Supplementary Material (ESI) for Organic & Biomolecular Chemistry
This journal is (c) The Royal Society of Chemistry 2009

Supporting Information

Facile synthesis of structurally diverse 5-oxopiperazine-2-carboxylates as dipeptide mimics and templates

Michael Limbach[a], Alexander V. Lygin,[a] Vadim S. Korotkov,[a] Mazen Es-Sayed[b] and Armin de Meijere[*a]

[a.] Institut für Organische und Biomolekulare Chemie, Georg-August-Universität Göttingen, Tammannstrasse 2, 37077 Göttingen, Germany. Fax: + 49(0)551/399475, Email: ameijer1@gwdg.de

[b.] Bayer CropScience AG, Alfred-Nobel-Strasse 50, 40789 Monheim, Germany.

Table of Contents:

Methyl 2-(1-(2-Bromo-N-(2-methoxyethyl)acetamido)-cyclopropyl)-2-chloroacetate (3b): To a solution of **1** (454 mg, 3.10 mmol) in THF (20 mL) was added at 0 °C methoxyethylamine (256 mg, 3.41 mmol), and the solution was stirred at this temperature for 5 h. Volatiles were removed under reduced pressure, the residue was taken up in 1,2-dichloroethane (50 mL), bromoacetyl chloride (876 mg, 6.20 mmol) and solid $NaHCO_3$ (328 mg, 3.10 mmol) were added with stirring at 20 °C and slowly water (1 mL). The suspension was vigorously stirred for 8 h, a saturated $NaHCO_3$ solution (10 mL) was added, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (1 × 50 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Chromatographic purification of the residue on silica gel (20 g, 2.5 × 14 cm, pentane/Et_2O 1 : 1, ninhydrine, R_f = 0.29) yielded 636 mg (66%) of **3b** as a colorless oil. – IR (film): nu(tilde) = 3484, 2887, 2953, 2895, 1752 (C=O), 1664 (C=O), 1436, 1398, 1354, 1195, 1167, 1112, 1016, 916, 733 cm^{-1}. – ^1H NMR ($CDCl_3$, 300 MHz, mixture of two rotamers): δ = 1.02–1.13 (m, 1 H, Cpr-*H*), 1.39–1.47 (m, 1 H, Cpr-*H*), 1.52–1.70 (m, 2 H, Cpr-*H*), 3.28 (s, 1.5 H, C*H*$_3$), 3.32 (s, 1.5 H, C*H*$_3$), 3.35 (s, 1 H, C*H*$_2$Br), 3.38–3.57 (m, 1 H, CH_2), 3.57–3.74 (m, 1 H, CH_2), 3.77 (s, 1.5 H, C*H*$_3$), 3.79 (s, 1.5 H, C*H*$_3$), 3.82 (s, 1 H, C*H*$_2$Br), 3.94–4.06 (m, 1 H), 4.29–4.40 (m, 1.5 H), 4.84 (s, 0.5 H). – ^{13}C NMR ($CDCl_3$, 75.5 MHz, APT): δ = 14.3 (–, Cpr-*C*), 14.6 (–, Cpr-*C*), 16.9 (–, Cpr-*C*), 19.0 (–, Cpr-*C*), 27.0 (–, CH_2), 27.2 (–, CH_2), 43.1 (C_{quat}, Cpr-*C*), 43.7 (C_{quat}, Cpr-*C*), 50.4 (–, N*C*H_2), 50.6 (–, N*C*H_2), 53.2 (+, *C*H), 53.3 (+, *C*H), 58.8 (O*C*H_3), 58.9 (O*C*H_3), 61.3 (O*C*H_3), 63.5 (O*C*H_3), 69.1 (–, CH_2), 69.3 (–, CH_2). – MS (ESI), *m*/*z* (%): 341.9/343.8 (43/62) [M^+], 363.9/365.8 (79/100) [M + Na]$^+$, 706.4/708.4/710.4 (24/25/5) [2M + Na]$^+$. – $C_{11}H_{17}BrClNO_4$ (342.6): calcd. C 38.56, H 5.00, N 4.09; found C 38.27, H 4.82, N 3.88.

Methyl (2-(2-Bromo-2-phenylacetyl)-(methoxymethyl)-amino)cyclopropyl)-2-chloroacetate (3c): To a solution of **1** (602 mg, 4.11 mmol) in THF (10 mL) was added at 0 °C glycinemethylester hydrochloride (469 mg, 3.73 mmol) and triethylamine (416 mg, 4.11 mmol), and the solution was stirred under rewarming to 20 °C for 7 h. The precipitate was filtered off, and the filtrate was concentrated under reduced pressure, the residue was taken up in 1,2-dichloroethane (20 mL), 2-bromo-2-phenylacetyl chloride (2.62 g, 11.2 mmol) and dropwise 1 n NaOH (11.2 mL, 11.2 mmol) were added at 0 °C. The suspension was vigorously stirred at 20 °C for 12 h, a saturated $NaHCO_3$ solution (10 mL)

was added, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic phases were dried over Na_2SO_4 and the solvent was removed under reduced pressure. Chromatographic purification of the residue on silica gel (20 g, 3 × 20 cm, pentane/EtOAc 3 : 2, ninhydrine, R_f = 0.64) yielded 1.59 g (86%) of **3c** as a colorless oil. – IR (film): nu(tilde) = 3440, 2954, 2253, 1749 (C=O), 1664 (C=O), 1438, 1391, 1214, 910, 740 cm^{-1}.– ^1H NMR ($CDCl_3$, 300 MHz, mixture of two diastereomers, rotamers): δ = 1.19–1.47 (m, 3 H, Cpr-*H*), 1.59–1.73 (m, 1 H, Cpr-*H*), 3.70 (s, 2 H, OC*H*$_3$), 3.70 (s, 1 H, OC*H*$_3$), 3.79 (s, 1 H, OC*H*$_3$), 3.81 (s, 2 H, OC*H*$_3$), 3.86–4.08 (m, 2 H), 4.28–4.45 (m, 1.5 H), 4.85 (d, *J* = 85 Hz, part of AB-system, 0.5 H), 7.10–7.18 (m, 1 H, aryl-*H*), 7.25–7.32 (m, 3 H, aryl-*H*), 7.53–7.59 (m, 1 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 75.5 MHz, APT): δ = 12.0 (–, Cpr-*C*), 13.5 (–, Cpr-*C*), 17.2 (–, Cpr-*C*), 21.5 (–, Cpr-*C*), 40.9 (C_{quat}, Cpr-*C*), 41.3 (C_{quat}, Cpr-*C*), 42.3 (C_{quat}, Cpr-*C*), 43.5 (C_{quat}, Cpr-*C*), 50.7 (–, *C*H$_2$), 51.2 (–, *C*H$_2$), 52.2 (+, *C*H), 52.6 (+, *C*H), 53.3 (+, *C*H), 53.4 (+, *C*H), 124.7 (C_{quat}, aryl-*C*), 124.8 (C_{quat}, aryl-*C*), 127.5 (+, aryl-*C*), 127.6 (+, aryl-*C*), 128.6 (+, aryl-*C*), 128.7 (+, aryl-*C*), 131.2 (+, aryl-*C*), 131.4 (+, aryl-*C*), 132.6 (+, aryl-*C*), 134.7 (C_{quat}, aryl-*C*), 134.9 (C_{quat}, aryl-*C*), 167.1 (C_{quat}), 168.5 (C_{quat}), 170.0 (C_{quat}), 170.1 (C_{quat}), 171.8 (C_{quat}), 172.2 (C_{quat}), 172.3 (C_{quat}). – MS (ESI), *m*/*z* (%): 454.0/456.0 (82/100) $[M + Na]^+$, 887.0 (90) $[2M + Na]^+$. – HRMS (ESI): calcd. for $C_{17}H_{19}BrClNO_5Na$ $[M + Na^+]$ 454.0033; found 454.0027.

Methyl 2-(1-(*N*-(4-Chlorobenzyl)-2-bromoacetamido)-cyclopropyl)-2-chloroacetate (3d): To a solution of **1** (500 mg, 3.41 mmol) in THF (50 mL) was added at 0 °C 4-chlorobenzylamine (531 mg, 3.75 mmol) and triethylamine (380 mg, 3.75 mmol), and the solution was stirred under rewarming to 20 °C for 12 h (Michael adduct, ninhydrine, MTBE/cyclohexane 1 : 1, R_f = 0.68). After removal of volatiles under reduced pressure, the residue was taken up in 1,2-dichloroethane (30 mL), bromoacetyl chloride (1.61 g, 10.2 mmol), solid $NaHCO_3$ (1.40 g, 3.41 mmol) and dropwise over 30 min water, (10 mL) were added at 0 °C. The suspension was vigorously stirred at 20 °C for 5 h, a saturated $NaHCO_3$ solution (10 mL) was added, the phases were separated, the aq. phase was extracted with CH_2Cl_2 (3 × 30 mL), the combined organic phases were dried over $MgSO_4$, and the solvent was removed under reduced pressure. Chromatographic purification of the residue on silica gel (30 g, 2 × 15 cm, MTBE/cyclohexane 1 : 1, ninhydrine, R_f = 0.50) yielded 1.01 g (72%) of **3d** as a colorless oil. – ^1H NMR ($CDCl_3$, 300 MHz, mixture of three rotamers):

δ = 0.92–1.12 (m, 2 H, Cpr-*H*), 1.18–1.32 (m, 1 H, Cpr-*H*), 1.40–1.70 (m, 1 H, Cpr-*H*), 3.49 (s, 1 H), 3.73 (s, 1 H, C*H*$_3$), 3.75 (s, 2 H, C*H*$_3$), 3.90–4.05 (m, 0.5 H), 4.10–4.50 (m, 2 H), 4.80 – 4.90 (m, 0.5 H), 4.84 (s, 1 H), 6.95–7.10 (m, 2 H, aryl-*H*), 7.15–7.32 (m, 2 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 13.2 (–, Cpr-*C*), 16.6 (–, Cpr-*C*), 18.8 (–, Cpr-*C*), 26.0 (–, CH_2), 26.5 (–, CH_2), 26.7 (–, CH_2), 27.2 (–, CH_2), 43.0 (C_{quat}, Cpr-*C*), 43.7 (C_{quat}, Cpr-*C*), 51.2 (–, N*C*H$_2$), 51.7 (–, N*C*H$_2$), 53.2 (+, *C*H), 53.4 (+, *C*H), 53.9 (–, N*C*H$_2$), 61.2 (O*C*H$_3$), 63.5 (O*C*H$_3$), 126.2 (+, aryl-*C*), 127.5 (+, aryl-*C*), 128.0 (+, aryl-*C*), 128.6 (+, aryl-*C*), 128.7 (+, aryl-*C*), 129.3 (C_{quat}, aryl-*C*), 132.7 (C_{quat}, aryl-*C*), 132.9 (C_{quat}, aryl-*C*), 133.4 (C_{quat}, aryl-*C*), 136.06 (C_{quat}, aryl-*C*), 136.11 (C_{quat}, aryl-*C*), 136.2 (C_{quat}, aryl-*C*), 167.2 (C_{quat}), 167.4 (C_{quat}), 167.8 (C_{quat}), 168.9 (C_{quat}), 169.8 (C_{quat}), 169.9 (C_{quat}). – MS (ESI), *m*/*z* (%): 434/432/430 (45/100/60) $[M + Na]^+$. – HRMS (ESI): calcd. for $C_{15}H_{17}BrClNO_3$ $[M + H^+]$ 407.9769; found 407.9763.

Methyl 2-(1-(N-(4-(Trifluoromethyl)benzyl)-2-bromo-2-phenylacetamido)cyclopropyl)-2-chloroacetate (3e): To a solution of **1** (1.00 g, 6.82 mmol) in THF (20 mL) was added at 0 °C *p*-(trifluoromethyl)benzylamine (1.29 g, 7.38 mmol), and the solution was stirred under rewarming to 20 °C for 19 h. Volatiles were removed under reduced pressure, the residue was taken up in 1,2-dichloroethane (20 mL), 2-bromo-2-phenylacetyl chloride (2.15 g, 10.0 mmol) in CH_2Cl_2 (10 mL) and solid $NaHCO_3$ (632 mg, 8.00 mmol) were added at 20 °C and slowly water (1 mL). The suspension was vigorously stirred for 17 h at 20 °C, a saturated $NaHCO_3$ solution (10 mL) was added, the phases were separated, the aqueous phase was extracted with CH_2Cl_2 (3 × 50 mL), the combined organic phases were dried over Na_2SO_4, and the solvent was removed under reduced pressure. Chromatographic purification of the residue on silica gel (20 g, 3 × 20 cm, cyclohexane/Et_2O 3 : 2 → 1 : 1, ninhydrine, R_f = 0.35) yielded 2.90 g (80%) of **3e** as a colorless oil. – IR (film): nu(tilde) = 1752 (C=O), 1669 (C=O), 1438, 1395, 1327, 1165, 1125, 1068, 1027, 1016, 911, 733 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 300 MHz, mixture of two diastereomers, rotamers): δ = 0.97–1.16 (m, 2 H, Cpr-*H*), 1.25–1.41 (m, 1 H, Cpr-*H*), 1.52–1.79 (m, 2 H, Cpr-*H*), 3.50 (d, *J* = 16.6 Hz, 0.5 H), 3.71 (s, 2 H, C*H*$_3$), 3.81 (s, 1 H, C*H*$_3$), 3.92–4.09 (m, 0.5 H), 4.23 (d, *J* = 16.6 Hz, 0.5 H), 4.40–4.58 (m, 0.5 H), 4.90 (d, *J* = 87 Hz, 0.6 H, PhC*H*$_2$), 5.01 (s, 1.4 H, PhC*H*$_2$), 7.06–7.17 (m, 1.5 H, aryl-*H*), 7.19–7.31 (m, 4 H, aryl-*H*), 7.47–7.59 (m, 2 H, aryl-*H*), 7.64 (d, J = 8.3 Hz, 1.5 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 75.5 MHz, APT): δ = 11.4 (–, Cpr-*C*), 12.9 (–, Cpr-*C*), 16.8 (–, Cpr-*C*),

21.3 (–, Cpr-*C*), 41.9 (C_{quat}, Cpr-*C*), 43.7 (C_{quat}, Cpr-*C*), 53.2 (+, 2 C, *C*H), 53.3 (+, *C*H), 53.4 (+, *C*H), 54.2 (–, N*C*H_2), 58.7 (O*C*H_3), 63.8 (O*C*H_3), 122.1 (C_{quat}, aryl-*C*), 124.7 (C_{quat}, aryl-*C*), 125.4 (+, aryl-*C*), 125.5 (+, aryl-*C*), 125.9 (+, aryl-*C*), 126.4 (+, aryl-*C*), 127.5 (+, aryl-*C*), 128.7 (+, aryl-*C*), 131.5 (+, aryl-*C*), 132.6 (+, aryl-*C*) 129.3 (C_{quat}, aryl-*C*), 134.5 (C_{quat}, aryl-*C*), 142.3 (C_{quat}, aryl-*C*), 167.0 (C_{quat}), 168.1 (C_{quat}), 168.6 (C_{quat}), 172.4 (C_{quat}). – MS (ESI), *m*/*z* (%): 542.0 (73) $[M + Na]^+$, 1059.0 (100) $[2M + Na]^+$. – $C_{22}H_{20}BrClF_3NO_3$ (518.7): calcd. C 50.94, H 3.89, N 2.70; found C 50.72, H 3.67, N 2.82.

Methyl 7-Benzyl-4-(2-methoxyethyl)-5-oxo-4,7-diazaspiro-[2.5]octane-8-carboxylate (2bf): The crude product from **3b** (1.15 g, 3.36 mmol), benzylamine (396 mg, 3.69 mmol) and triethylamine (1.02 g, 10.1 mmol) was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, pentane/Et_2O 1 : 1 → 0 : 1; R_f = 0.23) to yield 898 g (81%) of **2bf** as a colorless oil. – IR (film): nu(tilde) = 3315, 2951, 2836, 1743 (C=O), 1678 (C=O), 1517, 1437, 1253, 1036, 879, 846 cm^{-1}. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.60–0.80 (m, 1 H, Cpr-*H*), 0.81–1.01 (m, 2 H, Cpr-*H*), 1.25–1.40 (m, 1 H, Cpr-*H*), 1.68 (s, 1 H, C*H*), 2.85–3.00 (m, 1 H, CH_2), 3.22–3.46 (m, 5 H, CH_3, CH_2), 3.52–3.81 (m, 8 H), 7.18–7.40 (s, 5 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.45 (–, Cpr-*C*), 12.7 (–, Cpr-*C*), 41.1 (–, 2 C, C_{quat}, Cpr-*C*, CH_2), 51.5 (–, Ph*C*H_2), 53.8 (–, *C*H_2), 58.8 (+, O*C*H_3), 58.9 (+, O*C*H_3), 66.1 (+, *C*HN), 70.0 (–, O*C*H_2), 127.5 (+, CH, aryl-*C*), 128.4 (+, 2 C, aryl-*C*), 128.8 (+, 2 C, aryl-*C*), 136.9 (C_{quat}, aryl-*C*), 169.6 (C_{quat}, *C*N=O), 171.0 (C_{quat}, *C*=O). – MS (EI, 70 eV), *m*/*z* (%): 333/332 (2/5) $[M]^+$, 274/273 (14/88), 91 (100). – $C_{18}H_{24}N_2O_4$ (332.4): calcd. C 65.04, H 7.28, N 8.43; found C 65.21, H 7.44, N 8.59.

Methyl 4-(2-Methoxyethyl)-5-oxo-7-m-tolyl-4,7-diazaspiro-[2.5]octane-8-carboxylate (2bg): The crude product from **3b** (1.02 g, 2.99 mmol), 3-methylaniline (384 mg, 3.58 mmol) and triethylamine (906 mg, 2.96 mmol) was prurified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, pentane/Et_2O 1 : 1 → 0 : 1; R_f = 0.45) to yield 793 g (80%) of **2bg** as a colorless solid, m.p. 115–116°C – IR (film): nu(tilde) = 3330, 3027, 2951, 1735 (C=O), 1654 (C=O), 1452, 1429, 1396, 1200, 1176, 1031, 732, 700 cm^{-1}. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.86–0.92 (m, 2 H, Cpr-*H*), 1.21–1.33 (m, 1 H, Cpr-*H*), 1.59–1.69 (m, 1 H, Cpr-*H*), 2.31 (s, 3 H, CH_3), 3.29 (s, 3 H, OCH_3), 3.32–3.46 (m, 4 H, OCH_2, NCH_2), 3.49 (s, 1 H, C*H*), 3.72 (s, 3 H, OCH_3), 4.20 (s, 2 H, CH_2), 6.38 (d, ^3J = 3.6 Hz, 1 H, aryl-*H*), 6.38 (s, 1 H, aryl-*H*),

6.63 (d, ^3J = 3.6 Hz, 1 H, aryl-*H*), 7.14 (t, ^3J = 3.8 Hz, 1 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 10.1 (–, Cpr-*C*), 14.0 (–, Cpr-*C*), 21.8 (+, *C*H_3), 41.8 (C_{quat}, Cpr-*C*), 43.4 (–, N*C*H_2), 50.2 (–, N*C*H_2), 52.4 (+, O*C*H_3), 58.8 (+, O*C*H_3), 64.9 (+, *C*HN), 70.3 (–, O*C*H_2), 108.6 (+, aryl-*C*), 112.2 (+, aryl-*C*), 119.1 (+, aryl-*C*), 129.3 (+, aryl-*C*), 139.3 (C_{quat}, aryl-*C*), 146.8 (C_{quat}, aryl-*C*), 169.6 (C_{quat}, *C*N=O), 171.9 (C_{quat}, *C*=O). – $C_{18}H_{24}N_2O_4$ (332.4): calcd. C 65.04, H 7.28, N 8.43; found C 64.93, H 7.41, N 8.57.

Methyl 7-(4-Phenylphenyl)-4-(2-methoxyethyl)-5-oxo-4,7-diazaspiro[2.5]octane-8-carboxylate (2bh): The crude product from **3b** (1.04 g, 3.02 mmol), 4-phenylaniline (614 mg, 3.63 mmol) and triethylamine (918 mg, 9.07 mmol) was prurified by chromatography on 50 g of silica gel (3 × 20 cm, Et_2O, R_f = 0.22) to yield 1.03 g (87%) of **2bh** as a colorless solid, m.p. 129–130 °C. – IR (KBr): nu(tilde) = 3197, 3082, 2945, 1674 (C=O), 1464, 1437, 1414, 1344, 1318, 1144, 1101, 750, 600 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.89–0.96 (m, 2 H, Cpr-*H*), 1.21–1.36 (m, 1 H, Cpr-*H*), 1.62–1.72 (m, 1 H, Cpr-*H*), 3.31–3.48 (m, 4 H, 2 CH_2), 3.54 (s, 1 H, C*H*), 3.74 (s, 3 H, CH_3), 4.26 (d, *J* = 2.8 Hz, 2 H, PhCH_2), 6.65 (d, *J* = 7.2 Hz, 2 H, aryl-*H*), 6.24–6.30 (m, 1 H, aryl-*H*), 7.40 (t, *J* = 7.2 Hz, 2 H, aryl-*H*), 7.50–7.58 (t, *J* = 7.2 Hz, 4 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 10.1 (–, Cpr-*C*), 14.0 (–, Cpr-*C*), 41.8 (C_{quat}, Cpr-*C*), 43.5 (–, *C*H_2), 50.2 (–, *C*H_2), 52.5 (+, N*C*H_3), 58.8 (+, O*C*H_3), 64.9 (+, *C*HN), 70.3 (–, O*C*H_2), 107.6 (+, aryl-*C*), 111.7 (+, 2 C, aryl-*C*), 126.3 (+, 2 C, aryl-*C*), 128.0 (+, 2 C, aryl-*C*), 128.6 (+, 2 C, aryl-*C*), 131.0 (+, aryl-*C*), 140.6 (C_{quat}, aryl-*C*), 146.0 (C_{quat}, aryl-*C*), 169.4 (C_{quat}, *C*N=O), 171.7 (C_{quat}, *C*=O). – MS (ESI), *m*/*z* (%): 417.2 (91) $[M+Na]^+$, 811.4 (100) $[2M+Na]^+$. –$C_{23}H_{26}N_2O_4$ (394.5): calcd. C 70.03, H 6.64, N 7.10; found C 70.25, H 6.74, N 7.29.

Methyl 4-(2-Methoxyethyl)-5-oxo-7-o-tolyl-4,7-diazaspiro-[2.5]octane-8-carboxylate (2bi): The crude product from **3b** (1.14 g, 3.32 mmol), 2-methylaniline (427 mg, 3.99 mmol) and triethylamine (1.01 g, 9.97 mmol) was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, pentane/Et_2O 1 : 1 → 0 : 1; R_f = 0.43) to yield 838 g (76%) of **2bi** as a colorless oil. – IR (film): nu(tilde) = 3264, 2957, 2929, 2870, 1676 (C=O), 1641 (C=O), 1460, 1423, 1326, 1235, 1042, 938, 795, 720, 607 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.92–1.20 (m, 3 H, Cpr-*H*), 1.47–1.51 (m, 1 H, Cpr-*H*), 2.28 (s, 3 H, CH_3), 3.15–3.75 (m, 9 H), 3.96 (d, ^3J = 7.96 Hz, A-part of an AB-system, 1 H, CH_2), 4.20 (d, ^3J = 7.96 Hz, B-part

of an AB-system, 1 H, C*H*$_2$), 7.00–7.26 (m, 4 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.4 (–, Cpr-*C*), 13.5 (–, Cpr-*C*), 18.2 (+, *C*H$_3$), 41.4 (C_{quat}, Cpr-*C*), 42.1 (–, N*C*H$_2$), 51.8 (–, O*C*H$_2$), 53.0 (+, O*C*H$_3$), 58.8 (+, O*C*H$_3$), 67.5 (+, *C*HN), 70.3 (–, O*C*H$_2$), 122.5 (+, aryl-*C*), 124.6 (+, aryl-*C*), 126.7 (+, aryl-*C*), 131.4 (+, aryl-*C*), 133.8 (C_{quat}, aryl-*C*), 147.4 (C_{quat}, aryl-*C*), 170.3 (C_{quat}, *C*NO), 171.4 (C_{quat}, *C*=O). – MS (EI, 70 eV), *m/z* (%): 333/332 (54/11) $[M]^+$, 304 (15), 273 (100), 245 (22), 140 (18), 119 (19). – $C_{18}H_{24}N_2O_4$ (332.4): calcd. C 65.04, H 7.28, N 8.43; found C 65.32, H 7.47, N 8.33.

***trans*-Methyl 4-Methoxycarbonylmethyl-7-(4-methoxy-phenyl)-5-oxo-6-phenyl-4,7-diazaspiro[2.5]-octane-8-carboxylate (2cj-Ph):** The crude product from **3c** (643 mg, 3.24 mmol), *p*-anisidine (468 mg, 3.80 mmol) and triethylamine (1.39 mL, 10.0 mmol) was purified by chromatography on 44 g of silica gel (3 × 24 cm; CH_2Cl_2/EtOAc 10 : 1; R_f = 0.42; MOPS) to yield 932 mg (68%) of **2cj-Ph** as a colorless solid, m.p. 133–136 °C. IR (KBr): nu(tilde) = 3002, 2953, 2835, 2362, 2337, 1740 (C=O), 1670 (C=O), 1513, 1371, 1252, 1207, 1036, 813, 774, 699, 668 cm^{-1}. – ^{1}H NMR (250 MHz, $CDCl_3$): δ = 0.71–1.42 (m, Cpr-*H*, 4 H), 3.46 (s, C*H*, 1 H), 3.66 (s, CO_2CH_3, 3 H), 3.69 (s, CO_2CH_3, 3 H), 3.76 (s, OCH_3, 3 H), 3.77 (s, C*H*, 1 H), 3.88 (d, C*H*, ^3J = 17.8 Hz, 1 H, A-part of an AB-system), 4.11 (d, C*H*, ^3J = 17.8 Hz, 1 H, B-part of an AB-system), 6.46 (d, aryl-*H*, 2 H, ^3J = 9 Hz), 6.75 (d, aryl-*H*, 2 H, ^3J = 9 Hz), 7.25–7.37 (m, aryl-*H*, 3 H), 7.59–7.62 (d, aryl-*H*, 2 H). – ^{13}C NMR (62.9 MHz, $CDCl_3$): δ = 9.6 (–, Cpr-*C*), 14.4 (–, Cpr-*C*), 40.7 (C_{quat}, Cpr-*C*), 43.9 (–, $CH_2CO_2CH_3$), 52.2 (+, *C*H), 52.5 (+, *C*H), 55.5 (+, OCH_3), 64.9 (+, CO_2CH_3), 65.4 (+, CO_2CH_3), 113.3 (+, aryl-*C*, 2 C), 114.8 (+, aryl-*C*, 2 C), 126.7 (+, aryl-*C*, 2 C), 127.3 (+, aryl-*C*), 128.5 (+, aryl-*C*, 2 C), 137.7 (C_{quat}, aryl-*C*), 140.3 (C_{quat}, aryl-*C*), 153.4 (C_{quat}, aryl-*C*), 169.0 (C_{quat}, N*C*=O), 170.0 (C_{quat}, CO_2CH_3), 172.1 (C_{quat}, CO_2CH_3). – MS (70eV); *m/z* (%): 438 (90) [M^+], 410 (12), 379 (100), 351 (25), 211 (20). $C_{24}H_{26}N_2O_6$ (438.5): calcd. C 62.38, H 5.24, N 6.41; found C 65.66, H 6.15, N 6.27.

Methyl 4-(4-Chlorobenzyl)-5-oxo-7-p-tolyl-4,7-diazaspiro-[2.5]octane-8-carboxylate (2dk): The crude product from **3d** (1.00 g, 2.44 mmol), 4-methylaniline (288 mg, 2.69 mmol) and triethylamine (764 mg, 5.91 mmol) was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, cyclohexane/MTBE 1 : 2 → 1 : 1; R_f = 0.23) to yield 706 mg (73%) of **2dk** as a colorless solid, m.p. 149 °C. – IR (KBr): nu(tilde) = 3433, 3269, 3027, 2973, 1675

(C=O), 1641 (C=O), 1444, 1422, 1326, 1040, 755, 699, 612 cm^{-1}. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.77-0.95 (m, 2 H, Cpr-*H*), 1.19-1.33 (m, 1 H, Cpr-*H*), 1.36-1.43 (m, 1 H, Cpr-*H*), 2.26 (s, 3 H, ArCH_3), 3.48 (s, 1 H, C*H*), 3.56 (s, 3 H, OCH_3), 4.18 (d, ^3J = 7.83 Hz, 1 H, A-part of an AB-system, PhCH_2), 4.33 (s, 2 H, CH_2), 4.71 (d, ^3J = 7.83 Hz, 1 H, B-part of an AB-system, PhCH_2), 6.52 (d, ^3J = 4.15 Hz, 2 H, aryl-*H*), 7.08 (d, ^3J = 4.15 Hz, 2 H, aryl-*H*), 7.15 (d, ^3J = 4.10 Hz, 2 H, aryl-*H*), 7.28 (d, ^3J = 4.10 Hz, 2 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.7 (–, Cpr-*C*), 12.9 (–, Cpr-*C*), 20.2 (+, *C*H_3), 41.5 (C_{quat}, Cpr-*C*), 45.0 (–, *C*H_2), 50.3 (–, Ph*C*H_2), 52.3 (+, O*C*H_3), 64.5 (+, *C*HN), 111.7 (+, 2 C, aryl-*C*), 127.8 (C_{quat}, aryl-*C*), 128.66 (+, 2 C, aryl-*C*), 128.69 (+, 2 C, aryl-*C*), 130.0 (+, 2 C, aryl-*C*), 133.1 (C_{quat}, aryl-*C*), 136.1 (C_{quat}, aryl-*C*), 144.5 (C_{quat}, aryl-*C*), 169.5 (C_{quat}, *C*N=O), 171.4 (C_{quat}, *C*=O). – MS (70eV); *m/z* (%): 398/400 (76/23) [M^+], 339/341 (100/32), 311/313 (24/8), 232 (48), 119 (48). – $C_{22}H_{23}ClN_2O_3$ (398.9): calcd. C 66.24, H 5.81, N 7.02; found C 66.12, H 5.66, N 6.89.

Methyl 4-(4-Chlorobenzyl)-5-oxo-7-(2-trifluoromethyl benzyl)-4,7-diazaspiro[2.5]octane-8-carboxylate (2dl): The crude product from **3d** (1.05 g, 2.57 mmol), 2-(trifluoromethyl)benzylamine (497 mg, 2.83 mmol) and triethylamine (779 mg, 7.70 mmol) was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, pentane/Et_2O 1 : 1 → 0 : 1; R_f = 0.20) to yield 1.04 g (87%) of **2dl** as a colorless solid, m.p. 178–180 °C. – IR (film): nu(tilde) = 3449, 3335, 3090, 2999, 2947, 2882, 2843, 1737 (C=O), 1435, 1370, 1326, 1309, 1288, 1256, 1203, 1033, 1013, 945, 839, 731, 649, 578 cm^{-1}. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.67–0.74 (m, 1 H, Cpr-*H*), 0.77–0.95 (m, 2 H, Cpr-*H*), 1.14–1.24 (m, 1 H, Cpr-*H*), 2.68 (s, 1 H, NC*H*), 3.60 (s, 3 H, OCH_3), 3.72 (d, ^3J = 8.42 Hz, 1 H, A-part of an AB-system, PhCH_2), 3.77 (d, ^3J = 7.99 Hz, 1 H, B-part of an AB-system, PhCH_2), 3.91 (s, 2 H, CH_2), 3.94 (d, ^3J = 8.42 Hz, 1 H, A-part of an AB-system, PhCH_2), 4.96 (d, ^3J = 7.99 Hz, 1 H, A-part of an AB-system, PhCH_2), 7.10 (d, ^3J = 4.15 Hz, 2 H, aryl-*H*), 7.26 (d, ^3J = 4.15 Hz, 2 H, aryl-*H*), 7.51 (d, ^3J = 4.21 Hz, 2 H, aryl-*H*), 8.19 (d, ^3J = 4.21 Hz, 2 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.5 (–, Cpr-*C*), 11.5 (–, Cpr-*C*), 41.4 (C_{quat}, Cpr-*C*), 43.3 (–, Ph*C*H_2), 51.7 (+, O*C*H_3), 53.4 (–, Ph*C*H_2), 55.0 (–, *C*H_2), 66.6 (+, *C*HN), 123.8 (+, 2 C, aryl-*C*), 128.2 (+, 2 C, aryl-*C*), 128.6 (+, 2 C, aryl-*C*), 129.2 (+, 2 C, aryl-*C*), 132.8 (C_{quat}, aryl-*C*), 136.3 (C_{quat}, aryl-*C*), 144.8 (C_{quat}, aryl-*C*), 147.4 (C_{quat}, aryl-*C*), 169.0 (C_{quat}, *C*N=O), 170.4 (C_{quat}, *C*=O). – MS (70eV); *m/z* (%): 466/468 (4/2) [M^+], 407/409 (50/15), 300

(47), 159 (78), 125 (100) – HRMS (ESI): calcd. for $C_{23}H_{23}ClF_3N_2O_3$ [M + H^+] 467.1349; found 467.1344.

Methyl 4-(4-Chlorobenzyl)-7-isobutyl-5-oxo-4,7-diaza-spiro[2.5]octane-8-carboxylate (2dm): The crude product from **3d** (1.10 g, 2.68 mmol), isobutylamine (216 mg, 2.95 mmol) and triethylamine (814 mg, 8.04 mmol) was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, pentane/Et_2O 1 : 1 → 0 : 1; R_f = 0.69) to yield 884 mg (90%) of **2dm** as a colorless solid, m.p. 63 °C. – IR (KBr): nu(tilde) = 3311, 3094, 3009, 2952, 1739 (C=O), 1669 (C=O), 1436, 1229, 1112, 1013, 946, 747 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.72–0.95 (m, 9 H, cpr-*H*, C*H*$_3$), 0.99–1.18 (m, 1 H, Cpr-*H*), 1.65–1.76 (m, 1 H, C*H*), 2.30–2.41 (m, 2 H, C*H*$_2$), 2.71 (s, 1 H, NC*H*), 3.57 (s, 3 H, OC*H*$_3$), 3.65–3.84 (m, 3 H, C*H*$_2$), 4.93 (d, *J* = 16 Hz, 1 H, CH_2), 7.08 (d, ^3J = 8.4 Hz, 2 H, aryl-*H*), 7.22 (d, ^3J = 8.4 Hz, 2 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.0 (–, Cpr-*C*), 11.6 (–, Cpr-*C*), 20.2 (+, *C*H$_3$), 20.3 (+, *C*H$_3$), 25.7 (+, *C*H), 41.2 (C_{quat}, Cpr-*C*), 43.3 (–, N*C*H$_2$), 51.3 (+, O*C*H$_3$), 53.7 (–, Ph*C*H$_2$), 63.2 (–, *C*H$_2$), 67.5 (+, *C*HN), 128.2 (+, 2 C, aryl-*C*), 128.5 (+, 2 C, aryl-*C*), 132.7 (C_{quat}, aryl-*C*), 136.6 (C_{quat}, aryl-*C*), 169.8 (C_{quat}, *C*N=O), 171.1 (C_{quat}, *C*=O). MS (70eV): *m/z* (%): 364/366 (5/2) [M^+], 305/307 (100/34), 198 (40), 125/127 (48/18). – $C_{19}H_{25}ClN_2O_3$ (364.9): calcd. C 62.55, H 6.91, N 7.68; found C 62.65, H 6.98, N 7.89.

Methyl 4-(4-Chlorobenzyl)-7-methoxycarbonylmethyl-5-oxo-4,7-diazaspiro[2.5]octane-8-carboxylate (2dd): The crude product obtained **3d** (3.00 g, 7.33 mmol) in MeOH (50 mL), glycine methyl ester hydrochloride (1.01 g, 8.07 mmol) and triethylamine (3.60 mL, 25.7 mmol) with heating under reflux at 85 °C for 48 h, was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, Et_2O; R_f = 0.26) to yield 1.79 g (64%) of **2dd** as a colorless solid, m.p. 109 °C.– IR (KBr): nu(tilde) = 3466, 3005, 2953, 1743 (C=O), 1436, 1337, 1272, 1203, 1176, 1018, 936, 875, 833, 777, 667, 554 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.76−0.85 (m, 1 H, Cpr-*H*), 0.93−1.10 (m, 2 H, Cpr-*H*), 1.18−1.26 (m, 1 H, Cpr-*H*), 3.08 (s, 1 H, C*H*), 3.48 (d, ^3J = 8.9 Hz, 1 H, A-part of an AB-system, C*H*$_2$), 3.58 (s, 3 H, OC*H*$_3$), 3.63 (d, ^3J = 8.9 Hz, 1 H, B-part of an AB-system, C*H*$_2$), 3.70 (s, 3 H, OC*H*$_3$), 3.76 (d, ^3J = 7.7 Hz, 1 H, A-part of an AB-system, C*H*$_2$), 4.02 (d, ^3J = 7.7 Hz, 1 H, B-part of an AB-system, C*H*$_2$), 4.08 (d, ^3J = 7.95 Hz, 1 H, A-part of an AB-system, PhC*H*$_2$), 4.73 (d, ^3J = 7.95 Hz, 1 H, B-part of an AB-system, PhC*H*$_2$), 7.10 (d, ^3J = 4.2 Hz, 2 H, aryl-*H*), 7.24

(d, ^3J = 4.2 Hz, 2 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.3 (–, Cpr-*C*), 13.4 (–, Cpr-*C*), 41.3 (C_{quat}, Cpr-*C*), 44.6 (–, Ph*C*H$_2$), 51.7 (+, O*C*H$_3$), 51.9 (+, O*C*H$_3$), 53.8 (–, *C*H$_2$), 54.3 (–, *C*H$_2$), 66.2 (+, *C*HN), 126.4 (+, 2 C, aryl-*C*), 128.6 (+, 2 C, aryl-*C*), 132.8 (C_{ipso}, aryl-*C*), 136.5 (C_{quat}, aryl-*C*), 170.2 (C_{quat}, *C*N=O), 170.6 (C_{quat}, *C*=O), 171.1 (C_{quat}, *C*=O). – MS (70eV): *m/z* (%): 380.2/382.2 (32/11) [M^+], 321.4/323.4 (100/30), 293.2/295.2 (36/12), 236.1/238.1 (50/15), 214.2 (100), 125.0/127.0 (84/26). – HRMS (ESI): calcd. for $C_{18}H_{22}ClN_2O_5$ [M + H^+] 381.1217; found 381.1212

Methyl 4-(4-Chlorobenzyl)-7-(methoxycarbonylphenyl-methyl)-5-oxo-4,7-diazaspiro[2.5]-octane-8-carboxylate (2dn): The crude product obtained from **3d** (3.00 g, 7.33 mmol) in MeOH (50 mL), (*S*)-phenylglycine methyl ester hydrochloride (1.63 g, 8.07 mmol) and triethylamine (2.60 g, 25.7 mmol) under reflux at 80 °C for 19 h, was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, pentane/Et_2O 1 : 10 → 1 : 1) to yield 2.30 g (70%) of **2dn** as a colorless solid (1:1 mixture of diastereomers, which were separated by column chromatography on silica gel). – *Diastereomer 1*: 1.15 g (35%) of a colorless solid, m.p. 124–126 °C, R_f = 0.76 (Et_2O) – IR (KBr): nu(tilde) = 3396, 3197, 3078, 2947, 1670 (C=O), 1467, 1458, 1420, 1340, 1329, 756 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.65–1.01 (m, 3 H, Cpr-H), 1.15–1.24 (m, 1 H, Cpr-H), 3.11 (s, 1 H, CH), 3.62 (s, 3 H, OCH_3), 3.56–3.69 (m, 2 H, CH_2), 3.65 (s, 3 H, OCH_3), 3.93 (d, ^3J = 7.96 Hz, 1 H, A-part of an AB-system), 4.63 (s, 1 H, CH), 4.77 (d, ^3J = 7.96 Hz, 1 H, B-part of an AB-system), 7.07–7.42 (m, 9 H, aryl-H). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.55 (–, Cpr-C), 12.3 (–, Cpr-C), 41.5 (C_{quat}, Cpr-C), 44.1 (–, CH_2), 50.9 (+, CH), 51.8 (+, CH), 52.1 (–, CH_2), 65.0 (+, OCH_3), 68.8 (+, OCH_3), 128.3 (+, 2 C, aryl-C), 128.6 (+, aryl-C), 128.7 (+, 2 C, aryl-C), 128.8 (+, 2 C, aryl-C), 129.0 (+, 2 C, aryl-C), 132.8 (C_{quat}, C_{ipso}), 134.7 (C_{quat}, C_{ipso}), 136.5 (C_{quat}, C_{ipso}), 169.8 (C_{quat}, C_{ipso}), 171.0 (C_{quat}, C=O), 171.4 (C_{quat}, C=O). – MS (EI, 70 eV), *m/z* (%): 456/459 (8/2) [$M]^+$, 428 (12), 397 (90), 369 (21), 290 (71), 236 (34), 149 (58), 125 (100), 121 (79), 91 (40). – $C_{24}H_{25}ClN_2O_5$ (456.93): calcd. C 63.09, H 5.51, N 6.13; found C 63.21, H 5.50, N 6.25. – *Diastereomer 2*: 1.15 g (35%) of a colorless solid, m.p. 127–128, R_f = 0.58 (Et_2O). – IR (KBr): nu(tilde) = 3396, 3197, 3078, 2947, 1670 (C=O), 1467, 1458, 1420, 1340, 1329, 756 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.79–0.84 (m, 3 H, Cpr-H), 1.09–1.13 (m, 1 H, Cpr-H), 2.68 (s, 1 H, CH), 3.41 (s, 3 H, OCH_3), 3.69 (s, 3 H, OCH_3), 3.91 (d, ^3J = 8.00 Hz, 1 H), 3.92 (d, ^3J = 8.00 Hz, 1 H, A-part of an AB-system), 4.61

(s, 1 H, CH), 4.06 (d, ^3J = 8.00 Hz, 1 H, B-part of an AB-system), 7.07–7.36 (m, 9 H, aryl-H). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.59 (–, Cpr-C), 12.4 (–, Cpr-C), 41.7 (C_{quat}, Cpr-C), 44.1 (–, CH_2), 51.5 (+, CH), 52.3 (+, CH), 52.7 (–, CH_2), 63.3 (+, OCH_3), 69.5 (+, OCH_3), 128.3 (+, 2 C, aryl-C), 128.6 (+, aryl-C), 128.8 (+, 2 C, aryl-C), 128.9 (+, 2 C, aryl-C), 129.0 (+, 2 C, aryl-C), 132.8 (C_{quat}, C_{ipso}), 134.5 (C_{quat}, C_{ipso}), 136.5 (C_{quat}, C_{ipso}), 169.5 (C_{quat}, C_{ipso}), 170.9 (C_{quat}, C=O), 171.1 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 456/459 (8/2) $[M]^+$, 428 (12), 397 (90), 369 (21), 290 (71), 236 (34), 149 (58), 125 (100), 121 (79), 91 (40). – $C_{24}H_{25}ClN_2O_5$ (456.9): calcd. C 63.09, H 5.51, N 6.13; found C 63.29, H 5.59, N 6.39.

Methyl 4-(4-Chlorobenzyl)-7-(1-methoxycarbonyl-2-methylpropyl)-5-oxo-4,7-diazaspiro-[2.5]octane-8-carboxylate (2do): The crude product obtained from **3d** (3.00 g, 7.33 mmol) in MeOH (50 mL), (*S*)-valine methyl ester hydrochloride (1.35 g, 8.07 mmol) and triethylamine (4.00 mL, 29.3 mmol) under reflux at 85 °C for 24 h, was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, pentane/Et_2O 3 : 1 → 0 : 1, R_f = 0.23 [pentane/Et_2O = 1 : 1]) to yield 2.23 g (70%) of **2do** as a colorless solid (1:1 mixture of diastereomers, which were separated by column chromatography on silica gel). – *Diastereomer 1*: IR (KBr): nu(tilde) = 3327, 3026, 2950, 2857, 1734 (C=O), 1706 (C=O), 1652 (C=O), 1456, 1419, 1272, 1207, 1143, 1029, 735, 701 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.69–0.79 (m, 3 H, Cpr-H), 0.85 (t, ^3J = 6.65 Hz, 3 H, CH_3), 0.97 (t, ^3J = 6.65 Hz, 3 H, CH_3), 1.10–1.24 (m, 1 H, Cpr-H), 2.00–2.05 (m, 1 H, CH), 2.80–2.87 (m, 2 H, CH_2), 3.58 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.73 (d, ^3J = 7.91 Hz, 1 H, CH), 4.00 (d, ^3J = 5.32 Hz, 1 H, A-part of an AB-system), 4.10 (d, ^3J = 5.32 Hz, 1 H, B-part of an AB-system), 4.65 (d, ^3J = 7.91 Hz, 1 H, CH), 7.07 (d, ^3J = 4.11 Hz, 2 H, aryl-H), 7.23 (d, ^3J = 4.11 Hz, 2 H, aryl-H). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.55 (–, Cpr-C), 12.3 (–, Cpr-C), 41.5 (C_{quat}, Cpr-C), 44.1 (–, CH_2), 50.9 (+, CH), 51.8 (+, CH), 52.1 (–, CH_2), 65.0 (+, OCH_3), 68.8 (+, OCH_3), 128.3 (+, 2 C, aryl-C), 128.6 (+, aryl-C), 128.7 (+, 2 C, aryl-C), 128.8 (+, 2 C, aryl-C), 129.0 (+, 2 C, aryl-C), 132.8 (C_{quat}, C_{ipso}), 134.7 (C_{quat}, C_{ipso}), 136.5 (C_{quat}, C_{ipso}), 169.8 (C_{quat}, C_{ipso}), 171.0 (C_{quat}, C=O), 171.4 (C_{quat}, C=O). – MS (70eV): *m/z* (%): 422/424 (16/6) $[M^+]$, 394/396 (11/4), 363/365 (100/32), 335/337 (22/7), 256 (83), 125.0/127.0 (52/17). – M.p. 100−101 °C – $C_{21}H_{27}ClN_2O_5$ (422.9): calcd. C 59.64, H 6.44, N 6.62; found C 59.34, H 6.23, N 6.55. – *Diastereomer 2*: IR (KBr): nu(tilde) = 3333 , 3023, 2930, 1730 (C=O), 1700 (C=O), 1444, 1413, 1122, 701 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.66–0.76 (m, 3 H,

Cpr-H), 0.86 (t, ^3J = 6.65 Hz, 3 H, CH_3), 0.92 (t, ^3J = 6.65 Hz, 3 H, CH_3), 1.12–1.26 (m, 1 H, Cpr-H), 2.02–2.05 (m, 1 H, CH), 2.82–2.90 (m, 2 H, CH_2), 3.58 (s, 3 H, OCH_3), 3.68 (s, 3 H, OCH_3), 3.75 (d, ^3J = 7.91 Hz, 1 H, CH), 3.99 (d, ^3J = 5.32 Hz, 1 H, A-part of an AB-system), 4.12 (d, ^3J = 5.32 Hz, 1 H, B-part of an AB-system), 4.66 (d, ^3J = 7.91 Hz, 1 H, CH), 7.07 (d, ^3J = 4.11 Hz, 2 H, aryl-H), 7.23 (d, ^3J = 4.11 Hz, 2 H, aryl-H). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.57 (–, Cpr-C), 12.6 (–, Cpr-C), 41.5 (C_{quat}, Cpr-C), 44.0 (–, CH_2), 51.0 (+, CH), 51.9 (+, CH), 52.2 (–, CH_2), 65.2 (+, OCH_3), 68.8 (+, OCH_3), 128.5 (+, 2 C, aryl-C), 128.6 (+, aryl-C), 128.7 (+, 2 C, aryl-C), 128.8 (+, 2 C, aryl-C), 128.9 (+, 2 C, aryl-C), 132.8 (C_{quat}, C_{ipso}), 134.7 (C_{quat}, C_{ipso}), 136.5 (C_{quat}, C_{ipso}), 170.0 (C_{quat}, C_{ipso}), 171.2 (C_{quat}, C=O), 171.3 (C_{quat}, C=O). – MS (70eV): *m/z* (%): 422/424 (16/6) [M^+], 394/396 (11/4), 363/365 (100/32), 335/337 (22/7), 256 (83), 125.0/127.0 (52/17). – M.p. 98−99 °C – $C_{21}H_{27}ClN_2O_5$ (422.9): calcd. C 59.64, H 6.44, N 6.62; found C 59.45, H 6.37, N 6.46.

Methyl 4-(4-Chlorobenzyl)-7-(methoxyphenylmethyl)-5-oxo-4,7-diazaspiro[2.5]octane-8-carboxylate (6dq): The crude product obtained from **3d** (1.12 g, 2.73 mmol) in MeOH (20 mL), (*S*)-α-phenylglycinol (412 mg, 3.00 mmol) and triethylamine (1.50 mL, 10.9 mmol) at 20 °C in 24 h, was purified by chormatography on 50 g of silica gel (3 × 20 cm, MOPS, Et_2O; R_f = 0.30) to yield 657 mg (65%) of **6dq** as a colorless oil (1:1 mixture of diastereomers, which were separated by column chromatography on silica gel). – *Diastereomer 1*: IR (KBr): nu(tilde) = 3319 , 3213, 3090, 3068, 2961, 2928, 1682 (C=O), 1495, 1462, 1443, 1325, 1229, 1092, 1016, 819, 813, 804, 735, 604, 553, 433 cm^{-1}. – ^{1}H NMR ($CDCl_3$, 250 MHz): δ = 0.26–0.35 (m, 1 H, Cpr-H), 0.55–0.64 (m, 1 H, Cpr-H), 0.95–1.04 (m, 1 H, Cpr-H), 1.12–1.23 (m, 1 H, Cpr-H), 2.38–2.61 (br s, 1 H, OH), 3.08 (s, 1 H, CH), 3.54 (s, 3 H, OCH_3), 3.68–3.81 (m, 4 H, 2×CH, CH_2), 3.83–3.91 (m, 1 H, CH), 3.92 (d, ^3J = 7.90 Hz, 1 H, A-part of an AB-system), 4.68 (d, ^3J = 7.90 Hz, 1 H, B-part of an AB-system), 7.06 (d, ^3J = 4.16 Hz, 2 H, aryl-H), 7.22–7.41 (m, 7 H, aryl-H). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.67 (–, Cpr-C), 12.6 (–, Cpr-C), 42.6 (C_{quat}, Cpr-C), 44.3 (–, CH_2), 52.0 (+, OCH_3), 53.1 (–, CH_2), 62.8 (–, CH_2), 63.7 (+, CH), 67.9 (+, CH), 128.1 (+, 2 C, aryl-C), 128.3 (+, aryl-C), 128.4 (+, 2 C, aryl-C), 128.6 (+, 2 C, aryl-C), 128.8 (+, 2 C, aryl-C), 128.9 (+, 2 C, aryl-C), 132.9 (C_{quat}, C_{ipso}), 136.4 (C_{quat}, C_{ipso}), 136.8 (C_{quat}, C_{ipso}), 170.5 (C_{quat}, C=O), 172.4 (C_{quat}, C=O). – MS (EI, 70 eV), *m/z* (%): 397 (100) $[M]^+$, 369 (19), 236 (15), 125 (50). – $C_{22}H_{21}ClN_2O_3$ (396.9): calcd. C 66.58, H 5.33, N 7.06; found C 66.72, H 5.55, N

7.16. – *Diastereomer 2*: IR (KBr): nu(tilde) = 3304, 3055, 2950, 1736 (C=O), 1659 (C=O), 1457, 1436, 1419, 1341, 1213, 745 cm^{-1}. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.44–0.48 (m, 1 H, Cpr-H), 0.63–0.67 (m, 1 H, Cpr-H), 0.86–0.93 (m, 1 H, Cpr-H), 1.12–1.25 (m, 1 H, Cpr-H), 2.76 (s, 1 H, OH), 3.08 (s, 1 H, CH), 3.52 (s, 3 H, OCH_3), 3.69–4.02 (m, 6 H, 2×CH, 2×CH_2), 4.72 (d, ^3J = 7.85 Hz, 1 H, B-part of an AB-system), 7.05 (d, ^3J = 4.13 Hz, 2 H, aryl-H), 7.21–7.36 (m, 7 H, aryl-H). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.53 (–, Cpr-C), 13.3 (–, Cpr-C), 41.3 (C_{quat}, Cpr-C), 44.4 (–, CH_2), 50.0 (+, CH), 52.0 (+, OCH_3), 62.0 (–, CH_2), 65.6 (–, CH_2), 67.8 (+, CH), 128.45 (+, 2 C, aryl-C), 128.52 (+, 3 C, aryl-C), 128.6 (+, 2 C, aryl-C), 128.9 (+, 2 C, aryl-C), 132.9 (C_{quat}, C_{ipso}), 136.3 (C_{quat}, C_{ipso}), 136.6 (C_{quat}, C_{ipso}), 170.4 (C_{quat}, C=O), 171.6 (C_{quat}, C=O). – MS (EI, 70 eV), *m*/*z* (%): 399/397 (32/100) $[M]^+$, 369 (21), 249 (16), 236 (24), 139 (19), 125 (100), 105 (100), 77 (62). – $C_{22}H_{21}ClN_2O_3$ (396.9): calcd. C 66.58, H 5.33, N 7.06; found C 66.73, H 5.55, N 7.26.

Methyl 4-(4-Chlorobenzyl)-5-oxo-7-(4-nitrobenzyl)-4,7-diazaspiro[2.5]octane-8-carboxylate (2dr): The crude product from **3d** (1.06 g, 2.60 mmol), 4-nitrobenzylamine (499 mg, 2.86 mmol) and triethylamine (788 mg, 7.79 mmol) was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, pentane/$CHCl_3$ 1 : 1 → 0 : 1; R_f = 0.62) to yield 963 mg (84%) of **2dr** as a colorless solid, m.p. 126 °C. – IR (KBr): nu(tilde) = 3146, 3073, 2954, 2931, 2905, 1732 (C=O), 1687 (C=O), 1617 (C=O), 1492, 1435, 1432, 1351, 1330, 1263, 1243, 1219, 1204, 1162, 1129, 1016, 976, 853, 839, 765, 703, 668, 569 cm^{-1}. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.67–0.74 (m, 1 H, Cpr-*H*), 0.77–0.95 (m, 2 H, Cpr-*H*), 1.14–1.24 (m, 1 H, Cpr-*H*), 2.68 (s, 1 H, NC*H*), 3.60 (s, 3 H, OCH_3), 3.72 (d, ^3J = 8.42 Hz, 1 H, A-part of an AB-system, PhCH_2), 3.77 (d, ^3J = 7.99 Hz, 1 H, A-part of an AB-system, PhCH_2), 3.91 (s, 2 H, CH_2), 3.94 (d, ^3J = 8.42 Hz, 1 H, B-part of an AB-system, PhCH_2), 4.96 (d, ^3J = 7.99 Hz, 1 H, B-part of an AB-system, PhCH_2), 7.10 (d, ^3J = 4.15 Hz, 2 H, aryl-*H*), 7.26 (d, ^3J = 4.15 Hz, 2 H, aryl-*H*), 7.51 (d, ^3J = 4.21 Hz, 2 H, aryl-*H*), 8.19 (d, ^3J = 4.21 Hz, 2 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.5 (–, Cpr-*C*), 11.6 (–, Cpr-*C*), 41.3 (C_{quat}, Cpr-*C*), 43.3 (–, Ph*C*H_2), 51.7 (+, O*C*H_3), 53.4 (–, Ph*C*H_2), 58.0 (–, *C*H_2), 66.3 (+, *C*HN), 123.8 (+, 2 C, aryl-*C*), 128.2 (+, 2 C, aryl-*C*), 128.6 (+, 2 C, aryl-*C*), 129.2 (+, 2 C, aryl-*C*), 132.8 (C_{quat}, aryl-*C*), 136.3 (C_{quat}, aryl-*C*), 144.8 (C_{quat}, aryl-*C*), 147.4 (C_{quat}, aryl-*C*), 169.0 (C_{quat}, *C*N=O), 170.4 (C_{quat}, *C*=O). MS (EI, 70 eV), *m*/*z* (%): 78 (14), 89 (20), 125/127 (94/26), 136 (23), 138 (13), 236 (36), 251 (13), 277 (100), 290 (16), 356 (24), 384

(79), 415 (14), 443/445 (14/5) $[M]^+$ – $C_{22}H_{24}ClN_3O_5$ (445.9): calcd. C 59.26, H 5.43, N 9.42; found C 59.45, H 5.66, N 9.73.

Methyl 4-(4-Chlorobenzyl)-7-naphthaline-2-ylmethyl-5-oxo-4,7-diazaspiro[2.5]octane-8-carboxylate (2ds): The crude product from **3d** (1.16 g, 2.84 mmol), 2-naphthylmethylamine (490 mg, 3.12 mmol) and triethylamine (861 mg, 8.51 mmol) was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, pentane/Et_2O 1 : 1 → 0 : 1; R_f = 0.62) to yield 1.08 g (85%) of **2ds** as a colorless foam. – IR (film): nu(tilde) = 3321, 3091, 2953, 2869, 1737 (C=O), 1666 (C=O), 1433, 1342, 1202, 1024, 971, 881, 789, 730 cm^{-1}. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.41–0.51 (m, 1 H, Cpr-*H*), 0.71–0.81 (m, 2 H, Cpr-*H*), 1.02–1.13 (m, 1 H, Cpr-*H*), 2.61 (s, 1 H, NC*H*), 3.58 (s, 3 H, OCH_3), 3.67 (d, ^3J = 8.01 Hz, 1 H, A-part of an AB-system, NC*H*), 3.84 (d, ^3J = 8.00 Hz, 1 H, A-part of an AB-system, PhCH_2), 4.10 (d, ^3J = 8.56 Hz, 1 H, B-part of an AB-system, PhCH_2), 4.17 (d, ^3J = 6.37 Hz, 1 H, A-part of an AB-system, PhCH_2), 4.30 (d, ^3J = 6.37 Hz, 1 H, B-part of an AB-system, PhCH_2), 4.98 (d, ^3J = 8.01 Hz, 1 H, B-part of an AB-system, NC*H*), 7.09 (d, ^3J = 3.94 Hz, 2 H, aryl-*H*), 7.25 (d, ^3J = 4.17 Hz, 2 H, aryl-*H*), 7.37–7.42 (m, 2 H, aryl-*H*), 7.46–7.55 (m, 2 H, aryl-*H*), 7.78–7.87 (m, 2 H, aryl-*H*), 8.21–8.24 (m, 1 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.5 (–, Cpr-*C*), 11.2 (–, Cpr-*C*), 41.5 (C_{quat}, Cpr-*C*), 43.1 (–, Ph*C*H_2), 51.4 (+, O*C*H_3), 53.7 (–, Ph*C*H_2), 57.0 (–, *C*H_2), 65.3 (+, *C*HN), 124.5 (+, aryl-*C*), 125.1 (+, aryl-*C*), 125.86 (+, aryl-*C*), 125.90 (+, aryl-*C*), 127.8 (+, aryl-*C*), 128.2 (+, 2 C, aryl-*C*), 128.4 (+, 2 C, aryl-*C*), 128.5 (+, aryl-*C*), 128.7 (+, aryl-*C*), 132.1 (C_{quat}, aryl-*C*), 132.2 (C_{quat}, aryl-*C*), 132.7 (C_{quat}, aryl-*C*), 133.8 (C_{quat}, aryl-*C*), 136.5 (C_{quat}, aryl-*C*), 169.5 (C_{quat}, *C*N=O), 170.9 (C_{quat}, *C*=O). – MS (EI, 70 eV), *m*/*z* (%): 448 (6) $[M]^+$, 420 (3), 389 (24), 282 (9), 141 (100), 125 (17), 115 (9). – HRMS (ESI): calcd. for $C_{26}H_{25}ClN_2O_3$ [M + H^+] 449.1632; found 449.1626.

Methyl 4-(4-Chlorobenzyl)-7-(3,4-dimethylphenyl)-5-oxo-4,7-diazaspiro[2.5]octane-8-carbo-xylate (2dt): The crude product from **3d** (1.00 g, 2.44 mmol), 3,4-dimethylaniline (326 mg, 2.69 mmol) and triethylamine (544 mg, 5.34 mmol) was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, cyclohexane/MTBE 1 : 2 → 1 : 1; R_f = 0.26) to yield 730 g (72%) of **2dt** as a colorless solid, m.p. 166–168 °C. – IR (KBr): nu(tilde) = 3269, 3139, 3091, 3071, 3004, 2974, 2956, 2931, 2835, 1677 (C=O), 1649 (C=O),

1514, 1459, 1417, 1325, 1246, 1176, 1055, 1033, 732, 553 cm^{-1}. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.80–0.89 (m, 2 H, Cpr-*H*), 1.19–1.40 (m, 2 H, Cpr-*H*), 2.17 (s, 3 H, C*H*$_3$), 2.23 (s, 3 H, C*H*$_3$), 3.49 (s, 1 H, C*H*), 3.56 (s, 3 H, OC*H*$_3$), 4.18 (d, ^3J = 7.8 Hz, 1 H, A-part of an AB-system, PhC*H*$_2$), 4.33 (s, 2 H, C*H*$_2$), 4.70 (d, ^3J = 7.8 Hz, 1 H, B-part of an AB-system, PhC*H*$_2$), 6.36 (d, ^3J = 4.1 Hz, 1 H, aryl-*H*), 6.43 (s, 1 H, aryl-*H*), 7.02 (d, ^3J = 4.1 Hz, 1 H, aryl-*H*), 7.14 (d, ^3J = 4.1 Hz, 2 H, aryl-*H*), 7.28 (d, ^3J = 4.25 Hz, 2 H, aryl-*H*). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 10.6 (–, Cpr-*C*), 13.7 (–, Cpr-*C*), 19.4 (+, Toluyl-*C*H$_3$), 21.2 (+, Toluyl-*C*H$_3$), 42.4 (C$_{quat}$, Cpr-*C*), 45.9 (–, *C*H$_2$), 51.2 (–, Ph*C*H$_2$), 53.1 (+, O*C*H$_3$), 65.2 (+, *C*HN), 110.0 (+, aryl-*C*), 114.2 (+, aryl-*C*), 127.6 (C$_{quat}$, aryl-*C*), 129.5 (+, 2 C, aryl-*C*), 129.6 (+, 2 C, aryl-*C*), 131.4 (C$_{quat}$, aryl-*C*), 134.0 (C$_{quat}$, aryl-*C*), 137.0 (C$_{quat}$, aryl-*C*), 138.5 (C$_{quat}$, aryl-*C*), 145.8 (C$_{quat}$, aryl-*C*), 170.4 (C$_{quat}$, *C*N=O), 172.4 (C$_{quat}$, *C*=O). – MS (70eV); *m/z* (%): 412/414 (75/22) [M^+], 351/353 (100/32), 325/327 (24/8), 246 (48), 125 (19). $C_{23}H_{25}ClN_2O_3$ (412.9): calcd. C 66.90, H 6.10, N 6.78; found C 66.99, H 6.15, N 6.82.

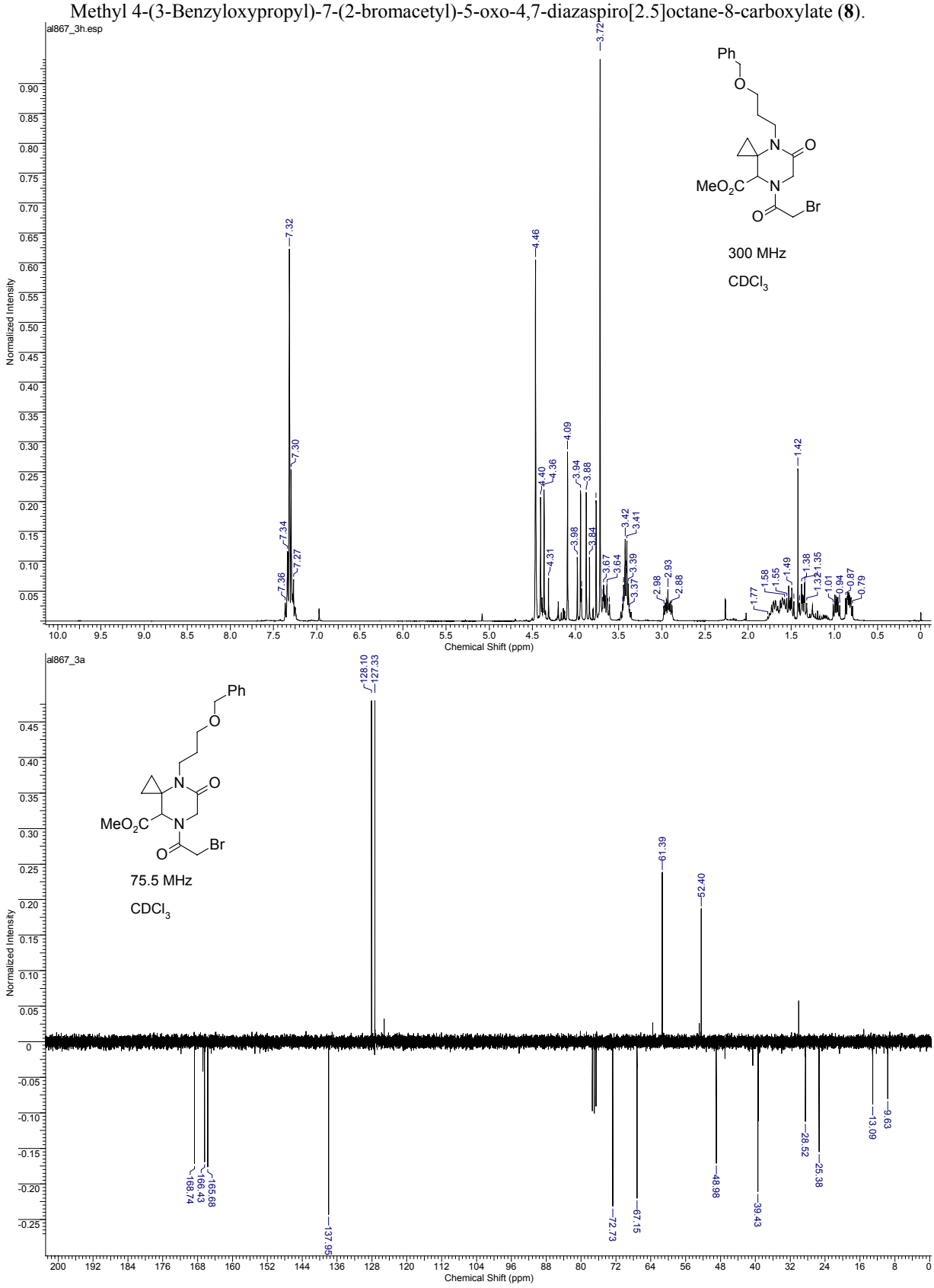
Methyl 4-(4-Chlorobenzyl)-5-oxo-7-(4-chlorophenyl)-4,7-diazaspiro[2.5]octane-8-carboxylate (2du): The crude product from **3d** (1.00 g, 2.44 mmol), *p*-chloroaniline (288 mg, 2.69 mmol) and triethylamine (764 mg, 5.91 mmol) was purified by chromatography on 50 g of silica gel (3 × 20 cm, MOPS, Et_2O; R_f = 32) to yield 399 mg (39%) of **2du** as a colorless solid, m.p. 165–166 °C – IR (KBr): nu(tilde) = 3443, 3323, 3052, 2951, 1739 (C=O), 1670 (C=O), 1492, 1435, 1404, 1337, 1221, 1093, 1015, 796, 736 cm^{-1}. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.75–0.82 (m, 1 H, Cpr-H), 0.85–0.91 (m, 1 H, Cpr-H), 1.21–1.27 (m, 1 H, Cpr-H), 1.35–1.43 (m, 1 H, Cpr-H), 2.26 (s, 3 H, $ArCH_3$), 3.48 (s, 1 H, CH), 3.54 (s, 3 H, OCH_3), 4.19 (d, ^3J = 7.83 Hz, 1 H, A-part of an AB-system), 4.31 (dd, ^2J = 9.93 Hz, 1 H, CH), 4.35 (dd, 1 H, ^2J = 9.95 Hz), 4.70 (d, ^3J = 7.83 Hz, 1 H, B-part of an AB-system), 6.50 (d, ^3J = 4.49 Hz, 2 H, aryl-H), 6.97–7.33 (m, 6 H, aryl-H). – ^{13}C NMR ($CDCl_3$, 62.9 MHz): δ = 9.80 (–, Cpr-*C*), 12.9 (–, Cpr-*C*), 41.4 (C$_{quat}$, Cpr-*C*), 45.1 (–, *C*H$_2$), 50.2 (–,*C*H$_2$Ph), 52.4 (+, O*C*H$_3$), 64.4 (+, *C*HN), 112.8 (+, 2 C, aryl-*C*), 123.5 (C$_{quat}$, aryl-*C*), 128.7 (+, 4 C, aryl-*C*), 129.3 (+, 2 C, aryl-*C*), 133.2 (C$_{quat}$, C$_{ipso}$), 135.9 (C$_{quat}$, C$_{ipso}$), 145.2 (C$_{quat}$, C$_{ipso}$), 169.0 (C$_{quat}$, *C*N=O), 170.9 (C$_{quat}$, *C*=O). – MS (70eV); *m/z* (%): 418/420 (36/23) [M^+], 359/361 (47/32), 252/254 (62/18), 236/238 (46/16), 125/127 (100/38) – $C_{21}H_{20}N_2O_3Cl_2$ (419.3). – HRMS (ESI): calcd. for $C_{21}H_{21}Cl_2N_2O_3$ [M + H^+] 419.0929; found 419.0924.

Methyl 4-(4-Chlorobenzyl)-7-[2-(1*H*-indol-3-yl)-ethyl]-5-oxo-4,7-diazaspiro[2.5]octane-8-carboxylate (2dv): The crude product obtained from **3d** (752 mg, 1.84 mmol), MeOH (20 mL), tryptamine (324 mg, 2.02 mmol), and triethylamine (1.02 mL, 7.35 mmol) at 40 °C within 3 d, was purified by chromatography on 50 g of silica gel (3 × 20 cm, CH_2Cl_2/MeOH 40 : 1, R_f = 0.38) to yield 825 mg (99%) of **2dv** as a colorless solid, m.p. 135–136 °C. – IR (KBr): nu(tilde) = 3454, 3088, 3000, 2947, 2876, 2844, 1739 (C=O), 1437, 1420, 1363, 1273, 1197, 1163, 1032, 934, 876, 811, 714, 659, 577 cm^{-1}. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.73–0.93 (m, 3 H, Cpr-H), 1.09–1.22 (m, 1 H, Cpr-H), 2.96 (s, 4 H, 2×CH_2), 3.59 (s, 3 H, OCH_3), 3.82 (d, ^2J = 7.93 Hz, 1 H), 3.93 (s, 2 H, CH_2), 4.94 (d, ^2J = 7.93 Hz, 1 H), 5.29 (s, 1 H, CH), 7.03–7.36 (m, 8 H, aryl-H), 7.57 (d, ^3J = 3.82 Hz, 1 H, aryl-H), 8.14–8.25 (br s, 1 H, NH). – ^{13}C NMR ($CDCl_3$, DEPT, 62.9 MHz): δ = 9.0 (–, Cpr-C), 11.9 (–, Cpr-C), 23.2 (–, CH_2), 41.1 (C_{quat}, Cpr-C), 43.5 (–, CH_2), 51.6 (+, OCH_3), 53.5 (–, CH_2), 55.5 (–, CH_2), 67.0 (+, CH), 111.1 (+, aryl-C), 113.2 (C_{quat}, aryl-C), 118.5 (+, aryl-C), 119.1 (+, aryl-C), 121.7 (+, aryl-C), 121.8 (+, aryl-C), 127.2 (C_{quat}, C_{ipso}), 128.2 (+, 2 C, aryl-C), 128.5 (+, 2 C, aryl-C), 131.8 (C_{quat}, C_{ipso}), 132.7 (C_{quat}, C_{ipso}), 136.1 (C_{quat}, C_{ipso}), 136.4 (C_{quat}, C_{ipso}), 169.8 (C_{quat}, C=O), 171.0 (C_{quat}, C=O). MS (ESI); *m/z* (%): 474/476 (100/32) [M+Na^+], 925/927 (47/17) [2M+Na^+] – $C_{25}H_{26}ClN_3O_3$ (451.96): calcd. C 66.44, H 5.80, N 9.30; found C 66.87, H 5.99, N 9.54.

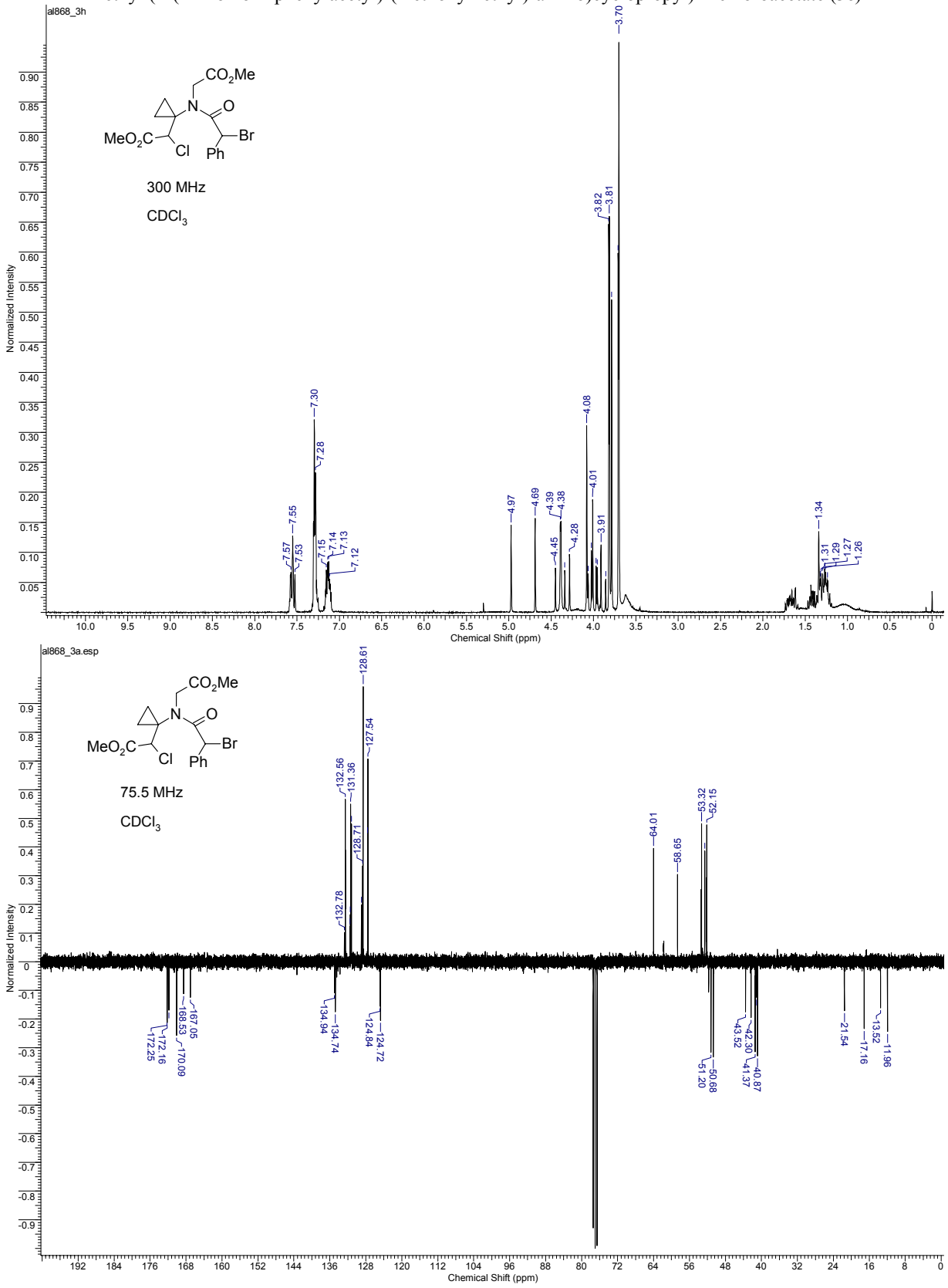
***trans*-Methyl 4-(4-Trifluoromethylbenzyl)-6-(4-phenyl)-5-oxo-7-(4-methoxyphenyl)-4,7-diazaspiro[2.5]octane-8-carboxylate (2ej-Ph).** The crude product obtained from **3e** (812 mg, 1.52 mmol) in THF (20 mL), *p*-anisidine (281 mg, 2.28 mmol) and triethylamine (1.50 mL, 10.9 mmol) under reflux for 12 h, was purified by chromatography on 30 g of silica gel (3 × 20 cm, pentane/Et_2O 1 : 0 → 1 : 2, R_f = 0.32, MOPS) and recrystallization from Et_2O to yield 250 mg (62%) of **2ef-Ph** as a slightly yellow solid, m.p. 132–133 °C. – IR (KBr): nu(tilde) = 3323, 2977, 2923, 1726 (C=O), 1670 (C=O), 1454, 1407, 1369, 1347, 1233, 1154, 843, 748, 701 cm^{-1}. – ^1H NMR ($CDCl_3$, 250 MHz): δ = 0.43–0.53 (m, 2 H, Cpr-H), 0.92–1.01 (m, 2 H, Cpr-H), 3.50 (s, 3 H, OCH_3), 3.70 (s, 3 H, OCH_3), 3.72 (s, 1 H, CH), 4.27 (d, ^2J = 7.76 Hz, 1 H, A-part of an AB-system), 4.50 (d, ^2J = 7.76 Hz, 1 H, B-part of an AB-system), 5.64 (s, 1 H, CH), 6.44 (m, 2 H, aryl-H), 6.75 (m, 2 H, aryl-H), 7.07–7.15 (m, 4 H, aryl-H), 7.28–7.41 (m, 2 H, aryl-H), 7.65–7.69 (m, 3 H, aryl-H). – ^{13}C NMR ($CDCl_3$,

DEPT, 62.9 MHz): δ = 9.75 (–, Cpr-C), 14.7 (–, Cpr-C), 40.8 (C_{quat}, Cpr-C), 47.5 (–, CH_2), 52.3 (+, OCH_3), 55.5 (+, OCH_3), 65.1 (+, CH), 65.7 (+, CH), 113.3 (+, 2 C, aryl-C), 114.9 (+, 2 C, aryl-C), 121.1 (+, 2 C, aryl-C), 126.8 (+, 2 C, aryl-C), 127.8 (+, aryl-C), 128.6 (+, 2 C, aryl-C), 128.8 (+, 2 C, aryl-C), 136.2 (C_{quat}, C_{ipso}), 137.9 (C_{quat}, C_{ipso}), 140.2 (C_{quat}, C_{ipso}), 148.3 (C_{quat}, C_{ipso}), 152.5 (C_{quat}, C_{ipso}), 170.4 (C_{quat}, C=O), 172.0 (C_{quat}, C=O). – MS (ESI), *m*/*z* (%): 547.2 (100) $[M+Na]^+$, 1071.4.4 (20) $[2M+Na]^+$. – $C_{29}H_{27}F_3N_2O_4$ (524.5): calcd. C 66.40, H 5.19, N 5.34; found C 66.22, H 5.14, N 5.25.

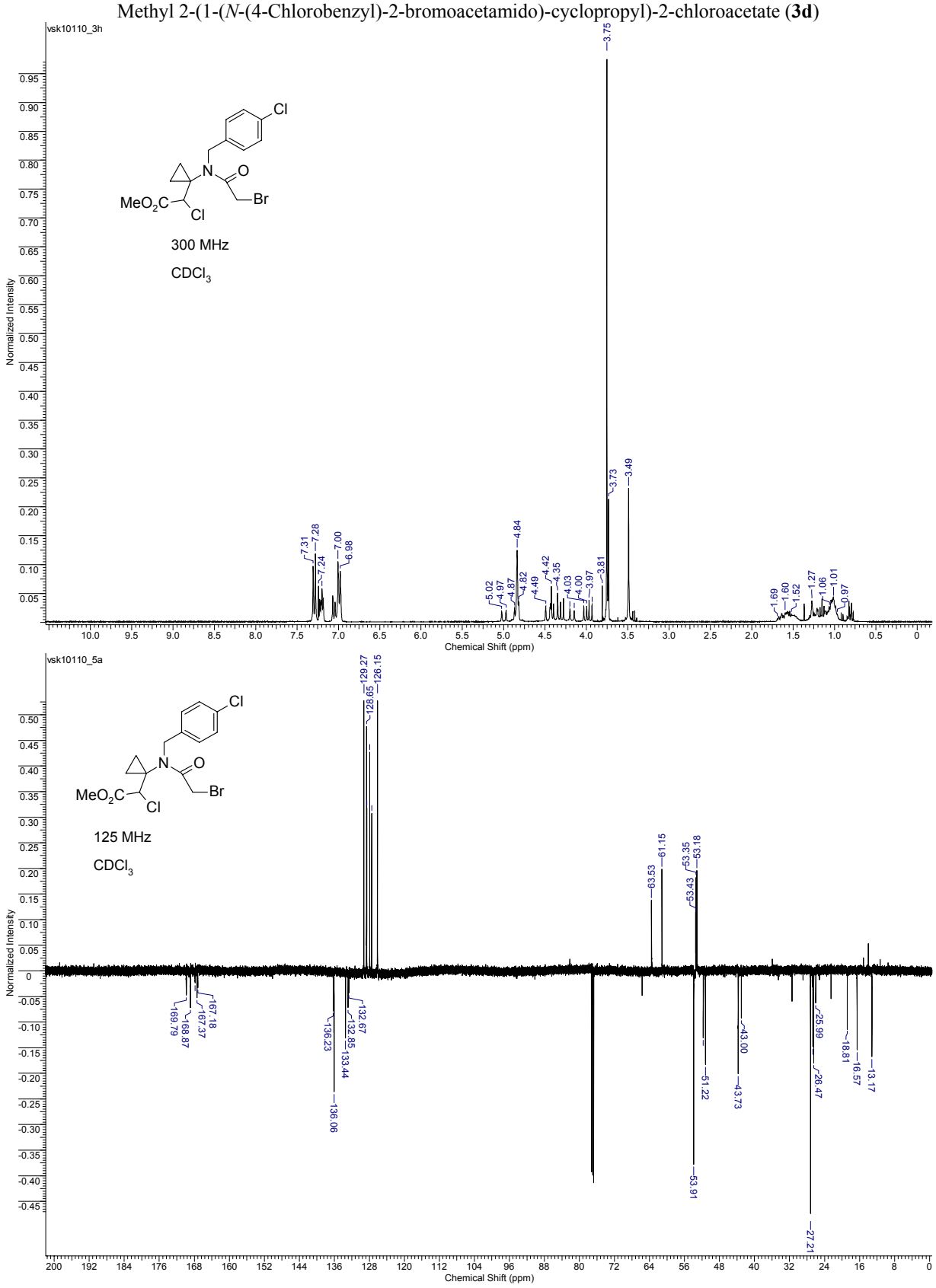
Methyl 4-(3-Benzyloxypropyl)-7-(2-bromacetyl)-5-oxo-4,7-diazaspiro[2.5]octane-8-carboxylate (**8**).



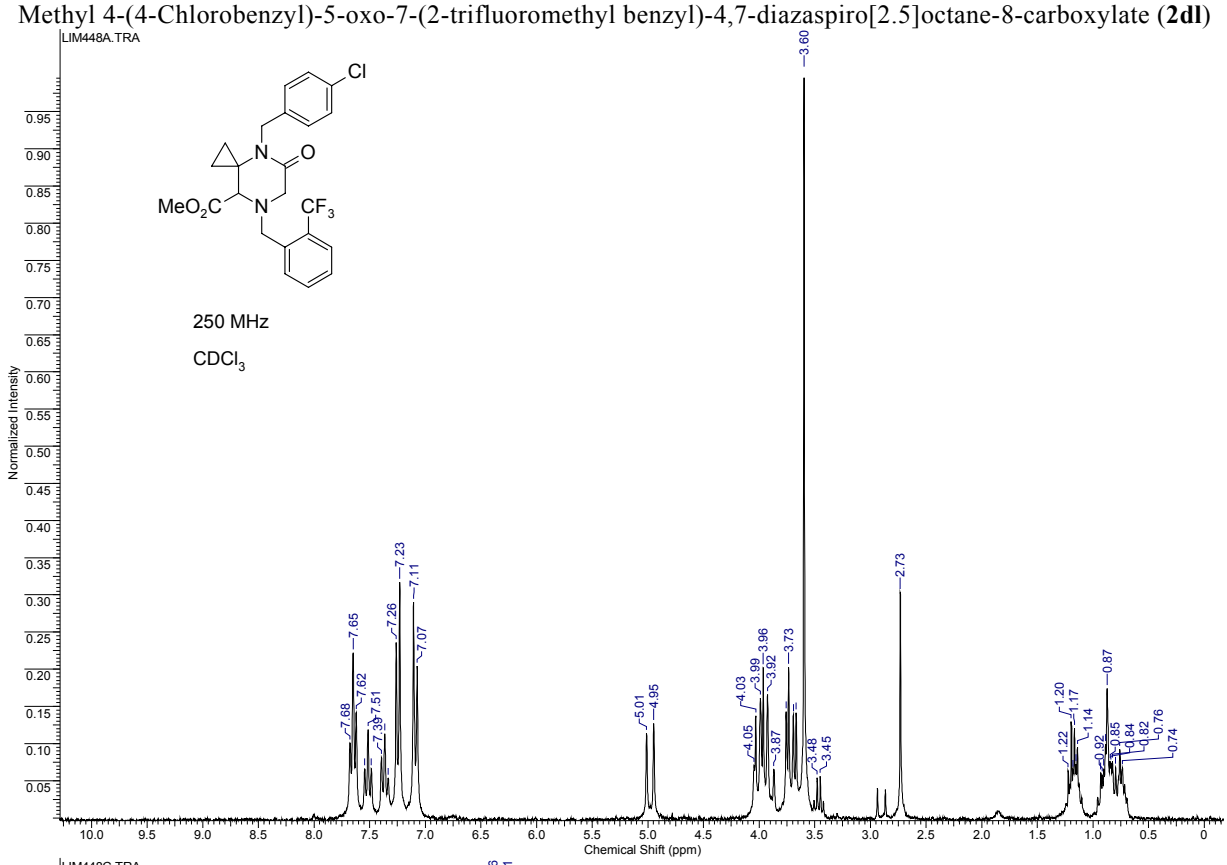
Methyl (2-(2-Bromo-2-phenylacetyl)-(methoxymethyl)-amino)cyclopropyl)-2-chloroacetate (**3c**)

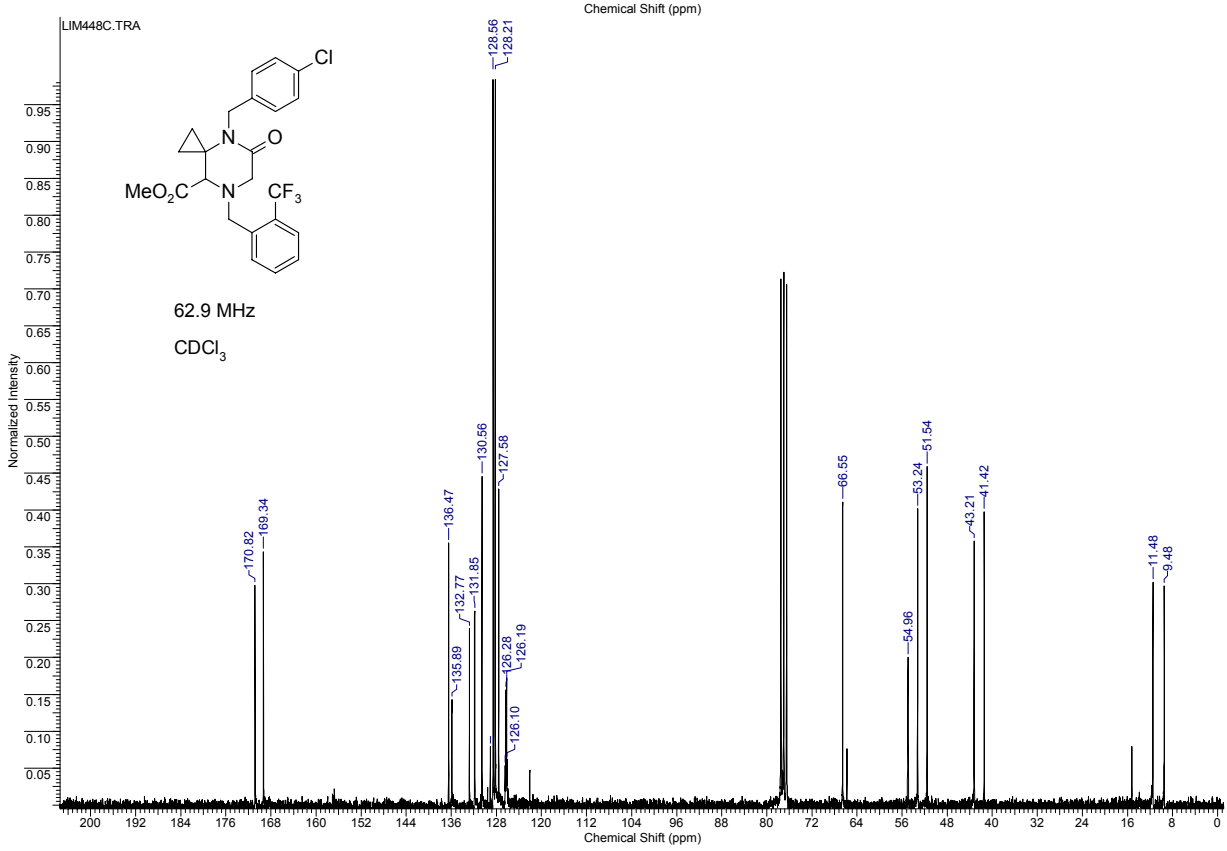


Methyl 2-(1-(*N*-(4-Chlorobenzyl)-2-bromoacetamido)-cyclopropyl)-2-chloroacetate (**3d**)

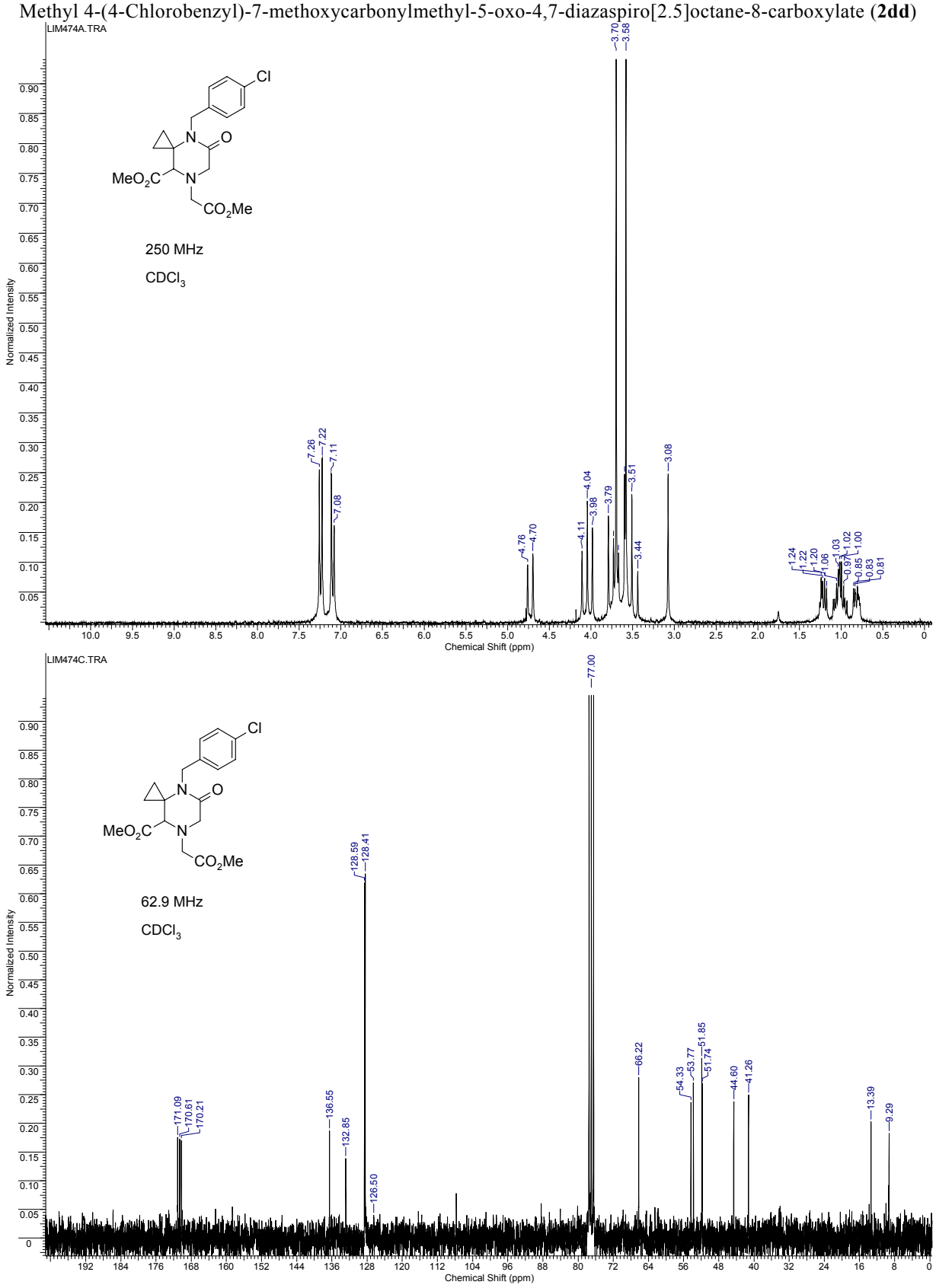


Methyl 4-(4-Chlorobenzyl)-5-oxo-7-(2-trifluoromethyl benzyl)-4,7-diazaspiro[2.5]octane-8-carboxylate (**2dl**)

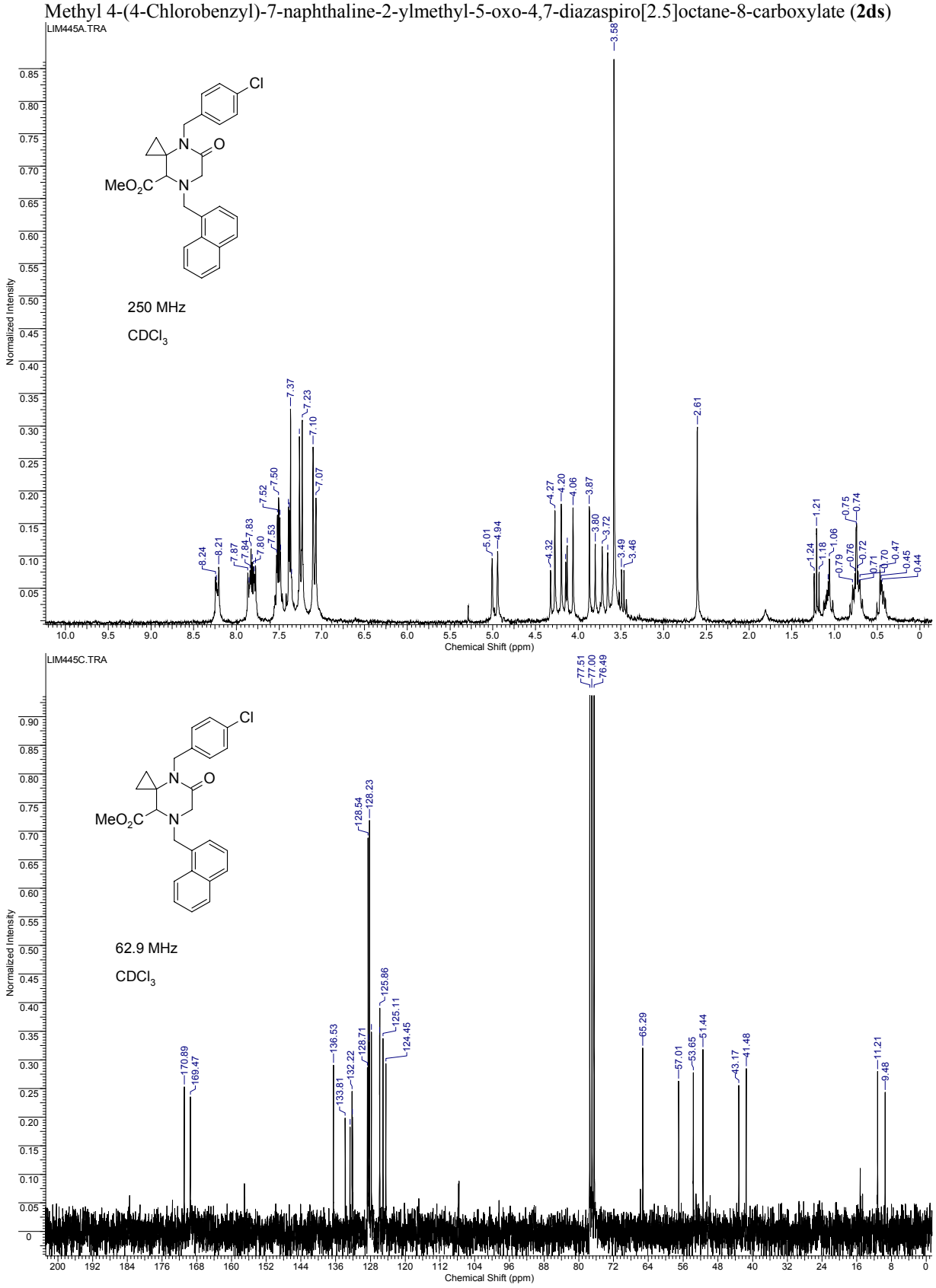




Methyl 4-(4-Chlorobenzyl)-7-methoxycarbonylmethyl-5-oxo-4,7-diazaspiro[2.5]octane-8-carboxylate (**2dd**)



Methyl 4-(4-Chlorobenzyl)-7-naphthaline-2-ylmethyl-5-oxo-4,7-diazaspiro[2.5]octane-8-carboxylate (**2ds**)



Methyl 4-(4-Chlorobenzyl)-5-oxo-7-(4-chlorophenyl)-4,7-diazaspiro[2.5]octane-8-carbo-xylate (**2du**)