Electronic Supplementary Information

Induction of Chirality: Experimental Evidence of Atropisomerism in Azapeptides

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S1. General Remarks

Solvents and reagents were obtained from Acros (Geel, Belgium), Fluka (Taufkirchen, Germany), Merck (Darmstadt, Germany), Grüssing (Filsum, Germany) or Sigma (Steinheim, Germany). Thin-layer chromatography was carried out on Merck aluminum sheets, silica gel 60 F_{254}. Preparative column chromatography was performed on Merck silica gel 60, 70–230 mesh. Melting points were determined on a Büchi 510 melting point apparatus and are uncorrected.

^{1}H and ^{13}C NMR spectra were acquired on a Bruker Avance DRX 500 spectrometer operating at 500 MHz for ^{1}H and 125 MHz for ^{13}C in DMSO-d_6 at 303 K if not denoted otherwise. Chemical shifts δ are given in ppm referring to the signal center using the solvent peak for reference: DMSO-d_6 2.49 ppm/39.7 ppm. The NMR signals were assigned by ^{1}H, ^{13}C correlation spectra (HMQC, HMBC) using standard pulse sequences. NOESY experiments of compound **9** were performed in DMSO-d_6 at 303 K using the following parameter values: Size of fid (TD) = 2048, 128; number of scans (NS) = 16; number of dummy scans (DS) = 16; mixing time (D8) = 2 s; acquisition time (AQ) = 0.36 s; and relaxation delay = 1.9 s.

Variable temperature (VT) ^{1}H NMR spectra for line-shape analysis were recorded at 500 MHz (compound **8)** on a Bruker Avance DRX 500 spectrometer or at 300 MHz (compounds **9** and **13**) on a Bruker DPX 300 spectrometer. Exchange rates k were determined upon line-shape analysis of the VT ^{1}H NMR measurements using the gNMR 5.0.6.0 software. Activation parameters $\Delta S^{\ddagger}$, $\Delta H^{\ddagger}$ and $\Delta G^{\ddagger}$ were determined from the slope and the ordinate intercept of linear fits to the Erying plots according to standard procedures. The overall error was estimated to be ± 10 kJ mol^{-1} for $\Delta G^{\ddagger}$.

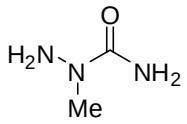
Elemental analyses were carried out with a Vario EL apparatus. HRMS (ESI+) was measured on a Bruker Daltonik micrOTOF-Q spectrometer. The purity was determined by HPLC-UV on an LCMS instrument (Applied Biosystems API 2000 LCMS/MS, HPLC Agilent 1100) using the following procedure: The compounds were dissolved at a concentration of 0.5 mg/mL in H_2O : MeOH (1 : 1), each containing 2 mM NH_4OAc. Then, 10 μL of the sample was injected into an HPLC column (Phenomenex Luna®, C18, 50 × 2.00 mm, 3 μm particle size). Elution was performed with a gradient of

H_2O (A) : MeOH (B) (each containing 2 mM NH_4OAc). For compounds *N*-(*tert*-butyloxycarbonyl)-glycyl-methylazaalanine-amide, glycyl-methylazaalanine-amide trifluoroacetate, **14,** *N*-(1*S,* 3*S,* 4*R*-menthyloxycarbonyl)-glycine, **15** and **16** (also see **S18**) the gradient table was: 0 min/10% B, 10 min/10% B, 20 min/100% B, 30 min/100% B; flowrate was 0.3 mL/min. For all other compounds the gradient table was: 0 min/10% B, 15 min/10% B, 30 min/100% B, 45 min/100% B; flowrate was 0.25 mL/min. UV absorption was detected using a diode array detector.

Chiral HPLC experiments (**S12**–**S17**) of compounds **9**, **12** and **16** were performed on a Jasco HPLC 2000 instrument. Chromatograms were obtained using ChromPass (version 1.8.6.1, Jasco) chromatography software. Chiral analyses of compounds **9**, **12** and **16** were performed with a Chiracel® OJ-RH column (150 × 4.6 mm, cellulose tris(4-methylbenzoate), 5 μm particle size, Daicel, Eschborn, Germany). For comparison purpose, achiral analyses of compound **9**, **12** and **16** were performed with a LiChroCART®, LiChrosorb® column (250-4, RP-18, 7 μm particle size) from Merck (Darmstadt, Germany). The samples were dissolved in acetonitrile at 1 mM if not mentioned otherwise, and 20 μL were injected into the HPLC device. A column temperature of 25 °C was applied. UV detection wavelength was 220 nm. For elution conditions, see text below chromatograms.

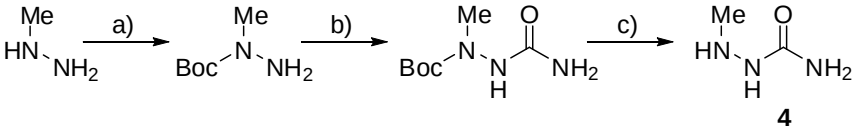
S2. Synthetic Procedures

2-Methylsemicarbazide (3)



HCl (8.85 mL of a 12 M solution, 105 mmol) was carefully given to a solution of *N*-methylhydrazine (4.837 g, 5.63 mL, 105 mmol), dissolved in H_2O (60 mL). Potassium cyanate (8.517g, 105 mmol) was added and the mixture was heated at 110 °C with an oil bath in an unsealed round-bottom flask until the water was driven off. The remaining white solid was taken up in toluene (50 mL), heated until reflux, and was then filtrated hot to remove inorganic salts. The white residue on the filter paper was treated with toluene (50 mL), heated until reflux, and filtrated hot again. The toluene extracts were combined and kept at room temperature to furnish **3** as colorless crystals (0.389 g, 4%): mp 101–102 °C (ref[1] 117 °C); ^{1}H NMR (500 MHz, DMSO-d_6): 2.91 (s, 3H, CH_3), 4.44 (s, 2H, CONH_2), 5.90 (s, 2H, NH_2N); ^{13}C NMR (125 MHz, DMSO-d_6): δ 37.49 (*C*H$_3$), 160.36 (*C*O). Anal. Calcd for $C_2H_7N_3O$: C, 26.96; H, 7.92; N, 47.16. Found: C, 26.71; H, 7.84; N, 45.70.

Synthesis of 1-Methylsemicarbazide (4).



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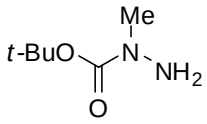
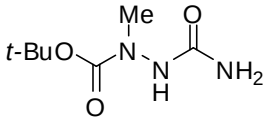
Reagents and conditions: a) Boc_2O, MeOH, rt, 40 min; b) TMSNCO, rt, 5 h, then H_2O, rt, 1 h; c) 1.0 M HCl (aq), reflux, 5 min, then rt, 10 min.

tert-Butyl 1-Methylhydrazinecarboxylate



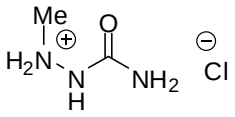
Di-*tert*-butyl dicarbonate (15.50 g, 71.02 mmol) was dissolved in MeOH (50 mL) and added dropwise to a solution of methyl hydrazine (4.335 g, 5.04 mL, 94.1 mmol) and MeOH (50 mL) over a period of 30 min at room temperature. Stirring was continued for 40 min and the mixture was concentrated in vacuo. The oily residue was taken up in EtOAc (100 mL) and washed with sat. $NaHCO_3$ (2 × 50 mL) and brine (1 × 30 mL). After drying (Na_2SO_4) the solvent was removed under reduced pressure to obtain *tert*-butyl 1-methylhydrazinecarboxylate as a colorless oil (7.625 g, 55%): ^{1}H NMR (500 MHz, DMSO-d_6): 1.39 (s, 9H, $(CH_3)_3C$), 2.91 (s, 3H, NCH_3), 4.46 (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 28.23 ($(CH_3)_3C$), 38.38 (NCH_3), 78.93 ($(CH_3)_3C$), 156.21 (CO); HRMS (ESI+) Calcd for $[C_6H_{14}N_2O_2Na]^+$: 169.0947. Found: 169.0942.

tert-Butyl 2-Carbamoyl-1-methylhydrazinecarboxylate



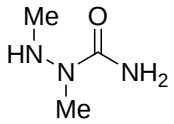
tert-Butyl 1-methylhydrazinecarboxylate (3.180 g, 21.75 mmol) and trimethylsilyl isocyanate (3.007 g, 3.54 mL, 26.10 mmol) were mixed under argon atmosphere. After stirring for 5 h at room temperature, H_2O (10 mL) was added and stirring was continued for 1 h. The meanwhile formed white suspension was evaporated to dryness and the white residue was placed in a fritted glass filter and washed with petroleum ether (3 × 30 mL) and diethyl ether (1 × 30 mL) to obtain *tert*-butyl 2-carbamoyl-1-methylhydrazinecarboxylate as a white solid (2.729 g, 66%): mp 129–131 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 1.37 (s, 9H, (CH_3)$_3$C), 2.93 (s, 3H, NCH_3), 5.87 (s, 2H, NH_2), 7.90 (s, 1H, N*H*CO); ^{13}C NMR (125 MHz, DMSO-d_6): δ 28.08 ((*C*H$_3$)$_3$C), 38.08 (N*C*H$_3$), 79.56 ((CH$_3$)$_3$*C*), 155.66 (O*C*ON), 158.30 (*C*ONH$_2$). Anal. Calcd for $C_7H_{15}N_3O_3$: C, 44.43; H, 7.99; N, 22.21. Found: C, 44.41; H, 8.42; N, 22.45.

1-Methylsemicarbazide Hydrochloride (4 × HCl)



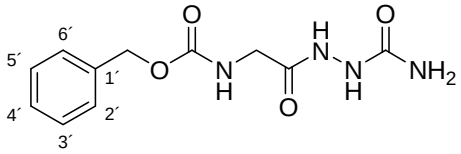
tert-Butyl 2-carbamoyl-1-methylhydrazinecarboxylate (0.946 g, 5.0 mmol) was suspended in HCl (1.0 M, 5 mL, 5.0 mmol) and refluxed for 5 min. Stirring was continued for 10 min in which the mixture was allowed to cool down. The obtained colorless solution was evaporated to dryness to obtain pure 1-methylsemicarbazide hydrochloride (**4** × HCl; 0.596 g, 95%): mp 174–175 °C; ^{1}H NMR (500 MHz, DMSO-d_6): 2.68 (s, 3H, CH_3), 6.61 (s, 2H, CONH_2), 9.28 (s, 1H, N*H*CO), 10.96 (br s, 2H, CH_3NH_2N); ^{13}C NMR (125 MHz, DMSO-d_6): δ 36.13 (*C*H_3), 156.94 (*C*O). Anal. Calcd for $C_2H_8ClN_3O$: C, 19.13; H, 6.42; N, 33.47. Found: C, 18.95; H, 6.64; N, 32.74.

1,2-Dimethylsemicarbazide (5)



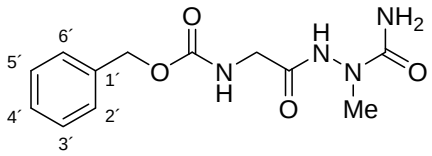
1,2-Dimethylhydrazine dihydrochloride (5.079 g, 38.18 mmol) was carefully added to a solution of NaOH (1.527 g, 38.18 mmol) and H_2O (30 mL) under ice cooling. Potassium cyanate (3.097 g, 38.18 mmol) was added and the mixture was heated at 100 °C with an oil bath in an unsealed round-bottom flask until the water was driven off. The remaining white solid was taken up in toluene (50 mL), heated until reflux, and was then filtrated hot to remove inorganic salts. The white residue on the filter paper was treated with toluene (50 mL), heated until reflux, and filtrated hot again. The toluene extracts were combined and kept at room temperature to furnish **5** as white needles (2.557 g, 65%): mp 117 °C (ref[2] 116 °C); ^{1}H NMR (500 MHz, DMSO-d_6): 2.39 (s, 3H, CH_3NH), 2.85 (s, 3H, CH_3NCO), 4.55 (s, 1H, CH$_3$NH), 5.95 (s, 2H, NH_2); ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.72 (*C*H$_3$NH or *C*H$_3$NCO), 34.43 (*C*H$_3$NH or *C*H$_3$NCO), 159.55 (*C*O). Anal. Calcd for $C_3H_9N_3O$: C, 34.94; H, 8.80; N, 40.75. Found: C, 34.84; H, 8.78; N, 38.39.

_N_-(Benzyloxycarbonyl)-glycyl-azaglycine-amide (6)



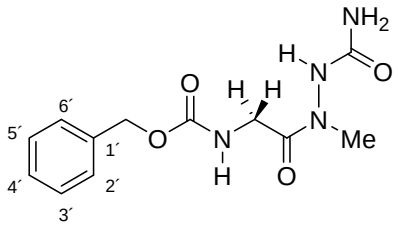
N-(Benzyloxycarbonyl)-glycine (0.418 g, 2.0 mmol) was dissolved in THF (5 mL) and cooled to –30 °C. *N*-Methylmorpholine (0.202 g, 0.22 mL, 2.0 mmol) and isobutyl chloroformate (0.273 g, 0.26 mL, 2.0 mmol) were given to the stirred solution. After precipitation of *N*-methylmorpholine hydrochloride, a solution of semicarbazide hydrochloride (**2** × HCl; 0.446 g, 4.0 mmol) and NaOH (0.160 g, 4.0 mmol) in H_2O (5 mL) was added to the reaction mixture. It was allowed to warm up to room temperature within 30 min and stirred additionally for 15 h. After evaporation of the organic solvent, the aqueous residue was diluted with H_2O (10 mL) and EtOAc (40 mL). A white precipitate was removed by suction filtration and represented crude compound **6** that was recrystallized from H_2O to obtain pure **6** (0.427 g, 80%): mp 184–188 °C (decomp.); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.65 (d, ^3J = 6.0 Hz, 2H, NCH_2CO), 5.02 (s, 2H, PhCH_2O), 5.89 (s, 2H, NH_2), 7.28–7.36 (m, 5H, H_{arom}), 7.43 (t, J = 6.0 Hz, 1H, N*H*CH$_2$CO), 7.72 (s, 1H, CN*H*NH or CNHN*H*), 9.57 (s, 1H, CN*H*NH or CNHN*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 42.34 (N*C*H$_2$CO), 65.64 (Ph*C*H$_2$O), 127.84 (C-2´, C-6´), 127.92 (C-4´), 128.47 (C-3´, C-5´), 137.14 (C-1´), 156.63 (O*C*ONH), 158.96 (*C*ONH$_2$), 169.02 (CH$_2$*C*ON). MS ESI-: *m/z* 265 ([$C_{11}H_{13}N_4O_4$]$^-$); HPLC purity: 99% (λ = 200–300 nm). Anal. Calcd for $C_{11}H_{14}N_4O_4$: C, 49.62; H, 5.30; N, 21.04. Found: 49.63; H, 5.06; N, 20.96.

_N_-(Benzyloxycarbonyl)-glycyl-azaalanine-amide (7)



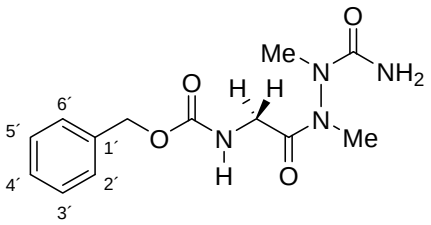
_N_-(Benzyloxycarbonyl)-glycine (0.418 g, 2.0 mmol) was dissolved in THF (5 mL) and cooled to –30 °C. _N_-Methylmorpholine (0.202 g, 0.22 mL, 2.0 mmol) and isobutyl chloroformate (0.273 g, 0.26 mL, 2.0 mmol) were given to the stirred solution. After precipitation of _N_-methylmorpholine hydrochloride, 2-methylsemicarbazide **3** (0.196 g, 2.20 mmol) was added to the reaction mixture. It was allowed to warm up to room temperature within 30 min and was further stirred for 15 h. After evaporation to dryness, the residue was taken up in EtOAc (120 mL) and the mixture was washed with sat. $NaHCO_3$ (1 × 15 mL), 10% $KHSO_4$ (1 × 15 mL), H_2O (1 × 15 mL), and brine (1 × 15 mL). The combined aqueous layers furnished pure **7** as white needles after keeping at room temperature for three days (0.281 g). To yield additional **7**, the organic layer of the extraction was dried (Na_2SO_4) and removed in vacuo to obtain crude compound **7** that was recrystallized from H_2O and yielded pure **7** (0.145 g, combined yield 0.426 g, 76%): mp 208–211 °C (decomp., recrystallized from H_2O); ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.89 (s, 3H, CH_3), 3.63 (d, J = 5.7 Hz, 2H, NCH_2CO), 5.02 (s, 2H, PhCH_2O), 6.03 (s , 2H, NH_2), 7.29–7.38 (m, 5H, H_{arom}), 7.49 (t, J = 5.7 Hz, 1H, NHCH_2CO), 9.97 (s, 1H, CONHN); ^{13}C NMR (125 MHz, DMSO-d_6): δ 35.31 (CH_3), 42.68 (NCH_2CO), 65.74 (PhCH_2O), 127.88 (C-2´, C-6´), 127.95 (C-4´), 128.46 (C-3´, C-5´), 137.04 (C-1´), 156.71 (OCONH), 158.74 (CONH$_2$), 168.62 (CH$_2C$ON); MS ESI+: _m/z_ 281 ([$C_{12}H_{17}N_4O_4$]$^+$); ESI-: _m/z_ 279 ([$C_{12}H_{15}N_4O_4$]$^-$); HPLC purity: 99% (λ = 200–400 nm). Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: 51.35; H, 5.79; N, 19.63.

_N_-(Benzyloxycarbonyl)-glycyl-azasarcosine-amide (8)



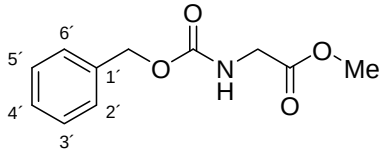
Synthesis has been performed using the procedure described for compound **6** with *N*-(benzyloxycarbonyl)-glycine (0.418 g, 2.0 mmol) and 1-methylsemicarbazide hydrochloride (**4** × HCl; 0.502 g, 4.0 mmol) as starting materials. The organic solvent was evaporated and the remaining aqueous residue was diluted with additional H_2O (10 mL) and EtOAc (40 mL). A white precipitate was removed by suction filtration and represented crude compound **8** that was recrystallized from H_2O to obtain pure **8** (0.342 g, 61%): mp 205–207 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.93 (s, 3H, CH_3), 3.63 (br s, 1H, NC*H*HCO), 3.97 (br s, 1H, NCH*H*CO), 5.02 (s, 2H, PhCH_2O), 6.20 (s, 2H, NH_2), 7.18 (t, J = 6.0 Hz, 1H, N*H*CH_2CO), 7.30–7.37 (m, 5H, H_{arom}), 8.31 (s, 1H, CONN*H*); ^{13}C NMR (125 MHz, DMSO-d_6): δ 35.63 (*C*H_3), 41.66 (N*C*H_2CO), 65.47 (Ph*C*H_2O), 127.78 (C-2´, C-6´), 127.86 (C-4´), 128.44 (C-3´, C-5´), 137.24 (C-1´), 156.54 (O*C*ONH), 157.45 (*C*ONH_2), 171.42 (CH_2*C*ON); MS ESI-: *m/z* 279 ([$C_{12}H_{15}N_4O_4$]$^-$); HPLC purity: 99% (λ = 200–400 nm). Anal. Calcd for $C_{12}H_{16}N_4O_4$: C, 51.42; H, 5.75; N, 19.99. Found: 51.18; H, 6.03; N, 20.13.

_N_-(Benzyloxycarbonyl)-glycyl-methylazaalanine-amide (9)



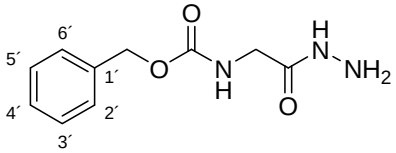
N-(Benzyloxycarbonyl)-glycine (0.418 g, 2.0 mmol) was dissolved in THF (5 mL) and cooled to –30 °C. *N*-Methylmorpholine (0.202 g, 0.22 mL, 2.0 mmol) and isobutyl chloroformate (0.273 g, 0.26 mL, 2.0 mmol) were given to the stirred solution. After precipitation of *N*-methylmorpholine hydrochloride, 1,2-dimethylsemicarbazide (**5**; 0.412 g, 4.0 mmol) was added to the reaction mixture. It was allowed to warm up to room temperature within 30 min and was further stirred for 15 h. After evaporation of the solvent, the residue was taken up with H_2O (40 mL), followed by extraction with EtOAc (3 × 40 mL). The combined organic layers were subsequently washed with sat. $NaHCO_3$ (1 × 25 mL), H_2O (1 × 25 mL), and brine (1 × 25 mL). After drying (Na_2SO_4) the solvent was removed in vacuo to obtain a white solid. Recrystallization from EtOH afforded pure **9** as white crystals (0.288 g, 49%): mp 152 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.92 (s, 3H, CH_2CONCH_3), 2.96 (s, 3H, CH_3NCONH_2), 3.69 (dd, ^2J = 17.3 Hz, ^3J = 6.3 Hz, 1H, NC*H*HCO), 3.85 (dd, ^2J = 17.4 Hz, ^3J = 5.7 Hz, 1H, NCH*H*CO), 5.03 (s, 2H, $PhCH_2O$), 6.47 (s, 2H, NH_2), 7.26 (t, J = 5.7 Hz, 1H, $NHCH_2$), 7.28–7.36 (m, 5H, H_{arom}); ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.32 (CH_2CONCH_3), 33.69 (CH_3NCONH_2), 41.41 (NCH_2CO), 65.56 ($PhCH_2O$), 127.81 (C-2´, C-6´), 127.90 (C-4´), 128.46 (C-3´, C-5´), 137.20 (C-1´), 156.57 (O*C*ONH), 157.65 ($CONH_2$), 171.13 (CH_2CON); MS ESI+: *m/z* 295 ($[C_{13}H_{19}N_4O_4]^+$); ESI-: *m/z* 293 ($[C_{13}H_{17}N_4O_4]^-$); HPLC purity: 99% (λ = 200–300 nm). Anal. Calcd for $C_{13}H_{18}N_4O_4$: C, 53.05; H, 6.16; N, 19.04. Found: 53.05; H, 5.96; N, 18.84.

_N_-(Benzyloxycarbonyl)-glycine Methyl Ester



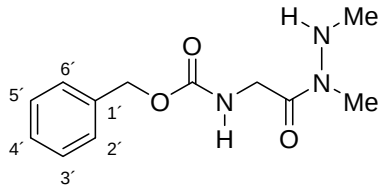
N-(Benzyloxycarbonyl)-glycine methyl ester was prepared from *N*-(benzyloxycarbonyl)-glycine (**1**) analogously to the procedure yielding *N*-(benzyloxycarbonyl)-phenylalanine methyl ester as described in ref.[3] Colorless oil; ^{1}H NMR (500 MHz, DMSO-d_6): 3.63 (s, 3H, OCH_3), 3.77 (d, J = 6.0 Hz, 2H, NCH_2CO), 5.04 (s, 2H, PhCH_2O), 7.27–7.38 (m, 5H, H_{arom}), 7.65 (t, J = 6.0 Hz, 1H, NHCH$_2$CO); ^{13}C NMR (125 MHz, DMSO-d_6): δ 42.24 (NHCH$_2$CO), 51.81 (OCH$_3$), 65.70 (PhCH$_2$O), 127.83 (C-2´, C-6´), 127.96 (C-4´), 128.48 (C-3´, C-5´), 137.08 (C-1´), 156.63 (OCONH), 170.76 (CH$_2$$CO_2$); MS ESI+: *m/z* 241 ([$C_{11}H_{13}NO_4$ + NH_4]$^+$); HPLC purity: 99% (λ = 210–300 nm).

_N_-(Benzyloxycarbonyl)-glycine Hydrazide (10)



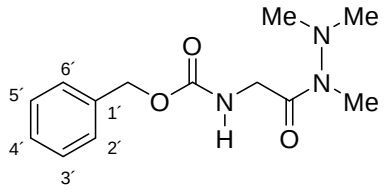
Hydrazine hydrate (4.361 g, 4.23 mL, 87.11 mmol) was added to a solution of *N*-(benzyloxycarbonyl)-glycine methyl ester (3.938 g, 17.42 mmol) in MeOH (15 mL) and stirred at room temperature. After 17 h the solvent was removed under reduced pressure and the residue was taken up in EtOAc (100 mL) and washed with 0.3 M HCl (1 × 100 mL, 2 × 50 mL). NaOH solution (2 M) was given to the aqueous layer until pH 11 was achieved, followed by extraction with ethyl acetate (3 × 150 mL). The organic layer was washed with water (1 × 100 mL) and brine (1 × 100 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure to obtain **10** as a colorless oil, that slowly crystallized to a white solid (1.883 g, 48%): mp 115–117 °C (ref[4] 115–117 °C); ^{1}H NMR (500 MHz, DMSO-d_6): δ 3.56 (d, J = 6.3 Hz, 2H, NCH_2CO), 4.17 (s, 2H, NH_2), 5.01 (s, 2H, PhCH_2O), 7.29–7.39 (m, 6H, H_{arom}, NHCH$_2$CO), 8.99 (s, 1H, CONHN); ^{13}C NMR (125 MHz, DMSO-d_6): δ 42.38 (NHCH$_2$CO), 65.57 (PhCH$_2$O), 127.83 (C-2´, C-6´), 127.88 (C-4´), 128.45 (C-3´, C-5´), 137.20 (C-1´), 156.52 (OCONH), 168.56 (CH$_2$$C$ONH); MS ESI-: *m/z* 222 ([$C_{10}H_{12}N_3O_3$]$^-$); HPLC purity: 93% (λ = 200–400 nm); Anal. Calcd for $C_{10}H_{13}N_3O_3$: C, 53.81; H, 5.87; N, 18.82. Found: 53.91; H, 5.93; N, 18.16.

_N_-(Benzyloxycarbonyl)-glycine 1,2-Dimethylhydrazide (11)



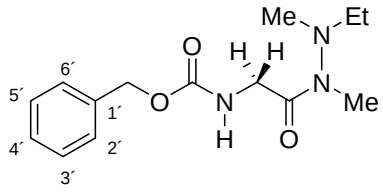
_N_-(Benzyloxycarbonyl)-glycine (1.464 g, 7.0 mmol) was dissolved in THF (15 mL) and cooled to –30 °C. _N_-Methylmorpholine (0.708 g, 0.77 mL, 7.0 mmol) and isobutyl chloroformate (0.956 g, 0.91 mL, 7.0 mmol) were given to the stirred solution. Another mixture, that was carefully prepared under ice cooling from NaOH (2.80 g, 70.0 mmol), H_2O (15 mL) and 1,2-dimethylhydrazine dihydrochloride (4.656 g, 35.0 mmol), was added to the reaction mixture after precipitation of _N_-methylmorpholine hydrochloride. It was allowed to warm to room temperature within 30 min and was stirred for further 15 h. After evaporation of the organic solvent, the aqueous residue was diluted with additional H_2O (20 mL), followed by extraction with EtOAc (3 × 30 mL). The combined organic layers were washed with H_2O (1 × 15 mL), sat. $NaHCO_3$ (1 × 15 mL), H_2O (1 × 15 mL), and brine (1 × 15 mL). After drying (Na_2SO_4) the solvent was removed in vacuo to obtain **11** as a colorless oil, that slowly crystallized to a white solid (1.683 g, 96%): mp 69–72 °C; ^{1}H NMR (500 MHz, DMSO-d_6): 2.44 (d, J = 5.7 Hz, 3H, NHCH_3), 2.93 (s, 3H, OCNCH_3), 3.93 (d, J = 6.3 Hz, 2H, NCH_2CO), 4.76 (q, J = 5.7 Hz, 1H, NHCH$_3$), 5.01 (s, 2H, PhCH_2O), 7.04 (t, J = 6.0 Hz, 1H, NHCH$_2$CO), 7.29–7.36 (m, 5H, H_{arom}); ^{13}C NMR (125 MHz, DMSO-d_6): δ 30.98, 34.82 (CH$_3$NH, CH$_3$N), 42.05 (NCH$_2$CO), 65.37 (PhCH$_2$O), 127.75 (C-2′, C-6′), 127.83 (C-4′), 128.43 (C-3′, C-5′), 137.33 (C-1′), 156.59 (OCONH), 170.34 (CH$_2$$C$ON); MS ESI+: _m/z_ 252 ([$C_{12}H_{17}N_3O_3$]$^+$); HPLC purity: 98% (λ = 200–300 nm). Anal. Calcd for $C_{12}H_{17}N_3O_3$: C, 57.36; H, 6.82; N, 16.72. Found: C, 57.23; H, 6.95; N, 16.14.

_N_-(Benzyloxycarbonyl)-glycine 1,2,2-Trimethylhydrazide (12)



N-(Benzyloxycarbonyl)-glycine 1,2-dimethylhydrazide (0.377 g, 1.50 mmol) was dissolved in 15 mL dry acetone. Cs_2CO_3 (0.489 g, 1.50 mmol) was added to the stirred solution. Then MeI (1.064 g, 0.47 mL, 7.50 mmol) was added and the suspension was refluxed. After 4 h additional MeI (1.064 g, 0.47 mL, 7.50 mmol) was given to the mixture and refluxing was continued for further 20 h. The solvent was evaporated, and the residue was suspended in EtOAc (60 mL), washed with sat. $NaHCO_3$ (2 × 20 mL) and brine (1 × 30 mL). After drying of the organic layer (Na_2SO_4) the solvent was removed under reduced pressure to obtain an oil that was subjected to column chromatography (CH_2Cl_2 / MeOH 19 + 1) to yield pure **12** as a colorless oil, that slowly crystallized to a white solid (0.146 g, 37%): mp 76–78 °C (decomp.); ^{1}H NMR (500 MHz, DMSO-d_6): 2.44 (s, 6H, N(CH_3)$_2$), 2.77 (s, 3H, OCNCH_3), 3.96 (d, J = 6.0 Hz, 2H, NCH_2CO), 5.01 (s, 2H, PhCH_2O), 7.04 (t, J = 5.7 Hz, 1H, NHCH$_2$CO), 7.28–7.39 (m, 5H, H_{arom}); ^{13}C NMR (125 MHz, DMSO-d_6): δ 22.03 (OCNCH$_3$), 42.20 (NCH$_2$CO), 42.62 (N(CH_3)$_2$), 65.39 (PhCH$_2$O), 127.77 (C-2´, C-6´), 127.84 (C-4´), 128.44 (C-3´, C-5´), 137.32 (C-1´), 156.56 (OCONH), 170.09 (CH$_2$$C$ON); MS ESI+: *m/z* 266 ([$C_{13}H_{20}N_3O_3$]$^+$); HPLC purity: 89 % (λ = 200–400 nm). Anal. Calcd for $C_{13}H_{19}N_3O_3$: C, 58.85; H, 7.22; N, 15.84. Found: C, 58.77; H, 7.16; N, 15.03.

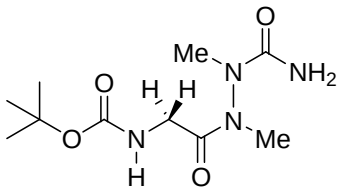
_N_-(Benzyloxycarbonyl)-glycine 2-Ethyl-1,2-dimethylhydrazide (13)



Mixture **A**: To a mixture of K_2CO_3 (12.438 g, 90.0 mmol) and H_2O (40 mL), 1,2-dimethylhydrazine dihydrochloride (3.961 g, 30.0 mmol) was carefully added under ice cooling. Then EtI (7.019 g, 3.60 mL, 45.0 mmol), dissolved in THF (10 mL), was added and the obtained solution was refluxed for 1 h. This mixture **A** was cooled to –30 °C.

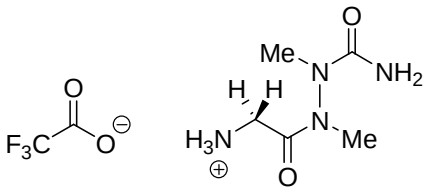
Mixture **B**: *N*-(Benzyloxycarbonyl)-glycine (1.255 g, 6.0 mmol), dissolved in THF (15 mL), was cooled to –30 °C. *N*-Methylmorpholine (0.607 g, 0.66 mL, 6.0 mmol) and isobutyl chloroformate (0.819 g, 0.78 mL, 6.0 mmol) were given to the stirred solution. After precipitation of *N*-methylmorpholine hydrochloride, the cooled mixture **A** was added to mixture **B**. The suspension was allowed to warm to room temperature within 30 min and was further stirred for 15 h. After evaporation of the organic solvent, the aqueous residue was extracted with EtOAc (1 × 60 mL, 1 × 30 mL). The combined organic layers were washed with sat. $NaHCO_3$ (1 × 30 mL), H_2O (1 × 30 mL), and brine (1 × 30 mL). After drying (Na_2SO_4) the solvent was removed in vacuo to obtain crude **13** as a colorless oil. This was purified by column chromatography (CH_2Cl_2 / MeOH 19 + 1) to yield pure **13** as a colorless oil, that slowly crystallized to a white solid (0.190 g, 11%): mp 81–82 °C; ^{1}H NMR (500 MHz, DMSO-d_6): 0.91 (t, J = 7.3 Hz, 3H, CH_2CH_3), 2.44 (s, 3H, CH_3NEt), 2.63 (q, J = 7.3 Hz, 2H, CH_2CH_3), 2.72 (s, 3H, CONCH_3), 3.88 (dd, ^2J = 17.4 Hz, ^3J = 6.0 Hz, 1H, NC*H*HCO), 4.01 (dd, ^2J = 17.7 Hz, ^3J = 6.0 Hz, 1H, NCH*H*CO), 5.01 (s, 2H, PhCH_2O), 7.07 (t, J = 6.0 Hz, 1H, N*H*CH_2CO), 7.29–7.36 (m, 5H, H_{arom}); ^{13}C NMR (125 MHz, DMSO-d_6): δ 12.15 (CH_2CH_3), 22.06 (CONCH_3) 41.35 (CH_3NEt), 42.31 (NCH_2CO), 48.21 (NCH_2CH_3), 65.37 (PhCH_2O), 127.75 (C-2´, C-6´), 127.84 (C-4´), 128.44 (C-3´, C-5´), 137.34 (C-1´), 156.57 (O*C*ONH), 170.84 (CH_2*C*ON); MS ESI+: *m/z* 280 ($[C_{12}H_{17}N_4O_4]^+$); HPLC purity: 92 % (λ = 200–400 nm).

_N_-(*tert*-Butyloxycarbonyl)-glycyl-methylazaalanine-amide



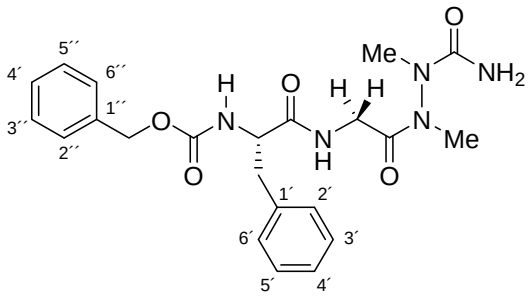
N-(*tert*-Butyloxycarbonyl)-glycine (0.701 g, 4.0 mmol) was dissolved in THF (10 mL) and cooled to –30 °C. *N*-Methylmorpholine (0.406 g, 0.44 mL, 4.0 mmol) and isobutyl chloroformate (0.546 g, 0.52 mL, 4.0 mmol) were given to the stirred solution. After precipitation of *N*-methylmorpholine hydrochloride, 1,2-dimethylsemicarbazide (**5**; 0.825 g, 8.0 mmol) was added to the reaction mixture. It was allowed to warm up to room temperature within 30 min and was further stirred for 15 h. After evaporation of the solvent, the residue was taken up with H_2O (80 mL), followed by extraction with EtOAc (3 × 80 mL). The combined organic layers were subsequently washed with sat. $NaHCO_3$ (1 × 50 mL), H_2O (1 × 50 mL), and brine (1 × 50 mL). After drying (Na_2SO_4) the solvent was removed in vacuo to obtain a white solid which was used without further purification (0.447 g, 43%): mp 140–142 °C; ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.91 (s, 3H, CH_2CONCH_3), 2.95 (s, 3H, CH_3NCONH_2), 3.62 (dd, ^2J = 17.1 Hz, ^3J = 6.0 Hz, 1H, NC*H*HCO), 3.75 (dd, ^2J = 17.4 Hz, ^3J = 5.7 Hz, 1H, NCH*H*CO), 6.44 (s, 2H, NH_2), 6.70 (t, J = 5.4 Hz, 1H, N*H*CH$_2$); ^{13}C NMR (125 MHz, DMSO-d_6): δ 28.33 ((*C*H$_3$)$_3$C), 31.31 (CH_2CONCH_3), 33.63 (CH_3NCONH_2), 41.07 (N*C*H$_2$CO), 78.13 ((CH$_3$)$_3$*C*), 155.86 (O*C*ONH), 157.62 ($CONH_2$), 171.34 (CH_2CON); MS ESI+: *m/z* 261 ($[C_{10}H_{21}N_4O_4]^+$); ESI-: *m/z* 259 ($[C_{10}H_{19}N_4O_4]^-$); HPLC purity: 97% (λ = 200–300 nm). Anal. Calcd for $C_{10}H_{20}N_4O_4$: C, 46.14; H, 7.74; N, 21.52. Found: C, 45.65; H, 7.84; N, 21.03.

Glycyl-methylazaalanine-amide Trifluoroacetate



N-(*tert*-Butyloxycarbonyl)-glycyl-methylazaalanine-amide (0.314 g, 1.21 mmol) was dissolved in dry CH_2Cl_2 (4 mL) and TFA (2 mL) and stirred at r.t. After 2 h, dry ether (30 mL) was added to the colorless solution and the mixture was stored at -18 °C for 10 min. A white viscous oil was isolated by suction filtration and dissolved in H_2O (60 mL). The solvent was removed under reduced pressure. The obtained residue was taken up in toluene (20 mL), followed by evaporation to dryness for four times to yield a colorless oil that was used without further purification (0.241 g, 73%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 2.96, 2.97 (each s, 3H, CH_2CONCH_3, CH_3NCONH_2), 3.53 (d, ^2J = 16.7 Hz, 1H, NC*H*HCO, overlapping with H_2O), 3.80 (d, ^2J = 16.4 Hz, 1H, NCH*H*CO), 6.60 (s, 2H, NH_2), 8.04 (s, 3, NH_3); ^{13}C NMR (125 MHz, DMSO-d_6): δ 31.02 (CH_2CONCH_3), 34.23 (CH_3NCONH_2), 157.59 ($CONH_2$), 158.08 (q, ^2J = 31.3 Hz), 168.63 (CH_2CON), NCH_2CO was not detected due to overlapping with DMSO, CF_3 was not detected; MS ESI+: *m/z* 161 ($[C_5H_{13}N_4O_2]^+$); ESI-: *m/z* 159 ($[C_5H_{11}N_4O_2]^-$); HPLC purity: 87% (λ = 200–300 nm).

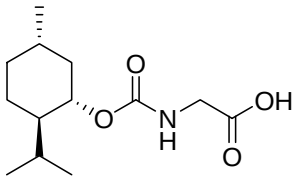
_N_-(Benzyloxycarbonyl)-L-phenylalanyl-glycyl-methylazaalanine-amide (14)



_N_-(Benzyloxycarbonyl)-L-phenylalanine (0.174 g, 0.58 mmol) was dissolved in dry THF (2 mL) and cooled to –30 °C. _N_-Methylmorpholine (0.059 g, 0.064 mL, 0.58 mmol) and isobutyl chloroformate (0.079 g, 0.076 mL, 0.58 mmol) were given to the stirred solution. After precipitation of _N_-methylmorpholine hydrochloride, a solution of glycyl-methylazaalanine-amide trifluoroacetate (0.192 g, 0.7 mmol), NaOH (1 M, 0.70 mL, 0.7 mmol) and H_2O (2 mL) was added to the reaction mixture. It was allowed to warm up to room temperature within 30 min and stirred additionally for 15 h. After evaporation of the solvent, the residue was taken up with H_2O (15 mL), followed by extraction with EtOAc (3 × 15 mL). The combined organic layers were subsequently washed with sat. $NaHCO_3$ (3 × 20 mL), H_2O (1 × 20 mL), and brine (1 × 20 mL). After drying (Na_2SO_4) the solvent was removed in vacuo to obtain **14** as a white solid (0.160 g, 62%): mp 91–92 °C; ^{1}H NMR (500 MHz, DMSO-d_6, mixture of atropdiastereomers, * = only one signal for both atropdiastereomers was detected): δ 2.73* (dd, ∑ 2H, ^2J = 13.3 Hz, ^3J = 11.4 Hz, PhC*H*HCH), 2.940, 2.942 (2 s (overlapping), ∑ 6H, CH_2CONCH_3), 2.98* (s, ∑ 6H, CH_3NCONH_2), 3.04* (dd, ∑ 2H, ^2J = 13.6 Hz, ^3J = 3.8 Hz, PhCH*H*CH), 3.82–3.86* (m, 2H, NC*H*HCO), 3.92–3.98* (m, ∑ 2H, NCH*H*CO), 4.31–4.36* (m, ∑ 2H, NHC*H*CO), 4.90–4.96* (m, ∑ 4H, PhCH_2O), 6.52* (s, ∑ 4H, NH_2), 7.17–7.33* (m, ∑ 20H, H_{arom}), 7.51 (d, ^3J = 8.5 Hz, 1H, N*H*CHCO), 7.53 (d, ^3J = 8.8 Hz, 1H, N*H*CHCO), 8.05–8.12* (m, ∑ 2H, N*H*CH_2CO); ^{13}C NMR (125 MHz, DMSO-d_6, mixture of atropdiastereomers, * = only one signal for both atropdiastereomers was detected): δ 31.16, 31.17 (CH_2CONCH_3), 33.67* (CH_3NCONH_2), 37.59, 37.61 (PhCH_2CH), 56.19* (PhCH_2CH), 65.30* (PhCH_2O), 126.32* (C-4′), 127.75* (C-4′′), 127.48*, 128.13*,

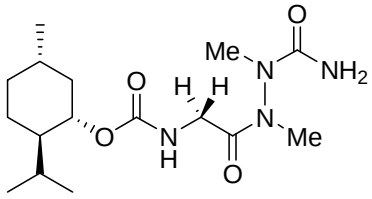
128.38*, 129.30*, (C-2′, C-6′, C-3′, C-5′, C-2′′, C-6′′, C-3′′, C-5′′), 137.13* (C-1′′), 138.30, 138.34 (C-1′), 155.95* (O*C*ONH), 157.70* (*C*ONH$_2$), 170.68, 171.88, 171.94 (NCH*C*ON, CH$_2$*C*ON), N*C*H$_2$CO was not detected due to overlapping with DMSO; MS ESI+: *m/z* 442 ([$C_{22}H_{28}N_5O_5$]$^+$); ESI-: *m/z* 440 ([$C_{22}H_{26}N_5O_5$]$^-$); HPLC purity: 99% (λ = 200–400 nm).

_N_-(1_S_, 3_S_, 4_R_-Menthyloxycarbonyl)-glycine



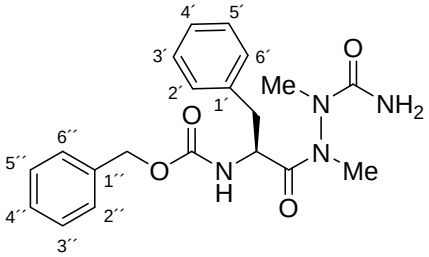
(1*S*, 3*S*, 4*R*)-Menthyl chloroformate (1.203 g, 1.18 mL, 5.5 mmol) in 1,4-dioxane (10 mL) was added dropwise to a solution of glycine (0.225 g, 3.0 mmol), $NaHCO_3$ (1.542 g, 18.4 mmol) and H_2O (20 mL) at room temperature. The reaction mixture was stirred at room temperature for 15 h. After the reaction time had elapsed, H_2O (20 mL) was given to the mixture, which was extracted with ether (2 × 60 mL). The aqueous layer was ice cooled, carefully acidified to pH 2–3 with 2 N HC1, and extracted with EtOAc (3 × 60 mL). The combined organic layers were dried (Na_2SO_4) and the solvent was removed in vacuo to obtain a crude product which was subjected to column chromatography (EtOAc / AcOH 99 + 1). The resulting oil was taken up in toluene (60 mL) and evaporated to dryness for four times to afford pure *N*-(1*S,* 3*S,* 4*R*-menthyloxycarbonyl)-glycine as a viscous oil (0.639 g, 83%):^{1}H NMR (500 MHz, DMSO-d_6): δ 0.72 (d, J = 6.9 Hz, 3H), 0.81–0.88 (m, 7H), 0.92 (q, J = 11.4 Hz, 1H), 1.01 (dq, J = 12.6, 2.9 Hz, 1H), 1.25–1.30 (m, 1H), 1.40–1.42 (m, 1H), 1.58–1.64 (m, 2H), 1.87–1.93 (m, 2H), 3.56–3.65 (m, 2H), 4.40 (dt, J = 11.1, 4.4 Hz, 1H), 7.22 (t, J = 6.3 Hz, 1H), 12.43 (br s, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 16.52, 20.66, 22.07, 23.28, 25.85, 31.02, 33.94, 41.40, 42.24, 47.01, 73.38, 156.58, 171.70; HRMS (ESI+) Calcd for $[C_{13}H_{23}NO_4Na]^+$: 280.1519. Found: 280.1521.

_N_-(1_S_, 3_S_, 4_R_-Menthyloxycarbonyl)-glycinyl-methylazaalanine-amide (15)



_N_-(1_S_, 3_S_, 4_R_-Menthyloxycarbonyl)-glycine (0.471 g, 1.83 mmol) was dissolved in dry THF (12 mL) and cooled to –30 °C. _N_-Methylmorpholine (0.185 g, 0.20 mL, 1.83 mmol) and isobutyl chloroformate (0.250 g, 0.24 mL, 1.83 mmol) were given to the stirred solution. After precipitation of _N_-methylmorpholine hydrochloride, 1,2-dimethylsemicarbazide (**5**; 0.379 g, 3.68 mmol) was added to the reaction mixture. It was allowed to warm up to room temperature within 30 min and was further stirred for 15 h. After evaporation of the solvent, the residue was taken up with H_2O (45 mL), followed by extraction with EtOAc (3 × 45 mL). The combined organic layers were subsequently washed with sat. $NaHCO_3$ (1 × 25 mL), H_2O (1 × 25 mL), and brine (1 × 25 mL). After drying (Na_2SO_4) the solvent was removed in vacuo to give a white solid which was subjected to column chromatography (EtOAc) to obtain pure **15** as a white solid (0.364 g, 58%): mp 54–57 °C; ^{1}H NMR (500 MHz, DMSO-d_6, mixture of atropdiastereomers, * = only one signal for both atropdiastereomers was detected): δ 0.72* (d, J = 7.0 Hz, ∑ 6H), 0.81–0.93* (m, ∑ 16H), 1.02* (dq, J = 14.5, 4.4 Hz, ∑ 2H), 1.23–1.31* (m, ∑ 2H), 1.38–1.44* (m, ∑ 2H), 1.58–1.64* (m, ∑ 4H), 1.86–1.93* (m, ∑ 4H), 2.91* (s, ∑ 6H), 2.95* (s, ∑ 6H), 3.62–3.71* (m, ∑ 2H), 3.80* (dt, J = 17.0, 5.7 Hz, ∑ 2H), 4.36–4.41* (m, ∑ 2H), 6.44, 6.50 (2 s (overlapping), ∑ 4H), 6.91–6.95* (m, ∑ 2H); ^{13}C NMR (125 MHz, DMSO-d_6, mixture of atropdiastereomers, * = only one signal for both atropdiastereomers was detected): δ 16.53, 16.56, 20.65*, 22.07*, 23.29, 23.31, 25.85*, 31.01*, 31.28*, 33.64*, 33.94*, 41.33, 41.38, 46.93*, 73.40, 73.43, 156.50*, 157.65*, 171.18, 171.22. Anal. Calcd for $C_{16}H_{30}N_4O_4$: C, 56.12; H, 8.83; N, 16.36. Found: C, 55.89; H, 9.18; N, 15.23.

_N_-(Benzyloxycarbonyl)-L-phenylalanyl-methylazaalanine-amide (16)

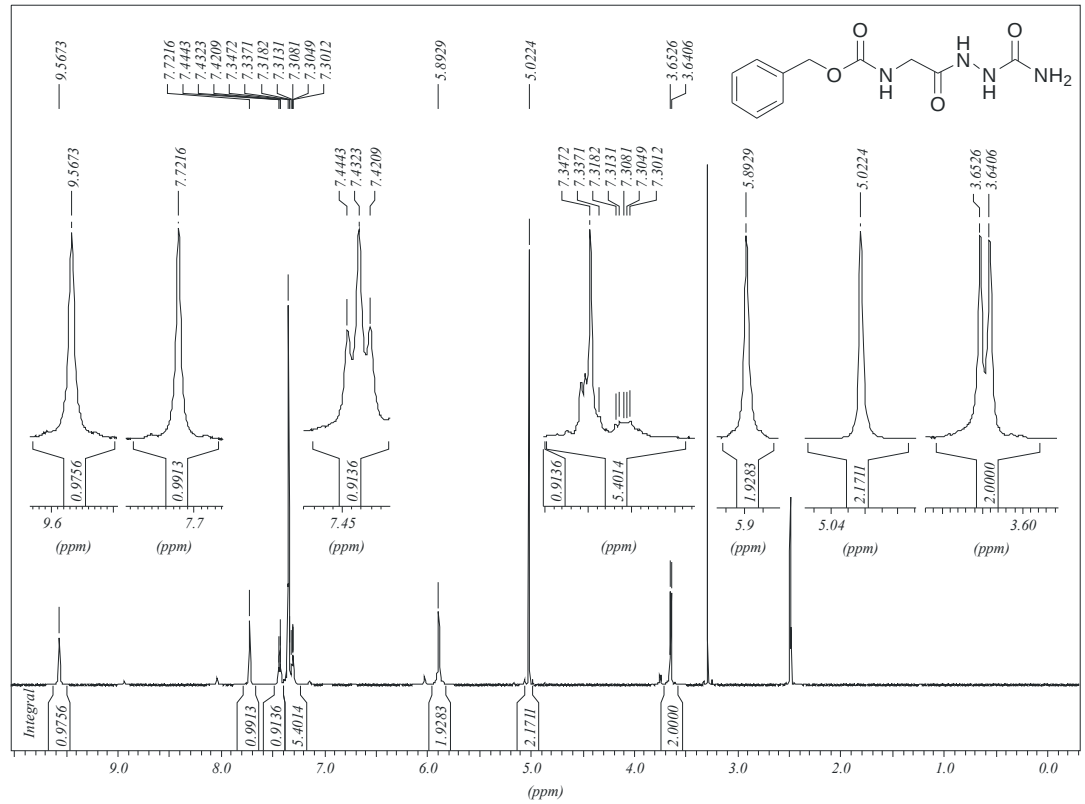


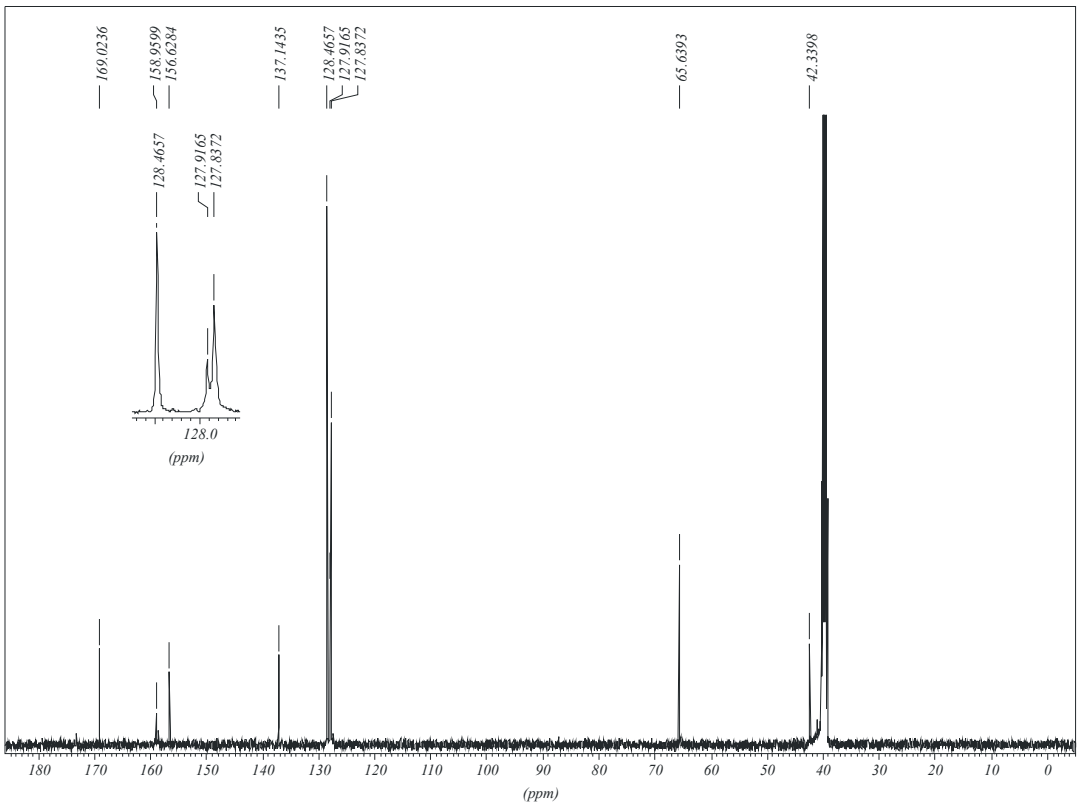
Synthesis has been performed applying the procedure described for compound **9** with *N*-(benzyloxycarbonyl)-L-phenylalanine (0.599 g, 2.0 mmol) and 1,2-dimethyl-semicarbazide (**5**; 1.031 g, 10.0 mmol) as starting materials. After drying (Na_2SO_4) and evaporation of the solvent the crude product was subjected to column chromatography (CH_2Cl_2 / MeOH 19 + 1) and subsequently recrystallized from toluene to obtain pure **16** as a white solid (0.392 g, 51%): mp 123 °C; ^{1}H NMR (500 MHz, DMSO-d_6, mixture of atropdiastereomers, ratio approximately 3+1 according to ^{1}H NMR, *w* = weak, refers to minor atropdiastereomer, *i* = intensive, refers to major atropdiastereomer) δ 2.63–2.69 (*w* + *i* overlapping) (m, 1H (*i*) + 1H (*w*), PhC*H*HCH), 2.82 (s, 3H (*w*), NCH_3), 2.93 (s, 3H (*w*), NCH_3), 2.98 (s, 3H (*i*), NCH_3), 3.00–3.02 (*w* + *i* overlapping) (m, 1H (*i*) + 1H (*w*), PhCH*H*CH), 3.09 (s, 3H (*i*), NCH_3), 4.50–4.55 (m, 1H (*i*), NHC*H*CO), 4.60–4.64 (m, 1H (*w*), NHC*H*CO), 4.92 (s, 2H (*i*), PhCH_2O), 4.95 (s, 2H (*w*), PhCH_2O), 6.50 (s, 2H (*w*), NH_2), 6.69 (s, 2H (*i*), NH_2), (*w* + *i* overlapping) 7.17–7.34 (10H (*i*) + 10H (*w*), H_{arom}), 7.68 (d, ^3J = 7.2 Hz, 1H (*w*), N*H*CHCO), 7.73 (d, ^3J = 8.5 Hz, 1H (*i*), N*H*CHCO); ^{13}C NMR (125 MHz, DMSO-d_6, *w* = weak, refers to minor atropdiastereomer; *i* = intensive, refers to major atropdiastereomer; * = only one signal for both atropdiastereomers was detected): δ 30.62 (*w*), 31.43 (*i*), (CHCON*C*H$_3$), 34.31 (*w*), 34.77 (*i*) (*C*H$_3$NCONH$_2$), 36.09 (*i*), 36.55 (*w*), (Ph*C*H$_2$CH), 52.81 (*w*), 53.44 (*i*), (NH*C*HCO), 65.43 (*i*), 65.69 (*w*), (Ph*C*H$_2$O), 126.45 (*i*), 126.69 (*w*), (C-4´), 127.85 (*i*), 127.91 (*w*), (C-4´´), 127.67 (*i*), 127.77 (*w*), 128.34*, 128.41*, 129.12 (*i*), 129.21 (*w*) (C-2´, C-6´, C-3´, C-5´, C-2´´, C-6´´, C-3´´, C-5´´), 137.04* (C-1´´), 138.83* (C-1´), 156.27 (*i*), 156.38 (*w*) (O*C*ONH), 157.85* (*C*ONH$_2$), 173.59 (*w*), 174.56 (*i*), (NCH*C*ON); LC/MS (see **S20**):

atropdiastereomer a, t_R = 9.98; ESI+: *m/z* 385 ($[C_{20}H_{25}N_4O_4]^+$); ESI-: *m/z* 383 ($[C_{20}H_{23}N_4O_4]^-$); atropdiastereomer b, t_R = 10.15 min; ESI+: *m/z* 385 ($[C_{20}H_{25}N_4O_4]^+$); ESI-: *m/z* 383 ($[C_{20}H_{23}N_4O_4]^-$); HPLC purity of atropdiastereomers a and b together: 100% (λ = 200–400 nm). Anal. Calcd for $C_{20}H_{24}N_4O_4$: C, 62.49; H, 6.29; N, 14.57. Found: C, 62.75; H, 6.03; N, 14.39.

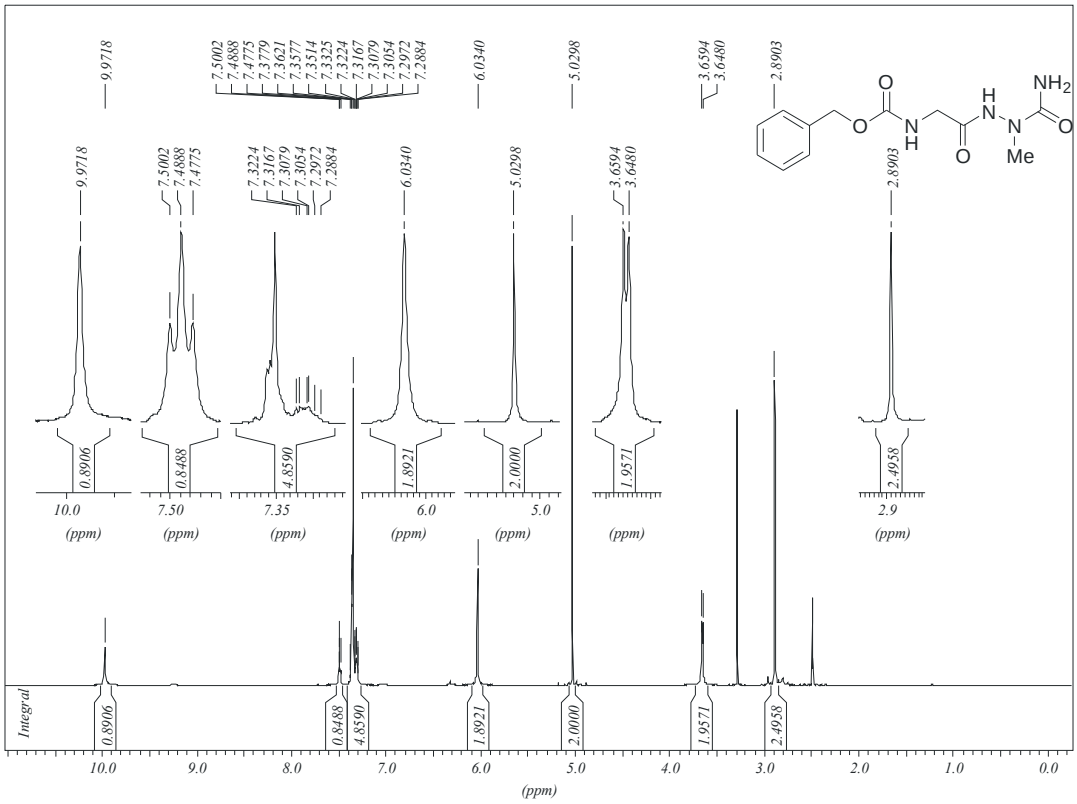
S3. ^{1}H NMR (500 MHz) and ^{13}C NMR (125 MHz) Spectra

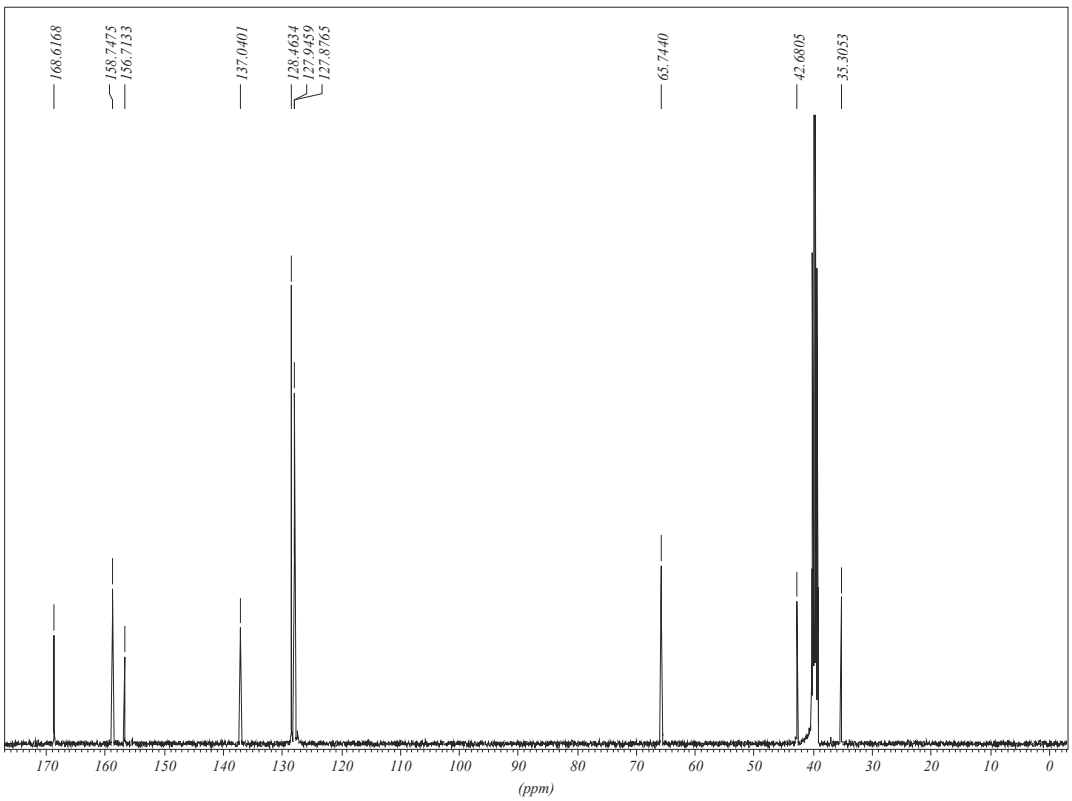
_N_-(Benzyloxycarbonyl)-glycyl-azaglycine-amide (6), DMSO-d_6, 303 K



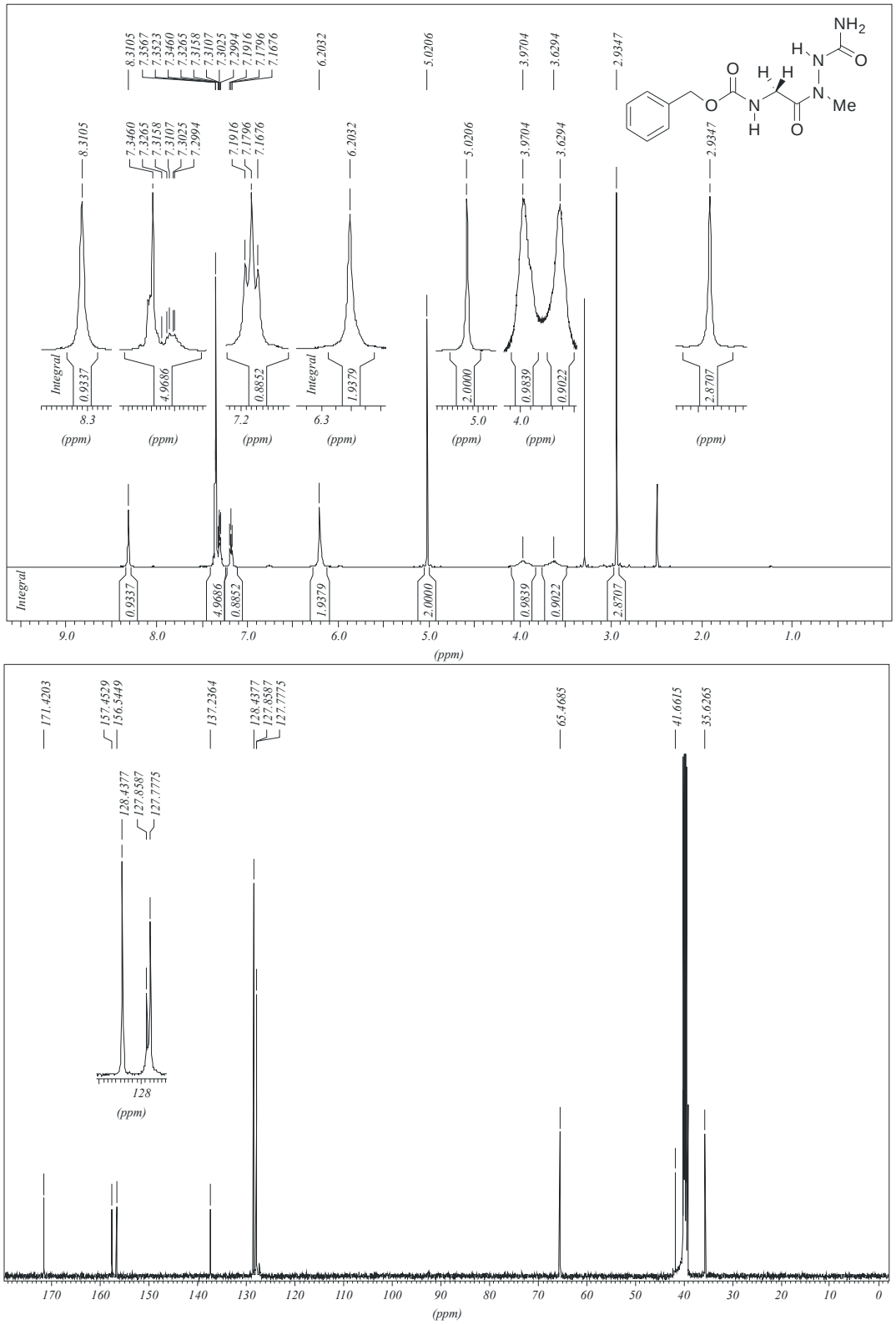


_N_-(Benzyloxycarbonyl)-glycyl-azaalanine-amide (7), DMSO-d_6, 303 K

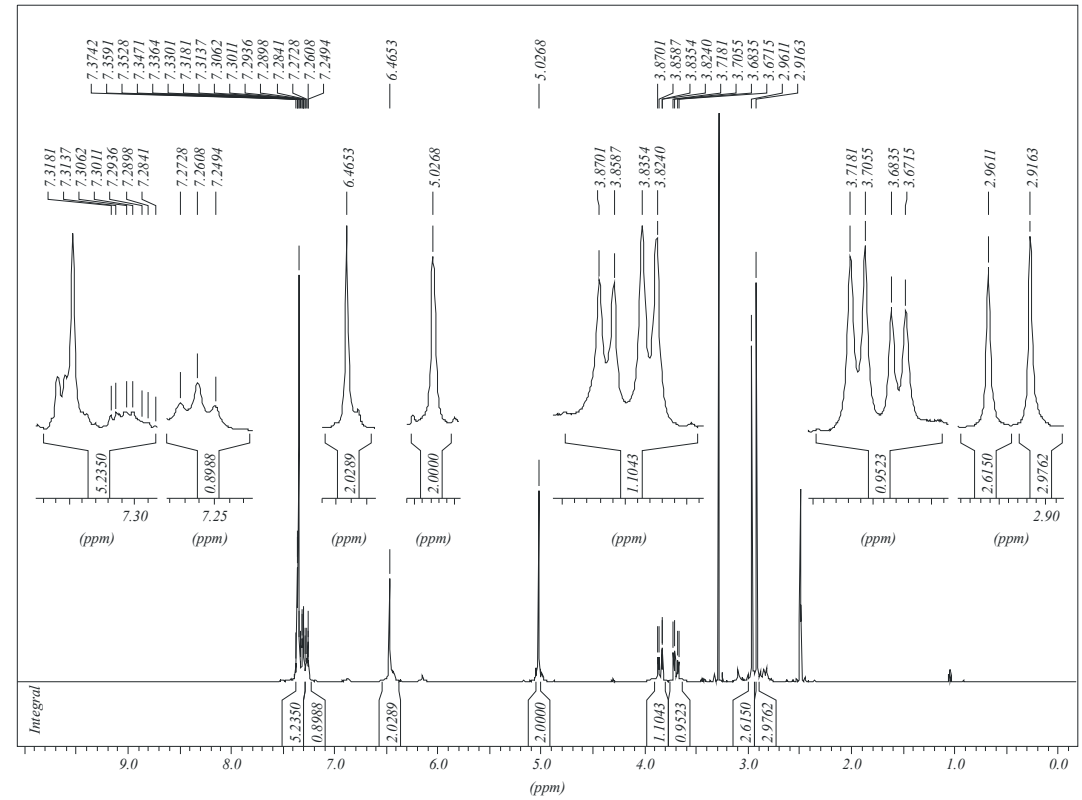


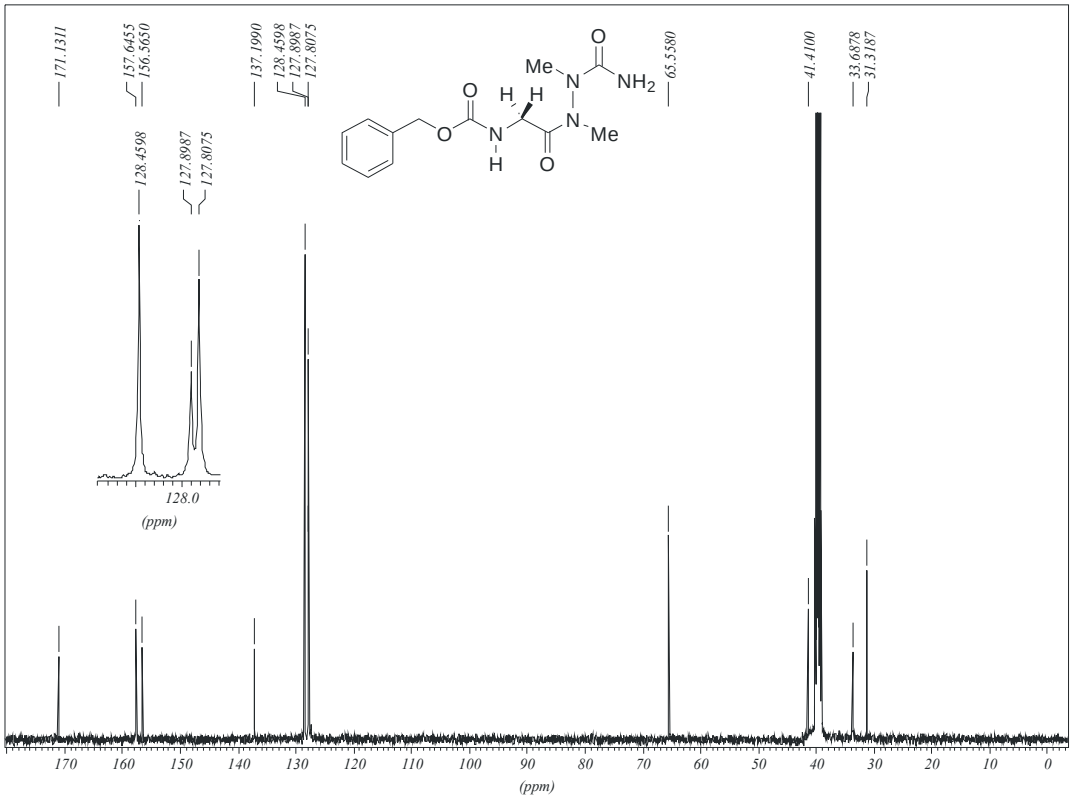


_N_-(Benzyloxycarbonyl)-glycyl-azasarcosine-amide (8), DMSO-d_6, 303 K

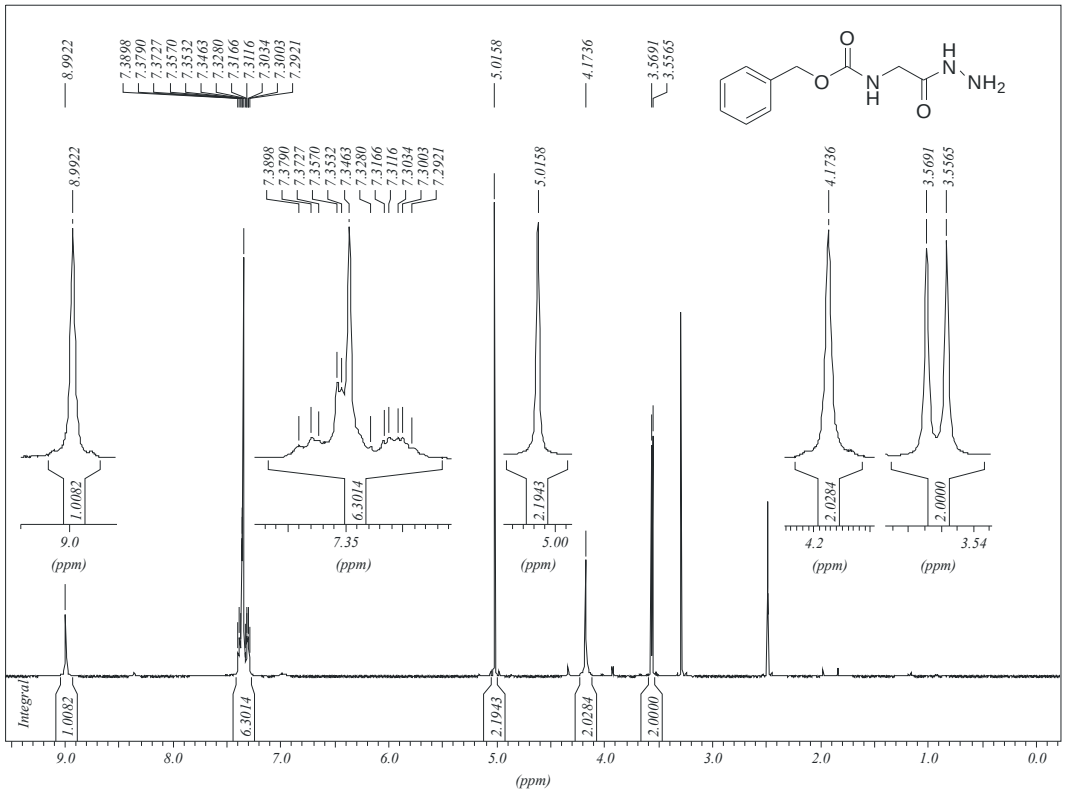


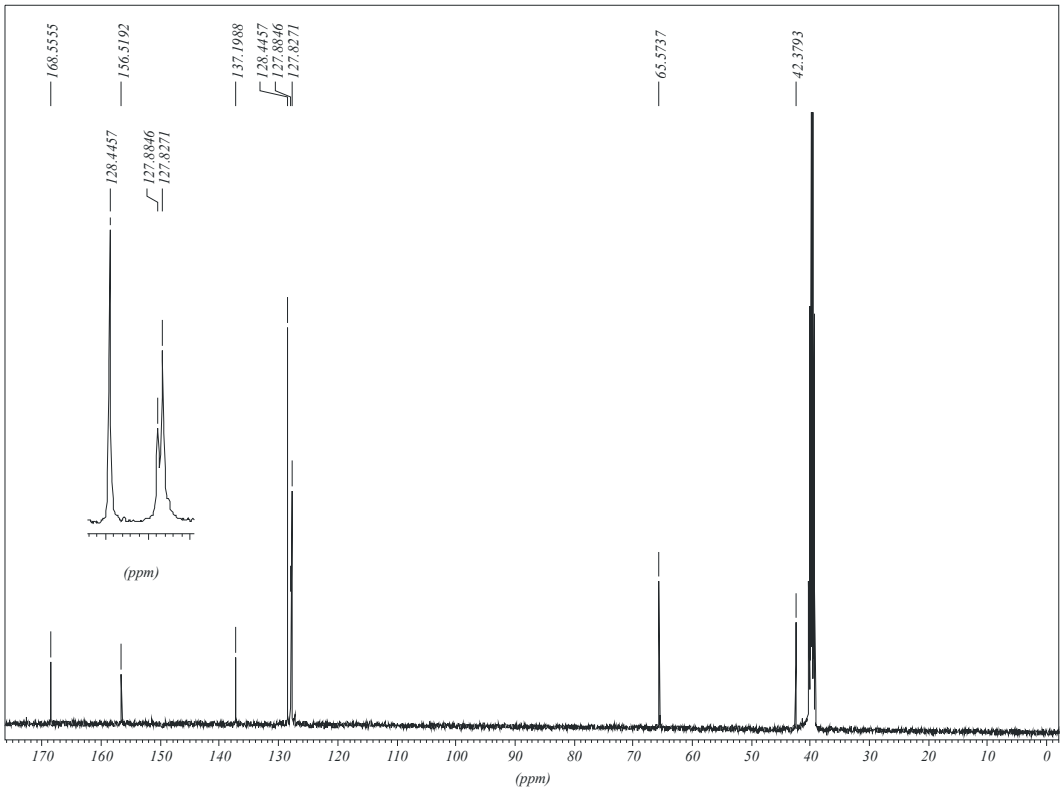
_N_-(Benzyloxycarbonyl)-glycyl-methylazaalanine-amide (9), DMSO-d_6, 303 K



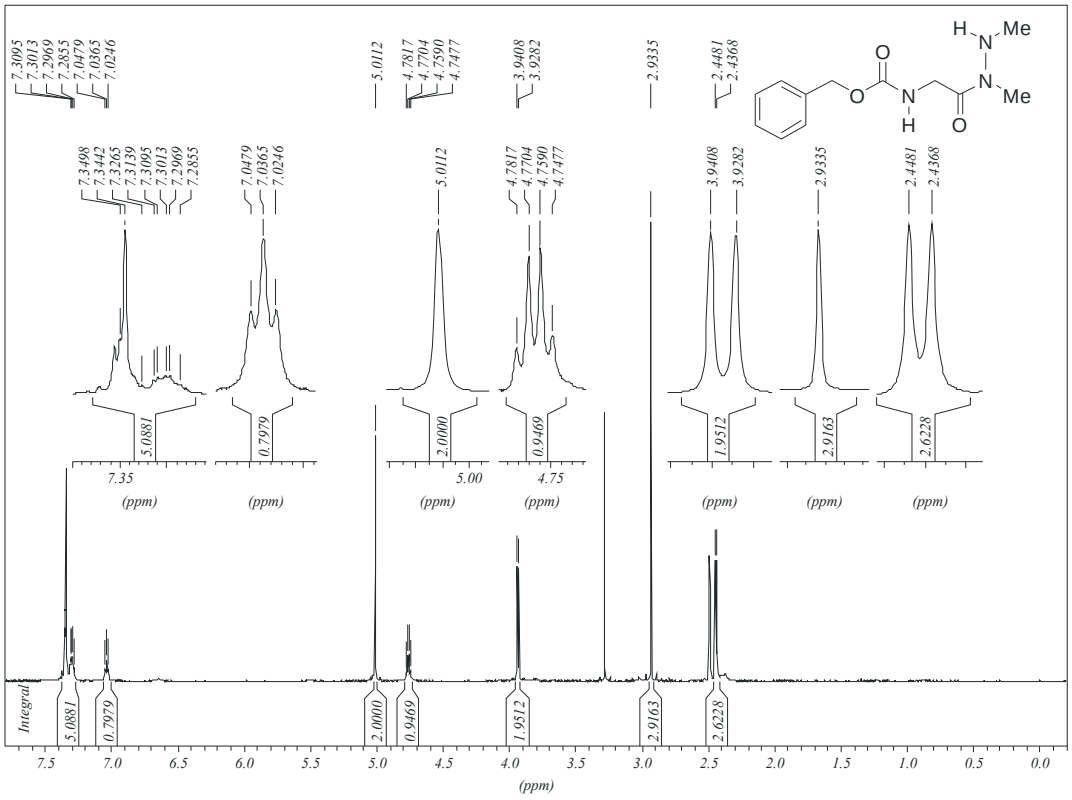


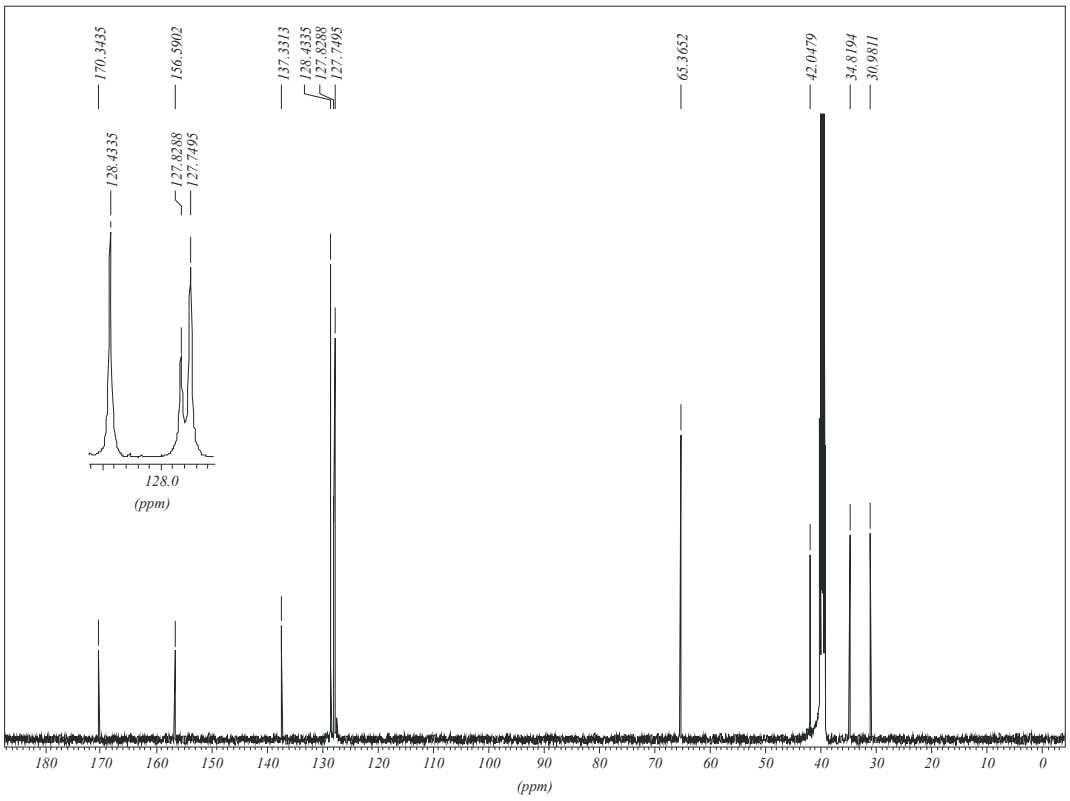
_N_-(Benzyloxycarbonyl)-glycine Hydrazide (10), DMSO-d_6, 303 K



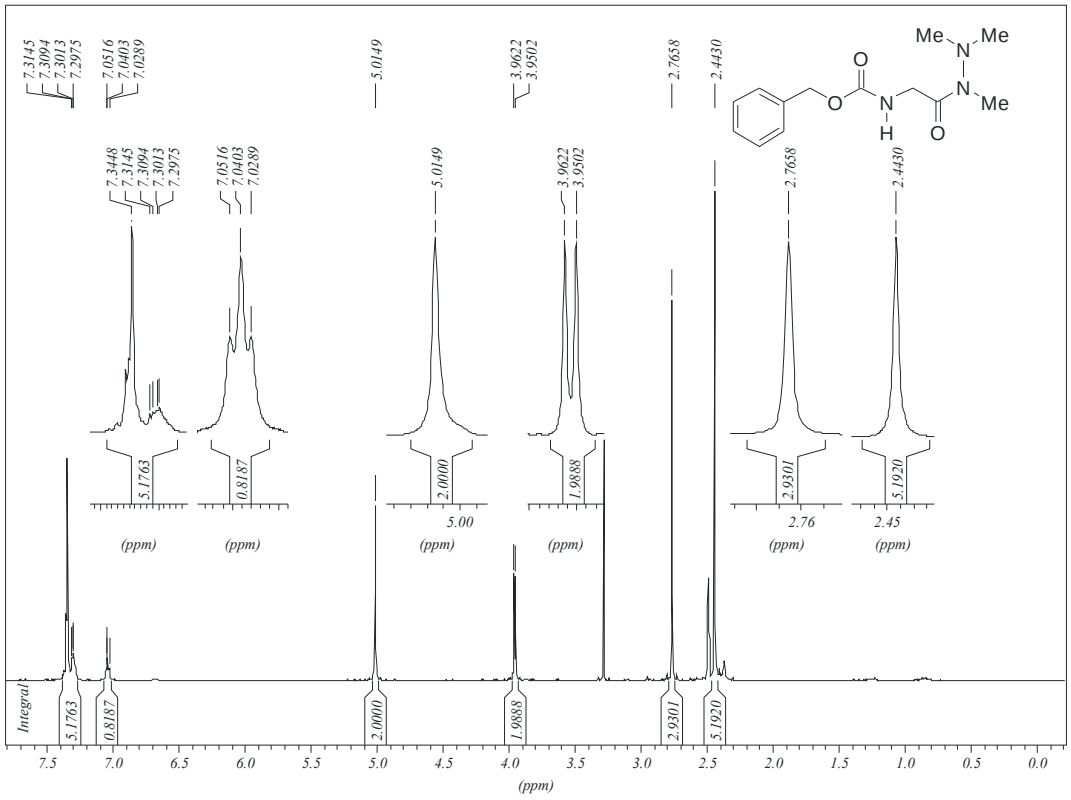


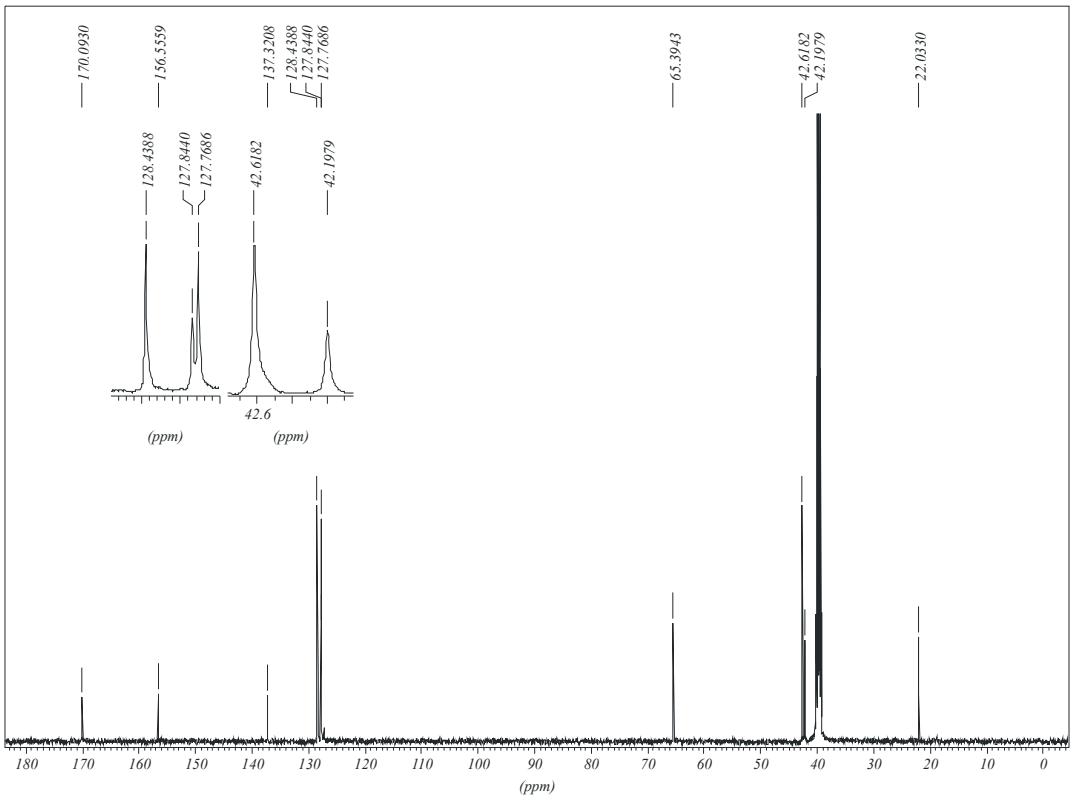
_N_-(Benzyloxycarbonyl)-glycine 1,2-Dimethylhydrazide (11), DMSO-d_6, 303 K





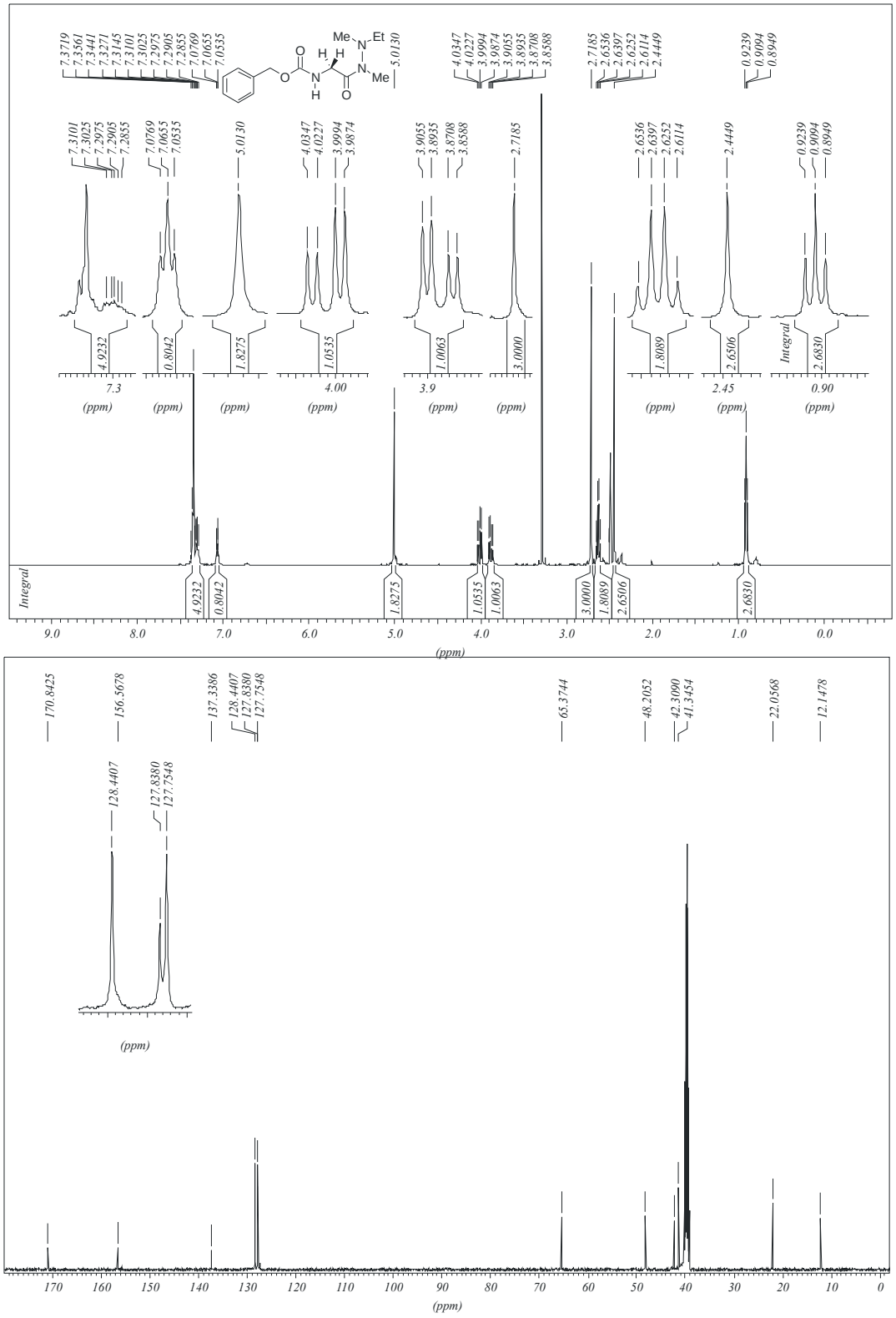
_N_-(Benzyloxycarbonyl)-glycine 1,2,2-Trimethylhydrazide (12), DMSO-d_6, 303 K



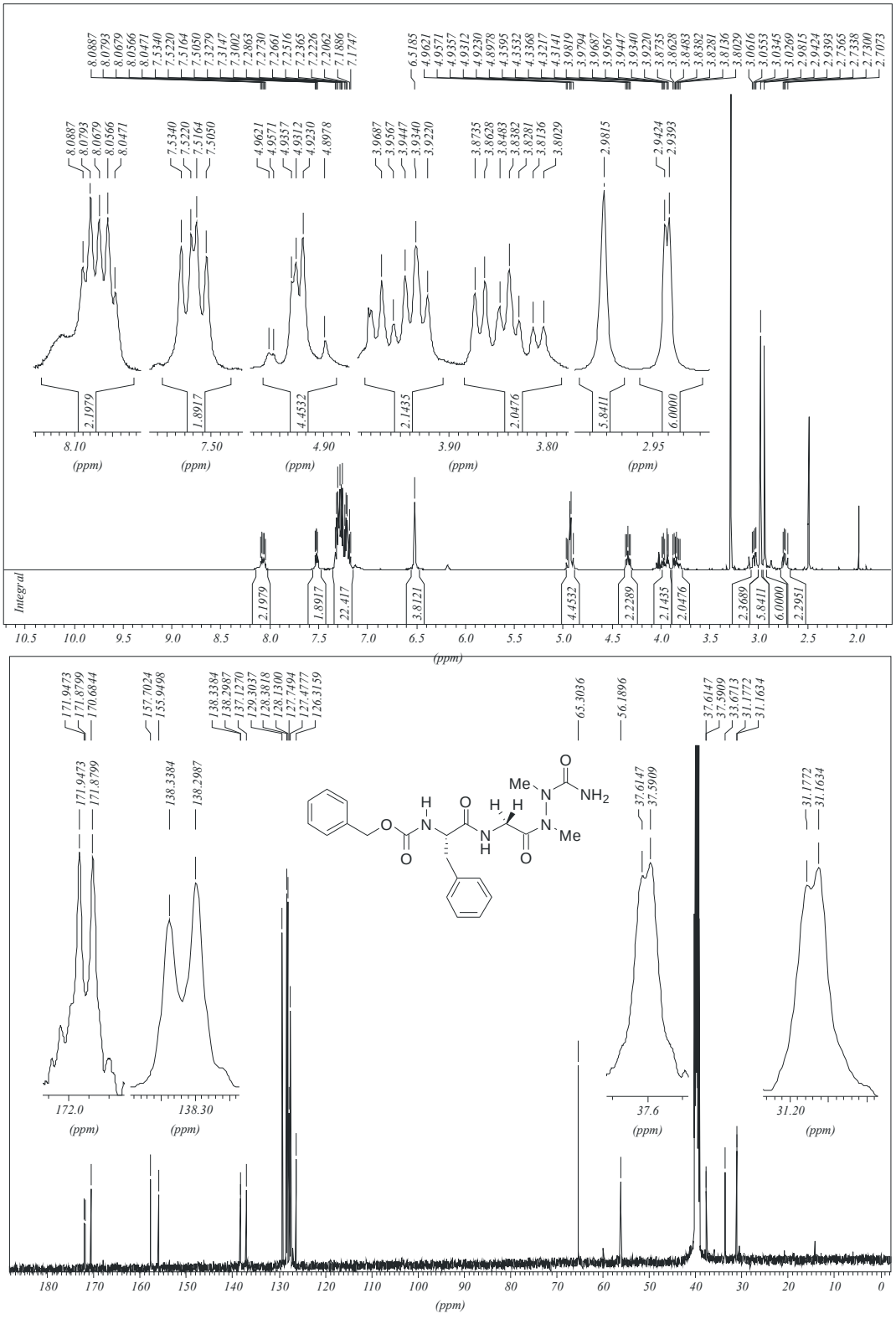


_N_-(Benzyloxycarbonyl)-glycine 2-Ethyl-1,2-dimethylhydrazide (13),

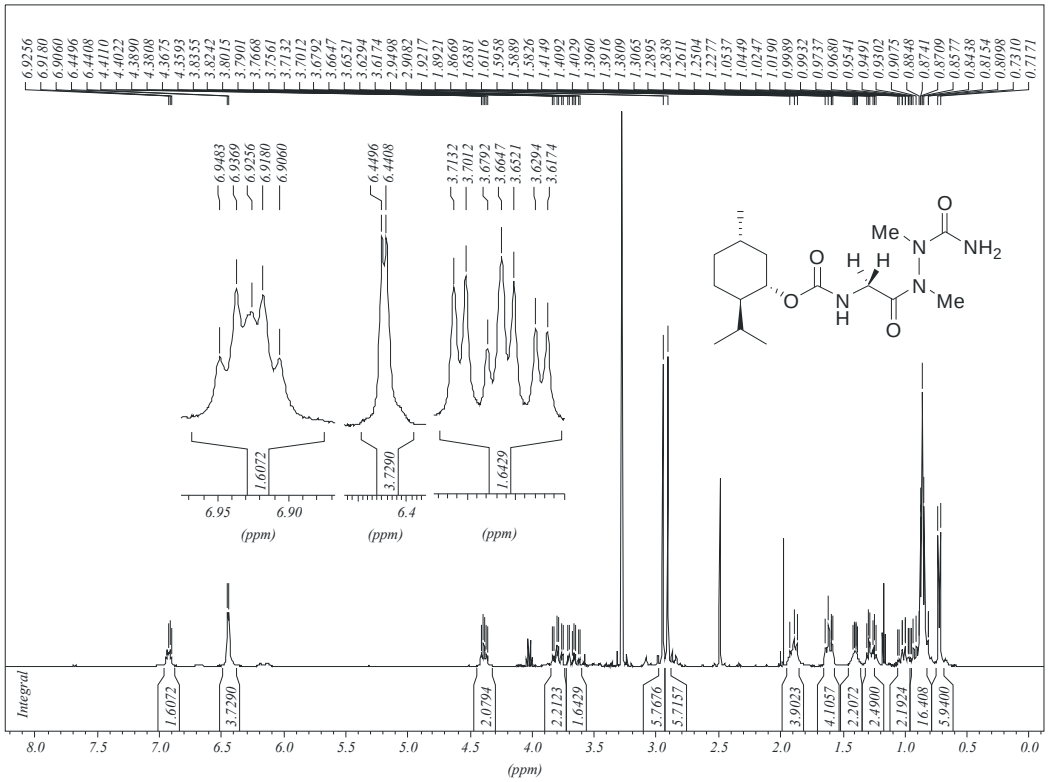
DMSO-d_6, 303 K

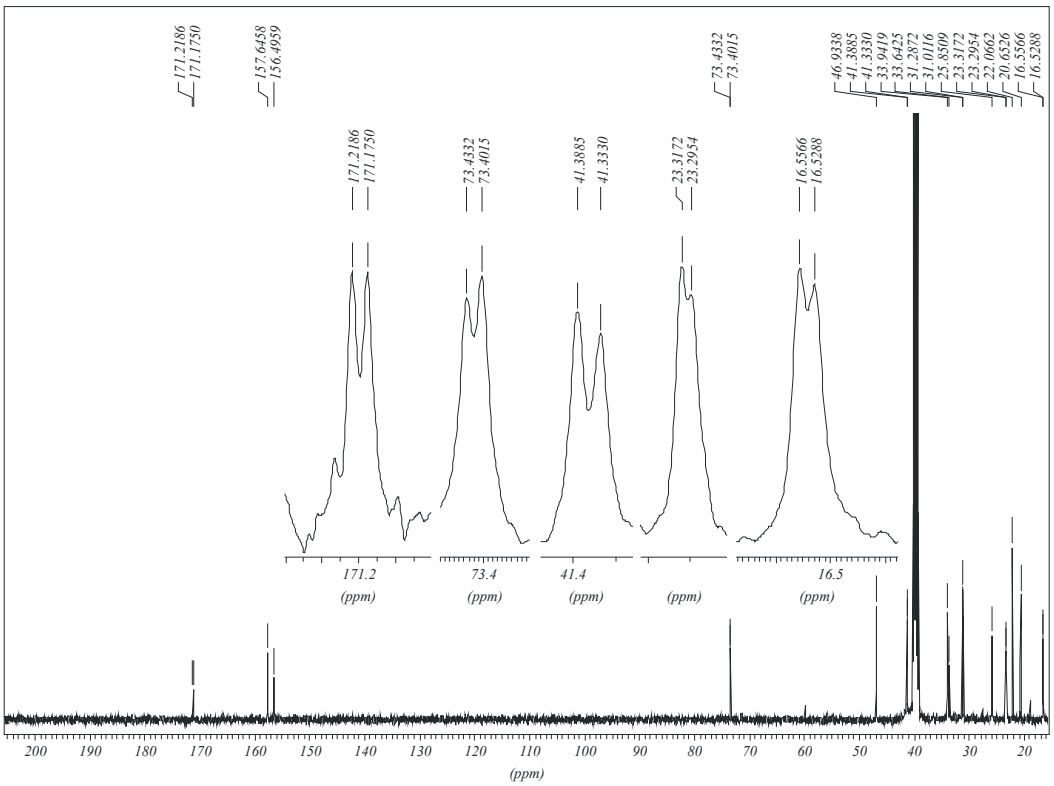


_N_-(Benzyloxycarbonyl)-L-phenylalanyl-glycyl-methylazaalanine-amide (14), DMSO-d_6, 303 K

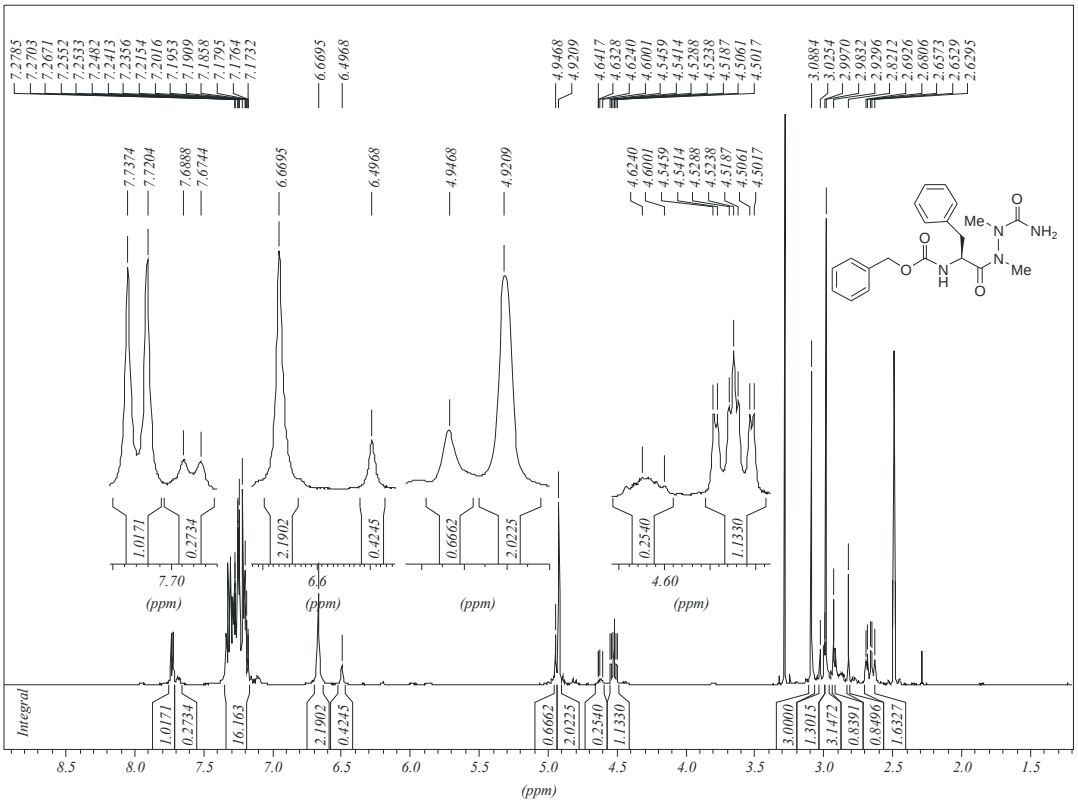


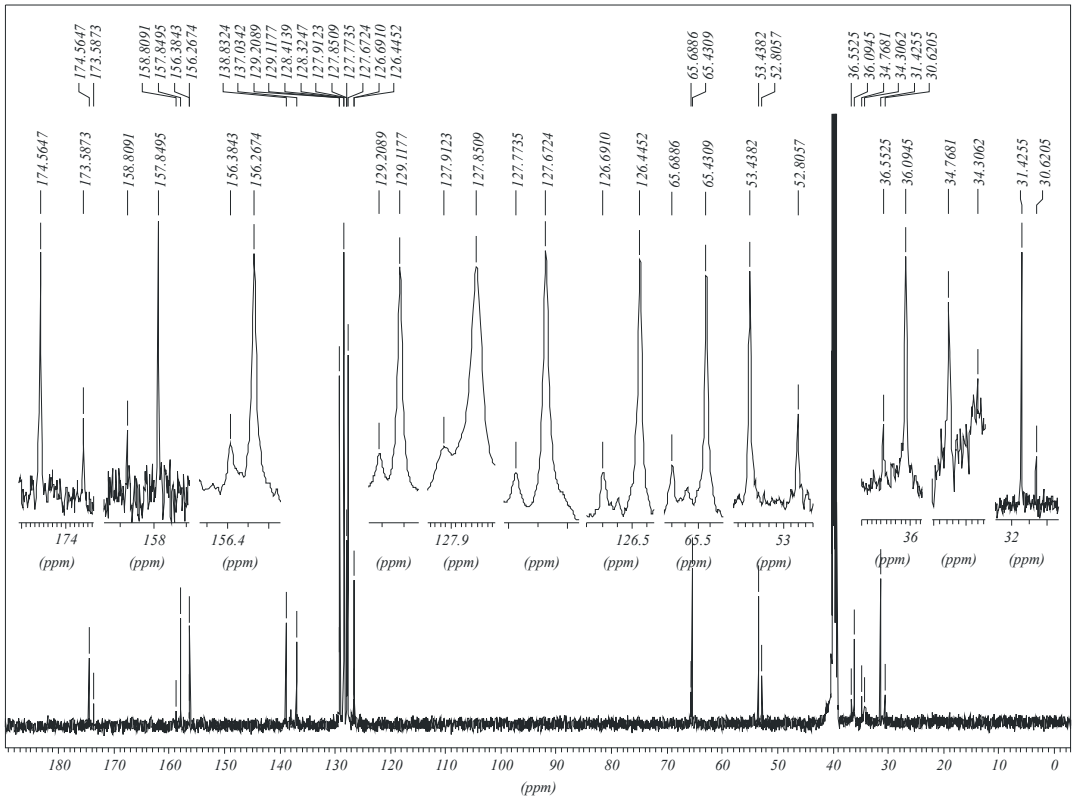
_N_-(1_S_, 3_S_, 4_R_-Menthyloxycarbonyl)-glycinyl-methylazaalanine-amide (15), DMSO-d_6, 303 K



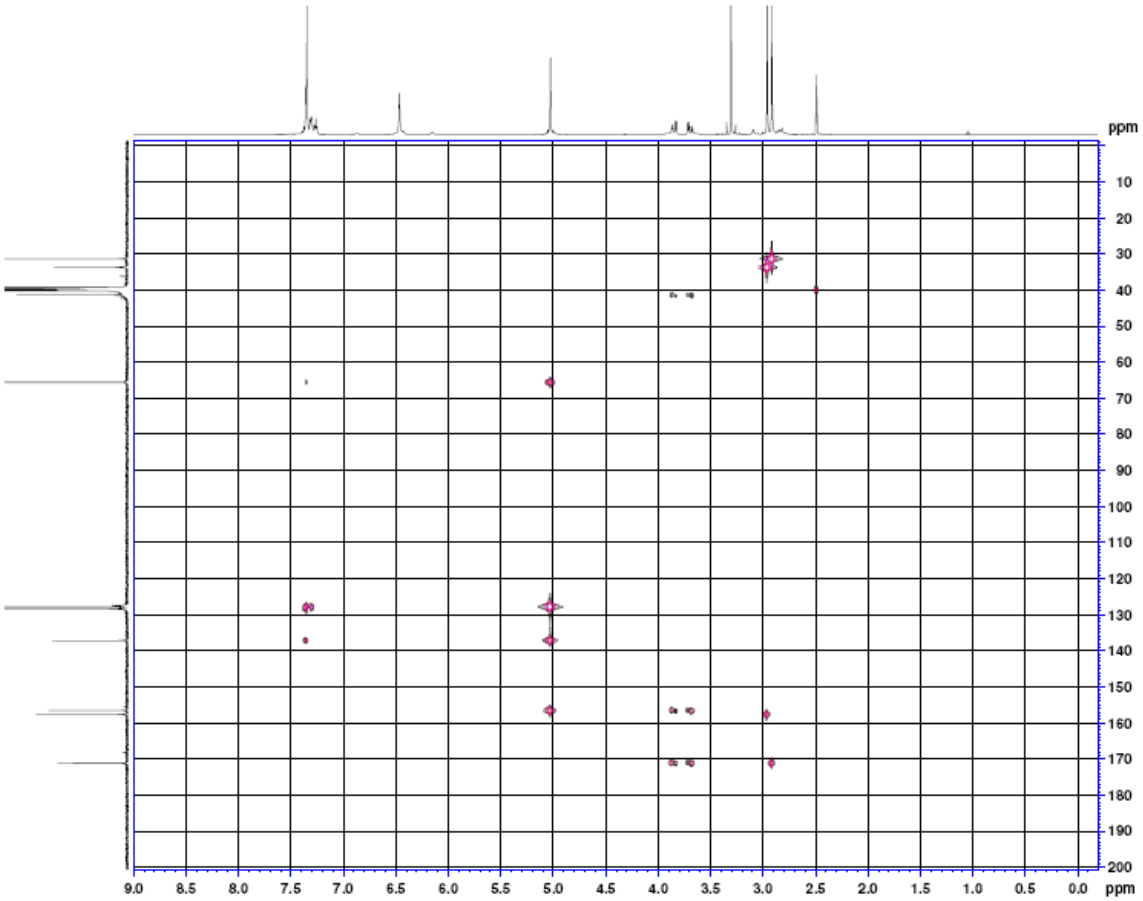


_N_-(Benzyloxycarbonyl)-L-phenyl-methylazaalanine-amide (16), DMSO-d_6, 303 K

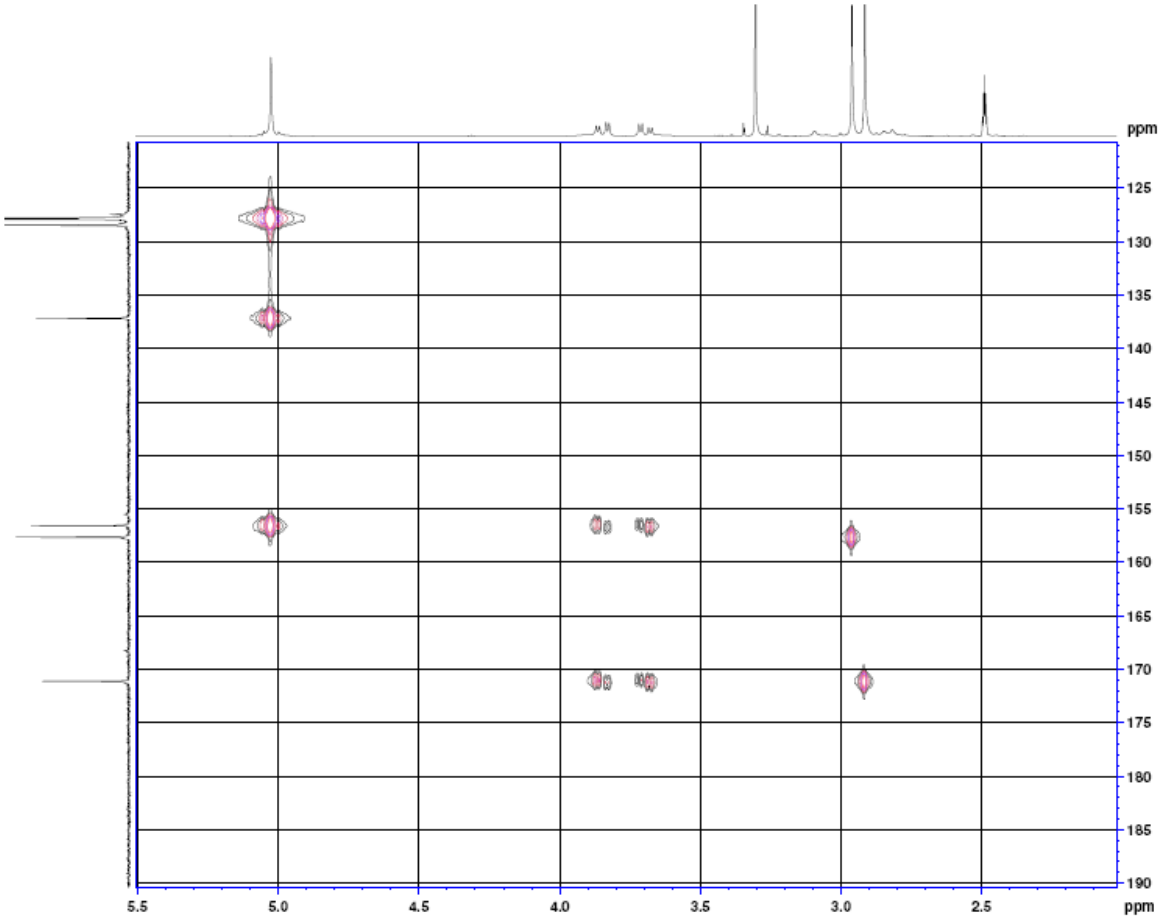


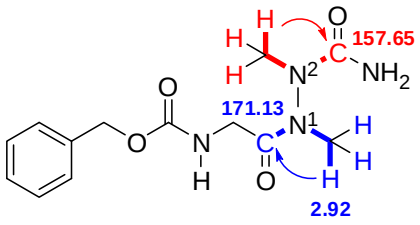


S4. HMBC Spectra of Cbz-Gly[ΨCONMe]-azaAla-NH_2 (9)



Complete HMBC spectrum (500 MHz, DMSO-d_6) of **9**.

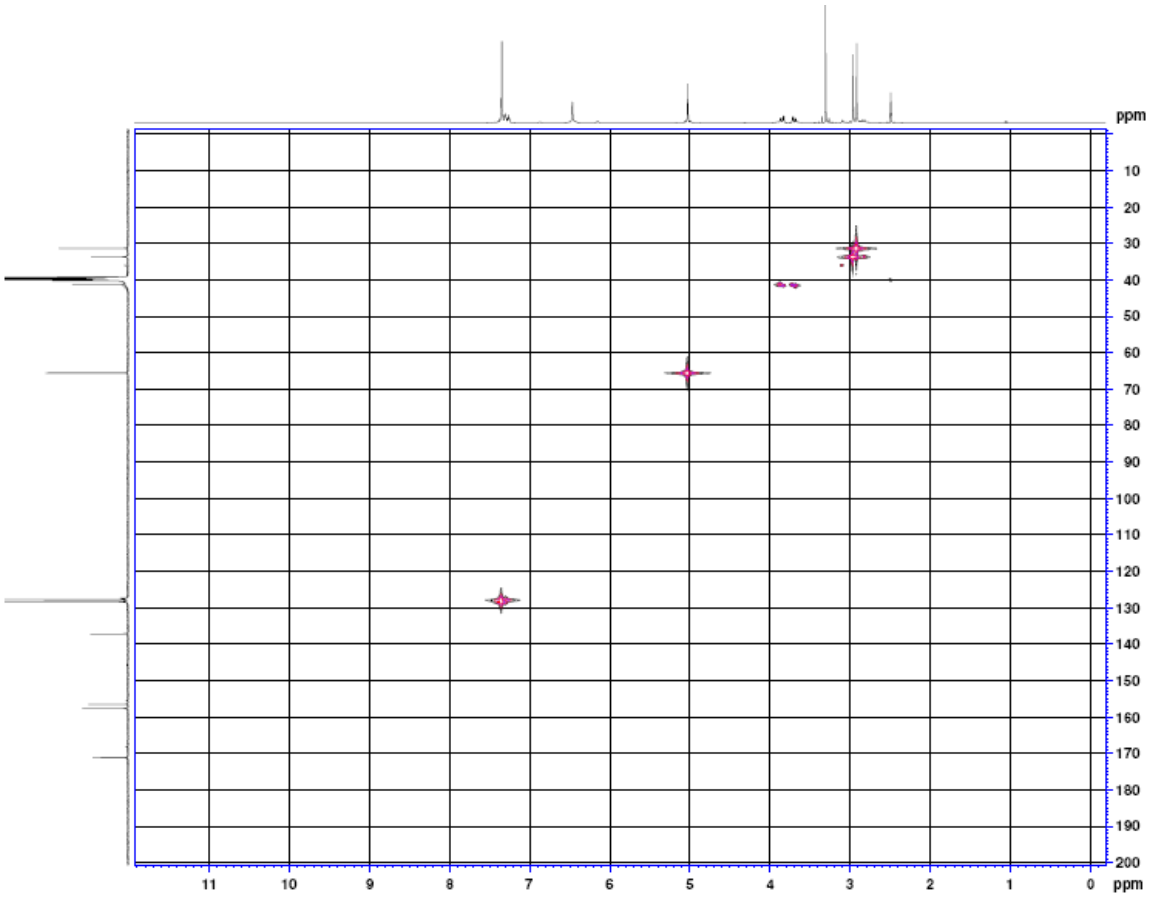




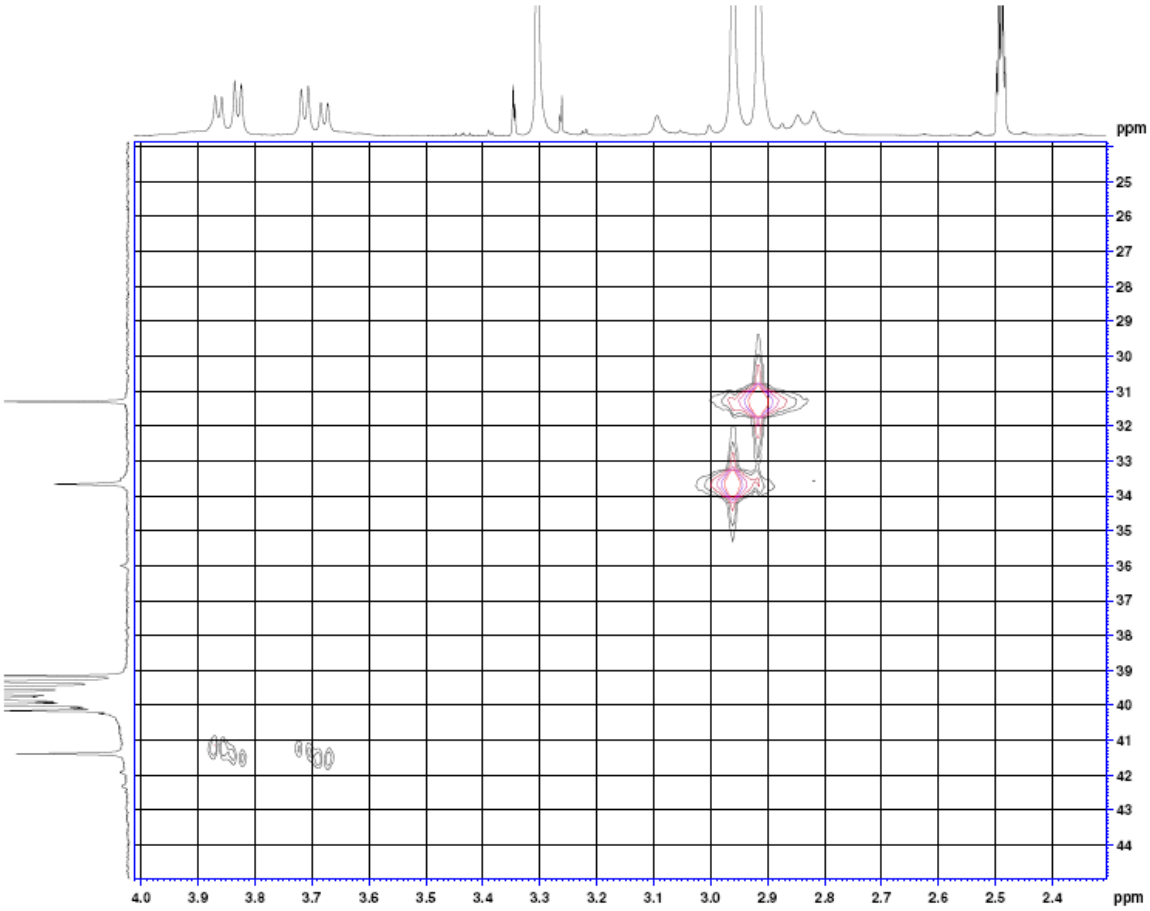
9

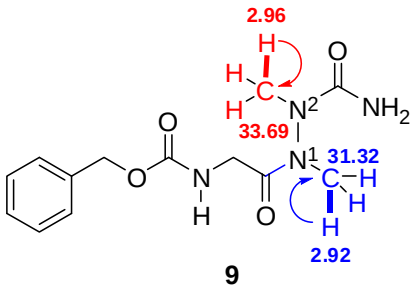
Detail of the HMBC spectrum (500 MHz, DMSO-d_6) of **9** for assignment of N^1*Me* and N^2*Me*.

S5. HMQC Spectra of Cbz-Gly[ΨCONMe]-azaAla-NH_2 (9)



Complete HMQC spectrum (500 MHz, DMSO-d_6) of **9**.

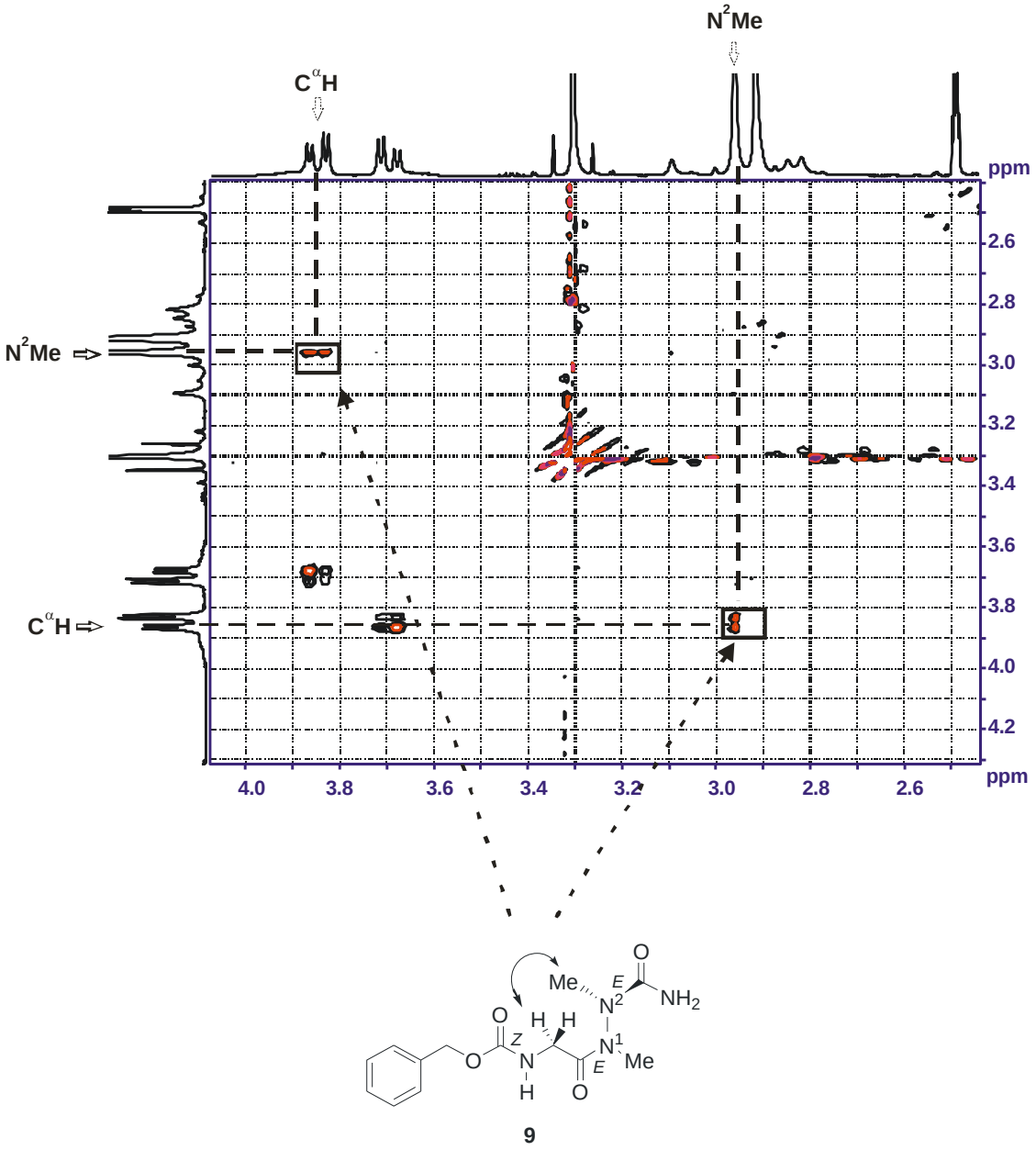




9

Detail of the HMQC spectrum (500 MHz, DMSO-d_6) of **9** for assignment of N^1*Me* and N^2*Me*.

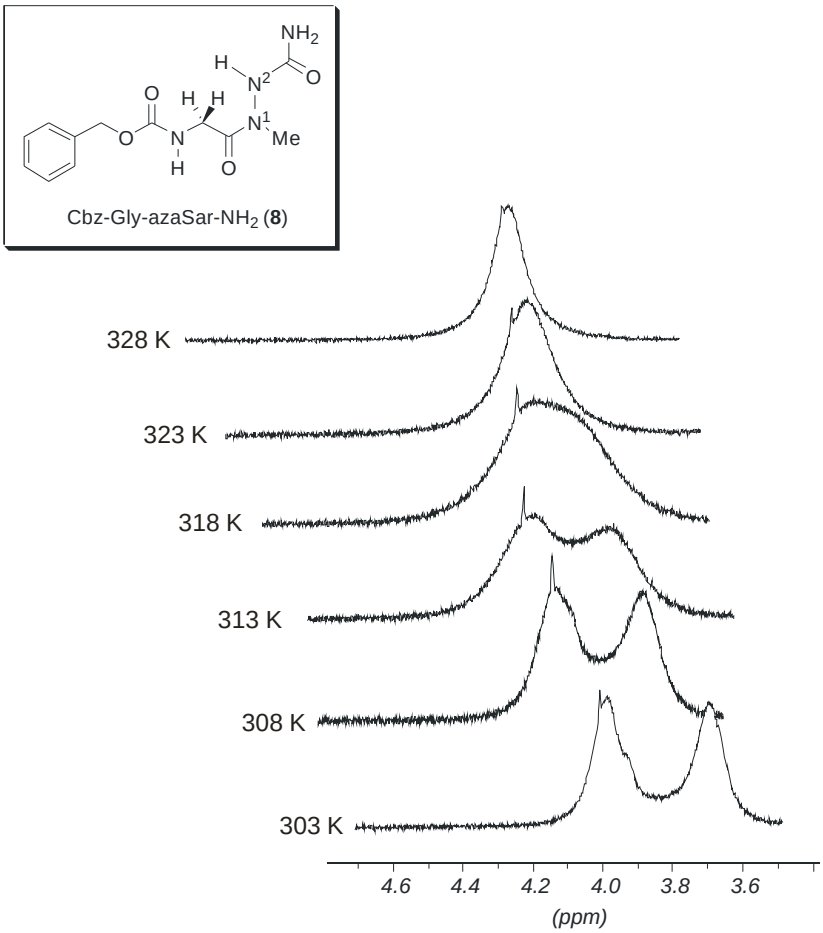
S6. NOESY Correlations of Cbz-Gly[ΨCONMe]-azaAla-NH_2 (9)



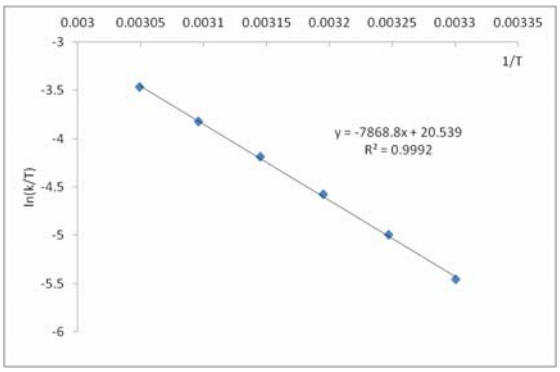
9

NOESY correlations demonstrating *E* configuration at the CO–N^1Me bond of Cbz-Gly[ΨCONMe]-azaAla-NH_2 (**9**) in DMSO-d_6.

S7. VT ^{1}H NMR Spectra (500 MHz) and Eyring Plot of 8 Based on Line-Shape Analysis



Cbz-Gly-azaSar-NH_2 (**8**)

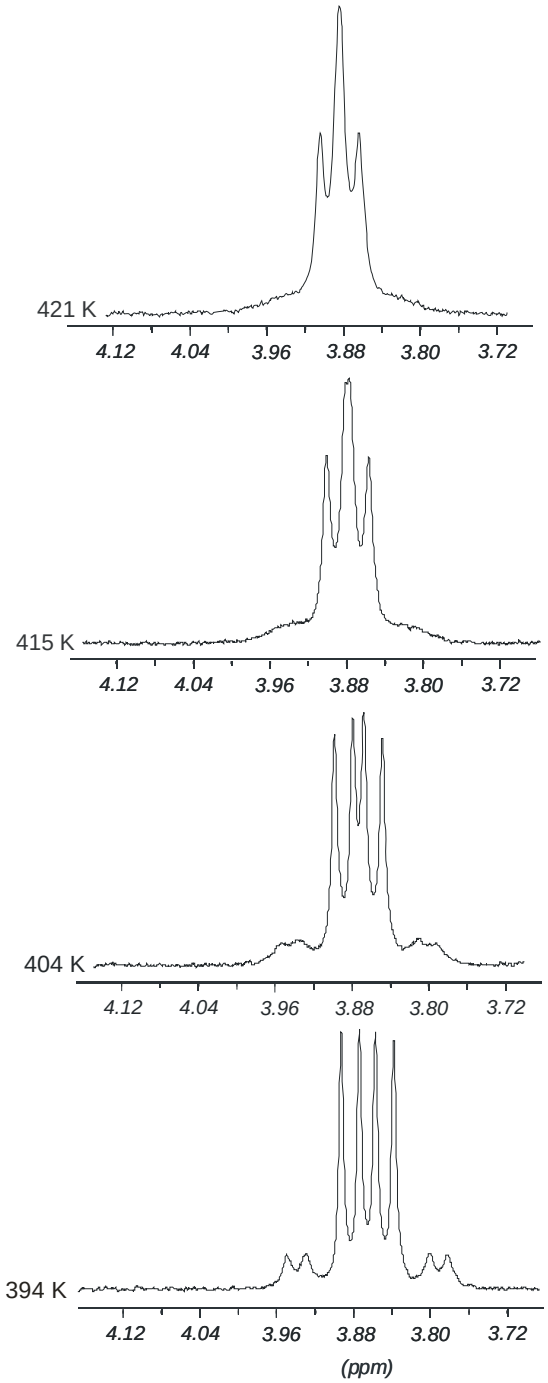


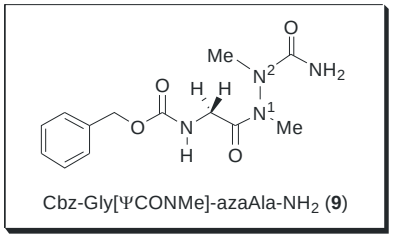
$\Delta S^{\ddagger}$ = -26.8 J mol^{-1} K^{-1}

$\Delta H^{\ddagger}$ = 65.4 kJ mol^{-1} K^{-1}

$\Delta G^{\ddagger}$ = 73.4 kJ mol^{-1}

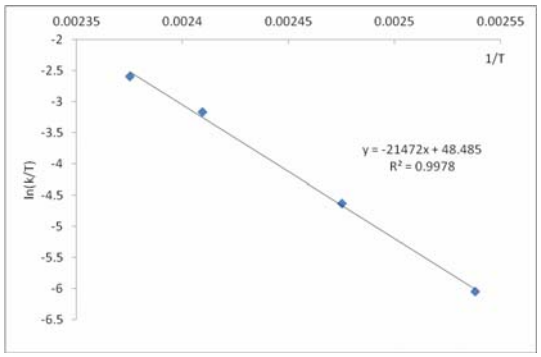
S8. VT ^{1}H NMR Spectra (300 MHz) and Eyring Plot of 9 Based on Line-Shape Analysis





Cbz-Gly[ΨCONMe]-azaAla-NH$_2$ (**9**)

Cbz-Gly[ΨCONMe]-azaAla-NH$_2$ (**9**)

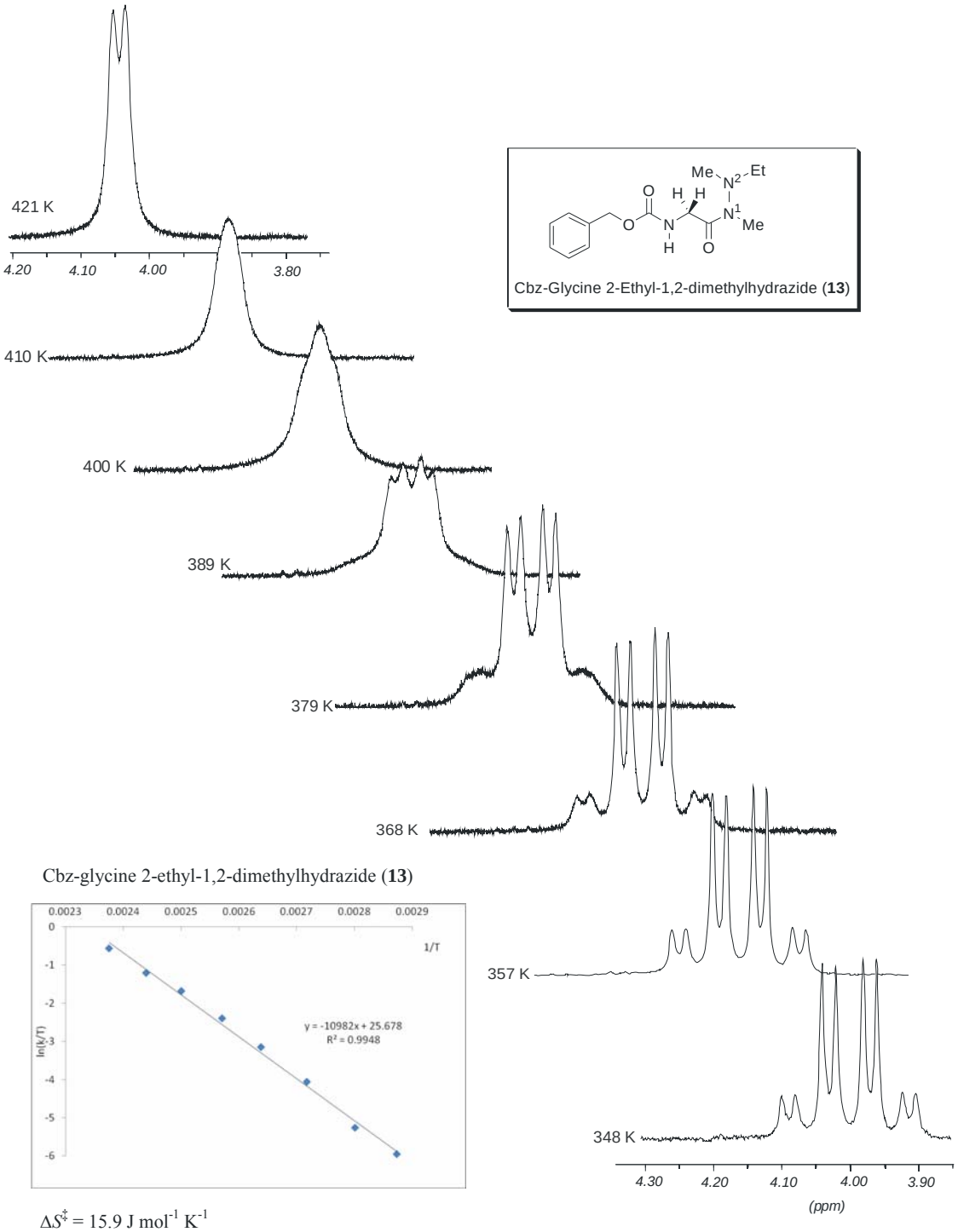


$\Delta S^{\ddagger}$ = 205.6 J mol^{-1} K^{-1}

$\Delta H^{\ddagger}$ = 178.5 kJ mol^{-1} K^{-1}

$\Delta G^{\ddagger}$ = 117.3 kJ mol^{-1}

S9. VT ^{1}H NMR Spectra (300 MHz) and Eyring Plot of 13 Based on Line-Shape Analysis



Cbz-Glycine 2-Ethyl-1,2-dimethylhydrazide (**13**)

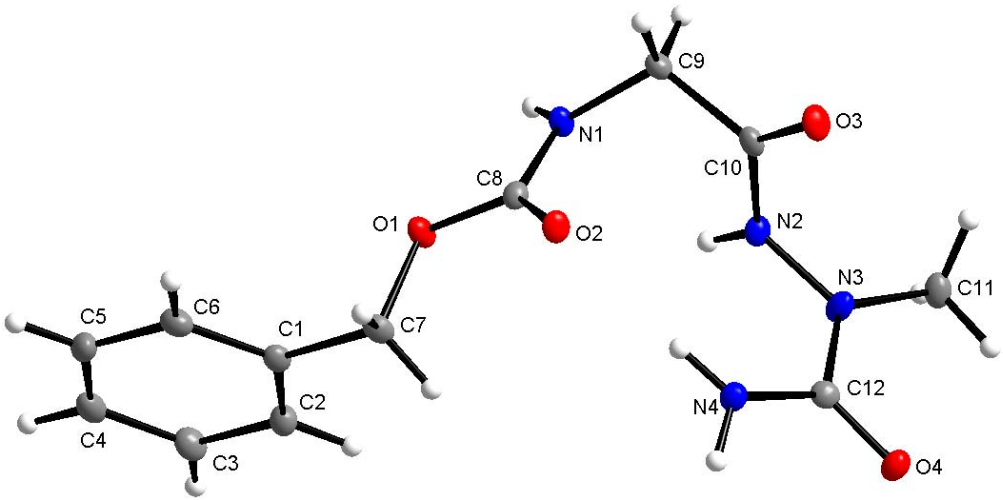
Cbz-glycine 2-ethyl-1,2-dimethylhydrazide (**13**)

$\Delta S^{\ddagger}$ = 15.9 J mol^{-1} K^{-1}

$\Delta H^{\ddagger}$ = 91.3 kJ mol^{-1} K^{-1}

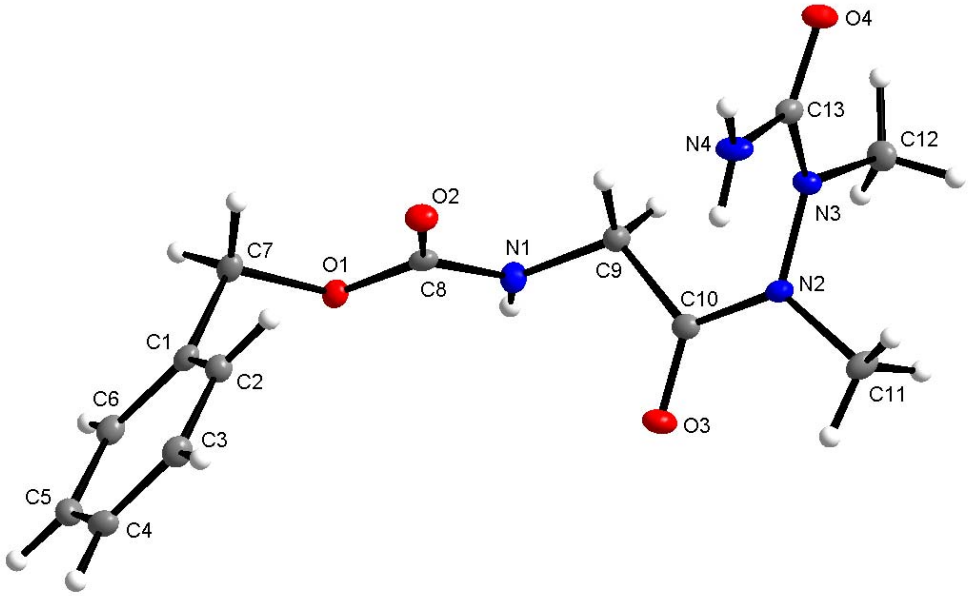
$\Delta G^{\ddagger}$ = 86.6 kJ mol^{-1}

S10. Molecular Plot of (*Z*,*Z*,*E*)-Cbz-Gly-azaAla-NH_2 (7)



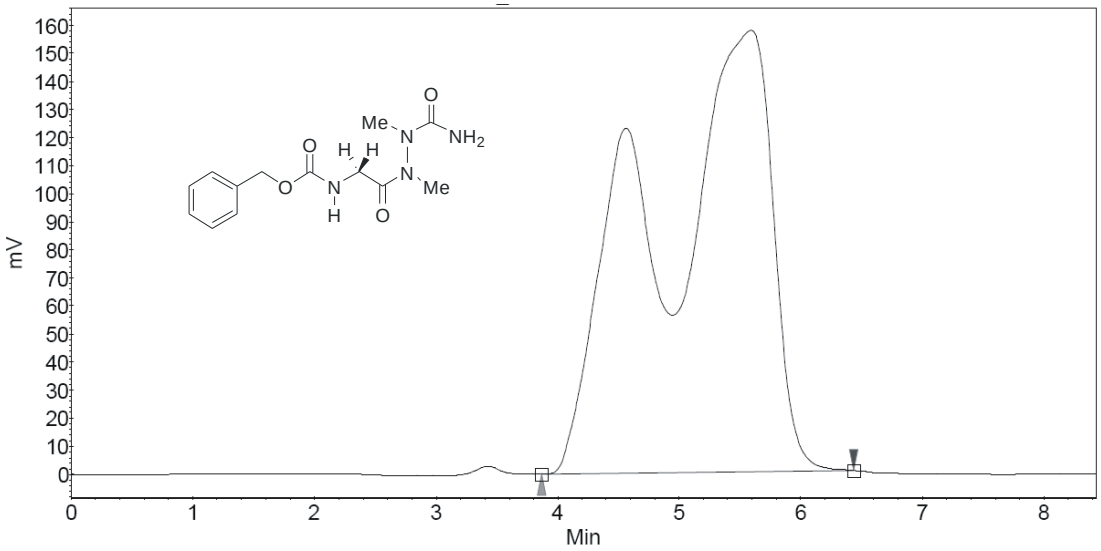
Molecular plot of (*Z*,*Z*,*E*)-Cbz-Gly-azaAla-NH_2 (**7**) showing the atom-labeling scheme and displacement ellipsoids at the 30% probability level for the non-H atoms. H atoms are depicted as white spheres of arbitrary radii. For bond lengths and angles, see CIF file.

S11. Molecular Plot of (a*S*,*Z*,*E*,*E*)-Cbz-Gly[ΨCONMe]-azaAla-NH$_2$ (9)



Molecular plot of (a*S*,*Z*,*E*,*E*)-Cbz-Gly[ΨCONMe]-azaAla-NH$_2$ (**9**) showing the atom-labeling scheme and displacement ellipsoids at the 30% probability level for the non-H atoms. H atoms are depicted as white spheres of arbitrary radii. For bond lengths and angles, see CIF file.

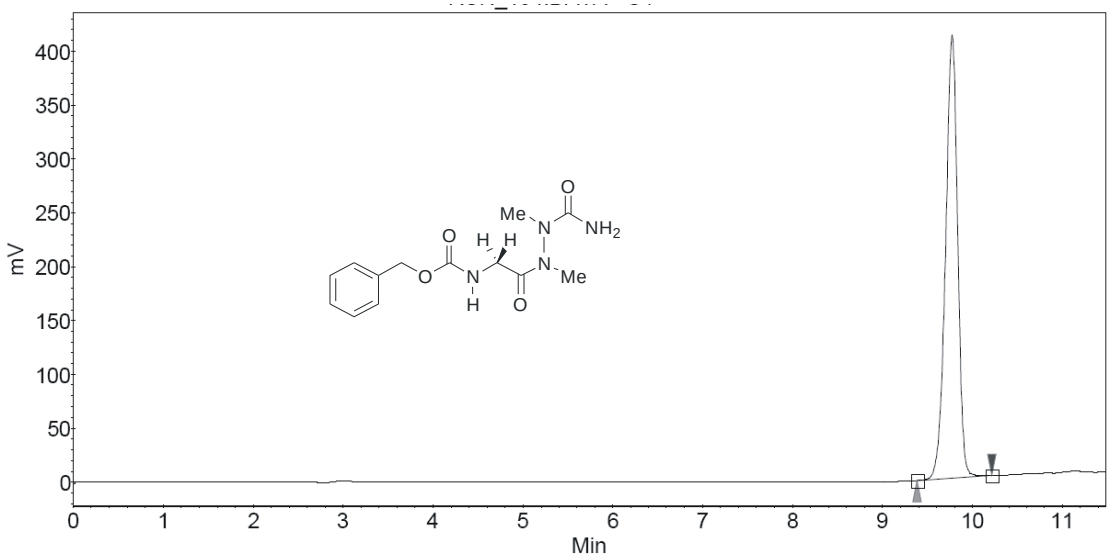
S12. Chiral HPLC of Cbz-Gly[ΨCONMe]-azaAla-NH_2 (9)



Chromatogram of Cbz-Gly[ΨCONMe]-azaAla-NH_2 (**9**) using chiral HPLC, indicating the existence of two atropenantiomers.

Conditions: Isocratic elution (H_2O /MeCN) 70 : 30; flow rate 0.45 mL/min.

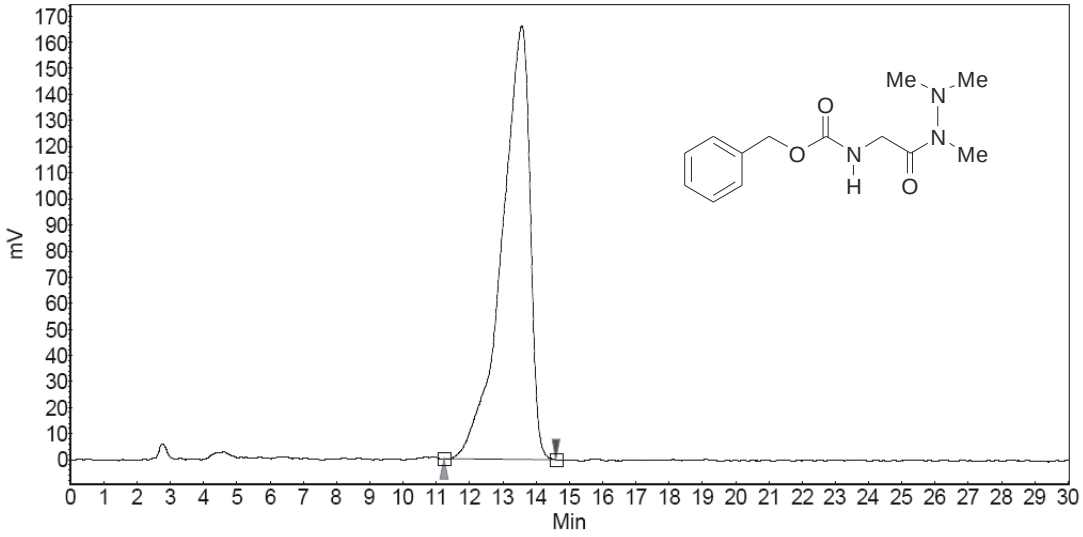
S13. Achiral HPLC of Cbz-Gly[ΨCONMe]-azaAla-NH_2 (9)



Chromatogram of **9** using achiral HPLC, indicating that the two peaks observed in **S12** derive from two atropenantiomers.

Conditions: Mobile phase gradient H_2O (A) : MeCN (B), gradient table was: 0 min/15% B, 5 min/15% B, 10 min/100% B, 30min/100%B; flow rate: 1.0 mL/min.

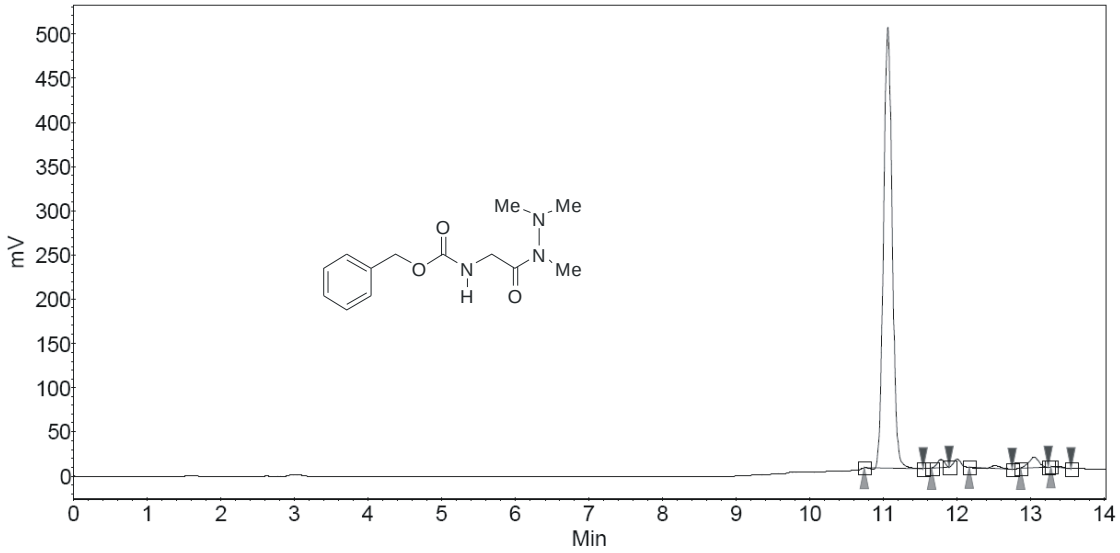
S14. Chiral HPLC of Cbz-Glycine 1,2,2-Trimethylhydrazide (12)



Chromatogram of compound **12** using chiral HPLC, indicating the *non*-existence of two atropenantiomers.

For conditions, see **S12**.

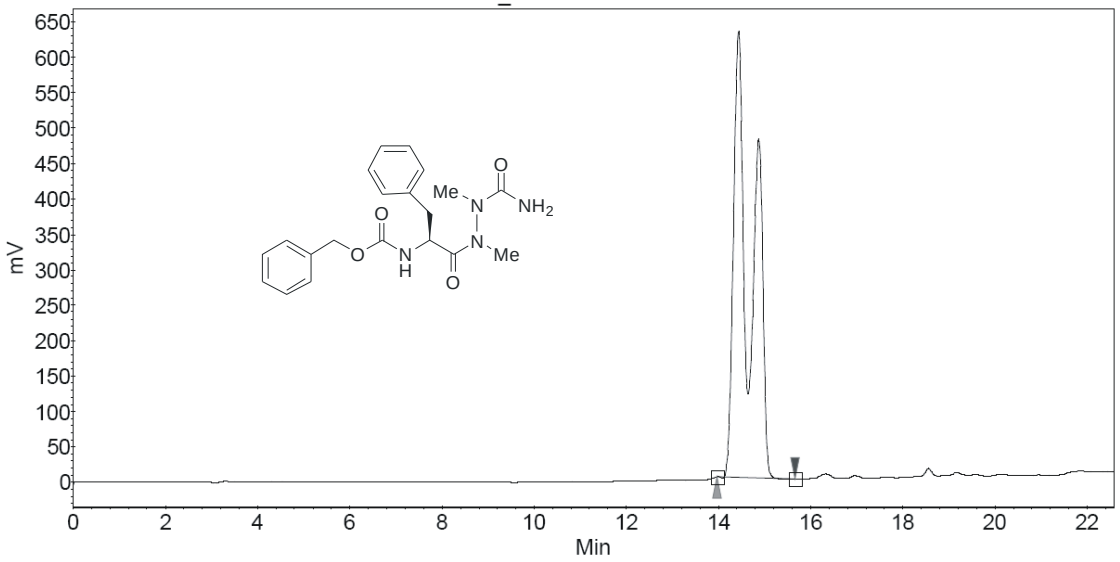
S15. Achiral HPLC of Cbz-Glycine 1,2,2-Trimethylhydrazide (12)



Chromatogram of compound **12** using achiral HPLC.

For conditions, see **S13**.

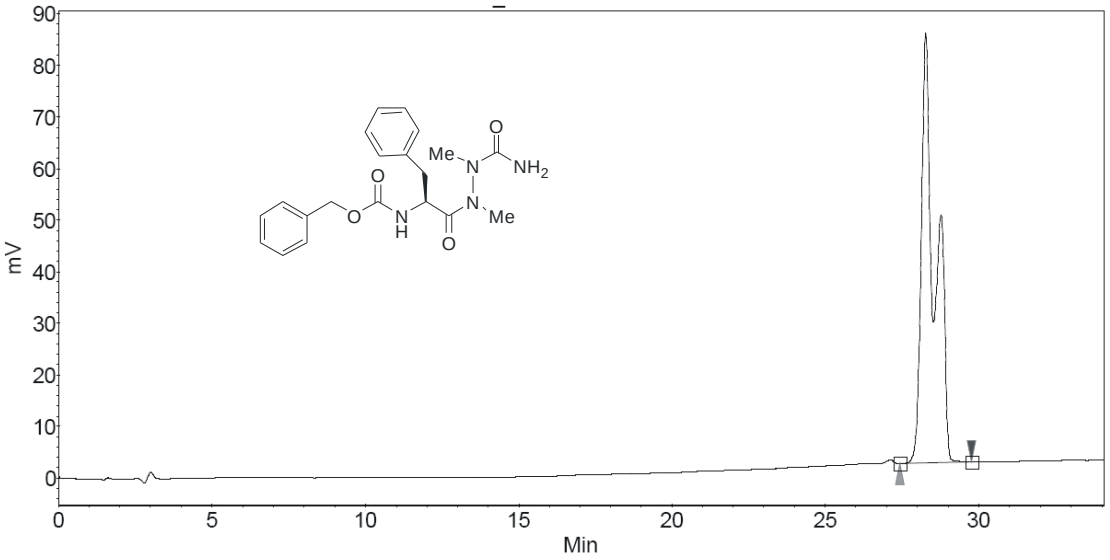
S16. Chiral HPLC of Cbz-L-Phe-[ΨCONMe]-azaAla-NH_2 (16)



Chromatogram of Cbz-L-Phe-[ΨCONMe]-azaAla-NH_2 (**16**) using chiral HPLC, indicating the existence of two atropdiastereomers.

Conditions: Mobile phase gradient H_2O (A) : MeCN (B), gradient table was: 0 min/10% B, 5 min/10% B, 20 min/100% B, 30min/100%B; flow rate 0.7 mL/min.

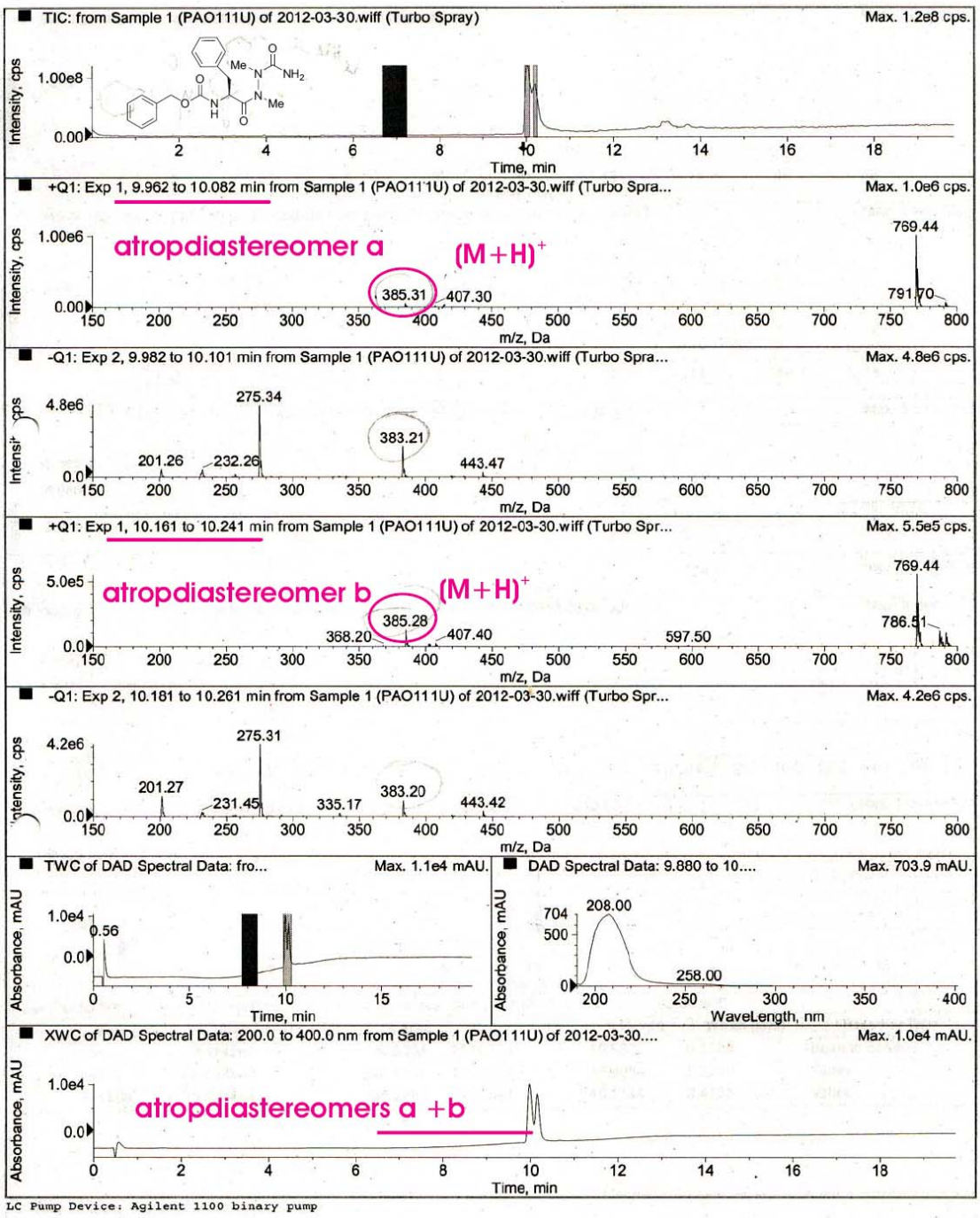
S17. Achiral HPLC of Cbz-L-Phe-[ΨCONMe]-azaAla-NH_2 (16)



Chromatogram of Cbz-L-Phe-[ΨCONMe]-azaAla-NH_2 (**16**) using achiral HPLC, indicating the existence of two atropdiastereomers.

Conditions: Concentration of **16**: 0.2 mM dissolved in MeCN; mobile phase gradient H_2O (A) : MeCN (B), gradient table was: 0 min/15% B, 10 min/15% B, 60 min/100% B; flow rate 1.0 mL/min.

S18. Copy of LC/MS Data of Cbz-L-Phe-[ΨCONMe]-azaAla-NH_2 (16)

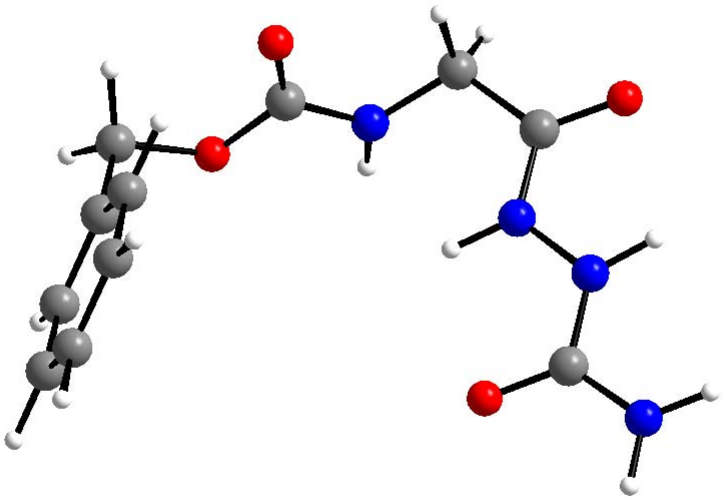


S19. Electronic Structure Calculations – Computational Methods

All calculations were carried out at the non-local density functional level of theory (DFT) using the exchange functional of Becke and the correlation functional of Perdew (BP86).[5] The LANL2DZ basis set was used, as implemented in Gaussian03. All geometry optimizations were carried out without symmetry restraints with the program package Gaussian03 using its standard convergence criteria.[6] The optimized geometries were verified as minima on the potential energy surface by evaluation of their harmonic vibrational frequencies, which were used to calculate the zero point vibrational energies. The Gibbs free energies of the barrier of rotations are corrected for the difference in the zero-point vibrational energies. The thermal corrections were carried out at standard conditions (T = 298.15 K, and P = 1 atmosphere). The transition states were calculated using the Berny algorithm implemented in Gaussian. The starting geometries were obtained from relaxed potential energy surface scans of the corresponding torsion of the N–N axis. These starting structures were further refined using the QST3 approach implemented in Gaussian03. IRC calculations in both directions were carried out to assure the right trajectory of the transition state.

Illustrations, Cartesian coordinates and energies of compounds **6**, **7**, **8**, **9**, **11**, **13** and of related transition states of the rotation around the N–N axis. Steric hindrance causing the barrier of rotation is denoted using thin dashed lines.

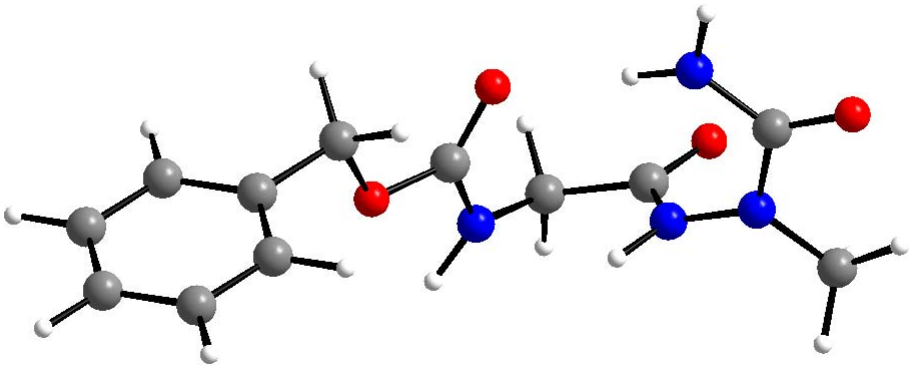
Optimized Geometry of Cbz-Gly-azaGly-NH_2 (6)



E(RB-P86) = -947.464243000 a.u.

C	-0.215425	-0.147375	3.294952
C	0.205650	1.192523	3.073530
H	-0.502955	1.911811	2.643892
C	1.527972	1.586802	3.385121
H	1.845629	2.622124	3.208094
C	2.441824	0.647647	3.924588
H	3.467703	0.954312	4.165774
C	2.029441	-0.688746	4.151407
H	2.734534	-1.418301	4.569442
C	0.706674	-1.081515	3.838504
H	0.388374	-2.118672	4.012003
C	-1.631968	-0.572341	2.958164
H	-1.951037	-1.450656	3.542981
H	-2.349337	0.258797	3.077165
C	-2.036653	-0.090819	0.572721
C	-2.456325	0.063329	-1.877539
H	-2.774820	1.069142	-1.545948
H	-3.325914	-0.420100	-2.362010
C	-1.382711	0.229823	-2.963039
C	2.211925	-0.253679	-3.215182
N	-2.023403	-0.677391	-0.686104
H	-1.901854	-1.692140	-0.725606
N	-0.090022	-0.039273	-2.594649
H	0.242861	-0.337859	-1.669995
N	0.916624	0.125331	-3.561468
N	3.167875	-0.085121	-4.209702
H	2.963565	0.297680	-5.131072
H	4.122823	-0.347583	-3.976504
O	-1.745386	-1.069660	1.534870
O	-2.276433	1.122071	0.814654
O	-1.662029	0.613968	-4.151074
O	2.469655	-0.713124	-2.054193
H	0.554034	0.466693	-4.458172

Optimized Geometry of Cbz-Gly-azaAla-NH_2 (7)

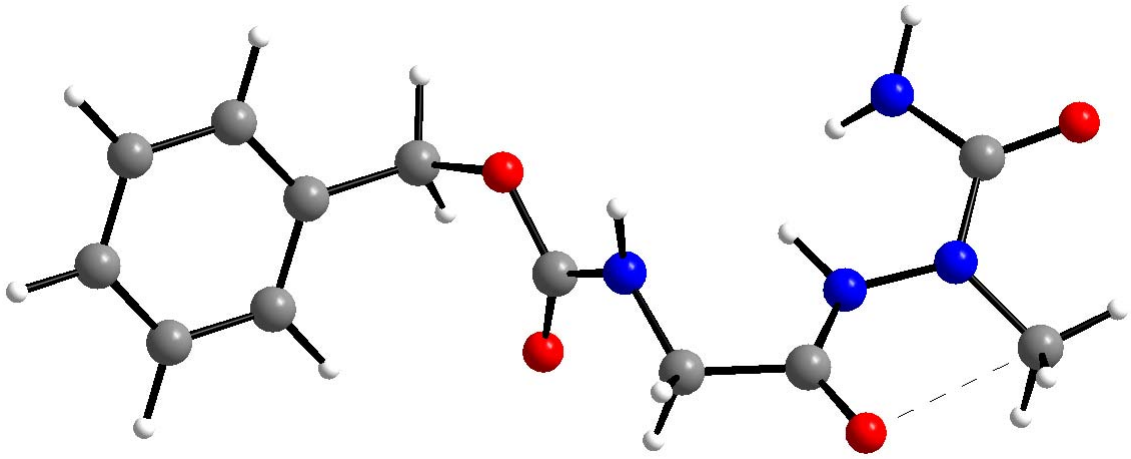


E(RB-P86) = -986.767707378 a.u.

C	-0.313969	-0.339942	3.692510
C	-1.408036	0.523083	3.967124
H	-2.122577	0.764447	3.168641
C	-1.584457	1.073781	5.258540
H	-2.435009	1.736863	5.459747
C	-0.665808	0.763945	6.291610
H	-0.803107	1.187168	7.294699
C	0.427581	-0.098338	6.028334
H	1.138385	-0.343965	6.827146
C	0.599199	-0.647934	4.736285
H	1.446637	-1.316939	4.535060
C	-0.128361	-0.927570	2.312624
H	0.343564	-1.926271	2.332474
H	-1.074540	-0.992000	1.746106
C	1.039302	-0.377311	0.221348
C	2.460868	0.286952	-1.711174
H	2.969396	-0.695343	-1.717641
H	3.221265	1.062189	-1.913930
C	1.484468	0.244766	-2.913034
C	-1.664028	-0.479190	-3.630514
C	-0.810415	1.622798	-4.736163
H	-1.671847	1.369075	-5.374790
H	0.124820	1.516945	-5.317291
H	-0.913417	2.662923	-4.372714
N	1.852835	0.559787	-0.394014
H	2.213260	1.317802	0.189938
N	0.212945	0.749323	-2.661843
H	0.004889	1.171377	-1.750916
N	-0.828411	0.675450	-3.602384
N	-1.445840	-1.408029	-2.625710
H	-0.663037	-1.390692	-1.961771
H	-2.052480	-2.225472	-2.651028
O	0.801574	-0.007852	1.547577
O	0.556203	-1.401339	-0.342838
O	1.857325	-0.220977	-4.024312
O	-2.575723	-0.595339	-4.506804

Transition State 1 (TS1) for the Rotation Around the N–N Axis of 7,

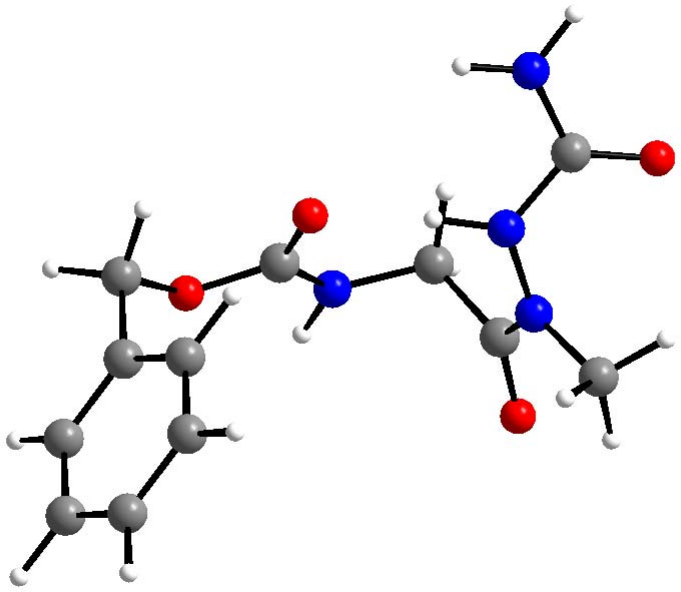
$\Delta G^{\ddagger}$ = +48 kJ mol^{-1}



E(RB-P86) = -986.749230593

C	-0.746836	0.266364	-3.830925
C	-1.268923	-0.725584	-4.704222
H	-2.182062	-1.268669	-4.424138
C	-0.622072	-1.019569	-5.927826
H	-1.034484	-1.785714	-6.596438
C	0.555278	-0.319577	-6.291090
H	1.056632	-0.544219	-7.241178
C	1.081650	0.672877	-5.427147
H	1.991796	1.217931	-5.707402
C	0.433235	0.965911	-4.204394
H	0.842404	1.726185	-3.527177
C	-1.441423	0.579567	-2.519417
H	-1.297798	1.632841	-2.220111
H	-2.512921	0.322172	-2.545275
C	0.193481	0.216141	-0.706275
C	1.857928	-0.544098	0.994946
H	2.345805	0.379150	0.631840
H	2.554036	-1.386760	0.832523
C	1.674340	-0.424958	2.531883
C	-1.474488	-0.009225	4.458110
C	0.827824	0.531032	5.292687
H	0.211418	0.646332	6.198230
H	1.312253	1.490927	5.031521
H	1.608174	-0.227323	5.454447
N	0.615355	-0.727349	0.225034
H	0.195282	-1.658273	0.157679
N	0.397815	-0.017861	2.885401
H	-0.319189	-0.082793	2.155298
N	-0.099314	0.121038	4.213016
N	-2.292916	-0.008813	3.299789
H	-2.164254	0.702502	2.574299
H	-3.263215	-0.266636	3.488406
O	-0.923454	-0.287827	-1.392662
O	0.703337	1.353926	-0.881186
O	2.648643	-0.632080	3.315704
O	-1.942327	-0.134025	5.630247

Optimized Geometry of Cbz-Gly-azaSar-NH_2 (8)

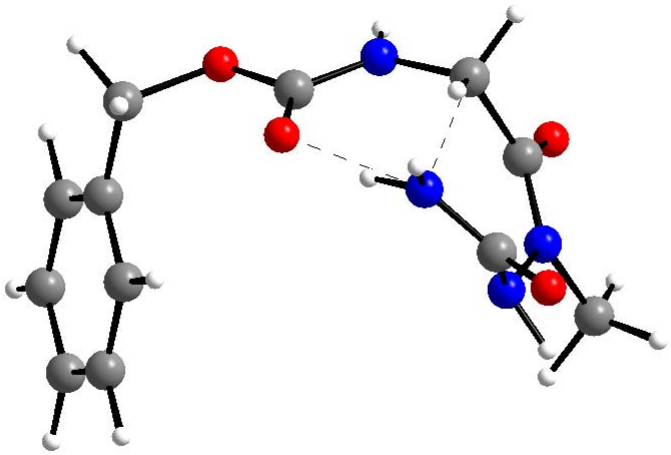


E(RB-P86) = -986.770536588 a.u.

C	-0.964011	-1.070223	-3.568325
C	-1.610632	1.920930	-2.675249
H	-1.227400	2.953353	-2.648913
H	-2.391533	1.787654	-1.903746
H	-2.023934	1.691949	-3.673006
C	0.810263	1.498152	-2.163176
C	1.923824	0.447460	-1.912748
H	1.685097	-0.529548	-2.362048
H	2.834888	0.851630	-2.384279
C	1.491934	-0.602388	0.316879
C	1.230512	-1.426383	2.632269
H	2.023993	-1.715854	3.340328
H	0.831265	-2.312315	2.108797
C	0.134224	-0.619268	3.300252
C	0.422229	0.182950	4.437202
H	1.447927	0.219321	4.828791
C	-0.598393	0.936696	5.062506
H	-0.366181	1.553502	5.939743
C	-1.921783	0.891398	4.557448
H	-2.715124	1.473739	5.043092
C	-2.218926	0.091913	3.425947
H	-3.243207	0.053978	3.034322
C	-1.195862	-0.659732	2.801347
H	-1.418017	-1.273360	1.919247
N	-1.096126	-2.446224	-3.379585
H	-1.289677	-3.010218	-4.204025
H	-1.024253	-2.893572	-2.466564
N	-0.748628	-0.370100	-2.362526
N	-0.472972	1.013971	-2.403371
N	2.203643	0.262647	-0.472758
H	2.874954	0.880986	-0.012887
O	-1.055080	-0.511361	-4.702285
O	1.071764	2.740179	-2.098187
O	0.522033	-1.333980	-0.072440
O	1.993476	-0.601524	1.618110
H	-0.478035	-0.848846	-1.478873

Transition State 1 (TS1) for the Rotation Around the N–N Axis of 8,

$\Delta G^{\ddagger}$ = +86 kJ mol^{-1}

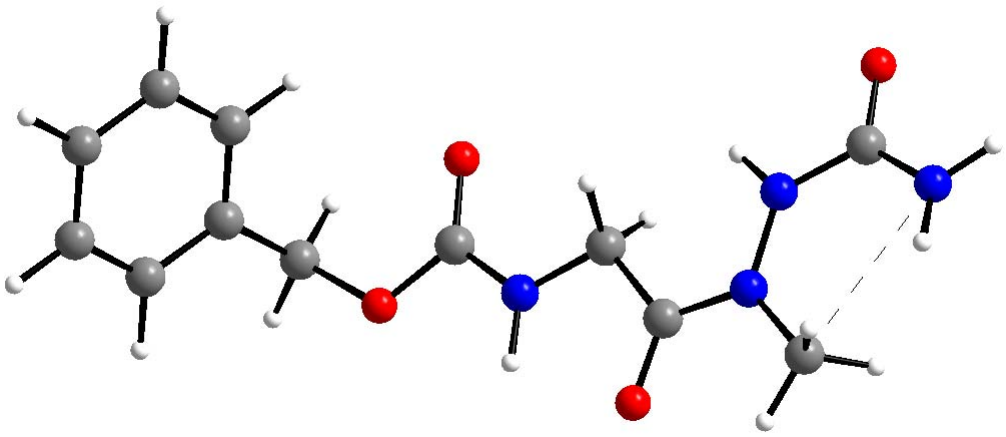


E(RB-P86) = -986.738876074 a.u.

C	0.949062	-1.438132	3.276598
C	1.518956	2.278869	3.027853
H	0.949365	3.211481	2.908806
H	2.352252	2.260563	2.299013
H	1.916298	2.209649	4.058884
C	-0.690952	1.446764	2.315307
C	-1.744644	0.367983	2.003726
H	-1.456556	-0.651859	2.286290
H	-2.639575	0.651131	2.587173
C	-1.597287	-0.493495	-0.332335
C	-1.489131	-1.058872	-2.733527
H	-2.322064	-1.072173	-3.455339
H	-1.314814	-2.066057	-2.317096
C	-0.227220	-0.464194	-3.327839
C	-0.306957	0.474443	-4.391568
H	-1.290932	0.770313	-4.780285
C	0.867749	1.032078	-4.948567
H	0.795596	1.755571	-5.770406
C	2.137491	0.651561	-4.447313
H	3.049971	1.081016	-4.880336
C	2.226609	-0.285494	-3.387926
H	3.208597	-0.582790	-2.998912
C	1.050345	-0.841464	-2.832071
H	1.113878	-1.559574	-2.004804
N	0.080933	-2.152915	2.488274
H	-0.141621	-3.093381	2.817426
H	-0.144933	-1.901020	1.502769
N	1.348280	-0.119194	2.798703
N	0.588346	1.147219	2.767310
N	-2.097872	0.406412	0.571822
H	-2.578399	1.234908	0.212209
O	1.537815	-1.904159	4.302294
O	-1.055172	2.669504	2.179870
O	-0.856458	-1.490048	-0.050355
O	-2.038908	-0.193385	-1.620645
H	2.202773	0.105984	3.328503

Transition State 2 (TS2) for the Rotation Around the N–N Axis of 8,

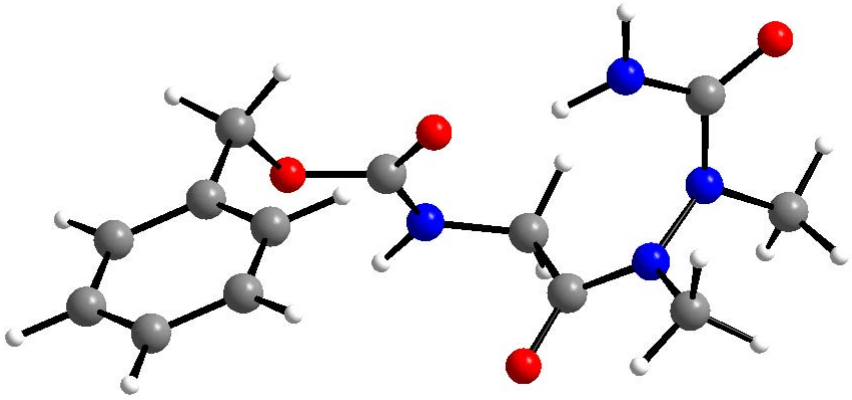
$\Delta G^{\ddagger}$ = +64 kJ mol^{-1}



E(RB-P86) = -986.744306392 a.u.

C	1.349022	0.011749	5.164676
C	-1.600019	1.053651	4.605949
H	-2.563427	1.207698	4.093705
H	-1.212058	2.044095	4.917258
H	-1.760085	0.393710	5.477549
C	-1.181196	0.212818	2.318440
C	-0.202656	-0.401321	1.300059
H	0.692373	0.246963	1.180094
H	0.158458	-1.394068	1.648186
C	-0.277179	-1.055518	-1.068799
C	-0.572805	-1.582406	-3.455155
H	-1.431612	-2.062413	-3.952962
H	0.204741	-2.328083	-3.211452
C	-0.010552	-0.435873	-4.276246
C	-0.824005	0.238680	-5.225726
H	-1.869029	-0.072421	-5.361034
C	-0.302162	1.307876	-5.992033
H	-0.939430	1.821230	-6.723381
C	1.044782	1.711636	-5.816910
H	1.452666	2.538697	-6.412324
C	1.864129	1.043413	-4.872841
H	2.908189	1.352842	-4.735976
C	1.340230	-0.025292	-4.107922
H	1.964222	-0.539346	-3.365995
N	0.850984	0.619517	6.307090
H	1.423806	0.512371	7.142506
H	0.045240	1.237326	6.332605
N	0.655722	0.109388	3.937440
N	-0.714161	0.423902	3.611627
N	-0.910611	-0.535857	0.032139
H	-1.886662	-0.220004	0.003467
O	2.458170	-0.608835	5.155125
O	-2.375990	0.515874	1.986929
O	0.925321	-1.448530	-1.096628
O	-1.167956	-1.101363	-2.156854
H	1.157179	-0.390898	3.200145

Optimized Geometry of Cbz-Gly[ΨCONMe]-azaAla-NH_2 (9)

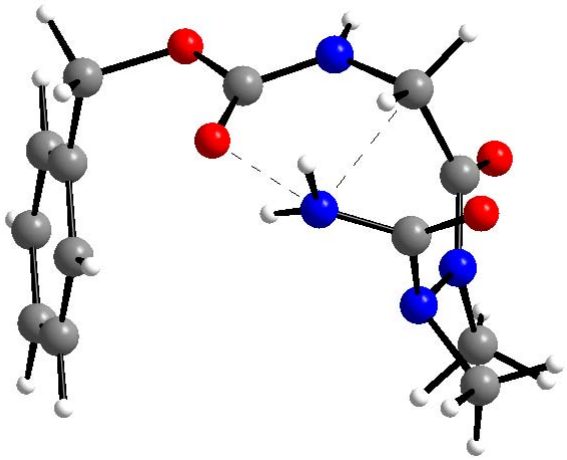


E(RB-P86) = -1026.07370093 a.u.

C	-0.046907	1.413833	-3.614869
C	0.112003	-0.701732	-4.954199
H	-0.479790	-0.079483	-5.643554
H	-0.356131	-1.696638	-4.843338
H	1.127860	-0.821754	-5.382387
C	2.390487	-0.463585	-2.697468
H	2.827637	-0.981055	-1.829075
H	2.642730	0.612198	-2.663825
H	2.790791	-0.908533	-3.627945
C	0.331649	-1.415436	-1.632420
C	-1.220213	-1.442562	-1.586695
H	-1.639410	-0.619576	-2.187493
H	-1.571450	-2.398372	-2.015165
C	-1.447246	-0.238447	0.547434
C	-1.687485	0.755051	2.797090
H	-2.604048	0.772236	3.409238
H	-1.604062	1.675726	2.193109
C	-0.448427	0.513281	3.637211
C	-0.557330	-0.051735	4.935704
H	-1.547411	-0.319312	5.329806
C	0.597709	-0.274900	5.722443
H	0.502932	-0.710203	6.725303
C	1.875529	0.065857	5.214591
H	2.772453	-0.106698	5.823115
C	1.993215	0.629338	3.919289
H	2.982092	0.891789	3.522856
C	0.837524	0.854741	3.136447
H	0.924053	1.282853	2.129742
N	0.010871	1.988775	-2.359727
H	-0.131549	2.998410	-2.343109
H	-0.125744	1.465115	-1.479027
N	0.137278	-0.011058	-3.642879
N	0.917275	-0.624982	-2.624127
N	-1.695303	-1.362921	-0.199530
H	-2.009585	-2.201076	0.290642
O	-0.272199	2.057602	-4.686712
O	1.027738	-2.056233	-0.790000
O	-0.871491	0.806952	0.112657
O	-1.943457	-0.389140	1.842504

Transition State 1 (TS1) for the Rotation Around the N–N Axis of 9,

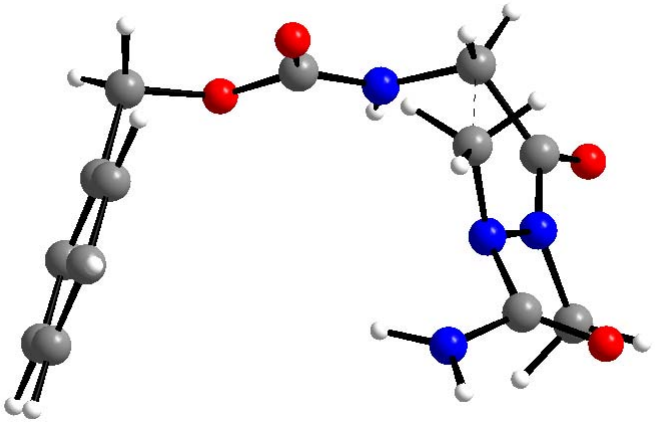
$\Delta G^{\ddagger}$ = +121 kJ mol^{-1}



E(RB-P86) = -1026.02927592 a.u.

C	-0.248747	-1.196500	3.346380
C	2.063704	-0.820262	3.890527
H	2.004817	-1.879367	4.194572
H	1.873490	-0.183095	4.776769
H	3.070875	-0.637137	3.486838
C	2.366423	1.322687	2.080298
H	2.236907	2.219227	1.455433
H	2.934747	0.549420	1.532132
H	2.906834	1.612287	2.998964
C	-0.067836	1.589658	1.974731
C	-1.515509	1.067639	1.805000
H	-1.710951	0.050036	2.155852
H	-2.169716	1.763372	2.357719
C	-1.679436	0.089783	-0.493106
C	-1.793297	-0.548859	-2.876959
H	-2.594007	-0.313689	-3.597337
H	-1.952977	-1.544050	-2.426379
C	-0.415327	-0.426531	-3.500021
C	-0.202625	0.431464	-4.612266
H	-1.042694	1.013099	-5.015789
C	1.079755	0.545541	-5.198949
H	1.233128	1.210754	-6.058059
C	2.164461	-0.203188	-4.678604
H	3.159358	-0.118274	-5.134259
C	1.961315	-1.062899	-3.570420
H	2.799315	-1.645447	-3.167050
C	0.678107	-1.174676	-2.985073
H	0.517273	-1.830941	-2.120464
N	-0.849242	-2.041653	2.451115
H	-1.710885	-2.506386	2.745840
H	-0.655316	-1.957597	1.441350
N	1.032072	-0.629379	2.803064
N	1.004995	0.799137	2.377408
N	-1.871347	1.139549	0.372072
H	-2.020416	2.065199	-0.037381
O	-0.634072	-1.008416	4.536077
O	0.132720	2.802652	1.606852
O	-1.292678	-1.080115	-0.184153
O	-2.011102	0.482863	-1.796726

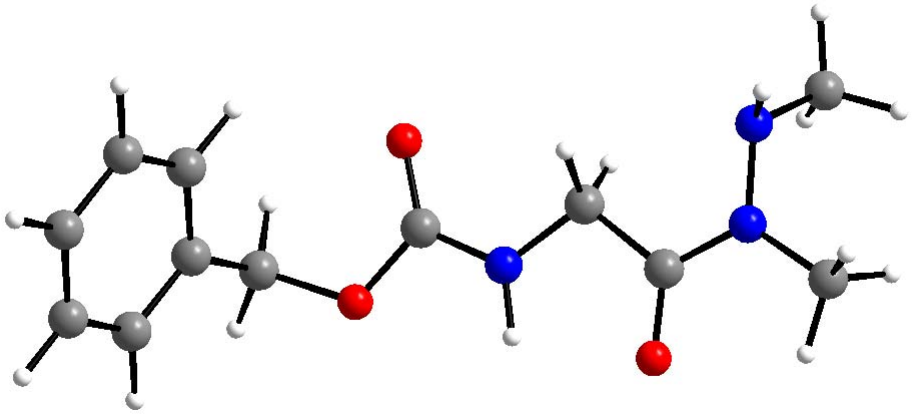
Transition State 2 (TS2) for the Rotation Around the N–N Axis of 9, $\Delta G^{\ddagger}$ = +124 kJ mol^{-1}



E(RB-P86) = -1026.02785953 a.u.

C	2.257625	-0.260892	2.617351
C	0.498881	-1.779948	1.844182
H	1.429177	-2.350135	1.686823
H	-0.122858	-1.891475	0.940974
H	-0.014297	-2.199329	2.735071
C	0.505417	1.780616	3.301598
H	-0.325862	2.496562	3.381685
H	1.266196	2.147693	2.587537
H	0.972908	1.633962	4.286935
C	-1.460759	0.414968	2.750196
C	-2.267729	-0.521207	1.816563
H	-1.887556	-1.541832	1.693589
H	-3.266786	-0.571175	2.285461
C	-1.996237	-0.555398	-0.678039
C	-1.826735	-0.268571	-3.119111
H	-2.509132	0.248117	-3.814282
H	-2.017843	-1.356086	-3.123380
C	-0.370326	0.041841	-3.418144
C	0.011606	1.328082	-3.886836
H	-0.753973	2.104355	-4.020157
C	1.365774	1.616061	-4.177243
H	1.649464	2.612552	-4.538866
C	2.354214	0.613561	-4.011390
H	3.403500	0.832410	-4.248181
C	1.982371	-0.672805	-3.547485
H	2.743675	-1.454492	-3.426965
C	0.627461	-0.955159	-3.249109
H	0.335136	-1.943542	-2.873454
N	3.174489	-0.502622	1.603546
H	4.158819	-0.589659	1.853299
H	2.889773	-0.467915	0.625482
N	0.894192	-0.351146	2.080919
N	-0.066464	0.503878	2.777565
N	-2.377699	0.085724	0.476662
H	-2.773063	1.025372	0.395488
O	2.581778	-0.016155	3.812354
O	-2.152335	1.261736	3.422582
O	-1.499790	-1.717487	-0.758439
O	-2.259438	0.275267	-1.783135

Optimized Geometry of Cbz-Glycine 1,2-dimethylhydrazide (11)

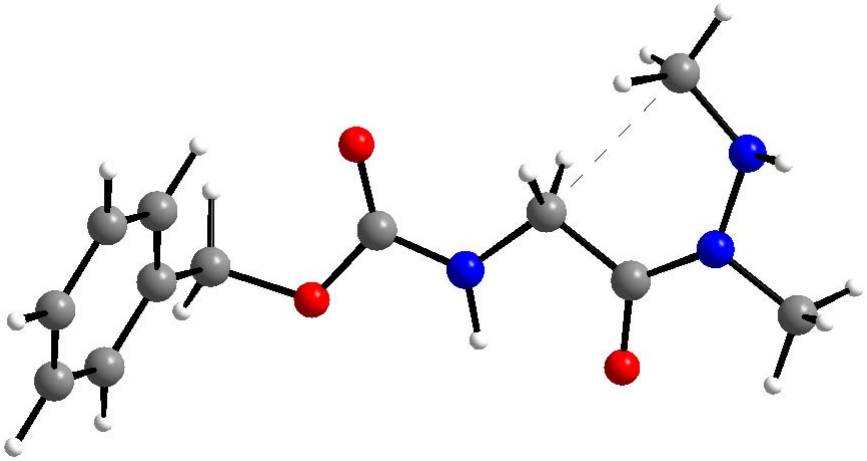


E(RB-P86) = -857.365115470 a.u.

C	1.646025	-0.303904	5.442880
H	2.747066	-0.212243	5.463699
H	1.392390	-1.331026	5.127225
H	1.258444	-0.144424	6.474580
C	-1.204485	1.051018	5.320686
H	-2.232988	0.982458	4.930761
H	-0.993215	2.096849	5.619831
H	-1.108138	0.393557	6.205684
C	-0.775526	0.194027	3.011719
C	0.271045	-0.196217	1.952486
H	0.948660	0.654181	1.749043
H	0.919123	-1.009482	2.331550
C	0.207284	-0.983549	-0.386231
C	-0.128109	-1.715627	-2.714101
H	-0.840307	-2.461050	-3.106069
H	0.856591	-2.178740	-2.523171
C	-0.007925	-0.514393	-3.636263
C	-1.050431	-0.197612	-4.547608
H	-1.951457	-0.825618	-4.578036
C	-0.941329	0.919609	-5.409603
H	-1.753207	1.154054	-6.110036
C	0.218004	1.733078	-5.368857
H	0.306027	2.599174	-6.037648
C	1.263870	1.424391	-4.463206
H	2.163887	2.051881	-4.430090
C	1.152867	0.306318	-3.603293
H	1.953051	0.067281	-2.891272
N	1.130897	0.659626	4.432866
N	-0.284497	0.629555	4.238065
N	-0.455569	-0.605574	0.749657
H	-1.481142	-0.580988	0.792034
O	-2.023825	0.122086	2.772588
O	1.464426	-1.024412	-0.530176
O	-0.725391	-1.344113	-1.385948
H	1.449972	1.627569	4.594435

Transition State 1 (TS1) for the Rotation Around the N–N Axis of 11,

$\Delta G^{\ddagger}$ = +62 kJ mol^{-1}

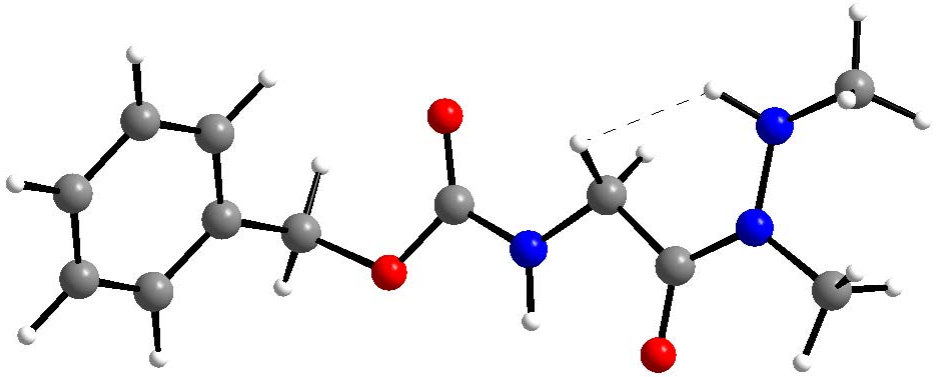


E(RB-P86) = -857.343878688 a.u.

C	2.257052	-0.423551	4.061045
H	3.100400	-0.587775	4.756946
H	2.629559	0.178122	3.203137
H	1.935768	-1.413326	3.702551
C	-0.897773	1.313095	5.326837
H	-1.879331	1.544937	4.889025
H	-0.405465	2.254409	5.645661
H	-1.010567	0.646100	6.200949
C	-0.678000	0.310529	3.082382
C	0.057315	-0.544169	2.024793
H	1.057843	-0.145533	1.786084
H	0.194958	-1.576760	2.406271
C	-0.304047	-1.097449	-0.345670
C	-0.872227	-1.499765	-2.707634
H	-1.822963	-1.853435	-3.140201
H	-0.174641	-2.342910	-2.556065
C	-0.243440	-0.403290	-3.550343
C	-1.038507	0.376208	-4.432463
H	-2.118581	0.185784	-4.498197
C	-0.453535	1.396208	-5.220325
H	-1.077707	1.991513	-5.899049
C	0.938685	1.645128	-5.134481
H	1.395013	2.433750	-5.746788
C	1.740036	0.871728	-4.257462
H	2.819114	1.061158	-4.189952
C	1.153149	-0.147779	-3.471638
H	1.763057	-0.743254	-2.780603
N	1.196687	0.216930	4.880024
N	-0.081745	0.636111	4.289966
N	-0.769688	-0.549883	0.818853
H	-1.700066	-0.121690	0.897597
O	-1.879096	0.690758	2.832610
O	0.836124	-1.628284	-0.502948
O	-1.287829	-0.998292	-1.351769
H	1.570974	1.071976	5.327330

Transition State 2 (TS2) for the Rotation Around the N–N Axis of 11,

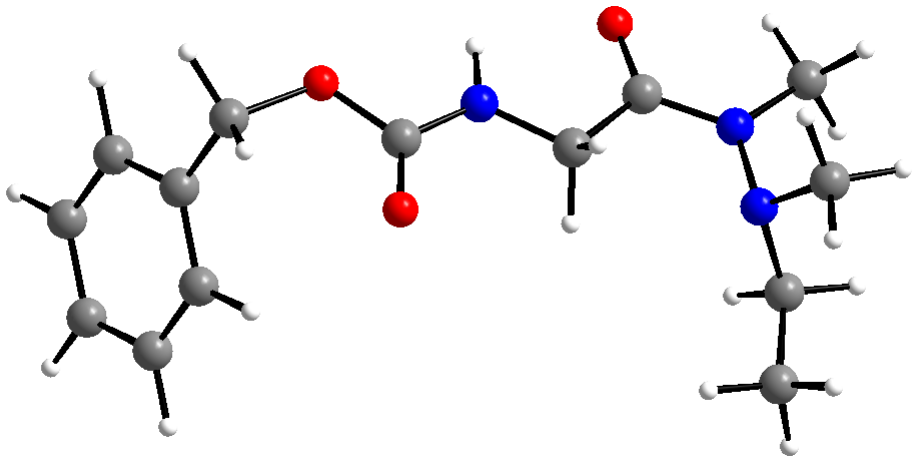
$\Delta G^{\ddagger}$ = +42 kJ mol^{-1}



E(RB-P86) = -857.352067332 a.u.

C	1.829473	0.055145	-5.755937
H	2.715611	0.714942	-5.775823
H	1.193169	0.330881	-6.612725
H	2.169494	-0.997879	-5.879631
C	-0.769674	-1.095220	-5.362240
H	-1.648805	-1.608345	-4.940308
H	-0.144522	-1.825586	-5.904739
H	-1.115270	-0.307467	-6.060181
C	-0.672568	-0.418409	-2.984032
C	0.050278	0.419526	-1.914729
H	1.065356	0.015070	-1.704433
H	0.196562	1.453114	-2.290785
C	-0.348593	1.012003	0.443138
C	-0.950965	1.421082	2.795765
H	-1.930197	1.702909	3.217381
H	-0.329953	2.317222	2.617628
C	-0.230920	0.410072	3.671408
C	-0.956841	-0.404183	4.581318
H	-2.048966	-0.302796	4.645550
C	-0.287189	-1.345794	5.398729
H	-0.858121	-1.969225	6.098760
C	1.120728	-1.480551	5.314518
H	1.641977	-2.208923	5.949231
C	1.853531	-0.671289	4.410329
H	2.944530	-0.771957	4.344387
C	1.182056	0.270001	3.595165
H	1.739357	0.892787	2.883964
N	1.130944	0.342193	-4.473187
N	-0.046957	-0.508977	-4.216373
N	-0.762787	0.389220	-0.703815
H	-1.636950	-0.148456	-0.749215
O	-1.780610	-1.005899	-2.730199
O	0.733344	1.655970	0.579332
O	-1.315737	0.842622	1.456222
H	1.786464	0.180815	-3.688855

Optimized Geometry of Cbz-Glycine 2-ethyl-1,2-dimethylhydrazide (13)

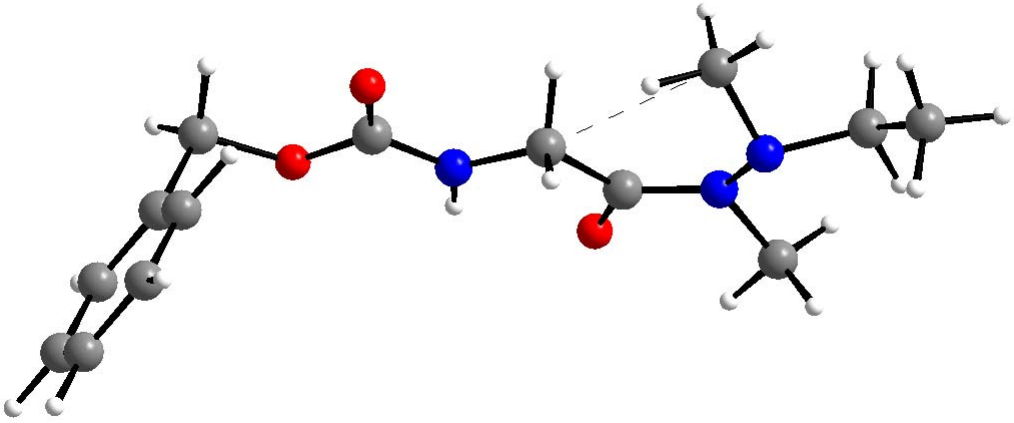


E(RB-P86) = -935.976908063 a.u.

C	0.285124	1.215011	-5.046352
H	1.136772	1.916294	-5.069549
H	-0.622084	1.783140	-4.777746
H	0.155193	0.788149	-6.069274
C	-1.265033	-1.457670	-4.726107
H	-2.123777	-1.955260	-4.246857
H	-0.552188	-2.223791	-5.085235
H	-1.624482	-0.862937	-5.587270
C	-1.167784	-0.504994	-2.421224
C	-0.435667	0.417515	-1.428925
H	0.623082	0.114188	-1.326683
H	-0.413862	1.454971	-1.813950
C	-0.683720	0.992700	0.958283
C	-1.103013	1.341770	3.359822
H	-2.058078	1.521307	3.881303
H	-0.593299	2.296703	3.139014
C	-0.203441	0.399939	4.142353
C	-0.756281	-0.514957	5.078051
H	-1.844162	-0.541467	5.229742
C	0.078675	-1.393867	5.808471
H	-0.360242	-2.095983	6.528974
C	1.481483	-1.363487	5.610950
H	2.131616	-2.042387	6.178035
C	2.042260	-0.452995	4.680508
H	3.128685	-0.426106	4.526054
C	1.205367	0.424741	3.951601
H	1.629816	1.122118	3.218402
N	0.542273	0.186290	-3.999988
N	-0.635875	-0.587339	-3.702299
N	-1.139737	0.330374	-0.148581
H	-1.969918	-0.272993	-0.112963
O	-2.205856	-1.158369	-2.075861
O	0.342498	1.732889	1.006933
O	-1.541726	0.741216	2.053795
C	1.737077	-0.683528	-4.256892
H	1.710673	-1.487962	-3.498357
H	1.686374	-1.166711	-5.263814
C	3.058101	0.105770	-4.126743
H	3.107905	0.615999	-3.147555
H	3.915288	-0.589333	-4.205322
H	3.171850	0.865219	-4.922587

Transition State 1 (TS1) for the Rotation Around the N–N Axis of 13,

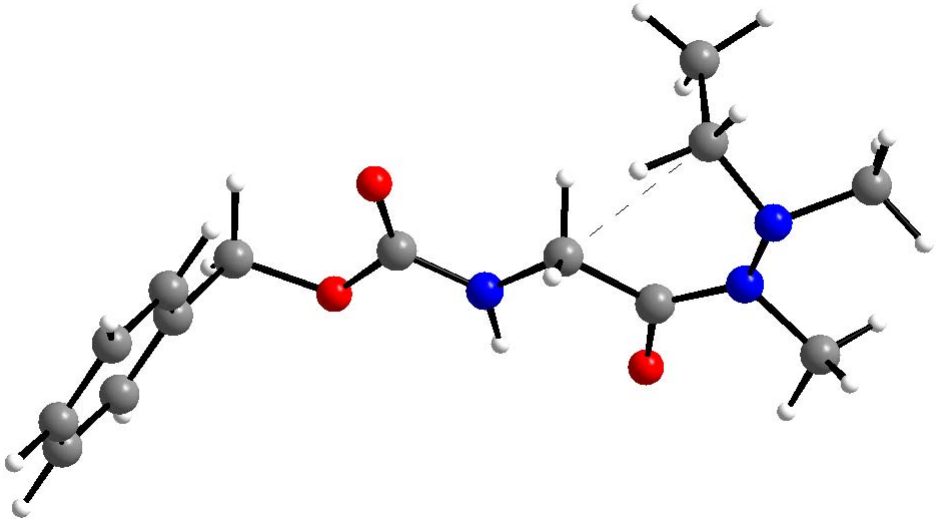
$\Delta G^{\ddagger}$ = +90 kJ mol^{-1}



E(RB-P86) = -935.947320315 a.u.

C	1.395055	-0.934578	3.682852
H	2.281071	-1.084857	4.319616
H	1.767635	-0.774437	2.662979
H	0.771871	-1.857154	3.726225
C	-1.528120	1.441097	4.368702
H	-2.296523	1.798599	3.666877
H	-0.896024	2.286306	4.698041
H	-2.040391	0.984824	5.234361
C	-1.103720	0.183463	2.326371
C	-0.176161	-0.438831	1.257839
H	0.738136	0.178813	1.148743
H	0.144078	-1.460933	1.525927
C	-0.364906	-1.031327	-1.120350
C	-0.752788	-1.481828	-3.509284
H	-1.665249	-1.849092	-4.007909
H	-0.063136	-2.317155	-3.292439
C	-0.068804	-0.393131	-4.318594
C	-0.801425	0.369647	-5.267099
H	-1.873117	0.172684	-5.407888
C	-0.165208	1.381255	-6.025408
H	-0.741089	1.963849	-6.755919
C	1.216196	1.638388	-5.843142
H	1.712074	2.420738	-6.432347
C	1.955363	0.881968	-4.899313
H	3.025698	1.078468	-4.756061
C	1.317336	-0.129057	-4.142893
H	1.878069	-0.710322	-3.400137
N	0.684581	0.271269	4.211910
N	-0.686733	0.455506	3.630613
N	-0.920031	-0.473036	-0.001514
H	-1.871435	-0.085975	0.015506
O	-2.288772	0.519028	1.958449
O	0.791472	-1.546234	-1.186871
O	-1.274755	-0.964353	-2.196826
C	0.588930	0.124483	5.720269
H	-0.117703	0.871932	6.106653
H	0.195650	-0.883333	5.997552
C	1.954554	0.391958	6.392812
H	2.361963	1.361774	6.053516
H	1.816737	0.432344	7.490108
H	2.705596	-0.391825	6.184952

Transition State 2 (TS2) for the Rotation Around the N–N Axis of 13, $\Delta G^{\ddagger}$ = +92 kJ mol^{-1}



E(RB-P86) = -935.947749526 a.u.

C	-0.484718	0.532506	-5.903271
H	-0.376221	-0.558922	-6.088695
H	0.298122	1.070037	-6.460255
H	-1.460806	0.866490	-6.297032
C	1.997381	0.758773	-4.646346
H	2.877167	0.678496	-3.991267
H	1.885695	1.795577	-5.013398
H	2.128650	0.066994	-5.496981
C	1.064314	0.029635	-2.510216
C	-0.016007	-0.005369	-1.404633
H	-0.406342	1.021061	-1.241495
H	-0.873812	-0.650584	-1.656976
C	-0.134573	-0.839828	0.906866
C	-0.006574	-1.680720	3.217818
H	0.607174	-2.504541	3.618707
H	-1.019411	-2.038489	2.959730
C	-0.060971	-0.502805	4.175325
C	0.944510	-0.328136	5.163413
H	1.772040	-1.048189	5.226415
C	0.892176	0.765146	6.060928
H	1.674436	0.889229	6.820775
C	-0.171988	1.696909	5.978775
H	-0.215586	2.544542	6.674969
C	-1.179975	1.530427	4.996150
H	-2.006357	2.249883	4.930818
C	-1.126445	0.436048	4.101273
H	-1.896890	0.305949	3.330687
N	-0.459537	0.904076	-4.448088
N	0.802035	0.404703	-3.827443
N	0.618792	-0.509605	-0.186502
H	1.638001	-0.634585	-0.219075
O	2.271749	-0.244917	-2.160227
O	-1.395523	-0.736859	0.988646
O	0.697045	-1.331325	1.935122
C	-1.749305	0.486170	-3.802098
H	-1.766989	0.855145	-2.767133
H	-2.517288	1.078665	-4.335382
C	-2.127228	-1.022126	-3.870692
H	-1.301815	-1.673169	-3.527684
H	-3.003589	-1.211752	-3.222447
H	-2.394968	-1.331042	-4.898117

S20. References

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[2] L. Knorr and A. Köhler, *Ber. Dtsch. Chem. Ges.* 1906, **39**, 3257.

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