IJPSR (2015), Vol. 6, Issue 1 (Research Article)

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 10 June, 2014; received in revised form, 15 August, 2014; accepted, 20 September, 2014; published 01 January, 2015

ANTIOXIDANT AND ANTIBACTERIAL ACTIVITIES OF THIAZOLIDINEDIONE DERIVATIVES

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Keywords:

Thiazolidinediones, antibacterial, antioxidant, ascorbic acid, DPPH, free radical scavenging activity, amoxicillin.

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ABSTRACT: The main aim of the present study was to synthesize new leads with potential antibacterial and antioxidant activities. As a part of systematic investigation of synthesis and biological activity, some of the new thiazoldinedione compounds **5a-e** were prepared and screened for their antibacterial and antioxidant activities. The antibacterial evaluation of newly synthesized compounds was carried out by cup-plate method. Antimicrobial activity results revealed that compound **5a** showed promising activity against bacteria *Staphylococcus aureus*, *Klebsiella pneumonia*, and *Pseudomonas aeruginosa*, **5e** was found to be more active aganist *Proteus vulgaris*. The antioxidant activity was performed by using free radical scavenging activity by DPPH (1, 1-diphenyl-2-picryl-hydrazil) assay method and Ferric ion reduction method, ascorbic acid was used as reference standard. All the tested derivatives show antioxidant activity but compound **5c** and **5d** show promising antioxidant activity concentration at 50µg /ml and can be further studied with modifications. Some novel thiazolidinediones derivatives **5(a–e)** were synthesized by reacting hydrazine hydrate in ethanol to form hydrazinecarboxylicacid [4-(2, 4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester and substituted derivatives were formed by further reaction. The target molecules have been characterized by IR, ^{1}H NMR, ^{13}C NMR, and mass spectral studies.

INTRODUCTION: The emergence and spread of antimicrobial resistance have become one of the most serious public health concerns across the world[1]. Thiazolidinone, a saturated form of thiazole with carbonyl group on fourth carbon, has been considered as a magic moiety (wonder nucleus) because it gives out novel derivatives with different types of biological activities. This diversity in the biological response profile has attracted the attention of many researchers to explore the potential biological activity, such as antibacterial[2], antifungal [3], and antioxidant [4, 5] activities of this skeleton.

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.6(1).421-28

Article can be accessed online on: www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.6(1).421-28

In the present study, an attempt was made towards the incorporation of various substituents into hydrazine moiety of thiazolidinediones, to probe how this moiety will influence the antibacterial activity and antioxidant activities. In view of all these valid observations and as a continuation of our work, prompted us to synthesize new thiazolidinedione derivatives and the synthesized compounds were screened for their antibacterial and antioxidant activity[6].

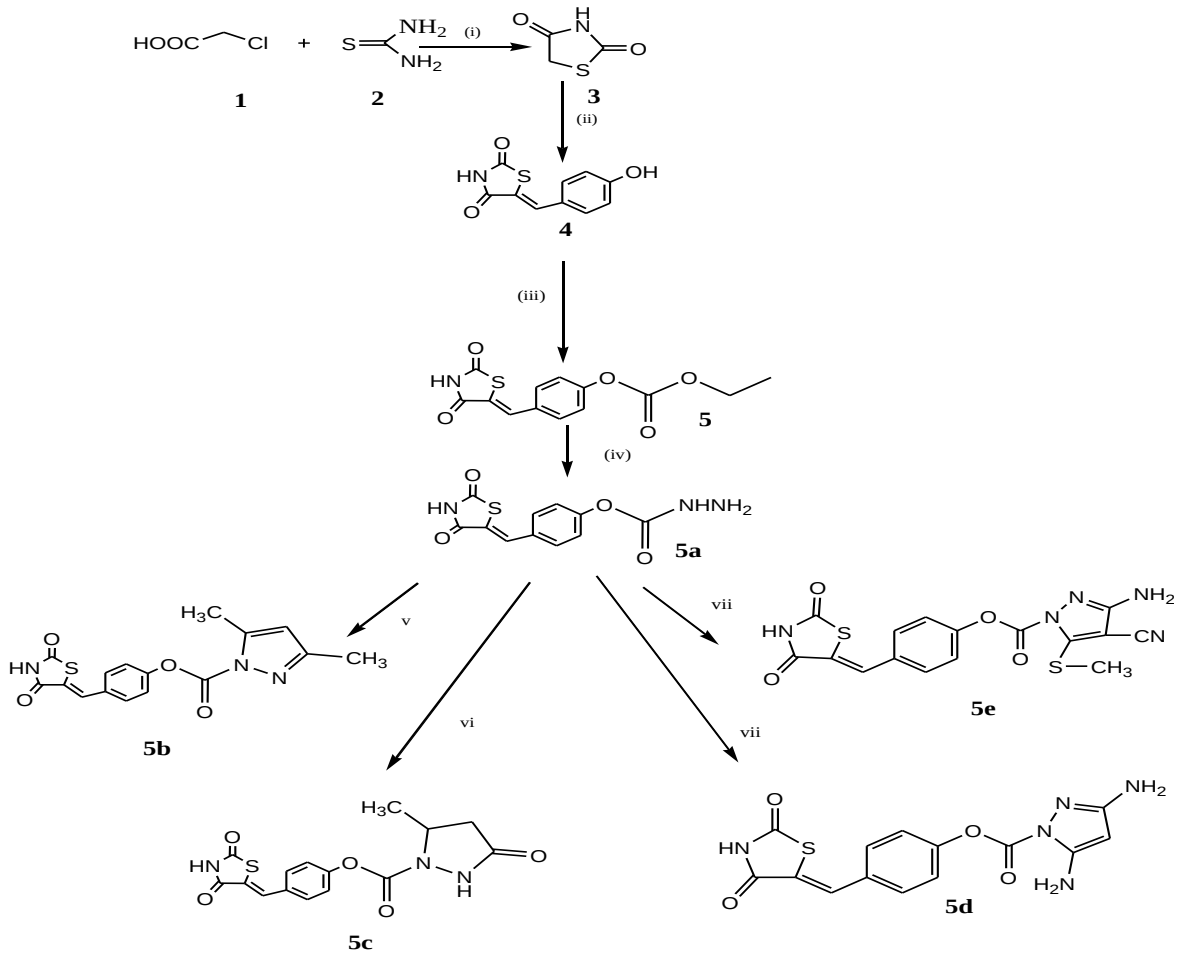
MATERIALS AND METHODS:

The chemicals used in the present project work were purchased from Rankem, Merck and Spectrochem. The melting point of the synthesized compound was determined by open capillary with Thiel's melting point tube (capillary tube method). TLC plates were prepared by using Merck Silica Gel 60 GF 254. Visualization was done in UV light chamber at 254 nm, iodine chamber.

The IR spectra of the synthesized compounds were recorded on a Fourier Transform Infra Red spectrometer (model Shimadzu 8400 S) in the range of 400-4000 cm^{-1} as KBr pellets. (^1H NMR) data of the compound was carried out in Bruker 200 spectrospin NMR at Astra Zeneca Pharma India Limited, Bangalore and Bruker 400 spectrospin NMR at Indian Institute of Science, Bangalore. The solvent used for NMR was $CDCl_3$.

PROTOCOL OF SYNTHESIS

Scheme I

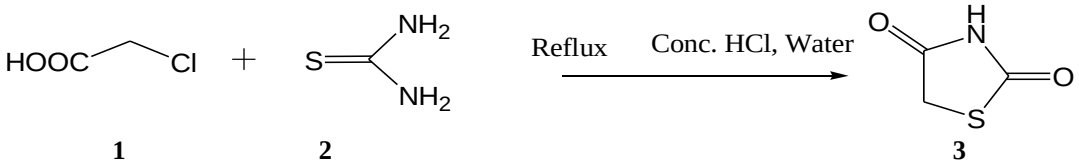


SCHEME1. Reagents and conditions: (i) Conc. HCl, H_2O, reflux 10 hrs. (ii) 4-hydroxybenzaldehyde, Benzoicacid, Piperidine, Toluene, stirred at 80 ◌̊C, 16 - 20 hrs. (iii) Ethyl chloro formate, Anhydrous K_2CO_3, Dry Acetone stirred over night. (iv) Hydrazine hydrate, Ethanol, refluxed 4hrs. (v) acetylacetone, ethanol, refluxed 4h. (vi) ethylacetoacetate, ethanol reflux 10h. (vii) malanonitrile, ethanol, refluxed, 8h.(viii) 2-(bismethy sulfanyl-methylene) malanonitrile, ethanol, refluxed, 8-12h.

EXPERIMENTAL PROCEDURE:

Preparation of thiazolidine-2, 4-dione[7]:

Scheme 1

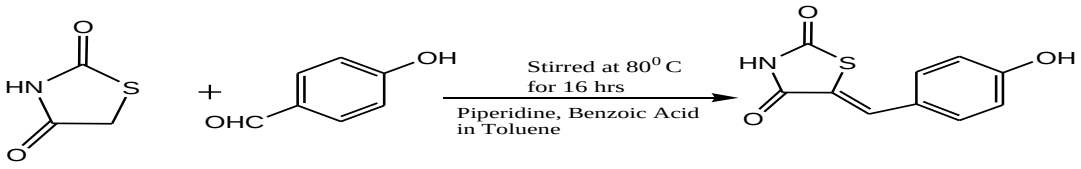


Procedure:

In a 250 ml round bottom flask place (1 g, 0.0131 mol) of Thiourea, Mono chloro acetic acid(2.046 g ,0.11 mol), (6.3 ml) of Hydrochloric acid and 5 ml of Water. The mixture was refluxed for 10 hrs and poured into 250 ml of beaker. The pH was adjusted to 7.0 by adding Sodium bicarbonate. The solution was extracted with 3×50 ml Ethyl acetate. The combined organic layer dried over anhydrous Sodium sulphate and solvent removed in vacuum to

obtain the product. The yield was 0.85g, (70%) m.p-126 ̊c.

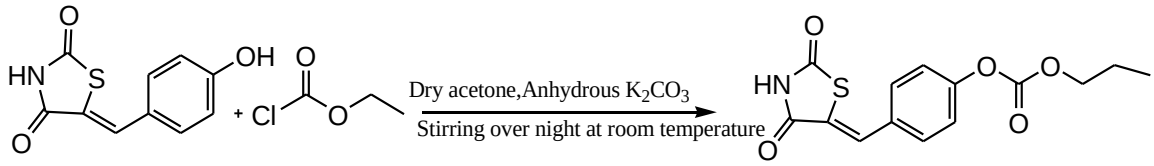
Preparation of 5-(4-hydroxybenzylidene) thiazolidine-2, 4-dione[7]:



3 **4**

In a 100 ml round bottom flask place 4-hydroxybenzaldehyde (0.244 g ,0.002 mol), Thiazolidine-2,4-dione (0.250 g 0.002 mol), Piperidine (0.010 g , 0.00017 mol) and Benzoic acid (0.013 g, 0.0001 mol) in 5 ml of Toluene was heated to 80˚C for 16 hrs, with stirring. Cooled at room temperature and filter off the yellow solid. Wash the solid with DCM (3×100 ml) and then with methanol: DCM (30:70) {2×100 ml}. Combine the organic layers and dried in vacuum at 35 ˚C until constant weight. The completion of the reaction was checked by TLC using mobile phase 10% methanol: 90% DCM. The yield was 0.46g (94%) m.p-294 ̊c.

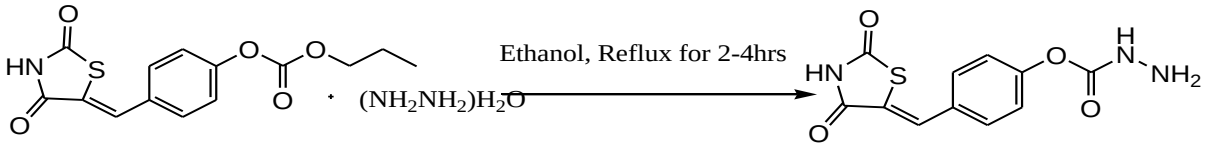
Preparation of [4-(2, 4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester ethylester[8]:



4 **5**

A mixture of 5 - (4-hydroxybenzylidene) thiazolidine - 2, 4-dione (0.05 mol) and Anhydrous K_2CO_3 (0.1mol) in excess of Dry Acetone (100ml) was stirred at reflux temperature for 4h. To stirred suspension mixture of Ethylchloroformate (0.05mol) in dry Acetone was added in a drop wise manner over a period of 30 min at reflux temperature, and the refluxing continued for 6h. After keeping the reaction mixture over night, the excess of solvent was removed to get the solid. The solid was re-crystallization from Acetone.

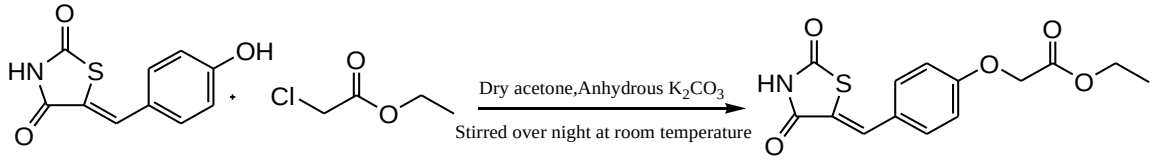
Preparation of Hydrazinecarboxylicacid [4-(2, 4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester[8]:



5 **5a**

To a suspension of [4-(2, 4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester ethyl ester (0.01mol) in 40 ml Ethanol 0.015 mol of Hydrazine hydrate was added and the reaction mixture was refluxed for 2h. The resulting mixture was allowed to cool and filtered. The solid obtained dried and re-crystallization with hot water.

Preparation of [4-(2, 4-Dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-aceticacid ethyl ester[8]:

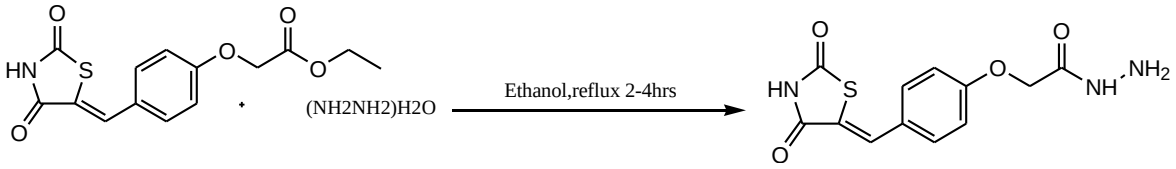


5 **6**

A mixture of 5 - (4-hydroxybenzylidene)thiazolidine-2,4-dione (0.05 mol) and anhydrous K_2CO_3 (0.1mol) in excess of dry Acetone (100ml) was stirred at reflux temperature for 4h.To stirred suspension mixture of Ethylchloroacetate (0.05mol) in dry Acetone was

added in a drop wise manner over a period of 30 min at reflux temperature, and the refluxing continued for 6h. After keeping the reaction mixture over night, the excess of solvent was removed to get the solid. The solid was re-crystallization from Acetone.

Preparation [4-(2, 4-Dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-aceticacid hydrazide[8]:



6 **6a**

To a suspension of **[**4-(2, 4-Dioxo-thiazolidin-5-ylidenemethyl)-phenoxy]-aceticacid ethyl ester (0.01mol) in 40 ml Ethanol 0.015 mol of Hydrazine hydrate was added and the reaction mixture was refluxed for 2h. The resulting mixture was allowed to cool and filtered. The solid obtained dried and re-crystallization with hot water.

***IN-VITRO* SCREENING FOR ANTIBACTERIAL AND ANTIOXIDANT ACTIVITIES:**

Antibacterial Activity[9]

Antibacterial activity of the synthesized compounds was determined, using a slightly modified cup plate method. Muller Hinton agar was used for the growth of bacterial strains Bacterial strains such as gram-positive (*S. aureus* and *B. subtilis*) and gram-negative (*E.coli & Proteus vulgaris*). Each organism was suspended in normal saline solution and transmittance (T) of 75 to 77% at 530 nm was made, which is equal to 10^6 CFU/ml.

All the test compounds were dissolved in DMSO at a concentration of 1 mg/ml. Each plate was inoculated with 20 µl of microbial suspension. 100 µl of the test compounds was added to each cup. The plates containing bacteria were incubated at 37^0C for 24 hrs, the positive antimicrobial activity were read based on the growth inhibition zone and compared with amoxicillin drug, as shown in **Table4.**

Antioxidant Activity Assay[10]

Free radical scavenging activity by DPPH assays method: DPPH (1, 1-diphenyl-2-picryl-hydrazil) is stable free radical. Methanol solution of DPPH is used to evaluate the antioxidant activity of several synthetic compounds. Antioxidant on interaction with DPPH, both transfer electron or hydrogen atom to DPPH, thus neutralizing its free radical character and convert it to1, 1-diphenyl-2-picryl hydrazine. The degree of discoloration indicates the scavenging activity of the drug .The change in absorbance produced at 517 nm has been used as measure of its antioxidant activity.

Chemicals used:

1, 1 – diphenyl - 2-picryl - hydrazil (DPPH) - Sigma Ltd., Ascorbic Acid - Qualigens, Methanol-Qualigens.

Preparation of DPPH solution: It was prepared by dissolving 33 mg of DPPH in 1 lit. Of methanol just before use and kept in dark amber colored bottle to protect from sunlight.

Sample preparation:

Preparation of stock solution of ligands:

It was prepared by dissolving 50 mg of ligand in 100 ml of methanol.

Standard preparation:

Preparation of Ascorbic Acid solution:

It was prepared by dissolving 50 mg of ascorbic acid in 100 ml of methanol.

PROCEDURE:

A 10, 20,30,40,50 µg/ml concentrations of ligands and ascorbic acid were prepared. From this stock solution 1ml has been pipette out and 5ml methanol solution of DPPH was added ,shaken well and the mixture was incubated at 370C for 30 minute absorbance of all samples were measured against blank at 517 nm. The absorbance of DPPH reagent alone was taken as control.

The % radical scavenging activity can be calculated following formula:

$$\% \text{ free radical Scavenging activity} = \frac{\text{Absorbance of control - Absorbance of sample}}{\text{Absorbance of control}} \times 100$$

& calculated IC_{50} value.

Ferric ion reduction method[11]:
The reaction mixture containing 1, 10-o-phenanthroline (0.5 mL), ferric chloride 1mL (0.02 mM) and test compound (solution of different concentration of synthesized compounds and ascorbic acid as standard drug) in a final volume of 5 mL with methanol was incubated for 15-20 min at ambient temperature and absorbance was measured at 510 nm. In another set, sodium dithionate (0.3 mM) was added instead of the compounds and absorbance was taken as equivalent to 100% reduction of all the ferric ions present.

Anti-oxidant activity by ferric ion reduction method can be calculated by the following formula:

$$\% \text{ Activity} = [At / As] \times 100$$

Where, **As** = absorbance by standard drug solution at 510 nm.
At = absorbance by the sample solution at 510 nm.

RESULT AND DISCUSSIONS:
The structure of new compounds prepared during present investigation has been authentically established by their UV, IR and ^{1}H NMR. In following reaction the spectral studies of some selected compounds have been dealt.

The synthesis of scaffold TZD (**3**) was done by refluxing Thiourea, Monochloroaceticacid and Con HCl. Which was proved by comparing observed m.p with literature m.p. IR **(Figure 1**) showed prominent carbonyl strechting at 1775.50 cm^{-1}, 1739.99 cm^{-1}. Further proof was obtained from ^{1}H NMR spectra **(Figure 10)** which clearly shows two singlets at 4.31 and 11.98 indicating the presence of –CH_2 and –NH. Further substitution reaction with 4-hydroxybenzaldehyde leads to 5 - (4-hydroxybenzylidene) thiazolidinediones. The formation of compounds were confirmed by visualizing agents (2, 4 DNP, Phosphomolybdicacid) and IR , which shows vinylic –CH stretching at 1664.31 cm-1 and 1562.91 cm-1 **(Figure 2)**.

The phenolic benzylidene intermediate was subjected to reaction with Ethylchloroformate and Ethylchloroacetate, Anhydrous K_2CO_3, Dry acetone with guard tube to obtain esters **5**. The IR **(Figure 3** and **7)** spectrum showed at 1442 cm^{-1} due to CH_3 str, 1654 cm^{-1} due to C=O str (carbonyl). This was then made to react with Hydrazine hydrate using ethanol as solvent to get respective hydrazino derivatives **5a**.

The IR **(Figure 4** and **8)** spectrum showed at 3290.67, 3178.79 (NH2 st), 3165.29 (NH st).These compounds were treated with different diketones Acetylacetone, ethylacetoacetate. Ethanol used as solvent to obtain compounds **5b-e** as described in **scheme 1**. The product formed by cyclo addition reaction determined from TLC by comparing R_f values of starting material and by IR and NMR data. The IR spectrum of **5b** showed at 3020.63 (aromatic C-H 3390.69, 3460.23 (N-H st), which showed the peaks at 5.84 indicating the presence of 1-pyrazole **(Figure 5)**. The IR spectrum of **5c** showed 693.56 cm^{-1}(C=O str.), 1205.55 cm^{-1}(C-O str.), 3468.13 cm^{-1}, 3398.69 cm^{-1} (N-H st), indicating presence of pyrazolidine (figure **6**).The other derivatives have been identified by similar manner.

In chemexper data + sign indicate favourable drug and – sign indicate unfavorable drug and mole inspiration shows vice versa. Physical and spectroscopical data described in **Table 1-3**. The compounds **5a-e** was screened for antibacterial activity using amoxicillin as standard reference (1µg/mL) as shown in **Table 4** and The antioxidant activity was performed by using free radical scavenging activity by DPPH (1, 1-diphenyl-2-picryl-hydrazil) assay method and Ferric ion reduction method, ascorbic acid was used as reference standard.

All the tested derivatives show antioxidant activity but compound **5c** and **5d** show promising antioxidant activity concentration at 50µg /ml and can be further studied with modifications. In general, most of the compounds showed significant antibacterial activity but some compounds are more specific to particular strains of bacteria. From the biological data, it was evident that the compound **5a** was found to be more active against *Staphylococcus aureus, Bacillus subtillus* and *E-Coli* and **5e** was found to be more active aganist *Proteus vulgaris*.

However the antimicrobial activity of the synthesized compounds against the tested

organisms was found to be less than that of respective standard drug at tested dose level. In future study the activity of the compounds may be manipulated by introducing unsaturation or heterocyclic ring at C_2 of thiazolidinediones.

TABLE 1 LIST OF COMPOUNDS SYNTHESIZED

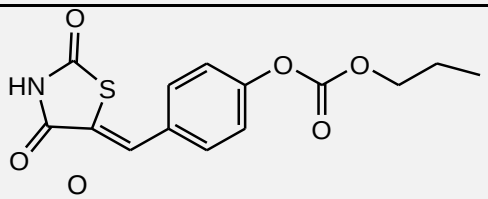
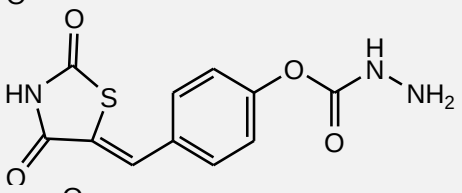
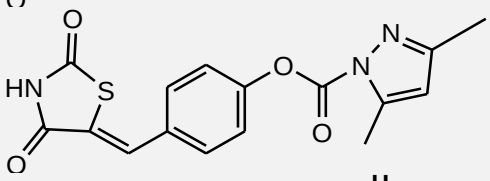
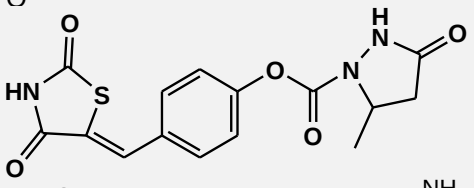
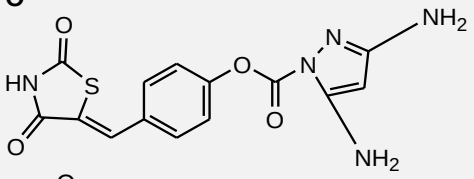
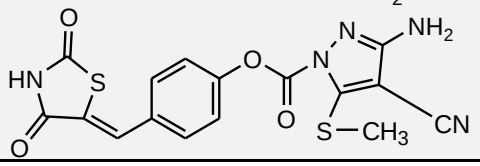
Sl. no	Comp code	Chemical Name	Structure
1	**5**	[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester ethyl ester	
2	**5a**	Hydrazinecarboxylic acid[4-(2,4-Dioxo-thiazolidin-5-ylidenemethyl)-phenyl-ester	
3	**5b**	3,5-Dimethyl-pyrazole-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester	
4	**5c**	5-Methyl-3-oxo-pyrazolidine-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester	
5	**5d**	Pyrazole-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester	
6	**5e**	3-Amino-4-cyano-5-methylsulfalyl -Pyrazole-1-carboxylic acid 4-(2,4-dioxo-thiazolidin-5-ylidenemethyl)-phenyl ester	

TABLE 2: PHYSICOCHEMICAL PROPERTIES OF SYNTHESIZED COMPOUNDS

Sl. no	C.C.*	Molecular formula	M.Wt.	% yield	State	R_f	Mobile Phase
1.	**5**	$C_{13}H_{11}NO_5S$	293.30	75.7 %	semisolid	0.68	n-Hex : EA 2 : 1
2.	**5a**	$C_{11}H_9N_3O_4S$	279.27	78.5%	semisolid	0.60	n-Hex :EA 2 : 1
3.	**5b**	$C_{16}H_{13}N_3O_4S$	343.36	65.7%	semisolid	0.62	n-Hex : EA 2 : 1
4.	**5c**	$C_{15}H_{13}N_3O_5S$	347.35	76.5%	semisolid	0.60	n-Hex : EA 2 : 1
5.	**5d**	$C_{14}H_9N_3O_4S$	315.30	66.7 %	semisolid	0.57	n-Hex : EA 2 : 1
6.	5e	$C_{15}H_{12}N_4O_4S$	355.33	63.2%	semisolid	0.69	n-Hex : EA 2: 1

C.C. * = Compound Code, n-Hex: EA = n-Hexane: Ethyl Acetate

TABLE 3 SPECTRAL DATA OF THE SYNTHESIZED COMPOUNDS

Comp Code	Elemental analysis	I.R. values (cm^{-1})
3	C=30.76; H= 2.58; N= 11.96; O= 27.32; S= 27.38	3470.06, (-N-H), 2915.19, 29 74.61 (C-H str.) 1776.50,1737.99 (keto C=O str.), 1522(C=C str.),
4	C=54.29; H=3.19; N= 6.33; O=21.70; S=14.49	3429.29, (-OH str.), 3236.66 (-NH str.), 1718,1703(C=O), 1680, 1664.31 (C=C str.), 1275(C-C)
5	C= 53.24; H=3.78; N= 4.78; O=27.28; S=10.93	3398.69(N-H str.), 2982.05, 2908.75(aliphatic C-H),1749.49,1732.13 (C=O str), 3020.63 (aromatic C-H str.), 1205.55,1242.20 (C-O str)
5a	C= 47.31; H=3.25; N=15.05; O=22.92; S, 11.48	3290.67, 3178.79 (NH2 str), 3165.29 (NH str), 2935.36 , 2812.31 (C-H str.) 1730.21 ,1685.8(C=O str.), 1269.55,1174.69 (C-O str.),
5b	C= 55.97; H=3.82; N= 12.24; O= 18.64; S=9.34 C=51.87; H=3.77;	3390.69, 3460.23 (N-H str), 2982.06, 2908.75 (aliphatic C-H str.), 3020.63 (aromatic C-H str.), 1749.49, 1732.13 (C=O str.), 1242.20 (C-O str.), 3468.13, 3398.69 (N-H str), 2982.05, (aliphatic C-H str.), 3020.63
5c	N=12.10; O=23.03; S= 9.23	(aromatic C-H str.), 1749.49, 1693.56 (C=O str.), 1205.55 (C-O str.),
5d	C=53.33; H= 2.88; N= 13.33; O=20.30; S= 10.17	3336.98,3166.51 (N-H str), 2980.08, 2905.85 (aliphatic C-H str.), 3020.63 (aromatic C-H str.), 1749.49, 1732.13 (C=O str.), 1242.20 (C-O str.),
5e	C= 50.70; H=2.55; N=19.71; O=18.01; S=9.02	3448.84 (N-H str), 3066.92, 3039.91 (aromatic C-H str.), 1707.06, 1610.61 (C=O str.), 763.84 (C-Hstr.).

Sl.no	Compound code	NMR In(DMSO-d6) (δ) value in ppm from TMS
1	3	4.130 (s, 2H,-S-CH_2-C=O) 11.98(1s, 1H, -NH-).
2	4	6.89-6.949 (d, 2H, Ar-H at 2, 6, J=8.6H_3), 7.44-7.48 (d, 2H, Ar at 3,5, J=8.6 H_3)7.70 (s, 1H, vinylic-H), 10.31 (s, 1H, Ar-OH), 12.46 (s,1H,NH).

TABLE 4 ANTIMICROBIAL ACTIVITY OF SYNTHESIZED COMPOUNDS

Compound	Zone of inhibition (mm)			
	Antibacterial activity			
	S.aureus	*B.subtilis*	*E.coli*	*P.vulgaris*
5a	20±2.53	25±0.23	14±1.23	12±1.59
5b	13±1.55	8±0.82	9±0.53	14±0.82
5c	23±0.86	13±0.49	16±2.03	27±0.23
5d	16±1.69	9±0.77	10±1.53	16±1.43
5e	15±0.94	14±1.25	15±0.81	28±1.23
Amoxicillin	25±1.34	28±1.23	17±0.99	31±0.41

TABLE 5 DPPH RADICAL SCAVENGING ASSAY OF SYNTHESIZED COMPOUNDS AND ASCORBIC ACID

Sl.no	Comp code	Mean abs±S.E.M	% inhibition
1	5a	0.5820±0.0006	56.40
2	5b	0.6216±0.0005	58.10
3	5c	0.5616±0.0005	66.80
4	5d	0.5140±0.0014	65.50
5	5e	0.5140±0.0014	59.90
6	Ascorbicacid	0.5260±0.05	68.50

TABLE 6 FERRIC REDUCING ACTIVITIES OF SYNTHESIZED COMPOUNDS AND ASCORBIC ACID

Sl.no	Comp code	Ferric reducing activity (100μg/mL) %
1	5a	0.28
2	5b	0.31
3	5c	0.34
4	5d	0.52
5	5e	0.53
6	Ascorbic acid	0.087

Absorbance by Sodium dithionite (100µg/ml) at 510 nm. = 0.571 (Standard, 100%) for ferric ion reduction.
Note: IC50 values were not detected at the highest concentration. It was determined by extrapolating the graph.

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How to cite this article:
Rekha S and Chandrashekhara S: Antioxidant and Antibacterial Activities of Thiazolidinedione Derivatives. Int J Pharm Sci Res 2015; 6(1): 421-28.doi: 10.13040/IJPSR.0975-8232.6 (1).421-28.