Synthesis of Novel pyrimido[4,5-b]quinoline-4-one Derivatives and Assessment as Antimicrobial and Antioxidant Agents

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ABSTRACT

Objective: Antimicrobial resistance has emerged as one of the serious global health problems of the 21st century that threatens the efficient treatment and prevention of an ever-increasing range of infections caused by bacteria, viruses, and fungi. Therefore, it would be favorable to find promising agents with antioxidant and antimicrobial activity combined in one molecule. Key findings: Pyrimido[4,5-b] quinolines are biologically active compounds that are known to rely primarily on the functional group’s existence and location. Quinolinobenzono[1,3]oxazin-4-one (3) was prepared and played as electrophilic interface/mediator for the synthesis of many compounds, such as pyrimido[4,5-b]quinoline, quinoline-carboxamide and oxoquinazolin-acetamide by reacting with nucleophilic reagent. Summary: Results revealed that pyrimido[4,5-b] quinoline derivatives (17b, 9d and 9c) are the most potent compounds that displayed significant antimicrobial activity along with compounds 17a, 29b, 5, 19, 23b, and 25b that appeared to be more promising as antioxidant agents than ascorbic acid. Key words: Quinoline, Benzoazinones, Pyrimidoquinolin, Antimicrobial agent, Antioxidant agent.

INTRODUCTION

The compounds based on scaffold of quinolines have been reported to possess a wide range of pharmaceutical properties1-7. Several structures based on quinoline have proved effective inhibitors of important proteins from microbial pathogens8. The modified classes of compounds based on quinolines have been studied recently for their antimicrobial9-10. Quinoline-carboxamide I, II, III were reported as the most potent EGFR inhibitors with IC50 2.6, 0.49 and 1.73 mM, respectively11. Iminosugar/Azasugars fused benzo [1,3]thiazin-4-one exhibited significant HIV-RT inhibitory activities12-13 (Figure 1).

Pyrimido[4,5-b]quinolin-4-ones were reported as analgesic, anti-inflammatory, and antimicrobial14 antioxidantmitotic agents and cytotoxic activity15. Pyrrolidine-2,5-dione showed antioxidant, antidiabetic activity16 analgesic and antialdolysmic activity17.

Benzoazinones which are widely used in pharmaceutics have a wide range of pharmaceutical activities for example, niphlogistic, anti fungal, antibacterial18, anti-human coronavirus19, inhibitor of human leucocyte elastase, anti-cathespin G, complement protein receptor blocker20 and chymotrypsin antagonist21. Benzo[1,3]oxazin-4-ones (IV) showed high significant against DNA-PK, PI3K, PDE3A enzymes and platelet aggregation22. Benzoazinones IV have showed antioxidant and anticancer activity23. Based on that, we decided to complete the work on pyrimido[4,5-b]quinoline and synthesis of benzo[d][1,3]oxazin-4-one as stating material for new compounds and evaluating their antioxidant and antimicrobial activity.

MATERIALS AND METHODS

 Equipments

All melting points are uncorrected and were taken on open capillary tubes using electropherical apparatus 9100. Elemental micro analyses were carried out at microanalytical unit, Central Services Laboratory, National Research Centre, Dokki, Cairo-Egypt, using Vario Elementar and were found within + or -0.3% of the theoretical values. Infrared spectra were recorded on a Jasco FT/IR-6100, Fourier Transform Infrared Spectrometer at cm-1 scale using KBr disc technique at the Central Services Lab. NRC, Dokki, Cairo, Egypt. 1HNMR spectra were determined by using a JEOL EX-270 NMR Spectrometer.

Chemistry synthesis

Synthesis of 2-(10-cyclohexyl-5-(3,4-dimethoxyphenyl)-4-oxo-3,4,5,6,7,8,9,10-octahydro pyrimido[4,5-b]quinolin-2-yl)-4H-benzo[d][1,3] oxazin-4-one (3)

To a solution of anthranilic acid (1.371 g, 0.01 mole) in dry pyridine (30 mL), 10-cyclohexyl-5-(3,4-dimethoxyphenyl)-4-oxo-3,4,5,6,7,8,9,10-
octahydropyrimido[4,5-b]quinoline-2-carbonyl chloride (1) (0.02 mole) was added portion wise with stirring at room temperature for 12 hrs. The reaction mixture was poured onto cold water (100 mL) and the precipitated solid was filtered off, washed with cold water, dried and recrystallized from ethanol to give benzod[1,3]azin-4-one derivative 3.

Yellow crystals; Yield 60%; m.p. 123–124 °C; IR (KBr, cm⁻¹): 3450 (NH), 1745 (C=O), 1715 (C=O), 1654, 1680 (C=N), 1243 (aryl ethers); 1 H-NMR (500 MHz, DMSO-d⁶, δ ppm): (relative abundance, %)): 566 (M + , 30); Anal. Calcd. for C₃₉ H₄₁ N₆ O₅: C, 70.07; H, 6.24; N, 19.8; Found: C, 69.42; H, 6.27; N, 12.45; S, 5.5.

Synthesis of N-(2-((2-aminophenyl)carbamoyl)phenyl)-10-cyclohexyl-5-(3,4-dimethoxyphenyl)-4-oxo-3,4,5,6,7,8,9,10-octahydropyrimido[4,5-b]quinolin-4(3H)-one (5)

A mixture of benzoxazinone 3 (3.93 g, 0.01 mole) and CH₃ COONH₄ (2.68 g, 0.01 mole) was fused in an oil bath. The reaction mixture was left to cool, washed with water several times, filtered off, dried and recrystallized from ethanol to give 5.

Yellow crystals; Yield 45%; m.p. 114–115 °C; IR (KBr, cm⁻¹): 3440, 3337 (NH), 1729, 1715 (C=O), 1637, 1624 (C=N), 1290 (OMe); 1 H-NMR (500 MHz, DMSO-d⁶, δ ppm): 1.45 (m, 2H, CH₂), 1.75-2.20 (q, 4H, 2CH₂), 1.82 (m, 2H, CH₂), 2.50 (m, 1H, CH), 3.72 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 4.40 (s, 1H, CH), 6.61-6.85 (m, 3H, Ar-H), 7.21-8.42 (d, 4H, Ar-H), 10.50 (s, 1H, NH); MS (m/z, relative abundance, %)): 566 (M⁺, 30); Anal. Calcld. for CₙH₁ₙN₂O₅: C, 69.95; H, 6.05; N, 9.89; Found: C, 69.79; H, 6.02; N, 12.38.

Synthesis of 10-cyclohexyl-5-(3,4-dimethoxyphenyl)-2-(4-thioxo-4H-dihydroquinazolin-2-yl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (6)

A mixture of benzoxazinone 3 (3.93 g, 0.01 mole) and P₂S₅ (8.9 g, 0.02 mole) in dry xylene (40 mL) was refluxed for 8 h. The reaction mixture was filtered off while hot, concentrated and the solid that separated on cooling was washed with petroleum ether (b.p. 80-100°), then recrystallized from ethanol to give 6.

Yellow crystals; Yield: 53%; m.p. 146–148 °C; IR (KBr, cm⁻¹): 3398 (NH), 1725 (C=O), 1646, 1633 (C=NH), 1121 (OMe), 1150 (C=S); 1 H-NMR (500 MHz, DMSO-d⁶, δ ppm): 1.45 (m, 2H, CH₂), 1.50-1.81 (m, 4H, 2CH₂), 1.52 (t, 2H, CH₂), 2.50 (m, 1H, CH), 3.78 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 4.20 (s, 1H, NH), 4.40 (s, 1H, CH), 5.50 (s, 1H, NH), 6.61-7.89 (m, 11H, Ar-H), 9.30 (s, 1H, NH), 10.10 (s, 1H, NH), 11.05 (s, 1H, NH); MS (m/z, relative abundance, %)): 674 (M⁺, 35); Anal. Calcld. for CₙH₁₅N₂O₅: C, 69.42; H, 6.27; N, 12.45; Found: C, 69.20; H, 5.79; N, 12.28.

Synthesis of 10-cyclohexyl-5-(3,4-dimethoxyphenyl)-2-(4-oxo-3,4-
Synthesis of compounds 9a-d

A solution of benzoazinone 2 (3.93 g, 0.01 mole) and amine derivatives namely, hydrazine hydrate, p-aminophenidine, 4-bromoaniline, or 4-aminoacetophenone (0.02 mole) in absolute EtOH (30 mL) was refluxed for 6 hours. The solid product that separated on cooling was filtered off, dried and recrystallized from ethanol to afford the quinazolinone derivative 9a-d.

2-(3-amino-4-oxo-3,4-dihydroquinazolin-2-yl)-10-cyclohexyl-5-(3,4-dimethoxyphenyl)-10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (9a)

Yellow crystals; Yield 63%; m.p. 109-110 °C; IR (KBr, cm⁻¹): 3500, 3477, 1748, 1728 (C=O), 1630, 1615 (C=N), 1220 (OMe); ¹H-NMR (500 MHz, DMSO-d₆, δ / ppm): 1.45 (m, 2H, CH₂), 1.50-1.81 (m, 4H, 2 CH₂), 1.52 (t, 2H, CH₃), 1.65 (m, 2H, CH₂), 1.74 (m, 2H, CH₂), 1.75-2.20 (q, 4H, 2CH₂), 1.82 (t, 2H, CH), 2.50 (m, 1H, CH), 3.78 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 4.40 (s, 1H, CH), 5.50 (s, 2H, NH), 6.61-7.70 (m, 7H, Ar-H), 11.30 (s, 1H, NH); MS (m/z, relative abundance, %): 580 (M⁺, 65); Anal. Calcd. for C₃₈H₃₈N₆O₄: C, 71.01; H, 5.96; N, 13.08; Found: C, 71.23; H, 5.98; N, 13.41.

Synthesis of 10-cyclohexyl-5-(3,4-dimethoxyphenyl)-2-(4-oxo-3-(pyridin-3-yl)-3,4-dihydro-quinazolin-2-yl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (13)

Yellow crystals; Yield 38%; m.p. 136-137 °C; IR (KBr, cm⁻¹): 3477 (NH), 1740, 1733 (C=O), 1690, 1683, 1665 (C=N), 1258 (OMe); ¹H-NMR (500 MHz, DMSO-d₆, δ / ppm): 1.45 (m, 2H, CH₂), 1.50-1.81 (m, 4H, 2 CH₂), 1.52 (t, 2H, CH), 1.65 (m, 2H, CH₂), 1.74 (m, 2H, CH₂), 1.75-2.20 (q, 4H, 2CH₂), 1.82 (t, 2H, CH), 2.50 (m, 1H, CH), 3.78 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 4.20 (s, 1H, CH), 6.61-8.30 (m, 11H, Ar-H), 11.20 (s, 1H, NH); MS (m/z, relative abundance, %): 642 (M⁺, 55); Anal. Calcd. for C₃₈H₃₈N₆O₄: C, 71.01; H, 5.96; N, 13.08; Found: C, 71.23; H, 5.98; N, 13.41.

Synthesis of compounds 17a-d

To a solution of benzoazinone 3 (2.35 g, 0.006 mole) in EtOH (30 mL), NH₂OH.HCl (0.417 g, 0.006 mole) and CH₃COONa (0.49 g, 0.006 mole) dissolved in the least amount of water. The reaction mixture was refluxed for 8 h, cooled and then concentrated. The solid product was filtered off and recrystallized from ethanol to give 15b.

Yellowish brown crystals; Yield 65%; m.p. 122-123 °C; IR (KBr, cm⁻¹): 3633 (OH), 3392 (NH), 1738, 1725 (C=O), 1630, 1612 (C=N), 1251 (OMe); ¹H-NMR (500 MHz, DMSO-d₆, δ / ppm): 1.45 (m, 2H, CH₂), 1.50-1.81 (m, 4H, 2 CH₂), 1.52 (t, 2H, CH), 1.65 (m, 2H, CH₂), 1.74 (m, 2H, CH₂), 1.75-2.20 (q, 4H, 2CH₂), 1.82 (t, 2H, CH), 2.50 (m, 1H, CH), 3.78 (s, 3H, OCH₃), 3.81 (s, 3H, OCH₃), 4.20 (s, 1H, CH), 6.10 (s, 1H, OH), 7.90-8.50 (m, 7H, Ar-H), 10.89 (s, 1H, NH); MS (m/z, relative abundance, %): 581 (M⁺, 20); Anal. Calcd. for C₂₃H₁₈N₄O₂: C, 75.57; H, 5.37; N, 16.66; Found: C, 75.70; H, 5.46; N, 16.51.

To a solution of benzoazinone 3 (3.93 g, 0.01 mole) in absolute EtOH (30 mL) containing few drops of piperidine, appropriate aldehydes namely, p-methoxybenzaldehyde, p-fluorobenzaldehyde, p-nitrobenzaldehyde, or 2-thiophenecarboxaldehyde (0.01 mole) was added. The reaction mixture was refluxed for 5 h, concentrated and left to cool. The precipitated product was filtered off and recrystallized from ethanol to give 17a-d.

10-cyclohexyl-5-(3,4-dimethoxyphenyl)-2-(3-hydroxy-4-oxo-3,4-dihydro-quinazolin-2-yl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (15)

To a solution of benzoazinone 3 (3.93 g, 0.01 mole) in absolute EtOH (30 mL) containing few drops of piperidine, appropriate aldehydes namely, p-methoxybenzaldehyde, p-fluorobenzaldehyde, p-nitrobenzaldehyde, or 2-thiophenecarboxaldehyde (0.01 mole) was added. The reaction mixture was refluxed for 5 h, concentrated and left to cool. The precipitated product was filtered off and recrystallized from ethanol to give 17a-d.
10-cyclohexyl-5-(3,4-dimethoxyphenyl)-2-(3-(4-fluorobenzylidene)amino)-4-oxo-3,4-dihydroquinazolin-2-yl)-5,6,7,8,9,10-hexahydropyrimidin-4(5H)-yl)amino)-4,4-dimethylpyrimidin-2(1H)-one (17b)

Yellow crystals; Yield 65%; m.p. 169-170 ºC; IR (KBr, cm⁻¹): 3501 (NH), 1730, 1721, 1718 (C=O), 1635, 1631 (C=N), 1225 (OMe); ¹H-NMR (500 MHz, DMSO-d₆, δ / ppm): 1.45 (m, 2H, CH₂), 1.50-1.81 (m, 4H, 2 CH₂), 1.52 (t, 2H, CH), 1.65 (2m, 2H, CH), 1.74 (m, 2H, CH), 1.75-2.20 (q, 4H, 2CH₂), 1.82 (t, 2H, CH), 2.50 (m, 1H, CH), 3.77 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 4.11 (s, 1H, CH=N), 4.40 (s, 1H, CH), 7.20-7.75 (m, 11H, Ar-H), 11.20 (s, 1H, NH); MS (m/z, relative abundance, %): 686 (M⁺, 45); Anal. Calcd. for C₄₁H₄₂N₆O₅: C, 70.69; H, 6.56; N, 10.54; Found: C, 71.83; H, 5.30; N, 10.54.

4-chloro-N-(4-chlorobenzoyl)-N-(4-(2-(10-cyclohexyl-5-(3,4-dimethoxyphenyl)-4-oxo-3,4,5,6,7,8,9,10-octahydropyrimido[4,5-b]quinolin-2-yl)-4-oxoquinazolin-3(4H)-yl)benzamide (21b)

Yellow crystals; Yield 50%; m.p. 129-130 ºC; IR (KBr, cm⁻¹): 3501 (NH), 1744, 1727, 1720, 1718 (C=O), 1650, 1635 (C=N), 1225 (OMe), 750 (C-Cl); ¹H-NMR (500 MHz, DMSO-d₆, δ / ppm): 1.45 (m, 2H, CH₂), 1.50-1.81 (m, 4H, 2 CH₂), 1.52 (t, 2H, CH), 1.65 (2m, 2H, CH), 1.74 (m, 2H, CH), 1.75-2.20 (q, 4H, 2CH₂), 1.82 (t, 2H, CH), 2.50 (m, 1H, CH), 3.76 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 4.40 (s, 1H, CH), 6.61-8.20 (m, 17H, Ar-H), 11.20 (s, 1H, NH); MS (m/z, relative abundance, %): 857 (M⁺, 20); Anal. Calcd. for C₄₇H₄₄Cl₂N₆O₆: C, 71.56; H, 5.62; N, 10.65; Found: C, 71.83; H, 5.30; N, 10.54.

Synthesis of 23a,b

A mixture of quinazolinone 7a (0.01 mole) and maleic anhydride or phthalic anhydride (0.01 mole) was fused in an oil bath at 6 hrs. The reaction mixture was triturated with ice/HCl. The solid product was filtered off, washed with water several times, dried and then recrystallized from ethanol affording 23a,b.

1-(2-(10-cyclohexyl-5-(3,4-dimethoxyphenyl)-4-oxo-3,4,5,6,7,8,9,10-octahydropyrimido[4,5-b]quinolin-2-yl)-4-oxoquinazolin-3(4H)-yl)pyrrole-2,5-dione (23a)

Yellow crystals; Yield 52%; m.p. 143-145 ºC; IR (KBr, cm⁻¹): 3444 (NH), 1745, 1730, 1722, 1715 (C=O), 1630, 1617 (C=N), 1217 (OMe); ¹H-NMR (500 MHz, DMSO-d₆, δ / ppm): 1.45 (m, 2H, CH₂), 1.50-1.81 (m, 4H, 2 CH₂), 1.52 (t, 2H, CH), 1.65 (2m, 2H, CH), 1.74 (m, 2H, CH), 1.75-2.20 (q, 4H, 2CH₂), 1.82 (t, 2H, CH), 2.50 (m, 1H, CH), 3.77 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 4.40 (s, 1H, CH), 5.30 (dd, 2H, CH=CH), 6.61-7.90 (m, 7H, Ar-H), 11.20 (s, 1H, NH); MS (m/z, relative abundance, %): 660 (M⁺, 60); Anal. Calcd. for C₄₇H₄₆N₆O₆: C, 70.69; H, 5.49; N, 12.72; Found: C, 70.56; H, 5.30; N, 12.91.

2-(2-(10-cyclohexyl-5-(3,4-dimethoxyphenyl)-4-oxo-3,4,5,6,7,8,9,10-octahydropyrimido[4,5-b]quinolin-2-yl)-4-oxoquinazolin-3(4H)-yl)isodoline-1,3-dione (23b)

Yellow crystals; Yield 65%; m.p. 162-163 ºC; IR (KBr, cm⁻¹): 3443 (NH), 1739, 1725, 1720, 1710 (C=O), 1650, 1644 (C=N), 1217 (OMe); ¹H-NMR (500 MHz, DMSO-d₆, δ / ppm): 1.45 (m, 2H, CH₂), 1.50-1.81 (m, 4H, 2 CH₂), 1.52 (t, 2H, CH), 1.65 (2m, 2H, CH), 1.74 (m, 2H, CH), 1.75-2.20 (q, 4H, 2CH₂), 1.82 (t, 2H, CH), 2.50 (m, 1H, CH), 3.77 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 4.40 (s, 1H, CH), 5.70-7.90 (m, 11H, Ar-H), 11.05 (s, 1H, NH); MS (m/z, relative abundance, %): 710 (M⁺, 55); Anal. Calcd. for C₄₇H₄₆N₆O₆: C, 70.28; H, 5.39; N, 11.82; Found: C, 69.46; H, 5.71; N, 11.38.
Synthesis of compound 25a,b

A mixture of 17a,b (0.01 mole), chloroacetyl chloride (1.13 g, 0.01 mole) and triethyl amine (5 drops) in dry dioxane (30 mL) was heated under reflux for 8 hours. The solid product that separated on cooling was filtered off, dried and recrystallized from ethanol to give 25a,b.

2-(3-(3-chloro-2-(4-fluorophenyl)-4-oxoazetidin-1-yl)-4-oxo-3,4-dihydro-quinazolin-2-yl)-10-cyclohexyl-5-(3,4-dimethoxyphenyl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (25a)

Yellow crystals; Yield 60%; m.p. 156-158 °C; IR (KBr, cm⁻¹): 3444 (NH), 1750, 1738, 1720 (C=O), 1644, 1620 (C=N), 1521 (CH, thiazole), 10.98 (s, 1H, NH); MS (m/z, (relative abundance, %)): 760 (M⁺, 35); Anal. Calcd. for C₄₂ H₄₁F N₆ O₅ S: C, 66.30; H, 5.43; N, 11.05; Found: C, 66.16; H, 5.46; N, 11.28.

2-(3-(2-(10-cyclohexyl-5-(3,4-dimethoxyphenyl)-4-oxo-3,4,5,6,7,8,9,10-octahydro-pyrimido[4,5-b]quinolin-2-yl)-4-oxoquinazolin-3(4H)-yl)-2-(4-fluorophenyl)-2H-benzo[e][1,3]thiazin-4(3H)-one (29a)

Yellow brown crystals; Yield 68%; m.p. 150-151 °C; IR (KBr, cm⁻¹): 3396 (NH), 1740, 1735, 1720 (C=O), 1690, 1650 (C=N), 1219 (O=O); 1'H-NMR (500 MHz, DMSO-d₆, δ / ppm): 1.45 (m, 2H, CH₂), 1.50-1.81 (m, 4H, 2 CH₂), 1.75-2.20 (q, 4H, 2 CH₂), 1.82 (t, 2H, CH₂), 2.50 (m, 1H, CH), 2.72 (s, 3H, OCH₃), 2.90 (d, 1H, CH), 3.50 (s, 1H, CH-Cl), 4.10 (s, 6H, 2 OCH₃), 4.40 (s, 1H, CH₂), 6.20 (s, 1H, NH), 6.98-7.90 (m, 11H, Ar-H); MS (m/z, (relative abundance, %)): 777 (M⁺, 15); Anal. Calcd. for C₂₃H₂₃ClFN₃O₅: C, 66.31; H, 5.59; N, 10.84; Found: C, 66.34; H, 5.37; N, 10.85.

Synthesis of 27a,b and 29a,b

A mixture of compound 17a,b (4.95 g, 0.01 mole) and thioglycolic acid (28) (0.01 mole) in dry benzene (20mL) was added drop wise with stirring at room temperature for 1 hour. The reaction mixture was heated under reflux for 6 hours, cooled and the precipitated product was filtered off and recrystallized from ethanol to give the desired products 27a,b and 29a,b respectively.

2-(3-(10-cyclohexyl-5-(3,4-dimethoxyphenyl)-4-oxo-3,4,5,6,7,8,9,10-octahydro-pyrimido[4,5-b]quinolin-2-yl)-4-oxoquinazolin-3(4H)-yl)-2-(4-fluorophenyl)-2H-benzo[e][1,3]thiazin-4(3H)-one (29b)

Yellow crystals; Yield 53%; m.p. 115-116 °C; IR (KBr, cm⁻¹): 3396 (NH), 1740, 1735, 1720 (C=O), 1690, 1650 (C=N), 1219 (O=O); 1'H-NMR (500 MHz, DMSO-d₆, δ / ppm): 1.45 (m, 2H, CH₂), 1.50-1.81 (m, 4H, 2 CH₂), 1.75-2.20 (q, 4H, 2 CH₂), 1.82 (t, 2H, CH₂), 2.50 (m, 1H, CH), 2.90 (d, 1H, CH), 3.50 (d, 1H, CH-Cl), 3.78 (s, 3H, OCH₃), 3.80 (s, 3H, OCH₃), 3.82 (s, 3H, OCH₃), 4.40 (s, 1H, CH₂), 6.98-7.90 (m, 11H, Ar-H), 10.95 (s, 1H, NH); MS (m/z, (relative abundance, %)): 763 (M⁺, 40); Anal. Calcd. for C₂₃H₂₃FN₃O₅: C, 68.60; H, 5.27; N, 10.21; Found: C, 68.10; H, 5.23; N, 10.02.

Biological activity

Test microorganisms

Standard strains used to evaluate antimicrobial activity; Gram positive bacteria; (Bacillus subtilis ATCC 6633 and Staphylococcus aureus ATCC 6538-P), Gram negative bacteria (Pseudomonas aeruginosa ATCC 27853 and Bordetella pertussis 6538-P), Gram negative bacteria (Escherichia coli); and fungi (Aspergillus niger NRRL A-326 and Trichoderma viride ATCC 9797). Yeasts; (Saccharomyces cervesiae ATCC 10231 and Candida albicans ATCC 10231 and Saccharomyces cerevisiae) and fungii (Aspergillus niger NRRL A-326 and Trichoderma viride NRC 314) were obtained from culture collection stocks maintained in the Department of Microbial Chemistry, National Research Centre, Egypt. Bacteria were maintained at 4 °C on nutrient agar slants containing (g/L): beef extract, 3; peptone, 5; and agar (SDA) and Potato dextrose agar (PDA) media, respectively. 

Antimicrobial activity

The antimicrobial activity of each chemical compound was investigated in vitro by the Department of Microbial Chemistry, National Research Centre using the agar well diffusion method (WDM) recommended by the Clinical and Laboratories Standards Institute (CLSI) to measure the in vitro susceptibility of bacteria to antimicrobial agents used in clinical settings. The accuracy of this test depends on the maintenance of standard procedures. In the present study, a stock solution containing 20 mg/mL in DMSO is prepared for each chemical compound. Dispense nutrient agar seeded with 1.5 x 10⁶ CFU/mL of each bacterial strain, DSA seeded with 2.0 x 10⁶ CFU/mL of each yeast and PDA seeded with 2.0 x 10⁶ CFU/mL for each fungal strain (cooled below 45 °C) into sterile Petri dishes, give a depth of 4 mm (~20 mL in Petri dish of 85 mm in diameter). Allow the agar to set before moving the plates. Agar
wells of diameter 8 mm were made in the agar plates with the help of a sterilized cork borer. Wells were loaded with 100 μL (20 mg/mL) of tested compound solutions and controls under aseptic condition. These plates were sealed with parafilm and kept in the refrigerator for 4 h at 5 °C for the complete diffusion of antimicrobial compounds, if any.

Thereafter, the sealed plates were incubated upright at 35 °C for 18-24 h for bacteria and yeasts, and 48-72 h at 28 °C for fungi. Positive control experiments were conducted under similar conditions using cefoxime (20 mg/mL), Ketonazole (20 mg/mL) and cyclosporine (10 mg/mL) as standard drugs for antibacterial and antifungal activity, respectively. Similarly, 10 μL DMSO was used as a negative control.

After the incubation period, antimicrobial activity was evaluated by measuring the diameter of inhibition zone in millimeters (mm) and compared to that of the standard (Positive controls). Inhibition zones with a diameter ≥ 16 mm were considered to have antimicrobial activity for further quantitative tests of their activity. The experiment was performed in triplicate and the average inhibition zone was calculated.

**Determination of minimal inhibitory concentration (MIC)**

In microbiology, the minimum inhibitory concentration (MIC) endpoints were defined as the lowest concentration of the assayed antimicrobial agent, which resulted in a 100% reduction in growth compared to the antimicrobial agent-free growth control test.23 The bacteriostatic activity of the active chemical compounds (with inhibition zones ≥ 16 mm) was evaluated using a two-fold serial dilution technique. Two-fold serial dilutions of the tested compound solutions were prepared using the proper nutrient broth. The final concentrations of the solutions were 25, 50, 75, 100, 150, 200 and 300 μg/mL. Each 5.0 mL received 0.1 mL of inoculums and incubated at 37 °C for 24 h for bacteria and yeasts, and 48 h at 28 °C for fungi. Tests were performed in triplicate and the average inhibition zone was calculated.

**Antioxidant activity of chemical compounds**

**Evaluation of antioxidant activity using the DPPH radical scavenging method**

The percentage of antioxidant activity of each chemical compound was measured by the Department of Microbial Chemistry, National Research Centre using the 1,1-Diphenyl-2-picrylhydrazyl (DPPH) radical scavenging assay. This assay is based on the measurement of the ability of antioxidants to reduce DPPH by measuring the decrease in its absorption wavelength at 515–520 nm. DPPH reacts with hydrogen/electron donor compounds and has a maximum UV–Vis absorption of 515–517 nm. Each 10 μL of freshly prepared DPPH radical solution (0.5 mM in ethanol). The reaction mixture consisted of 50 μL of each chemical compound dissolved in dimethyl sulfoxide (DMSO), as well as the reference standard ascorbic acid and the volume was made uniform to 150 μL using ethanol, 3 mL of absolute ethanol and 150 μL of freshly prepared DPPH radical solution (0.5 mM in ethanol). The mixtures were shaken vigorously and left to stand in the dark for 30 min at room temperature, and the absorbance was measured at 517 nm in Cary-100 UV–Vis spectrophotometer (Agilent Technologies, Frankfurt, Germany) using ethanol as a blank. Control reactions were performed without the test sample (i.e. 150 μL of DPPH + 3.0 mL ethanol). The experiment was carried out in triplicate for each chemical compound. Radical scavenging capacity was expressed as a percentage (%) and was calculated using the following formula:

\[
\text{Radical scavenging activity (\%)} = \frac{(\text{Abs control} - \text{Abs sample}) \times 100}{\text{Abs control}}
\]

The antioxidant activity of each chemical compound and ascorbic acid was expressed as EC50, (the effective micromolar concentration required to scavenge 50% of DPPH radicals) is a typically employed parameter to express the antioxidant capacity and to compare the activity of different compounds (Table 1). It is worth note that EDTA was added to prevent ascorbic acid oxidation.

**RESULTS AND DISCUSSION**

**Chemistry**

Compound 1 was synthesized previously by the author.24 In scheme 1, anthranilic acid (2) reacted with excess of acid chloride derivatives (1) in presence of dry pyridine to afford quinolin-oxazin-4-one derivative (3). IR spectrum of compound 3 demonstrated two bands of C=O and NH at 1715, 1745 and 3450 cm⁻¹, respectively (Scheme 1). 1H-NMR of 3 showed singlet tow OCH3 and NH signals occurring at 3.72, 8.30 and 10.5 ppm, respectively. Compound 3 play as electrophilic intermediate key for the synthesis of interest pharmaceutical derivatives.

In scheme 2, also, the compound 3 refluxed with compound 4 in absolute EtOH to afford carboxamidine compounds (5). IR of compound 5 revealed 3 groups C=O at 1770, 1750, 1745 and two NH, and only one NH. (Scheme 2). 1H-NMR of 5 revealed NH at 5.5 ppm. Moreover, compound 3 refluxed with CH3COONH4 afford quinazolin-4(3H)-one (6). Moreover, in dry xylene/toluene compound 3 refluxed with P2S5 to afford thiazin-4-one (7). Where elemental analysis of 7 revealed S 4.48%.

In scheme 3, compound 3 allowed to react with a series of primary heterocyclic amines and hydrazine hydrate (8a-d) to afford potent antifungal activity against Trichoderma viride that produced the most potent inhibitory activity against the growth of the strains tested. The MIC of compound 17b was equivalent to that of all heterocyclic amines and hydrazine hydrate (8a-d) to afford potent antifungal activity (Table 1). In scheme 4, The nucleophilic amino group of compound 9a condensed with series of aldehydes (16a-d) in presence of piperidine to afford benzylidene-quinazoline (17a-d). Also, 9a refluxed in dry pyridine with CH3COCl or phCOCl to afford 19, 21a, b, respectively (Scheme 4). In addition to, 9a fused with succinic anhydride and phthalic anhydride (22a, b) to yield the corresponding compounds 23a, b.

In last scheme 5, hexahydropyrimidine[4,5-b]quinolin was prepared by refluxing of compound 17a, b with CH3COCl in EtOH in presence of Et3N to afford compounds 25a, b. In addition to, compound 17a, b refluxed with thioglycolic acid or thiosalicic acid in dry benzene to yield new thiazolin-4-one 27a, b and thiazin-one 29a, b, respectively.

**Biological activity**

**In vitro antimicrobial Screening**

The newly synthesized compounds were evaluated as antimicrobial agents. It was observed that from Table 1 and 2, the compound 17b produced the most potent inhibitory activity against the growth of the strains tested. The MIC of compound 17b was equivalent to that of all standard drugs used (25-50 μg/mL). Interestingly, the compound 17b produced potent antifungal activity against Trichoderma viride that is greater than the Cyclosporine reference drug (MIC Cyclosporine: 50μg/mL, MIC compound 17b; 25μg/mL).
Table 1: Antimicrobial activity of based on well diffusion method (100 µL = 2000 µg).

| Compound | Staphylococcus aureus ATCC 6538-P | Bacillus subtilis ATCC 6633 | Pseudomonas aeruginosa ATCC 27853 | Bordetella pertussis | Candida albicans ATCC- 10231 | Saccharomyces cerevisiae | Aspergillus niger NRRL A-326 | Trichoderma viride NRC 314 |
|----------|-----------------------------------|-----------------------------|-----------------------------------|---------------------|-----------------------------|-----------------------------|-----------------------------|-----------------------------|
| 3        | R                                 | R                           | R                                 | R                   | R                           | R                           | R                           | R                           |
| 5        | R                                 | R                           | R                                 | R                   | R                           | R                           | R                           | R                           |
| 6        | R                                 | R                           | R                                 | 20                  | 18                          | R                           | R                           | R                           |
| 7        | R                                 | R                           | R                                 | 13                  | 14                          | R                           | R                           | R                           |
| 9a       | R                                 | R                           | R                                 | 21                  | 20                          | R                           | R                           | R                           |
| 9b       | R                                 | R                           | R                                 | 22                  | 25                          | R                           | R                           | R                           |
| 9c       | 23                                | 25                          | 18                                | 16                  | 25                          | 26                          | R                           | R                           |
| 9d       | 31                                | 33                          | 32                                | 30                  | 27                          | 30                          | 28                          | 31                          |
| 11       | R                                 | R                           | R                                 | R                   | R                           | R                           | R                           | R                           |
| 13       | R                                 | R                           | R                                 | 12                  | 25                          | 20                          | R                           | R                           |
| 15       | R                                 | 16                          | 22                                | 25                  | 27                          | 25                          | 24                          | 30                          |
| 17a      | R                                 | R                           | R                                 | 21                  | 20                          | R                           | R                           | R                           |
| 17b      | 36                                | 35                          | 33                                | 37                  | 29                          | 33                          | 34                          | 35                          |
| 17c      | 23                                | 30                          | 14                                | 16                  | 20                          | 16                          | R                           | R                           |
| 17d      | R                                 | R                           | R                                 | R                   | R                           | R                           | R                           | R                           |
| 19       | 20                                | 23                          | 16                                | 18                  | 20                          | 17                          | R                           | R                           |
| 21a      | R                                 | R                           | R                                 | 15                  | 12                          | R                           | R                           | R                           |
| 21b      | R                                 | 12                          | R                                 | R                   | 13                          | R                           | R                           | R                           |
| 23a      | 11                                | 15                          | 22                                | 24                  | 20                          | 20                          | R                           | R                           |
| 23b      | R                                 | 14                          | 15                                | 22                  | 20                          | 20                          | R                           | R                           |
| 25a      | R                                 | R                           | R                                 | 20                  | 17                          | R                           | R                           | R                           |
| 25b      | R                                 | 12                          | 18                                | 20                  | 22                          | 20                          | R                           | R                           |
| 27a      | R                                 | R                           | R                                 | 20                  | 16                          | 16                          | R                           | R                           |
| 27b      | R                                 | R                           | R                                 | 12                  | 16                          | 16                          | R                           | R                           |
| 29a      | 12                                | 13                          | 12                                | 24                  | 20                          | 20                          | R                           | R                           |
| 29b      | 16                                | 14                          | 17                                | 19                  | 31                          | 26                          | R                           | R                           |
| Negative Control | R                      | R                           | R                                 | R                   | R                           | R                           | R                           | R                           |
| Cefaxone        | 38                                | 36                          | 34                                | 39                  | NT                          | NT                          | NT                          | NT                          |
| Ketoconazole     | NT                                | NT                          | NT                                 | NT                  | NT                          | NT                          | NT                          | NT                          |

R = Resistant. NT = Not tested.

Scheme 1: Synthesis of quinoline-oxazin-4-one derivative.
Scheme 2: Synthesis of quinazoline-carboxamide and thiazine derivatives.

Scheme 3: Synthesis of pyridine-quinazolin and hydroxyquinazolin.
Scheme 4: Synthesis of 4-oxoquinazolin derivatives.

Scheme 5: Synthesis of thiazolidin and thiazin derivatives.
Table 2: MIC (µg/mL) against the pathological strains based on two folds serial dilution technique.

| Compound | Staphylococcus aureus ATCC 6538-P | Bacillus subtilis ATCC 6633 | Pseudomonas aeruginosa ATCC 27853 | Bordetella pertussis ATCC 9797 | Candida albicans ATCC 10231 | Saccharomyces cerevisiae | Aspergillus niger NRRL A-326 | Trichoderma viride NRC 314 |
|----------|----------------------------------|-----------------------------|-----------------------------------|-----------------------------|----------------------------|---------------------------|-----------------------------|---------------------------|
| 3        | NT                               | NT                          | NT                                 | NT                          | NT                        | NT                        | NT                          | NT                        |
| 5        | NT                               | NT                          | NT                                 | NT                          | NT                        | NT                        | NT                          | NT                        |
| 6        | NT                               | NT                          | NT                                 | NT                          | 100                       | 150                       | NT                          | NT                        |
| 7        | NT                               | NT                          | NT                                 | NT                          | NT                        | NT                        | NT                          | NT                        |
| 9a       | NT                               | NT                          | NT                                 | NT                          | NT                        | NT                        | NT                          | NT                        |
| 9b       | NT                               | NT                          | NT                                 | NT                          | 100                       | NT                        | NT                          | NT                        |
| 9c       | 75                               | 75                          | 200                                | 300                         | 75                        | 50                        | NT                          | NT                        |
| 9d       | 50                               | 50                          | 50                                 | 50                          | 50                        | 50                        | 75                          | 50                        |
| 11       | NT                               | NT                          | NT                                 | NT                          | NT                        | NT                        | NT                          | NT                        |
| 13       | NT                               | NT                          | NT                                 | NT                          | 100                       | 150                       | NT                          | NT                        |
| 15       | NT                               | NT                          | NT                                 | NT                          | 100                       | 150                       | NT                          | NT                        |
| 17a      | NT                               | NT                          | NT                                 | NT                          | 100                       | 150                       | NT                          | NT                        |
| 17b      | 50                               | 25                          | 25                                 | 50                          | 25                        | 25                        | 25                          | 25                        |
| 17c      | NT                               | NT                          | NT                                 | NT                          | NT                        | NT                        | NT                          | NT                        |
| 17d      | NT                               | NT                          | NT                                 | NT                          | NT                        | NT                        | NT                          | NT                        |
| 19       | 100                              | 75                          | 300                                | 200                         | 150                       | 200                       | NT                          | NT                        |
| 21a      | NT                               | NT                          | NT                                 | NT                          | NT                        | NT                        | NT                          | NT                        |
| 21b      | NT                               | NT                          | NT                                 | NT                          | NT                        | NT                        | NT                          | NT                        |
| 23a      | NT                               | NT                          | 100                                | 200                         | 200                       | 200                       | NT                          | NT                        |
| 23b      | NT                               | NT                          | NT                                 | NT                          | 100                       | 200                       | NT                          | NT                        |
| 25a      | NT                               | NT                          | NT                                 | NT                          | 200                       | 300                       | NT                          | NT                        |
| 25b      | NT                               | NT                          | 200                                | 100                         | 100                       | 200                       | NT                          | NT                        |
| 27a      | NT                               | NT                          | NT                                 | NT                          | 200                       | NT                        | NT                          | NT                        |
| 27b      | NT                               | NT                          | NT                                 | NT                          | 200                       | NT                        | NT                          | NT                        |
| 29a      | NT                               | NT                          | NT                                 | NT                          | 75                        | 200                       | NT                          | NT                        |
| 29b      | 300                              | NT                          | 300                                | 200                         | 50                        | 75                        | NT                          | NT                        |
| Cefaxone | 25                               | 25                          | 25                                 | 25                          | NT                        | NT                        | NT                          | NT                        |
| Ketoconazole | NT                       | NT                          | NT                                 | NT                          | 50                        | 25                        | NT                          | NT                        |
| Cyclosporine | NT                      | NT                          | NT                                 | NT                          | NT                        | NT                        | 25                          | 50                        |

NT = Not tested.

Figure 2: EC50 (µg/mL) of the synthesized compounds.
Table 3: EC<sub>50</sub> for DPPH inhibition of chemical compounds.

| Chemical compound | EC<sub>50</sub> (µg/mL) |
|-------------------|----------------------|
| 3                 | 100                  |
| 5                 | 15                   |
| 6                 | 60                   |
| 7                 | 75                   |
| 9a                | 45                   |
| 9b                | 25                   |
| 9c                | 90                   |
| 9d                | 45                   |
| 11                | 25                   |
| 13                | 70                   |
| 15                | 35                   |
| 17a               | 10                   |
| 17b               | 70                   |
| 17c               | 40                   |
| 17d               | 35                   |
| 19                | 15                   |
| 21a               | 40                   |
| 21b               | NA                   |
| 23a               | NA                   |
| 23b               | 20                   |
| 25a               | 45                   |
| 25b               | 20                   |
| 27a               | 35                   |
| 27b               | 25                   |
| 29a               | 35                   |
| 29b               | 10                   |
| Ascorbic acid (Control) | 55            |

NA= Not active.

Antioxidant activity

The compounds were evaluated as antioxidant agents and compared with reference drug (ascorbic acid) (Table 3). The obtained potency was as follows: 17a = 29b = 10 µg/mL > 5 = 19 = 15µg/mL > 23b = 25b = 20 µg/mL > 9b = 11 = 27b = 25 µg/mL > 15 = 17d = 27a = 29a = 35 µg/mL > 17c = 21a = 40 µg/mL > 9a = 9d = 25a = 45 µg/mL > Ascorbic acid (EC<sub>50</sub> 55 µg/mL) > 6 = 60 µg/mL > 13 = 17b (EC<sub>50</sub> 70 µg/mL). The remaining derivative compounds (7, 8c, 3, 21b, 23a) exhibited moderate to non-antioxidant activity.

CONCLUSION

A new series of pyrimido[4,5-b] quinoline and benzoxazinones derivatives were synthesized and tested to antioxidant and antimicrobial activity. Results revealed that some of these novel compounds displayed significant biological activity. The compounds 17b, 9d and 9c, showed high promising antimicrobial activity along with several compounds, in addition to, the compounds 17a = 29b = 10 µg/mL showed the most potent antioxidant agents than ascorbic acid.

In the study of the relationship SARs, very good antimicrobial activity was found at the compounds pyrimido[4,5-b] quinoline derivatives (17b, 9d and 9c) against the test microorganisms. Also, pyrimido[4,5-b]quinoline derivatives and oxoquinazolin-benzo[1,3]thiazin (17a = 29b = 10 µg/mL) possess high antioxidant than ascorbic acid.

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