INTRODUCTION

It has been recently shown that, pyrimidine and quinazoline derivatives 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 therapeutic activities. Pyrimidine compounds have been used as hypnotic drugs for the nervous system. Moreover, they exhibit range of pharmacological activities such as antibacterial, antifungal, anticancer and anti-inflammatory. 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 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 ¹H and ¹³C NMR spectra were recorded in DMSO-d₆ on a Varian EM 390 spectrometer (200 and 300 MHz for ¹H and 300 MHz for ¹³C); 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-tetrahydrodibenzofuran-1,3-dione (5 mmol), benzo[1,2-c:4,5-c’]difuran-1,3,5,7-tetraone (2.5 mmol), benzo[d]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 sp² C-H) 2955; (ν sp³ C-H aromatic) 3060; (ν NH) 3293. ¹H NMR (300 MHz, DMSO-d₆): δ 2.37 (m, 2H, 2CHA); 2.5 (m, 2H, 2CHb); 3.5 (m, 2H, 2CHc sp³); 5.9 (m, 2H, 2CH sp³); 7.29-7.96 (m, 4H, arom.H); 12.12 (s, 1H, NH). Anal.Calcld for C₁₈H₁₈N₂O₅: C, 61.73; H, 4.22; 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, 1656; (ν NH) 3308. ¹H NMR (300 MHz, DMSO-d₆): δ 7.18-8.05 (m, 8H, arom.H); 8.76 (s, 2H, 2HA); 12.43 (s, 2H, NH). ¹³C NMR (300 MHz, DMSO-d₆, 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.Calcld for C₁₉H₁₆N₂O₅: 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. ¹H NMR (300 MHz, DMSO-d₆): 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 (C₁₈H₁₈N₂O₅). Anal.Calcld for
C₆H₃N₂O₂: 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 NaNO₂ (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. 224°C, FT-IR (KBr, cm⁻¹): (νC=O’s) 1741, 1695, 1685; (νNH) 3308. ¹H NMR (300 MHz, DMSO-d₆): δ 2.57 (t, 2H, 2CH₂); 3.17 (s, 2H, CH₂); 3.65 (t, 4H, 2CH₂-O); 7.22-7.95 (m, 4H, arom.H); 10.3 (s, 1H, NH); 11.6 (s, 1H, NH). Anal.Calcd.for C₁₅H₁₂N₂O₂: C, 59.59; H, 6.0; N, 18.53. Found: C, 60.05; H, 5.98; N, 18.51 %.

Compounds (6-9)

Compound 6 (0.5 gm., 2 mmol) was added to a solution of 1H-quinazolin-2,4-dione (1 mmol) in absolute ethanol (30 ml) in presence of K₂CO₃ (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 1H,3H-quinazolin-2,4-dione 6 (1 gm., 4 mmol) and thiourea (4 mmol) in ethanol (20 ml) in presence of anhydrous K₂CO₃ (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 dichloromethane 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): (νC=O’s) 1760, 1690; (νNH) 3431. ¹H NMR (300 MHz, DMSO-d₆): δ 2.40 (s, 4H, 2CH₂); 6.88-7.79 (s, 2H, arom.H); 9.87 (s, 1H, NH). MS showed protonated molecular ion peak (M+H)+ at (m/z, %): 255 (100 %) correspond to the molecular formula (C₁₃H₁₁NO₂Cl). Anal.Calcd.for C₁₃H₁₁NO₂Cl: C, 47.43; H, 3.51; N, 17.10. Found: C, 47.50; H, 3.53; N, 17.19 %.

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 K₂CO₃ (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).
An equimolar amounts of compound 6 (0.5 gm., 2 mmol) and 2-mercaptopbenzothiazole (0.5gm., 3mmol) in acetone (30 ml) in presence of dry K$_2$CO$_3$ (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-quinoxalin-5-one 10 in yield 90% as yellow crystals (Scheme 4). M.P. 260°C FT-IR (KBr, cm$^{-1}$): (v C=O) 1715, 1685; (v NH) 3230-3200. $^1$H NMR (200 MHz, DMSO-d$_6$): δ 6.17 (s, 2H, CH$_2$); 7.19-7.97 (m, 5H, arom.HH); 10.72 (s, 1H, NH); 11.7 (s, 1H, NH). MS (m/z,%): 275 (1.44 %) correspond to the molecular formula (C$_{12}$H$_7$N$_2$O$_5$S). Anal.Calcd.for C$_{12}$H$_7$N$_2$O$_5$S: C, 47.99; H, 3.30; N, 25.42; S, 11.63 %.

RESULTS AND DISCUSSION

Owing to the important of quinoxaline derivatives which documented in our previous studies, here we have developed the synthesis of some new interesting derivatives of quinoxalin-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-quinoxalin-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-tetraene and 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. Diazotation 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-fquinozalin-2,4-dione. Scheme3 illustrates the way used to synthesize the requisite starting material 2-chloro-N-(2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-yl)acetamide 6 which was used in the synthesis of several quinoxalin-2,4-one derivatives. Treatment of 3-amino-1H-quinozingalin-2,4-dione 1 with chloroacetyl chloride drop by drop with stirring in DMF followed by addition of H$_2$O gave 2-chloro-N-(2,4-dioxo-1,4-dihydro-2H-quinoxalin-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$_2$CO$_3$, it gave the corresponding imides N-(2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-yl)-2-piperidin-1-yl-acetamide 7a, N-(2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-yl)-2-morpholin-4-yl-acetamide 7b and 1,4-bis[(2,4-dioxo-1,4-dihydro-2H-quinoxalin-3-yl-carbamoyl)-methyl]piperazine 8 respectively. Furthermore, we investigated the effect of urea, thiourea and thiocyanates on compound 6 as shown in (Scheme 4). Addition of urea to starting material under reflux until ammonia odour has ceased, it afforded 3-(2,5-dioxo-imidazolin-1-yl)-1H-quinozingalin-2,4-dione 9a. Similarly when compound 6 was added to thiourea, it afforded 3-(2-thioxo-2,5-dihydro-1H-imidazid-4-yl-amino)-1H-quinozingalin-2,4-dione 9b. The reaction of compound 6 with 2-mercaptopbenzothiazole in acetone yielded 2-(Benzothiazol-2-yl-sulfanyl-methyl)(1,3,4)oxadiazolo[2,3-b]-4H,5H-quinoxalin-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-3-yl)-1H-quinozingalin-2,4-dione (E-form) 11a and (Z-form) 11b in a ratio of 2:1 respectively. 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.
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REFERENCES


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