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Original article

# Microwave assisted synthesis and structure–activity relationship of 4-hydroxy-*N*′-[1-phenylethylidene]-2*H*/2-methyl-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides as anti-microbial agents

Naveed Ahmad [a], Muhammad Zia-ur-Rehman [b,*], Hamid Latif Siddiqui [a], Muhammad Fasih Ullah [a], Masood Parvez [c]

[a] Institute of Chemistry, University of the Punjab, Lahore 54590, Pakistan
[b] Applied Chemistry Research Centre, PCSIR Laboratories Complex, Ferozpur Road, Lahore 54600, Pakistan
[c] Department of Chemistry, The University of Calgary, 2500 University Drive, NW, Calgary, Alberta, Canada T2N 1N4

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ABSTRACT

A series of 4-hydroxy-*N*′-[1-phenylethylidene]-2*H*/2-methyl, 1,2-benzothiazine-3-carbohydrazide 1,1-dioxides was synthesized from commercially available sodium saccharin. Base catalyzed ring expansion of methyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl)acetate followed by ultrasound mediated hydrazinolysis and subsequent reaction with 1-phenylethanones under the influence of microwaves yielded the title compounds. Besides, microwave assisted synthesis of 1,4-dihydropyrazolo[4,3-*c*][1,2]benzothiazin-3-ol 5,5-dioxide and 4-methyl-1,4-dihydropyrazolo[4,3-*c*][1,2]benzothiazin-3-ol 5,5-dioxide is also discussed. Most of the synthesized compounds were found to possess moderate to significant anti-microbial (anti-bacterial and anti-fungal) activities. It is found that compounds with greater lipophilicity (*N*-methyl analogues) possessed higher anti-bacterial activities.



## 1. Introduction

Among condensed sulfur–nitrogen heterocycles, sulfones and sultams (cyclic sulfonamides) possess enormous potential as pharmaceutical and agricultural agents [1–3], chiral auxiliaries [4,5] and therapeutic compounds [6]. Benzothiazepines and benzothiazines are the most familiar classes of such compounds and are under investigation since a long. The six-membered homologues, 1,4-benzothiazine 1,1-dioxides, generally possess significant anti-fungal activities [7], while 1,2-benzothiazine 1,1-dioxides [8] correspond to the most familiar class of non-steroidal anti-inflammatory drugs (NSAIDs) available in the market (Fig. 1). Some of the 3,4-dihydro-1,2-benzothiazine-3-carboxylate 1,1-dioxide α-ketomide and P(2)–P(3) peptide mimetic aldehydes act as potent calpain I inhibitors [9,10]. These are also found useful for the treatment of rheumatoid arthritis, ankylosing spondylitis and osteoarthritis [11].

Carbohydrazides are becoming popular day by day in the field of drug development due to their condensation and cyclization reactions [12,13]. Up till now, a large number of such compounds have been synthesized with significant anti-microbial [14], anti-tubercular [15], anti-inflammatory [16], anti-cancer [17], anti-fungal [18], anti-bacterial [19] and anti-malarial [20] activities.

In continuation of our on-going research on various biologically active benzothiazine derivatives [21,22] and due to versatile anti-microbial activities of carbohydrazides, synthesis of a series of novel 4-hydroxy-*N*′-[1-phenylethylidene]-2*H*/2-methyl-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides has been contemplated with the perception of getting biologically active compounds. Besides the characterization of newly synthesized compounds through spectroscopic techniques and single crystal X-ray analysis, these have been evaluated for their anti-bacterial and anti-fungal potential. In addition to synthesis of the title compounds, microwave assisted synthesis of novel cyclized products [1,4-dihydropyrazolo[4,3-*c*][1,2]benzothiazin-3-ol 5,5-dioxide **5** and 4-methyl-1,4-dihydropyrazolo[4,3-*c*][1,2]benzothiazin-3-ol 5,5-dioxide (**10**)] is also described.

* Corresponding author. Tel.: +92 333 4571977.
*E-mail address:* rehman_pcsir@hotmail.com (M. Zia-ur-Rehman).

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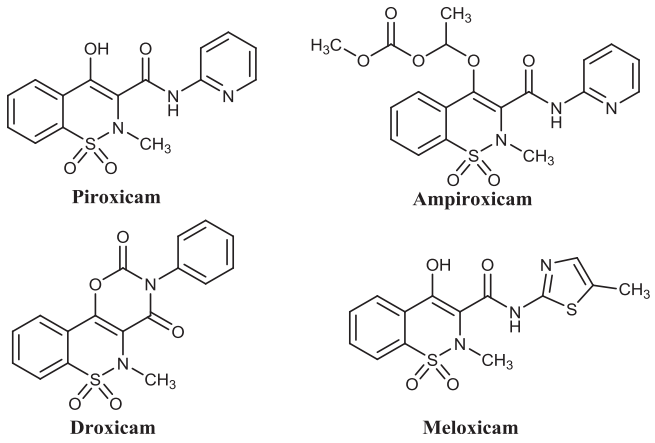
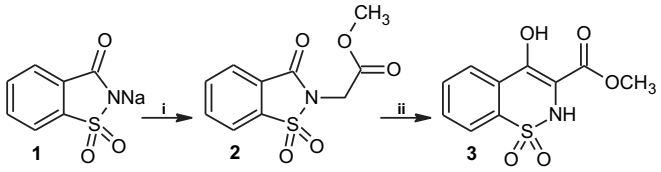



**Fig. 1.** Structures of some 1,2-benzothiazines 1,1-dioxide based drugs.



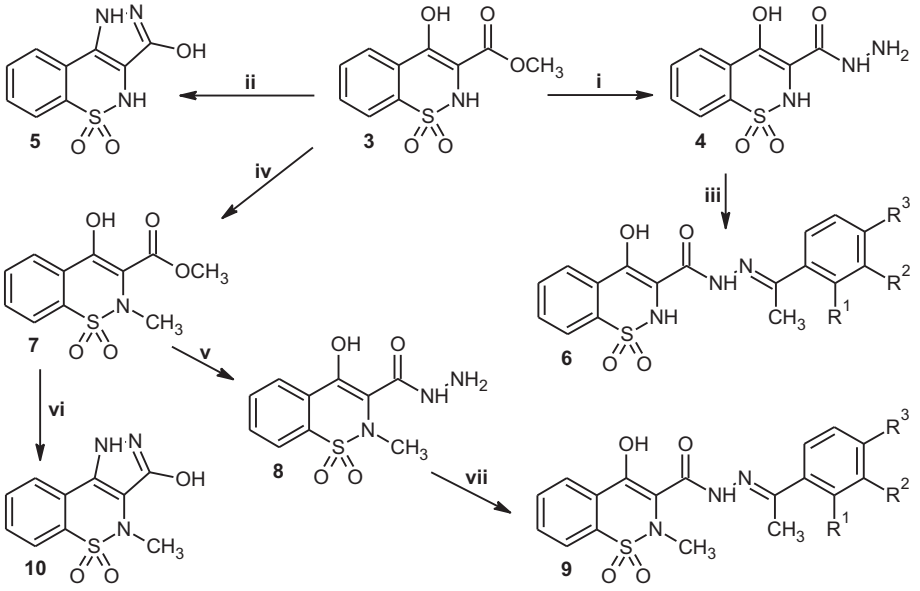

**Reaction conditions: i-** Methyl chloroacetate/ DMF **ii-** Sodium methoxide/ methanol

**Scheme 1.** Synthesis of methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide from commercially available sodium saccharin.

## 2. Results and discussion

### 2.1. Chemistry

4-Hydroxy-*N*′-[1-phenylethylidene]-2*H*-1,2-benzothiazine-3-ca -rbohydrazide 1,1-dioxides (**6a**–**n**) and 4-hydroxy-2-methyl-*N*′-[1-phenylethylidene]-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dio -xides (**9a**–**n**) were synthesized from commercially available sodium 3-oxo-3*H*-1,2-benzisothiazol-2-ide 1,1-dioxide **1**. The later, **1**, was reacted with methyl chloroacetate in microwave conditions to get methyl (1,1-dioxido-3-oxo-1,2-benzisothiazol-2(3*H*)-yl) acetate **2** in excellent yield. Gabriel–Colman type ring expansion of five membered isothiazole ring of **2** to the six-membered thiazine ring, having synchronous ring cleavage and ring closure steps, in an inert (nitrogen) atmosphere yielded 1,2-benzothiazine 1,1-dioxide [23]. Methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide **3**, synthesized as outlined in Scheme 1, was reacted with hydrazine hydrate in methanol to get 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide **4**. However, it was found that prolonged induction of microwave radiations to this reaction facilitated the intramolecular cyclization yielding 1,4-dihydropyrazolo[4,3-*c*][1,2]benzothiazin-3-ol 5,5-dioxide **5**, which may be attributed to greater energy associated with microwaves. 4-Hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide **4** and its 2-methyl analogue **7**, synthesized by N-methylation of **3** with dimethyl sulfate using literature procedure [18], were then reacted with a number of 1-phenylethanones to get series of novel 4-hydroxy-*N*′-[1-phenylethylidene]-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides **6a**–**n** and 4-hydroxy-2-methyl-*N*′-[1-phenylethylidene]-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides **9a**–**n** [Scheme 2]. All the condensation reactions were also attempted under microwaves and were found more effective than in thermal conditions due to greater yields and lesser reaction times [Table 1]. Induction of microwaves to the reaction of methyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide facilitated the formation of




**Reaction conditions: i-** $NH_2NH_2$/ MeOH; reflux **ii-** $NH_2NH_2$/ microwaves **iii-** 1-Phenyl ethanones/ MeOH/ $H_3PO_4$ / microwaves **iv-** $(Me)_2SO_4$ / $CH_3COCH_3$ **v-** $NH_2NH_2$/ MeOH; reflux **vi-** $NH_2NH_2$/ microwaves **vii-** 1-Phenyl ethanones/ MeOH/ $H_3PO_4$ / microwaves

**Scheme 2.** Conversion of methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide to 4-hydroxy-*N*′-[1-phenylethylidene]-2*H*/2-methyl-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides, 1,4-dihydropyrazolo[4,3-*c*][1,2]benzothiazin-3-ol 5,5-dioxide and 4-methyl-1,4-dihydropyrazolo[4,3-*c*][1,2]benzothiazin-3-ol 5,5-dioxide.

cyclized product **10** as in the previous reaction for the synthesis of **5**. All of the newly synthesized compounds were characterized through spectroscopic techniques (FT-IR, $^{1}$H NMR, $^{13}$C NMR and mass spectrometry) along with their elemental analyses and were found in accordance with the calculated values [Table 2].

### 2.2. Stereochemistry and X-ray crystallography

To explore the stereochemistry (*E* or *Z* configuration) of C=N bond of the compounds under investigation **6a**–**n** and **9a**–**n**, a single crystal of *N*′-[1-(4-chlorophenyl)ethylidene]-4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide **6b** (as a representative compound) was grown by dissolving the compound in 90% ethanol and was studied by single crystal X-ray crystallography. It was found that C=N bond exhibits *E* configuration and the compound **6b** crystallizes in an orthorhombic space group *P*ccn with $Z = 8$. The heterocyclic thiazine ring (Fig. 2) adopts half-chair conformation wherein S1 and N1 are displaced by 0.467 (5) Å and 0.255 (5) Å respectively from the plane defined by the remaining atoms of the ring. Rest of the molecule is more or less planar. Supplementary crystallographic data have been deposited with the CCDC number 785553. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. Details of crystal data and structure refinement have been provided in Table 3.

### 2.3. Biological activities

#### 2.3.1. Anti-bacterial activities

All the newly synthesized compounds (dissolved in dimethylformamide) were subjected to anti-bacterial screening against four gram positive bacteria (*Bacillus cereus*, *Bacillus subtilis*, *Bacillus thuringiensis* and *Staphylococcus aureus*) and three gram negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi*) by determining their minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MBCs) using the agar dilution technique [24] and streptomycin as reference drug. The choice of streptomycin as a clinical standard was based on the fact that at low concentrations, it only inhibits growth of the bacteria through induction of prokaryotic ribosomes to misread mRNA [25]. Streptomycin also prevents initiation of protein synthesis and leads to death of microbial cells. Also, in humans, they have structurally different ribosomes from bacteria, thereby allowing the selectivity of this antibiotic for bacteria.

**Table 1**
Synthesis of 4-hydroxy-2*H*/2-methyl-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides and various 1-phenylethanones under normal and microwave conditions.

| Entry | Reactant | Product | Conventional | | Microwave | |
|---|---|---|---|---|---|---|
| | | | Reaction conditions | Yield (%)[a] | Reaction conditions | Yield (%)[a] |
| 1 | 4 | **6a** | Reflux; 6 h | 78 | 200 W; 5 min | 92 |
| 2 | 4 | **6b** | Reflux; 6 h | 75 | 200 W; 8 min | 90 |
| 3 | 4 | **6c** | Reflux; 7 h | 80 | 200 W; 8 min | 93 |
| 4 | 4 | **6d** | Reflux; 6.5 h | 77 | 200 W; 7 min | 90 |
| 5 | 4 | **6e** | Reflux; 7 h | 80 | 200 W; 7 min | 92 |
| 6 | 4 | **6f** | Reflux; 7 h | 82 | 200 W; 8 min | 92 |
| 7 | 4 | **6g** | Reflux; 6 h | 80 | 200 W; 8 min | 91 |
| 8 | 4 | **6h** | Reflux; 6 h | 75 | 200 W; 7 min | 90 |
| 9 | 4 | **6i** | Reflux; 6 h | 75 | 200 W; 9 min | 89 |
| 10 | 4 | **6J** | Reflux; 6 h | 80 | 200 W; 7 min | 94 |
| 11 | 4 | **6k** | Reflux; 6.5 h | 77 | 200 W; 8 min | 93 |
| 12 | 4 | **6l** | Reflux; 7 h | 82 | 200 W; 7 min | 91 |
| 13 | 4 | **6m** | Reflux; 7 h | 80 | 200 W; 5 min | 94 |
| 14 | 4 | **6n** | Reflux; 7 h | 82 | 200 W; 7 min | 92 |
| 15 | 6 | **9a** | Reflux; 8 h | 78 | 200 W; 10 min | 90 |
| 16 | 6 | **9b** | Reflux; 7.5 h | 82 | 200 W; 7 min | 94 |
| 17 | 6 | **9c** | Reflux; 8 h | 70 | 200 W; 10 min | 92 |
| 18 | 6 | **9d** | Reflux; 8 h | 77 | 200 W; 6 min | 89 |
| 19 | 6 | **9e** | Reflux; 8 h | 79 | 200 W; 10 min | 93 |
| 20 | 6 | **9f** | Reflux; 7.5 h | 84 | 200 W; 8 min | 95 |
| 21 | 6 | **9g** | Reflux; 8 h | 75 | 200 W; 10 min | 92 |
| 22 | 6 | **9h** | Reflux; 8 h | 80 | 200 W; 8 min | 90 |
| 23 | 6 | **9i** | Reflux; 8 h | 80 | 200 W; 8 min | 90 |
| 24 | 6 | **9J** | Reflux; 6 h | 75 | 200 W; 10 min | 87 |
| 25 | 6 | **9k** | Reflux; 6 h | 80 | 200 W; 10 min | 91 |
| 26 | 6 | **9l** | Reflux; 7 h | 78 | 200 W; 8 min | 86 |
| 27 | 6 | **9m** | Reflux; 7 h | 77 | 200 W; 10 min | 87 |
| 28 | 6 | **9n** | Reflux; 7 h | 76 | 200 W; 9 min | 89 |

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

The MICs of the active compounds against a panel of selected Gram positive and Gram negative bacteria are presented in Table 4. Results of anti-bacterial activity of compounds show that the minimum inhibitory concentration (MIC) of compounds varies in the range of 4.0–33.4 $\times$ $10^{-2}$ μmol/ml, while minimum bactericidal concentration (MBC) varies between 7.3–67.2 $\times$ $10^{-2}$ μmol/ml. It was found that the title compounds were found more active against gram positive bacteria than gram negative bacteria. The most sensitive bacterial species on these compounds is *B. cereus*, while *S. typhi* is the most resistant species. An insight to the structure–activity relationship gives an idea that activity generally increases with the incorporation of hydroxyl and methoxy groups at the benzene ring of the 4-hydroxy-*N*′-[1-phenylethylidene]-2*H*/2-methyl, 1,2-benzothiazine-3-carbohydrazide 1,1-dioxides. Hydroxy derivatives (**6i**–**k** and **9i**–**k**) were found the most active with MIC values comparable to the standard and this may be attributed to the presence of lone pairs on oxygen atoms of hydroxyl and methoxy groups perhaps by blocking the active sites through hydrogen bonding. Compounds possessing amino (**6n** and **9n**) and fluoro (**6h** and **9h**) groups were found moderately active against the gram positive strains. It was found that incorporation of second chlorine atom to moderately active monosubstituted chloro compounds (**6a**, **6b** and **9a**, **9b**) decreased the activity making the compounds (**6c**, **6d** and **9c**, **9d**) weakly active. Further, it is observed that bromo substituted compounds (**6e**, **6f** and **9e**, **9f**) were found inactive probably due to steric hindrance, while the rest of compounds were found weakly active. Groups substituted on the benzene ring may be arranged in the following order with respect to their anti-bacterial activities: OH > $OCH_3$ > $NH_2$ > F > Br > Cl > I while activities for the same substituents follow the order: ortho > meta > para. It is found that higher the Clog*P* values of the compounds under investigation, greater are the anti-bacterial activities [Table 4]. Series of more active compounds, with *N*-methyl group on thiazine ring, (**9a**–**n**) have higher Clog*P* values than the un-substituted ones (**6a**–**n**) supporting the fact that increase in activity goes in parallel with their lipophilic character [26].

#### 2.3.2. Anti-fungal activities

All the newly synthesized compounds **6a**–**n** and **9a**–**n** (dissolved in dimethylsulfoxide) along with (4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide **4** and 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide **8**), bifonazole (reference drug) and control **0** were subjected to *in vitro* anti-fungal screening by determining the minimum inhibitory concentration (MICs) and minimum fungicidal concentrations (MFCs)through microdilution technique [27] against a panel of six strains of fungi i.e., *Aspergillus niger*, *Aspergillus flavus*, *Aspergillus fumigates*, *Trichoderma viride*, *Trichoderma reesei* and *Drechslera australiensis*.

Results of anti-fungal activity of compounds show that the minimum inhibitory concentration (MIC) of compounds varies in the range of 59.0–131 $\times$ $10^{-2}$ μmol/ml, while minimum fungicidal concentration (MFC) varies between 117.2–261 $\times$ $10^{-2}$ μmol/ml. Compounds **6c**, **6d**, **9c** and **9d** showed the best activity against all the

**Table 2**
Reaction parameters and CHN analysis of 4-hydroxy-*N*′-[(1*E*)-1-phenylethylidene]-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides **6a**–**n** and 4-hydroxy-2-methyl-*N*′-[(1*E*)-1-phenylethylidene]-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides **9a**–**n**.

| Compd | $R_1$ | $R_2$ | $R_3$ | Mol. formula | Analysis % | | |
|---|---|---|---|---|---|---|---|
| | | | | | Calculated (found) | | |
| | | | | | C | H | N |
| **6a** | Cl | H | H | $C_{17}H_{14}ClN_3O_4S$ | 52.11 (52.08) | 3.60 (3.62) | 10.72 (10.73) |
| **6b** | H | H | Cl | $C_{17}H_{14}ClN_3O_4S$ | 52.11 (52.09) | 3.60 (3.61) | 10.72 (10.73) |
| **6c** | Cl | H | Cl | $C_{17}H_{13}Cl_2N_3O_4S$ | 47.90 (47.88) | 3.07 (3.08) | 9.86 (9.87) |
| **6d** | H | Cl | Cl | $C_{17}H_{13}Cl_2N_3O_4S$ | 47.90 (47.87) | 3.07 (3.09) | 9.86 (9.87) |
| **6e** | Br | H | H | $C_{17}H_{14}BrN_3O_4S$ | 46.80 (46.82) | 3.23 (3.22) | 9.63 (9.62) |
| **6f** | H | H | Br | $C_{17}H_{14}BrN_3O_4S$ | 46.80 (46.77) | 3.23 (3.25) | 9.63 (9.64) |
| **6g** | H | H | I | $C_{17}H_{14}IN_3O_4S$ | 42.25 (42.27) | 2.92 (2.94) | 8.69 (8.69) |
| **6h** | F | H | F | $C_{17}H_{13}F_2N_3O_4S$ | 51.91 (51.89) | 3.33 (3.34) | 10.68 (10.69) |
| **6i** | OH | H | H | $C_{17}H_{15}N_3O_5S$ | 54.68 (54.70) | 4.05 (4.04) | 11.25 (11.24) |
| **6J** | H | OH | H | $C_{17}H_{15}N_3O_5S$ | 54.68 (54.66) | 4.05 (4.05) | 11.25 (11.27) |
| **6k** | H | H | OH | $C_{17}H_{15}N_3O_5S$ | 54.68 (54.71) | 4.05 (4.03) | 11.25 (11.24) |
| **6l** | H | $OCH_3$ | H | $C_{18}H_{17}N_3O_5S$ | 55.80 (55.76) | 4.42 (4.43) | 10.85 (10.87) |
| **6m** | H | H | $OCH_3$ | $C_{18}H_{17}N_3O_5S$ | 55.80 (55.77) | 4.42 (4.44) | 10.85 (10.86) |
| **6n** | H | H | $NH_2$ | $C_{17}H_{16}N_4O_4S$ | 54.83 (54.86) | 4.33 (4.31) | 15.04 (15.03) |
| **9a** | Cl | H | H | $C_{18}H_{16}ClN_3O_4S$ | 53.27 (53.31) | 3.97 (3.95) | 10.35 (10.33) |
| **9b** | H | H | Cl | $C_{18}H_{16}ClN_3O_4S$ | 53.27 (53.29) | 3.97 (3.95) | 10.35 (10.35) |
| **9c** | Cl | H | Cl | $C_{18}H_{15}Cl_2N_3O_4S$ | 49.10 (49.07) | 3.43 (3.45) | 9.54 (9.55) |
| **9d** | H | Cl | Cl | $C_{18}H_{15}Cl_2N_3O_4S$ | 49.10 (49.08) | 3.43 (3.45) | 9.54 (9.54) |
| **9e** | Br | H | H | $C_{18}H_{16}BrN_3O_4S$ | 48.01 (47.97) | 3.58 (3.60) | 9.33 (9.35) |
| **9f** | H | H | Br | $C_{18}H_{16}BrN_3O_4S$ | 48.01 (48.03) | 3.58 (3.58) | 9.33 (9.35) |
| **9g** | H | H | I | $C_{18}H_{16}IN_3O_4S$ | 43.47 (43.43) | 3.24 (3.25) | 8.45 (8.48) |
| **9h** | F | H | F | $C_{18}H_{15}F_2N_3O_4S$ | 53.07 (53.08) | 3.71 (3.73) | 10.31 (10.28) |
| **9i** | OH | H | H | $C_{18}H_{17}N_3O_5S$ | 55.80 (55.79) | 4.40 (4.43) | 10.85 (10.83) |
| **9J** | H | OH | H | $C_{18}H_{17}N_3O_5S$ | 55.80 (55.77) | 4.40 (4.42) | 10.85 (10.86) |
| **9k** | H | H | OH | $C_{18}H_{17}N_3O_5S$ | 55.80 (55.83) | 4.40 (4.38) | 10.85 (10.84) |
| **9l** | H | $OCH_3$ | H | $C_{19}H_{19}N_3O_5S$ | 56.85 (56.84) | 4.77 (4.75) | 10.47 (10.50) |
| **9m** | H | H | $OCH_3$ | $C_{19}H_{19}N_3O_5S$ | 56.85 (56.86) | 4.77 (4.76) | 10.47 (10.47) |
| **9n** | H | H | $NH_2$ | $C_{18}H_{18}N_4O_4S$ | 55.95 (55.93) | 4.70 (4.74) | 14.50 (14.48) |

fungi, with **9d** exhibiting the highest anti-fungal potential (MIC 59.0 × $10^{-2}$ μmol/ml and MFC 158.1 × $10^{-2}$ μmol/ml, while compounds **6i**, **6j**, **6k**, **9i**, **9j** and **9k** were found almost inactive (with MIC >100 × $10^{-2}$ μmol/ml). A closer look into the anti-fungal activities of the compounds (Table 5) indicates that, in general, the compounds bearing methyl group at 2-position of benzothiazine nucleus (**9a**–**n**) are more active than with those having no substituent (**6a**–**n**) and this is of same pattern previously reported activities of 1,2-benzothiazine 1,1-dioxide based oxicams [17]. Results showed moderate to significant activity of almost all the compounds against *T. viride*, *T. reesei* and *D. australiensis* while these were found less active against *Aspergillus* species except compounds bearing hydroxyl and methoxy groups on benzene ring (**6i**–**m** and **9i**–**m**), which were either found inactive or with MIC greater than 100. The majority of compounds showed the best activity against *T. viride* while *A. niger* is the most resistant species. An insight to the structure–activity relationship gives an idea that activity generally increases with number and strength of electron withdrawing groups. Compounds bearing two chloro groups (**6c**, **6d** and **9c**, **9d**) were found highly active with MIC values even lower than the standard, while the compounds (**6a**, **6b**, **6e**–**h** and **9a**, **9b**, **9e**–**h**) were found significantly active with MIC values comparable to the standard drug; Rest of the compounds were found moderately active.

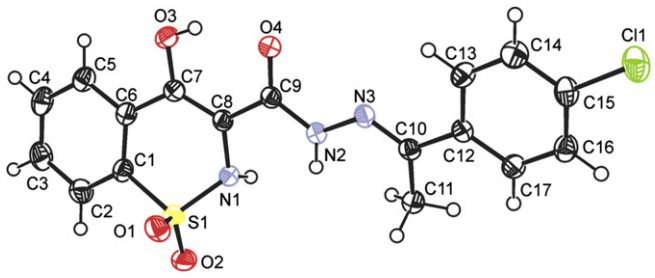



**Fig. 2.** ORTEP3 diagram of compound **6b** with the numbering scheme. Displacement ellipsoids are drawn at the 50% probability level; H atoms are represented by circles of arbitrary radii.

## 3. Conclusion

Prompted by the well established anti-bacterial and anti-fungal properties of carbohydrazides, series of novel 4-hydroxy-*N*′-[1-phenylethylidene]-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides (**6a**–**n**) and 4-hydroxy-2-methyl-*N*′-[1-phenylethylidene]-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides (**9a**–**n**) are synthesized emphasizing, in particular, on the strategy of combining two chemically different but pharmacologically compatible molecules (1,2-benzothiazine 1,1-dioxide nucleus and 1-phenylethylidene carbohydrazides) in one frame. The title compounds were synthesized under the influence of microwaves and assayed *in vitro* for the evaluation of their anti-microbial activity against Gram positive, Gram negative bacteria and fungi. It revealed that the compounds obtained by the synergism were found biologically active (anti-fungal, anti-bacterial) and could be useful as a template for further development through modification or derivatization to design more potent biologically active compounds. Facilitation of the syntheses with microwaves was found quite useful to obtain higher yields and purity than those which were carried out by simple thermal condensation in methanol and the duration of reactions was reduced considerably (from 6 to 8 h to 5–10 min).

## 4. Experimental

### 4.1. Chemistry

All the chemicals were purchased from E. Merck, BDH or Fluka and used without purification. However, solvents were purified

**Table 3**
Crystallographic parameters for compound **6a**.

| Structural formula | $C_{17}H_{14}ClN_3O_4S{\cdot}H_2O{\cdot}CH_3OH$ | Cell volume | 3851. 2 (3) Å$^3$ |
|---|---|---|---|
| Formula weight | 441.88 | Z | 8 |
| Crystal system | Orthorhombic | Absorption correction | Multi-scan method |
| Space group | *P*nnc | Calculated density | 1.524 Mg/m$^3$ |
| *T* (K) | 173 (2) K | Crystal size | 0.12 × 0.10 × 0.06 mm$^3$ |
| *a* (Å); α | 15.7936 (6); 90° | Reflections collected | 7472 |
| *b* (Å); α | 30.5165 (13); 90° | Independent reflections | 4283 [*R*(int) = 0.0264] |
| *c* (Å); γ | 7.9907 (3); 90° | Goodness-of-fit on *F*2 | 1.094 |
| θ min; θ max | 2.90°; 27.47° | *F*(000) | 1840 |

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. 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, 300W, DU-4) made by Nickel Electro Ltd, Weston-S-Mare Somerset, England. Microwave assisted reactions were carried out in a household MW oven (Orient–NN–781JF) equipped with inverter technology (generating fixed frequency throughout the required time) for realistic control of the microwaves operating at multiples of 100 W up to 1000 W generating 2450 MHz frequency. The apparatus was modified for laboratory applications, equipped with magnetic stirrer and an external reflux condenser. X-ray crystallography was carried out on Bruker Nonius Kappa CCD diffractometer with graphite monochromated Mo-Kα radiation and the data were corrected for Lorentz and polarization effects and for absorption using multi-scan method.

#### 4.1.1. 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 allowed to react in microwave oven at 200 W for a period of 3 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; 96.2%); m.p. 116–117 °C (lit. m.p. 115–116 °C) [18]; 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, ArH).

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

Compound **3** was synthesized according to literature procedure [21]. 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 reaction. The contents were then 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

**Table 4**
Anti-bacterial activity of compounds **6a**–**n** and **9a**–**n** tested by Micro dilution method (MIC and MFC μmol × 10$^{-2}$).

| Entry | Compound | Susceptible microorganism | | | | | | | ClogP |
|---|---|---|---|---|---|---|---|---|---|
| | | *B. cereus* | *B. subtilis* | *B. thuringiensis* | *S. aureus* | *E. coli* | *P. aeruginosa* | *S. typhi* | |
| | | MIC/MBC | MIC/MBC | MIC/MBC | MIC/MBC | MIC/MBC | MIC/MBC | MIC/MBC | |
| 1 | **6a** | 11.5/23.1 | 11.4/22.6 | 12.1/24.1 | 31.3/59.2 | 32.5/63.6 | – | – | 1.97 |
| 2 | **6b** | 11.7/23.1 | 12.5/24.8 | 12.3/24.3 | 30.8/58.7 | 31.2/62.4 | 32.4/64.8 | – | 2.55 |
| 3 | **6c** | – | – | – | – | – | – | – | 2.74 |
| 4 | **6d** | – | – | – | – | – | – | – | 3.23 |
| 5 | **6e** | – | – | – | – | – | – | – | 2.14 |
| 6 | **6f** | – | – | – | – | – | – | – | 2.74 |
| 7 | **6g** | 9.1/18.0 | 9.5/18.6 | 9.4/18.8 | 28.2/56.0 | 29.5/58.9 | 30.9/61.8 | 33.4/57.3 | 3.00 |
| 8 | **6h** | 7.8/14.9 | 8.0/14.8 | 8.2/16.4 | 28.1/55.9 | 29.2/58.4 | 30.6/61.6 | 33.2/71.5 | 1.68 |
| 9 | **6i** | 4.2/7.8 | 4.4/9.3 | 4.1/7.6 | 17.8/33.2 | 19.9/42.1 | 20.6/39.5 | 22.7/45.3 | 2.06 |
| 10 | **6j** | 4.5/9.4 | 4.6/7.3 | 4.4/8.1 | 18.4/37.0 | 19.7/39.4 | 21.2/39.7 | 23.5/46.3 | 1.45 |
| 11 | **6k** | 4.8/8.9 | 4.9/9.4 | 5.0/8.7 | 19.0/38.6 | 21.3/42.6 | 22.6/43.2 | 25.2/50.3 | 1.43 |
| 12 | **6l** | 7.2/14.2 | 7.5/15.0 | 7.7/15.9 | 24.5/42.9 | 25.6/46.5 | 26.7/52.1 | 29.3/63.1 | 1.52 |
| 13 | **6m** | 7.8/15.5 | 7.5/14.7 | 7.8/15.3 | 26.7/53.4 | 27.8/54.5 | 29.3/58.5 | 32.7/60.2 | 1.96 |
| 14 | **6n** | 6.2/12.6 | 6.0/11.8 | 6.1/12.2 | 20.5/41.1 | 22.9/46.5 | 24.5/49.8 | 27.7/57.5 | 1.04 |
| 15 | **9a** | 10.8/19.1 | 11.0/20.2 | 12.0/23.6 | 30.7/56.1 | 31.7/58.3 | 32.6/56.8 | – | 3.46 |
| 16 | **9b** | 11.0/20.2 | 11.6/22.7 | 12.3/24.3 | 30.9/57.4 | 31.0/48.4 | 32.3/64.3 | – | 4.05 |
| 17 | **9c** | – | – | – | – | – | – | – | 4.24 |
| 18 | **9d** | – | – | – | – | – | – | – | 4.72 |
| 19 | **9e** | – | – | – | – | – | – | – | 3.64 |
| 20 | **9f** | – | – | – | – | – | – | – | 4.23 |
| 21 | **9g** | 9.0/18.0 | 9.3/18.2 | 9.2/17.8 | 28.0/48.0 | 29.3/50.9 | 30.5/56.0 | 33.2/56.2 | 4.49 |
| 22 | **9h** | 7.5/14.4 | 7.8/15.2 | 8.0/15.2 | 27.6/47.6 | 28.9/58.7 | 30.5/57.3 | 33.1/64.3 | 3.17 |
| 23 | **9i** | 4.0/7.7 | 4.2/8.4 | 4.0/7.8 | 17.7/33.2 | 19.6/39.0 | 20.2/38.3 | 22.3/44.3 | 3.55 |
| 24 | **9j** | 4.2/8.2 | 4.5/8.9 | 4.3/8.6 | 18.2/36.4 | 19.3/38.6 | 21.0/41.2 | 23.1/39.6 | 2.94 |
| 25 | **9k** | 4.6/9.1 | 4.8/9.4 | 5.0/9.9 | 18.9/32.4 | 21.0/42.9 | 22.1/44.8 | 25.1/58.2 | 2.92 |
| 26 | **9l** | 7.0/14.7 | 7.7/13.1 | 7.8/14.1 | 24.1/40.6 | 25.6/54.7 | 26.8/58.4 | 29.4/61.8 | 3.02 |
| 27 | **9m** | 7.9/15.8 | 7.6/15.0 | 7.8/15.1 | 26.3/52.6 | 27.9/49.7 | 29.2/47.6 | 32.4/67.2 | 3.45 |
| 28 | **9n** | 6.2/10.9 | 6.2/12.1 | 6.3/12.6 | 20.4/35.2 | 22.4/39.2 | 24.3/51.9 | 27.5/58.3 | 2.53 |
| 29 | **4** | – | – | – | – | – | – | – | |
| 30 | **8** | – | – | – | – | – | – | – | |
| 31 | **Control** | 0 | 0 | 0 | 0 | 0 | 0 | 0 | |
| 32 | **Streptomycin** | 4.3/8.6 | 4.2/8.3 | 4.4/8.8 | 16.5/33.0 | 16.5/33.0 | 16.5/33.0 | 16.5/33.0 | |

**Table 5**
Anti-fungal activity of compounds **6a**–**n** and **9a**–**n** tested by microdilution Method (MIC and MBC in μmol × $10^{-2}$).

| Entry | Compound | Susceptible microorganism | | | | | |
|---|---|---|---|---|---|---|---|
| | | *Aspergillus niger* | *Aspergillus flavus* | *Aspergillus fumigatus* | *Trichoderma viride* | *Trichoderma reesei* | *Drechslera australiensis* |
| | | MIC/MFC | MIC/MFC | MIC/MFC | MIC/MFC | MIC/MFC | MIC/MFC |
| 1 | **6a** | 89.6/179.1 | 87.3/164.6 | 76.2/150.4 | 66.8/123.9 | 61.4/122.9 | 63.8/125.1 |
| 2 | **6b** | 82.9/145.4 | 81.9/163.0 | 72.7/140.1 | 67.3/114.7 | 62.5/124.8 | 64.4/130.5 |
| 3 | **6c** | 74.6/149.0 | 71.8/143.5 | 67.4/142.5 | 62.9/125.7 | 59.4/118.6 | 62.0/123.9 |
| 4 | **6d** | 75.2/150.2 | 75.2/150.3 | 68.1/136.2 | 61.3/118.7 | 59.2/108.0 | 61.8/123.4 |
| 5 | **6e** | 93.2/186.8 | 90.0/177.7 | 83.8/157.3 | 75.6/142.4 | 74.8/146.6 | 76.3/158.4 |
| 6 | **6f** | 96.4/188.5 | 93.7/173.2 | 85.7/191.0 | 74.4/188.2 | 74.9/129.7 | 77.5/143.9 |
| 7 | **6g** | 91.5/166.1 | 89.9/179.8 | 82.0/159.2 | 71.3/139.7 | 70.3/133.5 | 74.0/145.8 |
| 8 | **6h** | 76.6/160.3 | 76.4/168.7 | 69.8/118.2 | 72.0/139.6 | 69.0/138.0 | 72.3/145.7 |
| 9 | **6i** | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 |
| 10 | **6j** | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 |
| 11 | **6k** | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 |
| 12 | **6l** | 90.1/176.3 | 92.7/198.4 | 85.9/181.2 | 80.7/149.9 | 80.0/160.7 | 82.0/162.7 |
| 13 | **6m** | 87.3/179.5 | 86.2/169.3 | 77.7/153.6 | 80.5/158.8 | 79.9/159.8 | 81.1/159.6 |
| 14 | **6n** | 83.8/177.5 | 82.9/175.9 | 74.0/150.1 | 71.3/142.8 | 70.3/138.4 | 70.0/129.5 |
| 15 | **9a** | 88.6/167.9 | 87.1/170.2 | 76.1/144.6 | 66.5/133.1 | 61.1/119.2 | 63.6/126.5 |
| 16 | **9b** | 82.0/166.4 | 81.7/162.3 | 72.6/143.6 | 67.2/134.4 | 62.2/124.4 | 64.3/128.6 |
| 17 | **9c** | 74.2/148.3 | 71.6/143.1 | 67.3/134.7 | 62.7/125.0 | 59.1/118.1 | 61.5/122.7 |
| 18 | **9d** | 75.0/149.5 | 75.0/150.0 | 68.1/136.3 | 61.2/122.5 | 59.0/158.1 | 61.5/122.6 |
| 19 | **9e** | 93.1/186.0 | 89.4/168.5 | 83.6/163.6 | 75.4/149.9 | 74.5/151.2 | 76.2/151.7 |
| 20 | **9f** | 96.0/>200 | 93.4/189.8 | 85.5/177.0 | 74.3/139.4 | 74.6/142.5 | 77.3/148.4 |
| 21 | **9g** | 91.4/198.4 | 89.8/190.7 | 81.9/159.8 | 71.1/139.2 | 70.1/122.7 | 74.0/150.6 |
| 22 | **9h** | 76.5/143.6 | 76.3/149.4 | 69.6/140.1 | 72.1/143.0 | 68.4/130.2 | 72.1/144.2 |
| 23 | **9i** | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 |
| 24 | **9j** | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 |
| 25 | **9k** | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 |
| 26 | **9l** | 90.1/190.0 | 92.6/188.9 | 85.7/168.2 | 80.5/160.4 | 79.6/159.2 | 81.7/154.8 |
| 27 | **9m** | 87.2/180.7 | 86.1/170.0 | 77.6/149.5 | 79.2/158.4 | 78.9/157.6 | 80.0/159.9 |
| 28 | **9n** | 83.7/167.0 | 82.9/166.3 | 73.6/151.6 | 71.1/142.0 | 68.0/135.8 | 69.8/133.7 |
| 29 | **4** | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 |
| 30 | **8** | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 | >100/>200 |
| 31 | **0** | 0 | 0 | 0 | 0 | 0 | 0 |
| 32 | **Bifonazole** | 48.0/64.0 | 48.0/64.0 | 48.0/64.0 | 64.0/80.0 | 60.2/78.0 | 57.5/75.0 |

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): 3182, 1668, 1340, 1182 $cm^{-1}$; $^1H$ NMR ($CDCl_3$) $\delta$: 3.84 (s, 3H, OC*H*$_3$), 7.77 (dd, $J$ = 5.6, 3.2 Hz, 2H, Ar*H*), 7.83 (dd, $J$ = 5.6, 3.2 Hz, 2H, Ar*H*), 12.33 (s, 1H, O*H*$_{enolic}$), 8.33 (br s, 1 H, N*H*); MS $m/z$ (%): 255 [$M^+$].

#### 4.1.3. 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 (30 ml) 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 ($CDCl_3$) $\delta$: 2.49 (br s, 2H, N*H*$_2$), 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, O*H*$_{enolic}$); HRMS/EI: calcd for $C_9H_9N_3O_4S$ 255.2505, found 255.2511.

#### 4.1.4. 1,4-Dihydropyrazolo[4,3-c][1,2]benzothiazin-3-ol 5,5-dioxide (**5**)

A mixture of methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**3**) (2.55 g; 10.0 mmol), hydrazine hydrate (2.50 g; 50.0 mmol), acetic acid (3.0 ml) and methyl alcohol (50 ml) was stirred and heated in microwave oven for a period of 4 min. After cooling to room temperature, the contents were poured over crushed ice and pH was maintained at 1 with conc. hydrochloric acid. Precipitates obtained were filtered, washed with water and dried (1.82 g; 77%); Light yellow solid; m.p. 230 °C. IR (KBr) $cm^{-1}$: 3355, 1599, 1322, 1142. $^1H$ NMR ($CDCl_3$) (400 MHz) $\delta$: 7.55 (1H, t, $J$ = 7.4 Hz, Ar*H*), 7.65 (1H, t, $J$ = 7.2 Hz, Ar*H*), 7.91 (2H, t, $J$ = 7.8 Hz, Ar*H*), 8.16 (1H, s, N*H*), 10.02 (1H, br s, N*H*), 11.16 (1H, s, O*H*), $^{13}C$ NMR: 121.8, 127.3, 127.6, 128.8, 132.3, 133.5, 134.5, 137.7, 151.9. MS $m/z$: 237 ($M^+$).

### 4.2. General procedure for the synthesis of 4-hydroxy-N′-[1-phenylethylidene]-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides (**6a**–**n**)

#### 4.2.1. Using conventional procedure

A mixture of 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**4**) (2.0 mmol), 1-phenylethanone (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.

#### 4.2.2. Using microwaves

A mixture of 4-hydroxy-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**4**) (2.0 mmol), 1-phenylethanone (2.0 mmol), ortho phosphoric acid (2 drops) and methanol (50 ml) was heated at 200 W 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.

#### 4.2.3. N′-[1-(2-Chlorophenyl)ethylidene]-4-hydroxy-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6a**)

Light yellow powder; m.p. 146–147 °C. IR (KBr) $cm^{-1}$: 3652, 3550, 2364, 1643, 1376, 1181, 1061. $^1H$ NMR (DMSO-$d_6$) $\delta$: 2.37 (3H, s, C*H*$_3$), 7.52 (2H, d, $J$ = 8.7 Hz, Ar*H*), 7.85–7.90 (5H, m, Ar*H*), 8.03 (1H,

dd, $J = 6.4$, 1.2 Hz, Ar*H*), 8.57 (1H, br s, N*H*), 9.79 (1H, br s, CON*H*), 13.73 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.2, 106.4, 123.5, 126.7, 128.8, 128.9, 130.1, 130.3, 130.6, 131.8, 132.4, 132.5, 137.2, 137.3, 155.1, 168.7, 168.8. MS *m*/*z*: 391 [M$^+$], 393 [M$^+$+2].

#### 4.2.4. N′-[1-(4-Chlorophenyl)ethylidene]-4-hydroxy-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6b**)

Off white crystalline powder; m.p. 140–141 °C. IR (KBr) cm$^{-1}$: 3674, 3566, 2363, 1639, 1399, 1172, 1094. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.35 (3H, s, C$H_3$), 7.62 (2H, d, $J = 8.7$ Hz, Ar*H*), 7.83–7.89 (5H, m, Ar*H*), 8.06 (1H, dd, $J = 6.4$, 1.2 Hz, Ar*H*), 8.64 (1H, br s, N*H*), 9.86 (1H, br s, CON*H*), 13.77 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.6, 106.3, 123.5, 126.8, 128.2, 128.3, 128.6, 128.9, 130.0, 131.7, 132.4, 135.6, 136.5, 137.1, 147.7, 155.0, 168.7. MS *m*/*z* 391 [M$^+$], 393 [M$^+$+2].

#### 4.2.5. N′-[1-(2,4-Dichlorophenyl)ethylidene]-4-hydroxy-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6c**)

Brownish gray powder; m.p. 216–217 °C. IR (KBr) cm$^{-1}$: 3676, 3597, 2364, 1642, 1378, 1171, 1059. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.28 (3H, s, C$H_3$), 6.85 (1H, m, Ar*H*), 7.24 (2H, m, Ar*H*), 7.59 (2H, t, $J = 7.8$ Hz, Ar*H*), 7.76 (2H, t, $J = 7.8$ Hz, Ar*H*), 8.58 (1H, br s, N*H*), 9.99 (1H, br s, CON*H*), 13.73 (1H, br s, O*H*). $^{13}$C NMR: 16.3, 106.4, 123.4, 126.6, 126.7, 128.4, 128.8, 129.0, 131.8, 132.3, 133.4, 134.7, 135.3, 137.1, 155.1, 168.6, 168.8; MS *m*/*z* 425 [M$^+$], 427 [M$^+$+2], 429 [M$^+$+4].

#### 4.2.6. N′-[1-(3,4-Dichlorophenyl)ethylidene]-4-hydroxy-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6d**)

Light yellow powder; m.p. 254 °C. IR (KBr) cm$^{-1}$: 3674, 3560, 2363, 1619, 1379, 1176, 1066. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.29 (3H, s, C$H_3$), 6.88 (1H, m, Ar*H*), 7.31 (2H, m, Ar*H*), 7.61 (2H, t, $J = 7.8$ Hz, Ar*H*), 7.77 (2H, t, $J = 7.8$ Hz, Ar*H*), 8.55 (1H, br s, N*H*), 9.89 (1H, br s, CON*H*), 13.77 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.7, 106.3, 123.6, 126.4, 126.6, 129.0, 130.3, 130.5, 131.7, 132.4, 133.5, 133.6, 135.6, 137.2, 147.8, 155.2, 168.8; MS *m*/*z*: 425 [M$^+$], 427 [M$^+$+2], 429 [M$^+$+4].

#### 4.2.7. N′-[1-(2-Bromophenyl)ethylidene]-4-hydroxy-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6e**)

Pale yellow powder; m.p. 262–264 °C. IR (KBr) cm$^{-1}$: 3674, 3566, 2363, 1639, 1399, 1172, 1078. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.34 (3H, s, C$H_3$), 7.55 (2H, d, $J = 8.7$ Hz, Ar*H*), 7.88–7.90 (5H, m, Ar*H*), 8.06 (1H, dd, $J = 6.4$, 1.2 Hz, Ar*H*), 8.67 (1H, br s, N*H*), 9.89 (1H, br s, CON*H*), 13.78 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.6, 106.2, 122.1, 123.5, 126.7, 127.7, 128.8, 130.1, 131.8, 132.3, 132.8, 134.6, 135.5, 137.2, 155.1, 168.6, 168.7; MS *m*/*z*: 435 [M$^+$], 437 [M$^+$+2].

#### 4.2.8. N′-[1-(4-Bromophenyl)ethylidene]-4-hydroxy-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6f**)

Light yellow powder; m.p. 272–274 °C. IR (KBr) cm$^{-1}$: 3675, 3539, 2364, 1632, 1355, 1182, 1069. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.35 (3H, s, C$H_3$), 7.53 (2H, d, $J = 8.7$ Hz, Ar*H*), 7.83–7.89 (5H, m, Ar*H*), 8.04 (1H, d, $J = 6.4$, 1.2 Hz, Ar*H*), 8.70 (1H, br s, N*H*), 9.87 (1H, br s, CON*H*), 13.74 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.6, 106.5, 123.7, 125.5, 126.7, 128.6, 128.7, 130.0, 131.6, 131.8, 131.9, 132.4, 136.6, 137.3, 147.7, 155.0, 168.8; MS *m*/*z*: 435 [M$^+$], 437 [M$^+$+2].

#### 4.2.9. 4-Hydroxy-N′-[1-(4-iodophenyl)ethylidene]-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6g**)

Pale yellow powder; m.p. 220 °C. IR (KBr) cm$^{-1}$: 3673, 3570, 2363, 1644, 1389, 1183, 1062. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.34 (3H, s, C$H_3$), 7.65 (2H, d, $J = 8.4$ Hz, Ar*H*), 7.82–7.84 (2H, d, $J = 8.4$ Hz, Ar*H*), 7.86–7.91 (3H, m, Ar*H*),8.07 (1H, dd, $J = 6.4$, 1.2 Hz, Ar*H*), 8.66 (1H, br s, N*H*), 9.80 (1H, br s, CON*H*), 13.72 (1H, br s, O$H_{enolic}$); $^{13}$C NMR: 16.5, 96.5, 106.3, 123.3, 126.5, 128.8, 130.7, 131.0, 131.6, 132.3, 136.2, 137.1, 137.5, 137.6, 147.5, 155.1, 168.6; MS *m*/*z*: 483 [M$^+$], 485 [M$^+$+2].

#### 4.2.10. N′-[1-(2,4-Difluorophenyl)ethylidene]-4-hydroxy-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6h**)

Off white powder; m.p. 140 °C. IR (KBr) cm$^{-1}$: 3670, 3531, 2362, 1616, 1350, 1182, 1068. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.30 (3H, s, C$H_3$), 6.89 (1H, m, Ar*H*), 7.27 (2H, m, Ar*H*), 7.59 (2H, t, $J = 7.8$ Hz, Ar*H*), 7.77 (2H, t, $J = 7.8$ Hz, Ar*H*), 8.58 (1H, br s, N*H*), 9.95 (1H, br s, CON*H*), 13.74 (1H, br s, O$H_{enolic}$); $^{13}$C NMR: 16.6, 106.5, 111.3, 112.7, 113.8, 123.6, 126.7, 128.9, 131.9, 132.4, 132.7, 137.3, 155.3, 161.4, 163.5, 168.7, 168.9; MS *m*/*z*: 393 [M$^+$].

#### 4.2.11. 4-Hydroxy-N′-[1-(2-hydroxyphenyl)ethylidene]-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6i**)

Off white crystals; m.p. 263–265 °C. IR (KBr) cm$^{-1}$: 3674, 3560, 2364, 1648, 1387, 1185, 1074. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.30 (3H, s, C$H_3$), 5.21 (1H, s, O*H*), 6.9–6.95 (2H, m, Ar*H*), 7.3–7.37 (1H, m, Ar*H*), 7.65–7.68 (1H, dd, $J = 6.4$, 1.2 Hz, Ar*H*), 7.80–7.92 (3H, m, Ar*H*), 8.05 (1H, m, Ar*H*), 8.59 (1H, br s, N*H*), 9.98 (1H, br s, CON*H*), 13.68 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 17.0, 106.3, 117.6, 118.8, 121.3, 123.5, 126.6, 128.8, 131.7, 132.0, 132.4, 132.5, 137.2, 155.0, 162.4, 168.6, 168.8; MS *m*/*z*: 373 [M$^+$].

#### 4.2.12. 4-Hydroxy-N′-[1-(3-hydroxyphenyl)ethylidene]-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6j**)

Light yellow powder; m.p. 253–255 °C. IR (KBr) cm$^{-1}$: 3674, 3550, 2363, 1657, 1354, 1190, 1062. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.33 (3H, s, C$H_3$), 5.24 (1H, s, O*H*), 6.85 (1H, m, Ar*H*), 7.24 (2H, m, Ar*H*), 7.59 (2H, t, $J = 7.8$ Hz, Ar*H*), 7.76 (2H, t, $J = 7.8$ Hz, Ar*H*), 8.03 (1H, m, Ar*H*), 8.57 (1H, br s, N*H*), 9.96 (1H, br s, CON*H*), 13.70 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.8, 106.4, 114.9, 118.3, 120.9, 123.6, 126.8, 128.9, 130.3, 131.8, 132.6, 135.4, 137.4, 147.8, 155.2, 158.7, 168.8; MS *m*/*z*: 373 [M$^+$].

#### 4.2.13. 4-Hydroxy-N′-[1-(4-hydroxyphenyl)ethylidene]-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6k**)

Off white powder; m.p. 268–269 °C. IR (KBr) cm$^{-1}$: 3674, 3547, 2363, 1642, 1379, 1180, 1065. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.30 (3H, s, C$H_3$), 5.22 (1H, s, O*H*), 6.91–6.94 (2H, m, Ar*H*), 7.29–7.34 (1H, m, Ar*H*), 7.63–7.66 (1H, dd, $J = 6.4$, 1.2 Hz, Ar*H*), 7.82–7.90 (3H, m, Ar*H*), 8.02 (1H, m, Ar*H*), 8.59 (1H, br s, N*H*), 9.97 (1H, br s, CON*H*), 13.68 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.7, 106.3, 115.9, 116.0, 123.4, 126.7, 128.7, 128.8, 129.0, 130.0, 131.7, 132.4, 137.1, 147.6, 155.0, 160.7, 168.7; MS *m*/*z*: 373 [M$^+$].

#### 4.2.14. 4-Hydroxy-N′-[1-(3-methoxyphenyl)ethylidene]-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6l**)

Off white powder; m.p. 205–207 °C. IR (KBr) cm$^{-1}$: 3674, 3547, 2363, 1642, 1379, 1180, 1068. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.33 (3H, s, C$H_3$), 3.94 (3H, s, OC$H_3$), 6.78 (1H, m, Ar*H*), 7.34 (2H, m, Ar*H*), 7.59 (2H, t, $J = 7.8$ Hz, Ar*H*), 7.76 (2H, t, $J = 7.8$ Hz, Ar*H*), 8.03 (1H, m, Ar*H*), 8.57 (1H, br s, N*H*), 9.96 (1H, br s, CON*H*), 13.73 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.8, 55.9, 106.5, 113.4, 116.7, 120.6, 123.5, 126.8, 128.9, 129.7, 131.7, 132.4, 135.2, 137.1, 147.8, 155.3, 160.8, 168.8; MS *m*/*z*: 387 [M$^+$].

#### 4.2.15. 4-Hydroxy-N′-[1-(4-methoxyphenyl)ethylidene]-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6m**)

Off white powder; m.p. 208–210 °C. IR (KBr) cm$^{-1}$: 3676, 3560, 2364, 1638, 1380, 1170, 1066. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.34 (3H, s, C$H_3$), 3.93 (3H, s, OC$H_3$), 7.62 (2H, d, $J = 8.7$ Hz, Ar*H*), 7.83–7.89 (5H, m, Ar*H*), 8.06 (1H, dd, $J = 6.4$, 1.2 Hz, Ar*H*), 8.56 (1H, br s, N*H*), 9.89 (1H, br s, CON*H*), 13.75 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.8, 60.0, 106.5, 114.4, 114.6, 123.5, 126.8, 128.7, 128.8, 128.9, 129.9, 131.9, 132.5, 137.3, 147.8, 155.2, 162.9, 168.9; MS *m*/*z*: 387 [M$^+$].

#### 4.2.16. N′-[1-(4-Aminophenyl)ethylidene]-4-hydroxy-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**6n**)

Yellow powder; m.p. 239–240 °C. IR (KBr) cm$^{-1}$: 3674, 3560, 2363, 1638, 1380, 1183, 1059. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.35 (3H, s,

$CH_3$), 7.60 (2H, d, $J = 8.7$ Hz, Ar*H*), 7.81–7.88 (5H, m, Ar*H*), 8.01 (1H,d d, $J = 6.4$, 1.2 Hz, Ar*H*), 8.58 (1H, br s, N*H*), 9.93 (1H, br s, CON*H*), 13.76 (1H, br s, $OH_{enolic}$). $^{13}$C NMR: 16.6, 106.3, 114.1, 114.2, 123.4, 125.2, 126.5, 128.8, 130.0, 130.0, 131.6, 132.3, 137.1, 147.6, 150.5, 155.0, 168.5; MS *m*/*z*: 372 [$M^+$].

#### 4.2.17. Methyl 4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carboxylate-1,1-dioxide (**7**)

Compound **7** was synthesized according to literature procedure [21]. A mixture of *Methyl 4-hydroxy-2H-1,2-benzothiazine-3-carboxylate 1,1-dioxide* (**3**) (5.0 g; 19.6 mmol), 20% aqueous sodium hydroxide (8.4 ml) and acetone (50 ml) was stirred at room temperature for 5min. Dimethyl sulfate (5.9 ml) was added to the mixture drop wise over a period of 5 min. The mixture was stirred for further half an hour followed by the careful addition of dilute HCl (20 ml; 5%) to get the white precipitates which were filtered, washed with water and dried. Yield: 91%; m.p. 167 °C. IR (KBr): 3439, 1667, 1319, 1160 $cm^{-1}$. $^1$H NMR ($CDCl_3$), $\delta$: 2.95 (3H, s, $NCH_3$), 3.95 (3H, s, $OCH_3$), 7.75–8.12 (4H, m, Ar*H*), 12.09 (1H, s, OH). MS *m*/*z*: 269 [$M^+$], 254 [$M^+ - CH_3$]. Anal. Calcd for $C_{11}H_{11}NO_5S$: C, 49.06; H, 4.12; N, 5.20; Found: C, 49.11; H, 4.20; N, 4.19.

#### 4.2.18. 4-Hydroxy-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**8**)

A mixture of methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate 1,1-dioxide (**7**) (5.38 g; 20.0 mmol), hydrazine hydrate (1.25 g, 25.0 mmol) and methyl alcohol (50 ml) was stirred and refluxed for a period of 40 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 (4.79 g; 93.2%); m.p. 222 °C; IR (KBr) 3467; 3364; 2982; 1615; 1331; 1171 $cm^{-1}$; $^1$H NMR $\delta$ 2.73 (3H, s, $NCH_3$), 4.69 (2H, br s, $NH_2$), 7.81–7.86 (3H, m, Ar*H*), 7.95 (1H, d, $J = 7.6$ Hz, Ar*H*), 10.04 (1H, br s, N*H*), 14.23 (s, 1H, $OH_{enolic}$); MS *m*/*z* 255 [$M^+$].

### 4.3. General procedure for the synthesis of 4-hydroxy-N′-[1-phenylethylidene]-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxides **9a**–**n**

A mixture of 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**8**) (2.0 mmol), 1-phenylethanone (2.0 mmol), ortho phosphoric acid (2 drops) and methanol (50 ml) was heated at 200 W 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.

#### 4.3.1. N′-[1-(2-Chlorophenyl)ethylidene]-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9a**)

Pale yellow powder; m.p. 235–236 °C. IR (KBr) $cm^{-1}$: 3678, 3573, 2926, 2365, 1657, 1420, 1173, 1067. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.37 (3H, s, $CH_3$), 2.92 (3H, s, $NCH_3$), 7.52 (2H, d, $J = 8.7$ Hz, Ar*H*), 7.85–7.90 (5H, m, Ar*H*), 8.03 (1H, dd, $J = 6.4$, 1.2 Hz, Ar*H*), 9.79 (1H, br s, N*H*), 13.73 (1H, br s, $OH_{enolic}$). $^{13}$C NMR: 16.1, 40.7, 111.2, 123.4, 126.7, 128., 128.9, 130.0, 130.3, 130.6, 131.9, 132.3, 132.4, 134.3, 137.1, 156.5, 168.6, 168.7; MS *m*/*z* 405 [$M^+$], 407 [$M^+$+2].

#### 4.3.2. N′-[1-(4-Chlorophenyl)ethylidene]-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9b**)

Light yellow powder; m.p. 240–242 °C. IR (KBr) $cm^{-1}$: 3677, 3573, 2923, 2365, 1657, 1409, 1170, 1070. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.35 (3H, s, $CH_3$), 2.93 (3H, s, $NCH_3$), 7.62 (2H, d, $J = 8.7$ Hz, Ar*H*), 7.83–7.89 (5H, m, Ar*H*), 8.06 (1H, dd, $J = 6.4$, 1.2 Hz, Ar*H*), 9.86 (1H, br s, N*H*), 13.77 (1H, br s, $OH_{enolic}$). $^{13}$C NMR: 16.8, 40.9, 111.5, 123.6, 126.8, 128.3, 128.5, 128.8, 128.9, 129.2, 131.8, 132.5, 134.4, 135.7, 136.8, 147.8, 156.6, 168.8; MS *m*/*z* 405 [$M^+$], 407 [$M^+$+2].

#### 4.3.3. N′-[1-(2,4-Dichlorophenyl)ethylidene]-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9c**)

Yellow powder; m.p. 178–180 °C. IR (KBr) $cm^{-1}$: 3678, 3572, 2929, 2365, 1656, 1423, 1122, 1042. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.28 (3H, s, $CH_3$), 2.95 (3H, s, $NCH_3$), 6.85 (1H, m, Ar*H*), 7.24 (3H, m, Ar*H*), 7.59 (2H, t, $J = 7.8$ Hz, Ar*H*), 7.76 (1H, s, Ar*H*), 9.98 (1H, br s, N*H*), 13.74 (1H, br s, $OH_{enolic}$). $^{13}$C NMR: 16.2, 40.7, 111.2, 123.4, 126.4, 126.6, 128.2, 128.9, 129.2, 131.9, 132.5, 133.5, 134.4, 134.7, 135.5, 156.6, 168.7, 168.9; MS *m*/*z* 439 [$M^+$], 441 [$M^+$+2], 443 [$M^+$+4].

#### 4.3.4. N′-[1-(3,4-Dichlorophenyl)ethylidene]-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9d**)

Light yellow powder; m.p. 222–224 °C. IR (KBr) $cm^{-1}$: 3678, 3573, 2932, 2364, 1653, 1424, 1178, 1062. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.30 (3H, s, $CH_3$), 2.94 (3H, s, $NCH_3$), 6.87 (1H, m, Ar*H*), 7.32–7.61 (4H, m, Ar*H*), 7.70 (1H, m, Ar*H*), 7.78 (1H, t, $J = 7.8$ Hz, Ar*H*), 9.94 (1H, br s, N*H*), 13.75 (1H, br s, $OH_{enolic}$). $^{13}$C NMR: 16.7, 40.9, 111.4, 123.6, 126.3, 126.8, 128.9, 130.3, 130.7, 131.8, 132.5, 133.5, 133.7, 134.6, 135.8, 147.8, 156.6, 168.7; MS *m*/*z* 439 [$M^+$], 441 [$M^+$+2], 443 [$M^+$+4].

#### 4.3.5. N′-[1-(2-Bromophenyl)ethylidene]-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9e**)

Off white powder; m.p. 219–220 °C. IR (KBr) $cm^{-1}$: 3677, 3574, 2923, 2364, 1653, 1424, 1167, 1067. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.34 (3H, s, $CH_3$), 2.93 (3H, s, $NCH_3$), 7.54 (2H, d, $J = 8.7$ Hz, Ar*H*), 7.86–7.90 (5H, m, Ar*H*), 8.05 (1H, d, $J = 6.4$, 1.2 Hz, Ar*H*), 9.96 (1H, br s, N*H*), 13.73 (1H, br s, $OH_{enolic}$). $^{13}$C NMR: 16.1, 40.8, 111.3, 122.3, 123.6, 126.7, 127.9, 128.9, 130.2, 131.9, 132.5, 132.8, 134.5, 134.7, 135.6, 156.7, 168.6, 168.8; MS *m*/*z* 449 [$M^+$], 451 [$M^+$+2].

#### 4.3.6. N′-[1-(4-Bromophenyl)ethylidene]-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9f**)

Off white powder; m.p. 231–233 °C. IR (KBr) $cm^{-1}$: 3677, 3574, 2923, 2364, 1653, 1424, 1167, 1067. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.35 (3H, s, $CH_3$), 2.95 (3H, s, $NCH_3$), 7.52 (2H, d, $J = 8.7$ Hz, Ar*H*), 7.85–7.89 (5H, m, Ar*H*), 8.01 (1H, d, $J = 6.4$, 1.2 Hz, Ar*H*), 9.91 (1H, br s, N*H*), 13.74 (1H, br s, $OH_{enolic}$). $^{13}$C NMR: 16.8, 40.9, 111.5, 123.7, 125.4, 126.8, 128.5, 128.8, 128.9, 131.6, 131.7, 131.9, 132.4, 134.5, 136.5, 147.8, 156.7, 168.9; MS *m*/*z* 449 [$M^+$], 451 [$M^+$+2].

#### 4.3.7. 4-Hydroxy-N′-[1-(4-iodophenyl)ethylidene]-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9g**)

Pale yellow powder; m.p. 239–240 °C. IR (KBr) $cm^{-1}$: 3677, 3594, 2935, 2364, 1652, 1423, 1175, 1058. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.34 (3H, s, $CH_3$), 2.96 (3H, s, $NCH_3$), 7.65 (2H, d, $J = 8.4$ Hz, Ar*H*), 7.84–7.91 (5H, m, Ar*H*), 8.09 (1H, d, $J = 6.4$, 1.2 Hz, Ar*H*), 9.94 (1H, br s, N*H*), 13.72 (1H, br s, $OH_{enolic}$). $^{13}$C NMR: 16.8, 40.9, 96.5, 111.4, 123.5, 126.7, 128.9, 130.8, 130.8, 131.9, 132.4, 134.5, 136.4, 137.8, 137.8, 147.8, 156.5, 168.8; MS *m*/*z* 497 [$M^+$], 499 [$M^+$+2].

#### 4.3.8. N′-[1-(2,4-Difluorophenyl)ethylidene]-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9h**)

Light yellow powder; m.p. 251 °C. IR (KBr) $cm^{-1}$: 3678, 3570, 2932, 2362, 1656, 1435, 1178, 1059. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.30 (3H, s, $CH_3$), 2.93 (3H, s, $NCH_3$), 6.89 (1H, m, Ar*H*), 7.27 (3H, m, Ar*H*), 7.61 (2H, t, $J = 7.8$ Hz, Ar*H*), 7.78 (1H, s, Ar*H*), 9.95 (1H, br s, N*H*), 13.73 (1H, br s, $OH_{enolic}$). $^{13}$C NMR: 16.7, 40.9, 111.3, 111.3, 112.7, 113.9, 123.5, 126.9, 128.9, 131.9, 132.6, 132.7, 134.4, 156.5, 161.4, 163.4, 168.7, 168.9; MS *m*/*z* 407 [$M^+$], 409 [$M^+$+2].

#### 4.3.9. 4-Hydroxy-N′-[1-(2-hydroxyphenyl)ethylidene]-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9i**)

Pale yellow powder; m.p. 255–256 °C. IR (KBr) $cm^{-1}$: 3677, 3573, 2935, 2361, 1658, 1429, 1176, 1060. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.30 (3H, s, $CH_3$), 2.94 (3H, s, $NCH_3$), 5.20 (1H, s, O*H*), 6.89–6.94 (2H, m, Ar*H*),

7.31–7.35 (1H, m, Ar*H*), 7.64–7.67 (1H, dd, $J$ = 6.4, 1.2 Hz, Ar*H*), 7.82–7.92 (3H, m, Ar*H*), 8.04 (1H, m, Ar*H*), 9.97 (1H, br s, N*H*), 13.69 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 17.0, 40.9, 111.4, 117.9, 118.6, 121.5, 123.4, 126.9, 128.7, 131.9, 132.0, 132.3, 132.4, 134.4, 156.7, 162.8, 168.9, 168.7; MS $m/z$ 387 [$M^+$].

#### 4.3.10. 4-Hydroxy-N′-[1-(3-hydroxyphenyl)ethylidene]-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9j**)

Pale yellow powder; m.p. 260–262 °C. IR (KBr) cm$^{-1}$: 3678, 3573, 2935, 2361, 1658, 1425, 1174, 1059. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.33 (3H, s, C$H_3$), 2.93 (3H, s, NC$H_3$), 5.23 (1H, s, O*H*), 6.85 (1H, m, Ar*H*), 7.24 (2H, m, Ar*H*), 7.67–7.75 (4H, m, Ar*H*), 8.03 (1H, m, Ar*H*), 9.96 (1H, br s, N*H*), 13.70 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.6, 40.8, 111.3, 115.0, 118.2, 120.9, 123.5, 126.7, 128.8, 130.3, 131.9, 132.5, 134.3, 135.6, 147.7, 156.6, 158.9, 168.8; MS $m/z$ 387 [$M^+$].

#### 4.3.11. 4-Hydroxy-N′-[1-(4-hydroxyphenyl)ethylidene]-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9k**)

Light yellow powder; m.p. 270–273 °C. IR (KBr) cm$^{-1}$: 3677, 3573, 2926, 2364, 1658, 1446, 1174, 1060. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.30 (3H, s, C$H_3$), 2.95 (3H, s, NC$H_3$), 5.24 (1H, s, O*H*), 6.90–6.95 (2H, m, Ar*H*), 7.29–7.33 (1H, m, Ar*H*), 7.64–7.66 (1H, dd, $J$ = 6.4, 1.2 Hz, Ar*H*), 7.80–7.89 (3H, m, Ar*H*), 8.01 (1H, m, Ar*H*), 9.94 (1H, br s, N*H*), 13.68 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.7, 40.7, 111.2, 115.9, 116.0, 123.2, 126.7, 128.7, 129.0, 129.1, 130.0, 131.8, 132.2, 134.3, 147.6, 156.4, 160.6, 168.6; MS $m/z$ 387 [$M^+$].

#### 4.3.12. 4-Hydroxy-N′-[1-(3-methoxyphenyl)ethylidene]-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9l**)

Off white powder; m.p. 271–274 °C. IR (KBr) cm$^{-1}$: 3678, 3571, 2927, 2364, 1659, 1437, 1171, 1064. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.36 (3H, s, C$H_3$), 2.97 (3H, s, NC$H_3$), 3.94 (3H, s, OC$H_3$), 6.77 (1H, m, Ar*H*), 7.35 (2H, m, Ar*H*), 7.60 (2H, t, $J$ = 7.8 Hz, Ar*H*), 7.76 (2H, t, $J$ = 7.8 Hz, Ar*H*), 8.05 (1H, m, Ar*H*), 9.97 (1H, br s, N*H*), 13.73 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.6, 40.6, 55.6, 111.2, 113.2, 116.5, 120.5, 123.3, 126.7, 128.8, 129.8, 131.6, 132.2, 134.3, 135.0, 147.7, 156.4, 160.6, 168.6; MS $m/z$ 401 [$M^+$].

#### 4.3.13. 4-Hydroxy-N′-[1-(4-methoxyphenyl)ethylidene]-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9m**)

Off white powder; m.p. 267–269 °C. IR (KBr) cm$^{-1}$: 3679, 3573, 2927, 2363, 1661, 1435, 1169, 1085. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.34 (3H, s, C$H_3$), 2.95 (3H, s, NC$H_3$), 3.93 (3H, s, OC$H_3$), 7.63 (2H, d, $J$ = 8.7 Hz, Ar*H*), 7.83–7.89 (5H, m, Ar*H*), 8.07 (1H, d, $J$ = 6.4, 1.2 Hz, Ar*H*), 9.93 (1H, br s, N*H*), 13.76 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.7, 55.9, 40.9, 111.3, 114.4, 114.5, 123.5, 126.9, 128.6, 128.7, 128.9, 129.9, 131.9, 132.5, 134.6, 147.9, 156.6, 162.9, 168.8; MS $m/z$ 401 [$M^+$].

#### 4.3.14. N′-[1-(4-Aminophenyl)ethylidene]-4-hydroxy-2-methyl-2H-1,2-benzothiazine-3-carbohydrazide 1,1-dioxide (**9n**)

Yellow powder; m.p. 258–260 °C. IR (KBr) cm$^{-1}$: 3677, 3573, 2925, 2363, 1657, 1425, 1173, 1059. $^1$H NMR (DMSO-$d_6$) $\delta$: 2.35 (3H, s, C$H_3$), 2.91 (3H, s, NC$H_3$), 6.40 (2H, s, N$H_2$), 7.61 (2H, d, $J$ = 8.7 Hz, Ar*H*), 7.84–7.88 (5H, m, Ar*H*), 8.04 (1H, m, Ar*H*), 9.97 (1H, br s, N*H*), 13.72 (1H, br s, O$H_{enolic}$). $^{13}$C NMR: 16.8, 40.9, 111.5, 114.5, 123.5, 126.7, 127.5, 128.8, 130.0, 131.9, 132.4, 134.5, 147.9, 156.7, 168.9; MS $m/z$ 386 [$M^+$].

#### 4.3.15. 4-Methyl-1,4-dihydropyrazolo[4,3-c][1,2]benzothiazin-3-ol 5,5-dioxide (**10**)

A mixture of methyl 4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide (**7**) (2.69 g; 10.0 mmol), hydrazine hydrate (2.50 g; 50.0 mmol), acetic acid (3.0 ml) and methyl alcohol (50 ml) was stirred and heated in microwave oven for a period of 4 min. After cooling to room temperature, the contents were poured over crushed ice and pH was maintained at 1 with conc. hydrochloric acid. Precipitates obtained were filtered, washed with water and dried (1.79 g; 75%); Light yellow solid; m.p. 258 °C. IR (KBr) cm$^{-1}$: 3353, 1601, 1319, 1140. $^1$H NMR ($CDCl_3$) (400 M Hz) $\delta$: 2.95 (3H, s, NC$H_3$), 7.55 (1H, t, $J$ = 7.4 Hz, Ar*H*), 7.65 (1H, t, $J$ = 7.2 Hz, Ar*H*), 7.91 (2H, t, $J$ = 7.8 Hz, Ar*H*), 9.99 (1H, br s, N*H*), 11.13 (1H, s, O*H*), $^{13}$C NMR: 31.7, 122.8, 127.5, 127.6, 128.8, 132.3, 133.6, 134.2, 137.7, 151.2; MS $m/z$: 251 ($M^+$).

### 4.4. Biological activities

#### 4.4.1. Anti-bacterial activity

The anti-bacterial assay was carried out by microdilution method [24,25] in order to determine the anti-bacterial activity of compounds tested against the human pathogenic bacteria. The bacterial suspensions were adjusted with sterile saline to a concentration of $1.0 \times 10^5$ colony forming unit (CFU)/ml. The inocula were prepared daily and stored at +4 °C until use. Dilutions of the inocula were cultured on solid medium to verify the absence of contamination and to check the validity of the inoculum. The minimum inhibitory concentrations (MICs) and minimum bactericidal concentrations (MIFs) were determined using 96-well microtitre plates. Compounds under investigation were dissolved in broth LB medium (100 μl) with bacterial inoculum ($1.0 \times 10^4$ cfu per well) to achieve the desired concentrations (1 mg/ml). All the microplates were incubated for 24 h at 48 °C. The lowest concentrations without visible growth (at the binocular microscope) were defined as concentrations that completely inhibited bacterial growth (MICs). Minimum bactericidal concentrations (MBCs) were determined by serial subcultivation of 2 μl into microtitre plates containing 100 μl of broth per well followed by incubation at and further incubation 48 °C for 72 h. The lowest concentration with no visible growth was defined as the MBC, indicating 99.5% killing of the original inoculum. The optical density of each well was measured at a wavelength of 655 nm and compared with a blank. Streptomycin was used as a positive control (1 mg/ml DMSO).

#### 4.4.2. Anti-fungal activity

Anti-fungal screening of the newly synthesized compounds was carried out by microdilution technique [24] against *A. niger*, *A. flavus*, *A. fumigates*, *T. viride*, *T. reesei* and *D. australiensis*. The micromycetes were maintained on malt agar and the cultures were stored at 4 °C and sub-cultured once a month [28]. The fungal spores were washed from the surface of agar plates with sterile 0.85% saline containing 0.1% Tween 80 (v/v). The spore suspension was adjusted with sterile saline to a concentration of approximately $1.0 \times 10^5$ in a final volume of 100 μl per well. The inocula were stored at 4 °C for further use. Dilutions of the inocula were cultured on solid malt agar to verify the absence of contamination and to check the validity of the inoculum. Minimum inhibitory concentration (MIC) determinations were performed by a serial dilution technique using 96-well microtiter plates. The compounds investigated were dissolved in DMSO (1 mg/ml) and added in broth Malt medium with inoculum. The microplates were incubated for 72 h at 28 °C, respectively. The lowest concentrations without visible growth (at the binocular microscope) were defined as MICs. Minimum fungicidal concentrations (MFCs) were determined by serial subcultivation of a 2 μl into microtiter plates containing 100 μl of broth per well and were further incubated for 72 h at 28 °C. The lowest concentration with no visible growth was defined as MFC indicating 99.5% killing of the original inoculum. DMSO was used as a negative control while commercially available fungicide, bifonazole, was used as positive controls (1–3000 μg/ml).

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