ISSN: 0974 - 7516 Volume 8 Issue 10

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 8(10), 2012 [373-380]

Design and synthesis of some new pyrazole derivatives as anti-inflammatory and antimicrobial agents

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Received: 20th January, 2012 ; Accepted: 20th February, 2012

ABSTRACT

2-(6,8-Dibromo-2-methylquinazolin-4-yloxy)-acetohydrazide **(4)** was prepared by the reaction of 6,8-dibromo-2-methylbenzo-[*d*][1,3]oxazin-4-one with formamide to afford quinazolinone **(2)**, followed by alkylation with ethyl chloroacetate to give the ester **(3)**. Treatment of ester **(3)** with hydrazine hydrate and benzaldehyde afforded **(4)** and styryl quinazoline **(5)**. The hydrazide was reacted with triethyl orthoformate, acetylacetone and ethyl acetoacetate and benzaldehyde derivatives to afford the corresponding pyrazoles **(6)**, **(7)**, **(9)** and hydrazone derivatives **(10a-c)**. Cyclization of hydrazone **(10a-c)** with thioglycolic acid afforded the thiazole derivatives **(11a-c)**. The newly synthesized compounds were characterized by their spectral (IR, ^{1}H, ^{13}C NMR), Selected derivatives of these compounds were screened for anti-inflammatory and antimicrobial agents.

KEYWORDS

Pyrazolone;
Pyrazole;
Thiazole;
Quinazolin-4(3*H*)-one;
Anti-inflammatory activity;
Antimicrobial activity.

INTRODUCTION

Currently, available non-steroidal anti-inflammatory drugs (NSAIDs) like, ibuprofen, flurbiprofen, fenbufen and naproxen exhibit gastric toxicity. Long-term use of these drugs has been associated with gastro-intestinal (GI) ulceration, bleeding and nephrotoxicity. Quinazolin-4(3*H*)-one and its derivatives are a class of heteroaromatic compounds that have drawn much attention due to biological and pharmaceutical activities[1-11]. A brief survey on the biological activities of quinazolin-4(3*H*)-one derivatives showed anti-inflammatory[12-14], antitumor[15-18], anti HIV[19], antibacterial[20-22], as well as CNS depressant and anticonvulsant activities[23,24]. Also, 4-substituted quinazolines were studied as anticancer agents for their strong ability to inhibit several receptor tyrosine kinases[25]. The derivatives of quinazolin-4-one are potential drugs which can possess hypnotic[26], analgesic[27], anthelmintic[28], neuroleptic[29], antiallergic, antimalarial and other effects[30,31]. On the other hand, it was found that not only quinazoline derivatives showed chemotherapeutic activity but also pyrazole[32], pyrazolone[33], thiadiazoles[34] as well as triazole[35,36] moieties possess this activity. Moreover, the increasing biological importance of quinazolinone derivatives particularly in chemotherapy, promoted us to develop and synthesize the new molecules as pyrazole.

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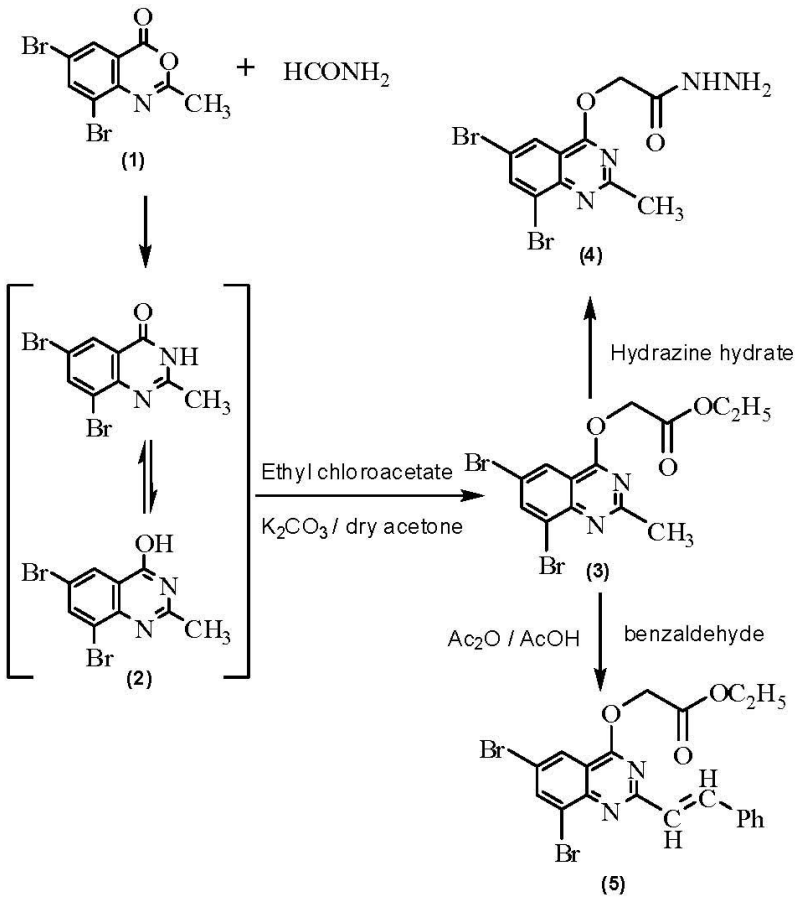
In the view of high biological and pharmacological activity of quinazoline derivatives[37], we synthesized some new pyrazole derivatives. 6,8-Dibromo-2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one 1 was refluxed with formamide to produce 6,8-dibromo-2-methylquinazolin-4(3*H*)one **(2)**. Reaction of compound **(2)** with ethyl chloroacetate in dry acetone in presence of potassium carbonate afforded ethyl 2-(6,8-dibromo-2-methylquinazolin-4- yloxy)acetate **(3)**. Hydrazinolysis of compound **(3)** with hydrazine hydrate gave the corresponding 2-(6,8- dibromo-2-methylquinazolin-4-yloxy)acetohydrazide **(4)** which used as starting material for preparation of some other quinazoline derivatives (Scheme 1). The IR spectrum of compound **(2)** showed bands at 3350, 1685 and 1620 cm^{-1} for (NH, C=O and C=N). Its ^{1}HNMR spectrum gave a signal at δ 2.40, 8.11, 8.21 and 12.30 ppm characteristic for CH_3, two aromatic protons and OH groups. IR, ^{1}H, ^{13}C NMR and microanalysis spectral data for compounds **(3)** and **(4)** are in agreements with their assigned structure. The condensation of **(3)** with benzaldehyde under Aldol type condensation afforded ethyl 2-(6,8- dibromo-2-styrylquinazolin-4-yloxy)acetate **(5)** (Scheme 1). ^{1}H NMR spectrum of compound **(5)** showed signals at 1.30, 4.12 and 4.90 ppm for CH_3, CH_2O and OCH_2CO groups with disappearance of signal for CH_3 of quinazoline ring, in addition, doublet signals at δ 6.95, 7.03 ppm characteristic for styryl group with coupling constant J = 15.98 and 16.01 Hz.

The synthesis of pyrazolone **(6)** and pyrazole derivatives **(7)** outlined in Scheme 2, were prepared by treating of 2-(6,8-dibromo-2-methylquinazolin-4-yloxy)acetohydrazide **(4)** with triethyl orthoformate and acetylacetone, respectively. IR spectrum of compound **(6)** showed bands at 3285, 1685 cm^{-1} for (NH and C=O), while, its ^{1}H NMR spectrum showed signals at δ 2.57, 4.83 ppm due to CH_3 and saturated CH in pyrazolone ring in addition to, a doublet signal at δ 7.50 ppm for CH=N of pyrazolone. ^{13}C NMR spectrum of compound **(6)** gave signals at δ 22.4 and 82.2 ppm characteristic for CH_3 and OCHCO groups. The structure of compound **(7)** was corroborated by IR, ^{1}H, ^{13}C NMR and elemental analysis. Furthermore, ethyl 3-(2-



Scheme 1 : Synthesis and reaction ethyl 2-(6,8-dibromo-2-methlquinazolin-4-yloxy)acetate 3.

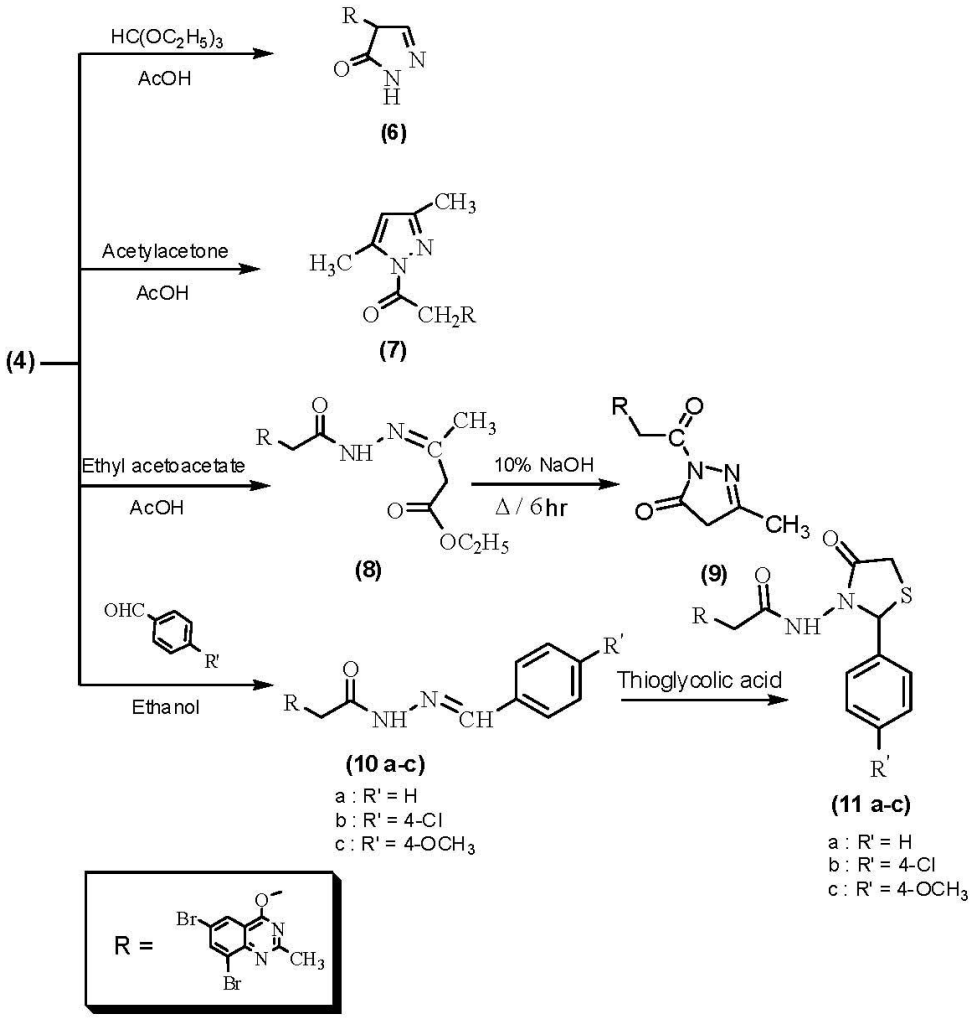
(2-(6,8-dibromo-2-methylquinazolin-4-yloxy)hydrazono)butanoate **(8)** was achieved employing reaction of **(4)** with ethyl acetoacetate. Compound **(8)** was intramolecular cyclized on treatment with 10% sodium hydroxide to yield **(9)** (Scheme 2).

Treatment of compound **(4)** with *p*-substituted benzaldehyde in absolute ethanol afforded benzylidine hydrazide derivatives **(10a-c)**, which were cyclized in the presence of thioglycolic acid to obtain thiazolidine derivatives **(11a-c)** (Scheme 2), respectively. The structure of compounds **(10a-c)** characterized by the presence of bands between 3280-3290 and 1680-1685 cm^{-1} for NH and C=O of amide groups in their IR spectra. ^1H NMR spectra of **(10a-c)** showed a singlet signal at δ 4.95 ppm characteristic for OCH_2CO, in addition, the important signal at δ 10.2 ppm for CH=N of Schiff 's base. The signals in ^{13}C NMR spectra of compounds **(10a-c)** assigned the structures and were mentioned in the experimental section. Compounds **(11a-c)** showed in ^1H NMR spectra a characteristic signals at δ 2.85-2.95, 3.67-3.69, and 4.89-4.98 ppm attributed to the CH_3, CH_2S and CH_2O groups, respectively. In addition, signals appeared at δ 5.79-5.92 ppm corresponds to CHAr group in thiazole ring. The IR spectra of compounds **(11a-c)** showed absorption bands at 3285-3310, 1690-1695 and 1680-1685 cm^{-1} for NH and 2 C=O groups, while in compound **(11b)** the ^{13}C NMR spectrum showed chemical shift signals at δ 23.3, 39.4, 57.7 and 61.9 ppm characteristic for CH_3, CH_2S, NCS and CH_2O groups which assigned the thiazole ring formation in **(11a-c)**.

PHARMACOLOGICAL STUDIES

Anti-inflammatory activity

The synthesized compounds were evaluated for their anti-inflammatory activity using carrageenan induced hind paw edema method of Winter et al[38]. The experi-



Scheme 2 : Reaction of 2-(6,8-dibromo-2-methylquinazolin-4-yloxy)acetohydrazide 4.

ment was performed on Albino rats of Wistar strain of either sex, weighing 180-200 gm. The animals were randomly allocated into groups of six animals each. One group was kept as control, received only 0.5% carboxymethyl cellulose solution. Group II and Group III were kept as standard and receives ibuprofen (70 mg/kg p.o.) and flurbiprofen (10 mg/kg p.o.) respectively. Carrageenan solution (0.1% in sterile 0.9% NaCl solution) in a volume of 0.1 mL was injected subcutaneously into the sub plantar region of the right hind paw of each rat, 1 h after the administration of the test compounds and standard drugs. The right hind paw volume was measured before and after 4 h of carrageenan treatment by means of a plethysmometer. The percent anti-inflammatory activity was calculated according to the following formula.

$$\text{Percent anti-inflammatory activity} = \left[V_c - \frac{V_t}{V_c}\right] \times 100$$

where, V_t represents the mean increase in paw volume in rats treated with test compounds and V_c represents the mean increase in paw volume in control group of rats.

Antibacterial and antifungal activities

Antibacterial activity of the synthesized compounds were determined in vitro by using dish diffusion method[39] against *Staphylococcus aureus* (gram-positive), *Escherichia coli* (gram negative) at 25, 50, 100 and 200 μg ml^{-1} concentration respectively, in the nutrient agar media by measuring the zone of inhibition in mm. Standard antibiotic Ofloxacin was used as reference drug at 25 and 50 μg ml^{-1} concentration. Similarly, the antifungal activity of the synthesized compounds were determined in vitro by dish diffusion method against fungal strain *A. niger* at 25, 50, 100 and 200 μg ml^{-1} concentration in sudroad dextrose medium by using ketoconazole as standarad drug at 25 and 50 μg ml^{-1} concentration. The zone of inhibition was measured in mm. The compounds which showed inhibition at 25 μg ml^{-1} concentration were further tested at 12.5 and 6.25 μg ml^{-1} concentrations. DMF was used as solvent to prepare the desired concentration of the synthesized compounds.

PHARMACOLOGICAL RESULTS AND DISCUSSION

The anti-inflammatory activity of the synthesized compounds **(6)**, **(7)**, **(9)** and **(10a-c)**, **(11a-b)** was evaluated by carrageenan induce paw edema method of Winter et al.[38]. The compounds **(6)**, **(7)**, **(9)** and **(10a)** were tested at an equimolar oral dose relative to 70 mg/kg ibuprofen. The tested compounds showed anti-inflammatory activity ranging from 18.17-80.29%, whereas standard drug ibuprofen and flurbiprofen showed 80.38 and 80.29% inhibition respectively after 4 h (TABLE 1). The anti-inflammatory activity of pyrazole derivatives is in the range of 18.17-80.29%. It was observed that the pyrazole derivatives **(6)** (80.29%) has shown the activity almost equal to standard drug, ibuprofen (80.38%). Compound **(10a)** and **(11a)** showed moderate activity.

Compounds **(6)**, **(7)**, **(9)** and **(10a-c)**, **(11a-b)** have been evaluated for their *in-vitro* anti-microbial activity against Staphylococcus aureus (S. aureus, ATCC-29737), as an example of gram-positive bacteria, Escherchia coli (E. coli, ATCC-8739) as an example of gram-negative bacteria and Aspergilus niger (A. niger) as a representative of fungi using cup plate technique. DMF (N,N-Dimethyl formamide) was run as a control and test was performed at 200, 100, 50, 25 μg/ml concentration. Ofloxacin and Ketoconazole was used as a standard drug. The micro dilution susceptibility test in nutrient agar media (Hi-Media), Sabroaud's dextrose agar media were used for determination of antibacterial and antifungal activities respectively. The minimal inhibitory concentration (MICs, μgmL^{-1}) of the tested compounds were recorded in TABLE 1. The antifungal screening results have shown that the compound **(6)**, **(10b)**, **(11a)** exhibited good activity (MIC 25 μgmL^{-1}) against *A. niger*, as compared with the standard drug Ketoconazole (MIC 12.5 μgmL^{-1}).

EXPERIMENTAL

Melting points are uncorrected and were recorded in open capillary tubes on a Stuart SMP3 melting point apparatus. Infrared spectra were recorded on FTIR 1600 spectrophotometer using (KBr discs) technique. ^1H, ^{13}C NMR spectra were measured on AC 250 MHz spectrometer. All chemical shifts were reported as δ (ppm) scale using TMS as the standard and coupling-constant values are given in Hz. The solvent for NMR spectra was deuterodimethylsulfoxide unless otherwise stated. The results of microanalysis were within ± 0.3% of the calculated values, the pharmacological study was carried out in National Research Center (Center of Excellence for Advanced Sciences, Cancer Biology

Research Laboratory).

6,8-Dibromo-2-methyl-4H-benzo[d][1,3]oxazin-4-one (1)

3,5-Dibromo-2-acetamidobenzoic acid (3.50 g) in (20 mL) acetic anhydride was heated on water bath for 1.5 hr, leaved to cool at room temperature to gave a pale yellow powder, which crystallized from ethanol. Yield 95%; m.p.: 140-142 C. IR (KBr): 1730 cm^{-1} (C=O), 1150 cm^{-1} (C-O, ether); ^1H NMR (DMSO-d_6): δ = 2.50 (s, 3H, CH_3),8.14,8.23 (2s, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): δ = 21.7 (CH_3), 119.1, 121.2, 122.5, 130.3, 142.4, 143.6, 164.1, 172.2 (Ar-C, C=N and C=O). Anal. Calcd for $C_9H_5Br_2NO_2$ (318.95): C, 33.89; H, 1.58; N, 4.39. Found: C, 33.88; H, 1.57; N, 4.39.

TABLE 1 : Anti-inflammatory and antimicrobial activity of the compounds

Compound	Anti-inflammatory activity[#]		Antimicrobial activity MIC[##]		
	Difference in paw volume (After 4 hr)	% inhibition ± SEM	*S. aureus*	*E. coli*	*C.albicans*
6	0.07 ± 0.008	80.29 ± 1.51	200	200	200
7	0.25 ± 0.016	37.63 ± 3.05 [d]	200	25	100
9	0.28 ± 0.007	56.57 ± 1.91[d]	200	100	12.5
10a	0.09 ± 0.008	78.78 ± 1.91	200	12.5	200
10b	0.36 ± 0.018	18.17 ± 4.21[d]	50	200	200
10c	0.16 ± 0.013	65.14 ± 3.03[c]	25	25	- -
11a	0.08 ± 0.013	78.78 ± 3.06	100	25	50
11b	0.23 ± 0.012	50.75 ± 2.73[d]	25	50	50
Ibuprofen	0.08 ± 0.012	80.38 ± 2.62	X X	X X	X X
Flurbipro- phen	0.08 ± 0.009	80.29 ± 2.25	X X	X X	X X
Ketocona- zole	X X	X X	X X	X X	6.25
Ofloxacin	X X	X X	6.25	6.25	- -
Control	0.44 ± 0.016		- -	- -	- -

- - Did not show any activity; X X Not tested; [#]Relative to their respective standard and data were analyzed by ANOVA followed by dunnett's multiple comparision test for n=6; [c]p<0.05, [d]p<0.01. [##]µg ml^{-1}

6,8-Dibromo-2-methylquinazolin-4(3H)-one (2)

Compound **(1)** (2.0 g) was refluxed in (10 mL) formamide for 2 hr, cooled, poured onto water to give a pale yellow powder, which crystallized from ethanol. Yield 75%; m.p.: 298-300 C. IR (KBr): 3350 cm^{-1} (NH), 1685 cm^{-1} (C=O), and 1620 cm^{-1} (C=N); ^1H NMR (DMSO-d_6): δ = 2.40 (s, 3H, CH_3), 8.11, 8.21 (2s, 2H, Ar-H), 12.3 (br,1H, NH); ^{13}C NMR (DMSO-d_6): δ = 21.8 (CH_3), 117.7, 123.4, 127.7, 139.2, 145.7, 146.7, 171.1 and 177.4 (Ar-C, C=N and C=O). Anal. Calcd for $C_9H_6Br_2N_2O$ (317.96): C, 34.00; H, 1.90; N, 8.81. Found: C, 34.01; H, 1.92; N, 8.79.

Ethyl 2-(6,8-dibromo-2-methylquinazolin-4-yloxy)acetate (3)

A mixture of **(2)** (10 mmol), ethyl chloroacetate (10mmol) in (20 mL) dry acetone and (2.0 g) of potassium carbonate was refluxed for 6 hr, cooled, poured onto water to afford a pale brown powder crystallized from ethanol. Yield 90%; m.p.: 124-126 C. IR (KBr): 1730 cm^{-1} (C=O), 1618 cm^{-1} (C=N) and 1185 cm^{-1} (C-O, ether); ^1H NMR (DMSO-d_6): δ = 1.30 (t, 3H, *J* = 7.0 Hz, CH_3CH_2), 2.59 (s, 3H, CH_3), 4.26 (q, 2H, *J* = 6.98 Hz, CH_2CH_3), 4.85 (s, 2H, CH_2O), 8.11, 8.21 (2s, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): δ = 14.1, 23.5 ($2CH_3$), 45.6, 62.3 ($2CH_2O$), 119.6, 129.1, 140.6, 144.8, 147.1, 155.0, 166.0 and 167.5 (Ar-C, C=N and C=O). Anal. Calcd for $C_{13}H_{12}Br_2N_2O_3$ (404.05): C, 38.64; H, 2.99; N, 6.93. Found: C, 38.63; H, 2.98; N, 6.95.

2-(6,8-Dibromo-2-methylquinazolin-4-yloxy)acetohydrazide (4)

A mixture of **(3)** (10 mmol), hydrazine hydrate (20 mmol) in (20 mL) ethanol was refluxed for 4 hr, the reaction mixture was concentrate and leaved to cool to give colorless crystals. Yield 80%; m.p.: 184-186 C. IR (KBr): 3280 cm^{-1} (br, NH and NH_2), 1675 cm^{-1} (C=O); ^1H NMR (DMSO-d_6): δ = 2.59 (s, 3H, CH_3), 4.64 (s, 2H, NH_2), 4.98 (s, 2H, CH_2O), 8.16, 8.35

(2s, 2H, Ar-H), 9.37 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 23.1 (CH_3), 61.5 (CH_2O), 118.6, 128.1, 139.5, 139.8, 143.7, 149.7, 165.8, 167.0 and 176.2 (Ar-C, 2C=N and C=O). Anal. Calcd for $C_{11}H_{10}Br_2N_4O_2$ (390.03): C, 33.87; H, 2.58; N, 14.36. Found: C, 33.85; H, 2.59; N, 14.33.

Ethyl 2-(6,8-Dibromo-2-methylquinazolin-4-yloxy)acetate (5)

A mixture of **(3)** (10 mmol) and benzaldehyde (10 mmol) was refluxed in (20 mL) acetic acid / acetic anhydride (1:1) for 5 hr, cooled and the reaction mixture was poured onto cold water to afford a colorless powder which crystallized from acetic acid. Yield 90%; m.p.: 148-150 C. IR (KBr): 1730 cm^{-1} (C=O), 1620 cm^{-1} (C=N) and 1180 cm^{-1} (C-O, ether); ^{1}H NMR (DMSO-d_6): δ = 1.30 (t, 3H, *J* = 7.02 Hz, CH_3CH_2), 4.12 (q, 2H, *J* = 6.99 Hz, CH_2CH_3), 4.90 (s, 2H, CH_2O), 6.95 (d, 1H, *J* = 15.9 Hz, CH=CH), 7.03 (d, 1H, *J* = 16.0 Hz, CH=CH), 7.33-7.60 (m, 5H, Ar-H), 7.95, 8.22 (2s, 2H, Ar-H). Anal. Calcd for $C_{20}H_{16}Br_2N_2O_3$ (492.16): C, 48.81; H, 3.28; N, 5.69. Found: C, 48.83; H, 3.29; N, 5.68.

4-(6,8-Dibromo-2-methylquinazolin-4-yloxy)-1H-pyrazol-5(4H)-one (6)

A mixture of **(4)** (10 mmol) and (16 mL) triethyl orthoformate in few drops of acetic acid was refluxed for 2 hr, after cooling the reaction mixture was poured onto water. The solid obtained was filtered off, dried and crystallized from ethanol to give colorless crystals. Yield 95%; m.p.: 168-170 C. IR (KBr): 3285 cm^{-1} (NH), 1685 cm^{-1} (C=O) and 1625 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6): δ = 2.57 (s, 3H, CH_3), 4.83 (d, 1H, OCH, pyrazolone), 7.50 (d, 1H, CH=N, pyrazolone), 7.95, 8.30 (2s, 2H, Ar-H), 9.66 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 23.4 (CH_3), 82.2 (OCHCO), 119.6, 122.4, 123.1, 129.1, 140.5, 144.1, 155.0, 166.8, 169.0 and 177.2 (Ar-C, 3C=N and C=O). Anal. Calcd for $C_{12}H_8Br_2N_4O_2$ (400.03): C, 36.03; H, 2.02; N, 14.01. Found: C, 36.02; H, 2.00; N, 14.00.

2-(6,8-Dibromo-2-methylquinazolin-4-yloxy)-1-(3,5-dimethyl-1H-pyrazol-1-yl)ethanone (7)

A mixture of **(4)** (10 mmol) and acetylacetone (10 mmol) in (10 mL) acetic acid was refluxed for 6 hr, after cooling, the reaction mixture was poured onto ice-water. The colorless powder obtained was crystallized from ethanol. Yield 80%; m.p.: 165-166 C. IR (KBr): 1680 cm^{-1} (C=O) and 1618 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6): δ = 2.56 (s, 3H, CH_3), 2.78, 2.99 (2s, 6H, 2CH_3, pyrazole), 4.90 (s, 2H, CH_2O), 6.65 (s, 1H, pyrazole), 8.11, 8.34 (2s, 2H, Ar-H); ^{13}C NMR (DMSO-d_6): δ = 23.4, 29.4, 45.9 and 61.9 (3CH_3 and CH_2O), 103.2, 119.2, 122.1, 122.9, 128.6, 140.0, 140.8, 147.2, 147.8, 166.1, 167.2 and 188.2 (Ar-C, 3C=N and C=O). Anal. Calcd for $C_{16}H_{14}Br_2N_4O_2$ (454.12): C, 42.32; H, 3.11; N, 12.34. Found: C, 42.33; H, 3.13; N, 12.32.

Ethyl 3-(2-(2-(6,8-dibromo-2-methylquinazolin-4-yloxy)acetyl) hydr-azono)butanoate (8)

A mixture of **(4)** (10 mmol) and ethyl acetoacetate (10 mmol) in (10 mL) acetic acid was refluxed for 5 hr, cooled and the reaction mixture was poured onto ice-water to give a colorless powder which was crystallized from ethanol/ acetic acid. Yield 75%; m.p.: 128-129 C. IR (KBr): 1735 cm^{-1} (C=O, ester), 1685 cm^{-1} (C=O, amide) and 1618 cm^{-1} (C=N); ^{1}H NMR (DMSO-d_6): δ =1.29 (t, 3H, CH_3CH_2), 1.94 (s, 3H, N=C-CH_3), 2.3 (s, 2H, CH_2CO), 2.44 (s, 3H, CH_3, quinazoline), 4.13 (q, 2H, CH_2CH_3), 4.63 (s, 2H, OCH_2CO), 7.95, 8.18 (2s, 2H, Ar-H), 10.68 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 8.9 (N=CCH_3), 14.1 (CH_3CH_2), 25.8 (CH_3, quinazoline), 43.5 (CH_2COO), 61.5 (CH_3CH_2O), 69.7 (OCH_2CO), 133.8, 119.6, 122.3, 123.5, 140.9, 149.5, 153.8, 168.3, 171.1, 173.3 and 181.4 (Ar-C, 3C=N and 2C=O). Anal. Calcd for $C_{17}H_{18}Br_2N_2O_4$ (502.16): C, 40.66; H, 3.61; N, 11.16. Found: C, 40.65; H, 3.60; N, 11.17.

1-(2-(6,8-Dibromo-2-methylquinazolin-4-yloxy)acetyl)-3-methyl-1H-pyrazol-5(4H)-one (9)

A solution of 8 (10 mmol) in (20 mL) sodium hydroxide (10%) was boiled under reflux for 6 hr, the reaction mixture was poured onto ice-water, then neutralized with dilute HCl. The solid obtained was collected by filtration, washed with water and crystallized from ethanol. Yield 68%; m.p.: 146-147 C. IR (KBr): 1685 and 1668 cm^{-1} (2 C=O, amide); ^{1}H NMR (DMSO-d_6): δ =1.94 (s, 3H, CH_3, pyrazole), 2.20 (s, 2H, CH_2CO, pyrazole), 2.44 (s, 3H, CH_3, quinazoline), 7.96, 8.19 (2s, 2H, Ar-H). ^{13}C NMR (DMSO-d_6): δ = 16.4 (CH_3, pyrazole), 25.4 (CH_3, quinazoline), 42.5 (CH_2O, pyrazole), 66.7 (OCH_2O), 113.7, 119.5, 122.1, 123.4, 140.9, 149.5, 159.3, 163.0, 170.6, 171.0 and 181.3 (Ar-C, 2C=O and

3C=N). Anal. Calcd for $C_{15}H_{12}Br_2N_4O_3$ (456.09): C, 39.50; H, 2.65; N, 12.28. Found: C, 39.52; H, 2.66; N, 12.26.

General procedure for synthesis of compounds (10a-c)

A mixture of **(4)** (10 mmol) and benzaldehyde derivatives (10 mmol) in (10 mL) absolute ethanol and few drops of acetic acid was refluxed for 10 hr, the reaction mixture leave to cool. The colorless solid was filtered off, and crystallized from ethanol / acetic acid.

N'-benzylidine-2-(6,8-dibromo-2-methylquinazolin-4-yloxy)ac-etohydrazide (10a)

Yield 80%; m.p.: 241-242 C. IR (KBr): 3285 cm^{-1} (NH), 1680 cm^{-1} (C=O) and 1623 cm^{-1} (C=N); ^1H NMR (DMSO- d_6): δ = 2.57 (s, 3H, CH_3), 4.95 (s, 2H, CH_2O), 7.80-8.38 (m, 7H, Ar-H), 10.2 (s, 1H, N=CH), 11.28 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 23.1 (CH_3), 61.5 (OCH_2CO), 118.6, 119.1, 120.8, 122.2, 127.8, 128.2, 132.5, 139.8, 143.6, 149.5, 155.8, 169.6, 170.3 and 176.8 (Ar-C, 3C=N and C=O). Anal. Calcd for $C_{18}H_{14}Br_2N_4O_2$ (478.14): C, 45.22; H, 2.95; N, 11.72. Found: C, 45.21; H, 2.93; N, 11.74.

N'-(4-Chlorobenzylidine)-2-(6,8-dibromo-2-methylquinazolin-4-yloxy)-acetohydrazide (10b)

Yield 85%; m.p.: 239-241 C. IR (KBr): 3290 cm^{-1} (NH), 1685 cm^{-1} (C=O) and 1628 cm^{-1} (C=N); ^1H NMR (DMSO-d_6): δ = 2.57 (s, 3H, CH_3), 4.94 (s, 2H, CH_2O), 7.52 (d, 2H, *J* = 8.20 Hz, Ar-H), 7.77 (d, 2H, *J* = 8.45 Hz, Ar-H), 8.15, 8.34 (2s, 2H, Ar-H), 10.20 (s, 1H, N=CH), 11.9 (s, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 23.2 (CH_3), 61.8 (OCH_2CO), 118.6, 119.4, 121.8, 122.7, 128.0, 128.5, 132.7, 139.8, 143.6, 149.8, 156.5, 168.6, 169.8 and 177.8 (Ar-C, 3C=N and C=O). Anal. Calcd for $C_{18}H_{13}Br_2ClN_4O_2$ (512.58): C, 42.18; H, 2.56; N, 10.93. Found: C, 42.19; H, 2.58; N, 10.95.

2-(6,8-Dibromo-2-methylquinazolin-4-yloxy)-N'-(4-methoxyben-zylidine)-acetohydrazide (10c)

Yield 84%; m.p.: 245-246 C. IR (KBr): 3280 cm^{-1} (NH), 1685 cm^{-1} (C=O) and 1618 cm^{-1} (C=N); ^1H NMR (DMSO-d_6): δ 2.58 (s, 3H, CH_3), 3.78 (s, 3H, OCH_3), 4.95 (s, 2H, OCH_2CO), 7.32 (d, 2H, *J* = 8.32 Hz, Ar-H), 7.78 (d, 2H, *J* = 8.48 Hz, Ar-H), 8.12, 8.33 (2s, 2H, Ar-H), 10.32 (s, 1H, N=CH), 11.85 (s, 1H, NH). Anal. Calcd for $C_{19}H_{16}Br_2N_4O_3$ (508.16): C, 44.91; H, 3.17; N, 11.03. Found: C, 44.93; H, 3.18; N, 11.05.

General procedure for synthesis of compounds 11a-c

A mixture of **(10a-c)** (10 mmol) and thioglycolic acid (10 mmol) in (10 mL) dry pyridine was refluxed for 6 hr, cooled, and the reaction mixture was poured onto cold dil. HCl. The solid obtained was filtered off, and crystallized from ethanol.

2-(6,8-Dibromo-2-methylquinazolin-4-yloxy)-N-(4-oxo-2-phenyl-thiazolidin-3-yl)acetamide (11a)

Yield 75%; m.p.: 153-15 C. IR (KBr): 3285 cm^{-1} (NH), 1695 and 1680 cm^{-1} (2C=O, amide); ^1H NMR (DMSO-d_6): δ = 2.59 (s, 3H, CH_3), 3.67 (s, 3H, CH_2S), 4.89 (s, 2H, OCH_2CO), 5.82 (s, 1H, CHPh), 7.82-8.52 (m, 7H, Ar-H), 10.40 (br, 1H, NH). Anal. Calcd for $C_{20}H_{16}Br_2N_4O_3S$ (552.24): C, 43.50; H, 2.92; N, 10.15. Found: C, 43.56; H, 2.85; N, 10.28.

N-(2-(4-Chlorophenyl)-4-oxothiazolidin-3-yl)-2-(6,8-dibromo-2-methylquinazolin-4-yloxy)acetamide (11b)

Yield 78%; m.p.: 158-160 C. IR (KBr): 3295 cm^{-1} (NH), 1690, 1682 cm^{-1} (2C=O, amide); ^1H NMR (DMSO-d_6): δ = 2.59 (s, 3H, CH_3), 3.69 (s, 3H, CH_2S), 4.89 (s, 2H, OCH_2CO), 5.79 (s, 1H, CHPh), 7.53 (d, 2H, *J* = 8.20 Hz, Ar-H), 7.78 (d, 2H, *J* = 8.28 Hz, Ar-H), 8.11 and 8.24 (2s, 2H, Ar- H), 10.50 (br, 1H, NH); ^{13}C NMR (DMSO-d_6): δ = 23.3 (CH_3), 39.4, 54.7, 61.9 (CH_2S, CHPh and OCH_2CO), 119.1, 122.2, 123.0, 128.7, 128.8, 134.8, 136.3, 140.1, 144.0, 148.5, 156.5, 168.6, 168.8,169.6 and 176.8 (Ar-C, 2C=N and 2C=O). Anal. Calcd for $C_{20}H_{15}Br_2ClN_4O_3S$ (586.68): C, 40.94; H, 2.58; N, 9.55. Found: C, 40.93; H, 2.57; N, 9.55.

2-(6,8-Dibromo-2-methylquinazolin-4-yloxy)-N-(2-(4-methoxyph-enyl) 4-oxothiazolidin-3-yl)acetamide (11c)

Yield 85%; m.p.: 168-170 C. IR (KBr): 3310 cm^{-1} (NH), 1695 and 1685 cm^{-1} (2C=O, amide); ^1H NMR (DMSO-d_6): δ = 2.58 (s, 3H, CH_3), 3.67 (s, 3H, CH_2S), 3.87 (s, 3H, OCH_3), 4.98 (s, 2H, OCH_2CO), 5.92 (s, 1H, CHPh), 7.33 (d, 2H, *J* = 8.30 Hz, Ar-H), 7.78 (d, 2H, *J* = 8.62 Hz, Ar-H), 8.15 and 8.36 (2s, 2H, Ar-H), 11.90 (br, 1H, NH). Anal. Calcd for $C_{21}H_{18}Br_2N_4O_4S$ (582.27): C, 43.32; H, 3.12; N, 9.62. Found: C, 43.33; H, 3.15; N, 9.62.

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CONCLUSIONS

We have used simple and convenient methods for synthesis of novel heterocycles such as pyrazolone, pyrazole and thiazole with 6,8-dibromo-2-methylquinazolin-4(3*H*)-one as substituent from 2-(6,8-Dibromo-2-methylquinazolin-4-yloxy) acetohydrazide with simple work up and clean products. All the tested compounds for antimicrobial and analgesic activities showed high, significant and moderate activity.

ACKNOWLEDGEMENT

The authors are thankful to C. B. Rawal, Chairman, RIET, Faridabad, Central Drug Research Institute (CDRI) for spectral analysis of the compounds and Majeedia Hospital, Hamdard University for providing necessary strains of bacteria and fungus. Authors are also thankful to Mrs. Shaukat Shah, in-charge animal house for providing Wistar rats.

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