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Synthesis and Antimicrobial Activities of Some 3,4-Dihydroquinazolinone-4-One, Quinoxaline, Benzoxazine, Benzothiazine, Pyran and Pyrrolidinedione Derivatives

[1]Nagwa M. Fawzy, [2]Samira A. Swelam and [1]Mohamed A. Farid
[1]Department of Natural and Microbial Products,
[2]Department of Photochemistry, National Research Centre, Tahrir Street, Dokki, Cairo, Egypt

Abstract: Synthesis of some 3,4-dihydroquinazolinone-4-one, quinoxaline, benzoxazine, benzothiazine, pyran and pyrrolidinedione derivatives using readily available starting materials were described. It has been found that compounds 4b, 8a and 8b were the most active compounds against the test organisms. Compound 8b was the most active against Gram positive and Gram negative bacteria (*B. subtilus* and *E. coli*) where compounds 4b and 8a were active against (*St. aureus*). Compound 12a is the least active member of this group. On the other hand, compound 14b showed a good activity compound against *St. aureus*.

Key words: Dihydroquinazolinone, pyran, quinoxaline, benzoxazine, benzothiazine, pyrrolidinedione, antimicrobial activities

INTRODUCTION

Quinoxaline derivatives have received much attention in recent years owing to their both biological properties and pharmaceutical applications (Ali *et al*., 2000). Some of them showed antimicrobial against several bacteria, viruses, fungi, etc. or anticancer activities. Furthermore, others are reported to be potent no-NMDA glutamate receptor antagonists, endowed with anxiolytic, deconditioning, analgesic, antispastic, antiallergic, antithrombotic activities.

It's known that α-keto acids, especially the α-keto acid analogues of naturally occurring amino acids, are of major importance in intermediary metabolism. Pyruvic acid, as an example, is known as a metabolite which is involved in a number of enzyme-catalyzed intercellular phenomena (http://www.freepatentsonline.com/4670042.html).

Recently, α-keto acids have been used in the therapy of certain conditions, for e.g., urenia and nitrogen accumulation disorders (Hishmat *et al*., 1999b).

Our interest was based on the preparation of new series of heterocyclic compounds based on furochromon derivatives with antimicrobial activity.

MATERIALS AND METHODS

Chemistry: The purity of the newly synthesized compounds was evidenced by TLC and their correct values in their elemental analyses were generally found to be within ±0.04% of the theoretical values. All melting points are uncorrected. IR spectra were recorded in KBr discs on a Jasco FT-IR 300 spectrophotometer. ^{1}H-NMR spectra were recorded on a JEOL-EX270(270 MHZ) spectrometer in $(CD_3)_2SO$ as a solvent, the chemical shifts (δ) are expressed in ppm using TMS as an internal standard. Splitting patterns are indicated as s, singlet; d, doublet; m, multiple; br, broad signal. Mass spectra were measured on a GCMS-Finnigan SSQ 7000 Digital DEC 3000 mass spectrometer, operating at 70 eV. Elemental analyses were carried out at the Microanalytical Laboratory of the National Research Centre, Cairo, Egypt. For Thin Layer Chromatographic (TLC) analysis, Merck TLC plates were used.

2-(2-aminophenyl)-3,4-dihydroquinazolin-4-one(4a): An ice-cooled ammonia solution 3a (10 mL) was poured into a stirred solution of 2 (3.20 g, 0.02 mol). The mixture was stirred at room temperature for 15 h and then was refluxed for 1 h. After cooling, the reaction mixture was filtered off and the solid product was collected and was crystallized from ethanol to give 4a.

Mol. formula: $C_{14}H_{11}N_3O$ = 237.54, m.p. 260-2°C. – IR (KBr): ν 3420-3390 cm^{-1} (NH2); 3310, 3300 cm^{-1} (NH); 1654 (C = O) cm^{-1}. – 1 H NMR (270 MHZ, [D6]-DMSO): δ = 9.89 (1 H, bs, NH exchangeable with D_2O); 7.05-7.85 (8 H, m, aromatic); 4.70 (2 H, s, NH_2 exchangeable with D_2O). MS (EI, 70 eV): m/z (%) = 237 (100); 221(54); 144(60).

General procedure for the preparation of 4b-d: To a solution of 2 (3.20 g, 0.02 mol) in chloroform (20 mL) was added the appropriate primary amine 3b-d (0.01 mol) with few drops of piperidine, the mixture was then refluxed for 3 h. The mixture was concentrated in vacuum to give a residue which was dissolved in 2 N hydrochloric acid and

Corresponding Author: Samira A. Swelam, Department of Photochemistry, National Research Centre, Dokki, Giza, Egypt

was extracted several times with chloroform after adjusting the pH carefully at 7. The organic layer was then dried over anhydrous $MgSO_4$ and concentrated in vacuum to give a crude product which was collected and was crystallized from the suitable solvent to afford 4b-d in good yields.

2-(2-aminophenyl)-3,4-dihydro-3-phenylaminoquinazolin-4-one (4b)

Mol. formula: $C_{20}H_{16}N_4O$ = 328.40; m.p. 240-2°C., crystallization from chloroform -IR (KBr): ν 3466-3359 cm^{-1} (NH_2), 33321, 3310 cm^{-1} (NH), 1661 (C = O) cm^{-1}. -^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 9.80 (1H, s, NH exchangeable D_2O); 7.65-7.10 (13H, m, aromatic), 5.10 (2H, s, NH_2 exchangeable D2O) -MS (EI, 70 eV): m/z (%) = 328 (10), 251 (60), 238 (100), 220(43), 144(21).

2-(2-aminophenyl)-3,4-dihydro-3-(4-methylphenyl) quinazolin-4-one (4c)

Mol. formula: $C_{21}H_{17}N_3O$ = 327.41; m.p. 200-2°C crystallization from ethanol-IR (KBr): ν 3440-3384 cm^{-1} (NH_2), 1641 (C=O) cm-^{1}. -^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 7.56-7.21 (12H, m, aromatic); 5.00 (2H, s, NH_2 exchangeable D_2O); 1.17 (3H, s, CH_3) - MS (EI, 70 eV): m/z (%) = 325 (20), 238 (100), 220 (13), 144 (32).

2-(2-aminophenyl)-3,4-dihydro-3-(4-nitrophenyl) quinazolin-4-one (4d)

Mol. formula: $C_{20}H_{14}N_4O_3$ = 358.38; m.p. 185-7°C crystallization from ethanol -IR (KBr): ν 3384 cm^{-1} (NH_2), 1644 (C = O) cm^{-1}. -^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 7.66-7.31 (12H, m, aromatic); 4.93 (2H, s, NH_2 exchangeable with D_2O) - MS (EI, 70 eV): m/z (%) = 357 (60), 238 (100).

General procedure for the preparation of 8a-d

Method A: A mixture of equimolecular amounts of 2-amino-N-substitutedbenzamide of type 6a-d (0.01 mol) and 4, 9-dimethoxy-5-oxo-5H-furo[3,2-g]chromene-4-carbaldehyde 7a (2.74 g, 0.01 mol) in ethanol (20 mL) was refluxed for 4 h in the presence of two drops of piperidine. The reaction mixture was cooled to room temperature and the solid that separated was collected and was crystallized from acetone to afford 8a-d in moderate yields.

Method B: A mixture of 9a (3.80 g, 0.01 mol) and the appropriate primary amine 5a-d (0.01 mol) in ethanol (100 mL) was refluxed for 6 h in the presence of two drops of piperidine. Similar treatment of the mixture as in method A gave products that were identical in all respects (m.p., IR, ^{1}H NMR, MS) with those obtained by method A.

3,4-dihydro-2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g] chromen-6-yl)-3-phenylquinazolin-4-one (8a):

Mol. formula: $C_{27}H_{18}N_2O_6$ = 466.47; m.p. 241-3°C., -IR (KBr): ν 1640,1632 (2C=O) cm^{-1}. -^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 8.11 (1H, s, H7); 7.92, 7.21 (2H, dd, H2,3, J = 2.3 Hz); 7.71-7.31 (9H, m, aromatic); 4.02, 4.00 (6H,s, $2OCH_3$) - MS (EI, 70 eV): m/z (%) = 466 (11), 389 (18), 245 (80), 215(76).

3,4-dihydro-2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g] chromen-6-yl)-3-(4-methylphenyl)quinazo-lin-4-one (8b)

Mol. formula: $C_{28}H_{20}N_2O_6$ = 480.46; m.p. 201-3°C. -IR (KBr): ν 1654, 1635 (2C = O) cm^{-1}. -^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 7.94 (1H, s, H7); 7.76, 7.13 (2H, dd, H2,3, J = 2.4 Hz); 7.74-733(8H, m, aromatic); 4.01, 3.98 (6H, s, $2OCH_3$); 1.56 (3H, s, CH_3)-MS (EI, 70 eV): m/z (%) = 480 (76), 391 (45), 339 (90), 297 (100), 283 (22), 271(64).

3,4-dihydro-2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g] chromen-6-yl)-3-(4-nitrophenyl)quinazo-lin-4-one (8c)

Mol. formula: $C_{27}H_{17}N_3O_8$ = 511.47; m.p. 215-7°C., crystallization from ethanol - IR (KBr): ν 1649, 1630 (2C = O) cm^{-1}. -^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 8.10 (1H, s, H7); 7.81, 7.21 (2H, dd, H2,3, J = 2.1 Hz); 7.62-7.11 (8H, m, aromatic.); 4.00, 3.91 (6H,s, 2 OCH_3)-MS (EI, 70 eV): m/z (%) = 510 (59), 465 (16), 389 (41), 266 (34), 359 (20), 245 (34).

3,4-dihydro-2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g] chromen-6-yl)-3-(4-methoxyphenyl)quinazo-lin-4-one (8d)

Mol. formula: $C_{28}H_{20}N_2O_7$ = 496.5; m.p. 243-5°C., crystallization from ethanol – IR (KBr): ν 1653, 1625 (2C = O) cm^{-1}. -^{1}H NMR (270 MHZ, [D6]-DMSO): δ = 8.10 (1H, s, H7); 7.76, 7.10 (2H, dd, H2,3, J = 2.0 Hz); 7.21-7.52 (8H, m, aromatic); 4.11, 4.01, 3.99 (9H, s, $3OCH_3$) – MS (EI, 70 eV): m/z (%) = 496 (43),466 (63), 436 (35), 389 (65), 245 (90), 221 (30).

General procedure for the preparation of 9a, b: To a solution of 2 (1.60 g, 0.01 mol) in ethanol (25 mL), was added aldehyde 7a,b (0.01 mol) and two drop of piperidine, the mixture was then refluxed for 4 h. The reaction mixture was cooled to room temperature and the precipitated product was filtered off and was crystallized from the suitable solvent to afford 9a, b in good yields.

2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl) methylidenaminobenzoyl chloride (9a)

Mol. formula: $C_{21}H_{14}Cl\ NO_6$ = 411.86; m.p. 210-2°C., crystallized from ethanol - IR (KBr): ν 1705, 1637 (2C = O) cm^{-1}. – ^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 8.13 (1H, s, H7); 7.89 7.23 (2H, dd, H2,3, J = 2.1HZ), 7.99

(1H, s, HC=N); 7.67-7.12-(4H, m, aromatic); 4.01, 3.98 (6H, s, $2OCH_3$). - MS (EI, 70 eV): m/z (%) = 412 (25), 376 (61), 264 (82), 237 (52), 271 (34), 256 (32), 244 (98), 215(53).

2-(4-cyanophenyl)methylidenaminobenzoyl chloride (9b)
Mol. formula: $C_{15}H_9ClN_2O$ = 268.26; m.p. 273-5°C., crystallized from ethanol - IR (KBr): ν 2200 (C≡N), 1681 (C = O) cm^{-1}. -^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 7.20-7.81 (8H, m, aromatic.), 7.87 (1H, s, HC=N). – MS (EI, 70 eV): m/z (%) = 268(42), 238 (10), 209(31), 241 (80), 164 (67), 137 (23), 131 (100).

4-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-2-oxobut-3-enoic acid (10): A solution of 40% NaOH was added to an equimolecular mixture of 7a (2.74 g, 0.01 mole) and pyruvic acid (0.74 g, 0.01 mole) in (50 mL) ethanol with stirring at 10-25°C and then was neutralized with 0.5 N HCl to give 55% of 10.

Mol. formula: $C_{17}H_{12}O_8$ = 344.27; m.p. 269-71°C.,. - IR (KBr): ν 3420 cm^{-1} (acidic OH); 1680, 1660, 1630 cm^{-1} (3C = O). – ^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 12.05 (1H, br, COOH); 8.16 (1H, s, H7); 7.82, 7.12 (2H, dd, H2,3, J = 2.1 HZ); 6.02,5.87(2H, dd, CH = CH, J = 1.8 HZ); 4.01 3.91 (6H, s, $2OCH_3$). - MS (EI, 70 eV): m/z (%) = 344 (90); 343 (84); 314 (66), 297 (31), 269 (56), 241 (77), 215 (100).

General procedure for the preparation of 11a, b: A mixture of 10 (3.44 g, 0.01 mol) and each of malononitrile and ethyl cyanoacetate (0.01 mol) in absolute ethanol (50 mL) using catalytic amounts of piperidine was heated under reflux for 6 h. The solid products that separated was filtered off and was crystallized from ethanol to give 11a,b, respectively.

6-amino-5-cyano-4-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-4H-pyran-2-carboxylic acid (11a)
Mol. formula: Wt $C_{20}H_{14}N_2O_8$ = 410.33; m.p. 284-6°C., -IR (KBr): ν 3460 cm^{-1} (acidic OH); 3420-3382 cm^{-1} (NH_2); 2210 cm^{-1} (CN); 1710, 1628 cm^{-1} (2C = O). -^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 13.11 (1H, br, exchangeable with D2O, COOH); 8.21 (1H, s,H7); 7.98, 6.52 (2H, dd,H2,3, J = 2.0 HZ); 5.67(2H, s, NH2, exchangeable with D2O); 6.14.80(2H, s, pyran H's); 4.00, 3.99 (6H, s, $2OCH_3$);- MS (EI, 70 eV): m/z (%) = 410 (85); 394(23); 381(34); 376(24); 354 (100); 350(66); 239(30); 245(90); 215(77); 165(22).

6-amino-5-(ethoxycarbonyl)-4-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-4H-pyran-2-carboxylic acid (11b)
Mol. formula: $C_{22}H_{19}NO_{10}$ = 457.42; m.p. 215-7°C., - IR (KBr): ν 3450 cm^{-1} (acidic OH); 3410-3375 cm^{-1} (NH_2); 1740, 1710, 1630 cm^{-1} (3C = O). – ^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 13.71 (1H, br, COOH); 8.01 (1H, s, H7); 7.99, 6.34 (2H, dd, H2,3, J=2.4 HZ); 5.36 (2H, s, NH_2); 5.26, 4.76 (2H, s, pyran-H's); 4.12, 3.98 (6H, s, $2OCH_3$); 3.41(2H, q, CH_2) and 1.20 (3H, t, CH_3). -MS (EI, 70 eV): m/z (%) = 456 (55); 412(43); 396(24); 380(21); 350 (100); 345(86); 211(30).

General procedure for the preparation of 12a-c: A mixture of 10 (3.44 g, 0.01 mole) and each of o-phenylenediamine and o-aminophenol (0.01 mole) was heated in glacial acetic acid (20 mL) at 70-75°C for 2 h. The reaction mixture was left overnight at room temperature. The solid that separated in each case was filtered off and was crystallized from ethanol to give 12a-c, respectively.

3-[2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-vinyl]-3,4-dihydroquinoxalin-2-one (12a)
Mol. formula: $C_{23}H_{18}N_2O_6$ = 418.39; m.p. 265-7°C., - IR (KBr): ν 3280, 3200 cm^{-1} (NH); 1680, 1633 cm^{-1} (2C = O). -^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 9.23 (2H, s, 2NH, exchangeable with D_2O); 7.88 (1H, s, H7); 7.84, 6.75 (2H, dd, H2,3, J = 2.0 HZ); 7.62-7.30 (4H, m, aromatic); 6.45, 6.42 (2H, dd, CH = CH); 4.32(1H, d, quinoxaline CH) and 3.97, 3.93 (6H, s, $2OCH_3$). - MS (EI, 70 eV): m/z (%) = 418 (89) 415(40); 398(34); 251(60); 240 (40); 228(33); 146(73).

3-[2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-vinyl]-3,4-dihydro-2H-1,4-benzoxazin-2-one (12b)
Mol. formula: $C_{23}H_{17}NO_7$ = 419.38; m.p. 271-3°C, – IR (KBr): ν 3310,3300 cm^{-1} (NH); 1700, 1640 cm^{-1} (2C = O). -^{1}H-NMR (270 MHZ, [D6]-DMSO): δ =9.01 (1H, br, NH exchangeable with D_2O); 8.01 (1H, s, H7); 7.99, 6.34 (2H, dd, H2,3, J = 2.4 HZ);7.81-7.21(4H, m, aromatic); 6.40, 6.26 (2H, dd, CH = CH-); 4.53 (1H, d, benzoxazine-CH) and 4.12, 3.98 (6H, s, $2OCH_3$). - MS (EI, 70 eV): m/z (%) = 420 (81); 388 (34); 254 (23); 240 (100); 215 (36); 148 (30).

3-[2-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-vinyl]-3,4-dihydro-2H-1,4-benzothia-zin-2-one (12c)
Mol. formula: $C_{23}H_{17}NSO_6$ = 435; m.p. 251-3°C., - IR (KBr): ν 3310,3300 cm^{-1} (NH); 1656, 1630 cm^{-1} (2C = O). – ^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 9.17 (1H, br, NH, exchangeable with D_2O); 8.00 (1H, s, H7); 7.98, 6.40 (2H, dd, H2,3, J = 2.1 HZ); 7.71-7.20(4H, m, aromatic); 6.30,6.20 (2H, dd, CH = CH) 4.23 (1H, d, benzothiazine-CH) and 4.00, 3.99 (6H, s, $2OCH_3$). - MS (EI, 70 eV): m/z (%) = 435 (75); 405 (37); 390 (30); 369 (56); 352 (10); 149 (100).

General procedure for the preparation of 13a,b, 14a, b: A mixture of compound 10 (3.44 g, 0.01 mole) and each of the aromatic amines (p-toludine and p-bromoaniline) (0.01 mole), in (25 mL) THF, in the presence of DMTMM

as a catalyst, was refluxed for 1 h on a steam-bath. The precipitation of each of compound 13a, b, respectively, usually started while the amine was added. When the mixture was then filtered off. It was actually a mixture of the carboxamide compound 13 and a small amount of 14. To obtain the pyrroledione 14a,b, the reaction mixture was not filtered off, instead, it was refluxed for 1-3 h. The reaction mixture was then allowed to cool and the solid was collected by filtration. The compound was washed thoroughly with ether then with cold absolute ethanol. The product was then crystallized from the suitable solvent to afford 14a, b, respectively.

N-(4-methylphenyl)-4-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-2-oxobut-3-enamide (13a)

Mol. formula: $C_{24}H_{19}NO_7$ = 433.38; m.p. 230-2°C, crystallization from chloroform - IR (KBr): ν 3340,3326 cm^{-1}(NH), 1770, 1714, 1620 cm^{-1} (3C = O). - ^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 9.01(1H, s, NH, exchangeable with D_2O); 7.79 (1H, s, H7); 7.62, 6.33 (2H, dd, H2,3, J = 2.1 HZ); 7.53-7.00 (4H, m, aromatic); 6.40, 6.21(2H, dd, CH = CH); 4.01, 3.97 (6H, s, 2 OCH_3) and 1.32 (3H, s, CH_3). MS (EI, 70 eV): m/z (%) = 433 (75); 431 (13); 416 (30); 403 (43); 388 (42), 296 (62), 245 (55); 215 (77); 188 (100); 156 (10).

N-(4-bromophenyl)-4-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-2-oxobut-3-enamide (13b)

Mol. formula: $C_{23}H_{16}NO_7Br$ = 499.38; m.p. 213-5°C, crystallization from chloroform/ethanol - IR (KBr): ν 1760, 1714, 1620 cm^{-1} (3C = O). -^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 9.17 (1H, s, NH, exchangeable with D_2O); 8.01 (1H, s, H7); 7.38, 6.20 (2H, dd, H2,3, J = 2.1 HZ); 7.41-7.10 (4H, s, aromatic); 6.30, 6.28 (1H, dd, CH = CH-) and 4.00, 3.99 (6H, s, 2 OCH_3). - MS (EI, 70 eV): m/z (%) = 499 (43); 484 (23); 420 (42), 344 (30); 327 (65), 299 (32), 271 (34), 254 (40); 245 (76); 192 (100); 177 (20); 100 (10).

5-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)-1-(4-methyl phenyl)-pyrrole-2,3-dione (14a)

Mol. formula: $C_{24}H_{17}NO_7$ = 431.39; m.p. 232-4°C, crystallization from chloroform - IR (KBr): ν 1767, 1710, 1628 cm^{-1} (3C = O). - ^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 7.87 (1H, s, H7); 7.62, 6.33 (2H, dd, H2,3, J = 2.1 HZ); 7.60-7.20 (4H, m, aromatic); 4.81(1H, s, pyrroledione-CH), 4.21, 4.02 (6H, s, 2 OCH_3) and 1.30 (3H, s, CH3). - MS (EI, 70 eV): m/z (%) = 432 (45); 431(10); 416(20); 400(23); 340(45), 245(72), 188 (87); 156(14).

1-(4-bromophenyl)-5-(4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromen-6-yl)pyrrole-2,3-dione (14b)

Mol. formula: $C_{23}H_{14}NO_7$, Br = 496.26; m.p. 255-7°C., crystallization from chloroform– IR (KBr): ν 1769, 1704, 1634 cm^{-1} (3C = O). – ^{1}H-NMR (270 MHZ, [D6]-DMSO): δ = 8.11 (1H, s, H7); 7.75, 6.42 (2H, dd, H2,3, J = 2.0 HZ); 7.41-7.10 (4H, m, aromatic.); 5.42 (1H, s, pyrroledione-CH) and 4.08, 3.99 (6H, s, 2 OCH_3). - MS (EI, 70 eV): m/z (%) = 497 (53); 418 (26); 342 (30), 254 (40); 245 (76), 299 (32), 188 (94), 160 (20); 156 (16).

Table 1: Test organisms used in experiment

Test organisms	
St. aur.	*Staphylococcus aureus* NRRL B-313
C. alb.	*Candida albicans* NRRL Y-477
B. s.	*Bacillus subtilus* NRRL B-543
E. coli	*Esherichia coli* NRRL B-210

Antimicrobial activities

Test organisms: The organisms used were: *Staphylococcus aureus* NRRL B-313, *Bacillus subtilus* NRRL B-543, *Esherichia coli* NRRL B-210, *Candida albicans* NRRL Y-477. These microorganisms were obtained from Northern Utilization Research and Development Division, US Department of Agriculture, Peoria, Illinois. USA (Table 1). Screening Tests For bacteria strains, the organisms were grown in 1% (w/v) oxide nutrient broth supplemented with separately heat sterilized glucose solution [0.5% (w/v) final concentration]. An in column (1.0 mL) of about 107 cells mL^{-1} were added to 9.0 mL of glucose–nutrient broth. During incubation, tubes containing the microorganisms were shaken at 200 rpm. in an incubator shaker for 24 h at the optimum growth temperature for each organism, after which the tubes were examined for visible growth. Preparation of the plates the sterilized nutrient agar medium was dissolved and maintained at 50-70°C and then added with 1 mL of each test organism separately. The media was distributed by 20 mL into petri dishes with an inner diameter of 9 cm to provide thin agar plates after being solidified of thickness 3.4-3.5 mm. After solidification, hollows of 10 mm in diameter were made using a cork poorer. An amount of 0.1 mL of the test solution was poured inside the hollow.

Three hollows were made for each sample to be assayed. The Petri dishes were incubated at 5-8°C for 2-3 h to permit good diffusion and then transferred to an incubator of 28°C for 2.3 h.

RESULTS AND DISCUSSION

Chemistry: In continuation of our interest in the synthesis of new series of heterocyclic compounds, most of which show considerable antimicrobial activities. We have been interested in identifying and synthesizing novel substituted quinazolinones which might have a broad spectrum of biological activity. In this study, we report our work on the synthesis of 2,3-disubstituted-3,4-dihydroquinazolin-4-ones 4a-d and 8a-d, most of them

Table 2: Newly synthesized compound showing variable antimicrobial activities

	Samples												
Organisms	4b	4c	4d	8a	8b	8c	8d	10	11a	12a	12c	13a	14b
St. aur.	+++	+	+	+++	++	+	+	-	+	+	+	-	+++
C. alb.	+	+	+	+++	+	+	+	+	+	-	+	-	+
B. s.	+	+	+	+	+++	+	+	+	+	-	+	-	-
E. coli	++	-	++	+++	+++	++	+	+	+	-	+	+++	-

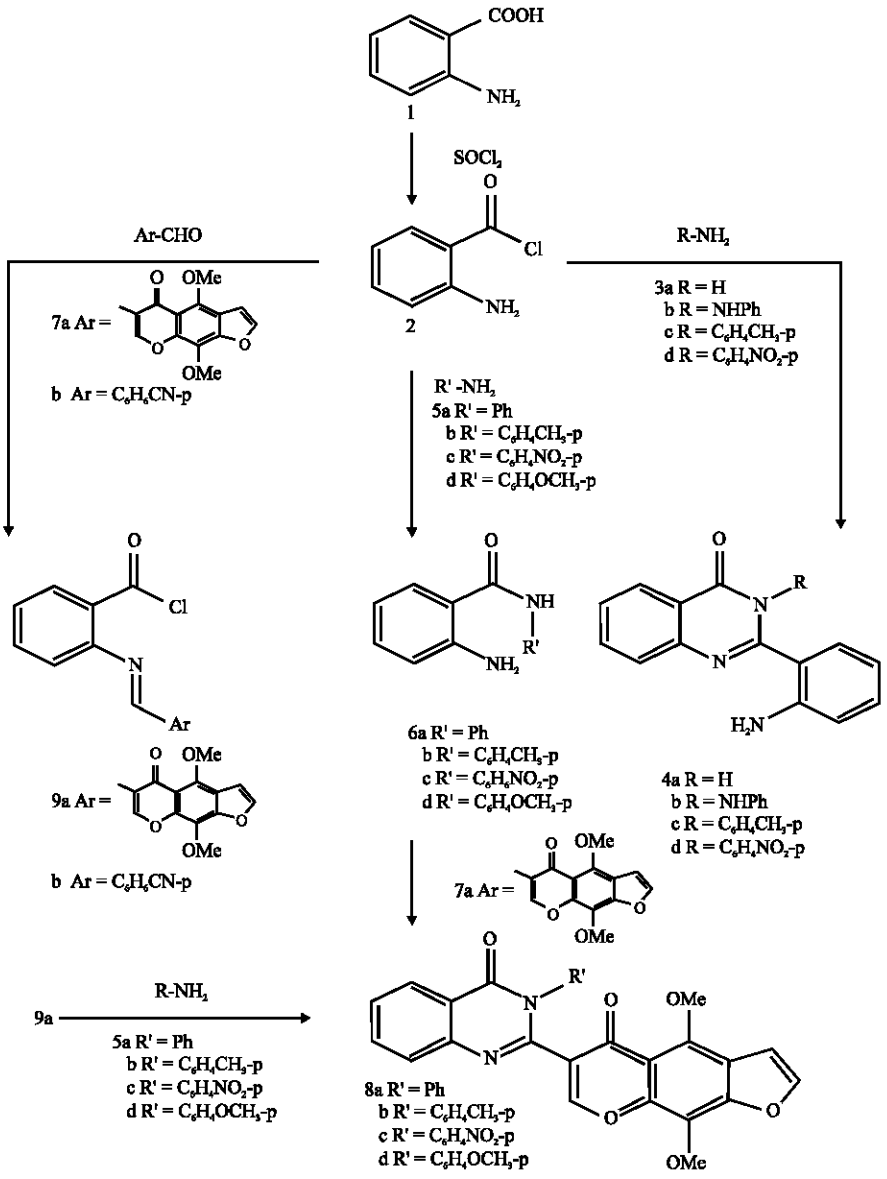
+: Refer to the inhibition zone less than 15 mm. ++: Refer to the inhibition zone of 1.5 to 20 mm, +++: Refer to the inhibition zone more than 20 mm

showed marked antimicrobial activities (Table 2). The starting 2-aminobenzoyl chloride 2 was readily prepared by reaction of anthranilic acid 1 with thionyl chloride. Treatment of two molecular equivalent of the starting 2 with one molecular equivalent of each of (ammonia, phenyl hydrazine and primary aromatic amines) 3a-d afforded the corresponding 3,4-dihydroquinazolin-4-one derivatives 4a-d in good yields (Scheme 1). Assignment of structures 4a-d was made on the basis of their elemental analyses and spectroscopic data (IR, 1H-NMR, MS). For example, the IR spectrum of compound 4a showed characteristic absorption bands at 3420-3390 cm^{-1} (NH_2) and another absorption band at 1654 cm^{-1} (C = O). Its 1H-NMR spectrum revealed a D_2O-exchageable singlet at δ 4.70 ppm, assignable to the (NH_2) protons and a broad D_2O-exchangeable singlet at δ 9.89 ppm, assignable to the (NH) proton. In addition to the typical aromatic multiple in the region δ 7.05-7.85 ppm, assignable to the 8 aromatic protons. The MS exhibited a molecular ion peak at m/z 237 with high intensity. Moreover, reacting of 2-amino-N-arylbenzamides 6a-d prepared according to the procedures reported in literature with 4,9-dimethoxy-5-oxo-5H-furo[3,2-g]chromene-6-carbaldehyde 7a prepared by the reported method (Hishmat *et al*., 1999a) under reflux in presence of piperidine afforded, in each case, the corresponding 3,4-dihydroquinazolin-4-one derivatives 8a-d in moderate yields, (Scheme 1). The structures of the products 8a-d were also identified from their elemental analyses and spectroscopic data (IR, 1H-NMR, MS). For example, the IR spectra showed, in each case, two characteristic absorption bands in the region 1654-1630 cm^{-1} and 1630-1620 cm^{-1} (2C = O). Both 1H-NMR and MS spectral data were in agreement with the assigned structures. Present investigation was also extended to study the reaction of 2 with the aromatic aldehydes 7a,b to give the corresponding 2-arylmethylidenaminobenzoyl chlorides 9a,b in good yields, in agreement with (Hishmat *et al*., 1999b) (Scheme 1). The IR spectra of the isolated products showed, in each case, a lack of the (NH_2) absorption bands and the presence of two (C = O) absorption bands at 1705 and 1637 cm^{-1} in 9a and the presence of (C = N) and (C = O) absorption bands at 2200 and 1681 cm^{-1}, respectively, in 9b. The1H-NMR spectra of the isolated products revealed, in each case, a characteristic singlet in the region δ7.99, 7.87 ppm, assignable to the (HC = N) proton.

Indeed, the structures of the products 8a-d were confirmed by their independent synthesis via the reaction of the product 9a with the appropriate amine 5a-d. In conclusion, reaction of 2-aminobenzoyl chloride 2 with ammonia, phenyl hydrazine and primary aromatic amines in 2:1 molar ratio provides an easy and convenient route to a variety of 2,3-disubstituted-3,4-dihydroquinazolin-4-ones 4a-d, while reaction with primary aromatic amines 5a-d in equimolecular ratio (1:1) gives access to various secondary amides of anthranilic acid 6a-d that can be readily converted into another series of 2,3-disubstituted-3,4-dihydro-quinazolin-4-ones 8a-d. The newly synthesized compounds showed variable antimicrobial activities (Table 2).

In present investigation, the starting α-keto acid 10, prepared from the reaction of 7a (Hishmat *et al*., 1999b) with pyruvic acid, was very useful in the preparation of a new series of various heterocyclic compounds (Scheme 2). In the first series of experiments, the reaction of 10 with each of malononitrile and ethyl cyanoacetate under the condition of Micheal-type reaction (El-Ashry, 1977a, b, 1978a,b,c) followed by cyclization afforded the substituted pyran-2-carboxylic acids 11a,b, respectively. The assigned structures were found to be in accordance with spectral data and elemental analyses. For example, the IR spectrum of compound 11a showed one characteristic absorption band at 2210 cm^{-1} (CN) and two bands at 1710, 1628 cm^{-1} (2C = O), while, compound 11b showed three characteristic absorption bands at 1740, 1710 and 1620 cm^{-1} (3C = O). The 1H-NMR spectrum of compound 11b revealed a singlet signal at δ 3.41 ppm (2H, q, CH_2) and another singlet signal at δ 1.20 ppm (3H, t, CH_3) characterized for ester group.

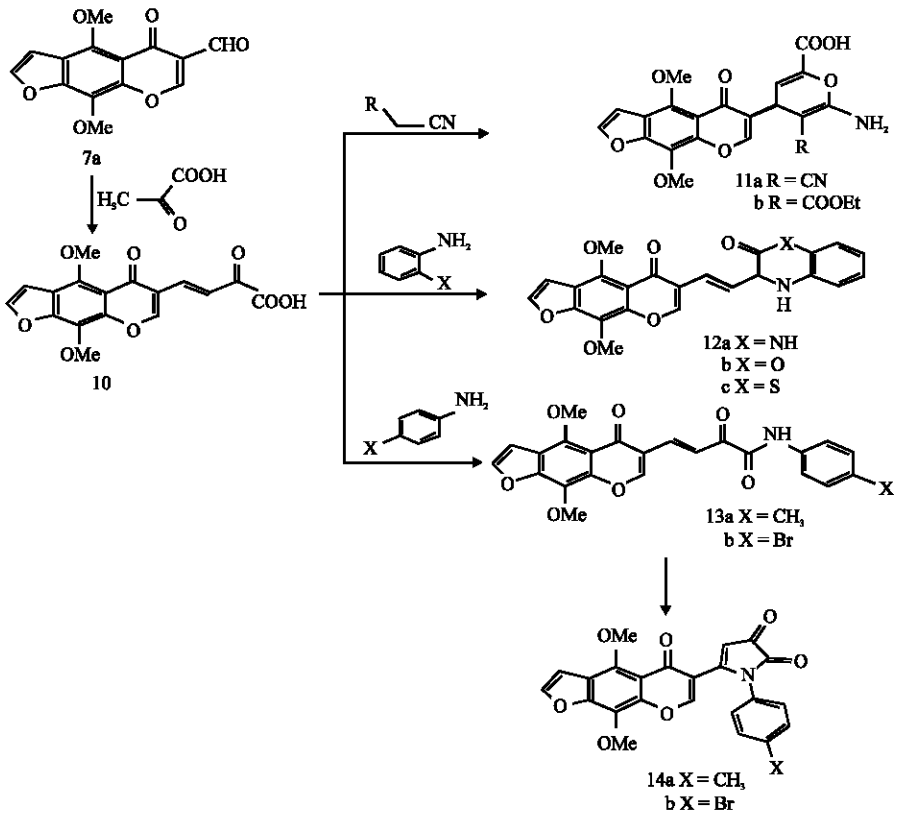
Moreover, α-keto acids were known to condense with aromatic diamines to yield very stable quinoxaline compounds (Katritzky *et al*., 2004; El-Ashry *et al*., 1978a, b, 2005). Here, we reported that the reaction of 10 with o-phenylenediamine to give the quinoxaline derivative 12a. Similarly, treatment of 10 with each of



Scheme 1:

o-aminophenol, o-aminothiophenol resulted in the formation of both of dihydrobenzoxazin-2-one 12b and dihydrobenzothiazin-2-one derivative 12c, respectively. Structures 12a-c were elucidated according to their elemental analyses and spectral data. In our investigation, condensation of compound 10 with primary aromatic amines (p-toludine and p-bromoaniline) in THF and in the presence of DMTMM [4-(4,6-dimethoxy-1,3,5-triazole-2-yl)-4-methyl morpholinium chloride] yielded the carboxamide derivatives 13a,b in good yields which gave rise to the pyrroledione derivatives 14a,b. Structures 13a,b and 14a,b were confirmed according to their elemental analyses and spectral data (IR,1H-NMR and MS).

Antimicrobial activities: Table 2 showed varying degrees of sensitivity of test organisms to the samples under investigation. Obviously, the newly synthesized 2,3-disubstituted-3,4-dihydroquinazolin-4-ones showed a high activity against Gram positive, Gram negative bacteria and fungi as well. The other group (pyruvic gp.) showed a little activity from the anthranilic gp. From the two series of products 4a-d and 8a-d, it has been found that compounds 4b, 8a and 8b were the most active compounds against the test organisms. Compound 8b was the most active against Gram positive and Gram negative bacteria (*B. subtilus* and *E. coli*) where compounds 4b and 8a were active against



Scheme 2:

(*St. aureus*). Compound 12a is the least active member of this group. On the other hand, compound 14b showed a good activity compound against *St. aureus*.

The diameter of the clear inhibition zone was measured for each sample.

CONCLUSION

In conclusion, reaction of the α-keto acid 10 with active methylenes afforded the corresponding pyran-2-carboxylic acid derivatives 11a,b. On the other hand, the condensation of compound 10 with each of o-phenylenediamine, o-aminophenol and o-aminothiophenol yielded the dihydroquinoxalinone, dihydrobenzoaxazinone and dihydrobenzothiazinone derivatives 12a-c. Also, treatment of 10 with primary aromatic amines afforded the carboxamide derivatives 13a,b which gave rise to the pyrroledione derivatives 14a,b in moderate yields.

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REFERENCES

Ali, M.M., M.M.F. Ismail, M.S.A. El-Gaby, M. A. Zahran and Y.A. Ammar, 2000. Synthesis and antimicrobial activities of some novel quinoxalinone derivatives. Molecules, 5: 864-873.

El-Ashry, E.S.H., M. Shaban, M. Nassr and V.N. Reinhold, 1977a. Org. Prep. Proceeding Int., 9 1977a. Sugar 1,3,4-oxadiazoles. The synthesis of sugar 1,3,4-oxadiazoline derivatives, pp: 267.

El-Ashry, E.S.H., Y. El-Kilany and F. Singab, 1977b. Synthesis of some pyrazole derivatives having L-threo and D-erythro side chains. Carbohydr. Res., pp: 56-93.

El-Ashry, E.S.H., I.E. El-Kholy and Y. El-Kilany, 1978a. Dehydrative ring closure of 3-substituted 2-quinoxalinones to give fused and nonfused pyrazoloquinoxalines. Carbohydr. Res., pp: 60-303.

El-Ashry, E.S.H., I.E. El-Kholy and Y. El Kilany, 1978b. Periodate oxidation products of 3-substitued 2-quinoxalinones, preparation of glyoxalyl quinoxalinones. Carbohydr. Res., pp: 60-396.

El-Ashry, E.S.H., I.E. El-Kholy and Y. El-Kilany, 1978c. Reactions of 3-(1-arylhydrazono-L-threo-2,3,4-trihydroxybutyl)-1-methyl-2-quinoxalinones. Carbohydr. Res., pp: 64-81.

El-Ashry, E.S.H., E. Ramadan, H. Abdel Hamid and M. Haggar, 2005. Microwave irradiation for enhancing the regioselective synthesis of 6H-indolo[2,3-b]quinoxaline. J. Chem. Res., pp: 229.

Hishmat, O.H., S.M.S. Atta, N.M. Fawzy and H.M.F. Roaiah, 1999a. The reaction of 2,3-diphenyl-5-methoxy-6-formylindole with active methylene, aromatic amines and hydrazines. Egypt J. Chem., 42: 189-197.

Hishmat, O.H., N.M. Fawzy, D.S. Farag and A.S. Abd El All, 1999b. Aminolysis and hydrolysis of chromonyl oxazolnes leading to new chromones. Roumanian J. Chem. 44: 161-167.

Katritzky, A.R., J.W. Rogers, R. M. Witek and S.K. Nair ARKIVOC, 2004. Novel syntheses of pyrido[1,2-a]pyrimidin-2-ones, 2H-quinolizin-2-ones, pyrido[1,2-a] quinolin-3-ones and thiazolo[3,2-a]pyrimidin-7-ones, pp: 52-60.