doi.org/10.36721/PJPS.2020.33.2.REG.575-579.1

Synthesis of (4*R*)-thiazolidine carboxylic acid and evaluation of antioxidant potential

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Abstract: We report here the synthesis as well as antioxidant activity of a series of 2-aryl thiazolidine-4-carboxylic acids, including two novel derivatives. They were synthesized by nucleophilic cyclic condensation of L-cysteine hydrochloride with a range of aromatic aldehydes. Their *in vitro* antioxidant activity was evaluated by DPPH radical scavenging assay. It was observed that the aromatic substituent at C-2 of thiazolidine ring effects the antioxidant potential of the thiazolidine derivatives. The nature and position of the substituents on aromatic ring were correlated with antioxidant activity. Compounds with $-OCH_3$ group on aromatic ring showed a better radical scavenging property than the other groups such as -Cl, -F, and $-NO_2$. The presence of phenyl ring thus enhanced radical scavenging activity.

Keywords: Antioxidant activity, DPPH, L-cysteine, free radical scavenging, (4*R*) Thiazolidine carboxylic acid

INTRODUCTION

Majority of biologically active molecules including drugs contain heterocyclic systems. Often the presence of hetero atoms renders specificities in their biological responses. Thiazolidines belong to a heterocyclic class of compounds, and regarded as biologically important scaffolds. Thiazolidines are known for several biological activities in medicinal chemistry (Samadhiya *et al*., 2012). Insulin sensitizers class of thiazolidines was developed in early 1980s (Fujita *et al*., 1983). Presently they are used for hypoglycemic effect *via* peroxisome proliferator-activated receptor c (PPARc) (Lehmann *et al*., 1995). Pioglitazone, and rosiglitazone are clinically used thiazolidines for the treatment of type 2 diabetes. Numerous naturally occurring molecules with significant pharmacological properties possess thiazolidine moiety in their structures. The presence of a thiazolidine ring in penicillin and its derivatives (Pulici and Quartieri, 2005) has established its presence in nature. Many pharmacologically active drugs contains substituted derivatives of thiazolidines. The significance of this nucleus in pharmacology and biochemistry is well known (Rathbun *et al*., 1996, Johnson *et al*., 1996, Butvin *et al*., 1999). Thiazolidine possess a range of biological activities, including antifungal, antibiotic, antidiabetic (Maccari *et al*., 2005, Kline *et al*., 2008, Xie *et al*., 2008, Mulwad and Mayekar, 2008), antioxidant, anticancer (Wtodek *et al*., 1996, Šubr and Ulbrich, 2006), antibacterial, antiviral, antihistaminic, hypoglycemic, anti-inflammatory, anticonvulsant, antidepressant, sedative, antihypertensive, and antiarthritic properties.

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Several substituted thiazolidine derivatives serve as intermediates for the production of pharmacologically active drugs (Nagasawa *et al*., 1984, Wonacott *et al*., 1993, Samanen *et al*., 1991). Many thiazolidines have been used as retroviral protease inhibitors (Iwakawa *et al*., 1978). Thiazolidine derivatives serve as alternatives for the carbohydrate moiety in the formation of novel antiviral nucleosides (Faury *et al*., 1994). Additionally thiazolidine derivatives serve as secondary structure disrupting building blocks in the synthesis of peptides (Haack and Mutter, 1992). Recent synthetic approaches and structure-activity relationship studies have made it possible to study novel drugs with diverse actions. In this context, the synthesis of thiazolidine derivatives has attracted interest of medicinal chemists. In view of the importance of the thiazolidine and its derivatives, the current study was designed to synthesize and evaluate their free radical scavenging activity by using DPPH assay.

MATERIALS AND METHODS

General Experimental Conditions

The aromatic aldehydes (4-nitro/4-pyrridinecarboxyldehyde/3, 4, 5-trimethoxy/4-chloro/isophthaldehyde/4-fluoro/formaldehyde/ benzaldehyde), organic solvents and reagents used for the antioxidant assays were obtained from Sigma Aldrich, and Fluka. All the reagents and solvents were used devoid of prior purification. The progress of reaction was monitored by 2.0×5.0 cm aluminium sheets pre-coated with silica gel (60 F254, with a 0.25 mm) (Merck, Germany) in EtOAC: hexane system 40:60). The

composition of the RM and purity of the achieved substances were monitored by TLC (silica gel). The spots were visualized by exposure to ultraviolet light (254–366 nm), followed by heating. FT-IR spectra were recorded on a Shimadzu-IR-prestige-21 spectrophotometer (Japan) as KBr pellets, and for $CHCl_3$ solutions (ν_{max} in cm^{-1}). ^{1}H-NMR spectra were acquired on a Bruker AV 300, and 400 MHz spectrometers (Switzerland). Tetramethylsilane (TMS) was taken as internal standard. The ^{1}H-NMR chemical shifts are stated in parts per million (δ scale) with coupling constants measured in Hertz (Hz). EI-MS Spectroscopic analysis was recorded on Finnigan-MAT-311-A mass spectrometer.

Thiazolidines **1-8** were synthesized by literature procedures, (Khan *et al*., 2006) and the spectral data of compounds **1-5** and **8** were in agreement with that reported in the literature.

General procedure for the preparation thiazolidine derivatives

L-Cysteine. HCl 0.19 g (0.94 mmol) was dissolved in 25 mL of distilled water and 0.067 g (0.64 mmol) of sodium acetate was added to it. Aldehyde (0.98 mmol) in 26 mL of ethanol was then added in a round bottom flask and stirred vigorously at room temperature for about 24 h. After the formation of precipitation, reaction mixture vessel was placed in ice cold water for precipitation. The precipitates was separated by suction filtration, and washed several times with cold ethanol (**Scheme 1**).

2-(3, 4, 5-Trimethoxyphenyl) thiazolidine-4-carboxylic acid (1)

Yield: (1.76 g, 5.88 mmol, 81%), ^{1}H-NMR (Acetone-d_6) (300 MHz), δ_H: 3.22 (m, 1H), 3.41 (m.1H), 3.70 (m, 3H), 3.81 (m, 6H), 4.40 (dd, $J_{4,\,5a}$ = 4.5 Hz, $J_{4,\,5b}$ = 7.2 Hz, 1H), 5.58 (s, 1H), 6.86 (d, $J_{2,6}$ =12.0 Hz, 2H); EI-MS (*m/z*) =299; FT-IR: (cm^{-1}) 3425 (NH), 2838 (CH stretch), 1593 (C=C), 1682 (C=C Aromatic), 1378 (C-O), 1132 (C-O-C).

2-(4-Nitrophenyl) thiazolidine-4-carboxylic acid (2)

Yield: (0.20 g, 0.81 mmol, 89%), ^{1}H-NMR (300 MHz, Acetone-d_6), δ_H (ppm): 3.21 (t, $J_{5a,\,4}$ = 9.2 Hz, 1H), 3.49 (t, $J_{5b,4}$ = 10.0 Hz, 1H), 4.09 (t, $J_{4,5a}$ = 7.6 Hz, 1H), 5.72 (s, 1H), 7.85 (d, $J_{2,6}$ = 8.0 Hz, 2H), 8.24 (d, $J_{3,5}$ = 8.0 Hz, 2H); EI-MS (*m/z*) = 254; FT-IR: (cm^{-1}) 3408 (NH), 2866 (CH stretch), 1525, 1348 (Ar-NO2), 1625 (C=C Aromatic), 850 (Para substitution).

2-(4-Flourophenyl) thiazolidine-4-carboxylic acid (3)

Yield: (1.01 g, 4.45 mmol, 82%), ^{1}H-NMR (300 MHz, Acetone-d_6), δ_H (ppm): 3.19 (m, 1H), 3.49 (m, 1H), 4.18 (dd, $J_{4,5a}$ = 7.5 Hz, $J_{4,5b}$ = 15.3 Hz, 1H), 5.67 (s, 1H), 7.06 (m, 1H), 7.14 (m, 1H), 7.52 (m, 1H), 7.60 (m, 1H); EI-MS (*m/z*) = 226; FT-IR: (cm^{-1}) 3385 (N-H), 1608 (C=O), 1511 (C=C), 1381 (C-O), 1233 (Ar-F).

2-(Phenyl) thiazolidine-4-carboxylic acid (4)

Yield: (0.16 g, 0.77 mmol, 87%), ^{1}H-NMR (300 MHz, Acetone-d_6), δ_H (ppm): 3.21 (m, 1H), 3.44 (m, 1H), 4.01 (t, $J_{4,5}$ = 7.5 Hz, 1H), 5.66 (s, 1H), 7.52 (m, 2H), 7.32 (m, 3H); EI-MS (*m/z*) = 209; FT-IR: (cm^{-1}) 3433 (N-H), 1575 (C=C), 1380 (C-O), 1137 (C-O-C).

2-(4-Chlorophenyl) thiazolidine-4-carboxylic acid (5)

Yield: (1.52 g, 6.25 mmol, 86%), ^{1}H-NMR (300 MHz, Acetone-d_6), δ_H (ppm): 3.29 (m, 1H), 3.46 (m, 1H), 4.19 (t, $J_{4,5}$ = 7.6 Hz, 1H), 5.63 (s, 1H), 7.53 (m, 2H), 7.37 (m, 2H); EI-MS (*m/z*) = 243; FT-IR: (cm^{-1}) 3418 (N-H), 1580 (C=C), 1319 (C-O), 1012 (Ar-Cl).

2-(Pyridine-4-yl) thiazolidine-4-carboxylic acid (6)

Yield: (0.90 g, 4.29 mmol, 79%), ^{1}H-NMR (300 MHz, Acetone-d_6), δ_H (ppm): 3.37 (m, 2H), 3.48 (m, 1H), 3.53 (m, 1H), 4.10 (t, $J_{4,5}$ =7.5 Hz, 1H), 4.40 (m, 1H) 5.60 (s, 1H), 5.77 (s, 1H), 7.43 (m. 1H) 7.53 (m, 1H), 7.59 (m, 1H), 7.75 (m, 1H); EI-MS (*m/z*) = 340; FT-IR: (cm^{-1}) 3425 (N-H), 1620 (C=C Aromatic), 1303 (C-O).

2, 2'-(1, 3-Phenylene)bis(thiazolidine-4-carboxylic acid) (7)

Yield: (0.27 g, 0.81 mmol, 87%), ^{1}H-NMR (300 MHz, Acetone-d_6), δ_H (ppm): 3.20 (m, 1H), 3.37 (m, 1H), 4.16 (t, $J_{4,5}$ = 6.3 Hz, 1H), 5.81 (s, 1H), 7.55 (d, $J_{2,6}$ = 5.7 Hz, 2H), 8.48 (d, $J_{3,5}$ = 6.0 Hz, 2H); EI-MS (*m/z*) = 210; FT-IR: (cm^{-1}) 3406 (N-H), 1691 (C=O), 1622 (C=C Aromatic), 1394 (C-O), 1209 (C-N stretching).

Thiazolidine-4-carboxylic acid (8)

Yield: (0.67 g, 5.09 mmol, 93%), ^{1}H-NMR (300 MHz, Acetone-d_6), δ_H (ppm): 3.20 (1H, m), 3.46 (1H, m), 4.12 (1H, m), 4.26 (1H, m), 4.43 (1H, m), 8.60 (1H, br,s) EI-MS *(m/z)* =133; FT-IR: (cm^{-1}) 3421 (N-H), 1625 (C=C Aromatic), 1386 (C-O).

Biological activity evaluation

The antioxidant potential of the synthesized compounds was assessed *in vitro* through DPPH assay. The scavenging of the DPPH radical is broadly used to estimate antioxidant assays in a lesser time, as compared to other approaches. DPPH act as a stable free radical and accept hydrogen radical or an electron from the specie being oxidized and hence transformed into a stable, diamagnetic molecule. DPPH radical showed a characteristic absorption band at 517 nm due to odd electron. As soon as this unpaired electron is paired off, the absorption falls stoichiometrically relating to the number of electrons occupied. This change in the absorbance represents the capability of various molecules to behave as free radical scavengers. The scavenging effect of the synthesized analogues **1-8** on the DPPH radical was evaluated according to the reported methods (Tataringa *et al*., 2014, Grădinariu *et al*., 2013) with slight modifications. Various concentrations of compounds **1**,

and **3-8** (0.1, 0.2, 0.3, and 0.4 mg/mL), and for compound **2** (0.2, 0.4, 0.6 and 0.8 mg/mL) in methanol were added to a 2.8 mL solution of DPPH (0.1 mM, A_{517} nm=1.0 ± 0.050) protected from light. The resulting mixture was shaken vigorously, and kept at room temperature for half an hour in the dark, and after this absorbance at 517 nm was measured by a Thermo Scientific UV-visible spectrometer (Germany), against using methanol as blank solution. The percentage of activity was calculated. The vitamin C (ascorbic acid) (2 mg/mL) was used as reference (positive control).

STATISTICAL ANALYSIS

Statistical analysis was performed by Minitab version 13.1. All analysis were carried out in triplicate and their arithmetic average ± standard deviation (SD) values were reported.

RESULTS

Synthesis

We report here the synthesis of thiazolidine derivatives **1-8** *via* the reactions of L-cysteine. HCl with a series of aldehydes. We selected different aromatic substituted thiazolidine analogues to study the influence of substituents on the cyclisation reaction.

To the best of our knowledge, compounds **6** and **7** are reported here for the first time. Compounds were prepared from the cyclization of L-cysteine. HCl with 4-pyrridine carboxyldehyde, and isophthaldehyde, respectively. The structures elucidation of compounds **1-8** were carried out with the help of their FT-IR, ^{1}H-NMR and mass spectrometry analyses.

Antioxidant assay

2, 2-Diphenyl-1-picrylhydrazyl (DPPH) assay is established on the spectrophotometric determination of the reduction of DPPH. DPPH is a purple colour stable free radical (Osman *et al*., 2012, Vasincu *et al*., 2014) that is transformed into radicles stable diamagnetic molecule (pale yellow compound) after accepting electron or hydrogen from test compounds. More the decolourization more is the reducing capability of test. This is a model for estimating the free radical scavenging activity of any test sample. The DPPH radical scavenging ability (%) of the synthesized thiazolidine derivatives **1-8** was evaluated.

DISCUSSION

Synthesis

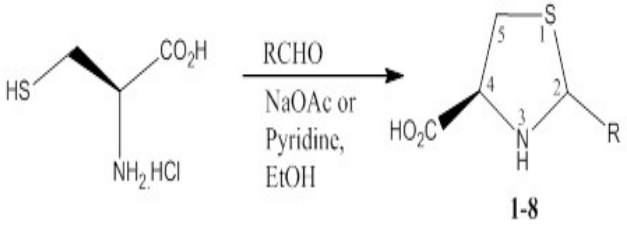
In our ongoing research to synthesize biologically active thiazolidine derivatives, we report here a series of thiazolidine derivatives (**Scheme-1**). Among these derivatives, compounds **6** and **7** were identified as new scaffolds.

Table 1: Synthesis of 2-substituted-(4*R*)-thiazolidine carboxylic acid derivatives

Compounds	R	Yield (%)
1	3,4,5-$(OMe)_3C_6H_5$–	81
2	4-$NO_2C_6H_4$–	89
3	4-FC_6H_4–	82
4	C_6H_5–	87
5	4-ClC_6H_4–	86
6	N-C_5H_4–	79
7	– C_6H_4–	78
8	H–	93

Table 2: *In vitro* DDH radical scavenging activity

Compounds	EC_{50} (µg/mL)
1	60.77 ± 0.39
2	110.08 ± 0.55
3	73.62 ± 0.61
4	50.34 ± 0.56
5	69.46 ± 0.51
6	84.49 ± 0.52
7	109.4 ± 0.54
8	79.24 ± 0.57
Ascorbic acid	23.46 ± 0.54



Scheme 1: General method for the preparation of (4*R*)-thiazolidine carboxylic acid derivatives.

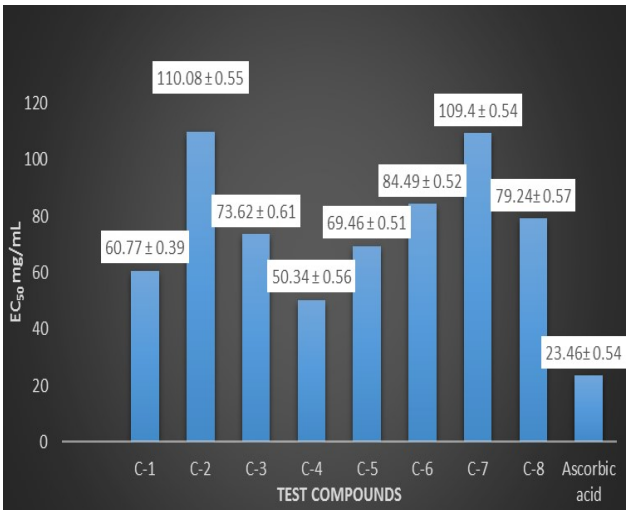


Fig. 1: Scavenging activity of thiazolidine derivatives 1-8 incubated 30 min with DPPH at 0.1mM concentration.

Compound **6** was characterized by using ^{1}H-NMR, FT-IR, and mass spectrometry. The ^{1}H-NMR of compound 6 displayed characteristic signals of methylene protons at δ 3.20 (1H, m) and 3.37 (1H, m). The characteristic signals of H-4 and H-2 was appeared at δ 4.16 (1H, t, $J_{4,5}$ = 6.3 Hz), and 5.81 (1H, s), respectively. The aromatic region of the spectrum displayed signals at δ 7.55 (2H, d, $J_{2',6'}$ = 5.7 Hz) and 8.48 (2H, d, $J_{3',5'}$ = 6.0 Hz) due to aromatic H-2′/H-6′ and H-3′/H-5′, respectively. The IR spectrum showed stretching vibration of C=C at 1620, and N-H at 3425 cm^{-1}. The molecular ion peak *m/z* 210 was observed in the EI-MS spectrum.

Compound **7** has two thiazolidine moieties as deduced from the integration of protons signals in ^{1}H-NMR spectrum. The ^{1}H-NMR spectrum displayed characteristic signals of two methylene groups at δ 3.37 (2H, m), 3.48 (1H, m) and 3.53 (1H, m), due to H-5a, H-5b respectively. The characteristic signals of two H-4 protons at δ 4.10 (1H, t, $J_{4,5}$ = 7.5 Hz), and 4.40 (1H, m) appeared in the downfield region of the spectrum. Signals at δ 5.60 (1H, s) and 5.77 (1H, s) were due to two methine H-2. The aromatic region displayed signals at δ 7.43 (1H, m), 7.53 (1H, m), 7.59 (1H, m) and 7.75 (1H, m) due to the aromatic protons.

The infrared spectrum of compound **7** indicated characteristic stretching of N-H at 3406, C=O at 1691, C=C at 1622 and C-N at 1209 cm^{-1}. The molecular ion peak *m/z* 340 was located in the EI-MS spectrum.

Antioxidant activity

The results revealed that the reaction of synthesized compounds with DPPH is time and concentration dependent. The radical scavenging activity was increased as the concentration of tested compound become higher and lower EC_{50} value (**Table-2**). Structure-activity relationship study indicated that the activity of these thiazolidine derivatives could be due to different substituents at the thiazolidine ring. The electron donating substituents, such as -C_6H_5, -OCH_3, -Cl and -F, increase the electron density on thiazolidine scaffold thus reduce the DPPH free radicals (Hashem, 2007, Cao *et al*., 1996). Whereas substituent like -NO_2 removes electron density from the thiazolidine moiety, making thiazolidine less reactive and lower its activity towards DPPH. The antioxidant activities of compounds measured by DPPH assay are shown in Table 2. The DPPH activity of all thiazolidine based derivatives was as **4** >**1** >**5** >**3** >**8** >**6** >**7** >**2**. The results indicated that among all the thiazolidine derivatives, compound **4** showed the highest antioxidant potential in DPPH assay, while compound **2** displayed the lowest activity.

CONCLUSION

We have synthesized a series of aryl substituted fused thiazolidine derivatives. The cyclo-condensation reactions of different analogues of thiazolidines occurred with a variety of aromatic and hetero-aromatic substituted thiazolidines in high yields, since electronic effects of aromatic rings. The synthesized compounds were characterized by their physical constants (yield, molecular formula, molecular weight and solubility in different organic solvents), and their structures ware evaluated using FT-IR, ^{1}H-NMR and mass spectrometry.

In vitro antioxidant activity of 2-aryl thiazolidine-4-carboxylic acids was evaluated by DPPH free radical scavenging method. The EC_{50} value was determined for each compound. Some of the tested compounds showed an appreciable antioxidant activity, as compared to ascorbic acid (standard), due to the influence of structural changes on the thiazolidine moiety. Antioxidants have significance in reducing or preventing the progress of aging, as well as oxidative stress-induced degenerative diseases.

REFERENCES

Butvin, P., Al-Ja'afreh, J., Svetlik, J. & Havranek, E. (1999). Solubility, Stability, and Dissociation Constants of (2*RS*, 4*R*)-2-Substituted Thiazolidine-4-carboxylic acids in Aqueous Solutions. *Chemical Papers-Slovak Academy of Sciences,* **53**(5): 315-322.

Cao G, Sofic E and Prior RL (1996). Antioxidant capacity of tea and common vegetables. *Journal of Agricultural and Food Chemistry,* **44**(11): 3426-3431.

Faury P, Camplo M, Charvet AS, Mourier N, Barthelemy P, Graciet JC and Kraus JL (1994). Approaches toward the synthesis of 2, 5-disubstituted-1, 3-thiazolidines. *Journal of Heterocyclic Chemistry,* **31**(6): 1465-1471.

Fujita T, Sugiyama Y, Taketomi S, Sohda T, Kawamatsu Y, Iwatsuka H and Suzuoki Z (1983). Reduction of insulin resistance in obese and/or diabetic animals by 5-[4-(1-methylcyclohexylmethoxy)benzyl]thiazolidine-2, 4-dione (ADD-3878, U-63,287, ciglitazone), a new antidiabetic agent. *Diabetes,* **32**(9): 804-810.

Gradinariu V, Cioanca O, Gille E, Aprotosoaie A, Hritcu L and Hancianu M (2013). The chemical profile of basil biovarieties and its implication on the biological activity. *Farmacia*, **61**(4): 532-639.

Haack T and Mutter M (1992). Serine derived oxazolidines as secondary structure disrupting, solubilizing building blocks in peptide synthesis. *Tetrahedron Letters,* **33**(12): 1589-1592.

Hashem F., (2007). Investigation of free radical scavenging activity by ESR for coumarins isolated from Tecoma radicans. *Journal of Medicinal Science*, **7**(6): 1027-1032.

Iwakawa M, Pinto BM and Szarek WA (1978). Synthetic routes to nucleoside analogs of N-substituted 1, 3-thiazolidines. *Canadian Journal of Chemistry,* **56**(3): 326-335.

Johnson D, Graham D, Amarnath V, Amarnath K, Valentine W (1996). The measurement of 2-thiothiazolidine-4-carboxylic acid as an index of the in vivo release of CS2 by dithiocarbamates. *Chemical Research in Toxicology,* **9**(5): 910-916.

Khan KM, Ullah Z, Lodhi MA, Ali M, Choudhary MI, ur Rahman A and ul Haq Z (2006). Successful computer guided planned synthesis of (4R)-thiazolidine carboxylic acid and its 2-substituted analogues as urease inhibitors. *Molecular Diversity,* **10**(2): 223-231.

Kline T, Felise HB, Barry KC, Jackson SR, Nguyen HV and Miller SI (2008). Substituted 2-imino-5-arylidenethiazolidin-4-one inhibitors of bacterial type III secretion. *Journal of Medicinal Chemistry,* **51**(22): 7065-7074.

Lehmann JM, Moore LB, Smith-Oliver TA, Wilkison WO, Willson TM and Kliewer SA (1995). An antidiabetic thiazolidinedione is a high affinity ligand for peroxisome proliferator-activated receptor γ (PPARγ). *Journal of Biological Chemistry,* **270**(22): 12953-12956.

Maccari R, Ottana R, Curinga C, Vigorita MG, Rakowitz D, Steindl T and Langer T (2005). Structure–activity relationships and molecular modelling of 5-arylidene-2, 4-thiazolidinediones active as aldose reductase inhibitors. *Bioorganic & Medicinal Chemistry,* **13**(8): 2809-2823.

Mulwad VV and Mayekar SA (2008). Synthesis of biologically active 3-(2-oxo-2H-benzopyran-6-yl)-2-(-2-oxo-2H-benzopyran-6-ylimino)-thiazolidin-4-one and its derivatives. *Indian Journal of Chemistry. Section B, Organic including Medicinal,* **47**(9): 1397.

Nagasawa HT, Goon DJ, Muldoon WP and Zera RT (1984). 2-Substituted thiazolidine-4 (R)-carboxylic acids as prodrugs of L-cysteine. Protection of mice against acetaminophen hepatotoxicity. *Journal of Medicinal Chemistry,* **27**(5): 591-596.

Osman H, Arshad A, Lam CK and Bagley MC (2012). Microwave-assisted synthesis and antioxidant properties of hydrazinyl thiazolyl coumarin derivatives. *Chemistry Central Journal,* **6** (1): 32.

Pulici M and Quartieri F (2005). Traceless solid-phase synthesis of 2-amino-5-alkylidene-thiazol-4-ones. *Tetrahedron Letters,* **46**(14): 2387-2391.

Rathbun WB, Killen CE, Holleschau AM, Nagasawa HT. (1996). Maintenance of hepatic glutathione homeostasis and prevention of acetaminophen-induced cataract in mice by L-cysteine prodrugs. *Biochemical Pharmacology,* **51**(9): 1111-1116.

Samadhiya P, Sharma R, Srivastav SK and Srivastava SD (2012). Synthesis of 4-Thiazolidine Derivatives of 6-Nitroindazole: Pharmaceutical Importance. *Journal of the Chilean Chemical Society,* **57**(1): 1036-1043.

Samanen J, Cash T, Narindray D, Brandeis E, Adams Jr W, Weideman H, Yellin T and Regoli D (1991). An investigation of angiotensin II agonist and antagonist analogs with 5, 5-dimethylthiazolidine-4-carboxylic acid and other constrained amino acids. *Journal of Medicinal Chemistry,* **34**(10): 3036-3043.

Subr V and Ulbrich K (2006). Synthesis and properties of new N-(2-hydroxypropyl) methacrylamide copolymers containing thiazolidine-2-thione reactive groups. *Reactive and Functional Polymers,* **66**(12): 1525-1538.

Tataringa G, Stan CD, Zbancioc AM, Jitareanu A and Tuchilus C (2014). Preliminary screening of biological activities of some new Schiff bases of isatins. *Farmacia,* **62**(1): 14-22.

Vasincu IM, Apotrosoaei M, Panzariu AT, Buron F, Routier S and Profire L (2014). Synthesis and biological evaluation of new 1, 3-thiazolidine-4-one derivatives of 2-(4-isobutylphenyl) propionic acid. *Molecules,* **19**(9): 15005-15025.

Wonacott A, Cooke R, Hayes FR, Hann MM, Jhoti H, McMeekin P, Mistry A, Murray-Rust P, Singh OM and Weir MP (1993). A series of penicillin-derived C2-symmetric inhibitors of HIV-1 proteinase: structural and modeling studies. *Journal of Medicinal Chemistry,* **36**(21): 3113-3119.

Wtodek L, Wrobel M and Czubak J (1996). Selective effect of 2-(Polyhydroxyalkyl)-thiazolidine-4-carboxylic acids on nonprotein sulfhydryl groups in tumor bearing mice. *General Pharmacology: The Vascular System,* **27**(8): 1373-1376.

Xie Y, Liu Y, Gong G, Rinderspacher A, Deng SX, Smith DH, Toebben U, Tzilianos E, Branden L and Vidovic D (2008) Discovery of a novel submicromolar inhibitor of the lymphoid specific tyrosine phosphatase. *Bioorganic & Medicinal Chemistry Letters,* **18**(9): 2840-2844.