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Research Article

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Synthesis, characterization and biological studies of some 3,5-diaryl-tetrahydro-N-formyl-1,4-thiazine-1,1-dioxide

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ABSTRCT

A series of some new 3, 5-diaryl-tetrahydro-N-formyl-1, 4-thiazine-1, 1-dioxides has been synthesized from their respective thiazine compounds. The structural assignments are based on their elemental and spectral data. All the synthesized compounds were preliminarily screened for their in vitro antimicrobial activity against Gram positive organisms (Bacillus subtilis, Staphylococcus aureus) and Gram negative organisms (Escherichia coli and Klebsiellapneumonia) and antifungal activity for Aspergillusnigerand Aspergillusfumigatus by disc diffusion method. Among the tested compounds, ***8*** *showed the most potent antibacterial and antifungal activities.*

Key words: 1,4-thiazine, N-formyl thiazine, antibacterial and antifungal activity, acute toxicity studies

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INTRODUCTION

Thiazines display diverse biological activities and act as tranquilizers, sedatives, antiepileptics and antitubercular, antitumour, bactericidal and parasiticidal agents[1-3]. They have also found use as cardiovascular agents,[4] herbicide antidote[5], antihypertensives,antithrombic agents[6,7] antibacterial[8,9], antihistaminic[10] and acute toxicity studies[11]. Thiazine derivatives are also used in the preparation of peptide resin inhibitors and good colour photographic materials[11,12], where they act as image stabilizers[13]. In view of the above bioapplications, we embarked on the synthesis of 3, 5-diaryl-tetrahydro-N-formyl-1, 4-thiazine-1, 1-dioxides (Scheme 1), which and we report our results in this article.

Baliah and Rangarajan (1954)[14] synthesized 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxides by he condensation of sulphonyldiacetic acid with aryl aldehydes and ammonia. The 3,5-diaryl tetrahydro-1,4-thiazine and its N-methyl derivatives were synthesized by Pandiarajan and Newton Benny (1994)[15].

EXPERIMENTAL SECTION

General

All the melting points were noted in open capillaries and are uncorrected. IR absorption spectra were recorded on a Perkin-Elmer spectrophotometer using KBr pellet and ^{1}HNMR spectra on a Bruker AMXC-500 FT NMR spectrometer (500 MHz) using $CDCl_3$ using TMS as an as internal standard. Purity of the compounds were routinely checked by TLC using silica gel coated aluminium plates (Merck).

General Method for the preparation of 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide(1a-e).
All the parent 3, 5-diaryl tetrahydro-1,4-thiazine-1,1-dioxides (**1-5**) were prepared according to the procedure of Baliah and Rangarajan (1954)[12] by the condensation of sulfonyldiacetic acid with araldehydes and ammonium acetate.

Benzaldehyde (1.06 g, 0.02 mole), sulphonyldiacetate (0.02 mole) and ammonium acetate (0.01 mole) were condensed in the presence of glacial acetic acid (25 ml).

General method for the preparation of 3,5-diaryl-N-formyl-tetrahydro-1,4-thiazine-1, 1-dioxide (2a):
To ice cold acetic anhydride (10 ml), 85% formic acid (5ml) was added slowly while stirring and the resulting solution was heated to 60°C. Immediately, the temperature of the solution rose steeply to about 90-100°C on its own and the solution was externally cooled and then maintained at 50-60°C for 1.5 h. The resulting acetic-formic anhydride was cooled to 5°C and added slowly to a cold solution of 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide **6** (3.87 g, 0.01 mole), in anhydrous benzene (30 ml). The reaction mixture was stirred at RT for 5 h and the solution was poured into water (250 ml). The benzene layer was separated and the aqueous layer was extracted with chloroform (4 x 25 ml). The organic extracts were combined, dried (anhydrous sodium sulphate) passed through a short column of silica and concentrated. Purification by crystallization from benzene: pet ether (60-80°C) mixture (1:1).

RESULTS AND DISCUSSION

In the present investigation, the synthesis of 3, 5-diaryl-tetrahydro-N-formyl-1, 4-thiazine-1, 1-dioxide (**2**) was performed. All the N-substituted thiazines obtained in the present work are hitherto unreported. The titled compounds **2a-e** have been synthesized by the reaction of formic and acetic acid mixture on 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide in the presence of benzene **(Scheme I)**. 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide has been synthesized by the chemoselective cyclization between aromatic aldehyde with sulphonyldiacetic acid and ammonium acetate in the presence of glacial acetic acid.The analytical data IR, ^{1}H and ^{13}C NMR data are in accordance with the structure proposed (**2**).

The IR spectrum of a representative example **2a** is discussed below. The characteristic infra red absorptions around 1340-1240 and 1165-1120 cm^{-1} which are assigned to asymmetric and symmetric stretching vibrations of sulphonyl group present. The bands at 710-700 and 1040-1015 cm^{-1} show the presence of C-S and S-O bonds. Aromatic C-H band displays a medium band at 3000-3100cm^{-1}. A weak band at 1620-1510 cm^{-1} is safely assigned to the C=C band of the aromatic ring. It is well known that C=O group has characteristic absorption between 2000-1600cm^{-1}. The CHO absorption has been observed in the range of 1650-1700cm^{-1}. The observed CHO and SO_2 stretching vibrational bands are supporting evidence for the formation of compounds.

The ^{1}H NMR spectrum of a representative example **6** is discussed below. The benzyl and methane protons (C-2 and C-6 nd C-3 and C-5) of the thiazine shows distinct doublet at 3.21-3.10 and a triplet at 4.40ppm. The aromatic protons are showed their peaks at 7.00-7.50ppm at multiplet. The N-CHO shows a singlet at 8.00 – 8.40ppm.

The ^{13}C NMR spectrum is also in agreement with the structure, showing the expected number of signals. The aromatic carbons appear in the range of 120-144ppm and ipso carbons at 138-144ppm. The signals of C-3 and C-5 and C-2 and C-6 appears in the range of 55-60 ppm. The carbonyl carbon of CHO appears in the range of 163-165ppm. All the other thiazines also give similar spectroscopic features.

The structures of all these new products were elucidated on the basis of their elemental analysis, IR, ^{1}H NMR and ^{13}C NMR data (Table 1 and 2). The antimicrobial activity of compounds **2a-e** are given in **Table 3.**

Antimicrobial activity

The compounds **2a-e** were evaluated *in vitro* for antibacterial activity against *E. Coli*, *K. pnemoniae*, *S. aureus*, *B. subtilis*and for antifungal activity against *Aspergillusniger* and *Aspergillusfumigatus* using acetone as solvent as 25 µg concentration by disc method. After 24 hr of incubation at 37°C the zone of inhibition were measured in mm. The activity was compared with the known antibiotics, viz., Norfloxacin, Griseofulvin at the same concentration, which is represented in **Table 1.**

To test for antibacterial activity, plates containing Nutrient Agar were seeded with different organisms at a concentration of 2-3 x 10^{-7} colony forming units (CFU) using a sterile swab. The filter paper discs containing the synthesized compounds were placed at different positions with the help of fine-pointed forceps. The plates were incubated at 37°C for 24 hours and the zone of inhibition was measured.

The antifungal activity of the synthesized compounds **2a-e** was also tested. The subculture and the viable count were carried out by the same procedure as for the antibacterial studies. The temperature maintained at 28±1°C and the results were noted after 72-96 hours. The concentration of the test compounds were as described previously and the solvent and Griesoflavin (standard drug) were used for the antifungal studies.

Of the compounds tested, **2c** (chloro substituted) inhibit the growth of tested bacteria and fungi at a minimum concentration of 25 µg/ml. The rest of the compounds show inhibition at higher concentration ranging from 50 to 200 µg/ml and **2a,2e**do not have inhibition even at 200 µg/ml. **2b**and **2d** showed moderate activity when compared to the standard Norfloxacin and Griseofulvin.

Acute Toxicity studies (LD_{50}) determination

Acute toxicity studies were undertaken to identify lethal dose 50 (LD_{50}) of the compounds **2b,2c** and **2d** respectively. According to the method of Miller and Tainter (1944)[16] with little modification except that different doses were used, colony-bred male albino mice weighing 20-30 g were taken and divided into five groups of ten animals each.

The observed percentage mortality results were converted into probit values, which were then plotted against dose. The LD_{50} values of the active compounds were found to be nontoxic in mice at oral doses of upto 1000 mg/kg.

TABLE I Physical data of 3,5-diaryl-tetrahydro-N-formyl-1,4-thiazine-1,1-dioxide (2)

Compound	m.p. (°C)	Yield (%)	Molecular formula	Calcd (found) (%)		
				C	H	N
2a	210	60	$C_{17}H_{17}NO_3S$	64.74	5.43	4.44
				(64.42	5.38	4.21)
2b	214	54	$C_{19}H_{21}NO_5S$	60.78	5.64	3.73
				(60.41	5.48	3.21)
2c	212	58	$C_{17}H_{15}NO_3SCl_2$	53.13	3.93	3.64
				(53.02	3.78	3.22)
2d	214	56	$C_{17}H_{15}N_3O_7S$	50.37	3.73	10.37
				(50.22	3.53	10.12)
2e	211	60	$C_{19}H_{21}NO_3S$	66.46	6.16	4.08
				(64.23	6.04	3.98)

TABLE II ^{1}H and ^{13}C NMR data of 3,5-diaryl-tetrahydro-N-formyl-1,4-thiazine-1,1-dioxide (2)

Compound	^{1}HNMR ($CDCl_3$)/TMS, δ (ppm)	^{13}C NMR ($CDCl_3$)/TMS, δ (ppm)
2a	3.13-3.21 (m, 2H) (C-2, C-5) 4.41 (t, 4H) (C3, C5) 7.21-7.45 (m, 10H) Aromatic 8.21 (s, 1H, CHO)	58.46 (C2, C6) 59.29 (C3,C5) 126.77-129.28 (Aromatic) 140.35 (ipso) 162.03(CHO)
2b	3.11-3.22 (m, 2H) (C-2, C-5) 3.81 (s, 6H, OCH_3) 4.45 (t, 4H) (C3, C5) 6.71 (d, 7.21-7.45 (m, 8H) Aromatic 8.21 (s, 1H, CHO)	55.44(-OCH_3), 58.46(C2,C 6), 114.77-130.06 (Aromatic) 159.75 (ipso) 162.03(CHO)
2c	3.03-3.21 (m, 2H) (C-2, C-5) 4.40 (t, 4H) (C3, C5), 6.8 (d, 7.21-7.52 (m, 10H) Aromatic 8.21 (s, 1H, CHO)	58.24 (C2, C6) 59.75 (C3,C5) 126.74-138.61 (Aromatic) 142.30 (ipso) 162.59(CHO)
2d	3.12-3.21 (m, 2H) (C-2, C-5) 4.40 (t, 4H) (C3, C5), 7.21-7.52 (m, 10H) Aromatic 8.22 (s, 1H, CHO)	58.47 (C2, C6) 59.09 (C3,C5) 126.67-129.14 (Aromatic) 140.34 (ipso) 163.60(CHO)
2e	2.32 (s, 6H, CH_3), 3.10-3.21 (m, 2H) (C-2, C-5) 4.40 (t, 4H) (C3, C5), 7.11-7.52 (m, 10H) Aromatic 8.12 (s, 1H, CHO)	22.68 (CH_3), 58.23 (C2, C6), 59.41 (C3,C5) 126.31-138.59 (Aromatic) 142.60 (ipso) 163.60(CHO)

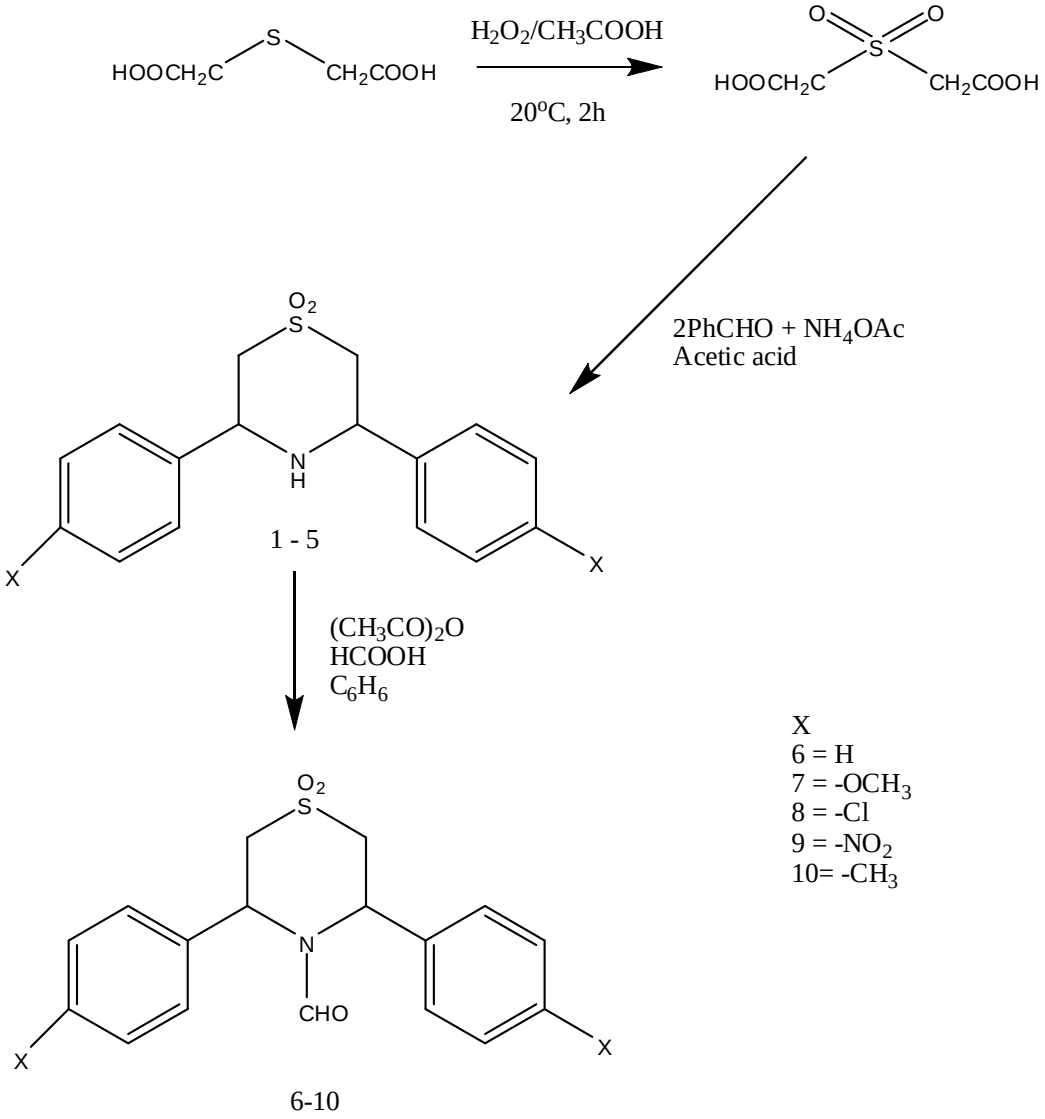
Table III Antibacterial activities of compounds 2a-e

(Diameter of the zone of inhibition in mm)

Compound No.	Gram positive		Gram negative		Fungi	
	A	**B**	**C**	**D**	**E**	**F**
2a	7	7	7	6	7	6
2b	9	10	10	11	10	9
2c	15	14	15	14	16	15
2d	12	13	14	12	14	14
2e	7	6	7	7	6	7
Norfloxacin	24	23	24	26	-	-
Griseoflavin	-	-	-	-	23	24
Acetone	-	-	-	-	-	-

A – Streptococci; B – Bacillus subtilis; C – Klebsiellapneumoniae; D – Escherchia coli; E – Aspergillusflavus, F – Aspergillusfumigatus.
Reference compound: Norfloxacin and Griseoflavin

Inactive < 8 mm; Moderate - 8-12 mm; Active > 12 mm



Scheme - 1

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