Synthesis, Characterization and Biological Activities of 3,5-Diaryltetrahydro-*N*-[(phenylamino) methyl]-1,4-thiazine-1,1-dioxide

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Abstract: Synthesis of 3,5-diaryltetrahydro-*N*- [(4'-nitroanilino)methyl]-thiazine-1,1-dioxide and *N*-[(4'-methylanilino)methyl]-1,4-thiazine-1,1-dioxides by condensing 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide with formaldehyde and 4-nitroaniline/4-methylaniline in the presence of hydrochloric acid is reported. The structures of the synthesized compounds have been confirmed by elemental and spectral analysis. The preliminary screening of the compounds for their biological activities gives significant results.

Keywords: Thiazines, Aromatic amines, Biological activities, Zone of inhibition.

Introduction

The studies related to 1,4-thiomorpholine-1,1-dioxides are of recent origin¹⁻³. Amongst the various methods known, condensation of either sulfonyl diacetic acid or dialkyl sulfonyl diacetate with araldehydes in the presence of ammonia or aliphatic amines was considered as an important route⁴. Heterocycles containing nitrogen and sulphur have potential pharmacological properties. One such class of compounds are 1,4-thiomorpholine-1,1-dioxides which possess two important pharmacophores *i.e.* -NH- and -SO₂-.

It is pertinent to note that the present investigation provides a facile route to synthesis of hitherto unknown substituted tetrahydro-1,4-thiazines that are in general used as sedatives, tranquilizers, antiepileptics, antitubercular, antitumour, bacteriocidal and parasiticidal agents⁵.

Tetrahydro-1,4-thiazine-1-oxide-3-carboxylic acid was isolated from algae⁶. Recently, tetrahydro-1,4-thiazine-3,5-dicarboxylic acid has been detected in the bovine brain⁷ and human urine^{8,9}.

A series of 1,4-thiomorpholine-1,1-dioxides have been synthesized and their biological activities were studied by Baskara Reddy *et al.*¹⁰. Thiazines display many important biological activities¹¹⁻²⁰. The derivatives of thiazine act as myocardial calcium channel inhibitors²¹ and also as matrix metalloproteinase inhibitors²². Mannich base derivatives have been reported to possess various biological activities including anti-inflammatory²³⁻²⁶. Tetrahydro-1,4-thiazine-1,1-dioxide derivatives showed antibacterial, antifungal, antihistamine activities²⁷⁻³⁰. In view of synthesizing potent therapeutic agents, the title compounds were prepared.

The title compounds **3a-j** were synthesized by the reaction of formaldehyde, aryl amine on 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide in the presence of hydrochloric acid (Scheme 1). 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide was synthesized by the chemoselective cyclization between aromatic aldehyde with sulphonyl diacetic acid and ammonium acetate in the presence of glacial acetic acid.

The structures of all these new products were elucidated by their elemental analysis, IR, ¹H NMR and ¹³C NMR data.

Scheme 1.

Compound	X	Y	Compound	X	Y
3a	H	NO ₂	3f	H	CH ₃
3b	<i>p</i> -OCH ₃	NO ₂	3g	<i>p</i> -OCH ₃	CH ₃
3c	<i>p</i> -Cl	NO ₂	3h	<i>p</i> -Cl	CH ₃
3d	<i>p</i> -NO ₂	NO ₂	3i	<i>p</i> -NO ₂	CH ₃
3e	<i>p</i> -Me	NO ₂	3j	<i>p</i> -Me	CH ₃

Experimental

All the melting points were noted in open capillaries and are uncorrected. IR absorption spectra were recorded on a FT-IR spectrophotometer using KBr pellet and ^1H NMR spectra on AV-300 spectrometer (300 MHz) using DMSO as internal standard. Purity of the compounds was routinely checked by TLC using silica gel G.

General methods of preparation of 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxide (2a-e)

Aromatic aldehyde (0.02 mole), sulphonyldiacetic acid (0.02 mole) and ammonium acetate (0.01 mole) were condensed in the presence of glacial acetic acid (25 mL) according to the earlier procedure reported⁴.

General methods of preparation of 3,5-diphenyl-N-[(phenylamino)methyl]-tetrahydro-1,4-thiazine-1,1-dioxide (3a-j)

A mixture of 3,5-diaryl-tetrahydro-1, 4-thiazine-1,1-dioxide (0.01 mole), formaldehyde (2.0 mL), aromatic amine (0.01 mole), hydrochloric acid (5.0 mL) and dioxan (25 mL) was refluxed for 5 h on an oil bath. The cold reaction mixture was filtered and poured into ice water. The precipitate obtained was filtered and recrystallized from dioxane.

3,5-Diphenyl-N-[(4'-nitroanilino)methyl]-tetrahydro-1,4-thiazine-1,1-dioxide (3a)

M.p. 202°C yield 50%. Anal. calcd for $\text{C}_{23}\text{H}_{23}\text{O}_4\text{N}_3\text{S}$: C, 63.14; H, 5.30; N, 9.60%, Found: C, 63.10, H, 5.25; N, 9.55. IR: 3329 (N-H str.), 3033 (Ar-C-H str), 2921 (C-H str., asym), 2852 (C-H str). 1114 and 1310 cm^{-1} (SO_2 str); ^1H NMR: δ 3.08-3.35 (m, 4H, $-\text{CH}_2$) (C_2 , C_6); 4.40-4.44 (t, $-\text{CH}$, C_3 , C_5), 3.90 (s, 2H, $-\text{N}-\text{CH}_2-\text{N}$), 5.54 (br s 1H, NH), 7.20- 7.67 (m, Ar-H) ^{13}C NMR: 40.12 (N- CH_2), 57.58 (C_2 , C_6), 59.93 (C_3 , C_5), 124.42-132.73 (Ar), 143.14 (ipso).

3,5-Bis(p-methoxyphenyl)-N-[(4'-nitroanilino)methyl]-tetrahydro-1,4-thiazine-1,1-dioxide (3b)

M.p. 218°C yield 48%. Anal. calcd for $\text{C}_{25}\text{H}_{27}\text{N}_3\text{O}_6\text{S}$: C, 60.35; H, 5.47; N, 8.45%, Found: C, 60.24, H, 5.39; N, 8.39. IR: 3329 (N-H str.), 3191 (Ar-C-H str), 2967 (C-H str.), 2918 (C-H str). 1139 and 1329 cm^{-1} (SO_2 str); ^1H NMR: δ 3.08-3.39 (m, 4H, $-\text{CH}_2$) (C_2 , C_6); 4.38-4.58 (t, $-\text{CH}$) (C_3 , C_5), 3.71 (s, 6H, $-\text{OCH}_3$), 3.94 (s, 2H, $-\text{N}-\text{CH}_2-\text{N}$), 5.50 (br s 1H, NH) 6.85, d, 7.00-8.05 (m, Ar-H). ^{13}C NMR: 40.67 (N- CH_2), 57.58 ($-\text{OCH}_3$), 59.52 (C_2 , C_6), 58.29 (C_3 , C_5), 126.84-132.94 (Ar), 143.93, 160.15 (ipso).

3,5-Bis(p-chlorophenyl)-N-[(4'-nitroanilino)methyl]-tetrahydro-1,4-thiazine-1,1-dioxide (3c)

M.p. 221°C yield 60%. Anal. calcd for $\text{C}_{23}\text{H}_{21}\text{Cl}_2\text{N}_3\text{O}_4\text{S}$: C, 54.55; H, 4.18; N, 8.30%, Found: C, 54.50, H, 4.12; N, 8.23. IR: 3329 (N-H str.), 3054 (Ar-C-H str), 2918 (C-H str., asym), 2866 (C-H str). 1115 and 1301 cm^{-1} (SO_2 str); ^1H NMR: δ 3.15-3.25 (m, 4H, $-\text{CH}_2$) (C_2 , C_6); 4.34-4.46 (t, $-\text{CH}$) (C_3 , C_5), 3.71 (s, 2H, $-\text{N}-\text{CH}_2-\text{N}$), 5.39 (br s 1H, NH) 6.83 d, 7.27-7.68 (m, Ar-H). ^{13}C NMR: 40.73 (N- CH_2), 57.48 (C_2 , C_6), 59.09 (C_3 , C_5), 127.12-131.34 (Ar), 140.85 (ipso).

3,5-Bis(p-Nitrophenyl)-N-[(4'-nitroanilino)methyl]-tetrahydro-1,4-thiazine-1,1-dioxide (3d)

M.p. 201°C yield 52%. Anal. calcd for $\text{C}_{23}\text{H}_{21}\text{N}_5\text{O}_8\text{S}$: C, 52.37; H, 4.01; N, 13.52%, Found: C, 52.32, H, 3.98; N, 13.46. IR: 3328 (N-H str.), 3054 (Ar-C-H str), 2921 (C-H str., asym), 2863 (C-H str). 1114 and 1300 cm^{-1} (SO_2 str); ^1H NMR: δ 3.16-3.24 (m, 4H, $-\text{CH}_2$) (C_2 , C_6); 3.94 (s,

2H, N-CH₂-N), 4.40-4.44 (t, -CH) (C₃, C₅), 5.49 (br s 1H, NH) 6.91, d, 7.27-7.46 (m, Ar-H). ¹³C NMR: 40.38 (N-CH₂), 58.28 (C₂, C₆), 59.23 (C₃, C₅), 126.59-131.46 (Ar), 140.15 (ipso).

3,5-Bis(*p*-methylphenyl)-*N*-[(4'-nitroanilino)methyl]-tetrahydro-1,4-thiazine-1,1-dioxide (3e**)**

M.p. 221°C yield 56%. Anal. calcd for C₂₃H₂₇N₃O₄S: C, 64.50; H, 5.85; N, 9.03%, Found: C, 64.12, H, 5.65; N, 8.93%. IR: 3328 (N-H str.), 3054 (Ar-C-H str), 2983 (C-H str., asym), 2865 (C-H str). 1114 and 1353 cm⁻¹ (SO₂ str); ¹H NMR: δ 2.18 (s, 6H -CH₃), 3.15-3.32 (m, 4H, -CH₂) (C₂, C₆); 3.89 (s, 2H, N-CH₂-N), 4.39-4.43 (t, -CH) (C₃, C₅), 5.71 (br s 1H, NH) 7.26-7.46 (m, Ar-H). ¹³C NMR: 20.12 (CH₃), 40.63 (N-CH₂), 58.42 (C₂, C₆), 59.09 (C₃, C₅), 126.79-129.11 (Ar), 140.35, 143.52 (ipso).

3,5-Diaryl-*N*-[(4'-methylanilino)methyl]-tetrahydro-1,4-thiazine-1,1-dioxide (3f**)**

M.p. 213°C yield 68%. Anal. calcd for C₂₄H₂₆O₂N₂S: C, 70.91; H, 6.45; N, 6.89%, Found: C, 70.62, H, 6.28; N, 6.59. IR: 3377 (N-H str.), 3098 (Ar-C-H str), 2970 (C-H str., asym), 2854 (C-H str). 1135 and 1332 cm⁻¹ (SO₂ str); ¹H NMR: δ 3.10-3.38 (m, 4H, -CH₂) (C₂, C₆); 4.41 (t, -CH) (C₃, C₅), 3.79 (s, 2H, -N-CH₂-N), 5.72 (br s 1H, NH), 7.12- 7.65 (m, Ar-H). ¹³C NMR: 20.09 (CH₃), 40.35 (N-CH₂), 58.46 (C₂, C₆), 59.09 (C₃, C₅), 126.75-129.09 (Ar), 140.35 (ipso).

3,5-Bis(*p*-methoxyphenyl)-*N*-[(4'-methylanilino)methyl]-tetrahydro-1,4-thiazine-1,1-dioxide (3g**)**

M.p. 213°C yield 65%. Anal. calcd for C₂₆H₃₀N₂O₄S: C, 66.93; H, 6.48; N, 6.00%, Found: C, 66.81, H, 5.28; N, 5.91. IR: 3328 (N-H str.), 3189 (Ar-C-H str), 2969 (C-H str., asym), 2858 (C-H str). 1157 and 1328 cm⁻¹ (SO₂ str); ¹H NMR: δ 1.61 (s, 6H, CH₃), 3.30 (m, 4H, -CH₂) (C₂, C₆); 4.40 (t, 2H, -CH) (C₃, C₅), 3.80 (s, 6H, -OCH₃), 3.90 (s, 2H, N-CH₂-N), 5.76 (br s 1H, NH) 6.81 d, 7.11-7.69 (m, Ar-H). ¹³C NMR: 20.74 (CH₃), 40.09 (N-CH₂), 55.44 (C₂, C₆), 59.51 (OCH₃), 58.49 (C₃, C₅), 114.26-159.75 (Ar), 162.93 (ipso).

3,5-Bis(*p*-chlorophenyl)-*N*-[(4'-methylanilino)methyl]-tetrahydro-1,4-thiazine-1,1-dioxide (3h**)**

M.p. 218°C yield 65%. Anal. calcd for C₂₄H₂₄Cl₂N₂O₂S: C, 60.63; H, 5.09; N, 5.89%, Found: C, 60.32, H, 5.01; N, 5.63. IR: 3377 (N-H str.), 3108 (Ar-C-H str), 2918 (C-H str., asym), 2855 (C-H str). 1139 and 1338 cm⁻¹ (SO₂ str); ¹H NMR: δ 1.67 (s, 6H, CH₃), 3.01-3.35 (m, 4H, -CH₂) (C₂, C₆); 4.41 (t, 2H, -CH, C₃, C₅), 3.89 (s, 2H, N-CH₂-N), 5.79 (br s 1H, NH) 6.82 d, 7.12-7.65 (m, Ar-H). ¹³C NMR: 20.09 (CH₃), 40.78 (N-CH₂), 58.24 (C₂, C₆), 59.41 (C₃, C₅), 126.74-138.26 (Ar), 142.30 (ipso).

3,5-Bis(*p*-Nitrophenyl)-*N*-[(4'-methylanilino)methyl]-tetrahydro-1,4-thiazine-1,1-dioxide (3i**)**

M.p. 218°C yield 65%. Anal. calcd for C₂₄H₂₄N₃O₄S: C, 63.98; H, 5.37; N, 9.33%, Found: C, 63.90, H, 5.30; N, 9.03. IR: 3326 (N-H str.), 3166 (Ar-C-H str), 2958 (C-H str., asym), 2830 (C-H str). 1145 and 1314 cm⁻¹ (SO₂ str); ¹H NMR: δ 1.61 (s, 6H, CH₃), 3.30 (m, 4H, -CH₂) (C₂, C₆); 3.90 (s, 2H, N-CH₂-N), 4.45 (t, 2H, -CH, C₃, C₅), 5.68 (br s 1H, NH) 6.81 d, 7.11-7.69 (m, Ar-H). ¹³C NMR: 20.29 (CH₃), 40.42 (N-CH₂), 53.93 (C₂, C₆), 59.86 (C₃, C₅), 124.93-129.93 (Ar), 159.65 (ipso).

3,5-Bis(p-methylphenyl)-N-[(4'-methylanilino)methyl]-tetrahydro-1,4-thiazine-1,1-dioxide (3j)

M.p. 206°C yield 61%. Anal. calcd for $C_{25}H_{23}N_2O_5S$: C, 71.86; H, 6.96; N, 6.45%, Found: C, 71.40, H, 6.78, N, 6.30%. IR: 3326 (N-H str.), 3040 (Ar-C-H str), 2932 (C-H str., asym), 2865 (C-H str). 1116 and 1300 cm^{-1} (SO_2 str); 1H NMR: δ 1.69 (s, 6H -CH₃), 3.10-3.38 (m, 4H, -CH₂) (C₂, C₆); 3.89 (s, 2H, N-CH₂-N), 4.451 (t, -CH) (C₃, C₅), 5.72 (br s 1H, NH) 6.82 d, 7.12-7.64 (m, Ar-H). ^{13}C NMR: 20.18 (CH₃), 40.94 (N-CH₂), 58.23 (C₂, C₆), 59.01 (C₃, C₅), 126.74-138.58 (Ar), 142.08 (ipso).

Results and Discussion

Antimicrobial activity

The compounds **3a-j** were evaluated *in vitro* for antibacterial activity against *Escherchia coli*, *Klebsiella pnemoniae*, *Staphylococcus aureus*, *Bacillus subtilis* and for antifungal activity against *Aspergillus niger* and *Aspergillus fumigatus* in acetone of 25 μg concentration by cup-plate method. After 24 h of incubation at 37°C the zones of inhibition were measured in mm. The activity was compared with the known antibiotics, viz., norfloxacin, griseofulvin at the same concentration. The results are given in Table 1.

Table 1. Antibacterial activities of compounds **3a-3j** (Diameter of the zone of inhibition in mm)

Compound No.	Gram positive		Gram negative		Fungi	
	A	B	C	D	E	F
3a	7	6	7	7	7	6
3b	10	9	10	9	10	10
3c	14	15	16	14	14	15
3d	13	12	14	12	13	12
3e	7	7	6	6	6	7
3f	7	6	6	6	6	7
3g	9	10	10	10	11	10
3h	14	15	15	14	13	16
3i	13	12	12	13	12	14
3j	7	6	7	6	7	7
Norfloxacin	24	23	24	26	-	-
Griseoflavin	-	-	-	-	23	24
Acetone	-	-	-	-	-	-

A – *Streptococci*; B – *Bacillus subtilis*; C – *Klebsiella pneumoniae*; D – *Escherchia coli*; E – *Aspergillus flavus*, F – *Aspergillus fumigatus*.

Reference compound: Norfloxacin and Griseoflavin Inactive < 8 mm; Moderate - 8-12 mm; Active > 12 mm

Of the compounds tested, **3c** and **3d**, **3h** and **3i** inhibit the growth of tested bacteria and fungi at a minimum concentration of 25 $\mu g/mL$. **3b** and **3g** showed moderate activity at higher concentrations ranging from 50 to 200 $\mu g/mL$. **3a**, **3f**, **3e** and **3j** do not have inhibition even at 200 $\mu g/mL$. when compared to the standard norfloxacin and griseofulvin.

Conclusion

From the present investigation, the following conclusions can be drawn:

- Thiazine compounds shows excellent biological activities
- Further studies in these field is needed

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