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A facile synthesis of novel biologically active 4-hydroxy-*N*′-(benzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxides

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ABSTRACT

A novel series of potentially biologically active 4-hydroxy-*N*′-(benzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxides were synthesized starting from ultrasonic mediated N-alkylation of sodium saccharin with methyl chloroacetate. Ring expansion of methyl(1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetate followed by its hydrazinolysis afforded 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide which was reacted in a straight forward manner with various benzaldehydes in an ultrasonic bath to get the title compounds. All of the synthesized compounds were subjected to preliminary evaluation for their antibacterial and DPPH radical scavenging activities.

1. Introduction

Various benzothiazine derivatives are known to possess a versatile range of biological activities and have been synthesized continuously since the very first synthesis by Abe et al. [1]. Among these, 1,2-benzothiazine-3-carboxamide-1,1-dioxides such as Piroxicam [2], Ampiroxicam [3] and Meloxicam [4] are familiar for their analgesic and anti-inflammatory activities and are being used worldwide as non-steroidal anti-inflammatory drugs (NSAIDs). Some of the 3,4-dihydro-1,2-benzothiazine-3-carboxylate 1,1-dioxide α-ketomide and P(2)–P(3) peptide mimetic aldehyde compounds act as potent calpain I inhibitors [5] while 1,2-benzothiazin-3-yl-quinazolin-4(3*H*)-ones possess antibacterial properties [6].

Various carbohydrazides and their derivatives are reported to show a plethora of biological activities. For example, some of these are found useful for the treatment of autoimmune and inflammatory diseases, tumors, osteoarthritis and hemorrhage [7] whereas some others exhibit antifungal [8], antiviral [9], bacteriostatic [10,11], antiparasitic [12], antituberculous [13–16], and insecticidal activities [17]. These have also been found useful as antifertility agents in pigeons and rats [18].

Prompted by the above mentioned biological properties of benzothiazines and hydrazides, it was contemplated to synthesize a novel series of *N*-arylmethylidene-4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides on the perception of getting biologically active compounds.

2. Chemistry

The synthetic route to prepare the 4-hydroxy-*N*′-(benzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxides **5a–o** (Scheme 1) employed N-alkylation of *o*-benzosulfimide **1** with methyl chloroacetate under ultrasonic waves followed by the known ring expansion of the five membered isothiazole ring to a six membered thiazine ring. The resulting methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide **3** was reacted with hydrazine hydrate followed by ultrasound mediated reaction with different aldehydes (Scheme 1).

3. Results and discussion

In recent years, synthetic applications of ultrasonic irradiation in various organic transformations have been widely demonstrated in literature [19]. Many procedures have been devised to carry out chemical reactions in shorter times and under milder and more environmentally benign conditions. Reduction of carbonyl

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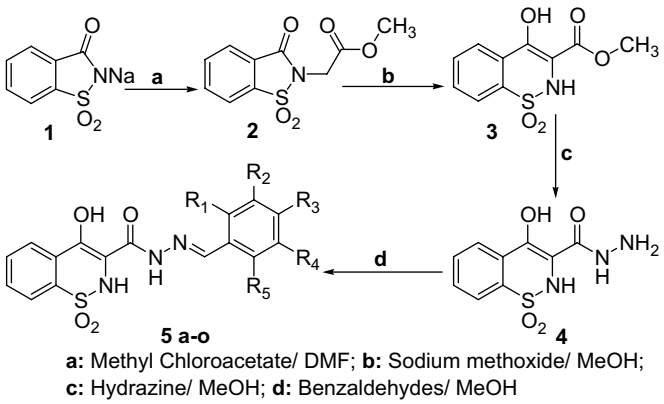

Scheme 1. Conversion of sodium saccharin to *N*-[(1*E*)-arylmethylidene]-4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides.

compounds [20], ring opening of epoxides [21], acetylation of alcohols [22], Suzuki cross-coupling reaction [23], aldol reaction [24] and oxime synthesis [25] are worth mentioning in this regard. Keeping in view the usefulness of this relatively unexplored technique, N-alkylation of 1,2-benzisothiazol-3(2*H*)-ones was carried out in an ultrasonic reaction bath; a mixture of sodium saccharin and methyl chloroacetate dissolved in dimethylformamide was subjected to ultrasonic irradiation. The reaction was completed in a shorter time and at lower temperature than the previously reported standard procedure [26].

In the next step, the five membered isothiazole ring was converted to a six membered thiazine ring using the known Gabriel–Colman type rearrangement having synchronous ring cleavage and ring closure steps in an inert atmosphere (nitrogen) [2] followed by its reaction with hydrazine. Hydrazinolysis of methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide **3** was carried out conventionally; it was heated to reflux along with hydrazine hydrate for 1 h and excess hydrazine was removed under vacuum. The resulting 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide **4** was then reacted with different benzaldehydes to get the respective 4-hydroxy-*N*′-(benzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxides.

In the first attempt, these condensations were affected in a polar medium (methanol) and the resulting compounds **5a**–**o** were characterized by spectroscopic techniques.

Due to the encouraging results obtained for ultrasonic mediated N-alkylation of sodium saccharin (in the first reaction), condensations of 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide **4** with different aldehydes were carried out in an ultrasonic bath with promising results.

Ultrasonic mediation shortened the reaction times considerably (reactions completed in only 1.5–3.0 min compared with 30–120 min under standard reflux conditions) and with improved yields (90.7–96.6% compared with 76.5–87.1% under reflux). Shortening of the reaction time may be attributed to cavitation, a physical process that creates, enlarges, and implodes gaseous and vaporous cavities in the irradiated medium. Cavitation creates very high local temperature and pressure inside the bubbles (cavities), leading to a turbulent flow in the liquid and enhanced mass transfer [27]. Results are shown in Table 1.

IR spectra of all the compounds **5a**–**o** showed an absorption band at 1630–1685 cm^{-1}, typical of the stretching vibrations of the carbon–nitrogen double bond. No peaks were found due to starting material amino or aldehydic functionalities. ^{1}H NMR spectra of all the compounds showed the broad singlets due CON*H* protons and a singlet due to C*H*–N protons. The singlet due to two amino protons disappeared, indicating the transformation of the reactant **4**. All of these compounds were further confirmed through mass spectrometry and C, H, N analyses which were found in accordance with the calculated values (Table 2)

In order to determine the stereochemistry (*E* or *Z* configuration) of the compounds under investigation, a single crystal of the product (**5e**) was grown by dissolving the compound in 90% ethanol and studied by X-ray crystallography. The crystal structure indicates that it crystallizes with $Z = 4$ (in space group $P2_1/c$; monoclinic) and except for the thiazine ring, the molecule deviates only slightly from being planar as shown by the values of six torsion angles defining the conformation (Tables 3 and 4); none of these angles deviates from 180° by more than 5°. The thiazine ring exhibits a half-chair conformation with S(1)–C(1)–C(6)–C(7) planar within ±0.041 Å and N(1) showing significant departure from planarity with pyramidal geometry [Fig. 1]. Also, a look on C=N bond indicates the *E* configuration of the compounds of this type. Crystallographic data have been deposited with the Cambridge Crystallographic Data Center (CCDC deposition number is 658397).

4. Biological activity

4.1. DPPH radical scavenging activities

Compounds **5a**–**o** were screened for DPPH radical scavenging activity using the procedure of Shaheen et al. [28]. All the compounds showed interesting antioxidant activity compared to the standard, 3-*tert* butyl-4-hydroxy anisole (Table 5). The reaction

Table 1
Condensation of 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide and various aldehydes under normal and ultrasonic conditions

Entry	Reactant	Product	Alcoholic medium		Ultrasonic mediation	
			Reaction conditions (min)	Yield (%)[a]	Reaction conditions (°C; min)	Yield (%)[a]
1	**4**	**5a**	Reflux; 60	80.1	40; 3	93.2
2	**4**	**5b**	Reflux; 30	81.9	25; 3	94.7
3	**4**	**5c**	Reflux; 60	82	25; 3	91.1
4	**4**	**5d**	Reflux; 60	83.4	35; 2	92.0
5	**4**	**5e**	Reflux; 35	83	40; 2.5	93.4
6	**4**	**5f**	Reflux; 60	80.1	35; 2	96.6
7	**4**	**5g**	Reflux; 120	83.4	35; 3	90.9
8	**4**	**5h**	Reflux; 90	85	35; 3	92.3
9	**4**	**5i**	Reflux; 120	85.2	30; 5	93.2
10	**4**	**5j**	Reflux; 60	77.2	30; 1.5	95.4
11	**4**	**5k**	Reflux; 60	79.1	30; 2	92.8
12	**4**	**5l**	Reflux; 60	77.3	30; 1.5	90.7
13	**4**	**5m**	Reflux; 60	76.5	30; 3	93.9
14	**4**	**5n**	Reflux; 30	76.2	30; 2	91.1
15	**4**	**5o**	Reflux; 120	87.1	30; 2.5	92.7

[a] Isolated yields based on 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide.

Table 2
Characterization table of *N*-[(1*E*)-arylmethylidene]-4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides (**5a–o**)

Compd	R_1	R_2	R_3	R_4	R_5	Mol. formula	Analysis%		
							Calculated (found)		
							C	H	N
5a	H	H	H	H	H	$C_{16}H_{13}N_3O_4S$	55.97 (56.03)	3.82 (3.85)	12.24 (12.27)
5b	OH	H	H	H	H	$C_{16}H_{13}N_3O_5S$	53.48 (53.54)	3.65 (3.69)	11.69 (11.73)
5c	OH	H	OH	H	H	$C_{16}H_{13}N_3O_6S$	51.20 (51.26)	3.49 (3.53)	11.19 (11.25)
5d	H	OH	OMe	H	H	$C_{17}H_{15}N_3O_6S$	52.44 (52.50)	3.88 (3.91)	10.79 (10.84)
5e	H	OMe	OH	H	H	$C_{17}H_{15}N_3O_6S$	52.44 (52.49)	3.88 (3.92)	10.79 (10.86)
5f	H	H	OMe	H	H	$C_{17}H_{15}N_3O_5S$	54.68 (54.73)	4.05 (4.10)	11.25 (11.30)
5g	OMe	H	OMe	H	H	$C_{18}H_{17}N_3O_6S$	53.59 (53.65)	4.25 (4.28)	10.42 (10.48)
5h	H	H	OMe	OMe	H	$C_{18}H_{17}N_3O_6S$	53.59 (53.66)	4.25 (4.30)	10.42 (10.47)
5i	H	H	OMe	OMe	OMe	$C_{19}H_{19}N_3O_7S$	52.65 (52.71)	4.42 (4.46)	9.69 (9.75)
5j	Cl	H	H	H	H	$C_{16}H_{12}ClN_3O_4S$	50.87 (50.90)	3.20 (3.23)	11.12 (11.16)
5k	H	Cl	H	H	H	$C_{16}H_{12}ClN_3O_4S$	50.87 (50.92)	3.20 (3.25)	11.12 (11.15)
5l	H	H	Cl	H	H	$C_{16}H_{12}ClN_3O_4S$	50.87 (50.93)	3.20 (3.24)	11.12 (11.18)
5m	Cl	H	Cl	H	H	$C_{16}H_{11}Cl_2N_3O_4S$	46.62 (46.67)	2.69 (2.73)	10.19 (10.24)
5n	NO_2	H	H	H	H	$C_{16}H_{12}N_4O_6S$	49.48 (49.52)	3.11 (3.15)	14.43 (14.48)
5o	H	H	NO_2	H	H	$C_{16}H_{12}N_4O_6S$	49.48 (49.54)	3.11 (3.13)	14.43 (14.48)

Table 3
Selected torsion angles (°)

Bond	Torsion angle	Bond	Torsion angle
C(4)–C(5)–C(6)–C(7)	−176.4 (5)	C(7)–C(8)–C(9)–N(2)	−175.0 (5)
C(8)–C(9)–N(2)–N(3)	179.7 (4)	C(9)–N(2)–N(3)–C(10)	−177.8 (5)
N(2)–N(3)–C(10)–C(11)	179.2 (5)	C(10)–C(11)–C(12)–C(13)	−179.0 (5)

Table 4
Crystallographic parameters for compound **5e**

Structural formula	$C_{17}H_{17}N_3O_7S$	Cell volume	1837.3(7) Å^3
Formula weight	407.40	Z	4
Crystal system	Monoclinic	Calculated density	1.473 g/cm^3
Space group	$P2_1/c$	Crystal size	0.33 × 0.11 × 0.02 mm^3
T (K)	150(2)	Reflections collected	8881
a (Å); α	9.444(2); 90°	Independent reflections	2393 (R_{int} = 0.1162)
b (Å); β	8.4079(18)	Reflections with $F^2 > 2\sigma$	1370
c (Å); γ	23.153(5); 90°	Goodness-of-fit on F^2	1.017

mixture containing 5 μL of test sample (0.5 mM in DMSO) and 95 μL of DPPH (300 mmoles 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. Results showed moderate to significant activity of almost all the compounds. An insight to the structure–activity relationship gives an idea that activity generally increases with number and strength of electron donating groups. Compounds having hydroxyl and methoxy groups in the benzene ring of carbohydrazides are found relatively more active e.g., compound **5c** (dihydroxy derivative; 65.014%) is more active than **5b** (monohydroxy derivative; 40.680%) which itself is more active than **5a** (bearing no substituent). Among the compounds bearing methoxy groups, 2,4-dimethoxy derivative is more active (68.147%) than 4-methoxy analogue. However, incorporation of one more methoxy group to the ring decreased the activity (2,3,4-trimethoxy derivative; 43.568%) perhaps due to steric reasons. Similarly, 3,4-dimethoxy derivative exhibits less activity (37.96%) than the 2,4-dimethoxy analogue (68.147%). For the chloro and nitro derivatives, compounds show percentage radical scavenging activity in the following order: $o > m > p$.

4.2. Antibacterial studies

Compounds **5a–o** were also subjected to antibacterial testing using the Agar Well Diffusion method [29]. The in vitro antibacterial activity of the compounds was checked against five strains of bacteria i.e., *Escherichia coli*, *Bacillus subtilis*, *Shigella flexneri*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Salmonella typhi*. The compounds were applied to the wells of 6 mm diameter at 1 mg per ml of DMSO in addition to 0 (control) and the standard Imipenum (10 μg per disc).

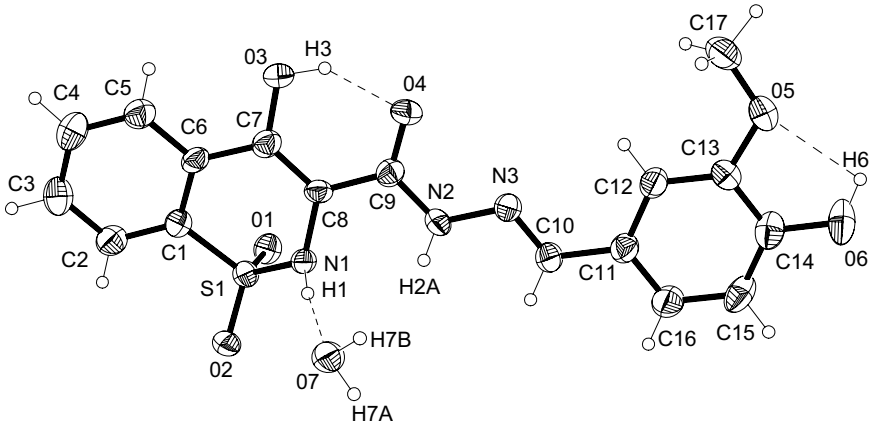

Fig. 1. *ORTEP* II diagram of compound **5e** with the numbering scheme. Displacement ellipsoids are drawn at the 50% probability level, H atoms are represented by circles of arbitrary radius and hydrogen bonds are shown as dashed lines.

Table 5
% radical scavenging activity

S. No.	Compound	% Radical scavenging activity
1	**5a**	37.652
2	**5b**	40.680
3	**5c**	65.014
4	**5d**	42.847
5	**5e**	34.998
6	**5f**	43.743
7	**5g**	68.147
8	**5h**	37.960
9	**5i**	43.568
10	**5j**	57.392
11	**5k**	23.762
12	**5l**	21.208
13	**5m**	43.808
14	**5n**	37.272
15	**5o**	30.945
16	3-*tert* Butyl-4-hydroxy anisole (standard oxidant)	92.601

Results showed that none of the compounds (**5a**–**o**) were active against *E. coli*, *B. subtilis* and *P. aeruginosa* (Table 6).

Compounds **5d** and **5m** were found weakly active against *S. flexneri* while **5h** and **5i** were found moderately active. Compounds **5h** and **5n** were found weakly active while **5c** and **5o** were found significantly active against *S. typhi*. Compounds **5d**, **5f** and **5n** were found weakly active, **5e** moderately active while **5i** was found significantly active against *S. aureus*. The remaining compounds were either inactive or had a zone of inhibition of less than 10 mm. A look on structure activity relationship reveals that compounds having electron donating groups are generally more active. For *S. flexneri,* 3,4,5-trimethoxy derivative, **5i**, is more active (22 mm) than the corresponding 3,4-dimethoxy derivative, **5h** (20 mm). Similar results were found for *S. aureus*; compound **5f**, (4-methoxy derivative) is moderately active. Incorporation of hydroxyl group at 3-position decreases the activity while upon reversing the position of substituents (**5e**), activity enhances. For *S. typhi,* compounds bearing 2,4-dihydroxy and 3-nitro substituents are found significantly active; however, all the other compounds showed no significant activity.

5. Conclusion

The present study revealed that the compounds obtained by synergism of the 4-hydroxy-1,2-benzothiazine-1,1-dioxide nucleus with carbohydrazide moieties were found to be biologically active 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. Ultrasonic mediation during the syntheses was found quite useful to obtain higher yields and purity than those which were carried out by simple condensation in methanol and reaction times were curtailed to a very considerable extent (from 0.5–3 h to 1.5–3 min).

Table 6
Antibacterial activity of compounds **5a**–**o**

S. No.	Compound	Susceptible micro organism					
		E. coli	*S. flexenari*	*B. subtilis*	*S. aureus*	*P. aeruginosa*	*S. typhi*
1	**5a**	–	–	–	–	–	–
2	**5b**	–	–	–	–	–	–
3	**5c**	–	–	–	–	–	28
4	**5d**	–	10	–	10	–	–
5	**5e**	–	–	–	15	–	–
6	**5f**	–	–	–	12	–	–
7	**5g**	–	–	–	–	–	–
8	**5h**	–	20	–	–	–	11
9	**5i**	–	22	–	21	–	–
10	**5j**	–	–	–	–	–	–
11	**5k**	–	–	–	–	–	–
12	**5l**	–	–	–	–	–	–
13	**5m**	–	10	–	–	–	–
14	**5n**	–	–	–	10	–	11
15	**5o**	–	–	–	–	–	26
16	0	–	–	–	–	–	–
17	Imipenum	30	37	36	26	32	30

6. Experimental

6.1. Chemistry

All the chemicals were purchased from E. Merck, BDH or Fluka and 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. Mass spectra were recorded on Agilent 5973N instrument using EI mode. X-ray crystallography was carried out on Bruker APEX II CCD diffractometer at 150 K. Melting points were recorded on a Gallenkamp melting point apparatus and are uncorrected. Ultrasonic mediated reactions were carried out in Clifton Ultrasonic Bath (2 x T2A, 300 W, DU-4) made by Nickel Electro Ltd, Weston-S-Mare Somerset, England.

6.1.1. Methyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3H)-yl) acetate **2**

A mixture of sodium saccharin (7.50 g; 36.55 mmol), *N*,*N*-dimethylformamide (50 ml) and methyl chloroacetate (3.942 g; 36.55 mmol) was taken in a round bottom flask and immersed in ultrasonic reaction bath at 60 °C for a period of 15 min. Contents were then cooled to room temperature and poured over ice cooled water (300 ml) resulting in the formation of a white solid, which was filtered and washed with cold water. The solid was dried and recrystallized from methyl alcohol to get the product (8.80 g; 94.4%); m.p. 116–117 °C (Lit. m.p. 115–116 °C) [26]; IR (KBr) 1754, 1671, 1344, 1189 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ: 3.81 (s, 3H, OCH_3), 4.42 (s, 2H, CH_2), 7.73–7.79 (m, 4H, Ar*H*).

6.1.2. Methyl 4-hydroxy-2H-1,2-benzothiazine-3-carboxylate 1, 1-dioxide (**3**)

Compound **3** was synthesized according to literature procedure [26]. Sodium metal (2.3 g; 100 mmol) and dry methanol (125 ml) was allowed to reflux until all the metal dissolved. To this solution, methyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl) acetate (**2**) (10.2 g; 40.0 mmol) was added in a single portion under inert conditions. Temperature of the mixture was maintained at 55 °C for 30 min till the completion of precipitation. The contents were then suddenly cooled to 5 °C and poured over an ice-water mixture. HCl (15%) was added to the mixture till the pH became approximately 3. The precipitates formed were filtered and dried at 70 °C to get the product as white crystalline solid (8.46 g, 82.9%); m.p. 172–173 °C; IR (KBr) 3184, 1669, 1341, 1180 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ: 3.85 (s, 3H, OCH_3), 7.75 (dd, $J = 5.6$, 3.2 Hz, 2H, Ar*H*), 7.82 (dd, $J = 5.6$, 3.2 Hz, 2H, Ar*H*), 12.35 (s, 1H, OH_{enolic}), 8.39 (br s, 1 H, N*H*); MS *m*/*z* (%): 255(100) [M$^+$], 254 (98) [M$^+$–H].

6.1.3. 4-Hydroxy-2H-1,2-benzothiazine-3-carbohydrazide 1, 1-dioxide (**4**)

A mixture of methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**3**) (5.1 g; 20.0 mmol), hydrazine hydrate (1.25 g, 25 mmol) and methyl alcohol was stirred and refluxed for a period of 35 min. After completion of the reaction (as indicated by

TLC), solvent was removed under vacuum and the residue obtained was treated with cold hydrochloric acid (5%) followed by washing with water to get the product (4.89 g; 96.4%); m.p. 292 °C decomp; IR (KBr) 3409, 3266, 1674, 1326, 1128, 1030 cm^{-1}; ^1H NMR ($CDCl_3$) δ: 2.49 (br s, 2H, NH_2), 7.55–7.87 (m, 4H, Ar*H*), 9.61 (br s, 1H, N*H*), 10.28 (br s, 1H, N*H*), 12.64 (s, 1H, OH_{enolic}); HRMS/EI ($g\,mol^{-1}$) calcd for CHNOS 255.2505, found 255.2511.

6.1.4. 4-Hydroxy-N′-(benzylidene)-2H-benzo[e][1,2] thiazine-3-carbohydrazide 1,1-dioxides ***5a–o***

6.1.4.1. Using methanol as solvent. A mixture of 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**4**) (2.0 mmol), aldehyde (2.0 mmol), ortho phosphoric acid (2 drops) and methanol (50 ml) was refluxed till completion of the reaction (for yields, reaction conditions and reaction times, see Table 1). The contents were cooled to 5 °C in an ice bath, filtered and the solids were washed with cold methanol to get the pure compound.

6.1.4.2. Using ultrasonic waves. A mixture of 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**4**) (0.51 g; 2.0 mmol), aldehyde (2.0 mmol), ortho phosphoric acid (1 drop) and methanol (2.5 ml) taken in a loosely screw capped test tube was immersed in an ultrasonic reaction bath (for yields, reaction conditions and reaction times, see Table 1). Contents were cooled to 10 °C and washed with cold methanol to get the pure compound.

4-Hydroxy-*N′*-(benzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxide (**5a**): Light yellow crystals (0.59 g; 93.2%). m.p. 251 °C decomp; IR (KBr) 3395, 3055, 1631, 1543, 1175, 1071 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.61–8.03 (m, 9H, Ar*H*), 8.57 (s, 1H, NC*H*), 9.51 (br s, 1H, N*H*), 11.78 (br s, 1H, N*H*), 13.12 (s, 1H, O*H* enolic); MS *m*/*z* (%): 359 (57.9) [M^+].

4-Hydroxy-*N′*-(2-hydroxybenzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxide (**5b**): Yellow crystals (0.68 g; 94.6%); m.p. 262–263 °C; IR (KBr) 3390, 2937, 1647, 1544, 1341, 1172, 1071 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 6.91 (d, $J = 6.6$ Hz, 1H, Ar*H*), 6.95 (m, 1H, Ar*H*), 7.32 (t, $J = 6.6$ Hz, 1H, Ar*H*), 7.54 (d, $J = 6.8$, 1H, Ar*H*), 7.85 (m, 3H, Ar*H*), 8.03 (dd, $J = 6.4$, 1.2 Hz, 1H, Ar*H*), 8.87 (s, 1H, NC*H*), 9.59 (br s, 1H, N*H*), 11.02 (s, 1H, ArO*H*), 12.14 (br s, 1H, N*H*), 13.77 (s, 1H, O*H* enolic); MS *m*/*z* (%): 359 (100) [M^+].

N′-(2,4-Dihydroxybenzylidene)-4-hydroxy-2*H*-benzo[*e*][1,2]-thiazine-3-carbohydrazide 1,1-dioxide (**5c**): Orange crystals (0.68 g; 91.1%); m.p. 270–272 °C; IR (KBr) 3392, 3284, 3052, 1633, 1541, 1320, 1170, 1069 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 6.31 (d, $J = 6.2$ Hz, 1H, Ar*H*), 6.35 (d, $J = 6.2$, 1H, Ar*H*), 7.31 (d, $J = 8.4$ Hz, 1H, Ar*H*), 7.78–8.03 (m, 4H, Ar*H*), 8.71 (s, 1H, NC*H*), 9.55 (br s, 1H, N*H*), 10.01 (s, 1H, ArO*H*), 11.20 (s, 1H, ArO*H*), 11.96 (br s, 1H, N*H*), 13.84 (s, 1H, O*H* enolic); MS *m*/*z* (%): 375 (82.8) [M^+], 137 (100).

4-Hydroxy-*N′*-(3-hydroxy-4-methoxybenzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxide (**5d**): Pale yellow crystals (0.70 g; 92.0%); m.p. 255 °C decomp; IR (KBr) 3389, 3280, 3049, 1637, 1544, 1326, 1174, 1073 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.80 (s, 3H, OCH_3), 6.82 (d, $J = 8.1$ Hz, 1H, Ar*H*), 7.09 (s, 1H, Ar*H*), 7.19 (dd, $J = 8.1$, 1.5 Hz, 1H, Ar*H*), 7.81–7.88 (m, 3H, Ar*H*), 8.02 (d, $J = 7.5$ Hz, 1H, Ar*H*), 8.50 (s, 1H, NC*H*), 9.53 (br s, 1H, N*H*), 9.59 (br s, 1H, N*H*), 14.11 (s, 1H, O*H* enolic); MS *m*/*z* (%): 389 (100) [M^+].

4-Hydroxy-*N′*-(4-hydroxy-3-methoxybenzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxide (**5e**): Dark yellow crystals (0.72 g; 93.4%); m.p. 262–263 °C; IR (KBr) 3379, 3272, 3054, 1631, 1595, 1332, 1176, 1031 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.83 (s, 3H, OCH_3), 6.85 (d, $J = 8.1$ Hz, 1H, Ar*H*), 7.07 (dd, $J = 8.1$, 1.5 Hz, 1H, Ar*H*), 7.29 (s, 1H, Ar*H*), 7.78–7.89 (m, 3H, Ar*H*), 8.02 (d, $J = 7.6$ Hz, 1H, Ar*H*), 8.52 (s, 1H, NC*H*), 9.53 (br s, 1H, N*H*), 9.61 (br s, 1H, N*H*), 14.08 (s, 1H, O*H* enolic); MS *m*/*z* (%): 389 (100) [M^+].

4-Hydroxy-*N′*-(4-methoxybenzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxide (**5f**): Yellow crystals (0.50 g; 96.6%); m.p. 250–251 °C; IR (KBr) 3281, 3170, 1651, 1590, 1330, 1174, 1128, 1037 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.81 (s, 3H, OCH_3), 7.03 (d, $J = 8.7$ Hz, 2H, Ar*H*), 7.66 (d, $J = 8.7$ Hz, 2H, Ar*H*), 7.81–7.88 (m, 3H, Ar*H*), 8.02 (d, $J = 7.7$ Hz, 1H, Ar*H*), 8.58 (s, 1H, NC*H*), 9.54 (br s, 1H, N*H*), 11.71 (br s, 1H, N*H*), 14.06 (s, 1H, O*H* enolic); MS *m*/*z* (%): 373 (100) [M^+].

N′-(2,4-Dimethoxybenzylidene)-4-hydroxy-2*H*-benzo[*e*][1,2]-thiazine-3-carbohydrazide 1,1-dioxide (**5g**): Light orange powder (0.73 g; 90.9%); m.p. 240 °C decomp; IR (KBr) 3285, 3168, 1669, 1604, 1327, 1177, 1132, 1034 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.82 (s, 3H, OCH_3), 3.87 (s, 3H, OCH_3), 6.61 (d, $J = 6.7$ Hz, 1H, Ar*H*), 6.64 (d, $J = 6.7$ Hz, 1H, Ar*H*), 7.78–7.89 (m, 4H, Ar*H*), 8.01 (d, $J = 6.6$ Hz, 1H, Ar*H*), 8.90 (s, 1H, NC*H*), 9.48 (br s, 1H, N*H*), 11.78 (br s, 1H, N*H*), 14.08 (s, 1H, O*H* enolic); MS *m*/*z* (%): 403 (100) [M^+].

N′-(2,3-Dimethoxybenzylidene)4-hydroxy-2*H*-benzo[*e*][1,2]-thiazine-3-carbohydrazide 1,1-dioxide (**5h**): Pale yellow powder (0.74 g; 92.3%); m.p. 248–249 °C; IR (KBr) 3299, 3101, 1668, 1589, 1322, 1171, 1128, 1071 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.81 (s, 3H, OCH_3), 3.83 (s, 3H, OCH_3), 7.04 (d, $J = 6.4$ Hz, 1H, Ar*H*), 7.60–8.03 (m, 6H, Ar*H*), 8.62 (s, 1H, NC*H*), 9.64 (br s, 1H, N*H*), 11.71 (br s, 1H, N*H*), 14.05 (s, 1H, O*H* enolic); MS *m*/*z* (%): 403 (100) [M^+].

4-Hydroxy-*N′*-(2,3,4-trimethoxybenzylidene)-2*H*-benzo[*e*][1,2] thiazine-3-carbohydrazide 1,1-dioxide (**5i**): Light yellow crystals (0.80 g; 93.2%); m.p. 254–257 °C decomp; IR (KBr) 3288, 2987, 1648, 1560, 1320, 1165, 1124, 1055 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 3.71 (s, 3H, $OCH_{3\ (para)}$), 3.84 (s, 6H, $OCH_{3\ (meta)}$), 7.0 (s, 2H, Ar*H*), 7.81–8.04 (m, 4H, Ar*H*), 8.56 (s, 1H, NC*H*), 9.56 (br s, 1H, NH), 11.81 (br s, 1H, N*H*), 13.99 (s, 1H, O*H* enolic); MS *m*/*z* (%): 433 (41.17) [M^+], 73 (100).

N′-(2-Chlorobenzylidene)-4-hydroxy-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxide (**5j**): Bright yellow crystals (0.71 g; 95.4%). m.p. 245 °C decomp; IR (KBr): 3390, 3078, 1678, 1545, 1340, 1173, 1067 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.52 (s, 1H, Ar*H*), 7.55 (s, 1H, Ar*H*), 7.73–8.04 (m, 6H, Ar*H*), 8.65 (s, 1H, NC*H*), 9.56 (br s, 1H, N*H*), 11.91 (br s, 1H, N*H*), 13.95 (s, 1H, O*H* enolic); MS *m*/*z* (%): 377 (100) [M^+], 379 (34.5) [$M^+ + 2$].

N′-(3-Chlorobenzylidene)-4-hydroxy-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxide (**5k**): Yellow powder (0.69 g; 92.8%); m.p. 253–254 °C; IR (KBr) 3391, 3074, 1674, 1540, 1339, 1172, 1067 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.55 (s, 1H, Ar*H*), 7.77–8.01 (m, 7H, Ar*H*), 8.63 (s, 1H, NC*H*), 9.58 (br s, 1H, N*H*), 11.90 (br s, 1H, N*H*), 13.91 (s, 1H, O*H* enolic); MS *m*/*z* (%): 377 (100) [M^+], 379 (34.6) [$M^+ + 2$].

N′-(4-Chlorobenzylidene)-4-hydroxy-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxide (**5l**): Dirty yellow powder (0.68 g; 90.7%); m.p. 255–256 °C; IR (KBr) 3388, 3076, 1675, 1544, 1342, 1175, 1063 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.07 (d, $J = 8.7$ Hz, 2H, Ar*H*), 7.69 (d, $J = 8.7$ Hz, 2H, Ar*H*), 7.84–7.87 (m, 3H, Ar*H*), 8.01 (d, $J = 7.7$ Hz, 1H, Ar*H*), 8.61 (s, 1H, NC*H*), 9.56 (br s, 1H, N*H*), 11.68 (br s, 1H, N*H*), 13.89 (s, 1H, O*H* enolic); MS *m*/*z* (%): 377 (100) [M^+], 379 (35.1) [$M^+ + 2$].

N′-(2,4-Dichloro benzylidene)-4-hydroxy-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxide (**5m**): Light yellow powder (0.77 g; 93.9%); m.p. 262 °C decomp; IR (KBr) 3395, 2944, 1684, 1564, 1347, 1181, 1073 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.52 (dd, 1H, $J = 6.6$, 1.2 Hz, 1H, Ar*H*), 7.54–8.04 (m, 6H, Ar*H*), 9.05 (s, 1H, NC*H*), 9.62 (br s, 1H, N*H*), 12.19 (br s, 1H, N*H*), 13.85 (s, 1H, O*H* enolic); MS *m*/*z* (%): 412 (100) [M^+], 414 (61.4) [$M^+ + 2$], 416 (15.0) [$M^+ + 4$].

4-Hydroxy-*N′*-(2-nitrobenzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxide (**5n**): Yellow powder (0.69 g; 92.6%); m.p. 280 ^{0}C decomp; IR (KBr) 3404, 3034, 1668, 1544, 1340, 1156, 1049 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.68–8.11 (m, 8H, Ar*H*), 9.07 (s, 1H, NC*H*), 9.60 (br s, 1H, N*H*), 12.24 (br s, 1H, N*H*), 13.84 (s, 1H, O*H* enolic); MS *m*/*z* (%): 388 (56.1) [M^+].

4-Hydroxy-*N′*-(3-nitrobenzylidene)-2*H*-benzo[*e*][1,2]thiazine-3-carbohydrazide 1,1-dioxide (**5o**): Light yellow powder (0.71 g; 92.7%); m.p. 255–256 °C; IR (KBr) 3385, 3074, 1671, 1543, 1340,

1175, 1065 cm^{-1}; ^1H NMR (DMSO-d_6) δ: 7.09 (d, $J = 8.7$ Hz, 2H, Ar*H*), 7.70 (d, $J = 8.7$ Hz, 2H, Ar*H*), 7.85–7.89 (m, 3H, Ar*H*), 8.0 (d, $J = 7.7$ Hz, 1H, Ar*H*), 8.58 (s, 1H, NC*H*), 9.52 (br s, 1H, N*H*), 11.70 (br s, 1H, N*H*), 13.90 (s, 1H, O*H* enolic); MS *m*/*z* (%): 388 (55.8) [M^+].

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