Available online at www.joac.info

ISSN: 2278-1862

Journal of Applicable Chemistry

2013, 2 (6): 1683-1689

(International Peer Reviewed Journal)

Applications of 3-Amino-1*H*-quinazolin-2,4-dione in Heterocyclic Chemistry

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Received on 8th November and finalized on 13th November 2013

ABSTRACT

Quinazoline moiety has been found in a wide variety of biologically and pharmacology active compounds. Many of 3-subsituted heterocyclic quinazolindione derivatives have been synthesized and characterized by NMR, MS, IR and elemental analysis.

Keywords: 3-subsituted quinazoline, anhydride, ethylchloroacetate, ammonium thiocyanate, spectral analysis.

INTRODUCTION

Quinazoline derivatives play a vital and interesting role in heterocyclic chemistry [1-4] due to their desirable biological and pharmaceutical properties [5]. Furthermore, literature survey reveals that quinazoline derivatives represent one of the most active classes of compounds possessing wide spectrum of biological and pharmacological activities such as antifungal, antibacterial[6,7], anticancer [8], anti-malarial, anticonvulsant against electroshock[9-13] and anti-inflammatory [14,15].Looking to the diversified biological activity of quinazolines and in order to achieve better therapeutic agents, it was contemplated to design and synthesize a series of interesting quinazoline derivatives. Our present invention has been devoted to the synthesis of novel derivatives of quinazoline derivatives of expected antibacterial and pharmaceutical activity.

MATERIALS AND METHODS

Instrumentation

All chemicals and reagents used for the synthesis were commercially available (Merck,Germany) and used without further purifications.Melting points were uncorrected determined on an electric melting point apparatus (Kofler). IR spectra (KBr) were recorded on a Shimadzu 408 spectrometer. The ^{1}HNMR spectra were recorded by 200 MHz Varian EM 390 spectrometer; chemical shifts are reported in ppm with TMS as an internal standard and are given in δ units. Electron impact mass spectra were obtained at 70 eV using a GC-MS sp. 1000 Shimadzu. Elemental analyses were carried out at Microanalysis Unit at Cairo University; purity of the compounds during reaction was detected by TLC.

Synthesis

***N*-(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl)phthalamic acid 2 and *N*-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-9,10-dihydro-11-amidoethanoanthracene-12-carboxylic acid 4.**

3-Amino-1*H*-quinazolin-2,4-dione **1** (0.9 gm., 5 mmol) was added to a suspension of phthalic anhydride and/or 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic anhydride (6 mmol) in glacial acetic acid (30 ml), the reaction mixture was heated under reflux for 6 hrs.; after cooling the solid formed was filtered off and crystallized from 1,4-dioxane to give *N*-(2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)phthalamic acid **2**and*N*-(2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)-9,10-dihydro-11-amidoethanoanthracene-12-carboxylic acid**4**respectively as white crystal.

Compound 2: Yield: 85 %. M.P.: > 360^{o}C. FT-IR (KBr, cm^{-1}): 1740, 1700 (ν C=O's);3300 (νNH); 3500 (νOH). ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.22-8.13 (m, 8H, arom.H); 10.56 (s, 1H, OH); 11.65 (s, 1H, NH); 12.25 (s, 1H, NH). Anal.Calcd.for $C_{16}H_{11}N_3O_5$: C, 59.08; H, 3.41; N, 12.92. Found: C, 59.05; H, 3.40; N, 12.94 %.

Compound 4:Yield: 65 %. M.P.: > 360^{o}C. FT-IR (KBr, cm^{-1}): 1736, 1680(ν C=O's); 3283 (ν NH); 3400 (ν OH).^{1}H NMR (200 MHz, DMSO-d_6): δ 3.72 (d, 2H, 2CH-11,12); 4.97 (d, 2H, 2CH-9,10); 7.23-8.04 (m, 12H, arom.H); 10.64 (s, 1H, OH); 11.84 (s, 1H, NH); 12.06 (s, 1H, NH). Anal. Calcd. for $C_{26}H_{19}N_3O_5$: C, 68.87; H, 4.22; N, 9.27. Found: C, 68.90; H, 4.20; N, 9.29 %.

3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-*1H*-quinazolin-2,4-dione 3 and 3-[*N*-(9,10-dihydro-9,10-ethano-anthracene-11,12-dicarboximidyl)]-*1H*-quinazolin-2,4-dione 5:

N-(2,4-dioxo-1,4-dihydro-2*H*-quinolin-3-yl)phthalamic acid **2** and/or *N*-(2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)-9,10-dihydro-11-amidoethanoanthracene-12-carboxylic acid **4** (0.65 gm., 2 mmol) was added to acetic anhydride (20 ml), then heated under reflux for 3 hrs.; after cooling, the reaction mixture was poured onto water, the solid formed was filtered off and crystallized from 1,4-dioxane to afford 3-(1,3-dioxo-1,3-dihydro-iso-indol-2-yl)-1*H*-quinazolin-2,4-dione **3** and 3-[*N*-(9,10-dihydro-9,10-ethano-anthracene-11,12-dicarboximidyl)]-1*H*-quinazolin-2,4-dione**5** respectively as white crystals .

Compound 3:Yield: 85%. M.P.:>360 ^{o}C. FT-IR (KBr, cm^{-1}):1736, 1700 (νC=O's);
3288 (νNH). ^{1}H NMR (200 MHz, DMSO-d_6):δ 7.32-8.1 (m, 8H, arom.H); 12.25 (s, 1H, NH). MS (m/z, %): 307 (19.80 %) correspond to the molecular formula ($C_{16}H_9N_3O_4$). Anal. Calcd. for$C_{16}H_9N_3O_4$: C, 62.54; H, 2.95; N,13.68. Found: C, 62.52; H, 2.96; N, 13.70 %.

Compound 5:Yield: 92%. M.P.:>360 ^{o}C. FT-IR (KBr, cm^{-1}): 1740, 1700(νC=O's); 3300 (νNH). ^{1}H NMR (200 MHz, DMSO-d_6):δ 3.65 (s, 2H, 2CH-11,12); 4.88 (s, 2H, 2CH-9,10); 7.09-7.89 (m, 12H, arom.H); 11.72 (s, 1H, NH). Anal. Calcd. for$C_{26}H_{17}N_3O_4$
: C, 71.72; H, 3.92; N, 9.65. Found: C, 71.75; H, 3.94; N, 9.66%.

(2,4-Dioxo-1,4-dihydro-*2H*-quinazolin-3-yl-amino)acetic acid ethyl ester 6:

3-Amino-1*H*-quinazolin-2,4-dione **1**(1.7 gm., 10 mmol) was added to a solution of ethylchloroacetate (15 mmol) in acetone (30 ml) in presence of finely grinded K_2CO_3 (2.76 gm., 20 mmol). The reaction mixture was heated under reflux for 5 hrs.; after cooling, the solid formed was filtered off and crystallized from benzene to give ethyl-*N*-(2,4-Dioxo-1,4-dihydro-2*H*-quinazolin-3-yl-amino)acetic acid ethyl ester**6** (2,3 gm., 9 mmol) as white needles.Yield: 90 %. M.P.: 164 ^{o}C. FT-IR (KBr, cm^{-1}): 3354, 3267 (NH), 1741, 1650 (C=O's). ^{1}H NMR (200 MHz, DMSO-d_6): 1.28 (t, 3H, CH_3); 4.24 (q, 2H, CH_2); 4.95 (s, 2H, CH_2); 6.98-7.25 (m, 4H, arom.H); 8.29 (d, 1H, NH)and also showed the disappearance of NH signal of quinazoline moiety in DMSO-d_6. MS (m/z, %): 263 (24.68 %) correspond to the molecular formula ($C_{12}H_{13}N_3O_4$). Anal. Calcd. for $C_{12}H_{13}N_3O_4$: C, 54.75; H, 4.98; N, 15.96. Found: C, 54.79; H, 4.97; N, 15.95 %.

(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl-amino)acetic acid hydrazide 7:

Ethyl-*N*-(2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)acetic acid ethyl ester**6** (1.31 gm., 5 mmol) was added to excess of hydrazine hydrate (1.25 ml, 10 mmol) in absolute ethanol (30 ml). The mixture was heated under reflux for 1 hr.; after cooling the precipitate formed was filtered off, crystallized from DMF to give (2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl-amino)acetic acid hydrazide **7**as white needles.Yield 95 %. M.P.: 262 ^{o}C. FT-IR (KBr, cm^{-1}): 1695, 1665 (C=O's); 3200 (NH_2); 3330(NH). ^{1}H NMR (200 MHz, DMSO-d_6): 4.27 (s, 1H, NH); 4.78 (s, 2H, CH_2); 5.62 (s, 2H, NH_2); 7.21-8.1 (m, 4H, arom.H); 9.37 (s, 1H, NH)and also showed the disappearance of NH signal of quinazoline moiety in DMSO-d_6. MS (m/z, %): 249

(10.50 %) correspond to the molecular formula ($C_{10}H_{11}N_5O_3$). Anal. Calcd. for $C_{10}H_{11}N_5O_3$: C, 48.19; H, 4.45; N, 28.10. Found: C, 48.22; H, 4.44; N, 28.09 %.

3-[(5-mercapto-[1,3,4]oxadiazol-2-yl-methyl)amino]-*1H*-quinazolin-2,4-dione 8:

(2,4-Dioxo-1,4-dihydro-2*H*-quinazolin-3-yl-amino)acetic acid hydrazide**7** (1.25 gm., 5 mmol) was added to a solution of carbon disulfide (0.46 ml, 6 mmol) in dry pyridine (20 ml), the reaction mixture was heated under reflux for 10 hrs.; after cooling the reaction mixture was poured onto ice cold diluted (1:1) HCl, the resulting solid formed was filtered off, dried and crystallized from acetic acid to give 3-[(5-mercapto-[1,3,4]oxadiazol-2-yl-methyl)amino]-1*H*-quinazolin-2,4-dione**8** as pale yellow crystals.Yield 60 %. M.P.: 242 ^oC. FT-IR (KBr, cm^{-1}): 1705, 1675 (C=O's); 3335, 3300 (NH). ^1H NMR (200 MHz, DMSO-d_6): 4.94 (s, 1H, NH); 5.53 (s, 2H, CH_2); 7.34-8.13 (m, 4H, arom.H); 8.65 (s, 1H, SH); 10.67 (s, 1H, NH). MS (m/z, %): 291 (24.64 %) correspond to the molecular formula ($C_{11}H_9N_5O_3S$). Anal. Calcd. for $C_{11}H_9N_5O_3S$: C, 45.36; H, 3.11; N, 24.04; S, 11.01. Found: C, 45.40; H, 3.1; N, 24.05; S, 10.98 %.

Ethyl-{5-[(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl-amino)-methyl][1,3,4]oxa-diazol-2-yl-sulfanyl}acetate 9:

Compound **8** (0.58 gm., 2 mmol) was added to ethylchloroacetate (0.36 ml, 3 mmol) in acetone (30 ml) in the presence of fine grinded anhydrous K_2CO_3 (0.41 gm., 3 mmol), the reaction mixture was heated under reflux for 12 hrs., after cooling, the solid was filtered off, washed with water and crystallized from benzene to give ethyl-{5-[(2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl-amino)-methyl]-[1,3,4]oxadiazol-2-yl-sulfanyl}acetate**9** as white crystals.Yield:55 %. M.P.:142-144 ^oC. FT-IR (KBr, cm^{-1}):1685, 1660 (C=O's);3330, 3280 (NH), ^1H NMR (200 MHz, DMSO-d_6):δ 1.26 (t, 3H, CH_3); 4.02 (s, 2H, CH_2-S); 4.21 (q, 2H, CH_2); 5.61 (s, 2H, CH_2-N); 7.27-8.29 (m, 4H, arom.H) (NH signal is not detected in DMSO). MS (m/z, %):377(18.40 %) correspond to the molecular formula ($C_{15}H_{15}N_5O_5S$). Anal. Calcd. for$C_{15}H_{15}N_5O_5S$: C,47.74; H,4.01; N, 18.56. Found: C, 47.77; H, 4.03; N, 18.55 %.

3-(4-oxo-*3H,4H,5H*-thiazolidin-2-yl-ideneamino)-*1H*-quinazolin-2,4-dione *E*-isomer 11a and *Z*-isomer 11b:

A mixture of 2-chloro-*N*-(2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)acetamide **10**(0.5 gm., 2 mmol) and ammonium thiocyanate (0.23 gm., 3 mmol) in ethanol (30 ml) is heated under reflux for 2 hrs. The solid was formed during the reaction was filtered off, crystallized from acetic acid to afford the isomeric mixture 3-(4-oxo-3*H*,4*H*,5*H*-thiazolidin-(2*E*)-ylideneamino)-1*H*-quinazolin-2,4-dione **11a** and 3-(4-oxo-3*H*,4*H*,5*H*-thiazolidin-(2*Z*)-ylideneamino)-1*H*-quinazolin-2,4-dione **11b** as white crystals.Yield: 70 %. M.P.:>360^oC. FT-IR (KBr, cm^{-1}):3230, 3200 (NH), 1700, 1687, 1660 (C=O's). ^1H NMR (200 MHz, DMSO-d_6):confirmed the proposed structures of **11a** and **11b** and it indicates different signals for the two isomers at δ 4.12 (s, 2H, CH_2) for **11a**; 4.21 (s, 2H, CH_2) for **11b**; 7.26-8.02 (m, 4H, arom.H) for both isomers; 11.72 (s, 1H, NH) for **11a**; 11.71 (s, 1H, NH) for **11b**; 12.48 (s, 1H, NH) for **11a** and 12.28 (s, 1H, NH) for **11b**. Anal. Calcd. for$C_{11}H_8N_4O_3S$: C,47.82; H, 2.92; N, 20.28. Found: C, 47.77; H, 2.94; N, 20.29 %.

3-(2-imino-4-oxo-*3H,4H,5H*-thiazolidin-3-yl)-*1H*-quinazolin-2,4-dione 12:

A mixture of 2-chloro-*N*-(2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)acetamide **10**(0.5 gm., 2 mmol) and potassium thiocyanate (0.29 gm., 3 mmol) in acetone (30 ml) is heated under reflux for 2 hrs. The solid formed during the reaction was filtered off, crystallized from ethanol to afford 3-(2-imino-4-oxo-3*H*,4*H*,5*H*-thiazolidin-3-yl)-1*H*-quinazolin-2,4-dione **12** as white crystals.Yield: 73%. M.P.:278-280 ^oC. FT-IR (KBr, cm^{-1}): 1715, 1685(ν C=O's); 3290(ν NH). ^1H NMR (200 MHz, DMSO-d_6): δ 4.32 (s, 2H, CH_2); 7.27-7.98 (m, 4H, arom.H); 9.59 (s, 1H, NH); 11.59 (s, 1H, NH). MS (m/z, %): 276 (29.30 %) correspond to the molecular formula ($C_{11}H_8N_4O_3S$). Anal. Calcd. for $C_{11}H_8N_4O_3S$: C, 47.82; H, 2.92; N, 20.28; S, 11.61. Found: C, 47.84; H, 2.93; N, 20.27; S, 11.60 %.

General procedure for synthesis of Arylidines 13a,b-15a,b:

An equimolar amount of 3-(2-Imino-4-oxo-thiazolidin-3-yl)-1*H*-quinazolin-2,4-dione **12**and aromatic aldehyde namely benzaldehyde, anisaldehyde and/or *p*-chlorobenzaldehyde in glacial acetic acid in presence anhydrous sodium acetate, is heated under reflux for 10-12 hrs., after which a precipitate is formed. After cooling, the formed solid is filtered off, recrystallized from acetic acid to afford the isomeric mixtures of 3-(5-benzylidine-2-imino-4-oxo-3*H*,4*H*,5*H*-thiazolidin-3-yl)-1*H*-quinazolin-2,4-dione **13a** (Z-form), **13b** (E-form), 3-[2-imino-5-(4-methoxybenzylidine)-4-oxo-3*H*,4*H*,5*H*-thiazolidin-3-yl]-1*H*-

quinazolin-2,4-dione **14a** (Z-form), **14b** (E-form) and 3-[5-(4-chlorobenzylidine)-2-imino-4-oxo-3*H*,4*H*,5*H*-thiazolidin-3-yl]-1*H*-quinazolin-2,4-dione **15a** (Z-form), **15b** (E-form) respectively as white crystals.

Arylidine13: Yield: 55 %. M.P.:>360 ^{o}C. FT-IR (KBr, cm^{-1}): 1700, 1670 (C=O's); 2934 (CH);3170, 3067 (NH's).^{1}H NMR (200 MHz, DMSO-d_6): δ 7.19-7.98 (m, 10H, 9-arom.H, CH sp^2); 11.72 (s, 1H, NH); 12.9 (s, 1H, NH). Anal. Calcd. for$C_{18}H_{12}N_4O_3S$: C, 59.33; H, 3.32; N, 15.38. Found: C, 59.37; H, 3.30; N, 15.35 %.

13b: ^{1}H NMR (200 MHz, DMSO-d_6): δ 7.19-7.98 (m, 10H, 9-arom.H, CH sp^2); 11.77 (s, 1H, NH); 13.2 (s, 1H, NH).

Arylidine14: Yield: 60 %. M.P.: >360^{o}C. FT-IR (KBr, cm^{-1}): 1741, 1650 (C=O's); 2929 (CH);3165, 3078 (NH's).^{1}H NMR (200 MHz, DMSO-d_6): 3.84 (s, 3H, CH_3); 7-7.99 (m, 9H, 8-arom.H, CH sp^2); 11.6 (s, 1H, NH); 12.75 (s, 1H, NH). MS (m/z, %): 394 (25.37 %) correspond to the molecular formula ($C_{19}H_{14}N_4O_4S$).Anal. Calcd. for$C_{19}H_{14}N_4O_4S$: C, 57.86; H, 3.58; N, 14.21. Found: C, 57.9; H, 3.59; N, 14.17 %.

***14b*:**^{1}H NMR (200 MHz, DMSO-d_6): δ 3.76 (s, 3H, CH_3); 7-7.99 (m, 9H, 8-arom.H, CH sp^2); 11.76 (s, 1H, NH); 13.03 (s, 1H, NH).

Arylidine 15: Yield: 68 %. M.P.: >360^{o}C. FT-IR (KBr, cm^{-1}): 1720, 1635 (C=O's); 3011 (CH); 3160, 3100 (NH's).^{1}H NMR (200 MHz, DMSO-d_6): 7.27-7.98 (m, 9H, 8-arom.H, CH sp^2); 11.57 (s, 1H, NH); 12.9 (s, 1H, NH). MS (m/z, %): (398, 26.83%) for ^{35}Cl and at (400, 11.23%) for ^{37}Cl corresponding to the formula ($C_{18}H_{11}N_4O_3SCl$). Anal. Calcd. for$C_{18}H_{11}N_4O_3SCl$: C, 54.21; H, 2.78; N, 14.05. Found: C, 54.4; H, 2.79; N, 13.99 %.

15b: ^{1}H NMR (200 MHz, DMSO-d_6):δ 7.27-7.98 (m, 9H, 8-arom.H, CH sp^2); 11.74 (s, 1H, NH); 13.2 (s, 1H, NH).

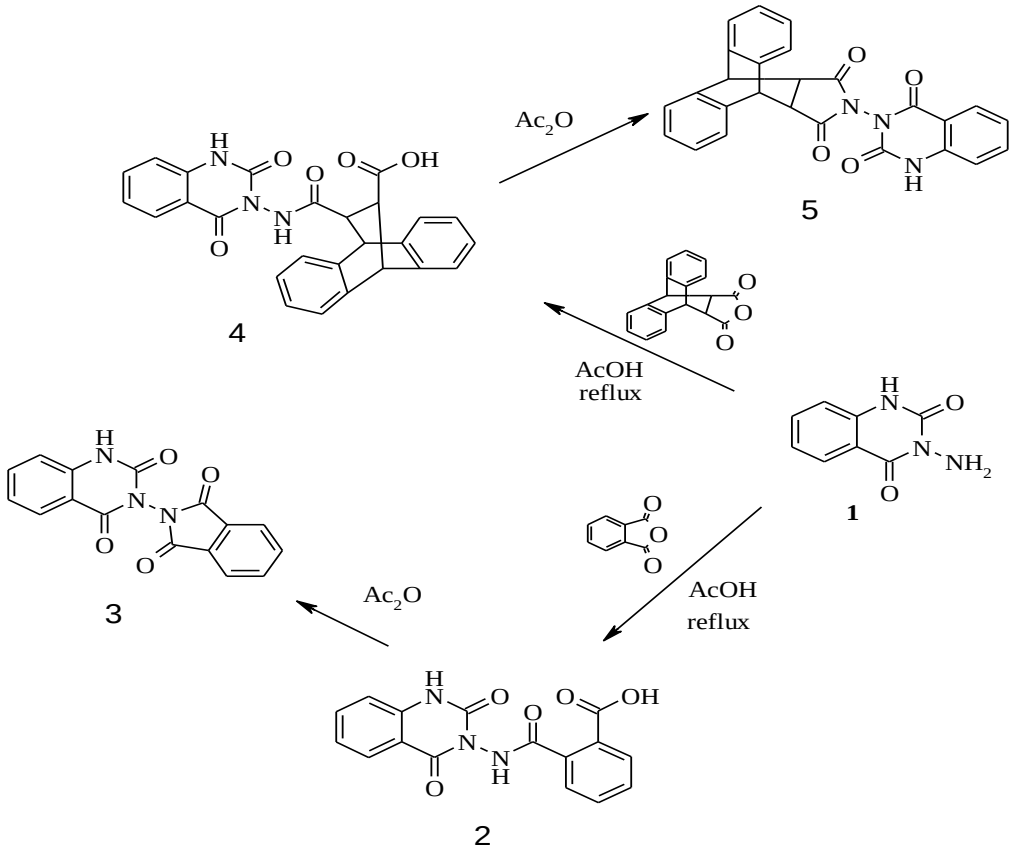
RESULTS AND DISCUSSION

According to the unique positionpyrimidines and quinazolindiones in medicinalchemistry, this encouraged us in this study to develop new synthetic route for the synthesis of new quinazoline derivatives as shown in schemes (1-3)by introducing directly or through side-chain heterocyclic moiety in position-3 starting with 3-amino-1*H*-quinazolin-2,4-dione **1** which may possess certain pharmacological activities.Synthetic scheme 1 illustrates the effect aromatic anhydrides on compound **1**, when3-amino-1*H*-quinazolin-2,4-dione **1**was reacted with phthalic anhydride and/or 9,10-dihydro-9,10-ethanoanthracene-11,12-dicarboxylic anhydride in acetic acid under reflux to give *N*-(2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)phthalamic acid **2** and *N*-(2,4-dioxo-1,4-dihydro-2*H*-quinazolin-3-yl)-9,10-dihydro-11-amidoethanoanthracene-12-carboxylic acid **4**respectively as open form. Cyclization of compound **2**and/or**4**takes place by heating under reflux with acetic anhydride afforded 3-(1,3-dioxo-1,3-dihydro-isoindol-2-yl)-1*H*-quinazolin-2,4-dione **3** and/or3-[*N*-(9,10-dihydro-9,10-ethano-anthracene-11,12-dicarboximidyl)]-1*H*-quinazolin-2,4-dione**5**(Scheme 1). Scheme 2 shows a linear synthesis for ethyl-{5-[(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl-amino)methyl]-[1,3,4]oxadiazol-2-yl-sulfanyl}-acetate **9** by addition ethylchloroacetate to starting compound **1** to give ester **6**, followed by addition of hydrazine to afford hydrazide **7** which by reacting with carbon disulfide yield 3-[(5-mercapto-[1,3,4]oxadiazol-2-yl-methyl)amino]-*1H*-quinazolin-2,4-dione**8** which finally reacted with ethylchloroacetate to give the final product **9** (Scheme 2). Furthermore, we investigated of the effect of ammonium thiocyanate on compound **10** to give 3-(4-oxo-3*H*,4*H*,5*H*-thiazolidin-2-yl-ideneamino)-1*H*-quinazolin-2,4-dione (*E*-form) **11a** and **(***Z*-form)**11b** in a ratio of 2:1 respectively(Scheme 3). Attempts to isolate the two isomers using column chromatography were unsuccessful. The presence of the two isomers and their ratio was indicated from the ^{1}H-NMR spectra. The integration curves of the signals confirmed the ratio, and it is suggested that the major product is structure **11a** due to: (1) the size of nitrogen atom is smaller than that of sulfur, thus **11a** is the more stable because it shows less steric hindrance with carbonyl oxygen atom than **11b** (2) the repulsive force between the atomic orbitals bearing the none bonding electrons is smaller in case of **11a** than **11b**. Separation of this mixture using column chromatography, HPLC and preparative TLC was not possible. Reaction of potassium thiocyanatewith compound

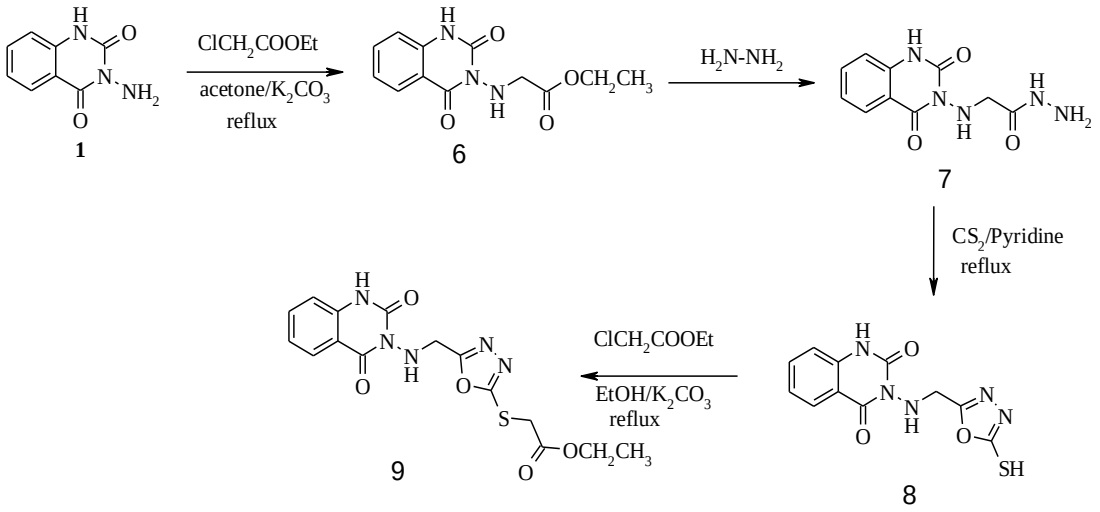
10gavecompound**12**(Scheme 3). Finally, we studied the effect of different aromatic aldehyde namely benzaldehyde, anisaldehyde and/or *p*-chlorobenzaldehyde on compound **12** to afford the corresponding arylidine in two isomeric structures 3-(5-benzylidine-2-imino-4-oxo-3*H*,4*H*,5*H*-thiazolidin-3-yl)-1*H*-quinazolin-2,4-dione **13a** (Z-form), **13b** (*E*-form),3-[2-imino-5-(4-methoxybenzylidine)-4-oxo-3*H*,4*H*,5*H*-thiazolidin-3-yl]-1*H*-quinazolin-2,4-dione **14a** (*Z*-form), **14b** (*E*-form) and 3-[5-(4-chlorobenzylidine)-2-imino-4-oxo-3*H*,4*H*,5*H*-thiazolidin-3-yl]-1*H*-quinazolin-2,4-dione **15a** (Z-form), **15b** (*E*-form)(Scheme 3).The formation of the two isomeric forms (*E*, *Z*) with a ratio (2: 3) respectively, was calculated from the integration curves of ^{1}H-NMR spectra. It was suggested that the major product is the (*Z*-form) which is the more stable stereoisomer. Separation of these mixtures using column chromatography, HPLC and preparative TLC was not possible owing to their comparable $\mathbf{R_f}$ values.

APPLICATIONS

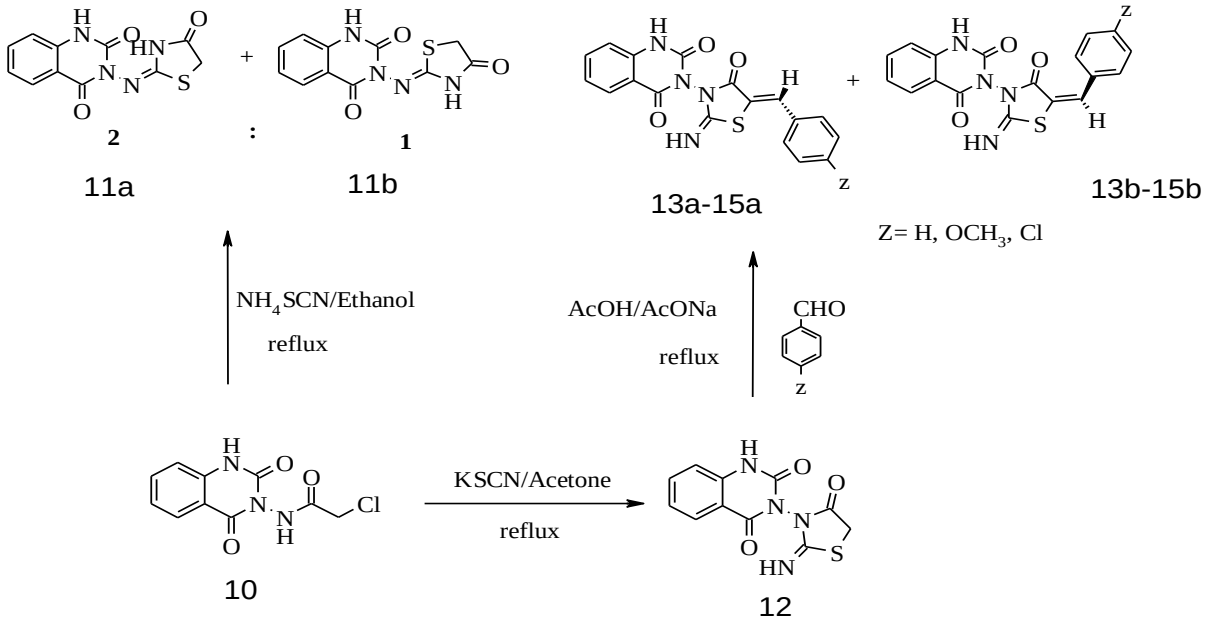
This study is to synthesize novel derivatives of quinazoline derivatives of expected antibacterial and pharmaceutical activity.



Scheme 1



Scheme2



Scheme 3

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