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Synthesis and evaluation of new 2,3- and 2,4-disubstituted quinazoline derivatives as potential antibacterial and antifungal agents

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ABSTRACT

We report here the sythesis of 2,3-disubstituted quinazolinone derivatives via interaction of 2-methyl-6,8-dibromo-(4H)-3,1-benzoxazinone with nitrogen nucleophiles namely, hydrazine hydrate, sulpha drugs, and 4-aminoacetophenone. Also Synthesis of 4-chloroquinazoline ***(11)*** *has been achieved via chlorination of the corresponding 6,8-dibromoquinazoline analog. The simple replacement of the chlorine atom at the 4-position of quinazoline nucleus with different nitrogen and carbon nucleophiles has produced derivatives of the 4-heteroaryl-quinazoline derivatives and fused quinazolines.Some of the synthesized compounds are tested for its antimicrobial activity.*

Keywords: 2,3-disubsituted quinazoline, 2,4-disubstituted quinazoline, 4-chloroquinazoline, antimicrobial activity.

INTRODUCTION

The recent literature reveals that the quinazolinone moiety associated with various aromatic as well as heterocyclic compounds possess wide range of pharmacological properties such as antibacterial[1], antifungal[1], analgesic[2], anti-inflammatory[3], antihelminthic[4], anticonvulsant[5], anti HIV[6], antitubercular[7], CNS depressent[8], cytotoxicity[9], diuretic[10], and hypolipidemic[11] activities.

The aim of the present work was to use the benzoxazinone derivatives as intermediates in the synthesis of 2,3- and/or 2,4-disubstituted quinazolinones, and to attach some interesting heterocycles with mixed and non-mixed system to quinazolin-4(3*H*)-one nucleus in order to find new biologically active pharmacophore, specially applied as antibacterial and anifungal 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-(4*H*)-3,1-benzoxazinone **(1)** via the reaction of freshely distilled acetic acid anhydride with 3,5-dibromoanthranilic acid[14].

MATERIALS AND METHODS

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 F254 with detection by UV quenching at 254nm. IR spectra (in KBr, cm^{-1}) were recorded on λ 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-d_6). TMS was used as an internal standard with chemical shifts δ in ppm from downfield to upfield. Chemical shifts (δ) are given in parts per million (ppm). EIMS were recorded on a gas chromatographic GCMS – Qploopx Shimadzu (Japan, 1990).

Benzoxazinone **1** and 2-aminoquinazolinone **2** were prepared according to literature[14].

6,8-Dibromo-2-methyl-3-benzylideneaminoquinazolin-4-one derivatives (3a,b)

A mixture of aminoquinazoline **2** (3.33 g, 0.01 mol) and aromatic aldehydes namely, 2,4-dichlorobenzaldehyde and/or 4-hydroxybenzaldehyde (0.01 mol) in ethanol (20 mL) was refluxed for 6h. The solid that separated after cooling was filtered off and recrystallized from ethanol to give **3a** and **3b** respectively.

6,8-Dibromo-3-[(2,4-dichlorobenzylidene)amino]-2-methylquinazolin-4(3*H*)-one (3a): Yield 73% (dark yellow). M.p. 210-211°C. IR (KBr): 558(C-Br), 1382(CH_3), 1580(C=N), 1646(C=O), 2854(CH-aliph), 3086(CH-arom), and devoid any band for NH. ^{1}H-NMR (DMSO-d_6)**:** δ 2.28(s, 3H, CH_3), 5.71(s, 1H, azamethine proton), 6.93-7.34(m, 7H, ArH). Anal. Calc. for $C_{16}H_9Br_2Cl_2N_3O$ (490) : C 39.22, H 1.85, Br 32.62, N 8.58; found: C 39.48, H 2.07, Br 32.79, N 8.92.

6,8-Dibromo-3-[(4-hydroxybenzylidene)amino]-2-methylquinazolin-4(3*H*)-one (3b): Yield 87% (yellow). M.p. 188-190°C. IR (KBr): 573(C-Br), 1395(CH_3), 1606(C=N), 1650(C=O), 2973(CH-aliph), 3069(CH-arom), 3416(OH), and devoid any band for NH. Anal. Calc. for $C_{16}H_{11}Br_2N_3O_2$ (437): C 43.97, H 2.54, Br 36.56, N 9.61; found: C 44.19, H 2.33, Br 36.84, N 9.42. MS: m/z 287[M^+- CO_2], 208, 156, 132, 77.

6,8-Dibromo-2-methyl-3-[4-sulphonamidophenyl]-quinazolin-4-one derivatives (4a-c)

A mixture of benzoxazinone **1** (3.19 g, 0.01 mol) and sulphadrugs namely, sulphacetamide, sulphaguanidine, and/or sulphadiimidine (0.01 mol) in *n*-butanol (15 mL) was heated under reflux for 10h. The solid that separated after concentrating and cooling was crystallized from the proper solvent to give **4a-c** respectively.

***N*-{[4-(6,8-dibromo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)phenyl]sulfonyl}acetamide(4a):** Yield 82% (pale yellow). M.p. 276-277°C (*n*-butanol). IR (KBr): 570(C-Br), 1230(S=O), 1397(CH_3), 1596(C=N), 1674(C=O), 2927(CH-aliph), 3070(CH-arom), 3338(NH). ^{1}H-NMR (DMSO-d_6)**:** δ 2.21(s, 3H , CH_3), 2.37(s, 3H , CH_3), 7.87-8.33(m, 6H, ArH), 12.58(brs, 1H, NH, D_2O exchangable). Anal. Calc. for $C_{17}H_{13}Br_2N_3O_4S$ (515) : C 39.63, H 2.54, Br 31.02, N 8.16; found: C 39.95, H 2.67, Br 31.33, N 8.31. MS: m/z 287[M^+- CO_2], 208, 156, 132, 77.

***N*-carbamimidoyl-4-(6,8-dibromo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)benzenesulfonamide (4b):** Yield 85% (pale yellow). M.p. 194°C (ethanol). IR (KBr): 562(C-Br), 1121(S=O), 1375(CH_3), 1594(C=N), 1664(C=O), 2871(CH-aliph), 3074(CH-arom), 3342(NH). Anal. Calc. for $C_{16}H_{13}Br_2N_5O_3S$ (515) : C 37.30, H 2.54, Br 31.02, N 13.59; found: C 37.12, H 2.73, Br 31.29, N 13.32. MS: m/z 515[M^+], 317, 319, 277, 199, 170, 141, 75, 62.

4-(6,8-dibromo-2-methyl-4-oxoquinazolin-3(4*H*)-yl)-*N*-(4,6-dimethylpyrimidin-2-yl)benzenesulfonamide (4c): Yield 79% (pale yellow). M.p. 164-166°C (acetic acid). IR (KBr): 582(C-Br), 1154(S=O), 1370(CH_3), 1598(C=N), 1665(C=O), 2870(CH-aliph), 3079(CH-arom), 3264(NH). Anal. Calc. for $C_{21}H_{17}Br_2N_5O_3S$ (579): C 43.54, H 2.96, Br 27.59, N 12.09; found: C 43.84, H 3.15, Br 27.77, N 12.31.

3-(4-Acetophenyl)-6,8-bibromo-2-methylquinazolin-4(3*H*)-one (5)

An equimolar amounts of benzoxazinone **1** and 4-aminoacetophenone (0.01 mol) in ethanol (20 mL) containing few drops of piperidine was heated at 70°C for 7h. The excess solvent was distilled off and the solid that separated after cooling was recrystallized from toleuene to give **5**.

Yield 81% (pale yellow). M.p. 203-204°C. IR (KBr): 580(C-Br), 1367(CH_3), 1583(C=N), 1667, 1709(C=O), 2925(CH-aliph), 3071(CH-arom). ^{1}H-NMR (DMSO-d_6)**:** δ 2.24(s, 3H , N=C-CH_3), 2.47(s, 3H , $COCH_3$), 7.74-8.11(m, 6H, ArH). Anal. Calc. for $C_{17}H_{12}Br_2N_2O_2$ (436): C 46.82, H 2.77, Br 36.65, N 6.42; found: C 47.09, H 2.92, Br 36.43, N 6.67. MS: m/z 438[M+2]$^+$, 436[M^+], 421, 350, 299, 246, 168, 120, 74, 65.

3-(4-Cinnamoylphenyl)-6,8-dibromo-2-methylquinazolin-4-one (6a-c)

A mixture of quinazolinone **5** (4.36 g, 0.01 mol) and aromatic aldehydes namely, 2,4-dichlorobenzaldehyde, 4-hydroxybenzaldehyde, and/or 4-methoxybenzaldehyde (0.01 mol) in 1,4-dioxane (20 mL) was heated under reflux for 4h. The solid that separated after concentration and cooling was crystallized from ethanol to give **6a-c** respectively.

6,8-dibromo-3-{4-[-3-(2,4-dichlorophenyl)prop-2-enoyl]phenyl}-2-methylquinazolin-4(3*H*)-one (6a) : Yield 89% (beige). M.p. 231-233°C. IR (KBr): 592(C-Br), 1365(CH_3), 1597(C=N), 1679(C=O), 2921(CH-aliph), 3080(CH-arom). ^{1}H-NMR (DMSO-d_6)**:** δ 2.27(s, 3H, CH_3), 6.74(d, *J=13.4Hz*, 1H, olefenic proton), 7.36-8.09(m, 10H, ArH & olefenic proton). Anal. Calc. for $C_{24}H_{14}Br_2Cl_2N_2O_2$ (593): C 48.60, H 2.38, Br 26.94, N 4.72; found: C 48.88, H 2.56, Br 27.34, N 5.03.

6,8-Dibromo-3-{4-[3-(4-hydroxyphenyl)prop-2-enoyl]phenyl}-2-methylquinazolin-4(3*H*)-one (6b): Yield 93% (beige). M.p. 245°C. IR (KBr): 589(C-Br), 1361(CH_3), 1595(C=N), 1666, 1678(C=O), 2874(CH-aliph), 3064(CH-arom), 3341(OH). Anal. Calc. for $C_{24}H_{16}Br_2N_2O_3$(540) : C 53.36, H 2.99, Br 29.58, N 5.19; found: C 53.54, H 3,31, Br 29.76, N 5.38.

6,8-dibromo-3-{4-[3-(4-methoxyphenyl)prop-2-enoyl]phenyl}-2-methylquinazolin-4(3*H*)-one (6c) : Yield 92% (beige). M.p. 254-256°C. IR (KBr): 590(C-Br), 1390(CH_3), 1591(C=N), 1662, 1693(C=O), 2854(CH-aliph), 3075(CH-arom). Anal. Calc. for $C_{25}H_{18}Br_2N_2O_3$ (554) : C 54.18, H 3.27, Br 28.83, N 5.05; found: C 54.38, H 3.53, Br 29.11, N 5.19.

Pyrazoles 7a-c

A solution of cinnamoylphenylquinazolines **6a-c** (0.01 mol) and hydrazine hydrate (0.75 g, 0.15 mol) in ethanol (20 mL) was heated under reflux for 6h. The solid that separated after concentration and cooling was filtered off, washed with pet. ether (60-80^0) and recrystallized from the proper solvent to afford **7a-c** respectively.

6,8-dibromo-3-{4-[5-(2,4-dichlorophenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]phenyl}-2-methylquinazolin-4(3*H*)-one (7a): Yield 77% (beige). M.p. 203-204°C. ^{1}H-NMR (DMSO-d_6)**:** δδ 3.12(s, 3H, CH_3), 3.34(dd, 1H, Ha of CH_2 of pyrazoline), 3.45(dd, 1H, Hb of CH_2 of pyrazoline), 5.47(dd, 1H, Hx of CH_2 of pyrazoline), 6.79-8.13(m, 9H, ArH), 8.45(brs, 1H, NH). Anal. Calc. for $C_{24}H_{16}Br_2Cl_2N_4O$ (607) : C 47.48, H 2.66 Br 26.32, Cl 11.68, N 9.23; found: C 47.74, H 2.51 Br 25.90, Cl 11.29, N 9.44.

6,8-dibromo-3-{4-[5-(4-hydroxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]phenyl}-2-methylquinazolin-4(3*H*)-one (7b): Yield 84% (beige). M.p. 211-213°C. Anal. Calc. for $C_{24}H_{18}Br_2N_4O_2$ (554) : C 52.01, H 3.27, Br 28.83, N 10.11; found: 52.32, H 3.42, Br 29.16, N 10.27.

3-{4-[5-(4-methoxyphenyl)-4,5-dihydro-1*H*-pyrazol-3-yl]phenyl}-2-methyl-5,6-dihydropyrimidin-4(3*H*)-one (7c) : Yield 68% (beige). M.p. 199-200°C. Anal. Calc. for $C_{25}H_{20}Br_2N_4O_2$ (568) : C 52.84, H 3.55, Br 28.12, N 9.86; found: C 52.69, H 3.62, Br 27.62, N 9.72.

3,5-Dibromo-2-(2-methyl-1,3,4,5-tetrazolo)-benzoic acid and/or 5,7-dibromo-1-acetyl-benzimidazol-2-one (8 and 9)

A mixture of compound **1** (3.19 g, 0.01 mol) and sodium azide (3.25 g, 0.05 mol) in glacial acetic acid (30 mL) was heated at 100°C for 5h. The reaction mixture was poured onto cold water, the solid that formed was filtered off and fractionally crystallized from ethanol to give **8**. While the residue was recrystallized from acetic acid to give **9**.

3,5-dibromo-2-(5-methyl-1*H*-tetrazol-1-yl)benzoic acid (8): Yield 64% (white). Mp 256-258°C. IR (KBr): 550(C-Br), 1365(CH_3), 1582(C=N), 1705(C=O), 2938(CH-aliph), 3421(OH). ^{1}H-NMR (DMSO-d_6)**:** δ 2.12(s, 3H, CH_3), 8.07(d, *J=2.4Hz*, 1H, ArH), 8.40(d, *J=2.4Hz*, 1H, ArH), 11.47(brs, 1H, OH). Anal. Calc. for $C_9H_6Br_2N_4O_2$ (362): C 29.86, H 1.67, Br 44.15, N 15.48; found: C 30.04, H 1.82, Br 44.48, N 15.21.

1-acetyl-5,7-dibromo-1,3-dihydro-2*H*-benzimidazol-2-one (9): Yield 66% (pale yellow). M.p. 191-193°C. IR (KBr): 594(C-Br), 1393(CH_3), 1600(C=N), 1642, 1678(C=O), 2928(CH-aliph), 3221(NH). Anal. Calc. for $C_9H_6Br_2N_2O_2$ (334) : C 32.37, H 1.81, Br 47.85, N 8.39; found: C 32.49, H 1.94, Br 48.14, N 8.28.

6,8-Dibromo-2-methylquinazolin-4(3*H*)-one (10)

A mixture of benzoxazinone **1** (3.19 g, 0.01 mol) and ammonium acetate (2.31g, 0.03mole) was heated in an oil bath at 170 °C for 2h. The reaction mixture after cooling was poured over crushed ice/water. The solid obtained was filtered off, washed with light petroleum ether (40-60^0), and crystallized from acetic acid to give **10**.

Yield 84% (Beige). M.p. 281-282°C. IR (KBr): 586(C-Br), 1389(CH_3), 1605(C=N), 1689(C=O), 2862(CH-aliph), 3071(CH-arom), 3394(NH). ^{1}H-NMR (DMSO-d_6)**:** δ 2.01(s, 3H, CH_3), 7.86(d, *J=2.4Hz*, 1H, ArH), 7.91(d, *J=2.4Hz*, 1H, ArH), 9.61(s, 1H, NH). Anal. Calc. for $C_9H_6Br_2N_2O$ (318) : C 34.00, H 1.90, Br 50.26, N 8.81; found: C 34.32, H 2.04, Br 50.07, N 8.67.

4-Chloro-6,8-dibromo-2-methylquinazoline (11)

A mixture of quinazoline **10** (3.18g, 0.01 mol), phosphorus oxychloride (10 mL), and phosphorus pentachloride (3.13 g, 0.15 mol) was heated in water bath at 80°C for 2h. The

reaction mixture after cooling was poured onto crushed ice and the solid that obtained was filtered of and crystallized from ethanol to give **11**.

Yield 59% (brown). M.p. >300°C. IR (KBr): 589(C-Br), 672(C-Cl), 1387(CH_3), 1604(C=N), 2852, 2920(CH-aliph), 3074(CH-arom). Anal. Calc. for $C_9H_5Br_2ClN_2$ (336.5) : C 32.13, H 1.50, Br 47.50, N 8.33; found: C 32.41, H 1.62, Br 47.83, N 8.56.

6,8-dibromo-2-methyl-4-phenylmethylaminoquinazoline (12)
To a solution of compound **11** (3.37 g, 0.01 mol) in 20 mL ethanol, benzyl amine (1.07 g, 0.01 mol) was added. The reaction mixture was heated under reflux for 6h. The solid that separated after concentration and cooling was filtered off and recrystallized from ethanol to give **12**.

Yield 69% (beige). M.p. 242-243°C. IR (KBr): 551(C-Br), 1375(CH_3), 1597(C=N), 2856(CH-aliph), 3078(CH-arom), 3324(NH). Anal. Calc. for $C_{16}H_{13}Br_2N_3$ (407): C 47.20, H 3.22, Br 39.25, N 10.32; found: C 47.38, H 3.31, Br 39.02, N 10.51.

6,8-dibromo-2-methyl-4-hydrazinoquinazoline (13)
To a solution of chloroquinazoline **11** (3.37 g, 0.01 mol) in 20 mL ethanol, hydrazine hydrate (0.75 g, 0.015 mol) was added. The reaction mixture was heated under reflux for 6h. The solid that separated after concentration and cooling was filtered off, washed with water, and crystallized from ethanol to give **13**.

Yield 57% (Beige). M.p. 273-275°C. IR (KBr): 550(C-Br), 1375(CH_3), 1598(C=N), 2852, 2922(CH-aliph), 3172, 3362(NH). Anal. Calc. for $C_9H_8Br_2N_4$ (332) : C 32.56, H 2.43, Br 48.14, N 16.88; found: C 32.36, H 2.35, Br 47.84, N 16.71.

6,8-dibromo-2-methyl-4-acylhydrazinoquinazoline derivatives (14a,b)
A mixture of compound **11** (3.37 g, 0.01 mol) and acyl hydrazides namely, acetyl hydrazide (0.58 g, 0.01 mol) and/or benzoyl hydrazide (1.04 g, 0.01 mol) in *n*-butanol (20 mL) was refluxed for 48h. The reaction mixture was leaved overnight and the solid that formed was collected and crystallized from ethanol to afford **14a** and **14b** respectively.

***N'*-(6,8-dibromo-2-methylquinazolin-4-yl)acetohydrazide (14a):** Yield 87% (Beige). M.p. 260°C. IR (KBr): 601(C-Br), 1401(CH_3), 1644(C=N), 1671(C=O), 2961(CH-aliph), 3068(CH-arom), 3221, 3399(NH). Anal. Calc. for $C_{11}H_{10}Br_2N_4O$ (374): C 35.32, H 2.69, Br 42.73, N 14.98; found: 35.62, H 2.89, Br 42.91, N 15.37.

***N'*-(6,8-dibromo-2-methylquinazolin-4-yl)benzohydrazide (14b):** Yield 76% (yellow). M.p. 273-274°C. IR (KBr): 579(C-Br), 1400(CH_3), 1651(C=N), 1679(C=O), 2925(CH-aliph), 3067(CH-arom), 3180, 3416(NH). Anal. Calc. for $C_{16}H_{12}Br_2N_4O$ (436) : C 44.07, H 2.77, Br 36.64, N 12.85; found: C 44.29, H 2.87, Br 36.43, N 12.98.

6,8-dibromo-2-methyl-4-*N*-substituted quinazoline derivatives (15a,b)
A mixture of compound **11** (3.37 g, 0.01 mol) and sulphadrugs namely,sulphacetamide and/or sulphaguanidine (0.01 mol) in 1,4-dioxane (20 mL) was refluxed for 4h. The reaction mixture was concentrated under reduced pressure and the solid that separated was filtered off and crystallized from proper solvent to afford **15a** and **15b** respectively.

***N*-({4-[(6,8-dibromo-2-methylquinazolin-4-yl)amino]phenyl}sulfonyl)acetamide(15a):** Yield 92% (yellow). M.p. 254-255°C (ethanol). IR (KBr): 551(C-Br), 1186(SO_2), 1373(CH_3),

1598(C=N), 1700(C=O), 2959(CH-aliph), 3074(CH-arom), 3223, 3363(NH). Anal. Calc. for $C_{17}H_{14}Br_2N_4O_3S$ (514) : C 39.71, H 2.74, Br 31.08, N 10.90; found: C 39.93, H 2.88, Br 30.81, N 10.76.

***N*-carbamimidoyl-4-[(6,8-dibromo-2-methylquinazolin-4-yl)amino]benzenesulfonamide (15b):** Yield 84% (yellow). M.p. 172-173°C. IR (KBr): 588(C-Br), 1148(SO_2), 1389(CH_3), 1599(C=N), 2916(CH-aliph), 3015(CH-arom), 3192, 3372(NH). Anal. Calc. for $C_{16}H_{14}Br_2N_6O_2S$ (514) : C 37.37, H 2.74, Br 31.08, N 16.34; found: C 37.64, H 2.91, Br 31.27, N 16.56.

7,9-Dibromo-5-methyl-tetrazolo[1,5-c]quinazoline (16)

A mixture of chloroquinazoline **11** (3.37 g, 0.01 mol), sodium azide (3.25 g, 0.05 mol), and sodium acetate (2 g) in glacial acetic acid (30 mL) was heated under reflux for 5h. The reaction mixture was poured on cold water and the solid that formed was collected, washed with water, filtered off, and crystallized from benzene to afford **16**. Yield 73% (beige). M.p. 136-137°C. IR (KBr) 553(C-Br), 1375(CH_3), 1596(C=N), , 2923(CH-aliph). Anal. Calc. for $C_9H_5Br_2N_5$ (343) : C 31.52, H 1.47, Br 46.59, N 20.42; found: C 31.75, H 1.56, Br 46.86, N 20.63.

6,8-Dibromo-2-methyl-4-[(ethoxycarbonyacetomethyl) and/or (diacetylmethyl)]quinazoline (17a and/or 17b)

0.01 mole of active methylene containing compounds namely, ethyl acetoacetate and/or acetyl acetone, 0.5g of sodium metal and 20 mL of methanol was added. The mixture was gently heated till alcohol is removed. Benzoxazinone **1** (0.01 mole) and 30 mL of ethanol was added. The reaction mixture was refluxed for 4h. Most of the solvent is distilled off and the residue was acidified with HCl to give a crude product which was filtered off, washed several times with cold water, dried, and recrystallized from AcOH to yield **17a** and **17b** respectively.

ethyl 2-(6,8-dibromo-2-methylquinazolin-4-yl)-3-oxobutanoate (17a): Yield 59% (beige). M.p. 248-250°C. IR (KBr): 532(C-Br), 1389(CH_3), 1582(C=N), 1730, 1759(C=O), 2924(CH-aliph), 3056(CH-arom). Anal. Calc. for $C_{15}H_{14}Br_2N_2O_3$ (430): C 41.89, H 3.28, Br 37.16, N 6.51; found: C 42.06, H 3.43, Br 37.38, N 6.67.

3-(6,8-dibromo-2-methylquinazolin-4-yl)pentane-2,4-dione (17b): Yield 72% (beige). M.p. 262-264°C. IR (KBr): 556(C-Br), 1413(CH_3), 1600(C=N), 1693(C=O), 2924(CH-aliph). Anal. Calc. for $C_{14}H_{12}Br_2N_2O_2$ (400): C 42.03, H 1.47, Br 39.95, N 7.00; found: C 42.21, H 1.69, Br 40.33, N 7.24.

6,8-dibromo-4-(3,5-dimethyl-1*H*-pyrazol-4-yl)-2-methylquinazoline (18)

A mixture of compound **17b** (4.00 g, 0.01 mol) and hydrazine hydrate (0.75 g, 0.015 mol) in ethanol (20 mL) was heated under reflux for 6h. The solid that separated after concentration and cooling was crystallized from ethanol/H_2O to give **18**.

Yield 64% (Beige). M.p. >300°C. IR (KBr) 564(C-Br), 1445(CH_3), 1601(C=N), 2963(CH-aliph), 3073(CH-arom), 3316(NH). ^{1}H-NMR (DMSO-d_6)**:** δ 2.01(s, 3H, CH_3), 8.19(d, *J=2.4Hz*, 1H, ArH), 8.36(d, *J=2.4Hz*, 1H, ArH), 9.61(s, 1H, NH). Anal. Calc. for $C_{14}H_{12}Br_2N_4$ (396) : C 42.45, H 3.05, Br 40.35, N 14.15; found: C 42.72, H 3.19, Br 40.64, N 14.34.

Antimicrobial activity

The in vitro antimicrobial activities of some compounds were carried out by the disc diffusion method[15]. Antibacterial activity was screened against two gram-positive bacteria S. aureus (ATC-6538-P) and B. cereus (NRRL-B-569), and two gram-negative bacteria S. marcesens

(IMRU-70) and P. merabitis (NTC-289), by measuring the zone inhibition on agar plates. While antifungal activity was tested by measuring the zone of inhibition on agar plates with two fungal species A. chraceus Wihelm (AUCC-230) and P. chrysogenum Thom (AUCC-530). Ampicillin was used as a standard antibacterial agent, whereas Mycostatin was used as a standard antifungal agent.

RESULTS AND DISCUSSION

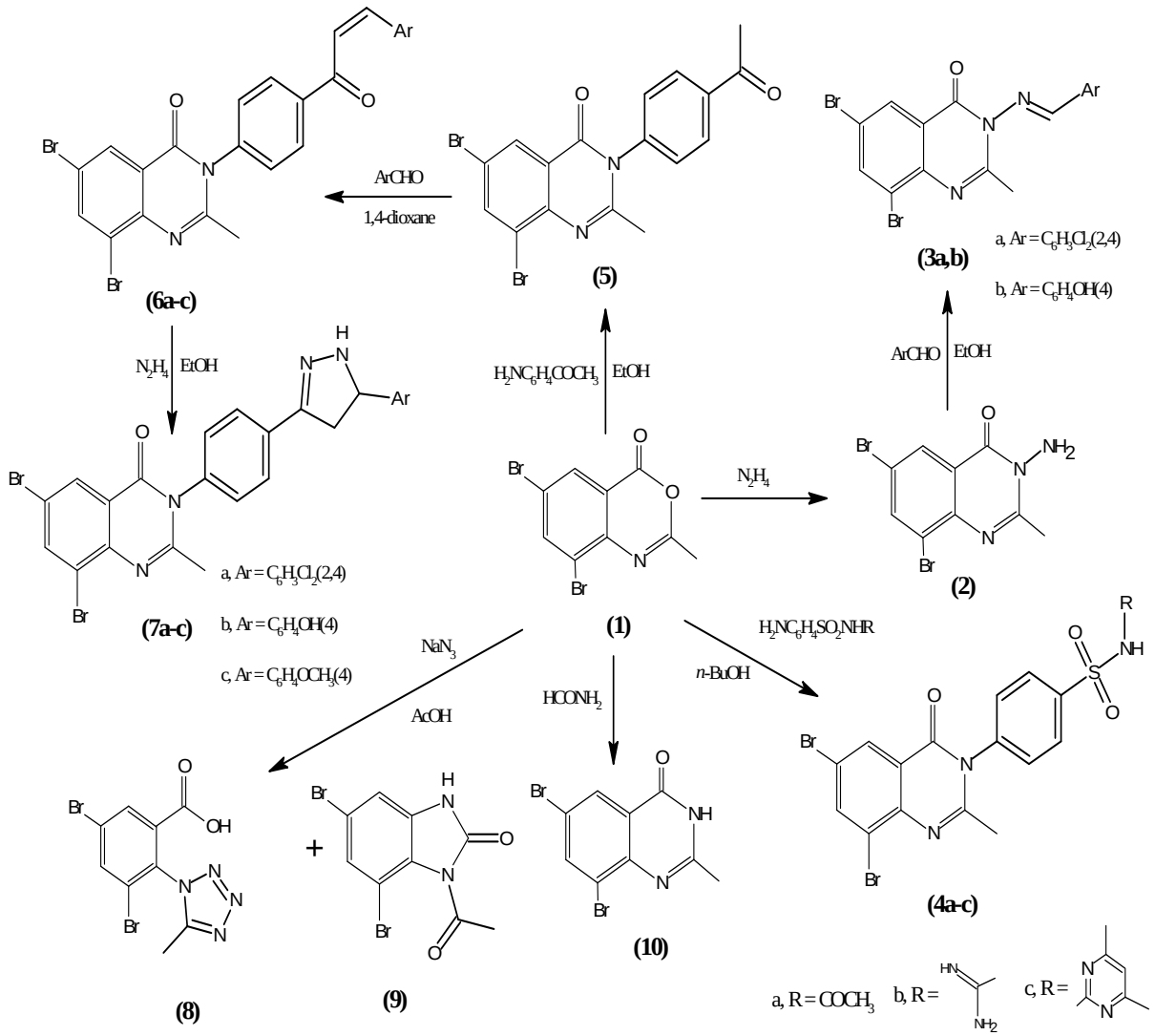
With the aim of extanding the synthetic potential of the 4*H*-3,1-benzoxazin-4-one formed, we have studied its hydrazinolysis using hydrazine hydrate in boiling ethanol. This is a simple and conventient route to the synthesis of 3-aminoquinazolin-4(3*H*)-one **2** which is a promising intermediate for diverse organic synthesis, (Scheme 1). Its IR(KBr)(cm^{-1}): 562(C-Br), 1615(C=N), 1670(C=O), 2910(CH), 3300(NH). ^{1}H-NMR (DMSO-d_6) of **2** exhibits signals at δ 3.52(s, 3H, CH_3), 5.52(brs, 2H, NH_2), 7.1(s, 1H, H_5), 7.3(s, 1H, H_6).

Thus, condensation of aminoquinazoline **2** with aromatic aldehydes such as 2,4-dichlorobenzaldehyde, 4-hydroxybenzaldehyde in boiling ethanol yielded 2-methyl-3-(2,4-dichloro and/or 4-hydroxybenzylidene)amino-6,8-dibromoquinazolin-4(3*H*)-one (**3a** and/or **3b**) respectively. These compounds were formed by nucleophilic attack of the amino group on the electronically deficient carbonyl carbon atom of the aldehyde followed by dehydration, a process in which the driving force of removing the bad leaving hydroxyl group is the conjugation with the aromatic nucleus in the more thermodynamically stable compounds **3a,b** (Scheme 1). IR(KBr)(cm^{-1}): 560-575(C-Br), 1615-1620(C=N), 1665-1675(C=O), 2900-2920(CH) and devoid any band for NH. ^{1}H-NMR(DMSO-d_6) of **3a** showed signals at δ 3.57(s, 3H , CH_3), 5.71(s, 1H, azamethine proton), 6.93-7.34(m, 7H, ArH).

When the benzoxazinone derivative **1** was allowed to react with sulphadrugs such as sulphacetamide, sulphaguanidine, and/or sulphadiimidine in boiling *n*-butanol the 6,8-dibromo-2-methyl-3-(substituted phenyl)quinazoline **(4a-c)** were furnished, (Scheme 1). The microanalytical data and spectral data are in good aggreement with the proposed structures for **4a-c**.

Aminolysis of the benzoxazinone derivative **1** using 4-aminoacetophenone in boiling ethanol was afforded the corresponding 4-acetophenyl quinazolinone derivative **5**, (Scheme 1). Its IR(KBr) revealed strong absorption bands at 1670, 1685 cm^{-1} corresponding to C=O stretching frequency. ^{1}H-NMR(DMSO-d_6) of **5** displayed signals at δ 2.14(s, 3H, CH_3CO), 3.32(s, 3H, CH_3), 6.91-7.48(m, 5H, ArH).

Thereafter, the behavior of activatated CH_3 in acetophenyl moiety of quinazolinone **5** was investigated by its reaction with different aromatic aldehydes like 2,4-dichlorobenzaldehyde, 4-hydroxybenzaldehyde, and/or 4-methoxybenzaldehyde and the corresponding chalcones **6a-c** bearing heterocyclic moiety were afforded, (Scheme 1). The structure of chalcones **6a-c** was inferred from correct microanalytical data and their IR(KBr)(cm^{-1}) exhibit absorption bands at 1660, 1675(CO) and broad band at 3350 (OH) for **6b**.



Scheme 1

Pyrazoline systems are known to be biologically active and are important constituents of many pharmacological products. These compounds are known for their antibacterial[16], antifungal[17], antimycobacterial[18], analgesic[19], anti-inflammatory[20], anticancer[21], antiamoebic[22], molluscicidal[23], hypotensive[24], antinociceptive[25], antidepressant[26], anticonvulsant[27], and antiviral[28] activities. In this circumacetance, the present investigation deals with the attachment of pyrazoline moiety to quinazolin-4(3*H*)-one in order to find new biologically active pharmacophore. Thus, the interaction of chalcone derivatives **6a-c** with hydrazine hydrate in boiling ethanol yielded 2-methyl-3[4-(5-substituted phenyl-4,5-dihydro-1*H*-pyrazol-3-yl)phenyl]-6,8-dibromoquinazolin-4(3*H*)-one **(7a-c)**. The structure of compounds **7a-c** was inferred other than from correct analytical data, the IR(KBr)(cm^{-1}) exhibit strong absorption bands at 560-570(C-Br), 1615-1620(C=N), 1670-1675(C=O), 3200-3250(NH), and 3330(OH). ^{1}H-NMR(DMSO-d_6) of **7a** showed signals at δ 3.12(s, 3H, CH_3), 3.34(dd, 1H, Ha of CH_2 of pyrazoline), 3.45(dd, 1H, Hb of CH_2 of pyrazoline), 5.47(dd, 1H, Hx of CH_2 of pyrazoline), 6.79-8.13(m, 9H, ArH), 8.45(brs, 1H, NH). This ^{1}H-NMR spectrum of **7a** indicated that the CH_2 protons of the pyrazoline ring (diastereotopic protons) are resonated as a pair of doublet of doublets (octet, Ha and Hb) due to geminal and vicinal coupling. The CH methine proton appeared as a doublet of doublet (quartet Hx) due to the vicinal coupling with the two magnetically nonequivalent protons of the methylene group at 4-position of pyrozoline ring. The

Ha proton which is cis to Hx resonates upfield as a doublet of doublet, while the other proton Hb which is trans to Hx resonates downfield as a doublet of doublet. The Hx proton which is vicinal to two methylene protons (Ha and Hb) resonates as a doublet of doublet.

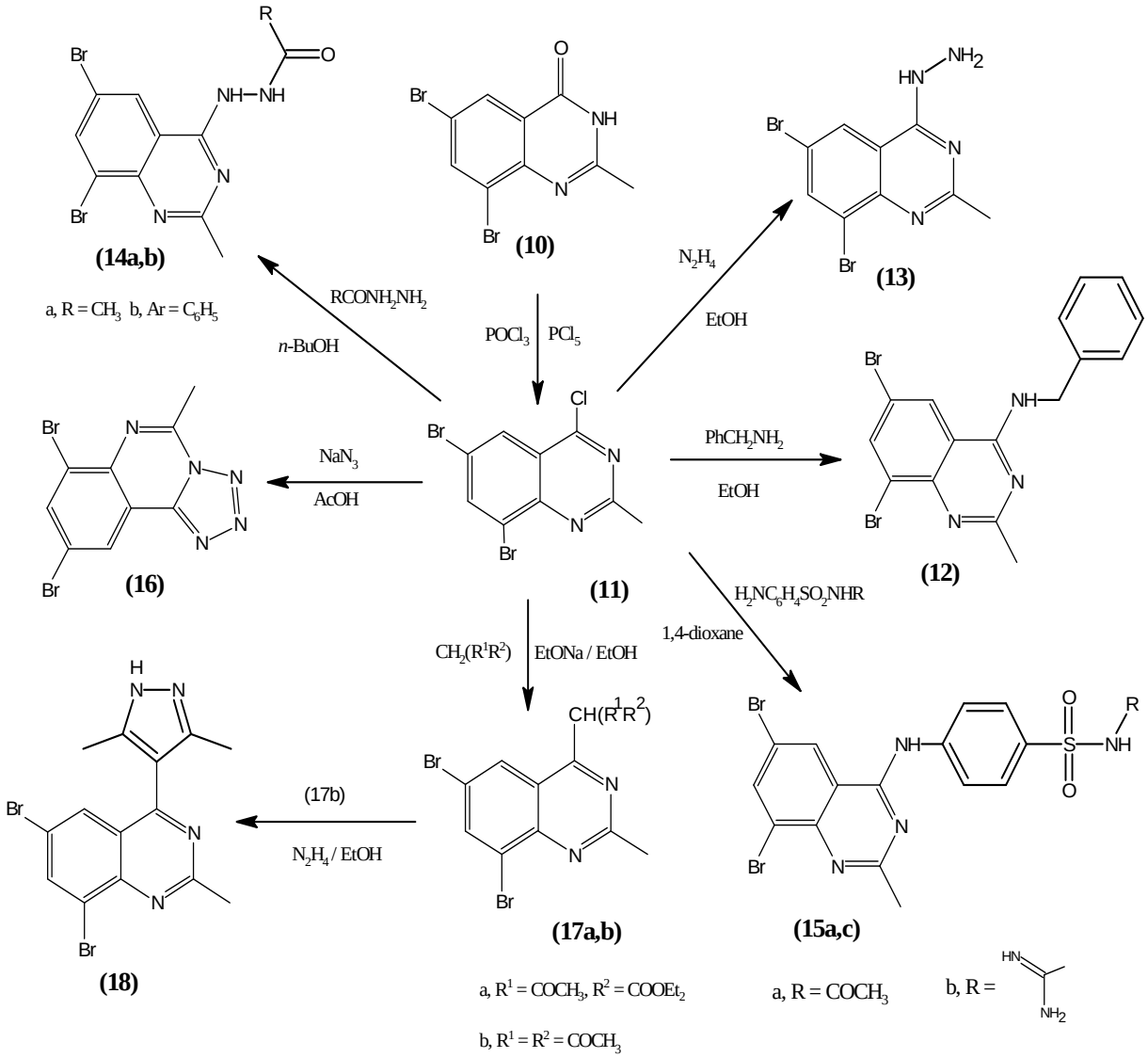
The abnormal heteroring opening of the benzoxazinone derivative **1** with sodium azide in boiling acetic acid has afforded the 3,5-dibromo-2-(5-methyl-1,2,3,4-tetrazolo-1-yl)benzoic acid **(8)** and 5,7-dibromo-1-acetylbenzimidazol-2-one **(9)**, (Scheme 1). Formation of compound **8** takes place via nucleophilic attack of azide ion at C-2 of oxazinone nucleus, according to our previous work[29] the N-nucleophiles are attacking the benzoxazinone 1 in a fashion in which it first undergoes H-bonding to N-atom of the heterocycle. Then, the nucleophilic addition at the azavinylic C(2) takes place.

On ther hand, formation of compound **9** takes place via heteroring opening of compound **1** with the nitrene derived from hydrazoic acid.

Recently, El-Hashash and coworkers [30-32] reported the behaviour of 2-substituted-4*H*-3,1-benzoxazin-4-one derivatives toward ammonia and/or formamide with the aim of converting benzoxazinone derivatives into the more stable quinazolinone derivatives by a facile one-step process. Similary, when 4*H*-3,1-benzoxazin-4-one **1** was allowed to react with formamide and/or ammonium acetate at 170 $^{\circ}$C in an oil bath, the quinazolinone **10** was isolated, (Scheme 1).

The synthesis of 2-methyl-4-chloro-6,8-dibromoquinazoline **(11)** was established based on chlorination of the corresponding 6,8-dibromoquinazoline analogue **10** using a mixture of phosphorus oxychloride and phosphorus pentachloride in boiling water bath [33]. The IR spectrum of **11** showed strong absorption bands at 589, 1604 cm^{-1} attributable to ν_{C-Br} and $\nu_{C=N}$ respectively and laked any absorption corresponding to $\nu_{C=O}$ and ν_{NH}.

Recently, it was reported that 4-substituted aminoquinazolines are exploited as a potent antitumor[34]. This enforced us to design and synthesis some 4-substituted amino quinazolines derived from 4-chloroquinazoline **11** via the simple replacement of the chlorine atom at 4-position of quinazoline nucleus with different amino compounds. In this circumstance, condensation of chloroquinazoline **11** with benzyl amine in boiling ethanol afforded the 4-phenylmethylamino-quinazoline **12**, (Scheme 2). The structure of compound **12** was inferred from correct analytical data and its IR(KBr)(cm^{-1}): 551(C-Br), 1375(CH_3), 1597(C=N), 3324(NH). Hydrazinolysis of chloroquinazoline **11** using hydrazine hydrate in boiling ethanol afforded the 4-hydrazinoquinazoline derivative **13**. IR(KBr)(cm^{-1}): 550(C-Br), 1598(C=N), 2922(CH), 3172, 3364(NH). Moreover, the present work also included the reactivity of 4-chloroquinazoline **11** towards acetyl and/or benzoyl hydrazides. Indeed, interaction of 6,8-dibromo-4-chloro-2-methylquinazoline **(11)** with acetyl and/or benzoyl hydrazides in boiling *n*-butanol furnished 6,8-dibromo-2-methyl-4-acylhydrazinoquinazoline **14a** and **14b** respectively, (Scheme 2). IR(KBr)(cm^{-1}): 579-601(C-Br), 1400-1401(CH_3), 1644-1651(C=N), 1671-1679(C=O), 3180-3222, 3399-3416(NH). Compounds have structure resembles **13**, **14a** and **14b** are reported as key starting materials for construction of triazoloquinazolines which proved as H_1-antihistaminic[35].



Sulphonamides and Schiff`s bases derived from them were proven therapeutic importance and are used against a wide spectrum of bacterial elements[36-38]. Since quinazoline derivatives too are associated with antibacterial activity, it was considered of interest to incorporate with sulpha drugs in the quinazoline nucleus to study if such compounds could have antibacterial activity. Indeed, interaction of sulphadrugs such as sulphacetamide or sulphaguanidine with chloroquinazoline **11** in 1,4-dioxane afforded the corresponding 4-*N*-substituted quinazoline derivatives **15a** and **b** respectively. IR(KBr)(cm^{-1}) of **15b**: 588(C-Br), 1148, 1438(SO_2), 1599(C=N), 2855, 3014(CH), 3192, 3372(NH). Successful attempt to construct a third heterocyclic ring condensed with quinazoline was achieved via reaction of chloroquinazoline **11** with sodium azide in glacial acetic acid to give the tetrazolo[4,5-c]quinazoline derivative **16,** (Scheme 2). IR(KBr)(cm^{-1}): 553(C-Br), 1596(C=N), 2854, 2923(CH).

It is interesting to investigate the behavior of the chloro derivative **11** towards carbon nucleophiles like active methylene containing compounds. Thus, interaction of the chloro derivatives with ethyl acetoacetate or acetyl acetone in boiling ethanol in the presence of sodium ethoxide as a catalyst afforded 4-substituted methyl quinazolines **17a** and **b** respectively. IR(KBr)(cm^{-1}) of **17b**: 556(C-Br), 1600(C=N), 1693(C=O), 2855-2924(CH). Finally, the behavior of diacetyl derivative **17b** which contains 2 C=O groups towards hydrazine hydrate in

boiling ethanol afforded the spiro compound **18**, (Scheme 2). ^{1}H NMR(DMSO-d_6) of **18** showed signals at δ 1.22(s, 3H, CH_3), 2.17(s, 3H, CH_3), 2.35(s, 3H, CH_3), 8.19-8.36(m, 2H, ArH), 12.70(brs, 1H, NH).

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
1	++	175	++	175	+++	125	++	175
2	+	175	+	175	++	125	++	175
3a	+++	75	+++	75	+++	125	+++	125
3b	+++	175	++	175	++	175	+++	175
4a	+++	175	+++	175	+++	175	+++	175
4b	++	250	+++	250	++	250	++	250
4c	+++	125	++	125	+++	125	+++	125
5	++	175	+	175	+	175	++	175
6a	++++	75	++++	75	+++	75	+++	125
6b	++	125	+++	125	+++	125	++	125
8	+++	250	++	250	++++	250	++	250
10	++	175	+++	175	+	175	+	250
11	++	125	++	175	++	175	++	175
15a	++	250	+++	250	+++	250	+++	250
15b	++	250	++	250	++	175	++	250
18	+++	250	++++	250	+++	250	++	250
Ampicillin	++++	25	++++	25	++++	25	++++	30

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
1	++	175	+	250
2	++	250	+	250
3a	+++	125	++	75
3b	++	175	++	175
4a	+++	175	+++	250
4b	++	250	++	250
4c	++	125	++	125
5	+++	250	++	250
6a	+++	125	+++	125
6b	++	125	++	125
8	+++	250	++	250
10	++	175	+	250
11	++	17	+	175
15a	+++	250	+++	250
15b	+++	250	+++	250
18	++	250	++	250
Mycostatin	++++	30	++++	30

Screening for antimicrobial activity

In this study, the antibacterial activity of some prepared compounds were tested by the disc diffusion method. The results are listed in table 1. It is clear that, compounds **3a**, **3b**, **4a**, **4c**, and

8 possessed high activity against G+ve bacteria except compound **6a** possessed very high activity, while compound **2** possessed low activity.

All compounds possessed high activity against G-ve, except compounds **5** and **10** possessed low activity.

Nearly all compounds possessed high to moderate activity against Fungi from which compounds **1**, **2**, **10**, and **11** have low activity (C.F. table 2).

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