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Short Communication

Microwave Assisted Synthesis of Some Novel Series of 4-Thiazolidinone Derivatives as Potent Antimicrobial Analogs

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Abstract: Several substituted 4-thiazolidinone derivatives **2a-q** have been synthesized from halogenohydroxy substituted Schiff bases **1a-q** under microwave irradiation technique. The reactions were carried out using ethanol: 2-methoxyethanol mixture as efficient reaction solvent system to afford high yield of product. The structures of newly synthesized compounds have been established on the basis of elemental analysis, IR, ^{1}H & ^{13}C NMR and mass spectral data. Further, all newly synthesized compounds were screened for their *in vitro* antimicrobial activity. The antifungal and antibacterial effects of the tested compounds are due to their molecular structure and substituent present.

Keywords: 4-thiazolidinones; halogenohydroxy Schiff bases; microwave irradiation; antimicrobial activity

1. INTRODUCTION

4-thiazolidinone nucleus is one of the most intensively investigated class of heterocyclic compounds having various remarkable biological activities such as analgesic [1], amoebicidal [2], nematicidal [3], antagonists [4], antihistamic [5], anti-HIV [6], antibacterial [7–12], antifungal [13,14], anti-inflammatory [15], antitubercular [16-18], antioxidant [19], antipsychotic agent. [20]. All these facts were driving force to develop novel thiazole derivatives with wide structural variation.

The use of microwave induced reactions in organic synthesis has increased dramatically in the last years, receiving widespread acceptance and becoming an indispensable tool [21]. Microwave technology has become a powerful tool in organic synthesis, since by employing this technique it is generally possible to prepare organic compounds very fast, with high purity and better yields compared to other more conventional method [22-24]. Additionally, in the search for economic and environmentally friendly synthetic methods, one-pot syntheses could offer a significant step ahead [25]. Since, the aim of our research has concerned on achieving reasonable yields of the synthesized heterocyclic compounds which might have prospective biological and pharmaceutical activities, we have synthesized new 4-thiazolidinone derivatives that may be of value in development of new, potent, selective and less toxic antimicrobial agents. As a part of our research work towards some green synthetic strategy **[**26-28], herein we plan to explore the possibility of a greater route with the help of microwave technique for the synthesis of 4-thiazolidinone derivatives (Figure **1**). The reaction between imines (Schiff bases) [29] and mercaptoacetic acid were carried out using ethanol: 2-methoxyethanol combination as efficient reaction solvent system to afford high yield of product. Therefore, present communication describes, microwave synthesis, characterization and study *in vitro* antimicrobial activity of novel 4-thiazolidinone derivatives.

2. MATERIAL AND METHODS

Melting points were determined in an open capillary tube and are uncorrected. The chemicals and solvents used were of laboratory grade and were purified. Purification of the compound was indicated using TLC (ethyl acetate / hexane, 0.25 mL: 0.25 mL,

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v/v as the mobile phase). FT-IR spectra were recorded in KBr pellets on a Perkin-Elmer (8201) spectrometer. ^{1}H NMR spectra were recorded on a Gemini 300-MHz instrument in DMSO-d_6 as the solvent and TMS was used as an internal standard. The mass spectra were recorded on SHIMADZU (GCMS-QP 1000 EX) GC-EI-MS spectrometer. Elemental analyses were performed on a Perkin-Elmer 240 CHN elemental analyzer. The reactions were carried out in EtOH: 2-methoxyethanol (10mL: 10mL, v/v) as reaction medium in QPro-M modified microwave oven, made in Canada at 200 watts and 2450 MHz frequency.

General procedure for synthesis of 4-thiazolidinone derivatives (2a-q)

Conventional method

A solution of halogenohydroxy substituted imines **1a-q** (0.001 mole) in EtOH: 2-methoxyethanol (10mL: 10mL, v/v) containing anhydrous $ZnCl_2$ (0.01 g) and thioglycolic acid (0.001 mole) was refluxed for 6-8 hrs. The reaction mixture was cooled and poured into ice cold water. The separated solid was filtered and recrystallized from ethanol to yield pure 4-thiazolidinone derivatives **2a-q** as reddish brown crystals.

Microwave method

A mixture of halogenohydroxy substituted imines **1a-q** (0.001 mole) in EtOH: 2-methoxyethanol (10mL: 10mL, v/v) containing anhydrous $ZnCl_2$ (0.01 g) and thioglycolic acid (0.001 mole) was irradiated in QPro-M microwave oven for about intermittently at 30 sec. interval for 2-6 min. Then reaction mixture was diluted with ice-cold water. The solid product thus formed was filtered, dried and recrystallized from ethanol to yield pure 4-thiazolidinone derivatives **2a-q** as reddish brown crystals.

3-(4-Chloro-2-iodo-phenyl)-2-(1-hydroxy-4-iodo-naphthalen-2-yl)-2-methyl-thiazolidin-4-one (2a): Colour (Reddish brown); FT-IR (KBr, ν, cm^{-1}): 3350 (OH), 2872 (C-H), 1778 (C=O), 1583, 1532, 1448 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.17 (s, 1H, OH), 1.24 (s, 3H, CH_3), 4.92 (s, 2H CH_2S), 7.13-8.05 (m, 8H, Aromatic proton); ^{13}C NMR: 34.69 (CH_3), 38.48 (CH_2), 60.12 (S-C-N of 4-thiazolidinone ring), 107-138 (C of Aromatic ring), 188 (CO); EIMS (*m/z*): 621.5 (M+); Anal. Calcd. For $C_{20}H_{14}O_2NSI_2Cl$: C, 38.61; H, 2.25; N, 2.25; S; 5.14; X (I, Cl); 46.58; Found: C, 38.68; H, 2.22; N, 2.27; S; 5.18; X (I, Cl); 46.55.

2-(4-Bromo-1-hydroxy-naphthalen-2-yl)-3-(4-chloro-2-iodo-phenyl)-2-methyl-thiazolidin-4-one (2b): Colour (Reddish brown); FT-IR (KBr, ν, cm^{-1}): 3346 (OH), 2881 (C-H), 1779 (C=O), 1580, 1537, 1442 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.16 (s, 1H,OH), 1.26 (s, 3H, CH_3), 4.90 (s, 2H CH_2S), 7.10-8.08 (m, 8H, Aromatic proton); ^{13}C NMR: 34.72 (CH_3), 38.51 (CH_2), 60.17 (S-C-N of 4-thiazolidinone ring), 109-136 (C of Aromatic ring), 186 (CO); EIMS (*m/z*): 574 (M+); Anal. Calcd. For $C_{20}H_{14}NO_2SClBrI$: C, 41.81; H, 2.43; N, 2.43; S; 5.57; X (Cl, Br, I,); 42.16; Found: C, 41.88; H, 2.45; N, 2.41; S; 5.60; X (Cl, Br, I,); 42.12.

2-(4-Chloro-1-hydroxy-naphthalen-2-yl)-3-(4-chloro-2-iodo-phenyl)-2-methyl-thiazolidin-4-one (2c): Colour (Reddish brown); FT-IR (KBr, ν, cm^{-1}): 3355 (OH), 2867 (C-H), 1777 (C=O), 1570, 1527, 1446 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.13 (s, 1H,OH), 1.24 (s, 3H, CH_3), 4.88 (s, 2H CH_2S), 7.10-8.12 (m, 8H, Aromatic proton); ^{13}C NMR: 34.72 (CH_3), 38.67 (CH_2), 60.27 (S-C-N of 4-thiazolidinone ring), 113-140 (C of Aromatic ring), 184 (CO); EIMS (*m/z*): 529 (M+); Anal. Calcd. For $C_{20}H_{14}NO_2SCl_2I$: C, 45.28; H, 2.64; N, 2.64; S, 6.03; X (Cl, I), 37.35; Found: C, 45.33; H, 2.62; N, 2.66; S, 6.08; X (Cl, I), 37.41.

2-(1-Hydroxy-4-iodo-naphthalen-2-yl)-3-(4-iodo-2-nitro-phenyl)-2-methyl-thiazolidin-4-one (2d): Colour (Reddish brown); FT-IR (KBr, ν, cm^{-1}): 3348 (OH), 2878 (C-H), 1776 (C=O), 1567, 1537, 1440 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.15 (s, 1H,OH), 1.22 (s, 3H, CH_3), 4.92 (s, 2H CH_2S), 7.17-8.13 (m, 8H, Aromatic proton); ^{13}C NMR: 34.69 (CH_3), 38.42 (CH_2), 60.20 (S-C-N of 4-thiazolidinone ring), 103-141 (C of Aromatic ring), 186 (CO); EIMS (*m/z*): 632 (M+); Anal. Calcd. For $C_{20}H_{14}O_4N_2SI_2$: C, 37.97; H, 2.21; N, 4.43; S, 5.06; X (I), 20.09; Found: C, 38.04; H, 2.20; N, 4.44; S, 5.10; X (I), 20.12.

2-(4-Bromo-1-hydroxy-naphthalen-2-yl)-3-(4-iodo-2-nitro-phenyl)-2-methyl-thiazolidin-4-one (2e): Colour (Reddish brown) FT-IR (KBr, ν, cm^{-1}): 3352 (OH), 2880 (C-H), 1775 (C=O), 1577, 1532, 1443 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.17 (s, 1H,OH), 1.23 (s, 3H, CH_3), 4.90 (s, 2H CH_2S), 7.12-8.10 (m, 8H, Aromatic proton); ^{13}C NMR: 34.63 (CH_3), 38.40 (CH_2), 60.23 (S-C-N of 4-thiazolidinone ring), 107-139 (C of Aromatic ring), 184 (CO); EIMS (*m/z*): 585 (M+); Anal. Calcd. For $C_{20}H_{14}O_4N_2SBrI$: C, 41.02; H, 2.39; N, 4.70; S, 5.47; X (Br, I), 35.38;

Found: C, 41.10; H, 2.35; N, 4.68; S, 5.42; X (Br, I), 35.46.

2-(4-Chloro-1-hydroxy-naphthalen-2-yl)-3-(4-iodo-2-nitro-phenyl)-2-methyl-thiazolidin-4-one (2f): Colour (Reddish brown) FT-IR (KBr, ν, cm^{-1}): 3348 (OH), 2892 (C-H), 1777 (C=O), 1565, 1542, 1448 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.16 (s, 1H,OH), 1.25 (s, 3H, CH_3), 4.89 (s, 2H CH_2S), 7.07-8.12 (m, 8H, Aromatic proton); ^{13}C NMR: 34.68 (CH_3), 38.37 (CH_2), 60.20 (S-C-N of 4-thiazolidinone ring), 112-137 (C of Aromatic ring), 186 (CO); EIMS (*m/z*): 540 (M+); Anal. Calcd. For $C_{20}H_{14}O_4N_2SClI$: C, 44.44; H, 2.59; N, 5.18; S, 5.92; X (Cl, I), 30.0; Found: C, 44.47; H, 2.55; N, 5.21; S, 5.90; X (Cl, I), 30.07.

3-(2-Chloro-4-iodo-phenyl)-2-(1-hydroxy-4-iodo-naphthalen-2-yl)-2-methyl-thiazolidin-4-one (2g): Colour (Reddish brown); FT-IR (KBr, ν, cm^{-1}): 3352 (OH), 2874 (C-H), 1775 (C=O), 1579, 1524, 1446 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.17 (s, 1H,OH), 1.23 (s, 3H, CH_3), 4.92 (s, 2H CH_2S), 7.13-8.08 (m, 8H, Aromatic proton); ^{13}C NMR: 34.69 (CH_3), 38.49 (CH_2), 60.15 (S-C-N of 4-thiazolidinone ring), 109-139 (C of Aromatic ring), 188 (CO); EIMS (*m/z*): 622 (M+); Anal. Calcd. For $C_{20}H_{14}O_2NSI_2Cl$: C, 38.58; H, 2.25; N, 2.25; S; 5.14; X (I, Cl); 46.54; Found: C, 38.55; H, 2.26; N, 2.23; S; 5.17; X (I, Cl); 46.60.

2-(4-Bromo-1-hydroxy-naphthalen-2-yl)-3-(2-chloro-4-iodo-phenyl)-2-methyl-thiazolidin-4-one (2h): Colour (Reddish brown); FT-IR (KBr, ν, cm^{-1}): 3347 (OH), 2876 (C-H), 1780 (C=O), 1587, 1531, 1440 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.17 (s, 1H,OH), 1.26 (s, 3H, CH_3), 4.90 (s, 2H CH_2S), 7.07-8.13 (m, 8H, Aromatic proton); ^{13}C NMR: 34.70 (CH_3), 38.58 (CH_2), 60.15 (S-C-N of 4-thiazolidinone ring), 106-138 (C of Aromatic ring), 186 (CO); EIMS (*m/z*): 574 (M+); Anal. Calcd. For $C_{20}H_{14}NO_2SClBrI$: C, 41.81; H, 2.43; N, 2.43; S; 5.57; X (Cl, Br, I,); 42.16; Found: C, 41.85; H, 2.42; N, 2.41; S; 5.55; X (Cl, Br, I,); 42.20.

2-(4-Chloro-1-hydroxy-naphthalen-2-yl)-3-(2-chloro-4-iodo-phenyl)-2-methyl-thiazolidin-4-one (2i): Colour (Reddish brown); FT-IR (KBr, ν, cm^{-1}): 3353 (OH), 2870 (C-H), 1776 (C=O), 1575, 1529, 1443 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.14 (s, 1H,OH), 1.22 (s, 3H, CH_3), 4.88 (s, 2H CH_2S), 7.13-8.12 (m, 8H, Aromatic proton); ^{13}C NMR: 34.72 (CH_3), 38.65 (CH_2), 60.30 (S-C-N of 4-thiazolidinone ring), 110-142 (C of Aromatic ring), 185 (CO); EIMS (*m/z*): 530 (M+); Anal. Calcd. For $C_{20}H_{14}NO_2SCl_2I$: C, 45.28; H, 2.64; N, 2.64; S, 6.03; X (Cl, I), 37.35; Found: C, 45.32; H, 2.62; N, 2.66; S, 6.10; X (Cl, I), 37.47.

2-(1-Hydroxy-4-iodo-naphthalen-2-yl)-3-(2-iodo-4-nitro-phenyl)-2-methyl-thiazolidin-4-one (2j): Colour (Reddish brown) FT-IR (KBr, ν, cm^{-1}): 3355 (OH), 2873 (C-H), 1778 (C=O), 1567, 1538, 1453 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.15 (s, 1H,OH), 1.23 (s, 3H, CH_3), 4.90 (s, 2H CH_2S), 7.10-8.09 (m, 8H, Aromatic proton); ^{13}C NMR: 34.65 (CH_3), 38.43 (CH_2), 60.27 (S-C-N of 4-thiazolidinone ring), 109-143 (C of Aromatic ring), 186 (CO); EIMS (*m/z*): 632 (M+); Anal. Calcd. For $C_{20}H_{14}O_4N_2SI_2$: C, 37.97; H, 2.21; N, 4.43; S, 5.06; X (I), 40.18; Found: C, 37.93; H, 2.23; N, 4.40; S, 5.11; X (I), 40.23.

2-(4-Bromo-1-hydroxy-naphthalen-2-yl)-3-(2-iodo-4-nitro-phenyl)-2-methyl-thiazolidin-4-one (2k): Colour (Reddish brown) FT-IR (KBr, ν, cm^{-1}): 3358 (OH), 2889 (C-H), 1778 (C=O), 1593, 1537, 1436 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.16 (s, 1H,OH), 1.25 (s, 3H, CH_3), 4.88 (s, 2H CH_2S), 7.06-8.12 (m, 8H, Aromatic proton); ^{13}C NMR: 34.72 (CH_3), 38.52 (CH_2), 60.40 (S-C-N of 4-thiazolidinone ring), 109-142 (C of Aromatic ring), 186 (CO); EIMS (*m/z*): 585 (M+); Anal. Calcd. For $C_{20}H_{14}O_4N_2SBrI$: C, 41.02; H, 2.39; N, 4.70; S, 5.47; X (Br, I), 35.38; Found: C, 41.15; H, 2.37; N, 4.72; S, 5.45; X (Br, I), 35.50.

2-(4-Chloro-1-hydroxy-naphthalen-2-yl)-3-(2-iodo-4-nitro-phenyl)-2-methyl-thiazolidin-4-one (2l): Colour (Reddish brown) FT-IR (KBr, ν, cm^{-1}): 3355 (OH), 2887 (C-H), 1780 (C=O), 1570, 1540, 1445 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.18 (s, 1H,OH), 1.23 (s, 3H, CH_3), 4.89 (s, 2H CH_2S), 7.10-8.14 (m, 8H, Aromatic proton); ^{13}C NMR: 34.80 (CH_3), 38.56 (CH_2), 60.32 (S-C-N of 4-thiazolidinone ring), 108-141 (C of Aromatic ring), 188 (CO); EIMS (*m/z*): 540 (M+); Anal. Calcd. For $C_{20}H_{14}O_4N_2SClI$: C, 44.44; H, 2.59; N, 5.18; S, 5.92; X (Cl, I), 30.0; Found: C, 44.52; H, 2.57; N, 5.22; S, 5.88; X (Cl, I), 30.10.

2-(4-Chloro-1-hydroxy-naphthalen-2-yl)-3-(2,6-dichloro-4-iodo-phenyl)-2-methyl-thiazolidin-4-one (2m): Colour (Reddish brown); FT-IR (KBr, ν, cm^{-1}): 3360 (OH), 2895 (C-H), 1775 (C=O), 1564, 1535, 1450 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.15 (s, 1H,OH), 1.24 (s, 3H, CH_3), 4.91 (s, 2H CH_2S), 7.08-8.18 (m, 8H, Aromatic proton); ^{13}C NMR: 34.72 (CH_3), 38.80 (CH_2), 60.43 (S-C-N of 4-thiazolidinone ring), 106-145 (C of Aromatic ring), 187 (CO); EIMS (*m/z*): 438.5 (M+); Anal. Calcd. For $C_{20}H_{14}NO_2SCl_3$:

C, 54.73; H, 3.19; N, 3.19; S, 7.29; X (Cl), 24.05; Found: C, 54.80; H, 3.15; N, 3.17; S, 7.26; X (Cl), 24.15.

3-(4-Bromo-2-chloro-phenyl)-2-(4-bromo-1-hydroxy-naphthalen-2-yl)-2-methyl-thiazolidin-4-one (2n): Colour (Reddish brown); FT-IR (KBr, ν, cm^{-1}): 3350 (OH), 2892 (C-H), 1777 (C=O), 1568, 1530, 1452 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 5.17 (s, 1H,OH), 1.26 (s, 3H, CH_3), 4.90 (s, 2H CH_2S), 7.13-8.21 (m, 8H, Aromatic proton); ^{13}C NMR: 34.72 (CH_3), 38.82 (CH_2), 60.40 (S-C-N of 4-thiazolidinone ring), 109-142 (C of Aromatic ring), 185 (CO); EIMS (*m/z*): 527.5 (M+); Anal. Calcd. For $C_{20}H_{14}NO_2SBr_2Cl$: C, 45.49; H, 2.65; N, 2.65; S, 6.06; X (Cl, Br), 37.06; Found: C, 45.58; H, 2.67; N, 2.66; S, 6.13; X (Cl, Br), 37.20.

4-[2-(4-Bromo-1-hydroxy-naphthalen-2-yl)-2-methyl-4-oxo-thiazolidin-3-yl]-3-iodo-benzoic acid (2o): Colour (Reddish brown) FT-IR (KBr, ν, cm^{-1}): 3365 (OH), 2892 (C-H), 1775 (C=O), 1572, 1548, 1430 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 12.08 (s, 1H, COOH), 5.13 (s, 1H,OH), 1.23 (s, 3H, CH_3), 4.90 (s, 2H CH_2S), 7.03-8.32 (m, 7H, Aromatic proton); ^{13}C NMR: 34.90 (CH_3), 38.65 (CH_2), 60.78 (S-C-N of 4-thiazolidinone ring), 112-157 (C of Aromatic ring), 184 (CO), 192 (COOH); EIMS (*m/z*): 710 (M+); Anal. Calcd. For $C_{21}H_{14}O_4NSBrI_2$: C, 35.50; H, 1.97; N, 1.97; S, 4.50; X (Br, I), 47.04; Found: C, 35.57; H, 1.94; N, 1.92; S, 4.56; X (Br, I), 47.21.

4-[2-(1-Hydroxy-4-iodo-naphthalen-2-yl)-2-methyl-4-oxo-thiazolidin-3-yl]-3,5-diiodo-benzoic acid (2p): Colour (Reddish brown) FT-IR (KBr, ν, cm^{-1}): 3378 (OH), 2932 (C-H), 1779 (C=O), 1587, 1543, 1454 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 12.06 (s, 1H, COOH), 5.16 (s, 1H,OH), 1.28 (s, 3H, CH_3), 4.86 (s, 2H CH_2S), 7.08-8.37 (m, 7H, Aromatic proton); ^{13}C NMR: 34.87 (CH_3), 38.73 (CH_2), 60.84 (S-C-N of 4-thiazolidinone ring), 109-154 (C of Aromatic ring), 183 (CO), 191 (COOH); EIMS (*m/z*): 757 (M+); Anal. Calcd. For $C_{21}H_{14}O_4NSI_3$: C, 33.02; H, 1.84; N, 1.84; S, 4.22; X (I), 50.33; Found: C, 33.24; H, 1.89; N, 1.87; S, 4.19; X (I), 50.42.

4-[2-(4-Chloro-1-hydroxy-naphthalen-2-yl)-2-methyl-4-oxo-thiazolidin-3-yl]-3,5-diiodo-benzoic acid (2q): Colour (Reddish brown) FT-IR (KBr, ν, cm^{-1}): 3384 (OH), 2937 (C-H), 1778 (C=O), 1579, 1548, 1462 (C=C); ^{1}H NMR (300 MHz, DMSO-*d*6, δ, ppm): 12.09 (s, 1H, COOH), 5.18 (s, 1H,OH), 1.26 (s, 3H, CH_3), 4.86 (s, 2H CH_2S), 7.11-8.39 (m, 7H, Aromatic proton); ^{13}C NMR: 34.82 (CH_3), 38.68 (CH_2), 60.92 (S-C-N of 4-thiazolidinone ring), 108-152 (C of Aromatic ring), 184 (CO), 193 (COOH); EIMS (*m/z*): 665.5 (M+); Anal. Calcd. For $C_{21}H_{14}O_4NSClI_2$: C, 37.86; H, 2.10; N, 2.10; S, 4.80; X (Cl, I), 43.50; Found: C, 37.92; H, 2.13; N, 2.12; S, 4.83; X (Cl, I), 43.57.

Antimicrobial activity

The antibacterial activities of the synthesized compounds (**2a-q**) were determined by agar well diffusion method[32]. The compounds were evaluated for antibacterial activity against *Escherichia coli* [MTCC 8742] and *Staphylococcus aureus* [MTCC 6535]. The antifungal activity performed against *Candia crusei* [MTCC 14264] and *Candida albicans* [MTCC 64558] were procured from Institute of Microbial Technology (IMTech), Chandigarh, India. The antibiotic streptomycin (12.5μ/mL & 10.5 μ/mL) and Nystatin (25 μ/mL) used as reference drug for antibacterial and antifungal activity, respectively. Dimethyl sulphoxide (1%, DMSO) in sterilized distilled water used a control for all sample treatment. The minimum inhibitory concentrations (MIC's) values were determined by comparison to streptomycin and Nystatin as the reference drugs for bacterial and fungal activity respectively, as shown in Table **2**.

3. RESULTS AND DISCUSSION

In view of the importance of this class of heterocycles and in continuation of our earlier investigation, reported the synthesis of 4-thiazolidinones from imines and some of the 4-thiazolidinone derivatives found to have significant antibacterial activity [30]. Therefore, in present paper, we have synthesized new class of 4-thiazolidinones (**2a-q**) by cyclocondensation reaction of imines (**Figure 1**). The starting iodo anilines required for the preparation of imines were prepared by iodination of substituted anilines using molecular iodine and iodic acid under refluxing technique [31]. Obtained different substituted iodo anilines on condensation with halogeno substituted 1-(1-Hydroxy-naphthalen-2-yl)-ethanone (ketones) under solvent-free grindstone technique to yield imines (Schiff bases) [29] **1a-q**.

The compounds (**1a-q**) on cyclocondensation with thioglycolic acid in ethanol: 2-methoxyethanol as mixture of solvent using microwave irradiation method to affords 4-thiazolidinones (**2a-q**). Initially, we attempted the cyclocondensation 4-Bromo-2-[1-(4-

chloro-2-iodophenylimino)-ethyl]-naphthalen-1-ol (**1b**, 0.001 mole) with mercapto-acetic acid (thioglycolic acid, 0.001 mole) in presence of $ZnCl_2$ (0.01 gm) to afford product **2b**. The reaction went to completion within 2 min and corresponding product **2b** was obtained in 96% yield. In order to optimize these reaction conditions, we carried out the above reaction using conventional heating method and obtained results are represented in Table **1**.

Microwave oven is used for syntheses of 4-thiazolidinone derivatives as a convenient source of heat in laboratory. The microwave assisted reactions occur more rapidly, safely, easy isolation of products and with more chemical yields and better time economy thus, render microwave method superior to conventional method. The structures of newly synthesized compounds (**2a-q**) are well established on the basis of spectral data.

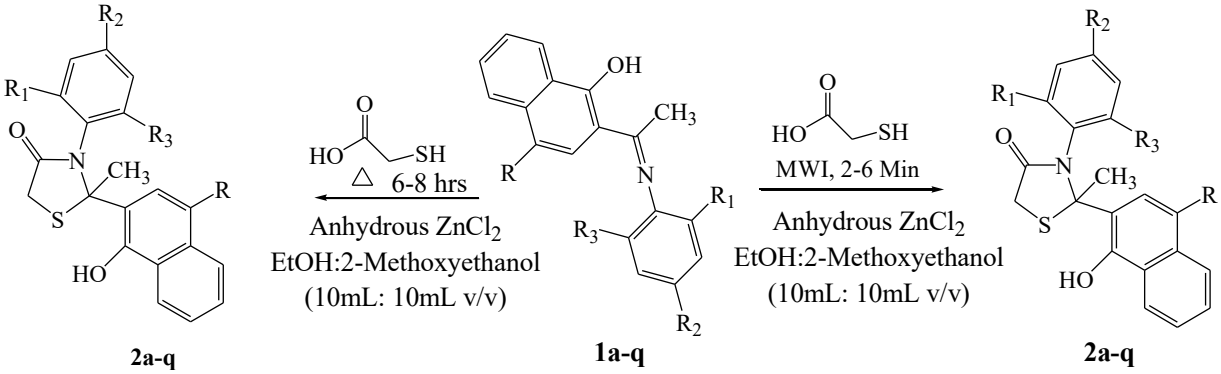


Figure 1. Microwave assisted synthesis of 4-thiazolidinones.

In IR spectra of corresponding product display the absence of characteristic absorption band near 1580-1588 cm^{-1} due to C=N stretching of imines and appearances of 1775-1780 cm^{-1} of C=O stretch indicate the formation of five-membered 4-thiazolidinone ring. The ^1H NMR spectra of 4-thiazolidinones show characteristics δ value at 4.90 ppm due to two protons of $-CH_2S$. In ^{13}C NMR spectra, the δ value near 38.60 ppm & 60.5 ppm reveals the presence of CH_2 & S-C-N of thiazolidin-4-one ring. Therefore, all synthesized compounds exhibited satisfactory spectral data consistent with their structures.

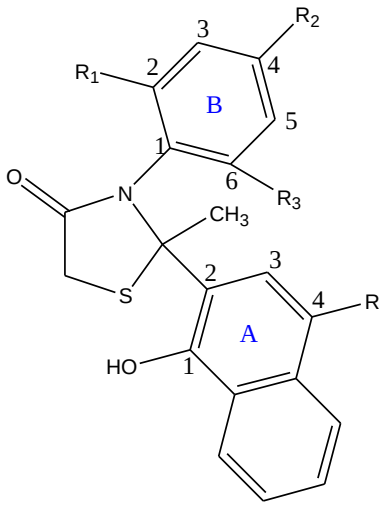
Table 1. Physical data of newly synthesized 4-thiazolidinon derivatives (**2a-q**).

Product	R	R_1	R_2	R_3	m.p. °C	Microwave method		Conventional method	
						Time (min)	Yield[a] (%)	Time (h)	Yield[b] (%)
2a	I	I	Cl	H	122-126	04	88	06	72
2b	Br	I	Cl	H	114-117	02	96	06	75
2c	Cl	I	Cl	H	129-132	05	90	08	78
2d	I	NO_2	I	H	143-146	03	85	06	68
2e	Br	NO_2	I	H	141-143	04	92	07	73
2f	Cl	NO_2	I	H	154-157	06	84	07	70
2g	I	Cl	I	H	137-140	04	92	06	75
2h	Br	Cl	I	H	142-145	03	85	06	68
2i	Cl	Cl	I	H	127-130	02	94	06	80
2j	I	I	NO_2	H	147-150	05	88	08	65
2k	Br	I	NO_2	H	157-160	06	82	08	67
2l	Cl	I	NO_2	H	149-152	05	84	07	70
2m	Cl	Cl	Cl	H	124-127	04	90	06	68
2n	Br	Cl	Br	H	118-121	03	87	06	72
2o	Br	I	COOH	I	162-165	06	80	07	65
2p	I	I	COOH	I	169-171	05	82	07	68
2q	Cl	I	COOH	I	185-187	06	84	08	74

a: Isolated yield of the product by microwave method.

b: Isolated yield of the product by conventional method.

Antimicrobial screening



All the synthesized 4-thiazolidinone derivatives (**2a-q**) were screened for their *in vitro* antimicrobial activity and showed good inhibitory activity at 10.5µg/mL, 12.5µg/mL & 25µg/mL concentration. Antimicrobial activity tested against *Escherichia coli* (MTCC 8742), *Staphylococcus aureus* (MTCC 6535), *Candia crusei* (MTCC 14264) and *Candida albicans* (MTCC 64558). The results of these studies in terms of zone of inhibition (ZOI) and minimum inhibitory concentrations (MICs) are summarized in Table **2**. The compounds **2a**, **2b**, **2c**, **2g**, **2h**, **2i**, **2m**, **2n** and **2p** shows good to moderate activity. The moderate antimicrobial activity is attributed due to presence of pharmacological active –I (2b, 2c,), -Cl (2g, 2h, 2n) at 2nd position of aromatic ring B. The compounds **2i** and **2m** has higher inhibitory activity in comparison with any other compounds due to presence of more activating group –Cl attached at 2nd and 4th position of ring A and B. The compounds **2d**, **2e**, **2f**, **2j**, **2k** and **2l** showed sharp decrease in activity due to replacement of active –Cl and –I group by NO_2 group at both positions of ring A & B. Thus 4-thiazolidinone derivatives which has activating functional group –Cl, -Br and –I showed antimicrobial inhibitory activity when compared with standard drug. The remaining **2o**, **2p** and **2q** compounds showed nearly equal inhibition activity.

Table 2. Antimicrobial activity of synthesized 4-thiazolidinone derivatives **2a-q** (MIC µg/mL).

Entry	Zone of inhibition in mm			
	E. coli	***S. aureus***	***C. crusei***	***C. albicans***
	MTCC 8742	**MTCC 6535**	**MTCC 14264**	**MTCC 64558**
2a	26(10.5)	27(10.5)	24(25)	26(25)
2b	27(10.5)	28(<10.5)	25(25)	25(25)
2c	25(12.5)	26(12.5)	27(25)	24(25)
2d	08(<200)	06(<200)	09(<200)	07(<200)
2e	06(<200)	05(<200)	07(<200)	06(<200)
2f	04(<200)	08(<200)	05(<200)	03(<200)
2g	28(10.5)	26(12.5)	27(25)	26(25)
2h	26(12.5)	25(12.5)	28(25)	27(25)
2i	30(<10.5)	32(<10.5)	28(25)	30(25)
2j	03(<200)	06(<200)	04(<200)	05(<200)
2k	06(<200)	04(<200)	06(<200)	05(<200)
2l	04(<200)	05(<200)	03(<200)	04(<200)
2m	32(<10.5)	30(<10.5)	28(25)	30(25)
2n	25(12.5)	26(12.5)	27(25)	24(25)
2o	18(100)	15(100)	14(50)	12(50)
2p	20(100)	17(100)	13(50)	15(50)
2q	17(100)	18(100)	17(50)	14(50)

4. CONCLUSION

In summary, 4-thiazolidinone derivatives have been synthesized from halogenohydroxy substituted imines using EtOH:2-methoxyethanol solvent system in Q-Pro-M modified microwave oven. The method is efficient, convenient in terms of simple reaction procedure, short reaction time, increasing the purity of resulting products, and enhances the quantitative yield in comparison with classical procedure. Further preliminary *in vitro a*ntimicrobial study of newly synthesized compounds reveals that, presence of Cl, Br

and I in basic nucleus of 4-thiazolidinones enhances the pharmacological activity. The electronic effect also plays an important role in pharmacological activity, as can be seen from compounds **2d**, **2e**, **2f**, **2j**, **2k** and **2l** which possess -NO_2 group has more electronic withdrawing character shows sharp decrease in antimicrobial activity. Owing to these results, the synthesized compounds **2i** and **2m** have broader value than standard drug used for screening of bacterial and fungal strains. Therefore, the present study is useful for drugs in medicinal investigation against bacterial and fungal diseases.

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