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A Synthetic Approach, Characterization and Biological Evaluation of Novel 5-(Arylidene)-2-(5-methyl-1,3,4-thiadiazol-2-ylimino)thiazolidin-4-one Derivatives

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The extensive biological potential of thiazolidin-4-one and 1,3,4-thiadiazole moieties, the novel string of 5-(arylidene)-2-(5-methyl-1,3,4-thiadiazol-2-ylimino)thiazolidin-4-one has been synthesized and characterized. The synthesized derivatives were screened for antimicrobial potential using serial tube dilution method. The results showed that all the synthesized compounds have significant biological activity against the microorganisms being tested. The antimicrobial activity of the compounds **TA$_2$**, **TA$_3$**, **TA$_4$**, **TA$_9$**, **TA$_{10}$** and **TA$_{20}$** against the tested microbial strains was promising. Compound **TA$_4$** (2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)-5-(4-nitrobenzylidene)- thiazolidin-4-one) and **TA$_2$** (5-(4-chlorobenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one) showed promising antimicrobial activity against microbial strains. Compound **TA$_9$** (5-(4-(benzyloxy)benzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one) was found to be the most effective towards *B. subtilis*. Compound **TA$_{10}$** (5-(3,4-dimethoxybenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one) was discovered to be the most potent against the Gram-negative bacteria. Compounds **TA$_3$** (5-(4-bromobenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one) and **TA$_{20}$** (5-(2-bromobenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one) were the most effective compounds against the fungal strain.

Keywords: Thiazolidin-4-ones, Thiadiazoles, Antimicrobial activity.

INTRODUCTION

Microbial infections are becoming a significant cause of human health problems, with a rise in the number of patients worldwide. Somewhere the main cause behind this occurrence is the development of microbial strain resistance. Although various antimicrobial drugs have been used for treatment, the detection of safe and effective drugs is still not common [1,2].

The nitrogen and sulfur compounds had shown their omnipresence in the field of heterocyclic compounds, due to their physical and chemical properties quite relevant to the development of new drug compounds. Rings known for their possible pharmaceutical uses include sulfur and nitrogen atoms such as thiazolidinone. The extensive biological potential of this thiazolidinone containing compounds such as anticancer [3], antifungal and antibacterial [4], anti-inflammatory [5], anti-urease [6], tyrosinase inhibitor [7], COX-2 inhibitor [8], anti-amoebic [9], antitubercular, antiviral, antimicrobial [10-13], *etc.* were reported.

Another five-membered 1,3,4-thiadiazole ring compounds play a major role and exist in various synthetic and natural compounds having biologically potential. Thiadiazoles have been reported to possess various pharmacological activities, according to the literature survey. Their derivatives also had a wide variety of pharmacological activities, including antibacterial [14,15], anti-HIV [16], antiproliferative [17-20], antimicrobial [21-23], *etc.*

To achieve better antimicrobial results, their biological activities have shown interest in the technique of combining substituted thiazolidinones linked with thiadiazoles within one system. A series of 5-(arylidene)-2-(5-methyl-1,3,4-thiadiazol-2-ylimino)thiazolidin-4-one derivatives were synthesized and characterized by IR, ^{1}H & ^{13}C NMR and mass spectral analysis (**TA$_1$-TA$_{20}$**). The antimicrobial potential of the resulting candidates towards *E. coli, P. aeruginosa, S. aureus, B. subtilis, C. albicans, A. niger* by using the serial tube dilution method were also studied.

EXPERIMENTAL

The analytical-grade chemicals were used without any further purification. Thin-layer chromatography (TLC) was used to confirm the reaction completion. The melting points of synthesized derivatives were determined without correction using a Decibel melting point apparatus. Using potassium bromide (KBr pellets), the Perkin Elmer IR spectrophotometer reported infrared spectra. There have been observations of ^{1}H NMR on the Bruker Avance III 400 NMR Spectrophotometer using the appropriate solvent. An LC-MS/MS QTOF Make-SCIEX mass spectrometer was used to record the mass spectra.

Synthesis of 2-amino-5-methyl-1,3,4-thiadiazoles (I): Acetic acid (0.06 mol) and thiosemicarbazide (0.072 mol) using concentrated H_2SO_4 (90 mL) on a water bath were refluxed for 9-11 h. Cooled the solution, after refluxing and further neutralized with ammonia solution. The product was collected after neutralization, which has been filtered and washed thoroughly with distilled water to eliminate any impurity, if any. Finally, recrystallization was done by using ethanol as a solvent [24].

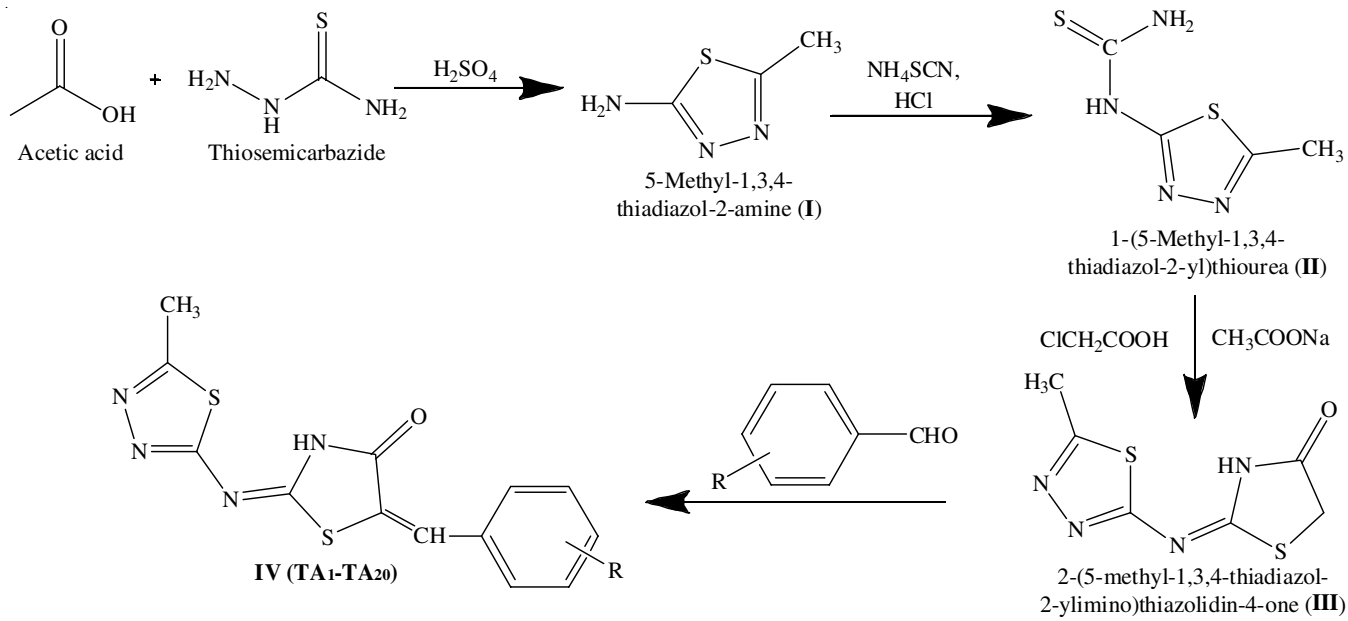
Synthesis of 1-(5-methyl-1,3,4-thiadiazol-2-yl)thiourea (II): Intermediate-I (0.04 mol) was dissolved in a minimum amount of dilute HCl in a round bottom flask; further then treated with ammonium thiocyanate (0.08 mol). The content of the flask was refluxed onto a water bath for 3-4 h. With vigorous shaking, the flask contents were poured into a beaker containing ice water. After filtering and washing the solid with distilled water, it was recrystallized with ethanol [25].

Synthesis of 2-(5-methyl-1,3,4-thiadiazol-2-ylimino)-thiazolidin-4-one (III): The refluxing of intermediate-II (0.02 mol) in dimethylformamide, chloroacetic acid (0.02 mol) and sodium acetate (0.02 mol) was carried for 16 to 18 h. The flask contents were poured into the beaker having crushed ice. The produced precipitate was filtered and washed several times with distilled water. The alcohol was used for recrystallization [26].

Synthesis of 5-(Arylidene)-2-(5-methyl-1,3,4-thiadiazol-2-ylimino)thiazolidin-4-one derivatives (TA_1-TA_{20}): In glacial acetic acid, a mixture of III (0.01mol), anhydrous sodium acetate (0.01 mol) and aldehyde derivatives (0.01 mol) were refluxed about 4-5 h. The resulting product was filtered after the reaction mixture had cooled (**Scheme-I**). Washed the obtained product with warm water give final compounds (TA_1-TA_{20}). The resulting product was recrystallized from ethanol [27].

5-(Benzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)-imino)thiazolidin-4-one (TA_1): Yield: 84.77%; m.p. 202-204 ºC; m.f. $C_{13}H_{10}N_4OS_2$; *m.w.*: 302.37; R_f: 0.60. IR (KBr, ν_{max}, cm^{-1}): 2801 (C-H *str.*, aliphatic), 617 (C-S bend), 1390 (C-N *str.*), 1635 (C=N *str.*), 3429 (N-H *str.*, thiazolidine ring), 1696 (C=O *str.*, thiazolidin-4-one), 1637 (C=C *str.*), 3154 (C-H *str.*, aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.97-7.89 (m, 5H, Ar-H), 7.81 (s, 1H, -CH=), 12.1 (s, 1H, NH), 2.5 (s, 3H, CH_3 of thiadiazole); ^{13}C NMR (DMSO-d_6): δ 171.0, 155.4, 145.2, 140.2, 133.4, 125.5, 124.9, 114.5, 17.2; MS: *m/z* (M^++1 303.03).

5-(4-Chlorobenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA_2): Yield: 78.52%; m.p. 228-230 ºC; m.f. $C_{13}H_9N_4OS_2Cl$; *m.w.*: 336.81; R_f: 0.72. IR (KBr, ν_{max}, cm^{-1}): 2902 (C-H *str.*, aliphatic), 637 (C-S bend), 1321 (C-N *str.*), 1694 (C=N *str.*), 3452 (N-H *str.*, thiazolidine ring), 1702 (C=O *str.*, thiazolidin-4-one), 1670 (C=C *str.*), 3162 (C-H *str.*, aromatic ring), 705(C-Cl bend); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.82-7.79 (m, 4H, Ar-H), 7.80 (s, 1H, -CH=),



R = **TA_1:** H; **TA_2:** 4-chloro; **TA_3:** 4-bromo; **TA_4:** 4-nitro; **TA_5:** 4-fluoro; **TA_6:** 4-hydroxy; **TA_7:** 4-methoxy; **TA_8:** 2-hydroxy; **TA_9:** 4-benzyloxy; **TA_{10}:** 3,4-dimethoxy; **TA_{11}:** 2- methoxy; **TA_{12}:** 2-fluoro; **TA_{13}:** 3-bromo; **TA_{14}:** 4-dimethylamino; **TA_{15}:** 4-methyl; **TA_{16}:** 3-hydroxy; **TA_{17}:** 2-nitro; **TA_{18}:** 3-chloro; **TA_{19}:** 2-chloro; **TA_{20}:** 2-bromo

Scheme-I: Synthesis of final compounds (TA_1-TA_{20})

12.19 (s, 1H, NH), 2.54 (s, 3H, CH_3 of thiadiazole); ^{13}C NMR (DMSO-d_6): δ 172.0, 157.3, 141.6, 141.3, 130.6, 130.4, 126.5, 125.4, 114.6, 17.5; MS: *m/z* (M^++1 337.89).

5-(4-Bromobenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA$_3$): Yield: 83.18%; m.p. 229-231 ºC; m.f. $C_{13}H_9N_4OS_2Br$; *m.w.*: 381.27; R_f: 0.74. IR (KBr, ν_{max}, cm^{-1}): 2860 (C-H *str.*, aliphatic), 617 (C-S bend), 1319 (C-N *str.*), 1690 (C=N *str.*), 3434 (N-H *str.*, thiazolidine ring), 1696 (C=O *str.*, thiazolidin-4-one), 1663 (C=C *str.*), 3135 (C-H *str.*, aromatic ring), 617 (C-Br bend); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.41-7.97 (m, 4H, Ar-H), 7.78 (s, 1H, -CH=), 12.39 (s, 1H, NH), 2.58 (s, 3H, CH_3 of thiadiazole); ^{13}C NMR (DMSO-d_6): δ 172.0, 155.3, 141.7, 140.3, 133.4, 133.3, 125.6, 120.2, 115.1, 17.9; MS: *m/z* (M^++1 382.02).

2-((5-Methyl-1,3,4-thiadiazol-2-yl)imino)-5-(4-nitrobenzylidene)thiazolidin-4-one (TA$_4$): Yield: 68.46%; m.p. 190-192 ºC; m.f. $C_{13}H_9N_5O_3S_2$; *m.w.*: 347.37; R_f: 0.70. IR (KBr, ν_{max}, cm^{-1}): 2803 (C-H *str.*, aliphatic), 617 (C-S bend), 1301 (C-N *str.*), 1636 (C=N *str.*), 3442 (N-H *str.*, thiazolidine ring), 1703 (C=O *str.*, thiazolidin-4-one), 1665 (C=C *str.*), 3164 (C-H *str.*, aromatic ring), 1558 (NO_2 assym. *str.*), 1299 (NO_2 symm. *Str.*); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.21-8.48 (m, 4H, Ar-H), 7.78 (s, 1H, -CH=), 12.12 (s, 1H, NH), 2.53 (s, 3H, CH_3 of thiadiazole); ^{13}C NMR (DMSO-d_6): δ 171.8, 158.3, 155.9, 149.3, 141.6, 140.2, 127.1, 120.6, 115.6, 17.9; MS: *m/z* (M^++1 348.05).

5-(4-Fluorobenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA$_5$): Yield: 85.62%; m.p. 245-247 ºC; m.f. $C_{13}H_9N_4OS_2F$; *m.w.*: 320.36; R_f: 0.71. IR (KBr, ν_{max}, cm^{-1}): 2904 (C-H *str.*, aliphatic), 612 (C-S bend), 1320 (C-N *str.*), 1637 (C=N *str.*), 3431 (N-H *str.*, thiazolidine ring), 1697 (C=O *str.*, thiazolidin-4-one), 1637 (C=C *str.*), 3154 (C-H *str.*, aromatic ring), 1269 (C-F bend); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.26-7.86 (m, 4H, Ar-H), 7.83 (s, 1H, -CH=), 12.35 (s, 1H, NH), 2.58 (s, 3H, CH_3 of thiadiazole); ^{13}C NMR (DMSO-d_6): δ 172.2, 156.4, 155.2, 141.4, 141.3, 126.8, 126.2, 115.9, 104.4, 18.2; MS: *m/z* (M^++1 321.06).

5-(4-Hydroxybenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA$_6$): Yield: 69.23%; m.p. 203-205 ºC; m.f. $C_{13}H_{10}N_4O_2S_2$; *m.w.*: 318.37; R_f: 0.58. IR (KBr, ν_{max}, cm^{-1}): 2862 (C-H *str.*, aliphatic), 638 (C-S bend), 1320 (C-N *str.*), 1632 (C=N *str.*), 3440 (N-H *str.*, thiazolidine ring), 1692 (C=O *str.*, thiazolidin-4-one), 1662 (C=C *str.*), 3140 (C-H *str.*, aromatic ring), 3402 (OH *str.*); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.5-7.7 (m, 4H, Ar-H), 7.77 (s, 1H, -CH=), 12.12 (s, 1H, NH), 2.52 (s, 3H, CH_3 of thiadiazole), 9.64 (s, 1H, OH); ^{13}C NMR (DMSO-d_6): δ 172.4, 169.8, 151.3, 141.4, 142.3, 140.7, 140.4, 137.8, 125.6, 115.6, 17.2; MS: *m/z* (M^++1 319.07).

5-(4-Methoxybenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA$_7$): Yield: 72.53%; m.p. 165-167 ºC; m.f. $C_{14}H_{12}N_4O_2S_2$; *m.w.*: 332.40; R_f: 0.62. IR (KBr, ν_{max}, cm^{-1}): 2800 (C-H *str.*, aliphatic), 658 (C-S bend), 1321 (C-N *str.*), 1636 (C=N *str.*), 3426 (N-H *str.*, thiazolidine ring), 1695 (C=O *str.*, thiazolidin-4-one), 1605 (C=C *str.*), 3164 (C-H *str.*, aromatic ring), 1245 & 1097 (O-CH_3 *str.*, *p*-substitution on phenyl ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.98-7.87 (m, 4H, Ar-H), 7.78 (s, 1H, -CH=), 11.92 (s, 1H, NH), 2.57 (s, 3H, CH_3 of thiadiazole), 3.78 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6): δ 172.0, 155.3, 141.6, 141.3, 139.8, 125.2, 115.2, 104.2, 42.5, 17.2; MS: *m/z* (M^++1 333.04).

5-(2-Hydroxybenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA$_8$): Yield: 68.59%; m.p. 189-191 ºC; m.f. $C_{13}H_{10}N_4O_2S_2$; *m.w.*: 318.37; R_f: 0.55. IR (KBr, ν_{max}, cm^{-1}): 2899 (C-H *str.*, aliphatic), 658 (C-S bend), 1321 (C-N *str.*), 1638 (C=N *str.*), 3420 (N-H *str.*, thiazolidine ring), 1696 (C=O *str.*, thiazolidin-4-one), 1578 (C=C *str.*), 3151 (C-H *str.*, aromatic ring), 3450 (OH *str.*); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.62-7.61 (m, 4H, Ar-H), 7.92 (s, 1H, -CH=), 12.14 (s, 1H, NH), 2.59 (s, 3H, CH_3 of thiadiazole), 10.21 (s, 1H, OH); ^{13}C NMR (DMSO-d_6): δ 171.8, 155.3, 150.1, 142.3, 141.7, 121.3, 120.9, 116.4, 115.8, 115.2, 17.3; MS: *m/z* (M^++1 319.02).

5-(4-(Benzyloxy)benzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA$_9$): Yield: 78.38%; m.p. 232-234 ºC; m.f. $C_{20}H_{16}N_4O_2S_2$; *m.w.*: 408.49; R_f: 0.82. IR (KBr, ν_{max}, cm^{-1}): 2803 (C-H *str.*, aliphatic), 656 (C-S bend), 1321 (C-N *str.*), 1601 (C=N *str.*), 3414 (N-H *str.*, thiazolidine ring), 1686 (C=O *str.*, thiazolidin-4-one), 1577 (C=C *str.*), 3159 (C-H *str.*, aromatic ring), 1262 & 1165 (O-CH_2 *str.*, *p*-substitution on phenyl ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.71-7.72 (m, 9H, Ar-H), 7.81 (s, 1H, -CH=), 11.96 (s, 1H, NH), 2.59 (s, 3H, CH_3 of thiadiazole), 4.97 (s, 2H, OCH_2); ^{13}C NMR (DMSO-d_6): δ 171.8, 160.4, 155.4, 142.3, 141.7, 132.4, 130.2, 129.1, 120.5, 117.2, 115.4, 115.3, 65.6, 17.4; MS: *m/z* (M^++1 409.08).

5-(3,4-Dimethoxybenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA$_{10}$): Yield: 69.21%; m.p. 186-188 ºC; m.f. $C_{15}H_{14}N_4O_3S_2$; *m.w.*: 362.42; R_f: 0.59. IR (KBr, ν_{max}, cm^{-1}): 2799 (C-H *str.*, aliph-atic), 638 (C-S bend), 1321 (C-N *str.*), 1637 (C=N *str.*), 3429 (N-H *str.*, thiazolidine ring), 1657 (C=O *str.*, thiazolidin-4-one), 1557 (C=C *str.*), 3153 (C-H *str.*, aromatic ring), 1245 & 1127 (O-CH_3 *str.*, substitution on phenyl ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.06-7.42 (m, 3H, Ar-H), 7.81 (s, 1H, -CH=), 12.04 (s, 1H, NH), 2.61 (s, 3H, CH_3 of thiadiazole), 3.82 (s, 3H, OCH_3 of *m*-position), 3.81 (s, 3H, OCH_3 of *p*-position); ^{13}C NMR (DMSO-d_6): δ 171.1, 156.3, 148.7, 148.1, 141.4, 140.3, 118.4, 115.6, 115.5, 51.4, 17.4; MS: *m/z* (M^++1 363.05).

5-(2-Methoxybenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA$_{11}$): Yield: 71.08%; m.p. 154-156 ºC; m.f. $C_{14}H_{12}N_4O_2S_2$; *m.w.*: 332.40; R_f: 0.64. IR (KBr, ν_{max}, cm^{-1}): 2792 (C-H *str.*, aliphatic), 658 (C-S bend), 1310 (C-N *str.*), 1650 (C=N *str.*), 3426 (N-H *str.*, thiazolidine ring), 1695 (C=O *str.*, thiazolidin-4-one), 1572 (C=C *str.*), 3164 (C-H *str.*, aromatic ring), 1243 & 1037 (O-CH_3 *str.*, *o*-substitution on phenyl ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.84-7.80 (m, 4H, Ar-H), 7.95 (s, 1H, -CH=), 11.94 (s, 1H, NH), 2.58 (s, 3H, CH_3 of thiadiazole), 3.85 (s, 3H, OCH_3); ^{13}C NMR (DMSO-d_6): δ 171.8, 155.6, 155.2, 142.3, 141.7, 120.5, 117.9, 116.4, 115.9, 115.6, 108.9, 53.5, 17.8; MS: *m/z* (M^++1 333.02).

5-(2-Fluorobenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA$_{12}$): Yield: 76.56%; m.p. 249-251 ºC; m.f. $C_{13}H_9N_4OS_2F$; *m.w.*: 320.36; R_f: 0.72. IR (KBr, ν_{max}, cm^{-1}): 2800 (C-H *str.*, aliphatic), 637 (C-S bend), 1321

(C-N *str.*), 1635 (C=N *str.*), 3429 (N-H *str.*, thiazolidine ring), 1605 (C=O *str.*, thiazolidin-4-one), 1557 (C=C *str.*), 3137 (C-H *str.*, aromatic ring), 1270 (C-F bend); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.05-7.42 (m, 4H, Ar-H), 7.93 (s, 1H, -CH=), 11.98 (s, 1H, NH), 2.62 (s, 3H, CH_3 of thia-diazole); ^{13}C NMR (DMSO-d_6): δ 172.1, 155.4, 152.4, 142.3, 141.6, 123.2, 119.2, 118.4, 117.6, 115.3, 112.4, 17.4; MS: *m/z* (M^++1 321.03).

5-(3-Bromobenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA_{13}): Yield: 85.65%; m.p. 161-163 ºC; m.f. $C_{13}H_9N_4OS_2Br$; *m.w.*: 381.27; R_f: 0.73. IR (KBr, ν_{max}, cm^{-1}): 2803 (C-H *str.*, aliphatic), 638 (C-S bend), 1262 (C-N *str.*), 1686 (C=N *str.*), 3414 (N-H *str.*, thiazolidine ring), 1687 (C=O *str.*, thiazolidin-4-one), 1601 (C=C *str.*), 3159 (C-H *str.*, aromatic ring), 656 (C-Br bend); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.07-7.64 (m, 4H, Ar-H), 7.67 (s, 1H, -CH=), 11.94 (s, 1H, NH), 2.57 (s, 3H, CH_3 of thiadiazole); ^{13}C NMR (DMSO-d_6): δ 171.9, 155.4, 141.6, 140.4, 132.5, 122.3, 122.1, 121.5, 120.8, 119.6, 114.8, 17.2; MS: *m/z* (M^++1 382).

5-((4-Dimethylamino)benzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA_{14}): Yield: 77.07%; m.p. 251-253 ºC; m.f. $C_{15}H_{15}N_5OS_2$; *m.w.*: 345.07; R_f: 0.61. IR (KBr, ν_{max}, cm^{-1}): 2792 (C-H *str.*, aliphatic), 637 (C-S bend), 1267 (C-N *str.*), 1645 (C=N *str.*), 3427 (N-H *str.*, thiazolidine ring), 1695 (C=O *str.*, thiazo-lidin-4-one), 1573s (C=C *str.*), 3165 (C-H *str.*, aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.73-7.52 (m, 4H, Ar-H), 7.58 (s, 1H, -CH=), 12.42 (s, 1H, NH), 2.61 (s, 3H, CH_3 of thiadiazole), 3.12 (s, 6H, 2 × CH_3),; ^{13}C NMR (DMSO-d_6): δ 171.6, 155.9, 142.4, 141.7, 140.4, 118.6, 115.6, 113.9, 107.6, 43.4, 17.9; MS: *m/z* (M^++1 346.07).

2-((5-Methyl-1,3,4-thiadiazol-2-yl)imino)-5-(4-methylbenzylidene)thiazolidin-4-one (TA_{15}): Yield: 75.91%; m.p. 170-172 ºC; m.f. $C_{14}H_{12}N_4OS_2$; *m.w.*: 316.40; R_f: 0.62. IR (KBr, ν_{max}, cm^{-1}): 2899 (C-H *str.*, aliphatic), 637 (C-S bend), 1269 (C-N *str.*), 1638 (C=N *str.*), 3432 (N-H *str.*, thiazolidine ring), 1637 (C=O *str.*, thiazolidin-4-one), 1657 (C=C *str.*), 3155 (C-H *str.*, aromatic ring); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.20-7.79 (m, 4H, Ar-H), 7.72 (s, 1H, -CH=), 12.32 (s, 1H, NH), 2.51 (s, 3H, CH_3 of thiadiazole), 2.85 (s, 3H, CH_3 adjacent to phenyl ring); ^{13}C NMR (DMSO-d_6): δ 171.8, 155.4, 141.7, 140.6, 138.3, 130.6, 130.1, 128.4, 115.9, 20.2, 17.4; MS: *m/z* (M^++1 317.03).

5-(3-Hydroxybenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA_{16}): Yield: 67.75%; m.p. 177-179 ºC; m.f. $C_{13}H_{10}N_4O_2S_2$; *m.w.*: 318.37; R_f: 0.56. IR (KBr, ν_{max}, cm^{-1}): 2899 (C-H *str.*, aliphatic), 658 (C-S bend), 1321 (C-N *str.*), 1638 (C=N *str.*), 3420 (N-H *str.*, thiazolidine ring), 1696 (C=O *str.*, thiazolidin-4-one), 1578 (C=C *str.*), 3151 (C-H *str.*, aromatic ring), 3450 (OH *str.*); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.62-7.61 (m, 4H, Ar-H), 7.92 (s, 1H, -CH=), 12.14 (s, 1H, NH), 2.59 (s, 3H, CH_3 of thiadiazole), 10.21 (s, 1H, OH); ^{13}C NMR (DMSO-d_6): δ 171.8, 155.3, 150.1, 142.3, 141.7, 121.3, 120.9, 116.4, 115.8, 115.2, 17.3; MS: *m/z* (M^++1 319.02).

2-((5-Methyl-1,3,4-thiadiazol-2-yl)imino)-5-(2-nitrobenzylidene)- thiazolidin-4-one (TA_{17}): Yield: 71.12%; m.p. 162-164 ºC; m.f. $C_{13}H_9N_5O_3S_2$; *m.w.*: 347.37; R_f: 0.78. IR (KBr, ν_{max}, cm^{-1}): 2801 (C-H *str.*, aliphatic), 637 (C-S bend), 1269 (C-N *str.*), 1637 (C=N *str.*), 3430 (N-H *str.*, thiazolidine ring), 1696 (C=O *str.*, thiazolidin-4-one), 1604 (C=C *str.*), 3130 (C-H *str.*, aromatic ring), 1402 (NO_2 assym. *str.*), 1321 (NO_2 symm. *str.*); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.65-7.98 (m, 4H, Ar-H), 8.18 (s, 1H, -CH=), 12.26 (s, 1H, NH), 2.59 (s, 3H, CH_3 of thiadiazole); ^{13}C NMR (DMSO-d_6): δ 172.1, 155.5, 145.6, 143.2, 141.4, 133.6, 126.4, 125.5, 125.3, 114.8, 18.2; MS: *m/z* (M^++1 348.03).

5-(3-Chlorobenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA_{18}): Yield: 82.15%; m.p. 209-211 ºC; m.f. $C_{13}H_9N_4OS_2Cl$; *m.w.*: 336.81; R_f: 0.74. IR (KBr, ν_{max}, cm^{-1}): 2801 (C-H *str.*, aliphatic), 617 (C-S bend), 1270 (C-N *str.*), 1635 (C=N *str.*), 3429 (N-H *str.*, thiazolidine ring), 1655 (C=O *str.*, thiazolidin-4-one), 1605 (C=C *str.*), 3137 (C-H *str.*, aromatic ring), 781 (C-Cl bend); ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.18-7.79 (m, 4H, Ar-H), 7.81 (s, 1H, -CH=), 12.56 (s, 1H, NH), 2.52 (s, 3H, CH_3 of thia-diazole); ^{13}C NMR (DMSO-d_6): δ 171.4, 155.4, 141.6, 140.4, 134.6, 132.3, 128.2, 127.4, 121.5, 121.2, 116.2, 16.9; MS: *m/z* (M^++1 337.92).

5-(2-Chlorobenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA_{19}): Yield: 72.34%; m.p. 221-223 ºC; m.f. $C_{13}H_9N_4OS_2Cl$; *m.w.*: 336.81; R_f: 0.63. IR (KBr, ν_{max}, cm^{-1}): 2800 (C-H *str.*, aliphatic), 637 (C-S bend), 1321 (C-N *str.*), 1636 (C=N *str.*), 3431 (N-H *str.*, thiazolidine ring), 1696 (C=O *str.*, thiazolidin-4-one), 1602 (C=C *str.*), 3130 (C-H *str.*, aromatic ring), 637 (C-Cl bend); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.87-7.89 (m, 4H, Ar-H), 7.92 (s, 1H, -CH=), 12.45 (s, 1H, NH), 2.61 (s, 3H, CH_3 of thiadiazole); ^{13}C NMR (DMSO-d_6): δ 172.1, 156.2, 141.6, 141.2, 129.2, 128.0, 126.5, 126.1, 125.6, 124.8, 114.9, 17.5; MS: *m/z* (M^++1 337.93).

5-(2-Bromobenzylidene)-2-((5-methyl-1,3,4-thiadiazol-2-yl)imino)thiazolidin-4-one (TA_{20}): Yield: 76.67%; m.p. 178-180 ºC; m.f. $C_{13}H_9N_4OS_2Br$; *m.w.*: 381.27; R_f: 0.75. IR (KBr, ν_{max}, cm^{-1}): 2803 (C-H *str.*, aliphatic), 638 (C-S bend), 1262 (C-N *str.*), 1601 (C=N *str.*), 3415(N-H *str.*, thiazolidine ring), 1687 (C=O *str.*, thiazolidin-4-one), 1577 (C=C *str.*), 3159 (C-H *str.*, aromatic ring), 652 (C-Br bend); ^{1}H NMR (400 MHz, DMSO-d_6): δ 6.72-7.76 (m, 4H, Ar-H), 7.91 (s, 1H, -CH=), 12.24 (s, 1H, NH), 2.63 (s, 3H, CH_3 of thiadiazole); ^{13}C NMR (DMSO-d_6): δ 171.8, 154.6, 141.6, 140.3, 138.5, 135.4, 129.5, 129.3, 121.3, 115.4,+ 17.2; MS: *m/z* (M^++1 382).

***in vitro* Antimicrobial screening:** Antimicrobial potential against elective strains *Escherichia coli* (MTCC 1652), *Bacillus subtilis* (MTCC 441), *Psuedomonas aeruginosa* (MTCC 424), *Staphylococcus aureus* (MTCC 7443) and *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 8189) were screened using the serial dilution process and the MIC (minimum inhibitory concentration) was determined. For bacterial and fungal development, double strength nutrient broth IP and Sabouraud's dextrose broth IP were used as nutrient media. For antibacterial and antifungal screening, ciprofloxacin and ketoconazole were used as a reference. To provide a concentration of 100 µg/mL, the test sample compounds were dissolved in dimethyl sulfoxide and were diluted in series to provide a concentration of 50, 25, 12.5, 6.25, 3.125 and 1.56 µg/mL in 1 mL nutrient medium culture tubes. For bacterial strains, test tubes were inoculated

with 0.1 mL of fresh inoculum and incubated for 24 h at 37 ± 1 ºC, 48 h for *Candida albicans* and 7 days for *A. niger* at 25 ± 1 ºC. Development was observed in the tubes and the absence of growth determined the inhibition [28].

RESULTS AND DISCUSSION

Substituted 4-thiazolidinones linked to 1,3,4-thiadiazoles have been synthesized (**Scheme-I**). Firstly, acetic acid and thiosemicarbazide were treated using concentrated sulphuric acid to obtain thiadiazole (**I**). Further, the ammonium thiocyanate and dilute HCl reacted with (**I**) resulted in 1-(5-methyl-1,3,4-thiadiazol-2-yl)thiourea (**II**). Further on reaction with chloroacetic acid and sodium acetate resulted in 2-(5-methyl-1,3,4-thiadiazol-2-ylimino)thiazolidin-4-one (**III**). Benzaldehyde derivatives were then treated with **III** to give final derivatives (**TA_1-TA_{20}**). Further synthesized derivatives (**TA_1-TA_{20}**) were characterized by spectral analysis.

The IR vibrations for N-H, C=O and C=N at 3442-3402, 1703-1605, 1694-1601 cm^{-1}, respectively, were shown by the IR spectra of final compounds (**TA_1-TA_{20}**). IR stretching at 1670-1557, 1390-1262 and 2904-2792 cm^{-1} confirmed the appearance of C=C, C-N and C-H aliphatic, respectively in the synthesized compounds. IR vibrations at 658-612 cm^{-1} also confirmed the appearance of C-S in the synthesized compounds. The asymmetric and symmetric vibrations appeared at 1558-1402 and 1321-1299 cm^{-1} confirmed the appearance of Ar-NO_2 group in compounds **TA_4** and **TA_{17}**. The appearance of Ar-OCH_3 group in the synthesized derivatives was confirmed by IR in compounds **TA_7**, **TA_9**, **TA_{10}**, **TA_{11}** by C-O-C stretching at 1262-1243 and 1165-1037 cm^{-1}. At 3421-3402 cm^{-1}, the OH stretch appeared. The presence of Ar-F group in the synthesized compounds **TA_5** and **TA_{12}** was indicated by IR vibrations at 1270-1269 cm^{-1}. The existence of chloro group was indicated by IR vibrations at 781-705 cm^{-1} in the compounds **TA_2**, **TA_{18}** and **TA_{19}**. The existence of bromo group in the compounds **TA_3**, **TA_{13}**, **TA_{20}** indicated by IR vibrations at 656-617 cm^{-1}.

Multiplet signals in the ^{1}H NMR (400 MHz, DMSO-d_6) spectra of the synthesized derivatives were observed at 6.50-8.48 ppm, confirming the existence of aromatic protons. Singlet(s) between 11.92-12.56 and 7.58-7.95 δ ppm suggested the presence of groups -NH and-CH=, respectively. The singlet(s) at 2.50-2.63 δ ppm in synthesized compounds suggested the presence of thiadiazole-adjacent CH_3. The presence of Ar-OH in the compounds **TA_6** and **TA_8** was confirmed at 9.47-10.21 δ ppm by the singlet (s). The occurrence of singlet(s) between 3.78-3.85 δ ppm implies that OCH_3 group is present in **TA_7**, **TA_{10}** and **TA_{11}** compounds. The ^{13}C NMR signals appeared at the predicted chemical shifts. The mass of the compounds synthesized showed M^++1 peaks.

Antimicrobial potential: The synthesized derivatives (**TA_1-TA_{20}**) were then further screened for their *in vitro* bacterial and fungal strains including *Escherichia coli*, *Psuedomonas aeruginosa*, *Bacillus subtilis*, *Staphylococcus aureus* and *Aspergillus niger*, *Candida albicans*; using ciprofloxacin and ketoconazole as standards, respectively.

The biological potential of compound **TA_{10}** against *E. coli* was tested that showed a $pMIC_{ec}$ value of 1.76 µM/mL, while $pMIC_{ec}$ values of 1.40 and 1.38 µM/mL were less active in compounds **TA_{15}** and **TA_1** (Table-1). The compounds **TA_3**, **TA_{13}**, **TA_4** and **TA_2** showed $pMIC_{pa}$ values of 1.78, 1.78, 1.74 and 1.72 µM/mL, respectively. Compounds **TA_9** and **TA_{13}** represented the maximum antibacterial activity against *B. subtilis*,

TABLE-1
ANTIMICROBIAL ACTIVITY OF 5-(ARYLIDENE)-2-(5-METHYL-1,3,4-THIADIAZOL-2-YLIMINO)THIAZOLIDIN-4-ONE DERIVATIVES (**TA_1-TA_{20}**)

Compound	Minimum inhibitory concentration (pMIC, µM/mL)					
	Escherichia coli	*Pseudomonas aeruginosa*	*Bacillus subtilis*	*Staphylococcus aureus*	*Aspergillus niger*	*Candida albicans*
TA_1	1.38	1.38	1.68	1.38	1.38	1.38
TA_2	1.73	1.73	1.73	1.73	1.73	1.73
TA_3	1.48	1.78	1.48	1.48	1.78	1.78
TA_4	1.74	1.74	1.74	1.74	1.74	1.74
TA_5	1.71	1.41	1.71	1.41	1.41	1.71
TA_6	1.71	1.71	1.41	1.71	1.71	1.71
TA_7	1.72	1.72	1.42	1.42	1.42	1.42
TA_8	1.41	1.41	1.71	1.41	1.71	1.41
TA_9	1.51	1.51	1.81	1.51	1.51	1.51
TA_{10}	1.76	1.76	1.46	1.46	1.46	1.46
TA_{11}	1.41	1.41	1.41	1.72	1.72	1.41
TA_{12}	1.41	1.41	1.41	1.71	1.41	1.41
TA_{13}	1.48	1.78	1.78	1.48	1.48	1.48
TA_{14}	1.44	1.44	1.74	1.44	1.44	1.44
TA_{15}	1.40	1.70	1.40	1.40	1.40	1.40
TA_{16}	1.71	1.41	1.71	1.41	1.41	1.71
TA_{17}	1.44	1.44	1.44	1.44	1.44	1.44
TA_{18}	1.43	1.43	1.73	1.73	1.43	1.43
TA_{19}	1.43	1.43	1.43	1.43	1.43	1.43
TA_{20}	1.48	1.48	1.48	1.48	1.78	1.78
Ciprofloxacin	2.32	2.32	2.02	2.02	–	–
Ketoconazole	–	–	–	–	1.93	1.93

with $pMIC_{bs}$ values of 1.81 and 1.78 μM/mL, respectively. Compound **TA_4** indicated the highest potential against *S. aureus* with a $pMIC_{sa}$ value of 1.74 μM/mL. The most potent antifungal activity was demonstrated by the **TA_3**, **TA_{20}** and **TA_4** compound with a pMIC value of 1.78, 1.78 and 1.74 μM/mL (Table-1). Compounds **TA_2** and **TA_5** have shown that antimicrobial activity is decreased by the substitution of the chloro group with the fluoro group. Replacing the chloro group in compound **TA_2** with the chloro (Cl) group at the *ortho* position (in **TA_{19}** compound) reduces activity. Results showed that compared to fluoro substituent; chloro substituent exerted greater activity against all microbial strains. The compound bearing methoxy group showed more antimicrobial activity as compared to the methyl substituted compound. The values observed suggested that the antibacterial/antifungal activity of these new analogs was significantly affected.

The antimicrobial activity of the compounds **TA_2**, **TA_3**, **TA_4**, **TA_9**, **TA_{10}** and **TA_{20}** against the tested microbial strains was promising. Compounds **TA_4** and **TA_2** possess appreciable antimicrobial activity. The most effective compound against the *B. subtilis* was **TA_9** with an electron-donating group among the synthesized derivatives. The derivative **TA_{10}** with an electron-donating group was found to be the most effective against Gram-negative strain. The most effective compounds against the fungal strain were **TA_3** and **TA_{20}** with bromo group substitution at *para* and *ortho* position. A closer look into the structure of the test compounds showed that the substituent serves to modulate their antimicrobial activity. As a result, these synthesized derivatives are being used as pharmacophore in the development of new antimicrobials with improved efficacy.

Structure-activity relationship (SAR): It is found that the synthesized derivatives (**TA_1-TA_{20}**) containing substituted benzaldehydes improved the bacterial and fungal activities significantly. By substituting electron-withdrawing groups including the nitro and chloro at the *para* position, the antimicrobial activity of the synthesized derivatives **TA_4** and **TA_2** was increased. Similarly, The electron-donating group; methoxy ($-OCH_3$) at the *meta* and *para* positions of compound **TA_{10}** increased its antibacterial potential against Gram-negative bacteria. The existence of an electron-withdrawing group having bromo group (-Br) at *ortho* and *para* positions increased the antifungal properties of the synthesized derivatives **TA_{20}** and **TA_3**. These molecules might be served as lead compounds in the development of more effective and less toxic antimicrobial agents.

Conclusion

A series of 5-(arylidene)-2-(5-methyl-1,3,4-thiadiazol-2-ylimino)thiazolidin-4-one derivatives were synthesized and characterized by IR, ^1H & ^{13}C NMR and mass spectral analysis (**TA_1-TA_{20}**). A serial dilution process was used to test all of the synthesized derivatives for antimicrobial activity. As a reference, ciprofloxacin and ketoconazole were used to determine the minimum inhibitory concentration. The antimicrobial screening revealed that the compounds **TA_2**, **TA_3**, **TA_4**, **TA_9**, **TA_{10}** and **TA_{20}** had promising antimicrobial activity against the tested microbial strains. Compounds **TA_4** and **TA_2** showed appreciable antimicrobial activity. Compound **TA_{10}**, which has an electron-donating group substitution on the aromatic ring, was found to be the most effective against Gram-negative bacteria. The most active compounds against the fungal strain were **TA_3** and **TA_{20}**, which had bromo substitutions at the *para* and *ortho* positions on the aromatic ring. These results suggested that further compounds should be synthesized and tested for antimicrobial activity using various aromatic or heteroaromatic aldehydes to see whether a new class of antimicrobials might be discovered.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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