Utility of (2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetic acid hydrazide in the synthesis of some heterocyclic nitrogen compounds

Mamdouh Adly Hassan a, Maghrabi Ali Seleem b, Ahmed Mohamed Mosalem Younes b, Mohamed Mobark Taha b and Abou-Bakr Haredi Abdel-Monsef b,*

1 Pharmaceutical Chemistry Department, Faculty of Pharmacy, Sinai University, 45518, Arish, Egypt
2 Chemistry Department, Faculty of Science, South Valley University, Qena, 83523, Egypt

*Corresponding author: Chemistry Department, Faculty of Science, South Valley University, Qena, 83523, Egypt.
Tel.: +20.96.5211281; fax: +20.96.5211279; E-mail address: bahosso2004@yahoo.com (A.H. Abdel-Monsef).

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1. Introduction
Quinazolines are made up of two fused six member simple aromatic rings which represents one of the most important class of heterocycles possessing wide spectrum of biological activities and it considered the building block of many biologically active compounds that possess antibacterial [1‐8], anti-inflammatory [1,2,7] and antifungal [5,9,10]. Quinazoline and pyrimidine derivatives are incorporated in a wide variety of pharmaceuticals. In addition, quinazoline and pyrimidine derivatives are attracting important applications in the field of medicinal chemistry; the pyrimidine ring is present in a large number of biological important compounds [11]. This encouraged us to synthesize new quinazoline derivatives attached to interesting heterocycles such as triazole, oxadiazole, pyrazole, pyrrole, pthalazine, and indol-2-one rings at position 3. The structures of the obtained compounds were confirmed by IR, 1H NMR, 13C NMR, MS spectral and elemental analysis.

2. Experimental

2.1. Instrumentation
Melting points were uncorrected and determined on an electric melting point apparatus (Kofler). The IR spectra (KBr) were recorded on a Shimadzu 408 spectrometer. The 1H NMR spectra were recorded using 300 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 with Shimadzu GC-MS (QP-2010 plus). 13C NMR spectra were measured on a JEOL ECA instrument 400 MHz in DMSO-δ6 and carried out at Jacobs University Bremen, Germany. Elemental analyses were carried out at the Microanalysis Unit at Cairo University. The purity of the compounds was detected by TLC.

2.2. Synthesis

2.2.1. 1-[(2,4-Dioxo-1,4-dihydro-2H-quinazolin-3-yl)-methylcarbonyl]-1H-pyrazole-4-thiosemicarbazide (4)

To a mixture of hydrazide 3 (Scheme 1) (2 g, 0.008 mol) in absolute ethanol (20 mL) phenyl isothiocyanate (0.011 mol) was added and the reaction mixture was heated under reflux for 4 hrs., then left to cool. The solid that separated was collected by filtration crystallized from ethanol to afford compound 4 (1.7 g, 0.004 mol) as white crystals (Scheme 2). Yield: 1.7 g, 54 %. M.p.: 220 °C. FT-IR (KBr, ν, cm⁻¹): 3339, 3304, 3292, 3265 (NH's), 1733, 1661, 1635 (C=O's). 1H NMR (300 MHz, DMSO-δ6, δ ppm): 4.7 (s, 2H, CH₂), 7.1-7.9 (m, arom.), 9.3 (s, 1H, NH), 9.7 (s, 1H, NH), 10.4 (s, 1H, NH), 11.6 (s, 1H, NH). 13C NMR (100 MHz, DMSO-δ6, δ ppm): 41.7, 113.6, 115.2, 120.8, 122.7, 124.4, 125.9, 127.3, 128.1, 135.2, 138.9, 139.3, 150.2, 162, 167. MS (m/z %): 369 (3.0 %). Anal. calc. for C₂₅H₁₁N₄O₂S: C, 55.28; H, 3.08; N, 19.02%.

2.2.2. 3-[(5-Mercapto-4-phenyl-1H-1,2,4-triazol-3-ylmethyl)-1H-quinazoline-2,4-dione (5)

Compound 4 was refluxed in NaOH solution (10 mL) for 6 hrs. The mixture was left to cool, filtered, and the filtrate was acidified with dil. HCl. The solid obtained was filtered off, and crystallized from benzene/ethanol to give compound 5 as white crystals (Scheme 2). M.p.: >300 °C. FT-IR (KBr, ν, cm⁻¹): 3126 (NH), 2510 (SH), 1721, 1663 (C=O's). 1H NMR (300 MHz, DMSO-δ6, δ ppm): 4.9 (s, 2H, CH₂), 7.1-7.9 (m, 9H, arom.), 11.6 (s, 1H, NH), 13.8 (s, 1H, SH).
2.2.3. 3-[(5-oxo-5H-[1,2,4]triazolo[3,4-a]isoindol-3-yl)methyl]quinazoline-2,4(1H,3H)-dione (6)

Heating of the hydrazide 3 (1 g, 0.004 mol) with phthalimide (0.75 g, 0.005 mol) in DMF (20 mL) under reflux for 14 hrs. gave a solid product which was filtered off and crystallized from benzene to give compound 6 as yellow crystals (Scheme 2). Yield: 0.4 g, 59 %. M.p.: 224 °C. FT-IR (KBr, v, cm⁻¹): 3300 (NH), 1661, 1635 (C=O's). ¹H NMR (200 MHz, DMSO-d₆, δ, ppm): 8.4 (s, 2H, NH), 7.3-7.9 (m, 8H, arom.), 4.7 (s, 2H, CH₂). Anal. calcd. for C₁₈H₁₃N₅O₄: C, 59.50; H, 3.61; N, 19.28. Found: C, 59.71; H, 3.63; N, 20.32%.

2.2.4. 3-Amino-1-[2-(2,4-dioxo-2H-quinazolin-3-yl)-acetyl]-5-phenyl-1H-pyrazole-4-carbonitrile (7)

Benzylidine malononitrile (0.27 g, 0.002 mol) in ethanol (20 mL) and piperidine as a catalyst was added to hydrazide 3 (0.4 g, 0.002 mol) and the reaction mixture was refluxed for 9 hrs. The formed solid product was filtered off and recrystallized from ethanol to afford compound 7 (0.16 g, 0.0004 mol) as white crystal (Scheme 3). Yield: 0.16 g, 66 %. M.p.: >310 °C. FT-IR (KBr, v, cm⁻¹): 3300 (NH), 1674, 1603 (C=O's). ¹H NMR (300 MHz, DMF-d₆, δ, ppm): 8.4 (s, 2H, CH₂), 7.2-7.9 (m, 9H, arom.), 11.5 (s, 2H, NH₂), 11.7 (s, 1H, NH). ¹³C NMR (100 MHz, DMSO-d₆, δ, ppm): 41.4, 113.4, 115.2, 118.8, 119.3, 122.6, 126.8, 127, 127.3, 128.7, 129.9, 133.9, 135.1, 139.2, 144, 150, 161.7, 168. Anal. calcd. for C₁₅H₁₁N₃O₂: C, 43.28; H, 3.67; N, 22.02%.

2.2.5. (2,4-Dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetic acid (2-oxo-1,2-dihydro-indol-3-ylidene)-hydrazide (8)

Treatment of hydrazide 3 (0.4 g, 0.002 mol) with isatine (0.25 g, 0.002 mol) in acetic acid (20 mL) and reflux for 9 hrs. afforded compound 8 (0.3 g, 0.001 mol) as yellow crystals (Scheme 3). Yield: 0.3 g, 50 %. M.p.: 119.4, 120.8, 122.5, 127.4, 131.7, 135.3, 139.3, 142.5, 149.9, 161.7, 162.4, 199.6, 205.3. MS (m/z, %): 363 (6.0 %). Anal. calcd. for C₁₈H₁₈Cl₄N₄O₅: C, 43.06; H, 1.90; N, 19.66. Found: C, 43.18; H, 1.94; N, 19.70%.

2.2.6. 3-[2-Oxo-2-(5,6,7,8-tetrachloro-1,4-dioxo-1H-phthalazin-2-yl)-ethyl]-1H-quinazoline-2,4-dione (9)

Tetrachlorophthalanic anhydride (1.2 g, 0.004 mol) in acetic acid (20 mL) was added to hydrazide 3 (1 g, 0.004 mol) then the reaction mixture was refluxed for 9 hrs, the formed solid product was filtered off and recrystallized from dioxane to give compound 9 as white crystals (Scheme 3). Yield: 1.2 g, 57 %. M.p.: 310 °C. FT-IR (KBr, v, cm⁻¹): 3304 (NH), 1661, 1635 (C=O's). ¹H NMR (300 MHz, DMSO-d₆, δ, ppm): 4.7 (s, 2H, CH₂), 7.0-7.9 (m, 4H, arom.), 11.2 (s, 1H, NH), 11.6 (s, 1H, NH). MS (m/z, %): 502 (1.27 %). Anal. calcd. for C₂₀H₁₈Cl₄N₄O₄: C, 43.06; H, 1.63; N, 11.92%.
2.2.7. Acetic acid N’-[2-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetyl]-hydrazide (10)

Reflexing of hydrazide 3 (0.5 g, 0.002 mol) with acetic acid (20 mL) for 8 hrs. On cooling, the separated solid was filtered off and crystallized from acetic acid to give compound 10 (0.4 g, 0.0015 mol) as white crystals (Scheme 3). Yield: 0.4 g, 66 %. M.p.: >300 °C. FT-IR (KBr, ν, cm⁻¹): 3304, 3282, 3265 (NH’s), 1733, 1732, 1635 (C=O’s). 1H NMR (300 MHz, DMSO-d₆, δ, ppm): 1.9 (s, 3H, CH₃), 4.5 (s, 2H, CH₂), 7.1-7.9 (m, 4H, arom.), 9.8 (s, 1H, NH), 10.1 (s, 1H, NH), 11.5 (s, 1H, NH). 13C NMR (100 MHz, DMSO-d₆, δ, ppm): 20.9, 41.6, 114.1, 115.7, 123.1, 127.9, 135.7, 139.9, 150.4, 162.3, 166.3, 168.4. MS (m/z, %): 276 (3.0 %). Anal. calcd. for C₁₂H₁₂N₄O₄: C, 52.18; H, 4.37; N, 20.28. Found: C, 52.39; H, 4.39; N, 20.35 %.

3. Results and discussion

In this work, we were able to introduce the amino group which is present in glycine ethyl ester hydrochloride into the sulphonyloxy system in N-phenylsulphonyloxyphthalimide 1 to obtain (2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetic acid ethyl ester 2 which on treatment with hydrazine hydrates in ethanol gave the hydrazide 3 (Scheme 1) [12]. Scheme 4 outlines the synthetic pathway used to obtain (2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetic acid hydrazide 3 [12]. The route outlined in Scheme 2 shown that hydrazide 3 used as a starting material for synthesis of some new quinazoline derivatives attached to interesting heterocycles such as triazole, oxadiazole, pyrazole and phthalazine rings which have biological effects [13,14], and many applications were they are used as fungicidal and bacterial reagents [15].
Scheme 5 and 6 outline the synthetic pathway used to synthesize 1-[[2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl]-methylcarbonyl]-4-phenylthiosemicarbazide 4 and 3-{[5-oxo-5H-1,2,4]triazolo[3,4-d]isoindol-3-yl][methyl]quinoxaline-2,4(1H, 3H)-dione (6). Scheme 3 shows the results of treatment of hydrazide 3 with benzylidine malononitrile, isatine, tetrachlorophthalic anhydride and acetic acid. Treatment of hydrazide 3 with benzylidine malononitrile in ethanol under reflux gave 3-amino-1-[2-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetyl]-5-phenyl-1H-pyrazole-4-carbonitrile, 7, which contains pyrazole ring. As a part of our program aimed to synthesize new rings attached to quinazoline ring as we notice in compounds 8 and 9 which contain indol-2-one and phthalazine rings, respectively, by reacting of hydrazide 3 with isatine and tetrachlorophthalic anhydride, respectively. Treatment of hydrazide 3 with acetic acid under reflux gave acetic acid N'-[2-(2,4-dioxo-1,4-dihydro-2H-quinazolin-3-yl)-acetyl]-hydrazide, 10.

4. Conclusion

The synthesis of new quinazolindione derivatives was achieved and structural verification was achieved by spectral and physical analysis.

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References