Synthesis and Antimicrobial Activity of Quinazolin-4(3*H*)-ones Incorporating Sulfonamido-4-thiazolidinone

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Some new derivatives 7-chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(2-substituted phenyl-4-oxo-thiazolidin-3-yl)phenyl]sulfonamido-quinazolin-4(3*H*)-ones **5a**—**5l** were synthesized from 2-[2-(2,6-dichlorophenyl)amino]phenyl acetic acid via acid chloride, benzoxazinone, amino quinazolin-4(3*H*)-one and Schiff base formation. The synthesized compounds were screened for *in vitro* antibacterial and antifungal activities by broth micro dilution method. Some of the Schiff base as well as 4-thiazolidinone derivatives showed promising antibacterial activity while pronounced antifungal activity was observed against *C. albicans*.

Keywords biological activity, quinazolin-4(3*H*)-one, sulfonamide, 4-thiazolidinone

Introduction

The heterocyclic compounds are important part of medicinal chemistry due to its rapid and diverse medicinal applications. It was reported that quinazolines have an interesting antimicrobial activity against different species of pathogenic gram positive bacteria, gram negative bacteria and fungi.[1-4] Quinazolin-4(3*H*)-one have emerged as an important class of nitrogenated heterocycle that have attracted synthetic interest because they possess pharmacological and therapeutic properties. A number of quinazolin-4(3*H*)-one derivatives have a wide range of biological applications including antibacterial, antifungal, antiviral, anticonvulsant, analgesic, antiinflammatory, antitubercular, anticancer and CNS depressant.[5-10] Schiff base has good biological importance and possesses variety of activities *i.e*. anticonvulsant, antimicrobial, antitubercular, anticancer, antitumor and antimalarial.[11-17] 4-Thiazolidinone is a sulfur atom containing 5-member heterocycle possessing antibacterial, antifungal, anti-HIV, anticonvulsant, anti-inflammatory and hypnotic activities.[18-24] Sulfonamide also showed broad spectrum of pharmacological properties such as antibacterial, antifungal, anticandidal, antinociceptive, anticancer and anti-inflammatory activities.[25-30]

The quinazolin-4(3*H*)-one incorporated with different type of aryl as well as heteryl linkers, showed wide range of pharmacological applications. In the present work we have synthesized quinazolin-4(3*H*)-one incorporated with 4-thiazolidinone and evaluated its *in vitro* antimicrobial activity.

Experimental

All chemicals were of analytical grade and used directly. Melting points were determined in PMP-DM scientific melting point apparatus and are uncorrected. The purity of compound was confirmed by TLC using Merck silica gel 60 F254 plates using toluene∶ethylacetate∶methanol (7∶2∶1, volume ratio) as a mobile phase and spots were visualized under UV radiation. IR spectra were recorded on a Perkin-Elmer RX 1 FTIR spectrophotometer, using potassium bromide pellets and the frequencies are expressed in cm^{-1}. The ^1H NMR and ^{13}C NMR spectra were recorded with a Bruker Avance II 400 NMR spectrometer, using tetramethylsilane as the internal reference, with deutero chloroform ($CDCl_3$) as a solvent. Elemental analyses were performed on a Heraeus Carlo Erba 1180 CHN analyzer. 2-[(2,6-Dichlorophenyl)amino]phenyl acetyl chloride (**1**) was synthesized by literature procedure.[31]

Synthesis of 7-chloro-2-[2-(2,6-dichlorophenyl)amino]-benzyl-4*H*-3,1-benzoxazin-4-one (2)

A mixture of acid chloride **1** (15 mmol) and 4-chloroanthranilic acid (15 mmol) in 20 mL pyridine were stirred at 0—5 ℃ for 1 h, further stirred for 1 h at room temperature. After completion of reaction, a pasty mass obtained was washed thoroughly with sodium bicarbonate (5% *w*/*v*) to remove unreacted acid. A solid separated was filtered, dried and recrystallized from methanol. Yield 53%, m.p. 183—188 ℃; ^1H NMR ($CDCl_3$, 400 MHz) δ: 3.58 (s, 2H, CH_2), 6.37—8.18 (m, 10H, Ar-H), 9.25 (bs, 1H, NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 32.26, 112.73, 116.12, 120.43, 121.42, 124.25, 126.47, 126.63, 127.28, 127.61, 129.32, 131.18, 134.24, 137.38, 141.72, 142.17, 149.86, 159.34, 164.29 cm^{-1}; IR (KBr) ν: 3440 (NH), 2921, 2848 (CH_2), 1735 (C=O), 1620 (C=N), 1145 (C—O), 754 (C—Cl). Anal. calcd for $C_{21}H_{13}Cl_3N_2O_2$ (M_r=431.7): C 58.43, H 3.04, N 6.49;

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found C 58.52, H 3.08, N 6.39.

Synthesis of 7-chloro-2-[2-(2,6-dichlorophenyl)amino]-benzyl-3-(4-aminophenyl)sulfonamido-quinazolin-4(3*H*)-one (3)

A mixture of benzoxazinone **2** (10 mmol) and 4-aminophenylsulfonyl hydrazide (10 mmol) was dissolve in 50 mL pyridine. The reaction mixture was refluxed for 5—6 h, cooled and poured into ice-cold water containing concentrated HCl. The separated solid was filtered, washed and recrystallised from ethanol. Yield 65%, m.p. 170—173 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.62 (s, 2H, CH_2), 5.71 (bs, 2H, NH_2), 6.37—8.17 (m, 14H, Ar-H), 9.22 (bs, 1H, NH), 11.82 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.23, 116.19, 117.15, 120.54, 121.57, 123.26, 124.35, 124.61, 126.82, 127.27, 127.52, 128.44, 129.44, 130.21, 131.04, 132.29, 136.43, 137.32, 141.84, 146.28, 150.74, 160.69, 162.76; IR (KBr) v: 3512—3386 (NH and NH_2), 2930, 2842 (CH_2), 1678 (C=O), 1618 (C=N), 1362, 1149 (SO_2), 750 (C—Cl) cm^{-1}. Anal. calcd for $C_{27}H_{20}Cl_3N_5O_3S$ (M_r=600.9): C 53.97, H 3.35, N 11.65; found C 54.16, H 3.28, N 11.77.

General procedure for the synthesis of Schiff base 4a—4l

A mixture of compound **3** (5 mmol) and substituted aromatic aldehyde (5 mmol) with catalytic amount of glacial acetic acid was refluxed in 40 mL absolute ethanol for 4—6 h on water bath. The excess solvent was distilled off, poured into ice cold water. The separated solid was filtered, washed and recrystallized from ethanol.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(2-chlorobenzylideneamino)phenyl]sulfonamido-quinazolin-4(3H)-one (4a) Yield 75%, m.p. 147—149 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.60 (s, 2H, CH_2), 6.36—8.16 (m, 18H, Ar-H), 8.60 (s, 1H, N=CH), 9.25 (bs, 1H, NH), 10.80 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.28, 116.05, 120.48, 121.53, 122.38, 123.33, 124.29, 124.57, 126.76, 127.32, 127.55, 127.77, 128.18, 128.62, 128.83, 129.39, 129.87, 131.23, 131.42, 132.36, 135.16, 136.41, 137.45, 139.17, 141.82, 146.25, 155.53, 157.73, 160.72, 162.86; IR (KBr) v: 3424 (NH), 2920, 2845 (CH_2), 1680 (C=O), 1635 (N=CH), 1610 (C=N), 1355, 1152 (SO_2), 750 (C—Cl) cm^{-1}. Anal. calcd for $C_{34}H_{23}Cl_4N_5O_3S$ (M_r=723.46): C 56.45, H 3.20, N 9.68; found C 56.27, H 3.16, N 9.74.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(4-chlorobenzylideneamino)phenyl]sulfonamido-quinazolin-4(3*H*)-one (4b) Yield 70%, m.p. 169—173 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.55 (s, 2H, CH_2), 6.37—8.16 (m, 18H, Ar-H), 8.55 (s, 1H, N=CH), 9.21 (bs, 1H, NH), 10.75 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.15, 116.24, 120.63, 121.46, 122.32, 123.33, 123.55, 124.26, 124.57, 126.91, 127.39, 127.58, 128.76, 129.31, 131.28, 131.76, 132.12, 133.38, 135.52, 136.25, 137.48, 139.36, 141.66, 146.42, 155.72, 157.64, 160.53, 162.89; IR (KBr) v: 3425 (NH), 2925, 2843 (CH_2), 1677 (C=O), 1637 (N=CH), 1608 (C=N), 1342, 1159 (SO_2), 743 (C—Cl) cm^{-1}. Anal. calcd for $C_{34}H_{23}Cl_4N_5O_3S$ (M_r=723.46): C 56.45, H 3.20, N 9.68; found C 56.34, H 3.25, N 9.61.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(2-hydroxybenzylideneamino)phenyl]sulfonamido-quinazolin-4(3*H*)-one (4c) Yield 66%, m.p. 153—155 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.57 (s, 2H, CH_2), 4.92 (bs, 1H, OH), 6.35—8.17 (m, 18H, Ar-H), 8.57 (s, 1H, N=CH), 9.24 (bs, 1H, NH), 10.77 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 30.86, 109.23, 116.07, 116.56, 119.75, 120.29, 121.32, 122.53, 123.48, 124.12, 124.45, 125.39, 127.04, 127.16, 127.43, 128.60, 129.58, 130.96, 131.28, 132.36, 136.11, 137.63, 139.27, 141.54, 146.46, 155.68, 156.73, 157.85, 160.62, 162.98; IR (KBr) v: 3434 (NH), 3252 (OH), 2927, 2850 (CH_2), 1678 (C=O), 1635 (N=CH), 1612 (C=N), 1340, 1155 (SO_2), 760 (C—Cl) cm^{-1}. Anal. calcd for $C_{34}H_{24}Cl_3N_5O_4S$ (M_r=705.01): C 57.92, H 3.43, N 9.93; found C 58.14, H 3.55, N 10.08.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(4-hydroxybenzylideneamino)phenyl]sulfonamido-quinazolin-4(3*H*)-one (4d) Yield 69%, m.p. 135—138 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.62 (s, 2H, CH_2), 4.98 (bs, 1H, OH), 6.36—8.18 (m, 18H, Ar-H), 8.63 (s, 1H, N=CH), 9.27 (bs, 1H, NH), 10.74 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.06, 115.96, 116.73, 118.27, 120.44, 121.25, 122.49, 123.57, 124.18, 124.37, 126.98, 127.24, 127.32, 128.42, 128.66, 129.64, 131.14, 132.47, 136.36, 137.59, 139.45, 141.76, 146.33, 155.83, 157.58, 159.86, 160.40, 163.13; IR (KBr) v: 3438 (NH), 3246 (OH), 2930, 2846 (CH_2), 1685 (C=O), 1632 (N=CH), 1614 (C=N), 1353, 1152 (SO_2), 753 (C—Cl) cm^{-1}. Anal. calcd for $C_{34}H_{24}Cl_3N_5O_4S$ (M_r=705.01): C 57.92, H 3.43, N 9.93; found C 57.78, H 3.46, N 9.87.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(2-nitrobenzylideneamino)phenyl]sulfonamido-quinazolin-4(3*H*)-one (4e) Yield 79%, m.p. 140—142 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.59 (s, 2H, CH_2), 6.37—8.17 (m, 18H, Ar-H), 8.57 (s, 1H, N=CH), 9.23 (bs, 1H, NH), 10.76 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 30.76, 115.85, 120.16, 121.38, 122.23, 123.34, 123.67, 124.03, 124.22, 126.82, 126.94, 127.18, 128.76, 129.17, 129.76, 130.53, 131.42, 132.24, 133.46, 134.14, 136.51, 137.28, 139.64, 142.12, 146.25, 149.86, 155.35, 157.66, 160.27, 163.26; IR (KBr) v: 3437 (NH), 2920, 2845 (CH2), 1679 (C=O), 1635 (N=CH), 1615 (C=N), 1540, 1362 (NO_2), 1342, 1154 (SO_2), 747 (C—Cl) cm^{-1}. Anal. calcd for $C_{34}H_{23}Cl_3N_6O_5S$ (M_r=734.01): C 55.63, H 3.16, N 11.45; found C 55.48, H 3.11, N 11.37.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(3-nitrobenzylideneamino)phenyl]sulfonamido-quinazolin-4(3*H*)-one (4f) Yield 71%, m.p. 155—157 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.60 (s, 2H, CH_2), 6.36—8.38 (m, 18H, Ar-H), 8.63 (s, 1H, N=CH), 9.27 (bs, 1H, NH), 10.78 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$,

100 MHz) δ: 30.81, 115.73, 120.02, 120.23, 121.19, 122.34, 123.42, 124.16, 124.38, 124.54, 125.65, 126.73, 126.96, 127.25, 129.04, 129.88, 130.62, 131.27, 132.15, 133.36, 136.43, 136.89, 139.23, 141.84, 146.37, 148.47, 155.52, 157.78, 160.41, 163.09; IR (KBr) *v*: 3435 (NH), 2927, 2842 (CH_2), 1680 (C=O), 1628 (N=CH), 1602 (C=N), 1548, 1365 (NO_2), 1338, 1161 (SO_2), 742 (C—Cl) cm^{-1}. Anal. calcd for $C_{34}H_{23}Cl_3N_6O_5S$ (M_r=734.01): C 55.63, H 3.16, N 11.45; found C 55.74, H 3.18, N 11.41.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(4-methoxybenzylideneamino)phenyl]sulfonamido-quinazolin-4(3*H*)-one (4g) Yield 75%, m.p. 172—175 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.30 (s, 3H, OCH_3), 3.55 (s, 2H, CH_2), 6.38—8.17 (m, 18H, Ar-H), 8.59 (s, 1H, N=CH), 9.23 (bs, 1H, NH), 10.73 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.14, 55.16, 114.43, 116.11, 116.84, 120.23, 121.38, 122.16, 123.54, 123.87, 124.22, 126.32, 126.54, 126.78, 127.21, 129.23, 130.12, 131.15, 132.35, 136.67, 137.03, 139.39, 141.73, 146.48, 155.74, 157.82, 159.93, 160.65, 163.17; IR (KBr) *v*: 3440 (NH), 2929, 2850 (CH_2), 1675 (C=O), 1635 (N=CH), 1607 (C=N), 1352, 1158 (SO_2), 1206, 1110 (C—O—C), 755 (C—Cl) cm^{-1}. Anal. calcd for $C_{35}H_{26}Cl_3N_5O_4S$ (M_r=719.04): C 58.46, H 3.64, N 9.74; found C 58.34, H 3.58, N 9.83.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(3,4,5-trimethoxybenzylideneamino)phenyl]sulfonamido-quinazolin-4(3*H*)-one (4h) Yield 65%, m.p. 164—166 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.32 (s, 33H, OCH_3), 3.58 (s, 2H, CH_2), 6.36—8.18 (m, 16H, Ar-H), 8.54 (s, 1H, N=CH), 9.22 (bs, 1H, NH), 10.76 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.26, 54.76, 55.23, 104.96, 116.32, 120.11, 121.29, 122.35, 123.47, 123.93, 124.19, 126.62, 126.81, 127.34, 127.87, 129.16, 130.25, 131.26, 132.54, 136.78, 137.15, 139.43, 140.68, 141.91, 146.32, 148.83, 156.12, 157.63, 160.18, 162.92; IR (KBr) *v*: 3438 (NH), 2927, 2842 (CH_2), 1673 (C=O), 1630 (N=CH), 1610 (C=N), 1350, 1162 (SO_2), 1210, 1114 (C—O—C), 746 (C—Cl) cm^{-1}. Anal. calcd for $C_{37}H_{30}Cl_3N_5O_6S$ (M_r=779.09): C 57.04, H 3.88, N 8.99; found C 56.87, H 3.96, N 8.92.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(2-hydroxy-4-methoxybenzylideneamino)phenyl]-sulfonamido-quinazolin-4(3*H*)-one (4i) Yield 66%, m.p. 153—156 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.35 (s, 3H, OCH_3), 3.56 (s, 2H, CH_2), 4.95 (bs, 1H, OH), 6.38—8.17 (m, 17H, Ar-H), 8.62 (s, 1H, N=CH), 9.25 (bs, 1H, NH), 10.79 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 30.92, 55.37, 104.19, 106.53, 108.74, 116.02, 119.97, 121.41, 122.54, 123.58, 123.88, 124.26, 126.89, 127.11, 127.15, 129.08, 129.85, 131.17, 131.83, 132.39, 136.44, 137.62, 139.71, 142.23, 146.29, 155.95, 157.52, 158.49, 160.22, 160.36, 163.24; IR (KBr) *v*: 3435 (NH), 3249 (OH), 2920, 2842 (CH_2), 1675 (C=O), 1629 (N=CH), 1608 (C=N), 1347, 1156 (SO_2), 1200, 1104 (C—O—C), 735 (C—Cl) cm^{-1}. Anal. calcd for $C_{35}H_{26}Cl_3N_5O_5S$ (M_r=735.04): C 57.19, H 3.57, N 9.53; found C 57.04, H 3.51, N 9.45.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(4-hydroxy-3-methoxybenzylideneamino)phenyl]-sulfonamido-quinazolin-4(3*H*)-one (4j) Yield 62%, m.p. 146—148 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.36 (s, 3H, OCH_3), 3.58 (s, 2H, CH_2), 4.92 (bs, 1H, OH), 6.36—8.16 (m, 17H, Ar-H), 8.61 (s, 1H, N=CH), 9.27 (bs, 1H, NH), 10.76 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.22, 54.98, 112.87, 116.25, 119.29, 120.61, 121.48, 122.33, 123.39, 123.67, 124.23, 124.62, 126.76, 126.93, 127.40, 127.72, 128.85, 129.32, 131.30, 132.23, 136.27, 137.52, 139.50, 141.68, 146.38, 147.56, 149.79, 155.86, 157.69, 160.55, 163.19; IR (KBr) *v*: 3442 (NH), 3254 (OH), 2930, 2856 (CH_2), 1677 (C=O), 1634 (N=CH), 1612 (C=N), 1353, 1147 (SO_2), 1210, 1106 (C—O—C), 742 (C—Cl) cm^{-1}. Anal. calcd for $C_{35}H_{26}Cl_3N_5O_5S$ (M_r=735.04): C 57.19, H 3.57, N 9.53; found C 57.08, H 3.62, N 9.59.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(4-dimethylaminobenzylideneamino)phenyl]sulfonamido-quinazolin-4(3*H*)-one (4k) Yield 60%, m.p. 141—143 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.10 [s, 23H, $N(CH_3)_2$], 3.56 (s, 2H, CH_2), 6.37—8.18 (m, 18H, Ar-H), 8.66 (s, 1H, N=CH), 9.20 (bs, 1H, NH), 10.75 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 30.84, 38.24, 112.72, 116.09, 120.32, 121.33, 122.56, 122.88, 123.49, 124.13, 124.58, 126.89, 127.22, 127.61, 128.73, 128.97, 129.56, 131.11, 132.42, 136.13, 137.49, 139.25, 141.56, 146.34, 150.65, 156.05, 157.74, 160.29, 163.32; IR (KBr) *v*: 3433 (NH), 2918, 2830 (CH_2), 1680 (C=O), 1632 (N=CH), 1610 (C=N), 1355, 1164 (SO_2), 756 (C—Cl) cm^{-1}. Anal. calcd for $C_{36}H_{29}Cl_3N_6O_3S$ (M_r=732.08): C 59.06, H 3.99, N 11.48; found C 59.23, H 4.07, N 11.42.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-[4-(2-hydroxy-4-diethylaminobenzylideneamino)-phenyl]sulfonamido-quinazolin-4(3*H*)-one (4l) Yield 78%, m.p. 143—146 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.35 [t, J=7.56 Hz, 23H, $N(CH_2CH_3)_2$], 2.82 [q, J=7.56 Hz, 22H, $N(CH_2CH_3)_2$], 3.54 (s, 2H, CH_2), 4.96 (bs, 1H, OH), 6.38—8.18 (m, 17H, Ar-H), 8.60 (s, 1H, N=CH), 9.29 (bs, 1H, NH), 10.69 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 14.86, 31.17, 43.27, 102.03, 108.34, 110.18, 115.92, 120.65, 121.63, 122.19, 123.31, 124.39, 124.50, 126.95, 127.36, 127.48, 129.11, 129.66, 130.46, 131.20, 132.14, 136.55, 137.43, 139.46, 142.14, 146.12, 151.69, 155.92, 157.92, 159.74, 160.32, 163.04; IR (KBr) *v*: 3442 (NH), 3258 (OH), 2925, 2849 (CH_2), 1679 (C=O), 1636 (N=CH), 1605 (C=N), 1358, 1165 (SO_2), 744 (C—Cl) cm^{-1}. Anal. calcd for $C_{38}H_{33}Cl_3N_6O_4S$ (M_r=776.13): C 58.81, H 4.29, N 10.83; found C 58.59, H 4.23, N 10.91.

General procedure for the synthesis of 4-thiazolidinonyl-quinazolin-4(3*H*)-ones 5a—5l

Thioglycolic acid (4 mmol) was added to a stirred solution of **4a**—**4l** (2 mmol) in 50 mL dry DMF, containing a pinch of anhydrous $ZnCl_2$ and refluxed for 8—

9 h. Excess of solvent was distilled off and the residual reaction mixture was cooled and poured into ice-cold water. The separated solid was filtered, washed and recrystallised from ethanol.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[2-(2-chlorophenyl)-4-oxo-thiazolidin-3-yl]phenyl}-sulfonamido-quinazolin-4(3*H*)-one (5a) Yield 78%, m.p. 156—158 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.61 (s, 2H, CH_2), 3.95 (s, 2H, CH_2-S), 5.22 (s, 1H, CH-S), 6.37—8.16 (m, 18H, Ar-H), 9.26 (bs, 1H, NH), 10.84 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.34, 35.75, 58.81, 105.87, 116.23, 120.47, 121.27, 121.64, 123.37, 124.41, 124.68, 125.74, 126.72, 127.01, 127.33, 127.45, 127.62, 127.94, 128.25, 129.59, 131.12, 132.36, 134.23, 135.32, 136.32, 137.53, 141.96, 145.47, 146.17, 160.51, 162.89, 173.38; IR (KBr) ν: 3436 (NH), 2925, 2839 (CH_2), 1758 (C=O, thiazolidinone), 1682 (C=O, quinazolinone), 1610 (C=N), 1362, 1150 (SO_2), 755 (C—Cl) cm^{-1}. Anal. calcd for $C_{36}H_{25}Cl_4N_5O_4S_2$ (M_r=797.56): C 54.21, H 3.16, N 8.78; found C 54.03, H 3.24, N 7.89.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[2-(4-chlorophenyl)-4-oxo-thiazolidin-3-yl]phenyl}-sulfonamido-quinazolin-4(3*H*)-one (5b) Yield 75%, m.p. 172—176 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.56 (s, 2H, CH_2), 3.93 (s, 2H, CH_2-S), 5.20 (s, 1H, CH-S), 6.37—8.17 (m, 18H, Ar-H), 9.20 (bs, 1H, NH), 10.70 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.22, 36.18, 63.77, 116.34, 120.54, 121.36, 121.58, 123.21, 123.49, 124.19, 124.67, 127.03, 127.13, 127.32, 127.71, 129.28, 130.68, 131.35, 131.53, 132.25, 133.97, 136.17, 137.53, 138.46, 141.76, 145.76, 146.38, 160.39, 163.06, 173.12; IR (KBr) ν: 3428 (NH), 2927, 2843 (CH_2), 1745 (C=O, thiazolidinone), 1672 (C=O, quinazolinone), 1606 (C=N), 1345, 1156 (SO_2), 746 (C—Cl) cm^{-1}. Anal. calcd for $C_{36}H_{25}Cl_4N_5O_4S_2$ (M_r=797.56): C 54.21, H 3.16, N 8.78; found C 54.32, H 3.19, N 8.72.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[2-(2-hydroxyphenyl)-4-oxo-thiazolidin-3-yl]-phenyl}sulfonamido-quinazolin-4(3*H*)-one (5c) Yield 76%, m.p. 160—162 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.60 (s, 2H, CH_2), 3.97 (s, 2H, CH_2-S), 5.22 (s, 1H, CH-S), 4.94 (bs, 1H, OH), 3.36—8.18 (m, 18H, Ar-H), 9.26 (bs, 1H, NH), 10.75 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 30.69, 35.92, 58.63, 108.96, 115.87, 116.15, 119.46, 120.35, 121.17, 121.23, 123.54, 124.26, 124.62, 124.83, 127.12, 127.19, 127.29, 127.56, 128.32, 129.42, 131.11, 132.53, 134.11, 136.19, 137.77, 141.65, 145.57, 146.37, 152.81, 160.59, 163.14, 172.78; IR (KBr) ν: 3440 (NH), 3252 (OH), 2924, 2847 (CH_2), 1750 (C=O, thiazolidinone), 1674 (C=O, quinazolinone), 1613 (C=N), 1340, 1155 (SO_2), 750 (C—Cl) cm^{-1}. Anal. calcd for $C_{36}H_{26}Cl_3N_5O_5S_2$ (M_r=779.11): C 55.50, H 3.36, N 8.99; found C 55.32, H 3.28, N 8.86.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[2-(4-hydroxyphenyl)-4-oxo-thiazolidin-3-yl]-phenyl}sulfonamido-quinazolin-4(3*H*)-one (5d) Yield 70%, m.p. 145—148 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.65 (s, 2H, CH_2), 3.94 (s, 2H, CH_2-S), 5.14 (s, 1H, CH-S), 4.97 (bs, 1H, OH), 6.36—8.19 (m, 18H, Ar-H), 9.25 (bs, 1H, NH), 10.78 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 30.89, 36.43, 64.26, 116.09, 116.48, 120.58, 121.23, 121.34, 122.16, 123.45, 124.22, 124.46, 126.86, 126.98, 127.19, 127.38, 128.14, 129.78, 131.12, 132.51, 134.29, 136.29, 137.69, 141.62, 145.51, 146.44, 156.75, 160.53, 163.25, 172.85; IR (KBr) ν: 3434 (NH), 3256 (OH), 2927, 2844 (CH_2), 1748 (C=O, thiazolidinone), 1680 (C=O, quinazolinone), 1611 (C=N), 1339, 1153 (SO_2), 742 (C—Cl) cm^{-1}. Anal. calcd for $C_{36}H_{26}Cl_3N_5O_5S_2$ (M_r=779.11): C 55.50, H 3.36, N 8.99; found C 55.38, H 3.41, N 9.07.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[2-(2-nitrophenyl)-4-oxo-thiazolidin-3-yl]phenyl}-sulfonamido-quinazolin-4(3*H*)-one (5e) Yield 82%, m.p. 151—154 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.58 (s, 2H, CH_2), 3.96 (s, 2H, CH_2-S), 5.23 (s, 1H, CH-S), 6.38—8.18 (m, 18H, Ar-H), 9.26 (bs, 1H, NH), 10.73 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 30.89, 35.42, 59.61, 115.78, 120.11, 121.19, 121.45, 122.92, 123.76, 124.13, 124.34, 126.69, 126.88, 127.10, 127.23, 128.36, 129.54, 129.73, 131.36, 132.29, 132.64, 134.18, 135.21, 136.59, 137.18, 142.15, 145.56, 146.26, 150.25, 160.36, 163.12, 172.67; IR (KBr) ν: 3447 (NH), 2915, 2840 (CH_2), 1746 (C=O, thiazolidinone), 1675 (C=O, quinazolinone), 1616 (C=N), 1545, 1365 (NO_2), 1342, 1157 (SO_2), 754 (C—Cl) cm^{-1}. Anal. calcd for $C_{36}H_{25}Cl_3N_6O_6S_2$ (M_r=808.11): C 53.51, H 3.12, N 10.40; found C 53.38, H 3.14, N 10.48.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[2-(3-nitrophenyl)-4-oxo-thiazolidin-3-yl]phenyl}-sulfonamido-quinazolin-4(3*H*)-one (5f) Yield 85%, m.p. 162—166 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.62 (s, 2H, CH_2), 3.97 (s, 2H, CH_2-S), 5.22 (s, 1H, CH-S), 6.37—8.40 (m, 18H, Ar-H), 9.28 (bs, 1H, NH), 10.77 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 30.95, 35.75, 66.28, 115.86, 120.14, 120.94, 121.10, 121.48, 122.74, 123.49, 124.22, 124.44, 125.28, 126.67, 126.87, 127.02, 127.31, 129.76, 131.32, 132.24, 133.12, 133.87, 135.53, 136.58, 136.92, 142.11, 145.64, 146.43, 148.30, 160.47, 162.93, 173.23; IR (KBr) ν: 3432 (NH), 2930, 2857 (CH_2), 1765 (C=O, thiazolidinone), 1682 (C=O, quinazolinone), 1605 (C=N), 1541, 1357 (NO_2), 1333, 1150 (SO_2), 750 (C—Cl) cm^{-1}. Anal. calcd for $C_{36}H_{25}Cl_3N_6O_6S_2$ (M_r=808.11): C 53.51, H 3.12, N 10.40; found C 53.36, H 3.07, N 10.34.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[2-(4-methoxyphenyl)-4-oxo-thiazolidin-3-yl]-phenyl}sulfonamido-quinazolin-4(3*H*)-one (5g) Yield 81%, m.p. 179—181 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.28 (s, 3H, OCH_3), 3.57 (s, 2H, CH_2), 3.96 (s, 2H, CH_2-S), 5.13 (s, 1H, CH-S), 6.37—8.18 (m, 18H, Ar-H), 9.20 (bs, 1H, NH), 10.71 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.25, 36.48, 55.33, 64.12, 114.19, 116.28, 120.17, 121.25, 121.52, 122.62, 123.68, 124.06, 124.42, 125.64, 126.46, 126.83, 126.95, 127.15, 129.94, 131.05, 132.40, 134.04, 136.75, 137.12, 141.88, 145.69,

146.59, 158.37, 160.56, 163.26, 173.46; IR (KBr) *v*: 3435 (NH), 2932, 2858 (CH_2), 1752 (C=O, thiazolidinone), 1674 (C=O, quinazolinone), 1610 (C=N), 1345, 1152 (SO_2), 1205, 1106 (C—O—C), 741 (C—Cl) cm^{-1}. Anal. calcd for $C_{37}H_{28}Cl_3N_5O_5S_2$ (M_r=793.14): C 56.03, H 3.56, N 8.83; found C 56.17, H 3.60, N 8.76.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[2-(3,4,5-trimethoxyphenyl)-4-oxo-thiazolidin-3-yl]phenyl}sulfonamido-quinazolin-4(3*H*)-one (5h) Yield 69%, m.p. 172—175 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.34 (s, 33H, OCH_3), 3.61 (s, 2H, CH_2), 3.95 (s, 2H, CH_2-S), 5.16 (s, 1H, CH-S), 6.36—8.17 (m, 16H, Ar-H), 9.24 (bs, 1H, NH), 10.78 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.34, 36.29, 54.65, 55.46, 64.32, 104.57, 116.37, 120.01, 121.12, 121.34, 123.53, 123.83, 124.25, 126.69, 126.92, 127.24, 127.41, 130.16, 131.22, 132.61, 133.92, 134.72, 135.86, 136.89, 137.22, 141.96, 145.48, 146.28, 148.59, 160.29, 163.07, 173.35; IR (KBr) *v*: 3431 (NH), 2927, 2846 (CH_2), 1755 (C=O, thiazolidinone), 1670 (C=O, quinazolinone), 1613 (C=N), 1348, 1152 (SO_2), 1210, 1108 (C—O—C), 736 (C—Cl) cm^{-1}. Anal. calcd for $C_{39}H_{32}Cl_3N_5O_7S_2$ (M_r=853.19): C 54.90, H 3.78, N 8.21; found C 54.82, H 3.76, N 8.25.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[2-(2-hydroxy-4-methoxyphenyl)-4-oxo-thiazolidin-3-yl]phenyl}sulfonamido-quinazolin-4(3*H*)-one (5i) Yield 79%, m.p. 163—167 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.32 (s, 3H, OCH_3), 3.55 (s, 2H, CH_2), 3.94 (s, 2H, CH_2-S), 5.19 (s, 1H, CH-S), 4.97 (bs, 1H, OH), 6.38—8.18 (m, 17H, Ar-H), 9.22 (bs, 1H, NH), 10.82 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.13, 35.74, 55.43, 58.56, 102.31, 105.42, 108.29, 116.10, 119.86, 121.38, 121.49, 123.64, 124.03, 124.33, 126.77, 126.97, 127.18, 127.35, 129.98, 131.37, 131.58, 132.45, 133.78, 136.54, 137.66, 142.17, 145.37, 146.38, 154.67, 159.15, 160.41, 163.35, 172.88; IR (KBr) *v*: 3442 (NH), 3255 (OH), 2924, 2845 (CH_2), 1753 (C=O, thiazolidinone), 1674 (C=O, quinazolinone), 1612 (C=N), 1347, 1154 (SO_2), 1218, 1097 (C—O—C), 748 (C—Cl) cm^{-1}. Anal. calcd for $C_{37}H_{28}Cl_3N_5O_6S_2$ (M_r=809.14): C 54.92, H 3.49, N 8.66; found C 55.14, H 3.57, N 8.62.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[2-(4-hydroxy-3-methoxyphenyl)-4-oxo-thiazolidin-3-yl]phenyl}sulfonamido-quinazolin-4(3*H*)-one (5j) Yield 68%, m.p. 154—158 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.35 (s, 3H, OCH_3), 3.59 (s, 2H, CH_2), 3.97 (s, 2H, CH_2-S), 5.16 (s, 1H, CH-S), 4.94 (bs, 1H, OH), 6.35—8.17 (m, 17H, Ar-H), 9.26 (bs, 1H, NH), 10.77 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 31.32, 35.66, 54.85, 63.96, 112.38, 116.39, 118.94, 120.43, 121.44, 121.65, 122.86, 123.47, 124.15, 124.57, 126.83, 127.06, 127.32, 127.64, 129.55, 130.72, 131.22, 132.31, 134.25, 136.40, 137.48, 141.45, 143.53, 145.45, 146.52, 149.30, 160.67, 163.24, 173.06; IR (KBr) *v*: 3435 (NH), 3246 (OH), 2920, 2842 (CH_2), 1750 (C=O, thiazolidinone), 1678 (C=O, quinazolinone), 1610 (C=N), 1350, 1144 (SO_2), 1228, 1087 (C—O—C), 745 (C—Cl) cm^{-1}. Anal. calcd for $C_{37}H_{28}Cl_3N_5O_6S_2$ (M_r=809.14): C 54.92, H 3.49, N 8.66; found C 54.78, H 3.43, N 8.58.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[2-(4-dimethylaminophenyl)-4-oxo-thiazolidin-3-yl]phenyl}sulfonamido-quinazolin-4(3*H*)-one (5k) Yield 70%, m.p. 150—152 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 3.12 [s, 23H, $N(CH_3)_2$], 3.57 (s, 2H, CH_2), 3.96 (s, 2H, CH_2-S), 5.18 (s, 1H, CH-S), 6.36—8.19 (m, 18H, Ar-H), 9.21 (bs, 1H, NH), 10.78 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 30.71, 36.14, 65.24, 38.37, 112.59, 116.11, 120.27, 121.32, 121.44, 123.56, 123.97, 124.39, 127.06, 127.22, 127.29, 127.78, 128.12, 129.04, 129.37, 130.89, 132.57, 133.84, 136.22, 137.66, 141.63, 145.76, 146.43, 149.28, 160.33, 163.28, 173.18; IR (KBr) *v*: 3430 (NH), 2915, 2836 (CH_2), 1743 (C=O, thiazolidinone), 1672 (C=O, quinazolinone), 1614 (C=N), 1352, 1156 (SO_2), 759 (C—Cl) cm^{-1}. Anal. calcd for $C_{38}H_{31}Cl_3N_6O_4S_2$ (M_r=806.18): C 56.61, H 3.88, N 10.42; found C 56.46, H 3.93, N 10.34.

7-Chloro-2-[2-(2,6-dichlorophenyl)amino]benzyl-3-{4-[2-(2-hydroxy-4-diethylaminophenyl)-4-oxo-thiazolidin-3-yl]phenyl}sulfonamido-quinazolin-4(3*H*)-one (5l) Yield 80%, m.p. 153—155 ℃; ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 1.34 [t, J=7.52 Hz, 23H, $N(CH_2CH_3)_2$], 2.83 [q, J=7.52 Hz, 22H, $N(CH_2CH_3)_2$], 3.56 (s, 2H, CH_2), 3.97 (s, 2H, CH_2-S), 5.25 (s, 1H, CH-S), 4.95 (bs, 1H, OH), 6.37—8.19 (m, 17H, Ar-H), 9.27 (bs, 1H, NH), 10.71 (bs, 1H, SO_2NH); ^{13}C NMR ($CDCl_3$, 100 MHz) δ: 15.13, 35.89, 31.24, 43.38, 58.42, 101.64, 106.92, 108.83, 115.85, 120.49, 121.28, 121.55, 123.48, 124.19, 124.65, 126.82, 127.28, 127.46, 127.67, 129.73, 130.06, 131.15, 132.26, 134.17, 136.69, 137.34, 141.98, 145.62, 146.23, 150.22, 158.53, 160.14, 163.16, 172.73; IR (KBr) *v*: 3438 (NH), 3248 (OH), 2928, 2853 (CH_2), 1750 (C=O, thiazolidinone), 1676 (C=O, quinazolinone), 1608 (C=N), 1353, 1159 (SO_2), 756 (C—Cl) cm^{-1}. Anal. calcd for $C_{40}H_{35}Cl_3N_6O_5S_2$ (M_r=850.23): C 56.51, H 4.15, N 9.88; found C 56.38, H 4.11, N 9.95.

Antimicrobial activity

The MICs of synthesized compounds were carried out by broth micro dilution method as described by Rattan.[32] Antibacterial activity was screened against two gram positive bacteria (*S. aureus* MTCC 96, *S. pyogenes* MTCC 442) and two gram negative bacteria (*E. coli* MTCC 443, *P. aeruginosa* MTCC 1688). Ampicillin was used as a standard antibacterial agent. Antifungal activity was screened against three fungal species *C. albicans* MTCC 227, *A. niger* MTCC 282 and *A. clavatus* MTCC 1323. Griseofulvin was used as a standard antifungal agent. All MTCC cultures were collected from Institute of Microbial Technology, Chandigarh and tested against above mentioned known drugs. Mueller hinton broth was used as nutrient medium to grow and dilute the drug suspension for the test. Inoculum size for test strain was adjusted to 10^8 CFU (Colony Forming Unit) per milliliter by comparing the turbidity. DMSO

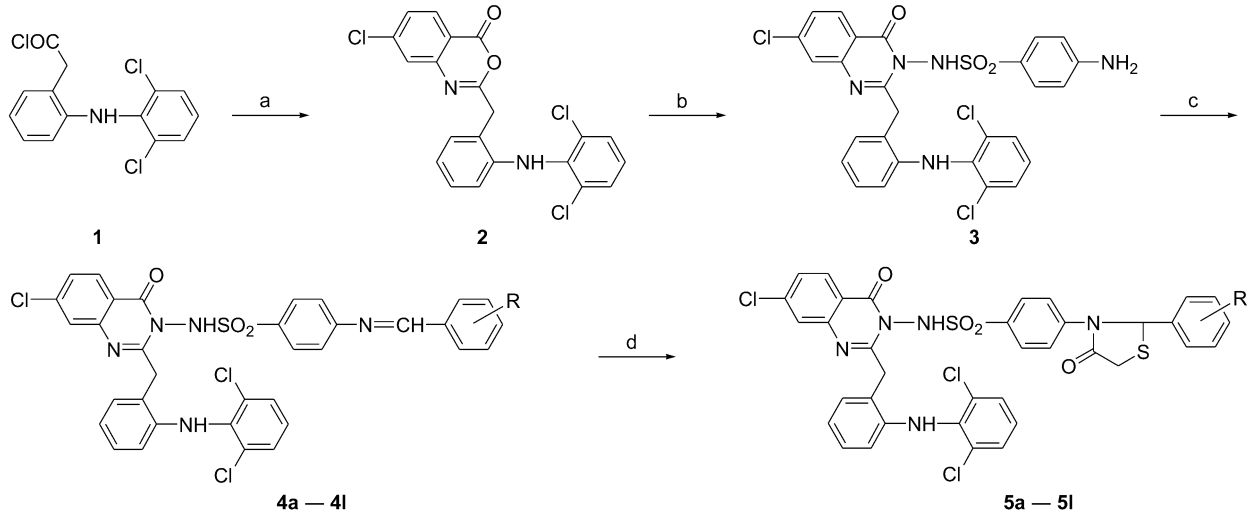
was used as diluents to get desired concentration of drugs to test upon standard bacterial strains. Serial dilutions were prepared in primary and secondary screening. The control tube containing no antibiotic was immediately sub cultured (before inoculation) by spreading a loopful evenly over a quarter of plate of medium suitable for the growth of the test organism and put for incubation at 37 ℃ overnight. The tubes were then incubated overnight. The MIC of the control organism was read to check the accuracy of the drug concentrations. The lowest concentration inhibiting growth of the organism was recorded as the MIC. All the tubes not showing visible growth (in the same manner as control tube described above) was sub cultured and incubated overnight at 37 ℃. The amount of growth from the control tube before incubation (which represents the original inoculum) was compared. Subcultures might show: similar number of colonies indicating bacteriostatic; a reduced number of colonies indicating a partial or slow bactericidal activity and no growth if the whole inoculum has been killed. The test must include a second set of the same dilutions inoculated with an organism of known sensitivity. Each synthesized drug was diluted obtaining 2000 μg/mL concentration, as a stock solution. In primary screening 500, 250 and 125 μg/mL concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution against all microorganisms. The drugs found active in primary screening were similarly diluted to obtain 100, 50, 25, 12.5, 6.250, 3.125 and 1.5625 μg/mL concentrations. The highest dilution showing at least 99% inhibition is taken as MIC.

Results and discussion

Chemistry

The compounds 7-chloro-2-[2-(2,6-dichlorophenyl)-amino]benzyl-3-[4-(2-substituted phenyl-4-oxo-thiazolidin-3-yl)phenyl]sulfonamido-quinazolin-4(3*H*)-ones **5a**—**5l** were synthesized from 2-[2-(2,6-dichlorophenyl)-amino]phenyl acetic acid by using efficient methods as described in Scheme 1. The benzoxazinone **2** was conveniently synthesized by the cyclization reaction of acid chloride **1** with 4-chloroanthranilic acid. The IR spectra showed strong C＝O and C＝N stretching vibration of benzoxazinone at 1735 and 1620 cm^{-1} respectively which was further confirmed by ^{13}C NMR spectra, showing C＝O and C＝N signals at δ 159.34 and 164.29, respectively. The condensation reaction of benzoxazinone **2** with 4-aminophenylsulfonyl hydrazide yielded amino-quinazolin-4(3*H*)-one (**3**), which showed strong C＝O stretching vibration at 1678 cm^{-1}, indicating the formation of quinazolinone moiety. The acid catalyzed condensation of amine **3** with substituted aromatic aldehydes afforded the Schiff base **4a**—**4l**. The Schiff base (N＝CH) showed C＝N stretching at around 1630 cm^{-1} in IR spectrum whereas in ^1H NMR spectrum the singlet equivalent to one proton was observed at around δ 8.6. The cyclization reaction of Schiff base with thioglycolic acid yielded the desired compounds thiazolidinonyl-quinazolin-4(3*H*)-ones **5a**—**5l**. The 4-thiazolidinone showed strong C＝O stretching at around 1750 cm^{-1}. ^1H NMR spectra showed singlet at around δ 3.95 and 5.20, confirming the presence of CH_2-S and CH-S of 4-thiazolidinone respectively. ^{13}C NMR spectra displayed the signals at around δ 36, 60 and 173 regarding CH_2-S, CH-S and C ＝ O of 4-thiazolidiones.

Scheme 1 Synthesis of 4-thiazolidinonyl-quinazolin-4(3*H*)-ones **5a**—**5l**



R = 2-Cl, 4-Cl, 2-OH, 4-OH, 2-NO_2, 3-NO_2, 4-OCH_3, 3,4,5-$(OCH_3)_3$, 2-OH-4-OCH_3, 4-OH-3-OCH_3, 4-$N(CH_3)_2$, 2-OH-4-$N(C_2H_5)_2$

Reagents and conditions: (a) 4-Chloro anthranilic acid, pyridine, 0 ℃ to r.t.; (b) 4-Aminophenylsulfonyl hydrazide, pyridine, 5 to 6 h; (c) Aromatic aldehyde, absolute ethanol, glacial acetic acid, 4 to 6 h; (d) Thioglycolic acid, DMF, $ZnCl_2$, 8 to 9 h.

Antimicrobial activity

The results of antibacterial and antifungal activity are summarized in Table 1. The result shows that some of the compounds showed very good antibacterial as well as antifungal activity. Schiff base derivatives **4a** (R＝2-Cl), **4b** (R＝4-Cl), **4c** (R＝2-OH), **4d** (R＝4-OH) and **4g** (R＝4-OCH_3) showed excellent activities (MIC: 50—125 μg/mL) against gram positive bacteria *S. aureus*. The results were found different when Schiff bases are converted to 4-thiazolidinone. The 4-thiazolidinone derivatives **5b** (R＝4-Cl) and **5h** [R＝3,4,5-$(OCH_3)_3$] exhibited excellent activities (MIC: 50 and 100 μg/mL, respectively) while **5a** (R＝2-Cl), **5c** (R＝2-OH), **5d** (R＝4-OH) and **5g** (R＝4-OCH_3) showed poor activity (MIC: 500 μg/mL) against gram positive bacteria *S. aureus*. Schiff bases **4g** (R＝4-OCH_3) and **4i** (R＝2-OH-4-OCH_3) showed good activities (MIC: 100 and 125 μg/mL, respectively) while its 4-thiazolidinone derivatives possessed poor activities (MIC: 500 and 250 μg/mL, respectively) against gram positive bacteria *S. pyogenes*. On the other hand Schiff bases **4h** [R＝3,4,5-$(OCH_3)_3$] and **4j** (R＝4-OH-3-OCH_3) displayed poor activities (MIC: 250 and 500 μg/mL, respectively) while its 4-thiazolidinone derivatives showed good activities (MIC: 100 and 125 μg/mL, respectively) against gram positive bacterial *S. pyogenes*. The Schiff base derivatives **4b** (R＝4-Cl), **4c** (R＝2-OH), **4d** (R＝4-OH) and **4g** (R＝4-OCH_3) as well as 4-thiazolidinone derivatives **5a** (R＝2-Cl) and **5b** (R＝4-Cl) possessed very good activities (MIC: 50—125 μg/mL) against gram negative bacteria *E. coli*. The Schiff base derivatives **4a** (R＝2-Cl), **4b** (R＝4-Cl), **4c** (R＝2-OH), **4d** (R＝4-OH) and **4g** (R＝4-OCH_3) exhibited very good activities (MIC: 62.5—125 μg/mL) while its 4-thiazolidinone derivatives showed poor activities except compound **5a** (R＝2-Cl) which showed good activity at 125 μg/mL against gram negative bacteria *P. aeruginosa*. The antifungal activity result reveals

Table 1 Antibacterial and antifungal activity of compounds **4a**—**4l** and **5a**—**5l**

Compd.	R	Antibacterial activity[a]				Antifungal activity		
		Gram positive bacteria		Gram negative bacteria		Fungal species		
		S. aureus MTCC96	S. *pyogenes* MTCC 442	*E. coli* MTCC443	*P. aeruginosa* MTCC 1688	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
4a	2-Cl	125	200	500	125	＞1000	＞1000	＞1000
4b	4-Cl	125	250	125	62.5	＞1000	＞1000	＞1000
4c	2-OH	62.5	500	62.5	100	＞1000	＞1000	＞1000
4d	4-OH	125	500	50	100	＞1000	＞1000	＞1000
4e	2-NO_2	500	500	500	1000	＞1000	＞1000	＞1000
4f	3-NO_2	500	500	250	500	＞1000	＞1000	＞1000
4g	4-OCH_3	50	100	100	125	＞1000	＞1000	＞1000
4h	3,4,5-$(OCH_3)_3$	250	250	250	250	200	200	500
4i	2-OH-4-OCH_3	500	125	500	500	500	＞1000	＞1000
4j	4-OH-3-OCH_3	1000	500	500	500	500	＞1000	＞1000
4k	4-$N(CH_3)_2$	250	500	500	500	＞1000	＞1000	＞1000
4l	2-OH-4-$N(C_2H_5)_2$	500	500	500	500	500	＞1000	＞1000
5a	2-Cl	500	500	62.5	125	500	250	500
5b	4-Cl	50	250	125	200	200	250	500
5c	2-OH	250	250	250	250	100	250	500
5d	4-OH	500	500	200	500	250	500	1000
5e	2-NO_2	250	250	500	500	1000	＞1000	＞1000
5f	3-NO_2	500	500	250	250	1000	＞1000	＞1000
5g	4-OCH_3	500	500	500	500	500	500	1000
5h	3,4,5-$(OCH_3)_3$	100	100	1000	500	125	＞1000	＞1000
5i	2-OH-4-OCH_3	500	250	500	500	500	＞1000	＞1000
5j	4-OH-3-OCH_3	2850	125	250	1000	1000	＞1000	＞1000
5k	4-$N(CH_3)_2$	500	500	500	500	1000	＞1000	＞1000
5l	2-OH-4-$N(C_2H_5)_2$	500	500	500	500	100	＞1000	＞1000
Ampicillin		250	100	100	100	NT	NT	NT
Griseofulvin		NT	NT	NT	NT	500	100	100

[a] Minimum inhibitory concentration (MIC, μg/mL): the lowest test concentration that completely inhibits microorganism growth; NT: not tested.

that some of the compounds showed excellent activity against *C. albicans* while moderate activities were observed against *A. niger*. All of the Schiff bases as well as 4-thiazolidinone derivatives displayed poor activities against *A. clavatus* compared to griseofulvin. Schiff bases **4h** [R＝3,4,5-$(OCH_3)_3$], **4i** (R＝2-OH-4-OCH_3), **4j** (R＝4-OH-3-OCH_3) and **4l** [R＝2-OH-4-N$(C_2H_5)_2$] as well as 4-thiazolidinones **5a** (R＝2-Cl), **5b** (R＝4-Cl), **5c** (R＝2-OH), **5d** (R＝4-OH), **5g** (R＝4-OCH_3), **5h** [R＝3,4,5-$(OCH_3)_3$], **5i** (R＝2-OH-4-OCH_3) and **5l** [R＝2-OH-4-N$(C_2H_5)_2$] showed very good activities (MIC: 100—500 μg/mL) against *C. albicans*. All Schiff base derivatives possessed poor activities against *A. niger* except compound **4h** [R＝3,4,5-$(OCH_3)_3$] which was found active at 200 μg/mL against *A. niger*. The 4-thiazolidinone derivatives **5a** (R＝2-Cl), **5b** (R＝4-Cl) and **5c** (R＝2-OH) exhibited moderate activity (MIC: 250 μg/mL) against *A. niger* compared to griseofulvin. The remaining compounds showed poor activities against *A. niger*.

Conclusion

The title compounds **5a**—**5l** were comprehensively synthesized using efficient methods and showed satisfactory analytical results. Furthermore some of the compounds showed good antimicrobial activity. The Schiff base derivative containing chloro and hydroxyl group showed good activity against gram positive bacteria *S. aureus* and gram negative bacteria *P. aeruginosa*. The Schiff base derivative containing 4-methoxy group was found active against all gram positive as well as gram negative bacteria. On the other hand 4-thiazolidinone derivative containing 3,4,5-trimethoxy and 4-hydroxy-3-methoxy group possessed good activity against gram positive bacteria while 2-chloro group containing 4-thiazolidinone was found active against gram negative bacteria. The 4-thiazolidinone derivatives exhibited very good activity against *C. albicans* than that of Schiff base derivatives. Hence, the overall result was found satisfactory and will guide to enhance these work with structural modification to improve biological activity.

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