SUPPORTING INFORMATION

Synthesis of $GABA_A$ Receptor Agonists and Evaluation of their α-Subunit Selectivity and Orientation in the GABA Binding Site

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Content:

Synthesis description and spectroscopic data

Infrared spectra were recorded on a Perkin Elmer 1310 infrared spectrophotometer or a Thermo Nicolet, Avatar 330 FT-IR spectrophotometer. ^{1}H (300 MHz, digital resolution 0.3768 Hz) and ^{13}C (75 MHz, digital resolution 1.1299 Hz) NMR were recorded on a Bruker AC 300: the data are reported as follows: chemical shift in ppm from Me_4Si as external standard, multiplicity and coupling constant (Hz). EI-Mass spectra were recorded on a Varian MAT 311A (70 eV) and FD-Mass spectra on a Finnigan MAT-95-spectrometer. For clarity only the highest measured signal is given for mass spectra. Elemental analyses were performed on an Elemental Analyzer Carlo Erba Strumentazione Mod. 1106. Combustion analyses agreed with the calculated data within ± 0.4% unless otherwise stated. Melting points / decomposition temperatures were determined on a Büchi apparatus after Dr. Tottoli and are uncorrected. Column chromatography was performed with Merck silica gel 60 (0,063-0,200 mm) or Acros organics silica gel (0,060-0,200 mm; pore diameter ca. 60 nm). Dichloromethane was dried and distilled over CaH_2, whereas THF was used after distillation over K/benzophenone. The progress of the reactions was monitored by thin-layer chromatography (TLC) performed with Merck silica gel 60 F-245 plates. Where necessary reactions were carried out in a nitrogen atmosphere.

General Procedures for Introducing a Boc-protective group: Procedure A (Compounds 1a,c,e,f). The amine (1 equiv) and $NaHCO_3$ (3 equiv) were dissolved in water (3 ml per mmol amine) and di-*tert*-butyl-dicarbonate was added. The resulting mixture was stirred at room temperature overnight. After separating the organic phase, the water was extracted with ethyl acetate. The combined organic extracts were washed with water, dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The Boc-protected amines were purified by column chromatography (70-89%).

Procedure B (Compounds 1a,g). The amine hydrochloride (1 equiv) and Et_3N (2.22 equiv) were dissolved in CH_2Cl_2 (4 ml per mmol amine) under nitrogen. After cooling to 0°C a solution of di-*tert*-butyl-dicarbonate (1.03 equiv) in a minimum amount of CH_2Cl_2 was added dropwise. The resulting solution was stirred at room temperature overnight, diluted with CH_2Cl_2 and washed with water. The combined organic extracts were dried (Na_2SO_4) and the solvent evaporated under reduced pressure. The Boc-protected amines were purified by column chromatography (94%).

Piperidine-1,4-dicarboxylic acid 4-ethyl 1-tert-butyl diester (1a). Starting from piperidine-4-carboxylic acid ethyl ester **1a** was synthesized as described in procedure A (78%) or procedure B (93%)[1]: colorless oil; R_f (petroleum ether / ethyl acetate = 5 / 1): 0.5; the NMR data agreed with literature[2, 3].

Piperidine-1,3-dicarboxylic acid 3-ethyl 1-tert-butyl diester (1b). Starting from piperidine-3-carboxylic acid ethyl ester **1b** was synthesized as described in literature[1]: colorless oil which crystallizes on standing (96%); mp = 31 °C; R_f (petroleum ether / ethyl acetate = 5 / 1): 0.5; the NMR data agreed with literature[4].

L-Pyrrolidine-1,2-dicarboxylic acid 1-tert-butyl 2-methyl diester (1c). Starting from L-proline methyl ester hydrochloride **1c** was synthesized as described in procedure A: colorless oil (70%); R_f (petroleum ether / ethyl acetate = 2 / 1): 0.5; the NMR data agreed with literature[5, 6]; $[\alpha]^D$ = -60.9 ° (RT, c = 1.05, MeOH).

***tert*-Butoxycarbonyl-amino-acetic acid methyl ester (1d). 1d** was obtained from Aldrich.

***tert*-Butoxycarbonyl-methyl-amino-acetic acid methyl ester (1e).** Starting from N-methyl-glycine ethyl ester **1e** was synthesized as described in procedure A: colorless oil (89%); R_f (petroleum ether / ethyl acetate = 5 / 1): 0.5; the NMR data agreed with literature[7].

D-*2-tert*-Butoxycarbonylamino-propionic acid methyl ester (1f). Starting from D-alanine methyl ester, **1f** was synthesized as described in procedure A, and chromatographed. The compound crystallized on standing: white crystals (79%); mp = 34 °C; R_f (petroleum ether / ethyl acetate = 1 / 2): 0.6; the NMR data agreed with literature[5, 8] ; $[\alpha]^D$ = +46.6 ° (RT, c = 0.55, MeOH).

***3-tert*-Butoxycarbonylamino-propionic acid ethyl ester (1g).** Starting from □-alanine ethyl ester, **1g** was synthesized as described in procedure B: colorless oil (94%); R_f (petroleum ether / ethyl acetate = 5 / 1): 0.4; ^{1}H NMR (DMSO-d_6) δ 1.17 (t, 7.15 Hz, 3H, CH_3), 1.36 (s, 9H, $C(CH_3)_3$), 2.39 (t, 6.91 Hz, 2H, CH_2CO), 3.14 (t, 6.91 Hz, 2H, CH_2N), 4.03 (t, 6.91 Hz, 2H, OCH_2), 6.84 (t, 5.0 Hz, 1H, NH); ^{13}C

NMR (DMSO-d_6) δ 14.35 (CH_3), 28.47 (3xCH_3), 34.57 (CH_2), 36.40 (CH_2), 60.14 (CH_2), 77.96 (Cq), 155.74 (CO), 171.51 (CO); EI-MS *m/z* 217 (M^+).

General Procedures for the Conversion of Esters to Hydrazides: Procedure C (Compounds 2a-g, 8a,c). The ester (1 equiv) and hydrazine hydrate (10-15 equiv) were refluxed for 3 hours. After standing at room temperature overnight, precipitated products were isolated by filtration. If no precipitate was formed, the solutions were extracted several times with CH_2CH_2. The combined organic extracts were dried (Na_2SO_4) and evaporated to dryness (33-92%).

4-Hydrazinocarbonyl-piperidine-1-carboxylic acid *tert*-butyl ester (2a). Starting from ester **1a** the compound was synthesized as described in procedure C, the product was isolated by filtration: white crystals (87%); mp = 105 °C; ^{1}H NMR (DMSO-d_6) δ 1.32-1.46 (m, 11H, $C(CH_3)_3$, 2CH), 1.56-1.60 (m, 2H, 2CH), 2.16-2.26 (m, 1H, CH), 2.62-2.74 (m, 2H, 2CH), 3.88-3.94 (m, 2H, 2CH), 4.17 (s, 2H, NH_2), 8.98 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.38 ($3CH_3$), 28.48 ($2CH_2$), 42.92 (CH), 43.49 ($2CH_2$), 78.90 (Cq), 154.11 (CO), 173.73 (CO); EI-MS *m/z* 243 (M^+).

3-Hydrazinocarbonyl-piperidine-1-carboxylic acid *tert*-butyl ester (2b). Starting from ester **1b** the compound was synthesized as described in procedure C, the product was isolated by extraction with CH_2Cl_2: colorless, vitreous compound (85%); mp = 55 °C; ^{1}H NMR ($CDCl_3$) δ 1.44 (m, 10H, $C(CH_3)_3$, CH), 1.57-1.69 (m, 1H, CH), 1.70-1.90 (m, 2H, 2CH), 2.20-2.34 (m, 1H, CH), 2.80-3.00 (m, 1H, CH), 3.07-3.18 (m, 1H, CH), 3.85-3.95 (m, 2H, 2CH); ^{13}C NMR (DMSO-d_6) δ 24.16 ($2CH_2$), 27.62 (CH_2), 28.46 ($3CH_3$), 41.42 (CH), 45.73 (CH_2), 80.08 (Cq), 154.82 (CO), 173.82 (CO); EI-MS *m/z* 187.1 (M^+-56).

L-2-Hydrazinocarbonyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester (2c). Starting from ester **1c** the compound was synthesized as described in procedure C, the product was isolated by extraction with CH_2Cl_2: colorless, vitreous compound, which crystallized on standing (87%); mp = 80 °C; ^{1}H NMR (DMSO-d_6) δ 1.31, 1.37 (s each, 9H, $C(CH_3)_3$), 1.67-1.87 (m, 3H, 3CH), 1.93-2.07 (m, 1H, CH), 3.21-3.35 (m, 1H, CH), 3.92-4.03 (m, 1H, CH), 4.16 (s, 2H, NH_2), 9.03 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.59, 24.21 (CH_2), 28.33, 28.48 ($3CH_3$), 30.39, 31.24 (CH_2), 46.70, 46.92 (CH_2), 58,48, 58.62 (CH), 78.69, 78.76 (Cq), 153.49, 153.79 (CN), 171.85, 172.20 (CO); EI-MS *m/z* 229 (M^+); $[\alpha]^D$ = -52.1 ° (RT, c = 0.60, MeOH).

Hydrazinocarbonylmethyl-carbamic acid *tert*-butyl ester (2d). Starting from ester **1d** the compound was synthesized as described in procedure C, the product was isolated by filtration (92%): white crystals; mp = 122 °C, the NMR data agreed with literature[9].

Hydrazinocarbonylmethyl-methyl-carbamic acid *tert*-butyl ester (2e). Starting from ester **1e** the compound was synthesized as described in procedure C, the product was isolated by extraction with CH_2Cl_2: white crystals (71%); mp = 72 °C; ^{1}H NMR (DMSO-d_6) δ 1.33, 1.38 (s each, 9H, $C(CH_3)_3$), 2.75, 2.79 (s each, 3H, NCH_3), 3.68, 3.71 (s each, 2H, CH_2), 4.18 (s, 2H, NH_2), 8.99, 9.02 (s each, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.31 ($3CH_3$), 35.56, 35.64 (CH_2), 49.77, 50.41 (CH_3), 78.94, 79.04 (Cq), 155.30, 155.48 (CN), 168.37, 168.43 (CO); EI-MS *m/z* 204 (M^+).

D-(1-Hydrazinocarbonyl-ethyl)-carbamic acid *tert*-butyl ester (2f). Starting from ester **1f** the compound was synthesized as described in procedure C, the product was isolated by extraction with CH_2Cl_2: white crystals (33%); mp = 89 °C; the NMR data agreed with its L-isomer in literature[9]; $[\alpha]^D$ = +22.1 ° (RT, c = 0.74, MeOH).

(2-Hydrazinocarbonyl-ethyl)-carbamic acid *tert*-butyl ester (2g). Starting from ester **1g** the compound was synthesized as described in procedure C, the product was isolated by filtration: white crystals (82%); mp = 102 °C[10]; ^{1}H NMR (DMSO-d_6) δ 1.35 (s, 9H, $C(CH_3)_3$), 2.14 (t, 7.21 Hz, 2H, CH_2CO), 3.09 (q, 2H, 6.99 Hz, CH_2), 4.15 (s, 2H, NH_2), 6.75 (t, 5.41 Hz, 1H, NHCO), 8.92 (s, 1H, NHNH$_2$); ^{13}C NMR (DMSO-d_6) δ 28.54 ($3CH_3$), 34.26 (CH_2), 37.04 (CH_2), 77.90 (Cq), 155.73 (CN), 170.05 (CO); EI-MS *m/z* 147 (M^+-56).

General Procedures for the Synthesis of Boc-protected Oxadiazol-2-ones: Procedure D (Compounds 3a-g). To a solution of hydrazide **2** (1 equiv) in a mixture of THF (10 ml per mmol) and DMF (1 ml per mmol) were added subsequently N,N'-carbonyldiimidazole (CDI) (1.5 equiv) and triethylamine (2 equiv). After refluxing for 15 hours, the solvent was removed by evaporation under

vacuum. The residue was treated with CH_2CH_2 and washed with water. The organic phase was dried (Na_2SO_4) and the solvent removed under reduced pressure. Chromatography yielded the pure compounds (33-94%).

4-(5-Oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-piperidine-1-carboxylic acid *tert*-butyl ester. (3a). Starting from **2a** the compound was synthesized as described in procedure D, the product was purified by chromatography: white crystals (78%); mp = 136 °C; R_f (petroleum ether / ethyl acetate = 1 / 1): 0.4; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H, $C(CH_3)_3$), 1.60-1.73 (m, 2H, 2CH), 1.92-1.98 (m, 2H, 2CH), 2.69-2.79 (m, 1H, CH), 2.85-2.93 (m, 2H, 2CH), 4.05-4.08 (m, 2H, 2CH), 9.77 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 27.95 (CH_2), 28.48 ($3CH_3$), 34.04 (CH), 42.82 (CH_2), 80.19 (Cq), 154.80 (Cq), 155.36 (Cq), 159.57 (Cq); EI-MS *m/z* 269 (M^+).

3-(5-Oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-piperidine-1-carboxylic acid *tert*-butyl ester. (3b). Starting from **2b** the compound was synthesized as described in procedure D, the product was purified by chromatography: white crystals (72%); mp = 136 °C; R_f (petroleum ether / ethyl acetate = 1 / 1): 0.4; ^{1}H NMR (DMSO-d_6) δ 1.46-1.47 (m, 11 H, 3CH, $C(CH_3)_3$), 1.66-1.86 (m, 2H, 2CH), 2.04-2.09 (m, 1H, CH), 2.70-2.79 (m, 1H, CH), 2.90-3.25 (m, 1.5H, 1.5CH), 3.80-4.25 (m, 1.5H, 1.5CH), 9.77 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 23.76 (CH_2), 27.13 (CH_2), 28.44 ($3CH_3$), 34.31 (CH), 44.03 (CH_2), 46.08 (CH_2), 80.41 (Cq), 154.73 (Cq), 155.17 (Cq), 158.19 (Cq); EI-MS *m/z* 269 (M^+).

L-2-(5-Oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester. (3c). Starting from **2c** the compound was synthesized as described in procedure D, the product was purified by chromatography: white crystals (33%); mp = 133 °C; R_f (petroleum ether / ethyl acetate = 2 / 1): 0.3; ^{1}H NMR (DMSO-d_6) δ 1.29, 1.38 (s each, 9H, $C(CH_3)_3$), 1.85-2.02 (m, 3H, 3CH), 2.11-2.29 (m, 1H, CH), 3.26-3.39 (m, 2H, 2CH), 4.55-4.63 (m, 1H, CH), 12.21 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 23.28, 23.96 (CH_2), 28.16, 28.34 ($3CH_3$), 30.00, 30.99 (CH_2), 46.44, 46.66 (CH_2), 53.17, 53.30 (CH), 79.44 (Cq), 153.04, 153.64 (Cq), 154.99 (Cq), 157.29, 157.60 (Cq); EI-MS *m/z* 199 (M^+-56); $[\alpha]^D$ = -89.0 ° (RT, c = 1.40, MeOH).

(5-Oxo-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-carbamic acid *tert*-butyl ester. (3d). Starting from **2d** the compound was synthesized as described in procedure D, the product was purified by chromatography: white crystals (49%); mp = 131 °C; R_f (petroleum ether / ethyl acetate = 1 / 1): 0.3; ^{1}H NMR (DMSO-d_6) δ 1.36 (s, 9H, $C(CH_3)_3$), 4.01 (d, 5.85 Hz, 2H, CH_2), 7.44 (t, 5.66 Hz, 1H, $CH_2\underline{NH}$), 12.18 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 28.41 ($3CH_3$), 36.25 (CH_2), 78.89 (Cq), 155.04 (Cq), 155.15 (Cq), 155.74 (Cq); EI-MS *m/z* 216 (M^++1).

Methyl-(5-oxo-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-carbamic acid *tert*-butyl ester. (3e). Starting from **2e** the compound was synthesized as described in procedure D, the product was purified by chromatography: colorless gum (44%); R_f (petroleum ether / ethyl acetate = 2 / 1): 0.3; ^{1}H NMR (DMSO-d_6) δ 1.35, 1.39 (s each, 9H, $C(CH_3)_3$), 2.81 (s, 3H, NCH_3), 4.28 (s, 2H, CH_2), 12.25 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.20 ($3CH_3$), 34.72 (CH_2), 43.73, 44.54 (CH_3), 79.85 (Cq), 154.06 (Cq), 154.16 (Cq), 155.13 (Cq); EI-MS *m/z* 229 (M^+).

D-[1-(5-Oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-ethyl]-carbamic acid *tert*-butyl ester. (3f). Starting from **2f** the compound was synthesized as described in procedure D, the product was purified by chromatography: white crystals (94%); mp = 114 °C; R_f (petroleum ether / ethyl acetate = 1 / 1): 0.4; ^{1}H NMR (DMSO-d_6) δ 1.29 (d, 7.05 Hz, 3H, $CH\underline{CH_3}$), 1.37 (s, 9H, $C(CH_3)_3$), 4.52 (q, 7.28 Hz, 1H, $\underline{CH}CH_3$), 7.45 (d, 7.86 Hz, 1H, NH), 12.17 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 17.47 (CH_3), 28.43 ($3CH_3$), 43.07 (CH), 78.78 (Cq), 155.10 (Cq), 155.17 (Cq), 157.84 (Cq); EI-MS *m/z* 214 (M^+-15); $[\alpha]^D$ = +64.2 ° (RT, c = 0.74, MeOH).

[2-(5-Oxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-ethyl]-carbamic acid *tert*-butyl ester. (3g). Starting from **2g** the compound was synthesized as described in procedure D, the product was purified by chromatography: white crystals (80%); mp = 91 °C; R_f (petroleum ether / ethyl acetate = 1 / 1): 0.3; ^{1}H NMR (DMSO-d_6) δ 1.34 (s, 9H, $C(CH_3)_3$), 2.58 (t, 6.46 Hz, 2H, $NHCH_2\underline{CH_2}$), 3.17 (t, 6.46 Hz, 2H, $NH\underline{CH_2}CH_2$), 6.98 (t, 5.84 Hz, $\underline{NH}CH_2$), 12.00 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 27.26 (CH_2), 28.48 ($3CH_3$), 36.88 (CH_2), 78.13 (Cq), 155.44 (Cq), 155.63 (Cq), 155.82 (Cq); EI-MS *m/z* 156 (M^+-73).

General Procedure for the Synthesis of Boc-protected Oxadiazol-2-thiones: Procedure E (Compounds 4a-g). To a mixture of hydrazide **2** (1 equiv) and KOH (1 equiv) in ethanol (1 ml per mmol) carbon disulfide (3.3 equiv) was added. After refluxing for 12 hours the mixture was poured on crushed ice, and the obtained mixture was brought to pH 7. The solution was extracted several times with ethyl acetate. The combined organic extracts were dried (Na_2SO_4), evaporated to dryness and purified by chromatography (24-85%).

4-(5-Thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-piperidine-1-carboxylic acid *tert*-butyl ester. (4a). Starting from **2a** the compound was synthesized as described in procedure E, the product was purified by chromatography and subsequent recrystallization in ethyl acetate: white crystals (85%); mp = 182 °C; R_f (petroleum ether / ethyl acetate = 1 / 1): 0.5; ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H, $C(CH_3)_3$), 1.66-1.79 (m, 2H, 2CH), 1.97-2.03 (m, 2H, 2CH), 2.84-1.97 (m, 3H, 3CH), 4.08-4.13 (m, 2H, 2CH), 12.01 (s, 1H, NH); ^{13}C NMR ($CDCl_3$) δ 28.21 (CH_2), 28.51 ($3CH_3$), 33.54 (CH), 42.86 (CH_2), 80.66 (Cq), 154.99 (Cq), 165.84 (Cq), 178.60 (Cq).

3-(5-Thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-piperidine-1-carboxylic acid *tert*-butyl ester. (4b). Starting from **2b** the compound was synthesized as described in procedure E, the product was purified by chromatography: white crystals (60%); mp = 161 °C; R_f (petroleum ether / ethyl acetate = 1 / 1): 0.5; ^{1}H NMR (DMSO-d_6) δ 1.46-1.60 (m, 12H, 3CH, $C(CH_3)_3$), 1.68-1.80 (m, 2H, 2CH), 2.10-2.16 (m, 1H, CH), 2.85-3.12 (m, 2H, 2CH), 3.73-4.33 (m, 1H, CH), 12.11 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.85 (CH_2), 27.43 (CH_2), 28.49 ($3CH_3$), 33.86 (CH), 44.26 (CH_2), 45.66 (CH_2), 81.08 (Cq), 155.01 (Cq), 164.26 (Cq), 178.49 (Cq); EI-MS *m/z* 285 (M^+).

L-2-(5-Thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-pyrrolidine-1-carboxylic acid *tert*-butyl ester. (4c). Starting from **2c** the compound was synthesized as described in procedure E, the product was purified by chromatography and subsequent recrystallization in ethyl acetate: white crystals (49%); mp = 192 °C; R_f (petroleum ether / ethyl acetate = 1 / 1): 0.4; ^{1}H NMR (DMSO-d_6) δ 1.26, 1.37 (s each, 9H, $C(CH_3)_3$), 1.86-1.89 (m, 2H, 2CH), 1.99-2.09 (m, 1H, CH), 2.17-2.29 (m, 1H, CH), 3.28-3.43 (m, 2H, 2CH), 4.75-4.82 (m, 1H, CH), 14.48 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 23.39, 24.06 (CH_2), 28.11, 28.31 ($3CH_3$), 30.33, 31.32 (CH_2), 46.52, 46.73 (CH), 52.70 (CH_2), 79.75 (Cq), 152.85, 153.71 (Cq), 164.38, 164.65 (Cq), 177.91 (Cq); EI-MS *m/z* 271 (M^+); $[\alpha]^D$ = -128.3 ° (RT, c = 0.75, MeOH).

(5-Thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-carbamic acid *tert*-butyl ester. (4d). Starting from **2d** the compound was synthesized as described in procedure E, the product was purified by chromatography: slightly yellow crystals (51%); mp = 106 °C; R_f (petroleum ether / ethyl acetate = 1 / 1): 0.4; ^{1}H NMR (DMSO-d_6) δ 1.37 (s, 9H, $C(CH_3)_3$), 4.19 (d, 5.80 Hz, 2H, CH_2), 7.56 (t, 5.69 Hz, 1H, $\underline{NH}CH_2$), 14.43 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.40 ($3CH_3$), 35.71 (CH_2), 79.12 (Cq), 155.75 (Cq), 162.00 (Cq), 178.11 (Cq); EI-MS *m/z* 231 (M^+).

Methyl-(5-thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-ylmethyl)-carbamic acid *tert*-butyl ester. (4e). Starting from **2e** the compound was synthesized as described in procedure E, the product was purified by chromatography: slightly yellow gum (64%); R_f (petroleum ether / ethyl acetate = 2 / 1): 0.3; ^{1}H NMR (DMSO-d_6) δ 1.33, 1.39 (s each, 9H, $C(CH_3)_3$), 2.84 (s, 3H, NCH_3), 4.46 (s, 2H, CH_2), 14.51 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.16 ($3CH_3$), 34.98 (CH_3), 43.35, 44.05 (CH_2), 80.08 (Cq), 154.70, 155.14 (Cq), 161.34 (Cq), 178.11 (Cq).

D-[1-(5-Thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-ethyl]-carbamic acid *tert*-butyl ester. (4f). Starting from **2f** the compound was synthesized as described in procedure E, with the exception that N,N'-thiocarbonyldiimidazole (TCDI) was used instead of CDI, the product was purified by chromatography: slightly yellow crystals (24%); mp = 136 °C; R_f (petroleum ether / ethyl acetate = 1 / 1): 0.6; ^{1}H NMR (DMSO-d_6) δ 1.35 (m, 12H, $C(CH_3)_3$,$CH\underline{CH_3}$), 4.70 (q, 7.36 Hz, 1H, $\underline{CH}CH_3$), 7.61 (d, 7.79 Hz, 1H, $CH\underline{NH}$), 14.44 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 17.75 (CH_3), 28.41 ($3CH_3$), 42.76 (CH_2), 79.03 (Cq), 164.91 (Cq), 161.34 (Cq), 178.14 (Cq); EI-MS *m/z* 245 (M^+); $[\alpha]^D$ = +71.0 ° (RT, c = 0.24, MeOH).

[2-(5-Thioxo-4,5-dihydro-[1,3,4]oxadiazol-2-yl)-ethyl]-carbamic acid *tert*-butyl ester. (4g). Starting from **2g** the compound was synthesized as described in procedure E, the product was purified

by chromatography: white crystals (73%); mp = 153 °C; R_f (petroleum ether / ethyl acetate = 1 / 1): 0.5; ^{1}H NMR (DMSO-d_6) δ 1.34 (s, 9H, $C(CH_3)_3$), 2.77 (t, 6.36 Hz, $\underline{CH_2}CH_2NH$), 3.22 (q, 6.29 Hz, $\underline{CH_2}NH$), 7.02 (t, 5.82 Hz, $NH\underline{CH_2}$), 14.27 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 26.50 (CH_2), 28.48 ($3CH_3$), 37.04 (CH_2), 78.21 (Cq), 155.83 (Cq), 162.70 (Cq), 178.16 (Cq); EI-MS *m/z* 245 (M^+).

1-Methyl-piperidine-4-carboxylic acid ethyl ester. (7a). Piperidine-4-carboxylic acid ethyl ester (1 equiv) was cooled in an ice-bath and formic acid (85%, 5 equiv) was added dropwise. After adding formalin (1.2 equiv) the mixture was refluxed overnight. The mixture was brought to pH 3 with conc. HCl and evaporated under reduced pressure. The residue was treated with aq. NaOH (25%) and extracted with ether. The combined organic extracts were dried ($MgSO_4$), evaporated to dryness and distilled under reduced pressure (Kugelrohr): colorless oil (47%); ^{1}H-NMR data agreed with literature[11]; ^{13}C NMR (DMSO-d_6) δ 14.40 (CH_3), 28.25 (CH_2), 46.40 (CH_3), 54.67 (CH_2), 60.06 (CH_2), 174.74 (Cq); EI-MS *m/z* 171 (M^+).

1-Benzyl-piperidine-4-carboxylic acid ethyl ester. (7b). Starting from piperidine-4-carboxylic acid ethyl ester compound **7b** was prepared as described in literature[11]. The NMR data agreed with literature[11, 12].

7c-e were commercially available.

1-Methyl-piperidine-4-carboxylic acid hydrazide. (8a). Starting from **7a** the compound was synthesized as described in procedure C: white crystals (45%); mp = 146 °C[13]; ^{1}H NMR (DMSO-d_6) δ 1.52-1.63 (m, 4H, 4CH), 1.72-1.80 (m, 2H, 2CH), 1.88-2.02 (m, 1H, CH), 2.10 (s, 3H, CH_3), 2.70-2.77 (m, 2H, 2CH), 4.11 (s, 2H, NH_2), 8.92 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.76 (CH_2), 40.12 (CH), 46.51 (CH_3), 55.15 (CH_2), 174.30 (Cq); EI-MS *m/z* 157 (M^+).

1-Benzyl-piperidine-4-carboxylic acid hydrazide. (8b). Was synthesized as described in literature[13]: Mp = 119 °C; ^{1}H NMR (DMSO-d_6) δ 1.53-1.64 (m, 4H, 4CH), 1.81-1.90 (m, 2H, 2CH), 1.95-2.06 (m, 1H, CH), 2.75-2.82 (m, 2H, 2CH), 3.40 (s, 2H, CH_2Ph), 4.15 (s, 2H, NH_2), 7.18-7.32 (m, 5H, CH_{Ar}), 8.92 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.81 ($2CH_2$), 40.62 (CH), 52.97 ($2CH_2$), 62.68 (CH_2-Ph), 127.12 (CH), 128.43 (2CH), 129.03 (2CH), 138.80 (Cq), 174.26 (Cq).

Dimethylamino acetic acid hydrazide. (8c). Starting from dimethylamino acetic acid ethyl ester **8c** was synthesized as described in procedure C: colorless oil (78%); ^{1}H NMR (DMSO-d_6) δ 2.15 (s, 6H, $N(CH_3)_2$), 2.82 (s, 2H, CH_2), 4.25 (s, 2H, NH_2), 8.87 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 45.65 (CH_3), 61.47 (CH_2), 168.81 (Cq); EI-MS *m/z* 118 (M^+).

Cyclohexanecarboxylic acid hydrazide (8d). Starting from ethyl cyclohexanecarboxylate compound **8d** was prepared according to procedure C: white needles (94%); mp = 158 °C[14]; ^{1}H NMR (DMSO-d_6) δ 1.08-1.37 (m, 5H, 5CH), 1.57-1.69 (m, 5H, 5CH), 1.96-2.07 (m, 1H, CH), 4.09 (s, 2H, NH_2), 8.86 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 25.58 ($2CH_2$), 25.72 (CH_2), 29.43 ($2CH_2$), 52.54 (CH), 174.97 (Cq); EI-MS *m/z* 142 (M^+).

Acetic acid hydrazide (8e) was obtained from Aldrich.

General Procedure for the Synthesis of acylated Semicarbazides: Procedure K (Compounds 12a,d, 13a,d). After adding isocyanate to a solution of hydrazide in N,N-dimethyl acetamide, the mixture was stirred at RT for 24 h. The solvent was removed under reduced pressure and the residue recrystallized or chromatographed (54-92%).

4-Benzyl-1-(4-formyl-piperidine-1-carboxylic acid *tert*-butyl ester) semicarbazide. (12a). Starting from **2a** (1 equiv) and benzylisocyanate (1 equiv) **12a** was synthesized as described in procedure K, and recrystallized from ethyl acetate: white crystals (84%); mp = 171 °C; ^{1}H NMR (DMSO-d_6) δ 1.32-1.45 (m, 11H, C(CH3)3, 2CH), 1.66-1.72 (m, 2H, 2CH), 2.25-2.40 (m, 1H, CH), 2.60-2.80 (m, 2H, 2CH), 3.85-3.97 (m, 2H, 2CH), 4.20 (d, 5.97 Hz, 2H, CH_2-Ph), 6.84 (t, 5.79 Hz, 1H, $\underline{NH}CH_2$), 7.17-7.31 (m, 5H, CH_{Ar}), 7.78 (s, 1H, NH), 9.52 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.25 ($2CH_2$), 28.39 ($3CH_3$), 40.04 (CH), 42.89 ($2CH_2$), 78.90 (Cq), 126.81 (CH), 127.18 (2CH), 128.40 (2CH), 140.87 (Cq), 154.14 (Cq), 158.55 (Cq), 174.20 (Cq); EI-MS *m/z* 319 (M^+-57).

4-Benzyl-1-(2-amino-acetyl-N-carboxylic acid *tert*-butyl ester) semicarbazide. (12d). Starting from **2d** (1 equiv) and benzylisocyanate (1 equiv) **12d** was synthesized as described in procedure K, and recrystallized from ethyl acetate / n-hexane: white crystals (92%); mp = 153 °C; ^{1}H NMR (DMSO-d_6)

δ 1.34 (s, 9H, $C(CH_3)_3$), 3.56 (d, 5.83 Hz, 2H, NCH_2CO), 4.21 (d, 5.97 Hz, 2H, CH_2-Ph), 6.88 (t, 5.60 Hz, 1H, NH), 7.04 (t, 5.71 Hz, 1H, NH), 7.17-7.30 (m, 5H, CH_{Ar}), 7.90 (s, 1H, NH), 9.63 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.47 ($3CH_3$), 42.28 (CH_2), 42.84 (CH_2), 78.44 (Cq), 126.80 (CH), 127.14 (2CH), 128.40 (2CH), 140.77 (Cq), 156.18 (Cq), 158.44 (Cq), 169.75 (Cq); EI-MS *m/z* 266 (M^+-56).

4-Benzyl-1-(4-thioformyl-piperidine-1-carboxylic acid *tert*-butyl ester) semicarbazide. (13a). Starting from **2a** (1 equiv) and benzylisothiocyanate (1 equiv) **13a** was synthesized as described in procedure K, and chromatographed: white crystals (68%); mp = 188 °C; R_f (ethyl acetate / petroleum ether = 1 / 1): 0.06; ^{1}H NMR (DMSO-d_6) δ 1.30-1.44 (m, 11H, C(CH3)3, 2CH), 1.72-1.76 (m, 2H, 2CH), 2.29-2.37 (m, 1H, CH), 2.62-2.79 (m, 2H, 2CH), 3.90-3.94 (m, 2H, 2CH), 4.70 (d, 5.74 Hz, 2H, CH_2-Ph), 7.19-7.31 (m, 5H, CH_{Ar}), 8.37 (t, 1H, $\underline{NH}CH_2$), 9.26 (s, 1H, NH), 9.76 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.12 ($2CH_2$), 28.39 ($3CH_3$), 40.19 (CH), 43.00 ($2CH_2$), 46.96 (CH_2), 78.92 (Cq), 126.69 (CH), 127.24 (2CH), 128.34 (2CH), 139.65 (Cq), 154.13 (Cq), 174.04 (Cq); FD-MS *m/z* 392 (M^+).

4-Benzyl-1-(2-amino-acetyl-N-carboxylic acid *tert*-butyl ester) semicarbazide. (13d). Starting from **2d** (1 equiv) and benzylisothiocyanate (1 equiv) **13d** was synthesized as described in procedure K, and chromatographed with petroleum ether / ethyl acetate = 1 / 5: white crystals (54%); mp = 153 °C; R_f: 0.6; ^{1}H NMR (DMSO-d_6) δ 1.37 (s, 9H, $C(CH_3)_3$), 3.59 (d, 5.48 Hz, 2H, NCH_2CO), 4.71 (d, 5.48 Hz, 2H, CH_2-Ph), 7.09 (t, 5.48 Hz, 1H, NH), 7.20-7.30 (m, 6H, NH, CH_{Ar}), 8.32 (t, 5.48 Hz, 1H, NH), 9.43 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.46 ($3CH_3$), 42.40 (CH_2), 46.92 (CH_2), 78.59 (Cq), 126.93 (CH), 127.24 (2CH), 128.36 (2CH), 139.43 (Cq), 156.29 (Cq), 169.47 (Cq), 182.27 (Cq); FD-MS *m/z* 338 (M^+).

General Procedure for the Synthesis of 1,2,4-triazol-ones and -thiones: Procedure L (Compounds 14a,15a). A solution of the semicarbazide derivative (1 equiv) in 2% NaOH aq. (5 ml / equiv) is refluxed for 2 h. The mixture is cooled in an ice bath and slowly neutralized with 2% HCl aq. The resulting precipitate is collected by filtration and dried under vacuum (44-82%).

4-(4-Benzyl-5-oxo-4,5-dihydro-1*H*-[1,2,4]triazol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester. (14a). Starting from **12a** compound **14a** was synthesized as described in procedure L: white crystals (55%); mp = 180 °C; ^{1}H NMR (DMSO-d_6) δ 1.26-1.39 (m, 11H, $C(CH_3)_3$, 2CH), 1.52-1.56 (m, 2H, 2CH), 2.66-2.73 (m, 3H, 3CH), 3.82-3.86 (m, 2H, 2CH), 4.01 (s, 2H, CH_2-Ph), 7.19-7.37 (m, 5H, CH_{Ar}), 11.62 (s, 1H, NH); ^{13}C NMR (DMSO-d_6) δ 28.35 ($3CH_3$), 29.52 ($2CH_2$), 32.46 (CH), 43.29 ($3CH_2$), 78.99 (Cq), 127.14 (2CH), 127.87 (CH), 129.03 (2CH), 137.39 (Cq), 150.31 (Cq), 154.09 (Cq), 155.44 (Cq); FD-MS *m/z* 358 (M^+).

4-(4-Benzyl-5-thioxo-4,5-dihydro-1*H*-[1,2,4]triazol-3-yl)-piperidine-1-carboxylic acid *tert*-butyl ester. (15a). Starting from **13a** compound **15a** was synthesized as described in procedure L: white crystals (82%); mp = 269 °C; ^{1}H NMR (DMSO-d_6) δ 1.32-1.49 (m, 13H, $C(CH_3)_3$, 4CH), 2.62-2.89 (m, 3H, 3CH), 3.80-3.58 (m, 2H, 2CH), 5.29 (s, 2H, CH_2-Ph), 7.22-7.37 (m, 5H, CH_{Ar}); EI-MS *m/z* 374 (M^+).

4-(5-Methyl-[1,3,4]oxadiazol-2-yl)-piperidine-1-carboxylic acid *tert*-butyl ester. (18). Starting from **2a** compound **18** was prepared according to procedure I, and chromatographed: white slightly green crystals (66%); mp = 69 °C; R_f (ethyl acetate / petroleum ether = 3 / 1): 0.2; ^{1}H NMR (DMSO-d_6) δ 1.38 (s, 9H, $C(CH_3)_3$), 1.46-1.59 (m, 2H, 2CH), 1.91-1.96 (m, 2H, 2CH), 2.44 (s, 3H, CH_3), 2.84-3.00 (m, 2H, 2CH), 3.06-3.16 (m, 1H, CH), 3.85-3.89 (m, 2H, 2CH); ^{13}C NMR (DMSO-d_6) δ 10.77 (CH_3), 28.37 ($3CH_3$), 28.94 ($2CH_2$), 32.37 (CH), 42.77 ($2CH_2$), 79.08 (Cq), 154.16 (Cq), 163.73 (Cq), 168.49 (Cq); EI-MS *m/z* 267 (M^+).

IR-Data (4000-1450 cm^{-1}):

3a (KBr) ν_{max} 3180, 3140, 2940, 2920, 2820,2780,1800,1760,1650,1610,1460 cm^{-1}.
3b (KBr) ν_{max} 3070, 2950, 2920, 2880, 2820, 2760, 1765, 1630, 1450 cm^{-1}.
3c (KBr) ν_{max} 3060, 2950, 2860, 2800, 1790, 1760, 1635, 1465 cm^{-1}.
3d (KBr) ν_{max} 3460, 3140, 2970, 2965, 2910, 2800, 1760, 1660, 1500 cm^{-1}.
3f (KBr) ν_{max} 3290, 3140, 2960, 2910, 1760, 1735, 1615, 1605, 1495 cm^{-1}.
3g (KBr) ν_{max} 3310, 3220, 2960, 2950, 2930, 2905, 1760, 1725, 1690, 1665, 1610, 1505 cm^{-1}.
4a (KBr) ν_{max} 3090, 3060, 2940, 2930, 2720, 1650, 1600, 1485, 1460 cm^{-1}.
4b (KBr) ν_{max} 3070, 2940, 2900, 1640, 1600, 1485 cm^{-1}.
4c (KBr) ν_{max} 3020, 2940, 2890, 2740, 1620, 1495 cm^{-1}.
4d (KBr) ν_{max} 3325, 3305, 3060, 2940, 2910, 1660, 1500 cm^{-1}.
4f (KBr) ν_{max} 3280, 3090, 2940, 2895, 1660, 1470 cm^{-1}.
4g (KBr) ν_{max} 3240, 3060, 2940, 2900, 1655, 1610, 1515, 1480 cm^{-1}.
5a (KBr) ν_{max} 3230, 2910, 800, 2770, 2700, 2470, 1765, 1735, 1620 cm^{-1}.
5b (KBr) ν_{max} 3060, 2910, 2790, 1760, 1610, 1575 cm^{-1}.
5c (KBr) ν_{max} 3120, 2820, 2670, 2500, 2400, 1755, 1720, 1610 cm^{-1}.
5d (KBr) ν_{max} 3160, 3060, 2970, 2920, 2600, 1750, 1615, 1570, 1535, 1475 cm^{-1}.
5e (KBr) ν_{max} 3000, 2880, 2750, 2690, 2460, 1730, 1620, 1575, 1450 cm^{-1}.
5f (KBr) ν_{max} 2960, 1730, 1615, 1570, 1485 cm^{-1}.
5g (KBr) ν_{max} 3060, 2895, 1755, 1610, 1580, 1465 cm^{-1}.
6a (KBr) ν_{max} 3380, 3020, 2990, 2930, 2820, 2760, 2740, 2380, 2455, 1600, 1555, 1500 cm^{-1}.
6b (KBr) ν_{max} 3000, 2890, 2790, 2740, 2600, 1600, 1550, 1475 cm^{-1}.
6c (KBr) ν_{max} 3410, 3120, 2920, 2710, 2540, 1475 cm^{-1}.
6d (KBr) ν_{max} 3410, 3300, 2880, 1485, 1465 cm^{-1}.
6e (KBr) ν_{max} 2900, 2380, 1610, 1565, 1475 cm^{-1}.
6g (KBr) ν_{max} 3150, 3060, 2940, 2860, 1610, 1545, 1475 cm^{-1}.
9a (KBr) ν_{max} 2970, 2920, 2770, 2600, 2530, 2500, 1760, 1620, 1460 cm^{-1}.
9b (KBr) ν_{max} 2980, 2910, 2610, 2580, 2520, 1760, 1600, 1485, 1465 cm^{-1}.
9c (KBr) ν_{max} 2955, 2920, 2800, 2755, 1800, 1760, 1620, 1460 cm^{-1}.
10a (KBr) ν_{max} 2990, 2930, 2630, 1560 cm^{-1}.
10b (KBr) ν_{max} 3000, 2930, 1565 cm^{-1}.
10c (KBr) ν_{max} 2960, 1570, 1485 cm^{-1}.
11 (KBr) ν_{max} 3070, 3000, 2975, 2910, 2780, 2740, 1565, 1500, 1480, 1455 cm^{-1}.
12a (KBr) ν_{max} 3250, 2940, 2900, 2830, 1670, 1640, 1590, 1535 cm^{-1}.
12d (KBr) ν_{max} 3320, 3220, 3050, 3000, 2940, 2900, 1685, 1660, 1630, 1530, 1450 cm^{-1}.
13a (KBr) ν_{max} 3210, 2940, 2900, 2830, 1650, 1530, 1460 cm^{-1}.
13d (KBr) ν_{max} 3256, 3148, 3040, 2971, 1682, 1559,1515 cm^{-1}.
14a (KBr) ν_{max} 3160, 3000, 2920, 2900, 2850, 2830, 1700, 1670, 1640, 1550 cm^{-1}.
15a (KBr) ν_{max} 3190, 3000, 2920, 2820, 1675, 1545, 1480 cm^{-1}.
16a (KBr) ν_{max} 3140, 2920, 2760, 2700, 2470, 1700, 1675, 1650, 1550 cm^{-1}.
16d (KBr) ν_{max} 3300, 3230, 3140, 3000, 2940, 2900, 2700, 1670, 1590, 1565, 1480 cm^{-1}.
17a (KBr) ν_{max} 3050, 3000, 2900, 2750, 2700, 2670, 2440, 1550, 1490 cm^{-1}.
17d (KBr) ν_{max} 3338, 2920, 2708, 2639, 1629, 1477 cm^{-1}.
18 (KBr) ν_{max} 2970, 2940, 2900, 2830, 1665, 1565, 1540 cm^{-1}.
19 (KBr) ν_{max} 3050, 2920, 2760, 1670, 1575, 1470 cm^{-1}.

Elemental analysis data

compound	found (calculated)			
5a	C 41.09	H 5.84	N 20.18	
	(C 40.88	H 5.88	N 20.43)	
5b	C 40.89	H 5.99	N 20.25	
	(C 40.88	H 5.88	N 20.43)	
5c	C 37.68	H 5.24	N 21.95	
	(C 37.61	H 5.26	N 21.93)	
5d	C 23.71	H 4.06	N 27.61	
	(C 23.79	H 3.99	N 27.73)	
5e	C 28.89	H 5.03	N 25.23	
	(C 29.02	H 4.87	N 25.38)	
5f	C 29.15	H 4.94	N 25.47	
	(C 29.02	H 4.87	N 25.38)	
5g	C 28.92	H 4.91	N 25.39	
	(C 29.02	H 4.87	N 25.38)	
6a	C 36.97	H 5.80	N 18.26	
	(C 36.92	H 5.61	N 18.45)	
6b	C 37.09	H 5.41	N 18.42	S 14.18
	(C 37.17	H 5.57	N 18.58	S 14.17)
6c	C 33.86	H 5.05	N 19.56	S 15.24
	(C 33.72	H 5.03	N 19.66	S 15.01)
6d	C 21.90	H 3.82	N 24.93	S 18.93
	(C 21.50	H 3.61	N 25.07	S 19.13)
6e	C 26.61	H 4.68	N 23.06	S 17.51
	(C 26.45	H 4.44	N 23.13	S 17.65)
6g	C 26.66	H 4.47	N 22.88	
	(C 26.45	H 4.44	N 23.13)	
9a	C 41.83	H 6.29	N 18.06	
	(C 42.02	H 6.61	N 18.38)	
9b	C 56.64	H 6.25	N 14.13	
	(C 56.85	H 6.13	N 14.21)	
9c	C 42.12	H 6.38	N 29.49	
	(C 41.95	H 6.35	N 29.35)	
9d	C 55.91	H 7.40	N 16.36	
	(C 55.93	H 7.19	N 16.66)	
9e	C 35.95	H 4.13	N 27.71	
	(C 36.00	H 4.03	N 27.99)	
10a	C 48.12	H 6.52	N 20.95	S 16.10
	(C 48.22	H 6.58	N 21.09	S 16.09)
10b	C 57.09	H 6.49	N 14.12	S 10.88
	(C 57.31	H 6.53	N 14.32	S 10.93)
10c	C 37.87	H 5.68	N 26.20	
	(C 37.72	H 5.70	N 26.39)	
10d	C 52.28	H 6.52	N 15.10	
	(C 52.15	H 6.56	N 15.20)	
10e	C 31.45	H 3.65	N 23.79	
	(C 31.02	H 3.47	N 24.12)	

compound	found (calculated)			
11	C 67.86 (C 68.19	H 7.12 H 7.31	N 16.96 N 16.73)	
16a	C 53.20 (C 52.99	H 6.56 H 6.83	N 17.60 N 17.66)	
16d	C 58.81 (C 59.09	H 5.92 H 5.99	N 27.43 N 27.47)	
17a	C 50.33 (C 50.21	H 6.29 H 6.52	N 16.53 N 16.81	S 9.99 S 9.62)
17d	C 50.94 (C 50.78	H 5.93 H 5.88	N 23.78 N 23.69	S 13.67 S 13.56)
19	C 41.12 (C 41.12	H 7.59 H 7.48	N 17.95 N 17.98)	

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