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Research Article

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL EVALUATION OF SOME NOVEL THIAZOLIDINONE DERIVATIVES

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ABSTRACT

Thiazolidine is a five membered ring with one nitrogen and one sulphur atoms. Hydrazides and their hetrocyclized derivatives also found to passes an important role in biological activities. Thiazolidinone derivatives showed good pharmacological properties. On the basis of literature study the objective of the present work was to prepare new derivatives of hydrazide containing thiazolidine moiety. In the present work we have prepared 12 novel thiazolidinone derivatives. The newly synthesized compounds were analyzed by IR, ^{1}H-NMR and Mass spectral analysis. The entire series of synthesized compounds was evaluated for their biological activities.

Keywords: Thiazolidinone Derivatives, Schiff Base, Thiomalic Acid, Biological Activities, MIC

1. INTRODUCTION

In medicinal research various heterocyclic compounds have contributed much to the unparallel progress of medicine and benefited numerous chemists and researchers. The Human immune system has long being implicated in the body's defense against various diseases. There is a constant requirement in the research of new drugs to overcome the increasing diseases and emerging anti drug resistant microbes. Today a large number of diseases are cured or at least controlled by drug therapy.

4-Thiazolidinones is a core of various pharmacological agents. The magical moiety of 4-Thiazolidinones have a broad spectrum of biological activities such as, Anti-inflammatory [1, 2], Anti-tubercular [3, 4], Anti-histamic [5, 6], Anti-Convulsant [7, 8], Anti-microbial [9], Anti HIV [10], Anti-viral [11], Anti-mycobacterial [12], cardiovascular effects [13]. Compound containing thiazolidinone moieties are also found to exhibit other broad spectrum Anti-microbial activities.

The structures of newly synthesized compounds were evaluated by spectral analysis and screened for their biological activities like anti-bacterial against (two gram positive and two gram negative bacteria) and anti-fungal activities.

2. MATERIAL AND METHODS

2.1. General

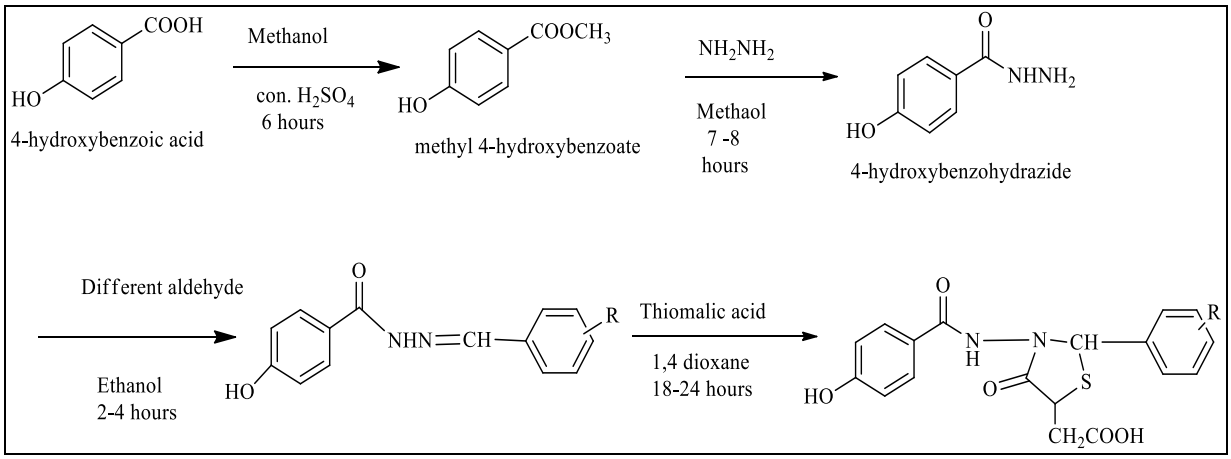
All chemicals used in the synthesis of the titled compounds were of analytical grade. Melting points were reported by the open capillary tube method and are uncorrected. Merck Kieselgel 60 F254 plates were used for TLC using mobile phase ethylacetate: chloroform (4:1). IR spectra were recorded on SHIMADZU FT-IR 8400 using potassium bromide pallets. The ^{1}H NMR spectra were recorded in DMSO d_6 solution in 5 mm tubes at room temperature, on a BRUKER 400 MHz FT-NMR, with TMS as internal standard. Mass spectra were recorded on SHIMADZU QP-2010. The antimicrobial activity was carried out using broth dilution method to determine minimum inhibitory concentration (MIC).

2.2. Synthesis of 4-hydroxy methyl benzoate

4-hydroxy benzoic acid (0.26 mol) was taken in a round bottom flask with 25 ml methanol followed by addition of sulfuric acid drop-wise through a dropping funnel. The solution was heated to reflux for 6-7 hours. It was then cooled to room temperature and poured into ice of cold water to precipitate the product methyl 4-hydroxy methyl benzoate. The product was re-crystallized from ethanol and the progress and completion of the reaction was confirmed by TLC.

2.3. Synthesis of 4-hydroxybenzohydrazide

A mixture of 4-hydroxymethylbenzoate (0.22mol) and hydrazine hydrate (0.22mol) in methanol was heated in a round bottom flask for 7-8 hours. The reaction mixture was cooled to room temperature. A white precipitates was obtained to form 4-hydroxybenzohydrazide.Finally the product was re-crystallized from ethanol and confirmed by TLC.



Scheme 1: Reaction scheme for the synthesis of the compounds I (a-l)

2.4. General procedure for the schiff bases

In a round bottom flask equimolar quantities (0.1mol) of different aromatic aldehydes and 4-hydroxybenzo hydrazide (0.1mol) were dissolved in ethanol and refluxed for 2-4 hours and solid product obtained are respectively Schiff bases.

Finally the products were re-crystallized from ethanol and the progress and completion of the reaction was confirmed by TLC.

2.5. General Procedure for the preparation of I(a-l)

A mixture of schiff bases (0.01mol) and thiomalic acid (0.01mol) were taken in round bottom flask followed by the addition of 1, 4-dioxane and a pinch of powder anhydrous $ZnCl_2$ was added to it. The reaction mass was heated for 18-24 hours the reaction mixture was poured into ice cold water with constant stirring. It was filtered then washed with sodium bicarbonate and to get the final product **I (a-l).**

Finally the products were re-crystallized from ethanol and the progress and completion of the reaction was confirmed by TLC.

3. RESULTS AND DISCUSSION

In the present work a new series of thiazolidines derivatives were prepared. The structures of newly synthesized compounds were confirmed by IR, ^{1}H NMR and mass spectral analysis. Compound **Ia** showed strong absorption at 1616 cm^{-1} due to carbonyl Group. In the ^{1}H-NMR compound **Ii** showed singlet at 10.4 δ ppm to two protons and one hydrogen at 6.8 ppm for thiazolidine ring.

Table 1.Physical properties of the synthesized compounds

Sr.No.	Compound Id	R	Molecular Formula	M.W. gm/mole	M.P.
1	Ia	-CHO	$C_{18}H_{16}N_2O_5S$	372.40	260°C
2	Ib	-3 NO_2	$C_{18}H_{15}N_3O_7S$	417.39	285°C
3	Ic	-4-Cl	$C_{18}H_{15}N_2O_5SCl$	406.84	295°C
4	Id	-4-OH	$C_{18}H_{16}N_2O_6S$	388.39	236°C
5	Ie	-2-OH	$C_{18}H_{16}N_2O_6S$	388.39	250°C
6	If	-4-OCH_3	$C_{19}H_{18}N_2O_6S$	402.42	264°C
7	Ig	-4-C_8H_7	$C_{21}H_{20}N_2O_5S$	412.11	275°C
8	Ih	-$N(CH_3)_2$	$C_{20}H_{21}N_3O_5S$	415.46	225°C
9	Ii	-3,4-$(OCH_3)_2$	$C_{20}H_{20}N_2O_7S$	432.5	259°C
10	Ij	-2-Cl	$C_{18}H_{15}N_2O_5SCl$	406.84	248°C
11	Ik	-2-NO_2	$C_{18}H_{15}N_3O_7S$	417.39	278°C
12	Il	-3-OCH_3,4-OH	$C_{19}H_{18}N_2O_7S$	418.42	235°C

3.1. Spectral data of some of the synthesized compounds:

3.1.1. 2-(3-(4-hydroxybenzamido phenyl) -4-oxo-2-phenylthiazolidine-5-yl)acetic acid (Ia)

IR (cm^{-1}, KBr):1552 (N-H bending, CONH), 1616 (C=O Thiazolidine ring), 667 (C-S-C Thiazolidine ring), 1431 (R-COOH), 3225 (Ar-OH); **^{1}H NMR:** (DMSO, 400MHz) (δ ppm)**:** 3.2(2H), 2.3 (1H), 6.6 (1H), 7.3 (2H), 7.6 (2H), 7.7 (2H), 7.9 (2H), 7.9 (2H,s), 8.3 (1H), 11.9 (1H); **Mass (m/z):**372.40.

3.1.2. 2-(3-(4-hydroxybenzamido)-2-(3-nitrophenyl) -4 oxo-thiazolidine-5-yl)-acetic acid (Ib)

IR (cm^{-1},KBr):1568(N-H bending, CONH), 1645 (C=O Thiazolidine ring), 1535(C-NO_2), 644(C-S-CThiazolidine ring), 1490 (R-COOH), 1365(-NO_2), 3354 (Ar-OH); **^{1}H NMR:** (DMSO, 400MHz) (δ ppm)**:** 2.04 (3H), 6.4 (1H), 7.5 (2H), 7.7 (2H), 7.9 (2H), 7.8 (1H), 8.2 (2H), 8.5 (1H), 11.2 (1H); **Mass (m/z):**417.39.

3.1.3. 2-(3-(4-hydroxybenzamido)-2-(3-chloro phenyl)-4-oxo-thiazolidine-5-yl)-acetic acid (Ic)

IR (cm^{-1}, KBr): 1541 (N-H bending, CONH), 1643 (C=O Thiazolidine ring), 731 (C-S-CThiazolidine ring), 1449 (R-COOH), 843 (C-Cl), 3319 (Ar-OH); **^{1}H NMR** (DMSO, 400MHz) (δ ppm)**:** 3.5 (3H), 6.6 (1H), 7.6 (2H), 7.7 (2H), 7.8 (2H), 7.9 (1H,d), 8.2 (2H) 8.5(1H),11.5 (1H); **Mass (m/z):**406.84.

3.1.4. 2-(3-(4-hydroxybenzamido)-2-(4-hydroxy phenyl)-4-oxothiazolidin-5-yl)-acetic acid (Id)

IR (cm^{-1}, KBr):1510 (N-H bending, CONH), 1647 (C=O Thiazolidine ring), 627 (C-S-C Thiazolidine ring), 1452 (R –COOH), 3238 (Ar-OH); **^{1}H NMR:** (DMSO, 400MHz) (δ ppm)**:** 3.2 (3H), 6.6 (1H), 7.5(2H), 7.7 (1H), 7.8 (2H), 7.9 (3H), 8.2 (2H) 8.39 (1H), 11.6 (1H); **Mass (m/z):**388.39.

3.1.5. 2-(3-(4-hydroxybenzamido)-2-(2-hydroxy phenyl)-4-oxothiazolidin-5-yl)-acetic acid (Ie)

IR (cm^{-1},KBr): 1568 (N-H bending, CONH), 1625 (C=O Thiazolidine ring), 629 (C-S-CThiazolidine ring), 1400 (R-COOH), 3049 (Ar-OH)**; ^{1}H NMR):** 3.2 (3H), 6.6 (1H), 7.5 (2H), 7.7 (1H), 7.8 (2H), 7.9 (3H), 8.2 (2H) 8.39 (1H),11.6 (1H)**; Mass (m/z):** 388.39

3.1.6. 2-(3-(4-hydroxybenzamido)-2-(4-methoxy phenyl)-4-oxothiazolidin-5-yl)acetic acid (If)

IR (cm^{-1}, KBr): 1564 (N-H bending, CONH), 1712 (C=O Thiazolidine ring), 760 (C-S-CThiazolidine ring), 1415 (R-COOH), 3057 (Ar-OH); **^{1}H NMR:** (DMSO, 400MHz) (δ ppm)**:** 2.4 (3H), 6.5 (1H), 6.97 (2H), 7.2 (1H), 7.4 (2H), 7.6 (3H), 8.1(2H), 8.2 (2H) 8.5 (1H),11.5 (1H); **Mass (m/z):**402.42.

3.1.7. 2-(3-(4-hydroxybenzamido)-2-cinnamyl-4-oxo thiazolidin-5-yl)-acetic acid (Ig)

IR (cm^{-1}, KBr): 1535 (N-H bending, CONH), 1638 (C=O Thiazolidine ring), 692 (C-S-C Thiazolidine ring), 1448 (R-COOH),1625(C=C Stretching), 3022(CH-Ar),1236 (Ar-OH); **^{1}H NMR:** (DMSO, 400MHz) (δ ppm)**:** 3.5(3H), 6.8 (1H), 7.0 (2H), 7.6 (2H), 7.7 (3H), 7.3 (2H), 8.2 (1H), 11.5 (1H); **Mass (m/z):412.11**

3.1.8. 2-(3-(4-hydroxybenzamido)-2-(4-dimethyl aminophenyl)-4-oxothiazolidin-5-yl)-acetic acid (Ih)

IR (cm^{-1}, KBr): 1535 (N-H bending, CONH), 1653 (C=O Thiazolidine ring), 642 (C-S-CThiazolidine ring), 1440 (R-COOH), 2806 (N-CH_3), 3271 (Ar-OH); **^{1}H NMR:** (DMSO, 400MHz) (δ ppm)**:** 3.3 (6H), 6.5 (1H), 6.7 (2H), 7.7 (3H), 7.9 (3H), 8.1(2H), 8.2 (2H) 8.5 (1H),11.5 (1H); **Mass (m/z):**415.46

3.1.9. 2-(3-(4-hydroxybenzamido)-2-(3,4-dimethoxy phenyl)-4-oxothiazolidin-5-yl)-acetic acid (Ii)

IR (cm^{-1}, KBr): 1553 (N-H bending, CONH), 1601 (C=OThiazolidine ring), 685 (C-S-C Thiazolidine ring), 2806(-OCH_3)' **^{1}H NMR:** (DMSO, 400MHz) (δ ppm)**:** 3.8(6H, s), 10.4(1H, s), 8.3(1H, s), 6.8(1H, s), 2.04(2H, t), 3.08(1H, d), 6.8 (1H), 7.0 (2H), 7.3 (2H), 7.8 (2H),,11.6(1H, s), **Mass (m/z):**432.

3.1.10. 2-(3-(4-hydroxybenzamido)-2-(2-chloro phenyl)-4-oxothiazolidin-5-yl)acetic acid (Ij)

IR (cm^{-1}, KBr): 1547(N-H bending, CONH), 1643 (C=O Thiazolidine ring), 655(C-S-C Thiazolidine ring), 1440 (R -COOH), 1356 (-NO_2), 3237 (Ar-OH), 758(C-Cl); **^{1}HNMR:** (DMSO, 400MHz (δppm)**:** 2.5 (2H), 3.4 (1H), 6.6 (1H), 7.2 (2H), 7.4 (2H), 7.892 H), 7.9 (2H), 8.1 (1H), 10.4 (1H), 11.5 (1H,); **Mass (m/z):**465.

3.1.11. 2-(3-(4-hydroxybenzamido)-2-(2-nitro phenyl) -4 oxo-thiazolidine-5-yl)-acetic acid (Ik)

IR (cm^{-1}, KBr): 1547 (N-H bending, CONH), 1643 (C=O Thiazolidine ring), 1356 (C-NO_2), 691(C-S-C Thiazolidine ring), 1487 (R-COOH), 1246(Ar-OH); **^{1}H NMR:** (DMSO, 400MHz) (δ ppm)**:** 2.3. (2H), 3.5 (1H),

6.5 (1H), 7.1 (2H), 7.5 (2H), 7.7 (2H), 7.8 (2H), 8.2 (1H), 10.3 (1H), 11.4(1H,); **Mass (m/z):**417.39

3.1.12. 2-(3-(4-hydroxybenzamido)-2-(3 metho--xy, 4-hydroxy phenyl) -4 oxo-thiazolidine- 5-yl)-acetic acid (Il)

IR (cm^{-1}, KBr): 1540(N-H bending, CONH), 1648 (C=O Thiazolidine ring), 690 (C-S-CThiazolidine ring), 1442 (R-COOH), 2845(-OCH_3)**;** ^{1}**H NMR:** (DMSO, 400MHz) (δ ppm)**:** 3.2 (3H), 6.5 (1H), 7.4 (2H), 7.5 (2H), 7.8 (3H), 7.9 (2H), 8.2 (2H), 10.2 (2H), 11.2 (1H,s)**; Mass (m/z):**418.42.

All the synthesized compounds were screened for antibacterial and antifungal activities by broth dilution method. From the study of the biological activity data in reference to Standard drug Ampicillin and Amphotericin B. It was found that compound, **Ij** and **Ii** exhibited moderate activity against *B.Cereus.*

Compounds **Ie and Ih**, exhibited moderate activity against *P.Seudomonas*.

Compounds **Id** and **Ik** exhibited moderate activity against *E.coli*.

Compounds **Ia**, **Ib**, **Id**, **Ie**, and **Ik** exhibited moderate activity against *A. niger*.

Table 2.Biological activities in the terms of the MIC of synthesized Compounds

Sr. No.	Compound Id	Anti-bacterial Activity				Anti-fungal activity
		Minimum inhibitory concentration (MIC) (µg/ml)				Minimum inhibitory concentration (MIC) (µg/ml)
		Gram Positives bacteria		Gram Negative bacteria		Fungus
		B. Cereus MTCC 430	*S. aureus* MTCC 737	*E. coli* MTCC 1687	*Pseudomonas* MTCC 1688	*Aspergillus-niger* ATCC 16404
1	Ia	256	256	512	256	128
2	Ib	256	128	256	512	256
3	Ic	512	64	1024	256	128
4	Id	128	128	64	1024	256
5	Ie	1024	256	256	128	256
6	If	512	128	1024	256	>1024
7	Ig	256	512	256	256	64
8	Ih	128	256	512	128	512
9	Ii	32	128	1024	256	>1024
10	Ij	64	1024	512	1024	64
11	Ik	512	512	64	512	512
12	Il	128	1024	128	256	512
	Ampicillin	10.0	12	2.0	8.0	-
	Amphotericin B	-	-	-	-	0.05

S.aureus:*Staphylococcus aureus, E. coli:Escherichia coli, Pseudomonas*:*Pseudomonas aeruginosa*

4. CONCLUSION

From the present study it was observed that thiazolidinone moiety can be considered as promising pharmacophore for better antibacterial activities. It was found that varying the substitution in the final structure affect the biological activities. Final compounds with chloro, hydroxy, nitro and methoxy were found to posses moderate antibacterial activity and some of the compounds e.g. **Ic**,**Ie** and **Ik ,Il** showed moderate activity against *Aspergillius niger.*

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