Synthesis and Biological Evaluation of Mannose Thiazolidinones

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Abstract

*In a one pot procedure , a series of novel mannose thiazolidinone derivatives 4**a-g** and 5**a-g** was prepared by condensation of (3aS,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxole-4-carbaldehyde **3** with mercapto acids and primary amines in presence of $ZnCl_2$ under both micro wave irradiation and conventional heating conditions. Compound **3** prepared from Methyl di acetone D- Mannose with primary acetonide deprotection and with oxidative cleavage .Characterization of new compounds has been done by means of IR, NMR, MS and elemental analysis. The nematicidal and anti bacterial activity of the compounds has also been evaluated.*

Keywords: *D-Mannose, Thiazolidinones, Microwave assisted synthesis, antimicrobial and nematicidal activity.*

1. Introduction

Thiazolidinone and its derivatives are known to possess significant pharmacological [1] and biological activities [2] like sedative [3,] anti inflammatory [4] anti tubercular [5] anticancer [6], anti tumor [7] , anti-HIV [8] , anti bacterial [9], anti fungal [10] , analgesic , hypotermic [11], anesthetic [12] ,nematicidal [13] and CNS stimulant [14.] Furthur more , thiazolidenones have been used for the treatment of cardiac diseases [15], diabetic complications like cataract nephropathy, neuropathy [16], and selective anti platelet activating factor [17].

Nematodes are tiny worms, some of them are plant parasites, and can play an important role in the predisposition of the host plant to the invansion by secondary pathogens [18]. Plants attacked by nematodes show retarded growth and development, as well as loss in the quality and quantity of the harvest. The namaticide use is slated for reduction due to environmental problems, and human and animals health concern. For example, effective namaticides such as dibromochloropropane (DBCD) and ethylene dibromide (EDB) have been withdrawn from the market due to their deleterious effects on human and the environment. Methyl bromide, the most effective and widely used fumigant for soil borne pests including nematodes, has already been banned.

The use of nonfumigant nematicides, based on organophosphates and carbamates, is expected to increase the withdrawal of methyl bromide, which will bring about new environmental concerns. In fact, the highly toxic Aldicarb used to control insects and nematodes has been detected in ground water [19]. Therefore alternative nematode control methods or less toxic nematicides need to be developed. One way of searching for such nematicidal compounds is to screen naturally occurring compounds in plants. Several such compounds, *e.g.* alkaloids, phenols, sesquiterpenes, diterpenes, polyacetylenes, and thienyl derivatives have nematicidal activity [20]. For example, α-terthienyl is a highly effective nematicidal compound [21]. Other compounds with nematicidal activity have been isolated from plants, mainly from the family *Asteraceae* [22]. However, compounds of plant origin and their analogs have not been developed into commercial nematicides; hence there is a need to develop commercial synthesis.

Following the successful introduction of antimicrobial and nematicidal agents, inspired by the biological profile of thiazolidenones , and in the continuation of our work on biological active heterocyclic's [23 – 35] we have developed a series of novel Mannose Thiazolidinone derivatives , and evaluated their nematicidal activity along with antimicrobial activity.

2.Result and discussion

O- Methyl Di acetone D- Mannose **(1)** prepared from D (+) – Mannose by treating with Acetone and methyl alcohol in presence of catalytic amount of sulphuricacid, Acid hydrolysis of 5,6 acetonide **1** in 60% AcOH furnished the diol **2** (85%) , which on oxidative cleavage with $NaIO_4$ gave the aldehyde **3** according to the literature procedure [36.] Subsequently one pot synthesis of Triazole linked Thiazolidenone glycosides was carried out by the condensation reaction between **3**, primary aromatic amine and a thio glycolic acid and thiomalic acid in presence of $ZnCl_2$ under microwave irradiation / conventional heating (**Scheme 1**) . In classical method, the reactions were performed in dry toluene at reflux for a long time (2-4 h), often leading to degradation processes and consequent low yields of isolated products, whereas the application of microwave assisted technology, the reaction is completed in only 5-10 minutes and the compounds, isolated by conventional work - up, are obtained in satisfactory yields , often higher than those achieved by traditional methods (**Table 1)** . The structures of synthesized compounds were confirmed by IR, NMR, MS and elemental analysis. Further the compounds were subject to nematicidal and anti bacterial testing.

3. Antibacterial Activity

Compounds **4a-g** and **5a-g** were screened for their antibacterial activity using the tube dilution method [37] by measuring the minimum inhibitory concentration (MIC) in µg /ML against four representative organisms viz Bacillus *subtilis, Staphylococcus aureus , Escherichia coli and Staphylococcus pyogenus.* Standard anti bacterial agents, such streptomycin and Neomycin, were also screened under identical condition for comparison. The minimum inhibitory concentrations are given in **Table 2.** It has been observed the test compounds however exhibited an interesting biological activity, with degree of variation.

Compounds in series **4** and **5**, which contain 4-Cl / 3- OH, displayed good antibacterial activity against all the organisms. Compounds **4b** and **5f** were highly active against all the

organisms. Compounds **4b** and **5f** were highly active against *B. Subtilis* , *S.aureus* and *S. pyogenus*, compound **5f** were highly active against *B. Subtilis* , *S.aureus* , *E.coli* , compound **5b** was highly active against *B. subtilis* , *E. coli and S. pyogenus* and the compound **4c** was highly active against *E. coli and S. pyogenus.* Compounds **5a** and **5d** did not exhibit any activity against *E. coli* even at 100 µg/ML concentration . The alkyl substituted derivatives displayed moderate level of anti bacterial activity (**Table 2**).

4.Nematicidal Activity.

The compounds **4a-g** and **5a-g** were also screened for their nematicidal activity against *Ditylenchus mycliophagus* and *Caenorhabditis elegans* by aqueous in vitro screening technique [38] at various concentrations . The results have been expressed in terms of LD_{50} i.e median lethl dose at which 50 % nematodes became immobile. The screened data reveal that compound **4f** and **5f** are the most effective against *D. myceliophagus* and *C. elegans* with LD_{50} value of 210 and 240 ppm, respectively.

5. Experimental

Commercial grade reagents were used as supplied. Solvents except analytical reagent grade were dried and purified according to literature when necessary. Reaction progress and purity of the compounds were checked by thin-layer chromatography (TLC) on pre-coated silica gel F254 plates from Merck and compounds visualized either by exposure to UV light or dipping in 1% aqueous potassium permanganate solution. Silica gel chromatographic columns (60–120 mesh) were used for separations. All melting points are uncorrected and measured using Fisher–Johns apparatus. IR spectra were recorded as KBr disks on a Perkin–Elmer FT IR spectrometer. The ^{1}HNMR and ^{13}C NMR spectra were recorded on a Varian Gemini spectrometer (300 MHz for ^{1}H and 75 MHz for^{13}C). Chemical shifts are reported as δ ppm against TMS as internal reference and coupling constants *(J)* are reported in Hz units. Mass spectra were recorded on a VG micro mass 7070H spectrometer. Elemental analyses (C, H, N) determined by a Perkin–Elmer 240 CHN elemental analyzer, were within ± 0.4% of theoretical.

2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-3-phenylthiazolidin-4-one (4a-g) To a solution of diol **2** (0.500 g, 2.13 mmol) in CH_2Cl_2 (5 mL), $NaIO_4$ (0.600 g, 2.81 mmol) was added at 0 °C and stirred at room temperature for 6 h. The

reaction mixture was filtered and washed with CH_2Cl_2 (2 x 10 mL). It was dried (Na_2SO_4) and evaporated to give aldehyde **3** (.520 g) in quantitative yield as a yellow liquid, which was used as such for the next reaction.

To a stirred mixture of **3** (0.520, 2.57 mmol), aromatic amine (2.57 mmol) and anhydrous thioglycolic acid (0.230g, 2.571 mmol) in dry toluene (5ml), $ZnCl_2$ (0.100g , 0.751mmol) was added after 2 min and irradiated in microwave bath reactor at 280 W for 4- 7 minutes at 110°C . After cooling, the filtrate was concentrated to dryness under reduced pressure and the residue was taken – up in ethyl acetate. The ethyl acetate layer was washed with 5% sodium bicarbonate solution and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness at reduced pressure. The crude product thus obtained was purified by column chromatography on silica gel (60- 120 mesh) with hexane - ethyl acetate as eluent. Under conventional method the reaction mixture in toluene (10 mL) was refluxed at 110°C for the appropriate time (**Table 1)**

2-((3aR,4S,6S,6aS)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-3-phenylthiazolidin-4-one (4a) mp137-139°C IR (KBr) ν 3432, 3230, 2986, 2944, 2836,2815, 1716, 1612, 1551, 1512, 1416, 1221, 687 cm^{-1} ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.52 – 6.90 (5H, m, Ar –H), 5.75 (d, *J* = 3.6 Hz,1H, C_1H) 4.93 (d, J = 5.2 Hz, CH-S), 4.62 (t, *J* = 3.9 Hz,1H, C_2H) , 3.98 – 3.95 (m, 1H,C_4H) , 3.75 (s, 2H, CH_2), 3.41 (s, 3H, OCH_3), 3.31 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 1.55 (s, 3H,CH_3), 1.32 (m, 3H,CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 141.2, 128.9, 128.2, 127.4, 119.6, 104.8, 81.2, 78.5, 74.4, 55.3, 52.0, 34.6, 26.5 ; MS: m/z (M^++Na) 358.10. Anal. Calcd for $C_{16}H_{18}NO_5S$: C, 57.13; H, 5.39; N, 4.16. Found: C, 57.03; H, 5.19; N, 4.03.

3-(4-chlorophenyl)-2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)thiazolidin-4-one (4b) mp 206-208 °C; IR (KBr) ν 3430, 3229,2984, 2832, 2817, 1712, 1610, 1549, 1510, 1412, 1219, 682 cm^{-1} ; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.50 (d, *J* = 9.2Hz, 2H, Ar-H) , 7.41 (d, *J* = 8.9Hz, 2H,Ar-H), 5.72 (d, *J* = 3.6 Hz,1H, C_1H) , 4.94 (d, *J* = 5.2 Hz, CH-S) 4.60 (t, *J* = 3.9 Hz,1H, C_2H) , 3.96 – 3.91 (m, 1H,C_4H,) , 3.76 (s, 2H, CH_2), 3.42 (s, 3H, OCH_3) , 3.31 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 1.55 (s, 3H,CH_3), 1.32 (m, 3H,CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 139.4, 133.2, 129.4,128.6, 125.6,111.2, 104.9, 81.5,

74.5,55.5, 52.6, 34.6, 26.5 ; MS: m/z (M^++H) 386.10. Anal. Calcd for $C_{17}H_{20}ClNO_5S$: C, 52.92; H, 5.22; N, 9.19. Found: C, 522.61; H, 5.16; N, 9.03.

2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-3-(4-nitrophenyl)thiazolidin-4-one (4c) mp 191-195°C ; IR (KBr) ν 3432, 3226, 2982, 2830,2819, 1710, 1608, 1546, 1512, 1414,1374, 1216, 865, 632 cm^{-1} ; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.7Hz, 2H) , 6.82 (d, *J* = 9.8 Hz, 2H, Ar-H) , 5.71 (d, *J* = 3.6 Hz,1H, C_1H) , 4.96 (d, *J* = 5.2 Hz, CH-S) 4.62 (t, *J* = 3.9 Hz,1H, C_2H) , 3.96 – 3.91 (m, 1H,C_4H) , 3.76 (s, 2H, CH_2),3.49 (s,3H, OCH_3), 3.28 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 1.52 (s, 3H,CH_3), 1.34 (m, 3H,CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 147.5, 143.2, 131.2, 124.6,111.8, 104.9, 81.5, 78.2, 74.8,55.8, 52.4, 34.6, 26.8 ; MS: m/z (M^++H) 397.10. Anal. Calcd for $C_{17}H_{20}N_2O_7S$: C, 55.51; H, 5.09; N, 7.07. Found: C, 54.96; H, 4.96; N, 6.91.

2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-3-o-tolylthiazolidin-4-one (4d) mp 161-163°C **;**IR (KBr) ν 3436, 3234, 2986, 2834,2820, 1710, 1705,1610, 1549, 1516, 1418, 1262, 865 cm^{-1} ; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.23 (d, *J* = 8.7Hz, 2H, Ar-H) , 7.45- 6.82 (m, 5H, Ar-H) ,5.74 (d, *J* = 3.6 Hz,1H, C_1H) , 4.94 (d, *J* = 5.2 Hz,1H, CH-S) 4.62 (t, *J* = 3.9 Hz,1H, C_2H) , 3.96 – 3.91 (m, 1H,C_4H) , 3.76 (s, 2H, CH_2), 3.51 s, 3H, OCH_3), 3.26 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 2.1 (s, 3H,CH_3) 1.53 (s, 3H,CH_3), 1.36 (m, 3H,CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 138.7, 130.6, 129.4, 125.8,111.6, 104.8, 81.7, 78.6, 74.7,55.6, 52.4, 26.6,16.5 ; MS: m/z (M^++H) 366.10. Anal. Calcd for $C_{18}H_{23}NO_5S$: C, 59.16; H, 6.34; N, 3.82. Found: C, 58.86; H, 6.19; N, 3.61.

2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-3-p-tolylthiazolidin-4-one (4e) mp 181-183°C **;** IR (KBr) ν 3428, 3230, 2986, 2832,2825,1708, 1698,1608, 1546, 1514, 1416, 1261, 859 cm^{-1} ; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 8.26 (d, *J* = 8.7Hz, 2H, Ar-H) , 7.15 (d, *J* = 8.3 Hz, 2H, Ar-H) , 5.76 (d, *J* = 3.6 Hz,1H, C_1H) , 4.96 (d, *J* = 5.2 Hz,1H, CH-S) 4.66 (t, *J* = 3.9 Hz,1H, C_2H) , 3.96 – 3.91 (m, 1H,C_4H) , 3.76 (s, 2, H, CH_2), 3.57(s, 3H, OCH_3) , 3.26 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 2.3 (s, 3H,CH_3) 1.53 (s, 3H,CH_3), 1.36 (m, 3H,CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 172.6, 137.4, 133.6,132.3, 131.2,127.9, 124.8, 111.2, 103.8, 81.2, 78.1, 74.1, 55.9, 51.4, 26.1,16.1 ; MS: m/z (M^++Na) 388.10. Anal. Calcd for $C_{18}H_{23}NO_5S$: C, 59.16; H, 6.34; N, 3.83. Found: C, 58.82; H, 6.15; N, 3.09.

3-(3-hydroxyphenyl)-2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)thiazolidin-4-one (4f) mp 198-200°C **;** IR (KBr) ν 3535, 3426, 3231, 2974,

2832, 1710, 1610, 1549,1516, 1418, 1261, 864 cm^{-1} ; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.14 - 6.70 (m, 5H,Ar-H), 5.76 (d, *J* = 3.6 Hz,1H, C_1H) , 5.40 (s, 1H, OH), 4.96 (d, *J* = 5.2 Hz,1H, CH-S) 4.66 (t, *J* = 3.9 Hz,1H, C_2H) , 3.93 – 3.96 (m, 1H,C_4H) , 3.74 (s, 2H, CH_2),3.59 (s, 3H, OCH_3) , 3.26 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 1.53 (s, 3H,CH_3), 1.38 (m, 3H,CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.6, 158.3, 144.2, 143.2, 130.6, 120.1, 114.6, 111.8, 107.6,106.8, 81.8, 78.6, 74.8, 55.7, 54.9, 41.1, 35.3; MS: m/z (M^++H) 368.20. Anal. Calcd for $C_{17}H_{21}NO_6S$: C, 55.57; H, 5.76; N, 3.81. Found: C, 54.82; H, 5.55; N, 3.19.

3-(4-hydroxyphenyl)-2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)thiazolidin-4-one (4g) mp 253-255°C **;**IR (KBr) ν 3541, 3425, 3232, 2987, 2834, 1710, 1612, 1546,1519, 1416, 1258, 862 cm^{-1} ; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 7.10 - 6.70 (m, 4H,Ar-H), 5.76 (d, *J* = 3.6 Hz,1H, C_1H) , 5.28 (s, 1H, OH), 4.92 (d, *J* = 5.2 Hz,1H, CH-S) 4.65 (t, *J* = 3.9 Hz,1H, C_2H) , 4.52(s, 2H, OCH_2) , 3.91 – 3.94 (m, 1H,C_4H) , 3.79 (s, 2H, CH_2), 3.62 (s, 3H, OCH_3), 3.34 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 1.52 (s, 3H,CH_3), 1.36 (m, 3H,CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 171.2, 157.8, 143.2, 133.4, 130.2, 121.9, 120.5, 114.2, 111.2, 106.8, 81.4, 78.2, 73.8, 55.2, 54.2, 40.9, 34.9; MS: m/z (M^++H) 368.20. Anal. Calcd for $C_{17}H_{21}NO_6S$: C, 55.57; H, 5.76; N, 3.81. Found: C, 55.12; H, 5.29; N, 3.22.

2-(2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-4-oxo-3-phenylthiazolidin-5-yl)acetic acid (5a-g) To a solution of diol **3** (0.500 g, 2.13 mmol) in CH_2Cl_2 (5 mL), $NaIO_4$ (0.600 g, 2.81 mmol) was added at 0 °C and stirred at room temperature for 6 h. The reaction mixture was filtered and washed with CH_2Cl_2 (2 x 10 mL). It was dried (Na_2SO_4) and evaporated to give aldehyde **5** (.520 g) in quantitative yield as a yellow liquid, which was used as such for the next reaction.

To a stirred mixture of 5 (0.520, 2.57 mmol) , aromatic amine (2.57 mmol) and thiomalic acid (0.375g, 2.57 mmol) in dry toluene (5ml), anhydrous $ZnCl_2$ (0.100g , 0.751mmol) was added after 2 min and irradiated in microwave bath reactor at 280 W for 4- 7 minutes at 110°C . After cooling, the filtrate was concentrated to dryness under reduced pressure and the residue was taken – up in ethyl acetate. The ethyl acetate layer was washed with 5% sodium bicarbonate solution and finally with brine. The organic layer was dried over Na_2SO_4 and evaporated to dryness at reduced pressure. The crude product thus obtained was purified by column chromatography on silica gel (60- 120 mesh) with hexane - ethyl acetate as eluent. Under

conventional method the reaction mixture in toluene (10 mL) was refluxed at 110°C for the appropriate time (**Table 1**)

2-(2-((3aR,4S,6S,6aS)-6-((1-(4-chlorophenyl)-1H-1,2,3-triazol-4-yl)methoxy)-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-4-oxo-3-phenylthiazolidin-5-yl)acetic acid (5a) mp201-204°C;

IR(KBr) ν 3436, 3226, 2984, 2942,2842, 2832, 1724, 1614, 1549, 1510, 1412, 1224, 685 cm^{-1} ^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.44 (s, 1H, CO_2H) , 6.73- 7.35 (m, 5H,Ar –H),) 6.15 (s,1H, CHS) ,5.73 (d, *J* = 4.2 Hz,1H, C_1H) , 4.69 (t, *J* = 3.9 Hz,1H, C_2H) ,4.65 (t, 1H,CH), 3.92 – 3.89 (m, 1H,C_4H) , 3.59 (s, 3H, OCH_3), 3.31 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 2.38 (d, 2H,CH_2), 1.53 (s, 3H,CH_3), 1.30 (m, 3H,CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.9, 141.2, 128.2, 126.8, 104.2, 80.4, 77.9, 73.8, 55.8, 52.0, 37.2, 33.9, 25.9 ; MS: m/z (M^++H) 410.20. Anal. Calcd for $C_{19}H_{23}NO_7S$: C, 55.74; H, 5.66; N, 3. 42 Found: C, 55.12; H, 4.99; N, 3.39.

2-(3-(4-chlorophenyl)-2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-4-oxothiazolidin-5-yl)acetic acid (5b) mp 239-241 °C

IR(KBr)ν 3438,3431, 3226, 2829,2815, 1724, 1716, 1608, 1539, 1509, 1410, 1216, 689cm^{-1} ^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.44 (s, 1H, CO_2H) , 7.45 (d, *J* = 9.2Hz, 2H, Ar-H) , 7.39 (d, J = 8.9 Hz, 2H,Ar-H), 6.14 (s,1H, CHS) ,5.73 (d, *J* = 4.2 Hz,1H, C_1H) , 4.69 (t, *J* = 3.9 Hz,1H, C_2H) ,4.65 (t, 1H,CH), 3.92 – 3.89 (m, 1H,C_4H) ,3.53 (s,3H, OCH_3) 3.20 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 2.34 (d, 2H,CH_2), 1.53 (s, 3H,CH_3), 1.30 (m, 3H,CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 170.6, 143.2, 141.6, 133.2, 128.8, 126.9,118.4, 104.5, 80.6, 77.6, 73.2, 55.9, 52.3, 36.9, 33.2, 25.6 ; MS: m/z (M^++H) 621.13. Anal. Calcd for $C_{27}H_{26}Cl_2N_4O_7S$: C, 52.18; H, 4.22; N, 9.01. Found: C, 52.02; H, 4.09; N, 8.95

2-(2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-3-(4-nitrophenyl)-4-oxothiazolidin-5-yl)acetic acid (5c) mp 226-228 °C;

IR(KBr)ν 3428,3434, 3225, 2820, 1725, 1710, 1610, 1536, 1510, 1412, 1373,1210, 863, 639 cm^{-1} ^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.45 (s, 1H, CO_2H) , 8.21 (d, J= 8.4 Hz, 2H) , 6.79 (d, J = 9.6 Hz, 2H,Ar-H) , 6.14 (s,1H, CHS) ,5.69 (d, *J* = 4.2 Hz,1H, C_1H) , 4.65 (t, 1H,CH), 4.53 (t, *J* = 3.9 Hz,1H, C_2H) , 3.90 – 3.86 (m, 1H,C_4H) , 3.61 (s, 3H, OCH_3) 3.19 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 2.30 (d, 2H,CH_2), 1.49 (s, 3H,CH_3), 1.25 (m, 3H,CH_3) ^{13}C NMR (75 MHz, $CDCl_3$): δ 190.2, 173.2, 143.6, 141.9, 126.5, 118.2, 104.3, 80.4, 77.2, 73.1, 55.9,51.2, 36.4, 33.1, 25.4 ;

MS: m/z (M^++H) 455.13. Anal. Calcd for $C_{19}H_{22}N_2O_9S$: C, 50.21; H, 4.85; N, 6.18. Found: C, 49.99; H, 4.49; N, 5.95.

2-(2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-4-oxo-3-o-tolylthiazolidin-5-yl)aceticacid(5d)mp237-239°C;

IR(KBr)ν 3431,3229, 2834, 2819, 1709, 1699, 1610, 1550, 1516, 1418, 1264, 853cm^{-1} ^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.45 (s, 1H, CO_2H) , 8.22 (d, J= 8.4 Hz, 2H, Ar-H) ,7.42-6.85(m, 2H,Ar-H) , 6.14 (s,1H, CHS) ,5.65 (d, *J* = 4.2 Hz,1H, C_1H) , 4.60 (t, 1H,CH), 4.53 (t, *J* = 3.9 Hz,1H, C_2H) , 3.92 – 3.86 (m, 1H,C_4H) ,3.62 (s, 3H, OCH_3) 3.22 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 2.34 (d, 2H,CH_2) ,2.21 (s, 3H,CH_3), 1.51 (s, 3H,CH_3), 1.29 (m, 3H,CH_3) ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.4, 173.4, 142.9, 133.9, 125.4, 105.6, 80.6, 77.4, 73.4, 53.1,55.2, 36.3, 33.2, 25.2,16.2 ; MS: m/z (M^++H) 409.13. Anal. Calcd for $C_{19}H_{22}NO_7S$: C, 55.85; H, 5.43; N, 3.42. Found: C, 55.19; H, 5.62; N, 3.15.

2-(2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-4-oxo-3-p-tolylthiazolidin-5-yl)aceticacid(5e)mp197-199°C

IR(KBr)ν 3435,3239, 2830, 1710, 1696, 1615, 1540, 1510, 1428, 1254, 843cm^{-1} ^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.45 (s, 1H, CO_2H) , 7.36 (d, J= 8.33Hz, 2H, Ar-H) , 7.12 (d, *J* = 8.3 Hz, 2H, Ar-H) , 6.14 (s,1H, CHS) ,5.65 (d, *J* = 4.2 Hz,1H, C_1H) , 4.60 (t, 1H,CH), 4.53 (t, *J* = 3.9 Hz,1H, C_2H) , 3.92 – 3.86 (m, 1H,C_4H) , 3.59 (s, 3H, OCH_3), 3.22 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 2.34 (d, 2H,CH_2) ,2.21 (s, 3H,CH_3), 1.51 (s, 3H,CH_3), 1.29 (m, 3H,CH_3) ^{13}C NMR (75 MHz, $CDCl_3$): δ 191.4, 173.4,142.9, 125.4, 105.6, 80.6, 77.4, 73.4,55.3, 53.1, 36.3, 33.2, 25.2,16.2 ; MS: m/z (M^++H) 424.13. Anal. Calcd for $C_{20}H_{25}NO_7S$: C, 56.72; H, 5.95; N, 3.31. Found: C, 55.19; H, 5.42; N, 3.05.

2-(3-(3-hydroxyphenyl)-2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-4-oxothiazolidin-5-yl)acetic acid (5f) mp217-219°C; IR (KBr) ν 3535, 3436, 3236, 2832, 2816, 1710, 1610, 1544,1516, 1418, 1261, 864 cm^{-1} ; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.42(s, 1H, CO_2H) , 7.14 - 6.70 (m, 4H,Ar-H), 6.14 (s,1H, CHS) , 5.76 (d, *J* = 3.6 Hz,1H, C_1H) , 5.42 (s, 1H, OH), 4.96 (d, *J* = 5.2 Hz,1H, CH) 4.51 (t, *J* = 3.9 Hz,1H, C_2H) , 4.54 (s, 2H, OCH_2) , 3.93 – 3.96 (m, 1H,C_4H) , 3.54 (s, 3H, OCH_3), 3.26 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 2.34 (d, 2H,CH_2) , 1.53 (s, 3H,CH_3), 1.38 (m, 3H,CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.6, 171.6, 158.3, 144.2, 143.2, 130.6,120.1, 114.6, 111.8, 107.6,106.8, 81.8, 78.6, 74.8, 55.7,

54.9, 41.1, 38.9 , 35.3; MS: m/z (M^++H) 425.20. Anal. Calcd for $C_{19}H_{23}NO_8S$: C, 53.64; H, 5.45; N, 3.29. Found: C, 53.42; H, 5.15; N, 3.09.

2-(3-(4-hydroxyphenyl)-2-((3aR,4S,6S,6aS)-6-methoxy-2,2-dimethyltetrahydrofuro[3,4-d][1,3]dioxol-4-yl)-4-oxothiazolidin-5-yl)acetic acid (5g) mp 256-258°C ; IR (KBr) ν 3532, 3430, 3226, 2830, 1710, 1616, 1534,1506, 1411, 1258, 854 cm^{-1} ; ^{1}H-NMR (300 MHz, $CDCl_3$): δ 11.39 (s, 1H, CO_2H) , 8.06 (s,1H,Ar-H) , 7.14 - 6.87 (m, 4H,Ar-H), 6.14 (s,1H, CHS) , 5.76 (d, *J* = 3.6 Hz,1H, C_1H) , 5.42 (s, 1H, OH), 4.96 (d, *J* = 5.2 Hz,1H, CH) 4.51 (t, *J* = 3.9 Hz,1H, C_2H) , 4.54 (s, 2H, OCH_2) , 3.93 – 3.96 (m, 1H,C_4H) , 3,70 (s, 3H, OCH_3), 3.26 (dd, *J* = 9.1,4.2 Hz, 1H, C_3H), 2.34 (d, 2H,CH_2) , 1.53 (s, 3H,CH_3), 1.38 (m, 3H,CH_3) ; ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 171.6, 154.1, 143.2, 142.1, 133.6, 131.4, 129.6, 128.1, 122.6, 120.5, 115.4, 112.6, 111.8, 107.6,106.8, 81.8, 78.6, 76.8, 65.9,55.2, 56.9, 42.1, 36.9 , 34.3; MS: m/z (M^++H) 545.20. Anal. Calcd for $C_{19}H_{23}NO_8S$: C, 53.64; H, 5.42; N, 3.29. Found: C, 53.42; H, 5.25; N, 3.09.

6. Conclusions

A series of novel Triazole linked thiazolidenone derivatives **4 a-g** and **5a-g** was prepared and evaluated for their antimicrobial, nematicidal activity against various bacteria's and nematodes . The screened compounds **4b, 5f** exhibited potent antimicrobial activity compared to standard drug at the tested concentrations and **4f, 5f** exhibited potent nematicidal activity compared to standard drug at the tested concentrations.

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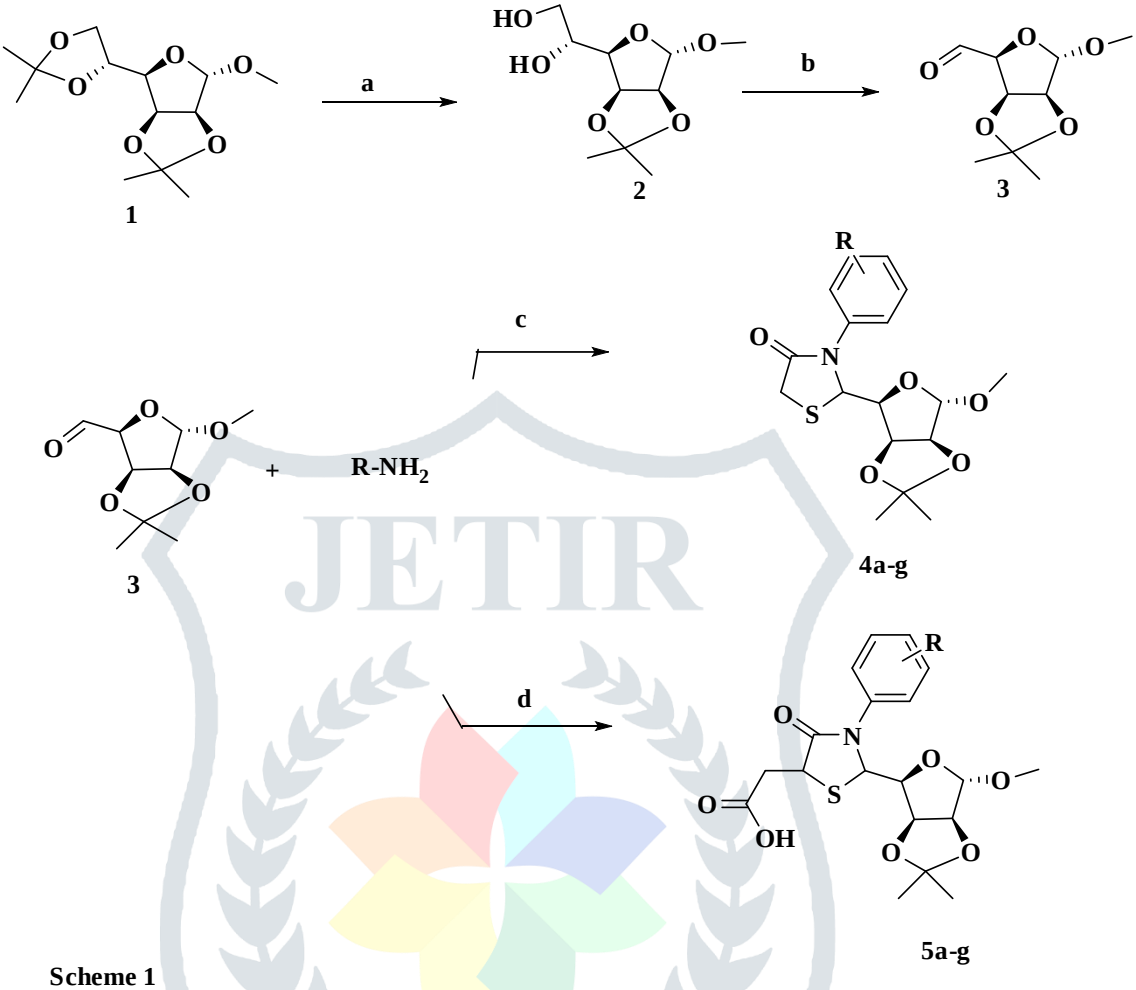

Scheme 1

Reagents and conditions ; a) 60%, AcOH; b) $NaIO_4$, CH_2Cl_2 ; c) Ar-NH_2 ,$SHCH_2COOH$, $ZnCl_2$, Toluene , 80 °C, MWI 110 °C ; d) Ar-NH_2 , Thio malic acid, $ZnCl_2$, Toluene, 80 °C , MWI 110 °C.

Table 1, Synthesis of Compounds 4(a-g) and 5 (a-g)

Compound	R	Mol. Formula	Reaction time		Yield	
			A (h)	B(min)	A	B
4a	C_6H_5	$C_{25}H_{25}ClN_4O_5S$	3.5	5	62	80
4b	4-Cl-C_6H_4	$C_{25}H_{24}Cl_2N_4O_5S$	2.5	6	71	89
4c	4-NO_2-C_6H_4	$C_{25}H_{24}ClN_5O_7S$	3.0	6	69	82
4d	2-CH_3-C_6H_4	$C_{26}H_{27}ClN_4O_5S$	2.0	5	63	86
4e	4-CH_3-C_6H_4	$C_{26}H_{27}ClN_4O_5S$	2.5	5	68	88
4f	3-OH – C_6H_4	$C_{25}H_{25}ClN_4O_6S$	3.0	5	79	86
4g	4-OH – C_6H_4	$C_{25}H_{25}ClN_4O_6S$	2.0	3	80	91
5a	C_6H_5	$C_{27}H_{27}ClN_4O_7S$	3.5	5	63	79
5b	4-Cl-C_6H_4	$C_{27}H_{26}Cl_2N_4O_7S$	2.5	6	65	82
5c	4-NO_2-C_6H_4	$C_{27}H_{26}Cl_2N_5O_9S$	3.0	7	61	79
5d	2-CH_3-C_6H_4	$C_{28}H_{29}ClN_4O_7S$	2.5	5	70	81
5e	4-CH_3-C_6H_4	$C_{28}H_{29}ClN_4O_7S$	2.0	5	67	82
5f	3-OH – C_6H_4	$C_{27}H_{27}ClN_4O_8S$	3.0	5	77	87
5g	4-OH – C_6H_4	$C_{27}H_{27}ClN_4O_8S$	2.5	4	79	90

A: Conventional heating. B : microwave irradiation

Table 2 Anti bacterial and nematicidal activity of 4 a-g and 5a-g

Compound	**Anti bacterial activity Minimum Inihibitory concentration (MIC, µg/mL)**				**Nematicidal activity** *D.mycelio phagus*	*C.elegans*
	B.Sublities	*S.aureas*	*E.coli*	*S.pyogenes*		
4a	50	25	50	50	940	960
4b	12.5	12.5	25	12.5	360	400
4c	25	25	12.5	12.5	440	390
4d	25	50	25	25	610	650
4e	100	50	50	50	1070	1010
4f	12.5	12.5	12.5	50	210	320
4g	50	50	100	25	420	670
5a	50	50	---	25	710	650
5b	12.5	25	12.5	12.5	400	350
5c	25	25	25	12.5	490	510
5d	50	100	---	50	1030	1050
5e	50	50	50	50	910	970
5f	12.5	12.5	25	12.5	360	240
5g	50	25	50	50	660	540
Strptomycin	10	10	10	10	----	----
Neomycin	30	30	30	30	----	----