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# Stereospecific synthesis of 2-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acids: enantiomeric excess evaluation by $^1$H NMR

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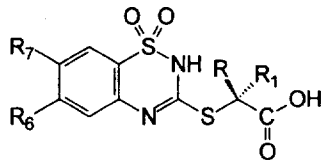
***Abstract:*** A method for the stereospecific synthesis of 2-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acids **1** has been developed. A new example of enantiomer self discrimination which can be conveniently used for the determination of enantiomeric purity by $^1$H NMR spectroscopy without a chiral auxiliary is also reported. © 1997 Elsevier Science Ltd

## Introduction

The stereospecific synthesis of 2-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acids **1** was performed. All these compounds, except for **1e**, were already obtained as racemic mixtures and showed an inhibitory effect on the activity of aldose reductase,[1] whose binding site can recognize inhibitors stereospecifically.[2,3] Moreover such compounds, as analogues of previously studied arylalkanoic acids,[4–7] could be also potential cyclooxygenase inhibitors.



R, $R_1$ = H, $CH_3$ $R_6$, $R_7$ = H, Cl, $CH_3$, $OCH_3$

**1**

| | $R_6$ | $R_7$ |
|---|---|---|
| **1a** | H | H |
| **1b** | Cl | H |
| **1c** | H | Cl |
| **1d** | $CH_3$ | H |
| **1e** | $OCH_3$ | H |

Compounds **1** were synthesized from the corresponding 3-mercaptoderivatives **2** by reaction with (R)- and (S)-2-bromopropanoic acid (**3**)[8] using 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) as dehydrohalogenating agent in acetonitrile at 80°C (Method A) or under mild conditions in DMF with sodium hydride (Method B) (Scheme 1). The enantiomeric excess of the synthesized compounds was evaluated on the methyl esters **4** owing to their improved $CDCl_3$ solubility. The evaluation was carried out by 200 MHz $^1$H NMR spectroscopy using the chiral shift reagent (CSR) Eu(hfc)$_3$ and also without a chiral auxiliary since compounds **4** show self-induced diastereomeric anisochronism (SIDA). This type of enantiomeric discrimination can be observed in NMR spectra of partially enriched enantiomers and the interacting non-racemic chiral influence is represented by aggregation of the same enantiomers.[9–17]

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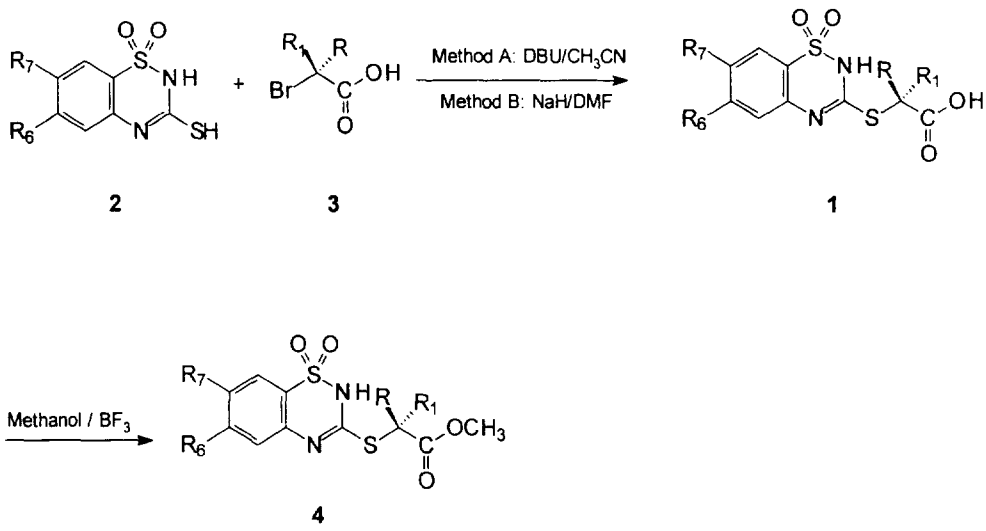


2 3 1 4

Scheme 1.

## Results and discussion

The nucleophilic substitution on 2-bromopropanoic acid (**3**) involves the stereogenic carbon and takes place with Walden inversion at the bromine-bearing atom.[18] With Method B the Walden inversion is almost complete and the title compounds are obtained with high yields and a good enantiomeric excess. Method A causes a racemization whose extent seems to be strongly influenced by benzene ring substitution (Table 1). $CDCl_3$ solutions (0.003–0.01 M) of enantiomer mixtures of esters **4** in the presence of shift reagent (0.5–1 CSR/compound molar ratio) show a large shift of the methoxyl resonance with signal splitting. The absolute configuration of compounds **4** was tentatively attributed by comparison between their $^1H$ NMR spectral data obtained with CSR and those of the previously studied 3-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acid methyl esters.[19] In both series the (S)-derivatives show a $\Delta\Delta\delta$ at higher field and the (R)-compounds at lower field (Figure 1).

Furthermore the $CDCl_3$ solutions of non-racemic mixtures of compounds **4** display separate signals in their $^1H$ NMR spectra due to each enantiomer. The ratio of intensities of these signals corresponds to the molar ratio of enantiomers present in the sample and the e.e.% obtained are in agreement with those obtained by the chiral shift reagent.

The signal separation ($\Delta\delta$) depends on temperature, and maximal $\Delta\delta$ values were measured at lower temperatures (Figure 2, Table 2). The SIDA effect appears to be present not only for methoxyl protons but also for NH and the aromatic ones.

The signals due to the protons of the enantiomer present in the higher concentration appear at lower fields for methoxy estereal and NH groups and at higher fields in the case of the aromatic ones.

The signal separations are directly related to enantiomer ratio, being maximum where the differences in enantiomer contents are also maximum, and are also directly related to overall solution concentration (Figure 3). In fact, pronounced solute–solute hydrogen binding appears to be essential to this phenomenon which is solvent dependent and was not observed in solvents like DMSO-$d_6$ strongly interacting with polar solutes.

It is noteworthy that for the higher homologues series of the 3-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acid methyl esters, above mentioned, the SIDA effect was not observed.

In conclusion the Method B appears to be suitable for obtaining 2-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acids **1** with high yields and relevant enantiomeric excess. The above-

**Table 1**. Comparison of e.e.%[a] calculated with CSR and SIDA

| Compd. | R | $R_1$ | $R_6$ | $R_7$ | e.e. % (Method A) | | e.e. % (Method B) | |
|---|---|---|---|---|---|---|---|---|
| | | | | | CSR | SIDA | CSR | SIDA |
| **(R)-4a** | H | $CH_3$ | H | H | 38.8 ± 2.4 | 38.8 ± 1.0 | 99.2 ± 0.6 | 98.9 ± 1.3 |
| **(S)-4a** | $CH_3$ | H | H | H | 49.3 ± 1.8 | 47.9 ± 1.6 | 91.4 ± 1.7 | 90.7 ± 1.6 |
| **(R)-4b** | H | $CH_3$ | Cl | H | 30.8 ± 0.9 | 31.2 ± 1.5 | 90.5 ± 1.2 | 92.6 ± 1.1 |
| **(S)-4b** | $CH_3$ | H | Cl | H | 43.0 ± 0.9 | 41.5 ± 2.7 | 83.9 ± 1.1 | 83.7 ± 1.3 |
| **(R)-4c** | H | $CH_3$ | H | Cl | rac | rac | 95.0 ± 1.0 | 94.9 ± 0.8 |
| **(S)-4c** | $CH_3$ | H | H | Cl | rac | rac | 80.4 ± 0.9 | 80.3 ± 0.9 |
| **(R)-4d** | H | $CH_3$ | $CH_3$ | H | rac | rac | 99.5 ± 0.4 | 99.5 ± 0.5 |
| **(S)-4d** | $CH_3$ | H | $CH_3$ | H | rac | rac | 90.2 ± 1.1 | 90.4 ± 1.0 |
| **(R)-4e** | H | $CH_3$ | $OCH_3$ | H | 43.0 ± 0.5 | 40.4 ± 0.8 | 96.7 ± 1.9 | 96,3 ± 0.7 |
| **(S)-4e** | $CH_3$ | H | $OCH_3$ | H | 42.2 ± 0.7 | 42.8 ± 0.5 | 92.3 ± 0.9 | 90,1 ± 1.0 |

[a] mean value ± s.d. The mean values were obtained from triplicate experiments.

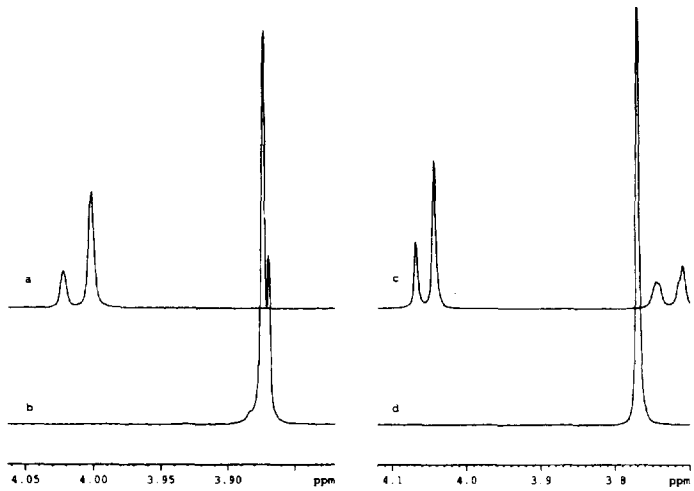


**Figure 1**. $^1H$ NMR signals of **(S)-4a** obtained from **(S)-1a** synthesized with Method A from (R)-2-bromopropanoic acid with CSR (a) and without CSR (b); $^1H$ NMR signals of a 3:7 mixture of (R)- and (S)-3-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]-2-methylpropanoic acid methyl esters with CSR (c) and without CSR (d).

mentioned example of self discrimination of enantiomers is useful for the determination of the enantiomeric purity of synthesized compounds without chiral auxiliary.

## Experimental

Melting points were determined with a Büchi 510 capillary apparatus and are uncorrected. $^1H$ NMR spectra were recorded with a Brucker DPX 200 and AMX-400 FT-NMR spectrometer using $CDCl_3$ and DMSO-$d_6$ as solvents and tetramethylsilane (TMS) as external standard. Chemical shifts are in ppm ($\delta$) and coupling constants (J) in Hz. Multiplicities are abbreviated as follows: s, singlet; d, doublet; m, multiplet; *, $D_2O$ changeable. IR spectra were recorded on a Perkin Elmer Model 1600 FT-IR spectrometer (Nujol mull) and are consistent with the assigned structures. Optical

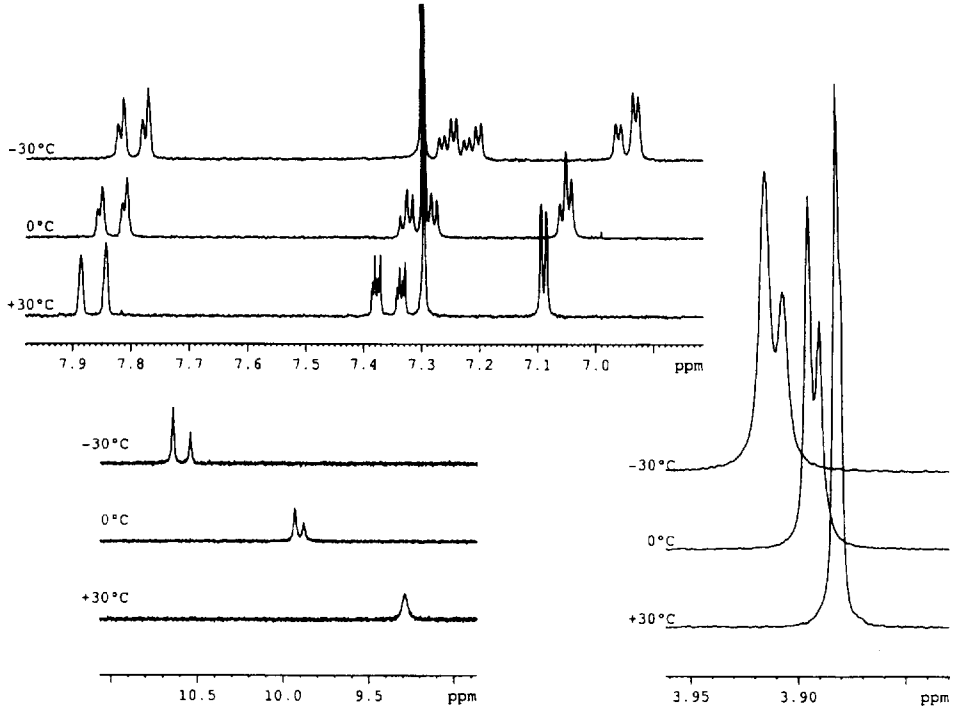


**Figure 2.** $^1$H NMR signals of methyl ester **(R)-4b** e.e. 31.2% at different temperatures.

rotations were measured using a Perkin Elmer 241 polarimeter. The progress of the reaction was followed by thin-layer chromatography (TLC) on aluminium sheets silica gel 60 $F_{254}$, 0.2 mm thick: eluent chloroform–methanol–ammonium hydroxide 6:4:0.5. Elemental analyses were performed in Microanalysis Laboratory of Dipartimento di Scienze Farmaceutiche of Modena University on a Carlo Erba Elemental Analyzer 1106 apparatus.

*2[(2H-1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acids* ***1***

*Method A*: to a solution of the appropriate 3-mercaptoderivative **2** (0.01 mol) in acetonitrile (20 ml per gram), 2-bromopropionic acid **3** (0.012 mol) and DBU (0.012 mol) were added dropwise under stirring at the temperature of 80°C. The reaction mixture was kept in the above conditions for 1 hour, then acetonitrile was evaporated under reduced pressure and the residue dissolved in NaOH 2% (20 ml). After cooling the alkaline solution supplied the title compounds on acidification with HCl until pH=4. The afforded compounds were filtered, washed with water, dried in vacuo and crystallized from appropriate solvents. Yields range between 53 and 92%.

*Method B*: to a suspension of NaH (80% dispersion in mineral oil) (0.01 mol) in DMF anhydrous (3–5 ml per gram) 3-mercaptoderivative **2** (0.005 mol) was added. The resulting mixture was stirred at 0°C for 30 minutes under a nitrogen atmosphere then 2-bromopropanoic acid **3** (0.006 mol) was added dropwise. The reaction mixture was stirred at room temperature for 1 hour then filtered. The filtrate on acidification with HCl afforded the title compounds which were washed with water and, after drying, crystallized from appropriate solvents.

Physicochemical data of compounds obtained with Method B are reported.

*(R)-2-[(2H-1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid* ***(R)-1a***

Yield: 68%. m.p.: 209–211°C (from water). $[\alpha]_D^{20}$=+44.7 (c 0.5, methanol). $^1$H NMR: (DMSO-$d_6$) δ 1.59 (d, J=7.3, 3H), 4.39 (q, J=7.3, 1H), 7.30 (dd, J=1.0, 8.2, 1H), 7.45 (ddd, J=1.0, 7.4, 7.9, 1H), 7.70 (ddd, J=1.3, 7.4, 8.2, 1H), 7.81 (dd, J=1.3, 7.9, 1H), 12.58 (s*, 1H), 13.11 (s*, 1H). IR (Nujol)

**Table 2.** $^1$H NMR chemical shifts of protons for methyl ester **(R)-4b**[a] e.e. 31.2% at different temperatures

| | δ NH (ppm) | | δ $H_8$ arom (ppm) | | δ $H_7$ arom (ppm) | | δ $H_5$ arom (ppm) | | δ $OCH_3$ (ppm) | |
|---|---|---|---|---|---|---|---|---|---|---|
| Temp.°C | R | S | R | S | R | S | R | S | R | S |
| -30 | 10.64 | 10.54 | 7.81 | 7.82 | 7.25 | 7.27 | 6.94 | 6.97 | 3.92 | 3.91 |
| | | | 7.77 | 7.78 | 7.24 | 7.26 | 6.93 | 6.96 | | |
| | | | | | 7.21 | 7.23 | | | | |
| | | | | | 7.20 | 7.22 | | | | |
| -20 | 10.38 | 10.30 | 7.83 | 7.84 | 7.24 | 7.25 | 6.99 | 7.01 | 3.91 | 3.90 |
| | | | 7.78 | 7.79 | 7.23 | 7.24 | 6.98 | 7.00 | | |
| | | | | | b | b | | | | |
| -10 | 10.14 | 10.07 | 7.84 | 7.85 | b | b | b | b | 3.90 | 3.90 |
| | | | 7.80 | 7.81 | | | | | | |
| 0 | 9.93 | 9.88 | 7.85 | 7.86 | b | b | b | b | 3.90 | 3.89 |
| | | | 7.81 | 7.82 | | | | | | |
| +10 | 9.71 | 9.68 | b | b | b | b | b | b | 3.89 | 3.89 |
| +20 | b | b | b | b | b | b | b | b | b | b |
| +30 | b | b | b | b | 7.38 | 7.39 | b | b | b | b |
| | | | | | 7.37 | 7.38 | | | | |
| | | | | | 7.34 | 7.34 | | | | |
| | | | | | 7.33 | 7.33 | | | | |

a $CDCl_3$ solution; total concentration $5.17 \times 10^{-3}$M

b Not resolved peaks

$\nu_{max}$: 3238, 1736, 1377, 1157 cm$^{-1}$. Anal. Calcd. for $C_{10}H_{10}N_2O_2S_4$: C, 41.95; H, 3.52; N, 9.78. Found: C, 41.95; H, 3.51; N, 9.74.

*(S)-2-[(2H-1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid (S)-1a*

Yield: 65%. m.p.: 204–205°C (from water). $[\alpha]_D^{20}$=−41.5 (c 0.5, methanol). $^1$H NMR: (DMSO-$d_6$) δ 1.59 (d, J=7.3, 3H), 4.39 (q, J=7.3, 1H), 7.30 (dd, J=1.0, 8.2,, 1H), 7.45 (ddd, J=1.0, 7.5, 8.0, 1H), 7.70 (ddd, J=1.3, 7.5, 8.0, 1H), 7.81 (dd, J=1.3, 8.0, 1H), 12.57 (s*, 1H), 13.11 (s*, 1H). IR (Nujol) $\nu_{max}$: 3237, 1736, 1377, 1157 cm$^{-1}$. Anal. Calcd. for $C_{10}H_{10}N_2O_2S_4$: C, 41.95; H, 3.52; N, 9.78. Found: C, 41.78; H, 3.54; N, 9.72.

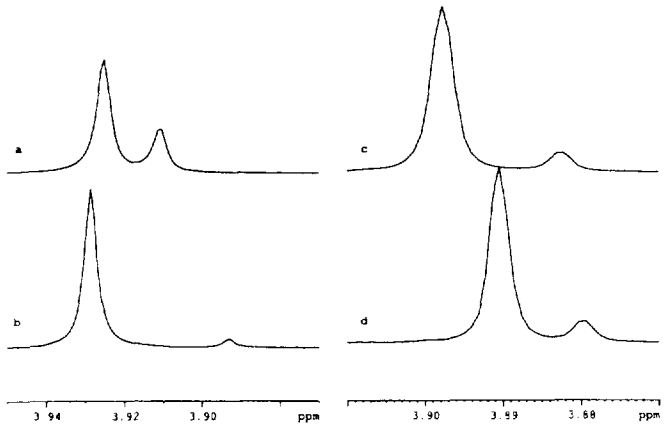


**Figure 3.** $^1$H NMR signals of **(S)-4a** e.e. 47.9% (a), **(S)-4a** e.e. 90.7% (b), **(S)-4c** e.e. 80.3%, total concentration $1.14\times10^{-2}$ M (c) and total concentration $5.1\times10^{-3}$M (d).

*(R)-2-[(6-Chloro-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid* ***(R)-1b***

Yield: 92%. m.p.: 222–225°C (from methanol/water). $[\alpha]_D^{20}$=+29.5 (c 0.5, methanol). $^1$H NMR: (DMSO-$d_6$) δ 1.66 (d, J=7.3, 3H), 4.46 (q, J=7.3, 1H), 7.37 (d, J=2.0, 1H), 7.57 (dd, J=2.0, 8.6, 1H), 7.93 (d, J=8.6, 1H), 12.88 (s*, 1H), 13.19 (s*, 1H). IR (Nujol) $\nu_{max}$: 3252, 1706, 1377, 1160 cm$^{-1}$. Anal. Calcd. for $C_{10}H_9ClN_2O_4S_2$: C, 37.44; H, 2.83; N, 8.73. Found: C, 37.64; H, 2.97; N, 8.52.

*(S)-2-[(6-Chloro-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid* ***(S)-1b***

Yield: 86%. m.p.: 226–229°C (from methanol/water). $[\alpha]_D^{20}$=−24.3 (c 0.5, methanol). $^1$H NMR: (DMSO-$d_6$) δ 1.66 (d, J=7.3, 3H), 4.46 (q, J=7.3, 1H), 7.37 (d, J=2.0, 1H), 7.58 (dd, J=2.0, 8.6, 1H), 7.93 (d, J=8.6, 1H), 12.80 (s*, 1H), 13.26 (s*, 1H). IR (Nujol) $\nu_{max}$: 3252, 1708, 1378, 1159 cm$^{-1}$. Anal. Calcd. for $C_{10}H_9ClN_2O_4S_2$: C, 37.44; H, 2.83; N, 8.73. Found: C, 37.72; H, 3.00; N, 8.84.

*(R)-2-[(7-Chloro-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid* ***(R)-1c***

Yield: 98%. m.p.: 209–211°C (from methanol/water). $[\alpha]_D^{20}$=+38.2 (c 0.5, methanol). $^1$H NMR: (DMSO-$d_6$) δ 1.59 (d, J=7.3, 3H), 4.39 (q, J=7.3, 1H), 7.32 (d, J=8.8, 1H), 7.76 (dd, J=2.3, 8.8, 1H), 7.87 (d, J=2.3, 1H), 12.76 (s*, 1H), 12.79 (s*, 1H). IR (Nujol) $\nu_{max}$: 3247, 1730, 1381, 1159 cm$^{-1}$. Anal. Calcd. for $C_{10}H_9ClN_2O_4S_2$: C, 37.44; H, 2.83; N, 8.73. Found: C, 37.41; H, 2.83; N, 8.66.

*(S)-2-[(7-Chloro-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid* ***(S)-1c***

Yield: 89%. m.p.: 205–208°C (from methanol/water). $[\alpha]_D^{20}$=−35.3 (c 0.5, methanol). $^1$H NMR: (DMSO-$d_6$) δ 1.59 (d, J=7.3, 3H), 4.39 (q, J=7.3, 1H), 7.32 (d, J=8.8, 1H), 7.76 (dd, J=2.3, 8.8, 1H), 7.86 (d, J=2.3, 1H), 12.77 (s*, 1H), 12.80 (s*, 1H). IR (Nujol) $\nu_{max}$: 3248, 1730, 1379, 1159 cm$^{-1}$. Anal. Calcd. for $C_{10}H_9ClN_2O_4S_2$: C, 37.44; H, 2.83; N, 8.73. Found: C, 37.51; H, 2.98; N, 8.47.

*(R)-2-[(6-Methyl-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid* ***(R)-1d***

Yield: 82%. m.p.: 218–220°C (from methanol/water). $[\alpha]_D^{20}$=+35.8 (c 0.5, methanol). $^1$H NMR: (DMSO-$d_6$) δ 1.66 (d, J=7.3, 3H), 2.48 (s, 3H), 4.46 (q, J=7.3, 1H), 7.14 (s, 1H), 7.35 (d, J=8.1, 1H), 7.77 (d, J=8.1, 1H), 12.55 (s*, 1H), 13.25 (s*, 1H). IR (Nujol) $\nu_{max}$: 3237, 1736, 1379, 1184 cm$^{-1}$. Anal. Calcd. for $C_{11}H_{12}N_2O_4S_2$: C, 43.84; H, 4.02; N, 9.30. Found: C, 43.81; H, 4.00; N, 9.20.

*(S)-2-[(6-Methyl-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid* ***(S)-1d***

Yield: 95%. m.p.: 215–217°C (from methanol/water). $[\alpha]_D^{20}$=−32.7 (c 0.5, methanol). $^1$H NMR: (DMSO-$d_6$) δ 1.59 (d, J=7.3, 3H), 2.40 (s, 3H), 4.38 (q, J=7.3, 1H), 7.06 (s, 1H), 7.27 (d, J=8.2, 1H), 7.69 (d, J=8.2, 1H), 12.45 (s*, 1H), 13.25 (s*, 1H). IR (Nujol) $\nu_{max}$: 3237, 1736, 1378, 1183 cm$^{-1}$. Anal. Calcd. for $C_{11}H_{12}N_2O_4S_2$: C, 43.84; H, 4.02; N, 9.30. Found: C, 43.99; H, 3.99; N, 9.27.

*(R)-2-[(6-Methoxy-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid* ***(R)-1e***

Yield: 67%. m.p.: 190–192°C (from methanol/water). $[\alpha]_D^{20}$=+28.4 (c 0.5, methanol). $^1$H NMR: (DMSO-$d_6$) δ 1.58 (d, J=7.3, 3H), 3.85 (s, 3H), 4.37 (q, J=7.3, 1H), 6.73 (d, J=2.4, 1H), 7.02 (dd, J=2.4, 8.9, 1H), 7.72 (d, J=8.9, 1H), 12.51 (s*, 2H). IR (Nujol) $\nu_{max}$: 3252, 1711, 1374, 1160 cm$^{-1}$. Anal. Calcd. for $C_{11}H_{12}N_2O_5S_2 \cdot 0.5H_2O$: C, 40.61; H, 4.03; N, 8.61. Found: C, 40.93; H, 3.93; N, 8.32.

*(S)-2-[(6-Methoxy-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid* ***(S)-1e***

Yield: 69%. m.p.: 195–198°C (from methanol/water). $[\alpha]_D^{20}$=−26.0 (c 0.5, methanol). $^1$H NMR: (DMSO-$d_6$) δ 1.58 (d, J=7.3, 3H), 3.85 (s, 3H), 4.37 (q, J=7.3, 1H), 6.73 (d, J=2.4, 1H), 7.03 (dd, J=2.4, 8.9, 1H), 7.72 (d, J=8.9, 1H), 12.43 (s*, 1H), 13.12 (s*, 1H). IR (Nujol) $\nu_{max}$: 3252, 1711, 1373, 1161 cm$^{-1}$. Anal. Calcd. for $C_{11}H_{12}N_2O_5S_2 \cdot 0.5H_2O$: C, 40.61; H, 4.03; N, 8.61. Found: C, 40.32; H, 3.73; N, 8.46.

*2-[(2H-1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid methyl esters* ***4***

A 0.1 g (0.3 mmol) amount of the appropriate 2-[(2*H*-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid was treated with methanol (3 ml) in the presence of boron trifluoride (3.9 mmol) and the obtained solution was refluxed for 20 minutes. After methanol excess removal under reduced pressure the crude product was tritured with 15 ml of water, filtered, dried and crystallized from methanol and water to obtain the corresponding ester.

*(R)-2-[(2H-1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid methyl ester* ***(R)-4a***

Yield: 96%. m.p.: 181°C. $[\alpha]_D^{20}$=+89.3. (c 0.5, methanol). $^1$H NMR ($CDCl_3$) δ 1.67 (d, J=7.4, 3H), 3.88 (s, 3H), 4.56 (q, J=7.4, 1H), 7.06 (dd, J=0.9, 8.0, 1H), 7.33 (ddd, J=0.9, 7.8, 7.9, 1H), 7.51 (ddd, J=1.5, 7.8, 8.0, 1H), 7.88 (dd, J=1.5, 7.9, 1H), 9.53 (s*, 1H). IR (Nujol) $\nu_{max}$: 3231, 1735, 1377, 1164 cm$^{-1}$. Anal. Calcd. for $C_{11}H_{12}N_2O_4S_2$: C, 43.99; H, 4.03; N, 9.33. Found: C, 44.06, H, 4.06 N, 9.26.

*(S)-2-[(2H-1,2,4-Benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid methyl ester* ***(S)-4a***

Yield: 96%. m.p.: 184°C. $[\alpha]_D^{20}$=−85.3 (c 0.5, methanol). $^1$H NMR ($CDCl_3$) δ 1.68 (d, J=7.4, 3H), 3.88 (s, 3H), 4.56 (q, J=7.4, 1H), 7.07 (dd, J=0.9,8.0, 1H), 7.34 (ddd, J=0.9, 7.8, 7.9, 1H), 7.52 (ddd, J=1.5, 7.8, 8.0, 1H), 7.89 (dd, J=1.5, 7.9, 1H), 9.44 (s*, 1H). IR (Nujol) $\nu_{max}$: 3228, 1730, 1376, 1156 cm$^{-1}$. Anal. Calcd. for $C_{11}H_{12}N_2O_4S_2$: C, 43.99; H, 4.03; N, 9.33. Found: C, 44.03, H, 4.05 N, 9.18.

*(R)-2-[(6-Chloro-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid methyl ester* ***(R)-4b***

Yield: 87%. m.p.: 212°C. $[\alpha]_D^{20}$=+71.4. (c 0.5, methanol). $^1$H NMR ($CDCl_3$) δ 1.69 (d, J=7.4, 3H), 3.88 (s, 3H), 4.56 (q, J=7.4, 1H), 7.07 (d, J=1.8, 1H), 7.32 (dd, J=1.8, 8.4, 1H), 7.84 (d, J=8.4, 1H), 9.78 (s*, 1H). IR (Nujol) $\nu_{max}$: 3219, 1741, 1388, 1160 cm$^{-1}$. Anal. Calcd. for $C_{11}H_{11}ClN_2O_4S_2$: C, 39.46 H, 3.31; N, 8.37. Found: C, 39.40, H, 3.31, N, 8.34.

*(S)-2-[(6-Chloro-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid methyl ester* ***(S)-4b***

Yield: 96%. m.p.: 206°C. $[\alpha]_D^{20}$=−60.0 (c 0.5, methanol). $^1$H NMR ($CDCl_3$) δ 1.69 (d, J=7.4, 3H), 3.88 (s, 3H), 4.55 (q, J=7.4, 1H), 7.07 (d, J=1.8, 1H), 7.31 (dd, J=1.8, 8.5, 1H), 7.84 (d, J=8.5, 1H), 9.76 (s*, 1H). IR (Nujol) $\nu_{max}$: 3218, 1742, 1384, 1158 cm$^{-1}$. Anal. Calcd. for $C_{11}H_{11}ClN_2O_4S_2$: C, 39.46 H, 3.31; N, 8.37. Found: C, 39.43, H, 3.35, N, 8.28.

*(R)-2-[(7-Chloro-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid methyl ester* ***(R)-4c***

Yield: 96%. m.p.: 135–137°C. $[\alpha]_D^{20}$=+84.7 (c 0.5, methanol). $^1$H NMR ($CDCl_3$) δ 1.69 (d, J=7.4, 3H), 3.90 (s, 3H), 4.55 (q, J=7.4, 1H), 6.98 (d, J=8.8, 1H), 7.43 (dd, J=2.3, 8.8, 1H), 7.82 (d, J=2.3, 1H), 9.88 (s*, 1H). IR (Nujol) $\nu_{max}$: 3239, 1751, 1378, 1160 cm$^{-1}$. Anal. Calcd. for $C_{11}H_{11}ClN_2O_4S_2$: C, 39.46; H, 3.31; N, 8.37. Found: C, 39.49, H, 3.44, N, 8.31.

*(S)-2-[(7-Chloro-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid methyl ester* ***(S)-4c***

Yield: 96%. m.p.: 143–148°C. $[\alpha]_D^{20}=-73.2$ (c 0.5, methanol). $^1$H NMR ($CDCl_3$) δ 1.69 (d, J=7.4, 3H), 3.89 (s, 3H), 4.54 (q, J=7.4, 1H), 7.02 (d, J=8.7, 1H), 7.47 (dd, J=2.2, 8.7 1H), 7.83 (d, J=2.2, 1H), 9.62 (s*, 1H). IR (Nujol) $\nu_{max}$: 3229, 1748, 1380, 1167 cm$^{-1}$. Anal. Calcd. for $C_{11}H_{11}ClN_2O_4S_2$: C, 39.46; H, 3.31; N, 8.37. Found: C, 39.47; H, 3.44; N, 8.29.

*(R)-2-[(6-Methyl-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid methyl ester* ***(R)-4d***

Yield: 96%. m.p.: 182–184°C. $[\alpha]_D^{20}=+83.2$ (c 0.5, methanol). $^1$H NMR ($CDCl_3$) δ 1.67 (d, J=7.4, 3H), 2.39 (s, 3H), 3.88 (s, 3H), 4.55 (q, J=7.4, 1H), 6.82 (s, 1H), 7.11 (d, J=8.1, 1H), 7.74 (d, J=8.1, 1H), 9.32 (s*, 1H). IR (Nujol) $\nu_{max}$: 3232, 1742, 1378, 1162 cm$^{-1}$. Anal. Calcd. for $C_{12}H_{14}N_2O_4S_2$: C, 45.85; H, 4.49; N, 8.91. Found: C, 45.87; H, 4.51; N, 8.85.

*(S)-2-[(6-Methyl-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid methyl ester* ***(S)-4d***

Yield: 96%. m.p.: 176–179°C. $[\alpha]_D^{20}=-72.5$. (c 0.5, methanol). $^1$H NMR ($CDCl_3$) δ 1.67 (d, J=7.4, 3H), 2.38 (s, 3H), 3.88 (s, 3H), 4.55 (q, J=7.4, 1H), 6.82 (s, 1H), 7.11 (d, J=8.1, 1H), 7.74 (d, J=8.1, 1H), 9.35 (s*, 1H). IR (Nujol) $\nu_{max}$: 3231, 1741, 1378, 1161 cm$^{-1}$. Anal. Calcd. for $C_{12}H_{14}N_2O_4S_2$: C, 45.85; H, 4.49; N, 8.91. Found: C, 45.90; H, 4.49; N, 8.82.

*(R)-2-[(6-Methoxy-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid methyl ester* ***(R)-4e***

Yield: 86%. m.p.: 166–167°C. $[\alpha]_D^{20}=+73.2$. (c 0.5, methanol). $^1$H NMR ($CDCl_3$) δ 1.67 (d, J=7.4, 3H), 3.87 (s, 6H), 4.54 (q, J=7.4, 1H), 6.49 (d, J=2.3, 1H), 6.86 (dd, J=2.3, 8.9, 1H), 7.76 (d, J=8.9, 1H), 9.38 (s*, 1H). IR (Nujol) $\nu_{max}$: 3241, 1740, 1360, 1158 cm$^{-1}$. Anal. Calcd. for $C_{12}H_{14}N_2O_5S_2$: C, 43.63; H, 4.27; N, 8.48. Found: C, 43.45; H, 4.14; N, 8.40.

*(S)-2-[(6-Methoxy-2H-1,2,4-benzothiadiazine-1,1-dioxide-3-yl)thio]propanoic acid methyl ester* ***(S)-4e***

Yield: 86%. m.p.: 163–165°C. $[\alpha]_D^{20}=-66.0$ (c 0.5, methanol). $^1$H NMR ($CDCl_3$) δ 1.67 (d, J=7.4, 3H), 3.87 (s, 6H), 4.54 (q, J=7.4, 1H), 6.50 (d, J=2.3, 1H), 6.86 (dd, J=2.3, 8.9, 1H), 7.76 (d, J=8.9, 1H), 9.35 (s*, 1H). IR (Nujol) $\nu_{max}$: 3242, 1740, 1360, 1159 cm$^{-1}$. Anal. Calcd. for $C_{12}H_{14}N_2O_5S_2$: C, 43.63; H, 4.27; N, 8.48. Found: C, 43.64; H, 4.21; N, 8.22.

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