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ORIGINAL ARTICLE

2nd Heterocyclic Update

Synthesis, characterization and antimicrobial screening of quinoline based quinazolinone-4-thiazolidinone heterocycles

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Abstract In an attempt to find new pharmacologically active molecules, we report here the synthesis and *in vitro* antimicrobial activity of various 2-(2-chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]-5-[(aryl)methylene]-1,3-thiazolidin-4-ones. *In vitro* antimicrobial activity of the title compounds are screened against two Gram positive bacteria (*Staphylococcus aureus*, *Streptococcus pyogenes*), two Gram negative bacteria (*Escherichia coli, Pseudomonas aeruginosa*) and three strains of fungi (*Candida albicans, Aspergillus niger*, *Aspergillus clavatus*) using broth micro dilution method. Some derivatives bearing chloro or hydroxy group exhibited very good antimicrobial activity.

1. Introduction

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); e.g. fluquinconazole fungicide for the control of agriculture diseases (Guang-Fang et al., 2007). Many reports have been published on the biological activity of quinazoline derivatives, including their bactericidal, herbal and antitumor 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 quinazolines exhibited very good antimicrobial activity (Alafeefy, 2008; Desai and Dodiya, 2010). Prompted by these findings, the present paper describes the synthesis of an extension series of 3-substituted-2-phenylquinazolin-4(3*H*)-one derivatives and testing of their antimicrobial activity.

Quinolines are known to inhibit DNA synthesis by promoting cleavage of bacterial DNA gyrase and type-IV topoisomer-

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ase, resulting in rapid bacterial death (Hooper and Wolfson, 1989; Hooper, 1995; Hardman et al., 2002). Certain drugs based on quinoline moiety such as doxorubicin and mitoxantrone have been established as one of the most effective classes of anticancer agents in clinical use today with broad application in the treatment of several leukemia and lymphomas as well as in combination chemotherapy of solid tumors (Wakelin and Waring, 1990). The potent anticancer activity as well as toxic effects described for these compounds are normally ascribed, at least, to two main mechanisms: one, which is associated with protein, involves trapping of a protein enzyme–DNA cleavable intermediate, whereas the other, a non-protein-associated mechanism, is related to redox cycling of the quinoline moiety, which produces damaging free-radical species (Murray, 2000).

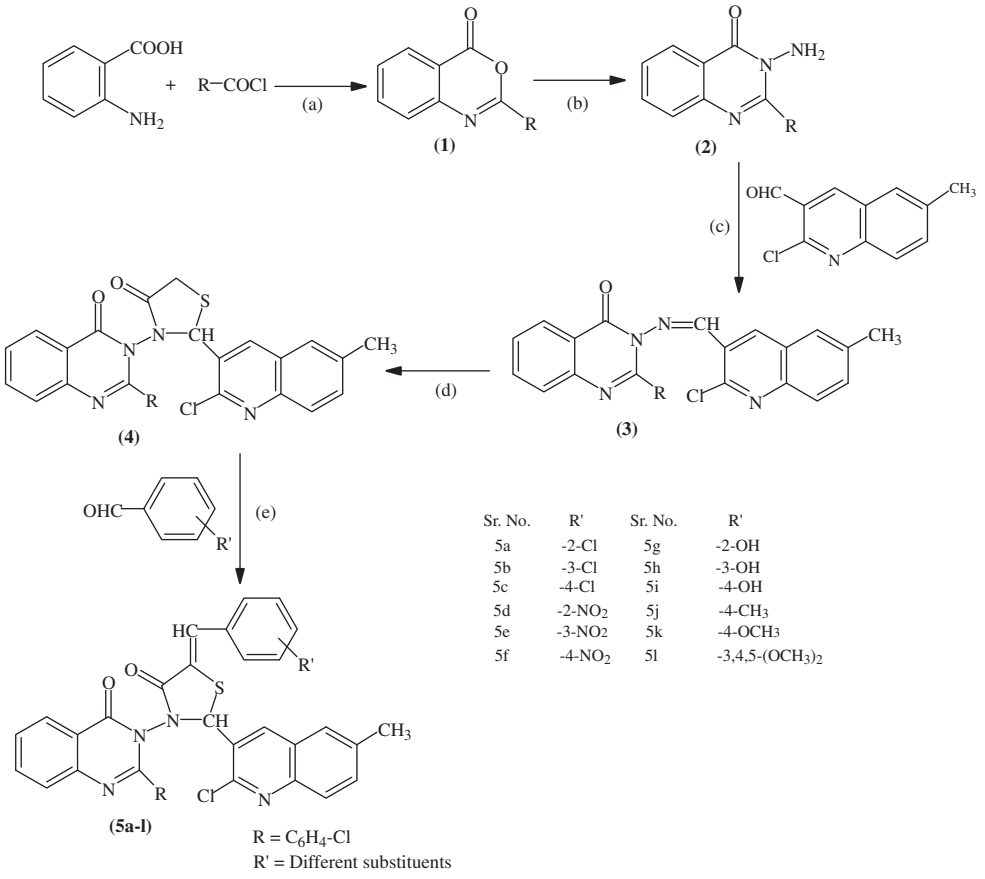
Similarly, various 4-thiazolidinones (Pan et al., 2010; Youssef et al., 2010) have attracted considerable attention as they are also endowed with a wide range of pharmaceutical activities including anesthetic (Surrey, 1949), anticonvulsant (Troutman and Long, 1948), antibacterial (Sayyed and Mokle, 2006) and antiviral (Rao and Zappala, 2004). Furthermore, drug research and development have led to the discovery of new pharmacologically active agents, including imidoxy compounds such as succinimidoxy (Farror et al., 1993). They also possess a strong anti-convulsant activity (Edafiogho 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(*3H*)-quinazolinone, 4-thiazolidinone and quinoline, we report here the synthesis of a new class of heterocyclic molecules in which all of these moieties are present and try to develop potential bioactive molecules. The structures of compounds synthesized are assigned on the basis of IR, ^{1}H NMR, ^{13}C NMR and Mass spectral data. These compounds are evaluated for their antimicrobial screening on different strains of bacteria and fungi Scheme 1.

2. Experimental

2.1. Materials and methods

All chemicals are of analytical grade and used directly. Melting points are determined in PMP-DM scientific melting point apparatus and are uncorrected. IR spectra are recorded on a Perkin-Elmer RX 1 FTIR spectrophotometer, using potassium bromide pellets and the frequencies are expressed in cm^{-1}. The ^{1}H NMR and ^{13}C NMR spectra are recorded with a Bruker



Sr. No.	R'	Sr. No.	R'
5a	-2-Cl	5g	-2-OH
5b	-3-Cl	5h	-3-OH
5c	-4-Cl	5i	-4-OH
5d	-2-NO_2	5j	-4-CH_3
5e	-3-NO_2	5k	-4-OCH_3
5f	-4-NO_2	5l	-3,4,5-$(OCH_3)_2$

Reagents : (a) Pyridine, 0-5°C, (b) Pyridine, $NH_2NH_2.H_2O$, (c) Ethanol, acetic acid, (d) 1,4-dioxane, thioglycolic acid, anhydrous $ZnCl_2$, (e) Ethanol, sodium ethoxide

Scheme 1 Preparation of compounds **5a**–**l**.

Avance II 400 MHz NMR spectrometer, using tetramethylsilane as the internal reference, with dimethylsulfoxide DMSO-d_6 as solvent. The chemical shifts are reported in parts per million (ppm). Elemental analysis is performed on a Heraeus Carlo Erba 1180 CHN analyzer. The purity of compounds is confirmed by TLC using Merck silica gel 60 F_{254} plates using *n*-hexane/ethyl acetate (7:3) as a mobile phase and spots are visualized under UV radiation. Compound 2-chloro-6-methylquinoline-3-carbaldehyde is synthesized by the literature method (Bawa and Suresh, 2009).

2.2. Chemistry

2-(4-Chlorophenyl)-4*H*-benzo[*d*][1,3]oxazin-4-one (**1**) (Eissa, 2007) and 3-amino-2-(4-chlorophenyl)quinazolin-4(3*H*)-one (**2**) were synthesized by the literature method (Gao et al., 2007). Reaction conditions were non-homogeneous and the use of an excess amount of hydrazine hydrate did not afford the desired results for procuring the products. When intermediate compound (**2**) reacted with 2-chloro-6-methylquinoline-3-carbaldehyde by using catalytic amount of acetic acid in ethanol, it furnished intermediate (**3**). Compound (**3**) reacted with thioglycolic acid by using anhydrous $ZnCl_2$ as a catalyst and 1,4-dioxan as solvent. Due to the chemical transformation of compound (**3**) it produced compound (**4**), which possessed 4-thiazolidinone nucleus. When compound (**4**) reacted with different aromatic aldehydes by using catalytic amount of sodium ethoxide and ethanol as a solvent, it produced final heterocyclic scaffolds (**5a**–**l**).

2.2.1. General procedure for 3-(1Z)-1-aza-[2-(2-chloro-6-methyl(3-quinolyl))vinyl]-2-(4-chlorophenyl)-3-hydroquinazolin-4-one (*3*)

To a solution of intermediate compound-(**2**) (0.01 mol) in ethanol (20 ml) and 2-chloro-6-methylquinoline-3-carbaldehyde (0.01 mol) was slowly added to it, in this reaction mixture glacial acetic acid was slowly added as a catalyst. Then reaction mixture was refluxed for 4–5 h, when the Schiff base came out, the excess solvent was distilled off and the separated solid mass filtered and washed with ice-cold methanol, dried and recrystallized in ethanol. Yield 65%, mp 228 °C; IR(KBr, cm^{-1}) *v*: 3051, 3063 (quinazolinone ring, quinoline ring Ar-H), 3072 (=CH stretching), 2959 (–CH_3 stretching), 1467 (–CH_3 bending), 1671 (C=O stretching), 1605, 1580 (C=N stretching), 1562–1439 (C=C, quinazolinone ring, quinoline ring, benzene ring), 838 (C–Cl stretching); ^{1}H NMR (DMSO): δ (ppm): 2.38 (s, 3H, –CH_3 group), 8.60 (s, 1H, =CH group), 7.51–9.22 (m, 8H, quinoline & quinazolinone-H), 7.29–7.83 (m, 4H, Ar-H); ^{13}C NMR (DMSO): 21.7, 121.9, 124.1, 126.4, 126.6, 126.7, 126.9, 127.3, 128.1, 129.1, 128.9, 132.5, 133.4, 135.7, 136.6, 137.2, 143.3, 147.7, 148.7, 151.6, 153.6, 165.1, 166.7; GCMS: *m*/*z*: 458.07 (M^+). Anal. calcd. for $C_{25}H_{16}Cl_2N_4O$: C, 65.37; H, 3.51; N, 12.19. Found: C, 65.24; H, 3.55; N, 12.23.

2.2.2. General procedure for 2-(2-chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl))-1,3-thiazolidin-4-one (*4*)

To a solution of compound (**3**) (0.01 mol) in 1,4 dioxane (50 ml) was added mercapto acetic acid (0.015mole) with stirring and a little amount of anhydrous $ZnCl_2$ was added. The mixture was refluxed for 10–12 h, after the completion of reaction, it was cooled and the excess solvent distilled and poured into sodium bicarbonate solution to neutralize it. The solid product was filtered and washed with cold water. The resulting solid was recrystallized in ethanol (99%). Yield 59%, mp 217 °C; IR (KBr, cm^{-1}) *v*: 3052, 3068 (quinazolinone ring, quinoline ring Ar-H), 2959 (–CH_3 stretching), 1467 (–CH_3 bending), 1677, 1686 (>C=O stretching), 1609, 1582 (>C=N stretching), 1564–1448 (C=C, quinazolinone ring, quinoline ring, benzene ring), 849 (C–Cl stretching); ^{1}H NMR (DMSO): δ (ppm): 2.37 (s, 3H, –CH_3 group), 3.85–3.95 (bs, 2H, CH_2 group), 5.92 (s, 1H, S–CH–N), 7.47–8.26 (m, 8H, quinoline & quinazolinone-H), 7.38–7.53 (m, 4H, Ar-H); ^{13}C NMR (DMSO): 21.7, 35.6, 57.4, 120.8, 125.8, 126.2, 126.5, 126.6, 126.7, 127.5, 127.3, 129.2, 128.6, 128.9, 130.8, 131.4, 133.4, 135.2, 135.7, 136.4, 143.4, 148.7, 150.8, 156.2, 160.8, 168.8; GCMS: *m*/*z*: 532.08 (M^+). Anal. calcd. for $C_{27}H_{18}Cl_2N_4O_2S$: C, 60.79; H, 3.40; N, 10.50. Found: C, 60.85; H, 3.44; N, 10.52.

2.2.3. General procedure for 2-(2-chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo(3-hydroquinazolin-3-yl)]-5-[(aryl)methylene]-1,3-thiazolidine-4-ones (*5a*–*l*)

A solution of intermediate compound-(**4**) (0.01 mol) was taken in ethanol (25 ml) and different aromatic aldehydes (0.01 mol) were slowly added to it with constant stirring and catalytic amount of sodium ethoxide (0.01 mol) was added along with it. The reaction mixture was refluxed for 6–7 h, after the completion of the reaction, the final products (**5a**–**l**) were obtained and excess amount of solvent was distilled out. The crude product was filtered off and washed with ethanol, dried and recrystallized in ethanol.

2.2.3.1. 2-(2-Chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo-(3-hydroquinazolin-3-yl)]-5-[(2-chlorophenyl)-methylene]-1,3-thiazolidin-4-one (*5a*).

Yield, 70%, yellow crystalline solid, mp 292–293 °C. IR (KBr, cm^{-1}) *v*: 3057, 3065 (C–H stret., quinazolinone ring, quinoline ring, Ar-H), 3080 (=CH stretching), 2957 (–CH_3 stretching), 1675, 1681 (>C=O stretching), 1605, 1589 (C=N stretching), 1568, 1445 (C=C, quinazolinone ring, quinoline ring, aromatic ring), 1464 (–CH_3 bending), 845, 832 (C–Cl stretching), 768 (=CH bending), 692 (mono substituted benzene ring); ^{1}H NMR (DMSO) δ (ppm): 2.34 (s, 3H, –CH_3), 5.92 (s, 1H, S–CH–N), 7.47–8.24 (m, 8H, quinoline & quinazolinone-H), 7.35–7.92 (m, 8H, Ar-H), 8.03 (s, 1H, =CH group); ^{13}C NMR (DMSO) δ (ppm): 21.7, 63.6, 120.8, 125.2, 125.8, 126.5, 126.6, 126.7, 126.9, 127.3, 127.5, 127.8, 128.9, 129.1, 129.3, 129.9, 130.7, 131.4, 133.0, 133.4, 134.0, 135.6, 135.7, 136.4, 138.3, 143.3, 148.7, 150.8, 156.2, 160.6, 164.4; GCMS: *m*/*z*: 654.08 (M^+). Anal. calcd. for $C_{34}H_{21}Cl_3N_4O_2S$: C, 62.25; H, 3.22; N, 8.54. Found: C, 62.28; H, 3.27; N, 8.60.

2.2.3.2. 2-(2-Chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo-(3-hydroquinazolin-3-yl)]-5-[(3-chlorophenyl)-methylene]-1,3-thiazolidin-4-one (*5b*).

Yield, 66%, light brown crystalline solid, mp 148–150 °C. IR (KBr, cm^{-1}) *v*: 3053, 3064 (C–H stret., quinazolinone ring, quinoline ring, Ar-H), 3083 (=CH stretching), 2952 (–CH_3 stretching), 1673, 1684 (>C=O stretching), 1607, 1582 (C=N stretching), 1569, 1440 (C=C, quinazolinone ring, quinoline ring, aromatic ring), 1462 (–CH_3 bending), 848, 833 (C–Cl stretching), 769 (=CH bending), 688 (mono substituted benzene ring); ^{1}H

NMR (DMSO) δ (ppm): 2.36 (s, 3H, –CH_3), 5.97 (s, 1H, S–CH–N), 7.42–8.24 (m, 8H, quinoline & quinazolinone-H), 7.32–7.82 (m, 8H, Ar-H), 8.08 (s, 1H, =CH group); ^{13}C NMR (DMSO) δ (ppm): 21.5, 63.7, 120.7, 125.2, 125.8, 126.4, 126.5, 126.6, 126.7, 127.3, 127.5, 128.0, 128.9, 129.1, 130.3, 130.7, 131.4, 133.4, 134.2, 135.7, 135.6, 136.4, 136.6, 138.3, 143.3, 148.7, 150.7, 156.4, 160.3, 164.6; GCMS: *m*/*z*: 654.08 (M^+). Anal. calcd. for $C_{34}H_{21}Cl_3N_4O_2S$: C, 62.25; H, 3.22; N, 8.54. Found: C, 62.29; H, 3.28; N, 8.58.

*2.2.3.3. 2-(2-Chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo-(3-hydroquinazolin-3-yl)]-5-[(4-chlorophenyl)-methylene]-1,3-thiazolidin-4-one (**5c**)*. Yield, 79%, yellow crystalline solid, mp 244–246 °C. IR (KBr, cm^{-1}) *v*: 3057, 3065 (C–H stret., quinazolinone ring, quinoline ring. Ar-H), 3085 (=CH stretching), 2957 (–CH_3 stretching), 1679, 1686 (>C=O stretching), 1609, 1594 (C=N stretching), 1572, 1450 (C=C, quinazolinone ring, quinoline ring, aromatic ring), 1454 (–CH_3 bending), 840, 831 (C–Cl stretching), 761 (=CH bending), 698 (mono substituted benzene ring); ^{1}H NMR (DMSO) δ (ppm): 2.32 (s, 3H, –CH_3), 5.94 (s, 1H, S–CH–N), 7.47–8.21 (m, 8H, quinoline & quinazolinone-H), 7.34–7.88 (m, 8H, Ar-H), 8.05 (s, 1H, =CH group); 13C NMR (DMSO) δ (ppm): 21.5, 63.6, 120.6, 125.2, 125.8, 126.5, 126.6, 126.7, 127.3, 127.5, 128.7, 128.9, 129.0, 129.1, 130.7, 131.4, 132.5, 133.3, 133.4, 135.7, 135.6, 136.4, 138.3, 143.3, 148.7, 150.8, 156.1, 160.5, 164.3; GCMS: *m*/*z*: 654.08 (M^+). Anal. calcd. for $C_{34}H_{21}Cl_3N_4O_2S$: C, 62.25; H, 3.22; N, 8.54. Found: C, 62.27; H, 3.31; N, 8.61.

*2.2.3.4. 2-(2-Chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo-(3-hydroquinazolin-3-yl)]-5-[(2-nitrophenyl)methylene]-1,3-thiazolidin-4-one (**5d**)*. Yield, 63%, light brown crystalline solid, mp 145–147 °C. IR (KBr, cm $^{-1}$) *v*: 3054, 3063 (C–H stret., quinazolinone ring, quinoline ring, Ar-H), 3089 (=CH stretching), 2957 (–CH_3 stretching), 1674, 1680 (>C=O stretching), 1611, 1583 (C=N stretching), 1555, 1440 (C=C, quinazolinone ring, quinoline ring, aromatic ring), 1456 (–CH_3 bending), 848, 836 (C–Cl stretching), 772 (=CH bending), 690 (mono substituted benzene ring); ^{1}H NMR (DMSO) δ (ppm): 2.35 (s, 3H, –CH_3), 5.90 (s, 1H, S–CH–N), 7.40–8.26 (m, 8H, quinoline & quinazolinone-H), 7.28–8.21 (m, 8H, Ar-H), 8.32 (s, 1H, =CH group); ^{13}C NMR (DMSO) δ (ppm): 21.8, 63.4, 120.6, 123.7, 125.2, 126.5, 126.6, 127.3, 127.4, 127.5, 128.8, 128.9, 129.1, 130.5, 131.4, 134.7, 135.6, 136.4, 147.7, 126.7, 125.8, 133.4, 135.7, 138.3, 143.3, 148.7, 150.8, 156.4, 160.5, 164.5; GCMS: *m*/*z*: 665.07(M^+). Anal. calcd. for $C_{34}H_{21}Cl_2N_5O_4S$: C, 61.26; H, 3.17; N, 10.50. Found: C, 61.29; H, 3.22; N, 10.55.

*2.2.3.5. 2-(2-Chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo-(3-hydroquinazolin-3-yl)]-5-[(3-nitrophenyl)-methylene]-1,3-thiazolidin-4-one (**5e**)*. Yield, 67%, dark yellow crystalline solid, mp 235–237 °C. IR (KBr, cm^{-1}) *v*: 3050, 3067 (C–H stret., quinazolinone ring, quinoline ring, Ar-H), 3080 (=CH stretching), 2956 (–CH_3 stretching), 1671, 1685 (>C=O stretching), 1604, 1583 (C=N stretching), 1562, 1452 (C=C, quinazolinone ring, quinoline ring, aromatic ring), 1462 (–CH_3 bending), 852, 840 (C–Cl stretching), 762 (=CH bending), 690 (mono substituted benzene ring); ^{1}H NMR (DMSO) δ (ppm): 2.38 (s, 3H, –CH_3), 5.95 (s, 1H, S–CH–N), 7.52–8.24 (m, 8H, quinoline & quinazolinone-H), 7.32–8.31 (m, 8H, Ar-H), 8.35 (s, 1H, =CH group); ^{13}C NMR (DMSO) δ (ppm): 21.4, 63.8, 120.4, 122.6, 123.1, 125.2, 125.8, 126.5, 126.6, 126.7, 127.3, 127.5, 128.9, 129.1, 129.5, 130.7, 131.4, 133.4, 135.7, 135.6, 134.6, 136.1, 136.4, 138.3, 143.3, 147.8, 148.7, 150.3, 156.0, 160.3, 164.7; GCMS: *m*/*z*: 665.07 (M^+). Anal. calcd. for $C_{34}H_{21}Cl_2N_5O_4S$: C, 61.26; H, 3.17; N, 10.50. Found: C, 61.32; H, 3.23; N, 10.56.

*2.2.3.6. 2-(2-Chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo-(3-hydroquinazolin-3-yl)]-5-[(4-nitrophenyl)-methylene]-1,3-thiazolidin-4-one (**5f**)*. Yield, 70%, light orange crystalline solid, mp 292–293 °C. IR (KBr, cm^{-1}) *v*: 3056, 3069 (C–H stret., quinazolinone ring, quinoline ring, Ar-H), 3080 (=CH stretching), 2957 (–CH_3 stretching), 1671, 1688 (>C=O stretching), 1612, 1592 (C=N stretching), 1562, 1451 (C=C, quinazolinone ring, quinoline ring, aromatic ring), 1458 (–CH_3 bending), 844, 832 (C–Cl stretching), 764 (=CH bending), 690 (mono substituted benzene ring); ^{1}H NMR (DMSO) δ (ppm): 2.32 (s, 3H, –CH_3), 5.98 (s, 1H, S–CH–N), 7.55–8.23 (m, 8H, quinoline & quinazolinone-H), 7.37–8.22 (m, 8H, Ar-H), 8.38 (s, 1H, =CH group); ^{13}C NMR (DMSO) δ (ppm): 21.4, 63.4, 120.5, 123.6, 125.2, 125.8, 126.5, 126.6, 126.7, 127.3, 127.5, 128.9, 129.0, 129.1, 130.7, 131.4, 133.4, 135.6, 135.7, 136.4, 138.3, 141.3, 143.3, 147.1, 148.7, 150.5, 156.2, 160.8, 164.4; GCMS: *m*/*z*: 665.07 (M^+). Anal. calcd. for $C_{34}H_{21}Cl_2N_5O_4S$: C, 61.26; H, 3.17; N, 10.50. Found: C, 61.33; H, 3.24; N, 10.57.

*2.2.3.7. 2-(2-Chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo-(3-hydroquinazolin-3-yl)]-5-[(2-hydroxyphenyl)-methylene]-1,3-thiazolidin-4-one (**5g**)*. Yield, 85%, light brown crystalline solid, mp 201–203 °C. IR (KBr, cm^{-1}) *v*: 3438 (–OH group stretching), 3053, 3069 (C–H stret., quinazolinone ring, quinoline ring, Ar-H), 3086 (=CH stretching), 2957 (–CH_3 stretching), 1668, 1684 (>C=O stretching), 1609, 1583 (C=N stretching), 1568, 1445 (C=C, quinazolinone ring, quinoline ring, aromatic ring), 1464 (–CH_3 bending), 841, 837 (C–Cl stretching), 769 (=CH bending), 692 (mono substituted benzene ring); ^{1}H NMR (DMSO) δ (ppm): 2.37 (s, 3H, –CH_3), 5.35 (s, 1H, –OH group), 5.92 (s, 1H, S–CH–N), 6.72–7.60 (m, 8H, Ar-H), 7.51–8.29 (m, 8H, quinoline & quinazolinone-H), 8.08 (s, 1H, =CH group); ^{13}C NMR (DMSO) δ (ppm): 21.9, 63.4, 116.2, 117.6, 120.8, 121.2, 125.2, 125.8, 126.5, 126.6, 126.7, 127.3, 127.5, 128.9, 129.1, 129.3, 130.7, 131.4, 133.4, 135.6, 135.7, 136.4, 138.3, 143.3, 148.7, 150.8, 157.5, 156.1, 160.4, 164.0; GCMS: *m*/*z*: 636.08 (M^+). Anal. calcd. for $C_{34}H_{22}Cl_2N4O_3S$: C, 64.05; H, 3.47; N, 8.78. Found: C, 64.09; H, 3.55; N, 8.85.

*2.2.3.8. 2-(2-Chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo-(3-hydroquinazolin-3-yl)]-5-[(3-hydroxyphenyl)-methylene]-1,3-thiazolidin-4-one (**5h**)*. Yield, 70%, off yellow crystalline solid, mp 252–253 °C. IR (KBr, cm^{-1}) *v*: 3432 (–OH group stretching), 3062, 3069 (C–H stret., quinazolinone ring, quinoline ring, Ar-H), 3080 (=CH stretching), 2951 (–CH_3 stretching), 1671, 1689 (>C=O stretching), 1608, 1580 (C=N stretching), 1563, 1442 (C=C, quinazolinone ring, quinoline ring, aromatic ring), 1463 (–CH_3 bending), 851, 842 (C–Cl stretching), 762 (=CH bending), 699 (mono substituted benzene ring); ^{1}H NMR (DMSO) δ (ppm): 2.34 (s, 3H, –CH_3), 5.38 (s, 1H, –OH group), 5.95 (s, 1H, S–CH–N), 7.68–8.26 (m, 8H, quinoline&quinazolinone-H),

7.36–8.31 (m, 8H, Ar-H), 8.09 (s, 1H, =CH group); ^{13}C NMR (DMSO) δ (ppm): 21.7, 63.6, 112.1, 115.1, 120.8, 121.1, 125.2, 125.8, 126.5, 126.6, 126.7, 127.3, 127.5, 128.9, 129.1, 130.0, 130.7, 131.4, 133.4, 135.6, 135.7, 136.4, 136.6, 138.3, 143.3, 148.7, 150.8, 156.2, 158.4, 160.6, 164.4; GCMS: *m*/*z*: 636.08 (M^+). Anal. calcd. for $C_{34}H_{22}Cl_2N_4O_3S$: C, 64.05; H, 3.47; N, 8.78. Found: C, 64.11; H, 3.53; N, 8.84.

*2.2.3.9. 2-(2-Chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo-(3-hydroquinazolin-3-yl)]-5-[(4-hydroxyphenyl)-methylene]-1,3-thiazolidin-4-one (**5i**)*. Yield, 53%, dark brown crystalline solid, mp 263–265 °C. IR (KBr, cm^{-1}) *v*: 3436 (–OH group stretching), 3056, 3069 (C–H stret., quinazolinone ring, quinoline ring, Ar-H), 3080 (=CH stretching), 1670, 1683 (>C=O stretching), 2956 (–CH_3 stretching), 1614, 1590 (C=N stretching), 1560, 1441 (C=C, quinazolinone ring, quinoline ring, aromatic ring), 1462 (–CH_3 bending), 846, 835 (C–Cl stretching), 769 (=CH bending), 691 (mono substituted benzene ring); ^{1}H NMR (DMSO) δ (ppm): 2.36 (s, 3H, –CH_3), 5.39 (s, 1H, –OH group), 5.96 (s, 1H, S–CH–N), 7.63–8.27 (m, 9H, quinoline & quinazolinone-H), 7.28–7.88 (m, 9H, Ar-H), 8.05 (s, 1H, =CH group); ^{13}C NMR (DMSO) δ (ppm): 21.4, 63.8, 115.2, 115.9, 120.9, 125.2, 125.8, 126.5, 126.6, 126.7, 127.3, 127.5, 127.8, 130.6, 130.7, 131.4, 133.4, 135.6, 135.7, 136.4, 138.3, 129.1, 128.9, 143.3, 148.7, 150.8, 156.0, 157.3, 160.9, 164.1; GCMS: *m*/*z*: 636.08 (M^+). Anal. calcd. for $C_{34}H_{22}Cl_2N_4O_3S$: C, 64.05; H, 3.47; N, 8.78. Found: C, 64.12; H, 3.53; N, 8.83.

*2.2.3.10. 2-(2-Chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo-(3-hydroquinazolin-3-yl)]-5-[(4-methylphenyl)-methylene]-1,3-thiazolidin-4-one (**5j**)*. Yield, 74%, off brown crystalline solid, mp 201–203 °C. IR (KBr, cm^{-1}) *v*: 3054, 3068 (C–H stret., quinazolinone ring, quinoline ring, Ar-H), 3082 (=CH stretching), 1675, 1681 (>C=O stretching), 2950 (–CH_3 stretching), 1605, 1589 (C=N stretching), 1567, 1442 (C=C, quinazolinone ring, quinoline ring, aromatic ring), 1460 (–CH_3 bending), 846, 839 (C–Cl stretching), 762 (=CH bending), 696 (mono substituted benzene ring); ^{1}H NMR (DMSO) δ (ppm): 2.34 (s, 6H, –CH_3), 2.39 (s, 3H, –CH_3 group), 5.91 (s, 1H, S–CH–N), 7.76 (s, 1H, =CH group), 7.47–8.24 (m, 8H, quinoline & quinazolinone-H), 7.18–7.60 (m, 8H, Ar-H); ^{13}C NMR (DMSO) δ (ppm): 21.3, 21.7, 63.6, 120.8, 125.2, 125.8, 126.5, 126.6, 126.7, 127.3, 127.5, 128.5, 128.9, 129.1, 130.7, 131.4, 132.2, 133.4, 135.6, 135.7, 136.4, 138.3, 143.3, 148.7, 150.8, 156.2, 157.6, 160.6, 164.4. Anal. calcd. for $C_{35}H_{24}Cl_2N_4O_2S$: C, 66.14; H, 3.80; N, 8.81; GCMS: *m*/*z*: 634.11 (M^+). Found: C, 66.20; H, 3.86; N, 8.87.

*2.2.3.11. 2-(2-Chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo-(3-hydroquinazolin-3-yl)]-5-[(4-methoxyphenyl)-methylene]-1,3-thiazolidin-4-one (**5k**)*. Yield, 72%, dark yellow crystalline solid, mp 224–226 °C. IR (KBr, cm^{-1}) *v*: 3057, 3062 (quinazolinone ring, quinoline ring Ar-H), 3075 (=CH stretching), 2945 (–OCH_3 stretching), 1672, 1684 (>C=O stretching), 1605, 1589 (C=N stretching), 1568, 1445 (C=C, quinazolinone ring, quinoline ring, aromatic ring), 1465 (–OCH_3 bending), 845, 838 (C–Cl stretching), 763 (=CH bending), 694 (mono substituted benzene ring); ^{1}H NMR (DMSO) δ (ppm): 2.33 (s, 3H, –CH_3), 3.83 (s, 3H, –OCH_3 group), 5.94 (s, 1H, S–CH–N), 6.94–7.62 (m, 8H, Ar-H), 7.76 (s, 1H, =CH group), 7.41–8.25 (m, 8H, quinoline & quinazolinone-H); ^{13}C NMR (DMSO) δ (ppm): 21.6, 55.8, 63.6, 114.2, 120.8, 125.2, 125.8, 126.5, 126.6, 126.7, 127.3, 127.4, 127.5, 128.9, 129.1, 130.0, 130.7, 131.4, 133.4, 135.6, 135.7, 136.4, 138.3, 114.2, 143.3, 148.7, 150.8, 156.2, 159.6, 160.2, 164.2; GCMS: *m*/*z*: 650.12 (M^+). Anal. calcd. for $C_{35}H_{24}Cl_2N_4O_3S$: C, 64.51; H, 3.71; N, 8.59. Found: C, 64.56; H, 3.77; N, 8.64.

*2.2.3.12. 2-(2-Chloro-6-methyl(3-quinolyl))-3-[2-(4-chlorophenyl)-4-oxo-(3-hydroquinazolin-3-yl)]-5-[(3,4,5-methoxyphenyl)methylene]-1,3-thiazolidin-4-one (**5l**)*. Yield, 69%, dark brown crystalline solid, mp 189–191 °C. IR (KBr, cm^{-1}) *v*: 3051, 3062 (quinazolinone ring, quinoline ring, Ar-H), 3080 (=CH stretching), 2942 (–OCH_3 stretching), 1671, 1682 (>C=O stretching), 1605, 1585 (C=N stretching), 1566, 1450 (C=C, quinazolinone ring, quinoline ring, aromatic ring), 1461 (–OCH_3 bending), 842 (C–Cl stretching), 763 (=CH bending), 694 (mono substituted benzene ring); ^{1}H NMR (DMSO) δ (ppm): 2.38 (s, 3H, –CH_3), 3.83 (s, 9H, –OCH_3 group), 5.96 (s, 1H, S–CH–N), 6.78–7.52 (m, 6H, Ar-H), 7.72 (s, 1H, =CH group), 7.49–8.29 (m, 8H, quinoline & quinazolinone-H); ^{13}C NMR (DMSO) δ (ppm): 21.2, 56.2, 60.8, 63.6, 103.8, 120.8, 125.2, 125.8, 126.5, 126.6, 126.7, 127.3, 127.5, 128.9, 129.1, 129.5, 130.7, 131.4, 133.4, 136.4, 135.7, 135.6, 138.3, 138.4, 143.3, 148.7, 150.8, 153.0, 153.4, 156.2, 160.4, 164.7; GCMS: *m*/*z*: 710.55 (M^+). Anal. calcd. for $C_{37}H_{28}Cl_2N_4O_5S$: C, 62.45; H, 3.96; N, 7.87. Found: C, 62.51; H, 3.99; N, 7.93.

3. Results and discussion

Characterization of newly synthesized compounds of the series is carried out by IR, NMR and Mass spectra and the data is discussed in the experimental section.

3.1. IR-DATA

IR spectrum of the final compound-**5h** (molecular formula $C_{34}H_{22}Cl_2N_4O_3S$, m.w. 636.08, structure and carbon numbering is given in Fig. 1) over the 3062 and 3069 cm^{-1} ranges showed multiple weak absorption peaks corresponding to Qu-H and Ar-H stretching vibration absorption peaks. The absorption peak at 3080 cm^{-1} is due to the stretching vibration of the methylene group. The absorption at 2851 cm^{-1} is due to stretching vibration of the methyl group. The strong absorption at 1689 cm^{-1} is due to >C=O stretching vibration, which

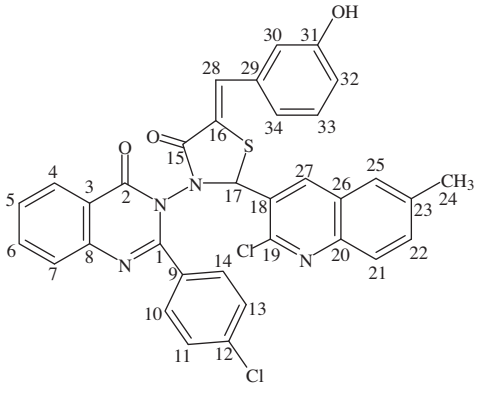


Figure 1 Carbon numbering of the final compound-**5h**.

is present in thiazolidine ring at position C-15, while another absorption peak at 1671 cm^{-1} is due to >C═O stretching vibration in quinazolinone ring, which is present at position C-2. Moderate intensity absorptions at 1608 and 1580 cm^{-1} correspond to a >C═N– stretching vibration. Absorptions at 1563 and 1442 cm^{-1} are due to the C═C and skeleton vibrations of aryl and heterocyclic rings. The absorption peak at 1463 cm^{-1} is due to bending vibration of the methyl group. The broad absorption peak at 3432 cm^{-1} is observed due to –OH stretching vibration. The absorption peaks at 851 and 842 cm^{-1} are due to chlorine atoms, which are attached to carbon atom at C-2 and C-15 in thiazolidine and quinazolinone rings. The vibration at 762 cm^{-1} is due to bending vibration of methylene group. The absorption peaks 699 cm^{-1} arise due to phenyl-substituted at position-3.

3.2. ^{1}H NMR-DATA

It can be seen from the chemical structure of compound-**5h** 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 appeared at 7.39, while protons which are attached to C-11 and C-13 appeared at 7.52 ppm. The proton attached to C-5 position appeared as a multiplet at δ = 7.63 ppm due to mutual coupling with protons attached to C-4 and C-6, while the proton attached to C-6 appeared as a multiplet at δ = 7.70 ppm due to mutual coupling with the protons attached to C-5 and C-7. The proton attached to C-4 position appeared as a doublet at δ = 8.03 ppm. A single peak that appeared at δ = 5.92 ppm must be for the proton attached at C-17 which is present in the thiazolidine ring. A single peak appeared at δ = 5.35 ppm of –OH group which is attached to C-31. The proton of the methylene group appeared as a singlet at δ = 7.76 ppm. Protons of the phenyl ring (C-30, C-32, C-33 and C-34) appeared between δ = 6.70–7.53 ppm, respectively. The protons of the methyl group appeared as a singlet at δ = 2.43 ppm. The proton of the C-30 appeared as a singlet at δ = 6.70 ppm due to the presence of a hydroxyl group at C-31, while the proton of the C-32 appeared as a doublet at δ = 6.83 ppm due to the presence of a hydroxyl group at C-31. The proton attached to C-33 position appeared as a multiplet at δ = 7.53 ppm due to mutual coupling with protons attached to C-32 and C-34. Proton of C-25 appeared as a singlet at δ = 7.63 ppm due to the presence of methyl group at C-23, while proton of C-22 appeared as a doublet at δ = 7.47 ppm due to the presence of methyl group at C-23.

3.3. ^{13}C NMR-DATA

The final compound-**5h** has quinazolinone ring, quinoline ring and thiazolidine ring. Chemical shifts of final compound carbons vary from δ = 164.4 to 21.7 ppm. The carbon nuclei under the influence of a strong electronegative environment appeared downfield, e.g. C-2 and C-15 carbonyl, which are directly linked to the ring nitrogen, have a chemical shift value of δ = 160.8 and 164.4 ppm, respectively, whereas C-19 linked to a chlorine atom appeared at δ = 150.8 ppm. Carbon C-1 which is attached on both sides to nitrogen atoms appeared at δ = 156.2. Carbon of methylene group C-28 appeared at δ = 125.2 ppm. Carbon of the methyl group C-24 appeared at δ = 21.7 ppm, while carbon C-23, where the methyl group is attached appeared at δ = 136.4 ppm. 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 δ = 120.8 and 138.3 ppm, respectively. Carbons of benzene ring which are attached to quinazolinone ring having equivalent carbons C-10 and C-14 appeared at δ = 129.1 ppm, C-11 and C-13 appeared at δ = 128.9 ppm respectively, while carbon C-12, which is directly attached with highly electro negative chlorine atom appeared at δ = 135.7 ppm. While the carbon atom C-17, which is present in the thiazolidine ring between the nitrogen atom and sulfur atom appeared at δ = 63.6 ppm. The carbon C-31 which is directly attached to hydroxyl group appeared at δ = 158.4 ppm, the other carbons of this ring (C-29, C-30, C-32, C-33 and C-34) appeared between δ = 112.1–136.6 ppm, respectively. The carbons of the quinoline ring (C-18, C-20, C-21, C-22, C-25, C-26 and C-27) appeared between δ = 125.8 and 143.4 ppm, respectively. Structure and carbon numbering of compound-**5h** is described in Fig. 1.

3.4. Antimicrobial activity

Many of the newly synthesized compounds are found to exhibit good to excellent antimicrobial activity. From antimicrobial activity data (Table 1), it is observed that compounds **5c**(-4-Cl), **5g**(-2-OH) and **5h**(-3-OH) are the most active compounds. Data of antibacterial activity reveals that, compounds **5a** (-2-Cl), **5d** (-2-NO_2), **5g** (-2-OH) and **5j** (-4-CH_3) are considered to be good active against *Escherichia coli*, while compounds **5c** (-4-Cl) and **5l** (-3,4,5-$(OCH_3)_2$) are considered as very good active against *E. coli*. Similarly when we have taken the -3-OH group as substitution in compound **5h,** it shows excellent activity against *E. coli*. Compounds **5b** (-3-Cl), **5c** (-4-Cl) and **5i** (-4-OH) are considered as good active against *Pseudomonas aeruginosa*. When we change the substitution in compounds **5h** and **5k** by 3-hydroxy and 4-methoxy groups, they exhibit very good activity against *P. aeruginosa*. Compounds **5d** (-2-NO_2) is considered as good active against *Staphylococcus aureus*, while compounds **5b** (-3-Cl), **5c** (-3-Cl), **5f** (-4-NO_2), **5h** (-3-OH), **5i** (-4-OH) and **5l** (-3,4,5-$(OCH_3)_2$) are considered as very good active against *S. aureus*. When we have replaced -2-OH group as a substitution in compound **5g**, it is an excellent active compound against *S. aureus*. Compounds **5b** (-3-Cl), **5h** (-3-OH) and **5k** (-4-OCH_3) are considered as good active against *Streptococcus pyogenes*, while compound **5i** (-4-OH) is considered as very good active against *S. pyogenes*. For the antifungal activity, we have screened the same compounds which are used for antibacterial activity. Compounds **5a** (-2-Cl), **5c** (-3-Cl), **5e** (-3-NO_2), **5g** (-2-OH), **5i** (-4-OH) and **5k** (-4-OCH_3) are considered as good active against *Candida albicans*, while compounds **5b** (-3-Cl), **5d** (-2-NO_2), **5f** (-4-NO_2) and **5h** (-3-OH) are considered as excellent active against *C. albicans*. Compounds **5c** (-3-Cl), **5g** (-2-OH), **5i** (-4-OH) and **5l** (-3,4,5-$(OCH_3)_2$) are considered as good active against *Aspergillus niger*. Compounds **5a** (-2-Cl), **5e** (-3-NO_2) and **5g** (-2-OH) are considered as good active against *Aspergillus clavatus*. Thus we have discussed and compared antibacterial and antifungal activities based on standard drugs ampicillin and griseofulvin, respectively.

3.4.1. Antibacterial activity

For the antibacterial activity, the newly synthesized compounds are screened for their antibacterial activity against Gram positive bacteria *S. aureus* (MTCC-96) and *S. pyogenes*

Table 1 Results of antibacterial and antifungal screening of the compounds (**5a–l**).

Sr. No.	-Ar	Minimum inhibitory concentration (MIC) μg/ml ± SD				Minimum inhibitory concentration (MIC) in μg/ml ± SD		
		E. coli MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
5a	-2-Cl	100 ± 3.56*	250 ± 4.04*	500 ± 4.93*	200 ± 3.46*	500 ± 3.15*	500 ± 3.60*	100 ± 3.05*
5b	-3-Cl	250 ± 3.05*	100 ± 3.51*	100 ± 4.72*	100 ± 3.15*	100 ± 4.04*	1000 ± 3.51*	1000 ± 4*
5c	-4-Cl	50 ± 4.04*	100 ± 4.50*	100 ± 4.93*	500 ± 4.04*	500 ± 3.21*	100 ± 4.35*	500 ± 3.78*
5d	-2-NO_2	100 ± 3.78*	125 ± 4*	250 ± 34.04*	500 ± 4.58*	100 ± 4.58*	500 ± 3.78*	500 ± 3.05*
5e	-3-NO_2	500 ± 3.05*	500 ± 1*	500 ± 3.78*	250 ± 4.08*	500 ± 4.04*	200 ± 4.50*	100 ± 3.60*
5f	-4-NO_2	250 ± 2.51*	500 ± 3.51*	100 ± 4.04*	500 ± 3.46*	100 ± 4.50*	1000 ± 4.58*	500 ± 4.04*
5g	-2-OH	100 ± 3.51*	500 ± 1*	50 ± 4.93*	500 ± 4.58*	500 ± 3.51*	100 ± 4.04*	100 ± 4.04*
5h	-3-OH	25 ± 4.04*	50 ± 1.32*	100 ± 4*	100 ± 3.60*	100 ± 3.21*	500 ± 3.05*	200 ± 4.16*
5i	-4-OH	250 ± 3*	100 ± 4.04*	100 ± 3.78*	50 ± 4.04*	500 ± 3.51*	100 ± 3.51*	500 ± 3*
5j	-4-CH_3	100 ± 3.21*	500 ± 4.16*	500 ± 3.21*	500 ± 3.51*	1000 ± 3.05*	1000 ± 3.05*	1000 ± 4.04*
5k	-4-OCH_3	500 ± 3.51*	50 ± 2.08*	500 ± 3.21*	100 ± 3.05*	500 ± 3.78*	500 ± 4.16*	200 ± 3.05*
5l	-3,4,5-$(OCH_3)_3$	62.5 ± 3.05*	500 ± 3.60*	100 ± 4.58*	500 ± 3.51*	1000 ± 3.05*	100 ± 4.04*	500 ± 2.51*
	Ampicillin	100 ± 1.52*	100 ± 2.08*	250 ± 2.0*	100 ± 1.0*	–	–	–
	Griseofulvin	–	–	–	–	500 ± 0.57*	100 ± 1*	100 ± 1.15*

SD = Standard deviation.
* $p \leqslant 0.0001$.

(MTCC-442) and Gram negative *E. coli* (MTCC-443) and *P. aeruginosa* (MTCC-1688)]. Antibacterial activity is carried out by serial broth dilution method (Ghalem and Mohamed, 2009; Desai and Trivedi, 1993). The standard strains used for antimicrobial activity were procured from Institute of Microbial Technology, Chandigarh. Compounds (**5a–l**) are screened for their antibacterial activity in triplicate against *E. coli*, *S. aureus*, *P. aeruginosa* and *S. pyogenes* at different concentrations of 1000, 500, 200, 100, 50, 25 μg/ml as shown in (Table 1). The drugs which are found to be active in primary screening are similarly diluted to obtain 100, 50, 25, 12.5 μg/ml concentrations. 10 μg/ml suspensions are further inoculated on appropriate media and growth is noted after 24 and 48 h. The lowest concentration, which showed no growth after spot subculture is considered as MIC for each drug. The highest dilution showing at least 99% inhibition is taken as (MIC). The test mixture should contain 10^8 cells/ml. The standard drug used in the present study is 'ampicillin' for evaluating antibacterial activity which shows (100, 100, 250 and 100 μg/mL) MIC against *E. coli, P. aeruginosa, S. aureus* and *S. pyogenes*, respectively. For bacterial growth, in the present protocol, we have used Muller Hinton broth at 37 °C in aerobic condition for 24 h to 48 h.

3.4.2. Antifungal activity

While for the antifungal activity, same compounds are tested for antifungal activity in triplicate against *C. albicans*, *A niger* and *A. clavatus* at various concentrations of 1000, 500, 200 and 100 μg/ml as shown in (Table 1). The results are recorded in the form of primary and secondary screening. Synthesized compounds are diluted at 1000 μg/ml concentration, as a stock solution. Synthesized compounds which are found to be active in this primary screening are further tested in a second set of dilution against all microorganisms. The lowest concentration, which shows no growth after spot subculture is considered as (MIC) for each drug. The highest dilution showing at least 99% inhibition is taken as MIC. The test mixture should contain 10^8 spores/ml MIC. 'Griseofulvin' is used as a standard drug for antifungal activity, which shows (500, 100 and 100 μg/mL) MIC against *C. albicans*, *A. niger* and *A. clavatus*, respectively. In the present protocol for fungal growth, we have used Sabourauds dextrose broth at 22 °C in aerobic condition for 72 h. The results of antimicrobial evaluation of derivatives (**5a–l**) are collected in (Table 1).

3.4.3. Statistical analysis

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

4. Conclusion

Some of the newly synthesized compounds exhibited promising antibacterial activity against *E. coli, P. aeruginosa, S. aureus* and *S. pyogenes strains*, while antifungal activity against *C. albicans, A. niger* and *A. clavatus* strains. Compounds **5g** and **5h** possess excellent activity against both bacterial and fungal species. It seems that the hydroxy group at ortho and meta position are very significant for enhancing activity against both bacterial and fungal species. Results biological activities of novel quinoline based quinazolinone,4-thiazolidine derivatives are interesting for optimization of lead molecules for further generation of antimicrobial agents.

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