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Synthesis of New 3-Phenyl-2-thioquinazoline Derivatives

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A new 3-phenyl-2-thioquinazoline derivatives have been synthesized by the reaction of hydrazide **1** with formic acid and diethylmalonate to give **2** and **3**, respectively. Compound **1** is reacted with sugar to give the sugar hydrazone (**4a-c**) which is converted to oxadiazole derivatives (**5a-c**). The final compounds **(6a-c)** were obtained by reacting the hydrazones **4a-c** with acetic anhydride in pyridine.

Key Words: Synthesis, 3-Phenyl-2-thioquinazoline derivatives, Sugar hydrazone.

INTRODUCTION

Substituted quinazoline derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity. They are widely used in pharmaceuticals and agrochemicals[1,2]. Alagarsamy *et al.*[3-6], developed a group of quinazoline-derivatives of intense current interest in commercial drugs with analgesic and antiinflammatory activity. A number of researches mention the utility of substituted quinazolines as important fungicide[7,8], herbicide[9,10] and anti-tumor agent[11]. Thus, their synthesis has been of great interest in the elaboration of biologically active heterocyclic compounds. Some high-bioactive compounds have been commercialized, for example, fluquinconazole fungicide for control of the agriculture disease[12,13]. Present interest involves in the synthesis of quinazoline derivatives with diversity at 1-position[14]. Recently, we reported the antimicrobial activity of novel 3-phenyl-2-thioquinazolin-4-one derivatives, some of which were found to possess good bioactivity prompted by these results and in an attempt to evaluate the modification of the antimicrobial induced by the change of the substituents at the quinazoline ring, we designed and synthesized a series of 2-alkylthio-3-phenylquinazoline derivatives.

EXPERIMENTAL

Melting points were determined using a Büchi apparatus. IR spectra (KBr) were recorded with a Bruker-Vector instrument (Bruker, Bremen, Germany). ^{1}H NMR spectra were recorded with a Varian Gemini spectrometer at 300 and 200 MHz with TMS as internal standard. Chemical shifts were reported in δ scale (ppm) relative to TMS as a standard and the coupling constants (*J* values) are given in Hz. The progress of the reactions was monitored by TLC using aluminum silica gel plates 60 F_{245}. EI-mass spectra were recorded with a HP D5988 A 1000 MHz instrument (Hewlett-Packard, Palo Alto, CA, USA).

N'-Formyl-2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylthio)acetohydrazide (2): A solution of hydrazide 1 0.33 g, 1 mmol) and formic acid (2.3 g, 0.05 mol) in ethanol (20 mL) was refluxed for 1 h. The mixture was poured on ice-cold water with stirring, precipitate formed, filtered off, dried and crystallized from ethanol to give white powder 0.1 g, (yield 50 %); IR (KBr, ν_{max}, cm^{-1}): 3207 (2NH), 1726 (CHO), 1655 (CH_2-CO), 1690 (C=O). ^{1}H NMR (DMSO-d_6): δ 3.98 (s, 2H, CH_2-S), 7.19-8.04 (m, 9H, Ar-H), 8.73 and 8.94 (2s, 2H, 2xNH), 9.54 (s, 1H, CHO).

1-[2-(4-Oxo-3-phenyl-3,4-dihydroquinazolin-2-ylsulfanyl)acetyl]pyrazolidine-3,5-dione (3): A mixture of the hydrazide **3** (0.33 g, 1 mmol), diethylmalonate (0.16 g, 1 mmol) and Et_3N (1 mL) was dissolved in dioxane (30 mL). The reaction mixture was heated under reflux for 6 h and then cooled at room temperature. The obtained precipitate was filtered off, dried and crystallized from ethanol as pale yellow powder; 0.15 g (41.6 %); m.p. 210 ºC; ^{1}H NMR (DMSO-d_6): δ 3.95 (s, 2H, CH_2-S), 4.36 (s, 2H, CH_2), 7.44-8.34 (m, 9H, Ar-H), 11.83 (s, 1H, NH).

Sugar hydrazone (4a-c): To a well stirred solution of the respective monosaccharide (0.01 mol) in water (2 mL)

and glacial acetic acid (0.2 mL) was added hydrazide derivative **4** (0.01 mol) in ethanol (10 mL). The mixture was heated under reflux for 3 h, the resulting solution was concentrated and left to cool. The precipitate formed was filtered off, washed with water and ethanol then dried and crystallized from ethanol.

D-(+)-Galactose 2-(4-oxo-3-phenyl-3,4-dihydro quinazolin-2-ylthio)aceto-hydrazone (4a): Yield 48 %; m.p. 98 ºC; IR (KBr, ν_{max}, cm^{-1}): 3390 (OH), 3300 (NH), 1673 (C=O), 1613 (CH_2-C=O); M/Z: m/z (%) = 478. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.49 (m, 2H, H-6', H-6''), 3.51 (m, 1H, H-5'), 3.82 (s, 2H, CH_2), 4.18 (m, 1H, H-4'), 4.36 (dd, 1H, *J* = 2.8 Hz, *J* = 5.8 Hz, H-3'), 4.46 (t, 1H, *J* = 5.8 Hz, H-2'), 4.61 (m, 1H, OH), 4.72 (d, 1H, *J* = 6.3 Hz, OH), 4.90 (m, 1H, OH), 4.97 (t, 1H, *J* = 4.5 Hz, OH), 5.36 (t, 1H, *J* = 4.5 Hz, OH), 7.20-8.16 (m, 9H, Ar-H), 10.21 (s, 1H, NH), MS (ESI): m/z = 490 [M^+ + 1].

D-(–)-Ribose 2-(4-oxo-3-phenyl-3,4-dihydro quinazolin-2-ylthio)aceto-hydrazone (4b): Yield 53 %; m.p. 100 ºC. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.39 (m, 1H, H-5'), 3.44 (dd, 1H, *J* = 9.8 Hz, *J* = 2.8 Hz, H-5''), 3.62 (m, 1H, H-4'), 3.81 (s, 2H, CH_2), 4.25 (t, 1H, *J* = 2.2 Hz, H-3'), 4.35 (dd, 1H, *J* = 5.8 Hz, *J* = 2.2 Hz, H-2'), 4.57 (d, 2H, *J* = 5.4 Hz, CH_2), 4.59 (m, 1H, OH), 4.86 (d, 1H, *J* = 2.8 Hz, *J* = 6.3 Hz, OH), 4.88 (t, 1H, *J* = 2.2 Hz, OH), 5.42 (d, 1H, *J* = 4.5 Hz, OH), 7.15-8.14 (m, 9H, Ar-H), 10.09 (s, 1H, NH), MS (ESI): m/z = 459 [M^+ + 1].

D-(+)-Xylose 2-(4-oxo-3-phenyl-3,4-dihydro quinazolin-2-ylthio)aceto-hydrazone (4c): Yield 43 %; m.p. 96 ºC. ^{1}H NMR (DMSO-d_6, 300 MHz): δ 3.43 (m, 1H, H-5'), 3.47 (dd, 1H, *J* = 9.8 Hz, *J* = 2.8 Hz, H-5''), 3.59 (m, 1H, H-4'), 3.80 (s, 2H, CH_2), 4.29 (t, 1H, *J* = 2.2 Hz, H-3'), 4.39 (dd, 1H, *J* = 5.8 Hz, *J* = 2.2 Hz, H-2'), 4.56 (d, 2H, *J* = 5.4 Hz, CH_2), 4.64 (m, 1H, OH), 4.93 (d, 1H, *J* = 2.8 Hz, *J* = 6.3 Hz, OH), 4.97 (t, 1H, *J* = 2.2 Hz, OH), 5.38 (d, 1H, *J* = 4.5 Hz, OH), 7.18-8.23 (m, 9H, Ar-H), 10.19 (s, 1H, NH), MS (ESI): m/z = 459 [M^+ + 1].

Oxadiazole derivatives (5a-c): To solution of compound **4** (1 mmol) in acetic anhydride (5 mL) was boiled under reflux for 1.5 h. The resulting solution was poured onto crushed ice and the product that separated out was filtered off, washed with solution of sodium hydrogen carbonate followed by water and then dried. The product was recrystallized from ethanol.

1-(3-Acetyl-5-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylthio)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)pentane-1,2,3,4,5-pentaaryl pentaacetate (5a): Yield 67 %; m.p. 108 ºC; IR (KBr, ν_{max}, cm^{-1}): 1745 (Ac), 1688 (C=O); ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.95, 1.96, 2.01, 2.07, 2.10, 2.19 (6s, 18H, 6CH_3), 3.85 (s, 2H, CH_2), 3.98 (dd, 1H, *J* = 11.2 Hz, *J* = 2.4 Hz, H-5'), 4.05 (dd, 1H, *J* = 10.6 Hz, *J* = 2.4 Hz, H-5''), 4.96 (dd, 1H, *J* = 2.8 Hz, *J* = 6.5 Hz, H-3'), 5.16 (dd, 1H, *J* = 2.8 Hz, *J* = 6.5 Hz, H-3'), 5.20 (dd, 1H, *J* = 3.2 Hz, *J* = 6.5 Hz, H-2'), 5.37 (dd, 1H, *J* = 3.2 Hz, *J* = 6.2 Hz, H-1'), 5.95 (d, 1H, *J* = 6.2 Hz, oxadiazoline-H),) 7.52-8.11 (m, 9H, Ar-H). MS (ESI): m/z = 741 [M^+ +1].

1-(3-Acetyl-5-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylthio)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)butane-1,2,3,4-tetraaryl tetraacetate (5b): Yield 63 %; m.p. 103 ºC; IR (KBr, ν_{max}, cm^{-1}): 1735 (CO-CH_3), 1657(C=O). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.95, 1.98, 2.03, 2.06, 2.18 (5s, 15H, 5CH_3), 3.77 (s, 2H, CH_2), 3.98 (dd, 1H, *J* = 10.2 Hz, *J* = 2.5 Hz, H-4'), 4.09 (dd, 1H, *J* = 10.4 Hz, *J* = 2.6 Hz, H-4''), 5.26 (dd, 1H, *J* = 2.7 Hz, *J* = 6.4 Hz, H-3'), 5.25 (dd, 1H, *J* = 3.2 Hz, *J* = 6.5 Hz, H-2'), 5.42 (dd, 1H, *J* = 3.2 Hz, *J* = 6.2 Hz, H-1'), 6.05 (d, 1H, *J* = 6.2 Hz, oxadiazoline-H)) 7.42-8.17 (m, 9H, Ar-H). MS (ESI): m/z = 669 [M^+ + 1].

1-(3-Acetyl-5-((4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylthio)methyl)-2,3-dihydro-1,3,4-oxadiazol-2-yl)butane-1,2,3,4-tetraaryl tetraacetate (5c): Yield 59 %; m.p. 89 ºC; ^{1}H NMR (DMSO-d_6, 300 MHz): δ 1.96, 1.98, 2.03, 2.06, 2.18 (5s, 15H, 5CH_3), 3.84 (s, 2H, CH_2), 3.97 (dd, 1H, *J* = 10.2 Hz, *J* = 2.5 Hz, H-4'), 4.09 (dd, 1H, *J* = 10.4 Hz, *J* = 2.6 Hz, H-4''), 5.13 (dd, 1H, *J* = 2.7 Hz, *J* = 6.4 Hz, H-3'), 5.29 (dd, 1H, *J* = 3.2 Hz, *J* = 6.5 Hz, H-2'), 5.47 (dd, 1H, *J* = 3.2 Hz, *J* = 6.2 Hz, H-1'), 6.01 (d, 1H, *J* = 6.2 Hz, oxadiazoline-H)) 7.32-8.10 (m, 9H, Ar-H). MS (ESI): m/z = 669 [M^+ - 1].

Acetylated sugar hydrazone (6a-c): To solution of compound **4** (0.5 mmol) in pyridine (7mL) was added acetic anhydride (0.01 mol) and stirred at room temperature for 5 h. The resulting solution was poured onto crushed ice and the product that separated out was filtered off, washed with solution of sodium hydrogen carbonate followed by water and then dried. The product was recrystallized from ethanol.

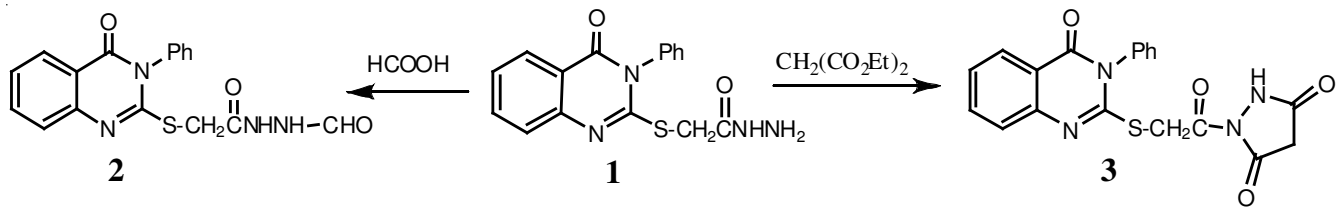
2,3,4,5,6-Penta-O-acetyl-D-(+)-galactose 2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylthio)aceto-hydrazone (6a): Yield 60 %; m.p. 125 ºC; IR (KBr, ν_{max}, cm^{-1}): 3441 (NH), 1744 (-$COCH_3$), 1691 (CO); ^{1}H NMR (DMSO-d_6): δ 1.95, 2.00, 2.04, 2.10, 2.12, 2.15 (6s, 18H, 6xCH_3CO), 3.89 (s, 2H, CH_2), 4.08-4.22 (m, 2H, H-6'), 4.59 (m, 1H, H-5'), 4.76 (m, 1H, H-4'), 5.18 (m, 1H, H-3'), 5.40 (m, 1H, H-2'), 7.13 (d, 1H, *J* = 2.5 Hz, H-1'), 7.37-8.21 (m, 9H, Ar-H), 10.03 (brs, 1H, NH). MS: m/z (%) = 699 [(M^+ +1].

2,3,4,5-Tetra-O-acetyl-D-(–)-ribose 2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylthio)aceto-hydrazone (6b): Black powder; (50 %); m.p. 105 ºC; IR (KBr, ν_{max}, cm^{-1}): 3435 (NH), 1730 (CO-CH_3), 1688 (C=O), 1606 (CH_2-CO). ^{1}H NMR (DMSO-d_6) δ: 1.95, 2.03, 2.11, 2.15 (4s, 12H, 4xCH_3CO), 3.86 (s, 2H, CH_2), 4.19 (m, 2H, H-5'), 4.33 (m, 1H, H-4'), 5.69 (m, 1H, H-3'), 5.77 (m, 1H, H-2'), 7.17 (d, 1H, *J* = 2.5 Hz, H-1'), 7.30-8.21 (m, 9H, Ar-H), 10.07 (brs, 1H, NH). MS: m/z (%) = 627 [(M^+ +1].

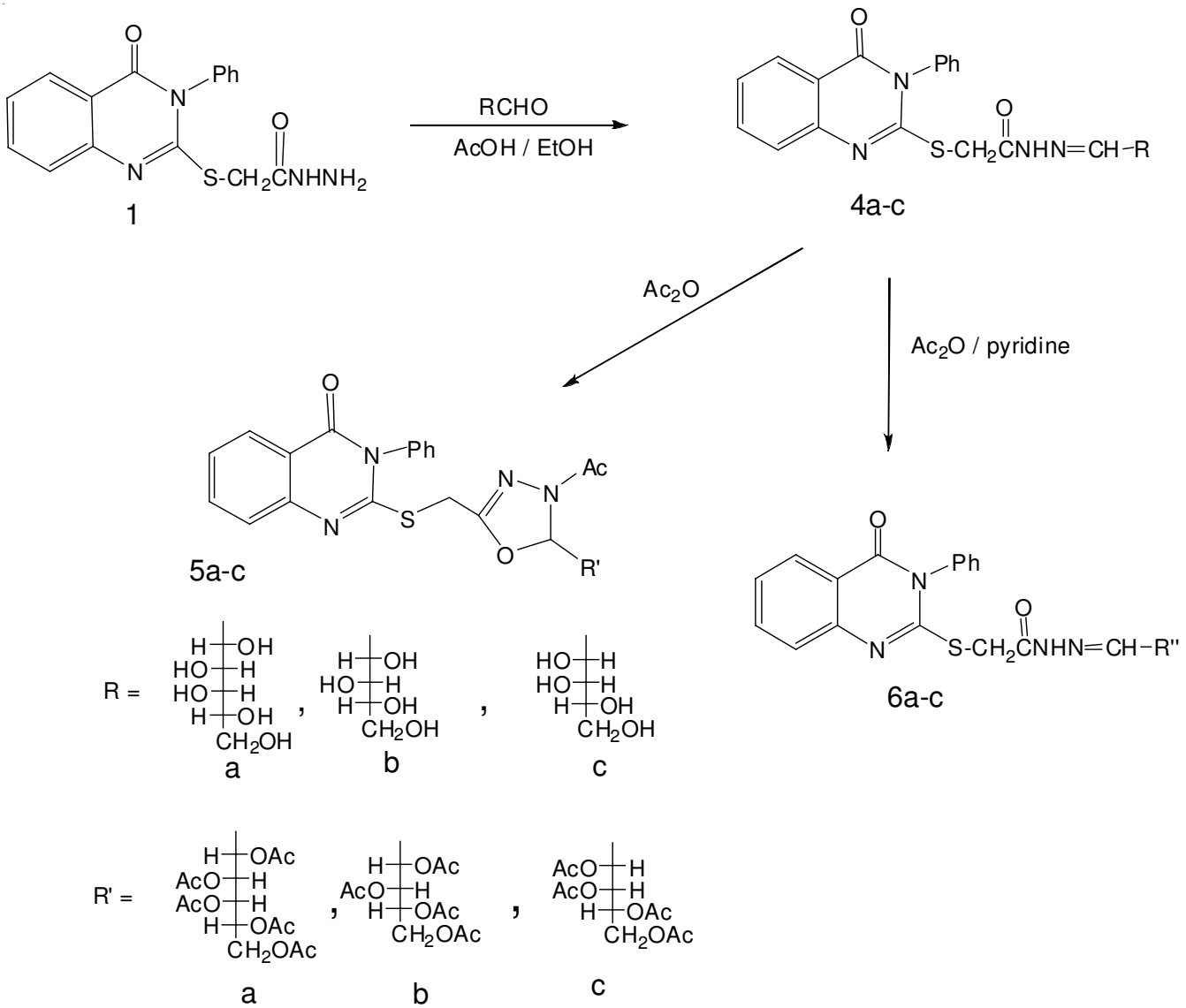
2,3,4,5-Tetra-O-acetyl-d-(+)-xylose 2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylthio)aceto-hydrazone (6c): Black powder; (48 %); m.p. 96 ºC; ^{1}H NMR (DMSO-d_6) δ: 1.95, 2.03, 2.11, 2.12, 2.15 (4s, 12H, 4xCH_3CO), 3.87 (s, 2H, CH_2), 4.29 (m, 2H, H-5'), 4.39 (m, 1H, H-4'), 5.74 (m, 1H, H-3'), 5.88 (m, 1H, H-2'), 7.12 (d, 1H, *J* = 2.5 Hz, H-1'), 7.31-8.23 (m, 9H, Ar-H), 10.00 (brs, 1H, NH). MS: m/z (%) = 627 [(M^+ + 1].

RESULTS AND DISCUSSION

The hydrazide[15] (**1**) was refluxed with formic acid or diethylmalonate to give the corresponding N'-formyl-2-(4-oxo-3-phenyl-3,4-dihydroquinazolin-2-ylthio)acetohydrazide (**2**) or 1-[2-(4-oxo-3-phenyl-3,4-dihydro-quinazolin-2-yl-sulfanyl)-acetyl]pyrazolidine-3,5-dione (**3**), respectively (**Scheme-I**).



Scheme-I



Scheme-II

In **Scheme-II**, the acid hydrazide (**1**) was allowed to react with a number of monosaccharides, the corresponding aldehydo-sugar hydrazones were obtained. Thus, reaction of (**1**) with D-galactose, D-xylose and D-arabinose in an aqueous ethanolic solution and catalytic amount of acetic acid gave the corresponding sugar hydrazones (**4a-c**). The structures of these compounds were confirmed by the analytical and spectral data. The sugar-hydrazone undergoes to form oxadiazolidine (**5a-c**) by refluxing with acetic anhydride or acetylated through the reaction with acetic anhydride in pyridine to form (**6a-c**).

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