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## Synthesis and pharmacological evaluation of 1-(2*H*-benzo [*b*] [1, 4] thiazin-3(4*H*)-ylidene) hydrazine-1, 1-dioxide derivatives as anti-inflammatory Agents

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### Abstract

Synthesis, physical and analytical properties of 1-(2*H*-benzo [*b*] [1, 4] thiazin-3(4*H*)-ylidene) hydrazine-1, 1-dioxide derivatives are described. These new compounds were synthesized through a sequence of almost quantitative reactions. The commercial starting material 2-aminothiophenol was condensed with  $\beta$ -haloesters, reacted with hydrazine derivatives and oxidized at sulfur atom to obtained sulfonyl derivatives. All the synthesized compounds were evaluated for anti-inflammatory activity using carrageenan induced rat paw oedema method.

**Keywords:** 1, 4-Benzothiazines; Hydrazine; 2-Aminothiophenol; Anti-inflammatory activity

### Introduction

1, 4-Benzothiazine derivatives represents one of the most important class of organic molecules and have been extensively studied because of wide spectrum of biological activities [1-5]. In particular the synthesis of the sulfoxide system, many sulfones have been reported to exhibit biological activity for industrial and pharmacological applications [6-8]. 1, 2-Benzothiazine have been widely used as Nonsteroidal anti-inflammatory drugs like piroxicam and meloxicam. Although they are effective in the treatment of inflammation, their routine and long-term administration is limited due to their gastrointestinal ulceration and renal side effects. Newer improved molecules are needed with lesser side effects and improved physical properties. With the aim to investigate more accurately anti-inflammatory properties of structurally related compounds, several 1-(2*H*-benzo [*b*] [1, 4] thiazin-3 (4*H*)-ylidene) hydrazine-1, 1-dioxide derivatives were synthesized from 2-aminothiophenol. Cyclisation of  $\beta$ -haloesters with this starting compound led to the 2*H*-benzo [*b*] [1, 4] thiazin-3 (4*H*)-ones which were reacted with hydrazines followed by oxidation at the sulfur to obtain Compounds 3a-f. The newly synthesized compounds have been screened for anti-inflammatory activity.

## 2. Result and discussion

### 2.1 Chemistry

The synthesis of 1-(2*H*-benzo [*b*] [1, 4] thiazin-3 (4*H*)-ylidene) hydrazine-1, 1-dioxide derivatives 3a-f started from cyclisation of  $\beta$ -haloesters with 2-aminothiophenol in presence of 10% potassium hydroxide in ethanolic solution as a base [10] to yield 2*H*-benzo [*b*] [1, 4] thiazin-3(4*H*)-one derivatives 1a-b, which were refluxed with some nitrogen containing nucleophilic hydrazines in methanol [11] to yield 1-(2*H*-benzo [*b*] [1, 4] thiazin-3 (4*H*)-ylidene) hydrazines 2a-f. The further step, i.e. the oxidation of the sulfur, was usually performed with 30% hydrogen peroxide in glacial acetic acid [6] to produce compounds 3a-f.

In IR spectra the synthesized 1-(2*H*-benzo [*b*] [1, 4] thiazin-3 (4*H*)-ylidene) hydrazines 2a-f exhibit a weak absorption band in the region 3360-3100  $\text{cm}^{-1}$  due to the stretching vibration of the secondary amino group. A weak N-N stretching absorption band in the region 1106-1052  $\text{cm}^{-1}$  and a strong C = N stretching absorption band in the 1640-1690  $\text{cm}^{-1}$  region are observed. In compound 2c, f the bands occur in the region 1404-1379  $\text{cm}^{-1}$  and 1577-1578  $\text{cm}^{-1}$  due to the symmetric and asymmetric stretching vibration of the nitro group.

<sup>1</sup>HNMR spectra of compounds 2a-f exhibit a multiplet in the region  $\delta$  8.5-6.8 ppm due to aromatic protons. The broad signal observed in the region  $\delta$  9-11 is attributed to -NH protons. The broad peak observed at  $\delta$  2.6-2.8 can be assigned to -CH proton.

In IR spectra the synthesized 1-(2*H*-benzo [*b*] [1, 4] thiazin-3 (4*H*)-ylidene) hydrazine-1, 1-dioxide derivatives 3a-f exhibit two sharp absorption bands in the region 1195-1135  $\text{cm}^{-1}$  and

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1380-1335  $\text{cm}^{-1}$  due to the symmetric and asymmetric stretching vibration of the  $\text{SO}_2$  group.

In  $^1\text{H-NMR}$  spectra a broad peak observed in the region  $\delta$  8-11 in all 1-(2*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene) hydrazine-1, 1-dioxides 3a-f is due to N-H proton. Aromatic protons show multiplet in the region  $\delta$  8.9-6.8 ppm. The sharp peak observed at  $\delta$  3.2-3.4 can be assigned to  $-\text{CH}$  proton. In compounds 3a, d a broad peak is observed in the region  $\delta$  8.2-8.5 due to  $-\text{NH}_2$  protons. In compounds 3d, e, f a doublet peak is observed in the region 1.2-1.3 due to  $\text{CH}_3$  protons at C-2.  $^{13}\text{C-NMR}$  spectra of compounds 3a-f have been recorded. In mass spectra of 1-(2*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene) hydrazine-1, 1-dioxides 3a-f, the molecular ion peak is in accordance to their molecular weight.

## 2.2. Biological activity

All the synthesized compounds 3a-f were screened for anti-inflammatory activity. The percentage inhibition of oedema as compared to the control was estimated in vivo for compounds 3a-f by using carrageenan induced rat paw oedema method [11]. The standard drug used for reference was Indomethacin (10mg/kg).

Results are collected in the Table 1.

## 3. Experimental protocols

### 3.1 Pharmacology

All the experimental procedures and protocol used in the study were reviewed by the Institutional Animal Ethics Committee and were in accordance with the guidelines of the Committee for the Purpose of Control and Supervision on Experiments on Animals (CPCSEA), Ministry of Forests and Environment, Govt. of India. The anti-inflammatory activity of all title compounds was carried out by carrageenan induced rat paw oedema method as described by Winter *et al.* The albino rats either sex weighing 150-200 g were randomly divided into various groups; each group consisted of a minimum of 6 animals. Animals were fastened for 12 h before the experiment and only water was allowed. The suspension of newly synthesized compounds, in 2% tween 80 was administered to the test animals intraperitoneally. The control group received the same experimental handling as test group but in place of test compounds equivalent dose of vehicle alone was administered. Acute oedema in hind paw of rat was induced by subplantar injection of freshly prepared 1% solution (0.1 ml of freshly prepared, w/v carrageenan in saline). Oedema was determined immediately and 30, 60, 120 and 180 minutes after the injection, using a mercury plethysmograph. Different dose of the test compounds 5mg/kg, 10mg/kg and 20mg/kg respectively and standard drug 10 mg/kg were administered 1 hr before the carrageenan injection. The control group receives 0.9% saline + tween80 solution. In standard group indomethacin was given, which at 10mg/kg showed significant inhibition of oedema when compared with control. The results were expressed as percent inhibition of the oedema. The mean increase of the paw volume at each time interval was compared with that of the control group. The statistical analysis was done by applying the ANOVA on the compounds in comparison with control.

### 3.2 Chemistry

All the chemicals used were of analytical grade. Melting points were determined in open capillary tubes and are uncorrected. Purity of the compounds was checked by thin layer chromatography on silica gel plates with a 0.2 mm

thickness. Compounds were powdered, mixed with KBr at 1% concentration and pressed into pellets before IR spectra be recorded on Bruker FT/IR Vertex spectrometer.  $^1\text{H}$ - and  $^{13}\text{C}$ -NMR spectra were recorded on a Bruker Avance II 400-NMR spectrometer using  $\text{DMSO-d}_6$  as solvent, TMS as an internal standard and the chemical shifts ( $\delta$ ) are expressed in parts per million (ppm), and coupling constants (J) are given in hertz (Hz). The Mass spectra were recorded on a Waters, Q-TOF MS-ES spectrometer. Elemental analysis was done on Carlo Erba 1108 Elemental Analyser.

Chemical data of compound 1a and 1b are given in Ref. [9, 10]

General method for the synthesis of compounds 2a-f 2-Substituted-benzo [b] [1, 4] thiazin-3 (4*H*)-one 1a-b (0.01 mol) and hydrazine derivative (0.01 mol) was dissolved in 15 ml methanol then 10 ml Conc. HCl was added into reaction mixture and heated on steam bath at 70-80  $^\circ\text{C}$  for 2 hour, the reaction mixture was concentrated and cooled in ice bath. Solid was separated out which was recrystallized from ethanol to obtain compound 2a-f 1-(2*H*-Benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene) hydrazine (2a).

The title compound was prepared from 2-*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-one 1a and hydrazine hydrate. Yield, 52%; m.p. 218-220  $^\circ\text{C}$ ;  $R_f$ , 0.52 (benzene-acetone, 1:3); IR ( $\nu$   $\text{cm}^{-1}$ ): 3358, 3319, 3192, 2973, 1652, 1575, 1525, 1473, 1336, 1072, 1024, 731, 685;  $^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{DMSO-d}_6$ ): 2.8 (s, 2H,  $\text{CH}_2$ ), 6.8-7.2 (m, 4H, Ar-H), 8.2 (br, 2H,  $\text{NH}_2$ ), 10.89 (br, 1H, NH);  $^{13}\text{C-NMR}$  ( $\delta$  ppm,  $\text{DMSO-d}_6$ ): 33.5 ( $\text{CH}_2$ ), 116.2 (CH), 119.5 (CH), 120.5 (C-S), 126.5 (CH), 127.1 (CH), 148.4 (C-N), 155.0 (C=N); MS m/z (%): 179 (22), 162 (51), 150 (35), 133 (23), 124 (100), 91 (15), 74 (10); Anal. Calcd for  $\text{C}_8\text{H}_9\text{N}_3\text{S}$ : C, 53.61; H, 5.06; N, 23.44; S, 17.89. Found: C, 53.63; H, 5.08; N, 23.42; S, 17.91.

1-(2*H*-Benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene)-2-phenylhydrazine (2b)

The title compound was prepared from 2-*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-one 1a and phenyl hydrazine hydrochloride. Yield, 66%; m.p. 190-192 $^\circ\text{C}$ ;  $R_f$ , 0.50 (benzene-acetone, 1:3); IR ( $\nu$   $\text{cm}^{-1}$ ): 3231, 3118, 2978, 1647, 1509, 1457, 1280, 1085, 1028, 781, 660  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{DMSO-d}_6$ ): 2.8 (s, 2H,  $\text{CH}_2$ ), 6.8-7.2 (m, 9H, Ar-H), 9.54 (br, 1H, NH), 10.22 (br, 1H, NH);  $^{13}\text{C-NMR}$  ( $\delta$  ppm,  $\text{DMSO-d}_6$ ): 33.8 ( $\text{CH}_2$ ), 116.5 (3CH), 119.0 (2CH), 120.5 (C-S), 126.2 (CH), 127.6 (CH), 129.0 (2CH), 147.4 (2C-N), 155.2 (C=N); MS m/z (%): 255 (26), 238 (21), 226 (13), 209 (51), 200 (24), 150 (100), 91 (10); Anal. Calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_3\text{S}$ : C, 65.85; H, 5.13; N, 16.46; S, 12.56. Found: C, 65.82; H, 5.16; N, 16.48; S, 12.54.

1-(2*H*-Benzo[b] [1, 4] thiazin-3 (4*H*)-ylidene) -2-(2, 4-dinitrophenyl) hydrazine (2c)

The title compound was prepared from 2-*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-one 1a and 2, 4-m-dinitrophenyl hydrazine. Yield, 78%; m.p. 140-142 $^\circ\text{C}$ ;  $R_f$ , value: 0.54 (benzene-acetone, 1:3); IR ( $\nu$   $\text{cm}^{-1}$ ): 3315, 2905, 1640, 1577, 1475, 1379, 1327, 1242, 1056, 835, 773, 736, 697  $\text{cm}^{-1}$ ;  $^1\text{H NMR}$  ( $\delta$  ppm,  $\text{DMSO-d}_6$ ): 2.9 (s,  $\text{CH}_2$ ), 6.9-8.8 (m, 7H, Ar-H), 9.60 (br, 1H, NH), 11.29 (br, 1H, NH);  $^{13}\text{CNMR}$  ( $\delta$  ppm,  $\text{DMSO-d}_6$ ): 33.9 ( $\text{CH}_2$ ), 116.5 (CH), 118.1 (CH), 119.3 (2CH), 120.4 (C-S), 126.2 (CH), 127.9 (2CH), 133.9 (C- $\text{NO}_2$ ), 142.2 (C- $\text{NO}_2$ ), 147.4 (2C-N), 154.8 (C=N); MS m/z (%): 345 (18), 328 (12), 316 (52), 299 (35), 290 (25), 240 (100), 91 (10); Anal. Calcd for  $\text{C}_{14}\text{H}_{11}\text{N}_5\text{O}_4\text{S}$ : C, 48.69; H, 3.21; N, 20.28; S, 9.29 Found: C, 48.65; H, 3.25; N, 20.25; S, 9.32.

1-(2-Methyl-2*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene) hydrazine (2d)

The title compound was prepared from 2-methyl-2*H*-benzo [b]

[1, 4] thiazin-3 (4*H*)-one 1b and hydrazine hydrate. Yield, 70%; m.p. 105-107°C;  $R_f$ , 0.42 (Toluene-ethylacetate 3:2); IR ( $\nu$   $\text{cm}^{-1}$ ): 3390, 3362, 3194, 2924, 2891, 1655, 1274, 1230, 1080, 1022, 921, 820, 790, 736, 649  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 1.2 (d, 3H,  $\text{CH}_3$ ,  $J = 6.2$ ), 2.6 (q, 1H, CH), 6.8-7.2 (m, 4H, Ar-H), 8.2 (br, 2H,  $\text{NH}_2$ ), 10.89 (br, 1H, NH);  $^{13}\text{C-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 15.2 ( $\text{CH}_3$ ), 42.5 ( $\text{CH}_2$ ), 116.3 (CH), 119.5 (CH), 120.5 (C-S), 126.5 (CH), 127.2 (CH), 148.4 (C-N), 154.9 (C = N); MS  $m/z$  (%): 193 (34), 176 (10), 150 (35), 133 (23), 124 (100), 91 (15); Anal. Calcd for  $\text{C}_9\text{H}_{11}\text{N}_3\text{S}$ : C, 55.93; H, 5.74; N, 21.74; S, 16.59. Found: C, 55.90; H, 5.72; N, 21.76; S, 16.62.

1-(2-Methyl-2*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene) -2-phenylhydrazine (2e)

The title compound was prepared from 2-methyl-2*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-one 1b and phenyl hydrazine hydrochloride. Yield, 68%; m.p. 95-97°C;  $R_f$ , 0.45 (Toluene-ethylacetate 3:2); IR ( $\nu$   $\text{cm}^{-1}$ ): 3189, 3107, 2976, 2884, 1657, 1472, 1276, 1231, 1080, 1023, 823, 787, 736, 649  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 1.2 (d, 3H,  $\text{CH}_3$ ,  $J = 6$ ), 2.6 (q, 1H, CH), 6.8-7.2 (m, 9H, Ar-H), 9.51 (br, 1H, NH), 10.21 (br, 1H, NH);  $^{13}\text{C-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 15.3 ( $\text{CH}_3$ ), 42.6 (CH), 116.5 (3CH), 119.2 (2CH), 120.5 (C-S), 126.4 (CH), 127.5 (CH), 129.6 (2CH), 147.7 (2C-N), 155.2 (C=N); MS  $m/z$  (%): 269 (100), 252 (51), 226 (13), 209 (51), 200 (24), 150 (100), 91 (10); Anal. Calcd for  $\text{C}_{15}\text{H}_{15}\text{N}_3\text{S}$ : C, 66.88; H, 5.81; N, 15.60; S, 11.90; Found: C, 66.92; H, 5.83; N, 15.58; S, 11.86.

1-(2-Methyl-2*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene) -2-(2, 4-dinitrophenyl) hydrazine (2f)

The title compound was prepared from 2-methyl-2*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-one 1b and 2, 4-dinitrophenyl hydrazine. Yield, 74%; m.p. 165-167°C;  $R_f$ , 0.88 (Toluene-ethylacetate 3:2); IR ( $\nu$   $\text{cm}^{-1}$ ): 3358, 3310, 2983, 1641, 1577, 1477, 1404, 1325, 1248, 1094, 1051, 837, 739, 695, 648  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 1.2 (d, 3H,  $\text{CH}_3$ ,  $J = 6.3$ ), 2.7 (q, 1H, CH), 6.8-8.9 (m, 7H, Ar-H), 9.55 (br, 1H, NH), 11.29 (br, 1H, NH);  $^{13}\text{C-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 15.2 ( $\text{CH}_3$ ), 42.5 (CH), 116.5 (CH), 118.2 (CH), 119.3 (2CH), 120.4 (C-S), 126.2 (CH), 127.9 (2CH), 133.9 (C- $\text{NO}_2$ ), 142.2 (C- $\text{NO}_2$ ), 147.5 (2C-N), 154.9 (C = N); MS  $m/z$  (%): 359 (20), 342 (16), 316 (52), 299 (35), 290 (26), 240 (100), 91 (10); Anal. Calcd for  $\text{C}_{15}\text{H}_{13}\text{N}_5\text{O}_4\text{S}$ : C, 50.13; H, 3.65; N, 19.59; S, 8.92. Found: C, 50.15; H, 3.68; N, 19.56; S, 8.90.

General method for the synthesis of compounds 3a-f

1-(2*H*-Benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene) hydrazine derivative 2a-f (0.01 mol) in glacial acetic acid (20 ml) and 30% hydrogen peroxide (5 ml) was added and refluxed for 15 min. heating was stopped and another lot of hydrogen peroxide (5 ml) was added. The reaction mixture was again refluxed for 3-4 hrs. The excess of solvent was removed by distillation under reduced pressure and poured into crushed ice. The residue obtained was filtered, washed with water and recrystallized from ethanol to obtain compound 3a-f

1-(2*H*-Benzo [b] [1, 4] thiazin-1, 1dioxide-3 (4*H*) ylidene) hydrazine (3a)

The title compound was prepared by oxidation of 1-(2*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene) hydrazine 2a. Yield, 36%; m.p. >300°C;  $R_f$ , 0.83 (Toluene-ethylacetate-ethanol 3:1:3); IR ( $\nu$   $\text{cm}^{-1}$ ): 3361, 3322, 3198, 2981, 1664, 1557, 1509, 1474, 1380, 1332, 1160, 1064, 1000, 742, 659  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 3.35 (s, 2H,  $\text{CH}_2$ ), 6.8-7.7 (m, 4H, Ar-H), 8.42 (br, 2H,  $\text{NH}_2$ ), 10.89 (br, 1H, NH);  $^{13}\text{C-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 53.1 ( $\text{CH}_2$ ), 117.1 (CH), 119.8 (CH), 126.9 (C-S), 127.3 (CH), 133.5 (CH), 143.1 (C-N), 154.4 (C = N); MS  $m/z$

(%): 211 (16), 176 (12), 146 (16), 150 (35), 133 (23), 124 (100), 91 (15), 74 (10); Anal. Calcd for  $\text{C}_8\text{H}_9\text{N}_3\text{O}_2\text{S}$ : C, 45.49; H, 4.29; N, 19.89; S, 15.18. Found: C, 45.45; H, 4.32; N, 19.86; S, 15.22.

1-(2*H*-Benzo [b] [1, 4] thiazin-1, 1dioxide-3 (4*H*)-ylidene) -2-phenylhydrazine (3b)

The title compound was prepared by oxidation of 1-(2*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene) -2-phenylhydrazine 2b. Yield, 46%; m.p. >300°C;  $R_f$ , 0.37 (Toluene-ethylacetate-ethanol 3:1:3); IR ( $\nu$   $\text{cm}^{-1}$ ): 3212, 3116, 1665, 1508, 1383, 1318, 1168, 1029, 745, 698, 662  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 3.37 (s, 2H,  $\text{CH}_2$ ), 6.4-8.0 (m, 9H, Ar-H), 10.23 (br, 1H, NH), 11.0 (br, 1H, NH);  $^{13}\text{C-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 53.4 ( $\text{CH}_2$ ), 116.7 (2CH), 118.1 (2CH), 119.1 (CH), 126.9 (CH), 127.5 (C-S), 130.1 (2CH), 133.3 (CH), 143.1 (2C-NH), 154.0 (C = N); MS  $m/z$  (%): 287 (14), 252 (7), 226 (14), 223 (53), 200 (39), 150 (100), 91 (5); Anal. Calcd for  $\text{C}_{14}\text{H}_{13}\text{N}_3\text{O}_2\text{S}$ : C, 58.52; H, 4.56; N, 14.62; S, 11.16. Found: C, 58.50; H, 4.58; N, 14.63; S, 11.15.

1-(2*H*-Benzo [b] [1, 4] thiazin-1, 1dioxide-3 (4*H*)-ylidene) -2-(2, 4-dinitrophenyl) hydrazine (3c)

The title compound was prepared by oxidation of 1-(2*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene) -2-(2, 4-dinitrophenyl) hydrazine 2c. Yield, 42%; m.p. >300°C;  $R_f$ , 0.27 (Toluene-ethylacetate-ethanol 3:1:3); IR ( $\nu$   $\text{cm}^{-1}$ ): 3321, 3298, 1694, 1591, 1427, 1322, 1249, 1144, 1063, 914, 831, 743, 658  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 3.3 (s, 2H,  $\text{CH}_2$ ), 6.9-8.9 (m, 7H, ArH), 11.0 (br, 1H, NH), 11.3 (br, 1H, NH);  $^{13}\text{C-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 53.1 ( $\text{CH}_2$ ), 117.9 (2CH), 119.8 (CH), 120.1 (CH), 126.1 (C-S), 127.6 (2CH), 133.1 (C- $\text{NO}_2$ ), 142.5 (C- $\text{NO}_2$ ), 147.4 (2C-NH), 153.9 (C = N); MS  $m/z$  (%): 377 (12), 342 (25), 316 (52), 299 (35), 290 (25), 240 (100), 91 (10); Anal. Calcd for  $\text{C}_{14}\text{H}_{11}\text{N}_5\text{O}_6\text{S}$ : C, 44.56; H, 2.94; N, 18.56; S, 8.50. Found: C, 44.53; H, 2.92; N, 18.58; S, 8.53.

1-(2-Methyl-2*H*-benzo [b] [1, 4] thiazin -1, 1dioxide-3 (4*H*)-ylidene) hydrazine (3d)

The title compound was prepared by oxidation of 1-(2-methyl-2*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene) hydrazine 2d. Yield, 31%; m.p. 188-190 °C;  $R_f$ , 0.28 (Toluene-ethylacetate-ethanol 3:1:3); IR ( $\nu$   $\text{cm}^{-1}$ ): 3396, 3359, 3166, 2924, 2853, 1669, 1556, 1421, 1356, 1255, 1155, 1060, 991, 858, 807, 764, 716, 648  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 1.23 (d, 3H,  $\text{CH}_3$ ,  $J=6.2$ ), 3.12 (q, 1H, CH), 6.8-7.6 (m, 4H, Ar-H), 8.39 (br, 1H, NH), 10.86 (br, 1H, NH);  $^{13}\text{C-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 7.5 ( $\text{CH}_3$ ), 52.1 (CH), 117.1 (CH), 119.8 (CH), 126.9 (C-S), 127.6 (CH), 133.1 (CH), 143.4 (C-N), 153.1 (C = N); MS  $m/z$  (%): 225 (14), 190 (27), 150 (35), 133 (23), 124 (100), 91 (15); Anal. Calcd for  $\text{C}_9\text{H}_{11}\text{N}_3\text{O}_2\text{S}$ : C, 47.99; H, 4.92; N, 18.65; S, 14.23. Found: C, 48.01; H, 4.90; N, 18.66; S, 14.22.

1-(2-Methyl-2*H*-benzo [b] [1, 4] thiazin-1, 1dioxide-3 (4*H*)-ylidene) -2-phenylhydrazine (3e)

The title compound was prepared by oxidation of 1-(2-methyl-2*H*-benzo [b] [1,4]thiazin-3 (4*H*)-ylidene) -2-phenylhydrazine 2e. Yield, 43%; m.p. 242-244°C;  $R_f$ , 0.70 (Toluene-ethylacetate-ethanol 3:1:3); IR ( $\nu$   $\text{cm}^{-1}$ ): 3249, 3104, 2853, 1670, 1508, 1378, 1318, 1163, 1025, 719, 698, 665  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 1.24 (d, 3H,  $\text{CH}_3$ ,  $J = 6$ ), 3.19 (q, 1H, CH), 6.4-8.0 (m, 9H, Ar-H), 10.23 (br, 1H, NH), 11.00 (br, 1H, NH);  $^{13}\text{C-NMR}$  ( $\delta$  ppm, DMSO- $d_6$ ): 7.4 ( $\text{CH}_3$ ), 52.1 (CH), 116.9 (2CH), 118.6 (2CH), 119.1 (CH), 126.9 (CH), 127.8 (C-S), 130.1 (2CH), 133.5 (CH), 143.1 (2C-NH), 153.1 (C = N); MS  $m/z$  (%): 301 (8), 266 (7), 226 (13), 209 (51), 200 (24), 150 (100), 91 (10); Anal. Calcd for  $\text{C}_{15}\text{H}_{15}\text{N}_3\text{O}_2\text{S}$ : C, 59.78; H, 5.02; N, 13.94; S, 10.64. Found: C, 59.76; H, 5.00;

N, 13.96; S, 10.66.

1-(2-Methyl-2*H*-benzo [b] [1, 4] thiazin-1, 1dioxide-3 (4*H*)-ylidene) -2-(2, 4-dinitrophenyl) hydrazine (3f)

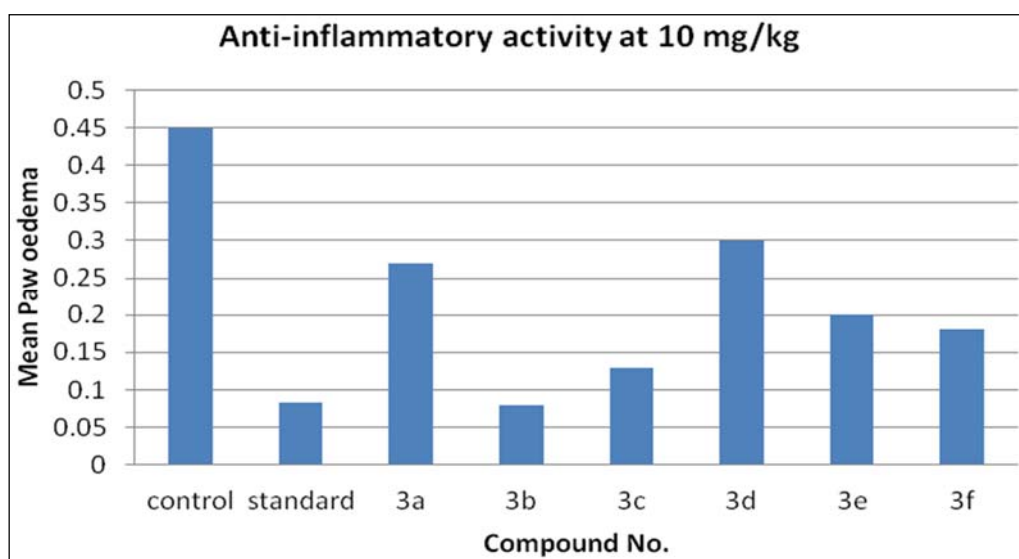
The title compound was prepared by oxidation of 1-(2-methyl-2*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene) -2-(2, 4-dinitrophenyl) hydrazine 2f. Yield, 56%; m.p. 274-276°C;  $R_f$ , 0.78 (Toluene-ethylacetate-ethanol 3:1:3); IR ( $\nu$   $\text{cm}^{-1}$ ): 3358, 3295, 2927, 1690, 1590, 1426, 1339, 1248, 1139, 1059, 905, 831, 765, 731, 647  $\text{cm}^{-1}$ ;  $^1\text{H-NMR}$  ( $\delta$  ppm,  $\text{DMSO-d}_6$ ): 1.25 (d, 3H,  $\text{CH}_3$ ,  $J = 6.3$ ), 3.22 (q, 1H, CH), 6.9-8.9 (m, 7H, ArH), 10.98 (br, 1H, NH), 11.30 (br, 1H, NH);  $^{13}\text{C-NMR}$  ( $\delta$  ppm,  $\text{DMSO-d}_6$ ): 7.6 ( $\text{CH}_3$ ), 52.1 (CH), 117.1 (CH), 119.6 (2CH), 120.1 (CH), 126.9 (C-S), 127.8 (2CH), 133.1 (CH), 142.8 (2C-NH), 147.6 (2C-NO<sub>2</sub>), 153.4 (C = N); MS  $m/z$  (%): 391 (14), 356 (25), 316 (47), 299 (35), 290 (26), 240 (100), 91 (10);

Anal. Calcd for  $\text{C}_{15}\text{H}_{13}\text{N}_5\text{O}_6\text{S}$ : C, 46.03; H, 3.35; N, 17.89; S, 8.19. Found: C, 46.06; H, 3.32; N, 17.85; S, 8.23.

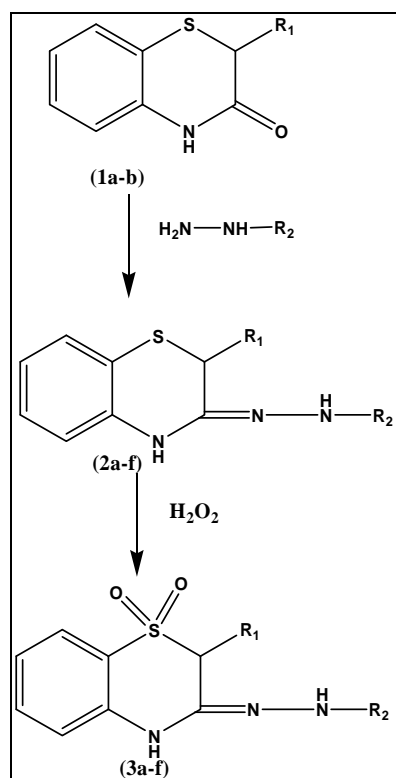
### 3. Tables, Figures and Equations

**Table 1:** Anti-inflammatory activity of compounds at dose 10mg/kg

Compound No.	Mean paw oedema (ml) $\pm$ SEM	Inhibition of oedema (%)
3a	0.27 $\pm$ 0.02	41.7
3b	0.08 $\pm$ 0.03	81.6
3c	0.13 $\pm$ 0.02	70.5
3d	0.30 $\pm$ 0.01	33.3
3e	0.20 $\pm$ 0.00	55.5
3f	0.18 $\pm$ 0.03	59.3



**Graph 1:** Anti-inflammatory activity at dose 10 mg/kg



**Fig 1:** Synthesis of 1-(2*H*-benzo [b] [1, 4] thiazine-3 (4*H*)-ylidene) hydrazine-1, 1-dioxide derivatives.

### 4. Conclusions

In conclusion, we have reported an easy method to prepare 1-(2*H*-benzo [b] [1, 4] thiazin-3 (4*H*)-ylidene) hydrazine-1, 1-dioxide derivatives, using inexpensive reagents and allowing to introduce different hydrazine derivative in the 3-position. It has been noted that compounds 3b and 3c showed the potent anti-inflammatory activity, whereas compounds 3e and 3f showed moderate anti-inflammatory activity. Compounds 3a and 3d showed weak activity as compared to reference.

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