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MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Synthesis and antioxidant studies of novel *N*-substituted benzyl/phenyl-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl)acetamides

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Abstract Two new series of twenty-two *N*-substituted benzyl/phenyl-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl)acetamides were synthesized by synergism of the dihydropyrazolo[4,3-*c*][1,2] benzothiazine 5,5-dioxide moiety with side chain of carboxamides. The routes of formation for these products have been discussed. All the compounds were characterized by NMR, mass and elemental analysis. Structures of compounds **6d** and **6l** have been elucidated by X-ray crystallography. The synthesized compounds were screened to the preliminary evaluation for their anti-oxidant activities and most of the compounds were found to possess moderate to significant radical scavenging activity. Furthermore, these compounds could be useful as a template for future development through modification or derivatization to design more potent biologically active compounds.

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Introduction

A wide range of 1,2-benzothiazine-3-carboxamides 1,1-dioxides are known for their potent anti-inflammatory and analgesic nature (Lomabardino *et al.*, 1971). Anti-inflammatory and analgesic drugs of this family are classified as oxicams in the main category of non-steroidal anti-inflammatory drugs (NSAID's). Oxicams include piroxicam, sudoxicam, ampiroxicam, and meloxicam (Lomabardino *et al.*, 1973; Turck *et al.*, 1995). These discoveries have led to the synthesis of a variety of carboxamides using aliphatic (Lomabardino *et al.*, 1973), aromatic (Lomabardino and Wiseman, 1972; Zinnes *et al.*, 1973) and heterocyclic amines (Lomabardino *et al.*, 1971; Turck *et al.*, 1995). Biological studies have revealed the versatile bioactive nature of benzothiazine derivatives as anti-allergic (Ikeda *et al.*, 1992), anti-microbial (Giuseppe *et al.*, 1987; Zia-ur-Rehman *et al.*, 2006), central nervous system depressants and tranquilizers (Krapcho and Somerset, 1968; Krapcho and Somerset, 1969a, b). Moreover, our previous studies have shown *N*′-arylmethylidene-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl)acetohydrazides are potent anti-oxidants and *N*′-[1-phenylethylidene]-2*H*/2-methyl-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides are anti-microbial (Ahmad *et al.*, 2010, 2011).

Pyrazole-containing compounds include numerous agents showing potent bioactivities including anti-bacterial, anti-fungal (Iovu *et al.*, 2003), anti-viral (Baraldi *et al.*, 1998), and anti-tumor efficacy (Riyadh, 2011). Some pyrazole derivatives have been reported to exhibit significant anti-arrhythmic and sedative (Bruno *et al.*, 1990),

hypoglycemic (Cottineau *et al.*, 2002), and anti-inflammatory activities (Smith *et al.*, 2001). Celecoxib (Fig. 1), for example, is a pyrazole-containing anti-inflammatory drug of recent significance due to its selective inhibition of COX-2 enzyme (Silverstein *et al.*, 2000).

This precedent for broad bioactivity profiles for these two different heterocyclic pharmacophores led us to perceive that fusion of benzothiazine and pyrazole nuclei may result in new bioactive molecules. The strategy envisioned starting from the inexpensive raw material sodium saccharine as a precursor to a common intermediate pyrazole-benzoathiazine fused ring system, 3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl acetic acid (**5**) which could then function as a common scaffold to generate a library of amide derivatives of the side chain carboxylate. Herein, we report the synthesis of **5** and reaction with a range of substituted benzylamines and anilines to afford two novel series of twenty-two *N*-(substituted)benzyl-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl) acetamides (**6a–l**) and 2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl)-*N*-phenylacetamides (**7a–j**). Structures of two representative compounds (**6d** and **6l**) were determined through XRD as well and preliminary evaluation as antioxidants provides useful SAR information for further development.

Results and discussion

Chemistry

One-pot synthesis of 3-acetyl-2*H*-1,2-benzothiazine 1,1-dioxide (**1**) was carried out in DMSO by condensation of sodium saccharine with monochloroacetone and subsequent ring expansion by sodium methoxide under anhydrous conditions (Scheme 1). This provided a significantly improved yield (80 %) over our prior stepwise process (62 %).

N-methylation of **1** with dimethylsulphate and cyclization with hydrazine hydrate afforded 3,4-dimethyl-2,4-dihydropyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxide (**3**) (Scheme 2). There are a number of literature reports of 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamides 1,1-dioxides showing as potent anti-inflammatory and analgesic agents. With ready access to this novel pyrazole, we thus prepared alkyl 3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl acetate (**4**) as a potential substrate for direct conversion to respective carboxamide derivatives. However, direct conversion of this ester (**4**) into respective anilides was unsuccessful due to lower reactivity of ester toward anilines. Therefore, ester (**4**) was hydrolyzed to 3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl acetic acid (**5**), to approach amide derivatives by amine-carboxylate coupling.

Finally, treatment of acid (**5**) with borane-THF complex resulted in the formation of a reactive intermediate, triacyloxyborane that reacted readily with substituted benzylamines to form respective carboxamides (Huang *et al.*, 2007). Parallel synthesizer equipment was efficiently used for the synthesis of libraries of these carboxamides, i.e., **6a–l** and **7a–j** (Scheme 2). The yields of the carboxamides (**6a–l**) were in the range of 60–75 %. It is worth mentioning here that the classical coupling agents DCC/HOBt (Sheehan and Hess, 1955) and EDC/HOBt (Boger *et al.*, 1999) were also employed, however, provided lower yields than use of borane-THF complex. Whereas, the yields of anilides (**7a–j**) from reactions using anilines were in the range of 15–20 % under the same reaction conditions which gave promising results using benzylamine

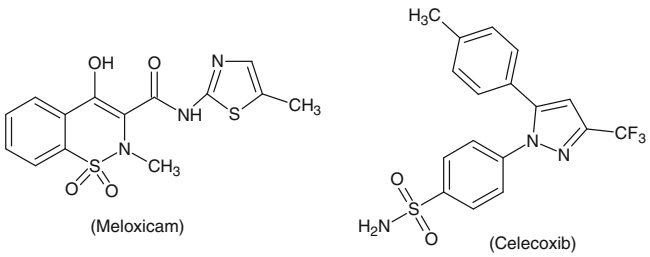
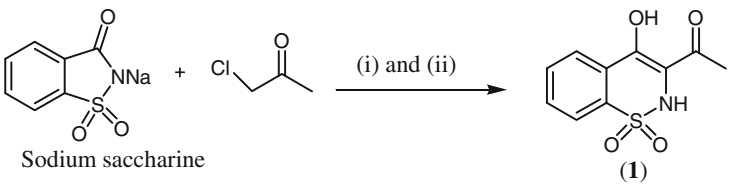


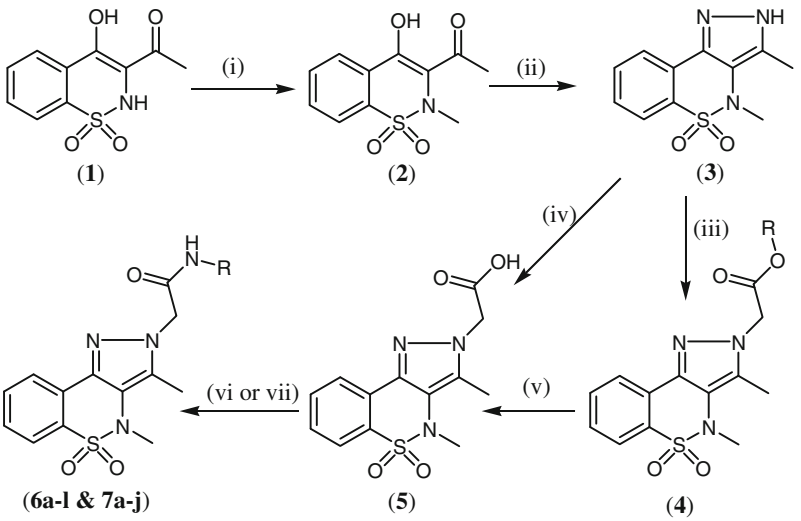
Fig. 1 Potent anti-inflammatory drugs based upon benzothiazine and pyrazole nuclei



(i) DMSO, 120 ºC, 1.5 hours (ii) NaOMe/ MeOH

Scheme 1 One-pot conversion of sodium saccharine to 3-acetyl-2*H*-1,2-benzothiazine 1,1-dioxide

Scheme 2 Synthesis of novel *N*-substituted benzyl/phenyl-2-(3,4-dimethyl-5,5 dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl)acetamides



(i) $(CH_3)_2SO_4/NaOH_{(aq)}$;Acetone (ii) $N_2H_4.H_2O$/EtOH (iii) alkyl chloroacetat/K_2CO_3; DMF (iv) $BrCH_2COOH/K_2CO_3$; DMF (v) $NaOH_{(aq)}$/MeOH (vi) BH_3-THF complex/Ar-CH_2-NH_2; Toluene:THF mixture (vii) $SOCl_2$; Ar-NH_2/Toluene:THF mixture

deriviatives. This may be due to better nucleophilicity of benzylamines compared to that of anilines. Thus, the more reactive intermediate acyl halide was prepared by using thionyl chloride as acylating reagent followed by its reaction with substituted anilines in the presence of triethyl amine as a base. The resulting novel *N*-substitutedphenyl-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl)acetamides (**7a–j**) were isolated in 75–86 % yields (Table 1). Unreacted benzylamines/anilines and carboxylic acid **5** were removed by dissolving residue in ethyl acetate and successively washing the solution with 1.0 N HCl and saturated $NaHCO_3$, respectively.

X-ray studies

The heterocyclic thiazine rings in both structures adopt half-chair conformation (Fig. 2), with atoms N1 and S1 displaced by 0.263(4) and −0.417(4) Å, respectively, in **6d** and 0.235(4) and −0.460(4) Å, respectively, in **6l** from the plane formed by atoms C1/C6/C7/C8; the puckering parameters (Cremer and Pople, 1975), respectively, are: $Q = 0.441(2)$ and 0.459(2) Å, $\theta = 118.7(3)°$ and 118.3(2) and $\varphi = 203.0(3)$ and 200.1(3)°. In both structures, the five-membered rings are essentially planar with maximum deviations being 0.0097(13) and 0.0112(13) Å for C7 in **6d** and **6l**, respectively. Crystallographic parameters are described in detail in Table 2. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center (CCDC deposition numbers are: **6d** = 817,158; **6l** = 817,157).

Antioxidant studies

Reactive oxygen species (ROS) and free radicals are involved in a wide range of human diseases (Gutteridge, 1993). ROS, including super oxide anion, hydrogen peroxide, and hydroxyl radical are byproducts of a variety of pathways of aerobic metabolism (Foroumadi *et al.*, 2007). These are unstable and react readily with a wide range of biological substrates, such as lipids, DNA, and protein molecules, consequently resulting in cell damage (Braughler *et al.*, 1986). The title compounds were subjected to antioxidant activity (superoxide anion and DPPH scavenging activity) and the results are described in Table 3.

Compound **6k** (%RSA = 81.51), having 2-methylbenzyl group, compound **7f** (%RSA = 79.09), bearing 2-bro mophenyl, and compound **7j** (%RSA = 78.32), with 2,4-dimethoxyphenyl group were found to be excellent superoxide anion radical scavengers. There is a reasonable structure–activity relationship among all the compounds. First, substituted aniline-based amides were more active as compared to the corresponding benzylamine derivatives. Second, compounds having electron donating substituents present at ortho and para positions were observed to be better scavengers. Among halogen substituted compounds, following relationship was present: Br > Cl > F.

During our previous work (Ahmad *et al.*, 2010), we reported the antioxidant studies of *N*′-arylmethylidene-2-(3,4-dimeth yl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl)acet ohydrazides. The comparison of superoxide scavenging studies of previously reported hydrazides (–CONHN=CHAr) and

Table 1 Characterization of *N*-substituted benzyl/phenyl-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl)acetamides (**6a–l** and **7a–j**)

Code name	R	Yield (%)	Analysis (%)		
			Calculated (found)		
			C	H	N
6a	2-Chlorobenzyl	70	55.75 (55.73)	4.44 (4.43)	13.00 (13.01)
6b	4-Chlorobenzyl	72	55.75 (55.74)	4.44 (4.46)	13.00 (12.99)
6c	2-Flourobenzyl	63	57.96 (57.95)	4.62 (4.63)	13.52 (13.49)
6d	4-Flourobenzyl	65	57.96 (57.92)	4.62 (4.61)	13.52 (13.53)
6e	2-Bromobenzyl	67	50.53 (50.54)	4.03 (4.01)	11.79 (11.78)
6f	3-Bromobenzyl	61	50.53 (50.50)	4.03 (4.05)	11.79 (11.80)
6g	2-Methoxybenzyl	73	59.14 (59.14)	5.20 (5.19)	13.14 (13.15)
6h	3-Methoxybenzyl	69	59.14 (59.15)	5.20 (5.22)	13.14 (13.15)
6i	4-Methoxybenzyl	71	59.14 (59.13)	5.20 (5.21)	13.14 (13.11)
6j	2,4-Dimethoxybenzyl	75	57.88 (57.86)	5.30 (5.31)	12.27 (12.25)
6k	2-Methylbenzyl	68	61.44 (61.43)	5.40 (5.42)	13.65 (13.66)
6l	4-Methylbenzyl	67	61.44 (61.45)	5.40 (5.39)	13.65 (13.63)
7a	Phenyl	78	59.67 (59.65)	4.74 (4.76)	14.65 (14.63)
7b	2-Chlorophenyl	82	54.74 (54.75)	4.11 (4.14)	13.44 (13.42)
7c	4-Chlorophenyl	85	54.74 (54.76)	4.11 (4.12)	13.44 (13.41)
7d	2-Flourophenyl	75	56.99 (56.97)	4.28 (4.27)	13.99 (14.01)
7e	4-Flourophenyl	77	56.99 (56.98)	4.28 (4.29)	13.99 (13.97)
7f	2-Bromophenyl	77	49.47 (49.45)	3.71 (3.71)	12.14 (12.13)
7g	3-Bromophenyl	75	49.47 (49.46)	3.71 (3.70)	12.14 (12.15)
7h	2-Methoxyphenyl	85	58.24 (58.22)	4.89 (4.87)	13.58 (13.60)
7i	3-Methoxyphenyl	84	58.24 (58.21)	4.89 (4.88)	13.58 (13.60)
7j	2,4-Dimethoxyphenyl	86	57.00 (57.01)	5.01 (5.02)	12.66 (12.65)

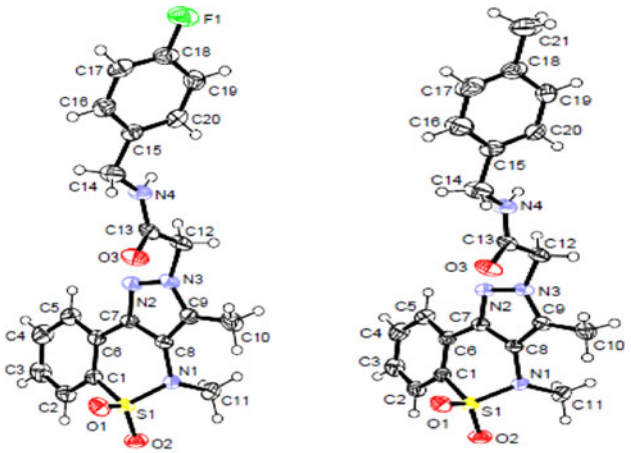


Fig. 2 ORTEP II diagram of compounds **6d** and **6l**, with the numbering scheme. Displacement ellipsoids are drawn at the 50 % probability level; H atoms are represented by *circles* of arbitrary radii

corresponding carboxamides (–CONHR; where R = $–CH_2Ar$ and –Ar)-posed interesting discussion. Overall, it is observed that anilides are the most potent scavengers of superoxide anion radical as compared to corresponding benzylamides and hydrazides. For example: compound **7j** (bearing 2-Cl phenyl moiety) is more active than corresponding compounds **6a** (benzylamide) and **6e** (hydrazide). Similar order of the activity was observed in the compounds possessing common substituents (i.e., 4-Cl, 4-F, 3-OMe, and 2,4-dimethoxy) in the corresponding benzylamide and hydrazides, respectively.

For DPPH radical scavenging activity, the compounds of both the series of carboxamides (i.e., **6a–l** and **7a–j**) were observed either weakly active or inactive. Among all the compounds, methoxy substituted compounds were the most active, e.g., **7j**, which contains a 2,4-dimethoxyphenyl moiety, (%RSA = 39.78) was more active than **7h** (2-methoxyphenyl; %RSA = 26.89) and **7i** (3-methoxyphenyl; %RSA = 20.18), however, the difference in activity was not as high as required to accomplish a satisfactorily structure–activity relationship. A similar behavior was observed among the benzyl substituted compounds (**6a–l**), i.e., compound **6j** (2,4-dimethoxybenzyl; %RSA = 27.31) has nearly same activity to the compounds **6g** (2-methoxybenzyl; %RSA = 25.58) and **6i** (4-methoxybenzyl; %RSA = 23.69).

Table 2 Crystallographic parameters for compounds **6d** and **6l**

Crystallographic parameters	**6d**	**6l**
CCDC numbers	817158	817157
Empirical formula	C_{20} H_{19} F N_4 O_3 S	C_{21} H_{22} N_4 O_3 S
Formula weight	414.45	410.49
Temperature	173(2) K	173(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Orthorhombic	Orthorhombic
Space group	$Pca2_1$	*Pbca*
Unit cell dimensions: *a*	17.7329(6) Å	17.8676(4) Å
b	12.3170(4) Å	8.6431(2) Å
c	8.7837(3) Å	26.4267(6) Å
Volume	1918.50(11) $Å^3$	4081.11(16) $Å^3$
Z	4	8
Density (calculated)	1.435 Mg/m^3	1.336 Mg/m^3
Absorption coefficient	0.209 mm^{-1}	0.189 mm^{-1}
F(000)	864	1728
Crystal size	0.18 × 0.16 × 0.06 mm^3	0.16 × 0.14 × 0.04 mm^3
Crystal habit	Colorless, prism	Colorless, plate
θ Range for data collection	2.0 to 25.0°	2.7 to 25.0°.
Reflections collected	3239	6640
Absorption correction	Multi-scan method	Multi-scan method
Max. and min. transmission	0.9876 and 0.9634	0.9925 and 0.9704
Goodness of fit	1.084	1.062
Final *R* indices [$I > 2\sigma(I)$]	$R1 = 0.0331$, w$R2 = 0.0761$	$R1 = 0.0448$, w$R2 = 0.0970$
R indices (all data)	$R1 = 0.0354$, w$R2 = 0.0798$	$R1 = 0.0556$, w$R2 = 0.1042$
Largest diff. peak and hole	0.160 and −0.253 e $Å^{-3}$	0.259 and −0.375 e $Å^{-3}$

Conclusion

This study revealed that the compounds obtained by synergism of the dihydropyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxide moiety with side chain carboxamides were found to possess anti-oxidant activities and could be useful as a template for future development through modification or derivatization to design more potent biologically active compounds. The new skeleton may also possess other biological activities of the parent ring systems.

Experimental

Chemistry

All the chemicals were purchased from Alfa Aesar and were used without purification. However, solvents were purified through distillation. ^{1}H NMR spectra were recorded on a Bruker DPX-400 instrument at 400 MHz. Chemical shifts are reported in ppm referenced to the residual solvent signal. FT-IR spectra were recorded on a Thermo Nicolet IR 200 spectrometer. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Ultrasonic mediated reactions were carried out in Clifton Ultrasonic Bath (2 × T2A, 300 W, DU-4) made by Nickel Electro Ltd, Weston-S-Mare Somerset, England.

*One-pot synthesis of 3-acetyl-4-hydroxy-2H-1,2-benzothiazine 1,1-dioxide (**1**)*

Sodium saccharin (10 g, 0.0488 mol) and monochloroacetone (4.3 mL, 0.054 mol) were mixed in DMSO and the reaction mixture was stirred at 110°C for 3 h under inert atmosphere maintained by nitrogen. A solution of sodium methoxide in methanol was added to this mixture and stirring was continued for another half hour. The reaction mixture was cooled to room temperature and was poured in ice cold 5 % HCl. The resulting precipitates were collected, washed with excess water and dried. Yield: 80 %, Brownish amorphous material, m.p:155–156 °C, IR (KBr): 3467, 3210, 1598, 1586, 1345, 1187 cm^{-1}, ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.22 (3H, s, CCH_3), 5.83 (1H, s, SO_2NH), 7.55 (1H, t, $J = 7.4$ Hz, Ar*H*), 7.67 (1H, t, $J = 7.2$ Hz, Ar*H*), 7.98 (2H, t, $J = 7.8$ Hz, Ar*H*), 14.95

Table 3 Percent radical scavenging activities (% RSA) of compounds **6a–l** and **7a–j**

Code name	R	% RSA (Superoxide anion)	% RSA (DPPH)
6a	2-Chlorobenzyl	52.49	17.10
6b	4-Chlorobenzyl	47.20	16.71
6c	2-Flourobenzyl	48.48	20.16
6d	4-Flourobenzyl	42.26	15.77
6e	2-Bromobenzyl	64.05	21.08
6f	3-Bromobenzyl	32.54	14.13
6g	2-Methoxybenzyl	38.79	25.58
6h	3-Methoxybenzyl	25.91	16.19
6i	4-Methoxybenzyl	33.11	23.69
6j	2,4-Dimethoxybenzyl	58.27	27.31
6k	2-Methylbenzyl	81.51	15.17
6l	4-Methylbenzyl	57.8	17.85
7a	Phenyl	28.61	18.29
7b	2-Chlorophenyl	60.95	21.76
7c	4-Chlorophenyl	55.56	25.37
7d	2-Flourophenyl	47.73	23.12
7e	4-Flourophenyl	44.10	22.14
7f	2-Bromophenyl	79.09	27.64
7g	3-Bromophenyl	47.11	26.09
7h	2-Methoxyphenyl	53.75	26.89
7i	3-Methoxyphenyl	47.44	20.18
7j	2,4-Dimethoxyphenyl	78.32	39.78
Standard	*n*-Propyl gallate	90.8	ND
Standard	3-*tert*-butyl-4-hydroxy anisole	ND	92.60

ND not determined

(1H, s, OH). ^{13}C NMR: 21.5, 69.2, 122.5, 123.4, 124.4, 127.2, 129.2, 133.4, 136.7, 167.2. HRMS (ESI) calculated for $C_{10}H_9NO_4S$: 240.0331 $(M + H)^+$, found: 240.0327.

*Synthesis of 3-acetyl-4-hydroxy-2-methyl-2H-1,2-benzothiazine 1,1-dioxide (**2**)*

The reaction was carried out according to our previously reported method [14]. A mixture of 3-acetyl-4-hydroxy-2*H*-1,2-benzothiazine 1,1-dioxide (**1**) (5.0 g; 20.9 mmol), aqueous sodium hydroxide (8.4 ml; 20 %), and acetone (50 ml) was stirred at room temperature for 5 min. After that dimethyl sulfate (5.9 ml) was added drop wise to the mixture over a period of 5 min and the contents were stirred for half an hour. White precipitates were obtained by careful addition of dilute HCl (20 ml; 5 %) to the resulting reaction mixture. These precipitates were filtered, washed with water and dried. Yield: 88 %. White crystalline material, m.p: 151–152 °C, IR (KBr): 3470, 1598, 1586, 1345, 1187 cm^{-1}, ^{1}H NMR ($CDCl_3$, 400 MHz): δ: 2.23 (3H, s, CCH_3), 3.09 (3H, s, NCH_3), 7.55 (1H, t, $J = 7.3$ Hz, Ar*H*), 7.66 (1H, t, $J = 7.2$ Hz, Ar*H*), 7.96 (2H, t, $J = 7.7$ Hz, Ar*H*), 12.22 (1H, s, OH). ^{13}C NMR: 21.5, 38.7, 117.9, 122.5, 123.4, 124.4, 127.2, 129.2, 133.4, 136.7, 167.2. HRMS (ESI) calculated for $C_{11}H_{11}NO_4S$: 254.0487 $(M + H)^+$, found: 254.0471.

*Synthesis of 3,4-dimethyl-2,4-dihydropyrazolo[4,3-c][1,2]benzo thiazine 5,5-dioxide (**3**)*

A mixture of 3-acetyl-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine 1,1-dioxide (**2**) (5.0 g, 19.8 mmol) and hydrazine monohydrate (4.8 mL, 99.0 mmol) was irradiated with ultrasonic waves for 10 min at 65 °C. Unreacted hydrazine was removed under vacuum and the residue obtained was poured over hydrochloric acid (20 mL, 10% v/v). Precipitates obtained were filtered, washed with excess water and cold ethanol. Brownish-yellow solid, yield; 83 %, m.p.: 230 °C, IR (KBr): 3359, 1599, 1322, 1142 cm^{-1}, ^{1}H NMR ($CDCl_3$, 400 MHz) δ: 2.39 (3H, s, CCH_3), 3.06 (3H, s, NCH_3), 7.53 (1H, t, $J = 7.4$ Hz, Ar*H*), 7.66 (1H, t, $J = 7.2$ Hz, Ar*H*), 7.94 (2H, t, $J = 7.8$ Hz, Ar*H*), 10.09 (1H, s, N*H*). ^{13}C NMR: 8.6, 38.8, 121.8, 123.3, 124.2, 128.8, 129.3, 131.1, 132.9, 133.2, 134.5. HRMS (ESI) calculated for $C_{11}H_{11}N_3O_2S$: 250.0650 $(M + H)^+$, found: 250.0650.

*Synthesis of methyl (3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2] benzothiazin-2(4H)-yl)acetate (**4**)*

A mixture of 3,4-dimethyl-2,4-dihydropyrazolo[4,3-*c*][1,2] benzothiazine 5,5-dioxide (**3**) (5.0 g, 0.020 mol), anhydrous potassium carbonate (3.31 g, 0.024 mol), methyl chloroacetate (2.60 g, 0.024 mol), and acetonitrile (30 mL) was refluxed for a period of 10 h, followed by the removal of solvent under vacuum. Residue obtained was washed with cold water to provide a white crystalline product. Yield: 80 %, m.p.: 180 °C, ^{1}H NMR ($CDCl_3$, 400 MHz): δ: 2.32 (3H, s, CCH_3), 3.04 (3H, s, NCH_3), 3.79 (3H, s, OCH_3), 4.91 (2H, s, NCH_2), 7.51 (1H, t, $J = 7.7$ Hz, Ar*H*), 7.63 (1H, t, $J = 7.7$ Hz, Ar*H*), 7.90 (1H, d, $J = 7.7$ Hz, Ar*H*), 7.97 (1H, d, $J = 7.7$ Hz, Ar*H*). ^{13}C NMR: 8.6, 38.7, 51.3, 52.4, 122.5, 123.4, 124.4, 127.7, 129.2, 131.5, 133.4, 134.4, 136.8, 167.6. HRMS (ESI) calculated for $C_{14}H_{15}N_3O_4S$: 322.0862 $(M + H)^+$, found: 322.0861.

*Synthesis of 3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2] benzothiazin-2(4H)-yl acetic acid (**5**)*

Method A A mixture of methyl (3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2] benzothiazin-2(4*H*)-yl) acetate (**4**) (5.0 g, 0.0156 mol), NaOH aqueous solution (2.49 g/10 mL H_2O), and methanol (30 mL) was refluxed for a period of 30 min. The solvent was removed under vacuum and residue obtained was acidified with 5 % HCl. The

resulting precipitates were washed with cold water to afford a white crystalline product, yield: 94 %.

Method B A mixture of 3,4-dimethyl-2,4-dihydropyrazolo[4,3-*c*][1,2]benzothiazine 5,5-dioxide (**3**) (5.0 g, 0.020 mol), anhydrous potassium carbonate (6.62 g, 0.048 mol), bromoacetic acid (3.31 g, 0.024 mol), and anhydrous DMF (15 mL) was stirred for a period of 3.0 h under nitrogen atmosphere. Contents of the flask were cooled to room temperature and then poured over ice cold 10 % HCl. White precipitates formed were filtered, washed with ice cold water and dried. Yield: 75 %, white crystalline product, ^{1}H NMR ($CDCl_3$) (400 MHz) δ: 2.30 (3H, s, CCH_3), 2.96 (3H, s, NCH_3), 5.07 (2H, s, NCH_2), 7.61 (1H, t, $J = 7.6$ Hz, Ar*H*), 7.76 (1H, t, $J = 7.6$ Hz, Ar*H*), 7.86(2H, dd, $J = 7.8$, 16.7 Hz, Ar*H*). ^{13}C NMR: 8.6, 38.7, 52.4, 122.5, 123.4, 124.4, 127.7, 129.2, 131.5, 133.4, 134.4, 136.8, 167.6. HRMS (ESI) calculated for $C_{13}H_{13}N_3O_4S$: 308.0705 $(M + H)^+$, found: 308.0701.

*Synthesis of N-substitutedbenzyl-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)acetamides (**6a–l**)*

Borane-THF complex (1.1 mmol) was added to the solution of 3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2] benzothiazin-2(4*H*)-yl acetic acid (**5**) (3.3 mmol) in toluene:THF (1:1) mixture and was added in it. The reaction mixture was stirred for 30 min at room temperature to generate triacyloxyborane as a reactive intermediate. The suitable benzylamine (3.4 mmol) was then added to the mixture followed which was reflux for 5 h. After completion of reaction, as indicated by TLC, solvent was removed under *vacuum* and the contents of the flask were dissolved in EtOAc. The solution was dried (Na_2SO_4), filtered and ethyl acetate removed under vacuum. Finally, the product was purified through column chromatography using EtOAc: *n*-hexane in (2:1) as eluent.

*N-(2-chlorobenzyl)-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)acetamide (**6a**)*

White crystalline solid; m.p.: 161 °C; IR (KBr): 3288; 1659; 1375; 1170 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.34(s, 3H, CCH_3), 2.97(s, 3H, NCH_3), 4.41 (d, 2H, $J = 5.7$ Hz, $ArCH_2$), 5.03 (s, 2H, NCH_2), 7.32–7.36 (m, 2H, Ar*H*), 7.43–7.48 (m, 2H, Ar*H*), 7.62 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.77 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.91 (dd, 2H, $J_1 = 7.5$ Hz, $J_2 = 17.4$ Hz, Ar*H*), 8.83 (brs, 1H, N*H*); ^{13}C NMR: 8.8, 30.9, 41.3, 52.5, 122.3, 123.4, 124.4, 127.2, 127.9, 128.9, 129.0, 129.2, 129.3, 131.5, 132.2, 133.3, 134.5, 135.8, 136.5, 166.3; HRMS (ESI) calculated for $C_{20}H_{19}ClN_4O_3S$: 431.0945 $(M + H)^+$, found: 431.0955.

*N-(4-chlorobenzyl)-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)acetamide (**6b**)*

White crystalline powder; m.p.:178 °C; IR (KBr): 3288; 1656; 1339; 1158 cm^{-1}; ^{1}H NMR(DMSO-d_6): 2.32 (s, 3H, CCH_3), 2.96 (s, 3H, NCH_3), 4.32 (d, 2H, $J = 5.7$ Hz, $ArCH_2$), 4.99 (s, 2H, NCH_2), 7.36 (dd, 2H, $J_1 = 8.4$ Hz, $J_2 = 26.1$ Hz, Ar*H*), 7.65 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.80 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.90 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 14.7$ Hz, Ar*H*), 8.85 (brs, 1H, N*H*); ^{13}C NMR: 8.8, 30.8, 41.1, 52.6, 122.3, 123.4, 124.4, 127.1, 127.9, 128.3, 129.0, 129.2, 131.5, 132.1, 133.3, 134.5, 135.7, 136.4, 138.0, 166.2; HRMS (ESI) calculated for $C_{20}H_{19}ClN_4O_3S$: 431.0945 $(M + H)^+$, found: 431.0953.

*2-(3,4-Dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)-N-(2-fluorobenzyl)acetamide (**6c**)*

White powder; m.p.146 °C; IR (KBr): 3279; 1656; 1334; 1168 cm^{-1}; ^{1}H NMR(DMSO-d_6): 2.32 (s, 3H, CCH_3), 2.96 (s, 3H, NCH_3), 4.37 (d, 2H, $J = 5.7$ Hz, $ArCH_2$), 5.01 (s, 2H, NCH_2),7.18–7.24 (m, 2H, Ar*H*), 7.33–7.42 (m, 2H,Ar*H*), 7.62 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.77 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.90 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 14.7$ Hz, Ar*H*), 8.84 (brs, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 41.4, 52.5, 115.0, 115.3, 121.3, 122.3, 123.4, 124.4, 125.5, 127.9, 128.2, 129.8, 129.9, 131.4, 133.3, 134.5, 136.4, 166.2; HRMS (ESI) calculated for $C_{20}H_{19}FN_4O_3S$: 415.1240 $(M + H)^+$, found: 415.1224.

*2-(3,4-Dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)-N-(4-fluorobenzyl)acetamide (**6d**)*

White crystals; m.p.178 °C; IR (KBr): 3269; 1662; 1335; 1156 cm^{-1}; ^{1}H NMR: 2.32 (s, 3H, CCH_3), 2.96 (s, 3H, NCH_3), 4.31 (d, 2H, $J = 6.0$ Hz, $ArCH_2$), 4.98 (s, 2H, NCH_2), 7.15 (t, 2H, $J = 8.7$ Hz, Ar*H*), 7.32 (dd, 2H, $J_1 = 5.7$ Hz, $J_2 = 8.4$ Hz, Ar*H*), 7.62 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.77 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.87 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 14.4$ Hz, Ar*H*), 8.82 (brs, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 41.6, 52.6, 114.9, 115.2, 121.2, 122.3, 123.4, 124.3, 125.4, 127.9, 129.0, 129.3, 129.4, 131.5, 133.3, 134.5, 135.1, 166.1; HRMS (ESI) calculated for $C_{20}H_{19}FN_4O_3S$: 415.1240 $(M + H)^+$, found: 415.1250.

*N-(2-Bromobenzyl)-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)acetamide (**6e**)*

White powder; m.p.169 °C; IR (KBr): 3282; 1660; 1335; 1170 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.34 (s, 3H, CCH_3),

2.96 (s, 3H, NCH_3), 4.37 (d, 2H, $J = 5.4$ Hz, $ArCH_2$), 5.03 (s, 2H, NCH_2), 7.25–7.30 (m, 1H, Ar*H*), 7.40–7.44 (m, 1H,Ar*H*), 7.62 (t, 2H, $J = 7.8$ Hz, Ar*H*), 7.77 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.87 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 18.0$ Hz, Ar*H*), 8.85 (brs, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 42.8, 52.5, 115.2, 122.3, 122.5, 123.4, 124.4, 127.8, 128.7, 129.2, 129.8, 130.4, 131.4, 132.5, 134.6, 137.3, 141.8, 166.3; HRMS (ESI) calculated for $C_{20}H_{19}BrN_4O_3S$: 475.0439 $(M + H)^+$, found: 475.0427.

*N-(3-bromobenzyl)-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)acetamide (**6f**)*

White powder; m.p.123 °C; IR (KBr): 3289; 1655; 1335; 1156 cm^{-1}; ^{1}H NMR(DMSO-d_6): 2.33 (s, 3H, C–CH_3), 2.96 (s, 3H, *N*–CH_3), 4.34 (d, 2H, $J = 6.0$ Hz, Ar–CH_2), 5.00 (s, 2H, *N*–CH_2), 7.31 (d, 2H, $J = 5.4$ Hz, ArH), 7.47–7.52 (m, 2H, Ar*H*), 7.62 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.77 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.91 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 18.9$ Hz, Ar*H*), 8.86 (brs, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 41.7, 52.6, 121.7, 122.3, 123.4, 124.3, 126.4, 127.9, 129.0, 129.8, 129.9, 130.5, 131.5, 133.3, 134.5, 136.5, 141.8, 166.3; HRMS (ESI) calculated for $C_{20}H_{19}BrN_4O_3S$: 475. 0439 $(M + H)^+$, found: 475.0428.

*2-(3,4-Dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)-N-(2-methoxybenzyl)acetamide (**6g**)*

White powder; m.p.121 °C; IR (KBr): 3261; 1661; 1335; 1156 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.34 (s, 3H, CCH_3), 2.96 (s, 3H, NCH_3), 3.81 (s, 3H, OCH_3), 4.30 (d, 2H, $J = 5.7$ Hz, $ArCH_2$), 4.99 (s, 2H, NCH_2), 6.91 (t, 1H, $J = 7.5$ Hz, Ar*H*), 6.99 (d, 1H, $J = 8.1$ Hz, Ar*H*), 7.24–7.30 (m, 2H, Ar*H*), 7.62 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.77 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.90 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 16.5$ Hz, Ar*H*), 8.56 (brs, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 37.6, 52.6, 55.3, 110.6, 120.1, 122.3, 123.4, 124.3, 126.1, 127.9, 128.2, 128.4, 129.0, 131.4, 133.3, 134.5, 136.4, 156.8, 166.1; HRMS (ESI) calculated for $C_{21}H_{22}N_4O_4S$: 427.1440 $(M + H)^+$, found: 427.1435.

*2-(3,4-Dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)-N-(3-methoxybenzyl)acetamide (**6h**)*

White powder; m.p.152 °C; IR (KBr): 3286; 1662; 1337; 1168 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.32 (s, 3H, CCH_3), 2.97 (s, 3H, NCH_3), 3.75 (s, 3H, OCH_3), 4.31 (d, 2H, $J = 6.0$ Hz, $ArCH_2$), 4.99 (s, 2H, NCH_2), 6.85–6.94 (m, 3H, Ar*H*), 7.24 (t, 1H, $J = 8.1$ Hz, Ar*H*), 7.62 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.77 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.88 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 16.5$ Hz, Ar*H*), 8.81 (brs, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 42.2, 52.6, 55.0, 112.3, 113.0, 119.5, 122.3, 123.4, 124.3, 127.9, 128.8, 129.0, 129.4, 131.5, 133.3, 134.5, 136.4, 159.3, 166.1; HRMS (ESI) calculated for $C_{21}H_{22}N_4O_4S$: 427.1440 $(M + H)^+$, found: 427.1439.

*2-(3,4-Dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)-N-(4-methoxybenzyl)acetamide (**6i**)*

Dirty yellow powder; m.p.178 °C; IR (KBr): 3341; 1658; 1337; 1155 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.33 (s, 3H, CCH_3), 2.97 (s, 3H, NCH_3), 3.74 (s, 3H, OCH_3), 4.26 (d, 2H, $J = 6.0$ Hz, $ArCH_2$), 4.96 (s, 2H, NCH_2), 6.89 (d, 2H, $J = 8.7$ Hz, Ar*H*), 7.22 (d, 2H, $J = 8.7$ Hz, Ar*H*), 7.62 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.77 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.88 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 14.7$ Hz, Ar*H*), 8.73 (brs, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 41.8, 52.6, 55.1, 113.8, 114.0, 122.3, 123.4, 124.3, 127.6, 127.9, 128.8, 129.0, 130.8, 131.4, 133.3, 134.5, 136.4, 158.3, 165.9; HRMS (ESI) calculated for $C_{21}H_{22}N_4O_4S$: 427.1440 $(M + H)^+$, found: 427.1432.

*N-(2,4-dimethoxybenzyl)-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)acetamide (**6j**)*

White powder; m.p. 201 °C; IR (KBr): 3285; 1657; 1337; 1156 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.09 (s, 3H, CCH_3), 2.96 (s, 3H, NCH_3), 3.75 (s, 3H, OCH_3), 3.80 (s, 3H, OCH_3), 4.21 (d, 2H, $J = 5.4$ Hz, $ArCH_2$), 4.96 (s, 2H, NCH_2), 6.49 (dd, 1H, $J_1 = 2.2$ Hz, $J_2 = 8.2$ Hz, Ar*H*), 6.57 (d, 1H, $J = 2.1$ Hz, Ar*H*), 7.13 (d, 1H, $J = 8.4$ Hz, Ar*H*), 7.62 (t, 1H, $J = 7.5$ Hz, Ar*H*), 7.77 (t, 1H, $J = 7.5$ Hz, Ar*H*), 7.90 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 14.4$ Hz, Ar*H*), 8.52 (brs, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 37.3, 52.5, 55.2, 55.4, 98.3, 118.3, 122.3, 123.4, 124.4, 127.9, 129.0, 129.3, 130.0, 131.4, 133.3, 134.5, 136.3, 157.8, 159.9, 166.2; HRMS (ESI) calculated for $C_{22}H_{24}N_4O_5S$: 457.1546 $(M + H)^+$, found: 457.1540.

*2-(3,4-Dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)-N-(2-methylbenzyl)acetamide (**6k**)*

White powder; m.p.190 °C; IR (KBr): 3292; 1661; 1335; 1156 cm^{-1}; ^{1}H NMR (DMSO-d_6): 2.34 (s, 3H, $ArCH_3$), 2.35 (s, 3H, CCH_3), 2.98 (s, 3H, NCH_3), 4.30 (d, 2H, $J = 5.7$ Hz, $ArCH_2$), 4.99 (s, 2H, NCH_2), 6.92 (t, 1H, $J = 7.5$ Hz, Ar*H*), 7.04 (d, 1H, $J = 8.0$ Hz, Ar*H*), 7.25–7.30 (m, 2H, Ar*H*), 7.64 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.79 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.89–7.96 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 16.5$ Hz, Ar*H*), 8.59 (brs, 1H, N*H*); ^{13}C NMR: 8.8,

21.2, 30.6, 42.2, 51.9, 115.1, 121.9, 122.5, 123.4, 124.4, 127.8, 128.8, 129.2, 129.9, 130.4, 131.1, 132.5, 134.1, 136.8, 141.2, 165.8; HRMS (ESI) calculated for $C_{21}H_{22}N_4O_3S$: 411.1491$(M + H)^+$, found: 411.1491.

*2-(3,4-Dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)-N-(4-methylbenzyl)acetamide (**6l**)*

White crystalline solid; m.p.150 °C; IR (KBr): 3281; 1656; 1336; 1157 cm^{-1}; ^1H NMR (DMSO-d_6): 2.31 (s, 3H, $ArCH_3$), 2.32 (s, 3H, CCH_3), 2.98 (s, 3H, NCH_3), 4.33 (d, 2H, $J = 6.0$ Hz, $ArCH_2$), 4.95 (s, 2H, NCH_2), 7.28 (t, 2H, $J = 8.7$ Hz, Ar*H*), 7.32 (dd, 2H, $J_1 = 5.7$ Hz, $J_2 = 8.4$ Hz, Ar*H*), 7.63 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.72 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.87 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 14.4$ Hz, Ar*H*), 8.79 (brs, 1H, N*H*); ^{13}C NMR: 8.7, 24.8, 30.4, 41.8, 51.9, 115.2, 122.4, 122.7, 123.3, 124.6, 127.3, 128.8, 129.2, 129.9, 130.5, 131.2, 132.1, 133.9, 136.7, 141.4, 165.3; HRMS (ESI) calculated for $C_{21}H_{22}N_4O_3S$: 411.1491 $(M + H)^+$, found: 411.1475.

*Synthesis of a series of 2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)-N-phenyl acetamides (**7a–j**)*

Procedure Thionyl chloride was added to the solution of 3,4-dimethyl-5,5-dioxidopyrazolo[4,3-*c*][1,2]benzothiazin-2(4*H*)-yl acetic acid (**5**) (3.3 mmol) in toluene under inert atmosphere. The reaction mixture was refluxed for 30 min to generate the respective acyl halide as a reactive intermediate. Unreacted thionyl chloride was removed from the reaction mixture by evaporation under a continuous stream of nitrogen gas. Respective anilines and triethyl amine were then added to the mixture was refluxed for 1 h along with continuous monitoring by mass spectrometry. Subsequently, the solvent was removed under vacuum and the contents of the flask were dissolved in EtOAc. In order to remove the impurities, the mixture was consecutively washed with excess water, 1.0 N HCl and saturated $NaHCO_3$ solution. The solution was dried (Na_2SO_4), filtered and the ethyl acetate removed in vacuo. Finally the product was purified through column chromatography using EtOAc: *n*-Hexane (2:1) as eluent.

*2-(3,4-Dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)-N-phenylacetamide (**7a**)*

White powder; m.p. 227 °C; IR (KBr): 3282; 1660; 1335; 1170 cm^{-1}; ^1H NMR (DMSO-d_6): 2.37 (s, 3H, CCH_3), 2.98 (s, 3H, NCH_3), 5.15 (s, 2H, NCH_2), 7.09 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.31 (t, 2H, $J = 7.8$ Hz, Ar*H*), 7.60–7.67 (m, 3H, Ar*H*), 7.79 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.88 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 16.2$ Hz, Ar*H*), 10.49 (s, 1H, N*H*); ^{13}C NMR: 8.9, 30.7, 53.1, 119.2, 122.3, 122.5, 123.4, 123.8, 124.4, 127.9, 128.9, 129.1, 129.8, 131.5, 133.3, 134.7, 136.6, 138.5, 164.8; HRMS (ESI) calculated for $C_{19}H_{18}N_4O_3S$: 383.1178 $(M + H)^+$, found: 383.1172.

*N-(2-Chlorophenyl)-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)acetamide (**7b**)*

White powder; m.p. 217 °C; IR (KBr): 3282; 1660; 1335; 1170 cm^{-1}; ^1H NMR (DMSO-d_6): 2.33 (s, 3H, CCH_3), 2.96 (s, 3H, NCH_3), 5.07 (s, 2H, NCH_2), 7.27–7.31 (m, 1H, Ar*H*), 7.35–7,41 (m, 2H, Ar*H*), 7.57 (t, 2H, $J = 7.8$ Hz, Ar*H*), 7.71 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.82 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 18.0$ Hz, Ar*H*), 10.43 (s, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 52.5, 115.2, 122.3, 122.5, 123.4, 124.4, 127.8, 128.7, 129.2, 129.8, 130.4, 131.4, 132.5, 134.6, 137.3, 141.8, 166.3; HRMS (ESI) calculated for $C_{19}H_{17}ClN_4O_3S$: 417.0788 $(M + H)^+$, found: 417.0775.

*N-(4-chlorophenyl)-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)acetamide (**7c**)*

White crystalline powder; m.p. 227 °C; IR (KBr): 3288; 1656; 1339; 1158 cm^{-1}; ^1H NMR (DMSO-d_6): 2.36 (s, 3H, CCH_3), 2.98 (s, 3H, NCH_3), 5.15 (s, 2H, NCH_2), 7.38 (d, 2H, $J = 7.8$ Hz, Ar*H*), 7.62 (t, 3H, $J = 8.4$ Hz, Ar*H*), 7.77 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.92–7.96 (dd, 2H, $J_1 = 8.1$ Hz, $J_2 = 15.0$ Hz, Ar*H*), 10.64 (s, 1H, N*H*); ^{13}C NMR: 8.8, 30.8, 53.1, 120.8, 122.1, 123.3, 124.4, 127.8, 127.9, 128.8, 129.1, 129.2, 129.4, 131.5, 133.3, 134.8, 135.7, 137.5, 165.0; HRMS (ESI) calculated for $C_{19}H_{17}ClN_4O_3S$: 417.0788 $(M + H)^+$, found: 417.0790.

*2-(3,4-Dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)-N-(2-fluorophenyl)acetamide (**7d**)*

Light yellow; m.p. 222 °C; IR (KBr): 3282; 1660; 1335; 1170 cm^{-1}; ^1H NMR (DMSO-d_6): 2.33 (s, 3H, CCH_3), 2.97 (s, 3H, NCH_3), 5.06 (s, 2H, NCH_2), 7.21–7.24 (m, 1H, Ar*H*), 7.29–7.35 (m, 2H, Ar*H*), 7.47 (t, 2H, $J = 7.8$ Hz, Ar*H*), 7.65 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.79 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 18.0$ Hz, Ar*H*), 10.41 (s, 1H, N*H*); ^{13}C NMR: 8.8, 30.6, 42.4, 51.8, 116.1, 121.2, 122.7, 123.7, 124.1, 127.0, 128.1, 129.5, 129.9, 130.4, 131.0, 131.8, 133.1, 137.5, 141.1, 165.9; HRMS (ESI) calculated for $C_{19}H_{17}FN_4O_3S$: 401.1084 $(M + H)^+$, found: 401.1086.

*2-(3,4-Dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)-N-(4-fluorophenyl)acetamide (**7e**)*

White powder; m.p. 237 °C; IR (KBr): 3288; 1656; 1339; 1158 cm^{-1}; ^1H NMR: 2.37 (s, 3H, CCH_3), 2.97 (s, 3H, NCH_3), 5.10 (s, 2H, NCH_2), 7.19 (d, 2H, $J = 7.8$ Hz, Ar*H*), 7.62 (d, 2H, $J = 7.8$ Hz, Ar*H*), 7.77 (t, 2H, $J = 7.8$ Hz, Ar*H*), 7.92 (dd, 2H, $J_1 = 8.1$ Hz, $J_2 = 15.5$ Hz, Ar*H*), 10.57 (s, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 52.6, 114.9, 115.2, 121.2, 122.3, 123.4, 124.3, 125.4, 127.9, 129.0, 129.4, 131.5, 133.3, 134.5, 135.1, 136.3, 166.1; HRMS (ESI) calculated for $C_{19}H_{17}FN_4O_3S$: 401.1084 $(M + H)^+$, found: 401.1081.

*N-(2-bromophenyl)-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)acetamide (**7f**)*

Off white powder; m.p. 205 °C; IR (KBr): 3276; 1671; 1337; 1168 cm^{-1}; ^1H NMR (DMSO-d_6): 2.38 (s, 3H, CCH_3), 2.97 (s, 3H, NCH_3), 5.25 (s, 2H, NCH_2), 7.14 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.36 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.66 (t, 3H, $J = 7.5$ Hz, Ar*H*), 7.78 (t, 1H, $J = 7.5$ Hz, Ar*H*), 7.89 (d, 1H, $J = 7.8$ Hz, Ar*H*), 7.96 (d, 1H, $J = 7.8$ Hz, Ar*H*), 9.92 (s, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 52.9, 122.5, 123.5, 124.4, 127.3, 127.4, 127.8, 128.1, 129.1, 129.8, 131.5, 132.8, 133.3, 134.7, 135.5, 136.6, 165.4; HRMS (ESI) calculated for $C_{19}H_{17}BrN_4O_3S$: 461.0283 $(M + H)^+$, found: 461.0285.

*N-(3-bromophenyl)-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)acetamide (**7g**)*

Dirty yellow; m.p. 204 °C; IR (KBr): 3280; 1651; 1337; 1150 cm^{-1}; ^1H NMR (DMSO-d_6): 2.41 (s, 3H, CCH_3), 3.01 (s, 3H, NCH_3), 5.25 (s, 2H, NCH_2), 7.28–7.32 (m, 2H, Ar*H*), 7.48 (d, 1H, $J = 7.2$ Hz, Ar*H*), 7.63 (t, 1H, $J = 7.5$ Hz, Ar*H*), 7.77 (t, 1H, $J = 7.5$ Hz, Ar*H*), 7.88 (t, 2H, $J = 7.2$ Hz, Ar*H*), 7.96 (d, 1H, $J = 3.9$ Hz, Ar*H*) 10.69 (s, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 52.6, 121.7, 122.3, 123.4, 124.3, 126.4, 127.9, 129.0, 129.8, 129.9, 130.5, 131.5, 133.3, 134.5, 136.5, 141.8, 165.3; HRMS (ESI) calculated for $C_{19}H_{17}BrN_4O_3S$: 461.0283 $(M + H)^+$, found: 461.0278.

*2-(3,4-Dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)-N-(2-methoxyphenyl)acetamide (**7h**)*

White powder; m.p. 189 °C; IR (KBr): 3259; 1671; 1337; 1157 cm^{-1}; ^1H NMR (DMSO-d_6): 2.36 (s, 3H, CCH_3), 2.98 (s, 3H, NCH_3), 3.86 (s, 3H, OCH_3), 5.26 (s, 2H, NCH_2), 6.91 (t, 1H, $J = 7.5$ Hz, Ar*H*), 7.09 (t, 2H, $J = 6.9$ Hz, Ar*H*), 7.65 (t, 1H, $J = 7.5$ Hz, Ar*H*), 7.80 (t, 1H, $J = 7.5$ Hz, Ar*H*), 7.89 (d, 1H, $J = 7.8$ Hz, Ar*H*), 7.98 (t, 2H, $J = 7.2$ Hz, Ar*H*), 9.65 (s, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 53.1, 55.7, 111.2, 120.3, 121.5, 122.4, 123.5, 124.4, 124.8, 126.6, 127.8, 129.1, 131.5, 133.3, 134.7, 136.6, 149.4, 165.1; HRMS (ESI) calculated for $C_{20}H_{20}N_4O_4S$: 413.1284 $(M + H)^+$, found: 413.1281.

*2-(3,4-Dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)-N-(3-methoxyphenyl)acetamide (**7i**)*

White powder; m.p. 185 °C; IR (KBr): 3286; 1662; 1337; 1168 cm^{-1}; ^1H NMR (DMSO-d_6): 2.36 (s, 3H, CCH_3), 2.97 (s, 3H, NCH_3), 3.75 (s, 3H, OCH_3), 5.14 (s, 2H, NCH_2), 6.87 (d, 1H, $J = 7.5$ Hz, Ar*H*), 7.12 (t, 2H, $J = 7.8$ Hz, Ar*H*), 7.25 (t, 1H, $J = 8.1$ Hz, Ar*H*), 7.54 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.71 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.82 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 15.5$ Hz, Ar*H*), 10.41 (s, 1H, N*H*); ^{13}C NMR: 8.8, 30.7, 52.7, 55.1, 107.3, 113.4, 120.5, 122.1, 123.4, 124.1, 126.8, 128.8, 129.2, 130.1, 131.2, 132.7, 134.8, 135.9, 159.7, 166.3; HRMS (ESI) calculated for $C_{20}H_{20}N_4O_4S$: 413.1284 $(M + H)^+$, found: 413.1278.

*N-(2,4-dimethoxyphenyl)-2-(3,4-dimethyl-5,5-dioxidopyrazolo[4,3-c][1,2]benzothiazin-2(4H)-yl)acetamide (**7j**)*

White powder; m.p. 203 °C; IR (KBr): 3277; 1657; 1343; 1147 cm^{-1}; ^1H NMR (DMSO-d_6): 2.42 (s, 3H, CCH_3), 3.03 (s, 3H, NCH_3), 3.80 (s, 3H, OCH_3), 3.90 (s, 3H, OCH_3), 5.26 (s, 2H, NCH_2), 6.52 (d, 1H, $J = 9.0$ Hz, Ar*H*), 6.70 (d, 1H, $J = 2.4$ Hz, Ar*H*), 7.68 (t, 1H, $J = 7.8$ Hz, Ar*H*), 7.80 (t, 2H, $J = 9.0$ Hz, Ar*H*), 7.97 (dd, 2H, $J_1 = 7.8$ Hz, $J_2 = 19.8$ Hz, Ar*H*), 9.59 (s, 1H, N*H*) ^{13}C NMR: 8.8, 30.7, 37.3, 52.9, 55.3, 55.8, 98.9, 104.1, 119.7, 122.3, 123.1, 123.4, 124.4, 127.9, 129.1, 131.5, 133.3, 136.5, 151.2, 156.9, 164.7; HRMS (ESI) calculated for $C_{21}H_{22}N_4O_5S$: 443.1389 $(M + H)^+$, found: 443.1377.

X-ray crystallography

The crystals of **6d** and **6l** suitable for X-ray crystallographic study were coated with Paratone 8277 oil (Exxon) and mounted on glass fibers. All measurements were made on a Bruker APEX2 CCD installed on a Nonius Kappa Goniometer diffractometer with graphite monochromated Mo-Kα radiation. The data were collected (Otwinowski and Minor, 1997) using ω and φ scans. The data were corrected for Lorentz and polarization effects and for absorption using multi-scan method (Hooft, 1998). The

structures were solved by the direct methods (Altomare *et al.*, 1993) and expanded using Fourier techniques (Beurskens *et al.*, 1994). The non-hydrogen atoms were refined anisotropically (Sheldrick, 2008). The H-atoms were included at geometrically idealized positions and were not refined. The weighting schemes were based on counting statistics and the final difference Fourier maps were essentially featureless. Details of crystal data and structure refinement have been provided in Table 1. The figures were plotted with the aid of ORTEP-3 for Windows (Farrugia, 1997). The crystals of **6d** were racemic twins with a BASF parameter = 0.54(8). Therefore, an absolute configuration of **6d** could not be determined. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center (CCDC deposition numbers are: **6d** = 817158; **6l** = 817157.

Antioxidant studies

Superoxide anion radical scavenging activity

Compounds were assessed by the method reported in literature (Gaulejac *et al.*, 1999). The reaction mixture comprises of 40 μL of 280 μM β-nicotinamide adenine dinucleotide reduced form (NADH), 40 μL of 80 μM nitro blue tetrazolium (NBT), 20 μL of 8 μM phenazine methosulphate (PMS), 10 μL of 1 mM sample and 90 μL of 0.1 M phosphate buffer (pH 7.4). The reagents were prepared in buffer and the sample in DMSO. The reactions were performed in 96-well microtitre plate at room temperature and absorbance was measured at 560 nm. The formation of superoxide was monitored by measuring the formation of water soluble blue formazan dye. A lower absorbance of reaction mixture indicates the higher scavenging activity of sample. Percent Radical Scavenging Activity was determined in comparison with control using the formula given below. The results are presented in Table 2.

$$\%\text{RSA} = 100 - (\text{OD test compound}/\text{OD control}) \times 100$$

DPPH radical scavenging activity

Compounds were assessed for DPPH radical scavenging activity using the procedure of Shaheen *et al.* (2005). The reaction mixture containing 5 μL of test sample (0.5 mM in DMSO) and 95 μL of DPPH (300 mmol in EtOH) was taken in a 96-well micro titer plate and incubated at 37 °C for 30 min. The absorbance was measured at 515 nm. Percent radical scavenging activity was determined by comparison with DMSO containing control, i.e., 3-*tert*-butyl-4-hydroxy anisole. The results are presented in Table 3.

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