Synthesis of Some Biologically Active 4(3*H*)-Quinazolinones Derived from 2,3-Pyridine Dicarboxylic Anhydride

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Abstract

A novel 3-amino-4(3*H*)-quinazolinone was synthesized *via* two routes. The first route involved interaction of 2,3-pyridine dicarboxylic anhydride with anthranilic acid in acetic acid under reflux to give the amide derivative which was subjected to cyclodehydration and treatment with hydrazine hydrate. The second route involved preparation of amide by treatment of 2,3-pyridine dicarboxylic anhydride with methyl anthranilate in glacial acetic acid under reflux, then treated with hydrazine hydrate. Treatment of 3-amino-4(3*H*)-quinazolinone with isocyanate, isothiocyanate, ethyl chloroacetate and diethyl malonate gave urea, thiourea, thiazole and pyrimidine derivatives, respectively. In addition, some bisquinazolines were synthesized. Antimicrobial activities of some selected compounds were screened.

Keywords: 4(3*H*)-Quinazolinone; 2,3-Pyridine dicarboxylic anhydride; Pyridine; Antimicrobial activities.

1. Introduction

The chemistry of 4(3*H*)-quinazolinone system has received an increasing interest because of its biological significance. Many derivatives of this system showed antifungal [1], antibacterial [2], antitumor [3] anti-inflammatory [4] anticonvulsant [5-7] analgesic [8,9] and antitubercular [10,11] activities. Furthermore, pyridine nucleus is well known to be found in a broad variety of drugs such as nicotinamide (3-pyridinecarboxamide) a well-known drug used as respiratory analeptic [12] as well as fungicides [13] pesticides [14] or for treatment of benign prostatic hyperplasia [15]. Considering all these factors it was tough to prepare a new series of 4(3*H*)-quinazolinone derivatives incorporating biologically active pyridine moiety.

2. Methods

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (ν, cm^{-1}). The ^1H NMR spectra were recorded in DMSO-d_6 at 300 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Elemental analyses were carried out by the Microanalytical Research Center, Faculty of Science, Cairo University.

Synthesis of nicotinamido derivatives **2** and **3**

A mixture of 2,3-pyridine dicarboxylic anhydride (**1**) (0.01 mol) and anthranilic acid or methyl anthranilate (0.01 mol) in acetic acid (20 ml) was heated under reflux for 3 hrs., then allowed to cool. The solid product was collected and recrystallized from acetic acid to give **2** and **3,** respectively.

2-(Nicotinamido)benzoic acid (**2**):

Yield 55%, m.p 269-270 °C. Anal. Calcd for $C_{13}H_{10}N_2O_3$: C, 64.46; H, 4.16; N, 11.56. Found: C, 64.50; H, 4.20; N, 11.60. IR: ν/cm^{-1}: 3168 (NH) and 1668 (C=O). ^{1}HNMR: δ/ppm: 7.58 – 8.80 (m, 8H, ArH + NH), 9.11 (s, 1H, ArH at C_2-H of pyridine), 12.08 (s, 1H, OH). MS,

m/z: 242 (M^+; 23.2%), 243 (M+1; 4.1%), 241 (M-1; 13.3%), 198 (M-CO_2; 2.1%), 197 (M-COOH; 4.7%), 119 (34.5%), 106 (100%), 79 (pyridine moiety; 8.9%), 77 (pyridyne; 47%).

Methyl 2-(nicotinamido)benzoate (**3**):

Yield 65%, m.p 104-105 °C. Anal. Calcd for $C_{14}H_{12}N_2O_3$: C, 65.62; H, 4.69; N, 10.94. Found: C, 65.60; H, 4.70; N, 11.00. IR: ν/cm^{-1}: 3302 (NH), 2956(CH-aliph.) and 1680 (C=O). ^{1}HNMR: δ/ppm: 3.8 (s, 3H, OCH_3), 7.2 (d, 1H, Ar-H), 7.3-7.8 (m, 6H, Ar-H + CH-pyridine), 9.2 (s, 1H, CH-pyridine), 11.2 (s, 1H, NH).

Synthesis of 2-(pyridin-3-yl)-4H-benzo[d][1,3]oxazin-4-one (**4**)

A solution of compound **2** (0.01 mol) in acetic anhydride (20 ml) was refluxed for 1 hr., then allowed to cool. The solid product was collected and recrystallized from ethanol to give **4** as pale yellow crystals, yield 80%, m.p 139-140 °C. Anal. Calcd for $C_{13}H_8N_2O_2$: C, 69.64; H, 3.60; N, 12.49. Found: C, 69.60; H, 3.60; N, 12.50. IR: ν/cm^{-1}: 1762 (C=O). ^{1}HNMR: δ/ppm: 7.7 (m, 3H, Ar-H), 7.9 (t, 1H, CH-pyridine), 8.2 (d, 1H, Ar-H), 8.5 (d, 1H, CH-pyridine), 8.8 (d, 1H, CH-pyridine), 9.3 (s, 1H, CH-pyridine). MS, m/z: 224 (M^+,96.4%) 180 (M-CO_2; 19.7%), 196 (M-CO; 43.6%), 146 (M-pyridinyl; 41.3%), 118 (4.2%), 78 (2-pyridinyl; 100%) and 77 (pyridyne; 11.7%).

Synthesis of 3-amino-2-(pyridin-3-yl)-4-quinazolinone (**5**)

A mixture of compound **3** or **4** (0.01 mol) and hydrazine hydrate (0.012 mol) in *n*-butanol (30 ml) was refluxed for 1 hr., then allowed to cool. The solid product was collected and recrystallized from ethanol to give **5** as colorless crystals, yield 80-85%. m.p 199-200 °C. Anal. Calcd for $C_{13}H_{10}N_4O$: C, 65.54; H, 4.23; N, 23.52. Found: C, 65.50; H, 4.20; N, 23.50. IR: ν/cm^{-1}: 3301, 3209 (NH_2), 3039 (CH-arom.) and 1643 (C=O). ^{1}HNMR: δ/ppm: 5.71 (b, 2H, NH_2, D_2O-exchangeable), 7.7 - 7.9 (m, 4H, Ar-H), 8.2 (d, 1H, Ar-H), 8.5 (d, 1H, CH-pyridine), 8.8 (d, 1H, CH-pyridine), 8.99 (s, 1H, CH-pyridine). MS, m/z: 224 (M^+;3.7%), 221 (50.0%), 209 (61.1%), 174 (20.9%), 119 (86.0%), 78 (53.2%), 77 (62.3%), 76 (70.2%) and 50 (92.6%).

2-(2-(Methoxycarbonyl)phenylcarbamoyl)nicotinic acid (**6**)

A mixture of 2,3-pyridine dicarboxylic anhydride **1** (0.01 mol) and methyl 2-aminobenzoate (0.01 mol) in glacial acetic acid (30 ml) was stirred for 0.5 hr at room temperature. The solid product was collected and recrystallized from the ethanol to give **6** as colorless crystals, yield 80-85%. m.p 174-176 °C. Anal. Calcd for $C_{15}H_{12}N_2O_5$: C, 60.00; H, 4.00; N, 9.30. Found: C, 60.30; H, 4.20; N, 9.50. IR: ν/cm-1: 3156 (OH,NH), 2968 (CH-aliph), and 1746, 1700, 1660 (νC=O). ^{1}HNMR: δ/ppm: 4.0 (s, 3H, OCH_3), 7.2-9.2 (m, 8H, Ar-H+NH), 13.8 (s, 1H, OH).

Synthesis of 5-hydroxy-1,6,6a,12-tetraaza-benzo[a]anth-acen-7-one (**7**)

A mixture of compound **6** (0.01 mol) and hydrazine hydrate (0.012 mol) in ethanol (30 ml) was refluxed for 6 hrs; then allowed to cool. The solid product was collected and recrystallized from acetic acid to give **7** as yellow crystals, yield 77%, m.p. >300 °C. Anal. Calcd for $C_{14}H_8N_4O_2$: C, 63.64; H, 3.05; N, 21.20. Found: C, 63.60; H, 2.90; N, 21.10. IR: ν/cm^{-1}: 3426 (OH) and 1694, 1634 (C=O). ^{1}HNMR: δ/ppm: 7.66 (t, 1H, pyridine-H), 7.93-7.99 (m, 4H, Ar-H), 8.3, 8.56(2d, 2H, pyridine-H), 9.22 (s, 1H,OH), MS, m/z: 264 (M^+; 100%), 265 (M+1; 23.6%), 236 (M-CO; 7.4%), 179 (81%), 153 (22.7%), 105 (16.1%), 92 (12.4%) and 77 (36.8%).

General procedure for the preparation of 4-oxo-2-pyridin-3-yl-4*H*-quinazolin-3-yl)-urea (or thiourea) derivatives (**8a-c**)

A mixture of compound **5** (0.01 mol) and isocyanate or isothiocyanate derivatives (0.01 mol) in dioxane (30 ml) was refluxed for 3 hrs., then allowed to cool, the solid product was collected and recrystallized from ethanol to give **8a-c**.

1-Ethyl-3-(4-oxo-2-(pyridin-3-yl-)-quinazolin-3(4*H*)-yl)thiourea (**8a**):

Yield 75%, m.p 218-220 °C. Anal. Calcd. for $C_{16}H_{15}N_5OS$: C, 59.06; H, 4.65; N, 21.52. Found: C, 59.00; H, 4.60; N, 21.50. IR: ν/cm^{-1}: 3308, 3274 (NH), 2942 (CH-aliph.) and 1666 (C=O). ^{1}HNMR: δ/ppm: 1.0 (t, 3H, CH_3), 3.4 (q, 2H, CH_2), 7.2 (t, 1H, Ar-H), 7.6 (t, 1H, Ar-H), 7.7 (d, 1H, Ar-H), 8.2(m, 2H, CH-pyridine), 9.3 (s, 1H, CH-pyridine), 10.6 (s, 1H, NH), 11.7 (s, 1H, NH), MS, m/z: 324(M^+; 23%), 51(100%).

1-(4-Oxo-2-(pyridin-3-yl)-quinazolin-3(4*H*)-yl)-3-phenylurea (**8b**):

Yield 70%, m.p 208-210 °C. Anal. Calcd. for $C_{20}H_{15}N_5O_2$: C, 67.22; H, 4.23; N, 19.60. Found: C, 67.10; H, 4.20; N, 19.50. IR: ν/cm^{-1}: 3298 (NH) and 1668 (C=O).

1-(4-Oxo-2-(pyridin-3-yl)-quinazolin-3(4*H*)-yl)-3-phenylthiourea (**8c**):

Yield 65%, m.p 213-215 °C. Anal. Calcd for $C_{20}H_{15}N_5OS$: C, 64.33; H, 4.05; N, 18.75. Found: C, 64.30; H, 4.00; N, 18.70. IR: ν/cm^{-1}: 3326 (NH) and 1664 (C=O). ^{1}HNMR: δ/ppm: 7.2 - 7.8 (m, 10H, Ar-H), 8.2 (m, 2H, CH-pyridine), 9.3 (s, 1H, CH-pyridine), 10.7 (s, 1H, NH), 11.6 (s, 1H, NH).

General procedure for the synthesis of 3-(3-substituted-4-hydroxy-3*H*-thiazol-2-ylideneamino)-2-pyridin-3-yl-3*H*-quinazolin-4-one derivatives (**9a,b**)

To a both solution of **8a** or **8c** (0.01 mol) in acetic acid (30 ml), ethyl chloroacetate (0.01 mol) was added. The reaction mixture was heated under reflux for 3 hrs, then allowed to cool, the solid product was collected and recrystallized from ethanol to give **9a,b**.

3-(3-Ethyl-4-hydroxythiazol-2(3*H*)-ylideneamino)-2-(pyridin-3-yl)-quinazolin-4(3*H*)-one (**9a**):

Yield 70%, m.p 164-165 °C. Anal. Calcd. for $C_{18}H_{15}N_5O_2S$: C, 59.16; H, 4.14; N, 19.17. Found: C, 59.10; H, 4.10; N, 19.10. IR: ν/cm^{-1}: 3418 (OH) and 1704, 1660 (C=O). ^{1}HNMR: δ/ppm: 1.1 (t, 3H, CH_3), 3.5 (q, 2H, CH_2), 4.00 (s, 2H, CH_2[thiazole]), 7.30-8.3 (m, 7H, ArH), 9.3 (s, 1H, CH-pyridine), 10.78 (s, 1H, OH, D_2O-exchangeable). MS, 365(M^+;23%), 290 (22.9%), 223 (82.7%) 119 (100%).

3-(4-Hydroxy-3-phenylthiazol-2(3*H*)-ylideneamino)-2-(pyridin-3-yl)-4(3*H*)-quinazolinone (**9b**):

Yield 70%, m.p 174-175 °C. Anal. Calcd. for $C_{22}H_{15}N_5O_2S$: C, 63.91; H, 3.66; N, 16.94. Found: C, 63.90; H, 3.70; N, 16.90. IR: ν/cm^{-1}: 1676 (C=O). MS, 413(M^+; 24%), 290 (55%), 268 (82%), 223 (20%), 149 (41%), 77 (100%).

General procedure for the synthesis of 1-alkyl or aryl-6-hydroxy-3-(4-thio(oxo)-2-pyridin-3-yl-4*H*-quinazolin-3-yl)-1*H*-pyrimidine-2,4-diones (**10a-c**)

To a mixture of **8a-c** (0.01 mol) and diethylmalonate (0.01 mol) in ethanol (30 ml) sodium ethoxide was added. The reaction mixture was heated under reflux for 3 hrs, then allowed to cool and poured into cold water. The solid product was collected and recrystallized from ethanol to give **10a-c**.

3-(3-Ethyl-4-hydroxy-6-oxo-2-thioxo-2,3-dihydropyrimidin-1(6*H*)-yl)-2-(pyridin-3-yl)-4(3*H*)-quinazolinone (**10a**):

Yield 70%, m.p 218-220 °C. Anal. Calcd. for $C_{19}H_{15}N_5O_3S$: C, 58.01; H, 3.84; N, 17.80. Found: C, 58.00; H, 3.80; N, 17.90. IR: ν/cm^{-1}: 3412 (OH), 2942 (CH-aliph.) and 1660 (C=O). ^{1}HNMR: δ/ppm: 1.2 (t, 3H, CH_3), 3.9 (q, 2H, CH_2), 7.43 (s, 1H, CH-olefinic), 7.47-8.9 (m, 8H, Ar-H), 10.59 (s, 1H,OH), MS, m/z 393(M^+; 24%), 368 (42.5%), 341 (30.3%), 303 (44.5%), 227 (50%), 200 (56.3%), 178 (40.4%), 115(100%).

6-Hydroxy-3-(4-oxo-2-(pyridin-3-yl)-quinazolin-3(4*H*)-yl)-1-phenyl pyrimidine-2,4(1*H*,3*H*)-dione (**10b**):

Yield 70%, m.p 238-240 °C. Anal. calcd for $C_{23}H_{15}N_5O_4$: C, 64.94; H, 3.55; N, 16.46. Found: C, 64.90; H, 3.60; N, 16.40. IR: ν/cm^{-1}: 1679 (C=O). MS, 525 (M^+), 289 (100%).

3-(4-Hydroxy-6-oxo-3-phenyl-2-thioxo-2,3-dihydropyrimidin-1(6*H*)-yl)-2-(pyridin-3-yl)quinazolin-4(3*H*)-one (**10c**)

Yield 70%, m.p 179-180 °C. Anal. Calcd. for $C_{23}H_{15}N_5O_3S$: C, 62.58; H, 3.42; N, 15.86. Found: C, 62.50; H, 3.40; N, 15.90.IR: ν/cm^{-1}: 3290 (OH) and 1648 (C=O). ^{1}HNMR: δ/ppm: 7.43 (s, 1H, CH-olefinic), 7.47-8.9 (m, 13H, Ar-H), 10.59 (s, 1H, OH).

General procedure for the synthesis of 3,3'-(1,4-phenylene or 4,4'-sulfonylbis(4,1-phenylene))bis(2-(pyridin-3-yl)quinazolin-4(3*H*)-one) (**11a,b**)

A mixture of compound **4** (0.02 mol) and 1,4-phenylenediamine or 4,4- diaminodiphenylsulfone (0.01 mol) in glacial acetic acid (30 ml) containing freshly prepared anhydrous sodium acetate was refluxed for 3 hrs., then allowed to cool and poured into cold water. The solid product was collected and recrystallized from ethanol to give **11a,b** as green crystals.

3,3'-(1,4-Phenylene)bis(2-(pyridin-3-yl)quinazolin-4(3*H*)-one) (**11a**):

Yield 70%, m.p 248-251 °C. Anal. calcd for $C_{32}H_{20}N_6O_2$: C, 73.84; H, 3.87; N, 16.14. Found: C, 73.80; H, 3.80; N, 16.10. IR: ν/cm^{-1}: 1678 (C=O). ^{1}HNMR: δ/ppm: 7.2-9.1 (m, 20H, Ar-H). MS, 530 (M^+) 289 (100%).

3,3'-(4,4'-Sulfonylbis(4,1-phenylene))bis(2-(pyridin-3-yl)-4(3*H*)-quinazolinone) (**11b**):

Yield 80%, m.p 258-261 °C. Anal. calcd for $C_{38}H_{24}N_6O_4S$: C, 69.08; H, 3.66; N, 12.72. Found: C, 69.00; H, 3.60; N, 12.70. IR: ν/cm^{-1}: 1661 (C=O). MS, z m/z 660 (M^+; 10.4) 224 (100%).

Synthesis of *N*1,*N*4-bis(4-oxo-2-(pyridin-3-yl)-3(4*H*)-quinazolinyl) terephthalamide (**12**)

A mixture of compound **5** (0.02 mol) and diethyl terephthalate (0.01 mol) in DMF (30 ml) was heated under reflux for 3 hrs., then allowed to cool and poured into cold water (100 ml). The solid product was collected and recrystallized from ethanol to give **12** as brown crystals, yield 85%, m.p >300°C. Anal. Calcd. for $C_{34}H_{22}N_8O_4$: C, 67.32; H, 3.66; N, 18.47. Found: C, 67.30; H, 3.60; N, 18.40. IR: ν/cm^{-1}: 3290 (NH) and 1660 (C=O). MS, 606 (M^+; 2.3%), 552 (10.55%), 524 (8.5%), 404 (8.5%), 367 (33.03%), 230 (53.20), 178 (95%), 97 (100%).

3,3'-(1,4-Phenylenebis(methan-1-yl-1-ylidene))bis(azan-1-yl-1-ylidene)bis(2-(pyridin-3-yl)-4(3*H*)-quinazolinone) (**13**)

A mixture of compound **5** (0.02 mol) and *ter*-phthalaaldehyde (0.01 mol) in ethanol (30 ml) was heated under reflux for 3 hrs., the solid which formed on heating was collected and recrystallized from methanol to give **13** as yellow green crystals, yield 85%, m.p 258-261 °C. Anal. Calcd. for $C_{34}H_{22}N_8O_2$: C, 71.07; H, 3.86; N, 19.50. Found: C, 71.00; H, 3.80; N, 19.60. IR: ν/cm^{-1}: 1669 (C=O). ^{1}HNMR: δ/ppm: 7.30-8.3 (m, 18H, ArH), 9.1 (s, 2H, CH=N), 9.3 (s, 2H, CH-pyridine), MS, 582 (M^+), 119 (100%).

3. Results and Discussion

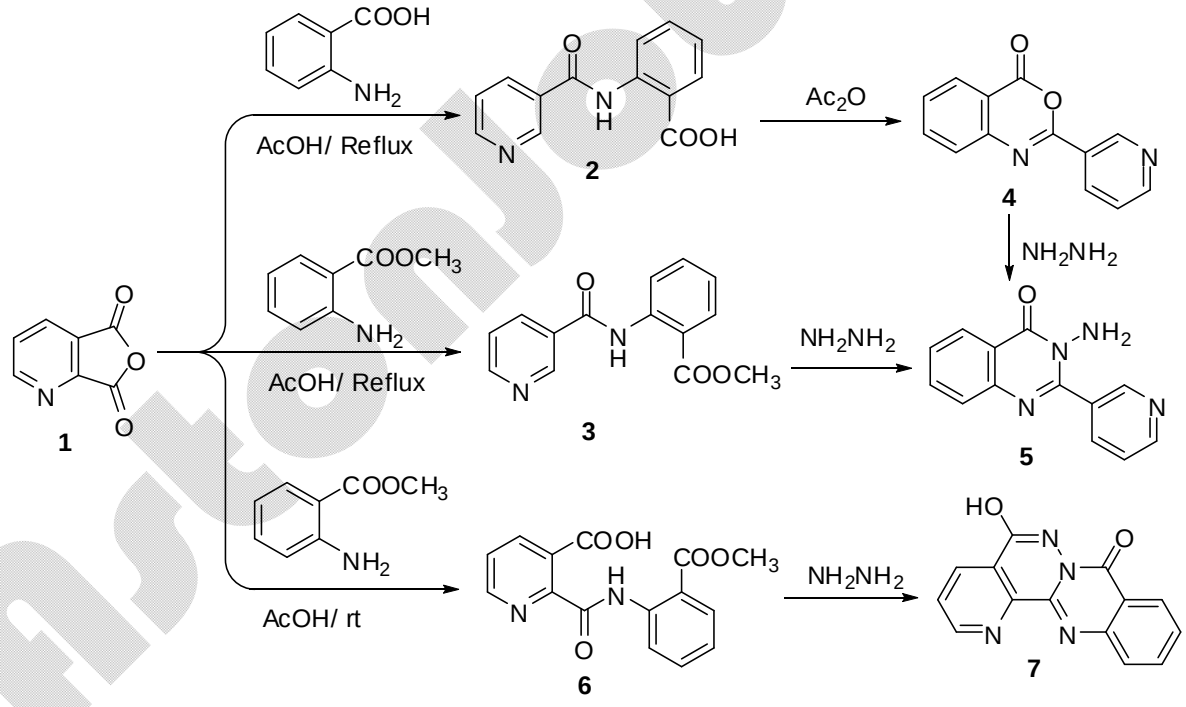
The most common approaches to synthesize 4(3*H*)-quinazolinone derivatives involve amidation of 2-aminobenzoic acid derivatives, then treatment of the amidated anthranilic acid derivatives with acetic anhydride to afford benzoxazinones, followed by their condensation with nitrogen nucleophiles. Here the amidated anthranilic acid was synthesized by novel route. Thus interaction of 2,3-pyridine dicarboxylic anhydride (**1**) with anthranilic acid in glacial acetic acid under reflux afforded amidated anthranilic acid **2**.

An important evidence for structure **2** was arrived at through its synthesis from nicotinyl chloride and anthranilic acid [16]. On the other hand, amidated methyl anthranilate **3** was prepared by treatment of pyridine dicarboxylic anhydride (**1**) with methyl anthranilate in the same condition (Scheme 1).

Structure of the nicotinamide **2** supported based on correct analytical data and by studying the IR and mass spectral data. Analytical and spectral data supported the suggested structure. Structures of the amide **3** was predicted by careful studying of there spectral data. IR spectrum showed bands at: 3302, 2956 and 1680 cm^{-1} attributed for NH, aliphatic proton, C=O. Its ^{1}HNMR spectrum showed peaks at 3.8 and 11.2 ppm characterized for OCH_3 and NH groups, respectively.

Cyclodehydration of the amide **2** upon heating under reflux in acetic anhydride afforded 3,1-benzoxazin-4-one **4**, in good yield. The structure of the benzoxazine **4** was inferred from their microanalysis and spectral data. Their IR spectrum was characterized by disappearance of the bands of OH, NH groups and appearance of strong band in the 1762 cm^{-1} characteristic of the lactone group. ^{1}HNMR spectrum revealed signals at: δ = 7.7 (m, 3H, Ar-H), 7.9 (t, 1H, CH-pyridine), 8.2 (d, 1H, Ar-H), 8.5 (d, 1H, CH-pyridine), 8.8 (d, 1H, CH-pyridine), 9.3 (s, 1H, CH-pyridine), the mass spectrum of compound ($C_{13}H_8N_2O_2$) displayed molecular ion peak at m/z 224 (M^+; 96.4%) and other significant peaks were observed at m/z 180 (M-CO_2; 19.7%), 196 (M-CO; 43.6%), 146 (M-pyridinyl; 41.3%), 78 (2-pyridinyl; 100%) and 77 (pyridyne; 11.7%),

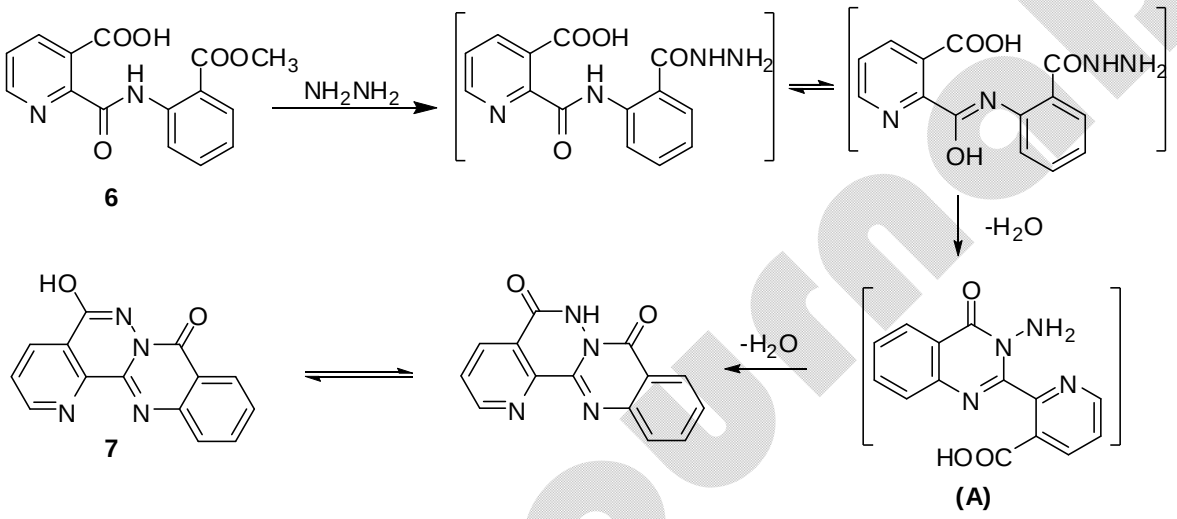
When 2-pyridinyl-3,1-benzoxazinones (**4**) was left to react with hydrazine hydrate in *n*-butanol under reflux, the corresponding 3-amino-2-pyridinyl-4(3*H*)-quinazolinone (**5**) was formed in good yield (Scheme 1). Also, the same product **5** was obtained by treatment of amide **3** with hydrazine hydrate (m.p. and mixed m.p.). IR spectrum of **5** showed characteristic absorption bands of amino group in 3301, 3209 cm^{-1} and band at 1677 cm^{-1} attributed for quinazolinone C=O group. Mass spectrum of compound **5** showed a molecular ion peak at: m/z = 238(M^+; 59.6%) corresponding to the molecular formula $C_{13}H_{10}N_4O$ with a base peak at: m/z = 78 (pyridine moiety).



Scheme 1. Preparation of 3-amino-2-pyridinyl-4(3*H*)-quinazolinone (**5**).

Treatment of pyridine dicarboxylic anhydride **1** with methyl 2-aminobenzoate in glacial acetic acid at room temperature gave **6**. The same products were arrived by repeating the same reaction in toluene at reflux conditions (m.p. and mixed m.p). Double cyclization

was occurred when compound **6** was heated with hydrazine hydrate in ethanol and produced the tetracyclic structure **7** on the basis of elemental and spectral data. IR spectrum of compound **7** showed absorption band at: 3426 (OH) and 1694 cm^{-1} (C=O). ^{1}HNMR spectrum displayed the following signals at: δ= 7.66 (t, 1H, pyridine-H), 7.93-7.99 (m, 4H, Ar-H), 8.3, 8.56(2d, 2H, pyridine-H), 9.22 (s, 1H, OH), Also, mass spectrum exhibited a molecular ion peak at m/z 264(M^+) which was the base peak in the spectrum. The formation of **7** on reaction of **6** with hydrazine hydrate was assumed to proceed through the formation of the 3-aminoquinazoline (A) as an intermediate, which readily cyclized through elimination of water (Scheme 2).



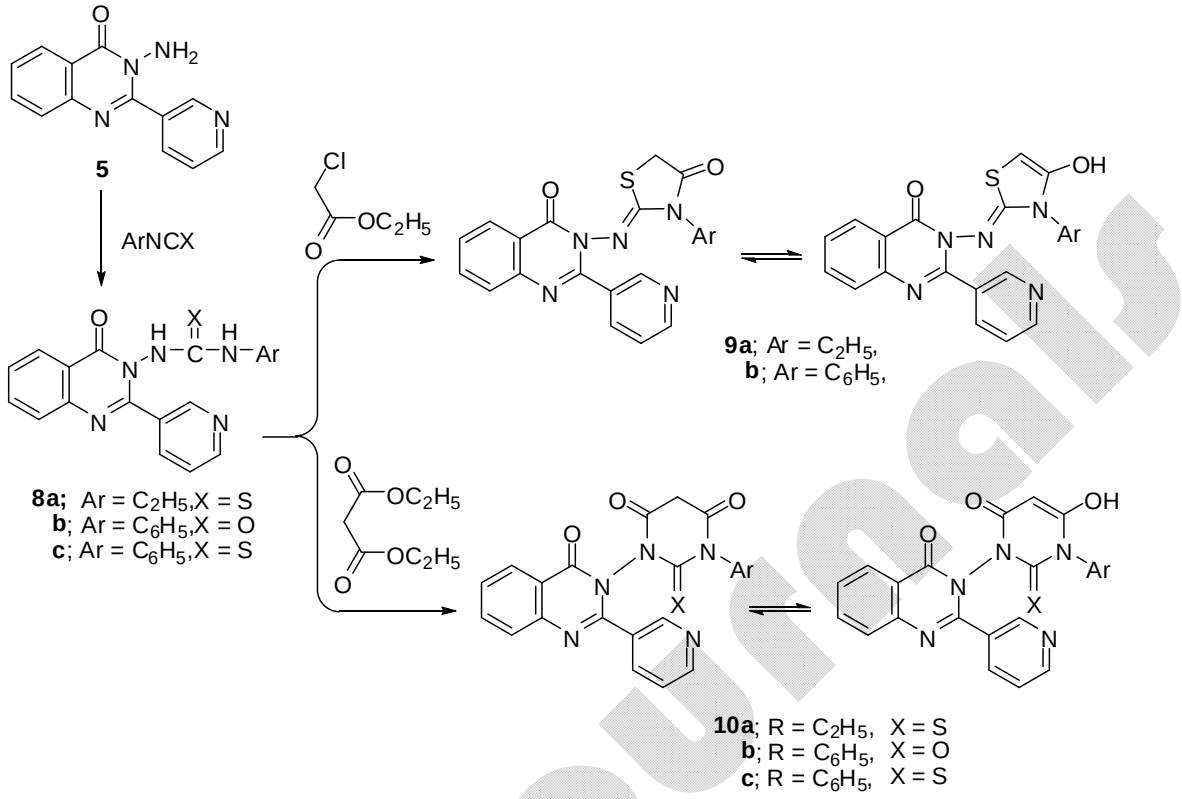
Scheme 2. Suggested mechanism for compound **7.**

Hypoglycemic [17] activity of some urea and thiourea derivatives led us to synthesize some quinazolinone derivatives containing urea or thiourea moieties. Thus, treatment of compound **5** with of isocyanate or isothiocyanate derivatives in dioxane under reflux gave compound **8a-c**. Structure of the urea and thiourea derivatives was deduced from their correct elemental analyses and spectral data. IR spectra were characterized by appearance of absorption bands at: 3326-3274 cm^{-1} region attributed to the stretching vibration of the NH group. All derivatives showed bands at 1668-1664 cm^{-1} for quinazolinone C=O group. ^{1}HNMR spectrum of **8a** was compatible with the assigned structure and revealed signals at: 1.0 (t, 3H, CH_3), 3.4 (q, 2H, CH_2), 7.2 (t, 1H, Ar-H), 7.6 (t, 1H, Ar-H), 7.7 (d, 1H, Ar-H), 8.2 (m, 2H, CH-pyridine), 9.3 (s, 1H, CH-pyridine), 10.6 (s, 1H, NH), 11.7 (s, 1H, NH). Its mass spectrum showed a molecular ion peak at m/z 309 (M^+) with a base peak at 51 (100%).

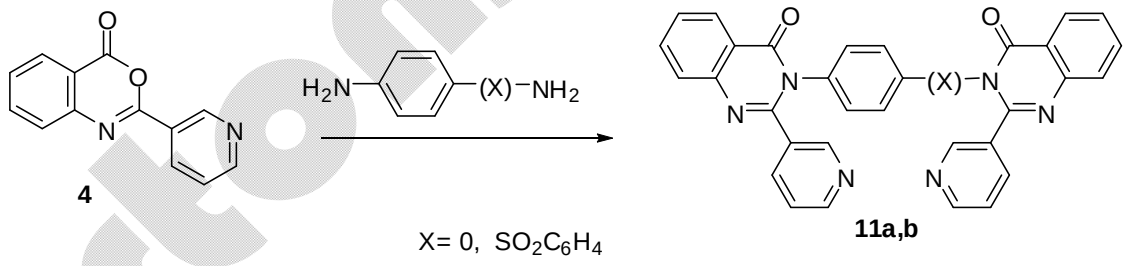
Remarkable pharmacological and biological activities of 4-thiazolidinone [18] and quinazolinone derivatives encourage the authors to prepare some new quinazolinone derivatives containing thiazolidinone moiety, which were expected to have better biological activities. Thus, when compounds **8a,c** were treated with ethyl chloroacetate in acetic acid under reflux gave thiazoles **9a,b**. All analytical and spectral data supported the suggested structures (Scheme 3).

Diverse biological activities are reported for barbiturates [19] and it was therefore desirable to synthesize some barbiturates containing quinazolinone and pyridine nucleus. When compounds **8a-c** were allowed to react with diethyl malonate in ethanol under reflux in presence of sodium ethoxide, the pyrimidine derivatives **10a-c** were formed. Also diagnostically important signals in the ^{1}HNMR spectrum of **10a** were three singlets, triplet at 1.20, quartet at 3.94 attributed to ethyl group and singlet at 10.59 for OH group. Mass spectrum of compound **10a** revealed a molecular ion peak at m/z 393(M^+) corresponding to the molecular formula $C_{19}H_{15}N_5O_3S$ with a base peak at: m/z 115.

Bisheterocyclic compounds exhibit various biological activities [20]. Condensation of two moles of compound **4** with one mole of a 1,4-phenylenediamine or 4,4`-diaminodiphenyl-sulfone in glacial acetic acid under reflux resulted in bisquinazolines **11a,b**. The formation of these products were supported by analytical and the spectral data (Scheme 4).

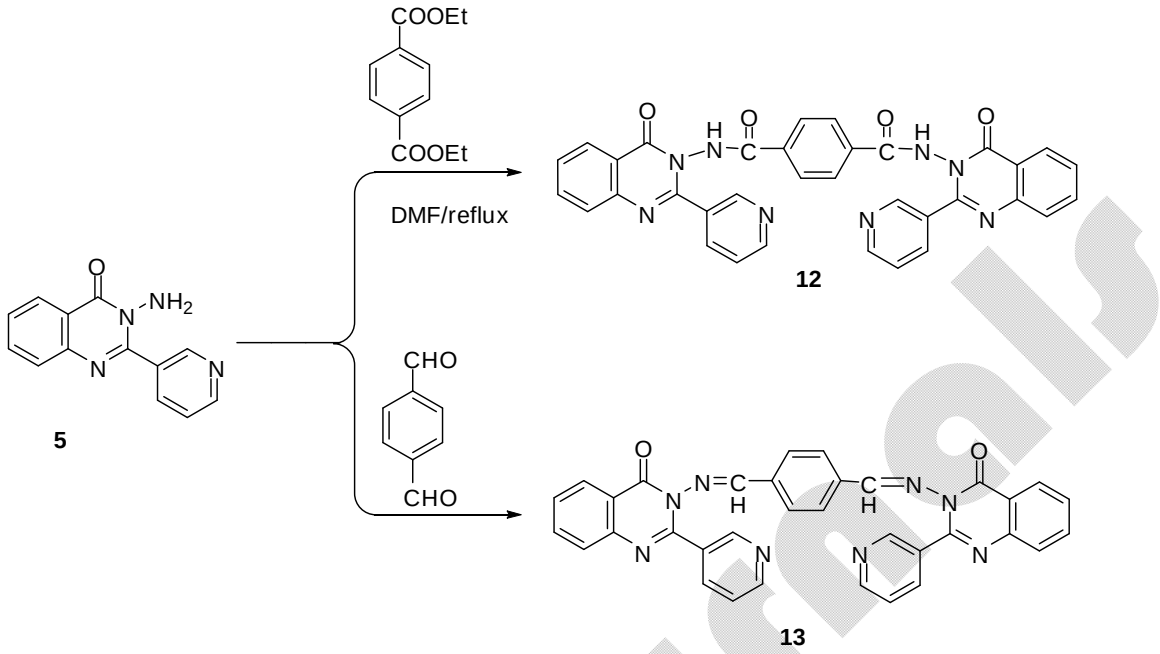


Scheme 3.



Scheme 4.

Bisquinazolinone **12** was obtained when two moles of compound **5** was condensed with one mole of diethyl terphthalate. Also, *ter*-phthaldehyde was condensed with amino-quinazolinone **5** in refluxing ethanol to give novel azomethine **13**. The structures of compound **12** and **13** were established by analytical and spectral data. The infrared spectrum of compound **12** showed bands at 3290 cm^{-1} (NH) and 1660 cm^{-1} (C=O). Its mass spectrum revealed a molecular ion peak at m/z 606 (M^+; 2.3%) which is corresponding to the molecular formula $C_{34}H_{22}N_8O_4$ with a base peak at m/z 97 (100%). IR spectrum of **13** was characterized by presence band of NH group and appearance of strong band at: 1669 cm^{-1}, characteristic of C=O group. Its mass spectrum exhibited a molecular ion peak at: m/z 578 (M^+; %) with a base at 119 (Scheme 5).



Scheme 5.

The preliminary *in vitro* antimicrobial activity screening for some selected examples of the synthesized compounds was carried out using paper disc method [21] against six test organisms representing three different microbial groups: Group 1: (Gram-positive bacteria) *Bacillus subtilis* and *Sarcina sp*. Group 2: (Gram-negative bacteria) *Salmonella typhi* and *Klebsiella pneunmonia*. Group 3: (Fungi) *Aspergillus ochraceus Wilhelm* and *Penicillium chrysogenum thom*. Fresh stock solutions (1mg/ml) of the tested compounds were prepared in redistilled DMSO according to the required concentrations. The results concerning *in vitro* antimicrobial activities of some synthesized compounds together with the inhibition zone (mm) and (MIC) values of comparative antibiotic and antifungal activities were presented in Table 1.

Table 1. Data of antimicrobial activities of some synthesized compounds.

Compound No.	Gram +ve		Gram –ve		Fungi	
	B. Sub.	***Sarcina sp.***	***Klebsiella pneunmoniae***	***Salmonella typhi***	***Penicillium* sp.**	***Aspergillus* sp.**
2	-	7	-	8	-	-
3	9	17 (12.5)	10	14	9	10
4	10	8	7	7	10	9
5	9	8	9	10	9	8
7	15 (12.5)	8	7	9	0	8
Erthromycin	30	19	15	16	-	-
Noroxin	35	27	17	15	-	-
Nystatin	-	-	-	-	16	20

The results indicated that most of the tested compounds showed moderate antimicrobial activity, in which compounds **3** and **7** exhibited good activity against standard organisms.

4. Conclusion

Novel 4(3*H*)-quinazolinone derivatives having pyridine, urea, thiourea, thiazole and pyrimidine moieties were synthesized and characterized. Screening of some selected compounds was carried out for their potential antimicrobial activity.

Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

YAA, YAM and AME made the plan, explained data, and dissected the results involved in the preparation of manuscript. MSAE and SYA carried out experimental work and reviewed the scientific background.

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Plant and Microbiology Department, Faculty of Science, Al-Azhar University, carried out antimicrobial screening.

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