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SYNTHESIS OF NEW THIAZOLIDINE-2,4-DIONE DERIVATIVES AND THEIR ANTIMICROBIAL AND ANTITUBERCULAR ACTIVITY

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ABSTRACT

New 1,3-thiazolidine-2,4-dione (TZD) derivatives **16-29** have been prepared by Knoevenagel condensation reaction between TZD and aromatic aldehydes followed by condensation with 3,4-dichloro benzoyl chloride. The structures of the newly synthesized compounds were assigned on the basis of elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectral data. All the synthesized compounds were tested for antibacterial activity against Gram-positive cocci and Gram-negative rods, antifungal activity and antitubercular activity. Moderate to good activity results were found for the newly synthesized compounds.

Key Words: 1,3-thiazolidine-2,4-dione, Knoevenagel condensation, antibacterial, antifungal, antitubercular activity

1. INTRODUCTION

One of the main objectives of organic and medicinal chemistry is to design, synthesize and produce molecules possessing value as human therapeutic agents. Compounds containing heterocyclic ring systems are of great importance receiving special attention as they belong to a class of compounds with proven utility in medicinal chemistry. Thiazolidine-2,4-dione (TZD) is a heterocyclic ring system with multiple applications. Thiazolidine-2,4-dione inhibits corrosion of mild steels in acidic solution. These are also used in analytical chemistry as highly sensitive reagents for heavy metals and as a brighter in electroplating industry. In 1982 a number of TZDs were intensively studied for their anti-hyperglycaemic property. The first representative of this class was ciglitazone, whereas other derivatives like englitazone, pioglitazone and troglitazone followed soon. The thiazolidine-2,4-dione nucleus has been reported for being responsible for majority of their pharmacological actions. Henceforth, thiazolidine-2,4-dione derivatives have been studied extensively and found to have diverse chemical reactivities and broad spectrum of biological activities (Jain, 2013).

Thiazolidinediones (TZD) are biologically active compounds having five membered rings, with two heteroatoms. Thiazolidinediones displayed a broad spectrum of biological activities including antimicrobial (Gouveia, 2009; Tuncbilek and Altanlar, 2006), antidiabetic (Murugan, 2009; Pattan, 2005), antiobesity (Bhattarai, 2009), anti-inflammatory (Youssef, 2010), antioxidant (Bozdag-Dundar, 2009), antiproliferative (Patil, 2010), antitumor (Shimazaki, 2008), etc.

Currently, the antibiotic era is threatened by the convergence of three adverse circumstances: high levels of antibiotic resistance among important pathogens, an uneven supply of novel classes of antibiotics, and a dramatic reduction in the number of pharmaceutical companies engaged in the discovery and development of anti-infective agents (Wenzel, 2004). As a result, multidrug-resistant, and therefore difficult-to-treat, infections continue to occur and are clearly increasing in some areas. New antibiotics can help stave off the catastrophe. But since 1987, no major antibiotic has been discovered. In this regard, it is important to develop new and safe nuclei to combat with multidrug-resistant bacterial and fungal infections. Substantial investment and research in the field of anti-infectives are now desperately needed if a public health crisis is to be averted. Looking towards this turmoil of situation in the field of antibiotics, we are reporting herewith synthesis and antibacterial, antifungal and antitubercular activity of new thiazolidinediones.

2. MATERIALS AND METHODS

2.1. General: Laboratory Chemicals were supplied by Rankem India Ltd. and Ficher Scientific Ltd. Melting points were determined by the open tube capillary method and are uncorrected. The purity of the compounds was determined by thin layer chromatography (TLC) plates (silica gel G) in the solvent system n-hexane: ethyl acetate (7.5:2.5). The spots were observed by exposure to iodine vapors or by UV light. The IR spectra were obtained on Thermo Scientific Nicolet iS10 FT-IR spectrometer (using KBr pellets). The ^{1}H-NMR & ^{13}C-NMR spectra were recorded on a Varian Gemini 200 spectrometer using TMS as an internal standard in DMSO-d_6. Elemental analyses of the newly

synthesized compounds were carried out on Carlo Erba 1108 analyzer**.**

2.2. Synthesis of (E)-5-(substitutedbenzylidene) thiazolidine-2,4-diones 2-15: These compounds were prepared according to previously reported procedure (fig.-1) (Scheme-1).

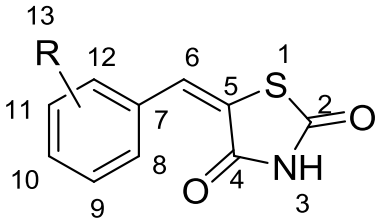

Fig.-1. (E)-5-(substitutedbenzylidene)thiazolidine-2,4-diones 2-15

2.3. Synthesis of (E)-5-substitutedbenzylidene-3-(3,4-dichlorobenzoyl) thiazolidine-2,4-diones 16-29: To a mixture of appropriate benzylidenes 2-15 (2 mmol) and pyridine (20 mL) was added dropwise 3,4-dichlorobenzoyl chloride (2.4 mmol) with stirring. The reaction was carried out for 3 h at room temperature with stirring and then heated for 4 h at 70 °C with stirring. When the mixture was cooled to room temperature, water (30 mL) was added. Then the mixture was neutralized with aqueous hydrochloric acid. The resultant solid was filtered off and washed three times with water. Product was obtained as a solid to give respective (E)-5-substitutedbenzylidene-3-(3,4-dichlorobenzoyl)thiazolidine-2,4-diones **16-29**. (Scheme-2)

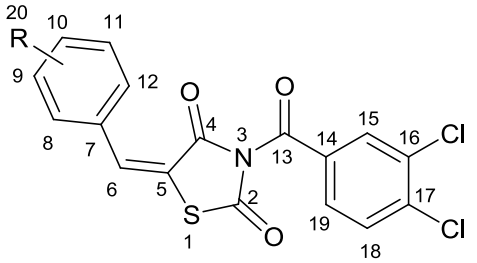

Fig.-2. Title compounds 16-29

2.3.1. (E) - 5- benzylidene - 3 - (3,4-dichlorobenzoyl) thiazolidine-2,4-dione 16: m.p. 241-242 °C, yield, 71 % ; IR (KBr) *v* cm^{-1}: 1756 and 1658 (>C=O str. of TZD), 1695 (>C=O str. of benzoyl chloride) 792 (C-S-C str.), 714 (C-Cl str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.02 (s, 1H, =CH), 7.24-8.11 (m, 8H, aromatic). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 171.6 (C_{13}), (>CO=), 169.5 (C_2), (>CO=), 168.6 (C_4), (>CO=), 144.7 (C_6), (=CH), 137.2 (C_{17}), 136.0 (C_7), 134.6 (C_{14}), 133.9 (C_{16}), 130.8 (C_{18}), 130.2 (C_{15}), 129.1 ($C_{9,11}$), 128.7 ($C_{8,12}$), 128.4 (C_{19}), 127.5 (C_{10}), 116.8 (C_5). Anal. calcd for $C_{17}H_9O_3NSCl_2$: C 53.98, H 2.40, N 3.70; found C 53.95, H 2.37, N 3.66.

2.3.2. (E) – 5 - (2-chlorobenzylidene) – 3 - (3,4-dichlorobenzoyl)thiazolidine-2,4-dione 17: m.p. 221-222 °C, yield, 60 % ; IR (KBr) *v* cm^{-1}: 1758 and 1655 (>C=O str. of TZD), 1698 (>C=O str. of benzoyl chloride) 790 (C-S-C str.), 719 (C-Cl str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.26 (s, 1H, =CH), 7.26-8.13 (m, 7H, aromatic). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 171.7 (C_{13}), (>CO=), 169.4 (C_2), (>CO=), 168.5 (C_4), (>CO=), 144.4 (C_6), (=CH), 137.1 (C_{17}), 134.6 (C_8), 134.0 (C_{14}), 133.6 (C_{16}), 133.1 (C_7), 130.9 (C_{18}), 130.3 (C_{15}), 129.6 (C_9), 128.5 (C_{19}), 127.9 (C_{10}), 127.3 (C_{12}), 126.2 (C_{11}), 116.7 (C_5). Anal. calcd for $C_{17}H_8O_3NSCl_3$: C 49.48, H 1.95, N 3.39; found C 49.45, H 1.93, N 3.38.

2.3.3. (E) – 5 - (4-chlorobenzylidene) – 3 - (3,4-dichlorobenzoyl)thiazolidine-2,4-dione 18: m.p. 250-252 °C, yield, 67 % ; IR (KBr) *v* cm^{-1}: 1757 and 1659 (>C=O str. of TZD), 1697 (>C=O str. of benzoyl chloride) 791 (C-S-C str.), 716 (C-Cl str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.03 (s, 1H, =CH), 7.40-8.21 (m, 7H, aromatic). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 171.2 (C_{13}), (>CO=), 169.1 (C_2), (>CO=), 168.4 (C_4), (>CO=), 144.1 (C_6), (=CH), 137.0 (C_{17}), 134.2 (C_{14}), 133.4 ($C_{10,16}$), 132.6 (C_7), 130.7 (C_{18}), 130.2 (C_{15}), 129.1 ($C_{8,12}$), 128.2 ($C_{9,11}$), 128.0 (C_{19}), 116.5 (C_5). Anal. calcd for $C_{17}H_8O_3NSCl_3$: C 49.48, H 1.95, N 3.39; found C 49.46, H 1.94, N 3.37.

2.3.4. (E) - 3 - (3,4-dichlorobenzoyl) -5- (4-fluorobenzylidene) thiazolidine-2,4-dione 19: m.p. 230-232 °C, yield, 70 % ; IR (KBr) *v* cm^{-1}: 1752 and 1662 (>C=O str. of TZD), 1702 (>C=O str. of benzoyl chloride) 798 (C-S-C str.), 715 (C-Cl str.), 678 (C-F str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.00 (s, 1H, =CH), 7.14-8.10 (m, 7H, aromatic). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 171.1 (C_{13}), (>CO=), 169.8 (C_2), (>CO=), 167.8 (C_4), (>CO=), 163.6 (C_{10}), 143.7 (C_6), (=CH), 137.3 (C_{17}), 134.4 (C_{14}), 133.2 (C_{16}), 132.4 ($C_{8,12}$), 132.0 (C_7), 131.1 (C_{18}), 130.2 (C_{15}), 128.1 (C_{19}), 116.2 (C_5), 112.6 ($C_{9,11}$). Anal. calcd for $C_{17}H_8O_3NSCl_2F$: C 51.53, H 2.04, N 3.54; found C 51.51, H 2.02, N 3.51.

2.3.5. (E) – 5 - (3-bromobenzylidene) – 3 - (3,4-dichlorobenzoyl) thiazolidine-2,4-dione 20: m.p. 258-259 °C, yield, 65 % ; IR (KBr) *v* cm^{-1}: 1750 and 1654 (>C=O str. of TZD), 1692 (>C=O str. of benzoyl chloride) 795 (C-S-C str.), 714 (C-Cl str.), 618 (C-Br str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.04 (s, 1H, =CH), 7.25-8.15 (m, 7H, aromatic). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 169.9 (C_{13}), (>CO=), 168.6 (C_2), (>CO=), 167.3 (C_4), (>CO=), 143.5 (C_6), (=CH), 138.3 (C_7), 137.3 (C_{17}), 134.2 (C_{14}), 133.5

(C_{16}), 131.5 (C_{10}), 130.8 (C_{18}), 130.1 (C_{15}), 129.7 (C_8), 129.5 (C_{11}), 128.4 (C_{19}), 127.7 (C_{12}), 122.6 (C_9), 116.2 (C_5). Anal. calcd for $C_{17}H_8O_3NSCl_2Br$: C 44.67, H 1.76, N 3.06; found C 44.65, H 1.75, N 3.03.

2.3.6. (E) – 3 - (3,4-dichlorobenzoyl) – 5 - (4-methylbenzylidene)thiazolidine -2, 4 - dione 21: m.p. 212-214 °C, yield, 75 % ; IR (KBr) *v* cm^{-1}: 2912 and 2825 (-CH_3 asym. and sym. str.), 1759 and 1652 (>C=O str. of TZD), 1699 (>C=O str. of benzoyl chloride) 790 (C-S-C str.), 719 (C-Cl str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.03 (s, 1H, =CH), 7.14-8.10 (m, 7H, aromatic), 2.26 (s, 3H, -CH_3). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 172.3 (C_{13}), (>CO=), 170.4 (C_2), (>CO=), 168.6 (C_4), (>CO=), 144.0 (C_6), (=CH), 138.4 (C_{10}), 137.2 (C_{17}), 134.7 (C_{14}), 133.5 (C_{16}), 132.0 (C_7), 131.3 (C_{18}), 130.2 (C_{15}), 129.0 ($C_{9,11}$), 128.3 ($C_{8,12}$), 127.7 (C_{19}), 115.6 (C_5), 21.6 (C_{20}) (-CH_3). Anal. calcd for $C_{18}H_{11}O_3NSCl_2$: C 55.12, H 2.83, N 3.57; found C 55.10, H 2.81, N 3.56.

2.3.7. (E) – 3 - (3,4-dichlorobenzoyl) – 5 - (4-methoxybenzylidene) thiazolidine - 2, 4-dione 22: m.p. 224-225 °C, yield, 70 % ; IR (KBr) *v* cm^{-1}: 1761 and 1650 (>C=O str. of TZD), 1705 (>C=O str. of benzoyl chloride) 789 (C-S-C str.), 721 (C-Cl str.), (-OCH_3 str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.05 (s, 1H, =CH), 6.86-8.12 (m, 7H, aromatic), 3.76 (s, 3H, -OCH_3). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 172.0 (C_{13}), (>CO=), 169.3 (C_2), (>CO=), 168.2 (C_4), (>CO=), 157.7 (C_{10}), 143.8 (C_6), (=CH), 137.3 (C_{17}), 134.5 (C_{14}), 133.4 (C_{16}), 131.6 (C_{18}), 130.7 (C_{15}), 129.9 ($C_{8,12}$), 128.4 (C_{19}), 127.1 (C_7), 115.5 (C_5), 112.1 ($C_{9,11}$), 55.3 (C_{20}) (-OCH_3). Anal. calcd for $C_{18}H_{11}O_4NSCl_2$: C 52.96, H 2.72, N 3.43; found C 52.93, H 2.70, N 3.41.

2.3.8.(E) – 3 - (3,4-dichlorobenzoyl) – 5 - (4-(dimethylamino) benzylidene) thiazolidine-2,4-dione 23: m.p. 268-269 °C, yield, 57 % ; IR (KBr) *v* cm^{-1}: 1751 and 1653 (>C=O str. of TZD), 1703 (>C=O str. of benzoyl chloride) 790 (C-S-C str.), 714 (C-Cl str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.04 (s, 1H, =CH), 6.68-8.15 (m, 7H, aromatic), 3.10 (s, 6H, -$N(CH_3)_2$). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 171.5 (C_{13}), (>CO=), 169.6 (C_2), (>CO=), 168.3 (C_4), (>CO=), 147.9 (C_{10}), 144.2 (C_6), (=CH), 137.3 (C_{17}), 134.5 (C_{14}), 133.7 (C_{16}), 131.4 (C_{18}), 130.6 (C_{19}), 124.4 (C_7), 116.3 (C_5), 111.1 ($C_{9,11}$), 40.7 ($C_{20,21}$) (-$N(CH_3)_2$). Anal. calcd for $C_{19}H_{14}O_3N_2SCl_2$: C 54.17, H 3.35, N 6.65; found C 54.15, H 3.35, N 6.63.

2.3.9.(E)-3-(3,4-dichlorobenzoyl)-5-(4-hydroxybenzylidene) thiazolidine-2,4-dione 24: m.p. 236-238 °C, yield, 78 % ; IR (KBr) *v* cm^{-1}: 3489 (-OH str.), 1749 and 1658 (>C=O str. of TZD), 1693 (>C=O str. of benzoyl chloride) 791 (C-S-C str.), 715 (C-Cl str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.02 (s, 1H, =CH), 6.62-8.14 (m, 7H, aromatic), 5.24 (s, 1H, -OH). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 170.3 (C_{13}), (>CO=), 168.7 (C_2), (>CO=), 167.3 (C_4), (>CO=), 157.1 (C_{10}), 143.8 (C_6), (=CH), 137.3 (C_{17}), 134.7 (C_{14}), 133.5 (C_{16}), 131.6 (C_{18}), 130.7 (C_{15}), 130.1 ($C_{8,12}$), 128.5 (C_{19}), 127.4 (C_7), 116.3 (C_5), 115.1 ($C_{9,11}$). Anal. calcd for $C_{17}H_9O_4NSCl_2$: C 51.79, H 2.30, N 3.55; found C 51.77, H 2.29, N 3.52.

2.3.10. (E) – 3 - (3,4-dichlorobenzoyl) – 5 - (4-hydroxy-3-methoxybenzylidene)thiazolidine-2,4-dione 25: m.p. 206-208 °C, yield, 61 % ; IR (KBr) *v* cm^{-1}: 3491 (-OH str.), 1751 and 1657 (>C=O str. of TZD), 1696 (>C=O str. of benzoyl chloride) 788 (C-S-C str.), 717 (C-Cl str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.08 (s, 1H, =CH), 6.64-8.13 (m, 6H, aromatic), 5.21 (s, 1H, -OH), 3.74 (s, 3H, -OCH_3). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 171.4 (C_{13}), (>CO=), 169.6 (C_2), (>CO=), 168.2 (C_4), (>CO=), 149.7 (C_9), 147.2 (C_{10}), 143.9 (C_6), (=CH), 137.4 (C_{17}), 134.8 (C_{14}), 133.3 (C_{16}), 131.5 (C_{18}), 130.6 (C_{15}), 129.3 (C_7), 128.4 (C_{19}), 122.7 (C_{12}), 117.5 (C_{11}), 116.3 (C_5), 111.5 (C_8), 55.7 (C_{20}) (-OCH_3). Anal. calcd for $C_{18}H_{11}O_5NSCl_2$: C 50.96, H 2.61, N 3.30; found C 50.94, H 2.59, N 3.27.

2.3.11. (E)-3-(3,4-dichlorobenzoyl)-5-(thiophen-2-ylmethylene)thiazolidine-2,4-dione 26: m.p. 214-215 °C, yield, 69 % ; IR (KBr) *v* cm^{-1}: 1755 and 1661 (>C=O str. of TZD), 1700 (>C=O str. of benzoyl chloride) 793 (C-S-C str.), 718 (C-Cl str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.22 (s, 1H, =CH), 7.46-8.18 (m, 6H, aromatic & thiophene). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 172.2 (C_{13}), (>CO=), 169.1 (C_2), (>CO=), 168.3 (C_4), (>CO=), 144.7 (C_6), (=CH), 136.9 (C_{17}), 134.5 (C_{14}), 133.8 (C_{16}), 130.8 (C_{18}), 130.1 (C_{15}), 128.0 (C_{19}), 138.3-128.1 (thiophene carbons), 115.9 (C_5). Anal. calcd for $C_{15}H_7O_3NS_2Cl_2$: C 46.89, H 1.84, N 3.65; found C 46.86, H 1.82, N 3.62.

2.3.12. (E) – 3 - (3,4-dichlorobenzoyl) – 5 - (3-phenoxybenzylidene) thiazolidine-2,4-dione 27: m.p. 221-223 °C, yield, 62 % ; IR (KBr) *v* cm^{-1}: 1750 and 1654 (>C=O str. of TZD), 1694 (>C=O str. of benzoyl chloride) 794 (C-S-C str.), 721 (C-Cl str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.08 (s, 1H, =CH), 6.98-8.12 (m, 12H, aromatic). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 171.6 (C_{13}), (>CO=), 169.3 (C_2), (>CO=), 168.6 (C_4), (>CO=), 156.5 (C_9), 143.9 (C_6), (=CH), 137.2 (C_{17}), 134.9 (C_7), 134.1 (C_{14}), 133.4 (C_{16}), 130.6 (C_{18}), 130.0 (C_{15}), 128.7 (C_{11}), 128.1 (C_{19}), 121.2 (C_{12}), 118.3 (C_{10}), 116.4 (C_5), 113.2 (C_8), 157.2-119.3 (C_{20-25}) (Phenoxy carbons). Anal. calcd

for $C_{23}H_{13}O_4NSCl_2$: C 58.74, H 2.79, N 2.98; found C 58.72, H 2.76, N 2.95.

2.3.13. (E) – 3 - (3,4-dichlorobenzoyl) – 5 - (3,4,5-trimethoxybenzylidene)thiazolidine-2,4-dione 28: m.p. 242-244 °C, yield, 66 % ; IR (KBr) *v* cm^{-1}: 1752 and 1656 (>C=O str. of TZD), 1692 (>C=O str. of benzoyl chloride) 788 (C-S-C str.), 720 (C-Cl str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.05 (s, 1H, =CH), 6.72-8.15 (m, 5H, aromatic), 3.79 (s, 9H, $(-OCH_3)_3$). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 171.5 (C_{13}), (>CO=), 169.6 (C_2), (>CO=), 168.3 (C_4), (>CO=), 152.2 ($C_{9,11}$), 143.7 (C_6), (=CH), 138.9 (C_{10}), 136.9 (C_{17}), 134.5 (C_{14}), 133.4 (C_{16}), 130.8 (C_{18}), 130.2 (C_{15}), 129.2 (C_7), 128.1 (C_{19}), 116.5 (C_5), 102.7 ($C_{8,12}$), 60.3 (C_{21}) ($-OCH_3$), 55.7 ($C_{20,22}$) $(-OCH_3)_2$. Anal. calcd for $C_{20}H_{15}O_6NSCl_2$: C 51.29, H 3.23, N 2.99; found C 51.28, H 3.20, N 2.97.

2.3.14. (E) – 3 - (3,4-dichlorobenzoyl) – 5 - (4-(dihexylamino) – 2 - methylbenzylidene) thiazolidine-2,4-dione 29: m.p. 246-247 °C, yield, 62 % ; IR (KBr) *v* cm^{-1}: 2910 and 2823 ($-CH_3$ asym. and sym. str.),1762 and 1664 (>C=O str. of TZD), 1704 (>C=O str. of benzoyl chloride) 795 (C-S-C str.), 721 (C-Cl str.). ^{1}H NMR (DMSO-d_6) δ (ppm): 8.32 (s, 1H, =CH), 6.46-8.17 (m, 6H, aromatic), 2.52 (s, 3H, $-CH_3$), 0.89-3.80 (m, 26H, dihexyl). ^{13}C NMR (100MHz, DMSO-d_6) δ(ppm): 171.2 (C_{13}), (>CO=), 169.1 (C_2), (>CO=), 168.6 (C_4), (>CO=), 150.5 (C_{10}), 143.7 (C_6), (=CH), 138.5 (C_8), 137.0 (C_{17}), 134.4 (C_{14}), 133.5 (C_{16}), 131.0 (C_{18}), 130.2 (C_{15}), 128.4 (C_{19}), 127.4 (C_{12}), 125.2 (C_7), 116.8 (C_5), 113.3 (C_9), 108.5 (C_{11}), 53.5 ($C_{21,22}$) ($N-CH_2-$), 31.3-14.2 (C_{23-32}) (methylene & methyl groups attached to N), 19.1 (C_{20}) ($-CH_3$), Anal. calcd for $C_{30}H_{36}O_3N_2SCl_2$: C 62.60, H 6.30, N 4.87; found C 62.57, H 6.26, N 4.86.

3. RESULTS AND DISCUSSION

3.1. Antimicrobial activity: The Minimum inhibitory concentrations (MICs) of synthesized compounds were carried out by broth micro dilution method as described by Rattan (Rattan, 2000). MICs of the tested compounds are shown in Table-1, 2 and 3. The different compounds 1-29 were tested for *in vitro* against two Gram positive (*Staphylococcus aureus* MTCC 96, *Streptococcus pyogenes* MTCC 442) and two Gram negative (*Escherichia coli* MTCC 443, *Pseudomonas aeruginosa* MTCC 741) bacteria for antibacterial, three fungal species (*Candida albicans* MTCC 227, *Aspergillus niger* MTCC 282 and *Aspergillus clavatus* MTCC 1323) for antifungal and. *M. tuberculosis* $H_{37}RV$ mycobacterium for antitubercular activity. Ampicillin, greseofulvin and rifampicin were used as standard antibacterial, antifungal and antitubercular agents respectively.

3.1.1. Antibacterial activity: The results of antibacterial activity of the synthesized compounds are presented in Table-1. Moderate to good antibacterial activity is observed with most of the tested compounds. Starting scaffold 1,3-thiazolidine-2,4-dione 1 exhibited good activity (MIC value 200 μg/ml) against *S. aureus* and moderate activity against other bacteria with ampicillin.

Compounds 9, 12 and 15 displayed good activity (MIC value 62.5–100 μg/ml) against *E. coli* relative to the reference drug ampicillin while other compounds showed modest to moderate activity. Additionally, compounds 17, 20 and 27 shows good biological activity (MIC value 62.5–125 μg/ml).

Compounds 6, 9, and 15 showed comparable activity (MIC value 100 μg/ml) against *P. aeruginosa* relative to the reference drug ampicillin while other compounds showed modest to moderate activity. These results confirming the importance of the presence of nitrogen atom of a tertiary amine at position-4 in antibacterial activity, on the other hand title compounds 17, 19, 20, 24, 27 and 28 exhibited excellent to good activity (MIC value 50-125 μg/ml).

Compounds 4, 5, 6, 7, 8, 11, 13 and 14 exhibited comparable to good activity (MIC value 100–250 μg/ml) against *S. aureus* relative to the reference drug ampicillin while other compounds showed modest to moderate activity. From final compounds; 17, 20, 21, 24, 25, 26, 27, 28 and 29 displayed good to very good activity (MIC value 62.5-250 μg/ml).

Finally, all the compounds (MIC value 200-500 μg/ml) exhibited modest to moderate activity against *S. pyogenus* relative to the reference drug ampicillin. Dramatically, from compounds (having 3,4-dichloro benzoyl core) 17, 20, 21 and 24 (MIC value 62.5-100 μg/ml) showed remarkable activity against *S. pyogenus*.

3.1.2. Antifungal activity: The results of antifungal activity of the synthesized compounds are presented in Table-2. Starting scaffold 1,3-thiazolidine-2,4-dione 1 exhibited good activity (MIC value 250 μg/ml) against *C. albicans* and moderate activity against other fungal species with greseofulvin.

Compounds 2, 3, 4, 7, 8, 12, 13 and 14 displayed comparable to good activity (MIC value 100–500 μg/ml) against *C. albicans* with reference drug greseofulvin while other compounds showed modest to moderate activity. Interestingly, addition of 3,4-dichloro benzoyl group also showed enhanced

antifungal activity for compounds 16, 17, 20, 21, 23, 24, 25, 26, 27, 28 and 29 (MIC value 100-500 μg/ml).

All the compounds with exception of 11 and 29 (MIC value 100 μg/ml) exhibited modest to moderate activity against *A. niger* with reference drug greseofulvin.

All the compounds (MIC value 250->1000 μg/ml) except 29 (MIC value 100 μg/ml) showed modest to moderate activity against *A. clavatus* relative to the reference drug greseofulvin.

3.2. Antitubercular activity: All the synthesized compounds were also screened against *M. tuberculosis* $H_{37}RV$ with reference drug rifampicin which is summarized in Table-3. Results indicate that compounds showed moderate to modest antitubercular activity, except compound 14, 22 and 23 that showed good to very good activity (MIC value 25-50 μg/ml) against *M. tuberculosis* and compounds 5, 11, 16, 21 and 28 that showed comparable (MIC value 62.5-100 μg/ml) activity whereas remaining compounds exhibited modest to moderate activity (MIC value 200-1000 μg/ml).

4. CONCLUSION

In summary, new compounds of 1,3-thiazolidine-2,4-diones were synthesized, which showed a variety of biological activities *in vitro* as potential antibacterial, antifungal and antitubercular agents. Particulary, 2,4-thiazolidinedione ring is a scaffold for development of new antibacterial and anti-giardiasis agents, and attachment of 3,4-dichlorobenzoyl chloride is a good strategy for development of new antibacterial, antifungal and antitubercular agents. Present work provides a good outline of structure activity relationships of 1,3-thiazolidine-2,4-diones.

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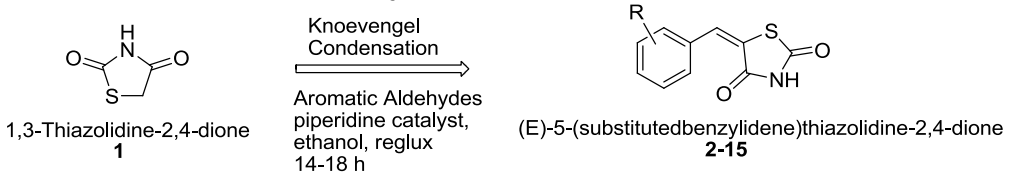
Table.1. Antibacterial activity (MICs, μg/ml) for the title compounds

Compound	Gram negative bacteria		Gram positive bacteria	
	E. coli	*P. aeruginosa*	*S. aureus*	*S. pyogenus*
	MTCC-443	MTCC-741	MTCC-96	MTCC-442
1	500	500	200	200
2	250	500	500	500
3	250	200	500	500
4	200	250	250	250
5	200	250	200	250
6	500	100	250	500
7	500	250	250	250
8	250	500	100	200
9	62.5	100	500	250
10	200	250	500	250
11	250	250	250	250
12	100	200	500	250
13	200	200	200	200
14	250	250	200	500
15	62.5	100	500	500
16	500	500	1000	500
17	62.5	50	100	62.5
18	500	250	500	500
19	250	50	500	200
20	125	62.5	200	100
21	500	500	125	100
22	500	250	500	500
23	500	500	1000	500
24	200	125	100	62.5
25	250	200	250	500
26	250	250	250	250
27	125	100	125	200
28	500	100	62.5	200
29	200	500	200	250
Ampicillin	100	100	250	100

Table.2. Antifungal activity (MICs, μg/ml) for the title compounds

Compound	Fungal species		
	C. albicans	*A. niger*	*A. clavatus*
	MTCC-227	MTCC-282	MTCC-1323
1	250	500	>1000
2	500	1000	1000
3	500	250	>1000
4	250	1000	500
5	1000	>1000	500
6	1000	>1000	>1000
7	250	500	1000
8	500	1000	1000
9	1000	>1000	>1000
10	1000	1000	1000
11	1000	100	500
12	500	1000	1000
13	250	1000	>1000
14	500	1000	1000
15	1000	>1000	>1000
16	500	1000	1000
17	200	500	>1000
18	>1000	500	>1000
19	>1000	>1000	>1000
20	500	500	>1000
21	500	>1000	500
22	>1000	>1000	>1000
23	200	500	>1000
24	500	500	>1000
25	500	500	>1000
26	500	500	500
27	200	250	250
28	250	500	500
29	100	100	100
Greseofulvin	500	100	100

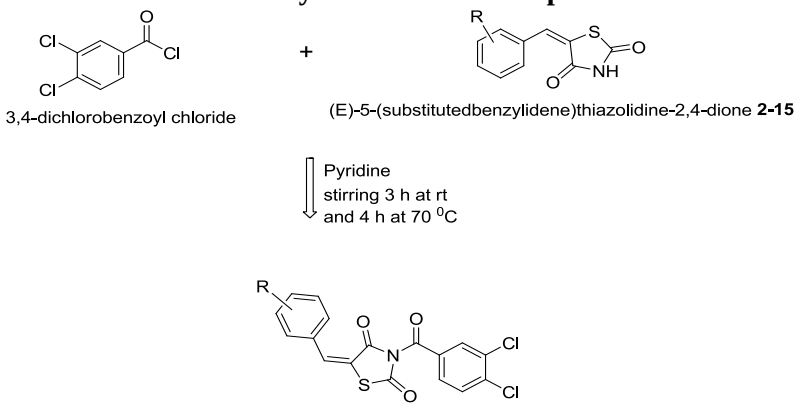
Scheme-1 Synthesis of intermediates 2-15



1,3-Thiazolidine-2,4-dione
1

(E)-5-(substitutedbenzylidene)thiazolidine-2,4-dione
2-15

Scheme-2 Synthesis of title compounds 16-29



3,4-dichlorobenzoyl chloride

(E)-5-(substitutedbenzylidene)thiazolidine-2,4-dione **2-15**

(E)-3-(3,4-dichlorobenzoyl)-5-substitutedbenzylidenethiazolidine-2,4-dione **16-29**

Table.3. Minimal tubercular concentrations (MICs, μg/ml) for the title compounds

Compound	MIC values (μg/ml) of *M. tuberculosis* $H_{37}Rv$	% Inhibition
2	250	98%
3	500	97%
4	250	99%
5	100	98%
6	250	99%
7	200	99%
8	250	98%
9	1000	98%
10	250	99%
11	100	99%
12	1000	98%
13	200	98%
14	50	99%
15	500	98%
16	62.5	98%
17	500	98%
18	1000	99%
19	500	98%
20	250	98%
21	100	99%
22	50	99%
23	25	99%
24	500	98%
25	1000	99%
26	1000	98%
27	250	98%
28	100	99%
29	1000	99%
Rifampicin	40	99%

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