Egyptian Journal of Chemistry

http://ejchem.journals.ekb.eg/

Synthesis of Some 2-Substituted Quinazolin-4(3*H*)-one Compounds from Methyl α-[(4-oxoquinazolin-2-yl)thio]acetate

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Abstract

A series of new quinazoline-4(3H)-one derivatives (2-15) have been synthesized using methyl α-[(4-oxoquinazolin-2-yl)thio]acetate (1) as precursor. The acid hydrazide (2) was synthesized via the reaction of the ester (1) with hydrazine hydrate, whereas the thiosemicarbazide (4) was synthesized either from the reaction of the acid hydrazide (2) with ammonium thiocyanate or from the reaction of the ester (1) with thiosemicabazide. The thiosemicarbazide (4) was used to synthesize 2-amino-1,3,4-thiadiazole (5) and 1,3,4-triazole-5-thiol (6) via the cyclization reaction under acidic and basic conditions respectively. On the other hand, the reaction of organic thiocyanates with the hydrazide (2) gave di-substituted thiosemicarbazide (13-15), while the reaction of carbon disulfide with the hydrazide (2) in presence of potassium hydroxide afforded the carbodithioate potassium salt (7). The carbodithioate potassium salt (7) was then treated with hydrazine hydrate to give 2-{[(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)methyl]thio}quinazolin-4(3H)-one (8). The later compound (8) was used as a precursor to synthesize fused heterocyclic compounds {namely 2-{[(6-mercapto[1,2,4]triazolo[3,4-b][1,3,4] thiadiazol-3-yl)methyl]thio}quinazolin-4(3H)-one (9), 2-{[(6-methyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl) methyl]thio} quinazolin-4(3H)-one (10) and 2-{[(6-(2,6-dichlorophenyl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl]thio} quinazolin-4(3H)-one (11), 2-{[(6-(3-nitrophenyl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl]thio}quinazolin-4(3H)-one (12) via the reaction of compound (8) with CS_2 / potassium hydroxide, acetyl chloride and aromatic aldehydes respectively. Elucidation of the structures of the compounds (4-15) was performed by using the FT-IR, ^{1}H-NMR and ^{13}C-NMR spectroscopic methods.

Keywords: Quinazolin-4-(3*H*)-one, acetohydrazide, thiosemicarbazide, 1,3,4-triazol-2-thiole, 2-amino-1,3,4-thiadiazole, 1,2,4-triazolo compound.

Introduction

Quinazolines are one of a significant class of fused heterocyclic compounds. The quinazoline skeleton, especially as quinazoline-4(3H)-one moiety, was considered to be the essential building block of numerous natural products [1], such as chrysogine [2,3], L-vasicinone [4], and also found in drugs such as methaqualone [5]. The quinazoline-4(3H)-one derivatives are of considerable interest owing to their activity in biological, pharmacological and medicinal chemistry fields, and also they shown an activity as antibacterial [6], antimicrobial [7,8], antitumor [9-11], anticancer [12-15], antifungal [16], antioxidant [17,-19], anti-inflammatory and analgesic [19,20], anti-HIV [21], anticonvulsant [22], antihypertensive [23], antitubercular [24,25], anti-diabetes [26] agents.

On the other hand, many heterocyclic moieties, other than quinazoline-4(3H)-one, such as 1,3,4-triazole, 1,3,4-oxadizole and 1,3,4-thiadiazole, have gained an importance in organic synthesis owing to their diverse biological and pharmacological activities like antimicrobial [27], anticancer and antitumoral [27-31] and anticonvulsant [32] activities.

Thus, on the basis of the previously mentioned facts, this manuscript dealing with the synthesis of a series of quinazoline-4(3H)-one derivatives containing quinazoline-4(3H)-one nucleus associated with different heterocyclic moieties starting from methyl α-[(4-oxoquinazolin-2-yl)thio]acetate as an essential synthesizing compound.

Experimental:

Melting points were recorded using a Stuart melting point SMP30 apparatus and were

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Receive Date: 31 May 2021, Revise Date: 19 June 2021, Accept Date: 04 July 2021
DOI: 10.21608/EJCHEM.2021.78538.3844

uncorrected. The FT-Infrared spectra were recorded as neat using Bruker system 2000 FT.IR spectrophotometer. The spectra of ^{1}H & ^{13}C NMR were measured on a Bruker BioSpin GmbH (400) super conducting NMR Spectrometer (400 MHz) using DMSO-d6 as a solvent and TMS as an internal standard. The methyl ester (1), the acetohydrazide compound (2) and oxadiazole (3) were synthesized according to our previously published paper [33].

Synthesis of [α-{(4-oxoquinazolin-2-yl)thio}aceto] thiosemicarbazide (4) [34]:

This compound was synthesized via two synthetic methods.

Method A: To a stirred solution of methyl α-[(4-oxoquinazolin-2-yl)thio]acetate (1) (0.01 mol, 2.5 g) in (50 ml) absolute ethanol, thiosemicarbazide (0.015 mol, 0.75 g) was added with stirring followed by reflux for 12h. The resulting solid product was filtered off, washed with cold water and dried then recrystallized from ethanol to give white crystals in 95% yield, m.p.176-177 ºC.

Method B: Concentrated hydrochloric acid (2 ml) was added to a stirred solution of the α-substituted acetohydrazide (2) (0.005 mol, 1.25 g) and ammonium thiocyanate (0.015 mol, 1.14 g) in absolute ethanol (25 ml). The resulting mixture was refluxed for 4h, and subsequently the solvent was evaporated under reduced pressure. The residue was washed with cold water, dried then recrystallized by using ethanol to afford white crystalline product in 95% yield, m.p.176-177 ºC.

Synthesis of 2-{[(5-amino-1,3,4-thiadiazol-2-yl) methyl]thio}quinazolin-4(3H)-one (5) [35]:

Concentrated sulfuric acid (10 ml) was added slowly with shaking and cooling (at 0 ºC) to α-{(4-oxoquinazolin-2-yl)thio}aceto]thiosemicarbazide (4) (0.001 mol, 0.309 g) within 15 min, then the stirring was continued for further 10min, and subsequently poured on crushed ice (100 g) with shaking then neutralized with conc. NH_4OH solution under cooling to produce a precipitate, which washed many times with cold water, dried then recrystallized from ethanol to afford pale yellow crystalline product in 80% yield, its m.p. is 320-321ºC.

Synthesis of 2-{[(5-mercapto-4H-1,2,4-triazol-3-yl) methyl]thio}quinazolin-4(3H)-one (6) [34]:

A solution of [α-{(4-oxoquinazolin-2-yl)thio} aceto]thiosemicarbazide (4) (0.001 mol, 0.309 g) in NaOH solution (4%, 25 ml) was stirred for 3h then refluxed for 3h. The solution was cooled to room temperature then filtered. The filtrate was then neutralized with diluted hydrochloric acid to produce a precipitate, which filtered off, washed with water, dried then recrystallized from ethanol to produce white crystalline product in 90% yield, its m.p. is 255-256 ºC.

Synthesis of potassium 2-[2-{(4'-oxoquinazolin-2'-yl)thio}acetyl]hydrazine-1-carbodithioate (7) [36]:

A solution of potassium hydroxide (0.01mol, 0.56 g) in (10 ml) absolute ethanol was added with stirring to an ice cooled solution of the acetohydrazide (2) (0.005 mol, 1.25g) in absolute ethanol (20 ml), followed by dropwise addition of CS_2 (0.02 mole, 1.8 ml). The resulting mixture was stirred over night at room temperature. The resulting precipitate of potassium carbodithioate (7) was filtered off, washed with cold dry diethyl ether then dried to produce white powder in 95% yield, its m.p. is more than 350 ºC. This carbodithioate salt was applied in the next step without further purification.

Synthesis of 2-{[(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)methyl]thio}quinazolin-4(3H)-one (8) [36]:

This compound was synthesized via one the following two synthetic methods:

A: Hydrazine hydrate (99%) (0.06 mol, 3 ml) was added to a solution of 2-{[(5-mercapto-1,3,4-oxadiazol-2-yl)methyl]thio}quinazolin-4(3H)-one (3) (0.001 mol, 0.292 g) in (10 ml) of absolute ethanol. The resulting mixture was refluxed for 12h, then cooled. The resulting precipitate was filtered off, washed with cold ethanol, then recrystallized from ethanol to afford shiny white crystalline product in 85% yield, its m.p. is 256-257 ºC.

B: The potassium carbodithioate salt (7) (0.003 mol, 1.091 g) was dissolved in water (8 ml), then an excess hydrazine hydrate (99.5%, 5 ml) was added with stirring followed by reflux until the emission of H_2S gas was stopped [(detected by using paper soaked with lead acetate (~ 2 h)], and accompanied by a change in the color to green, then became homogenous solution. The resulting solution was cooled to ambient temperature then poured on crushed ice (50 g) then neutralized with acetic acid to afford a precipitated material which was filtered off, washed with cold water, dried, and finally recrystallized from ethanol:DMF (1:2) mixture to afford compound (8) as shiny white crystalline material in 98% yield, m.p. 256-257 ºC.

Synthesis of 2-{[(6-mercapto[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl]thio}quinazolin-4(3H)-one (9) [36]:

To a mixture of the triazole (8) (0.001 mol, 0.306 g) in dry pyridine (20 ml), CS_2 (0.01 mol, 0.76 g) was added with stirring. The resulting mixture was heated

under reflux for 3h., then let to cool to ambient temperature and poured on crushed ice-water. The resulting precipitate was filtered off, and recrystallized from ethanol to give pale green crystals in 90% yield, its m.p. is 298-299 °C.

Synthesis of 2-{[(6-methyl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl]thio}quinazolin-4(3H)-one (10):

A mixture of compound (8) (0.002 mol, 0.612 g) and acetyl chloride (0.002 mol, 0.157 g) in pyridine (5 ml) was heated under reflux for 12h, then left to cool, then basified with cold saturated sodium acetate solution till pH 8. The precipitate was formed after leaving the mixture overnight in refrigerator. The solid product wasfiltered off, washed with water, then recrystallized from ethanol-water to afford white crystals in 92% yield, its m.p.is 267-268 °C.

Synthesis 2-{[(6-aryl[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl]thio}quinazolin-4(3H)-one (11, 12): General procedure:

To an ice cooled solution of compound (8) (0.002 mol, 0.612 g) in (50 ml) of ethanol, 2,4-dichloro- and 3-nitrobenzaldehyde (0.002 mol) was added with stirring. The stirring was continued for further 12h. The resulting precipitate was filtred off, washed with cold ethanol then recrystallized from ethanol.

2-{[(6-(2,6-dichlorophenyl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl]thio}quinazolin-4(3H)-one (11):

m.p. 210-211 °C, yellow powder, yield 85%.

2-{[(6-(3-nitrophenyl)[1,2,4]triazolo[3,4-b][1,3,4]thiadiazol-3-yl)methyl]thio}quinazolin-4(3H)-one (12):

m.p. 178-179 °C, pale yellow powder, yield 90%.

Synthesis of 1-[α{(4'-oxoquinazolin-2'-yl)thio}acetyl]-4-substituted thiosemicarbazide (13-15) [37]: General procedure:

To a solution of the acetohydrazide (2) (0.005 mol, 1.25 g) in absolute ethanol (30 ml), organic isothiocyanate compound (0.005 mol) was added with stirring. The resulting mixture was heated under reflux for 12 h then cooled, to afford a precipitate, which filtred off and recrystallized from ethanol.

1-[α{(4'-oxoquinazolin-2'-yl)thio}acetyl]-4-allyl thiosemicarbazide (13):

m.p. 225-226 °C, white powder, yield 85%.

1-[α{(4'-oxoquinazolin-2'-yl)thio}acetyl]-4-methyl thiosemicarbazide (14):

m.p. 199-200 °C, pale yellow powder, yield 88%.

1-[α{(4'-oxoquinazolin-2'-yl)thio}acetyl]-4-phenyl thiosemicarbazide (15):

m.p. 68-69 °C, white powder, yield 80%..

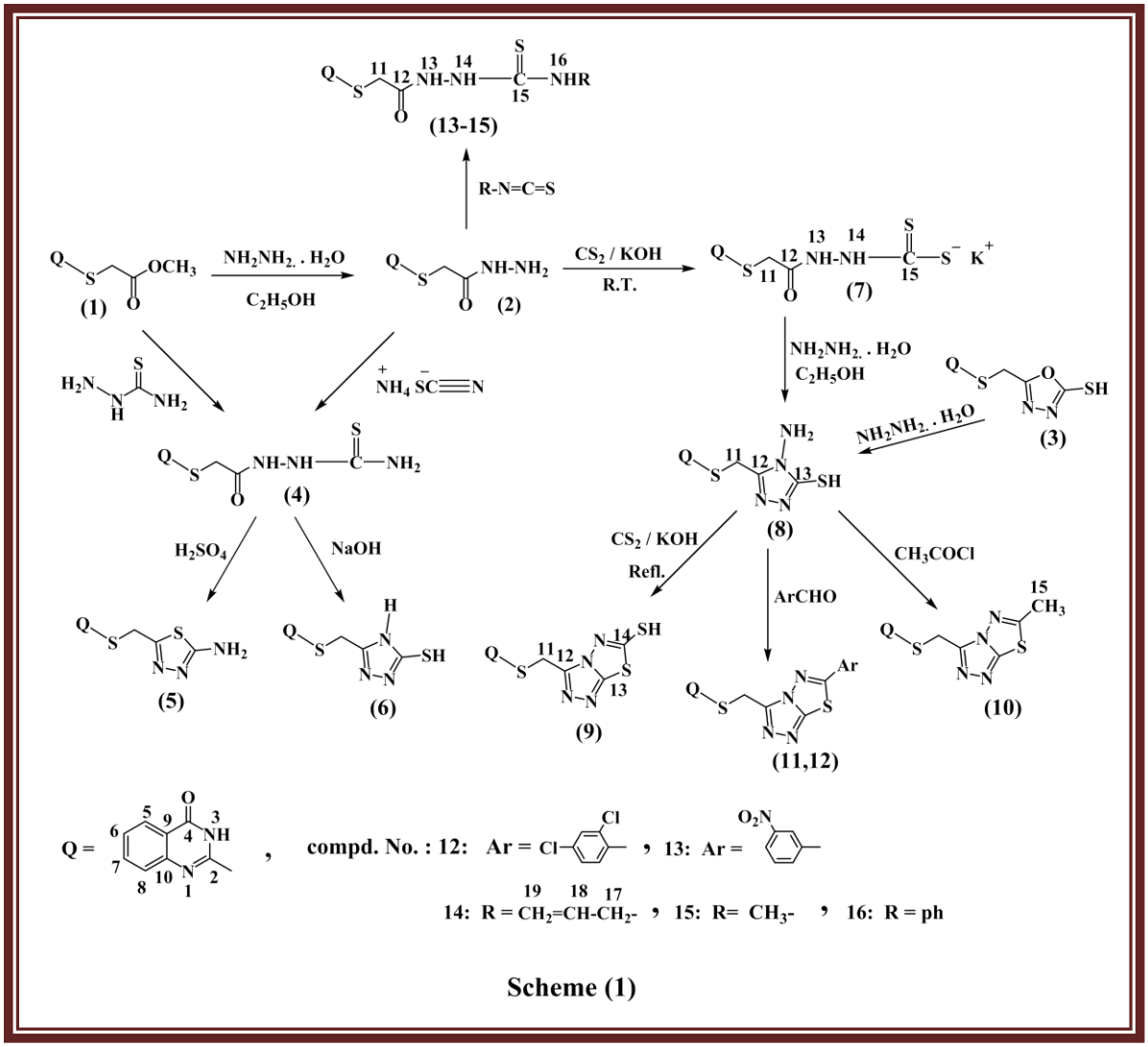
Results and Discussion:

In the present study 4-quinazolinone derivatives (4-15) were synthesized as shown in Scheme (1).

The essential precursor compound applied in synthesizing compounds (4-15), in this research, is the ester (1), which synthesized from anthranilic acid according to the procedure listed previously [33]. This ester was transformed to the corresponding carbohydrazide (2) via the reaction of the ester (1) with hydrazine hydrate according to the procedure stated previously [33]. Thiosemicabazide compound (4) was synthesized either via the reaction of the acetohydrazide (2) with ammonium thiocyanate in existence of conc. HCl , or via the reaction of the ester (1) with the thiosemicarbazide in absolute ethanol.

The structure of the thiosemicabazide compound (4) was confirmed according to (IR, ^{1}H NMR,^{13}C NMR) spectral data [38-40]. The appearance of a characteristic stretching absorption band, in the IR spectrum, at 1164 cm^{-1} for C=S functional group gives an excellent evidence about thiosemicabazide moiety formation, in addition to appearance of stretching absorption at 3419,3176 cm^{-1} for (N-H), at 1741,1679 cm^{-1} for (C=O) , at 1612 cm^{-1} for (C=N) and at 892 cm^{-1} for (C-S). The ^{1}H NMR spectrum of compound (4) showed the following chemical shifts (δ, ppm): 3.84 (s, 2H, CH_2), 7.42 (t, 1H, H6), 7.61 (d, 1H, H8), 7.77 (t, 1H, H7), 8.02 (d, 1H, H5), 8.23 (s, 1H, CONH), 9.53 (s, 2H, NH_2), 10.4 (s, 1H, CSNH), 12.65 (s, 2H, H3). Whereas, the ^{13}C NMR spectrum showed the following chemical shifts (δ, ppm): 30.7 (C11), 120.8 (C10), 126.6 (C8), 126.7 (C6), 127.3 (C5), 133.4 (C7), 146.9 (C9), 159.3 (C2), 161.0 (C4), 170.3 (C=O), 182.5 (C=S). stretching absorption at 3419,3176 cm^{-1} for (N-H), at 1741,1679 cm^{-1} for (C=O) , at 1612 cm^{-1} for (C=N) and at 892 cm^{-1} for (C-S). The ^{1}H NMR spectrum of compound (4) showed the following chemical shifts (δ, ppm): 3.84 (s, 2H, CH_2), 7.42 (t, 1H, H6), 7.61 (d, 1H, H8), 7.77 (t, 1H, H7), 8.02 (d, 1H, H5), 8.23 (s, 1H, CONH), 9.53 (s, 2H, NH_2), 10.4 (s, 1H, CSNH), 12.65 (s, 2H, H3). Whereas, the ^{13}C NMR spectrum showed the following chemical shifts (δ, ppm): 30.7 (C11), 120.8 (C10), 126.6 (C8), 126.7 (C6), 127.3 (C5), 133.4 (C7), 146.9 (C9), 159.3 (C2), 161.0 (C4), 170.3 (C=O), 182.5 (C=S).

The thiosemicabazide (4) was cyclized under acidic conditions (conc. H_2SO_4) to 1,3,4-thiadiazole compound (5) or under basic conditions (NaOH) to 1,3,4-triazole compound (6). The IR spectrum of compound (5) showed the following stretching absorption bands (ν, cm^{-1}): at 3369, 3242 cm^{-1} related to the N-H of NH_2 and NH moieties, at 1665 cm^{-1} for



Scheme (1)

the C=O, at 1602 cm^{-1} due to the combination of C=C and C=N and at 685 cm^{-1} for the stretching vibration

of C-S functional group, and its ^{1}H NMR spectrum showed the following chemical shifts (δ, ppm): 4.13 (s, 2H, H11), 6.86 (s, 2H, NH_2), 7.42 (t, 1H, H6), 7.61 (d, 1H, H8), 7.77 (t, 1H, H7), 8.02 (d, 1H, H5), 12.59 (s, 1H, NH). While its ^{13}C NMR spectrum showed the following chemical shifts (δ, ppm): 24.1(C11), 120.8 (C10), 126.6 (C8), 126.7 (C6), 127.3(C5), 133.4 (C7), 146.9 (C9), 159.3 (C2), 161.0 (C12), 161.1(C4), 168.6 (C13).

The compound (6) is present in two tautomeric structures (thiol-thione tautomerism) and its structure was confirmed according to the spectral data. In IR spectrum the following stretching absorption bands (ν, cm^{-1}) were shown: at 3321 cm^{-1} for the N-H, at 2582 cm^{-1} for S-H, at 1668 cm^{-1} for the C=O, at 1612 cm^{-1} due to combination of C=C and C=N and at 682 cm^{-1} for C-S. Whereas, ^{1}H NMR spectrum involved the following chemical shifts (δ, ppm): 4.13 (s, 2H, CH_2), 7.42 (t, 1H, H6), 7.61 (d, 1H, H8), 7.77 (t, 1H, H7), 8.02 (d, 1H, H5), 11.12 (s, 1H,NH), 12.63 (s,1H, H3), 13.05 (s,1H, SH). While the ^{13}C NMR spectrum showed the chemical shifts (δ, ppm) as follows: 23.7 (C11), 120.8 (C10), 126.6 (C8), 126.7 (C6), 127.3 (C5), 133.4 (C7), 146.9 (C9), 158.6 (C12), 159.3 (C2), 159.8 (C4), 161.5 (C13).

The preparation of **2-{[(4-amino-5-mercapto-4H-1,2,4-triazol-3-yl)methyl]thio}quinazolin-4(3H)-one** (8) was performed either by the reaction of 1,3,4-oxadiazole-2-thiole (3) with hydrazine hydrate, or by two steps synthetic pathway via the reaction of the acetohydrazide (2) with CS_2 in existence of alcoholic potassium hydroxide, in primal step, to synthesize potassium carbodithioate salt (7), while the second step, involves the reaction of the isolated carbodithioate salt (7) with hydrazine hydrate to produce compound (8). The IR spectrum of the carbodithioate salt (7) showed the following stretching absorption (ν, cm^{-1}): at 3467 cm^{-1} for the N-H, at 1678 cm^{-1} for C=O at 1597 cm^{-1} for the C=N, at 1248 cm^{-1} for C=S and 650 cm^{-1} for C-S. its

^{1}H NMR spectrum showed the chemical shifts (δ, ppm) as follows: 3.84 (s, 2H, CH_2), 7.42 (t, 1H, H6), 7.61 (d, 1H, H8), 7.68 (s, 1H, H13), 7.75 (t, 1H, H7), 8.02 (d, 1H, H5), 11.3 (s,1H, H14), 12.65 (H3). While in its ^{13}C NMR spectrum the following chemical shifts (δ, ppm) are shown: 23.7 (C11), 120.8 (C10), 126.6 (C8), 126.7 (C6), 127.3 (C5), 133.4 (C7), 146.9 (C9), 158.2 (C2), 159.3 (C12), 163.4 (C4), 212 (C15).

The IR spectrum compound (8) showed the following stretching absorption (ν, cm^{-1}): at 3271 and 3161 cm^{-1} for the N-H, at 2505 cm^{-1} for S-H, at 1667 cm^{-1} for C=O, at 1607 cm^{-1} for the C=N and 658 cm^{-1} for C-S. The ^{1}H NMR spectrum of compound (8) showed the following chemical shifts (δ, ppm): 4.82 (s, 2H, C11), 4.96 (s, 2H, NH_2), 7.22 (t, 1H, H6), 7.30 (d, 1H, H8), 7.45 (t, 1H, H7), 8.03 (d, 1H, H5), 8.21 (s,1H, H3), 12.05 (s, 1H, SH). In ^{13}C NMR spectrum the following chemical shifts (δ, ppm) are shown: 18.6 (C11), 120.8 (C10), 126.6 (C8), 126.7 (C6), 127.3 (C5), 133.4 (C7), 146.9 (C9), 152.2 (C12), 159.3 (C2), 163.4 (C4), 166.8 (C13).

The 1-amino-1,3,4-triazol-2-thiole compound (8) was used to synthesize different fused heterocyclic compounds (9-12) via three synthetic routes. The first one involves the reaction of the compound (8) with CS_2 to form compound (9). The structure of compound (9) was confirmed according to the spectral data. In IR spectroscopy the following stretching absorptions (ν, cm^{-1}) are shown: at 3317 cm^{-1} for the N-H, at 1670 cm^{-1} for the C=O stretching absorption, at 1633 cm^{-1} for the C=N, at 1176 cm^{-1} for C=S and at 690 cm^{-1} for the C-S. ^{1}H NMR spectrum of compound (9) showed the chemical shifts (δ, ppm) as follows: 4.13 (s, 2H, H11), 7.42 (t,1H, H6), 7.61 (d, 1H, H8), 7.75 (t, 1H, H7), 7.82 (d, 1H, H5), 8.35 (s, 1H, H3), 12.28 (s,1H, SH), while in ^{13}C NMR spectroscopy it showed the following chemical shifts (δ, ppm): 18.9 (C11), 120.8 (C10), 126.6 (C8), 126.7(C6), 127.3 (C5), 133.4 (C7), 146.9 (C9), 159.3 (C12), 160.4 (C2), 164.4 (C4), 167.3 (C13), 184.0 (C14).

On the other hand, the second route involves the reaction of compound (8) with acetyl chloride to form compound (10). The IR spectrum of compound (10) showed stretching absorptions as follows: at 3383 cm^{-1} for the N-H, at 1678 cm^{-1} for the C=O, at 1602 cm^{-1} for the C=N, at 692 cm^{-1} for the C-S, in addition to absorption vibration at 1473 cm^{-1} for bending of C-H bond of methyl group. The ^{1}H NMR spectrum of compound (10) showed the following chemical shifts (δ, ppm): 2.64 (s, 3H, H15), 4.13 (t, 2H, C11), 7.42 (t, 1H, H6), 7.61(d, 1H, H8), 7.75 (t, 1H, H7), 8.02 (d, 1H, H5), 12.59 (s,1H,H3). Whereas in ^{13}C NMR spectroscopy of it showed the following chemical shifts (δ, ppm): 18.9 (C15), 19.0 (C11), 120.8 (C10), 126.6 (C8), 127.7 (C6), 127.3 (C5), 133.4 (C7), 142.7 (C9), 146.9 (C9), 159.3 (C12), 160.4 (C2), 164.4 (C4), 167.3 (C13).

The third route involves the reaction of compound (8) with alcoholic solution of 2,4-dichloro- and 3-nitro benzaldehyde to form compounds (11,12) respectively. The IR spectrum of compound (11) showed stretching absorptions bands (ν, cm^{-1}) as follows: at 3383 cm^{-1} for N-H, at 1678 cm^{-1} for the C=O, at 1602 cm^{-1} for the C=N, at 750 cm^{-1} for C-Cl, and at 590 cm^{-1} for the C-S. ^{1}H NMR spectrum of compound (11) showed the following chemical shifts (δ, ppm): 4.13 (s, 2H, H11), 7.41 (d, 1H, H8), 7.42 (t, 1H, H6), 7.61 (t, 1H, H7), 7.65-7.75 (m, 3H, ph-H), 8.02 (d, 1H, H5), 12.59 (s, 1H, H3). whereas ^{13}C NMR spectrum showed the following chemical shifts (δ, ppm): 18.9 (C11), 120.8 (C10), 126.6 (C8), 126.7 (C6), 127.3 (C5), [127.4, 130.3, 130.9, 133.6, 135.0, 135.7] (phenyl carbons), 133.4 (C7), 146.9 (C9), 148..2 (C14), 159.3 (C12), 160.4 (C2), 164.4 (C4), 167.3 (C13).

While the IR spectrum of compound (12) showed the following stretching absorptions (ν, cm^{-1}): at 3378 cm^{-1} for N-H, at 1678 cm^{-1} for the C=O, at 1595 cm^{-1} for the C=N, at 1527&1321 cm^{-1} for the sy. and asy. for NO_2, and at 658 cm^{-1} for the C-S. The ^{1}H NMR spectrum of compound (12) showed the following chemical shifts (δ, ppm): 4.13 (s, 2H, H11), 7.42 (t, 1H, H6), 7.61 (d, 1H, H8), 7.75 (t,1H, H7), 7.83-8.66 (m, 4H, ph-H), 8.02 (d, 1H, H5), 12.59 (s, 1H, H3). Whereas ^{13}C NMR spectrum showed the following chemical shifts (δ, ppm): 18.9 (C11), 120.8 (C10), 126.6 (C8), 126.7 (C6), 127.3 (C5), 133.4 (C7), 146.9 (C9), 148.4 (C14), 159.3 (C12), 160.4 (C2), 164.4 (C4), 167.3 (C13) and [122.8, 123.9, 130.1, 134.4, 137.0, 143.3] (ph-carbons).

Lastly, the reaction of the hydrazide (2) with organic isothiocyanate compounds, namely allyl-, methyl- and phenyl- isothiocyanate in boiling ethanol afforded the corresponding thiosemicarbazide derivatives (13-15) in good yields.

The IR spectrum of compound (13) showed the following stretching absorptions (ν, cm^{-1}): at 3300 cm^{-1} for N-H, at 1670 cm^{-1} for the C=O, at 1608 cm^{-1} for combination of C=C and C=N, at 1255 cm^{-1} for C=S, at 616 cm^{-1} for the C-S. The ^{1}H NMR spectrum of compound (13) showed the following chemical shifts (δ, ppm): 3.84 (s, 2H, H11), 4.13 (d, 2H, H17), 5.06 (d, 1H, H19 cis), 5.19 (d, 1H, H19 trans), 5.83 (m,1H, H18), 7.42 (t, 1H, H6), 7.61 (d, 1H, H8),7.68 (s, 1H, H13), 7.75 (t, 1H, H7), 7.82 (s, 1H, H16), 8.02 (d, 1H, H5), 10.4 (s, 1H, H14), 12.59 (s, 1H, H3). Whereas ^{13}C NMR spectrum showed the following chemical shifts (δ, ppm): 30.7 (C11), 46.7 (C17), 117.4 (C19), 120.8 (C10), 126.6 (C8), 126.7 (C6), 127.3 (C5), 133.4 (C7), 134.2 (C18), 146.9 (C9), 159.3 (C2), 164.4 (C4) 170.3 (C12), 184.2 (C15).

The IR spectrum of compound (14) showed the following stretching absorptions (ν, cm^{-1}): at 3325 cm^{-1} for N-H, at 1678 cm^{-1} for the C=O, at 1601 cm^{-1} for combination of C=C and C=N, , at 1267 cm^{-1} for C=S, at 658 cm^{-1} for the C-S, in addition to absorption vibration at 1473 cm^{-1} for bending vibration of C-H bond of CH_3 group. The ^1H NMR spectrum of compound (14) showed the following chemical shifts (δ, ppm): 2.81 (s, 3H, CH_3), 3.84 (s, 2H, H11), 7.31 (s, 1H, H13), 7.42 (t, 1H, H6), 7.61 (d, 1H, H8), 7.68 (s, 1H, H16), 7.77 (t, 1H, H7), 8.02 (d, 1H, H5), 10.4 (s, 1H, H14), 12.59 (s, 1H, H3). Whereas ^{13}C NMR spectrum showed the following chemical shifts (δ, ppm): 30.7 (C11), 31.1 (**C**H3), 120.8 (C10), 126.6 (C8), 126.7 (C6), 127.3 (C5), 133.4 (C7), 146.9 (C9), 159.3 (C2), 164.4 (C4), 170.3 (C12), 184.2 (C15).

The IR spectrum of compound (15) showed the following stretching absorptions (ν, cm^{-1}): at 3483, 3352 cm^{-1} for N-H, at 1672 cm^{-1} for the C=O, at 1593 cm^{-1} for combination of C=C and C=N, at 1278 cm^{-1} for C=S, at 592 cm^{-1} for the C-S. ^1H NMR spectrum of compound (15) showed the following chemical shifts (δ, ppm): 3.84 (s, 2H, H11), 7.08 (s, 1H, H13), 7.42 (t, 1H, H6), 7.43- 7.7 (m, 5H, ph-H), 7.61(d, 1H, H8), 7.75 (t, 1H, H7), 8.02 (d, 1H, H5), 10.4 (s,1H, H16), 11.32 (s, 1H, H14), 12.59 (s, 1H, H3). Whereas in^{13}C NMR spectrum the following chemical shifts (δ, ppm) were shown: 30.7 (C11), 120.8 (C10), [126.5, 128.4, 129.0, 138.5] (ph-carbons), 126.6 (C8), 126.7 (C6), 127.3 (C5), 133.4 (C7), 146.9 (C9), 159.3 (C2), 164.4 (C4), 170.3 (C12), 181.1 (C15).

Conclusions

In conclusion, the present study describes the synthesis of newly diverse 2-substituted quinazoline-4(3*H*)-one derivatives by using α-substituted acetate ester or α- acetohydrazide as active functional groups, via their reaction with various reagents. All the compounds have been obtained in good yields, and their FT-IR, ^1H-NMR and ^{13}C-NMR spectral confirmed their structures.

References

1. Michael J.P., Quinoline, quinazoline and acridone alkaloids. *Nat. Prod. Rep.*, **20**(5), 476-493 (2003). doi.org/10.1039/B208140G
2. Bergman J. and Brynoef A., Synthesis of Chrysogine, a Metabolite of *Penicillium chrysogenum* and some related 2-substituted 4-(3H)-Quinazolinones, *Tetrahedron*, **46**(4), 1295-1310 (1990). doi.org/10.1016/S0040-4020(01)86694-1
3. Bergman J., "Comments on the Asymmetric Synthesis of Chrysogine", *J. Chem. Res.*(s), (6),224, (1997). doi.org/10.1039/A701012E
4. Eguchi S.; Suzuki T.; Okawa T.; Matsushita Y.; Yashima E.; Okamoto Y., Synthesis of optically active vasicinone based on intramdecular Aza-witting reaction asymmetric oxidation. *J.Org. Chem.*, **61**, 7316-7319, (1996). doi.org/10.1021/jo9609283
5. John S., "In supplements to the 2nd edition of rodd's chemistry of carbon compounds", M.F. Ansell. ed, Elsevier: Amsterdam, 223, 1955.
6. Lafta S.J., Ayram N.B., Baqer S.M., Synthesis and Characterization of New 2,3-Disubstituted Quinazolinone Derivatives as Antibacterial Agents, *Journal of Al-Nahrain University*, 19 (1), 1-12 (2016) .
7. Saravanan G., Alagarsamy V., Prakash C.R., Synthesis, characterization and in vitro antimicrobial activity of some 1-(substituted benzylidene)-4-(4-(2-(methyl / phenyl)-4-oxoquinazolin-3(4H)-yl)phenyl)semicarbazide derivatives, *J. Saudi Chem. Soc.* **19**, 3–11 (2015). doi.org/10.1016/j.jscs.2011.12.010
8. Patel N.B., Patel J.C., Synthesis and antimicrobial activity of Schiff bases and 2-azetidinones derived from quinazolin-4(3H)-one *Arabian J. of Chemistry*.; **4**: 403–411 (2011). doi:10.1016/j.arabjc.2010.07.005
9. Abbas S.E., Barsoum F.F, Georgey H.H., Mohammed E.R., Synthesis and antitumor activity of certain 2,3,6-trisubstituted quinazoline-4(3H)-one derivatives, *Bulletin of Faculty of Pharmacy, Cairo University* **51**, 273–282 (2013). doi.org/10.1016/j.bfopcu.2013.08.003
10. Luo H., Yang S., Cai Y., Peng Z., Liu T., Synthesis and biological evaluation of novel 6-chloro-quinazolin derivatives as potential antitumor agents, *Eur. J. Med. Chem.*, **84**: 746-52 (2014). doi:org/10.1016/j.ejmech.2014.07.053
11. Pagilla S., Marupati S., Nani K., Green synthesis and in vitro anti-oxidant activity of 6-aryl-quinazolin-4(3H)-ones via Suzuki cross coupling, *Orient. J. Chem*., **33**(6), 3056-3062 (2017). dx.doi.org/10.13005/ojc/330645.
12. Dohle W.; Jourdan, F.L.; Menchon, G.; Prota, A.E.; Foster, P.A.; Mannion, P.; Hamel, E.; Thomas, M.P.; Kasprzyk, P.G.; Ferrandis, E.; Steinmetz, M.O.; Leese, M.P.; Potter.B.V.L. Quinazolinone-based anticancer agents: Synthesis, antiproliferative SAR, antitubulin activity, and tubulin Co-crystal structure, *J. Med. Chem.*, **61**: 1031–1044 (2018). doi:org/10.1021/acs.jmedchem.7b01474
13. Rakesh K.P.; Kumara, H.K.; Manukumar, H.M.; Gowda, D.C., Anticancer and DNA binding studies of potential amino acids based

quinazolinone analogs: Synthesis, SAR and molecular docking, *Bioorg. Chem.* **87**: 252-264 (2019). doi: org/10.1016/j.bioorg.2019.03.038

14. Abuelizz H.A.; Marzouk M.; Ghabbour H.; Al-Salahi R., synthesis and anticancer activity of new quinazoline derivatives, *saudi pharmaceutical journal,*; **25**(7), 1047-1054 (2017). doi.org/10.1016/j.jsps.2017.04.022
15. Hosseinzadeh L.; Aliabadi A.; Rahnama M., Sadeghi H.M.M., Khajouei M.R., synthesis and cytotoxic evaluation of some new 3-(2-(2-phenylthiazol-4-yl)ethyl)-quinazolin-4(3H)one derivatives with potential anticancer effects. *Research in pharmaceutical sciences*,; **12**(4): 290-298 (2017). doi**:** 10.4103/1735-5362.212046
16. Mohamed, M.S.; Kamel, M.M.; Kassem, E.M.M.; Abotaleb, N.; Abd El-moez, S.I.; Ahmed, M.F., Novel 6,8-dibromo-4(3H)quinazolinone derivative of anti-bacterial and anti-fungal activities, *Eur. J. Med. Chem*., **45**(8): 3311-3319 (2010). doi:org/10.1016/j.ejmech.2010.04.014
17. Saravanan G., Alagarsamy V., Prakash C.R.; Synthesis and evaluation of antioxidant activities of novel quinazolinone derivatives, *Int. J. Pharm. Pharm. Sci.*, **2** (suppl. 4): 83–86 (2010).
18. Al-Omer M.A., El-Azab A.S., El-Obeid H.A., Abdel Hamide S.G., Synthesis of Some New 4-(3H)-Quinazoline Analogs as Potential Antioxidant Agents, *J. Saudi Chem. Soc.*, **10**: 111-128 (2006).
19. Rakesh K.P., Manukumar H.M. , Gowda D.C., schiff's bases of quinazolinone derivatives: synthesis and SAR studies of a novel series of potential anti-inflammatory and antioxidants. *Bioorganic & Medicinal chemistry letters*, **25:** 1072-1077(2015). doi:10.1016/j.bmcl.2015.01.010
20. Amin K.M., Kamel M.M., Anwar M.M., Khedr M., Syam Y.M., Synthesis, biological evaluation and molecular docking of novel series of spiro [(2H,3H) quinazoline-2,1′-cyclohexan]-4(1H)-one derivatives as anti-inflammatory and analgesic agents. *Eur. J. Med. Chem.*, **45**: 2117–2131. (2010). doi:10.1016/j.ejmech.2009.12.078
21. Selvam P., Girija K., Nagarajan G., De Clercq E., Synthesis, antibacterial and antiHIV activities of 3-(5-amino-6-(2-3-dichlorophenyl)-(1,2,4)triazin-3-yl)-6,8-dibromo-2-substituted-3H-quinozolin-4-one, *Indian J. Pharm. Sci.*, **67**(4): 484–487 (2005).
22. Geordey H., Abdel-Gawad N., Abbas S., Synthesis and anticonvulsant activity of some quinazoline-4-(3H)-one derivatives, *Molecules*, **13**(10): 2557-2569 (2008). doi:org/10.3390/molecules13102557
23. Alagarsamy V. and Pathak U.S.; Synthesis and antihypertensive activity of novel 3-benzyl-2-substituted-3*H*-[1,2,4]triazolo[5,1-*b*]quinazolin-9-ones, *Bioorg. & Med. Chem.*, **15**(10): 3457–3462 (2007). doi.org/10.1016/j.bmc.2007.03.007
24. Devi K. and Kachroo M., synthesis and antitubercular activity of some new 2,3-disubstituted quinazolinones, *Der pharma chemica*, **6**(5): 353-359 (2014).
25. Rajasekhar, K.K.; Nizamuddin N.D.; surur A.S., Mekonnen Y.T., synthesis, characterization, anti-tubercular and antibacterial activity, and molecular docking of 2,3-disubstituted quinazolinone derivatives, *Research and Reports in Medicinal chemistry*, **6**: 15-26 (2016) doi.org/10.2147/RRMC.S91474
26. Malamas M.S., Millen J., Quinazolineacetic acids and related analogs as aldose reductase inhibitors. *J. Med. Chem.*, **34**(4):1492–1503 (1991). doi.org/10.1021/jm00108a038
27. Demirbas N., Karaoglu S.A., Demirbas A. and Sancak K., Synthesis and antimicrobial activities of some new 1-(5-phenylamino-[1,3,4]thiadiazol-2-yl)methyl-5-oxo-[1,2,4] triazole and 1-(4-phenyl-5-thioxo-[1,2,4]triazol-3-yl)methyl-5-oxo-[1,2,4]triazole derivatives. *Eur. J. Med. Chem.*, **39**(9), 793-804 (2004). doi.org/10.1016/j.ejmech.2004.06.007
28. Demirbaş N., Ugurluoglu R., Demirbaş A., Synthesis of 3-alkyl(aryl)-4-alkylidenamino-4,5-dihydro(1H)-1,2,4-triazol-5-ones and 3-alkyl-4-alkylamino-4,5-dihydro(1H)-1,2,4-triazol-5-ones as antitumor agents, *Bioorg. Med. Chem.*, **10**(12), 3717-23 (2002). doi: 10.1016/s0968-0896(02)00420-0
29. Jatav, V.; Mishra, P.; Kashaw, S.; Stables, J.P., CNS depressant and anticonvulsant activities of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones Eur. J. Med.Chem., 43(9), 1945-1954 (2008). doi: 10.1016/j.ejmech.2007.12.003.
30. Rzeski W.; Matysiak, J.; Kandefer-Szerszen, M., Anticancer, neuroprotective activities and computational studies of 2-amino-1,3,4-thiadiazole based compound, *Bioorg. & Med. Chem.*, **15**(9), 3201-3207(2007). doi: 10.1016/j.bmc.2007.02.041
31. Al-Soud, Y.A.; Al-Masoudi, N.A.; Ferwanah, A.S., Synthesis and properties of new substituted 1,2,4-triazoles: potential antitumor agents *Bioorg. & Med. Chem.*, **11**(8): 1701-1708 (2003). doi: 10.1016/S0968-0896(03)00043-9

32. Jatav, V.; Mishra, P.; Kashaw, S.; Stables, J.P., CNS depressant and anticonvulsant activities of some novel 3-[5-substituted 1,3,4-thiadiazole-2-yl]-2-styryl quinazoline-4(3H)-ones, *Eur. J. Med. Chem.*, **43**(9), 1945-1954 (2008). doi:10.1016/j.ejmech.2007.12.003
33. Al-Alaaf H.A., Al-Iraqi M.M. Methyl α-[(4-oxoquinazolin-2-yl)thio]acetate as precursor to new heterocyclic compounds, *The Eurasia Proceedings of Science, Technology, Engineering & Mathematics (EPSTEM)*, **7**, 63-67 (2019).
34. Al-Iraqi M.A. and Saad-Aldeen R.A., Synthesis of new 3-substituted quinazolin-4(3H)-one compounds via linking of some five-membered ring heterocyclic moieties with quinazolin-4(3H)-one nucleus, *Journal of Education and Science*, **30**(1), 158-172 (2021). doi: 10.33899/edusj.2020.127904.1101
35. Shamroukh A.H., Hegab M.I., A review on synthesis, therapeutic, and computational studies of substituted 1, 3, 4- thiadiazole derivatives, *Egypt. J. Chem.* 63(11), 4387-4408 (2020). doi: 10.21608/EJCHEM.2020.25343.2492
36. Othman M.A., Synthesis and study of Some fused substituted 1,3,4-thiadiazoles and 1,2,4-triazoles from 4-chloro- phenoxy acetic acid and 2,4-dichlorophenoxy acetic acid, *Journal of Education and Science*, **29**(3), 218-226 (2020). doi:10.33899/edusj.2020.166251
37. Abdel-Wahab B.F, Mohaned H.A., Awad Gh. E.A., Synthesis of 5-(1,2,3-triazol-4-yl)-1,3,4-oxa(thia)diazol-2-amines as antimicrobial agents, *Egypt. J. Chem.* 57(4), 257–266 (2014).
38. Crews Ph., Rodriguez, J.; Jaspars, M., "Organic Structure Analysis", New York, Oxford, Oxford University Press, (1998).
39. Parikh V.M., " Absorption Spectroscopy of Organic Molecules" Addison-Wesley Publishing Company Inc. USA. (1974).
40. Levy G.C., Lichter, R. L., Nelson, G. L., "Carbon-13 Nuclear Magnetic Resonance-Spectroscopy". John Wiley & Sons Ltd., New York, Chichester, Brisbane, Toronto (1980).