Journal of Applied and Advanced Research 2016, 1(4): 8–13
doi.: 10.21839/jaar.2016.v1i4.36
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Research Article – Chemistry

Synthesis and biological activities of some 3,5-diaryl-*N*-hydroxy-tetrahydro-1,4-thiazine-1,1-dioxides

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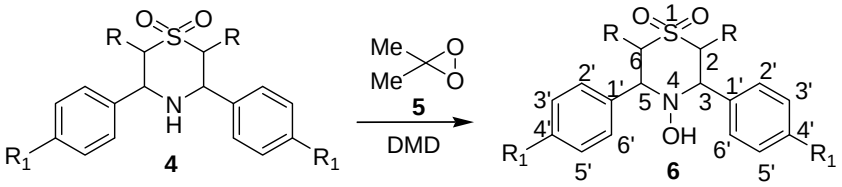
Abstract

Some new 3,5-diaryl-*N*-hydroxy-tetrahydro-1,4-thiazine-1,1-dioxides **(6a-i)** have been synthesized by reacting thiazines **(4)** with dimethyldioxirane **(5)** and tested for their antibacterial and acute toxicity studies. The synthesized compounds were characterized by elemental analysis, IR and NMR spectral data.



Key words: Thiazines, dimethyldioxirane, *N*-hydroxythiazines, Antibacterial activity, Acute toxicity

Introduction

Molecules with heteroaromatic rings as part structures are widely available in nature apart from their synthetic viability as valuable compounds. Incorporation of heteroatoms within the frame work of donor systems has been regarded as an important aspect of designing new molecules. It is well known that molecules containing nitrogen, sulfur and other members of heteroatoms exhibit a variety of biological activities (Katritzky, 1965; Prot and Thomson, 1976; Faria *et al.,* 1979). A large group of thiazines, benzothiazines and phenothiazines have antihistaminic, antihyper––tensive, diuretic, antipsychotic and antimicrobial effects (Matier *et al.,* 1974; Kaverling Busiman, 1982; Klaus and Erik, 1982; Bertran Katzen, 1995; Dayle; Dengle *et al.,* 1999).

Received: 23-09-2016; Revised: 02-11-2016: Accepted 14-11-2016; Published Online 30-11-2016

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Recently the antiviral activity of benzothia––zines against human immuno-deficiency virus-1 and 2 (HIV-1 and HIV-2) has been reported (Duckworth and Handerz, 1991; Seraginoedk *et al.,* 1995).

Similarly, Dimethyldioxirane (DMD) is an efficient and powerful electrophilic oxidant (Thenmozhiyal *et al.,* 2006) and it is known to oxidize primary amines to nitro compounds, secondary amines to hydroxylamines and nitrones. Heterocyclic hydroxylamines are of much importance because of their pharmacological and physiological activity. Many potential central nervous system depressants exhibit more activity in their *N*-hydroxylamine form than in their amino or *N*-aryloxy derivatives.

Baliah and Rangarajan (1954) have synthesized 3,5-diaryltetrahydro-1,4-thiazine-1,1-dioxides and 2,6-dialkoxycarbonyl-3,5-diarylte trahydro-1,4-thiazine-1,1-dioxides by the condensation of sulphonyldiacetic acids/ sulphonyldiacetates with aryl aldehydes and ammonia. The *N*-methyl derivatives of substituted

tetahydro-1,4-thiazine-1,1-dioxides were synthesized by Pandiarajan and Christopher Benny (1994).

In the present study, the oxidation of di- and tetra substituted thiazines **(4)** using excess dimethyldioxirane **(5)** (*in situ*) were carried out with a view to get *N*-hydroxy thiazines **(6)**.

Chemistry

The *N*-hydroxy derivatives of 2,6-diphenylpiperidin-4-ones and *N*-hydroxy -r-2,c-6-diphenylpiperidines (Thenmozhiyal *et al.,* 2006) were synthesized and characterized by elemental analysis and spectral data.

In the similar way we have synthesized the *N*-hydroxy-1,4-thiazine-1,1-dioxides **(6a-i)**. This transformation is carried out by treating thiazines (**4**) with excess dimethyldioxirane (**5**) as shown in Scheme 1.

The formation of *N*-hydroxy compounds **(6a-i)** was confirmed from the IR spectra by the absence of *N*-H stretching bands around 3300 cm^{-1} in the IR spectra and the appearance of medium band in the region 3322-3437 cm^{-1} due to the *N*-OH vibration and the asymmetric and symmetric stretching vibrations of the sulfonyl group in the region 1322-1349, 1302-1317 and 1115-1146 cm^{-1}. Further a singlet around 4.60-4.63 ppm, in the ^{1}H NMR spectra also confirms the product.

It is well known that the C=O group has characteristic absorption between 1600-1800 cm^{-1}. The C=O absorption depends upon the functional group which it is present. The *N*-hydroxy compounds **(6d-i),** the presence of C=O absorption in carbonyls of the ester group was found to be in the range of 1628-1656 cm^{-1}.

The assignments for the six membered heterocyclic ring carbons with the side chain methylene carbons are made by comparing the signals with that of parent thiazine compounds (Pandiarajan and Chrisotpher, 1994; Sundari and Valliappan, 2004).

Results and discussion

In vitro antibacterial activity

The preliminary antibacterial screening of the synthesized compounds was carried out by using disc method. The bacteria *viz., Staphylococcus aureus* (Gram positive) and *Klebsiella pneumoniae* (Gram negative) is used for the study. Acetone is used as a control and Norfloxacin is used as standard. The antibacterial activity of the compounds (**6a-i)** is given in Table-1.

Of the compounds tested **6c, 6f** and **6i** inhibit the growth of tested bacteria and fungi at a minimum concentration 25μgml^{-1}. The rest of the compounds show inhibition at higher concentration ranging from 50 to 80 μgml^{-1} and **6a**, **6d** and **6g** do not have inhibition action even at 200 μgml^{-1}. **6c** and **6f** showed good activity against *Staphylococcus aureus*. **6b**, **6e** and **6h** showed moderate activityand **6a**, **6d** and **6g** showed less active when compared to the standard Norfloxacin.

Table 1. Antibacterial activity of compounds (**6a-i)**

Compound	*K. pneumoniae*	*S. aureus*
6a	7	9
6b	11	11
6c	16	16
6d	8	8
6e	10	11
6f	17	17
6g	8	7
6h	11	11
6i	17	15
Norfloxacin	22	21

Zone of inhibition in (mm): inactive < 8 mm; moderate 9-12 mm; active > 12 mm

Acute toxicity studies

Acute toxicity studies were carried out for compounds **6c, 6f** and **6i** using 5 groups of albino mice for each compound and each group comprise 10 animals.

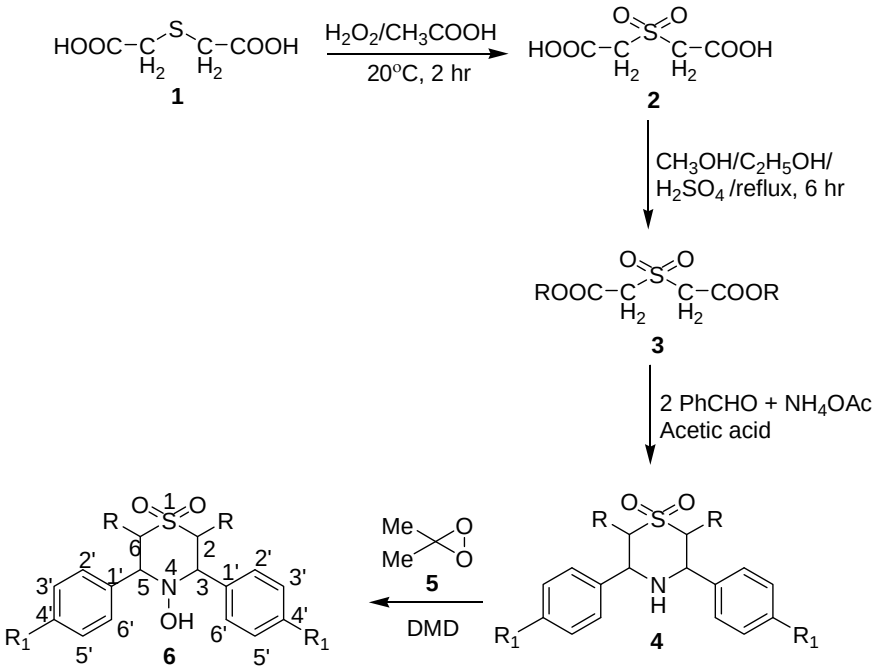
The LD_{50} values of the active compounds were found to be > 1000 mg/kg b.w. All the compounds were found to be non-toxic to mice upto 1000 mg/kg p.o. dose.

Experimental

Chemistry

Thin-layer chromatography (TLC) was used to monitor the progress of the reaction and the purity of the products. The melting points were recorded in open capillaries and are uncorrected. IR spectra were recorded in AVATAR-330 FT-IR spectrophotometer (Thermo Nicolet) and only strong absorption bands (reciprocal centimeters) are listed.

Scheme 1: Synthesis of 3,5-diaryl-*N*-hydroxy-tetrahydro-1,4-thiazine-1,1-dioxides **(6a-i)**



	R	R^1
6a	H	H
6b	H	4-OCH_3
6c	H	4-Cl
6d	$COOCH_3$	H
6e	$COOCH_3$	4-OCH_3
6f	$COOCH_3$	4-Cl
6g	$COOC_2H_5$	H
6h	$COOC_2H_5$	4-OCH_3
6i	$COOC_2H_5$	4-Cl

^{1}H NMR spectra were recorded at 400 MHz on BRUKER DRX 400 MHz spectrophotometer; $CDCl_3$ was used as solvent and TMS as internal standard. ^{13}C NMR spectra were recorded at 100 MHz on BRUKER DRX 400 MHz spectrometer; $CDCl_3$ was used as solvent. Unless otherwise stated, all the reagents and solvents used were of high grade and purchased from Fluka and Merck. All the solvents were distilled before use. The abbreviations used to indicate the peak multiplicity were: s-singlet; d-doublet; dd-doublet of doublet; t-triplet; q-quartet and m-multiplet.

General method of preparation of 2,6-dialkoxycarbonyl-3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxides and 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxides

*Preparation of thiodiglycollic acid **(1)***

This compound was prepared by the method employed by Bearse (1947). Monochloroacetic acid (94.5 g) was taken in a one litre beaker and dissolved in water (75 ml). This solution was neutralized with saturated sodium carbonate solution.A solution of sodium sulphide monohydrate (142 g) in water (100 ml) was added slowly with constant stirring. There was considerable evolution of heat. The mixture was allowed to stand for 3 hr and filtered to remove the small amount of dark green flocculent precipitate. Concentrated sulphuric acid (75 ml) was added with stirring, keeping the temperature at 25-30°C. Ethyl methyl ketone (100 ml) was added to the resulting solution and shaken well in a separatory funnel. The ketone layer was drawn off and dried over anhydrous sodium sulphate. The ethyl methyl ketone layer was filtered and distilled with a recovery of 75 ml of ethyl methyl ketone. The remaining solution in the flask mainly containing a concentrated aqueous solution of thiodiglycollic acid was poured, while hot, into a beaker and cooled in ice water. The acid soon solidified and it was dried and weighed 60 g (80%). After recrystallizing it from hot water, it had a melting point of 127-129°C. Baliah and Rangarajan (1954) report the same melting point.

*Preparation of sulphonyldiacetic acid **(2)***

Thiodiglycollic acid **(1)** 100 g was slowly added to a solution of hydrogen peroxide (30%, 300 ml) and glacial acetic acid (5 ml), taken in a one litre conical flask. The rise in temperature during the addition of thiodiglycollic acid was controlled by cooling the solution in ice water. After the addition was complete, the reaction mixture was kept at 20°C for 3 hr, then at room temperature for 48 hr. Finally, it was evaporated on a steam bath to dryness. Sulphonyldiacetic acid was purified by boiling an aqueous solution with decolourising carbon. The carbon was then filtered off and the water was evaporated on a steam bath. The yield was almost theoretical. It had a melting point of 182-184°C.

*Preparation of di-n-methyl sulphonyldiacetate/di-n-ethyl sulphonyldiacetate **(3)***

Sulphonyldicetic acid **(2)** (20 g), methanol/ ethanol (75 ml) and sulphuric acid (1 ml) were refluxed for 6 hr. The excess alcohol was removed by distillation and the residual solution was poured into water (150 ml). The separated ester was taken up in ether and dried ($CaCl_2$); the solvent was removed and the residue was distilled, giving the ester.

*General method of preparation of 2,6-dialkoxycarbonyl-3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxides and 3,5-diaryl-tetrahydro-1,4-thiazine-1,1-dioxides **(4)***

All the parent di- and tetra- substituted tetrahydro-1,4-thiazine-1,1-dioxides were prepared according to the procedure of Baliah and Rangarajan (1954). A mixture of sulphonyl diacetic acid/sulphonyldiacetate **(3)** (0.02 mol) with araldehydes (0.04 mol) and ammonium acetate (0.02 mol) were refluxed for 15 minutes. There was a brisk evolution of carbon dioxide at the beginning but it slowly subsided. The completion of the reaction was indicated by the change of colour to brownish yellow. The reaction mixture was cooled and ether 30 ml was added. On shaking well and leaving aside, the turbid ethereal layer cleared leaving a small aqueous layer below. The ethereal layer was separated; dry hydrogen chloride was passed into it. The precipitated thiazine hydrochloride was separated by filtration, washed with ether and dried. The free base was liberated by dissolving the thiazine hydrochloride in ethanol, adding aqueous ammonia and diluting with water. On recrystallizing from ethanol, it melted at 202-203°C.

*General method of preparation of and 3,5-diaryl-N-hydroxy-tetrahydro-1,4-thiazine-1,1-dioxides and 2,6-dialkoxycarbonyl-3,5-diaryl-N-hydroxy-tetrahydro-1,4-thiazine-1,1-dioxides **(6)***

The respective thiazines **(4)** (5 mmol) in dichloromethane (40 ml) and acetone (80 ml) was kept at 0°C in an ice bath for freshly prepared solution of dimethyldioxirane **(5)** (oxone) (6.14 g, 100 mmole) in water (25 ml) was added in drops for a period of 1 hr with constant stirring. The pH was maintained between 7.0-8.0 by adding drops of potassium hydroxide solution. The reaction mixture was allowed to stir vigorously for about 40 minutes. After the separation of dichloromethane layer, the aqueous layer was extracted with two 50 ml portions of

dichloromethane the combined dichloromethane extract was washed with water, dried over anhydrous sodium sulphate, filtered and evaporated. The solid left behind was recrystallized from 1:2 mixture of benzene and petroleum ether (60-80°C) to get colourless crystals of *N*-hydroxy derivative.

3,5-diphenyl-*N*-hydroxy-tetrahydro-1,4-thiazine -1,1-dioxide (6a).

m.p. 219-221ºC, yield 70%. IR: ν_{max} (KBr, cm^{-1}): 3327 (*N*-OH), 1348, 1302, 1146 (SO_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 3.10-3.21 (H-2 & H-6) (m, 4H), 4.40 (H-3 & H-5) (t, 2H), 4.60 (*N*-OH) (s, 1H), 7.25-7.45 (m, 10H, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 58.41 (C-2 & C-6), 59.06 (C-3 & C-5), 126.70, 128.70, 129.00, 140.30. Anal. Calcd. for $C_{16}H_{17}NO_3S$: C, 63.34; H, 5.65; N, 4.62 %. Found: C, 63.44; H, 5.69; N, 4.67 %. Mass spectrum EIMS (M^+): 303.

3,5-bis(*p*-methoxyphenyl)-*N*-hydroxy-tetrahydro -1,4-thiazine-1,1-dioxide (6b).

m.p. 222-224ºC, yield 50%. IR: ν_{max} (KBr, cm^{-1}): 3331 (*N*-OH), 1342, 1309, 1131 (SO_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 3.12 (H-2 & H-6) (dd, 4H), 3.80 (OCH_3) (s, 6H), 4.35 (H-3 & H-5) (t, 2H), 4.60 (*N*-OH) (s, 1H), 6.38 (H-3' & H-5') (d, 4H, *J* = 8.8 Hz, -Ar-H), 7.35 (H-2' & H-6') (d, 4H, *J* = 8.8 Hz, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 55.27 (C-2 & C-6), 53.27 (OCH_3), 58.39 (C-3 & C-5), 116.22, 131.78, 135.07, 159.16. Anal. Calcd. for $C_{18}H_{21}NO_5S$: C, 59.49; H, 5.82; N, 3.85 %. Found: C, 55.69; H, 5.92; N, 3.88 %. Mass spectrum EIMS (M^+): 363.

3,5-bis(*p*-chlorophenyl)-*N*-hydroxy-tetrahydro-1,4-thiazine-1,1-dioxide (6c).

m.p. 225-227ºC, yield 62%. IR: ν_{max} (KBr, cm^{-1}): 3340 (*N*-OH), 1344, 1305, 1140 (SO_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 3.10- 3.13 (H-2 & H-6) (m, 4H), 4.41 (H-3 & H-5) (t, 2H), 4.61 (*N*-OH) (s, 1H), 7.20-7.40 (m, 8H, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 55.22 (C-2 & C-6), 58.49 (C-3 & C-5), 114.22, 132.78, 134.06, 159.66. Anal. Calcd. for $C_{16}H_{15}NO_3SCl_2$: C, 51.62; H, 4.06; N, 3.76 %. Found: C, 51.72; H, 4.10; N, 3.82 %. Mass spectrum EIMS (M^+): 372.

2,6-dimethoxycarbonyl-3,5-diphenyl-*N*-hydroxy -tetrahydro-1,4-thiazine-1,1-dioxide (6d).

m.p. 230-232ºC, yield 70%. IR: ν_{max} (KBr, cm^{-1}): 3322 (*N*-OH), 1645 (C=O), 1335, 1308, 1128 (SO_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 3.52 (COOC**H**$_3$) (s, 6H), 4.21 (H-2 & H-6) (d, 2H), 4.74 (H-3 & H-5) (d, 2H), 4.60 (*N*-OH) (s, 1H), 7.20-7.50 (m, 10H, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 53.21 (COO**C**H_3), 59.21 (C-3 & C-5), 69.92 (C-2 & C-6), 127.63, 128.40, 138.98, 163.70 (C=O). Anal. Calcd. for $C_{20}H_{21}NO_7S$: C, 57.27; H, 5.05; N, 3.34 %. Found: C, 57.38; H, 5.15; N, 3.40 %. Mass spectrum EIMS (M^+): 419.

2,6-dimethoxycarbonyl-3,5-bis(*p*-methoxyphenyl) -*N*-hydroxy-tetrahydro-1,4-thiazine-1,1-dioxide (6e).

m.p. 225-227ºC, yield 52%. IR: ν_{max} (KBr, cm^{-1}): 3340 (*N*-OH), 1628 (C=O), 1348, 1305, 1125 (SO_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 3.54 (COOC**H**$_3$), (s, 6H), 3.80 (OCH_3) (s, 6H), 4.27 (H-2 & H-6) (d, 2H), 4.63 (*N*-OH) (s, 1H), 4.70 (H-3 & H-5) (d, 2H), 6.80 (H-3' & H-5') (d, 4H, *J* = 7.8 Hz, -Ar-H), 7.35 (H-2' & H-6') (d, 4H, *J* = 7.8 Hz, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 52.41 (O**C**H_3), 53.13 (COO**C**H_3), 59.94 (C-3 & C-5), 69.96 (C-2 & C-6), 114.01, 132.01, 134.41, 159.00, 164.02 (C=O). Anal. Calcd. for $C_{22}H_{24}NO_9S$: C, 55.11; H, 5.26; N, 2.92 %. Found: C, 55.20; H, 5.30; N, 3.00 %. Mass spectrum EIMS (M^+): 479.

2,6-dimethoxycarbonyl-3,5-bis(*p*-chlorophenyl)-*N*-hydroxy-tetrahydro-1,4-thiazine-1,1-dioxide (6f).

m.p. 235-237ºC, yield 75%. IR: ν_{max} (KBr, cm^{-1}): 3327 (*N*-OH), 1690 (C=O), 1332, 1309, 1135 (SO_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 3.52 (COOC**H**$_3$), (s, 6H), 4.22 (H-2 & H-6) (d, 2H), 4.62 (*N*-OH) (s, 1H), 4.72 (H-3 & H-5) (d, 2H), 7.25-7.40 (m, 8H, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 53.43 (COO**C**H_3), 58.92 (C-3 & C-5), 69.16 (C-2 & C-6), 114.71, 132.91, 136.43, 158.70, 162.42 (C=O). Anal. Calcd. for $C_{20}H_{19}NO_7SCl_2$: C, 49.19; H, 3.92; N, 2.87 %. Found: C, 49.29; H, 3.99; N, 2.95 %. Mass spectrum EIMS (M^+): 488.

2,6-diethoxycarbonyl-3,5-diphenyl-*N*-hydroxy-tetrahydro-1,4-thiazine-1,1-dioxides (6g).

m.p. 197-199ºC, yield 65%. IR: ν_{max} (KBr, cm^{-1}): 3437 (*N*-OH), 1634 (C=O), 1349, 1312, 1115 (SO_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 1.20 ($COOCH_2C\mathbf{H_3}$), (t, 3H, *J* = 7.2 Hz), 4.10 ($COOC\mathbf{H}_2CH_3$) (q, 2H, *J* = 7.2 Hz), 4.19 (H-2 & H-6) (d, 2H), 4.61 (*N*-OH) (s, 1H), 4.73 (H-3 & H-5) (d, 2H), 7.23-7.38 (m, 10H, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 13.54 ($COOCH_2\mathbf{C}H_3$), 61.01 (C-3 & C-5), 61.04 ($COO\mathbf{C}H_2CH_3$), 65.94 (C-2 & C-6), 126.14, 134.91, 136.43, 159.72, 167.26 (C=O). Anal. Calcd. for $C_{22}H_{25}NO_7S$: C, 59.05; H, 5.63; N, 3.13 %. Found: C, 59.15; H, 5.69; N, 3.18 %. Mass spectrum EIMS (M^+): 447.

2,6-diethoxycarbonyl-3,5-bis(*p*-methoxyphenyl) -*N*-hydroxy-tetrahydro-1,4-thiazine-1,1-dioxide (6h).

m.p. 192-194ºC, yield 53%. IR: ν_{max} (KBr, cm^{-1}): 3410 (*N*-OH), 1628 (C=O), 1336, 1310, 1120 (SO_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 1.21 ($COOCH_2C\mathbf{H_3}$), (t, 3H, *J* = 7.2 Hz), 3.80 (OCH_3) (s, 6H), 4.13 ($COOC\mathbf{H}_2CH_3$) (q, 2H, *J* = 7.2 Hz), 4.24 (H-2 & H-6) (d, 2H), 4.62 (*N*-OH) (s, 1H), 4.73 (H-3 & H-5) (d, 2H), 6.80 (H-3' & H-5') (d, 4H, *J* = 7.8 Hz,-Ar-H), 7.32 (H-2' & H-6') (d, 4H, *J* = 7.8 Hz,-Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 13.01 ($COOCH_2\mathbf{C}H_3$), 55.05 ($O\mathbf{C}H_3$), 62.03 ($COO\mathbf{C}H_2CH_3$), 62.41 (C-3 & C-5), 69.82 (C-2 & C-6), 126.74, 134.92, 136.74, 159.41, 167.62 (C=O). Anal. Calcd. for $C_{24}H_{29}NO_9S$: C, 56.79; H, 5.76; N, 2.76 %. Found: C, 56.88; H, 5.79; N, 3.01 %. Mass spectrum EIMS (M^+): 507.

2,6-diethoxycarbonyl-3,5-bis(*p*-chlorophenyl)-*N*-hydroxy-tetrahydro-1,4-thiazine-1,1-dioxide (6i).

m.p. 190-192ºC, yield 55%. IR: ν_{max} (KBr, cm^{-1}): 3430 (*N*-OH), 1656 (C=O), 1345, 1317, 1121 (SO_2). ^{1}H-NMR (400 MHz, $CDCl_3$) δ_H: 1.22 ($COOCH_2C\mathbf{H_3}$), (t, 3H, *J* = 7.2 Hz), 4.09 ($COOC\mathbf{H}_2CH_3$) (q, 2H, *J* = 7.2 Hz), 4.20 (H-2 & H-6) (d, 2H), 4.62 (*N*-OH) (s, 1H), 4.70 (H-3 & H-5) (d, 2H), 7.25-7.38 (m, 8H, -Ar-H). ^{13}C-NMR (100 MHz, $CDCl_3$) δ_C: 13.64 ($COOCH_2\mathbf{C}H_3$), 61.01 ($COO\mathbf{C}H_2CH_3$), 62.62 (C-3 & C-5), 69.34 (C-2 & C-6), 124.72, 133.22, 136.54, 159.89, 167.82 (C=O). Anal. Calcd. for $C_{22}H_{23}NO_7SCl_2$: C, 51.17; H, 4.49; N, 2.71 %. Found: C, 51.29; H, 4.60; N, 2.80 %. Mass spectrum EIMS (M^+): 516.

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