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Synthesis and antihypotensive properties of 2-amino-2-thiazoline analogues with enhanced lipophilicity

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Chemistry

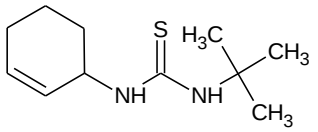
General information

All starting materials, reagents and solvents were purchased as high-grade commercial products and used without further purification. Reactions sensitive to moisture and/or oxygen were carried out under an inert atmosphere of anhydrous argon. Liquid column chromatography was performed using silica gel Acros (40–60 μm). Thin-layer chromatography (TLC) was performed on Silufol-UV254 silica gel sheets, and spots were visualized with UV light (λ = 254 nm) or stained with iodine vapor or aqueous potassium permanganate solution.

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance 400 spectrometer at 28°C in $CDCl_3$ at 400 and 100 MHz correspondingly. Chemical shifts (δ) are reported in parts per million (ppm) referenced to residual protonated solvent peak ($CDCl_3$, δ = 7.26 for ^{1}H NMR) or to carbon resonances in the NMR solvent ($CDCl_3$, δ = 77.0 for ^{13}C NMR). Electron impact mass spectra (EI-MS) were recorded on a Finnigan MAT INCOSSO spectrometer (electron impact, 70 eV). CHN elemental analysis was performed using a Carlo-Erba ER-20 analyzer. Infrared spectra (IR) were registered on a Thermo Nicolet IR200 apparatus using KBr disks. Melting points were determined using a capillary melting point apparatus and were uncorrected.

Synthetic procedures and characteristics of the compounds

1-*tert*-Butyl-3-(cyclohex-2-en-1-yl)thiourea (5a). Cyclohex-2-en-1-amine hydrochloride (180 mg, 1.35 mmol) dissolved in CH_2Cl_2 (10 ml) was treated with DIPEA (240 μl, 1.38 mmol) and *tert*-butyl isothiocyanate (180 μl, 1.42 mmol). The reaction mass was stirred overnight at room temperature, concentrated and purified by column chromatography (eluent: 2% methanol in $CHCl_3$) to give **5a** as white solid (214 mg, yield 75%). M.p. 61–63°C.



^{1}H NMR (δ, $CDCl_3$): 1.40 (s, 9H, *t*-Bu), 1.55–1.74 (m, 3H), 1.95–2.06 (m, 3H), 4.87 (m, 1H, H^1), 5.69 (m, 1H, H^2, *J*=9.9 Hz), 5.80 (br s, 2H, 2NH), 5.90 (m, 1H, H^3, *J*=9.9 Hz).

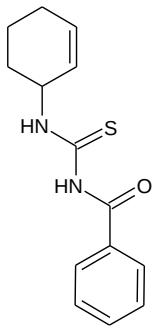
^{13}C NMR (δ, $CDCl_3$): 19.66 (C^5), 24.79 (C^4), 28.96 (C^6), 29.52 ($C(\underline{C}H_3)_3$), 50.61 (C^1), 52.63 ($\underline{C}(CH_3)_3$), 126.88 (C^3), 131.71 (C^2), 179.86 (C=S).

IR (KBr, cm^{-1}): 1202, 1318 (C=S), 1346, 1360, 1394, 1529 (C-N), 2834–2975, 3025–3101, 3258.

MS (EI): 212 $(M)^+$, 156 $(M\text{-}t\text{-}Bu)^+$, 133 $(t\text{-}BuNHC(S)NH_3)^+$, 96 $(C_6H_{11}N)^+$, 77 $(NH_2C(S)NH_3)^+$, 57 $(t\text{-}Bu)^+$.

Anal. Calcd for $C_{11}H_{20}N_2S$: C, 62.22, H, 9.49, N, 13.19, S, 15.10. Found: C, 62.21, H, 9.54, N, 13.08, S, 14.91.

***N*-[(Cyclohex-2-en-1-yl)aminocarbonothioyl]benzamide (5b)**. Cyclohex-2-en-1-amine hydrochloride (220 mg, 1.65 mmol) dissolved in CH_2Cl_2 (10 ml) was treated with DIPEA (580 µl, 3.34 mmol) and benzoyl isothiocyanate (224 µl, 1.67 mmol). The reaction mass was stirred overnight at room temperature, concentrated and purified by column chromatography (eluent: 2% methanol in $CHCl_3$) to give **5b** as white solid (380 mg, yield 89%). M.p. 76–78°C.



^{1}H NMR (δ, $CDCl_3$): 1.69–1.82 (m, 3H), 2.02–2.14 (m, 3H), 4.97 (m, 1H, *J*=6.1, 7.7 Hz, H^1), 5.77 (m, 1H, *J*=10.0 Hz, H^2), 5.95 (m, 1H, *J*=10.0 Hz, H^3), 7.50 (m, 2H, *J*=8.1, 7.4 Hz, 3,5-Ph), 7.64 (m, 1H, *J*=7.4 Hz, 4-Ph), 8.15 (m, 2H, *J*=8.1 Hz, 2,6-Ph).

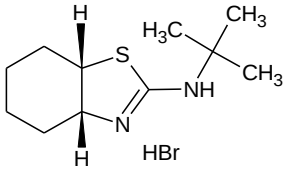
^{13}C NMR (δ, $CDCl_3$): 19.54, 24.74, 27.96, 50.92 (C^1), 125,63 (C^2), 127.33 (2,6-Ph), 129.04 (3,5-Ph), 130.49 (1-Ph), 131.92 (4-Ph), 133.42 (C^3), 166.66 (C=O), 178.56 (C=S).

MS (EI): 259 $(M\text{-}H^+)$, 183 $(M\text{-}Ph^+)$, 105 $(PhCO^+)$, 77 $(NH_2C(S)NH_3^+)$.

IR (KBr, cm^{-1}): 1172, 1256, 1341, 1521 (C-N), 1672 (C=O), 2860–2946, 3033, 3170–3223 cm^{-1}.

Anal. Calcd for $C_{14}H_{16}N_2OS$: C, 64.58, H, 6.19, N, 10.76, S, 12.32. Found: C, 64.65, H, 6.21, N, 10.56, S, 12.22.

(3a*RS*,7a*SR*)-*N*-*tert*-Butyl-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazol-2-amine hydrobromide (6a). A solution of acetyl bromide (40 µl, 0.54 mmol) in CH_2Cl_2 (2 ml) was treated with methanol (22 µl, 0.54 mmol) and stirred at room temperature in darkness. In 10 min a solution of **5a** (106 mg, 0.50 mmol) in CH_2Cl_2 (5 ml) was added and stirring was continued for 12 h. The reaction mass was concentrated and the residue purified by column chromatography (eluent: 2% methanol in $CHCl_3$) to yield **6a** as colourless oil (109 mg, 74%).



^{1}H NMR (δ, $CDCl_3$): 1.16–1.57 (m, 6H), 1.33 (s, 9H, *t*-Bu), 1.90 (m, 2H), 3.80 (dt, 1H, *J*=7.8, 5.3 Hz, H^{7a}), 3.93 (m, 1H, H^{3a}), 9.79 (br s, 2H, 2NH).

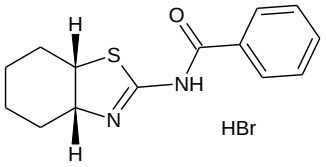
^{13}C NMR (δ, $CDCl_3$): 19.64, 21.87, 26.56, 28.40 ($C(\underline{C}H_3)_3$), 28.49, 48.58 (C^{7a}), 55.08 ($\underline{C}(CH_3)_3$), 58.18 (C^{3a}), 171.29 (C^2).

IR (neat, cm^{-1}): 1203, 1239, 1267, 1375, 1405, 1447, 1471, 1527, 1533, 1615 (C=N), 2757, 2859, 2934, 2972, 3127, 3170, 3408 cm^{-1}.

MS (EI): 212 $(M)^+$, 211 $(M\text{-}H)^+$, 197 $(M\text{-}Me)^+$, 183 $(M\text{-}Et)^+$, 156 $(C_7H_{12}N_2S)^+$, 131 $(C_5H_{11}N_2S)^+$, 113 $(C_6H_9S)^+$, 57 $(t\text{Bu})^+$, 41 $(C_3H_5)^+$, 29 $(Et)^+$, 15 $(Me)^+$.

Anal. Calcd for $C_{11}H_{21}BrN_2S$: C, 45.05, H, 7.22, N, 9.55, S, 10.93. Found: C, 45.08, H, 7.35, N, 9.67, S, 10.81.

***N*-[(3a*RS*,7a*SR*)-3a,4,5,6,7,7a-Hexahydro-1,3-benzothiazol-2-yl]benzamide hydrobromide (6b).** A solution of acetyl bromide (40 μl, 0.54 mmol) in CH_2Cl_2 (2 ml) was treated with methanol (22 μl, 0.54 mmol) and stirred at room temperature in the dark. In 10 min a solution of **5b** (130 mg, 0.50 mmol) in CH_2Cl_2 (5 ml) was added and stirring was continued for 12 h. The reaction mass was concentrated and the residue purified by column chromatography (eluent: 2% methanol in $CHCl_3$) to yield **6b** as white solid (128 mg, 75%). M.p. 165–167°C.



^{1}H NMR (δ, $CDCl_3$): 1.44–1.58 (m, 2H), 1.63–1.76 (m, 2H), 1.80–1.89 (m, 1H), 1.91–1.99 (m, 1H), 2.03–2.15 (m, 2H), 3.88 (dt, 1H, *J*=7.6, 6.1 Hz, H^{7a}), 4.28 (dt, 1H, *J*=6.4, 5.6 Hz, H^{3a}), 7.57 (m, 2H, *J*=7.7, 7.4 Hz, 3,5-Ph), 7.68 (m, 1H, *J*=7.4, 1.9, Hz, 4-Ph), 8.36 (m, 2H, *J*=7.7, 1.9, Hz, 2,6-Ph).

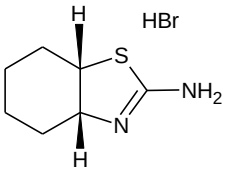
^{13}C NMR (δ, $CDCl_3$): 20.21, 21.74, 26.64, 28.05, 46.86 (C^{7a}), 59.22 (C^{3a}), 129.00 (3,5-Ph), 129.28 (2,6-Ph), 130.00 (1-Ph), 134.40 (4-Ph), 166.83 (C=O), 174.57 (C^{2}).

MS (EI): 260 (M^+), 259 $(M-H)^+$, 243 $(M-OH)^+$, 231 $(M-H-CO)^+$, 183 $(M-Ph)^+$, 179 $(C_8H_7N_2OS)^+$, 147 $(C_8H_7N_2O)^+$, 105 $(PhCO)^+$, 77 $(Ph)^+$, 51 $(C_4H_3)^+$.

Anal. Calcd for $C_{14}H_{17}BrN_2OS$: C, 49.27, H, 5.09, N, 8.21, S, 9.40. Found: C, 49.23, H, 4.98, N, 8.44, S, 9.12.

(3a*RS*,7a*SR*)-3a,4,5,6,7,7a-Hexahydro-1,3-benzothiazol-2-amine hydrobromide (7).

Method 1: A solution of **6a** (45 mg, 0.15 mmol) was refluxed in aqueous 20% HBr (5 ml) for 3 h. The reaction mass was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: 5% methanol in $CHCl_3$) to give **7** as white solid (27 mg, 93%). M.p. 185–187°C.



Method 2: A solution of **6b** (58 mg, 0.17 mmol) in methanol (5 ml) was stirred with 1,8-diazabicyclo[5.4.0]undec-7-en (DBU, 52 μl, 0.34 mmol) at room temperature for 12 h. The mixture was concentrated under reduced pressure and purified by column chromatography on silica gel (gradient elution by solution of 1% to 5% methanol in $CHCl_3$), the target fraction was treated with aqueous 20% HBr (10 ml), then evaporated, triturated with Et_2O (2×10 ml), decanted and dried to give **7** as white solid (10 mg, 25%).

^{1}H NMR (δ, $CDCl_3$ + methanol-d_4): 1.23–1.38 (m, 2H), 1.41–1.55 (m, 2H), 1.62–1.73 (m, 2H), 1.89 (m, 2H), 3.79 (dt, 1H, *J*=5.3, 7.8 Hz, H^{7a}), 4.03 (dt, 1H, *J*=4.9, 5.3 Hz, H^{3a}).

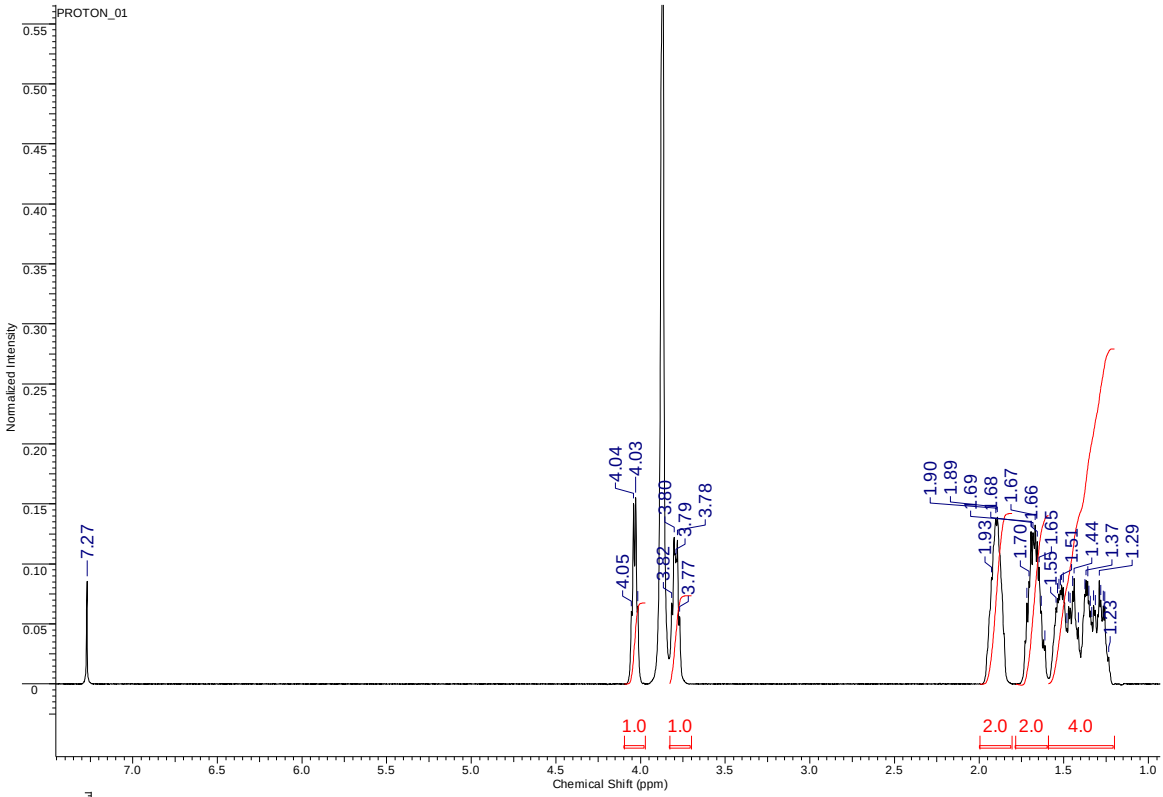
^{13}C NMR (δ, $CDCl_3$ + methanol-d4): 19.87, 21.88, 26.71, 28.51, 48.36 (C^{7a}), 60.37 (C^{3a}), 173.21 (C^{2}).

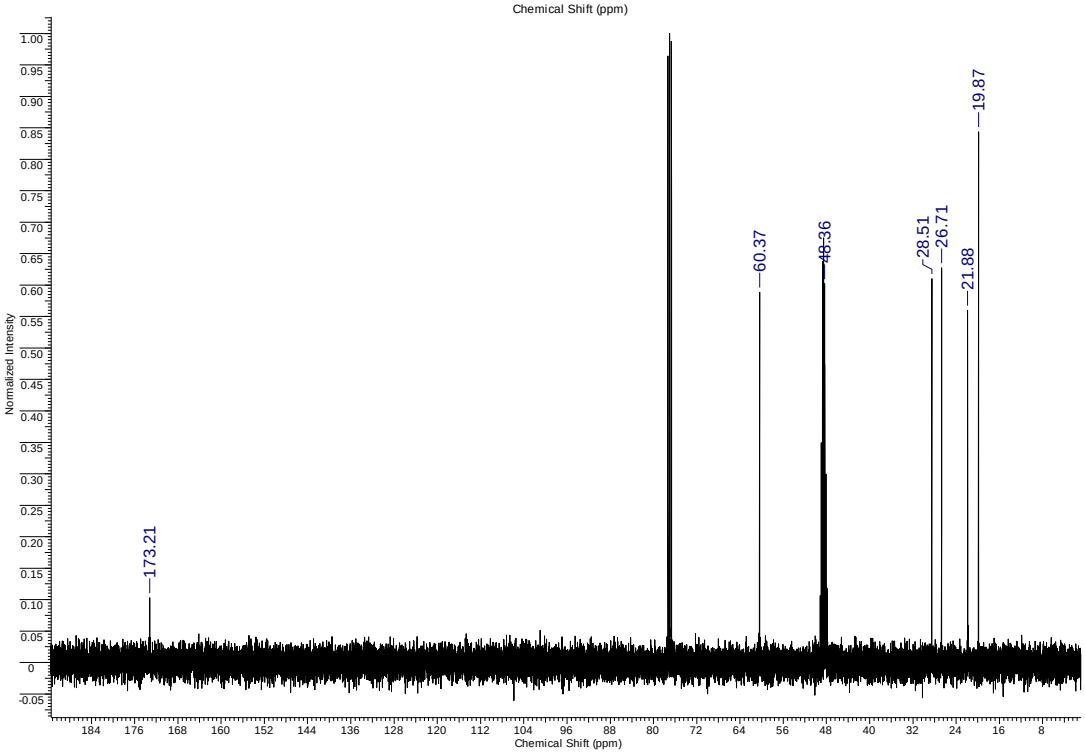
^{1}H NMR (δ, D_2O): 1.32 (m, 1H), 1.41–1.46 (m, 2H), 1.58 (m, 1H), 1.65–1.78 (m, 2H), 1.91–2.01 (m, 2H), 3.95 (dt, 1H, *J*=9.0, 5.5 Hz, H^{7a}), 4.18 (dt, 1H, *J*=5.6, 5.1 Hz, H^{3a}).

^{13}C NMR (δ, D_2O): 19.57, 21.95, 26.26, 28.54, 48.71 (C^{7a}), 60.77 (C^{3a}), 173.20 (C^{2}).

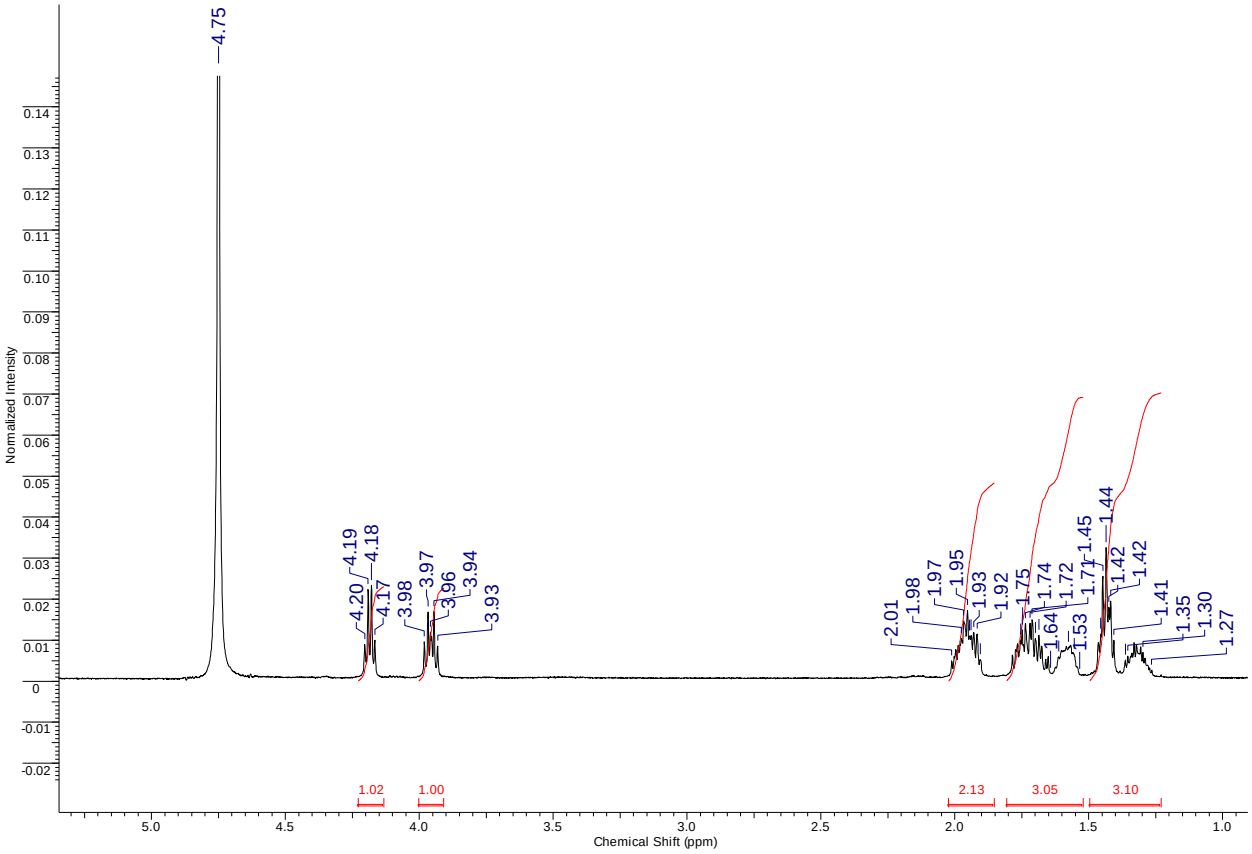
Anal. Calcd for $C_7H_{13}BrN_2S$: C, 35.45, H, 5.53, N, 11.81, S, 13.52. Found: C, 35.40, H, 5.55, N, 11.71, S, 13.43.

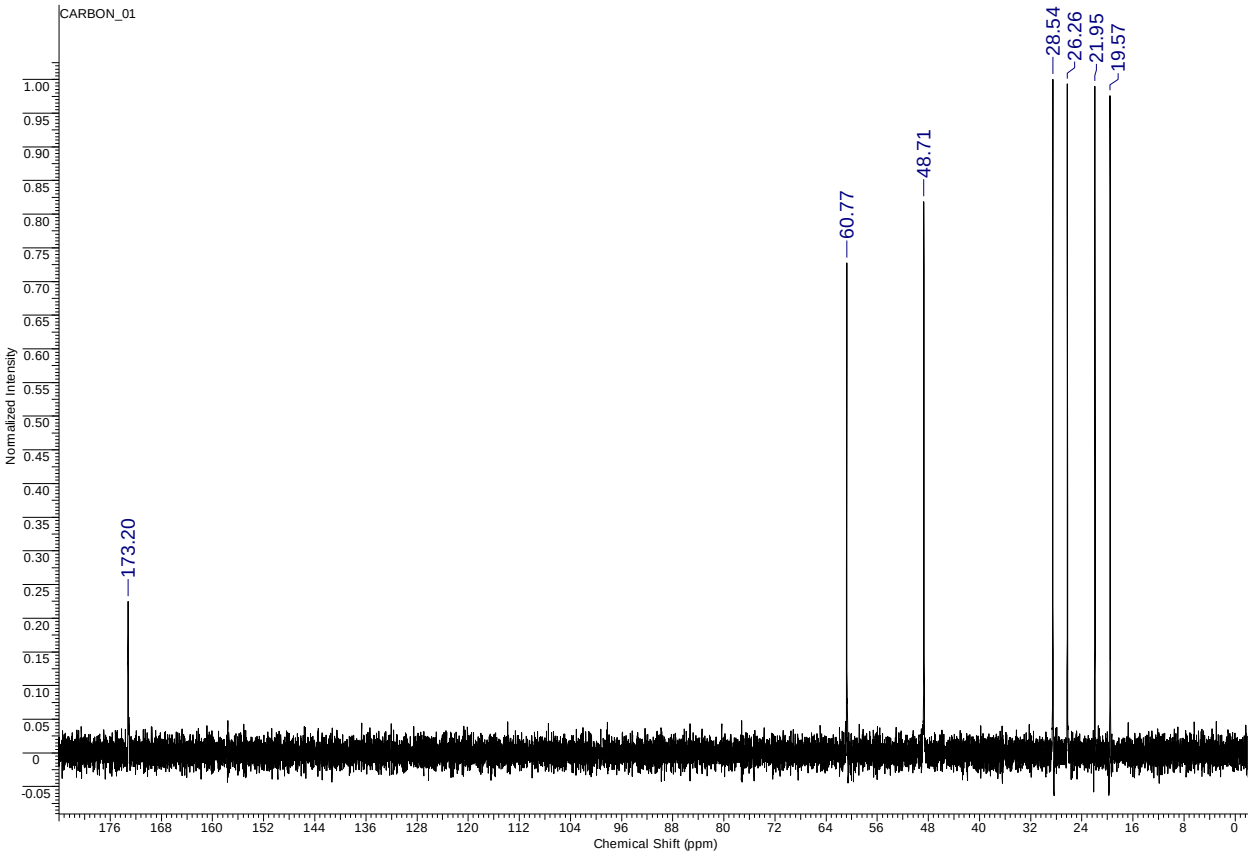
^{1}H NMR and ^{13}C NMR spectra of compound **7** in $CDCl_3$+methanol-d_4





^{1}H NMR and ^{13}C NMR spectra of compound **7** in D_2O



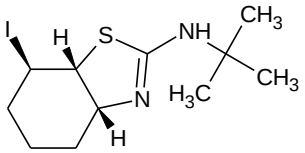


(3a*RS*,7a*SR*)-*N*-*tert*-Butyl-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazol-2-amine (6'a), free base**.** A solution of **11a** (47 mg, 0.14 mmol) or **8a** (52 mg, 0.14 mmol) in toluene (10 ml) was treated with tri-*n*-butyltin hydride (94 µl, 0.35 mmol) and azobisisobutyronitrile (AIBN, 2 mg, 0.12 mmol). The mixture was heated at 100°C under argon atmosphere for 6 h, then washed with saturated aq. $NaHCO_3$ solution (10 ml), dried over Na_2SO_4, concentrated under reduced pressure and purified by column chromatography (eluent: CH_2Cl_2, then 2% methanol in $CHCl_3$) to yield free base of **6'a** as a colourless oil (27 mg, 92% from **11a**; 25 mg, 84% from **8a**).

^{1}H NMR (δ, $CDCl_3$): 1.29–1.42 (m, 2H), 1.37 (s, 9H, *t*-Bu), 1.48–1.62 (m, 2H), 1.65–1.76 (m, 2H), 1.91–1.98 (m, 2H), 3.79 (dt, 1H, *J*=8.3, 5.1 Hz, H^{7a}), 3.93 (m, *J*=5.1, 3.3 Hz, 1H, H^{3a}), 9.00–10.00 (br s, 2H, 2NH).

^{13}C NMR (δ, $CDCl_3$): 19.90, 22.14, 26.88, 28.63 ($C(\underline{C}H_3)_3$), 28.72, 48.84 (C^{7a}), 54.84 ($\underline{C}(CH_3)_3$), 58.47 (C^{3a}), 171.04 (C^2).

(3a*RS*,7*RS*,7a*RS*)-*N*-*tert*-Butyl-7-iodo-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazol-2-amine (11a). A solution of **5a** (52 mg, 0.25 mmol) in Et_2O (10 ml) was treated with K_2CO_3 (68 mg, 0.49 mmol) and I_2 (124 mg, 0.49 mmol). The reaction mixture was stirred in darkness at room temperature for 24 h, then concentrated and the residue was dissolved in $CHCl_3$ (20 ml) and washed with aqueous saturated solution of Na_2SO_3 (3×20ml). The organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography (eluent: 1% methanol in $CHCl_3$) to yield **11a** as yellowish crystals (60 mg, 71%). M.p. 110°C (decomp.).



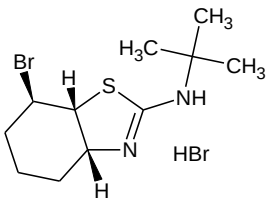
^{1}H NMR (δ, $CDCl_3$): 1.38 (s, 9H, *t*-Bu), 1.47-1.61 (m, 2H), 1.66–1.74 (m, 1H), 1.90–2.00 (m, 2H), 2.30–2.39 (m, 1H), 3.94 (dd, 1H, *J*=9.8, 5.1 Hz, H^{7a}), 3.97 (m, 1H, H^{3a}), 4.11 (ddd, *J*=11.9, 9.8, 4.1 Hz, H^7), 4.81 (br s, 1H, NH).

^{13}C NMR (δ, $CDCl_3$): 22.54 (C^5), 28.82 (C^4), 28.92 ($C(\underline{C}H_3)_3$), 37.05 (C^6), 37.86 (C^7), 52.73 ($\underline{C}(CH_3)_3$), 63.21 (C^{7a}), 71.28 (C^{3a}), 156.85(C^2).

IR (KBr, cm^{-1}): 1449, 1622 (C=N), 2866, 2932, 3113 (NH).

Anal. Calcd for $C_{11}H_{19}IN_2S$: C, 39.06, H, 5.66, N, 8.28, S, 9.48. Found: C, 39.11, H, 5.63, N, 8.19, S, 9.46.

(3a*RS*,7*RS*,7a*RS*)-7-Bromo-*N*-*tert*-butyl-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazol-2-amine hydrobromide (8a). A solution of **5a** (30 mg, 0.14 mmol) in CH_2Cl_2 (4 ml) was treated with Br_2 (22 µl, 0.43 mmol) and stirred in darkness at room temperature for 24 h. The reaction mass was concentrated and the residue purified by column chromatography (eluent: 2% methanol in CH_2Cl_2) to yield **8a** as yellowish crystals (51 mg, 97%). M.p. 199–201°C.



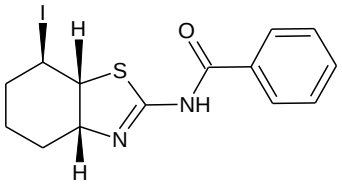
^{1}H NMR (δ, $CDCl_3$): 1.45 (s, 9H, *t*-Bu), 1.58-1.84 (m, 4H, H^4), 2.32 (m, 2H, *J*=12.8 Hz), 3.82 (dd, 1H, *J*=10.0, 5.3 Hz, H^{7a}), 3.91 (ddd, *J*=11.7, 10.0, 3.9 Hz, H^7), 4.16 (m, 1H, H^{3a}), 8.7 (br s, 2H, NH).

^{13}C NMR (δ, $CDCl_3$): 20.47 (C^5), 25.68 (C^4), 28.64 ($C(\underline{C}H_3)_3$), 34.76 (C^6), 52.43 (C^{7a}), 55.69 ($\underline{C}(CH_3)_3$), 57.31 (C^7), 59.95 (C^{3a}), 171.00 (C=N). IR (KBr): 1449, 1622 (C=N), 2866, 2932, 3113 (NH).

MS (EI): 292 $(M+2)^+$, 290 (M^+), 277 $(M+2\text{-}Me)^+$, 275 $(M\text{-}Me)^+$, 235 $(M+2\text{-}t\text{Bu})^+$, 233 $(M\text{-}t\text{Bu})^+$, 211 $(M\text{-}Br)^+$, 155 $(M\text{-}Br\text{-}tBu)^+$, 113 $(C_6H_9S)^+$, 57 $(tBu)^+$, 41 $(C_3H_5)^+$.

Anal. Calcd for $C_{11}H_{20}Br_2N_2S$: C, 35.50, H, 5.42, N, 7.53, S, 8.62. Found: C, 35.49, H, 5.43, N, 7.38, S, 8.57.

***N*-[(3a*RS*,7*RS*,7a*RS*)-7-Iodo-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazol-2-yl]benzamide (11b).** A solution of **5b** (30 mg, 0.12 mmol) in Et_2O (10 ml) was treated with K_2CO_3 (40 mg, 0.29 mmol) and I_2 (74 mg, 0.29 mmol). The reaction mixture was stirred in darkness at room temperature for 24 h, then concentrated and the residue was dissolved in $CHCl_3$ (20 ml) and washed with aqueous saturated solution of Na_2SO_3 (3×20ml). The organic layer was dried over Na_2SO_4, concentrated and purified by column chromatography (eluent: 1% methanol in $CHCl_3$) to yield **11b** as yellowish crystals (32 mg, 72%). M.p. 110°C (decomp.).

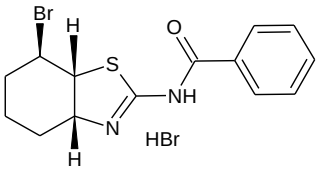


^{1}H NMR (δ, $CDCl_3$): 1.59 (m, 2H), 1.83 (m, 1H), 1.98 (m, 1H), 2.16 (m, 1H), 2.33 (m, 1H, *J*=13.5 Hz, H^6), 3.93 (dd, 1H, *J*=9.5, 5.6 Hz, H^{7a}), 4.07 (m, 1H, *J*=9.1, 5.6 Hz H^{3a}), 4.23 (ddd, 1H, *J*=11.5, 9.5, 3.8 Hz, H^7), 7.46 (m, 2H, *J*=7.9, 7.3 Hz, 3,5-Ph), 7.55 (m, 1H, *J*=7.3 Hz, 4-Ph), 8.19 (d, 2H, *J*=7.9 Hz, 2,6-Ph). ^{13}C NMR (δ, $CDCl_3$): 21.75, 26.69, 31.52, 36.27 (C^7), 56.39 (C^{7a}), 59.02 (C^{3a}), 128.40 (3,5-Ph), 129.23 (2,6-Ph), 132.65 (4-Ph), 134.64 (1-Ph), 148.96 (C=O), 173.65 (C^2).

MS (EI): 386 $(M)^+$, 385 $(M\text{-}H)^+$, 309 $(M\text{-}Ph)^+$, 259 $(M\text{-}I)^+$, 231 $(M\text{-}CO)^+$, 179 $(C_8H_7N_2OS)^+$, 147 $(C_8H_7N_2O)^+$, 128 $(HI)^{+\cdot}$, 127 $(I)^+$, 113 $(C_6H_9S)^+$, 105 $(PhCO)^+$, 77 $(Ph)^+$, 51 $(C_4H_3)^+$.

Anal. Calcd for $C_{14}H_{15}IN_2OS$: C, 45.53, H, 3.91, N, 7.25, S, 8.30. Found: C, 45.58, H, 3.90, N, 7.04, S, 8.19.

***N*-[(3a*RS*,7*RS*,7a*RS*)-7-Bromo-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazol-2-yl]benzamide hydrobromide (8b)** A solution of **5b** (30 mg, 0.12 mmol) in CH_2Cl_2 (4 ml) was treated with Br_2 (13 μl, 0.24 mmol) and stirred in darkness at room temperature for 24 h. The reaction mass was concentrated and the residue purified by column chromatography (eluent: 2%

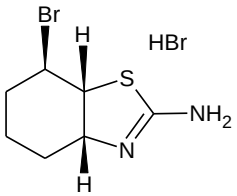


methanol in CH_2Cl_2) to yield **8b** as white crystals (32 mg, 66%). M.p. 194–196°C. ^{1}H NMR (δ, $CDCl_3$): 1.45–1.54 (m, 1H), 1.61–1.70 (m, 2H), 1.75–1.84 (m, 1H), 1.92 (m, 1H, *J*=13.7 Hz, H^6), 2.27 (m, 1H, *J*=13.7 Hz, H^6), 3.70 (dd, 1H, *J*=8.8, 5.8 Hz, H^{7a}), 4.07–4.13 (m, 2H, H^{3a}+H^7), 7.43 (m, 2H, *J*=7.4, 7.3 Hz, 3,5-Ph), 7.52 (m, 1H, *J*=7.3 Hz, 4-Ph), 8.36 (d, 2H, *J*=7.4 Hz, 2,6-Ph). ^{13}C NMR (δ, $CDCl_3$): 20.49, 26.63, 34.34, 53.38 (C^{7a}), 54.51 (C^7), 59.08 (C^{3a}), 128.33 (3,5-Ph), 129.21 (2,6-Ph), 132.46 (4-Ph), 135.16 (1-Ph), 174.15 (C=O), 174.50 (C^2).

MS (EI): 340 $(M+2)^+$, 338 $(M)^+$, 311 $(M+2\text{-}HCO)^+$, 309 $(M\text{-}HCO)^+$, 263 $(M+2\text{-}Ph)^+$, 261 $(M\text{-}Ph)^+$, 259 $(M\text{-}Br)^+$, 231 $(M\text{-}Br\text{-}CO)^+$, 179 $(C_8H_7N_2OS)^+$, 147 $(C_8H_7N_2O)^+$, 113 $(C_6H_9S)^+$, 105 $(PhCO)^+$, 77 $(Ph)^+$, 51 $(C_4H_3)^+$.

Anal. Calcd for $C_{14}H_{16}Br_2N_2OS$: C, 40.02, H, 3.84, N, 6.67, S, 7.63. Found: C, 40.03, H, 3.80, N, 6.54, S, 7.53.

(3a*RS*,7*RS*,7a*RS*)-7-Bromo-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazol-2-amine hydrobromide (9). A solution of **8a** (100 mg, 0.27 mmol) in aqueous 10% HBr (5 ml) was refluxed for 3 h. The reaction mass was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: 5% methanol in $CHCl_3$) to give **9** as white solid (78 mg, 92%). M.p. 206–208°C.



^{1}H NMR (δ, D_2O): 1.42–1.53 (m, 1H), 1.66–1.82 (m, 3H), 2.10–2.14 (m, 1H), 2.23–2.26 (m, 1H), 4.08 (dd, 1H, *J*=10.1, 5.3 Hz, H^{7a}), 4.18 (ddd, 1H, *J*=11.6, 10.1, 4.3 Hz, H^7), 4.33 (m, 1H, H^{3a}).

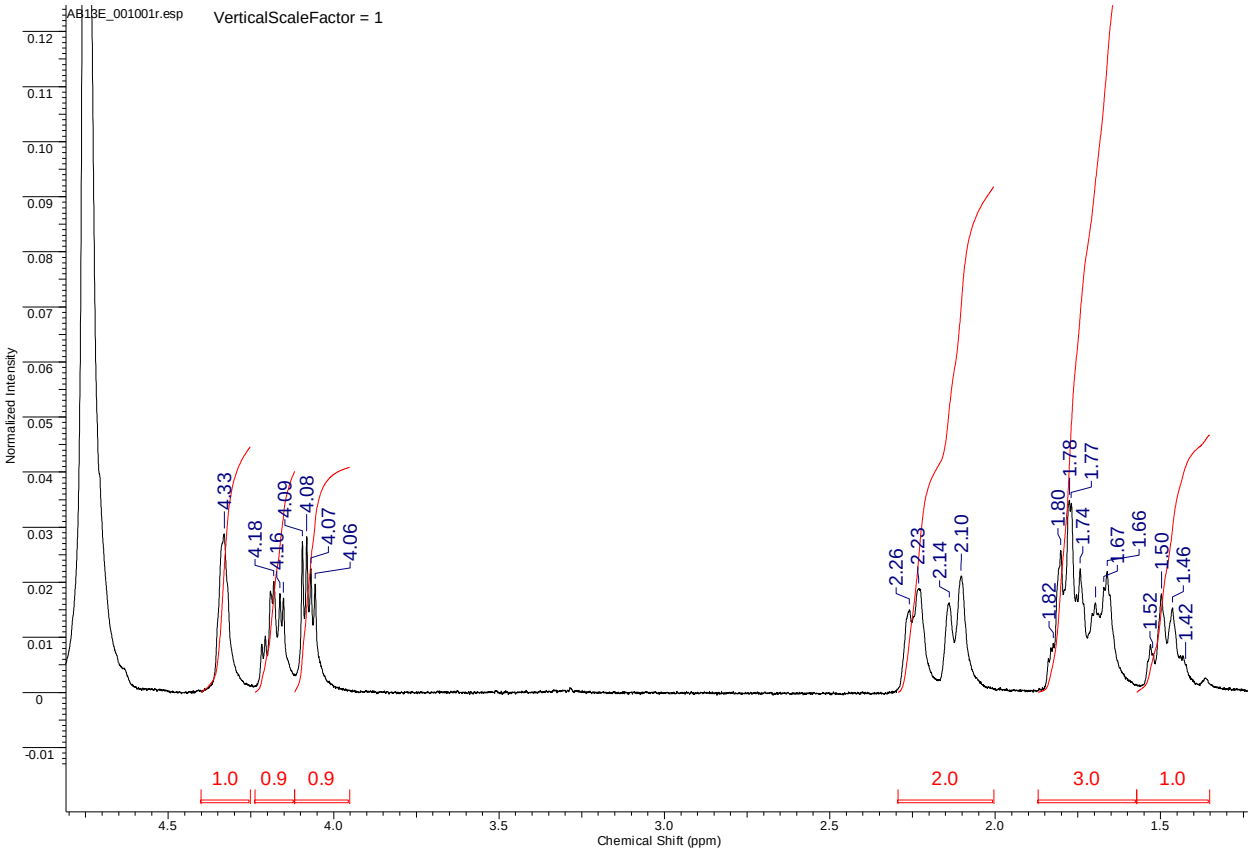
^{13}C NMR (δ, D_2O): 20.32, 25.15, 34.55, 53.95 (C^{7a}), 57.19 (C^7), 62.49 (C^{3a}), 173.03 (C^2).

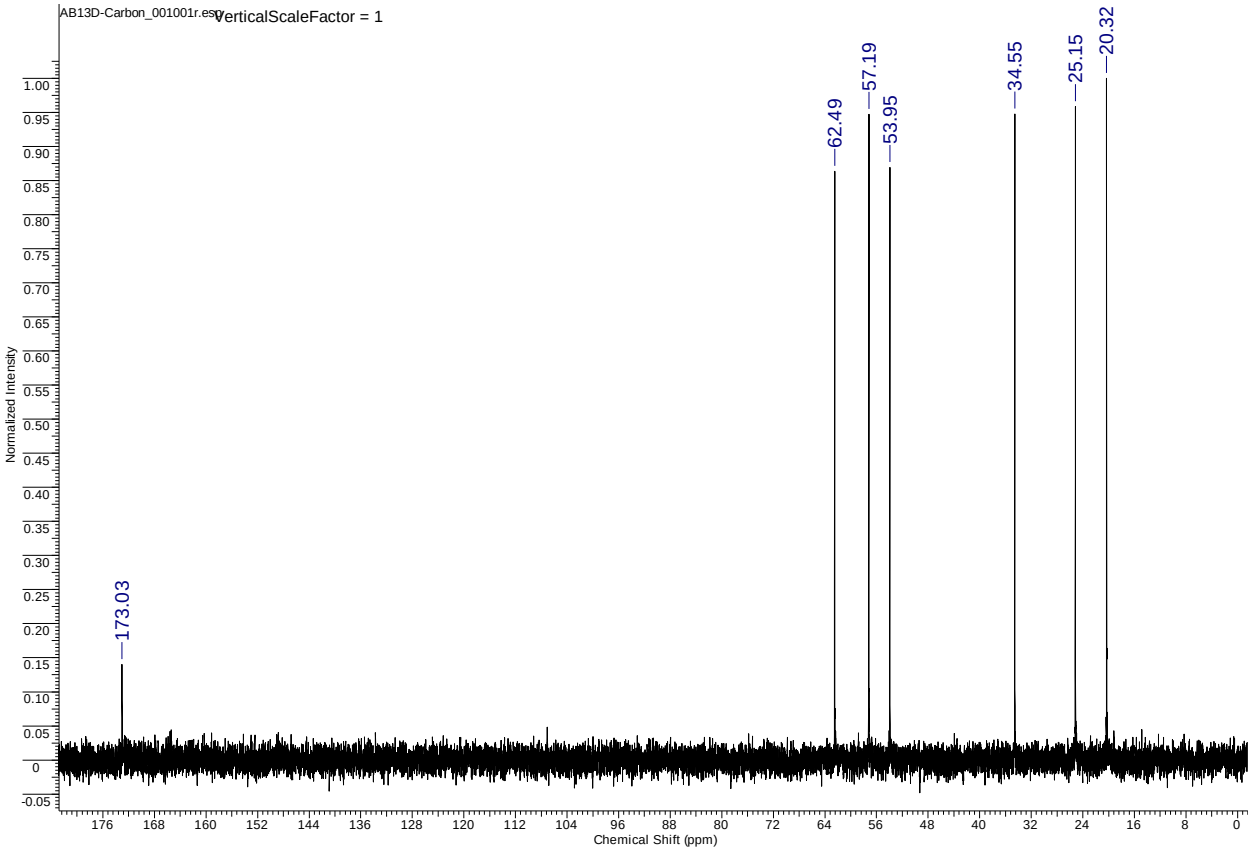
IR (KBr, cm^{-1}): 1000, 1197, 1324, 1348, 1376, 1405, 1448, 1471, 1550, 1621 (S-C=N), 1731, 2753-3469 (C-H).

MS (EI): 236 $(M+2)^+$, 234 (M^+), 155 $(M\text{-}Br)^+$, 128 $(M\text{-}C_2H_3Br)^+$, 113, 81 $(Br)^+$, 79 $(Br)^+$.

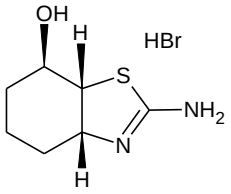
Anal. Calcd for $C_7H_{12}Br_2N_2S$: C, 26.60, H, 3.83, N, 8.86, S, 10.15. Found: C, 26.59, H, 3.80, N, 8.75, S, 10.18.

^{1}H NMR and ^{13}C NMR spectra of compound **9** in D_2O





(3a*RS*,7*RS*,7a*RS*)-7-Hydroxy-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazol-2-amine hydrobromide (10). A suspension of **9** (111 mg, 0.351 mmol) and PbO (280 mg, 1.25 mmol) in water (10 ml) was stirred at 50 °C for 10 h. The reaction mass was filtered, the filtrate was concentrated under reduced pressure, triturated with Et_2O (10 ml), the solution was decanted and the residue was dried to give **10** as white solid (76 mg, 86%). White crystals, M.p. 205–207°C.



^{1}H NMR (δ, D_2O): 1.18–1.28 (m, 1H, H^6), 1.34–1.44 (m, 1H, H^5), 1.56-166 (m, 2H, H^{4+5}), 1.87 (m, 1H, H^6), 2.04 (m, 1H, H^4), 3.42 (dd, 1H, *J*=9.6, 5.3 Hz, H^{7a}), 3.54 (ddd, 1H, *J*=11.5, 9.6, 4.3 Hz, H^7), 4.27 (m, 1H, H^{3a}).

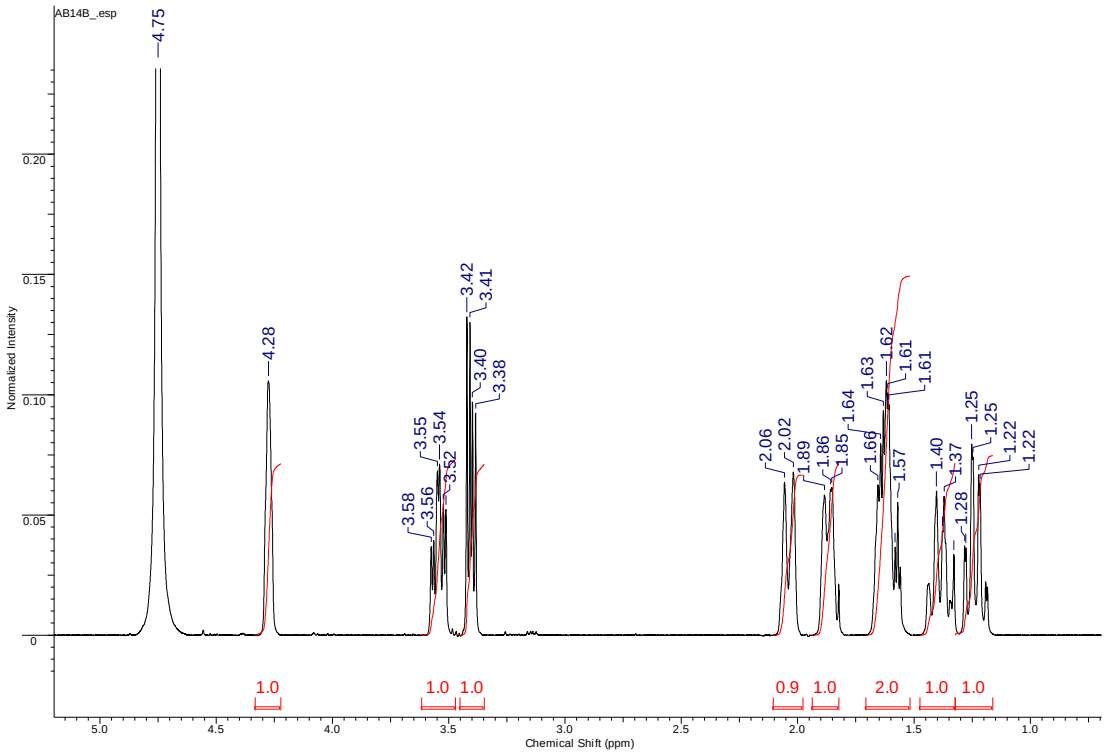
NOESY 1D (D_2O): H^{3a}–H^{7a} (1.7%), H^{3a}–H^{5ax} (1.4%).

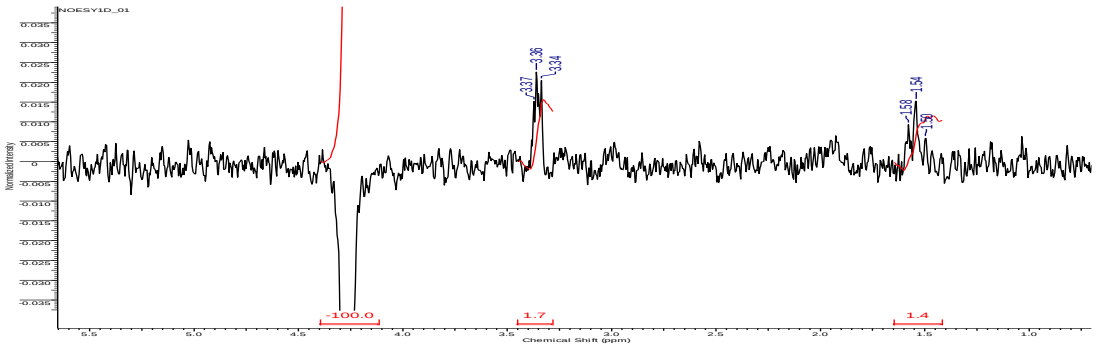
^{13}C NMR (δ, D_2O): 18.82, 26.23, 32.32, 56.63 (C^{7a}), 65.19 (C^{3a}), 72.67 (C^7), 171.12 (C^2).

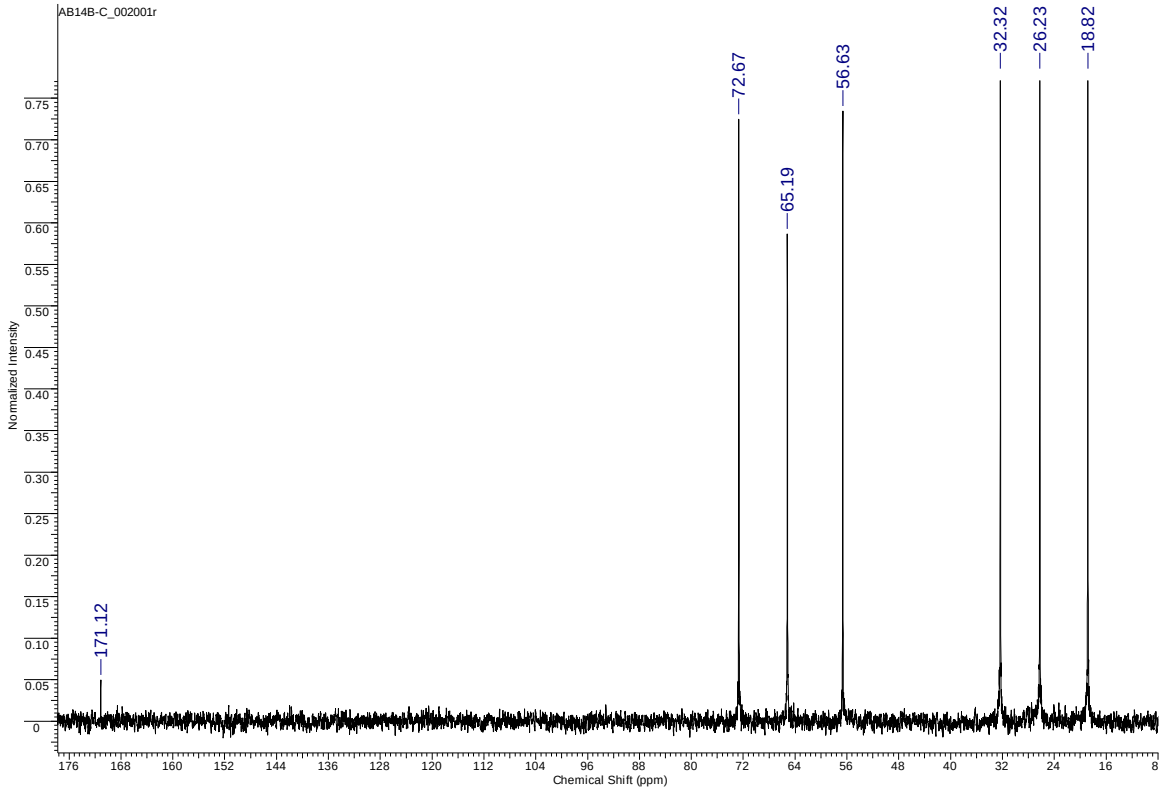
IR (KBr, cm^{-1}): 1313, 1446, 1583, 1648 (S-C=N), 1729, 2850–3417 (C-H, O-H).

Anal. Calcd for $C_7H_{13}BrN_2OS$: C, 33.21, H, 5.18, N, 11.07, S, 12.67. Found: C, 33.20, H, 5.12, N, 11.11, S, 12.51.

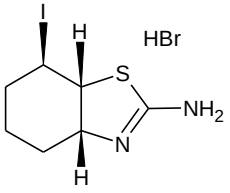
^{1}H NMR, NOESY 1D (irradiation of H^{3a} proton resonance) and ^{13}C NMR spectra of compound **10** in D_2O







(3a*RS*,7*RS*,7a*RS*)-7-Iodo-3a,4,5,6,7,7a-hexahydro-1,3-benzothiazol-2-amine hydrobromide (12). A solution of **11a** (45 mg, 0.133 mmol) in aqueous 10% HBr (5 ml) was refluxed for 3 h. The reaction mass was concentrated under reduced pressure and purified by column chromatography on silica gel (eluent: 5% methanol in $CHCl_3$) to give **12** as light yellow solid (27 mg, 56%). M.p. 145 °C (decomp.).

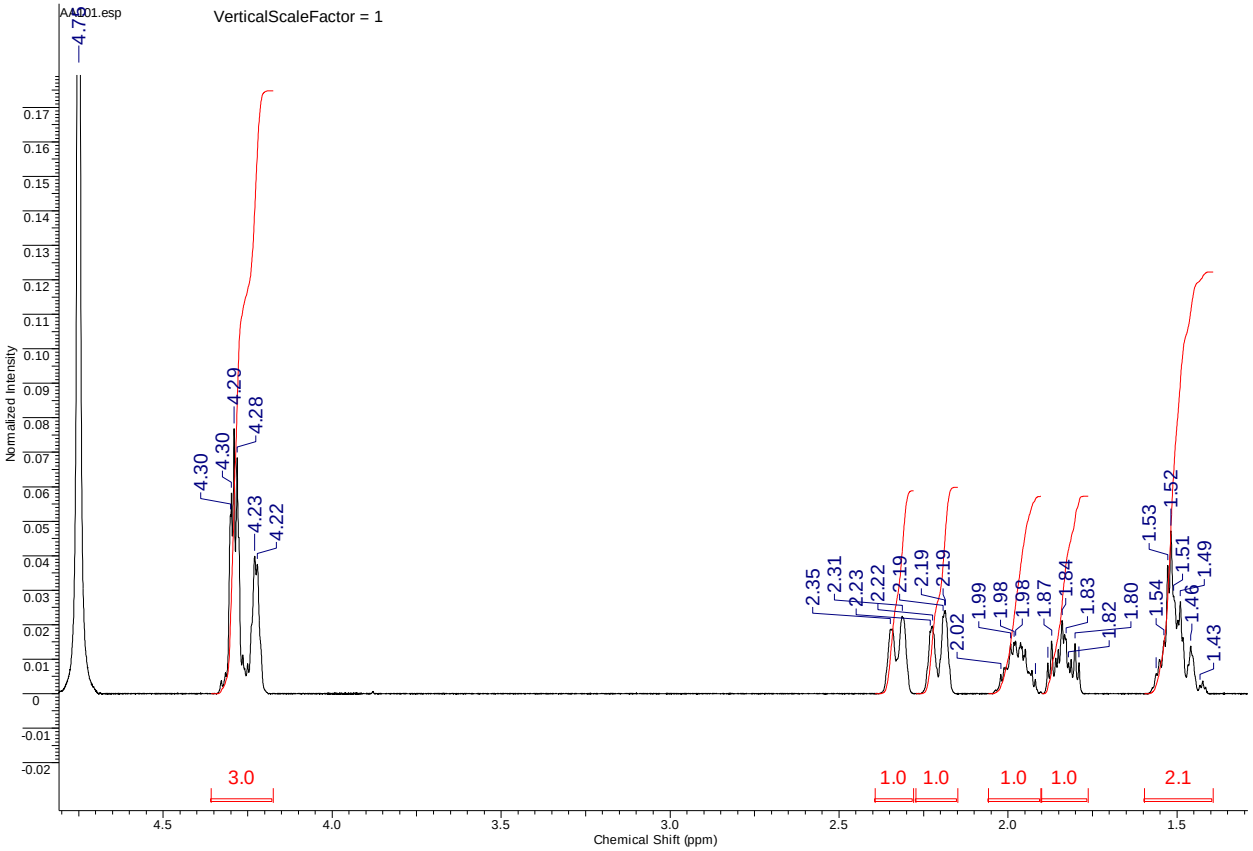


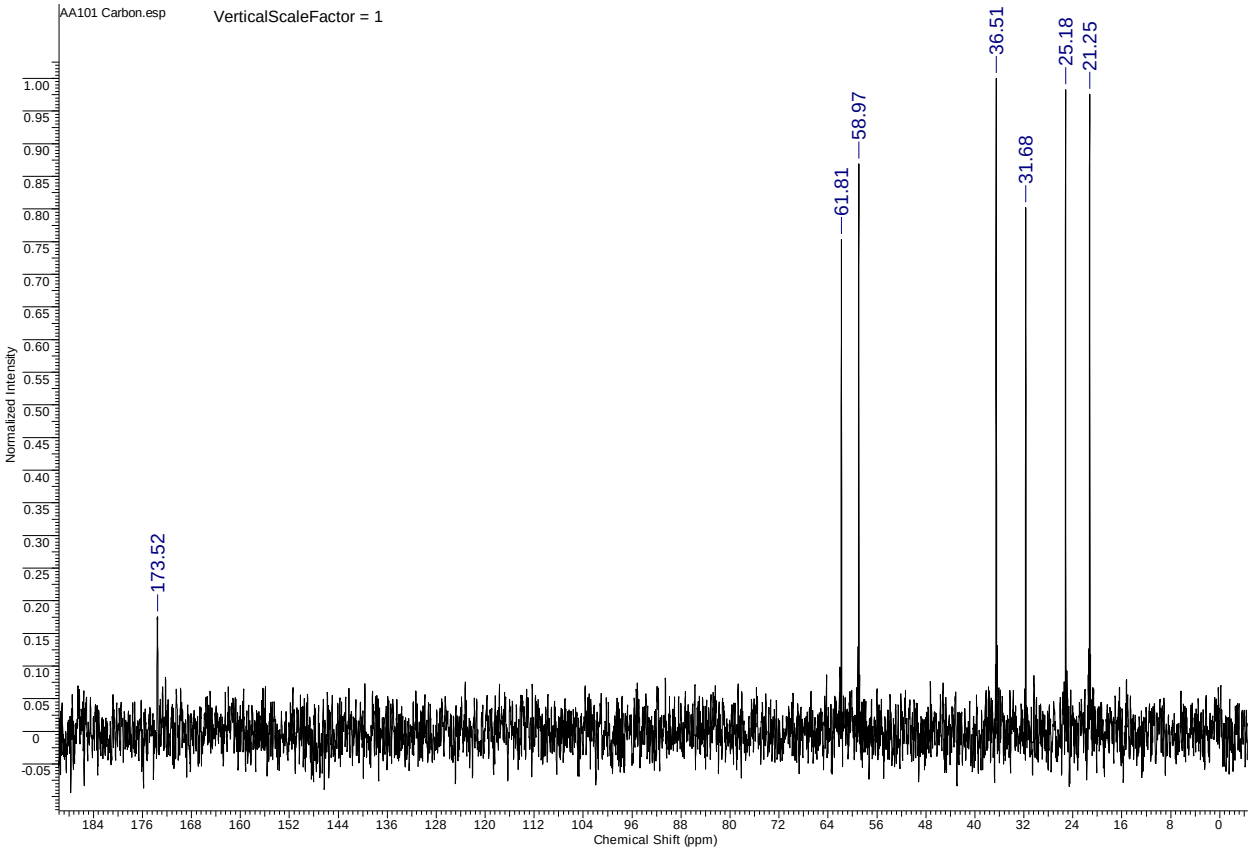
^{1}H NMR (δ, D_2O): 1.43 - 1.56 (m, 2H), 1.79 - 1.88 (m, 1H), 1.92- 2.02 (m, 1H), 2.20 (m, *J* = 14.0 Hz, 1H), 2.33 (m, *J* = 14.0 Hz, 1H), 4.23 (m, 1H, H^{7a}), 4.28-4.30 (m, 2H, H^{3a}+H^{7}).

^{13}C NMR (δ, D_2O): 21.25, 25.18, 31.68, 36.51 (C^7), 58.97 (C^{7a}), 61.81 (C^{3a}), 173.52 (C^2).

Anal. Calcd for $C_7H_{12}BrIN_2S$: C, 23.16, H, 3.33, N, 7.72, S, 8.83. Found: C, 26.08, H, 3.27, N, 7.72, S, 8.52.

^{1}H NMR and ^{13}C NMR spectra of compound **12** in D_2O





Biotesting *in vivo*.

The vasopressor action of compounds **7**, **9** and **10** on the model of severe septic shock was studied on Wistar rats (KYO, males, 3–4 months, mass 240–270 g). Before the operative intervention each animal was anesthetized with sodium thiopental (60 mg kg^{-1}, intraperitoneally). A tracheostome was placed, catheterization was performed with the jugular vein and carotid arteries, invasive sensors of blood pressure and electrodes of ECG registration were connected. Heparin (100 units ml^{-1}) was injected intravenously. After the state of the animal stabilized the following initial parameters were registered using PowerLab 8/30 system (ADInstruments, Australia): the heart rate (beats per minute), respiratory rate (breaths per minute), systolic (SBP) and diastolic (DBP) blood pressure (mm Hg) in the left carotid artery. The acute endotoxic (vasodilatation) shock was induced by intravenous injection of lipopolysaccharide *E. coli* (0111:B4; Sigma–Aldrich, USA) in a dose 18 mg/kg. After development of a stable hypotension – in 20–30 minutes after lipopolysaccharide injection (blood pressure reduction to 60–70% of initial values) – the physiologic parameters were repeatedly measured. Tested compounds **7**, **9** and **10** were dissolved in isotonic sodium chloride solution and were syringed intraperitoneally in one dose 20 mg kg^{-1} (0.1 ml per 100 g of body weight). Further monitoring of the parameters was being continued within the following 90 min. Animals survived in the end of the test were derived from the experience by air embolism.

The *in vivo* trials were conducted according to current legislation in Russian Federation concerning humanitarian handling of laboratory animals, namely GOST P53434-2009, “Principles of Laboratory Practices” and Russian Ministry of Health and Social Development Order of Aug. 23, 2010, No. 708n “On Approval of Laboratory Practice Rules”.