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Preparation, Characterization of some Thiazolidine Derived from Penicillamine and their Antioxidants Activity

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ABSTRACT

A new series of thiazolidine-4-carboxylic acid derivatives of penicillamine have been synthesized in one step by cyclization of penicillamine with different aromatic aldehydes. The optimized reaction conditions for this one -pot reaction were achieved. The products were obtained in short reaction times, high yields and high purities". All products were characterized and identified by FT.I.R and ^{1}H-NMR spectroscopy and Finally in vitro antioxidant potential for the new prepared products was evaluated according to the 1,1-diphenyl-2-picrylhydrazyl (DPPH)"radical scavenging assays. Some of synthesized compounds showed a good antioxidant activity which supports the favorable influence of the structural modulation on the antioxidant effects of the aromatic aldehydes".

KEYWORDS

D-penicillamine, Thiazolidine, Antioxidants, DPPH.

Introduction

In recent years, heterocyclic compounds containing sulfur and nitrogen as heteroatoms have received considerable attention because of their medicinal and pesticidal importance, thiazolidine belongs to a class of heterocyclic compounds having two hetero atoms a sulfur and nitrogen as part of the saturated five-member ring, in the form of thio-ether group at position 1 and amine group at position3, with three carbon atoms. Also called by name tetrahydrothiazoles (Victoria *et al* 2013). Thiazolidine derivatives "attracted attention of researchers in recent years because, this class of compound has an important properties and applications, especially in natural product, medicinal chemistry, agrochemical agents, bioorganic and organocatalytic, where many of them have been used as synthetic intermediates, auxiliary reagents, ligands or asymmetric synthesis catalyst(Lodhi et al., 2014; Rambo et al., 2015)."Scientists had developed a myriad of new compounds related to this moiety and investigated for different "pharmacological "activities with least side effects. Thiazolidine-4-carboxylic acid (TC)"and 2-substituted are unnatural amino acid analogs of L-proline, in which a sulfur atom replaces the $^{\gamma}$-carbon in the 5-member ring of proline, sporting a thiazolidine instead of a pyrrolidine ring (Choudhary et al., 2011). To be particular, 2-arylthiazolidine carboxylic acids and derivatives are an important thiazolidine derivatives, are immensely important due to their multiple activities as antimicrobial(Song *et al*, 2015), anti-inflammatory (Hansen, *et al*, 2018) & (Jagtap *et al*, 2018), anticancer (Gududuru, *et al*., 2005) & (Onen-Bayram *et al*, 2012), and has utility as a therapeutic agent for the treatment of dementia and amnesia disorders(Furukawa *et al* 1989), HIV protease inhibitor (Hidaka, *et al*, 2009), immunomodulators (Pellegrini *et al*, 1999), antifungal (Abid *et al*, 2019), antitubercular (Nagasree *et al* 2018), analgesic, anti-viral, antiplatelet, antimalarial, anticonvulsant, cardio protective (Bayram, *et al*, 2016), DPP-IV inhibitor for treatment of type 2 diabetes, antioxidants etc (Yoshida *et al*, 2007).

The discovery of thiazolidines-4-carboxylics was accidentally made by Birch and Harris (Harris & Birch 1930), during the study of the effect of formaldehyde on the amino acid titration curves". "Later, in 1936, Schubert (Schubert, 1935) was the first to explain the formation of thiazolidines through the condensation of cysteine and formaldehyde followed by an intramolecular cyclization. Consequently, a large number of thiazolidine-4-carboxylic acid can be synthesized by condensation of aldehydes or ketones with cysteine and / or penicillamine, according to Scheme 1. When an aldehyde or a non-symmetric ketone is used, the cyclization results in a new chiral center in C2 thus creating a mixture of diastereoisomers (Kallen, 1971).

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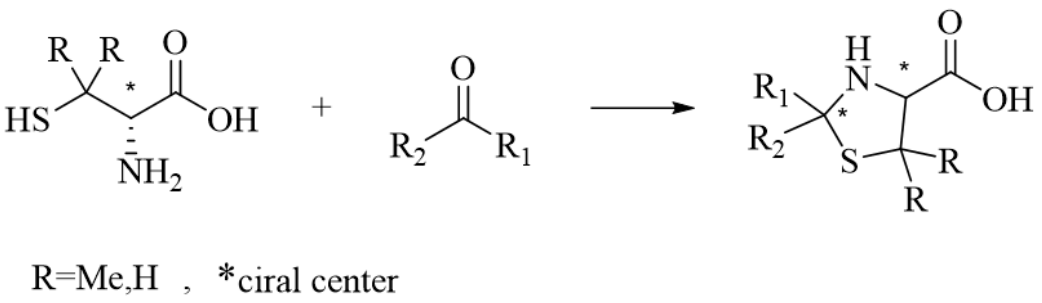

Scheme 1. Stereochemistry in the synthesis of thiazolidine

"The term 'antioxidant' is frequently used in the biomedical literature, An antioxidant may be defined as:' Any substance that when present at low concentrations, compared to those of the oxidizable substrate, significantly delays, or inhibits, oxidation of that substrate (Halliwell, & Gutteridge, 2015).

"Antioxidants can act at several different stages in an oxidative sequence, and we can illustrate this by considering lipid peroxidation in cell membranes or food products. Antioxidants can act by":

1. "removing oxygen or decreasing local 02 concentrations";
2. "removing catalytic metalions";
3. "removing key (reactive oxygen species (ROS) such as $O_2^-$and H_2O.
4. "scavenging initiating radicals such as $^{\cdot}OH$, $RO^{\cdot}$, $RO^{\cdot\cdot}$.
5. "breaking the chain of an initiated sequence".
6. "quenching or scavenging singlet oxygen".

"antioxidant used by the food industry, is a chain-breaking antioxidant, a powerful scavenger of" OH radicals and an iron-binding agent" (Gutteridge, 1994)."Although natural antioxidants (fruits and vegetables) help to curb the free radical attack, they often fall short of their requirement .development of synthetic antioxidant supplements has grabbed much attention of medicinal chemist which also constitutes the prime content of the present work .In this study we aimed to generate a series of thiazoldine-4-carboxylic acids" from D-penicillamine and series of substituted benzaldehydes comprising diverse" hydroxyl "groups were chosen, so that the impact of substitution on the thiazolidine pattern and the antioxidant activity could be further discussed. After being synthesized and characterized, the molecules' antioxidative properties were evaluated using radical scavenging methods on the DPPH free radical".

Experimental

All chemical were supplied from merck, sigma and fluka chemicals companies. Uncorrected melting points were determined by using thermal scientific apparatus. Fourier transfrom infrared spectra were recorded using KBr discs on 8400s, shimadzu, Japan. Spectrophotometer and the measurement were done in chem. Dept. Basrah University. ^{1}H-nmr spectra were recorded at 400 MHz on Iran by using Bruker (400MHz) in a DMSO-*d*6 solution with tetramethylsilaneas an internal standard. Mass spectra were recorded using the (El) Impact Electron technique at (70 ev) on Amirkabir University- Iran. Using an Agilent mass 5975 spectrometer analyzer quadropole. "Thin-layer chromatography (TLC) was performed on Merck Kieselgel 60 plates (0.25 mm thick, art 1.05714".)

1) "1. Synthesis of 2-aryl-thiazolidine-4-carboxylic Acids"

All thiazolidine compounds were is prepared from the condensation of D-penicillamine with a variety of aromatic aldehydes. performing modifications in already reported method (Serra, *et al*, 2016). In excellent yields (Scheme 2).

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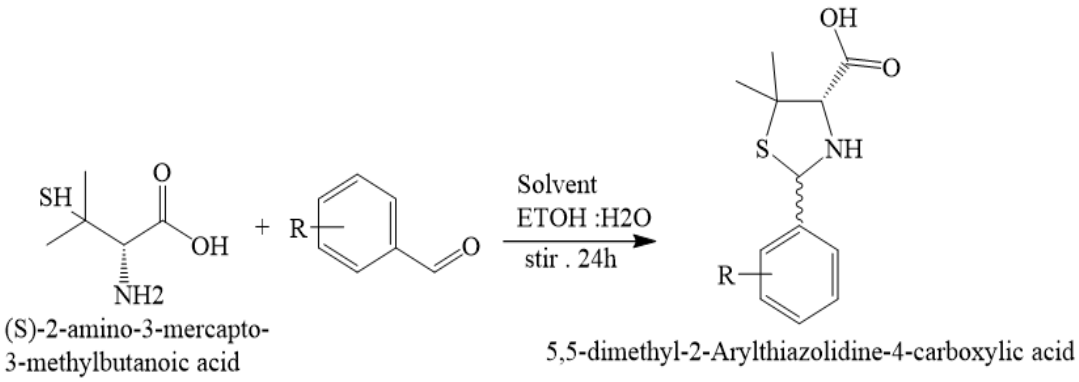

Scheme 2. General method for the preparation of thiazolidine carboxylic acid derivative from penicillamine

Table 1. Synthesis of 2-substituted thiazolidine carboxylic acid derivatives

Com.	Ar	m.p	Yield (%)	2R,4R/ 2S, 4R ratio
A1	Benzaldehyd	159-160	89	40/60
A2	2-hydroxyphenyl	170-171	84	31/69
A3	3-hydroxyphenyl	179-181	69	41/59
A4	4-hydroxyphenyl	199-200	86	32/68
A5	2,4-hydroxyphenyl	209-110dec	84	40/60
A6	3,4-hydroxyphenyl	198-200	76	32/68
A7	3,4,5-trihydroxyphenyl	205-207dec	75	32/68
A8	2-hydroxynaphthyl	167-169	78.6	25/75
A9	4-hydroxy-3 methoxyphenyl	197-198	82	30/70
A10	2-hydroxy-3 methoxyphenyl	138-140	74	40/60
A11	4-hydroxy-3 ethoxyphenyl	169-171	73	40/60
A12	3-carboxy-2-hydroxyphenyl	170-172	72	44.5/55.5
A13	5-carboxy-2-hydroxyphenyl	188-190	78	44/55

5, 5- "dimethyl-2-phenylthiazolidine-4-carboxylic Acid" (1A)

A solution containing benzaldehyde (1.06 g, 10 mmole) in ethanol (10 mL) is dropped to the solution containing D-penicillamine (1.491 g, 10 mmole) in (30ml) of ion-free water under continuous stirring at room temperature within1 hour. The mixture is stirred for additional 10 hour, whilst a beige-colored product starts to precipitate, during which the progress of the reaction was monitored by TLC. The precipitated solids were collected by filtration, washed with EtOH, diethyl ether, and air-dried at an oven temperature of 50°C overnight to give A1 (52.1 g, 96.4%) as white crystals: mp158–160".°C (lit.:18 mp 194–196°C); IR _max (KBr)3290,3050,2968,2497, 1724,1492, 1452, 1287, 1125, 1003, 902, 785, 686cm−1; The 1H NMR spectrum((400 MHz, (DMSO-d6)"showed the presence of the two diastereoisomers (2S,4S) and (2R, 4S) (ratio 38:62); Minor isomer: 1H NMR (400 MHz, (DMSO-d6):δ=1.26 (s, 3H), 1.47 (s, 3H), 3.63 (s, 1H), 5.87 (s, 1H),7.54-7.55 (5H, m, ArH) ; Major isomer: 1H NMR (400 MHz, (DMSO-d6): δ=1.31 (3H, s), 1.61 (3H,s), 3.59 (1H, s), 5.75(1H, s), 7.37-7.41 (5H, m).EIMS (EI): m/z [M+H]+:237,08".

(2-hydroxyphenyl)-5,5-dimethylthiazolidine-4-carboxylic Acid (A2)

Compound A2 was prepared from D-penicillamine (1.5g, 10 mmole) and 2-hydroxy benzaldehyde (1.23 g, 10 mmole) according to the procedure described for compound A1.IR _max (KBr) 3440b, 3340b3045w2968m1641s1598s1458w1344m; 1HNMR spectrum ((400 MHz, (DMSO-d6)"showed the presence of the two diastereoisomers (2S,4S) and (2R,4S) (ratio38:62); Minor isomer: 1H NMR (400 MHz, (DMSO-d6):δ=1.26 (s, 3H), 1.47 (s, 3H), 3.63 (s, 1H), 5.87 (s, 1H),7.54-7.55 (4H, m, ArH) ; Major isomer: 1H NMR (400 MHz, (DMSO-d6): δ=1.31 (3H, s), 1.61 (3H,s), 3.59 (1H, s), 5.75(1H, s), 7.37-7.41 (4H, m)".EIMS (EI): m/z [M+H]+: (253.08 m/z, 21.16%); Mwt=253.32.

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(3-hydroxyphenyl)-5,5-dimethylthiazolidine-4-carboxylic Acid(A3)

Compound A3 was prepared from D-penicillamine(1.5g, 10 m mole) and 3-hydroxy benzaldehyde(1.23 g, 10 mmole) according to theprocedure described for compound A1.IR _max (KBr)3163b, 3163b, 3045w, 2976m,1637s,1587s, 1460w, 1249m;1H NMR spectrum((400 MHz, (DMSO-d6)showed the presence of the two diastereoisomers (2S,4S) and (2R,4S) (ratio38:62); Minor isomer: 1H NMR (400 MHz, (DMSO-d6):δ=1.26 (s, 3H), 1.47 (s, 3H), 3.63 (s, 1H), 5.87 (s, 1H),7.54-7.55 (4H, m, ArH) ; Major isomer: 1H NMR (400 MHz, (DMSO-d6): δ=1.31 (3H, s), 1.61 (3H,s), 3.59 (1H, s), 5.75(1H, s), 7.37-7.41 (4H, m).EIMS (EI): m/z [M+H]+:(253.08 m/z, 32.44%); Mwt=253.32.

(4-hydroxyphenyl)-5,5-dimethylthiazolidine-4-carboxylic acid(A4)

Compound A4 was prepared from D-penicillamine (1.5g, 10 mmole) and 4-hydroxy benzaldehyde (1.23 g, 10 mmole) according to the procedure described for compound A1. (KBr)3244b, 2400-3200, 3045w, 2966m, 1633s, 1610, 1593s, 1263w; 1H NMR spectrum ((400 MHz, (DMSO-d6) "showed the presence of the two diastereoisomers (2S,4S) and (2R,4S) (ratio38:62); Minor isomer: 1H NMR (400 MHz, (DMSO-d6):δ=1.45 (s, 3H), 1.56 (s, 3H), 3.94 (s, 1H), 6.62 (s, 1H),6.69-6.74 (2H, d, ArH) ; Major isomer: 1H NMR (400 MHz, (DMSO-d6): δ=1.31 (3H, s), 1.61 (3H,s), 3.59 (1H, s), 5.75(1H, s), 7.18-7.34 (2H, d)";EIMS (EI): m/z [M+H]+:(253.08m/z,42.19%); Mwt=253.32.

(2,4-dihydroxyphenyl)-5,5-dimethylthiazolidine-4-carboxylic Acid(A5)

Compound (A5) was prepared from D-penicillamine (1.5g, 10 mmole) and 2,4-dihydroxy benzaldehyde (1.38g, 10 mmole) according to the procedure described for compound A1. IR _max (KBr)3163b, 3163b, 3045w, 2976m, 1637s, 1587s, 1460w, 1249m; 1H NMR spectrum((400 MHz, (DMSO-d6)"showed the presence of the two diastereoisomers (2S, 4S) and (2R, 4S) (ratio38:62); Minor isomer: 1H NMR (400 MHz, (DMSO-d6):δ=1.25 (s, 3H), 1.46 (s, 3H), 3.63 (s, 1H), 5.82 (s, 1H),6.43-7.38 (3H, m, ArH) ; Major isomer: 1H NMR (400 MHz, (DMSO-d6): δ=1.31 (3H, s), 1.62 (3H,s), 3.59 (1H, s), 5.76(1H, s), 6.43-7.38 (3H, m, ArH).EIMS (EI): m/z [M+H]+: (269.08m/z,1.77%); Mwt=269.32".

(3,4-dihydroxyphenyl)-5,5-dimethylthiazolidine-4-carboxylic Acid(A6)

Compound (A6) was prepared from D-penicillamine(1.5g, 10 mmole) and 3,4-dihydroxy benzaldehyde(1.38g, 10 mmole) according to the procedure described for compound A1.IR _max (KBr) 3250b, 3045b, 2968, 2310b dimer, 1637s, 1612w,1519w,1292w;1H NMR spectrum((400 MHz, (DMSO-d6)"showed the presence of the two diastereoisomers (2S,4S) and (2R,4S) (ratio38:62); Minor isomer: 1H NMR (400 MHz, (DMSO-d6):δ=1.28 (s, 3H), 1.55 (s, 3H), 3.55 (s, 1H), 5.70 (s, 1H),6.90-7.38 (3H, m, ArH) ; Major isomer: 1H NMR (400 MHz, (DMSO-d6): δ=1.32(3H, s), 1.62 (3H,s), 3.60 (1H, s), 5.47(1H, s), 6.90 (s, 2H), 6.81 (s, 1H), 6.73 (d, *J* = 9.3 Hz, 2H), 6.69 (d, *J* = 8.1 Hz, 2H), 6.63 (s, 2H) (3H, m, ArH). EIMS (EI,70ev): m/z [M]+:(269.08m/z,1.60%); Mwt=269.32".

5,5-dimethyl-2-(3,4,5-trihydroxyphenyl) Thiazolidine-4-carboxylic Acid(A7)

Compound (A7) was prepared from D-penicillamine (1.5g, 10 mmole) and 3,4,5-trihydroxy benzaldehyde (1.54g, 10 mmole) according to the procedure described for compound A1. IR _max (KBr)3128-3286b, 3128,3047,2974,1631s, 1546w, 1454m, 1207m;1H NMR spectrum((400 MHz, (DMSO-d6)"showed the presence of the two diastereoisomers (2S,4S) and (2R,4S) (ratio38:62); Minor isomer:δ=1.28 (s, 3H), 1.54 (s, 3H), 3.58 (s, 1H), 5.67 (s, 1H), 6.352-6.48 (2H, d, ArH); Major isomer:: δ=1.32(3H, s), 1.619 (3H,s), 3.60 (1H, s), 5.47(1H, s), 6.352 (s, 2H), 6.481 (s, 2H), (2H, d,ArH). EIMS (EI,70ev): m/z [M]+: (285.08m/z,18.5%); Mwt=285.32"

(2-hydroxynaphthalen-1-yl)-5,5-dimethylthiazolidine-4-carboxylic Acid (A8)

Compound (A8) was prepared from D-penicillamine(1.5g, "10mmole) and" 2-hydroxy naphthaldehyde("1.38 g, 10 mmole) according to the procedure described for compound A1.IR _max (KBr), 3429b,3200-2400,3041,2968,1643s,1629, 1585w, 1274m, 1207m;"1H NMR spectrum((400 MHz, (DMSO-d6)"showed the presence of the two diastereoisomers (2S,4S) and (2R,4S) (ratio38:62); Minor isomer::δ=1.45 (s, 3H), 1.56 (s, 3H), 3.94 (s, 1H), 6.62 (s, 1H),6.97-7.85 (9H, m, ArH); Major isomer:: δ=1.42(3H, s), 1.68 (3H,s), 3.78 (1H, s),6.45(1H, s), 6.97-7.85 (9H, m, ArH). EIMS (EI,70ev): m/z [M]+:(303.08m/z,65.36%); Mwt=303.32"".

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(4-hydroxy-3-methoxyphenyl")-5,5-dimethylthiazolidine-4-carboxylic acid(A9)

Compound (A9) was prepared from D-penicillamine (1.5g, 10 mmole) and 4-hydroxy-3 methoxybenzaldehyde (1.52 g, 10 mmole) according to the procedure described for compound A1.IR _max (KBr), 3462, 3234, 3057, 2954, 1714, 1610, 1519, 1273, 1207cm^{-1};"1H NMR spectrum((400 MHz, (DMSO-d6)showed the presence of the two diastereoisomers (2S,4S) and (2R,4S) (ratio38:62); Minor isomer::δ=1.29 (s, 3H), 1.55 (s, 3H), 3.58 (s, 1H), 5.76 (s, 1H),6.574-7.13 (3H, m, ArH) ; Major isomer:: δ=1.34(3H, s), 1.63 (3H,s), 3.59 (1H, s),5.514(1H, s), 6.574-7.13 (3H, m,ArH). EIMS (EI,70ev): m/z [M]+:(283.08 m/z,93.77%); Mwt=283.32".

(2-hydroxy-3-methoxyphenyl)-5,5-dimethylthiazolidine-4-carboxylic acid(A10)

Compound (A10) was prepared from D-penicillamine (1.5g, 10 mmole) and 2-hydroxy-3 methoxybenzaldehyde (1.52 g, 10mmole) according to the procedure described for compound A1.IR _max (KBr), 3456, 3192,3045, 2976, 1629, 1595, 1485, 1267, 1207cm^{-1};"1H NMR spectrum((400 MHz, (DMSO-d6)showed the presence of the two diastereoisomers (2S,4S) and (2R,4S) (ratio38:62); Minor isomer::δ=1.26 (s, 3H), 1.54 (s, 3H), 3.53(s, 1H), 5.62 (s, 1H),6.71-6.91(3H, m, ArH)"; Major isomer:: δ=1.31(3H, s), 1.62 (3H,s), 3.59 (1H, s),5.96(1H, s), 6.71-6.91 (3H, m,ArH).EIMS (EI,70ev): m/z [M]+:(283.08m/z,72.34%); Mwt=283.32.

(3-ethoxy-4-hydroxyphenyl)-5,5-dimethylthiazolidine-4-carboxylic Acid(A11)

Compound (A11) was prepared from D-penicillamine(1.5g, 0.01mol) and 3-ethoxy-4-hydroxybenzaldehyde (1.66 g, 0.01mol) according to the procedure described for compound A1.IR _max (KBr), 3383, 3186, 3046, 2970, 1656, 1610, 1458, 1292cm^{-1};"1H NMR spectrum((400 MHz, (DMSO-d6)showed the presence of the two diastereoisomers (2S,4S) and (2R,4S) (ratio38:62); Minor isomer::δ=1.25 (s, 3H), 1.46 (s, 3H), 3.63 (s, 1H), 5.82 (s, 1H),6.43-738 (d, *J* = 8.4 Hz, 1H), (d, *J* = 8.4 Hz, 1H), (m, 1H)(3H,ArH);Major isomer:: δ=1.31(3H, s), 1.62 (3H,s), 3.59 (1H, s),5.76(1H, s), 6.43-738 (d, *J* = 8.4 Hz, 1H), (d, *J* = 8.4 Hz, 1H), (m, 1H)(3H,ArH).EIMS (EI,70ev): m/z [M]+:(297.04m/z,17.57%); Mwt=297.32".

(3-carboxy-2-hydroxyphenyl)-5,5-dimethylthiazolidine-4-carboxylic Acid(A12)

Compound (A12) was prepared from D-penicillamine(1.5g, 0.01mol) 3-carboxy-2-hydroxybenz aldehyde (1.66 g, 0.01mol) according to the procedure described for compound A1,IR _max (KBr), 3514, 3248,3061, 2978,1726 ,1604, 1514, 1269cm^{-1}; "1H NMR spectrum((400 MHz, (DMSO-d6)showed the presence of the two diastereoisomers (2S,4S) and (2R,4S) (ratio38:62); Minor isomer::δ=1.26 (s, 3H), 1.47 (s, 3H), 3.64 (s, 1H), 5.91 (s, 1H),6.91 (t, *J* = 7.7 Hz, 4H), 6.78 (dt, *J* = 15.9, 8.0 Hz, 3H), 6.71 (t, *J* = 8.0 Hz, 1H)(3H,ArH);Major isomer:: δ=1.32(3H, s), 1.62 (3H,s), 3.6 (1H, s),5.79(1H, s), 6.91 (t, *J* = 7.7 Hz, 4H), 6.78 (dt, *J* = 15.9, 8.0 Hz, 3H), 6.71 (t, *J* = 8.0 Hz, 1H) (3H,ArH).EIMS (EI,70ev): m/z [M]+:(297.4m/z,1.62%); Mwt=297.32"

(5-carboxy-4-hydroxyphenyl)-5,5-dimethylthiazolidine-4-carboxylic Acid (A13)

Compound (A13) was prepared from D-penicillamine (1.5g, 0.01mol) and 3-carboxy-4-hydroxybenzaldehyde (1.66 g, 0.01mol) according to the procedure described for compound A1IR _max (KBr), 3514, 3248, 3061, 2978, 1726, 1604, 1514, 1269cm^{-1};"1H NMR spectrum((400 MHz, (DMSO-d6)showed the presence of the two diastereoisomers (2S,4S) and (2R,4S) (ratio38:62); Minor isomer::δ=1.27 (s, 3H), 1.54 (s, 3H), 3.53 (s, 1H), 5.62 (s, 1H),6.91 (t, *J* = 7.7 Hz, 4H), 6.78 (dt, *J* = 15.9, 8.0 Hz, 3H), 6.71 (t, *J* = 8.0 Hz, 1H)(3H, ArH); Major isomer:: δ=1.31(3H, s), 1.62 (3H,s), 3.59 (1H, s), 5.96(1H, s), 6.91 (t, *J* = 7.7 Hz, 4H), 6.78 (dt, *J* = 15.9, 8.0 Hz, 3H), 6.71 (t, *J* = 8.0 Hz, 1H) (3H, ArH). EIMS (EI,70ev): m/z [M]+:(297.4m/z,37.65%); Mwt=297.32".

2). Scavenging Effect of Antioxidant Activity on DPPH Radical"[21-22]

"The scavenging effect of the synthesized compounds A1–A13 on the DPPH radical was evaluated according to the methods of literature (Braca, *et al*, 2002) & (Shih, 2004).

The model of the scavenging of the stable DPPH radical is extensively used to evaluate antioxidant activities in less time than other methods. DPPH is a stable free radical that can accept an electron or hydrogen radical and thus be

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converted into a stable, diamagnetic molecule. DPPH has an odd electron and so has a strong absorption band at 517nm". "When this electron becomes pairedoff, the absorption decreases stoichiometrically with respect to the number of electrons taken up. Such a change in the absorbance produced in this reaction has been widely applied to test the capacity of numerous molecules to act as free radical scavengers". The scavenging effect of the synthesized compounds A1–A13 on the DPPH radical test was "first performed with a rapid TLC screening method using a 0.2% DPPH in EtOH. Thirty minute after spraying active compounds appear as yellow spots against purple background. In a second time, spectrophotometric assay was carried out by the following method": "The diluted working solutions of the synthesized compounds are prepared in ethanol (20, 40, 60, 80and 100 µg/mL).One mL of methanol solution of DPPH (0.002 %) is mixed with 1 mL solution of test compound vigorously and allowed to stand for 30min; absorbance at 517nm was determined by a Hitachi U-2001 spectrophotometer, and The percent of % of scavenging of free radical production from DPPH was calculated by the following equation",

$$\% \text{ of scavenging} = [(A \text{ control} - A \text{ sample})/A \text{ blank}] \times 100.$$

"Vitamin C (Ascorbic acid) was used as a reference compound. The effective concentration of sample required to scavenge DPPH radical by 50% (IC50 value) was obtained by linear regression analysis of dose-response curve plotting between % inhibition and concentration.

Table 2. Antioxidant activities of the synthesized compounds (A1-A13) Concentration in µg / ml

Compound	% inhibition					IC 50µg/mL
	20 µg/ml	40 µg/ml	60 µg/ml	80 µg/ml	100 µg/ml	
A1	34.91	44.61	47.14	51.78	53.76	73.50
A2	37.88	43.65	49.87	53.49	56.31	60.48
A3	43.28	46.55	51.34	54.12	57.58	53.95
A4	43.22	47.89	50.88	53.34	56.88	55.23
A5	51.34	55.68	57.59	60.48	63.68	18.61
A6	78.19	82.24	84.33	86.47	88.86	9.35
A7	87.51	88.88	89.76	90.313	91.7	8.23
A8	47.53	52.17	56.18	61.35	62.99	30.13
A9	46.36	48.04	52.73	55.69	53.83	48.90
A10	46.19	48.86	53.02	56.31	59.26	42.98
A11	44.96	48.73	51.61	53.97	56.04	68.62
A12	46.66	48.56	51.3	54.70	57.24	53.39
A13	44.39	46.86	50.78	53.45	56.16	61.02
AA	86.51	87.77	88.02	87.35	90.01	8.7

AA – ascorbic acid

Results and Discussion

"Thiazolidine carboxylic acid derivatives were synthesized with good yields by condensing (S)-2-amino-3-mercapto-3-methylbutanoic acid with a series of benzaldehyde derivatives (Table 1).The typical cyclization reaction was carried out in room temperatures in a water/ethanol mixture"(75:25,v:v); after purification by recrystallization from aqueous ethanol; Pure thiazolidine was obtained (60-95%) yield ,"Thus thiazolidine derivatives are obtained as diasteromeric mixtures because cyclization of D-penicillamine to build 2-substitution thiazolidine , gives rise to anew chiral center at C-2 position of the thiazolidine ring, affording mixtures of two diasteroisomer; with respect to C2(2S,4S) (2R,4S). In solution these diastereoisomers interconvert through a mechanism involving opening of the thiazolidine ring (Refouvelet *et al*, 2000) (schem3).

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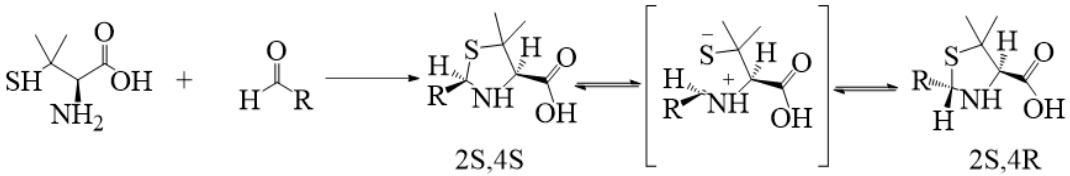
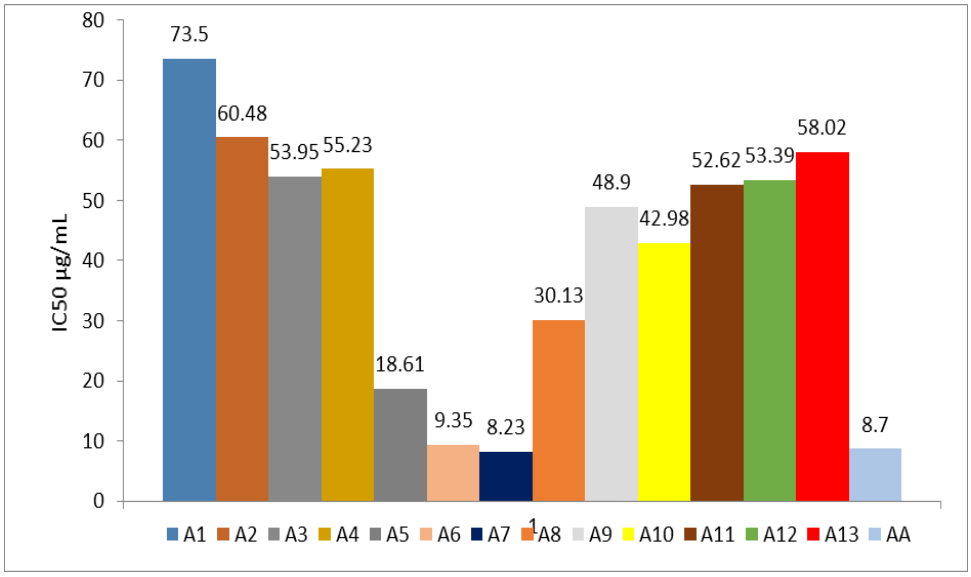


Scheme 3. Proposed isomerisation pathway for C-(2) isomers in thiazolidine

The structure was cheeked by mass, FT.IR and ^{1}H-NMRspectra. The FT.IR spectra of thiazolidine compound were detected by the disappear of the thiol band (S-H strt) which appeared at 2600 cm^{-1}. These facts confirmed the correct expected structure also it showed one a peak at 3200-3400 cm^{-1} which related to the (NH) stretching band, also in the range of ν_{max} 1630-1724cm^{-1} which appeared to the C=O stretching. 1059 cm^{-1} peak for the C-O start and finally a peak at 2999cm^{-1} for the aromatic C-H str. The ^{1}H-NMR spectra for the formation of the 2-arylthiazolidine-4-carboxylic acid system has shows, two sets of resonance with different intensities were observed for H-2, H-4, α-CH3-5 and β-CH3-5 proton; the presence of integrals of this signals were used for the determination of ratio of epimers. α-CH_3-5in the region 1.25-1.45ppm (s, 3H), β-CH_3in the region 1.46-1.68ppm (s, 3H), (C-2) of thiazolidine ring showed singlet in the region 5.47-6.62ppm ,(C-4) of thiazolidine ring showed singlet in the region 3.53-3.94 ppm, and aromatic protons showed two multiple signals within the range of (6.31-8.45) ppm.MS(70 eV), **m/z** (%):1.6-93%

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 IC50 value". "From the results obtained (Table 2) it was observed that the activity of these thiazolidine derivatives depends on the substitution of the phenyl ring of 2-phenyl-thiazolidine-4-carboxylic acid derivatives", show that substituents on the phenyl ring have a great influence on antioxidant activity ,The electron donating substituents, such as -OH increase the electron density on thiazolidine scaffold thus reduce the DPPH free radicals, the most favorable influence was exerted by 3-OH-4-OH-5-OH radicals, and the corresponding compounds A6which has the equivalent in activity, is ascorbic acid (AA)".In descending order the effects of the various substituents on the phenyl ring of the thiazolidine derivatives bases were found to be: 2,3,5$(OH)_3$ (A7) >3,4-$(OH)_2$ (A6) >2,4-$(OH)_2$ (A5)>>2-OH-naphthal (A8) > 3-OCH_3-2-OH (A10) > 4-OH-3-OCH_3(A9) > 4-OH-3-OC_2H_5(A11) > 3 - COOH-2-OH (A12) > 3-OH (A3) >4-OH (A4) >5 - COOH-2-OH (A13) > 2-OH (A2) > ph (A1). The results indicated that among all the thiazolidine derivatives, compound (A7) showed the highest antioxidant potential in DPPH assay, while compound (A1) lowest.



(IC50) value of compounds A1–A13 (µg/mL) incubated 30min with DPPH at 200 µg/mL concentration

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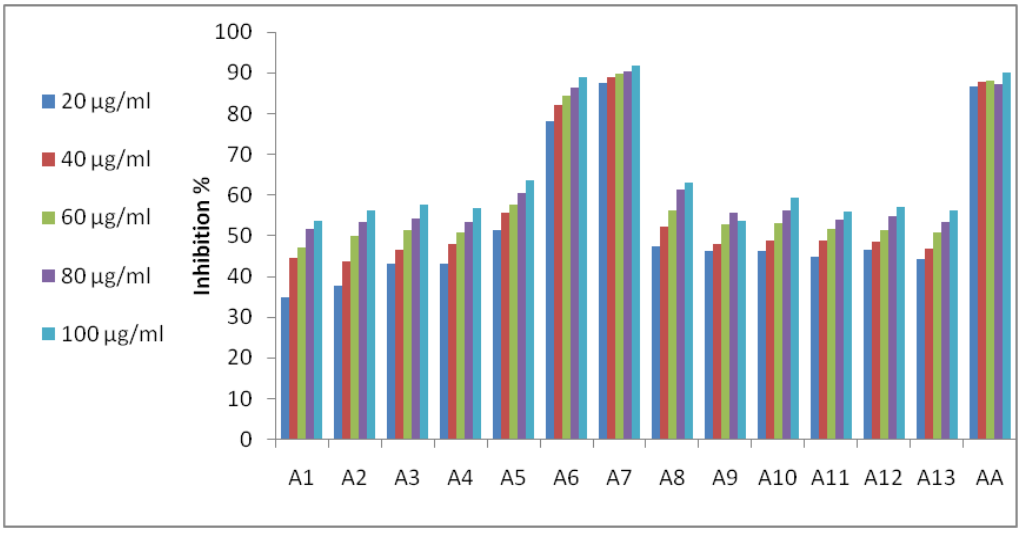
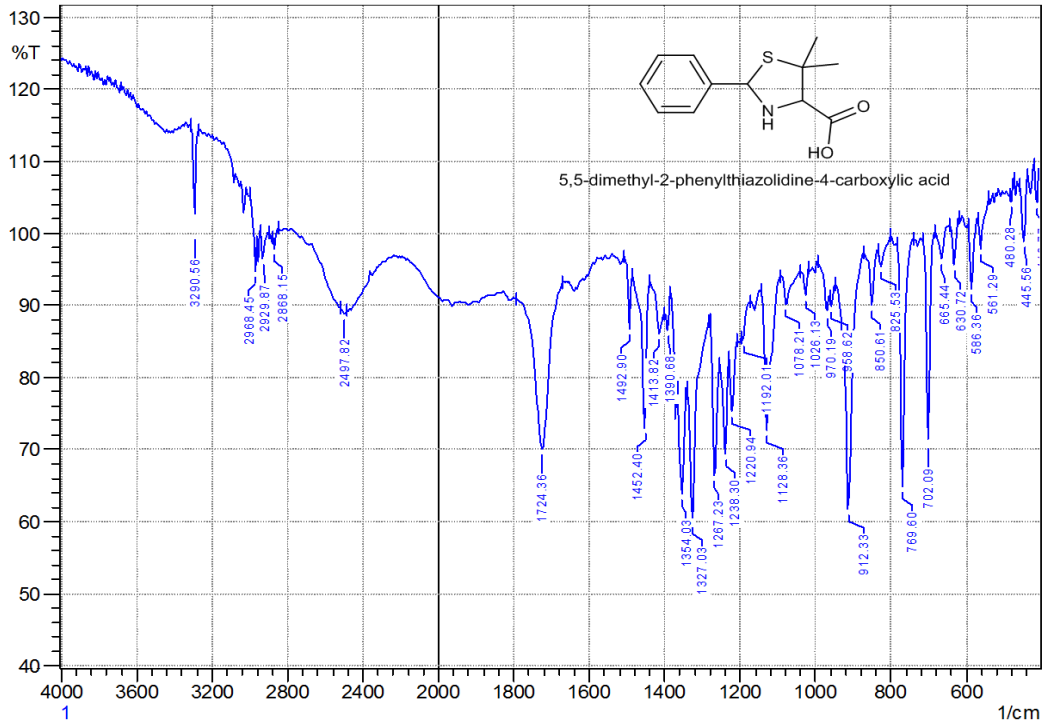


Scavenging activity of compounds A1–A13 (µg/mL) incubated 30min with DPPH at 200 µg/mL concentration

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 ((melting point, yield, molecular formula, molecular weight and solubility in different organic solvents), and their structures were evaluated using "FT-IR, 1H-NMR and mass spectrometry". In vitro antioxidant activity of 2-aryl thiazolidine-4- carboxylic acids was evaluated by DPPH free radical scavenging method. The IC50 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".



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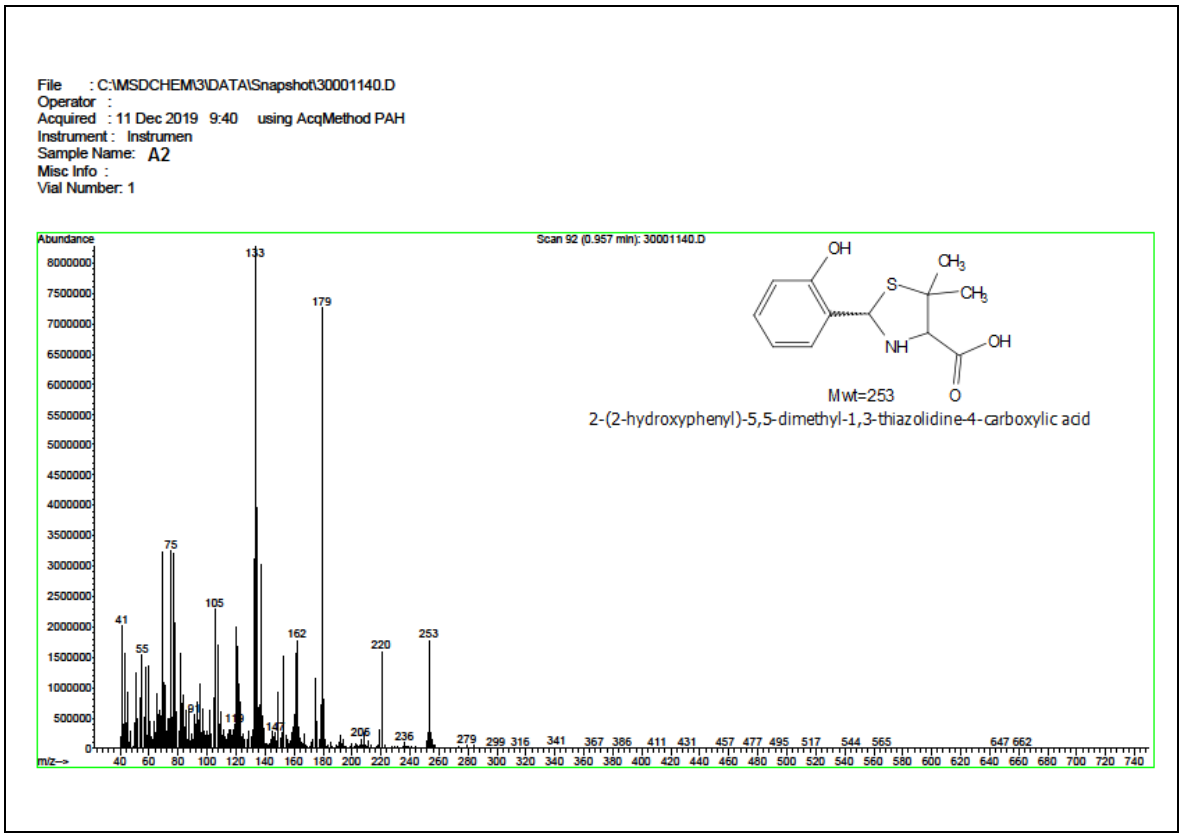

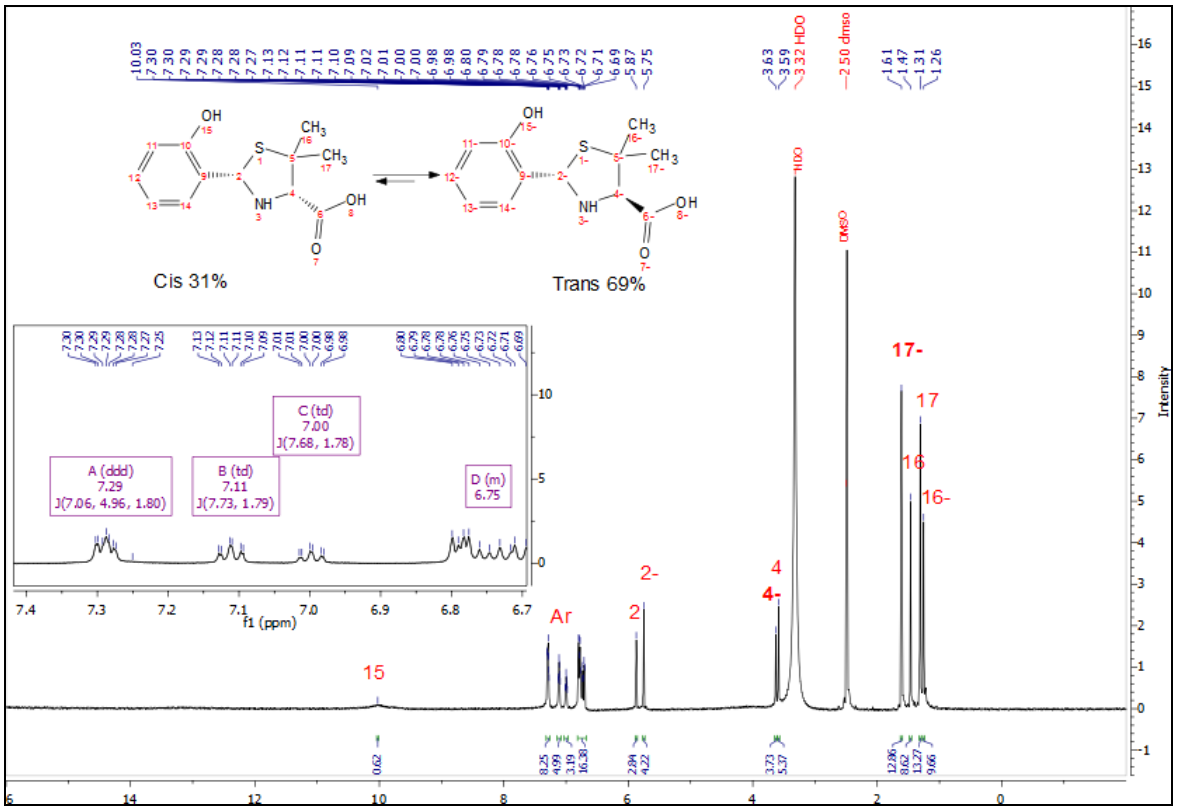

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