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One pot three components microwave assisted and conventional synthesis of new Thiazolidin-4-one derivatives as antimicrobial agents

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ABSTRACT

A one-pot, three-component, microwave assisted and conventional synthesis of new 3-(4-chloro-2-hydroxyphenyl)-2-(substituted) thiazolidin-4-one derivatives (**4a-n**) were carried out without solvent with high product yield and less reaction time. Among these synthesized compounds (**4f**, **4g**, **4l** and **4m**) were found to be broad spectrum molecule active against all bacterial and fungus strain tested, except fungus *A. niger*. Amongst the compounds (**4g**, **4l** and **4m**) were found to be much more potent than respective standard drugs used in experiment against *C. albicans*, *S. aureus* and *A. flavus* respectively.

Keywords: Thiazolidin-4-one, microwave-assisted synthesis, 2-amino-5-chlorophenol, antimicrobial.

INTRODUCTION

The structural and therapeutic diversity coupled with commercial viability of different types of small molecules has fascinated organic and medicinal chemists. There has been considerable most of interest in the chemistry of thiazolidin-4-one moiety. The derivatives of 4-thiazolidinone nucleus have also occupied a unique place in the field of medicinal chemistry.[1] The thiazolidin-4-one moiety display a wide range of biological activities like antibacterial,[2] anti-inflammatory,[3,4] anticancer,[5-8] anti-tuberculosis,[9] anticonvulsant[10] and analgesic[11] activities.

Earlier studies on the pharmacological activities of thiazolidin-4-ones showed wide spectrums of antimicrobial activities.[12-14] Microwave assisted reactions have become an established tool for the high-speed synthesis of novel chemical entities.[15] Many chemical reactions are accelerated rate of reaction because of selective absorption of MW energy. The application of microwave irradiation is the use of catalysts or mineral supported reagents, under solvent-free conditions, enables organic reactions to occur expeditiously at ambient pressure, thus providing unique chemical processes with special attributes such as enhanced reaction rates and higher yields.[16,17] The thiazolidin-4-ones derivatives has been known for over 50 years, so there have been several attempts to design antimicrobial agents based on this heterocycle. In continuation of our work,[18] on the synthesis of bioactive compounds, we have synthesized some thiazolidin-4-ones analogues. On the development of new heterocyclic compounds and antimicrobial screening, we have discovered efficient method for the synthesized of thiazolidin-4-ones analogues. There are various reports available on thiazolidin-4-ones derivatives as antimicrobial agents.[19-22] With this in mind, we initiated a program to synthesized thiazolidin-4-ones derivatives as antimicrobial agent by preparing hybrid molecules having the similar features of reported potent antimicrobial agents (**Figure 1**).

MATERIALS AND METHODS

2-amino-5-chlorophenol, substituted aldehydes, thioglycolic acid and various solvents were commercially available. The major chemicals were purchased from Sigma Aldrich and Avra labs. Reaction progress was monitored by TLC on silica gel precoated F254 Merck plates. Developed plates were examined with ultraviolet lamps (254 nm). IR spectra were recorded on a FT-IR (Bruker). Melting points were recorded on SRS Optimelt, melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a 400 MHz Bruker spectrometer and ^{13}C NMR spectra were recorded on a 100 MHz Bruker spectrometer are reported as parts per million (ppm) downfield from a tetramethylsilane internal standard. The following abbreviations are used, singlet (s), doublet (d), triplet (t), quartet (q), multiplate (m) and broad (br). Mass spectra were taken with Micromass-QUATTRO-II of WATER mass spectrometer. Microwave reactions were carried out in MicroSYNTH Lab station of Ethusi Mileston

RESULT AND DISCUSSION

To synthesize a series of new thiazolidin-4-ones, which have different pharmacologically active groups, these are exhibit antimicrobial activities. We have successfully synthesized series of new 3-(4-chloro-2-hydroxyphenyl)-2-(substituted) thiazolidin-4-one (**4a-n**) (**Scheme 1**) by using one-pot, three-component system, under microwave assisted technique as well as conventional method without any solvent. The synthesized compounds are tested for their in vitro antimicrobial activities against fungal and bacterial strains. The synthesized compounds were characterized on the basis of IR, ^{1}H NMR, ^{13}C NMR, Elemental analysis and mass spectral data.

Our current investigation describes the convenient synthesis of 3-(4-chloro-2-hydroxyphenyl)-2-(substituted)thiazolidin-4-one, without solvent under microwave assisted as well as conventional synthesis with high yield in short time period. This method is unique, rapid and convenient for the synthesis of new thiazolidin-4-one compounds. We herein report the synthesis and screening of antimicrobial activity of a series of new 3-(4-chloro-2-hydroxyphenyl)-2-(substituted) thiazolidin-4-one. The syntheses of new 3-(4-chloro-2-hydroxyphenyl)-2-(substituted) thiazolidin-4-one were achieved following the step outlined (**Scheme 1**). Microwave used in the study was MicroSYNTH Lab station of Ethusi Milestone with temperature control (**Scheme 1**, **Method A**). A one-pot, three-component, microwave assisted as well as conventional synthesis by using 2-amino-5-chlorophenol with substituted aldehydes and thioglycolic acid reacted with them to give the compounds (**4a-n**) (**Table 1**). The possible mechanism of the reaction is shown in **Scheme 2**. All of the compounds were obtained in good yield with short reaction time period in microwave assisted synthesis. These compounds were characterized on the basis of spectral analysis. The IR spectrum of representative compound 3-(4-chloro-2-hydroxyphenyl)-2-phenylthiazolidin-4-one (**4a**), IR absorption bands in the wavenumber show 3380 cm^{-1} that is due to a hydroxyl group, 1683 cm^{-1} that is due to a carbonyl group. The mass spectrum revealed a molecular ion peak at m/z was 306 (M+1) corresponding to a molecular formula $C_{15}H_{12}ClNO_2S$. The ^{1}H NMR spectrum of the compound (**4a**) has been shown doublet of methylene proton in the range of δ 4.46–4.57 (d, 1H, CH_2), 4.60–

4.69 (d, 1H, CH_2), 5.72 (s, 1H, OH), 6.20 (s, 1H, S–CH–N), 7.01–7.20 (m, 3H, Ar-H), 7.23–7.38 (m, 5H, Ar-H).

General procedure for microwave-assisted synthesis of 3-(4-chloro-2-hydroxyphenyl)-2-(substituted)thiazolidin-4-one (4a-n), Method A.

An equimolar amount of substituted aldehydes (**1a-n**) (1 mmol), 2-amino-5-chlorophenol **(2)** (1 mmol), thioglycolic acid (**3**) (1 mmol) were added in a 100 mL round bottom flask subjected to MW irradiation (800 W), at 120 ºC temperature for 7-9 min. The completion of the reaction progress was monitored by using TLC (5 % Ethyl acetate: n-hexane). The product obtained was poured into crushed ice, filtered and extracted with petroleum ether and ethyl acetate (2:8), (3×15 mL). The combined solvents extracted were concentrated in vacuo. The compounds were recrystallized from ethanol to obtain pure product (**4a-n**).

General procedure for Conventional synthesis of 3-(4-chloro-2-hydroxyphenyl)-2-(substituted)thiazolidin-4-one (4a-n), Method B.

An equimolar amounts of substituted aldehydes (**1a-n**) (1 mmol), 2-amino-5-chlorophenol (**2**) (1 mmol), thioglycolic acid (**3**) (1 mmol) were added in a 100 mL round bottom flask and heating with stirring at reflux condition for 2-3 h. The completion of the reaction progress was monitored by using TLC (5 % Ethyl acetate: n-hexane). The product obtained was poured into crushed ice, filtered and extracted with petroleum ether and ethyl acetate (2:8), (3×15 mL). The combined solvent extracts were concentrated in vacuo. The compounds were recrystallized from ethanol to give pure product (**4a-n**).

*3-(4-chloro-2-hydroxyphenyl)-2-phenylthiazolidin-4-one (**4a**)*

Yellow solid, Yield: 97%, mp 88–90 ºC; ES-MS m/z: 306 (M+1); IR (νmax/ cm^{-1}): 3380 (OH), 3057 (Ar-H stretch.), 2936 (aliphatic CH stretch.), 1683 (C=O); ^{1}H NMR: δppm = 4.46–4.57 (d, 1H, CH_2), 4.60–4.69 (d, 1H, CH_2), 5.72 (s, 1H, OH), 6.20 (s, 1H, S–CH–N), 7.01–7.20 (m, 3H, Ar-H), 7.23–7.38 (m, 5H, Ar-H); ^{13}C NMR: δppm = 33.2, 73.3, 116.8, 121.8, 124.2, 126.3, 127.2, 128.8, 129.1, 132.8, 139.4, 151.2, 171.9.; Anal. Calcd for $C_{15}H_{12}ClNO_2S$ (305.03): C, 58.92; H, 3.96; Cl, 11.59; N, 4.58; S, 10.49. Found: C, 58.90; H, 3.93; Cl, 11.57; N, 4.56; S, 10.47.

*3-(4-chloro-2-hydroxyphenyl)-2-(4-nitrophenyl)thiazolidin-4-one (**4b**)*

Yellow solid, Yield: 97%, mp 190–192 ºC; ES-MS m/z: 350; IR (νmax/ cm^{-1}): 3383 (OH), 3052 (Ar-H stretch.), 2939 (aliphatic CH stretch.), 1681 (C=O), 1516, 1481 (NO_2); ^{1}H NMR: δppm = 4.47–4.57 (d, 1H, CH_2), 4.58–4.69 (d, 1H, CH_2), 5.30 (s, 1H, OH), 6.61 (s, 1H, S–CH–N), 7.04–7.24 (m, 3H, Ar-H), 7.40–7.58 (d, 2H, Ar-H), 8.13–8.28 (d, 2H, Ar-H); ^{13}C NMR: δppm = 33.1, 73.5, 116.1, 121.3, 124.9, 126.8, 127.1, 128.2, 129.4,132.2, 132.4,152.2, 172.5.; Anal. Calcd for $C_{15}H_{11}ClN_2O_4S$ (350.01): C, 51.36; H, 3.16; Cl, 10.11; N, 7.99; S, 9.14. Found: C, 51.33; H, 3.14; Cl, 10.08; N, 7.96; S, 9.12.

*3-(4-chloro-2-hydroxyphenyl)-2-(2,4-dichlorophenyl)thiazolidin-4-one (**4c**)*

Yellow solid, Yield: 98%, mp 131–133 ºC; ES-MS m/z: 374; IR (νmax/ cm^{-1}): 3393 (OH), 3051 (Ar-H stretch.), 2931 (aliphatic CH stretch.), 1685 (C=O); ^{1}H NMR: δppm = 4.46–4.56 (d, 1H, CH_2), 4.57–4.68 (d, 1H, CH_2), 5.32 (s, 1H, OH), 6.41 (s, 1H, S–CH–N), 7.04–7.24 (m, 3H, Ar-H), 7.27–7.35 (d, 2H, Ar-H), 7.63 (s, 1H, Ar-H); ^{13}C NMR: δppm = 33.6, 67.3, 100.8, 116.9, 121.8, 124.1, 126.8, 128.5, 129.9, 130.1, 131.4, 132.4, 135.4, 151.5, 172.1.; Anal. Calcd for $C_{15}H_{10}Cl_3NO_2S$ (374.07): C, 48.09; H, 2.69; Cl, 28.39; N, 3.74; S, 8.56. Found: C, 48.05; H, 2.66; Cl, 28.37; N, 3.72; S, 8.53.

*3-(4-chloro-2-hydroxyphenyl)-2-(4-chlorophenyl)thiazolidin-4-one (**4d**)*

Yellow solid, Yield: 98%, mp 118–120 ºC; ES-MS m/z: 340; IR (νmax/ cm^{-1}): 3387 (OH), 3045 (Ar-H stretch.), 2935 (aliphatic CH stretch.), 1689 (C=O); ^{1}H NMR: δppm = 4.04–4.15 (d, 1H, CH_2), 4.18–4.28 (d, 1H, CH_2), 5.31 (s, 1H, OH), 6.45 (s, 1H, S–CH–N), 7.05–7.27 (m, 3H, Ar-H), 7.27–7.37 (d, 2H, Ar-H), 7.38–7.48 (d, 2H, Ar-H); ^{13}C NMR: δppm = 33.5, 72.3, 116.9, 124.4, 126.8, 128.7, 130.1, 131.4, 132.7, 132.9, 137.7, 151.3, 172.4.; Anal. Calcd for $C_{15}H_{11}Cl_2NO_2S$ (340.22): C, 52.95; H, 3.26; Cl, 20.84; N, 4.12; S, 9.42. Found: C, 52.93; H, 3.23; Cl, 20.82; N, 4.10; S, 9.40.

*3-(4-chloro-2-hydroxyphenyl)-2-(2-chlorophenyl)thiazolidin-4-one (**4e**)*

Yellow solid, Yield: 97%, mp 127–129 ºC; ES-MS m/z: 340; IR (νmax/ cm^{-1}): 3384 (OH), 3046 (Ar-H stretch.), 2937 (aliphatic CH stretch.), 1681 (C=O); ^{1}H NMR: δppm = 3.99–4.09 (d, 1H, CH_2), 4.13–4.23 (d, 1H, CH_2), 5.30 (s, 1H, OH), 6.45 (s, 1H, S–CH–N), 7.02–7.23 (m, 3H, Ar-H), 7.24–7.37 (m, 4H, Ar-H); ^{13}C NMR: δppm = 33.3, 68.3, 102.3, 116.8, 121.4, 124.3, 126.6, 128.2, 130.5, 131.4, 132.1, 132.3, 137.7, 151.1, 172.1.; Anal. Calcd for $C_{15}H_{11}Cl_2NO_2S$

(340.22): C, 52.95; H, 3.26; Cl, 20.84; N, 4.12; O, 9.41; S, 9.42. Found: C, 52.92; H, 3.23; Cl, 20.81; N, 4.10; S, 9.41.

*3-(4-chloro-2-hydroxyphenyl)-2-(4-methoxyphenyl)thiazolidin-4-one (**4f**)*

Yellow solid, Yield: 98%, mp 48–50 ºC; ES-MS m/z: 335; IR (νmax/ cm^{-1}): 3383 (OH), 3044 (Ar-H stretch.), 2939 (aliphatic CH stretch.), 1686 (C=O); ^{1}H NMR: δppm = 3.75 (s, 3H, CH_3), 3.89–3.98 (d, 1H, CH_2), 4.01–4.12 (d, 1H, CH_2), 5.29 (s, 1H, OH), 6.44 (s, 1H, S–CH–N), 6.81–6.97 (d, 2H, Ar-H), 7.02–7.24 (m, 3H, Ar-H), 7.84–7.90 (d, 2H, Ar-H); ^{13}C NMR: δppm = 33.5, 55.8, 72.3, 102.3, 116.8, 121.4, 124.3, 126.6, 128.2, 130.5, 131.4, 132.3, 137.7, 151.1, 159.1, 171.1.; Anal. Calcd for $C_{16}H_{14}ClNO_3S$ (335.81): C, 57.23; H, 4.20; Cl, 10.56; N, 4.17; S, 9.55. Found: C, 57.20; H, 4.18; Cl, 10.54; N, 4.13; S, 9.52.

*3-(4-chloro-2-hydroxyphenyl)-2-(2,4-dimethoxyphenyl)thiazolidin-4-one (**4g**)*

Yellow solid, Yield: 96%, mp 46–48 ºC; ES-MS m/z: 365; IR (νmax/ cm^{-1}): 3385 (OH), 3039 (Ar-H stretch.), 2935 (aliphatic CH stretch.), 1691 (C=O); ^{1}H NMR: δppm = 3.75 (s, 6H, CH_3), 3.98–4.08 (d, 1H, CH_2), 4.10–4.19 (d, 1H, CH_2), 5.32 (s, 1H, OH), 6.47 (s, 1H, S–CH–N), 6.57 (s, 1H, Ar-H), 7.02–7.24 (m, 3H, Ar-H), 7.24–7.32 (d, 2H, Ar-H); ^{13}C NMR: δppm = 33.5, 55.9, 67.3, 100.3, 116.9, 121.4, 124.3, 126.6, 128.2, 130.5, 131.4, 132.3, 137.7, 151.2, 159.3, 171.1.; Anal. Calcd for $C_{17}H_{16}ClNO_4S$ (365.83): C, 55.81; H, 4.41; Cl, 9.69; N, 3.83; S, 8.76. Found: C, 55.83; H, 4.42; Cl, 9.65; N, 3.81; S, 8.74.

*3-(4-chloro-2-hydroxyphenyl)-2-(4-fluorophenyl)thiazolidin-4-one (**4h**)*

Yellow solid, Yield: 96%, mp 126–128 ºC; ES-MS m/z: 323; IR (νmax/ cm^{-1}): 3382 (OH), 3044 (Ar-H stretch.), 2931 (aliphatic CH stretch.), 1683 (C=O); ^{1}H NMR: δppm = 3.96–4.04 (d, 1H, CH_2), 4.08–4.16 (d, 1H, CH_2), 5.34 (s, 1H, OH), 6.46 (s, 1H, S–CH–N), 7.05–7.20 (m, 3H, Ar-H), 7.22–7.32 (d, 2H, Ar-H), 7.32–7.41 (d, 2H, Ar-H); ^{13}C NMR: δppm = 33.5, 71.3, 116.9, 124.2, 126.3, 128.7, 130.4, 131.1, 132.7, 132.6, 137.7, 151.7, 172.4.; Anal. Calcd for $C_{15}H_{11}ClFNO_2S$ (323.03): C, 55.64; H, 3.42; Cl, 10.95; F, 5.87; N, 4.33; S, 9.90. Found: C, 55.62; H, 3.40; Cl, 10.92; F, 5.84; N, 4.30; S, 9.86.

*3-(4-chloro-2-hydroxyphenyl)-2-(3-fluorophenyl)thiazolidin-4-one (**4i**)*

Yellow solid, Yield: 97%, mp 138–140 ºC; ES-MS m/z: 323; IR (νmax/ cm^{-1}): 3388 (OH), 3039 (Ar-H stretch.), 2934 (aliphatic CH stretch.), 1687 (C=O); ^{1}H NMR: δppm = 3.97–4.06 (d,

1H, CH_2), 4.10–4.18 (d, 1H, CH_2), 5.30 (s, 1H, OH), 6.42 (s, 1H, S–CH–N), 6.77 (s, 1H, Ar-H), 7.06–7.21 (m, 3H, Ar-H), 7.22–7.33 (m, 3H, Ar-H); ^{13}C NMR: δppm = 33.5, 72.3, 113.2, 116.9, 124.2, 126.3, 128.7, 130.4, 131.1, 132.7, 132.6, 137.7, 151.7, 162.3, 171.4.; Anal. Calcd for $C_{15}H_{11}ClFNO_2S$ (323.03): C, 55.64; H, 3.42; Cl, 10.95; F, 5.87; N, 4.33; S, 9.90. Found: C, 55.61; H, 3.40; Cl, 10.93; F, 5.87; N, 4.31; S, 9.92.

*3-(4-chloro-2-hydroxyphenyl)-2-(thiophen-2-yl)thiazolidin-4-one (**4j**)*

Yellow solid, Yield: 96%, mp 86–88 ºC; ES-MS m/z: 311; IR (νmax/ cm^{-1}): 3389 (OH), 3050 (Ar-H stretch.), 2936 (aliphatic CH stretch.), 1691 (C=O); ^{1}H NMR: δppm = 3.95–4.04 (d, 1H, CH_2), 4.10–4.19 (d, 1H, CH_2), 5.21 (s, 1H, OH), 6.30 (s, 1H, S–CH–N), 6.87–6.97 (m, 2H, Ar-H), 7.06–7.21 (m, 3H, Ar-H), 7.40–7.51 (m, 1H, Ar-H); ^{13}C NMR: δppm = 33.5, 64.3, 116.9, 124.4, 125.3, 126.7, 127.2, 130.4, 131.1, 132.7, 139.7, 151.7, 171.4.; Anal. Calcd for $C_{13}H_{10}ClNO_2S_2$ (311.81): C, 50.08; H, 3.23; Cl, 11.37; N, 4.49; S, 20.57. Found: C, 50.06; H, 3.20; Cl, 11.34; N, 4.45; S, 20.53.

*3-(4-chloro-2-hydroxyphenyl)-2-(pyridin-2-yl)thiazolidin-4-one (**4k**)*

Yellow solid, Yield: 98%, mp 106–108 ºC; ES-MS m/z: 306; IR (νmax/cm^{-1}): 3394 (OH), 3059 (Ar-H stretch.), 2937 (aliphatic CH stretch.), 1685 (C=O); ^{1}H NMR: δppm = 3.91–3.99 (d, 1H, CH_2), 4.10–4.18 (d, 1H, CH_2), 5.38 (s, 1H, OH), 6.11 (s, 1H, S–CH–N), 7.02–7.20 (m, 3H, Ar-H), 7.33–7.48 (m, 4H, Ar-H); ^{13}C NMR: δppm = 33.2, 73.3, 116.8, 121.8, 124.2, 126.3, 127.2, 128.8, 132.8, 136.4, 148.3, 151.1, 158.6, 171.9.; Anal. Calcd for $C_{14}H_{11}ClN_2O_2S$ (306.07): C, 54.81; H, 3.61; Cl, 11.56; N, 9.13; S, 10.45. Found: C, 54.78; H, 3.58; Cl, 11.54; N, 9.11; S, 10.42.

*3-(4-chloro-2-hydroxyphenyl)-2-(4-hydroxyphenyl)thiazolidin-4-one (**4l**)*

Yellow solid, Yield: 98%, mp 42–44 ºC; ES-MS m/z: 321; IR (νmax/ cm^{-1}): 3389 (OH), 3052 (Ar-H stretch.), 2932 (aliphatic CH stretch.), 1681 (C=O); ^{1}H NMR: δppm = 3.93–4.02 (d, 1H, CH_2), 4.11–4.21 (d, 1H, CH_2), 5.35 (s, 2H, OH), 6.60 (s, 1H, S–CH–N), 6.63–6.78 (d, 2H, Ar-H), 7.01–7.20 (m, 3H, Ar-H), 7.73–7.88 (d, 2H, Ar-H); ^{13}C NMR: δppm = 33.2, 72.3, 115.8, 116.8, 124.2, 126.3, 127.2, 130.2, 131.8, 132.4, 151.2, 156.8, 171.9.; Anal. Calcd for $C_{15}H_{12}ClNO_3S$ (321.78): C, 55.99; H, 3.76; Cl, 11.02; N, 4.35; S, 9.96. Found: C, 55.95; H, 3.73; Cl, 11.01; N, 4.32; S, 9.94.

*3-(4-chloro-2-hydroxyphenyl)-2-(4-methylthiazol-5-yl)thiazolidin-4-one (**4m**)*

Yellow solid, Yield: 98%, mp 47–49 ºC; ES-MS m/z: 326; IR (νmax/ cm^{-1}): 3388 (OH), 3051 (Ar-H stretch.), 2937 (aliphatic CH stretch.), 1692 (C=O); ^{1}H NMR: δppm = 2.45 (s, 3H, CH_3), 3.80–3.91 (d, 1H, CH_2), 4.01–4.11 (d, 1H, CH_2), 5.23 (s, 1H, OH), 5.91 (s, 1H, S–CH–N), 7.06–7.21 (m, 3H, Ar-H), 8.67 (s, 1H, Ar-H); ^{13}C NMR: δppm = 14.2, 33.5, 61.3, 116.9, 121.5, 124.4, 126.7, 128.2, 132.7, 148.9, 150.3, 151.7, 171.4.; Anal. Calcd for $C_{13}H_{11}ClN_2O_2S_2$ (326.02): C, 47.78; H, 3.39; Cl, 10.85; N, 8.57; S, 19.62. Found: C, 47.75; H, 3.36; Cl, 10.82; N, 8.57; S, 19.62.

*4-(3-(4-chloro-2-hydroxyphenyl)-4-oxothiazolidin-2-yl)benzonitrile (**4n**)*

Yellow solid, Yield: 97%, mp 141–143 ºC; ES-MS m/z: 330; IR (νmax/ cm^{-1}): 3335 (OH), 3059 (Ar-H stretch.), 2931 (aliphatic CH stretch.), 2227 (CN), 1692 (C=O); ^{1}H NMR: δppm = 3.80–3.91 (d, 1H, CH_2), 4.11–4.22 (d, 1H, CH_2), 5.35 (s, 1H, OH), 6.44 (s, 1H, S–CH–N), 7.21–7.29 (m, 3H, Ar-H), 7.40–7.49 (d, 2H, Ar-H), 7.51–7.60 (m, 2H, Ar-H); ^{13}C NMR: δppm = 33.2, 72.8, 111.3, 116.8, 118.8, 124.2, 126.3, 127.2, 130.2, 132.1, 132.6, 151.2, 156.8, 171.9.; Anal. Calcd for $C_{16}H_{11}ClN_2O_2S$ (330.02): C, 58.09; H, 3.35; Cl, 10.72; N, 8.47; S, 9.69. Found: C, 58.05; H, 3.33; Cl, 10.70; N, 8.43; S, 9.65.

PHARMACOLOGY

Antimicrobial evaluation

All the synthesized compounds (**4a-n**) were screened for their in vitro antimicrobial activity against two gram positive bacteria; *Bacillus subtilis* (NCIM-2063) and *Staphylococcus aureus* (NCIM-2901), two gram negative bacteria; *Escherichia coli* (NCIM-2256), *Salmonella typhimurium* (NCIM-3471) and four fungal strains; *Candida albicans* (NCIM-3471), *Aspergillus flavus* (NCIM-539) *Aspergillus niger* (NCIM-1196) and *Cryptococcus neoformans* (NCIM-3378). In order to investigate the antimicrobial properties of the compounds, Minimum Inhibitory Concentration (MIC), Minimum Bactericidal Concentration (MBC) and Minimum Fungicidal Concentration (MFC) were found out by modified macrodilution technique.[23-27] For the Bacterial strains MIC determinations were performed by a serial macrodilution technique using 96-well microtiter plate reader. Investigated compounds were prepared in saline (0.8%

NaCl) solution, containing 5% Dimethyl sulfoxide (DMSO) for dissolution of compounds. All microbial strains were incubated with different concentration of each compound in 96-well microtiter plate for 20 h at 37 ºC on Rotary shaker (160 rpm). After incubation the lowest concentrations value without growth were defined as MICs. For the Fungal strains agar dilution technique, on Potato Dextros Agar (PDA) Medium, were used for MIC determination. The MBC and MFC of compounds were determined by serial subcultivation after inoculated for 72 h with tested compounds dissolved in saline containing 5% DMSO. The lowest concentration with no visible growth was defined as MBC/MFC indicating 99.5% killing of the original inoculum. All the experiments performed in triplicates and mean reading is taken as final reading. 5% DMSO was used as a negative control along with Ciprofloxacin and Ampicillin as standard antibacterial drug, and Fluconazole and Miconazole as standard antifungal drug (**Table 2**). Thiazolidin-4-one based compounds were synthesized by microwave irradiation as well as conventional heating.

From the antimicrobial activity data (**Table 2**) it is clearly observed that many of the synthesized compounds were shows prominent antimicrobial activity. Some compounds were narrow spectrum, active against only one fungal or bacterial strain while some of them were found to be broad spectrum active against both fungal and bacterial strains. Among the series compounds (**4f**, **4g**, **4l** and **4m**) were found to broad spectrum molecule as they all were active against all tested bacteria strains and, fungus *A. flavus* and *C. albicans*. They are also most active molecules among the series with (**4g**) and (**4m**) were more potent than standard antifungal drugs Fluconazole and Miconazole, against *C. albicans* and *A. flavus* respectively, having MIC value 3.5 µg/mL each. The compound (**4l**) was more potent than standard drugs Ciprofloxacin and Ampicillin against *S. aureus* with MIC 5.5 µg/mL. MIC value of this group of molecules for remaining bacterial and fungal strains are in range of 15 to 35 µg/mL, except for *A. niger*. The fungal strain, *A. niger* shows higher level of resistance to nearly all synthesized compounds and in most of the cases this resistance was reported up to MIC of 100 µg/mL. In the series, on the other hand, some narrow spectrum molecules including compounds **(4a, 4d, 4e, 4h, 4j** and **4n)** were also obtained which are active against selective strains. Among them (**4a**) was specifically active towards *S. aureus* (MIC 35 µg/mL), (**4d**) was active towards against Gram positive bacteria (MIC 20 to 25 µg/mL), compound (**4e**) active against Gram positive bacteria (MIC 20 to

35 µg/mL), and *A. flavus* (MIC 35 µg/mL), compounds (**4h**) and (**4n**) active against *S. aureus* (MIC 25 and 35 µg/mL respectively). The compound (**4j**) has been active against *A. flavus* (MIC 25 µg/mL) with *B. subtilis* (MIC 35 µg/mL). The remaining compounds (**4b, 4c, 4i** and **4k**) were having very high MIC values and therefore these are considered as inactive compounds as per as antimicrobial activity concerned.

The structure activity relationship of the series can be explained as,

The results of the antimicrobial screening demonstrated some definite and interesting facts about the structural activity relationship (SAR) of synthesized molecules. In majority of cases, dependence of activity profile on structural modifications of the molecule is clear and fascinating. Strain specificity and variation in activity profile of molecules are also directly attributed with the structural variations in molecules. The important highlights of structure-activity relationship are.

- *Effect of substituent on phenyl ring:* The presence of phenyl ring (**4a**) at C2 position on the thiazolidinone nucleus, without any substitution at *para* and *ortho* position, makes the molecule specifically active towards bacterium *S. aureus.*
- *Effect of nitro group:* The electron withdrawing nitro group substitution on phenyl ring at the *para* position (**4b**) make the molecule inactivate. This may due to its electron withdrawing effect on phenyl ring.
- *Effect of chloro group:* The chloro group have a crucial role in determined the activity of molecule. This group affect the activity of molecule by its number as well as its position to phenyl ring. Substitution of chloro group at *para* positions on phenyl ring (**4d**) make the molecule specifically active towards Gram positive bacteria *B. subtilis* and *S. aureus.* On the other hand, substitution of chloro group at ortho positions (**4e**) makes the molecule active against Gram positive bacteria as well as against *A. flavus.* This clearly indicates that change in position of chloro group from *para* to *ortho* on phenyl ring preserve its effects against Gram positive bacteria and a make molecule additionally active against *A. flavus*. These changes of *para* to *ortho* are favorable regarding the development of broad spectrum molecule active against bacteria and fungi. However the substitution of two chloro group at *ortho* and *para* position (**4c**) gives inactive molecule,

not even active against Gram positive bacteria. This may be due to larger size of molecule or increase in total electronegative effect on phenyl ring caused by addition of extra chloro group, in either way hampering the binding of molecule to its target site and make it inactive in nature.

- *Effect of methoxy group:* The substitution of electron donating methoxy group at *ortho* (**4f**) and *ortho*, *para* position (**4g**) on phenyl ring gives the broad spectrum properties of molecules, which is active against all bacterial and fungal strains tested, except *A. niger*. This observations clearly shows that, for the development broad spectrum antimicrobial molecule, electron donating group is better than electron withdrawing group (nitro group which make molecule inactive and chloro group make molecule active against Gram positive bacteria and *A. flavus*) on phenyl ring. Further, the MIC data shows that (**4g**) is more potent than (**4f**), indicates that addition of extra methoxy group at para position somehow increases the activity of molecule.
- *Effect of fluoro group***:** Substitution of fluoro group at *para* positions (**4h**) make the molecule narrow spectrum, active only against *S. aureus*, while substitution at *meta* position (**4i**) make the molecule inactive. This variation in activity may be attributed to the change in position of fluoro group, from *para* to *meta* on phenyl ring.
- *Effect of heterocyclic ring:* The presence of thiophenyl moiety instead of phenyl ring at C2 position on the thiazolidinone nucleus (**4j**) give the molecule specificity against *B. subtilis* and *A. flavus*. However substitution of pyridinyl moiety instead of phenyl rings at C2 position on the thiazolidinone nucleus (**4k**) resulted in formation of inactive molecule and therefore this heterocyclic ring is not suitable to develop antimicrobial compounds. On the other hand the substitution of 4-methylthiazole moiety (**4m)** make the molecule broad spectrum, and its activity is intermediate between the (**4l**) and (**4f**) i.e. lower than (**4l**) but higher than (**4f**).
- *Effect of hydroxyl group:* Substitution of electron donating hydroxyl group attached to phenyl ring at *para* position (**4l**) gives the most potent and broad spectrum molecule of the series. The compound (**4l**) is more active than (**4f**) and (**4g**), indicates that hydroxyl

group at *para* position is better option than methoxy group at ortho (**4f**) or *ortho* and *para* (**4g**) position, as per as antimicrobial potential molecules.

- *Effect of nitrile groups***:** The electron withdrawing nitrile group substitution on phenyl ring at the *para* position (**4n**) render the molecule narrow spectrum, active only against *S. aureus*.

CONCLUSION

The compounds were synthesized by both conventional as well as microwave irradiation techniques with reduce reaction time and increase the yield of product. Among the synthesized compounds (**4f**, **4g**, **4l** and **4m**) were found to be broad spectrum molecule as they all were active against all tested bacteria strains and fungus *A. flavus* and *C. albicans*. Important finding is that the compounds (**4g**) and (**4m**) more potent than standard antifungal drugs. The compound (**4l**) was more potent than standard drugs Ciprofloxacin and Ampicillin against *S. aureus*. SAR observations confirms that, electron donating group, such as methoxy, is suitable over electron withdrawing group, including nitro and chloro groups, on phenyl ring for the development of broad spectrum antimicrobial compounds. For all active molecules, values for MBC and MFC are higher than corresponding MIC value in all cases. This may be due to the 'static' and not the cidal, mode of action of molecules on all strains. Thus the outstanding antimicrobial properties of this new class of substances are diverse and vary considerably with antimicrobial strains.

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Table 1: Synthesis of 3-(4-chloro-2-hydroxyphenyl)-2-(substituted) thiazolidin-4-one (**4a-n**)[a].

Sr. No.	Aldehydes	Time		Yield[b] (%)		Melting point (ºC)
		MW[c] (min)	Con.[d] (h)	MW[c]	Con.[d]	
4a	Benzaldehyde	7	2	97	92	88-90
4b	4-nitrobenzaldehyde	7	2	97	90	190-192
4c	2,4-dichlorobenzaldehyde	8	2	98	91	131-133
4d	4-chlorobenzaldehyde	8	3	98	91	118-120
4e	2-chlorobenzaldehyde	8	3	97	92	127-129
4f	4-methoxybenzaldehyde	7	3	98	92	48-50
4g	2,4-dimethoxybenzaldehyde	7	3	96	90	46-48
4h	4-fluorobenzaldehyde	7	3	96	92	126-128
4i	3-fluorobenzaldehyde	7	2	97	90	138-140
4j	thiophene-2-carbaldehyde	9	2	96	92	86-88
4k	2-Pyridinecarbaldehyde	7	2	98	92	106-108
4l	4-hydroxybenzaldehyde	7	2	98	92	42-44
4m	4-methylthiazole-5-carbaldehyde	8	2	98	90	47-49
4n	4-formylbenzonitrile	7	3	97	90	141-143

[a]Reaction condition (**4a-n**)

Method A: Microwave-assisted synthesis: 120 ºC, 7-9 min.

Method B: Conventional synthesis: reflux 2-3 h.

[b]Isolated yields.

[c]Microwave

[d]Conventional

B.s.- *Bacillus subtilis* (NCIM-2063); ***S.a.***- *Staphylococcus aureus* (NCIM-2901)*;* ***E.c.***- *Escherichia coli* (NCIM-2256); ***S. t.***- *Salmonella typhimurium* (NCIM-3471);***C.a.***- *Candida albicans* (NCIM-3471); ***A.f.***- *Aspergillus flavus* (NCIM-539); ***A.n.***- *Aspergillus niger* (NCIM-1196); ***C. n.***- *Cryptococcus neoformans* (NCIM- 3378).
(-) denotes not tested.

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Compound		MIC, MBC and MFC Values (µg/mL)[a]							
		B.s.	***S.a.***	***E.c.***	***S. t.***	***C.a.***	***A.f.***	***A.n.***	***C. n.***
4a	MIC	66	35	60	50	60	80	90	70
	MBC/MFC	80	45	120	115	110	110	125	125
4b	MIC	100	80	90	80	95	75	100	90
	MBC/MFC	140	140	155	135	155	135	160	135
4c	MIC	80	90	70	75	90	85	70	100
	MBC/MFC	160	160	150	155	160	140	145	150
4d	MIC	25	20	25	25	70	90	65	95
	MBC/MFC	45	45	165	155	160	155	165	160
4e	MIC	20	35	80	65	55	35	100	90
	MBC/MFC	40	55	140	135	140	50	155	135
4f	MIC	30	30	35	25	15	15	80	65
	MBC/MFC	40	40	45	110	20	20	150	155
4g	MIC	30	15	30	35	**3.5**	10	65	70
	MBC/MFC	45	25	50	45	17.5	15	120	120
4h	MIC	55	25	70	60	65	90	50	90
	MBC/MFC	150	45	145	140	150	140	140	145
4i	MIC	100	80	70	90	95	90	100	85
	MBC/MFC	155	160	145	155	165	140	165	140
4j	MIC	35	60	85	70	100	25	70	95
	MBC/MFC	55	150	160	155	160	45	155	160
4k	MIC	85	60	90	85	55	100	80	75
	MBC/MFC	165	155	165	150	155	165	155	150
4l	MIC	15	**5.5**	20	25	25	20	55	60
	MBC/MFC	25	20	35	45	40	35	115	115
4m	MIC	30	15	15	20	30	**3.5**	80	55
	MBC/MFC	55	20	20	40	45	20	135	95
4n	MIC	100	35	90	55	90	60	100	85
	MBC/MFC	140	145	120	115	140	115	145	125
Ciprofloxacin	MIC	**6.0**	**6.0**	**7.0**	**7.0**	-	-	-	-
	MBC	**13.5**	**13.5**	**8.5**	**8.5**	-	-	-	-
Ampicillin	MIC	**11.5**	**11.5**	**11.5**	**11.5**	-	-	-	-
	MBC	**16.5**	**16.5**	**16.5**	**16.5**	-	-	-	-
Fluconazole	MIC	-	-	-	-	**11.0**	**6.0**	**6.0**	**6.0**
	MFC	-	-	-	-	**21.5**	**15.5**	**15.5**	**15.5**
Miconazole	MIC	-	-	-	-	**4.25**	**4.25**	**4.25**	**4.25**
	MFC	-	-	-	-	**11.5**	**11.5**	**11.5**	**11.5**

[a]All values are the average of three readings and expressed in µg/mL.

Table 2 Antimicrobial activity of the synthesized compounds (**4a-n**).

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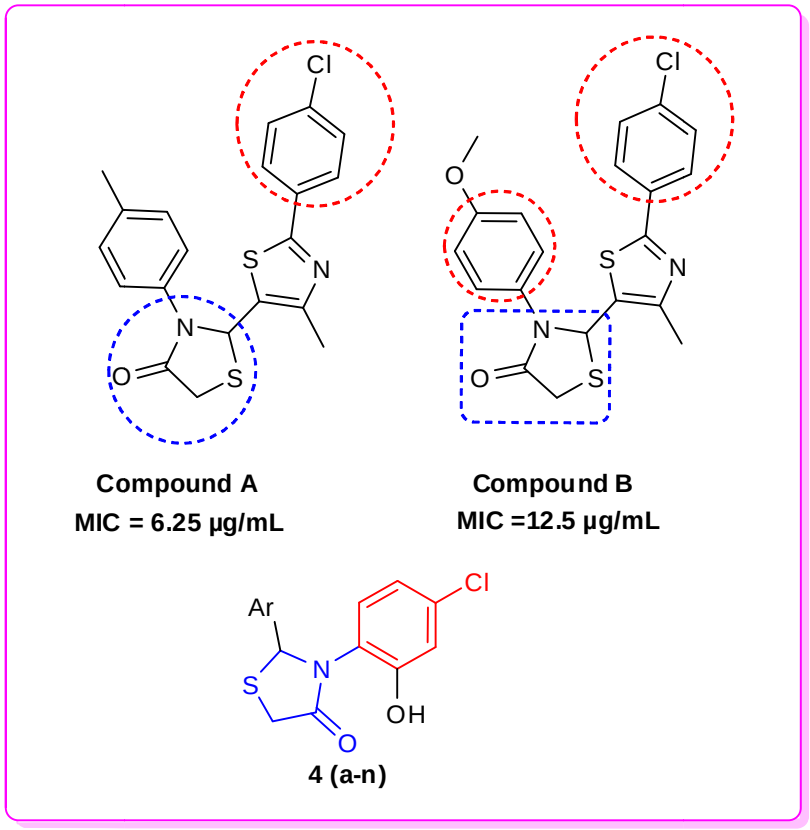
Fig. 1. Previously reported antimicrobial agents and synthesized compounds.



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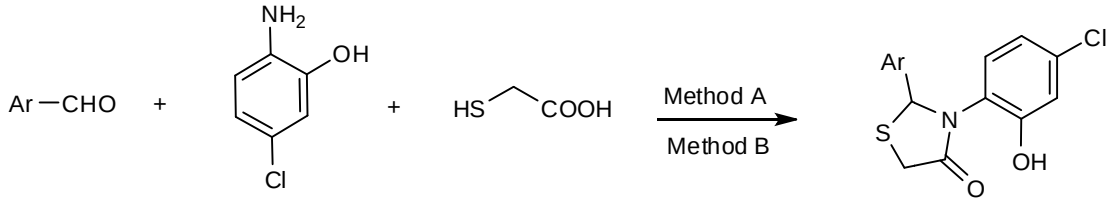
Scheme 1. Synthesis of 3-(4-chloro-2-hydroxyphenyl)-2-(substituted) thiazolidin-4-one (**4a-n**).



1 (a-n) 2 3 4 (a-n)

Ar = 1a = 4a = phenyl
1b = 4b = 4-nitrophenyl
1c = 4c = 2,4-dichlorophenyl
1d = 4d = 4-chlorophenyl
1e = 4e = 2-chlorophenyl
1f = 4f = 4-methylphenyl
1g = 4g = 2,4-dimethoxyphenyl
1h = 4h = 4-fluorophenyl
1i = 4i = 3-fluorophenyl
1j = 4j = thiophen-2-yl
1k = 4k = pyridin-2-yl
1l = 4l = 4-hydroxybenzyl
1m= 4m = 4-methylthiazol-5-yl
1n = 4n = benzonitrile

Method A: Microwave-assisted synthesis: 120 ºC, 7-9 min.

Method B: Conventional synthesis: reflux 2-3 h.

Scheme 2. Plausible reaction mechanism for the synthesis of thiazolidin-4-one