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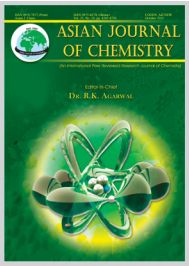

Synthesis of Novel Quinazoline-4-one Derivatives and their Acyclonucleoside Analogs

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A number of quinazolin-4-one derivatives were synthesized. Reaction of the 2-hydrazonoquinazoline-4-one derivatives with aldoses afforded the corresponding sugar hydrazones which on treatment with ferric chloride to afford the corresponding acyclic nucleoside analogues.

Key Words: Quinazoline-4-one, Acyclonucleoside.

INTRODUCTION

Quinazoline or isoquinazoline derivatives belong to a broad class of compounds, which have received a considerable attention over the past years due to their wide range of biological properties[1,2]. Some of the aminoquinazoline derivatives were found to be inhibitors of the tyrosine kinase[3,4] or dihydrofolate reductase enzymes[5], so they work as potent anticancer agents. They are also used to work out medicines against hypertension, malaria and to fight infections involving AIDS[6,7]. Furthermore, quinazoline derivatives are potential drugs which can possess antimalarial[8] sedative-hypnotic, CNS depressant[9-11], antimicrobial[12] and antiinflammatory[13] activities. A number of quinazoline derivatives were shown to act as anticancer active agents and antimetabolites from the group of analogues of folic acid; they are antifolate thymidylate synthase (TS) inhibitors[14]. On the other hand, many synthetic acyclo C-nucleosides have also been found to possess important biological activates including antiviral[15], antibacterial[16], antifungal[17] and protein kinase inhibition activity[18]. Consequently, we have considered that the attachment of quinazolin-4-one heterocycles to some sugar moieties or open chain analogues will produce their respective acyclic nucleosides analogues with enhancing the biological activity.

EXPERIMENTAL

Melting points were taken on a digital melting point apparatus. Infrared spectra were measured on KBr using a Bruker-Vector 22. Mass spectra were measured on a Hewlett-Packard 5988 A (1000 Hz) instrument. ^{1}H NMR spectra were obtained using a Varian Gemini (300 MHz) spectrometer (DMSO-d_6) with TMS as internal standard. All reactions were monitored by TLC. The microanalyses were performed at the microanalytical unit, Cairo University, Egypt and were found to agree favourably with the calculated values. The antimicrobial test was carried out at National Research Centre (NRC) Dokki, Cairo, Egypt.

2-Mercapto-3-alkyl-4a,8a-dihydro-3*H*-quinazoline-4-one (3a,b): A mixture of anthranilic acid (100 mmol, 13.7 g) and the corresponding isocynate derivative 0.1 mol in absolute ethanol (120 mL) was refluxed for 12 h. The reaction mixture was cooled to room temperature. The precipitate was filtered off, washed with ethanol and dissolved in 2 N sodium hydroxide (200 cm^3). The reaction was boiled for 20 min and then cooled. The alkaline solution was neutralized by conc. hydrochloric acid to give pale yellow precipitate.

3-Methyl-2-(methylthio)quinazolin-4(3*H*)-one (3a): Pale yellow powder; yield 79 %; m.p. 255-258 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3431 (NH), 1688 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 2.52 (s, 3H, CH_3), 3.66 (s, 3H, CH_3), 7.30 (m, 2H, Ar-H), 7.54 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.97 (d, 1H, *J* = 7.8 Hz, Ar-H). ^{13}C NMR (DMSO) δ = 26.25, 33.20 (2CH_3), 115.17-138.91 (Ar-C), 167.50 (C=O). Mass : m/z (%) = 207 [(M^+ + 1)].

3-Ethyl-2-(methylthio)quinazolin-4(3*H*)-one (3b): Pale yellow powder; yield 79 %; m.p. 270-272 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3464 (NH), 1708 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.21 (t, 3H, *J* = 5.6 Hz, CH_3), 2.57 (s, 3H, CH_3), 4.50 (q, 2H, *J* = 5.6 Hz, CH_2), 7.30 (m, 2H, Ar-H), 7.54 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.97 (d, 1H, *J* = 7.8 Hz, Ar-H). Mass: m/z (%) = 220 [M^+].

2-Hydrazino-3-methyl-4a,8a-dihydro-3*H*-quinazolin-4-one (4): A mixture of 2-methyl sulfonyl quinazolin-4-one derivative **4** (10 mmol, 2 g) and 1 mol (32 mL) hydrazine hydrate in 20 mL ethanol was heated under reflux for 6 h. The solid product obtained after cooling was filtered off, washed

with water and recrystallized from (EtOH/DMF) dried to give compound **5**. White powder; yield 63 %; m.p. 167-170 ºC. IR (KBr, ν_{max}, cm^{-1}) = 3319 (NH_2), 3300 (NH), 1667, (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.28 (s, 3H, CH_3), 5.40 (s, 2H, NH_2), 7.11 (m, 2H, Ar-H), 7.56 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.49 (d, 1H, *J* = 7.8 Hz, Ar-H), 8.13 (s, 1H, NH).

Sugar-2-hydrazonoquinazoline derivatives (5a-c): A solution of the respective sugar (100 mmol) in 5 mL H_2O was treated with a solution of 2-hydrazino-3-methylquinazolin-4-one (**5**) (10 mmol, 1.9 g) in 50 mL ethanol and few drops of acetic acid, the mixture was boiled under reflux for 2 h. The product that separated out after cooling was filtered, washed with water, ethanol and recrystallized from EtOH/DMF to give compounds (**5a-c**).

D-Galactose-[(3-methyl-4a,8a-dihydro-3*H*-quinazolin-4-one)-2-yl]hydrazone (5a): White powder; yield 66 %; m.p. 186-187 ºC. IR (KBr, ν_{max}, cm^{-1}) = 3260 (NH and OH); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.16 (s, 3H, CH_3), 3.17 (m, 2H, H-6', H-6''), 3.28 (m, 1H, H-5'), 3.62 (m, 1H, H-3',4'), 4.14 (dd, 1H, *J* = 8.8 Hz, *J* = 3.8 Hz, H-2'), 4.49 (t, 1H, *J* = 6.2 Hz, OH), 4.60 (t, 1H, *J* = 5.8 Hz, OH), 4.82 (m, 1H, OH), 5.11 (m, 1H, OH), 5.20 (m, 1H, OH), 7.10 (m, 1H, Ar-H), 7.39 (d, 1H, *J* = 9.5 Hz, H-1'), 7.66 (d, 1H, *J* = 7.8 Hz, Ar-H), 7.90 (m, 2H, Ar-H), 9.78 (s, 1H, NH); mass: m/z (%) = 352 [M^+].

D-Mannose-[(3-methyl-4a,8a-dihydro-3*H*-quinazoline-4-one)-2-yl]hydrazone (5b): White powder; yield 65 %; m.p. 194-195 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3260 (NH and OH), 1693 (C=O), 1606 (C=N), ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.40 (s, 3H, CH_3) 3.42 (m, 2H, H-6', H-6''), 3.50 (m, 1H, H-5'), 3.70 (m, 1H, H-3',4'), 4.20 (dd, 1H, *J* = 6.8 Hz, *J* = 2.6 Hz, H-2'), 4.30 (m, 1H, OH), 4.44 (t, 1H, *J* = 4.8 Hz, OH), 5.0 (d, 1H, *J* = 4.8 Hz, OH), 5.02 (m, 1H, OH), 7.25 (m, 2H, Ar-H), 7.29 (d, 1H, *J* = 8.8 Hz, H-1'), 7.76 (d, 1H, *J* = 8.2 Hz, Ar-H), 7.98 (d, 1H, Ar-H), 9.79 (bs, 1H, NH); mass: m/z (%) = 353 [(M^+ + 1)].

D-Arabinose[(3-methyl-4a,8a-dihydro-3*H*-quinazoline-4-one)-2-yl]hydrazone (5c): White powder; yield 56 %; m.p. 170-171 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3267 (NH and OH), 1677 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.33 (s, 3H, CH_3), 3.38 (m, 2H, H-5', H-5'), 3.60 (m, 2H, H-3',4'), 4.19 (t, 1H, *J* = 6.8 Hz, H-2'), 4.76 (d, *J* = 6.2 Hz, 1H, OH), 4.80 (m, 1H, OH), 4.90 (m, 1H, OH), 5.12 (d, *J* = 6.4 Hz, 1H, OH), 7.30 (m, 2H, Ar-H), 7.39 (d, 1H, *J* = 8.8 Hz, H-1'), 7.86 (d, 1H, *J* = 8.58 Hz, Ar-H), 7.92 (d, 1H, *J* = 8.58 Hz, Ar-H), 10.56 (s, 1H, NH). ^{13}C NMR (DMSO, 300 MHz), δ = 63.54 (C-6'), 70.50 (C-5'), 70.94 (C-4'), 72.67 (C-3'), 113.26 (C-2'), 114.88-157.05 (Ar-C and C-1'), 157.8 (C=O).

3-Methyl-4a,8a-dihydro-3*H*-2-[3-(sugar)-1,2,4-triazole-2-ylamino]quinazolin-4-one (6a-c): 2 M solution of ferric chloride (0.4 g) in 1 mL ethanol was added dropwise to a boiling solution of sugar hydrazone of 3-methylquina-zoline-4-one derivative **6a-c** (3 mmol) in 80 cm^3 ethanol, heating was continued for 15 min and the mixture was kept over night at room temperature. The precipitate was filtered, washed with water and ethanol and recrystallized from (EtOH/DMF).

3-Methyl-4a,8a-dihydro-3*H*-2-[3-(D-galactose)-1,2,4-triazole-2-ylamino]quinazolin-4-one (6a): Pale yellow powder; yield 66 %; m.p. 155-157 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3560-3150 (OH), 3405 (NH_2) 1696 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.34 (s, 3H, CH_3), 3.65 (m, 2H, H-5', H-5''), 3.70 (m, 1H, H-3',4'), 4.10 (m 1H, H-2'), 4.26-4.42 (m, 2H, 2OH), 5.26 (m, 1H, OH), 4.70 (m, 1H, OH), 5.16 (m, 1H, OH), 5.37 (t, 1H, *J* = 8.5 Hz, H-1'), 5.77 (dd, 1H, *J* = 8.5 Hz, *J* = 4.2 Hz, triazole H-3), 7.45 (m, 2H, Ar-H), 7.67 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.86 (d, 1H, *J* = 8.4 Hz, Ar-H). ^{13}C NMR (DMSO), δ = 29.25 (CH_3), 62.88 (C-5'), 65.46 (C-5'), 68.56 (C-4'), 69.51 (C-3'), 71.12 (C-2'), 77.42 (C-1') 96.50 (triazole C-3), 118.84-155.79 (Ar-C), 165.76 (C=O).

3-Methyl-4a,8a-dihydro-3*H*-2-[3-(D-arabinose)-1,2,4-triazole-2-ylamino]quinazoline-4-one (6b): Pale yellow powder; yield 61 %; m.p. 158-159 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3562-3147 (OH), 3419 (NH_2) 1690 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.47 (s, 3H, CH_3), 3.67 (m, 2H, H-4', H-4''), 3.71 (m, 1H, H-2',3'), 4.12 (m, 1H, H-1'), 4.33 (m, 2H, OH), 5.24 (m, 1H, OH), 4.75 (m, 1H, OH), 5.75 (dd, 1H, *J* = 8.8 Hz, *J* = 4.0 Hz, triazole H-3), 7.46 (m, 2H, Ar-H), 7.72 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.89 (d, 1H, *J* = 8.4 Hz, Ar-H).

3-Methyl-4a,8a-dihydro-3*H*-2-[3-(D-mannose)-1,2,4-triazole-2-ylamino]quinazoline-4-one (6c): Pale yellow powder; yield 68 %; m.p. 159-160 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3555-3142 (OH), 3412 (NH_2) 1690 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.36 (s, 3H, CH_3), 3.67 (m, 2H, H-5', H-5''), 3.71 (m, 1H, H-3',4'), 4.12 (m 1H, H-2'), 4.20-4.45 (m, 2H, 2OH), 5.24 (m, 1H, OH), 4.72 (m, 1H, OH), 5.18 (m, 1H, OH), 5.37 (t, 1H, *J* = 8.5 Hz, H-1'), 5.82 (dd, 1H, *J* = 8.5 Hz, *J* = 4.2 Hz, triazole H-3), 7.46 (m, 2H, Ar-H), 7.72 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.89 (d, 1H, *J* = 8.4 Hz, Ar-H).

D-Glucose [(3-methyl-4a,8a-dihydro-3H-quinazoline-4-one)-2-yl]hydrazone (7): White powder (68 %); m.p. 149-125 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3490 (NH); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.33 (s, 3H, CH_3), 3.42 (m, 2H, H-6',6''), 3.50 (m, 1H, H-5'), 3.70 (m, 1H, H-4',3'), 4.20 (t, 1H, *J* = 8.8 Hz, H-2'), 4.30-4.44 (m, 2H, 2OH), 5.02 (d, 1H, *J* = 6.8 Hz, OH), 5.02 (m, 1H, OH), 6.05 (d, 1H, *J* = 9.8 Hz, H-1'), 7.45 (d, 1H, *J* = 8.9 Hz Ar-H), 7.86 (m, 2H, Ar-H), 7.95 (d, 1H, *J* = 8.9 Hz Ar-H), 10.96-11.05 (bs, 2H, 2NH). ^{13}C NMR (DMSO), δ = 29.25 (CH_3), 60.33 (C-6'), 68.18 (C-5'), 68.58 (C-4'), 73.61 (C-3'), 76.39 (C-2'), 92.14 (C-1'), 113.44-156.22 (Ar-C), 166.29 (C=O).

3-Alkylquinazolin-2,4-(1H,3H)dione (8a, b): To a solution of 2-mercaptoquinazoline-4-one derivatives **3a, b** (10 mmol) in 10 % aqueous potasium hydroxide (30 mL) at 50 ºC was added hydrogen peroxide (15 mL) over a period of 1 h, the reaction mixture was warmed at 60-70 ºC for an additional 1 h, the solution that obtained after cooling and filterating was acidified by acetic acid to give white precipitate, which was filtered, washed with water dried, recrystallized from ethanol to afford compound (**8a, b**).

3-Methylquinazolin-2,4-(1*H*, 3*H*)dione (8a): Pale yellow powder; yield 73 %; m.p. 270-272 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3405 (NH), 1681 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.25 (s, 3H, CH_3), 7.54 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.55 (m, 2H, Ar-H), 7.65 (d, 1H, *J* = 8.4 Hz, Ar-H), 11.05 (s, 1H, NH), ^{13}C NMR (DMSO, 300 MHz): δ = 26.91 (CH_3) 113.59-155.23 (Ar-C), 167.27, 168.07 (2C=O); mass: m/z (%) = 176 [M^+].

3-Ethylquinazolin-2,4-(1*H*, 3*H*)dione (8b): White powder; yield 72 %; m.p. 270-272 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3405 (NH), 1681 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ

1.14 (t, 3H, *J* = 5.4 Hz, CH_3), 4.44 (q, 2H, *J* = 5.4 Hz, CH_2), 7.48 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.57 (m, 1H, Ar-H), 7.65 (d, 1H, *J* = 8.4 Hz, Ar-H), 11.08 (s, 1H, NH); mass: m/z (%) = 190 [M^+].

Preparation of *N*-derivatives of *N*-methyl and *N*-ethyl quinazoline-2,4-dione (9a-h): A mixture of the quinazoline-2,4-dione derivatives (**9a,b**) (10 mmol) and potassium carbonate (12 mmol) in 20 mL dry acetone stirred for 3 h, then the alkylating agent (15 mmol) was added and reaction mixture was stirred for 48 h at room temperature the solvent was evaporate recrystallized from ethanol.

1-(2-Hydroxyethyl)-3-methlquinazoline-2,4(1*H*, 3*H*)-dione (9a): Pale yellow powder; yield 65 %; m.p. 115-118 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3467 (OH), 3100 (NH), 1680 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.35 (s, 1H, CH_3), 3.95 (s, 2H, CH_2), 4.55 (t, 1H, *J* = 6.4 Hz, OH), 7.45 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.55 (m, 2H, Ar-H), 7.89 (d, 1H, *J* = 8.4 Hz, Ar-H). ^{13}C NMR (DMSO) δ = 29.91 (CH_3), 62.75 (CH_2), 121.16-150.27 (Ar-C), 165.49 (C-2), 167.08 (C-4); mass: m/z (%) = 206 [M^+].

3-Methyl-1-(oxiran-2-ylmethyl)quinazoline-2,4(1*H*, 3*H*)-dione (9b): Pale yellow powder; yield 55 %; m.p. 98-100 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3110 (NH), 1687 (C=O) ; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.41 (s, 3H, CH_3), 3.42 (d, 2H, *J* = 5.8 Hz, CH_2), 4.17 (d, 2H, *J* = 6.4 Hz, CH_2), 4.25 (m, 1H, CH-O), 7.26 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.65 (m, 2H, Ar-H), 7.92 (d, 1H, *J* = 8.4 Hz, Ar-H); mass: m/z (%) = 232 [M^+].

1-(2-Methoxyethyl)-3-methylquinazoline-2,4(1*H*, 3*H*)-dione (9c): Pale yellow powder; yield 55 %; m.p. 96-98 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3115 (NH), 1666 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.36 (s, 3H, CH_3), 3.78 (s, 3H, CH_3), 3.62 (t, 2H, *J* = 6.4 Hz, CH_2), 3.87 (t, 2H, *J* = 6.4 Hz, CH_2), 7.44 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.64 (m, 2H, Ar-H), 7.88 (d, 1H, *J* = 8.4 Hz, Ar-H); mass: m/z (%) = 234 [M^+].

1,3-Diethylquinazoline-2,4(1*H*,3*H*)-dione (9d): White powder; yield 66 %; m.p. 102-103 ºC; IR (KBr, ν_{max}, cm^{-1}) = 33600 (NH), 1684 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.13 (t, 3H, *J* = 5.4 Hz, CH_3), 1.22 (t, 3H, *J* = 6.2 Hz, CH_3), 3.99 (q, 2H, *J* = 5.4 Hz, CH_2), 4.15 (q, 2H, *J* = 6.2 Hz, CH_2), 7.43 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.35 (m, 2H, Ar-H), 7.91 (d, 1H, *J* = 8.4 Hz, Ar-H); mass: m/z (%) = 218 [M^+].

1-Benzyl-3-ethylquinazoline-2,4(1*H*,3*H*)-dione (9e): White powder; yield 60 %; m.p. 192-194 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3224 (NH), 1641 (C=O); ^{1}H NMR (DMSO-δ_6, 300 MHz): δ 1.16 (t, 3H, *J* = 5.8 Hz, CH_3), 3.25 (q, 2H, *J* = 5.8 Hz, CH_2), 3.96 (s, 2H, CH_2), 7.54 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.57 (m, 2H, Ar-H), 7.62 (m, 2H, Ar-H), 7.67 (m, 3H, Ar-H), 7.95 (d, 1H, *J* = 8.4 Hz, Ar-H); mass: m/z (%) = 280 [M^+].

3-Ethyl-1-(2-hydroxymethylquinazoline-2,4(1*H*,3*H*)-dione (9f): Pale yellow powder; yield 66 %; m.p. 189-190 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3454 (OH), 3324 (NH), 1678 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.16 (t, 3H, *J* = 6.4 Hz, CH_3), 3.96 (q, 2H, *J* = 4.6 Hz, CH_2), 4.42 (t, 2H, *J* = 5.6 Hz, CH_2), 4.46 (m, 1H, OH), 7.43 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.39 (m, 2H, Ar-H), 7.95 (d, 1H, *J* = 8.4 Hz, Ar-H).

3-Ethyl-1-(oxiran-2-ylmethyl)quinazoline-2,4(1*H*-3*H*)-dione (9g): Pale yellow powder; yield 66 %; m.p. 173-175 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3387 (NH), 1698 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.16 (t, 3H, *J* = 6.4 Hz, CH_3), 3.63 (q, 2H, *J* = 6.4 Hz, CH_2), 3.75 (d, 2H, *J* = 6.2 Hz, CH_2), 4.25 (d, 2H, *J* = 6.2 Hz, CH_2), 4.97 (m, H, CH-O), 7.45 (d, 1H, *J* = 8.4 Hz, Ar-H), 7.62 (m, 2H, Ar-H), 7.93 (d, 1H, *J* = 8.4 Hz, Ar-H).

3-Ethyl-1-(2-methoxyethyl)quinazoline-2,4(1*H*-3*H*)-dione (9h): Pale yellow powder; yield 66 %; m.p. 145-147 ºC; IR (KBr, ν_{max}, cm^{-1}) = 3365 (NH), 1706 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.21 (t, 3H, *J* = 6.2 Hz, CH_3), 3.72 (s, 3H, CH_3), 3.49 (q, 2H, *J* = 6.2 Hz, CH_2), 4.18 (t, 2H, *J* = 5.8 Hz, CH_2), 4.50 (t, 2H, *J* = 5.8 Hz, CH_2), 7.45 (d, 1H, Ar-H), 7.49 (m, 2H, Ar-H), 7.97 (d, 1H, Ar-H).

RESULTS AND DISCUSSION

The quinazoline derivatives **2a, b** were synthesized by the reaction of anthranilic acid with the corresponding isothiocyanate derivative in ethanol to give thiourea derivatives which underwent cyclization in presence of sodium hydroxide. Methylation of 2-thioquinazolines **2a, b** with one equivalent methyl iodide gave 2-methyl thioquinazoline **3a, b**. Treatment of compound **3a** with hydrazine hydrate resulted in nucleophilic displacement of the thiomethyl group with hydrazine hydrate to give the corresponding hydrazino derivative **4**.

Reaction of the 2-hydrazinoquinazoline derivative **4** with the aldoses (D-galactose, D-mannose and D-arabinose) gave the corresponding sugar hydrazone **5a-c** respectively. The structure of the products was confirmed by means of IR, ^{1}H NMR, mass spectra and elemental analysis. The IR spectrum showed an absorption at 3467-3260 cm^{-1} characterized for the OH and NH groups. The ^{1}H NMR spectrum showed signals of the protons of the sugar moiety at d 3.17-5.20 ppm in addition to signals at 10.54-9.98 ppm for the NH group. The C-1 methine proton signal appeared at higher chemical shift greater than 7 ppm.

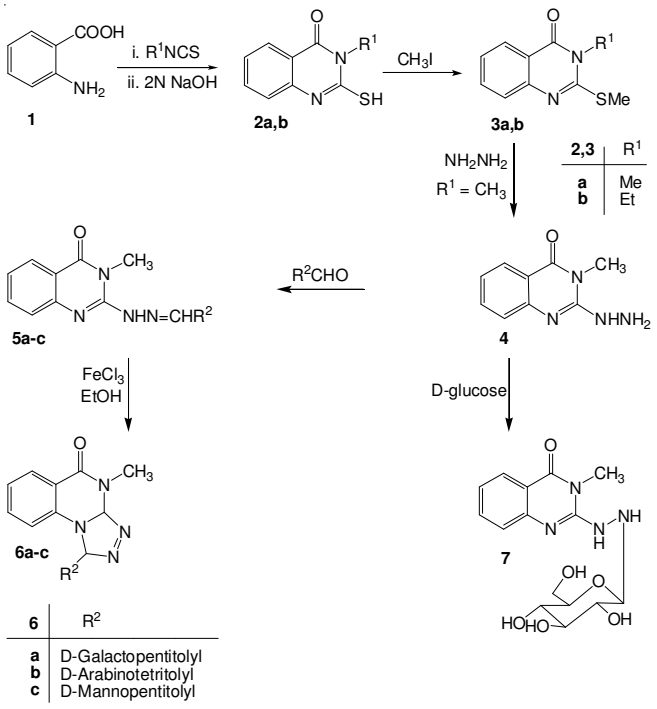
Oxidative cyclization of the sugar hydrazone **5a-c** with ferric chloride in ethanol gave the corresponding triazoloquinazoline derivatives **6a-c**, which have been assigned from their spectral and analytical data. Thus, the ^{1}H NMR spectra showed the signal of the H-3 in the triazole ring as doublet at δ 5.75-5.82 ppm (**Scheme-I**).

When the 2-hydrazinoquinazoline derivative **4a** was allowed to react with D-glucose, it gave the hydrazino sugar **7**, which has been shown to be in the cyclic pyranose form. The ^{13}C NMR spectrum showed the signal at δ 91.14 ppm, assigned for the anomeric carbon, which indicates that the hydrazine sugar presences in the pyranose form. The signals at δ 68.18-76.39 were assigned for the carbons of the sugar moiety.

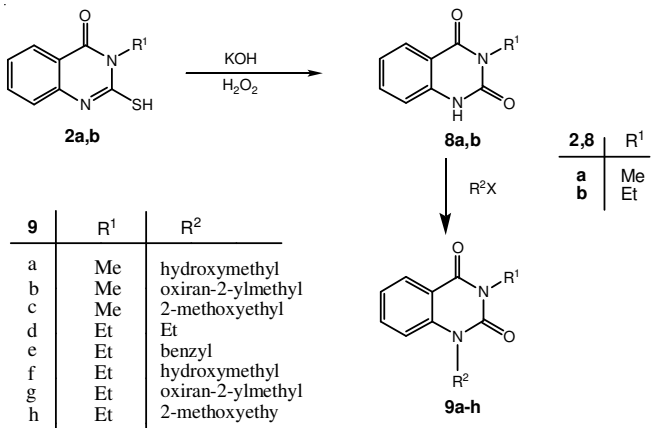
Oxidation of **2a, b** using H_2O_2 and KOH afforded the oxoquinazoline **8a,b**. Alkylation of the oxoquinazoline **8a,b** with different alkyl or oxegentaed alkyl halides in dry acetone in presence of K_2CO_3 gave the oxoquinazoline derivatives **9a-h** (**Scheme-II**). Their ^{1}H NMR spectra showed signals corresponding to the substituted alkyl chain protons and IR spectra agreed with the assigned structures.

Antimicrobial activity: The newly synthesized compounds were tested for their antimicrobial action against important pathogenic microorganisms namely *Escherichia coli*

(Gram-negative bacterium), *Staphlococcusaureus* (Gram-positive bacterium), *Candida albicans* and *Aspirgillus flavus* (two of the important Fungi). All of the tested compounds exhibited different degrees of antibacterial activity or inhibitory action. The most susceptible organism was the Gram-positive bacteria Staphlococcusaureus, followed by *Escherichia coli* while the lowest inhibitory effect was encountered in the case of *Aspirgillus flavus*. The highest degrees of inhibition were recorded for compounds **9e** and **8a** followed by **3b, 3a** and **9d** (Table-1). The results were compared to amoxicillin (penicillin) as a reference drug.



Scheme-I



Scheme-II

TABLE-1
ANTIMICROBIAL ACTIVITY OF THE NEWLY SYNTHESIZED COMPOUNDS

Compound	*Escherichia coli* (G^-)	*Staphlococcusaureus* (G^+)	*Candida albicans* (Fungus)	*Aspergillus flavus* (Fungus)
Control	0.0	0.0	0.0	0.0
3a	11	12	12	0.0
3b	12	12	12	0.0
8a	10	13	10	0.0
9b	12	12	10	0.0
9d	12	12	11	0.0
9e	13	17	13	0.0

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