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Synthesis, Characterization and Biological Evaluation of Substituted Thiazolidin-4-Ones as Antimicrobial Agents

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Abstract: **A new series of substituted thiazolidin-4-ones were synthesized and evaluated for antimicrobial activity by means of zone of inhibition by cup plate method. The structures of these compounds were established by means by IR, H NMR analysis. All the compounds were evaluated for their antibacterial activity against gram positive and gram negative species and antifungal activity .Compounds TH09 & TH17 were found most active due to presence of electron withdrawing groups at appropriate position.**

Keywords: **Antibacterial, antifungal, Thiazolidin-4-ones.**

1. INTRODUCTION

There are number of five membered hetrocycles containing nitrogen and sulphur atom, have turned out to be potential chemotherapeutics and pharmaco therapeutics agents.[1,2] The development of antibacterial agents has been a very important step for research, most of the research programme efforts are directed toward the design of new drugs, because of the unsatisfactory status of present drugs side effects and the acquisition of resistance by the infecting organism to present drugs.[3] The massive use of antibacterial drugs by mankind leads to a major problem i.e. drug resistance.[4] A potential approach to overcome the resistance problem may be represented by the design of innovative agents having a different mechanism of action, so that it can't occur any cross-resistance with the therapeutic agents in use.[5] In spite of a large number of antibiotics and chemotherapeutics available today, due to the widespread and excess use of antibiotics, bacterial resistance has become a serious public health problem, always demanding new classes of antibacterial agents. The development of new potential drugs, will be one of the possible solutions to treat various infectious diseases with multi drug treatment and will be devoid of side effect and resistance profile of currently available drugs6.Thiazolidin-4-ones have attracted a great deal of interest owing to their antimicrobial7, anti-inflammatory8-9,CNS depresent10, antitubercular11, antitumor12, anthelmintic13, sedative14, antiretroviral properties15 and antineoplastic16 activity.

Experiment:

Melting points were recorded on a cintexm .p. Apparatus, in open capillaries and are uncorrected .I .R. spectra recorded in KBr on Thermo scientific, Nicolet-155.H1-NMR spectra on JNM-ECS400 300MHz spectrophotometer using TMS as internal standard(chemical shift in – ppm)

General Procedure for synthesis of Substituted thiazolidin-4-ones:

Step1-prepration of ethyl-4-aryl-benzoate (2):

To the substituted benzoic acids in absolute ethanol add 1 ml H2SO4 dropwise and refluxed for 3.5 hrs. The solvent was evaporated on water bath and the precipitate washed with cooled water and recrystallized with ethanol.

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Step2-prepration of aryl substituted benzohydrazide(3):

To the equimolar quantities of (2) and hydrazine-hydrate in ethanol refluxed for 3hrsThe solvent was evaporated on water bath and the precipitate washed with cooled water and recrystallized with ethanol.

Step3-prepration of aryl-N-substituted phenyl-methylidene-benzohydrazide (4):

To the equimolar quantities of(3) and aromatic substituted benzaldehyde in methanol refluxed for 3hrs.The solvent was evaporated on water bath and the precipitate washed with diethyl ether and recrystallized with ethanol.

Step4-prepration of aryl-N[2-(substituted phenyl)-4-oxo-1,3-thiazolidin-3-yl]-benzamide(5):

To I mol of (4) add 0.9 mol of thioglycollic acid in DMF with a pinch of ZnCl2 refluxed for 6 hrs .The product so formed cooled& poured on crushed ice. The solid product filtered, washed & recrystallized from ethanol.

2. SCHEME

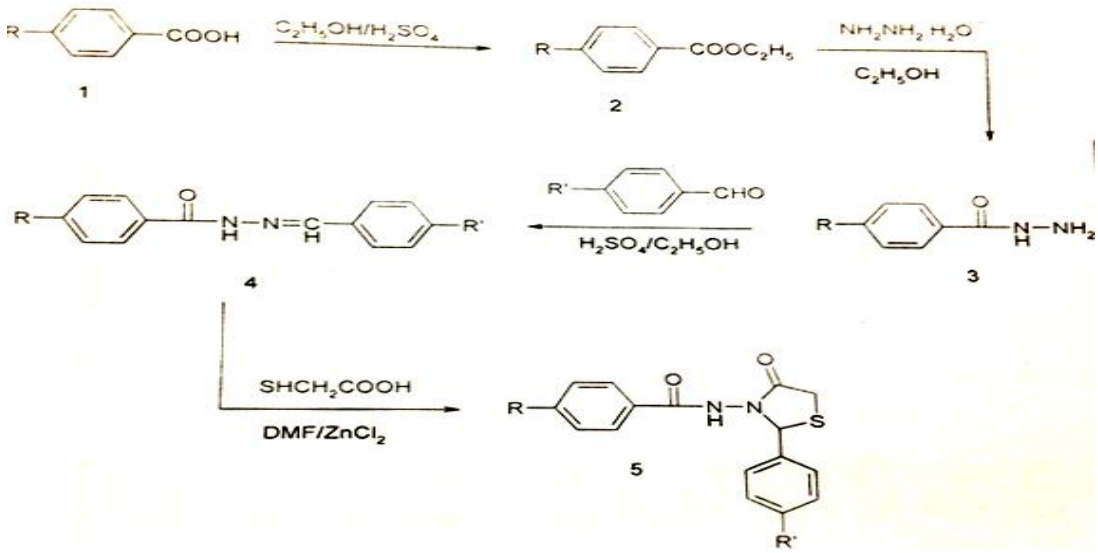

Table-I: Physicochemical characteristics of synthesized substituted thiazolidin-4-ones derivatives

Compound	-R	-R`	MOLECULAR FORMULA	MOLECULAR WEIGHT	M.P. (C`)	Rf	% yield
TH01	-H	-H	C16H14N2O2 S	298.37	136-138	0.56	54
TH02	-H	-NO2	C16H14N3O4S	343.36	133-135	0.54	45
TH03	-H	-Cl	C16H13N2O2SCl	332.81	141-143	0.70	51
TH04	-H	-OH	C16H14N2O3S	314.37	138-140	0.53	60
TH05	-OH	-H	C16H14N2O3 S	314.37	1142-143	0.65	65
TH06	-OH	-NO2	C16H14N3O4S	359.36	133-135	0.68	70
TH07	-OH	-Cl	C16H13ClN2O2 S	348.81	134-136	0.72	45
TH08	-OH	-OH	C16H14N2O4S	330.36	131-133	0.49	60
TH09	-Cl	-H	C16H12ClN2O2 S	332.81	140-142	0.39	60
TH10	-Cl	-NO2	C16H12ClN3O4 S	377.81	132-134	0.59	45
TH11	-Cl	-Cl	C16H12ClN2O2 S	367.26	136-138	0.56	85
TH12	-Cl	-OH	C16H13ClN2O3 S	348.81	140-142	0.72	65
TH13	-NH2	-H	C16H15N3O2S	313.38	132-134	0.66	45
TH14	-NH2	-NO2	C16H14N4O4S	358.38	131-133	0.47	45
TH15	-NH2	-Cl	C16H14ClN3O2 S	347.38	134-135	0.65	70
TH16	-NH2	-OH	C16H15N3O3 S	329.38	132-134	0.58	55
TH17	-NO2	-H	C16H13N3O4 S	343.36	131-133	0.52	60
TH18	-NO2	-NO2	C16H12N4O6 S	388.36	138-140	0.62	75
TH19	-NO2	-Cl	C16H12ClN3O4 S	377.81	138-140	0.35	75
TH20	-NO2	-OH	C16H13N3O5 S	359.36	139-140	0.56	55

Spectral data of **substitutedsynthesized 1,3-thiazolidin-4-ones**

TH02-IR(KBr):1684(C=O str.,ketonic),3058(C-H str.,aromatic),3147(N-H str.),768(C-S str.,aromatic),1520(N=O str.,aromatic) and 1245 (C-N str.)

H-NMR:2.64(s,2H,-S-CH2),7.86-6.52 (m,5H,ArH),1.91(s,1H,-CHN-),4.74(s,1H,-CONH-),6.84-6.82(d,2H,ArH);6.54-6.52(d,2H,ArH).

TH07-IR(KBr):1665(C=O str.,ketonic),2874(C-H str.,aromatic),3138(O-H str.),2973(N-H str.),759,837(C-Sstr.,aromatic) and 1125 (C-N str.).

H-NMR:8.09(s, 1H,OH),2.85(s,2H,-S-CH2),1.25(s,1H,-CHN-),4.38(s,1H,-CONH-),8.094-8.089(d,2H,ArH);7.585-7.582(d,2H,ArH),7.581-7.447(d,2H,ArH);7.427-7.408(d,H,ArH).

TH09-IR(KBr):1685(C=O str.,ketonic),2873(C-H str.,aromatic),3412(O-H str.),3284(N-H str.),886(C-S str.,aromatic),510(C-1 str., aromatic).

H-NMR:2.503(s,2H,-S-CH2),,1.18(s,1H,-CHN-),3.165(s,1H,-CONH-),6.98-6.94(m,5H,ArH);8.18-8.07(d,2H,ArH),7.64-763(d,2H,ArH).

TH10-IR(KBr):1673(C=O str.,ketonic),2994(C-H str.,aromatic),3285(N-H str.),524(Clstr.,aromatic),745 (C-S str. Aromatic), 1168 (C-N str.)and 542 (N=O str. Aromatic).

H-NMR:3.36(s,2H,-S-CH2),1.27(s,1H,-CHN-),2.5(s,1H,-CONH-),8.24-8.08(d,2H,ArH);8.02-7.84(d,2H,ArH),7.45-7.43(d,2H,ArH);6.84-6.82(d,H,ArH).

TH13-IR(KBr):1745(C=O str.,ketonic),2953(C-H str.,aromatic),3137(N-H str.)

,734 (C-S str. Aromatic), 1087 (C-N str.).

H-NMR:3.808(s,2H,-S-CH2),1.103(s,1H,-CHN-),2.5(s,1H,-CONH-),5.624(m,5H,ArH);7.89-7.87(d,2H,ArH),7.00-6.91(d,2H,ArH).

TH15-IR(KBr):1783(C=O str.,ketonic),3084(C-H str.,aromatic),3515(N-H str.),735 (C-S str. Aromatic), 1268 (C-N str.)and 514 (Cl str.).

H-NMR:1.137(s,2H,-S-CH2),0.75(s,1H,-CHN-),3.016(s,1H,-CONH-),3.845(s,2H,-NH2-)7.745-7.722(d,2H,ArH);7.488-7.411(d,2H,ArH),6.928-6.904(d,2H,ArH);6.84-6.85(d,H,ArH).

TH16-IR(KBr):1725(C=O str.,ketonic),3168(C-H str.,aromatic),3478(O-H str.),2927(N-H str.),794(C-S str.,aromatic).

H-NMR:2.385(s,2H,-S-CH2),,1.258(s,1H,-CHN-),4.225(s,1H,-CONH-),3.363(s,2H,NH2-),8.394-8.380(m,5H,ArH),7.2(s,1H,OH),6.917-6.874(d,2H,ArH),7.670-7.650(d,2H,ArH).

TH17-IR(KBr):1759(C=O str.,ketonic),3065(C-H str.,aromatic),1365(N=O str.),3476(N-H str.),748(C-S str.,aromatic),1048(C-N str.) .

H-NMR:2.5(s,2H,-S-CH2),,1.194(s,1H,-CHN-),3.478(s,1H,-CONH-),7.763-7.742(d,2H,ArH),7.29-7.20(d,2H,ArH),6.938-6.917(d,2H,ArH),6.755-6.734(d,2H,ArH).

TH19-IR(KBr):1835(C=O str.,ketonic),1246(C-Nstr.)3154(C-H str.,aromatic),1586(N=O str.),3438(N-H str.),826(C-S str.,aromatic),694(Cl) .

H-NMR:2.5(s,2H,-S-CH2),2.3(s,1H,-CHN-),3.35(s,1H,-CONH-),8.18-8.02(d,2H,ArH),7.64-7.63(d,2H,ArH),7.13-7.11(d,2H,ArH),6.98-6.96(d,2H,ArH).

TH20-IR(KBr):1726(C=O str.,ketonic),1175(C-Nstr.)3154(C-H str.,aromatic),1586(N=O str.),3495(N-H str.),826(C-S str.,aromatic),3152(OH str.) .

H-NMR:2.5(s,2H,-S-CH2),1.3(s,1H,-CHN-),3.91(s,1H,-CONH-),7.514(s,1H,OH),8.29-8.16(d,2H,ArH),8.141-7.951(d,2H,ArH),7.636-7.635(d,2H,ArH),7.494-7.475(d,2H,ArH).

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3. ANTIMICROBIAL ACTIVITY

For bacterial growth nutrient agar media was used having composition beef extract, 3g; bacteriological peptones, 5g; agar, 20g, the pH was adjusted to 6.2 + 0.2 at 25 (+2) °C and for fungal growth malt extract agar (MEA) was used composed of malt extract, 20 g; bacteriological peptone, 5g; agar, 20g, the pH was adjusted to 5.4 + 0.2 at 25 (+2) °C. Media was prepared by dissolving the all ingredients in 1L distilled water and heated upto 60-70°C and was sterilized in an autoclave at 121°C for 15-20 mins. Against the several species the antibacterial and antifungal activity was expressed by the measurement of zone of inhibition by diffusion agar method. At equal distance four holes were made in the sterile agar plates with the help of sterile cork borer in both media i.e. in nutrient agar and in malt extract agar. The synthesized compounds were dissolved in DMSO and 100µg/ml concentration of each compound were filled in the holes. Controlled holes were filled with DMSO solvent. For bacterial isolates plates were placed in a BOD at 37°C ± 2°C and on the other hand fungal isolates were incubated at 28°C ± 2°C for 24-48 hrs. Zone of inhibition created by active compounds were measured after 24-48 hrs. Ciprofloxacin was used as standard antibacterial agent while Miconazole was used as a standard antifungal agent.

Table II: In –vitro antimicrobial activity of novel 1,3-thiazolidin-4-ones against bacterial and fungal strains.

Compound	**Concentration (µg/ml)**	**Zone of inhibition (mm)**					
		Gram positive		**Gram negative**		**Fungal strain**	
		B. subtilis (MTCC 96)	*S. aureus* (MTCC 121)	*P. aeruginosa* (MTCC 2453)	*E. coli* (MTCC 40)	*C. albicans* (MTCC 8184)	*A. niger* (MTCC 8189)
TH01	100	25	21	13	29	30	30
TH02	100	28	17	11	27	27	28
TH03	100	27	16	10	26	25	27
TH04	100	22	15	11	24	22	24
TH05	100	26	24	14	21	24	27
TH06	100	30	23	12	17	24	24
TH07	100	28	19	11	16	22	22
TH08	100	25	16	10	15	20	20
TH09	100	22	29	16	29	30	30
TH10	100	25	27	13	28	29	29
TH11	100	23	25	12	26	28	26
TH12	100	20	23	11	25	25	26
TH13	100	24	28	14	23	28	29
TH14	100	29	15	12	21	26	27
TH15	100	28	14	11	19	23	25
TH16	100	24	12	10	17	20	21
TH17	100	20	24	15	30	21	30
TH18	100	24	21	13	29	27	27
TH19	100	22	14	10	28	26	24
TH20	100	19	17	10	23	25	23
Ciprofloxacin	50	29	28	26	27	-	-
Miconazole	50	-	-	-	-	26	28

4. RESULTS

The antimicrobial activity of the synthesized compounds were assayed using cup plate technique in the nutrient agar at 100 µg/ml concentration is shown in table 2. Ciprofloxacin standard were active at 50 µg/ml on all theGram (+ve) bacteria with a zone of inhibition for *Bacillus subtilis*, *Staphylococcus aureus*and Gram (-ve)bacteria *Pseudomonas aeruginosa*, *Escherichia coli*. From the antibacterial screening, it was concluded thatcompounds TH09 and TH17showed larger zone of inhibition as compare to standard drug Ciprofloxacin andMiconazole.

5. CONCLUSION

Results obtained from antimicrobial activity showed that compound TH09 and TH17 were highest active against Gram positive species *Staphylococcus aeuras*and Gram negative species *Pseudomonas aeruginosa,Escherichia coli.* .These both compounds have highest zone of inhibition among all the synthesized compoundsdue to appropriate presence of electron withdrawing and electron donating groups at –R and no substitution at position –R". Compounds TH08 and RH16 were substituted with electron donating groups both at –R and –R"position . This may be the reason for lowest activity of these compounds, i.e. wrong side (-R and –R') substitution by electron donating groups. So we can say that at –R position electron withdrawing and at -R' position electron donating groups are good to increase the binding of molecule with the target.

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