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Syntheses of New Thiazolidinones and Their Microbial Activity

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ABSTRACT

The acid hydrazide (I & IV) on condensation with different aromatic aldehydes yielded the substituted benzal hydrazines (IIa-e & Va-e) which on cyclization with thioglycolic acid in presence of anhydrous aluminium chloride as catalyst afforded 2-(substituted phenyl)-5-H-thiazolidin-4-ones (IIIa-e & VIa-e). The structures of the newly synthesized compounds have been confirmed by IR, ^{1}HNMR and Mass spectra. The compounds have also been screened for their biological activity.

Key words: Biological activity, Synthesis, IR, and ^{1}HNMR and Mass spectra.

INTRODUCTION

Thiazolidin-4-one derivatives are known to possess a variety of physiological properties, viz. anticonvulsant[1], sciatic nerve block[2], spiral anaesthesia[2], CNS-stimulant[3], local anaesthesia[4], analgesic[5], choleretic[5], sedative[6], antiphlogistic[7] activities and cardiovascular effects[8]. In addition they are also effective antifungal[9,10], antibacterial[11] and antihelmentic[12] agents. These observations suggested that it would be of interest to study the activity of some new thiazolidin-4-one derivatives (IIIa-e & VIa-e). A series of these compounds have been synthesized and tested for their biological activity.

EXPERIMENTAL SECTION

Melting points were taken in open capillaries and are uncorrected. IR spectra (KBr in cm^{-1}) were recorded on Jasco 410 plus FTIR spectrophotometer. ^{1}H NMR spectra were recorded on a Bruker 500 MHz NMR spectrophotometer using DMSO-d_6 as solvent and TMS as internal

standard (chemical shifts in δ ppm). Mass spectra were recorded on LC-MS Schimadzu 2010A using dimethyl sulfoxide as solvent. The elemental analysis was carried out on a Perkin Elmer CHN analyzer. The purity of the compounds was monitored by thin layer chromatography. TLC was carried out on precoated 0.2 mm silica gel $_{60}F^{254}$ plates.

Substituted benzal-(2'-naphthoxyacetylamido) hydrazines (IIa-e) :
2'-Naphthoxyacetic acid hydrazide (I, 2.49 g, 0.01 moles) was dissolved in 30 cm^3 ethanol containing few drops of glacial acetic acid. The appropriate aromatic aldehyde (0.01 mole) was added and the reaction mixture was refluxed for 3 hours, cooled and then poured into crushed ice. The solid obtained was filtered, washed with water and recrystallised from N,N-dimethylformamide to afford desire products **(IIa-e)**.

The melting points, yields and analytical data are given in Table (II)

Substituted benzal-(2',4'-dichlorophenoxy acetyl) hydrazines (Va-e):
The benzal hydrazines **(Va-e)** were obtained in a similar way as given in synthesis of benzal hydrazines (**IIa-e**).

The melting points, yields and analytical data are given in Table (II)

2-(Substituted phenyl)-3-(2'-naphthoxyacetylamido)-5H-thiazolidin- 4-ones (IIIa-e) :
The benzal hydrazine (**II** ; 0.01 mole) was refluxed with thioglycolic acid (1.40 cm^3, 0.02 mole) in presence of anhydrous aluminum chloride (0.5g) at 120°C for 10-12 hours. The reaction mixture was then cooled and triturated with 10% sodium bicarbonate solution. The product (III) obtained was filtered, washed several times with water and recrystallised from methanol to get desire compounds.

The melting points, yields and analytical data are given in Table (II).

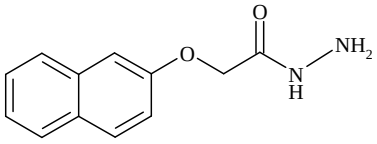
4-(Substituted phenyl)-3-(2',4'-dichlorophenoxyacetylamido)-5H-thiazolidin-4-ones (VIa-e) :
The products **(VIa-e)** were synthesized similarly as synthesis of 2-(substituted phenyl)-3-(2'-naphthoxyacetylamido)-5H-thiazolidin-4-ones **(IIIa-e)**.

The melting points, yields and analytical data are given in Table (II).

RESULTS AND DISCUSSION

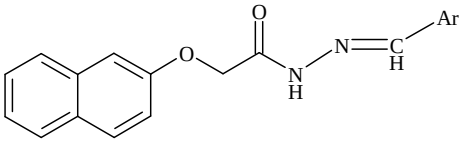
The substituted aryl acid hydrazides required were prepared from the corresponding esters of different aromatic acids by reaction with hydrazine hydrate following the reported method[13,14]. The acid hydrazides (**I & IV**) were reacted with various aromatic aldehydes to obtain benzal hydrazines (**IIa-e & Va-e**) which on cyclization with thioglycolic acid in presence of anhydrous aluminium chloride as catalyst afforded 2-(substituted phenyl)-5H-thiazolidin-4-ones **(IIIa-e & VIa-e) [SCHEMES – 1 and 2].**

SCHEME 1



(I)

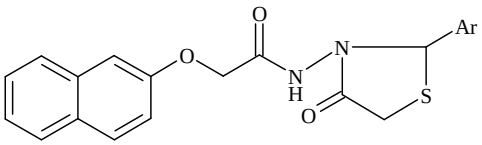
ArCHO / EtOH



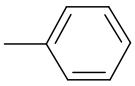
(IIa-e)

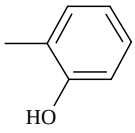
i) $HSCH_2COOH$

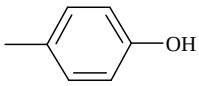
ii) Anhydrous $AlCl_3$

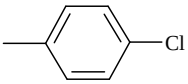


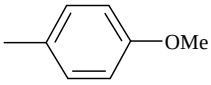
(IIIa-e)

(a) Ar = 

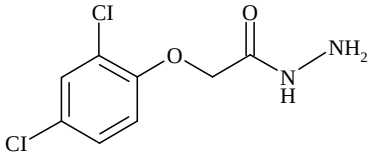
(b) Ar = 

(c) Ar = 

(d) Ar = 

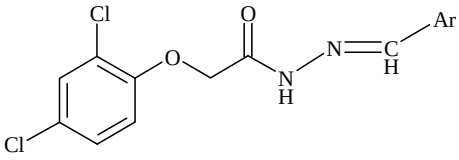
(e) Ar = 

SCHEME 2



(IV)

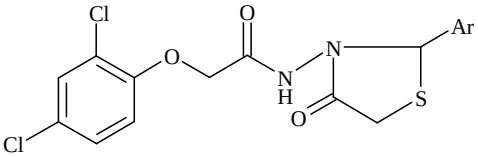
CS_2 / ethanolic KOH



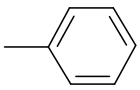
(Va-e)

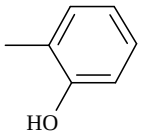
i) $HSCH_2COOH$

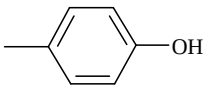
ii) Anhydrous $AlCl_3$

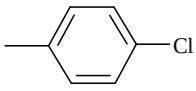


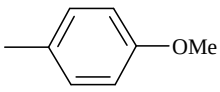
(VIa-e)

(a) Ar = 

(b) Ar = 

(c) Ar = 

(d) Ar = 

(e) Ar = 

Biological Activity

Antibacterial activity

All the newly synthesized compounds **(IIIa-e & VIa-e)** were screened in **vitro** for their antibacterial activity against **Staphylococcus aureus, Escherichia coli, Bacillus subtilis and Salmonella typhosa** by the ditch-plate technique [15] using concentrations of 2 mg/ml and 5 mg/ml. Nutrient agar was employed as culture media and DMF was used as solvent control for antibacterial activity.

The known compounds such as ampicillin, amoxicillin, norfloxacin, penicillin and griseofulvin were used for comparison studies. The diameter of zone of inhibition was measured in mm. The antibacterial screening data are recorded in **Table I.**

TABLE I: Biological Activity Data

Compounds	S. aureus		E. coli		B. subtilis		S. typhosa	
	2 mg	5 mg	2 mg	5 mg	2 mg	5 mg	2 mg	5 mg
IIIa	-	+	+	+	-	+	-	+
IIIb	+	++	+	++	+	++	+	++
IIIc	-	+	+	+	-	-	-	-
IIId	+	+	+	+	+	+	+	+
IIIe	-	+	+	+	-	-	-	-
VIa	-	+	+	+	+	++	+	++
VIb	-	+	+	++	-	+	+	++
VIc	+	+	+	++	+	+	+	++
VId	-	+	-	+	-	+	+	++
VIe	-	+	+	+	+	++	+	++

Inhibition zone diameter in mm :
(-) <11 mm; (+) 11-14 mm; (++) 15-18 mm

TABLE II: Physical and Spectral data of compounds

Compounds	Ar	M.P. °C	Yield %	Molecular Formula	Analysis %N		IR
					Requires	Found	
IIa	Phenyl	191	70	$C_{19}H_{16}N_2O_2$	9.21	9.24	3340 (N-H str.), 1695 (C=O str.), 1672 (C=N str.).
IIb	2-Hydroxyphenyl	155	72	$C_{19}H_{16}N_2O_3$	8.75	8.79	3490 (O-H str.), 3355 (N-H str.), 1705 (C=O str.), 1675 (C=N str.).
IIc	4-Hydroxyphenyl	160	70	$C_{19}H_{16}N_2O_3$	8.75	8.78	3495 (O-H str.), 3350 (N-H str.), 1710 (C=O str.), 1680 (C=N str.).
IId	4-Chlorophenyl	185	80	$C_{19}H_{15}N_2O_2Cl$	8.28	8.31	3350 (N-H str.), 1715 (C=O str.), 1676 (C=N str.), 752 (C-Cl str.).
IIe	4-Methoxyphenyl	175	81	$C_{20}H_{18}N_2O_3$	8.38	8.41	3340 (N-H str.), 1700 (C=O str.), 1673 (C=N str.), 1175 (C-O-C str.).
Va	Phenyl	182	59	$C_{15}H_{12}N_2O_2Cl_2$	8.67	8.70	3350 (N-H str.), 1715 (C=O str.), 1683 (C=N str.).
Vb	2-Hydroxyphenyl	138	62	$C_{15}H_{12}N_2O_3Cl_2$	8.26	8.28	3515 (O-H str.), 3360 (N-H str.), 1715 (C=O str.), 1685 (C=N str.).
Vc	4-Hydroxyphenyl	146	60	$C_{15}H_{12}N_2O_3Cl_2$	8.26	8.30	3510 (O-H str.), 3363 (N-H str.), 1712 (C=O str.), 1687 (C=N str.).
Vd	4-Chlorophenyl	170	55	$C_{15}H_{11}N_2O_3Cl_3$	7.83	7.85	3360 (N-H str.), 1714 (C=O str.), 1688 (C=N str.), 754 (C-Cl str.).
Ve	4-Methoxyphenyl	142	65	$C_{16}H_{14}N_2O_3Cl_2$	7.93	7.95	3375 (N-H str.), 1712 (C=O str.), 1682 (C=N str.), 1176 (C-O-C str.).

TABLE III: Physical data of compounds

Compounds	Ar	M.P. °C	Yield %	Molecular Formula	Analysis %N	
					Requires	Found
IIIa	Phenyl	195	59	$C_{21}H_{18}N_2O_3S$	7.40	7.43
IIIb	2-Hydroxyphenyl	170	62	$C_{21}H_{18}N_2O_4S$	7.10	7.13
IIIc	4-Hydroxyphenyl	190	55	$C_{21}H_{17}N_2O_3S$	7.10	7.12
IIId	4-Chlorophenyl	142	65	$C_{21}H_{17}N_2O_3SCl$	6.78	6.80
IIIe	4-Methoxyphenyl	132	60	$C_{22}H_{20}N_2O_4S$	6.86	6.89
VIa	Phenyl	255	65	$C_{17}H_{14}N_2O_3SCl_2$	7.05	7.09
VIb	2-Hydroxyphenyl	223	58	$C_{17}H_{14}N_2O_4SCl_2$	6.78	6.80
VIc	4-Hydroxyphenyl	232	60	$C_{17}H_{14}N_2O_4SCl_2$	6.78	6.81
VId	4-Chlorophenyl	211	70	$C_{17}H_{13}N_2O_3SCl_3$	6.49	6.52
VIe	4-Methoxyphenyl	145	69	$C_{18}H_{16}N_2O_4S_2Cl_2$	6.56	6.60

TABLE IV: Spectral data of compounds

Compds	Ar	IR, KBr	^{1}H NMR (DMSO-d6)	Mass Ms: m/z [M^+]
IIIa	Phenyl	3345 (N-H str.), 1698 (C=O str.), 1104 (C-S-C str.).	4.4 (s, 2H, O·CH_2·C), 4.9 (s, 2H, C-CH_2-S), 7.2-8.05 (m, 12H, ArH), 8.11 (s, 1H, N-CH-S), 10.80 (s, 1H, CONH-N).	378
IIIb	2-Hydroxyphenyl	3495 (O-H str.), 3358 (N-H str.), 1700 (C=O str.), 1107 (C-S-C str.).	4.52 (s, 2H, O·CH_2·C), 4.98 (s, 2H, C-CH_2-S), 7.3-8.10 (m, 11H, ArH), 8.15 (s, 1H, N-CH-S), 10.62 (s, 1H, CONH-N), 11.20 (s, 1H, -OH),	394
IIIc	4-Hydroxyphenyl	3499 (O-H str.), 3361 (N-H str.), 1703 (C=O str.), 1110 (C-S-C str.).	4.58 (s, 2H, O·CH_2·C), 5.02 (s, 2H, C-CH_2-S), 7.25-8.10 (m, 11H, ArH), 8.14 (s, 1H, N-CH-S), 10.65 (s, 1H, CONH-N), 11.24 (s, 1H, -OH),	394
IIId	4-Chlorophenyl	3355 (N-H str.), 1705 (C=O str.), 1108 (C-S-C str.). 752 (C-Cl str.).	4.6 (s, 2H, O·CH_2·C), 5.10 (s, 2H, C-CH_2-S), 7.3-8.15 (m, 11H, ArH), 8.2 (s, 1H, N-CH-S), 10.75 (s, 1H, CONH-N).	412
IIIe	4-Methoxyphenyl	3355 (N-H str.), 1706 (C=O str.), 1175 (C-O-C str.), 1098 (C-S-C str.).	3.8 (s, 3H, -OCH_3), 4.5 (s, 2H, O·CH_2·C), 5.0 (s, 2H, C-CH_2-S), 7.2-8.0 (m, 11H, ArH), 8.12 (s, 1H, N-CH-S), 10.70 (s, 1H, CONH-N).	408
VIa	Phenyl	3360 (N-H str.), 1711 (C=O str.), 1101 (C-S-C str.).	4.6 (s, 2H, O·CH_2·C), 5.1 (s, 2H, C-CH_2-S), 7.1-7.6 (m, 8H, ArH), 8.2 (s, 1H, N-CH-S), 10.85 (s, 1H, CONH-N).	397
VIb	2-Hydroxyphenyl	3510 (O-H str.), 3365 (N-H str.), 1714 (C=O str.), 1111 (C-S-C str.).	4.64 (s, 2H, O·CH_2·C), 5.11 (s, 2H, C-CH_2-S), 7.1-7.65 (m, 7H, ArH), 8.25 (s, 1H, N-CH-S), 10.95 (s, 1H, CONH-N), 11.35 (s, 1H, -OH),	413
VIc	4-Hydroxyphenyl	3515 (O-H str.), 3363 (N-H str.), 1712 (C=O str.), 1117 (C-S-C str.).	4.7 (s, 2H, O·CH_2·C), 5.15 (s, 2H, C-CH_2-S), 7.14-7.63 (m, 7H, ArH), 8.27 (s, 1H, N-CH-S), 11.0 (s, 1H, CONH-N), 11.40 (s, 1H, -OH),	413
VId	4-Chlorophenyl	3362 (N-H str.), 1704 (C=O str.), 754 (C-Cl str.). 1120 (C-S-C str.).	4.73 (s, 2H, O·CH_2·C), 5.2 (s, 2H, C-CH_2-S), 7.2-7.65 (m, 7H, ArH), 8.45 (s, 1H, N-CH-S), 11.05 (s, 1H, CONH-N).	431
VIe	4-Methoxyphenyl	3370 (N-H str.), 1702 (C=O str.), 1182 (C-O-C str.), 1113 (C-S-C str.).	3.85 (s, 3H, -OCH_3), 4.6 (s, 2H, O·CH_2·C), 5.0 (s, 2H, C-CH_2-S), 7.2-7.6 (m, 7H, ArH), 8.40 (s, 1H, N-CH-S), 10.94 (s, 1H, CONH-N).	427

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