Research Article

Facile Syntheses of Pharmaceutically Active Quniazolin-2,4-Diones

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ABSTRACT

Our aim is to design and synthesize new and effective derivatives of quinazolin-2,4-dione which may possess greater certain pharmacological activities. A new series of quinazolin-2,4-diones have been synthesized starting from 3-amino-*1H*-quinazolin-2,4-dione 1 which reacted with chloroacetylchloride to give compound 6, followed by reaction with different reagents to yield heterocyclic moieties attached to pyrimidine ring in position 3.Characterization of the newly synthesized compounds was by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis technique.

Keywords: Anti-inflammatory, Aromatic anhydride, Pharmaceutical, Isomer, 3-amino-*1H*-quinazolin-2,4-dione.

INTRODUCTION

It has been recently shown that, pyrimidine and quinazoline derivatives[1,2] are most popular compounds and they are promising structural moieties which form components in a number of useful drugs and are associated with many attractive biological and therapeutical activities.[3] Pyrimidine compounds have been used as hypnotic drugs for the nervous system.[4] Moreover, they exhibit range of pharmacological activities such as antibacterial[5,6], antifungal[7,8], anticancer[9] and anti-inflammatory.[10,11] In the continuation of our search for more potent antibacterial agents, we have documented that pyrimidine and quinazoline derivatives exhibited good antibacterial activity. Our research has been devoted to the development of a new class of quinazoline moiety which attached to interesting heterocyclic moieties using 2-Chloro-*N*-(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl)-acetamide 6 as a requisite starting substrate. The incorporation of the two resulted moieties increases the biological activity of the newly synthesized compounds.

MATERIALS AND METHODS

Instrumentation

Melting points were uncorrected determined on an electric melting point apparatus (Kofler). IR spectra (KBr) were recorded on a Shimadzu 408 spectrometer. The ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 on Varian EM 390 spectrometer (200 and 300 MHz for ^{1}H and 300 MHz for ^{13}C); chemical shifts are reported in ppm with TMS as an internal standard and are given in δ units. The mass spectra were determined using a HP Model, MS 5988 and AmD 402/3 mass spectrometers at ionization energy 70 eV. Elemental analyses were carried out at Microanalysis Unit at Cairo University and the Chemistry Department at Regensburg University, Germany; purity of the compounds was detected by TLC.

Synthesis

General procedures *for synthesis of imides (2-4)*

A mixture of 3-amino-*1H*-quinazolin-2,4-dione 1 (0.9 gm., 5 mmol) and the appropriate anhydrides namely 3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione (5 mmol), benzo[1,2-c;4,5-c`]difuran-1,3,5,7-tetraone (2,5 mmol), benzo[de]isochromen-1,3-dione (5 mmol) in glacial acetic acid (20 ml) was refluxed for (4-6) hrs. After cooling, the solid crystals were filtered off and collected; then crystallized from the appropriate solvent to give 2-4 respectively (Scheme 1).

Compound 2

Yield 70 % M.P. 270°C FT-IR (KBr, cm^{-1}): (ν C=O's) 1741, 1695; (ν sp^3 C-H) 2955; (ν sp^2 C-H aromatic) 3060; (ν NH) 3231.^{1}H NMR (300 MHz, DMSO-d_6): δ 2.37 (m, 2H, 2CHa); 2.5 (m, 2H, 2CHb); 3.5 (m, 2H, 2CHc sp^3); 5.9 (m, 2H, 2CH sp^2); 7.29-7.96 (m, 4H, arom.H); 12.12 (s, 1H, NH). Anal.Calcd.for $C_{16}H_{13}N_3O_4$: C,61.73; H, 4.21; N, 13.50. Found: C, 61.76; H, 4.22; N, 13.52 %.

Compound 3

Yield 60 % M.P. > 360°C FT-IR (KBr, cm^{-1}): (ν C=O's) 1746, 1695, 1685; (ν NH) 3308.^{1}H NMR (300 MHz, DMSO-d_6): δ 7.18-8.05 (m, 8H, arom.H); 8.76 (s, 2H, 2Ha); 12.43 (s, 2H, NH).^{13}C NMR (300 MHz, DMSO-d_6, δ, ppm):112.6, 116.3, 120.9, 123.9, 127.9, 135.0, 136.9, 139.3, 147.1, 159.1, 161.6.Anal.Calcd.for $C_{26}H_{12}N_6O_8$: C,58.22; H, 2.25; N, 15.67. Found: C, 58.19; H, 2.26; N, 15.66 %.

Compound 4

Yield 68% M.P. > 360°C FT-IR (KBr, cm^{-1}): (ν C=O's) 1757, 1669; (ν NH) 3293.^{1}H NMR (300 MHz, DMSO-d_6): δ 7.34-8.61 (m, 10H, arom.H). MS showed protonated molecular ion peak $(M+H)^+$ [12] at (m/z, %): 357 (100 %) correspond to the molecular formula ($C_{20}H_{11}N_3O_4$). Anal.Calcd. for

$C_{20}H_{11}N_3O_4$: C, 67.23; H, 3.10; N, 11.76. Found: C, 67.25; H, 3.11; N, 11.74 %.

1H,3H-quinazolin-2,4-dione (5)

A cooled solution of $NaNO_2$ (0.7 gm.) in water (10 ml) was added drop by drop during 30 minutes to a cooled solution of compound **1** (1.7gm., 10 mmol) in HCl (30 ml) with stirring at 0°C. Stirring continues for 2 hrs., the precipitate formed was isolated by filtration, washed with water; then crystallized from commercial ethanol to give *1H,3H*-quinazolin-2,4-dione **5** (1.33 gm., 8 mmol) as white needles (Scheme 2). Yield 85 % M.P. 320°C FT-IR (KBr, cm^{-1}): (ν C=O's) 1705, 1675; (ν NH) 3247. MS showed protonated molecular ion peak $(M+H)^+$at (m/z, %): 162 (100 %) correspond to the molecular formula ($C_8H_6N_2O_2$). Anal.Calcd.for $C_8H_6N_2O_2$: C, 59.26; H, 3.73; N, 17.28. Found: C, 59.23; H, 3.74; N, 17.29 %.

2-chloro-N-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetamide (6)

Treatment of a solution of 3-amino-*1H*-quinazolin-2,4-dione 1 (0.53 gm., 3 mmol) in 10 ml DMF with chloro acetylchloride (0.16 ml) drop wisely during stirring at room temperature. The reaction mixture was further stirred for 2 hrs., then diluted with cold water. The solid formed was filtered off; then crystallized from benzene to give 2-Chloro-*N*-(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl) acetamide 6 in yield 85% as white crystals (Scheme 3). M.P. 216 °C FT-IR (KBr, cm^{-1}): (νC=O's) 1740, 1670; (νNH) 3200. ^{1}H NMR (300 MHz, DMSO-d_6): δ 4.33 (s, 2H, CH_2); 7.22-7.96 (m, 4H, arom.H); 10.94 (s, 1H, NH); 11.68 (s, 1H, NH). MS showed molecular ion peak at (m/z=253, 28.83%) for ^{35}Cl and at (m/z=255, 10.23%) for ^{37}Cl correspond to the molecular formula ($C_{10}H_8N_3O_3Cl$). Anal.Calcd.for $C_{10}H_8N_3O_3Cl$: C, 47.35; H, 3.18; N, 16.57; Cl, 13.98. Found: C, 47.55; H, 3.15; N, 16.52; Cl, 13.94 %.

General procedures for synthesis of N-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-2-piperidin-1-yl-acetamide (7a)and N-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-2-morpholin-4-yl-acetamide (7b)

2-Chloro-N-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl) acetamide 6 (0.5 gm., 2 mmol) was added to a solution of piperidine and/ or morpholine (2 mmol) in absolute ethanol (30 ml) in presence of K_2CO_3 (0.42 gm., 3 mmol). The reaction mixture was stirred for 6 hrs., the solid formed was filtered off, washed with water; then crystallized from toluene to afford *N*-(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl)-2-piperidin-1-yl-acetamide 7a in yield 55% as white crystals and *N*-(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl)-2-morpholin-4-yl-acetamide **7b** in yield 45% as yellow crystals (Scheme 3).

Compound (7a)

M.P. 224°C FT-IR (KBr, cm^{-1}): (νC=O's) 1741, 1695; (νNH) 3231. ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.41 (m, 2H, CH_2); 1.57 (m, 4H, $2CH_2$); 2.5 (t, 4H, $2CH_2$); 3.1 (s, 2H, CH_2); 7.2-7.95 (m, 4H, arom.H); 10.2 (s, 1H, NH); 11.7 (s, 1H, NH). MS showed protonated molecular ion peak $(M+H)^+$at (m/z, %): 303 (5.00 %) correspond to the molecular formula ($C_{15}H_{19}N_4O_3$). Anal.Calcd.for $C_{15}H_{18}N_4O_3$: C, 59.59; H, 6.0; N, 18.53. Found: C, 60.05; H, 5.98; N, 18.51 %.

Compound (7b)

M.P. 236 °C FT-IR (KBr, cm^{-1}): (νC=O's) 1746, 1695, 1685; (νNH) 3308. ^{1}H NMR (300 MHz, DMSO-d_6): δ 2.57 (t, 2H, $2CH_2$-N); 3.17 (s, 2H, CH_2); 3.65 (t, 4H, $2CH_2$-O); 7.22-7.95 (m, 4H, arom.H); 10.3 (s, 1H, NH); 11.6 (s, 1H, NH). Anal.Calcd.for $C_{14}H_{16}N_4O_4$: C, 55.26; H, 5.30; N, 18.41. Found: C, 55.23; H, 5.31; N, 18.39 %.

1,4-bis[(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl-carbamoyl)-methyl]-piperazine (8)

Compound 6 (0.5 gm., 2 mmol) was added to a solution of piperazine (1 mmol) in absolute ethanol (30 ml) in presence of K_2CO_3 (0.42 gm., 3 mmol). The reaction mixture was stirred for 6 hrs., the solid formed was filtered off, washed with water; then crystallized from DMF to afford 1,4-bis[(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl-carbamoyl)-methyl]piperazine 8 in yield 48% as white crystals (Scheme 3). M.P. > 360°C FT-IR (KBr, cm^{-1}): (νC=O's) 1757, 1669; (νNH) 3293.^{1}H NMR (300 MHz, DMSO-d_6): δ 2.68 (s, 8H, $4CH_2$); 3.35 (s, 4H, $2CH_2$); 7.22-7.96 (m, 8H, arom.H); 10.27 (broad s, 2H, 2NH); 11.6 (broad s, 2H, 2 NH). MS showed protonated molecular ion peak $(M+H)^+$at (m/z, %): 521 (100 %) correspond to the molecular formula ($C_{24}H_{25}N_8O_6$). Anal.Calcd.for $C_{24}H_{24}N_8O_6$: C, 55.38; H, 4.65; N, 21.53. Found: C, 55.43; H, 4.63; N, 21.52 %.

3-(2,5-dioxo-imidazolidin-1-yl)-1H-quinazolin-2,4-dione (9a)

A mixture of 2-chloro-*N*-(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl)-acetamide 6 (1 gm., 4 mmol) and urea (4 mmol) in ethanol (20 ml) in presence of anhydrous K_2CO_3 (0.7 gm., 5 mmol), was refluxed until ammonia odour has stopped (10 hrs.). The solid formed was filtered off, washed with water, then crystallized from 1,4-dioxane to afford 3-(2,5-dioxo-imidazolidin-1-yl)-*1H*-quinazolin-2,4-dione 9a in yield 62 % as white crystals (Scheme 4).M.P. > 360 °C. FT-IR (KBr, cm^{-1}): (ν C=O's) 1760, 1690; (ν NH) 3320, 3290. ^{1}H NMR (200 MHz, DMSO-d_6): δ 4.54 (s, 2H, CH_2); 7.26-8.0 (m, 4H, arom.H). MS (m/z, %): 260 (29.20%) correspond to the molecular formula ($C_{11}H_8N_4O_4$). Anal.Calcd.for $C_{11}H_8N_4O_4$: C, 50.78; H, 3.10; N, 21.53. Found: C, 50.84; H, 3.08; N, 21.51 %.

3-(2-thioxo-2,5-dihydro-1H-imidazol-4-ylamino)-1H-quinazolin-2,4-dione (9b)

When 2-chloro-*N*-(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl) acetamide 6 (1 gm., 4 mmol) and thiourea (4 mmol) in ethanol (20 ml) in presence of anhydrous K_2CO_3 (0.7 gm., 5 mmol), were heated under reflux for 12 hrs. After cooling the reaction mixture was neutralized with concentrated HCl. The precipitated solid was filtered off, crystallized from ethanol to give 3-(2-thioxo-2,5-dihydro-*1H*-imidazol-4-yl-amino)-1H-quinazolin-2,4-dione 9b in yield 55 % as deep yellow crystals (Scheme 4). M.P. > 360

°C. FT-IR (KBr, cm^{-1}):(ν C=O's) 1710, 1650; (ν NH's) 3290, 3200. ^{1}H NMR (200 MHz, DMSO-d6): δ 3.6 (s, 2H, CH_2); 7.19-7.97 (m, 5H, arom.H+NH); 10.72 (s, 1H, NH); 11.7 (s, 1H, NH). MS (m/z, %): 275 (1.44 %) correspond to the molecular formula ($C_{11}H_9N_5O_2S$). Anal.Calcd.for $C_{11}H_9N_5O_2S$: C, 47.99; H, 3.30; N, 25.44; S, 11.65. Found: C, 48.04; H, 3.31; N, 25.42; S, 11.63 %.

2-(Benzothiazol-2-yl-sulfanylmethyl)(1,3,4)-oxadiazolo [2,3-b]-4H,5H-quinazolin-5-one (10)

An equimolar amounts of compound 6 (0.5 gm., 2 mmol) and 2-mercaptobenzothiazole (0.5gm., 3mmol) in acetone (30 ml) in presence of dry K_2CO_3 (0.55 gm., 4 mmol), was heated under reflux for 5 hrs. After cooling, the solid formed was filtered off, washed with water, then crystallized from ethanol to give 2-(Benzothiazol-2-yl-sulfanyl-methyl)(1,3,4)oxadiazolo[2,3-b](*4H,5H*) quinazolin-5-one 10 in yield 90% as yellow crystals (Scheme 4). M.P. 260°C FT-IR (KBr, cm^{-1}): (ν C=O) 1695; and the absence of any band due to NH vibration. ^{1}H NMR (200 MHz, DMSO-d_6): δ 4.25 (s, 2H, CH_2); 6.88-8.03 (m, 8H, arom.H). MS (m/z, %): 366 (27.60%) correspond to the molecular formula ($C_{17}H_{10}N_4O_2S_2$). Anal.Calcd.for $C_{17}H_{10}N_4O_2S_2$: C, 55.73; H, 2.75; N, 15.29; S, 8.73. Found: C, 55.76; H, 2.74; N, 15.30; S, 8.71 %.

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

A mixture of 2-chloro-*N*-(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl)acetamide 6 (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 of 3-(4-oxo-3H,4H,5H-thiazolidin-(2E)-ylideneamino)-*1H*-quinazolin-2,4-dione 11a and 3-(4-oxo-3H,4H,5H-thiazolidin-(2Z)-ylideneamino)-*1H*-quinazolin-2,4-dione 11b in yield 70% as white crystals(Scheme 4). M.P. > 360 °C. FT-IR (KBr, cm^{-1}): (ν C=O's) 1735, 1695, 1660; (ν NH) 3230-3200. ^{1}H 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; S, 11.61. Found: C, 47.77; H, 2.94; N, 20.29; S, 11.60 %.

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-*2H*-quinazolin-3-yl)acetamide 6 (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-3H,4H,5H-thiazolidin-3-yl)-*1H*-quinazolin-2,4-dione 12 in yield 75% as white crystals (Scheme 4).M.P. 280°C FT-IR (KBr, cm^{-1}): (ν C=O's) 1715, 1685; (ν NH) 3290. ^{1}H 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 %.

RESULTS AND DISCUSSION

Owing to the importance of quinazoline derivatives which documented in our previous studies[13-17], here we have developed the synthesis of some new interesting derivatives of quinazolin-2,4-dione which may use as potential pharmaceuticals. Synthetic scheme 1 illustrates the effect of different aromatic anhydrides on compound **1** in different ratios like (1:1) and (2:1). Treatment of 3-amino-*1H*-quinazolin-2,4-dione **1** with different aromatic anhydride namely 3a,4,7,7a-tetrahydroisobenzofuran-1,3-dione, benzo[1,2-c;4,5-c`]difuran-1,3,5,7-tetraoneand benzo[de]isochromen-1,3-dione in acetic acid under reflux gave the corresponding imides 2, 3 and 4 respectively. Scheme 2 shows the effect of nitrous acid on compound **1**. Diazotization of compound **1** followed by addition of malononitrile or diethyl malonate to introduce diazo group in position-3 was unsuccessful. The only formed product was identified as *1H,3H*-quinazolin-2,4-dione. Scheme3 illustrates the way used to synthesize the requisite starting material 2-chloro-*N*-(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl) acetamide **6** which was used in the synthesis of several quinazolin-2,4-one derivatives. Treatment of 3-amino-*1H*-quinazolin-2,4-dione **1** with chloroacetyl chloride drop by drop with stirring in DMF followed by addition of H_2O gave 2-chloro-*N*-(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl)acetamide **6** in an excellent yield. When compound **6** is stirred with piperidine, morpholine and/or piperazine in ethanol in presence of anhydrous K_2CO_3, it gave the corresponding imides N-(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl)-2-piperidin-1-yl-acetamide **7a**, N-(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl)-2-morpholin-4-yl-acetamide **7b** and 1,4-bis[(2,4-dioxo-1,4-dihydro-*2H*-quinazolin-3-yl-carbamoyl)-methyl]piperazine **8** respectively. Furthermore, we investigated of the effect of urea, thiourea and thiocyanates on compound **6** as shown in (Scheme 4). Addition of urea to starting material**6**under reflux until ammonia odour has ceased, it afforded 3-(2,5-dioxo-imidazolidin-1-yl)-*1H*-quinazolin-2,4-dione **9a**. Similarly when compound **6** was added to thiourea, it afforded 3-(2-thioxo-2,5-dihydro-1H-imidazol-4-yl-amino)-*1H*-quinazolin-2,4-dione **9b**.The reaction of compound **6** with 2-mercaptobenzothiazole in acetone yielded 2-(Benzothiazol-2-yl-sulfanylmethyl) (1,3,4)oxadiazolo[2,3-b]-*4H,5H*-quinazolin-5-one **10** in a good yield. On treatment of compound **6** with ammonium thiocyanate under reflux, it gave two isomeric forms of compound 3-(4-oxo-3H,4H,5H-thiazolidin-2-yl-ideneamino)-*1H*-quinazolin-2,4-dione (E-form) **11a** and (Z-form) **11b** in a ratio of 2:1 respectively[18]. Attempts to isolate the two isomers using column chromatography and HPLC were unsuccessful. The presence of the two isomers and their

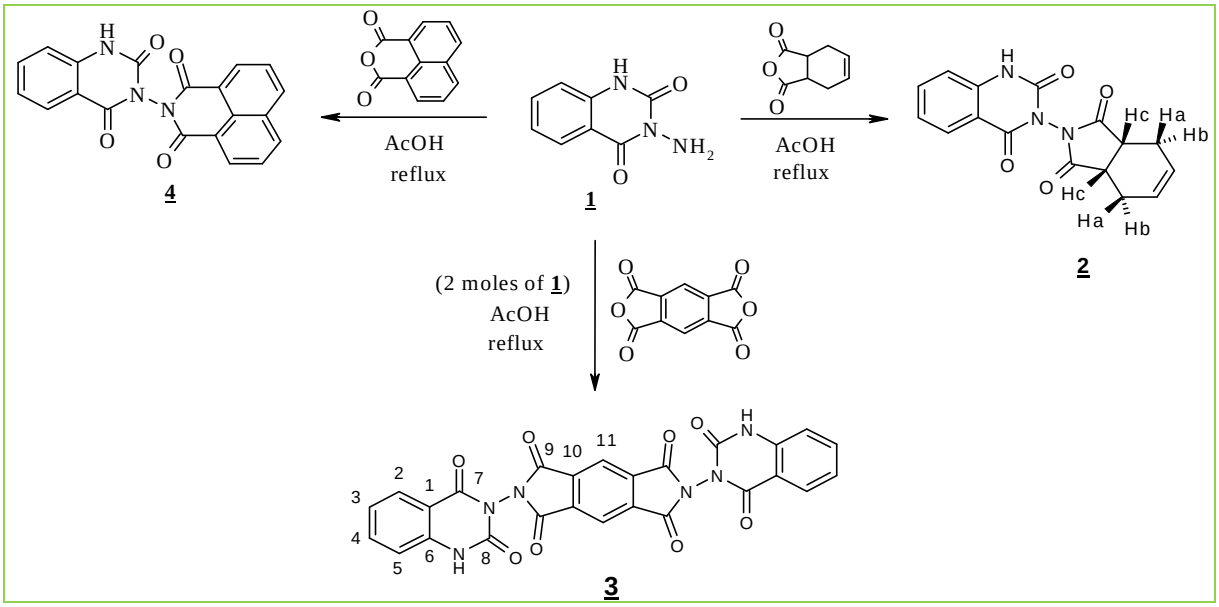
ratio was indicated from the ^{1}H-NMR spectra. The integration curves of the signals confirmed the ratio, and it is suggested that the major product is structure **11a** due to:-

(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**.

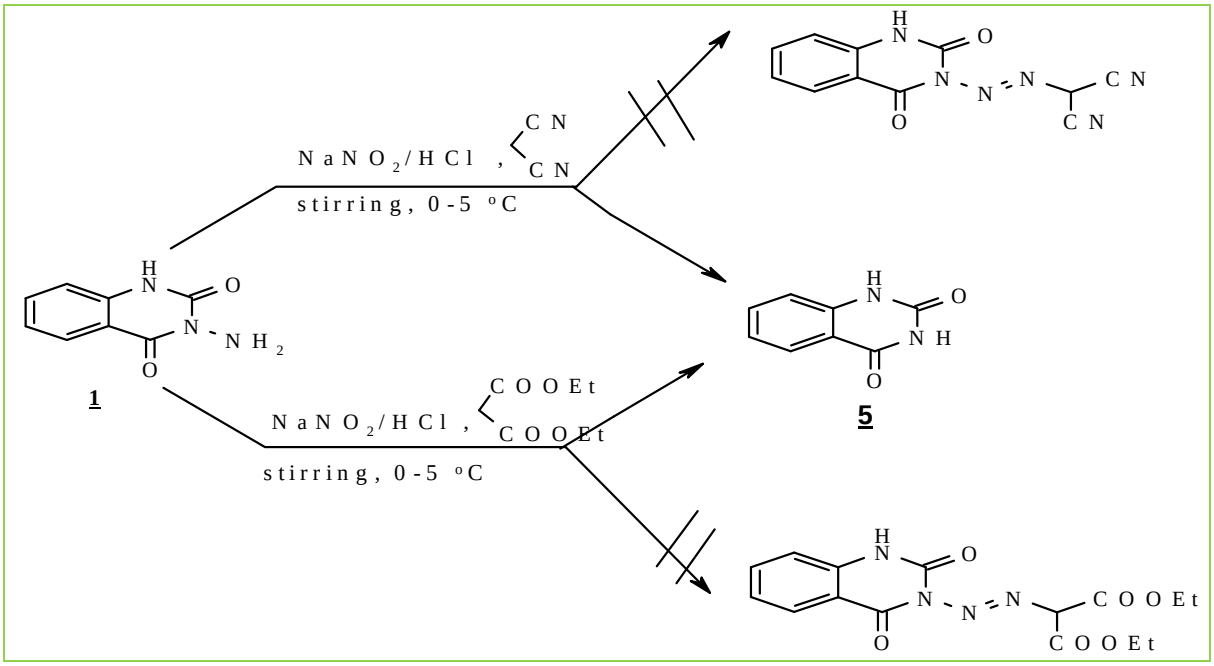
(2) The repulsive force between the atomic orbitals bearing the none bonding electrons is smaller in case of **11a** than **11b**.

Separation of this mixture using various chromatographic methods such as column chromatography, HPLC and preparative TLC was not possible.

Finally, when compound **6** was allowed to react with potassium thiocyanate under reflux, it gave 3-(2-imino-4-oxo-3H, 4H, 5H-thiazolidin-3-yl)-*1H*-quinazolin-2,4-dione **12**. It was expected that the imino group could be hydrolyzed but ammonia odour was not detected during the reaction[19]. The Formation of Compound **12** may proceed according to the Dimroth type Rearrangement mechanism[20] as illustrated in (Scheme 5). **In conclusion**, the recent study focused primarily on the synthesis of several and effective quinazoline derivatives which may have significant role in drug design. Diverse chemical structures were evaluated by IR, ^{1}H NMR, ^{13}C NMR, MS, and elemental analysis technique.



Scheme 1



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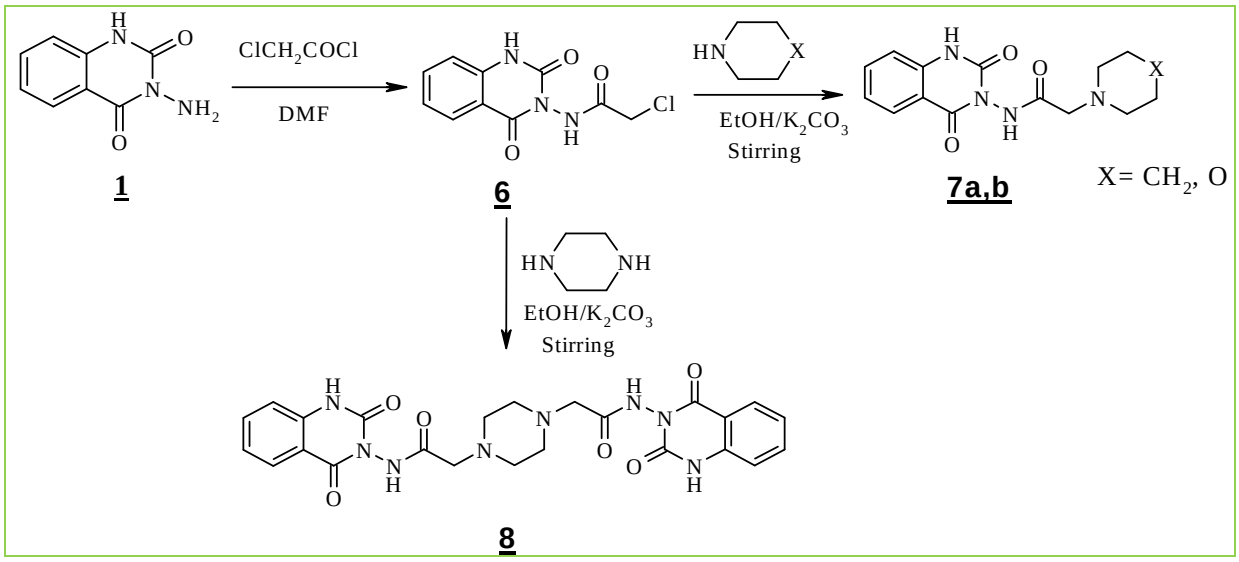
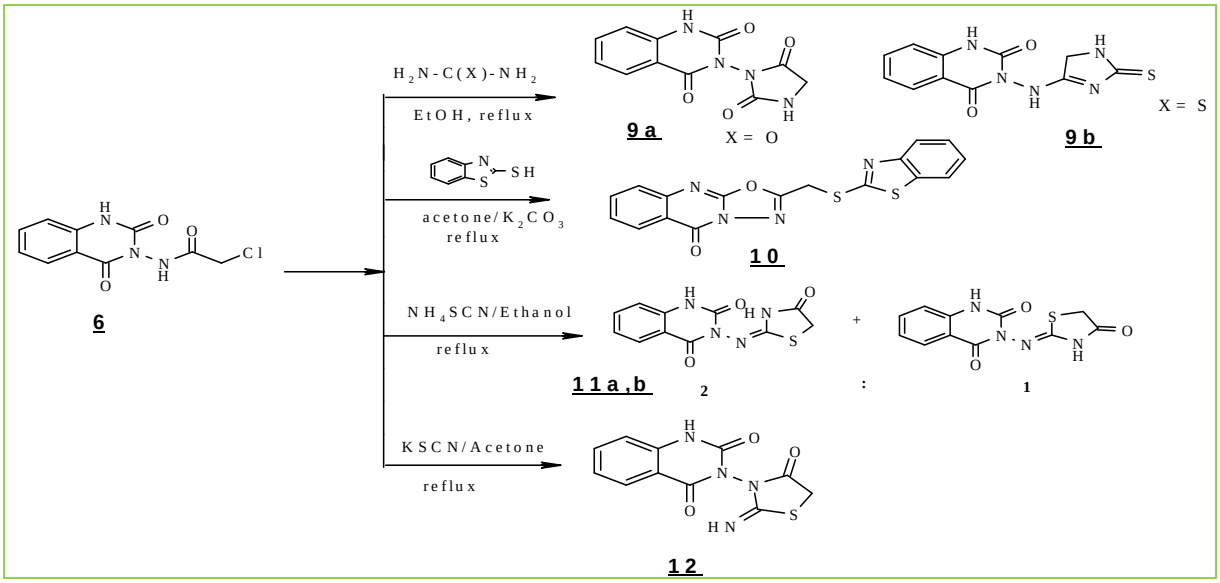
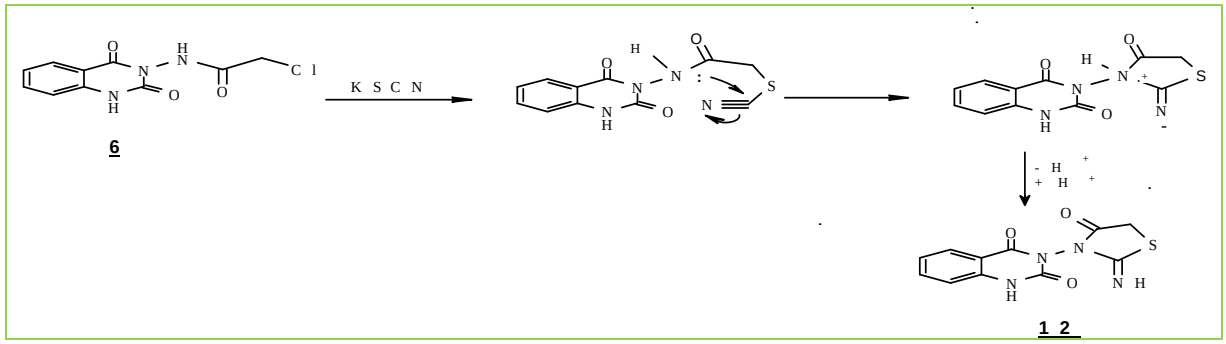


Scheme 3



Scheme 4



Scheme 5

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REFERENCES

1. Hassan AM, Seleem AM, Younes MMA, Taha MM, Abdel-MonsefHA, Synthesis and spectral characterization of some heterocyclic nitrogen compounds, Eur. J. Chem, 4(2), 2013, 121-123.
2. Hassan AM, Seleem AM, Younes MMA, Taha MM, Abdel-Monsef HA, Utility of (2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetic acid hydrazidein the synthesis of some heterocyclic nitrogen compounds, Eur. J. Chem., 4(2), 2013, 168-171.
3. Patel R, Desai K, Chikhalia K, Synthesis and evaluation of novel quinolylchalcone as antibacterial agents, J. Ind. Chem. Soc., 80, 2003, 138-145.

4. Wang SQ, Fang L, Liu XJ, Zhao K, Design, synthesis, and hypnotic activity of pyrazolo[1,5-a] pyrimidine derivatives, Chinese Chem. Lett., 15, 2004, 885-888.
5. Sharma P, Rane N, Gurram VK, Synthesis and QSAR studies of pyrimido[4,5-d]pyrimidine-2,5-dione derivatives as potential antimicrobial agents, Bioorg. Med. Chem. Lett., 14, 2004, 4185-4190.
6. Elkholy YM, Morsy MA, Facile Synthesis of 5, 6, 7, 8-Tetrahydropyrimido[4,5-b]-quinoline Derivatives, Molecules, 11, 2006, 890-903.
7. Holla BS, Mahalinga M, Karthikeyan MS, Akberali PM, Shetty NS, Synthesis of some novel pyrazolo[3,4-d]pyrimidine derivatives as potential antimicrobial agents, Bioorg. Med.Chem., 14, 2006, 2040-2047.
8. Ingarsal N, Saravanan G, Amutha P, Nagarajan S, Synthesis, *in vitro* antibacterial and antifungal evaluations of 2-amino-4-(1-naphthyl)-6-arylpyrimidines, Eur. J. Med .Chem., 42, 2007, 517-520.
9. Zhao XL, Zhao YF, Guo SC, Song HS, Wang D, Gong P, Synthesis and anti-tumour activities of novel [1,2,4]triazolo[1,5-a]pyrimidines, Molecules, 12, 2007, 1136-1146.
10. Sondhi SM, Singh N, Johar M, Kumar A, Synthesis, anti-inflammatory and analgesic activities evaluation of some mono, bi, tricyclic pyrimidine derivatives, Bioorg. Med. Chem., 13, 2005, 6158-6166.
11. Amin KM, Hanna MM, Abo-Youssef HE, George RF, Synthesis, analgesic and anti-inflammatory activities of some bi-, tri- and tetracyclic condensed pyrimidines, Eur. J. Med. Chem., XXX, 2009, 1-13.
12. Pndrew D, Hammoud J, Major H, Eur. J. of Mass Spectrometry, 16, 2, 2010, 169.
13. Hassan AM, Younes MMA, Taha MM, Abdel-Monsef HA, Synthesis and reactions of 3-aminotetrachloro quinazolin-2,4-dione, Eur. J. Chem., 2(4), 2011, 514-518.
14. Hassan AM, Younes MMA, Taha MM, Abdel-Monsef HA, Action of Some Heterocyclic Amines and Difunctional Nucleophiles on *N*-Phenylsulphonyloxy-tetrachloro phthalimide, Chemistry Journal, 2 (5), 2012, 158-165.
15. Hassan AM, Younes MMA, Taha MM, Salem MW, Abdel-Monsef HA, An Efficient Synthesis of Biologically Active Tetrachloroquinazolin-2,4-dione, Chem. Sci Journal, 2012, CSJ-87.
16. Younes MMA, Taha MM, Abdel-Monsef HA, (2,4-Dioxo-1,4-Dihydro-2H-Quinazolin-3-yl)-acetic acid hydrazide: Synthesisand Reactions, J. Asian Sci. Res., 3 (8), 2013, 800-809.
17. Hassan AM, Younes MMA, Taha MM, Abboudy MS, Abdel-Monsef HA, Applications of 3-Amino-1H-quinazolin-2,4-dione in Heterocyclic Chemistry, journal of Applicable Chemistry, 2013 (Accepted).
18. Antintas H, Ates O, Kocabalkanli A, Birteksoz S, Otuk G, Indian J. Chem. Sect. B: Org. Chem. Incl. Med. Chem., 2005, 44, 585-590.
19. Liu HL, Li Z, Anthonsen T, Synthesis and Fungicidal Activity of 2-Imino-3-(4-aryl-thiazol-2-yl)-thiazolidin-4-ones and their 5-Arylidene Derivatives, Molecules, 5, 2000, 1055-1061.
20. Hassan AM, Younes MMA, Taha MM, Abdel-Monsef HA, Synthesis and Reactions of 3-(2-Chloromethyl-carbonylamino)-tetrachloroquinazolin-2,4-dione, Org. Chem. Int., 2012, Article ID 284947, 4 pages, doi:10.1155/2012/284947.

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