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Synthesis of acetamides bearing 3-aryl-3,4-dihydroquinazolin-4-one and 2-thioxothiazolidin-4-one moieties as novel derivatives

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Abstract:

Five new derivatives of *N*-(4-oxo-2-thioxothiazolidin-3-yl)-2-((3-aryl-4-oxo-3,4-dihydroquinazolin-2-yl)thio) acetamides have been synthesized successfully through a four-step process from anthranilic acid and aryl isothiocyanates as starting materials. The total yields ranged from 29 to 31% and these structures were determined by IR, ^{1}H-NMR, ^{13}C-NMR, and HR-MS spectra.

Keywords: **acetamide, hydrazide, quinazolin-4(3*H*)-one, thiocarbonyl-*bis*-thioglycolic, 2-thioxothiazolidin-4-one.**

Classification number: **2.2**

Introduction

3-aryl-3,4-dihydroquinazolin-4-one derivatives have been of great interest in medicinal chemistry for their role as potential biological agents. These derivatives exhibit a wide range of biological effects such as antimicrobial [1-3], antifungal [1], anticonvulsant [4], antihistamine [5], an inhibitor for methionine synthase [6], and increasing HDL cholesterol [7]. Specifically, compounds containing 3-aryl-3,4-dihydroquinazolin-4-one nuclei also show promising anticancer potency [8, 9]. Besides that, the 5-arylidene-2-thioxothiazolidine-4-one scaffold is present in the molecular composition of some compounds that inhibit the hepatitis C virus (HCV) [10], human immunodeficiency virus (HIV) [11], aldose reductase [12, 13], glycogen synthase kinase-3 (GSK-3) [14], JNK-stimulating phosphatase-1 (JSP-1) [15], histone acetyltransferases (HATs) [16], and 17β-hydroxysteroid dehydrogenase type 3 [17]. A variety of biological activities like anticonvulsant [18], antimicrobial [19], anti-diabetic [20], antitumor [21, 22] and anticancer activities [23, 24], etc., have been found in compounds containing the 2-thioxothiazolidine-4-one moiety. The combination of 3-aryl-3,4-dihydroquinazolin-4-one and 2-thioxothiazolidine-4-one moieties thus promise to produce organic molecules bearing precious biological activities of both these heterocycles. This work reports the synthesis of some *N*-(4-oxo-2-thioxothiazolidin-3-yl)-2-((4-oxo-3-aryl-3,4-dihydroquinazolin-2-yl)thio) acetamide compounds. Their biological activity has been studied and is being reported soon.

Materials and methods

All reagents and chemicals were obtained from commercial sources and were used without purification. Melting points were recorded on a Gallenkamp melting point apparatus and were uncorrected. Fourier transform infrared (FTIR) spectra (ν, cm^{-1}) were recorded in KBr discs on a FTIR-8400S-SHIMADZU spectrometer. All the NMR spectra were recorded on a Bruker Avance III spectrometer (500 MHz for ^{1}H-NMR and 125 MHz for ^{13}C-NMR). The residual solvent DMSO-d_6 signals (δ_H 2.50, δ_C 39.52) are used as internal references. The abbreviations *s* (singlet), *d* (doublet), *dd* (doublet of doublet), *t* (triplet), *q* (quartet), and *m* (multiplet) are used to describe the splitting of the peaks. The HR-ESI-MS spectra were recorded on an Agilent 6500 series Q-TOF spectrometer.

The target compounds (**5a-e**) were synthesized via a four-step pathway as illustrated in Scheme 1.

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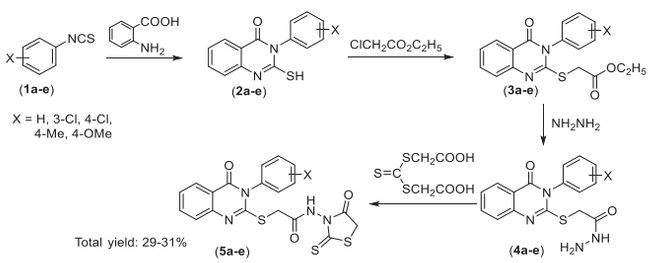

Scheme 1. The pathway for synthesis of the target compounds.

The synthesis, physical characteristics as well as spectral data of the **2a**, **3a**, **4a** and **5a** compounds were reported in our previous work [24].

General procedure for synthesis of 3-aryl-2-mercaptoquinazolin-4-one compounds (2a-e)

Anthranilic acid (13.7 g, 0.1 mol) was dissolved in absolute ethanol (200 ml), then triethylamine (3 ml) and appropriate aryl isothiocyanate (0.1 mol) were added and the reaction mixture was refluxed for 4 h. Upon completion, the reaction mixture was cooled and poured into ice-cold water. The solid was filtered and then recrystallized from a mixture of DMF and water, then washed with cold ethanol to afford crystals.

*3-(3-chlorophenyl)-2-mercaptoquinazolin-4-one (**2b**):* yield: 78.0%. Mp. 269.5-270.7°C (lit. [7] 270°C); IR (ν, cm^{-1}): 3219, 3136 (N-H), 3030 (C-H aromatic), 1661 (C=O), 1618, 1526, 1485 (C=N, C=C aromatic), 1227 (C=S); ^{1}H-NMR (δ, ppm): 13.10 (1H, *s*, SH), 7.97 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.79 (1H, J_1=J_2=7.5 Hz, Ar-H), 7.49 (4H, *m,* Ar-H), 7.36 (1H, *dd*, J_1=J_2=7.5 Hz, Ar-H), 7.31 (1H, *d*, *J*=7.0 Hz, Ar-H); ^{13}C-NMR (δ, ppm): 176.3, 160.2, 141.1, 140.1, 136.1, 133.4, 130.9, 129.8, 128.7, 128.6, 127.9, 124.9, 116.7, 116.3.

*3-(4-chlorophenyl)-2-mercaptoquinazolin-4-one (**2c**):* yield: 81.0%. Mp. 312.4-313.6°C (lit. [7] 315°C); IR (ν, cm^{-1}): 3265, 3138 (N-H), 3032 (C-H aromatic), 1681 (C=O), 1616, 1528, 1485 (C=N, C=C aromatic), 1229 (C=S); ^{1}H-NMR (δ, ppm): 13.08 (1H, *s*, SH), 7.96 (1H, *dd*, J_1=8.0 Hz, J_2=1.0 Hz, Ar-H), 7.79 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.55 (2H, *d*, *J*=8.0 Hz, Ar-H), 7.46 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.36 (3H, *m*, Ar-H); ^{13}C-NMR (δ, ppm): 176.4, 160.2, 140.1, 138.7, 136.1, 133.2, 131.5, 129.5, 127.9, 124.9, 116.7, 116.2.

*3-(4-methylphenyl)-2-mercaptoquinazolin-4-one (**2d**):* yield: 87.0%. Mp. 300.1-301.4°C (lit. [7] 302°C); IR (ν, cm^{-1}): 3242, 3123 (N-H), 3028 (C-H aromatic), 1659 (C=O), 1620, 1522, 1485 (C=N, C=C aromatic), 1229 (C=S); ^{1}H-NMR (δ, ppm): 13.01 (1H, *s*, SH), 7.95 (1H, *dd*, J_1=8.0 Hz, J_1=1.0 Hz, Ar-H), 7.78 (1H, *ddd*, J_1=J_2=8.0 Hz, J_3=1.5 Hz, Ar-H), 7.45 (1H, *d*, *J*=7.5 Hz, Ar-H), 7.35 (1H, *dd*, J_1=J_2=7.5 Hz, Ar-H), 7.28 (2H, *d*, *J*=8.0 Hz, Ar-H), 7.14 (2H, *d*, *J*=8.0 Hz, Ar-H), 2.38 (3H, *s*, CH_3); ^{13}C-NMR (δ, ppm): 176.7, 160.3, 140.1, 137.9, 137.2, 136.0, 129.9, 129.2, 127.9, 124.8, 116.7, 116.2, 21.3.

*3-(4-methoxyphenyl)-2-mercaptoquinazolin-4-one (**2e**):* yield: 75.0%. Mp. 272.7-273.5°C (lit. [7] 273°C); IR (ν, cm^{-1}): 3240, 3136 (N-H), 3036 (C-H aromatic), 1659 (C=O), 1618, 1528, 1485 (C=N, C=C aromatic), 1231 (C=S); ^{1}H-NMR (δ, ppm): 13.00 (1H, *s*, SH), 7.96 (1H, *d*, *J*=7.0 Hz, Ar-H), 7.78 (1H, *dd*, J_1=J_2=7.5 Hz, Ar-H), 7.45 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.35 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.18 (2H, *d*, *J*=8.5 Hz, Ar-H), 7.01 (1H, *d*, *J*=8.0 Hz, Ar-H), 3.82 (3H, *s*, CH_3O); ^{13}C-NMR (δ, ppm): 177.0, 162.8, 160.4, 159.2, 140.0, 136.0, 132.4, 130.4, 127.9, 124.8, 116.7, 116.3, 114.6, 55.8.

General procedure for synthesis of ethyl 2-[(3-aryl-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetate compounds (3a-e)

After stirring the solution of a definite 3-aryl-2-mercaptoquinazolin-4-one (**2a-e**) (20 mmol) and anhydrous potassium carbonate (2.76 g, 20 mmol) in dry DMF (30 ml) for 30 min, ethyl chloroacetate (2.45 g, 20 mmol) was added and the reaction mixture was refluxed for 5 h. Upon completion, the reaction mixture was cooled and poured into ice-cold water. The white solid was filtered and recrystallized from ethanol to give pure product **3a-e**, respectively.

*Ethyl 2-[(3-(3-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetate (**3b**):* yield: 75.0%. Mp. 86.6-87.2°C (lit. [7]: 86.0°C); IR (ν, cm^{-1}): 3061 (C-H aromatic), 2976, 2922 (C-H aliphatic), 1732, 1690 (C=O), 1607, 1574, 1547, 1468 (C=N, C=C aromatic); ^{1}H-NMR (δ, ppm): 8.09 (1H, *dd*, J_1=8.0 Hz, J_2=1.5 Hz, Ar-H), 7.85 (1H, *ddd*, J_1=J_2=8.0 Hz, J_3=1.5 Hz, Ar-H), 7.73 (1H, *m*, Ar-H), 7.69 (1H, *m*, Ar-H), 7.65 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.51 (3H, *m*, Ar-H), 4.15 (2H, *q*, -CH_2CH_3), 4.01 (2H, *s*, -SCH_2-), 1.24 (3H, *t*, CH_3); ^{13}C-NMR (δ, ppm): 168.7, 161.0, 156.4, 147.4, 137.5, 135.6, 134.0, 131.6, 130.7, 130.0, 128.9, 127.1, 126.7, 126.4, 120.0, 61.6, 34.9, 14.6.

*Ethyl 2-[(3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetate (**3c**):* yield: 69.0%. Mp. 96.7-97.5°C (lit. [7]: 98.0°C); IR (ν, cm^{-1}): 3090 (C-H aromatic), 2980, 2932 (C-H aliphatic), 1732,

1684 (C=O), 1605, 1549, 1468 (C=N, C=C aromatic); ^{1}H-NMR (δ, ppm): 8.09 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.85 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.69 (2H, *d*, *J*=8.0 Hz, Ar-H), 7.56 (2H, *d*, *J*=8.0 Hz, Ar-H), 7.56 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.50 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 4.15 (2H, *q*, *J*=7.0 Hz, -CH_2CH_3), 4.01 (2H, *s*, -SCH_2-), 1.23 (3H, *t*, *J*=7.0 Hz, -CH_2CH_3); ^{13}C-NMR (δ, ppm): 168.7, 161.0, 156.6, 147.5, 135.6, 135.3, 135.1, 131.9, 130.2, 127.1, 126.7, 126.4, 120.0, 61.6, 34.9, 14.6.

*Ethyl 2-[(3-(4-methylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetate (**3d**):* yield: 73.0%. Mp. 102.6-103.7°C (lit. [7]: 102.0°C); IR (ν, cm^{-1}): 3061 (C-H aromatic), 2986, 2914 (C-H aliphatic), 1728, 1694 (C=O), 1607, 1547, 1466 (C=N, C=C aromatic); ^{1}H-NMR (δ, ppm): 8.07 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.83 (1H, *dd*, J_1=J_2=7.5, Ar-H), 7.50 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.47 (1H, *dd*, J_1=J_2=7.5 Hz, Ar-H), 7.40 (2H, *d*, *J*=8.0 Hz, Ar-H), 7.34 (2H, *d*, *J*=8.0 Hz, Ar-H), 4.15 (2H, *q*, *J*=7.0 Hz, -CH_2CH_3), 3.98 (2H, *s*, -SCH_2-), 2.43 (3H, s, Ar-CH_3), 1.23 (3H, *t*, *J*=7.0 Hz, -CH_2CH_3); ^{13}C-NMR (δ, ppm): 168.8, 161.1, 157.3, 147.5, 140.3, 135.4, 133.5, 130.6, 129.5, 127.1, 126.6, 126.3, 119.9, 61.5, 34.9, 21.3, 14.6.

*Ethyl 2-[(3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetate (**3e**):* yield: 77.0%. Mp. 120.8-122.1°C (lit. [7]: 122.0°C); IR (ν, cm^{-1}): 3071 (C-H aromatic), 2974, 2926 (C-H aliphatic), 1734, 1682 (C=O), 1607, 1551, 1508, 1470 (C=N, C=C aromatic); ^{1}H-NMR (δ, ppm): 8.08 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.85 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.51 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.49 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.39 (2H, *d*, *J*=8.0 Hz, Ar-H), 7.13 (2H, *d*, *J*=8.0 Hz, Ar-H), 4.15 (2H, *q*, *J*=7.0 Hz, -CH_2CH_3), 3.97 (2H, *s*, -SCH_2-), 3.86 (3H, *s*, OCH_3), 1.22 (3H, *t*, *J*=7.0 Hz, -CH_2CH_3); ^{13}C-NMR (δ, ppm): 168.8, 161.2, 160.7, 157.7, 147.5, 135.4, 131.1, 128.5, 127.1, 126.6, 126.3, 120.0, 115.2, 61.5, 56.0, 34.9, 14.6.

General procedure for synthesis of 2-[(3-aryl-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetohydrazide compounds (4a-e)

Refluxing a solution of ethanol (50 ml) dissolved a definite ester **3a-e** (20 mmol) and an excess of hydrazine hydrate 80% (1.5 g, 30 mmol) for 6.0 h. The reaction mixture was cooled to room temperature and the resulting solid was filtered then recrystallized from ethanol to afford crystals of **4a-e** compounds, respectively.

*2-[(3-(3-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetohydrazide (**4b**):* yield: 78%. Mp: 184.7-185.6°C (lit. [7]: 186.0°C); IR (ν, cm^{-1}): 3314 (N-H), 3063 (C-H aromatic), 2986 (C-H aliphatic), 1695, 1638 (C=O), 1605, 1553, 1470 (C=N, C=C aromatic); ^{1}H-NMR (δ, ppm): 9.32 (1H, *s*, NH), 8.09 (1H, *d*, *J*=7.0 Hz, Ar-H), 7.87 (1H, *dd*, J_1=J_2=7.5 Hz, Ar-H), 7.72 (1H, *s*, Ar-H), 7.64 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.63 (2H, *m*, Ar-H), 7.50 (2H, *m*, Ar-H), 4.28 ppm (2H, *br*, -NH_2), 3.87 (2H, *s*, -SCH_2-); ^{13}C-NMR (δ, ppm): 166.5, 161.1, 156.6, 147.6, 137.6, 135.5, 134.0, 131.6, 130.6, 130.1, 129.0, 127.0, 126.6, 126.5, 120.0, 35.0.

*2-[(3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetohydrazide (**4c**):* yield: 81%. Mp: 173.2-174.5°C (lit. [7]: 175.0°C); IR (ν, cm^{-1}): 3339, 3298 (N-H), 3049 (C-H aromatic), 2982 (C-H aliphatic), 1684, 1647 (C=O), 1609, 1547, 1470 (C=N, C=C aromatic); ^{1}H-NMR (δ, ppm): 9.32 (1H, *br*, NH), 8.09 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.86 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.67 (2H, *d*, *J*=8.5 Hz, Ar-H), 7.63 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.55 (2H, *d*, *J*=8.0 Hz, Ar-H), 7.50 (2H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 4.28 (2H, *br*, -NH_2), 3.87 (2H, *s*, -SCH_2-); ^{13}C-NMR (δ, ppm): 166.5, 161.1, 156.8, 147.6, 135.4, 135.2, 135.1, 132.0, 130.1, 127.0, 126.6, 126.5, 120.0, 35.0.

*2-[(3-(4-methylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetohydrazide (**4d**)*: yield: 77%. Mp: 147.5-158.6°C (lit. [7]: 148.0°C); IR (ν, cm^{-1}):
3341, 3271 (N-H), 3063 (C-H aromatic), 2974 (C-H aliphatic), 1678, 1643 (C=O), 1609, 1549, 1468 (C=N, C=C aromatic); ^{1}H-NMR (δ, ppm): 9.30 (1H, *br*, NH), 8.08 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.85 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.62 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.49 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.39 (2H, *d*, *J*=8.0 Hz, Ar-H), 7.39 (2H, *d*, *J*=8.0 Hz, Ar-H), 4.26 (2H, *br*, -NH_2-), 3.84 (2H, *s*, -SCH_2-), 2.43 (3H, *s*, CH_3-Ar); ^{13}C-NMR (δ, ppm): 166.6, 161.2, 157.5, 147.6, 140.1, 135.3, 133.6, 130.5, 129.6, 127.0, 126.6, 126.5, 120.0, 35.0, 21.3.

*2-[(3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetohydrazide (**4e**):* yield: 82%. Mp: 154.4-155.6°C (lit. [7]: 149.0°C); IR (ν, cm^{-1}): 3335, 3294 (N-H), 3069 (C-H aromatic), 2970, 2914 (C-H aliphatic), 1686, 1645 (C=O), 1607, 1545, 1508, 1468 (C=N, C=C aromatic); ^{1}H-NMR (δ, ppm): 9.30 (1H, *s*, NH), 8.08 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.84 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.62 (1H, *d*, *J*=7.5 Hz, Ar-H), 7.48 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.38 (2H, *d*, *J*=7.0 Hz, Ar-H), 7.11 (2H, *d*, *J*=8.0 Hz, Ar-H), 4.27 (2H, *br*, -NH_2-), 3.86 (3H, *s*, -OCH_3), 3.84 (2H, *s*, -SCH_2-); ^{13}C-NMR (δ,

ppm): 166.7, 161.3, 160.6, 157.9, 147.6, 135.3, 131.1, 128.6, 127.0, 126.6, 126.4, 120.0, 115.1, 56.0, 35.0.

General procedure for synthesis of N-(4-oxo-2-thioxothiazolidin-3-yl)-2-[(3-aryl-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetamide compounds (5a-e)

A definite **4a-e** compound (5 mmol) and thiocarbonyl-*bis*-thioglycolic acid (1.13 g, 5 mmol) were dissolved in absolute ethanol (15 ml) and the solution was refluxed for 8 h. The reaction mixture was cooled to room temperature and the solid separated was filtered, dried, and recrystallized from AcOH. The pure products **5a-e** were formed as a yellowish powder.

*N-(4-oxo-2-thioxothiazolidin-3-yl)-2-[(3-(3-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio] acetamide compounds (**5b**):* yield: 67.0%. Mp: 223.7-224.3°C. IR (ν, cm^{-1}): 3188 (N-H), 3067 (C-H aromatic), 2974 (C-H aliphatic), 1761, 1684 (C=O), 1551, 1466 (C=C aromatic, C=N), 1242 (-N-C=S); ^{1}H-NMR (δ, ppm): 11.32 (1H, *s*, NH), 8.09 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.87 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.76 (1H, *dd*, J_1=8.0 Hz, J_2=3.0 Hz, Ar-H), 7.72 (1H, *m*, Ar-H), 7.68 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.65 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), 7.50 (2H, *m*, Ar-H), [4.44 (1H, *J*=19.0 Hz) and 4.39 (1H, *J*=19.0 Hz)] (-CH_2- in the thiazolidine ring), [4.18 (1H, *J*=20.0 Hz) and 4.13 (1H, *J*=20.0 Hz)] (-CH_2- in the -S-CH_2-CONH- group); ^{13}C-NMR (δ, ppm): 200.1 (C=S), 170.5, 165.9, 161.1 (C=O), 155.9, 147.6, 137.5, 135.3, 134.0, 131.6, 130.7, 130.1, 129.0, 127.0, 126.9, 126.7, 120.0 (C_{Ar}), 34.6 (-SCH_2-), 33.8 (-CH_2- thiazolidine ring); HR-ESI-MS *m/z* 476.9912 $(M+H)^+$ calcd. for ($C_{19}H_{14}ClN_4O_3S_3$) 476.9917.

*N-(4-oxo-2-thioxothiazolidin-3-yl)-2-[(3-(4-chlorophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio] acetamide compounds (**5c**):* yield: 69.0%. Mp: 247.3-248.6°C. IR (ν, cm^{-1}): 3211 (N-H), 3086 (C-H aromatic), 2980 (C-H aliphatic), 1763, 1690 (C=O), 1549, 1466 (C=C aromatic, C=N), 1233 (-N-C=S); ^{1}H-NMR (δ, ppm): 11.31 (1H, *s*, NH), 8.09 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.86 (1H, *dd*, J_1=J_2=7.0 Hz, Ar-H), 7.76 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.68 (2H, *d*, *J*=9.0 Hz, Ar-H), 7.56 (2H, *m*, Ar-H), 7.50 (1H, *dd*, J_1=J_2=8.0 Hz, Ar-H), [4.43 (1H, *J*=18.5 Hz) and 4.38 (1H, *J*=18.5 Hz)] (-CH_2- in the thiazolidine ring), [4.17 (1H, *J*=15.5 Hz) and 4.12 (1H, *J*=15.5 Hz)] (-CH_2- in the -S-CH_2-CONH- group); ^{13}C-NMR (δ, ppm): 200.1 (C=S), 170.5, 165.9, 161.1 (C=O), 156.1, 147.6, 135.3, 135.1, 131.9, 130.2, 127.0, 126.9, 126.6, 120.0 (C_{Ar}), 34.6 (-SCH_2-), 33.8 (-CH_2- thiazolidine ring); HR-ESI-MS *m/z* 476.9923 $(M+H)^+$ calcd. for ($C_{19}H_{14}ClN_4O_3S_3$) 476.9917.

*N-(4-oxo-2-thioxothiazolidin-3-yl)-2-[(3-(4-methylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio] acetamide compounds (**5d**):* yield: 72.0%. Mp: 246.4-247.2°C. IR (ν, cm^{-1}): 3210 (N-H), 3093 (C-H aromatic), 2918 (C-H aliphatic), 1761, 1688 (C=O), 1609, 1549, 1466 (C=C aromatic, C=N), 1233 (-N-C=S); ^{1}H-NMR (δ, ppm): 11.29 (1H, *s*, NH), 8.08 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.85 (1H, *dd*, J_1=J_2=7.5 Hz, Ar-H), 7.75 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.49 (1H, *dd*, J_1=J_2=7.5 Hz, Ar-H), 7.40 (2H, *d*, *J*=8.0 Hz, Ar-H), 7.34 (2H, *d*, *J*=8.0 Hz, Ar-H), [4.43 (1H, *J*=18.5 Hz) and 4.38 (1H, *J*=18.5 Hz)] (-CH_2- in the thiazolidine ring), [4.14 (1H, *J*=16.0 Hz) and 4.09 (1H, *J*=16.0 Hz)] (-CH_2- in the -S-CH_2-CONH- group), 2.43 (3H, *s*, CH_3-Ar); ^{13}C-NMR (δ, ppm): 200.1 (C=S), 170.5, 166.0, 161.2 (C=O), 156.8, 147.6, 140.3, 135.2, 133.5, 130.5, 129.6, 126.9, 126.5, 120.0 (C_{Ar}), 34.5 (-SCH_2-), 33.8 (-CH_2- thiazolidine ring), 21.3 (CH_3-Ar); HR-ESI-MS *m/z* 479.0275 $(M+Na)^+$ calcd. for ($C_{20}H_{16}N_4NaO_3S_3$) 479.0282.

*N-(4-oxo-2-thioxothiazolidin-3-yl)-2-[(3-(4-methoxyphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)thio] acetamide compounds (**5e**):* yield: 58.0%. Mp: 234.6-235.1°C. IR (ν, cm^{-1}): 3213 (N-H), 2978 (C-H aliphatic), 1765, 1682 (C=O), 1549, 1466 (C=C aromatic, C=N), 1231 (-N-C=S); ^{1}H-NMR (δ, ppm): 11.29 (1H, *s*, NH), 8.08 (1H, *d*, *J*=7.5 Hz, Ar-H), 7.85 (1H, *dd*, J_1=J_2=7.5 Hz, Ar-H), 7.74 (1H, *d*, *J*=8.0 Hz, Ar-H), 7.49 (1H, *dd*, J_1=J_2=7.5 Hz, Ar-H), 7.38 (2H, *d*, *J*=7.0 Hz, Ar-H), 7.13 (2H, *d*, *J*=7.0 Hz, Ar-H), [4.43 (1H, *J*=18.5 Hz) and 4.38 (1H, *J*=18.5 Hz)] (-CH_2- in the thiazolidine ring), [4.14 (1H, *J*=15.5 Hz) and 4.09 (1H, *J*=15.5 Hz)] (-CH_2- in the -S-CH_2-CONH- group), 3.86 (3H, *s*, OCH_3); ^{13}C-NMR (δ, ppm): 200.1 (C=S), 170.5, 166.0, 161.3 (C=O), 160.7, 157.2, 147.6, 135.1, 131.1, 128.5, 126.9, 126.5, 120.0, 115.2 (C_{Ar}), 56.0 (CH_3O), 34.6 (-SCH_2-), 33.8 (-CH_2- thiazolidine ring); HR-ESI-MS *m/z* 473.0402 $(M+H)^+$ calcd. for ($C_{20}H_{17}N_4O_4S_3$) 473.0412.

Cytotoxicity assay: compounds **5a-e** were tested for cytotoxicity in three human cancer cell lines including Hep-G2 (Human hepatocellular carcinoma), LU-1 (Human lung adenocarcinoma), and HeLa (HeLa cervical cancer cells). The cell lines were cultured in vitro under standard cell culture conditions (humidified air, 5% CO_2, 37°C) according to the method of Skehan, et al. (1991)

[25]. The cytotoxicity assay on cancer cell lines was conducted by the Sulforhodamine B (SRB) method as described by K. Likhitwitayawuid, et al. (1993) [26]. Ellipticine was used as the positive control and dimethyl sulfoxide (DMSO) in culture media was used as the negative control. The optical density (OD) was measured by using an automated 96-well plate reader (Infinite Tecan, Switzerland) at 550 nm. The percentage of cell survival (CS%) was determined based on the absorbances of the test sample and negative control (DMSO-treated cells) as the following equation:

$$CS\% = \frac{(OD_{Sample} - OD_{day\,0})}{(OD_{DMSO} - OD_{day\,0})} * 100$$

where OD_{Sample}: optical density of sample at 550 nm; OD_{DMSO}: optical density of negative control at 550 nm; $OD_{day\,0}$: optical density of sample or DMSO at time zero (start of sample exposure).

Each sample was assayed with three replications and the result was taken as mean ± standard deviation (SD). The results are recorded in Table 1.

Table 1. The cytotoxicity of 5a-e compounds in Hep-G2, LU-1 and HeLa cell lines.

No.	Compounds	Concentration (µg/ml)	CS (%)		
			Hep-G2	*LU-1*	*HeLa*
1	DMSO	-	100	100	100
2	Ellipticine	5	2.05±1.15	3.06±1.26	2.33±1.23
3	**5a**	5	99.75±0.16	78.62±2.52	94.45±2.14
4	**5b**	5	99.26±0.66	98.74±0.90	95.52±0.63
5	**5c**	5	98.48±1.03	86.20±2.22	81.23±1.56
6	**5d**	5	95.79±0.38	66.52±2.19	65.24±1.04
7	**5e**	5	98.05±0.29	76.35±1.15	78.89±2.42

Results and discussion

The reaction of anthranilic acid and appropriately substituted phenyl isothiocyanates gave five 3-aryl-2-mercaptoquinazolin-4(3*H*)-one compounds with good yield. In the fact, the **2a-e** compounds existed in the thione form, namely 3-aryl-2-thioxo-2,3-dihydroquinazolin-4(1*H*)-one by tautomerization. This was confirmed not only by their IR spectra with an absorption band around 1200-1300 cm^{-1}, which was attributed to the C=S bond but also by both their ^{1}H-NMR and ^{13}C-NMR spectra. The ^{1}H-NMR spectra of the **2a-e** compounds displayed a signal at around δ 13.00, which is attributed to the N-H proton [27]. The signal appeared at high field (near 176.5 ppm) in the ^{13}C-NMR spectra of the **2a-e** compounds but was not seen in the ^{13}C-NMR spectra of the **3a-e** compounds, which must be assigned to carbon in the C=S group. However, in an alkaline environment, the **2a-e** compounds transformed into thiolate form and reacted with ethyl chloroacetate in the role of nucleophile agents to form *S*-substituted products, namely, ethyl 2-[(3-aryl-4-oxo-3,4-dihydroquinazolin-2-yl)thio]acetate. Existence of **2a-e** compounds in thione form and their transformation into *S*-substituted products were reported in our recent work [28]. The esters, in turn, reacted with hydrazine hydrate to form hydrazide compounds. The reaction sequence used to synthesize the 2-[(4-oxo-3-aryl-3,4-dihydroquinazolin-2-yl)thio] acetohydrazide compounds from anthranilic acid and aryl isothiocyanates has been reported in some works [7, 24]. However, spectral data of the synthesized compounds including both ester and hydrazide compounds, especially data on the ^{13}C-NMR spectrum, were not fully available. The formation of these compounds was confirmed by the similarity in both melting point and spectral characteristics of them with the ones of the corresponding compounds in the literature [2, 7, 24]. Furthermore, the ^{13}C-NMR spectra of the **3b-e** and **4b-e** compounds have been presented.

To form a 2-thioxothiazolidine-4-one compound, the reaction of a hydrazide with thiocarbonyl-*bis*-thioglycolic acid has been mentioned [19-24]. This method was used to prepare the *N*-(4-oxo-2-thioxothiazolidin-3-yl)-2-[(4-oxo-3-aryl-3,4-dihydroquinazolin-2-yl)thio]acetamide compounds (**5a-e**) based on the reaction of thiocarbonyl-*bis*-thioglycolic acid with appropriate hydrazides **4a-e**. Except for the **5a** compound that was synthesized and reported in our recent work [24], the **5b-e** compounds have not been found in the literature. In the IR spectra of the **5a-e** compounds, the vibration of the N-H bond appeared around 3200 cm^{-1}, which is the absorption region of the C=O bond. Besides the absorption of the lactam and amide carbonyl groups around 1690 cm^{-1}, there is an appearance of a new band around 1760 cm^{-1} assigned to the absorption of the C=O group in the 2-thioxothiazolidin-4-one ring. The pseudo-molecular ion peaks $[M+H]^+$ or $[M+Na]^+$ in the mass spectra of the products matched with theoretical calculations. In the ^{1}H-NMR spectra of the **5a-e** compounds, in addition to the signal at 4.13 ppm characterized as the -SCH_2- group bonding with quinazoline ring, there is the new signal at 4.41 ppm that was assigned to the methylene group on the thiazolidinone ring. Notably, the signals of these methylene groups did not appear in the expected *singlet* type, but both of them were split into two doublets, which is similar to what happened to the compound containing

a 2-thioxo-1,3-thiozolidin-4-one ring synthesized from 7-hydroxy-4-methylcoumarin [19]. Thus, the thiazolidine ring not only contains non-equivalent methylene protons but also makes the methylene protons of the -SCH_2CONH- group become diastereotopic protons. Protons in each of these methylene groups interact with each other and form doublet signals. Due to the proximity of chemical shifts, these signals are influenced by the roof effect and appear in the special shape as described. The signals appearing in the ^{13}C-NMR spectra of the **5a-e** compounds include 2 signals at 34.5 ppm and 33.8 ppm (2 methylene carbons), a signal at 200.1 ppm (carbon in the thioxo group), 3 signals at about 161-170 ppm (3 carbonyl carbons), and 14 signals at 120.0-156.5 ppm (unsaturated and aromatic carbons). In addition, the signals of the carbon atoms in the aromatic rings appear fully in the spectra. Particularly, the spectrum of the **5d** compound has a signal at 21.3 ppm while the spectrum of the **5e** compound has a signal at 56.0 ppm. These signals are assigned to carbon atoms in the methyl and methoxy groups in their molecules, respectively. All data showed that the structure of the **5a-e** compounds matches their desired molecular formula.

All compounds containing a 2-thioxothiazolidin-4-one ring (**5a-e**) were evaluated for their potential cytotoxicity against Hep-G2, LU-1, and HeLa cancer cell lines using Ellipticine as a positive control. The results were expressed in terms of the percentage of cell survival (CS%) (see Table 1). Disappointingly, all of the (**5a-e**) compounds possessed low toxicity against the three human cancer cell lines tested. Other biological activities of these compounds such as antimicrobial and antioxidant activities are continuing to be investigated.

Conclusions

In the present work, five new *N*-(4-oxo-2-thioxothiazolidin-3-yl)-2-[(4-oxo-3-aryl-3,4-dihydroquinazolin-2-yl)thio]acetamide compounds were synthesized and their structures were confirmed by IR, HR-MS, ^{1}H-NMR, and ^{13}C-NMR spectral data. However, the initial survey showed that all of these hybrid compounds based 3-aryl-2-sulfanylquinazolin-4(3*H*)-one heterocycle and 2-thioxothiazolidin-4-one heterocycle did not exhibit cytotoxic active against Hep-G2, LU-1, and HeLa cancer cell lines.

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COMPETING INTERESTS

The authors declare that there is no conflict of interest regarding the publication of this paper.

REFERENCES

[1] Al-Alshaikh Monirah, Al-Shammary Danah, El-Baih Fatima (2013), "Synthesis of some-2-thioxo-3-substituted-2,3-dihydro-1*H*-quinazolin-4-one derivatives as potential antibacterial and antifungal agents", *Res. J. Chem. Environ.*, **17(9)**, pp.48-52.

[2] S.M.H. Al-Majidi, M.G.A. Al-Khuzaie (2015), "Synthesis and antimicrobial activity of some new S-substituted quinazolinones containing different heterocyclic rings", *Asian Journal of Chemistry*, **27(2)**, pp.756-762.

[3] X. Lv, L. Yang, Z. Fan, X. Bao (2018), "Synthesis and antimicrobial activities of novel quinazolin-4(3*H*)-one derivatives containing a 1,2,4-triazolo[3,4-*b*][1,3,4]thiadiazole moiety", *Journal of Saudi Chemistry Society*, **22(1)**, pp.101-109.

[4] A.S. El-Azab, S.G. Abdel-Hamide, M.M. Sayed-Ahmed, G. Hassan, T.M. El-Hadiyah, O. Al Shabanah, O.A. Al-Deeb, H. El-Subbagh (2013), "Novel 4(3*H*)-quinazolinone analogs: synthesis and anticonvulsant activity", *Medicinal Chemistry Research*, **22(6)**, pp.2815-2827.

[5] M. Gobinath, N. Subramanian, V. Alagarsamy (2015), "Design, synthesis and H1-antihistaminic activity of novel 1-substituted-4-(3-chlorophenyl)-[1,2,4]triazolo [4,3-a] quinazolin-5(4*H*)-ones", *Journal of Saudi Chemistry Society*, **19(3)**, pp.282-286.

[6] I.M. Elfekki, W.F.M. Hassan, H.E.A.E. Elshihawy, I.A.I. Ali, E.H.M. Eltamany (2014), "Molecular modeling studies and synthesis of novel methyl 2-(2-(4-oxo3-aryl-3,4-dihydroquinazolin-2-ylthio) acetamido)alkanoates with potential anti-cancer activity as inhibitors for methionine synthase", *Chemical and Pharmaceutical Bulletin*, **62(7)**, pp.675-694.

[7] M.B. Deshmukh, Savita Dhongade (2004), "Synthesis and QSAR study of some HDL cholesterol increasing quinazolinone derivatives", *E-Journal of Chemistry*, **1(1)**, pp.17-31.

[8] S. ElSayed, K. Metwally, A.A. ElShanawani, L.M. Abdel-Aziz, H. Pratsinis, D. Kletsas (2017), "Synthesis and anticancer activity of novel quinazolinonebased rhodanines", *Chemistry Central Journal*, **11**, pp.102-111.

[9] I.A. Khodair, M.A. Alsaf, M.S. Nafe (2019), "Synthesis, molecular modeling and anti-cancer evaluation of a series of quinazoline derivatives", *Carbohydrate Research*, **486**, DOI: 10.1016/j.carres.2019.107832.

[10] T.T. Talele, P. Arora, S.S. Kulkarni, M.R. Patel, S. Singh, M. Chudayeu, N. Kaushik-Basu (2010), "Structure-based virtual screening, synthesis and SAR of novel inhibitors of hepatitis C virus NS5B polymerase", *Bioorganic and Medicinal Chemistry*, **18(13)**, pp.4630-4638.

[11] K. Ramkumar, V.N. Yarovenko, A.S. Nikitina, I.V. Zavarzin, M.M. Krayushkin, L.V. Kovalenko, A. Esqueda, S. Odde, N. Neamati (2010), "Design, synthesis and structure-activity studies of rhodanine derivatives as HIV-1 integrase inhibitors", *Molecules*, **15(6)**, pp.3958-3992.

[12] S. Jiang, S.R. Tala, H. Lu, N.E. Abo-Dya, I. Avan, K. Gyanda, L. Lu, A.R. Katritzky, A.K. Debnath (2011), "Design, synthesis, and biological activity of novel 5-((arylfuran/1H-pyrrol-2-yl)methylene)-2-thioxo-3-(3-(trifluoromethyl)phenyl) thiazolidin-4-ones as HIV-1 fusion inhibitors targeting GP41", *Journal of Medicinal Chemistry*, **54(2)**, pp.572-579.

[13] M. Murata, B. Fujitani, H. Mizuta (1999), "Synthesis and aldose reductase inhibitory activity of a new series of 5-[[2-(**ω**-carboxyalkoxy)aryl]methylene]-4-oxo-2-thioxothiazolidine derivatives", *European Journal of Medicinal Chemistry*, **34(12)**, pp.1061-1070.

[14] S. Guiheneuf, L. Paquin, F. Carreaux, E. Durieu, T. Roisnel, L. Meijer, J-P. Bazureau (2014), "New 5-ylidene rhodanine derivatives based on the dispacamide A model", *Molecular Diversity*, **18(2)**, pp.375-388.

[15] N.S. Cutshall, C. O'Day, M. Prezhdo (2005), "Rhodanine derivatives as inhibitors of JSP-1", *Bioorganic and Medicinal Chemistry Letters*, **15(14)**, pp.3374-3379.

[16] S.D. Furdas, S. Shekfeh, S. Kannan, W. Sippl, M. Jung (2012), "Rhodanine carboxylic acids as novel inhibitors of histone acetyltransferases", *Med. Chem. Comm.*, **3**, pp.305-311.

[17] K. Harada, H. Kubo, J. Abe, M. Haneta, A. Conception, S. Inoue, S. Okada, K. Nishioka (2012), "Discovery of potent and orally bioavailable 17β-hydroxysteroid dehydrogenase type 3 inhibitors", *Bioorganic and Medicinal Chemistry*, **20(10)**, pp.3242-3254.

[18] J. Gagoria, K. Singh, S.K. Jain, Gautam, a. Khatkar (2008), "Synthesis and anticonvulsant study of benzylidine rhodanine derivatives", *Oriental Journal of Chemistry*, **24(2)**, pp.713-716.

[19] T.C. Nguyen, T.N. Huynh, V.H. Luong, D.T. Tran, P.C. Kuo (2014), "Synthesis and antibacterial activity of analogs of 5-arylidene-3-(4-methylcoumarin-7-yloxyacetylamino)-2-thioxo-1,3-thiazolidin-4-one", *Molecules*, **19(19)**, pp.13577-13586.

[20] S.S. Alneyadi (2018), "Rhodanine as scaffold: a short review on its synthesis and anti-diabetic activities", *Heterocycles*, **96(5)**, pp.803-838.

[21] L. Mosula, B. Zimenkovsky, D. Havrylyuk, A-V. Missir, I.C. Chirita, R. Lesyk (2009), "Synthesis and antitumor activity of novel 2-thioxo-4-thiazolidinones with benzothiazole moieties", *Farmacia*, **57(3)**, pp.321-330.

[22] O. Roman, R. Lesyk (2007), "Synthesis and anticancer activity in vitro of some 2-thioxo-4-thiazolidone derivatives", *Farmacia*, **55(6)**, pp.640-648.

[23] G.N. Masoud, A.M. Youssef, M.M.A. Khalek, A.E.A. Wahab, I.M. Labouta, A.A.B. Hazzaa (2013), "Design, synthesis, and biological evaluation of new 4-thiazolidinone derivatives substituted with benzimidazole ring as potential chemotherapeutic agents", *Medicinal Chemistry Research*, **22(2)**, pp.707-725.

[24] T.C. Nguyen, T.Q. Nguyen, H.P. Dao, L.T. Nguyen, T.P. Nguyen, H.H. Nguyen (2019), "Synthesis and cytotoxic activity against K562 and MCF7 cell lines of some *N*-(5-arylidene-4-oxo-2-thioxothiazolidin-3-yl)-2-((4-oxo-3-phenyl-3,4-dihydroquinazoline-2-yl)thio)acetamide compounds", *Journal of Chemistry*, **2019(2b)**, pp.1-8.

[25] P. Skehan, R. Storeng, D. Scudiero, A. Monks, J. McMahon, D. Victica (1991), "New colorimetric cytotoxicity assay for anticancer agents", *European Journal of Cancer*, **27**, pp.1162-1168.

[26] K. Likhitwitayawuid, C.K. Angerhofer (1993), "Cytotoxic and antimalarial bisbenzylisoquinoline alkaloids from *Sephania evecta*", *Jounal of Natural Products*, **56(1)**, pp.30-38.

[27] M.M. Wang, G.L. Dou, D.Q. Shi (2010), "One-pot synthesis of 2,3-dihydro-2-thioxoquinazolin-4(1*H*)-ones from nitro-compounds with the aid of tin(II) chloride", *J. Heterocyclic Chem.*, **47(4)**, pp.939-943.

[28] T.C. Nguyen, T.Q. Nguyen, D.D. Pham, H.P. Tran, D.D. Nguyen, M.L. Truong, L.V. Meervelt (2020), "Synthesis and structure of ethyl 2-[(4-oxo-3phenyl-3,4-dihydroquinazolin-2-yl)sulfanyl] acetate", *Acta Cryst.*, **76(5)**, pp.668-672.