Synthesis of Potential Biologically Active 1,2-Benzothiazin-3-yl-quinazolin-4(3*H*)-ones

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A series of potential biologically active 2-(4-hydroxy-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl)quinazolin-4(3*H*)-ones was synthesized in a straight forward manner by condensation of respective 4-hydroxy-1,2-benzothiazine-1,1-dioxides with anthranilamide followed by simple and high throughput cyclization of *N*-[2-(aminocarbonyl)phenyl]-4-hydroxy-1,2-benzothiazine-3-carboxamide-1,1-dioxides. All the synthesized compounds were subjected to preliminary evaluation for their biological activity against Gram positive and Gram negative bacteria. Some of the assayed compounds showed marked activity against *Bacillus subtilis*.

Key words 1,2-benzothiazin-3-yl-quinazolin-4(3*H*)-one; anthranilamide; antibacterial agent; 1,2-benzothiazine-3-carboxamide; potassium tertiary butoxide

Benzothiazine derivatives possess versatile type of biological activities.[1)] Among these, 1,2-benzothiazine-3-carboxamide-1,1-dioxides such as piroxicam,[2)] ampiroxicam[3)] and meloxicam[4)] are well known for their analgesic and anti-inflammatory activities. Some of the 3,4-dihydro-1,2-benzothiazine-3-carboxylate 1,1-dioxide α-ketomide[5)] and P(2)–P(3) peptide mimetic aldehyde[6)] compounds act as potent calpain I inhibitors, while 1,4-benzothiazines generally possess significant antifungal activities.[7,8)]

Similarly, 3*H*-quinazolin-4-ones and their derivatives are found to be antihypertensive, antifibrillatory, choleretic, antiphlogistic,[9)] antimitotic, anticancer, and anticonvulsant agents.[10)] They have also been successfully tested as CNS depressants,[11)] muscle relaxants[12)] and for their antineoplastic activity.[13)] Another interesting characteristic of quinazolines is their antimicrobial activity against different species of pathogenic Gram negative bacteria, Gram positive bacteria and fungi.[14—20)]

Keeping in view the potential biological activities of 4-hydroxy-1,2-benzothiazine-1,1-dioxides and 3*H*-quinazolin-4-ones, it was perceived that if both the heterocyclic moieties are synergized in a single nucleus, the new compounds obtained were likely to possess significant biological activities. In this quest, novel 1,2-benzothiazin-3-yl-quinazolin-4(3*H*)-ones (**4a** to **h**) were synthesized from various alkyl 4-hydroxy-1,2-benzothiazine-1,1-dioxides (**1**, **2a—d**), prepared by literature methods,[21,22)] from simple substituted toluenes (Chart 1) and subjected to antibacterial activity.

Chemistry *N*-Methylation of methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxides (**1a—d**) was carried by reaction with methyl iodide to get the corresponding methylated compounds (**2a—d**). Usually for the alkylation of such compounds, solvent such as DMF or DMSO is used in the presence of strong bases such as NaH, metal alkoxides or alkyl lithiums.[23)] Due to high boiling points of these solvents, their thermal instability, and the environmental issues, butyl pyridinium tetrafluoroborate [BuPy]BF_4, a room temperature ionic liquid (RTIL) was used as a catalyst for these transformations. It is environmentally benign, easy to use due to simple product isolation, high yields and is economically friendly having potential for recyclization.[24)] In the next step, 1,2-benzothiazine-1,1-dioxides, (**1a—d**) and (**2a—d**) were reacted with anthranilamide *via* condensation reaction in an inert medium (toluene or xylene) using 4 Å molecular sieves in a Soxhelt apparatus. It provided highly pure products in good yields to form respective *N*-[2-(aminocarbonyl)phenyl]-4-hydroxy-1,2-benzothiazine-3-carboxamide-1,1-dioxides (Chart 2). Intramolecular cyclization of *N*-[2-(aminocarbonyl)phenyl]-4-hydroxy-1,2-benzothiazine-3-carboxamide-1,1-dioxides was then effected by their reaction with a base (NaOH) in the presence of hydrogen peroxide. Carboxamides (**3a—h**) were added in aliquots to a mixture of aqueous sodium hydroxide, hydrogen peroxide and ethanol; the contents were refluxed for three to four hours. Products [(1,2-benzothiazin-3-yl-quinazolin-4(3*H*)-ones (**4a—h**)] were obtained by acidifying the mixtures with dilute hydrochloric acid in cold followed by extraction with an organic solvent such as dichloromethane. However, the reaction was found sensitive to the amount of sodium hydroxide used and the portion-wise addition of the reactants. Sometimes, an orange coloured impurity appeared in the product in small amounts, perhaps due to the hydrolysis of the amides (**3a—h**) with base. To avoid the difficulty, reaction was modified and conducted under anhydrous conditions; reaction was performed by heating the amides (**3a—h**) with 1.2 equiv of potassium

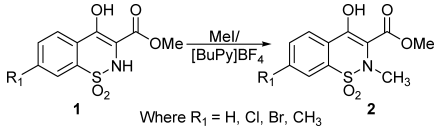

Chart 1. *N*-Methylation of 1,2-Benzothiazine-3-carboxylate-1,1-dioxides

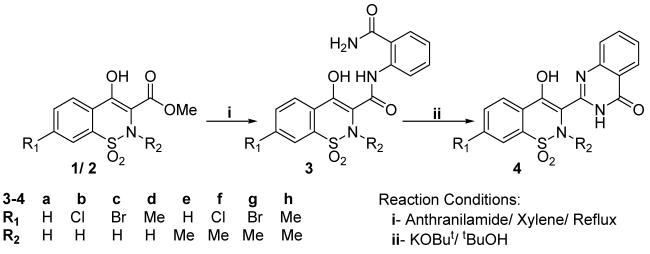

Chart 2. Synthesis of 2-(4-Hydroxy-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl)quinazolin-4(3*H*)-ones

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tert-butoxide in anhydrous *tert*-butyl alcohol at 80 °C. By conducting the cyclization under these conditions, the hydrolysis side products were avoided, and the reaction proceeded in very good isolated yields with no impurities detected. Simple high throughput isolation was devised, in which the reaction was diluted with water and acidified with 3 M hydrochloric acid to pH 5.5.

Antimicrobial Testing All the newly synthesized compounds (dissolved in dimethylformamide) were subjected to antimicrobial screening by determining the minimum inhibitory concentration (MIC) using the agar dilution technique.[25)]

The *in vitro* antimicrobial activity of the prepared compounds (**4a**—**h**) against the Gram positive bacterium, *Bacillus subtilis* and a Gram negative bacterium, *Escherichia coli* was determined by preparing suspensions of each microorganism to contain approximately 10^5—10^6 CFU (colony forming units)/well. The test compounds were applied to the wells at concentrations ranging from 200 to about 3.0 μg ml^{-1} in dimethyl formamide solution, in addition to the 0 (control), 1,2-benzothiazine-1,1-dioxides (**1**, **2a—d**) and the standard Tetracycline. The plates were incubated for 24 h at 37 °C and growth assessed by visual inspection. The minimum inhibitory concentration (MIC) was defined as the lowest concentration of inhibitor at which microbial growth was not apparent disregarding a single colony or a faint haze caused by the inoculums.

Results

The MICs of the active compounds against the susceptible pathogenic organisms are presented in Table 1. It was found that all the newly synthesized compounds except **4h** have inhibitory activity against *Bacillus subtilis*. The compounds **4b** and **c** caused inhibition against *Escherichia coli*, while compounds **4a**, **d**, **f**, **g** and **h** were found inactive or presented a MIC more than 200 μg ml^{-1}.

Compound **4b** showed highest activity against both the strains (MIC = 7.0 μg ml^{-1} and 57.0 μg ml^{-1}). An insight to the activities of different compounds obtained reveals that these are more active against *Bacillus subtilis* (a gram positive bacterium) than that of *Escherichia coli*. Only the two compounds **4b** and **c** showed some activity against the later. Also it is evident that compounds **4a**—**d** are relatively more active against *Bacillus subtilis* than **4e**—**h** (*N*-methyl derivatives of **4a**—**d**) and this higher activity may be attributed to the presence of two NH groups. Further, it seems that incorporation of an electronegative halogen atom at 7-position of benzothiazine nucleus enhances the antimicrobial activity; chloro compound **4b** showed maximum (MIC = 7.0 μg ml^{-1}) while electron donating methyl substituted compound **4h** exhibited no activity.

In conclusion, the present study revealed that synergism of two different heterocyclic systems, 4-hydroxy-1,2-benzothiazine-1,1-dioxide and quinazolin-4(3*H*)-one to a new system 2-(4-hydroxy-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl)quinazolin-4(3*H*)-ones could be useful as a template for future development through modification or derivatization to design a more potent biologically active compounds. The new skeleton may also possess other biological activities of the parent ring systems.[2—20)]

Table 1. Antibacterial Activity (MIC, μg ml^{-1})

Compound	Susceptible microorganisms	
	Bacillus subtilis	*Escherichia coli*
4a	20	—
4b	7	57
4c	12	69
4d	40	—
4e	41	—
4f	21	—
4g	23	—
4h	—	—
1a—d	—	—
2a—d	—	—
Tetracycline	0.25	0.35

Table 2. *N*-Methylation of 4-Hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxides

Entry	Reactant	Product	Reaction conditions	Yield (%)[a)]
1	**1a**	**2a**	40 °C, 6 h	94
2	**1b**	**2b**	40 °C, 5 h	93
3	**1c**	**2c**	50 °C, 6 h	94
4	**1d**	**2d**	50 °C, 6 h	93

a) Isolated yields based on corresponding 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide.

Table 3. Reaction of Methyl-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxides with Anthranilamide

Entry	Reactant	Product	Reaction time	Yield (%)[a)]
1	**1a**	**3a**	8 h	75
2	**1b**	**3b**	8 h	73
3	**1c**	**3c**	8 h	72
4	**1d**	**3d**	8 h	76
5	**2a**	**3e**	12 h	72
6	**2b**	**3f**	12 h	71
7	**2c**	**3g**	12 h	75
8	**2d**	**3h**	12 h	70

a) Isolated yield based on corresponding methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide.

Table 4. Synthesis of 2-(4-Hydroxy-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl)quinazoline-4(3*H*)-ones

Entry	Reactant	Product	Reaction time	Yield (%)[a)]
1	**3a**	**4a**	2.5 h	93
2	**3b**	**4b**	2.5 h	92
3	**3c**	**4c**	2.5 h	90
4	**3d**	**4d**	2.5 h	94
5	**3e**	**4e**	3 h	92
6	**3f**	**4f**	3 h	90
7	**3g**	**4g**	3 h	92
8	**3h**	**4h**	3 h	90

a) Isolated yield based on corresponding *N*-[2-(aminocarbonyl)phenyl]-4-hydroxy-1,2-benzothiazine-3-carboxamide-1,1-dioxide.

Experimental

Melting points were taken on Gallenkemp melting point apparatus and are uncorrected. ^{1}H-NMR spectra were taken on the Bruker DPX-400 NMR spectrometer, and chemical shifts are given in ppm downfield from TMS as the internal standard. IR spectra were recorded in the spectral range of 4000—400 cm^{-1} on Hitachi spectrometer, model 270-30. Mass spectra were

taken on Jeol JMS-HX110 H spectrometer. All the chemicals were purchased from E. Merck, BDH or Fluka and used without purification. However, solvents were purified through distillation. Butyl pyridinium tetrafluoroborate was synthesized according to the method described by Owens *et al.*[26] while methyl 4-hydroxy-1,2-benzothiazine-3-carboxylate-1,1-dioxides (**1a**—**d**) were synthesized according to procedures given in literature.[21,22] (Chart 1).

General Procedure of *N*-Methylation of Methyl 4-Hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxides Methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide (10.0 mmol) and KOH (1.12 g; 20.0 mmol) was added to butyl pyridinium tetrafluoroborate (6.0 ml), and the mixture was stirred magnetically for 5 min. Then, methyl iodide (20.0 mmol) was added in a single portion and stirring continued for 2—3 h (for reaction conditions, see Table 2). After completion of the reaction, product was extracted with chloroform (3×25 ml). The combined organic phases were evaporated under reduced pressure to get the crude product which was crystallized from methanol. After isolation of the product, remainder of the ionic liquid was recovered by drying at vacuum followed by filtration of the suspension to remove the residual KOH and the formed potassium iodide.

Methyl 4-Hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide (**2a**): White crystalline solid; mp 165 °C. IR (KBr): 3439, 1667, 1319, 1160 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.95, (s, 3H, NC$\underline{H}_3$), 3.95 (s, 3H, OC$\underline{H}_3$), 7.75—8.12 (m, 4H, Ar$\underline{H}$), 12.09 (s, 1H, O$\underline{H}$). MS *m/z*: 269 [M^+], 254 [M^+-CH_3], 238 [M^+-OCH_3]. *Anal.* Calcd for $C_{11}H_{11}NO_5S$: C, 49.06; H, 4.12; N, 5.20; Found: C, 49.21; H, 4.24; N, 4.99.

Methyl 7-Chloro-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide (**2b**): White crystalline solid; mp 295—296 °C. IR (KBr): 3450, 1678, 1329, 1160, 1074 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 3.16, (s, 3H, NC$\underline{H}_3$), 4.08 (s, 3H, OC$\underline{H}_3$), 7.89—8.34 (m, 3H, Ar$\underline{H}$), 12.17 (s, 1H, O$\underline{H}$). MS *m/z*: 305 [M^++2], 303 [M^+], 288 [M^+-CH_3], 272 [M^+-OCH_3]. *Anal.* Calcd for $C_{11}H_{10}ClNO_5S$: C, 43.50; H, 3.32; N, 4.61; Found: C, 43.39; H, 3.35; N, 4.78.

Methyl 7-Bromo-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide (**2c**): White crystalline solid; mp 189—190 °C. IR (KBr): 3447, 1680, 1325, 1162, 1053 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 3.09, (s, 3H, NC$\underline{H}_3$), 3.98 (s, 3H, OC$\underline{H}_3$), 7.81—8.22 (m, 3H, Ar$\underline{H}$), 12.22 (s, 1H, O$\underline{H}$). MS *m/z*: 349 [M^++2], 347 [M^+], 332 [M^+-CH_3], 316 [M^+-OCH_3]. *Anal.* Calcd for $C_{11}H_{10}BrNO_5S$: C, 37.95; H, 2.89; N, 4.02; Found: C, 38.06; H, 3.01; N, 4.11.

Methyl 4-Hydroxy-2,7-dimethyl-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide (**2d**): White crystalline solid; mp 141 °C. IR (KBr): 3393, 1675, 1322, 1157 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.44 (s, 3H, ArC$\underline{H}_3$), 3.26, (s, 3H, NC$\underline{H}_3$), 3.93 (s, 3H, OC$\underline{H}_3$), 7.71—7.96 (m, 3H, Ar$\underline{H}$), 12.13 (s, 1H, O$\underline{H}$). MS *m/z*: 283 [M^+], 268 [M^+-CH_3], 252 [M^+-OCH_3]. *Anal.* Calcd for $C_{12}H_{13}NO_5S$: C, 50.87; H, 4.63; N, 4.94; Found: C, 50.88; H, 4.57; N, 4.88.

General Procedure of Synthesis of *N*-(2-Carbamoylphenyl)-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxides A mixture of methyl 4-hydroxy-2*H*-1,2-benzothiazine-3-carboxylate-1,1-dioxide (8.51 g; 33.33 mmol), anthranilamide (5.0 g; 36.72 mmol) and xylene (250 ml) was refluxed (for reaction conditions, see Table 3) under nitrogen atmosphere in a Soxhlet apparatus having Linde type 4 Å molecular sieves. Three fourth of the xylene was then distilled off and the remaining contents were allowed to stand overnight at room temperature. Crystals were filtered off, washed with diethyl ether and recrystallized from ethanol to get the required compound.

N-(2-Carbamoylphenyl)-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide (**3a**): Bright yellow crystalline solid, mp 265 °C. IR (KBr): 3358, 1666, 1344, 1180 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.88 (s, 1H, N$\underline{H}$); 7.20—7.64 (m, 4H, anthranilamide ring), 7.84—8.10 (m, 4H, $C_6\underline{H}_4$); 8.47 (s, 2H, CON$\underline{H}_2$), 8.58 (br s, 1H, N$\underline{H}$), 13.12 (s,1H, O$\underline{H}$); MS *m/z*: 359 [M^+], 315 [M^+-CONH_2], 196 [$M^+-CONHC_6H_4CONH_2$]. *Anal.* Calcd for $C_{16}H_{13}N_3O_5S$: C, 53.48; H, 3.65; N, 11.69; Found: C, 53.51; H, 3.58; N, 11.73.

N-(2-Carbamoylphenyl)-7-chloro-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide (**3b**): Light yellow crystalline solid, mp 289—290 °C. IR (KBr): 3358, 1670, 1341, 1181, 1078 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.92 (s, 1H, N$\underline{H}$); 7.19—7.66 (m, 4H, anthranilamide ring), 7.81—8.14 (m, 3H, $C_6\underline{H}_3$); 8.44 (s, 2H, CON$\underline{H}_2$), 8.57 (br s, 1H, CON$\underline{H}$), 12.98 (s, 1H, O$\underline{H}$); MS *m/z*: 395 [M^++2], 393 [M^+], 349 [M^+-CONH_2], 230 [$M^+-CONHC_6H_4CONH_2$]. *Anal.* Calcd for $C_{16}H_{12}ClN_2O_5S$: C, 48.80; H, 3.07; N, 10.67; Found: C, 48.73; H, 3.13; N, 10.77.

7-Bromo-*N*-(2-carbamoylphenyl)-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide (**3c**): Cream coloured crystalline solid, mp 271—273 °C. IR (KBr): 3275, 1676, 1337, 1184, 1039 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.95 (br s, 1H, N$\underline{H}$); 7.21—7.72 (m, 4H, anthranilamide ring), 7.78—8.19 (m, 3H, $C_6\underline{H}_3$); 8.48 (s, 2H, CON$\underline{H}_2$), 8.61 (br s, 1H, CON$\underline{H}$), 13.09 (s, 1H, O$\underline{H}$); MS *m/z*: 439 [M^++2], 437, [M^+], 392.97 [M^+-CONH_2], 273.97 [$M^+-CONHC_6H_4CONH_2$]. *Anal.* Calcd for $C_{16}H_{12}BrN_3O_5S$: C, 43.85; H, 2.76; N, 9.59; Found: C, 43.77; H, 2.75; N, 9.70.

N-(2-Carbamoylphenyl)-4-hydroxy-7-methyl-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide (**3d**): Yellow crystalline solid, mp 280—281 °C decomp; IR (KBr): 3367, 1673, 1337, 1178 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.34 (s, 3H, ArC$\underline{H}_3$), 2.90 (s, 1H, N$\underline{H}$), 7.21—7.63 (m, 4H, anthranilamide ring), 7.83—8.10 (m, 3H, $C_6\underline{H}_3$); 8.46 (s, 2H, CON$\underline{H}_2$), 8.61 (br s, 1H, CON$\underline{H}$), 13.08 (s, 1H, O$\underline{H}$); MS *m/z*: 373 [M^+], 329 [M^+-CONH_2], 210 [$M^+-CONHC_6H_4CONH_2$]. *Anal.* Calcd for $C_{17}H_{15}N_3O_5S$: C, 54.68; H, 4.05; N, 11.25; Found: C, 54.75; H, 3.96; N, 11.19.

N-(2-Carbamoylphenyl)-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide (**3e**): White crystalline solid, mp 250—252 °C. IR (KBr): 3376, 1669, 1330, 1169 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.72 (s, 3H, NC$\underline{H}_3$); 7.37—7.74 (m, 4H, anthranilamide ring), 7.79—8.03 (m, 4H, $C_6\underline{H}_4$); 8.41 (s, 2H, CON$\underline{H}_2$), 8.60 (br s, 1H, CON$\underline{H}$), 13.10 (s, 1H, O$\underline{H}$); MS *m/z*: 373 [M^+], 315 [M^+-CONH_2], 196 [$M^+-CONHC_6H_4CONH_2$]. *Anal.* Calcd for $C_{17}H_{15}N_3O_5S$: C, 54.68; H, 4.05; N, 11.25; Found: C, 54.70; H, 3.95; N, 11.20.

N-(2-Carbamoylphenyl)-7-chloro-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide (**3f**): Pale yellow crystalline solid, mp 277 °C. IR (KBr): 3344, 1668, 1335, 1140, 1051 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 3.21 (s, 3H, NC$\underline{H}_3$); 7.32—7.71 (m, 4H, anthranilamide ring), 7.87—8.18 (m, 3H, $C_6\underline{H}_3$); 8.42 (s, 2H, CON$\underline{H}_2$), 8.58 (br s, 1H, N$\underline{H}$), 13.07 (s, 1H, O$\underline{H}$); MS *m/z*: 409 [M^++2], 407 [M^+], 363 [M^+-CONH_2], 244 [$M^+-CONHC_6H_4CONH_2$]. *Anal.* Calcd for $C_{17}H_{14}ClN_3O_5S$: C, 50.07; H, 3.46; N, 10.30; Found: C, 50.14; H, 3.38; N, 10.36.

7-Bromo-*N*-(2-carbamoylphenyl)-4-hydroxy-2-methyl-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide (**3g**): Light yellow crystalline solid, mp 269 °C. IR (KBr): 3408, 1673, 1332, 1125, 1035 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 3.12 (s, 3H, NC$\underline{H}_3$); 7.35—7.70 (m, 4H, anthranilamide ring), 7.91—8.21 (m, 3H, $C_6\underline{H}_3$); 8.39 (s, 2H, CON$\underline{H}_2$), 8.64 (br s, 1H, N$\underline{H}$), 13.17 (s, 1H, O$\underline{H}$); MS *m/z*: 453 [M^++2], 451 [M^+], 407 [M^+-CONH_2], 288 [$M^+-CONHC_6H_4CONH_2$]. *Anal.* Calcd for $C_{17}H_{14}BrN_3O_5S$: C, 45.15; H, 3.12; N, 9.29; Found: C, 45.06; H, 3.05; N, 9.37.

N-(2-Carbamoylphenyl)-4-hydroxy-2,7-dimethyl-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide (**3h**): White crystalline solid, mp 264 °C. IR (KBr): 3360, 1666, 1328, 1149 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.49 (s, 3H, ArC$\underline{H}_3$), 2.95 (s, 3H, NC$\underline{H}_3$); 7.36—7.73 (m, 4H, anthranilamide ring), 7.77—8.10 (m, 3H, $C_6\underline{H}_3$); 8.44 (s, 2H, CON$\underline{H}_2$), 8.58 (br s, 1H, CON$\underline{H}$), 13.15 (s, 1H, OH); MS *m/z*: 387 [M^+], 343 [M^+-CONH_2], 224 [$M^+-CONHC_6H_4CONH_2$]. *Anal.* Calcd for $C_{18}H_{17}N_3O_5S$: C, 55.80; H, 4.42; N, 10.85; Found: C, 55.71; H, 4.48; N, 10.91.

General Procedure of Synthesis of 2-(4-Hydroxy-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl)quinazolin-4(3*H*)-ones. A. Using H_2O_2 *N*-[2-(Aminocarbonyl)phenyl]-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide (6.76 mmol) was added portion-wise to a solution of sodium hydroxide (0.54 g; 13.5 mmol) and hydrogen peroxide solution (2.5 ml; 30%) in water (20 ml). Ethanol (7.0 ml) was added and the resulting mixture was heated under reflux for 3 h, cooled and evaporated under vacuum. The resulted solid was treated with 2 N hydrochloric acid (4.0 ml) followed by extraction with dichloromethane (3×15 ml). The combined organic extracts were washed successively with saturated aqueous sodium bicarbonate solution (3×10 ml) and brine (5 ml) followed by drying with magnesium sulphate and evaporation of solvent under vacuum. Recrystallization from chloroform afforded light yellow product.

B. Using KOBu^t/^{t}BuOH *N*-[2-(Aminocarbonyl)phenyl]-4-hydroxy-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide (5.0 mmol) was suspended in *tert*-butyl alcohol (10.0 ml) followed by addition of potassium *tert*-butoxide (6.0 mmol). The resulting mixture was heated at reflux for a time till completion (given in Table 4). Water (15 ml) was added after cooling the mixture and subsequently the contents were acidified by adding dilute HCl to Congo Red. Precipitates were washed with water and dried in vacuum to get the crystalline product.

2-(4-Hydroxy-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl)quinazolin-4(3*H*)-one (**4a**): Yellow crystalline solid, mp 263—265 °C. IR (KBr): 3398, 1668, 1331, 1170 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.91 (s, 1H, N$\underline{H}$); 7.42—7.92 (m, 8H, Ar$\underline{H}$); 9.02 (br s, CON$\underline{H}$), 13.07 (s, 1H, O$\underline{H}$). MS *m/z*: 341 [M^+], 196 [M^+−quinazolin-4(3*H*)-one]. *Anal.* Calcd for $C_{16}H_{11}N_3O_4S$: C, 50.07; H, 3.46; N, 10.30; Found: C, 50.11; H, 3.38; N, 10.24.

2-(7-Chloro-4-hydroxy-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl)quinazolin-4(3*H*)-one (**4b**): Light yellow crystalline solid, mp 249—254 °C. IR (KBr): 3408, 1671, 1321, 1165, 1057 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.99 (s, 1H, N$\underline{H}$);

7.51—7.95 (m, 7H, ArH); 9.08 (br s, CONH), 13.10 (s, 1H, OH). MS *m/z*: 377 [M^++2], 375 [M^+], 229.96 [M^+−quinazolin-4(3*H*)-one]. *Anal.* Calcd for $C_{16}H_{10}ClN_3O_4S$: C, 51.14; H, 2.68; N, 11.18; Found: C, 50.99; H, 2.74; N, 11.07.

2-(7-Bromo-4-hydroxy-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl)quinazolin-4(3*H*)-one (**4c**): Off white crystalline solid, mp 245—248 °C. IR (KBr): 3395, 2934, 1666, 1328, 1160, 1032 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.91 (s, 1H, NH); 7.32—8.08 (m, 7H, ArH); 9.16 (br s, CONH), 13.14 (s, 1H, OH). MS *m/z*: 421 [M^++2], 419 [M^+], 273.92 [M^+−quinazolin-4(3*H*)-one]. *Anal.* Calcd for $C_{16}H_{10}BrN_3O_4S$: C, 45.73; H, 2.40; N, 10.00; Found: C, 45.65; H, 2.49; N, 9.92.

2-(4-Hydroxy-7-methyl-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl)quinazolin-4(3*H*)-one (**4d**): Off white crystalline solid, mp 254 °C. IR (KBr): 3390, 1670, 1328, 1166 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.38 (s, 3H, $ArCH_3$), 2.94 (s, 1H, NH); 7.47—7.87 (m, 7H, ArH); 8.98 (br s, CONH), 13.00 (s, 1H, OH). MS *m/z*: 355 [M^+], 210 [M^+−quinazolin-4(3*H*)-one]. *Anal.* Calcd for $C_{17}H_{13}N_3O_4S$: C, 57.46; H, 3.69; N, 11.82; Found: C, 57.39; H, 3.77; N, 11.86.

2-(4-Hydroxy-2-methyl-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl)quinazolin-4(3*H*)-one (**4e**): White crystalline solid, mp 320 °C decomp. IR (KBr): 3406, 2927, 1678, 1332, 1169 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.63 (s, 1H, NCH_3), 3.07 (s, 1H, NH); 7.44—7.89 (m, 8H, ArH), 9.09 (br s, CONH), 13.11 (s, 1H, OH). MS *m/z*: 355 [M^+], 210 [M^+−quinazolin-4(3*H*)-one]. *Anal.* Calcd for $C_{17}H_{13}N_3O_4S$: C, 57.46; H, 3.69; N, 11.82; Found: C, 57.39; H, 3.76; N, 11.90.

2-(7-Chloro-4-hydroxy-2-methyl-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl)quinazolin-4(3*H*)-one (**4f**): Pale yellow crystalline solid, mp 300 °C decomp. IR (KBr): 3395, 2939, 1678, 1342, 1175, 1071 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.69 (s, 3H, NCH_3), 7.51—8.13 (m, 7H, ArH), 9.09 (br s, CONH), 13.12 (s, 1H, OH). MS *m/z*: 391 [M^++2], 389 [M^+], 244 [M^+−quinazolin-4(3*H*)-one]. *Anal.* Calcd for $C_{17}H_{12}ClN_3O_4S$: C, 52.38; H, 3.10; N, 10.78; Found: C, 52.47; H, 3.04; N, 10.85.

2-(7-Bromo-4-hydroxy-2-methyl-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl)quinazolin-4(3*H*)-one (**4g**): Yellow crystalline solid, mp 290—293 °C. IR (KBr): 3403, 2937, 1675, 1339, 1175, 1028 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.70 (s, 3H, NCH_3), 7.48—8.08 (m, 7H, ArH), 9.17 (br s, CONH), 13.08 (s, 1H, OH). MS *m/z*: 499 [M^++2], 497 [M^+], 288 [M^+−quinazolin-4(3*H*)-one]. *Anal.* Calcd for $C_{17}H_{12}BrN_3O_4S$: C, 47.02; H, 2.79; N, 9.68; Found: C, 46.94; H, 2.86; N, 9.75.

2-(4-Hydroxy-2,7-dimethyl-1,1-dioxido-2*H*-1,2-benzothiazin-3-yl)quinazolin-4(3*H*)-one (**4h**): White crystalline solid, mp 280 °C decomp. IR (KBr): 3391, 2930, 1662, 1336, 1174 cm^{-1}. ^{1}H-NMR ($CDCl_3$), δ: 2.38 (s, 3H, $ArCH_3$), 2.74 (s, 3H, NCH_3), 7.46—7.95 (m, 7H, ArH), 8.99 (br s, CONH), 13.04 (s, 1H, OH). MS *m/z*: 369 [M^+], 224 [M^+−quinazolin-4(3*H*)-one]. *Anal.* Calcd for $C_{18}H_{15}N_3O_4S$: C, 58.53; H, 4.09; N, 11.38; Found: C, 58.46; H, 4.16; N, 11.47.

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