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Research Article

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. Quinolin-benzo-[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. S**ummary:** 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, Benzoxazinones, Pyrimidoquinolin, Antimicrobial agent, Antioxidant agent.

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INTRODUCTION

The compounds based on scaffold of quinolines have been reported to possess a wide range of pharmaceutical properties[1-7]. Several structures based on quinoline have proved effective inhibitors of important proteins from microbial pathogens[8]. The modified classes of compounds based on quinolines have been studied recently for their antimicrobial[9,10]. Quinoline-carboxamide I, II, III were reported as the most potent EGFR inhibitors with IC_{50} 2.6, 0.49 and 1.73 mM, respectively[11]. Iminosugar/Azasugars fused benzo [1,3]thiazin-4-one exhibited significant HIV-RT inhibitory activities[12,13] (Figure 1).

Pyrimido[4,5-b]quinolin-4-ones were reported as analgesic, anti-inflammatory, and antimicrobial[14] antimitotic agents and cytotoxic activity[15]. Pyrrolidine-2,5-dione showed antioxidant, antidiabetic activity[16] analgesic and antiallodynic activity[17].

Benzoxazinones which are widely used in pharmaceutics have a wide range of pharmaceutical activities for example, ntiphlogistic,, antifungal, antibacterial[18], anti-human coronavirus[19], inhibitor of human leucocyte elastase, anti-cathepsin G, complement protein receptor blocker[20] and chymotrypsin antagonist[21]. Benzo[1,3]oxazin-4-ones (IV) showed high significant against DNA-PK, PI3K,PDE3A enzymes and platelet aggregation[22]. Benzoxazinones IV have showed antioxidant and anticancer activity[20] (Figure 1).

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 electrothermal 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 -0.5% 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. ^{1}HNMR spectra were determined by using a JEOL EX-270 NMR Spectrometer at Central Services Lab, NRC. Mass spectra were measured with Finnigan M A T SSQ-7000 mass spectrometer at the Central Services, NRC Dokki, Cairo, Egypt. Follow up of the reactions and checking the purity of the compounds were made by TLC on silica gel-precoated aluminum sheets (Type 60 F254-Merck, Darmstadt, Germany) and the spots were detected by exposure to UV Lamp at 254 nanometer for few seconds.

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-

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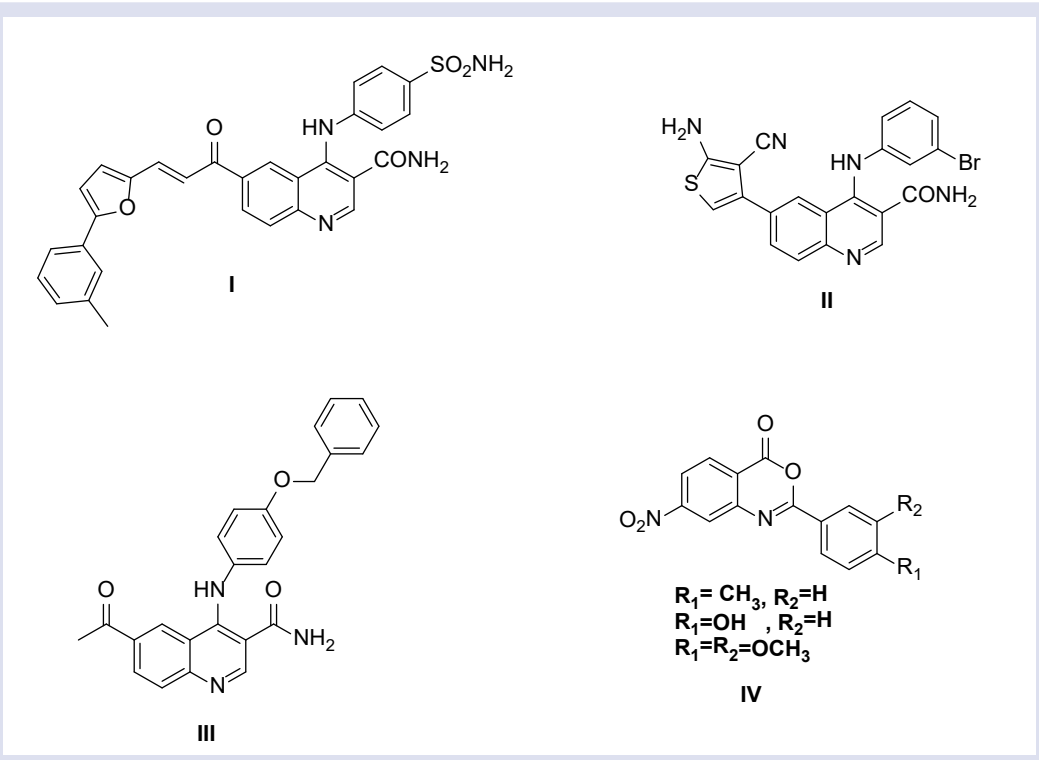


Figure 1: Structure of quinoline carboxamide and benzoxazinones derivatives.

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 benzo[d][1,3]xazin-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-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, $2CH_2$), 1.52 (*m*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, $2CH_2$), 1.82 (*m*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.72 (*s*, 3H, OCH_3), 3.80 (*s*, 3H, OCH_3), 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. Calcd. for $C_{33}H_{34}N_4O_5$: C, 69.95; H, 6.05; N, 9.89; Found: C, 69.98; H, 6.02; N, 9.90.

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]quinoline-2-carboxamide (5)

A mixture of benzoxazinone 2 (1.18 g, 0.003 mole) and *o*-phenylenediamine (0.32gm, 0.003 mole) in EtOH (20 mL) was refluxed for 8 hours. The solid product that separated on cooling was filtered off and recrystallized from ethanol to give **5.**

Reddish brown crystals; Yield 40%; m.p. 101-103 °C; IR (KBr, cm^{-1}): 3521 (NH_2), 3450, 3425, 3390 (NH), 1750, 1740, 1720 (C=O), 1690, 1665 (C=N), 1265 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, $2CH_2$), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.78 (*s*, 3H, OCH_3), 3.80 (*s*, 3H, OCH_3), 4.20 (*s*, 1H, NH), 4.40 (*s*, 1H, CH), 5.50 (*s*, 1H, NH_2), 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. Calcd. for $C_{39}H_{42}N_6O_5$: 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-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 CH_3COONH_4 (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 6.

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-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, $2CH_2$), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.78 (*s*, 3H, OCH_3), 3.81 (*s*, 3H, OCH_3), 4.40 (*s*, 1H, CH), 6.61-7.90 (*m*, 7H, Ar-H), 11.10 (*s*, 1H, NH), 11.20 (*s*, 1H, NH); MS (*m/z*, (relative abundance, %)): 565 (M^+, 55); Anal. Calcd. for $C_{33}H_{35}N_5O_4$: C, 70.07; H, 6.24; N, 12.38; Found: C, 69.79; H, 6.60; N, 12.02.

Synthesis of 10-cyclohexyl-5-(3,4-dimethoxyphenyl)-2-(4-thioxo-4H-benzo[d][1,3]thiazin-2-yl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (7)

A mixture of benzoxazinone 3 (3.93g, 0.01 mole) and P_2S_5 (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 **7**.

Yellow crystals; Yield 53%; m.p. 146-148 °C; IR (KBr, cm^{-1}): 3398 (NH), 1725 (C=O), 1646, 1633 (C=N), 1219 (OMe), 1150 (C=S); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, $2CH_2$), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.78 (*s*, 3H, OCH_3), 3.82 (*s*, 3H, OCH_3), 4.40 (*s*, 1H, CH), 6.91-7.30 (*m*, 7H, Ar-H), 11.20 (*s*, 1H, NH),; MS (*m/z*, (relative abundance, %)): 598 (M^+, 29); Anal. Calcd. for $C_{33}H_{34}N_4O_3S_2$: C, 68.19; H, 5.88; N, 9.61; S, 5.5 Found: C, 66.48; H, 5.23; N, 9.32, S, 4.48.

Synthesis of compounds 9a-d

A solution of benzoxazinone **2** (3.93 g, 0.01 mole) and amine derivatives namely, hydrazine hydrate, *p*-aminopyridine, 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) -5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (9a)

Yellow crystals; Yield 63%; m.p. 109-110 °C; IR (KBr, cm^{-1}): 3500, 3437 (NH), 1744, 1728 (C=O), 1630, 1615 (C=N), 1220 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.78 (*s*, 3H, OCH_3), 3.80 (*s*, 3H, OCH_3), 4.40 (*s*, 1H, CH), 5.50 (*s*, 2H, NH_2), 6.61-7.70 (*m*, 7H, Ar-H), 11.30 (*s*, 1H, NH); MS (*m/z*, (relative abundance, %)): 580 (M^+, 65); Anal. Calcd. for $C_{33}H_{36}N_6O_4$: C, 68.26; H, 6.25; N, 14.47; Found: C, 68.76; H, 6.35; N, 14.83.

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

Yellow crystals; Yield 58%; m.p. 116-117 °C; IR (KBr, cm^{-1}): 3444 (NH), 1722, 1718 (C=O), 1650, 1635, 1629 (C=N), 1217 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.79 (*s*, 3H, OCH_3), 3.82 (*s*, 3H, OCH_3), 4.40 (*s*, 1H, CH), 6.61-8.70 (*m*, 11H, Ar-H), 11.30 (*s*, 1H, NH),; MS (*m/z*, (relative abundance, %)): 642 (M^+, 35); Anal. Calcd. for $C_{38}H_{38}N_6O_4$: C, 71.01; H, 5.96; N, 13.08; Found: C, 71.45; H, 5.78; N, 13.30.

2-(3-(4-bromophenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-10-cyclohexyl-5-(3,4-dimethoxy-phenyl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (9c)

Yellow crystals; Yield 52%; m.p. 136-137 °C; IR (KBr, cm^{-1}): 3450 (NH), 1730, 1717 (C=O), 1624, 1619 (C=N), 1225 (OMe), 600 (C-Br); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.77 (*s*, 3H, OCH_3), 3.80 (*s*, 3H, OCH_3), 4.40 (*s*, 1H, CH), 6.61-7.50 (*m*, 11H, Ar-H), 11.12 (*s*, 1H, NH); MS (*m/z*, (relative abundance, %)): 719 (M^+, 45), 722 (M^{+3}, 15); Anal. Calcd. for $C_{39}H_{38}BrN_5O_4$: C, 65.00; H, 5.31; N, 9.72; Found: C, 65.34; H, 5.81; N, 9.48.

2-(3-(4-acetylphenyl)-4-oxo-3,4-dihydroquinazolin-2-yl)-10-cyclohexyl-5-(3,4-di-methoxy-phenyl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b] quinolin-4(3H)-one (9d)

Yellow crystals; Yield 48%; m.p. 126-127 °C; IR (KBr, cm^{-1}): 3445 (NH), 1735, 1720, 1718 (C=O), 1625, 1619 (C=N), 1220 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*s*, 3H, CH_3), 2.55 (*m*, 1H, CH), 3.78 (*s*, 3H, OCH_3), 3.80 (*s*, 3H, OCH_3), 4.40 (*s*, 1H, CH), 7.15-8.80 (*m*, 11H, Ar-H), 11.20 (*s*, 1H, NH); MS (*m/z*, (relative abundance, %)): 683 (M^+, 65); Anal. Calcd. for $C_{41}H_{41}N_5O_5$: C, 72.02; H, 6.04; N, 10.24; Found: C, 72.35; H, 6.48; N, 9.74.

Synthesis of 10-cyclohexyl-5-(3,4-dimethoxyphenyl)-2-(4-oxo-3-(pyridin-2-yl)-3,4-dihydro-quinazolin-2-yl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (11)

A mixture of benzoxazinone 3 (3.93 g, 0.01 mole) and 2-aminopyridine or 3- aminopyridine (0.94 g, 0.01 mole) was fused in an oil bath in presence of anhydrous $ZnCl_2$ (1 g) for 4 h. The reaction mixture was triturated with ice/HCl. The formed solid product was filtered off, washed with water several times, dried and recrystallized from methanol to give 11 or 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); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.78 (*s*, 3H, OCH_3), 3.81 (*s*, 3H, OCH_3), 4.40 (*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 $C_{38}H_{38}N_6O_4$: 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); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.77 (*s*, 3H, OCH_3), 3.80 (*s*, 3H, OCH_3), 4.40 (*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 $C_{38}H_{38}N_6O_4$: 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-(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 benzoxazinone 3 (2.35 g, 0.006 mole) in EtOH (30 mL), $NH_2OH.HCl$ (0.417 g, 0.006 mole) and CH_3COONa (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 **15**.

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); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.78 (*s*, 3H, OCH_3), 3.81 (*s*, 3H, OCH_3), 4.40 (*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 $C_{33}H_{35}N_5O_5$: C, 68.14; H, 6.07; N, 12.04; Found: C, 68.20; H, 6.18; N, 12.26.

Synthesis of compounds 17a-d

To a solution of 9a (0.01 mole) in absolute EtOH (30 mL) containing few drops of piperidine, appropriate aldehydes namely, p-methoxybenzaldehyde, p-fluorobenzaldehyde, p-nitrobenzaldehyde, or 2-thiophenealdehyde (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-methoxybenzylidene) amino)-4-oxo-3,4-dihydro-quinazolin-2-yl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (17a)

Yellow crystals; Yield 65%; m.p. 174-175 °C; IR (KBr, cm^{-1}): 3442 (NH), 1733, 1722 (C=O), 1650, 1635, 1619 (C=N), 1226, 1210, 1205 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH),

3.78 (*s,* 3H, OCH_3), 3.80 (*s,* 3H, OCH_3), 3.82 (*s,* 3H, OCH_3), 4.40 (*s,* 1H, CH), 4.50 (*s*, 1H, CH=N-), 6.81-7.50 (*m*, 11H, Ar-H), 10.75 (*s*, 1H, NH); MS (*m/z*, (relative abundance, %)): 698 (M^+, 35); Anal. Calcd. for $C_{41}H_{42}N_6O_5$: C, 70.47; H, 6.06; N, 12.03; Found: C, 70.69; H, 6.56; N, 12.00.

10-cyclohexyl-5-(3,4-dimethoxyphenyl)-2-(3-((4-fluorobenzylidene) amino)-4-oxo-3,4-dihydro-quinazolin-2-yl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (17b)

Yellow crystals; Yield 65%; m.p. 169-170 °C; IR (KBr, cm^{-1}): 3441 (NH), 1733, 1723 (C=O), 1632, 1623, 1615 (C=N), 1220 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.77 (*s,* 3H, OCH_3), 3.80 (*s,* 3H, OCH_3), 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 $C_{40}H_{39}FN_6O_4$: C, 69.95; H, 5.72; N, 12.24; Found: C, 69.97; H, 5.36; N, 12.18.

10-cyclohexyl-5-(3,4-dimethoxyphenyl)-2-(3-((4-nitrobenzylidene) amino)-4-oxo-3,4-dihydro-quinazolin-2-yl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (17c)

Yellow crystals; Yield 53%; m.p. 106-107 °C; IR (KBr, cm^{-1}): 3448 (NH), 1753, 1740 (C=O), 1642, 1622, 1610 (C=N), 1226 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.78 (*s,* 3H, OCH_3), 3.81 (*s,* 3H, OCH_3), 4.20 (*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, %)): 713 (M^+, 40); Anal. Calcd. for $C_{40}H_{39}N_7O_6$: C, 67.31; H, 5.51; N, 13.74; Found: C, 67.81; H, 5.39; N, 13.41.

10-cyclohexyl-5-(3,4-dimethoxyphenyl)-2-(4-oxo-3-((thiophen-2-ylmethylene)amino)-3,4-dihydroquinazolin-2-yl)-5,6,7,8,9,10-hexahydropyrimido[4,5-b]quinolin-4(3H)-one (17d)

Yellow crystals; Yield 50%; m.p. 116-118 °C; IR (KBr, cm^{-1}): 3450 (NH), 1720, 1712 (C=O), 1640, 1638, 1622 (C=N), 1225 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.78 (*s,* 3H, OCH_3), 3.80 (*s,* 3H, OCH_3), 4.40 (*s,* 1H, CH), 4.60 (*s*, 1H, CH=N-), 7.50-7.95 (*m*, 10H, Ar-H, thiophene H), 11.20 (*s*, 1H, NH); MS (*m/z*, (relative abundance, %)): 674 (M^+, 40); Anal. Calcd. for $C_{38}H_{38}N_6O_4S$: C, 67.63; H, 5.68; N, 12.45; Found: C, 67.53; H, 5.21; N, 12.18.

Synthesis of 19, 21a,b

A solution of quinazolinone 9a (4.07 g, 0.01 mole), acetyl chloride, benzoyl chloride, and *p*-chlorobenzoyl chloride (0.02 mole) in dry pyridine (30 mL) was heated under reflux for 3 hours. The reaction mixture was cooled, then poured over ice/ HCl and the solid that separated out was filtered off, washed with water several times, dried and then recrystallized from methanol to afford 19 and 21a,b, respectively.

N-acetyl-N-(2-(10-cyclohexyl-5-(3,4-dimethoxyphenyl)-4-oxo-3,4,5,6,7,8,9,10-octa-hydro-pyrimido[4,5-b]quinolin-2-yl)-4-oxoquinazolin-3(4H)-yl)acetamide (19)

Yellow crystals; Yield 63%; m.p. 133-134 °C; IR (KBr, cm^{-1}): 3390 (NH), 1758, 1743, 1735, 1720 (C=O), 1632, 1618 (C=N), 1217 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.40 (*s*, 6H, 2 $COCH_3$), 2.50 (*m*, 1H, CH), 3.78 (*s,* 3H, OCH_3), 3.80 (*s,* 3H, OCH_3), 4.40 (*s,* 1H, CH), 6.61-7.90 (*m*, 7H, Ar-H), 11.20 (*s*, 1H, NH); MS (*m/z*, (relative abundance, %)): 664 (M^+, 30); Anal. Calcd. for $C_{37}H_{40}N_6O_6$: C, 66.85; H, 6.07; N, 12.64; Found: C, 66.55; H, 6.10; N, 12.45.

N-benzoyl-N-(2-(10-cyclohexyl-5-(3,4-dimethoxyphenyl)-4-oxo-3,4,5,6,7,8,9,10-octa-hydro-pyrimido[4,5-b]quinolin-2-yl)-4-oxoquinazolin-3(4H)-yl)benzamide (21a)

Yellow crystals; Yield 50%; m.p. 112-113 °C; IR (KBr, cm^{-1}): 3453 (NH), 1750, 1731, 1728, 1718 (C=O), 1633, 1619 (C=N), 1218 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.77 (*s,* 3H, OCH_3), 3.80 (*s,* 3H, OCH_3), 4.40 (*s,* 1H, CH), 6.61-8.20 (*m*, 17H, Ar-H), 11.20 (*s*, 1H, NH); MS (*m/z*, (relative abundance, %)): 788 (M^+, 20); Anal. Calcd. for $C_{47}H_{44}N_6O_6$: C, 71.56; H, 5.62; N, 10.65; Found: C, 71.83; H, 5.30; N, 10.54.

4-chloro-N-(4-chlorobenzoyl)-N-(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 °C; IR (KBr, cm^{-1}): 3501 (NH), 1744, 1727, 1720, 1718 (C=O), 1650, 1635 (C=N), 1225 (OMe), 750, 733 (C-Cl); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.76 (*s,* 3H, OCH_3), 3.80 (*s,* 3H, OCH_3), 4.40 (*s,* 1H, CH), 6.61-8.20 (*m*, 15H, Ar-H), 11.10 (*s*, 1H, NH); MS (*m/z*, (relative abundance, %)): 857 (M^+, 20); Anal. Calcd. for $C_{47}H_{42}Cl_2N_6O_6$: C, 65.81; H, 4.94; N, 9.80; Found: C, 65.51; H, 4.92; N, 9.83.

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 for 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-octahydro-pyrimido[4,5-b]quinolin-2-yl)-4-oxoquinazolin-3(4H)-yl)-1H-pyrrole-2,5-dione (23a)

Yellow crystals; Yield 52%; m.p. 143-145 °C; IR (KBr, cm^{-1}): 3444 (NH), 1745, 1730, 1722, 1715 (C=O), 1630, 1617 (C=N), 1217 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.77 (*s,* 3H, OCH_3), 3.80 (*s,* 3H, OCH_3), 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 $C_{37}H_{36}N_6O_6$: C, 67.26; H, 5.49; N, 12.72; Found: C, 67.15; H, 5.30; N, 12.91.

2-(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) isoindoline-1,3-dione (23b)

Yellow crystals; Yield 65%; m.p. 162-163 °C; IR (KBr, cm^{-1}): 3443 (NH), 1739, 1725, 1720, 1710 (C=O), 1650, 1644 (C=N), 1217 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.79 (*s,* 3H, OCH_3), 3.81 (*s,* 3H, OCH_3), 4.40 (*s,* 1H, CH), 6.61-8.80 (*m*, 11H, Ar-H), 11.05 (*s*, 1H, NH); MS (*m/z*, (relative abundance, %)): 710 (M^+, 55); Anal. Calcd. for $C_{41}H_{38}N_6O_6$: C, 69.28; 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-methoxyphenyl)-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), 1219 (OMe), 750 (C-Cl); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 2.72 (*s*, 3H, OCH_3), 2.90 (*d*, 1H, CH), 3.50 (*d*, 1H, CH-Cl), 4.10 (*s*, 6H, 2 OCH_3), 4.40 (*s*, 1H, CH), 6.20 (*s*, 1H, NH), 6.98-7.90 (*m*, 11H, Ar-H); MS (*m/z*, (relative abundance, %)): 775 (M^+, 45), 777 (M^{+2}, 15); Anal. Calcd. for $C_{43}H_{43}ClN_6O_6$: C, 66.61; H, 5.59; N, 10.84; Found: C, 66.34; H, 5.37; N, 10.85.

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

Yellow crystals; Yield 50%; m.p. 102-103°C; IR (KBr, cm^{-1}): 3444 (NH), 1750, 1738, 1720 (C=O), 1644, 1620 (C=N), 1219 (OMe), 750 (C-Cl); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 2.90 (*d*, 1H, CH), 3.50 (*d*, 1H, CH-Cl), 3.78 (*s*, 3H, OCH_3), 3.80 (*s*, 3H, OCH_3), 3.82 (*s*, 3H, OCH_3), 4.40 (*s*, 1H, CH), , 6.98-7.90 (*m*, 11H, Ar-H), 10.95 (*s*, 1H, NH); MS (*m/z*, (relative abundance, %)): 763 (M^+, 40); Anal. Calcd. for $C_{42}H_{40}ClFN_6O_5$: C, 66.09; H, 5.28; N, 11.01; Found: C, 65.66; H, 5.07; N, 11.51.

Synthesis of 27a,b and 29a,b

A mixture of compound 17a,b (4.95 g, 0.01 mole) and thioglycolic acid (26) or thiosalicylic 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.

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-methoxyphenyl)thiazolidin-4-one (27a)

Yellow crystals; Yield 58%; m.p. 126-128 °C; IR (KBr, cm^{-1}): 3414 (NH), 1780, 1737, 1720 (C=O), 1630, 1619 (C=N), 1223 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.20 (*s*, 1H, CH, thiazole), 3.76 (*s*, 3H, OCH_3), 3.79 (*s*, 3H, OCH_3), 3.81 (*s*, 3H, OCH_3), 4.40 (*s*, 1H, CH), 4.45 (*s*, 2H, CH_2, thiazole), 6.61-7.10 (*m*, 11H, Ar-H), 10.95 (*s*, 1H, NH); MS (*m/z*, (relative abundance, %)): 772 (M^+, 35); Anal. Calcd. for $C_{43}H_{44}N_6O_6S$: C, 66.82; H, 5.74; N, 10.87; Found: C, 66.63; H, 5.46; N, 10.86.

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)thiazolidin-4-one (27b)

Yellow crystals; Yield 55%; m.p. 135-137 °C; IR (KBr, cm^{-1}): 3414 (NH), 1780, 1737, 1720 (C=O), 1630, 1619 (C=N), 1223 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.20 (*s*, 1H, CH, thiazole), 3.77 (*s*, 3H, OCH_3), 3.80 (*s*, 3H, OCH_3), 4.40 (*s*, 1H, CH), 4.45 (*s*, 2H, CH_2, thiazole), 6.61-7.10 (*m*, 11H, Ar-H), 11.05 (*s*, 1H, NH); MS (*m/z*, (relative abundance, %)): 760 (M^+, 35); Anal. Calcd. for $C_{42}H_{41F}N_6O_5S$: C, 66.30; H, 5.43; N, 11.05; Found: C, 66.16; H, 5.46; N, 11.28.

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-methoxyphenyl)-2H-benzo[e][1,3]thiazin-4(3H)-one (29a)

Yellowish 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 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.77 (*s*, 3H, OCH_3), 3.80 (*s*, 3H, OCH_3), 3.83 (*s*, 3H, OCH_3), 4.45 (*s*, 1H, CH, thiazine), 10.98 (*s*, 1H, NH), 6.61-7.90 (*m*, 15H, Ar-H); MS (*m/z*, (relative abundance, %)): 834 (M^+, 40); Anal. Calcd. for $C_{48}H_{46}N_6O_6S$: C, 69.05; H, 5.55; N, 10.06; Found: C, 69.10; H, 5.23; N, 10.02.

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 (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 (OMe); ^{1}H-NMR (500 MHz, DMSO-d_6, δ / ppm): 1.45 (*m*, 2H, CH_2), 1.50-1.81 (*m*, 4H, 2 CH_2), 1.52 (*t*, 2H, CH_2), 1.65 (*m*, 2H, CH_2), 1.74 (*m*, 2H, CH_2), 1.75-2.20 (*q*, 4H, 2CH_2), 1.82 (*t*, 2H, CH_2), 2.50 (*m*, 1H, CH), 3.78 (*s*, 3H, OCH_3), 3.80 (*s*, 3H, OCH_3), 4.45 (*s*, 1H, CH, thiazine), 10.98 (*s*, 1H, NH), 6.61-7.90 (*m*, 15H, Ar-H); MS (*m/z*, (relative abundance, %)): 822 (M^+, 40); Anal. Calcd. for $C_{47}H_{43}FN_6O_5S$: 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* ATCC 9797), yeasts (*Candida albicans* ATCC 10231 and *Saccharomyces cervesiae*) and fungi *(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 1 L of distilled water, and adjusted at pH 7.2 before autoclaving (LAC-J0805 autoclave, Daihan Labtech Co., Korea) at 121 °C for 15 min, while yeast and fungi were maintained on Sabouraud dextrose 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 *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 1.5×10^8 CFU/mL of each bacterial strain, SDA seeded with 2.0×10^5 CFU/mL of each yeast and PDA seeded with 2.0×10^4 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 cefaxone (20 mg/mL), Ketoconazole (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[24]. 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 300µg/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 repeated twice. The lowest concentration showing no growth was considered the minimum inhibitory concentration (MIC) (Table 3).

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[25]. This assay is based on the measurement of the ability of antioxidants to reduce DPPH by measuring the decrease in its absorption[26]. DPPH reacts with hydrogen/electron donor compounds and has a maximum UV–Vis absorption of 515–520 nm[27]. The reaction mixture consisted of 50 µL (10-200 µg/mL) of each chemical compound dissolved in dimethyl sulfoxide (DMSO), as well as the reference standard ascorbic acid and the volume was made uniformly 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:

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

$\text{Abs}_{\text{control}}$ and $\text{Abs}_{\text{sample}}$: the absorbance values of the control as well as the sample.

\The antioxidant activity of each chemical compound and ascorbic acid was expressed as EC_{50} (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[28] (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[29]. 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[30] (3). IR spectrum of compound 3 demonstrated two bands of C=O and NH at ≈ 1715, 1745 and 3450 cm^{-1}, respectively (Scheme 1). ^{1}H-NMR of 3 showed singlet tow OCH_3 and NH signals occurring at 3.72, 3.80 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 carboxamide compounds (5). IR of compound 5 revealed 3 groups C=O at ≈ 1750, 1740, 1725 and two NH_2 and only one NH. (Scheme 2). ^{1}H-NMR of 5 revealed NH_2 at 5.5 ppm. Moreover, compound 3 refluxed with CH_3COONH_4 afford quinazolin-4(3*H*)-one (6). Moreover, in dry xylene/toluene compound 3 refluxed with P_2S_5 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 9a-d and fused with 2/3-aminopyridine (10, 12) in presence of $ZnCl_2$ to yielded 11,13, respectively. Also, compound 3 refluxed with $NH_2OH.HCl$ in presence of CH_3COONa to afford 3-hydroxyquinazolin-4-one (15). IR of compound 15 revealed the presence of -OH group at ≈ 3635 cm^{-1}, where ^{1}H-NMR of 15 proved the presence of OH at 6.1 ppm (Scheme 3).

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 CH_3COCl 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, hexahydropyrimido[4,5-b]quinolin was prepared by refluxing of compound 17a, b with CH_2COCl_2 in EtOH in presence of Et_3N to afford compounds 25a, b. In addition to, compound 17a, b refluxed with thioglycolic acid or thiosalicylic acid in dry benzene to yield new thiazolidin-4-one 27a, b and *thiazin-one* 29a, b, respectively.

Biological activity

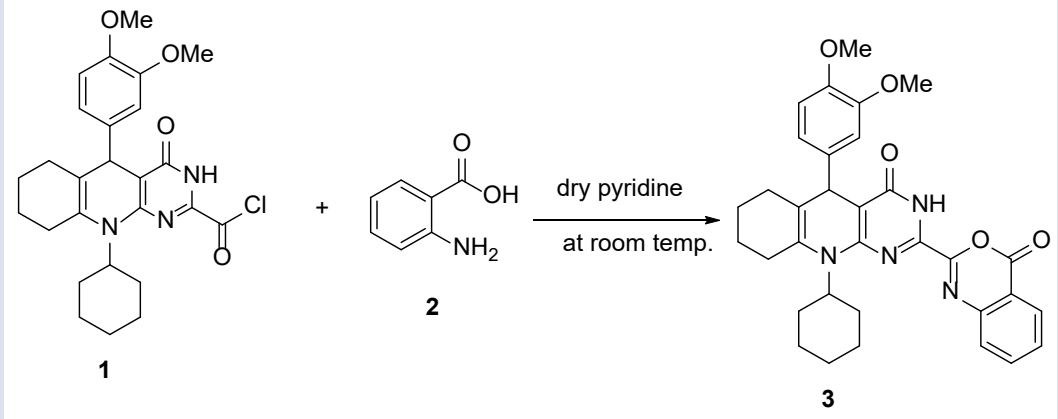
In vitro antimicrobial Screening

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).

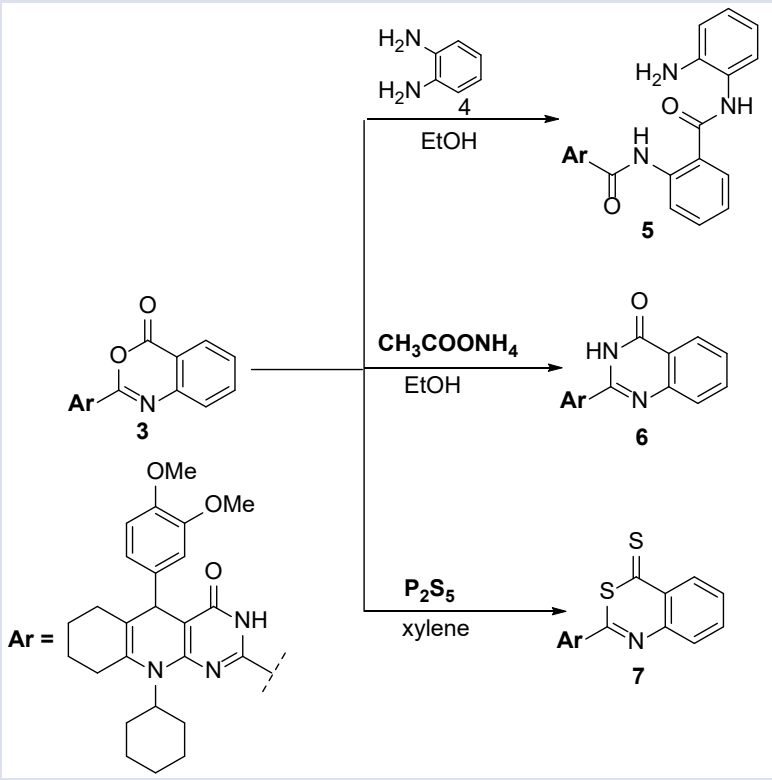
Table 1: Antimicrobial activity of based on well diffusion method (100 µL= 2000 µg).

Compound	Staphylococcus aureus ATCC 6538-P	Bacillus subtilis ATCC 6633	Pseudomonas aeruginosa ATCC 27853	Bordetella pertussis ATCC- 9797	Candida albicans ATCC-10231	Saccharomyces cervesiae	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	R	20	18	R	R
7	R	R	R	13	14	R	R	R
9a	R	R	R	R	21	20	R	R
9b	R	R	R	R	22	25	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	R	21	20	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	R	15	12	R	R
21b	R	12	R	R	13	R	R	R
23a	11	15	22	24	20	20	R	R
23b	R	R	14	15	22	20	R	R
25a	R	R	R	R	20	17	R	R
25b	R	12	18	20	22	20	R	R
27a	R	R	R	R	20	R	R	R
27b	R	R	R	12	20	16	R	R
29a	12	13	12	15	24	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	31	34	NT	NT
Cyclosporine	NT	NT	NT	NT	NT	NT	35	32

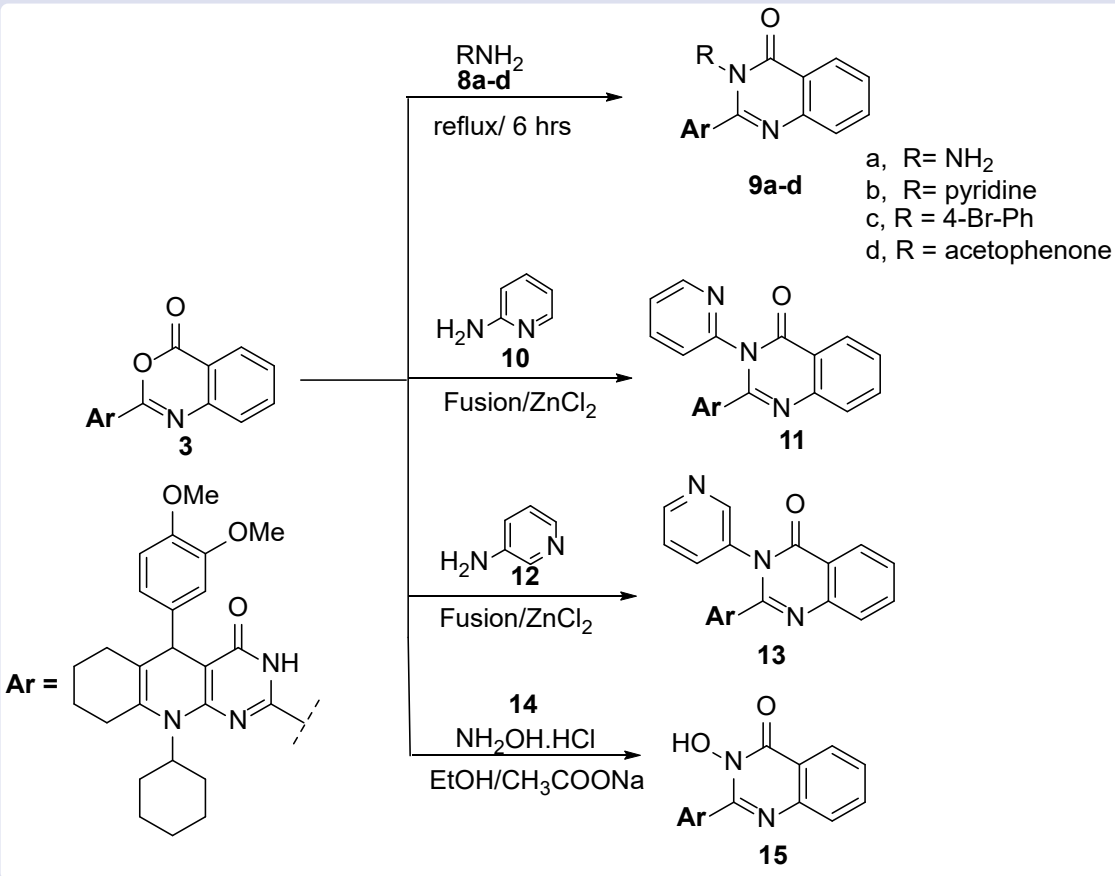
R = Resistant. NT = Not tested.



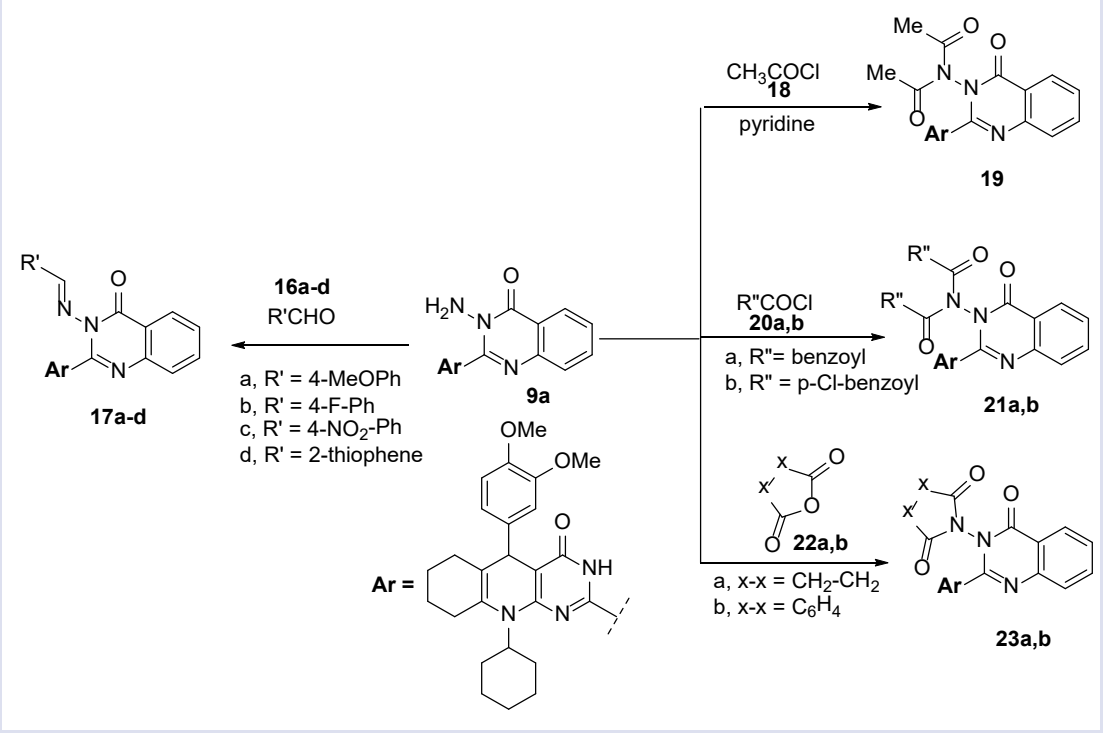
Scheme 1: Synthesis of quinoline-oxazin-4-one derivative.



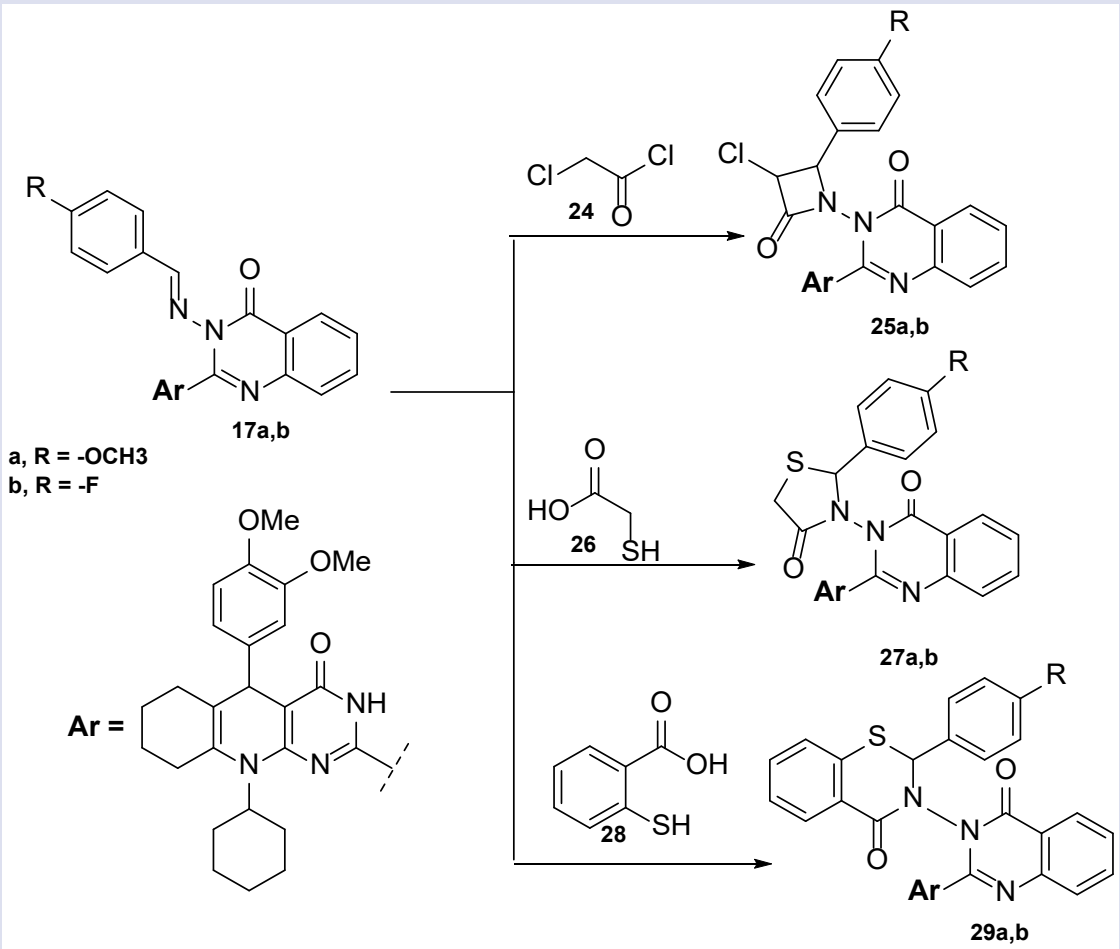
Scheme 2: Synthesis of quinazoline-carboxamide and thiazine derivatives.



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 cervesiae	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	75	100	NT	NT
9b	NT	NT	200	NT	NT	50	NT	NT
9c	75	75	200	300	75	50	NT	NT
9d	50	50	50	75	50	50	75	50
11	NT	NT	NT	NT	NT	NT	NT	NT
13	NT	NT	NT	NT	75	100	NT	NT
15	NT	300	100	75	50	75	75	50
17a	NT	NT	NT	NT	100	150	NT	NT
17b	50	25	25	50	50	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	75	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	300	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.

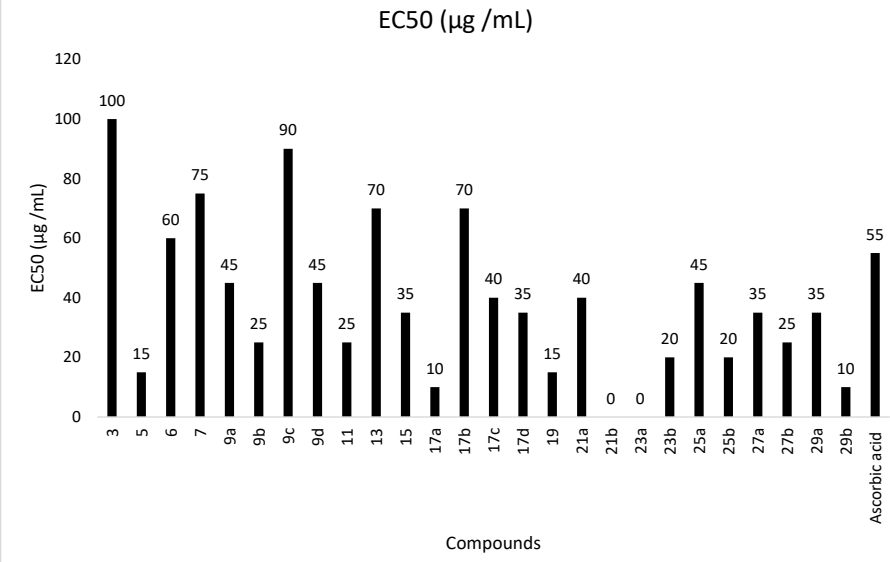


Figure 2: EC_{50} of the synthesized compounds

Table 3: EC_{50} for DPPH inhibition of chemical compounds.

Chemical compound	EC_{50} (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_{50}; 55 µg/mL) > 6 = 60 µg /mL > 13 =17b (EC_{50}; 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 agents than ascorbic acid.

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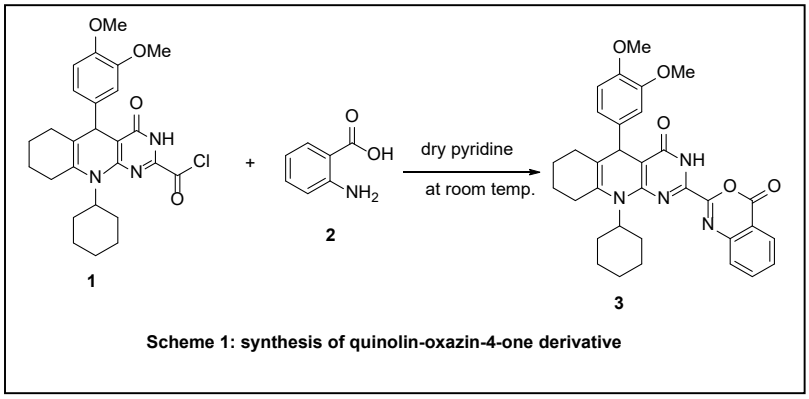
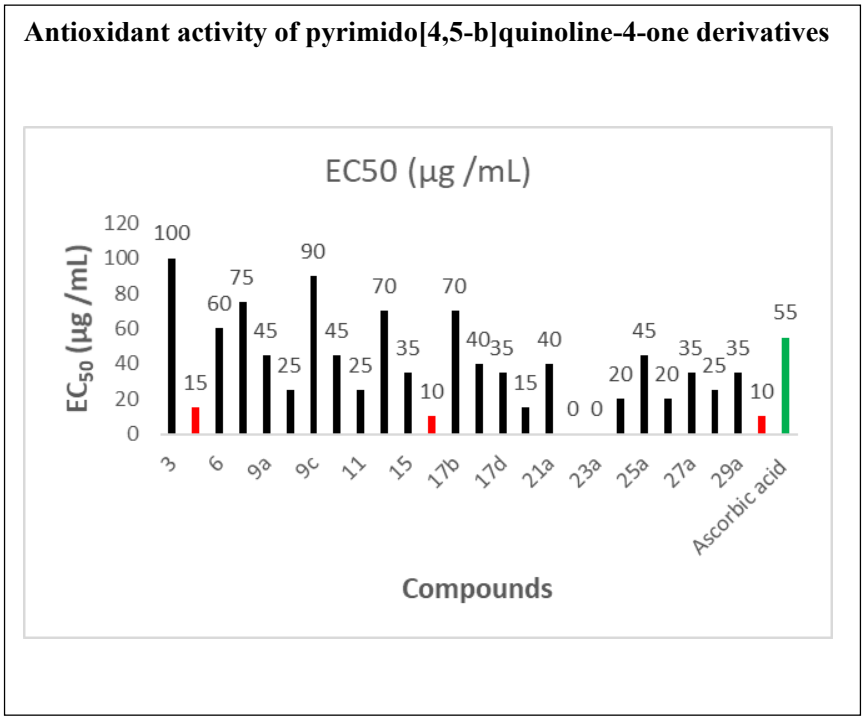
GRAPHICAL ABSTRACT



Scheme 1: synthesis of quinolin-oxazin-4-one derivative



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