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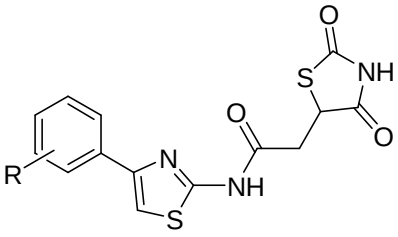
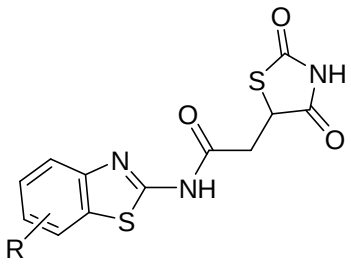


4a-k



4l-o

A new series of *N*-thiazolyl-thiazolidinedione-2-acetamides are synthesized and evaluated for DPPH radical scavenging, SASA, LPI, EHI, IL-1ß and MCP-1 secretion inhibition activities. Some of them have exhibited good antioxidant and anti-inflammatory potential.

Anti-inflammatory activity

IC_{50} (µM) values

	R	IL-1β	MCP-1
4h	*o*-Me	7.6	18.7
4m	6-NO_2	6.8	20.2
4n	6-OMe	7.0	39.6

Novel 2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamides as antioxidant and/or anti-inflammatory compounds

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ABSTRACT

A series of novel *N-(4-aryl-1,3-thiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamides* (**4a**-**k**) and *N-(1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide* derivatives (**4l**-**o**) are synthesized and evaluated for their anti-inflammatory and antioxidant activity (DPPH radical scavenging, superoxide anion scavenging, lipid peroxide inhibition, erythrocyte hemolytic inhibition). The structure of the compound **4j** is confirmed by X-ray crystallography. Compounds **4k** and **4l** have exhibited good antioxidant activity in four assays, while compounds **4c**, **4d**, **4m, 4n** and **4o** have shown good DPPH radical scavenging efficacy. Compounds **4a**, **4h**, **4i**, **4k**, **4m** and **4n** have possessed excellent anti-inflammatory activity. *N-[4-(o-Methoxyphenyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide* (**4k**) and *N-(6-nitro-/methoxy-1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide* (**4m** and **4n**) have exhibited both antioxidant and anti-inflammatory activities.

Keywords:
Anti-inflammatory activity; Lipid peroxidation; Erythrocyte hemolysis;
Superoxide anion and DPPH radical scavenging;
N-(1,3-Benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide;
N-(4-Aryl-1,3-thiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide.

1. Introduction

Antioxidant therapies are gaining importance due to their ability to retard disease progression by reducing the damage caused by free radical oxidative stress in a patient [1]. Physiological levels of reactive oxygen species (ROS) play vital role as signaling molecules to mediate numerous biological functions causing alterations in cell growth, gene expression and host defense [2]. Under inflammatory conditions, presence of excess reactive oxygen species ($O_2^{\cdot -}$, $^{\cdot}OH$, H_2O_2, $NO^{\cdot}$, $ONOO^-$) can initiate damage to nucleic acids, proteins, carbohydrates and lipids in many types of cells including macrophages [3]. Increased oxidative stress induced production of ROS, overwhelming the antioxidant defense system, has been implicated in the pathogenesis of various disorders including atherosclerosis [4,5], cancer [6,7], asthma [8], rheumatoid arthritis [9], ischemia-reperfusion injury [10], neurodegenerative diseases [11,12], inflammation [13], myocardial infarction and also aging [14,15].

Inflammation, on the other hand, is a multifactorial process. In response to infection stimulus, monocytes/ macrophage lineage cells activate and generate an inflammatory environment by secreting many pro-inflammatory cytokines. Among the cytokines, IL-1β is a multipotent, proinflammatory and procoagulant cytokine affecting most cell types causing alzheimer's [16], rheumatoid arthritis [17], atherosclerosis [18], diabetes, etc. The onset of diabetes is believed to open a gateway to several other complications associated with increased oxidative stress and elevated inflammatory processes. Monocyte chemoattractant protein-1 (MCP-1) is a key regulator of monocyte recruitment to sites of inflammation and plays an important role in initiating local inflammation at the damaged site. MCP-1 levels are known to be elevated in various disorders including cardiovascular and neurodegeneration [19, 20]. In addition, MCP-1 induces several proinflammatory changes including secretion of cytokines and expression of adhesion molecules like intracellular adhesion molecule (ICAM), Vascular cell adhesion molecule (VCAM) etc., which in turn facilitates the binding of immune cells to endothelial cells and may promote an inflammatory environment within the vasculature [19]. It is desirable to develop small molecules containing two or three biologically active scaffolds possessing good antioxidant, anti-inflammatory and/or anti-diabetic activities [21,22].

Anti-diabetic drugs and drug candidates such as ciglitazones [23,24], englitazone [25], pioglitazone [26], rosiglitazone [27] and KRP-297 [28] contain thiazolidinedione scaffold. These compounds have been reported to be acting as ligands for peroxisome proliferator-activated

receptors (PPAR) [29]. Many compounds belonging to this class are believed to be potential anti-inflammatory agents [30]. Pyrazolyl-2,4-thiazolidinediones are reported to exhibit anti-inflammatory activity [31]. However, the exact mechanism of their action is not completely understood. Similarly, thiazole ring has been identified as a central feature of myriad natural products and their synthetic analogues have been pursued by medicinal chemistry researchers [32]. 2-Amino-1,3-thiazole based amide compounds have been reported as potential radical scavengers [33] and P53 inactivators [34]. 2-Amino-5-methyl-1,3-thiazole scaffold is present as an amide in the nonsteroidal anti-inflammatory drug, meloxicam [35]. By incorporating both these pharmacophores into a single molecule, we intend to synthesize a new series of 2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamides of 2-aminothiazoles and 2-aminobenzimidazoles having antioxidant and/or anti-inflammatory properties.

2 Results and Discussion

2.1. Chemistry

2-(2,4-Dioxo-1,3-thiazolidin-5-yl)acetic acid (**1**) is obtained in good yield by refluxing maleic anhydride and thiourea in concentrated hydrochloric acid for 5 h as reported earlier [36]. Iodine catalyzed condensation-cyclisation of thiourea with the respective acetophenone (**2a**-**k**) at 100^{o}C for 8 h [37] has resulted in the formation of the corresponding *4-aryl-1,3-thiazol-2-amine* (**3a**-**k**) in good yield. The target molecules *viz.*, *N-(4-aryl-1,3-thiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamides* **4a**-**k** are synthesized in 65-71% yield by treating a dry dichloromethane (DCM) solution of *2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetic acid* (**1**), *N-hydroxybenzotriazole* (HOBT) and *O-(1H-benzotriazol-1-yl)-N,N,N',N'-tetramethyluronium hexafluorophosphate* (HBTU) with the corresponding 4-aryl-1,3-thiazol-2-amine (**3a**-**k**) and *N,N*-diisopropylethylamine (DIEA) in dry dimethylformamide (DMF) under stirring for 12 h. In a similar reaction, *2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetic acid* (**1**) is initially activated with HOBT and HBTU in dry DCM and then reacted *in situ* with commercially available 2-aminobenzothiazoles **3l**-**o** in dry DMF in presence of DIEA for 12 h to obtain *N-(1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide* derivatives **4l**-**o** in 54-61% yield. The detailed reaction sequence is depicted in Scheme 1. The thiazolidinedioneacetic acid and thiazolamine/ benzothiazolamine scaffolds present in the target molecules **4a**-**o** are attached through an amide linkage.

> Scheme 1 <

The newly synthesized *2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide* derivatives **4a**-**o** are well characterized by IR, ^{1}H NMR, ^{13}C NMR and Mass spectroscopy including HRMS. The IR spectra of these compounds consisted of absorption bands ranging from 1660 - 1760 cm^{-1} due to secondary amide C=O stretching, 3140 - 3450 cm^{-1} of N-H stretching of amide group and at 3040 - 3130 cm^{-1} due to the aromatic C-H stretching frequency. The presence of C-S bond stretching absorption is seen in the range 624 - 757 cm^{-1}. The ^{1}H NMR spectra of all the compounds showed signals for aromatic protons between δ 7.0 - 8.7 ppm. The two N-H protons appeared as two singlets around δ 11.5 and 12.5 ppm and are D_2O exchangeable. The thiazole ring proton signal appeared as a singlet at δ 6.9 - 7.9 ppm. Interestingly, the active methylene protons of acetamide compounds **4a**-**o** are diastereotropic and their signals appeared as ABX pattern. The C*HAHBHX* pattern for all the thiazolidinedioneacetic acid derivatives is seen as doublet of doublet around δ 3.0 - 3.5 ppm and δ 4.6 ppm with coupling constants, J_{AB} = 16.8 - 17.9 H_Z, J_{AX} = 7.9 - 10.1 H_Z, J_{BX} = 3.1 - 4.1 H_Z. High coupling constant of J_{AB} compromises with the data of Takahashi [38]. The molecular formula and elemental composition are confirmed by high resolution mass spectral analysis. The structural assignment of these compounds is further supported by ^{13}C NMR data. The physical characteristics of individual compounds, **4a**-**o** is presented in Table 1.

> Table 1 <

*2.2. Crystal structure of compound **4j***

> Fig. 1 <

In addition to the spectral characterization, a single crystal of compound **4j** is obtained from ethyl acetate/hexane (80:20). The crystal structure of compound **4j** has been determined by X-ray crystallography. The ORTEP view of compound **4j** is displayed in Fig. 1. The crystal data and

structural refinement parameters are presented in Table 2, while selected bond lengths and bond angles are listed in Table 3.

> Table 2 <

> Table 3 <

2.3. *Biology*

2.3.1. Antioxidant activities

The antioxidant efficacy of the newly synthesized thiazolidinedione derivatives is assayed by applying DPPH method. Superoxide anion scavenging activity (SASA), inhibition of lipid peroxidation (LPI) and hemolysis in erythrocyte membrane stabilization or erythrocyte hemolysis inhibition (EHI) assays are performed only for selected compounds showing good radical scavenging activity in DPPH method. The sample solutions are prepared at concentrations of 60, 80, 100 µg/mL and their EC_{50} values are obtained. Ascorbic acid and luteolin are employed as standards in these assays. The results of the antioxidant activities of these compounds are shown in Table 3. The thiazolidinedione-5-acetamides of 4-(p-fluorophenyl)-thiazol-2-amine (**4c**), 4-(p-bromophenyl)-thiazol-2-amine (**4d**), 4-(o-methoxyphenyl)-thiazol-2-amine (**4k**) and all the benzimidazol-2-amine derivatives (**4l**-**o**) have exhibited good DPPH radical scavenging potential with EC_{50} values ranging from 20 - 60 µM as compared to ascorbic acid (40.28 µM) and luteolin (44.18 µM) as positive controls. Compounds **4k** and **4l** have also shown good LPI and EHI along with moderate SASA. Among the structural features, the presence of benzothiazole moiety (**4l**-**o**) and/or NO_2 or OMe substituent at suitable position as seen in **4h**, **4k**, **4m** and **4n** seem to be desirable.

> Table 4 <

2.3.2. Anti-inflammatory activity

The thiazolidinedione derivatives **4a**-**o** along with pioglitazone are assayed for their anti-inflammatory potential in the presence of PMA (phorbol 13-myristate 12-acetate)-induced

inflammation using THP1 monocyte cell system (Table 5). This method is conventional, sensitive and well accepted for screening of newer anti-inflammatory agents. Compounds **4b**, **4d**, **4f**, **4g** with IC_{50} values of 16.31 µM, 33.12 µM, 18.23 µM and 23.4 µM respectively, showed reasonable anti-inflammatory activities (Table 6). Compounds **4a** and **4i** showed good activity with IC_{50} values of 9.6 µM and 11.72 µM. The thiazolidine-2,4-dione-5-acetamides of 4-(o-tolyl)-thiazol-2-amine (**4h**), 4-(o-methoxyphenyl)-thiazol-2-amine (**4k**), 6-nitro-benzimidazol-2-amine (**4m**) and 6-methoxy-benzimidazol-2-amine (**4n**) have shown excellent IL-1β inhibitory activity with IC_{50} values between 6.83 µM - 7.66 µM with respect to piroxicam (21.33 µM) as standard. However, compounds **4c**, **4e**, **4j**, **4l**, **4o** and pioglitazone (Table 6) did not show appreciable activity. In terms of MCP-1 inhibition, compounds **4a**, **4d**, **4e**, **4g**, **4n** and **4o** with IC_{50} values of 30.4 µM, 49.13 µM, 31.7 µM, 34.24 µM, 39.6 µM and 63.06 µM, respectively showed reasonable activities against MCP-1 (Table 4). Compounds **4c**, **4h**, **4i**, **4j**, **4l** and **4m** have shown good MCP-1 inhibition activity with IC_{50} values between 16.68 µM – 20.29 µM which are well comparable to pioglitazone with IC_{50} of 18.84 µM. MCP-1 levels are significantly attenuated in pioglitazone treatment animals compared to placebo group in stent implantation animals [39]. However, neither pioglitazone nor the thiazolidinedione compounds have shown activity on PMA induced TNF-α production. This result corresponds with the report of Thieringer, *et al*., which says that PPAR agonists do not inhibit TNF-α production [40].

> Table 5 <

> Table 6 <

3. Conclusion

We have reported here a simple synthesis of a collection of novel 2,4-thiazolidinedione-5-acetamides of 4-aryl-1,3-thiazol-2-amines and 6-substituted-benzothiazol-2-amines. These compounds are screened *in vitro* for their DPPH radical scavenging activity along with IL-1β and MCP-1 secretion inhibition efficacy. The compounds having DPPH radical scavenging potential are further assayed for their superoxide anion scavenging, lipid peroxidation inhibition and

erythrocyte hemolysis inhibition activities with reasonable success. Some of the compounds having methoxy- or nitro- substituent, especially on benzothiazole moiety have exhibited very good anti-inflammatory activity while showing good antioxidant potential. Further research on such molecules embedded with two biologically active scaffolds and exhibiting multiple activities may be useful in development of therapeutic applications where free radical induced inflammation plays a role in diseases.

4. Experimental Protocols

4.1. Synthetic Chemistry

All the reagents and solvents are purchased from commercial suppliers. Solvents are distilled and dried before use. Melting points are determined on the Veego (VMP-MP) melting point apparatus and are uncorrected. Merck 60 F_{254} silica gel coated glass sheets are used for thin layer chromatography. The compounds are purified by using column chromatography on silica gel (60-120 mesh) with ethyl acetate/ petroleum ether (1:2) as eluent. Infrared spectra are recorded on Perkin-Elmer FT-IR 1600 spectrometer. ^{1}H NMR and ^{13}C NMR spectra are recorded on Bruker Avance 300 MHz and Bruker Inova 400 MHz spectrometer with TMS as internal standard. Chemical shifts (δ) are given in parts per million and coupling constants are given as absolute values expressed in Hertz. Mass spectral analysis using electrospray ionization (ESI) and high resolution mass spectrometry (HRMS) experiments are performed using a quadrupole time-of-flight mass spectrometer (QSTAR XL, Applied Biosystems/MDS Sciex, Foster City, CA, USA), equipped with an ESI source.

*4.1.1. Synthesis of 2, 4-dioxo-1,3-thiazolidine-5-acetic acid (**1**).* A mixture of thiourea (10 g, 131 mmol) and of maleic anhydride (12.8 g, 131 mmol) in 33 mL of concentrated hydrochloric acid is refluxed for 5 h and cooled to room temperature. The precipitate is separated by filtration, washed with cold water (5 mL) and crystallized from hot water to yield compound **1**. Yield 70%; mp 167-169 ^{0}C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.82-2.91 (dd, *J* = 17.7, 9.2 Hz, 1H, CH_2), 3.05-3.12 (dd, *J* = 17.5, 3.7 Hz, 1H, CH_2), 4.43-4.48 (m, 1H, CH), 11.95 (s, 1H, NH), 12.60 (s, 1H, COOH).

*4.1.2. General procedure for synthesis of 2-amino-4-(substituted-phenyl)-1,3-thiazoles (**3a**-**k**).*

A mixture of thiourea (50 mmol), the corresponding acetophenone (25 mmol) and iodine (25 mmol) is stirred at 100 ^{0}C for 8 h. Then the reaction mixture is cooled, extracted with diethyl ether to remove excess of acetophenone, and then washed with aqueous sodium thiosulfate to remove excess iodine and later with cold water. The crude product is dissolved in hot water, filtered to remove sulphone, and the filtrate is basified with aqueous Na_2CO_3 to yield the corresponding 2-amino-4-(substituted-phenyl)-1,3-thiazole. The crude product is purified by recrystallization from alcohol.

*4.1.2.1. 4-Phenyl-1,3-thiazol-2-amine (**3a**)*. Yield 70%; mp 146-148 ^{o}C (lit [41] mp 146-148 ^{o}C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 5.13 (br s, 2H, NH_2, D_2O exchangeable), 6.66 (s, 1H, thiazole-H), 7.23-7.35 (m, 3H, Ar-H), 7.70-7.73 (m, 2H, Ar-H); ESI-MS(positive): 177.0 $[M+H]^+$.

*4.1.2.2. 4-(p-Chlorophenyl)-1,3-thiazol-2-amine (**3b**)*. Yield 68%; mp 164-166 ^{o}C (lit [37] mp 163-164 ^{o}C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 6.23 (br s, 2H, NH_2, D_2O exchangeable), 6.70 (s, 1H, thiazole-H), 7.30 (d, *J* = 8.4 Hz, 2H, Ar-H), 7. 71 (d, *J* = 8.4 Hz, 2H, Ar-H); ESI-MS(positive): 211.0 $[M+H]^+$.

*4.1.2.3. 4-(p-Fluorophenyl)-1,3-thiazol-2-amine (**3c**)*. Yield 69%; mp 108-110 ^{o}C (lit [42] mp 106 ^{o}C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 5.94 (br s, 2H, NH_2, D_2O exchangeable), 6.60 (s, 1H, thiazole-H), 7.01-7.07 (m, 2H, Ar-H), 7.72-7.77 (m, 2H, Ar-H); ESI-MS(positive): 195.0 $[M+H]^+$.

*4.1.2.4. 4-(p-Bromophenyl)-1,3-thiazol-2-amine (**3d**)*. Yield 65%; mp 178-180 ^{o}C (lit [37] mp 180-181 ^{o}C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 6.32 (br s, 2H, NH_2, D_2O exchangeable), 6.73 (s, 1H, thiazole-H), 7.45 (d, *J* = 8.4 Hz, 2H, Ar-H), 7. 65 (d, *J* = 8.4 Hz, 2H, Ar-H); ESI-MS(positive): 256.0 $[M+H]^+$.

*4.1.2.5. 4-(p-Iodophenyl)-1,3-thiazol-2-amine (**3e**)*. Yield 65%; mp 190-192 ^{o}C (lit [37] mp 176-177 ^{o}C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 6.85 (s, 1H, thiazole-H), 7.44 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.74 (d, *J* = 8.4 Hz, 2H, Ar-H); ESI-MS(positive): 303.0 $[M+H]^+$.

*4.1.2.6. 4-(o-Chlorophenyl)-1,3-thiazol-2-amine (**3f**).* Yield 66%; mp 142-144 ^{o}C (lit [43] mp 126 ^{o}C); ^{1}H NMR (DMSO-d_6, 300 MHz) δ (ppm): 5.15 (br s, 2H, NH_2, D_2O exchangeable), 7.03

(s, 1H, thiazole-H), 7.20-7.30 (m, 2H, Ar-H), 7.41 (d, *J* = 7.9 Hz, 1H, Ar-H), 7. 81 (d, *J* = 6.9 Hz, 1H, Ar-H); ESI-MS (positive): 211.0 $[M+H]^+$.

*4.1.2.7. 4-(m-Chlorophenyl)-1,3-thiazol-2-amine (**3g**)*. Yield 65%; mp 126-128 ^oC (lit [43] mp 112 ^oC); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 5.70 (s, 2H, NH_2, D_2O exchangeable), 6.73 (s, 1H, thiazole-H), 7.24-7.37 (m, 2H, Ar-H), 7.63 (d, *J* = 7.3 Hz, 1H, Ar-H), 7.78 (s, 1H, Ar-H); ESI-MS(positive): 211.0 $[M+H]^+$.

*4.1.2.8. 4-(o-Tolyl)-1,3-thiazol-2-amine (**3h**)*. Yield 68%; mp 81-83 ^oC (lit [37] mp 81-82 ^oC); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.43 (s, 3H, CH_3) 5.14 (br s, 2H, NH_2, D_2O exchangeable), 6.45 (s, 1H, thiazole-H), 7.18-7.25 (m, 3H, Ar-H), 7.50-7.53 (m, 1H, Ar-H); ESI-MS(positive): 191.0 $[M+H]^+$.

*4.1.2.9. 4-(m-Tolyl)-1,3-thiazol-2-amine (**3i**)*. Yield 67%; mp 86-88 ^oC (lit [37] mp 79-92 ^oC); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 2.41 (s, 3H, CH_3) 6.86 (s, 1H, thiazole-H), 7.24 (d, *J* = 7.3 Hz, 1H, Ar-H), 7.32-7.45 (m, 3H, Ar-H); ESI-MS(positive): 191.0 $[M+H]^+$.

*4.1.2.10. 4-(o-Fluorophenyl)-1,3-thiazol-2-amine (**3j**)*. Yield 66%; mp 98-100 ^oC (lit [44] mp 95-96 ^oC); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 6.25 (s, 2H, NH_2, D_2O exchangeable) 6.92 (s, 1H, thiazole-H), 7.06-7.22 (m, 3H, Ar-H), 8.0-8.20 (m, 1H, Ar-H); ESI-MS(positive): 195.0 $[M+H]^+$.

*4.1.2.11. 4-(o-Methoxyphenyl)-1,3-thiazol-2-amine (**3k**)*. Yield 58%; mp 180-182 ^oC (lit [45] liquid); ^1H NMR (DMSO-d_6, 300 MHz) δ (ppm): 3.98 (s, 3H, CH_3), 6.96 (s, 1H, thiazole-H), 7.03-7.07 (m, 2H, Ar-H), 7.39-7.44 (m, 1H, Ar-H), 7.60-7.64 (m, 1H, Ar-H); ESI-MS(positive): 207.0 $[M+H]^+$.

4.1.3. General procedure for the synthesis of N-*(4-aryl-1,3-thiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamides (**4a-k**) and* N-*(1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide derivatives (**4l-o**).*

The general protocol followed by us in obtaining 2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide compounds **4a-o** is illustrated for the synthesis of N-(4-phenyl-1,3-thiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (**4a**) as an example. A solution of compound **1** (0.4 g, 2.55 mmol) in DCM (10 mL) is cooled to 0 ^oC and then charged with HOBT (0.36 g, 2.4 mmol), followed by HBTU (0.90 g, 2.4 mmol). The reaction mixture is stirred at 0 ^oC for 45 minutes.

After that, a solution of 4-phenylthiazol-2-amine, **3a** (0.29 g, 1.70 mmol) and DIEA (0.8 mL, 5.1 mmol) in a mixture of DCM (5 mL) and DMF (2.5 mL) is added drop wise over 5 minutes. The reaction temperature is initially maintained at 0 ^{o}C for 1 h and later at RT for 10 h. Completion of reaction is evidenced by TLC analysis. After evaporating the DCM solvent on rotavapor, the reaction mixture is diluted with 40 mL of distilled water and extracted with (3 x 15 mL) of ethyl acetate. The combined organic layer is washed with saturated aqueous sodium bicarbonate solution (2 x 10 mL), followed by saturated aqueous sodium chloride solution (2 x 20 mL). After drying over anhydrous sodium sulfate, the organic layer is filtered and the filtrate is stripped off the solvent. The crude product thus obtained is purified by column chromatography over silica gel. The rest of the 2-(thiazolidinedion-5-yl)acetamide derivatives (**4b**-**o**) are prepared similarly by reacting 2,4-dioxo-1,3-thiazolidine-5-acetic acid (**1**) with the appropriate amine (**3b**-**o)**.

*4.1.3.1. N-(4-Phenyl-1,3-thiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (**4a**).*

IR (KBr) cm^{-1}: 3340, 3170 (NH), 3040 (Ar-H), 1750, 1692 (C=O), 1556 (C=C), 1407 (C-N), 1060; ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ (ppm): 3.06-3.14 (m, 1H, CH_2), 3.38 (dd, *J* = 17.1, 3.5 Hz, 1H, CH_2), 4.56 (dd, *J* = 9.2, 3.5 Hz, 1H, CH), 7.20 (s, 1H, thiazole-H), 7.23-7.38 (m, 3H, Ar-H), 7.78 (d, *J* = 7.1 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 37.5 (CH_2), 45.8 (CH), 106.7 (thiazole-C-5), 125.1, 127.0, 127.8, 133.7 (aromatic carbons), 149.0 (thiazole-C-4), 157.0 (thiazole-C-2), 167.0 (C=O), 171.4 (C=O), 174.0(C=O).

HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{14}H_{12}O_3N_3S_2$: 334.0320; found: 334.0312.

*4.1.3.2. N-[4-(p-Chlorophenyl)-1,3-thiazol-2yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide **(4b).*** IR (KBr) cm^{-1}: 3379, 3136 (NH), 3042 (Ar-H), 1747, 1673 (C=O), 1154, 1075, 747 (C-S-C); ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ (ppm): 3.15 (dd, *J* = 17.1, 8.6 Hz, 1H, CH_2), 3.38-3.40 (m, 1H, CH_2), 4.77 (dd, *J* = 8.6, 3.7 Hz, 1H, CH), 7.47 (d, *J* = 8.4 Hz, 2H, Ar-H), 7.72 (s, 1H, thiazole-H), 7.89 (d, *J* = 8.4 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 37.1 (CH_2), 45.5 (CH), 107.0 (thiazole-C-5), 126.2, 127.6, 132.1 (aromatic carbons), 147.0 (thiazole-C-4), 156.8 (thiazole-C-2), 166.8 (C=O), 171.1(C=O), 174.4(C=O). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{14}H_{11}O_3N_3ClS_2$: 367.9930; found: 367.9929.

*4.1.3.3. N-[4-(p-Fluorophenyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide **(4c)**.* IR (KBr) cm^{-1}: 3240, 3162 (NH), 3041 (Ar-H), 1760, 1680 (C=O), 1560 (C=C), 1410 (C-N), 1090 (C-N); ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ (ppm): 3.15-3.23 (m, 1H, CH_2), 3.37

(dd, *J* = 17.7, 3.7 Hz, 1H, CH_2), 4.59-4.62 (m, 1H, CH), 7.06-7.11 (m, 2H, Ar-H), 7.23 (s, 1H, thiazole-H), 7.81-7.85 (m, 2H, Ar-H), 11.96 (br s, 1H, NH, D_2O exchangeable), 12.37 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 35.5 (CH_2), 44.5 (CH), 105.8 (thiazole-C-5), 113.4, 113.7, 125.7, 129.0 (aromatic carbons), 146.2 (thiazole-C-4), 155.7 (thiazole-C-2), 166.2 (C=O), 170.4 (C=O), 173.7 (C=O). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{14}H_{11}O_3N_3FS_2$: 352.0226; found: 352.0220.

4.1.3.4. N-[4-(p-Bromophenyl)-1,3-thiazol-2yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide ***(4d)***. IR (KBr) cm^{-1}: 3371, 3140 (NH), 3043 (Ar-H), 1748, 1677 (C=O), 1155, 1065, 600 (C-S-C); ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ (ppm): 3.14-3.18 (m, 1H, CH_2), 3.36 (dd, *J* = 17.1, 3.5 Hz, 1H, CH_2), 4.58 (dd, *J* = 8.6, 3.0 Hz, 1H, CH), 7.34 (s, 1H, thiazole-H), 7.49 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.73 (d, *J* = 8.4 Hz, 2H, Ar-H), 11.95 (br s, 1H, NH, D_2O exchangeable), 12.39 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 36.3 (CH_2), 45.0 (CH), 106.9 (thiazole-C-5), 119.8, 126.1, 130.1, 132.1 (aromatic carbons), 146.8 (thiazole-C-4), 156.3(thiazole-C-2), 166.4 (C=O), 170.7 (C=O), 174.0 (C=O). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{14}H_{11}O_3N_3BrS_2$: 411.9425; found: 411.9425.

4.1.3.5. N-[4-(p-Iodophenyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide ***(4e)***. IR (KBr) cm^{-1}: 3200, 3112 (NH), 3040 (Ar-H), 1747, 1680 (C=O), 1159, 1065, 625 (C-S-C); ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ (ppm): 3.05 (dd, *J* = 17.1, 9.6 Hz, 1H, CH_2), 3.37 (dd, *J* = 17.3, 3.3 Hz, 1H, CH_2), 4.55-4.59 (m, 1H, CH), 7.25 (s, 1H, thiazole-H), 7.57 (d, *J* = 8.3 Hz, 2H, Ar-H), 7.68 (d, *J* = 8.4 Hz, 2H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 36.9 (CH_2), 45.4 (CH), 99.2(Ar-C-I), 107.2 (thiazole-C-5), 126.7, 132.9, 136.5 (aromatic carbons), 156.8 (thiazole-C-2), 169.9 (C=O), 174.4 (C=O). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{14}H_{11}O_3N_3IS_2$: 459.9287; found: 459.9281.

4.1.3.6. N-[4-(o-Chlorophenyl)-1,3-thiazol-2yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide ***(4f)***. IR (KBr) cm^{-1}: 3211, 3134 (NH), 3075 (Ar-H), 1756, 1701(C=O), 1138, 1039, 748 (C-S-C); ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ (ppm): 3.09 (dd, *J* = 17.1, 9.2 Hz, 1H, CH_2), 3.40 (dd, *J* = 17.1, 3.7 Hz, 1H, CH_2), 4.61 (dd, *J* = 9.2, 3.7 Hz, 1H, CH), 7.25-7.37 (m, 2H, Ar-H) 7.44-7.47 (m, 2H, Ar-H, thiazole-H), 7.81-7.85 (m, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 37.5 (CH_2), 45.8 (CH), 111.9 (thiazole-C-5), 126.0, 128.0, 129.6, 130.3, 131.0, 132.6 (aromatic carbons), 145.5 (thiazole-C-4), 156.0 (thiazole-C-2), 167.1 (C=O),

171.5(C=O), 174.7 (C=O). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{14}H_{11}O_3N_3ClS_2$: 367.9930; found: 367.9924.

4.1.3.7. N-[4-(m-Chlorophenyl)-1,3-thiazol-2yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide ***(4g)***. IR (KBr) cm^{-1}: 3288, 3174 (NH), 3052 (Ar-H), 1753, 1676 (C=O), 1156, 1074, 741 (C-S-C); ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ (ppm): 3.16 (dd, *J* = 17.1, 8.4 Hz, 1H, CH_2), 3.99 (dd, *J* = 14.1, 6.9 Hz, 1H, CH_2), 4.78 (dd, *J* = 8.6, 3.9 Hz, 1H, CH), 7.37 (d, *J* = 8.4 Hz, 1H, Ar-H), 7.44 (t, *J* = 7.7, 7.9 Hz, 1H, Ar-H), 7.82 (s,1H, thiazole-H), 7.85 (d, *J* = 7.7 Hz, 1H, Ar-H), 7.95 (s, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 37.7 (CH_2), 45.9 (CH_2), 108.0 (thiazole-C-5), 123.3, 125.5, 127.0, 129.4, 133.7, 135.7 (aromatic carbons), 143.0 (thiazole-C-4), 158.9 (thiazole-C-2), 167.3 (C=O), 171.6 (C=O), 174.8 (C=O). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{14}H_{11}O_3N_3ClS_2$: 367.9930; found: 367.9928.

4.1.3.8. N-[4-(o-Tolyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3thiazolidin-5-yl)acetamide ***(4h)***.
IR (KBr) cm^{-1}: 3291, 3155 (NH), 3054 (Ar-H), 1739, 1687 (C=O), 1167, 1064, 740 (C-S-C); ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ (ppm): 2.44 (s, 3H, CH_3), 3.07(dd, *J* = 17.5, 9.3 Hz, 1H, CH_2), 3.42 (dd, *J* = 16.5, 4.1 Hz, 1H, CH_2), 4.59-4.61 (m, 1H, CH), 6.92 (s, 1H, thiazole-H), 7.19-7.21 (m, 3H, Ar-H), 7.53 (d, *J* = 7.2 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 20.1 (CH_3), 37.1 (CH_2), 45.5 (CH), 109.5 (thiazole-C-5), 124.7, 126.8, 128.5, 129.8, 133.7, 134.7 (aromatic carbons), 148.8 (thiazole-C-4), 155.9 (thiazole-C-2), 166.7 (C=O), 171.2 (C=O), 174.4 (C=O). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{15}H_{14}O_3N_3S_2$: 348.0477; found: 348.0466.

4.1.3.9. N-[4-(m-Tolyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide ***(4i)***.
IR (KBr) cm^{-1}: 3275, 3154 (NH), 3050 (Ar-H), 1748, 1699 (C=O), 1161, 1091; ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ (ppm): 2.39 (s, 3H, CH_3), 3.08 (dd, *J* = 17.1, 9.6 Hz, 1H, CH_2), 3.44 (dd, *J* = 17.1, 3.7 Hz, 1H, CH_2), 4.58 (dd, *J* = 9.8, 3.7 Hz, 1H, CH), 7.11 (d, *J* = 8.1 Hz, 1H, Ar-H), 7.17 (s, 1H, thiazole-H), 7.26 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.59 (s, 1H, Ar-H), 7.63 (d, *J* = 6.2 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 21.0 (CH_3), 36.9 (CH_2), 46.3 (CH), 108.0 (thiazole-C-5), 122.7, 126.2, 128.4, 128.5, 134.0, 137.7 (aromatic carbons), 148.9 (thiazole-C-4), 157.2 (thiazole-C-2), 168.1 (C=O), 172.4 (C=O), 175.7 (C=O). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{15}H_{14}O_3N_3S_2$: 348.0477; found: 348.0470.

4.1.3.10. N-[4-(o-Fluorophenyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide ***(4j)***. IR (KBr) cm^{-1}: 3226, 3153 (NH), 3053 (Ar-H), 1739, 1687 (C=O), 1169, 1062, 739 (C-S-C); ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ (ppm): 3.09 (dd, *J* = 17.1, 9.6 Hz, 1H, CH_2), 3.45 (dd, *J* = 17.1, 3.5 Hz, 1H, CH_2), 4.59 (dd, *J* = 9.8, 3.5 Hz, 1H, CH), 7.11-7.23 (m, 2H, Ar-H), 7.39 (d, *J* = 1.8 Hz, 1H, Ar-H),7.56 (s, 1H, thiazole-H), 8.01 (t, *J* = 7.5, 7.7 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 37.2 (CH_2), 45.6 (CH), 108.3 (thiazole-C-5), 111.1 (d, *J* = 13.7 Hz), 114.9, 115.2, 123.3, 128.0, (d, J = 8.8 Hz), 128.4 (aromatic carbons), 142.5 (thiazole-C-4), 156.0 (thiazole-C-2), 166.9 (C=O), 171.3 (C=O), 174.6 (C=O). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{14}H_{11}O_3N_3FS_2$: 352.0226; found: 352.0220.

4.1.3.11. N-[4-(o-Methoxyphenyl)-1,3-thiazol-2-yl]-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide ***(4k)***. IR (KBr) cm^{-1}: 3251, 3184 (NH), 3070 (Ar-H), 1759, 1670 (C=O), 1115, 1056, 750 (C-S-C); ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz) δ (ppm): 3.09-3.14 (m, 1H, CH_2), 3.45 (dd, *J* = 16.8, 3.3 Hz, 1H, CH_2), 3.95 (s, 3H, OCH_3), 4.59 (dd, *J* = 10.1, 3.3 Hz, 1H, CH), 6.99-7.02 (m, 2H, Ar-H) 7.26 (t, *J* = 7.8 Hz, 1H, Ar-H), 7.59 (s, 1H, thiazole-H), 8.08 (d, *J* = 6.7 Hz, 1H, Ar-H) 11.8 (br s, 1H, NH, D_2O exchangeable), 12.1 (br s, 1H, NH, D_2O exchangeable); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 36.9 (CH_2), 46.3 (CH), 55.3(OCH_3), 111.6 (thiazole-C-5), 111.8, 120.4, 122.4, 128.8, 155.7 (aromatic carbons), 144.7 (thiazole-C-4), 156.5 (thiazole-C-2), 168.0 (C=O), 172.5 (C=O), 175.7 (C=O). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{15}H_{14}O_4N_3S_2$: 364.0426; found 364.0421.

4.1.3.12. N-(1,3-Benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide ***(4l)***.
IR (KBr) cm^{-1}: 3192, 3110 (NH), 2924 (Ar-H), 1742, 1677 (C=O), 1182, 1069, 757 (C-S-C); ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ (ppm): 3.39-3.40 (m, 1H, CH_2), 3.44-3.46 (m, 1H, CH_2), 4.62-4.67 (m, 1H, CH), 7.23 (t, *J* = 7.5 Hz, 1H, Ar-H), 7.35-7.40 (m, 1H, Ar-H), 7.68 (d, *J* = 7.9 Hz, 1H, Ar-H) 7.81 (d, *J* = 7.9 Hz, 1H, Ar-H). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{12}H_{10}O_3N_3S_2$: 308.0164, found 308.0159.

4.1.3.13. N-(6-Nitro-1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide ***(4m)***.
IR (KBr) cm^{-1}: 3275, 3193 (NH), 2917 (Ar-H), 1747, 1704 (C=O), 1165, 1044, 749 (C-S-C); ^{1}H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ (ppm): 3.17 (dd, *J* = 17.9, 8.9 Hz, 1H, CH_2), 3.50 (dd, *J* = 17.9, 2.9 Hz, 1H, CH_2), 4.62 (dd, *J* = 8.9, 3.9 Hz, 1H, CH), 7.81 (d, *J* = 8.9 Hz, 1H, Ar-H), 8.27 (d, *J* = 8.9 Hz, 1H, Ar-H), 8.77 (s, 1H, Ar-H), 11.96 (brs, 1H, D_2O exchangeable), 12.84

(brs, 1H, D_2O exchangeable); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 37.2 (CH_2), 46.0 (CH), 118.8, 120.6, 121.7, 132.1, 143.0, 153.2, 162.8 (benzothiazole), 169.7 (C=O), 172.3 (C=O), 175.5 (C=O). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{12}H_9O_5N_4S_2$: 353.0014; found 353.0015.

*4.1.3.14. N-(6-Methoxy-1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (**4n**).* IR (KBr) cm^{-1}: 3207, 3094(NH), 3008 (Ar-H), 1738, 1675 (C=O), 1172, 1060, 639 (C-S-C); ^1H NMR ($CDCl_3$ + DMSO-d_6, 400 MHz) δ (ppm): 3.05 (dd, *J* = 17.1, 9.6 Hz, 1H, CH_2), 3.40 (dd, *J* = 17.1, 3.5 Hz, 1H, CH_2), 3.85 (s, 3H, OCH_3), 4.54 (dd, *J* = 9.4, 3.3 Hz, 1H, CH), 6.92-6.96 (m, 1H, Ar-H), 7.26 (s, 1H, Ar-H), 7.55 (d, *J* = 8.6 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 38.8 (CH_2), 49.6 (CH), 53.4(OCH_3), 102.0, 112.0, 118.0, 130.6, 140.5 (benzothiazole), 153.9 (C=O), 168.3 (C=O), 188 (C=O). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{13}H_{12}O_4N_3S_2$: 338.0269; found 338.0261.

*4.1.3.15. N-(6-Ethoxy-1,3-benzothiazol-2-yl)-2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamide (**4o**).* IR (KBr) cm^{-1}: 3205, 3100 (NH), 2928 (Ar-H), 1743, 1681 (C=O), 1175, 1060, 717 (C-S-C); ^1H NMR ($CDCl_3$ + DMSO-d_6, 300 MHz) δ (ppm): 1.39 (t, *J* = 6.9 Hz, 3H, CH_3), 3.06-3.15 (m, 1H, CH_2), 3.37 (dd, *J* = 17.1, 3.7 Hz, 1H, CH_2), 4.02 (q, *J* = 6.7, 6.9 Hz, 2H, OCH_2), 4.59 (dd, *J* = 9.2, 2.8 Hz, 1H, CH), 6.91 (dd, *J* = 11.1, 2.2 Hz 1H, Ar-H), 7.28 (s, 1H, Ar-H), 7.55 (d, *J* = 8.8 Hz, 1H, Ar-H); ^{13}C NMR ($CDCl_3$ + DMSO-d_6, 75 MHz) δ (ppm): 13.21 (CH_3), 36.2 (CH_2), 44.7 (CH), 62.2(OCH_2), 103.0, 113.0, 119.0, 131.6, 141.5, 153.8, 154.1(benzothiazole), 166.7 (C=O), 170.5 (C=O), 173.9 (C=O). HRMS-ESI m/z $[M+H]^+$ calcd. for $C_{14}H_{14}O_4N_3S_2$: 352.0426; found 352.0423.

4.1.4. X-ray structure analysis

X-ray data for the compound **4j** is collected at room temperature using a Bruker Smart Apex CCD diffractometer with graphite monochromated MoKα radiation (λ=0.71073Å) with ω-scan method [46]. Preliminary lattice parameters and orientation matrices are obtained from four sets of frames. Unit cell dimensions are determined using 6121 reflections for **4j** data. Integration and scaling of intensity data are accomplished using SAINT program [46]. The structures are solved by Direct Methods using SHELXS97 [47] and refinement is carried out by full-matrix least-squares technique using SHELXL97 [47]. Anisotropic displacement parameters are included for all non-hydrogen atoms. All H atoms are positioned geometrically and treated as

riding on their parent C atoms, with C-H distances of 0.93--0.97 Å, and with $U_{iso}(H) = 1.2U_{eq}$ (C) or $1.5U_{eq}$ for methyl atoms. CCDC 905873 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge at www.ccdc.cam.ac.uk/conts/retrieving.html [or from the Cambridge Crystallographic Data Centre (CCDC), 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44(0) 1223 336 033; email: deposit@ccdc.cam.ac.uk].

4.2. Biological experiments

4.2.1. Experiments in vitro

In the *in vitro* assays, each experiment is performed at least in triplicate and the standard deviation of absorbance is less than 10% of the mean.

4.2.2. DPPH radical scavenging assay

Antioxidant activity of synthesized thiazolidinedione-5-acetamide derivatives is assessed on the basis of the free radical scavenging effect of the stable 1,1-diphenyl-picrylhydrazyl (DPPH) following a previously described method [48] with some modifications. The diluted working solutions of the synthesized compounds are prepared in methanol (5, 10, 20, 40, 60 and 180 µg/mL). One mL of methanol solution of DPPH (0.002 %) is mixed with 1 mL solution of test compound. The mixture is shaken vigorously and left to stand in dark for 30 min. Absorbance of the resulting solution is measured at 517 nm in a Lambda 25 UV-visible spectrophotometer (Perkin-Elmer, Shelton, CT, USA). Ascorbic acid and luteolin are used as positive controls. The radical scavenging ability is measured as a decrease in the absorbance of DPPH. Lower absorbance of the reaction mixture has indicated higher free radical scavenging activity. DPPH radical scavenging activity is calculated using the following formula: DPPH radical scavenging activity (%) = [(absorbance of control – absorbance of test sample)/ (absorbance of control)] x 100. Radical scavenging potential is expressed as EC_{50} value, which represents the test compound concentration at which 50% of the DPPH radicals are scavenged [49].

4.2.3. Superoxide radical scavenging assay

The superoxide radical scavenging assay of samples is done according to the protocol described by Liu, *et al*., [50].The superoxide radical is generated by phenazine methosulfate - nicotinamide adenine dinucleotide (PMS/NADH) system, which reduces nitro blue tetrazolium (NBT) forming a purple coloured formazan. The reaction mixture consisted of 3.0 mL of 16 mM

tris-HCl buffer (pH 8.0) containing 78 mM NADH, 50 µM NBT, 10 µM PMS and various concentrations (5, 10, 20, 40, 60 and 180 µg/mL) of test compound. After incubation for 5 min at room temperature the absorbance is read at 560 nm. Ascorbic acid is run in parallel as a positive control. The scavenging activity of superoxide radical (%) is calculated using the equation:

$$[(A_{560} \text{ of control} - A_{560} \text{ of sample})/A_{560} \text{ of control}] * 100$$

4.2.4. Inhibition of lipid peroxidation assay

The inhibition of lipid peroxidation is assayed by measuring malondialdehyde (MDA) thiobarbituric acid adduct formation using egg yolk as the oxidizable substrate [51]. The yolk is taken out from an egg and same volume of PBS (0.1 M, pH 7.45) is added to it and stirred vigorously. The yolk suspension is mixed with 0.5 mL of test sample at various concentrations (50, 100, 150 and 300 µg/mL), 0.2 mL of 25 mM $FeSO_4$ and 1.3 mL of PBS and incubated at 37 ^{o}C for 15 min before the reaction is quenched by adding 0.5 mL of 20% trichloroacetic acid and 1 mL of 0.8% thiobarbituric acid, and then the mixture is heated at 100 ^{0}C for 15 min. The samples are read at 532 nm. Ascorbic acid is used as positive control. The inhibition of lipid peroxidation is calculated from the following equation:

$$\text{Inhibition effect (\%)} = A_{control} - A_{sample} / A_{control} * 100\%$$

4.2.5. Inhibition of erythrocyte hemolysis assay

The inhibition of erythrocyte hemolysis is measured according to the modified protocol described by Ng, et al., [52]. The human blood sample is collected in a tube with 3% sodium citrate. The blood sample is centrifuged at 3,000 g for 10 min to separate erythrocytes from the plasma and washed with PBS buffer (pH 7.4) and 1.25% erythrocyte suspension is prepared. Different concentrations of compounds (50, 100, 150 and 300 µg/mL) are added to the mixture containing 1.0 mL erythrocyte suspension and 0.5 mL H_2O_2 (2.5 mM) and incubated at 37 ^{o}C for 30 min. After incubation, the reaction is terminated by incubating in ice water bath at 4 ^{o}C and then centrifuged at 3,000 g for 10 min. The absorbance of the precipitated protein is measured at 540 nm. Ascorbic acid is used as positive control. The inhibition rate of the hemolysis is calculated using the following equation:

$$\text{Inhibition rate (\%)} = (A_{H2O2} - A_{sample}) / (A_{H2O2} - A_{normal}) * 100$$

4.2.6. THP1 cell culture

THP1 monocytes are obtained from ATCC and grown in RPMI 1640 (Sigma) containing 10% FBS (Lonza), non essential amino acids, penicillin (100 U/mL), and streptomycin (100 µg/mL) in 75-cm^2 filter vent flasks (Costar), incubated at 37°C in a humidified atmosphere containing 5% CO_2 and 95% air .

4.2.7. Measurement of cell viability

The effect of synthesized compounds on cell viability is determined by Trypan blue dye exclusion assay. THP1 cells are seeded at a density of 2 x 10^5 cells/ mL in 24-well plates in triplicates and are treated with test compounds (10 µM) for 48 h. At the end of the treatments, cells are harvested and resuspended in 0.4 % Trypan blue (Sigma) and live/dead cells are counted using cell countess chamber (Invitrogen).

4.2.8. Enzyme-linked immunosorbent assay for IL-1β and MCP-1 inhibition

To check the inhibitory effects of thiazole derivatives (**4a-o**) on PMA induced inhibition of inflammation, THP1 monocytes are seeded at a density of 2 x 10^5 cells/ mL in 24 well plates. Cells are pre-treated with 5, 10 and 20 µM concentrations of compounds for 1 h before they are stimulated with 10 ng/mL of PMA. After 48 h of PMA stimulation supernatants are harvested and assayed for IL-1β , MCP-1 and TNF-α using an enzyme-linked immunosorbent assay (ELISA) kit following the manufacturer's instructions (eBiosciences, San Diego, CA, USA). The absorbance in each well is measured with a microplate reader at 450 nm and corrected at 570 nm. Concentrations of cytokines released are obtained and the percentage of inhibition of cytokines production is calculated as compared to control conditions. IC_{50} is also obtained as a mean of anti-inflammatory potency, expressing the predicted concentration of the correspondent compound able to reach 50% inhibition. The standard curves are calculated by plotting the pg/mL concentrations *versus* absorbance values from the standards, and are used to quantify the amount of cytokines released by the cells.

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activity data. The authors are grateful to the Council of Scientific and Industrial Research (CSIR), New Delhi, for the financial assistance.

Appendix A. Supplementary data

Supplementary data related to this article can be found at http://dx.doi.org/10.1016/j.ejmech.2013.

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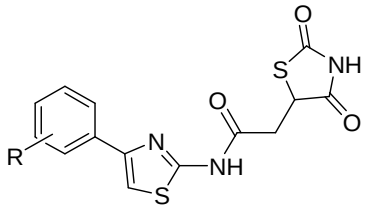
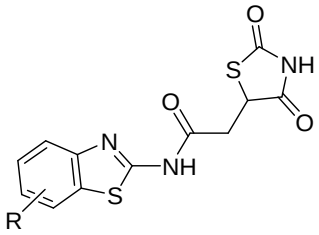
Table 1

Structure and physicochemical characteristics of target compounds **4a-o**.



4a-k



4l-o

Entry	Product[a]	R	Mol. Formula/ Mol. Wt.	R_f[b]	C log P*	mp ^oC	Yield (%)
1	**4a**	H	$C_{14}H_{11}N_3O_3S_2$ 333	0.51	2.28	236-238	71
2	**4b**	*p*-Cl	$C_{14}H_{10}N_3O_3S_2Cl$ 367	0.56	3.00	>260	67
3	**4c**	*p*-F	$C_{14}H_{10}N_3O_3S_2F$ 351	0.54	2.43	212-216	69
4	**4d**	*p*-Br	$C_{14}H_{10}BrN_3O_3S_2$ 412	0.57	3.15	252-254	67
5	**4e**	*p*-I	$C_{14}H_{10}IN_3O_3S_2$ 459	0.59	3.41	242-244	62
6	**4f**	*o*-Cl	$C_{14}H_{10}N_3O_3S_2Cl$ 367	0.55	2.75	216-218	68
7	**4g**	*m*-Cl	$C_{14}H_{10}N_3O_3S_2Cl$ 367	0.55	3.00	212-214	68
8	**4h**	*o*-Me	$C_{15}H_{13}N_3O_3S_2$ 347	0.50	2.48	192-194	69
9	**4i**	*m*-Me	$C_{15}H_{13}N_3O_3S_2$ 347	0.51	2.78	218-220	69
10	**4j**	*o*-F	$C_{14}H_{10}N_3O_3S_2F$ 351	0.53	2.43	220-222	68
11	**4k**	*o*-OMe	$C_{15}H_{13}N_3O_4S_2$ 363	0.56	1.74	228-230	65
12	**4l**	H	$C_{12}H_9N_3O_3S_2$ 307	0.57	1.78	266-268	61
13	**4m**	6-NO_2	$C_{12}H_8N_4O_5S_2$ 352	0.60	1.62	272-274	56
14	**4n**	6-OMe	$C_{13}H_{11}N_3O_4S_2$ 337	0.59	2.08	262-264	54
15	**4o**	6-OEt	$C_{14}H_{13}N_3O_4S_2$ 351	0.58	2.61	246-248	58

[a] All products are characterized by IR, NMR, ESI-MS and HRMS analysis; [b] Ethyl acetate: Petroleum ether (2:1);
* C log P values are calculated using ChemDraw Ultra 10.0.

Table 2
Crystal data and structure refinement parameters for compound **4j**.

Empirical formula	$C_{14}H_{10}FN_3O_3S_2$
Formula weight	351.37
Temperature (K)	293
Color	Colorless, needle
Wavelength (Å)	0.71073
Crystal system	Monoclinic
Space group	C2/c
a(Å)	30.877(4)
b(Å)	5.7127(6)
c(Å)	18.357(3)
β(deg)	117.036(3)
Volume ($Å^3$)	2884.2(6)
Z	8
D_{calc} (mg m^{-3})	1.618
Absorption Coefficient (mm^{-1})	0.40
F(000)	1440.0
Crystal size ($mm^{3)}$	0.60 × 0.20 × 0.10
θ Range for data collection (deg)	2.3-28.0
Index ranges	h= -36 →36, k= -6 → 6, l= -21 →21.
Reflections collected	12857
Independent Reflections(Rint)	2538 (R_{int} = 0.0346)
Data/restraints/Parameters	2538/0/216
No. of parameters	216
Goodness-on-fit on F^2	1.18
Final R indices [I > 2σ(I)]	R1 = 0.0504, wR2 = 0.1241
R indices (all data)	R1 = 0.0527, wR2 = 0.1256
Largest diffraction peak and hole (Å e^3)	0.49 and -0.25
CCDC number	905873

Table 3

Selected bond distances (Å**)** and bond angles (^{0}) for the compound **4j**.

Bond lengths		Bond angles	
S1–C1	1.766(3)	O1–C2– N1	124.7(3)
S1–C3	1.824(3)	O1–C2– C3	111.5(2)
O1–C2	1.216(3)	C2–N1–C1	118.5(3)
O2–C1	1.197(4)	N1–C1– S1	109.8(2)
N1–C1	1.383(4)	O2–C1– N1	125.2(3)
C2–N1	1.360(4)	O2–C1– S1	125.0(3)
O3–C5	1.217(3)	C4–C3– S1	114.3(2)
N2–C5	1.360(3)	O3–C5– N2	112.7(3)
N2–C6	1.379(4)	O3–C5– C4	124.3(2)
S2–C7	1.722(3)	N2–C6– S2	123.77(19)
S2–C6	1.729(3)	N3–C6– N2	120.4(2)
N3–C6	1.295(3)	N3–C6– S2	115.9(2)
N3–C8	1.381(4)	F1–C10–C9	118.5(3)
F1–C10	1.361(4)	F1–C10–C11	118.1(3)
		C14–C9–C8	119.8(3)

Table 4

Antioxidant activities of the synthesized compounds (**4a-o**).

Compound	**EC_{50}** (μg/ mL)[a]			
	DPPH radical scavenging activity	Superoxide anion scavenging activity	Lipid peroxidation inhibition	Erythrocyte hemolysis inhibition
4a	NA	NT	NT	NT
4b	NA	NT	NT	NT
4c	52.69	NA	NA	NA
4d	49.71	NA	NA	NA
4e	NA	NT	NT	NA
4f	NA	NT	NT	NT
4g	NA	NT	NT	NT
4h	NA	NT	NT	NT
4i	90.16	NA	NT	NA
4j	82.50	NA	NA	NA
4k	58.68	79.94	131.79	96.62
4l	52.18	101.18	149.70	107.28
4m	39.76	NA	NA	NA
4n	51.82	NA	NA	NA
4o	62.90	NA	NA	NA
Ascorbic acid [b]	40.28	21.01	139.97	96.625
Luteolin [b]	44.18	31.01	149.70	107.28

[a] EC_{50} values are mean of three experiments; [b] Positive control; NA: not active; NT: not tested.

Table 5

Effect of pioglitazone on PMA-induced IL-1β, MCP-1 levels in THP1 cells.[a]

Treatment conditions	**Secreted IL-1β levels** (pg/ mL)	**Secreted MCP-1 levels** (pg/ mL)
Without PMA	12 ± 0.38	28.12 ±3.18
PMA (10 ng/mL)	172 ± 0.71	3521.63 ±79.78
PMA+ Pioglitazone (10 µM)	165 ± 1.56	2588.33 ±11.64

[a] 2 x 10^5/mL THP1 monocytes are seeded in 24 well cell culture plates and stimulated with 10 ng/ mL of PMA for IL-1β, MCP-1 production. Cells are incubated for a period of 48 h. At the end of the treatment, conditioned media is collected and IL-1β, MCP-1 levels are measured by ELISA as described in the materials and methods.

Table 6

IL-1β and MCP-1 secretion inhibition efficacy of the synthesized compounds (**4a-o**).[a]

Compound	**IC_{50}** (μM) [b]	
	IL-1β secretion inhibition efficacy	MCP-1 secretion inhibition efficacy
4a	9.6 ± 2.96	30.4± 3.4
4b	16.31 ± 0.91	NA
4c	NA	17.58± 1.58
4d	33.12 ± 5.57	49.13± 3.46
4e	NA	31.7± 1.86
4f	18.23 ± 1.53	26.49± 2.54
4g	23.4 ± 6.66	34.24± 1.86
4h	7.66 ± 0.46	18.79± 2.45
4i	11.72 ± 4.05	18.94± 0.86
4j	NA	16.68± 1.11
4k	7.23 ± 0.99	NA
4l	NA	20.8± 2.21
4m	6.83 ± 0.24	20.29± 3.21
4n	7.03 ± 0.06	39.6± 1.66
4o	NA	63.06± 4.21
Pioglitazone	NA	18.84± 2.16
Piroxicam [c]	21.33 ± 3.2	NT

[a] THP1 monocytes are pretreated with 5, 10 and 20 μM concentrations of the above mentioned thiazole substituents (**4a-o**) for 1 h before simulation with 10 ng/ mL of Phorbol 13-myristate 12-acetate (PMA) to induce inflammation for a period of 48 h. At the end of the treatment, conditioned media is collected and levels of IL-1β and MCP-1 are measured by ELISA as described in the materials and methods. [b] IC_{50} values are Mean ± SD of three independent experiments; [c] Piroxicam, a known anti-inflammatory agent is used as a positive control; NA: denotes activity >50 μM; NT: indicates 'not tested'.

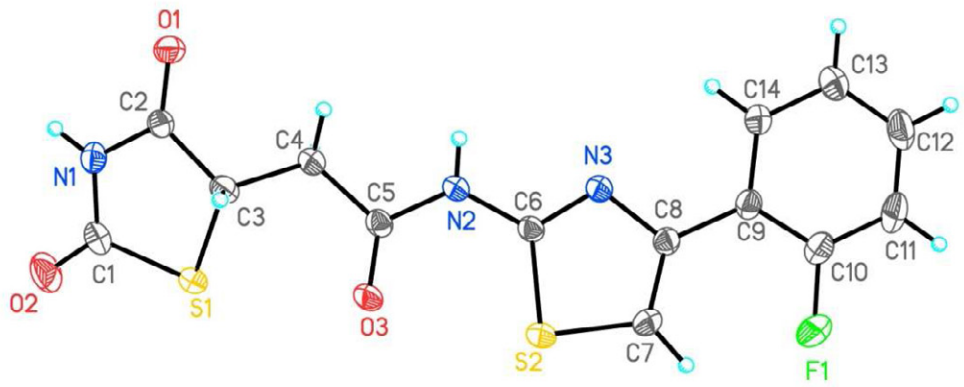
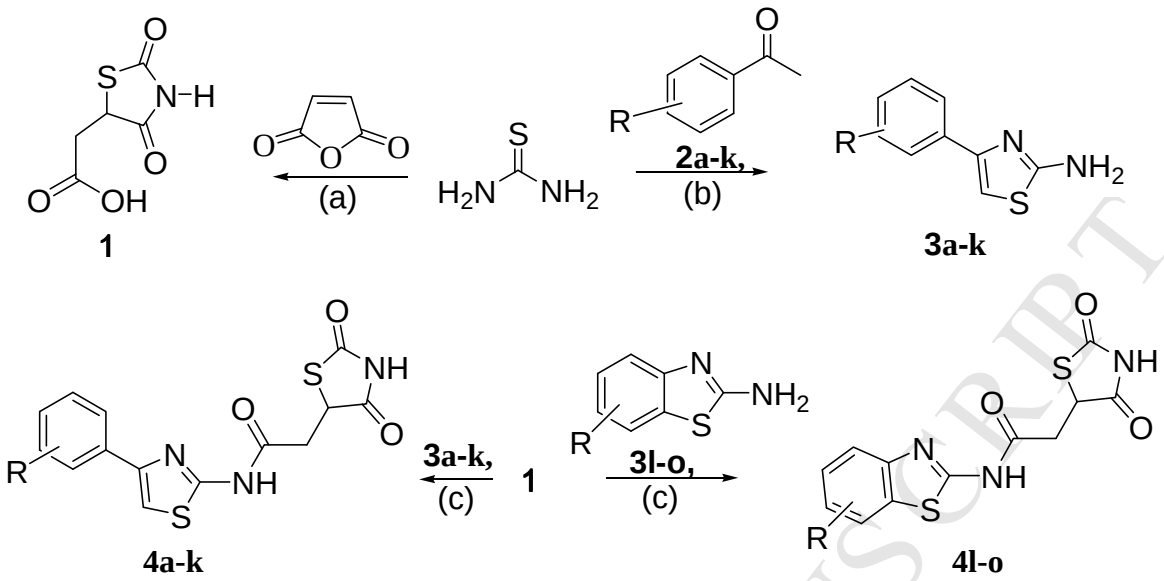
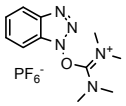


Fig. 1. An ORTEP view of the molecular structure and atom-numbering of compound **4j**. Displacement ellipsoids are drawn at the 30% probability level and H atoms are shown as small spheres of arbitrary radius.



Scheme 1. Synthesis of target compounds **4a-o**; Reagents and conditions:
(a) Conc. HCl, 100 ^{0}C, 5 h; (b) I_2, 90 ^{0}C, 12 h;
(c) *N*-Hydroxybenzotriazole (HOBT),



O-(1*H*-Benzotriazol-1-yl)-*N*,*N*,*N*',*N*'-tetramethyluronium hexafluorophosphate (HBTU),

and *N*,*N*-Diisopropylethylamine (DIEA), DCM, DMF, 0 ^{0}C - RT, 12 h.

R = H, F, Cl, Br, I, Me, OMe, OEt, NO_2.

Supporting information for

Novel 2-(2,4-dioxo-1,3-thiazolidin-5-yl)acetamides as antioxidant and/or anti-inflammatory compounds

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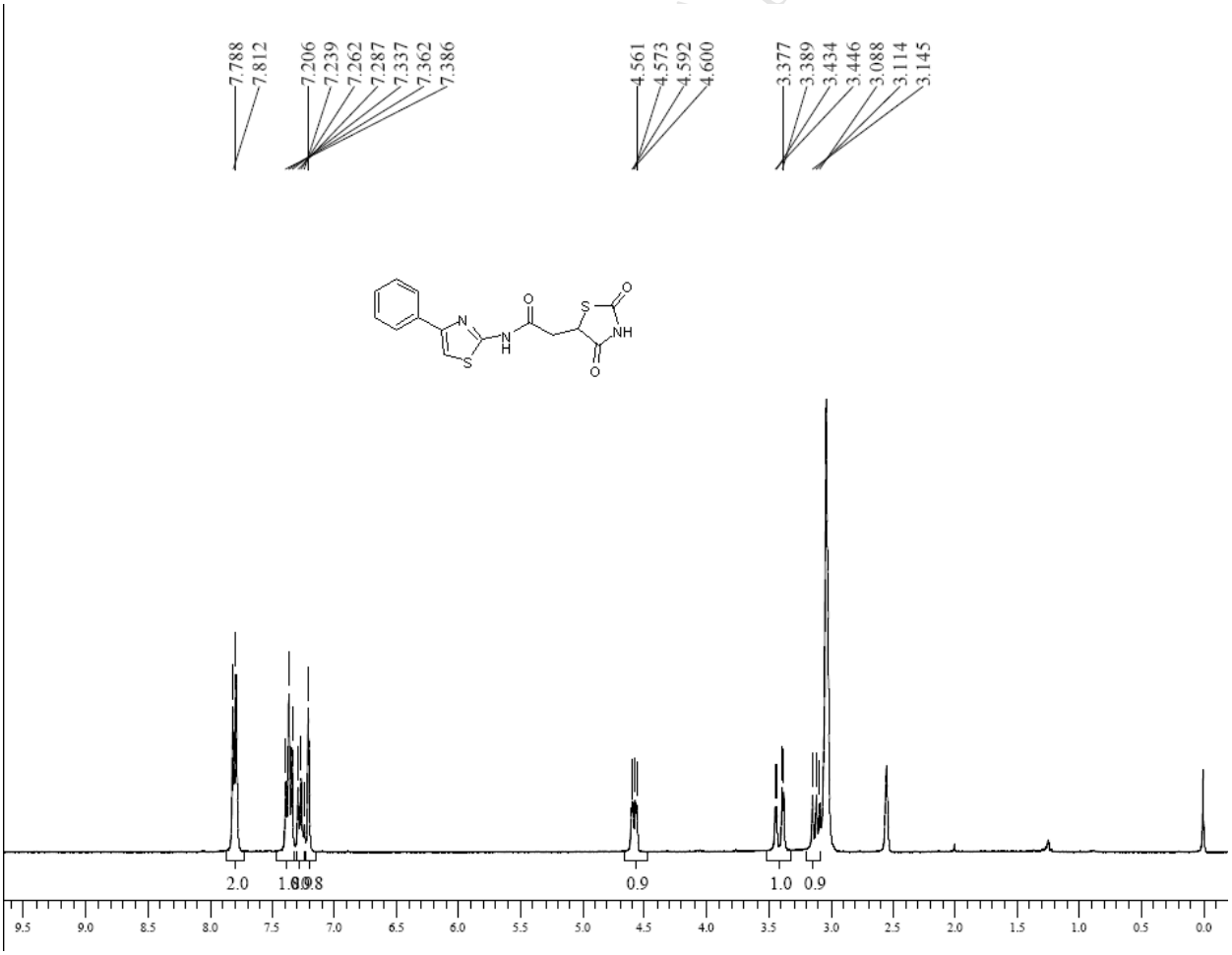
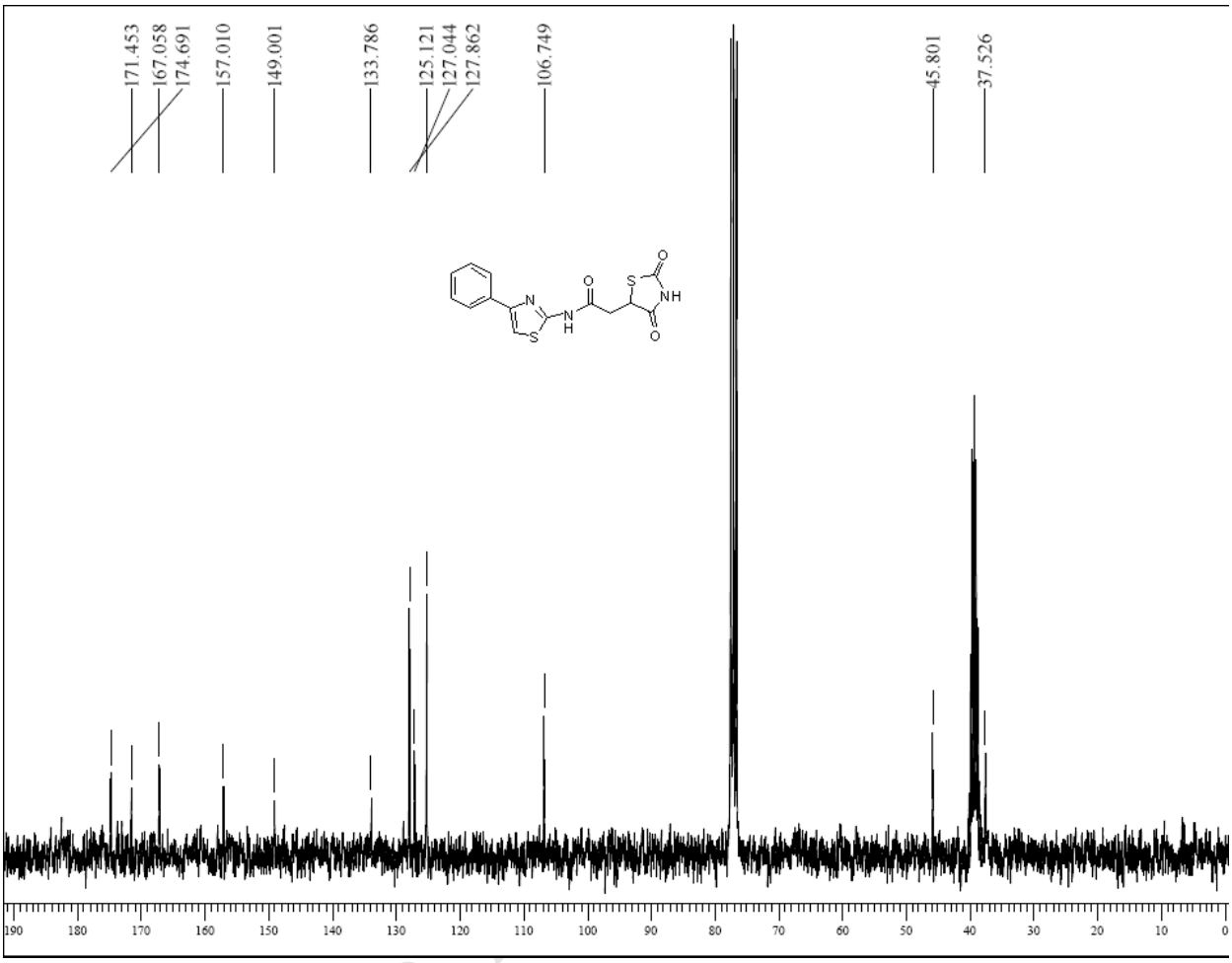
^{1}H NMR and ^{13}C NMR spectra of *N*-thiazolyl-thiazolidinedione-2-acetamides 4a-o

^{1}H NMR and ^{13}C NMR charts of representative compounds (4a-4o)

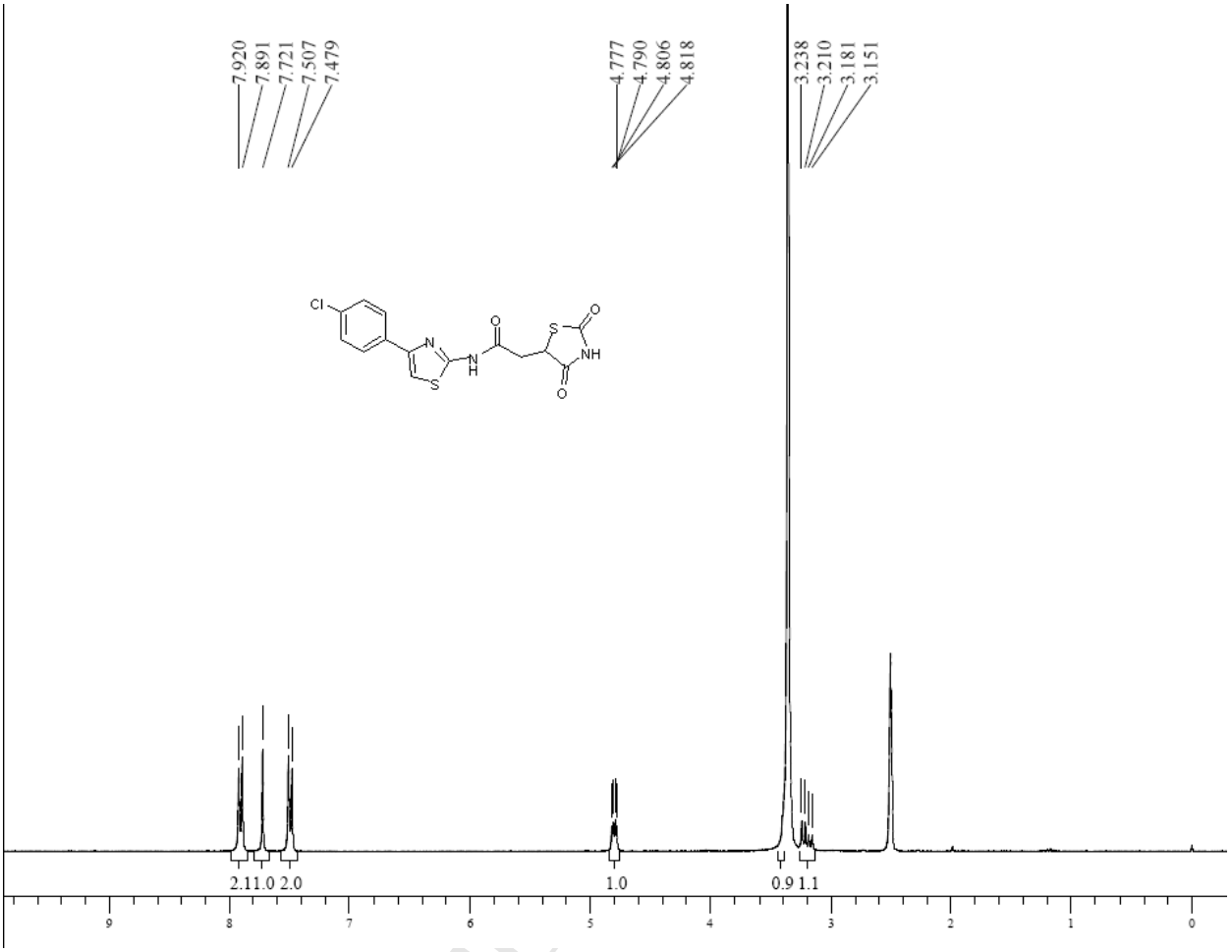
^{1}H NMR spectrum of **4a**



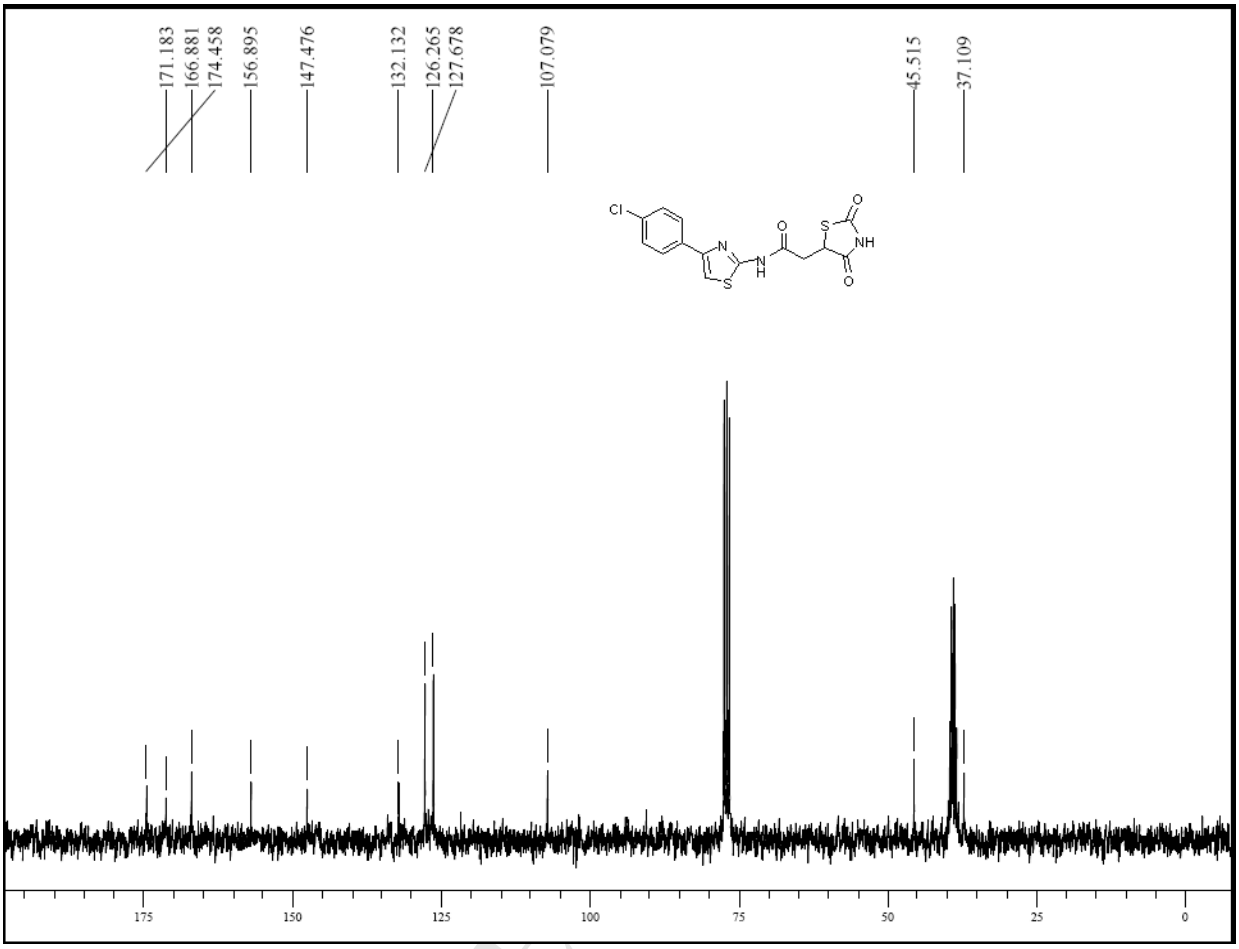
^{13}C NMR spectrum of **4a**



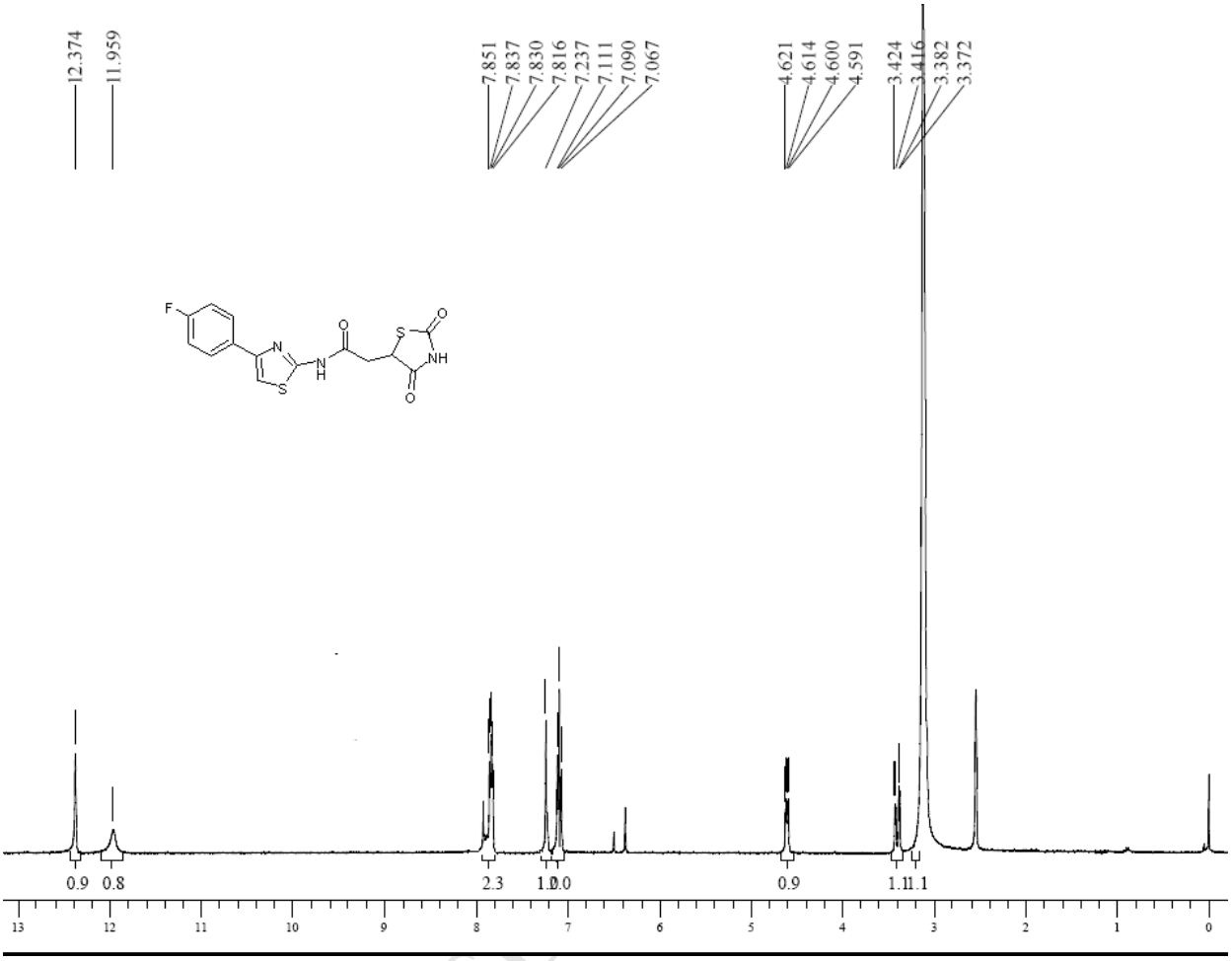
^{1}H NMR spectrum of **4b**



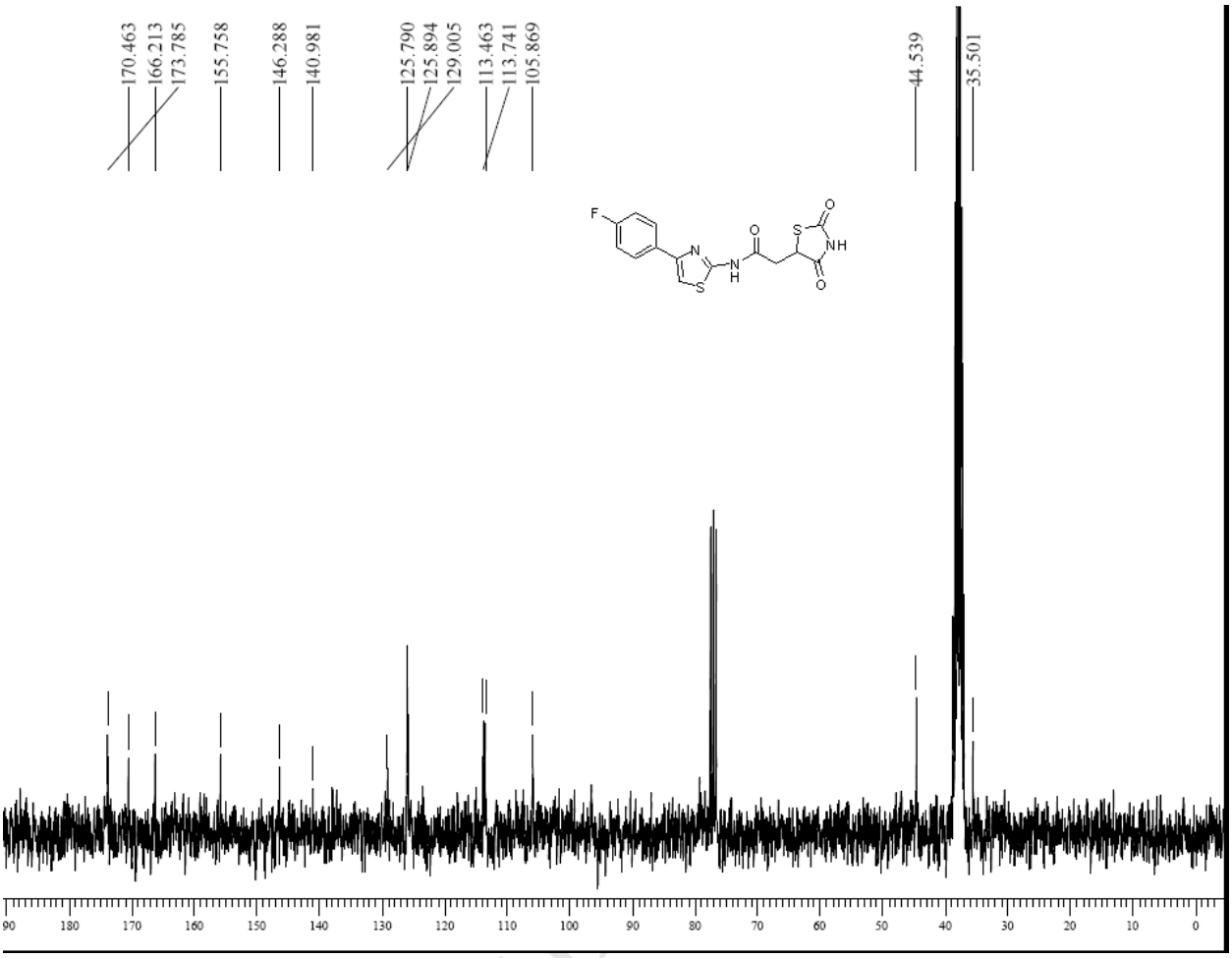
^{13}C NMR spectrum of **4b**



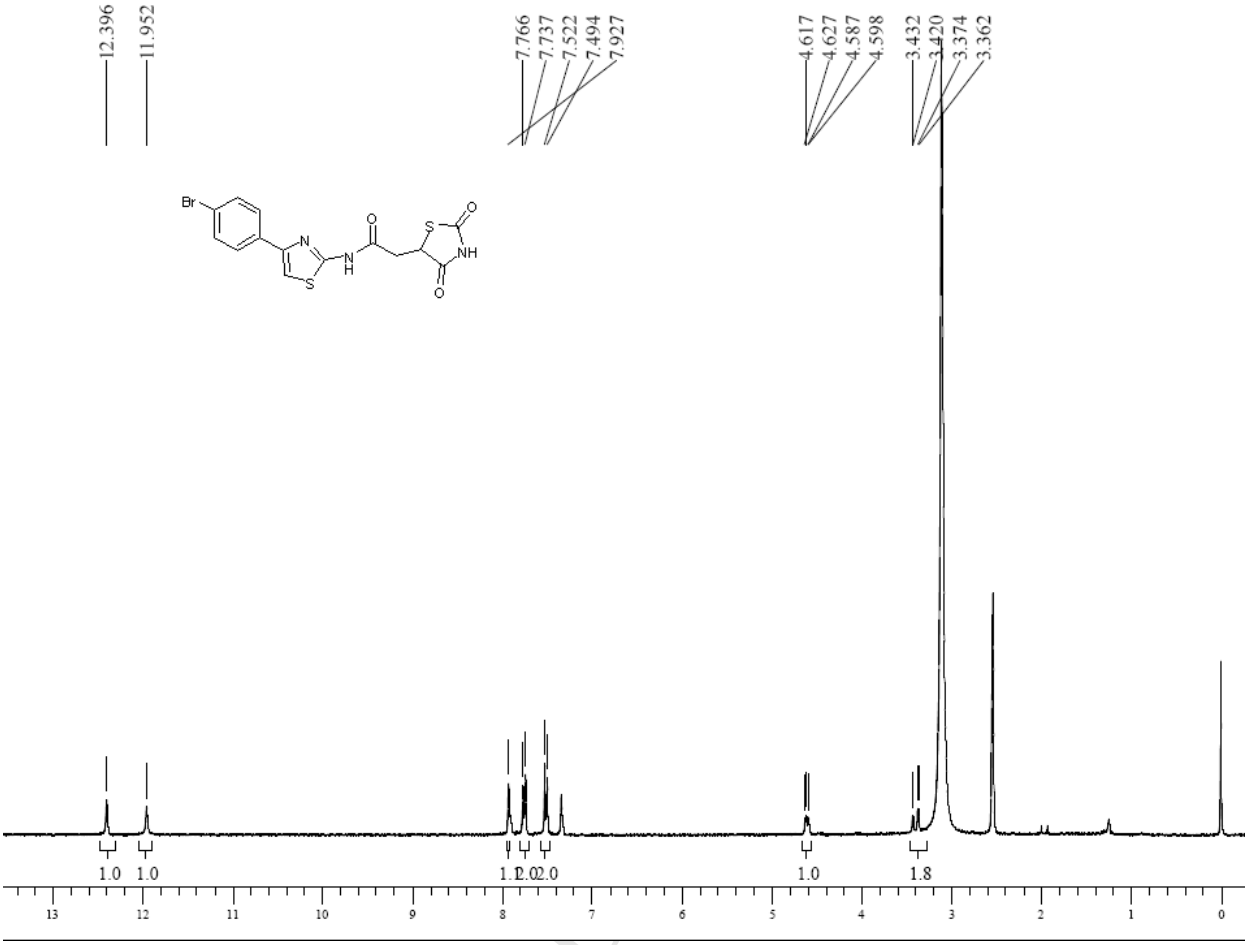
^{1}H NMR spectrum of **4c**



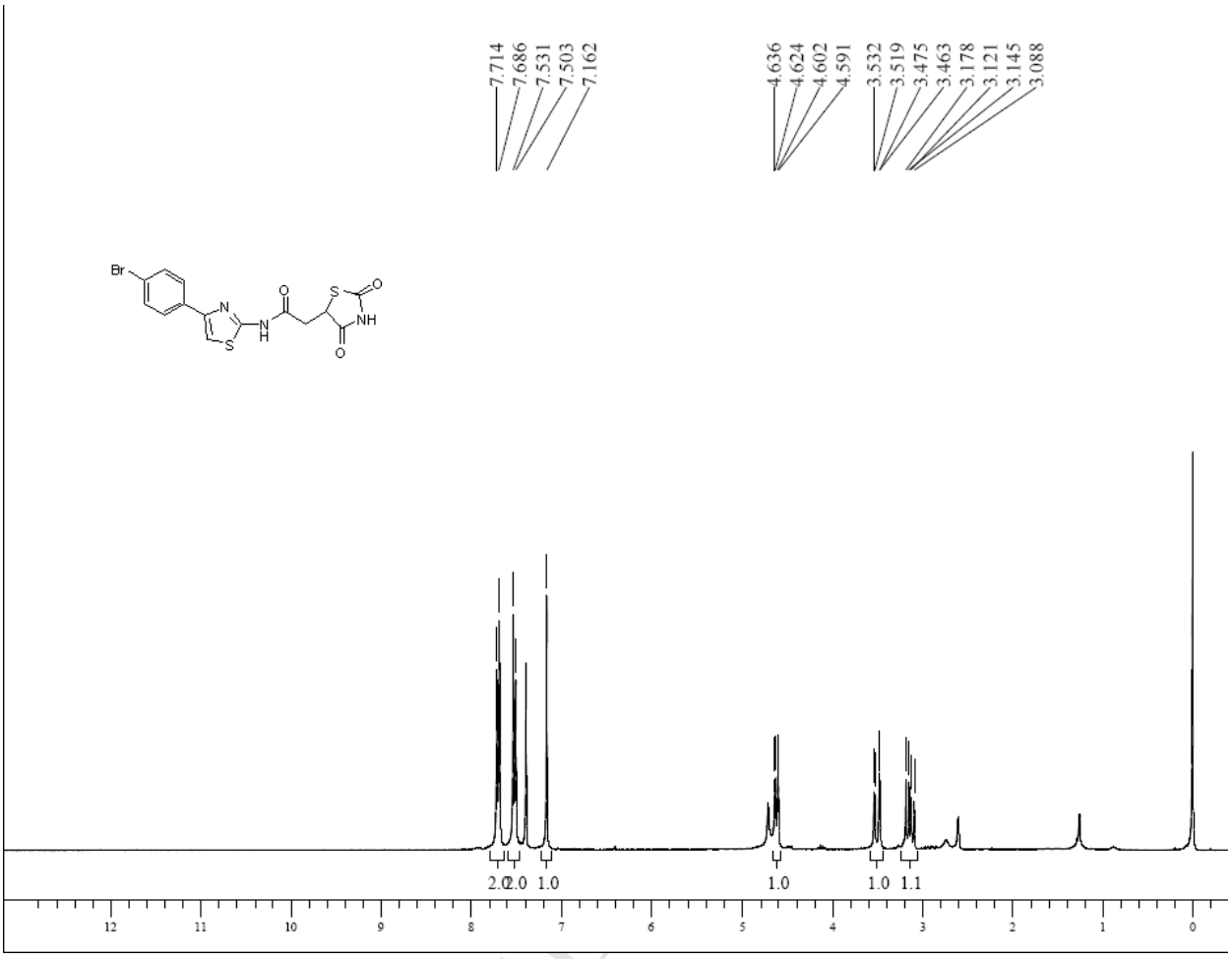
^{13}C NMR spectrum of **4c**



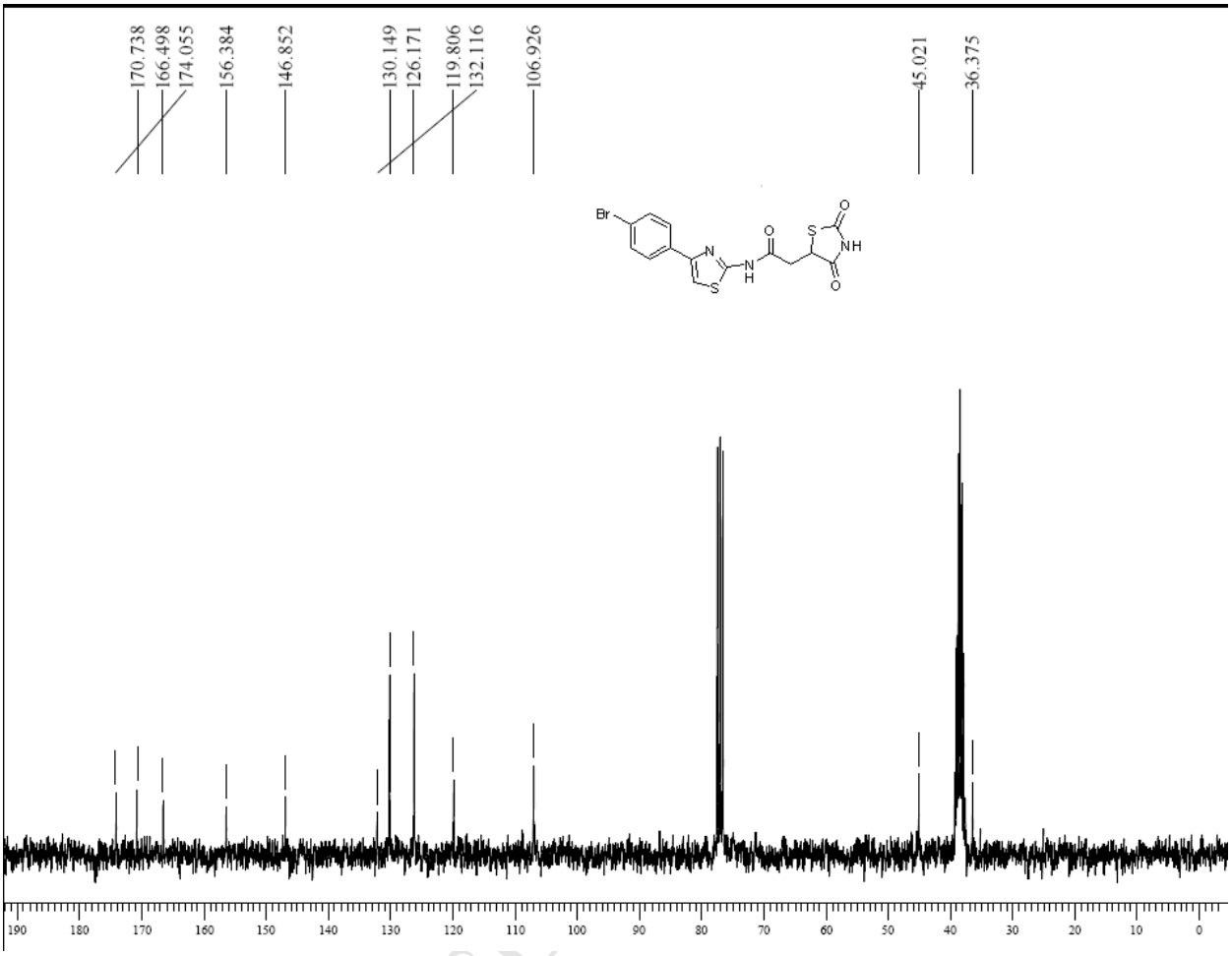
^{1}H NMR spectrum of **4d**



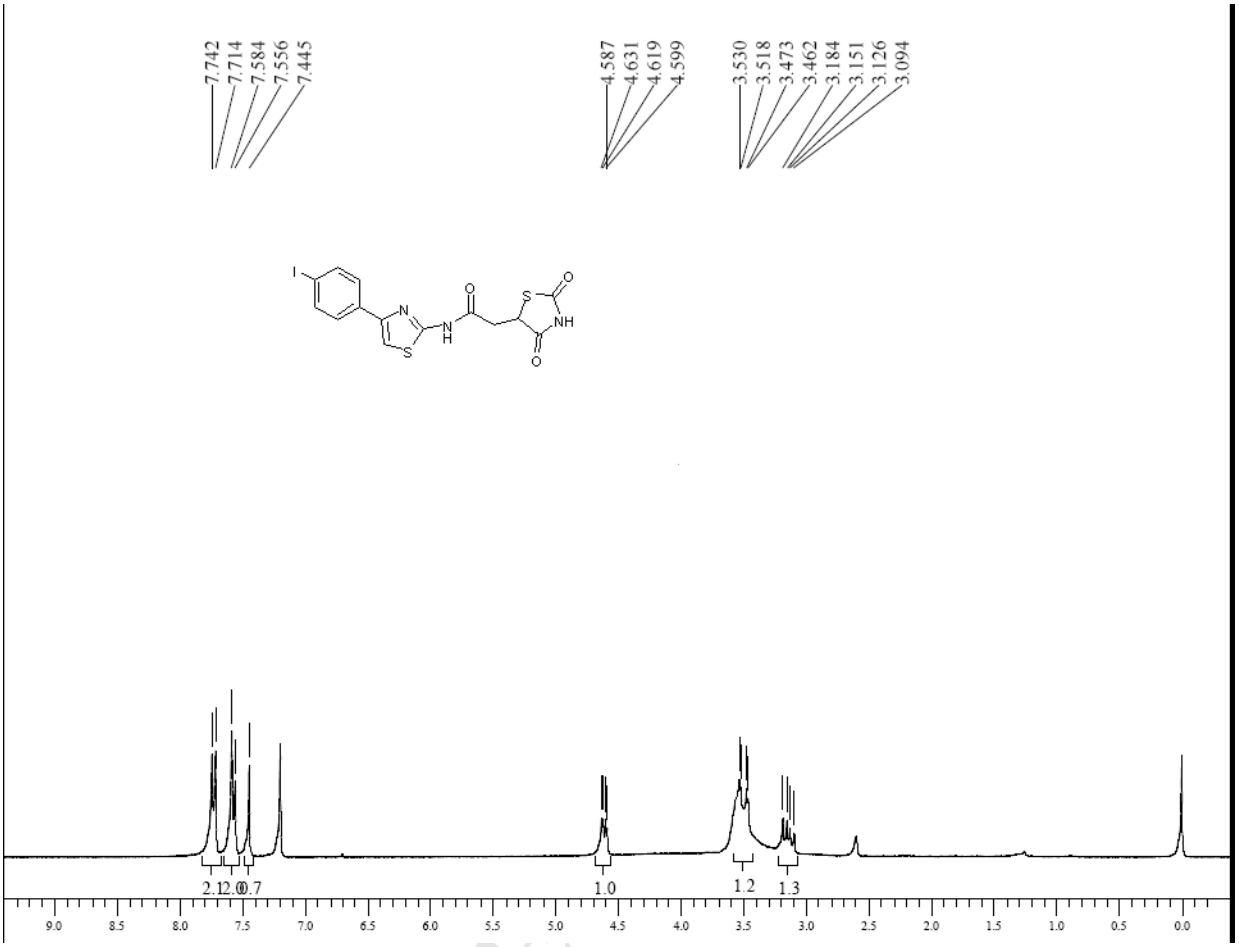
^{1}H NMR spectrum of **4d** (D_2O exchanged)



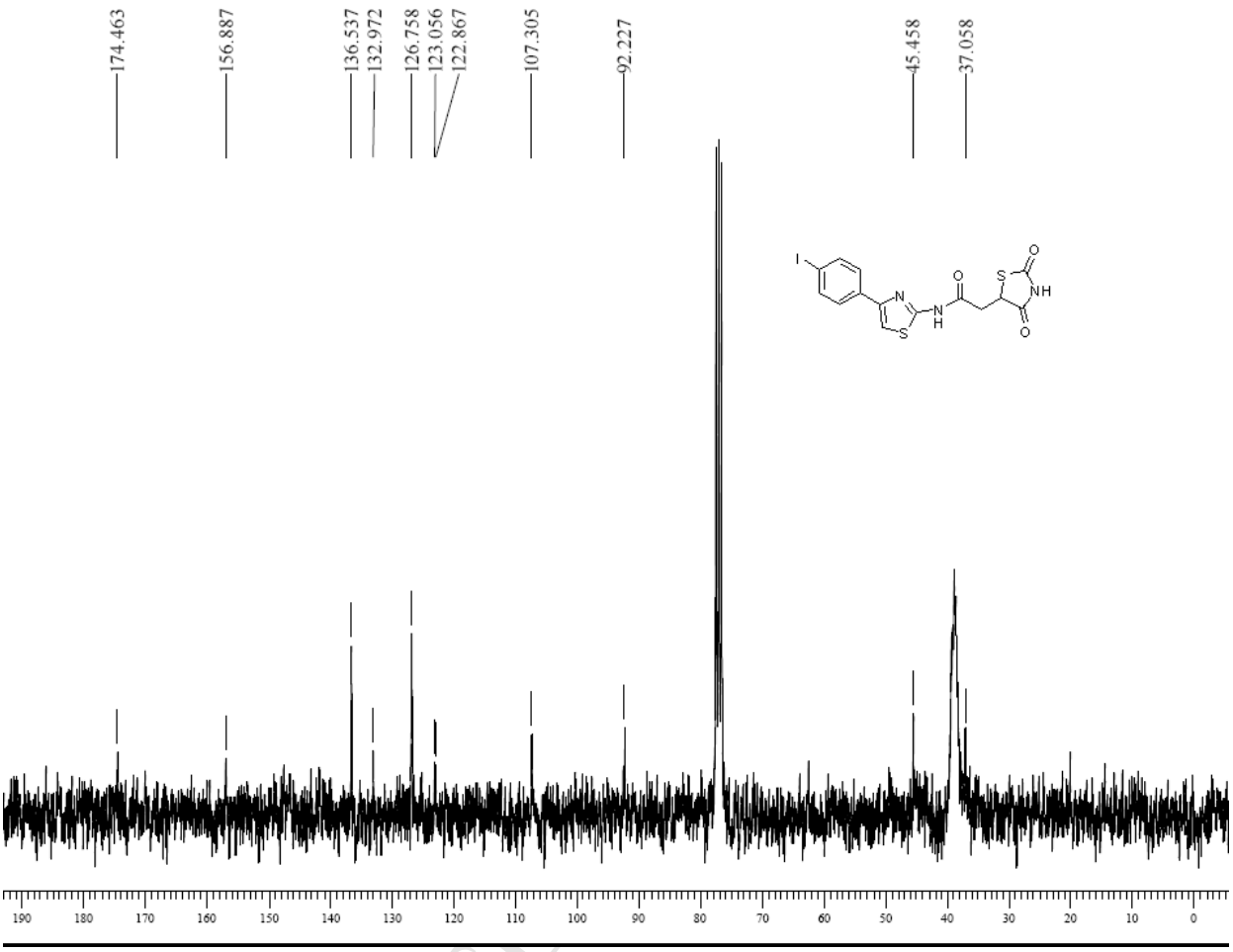
^{13}C NMR spectrum of **4d**



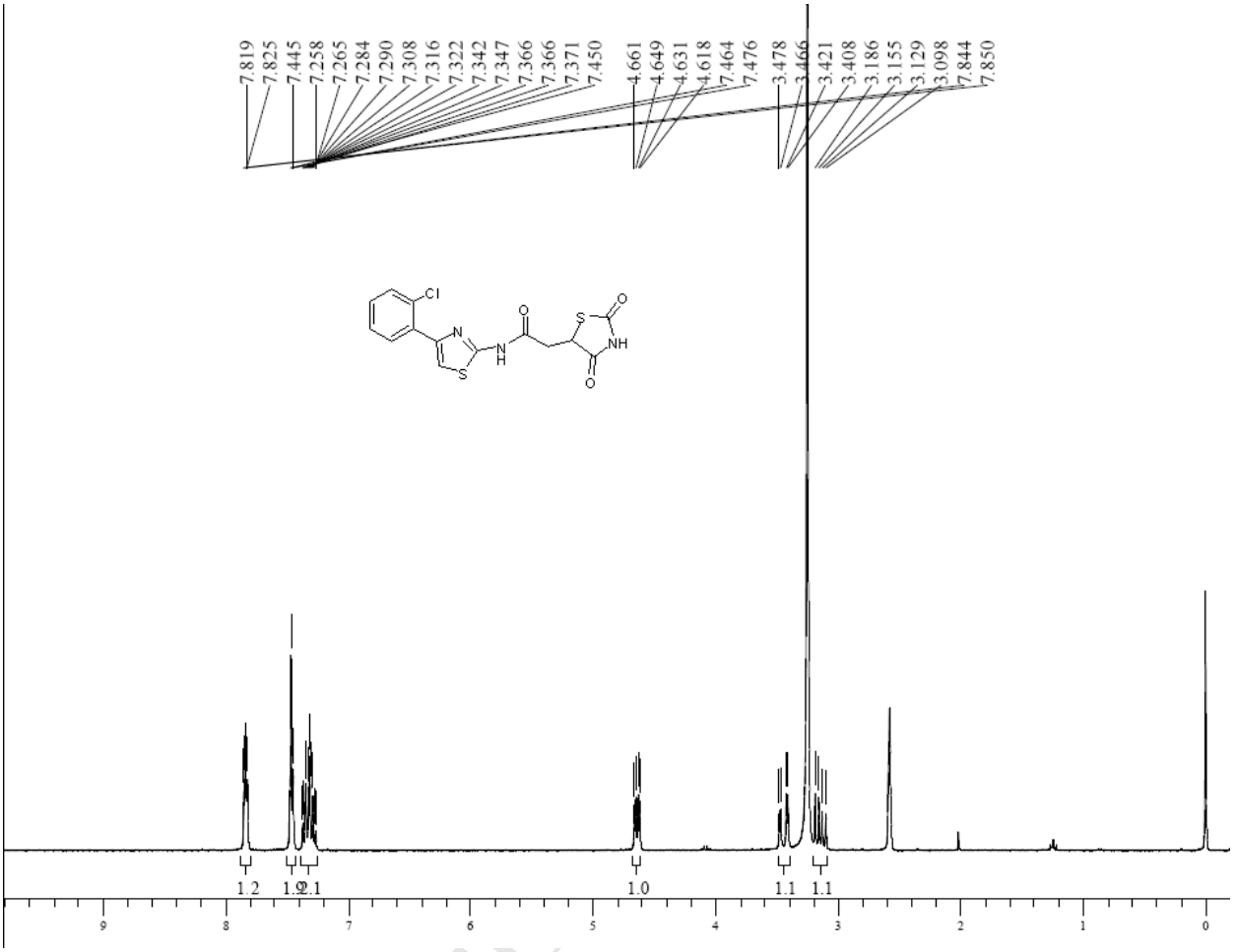
^{1}H NMR spectrum of **4e**



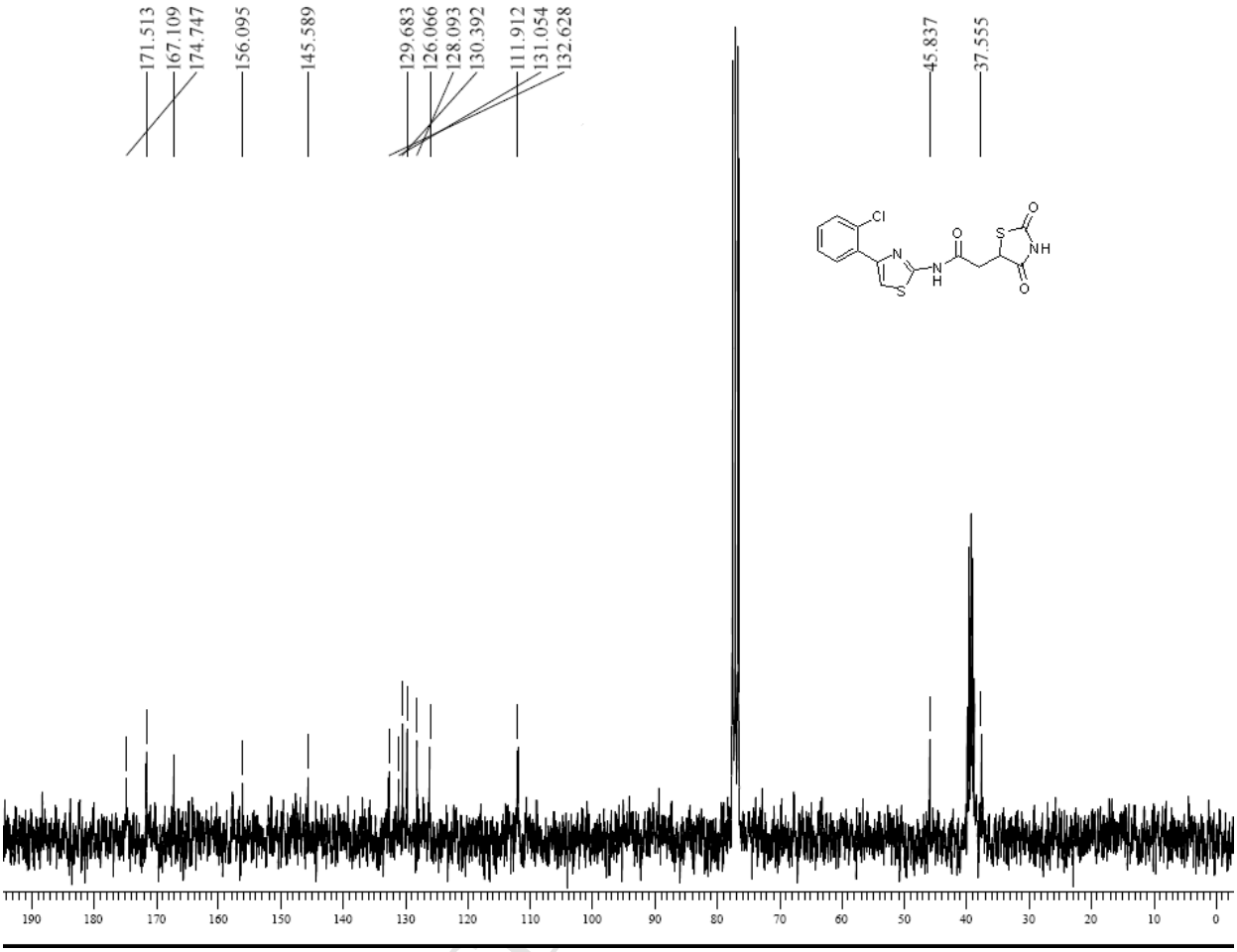
^{13}C NMR spectrum of **4e**



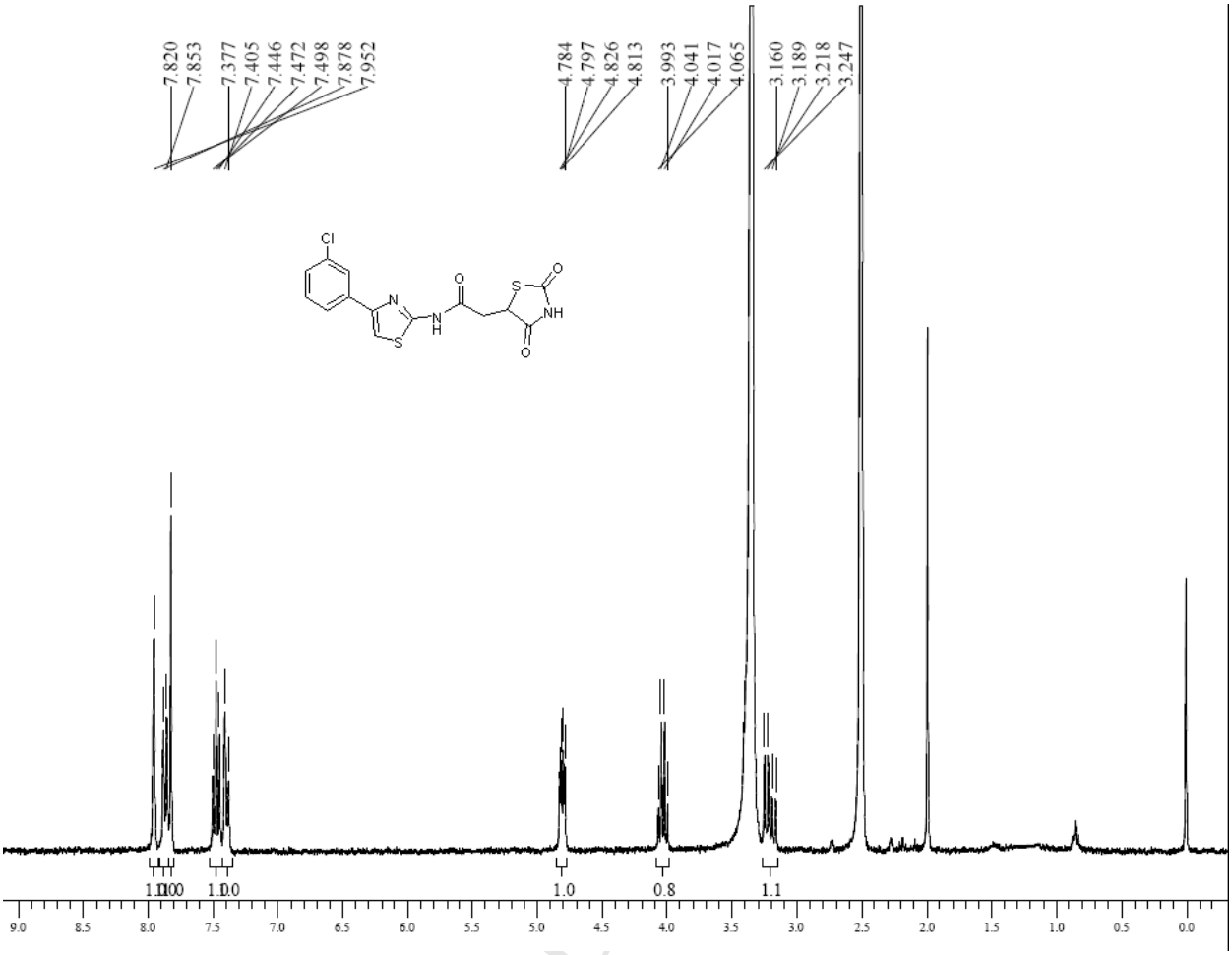
^{1}H NMR spectrum of **4f**



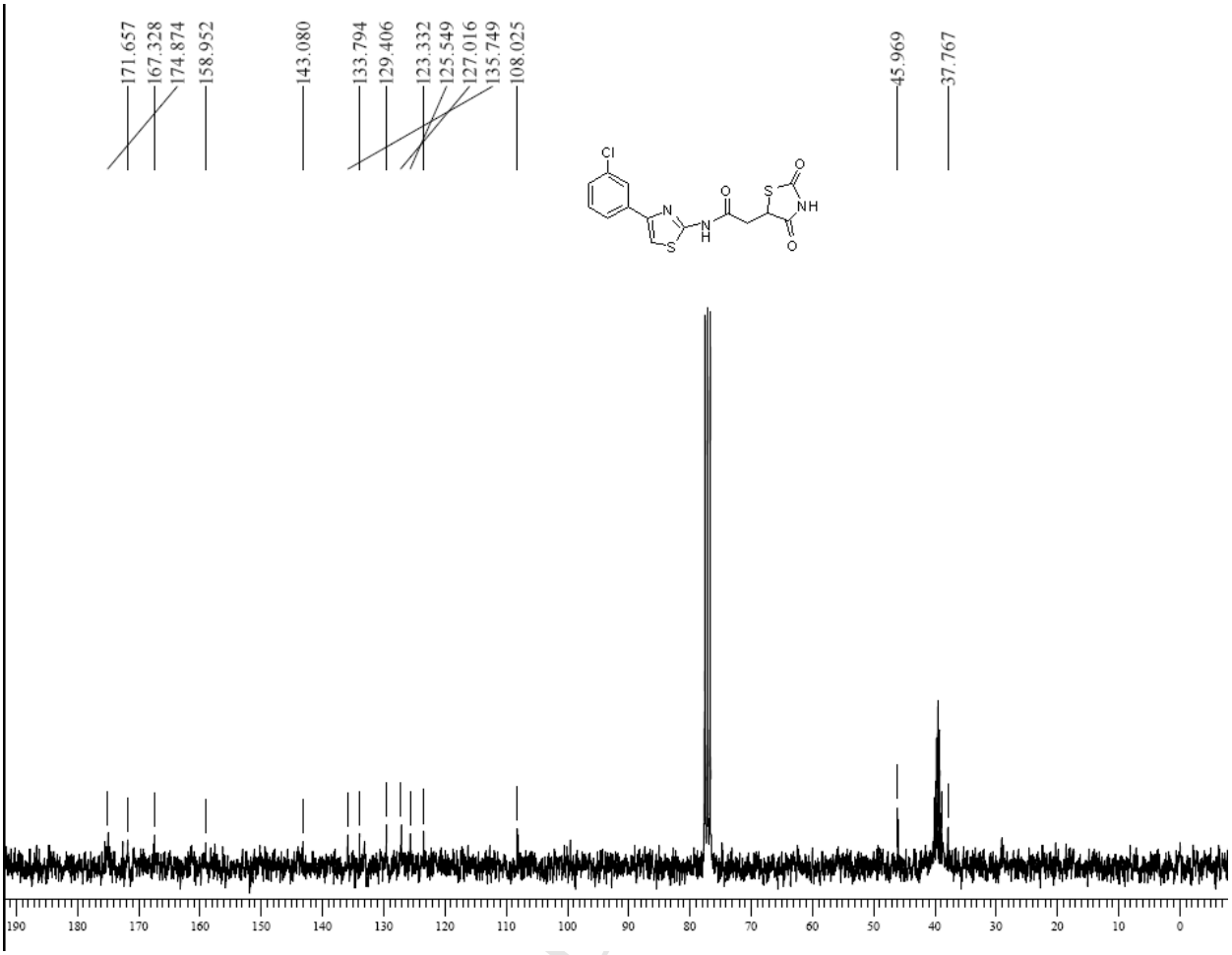
^{13}C NMR spectrum of **4f**



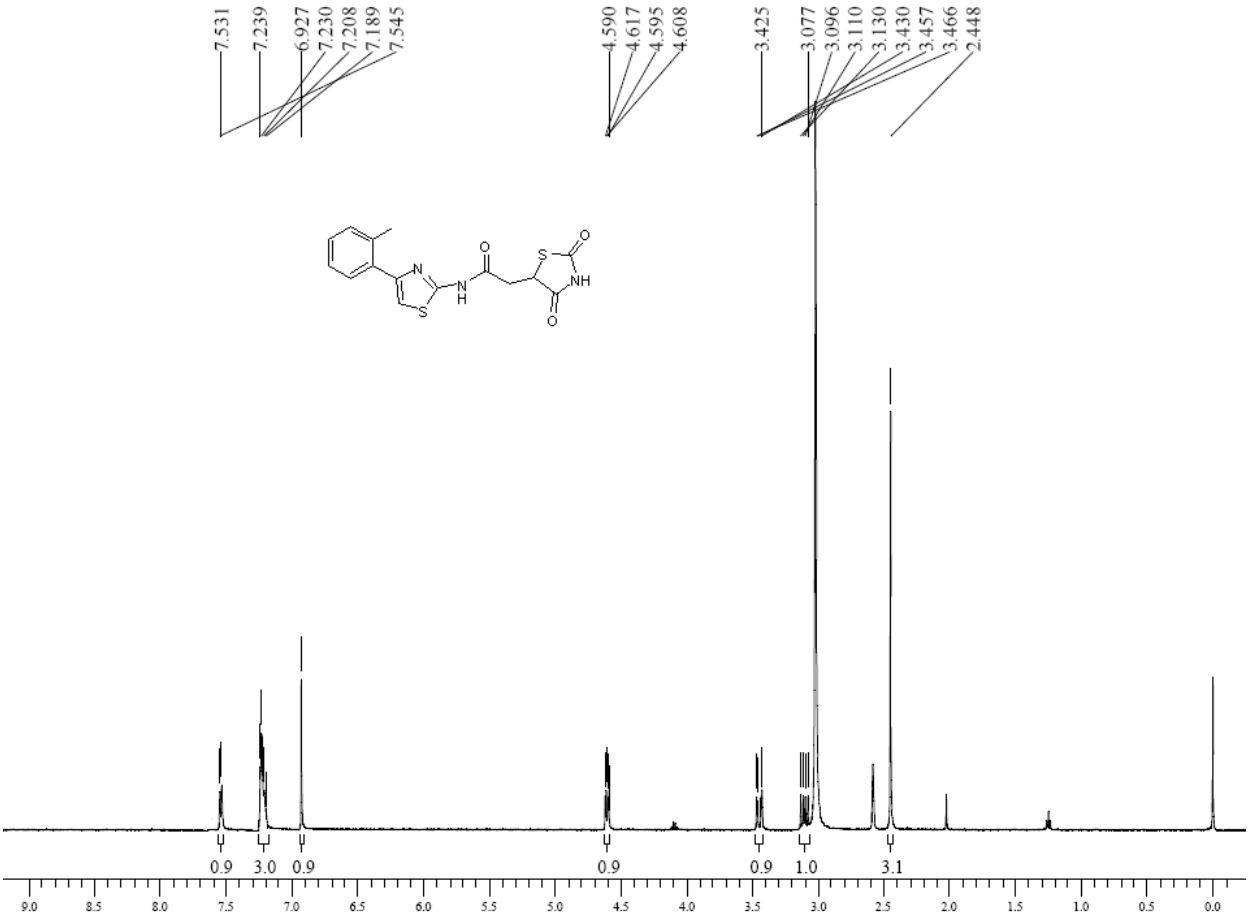
^{1}H NMR spectrum of **4g**



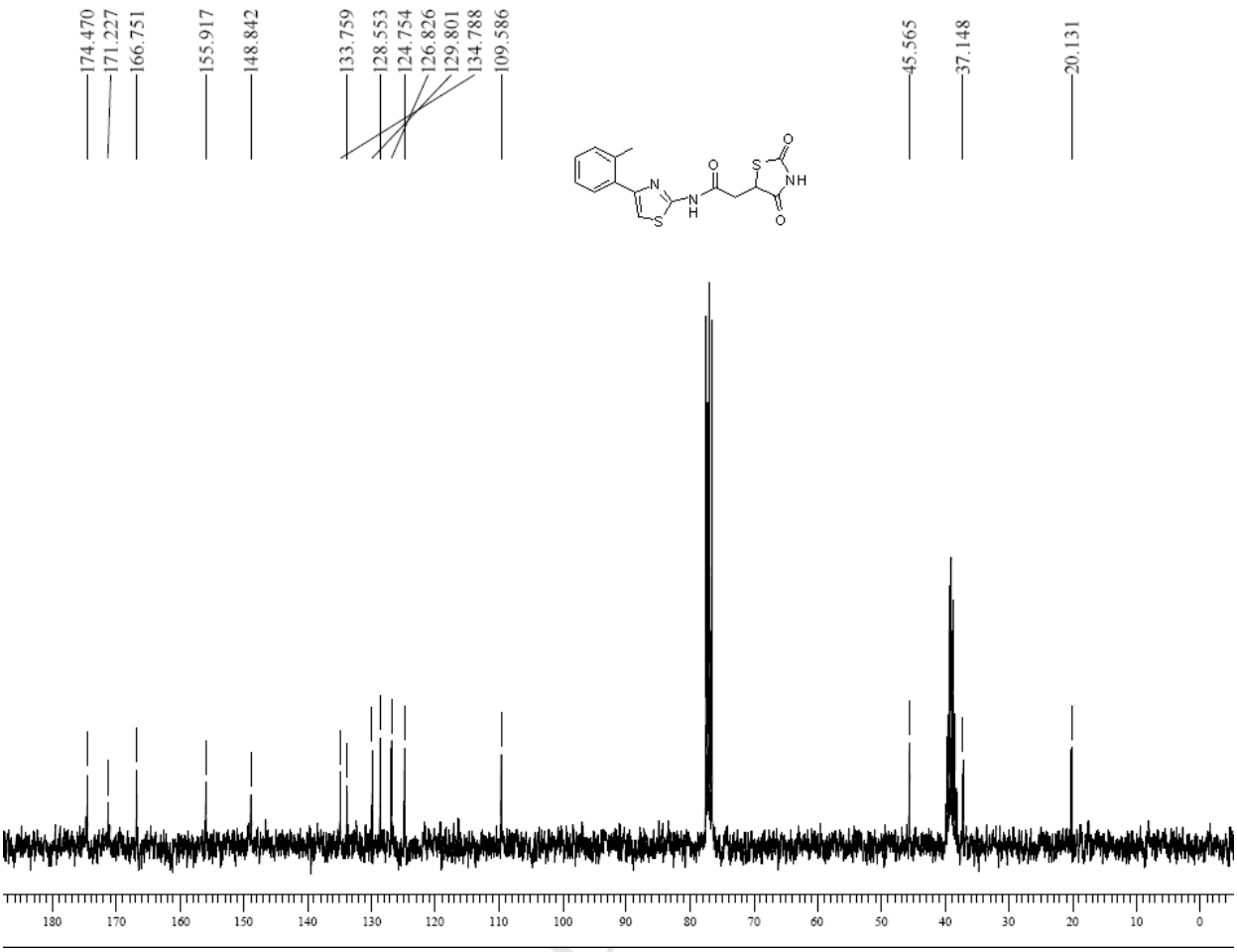
^{13}CNMR spectrum of **4g**



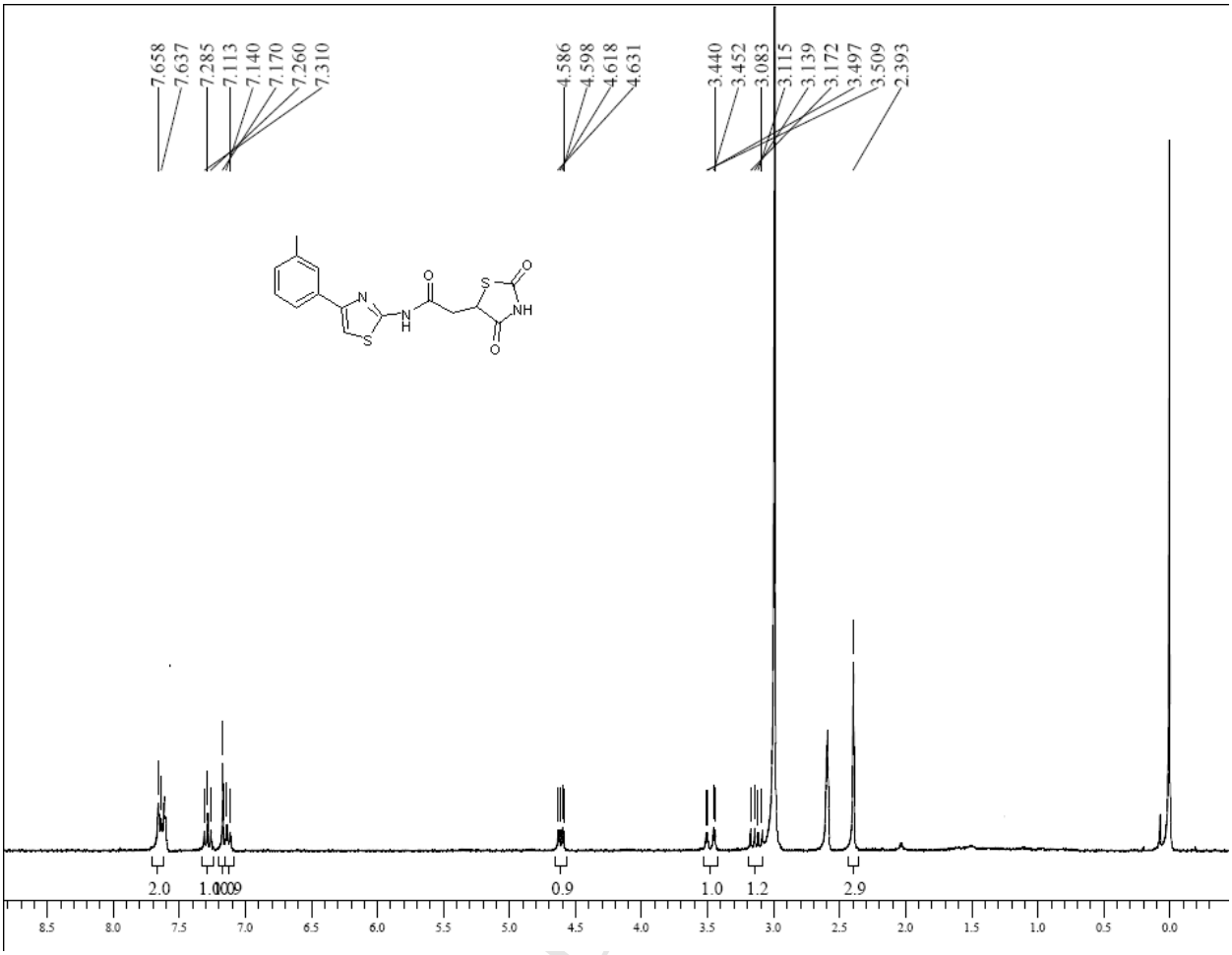
^{1}H NMR spectrum of **4h**



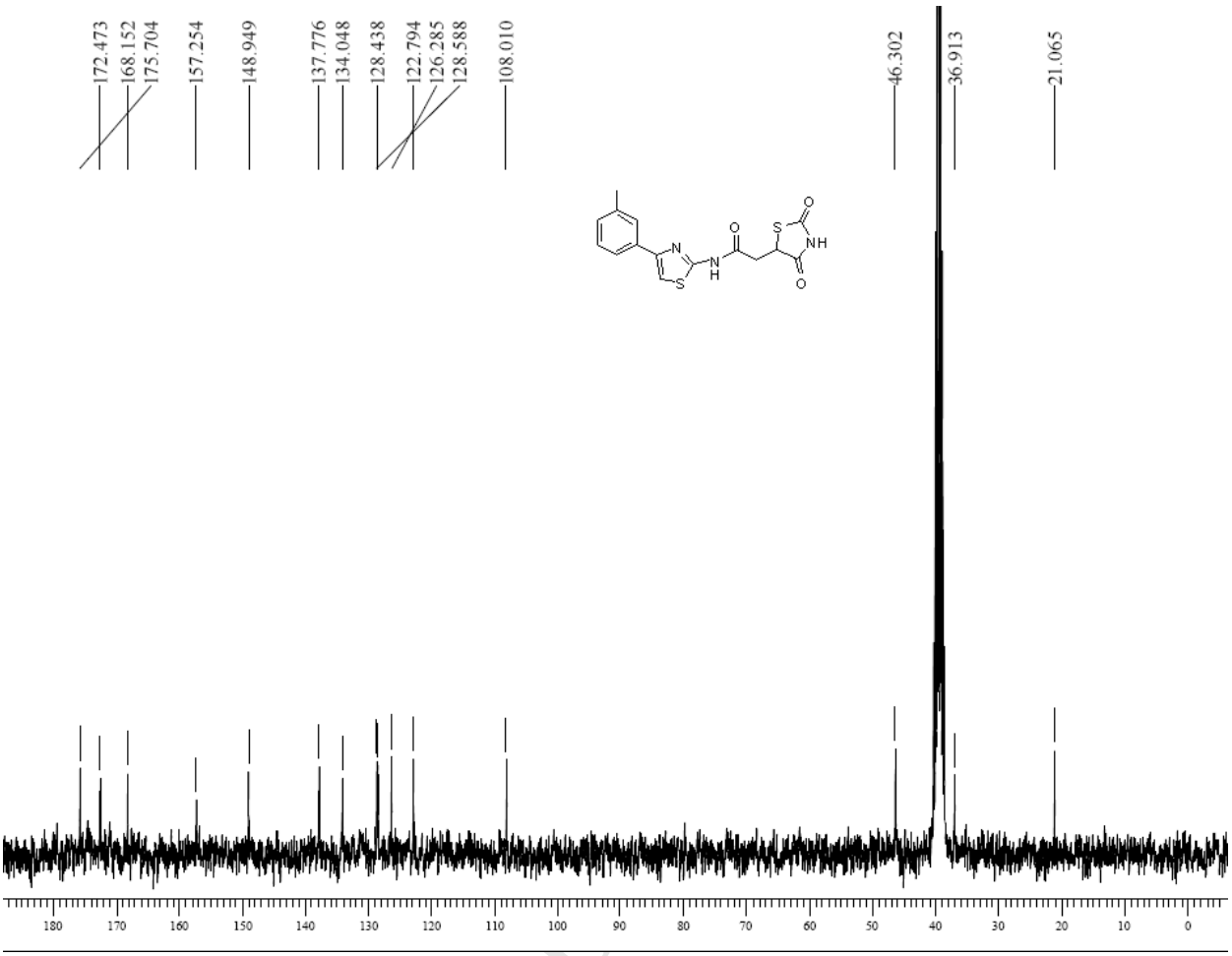
^{13}C NMR spectrum of **4h**



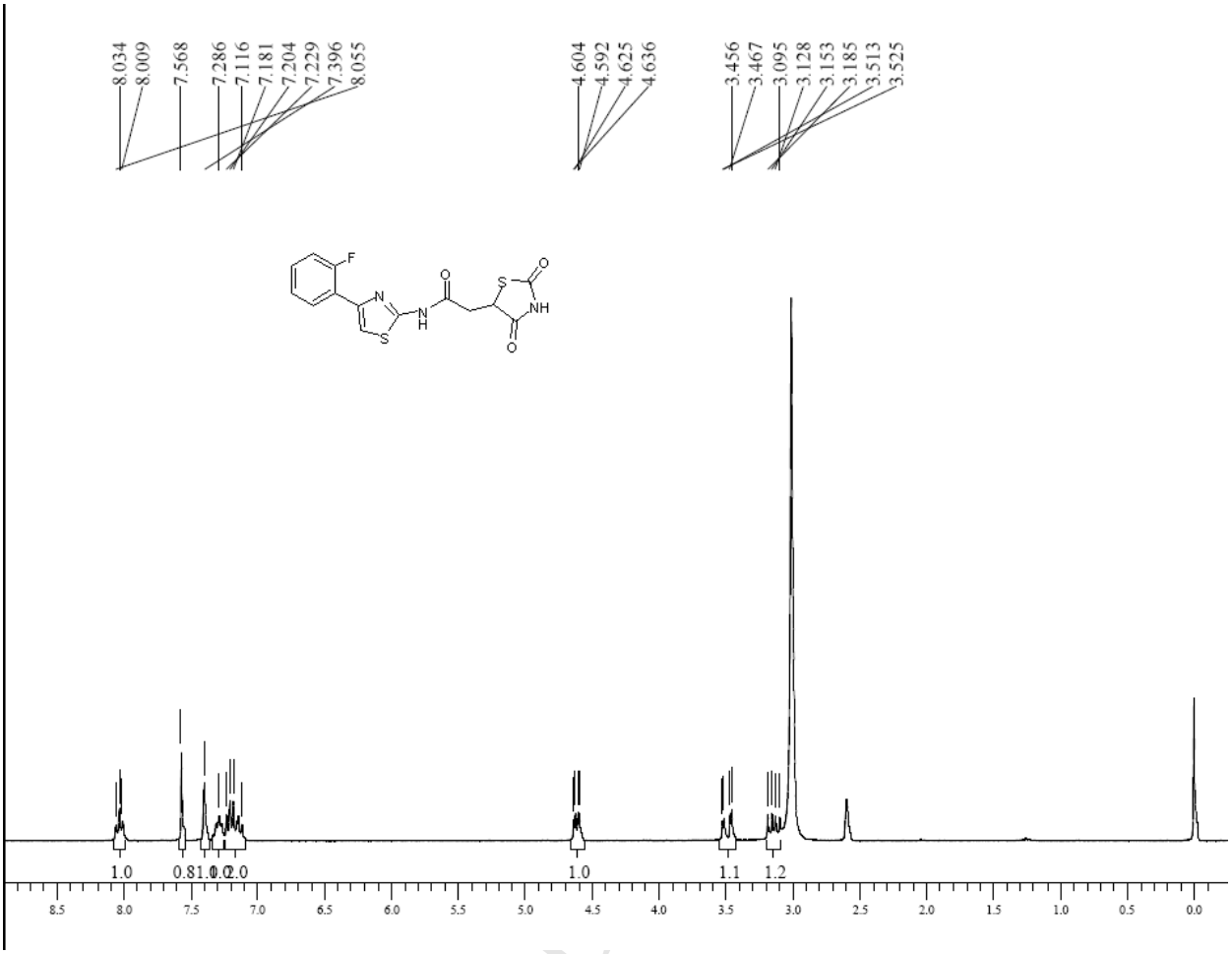
^{1}H NMR spectrum of **4i**



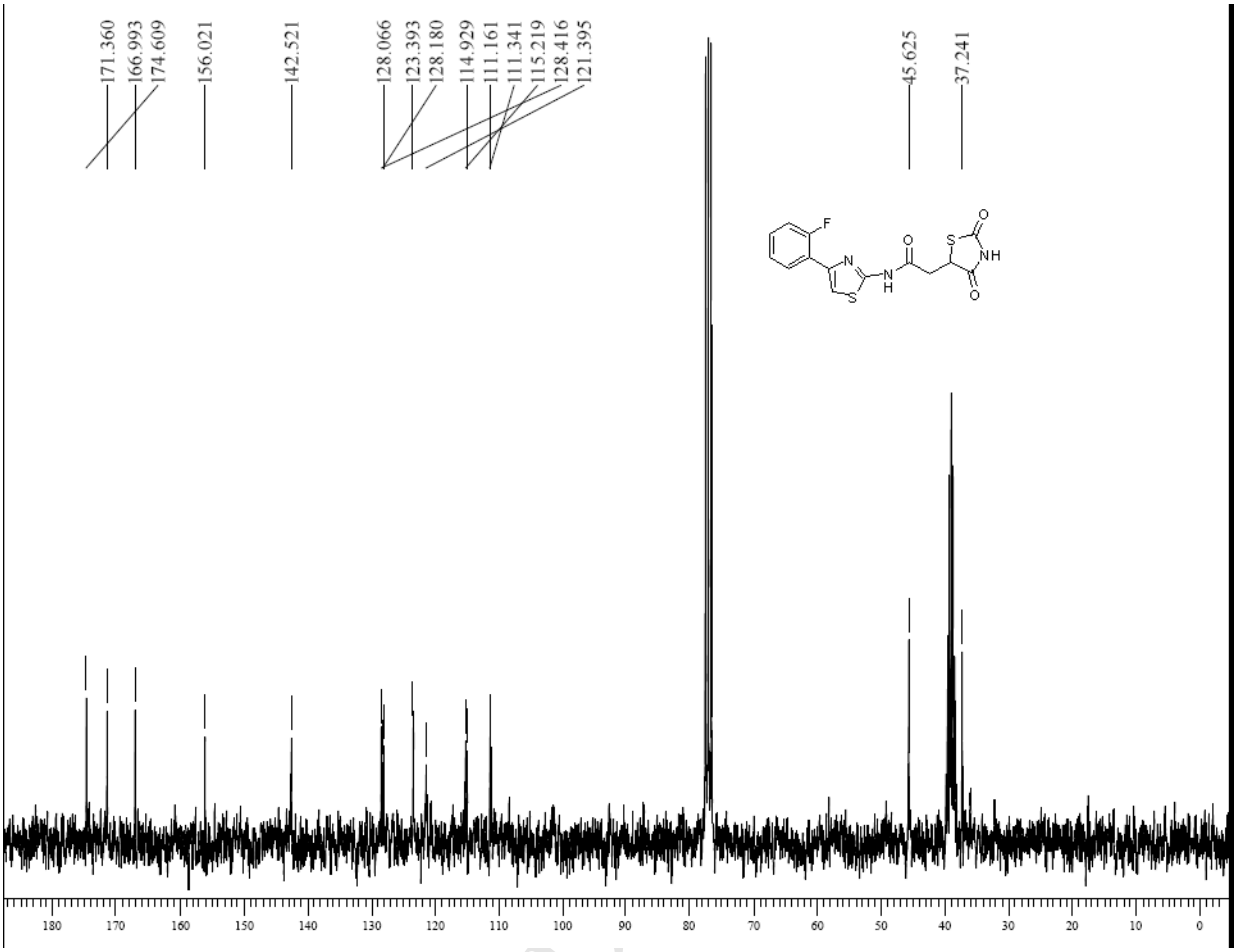
^{13}C NMR spectrum of **4i**



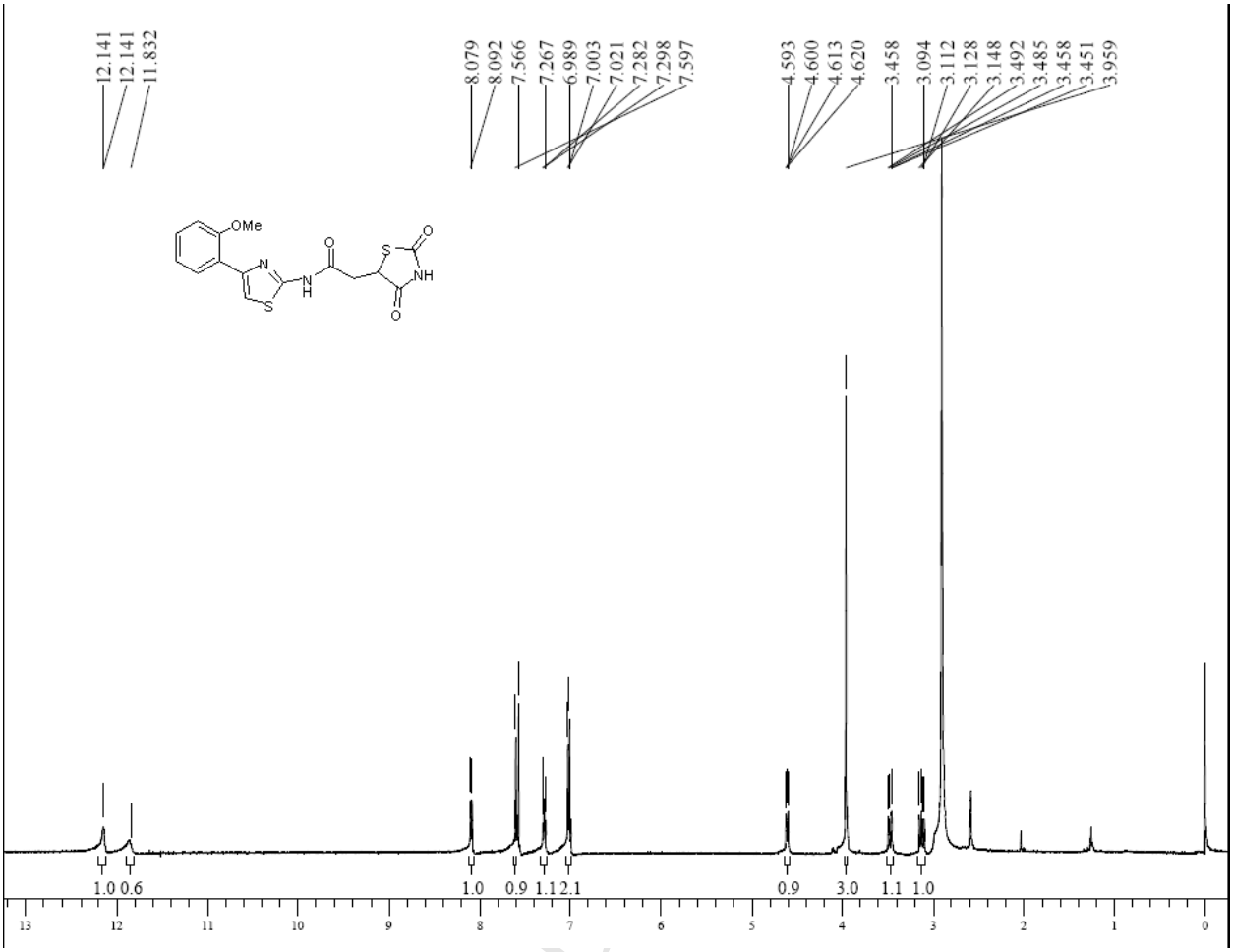
^{1}H NMR spectrum of **4j**



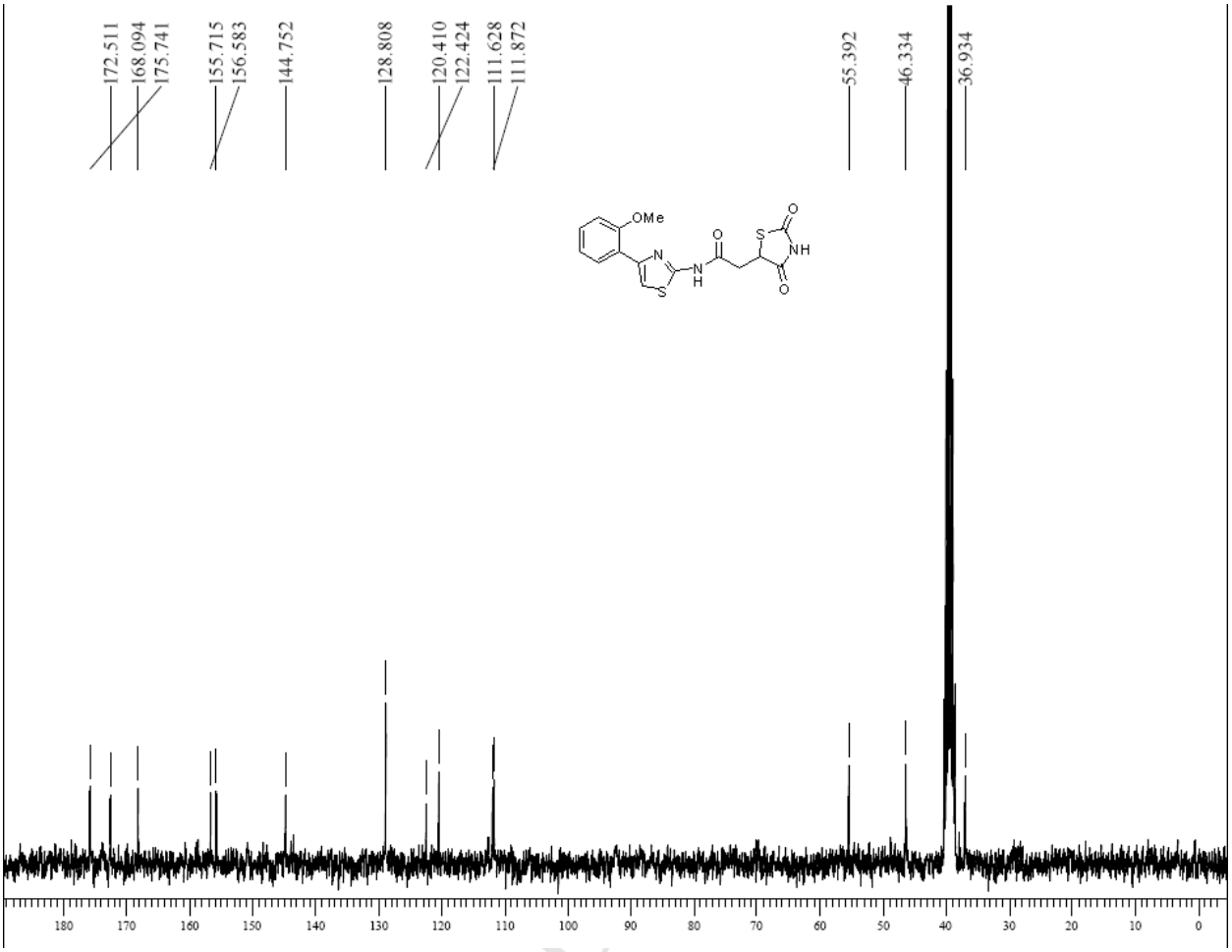
^{13}C NMR spectrum of **4j**



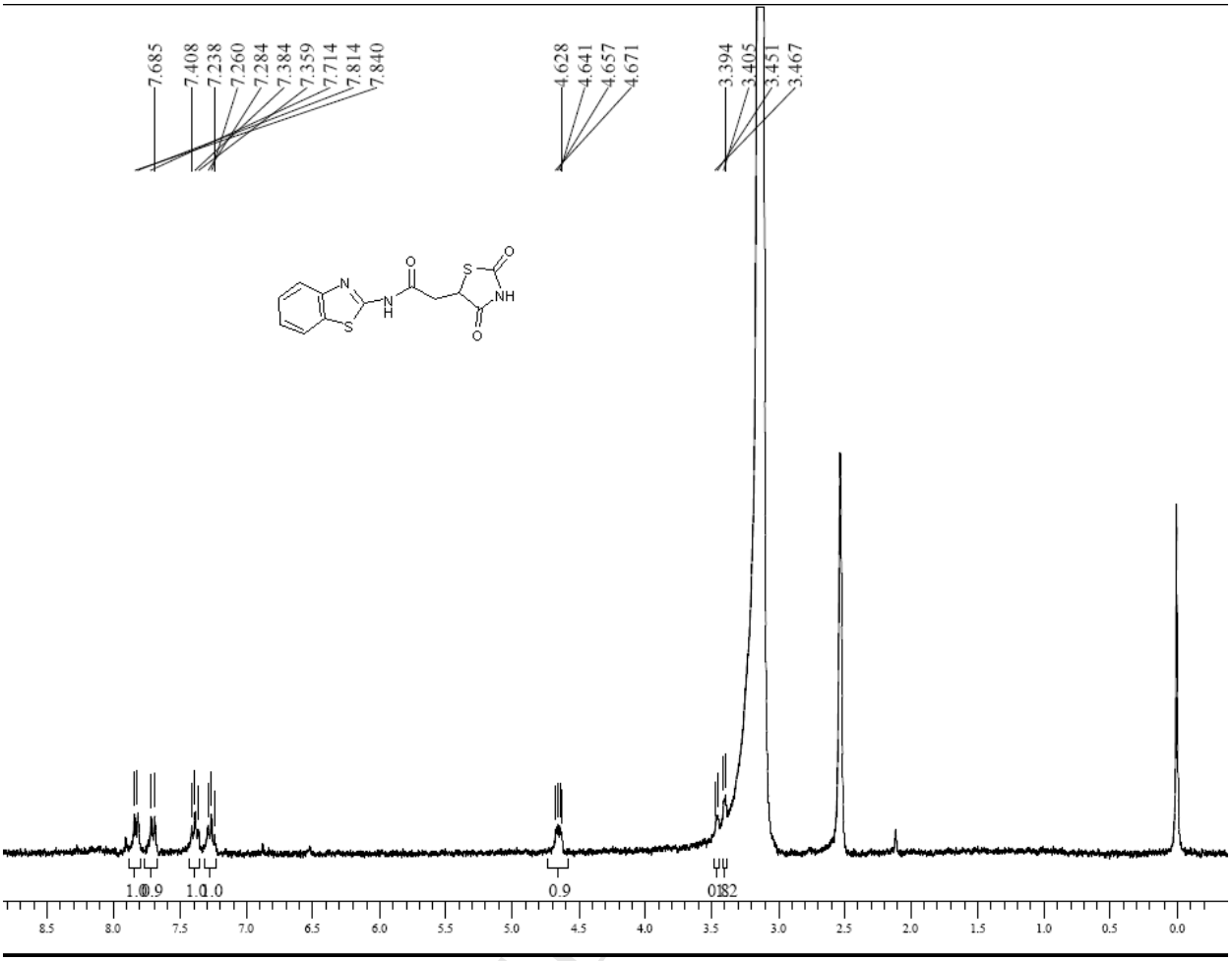
^{1}H NMR spectrum of **4k**



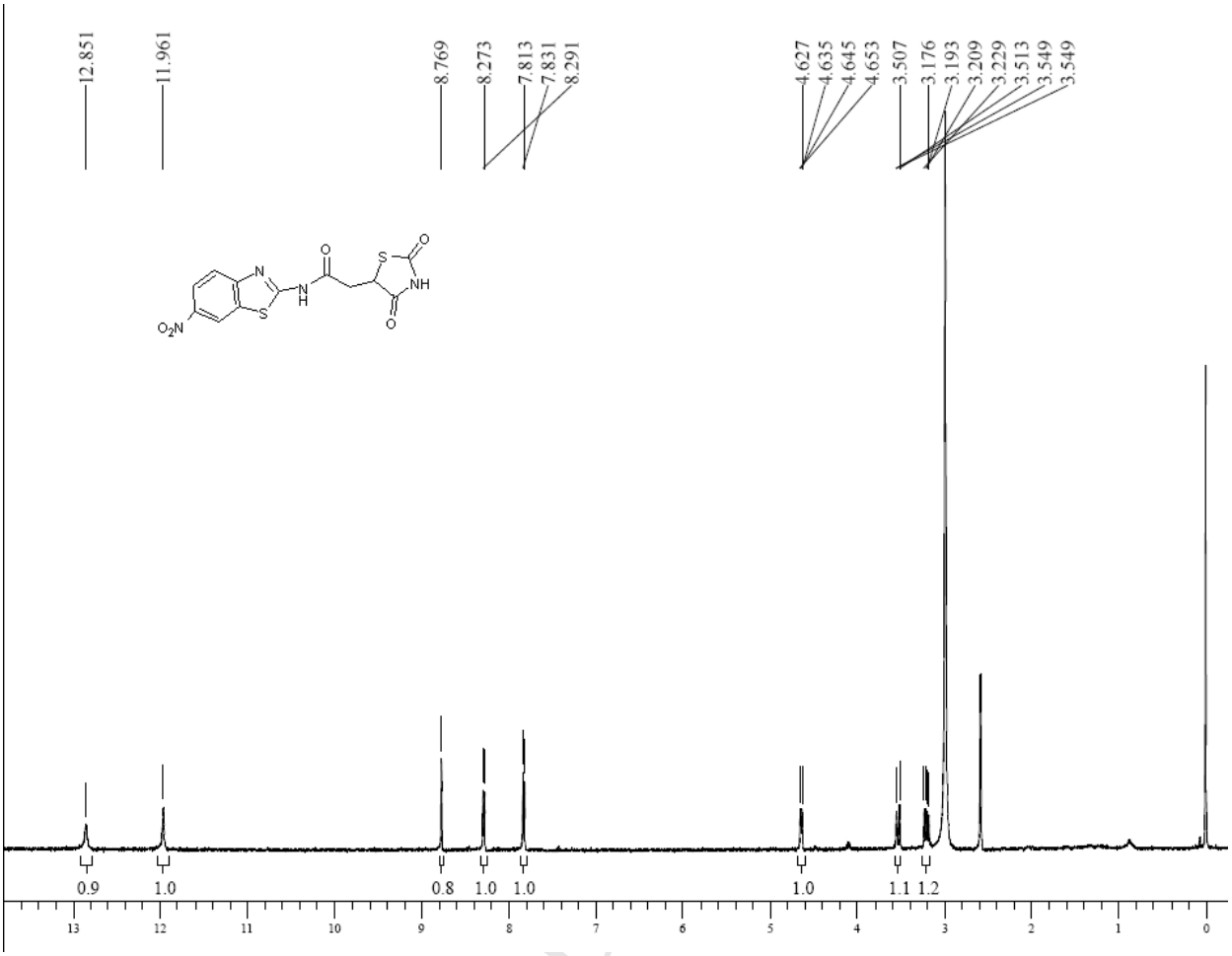
^{13}C NMR spectrum of **4k**



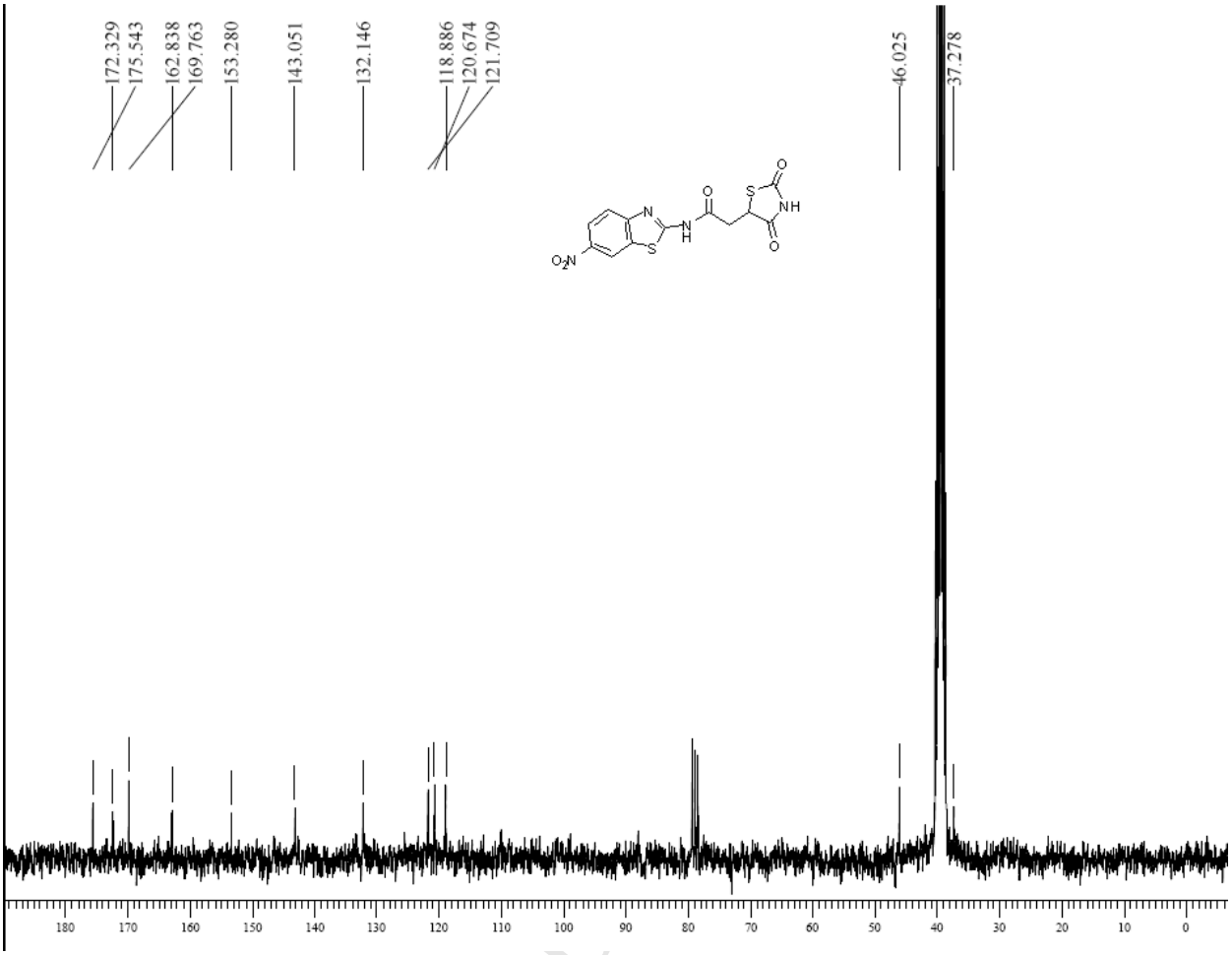
^{1}H NMR spectrum of **4l**



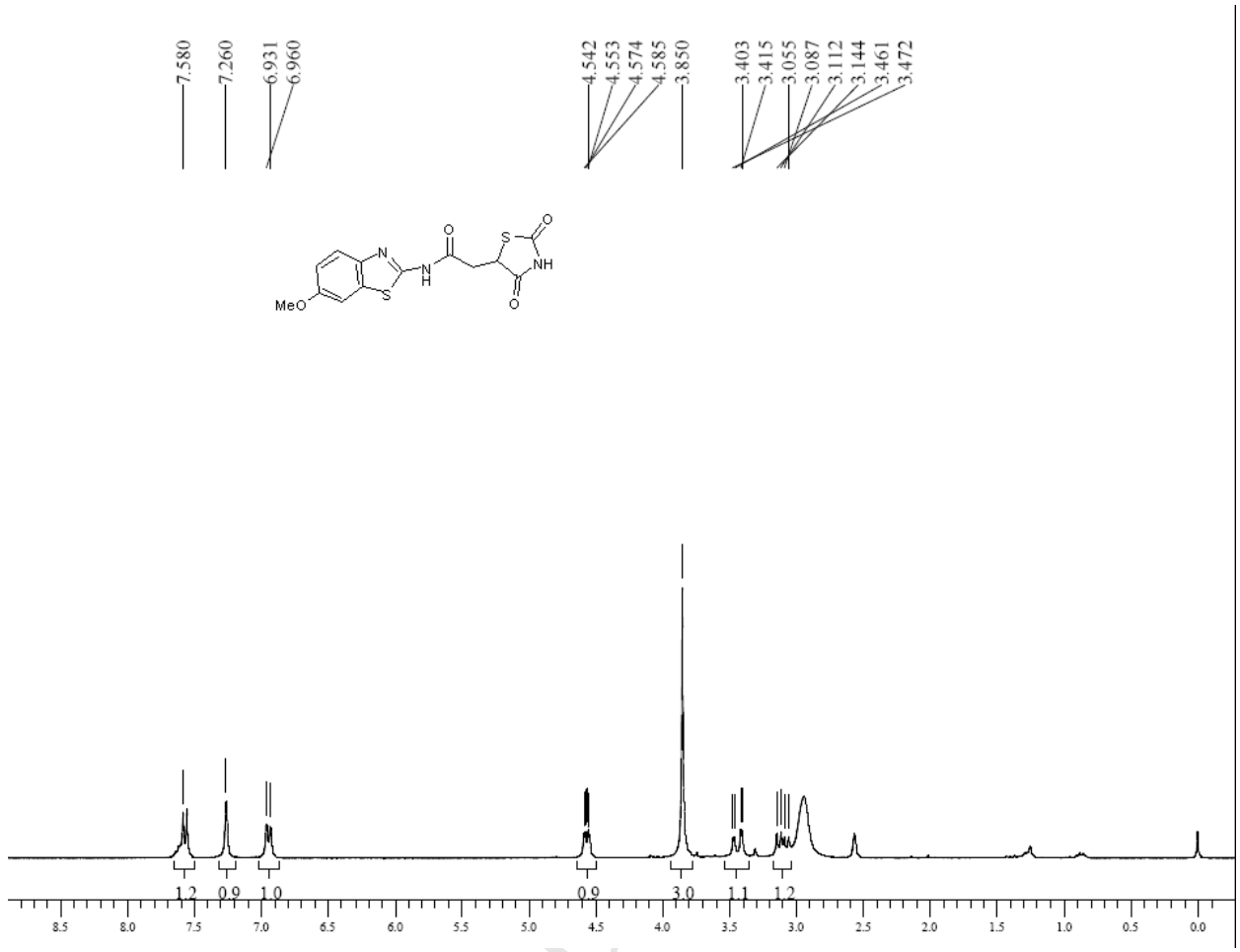
^{1}H NMR spectrum of **4m**



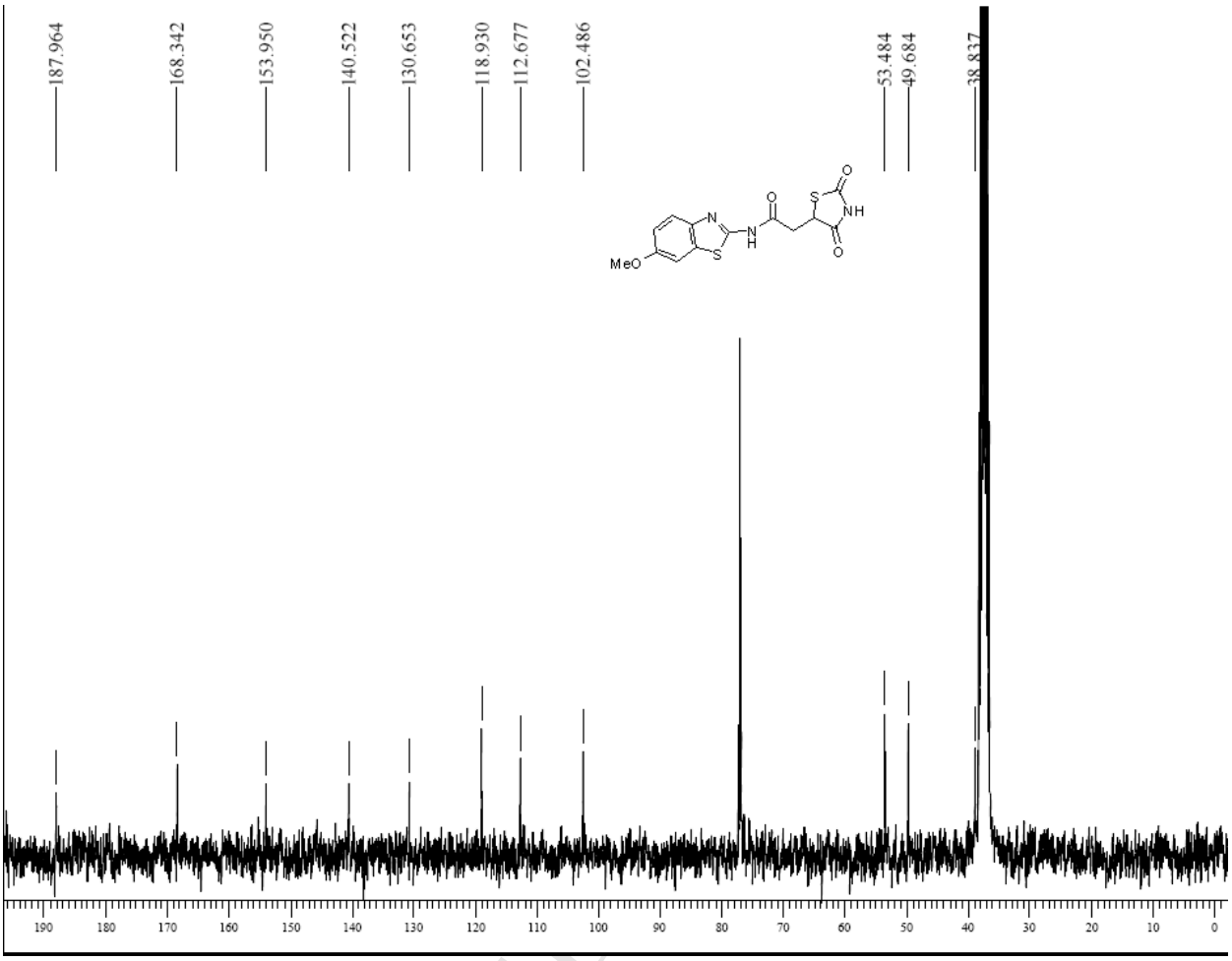
^{13}C NMR spectrum of **4m**



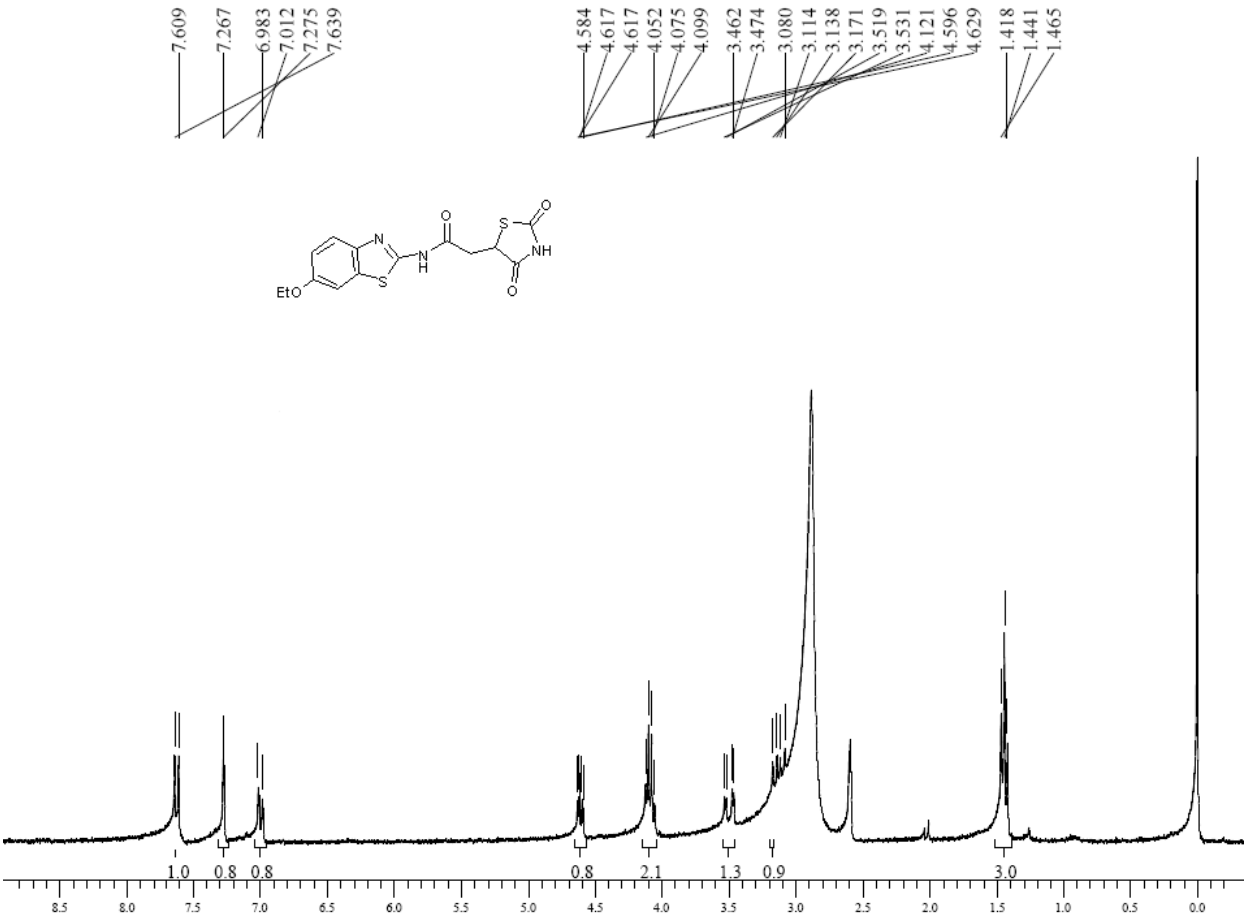
^{1}H NMR spectrum of **4n**



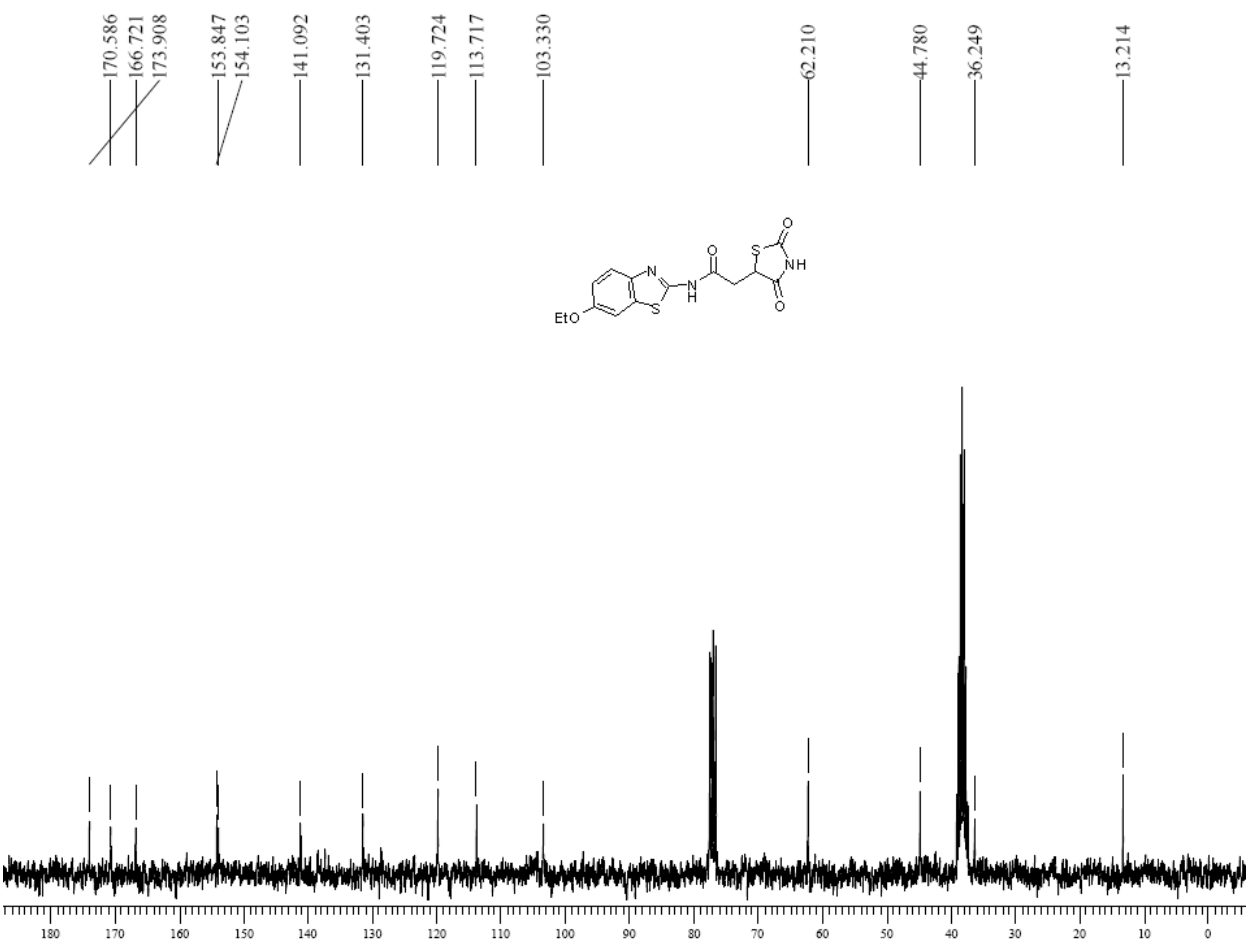
^{13}CNMR spectrum of **4n**



^{1}H NMR spectrum of **4o**



^{13}C NMR spectrum of **4o**


170.586
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173.908
153.847
154.103
141.092
131.403
119.724
113.717
103.330
62.210
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13.214
EtO
N
S
N
H
O
S
NH
O
O
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0

High lights

- Novel N-thiazolyl/ benzothiazolyl-thiazolidinedione-2-acetamides are prepared.
- Essayed for DPPH RSA, SASA, LPI, EHI, IL-1ß & MCP-1 secretion inhibition.
- Some of them show both anti-inflammatory and antioxidant potential.
- Structure of one of the target compounds is confirmed by X-ray.