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Synthesis and evaluation of new polysubstituted quinazoline derivatives as potential antimicrobial agents

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ABSTRACT

A new series of polysubstituted quinazoline derivatives has been furnished as a product of N-acylation, O-acylation and/or O-alkylation of the corresponding 2-methylquinazolinones; based on using the principles of lactam-lactim dynamic equilibrium phenomena and the role of solvent polarity in shifting such equilibrium. The reaction of the prepared polysubstituted quinazolines with different nitrogen, carbon, and sulphur nucleophiles has produced derivatives of 4-heteroaryl-quinazoline derivatives and interesting moieties such as oxadiazoles, triazoles, fused triazolo-thiadiazole, thiazole, furyl, and pyrazole were introduced at the 4-position of the quinazoline skeleton. Some of the synthesized compounds are tested for its antimicrobial activity.

Keywords: 1,3,4-oxadiazol-quinazoline, 1,2,4-triazolo quinazoline, triazolo[3,4-b]thiadiazol-quinazoline, antimicrobial activity.

INTRODUCTION

The recent literature reveals that the quinazoline moiety associated with various aromatic as well as heterocyclic compounds possess wide range of pharmacological activities [1-11]. The present study deals with the use of 2-methylquinazolin-4(3*H*)-one derivatives as starting intermediates in the synthesis of polysubstituted-quinazolines and attaching some interesting heterocycles (with mixed and non-mixed system) to the 4-position of quinazoline nucleus in order to find new biologically active pharmacophores, specially introduced as antimicrobial agents. Where, the entire structure of them was required, but activity is further enhanced by introducing halide substituent at 6- and 8-position [12,13]. Herein, we report the synthesis of 2-methyl-(6,8-dibromo and/or 6-bromo)-quinazolin-4(3*H*)-one **1a,b** as the starting intermediate followed by O-alkylation depending on the lactam-lactim dynamic equilibrium phenomena.

MATERIALS AND METHODS

Experimental

General procedure

Reagents and solvents were used as obtained from the supplier without further purification. All melting points reported are uncorrected and were determined on a Stuart electric melting point apparatus. Elemental analysis were carried out in the Micro Analytical Center, Cairo University, Giza, Egypt. Thin-layer chromatography (TLC) was performed on Merk TLC aluminium sheets silica gel 60 F_{254} with detection by UV quenching at 254nm. IR spectra (in KBr, cm^{-1}) were recorded on FTIR 8201PC Shimadzu (Japan, 1995). ^{1}H NMR spectra were recorded on a Varian 300 MHz (Germany, 1999) with residual proton signal of the deuterated solvent as the internal reference (δ_H=7.26 ppm for $CDCl_3$ and δ_H=2.51 ppm for DMSO-*d6*). TMS was used as an internal standard with chemical shifts δ in

ppm from downfield to upfield. EIMS were recorded on a gas chromatographic GCMS –Qploopx Shimadzu (Japan, 1990).

Formation of 1a,b: were prepared according to literature [14].

4-Acetoxy-6,8-dibromo-2-methylquinazolin-4(3*H*)-one (2)

A solution of quinazolinone **1a** (3.18g, 0.01mol) in acetyl chloride (20 mL) was heated at 60°C in water bath for 2 h. The solid that separated after cooling was washed with ligh pet. ether (60-80°), filtered off and crystallized from benzene to give 2.25g (63%) of **2**.

M.p. 117-118 °C. IR (KBr): 1733 (CO), 2940 (CH-aliph.), 3012, 3059 cm^{-1} (CH-arom.). Anal. Calc. for $C_{11}H_8Br_2N_2O_2$ (360): C 36.70, H 2.24, Br 44.39, N 7.78; found: C 36.34, H 2.45, Br 44.13, N 7.64.

3-Acetyl-6,8-dibromo-2-methylquinazolin-4(3*H*)-one (3)

A mixture of quinazolinone **1a** (3.18g, 0.01mol) and acetyl chloride (0.79g, 0.01mol) in dry pyridine (20 mL) was heated under reflux for 2h. The reaction mixture after cooling was poured over HCl/crushed ice. The solid obtained was filtered off and crystallized from acetic acid to give 2.41g (68%) of **3**.

M.p. 178 °C. IR (KBr): 1683 (CO), 2937 (CH-aliph.), and 3061 cm^{-1} (CH-arom.). ^1H NMR ($CDCl_3$): δ 1.85(s, 3H, CH_3), 2.18(s, 3H, CH_3), 7.82-7.94 (m, 2H, Ar-H). Anal. Calc. for $C_{11}H_8Br_2N_2O_2$ (360): C 36.70, H 2.24, Br 44.39, N 7.78; found: C 36.97, H 2.38, Br 44.04, N 8.12.

3-(2-Chloroacetyl)-6,8-dibromo-2-methylquinazolin-4(3*H*)-one (4)

Quinazolinone derivative **1a** (3.18g, 0.01mol) was dissolved in 1,4-dioxane (20 mL) then chloro acetylchloride (2.26g, 0.02mol) was added drop wise with stirring at 0°C. Then the reaction mixture was stirred at room temperature for 2h. The solid that separated was collected and washed with pet. ether (40-60°), The crude product was recrystallized from ethanol to give 2.24g (56%) of **4**.

M.p. 258-260 °C. IR (KBr): 1714, 1720 (CO), 2920(CH-aliph.), and 3051cm^{-1} (CH arom.). Anal. Calc. for $C_{11}H_7Br_2ClN_2O_2$ (394.5): C 33.49, H 1.79, Br 40.51, N 7.10; found: C 33.70, H 2.11, Br 40.25, N 7.36.

6,8-Dibromo-3-(hydrazinylacetyl)-2-methylquinazolin-4(3*H*)-one (5)

A mixture of **4** (3.95g, 0.01mol) and hydrazine hydrate (0.015mol) in ethanol (30 mL) was refluxed for 5 h. The reaction mixture was concentrated, cooled and the solid obtained was filtered off and recrystallized from benzene to give 2.74g (71%) of **5**. M.P. 178 °C. IR (KBr): 1688 (CO), 2939 (CH-aliph.), 3013, 3058 (CH-arom.), 3158, 3305 (NH), and 3450 cm^{-1} (OH). Anal. Calc. for $C_{11}H_{10}Br_2N_4O_2$ (390): C 33.87, H 2.58, Br 40.97, N 14.36; found: C 34.21, H 2.84, Br 40.62, N 14.58.

Formation of (6a,b)

A mixture of **4** (3.95g, 0.01mol) and piperidine and/or morpholine (0.01mol) in ethanol (30 mL) was refluxed for 6 h. The reaction mixture was concentrated and cooled to yield a solid which recrystallized from ethanol to furnish **6a,b** repectively.

6,8-Dibromo-2-methyl-3-(piperidin-1-ylacetyl)quinazolin-4(3*H*)-one (6a): Yield 3.44g (78%). M.p. 241-243 °C. IR (KBr): 1688(CO), 2936(CH-aliph.), 3058 cm^{-1} (CH-arom.). Anal. Calc. for $C_{16}H_{17}Br_2N_3O_2$ (443): C 43.37, H 3.87, Br 36.06, N 9.48; found: C 43.61, H 3.96, Br 36.38, N 9.15.

6,8-Dibromo-2-methyl-3-(morpholin-4-ylacetyl)quinazolin-4(3*H*)-one (6b): Yield 3.22g (72%). M.p. 233-235 °C. IR (KBr): 1687(CO), 2939(CH-aliph.), 3061 cm^{-1} (CH-arom.). Anal. Calc. for $C_{15}H_{15}Br_2N_3O_3$ (445): C 40.48, H 3.40, Br 35.90, N 9.44; found: C 40.73, H 3.67, Br 35.45, N 9.59. MS: m/z 445[M^+], 359, 316, 263, 236, 129.

6,8-Dibromo-2-methyl-3-[(1,3-thiazol-2-ylamino)acetyl]quinazolin-4(3*H*)-one (7)

A solution of **4** (3.95g, 0.01mol) and 2-aminothiazole (1.00g, 0.01mol) in glacial acetic acid (40 mL) was heated under reflux for 3 h. The reaction mixture cooled then poured upon crushed ice and leaved overnight. The solid formed was filtered off and recrystallized from xylene to give 2.12g (46%) of **7**.

M.P. 236-238 °C. IR (KBr): 1687(CO), 2945(CH-aliph.), 3057 cm^{-1} (CH-arom.). Anal. Calc. for $C_{14}H_{10}Br_2N_4O_2S$ (458): C 36.70, H 2.20, Br 34.88, N 12.23, S 7.00; found: C 38.12, H 2.43, Br 35.17, N 12.51, S 6.79.

Formation of (8a,b)

A mixture of quinazolinone derivatives **1a** and/or **1b** (0.01 mol), ethyl chloroacetate (5.42 g, 0.05 mol), and anhydrous K_2CO_3 (5 g, 0.04 mol) in dry acetone (80 mL) was heated in water bath at 60°C for 24h. The excess solvent was removed by distillation and water was added upon the reaction mixture. The reaction mixture was partitioned between H_2O and diethyl ether and the liquid phase was extracted 3x with 30 mL Et_2O. The combined

organic extracts were dried by sodium sulphate and the solvent was removed by distillation at atmospheric pressure. The solid obtained was crystallized from ethanol to give 2.74g (68%) of **8a** and 2.69g (83%) of **8b** respectively.

6,8-Dibromo-4-(ethoxycarbonylmethoxy)-2-methylquinazoline (8a): M.p. 155-157 °C. IR (KBr): 1736 (CO), 2856 (CH-aliph.), and 3074 cm^{-1} (CH-arom.). ^1H NMR (DMSO-*d6*): δ 1.43 (t, 3H, $CH_2\underline{CH_3}$), 2.18 (s, 3H, CH_3), 3.96 (s, 2H, CH_2), 4.95 (q, 2H, CH_2), 8.16-8.34 (m, 2H, Ar-H). Anal. Calc. for $C_{13}H_{12}Br_2N_2O_3$ (404): C 38.61, H 2.97, Br 39.60, N 6.93; found: C 38.94, H 2.83, Br 39.86, N 7.18.

6-Bromo-4-(ethoxycarbonylmethoxy)-2-methylquinazoline (8b): M.p. 127-128 °C. IR (KBr): 1734 (CO), 2856 (CH-aliph.), and 3076 cm^{-1} (CH-arom.). Anal. Calc. for $C_{13}H_{13}BrN_2O_3$ (325): C 48.00, H 4.00, Br 24.61, N 8.61; found: C 48.31, H 4.19, Br 24.15, N 8.47.

Formation of (9a,b)
A solution of **8a** (4.04g, 0.01mol) and/or **8b** (3.25g, 0.01mol) and hydrazine hydrate (0.75g, 0.015mol) in ethanol (40 mL) was heated under reflux for 7h. The solid that separated after concentration and cooling was filtered off, dried, and recrystallized from the proper solvent to give 3.58g (92%) of **9a** and 2.63g (84%) of **9b** respectively.

4-(Acetohydrazide)-6,8-dibromo-2-methylquinazoline (9a): M.p. 264-267 °C (DMF). IR (KBr): 1683 (CO), 2855 (CH-aliph.), 3055 (CH-arom.), and 3220, 3425 cm^{-1} (NH). Anal. Calc. for $C_{11}H_{10}Br_2N_4O_2$ (390): C 33.84, H 2.56, Br 41.02, N 14.35; found: C 34.11, H 2.80, Br 41.42, N 14.62. MS: m/z 359[M^+ - N_2H_4], 317, 236, 129.

4-(Acetohydrazide)-6-bromo-2-methylquinazoline (9b): M.p. 240-241 °C (*n*-BuOH). IR (KBr): 1667 (CO), 2853 (CH-aliph.), 3038 (CH-arom.), and 3206, 3435 cm^{-1} (NH). Anal. Calc. for $C_{11}H_{10}BrN_4O_2$ (311): C 42.44, H 3.53, Br 25.72, N 18.00; found: C 42.70, H 3.32, Br 26.04, N 18.36.

Formation of (10a,b)
To a solution of **9a** (3.90 g, 0.01 mol) and/or **9b** (3.11 g, 0.01 mol) in dry pyridine (30 mL), carbon disulphide (1.52g, 0.02 mol) was added and the reaction mixture was heated under reflux for 8h. After cooling the reaction mixture was poured onto ice/HCl mixture and the solid that separated was washed with cold water, filtered off, and crystallized from EtOH to give 2.60g (61%) of **10a** and 2.55g (72%) of **10b** respectively.

6,8-Dibromo-2-methyl-4-(5-mercapto-2-methoxy-1,3,4-oxadiazole)quinazoline (10a): M.p. 278 °C. IR (KBr): 1463 (C=S), 1632 (C=N), 2856 (CH-aliph.), and 3070 cm^{-1} (CH-arom.). Anal. Calc. for $C_{12}H_8Br_2N_4O_2S$ (432): C 33.33, H 1.85, Br 37.03, N 12.69, S 7.40; found: C 33.58, H 2.09, Br 37.28, N 12.94, S 7.16.

6-Bromo-2-methyl-4-(5-mercapto-2-methoxy-1,3,4-oxadiazole)quinazoline (10b): M.p. 290-292 °C. IR (KBr): 1461 (C=S), 1636 (C=N), and 2851 cm^{-1} (CH-aliph.). ^1H NMR (DMSO-*d6*): δ 2.27 (s, 3H, CH_3), 5.35 (s, 2H, CH_2) 7.36-7.97 (m, 3H, Ar-H), 8.51 (s, 1H, SH). Anal. Calc. for $C_{12}H_9BrN_4O_2S$ (353): C 40.79, H 2.54, Br 22.66, N 15.86, S 9.06; found: C 41.05, H 2.79, Br 22.15, N 15.55, S 9.31.

Formation of (11a,b)
To an ice cold solution of **9a** (3.9 g, 0.01 mol) and/or **9b** (3.11 g, 0.01mol) in ethanolic KOH (1.12 g, 0.02 mol) in 50 mL EtOH), 1.14g (0.15 mol) of CS_2 was added gradually with stirring during 15min. The reaction mixture was further stirred for 2h then dry ether was added. The solid that separated was filtered and crystallized from EtOH/H_2O to give 2.12g (42%) of **11a** and 2.07g (48%) of **11b** respectively.

Potassium[6,8-dibromo-2-methylquinazolinloxy-4-yl]acetohydrazide dithiocarbamic acid (11a): M.p. >300 °C. IR (KBr): 1451 (C=S), 1594 (C=N), 1659 (CO), 2968 (CH-aliph.), 3073 (CH-arom.), and 3427 cm^{-1} (NH). Anal. Calc. for $C_{12}H_9Br_2N_4O_2KS_2$ (504): C 28.57, H 1.78, Br 31.74, N 11.11, S 12.69; found: C 28.94, H 2.15, Br 31.25, N 11.30, S 12.87.

Potassium[6-bromo-2-methylquinazolinloxy-4-yl]acetohydrazide dithiocarbamic acid (11b): M.p. >300 °C. IR (KBr): 1469 (C=S), 1603 (C=N), 1660 (CO), 2951 (CH-aliph.), 3063 (CH-arom.), and 3209 cm^{-1} (NH). Anal. Calc. for $C_{12}H_{10}Br_2N_4O_2KS_2$ (425): C 33.88, H 2.35, Br 18.82, N 13.17, S 15.05; found: C 34.17, H 2.59, Br 19.20, N 13.30, S 15.31.

Formation of (12a,b)
A mixture of **11a** and/or **11b** (0.01 mol) and hydrazine hydrate (0.015 mol) in ethanol (30 mL) was heated under reflux for 4h. After cooling 5 mL of water was added and the reaction mixture was neutralized with dilute HCl. The solid that formed was filtered off and crystallized from *n*-butanol to give 3.58g (81%) of **12a** and 2.90g (78%) of **12b** respectively.

6,8-Dibromo-2-methyl-4-(4-Amino-5-mercapto-1,2,4-triazolo-3-yl)methoxyquinazoline (12a): M.p. 226-227 °C. IR (KBr): 1598 (C=N), 2858 (CH-aliph.), 3074 (CH-arom.), and 3196, 3427 cm^{-1} (NH). Anal. Calc. for $C_{12}H_{10}Br_2N_6OS$ (446): C 32.28, H 2.24, Br 35.87, N 18.83, S 7.17; found: C 32.58, H 2.42, Br 36.15, N 18.44, S 7.35.

6-bromo-2-methyl-4-(4-Amino-5-mercapto-1,2,4-triazolo-3-yl)methoxyquinazoline (12b): M.p. 209-211 °C. IR (KBr): 1598 (C=N), 2858 (CH-aliph.), 3074 (CH-arom.), and 3196, 3427 cm^{-1} (NH). Anal. Calc. for $C_{12}H_{11}BrN_6OS$ (367): C 39.23, H 2.99, Br 21.79, N 22.88, S 8.71; found: C 39.41, H 3.20, Br 21.45, N 22.54, S 8.18.

6,8-Dibromo-2-methyl-4-[(6-methyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methoxy]quinazoline (13)
A suspension of **12a** (4.46g, 0.01mol) in mixture of 5 mL acetic acid and 10 mL $POCl_3$ was stirred at room temperature for 10h. The reaction mixture was poured onto cold ice/water and the solid that formed was collected, washed with water, and crystallized from acetic acid to give 2.40g (51%) of **13**.
M.p. 261 °C. IR (KBr): 1584, 1627 (C=N), 2852 (CH-aliph.), 3061 cm^{-1} (CH-arom.). Anal. Calc. for $C_{14}H_{10}Br_2N_6OS$ (470): C 35.74, H 2.12, Br 34.00, N 17.87, S 6.80; found: C 35.89, H 2.29, Br 33.75, N 17.96, S 7.08. MS: m/z 470[M^+], 432, 414, 317, 236, 153, 128.

Formation of (14a-c)
A mixture of **9a** (3.90 g, 0.01 mol) and/or **9b** (3.10 g, 0.01 mol) and acetyl chloride (0.58 g, 0.01 mol) and/or benzoyl chloride (1.40 g, 0.01 mol) in dry benzene (40 mL) was heated under reflux for 4h. The solid that separated after concentration and cooling was filtered off and recrystallized from the proper solvent to give **14a-c** respectively.

4-Acetylhydrazinocarbonylmethoxy-6,8-dibromo-2-methylquinazoline (14a): Yield 3.70g (86%). M.p. 263-265 °C (EtOH). IR (KBr): 1608 (C=N), 1676 (CO), 2854 (CH-aliph.), 3066 (CH-arom.), and 3258, 3430 cm^{-1} (NH). Anal. Calc. for $C_{13}H_{12}Br_2N_4O_3$ (432): C 36.11, H 2.77, Br 37.03, N 12.96; found: C 36.38, H 2.95, Br 37.28, N 13.21.

4-Benzoylhydrazinocarbonylmethoxy-6,8-dibromo-2-methylquinazoline (14b): Yield 4.38g (89%). M.p. 287-288 °C (EtOH). IR (KBr): 1602 (C=N), 1689 (CO), 2843 (CH-aliph.), 3070 (CH-arom.), and 3425 cm^{-1} (NH). Anal. Calc. for $C_{18}H_{14}Br_2N_4O_3$ (494): C 43.72, H 2.83, Br 32.38, N 11.33; found: C 43.94, H 3.07, Br 32.64, N 11.12.

4-Acetylhydrazinocarbonylmethoxy-6-bromo-2-methylquinazoline (14c): Yield 2.58g (73%). M.p. 254-255 °C (AcOH). IR (KBr): 1595 (C=N), 1668 (CO), 2831 (CH-aliph.), and 3301 cm^{-1} (NH). Anal. Calc. for $C_{13}H_{13}BrN_4O_3$ (353): C 44.19, H 3.86, Br 22.66, N 15.86; found: C 44.39, H 3.95, Br 22.24, N 16.14.

Formation of (15a-c)
To a suspension of **14a-c** (0.01 mol) in 20 mL 1,4-dioxane, 10 mL of $POCl_3$ was added portion wise with stirring at 0 °C. The temperature was elevated gradually to 120 °C and kept for 10min. After cooling the reaction mixture was poured onto ice/water mixture and the solid that separated was filtered off and crystallized from the proper solvent to give **15a-c** respectively.

6,8-Dibromo-2-methyl-4-[(5-methyl-1,3,4-oxadiazol-2-yl)methoxy]quinazoline (15a): Yield 3.51g (85%). M.p. 231 °C (*n*-BuOH). IR (KBr): 1615 (C=N), 2929 (CH-aliph.), and 3059 cm^{-1} (CH-arom.). Anal. Calc. for $C_{13}H_{10}Br_2N_4O_2$ (414): C 37.68, H 2.41, Br 38.64, N 13.52; found: C 37.91, H 2.57, Br 38.97, N 13.73.

6-Bromo-2-methyl-4-[(5-methyl-1,3,4-oxadiazol-2-yl)methoxy]quinazoline (15b): Yield 3.37g (71%). M.p. 227-229 °C (AcOH). IR (KBr): 1601 (C=N), 2921 (CH-aliph.), and 3047 cm^{-1} (CH-arom.). Anal. Calc. for $C_{18}H_{12}Br_2N_4O_2$ (476): C 45.37, H 2.52, Br 33.61, N 11.76; found: C 45.76, H 2.77, Br 33.90, N 11.41.

6,8-Dibromo-2-methyl-4-[(5-phenyl-1,3,4-oxadiazol-2-yl)methoxy]quinazoline (15c): Yield 2.46g (73%). M.p. 189-191 °C (toluene). IR (KBr): 1604 (C=N), 2921 (CH-aliph.), and 3068 cm^{-1} (CH-arom.). Anal. Calc. for $C_{13}H_{11}BrN_4O_2$ (335): C 46.56, H 3.28, Br 23.88, N 16.71; found: C 46.79, H 3.12, Br 23.56, N 16.89.

Formation of (16a,b)
A mixture of **9a** (3.96 g, 0.01 mol), cinnamaldehyde (1.32 g, 0.01 mol) and/or furaldehyde (0.9 g, 0.01 mol), and few drops of piperidine in ethanol (30 mL) was refluxed for 6h. The solid that separated after concentration and cooling was recrystallized from ethanol to give 4.60g (91%) of **16a** and 3.65g (78%) of **16b** respectively.

2-[(6,8-Dibromo-2-methylquinazolin-4-yl)oxy]-*N'*-[3-phenylprop-2-en-1-ylidene]acetohydrazide (16a): M.p. 187-188 °C. IR (KBr): 1597 (C=N), 1682 (CO), 2852 (CH-aliph.), 3059 (CH-arom.), and 3428 cm^{-1} (NH). Anal. Calc. for $C_{20}H_{16}Br_2N_4O_2$ (504): C 47.61, H 3.17, Br 31.74, N 11.11; found: C 47.92, H 3.36, Br 31.43, N 10.84.

2-[(6,8-Dibromo-2-methylquinazolin-4-yl)oxy]-*N'*-[furan-2-ylmethylidene]acetohydrazide (16b): M.p. 195-196 °C. IR (KBr): 1600 (C=N), 1686 (CO), 2855 (CH-aliph.), 3059 (CH-arom.), and 3429 cm^{-1} (NH). ^{1}H NMR (DMSO-*d6*): δ 2.21 (s, 3H, CH_3), 3.08 (s, 1H, CH=N), 3.69 (s,2H, OCH_2), 7.61-8.12 (m, 5H, Ar-H), 9.98 (s, 1H, NH).Anal. Calc. for $C_{16}H_{12}Br_2N_4O_3$ (468): C 41.02, H 2.56, Br 34.18, N 11.96; found: C 41.27, H 2.70, Br 34.03, N 12.26. MS: m/z 468[M^+], 401, 360, 236, 152.

2-[(6,8-Dibromo-2-methylquinazolin-4-yl)oxy]-*N*-[2-(furan-2-yl)-4-oxo-1,3-thiazolidin-3-yl]acetamide (17)
An equimolar ratio of **16b** (4.68g, 0.01mol) and thioglycolic acid (0.92g, 0.01mol) in benzene (30 mL) in presence of few drops of piperidine was heated under reflux for 8h. The solid that formed after concentration and cooling was filtered off and crystallized from ethanol to give 3.58g (66%) of **17**.
M.p. 117-119 °C. IR (KBr): 1604 (C=N), 1689, 1731 (CO), 2836 (CH-aliph.), 3057 (CH-arom.), and 3248 (NH), 3469 cm^{-1} (OH). Anal. Calc. for $C_{18}H_{14}Br_2N_4O_4S$ (542): C 38.85, H 2.58, Br 29.52, N 10.33, S 5.90; found: C 39.12, H 2.74, Br 29.16, N 10.09, S 5.61.

2-[(6,8-Dibromo-2-methylquinazolin-4-yl)oxy]-N'-[furan-2-yl(phenylsulfanyl)methyl] acetohydrazide (18)
A mixture of **16b** (4.68g, 0.01mol) and thiophenol (1.10g, 0.01mol) in benzene (30 mL) in presence of few drops of piperidine was stirred at room temperature for 4d. The solid that formed was collected and crystallized from benzene to give 4.48g (78%) of **18**.
M.p. 144-146 °C. IR (KBr): 1627 (C=N), 1661 (CO), 2857 (CH-aliph.), 3068 (CH-arom.), and 3250 cm^{-1} (NH). Anal. Calc. for $C_{22}H_{18}Br_2N_4O_3S$ (578): C 45.67, H 3.11, Br 27.68, N 9.68, S 5.53; found: C 45.85, H 3.28, Br 27.50, N 9.24, S 5.11.

Formation of (19) and/or (20)
A mixture of **9a** (3.96 g, 0.01 mol), ethyl acetoacetate (0.70g, 0.01mol) and/or acetyl acetone (0.54g, 0.01mol), and few drops of piperidine in 30 mL ethanol was heated at 70°C for 5h. The solid that separated after concentration and cooling was filtered off and recrystallized from light pet. ether (60-80°) to give 2.19g (48%) of **19** and 2.47g (53%) of **20** respectively.

1-{[(6,8-Dibromo-2-methylquinazolin-4-yl)oxy]acetyl}-5-methyl-1,2-dihydro-3*H*-pyrazol-3-one (19): M.p. 96-98 °C. IR (KBr): 1600 (C=N), 1684 (CO), 2874 (CH-aliph.), 3073 (CH-arom.), 3259 (NH), and 3424 cm^{-1} (OH) due to the presence of two tautomeric keto-enol forms. ^{1}H NMR (DMSO-*d6*): δ 1.34 (s, 3H, CH_3), 2.28 (s, 3H, CH_3), 3.77 (s, 2H, CH_2), 4.92 (s, 1H, CH-pyrazole), 7.73-8.22 (m, 2H, Ar-H), 9.57 (s, 1H, NH). Anal. Calc. for $C_{15}H_{12}Br_2N_4O_3$ (456): C 39.47, H 2.63, Br 35.08, N 12.28; found: C 39.25, H 2.72, Br 38.84, N 12.00.

2-[(6,8-Dibromo-2-methylquinazolin-4-yl)oxy]-*N*'-[4-oxopentan-2-ylidene]acetohydrazide (20): M.p. 154-156 °C. IR (KBr): 1609 (C=N), 1688, 1739 (CO), 2854 (CH-aliph.), 3070 (CH-arom.), 3238 cm^{-1} (NH). Anal. Calc. for $C_{16}H_{16}Br_2N_4O_3$ (472): C 40.67, H 3.38, Br 33.89, N 11.86; found: C 40.98, H 3.54, Br 34.16, N 12.07.

Antimicrobial activity
Some of the synthesized compounds were tested for their in vitro antibacterial activity against *Staphylococcus aureus*, *Bacillus cereus* (Gram positive) and *Serratia marcesens*, *Proteus merabitis* (Gram negative) and the antifungal activity was screened against *Aspergillus chraceus*, *Penicillium chrysogenum* by disc diffusion method [15].

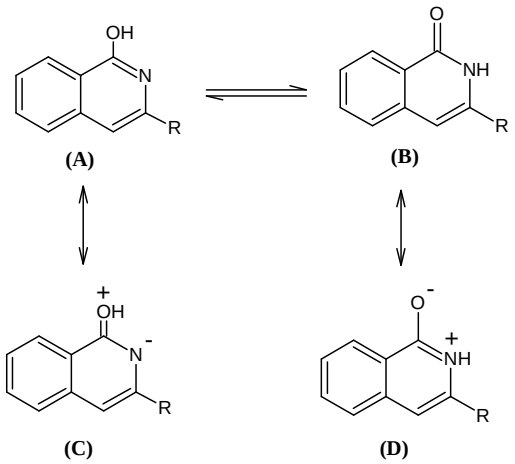
Ampicillin and mycostatin were used as standard drugs for antibacterial and antifungal activity respectively. Sterile disc of 5 mm in diameter made from Whatmann filter paper which is previously sterilized in U.V lamp was dipped in solution of synthesized compound and standard and placed the disc on the surface of agar plates.
Allowed the plates to stand for 1h at room temperature as a period of pre-incubation to obtain minimize the effects of variation in time between the applications of different solutions. Then the plates were incubated for 24h at 37 °C for bacteria and 72h at 25 °C for fungi. The diameter of zone of inhibition was measured.

RESULTS AND DISCUSSION

The titled compounds 2-methyl-(6,8-dibromo and/or 6-bromo)-quinazolin-4(3*H*)-one **1a,b** were prepared by a facile one-step process according to reported method [14]. In spite of the high stability of quinazolin-4(3*H*)-one derivatives **1a,b** (with respect to the corresponding benzoxazinone derivatives) they can be used as versatile building blocks in the synthesis of new series of 2,4-disubstituted quinazoline derivatives with high functionality at the heterocyclic system; using the principles of lactam-lactim dynamic equilibrium phenomena.

It was reported that, polar solvent (e.g. pyridine and DMF) strongly affects and favors the amide-like structure of the α– and γ–pyridinone tautomers, the same was shown with pyrimidinone system which very closed to our quinazolone system [16, 17]. Therefore, one can consider our quinazolone system to exhibit this phenomena, specially when discussing the nature of that system. Latam-lactim dynamic equilibrium is a classical medium-dependent equilibrium.

This compounds found normally in the lactam form (B); where from the canonical forms (D) & (C), the (D) form is much greater stabilized than the (C) form. Since The (D) form possess the oxygen with –ve charge and nitrogen has +ve charge, which is more favored than the reverse [form (C); the oxygen has +ve charge and nitrogen has –ve charge] (scheme 1).



Scheme 1

As shown, form (B) is the more polar conformer and has higher dipole moment, so it will be more stable in polar solvent or in aqueous media. Form (A) will be found only in non-polar solvent or in gas phase. In aqueous solution it is preferred to have $^{+}$NH (lower acidity than $^{+}$OH) rather than $^{+}$OH and so the lactam form is more preferable (scheme 1).

In order to give a practical prove for the solvent polarity effect on lactam-lactim dynamic equilibrium of quinazolin-4(3*H*)-one, acylation of quinazolin-4(3*H*)-one **1a** with acetyl chloride (as solvent also) afforded 4-acetoxyquinazoline **2** as sole product and no *N*-acetyl derivative is obtained. On the other hand, when the above reaction was conducted in presence of pyridine, the 3-acetyl quinazolinone derivative **3** was produced (scheme 2). This clarify that, in presence of acetyl chloride as solvent this quinazolinone **1a** exist in lactim form, while in pyridine (polar solvent) it exist in lactam form.

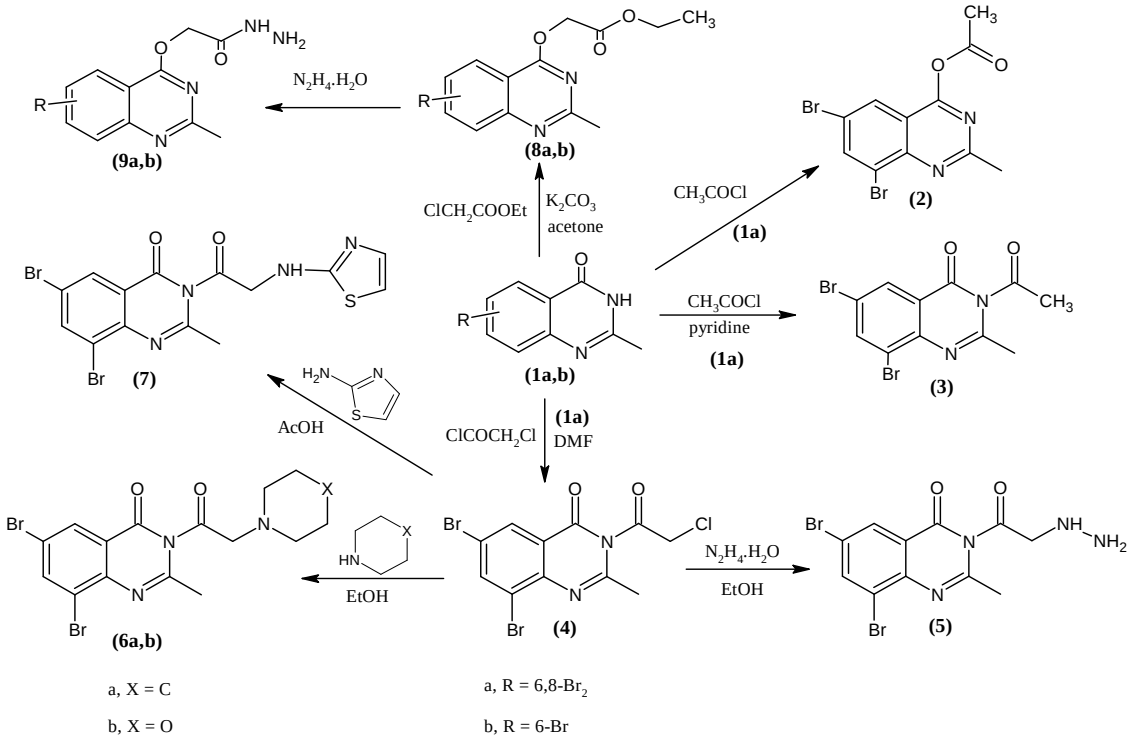
Moreover, quinazolin-4(3*H*)-one **1a** was reacted with chloroacetyl chloride in presence of *N*,*N*-dimethyl formamide and the 3-chloroacetyl quinazolinone derivative **4** was produced as a sole product. Clearly, the lactam form is the more predominant tautomer in DMF.

Compound **4** is considered as key starting material for a diversity of heterocyclic compounds; it has a hydrolysable chloro-atom which can be easily exchanged. In this context, compound **4** was converted to the corresponding hydrazine **5** on treatment with hydrazine hydrate in boiling ethanol. Furthermore, compound **4** was converted into more interesting derivatives via treatment with secondary amines like piperidine and morpholine; compounds **6a,b** were produced in good yield. Refluxing **4** with 2-aminothiazole in glacial acetic acid furnished the thiazole-quinazoline derivative **7** (scheme 2).

The behaviour of compounds **1a,b** towards carbon electrophiles has been investigated with a view for obtaining some interesting 2,4-disubtituted quinazoline derivatives and to throw more precise information about the concept of amide-iminol dynamic equilibrium. Thus, alkylation of **1a,b** with ethyl chloroacetate in presence of anhydrous potassium carbonate in dry acetone [18], afforded 4-ethoxycarbonylmethoxy quinazoline derivative **8a,b** (scheme 2).

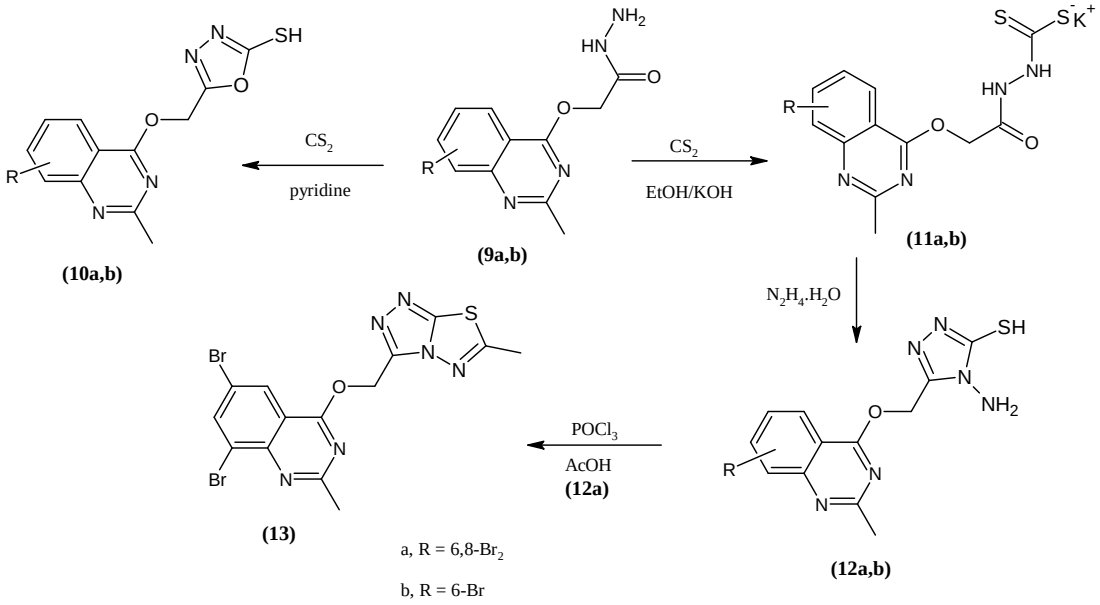
Here alkylation took place at 4-position, the activities of amide and iminol tautomers based on their thermodynamic and kinetic control under experimental conditions have been explained. The conjugate base of the iminol tautomer has been found to be thermodynamically more stable than the conjugate base of the amide tautomer (basisity is thermodynamic control) in the presence of anhydrous K_2CO_3 and dry acetone due to stabilization by aromaticity of the quinazoline nucleus. This making the iminol tautomer easily formed, which practically spells out the reactivity of the iminol tautomer under these experimental conditions. The reaction takes place via direct nucleophilic displacement mechanism by the oxygen nucleophile of the predominant lactim form on the partially positive saturated carbon of the ethyl chloroacetate via S_N2 mechanism. Which in agreement with literature foundations [19]. The reaction of the esters **8a,b** with hydrazine hydrate in boiling ethanol yielded the corresponding hydrazide derivatives **9a,b** (scheme 2).

It was reported that 2,5-disubstituted 1,3,4 oxadiazoles possess multi-range of biological actions, specially as antimicrobial agents [20]. In this respects, trials for introducing 1,3,4-oxadiazoles into the 4-position of quinazoline system has been achieved.



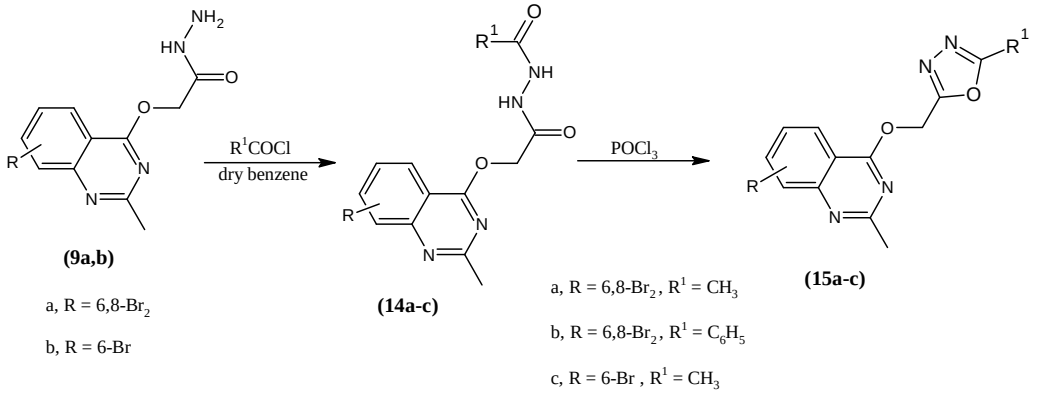
Scheme 2

It is interesting to investigate the behavior of hydrazides **9a,b** towards CS_2 in different media. When compounds **9a,b** were allowed to react with CS_2 in boiling pyridine gave [6,8-dibromo and/or 6-bromo-2-methyl-4-(5-mercapto-2-methoxy-1,3,4-oxadiazole)]quinazoline derivatives **(10a,b)** respectively. This reaction takes place via nucleophilic addition of NH_2 of the hydrazides **9a,b** to S=C=S followed by cyclization to form oxadiazole moiety. On the other hand, when hydrazides **9a,b** were allowed to react with CS_2 in cold ethanolic KOH solution afforded potassium[6,8-dibromo and/or 6-bromo-2-methylquinazolinloxy-4-yl]-acetohydrazide dithiocarbamic acid **(11a,b)**. The structure of compounds **11a,b** were further supported by their hydrazinolysis and they afforded mercapto-1,2,4-trizolo-methoxyquinazoline derivatives **12a,b**. The bridgehead nitrogen analog **13** was obtained via treatment of **12a** with acetic acid in the presence of phosphuros oxychloride (scheme 3).



Scheme 3

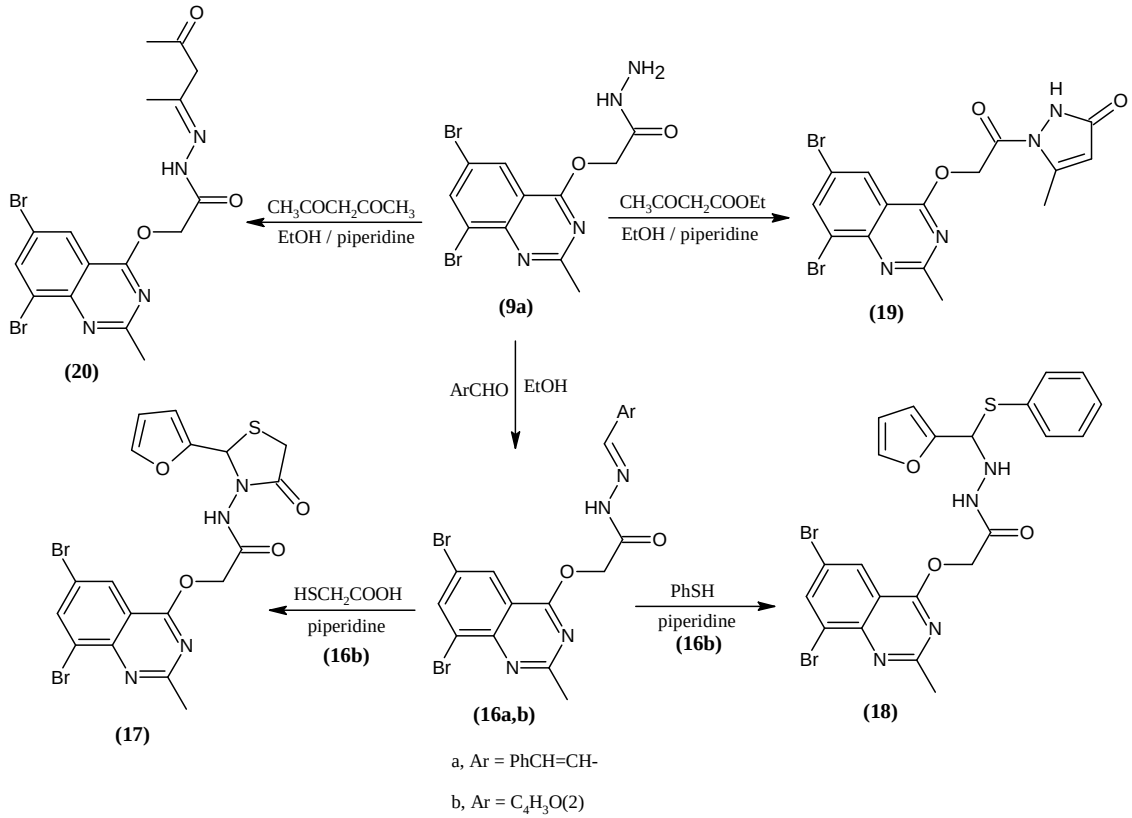
In the same fashion, it is interesting to investigate the acylation of the hydrazide derivatives **9a,b** with the aim of using them as precursor for introducing mixed heterocycles at 4-position of the titled quinazoline derivatives. Indeed, interaction of hydrazide derivatives **9a,b** with acyl chlorides like acetyl chloride and/or benzoyl chloride in dry benzene afforded the 4-acylhydrazinocarbonylmethoxyquinazoline derivatives **14a-c**, Which followed by warming compounds **14a-c** with $POCl_3$ in water bath at 50°C to afford the desired oxadiazolo-quinazolines **15a-c** (scheme 4).



Scheme 4

As a point of interest in this investigation is to study the behavior of the hydrazide derivatives **9a,b** towards aromatic aldehydes to obtain compounds of the type **16a,b** which contain C=N to investigate its behviour towards aliphatic and aromatic mercaptans under Michael reaction conditions [21]. Thus, by treatment of hydrazide **9a** with cinnamaldehyde and/or furaldehyde, the 4-(arylidenehydrazinocarbonylmethoxy)-quinazoline derivatives **16a,b** were obtained. Compound **16b** was allowed to react with thioglycolic acid in the presence of piperidine; firstly, the addition on C=N took place followed by cyclization and the thiazole nucleus was furnished as a constituent of the side chain at 4-position of the quinazoline derivative to afford compound **17**. On the other hand, when hydrazone derivative **16b** was allowed to react with thiophenol in the presence of few drops of piperidine, the adduct **18** was produced (Scheme 5).

Finally, the hydrazide **9a** underwent condensation with active methylene containing compounds like ethyl acetoacetate and acetyl acetone and afforded 4-(1-methoxycarbonyl-5-methyl-2-pyrazolin-3-one)quinazoline **19** and 4-(methoxycarbonylhydrazinoacetylacetone) quinazoline **20**, respectively (Scheme 5).



Scheme 5

Table 1 . Antibacterial activity of some synthesized compounds

Comp. No.	Zone of inhibition							
	Grampositive				Gramnegative			
	Staphlococcus aureus (ATC-6538-P)		Bacillus cereus (NRRL-B-569)		Serratia marcesens (IMRU-70)		Proteus merabitis (NTC-289)	
	Zone	MIC	Zone	MIC	Zone	MIC	Zone	MIC
7	17	175	9	175	17	125	19	175
8a	16	125	8	125	10	175	8	175
10a	21	175	11	175	8	175	6	175
10b	19	175	9	250	12	150	12	250
11b	18	175	16	150	19	175	15	175
14b	20	175	19	125	16	75	21	75
16b	17	125	11	125	18	175	17	175
18	22	175	20	175	21	175	24	175
Ampicillin	**30**	**25**	**33**	**25**	**24**	**25**	**28**	**25**

Screening for antimicrobial activity

In this study, some of the prepared compounds were screened for their in vitro antibacterial and antifungal activities. The zone of inhibition (mm) and MIC (minimum inhibitory concentration, in µg/mL) of the compounds are presented in table (1 and 2).

All the compounds shown good antibacterial activity against gram positive bacteria especially *Staphylococcus aureus* and the compounds **11b**, **14b**, **16b** and **18** could show better action against gram negative bacterial species. About antifungal screening the compounds **14b** and **18** possessed high activities against the fungal species (*Aspergillus chraceus*, *Penicillium chrysogenum*), the compounds **7**, **8a**, **10a**, **10b** and **11b** possessed moderate activity against the same fungal species.

Table 2 . Antifungal activity of some synthesized compounds

Comp. No.	Zone of inhibition Antifungal activity			
	Aspergillus chraceus Wihelm (AUCC-230)		Penicillium Chrysogenum Thom (AUCC-530)	
	Zone	MIC	Zone	MIC
7	7	150	9	250
8a	10	175	13	175
10a	11	175	14	175
10b	10	125	13	175
11b	8	175	12	250
14b	18	175	23	175
16b	12	175	14	75
18	17	175	21	150
Mycostatin	**20**	**30**	**25**	**30**

CONCLUSION

We successfully obtained a novel series of interesting polysubstituted quinazoline derivatives with high functionality. Also the plethora of research described in this manuscript indicates a wide spectrum of pharmacological activities exhibited by poly substituted quinazolines produced here as antimicrobial agents.

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