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Synthesis and Characterization of 4-Thiazolidinones Derivatives with 6-Chlorobenzothiazole Moiety

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ABSTRACT

The 4-thiazolidinone ring system is a fundamental structure which is present in a large variety of synthetic pharmaceuticals that has a wide range of potential biological effects. In this work, thioglycolic acid and 6-chloro-*N*-(substituted benzylidene)benzothiazol-2-amine were condensed in DMF solvent in the presence of $ZnCl_2$ to obtain novel 3-(6-chlorobenzo[*d*]thiazol-2-yl)-2-(substituted aryl)thiazolidin-4-one derivatives. The structure of the synthesized compounds (**3a-j**) were confirmed using IR, ^1H & ^{13}C NMR and mass spectroscopy.

KEYWORDS

Benzothiazole, 4-Thiazolidinone, Thioglycolic acid, Schiff bases, Biological activities.

Asian Journal of Organic & Medicinal Chemistry

Volume: 8 Year: 2023
Issue: 3–4 Month: July–December
pp: 35–38
DOI: https://doi.org/10.14233/ajomc.2023.AJOMC-P30726

Received: 14 December 2023
Accepted: 30 December 2023
Published: 9 January 2024

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Available online at: http://ajomc.asianpubs.org

INTRODUCTION

It has been revealed that integrating two or more heterocyclic scaffolds in a single molecule can enable access to a wide range of molecules with various biological functions. As a result, developing an efficient and simple method for accessing new compounds containing thiazolidinone and benzothiazole rings is important. A significant variety of drugs on the market have well-proven the antimicrobial, antimalarial, antidiabetic, anticonvulsant, anti-inflammatory, anthelmintic, analgesic, antitubercular agent and other biological activities of benzothiazole compounds [1]. Thiazolidinones are five-membered unsaturated heterocyclic compounds that contain a carbonyl group and have one nitrogen, one sulfur and three carbon atoms. The 4-thiazolidinones are found in a diverse spectrum of physiologically active molecules from several pharmacological classes, earning them a special place in the field of medicinal chemistry. Anti-inflammatory [2-4], antihistaminic [5], anti-HIV [6], anticancer [7], anticonvulsant [8,9], analgesic, antimicrobial [10] and CNS stimulants are the examples [11]. Thiazolidinone-linked benzothiazole derivatives, in particular, have recently been shown to be intriguing compounds with a diverse set of pharmacological actions [12-14]. In melanoma, leukemia, lung, colon, ovarian, CNS, renal, prostate and breast cancers, benzothiazole substituted 4-thiazolidinone has shown considerable anticancer activity [15]. *In vitro* action of 2,4-thiazolidinedione with benzothiazole moiety against NSC lung cancer [16] has been demonstrated. 4-Thiazolidinone and benzothiazole have

also been shown to exhibit anticancer properties against colon HCT-116 and breast MCF-7 cancer cell lines [17].

Following these considerations, it seemed worthwhile to synthesize novel 4-thiazolidinone derivatives from Schiff bases, with thioglycolic acid integrating with a 6-chlorobenzothiazole moiety. These approaches may also provide valuable information for the subsequent design and development of more active biological agents through various modifications and derivatizations. The structures of the synthesized compounds (**3a-j**) were confirmed using IR, ^{1}H NMR, ^{13}C NMR and MS spectroscopy.

EXPERIMENTAL

All reagents were commercially available and used without further purification. The melting points were taken with the help of an open capillary tube and are uncorrected. The purity of the synthesized compounds was checked by TLC on precoated silica gel aluminum plates (E-Merck) using ethyl acetate: *n*-hexane (3:7) and visualized in a UV chamber. The IR spectra were recorded on Perkin-Elmer FTIR spectrum 2 with UATR accessory. ^{1}H and ^{13}C NMR spectra were recorded in DMSO with tetramethylsilane (TMS) as internal standard at 400 MHz on a Brucker spectrophotometer. The chemical shifts are reported as parts per million (ppm). Mass spectroscopy was recorded on Shimadzu GCMS QP 5000 instrument.

Procedure: 2-Amino-6-chlorobenzothiazole (**1**) and 6-chloro-*N*-(substituted benzylidene)benzo[*d*]thiazol-2-amine (**2**) was synthesized as per the reported procedure [18].

Synthesis of 3-(6-chlorobenzo[*d*]thiazol-2-yl)-2-(substituted aryl)thiazolidin-4-one (3a-j): In the Dean-Stark apparatus, 25 mL of DMF containing a pinch of anhydrous zinc chloride was added to a mixture of Schiff base (0.01 mol) and mercaptoacetic acid (0.012 mol). The mixture of the reaction was then refluxed for 8 h. On TLC, the progress of the reaction was monitored. After cooling, the reaction mixture was poured into ice-water. The obtained residue was dissolved in dichloromethane/ethylacetate and then the organic layer was washed with a 10 % Na_2CO_3 solution and finally with a brine solution to remove excess acid (**Scheme-I**). After filtering and multiple water washes, the resultant solid was dried over Na_2SO_4 and recrystallized from ethanol [19].

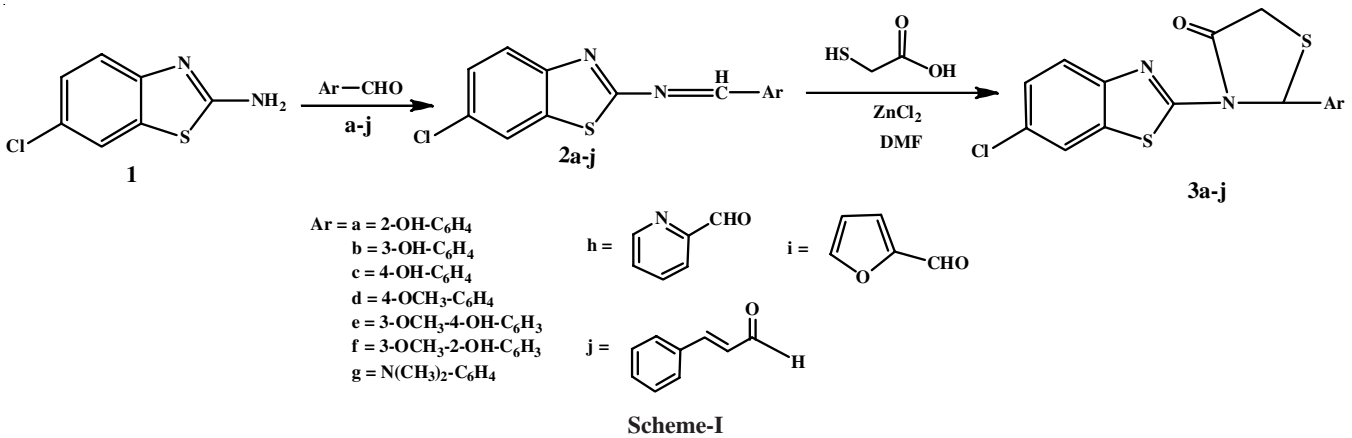
3-(6-Chlorobenzo[*d*]thiazol-2-yl)-2-(2-hydroxyphenyl)-thiazolidin-4-one (3a): Yield: 52%, m.p.: 161-163 ºC, m.f.: $C_{16}H_{11}N_2O_2S_2Cl$ (*m.w.* 362.85 g/mol); IR (KBr, ν_{max}, cm^{-1}): 3498 (-OH), 1773 (C=O), 1277 (C-N), 817 (C-Cl), 762; ^{1}H NMR (400 MHz, DMSO, δ ppm): 8.45 (1H, s), 8.13 (1H, d, *J* = 2.2 Hz), 7.95 (1H, d, *J* = 8.5 Hz), 7.39 (1H, dd, *J* = 7.2, 2.1 Hz), 7.13 (1H, s), 7.03-6.94 (2H, m), 6.80-6.67 (2H, m), 3.39 (2H, q, *J* = 13.4); ^{13}C NMR (100 MHz, DMSO, δ ppm): 177.39, 156.19, 154.64, 154.11, 136.97, 132.63, 132.42, 131.74, 129.62, 126.13, 124.66, 123.48, 122.57, 119.56, 60.53, 38.25; EI-MS (*m/z*): 363.96 (M^{+1}), 351.76, 209.35, 197.05.

3-(6-Chlorobenzo[*d*]thiazol-2-yl)-2-(2-hydroxyphenyl)-thiazolidin-4-one (3b): Yield: 56%, m.p.: 145-147 ºC, m.f.: $C_{16}H_{11}N_2O_2S_2Cl$ (*m.w.* 362.85 g/mol); IR (KBr, ν_{max}, cm^{-1}): 3412 (-OH), 1770 (C=O), 1277 (C-N), 810 (C-Cl), 761; ^{1}H NMR (400 MHz, DMSO, δ ppm): 8.00 (1H, d, *J* = 1.7 Hz), 7.82 (1H, d, *J* = 7.6 Hz), 7.26 (1H, dd, *J* = 7.2, 1.3 Hz), 6.90 (1H, t, *J* = 8.1 Hz), 6.67 (1H, t, *J* = 1.5 Hz), 6.63-6.57 (1H, m), 6.48 (1H, dt, *J* = 8.3, 2.2 Hz), 5.40 (1H, s), 3.25 (2H, q, *J* = 12.5 Hz); ^{13}C NMR (100 MHz, DMSO, δ ppm): 176.66, 159.33, 155.38, 153.84, 143.05, 136.27, 132.38, 131.76, 128.83, 123.97, 121.88, 120.39, 119.33, 115.83, 67.86; EI-MS (*m/z*): 363.15 (M^{+1}), 350.10, 209.35, 197.05.

3-(6-Chlorobenzo[*d*]thiazol-2-yl)-2-(4-hydroxyphenyl)-thiazolidin-4-one (3c): Yield: 58%, m.p.: 160-162 ºC, m.f.: $C_{16}H_{11}N_2O_2S_2Cl$ (*m.w.* 362.85 g/mol); IR (KBr, ν_{max}, cm^{-1}): 3491 (-OH), 1773 (C=O), 817 (C-Cl), 762; ^{1}H NMR (400 MHz, DMSO, δ ppm): 8.62 (1H, d, *J* = 2.1 Hz), 8.44 (1H, d, *J* = 7.8 Hz), 7.88 (1H, dd, *J* = 8.1, 1.8 Hz), 7.53 (2H, d, *J* = 8.1 Hz), 7.18 (2H, d, *J* = 7.9 Hz), 7.12 (1H, s), 5.31 (1H, s), 3.87 (2H, q, *J* = 12.8 Hz); ^{13}C NMR (100 MHz, DMSO, δ ppm): 174.27, 158.68, 152.27, 150.74, 133.17, 131.48, 128.64, 127.43, 125.77, 120.88, 118.72, 115.27, 64.54, 34.38; EI-MS (*m/z*): 363.15 (M+1).

3-(6-Chlorobenzo[*d*]thiazol-2-yl)-2-(4-methoxyphenyl)-thiazolidin-4-one (3d): Yield: 58%, m.p.: 173-175 ºC, m.f.: $C_{17}H_{13}N_2O_2S_2Cl$ (*m.w.* 376.88 g/mol); IR (KBr, ν_{max}, cm^{-1}): 3216, 1755 (C=O), 1537 (Ar C=C), 813 (C-Cl), 712, 583; ^{1}H NMR (400 MHz, DMSO, δ ppm): 7.95 (1H, d, *J* = 2.9 Hz), 7.78 (1H, d, *J* = 8.6 Hz), 7.22 (1H, dd, *J* = 9.1, 2.8 Hz), 7.00 (2H, d, *J* = 8.4 Hz), 6.64 (2H, d, *J* = 9.5 Hz), 6.47 (1H, s), 3.20 (2H, q, *J* = 13.2 Hz), 2.71 (3 H, s); ^{13}C NMR (100 MHz, DMSO, δ ppm): 175.75, 162.16, 154.45, 153.00, 136.08, 135.39, 130.83, 128.38, 128.05, 123.05, 120.96, 115.66, 66.75, 57.37, 36.62; EI-MS (*m/z*): 377.01 (M^{+1}), 280.77, 268.93, 208.12, 183.66, 167.92.

3-(6-Chlorobenzo[*d*]thiazol-2-yl)-2-(4-hydroxy-3-methoxyphenyl)thiazolidin-4-one (3e): Yield: 61%, m.p.: 156-



Scheme-I

158 ºC, m.f.: $C_{17}H_{13}N_2O_3S_2Cl$ (*m.w*. 392.88 g/mol); IR (KBr, ν_{max}, cm^{-1}): 3491 (-OH), 1750 (C=O), 817, 762; ^{1}H NMR (400 MHz, DMSO, δ ppm): 8.05 (1H, d, *J* = 1.1 Hz), 7.88 (1H, d, *J* = 7.2 Hz), 7.32 (1H, dd, *J* = 8.3, 1.6 Hz), 6.67 (1H, d, *J* = 2.0 Hz), 6.61-6.53 (3H, m), 5.22 (1H, s), 3.31 (2H, q, *J* = 12.9 Hz), 3.05 (3 H, s); ^{13}C NMR (100 MHz, DMSO, δ ppm): 178.38, 157.07, 155.66, 152.46, 150.45, 137, 93, 136.36, 133.45, 130.64, 125.64, 123.51, 123.06, 117.58, 116.50, 69.59, 60.65; EI-MS (*m/z*): 392.16 (M+1), 268.93, 242.65, 209.98, 182.04, 167.98.

3-(6-Chlorobenzo[*d*]thiazol-2-yl)-2-(2-hydroxy-3-methoxyphenyl)thiazolidin-4-one (3f): Yield: 54%, m.p.: 189-1191 ºC, m.f.: $C_{17}H_{13}N_2O_3S_2Cl$ (*m.w*. 392.85 g/mol); IR (KBr, ν_{max}, cm^{-1}): 3491 (-OH), 1773 (C=O), 823 (C-Cl), 762; ^{1}H NMR (400 MHz, DMSO, δ ppm): 8.26 (1H, s), 7.94 (1H, d, *J* = 1.9 Hz), 7.76 (1H, d, *J* = 8.1 Hz), 7.20 (1H, dd, *J* = 8.1, 1.8 Hz), 6.68 (1H, s), 6.54 (1H, t, *J* = 7.9 Hz), 6.47 (1H, dd, *J* = 8.2, 1.9 Hz), 6.38 (1H, dd, *J* = 7.3, 2.1 Hz), 3.19 (2H, q, *J* = 13.6 Hz), 2.91 (3 H, s); ^{13}C NMR (100 MHz, DMSO, δ ppm): 173.88, 152.59, 151.02, 147.96, 141.07, 133.46, 128.99, 126.07, 121.13, 119.02, 117.63, 117.64, 114.06, 57.64, 56.15, 34.68; EI-MS (*m/z*): 392.16 (M+1).

3-(6-Chlorobenzo[*d*]thiazol-2-yl)-2-(4-(dimethylamino)-phenyl)thiazolidin-4-one (3g): Yield: 52%, m.p.: 144-146 ºC, m.f.: $C_{18}H_{16}N_3OS_2Cl$ (*m.w*. 389.92 g/mol); IR (KBr, ν_{max}, cm^{-1}): 3440, 1752 (C=O), 1240 (C-O), 815 (C-Cl), 756; ^{1}H NMR (400 MHz, DMSO, δ ppm): 8.00 (1H, d, *J* = 1.3 Hz), 7.82 (1H, d, *J* = 8.4 Hz), 7.26 (1H, dd, *J* = 8.5, 2.1 Hz), 6.88 (2H, d, *J* = 9.1 Hz), 6.46 (1H, s), 6.40 (2H, d, *J* = 8.3 Hz), 3.25 (2H, q, *J* = 13.2 Hz), 2.66 (6 H, s); ^{13}C NMR (100 MHz, DMSO, δ, ppm): 176.59, 157.65, 155.22, 153.88, 136.17, 135.08, 131.69, 129.49, 128.82, 123.86, 121.75, 115.38, 67.56, 44.01, 37.44; EI-MS (*m/z*): 390.85 (M+1), 379.11, 344.09, 242.17, 221.42, 209.31, 179.32, 163.97.

3-(6-Chlorobenzo[*d*]thiazol-2-yl)-2-(pyridin-2-yl)thiazolidin-4-one (3h): Yield: 48%, m.p.: 136-138 ºC, m.f.: $C_{15}H_{10}N_3OS_2Cl$ (*m.w*. 347.84 g/mol); IR (KBr, ν_{max}, cm^{-1}): 3450, 1746 (C=O), 1294 (C-N), 856 (C-Cl), 813, 777; ^{1}H NMR (400 MHz, DMSO, δ ppm): 8.48 (1H, dd, *J* = 7.9, 2.1 Hz), 8.17 (1H, d, *J* = 1.9 Hz), 7.87 (1H, d, *J* = 8.1 Hz), 7.65 (1H, td, *J* = 8.2, 1.7 Hz), 7.38 (2H, ddd, *J* = 7.8, 2.1, 1.7 Hz), 7.18 (1H, td, *J* = 8.1, 1.9 Hz), 6.96 (1H, s), 3.37 (2H, q, *J* = 13.6 Hz); ^{13}C NMR (100 MHz, DMSO, δ ppm): 175.47, 154.20, 152.75, 152.64, 150.45, 140.41, 135.09, 130.57, 128.96, 127.76, 125.02, 122.75, 120.66, 69.14, 36.32; EI-MS (*m/z*): 348.47 (M+1), 293.51, 268.85.

3-(6-Chlorobenzo[*d*]thiazol-2-yl)-2-(furan-2-yl)thiazolidin-4-one (3i): Yield: 59%, m.p.: 166-168 ºC, m.f.: $C_{14}H_9N_2O_2S_2Cl$ (*m.w*. 336.82 g/mol); IR (KBr, ν_{max}, cm^{-1}): 3116, 1750 (C=O), 1533(Ar C=C), 1280 (C-N), 815 (C-Cl), 713; ^{1}H NMR (400 MHz, DMSO, δ ppm): 8.35 (1H, d, *J* = 2.1 Hz), 8.15 (1H, d, *J* = 8.2 Hz), 7.59 (1H, dd, *J* = 7.3, 1.8 Hz), 7.38 (1H, dd, *J* = 7.6, 1.8 Hz), 6.43 (1H, dd, *J* = 8.3, 1.5 Hz), 6.38 (1H, t, *J* = 7.9 Hz), 6.31 (1H, s), 3.60 (2H, q, *J* = 12.5 Hz); ^{13}C NMR (100 MHz, DMSO, δ ppm): 174.84, 155.95, 152.27, 151.59, 139.56, 133.15, 128.62, 125.75, 120.79, 118.73, 110.48, 109.99, 57.33, 33.40; EI-MS (*m/z*): 337.90 (M^{+1}), 304.9, 274.1.

3-(6-Chlorobenzo[*d*]thiazol-2-yl)-2-styrylthiazolidin-4-one (3j): Yield: 44%, m.p.: 198-200 ºC, m.f.: $C_{18}H_{13}N_2OS_2Cl$ (*m.w*. 372.02 g/mol); IR (KBr, ν_{max}, cm^{-1}): 3264, 869, 767; ^{1}H NMR (400 MHz, DMSO, δ ppm): 8.20 (1H, d, *J* = 1.6 Hz), 8.02 (1H, d, *J* = 7.9 Hz), 7.46 (1H, dd, *J* = 8.1, 1.9 Hz), 7.26 (2H, dd, *J* = 7.5, 1.3 Hz), 7.19 (2H, t, *J* = 8.6 Hz), 7.16-7.10 (1H, m), 6.59 (1H, dd, *J* = 14.8, 0.8 Hz), 5.98 (1H, dd, *J* = 15.1, 7.1 Hz), 5.29 (1H, dd, *J* = 6.8, 0.7 Hz), 3.40 (2H, q, *J* = 13.5 Hz); ^{13}C NMR (100 MHz, DMSO, δ ppm): 177.11, 154.98, 151.81, 139.08, 138.55, 135.84, 130.83, 130.53, 129.33, 128.48, 123.52, 121.45, 119.48, 36.26; EI-MS (*m/z*): 373.01(M+1), 204.12, 268.93, 162.9.

RESULTS AND DISCUSSION

When equimolar amounts of Schiff base and thioglycolic acid in DMF as solvent were refluxed for 8 h in the presence of catalytic Lewis acid anhydrous $ZnCl_2$, 3-(6-chlorobenzo[*d*]-thiazol-2-yl)-2-(substituted) thiazolidine-4-one (**3a-j**) were obtained. By increasing the rate of the multicomponent reaction, zinc chloride can catalyze the model reaction by generating a better-activated intermediate. In this case, the reaction begins with a nucleophilic attack of the sulfur atom on the carbon atom of the imino group, followed by intramolecular cyclization, which results in the elimination of water molecule. As a result, high yields were obtained when anhydrous $ZnCl_2$ was utilized as a dehydrating agent as well as to speed up the final stage of the cyclization reaction [20]. Overall, the reactions went successfully, with modest yields and no unwanted byproducts formed.

The C=N stretching frequency from the imine group has completely disappeared from the contemporary IR spectra. The strong infrared absorption band in the area 1850-1650 cm^{-1}, which corresponds to the stretching vibration of the carbon-oxygen double bond, can positively identify a carbonyl group in a molecule. The position of the band within this frequency range is determined by the carbonyl group's molecular environment. All of the compounds have a carbonyl frequency between 1773-1746 cm^{-1} range. A significant peak for aryl alcohol, which is present in compounds **3a**, **3b**, **3c**, **3e** and **3f**, can be found at 3412-3498 cm^{-1}. The C-Cl stretching causes the typical sharp bands at 820-800 cm^{-1} and there is some stretching frequency at 750-700 cm^{-1} due to the presence of the C-Cl group in the molecule. For aromatic C=C groups, several compounds exhibit unique strong stretching bands at 1583 cm^{-1}.

The presence of daughter ions in the mass spectra is indicated by fragmentation patterns that correspond to findings from relevant compound investigations. In all of the compounds, a base peak and a molecular ion peak were observed in the mass spectrum. Furthermore, there are some daughter ion peaks at 167 (*m/z*), indicating that 6-chlorobenzothiazole groups have been removed from the entire molecule. Compound **3g** has a superior fragmentation pattern, with a base peak at *m/z* 390.8 (M+1) and several daughter ion peaks showing fragmentation at 344.09 (*m/z*) for elimination of the -$N(CH_3)_2$ group, 209.31 (*m/z*) and 179.32 (*m/z*) for breaking the thiazolidinone ring. Using electron bombardment, several daughter ion peaks reveal fragmentation at *m/z* 268.93 for anisole. With the use of electron bombardment, certain daughter ion peaks from compound **3d** show fragmentation at 268.93 (*m/z*).

The ^{1}H NMR spectra of compounds studied in DMSO revealed distinct signals in a separate area. Compounds **3b**, **3c** and **3e** have hydroxyl (-OH) peaks at δ 5.40 ppm, δ 5.31 ppm and δ 5.22 ppm, respectively, whereas compounds **3a** and **3f** have a hydroxyl (-OH) peaks at δ 8.45 ppm and δ 8.26 ppm, respectively, due to hydrogen bonding of thiazolidinone rings C-H group. Compounds **3d**, **3e** and **3f** exhibit a singlet for the methoxy (-OCH_3) group in the downfield area at around δ 2.71 ppm, δ 3.05 ppm and δ 2.91 ppm, respectively. The thiazolidinone ring's -N-C- bond exhibits a singlet before the aromatic region, with values of δ 6.60 ppm, δ 6.47 ppm, δ 6.59 ppm, δ 6.46 ppm and δ 6.37 ppm for compounds **3b**, **3d**, **3e** and **3i**, respectively, whereas compounds **3a**, **3f**, **3h** and **3j** exhibit above seven simply due to hydrogen bonding with nearby -OH groups or due to conjugation with heteroatoms present in the ring. A downfield peak for the -$N(CH_3)_2$ group appears for the compound **3g** at about δ 2.66 ppm. All compounds exhibit a quartet-like peak for the -CH_2 (from the thiazolidinone ring) group in the range of δ 3.16-3.84 ppm, confirming that these are diastereotopic protons. The two doublets for *meta* and *ortho* coupling, as well as a doublet of doublet for both *meta* and *ortho* coupling, are shown by the benzothiazole ring's highest significant shift values. The aromatic zone, which is located at about 7 ppm, contains all of the benzene ring peaks.

In ^{13}C NMR spectra, the -OCH_3 group shows a signal in the downfield region, *i.e.* at δ 57.37 ppm for compound **3d**, δ 60.65 ppm for compound **3e** and δ 56.15 ppm for compound **3f**. Because of the shielding effect of methyl group, molecule **3g** shows a signal at δ 44.01 ppm for the -$N(CH_3)_2$ group, which is in the far downfield area. The –CH_2 group from thiazolidinone ring shows a peak at the extreme downfield region and appears between δ 33 ppm to δ 38 ppm. Due to the electron cloud on the oxygen atom, compounds **3a**, **3b**, **3c**, **3e** and **3f** exhibit signals for the -OH group in the upfield area of about δ 160-170 ppm. The signal for carbonyl carbon (-C=O), which is close to the -N=C group in the upfield area, is also higher than δ 170.0 ppm. Depending on the groups attached to the benzene ring, the ^{13}C NMR signal for the ring ranges from δ 111.6 ppm.

Conclusion

In this study, the synthesis of novel derivatives of 3-(6-chlorobenzo[*d*]thiazol-2-yl)-2-(substituted aryl)thiazolidin-4-one were carried out. The current method offers a number of benefits, including easy experimental setup, non-hazardous method, mild reaction conditions and basic workup procedure. However, the evaluated compounds' activity is substantially lower than those of standard antibacterial agents.

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