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Synthesis and antimicrobial activity of novel quinazolinone–thiazolidine–quinoline compounds

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Abstract A series of 2-(2-chloroquinolin-3-yl)-5-((aryl)benzylidene)-3-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)thiazolidin-4-ones (**V**)_{1–12} have been synthesized. In order to establish optimization of different parameters of chemical transformation, that is the reaction pathway for each step and reaction conditions in the each step, in the present paper, different solvents and catalysts were used. The structures of the synthesized compounds were assigned on the basis of elemental analysis, IR, ¹H NMR and ¹³C NMR spectral data. All the newly synthesized compounds were screened against various strains of bacteria and fungi.

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1. Introduction

The number of life-threatening infectious diseases caused by multidrug-resistant bacteria has reached an alarming level in many countries around the world. Recently, the Severe Acute Respiratory Syndrome (SARS) caused by the novel corona virus SARS-CoV (Chang et al., 2007; Yeung and Meanwell, 2007) and bird flu caused by avian influenza (H5N1) virus

(Gary and Ting, 2007) have emerged as two important infectious diseases with pandemic potential. Both infections crossed the species barrier to infect humans. Also, the ever growing demand for material protection from microbial contamination is a serious challenge (Berber et al., 2003). The aforementioned facts are a cause of great concern and create a pressing need for new anti-bacterial agents. Despite great effort from the pharmaceutical industry to manage the resistance problem, the discovery and development of new mechanistic classes of antibiotics has found very little success (Taun et al., 2007). The difficulty of this task is demonstrated by the fact that only two antibiotics of new classes, linezolid (an oxazolidinone) and daptomycin (a cyclic lipopeptide), have been successfully developed in the past three decades (Carpenter and Champers, 2004; Weigelt et al., 2005).

Quinazoline derivatives represent one of the most active classes of compounds possessing a wide spectrum of biological activity (Apfel et al., 2001). They are widely used in pharmaceuticals and agrochemicals (Tobe et al., 2003); for example, fluquinconazole fungicide for the control of agriculture diseases (Guang-Fang et al., 2007). Several reports have been published

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on the biological activity of quinazoline derivatives, including their bactericidal, herbal and anti-tumour activity (Raffa et al., 1999; Chenard et al., 2001). Thus, their synthesis has been of great interest in the elaboration of biologically active heterocyclic compounds. Recently, it was reported that some iodoquinazolines exhibited moderate antibacterial activity (Alafeefy, 2008). Prompted by these findings, this article reports the design and synthesis of an extension series of 3-substituted 2-phenylquinazolin-4(3*H*)-one derivatives and tested their antibacterial activities.

Quinolines are known to inhibit DNA synthesis by promoting cleavage of bacterial DNA gyrase and type-IV topoisomerase, resulting in rapid bacterial death (Hooper and Wolfson, 1989; Hooper, 1995; Hardman et al., 2002). Quinolones with substituents at C-6 position, albeit less activity than fluorine, are essential for high activity as evidenced by its enhanced gyrase inhibition and cell penetration (Bhanot et al., 2001). A number of substituents for fluorine replacement have been introduced into that position. Garenoxacin showed greater potency than the newer fluoroquinolone and moxifloxacin against both sensitive and resistant gram positive organisms, thus casting doubt on the validity of necessity of C-6 fluorine (Emami et al., 2006). Several efforts to further modify non-fluoroquinolone and their biological activities were also investigated (Ctoen-Chackal et al., 2004; Chevalier et al., 2001).

Similarly, various 4-thiazolidinones (Pan et al., 2010; Youssef et al., 2010) have attracted considerable attention as they are also endowed with a wide range of pharmaceutical activities including anaesthetic (Surrey, 1949), anticonvulsant (Troutman and Long, 1948), antibacterial (Sayyed and Mokle, 2006) and antiviral (Rao and Zappala, 2004). Furthermore, drug research and development have led to the discovery of new pharmacologically active agents, including imidoxo (Wolfgang, 1998) compounds such as succinimidoxy (Farror et al., 1993). They also possess a strong anti-convulsant activity (Edafiohgo et al., 1991). 4-Thiazolidinones may be considered as phosphate bioisosteres and therefore inhibit the bacterial enzyme MurB which is involved in the biosynthesis of peptidoglycan layer of the cell wall (Gursoy et al., 2005). In addition, some thiazolidinones were recently reported as novel inhibitors of mycobacterial rhamnose synthetic enzymes (Gursoy et al., 2005). This new approach is believed to be selective as rhamnose is not found in humans, but is essential for mycobacterial cell wall synthesis in animals (Andres et al., 2000).

Looking to the medicinal importance of 4(3*H*)-quinazolinone, 4-thiazolidinone and quinoline, we report here the synthesis of new class of heterocyclic molecules in which all of these moieties are present and try to develop potential bioactive molecules. The structures of the compounds synthesized were assigned on the basis of elemental analysis, IR, ¹H NMR, ¹³C NMR and Mass spectral data. These compounds were evaluated for their antimicrobial screening on different strains of bacteria and fungi.

2. Experimental part

2.1. Materials and physical measurements

General Procedures. Laboratory Chemicals were supplied by Merck Ltd. Melting points were determined by the open tube

capillary method and are uncorrected. The purity of the compounds was monitored by thin layer chromatography (TLC) plates (silica gel G) in the solvent system n-hexane: ethyl acetate (V/V = 1:3). The spots were observed by exposure to iodine vapour or by UV light. The IR spectra were obtained on a Perkin-Elmer 1720 FT-IR spectrometer (KBr pellets). The ¹H NMR and ¹³C NMR spectra were recorded on a Bruker Avance II 400 spectrometer using TMS as the internal standard in DMSO. Elemental analysis of the newly synthesized compounds was carried out on Carlo Erba 1108 analyzer.

2.2. Preparation methods and physical data of synthesized compounds (I to V₁₋₁₂)

2.2.1. Procedure for the synthesis of 3-((2-chloroquinolin-3-yl)methyleneamino)-2-phenylquinazolin-4(3*H*)-one (III)

To a solution of the 2-chloroquinoline-3-carbaldehyde (1.0 mmol) in ethanol (15 mL) was added 3-amino-2-phenyl-4(3*H*)-quinazolinone (1.0 mmol) and a few drops of glacial acetic acid was added. The reaction mixture was refluxed for 3–8 h and the course of the reaction was monitored by TLC [*n*-hexane/ethyl acetate (V/V = 1:2)] to its completion. The reaction mixture was cooled. The crude product was recrystallized from 95% ethanol to give the intermediate compound-(III). Yield 73%, m.p. 178 °C; IR (KBr, cm⁻¹) ν : 3051, 3063 (quinazolinone ring, quinoline ring Ar-H), 3072 (=CH stretching), 1671 (C=O stretching), 1605, 1580 (C=N stretching), 1562–1439 (C=C, quinazolinone ring, quinoline ring, benzene ring), 838 (C-Cl stretching). ¹H NMR (DMSO): δ (ppm): 8.60 (s, 1H, =CH group), 7.60–9.27 (m, 9H, quinoline and quinazolinone-H), 7.29–7.83 (m, 5H, Ar-H). ¹³C NMR (DMSO): 121.9, 124.3, 126.6, 126.7, 126.8, 127.2, 127.3, 127.8, 128.1, 128.2, 128.8, 130.1, 133.4, 131.0, 137.8, 143.3, 148.7, 149.7, 152.7, 153.6, 166.7, 167.0. Anal. Calcd for C₂₄H₁₅ClN₄O: C, 70.16; H, 3.68; N, 13.64. Found: C, 70.22; H, 3.74; N, 13.67.

2.2.2. Procedure for the synthesis of 2-(2-chloroquinolin-3-yl)-3-(4-oxo-2-phenylquinazolin-3(4*H*)-yl)thiazolidin-4-one (IV)

To a solution of compound-(III) (0.01 mol) in 1,4-dioxane (50 ml) was added mercapto acetic acid (0.01 mol) with stirring and a little amount of anhydrous ZnCl₂ was added. The mixture was refluxed for 10–12 h, after the completion of the reaction, it was cooled and the excess solvent distilled and poured into sodium bicarbonate solution to neutralize it. The solid product was filtered, washed with cold water. The resulting light brown colour product was obtained. The completion of the reaction was checked by TLC [*n*-hexane/ethyl acetate (V/V = 1:3)]. The crude product was recrystallized from 95% ethanol to give the intermediate compound-(IV). Yield 73%, m.p. 178 °C; IR(KBr, cm⁻¹) ν : 3052, 3068 (quinazolinone ring, quinoline ring Ar-H), 1677, 1686 (C=O stretching), 1609, 1582 (C=N stretching), 1564–1448 (C=C, quinazolinone ring, quinoline ring, benzene ring), 849 (C-Cl stretching): ¹H NMR (DMSO): δ (ppm): 3.85–3.95 (s, 1H, CH₂ group), 5.92 (s, 1H, S-CH-N), 7.63–8.27 (m, 9H, quinoline and quinazolinone-H), 7.27–7.83 (m, 5H, Ar-H). ¹³C NMR (DMSO): 35.6, 57.7, 120.8, 126.6, 126.7, 127.5 (C-21), 127.3, 127.0, 128.2, 128.6, 128.8, 129.9, 130.1, 130.9, 133.4, 136.2, 145.4, 148.7, 151.9, 156.2, 160.8, 168.8. Anal. Calcd for C₂₆H₁₇ClN₄O₂S: C, 64.39; H, 3.53; N, 11.55. Found: C, 64.42; H, 3.58; N, 11.61.

2.2.3. General procedure for the synthesis of 2-(2-chloroquinolin-3-yl)-5-((aryl)benzylidene)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-ones (V)₁₋₁₂

Compound-(IV) (0.01 mol) was taken in ethanol (25 ml) and substituted aromatic aldehydes (0.01 mol) were slowly added to it with stirring and a catalytic amount of sodium ethoxide was added. The reaction mixture was refluxed for 6–7 h, after the completion of the reaction, the product came out and excess amount of solvent was distilled out and the crude product was filtered off and washed with ethanol, dried and recrystallized in ethanol. The completion of the reaction was checked by TLC [*n*-hexane/ethyl acetate (V/V = 1:3)] to give the final product (V₁₋₁₂).

2.2.3.1. 5-(2-Chlorobenzylidene)-2-(2-chloroquinolin-3-yl)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-one (V)₁

Yield, 70%, off yellow crystalline solid, mp 292–293 °C. IR (KBr, cm⁻¹): 3057, 3065 (quinazolinone ring, quinoline ring Ar-H), 3080 (=CH stretching), 1675, 1681 (C=O stretching), 1605, 1589 (C=N stretching), 1568–1445 (C=C, quinazolinone ring, quinoline ring, benzene ring), 845 (C–Cl stretching), 768, 692 (mono substituted benzene ring). ¹H NMR (DMSO) δ (ppm): 8.03 (s, 1H, =CH group), 5.92 (s, 1H, S–CH–N), 7.63–8.27 (m, 9H, quinoline and quinazolinone-H), 7.27–7.83 (m, 9H, Ar-H). ¹³C NMR (DMSO) δ (ppm): 164.4, 160.8, 156.2, 148.7, 145.4, 136.2, 134.0, 133.4, 133.0, 134.0, 133.4, 133.0, 131.9, 130.9, 130.1, 129.9, 129.3, 128.8, 128.6, 128.2, 127.8, 127.5, 127.3, 127.0, 126.7, 126.6, 125.2, 63.5. Anal. Calcd for C₃₃H₂₀Cl₂N₄O₂S: C, 65.24; H, 3.31; N, 9.22. Found: C, 65.32; H, 3.35; N, 9.30.

2.2.3.2. 5-(3-Chlorobenzylidene)-2-(2-chloroquinolin-3-yl)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-one (V)₂

Yield, 66%, light brown crystalline solid, mp 148–150 °C. IR (KBr, cm⁻¹): 3053, 3064 (quinazolinone ring, quinoline ring Ar-H), 3083 (=CH stretching), 1673, 1684 (C=O stretching), 1607, 1582 (C=N stretching), 1569–1440 (C=C, quinazolinone ring, quinoline ring, benzene ring), 848 (C–Cl stretching), 769, 688 (mono substituted benzene ring). ¹H NMR (DMSO) δ (ppm): 8.08 (s, 1H, =CH group), 5.97 (s, 1H, S–CH–N), 7.66–8.28 (m, 9H, quinoline and quinazolinone-H), 7.27–7.83 (m, 9H, Ar-H). ¹³C NMR (DMSO) δ (ppm): 164.4, 160.8, 156.2, 148.7, 145.4, 138.3, 136.2, 133.4, 136.6, 134.2, 126.4, 131.9, 130.9, 130.1, 130.0, 129.9, 128.0, 128.8, 128.6, 128.2, 127.5, 127.3, 127.0, 126.7, 126.6, 125.2, 120.8, 63.5. Anal. Calcd for C₃₃H₂₀Cl₂N₄O₂S: C, 65.24; H, 3.31; N, 9.22. Found: C, 65.31; H, 3.33; N, 9.29.

2.2.3.3. 5-(4-Chlorobenzylidene)-2-(2-chloroquinolin-3-yl)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-one (V)₃

Yield, 79%, off yellow crystalline solid, mp 244–246 °C. IR (KBr, cm⁻¹): 3057, 3065 (quinazolinone ring, quinoline ring Ar-H), 3085 (=CH stretching), 1679, 1686 (C=O stretching), 1609, 1594 (C=N stretching), 1572–1450 (C=C, quinazolinone ring, quinoline ring, benzene ring), 840 (C–Cl stretching), 761, 698 (mono substituted benzene ring). ¹H NMR (DMSO) δ (ppm): 8.05 (s, 1H, =CH group), 5.94 (s, 1H, S–CH–N), 7.65–8.29 (m, 9H, quinoline and quinazolinone-H), 7.28–7.81 (m, 9H, Ar-H). ¹³C NMR (DMSO) δ (ppm): 164.4, 160.8, 156.2, 148.7, 145.4, 138.3, 136.2, 133.5, 133.4, 133.3, 131.9, 130.9, 130.1, 129.9, 129.0, 128.8, 128.7, 128.6, 128.2, 127.5, 127.3, 127.0, 126.7, 126.6, 125.2, 120.8, 63.5. Anal. Calcd for

C₃₃H₂₀Cl₂N₄O₂S: C, 65.24; H, 3.31; N, 9.22. Found: C, 65.33; H, 3.38; N, 9.28.

2.2.3.4. 2-(2-Chloroquinolin-3-yl)-5-(2-nitrobenzylidene)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-one (V)₄

Yield, 63%, light brown crystalline solid, mp 145–147 °C. IR (KBr, cm⁻¹): 3054, 3063 (quinazolinone ring, quinoline ring Ar-H), 3089 (=CH stretching), 1674, 1680 (C=O stretching), 1611, 1583 (C=N stretching), 1555–1440 (C=C, quinazolinone ring, quinoline ring, benzene ring), 848 (C–Cl stretching), 772, 690 (mono substituted benzene ring). ¹H NMR (DMSO) δ (ppm): 8.32 (s, 1H, =CH group), 5.90 (s, 1H, S–CH–N), 7.67–8.35 (m, 9H, quinoline and quinazolinone-H), 7.25–7.86 (m, 9H, Ar-H). ¹³C NMR (DMSO) δ (ppm): 164.4, 160.8, 156.2, 148.7, 147.7, 145.4, 138.3, 136.2, 134.7, 133.4, 131.9, 130.9, 130.1, 129.9, 128.8, 128.8, 128.6, 128.2, 127.5, 127.3, 127.2, 127.1, 127.0, 126.7, 126.6, 125.2, 123.8, 120.8, 63.5. Anal. Calcd for C₃₃H₂₀ClN₅O₄S: C, 64.12; H, 3.26; N, 11.33. Found: C, 64.22; H, 3.34; N, 11.35.

2.2.3.5. 2-(2-Chloroquinolin-3-yl)-5-(3-nitrobenzylidene)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-one (V)₅

Yield, 67%, dark yellow crystalline solid, mp 235–237 °C. IR (KBr, cm⁻¹): 3050, 3067 (quinazolinone ring, quinoline ring Ar-H), 3080 (=CH stretching), 1671, 1685 (C=O stretching), 1604, 1583 (C=N stretching), 1562–1452 (C=C, quinazolinone ring, quinoline ring, benzene ring), 852 (C–Cl stretching), 762, 690 (mono substituted benzene ring). ¹H NMR (DMSO) δ (ppm): 8.35 (s, 1H, =CH group), 5.95 (s, 1H, S–CH–N), 7.60–8.32 (m, 9H, quinoline and quinazolinone-H), 7.24–7.87 (m, 9H, Ar-H). ¹³C NMR (DMSO) δ (ppm): 164.4, 160.8, 156.2, 148.7, 147.8, 145.4, 138.3, 136.2, 136.1, 133.4, 131.9, 130.9, 130.1, 129.9, 129.5, 128.8, 128.6, 128.2, 134.6, 127.5, 127.3, 127.0, 126.7, 126.6, 125.2, 123.1, 122.7, 120.8, 63.5. Anal. Calcd for C₃₃H₂₀ClN₅O₄S: C, 64.12; H, 3.26; N, 11.33. Found: C, 64.21; H, 3.36; N, 11.38.

2.2.3.6. 2-(2-Chloroquinolin-3-yl)-5-(4-nitrobenzylidene)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-one (V)₆

Yield, 70%, light orange crystalline solid, mp 292–293 °C. IR (KBr, cm⁻¹): 3056, 3069 (quinazolinone ring, quinoline ring Ar-H), 3080 (=CH stretching), 1671, 1688 (C=O stretching), 1612, 1592 (C=N stretching), 1562–1451 (C=C, quinazolinone ring, quinoline ring, benzene ring), 844 (C–Cl stretching), 764, 690 (mono substituted benzene ring). ¹H NMR (DMSO) δ (ppm): 8.38 (s, 1H, =CH group), 5.98 (s, 1H, S–CH–N), 7.64–8.22 (m, 9H, quinoline and quinazolinone-H), 7.23–7.86 (m, 9H, Ar-H). ¹³C NMR (DMSO) δ (ppm): 164.4, 160.8, 156.2, 147.1, 141.3, 148.7, 145.4, 138.3, 136.2, 133.4, 131.9, 130.9, 130.1, 129.9, 129.0, 128.8, 128.6, 128.2, 127.5, 127.3, 127.0, 126.7, 123.8, 126.6, 125.2, 123.8, 120.8, 63.5. Anal. Calcd for C₃₃H₂₀ClN₅O₄S: C, 64.12; H, 3.26; N, 11.33. Found: C, 64.18; H, 3.35; N, 11.37.

2.2.3.7. 2-(2-Chloroquinolin-3-yl)-5-(2-hydroxybenzylidene)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-one (V)₇

Yield, 85%, light brown crystalline solid, mp 201–203 °C. IR (KBr, cm⁻¹): 3053, 3069 (quinazolinone ring, quinoline ring Ar-H), 3086 (=CH stretching), 1668, 1684 (C=O stretching), 1609, 158- (C=N stretching), 1568–1445 (C=C, quinazolinone ring, quinoline ring, benzene ring), 841 (C–Cl stretching), 769, 692 (mono substituted benzene ring). ¹H NMR (DMSO)

δ (ppm): 8.08 (s, 1H, =CH group), 5.92 (s, 1H, S-CH-N), 7.63–8.27 (m, 9H, quinoline and quinazolinone-H), 7.27–7.83 (m, 9H, Ar-H), 5.35 (s, 1H, -OH group). ^{13}C NMR (DMSO) δ (ppm): 164.4, 160.8, 157.1, 156.2, 148.7, 145.4, 138.3, 136.2, 133.4, 131.9, 130.9, 130.1, 129.9, 129.3, 128.9, 128.8, 128.6, 128.2, 127.5, 127.3, 127.0, 126.7, 126.6, 125.2, 121.2, 120.8, 117.6, 116.5, 63.5. Anal. Calcd for $\text{C}_{33}\text{H}_{21}\text{ClN}_4\text{O}_3\text{S}$: C, 67.28; H, 3.59; N, 9.51. Found: C, 67.37; H, 3.67; N, 9.61.

2.2.3.8. 2-(2-Chloroquinolin-3-yl)-5-(3-hydroxybenzylidene)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-one (**V**)₈. Yield, 70%, off yellow crystalline solid, mp 252–253 °C. IR (KBr, cm^{-1}) ν : 3062, 3069 (quinazolinone ring, quinoline ring Ar-H), 3080 (=CH stretching), 1674, 1684 (>C=O stretching), 1608, 1580 (C=N stretching), 1563–1442 (C=C, quinazolinone ring, quinoline ring, benzene ring), 851 (C-Cl stretching), 762, 699 (mono substituted benzene ring). ^1H NMR (DMSO) δ (ppm): 8.09 (s, 1H, =CH group), 5.95 (s, 1H, S-CH-N), 7.68–8.31 (m, 9H, quinoline and quinazolinone-H), 7.28–7.82 (m, 9H, Ar-H), 5.38 (s, 1H, -OH group). ^{13}C NMR (DMSO) δ (ppm): 164.4, 160.8, 158.4, 156.2, 148.7, 145.4, 138.3, 136.2, 133.4, 131.9, 130.9, 130.0, 130.1, 129.9, 128.8, 128.6, 128.6, 128.2, 127.5, 127.3, 127.0, 126.7, 126.6, 125.2, 121.1, 120.8, 115.1, 112.1, 63.5. Anal. Calcd for $\text{C}_{33}\text{H}_{21}\text{ClN}_4\text{O}_3\text{S}$: C, 67.28; H, 3.59; N, 9.51. Found: C, 67.24; H, 3.63; N, 9.58.

2.2.3.9. 2-(2-Chloroquinolin-3-yl)-5-(4-hydroxybenzylidene)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-one (**V**)₉. Yield, 53%, dark brown crystalline solid, mp 263–265 °C. IR (KBr, cm^{-1}) ν : 3056, 3069 (quinazolinone ring, quinoline ring Ar-H), 3080 (=CH stretching), 1670, 1683 (C=O stretching), 1614, 1590 (C=N stretching), 1560–1441 (C=C, quinazolinone ring, quinoline ring, benzene ring), 846 (C-Cl stretching), 769, 691 (mono substituted benzene ring). ^1H NMR (DMSO) δ (ppm): 8.05 (s, 1H, =CH group), 5.96 (s, 1H, S-CH-N), 7.63–8.27 (m, 9H, quinoline and quinazolinone-H), 7.28–7.88 (m, 9H, Ar-H), 5.39 (s, 1H, -OH group). ^{13}C NMR (DMSO) δ (ppm): 164.4, 160.8, 157.7, 156.2, 148.7, 145.4, 138.3, 136.2, 133.4, 131.9, 130.9, 130.6, 130.1, 129.9, 128.8, 128.6, 128.2, 127.8, 127.5, 127.3, 127.0, 126.7, 126.6, 125.2, 120.8, 115.8, 63.5. Anal. Calcd for $\text{C}_{33}\text{H}_{21}\text{ClN}_4\text{O}_3\text{S}$: C, 67.28; H, 3.59; N, 9.51. Found: C, 67.35; H, 3.63; N, 9.56.

2.2.3.10. 2-(2-Chloroquinolin-3-yl)-5-(4-methylbenzylidene)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-one (**V**)₁₀. Yield, 74%, off brown crystalline solid, mp 201–203 °C. IR (KBr, cm^{-1}) ν : 3054, 3068 (quinazolinone ring, quinoline ring Ar-H), 3082 (=CH stretching), 2950 (-CH₃ stretching), 1675, 1681 (C=O stretching), 1605, 1589 (C=N stretching), 1567–1442 (C=C, quinazolinone ring, quinoline ring, benzene ring), 1460 (-CH₃ bending), 846 (C-Cl stretching), 762, 696 (mono substituted benzene ring). ^1H NMR (DMSO) δ (ppm): 7.76 (s, 1H, =CH group), 5.91 (s, 1H, S-CH-N), 7.65–8.21 (m, 9H, quinoline and quinazolinone-H), 7.29–7.86 (m, 9H, Ar-H), 2.35 (s, 3H, -CH₃ group). ^{13}C NMR (DMSO) δ (ppm): 164.4, 160.8, 156.2, 148.7, 145.4, 138.3, 137.6, 136.2, 133.4, 132.2, 131.9, 130.9, 130.1, 129.9, 128.9, 128.9, 128.8, 128.6, 128.5, 128.2, 127.5, 127.3, 127.0, 126.7, 126.6, 125.2, 120.8, 63.5, 21.3. Anal. Calcd for $\text{C}_{34}\text{H}_{23}\text{ClN}_4\text{O}_2\text{S}$: C, 69.55; H, 3.94; N, 9.54. Found: C, 69.56; H, 3.99; N, 9.62.

2.2.3.11. 2-(2-Chloroquinolin-3-yl)-5-(4-methoxybenzylidene)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)thiazolidin-4-one (**V**)₁₁. Yield, 72%, dark yellow crystalline solid, mp 224–226 °C. IR (KBr, cm^{-1}) ν : 3057, 3062 (quinazolinone ring, quinoline ring Ar-H), 3075 (=CH stretching), 2945 (-OCH₃ stretching), 1672, 1684 (C=O stretching), 1605, 1589 (C=N stretching), 1568–1445 (C=C, quinazolinone ring, quinoline ring, benzene ring), 838 (C-Cl stretching), 1465 (-OCH₃ bending), 763, 694 (mono substituted benzene ring). ^1H NMR (DMSO) δ (ppm): 7.76 (s, 1H, =CH group), 5.94 (s, 1H, S-CH-N), 7.63–8.27 (m, 9H, quinoline and quinazolinone-H), 7.27–7.86 (m, 9H, Ar-H), 3.83 (s, 3H, -OCH₃ group). ^{13}C NMR (DMSO) δ (ppm): 164.4, 160.8, 159.8, 156.2, 148.7, 145.4, 138.3, 136.2, 133.4, 130.2, 131.9, 130.9, 130.1, 129.9, 128.8, 128.6, 128.2, 127.5, 127.3, 127.0, 126.7, 114.2, 126.6, 125.2, 120.8, 114.2, 63.5, 55.8. Anal. Calcd for $\text{C}_{34}\text{H}_{23}\text{ClN}_4\text{O}_3\text{S}$: C, 67.71; H, 3.84; N, 9.29. Found: C, 67.78; H, 3.89; N, 9.33.

2.2.3.12. 2-(2-Chloroquinolin-3-yl)-3-(4-oxo-2-phenylquinazolin-3(4H)-yl)-5-(3,4,5-trimethoxybenzylidene)thiazolidin-4-one (**V**)₁₂. Yield, 69%, dark brown solid, mp 189–191 °C. IR (KBr, cm^{-1}) ν : 3051, 3062 (quinazolinone ring, quinoline ring Ar-H), 3080 (=CH stretching), 2939 (-OCH₃ stretching), 1671, 1682 (C=O stretching), 1605, 1585 (C=N stretching), 1566–1450 (C=C, quinazolinone ring, quinoline ring, benzene ring), 1462 (-OCH₃ bending), 842 (C-Cl stretching), 763, 694 (mono substituted benzene ring). ^1H NMR (DMSO) δ (ppm): 7.72 (s, 1H, =CH group), 5.96 (s, 1H, S-CH-N), 7.65–8.24 (m, 9H, quinoline and quinazolinone-H), 7.21–7.85 (m, 7H, Ar-H), 3.83 (s, 9H, -OCH₃ group). ^{13}C NMR (DMSO) δ (ppm): 164.4, 160.8, 156.2, 153.0, 148.7, 145.4, 138.4, 138.3, 136.2, 133.4, 131.9, 130.9, 130.1, 129.9, 129.5, 128.8, 128.6, 128.2, 127.5, 127.3, 127.0, 126.7, 153.0, 126.6, 125.2, 120.8, 103.8, 63.5, 60.8, 56.1. Anal. Calcd for $\text{C}_{36}\text{H}_{27}\text{ClN}_4\text{O}_5\text{S}$: C, 65.20; H, 4.10; N, 8.44. Found: C, 65.25; H, 4.17; N, 8.49.

3. Results and discussion

3.1. Synthesis

Intermediate compound (**I**) (2-phenylbenzo[d]1,3-oxazin-4-one) (Bogert and Coriner, 1909) and compound (**II**) (3-amino-2-phenyl-3-hydroquinazolin-4-one) were prepared by following literature procedures (Siddappa et al., 2008). Reaction conditions were non-homogeneous and the use of an excess amount of hydrazine hydrate did not afford desired results. The reaction conditions for the synthesis of (**II**) were optimized in various solvents at different temperatures and different time. The results were observed and data was reported in Table 1. In step-(II), ethanol was used as a solvent and refluxed at 78 °C, reaction was completed in 4 h and yield was found to be 24% (Table 2, step-(II), entry-1). When we used isopropanol as a solvent and at 85 °C temperature for 4 h, we found that 31% yield was obtained (Table 2, step-(II), entry-2). Pyridine was used as a solvent and reaction mixture was refluxed at 116 °C for 3 h, we found that 87% yield was obtained (Table 2, step-II, entry-3). Thus for the synthesis of intermediate compound-(2), pyridine is considered to be appropriate solvent and higher temperature (more than 100 °C) was the perfect parameter for step-2.

Table 1 Antimicrobial activity of the final synthesized compounds (V)_{1–12}.

S. No.	Compd.	-3-Cl	Minimum inhibitory concentration for bacteria µg/ml ± SD						Minimum inhibitory concentration for fungi µg/ml ± SD					
			Gram positive			Gram negative			C. albicans		A. niger		A. clavatus	
			<i>E. coli</i> MTCC-443	<i>P. aeruginosa</i> MTCC-1688	<i>S. aureus</i> MTCC-96	<i>S. aureus</i> MTCC-96	<i>S. pyogenes</i> MTCC-442	<i>C. albicans</i> MTCC-227	<i>C. albicans</i> MTCC-227	<i>A. niger</i> MTCC-282	<i>A. niger</i> MTCC-282	<i>A. clavatus</i> MTCC-1323	<i>A. clavatus</i> MTCC-1323	
1	(V) ₁	-4-Cl	250 ± 2.64	250 ± 3.05	250 ± 3	250 ± 3.05	200 ± 4.16	500 ± 3.60	500 ± 3.21	500 ± 3.21	500 ± 3.21			
2	(V) ₂		100 ± 3	250 ± 3.51	500 ± 4.04	100 ± 3.51	250 ± 3.05	1000 ± 2.6	100 ± 3.24	100 ± 3.24				
3	(V) ₃		150 ± 2.30	25 ± 1	100 ± 3.60	200 ± 4.16	500 ± 4.04	100 ± 3.05	1000 ± 3.21	1000 ± 3.21				
4	(V) ₄	-2-NO ₂	100 ± 3.05	200 ± 4	250 ± 2.64	250 ± 2.64	250 ± 2.08	500 ± 3.51	500 ± 3.46	500 ± 3.46				
5	(V) ₅	-3-NO ₂	100 ± 3.51	250 ± 2.08	500 ± 3.05	500 ± 4.58	500 ± 4.04	100 ± 3.60	1000 ± 3.51	1000 ± 3.51				
6	(V) ₆	-4-NO ₂	200 ± 2.64	250 ± 2.51	250 ± 3.60	250 ± 2.51	100 ± 4.04	100 ± 3.05	500 ± 3.21	500 ± 3.21				
7	(V) ₇	-2-OH	500 ± 3	50 ± 2.64	500 ± 4.16	250 ± 3.05	100 ± 3.51	500 ± 2.08	100 ± 3.05	100 ± 3.05				
8	(V) ₈	-3-OH	100 ± 3.51	100 ± 4.50	200 ± 4.16	100 ± 4.93	500 ± 3	500 ± 3.05	100 ± 3.51	100 ± 3.51				
9	(V) ₉	-4-OH	50 ± 2.64	200 ± 2.64	100 ± 3.60	100 ± 4.72	500 ± 3.51	100 ± 3.05	500 ± 3	500 ± 3				
10	(V) ₁₀	-4-CH ₃	500 ± 4.72	50 ± 2.51	250 ± 3.21	250 ± 3	500 ± 3.78	1000 ± 3	100 ± 3.60	100 ± 3.60				
11	(V) ₁₁	-4-OCH ₃	500 ± 4.04	100 ± 4.16	500 ± 3.51	500 ± 4.04	200 ± 4	1000 ± 3.5	1000 ± 2.30	1000 ± 2.30				
12	(V) ₁₂	3,4,5-(OCH ₃) ₃	250 ± 4.04	250 ± 2.51	500 ± 3.05	1000 ± 3.51	500 ± 3.46	1000 ± 3	100 ± 4.16	100 ± 4.16				
	Ampicillin		100 ± 4	100 ± 4.04	250 ± 4.04	100 ± 3.51	500 ± 2.64	100 ± 3	100 ± 3.46	100 ± 3.46				
	Griseofulvin		—	—	—	—	—	—	—	—				

±SD = Standard deviation; *p ≤ 0.0001.

In order to optimize the reaction conditions for the synthesis of (III), the different conditions were employed. First, the role of the catalyst (Acetic acid) in accelerating the reaction rate was ascertained. While in the presence of catalyst, a 72% yield of (III) was achieved in 10 h (Table 2, step-(III), entry-1), In the absence of the catalyst, only 52% yield was obtained with a prolonged reaction period of 30 h (Table 2, step-(III), entry-2). In addition, we also examined the effect of time taken for the completion of reaction. When the reaction time was decreased to 20 h, suddenly yield was improved (75%) (Table 2, step-(III), entry-3). We have also noted that the time decreased to 10 h, the yield was found to be (72%). Also, it could be observed that the yield was significantly lower at room temperature (Table 2, step-(III), entry-4). Thus the best condition for the synthesis of intermediate compound (III) may be at 78 °C temperature, using solvent ethanol and acetic acid as the catalyst.

The different reaction conditions for intermediate step (IV) were also employed. For this step, we have used different solvents and reaction was carried out at different temperature. In this step 1,4-dioxane was used as a solvent and fused ZnCl₂ used as a catalyst and refluxed at 90 °C, 76% yield of (IV) was achieved in 15 h (Table 2, step-(IV), entry-1), It was our observation, when the same reaction was carried out in the same solvent at 90 °C without catalyst ZnCl₂ it took 18 h, 52% yield was obtained (Table 2, step-(IV), entry2), when we have used ethanol as a solvent at 65 °C, reaction completed after 20 h and 32% yield was found (Table 2, step-(IV), entry-3). While reaction is carried out in benzene as a solvent at 78 °C, reaction completed after 15 h and 56% yield observed (Table 2, step-(IV), entry-4). So, this led to the conclusion that good result was obtained in 1,4-dioxane used as a solvent and fused ZnCl₂ used as a catalyst and refluxed at 90 °C temperature.

In the last step, in order to optimize the reaction conditions for the final step, three different catalysts in the same solvent ethanol at different temperature were used. The ethanol taken as a solvent and sodium ethoxide was used as catalyst at 75 °C for 8 h. Yield (74%) was found (Table 2, step-(V), entry-1), while in the same solvent sodium methoxide as catalyst was used at 70 °C for 12 h, only 43% yield was found (Table 2, step-(V), entry-2), If we used the same solvent but fused sodium acetate as a catalyst at 72 °C for 10 h, we have obtained 52% yield (Table 2, step-(V), entry-3). From the above observations, we have concluded that if, we want to get a better yield in the final step, ethanol as solvent and sodium ethoxide as a catalyst will be appropriate (see Scheme 1).

The IR spectrum of the final compound-(V)₈ (molecular formula C₃₃H₂₁ClN₄O₃S, m.w. 589.07, structure and carbon numbering is given in Fig. 1) over the 3077 cm⁻¹ range showed multiple weak absorption peak corresponding to Qu-H and Ar-H stretching vibration absorption peaks. The absorption peak at 3002 cm⁻¹ is due to the stretching vibration of methylene group. The strong absorption at 1671 cm⁻¹ is due to the >C=O stretching vibration, which is present in quinazolinone on position C-2, while another absorption peak at 1663 cm⁻¹ is due to the >C=O stretching vibration in thiazolidine ring and the moderate intensity absorption at 1623 cm⁻¹ corresponds to a >C=N- stretching vibration. The 1605–1580 cm⁻¹ absorptions are due to the skeleton vibration of the aryl and heterocyclic rings. The broad absorption peak at 3432 cm⁻¹ is observed due to the –OH stretching vibration.

Table 2 The effect of reaction condition on yield of step (II) to (V)₁₋₁₂.

Reaction step	Entry	Solvent	Catalyst	Reaction temp. (°C)	Reaction time (h)	Yield (%)
(II)	1	Absolute Ethanol	–	78	4	24
	2	Isopropanol	–	85	5	31
	3	Pyridine	–	116	3	87
(III)	1	Absolute Ethanol	Acetic acid	78	10	71.9
	2	Absolute Ethanol	–	78	30	52.4
	3	Absolute Ethanol	Acetic acid	78	20	74.8
	4	Absolute Ethanol	Acetic acid	r.t.	10	22.1
(IV)	1	1,4-dioxane	ZnCl ₂	90	12	76
	2	1,4-dioxane	–	90	18	52
	3	Absolute Ethanol	ZnCl ₂	65	20	32
	4	Benzene	–	78	24	52
(V) ₁₋₁₂	1	Absolute Ethanol	C ₂ H ₅ ONa	75	8	74
	2	Absolute Ethanol	CH ₃ ONa	70	12	43
	3	Absolute Ethanol	CH ₃ COONa	72	10	52

The absorption peak at 756 cm⁻¹ is due to the chlorine atom, which is attached with a carbon atom at C-19. The vibration at 845 cm⁻¹ is due to the bending vibration of methylene group. The absorption peaks 696 cm⁻¹ arise due to phenyl-substituted at position-3.

It can be seen from the chemical structure of compound-(V)₈ that different pairs of carbons e.g. C-10 and C-14, C-11 and C-13 are attached to chemically equivalent protons. The protons which are attached to C-10 and C-14 appear at 7.83, while the protons which are attached to C-11 and C-13 appear at 7.52 ppm. The protons attached at C-5 position appeared as a multiplet at $\delta = 7.63$ ppm due to mutual coupling with C4-H and C6-H, while protons attached at C-6 appeared as a multiplet at $\delta = 7.70$ ppm due to mutual coupling with C5-H and C7-H. The protons attached at C-4 position appeared as a doublet at $\delta = 8.03$ ppm. The protons which are attached with C-12 appeared as a multiplet at $\delta = 7.55$ ppm due to mutual coupling with C-11 and C-13 which are present in the phenyl ring directly attached to the quinazolinone ring. A single peak that appeared at $\delta = 5.97$ ppm must be for proton attached at C-17 which is present in thiazolidine ring. A single peak appeared at $\delta = 5.35$ ppm of -OH group which is attached with C-32. The proton of the methylene group appear as a singlet at $\delta = 7.33$ ppm. The protons of the phenyl ring (C-29, C-30, C-31 and C-33) appeared between $\delta = 6.70$ and 7.16 ppm, respectively. The proton attached at C-23 position appeared as a multiplet at $\delta = 7.59$ ppm due to mutual coupling with protons attached at C-22 and C-24, while proton attached at C-22 position appeared as a multiplet at $\delta = 7.74$ ppm due to mutual coupling with C-21 and C-23. The proton at C-21 appeared as a doublet at $\delta = 7.99$ ppm, while proton at C-24 appeared at $\delta = 8.03$ ppm and proton at C-26 appeared at $\delta = 8.27$ ppm.

The final compound-(V)₈ has quinazolinone ring, quinoline ring and thiazolidine ring. The chemical shifts of the final compound carbons vary from $\delta = 164.2$ –63.6 ppm. The carbon nuclei under the influence of a strong electronegative environment appeared downfield, e.g. the C-2 and C-15 carbonyl, which are directly linked to the ring nitrogen, has a chemical shift value of $\delta = 160.6$ and 164.4 ppm, respectively, whereas C-19 linked to a chlorine atom appeared at $\delta = 151.9$ ppm. The carbon C-1 which is attached on both sides to nitrogen atoms appeared at $\delta = 156.0$. The carbon of the methylene

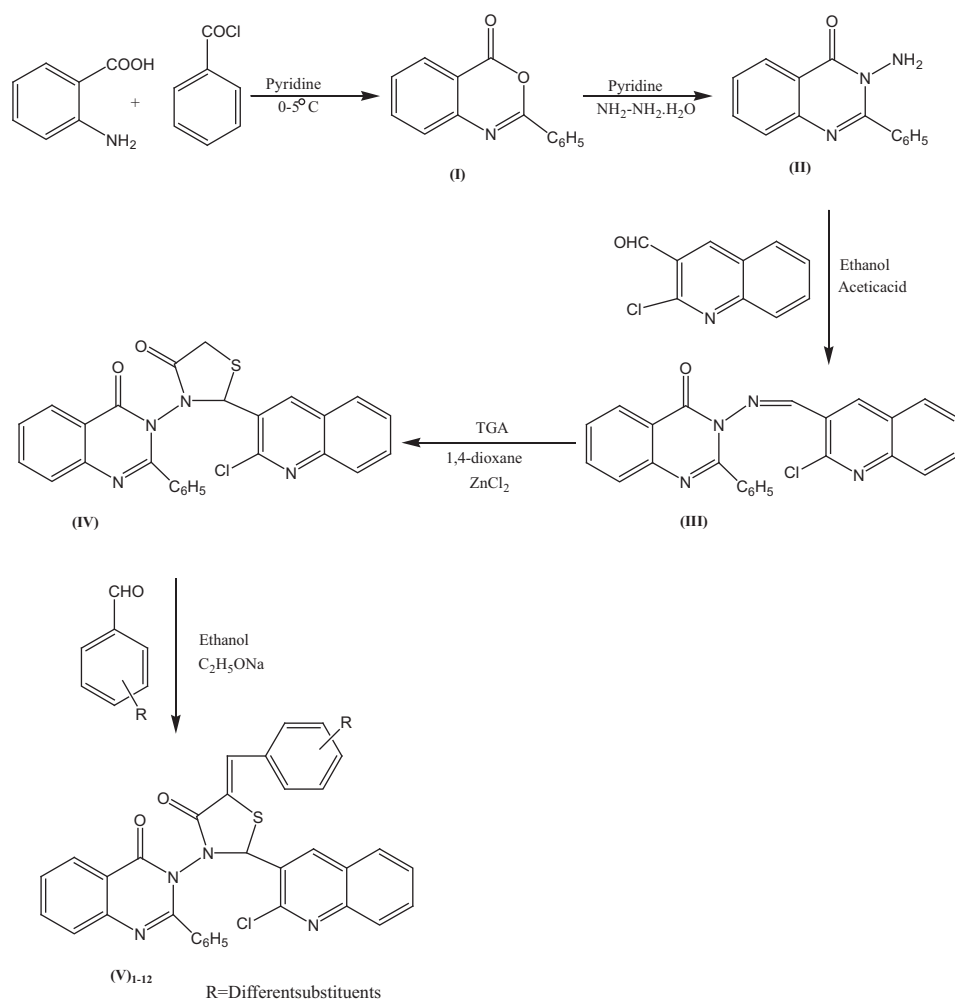
group C-27 appeared at $\delta = 125.1$ ppm. The chemical shift of the ring carbons at C-3 and C-16 which are affected by the presence of the nearest carbonyl group appeared at $\delta = 120.7$ and 138.4 ppm, respectively. The carbons of the benzene ring which are attached to the quinazolinone ring having equivalent carbons C-10 and C-14 appeared at $\delta = 128.2$ ppm, C-11 and C-13 appeared at $\delta = 128.8$ ppm, respectively, while carbon C-12 appeared at $\delta = 130.1$ ppm, respectively, while the carbon atom which is present in thiazolidine ring between nitrogen atom and sulfur atom appeared at $\delta = 63.6$ ppm. The carbon C-32 which is directly attached to hydroxyl group appeared at $\delta = 158.4$ ppm, the other carbons of this ring (C-28, C-29, C-30, C-31 and C-33) appeared between $\delta = 115.0$ and 136.6 ppm, respectively. The carbons of the quinoline ring (C-18, C-20, C-21, C-22, C-23, C-24, C-25 and C-26) appeared between $\delta = 126.6$ and 151.9 ppm, respectively. The structure and carbon numbering of compound-(V)₈ is described in Fig. 1.

3.2. Antimicrobial activity

Minimum Inhibitory Concentration for bacteria (MIC_b) of all the synthesized compounds was determined against four different strains, viz two Gram positive bacteria (*Staphylococcus aureus* and *S. pyogenes*) and two Gram negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) compared with standard drug. Ampicillin by broth dilution method (Rattan, 2000). For Antifungal activities, minimum inhibitory concentration for fungi (MIC_f) of all the synthesized compounds was determined against *Candida albicans*, *Aspergillus niger* and *A. clavatus* organisms were compared with standard drugs Griseofulvin by same method, which showed 100 μ g/ml MIC_f against all fungi used for the antifungal activity. We have synthesized 2-(2-Chloro(3-quinoly))-5-[(2-aryl)methylene]-3-(4-oxo-2-phenyl(3-hydroquinazolin-3-yl))-1,3-thiazolidin-4-one (V)₁₋₁₂ derivatives.

3.2.1. Antibacterial activity

From screening results, final compound (V)₉ possesses very good activity against *E. coli*. Compounds (V)₂, (V)₄, (V)₅ and (V)₈ were good active against *E. coli* compared with standard ampicillin. Final compound (V)₃ possesses an excellent activity against *P. aeruginosa* and compound (V)₇ and (V)₁₀



Scheme 1 Synthetic route of the title compounds.

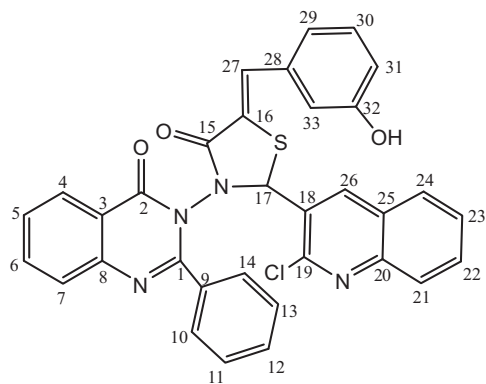


Figure 1 Carbon numbering of the final compound-(V)₈.

possesses very good activity against *P. aeruginosa*, while compound (V)₈ and (V)₁₁ possesses good activity against *P. aeruginosa* as compared to standard ampicillin. Final compounds (V)₃ and (V)₉ possesses very good activity against *S. aureus*, while compounds (V)₁, (V)₄, (V)₆, (V)₈ and (V)₁₀ possesses good activity against *S. aureus* as compared to standard ampicillin. Final compounds (V)₂, (V)₈ and (V)₉ are considered as

good active against *S. pyogenus* as compared to ampicillin. The remaining compounds of the entire series possesses only moderate to poor antibacterial activity.

3.2.2. Antifungal activity

Antifungal screening data showed that final compounds (V)₆ and (V)₇ possesses very good activity against *C. albicans*, while compounds (V)₁, (V)₃, (V)₄ and (V)₁₁ possess good activity against *C. albicans* as compared to the standard griseofulvin. Compounds (V)₃, (V)₅, (V)₆ and (V)₉ possesses good activity against *A. niger* as compared to the standard griseofulvin. Compounds (V)₃, (V)₇, (V)₈, (V)₁₀ and (V)₁₂ possesses good activity against *A. clavatus* as compared to the standard griseofulvin. The remaining compounds of the entire series possesses moderate to poor antifungal activity.

3.3. Statistical analysis

The standard deviation value is express in the terms of \pm SD. On the basis of the calculated value by using ANOVA method, it has been observed that the differences below to 0.0001 level ($p \leq 0.0001$) were considered as statistically significant.

4. Conclusion

Some of the newly synthesized compounds exhibited promising antibacterial activities against *E. coli*, *S. aureus*, *P. aeruginosa* and *S. pyogenes*. Some exhibited very good antifungal activity against *C. albicans*, *A. niger* and *A. clavatus*. Compounds (V)₇ and (V)₁₀ possessed very good activity against both bacterial and fungal species. It seems that the methyl group at para position and hydroxy group at second position are very significant for activity against both bacterial and fungal species. These results make novel quinazolinone, thiazolidine and quinoline derivatives interesting lead molecules for further synthetic and biological evaluation.

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References

- Alafeefy, A.M., 2008. Synthesis and antimicrobial activity of some new quinazolin-4(3*H*)-one derivatives. *Pharm. Biol.* 46 (10), 751–756.
- Andres, C.J., Bronson, J.J., D'Andrea, S.V., Deshpande, M.S., Falk, P.J., Grant-Young, K.A., Harte, W.E., Ho, H., Misco, P.F., Robertson, J.G., Stock, D., Sun, Y., Walsh, A.W., 2000. 4-Thiazolidinones: novel inhibitors of the bacterial enzyme MurB. *Bioorg. Med. Chem. Lett.* 10, 715–717.
- Apfel, C., Banner, D.W., Bur, D., Dietz, M., Hubschwerlen, C., Locher, H., Marlin, F., Masciadri, R., Pirson, W., Stalder, H., 2001. 2-(2-Oxo-1,4-dihydro-2*H*-quinazoli-3-yl)- and 2-(2,2-dioxo-1,4-dihydro-2*H*-6-benzo[1,2,6]thiadiazin-3-yl)-*N*-hydroxy-acetamides as potent and selective peptide deformylase inhibitors. *J. Med. Chem.* 44, 1847–1852.
- Berber, I., Cokmus, C., Atalan, E., 2003. Comparison of *Staphylococcus* spp. cellular and extracellular proteins. *Mikrobiologia* 72, 54–59.
- Bhanot, S.K., Singh, M., Chatterjee, N.R., 2001. The chemical and biological aspects of fluoroquinolones: reality and dreams. *Curr. Pharm. Des.* 7, 311–335.
- Bogert, M.T., Coriner, R.A., 1909. Researches on quinazolines (Twenty-second paper). On 2-methyl-3-amino-4-quinazolinone and certain of its derivatives. *J. Am. Chem. Soc.* 31, 943–947.
- Carpenter, C.F., Chambers, H.F., 2004. Daptomycin: another novel agent for treating infections due to drug-resistant gram-positive pathogens. *Clin. Infect. Dis.* 38, 994–1000.
- Chang, Z., Babiuk, L.A., Hu, J., 2007. Therapeutic and prophylactic potential of small interfering RNAs against severe acute respiratory syndrome: progress to date. *Bio. Drugs* 21, 9–15.
- Chevalier, J., Atifi, S., Eyraud, A., Mahamoud, A., Barbe, J., Pajes, J., 2001. New pyridoquinoline derivatives as potential inhibitors of the fluoroquinolone efflux pump in resistant *Enterobacter aerogenes* strains. *J. Med. Chem.* 44, 4023–4026.
- Chenard, B.L., Welch, W.M., Blake, J.F., Butler, T.W., Reinhold, A., Ewing, F.E., Menniti, F.S., Pagnozzi, M.J., 2001. Quinazolin-4-one *a*-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) receptor antagonists: structure–activity relationship of the C-2 side chain tether. *J. Med. Chem.* 44, 1710–1717.
- Ctoen-Chackal, S., Facompre, M., Houssin, R., Pommery, N., Gossens, J.F., Colson, P., Bailly, C., Henichart, J.P., 2004. DNA binding to guide the development of tetrahydroindeno[1,2-*b*]pyridido[4,3,2-*de*]quinoline derivatives as cytotoxic agents. *J. Med. Chem.* 47 (14), 3665–3673.
- Edafigo, I.O., Scott, K.R., Moore, J.A., Farrar, Y.A., Nicholson, J.M., 1991. Synthesis and anticonvulsant activity of imidooxy derivatives. *J. Med. Chem.* 34, 387–392.
- Emami, S., Shafiee, A., Alireza, F., 2006. Structural features of new quinolones and relationship to antibacterial activity against gram-positive bacteria. *Mini Rev. Med. Chem.* 6, 375–386.
- Farrar, Y.A., Rutkowaka, M.C., Grochowski, J., Serda, P., Pilati, T., Cory, M., Nicholson, J.M., Scott, K.R., 1993. Synthesis and calculated log P correlation of imidooxy anticonvulsants. *J. Med. Chem.* 36, 3517–3525.
- Gary, W.W.K., Ting, L.F., 2007. Bird flu: lessons from SARS. *Paediatr. Respir. Rev.* 8, 171–176.
- Guang-Fang, X., Bao-An, S., Pinaki, S.B., Song, Y., Pei-Quan, Z., Lin-Hong, J., Wei, X., De-Yu, H., Ping, L., 2007. Synthesis and antifungal activity of novel *S*-substituted 6-fluoro-4-alkyl(aryl)thioquinazolinone derivatives. *Bioorg. Med. Chem.* 15, 3768–3774.
- Gursoy, A., Otuk, G., Terzioglu, N., 2005. Synthesis and antimicrobial evaluation of some novel imidazolylmercaptoacetylthiosemicarbazide and 4-thiazolidinone analogs. *Turkish J. Pharm. Sci.* 2, 1–10.
- Hardman, J.G., Limbird, E.L., Molinoff, P.B., Ruddon, R.W., Gilman, A.G., 2002. Goodman and Gilman's, ninth ed.. *The Pharmacological Basis of Therapeutics* Springer, p. 1065.
- Hooper, D.C., 1995. Quinolones. In: Mandell, Douglas (Eds.), *Bennett's Principles and Practice of Infectious Diseases*, fourth ed. Churchill Livingstone Inc., New York, p. 364.
- Hooper, D.C., Wolfson, J.S., 1989. Fluoroquinolone antimicrobial agents. *Clin. Microbiol. Rev.* 2, 378–424.
- Pan, B., Huang, R.Z., Ying, H.J., 2010. Design, synthesis and antibiofilm activity of 2-arylimino-3-aryl-thiazolidine-4-ones. *Bioorg. Med. Chem. Lett.* 20, 2461–2464.
- Raffa, D., Daidone, G., Schillaci, D., Maggio, B., Plescia, F., 1999. Synthesis of new 3-(3-phenyl-isoxazo-5-yl) or 3-[(3-phenylisoxazol-5-yl)-amino]-substituted 4(3*H*)quinazolinone derivatives with antineoplastic activity. *Pharmazie* 54, 251–254.
- Rao, A., Zappala, M., 2004. Microwave-assisted synthesis of benzimidazole and thiazolidinone derivatives as HIV-1 RT inhibitors. *Arkivoc* v, 147–155.
- Rattan, A., 2000. *Antimicrobials in laboratory medicine*. Churchill, B.I., Livingstone, New Delhi, pp. 85–105.
- Sayed, M., Mokle, S., 2006. Synthesis of some new 2,3-diaryl-1,3-thiazolidin-4-ones as antibacterial agents. *Arkivoc* ii, 187–192.
- Siddappa, K., Reddy, K., Reddy, C.V., 2008. Synthesis, characterization and antimicrobial studies of 3-[(2-hydroxy-quinolin-3-ylmethylene)-amino]-2-phenyl-3*H*-quinazolin-4-one and its Metal(II) complexes. *E-J. chem.* 5, 155–162.
- Surrey, A.R., 1949. 4-Thiazolidinones. IV. The preparation of some 3-alkylaminoalkyl-2-aryl derivatives. *J. Am. Chem. Soc.* 71, 3354–3356.
- Taun, P.T., Edmund, L.E., Joseph, P.S., Brian, M.W., Michael, A.S., Hollis, S., John, M.D., Martin, A.S., Themis, J., Stephen, J.G., Dai, Q.N., Paul, B., Judy, Y., Anurag, S., Chan, H., Saeed, R., Xiujuan, W., Rajeshwar, S., 2007. Structure activity relationships of 3-aminoquinazolinones, a new class of bacterial type-2 topoisomerase (DNA gyrase and topo IV) inhibitors. *Bioorg. Med. Chem. Lett.* 17, 1312–1320.
- Troutman, H.D., Long, L.M., 1948. The Synthesis of 2,3-disubstituted-4-thiazolidinones. *J. Am. Chem. Soc.* 70, 3436–3439.
- Tobe, M., Isobe, Y., Tomizawa, H., Nagasaki, T., Obara, F., Hayashi, H., 2003. Structure–activity relationships of 6-fluoroquinazolines: dual-acting compounds with inhibitory activities toward both TNF alpha production and T cell proliferation. *Bioorg. Med. Chem.* 11, 609–616.
- Weigelt, J., Itani, K., Stevens, D., Lau, W., Dryden, M., Knirsch, C., 2005. Linezolid versus vancomycin in treatment of complicated skin and soft tissue infections. *Antimicrob. Agents Chemother.* 49, 2260–2266.

- Wolfgang, L., 1998. New visions in the pharmacology of anticonvulsion. *Eur. J. Pharmacol.* 342, 1–13.
- Yeung, K.S., Meanwell, N.A., 2007. Recent developments in the virology and antiviral research of severe acute respiratory syndrome coronavirus. *Infect. Dis.* 7, 29–41.
- Youssef, A.M., White, M.S., Klegeris, A., 2010. Synthesis and biological evaluation of novel pyrazolyl-2,4-thiazolidinediones as anti-inflammatory and neuroprotective agents. *Biorg. Med. Chem.* 20, 2019–2028.