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Synthesis and antimicrobial activity of some new 2,3-disubstituted quinazoline-4(3*H*)-ones derivatives

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ABSTRACT

A new series of 2, 3-substituted quinazoline-4(3H)-ones were prepared by condensation of different amino acids with either 2-methyl or 2-phenyl- 4H-3,1-benzoxazin-4-one in refluxing pyridine. The structures of all compounds have been evaluated by elemental analysis and spectral analysis (IR, MS and 1H NMR). The antimicrobial activity of the newly synthesized compounds was tested and finally the structure activity relationship was described.

Keywords: Quinazolin-4(3H)-ones, 4H-3,1-benzoxazin-4-one,Synthesis, Antimicrobial.

INTRODUCTION

The quinazolin-4-onesare an important group of heterocyclic compounds which have attracted interest due to the wide range of therapeutic activities of these compounds includingantiviral[1],antimicrobial [2-5] , antimalarial [6],analgesic [7-8], anticonvulsant [9], anti-inflammatory [10], anti-diabetic [11]and anticancer [12].

Several reports relate the good antimicrobial activity with 2,3-disubstituted 4(3H)-quinazolinones. Structure activity relationship (SAR) studies have shown that positions 2 and 6 of quinazoline structure are important and position 3 should be presented for better antimicrobial activities [13].

Due to the structure similarity between quinazolinones and quinolones, their antimicrobial activity is supposed to be occurred by the same mechanism. It has been reported that the antimicrobial activity of quinolones is due to inhibition of DNA replication. Quinolonesinhibit the bacterial DNA gyrasewhich is an enzyme essential for bacterial DNA replication [14].

In a previous work [15] we have reported that the antimicrobial activity increases with the presence of polar group at position 3 and bulk group at position 2. To continue this work, a series of new quinazolin-4-one derivatives were synthesized and tested as antimicrobial agent.

EXPERIMENTAL SECTION

The melting points were determined on a Stuart melting point apparatus and are uncorrected. The IR spectra were recorded as KBr pellets using Buck scientific model 500 IR spectrophotometer. The proton NMR spectra were recorded in DMSO-d6 as solvent at 300, 350 MHz, on Varian Gemini NMR spectrophotometer using TMS as internal standard, chemical shifts are recorded as units (δppm)The chemical shifts are reported as parts per million (ppm). Mass

spectra were measured on Shimadzu GCMS-QP 1000 Ex mass spectrometer at 70 eV. Microanalyses were performed at the micro-analytical center, Cairo University.

Synthesis of 2-methyl-4*H*-3,1-benzoxazin-4-one (1)
Anthranilic acid (0.01 mole) was dissolved in 20 ml acetic anhydride. The reaction medium was gently heated for one hour. The excess of acetic anhydride was removed by evaporation under reduced pressure and cooled to room temperature. The solid residue was collected, washed by ice cold water, dried and crystallized from ethanol(m.p.81- 82 ^{o}C; yield 83%).

Synthesis of 2-phenyl-4*H*-3,1-benzoxazin-4-one(2)
To a stirred solution of anthranilic acid (0.01 mole) in pyridine (60 ml), benzoyl chloride (0.01 mol) was added drop wise maintaining the temperature near 8° C for one hour. The reaction mixture was stirred for another 2 h at room temperature. While stirring, a solid product separated out. The whole reaction mixture was neutralized with $NaHCO_3$ solution. A pale yellow solid deposited was filtered, washed with water and recrystallized from ethanol (m.p. 120 - 121^{o}C;yield 78%).

General procedure for synthesis substituted quinazolin-4ones derivatives (3-16)
A mixture of 2-substituted-4H-3, 1-benzoxazin-4-one**1, 2** (0.01 mol) and selected amino acids namely, aspartic acid, arginine, histidine, tyrosine, threonine, valine and methionine (0.01 mol) were refluxed in a pyridine for 6 h. The mixture was then poured in an ice/water mixture, stirred and left to allow the white solid precipitate to settle down. The solid was filtered, washed, dried and finally crystallized from the proper solvent to yield compounds **3-14**, respectively.

2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)butanedioic acid (3)
White crystals from DMF ; m.p. 253 °C; yield 85%;IR (υ_{max} cm^{-1}) 3420 (OH), 1702 (C=O). MS: m/z 276 [M^{+}]; Anal. Calcd for $C_{13}H_{12}N_2O_5$: C, 56.52; H, 4.38; N, 10.14, O 28.96. Found: C, 56.31; H, 4.39; N, 10.33%.^{1}H-NMR (DMSO-d_6) δ 2.40 (s, 3H), 3.10 (d, 2H), 5.69 (t, 1H), 7.29 -8.11 (m, 4H, ArH).

2-(4-oxo-2-phenylquinazolin-3(4H)-yl)butanedioic acid (4)
Yellow crystals from DMF; m.p. 245 °C; IR (υ_{max} cm^{-1}) 3410 (OH), 1705 (C=O). MS: m/z 338 [M^{+}]; Anal. Calcd for $C_{18}H_{14}N_2O_5$: C, 63.90; H, 4.17; N, 8.28, O 23.65. Found: C, 56.11; H, 4.39; N, 10.33%. ^{1}H-NMR (DMSO-d_6) δ 3.21 (d, 2H), 5.77 (t, 1H), 7.31- 8.34 (m, 10H, ArH)

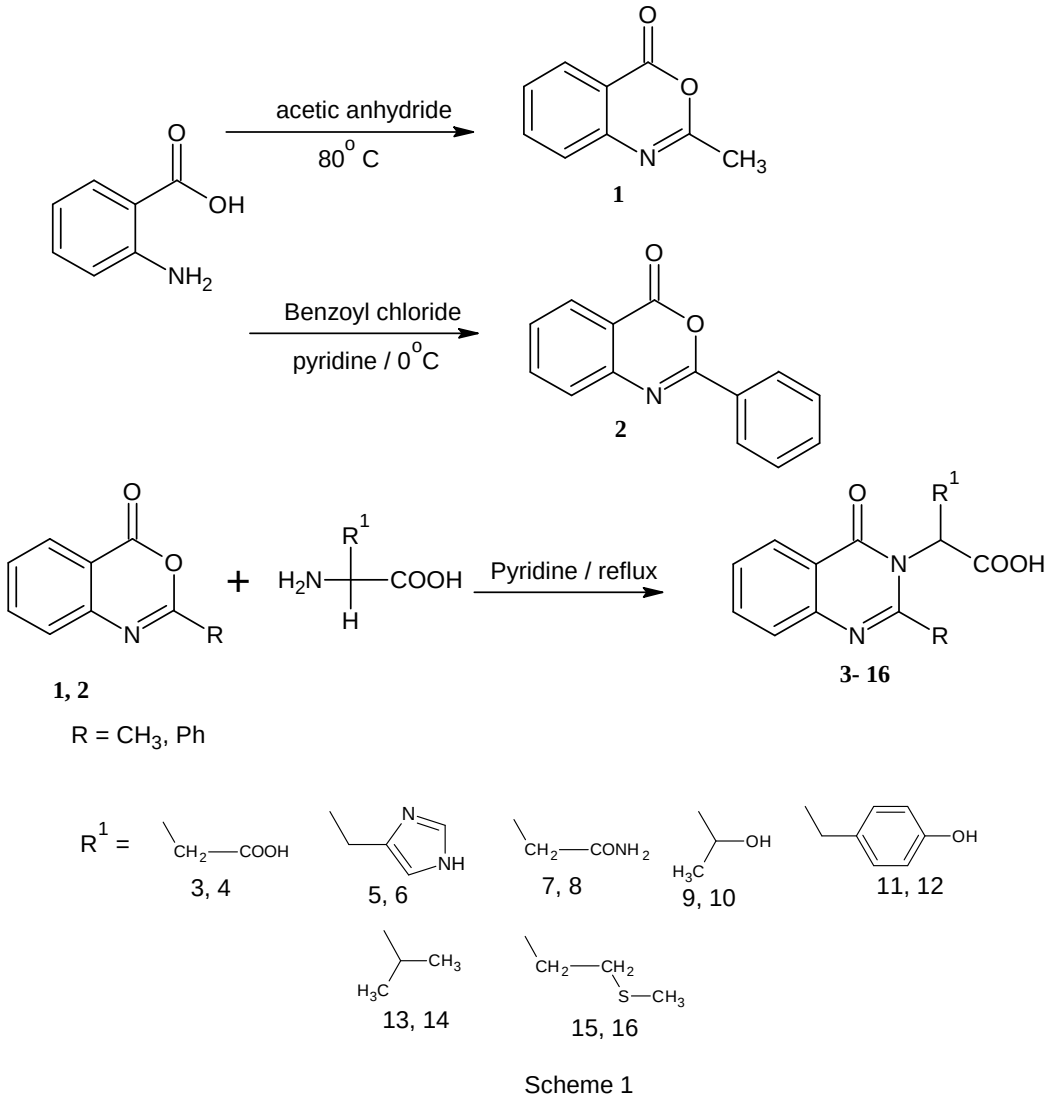
3-(1H-imidazol-4-yl)-2-(2-methyl-4-oxoquinazolin-3(4H)-yl) propanoic acid (5)
Yellow crystals from DMF; m.p. 189 °C; IR (υ_{max} cm^{-1}) 3442 (OH), 1695 (C=O). MS: m/z 298 [M^{+}]; Anal. Calcd for $C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78Found: C, 60.10; H, 4.71; N, 18.66. ^{1}H-NMR (DMSO-d_6) δ 2.411 (s, 3H), 3.206 (d,2H), 5.58 (t,1H), 7.29 - 8.11 (m, 6H, ArH and imidazole H).

3-(1H-imidazol-4-yl)-2-(4-oxo-2-phenylquinazolin-3(4H)-yl)propanoic acid (6)
Yellow crystals from DMF; m.p. 173 °C; IR (υ_{max} cm^{-1}) 3450 (OH), 1697 (C=O). MS: m/z 360 [M^{+}]; Anal. Calcd for $C_{20}H_{16}N_4O_3$: C, 66.66; H, 4.48; N, 15.55 Found: C, 66.61; H, 4.51; N, 15.66. ^{1}H-NMR (DMSO-d_6) δ 3.24 (d, 2H), 5.59 (t, 1H), 6.91- 8.34 (m, 11H, ArH and imidazole H).

4-amino-2-(2-methyl-4-oxoquinazolin-3(4H)-yl)-4-oxobutanoic acid (7)
Yellow crystals from DMF; m.p. 245 °C; IR (υ_{max} cm^{-1}) 3350 (OH). 1670, 1675, 1705 (C=O). MS: *m/z* 275 [M^{+}]; Anal. Calcd for $C_{13}H_{13}N_3O_4$: C, 56.72; H, 4.76; N, 15.27; Found: C, 56.76; H, 4.82; N, 15.39. 1H-NMR (DMSO-d_6) δ 2.40 (s, 3H), 3.00 (br, NH), 3.19 (d, 2H) 5.7 (t, 1H), 7.45-8.17 (m, 4H, Ar-H).

4-amino-4-oxo-2-(4-oxo-2-phenylquinazolin-3(4H)-yl)butanoic acid (8)
Yellow crystals from DMF; m.p. 227 °C; IR (υ_{max} cm^{-1}) 3390 (OH). 1675, 1689, 1706 (C=O). MS: *m/z* 337 [M^{+}]; Anal. Calcd for $C_{18}H_{15}N_3O_4$: C, 64.09; H, 4.48; N, 12.46; Found: C, 64.16; H, 4.35; N, 12.32. 1H-NMR (DMSO-d_6) δ 3.10 (br, NH), 3.24 (d, 2H), 5.67 (t, 1H), 7.32-8.42 (m, 9H, Ar-H).

3-hydroxy-2-(2-methyl-4-oxoquinazolin-3(4H)-yl)butanoic acid (9)
Yellow crystals from DMF; m.p. 231 °C; IR (υ_{max} cm^{-1}) 3405 (OH), 1699 (C=O). MS: m/z 262 [M^{+}]; Anal. Calcd for $C_{13}H_{14}N_2O_4$: C, 59.54; H, 5.38; N, 10.68; O 24.40 Found: C, 59.23; H, 5.37; N, 10.71. ^{1}H-NMR (DMSO-d_6) δ1.20 (d, 3H), 2.41 (s, 3H), 3.95 (dq, 1H), 5.52 (d,1H), 7.30- 8.11 (m, 4H, ArH).



Scheme 1

3-hydroxy-2-(4-oxo-2-phenylquinazolin-3(4H)-yl)butanoic acid (10)
Yellow crystals from DMF; m.p. 217 °C; IR (υ_{max} cm^{-1}) 3409 (OH), 1696 (C=O). MS: m/z 324 [M^+]; Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64; O 19.73 Found: C, 66.45; H, 4.96; N, 8.57. ^{1}H-NMR (DMSO-d_6) δ1.22 (d,3H), 3.91 (dq, 1H), 5.608 (d, 1H), 7.31- 8.34 (m, 9H, ArH)

3-(4-hydroxyphenyl)-2-(2-methyl-4-oxoquinazolin-3(4H)-yl)propanoic acid (11)
Yellow crystals from DMF; m.p. 262 °C; IR (υ_{max} cm^{-1}) 3392 (OH), 1653, 1697 (C=O). MS: m/z 324 [M^+]; Anal. Calcd for $C_{18}H_{16}N_2O_4$: C, 66.66; H, 4.97; N, 8.64;O 19.73Found: C, 66.84; H, 4.98; N, 8.48.^{1}H-NMR (DMSO-d_6) δ 2.41 (s,3H), 2.87 (d, 2H), 5.50 (t,1H), 6.70 – 8.19 (m, 8H, ArH)

3-(4-hydroxyphenyl)-2-(4-oxo-2-phenylquinazolin-3(4H)-yl) propanoic acid (12)
Brown crystals from DMF; m.p. 249 °C;IR (υ_{max} cm^{-1}) 3392 (OH), 1653, 1697 (C=O). MS: m/z 386 [M^+]; Anal. Calcd for $C_{23}H_{18}N_2O_4$: C, 71.49; H, 4.70; N, 7.25; O 16.56 Found: C, 71.55; H, 4.71; N, 7.31. ^{1}H-NMR (DMSO-d_6) δ 2.89 (d, 2H), 5.54 (t, 1H)**,** 6.70- 8.34(m, 13H, ArH)**.**

3-methyl-2-(2-methyl-4-oxoquinazolin-3(4H)-yl)butanoic acid (13)
brown crystals from DMF; m.p. 202 °C; IR (υ_{max} cm^{-1}) 3392 (OH), 1653, 1697 (C=O). MS: m/z 260 [M^+]; Anal. Calcd for $C_{14}H_{16}N_2O_3$: C, 64.60; H, 6.2; N, 10.76 Found: C, 64.44; H, 6.11; N, 10.83. ^{1}H-NMR (DMSO-d_6) δ 1.36 (d,6H), 2.08 (sept,1H), 2.48 (s, 3H), 5.30 (d, 1H), 7.29-8.15 (m, 4H, ArH)

3-methyl-2-(4-oxo-2-phenylquinazolin-3(4H)-yl)butanoic acid (14)
Yellow crystals from DMF; m.p. 188 °C; IR (υ_{max} cm^{-1}) 3399 (OH), 1651, 1695 (C=O).MS: m/z 322 [M^+]; Anal. Calcd for $C_{19}H_{18}N_2O_3$: C, 70.79; H, 5.63; N, 8.69; O 14.89 Found: C, 70.61; H, 5.55; N, 8.74. ^{1}H-NMR (DMSO-d_6) δ 0.98 (d, 3H), 2.09 (dhept, 1H), 5.33 (d, 1H), 7.31- 8.34 (m, 9H, ArH)

2-(2-methyl-4-oxoquinazolin-3(4*H*)-yl)-4-(methylsulfanyl)butanoic acid (15)
Light brown crystals from DMF; m.p. 210-211 °C; IR (υ_{max} cm^{-1}) 3443 (OH), 1689 (C=O). MS: m/z 292 [M^+]; Anal. Calcd for $C_{14}H_{16}N_2O_3S$: C, 57.52; H, 5.52; N, 9.58, O 16.42; S, 10.97. Found: C, 57.83; H, 5.50; N, 10.13%, S, 10.70. ^{1}H-NMR (DMSO-d_6) δ 2.20 (s, 3H), 2.41 (s, 3H), 2.62 (t, 2H), 2.13(td,2H), 5.35 (t, 1H), 7.29- 8.06 (m, 4H, ArH).

4-(methylsulfanyl)-2-(4-oxo-2-phenylquinazolin-3(4H)-yl)butanoic acid (16)
Light brown crystals from DMF; m.p. 224-225 °C; IR (υ_{max} cm^{-1}) 3450 (OH), 1694 (C=O). MS: m/z 354 [M^+]; Anal. Calcd for $C_{19}H_{18}N_2O_3S$: C, 64.39; H, 5.12; N, 7.90, O 13.54; S, 9.05. Found: C, 64.52; H, 5.07; N, 8.01, S, 8.89. ^{1}H-NMR (DMSO-d_6) δ2.16 (td,2H), 2.20 (s, 3H), 2.63 (t, 2H), 5.38 (t, 1H), 7.31- 8.34 (m, 9H, ArH).

Antimicrobial activity test
Sterile filter paper disks (8 mm diameter) were moistened with the test compound solution in DMSO of specific concentration (200µg/disk). The disks were carefully placed on the agar culture plates that had been previously inoculated separately with the microorganisms suspension at 106 Colony Forming Unit/mL (CFU/mL) concentration. The plates were incubated at 37^{o}C, for 24 h in case of bacteria and 48 h in case of *C. albicans*and *Aspergillus niger*. The diameters of the clear area around the discs (in mm) have been taken as an indication for the antimicrobial activity.

RESULTS AND DISCUSSION

Chemistry:
Variously substituted quinazolin-4(3H)-one derivatives**3-14** were prepared according to Scheme 1. 2-methyl-4H-3,1-benzoxazin-4-one **1** is a well identified compound that conventionally synthesized via heating of Anthranilic acid in acetic anhydride. 2-phenyl 4H-3, 1-benzoxazin-4-one **2** synthesis has been reported in the literature. It was preparedby stirring an equimolar amount anthranilic acid and benzoyl chloride in an anhydrous pyridine. 4H-3,1-Benzoxazin-4-one derivatives **1, 2** were reacted with acidic, basic, polar, and nonpolar, amino acids namely aspartic acid, histidine, asparagine, threonine, tyrosine, valine, and methionine in a refluxing pyridine for 6-8 h to give the corresponding quiazolin-4-one derivatives **3-16** in a good yield. All the synthesized compounds were characterized by their physical and spectral data.

Table 1.Antimicrobial activity of the new synthesized compounds, expressed as inhibitory zone diameter in mm.

Compound name	*S. aureus*	*B. subtilis*	*E. coli*	*K. pneumoniae*	*C. albicans*	*A. niger*
3.	8	7	5	6	-	6
4.	12	14	10	11	8	12
5.	33	35	25	21	13	18
6.	38	37	28	24	14	18
7.	30	29	20	21	9	14
8.	29	31	22	18	12	22
9.	16	15	14	10	6	10
10.	23	25	17	11	6	11
11.	23	26	10	15	4	16
12.	27	29	21	20	-	9
13.	15	14	17	11	10	13
14.	18	17	18	15	9	14
15.	11	18	12	6	2	12
16.	15	21	15	16	12	20

Antimicrobial activity:

All the synthesized compounds were tested for their in vitro antimicrobial activity against the Gram-positive bacteria, *Staphylococcus aureus* and *Bacillus subtilis*, the Gram negative bacteria, *Escherichia coli* and *Klebsiella pneumoniae*, the yeast*Candida albicans* and finally thefungus*Aspergillus niger*. The primary screening was carried out using the agar-disk diffusion method using Muller-Hinton agar medium [17]. From the obtained data (Table 1), it is clear that all new synthesized compounds show wide spectrum activity of different degrees against the tested microorganisms. In general, the tested compounds showed higheractivity against Gram positive bacteria than Gram negative one. In addition, these derivatives showed weak activity against *C. albicans* and medium activity against *Aspergillus niger*. Also the 2-phenyl derivatives recorded higher activity than 2-methyl derivatives. In more details quinazoline-4(3H)-onederivatives **(5-8)** of basic side chain showed the highest activity while the lowest activity was obtained by the quinazoline-4(3H)-ones of acidic side chain**(3,4)**. Finally derivatives **(9-12)** of polar side chain showed a slightly higher activity than compounds **(13-16)** of nonpolar side chain.

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