N-Alkyl-4-chloro-1*H*-benzo[*c*][1,2]thiazine-3-carbaldehyde-2,2-dioxides - New Functional Benzothiazine Derivatives

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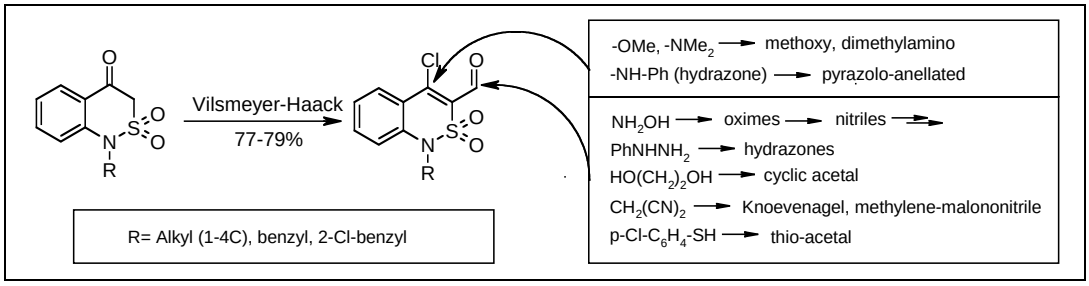

A synthesis of *N*-alkyl-4-chloro-1*H*-benzo[*c*][1,2]thiazine-3-carbaldehyde-2,2-dioxides is described. Reactivity of new β-chloroaldehydes is investigated, a number of novel benzo[*c*][1,2]thiazine derivatives are synthesized and characterized using ^{1}H, ^{13}C-NMR, MS and elemental analysis.

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INTRODUCTION

Benzo[*c*][1,2]thiazine nucleus is present in many synthetic pharmacologically active compounds. The derivatives of this heterocycle are shown to possess anti-inflammatory, antiviral, CNS-depressive properties [1].

Much attention has been focused on approaches for the construction of the 1*H*-benzo[*c*][1,2]thiazin-4-one system. The synthesis of this compound starting from sulfoacetic acid was reported [2a-b]. Also, new methods of accessing these important compounds continue to be developed. Several hetero-annelated benzothiazine analogues were synthesized [3-4].

Nevertheless, the methylene group, carbonyl moiety and the fused benzene ring of benzothiazinone provide an opportunity for further modification. The introduction of functional groups in the unsubstituted positions of thiazine, and heterocycles fused at the [c] side of thiazine ring are the objectives of actual research.

RESULTS AND DISCUSSION

We have carried out the synthesis [5] of several N-alkyl substituted benzothiazines (Scheme I, Table 2). Sulfonylation of 2-aminobenzoic acid ethyl ester **1** with methanesulfonylchloride in dry dioxane provided 2-methanesulfonylamino-benzoic acid ethyl ester **2** in high yield. Triethylamine was used as the base.

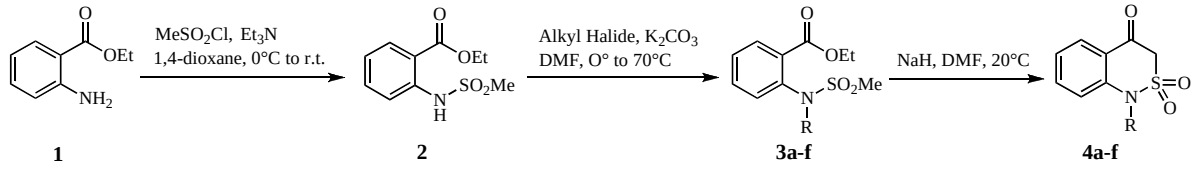
Subsequent alkylation of **2** with a range of alkyl halides in DMF afforded ethyl N-alkyl-methylsulfonylamino-benzoates **3a-f** and was followed by their treatment with sodium hydride in dry DMF to produce *N*-alkyl-1*H*-benzo[*c*][1,2]thiazin-4-one-2,2-dioxides **4a-f**. The ring closure occurred in good to excellent yields.

The Vilsmeier-Haack reaction performed with ketones **4a-b,d-e** led to β-chloroaldehydes **5** (Scheme II, Table 1). It was discovered, that if the molar ratio of **4** and the Vilsmeier reagent is 1:4, then pure *N*-alkyl-4-chloro-1*H*-benzo[*c*][1,2]thiazine-3-carbaldehyde-2,2-dioxides **5a-b,d-e** could be obtained and in good to excellent yields.

During the last 25 years, chloroformylation became a convenient transformation providing access to the intermediates widely used in pharmaceutical-directed organic synthesis [6-10]. The novel β-chloroaldehyde compounds **5** contain two electrophilic centers: the carbon atom C-4 of the benzothiazine system and the carbon atom of the aldehyde group. We have investigated the reactivity of both centers.

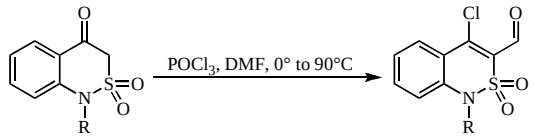
Scheme 3 illustrates reactions of β-chloroaldehydes **5a-d** with hydroxylamine, phenyl-hydrazine, ethane-1,2-diol,

Scheme I



Synthesis of benzothiazinone derivatives

Scheme II



4a-b, d-e **5a-b, d-e**

Synthesis of chloroaldehydes by Vilsmeier-Haack reaction

dioxane to obtain the corresponding methoxy-aldehyde **13e** in quantitative yield (Scheme IV).

Treatment of the protected compound **8b** with nucleophiles (potassium thiophenolate, sodium ethoxide) forced the deprotection and the mixture of corresponding thioacetals and acetals with the aldehyde and starting dioxolane was isolated.

The chlorine atom could also be substituted intramolecularly. Refluxing hydrazone **7b** in DMF for 3 h

Table 1

Physical Data of *N*-Alkyl-4-chloro-1*H*-benzo[*c*][1,2]thiazine-3-carbaldehyde-2,2-dioxides **5a-b,d-e**

Yield, (%)	R	^{1}H NMR (DMSO/TMS) δ, *J* (Hz)	^{13}C NMR (DMSO/TMS) δ, *J* (Hz)	m.p., ° C	Mass (CI)	Analysis(%) Calcd/Found S,Cl,C,H,N
5a (91)	CH_3	3.501 (s, 3H, CH_3), 7.492 (t, *J* = 7.6 Hz, 1H), 7.58 (d, *J* = 7.8 Hz, 1H), 7.87 (t, *J* = 8 Hz, 1H), 8,17 (d, *J* = 7.8 Hz, 1H) 10.107 (s, 1H, CH)	32.1, 119.1, 120.5, 125.1, 129.6, 129.8, 136.6, 141.3, 149.5, 184.2	109-111	238 $(M+H)^+$	12.43 13.79 12.42 13.79 46.61 3.13 46.58 3.10 5.44 5.50
5b (77)	C_2H_5	1.33 (t, *J* = 6.8 Hz, 3H), 4.11 (q, *J* = 7.2 Hz, 2H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.807 (t, *J* = 8.2 Hz, 1H), 8,14 (d, *J* = 8.2 Hz, 1H) 10.10 (s, 1H, CH)	15.0, 43.2, 119.9, 121.4, 125.3, 129.7, 130.5, 136.4, 140.3, 149.3, 183.9	85-87	252 $(M+H)^+$	11.78 13.07 11.77 13.08 48.62 3.71 48.70 3.80 5.15 5.12
5d (97)	*n*-C_4H_9	0.95 (t, *J* = 7.6 Hz, 3H), 1.32 (m, 2H), 1.65 (m, 2H), 4.06 (q, *J* = 7.8 Hz, 2H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.60 (d, *J* = 7.6 Hz, 1H), 7.81 (t, *J* = 8.2 Hz, 1H), 8,15 (d, *J* = 7.8 Hz, 1H) 10.11 (s, 1H, CH)	13.9, 19.8, 30.8, 46.9, 120.0, 121.4, 125.3, 129.7, 130.3, 136.4, 140.3, 149.2, 183.9	52-53	296 $(M+H)^+$	10.68 11.85 10.70 11.83 52.09 4.71 52.19 4.79 4.67 4.72
5e (87)	$C_6H_5CH_2$	5.28 (s, 2H), 7.23-7.30 (m, 5H), 7.42 (t, *J* = 7.8 Hz, 1H), 7.48 (d, *J* = 7.6 Hz, 1H), 7,707 (t, *J* = 7.6 Hz, 1H), 8.12 (d, *J* = 7.8 Hz, 1H), 10.125 (s, 1H, CH)	50.4, 120.6, 121.8, 125.7, 127.8, 128.6, 129.5, 129.7, 130.8, 136.3, 140.2, 149.4, 183.9	114-116	314 $(M+H)^+$	09.60 10.64 09.60 10.63 57.57 3.62 57.52 3.68 4.20 4.24

malononitrile and the 4-chloro-benzenethiol, which accordingly lead to oximes **6a-b,d-e**, hydrazones **7b,e**, [1,3]-dioxolanes **8b,e**, methylene-malononitrile **9b** and the (4-chlorophenylsulfanyl)-methanol **10b** respectively. The aldehyde group is a target for all these nucleophiles (Scheme III).

Our attempt to substitute the chlorine atom in **5b** by the 4-chlorophenylthio group failed. Reaction with sodium methoxide led to an unidentified mixture and so it was decided to use the protected compounds **8** in all transformations, concerning the substitution of the chlorine atom.

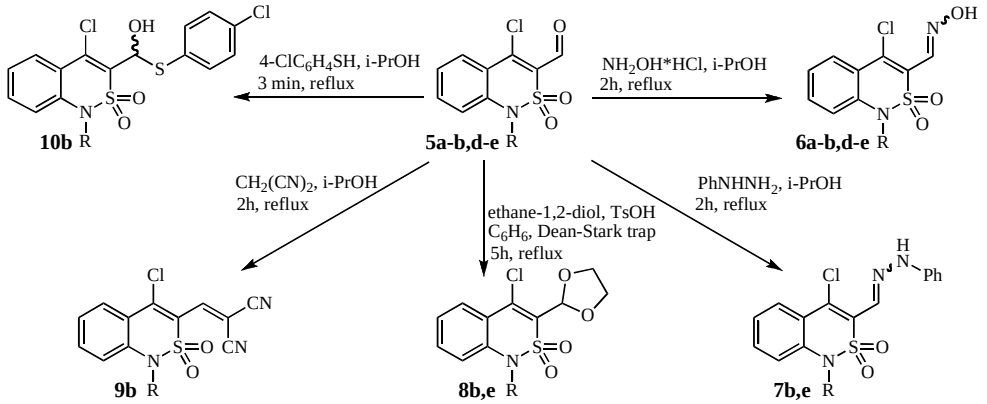
For example, the reaction of **8b** with sodium methoxide in methanol leads to the methoxy-dioxolane **8e**, followed by deprotection of **8e** by refluxing with HCl in 1,4-

afforded 5-ethyl-1-phenyl-1,5-dihydrobenzo[*c*]pyrazolo [3,4-*e*][1,2]thiazine **11b**. This compound is the first representative of the new heterocyclic system (SchemeV).

An attempt to employ oxime **6e** for analogous transformation to obtain the corresponding isoxazole did not succeed and led to β-chloronitrile **12e**. The nitrile was also the product of the reaction of **6e** with sodium hydride in dry DMF (Scheme V).

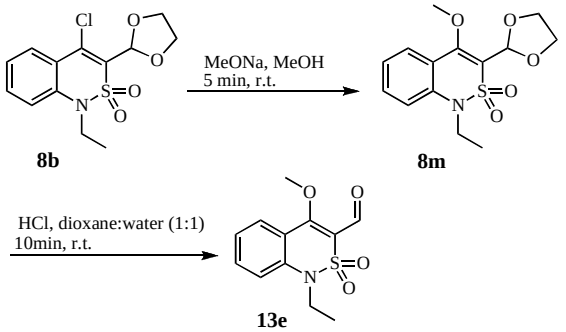
Chloronitriles of the type **12**, like chloroaldehydes **5**, include 1,3-electrophilic system and could serve as useful intermediates for the synthesis of more elaborate structures. In addition to the methods described above, compounds **12** are accessible by stirring a suspension of the oxime **6** in benzene with 5 equivalents of excess thionyl chloride at room temperature overnight (Scheme V). The yield of target compounds **12** is quantitative.

Scheme III



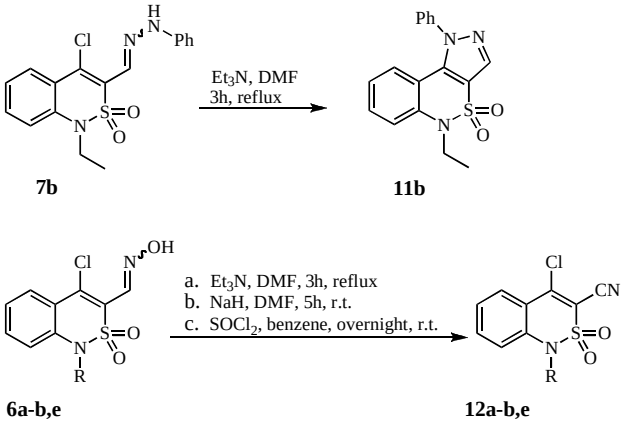
Nucleophilic reactions of the carbonyl moiety

Scheme IV



Selectivity achieved using protected intermediate

Scheme V

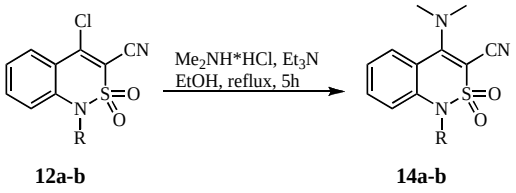


Benzothiazine derivatives transformations

There is important distinction between **12** and **5** that has to be considered when planning synthesis. In chloroaldehydes, carbonyl is more reactive toward nucleophiles than C-4 center, but we assumed that in chloronitriles the substitution of the chlorine atom would be much faster then the nucleophilic addition to the nitrile group. This assumption was verified experimentally. Thus, by refluxing the mixture of **12**, dimethylamine and triethylamine in ethanol dimethylamino-derivatives **14** were obtained (Scheme VI).

Consequently, every two-stage heterocyclisation process starts with nucleophilic attack at the C-4 position of the β-chloronitrile followed by the addition to the nitrile group resulting in the ring closure. The reaction of **12** with methyl thioglycolate proceeds by reflux in isopropanol with potassium carbonate in two stages (Scheme VII). The nucleophilic substitution by the thioglycolate anion led to sulfanylacetic acid methyl ester **15** which is not isolated pure but is rapidly converted to the thiophene-amino carboxylic acid ester **16**. The progress of the heterocyclisation is easy to control by means of ^{1}H-NMR, measured from the mixture.

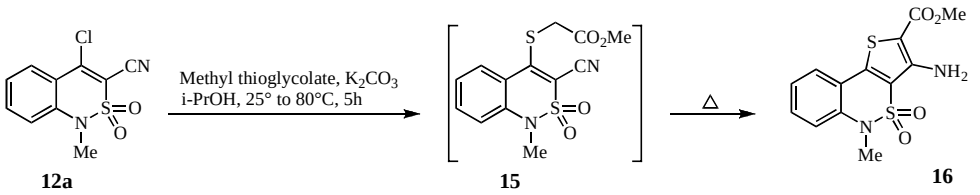
Scheme VI



Displacement of chlorine by dimetylamine

Aminopyrazoles **17** are accessible by refluxing **12** with the corresponding hydrazine in isopropanol with potassium carbonate With N-substituted hydrazine only one isomer is formed in both cases. The two-step process starting from fast chlorine substitution (Scheme VIII) is analogous to the thioglycolic ester cyclisation.

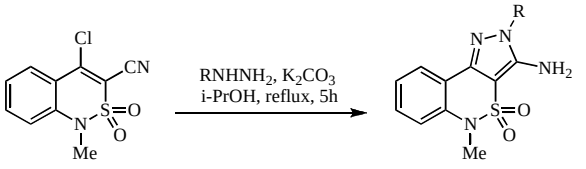
Scheme VII



12a **15** **16**

Synthesis of thieno-annelated benzothiazine

Scheme VIII



12a

17a (R=H)
17b (R=Ph)
17c (R= $-C_6H_4-NO_2$)

Synthesis of pyrazolo-annelated benzothiazine

EXPERIMENTAL

The NMR spectra were measured on a Varian 400 spectrometer at 25℃ using DMSO-d_6. All chemical shifts are reported in ppm relative to TMS. Starting materials used were obtained from Makrochim and used without further purification. Dry solvents were prepared according to the standard methods.

Ethyl 2-alkylmethylsulfonylamido-benzoates (3a-f); General Procedure. To a magnetically stirred solution of ethyl 2-methylsulfonylamidobenzoate (19.3 g, 78 mmol) in dry DMF (35 mL) at 0 ℃ was added potassium carbonate (22 g, 0.16 mol). The reaction mixture was stirred for 15 min at 0 ℃, then the alkyl halide (100 mmol) was added dropwise. The mixture was slowly heated to 70 ℃. After 8 hours, the inorganics were filtered off, the solution was concentrated *in vacuo* and the crude product was washed with water and filtered (oily products were extracted in chloroform 3x150mL, washed with water, dried and the solvent evaporated *in vacuo*). The pure product was obtained by crystallisation from i-PrOH (61-88%).

Product 3a (73%): m.p.: 56-58 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 1.29 (t, *J* = 7.6 Hz, 3H), 2.98 (s, 3H), 3.22 (s, 3H), 4.25 (q, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 8 Hz, 1H), 7.57 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H); MS (CI): 258(M+H)$^+$.

Product 3b (82%): m.p.: 61-63 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 1.06 (t, *J* = 7.8 Hz, 3H), 1.29 (t, *J* = 8.2 Hz, 3H),

Table 2

Physical Data of *N*-Alkyl-1*H*-benzo[*c*][1,2]thiazin-4-one-2,2-dioxides **4a-f**

Yield, (%)	R	m.p., ˚ C	^{1}H NMR (DMSO/TMS) δ, *J* (Hz)	IR (KBr)
4a (67)	CH_3	107-108	3.37 (s, 3H, CH_3), 4.96 (s, 2H, CH_2), 7.30 (t, *J* = 7.6 Hz, 1H), 7.42 (d, *J* = 8.4 Hz, 1H), 7.78 (t, *J* = 8 Hz, 1H), 8.00 (d, *J* = 8 Hz, 1H)	2973, 2920, 1687, 1599, 1457,1332, 1318, 1146 cm^{-1}
4b (66)	C_2H_5	86-88	1.28 (t, *J* = 6.8 Hz, 3H), 4.02 (q, *J* = 7.2 Hz, 2H), 4.91 (s, 2H, CH_2), 7.28 (t, *J* = 7.2 Hz, 1H), 7.47 (d, *J* = 8.8 Hz, 1H), 7.76 (t, *J* = 7.2 Hz, 1H), 8.00 (d, *J* = 8 Hz, 1H)	2987, 2925, 1680, 1579, 1453,1342, 1321, 1151 cm^{-1}
4c (98)	*n*-C_3H_7	84-86	0.99 (t, *J* = 6.7 Hz, 3H), 1.75 (m, 2H), 3.88 (t, *J* = 7 Hz, 2H), 4.70 (s, 2H, CH_2), 7.23 (t, *J* = 7.2 Hz, 1H), 7.36 (d, *J* = 8.2 Hz, 1H), 7.70 (t, *J* = 6.8 Hz, 1H), 8.01 (d, *J* = 8 Hz, 1H)	2987, 2925, 1682, 1589, 1467,1340, 1289, 1157 cm^{-1}
4d (70)	*n*-C_4H_9	49-51	0.92 (q, *J* = 7.2 Hz, 3H), 1.31 (m, 2H), 1.65 (m, 2H), 4.06 (t, *J* = 8 Hz, 2H), 4.70 (s, 2H, CH_2), 7.46 (t, *J* = 7.6 Hz, 1H), 7.70 (d, *J* = 8.4 Hz, 1H), 7.82 (t, *J* = 8 Hz, 1H), 8.02 (d, *J* = 7.6 Hz, 1H)	2961, 2873, 1684, 1598, 1477,1339, 1297, 1154 cm^{-1}
4e (90)	$C_6H_5CH_2$	79-81	4.69 (s, 2H), 5.35 (s, 2H, CH_2), 7.29-7.37 (m, 5H, phenyl), 7.51 (t, *J* = 6.8 Hz, 1H), 7.62 (d, *J* = 8 Hz, 1H), 7.71 (t, *J* = 7.6 Hz, 1H), 8.02 (d, *J* = 6.8 Hz, 1H)	2926, 1687, 1598, 1349, 1226, 1162 cm^{-1}
4f (94)	2-$ClC_6H_4CH_2$	72-73	4.72 (s, 2H), 5.41 (s, 2H), 7.24-7.32 (m, 4H), 7.54 (t, *J* = 6.8 Hz, 1H), 7.65 (d, *J* = 6.8 Hz, 1H), 7.72 (t, *J* = 6.8 Hz, 1H), 8.04 (d, *J* = 6.8 Hz, 1H)	3435, 2985, 1689, 1476, 1347, 1160 cm^{-1}

Structures of all above-mentioned compounds were established on the basis of their ^{1}H NMR, ^{13}C NMR, IR spectral data, mass spectrometry data and elemental microanalyses.

In conclusion, a synthesis of *N*-alkyl-4-chloro-1*H*-benzo[*c*][1,2]thiazine-3-carbaldehyde-2,2-dioxides **5a-b, d-e** from *N*-alkyl-1*H*-benzo[*c*][1,2]thiazin-4-one-2,2-dioxides is disclosed. The investigation of the reactivity of the new β-chloroaldehydes was carried out resulting in the preparation of a number of previously unknown benzo[*c*]-[1,2]thiazine derivatives.

2.95 (s, 3H), 3.67 (q, *J* = 8 Hz, 2H), 4.25 (q, *J* = 7.8 Hz, 2H), 7.48 (t, *J* = 7.6 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.77 (d, *J* = 7.8 Hz, 1H); MS (CI): 273(M+H)$^+$.

Product 3c (75%): m.p.: 35-37 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 0.82 (t, *J* = 7.6 Hz, 3H), 1.29 (t, *J* = 7.4 Hz, 3H), 1.46 (m, 2H), 2.95 (s, 3H), 3.56 (br.s, 2H), 4.24 (q, *J* = 7.8 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.55 (s, 1H), 7.63 (t, *J* = 8.2 Hz, 1H), 7.77 (d, *J* = 8 Hz, 1H); MS (CI): 287(M+H)$^+$.

Product 3d (oil, 61%): ^{1}H NMR (400 MHz, DMSO): δ = 0.92 (t, *J* = 8.2 Hz, 3H), 1.29 (t, *J* = 8 Hz, 3H), 1.31 (m, 2H), 1.65 (m, 2H), 2.90 (s, 3H), 4.06 (br.s, 2H), 4.23 (q, *J* = 7.8 Hz, 2H,), 7.45 (t, *J* = 7.6 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.79 (t, *J* = 7.6 Hz, 1H), 7.89 (d, *J* = 8 Hz, 1H); MS (CI): 300(M+H)$^+$.

Product 3e (oil, 88%): ^{1}H NMR (400 MHz, DMSO): δ = 2.92 s, 3H), 5.25 (br.s, 2H), 7.28-7.35 (m, 5H), 7.45 (t, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.61 (t, *J* = 7.6 Hz, 1H), 7.81 (s, 1H); MS (CI): 334(M+H)$^+$.

Product 3f (oil, 78%): ^{1}H NMR (400 MHz, DMSO): δ = 2.96 (s, 3H), 5.34 (br.s, 2H), 7.23-7.30 (m, 4H), 7.44 (t, *J* = 7.6 Hz, 1H), 7.55 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 8 Hz, 1H), 7.83 (d, *J* = 7.6 Hz, 1H); MS (CI): 368(M+H)$^+$.

***N*-Alkyl-3,4-dihydro-(1*H*)-2,1-benzothiazin-4-one-2,2-dioxides (4a-f), Table 2; General Procedure.** To a magnetically stirred suspension of sodium hydride (120 mmol) in dry DMF (15 mL) at r.t., the solution of alkylated product (**3a-f**) (60 mmol) in dry DMF was added dropwise (25 mL). After hydrogen evolution was over, the mixture was stirred for 4 hours, DMF was evaporated, and dilute hydrochloric acid (250 mL) was added to the residue. The crude product was collected by filtered and washed with water. Recrystallisation from i-PrOH afforded pure target products (67-98%).

4-Chloro-1-alkyl-(1*H*)-2,1-benzothiazin-3-carbaldehyde-2,2-dioxides (5a-b,d-e), Table 1; General Procedure. To magnetically stirred dry DMF (14 mL) at 0 ˚C was added phosphorus oxychloride (8.3 mL, 40 mmol). After 30 minutes at 0 ˚C the solution of benzothiazine-4-one (**4a-b,d-e**, 10 mmol) in dry DMF was added dropwise. The mixture obtained was stirred for 10 hours, then the temperature was gradually raised to 75 ˚C. The solution was concentrated *in vacuo*. To the resulting brown oil ice was added (250 mL) and the mixture was filtered to yield pure product (77-97%).

4-Chloro-1-alkyl-(1*H*)-2,1-benzothiazin-3-carbaldehyde-2,2-dioxide oximes (6a-b,d-e); General Procedure. To a solution of β-chloroaldehyde (**5a-b,d-e**) (250 mg, 1 mmol) in i-PrOH (2 mL) was added hydroxylamine hydrochloride (90 mg, 3 mmol). The mixture was heated to reflux for 3 hours. After cooling to r.t the solid product was filtered and washed with i-PrOH to afford pure target compound (62-89%).

Product 6a (80%): m.p.: 203-205 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 3.50 (s, 3H), 7.36 (t, *J* =7.6 Hz, 1H), 7.46 (d, *J* = 7.8 Hz, 1H), 7.66 (t, *J* = 8 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H) 8.19 (s, 1H), 12.37 (s, 1H);

^{13}C NMR (100 MHz, DMSO): δ = 33.0, 119.2, 121.3, 124.9, 128.3, 128.8, 133.9, 137.5, 139.5, 141.3; *Anal.*calcd. S, 11.73; Cl, 13.02; C, 44.04; H, 3.33; N, 10.27; found S, 11.75; Cl, 13.02; C, 44.09; H, 3.38; N, 10.32.

Product 6b (89%): m.p.: 179-181 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 1.30 (t, *J* = 6.8 Hz, 3H), 4.08 (q, *J* = 7 Hz, 2H), 7.37 (t, *J* = 6.8 Hz, 2H), 7.54 (d, *J* = 7.6 Hz, 1H), 7.66 (t, *J* = 7.8 Hz, 1H), 7.98 (d, *J* = 8.2 Hz, 1H) 8.19 (s, 1H), 12.40 (s, 1H);

^{13}C NMR (100 MHz, DMSO): δ = 14.7, 44.2, 120.3, 122.4, 125.2, 128.4, 129.9, 133.7, 137.2, 138.5, 141.3; *Anal.* calcd. S, 11.16; Cl, 12.38; C, 46.08; H, 3.87; N, 9.77; found S, 11.17; Cl, 12.45; C, 46.12; H, 3.91; N, 9.80.

Product 6d (67%): m.p.: 142-143 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 0.90 (t, *J* = 6.8 Hz, 3H), 1.28 (sex, *J* = 6.8 Hz, 2H), 1.61 (q, *J* = 7 Hz, 2H), 4.01 (t, *J* = 7.6 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.51 (d, *J* = 7.8 Hz, 1H), 7.63 (t, *J* = 7.8 Hz, 1H), 7.97 (d, *J* = 8 Hz, 1H) 8.19 (s, 1H), 12.36 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ = 13.9, 19.7, 30.6, 47.8, 120.4, 122.5, 125.2, 128.4, 129.7, 133.7, 137.0, 138.5, 141.2; *Anal.*calcd. S, 10.16; Cl, 11.27; C, 49.60; H, 4.80; N, 8.90; found S, 10.17; Cl, 11.3; C, 49.63; H, 4.85; N, 8.92.

Product 6e (62%): m.p.: 210-212 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 5.22 (s, 2H), 7.20-7.32 (m, 5H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.55 (t, *J* = 7.6 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 8.18 (s, 1H), 12.43 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ = 50.5, 119.9, 122.1, 124.9, 125.1, 126.3, 126.9, 127.5, 128.0, 129.5, 133.3, 136.9, 138.2, 140.9; *Anal.* calcd. S, 9.17; Cl, 10.17; C, 49.10; H, 3.96; N, 9.16; found S, 9.17; Cl, 10.18; C, 49.14; H, 4.02; N, 9.19.

4-Chloro-1-alkyl-(1*H*)-2,1-benzothiazin-3-carbaldehyde-2,2-dioxide N-phenylhydrazones (7b,e); General Procedure. To a solution of β-chloroaldehyde (**5b,e**) (250 mg, 1 mmol) in i-PrOH (2 mL) was added phenylhydrazine (120 mg, 1.2 mmol). The mixture was heated to reflux for 5 hours. After cooling to rt. the solid product was filtered and washed with i-PrOH to afford pure target compound (68-75%).

Product 7b (75%): ^{1}H NMR (400 MHz, DMSO): δ = 1.31 (t, *J* = 6.8 Hz, 3H), 4.08 (q, *J* = 6.8 Hz, 2H), 6.84 (t, *J* = 7 Hz, 1H), 7.13 (d, *J* = 7.8 Hz, 2H), 7.235 (t, *J* = 7.8 Hz ,2H), 7.35 (t, *J* = 7.6 Hz, 1H), 7.48 (d, *J* = 7.8 Hz, 1H), 7.56 (t, *J* = 8 Hz, 1H), 7.94 (d, *J* = 7.8 Hz, 1H), 7.99 (s, 1H), 11.02 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ = 14.7, 44.2, 113.6, 120.3, 121.3, 123.2, 125.2, 127.5, 127.9, 130.0, 131.1, 132.3, 133.0, 137.9, 144.6; *Anal.* calcd. S, 8.84; Cl, 9.81; C, 56.43; H, 4.46; N, 11.61; found S, 8.8; Cl, 9.82; C, 56.47; H, 4.42; N, 11.57.

Product 7e (68%): ^{1}H NMR (400 MHz, DMSO): δ = 5.21 (s, 2H), 6.82 (t, *J* = 6.8 Hz, 2H), 7.12- 7.35 (m, 11H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.89 (d, *J* = 7.6 Hz, 1H) 8.0 (s, 1H), 11.0 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ = 51.6, 113.6, 120.6, 121.3, 123.3, 125.3, 127.5, 127.7, 127.9, 128.4, 128.5, 129.0, 129.3, 130.0, 131.1, 132.1, 133.1, 136.7, 137.8, 144.6; *Anal.* calcd. S, 7.55; Cl, 8.37; C, 62.33; H, 4.28; N, 9.91; found S, 7.55; Cl, 8.4; C, 62.31; H, 4.24; N, 9.95.

4-Chloro-3-(1,3-dioxolan-2-yl)-1-alkyl-(1*H*)-2,1-benzothiazin-2,2-dioxides; General Procedure (8b,e). To a mixture of β-chloroaldehyde (**5b,e**) (500 mg, 2 mmol) and ethane-1,2-diol (3 mmol) in dry benzene (15 mL) the catalytic amount of 4-tolylsulfonic acid (5 mol%) was added. The reaction flask was equipped with a Dean-Stark trap and the mixture was refluxed for 5 hours. After cooling to r.t. the organic layer was separated, washed extensively with water and evaporated *in vacuo* to afford yellow solid, which was puified by crystallysation from i-PrOH.

Product 8b (87%): m.p.: 121-123 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 1.24 (t, *J* = 7 Hz, 3H), 3.97-4.05 (m, 4H), 4.20 (q, *J* = 7.2 Hz, 2H), 6.29 (s, 1H), 7.37 (t, *J* = 7.8 Hz, 1H), 7.52 (d, *J* = 7.6 Hz, 1H), 7.64 (t, *J* = 7.6 Hz, 1H), 7.98 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO): δ = 14.3, 44.2, 66.4, 100.9, 112.2, 120.5, 122.6, 125.2, 128.5, 132.7, 133.8, 138.9, 139.4; *Anal.* calcd. S, 10.13; Cl, 11.24; C, 49.45; H, 4.47; N, 4.44; found S, 10.12; Cl, 11.04; C, 49.49; H, 4.43; N, 4.45.

Product 8e (70%): m.p.: 149-151 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 4.01 (m, 2H), 4.22 (m, 2H), 5.21 (s, 2H), 6.33 (s,

1H), 7.22-7.33 (m, 6H), 7.41 (d, *J* = 7.8 Hz, 1H) 7.53 (t, *J* = 7.8 Hz, 1H), 7.93 (d, *J* = 8.2 Hz, 1H); ^{13}C NMR (100 MHz, DMSO): δ = 50.7, 66.1, 100.6, 111.9, 120.2, 122.3, 125.1, 126.8, 127.5, 127.6, 128.1, 128.2, 132.4, 133.4, 138.5, 139.1; *Anal*.calcd. S, 8.47; Cl, 9.39; C, 57.22; H, 4.27; N, 3.71; found S, 8.51; Cl, 9.42; C, 57.12; H, 4.31; N, 3.77.

2-(4-Chloro-1-ethyl-(1*H*)-2,1-benzothiazin-2,2-dioxide-3-yl-methylene)malononotrile (9b). To a solution of β-chloroaldehyde (**5b**) (250 mg, 1 mmol) in i-PrOH (2 mL) was added malononitrile (1 mmol). The mixture was heated to reflux for 2 hours. After cooling to r.t the solid product was filtered and washed with i-PrOH to afford pure target compound (73%). M.p.: 109-111 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 1.30 (t, *J* = 8 Hz, 3H), 4.12 (q, *J* = 8 Hz, 2H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.68 (d, *J* = 7.6 Hz, 1H), 7.81 (t, *J* = 7.8 Hz, 1H), 8.10 (d, *J* = 7.8 Hz, 1H), 8.92 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ = 14.3, 44.8, 91.2, 111.8, 113.3, 120.7, 122.3, 125.8, 128.5, 129.7, 135.6, 139.3, 144.6, 149.2; *Anal*.calcd. S, 10; Cl, 11.1; C, 52.59; H, 3.15; N, 13.14; found S, 9.88; Cl, 10.9; C, 52.63; H, 3.20; N, 13.19.

4-Chloro-1-ethyl-(1*H*)-2,1-benzothiazin-2,2-dioxide-3-yl-(4-chlorophenylsulfanyl)methanol (10b). To a solution of β-chloroaldehyde (**5b**) (250 mg, 1 mmol) in i-PrOH (2 mL) was added 4-chlorothiophenol (1 mmol). The mixture was heated to reflux for 3 minutes. After cooling to r.t the solid product was filtered and washed with i-PrOH to afford pure target compound (96%). M.p.: 184-186 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 1.31 (t, *J* = 8 Hz, 3H), 4.01 (q, *J* = 7.8 Hz, 2H), 6.13 (s, 1H), 7.29 (t, *J* = 7.8 Hz, 1H) 7.48 (d, *J* = 7.6 Hz, 1H), 7.53-7.62 (m, 6H), 7.93 (d, *J* = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, DMSO): δ = 14.7, 41.5, 119.5, 119.6, 121.2, 124.1, 127.2, 128.0, 131.2, 133.0, 136.1, 136.9, 138.9, 146.5; *Anal*.calcd. S, 15.37; Cl, 17.05; C, 49.04; H, 3.63; N, 3.36; found S, 15.24; Cl, 17.1; C, 49.14; H, 3.58; N, 3.41.

***N*-Phenyl-5-ethyl-1,5-dihydrobenzo[*C*]pyrazolo[3,4-*e*][1,2]-thiazin-2,2-dioxide (11b).** 4-Chloro-1-ethyl-(1*H*)-2,1-benzothiazine-3-carbaldehyde-2,2-dioxide N-phenylhydrazone (**7b**) (300 mg, 0.9 mmol) was dissolved in dry DMF (1.5 mL), the catalytic amount of triethylamine was added and the mixture obtained was heated to reflux for 2 hours. The solution was concentrated *in vacuo*, solid product was washed with ethanol and filtered, which gave the title pure product (74%). M.p.: 151-153 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 1.25 (t, *J* = 6.8 Hz, 3H), 4.01 (q, *J* = 7 Hz, 2H), 6.99-7.05 (m, 2H), 7.46-7.63 (m, 7H) 8.17 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ = 14.1, 43.6, 117.0, 119.7, 122.7, 124.9, 125.2, 127.4, 130.7, 130.9, 131.8, 133.6, 138.1, 138.8, 139.7; *Anal*.calcd. S, 9.83; N, 12.91; C, 62.75; H, 4.65; N, 12.91; found S, 9.84; N, 12.94; C, 62.81; H, 4.70; N, 12.97.

1-Benzyl-4-chloro-1*H*-2,1-benzothiazine-3-carbonitrile 2,2-dioxide (12e). 4-Chloro-1-benzyl-(1H)-2,1-benzothiazine-3-carbaldehyde-2,2-dioxide oxime (**6e**) (300 mg, 0.9 mmol) was dissolved in dry DMF (1 mL), catalytic amount of triethylamine was added and the mixture obtained was heated to reflux for 12 hours. The solution was concentrated *in vacuo*, solid product filtered, which gave the title pure product (65%). ^{1}H NMR (400 MHz, DMSO): δ = 5.01 (s, 2H), 7.07 (d, 1H), 7.16 (t, 1H), 7.2-7.34 (m, 5H), 7.38 (t, 1H), 7.91 (d, 1H); ^{13}C NMR (100 MHz, DMSO): δ = 50.5, 111.9, 119.3, 120.2, 122.3, 124.9, 126.3, 127.1, 127.6, 128.3, 129.8, 129.0, 132.4, 133.4, 138.54, 139.1; *Anal*.calcd. S, 9.67; Cl, 10.73; C, 58.10; H, 3.35; N, 8.47; found S, 9.65; Cl. 10.74; C, 58.16; H, 3.39; N, 8.52.

1-Benzyl-4-chloro-1*H*-2,1-benzothiazin-3-carbonitrile 2,2-dioxide (12e); Alternative Method. A solution of 4-chloro-1-benzyl-(1*H*)-2,1-benzothiazine-3-carbaldehyde-2,2-dioxide oxime (**6e**) (300 mg, 0.9 mmol) in dry DMF (0.5 mL) was added dropwise to a suspension of sodium hydride in dry DMF (1 mL). The resulting mixture was stirred for 2 hours. The solution was concentrated *in vacuo*, solid product filtered, which gave the title pure product (97%).

1-Alkyl-4-chloro-1*H*-2,1-benzothiazin-3-carbonitrile 2,2-dioxides (12a,b); General Procedure. Thionyl chloride (3.6 mL, 0.05 mol) was added dropwise to a suspension of 4-chloro-1-alkyl-(1*H*)-2,1-benzothiazine-3-carbaldehyde-2,2-dioxide oxime (**6a,b**) (2.5 g, 0.01 mol) in dry benzene (10 mL). The resulting mixture was stirred at room temperature overnight. The excess thionyl chloride and benzene were distilled off *in vacuo*, solid product washed with ethanol, collected by filtration and dried which gave the title pure compound (quantitative).

Product 12a (99%): m.p.: 153-154 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 3.61 (s, 3H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.64 (d, *J* = 8 Hz, 1H), 7.86 (t, *J* = 8.2 Hz, 1H), 8.06 (d, *J* = 7.8 Hz, 1H); MS (CI): 255(M+H)$^+$; *Anal*. calcd. S, 12.59; N, 11.00; C, 47.16; H, 2.77; N, 11.00; found S, 12.88; N, 10.91; C, 47.19; H, 2.82; N, 11.15.

Product 12b (99%): m.p.: 130-132 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 1.25 (t, *J* = 7.4 Hz, 3H), 3.92 (q, *J* = 7.4 Hz, 2H), 7.47 (t, *J* = 7.8 Hz, 1H), 7.61 (d, *J* = 8 Hz, 1H), 7.82 (t, *J* = 8.2 Hz, 1H), 8.02 (d, *J* = 8.2 Hz, 1H); MS (CI): 269(M+H)$^+$; *Anal*. calcd. S, 11.93; N, 10.42; C, 49.17; H, 3.38; N, 10.42; found S, 11.81; N, 10.13; C, 49.21; H, 3.44; N, 10.49.

1-Ethyl-4-methoxy-1*H*-2,1-benzothiazin-3-carbaldehyde 2,2-dioxide (13e). 4-Methoxy-3-(1,3-dioxolan-2-yl)-1-ethyl-(1*H*)-2,1-benzothiazin-2,2-dioxide (**8m**) (0.5 g, 0.16 mmol) was dissolved in 1,4-dioxane:water (1:1). Hydrochloric acid (3mL, conc.) was added to the solution and the mixture was stirred for 10min at room temperature. Solution was concentrated, solid product filtered and dried to give the pure title compound (97%). M.p.: 134-135 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 1.30 (t, *J* = 6.8 Hz, 3H), 3.87 (s, 3H), 4.08 (q, *J* = 7.2 Hz, 2H), 7.46 (t, *J* = 7.8 Hz, 1H), 7.63 (d, *J* = 7.8 Hz, 1H), 7.84 (t, *J* = 8.2 Hz, 1H), 8,02 (d, *J* = 8.2 Hz, 1H), 9.75 (s, 1H); MS (CI): 268 (M+H)$^+$; *Anal*.calcd. S, 12.00; N, 5.24; C, 53.92; H, 4.90; N, 5.24; found S, 12.17; N, 5.65; C, 53.98; H, 4.93; N, 5.29.

1-Alkyl-4-(*N*,*N*-dimethylamino)-1*H*-2,1-benzothiazin-3-carbonitrile 2,2-dioxides (14a,b); General Procedure. A solution of 4-chloro-1-alkyl-(1*H*)-2,1-benzothiazine-3-carbonitrile-2,2-dioxide (**12a,b**) (250 mg, 0.1 mmol), dimethylamine hydrochloride (100 mg, 0.12 mmol) and triethylamine (3 mL) in ethanol (10 mL) was refluxed for 5 hours. Solid product was collected by filtration, washed with ethanol and dried, which gave the title pure compound.

Product 14a (89%): m.p.: 161-162 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 3.26 (s, 6H), 3.35 (s, 3H), 7.33 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 8 Hz, 1H), 7.68 (t, *J* = 7.8 Hz, 1H), 7.79 (d, *J* = 8 Hz, 1H); MS (CI): 264(M+H)$^+$; *Anal*. calcd. S, 12.18; N, 15.96; C, 54.74; H, 4.98; N, 15.96; found S, 11.89; N, 15.94; C, 54.80; H, 5.12; N, 16.08.

Product 14b (94%): m.p.: 142 ˚C; ^{1}H NMR (400 MHz, DMSO): δ = 1.27 (t, *J* = 7.4 Hz, 3H), 3.24 (s, 6H), 3.95(q, *J* = 7.4 Hz, 2H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 7.8 Hz, 1H), 7.71 (t, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8 Hz, 1H); MS (CI): 278(M+H)$^+$; *Anal*. calcd. S, 11.56; N, 15.15; C, 56.30; H, 5.45; N, 15.15; found S,11.50; N, 15.10; C, 56.36; H, 5.49; N, 15.21.

Methyl 3-amino-5-methyl-5*H*-thieno[3,2-*c*][2,1]benzothiazine-2-carboxylate 2,2-dioxide (16). A mixture of 4-chloro-1-methyl-(1*H*)-2,1-benzothiazine-3-carbonitrile-2,2-dioxide (**12a**) (250 mg, 0.1 mmol), methyl thioglycolate (0.1 mL, 0.12 mmol) and potassium carbonate (200 mg, 0.15 mmol) in isopropanol (10 mL) was stirred at gradual temperature raise of 25 °C to 80 °C for 5 hours. Solid product was filtered, washed with water, dried and recrystallized from acetic acid to give the title pure compound (86%). M.p.: 189-191 °C; ^{1}H NMR (400 MHz, DMSO): δ = 3.46 (s, 3H), 3.84 (s, 3H), 6.46 (s, 2H, NH2), 7.33 (t, *J* = 7.8 Hz, 1H), 7.47 (d, *J* = 8.2 Hz, 1H), 7.61 (t, *J* = 8 Hz, 1H), 7.73 (d, *J* = 8.2 Hz, 1H); MS (CI): 326(M+H)$^+$; IR (KBr): 1150, 1300cm-1 (SO2), 1692cm-1 (C=O), 3360, 3480cm-1 (NH2); *Anal.* calcd. S, 19.77; N, 8.64; C, 48.14; H, 3.73; N, 8.64; found S, 19.87; N, 8.72; C, 48.20; H, 3.81; N, 8.68.

2-R-5-methyl-2,5-dihydropyrazolo[4,3-*c*][2,1]benzothiazin-3-amine 2,2-dioxides (17a,b,c); General Procedure. A mixture of 4-chloro-1-methyl-(1*H*)-2,1-benzothiazine-3-carbonitrile-2,2-dioxide (**12a**) (250 mg, 0.1 mmol), corresponding hydrazine (0.12 mmol) and potassium carbonate (200 mg, 0.15 mmol) in isopropanol (10 mL) was refluxed for 10 hours. Solid product was collected by filtration, washed with water and recrystallized from isopropanol to give the title pure compound.

Product 17a (75%): m.p.: 201-203 °C; ^{1}H NMR (400 MHz, DMSO): δ = 3.27 (s, 3H), 5.75-5.90 (br.s, 3H, NH2+NH), 7.20-7.27 (m, 2H, arom), 7.43 (t, *J* = 7.8 Hz, 1H), 7.90 (d, *J* = 8.2 Hz, 1H); MS (CI): 251(M+H)$^+$; *Anal.* calcd. S, 12.81; C, 47.99; H, 4.03; N, 22.39; found S, 12.92; C, 47.92; H, 4.00; N, 22.91.

Product 17b (72%): m.p.: 166-167 °C; ^{1}H NMR (400 MHz, DMSO): δ = 3.26 (s, 3H), 6.17 (s, 2H, NH2), 7.23 (t, *J* = 7.8 Hz, 1H), 7.27 (d, *J* = 8.2 Hz, 1H), 7.45-7.63 (m, 6H, Ph+H), 7.94 (d, *J* = 8.2 Hz, 1H); MS (CI): 327(M+H)$^+$; *Anal.* calcd. S, 9.82; C, 58.88; H, 4.32; N, 17.17; found S, 9.88; C, 58.81; H, 4.26; N, 17.54.

Product 17c (67%): m.p.: 240-241 °C; ^{1}H NMR (400 MHz, DMSO): δ = 3.28 (s, 3H), 6.72 (s, 2H, NH2), 7.28 (t, *J* = 7.8 Hz, 1H), 7.34 (d, *J* = 8 Hz, 1H), 7.49 (t, *J* = 8.2 Hz, 1H), 7.93-7.95 (m, 3H, Ph+H), 8.37 (m, 2H, Ph); MS (CI): 371(M+H)$^+$; *Anal.* calcd. S, 8.63; C, 51.75; H, 3.53; N, 18.86; found S, 8.43; C, 51.70; H, 3.58; N, 18.98.

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