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Design, Synthesis and Evaluation of Antibacterial and Antifungal Quinazolinone Derivatives bearing Thiazole Schiff Base Moiety

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Abstract

Various quinazolinone derivatives with thiazole substituent was synthesised in good yields starting from 4-chloroanthranilic acid and ethyl-2-aminothiazole acetate in condensation reactions. The synthesized compounds were characterised using proton and carbon-13 nuclear magnetic resonance (^{1}H NMR, ^{13}C NMR), Fourier Transform Infrared (FT-IR), and mass spectrometry (GCMS) analyses. The antibacterial activity of the compounds against a number of micro-organisms was tested by the Micro broth dilution method. It was found that the synthesised compounds exhibited variable antimicrobial activity against Gram-negative bacteria (*Escherichia coli* and *Pseudomonas aeruginosa*) and Gram-positive bacteria (*Bacillus subtilis* and *Staphylococcus aureus*) as well as the fungus (*Candida pseudotropicalis*). It was also found that compounds **6c** and **6d** among others were the most effective on both Gram-negative and Gram-positive bacteria. The two compounds were also found to be the most effective against the fungus, *Candida pseudotropicalis*. The results of the antimicrobial activity suggest that compounds **6c** and **6d** are potent antimicrobial agents.

Keywords: Synthesis, Antimicrobial, Characterization, Quinazolinone derivative, Condensation reactions, Heterocycles.

Introduction

The chemistry of the heterocyclic compounds has attracted a lot of attention by the scientific community, due to their utility in the development of various drugs. Researchers have shown that about 68% of the heterocycles (Dahiya *et al.*, 2008; Ansari and Lai, 2009) possess chemotherapeutic attributes. They show widespread pharmaceutical and non-pharmaceutical applications. Of particular interest as far as this study is concerned, are the quinazolinone and thiazole derivatives.

The structure of the quinazolinone nucleus is such that it can undergo condensation reactions with a variety of reactants to give several products (derivatives). This has enabled many bioactive moieties to be introduced into the nucleus to further increase or modify their therapeutic activities (Patel and Patel, 2011). Thus, it has been reported that various quinazolinone derivatives exhibit anti-cancer (Nandy *et al.*, 2006), anti-bacterial (Rohini *et al.*, 2010; Antipenko *et al.*, 2009; Gupta *et al.*, 2008; Ally, 2003), analgelsic (Alagarsamy *et al.*, 2007), anti-obesity (Sasmal *et al.*, 2012) anti-oxidation (Saravanan *et al.*, 2010) activities and other potential applications in the field of biology, pesticides and medicine.

The thiazole derivatives on the other hand have also been reported (Nadeem and Satish, 2010; Lakshmana and Lalitha, 2011; Tabbi *et al.*, 2016) to exhibit brilliant medicinal properties against various

common human diseases linked with the skin, blood, urinary, cardiac pulmonary systems, etc. The condensation products of aromatic amines with aryl or hetaryl aldehydes, known as Schiff bases, have also been reported to exhibit a wide range of pharmacological activities such as anti-bacterial, antifungal, antitumor, analgesic, anti-hypertension and anti-inflammatory activities (Kumar *et al.*, 2010; Mistry and Desai, 2014). The bioactivity of Schiff bases is believed to be associated with the azomethine (-C=N-) group.

Thus, the search for new antimicrobial agents is a continuous process because, apart from the host defense mechanism which reduces the effectiveness of the anti-microbial agents with time, there is also the problem of resistance of pathogenic bacteria or fungi to existing drugs.

The authors now report the design and synthesis of new quinazolinone derivatives bearing a thiazole Schiff base moiety, their characterisation by spectroscopic methods (IR, ^{1}H NMR, ^{13}C NMR and GC/MS) and their effectiveness against selected microorganisms in comparison with a standard drug.

Experimental Section

All melting points (uncorrected) were determined on a Veego melting point apparatus (model number). Infrared (IR) spectra were recorded on a Perkin-Elmer FTIR-8400S spectrometer using KBr pellets, ^{1}H NMR (400MHz) and Carbon-13 NMR (100 MHz) spectra were obtained on an Agilent spectrometer (Agilent Technology, USA) using tetramethylsilane (TMS) as internal standard and chemical shift are in δ. Mass spectra were recorded on a GC/MS-QP 2010 series. All reagents were obtained from commercial suppliers unless otherwise stated and were used as such without further purification.

7-Chloro-2-methyl-4H-1,3-benzoxazin-4-one 2-methyl-4H-1,3-benzoxazin-4-one (2)

A mixture of 2-amino-4-chlorobenzoic acid (4.6 g, 27 mmol) and acetic anhydride (20 mL) were added to acetic acid (0.01 M). The mixture was refluxed for 4 h. after which the acetic anhydride and acetic acid were distilled off under reduced pressure. The solid product was isolated by filtration and purified by recrystallization twice from hot ethanol to give compound **2**. Thus, the yield of compound 2 is 5.046 g (mass) and 88 % (percentage yield) (Kohli, *et al.*, 2009).

2-Phenyl-4H-1,3-benzoxazin-4-one (3)

To the solution of 2-amino-4-chlorobenzoic acid (7.0 g, 41 mmol) in pyridine (60 mL), benzoyl chloride (10 mL) was added dropwise with stirring for 1 h. The reaction mixture was stirred at room temperature for another 1 h and neutralised with sodium bicarbonate solution (10 % w/v). The precipitated crude product was filtered, washed with distilled water and recrystallized twice from chloroform/ethanol mixture to give the desired compound **3**. The final product was obtained with a yield of 12.49 g, corresponding to a 98 % yield based on the starting material (2-amino-4-chlorobenzoic acid) (Kohli, *et al.*, 2009).

7-Chloro-2-methyl/phenyl-4-(3H)-quinazolinone (2,5-thiazol-3yl)-acetate 2-methyl-4(3H)-quinazolinone-(2,5-thiazole-3yl)-acetate (4)

A mixture of compound **2** (3.8 g, 19 mmol), ethyl-2-amino-thiazole acetate (3.0 g, 16 mmol) in acetic acid (40 mL) was stirred and refluxed for 1 hour. The reaction mixture was allowed to cool and poured onto crushed ice (5 g). The precipitated compound was filtered and recrystallized from ethanol to give compound **4**. The final product was obtained with a 6.17 g (mass) and 87 % (percentage yield).

2-phenyl-4-(3H)-quinazolinone-(2,5-thiazol-3yl)-acetate (5)

A mixture of compound **3** (6.50 g, 25 mmol) and ethyl 2-amino-thiazole acetate (5.0 g, 14 mmol) in acetic acid (40 mL) was stirred thoroughly and heated to reflux for 1 hour. The reaction mixture was allowed to cool and then poured onto crushed ice (5 g). The solid compound (5) obtained was

filtered and recrystallized from ethanol. The product was obtained with a mass yield of 9.10 g, corresponding to a 68 % yield.

Synthesis of Schiff-Bases

The synthesis of the Schiff bases **5a – 5d** and **6a – 6d** were carried out by the following method:

A solution of compound **3a** (8 mmol) in absolute ethanol, was mixed with hydrazine hydrate (15 mL) and the resultant mixture was stirred at reflux for 4 hours. The reaction mixture was then cooled to room temperature. The brown precipitate was filtered, dried and recrystallized from ethanol to give compound **4a.** A 2 mmol of compound **4a** in ethanol (10 mL) and acetic acid (6 mL) were refluxed for 1 hour with 8 mmol each of 3-chlorobenzyl aldehyde, 2-methoxylbenzyl aldehyde, 2-hydroxylbenzyl aldehyde and 4-hydroxylbenzyl aldehyde to give the Schiff bases **5a** – **5d** respectively. Each of the crude products was filtered and recrystallized from ethanol or methanol.

Similarly, compounds **6a** to **6d** were obtained by first synthesizing compound **4b** from compound **3b** as described for compound **4a** and then heating a mixture of the intermediate (8 mmol) formed with the appropriate aldehyde in ethanol (10 mL) and acetic acid (6 mL) under reflux for 1 hour. The products were further purified by recrystallization from ethanol or methanol to afford the Schiff base compounds.

7-Chloro-(2-methoxyphenyl)-1,3-thiazol-2yl)-4-acetylhydrazone)-2-methylquinazolinon-4-(3H)-one (5a)

Yellow solid, mp = 140 – 142 ^{o}C, 87 % yield; ^{1}H NMR (DMSO-d_6) δ_H ppm: 6.61 – 7.07 (7H, m, ArH), 8.36 – 8.39 (1H, s, N=CH) and 11.0 (1H, broad s, OH); ^{13}C NMR (DMSO-d_6) δ_C ppm: 165.0, 163.2, 160.1, 142.0, 133.8, 132.9, 120.1, 117.6, 117.5, 77.6, 77.3, 77.0, 30.0, 29.9, 29.8, 29.7, 29.6, 29.4 and 29.2; IR (KBr) cm^{-1}: 3421 (NH), 2951 (C-H_{str}), 1618 (N-CH_{str}), 1486 (ArC=C), 1398 (ArC-N), 1119 (C-S) and 597 (C-Cl_{str})**;** m/z (%): 72 (0.70), 72 (8.47), 109 (0.71), 111 (6.94), 112 (0.13), 114 (0.53), 123 (1.14), 127 (0.20), 127 (0.59), 149 (0.13), 240 (57.7), 240 (16.2), 240 (5.70) and 279 (0.59).

7-Chloro-(4-hydroxyphenyl)-1,3-thiazol-2yl)-4-acetylhydrazone)-2-methylquinazolinon-4-(3H)-one (5b)

Orange solid, mp = 140 – 142 ^{o}C, 93 % yield; ^{1}H NMR (DMSO-d_6,) δ_H ppm: 3.13 (3H, s, CH_3), 3.92 (3H, s, OCH_3), 4.0 (2H, s, CH_2), 8.20 (1H, s, thiazole-H), 8.62 – 9.02 (1H, s, N=CH) and 9.74 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C ppm: 206.6 (C=O), 161.9, 132.3, 131.9, 129.0, 128.4, 30.6, 30.4, 30.1, 29.9 and 29.7; IR (KBr)cm^{-1}: 3405 (N-H_{str}), 1627 (N=CH), 1431 (ArC=C_{str}), 1084 (C-S_{str}), 1220 (ArC-N) and 587 (C-Cl_{str}); m/z (%): 85 (1.51), 95 (3.39), 99 (1.12), 101 (2.16), 113 (1.42), 113 (0.78), 113 (1.58), 113 (1.06), 121 (1.35), 139 (12.32), 194 (20.82), 240 (11.83), 258 (5.96) and 276 (34.70).

7-Chloro-(3-chlorophenyl)-1,3-thiazol-2yl)-4-acetylhydrazone)-2-methylquinazolinon-4-(3H)-one (5c)

Light brown solid, mp = 215 – 219 ^{o}C, 34% yield; ^{1}H NMR (DMSO-d_6) δ_H ppm: 2.14 – 2.18 (3H, s, CH_3), 4.01 – 4.07 (2H, s, CH_2), 7.14 – 7.59 (7H, m, ArH), 8.19 – 8.22 (1H, s, N=CH) and 9.11 – 9.16 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_C ppm: 205.9 (C=O), 159.8, 157.3, 133.8, 133.3, 127.4, 123.2, 121.3, 115.7, 112.2, 55.9, 30.2, 30.0, 29.8, 29.6, 29.4, 29.2 and 29.0; IR (KBr)cm^{-1}: 3437 (O-H_{str}), 3402 (NH), 2969 (C-H_{str}), 1610 (N=CH), 1464 (ArC=C), 1026 (C-S), 1249 (ArC-N) and 575(C-Cl_{str}); m/z (%): 84 (3.33), 87 (0.71), 87 (0.82), 97 (3.91), 136 (1.29), 151 (10.70), 159 (11.35), 161 (17.07), 188 (12.46), 197 (2.52), 237 (17.75), 256 (5.84), 277 (6.33), 284 (1.90) and 348 (4.01).

7-Chloro-(2-hydroxyphenyl)-1,3-thiazol-2yl)-4-acetylhydrazone)-2-methylquinazolinon-4-(3H)-one (5d)

Brown solid, mp = 199 – 201 ^{o}C, 85% yield; ^{1}H NMR (DMSO-d_6) δ_H (ppm): 2.49 (3H, s, CH_3), 7.42 – 8.08 (7H, m, ArH), 45 – 8.47 (1H, thiazole-H), 8.59 – 8.60 (1H, s, N=CH), 9.49 (1H, s, NH) and 12.80 (AH, s, ArOH); ^{13}C NMR (DMSO-d_6, 100 MHz), δ_C ppm: 206.2 (C-O), 169.8, 165.6, 161.9, 161.8, 158.1, 143.6, 140.3, 136.1, 134.9, 133.4, 132.7, 130.2, 129.3, 127.6, 122.9, 120.7, 119.8, 118.8, 114.7, 114.4, 29.9, 29.8, 29.6, 29.4, 29.2, 29.0 and 28.8; IR (KBr)cm^{-1}: 3329 (O-H_{str}), 3143 (N=H_{str}), 1662 (N=CH), 1501 (ArC=C), 1246 (ArC-N), 969 (C – S) and 551(C-Cl_{str}); m/z (%): 85 (1.36), 85 (0.86), 87 (4.93), 112 (10.49), 113 (0.94), 113 (1.14), 113 (1.04), 122 (13.92), 137 (1.49), 162 (10.66), 174 (9.07), 176 (1.62), 202 (4.56), 218 (3.67), 256 (1.91), 257 (26.12), 275 (4.30), 289 (1.24) and 317 (0.70).

7-Chloro-(4-methoxyphenyl)-1,3-thiazol-2yl)-4-acetylhydrazone)-2-phenylquinazolinon-4-(3H)-one (6a)

Brown solid, mp = 218 – 220 ^{o}C, 97% yield; ^{1}H NMR (DMSO-d_6) δ_H (ppm): 1.31 (2H, s, CH_2), 7.22 – 7.59 (7H, m, ArH), 8.94(1H, s, NH) and 10.31 (1H, broad s, OH); ^{13}C NMR (DMSO-d_6) δ_C (ppm): 165.0, 163.2, 160.11, 154.3, 144.0, 33.8, 132.9, 120.1, 117.6, 77.7, 77.3, 77.0, 29.9, 29.7, 29.4 and 29.3; IR (KBr)cm^{-1}: 3424, 3313 (NH), 3049 (ArC=H_{str}), 1604 (N=CH), 1498 (ArC=C), 1248 (ArC-N), 1112 (C – S_{str}) and 547(C-Cl_{str}); m/z (%): 98 (4.33), 112 (1.44), 129 (4.28), 129 (1.57), 240 (50.89), 240 (11.78), 240 (7.43), 257 (13.71), 279 (2.10) and 289 (1.30).

7-Chloro-(2-hydroxyphenyl)-1,3-thiazol-2yl)-4-acetylhydrazone)-2-phenylquinazolinon-4-(3H)-one (6b)

Yellow solid, mp = 170 - 172 ^{o}C, 64% yield; ^{1}H NMR (DMSO-d_6) δ_H (ppm): 1.57 (2H, s, CH_2), 4.71 (1H, OH), 7.71 – 7.99 (7H, m, ArH), 8.18 (1H, s, thiazole-H), 8.31 (1H, N=CH) and 8.90 (1H, s, NH); ^{13}C NMR (DMSO-d_6) δ_c (ppm): 161.5, 131.7, 130.5, 128.6, 127.8, 77.7, 77.5 and 77.1; IR (KBr) cm^{-1}: 3420 (N-H_{str}), 597 (N=CH), 1420 (ArC=C), 1202 (ArC-N), 882 (C-S) and 685 (C-Cl_{str}); m/z(%): 87 (5.54), 109 (4.07), 111 (0.55), 111 (0.84), 113 (0.58), 123 (0.35), 123 (5.68), 125 (0.47), 129 (5.47), 129 (2.77), 139 (0.76), 194 (2.13), 206 (1.56), 255 (4.23), 257 916.18), 258 (1.17), 276 (5.38), 276 (11.27), 277 (18.38) and 289 (1.08).

7-Chloro-(3-hydroxyphenyl)-1,3-thiazol-2yl)-4-acetylhydrazone)-2-phenylquinazolinon-4-(3H)-one (6c)

Yellowish brown solid, mp = 195 – 197 ^{0}C, 44% yield; ^{1}H NMR (DMSO-d_6) δ_H (ppm): 2.37 (3H, s, CH_3), 4.0 (1H, d, OH), 4.12 – 4.24 (2H, s, CH_2), 7.24 – 8.07 (7H, m, ArH), 8.33 – 8.49 (1H, s, thiazole-H), 8.87(1H, m, N=CH), 9.37 (1H, S, NH) and 12.68 (1H, s, ArOH); ^{13}C NMR (DMSO-d_6) δ_c (ppm): 205.5 (C = O), 165.5, 160.8, 140.3, 133.3, 132.6, 130.5, 129.2, 127.5, 126.5, 122.9, 119.7, 116.0, 29.9, 29.7, 29.5, 29.1, 28.9 and 28.7. IR (KBr) cm^{-1}: 3326 (OH_{str}), 3081 (ArC-H_{str}), 1593 (N=CH), 1506 (ArC=C), 1248 (ArC-N), 886 (C-S) and 689 (C-Cl_{str}); m/z (%): 83 (1.15), 85 (0.88), 87 (2.60), 113 (0.80), 113 (0.47), 121 (60.22), 129 (2.57), 161 (1.09), 162 (6.14), 257 (18.05) and 432 (5.22).

7-Chloro-(3-chlorophenyl)-1,3-thiazol-2yl)-4-acetylhydrazone)-2-phenylquinazolinon-4-(3H)-one (6d)

Brown solid, mp = 199 – 201 ^{0}C, 85% yield; ^{1}H NMR (DMSO-d_6) δ_H (ppm): 2.49 (3H, s, CH_3), 7.42 – 8.08 (7H, m, ArH) 8.45 – 8.47 (1H, thiazole-H), 8.58 – 8.60 (1H, s, N=CH), 9.49 (1H, s, NH) and 12.80 (1H, s, OH); ^{13}C NMR (DMSO-d_6), δ_c (ppm): 206.0 (C-O), 169.8, 165.6, 161.9, 161.8, 158, 143.6, 140.3, 136.1, 134.9, 133.4, 132.7, 130.2, 129.3, 127.6, 122.9, 120.7, 119.8, 118.8, 114.7, 114.4, 29.9, 29.8, 29.6, 29.4, 29.0 and 28.8; IR (KBr)cm^{-1}: 3329 (O-H_{str}), 3143 (N=H_{str}), 1662 (N=CH_{str}), 1501 (ArC=C), 1246 (ArC-N), 969 (C – S) and, 551 (C-Cl_{str});

m/z (%): 85 (1.36), 85 (0.86), 87 (4.93), 112 (10.49), 113 (0.94), 113 (1.14), 113 (1.04), 122 (13.92), 137 (1.49), 162 (10.66), 174 (9.07), 176 (1.62), 202 (4.56), 218 (3.67), 256 (1.91), 257 (26.12), 275 (4.30), 289 (1.24) and 317 (0.70).

Antibacterial Activity

The minimum inhibitory concentration (MIC) was carried out in a 96-well microplate. The double strength Mueller Hinton Broth, using 100 µL, was dispensed into each well of the plate, and 100 µL of a solution of sample was added into the first well to afford a concentration of 40 mg/mL. Serial dilutions were carried out until a final concentration of 0.08 mg/ml was obtained. A volume of 100 µL was then withdrawn from the tenth well and discarded. The eleventh well had no test compound to serve as the negative control while the twelfth well had ciprofloxacin at 2 mg/ml as the positive control. This was carried out for all the rows of the microplates. A volume of 5 µL of the suspension of each test organism containing 10^5 cfu/mL was then added to the respective wells. The experiment was carried out in duplicate and the plates were incubated in the upright position at 37 ^oC for 36 hours. After this, the wells were sub-cultured over dried duplicate Mueller Hinton Agar plates using a multi-inoculator before adding a drop of tetrazolium salt to each well. The minimum concentration inhibiting the growth of the test organisms were measured using mm scale. The minimum bacteriacidal concentration was carried out by incubating a fresh duplicate of Mueller Hinton agar plates at 37 ^oC for 72 hours and the growth of organisms were measured[19].

Antifungal Activity

The microbroth dilution method was used to determine the minimum inhibitory concentration (MIC). The yeast, and medium used was Sarbourand Dextrose medium and the incubation was done at 25 ^oC for 72 hours. The negative control had no test compound while ketoconazole at 4 µg/mL was used as the positive control.

Samples of reaction mixture from each well were transferred by using multi-inoculator on to fresh duplicate of Sarbourand Dextrose agar plate. The plates containing the test organisms were incubated at 25 ^oC for 72 hours and the same procedure as described above was then followed to obtain the minimum fungicidal concentration (Tabbi *et al.*, 2016).

Results and Discussion

This paper describes the synthesis and antimicrobial activity of quinazolinone derivatives bearing thiazole Schiff base moiety. As human pathogens continue to develop defensive mechanisms against existing drugs, thus rendering them gradually ineffective with time, there is need to explore and develop new compounds that could be used to inhibit their growth.

Eight quinazolinone derivatives bearing thiazole substituents were synthesized. The yields of the compounds varied considerably due to the structural differences that exist among them. The low yields of compounds **5c** and **6c** could be attributed to the methyl substituent at the 2-position of the quinazolinone nucleus but that of **6c** is not immediately understood. However, the hydroxyl-group at the benzylidene nucleus of **6c** could be responsible for this.

The chemical structures of the compounds were confirmed with FT-IR, ^{1}H NMR, ^{13}C NMR and GC/MS analysis. The functional groups, chemical shifts, multiplicities and integration of the relevant groups of protons are in accordance with the structures of the molecules. However, the ^{13}C NMR spectra of compounds **5a, 6a** and **6b** showed the absence of sp^2 carbonyl carbons. This suggests that there may be the transformation of the carbonyl group to the enol form. This probably explains the presence of OH signals in the ^{1}H NMR spectra of **5a, 6a** and **6b**. Regarding the antimicrobial activity of the compounds, the results of the study showed that **6c** and

6d were found to be the most potent antibacterial agents against gram-positive bacteria compared with the standard drug, Ciprofloxacin. The two compounds were also observed to be the most effective agents against the fungus, *Candida pseudotropicalis*. Their success may be attributed to the peculiar structures of the compounds, having the phenyl group at the 2-position of the quinazolinone nucleus as well as the OH group at the 2- and 3-positions of the benzylidine nucleus. However, compounds **5c** also exhibited the same inhibitory effect on the *Candida pseudotropicalis* fungus even though it possesses the methyl (CH_3) group at the 2-position of the quinazolinone nucleus instead of the phenyl group.

This study therefore demonstrates that compounds **6c** and **6d** could be potential antibacterial agents especially against Gram-positive bacteria.

The eight newly synthesized compounds were screened for their antibacterial activity against *Bacillus subtilis* (NCTC 8236), *Staphylococcus aerus* (NCTC 6571), *Escherichia coli* (ATCC 25992) and *Pseudomonas aeruginosa* (ATCC 10145) using tube dilution method. The antibacterial activity was determined by measuring the minimum inhibitory concentration (MIC). The compounds were also tested for their antifungal activity. The results set out in Tables 1, 2 and 3 show that the potency of the inhibitions against gram-positive and gram-negative bacteria increased in the order **5a < 5b < 5c < 5d < 6a < 6b < 6c < 6d**. Thus, according to the inhibitory activity of the compounds, **6c** and **6d** exhibited stronger inhibitory effects compared with the other compounds. It was also observed that the inhibitory effects of the synthesized compounds against *Candida pseudotropicalis* fungus (Table 3) are in the order **5a, 6b < 5b**, **5d < 6a < 5c, 6c, 6d**. Hence, compounds **5c, 6c** and **6d** showed the highest inhibitory effects against *Candida pseudotropicalis* compared with **5a, 5b, 5d** and **6a.**

Table 1: Antibacterial activity data of synthesized compounds expressed as MIC (mg/ml)

Compounds	Gram-Positive Bacteria		Gram-Negative Bacteria	
	Bacillus subtilis **NCTC 8236**	***Staphylococcus aureus*** **NCTC 6571**	***Escherichia coli*** **ATCC 25922**	***Pseudomonas aeruginosa*** **ATCC 10145**
5a	20	40	40	40
5b	20	>40	20	20
5c	40	40	20	20
5d	40	40	40	40
6a	20	2.5	40	20
6b	5	40	10	10
6c	2.5	1.25	5	40
6d	1.25	1.25	10	20
Ciprofloxacin	2	2	2	2

MIC = Minimum inhibitory concentration

Table 2: Antibacterial activity data of synthesized compounds expressed as MBC (mg/ml)

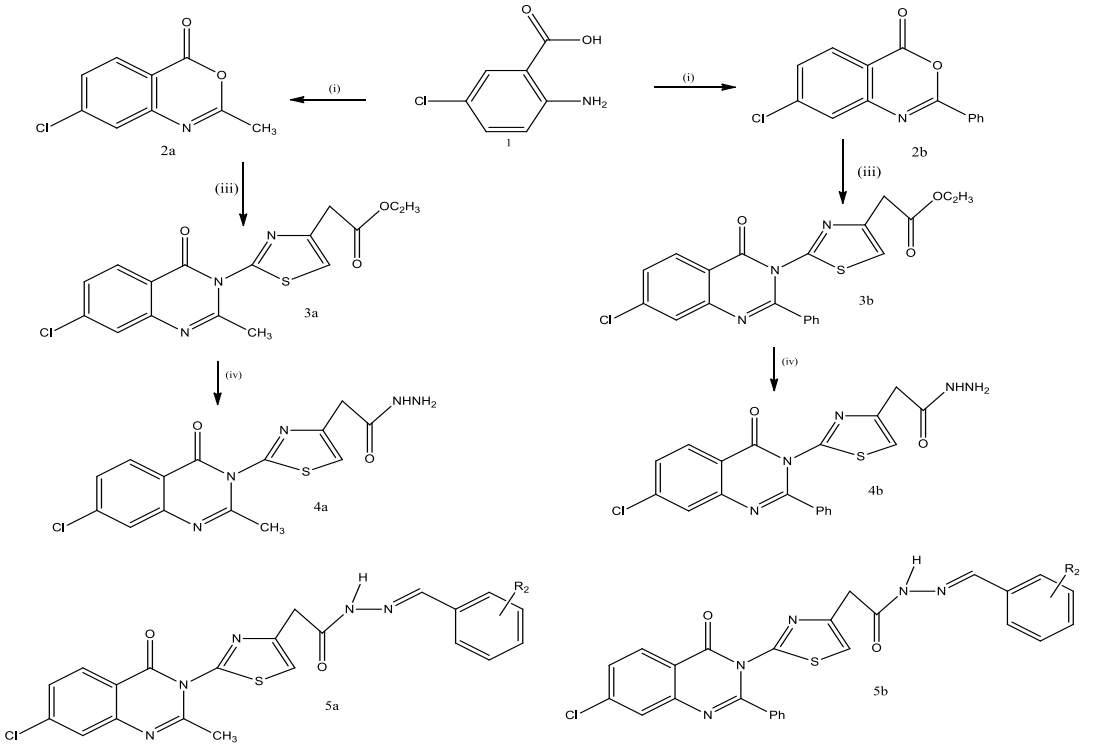
Compounds	Gram-Positive Bacteria		Gram-Negative Bacteria	
	***Bacillus subtilis* NCTC 8236**	***Staphylococcus aureus* NCTC 6571**	***Escherichia coli* ATCC 25922**	***Pseudomonas aeruginosa* ATCC 10145**
5a	>40	>40	40	40
5b	>40	>40	20	>40
5c	>40	>40	20	40
5d	>40	>40	40	40
6a	>40	>40	40	>40
6b	>40	>40	40	>40
6c	40	1.25	>40	40
6d	40	1.25	40	40

MBC = Minimum bacterial concentration

Table 3: Anti-fungal activity of synthesized compounds

Compounds	*Candida pseudotropicalis*	
	MIC	**MFC**
5a	40	40
5b	20	40
5c	10	20
5d	20	40
6a	20	20
6b	40	40
6c	10	20
6d	10	20
Ketoconazole	4	-

MIC = Minimum inhibitory concentration
MFC = Minimum fungicidal concentration



R_1	R_2
5a = 2-OCH_3	**6a = 4-OCH_3**
5b = 4-OH	**6b = 2-OH**
5c = 3-Cl	**6c = 3-OH**
5d = 2-OH	**6d = 3-Cl**

Scheme 1: (i) $(CH_3CO)_2O$, reflux for 4h or C_6H_5COCl/pyridine, reflux for 4h, (ii) ethyl 2-amino-4-thiazoleacetate/CH_3COOH, reflux 1h, (iii) $NH_2NH_2.H_2O$, reflux 4h, (iv) Aromatic aldehyde, reflux 1h

Conclusion

This study involved the synthesis of eight quinazolinone derivatives bearing thiazole Schiff base moieties. Investigation of the antibacterial and antifungal activities of these compounds showed that the positions of the substituents such as the phenyl, free hydroxyl and chloro groups affected their biological activities. Compounds **5a** – **5d** exhibited low antibacterial activity and also low antifungal activity except **5c,** which can compare with **6c** and **6d** against *Candida pseudotropicalis*. However, compounds **6c** and **6d** showed the most effective antibacterial and moderate antifungal activities. The performance of compounds **6c** and **6d** are very promising compared with the standard compound.

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