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Synthesis, Characterization and Antimicrobial Activity of Thiazolidiine-Based Compounds

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ABSTRACT

In the present investigation, an attempt was made to synthesize and evaluate the anti-inflammatory properties of some new thiazolidinedione congeners. The synthesis of the N-benzylated thiazolidinedione derivatives (SD1 -SD5) was accomplished in three distinct steps involving the formation of thiazolidine-2,4-dioneform thiourea and monochloroacetic acid, followed by novena gel condensation with aryl aldehyde and ultimately the formation of N-benzylated compound in the final step. The MIC value of the synthesized thiazolidinedione congeners was evaluated using broth dilution method. The optical density of each broth tube was measured and 600nm and the concentration that presented almost half of the optical density of control was considered as MIC. The MIC of compounds against P. mirabilis and P. aeuroginosa was approximately6.3, 50, 50, 6.3 and 50 µg/mL and for B. subtilis and S. aureus it was approximately6.5, 40, 20, 6.5 and 40 µg/mL for SD 1 to SD 5 respectively. The results also exhibited that compounds SD 1 and SD 4 were having higher antibacterial activity in comparison to the remaining compounds which could be due the presence of cytotoxic fluorine and nitro groups in these compounds.

INTRODUCTION

Antimicrobials

Antimicrobial drugs have caused a dramatic change not only in the treatment of infectious diseases but of the fate of mankind. Antimicrobial chemotherapy made remarkable advances, resulting in the overly optimistic view that infectious diseases would be conquered soon.[1] A dose of anticancer drug sufficient to kill tumor cells is often toxic to the normal tissue and leads to many side effects, which in turn, limits its treatment efficacy. In recent years, there has been a concerted search for the discovery and development of novel selective anti-tumor agents, devoid of many of the unpleasant side effects of conventional antimicrobial and antitumor agents. [2,3]

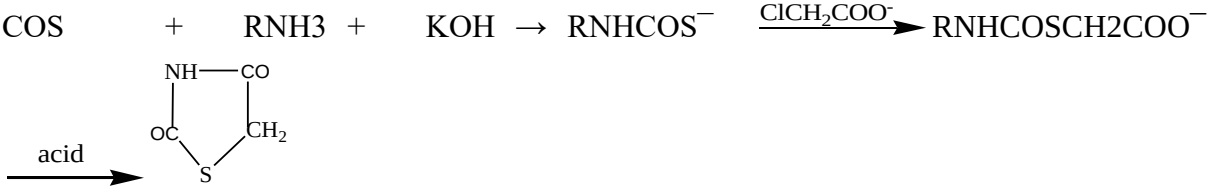
Thiazolidinediones

Thiazolidin-2,4-dione, also called glitazone, is a heterocyclic moiety that consists of a five-membered saturated thiazolidine ring with sulfur at 1 and nitrogen at 3, along with two carbonyl functional groups at the 2 and 4 positions. Substitutions of various moieties are possible only at the third and fifth positions of the Thiazolidin-2,4-dione (TZD) scaffold. 2,4-thiazolidinedione (TZD) is an attractive scaffold because of its prestigious position in medicinal chemistry as this unit is responsible for numerous pharmacological and biological activities, e.g., antidiabetic, antidiarrheal, anticonvulsant, antimicrobial, antihistaminic, anticancer, anti- HIV, 15-hydroxyprostaglandin dehydrogenase inhibitors, and anti-ischemic.[4]

Synthetic methods for 2-azetidinones

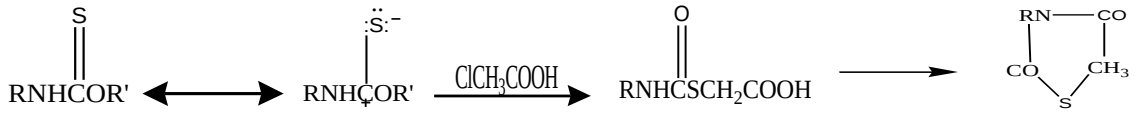
Reaction with acyclic thiocarbamates

In an analogous series of reactions, the substitution of carbon oxysulfide for carbon disulfide yields 2, 4-thiazolidinedione. With the use of primary amines instead of ammonia, the procedure can be adapted to the synthesis of 3- substituted 2, 4-thiazolidinediones.[5]



In the reaction, the sulfur of the thione group displaces the halogen of the α-haloalkanoic acid and the R' alkyl group is lost as a carbonium ion. Cyclization of the S- carboxymethyl

thiocarbamate produces 2, 4-thiazolidinedione. Isothiocyanates in alcoholic solution can be substituted for the alkyl thiocarbamate.



***Reaction with Thiosemicarbazones*[6]**

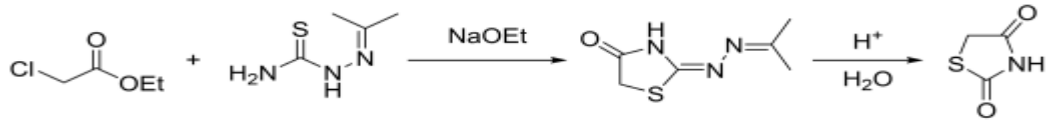
Heating an alcoholic solution of the thiosemicarbazone with chloroacetic acid and sodium acetate, with ethyl chloroacetate and N- ethylpiperidine, or with chloroacetanilide in ethanol or butanol. Refluxing the 4-oxo-2-thiazoline-2-ylhydrazone of acetone for 15 min. with dilute hydrochloric acid gives the salt of 2-hydrazino-4-thiazolidinedione, while longer refluxing with concentrated acid produces 2, 4-thiazolidinedione.[5]

***Reaction with Alkali Thiocynates*[6]**

The first 4-thiazolidinedione to be reported was 2, 4-thiazolidinedione, which was synthesized by treating the product of the reaction of ethyl chloroacetate and potassium thiocynate with dilute hydrochloric acid.[6]

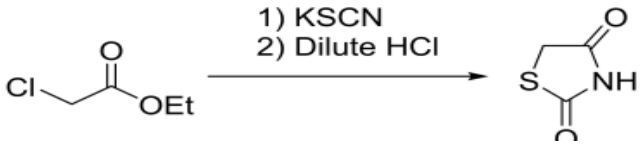
***Using thiosemicarbazone and ethylchloroacetate*[6]**

This method involves the reaction of ethyl chloroacetate with thiosemicarbazone, which in the presence of NaOEt, generates 2-hydrazino-4-thiazolidinedione; this, in turn, can be refluxed in dilute hydrochloric acid to give the desired TZD.[6]



Using potassium thiocyanate and ethylchloroacetate[7]

In this method, acidification of the product obtained from the reaction with potassium thiocyanate yields. It should be noted that during this process significant care must be taken due to the liberation of toxic HCN gas as a by-product.[7]



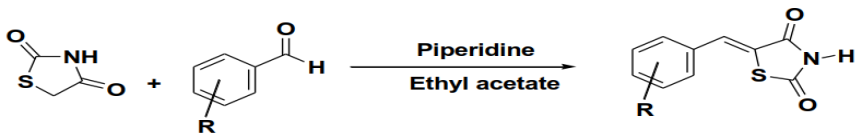
Structure and reactivity of thiazolidine-2,4-diones

Thiazolidine-2, 4-diones are derivatives of thiazolidine with a carbonyl group in the 2 and 4th positions. Substituent in the 3rd and 5th positions may be varied, but the greatest difference in the structure and properties is exerted by the group attached to the carbon atom in the 2nd position.

Reactions of thiazolidine-2,4-diones

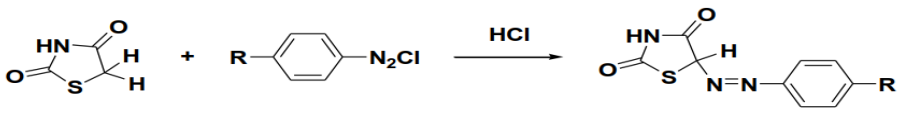
Knoevenagel condensation with aldehyde and ketones

Aromatic aldehyde react with 2,4-thiazolidinedione and forms the 5-arylidine derivatives of the later. The reaction takes place in the presence of mineral acid, or few drops of piperidine, or anhydrous sodium acetate in glacial acetic acid.[8]



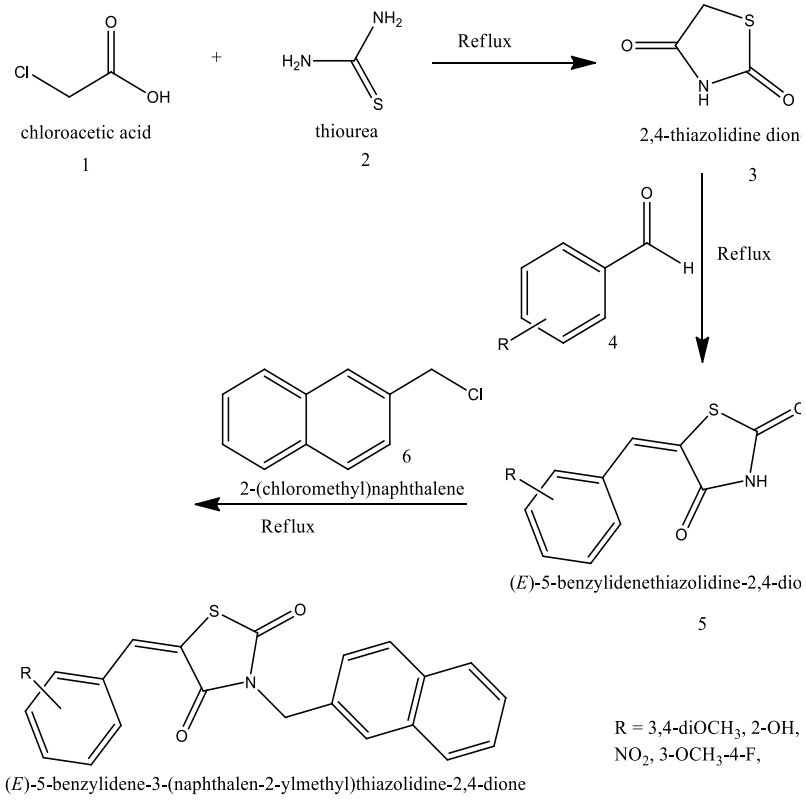
Reaction with diazonium salt

Diazonium salts undergo a coupling reaction with the 5-methylene group of rhodanines, 2,4-thiazolidinediones and 2-substituted- imino-3-substituted (or hydrogen)-4-thiazolidinediones.[9]



METHODOLOGY

The steps involved in the synthesis of thiazolidinedione derivatives has been presented in Scheme 1 below.



Scheme 1: Scheme for synthesis of thiazolidinedione derivatives

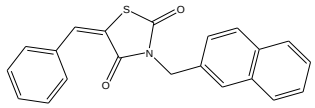
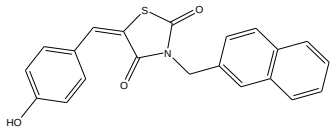
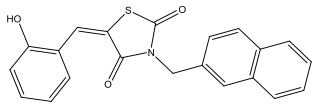
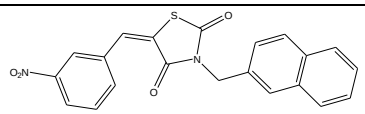
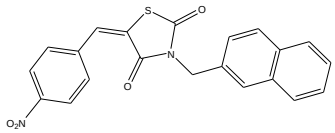
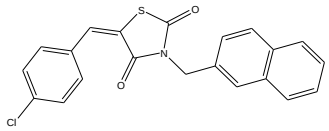
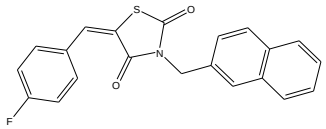
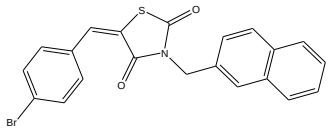
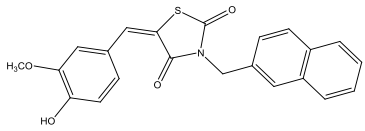
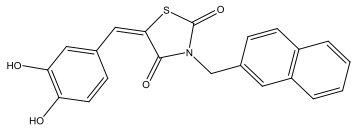
The entire scheme comprises of 3 steps leading to the formation of the title compounds.

Step 1 - Synthesis of 2,4-thiazolidinedione

Step 2 - Synthesis of (E)-5-benzylidenethiazolidine-2,4-dione

Step 3 - Synthesis of (E)-5-benzylidene-3-(naphthalen-2-ylmethyl)thiazolidine-2,4-dione compounds.

Table 01: List of proposed thiazolidinedione congeners to be synthesized

S. No.	Structure	IUPAC Name
1		(E)-5-benzylidene-3-(naphthalen-2-ylmethyl)thiazolidine-2,4-dione
2		(E)-5-(4-hydroxybenzylidene)-3-(naphthalen-2-ylmethyl)thiazolidine-2,4-dione
3		(E)-5-(2-hydroxybenzylidene)-3-(naphthalen-2-ylmethyl)thiazolidine-2,4-dione
4		(E)-5-(3-nitrobenzylidene)-3-(naphthalen-2-ylmethyl)thiazolidine-2,4-dione
5		(E)-5-(4-nitrobenzylidene)-3-(naphthalen-2-ylmethyl)thiazolidine-2,4-dione
6		(E)-5-(4-chlorobenzylidene)-3-(naphthalen-2-ylmethyl)thiazolidine-2,4-dione
7		(E)-5-(4-fluorobenzylidene)-3-(naphthalen-2-ylmethyl)thiazolidine-2,4-dione
8		(E)-5-(4-bromobenzylidene)-3-(naphthalen-2-ylmethyl)thiazolidine-2,4-dione
9		(E)-5-(3-methoxy-4-hydroxybenzylidene)-3-(naphthalen-2-ylmethyl)thiazolidine-2,4-dione
10		(E)-5-(3,4-dihydroxybenzylidene)-3-(naphthalen-2-ylmethyl)thiazolidine-2,4-dione

Synthesis of 2,4-thiazolidinedione, 3

To 0.6 mole of chloroacetic acid, **1** in 60 ml of water, followed by the addition of 0.6 mole of thiourea, **2**. The reaction mixture was stirred until the completion of the reaction (white precipitate was formed, approximately 15 min.) and refluxed until the completion of the reaction (approximately 40 hours). On cooling, a solid separated, which was recrystallized from ethyl alcohol to give the pure thiazolidine-2,4-dione.[10]

General method for synthesis of 5-benzylidenethiazolidine-2,4-dione, 5a-e

A mixture of aromatic aldehyde, **4a-e** (0.5 mmol), thiazolidine-2,4-dione, **3** (0.5 mmol), and sodium acetate (0.5 mmol) were dissolved in glacial acetic acid (5 mL) and was reflux at 100 °C for 5 h. The progress of the reaction was monitored by TLC using ethyl acetate/hexane as a solvent system. The reaction was quenched by crushed ice and extracted in ethyl acetate (20 mL × 3). The combined organic layers wash with brine solution (2 × 15 mL) and dried over $NaSO_4$. The solvent was removed under reduced pressure. The solvent was removed under reduced pressure and used for further reaction without purification.[11]

Synthesis of 5a

A mixture of 4-fluoro benzaldehyde (0.5 mmol), thiazolidine-2,4-dione, **3** (0.5 mmol), and sodium acetate (0.5 mmol) were dissolved in glacial acetic acid (5 mL) and were reflux at 100 °C for 5 h. The progress of the reaction was monitored by TLC using ethyl acetate/hexane as a solvent system. The reaction was quenched by crushed ice and extracted in ethyl acetate (20 mL × 3). The combined organic layers wash with brine solution (2 × 15 mL) and dried over $NaSO_4$. The solvent was removed under reduced pressure. The solvent was removed under reduced pressure and used for further reaction without purification.

Synthesis of 5b

A mixture of 2-hydroxybenzaldehyde (0.5 mmol), thiazolidine-2,4-dione, **3** (0.5 mmol), and sodium acetate (0.5 mmol) were dissolved in glacial acetic acid (5 mL) and was reflux at 100 °C for 5 h. The progress of the reaction was monitored by TLC using ethyl acetate/hexane as a solvent system. The reaction was quenched by crushed ice and extracted in ethyl acetate (20 mL × 3). The combined organic layers wash with brine solution (2 ×

15 mL) and dried over $NaSO_4$. The solvent was removed under reduced pressure. The solvent was removed under reduced pressure and used for the further reaction without purification.

Synthesis of 5c

A mixture of 3,4-dimethoxybenzaldehyde (0.5 mmol), thiazolidine-2,4-dione, **3** (0.5 mmol), and sodium acetate (0.5 mmol) was dissolved in glacial acetic acid (5 mL) and were reflux at 100 °C for 5 h. The progress of the reaction was monitored by TLC using ethyl acetate/hexane as a solvent system. The reaction was quenched by crushed ice and extracted in ethyl acetate (20 mL × 3). The combined organic layers wash with brine solution (2 × 15 mL) and dried over $NaSO_4$. The solvent was removed under reduced pressure. The solvent was removed under reduced pressure and used for further reaction without purification.

Synthesis of 5d

A mixture of 3-nitrobenzaldehyde (0.5 mmol), thiazolidine-2,4-dione, **3** (0.5 mmol), and sodium acetate (0.5 mmol) were dissolved in glacial acetic acid (5 mL) and was reflux at 100 °C for 5 h. The progress of the reaction was monitored by TLC using ethyl acetate/hexane as a solvent system. The reaction was quenched by crushed ice and extracted in ethyl acetate (20 mL × 3). The combined organic layers wash with brine solution (2 × 15 mL) and dried over $NaSO_4$. The solvent was removed under reduced pressure. The solvent was removed under reduced pressure and used for further reaction without purification.

Synthesis of 5e

A mixture of 3-methoxy-4-hydroxybenzaldehyde (0.5 mmol), thiazolidine-2,4-dione, **3** (0.5 mmol), and sodium acetate (0.5 mmol) were dissolved in glacial acetic acid (5 mL) and were reflux at 100 °C for 5 h. The progress of the reaction was monitored by TLC using ethyl acetate/hexane as a solvent system. The reaction was quenched by crushed ice and extracted in ethyl acetate (20 mL × 3). The combined organic layers wash with brine solution (2 × 15 mL) and dried over $NaSO_4$. The solvent was removed under reduced pressure. The solvent was removed under reduced pressure and used for the further reaction without purification.

Synthesis of 5-benzylidene-3-(naphthalen-2-ylmethyl)thiazolidine-2,4-dione compounds, 7a-e

A mixture of each of the 5-benzylidenethiazolidine-2,4-dione, **5a-e** (1.3 mM) and 2-(choloromethyl) naphthalene, **6** (1.3 mM) in acetone (10 mL) containing K_2CO_3 (3.9 mM) were refluxed for 5–6 h. After this time, the mixture was poured onto crushed ice. The precipitate thus obtained was filtered and washed with water and recrystallized from a mixture of ethanol and acetic acid.[12]

Chemical Characterization

All the synthesized compounds were characterized for melting point, solubility, yield, and elucidation of the structure. The structure elucidation was performed by spectroscopic analysis (NMR, and IR). The melting points were determined by open capillary method and are uncorrected using an electrically heated melting point determination apparatus.[13] The purity and homogeneity of the compounds were determined by thin layer chromatography, using silica gel G as the stationary phase on glass plates. TLC cabinet with long and short UV light were used for visualization of the spots.[14]

Anti-bacterial Study

The antibacterial action of the synthesized compounds was evaluated against two gram-positive (*Staphylococcus aureus* and *Bacillus subtilis*) and two-gram negative bacteria (*Psuedomonas aeruginosa* and *Proteus mirabilis*). [15]

Preparation of test solutions

The synthesized derivatives (**SD_1-SD_5**) were dissolved in dimethyl sulfoxide (DMSO) and the further dilutions of the test compounds were prepared at the required quantities of 1000 µg/mL concentrations with Mueller-Hinton broth medium.

Preparation of Inoculum

Overnight culture of all four bacteria were prepared separately in nutrient broth, and used as a microbial source for the determination of MIC.

RESULTS AND DISCUSSION

The synthesis of novel thiazolidine-2,4-dione congeners was accomplished as per the scheme 1 utilizing the procedures presented in the previous chapter.

Physicochemical characterization

The yield of the synthesized compounds is presented in table 02. The yield of the compounds was calculated based on the dry weight of the final product and the theoretical yield that could be obtained for the reaction. The retention factor value (R_f) was calculated as the ratio of the distance travelled by the sample to the distance travelled by the solvent in the selected solvent system for TLC.

Table 02: Physicochemical characterization of Yield SD_1-SD_5

Compound	R	Molecular Formula	Melting Point (°C)	Yield (%)	R_f value	Solvent System Used
SD_1	4-F	$C_{21}H_{1f}FNO_2S$	212-215	69.3	0.57	Chloroform:methanol (9:1)
SD_2	2-OH	$C_{21}H_{15}NO_3S$	221-222	65.2	0.53	Chloroform:methanol (9:1)
SD_3	3,4-OCH_3	$C_{22}H_{17}NO_4S$	201-203	70.1	0.61	Chloroform:methanol (9:1)
SD_4	3-NO_2	$C_{21}H_{14}N_2O_4S$	199-201	69.7	0.66	Chloroform:methanol (9:1)
SD_5	3-OCH_3, 4-OH	$C_{21}H_{15}NO_4S$	204-206	70.1	0.62	Chloroform:methanol (9:1)

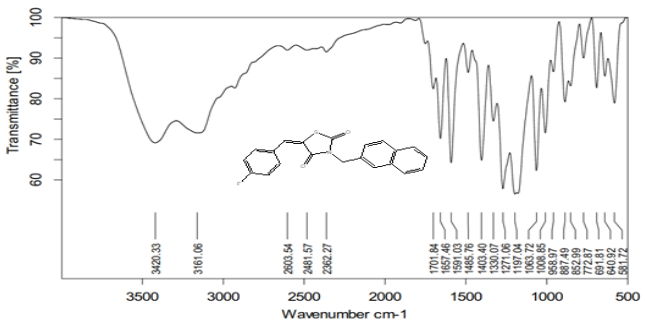
Spectral characterization of compounds

(E)-5-(4-fluorobenzylidene)-3-(naphthalen-2-ylmethyl) thiazolidine-2,4-dione, SD_1

Table 03: Interpretation of IR spectra of SD_1

IR peaks (cm^{-1})	Occurs due to
1197.04	C-F stretch
3161.06	C-H (aromatic) stretch
1701.84	C=O stretch
1591.03	C-C/C=C (aromatic) stretch
1271.06	C-N stretch
772.87	C-S-C stretch (assymetric)

Graph 1: FTIR Spectra of SD_1

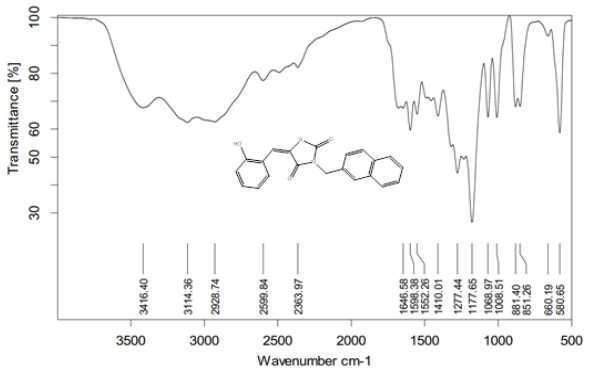


(E)-5-(2-hydroxybenzylidene)-3-(naphthalen-2-ylmethyl) thiazolidine-2,4-dione, SD 2

Table 04: Interpretation of IR spectra of SD_2

IR peaks (cm^{-1})	Occurs due to
3416.40	O-H stretch
3114.36, 2928.74	C-H (aromatic) stretch
1646.58	C=O stretch
1598.38	C-C/C=C (aromatic) stretch
1277.44	C-N stretch
660.19	C-S-C stretch (assymetric)

Graph 2: FTIR Spectra of SD_2

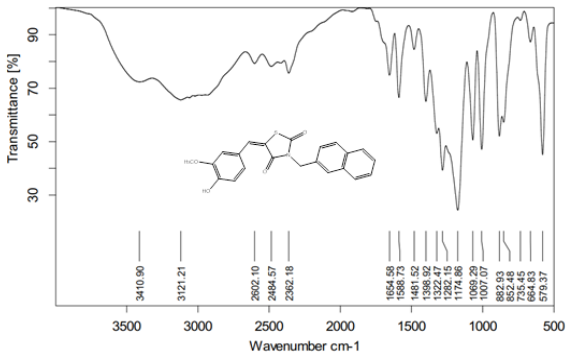


(E)-5-(3-methoxy-4-hydroxybenzylidene)-3-(naphthalen-2-ylmethyl) thiazolidine-2,4-dione, SD_3

Table 05: Interpretation of IR spectra of SD_3

IR peaks (cm^{-1})	Occurs due to
3410.90	O-H stretch
3121.21	C-H (aromatic) stretch
2602.10	C-H stretch
1654.58	C=O stretch
1588.73	C-C/C=C (aromatic) stretch
1282.15	C-N stretch
660.19	C-S-C stretch (assymetric)

Graph 3: FTIR Spectra of SD_3

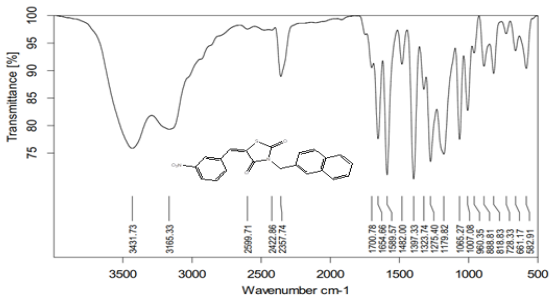


(E)-5-(3-nitrobenzylidene)-3-(naphthalen-2-ylmethyl) thiazolidine-2,4-dione, SD_4

Table 06: Interpretation of IR spectra of SD_4

IR peaks (cm^{-1})	Occurs due to
3165.33	C-H (aromatic) stretch
2599.71	C-H stretch
1700.78	C=O stretch
1589.57	C-C/C=C (aromatic) stretch
1275.40	C-N stretch
728.33	C-S-C stretch (assymetric)

Graph 4: FTIR Spectra of SD_4

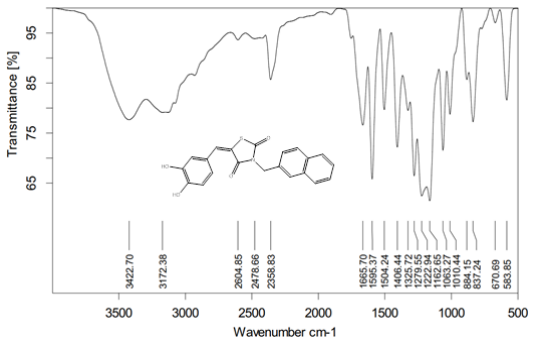


(E)-5-(3,4-dihydroxybenzylidene)-3-(naphthalen-2-ylmethyl) thiazolidine-2,4-dione, SD_5

Table 07: Interpretation of IR spectra of SD_5

IR peaks (cm^{-1})	Occurs due to
3422.70	O-H stretch
3172.38	C-H (aromatic) stretch
2604.85	C-H stretch
1665.70	C=O stretch
1595.37	C-C/C=C (aromatic) stretch
1279.55	C-N stretch
670.69	C-S-C stretch (assymetric)

Graph 5: FTIR Spectra of SD_5



The synthesis of the thiazolidinedione congeners (**SD_1-SD_5**) was achieved in three definitive steps involving formation of thiazolidine-2,4-dione form thiourea and monochloroacetic acid, followed by knoevenagel condensation with aryl aldehyde and ultimately formation of N-benzylated compound in the final step (Table 03-07). The IR spectrum is an indicator of the relevant functional groups present in the compounds, while the mass spectrum is a representation of the molecular mass of the compounds.

All the compounds exhibited peaks of N-C stretching (1000-1100 cm^{-1}), C-S stretching (600-700 cm^{-1}), and aromatic C-H stretching (3000-3200 cm^{-1}). The vibrations of O-H stretching (3300-3500 cm^{-1}), C=O stretching (1670-1340 cm^{-1}), C-N stretching (1215-1260 cm^{-1}) and C-F (820-850 cm^{-1}) stretching were also found in the compounds.

Antibacterial activity

The MIC value of the synthesized thiazolidinedione congeners was evaluated using the broth dilution method. The optical density of each broth tube was measured and 600 nm and the concentration that presented almost half of the optical density of control was considered as MIC. The results obtained are presented in Table 08-09.

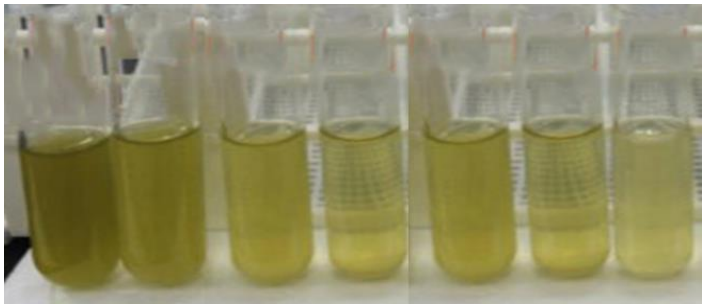


Figure 01: Broth depicting varying amount of viable microbes

The optical density observed in the control sample with no test sample was found to be 0.547, 0.553, 0.529 and 0.517 for *P. mirabilis, P. aeuroginosa, B. sutilis* and *S. aureus* respectively.

Table 08: Optical density by SD_1

S. No.	Concentration (µg/ml)	Optical Density at 600 nm			
		Proteus mirabilis	*Pseudomonas aeruginosa*	*Bacillus subtilis*	*Staphylococcus aureus*
1	**100**	0.112	0.113	0.099	0.101
2	**50**	0.151	0.145	0.137	0.131
3	**25**	0.182	0.182	0.168	0.166
4	**12.5**	0.213	0.215	0.193	0.199
5	**6.25**	0.269	0.275	0.241	0.246
6	**3.125**	0.318	0.335	0.298	0.304
7	**1.5625**	0.377	0.379	0.337	0.346

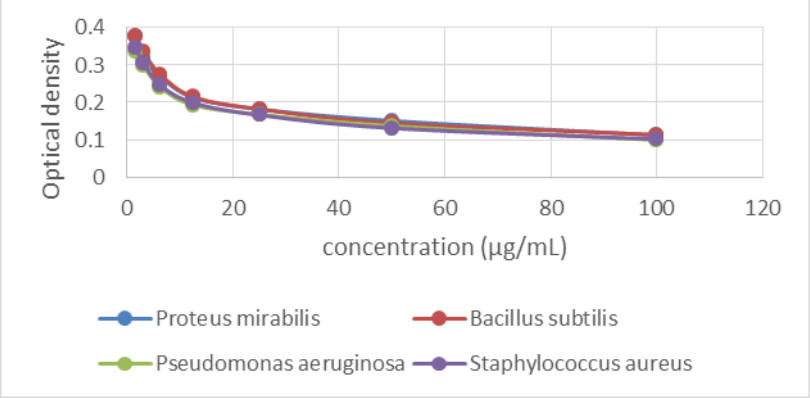


Figure 02: Graph of optical density vs. concentration of SD_1

Table 09: Optical density by SD_4

S. No.	Concentration (µg/ml)	Optical Density at 600 nm			
		Proteus mirabilis	*Pseudomonas aeruginosa*	*Bacillus subtilis*	*Staphylococcus aureus*
1	**100**	0.121	0.123	0.109	0.111
2	**50**	0.159	0.155	0.147	0.151
3	**25**	0.192	0.19	0.178	0.179
4	**12.5**	0.221	0.225	0.203	0.209
5	**6.25**	0.278	0.283	0.256	0.262
6	**3.125**	0.336	0.345	0.311	0.324
7	**1.5625**	0.396	0.399	0.354	0.361

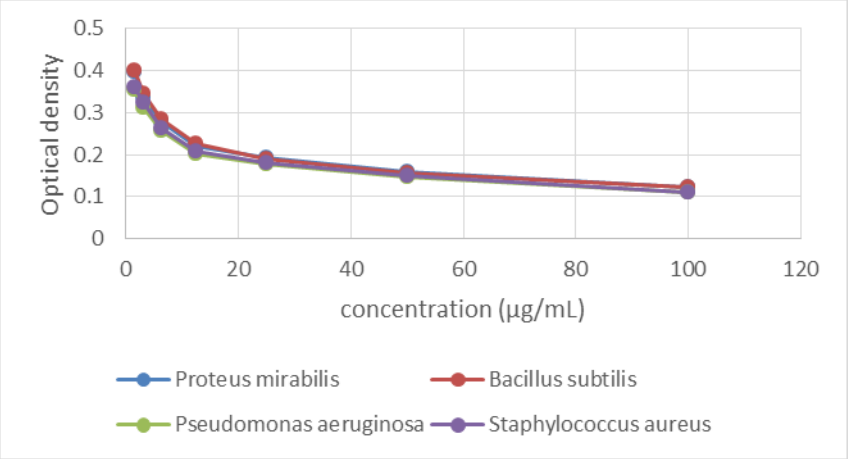


Figure 03: Graph of optical density vs. concentration of SD_4

From the results it was found that the MIC of compounds against *P. mirabilis* and P. *aeuroginosa* was approximately 6.3, 50, 50, 6.3 and 50 µg/mL for SD_1 to SD_5 respectively. The MIC of compounds against *B. subtilis and S. aureus* was approximately 6.5, 40, 20, 6.5 and 40 µg/mL for SD_1 to SD_5 respectively.

It could be observed that all the compounds were active against both gram negative and gram-positive bacteria. Also it was concluded that compounds **SD_1** and **SD_4** had higher antibacterial activity in comparison to the remaining compounds which could be due to the presence of cytotoxic fluorine and nitro groups in these compounds.

CONCLUSION

The preliminary object of this research work was to prepare thiazolidinedione congeners and assess them for anti-bacterial action using gram positive and gram-negative bacteria. It could be concluded from the results that the compounds possessed anti-bacterial activity. In future a further extended congeneric series would be developed and molecular modeling approached would be used for designing lead molecule and defining the structure-activity relationship of the molecules.

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