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Synthesis of 6- and 7-acyl-4*H*-benzothiazin-3-ones

Pascal Carato,[a,*] Ziaeddine Moussavi,[b] Ahmed Sabaouni,[a] Nicolas Lebegue,[a] Pascal Berthelot[a] and Saïd Yous[a]

[a]*Laboratoire de Chimie Thérapeutique, Faculté de Pharmacie, EA 1043, 3, rue du Professeur Laguesse, BP 83, 59006 Lille Cedex, France*
[b]*Faculty of Pharmacy, Salman Street, Sari, Iran*

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Abstract—Synthesis of 6- and 7-substituted benzoxazin-3-ones was already described in the literature by acylation of the corresponding benzoxazin-3-ones or cyclization of the corresponding 4- or 5-acyl-2-aminophenols. This paper describes original synthetic pathways to afford the 6- and 7-acyl products in the benzothiazin-3-one series, respectively, via Stille coupling reaction and by acylation.
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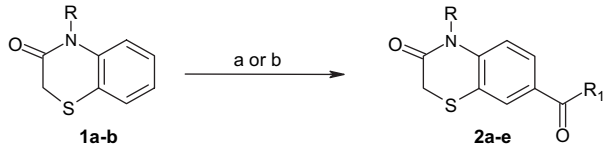
1. Introduction

The chemistry of benzoxazin-3-one and benzothiazin-3-one heterocycles has been offering for years an attractive pathway to lots of new synthetic methods and transformations. Benzothiazin-3-ones, in fact, have gained substantial interest in the scientific community not only due to their meaningful biological activity, but also as reactive intermediates and as starting materials in a wide range of synthesis.[1–3]

Direct acylation of the benzoxazin-3-one heterocycle at the C-6 position is well described in the literature[4–7] and leads to products in accordance with theoretical study of the electronic effects.[8] Indeed, two distinct electronic effects were generated by a substituent: the mesomeric and the inductive effects. The basis of the inductive effect is probably complex but originates in part from differences in electronegativity. For the benzoxazin-3-one heterocycle, not only the withdrawing effect of the amide but also the donating and the inductive effects of the oxygen allowed the introduction of the electrophile group logically towards the *para* position of the oxygen to give 6-acylbenzoxazin-3-ones. However, the direct acylation of benzothiazin-3-one at the C-6 position is less described in the literature. We have only found some patents[9–11] describing results that are not consistent with the expected electronic effects-related reactivity.[8] In Friedel–Crafts conditions, the mesomeric effects, with benzothiazin-3-one or benzoxazin-3-one, of the amide and the sulfur or oxygen are quite identical. However, the electronegativities, implicated in the inductive effect, of oxygen and sulfur atoms are strongly different (S: 2.5, N: 3.0, O: 3.5). Therefore, the electrophile group could be introduced at the *para* position of the nitrogen affording the corresponding 7-acylbenzothiazin-3-ones.

The obvious disagreement between literature and theoretical electronic effects has prompted us to study the acylation of the benzothiazinonic ring. In the first attempt, we acylated this heterocycle directly, according to different methods, in polyphosphoric acid (PPA) and in the mixture $AlCl_3$–DMF with the corresponding carboxylic acid or acid chloride, respectively; the structures of obtained compounds **2a–d** (Scheme 1) were confirmed by full spectral data. In the second attempt, we have realized two unequivocal syntheses to afford 6- or 7-acylbenzothiazin-3-ones (Schemes 2 and 3) in order to have a reference of each position isomer.



Scheme 1. Synthesis of 7-acylbenzothiazin-3-ones **2a–e** by direct acylation. (a) PPA, R_1CO_2H; (b) $AlCl_3$–DMF, R_1COCl.

Keywords: Benzothiazin-3-one; Friedel–Crafts acylation; Stille coupling.
* Corresponding author. Tel.: +33 320964040; fax: +33 320964913; e-mail: pascal.carato@univ-lille2.fr

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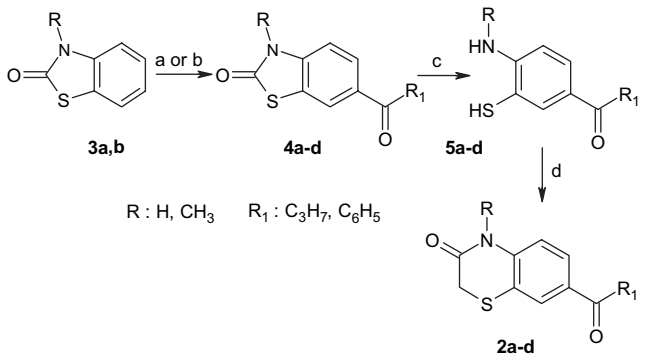
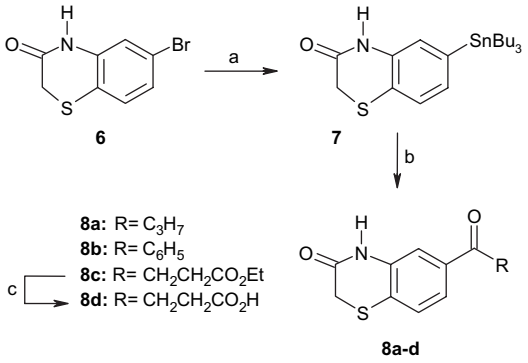


Scheme 2. Synthesis of 7-acylbenzothiazin-3-ones **2a–d** by cyclization of the 5-acyl-2-aminothiophenols **5a–d**. (a) PPA, $C_6H_5CO_2H$; (b) $AlCl_3$–DMF, $C_3H_7CO_2Cl$; (c) (i) KOH, (ii) HCl, (iii) $NaHCO_3$; (d) EtONa, $BrCH_2CO_2C_2H_5$, DMSO.



Scheme 3. Synthesis of 6-acylbenzothiazin-3-one **8a–d** via 6-tributyltin benzothiazin-3-one **7**. (a) $(Bu_3Sn)_2$, $Pd(PPh_3)_4$, toluene under argon; (b) RCOCl, $PdCl_2(PPh_3)_2$, toluene under argon; (c) (i) KOH, EtOH, H_2O, (ii) HCl.

2. Results and discussion

2.1. Synthesis of 7-acylbenzothiazin-3-ones by direct acylation

Benzothiazin-3-one derivatives **1a** and **b** were acylated by using either acyl chloride in the mixture $AlCl_3$–DMF or carboxylic acid in PPA to give the corresponding 7-acylbenzothiazin-3-one derivatives **2a–d** (Scheme 1). It was confirmed by full NMR spectral data (^{2}H COESY, ROESY, HMBC, HSQC) that compounds **2a–d** obtained by Friedel–Crafts conditions were not substituted in the C-6 position but in the C-7 position, in accordance with theoretical study of the electronic effects.

2.2. Synthesis of 7-acylbenzothiazin-3-ones 2a–d by unequivocal way

In order to confirm these structural data, we have realized the unequivocal synthesis of 7-acylbenzothiazin-3-ones **2a–d** by cyclization of the corresponding 5-acyl-2-aminothiophenols **5a–d** (Scheme 2).

6-Acylbenzothiazolin-2-ones **4a–d** were prepared according to literature procedure[12] from the corresponding benzothiazolin-2-ones **3a** and **b**. Ring opening under strong basic conditions of 6-acylbenzothiazolin-2-ones **4a–d** afforded the corresponding 5-acyl-2-aminothiophenols **5a–d** followed by cyclization using ethyl bromoacetate and sodium ethylate in DMSO,[13] which supplied compounds **2a–d** (Scheme 2) with identical physico-chemical characteristics as compounds obtained by direct acylation (Scheme 1).

6-Acylbenzothiazin-3-ones were described in the literature by cyclization of the corresponding 4-chloro-3-nitrophenylacyl derivatives.[14,15] A new approach was developed in two steps to afford original 6-acylbenzothiazin-3-ones **8a–c** (Scheme 3).

2.3. Synthesis of 6-acylbenzothiazin-3-ones 8a–c

6-Bromobenzothiazin-3-one[16] (**6**) was treated with $Pd(PPh_3)_4$ and $(Bu_3Sn)_2$ in toluene under argon to afford 6-tributyltinbenzothiazin-3-one (**7**). Reaction of derivative **7** with the corresponding acid chloride was then performed in toluene under argon with $PdCl_2(PPh_3)_2$ to give the 6-acylbenzothiazin-3-ones **8a–c**. This synthetic pathway developed, in two steps, allows access to various 6-acylbenzothiazin-3-ones (Scheme 3).

Spectral data of compounds **8a** and **b** obtained in Scheme 3 were strongly different from those found for compounds **2a** and **c** obtained by direct acylation (Scheme 1). Melting points differed for compounds **8a**, **2a** and for compounds **2c**, **8b** from 20 to 30 °C.

Combs[9,10] described the synthesis of 6-(4-oxobutyric)benzothiazin-3-one (**8d**) by acylation of the corresponding benzothiazin-3-ones in the mixture $AlCl_3$–DMF with succinic anhydride, which was not in agreement with our results. We have realized the acylation of the benzothiazin-3-one in the Combs conditions, who used ethylsuccinyl chloride and obtained derivative **2e** (Scheme 1). Full NMR spectral data confirmed that the substitution occurred at the C-7 position of the benzothiazin-3-one, as in all derivatives **2a–d** synthesized in Schemes 1 and 2. (4-Oxobutyric)benzothiazin-3-one substituted at the C-6 position was also synthesized by the unequivocal way described in Scheme 3, starting from the stannic intermediate **7** and ethylsuccinyl chloride. The 6-(ethyl-4-oxobutyrate) intermediate **8c** was obtained, followed by hydrolysis in a solution of ethanol/water with KOH leading to acid **8d** whose physico-chemical characteristics were strongly different from those for 7-(4-oxobutyric)benzothiazin-3-one **2e**.

3. Conclusion

Friedel–Crafts acylations of benzothiazin-3-ones using either $AlCl_3$–DMF mixture or PPA led to the 7-acyl derivatives **2a–d**, in accordance with the theoretical study of the electronic effects. It was confirmed by full NMR spectral data and unambiguous synthesis. In order to access 6-acylbenzothiazin-3-ones **8a–c**, we have developed a new synthetic pathway using Stille coupling with 6-tributyltinbenzothiazin-3-one intermediate. This work proves that synthesis of 6-acylbenzothiazin-3-ones from direct acylation of benzothiazin-3-one, as Combs described in the literature,[9,10] is not in agreement with our results and the electronic effect rules on this heterocycle ring.

4. Experimental

4.1. General

All compounds were purified by recrystallization in different solvents and their purity was determined by TLC. Melting points were determined by a Büchi 510 capillary apparatus and are uncorrected. Elemental analyses were performed at C.N.R.S centre Vernaison, France and were within ±0.4% of the theoretical values. Infrared spectra were obtained on a Nicolet 550-FT spectrometer on KBr paths. ^{1}H and ^{2}H NMR proton spectra were recorded on a Bruker FT-80 spectrometer and chemical shifts are in parts per million with TMS as internal standard.

4.2. General procedure for the synthesis of 7-acyl-4*H*-benzothiazin-3-one derivatives (2a–e)

The method adopted for the synthesis of 7-acyl-4*H*-benzothiazin-3-ones (**2a–e**) is described in PPA and in the mixture $AlCl_3$–DMF. Under mechanical stirring, to a mixture of benzothiazin-3-one **1a** (16.4 g, 100 mmol) in 100 g of polyphosphoric acid was added portionwise the corresponding acid (130 mmol). The resulting mixture was heated at 110 °C for 4 h. After cooling, the reaction mixture was poured into ice-water (1 L), and the resulting precipitate was filtered, washed with water, dried and recrystallized.

Reaction with $AlCl_3$–DMF: to 112 g of $AlCl_3$ (53.5 g, 400 mmol) was added dropwise anhydrous DMF (17.2 mL, 230 mmol) under stirring. To the mixture heated at 50 °C, benzothiazin-3-one **1a** (16.4 g, 100 mmol) and the corresponding acid chloride (130 mmol) were added. The mixture was heated at 90 °C for 4 h, poured into ice-water (1 L), and the resulting precipitate was filtered, washed with water, dried and recrystallized.

4.2.1. 7-Butyryl-4*H*-benzothiazin-3-one (2a). Recrystallization from acetone gave **2a** in 81% yield; mp 191–193 °C; IR (KBr, ν cm^{-1}) 3200 (NH), 1670 and 1645 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.95 (t, 3H, J=5.90 Hz, CH_3), 1.55 (m, 2H, CH_2), 2.75 (t, 2H, J=6.05 Hz, CH_2), 3.50 (s, 2H, CH_2), 6.95 (d, 1H, J=8.15 Hz, H_5), 7.55 (d, 1H, J=1.25 Hz, H_8), 7.70 (dd, 1H, J=8.15 Hz, J=1.25 Hz, H_6), 10.50 (s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.27; H, 5.57; N, 5.91; S, 13.61. Found: C, 61.03; H, 5.54; N, 5.74; S, 13.84.

4.2.2. 7-Butyryl-4-methyl-4*H*-benzothiazin-3-one (2b). Recrystallization from ethanol gave **2b** in 80% yield; mp 109–111 °C; IR (KBr, ν cm^{-1}) 1670 and 1640 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.00 (t, 3H, J=5.50 Hz, CH_3), 1.50 (m, 2H, CH_2), 2.80 (t, 2H, J=6.50 Hz, CH_2), 3.40 (s, 3H, CH_3), 3.50 (s, 2H, CH_2), 7.10 (d, 1H, J=8.00 Hz, H_5), 7.60 (d, 1H, J=1.40 Hz, H_8), 7.75 (dd, 1H, J=8.00 Hz, J=1.40 Hz, H_6). Anal. Calcd for $C_{13}H_{15}NO_2S$: C, 62.64; H, 6.07; N, 5.62; S, 13.61. Found: C, 62.90; H, 6.02; N, 5.67; S, 12.93.

4.2.3. 7-Benzoyl-4*H*-benzothiazin-3-one (2c). Recrystallization from acetone gave **2c** in 55% yield; mp 210–212 °C; IR (KBr, ν cm^{-1}) 3196 (NH), 1694 and 1645 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.50 (s, 2H, CH_2), 7.10 (d, 1H, J=8.30 Hz, H_5), 7.50–7.60 (m, 3H, H_6, H_{Ar}), 7.70–7.80 (m, 4H, H_8, H_{Ar}), 10.50 (s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.91; H, 4.12; N, 5.20; S, 11.88. Found: C, 66.81; H, 4.27; N, 5.06; S, 11.23.

4.2.4. 7-Benzoyl-4-methyl-4*H*-benzothiazin-3-one (2d). Recrystallization from ethanol gave **2d** in 75% yield; mp 130–132 °C; IR (KBr, ν cm^{-1}) 1670 and 1640 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ=3.40 (s, 3H, CH_3), 3.50 (s, 2H, CH_2), 7.10 (d, 1H, J=8.20 Hz, H_5), 7.50–7.80 (m, 7H, H_6, H_8, H_{Ar}). Anal. Calcd for $C_{16}H_{13}NO_2S$: C, 66.44; H, 4.84; N, 5.16; S, 11.79. Found: C, 66.61; H, 4.70; N, 5.52; S, 11.70.

4.2.5. 7-(4-Oxobutyric)-4*H*-benzothiazin-3-one (2e). Recrystallization from ethanol gave **2e** in 63% yield; mp 173–174 °C; IR (KBr, ν cm^{-1}) 3189 (NH), 1701 (COO), 1678 (CON), 1647 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.60 (t, 2H, J=7.00 Hz, CH_2COO), 3.20 (t, 2H, J=7.00 Hz, CH_2CO), 2.55 (s, 2H, CH_2), 7.45 (d, 1H, J=8.20 Hz, H_5), 7.55 (d, 1H, J=1.75 Hz, H_8), 7.60 (d, 1H, J=8.20 Hz, J=1.75 Hz, H_6), 11.75 (s, 1H, NH, exchangeable with D_2O), 12.30 (br s, 1H, OH, exchangeable with D_2O). Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28; S, 12.09. Found: C, 54.64; H, 4.41; N, 5.14; S, 12.35.

4.3. General procedure for the synthesis of 5-acyl-2-aminothiophenol derivatives (5a–d)

6-Acyl-2(3*H*)-benzothiazolone (**4a–d**) (20 mmol) and KOH powder (5.6 g, 100 mmol) were heated at fusion during 1 h under nitrogen. The residue was poured into 100 mL of cold water and filtered. The aqueous solution was extracted with diethyl ether, acidified (pH=3) by 12 M HCl solution, then the pH adjusted to 8 with aqueous solution of sodium hydrogen carbonate. The precipitate was filtered, washed with water and recrystallized.

4.3.1. 5-Butyryl-2-aminothiophenol (5a). Recrystallization from acetone gave **5a** in 60% yield; mp 187–188 °C; IR (KBr, ν cm^{-1}) 3410 (NH), 3350 (SH), 1645 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ=0.90 (t, 3H, CH_3), 1.50 (m, 2H, CH_2), 2.60 (t, 2H, CH_2), 6.25 (br s, 3H, NH_2 and SH, exchangeable with D_2O), 6.75 (d, 1H, J=7.80 Hz, H_3), 7.40 (d, 1H, J=1.10 Hz, H_6), 7.70 (dd, 1H, J=7.80 Hz, J=1.10 Hz, H_4). Anal. Calcd for $C_{10}H_{13}NOS$: C, 60.14; H, 6.81; N, 7.10; S, 16.02. Found: C, 60.42; H, 6.41; N, 6.92; S, 16.33.

4.3.2. 5-Butyryl-2-methylaminothiophenol (5b). Recrystallization from ethanol gave **5b** in 70% yield; mp 117–118 °C; IR (KBr, ν cm^{-1}) 3400 (NH), 3350 (SH), 1640 (CO), 1580 (C=C); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.90 (t, 3H, J=6.20 Hz, CH_3), 2.45 (m, 2H, CH_2), 2.65 (t, 2H, J=6.05 Hz, CH_2), 2.95 (s, 3H, CH_3), 4.20–3.80 (br s, 2H, NH and SH, exchangeable with D_2O), 6.60 (d, 1H, J=8.00 Hz, H_3), 7.70 (d, 1H, J=1.20 Hz, H_6), 7.90 (dd, 1H, J=8.00 Hz, J=1.20 Hz, H_4). Anal. Calcd for $C_{11}H_{15}NOS$: C, 63.14; H, 6.71; N, 6.69; S, 15.29. Found: C, 63.50; H, 6.71; N, 6.55; S, 15.35.

4.3.3. 5-Benzoyl-2-aminothiophenol (5c). Recrystallization from acetone gave **5c** in 60% yield; mp 208–210 °C; IR (KBr, ν cm^{-1}) 3500 (NH), 3300 (SH), 1650 (CO), 1590 (C=C); ^{1}H NMR (300 MHz, DMSO-d_6): δ=6.25 (br s, 3H, NH_2 and SH, exchangeable with D_2O), 6.75 (d, 1H, J=8.30 Hz, H_3), 7.45–7.60 (m, 6H, H_6, H_{Ar}), 7.80 (dd, 1H, J=8.30 Hz, J=1.05 Hz, H_4). Anal. Calcd for $C_{13}H_{11}NOS$: C, 68.41; H, 4.83; N, 6.13; S, 14.02. Found: C, 68.32; H, 4.52; N, 6.02; S, 14.12.

4.3.4. 5-Benzoyl-2-methylaminothiophenol (5d). Recrystallization from ethanol gave **5d** in 60% yield; mp 70–71 °C; IR (KBr, ν cm^{-1}) 3400 (NH), 3350 (SH), 1650 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ=2.95 (s, 1H, NH, exchangeable with D_2O), 3.20 (s, 3H, CH_3), 6.75 (s, 1H, SH, exchangeable with D_2O), 7.20 (d, 1H, J=8.15 Hz, H_3), 7.50 (m, 6H, H_6, H_{Ar}), 7.80 (dd, 1H, J=8.15 Hz, J=1.30 Hz, H_4). Anal. Calcd for $C_{14}H_{13}NOS$: C, 69.12; H, 5.38; N, 5.75; S, 13.15. Found: C, 69.01; H, 5.55; N, 5.92; S, 13.02.

4.4. General procedure for the synthesis of 7-acyl-4*H*-benzothiazin-3-one derivatives (2a–d) from compounds 5a–d

The method adopted for the synthesis of 7-butyryl-4*H*-benzothiazin-3-one (**2a**) is described. To a solution of compound **5a** (3.9 g, 20 mmol) in DMSO was added sodium ethylate (1.36 g, 20 mmol). After 1 h, ethyl bromoacetate (2.45 mL, 22 mmol) was added and the mixture was stirred for 2 h at room temperature. The solution was poured into cold water and acidified with 6 M HCl solution (pH=5), filtered, washed with water and recrystallized from acetone to give **2a** in 65% yield (**2b–d**: 56–76% yield).

4.5. 6-Tributyltin-4*H*-benzothiazin-3-one (7)

To a mixture of 6-bromo-3-methyl-4*H*-benzothiazin-3-one (**6**) (4.4 g, 18 mmol) in toluene (20 mL) under argon, tetrakis(triphenyl phosphine) palladium (1.86 g, 1.8 mmol) and bis(tributyltin) (11.80 mL, 27 mmol) were added. The reaction mixture was stirred at reflux for 6 h. The solution was evaporated under reduced pressure. The oily residue was purified by flash column chromatography with petroleum ether/EtOAc (9/1) to give an oily product. Yield 53%; IR (KBr, ν cm^{-1}) 3211 (NH), 2852–2956 (CH), 1679 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.80 (t, 9H, J=5.70 Hz, $(CH_3)_3$), 1.05 (t, 6H, J=6.00 Hz, $(COCH_2)_3$), 1.30 (m, 6H, $(CH_2)_3$), 1.50 (m, 6H, $(CH_2)_3$), 3.45 (s, 2H, CH_2CO), 6.90 (d, 1H, J=0.95 Hz, H_5), 7.10 (dd, 1H, J=7.30 Hz, J=0.95 Hz, H_7), 7.30 (d, 1H, J=7.30 Hz, H_8), 8.50 (br s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{20}H_{33}NOSSn$: C, 52.88; H, 7.32; N, 3.08; S, 7.06. Found: C, 52.63; H, 7.50; N, 2.86; S, 7.32.

4.6. General procedure for the synthesis of 6-acyl-4*H*-benzothiazin-3-one derivatives (8a–c)

Compound **7** (1.04 g, 2.3 mmol) in toluene (10 mL) was placed under argon, dichlorobis(triphenyl phosphine) palladium (0.16 g, 0.23 mmol) and the corresponding acid chloride (4.6 mmol) were added. The reaction was refluxed for 2 h. The solution was evaporated under reduced pressure. The residue was purified by flash column chromatography with dichloromethane/EtOAc (9/1) and recrystallized.

4.6.1. 6-Butyryl-4*H*-benzothiazin-3-one (8a). Recrystallization from ethanol gave **8a** in 40% yield; mp 214–215 °C; IR (KBr, ν cm^{-1}) 3194 (NH), 1672 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ=0.90 (t, 3H, J=7.00 Hz, CH_3), 1.60 (m, 2H, CH_2), 2.90 (t, 2H, J=7.00 Hz, CH_2CO), 3.55 (s, 2H, CH_2S), 7.45 (d, 1H, J=8.20 Hz, H_8), 7.50 (s, 1H, H_5), 7.55 (dd, 1H, J=8.20 Hz, J=1.75 Hz, H_7), 10.60 (br s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{12}H_{13}NO_2S$: C, 61.25; H, 5.57; N, 5.95; S, 13.63. Found: C, 61.05; H, 5.70; N, 5.68; S, 13.50.

4.6.2. 6-Benzoyl-4*H*-benzothiazin-3-one (8b). Recrystallization from ethanol gave **8b** in 69% yield, mp 180–181 °C; IR (KBr, ν cm^{-1}) 3140 (NH), 1678 and 1640 (CO); ^{1}H NMR (300 MHz, DMSO-d_6): δ=3.35 (s, 2H, CH_2CO), 7.30 (dd, 1H, J=7.90 Hz, J=1.50 Hz, H_7), 7.40 (d, 1H, J=1.50 Hz, H_5), 7.50 (d, 1H, J=7.90 Hz, H_8), 7.60 (m, 2H, H_{Ar}), 7.65–7.75 (m, 3H, H_{Ar}), 10.75 (br s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{15}H_{11}NO_2S$: C, 66.89; H, 4.12; N, 5.20; S, 11.91. Found: C, 66.74; H, 4.24; N, 5.03; S, 12.13.

4.6.3. 6-(Ethyl-4-oxobutyrate)-4*H*-benzothiazin-3-one (8c). Recrystallization from ethanol gave **8c** in 57% yield; mp 162–163 °C; IR (KBr, ν cm^{-1}) 3315 (NH), 1723 (COO), 1672 (CON); ^{1}H NMR (300 MHz, $CDCl_3$): δ=1.30 (t, 3H, J=7.00 Hz, CH_3), 2.80 (t, 2H, J=6.45 Hz, CH_2CO), 3.30 (t, 2H, J=6.45 Hz, CH_2COO), 3.50 (s, 2H, CH_2S), 4.20 (q, 2H, J=7.00 Hz, CH_3), 7.40 (d, 1H, J=8.20 Hz, H_7), 7.50 (d, 1H, J=1.75 Hz, H_4), 7.65 (dd, 1H, J=8.20 Hz, J=1.75 Hz, H_6), 8.50 (br s, 1H, NH, exchangeable with D_2O). Anal. Calcd for $C_{14}H_{15}NO_4S$: C, 57.32; H, 5.15; N, 4.77; S, 10.93. Found: C, 57.15; H, 5.28; N, 4.63; S, 10.78.

4.7. 6-(4-Oxobutyric)-4*H*-benzothiazin-3-one (8d)

To sodium hydroxide (0.21 g, 5.13 mmol) dissolved in a solution of ethanol/water (15/15 mL) was added compound **8c** (0.50 g, 1.71 mmol). The reaction mixture was refluxed for 2 h and then evaporated under reduced pressure. The residue was dissolved in water (30 mL). The solution was acidified with 6 N HCl to pH=1, and extracted with dichloromethane. The organic layer was dried over magnesium sulfate and evaporated under reduced pressure. The compound was recrystallized from ethanol to give **8d** in 65% yield; mp 189–190 °C; IR (KBr, ν cm^{-1}) 3254 (NH), 1701 (COO), 1669 (CON), 1650 (CO); ^{1}H NMR (300 MHz, $CDCl_3$): δ=2.60 (m, 2H, CH_2CO), 3.15 (m, 2H, CH_2COO), 3.60 (s, 2H, CH_2S), 7.40–7.60 (m, 3H, H_4, H_6, H_7), 10.60 (br s, 1H, NH, exchangeable with D_2O), 12.10 (br s, 1H, OH, exchangeable with D_2O). Anal. Calcd for $C_{12}H_{11}NO_4S$: C, 54.33; H, 4.18; N, 5.28; S, 12.09. Found: C, 54.57; H, 4.35; N, 5.08; S, 12.24.

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