Synthesis, characterization and antimicrobial efficacy of some novel thiazolidinone-1,3,5-triazine derivatives

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Abstract: The newly synthesised series of Thiazolidinone 1,3,5 triazine by reacting differently substituted aldehydes with triazine to produce Schiff base. Further when reacted with thioglycolic acid to give corresponding Thiazolidinone subsidiaries. These newly synthesised compounds were confirmed by spectroscopy techniques like NMR. After the confirmation of these compounds they were subjected for their anti-microbial activity using disc diffusing method and Mueller Hinton Agar.

Keywords: 1,3,5-triazine derivatives, Schiff base, Thiazolidinone derivative, Anti-microbial activity, Disc Diffusing Method, Mueller Hinton Agar, NMR Characterization.

1. Introduction:

Heterocyclic compounds with various substituents are proved to be therapeutic agents [1]. Specifically 1,3,5 triazine and its analogues are well known for their antimicrobial effects and an important class for the study against the biological terrors such as microbes.[2], [3].

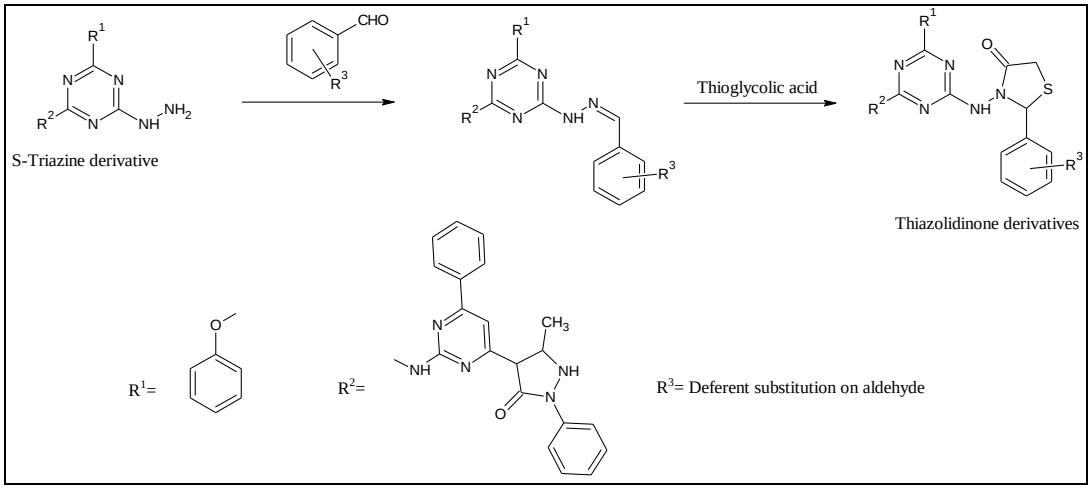
Moreover, the Thiazolidinone itself considered to be broad spectrum biologically active component [4], [5], [6]. Thiazolidinone derivative have potential to work as antifungal [7] as well as antibacterial [8]. According to some of the literatures they considered to be anticonvulsant also [9], [10].

Today's world is more prone to micro pathogens and these pathogens are developing resistance to presently available antimicrobial drugs [11], [12], [13]. Thus considering all the aspects, the heterocyclic component inspired the researchers to synthesis such derivatives and evaluate their medicinal properties [14], [15], [16], [17], [18], [19].

In the present invention we have synthesis Thiazolidinone derivatives of S-triazine by first reacting differently substituted aldehyde with corresponding triazine to give Schiff base. These Schiff base further reacted with thioglycolic acid in presence of zinc chloride to give corresponding Thiazolidinone derivatives. All these compounds then characterised by spectroscopy techniques as shown in Table-1. After the confirmation of these new moieties they were subjected for their anti- microbial studies.

Using Mueller Hinton Agar disc-diffusion method these compounds were screened for their anti-bacterial as well as anti-fungal properties [20]. The antimicrobial activity was done on both the stains i.e. Gram positive and gram negative bacteria/ fungi considering standards Norfloxacin and Amphotericin-B respectively. The results obtained as shown in Table-2 were in favour to the subject of study.

2. Research Design:



3. Experimental work:

3.1 Sep-I: Synthesis of Schiff base derivatives

Tri-substituted S-triazine derivative was synthesized and reacted with different substituted Aldehydes in denatured alcohol. The mixture was stirred at room temperature which resulted in Schiff base formation. The product was filtered off and washed with hot water and purified in ethyl alcohol.

3.2 Step-II: Synthesis of Thiazolidinone derivative

The Schiff base which obtained from step-I was then reacted with thioglycolic acid in equimolar ratio in required volume of methanol in presence of ZnCl2. The method was performed in 2-steps:

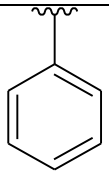
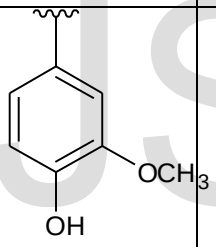
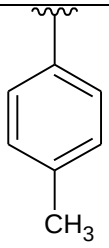
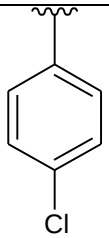
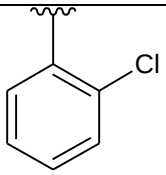
(1) The above reaction mix was stirred at RT for 2-3 hours and

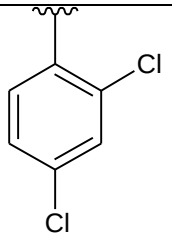
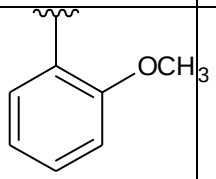
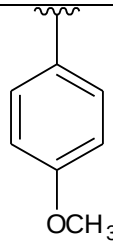
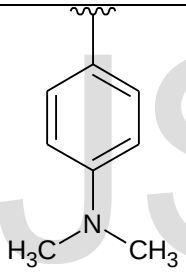
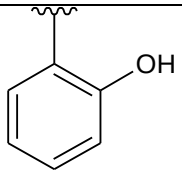
(2) Then in water bath for RT 3-4 hours.

The resulting product Thiazolidinone was recrystallized using denatured alcohol.

Final compounds shown in Table-1

TABLE-1: SHOWS DIFFERENT DERIVATIVES OF S-TRIAZINE THIAZOLIDINONE

No	Substitution	Structure	M.F	C %	H %	O %	N %	Cl %	S %
a	-H		$C_{38}H_{32}N_{10}O_3S$	64.39	4.55	6.77	19.67	-	4.52
b	-3-OCH_3-4-OH		$C_{39}H_{34}N_{10}O_5S$	62.06	4.54	10.60	18.56	-	4.25
c	-4-CH_3		$C_{39}H_{34}N_{10}O_3S$	64.8	4.74	6.64	19.38	-	4.44
d	-4-Cl		$C_{38}H_{31}ClN_{10}O_3S$	61.41	4.20	6.46	18.85	4.77	4.31
e	-2-Cl		$C_{38}H_{31}ClN_{10}O_3S$	61.41	4.20	6.46	18.85	4.77	4.31

f	-2-Cl-4-Cl		$C_{38}H_{30}Cl_2N_{10}O_3S$	58.69	3.89	6.17	18.01	9.12	4.12
g	-2-OCH_3		$C_{39}H_{34}N_{10}O_4S$	63.40	4.64	8.66	18.96	-	4.34
h	-4-OCH_3		$C_{39}H_{34}N_{10}O_4S$	63.40	4.64	8.66	18.96	-	4.34
i	-4-$N(CH_3)_2$		$C_{40}H_{37}N_{11}O_3S$	63.90	4.96	6.38	20.49	-	4.26
j	-2-OH		$C_{38}H_{32}N_{10}O_4S$	62.97	4.45	8.83	19.33	-	4.42

4. Antimicrobial Activity:

Compounds (a-j) Shown in Table-1 were screened for their antimicrobial activity using Mueller Hinton Agar (MHA) and disc diffusion method. The compounds were dissolved in DMSO for the preparation of stock solution. 20mg/100ml concentration was used as stock solution for each compound. The disc diffusion technique used to check the inhibition of the growth of the microbes at minimum inhibitory concentration (MIC). The medium used for the growth of microbes was Mueller Hinton Agar. The zone of inhibition measured in mm. The bacteria used as inoculum on agar plate petri dish were Staphylococcus aureus MTCC-96 a gram positive bacteria and Escherichia coli MTCC-442 a gram negative bacteria. Similarly fungi used were Aspergillus flavus MTCC-9390 a gram-positive fungus and Aspergillus niger MTCC-282 a gram-negative fungus.

The bacterial growth and zone of inhibition was compared with the standard such as Norfloxacin and Amphotericin-B for bacteria and fungi respectively.

The obtained results are shown in Table-2.

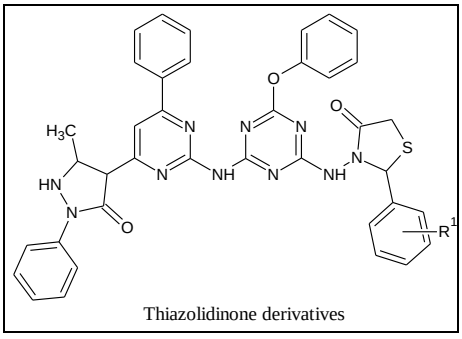
TABLE-2: SHOWING BACTERICIDAL AND FUNGICIDAL EFFECTS OF COMPOUND SYNTHESIZED (A-J)

Thiazolidinone as per table no.-1	**Antibacterial activity** Zone of Inhibition (mm)		**Antifungal activity** Zone of Inhibition (mm)	
	Staphylococcus aureus MTCC-96	*Escherichia coli MTCC-442*	*Aspergillusflavus MTCC-9390*	*Aspergillus niger MTCC-282*
a	11.0	10.6	-	-
b	2.8	3.6	9.3	9.2
c	1.6	1.2	7.1	6.3
d	9.3	8.1	9.8	9.1
e	4.6	3.3	1.2	3.2
f	8.9	9.0	6.9	3.9
g	6.3	5.2	5.6	5.1
h	2.1	2.3	-	-
i	4.5	3.9	9.8	11.2
j	6.3	6.2	2.7	2.6
Amphotericin-B	-	-	12.9	16.6
Norfloxacin	18.0	15.0	-	-

No zone of inhibition shown by dash

5. Characterization data:

NMR Data of the synthesized compounds:



Thiazolidinone derivatives

a) R1= Hydrogen : 1H NMR (400 MHz) : δ 7.333 (2H, dd), 7.375 (1H, t), 7.297 (1H, s), 7.192 (2H, dd), 3.603 (1 H, q), 3.754 (1H, d), 3.549 (1H, d), 7.606 (2H, dd), 7.227 (2H, dd), 7.445 (2H, dd), 7.282 (1H, t), 7.484 (2H, dd), 7.343 (1H, tt), 7.380 (2H, dd), 4.885 (1H, d), 6.236 (1H, s), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd).

b) R1= 3-OCH3-4-OH : 1H NMR (400 MHz) : δ 7.333 (2H, dd), 7.375 (1H, t), 7.297 (1H, s), 7.192 (2H, dd), 6.967 (1H, dd), 6.673 (1H, dd), 3.794 (3H, s), 3.603 (1H, q), 3.740 (1H, d), 3.550 (1H,

d), 7.606 (2H, dd), 7.227 (2H, dd), 7.445 (2H, dd), 7.282 (1H, t), 6.865 (1H, dd), 4.884 (1H, d), 6.152 (1H, s), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd).

c) R1= 4-CH3 : 1H NMR (400 MHz) : δ 7.333 (2H, dd), 7.375 (1H, t), 7.297 (1H, s), 7.192 (2H, dd), 3.603 (1H, q), 2.266 (3H, s), 7.222 (2H, dd), 3.739 (1H, d), 3.550 (1H, d), 7.606 (2H, dd), 7.176 (2H, dd), 7.227 (2H, dd), 7.445 (2H, dd), 7.282 (1H, t), 4.885 (1H, d), 6.232 (1H, s), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd).

d) R1= 4-Cl : 1H NMR (400 MHz) : δ 7.333 (2H, dd), 7.375 (1H, t), 7.297 (1H, s), 7.192 (2H, dd), 3.603 (1H, q), 7.549 (2H, dd), 3.740 (1H, d), 3.550 (1H, d), 7.606 (2H, dd), 7.565 (2H, dd), 7.227 (2H, dd), 7.445 (2H, dd), 7.282 (1H, t), 4.884 (1H, d), 6.216 (1H, s), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd).

e) R1= 2-Cl : 1H NMR (400 MHz) : δ 7.333 (2H, dd), 7.375 (1H, t), 7.297 (1H, s), 7.192 (2H, dd), 3.603 (1H, q), 7.258 (1H, dd), 7.553 91H, dd), 7.273 (1H, dd), 7.640 (1H, dd), 3.761 (1H, d), 3.554 (1H, d), 7.606 (2H, dd), 7.227 (2H, dd), 7.445 (2H, dd), 7.282 (1H, t), 4.884 (1H, d), 6.213 (1H, s), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd).

f) R1= 2-Cl-4-Cl : 1H NMR (400 MHz) : δ 7.333 (2H, dd), 7.375 (1H, t), 7.297 (1H, s), 7.192 (2H, dd), 3.603 (1H, q), 7.569 (1H, dd), 3.764 (1H, d), 3.556 (1H, d), 7.606 (2H, dd), 7.227 (2H, dd), 7.445 (2H, dd), 7.282 (1H, t), 4.884 (1H, d), 6.191 (1H, s), 1.131 (3H, d), 7.221 (1H, dd), 7.186 (1H, dd), 7.319 (1H, t), 7.836 (2H, dd).

g) R1= 2-OCH3: 1H NMR (400 MHz) : δ 7.333 (2H, dd), 7.375 (1H, t), 7.297 (1H, s), 7.192 (2H, dd), 3.603 (1H, q), 7.006 (1H, dd), 7.376 (1H, dd), 3.758 (1H, d), 3.551 (1H, d), 7.606 (2H, dd), 7.227 (2H, dd), 7.445 (2H, dd), 7.282 (1H, t), 4.884 (1H, d), 6.083 (1H, s), 1.131 (3H, d), 6.902 (1H, dd), 3.799 (3H, s), 7.231 (1H, dd), 7.319 (1H, t), 7.836 (2H, dd).

h) R1= 4-OCH3 : 1H NMR (400 MHz): δ 7.333 (2H, dd), 7.375 (1H, t), 7.297 (1H, s), 7.192 (2H, dd), 3.603 (1H, q), 3.738 (1H, d), 3.550 (1H, d), 7.606 (2H, dd), 7.308 (2H, dd), 7.227 (2H, dd)7.445 (2H, dd), 7.282 (1H, t), 4.885 (1H, d), 6.035 (1H, s), 1.131 (3H, d), 6.953 (2H, dd), 3.759 (3H, s), 7.319 (1H, t), 7.836 (2H, dd).

i) R1= 4-N(CH3)2: 1H NMR (400 MHz): δ 7.333 (2H, dd), 7.375 (1H, t), 6.660 (2H, dd), 7.297 (1H, s), 7.192 (2H, dd), 2.746 (6H, s), 3.603 (1H, q), 3.740 (1H, d), 3.550 (1H, d), 7.606 (2H, dd), 7.250 (2H, dd), 7.227 (2H, d), 7.445 (2H, dd), 7.282 (1H, t), 4.884 (1H, d), 5.998 (1H, s), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, dd).

j) R1= 2-OH : 1H NMR (400 MHz): δ 7.333 (2H, dd), 7.375 (1H, t), 7.297 (1H, s), 7.192 (2H, dd), 3.603 (1H, q), 6.968 (1H, dd), 6.691 (1H, dd), 7.247 (1H, dd), 7.727 (1H, dd), 3.740 (1H, d), 3.550 (1H, d), 7.606 (2H, dd), 7.227 (2H, dd), 7.445 (2H, dd), 7.282 (1H, t), 4.884 (1H, d), 6.050 (1H, s), 1.131 (3H, d), 7.319 (1H, t), 7.836 (2H, d).

6. Acknowledgment:

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8. Conclusion:

The compound synthesised above (a-j) confirmed by spectroscopy instruments (NMR). These compound (a-j) showed potential bactericidal as well as fungicidal effects as per accumulated data depicted in table-2. Thus the invention favoured that the Thiazolidinone derivatives of 1,3,5 triazine/s-triazine could be next series of drugs that considered to be antimicrobial drugs.

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