Electronic Supplementary Material (ESI) for RSC Advances

Supporting Information

Minimalistic amino amides as models to study N-H···π interactions and their implication in the side chain folding of pseudopeptidic molecules

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Synthetic procedures and characterization of new compounds

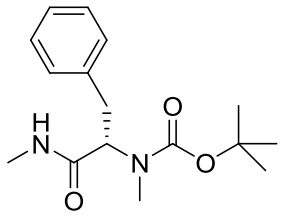
General

Reagents and solvents were purchased from commercial suppliers (Aldrich, Fluka, or Merck) and were used without further purification. Flash chromatographic purifications and preparative reversed-phase purifications were performed on a Biotage® Isolera Prime™ equipment. TLCs were performed using 6x3 cm SiO_2 pre-coated aluminium plates (ALUGRAM® SIL G/UV_{254}).

The NMR spectroscopic experiments were carried out either on an Agilent VNMRS Direct Drive 400 (400 and 101 MHz for ^{1}H and ^{13}C NMR, respectively) or on Agilent Inova 500 (500 and 125 MHz for ^{1}H and ^{13}C NMR, respectively) spectrometers. The chemical shifts are reported in ppm, using the solvent signal as internal standard ($CDCl_3$ = 7.26 ppm; CD_3CN = 1.94 ppm; dmso-d_6 = 2.50 ppm). In the experiment in which the dmso/$CDCl_3$ ratio was varied, Tetrakis(trimethylsilyl)silane was used as a reference (0.00 ppm).

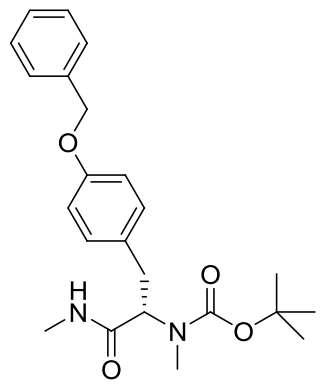
Scanning Electron Microscopy was performed on a FEI Quanta 200 microscope with a digital camera. Samples were obtained by slow evaporation of a 20 mM solution of compound X in different solvents, directly onto the glass sample holder, followed by conventional gold coating.

High Resolution Mass Spectrometry analyses were carried out at the IQAC Mass Spectrometry Facility, using an UPLC-ESI-TOF equipment: [Acquity UPLC® BEH C_{18} 1.7 mm, 2.1x100 mm, LCT Premier Xe, Watters]. (CH_3CN + 20 mM HCOOH and H_2O + 20 mM HCOOH) mixtures at 0.3 mL/min were used as mobile phase.



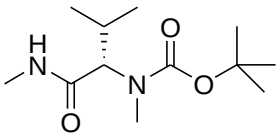
Boc,Me-Phe-NHMe (2c). To a solution of N-α-Boc-N-α-methyl-Phenylalanine (Boc,Me,Phe-OH, 500 mg, 1.79 mmol) in dry Tetrahydrofuran (15 ml) were added *N*,*N*-Diisopropylethylamine (410 µl, 2.33 mmol) and 1-[Bis(dimethylamino)methylene]-1*H*-1,2,3-triazolo[4,5-*b*]pyridinium 3-oxid hexafluorophosphate (HATU, 750 mg, 1.97 mmol). The mix was stirred at room temperature under Argon for 10 minutes, and then a solution of methylamine in Tetrahydrofuran (2.0 M, 3.6 ml, 7.2 mmol) was added. The reaction mix was stirred at room temperature for 18 hours. Solvents were removed at reduced pressure and the residue dissolved in chloroform and washed twice with water. Organic layer was dried over $MgSO_4$ and evaporated at reduced pressure. The crude product was purified by flash column chromatography (SiO_2; hexane:AcOEt 1:1 to 1:2), affording the desired product as a colorless oil (418 mg, 1.43 mmol, 80% yield). Two rotamers (A and B) are observed.

^{1}H-NMR (CD_3OD, 400 MHz) δ 7.28-7.15 (m, 5H), 4.66 (d, *J* = 7.5 Hz, 1H), 3.28 (dd, *J* = 14.2, 4.9 Hz, 1H), 2.94 (dd, *J* = 14.2, 11.0 Hz, 1H), 2.75 (s, 3H), 2.73 (s, 3H), 1.33 (s, 3H), 1.28 (s, 6H). ^{13}C-NMR (CD_3OD, 101 MHz) δ 173.2 (A), 172.8 (B), 157.5 (A), 156.9 (B), 139.5 (A), 138.9 (B), 130.2 (A), 130.1 (B), 129.5 (A), 129.3 (B), 127.5, 81.5 (A), 81.3 (B), 63.2, 61.0, 35.7 (A), 35.6 (B), 32.1 (A), 31.7 (B), 28.5 (A), 28.4 (B), 26.5 (A), 26.4 (B). HRMS: m/z calculated for $C_{16}H_{24}N_2O_3Na$: 315.1685, found 315.1713 $(M+Na)^+$; m/z calculated for $C_{32}H_{48}N_4O_6Na$: 607.3472, found 607.3500 $(2M+Na)^+$.



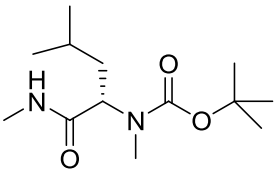
Boc,Me-(OBn)Tyr-NHMe (2d). Prepared following the same procedure of **2c**. Starting from 500 mg (1.30 mmol) of Boc,Me-(OBn)Tyr-OH, desired product was obtained as a pale yellow waxy solid (320 mg, 0.80 mmol, 62% yield). Two rotamers (A and B) are observed.

^{1}H-NMR (CD_3OD, 400 MHz) δ 7.81 (bs, 1H), 7.42-7.26 (m, 5H), 7.11 (d, *J* = 8.5 Hz, 2H), 6.91 (d, *J* = 8.5 Hz, 2H), 5.04 (s, 2H), 4.60 (d, *J* = 10.5 Hz, 1H), 3.20 (dd, *J* = 14.3, 5.0 Hz, 1H), 2.87 (dd, *J* = 14.3, 10.9 Hz, 1H), 2.72 (s, 6H), 1.33 (s, 3H), 1.27 (s, 6H). ^{13}C-NMR (CD_3OD, 101 MHz) δ 173.4, 159.0, 157.7 (A), 157.1 (B), 138.8, 131.1, 129.5, 128.8, 128.5, 116.0, 81.7 (A), 81.4 (B), 71.0, 63.4, 61.2, 34.9, 32.0 (A), 31.7 (B), 28.5 (3C), 26.5. HRMS: m/z calculated for $C_{23}H_{30}N_2NaO_4$ $(M+Na)^+$: 421.2103, found 421.2122.



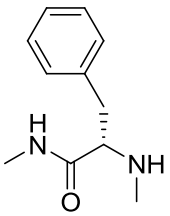
Boc,Me-Val-NHMe (2a). Prepared following the same procedure of **2c**. Starting from 500 mg (2.16 mmol) of Boc,Me-Val-OH, desired product was obtained as a white solid (430 mg, 1.76 mmol, 81% yield).

^{1}H-NMR ($CDCl_3$, 400 MHz) δ 6.34 (bs, 1H), 3.98 (d, *J* = Hz, 1H), 2.76 (s, 3H), 2.70 (d, *J* = 4.9 Hz, 3H), 2.26-2.14 (m, 1H), 1.39 (s, 9H), 0.86 (d, *J* = 6.6 Hz, 3H), 0.79 (d, *J* = 6.7 Hz, 3H). ^{13}C-NMR ($CDCl_3$, 101 MHz) δ 171.2, 156.5, 79.6, 64.0, 29.8, 28.1 (3C), 26.2, 25.6, 19.4, 18.4. HRMS: m/z calculated for $C_{24}H_{48}N_4NaO_6$ $(2M+Na)^+$: 511.3472, found 511.3509.

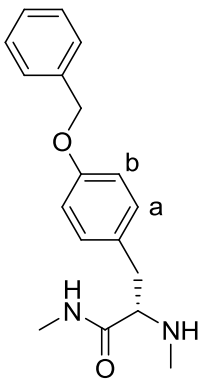


Boc,Me,Leu-NHMe (2b). Prepared following the same procedure of **2c**. Starting from 500 mg (2.04 mmol) of Boc,Me-Leu-OH, desired product was obtained as a pale yellow oil (350 mg, 1.36 mmol, 66% yield). Two rotamers are observed.

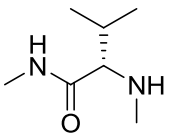
^{1}H-NMR (CD_3OD, 400 MHz) δ 7.79 (bs, 1H), 4.70 (bs, 1H), 4.64 (bs, 1H), 2.80 (s, 3H), 2.75 (d, *J* = 4.5 Hz, 3H), 1.72-1.63 (m, 2H), 1.49 (s, 9H), 0.98 (d, *J* = 6.7 Hz, 6H). ^{13}C-NMR (CD_3OD, 101 MHz) δ 174.1, 157.71 (A), 157.2 (B), 81.5 (A), 81.2 (B), 59.0 (A), 57.4 (B), 38.9 (A), 38.5 (B), 30.7 (A), 30.6 (B), 28.7 (3C), 26.4 (A), 26.0 (B), 23.7, 21.9 (2C). HRMS: m/z calculated for $C_{13}H_{26}N_2NaO_3$ $(M+Na)^+$: 281.1841, found 281.1866; calculated for $C_{26}H_{52}N_4NaO_6$ $(2M+Na)^+$: 539.3785, found 5539.3829.



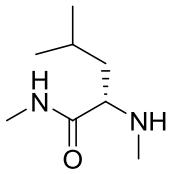
Me-Phe-NHMe (3c). To a solution of **2c**, 400 mg, 1.37 mmol) in dry Dichloromethane (4 ml) was added Trifluoroacetic Acid (3 ml) and the mix was stirred at room temperature under Argon for 3 hours. Solvents were removed at reduced pressure and the residue dissolved in 10% aqueous NaOH and extracted three times with DCM. Organic layers were combined, dried over $MgSO_4$ and evaporated at reduced pressure, affording the desired product as a pale-yellow oil (184 mg, 0.96 mmol, 70% yield). $[\alpha]_D$ = +19.7 (c 0.005, MeOH). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.33-7.20 (m, 5H, Ph), 7.13 (bs, 1H, amide NH), 3.27 (dd, *J* = 9.0, 4.5 Hz, 1H, Hα), 3.21 (dd, *J* = 13.6, 4.5 Hz, 1H, Hβ), 2.81 (d, *J* = 5.1 Hz, 3H, amide Me), 2.73 (dd, *J* = 13.6, 9.0 Hz, 1H, Hβ'), 2.29 (s, 3H, amine Me). ^{13}C-NMR ($CDCl_3$, 101 MHz) δ 174.0, 137.6, 129.1, 128.7, 126.9, 66.0, 39.3, 35.4, 25.8. HRMS: m/z calculated for $C_{11}H_{17}N_2O$ $(M+H)^+$: 193.1341, found 193.1355; calculated for $C_{11}H_{16}N_2NaO$ $(M+Na)^+$: 215.1160, found 215.1193.



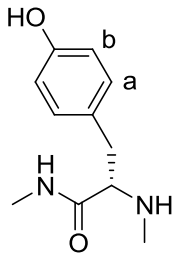
Me-(OBn)Tyr-NHMe (3d). Prepared following the same procedure of **3c**. Starting from 300 mg (0.75 mmol) of **2d**, desired product obtained as a white solid (202 mg, 0.68 mmol, 90% yield). $[\alpha]_D$ = +11.0 (c 0.002, MeOH). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.44-7.31 (m, 5H, Bn), 7.12 (d, *J* = 8.6 Hz, 2H, Ph Ha), 6.92 (d, *J* = 8.5 Hz, 2H, Ph Hb), 5.05 (s, 2H, CH_2 Bn), 3.18 (dd, *J* = 8.9, 4.3 Hz, 1H, Hα), 3.14 (dd, *J* = 13.6, 4.3 Hz, 1H, Hβ), 2.82 (d, *J* = 4.9 Hz, 3H, amide Me), 2.64 (dd, *J* = 13.6, 8.9 Hz, 1H, Hβ'), 2.27 (s, 3H, amine Me). ^{13}C-NMR ($CDCl_3$, 101 MHz) δ 174.1, 157.9, 137.1, 130.2, 129.8, 128.7, 128.1, 127.6, 115.2, 70.1, 66.3, 38.5, 35.6, 25.9. HRMS: m/z calculated for $C_{18}H_{23}N_2O_2$ $(M+H)^+$: 299.1760, found 299.1784; calculated for $C_{18}H_{22}N_2NaO_2$ $(M+Na)^+$: 221.1579, found 221.1604.



Me,Val-NHMe (3a). Prepared following the same procedure of **3c**. Starting from 239 mg (0.98 mmol) of **2a**, desired product obtained as a white solid (123 mg, 0.85 mmol, 87% yield). $[\alpha]_D$ = -15.5 (c 0.008, MeOH). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.16 (bs, 1H, amide NH), 2.84 (d, *J* = 5.1 Hz, 3H, amide Me), 2.82 (d, *J* = 4.5 Hz, 1H, Hα), 2.39 (s, 3H, amine Me), 2.16-2.08 (m, 1H, Hβ), 1.67 (bs, 1H, amine NH), 0.99 (d, *J* = 7.0 Hz, 3H, Hγ), 0.89 (d, *J* = 6.9 Hz, 3H, Hγ'). ^{13}C-NMR ($CDCl_3$, 101 MHz) δ 174.2, 70.7, 36.0, 31.2, 25.4, 19.4, 17.8. HRMS: m/z calculated for $C_7H_{17}N_2O$ $(M+H)^+$: 145.1341, found 145.1367; calculated for $C_7H_{16}N_2NaO$ $(M+Na)^+$: 167.1160, found 167.0890.



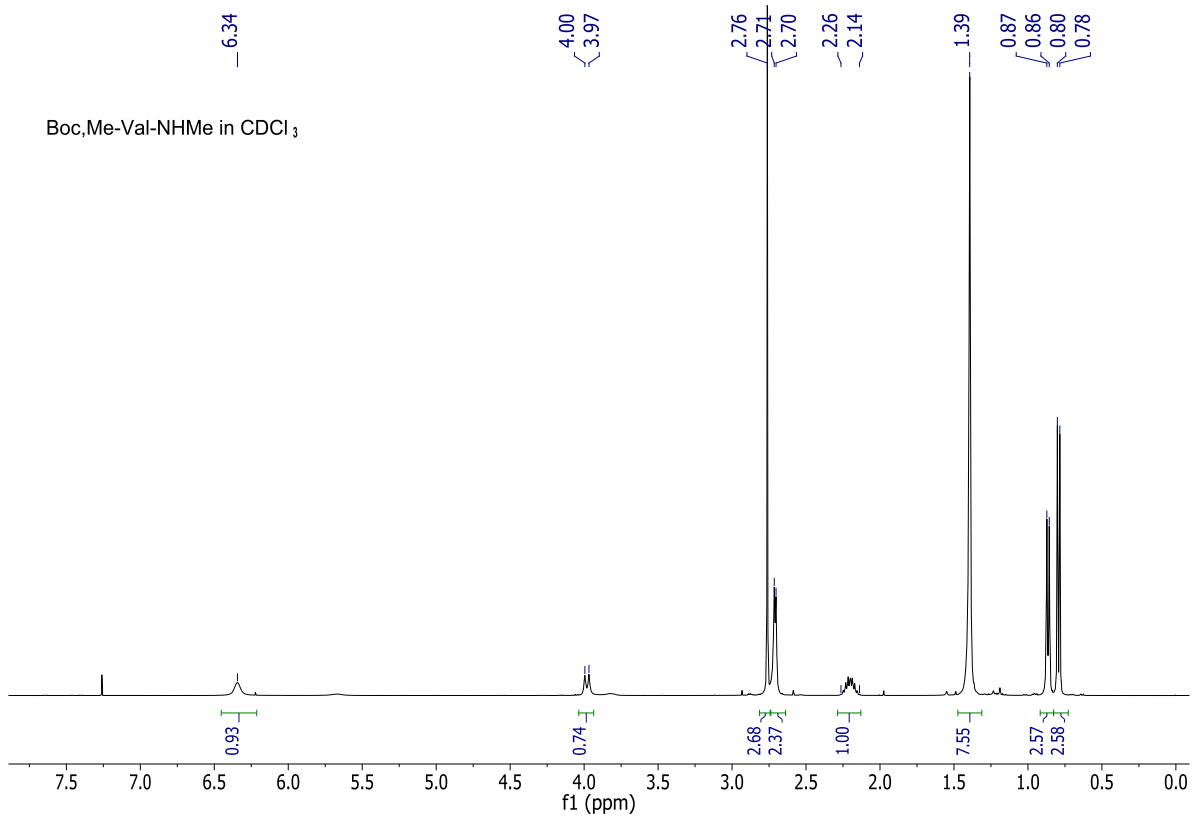
Me-Leu-NHMe (3b). Prepared following the same procedure of **3c**. Starting from 190 mg (0.74 mmol) of **2b**, desired product was obtained as a pale-yellow oil (109 mg, 0.69 mmol, 94% yield). $[\alpha]_D$ = -5.0 (c 0.005, MeOH). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.20 (bs, 1H, amide NH), 3.04 (dd, *J* = 8.9, 4.9 Hz, Hα), 2.83 (d, *J* = 5.1 Hz, 3H, amide Me), 1.72-1.57 (m, 2H, Hβ and Hγ), 1.39 (ddd, *J* = 13.3, 8.8, 5.6 Hz, 1H, Hβ'), 0.95 (d, *J* = 6.7 Hz, 3H, Hδ), 0.93 (d, *J* = 6.7 Hz, 3H, Hδ'). ^{13}C-NMR ($CDCl_3$, 101 MHz) δ 175.4, 63.3, 42.8, 35.2, 25.6, 24.9, 23.0, 21.9. HRMS: m/z calculated for $C_{16}H_{36}N_4NaO_2$ $(2M+Na)^+$: 339.2736, found 339.3386.

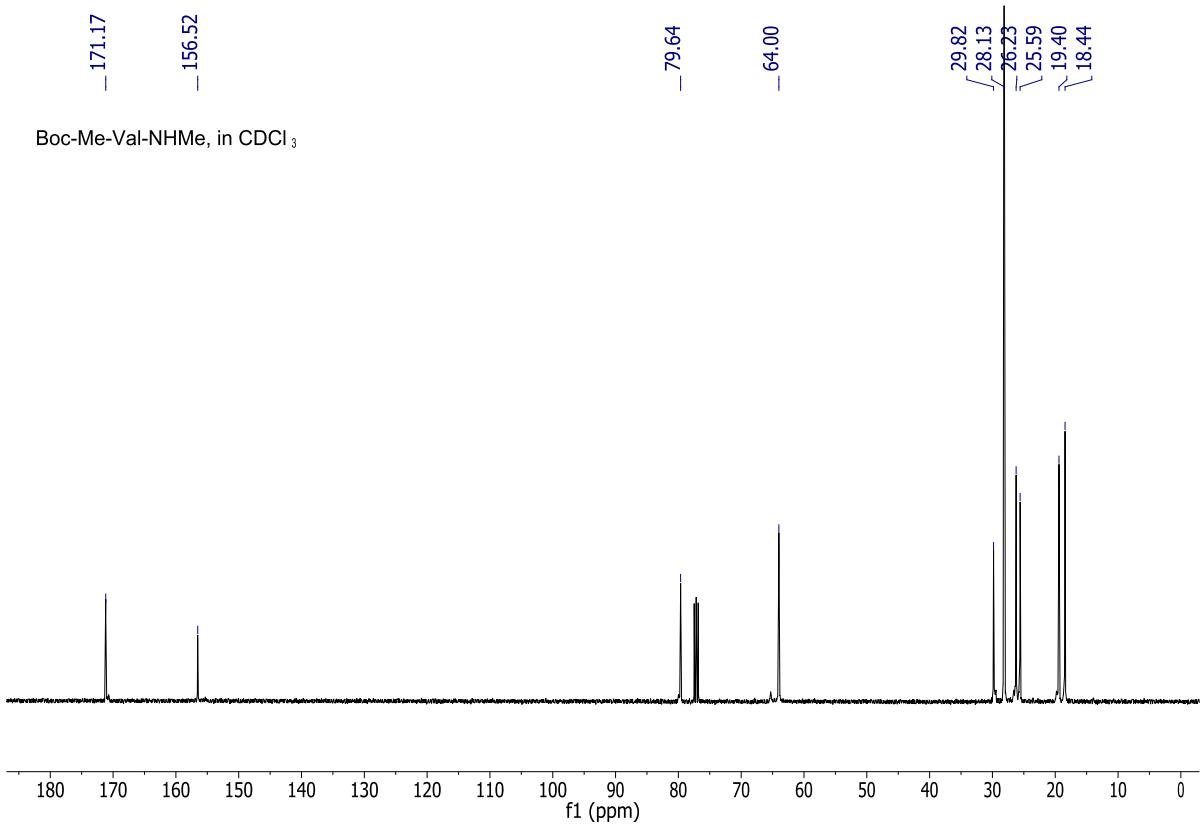


Me-Tyr-NHMe (3e). To a solution of **3d** (155 mg, 0.52 mmol) in THF (5.0 ml) and methanol (2.0 ml), in Argon atmosphere, was added Pd/C (10% Pd, 50 mg). Argon was replaced by hydrogen (2 atm) and the black suspension was stirred for 20 hours at room temperature. The catalyst was filtered through celite and washed thoroughly with methanol. The filtrate was concentrated under reduced pressure, affording the desired product as a pale yellow solid (106 mg, 0.51 mmol, 98% yield). $[\alpha]_D$ = +32.6 (c 0.005, MeOH). ^{1}H-NMR ($CDCl_3$, 400 MHz) δ 7.14 (bs, 1H, amide NH), 7.06 (d, *J* = 8.5 Hz, 2H, Ph Ha), 6.79 (d, *J* = 8.5 Hz, 2H, Ph Hb), 3.15 (dd, *J* = 8.5, 4.3 Hz, 1H, Hα), 3.13 (dd, *J* = 13.2, 4.3 Hz, 1H, Hβ), 2.83 (d, *J* = 5.0 Hz, 3H, amide Me), 2.62 (dd, *J* = 13.2, 8.5 Hz, 1H, Hβ'), 2.26 (s, 3H, amine Me). ^{13}C-NMR ($CDCl_3$, 101 MHz) δ 174.9, 155.7, 130.2, 128.6, 115.9, 66.4, 38.6, 35.6, 26.0. HRMS: m/z calculated for $C_{11}H_{17}N_2O_2$ $(M+H)^+$: 209.1290, found 209.1287; calculated for $C_{11}H_{16}N_2NaO_2$ $(M+Na)^+$: 231.1109, found 231.1087; calculated for $C_{22}H_{32}N_4NaO_4$ $(2M+Na)^+$: 439.2321, found 439.2285.

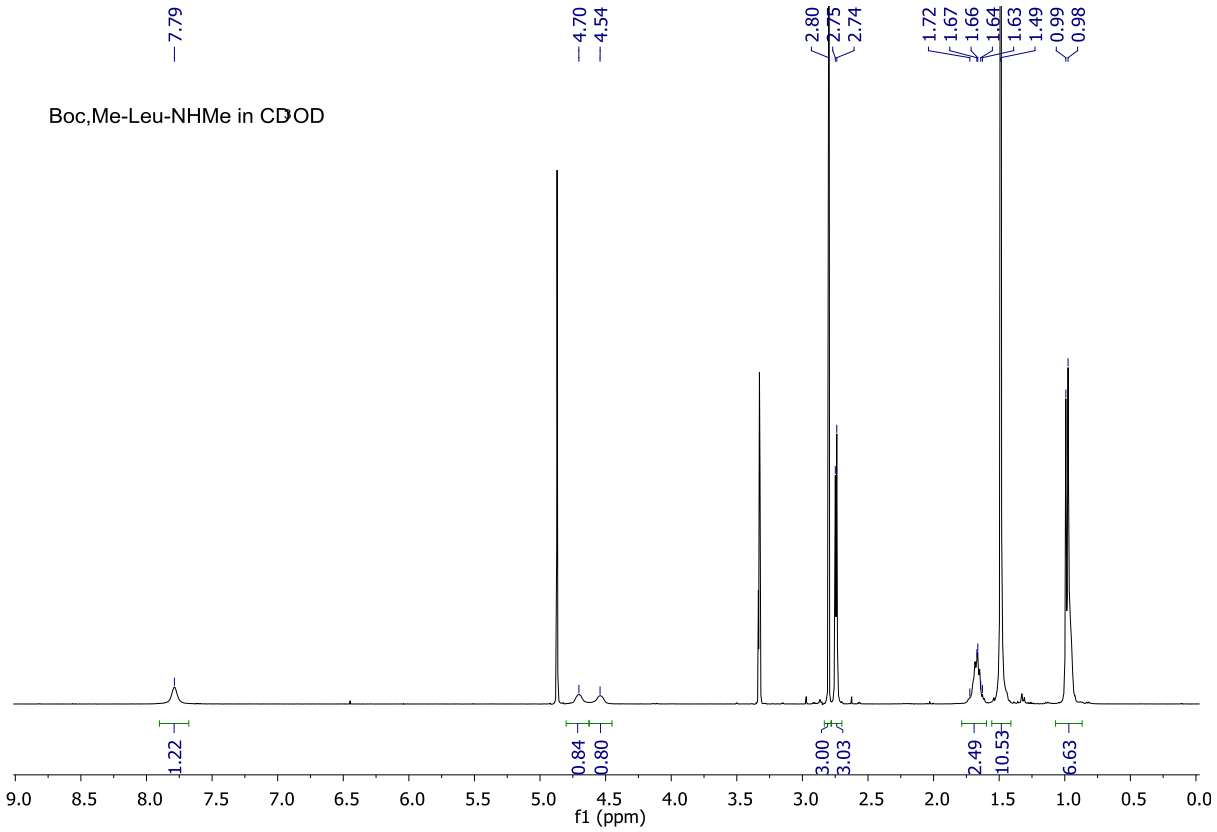
NMR Spectra: unless otherwise stated at 400 MHz (^{1}H) or 101 MHz (^{13}C) and at 298K

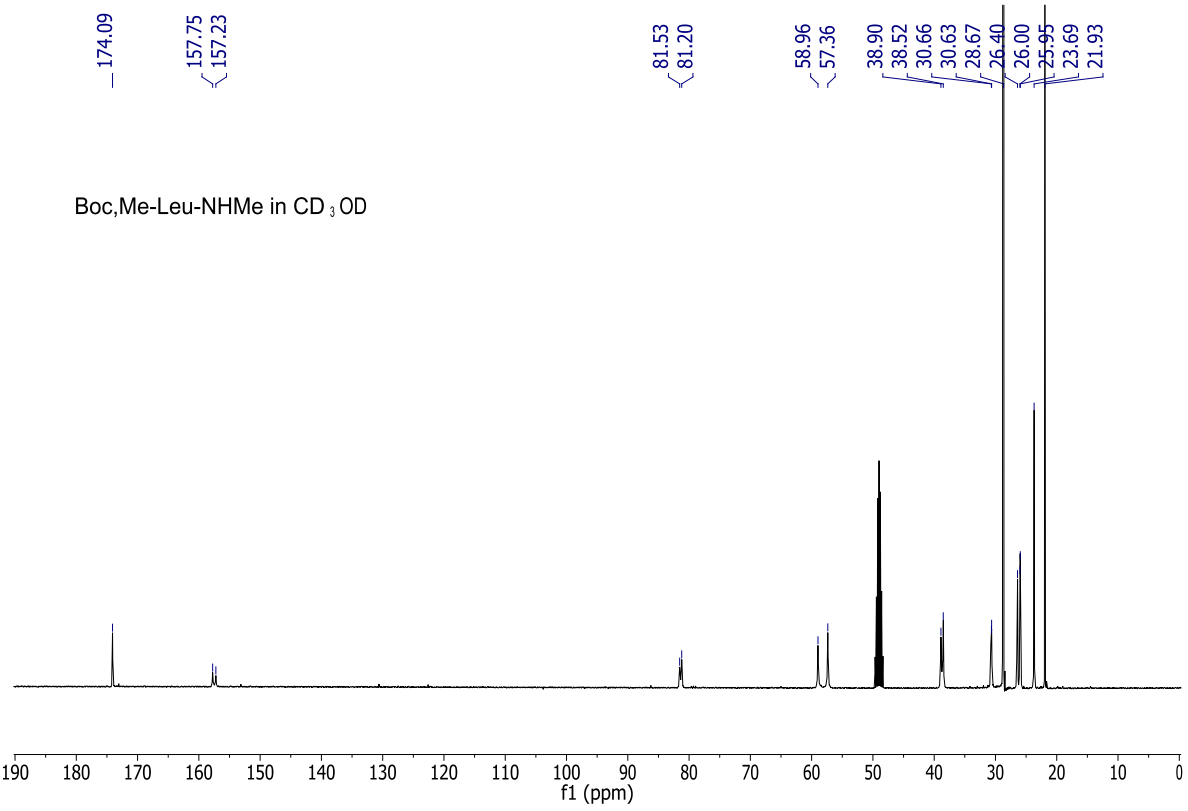
^{1}H and ^{13}C NMR spectra of **2a**.



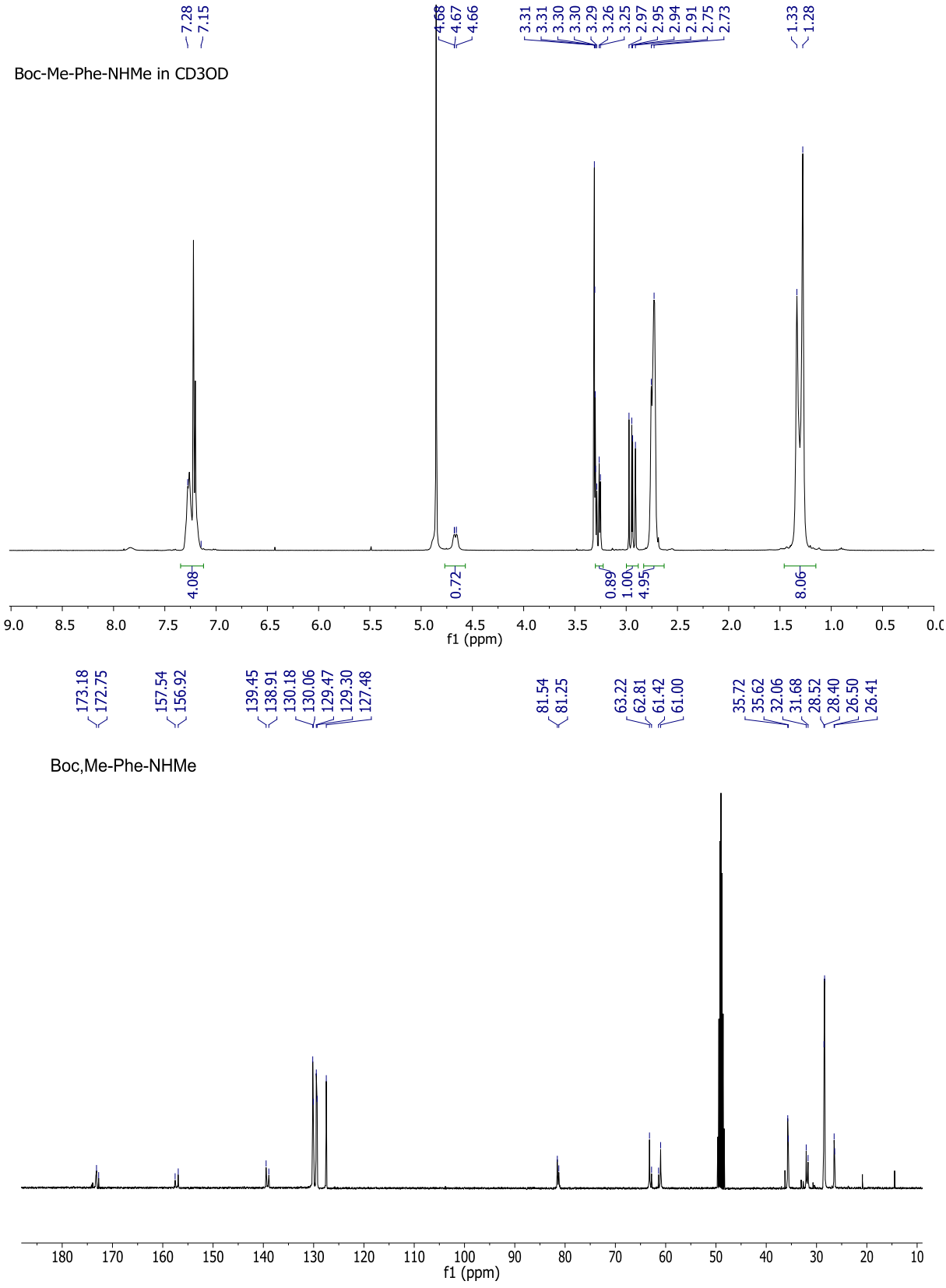


^{1}H and ^{13}C NMR spectra of **2b**.

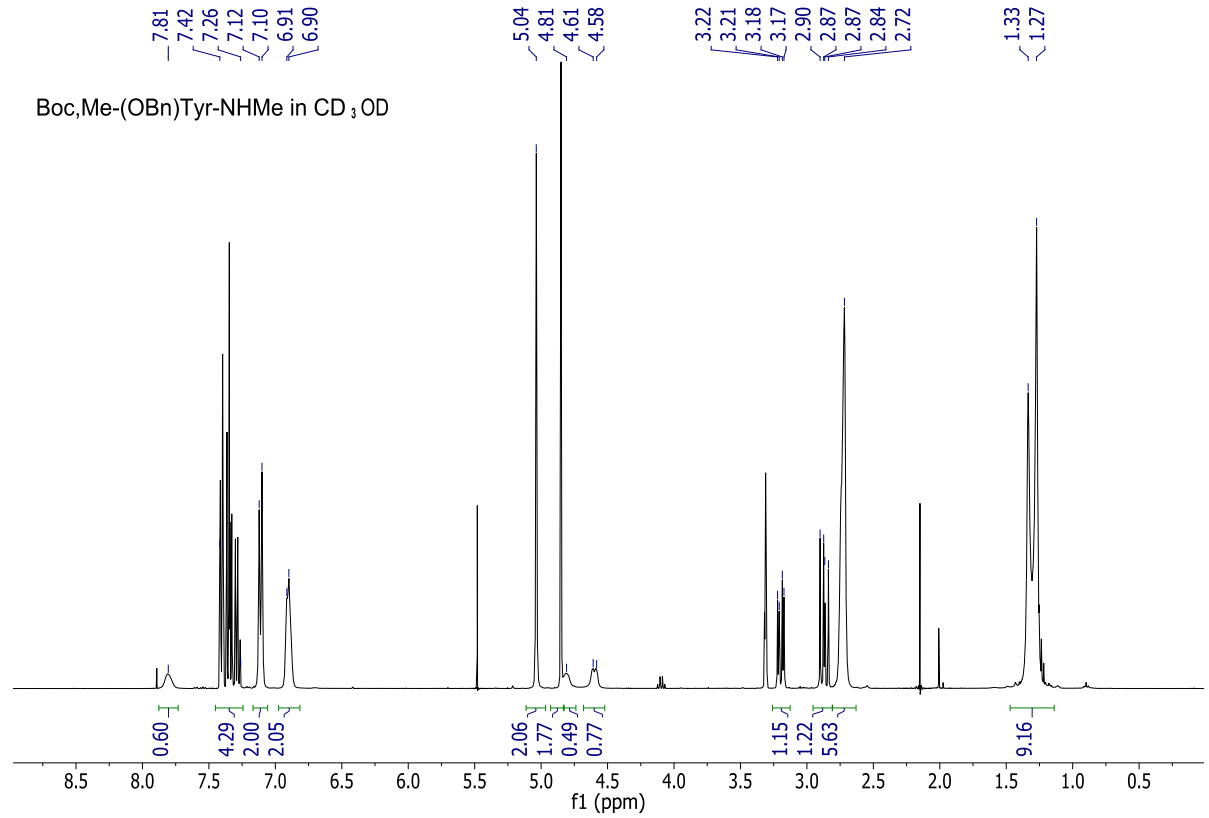


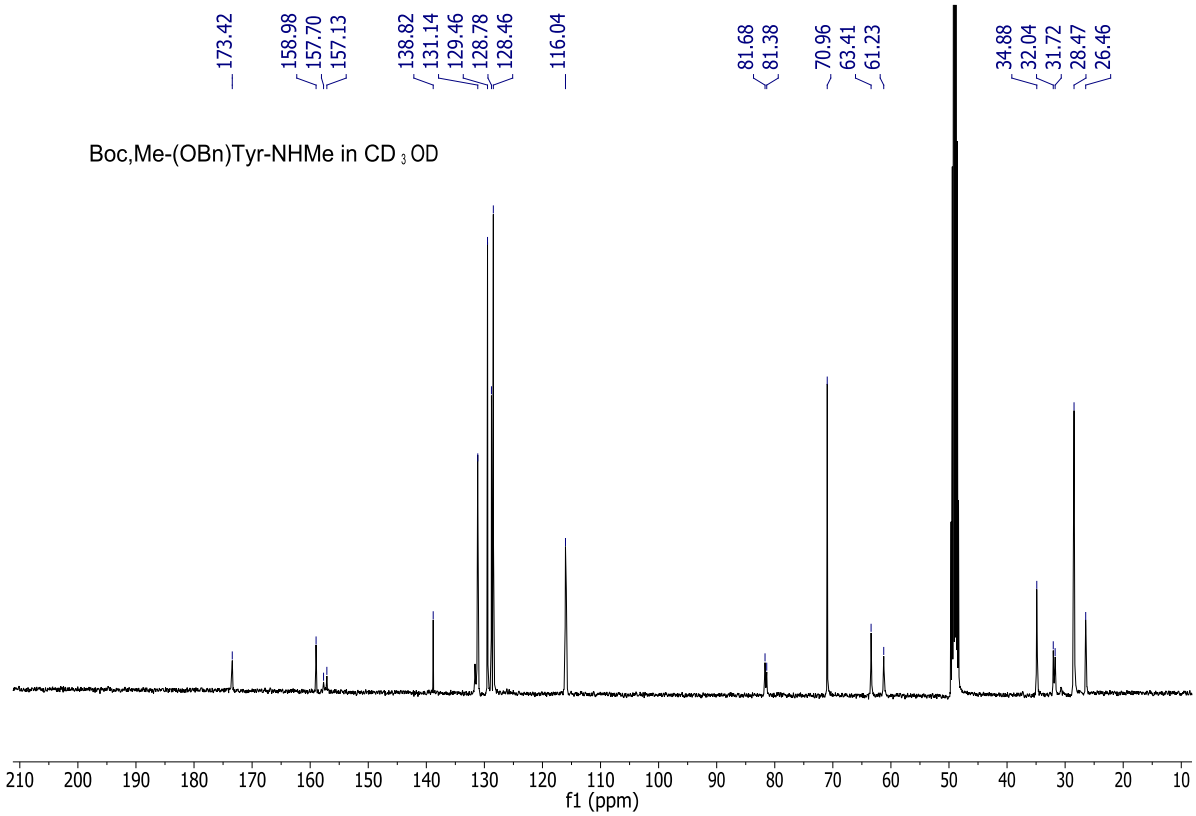


^{1}H and ^{13}C NMR spectra of **2c**.

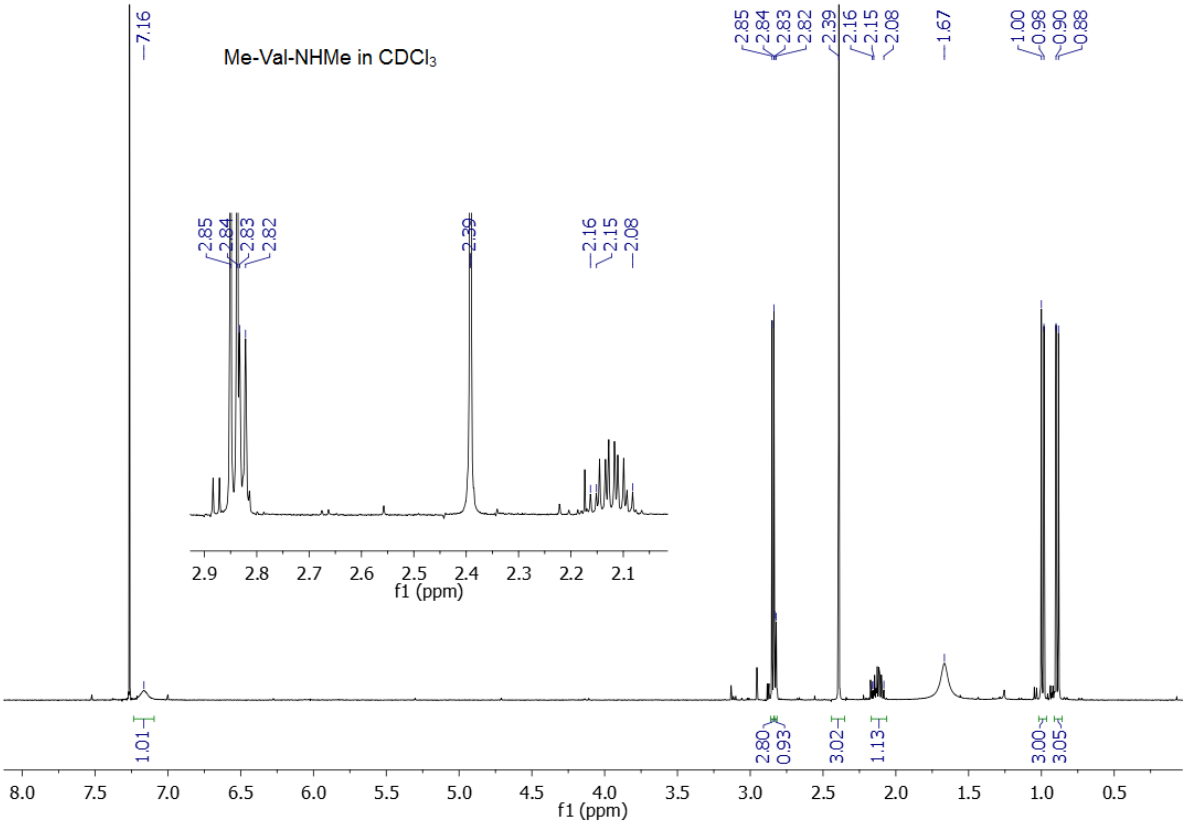


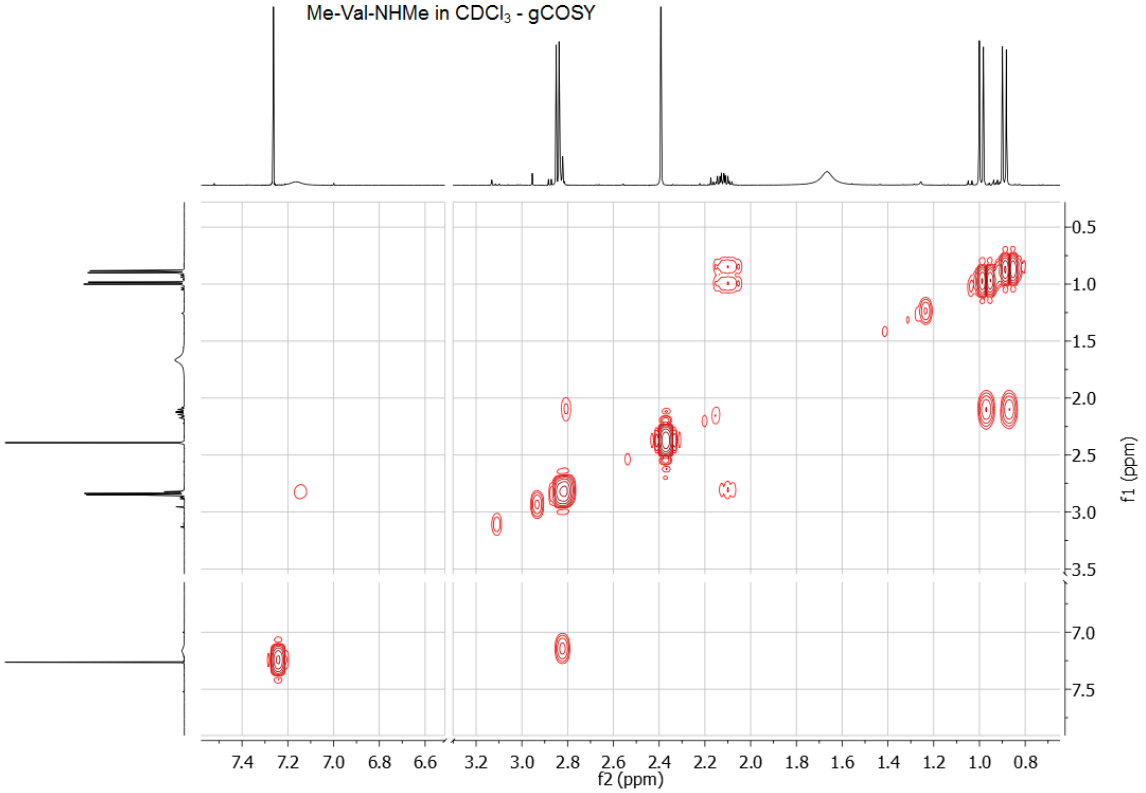
^{1}H and ^{13}C NMR spectra of **2d**.

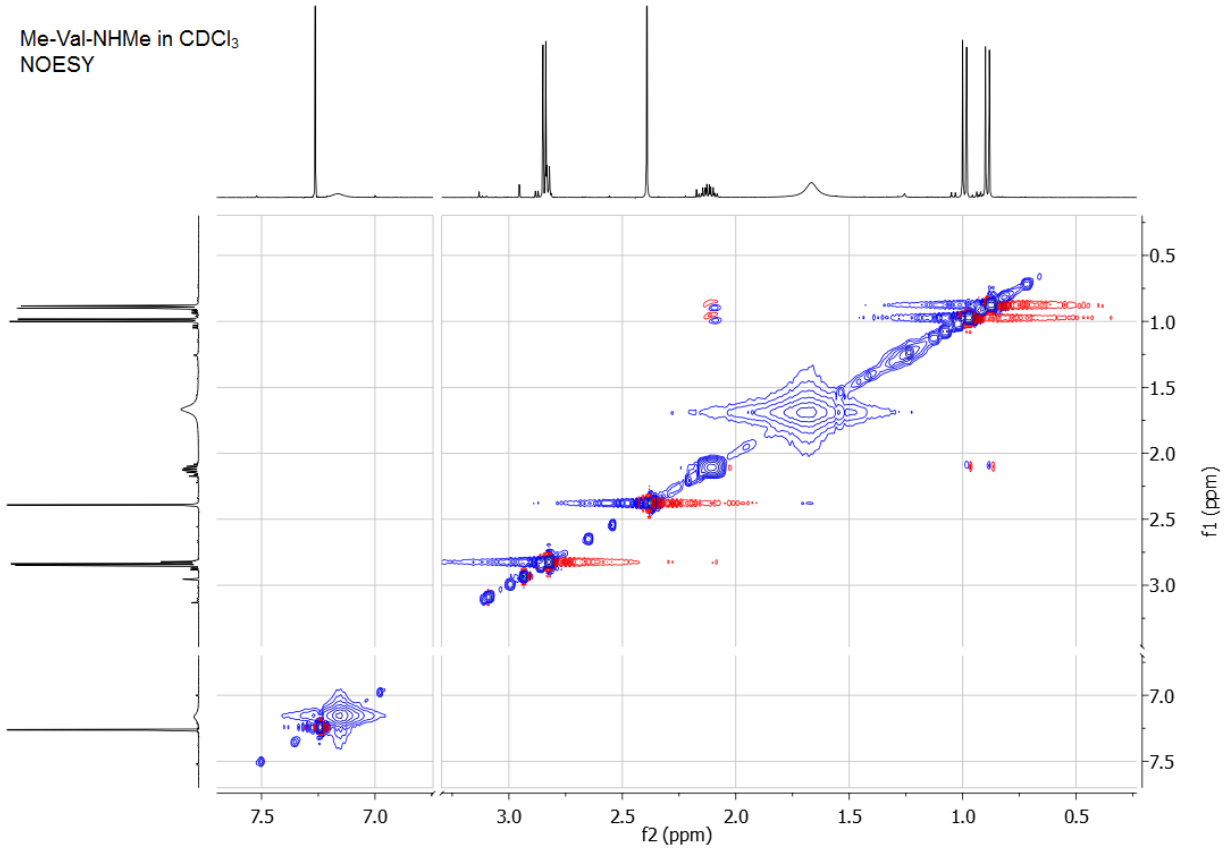


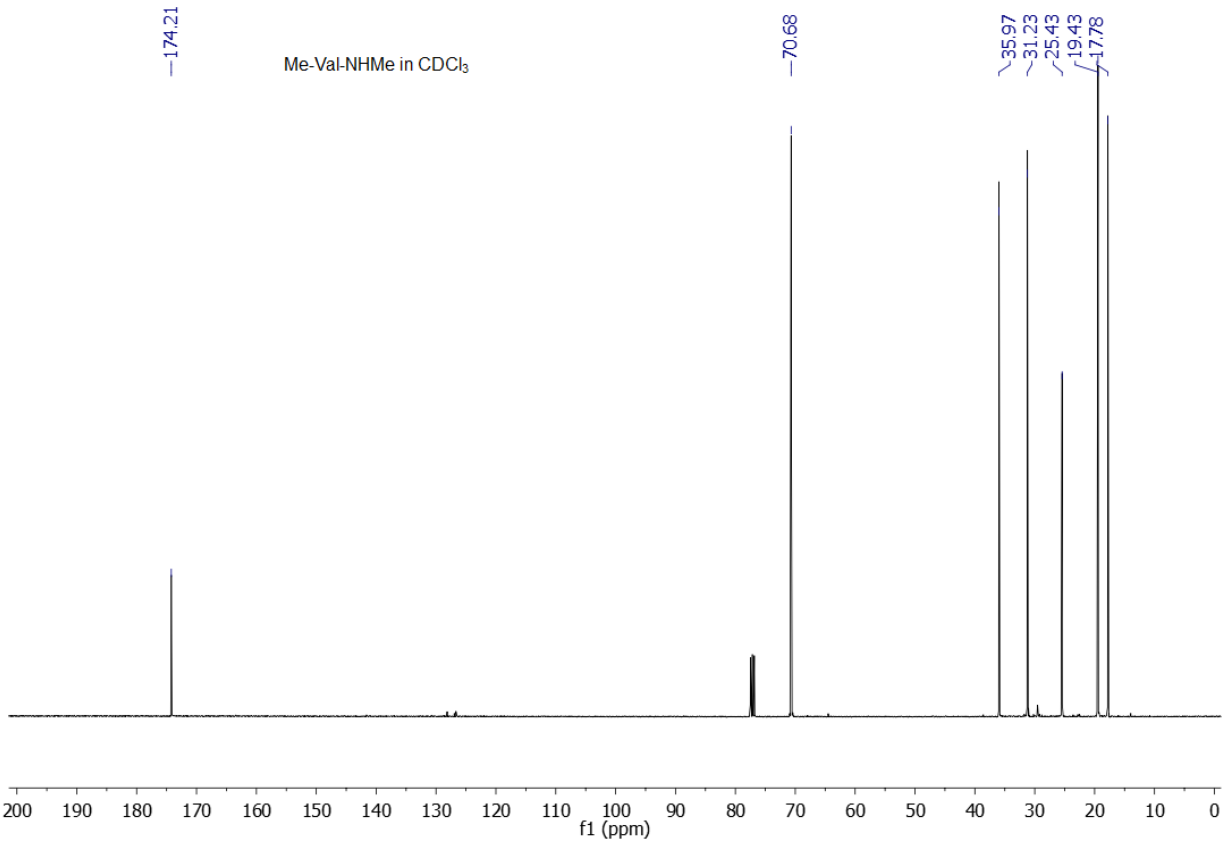


^{1}H, gCOSY, gNOESY and ^{13}C NMR spectra of **3a** in $CDCl_3$

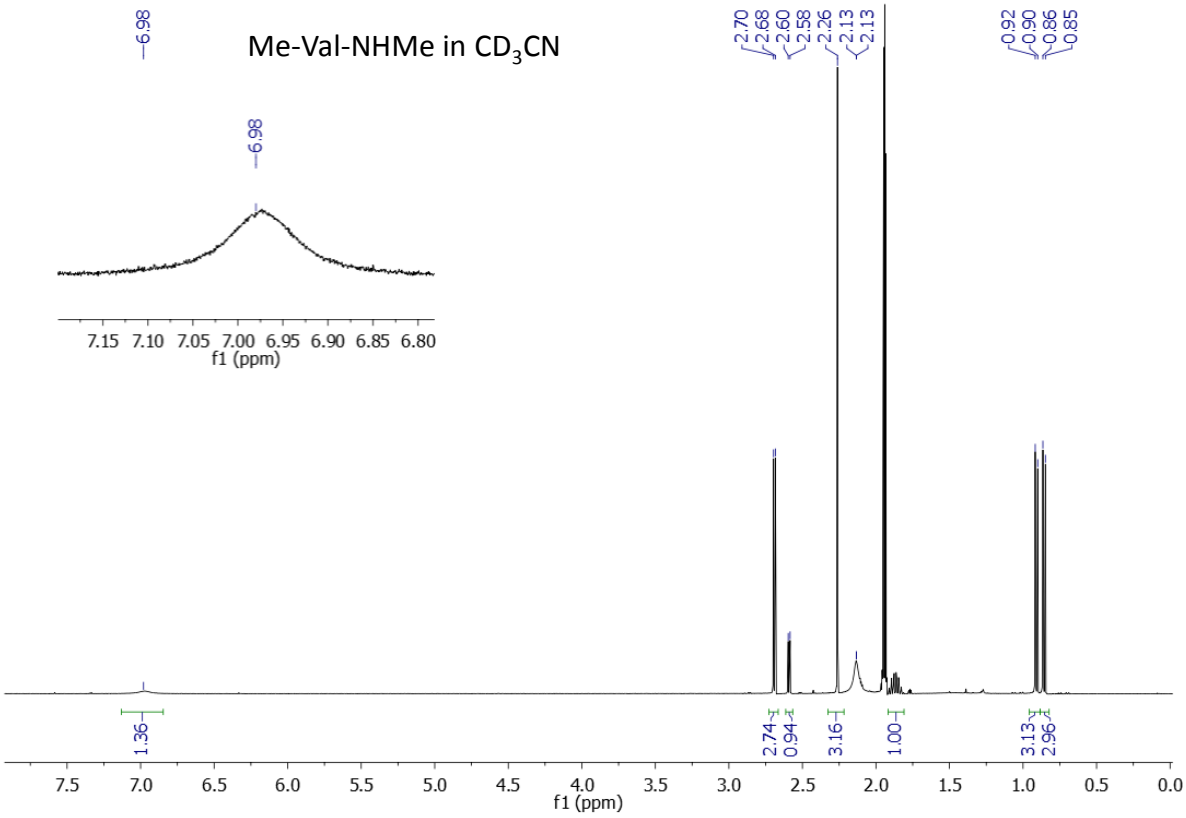


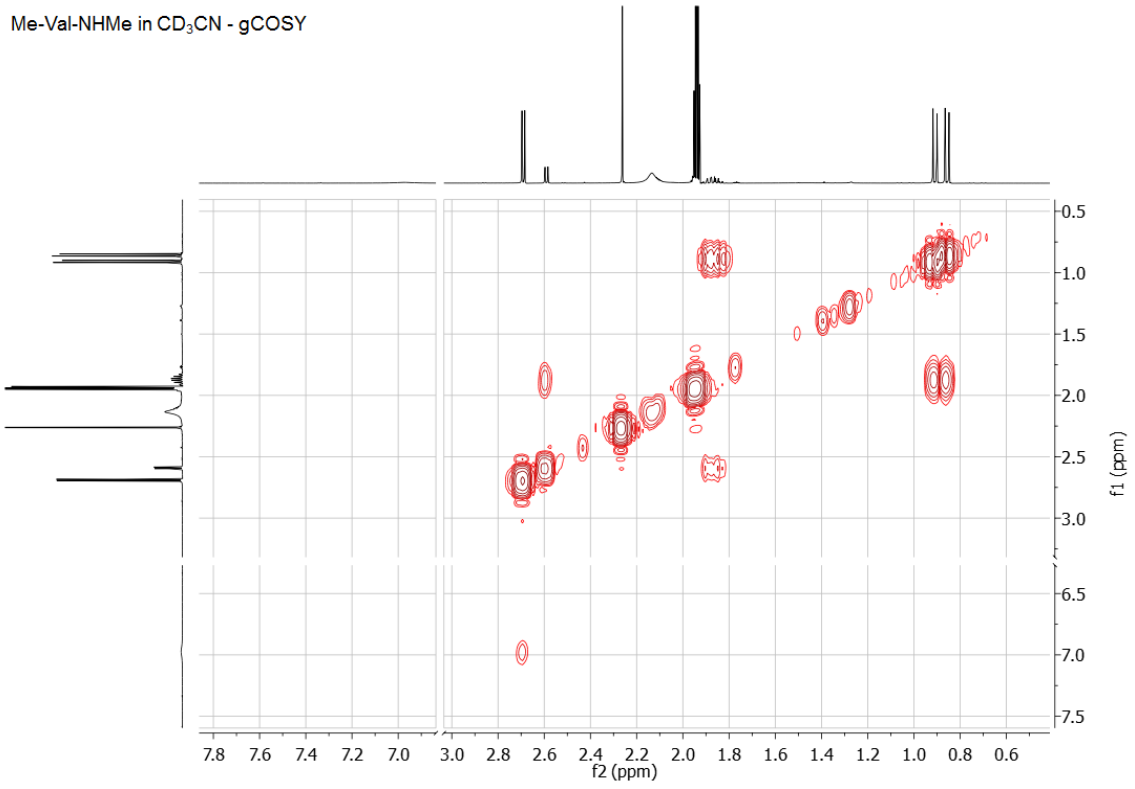


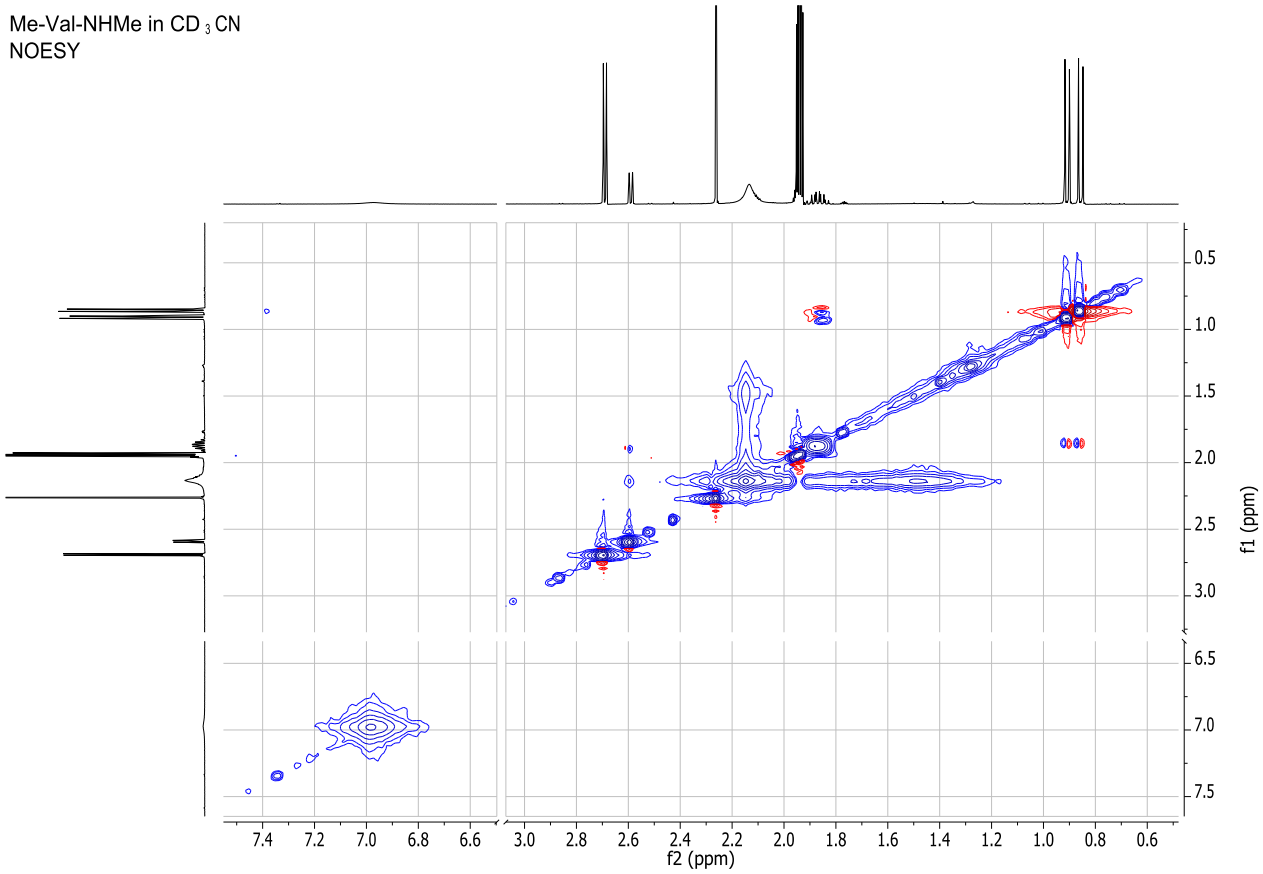




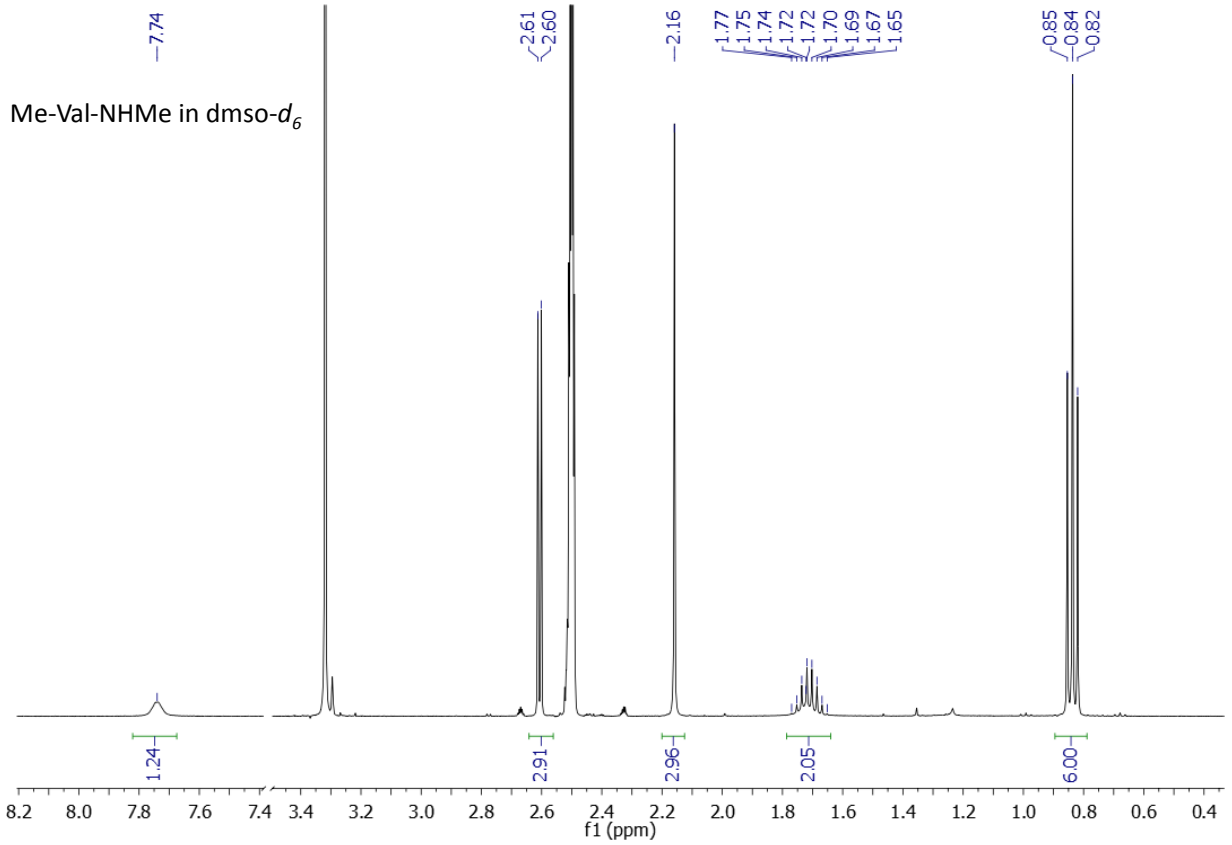
^{1}H, gCOSY and gNOESY NMR spectra of **3a** in CD_3CN

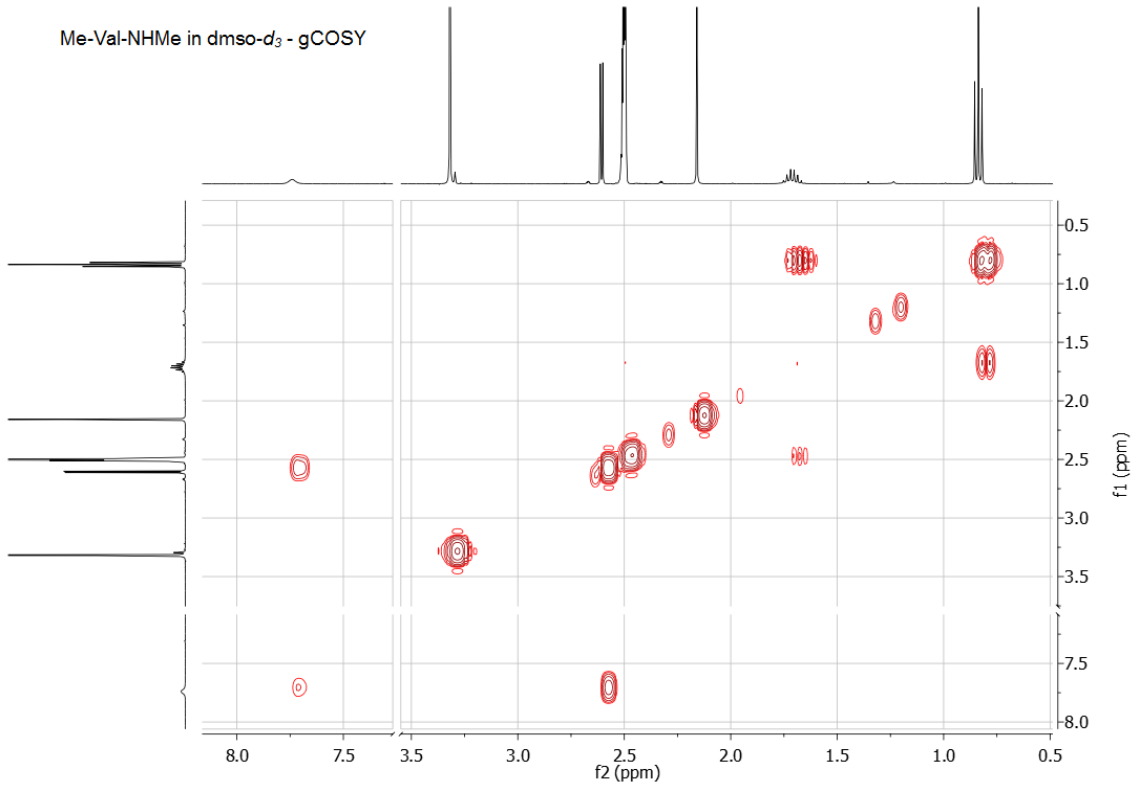


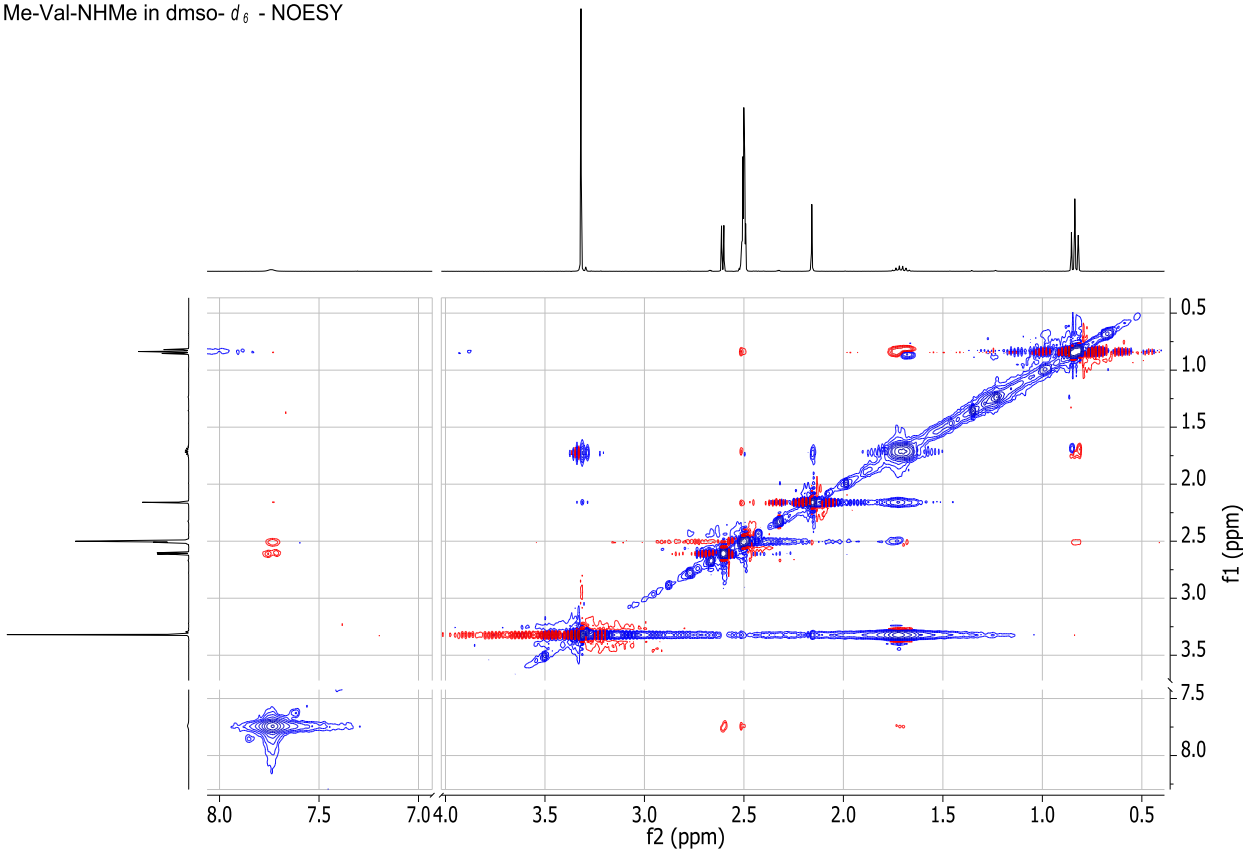




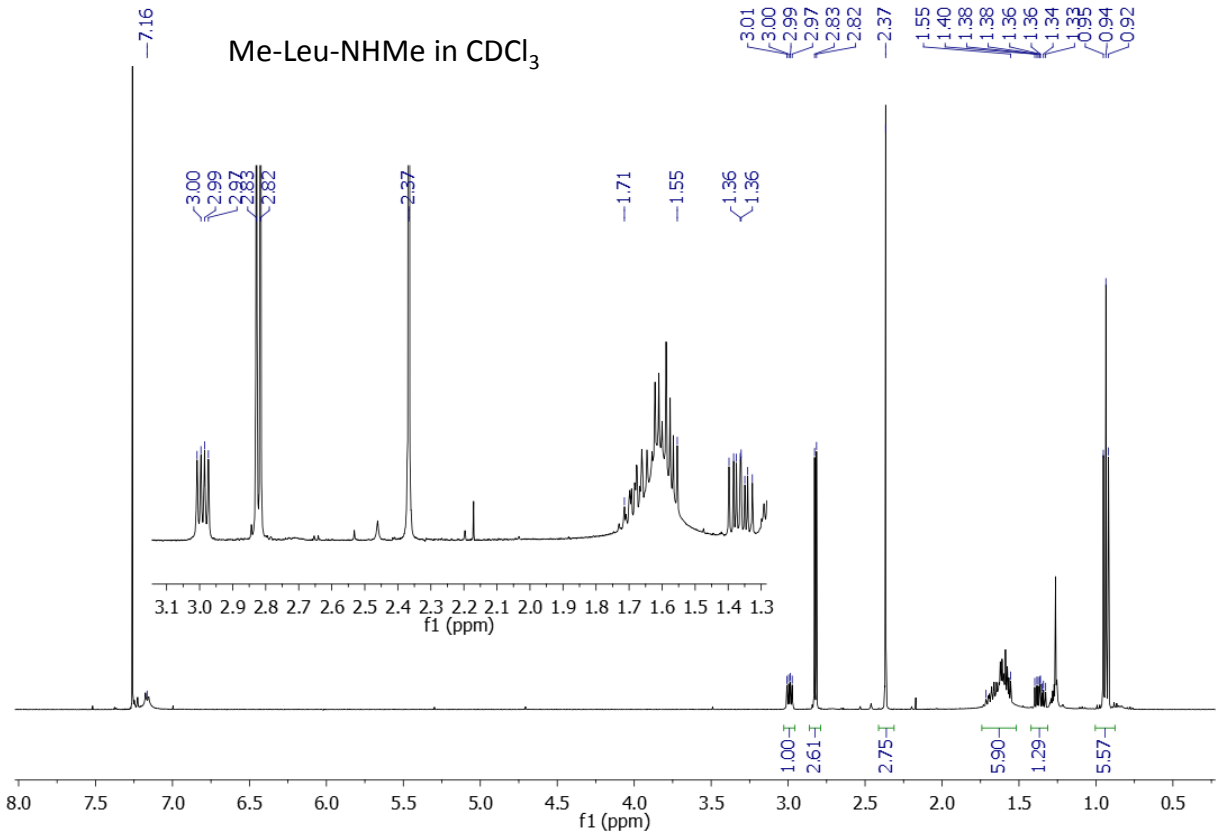
^{1}H, gCOSY and gNOESY NMR spectra of **3a** in dmso-d_6

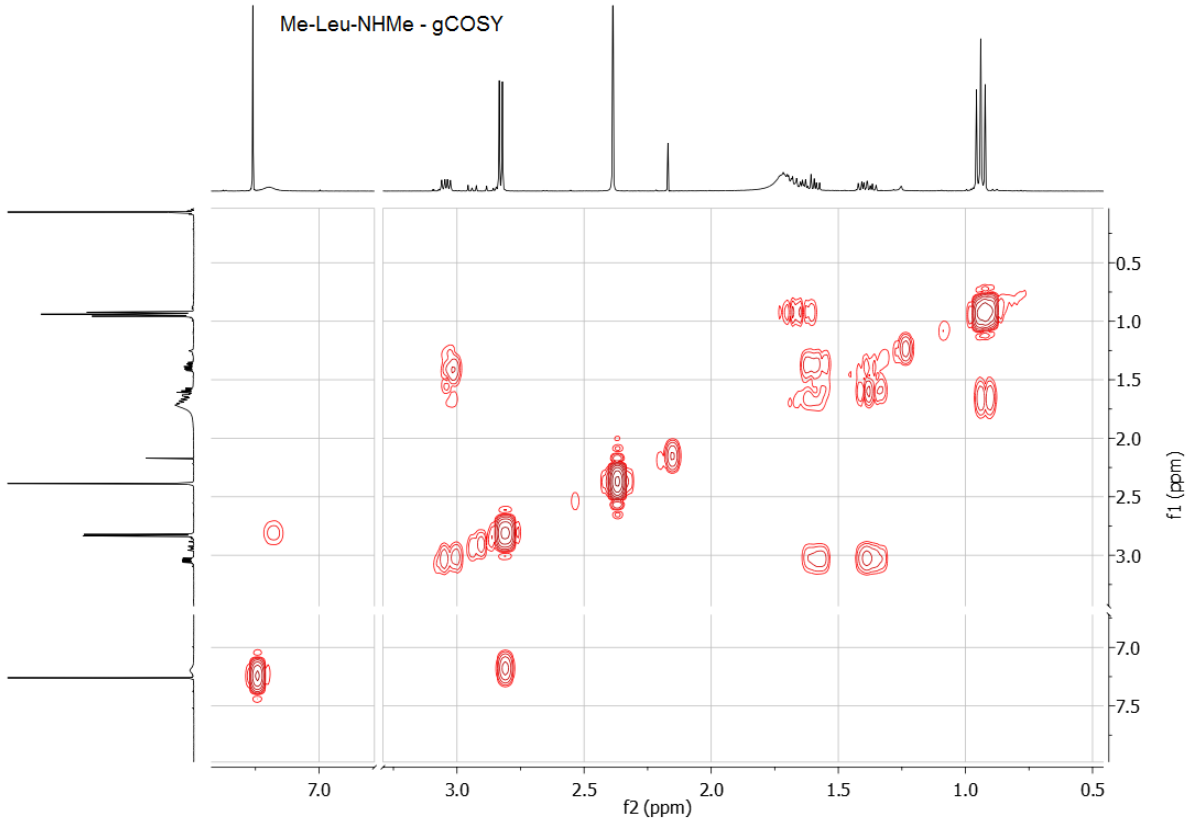


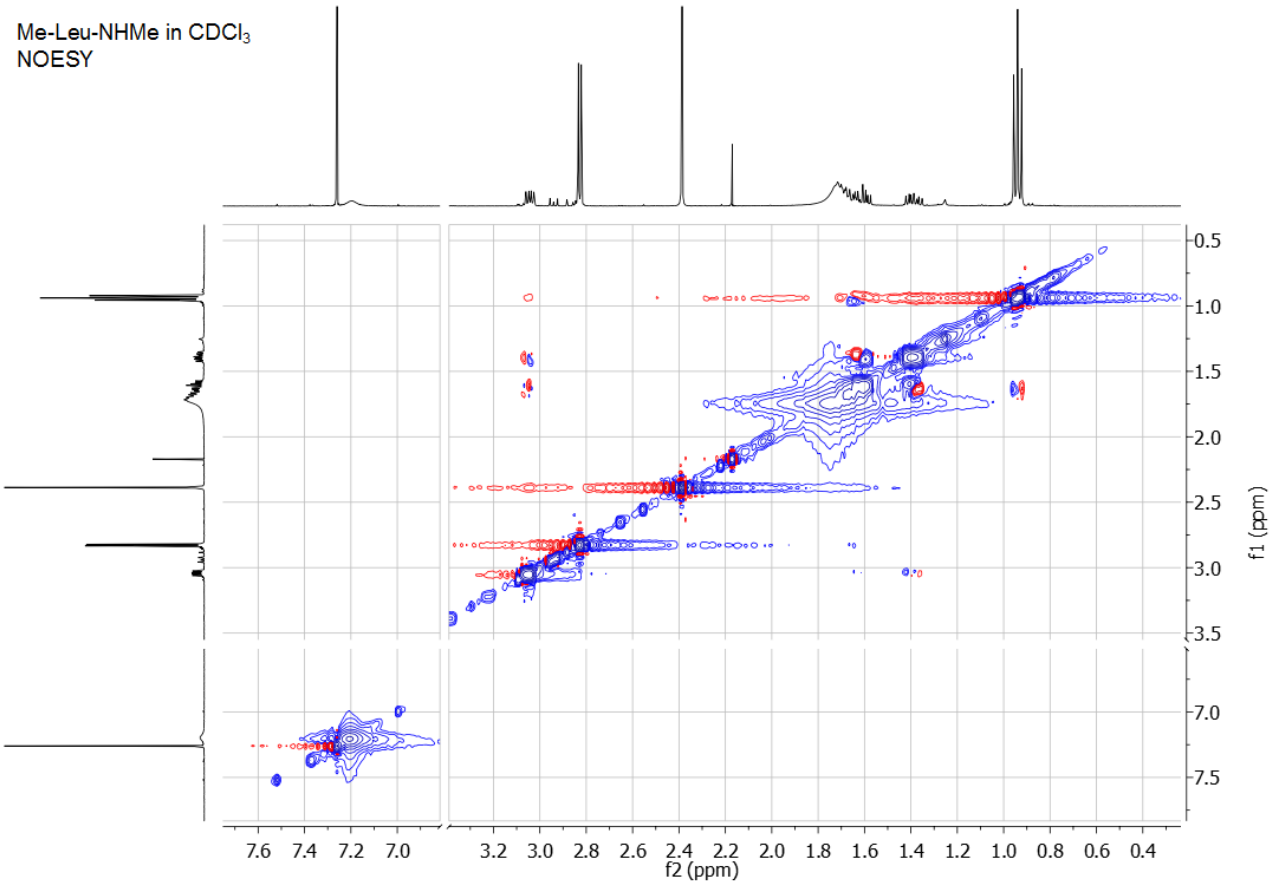


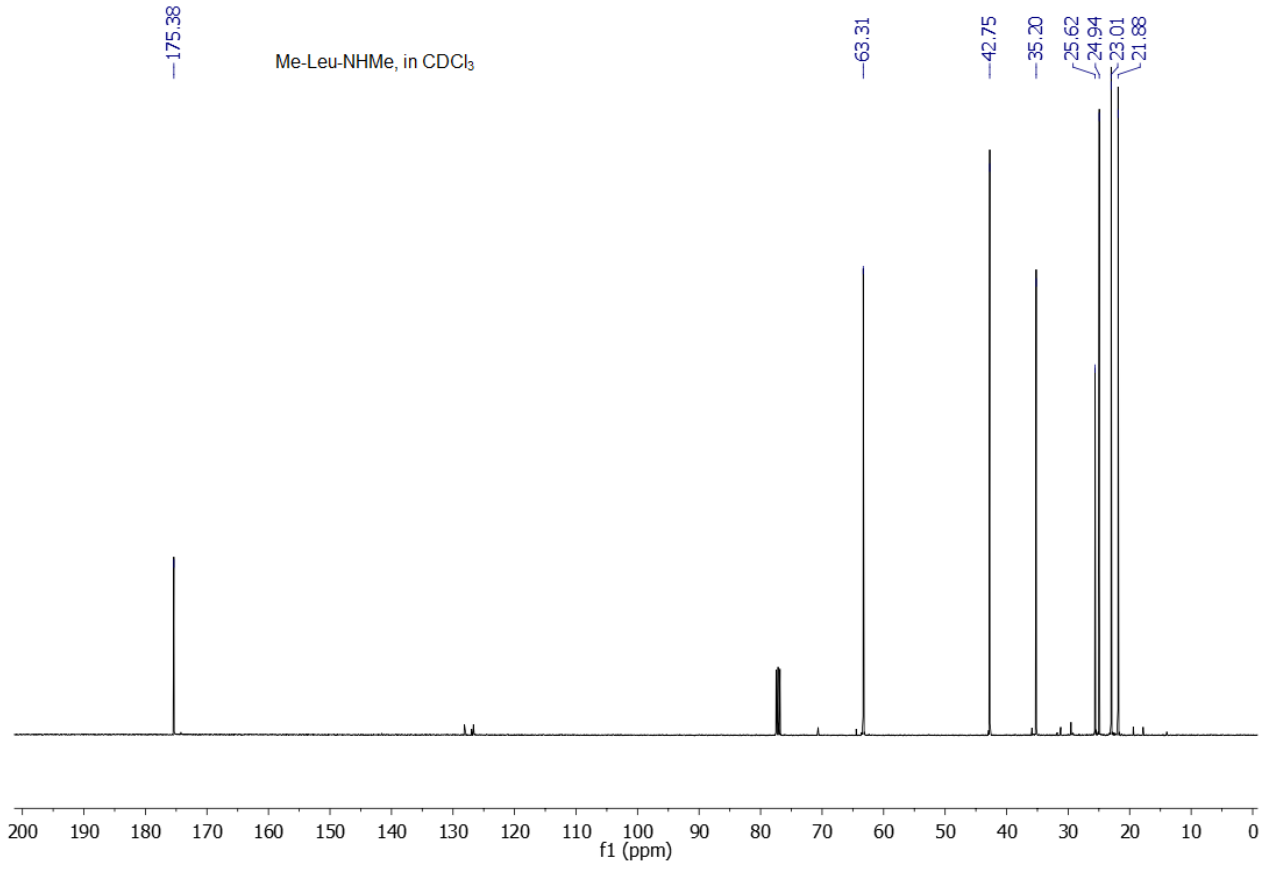


^{1}H, gCOSY, gNOESY and ^{13}C NMR spectra of **3b** in $CDCl_3$

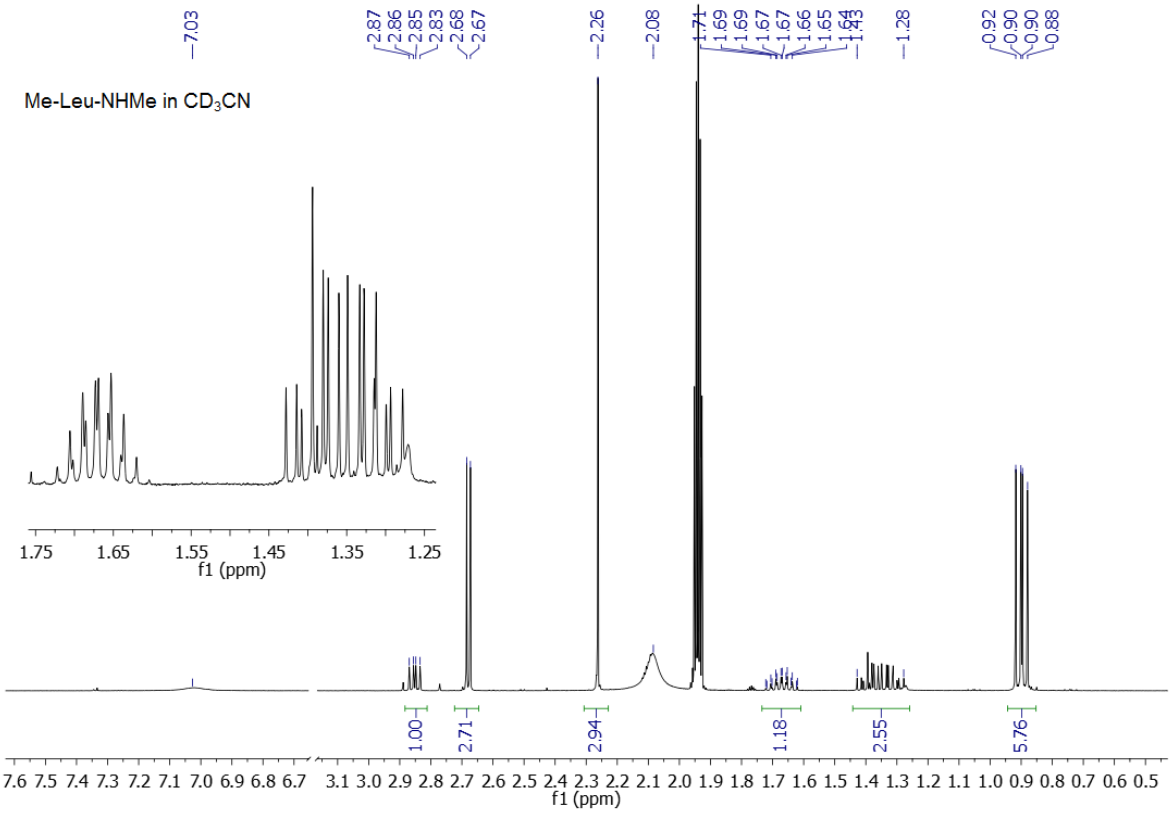


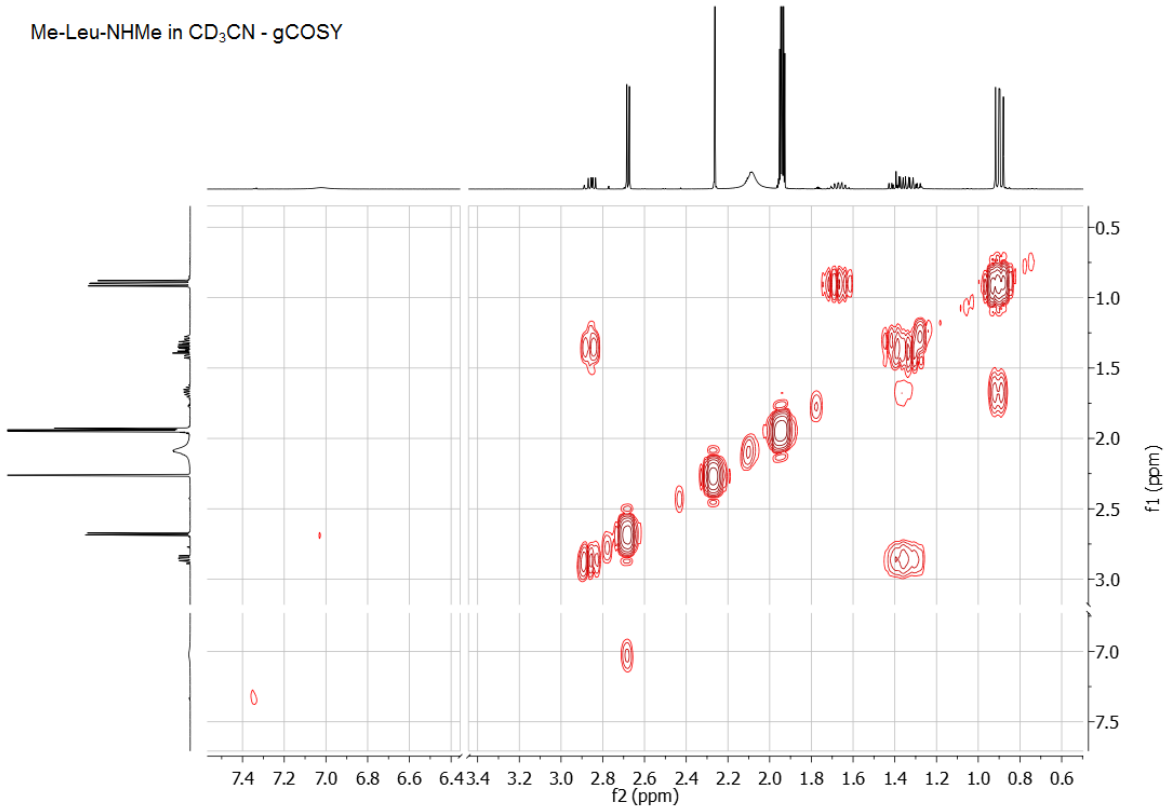


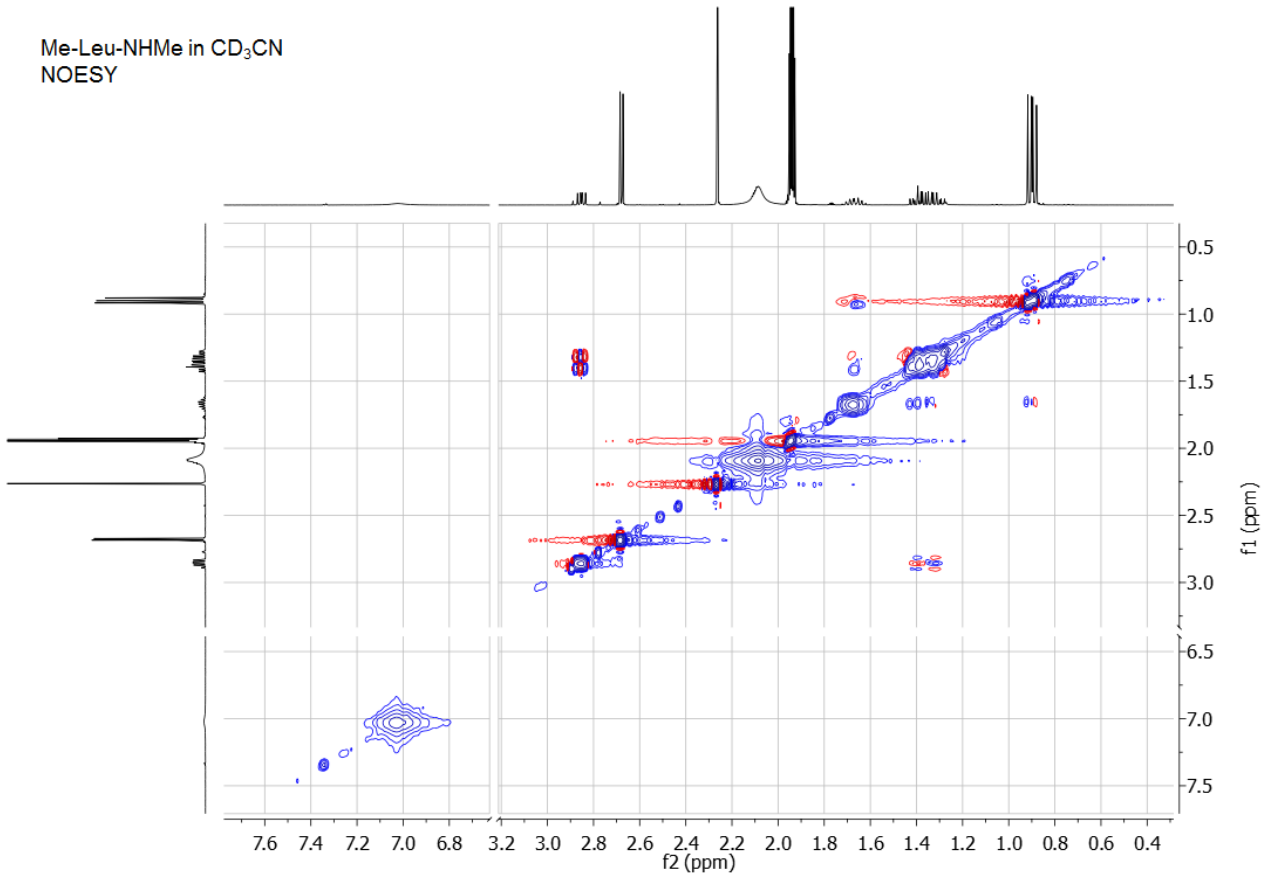

Me-Leu-NHMe in CDCl3
NOESY
f1 (ppm)
f2 (ppm)


Me-Leu-NHMe, in CDCl3
175.38
63.31
42.75
35.20
25.62
24.94
23.01
21.88
f1 (ppm)

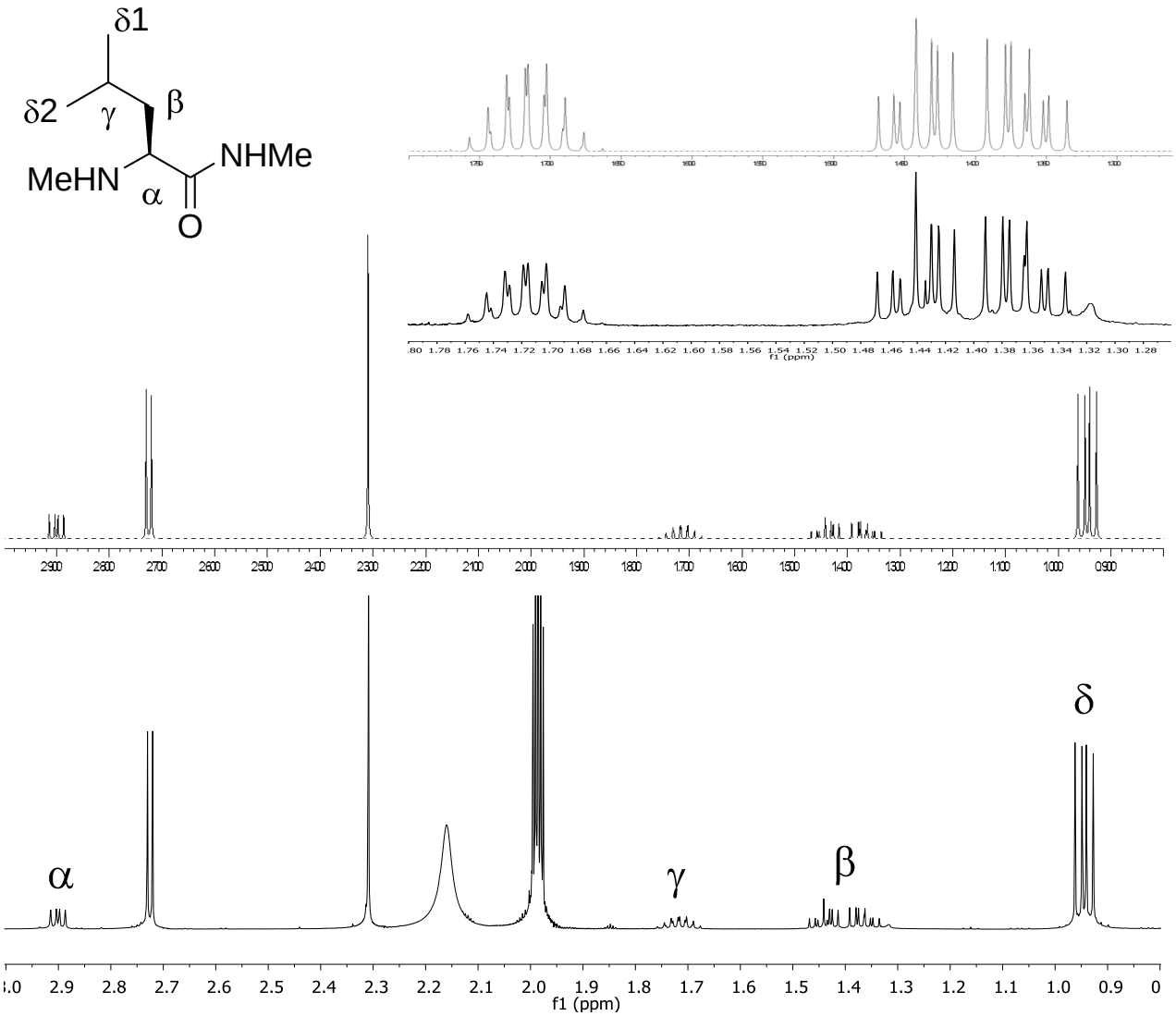
^{1}H, gCOSY and gNOESY NMR spectra of **3b** in CD_3CN



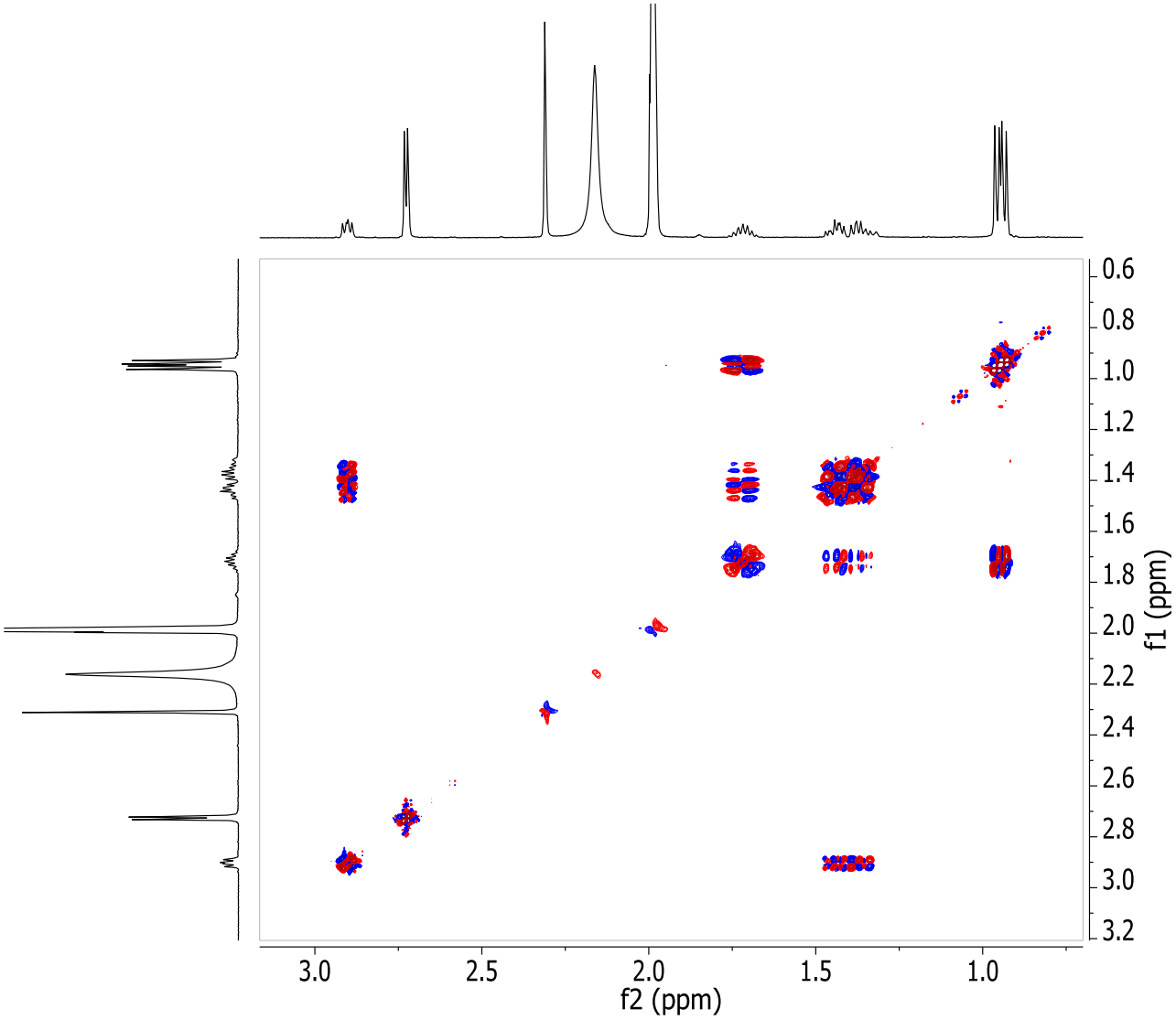



Me-Leu-NHMe in CD3CN
NOESY
0.5
1.0
1.5
2.0
2.5
3.0
6.5
7.0
7.5
f1 (ppm)
7.6 7.4 7.2 7.0 6.8 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4 1.2 1.0 0.8 0.6 0.4
f2 (ppm)

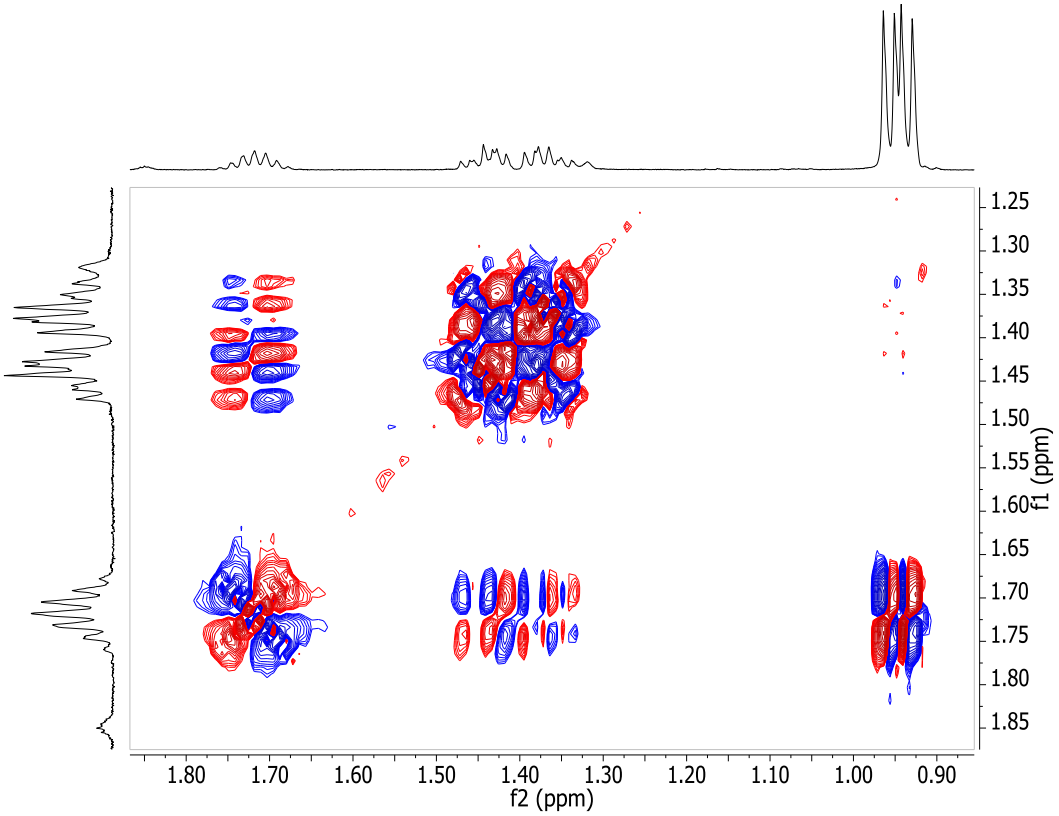
Experimental (down) and simulated (gNMR, up) ^{1}H NMR spectra of **3b** in CD_3CN (500 MHz)

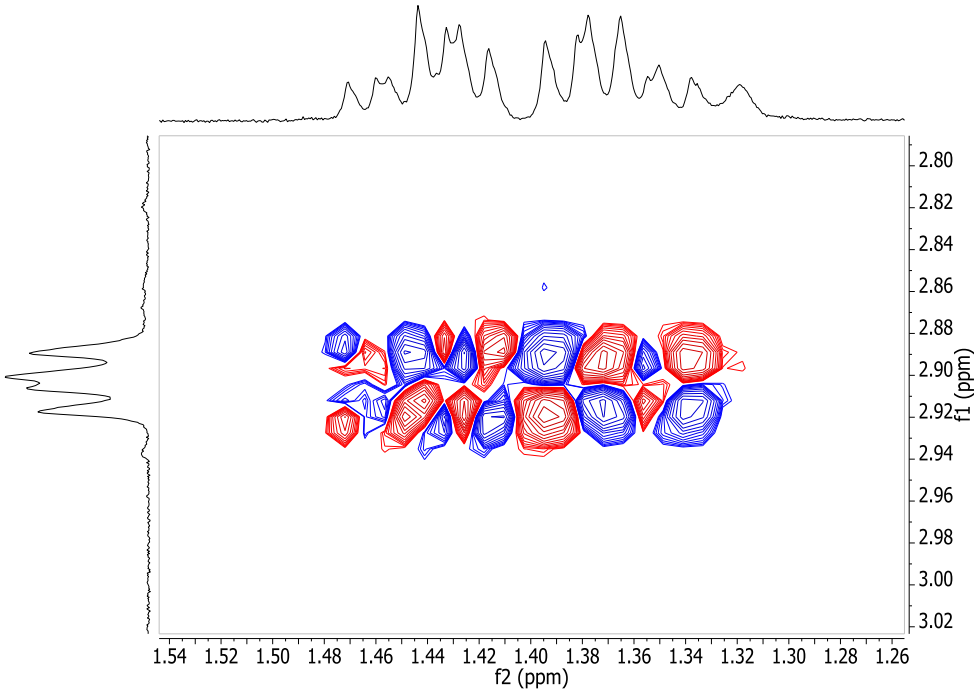


gDQCOSY spectrum of **3b** in CD_3CN (500 MHz)

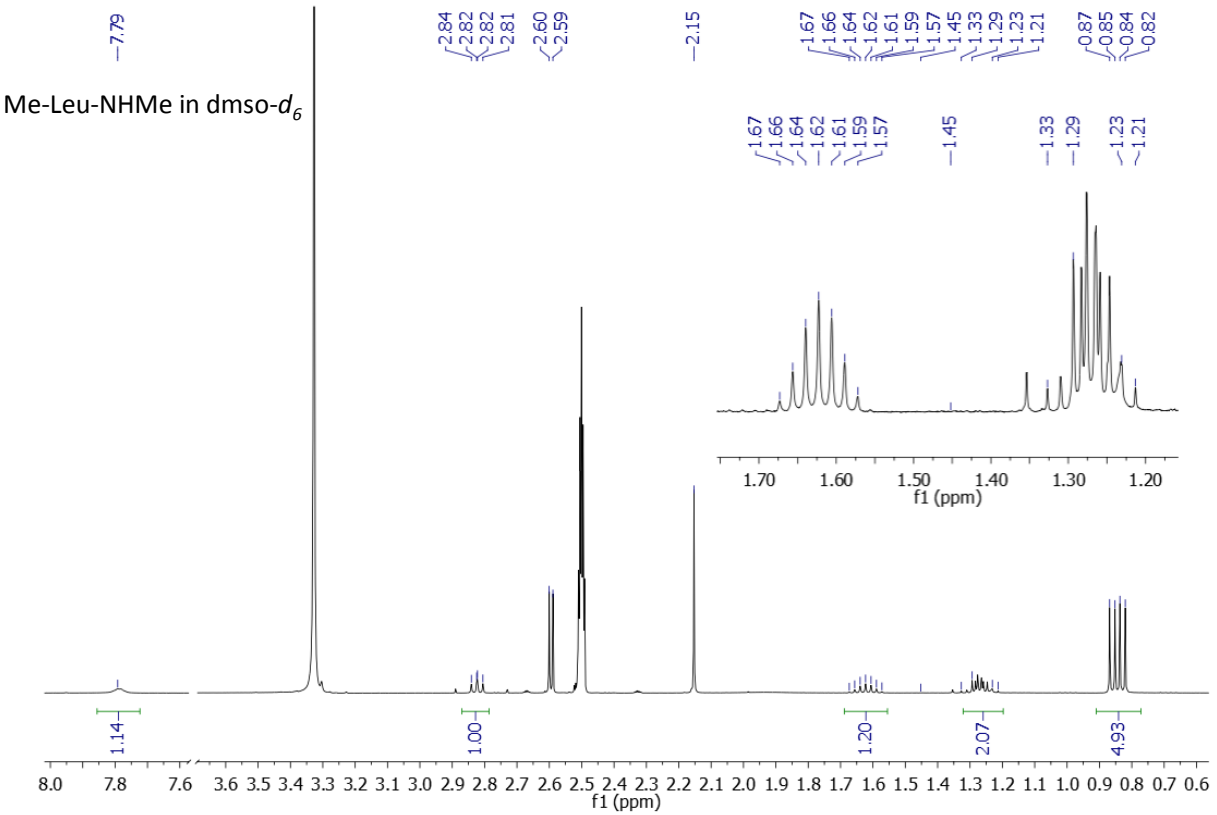


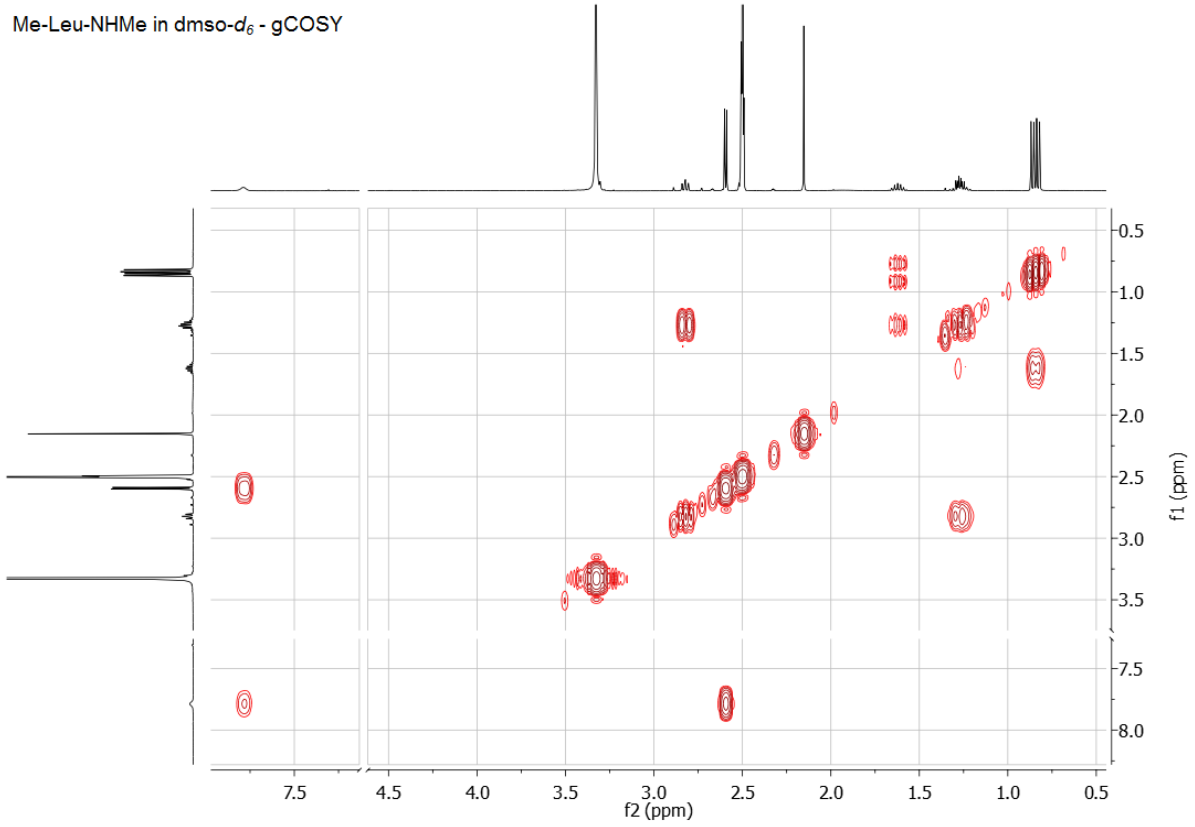
Zoomed regions of the gDQCOSY spectrum of **3b** in CD_3CN (500 MHz)

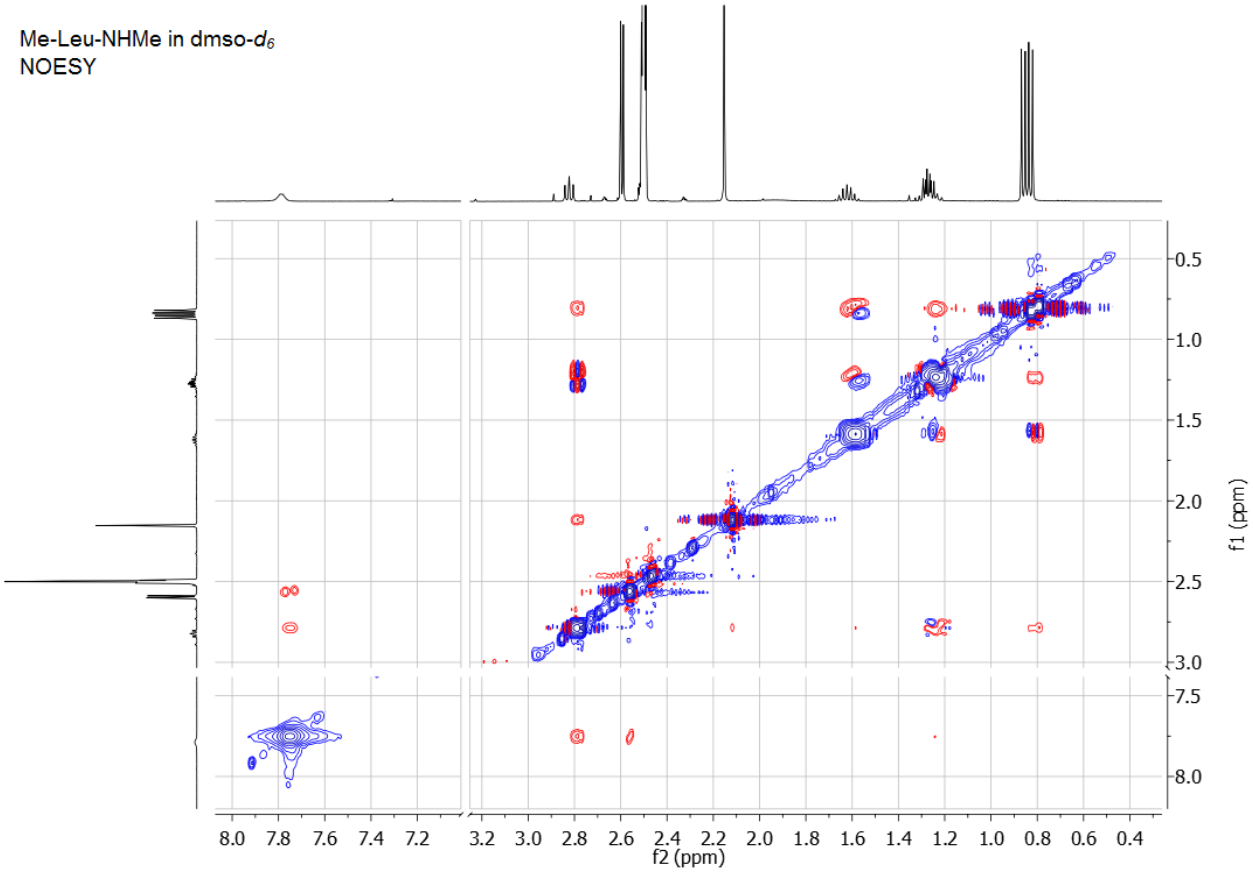




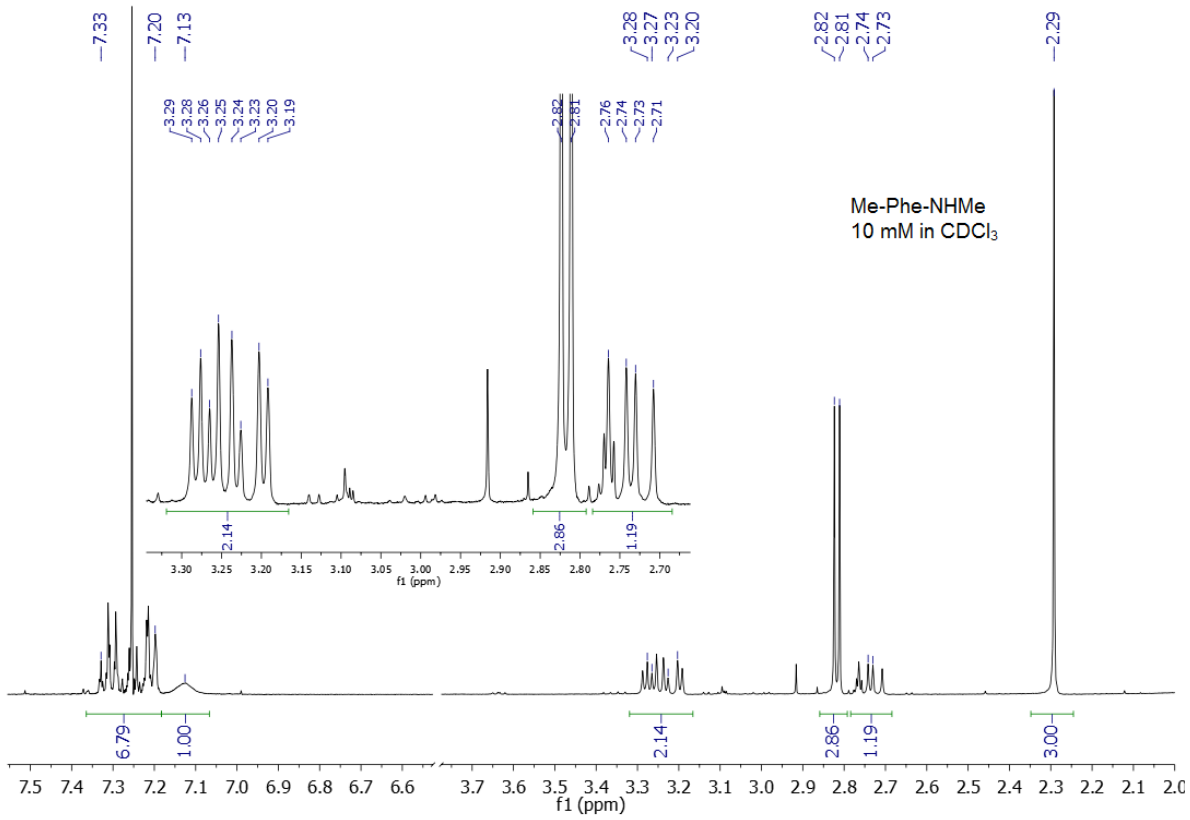
^{1}H, gCOSY and gNOESY NMR spectra of **3b** in dmso-d6

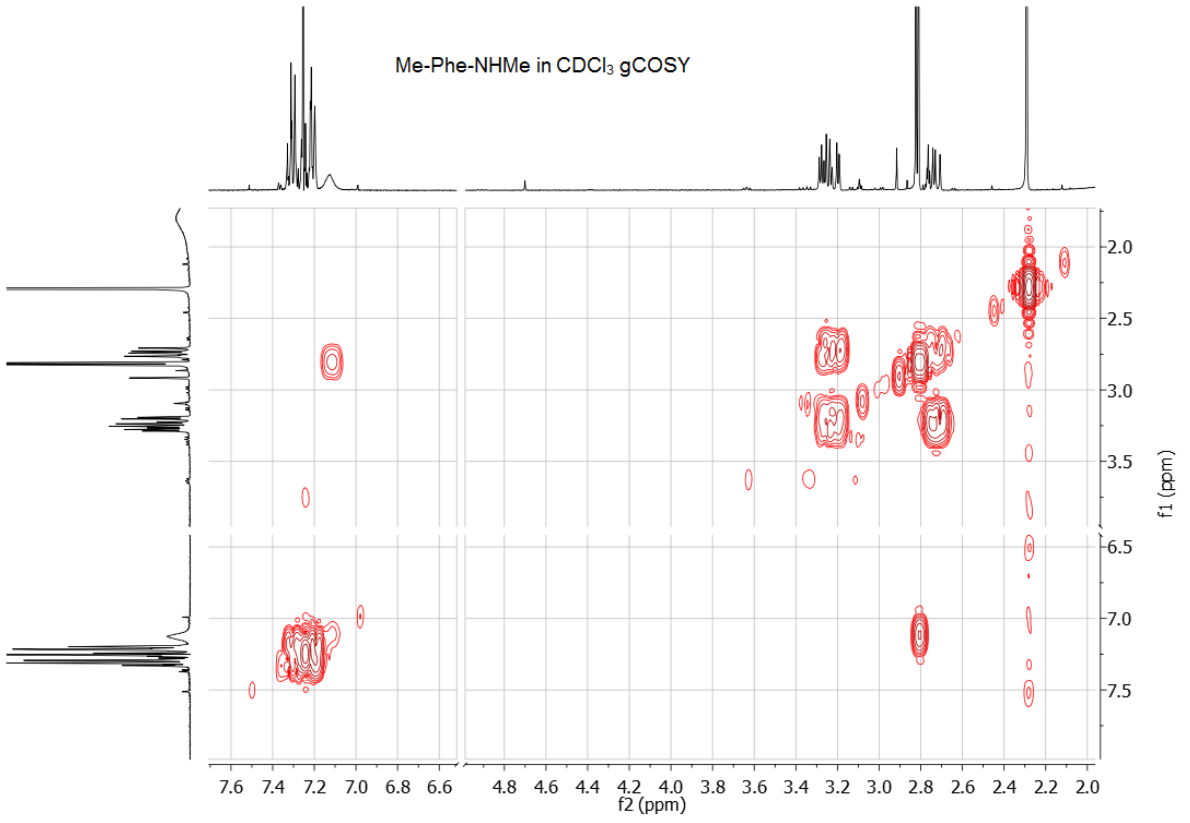


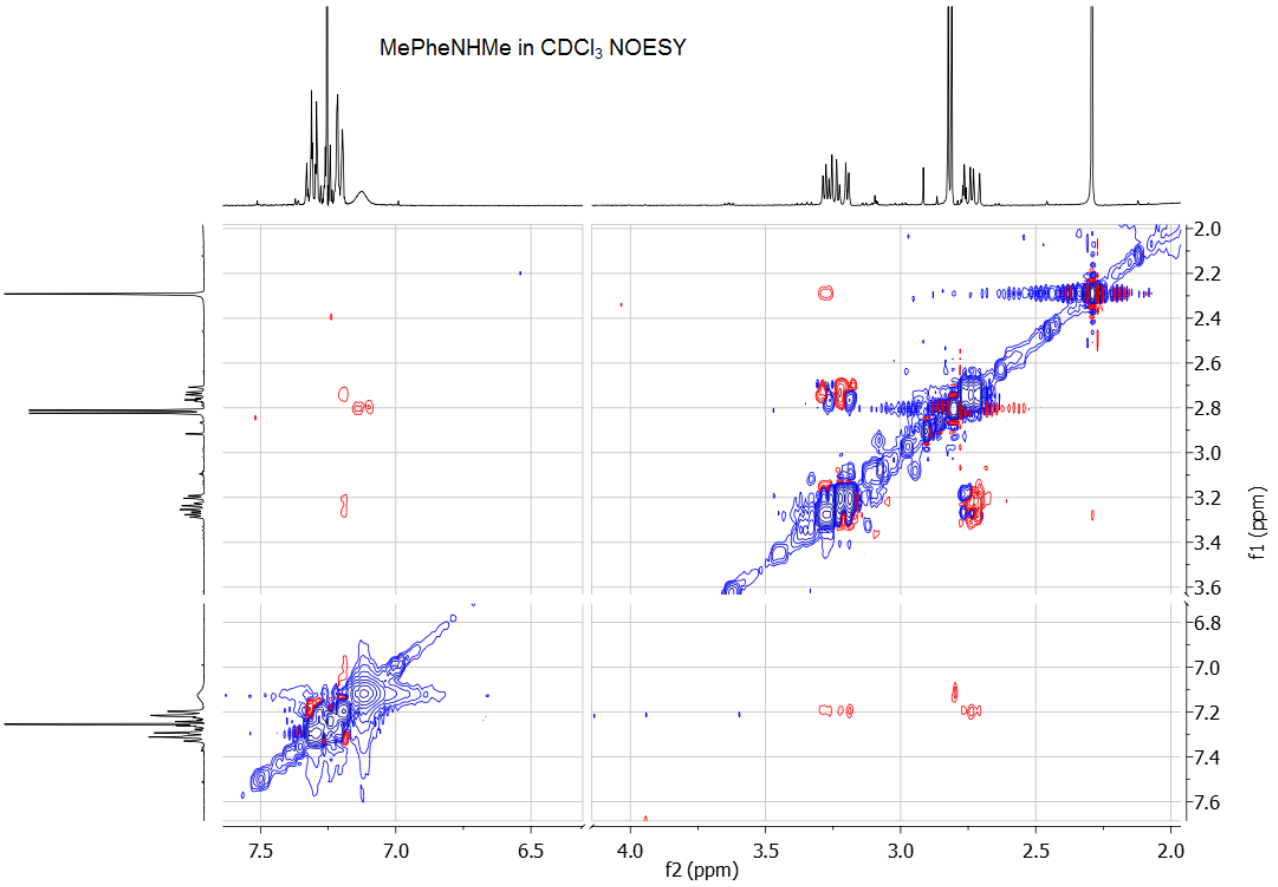


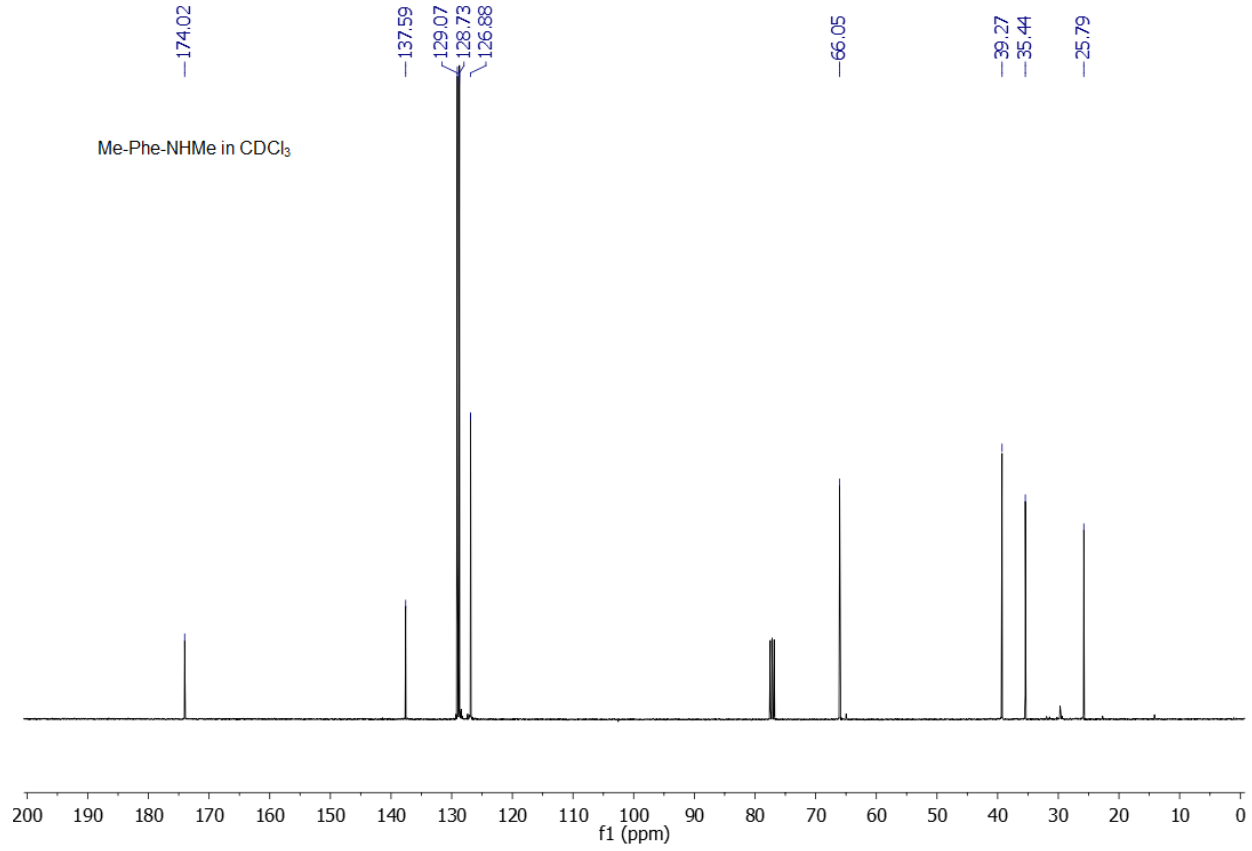


^{1}H, gCOSY, gNOESY and ^{13}C NMR spectra of **3c** in $CDCl_3$

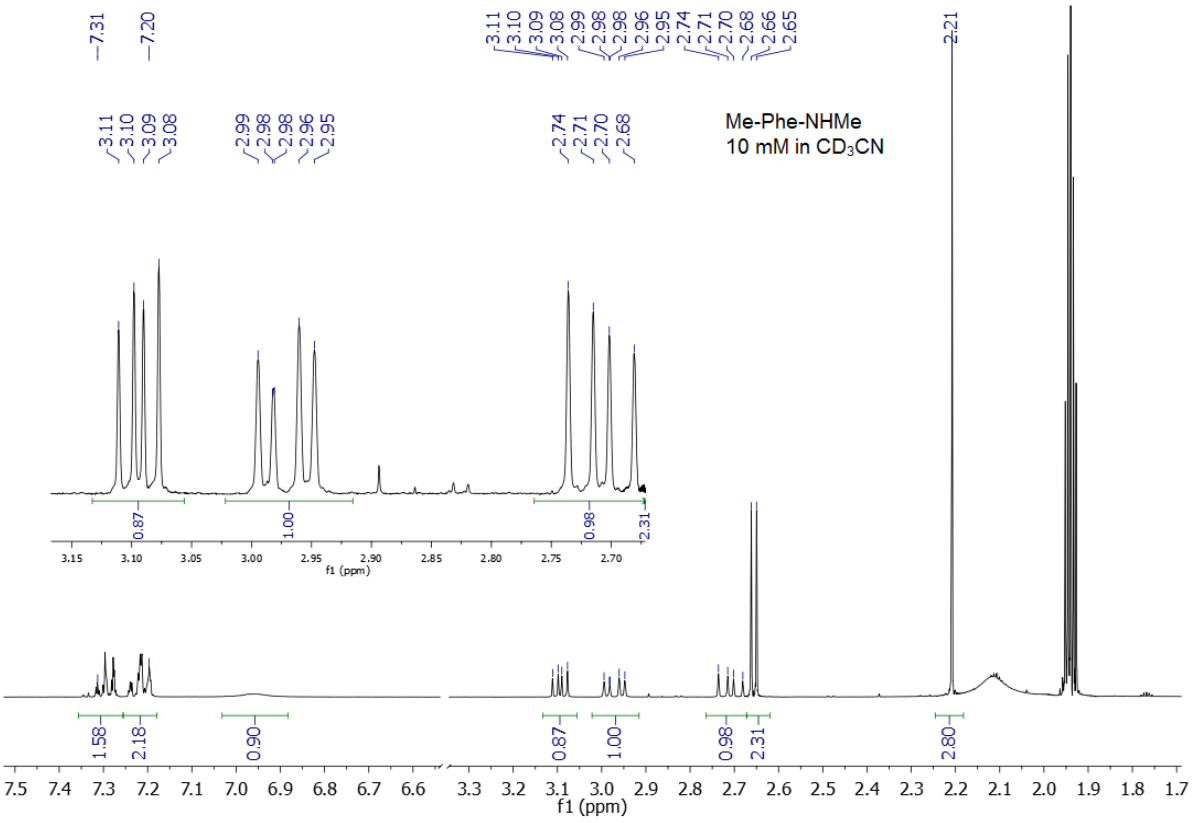


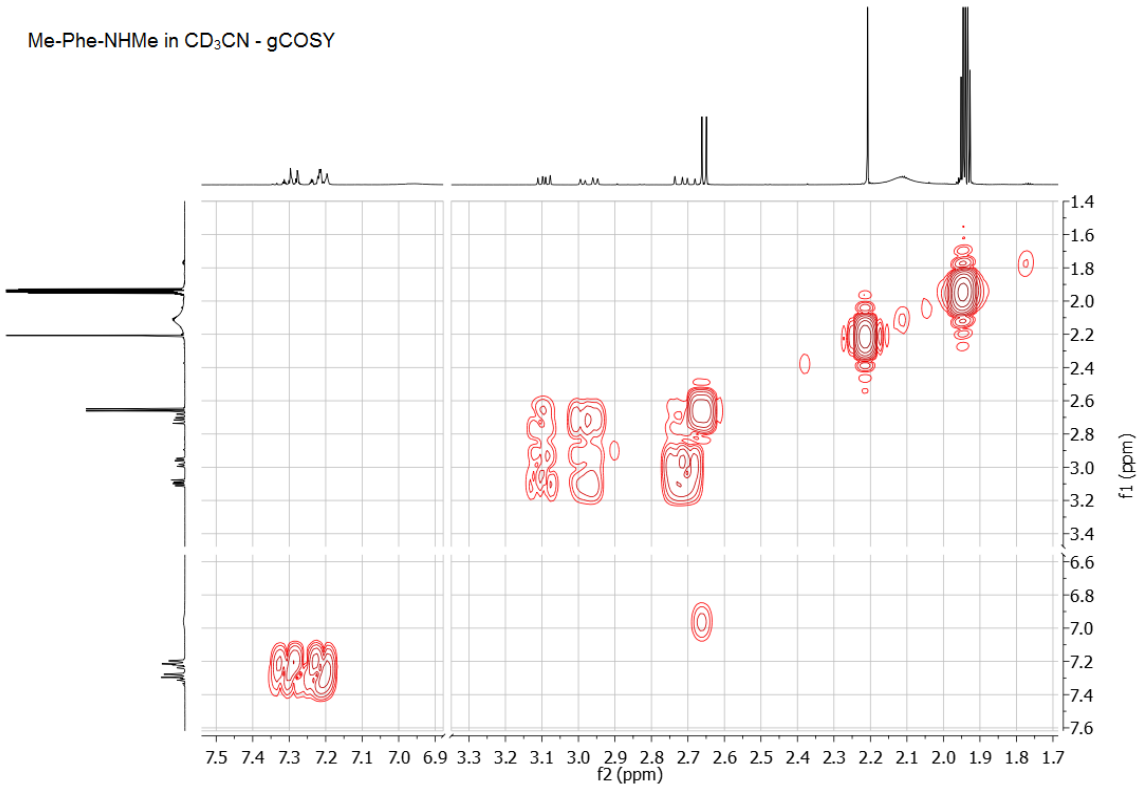


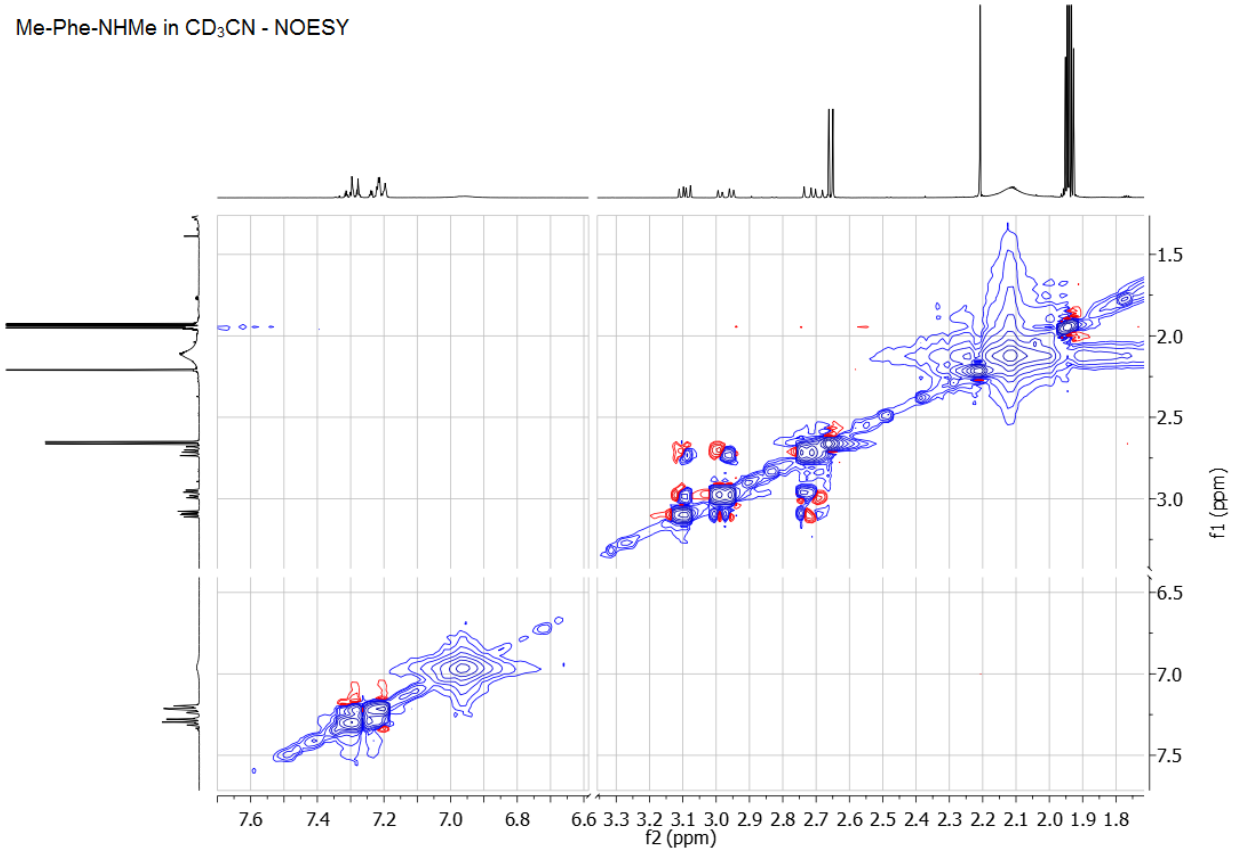




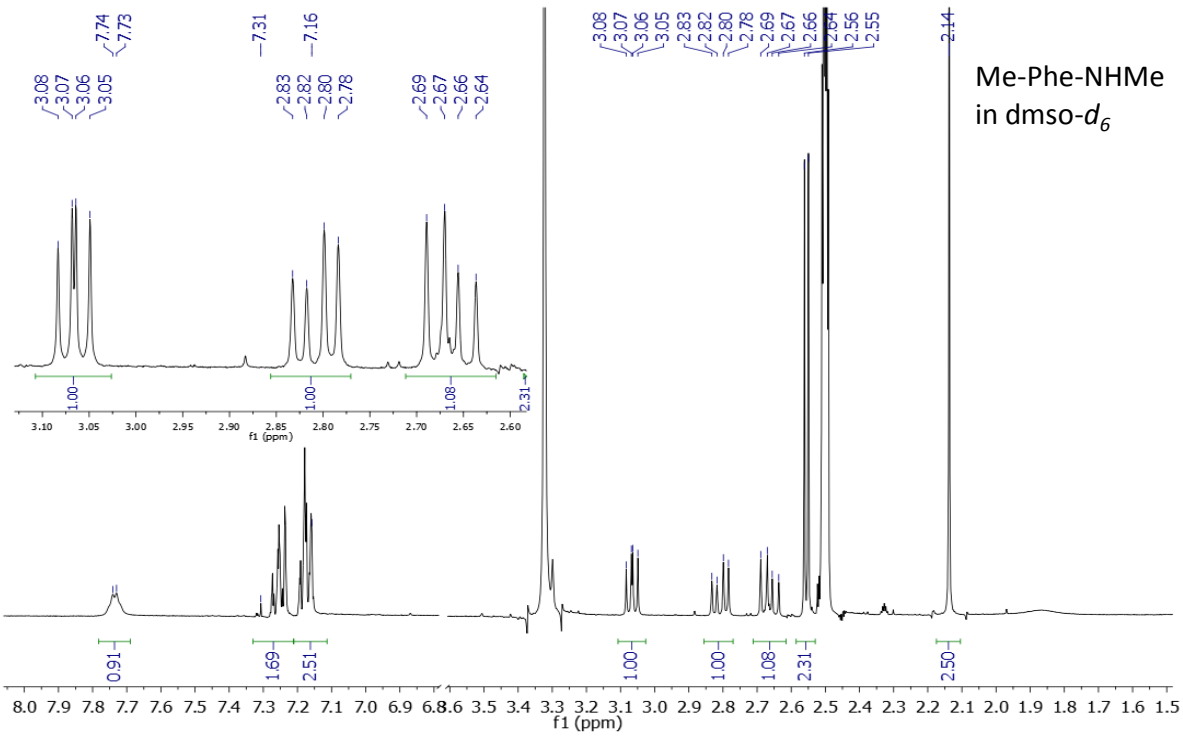
^{1}H, gCOSY and gNOESY spectra of **3c** in CD_3CN

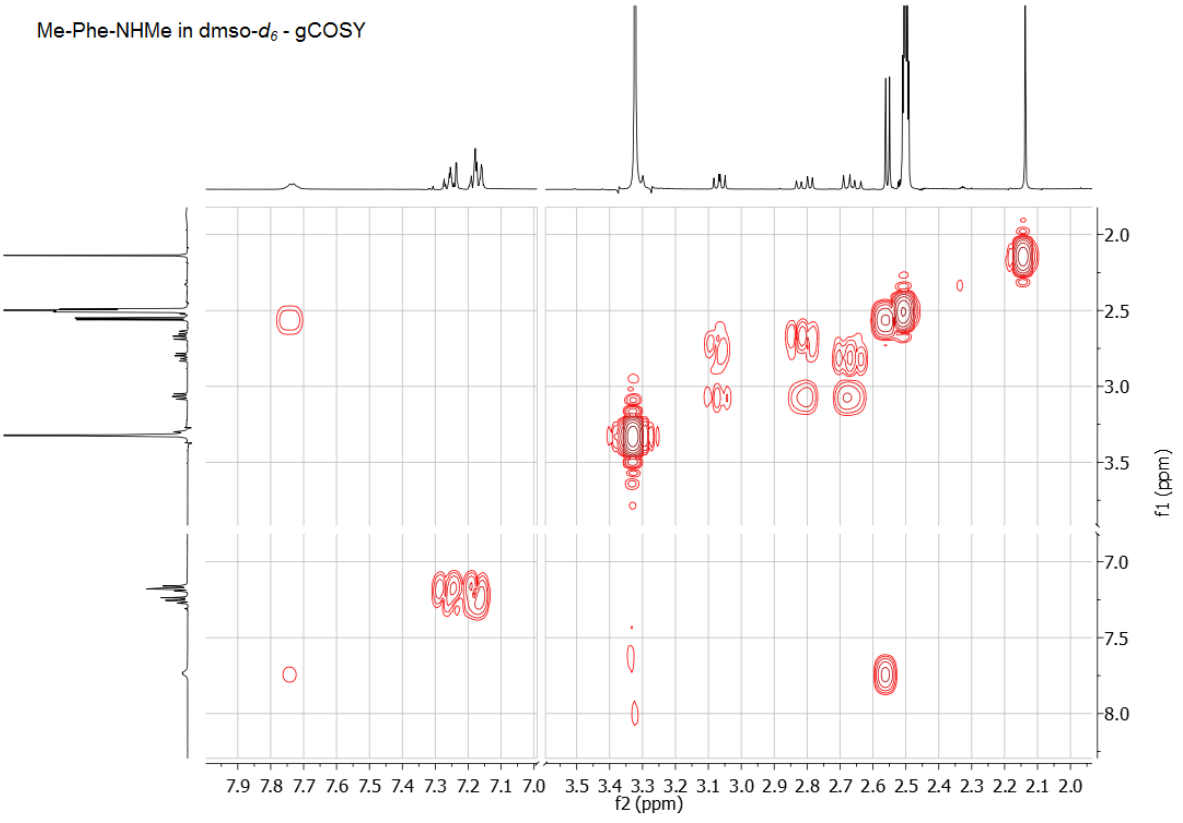


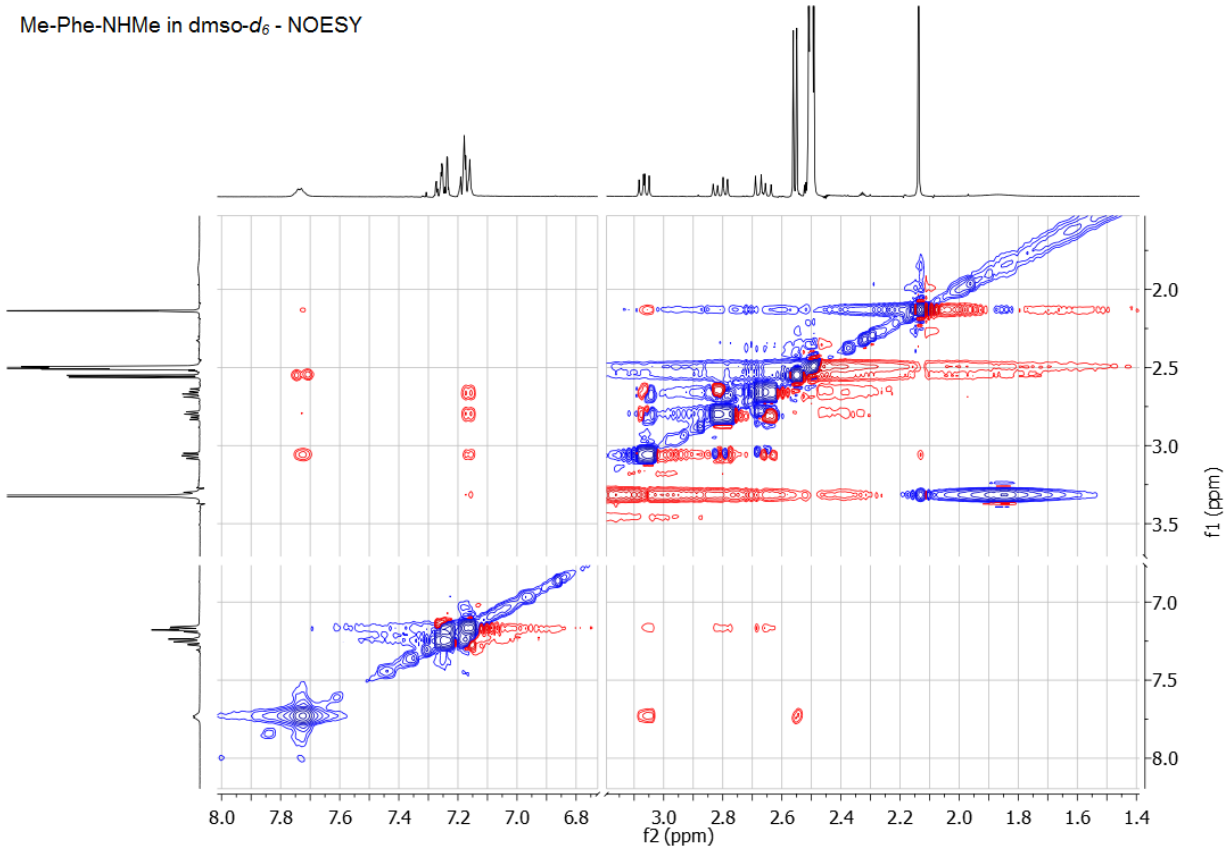




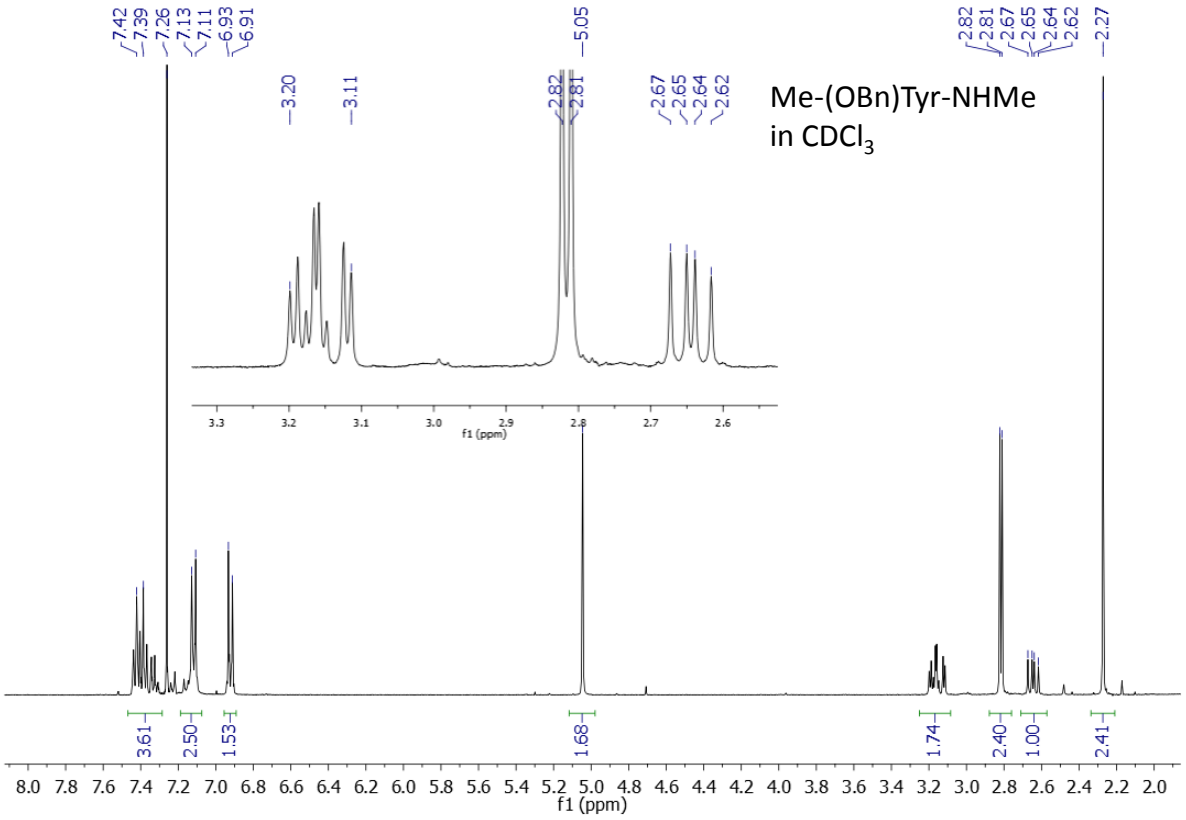
^{1}H, gCOSY and gNOESY spectra of **3c** in dmso-d_6

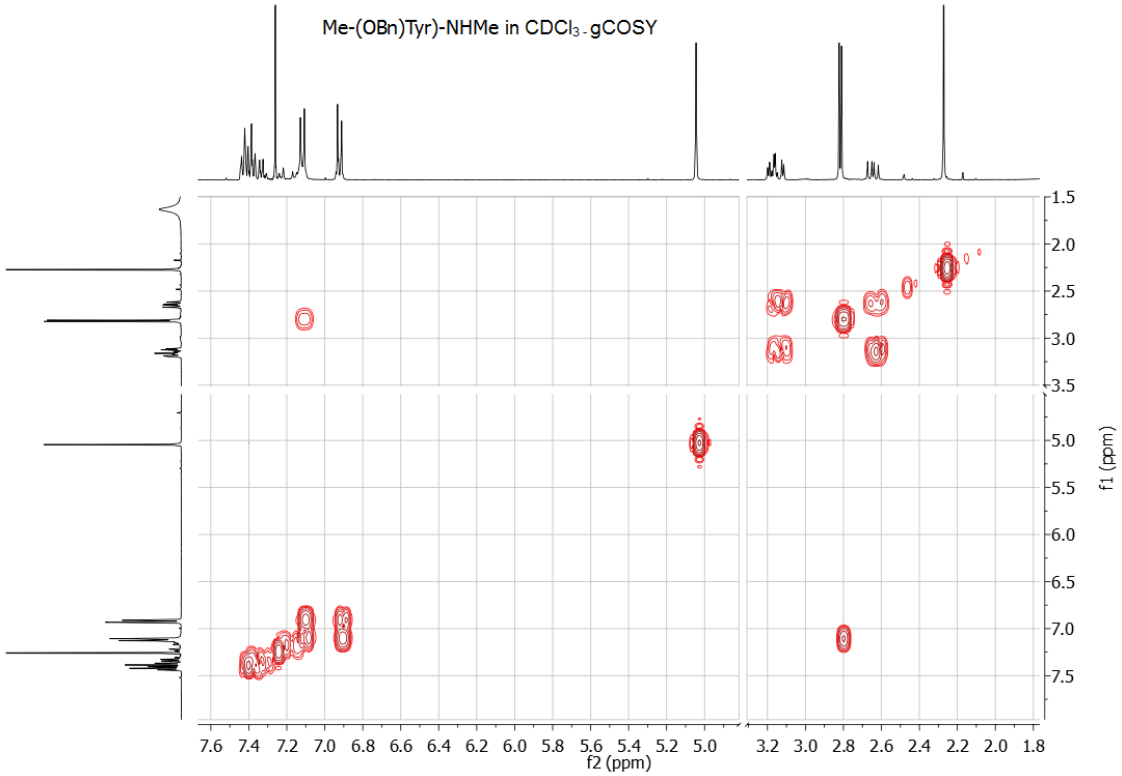


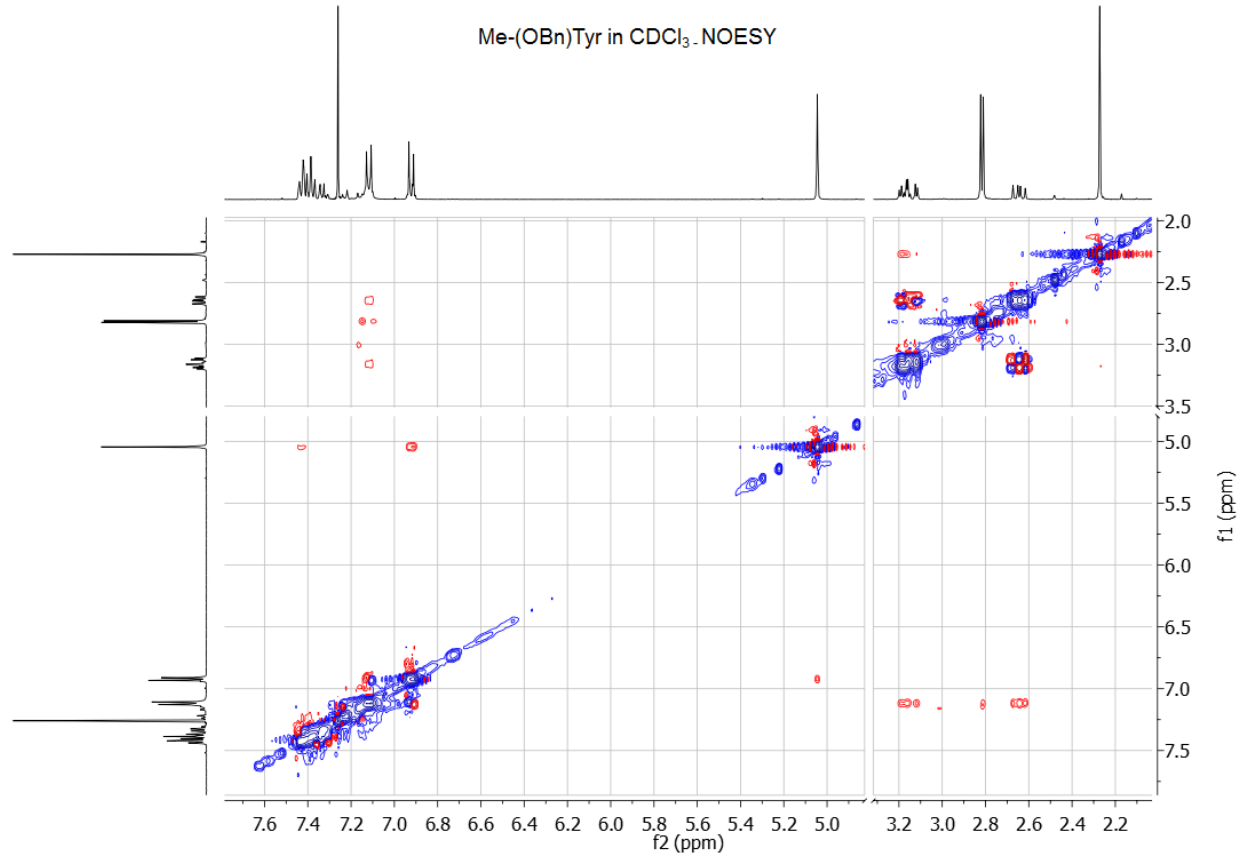


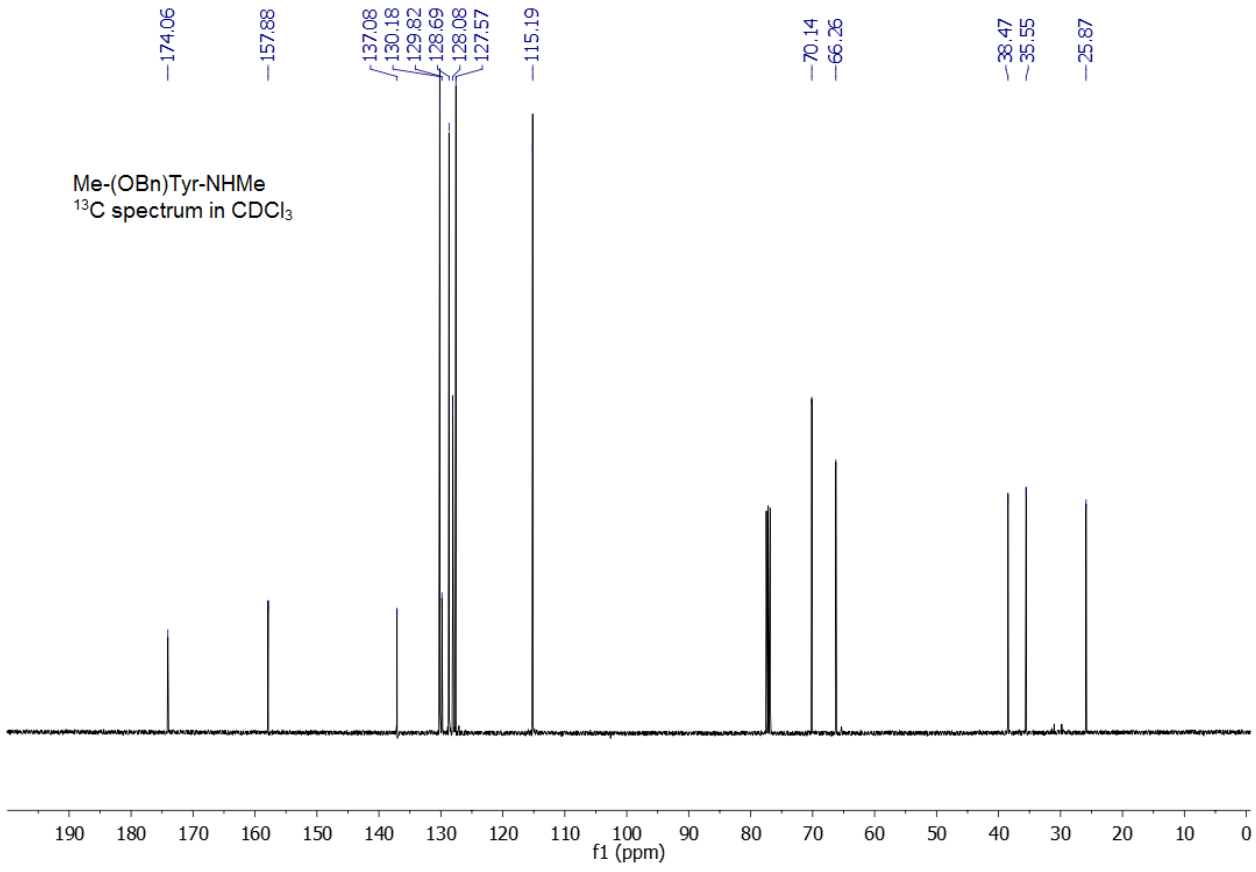


^{1}H, gCOSY, gNOESY and ^{13}C NMR spectra of **3d** in $CDCl_3$

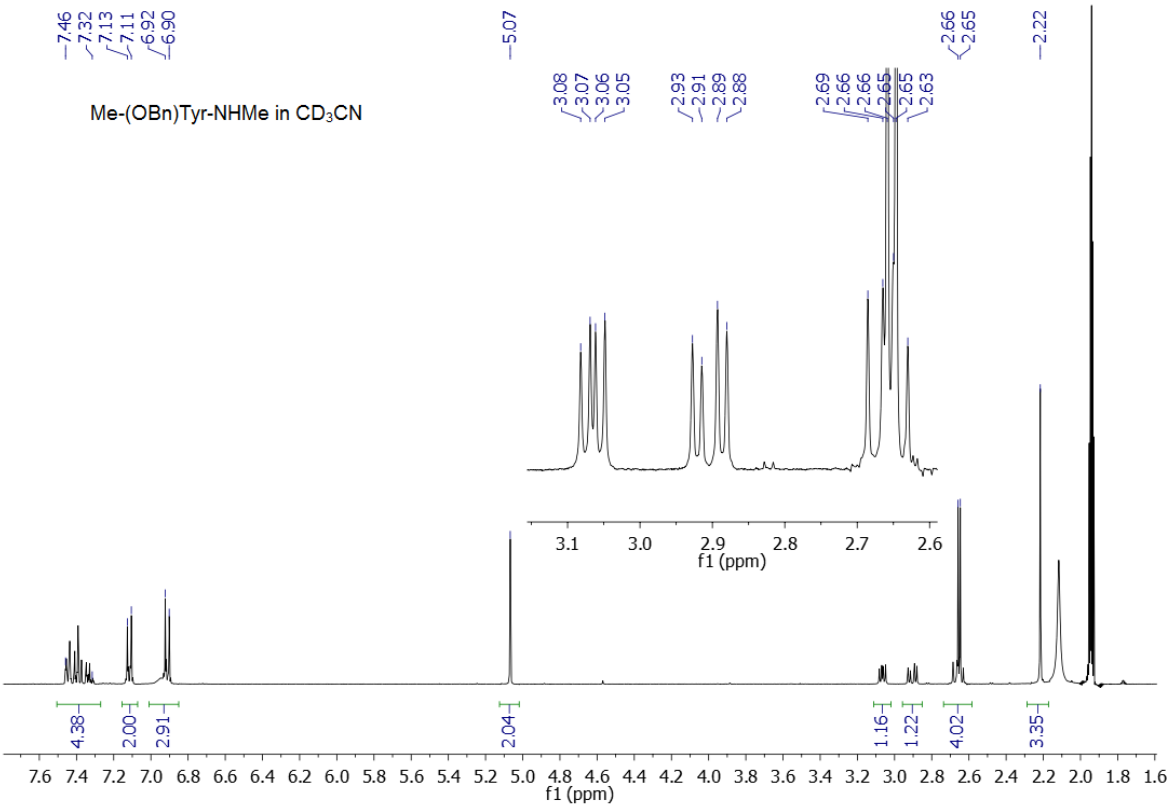


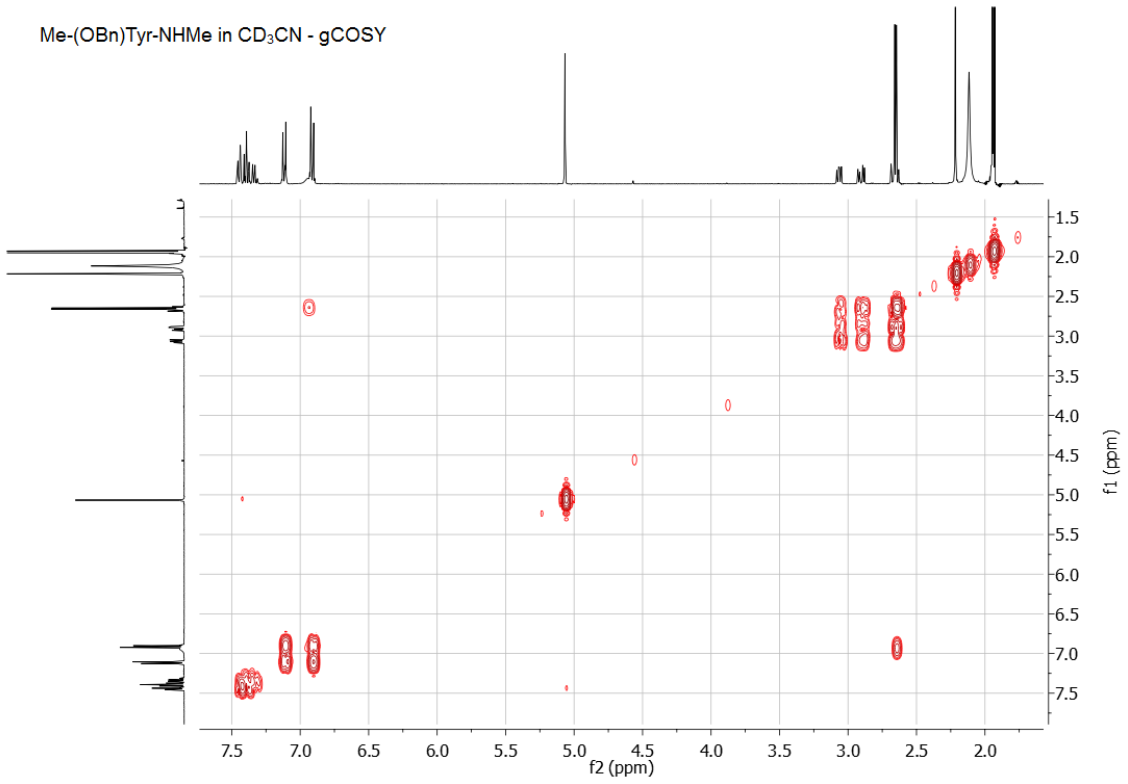


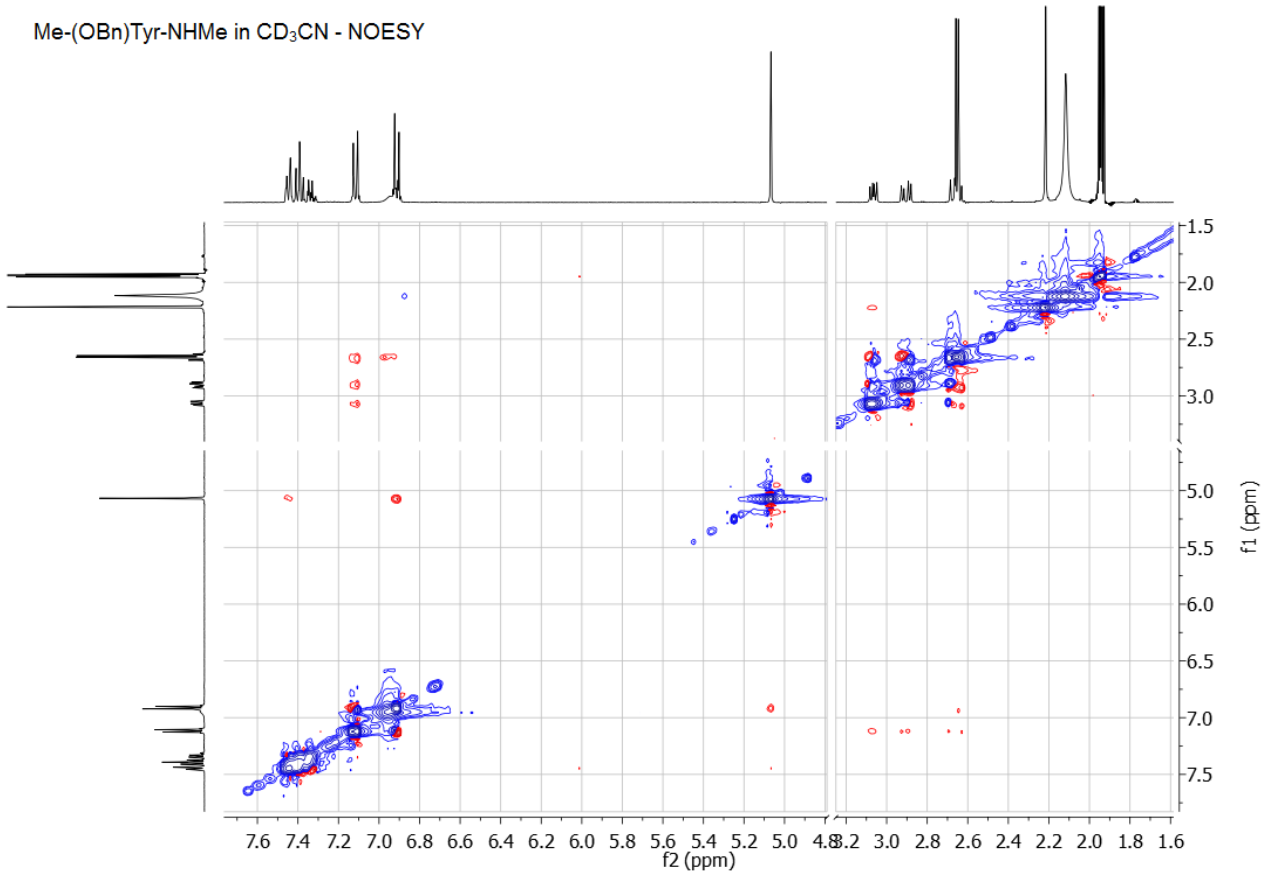

Me-(OBn)Tyr in CDCl3 - NOESY
f2 (ppm)
f1 (ppm)


174.06
157.88
137.08
130.18
129.82
128.69
128.08
127.57
115.19
70.14
66.26
38.47
35.55
25.87
Me-(OBn)Tyr-NHMe
13C spectrum in CDCl3
f1 (ppm)

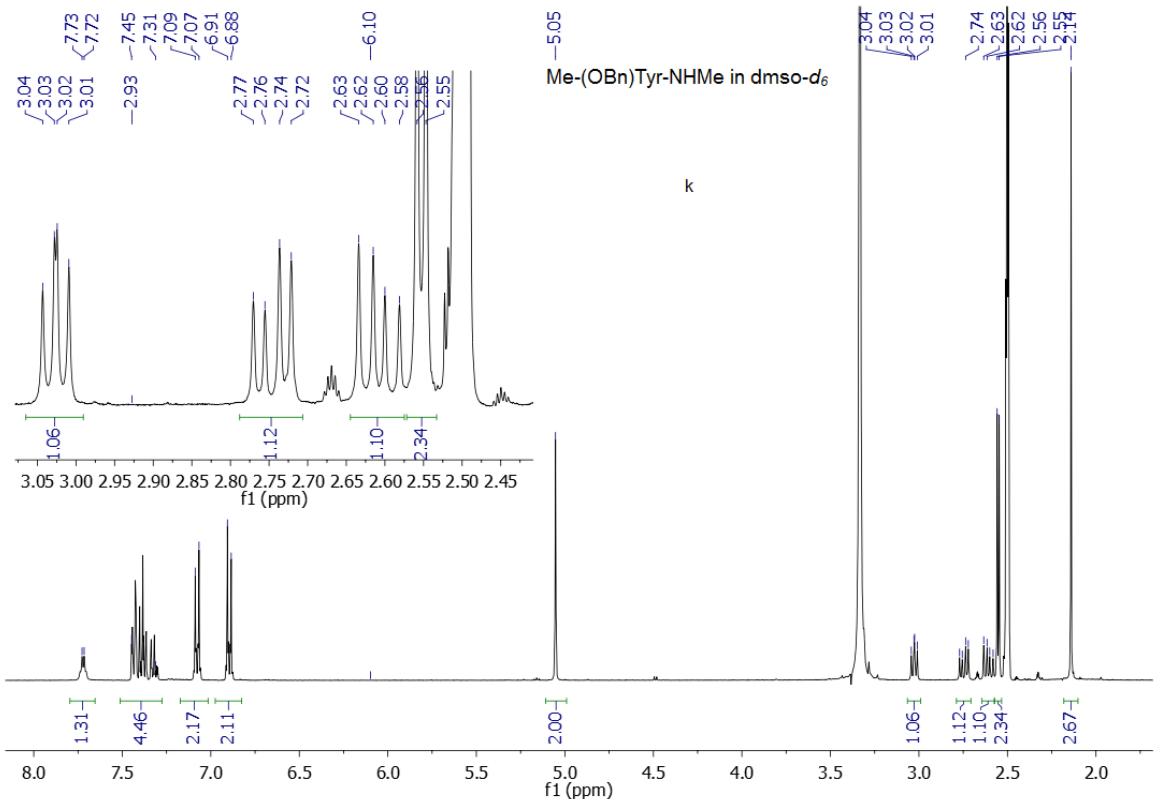
^{1}H, gCOSY and gNOESY spectra of **3d** in CD_3CN

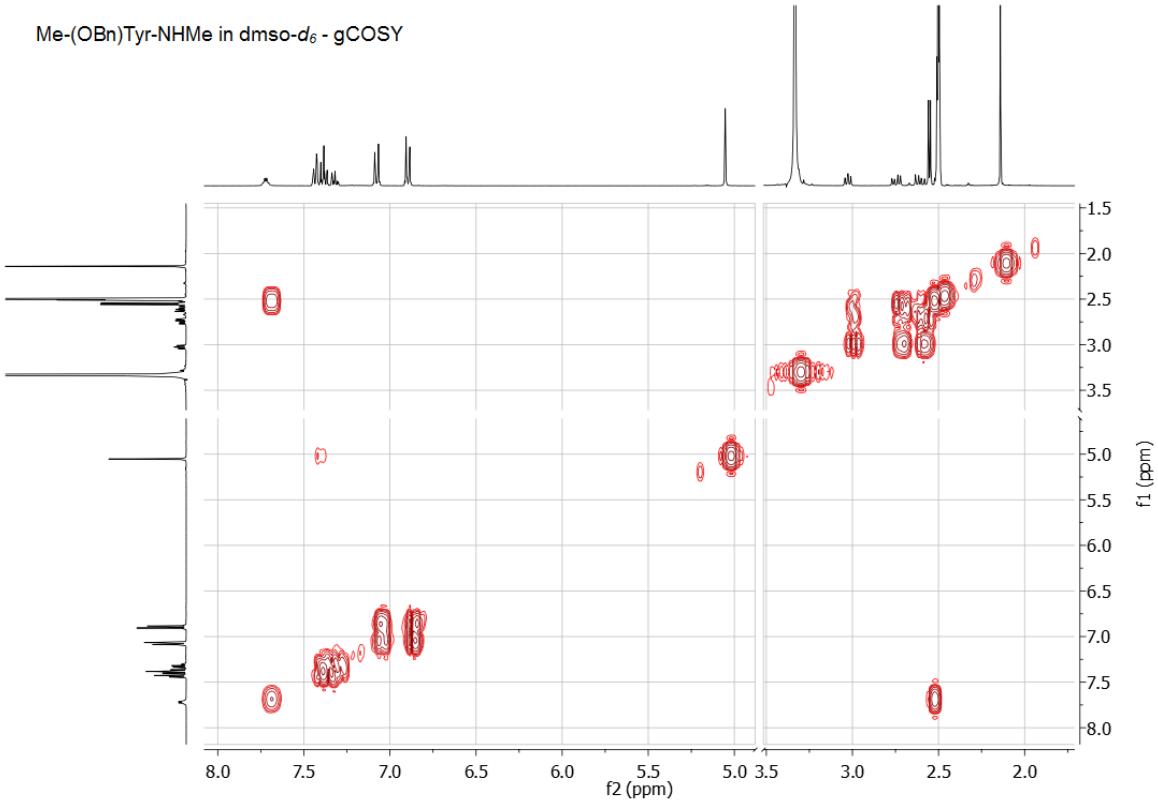


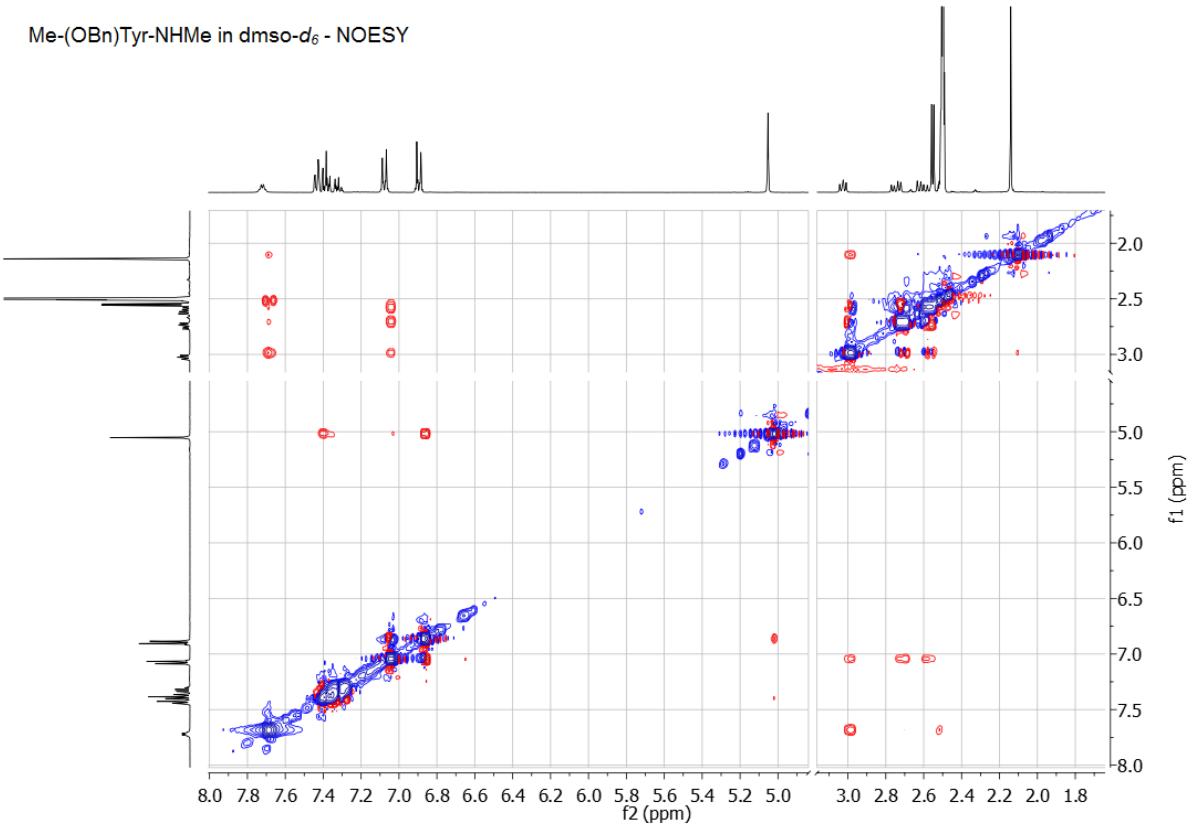




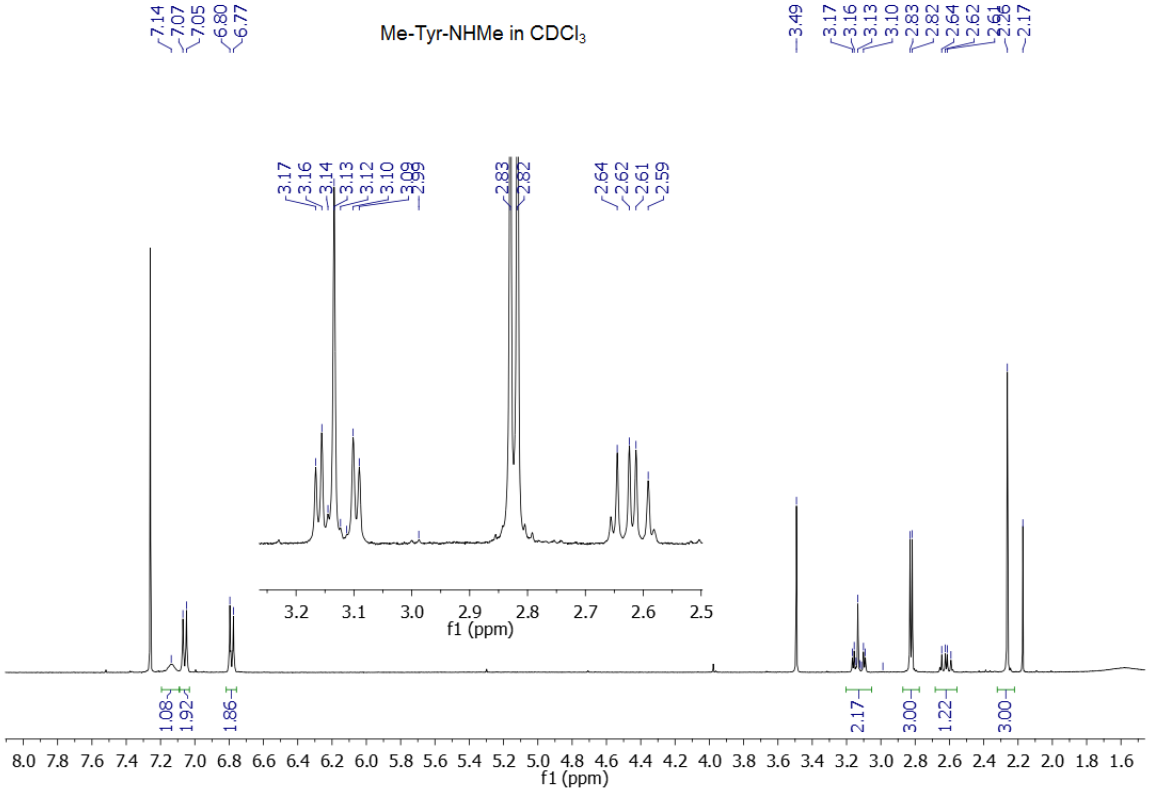
^{1}H, gCOSY and gNOESY spectra of **3d** in dmso-d_6

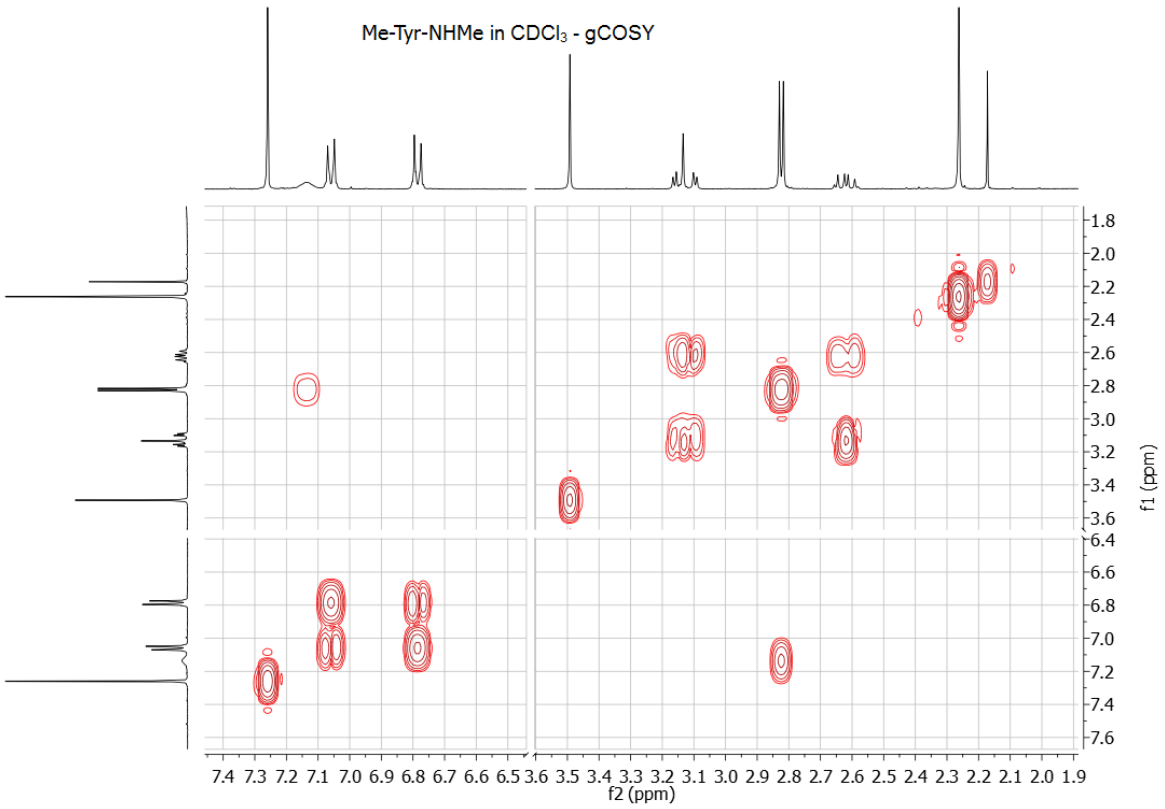


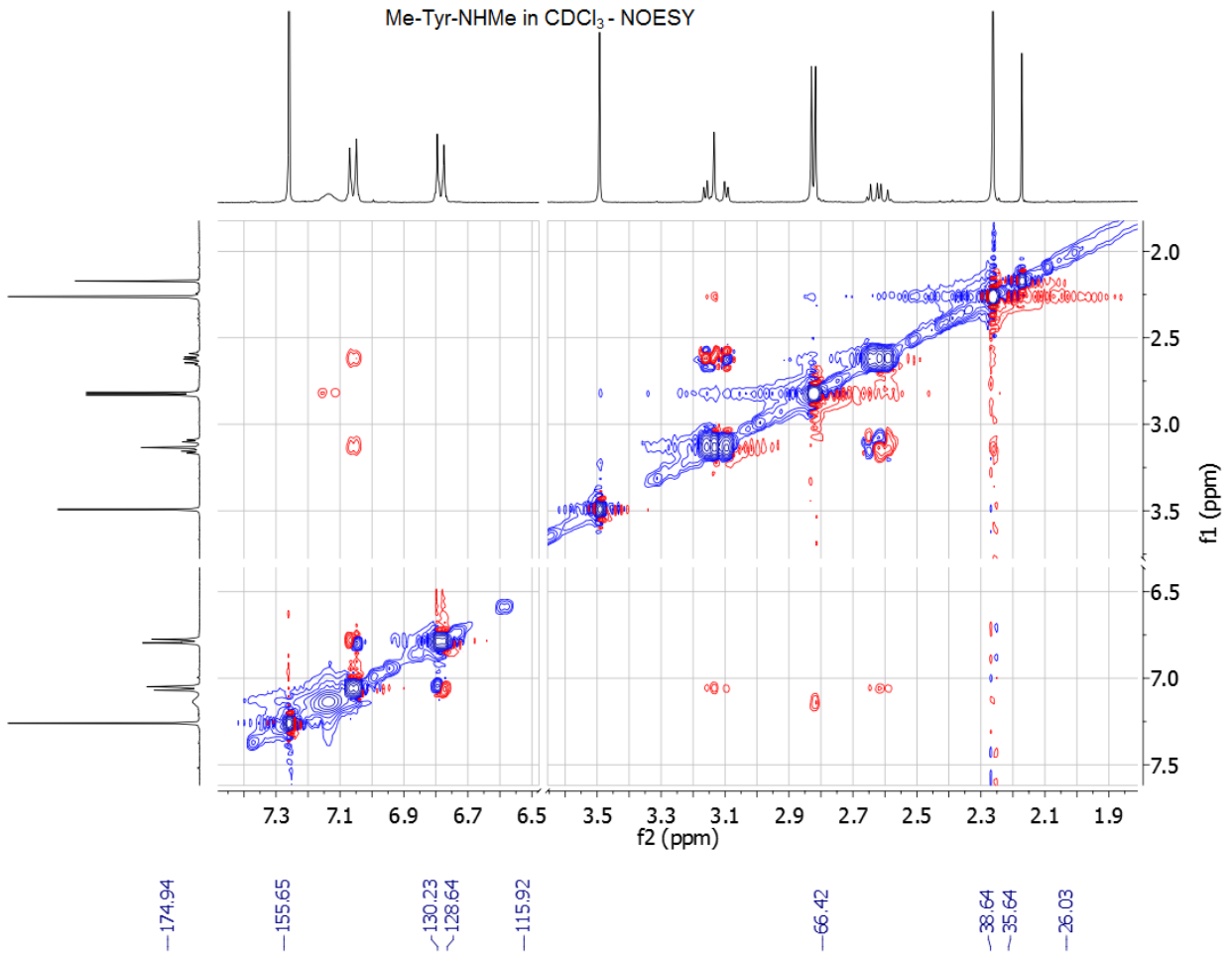




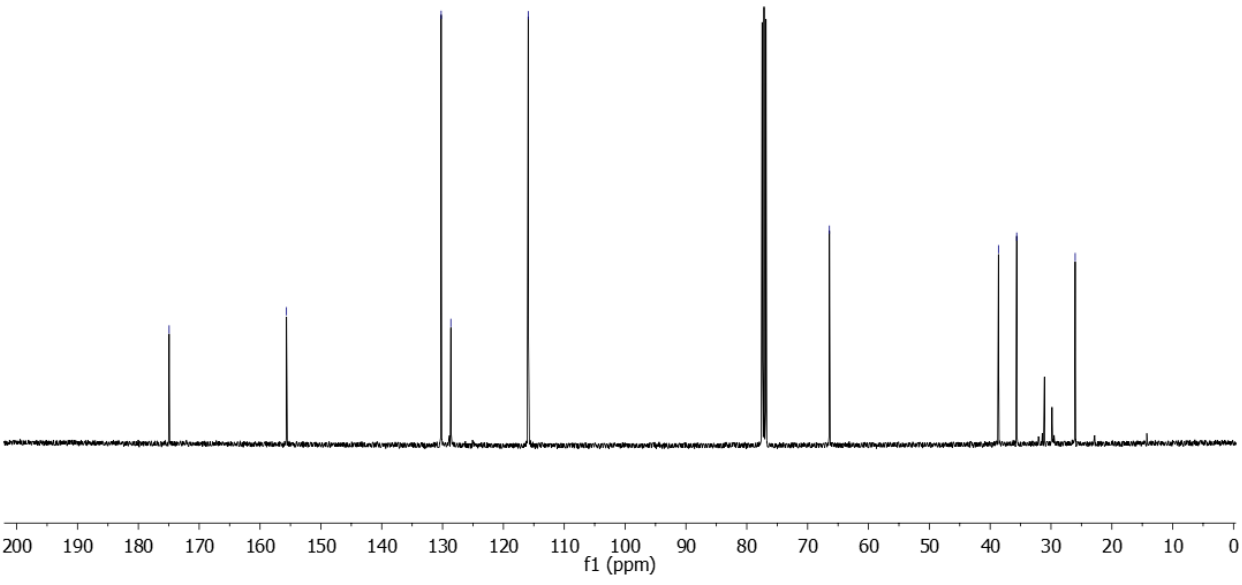
^{1}H, gCOSY, gNOESY and ^{13}C NMR spectra of **3e** in $CDCl_3$



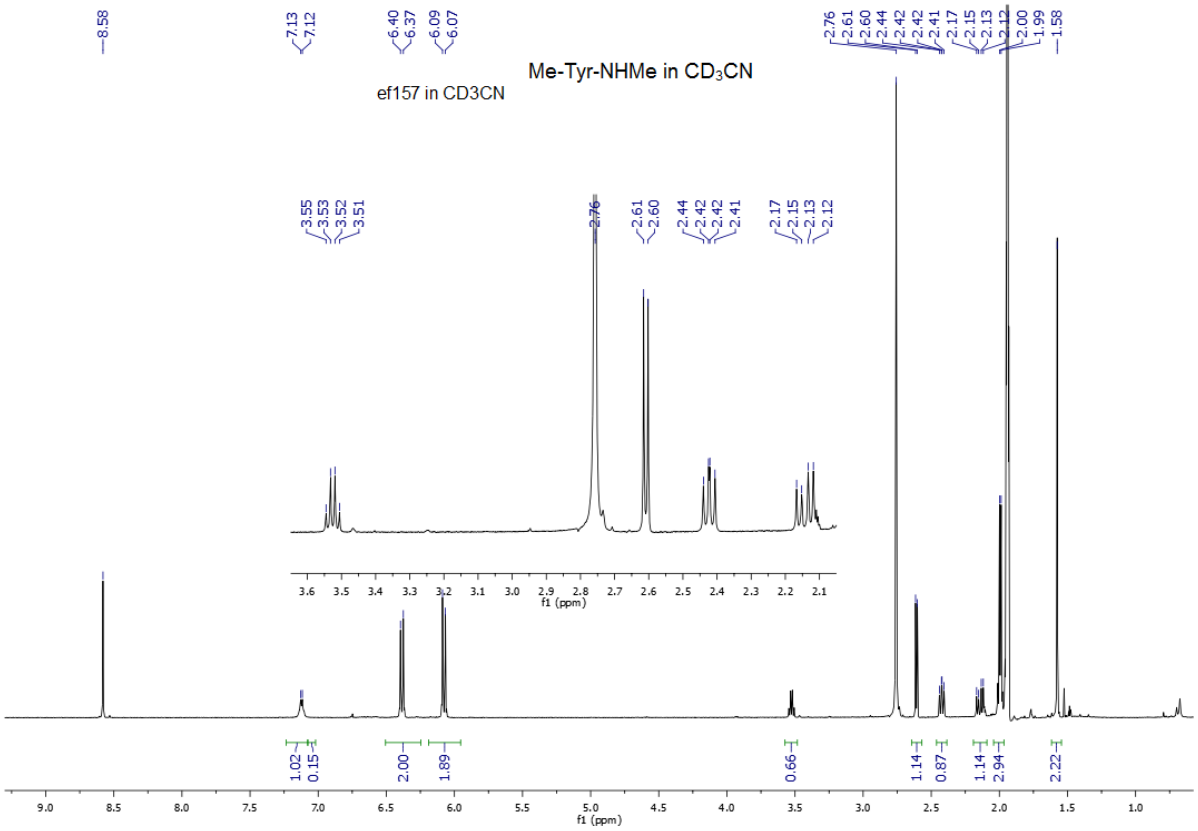


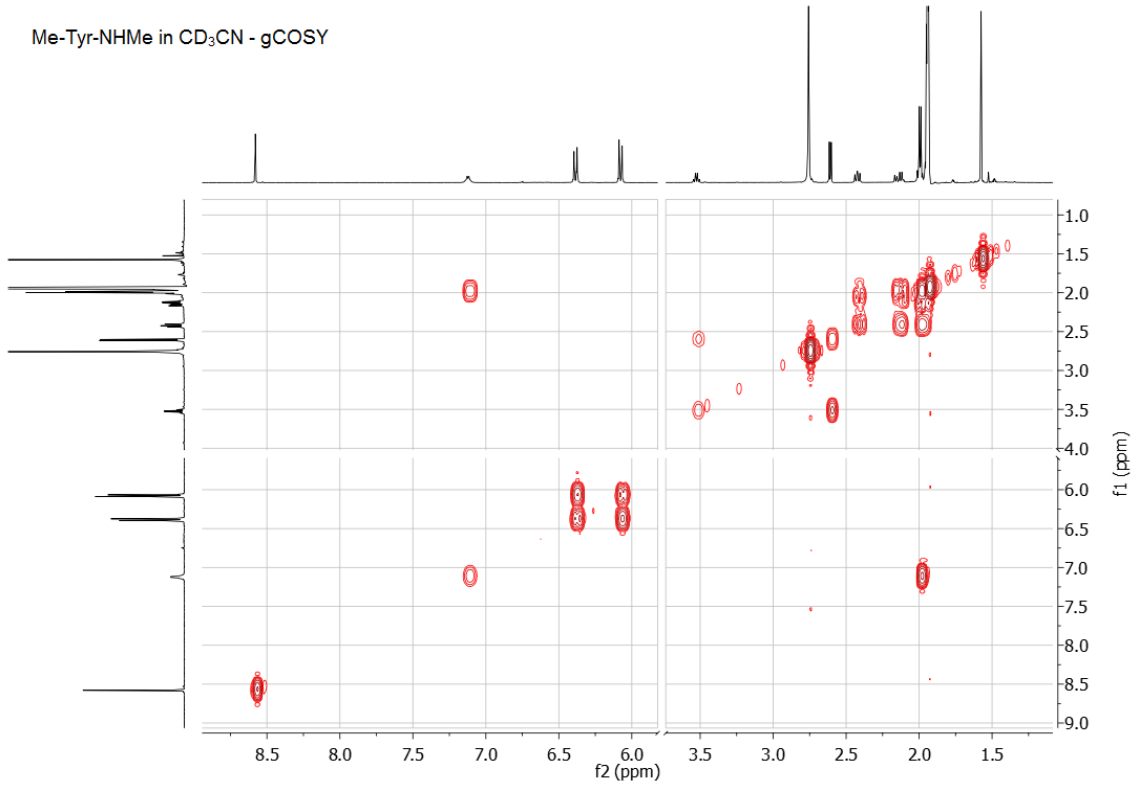


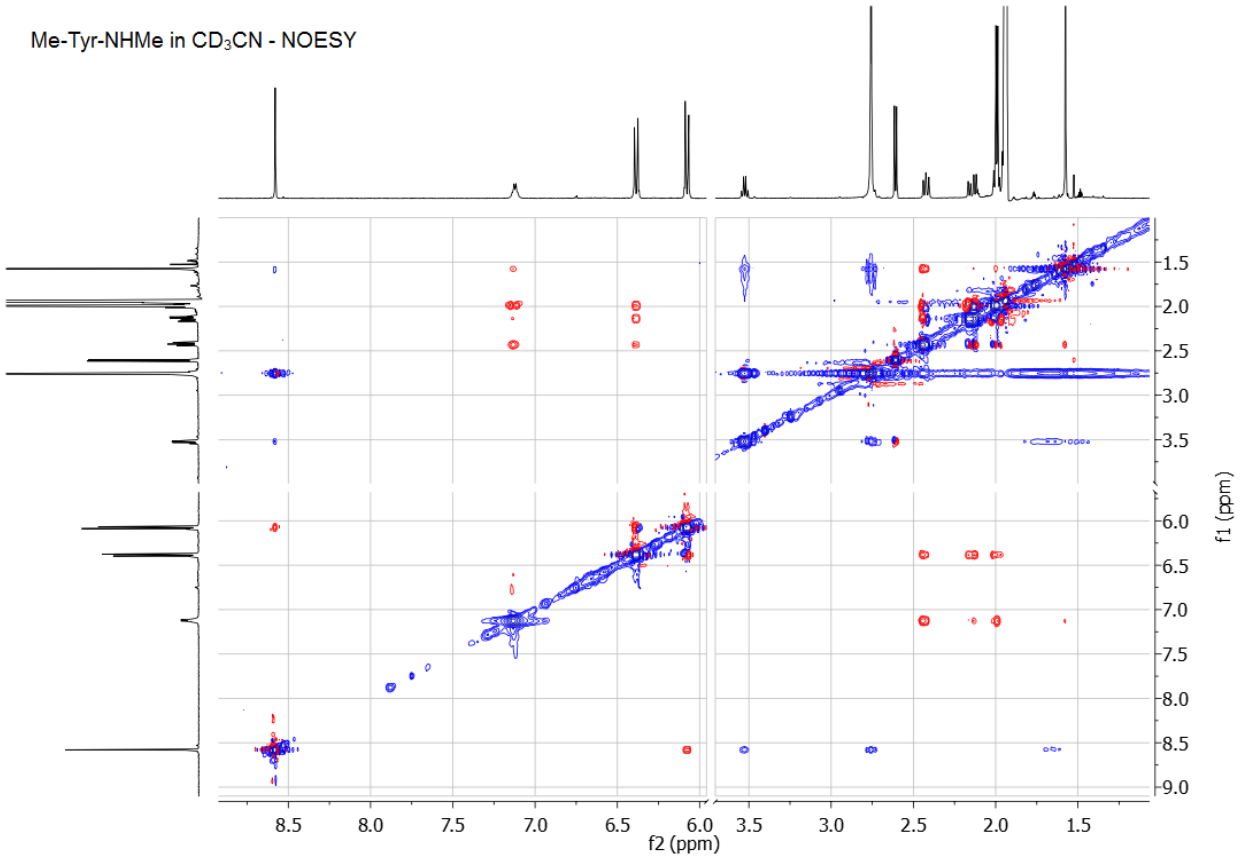
Me-Tyr-NHMe
^{13}C spectrum in $CDCl_3$



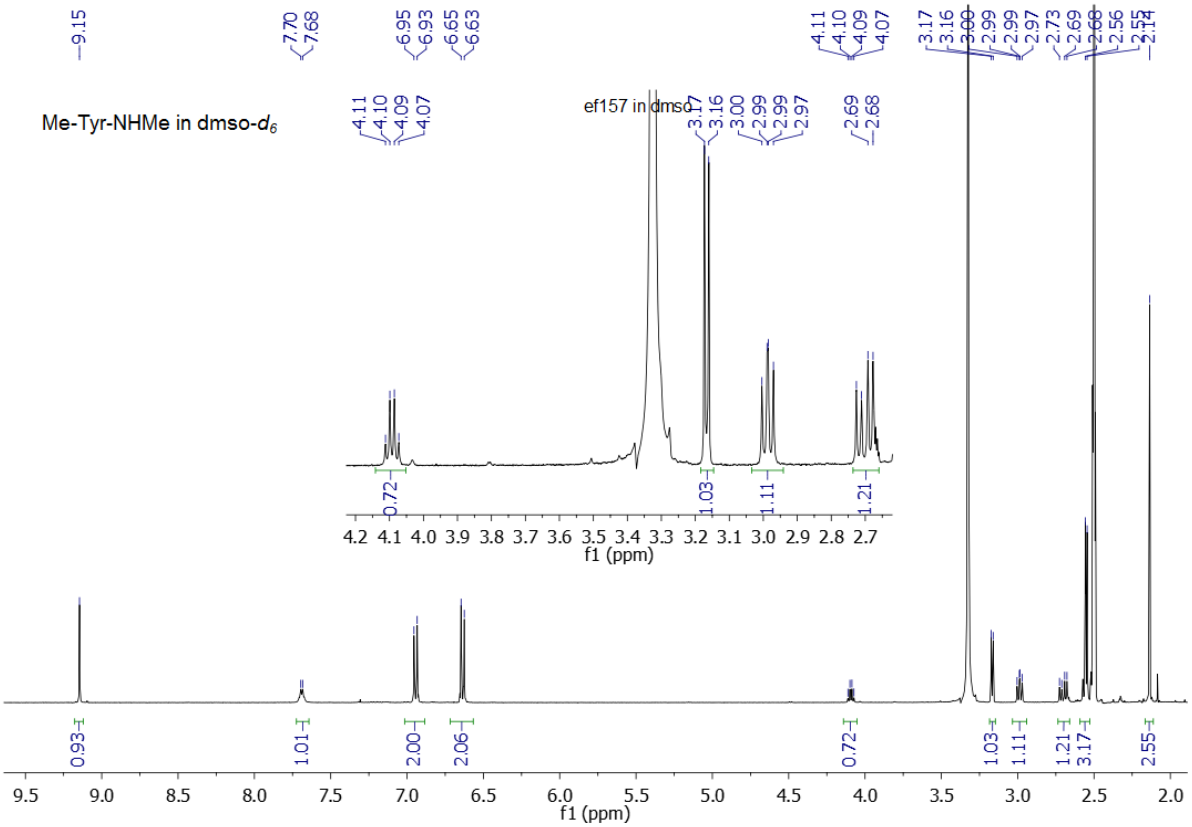
^{1}H, gCOSY and gNOESY NMR spectra of **3e** in CD_3CN

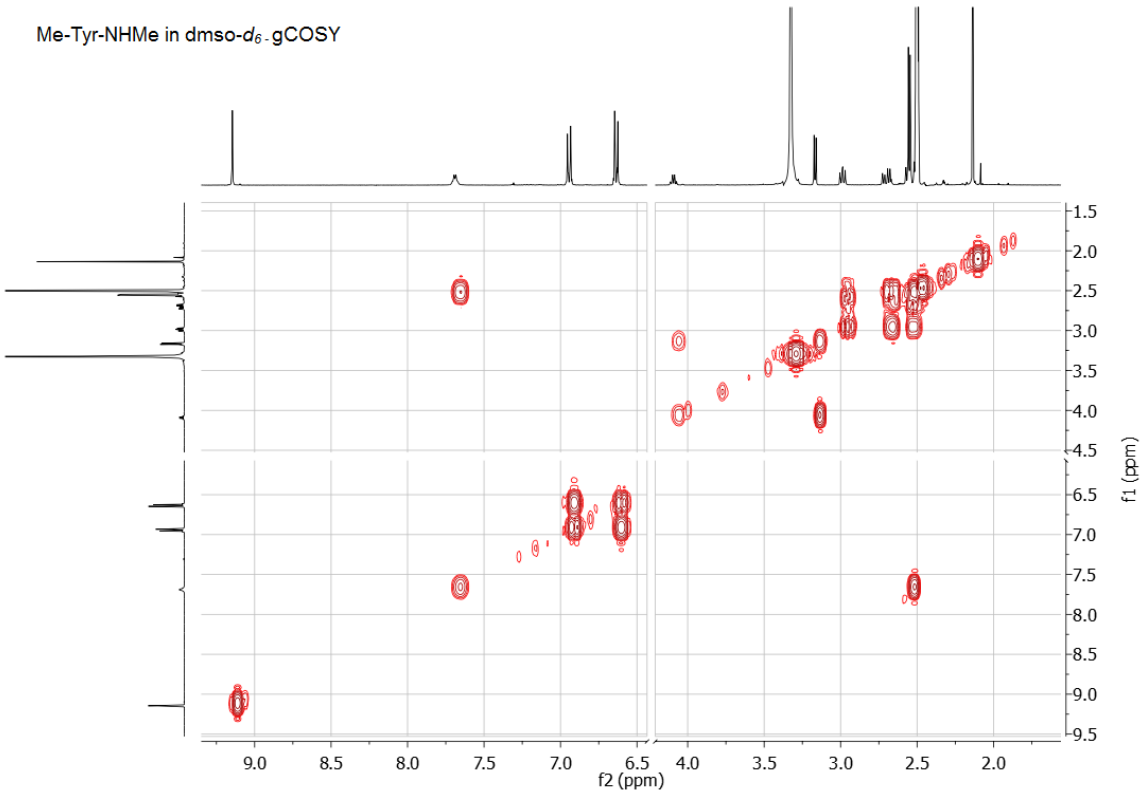


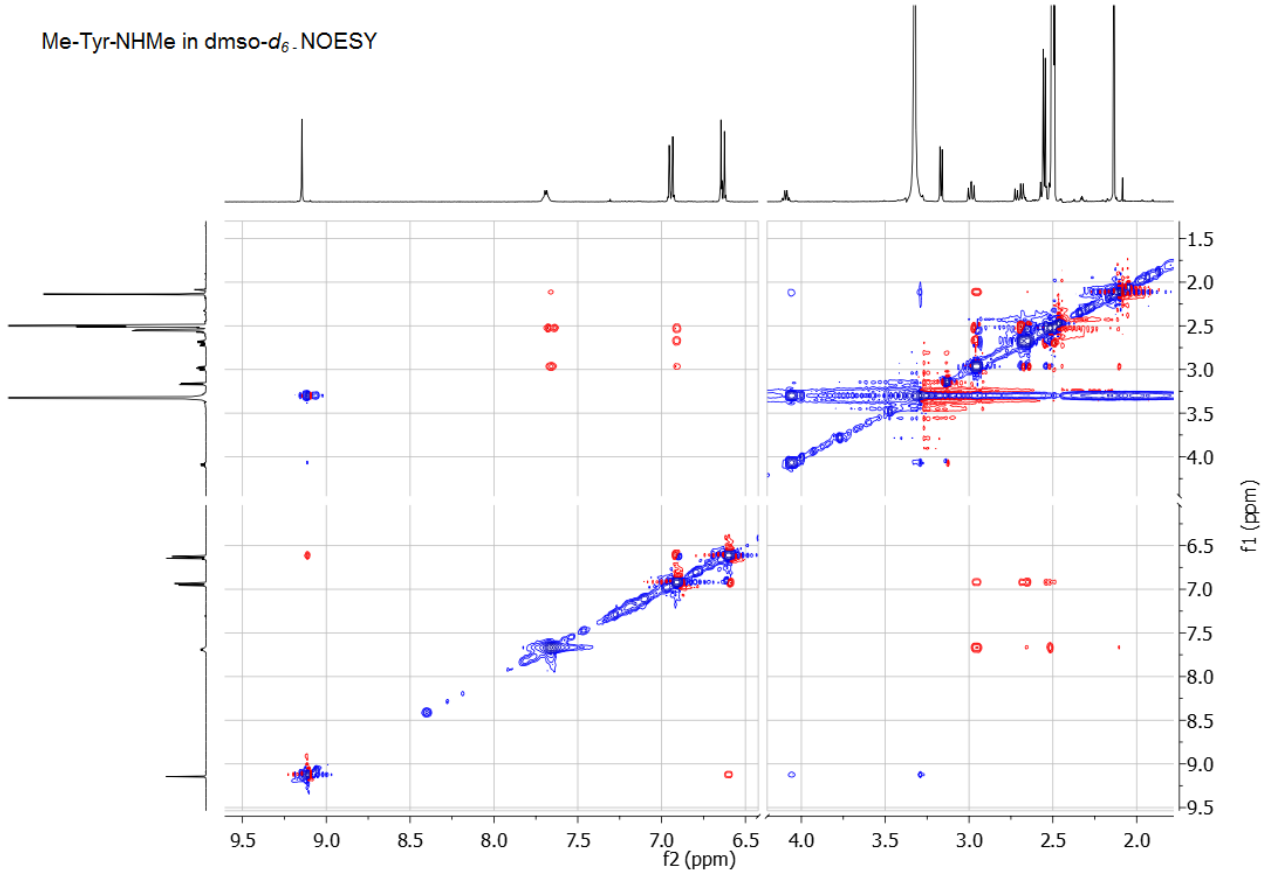




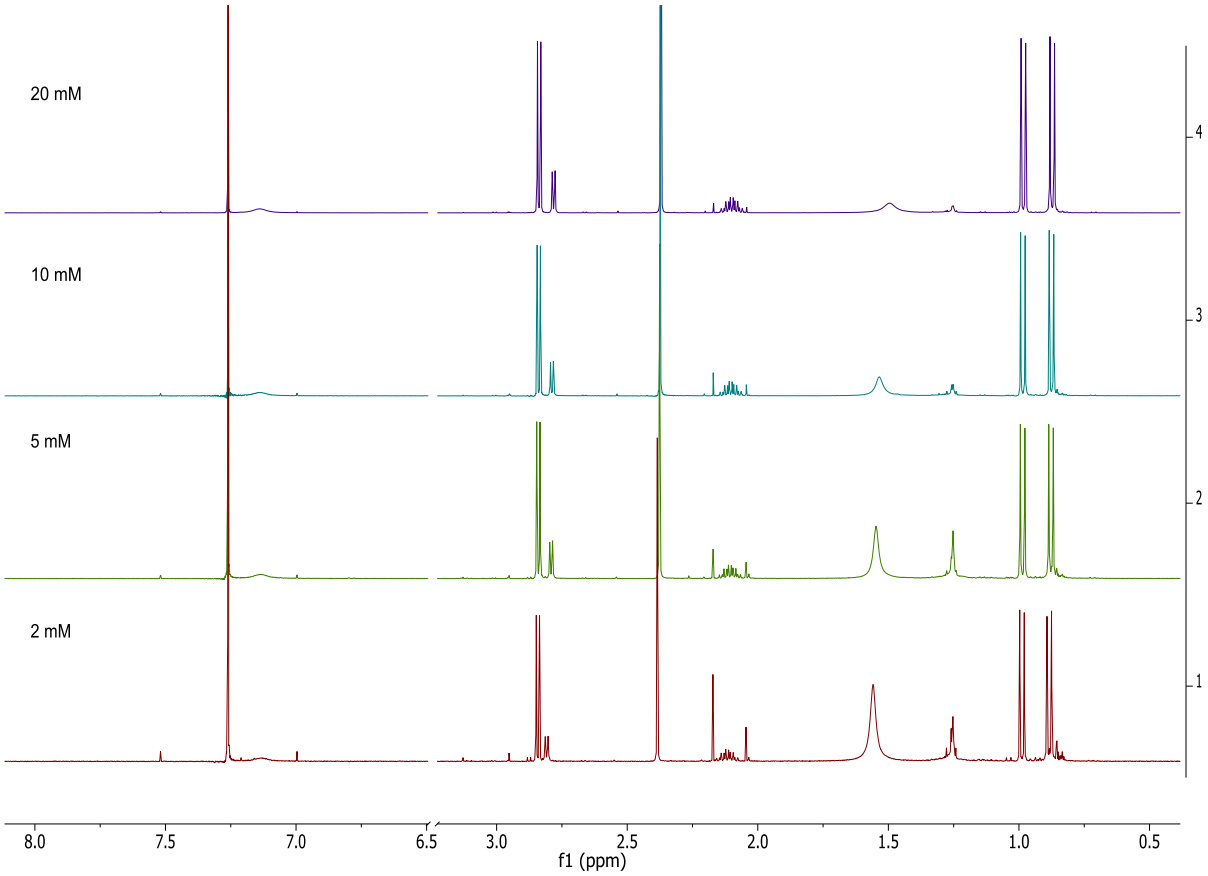
^{1}H, gCOSY and gNOESY NMR spectra of **3e** in dmso-d_6



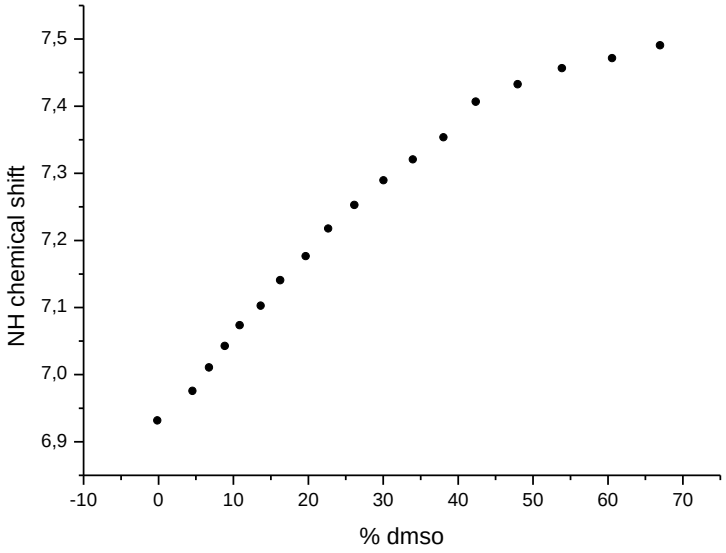




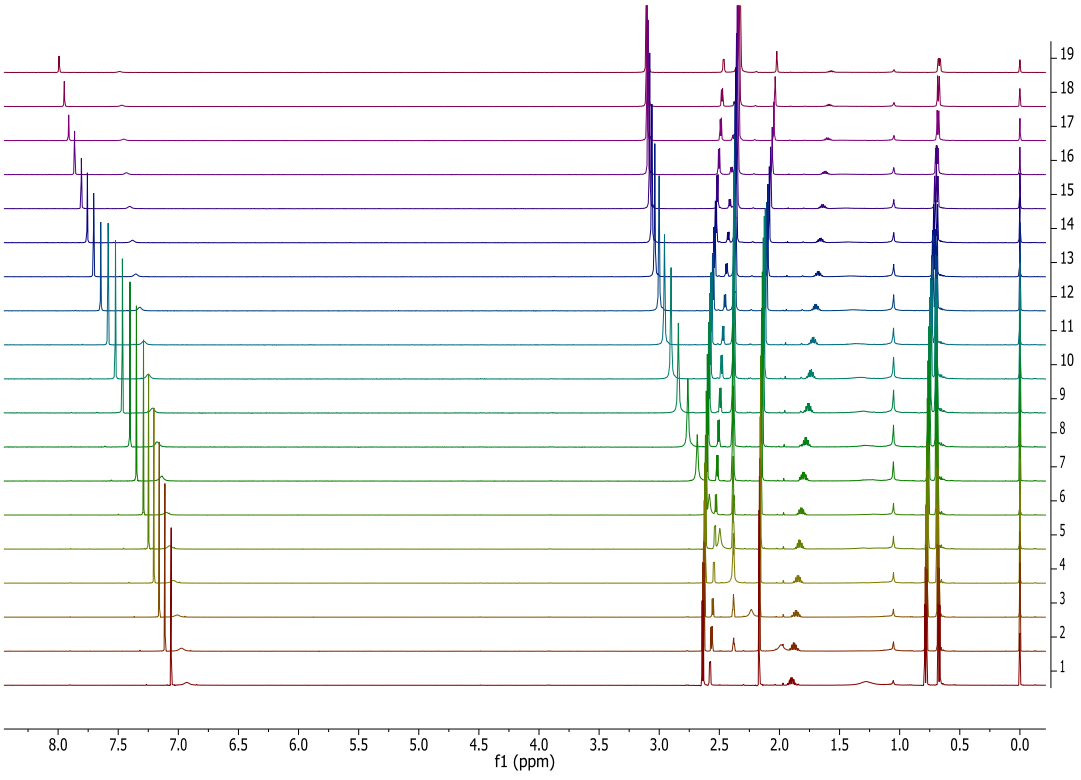
^{1}H-NMR spectra of **3a** in $CDCl_3$ at different concentrations



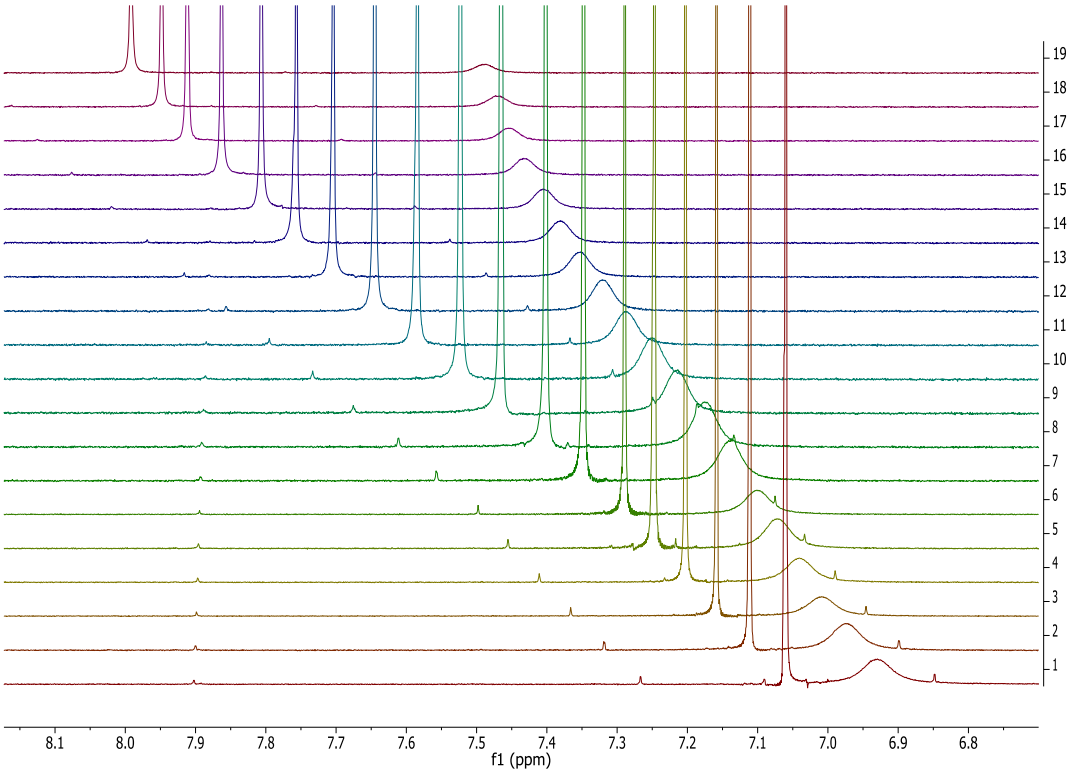
Chemical shift of the amide NH signal (in ppm) of **3a** in a $CDCl_3$/dmso-d_6 mixture as a function of the percentage of dmso-d_6.



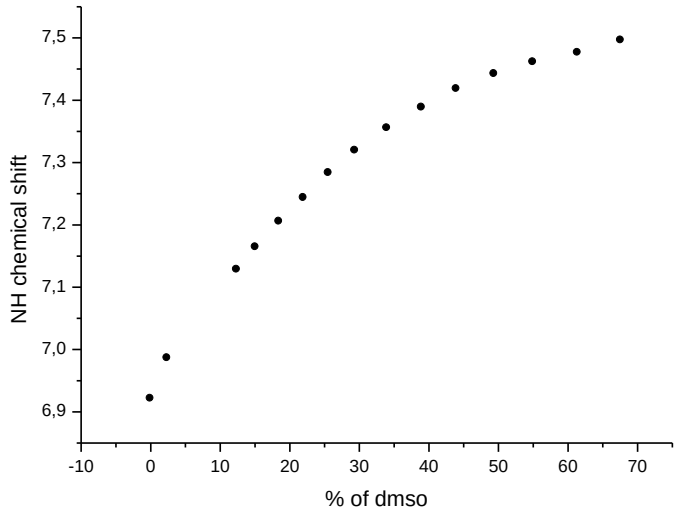
^{1}H-NMR (500 MHz) spectra of **3a** with increasing amounts of dmso-d_6 in $CDCl_3$ (bottom: 0% dmso-d_6, top: 67.1% dmso-d_6).



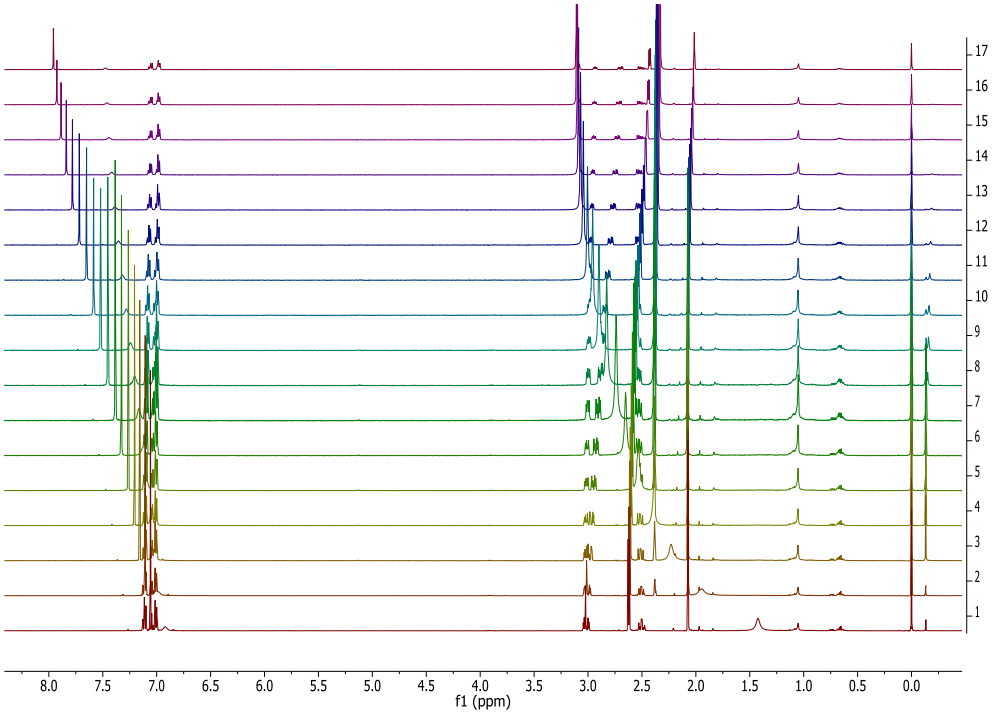
Amide NH region of the ^{1}H-NMR (500 MHz) spectra of **3a** with increasing amounts of dmso-d_6 in $CDCl_3$ (bottom: 0% dmso-d_6, top: 67.1% dmso-d_6).



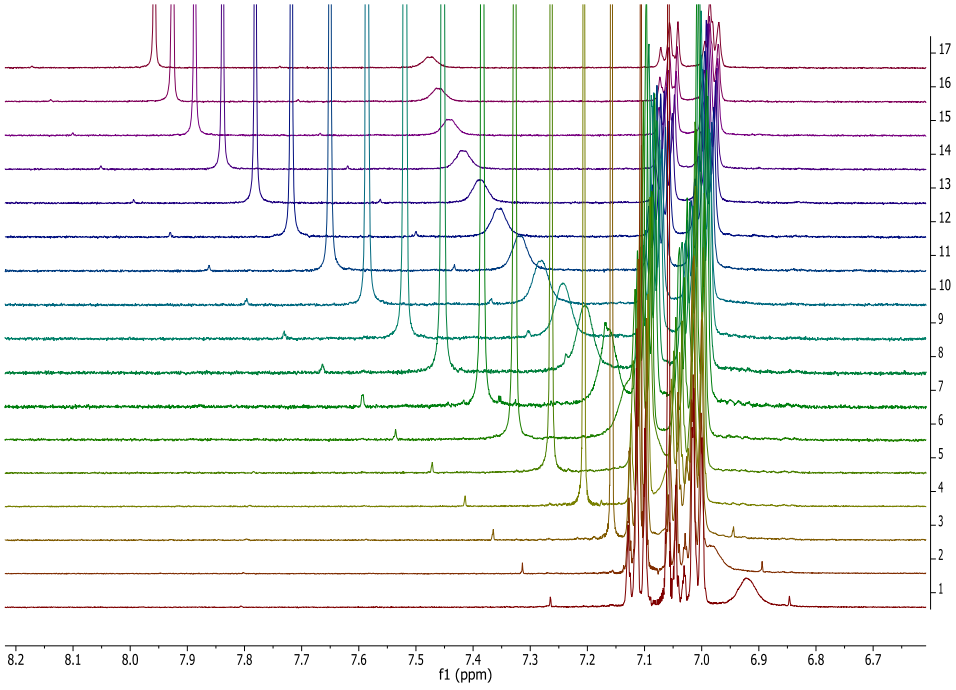
Chemical shift of the amide NH signal (in ppm) of **3c** in a $CDCl_3$/ dmso-d_6 mixture as a function of the percentage of dmso-d_6.



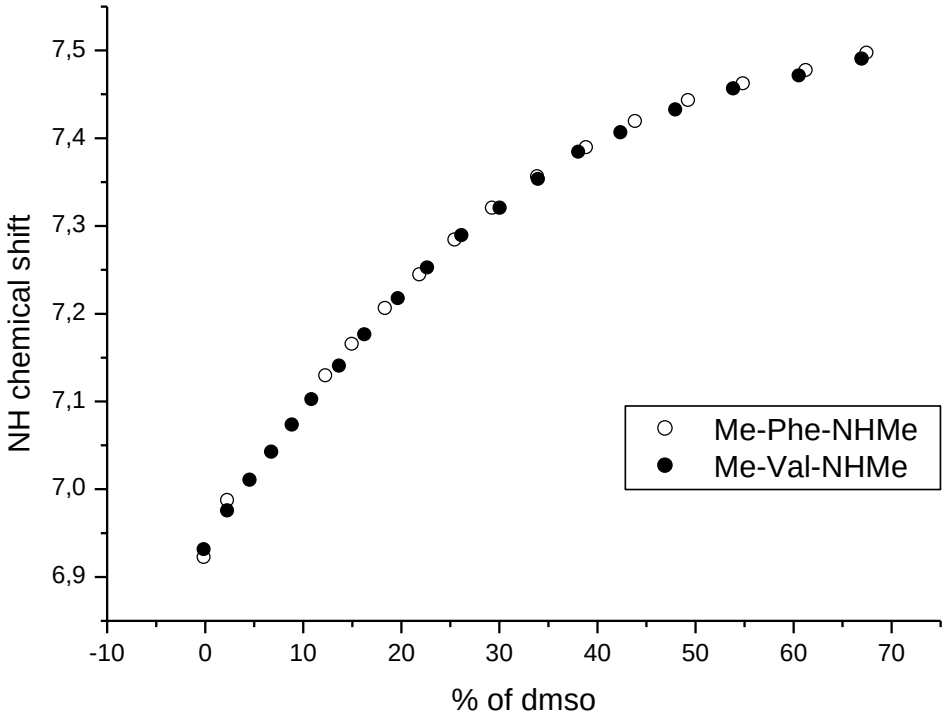
^{1}H-NMR (500 MHz) spectra of **3c** with increasing amounts of dmso-d_6 in $CDCl_3$ (bottom: 0% dmso-d_6, top: 67.1% dmso-d_6).



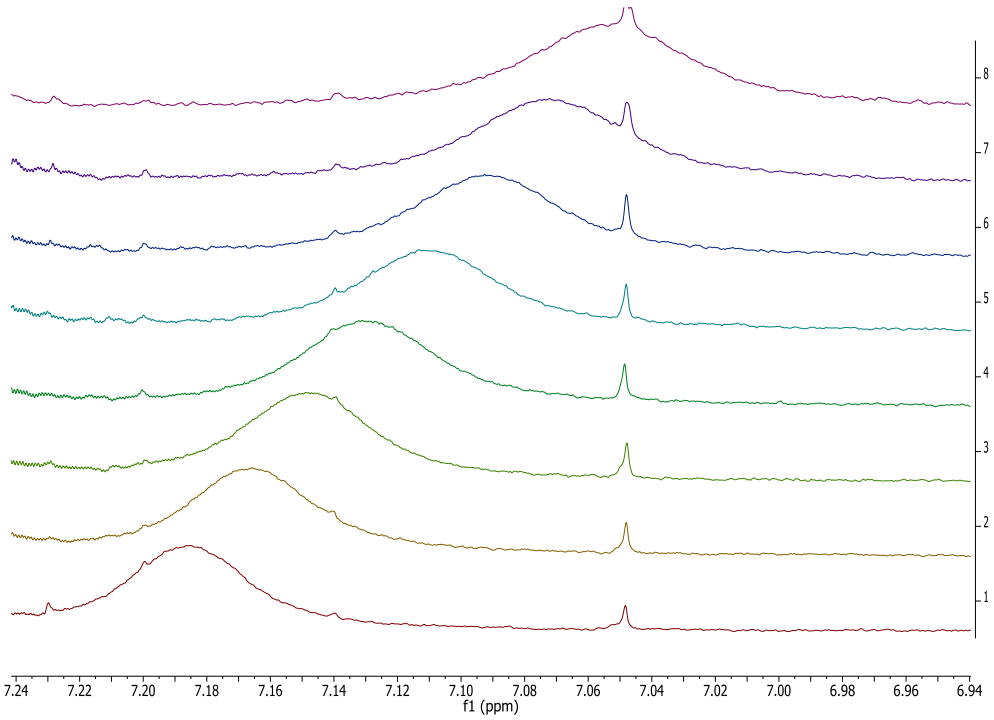
Amide NH region of the ^{1}H-NMR spectra of **3c** with increasing amounts of dmso-d_6 in $CDCl_3$ (bottom: 0% dmso-d_6, top: 61.4% dmso-d_6).



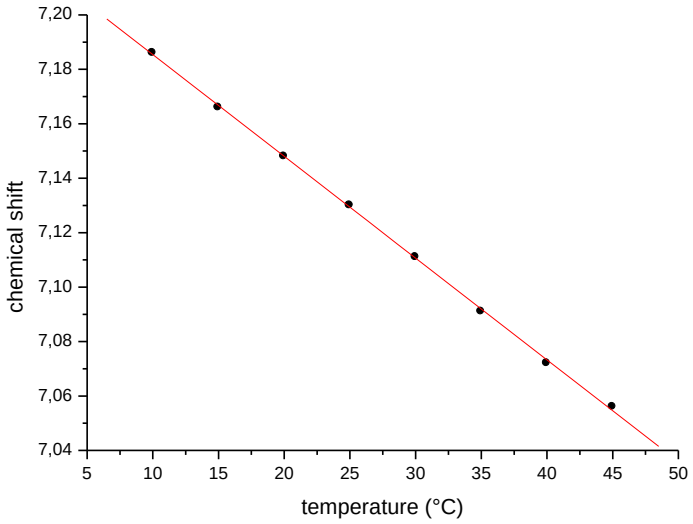
Comparison of the amide NH chemical shift (in ppm) of **3c** (o) and **3a** (•) as a function of the percentage of dmso-d_6 in $CDCl_3$.



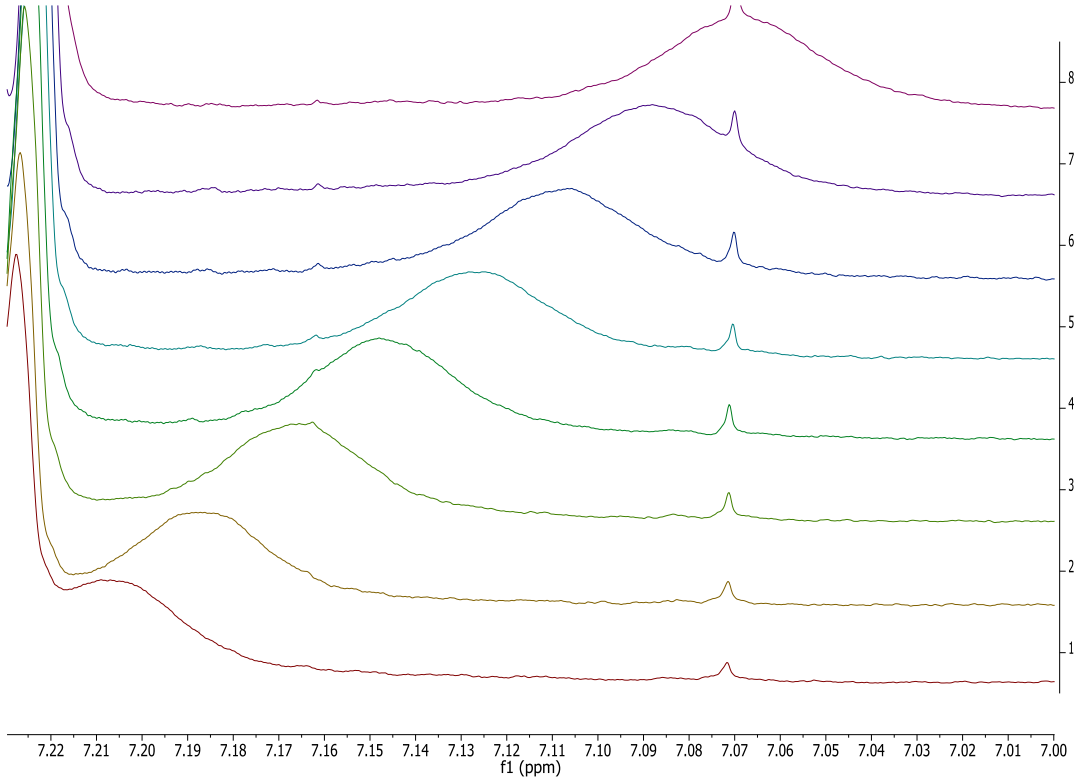
Amide NH region of the ^{1}H-NMR (500 MHz) spectra of **3a** at different temperatures; from 45°C (top) to 10°C (bottom).



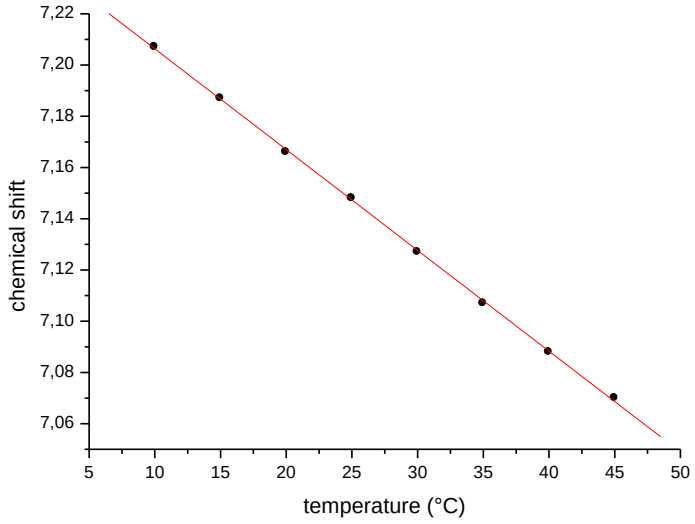
Chemical shift of the amide NH of **3a** as a function of temperature. Experimental points (black circles) and linear fitting (red line). The fitting provides a value of Δδ = -3.74 ppb/°C



Amide NH region of the ^{1}H-NMR (500 MHz) spectra of **3c** at different temperatures; from 45°C (top) to 10°C (bottom).



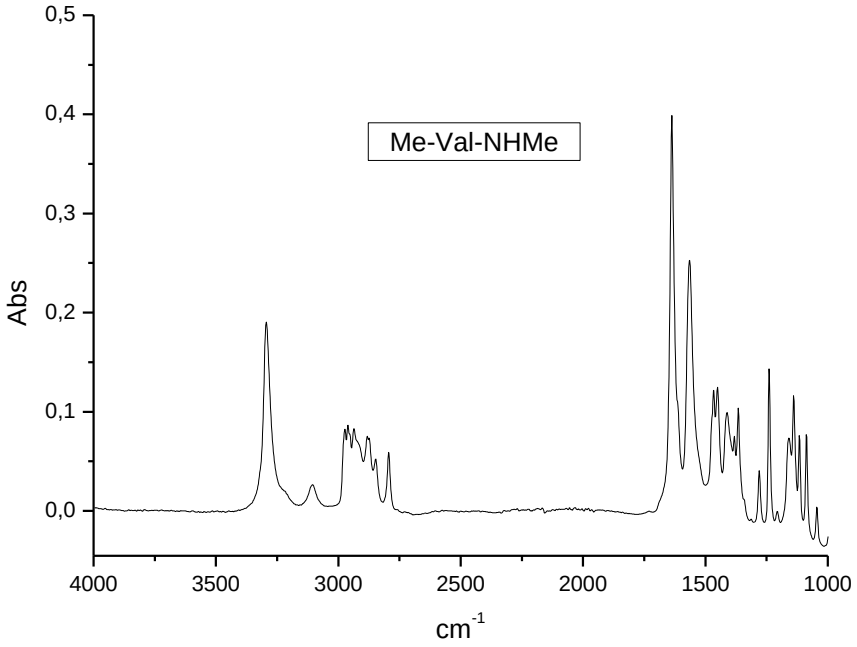
Chemical shift of the amide NH of **3c** as a function of temperature. Experimental points (black circles) and linear fitting (red line). The fitting provides a value of Δδ = -3.93 ppb/°C



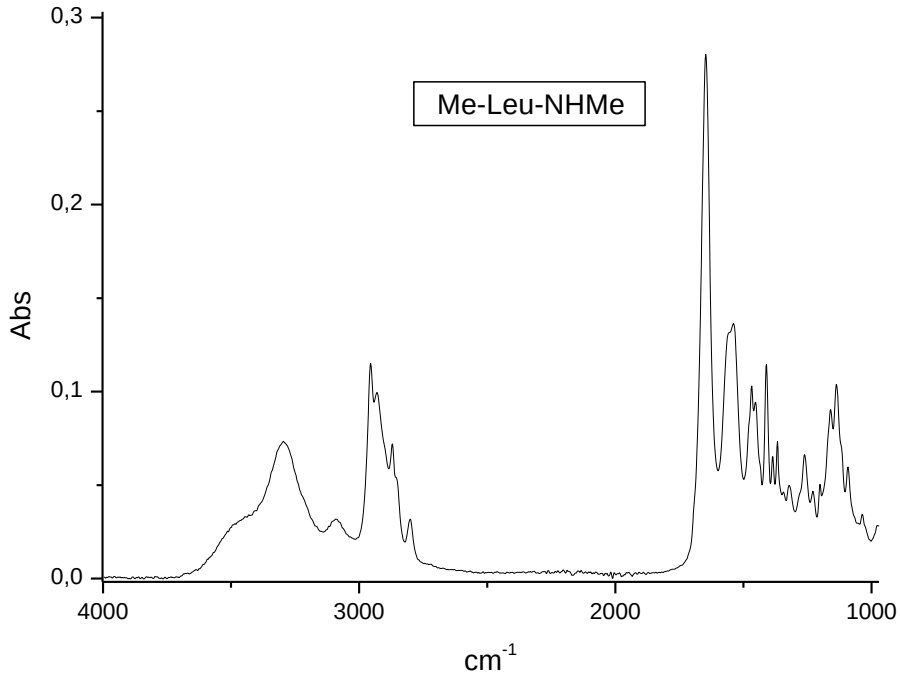
ATR-IR Spectra

Attenuated total reflectance infrared (ATR-IR) spectra were recorded on a Bruker Vertex 70 spectrophotometer equipped with a Specac Golden Gate ATR accessory. The spectra were acquired either using bulk materials or by slow evaporation of the sample onto the ATR sample holder. To do that, 2-3 drops of a 20 mM solution of the sample in chloroform were placed on the ATR sample holder, and spectra were collected sequentially, approximately every 40 seconds, until complete solvent evaporation was achieved.

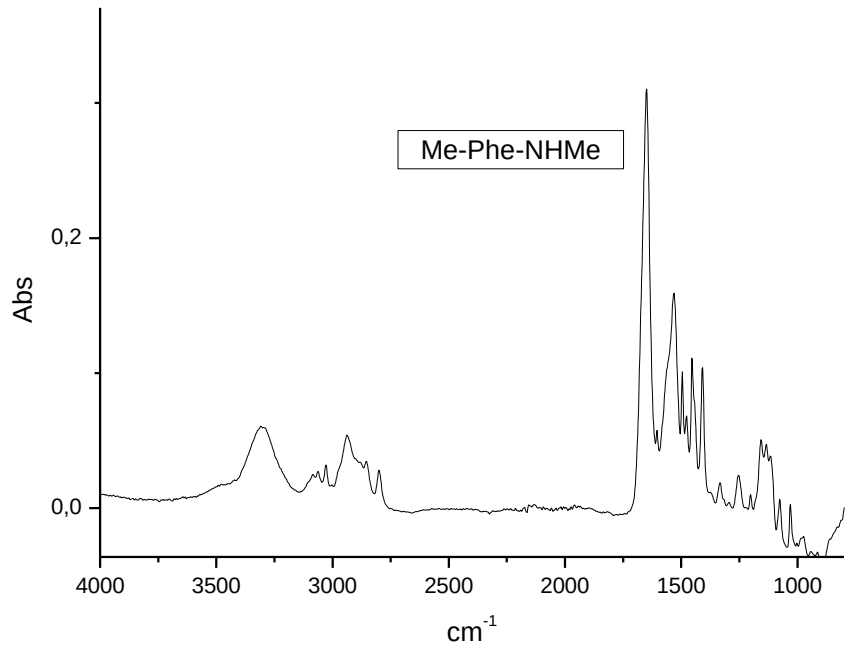
ATR-IR spectrm of **3a** (solid), maxima at: 3293, 2963, 1637, 1565 cm^{-1}.



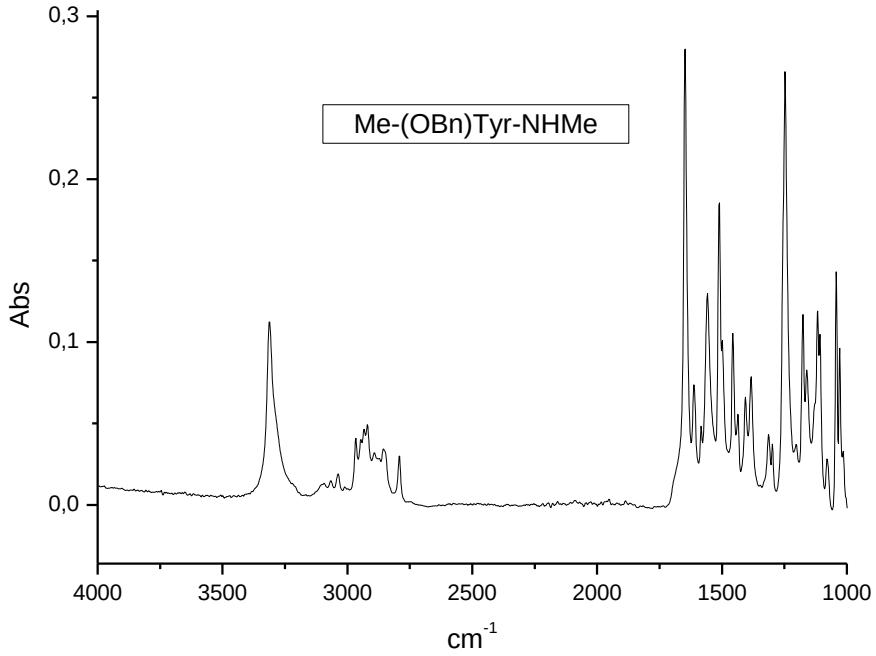
ATR-IR Spectra of **3b** (oil), maxima at 3295, 2954, 1647 and 1535 cm^{-1}.



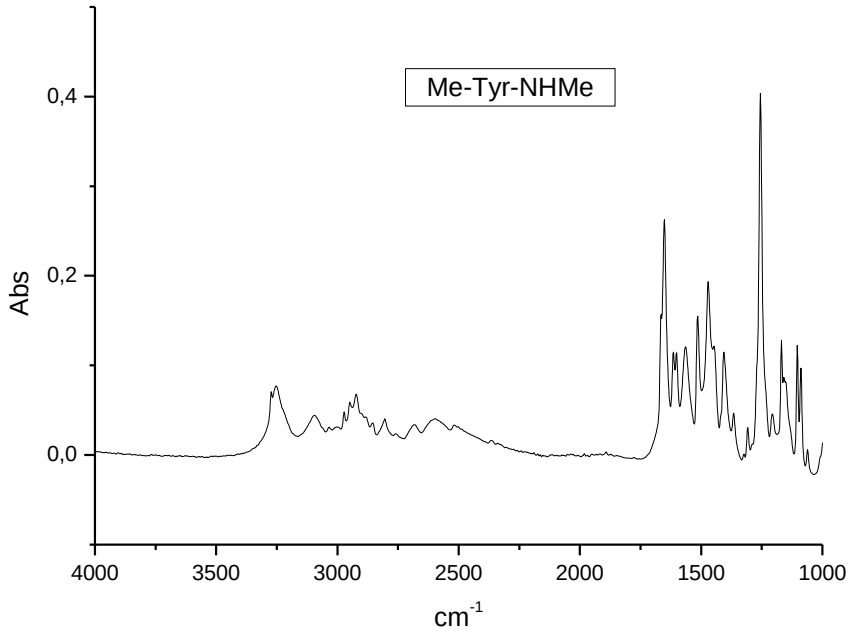
ATR-IR Spectra of **3c** (oil), maxima at 3300, 2935, 1648 and 1531 cm^{-1}.



ATR-IR Spectra of **3d** (solid), maxima at 3314, 2914, 1648, 1565 and 1510 cm^{-1}.

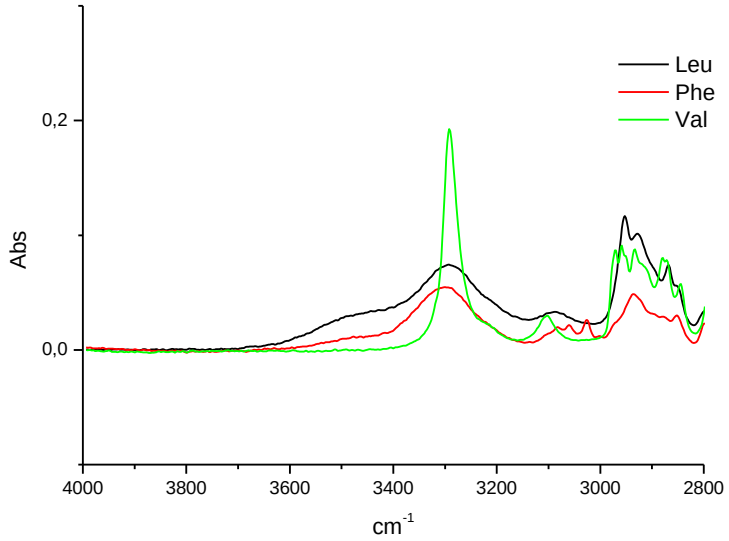


ATR-IR spectrm of **3e** (solid), maxima at 3252, 3094, 2921, 1648, 1469 and 1256 cm^{-1}.

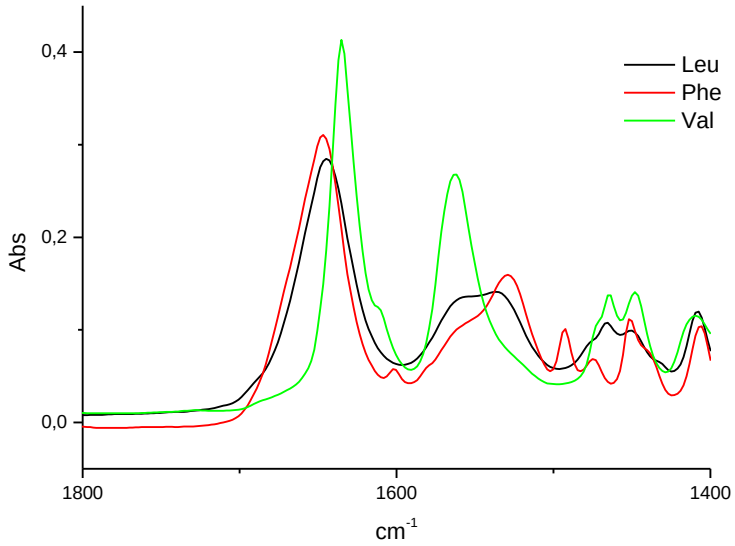


Comparison between **3a**, **3b** and **3c**

4000-2800 cm^{-1} region



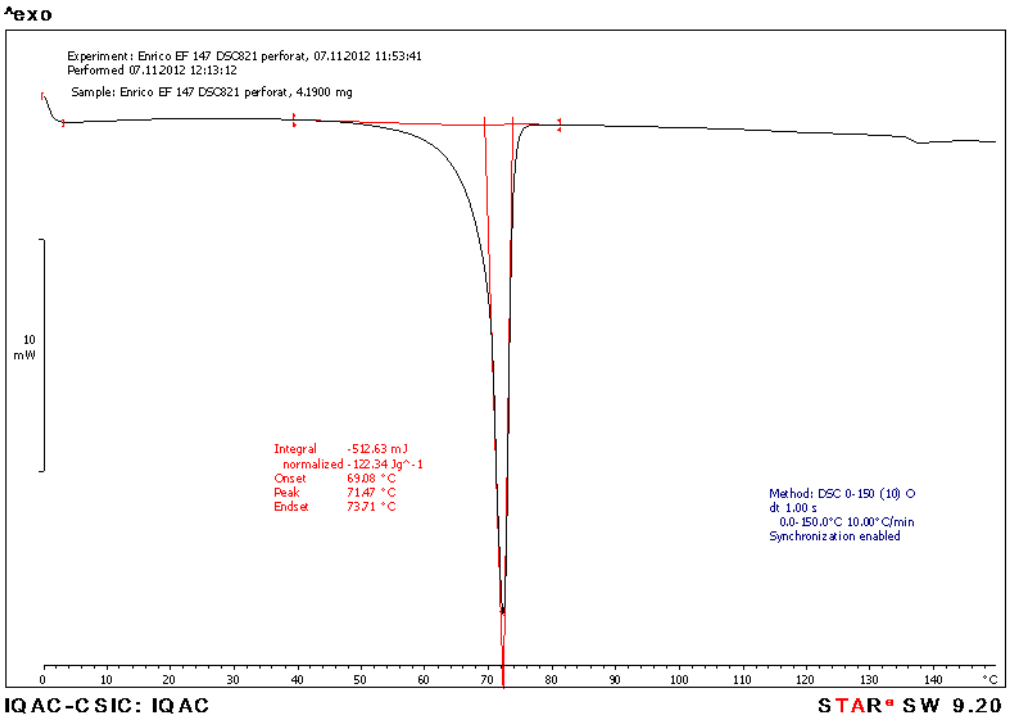
1800-1400 cm^{-1} region



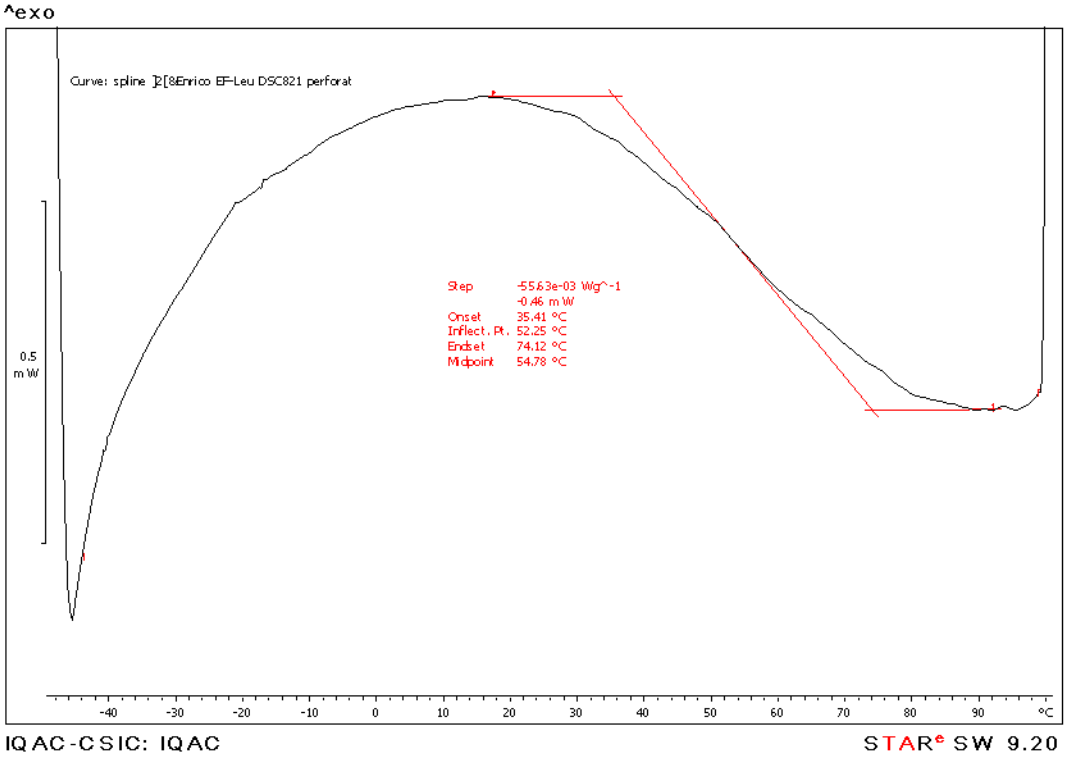
Thermal analysis

Differential Scanning Calorimetry (DSC) analyses were performed on a Mettler Toledo DSC821 apparatus. Samples were cooled down to -50°C and then heated up to +150°C.

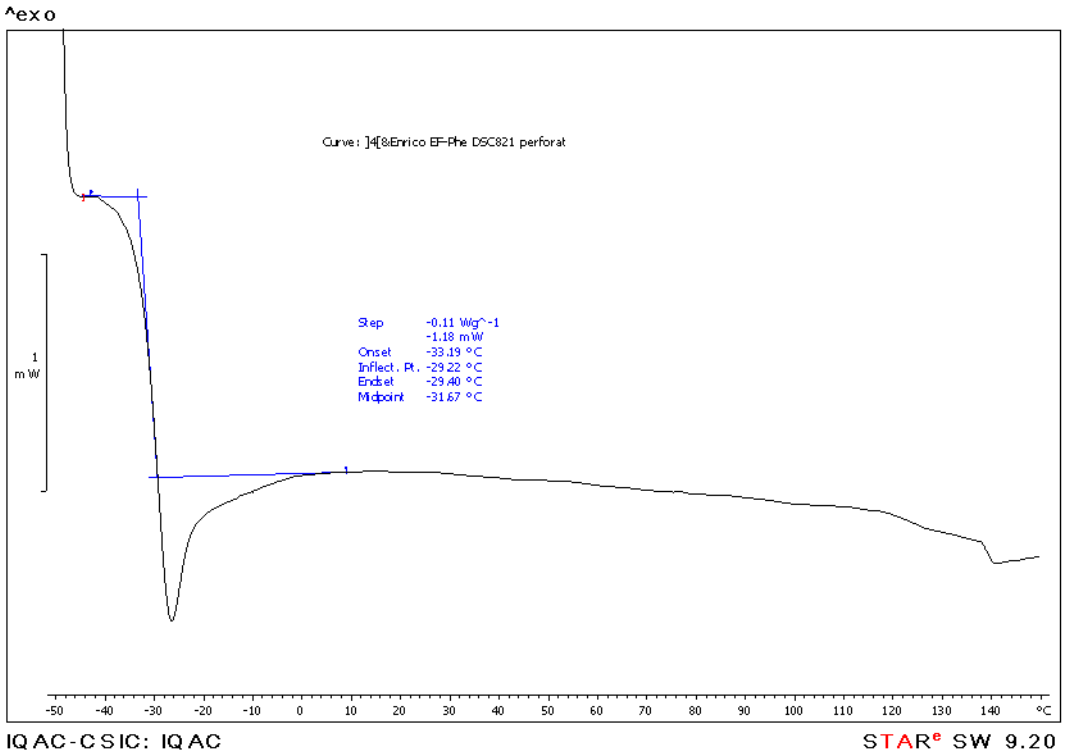
DSC curve of **3a** (white solid at room temperature)**,** showing its melting point at 69.0 °C.



DSC curve of **3b** (pale yellow oil at room temperature), showing a vitreous transition between 35.4 °C and 74.1 °C.



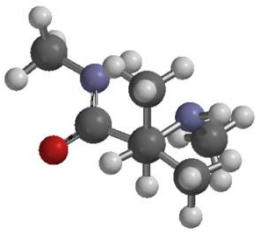
DSC curve of **3c** (pale yellow oil at room temperature), showing a vitreous transition between -34.3 °C and -30.9 °C.



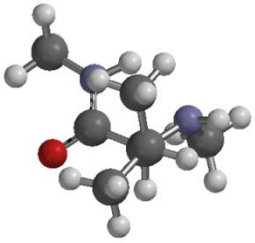
Molecular modelling

All the theoretical calculations were performed with the Spartan 06 program on a Dell workstation. An initial conformational analysis was performed at the HF/6-31G* level of theory by a Monte Carlo search followed by full unrestricted minimization. In this way, we obtained about 15-20 geometries for each molecule within a 10 kcal/mol cut-off. The representative local minima thus obtained were fully re-optimized by DFT calculations at the B3LYP/6-311+G** level of theory, including the frequency analysis. All the optimized geometries showed positive frequencies and thus, they are minima of energy. The energetically accessible conformers thus obtained were ordered according to their relative energy and the corresponding Boltzmann distribution at 298 K calculated using the same software. Besides, for every minimum, we computed the corresponding CPK areas and the polar surface area (PSA). The obtained values for every compound, as well as the Cartesian coordinates for every minimum, are shown following. All the calculations were performed in the gas phase. The electrostatic potential (ESP) mapped onto the global electron density surfaces was computed at Isoval = 0.002, 0.003, 0.004, 0.005, 0.006, 0.007, 0.008, 0.009, 0.010, 0.015, and 0.020 au using the B3LYP/6-311+G** wavefunction and with the facilities also available in this package. The graphics of the ESP electron densities were displayed using Spartan 06. The dimers of **3a** were manually built from two isolated molecules of the conformer I, by the rotation of the CO-Cα bond in order to form an extended conformation of the backbone. The possible parallel and anti-parallel dimeric non-covalent complexes were fully optimized at the B3LYP/6-31+G* level of theory also using the Spartan 06 software.

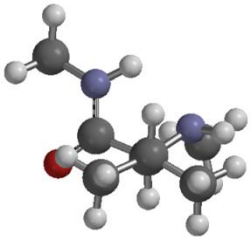
Conformer distribution for **3a** (Val)



Conf. I (0.00)



Conf. II (0.55)



Conf. III (0.75)

Val	E (kcal/mol)	rel. E (kcal/mol)	Boltzm. Dist.	CPK Area (Å²)	PSA (Å²)	PSA/CPKA
conformer I	-289446.45	0	0.594362899	201.434559	33.734603	0.16747
conformer II	-289445.904	0.545707796	0.236631686	200.942952	33.935504	0.16888
conformer III	-289445.705	0.74513675	0.169005415	199.819661	34.053257	0.17042

Conformer I

Cartesian Coordinates (Angstroms)

	Atom		X	Y	Z
1	C	CA	-0.2561979	-0.2038962	-0.5977569
2	C	C	1.1628902	0.3886750	-0.7282694
3	O	O	1.4548855	1.0952133	-1.6852947
4	H	HA	-0.4823197	-0.5979079	-1.6000211

5	C	CB	-1.2695259	0.9417503	-0.3324588
6	N	N2	2.0108124	0.0783812	0.2817065
7	H	H4	1.6158835	-0.4916289	1.0199263
8	C	C1	3.3744965	0.5684757	0.3569875
9	H	H2	4.0759175	-0.2572882	0.5045954
10	H	H5	3.4976206	1.2839579	1.1765333
11	H	H6	3.6053253	1.0703105	-0.5819282
12	C	C2	-0.0435820	-2.6082032	-0.1150367
13	H	H3	-0.1555776	-3.3436338	0.6849257
14	H	H7	0.9882453	-2.6602414	-0.4725091
15	H	H8	-0.7017639	-2.8948467	-0.9500289
16	N	N1	-0.3206945	-1.2694486	0.4081708
17	H	H11	-1.2216896	-1.2635411	0.8699500
18	H	H1	-1.0386520	1.6958852	-1.0906036
19	C	C3	-2.7161753	0.4788901	-0.5592180
20	H	H9	-3.0280813	-0.2840525	0.1630625
21	H	H10	-2.8500503	0.0644746	-1.5625654
22	H	H12	-3.4063999	1.3199271	-0.4493613
23	C	C4	-1.1015566	1.5921678	1.0493000
24	H	H13	-0.0883208	1.9743735	1.1934740
25	H	H14	-1.3124509	0.8896944	1.8618715
26	H	H15	-1.7930386	2.4325119	1.1545485

Conformer II

Cartesian Coordinates (Angstroms)

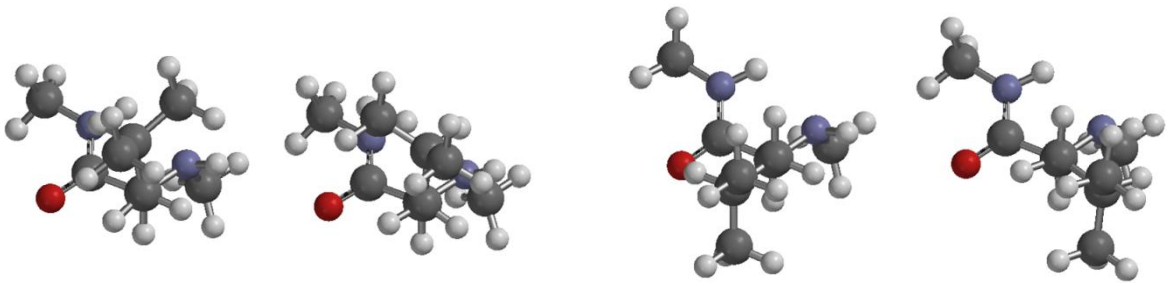
Atom			X	Y	Z
1	C	CA	-0.3370652	0.4886670	0.5247379
2	C	C	0.7664313	-0.5865558	0.6214175
3	O	O	0.7389908	-1.4469408	1.4930448
4	H	HA	-0.5481983	0.7741191	1.5659967
5	C	CB	-1.6539099	-0.0920371	-0.0650327
6	N	N2	1.7224865	-0.5001502	-0.3359682
7	H	H4	1.6208656	0.2774246	-0.9764450
8	C	C1	2.8392774	-1.4205565	-0.4370678
9	H	H2	2.8686453	-1.8920419	-1.4233969
10	H	H5	2.7124114	-2.1924786	0.3210543
11	H	H6	3.7916827	-0.9100133	-0.2641336
12	C	C2	0.8580624	2.6450499	0.5120852
13	H	H3	1.1013943	3.4937276	-0.1312335
14	H	H7	1.7995414	2.2168622	0.8662189
15	H	H8	0.3078526	3.0167074	1.3904118
16	N	N1	0.1133019	1.6475701	-0.2587185
17	H	H11	-0.6853480	2.0862964	-0.7030272
18	H	H1	-2.3160345	0.7789648	-0.1813108
19	C	C3	-1.4714998	-0.7270654	-1.4513099
20	H	H9	-0.8690946	-1.6379791	-1.3898684
21	H	H10	-0.9824762	-0.0470021	-2.1533818
22	H	H12	-2.4436838	-1.0012229	-1.8702890
23	C	C4	-2.3478852	-1.0598884	0.9023399
24	H	H13	-2.5430053	-0.5843559	1.8675834
25	H	H14	-1.7360869	-1.9442227	1.0906247
26	H	H15	-3.3066556	-1.3828786	0.4856680

Conformer III

Cartesian Coordinates (Angstroms)

	Atom	X	Y	Z
1	C CA	-0.3074435	-0.2548508	-0.4043017
2	C C	1.0887884	0.3904189	-0.5209478
3	O O	1.4093766	1.0678325	-1.4882812
4	H HA	-0.6506496	-0.3832238	-1.4430047
5	C CB	-1.3061179	0.6899202	0.3197582
6	N N2	1.8931882	0.1781963	0.5510658
7	H H4	1.5659251	-0.5135995	1.2133463
8	C C1	3.2558234	0.6767323	0.6173072
9	H H2	3.2962459	1.6817397	0.1965467
10	H H5	3.9528867	0.0464037	0.0536801
11	H H6	3.5756373	0.7119617	1.6598814
12	C C2	0.3259443	-2.6297858	-0.5163388
13	H H3	0.3418686	-3.5493451	0.0729254
14	H H7	1.3543481	-2.4063721	-0.8123884
15	H H8	-0.2536959	-2.8112256	-1.4348674
16	N N1	-0.2044166	-1.5374215	0.3016551
17	H H11	-1.1074121	-1.8017653	0.6743672
18	H H1	-0.9966516	0.7307172	1.3719374
19	C C3	-1.2828165	2.1177810	-0.2426730
20	H H9	-1.5489039	2.1297692	-1.3039220
21	H H10	-0.3011749	2.5833609	-0.1498248
22	H H12	-2.0060595	2.7384741	0.2936920
23	C C4	-2.7399128	0.1348554	0.2595308
24	H H13	-2.8498837	-0.8411171	0.7421102
25	H H14	-3.0754975	0.0355325	-0.7780914
26	H H15	-3.4293967	0.8150110	0.7668374

Conformer distribution for **3b** (Leu)



Conf. Ia (1.78) Conf. Ib (2.13) Conf. II (0.26) Conf. III (0.00)

Leu	E (kcal/mol)	rel. E (kcal/mol)	Boltzm. Dist.	CPK Area (Å²)	PSA (Å²)	PSA/CPKA
Conformer III	-314123.385	0	0.580587011	221.727161	34.089998	0.15375
Conformer II	-314123.126	0.25918673	0.374882637	221.642363	34.937194	0.15763
Conformer Ia	-314121.603	1.78201545	0.028690076	220.540544	33.796751	0.15325
Conformer Ib	-314121.251	2.13397326	0.015840277	219.797974	34.340184	0.15624

Conformer Ia

Cartesian Coordinates (Angstroms)

	Atom		X	Y	Z
1	C	CA	-0.4169804	-0.6636524	0.9217861
2	C	C	-1.2127957	0.6569232	0.8797153
3	O	O	-1.2370837	1.4047206	1.8491645
4	H	HA	-0.6669442	-1.1025146	1.8997222
5	C	CB	1.0967182	-0.3546923	0.9654545
6	N	N2	-1.8474205	0.9102866	-0.2897905
7	H	H4	-1.7096037	0.2248791	-1.0212607
8	C	C1	-2.6035513	2.1267066	-0.5275391
9	H	H2	-1.9764635	2.9245641	-0.9404353
10	H	H5	-3.0169821	2.4761392	0.4185694
11	H	H6	-3.4180606	1.9231986	-1.2249342
12	C	C2	-1.9515426	-2.4258613	0.1504865
13	H	H3	-2.1291755	-3.1171740	-0.6762796
14	H	H7	-2.8467902	-1.8096133	0.2669275
15	H	H8	-1.8236135	-3.0097442	1.0755632
16	N	N1	-0.7986267	-1.5782433	-0.1629264
17	H	H11	-0.0081443	-2.1602840	-0.4126528
18	H	H1	1.6383817	-1.3078832	1.0436435
19	C	C3	1.7145374	0.4927390	-0.1669296
20	H	H9	1.0728305	1.3698098	-0.3177284
21	C	C5	3.0948178	1.0037999	0.2741577
22	H	H12	3.0245205	1.5988317	1.1888848
23	H	H16	3.5484359	1.6292882	-0.5001966
24	H	H17	3.7792561	0.1700721	0.4688795
25	C	C6	1.8276506	-0.2472456	-1.5085225
26	H	H10	0.8543778	-0.5585602	-1.8914921
27	H	H18	2.4565436	-1.1406081	-1.4101378
28	H	H19	2.2938074	0.3944351	-2.2622901
29	H	H20	1.2619012	0.1696829	1.9101610

Conformer Ib

Cartesian Coordinates (Angstroms)

	Atom		X	Y	Z
1	C	CA	-0.3972503	-0.7765798	0.7692512
2	C	C	-1.2937244	0.4792985	0.7759314
3	O	O	-1.3580290	1.1951664	1.7670608
4	H	HA	-0.6834421	-1.3020621	1.6930806
5	C	CB	1.0979116	-0.4265589	0.9416250
6	N	N2	-1.9945288	0.6960828	-0.3630390
7	H	H4	-1.7889345	0.0663433	-1.1285349
8	C	C1	-2.8552909	1.8504910	-0.5463099
9	H	H2	-2.3020886	2.7175893	-0.9249222
10	H	H5	-3.2931641	2.1232889	0.4138988
11	H	H6	-3.6515842	1.6054799	-1.2510923
12	C	C2	-1.6643950	-2.6587545	-0.1932021
13	H	H3	-1.7501832	-3.2753198	-1.0908968
14	H	H7	-2.6338993	-2.1838741	-0.0215356
15	H	H8	-1.4563890	-3.3164071	0.6654023
16	N	N1	-0.6406386	-1.6325761	-0.3989797
17	H	H11	0.2250261	-2.0641919	-0.6990819
18	H	H1	1.6056989	-1.3616499	1.2081280

19	C	C3	1.8533714	0.2086181	-0.2471514
20	H	H9	1.6351515	-0.3694471	-1.1550569
21	C	C5	1.4550846	1.6680761	-0.5123158
22	H	H12	0.4026727	1.7677278	-0.7809379
23	H	H16	2.0478774	2.0827742	-1.3332230
24	H	H17	1.6290109	2.2862080	0.3741057
25	C	C6	3.3664528	0.1127428	0.0059373
26	H	H10	3.6882097	-0.9239473	0.1452208
27	H	H18	3.6456531	0.6717518	0.9056725
28	H	H19	3.9324567	0.5294519	-0.8321399
29	H	H20	1.1789643	0.2302780	1.8131049

Conformer II

Cartesian Coordinates (Angstroms)

	Atom		X	Y	Z
1	C	CA	-0.4111472	-0.6537511	0.2407689
2	C	C	-1.0808799	0.7154748	0.4734724
3	O	O	-0.7621835	1.4311726	1.4151624
4	H	HA	-0.1681411	-1.0305019	1.2436578
5	C	CB	0.8918728	-0.4953382	-0.5713623
6	N	N2	-1.9937033	1.0596582	-0.4683525
7	H	H4	-2.2304782	0.3300121	-1.1290544
8	C	C1	-2.7378085	2.3056669	-0.4285816
9	H	H2	-2.1285938	3.0649659	0.0611457
10	H	H5	-3.6745256	2.2068532	0.1316335
11	H	H6	-2.9681552	2.6288038	-1.4455235
12	C	C2	-2.3007430	-2.2280113	0.3852400
13	H	H3	-2.8966642	-2.9211900	-0.2127691
14	H	H7	-2.9815495	-1.4846877	0.8091241
15	H	H8	-1.8500508	-2.7843781	1.2217852
16	N	N1	-1.3153898	-1.5661280	-0.4714233
17	H	H11	-0.7726857	-2.2594699	-0.9739590
18	H	H1	0.6251168	-0.1304349	-1.5702891
19	C	C3	1.9881878	0.4084138	0.0228031
20	H	H9	1.5580363	1.4007870	0.1925142
21	C	C5	2.5094477	-0.1094246	1.3701231
22	H	H12	1.7286750	-0.1051380	2.1329110
23	H	H16	3.3251754	0.5222156	1.7334459
24	H	H17	2.8982691	-1.1305965	1.2761954
25	C	C6	3.1352516	0.5539649	-0.9879349
26	H	H10	2.7826235	0.9694688	-1.9369431
27	H	H18	3.6016783	-0.4150323	-1.2008656
28	H	H19	3.9145333	1.2180192	-0.6028899
29	H	H20	1.3138320	-1.5013942	-0.7100345

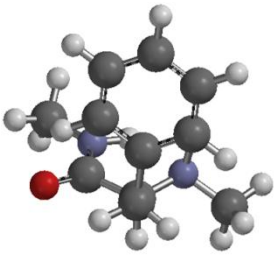
Conformer III

Cartesian Coordinates (Angstroms)

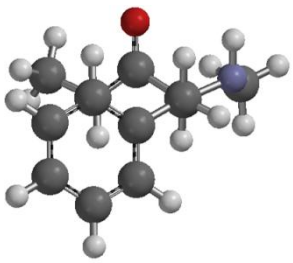
	Atom		X	Y	Z
1	C	CA	-0.3754780	-0.2481552	0.3176836
2	C	C	-1.6599888	0.5651692	0.5850473
3	O	O	-1.7573886	1.2716512	1.5801631
4	H	HA	-0.0930187	-0.6551657	1.2985305

5	C	CB	0.7230223	0.7240677	-0.1538176
6	N	N2	-2.6114333	0.4477609	-0.3721819
7	H	H4	-2.3785517	-0.1766807	-1.1345067
8	C	C1	-3.8704026	1.1680095	-0.3402585
9	H	H2	-3.9258901	1.9113086	-1.1421089
10	H	H5	-3.9407488	1.6819015	0.6177496
11	H	H6	-4.7146554	0.4802349	-0.4405839
12	C	C2	-1.0767079	-2.5778691	-0.0863703
13	H	H3	-1.1797988	-3.3228726	-0.8785498
14	H	H7	-2.0629658	-2.4299131	0.3613802
15	H	H8	-0.4122153	-2.9833321	0.6920660
16	N	N1	-0.5981051	-1.3191199	-0.6606972
17	H	H11	0.2465888	-1.4841102	-1.1943618
18	H	H1	0.6714354	1.6146418	0.4795140
19	C	C3	2.1674802	0.1822900	-0.1257319
20	H	H9	2.2086413	-0.7615425	-0.6879433
21	C	C6	2.6558475	-0.0984633	1.3024078
22	H	H10	2.0463970	-0.8493056	1.8111793
23	H	H18	2.6240194	0.8155792	1.9043861
24	H	H19	3.6878835	-0.4608418	1.2962927
25	H	H20	0.4752801	1.0448758	-1.1734328
26	C	C4	3.1066851	1.1722429	-0.8307171
27	H	H12	4.1377868	0.8072254	-0.8301854
28	H	H13	3.0977552	2.1434876	-0.3245145
29	H	H14	2.8085262	1.3369257	-1.8704387

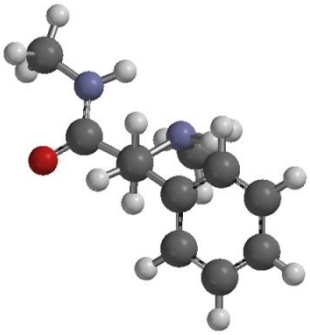
Conformer distribution for **3c** (Phe)



Conf. I (0.74)



Conf. II (2.33)



Conf. III (0.00)

Phe	E (kcal/mol)	rel. E (kcal/mol)	Boltzm. Dist.	CPK Area (Å²)	PSA (Å²)	PSA/CPKA
conformer III	-385116.925	0	0.765144281	244.67005	33.749913	0.13794
conformer I	-385116.186	0.739162854	0.219771238	242.361124	32.672415	0.13481
conformer II	-385114.599	2.32649333	0.015084482	246.010173	37.439279	0.15219

Conformer I

Cartesian Coordinates (Angstroms)

	Atom		X	Y	Z
1	C	CA	1.2513372	-0.5904526	-0.5996017
2	C	C	1.6878397	0.8870737	-0.4655390

3	O	O	1.6467812	1.6474257	-1.4261877
4	H	HA	2.0856322	-1.0662193	-1.1297323
5	C	CB	0.0035496	-0.7192931	-1.5186218
6	C	CG	-1.2826794	-0.2379856	-0.8842787
7	H	2HB	-0.1018560	-1.7702372	-1.8024556
8	H	1HB	0.2112264	-0.1540691	-2.4290134
9	C	CZ	-3.6540539	0.6520728	0.3466262
10	C	CD1	-2.1450273	-1.1379692	-0.2447172
11	C	CD2	-1.6366298	1.1186365	-0.9043424
12	C	CE2	-2.8097852	1.5582180	-0.2950170
13	C	CE1	-3.3192092	-0.6997554	0.3680661
14	H	HD1	-1.9053946	-2.1971815	-0.2422445
15	H	HD2	-0.9837495	1.8269333	-1.4016083
16	H	HE2	-3.0683377	2.6110833	-0.3265489
17	H	HE1	-3.9744452	-1.4152668	0.8530542
18	N	N2	2.1419742	1.2330424	0.7599817
19	H	H4	2.1561012	0.4843496	1.4417069
20	C	C1	2.6805877	2.5455110	1.0649339
21	H	H2	3.7759360	2.5430283	1.0668161
22	H	H5	2.3283175	2.8788362	2.0437724
23	H	H6	2.3398499	3.2447176	0.3020360
24	N	N1	1.1455255	-1.2504311	0.7055286
25	H	H1	0.2322339	-1.0551682	1.1065168
26	C	C2	1.3809610	-2.6946222	0.6901877
27	H	H3	0.7090931	-3.2582946	0.0252296
28	H	H7	1.2630043	-3.0885013	1.7020942
29	H	H8	2.4092618	-2.8909228	0.3751697
30	H	H10	-4.5680447	0.9954412	0.8181883

Conformer II

Cartesian Coordinates (Angstroms)

	Atom		X	Y	Z
1	C	CA	1.2327482	-0.7941349	0.0120703
2	C	C	1.3154620	0.7239957	0.2873694
3	O	O	1.8015978	1.1441488	1.3298584
4	H	HA	1.0137610	-0.9653431	-1.0487876
5	C	CB	0.0946173	-1.4144925	0.8582716
6	C	CG	-1.2852458	-0.8994943	0.5155789
7	H	2HB	0.3143007	-1.2214585	1.9124377
8	H	1HB	0.1471582	-2.4954306	0.7066523
9	C	CZ	-3.8362436	0.0738921	-0.1671511
10	C	CD1	-1.8854423	0.1223630	1.2600905
11	C	CD2	-1.9891623	-1.4282634	-0.5738257
12	C	CE2	-3.2520393	-0.9477600	-0.9149174
13	C	CE1	-3.1489021	0.6063171	0.9224300
14	H	HD1	-1.3578644	0.5392647	2.1121228
15	H	HD2	-1.5475889	-2.2342319	-1.1524262
16	H	HE2	-3.7835693	-1.3770025	-1.7573743
17	H	HE1	-3.5985881	1.3957864	1.5148152
18	H	HZ	-4.8211610	0.4459249	-0.4263950
19	N	N2	0.8383034	1.5407903	-0.6889672
20	H	H4	0.3421413	1.1164985	-1.4571476
21	C	C1	0.7352672	2.9823571	-0.5130645

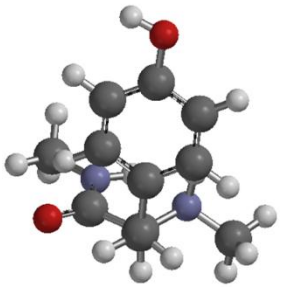
22	H	H2	-0.1886305	3.2636785	0.0032668
23	H	H5	0.7621603	3.4707786	-1.4882345
24	H	H6	1.5800328	3.3228743	0.0841553
25	C	C2	3.5998832	-1.1132314	-0.5546182
26	H	H3	4.4927516	-1.6529063	-0.2321465
27	H	H7	3.8351061	-0.0379425	-0.5662904
28	H	H8	3.3772489	-1.4266946	-1.5790494
29	N	N1	2.4835061	-1.4760152	0.3188333
30	H	H11	2.7283911	-1.2642682	1.2824432

Conformer III

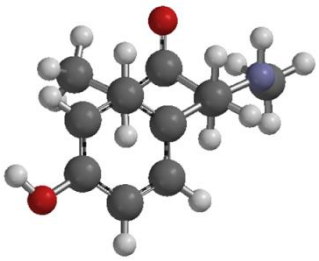
Cartesian Coordinates (Angstroms)

	Atom		X	Y	Z
1	C	CA	-0.7730896	0.1683021	0.4303920
2	C	C	-2.1997137	0.7354943	0.2999866
3	O	O	-2.5370696	1.7499260	0.8965966
4	H	HA	-0.4862031	0.3357341	1.4790931
5	C	CB	0.1618667	1.0155587	-0.4660850
6	C	CG	1.6285599	0.6862749	-0.2946960
7	H	2HB	-0.0176520	2.0647927	-0.2197422
8	H	1HB	-0.1321803	0.8711098	-1.5105581
9	C	CZ	4.3504156	0.0605375	0.0473436
10	C	CD1	2.3203368	1.0934387	0.8539392
11	C	CD2	2.3276907	-0.0342982	-1.2690144
12	C	CE2	3.6776539	-0.3462606	-1.1014510
13	C	CE1	3.6666422	0.7843042	1.0249165
14	H	HD1	1.7998636	1.6668428	1.6146368
15	H	HD2	1.8151250	-0.3417005	-2.1753444
16	H	HE2	4.2023837	-0.9011103	-1.8714860
17	H	HE1	4.1859038	1.1141072	1.9180538
18	H	HZ	5.4000043	-0.1771404	0.1790072
19	N	N2	-3.0055747	0.0598664	-0.5508778
20	H	H4	-2.6137970	-0.7752576	-0.9659698
21	C	C1	-4.3653971	0.4853509	-0.8355679
22	H	H2	-4.3790133	1.4934321	-1.2577789
23	H	H5	-4.9715888	0.4951635	0.0739989
24	H	H6	-4.8086222	-0.2070394	-1.5515582
25	C	C2	-1.1040808	-2.1574797	1.1471301
26	H	H3	-0.9901739	-3.1900860	0.8104419
27	H	H7	-2.1564240	-2.0033663	1.3998044
28	H	H8	-0.5138635	-2.0208460	2.0660867
29	N	N1	-0.7106694	-1.2481457	0.0676622
30	H	H11	0.2286668	-1.4775054	-0.2389601

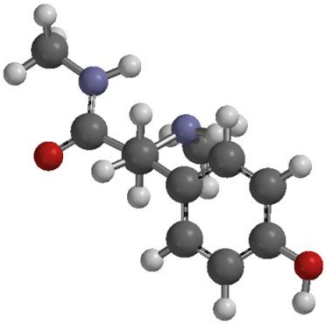
Conformer distribution for **3e** (Tyr)



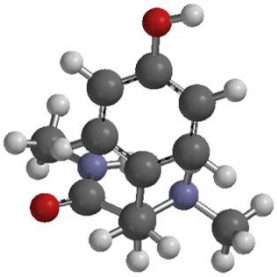
Conf. Ia (0.68)



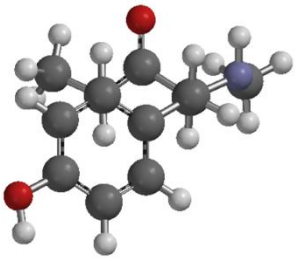
Conf. IIa (2.42)



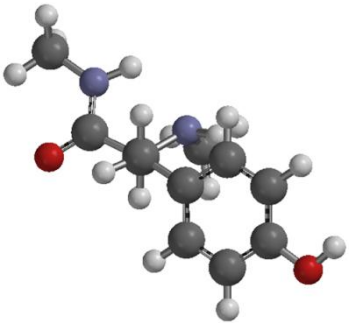
Conf. IIIa (0.00)



Conf. Ib (0.92)



Conf. IIb (2.54)



Conf. IIIb (0.03)

Tyr	E (kcal/mol)	rel. E (kcal/mol)	Boltzm. Dist.	CPK Area (Å²)	PSA (Å²)	PSA/CPKA
conformer IIIa	-432335.311	0	0.397239751	253.547423	53.249317	0.21002
conformer IIIb	-432335.284	0.026763302	0.379696355	253.545255	53.24676	0.21001
Conformer Ia	-432334.634	0.677616673	0.126587478	251.175877	52.267903	0.20809
conformer Ib	-432334.393	0.918442461	0.084309495	251.388224	52.46461	0.2087
conformer IIa	-432332.896	2.41551817	0.006738894	254.994364	57.194246	0.2243
conformer IIb	-432332.768	2.54369336	0.005428028	254.877466	57.171952	0.22431

Conformer Ia

Cartesian Coordinates (Angstroms)

	Atom	X	Y	Z
1	C CA	1.4251122	-0.6596514	-0.6208959
2	C C	1.8577941	0.8196785	-0.4899728
3	O O	1.8027526	1.5818610	-1.4489059
4	H HA	2.2639199	-1.1368480	-1.1428923
5	C CB	0.1815290	-0.7950962	-1.5430393
6	C CG	-1.1086453	-0.3077165	-0.9211412
7	H 2HB	0.0767660	-1.8485379	-1.8182706
8	H 1HB	0.3938112	-0.2407008	-2.4590751
9	C CZ	-3.4931415	0.5928222	0.2821999
10	C CD1	-1.9871615	-1.1966220	-0.2870781
11	C CD2	-1.4628631	1.0471251	-0.9457973
12	C CE2	-2.6396277	1.4967207	-0.3522621
13	C CE1	-3.1660555	-0.7614682	0.3121042
14	H HD1	-1.7569248	-2.2577467	-0.2752679

15	H	HD2	-0.8065302	1.7575077	-1.4352713
16	H	HE2	-2.8954697	2.5520609	-0.3887884
17	H	HE1	-3.8423550	-1.4572810	0.7941848
18	N	N2	2.3289883	1.1619306	0.7304144
19	H	H4	2.3264387	0.4163061	1.4159769
20	C	C1	2.8532272	2.4779830	1.0437447
21	H	H2	3.9192797	2.4312039	1.2866874
22	H	H5	2.3194235	2.9188648	1.8904505
23	H	H6	2.7194822	3.1129658	0.1688651
24	N	N1	1.3122718	-1.3122207	0.6878764
25	H	H1	0.3954872	-1.1152384	1.0801931
26	C	C2	1.5480408	-2.7564774	0.6819958
27	H	H3	0.8826294	-3.3234924	0.0134225
28	H	H7	1.4202345	-3.1451860	1.6947061
29	H	H8	2.5792940	-2.9544267	0.3777679
30	O	O1	-4.6639627	0.9758352	0.8836680
31	H	H9	-4.7837452	1.9258448	0.7844005

Conformer Ib

Cartesian Coordinates (Angstroms)

	Atom		X	Y	Z
1	C	CA	1.4376897	-0.6031426	-0.6436417
2	C	C	1.8667045	0.8764546	-0.5093828
3	O	O	1.8143879	1.6396559	-1.4674716
4	H	HA	2.2751334	-1.0759325	-1.1717061
5	C	CB	0.1901792	-0.7385273	-1.5611491
6	C	CG	-1.0999600	-0.2645621	-0.9291121
7	H	2HB	0.0908228	-1.7901426	-1.8452189
8	H	1HB	0.3951435	-0.1748722	-2.4733487
9	C	CZ	-3.4825167	0.6175070	0.2917890
10	C	CD1	-1.9725883	-1.1645517	-0.3094960
11	C	CD2	-1.4591415	1.0924938	-0.9307156
12	C	CE2	-2.6318465	1.5332182	-0.3296953
13	C	CE1	-3.1533077	-0.7366061	0.2987075
14	H	HD1	-1.7415741	-2.2254507	-0.3132704
15	H	HD2	-0.8049331	1.8103178	-1.4122534
16	H	HE2	-2.9051258	2.5816880	-0.3389686
17	H	HE1	-3.8177662	-1.4577017	0.7667274
18	N	N2	2.3262881	1.2236062	0.7136124
19	H	H4	2.3471059	0.4755729	1.3957004
20	C	C1	2.8540264	2.5408860	1.0170145
21	H	H2	3.9482488	2.5626302	0.9616027
22	H	H5	2.5462735	2.8446603	2.0203725
23	H	H6	2.4598556	3.2495969	0.2887857
24	N	N1	1.3326336	-1.2614965	0.6628202
25	H	H1	0.4175144	-1.0668922	1.0601838
26	C	C2	1.5698157	-2.7053076	0.6493078
27	H	H3	0.9011677	-3.2706813	-0.0175816
28	H	H7	1.4491539	-3.0986720	1.6611661
29	H	H8	2.5993315	-2.9008108	0.3377600
30	O	O1	-4.6259398	1.1056224	0.8692381
31	H	H9	-5.1267763	0.3814396	1.2582238

Conformer IIa

Cartesian Coordinates (Angstroms)

	Atom		X	Y	Z
1	C	CA	1.4173864	-0.8431140	0.0096604
2	C	C	1.4924588	0.6752361	0.2839432
3	O	O	1.9645235	1.0995237	1.3314532
4	H	HA	1.2072816	-1.0151497	-1.0529600
5	C	CB	0.2746620	-1.4666069	0.8469806
6	C	CG	-1.1034846	-0.9424175	0.5126941
7	H	2HB	0.4957110	-1.2862370	1.9032972
8	H	1HB	0.3235769	-2.5465138	0.6860186
9	C	CZ	-3.6540331	0.0499363	-0.1548730
10	C	CD1	-1.7018843	0.0714650	1.2656705
11	C	CD2	-1.8192933	-1.4504408	-0.5798521
12	C	CE2	-3.0781989	-0.9662608	-0.9182799
13	C	CE1	-2.9633402	0.5681323	0.9403889
14	H	HD1	-1.1762896	0.4819841	2.1217497
15	H	HD2	-1.3881041	-2.2519240	-1.1721570
16	H	HE2	-3.6296495	-1.3705656	-1.7587609
17	H	HE1	-3.4095650	1.3537913	1.5437855
18	N	N2	1.0242327	1.4893466	-0.6990652
19	H	H4	0.5385550	1.0626568	-1.4725414
20	C	C1	0.9203246	2.9312660	-0.5287560
21	H	H2	-0.0035013	3.2144478	-0.0131388
22	H	H5	0.9465906	3.4158540	-1.5058517
23	H	H6	1.7648420	3.2750402	0.0670352
24	C	C2	3.7922013	-1.1515979	-0.5341509
25	H	H3	4.6830967	-1.6907460	-0.2052853
26	H	H7	4.0251420	-0.0757153	-0.5386329
27	H	H8	3.5805476	-1.4607729	-1.5622164
28	N	N1	2.6679535	-1.5208554	0.3261608
29	H	H11	2.9020461	-1.3130494	1.2932427
30	O	O1	-4.8965114	0.4938795	-0.5259935
31	H	H1	-5.1972771	1.1694075	0.0904344

Conformer IIb

Cartesian Coordinates (Angstroms)

	Atom		X	Y	Z
1	C	CA	1.7058429	-0.7729803	-0.1320933
2	C	C	1.7512958	0.7436183	0.1577877
3	O	O	2.2403317	1.1652176	1.1985378
4	H	HA	1.4604072	-0.9403400	-1.1879343
5	C	CB	0.6127652	-1.4360006	0.7403641
6	C	CG	-0.7911510	-0.9522695	0.4558559
7	H	2HB	0.8652921	-1.2539992	1.7893256
8	H	1HB	0.6886720	-2.5129950	0.5711446
9	C	CZ	-3.3907390	-0.0306406	-0.1165917
10	C	CD1	-1.3834425	0.0664462	1.2133633
11	C	CD2	-1.5380568	-1.5009134	-0.5912126
12	C	CE2	-2.8243754	-1.0498064	-0.8824839
13	C	CE1	-2.6663149	0.5274024	0.9368239
14	H	HD1	-0.8300103	0.5057400	2.0370840

15	H	HD2	-1.1151521	-2.3048688	-1.1858177
16	H	HE2	-3.3882606	-1.4982837	-1.6956178
17	H	HE1	-3.1208587	1.3117231	1.5303181
18	N	N2	1.2397596	1.5583127	-0.8028635
19	H	H4	0.7510156	1.1295900	-1.5731400
20	C	C1	1.1061793	2.9958531	-0.6148747
21	H	H2	0.1705104	3.2543822	-0.1079362
22	H	H5	1.1360672	3.4949900	-1.5846971
23	H	H6	1.9368362	3.3458830	-0.0036452
24	C	C2	4.0634750	-1.0103652	-0.7733822
25	H	H3	4.9851821	-1.5161989	-0.4782712
26	H	H7	4.2572499	0.0732442	-0.7884018
27	H	H8	3.8239842	-1.3296158	-1.7922322
28	N	N1	2.9868681	-1.4173882	0.1299611
29	H	H11	3.2538194	-1.2043586	1.0874782
30	O	O1	-4.6502282	0.4586240	-0.3469487
31	H	H1	-5.0548483	-0.0141626	-1.0813928

Conformer IIIa

Cartesian Coordinates (Angstroms)

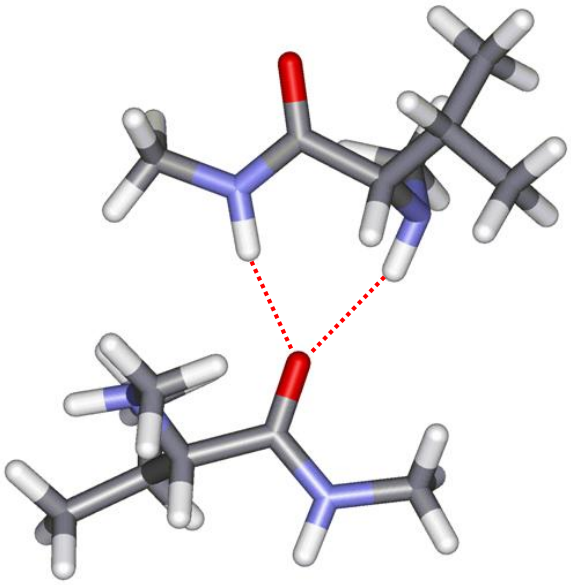
	Atom		X	Y	Z
1	C	CA	0.9786722	0.1531733	-0.4075786
2	C	C	2.4139489	0.7061133	-0.3038585
3	O	O	2.7427617	1.7134170	-0.9167993
4	H	HA	0.6812882	0.3137200	-1.4544744
5	C	CB	0.0642149	1.0213300	0.4904420
6	C	CG	-1.4092509	0.7153264	0.3360123
7	H	2HB	0.2613701	2.0657606	0.2373452
8	H	1HB	0.3653101	0.8787632	1.5333311
9	C	CZ	-4.1472731	0.1290692	0.0261618
10	C	CD1	-2.1168613	0.0081808	1.3153869
11	C	CD2	-2.1120471	1.1283938	-0.8017405
12	C	CE2	-3.4644290	0.8417380	-0.9617628
13	C	CE1	-3.4701111	-0.2868956	1.1707082
14	H	HD1	-1.6046031	-0.3081437	2.2187141
15	H	HD2	-1.5984276	1.6926089	-1.5736651
16	H	HE2	-3.9902742	1.1791987	-1.8504407
17	H	HE1	-4.0118981	-0.8299079	1.9357800
18	N	N2	3.2213654	0.0198757	0.5410866
19	H	H4	2.8095978	-0.8047697	0.9605054
20	C	C1	4.5951467	0.3967469	0.8189294
21	H	H2	4.8089196	1.3171851	0.2769590
22	H	H5	5.2931835	-0.3786154	0.4885733
23	H	H6	4.7440822	0.5707285	1.8885912
24	N	N1	0.9011372	-1.2583138	-0.0304482
25	H	H1	-0.0377795	-1.4698048	0.2899845
26	C	C2	1.2663502	-2.1840706	-1.1057089
27	H	H3	1.1391080	-3.2116133	-0.7583304
28	H	H7	2.3180144	-2.0497942	-1.3720198
29	H	H8	0.6678505	-2.0460928	-2.0192530
30	O	O1	-5.4774027	-0.1826982	-0.0726541
31	H	H9	-5.8319642	0.1593905	-0.8997769

Conformer IIIb

Cartesian Coordinates (Angstroms)

	Atom		X	Y	Z
1	C	CA	0.9791432	0.1644715	-0.4624060
2	C	C	2.4155714	0.7172609	-0.3747697
3	O	O	2.7475149	1.7036732	-1.0188854
4	H	HA	0.6832822	0.2923221	-1.5141352
5	C	CB	0.0663504	1.0623547	0.4075809
6	C	CG	-1.4068157	0.7471295	0.2705702
7	H	2HB	0.2588973	2.0974129	0.1152835
8	H	1HB	0.3722473	0.9584151	1.4536782
9	C	CZ	-4.1452494	0.1501185	-0.0126900
10	C	CD1	-2.1084671	0.0826840	1.2790297
11	C	CD2	-2.1151743	1.1102835	-0.8847655
12	C	CE2	-3.4646665	0.8193549	-1.0324507
13	C	CE1	-3.4653098	-0.2174994	1.1463696
14	H	HD1	-1.5955968	-0.1972435	2.1937720
15	H	HD2	-1.6011997	1.6402010	-1.6805893
16	H	HE2	-4.0078444	1.1091865	-1.9239663
17	H	HE1	-3.9900013	-0.7305241	1.9474026
18	N	N2	3.2205365	0.0568053	0.4929107
19	H	H4	2.8069664	-0.7536286	0.9374499
20	C	C1	4.5956838	0.4382513	0.7576347
21	H	H2	4.8033001	1.3563824	0.2093697
22	H	H5	5.2939744	-0.3364929	0.4260421
23	H	H6	4.7515493	0.6176339	1.8253404
24	N	N1	0.8976168	-1.2343247	-0.0408179
25	H	H1	-0.0432167	-1.4317829	0.2831826
26	C	C2	1.2606289	-2.1944002	-1.0866658
27	H	H3	1.1291773	-3.2102392	-0.7077509
28	H	H7	2.3130939	-2.0724985	-1.3556424
29	H	H8	0.6635845	-2.0825153	-2.0045677
30	O	O1	-5.4753716	-0.1105249	-0.2095833
31	H	H9	-5.8402054	-0.5522671	0.5640698

Val dimer in antiparallel β-sheet

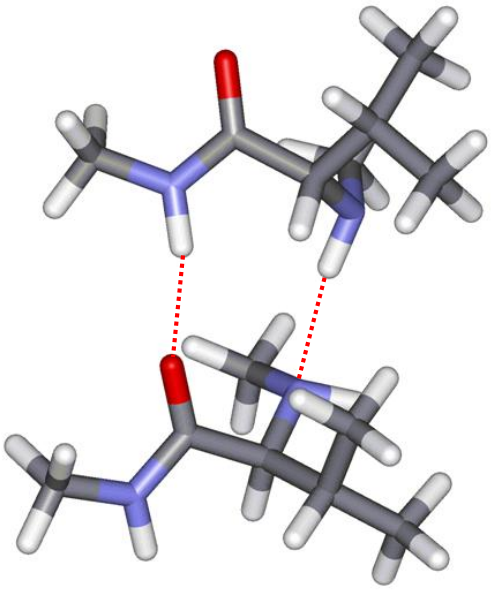


E = -578732.695 kcal/mol
Cartesian Coordinates (Angstroms)

	Atom		X	Y	Z
1	C	CA	2.5182249	-0.1271635	0.1999406
2	C	C	2.2325546	1.3965650	0.1658068
3	O	O	3.1151007	2.2590696	0.1799360
4	H	HA	1.8146787	-0.5422120	0.9346294
5	C	CB	3.9341943	-0.4561826	0.7385682
6	N	N2	0.9113929	1.7196019	0.1155138
7	C	C1	0.4676199	3.1008411	0.0335470
8	H	H2	0.9261031	3.6980952	0.8290177
9	H	H5	-0.6194118	3.1152056	0.1449787
10	H	H6	0.7420635	3.5577759	-0.9260721
11	C	C2	2.4787128	-0.1235955	-2.3210487
12	H	H3	2.1466896	-0.7618440	-3.1483416
13	H	H7	3.5540298	0.0311731	-2.4326799
14	H	H8	1.9857024	0.8586712	-2.4288946
15	N	N1	2.1813240	-0.8150619	-1.0638951
16	H	H11	1.1910470	-1.0437349	-1.0422277
17	H	H1	4.0875868	0.2121033	1.5976565
18	C	C3	3.9761626	-1.9069062	1.2454402
19	H	H9	3.7583181	-2.6065614	0.4295876
20	H	H10	3.2412009	-2.0783812	2.0437675
21	H	H12	4.9675325	-2.1500426	1.6483005
22	C	C4	5.0902524	-0.2052507	-0.2430540
23	H	H13	5.0759055	0.8193734	-0.6238426
24	H	H14	5.0516225	-0.9060759	-1.0860540
25	H	H15	6.0493105	-0.3636348	0.2674539
26	O	O1	-0.8339021	-0.7743801	-0.1595410
27	C	C5	-1.9579870	-1.1796729	0.1489066
28	N	N3	-2.2573898	-2.5035450	0.1661715
29	H	H18	-3.1929396	-2.7851197	0.4255399
30	C	C6	-1.3062939	-3.5303235	-0.2436476

31	H	H17	-1.2026617	-3.5682000	-1.3345907
32	H	H19	-1.6572819	-4.4996539	0.1177239
33	H	H20	-0.3248573	-3.3186870	0.1873135
34	C	C7	-3.1273740	-0.2397998	0.5067836
35	H	H21	-3.8166153	-0.8218564	1.1563988
36	N	N4	-2.6251277	0.9362176	1.1969344
37	H	H16	-3.3642903	1.6313199	1.2551091
38	C	C8	-2.1032260	0.6692294	2.5376147
39	H	H23	-1.1815244	0.0832355	2.4659365
40	H	H24	-2.8134002	0.1207987	3.1845988
41	H	H25	-1.8549199	1.6183438	3.0220215
42	C	C9	-3.9322344	0.1275472	-0.7777912
43	H	H22	-4.1908121	-0.8319783	-1.2490439
44	C	C10	-3.1277648	0.9519168	-1.7948332
45	H	H26	-2.1930843	0.4559405	-2.0718850
46	H	H28	-2.8711465	1.9380790	-1.3937525
47	H	H29	-3.7201188	1.1011614	-2.7057661
48	C	C11	-5.2595476	0.8226084	-0.4251181
49	H	H27	-5.8373530	0.2505068	0.3120675
50	H	H30	-5.8787962	0.9325382	-1.3230423
51	H	H31	-5.1034517	1.8329368	-0.0252396
52	H	H32	0.2101278	0.9838407	0.0764083

Val dimer in parallel β-sheet

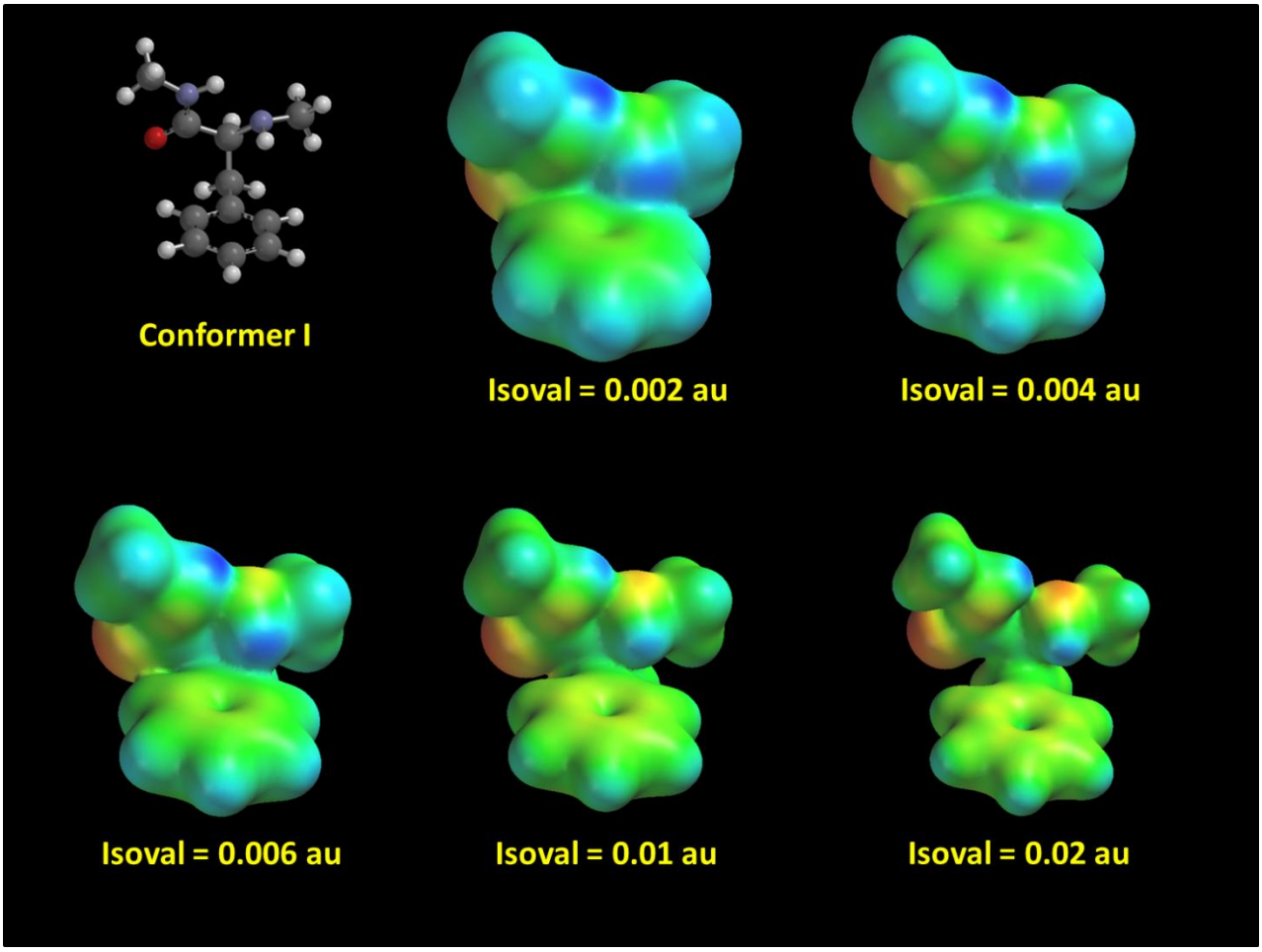


E = -578732.638 kcal/mol
Cartesian Coordinates (Angstroms)

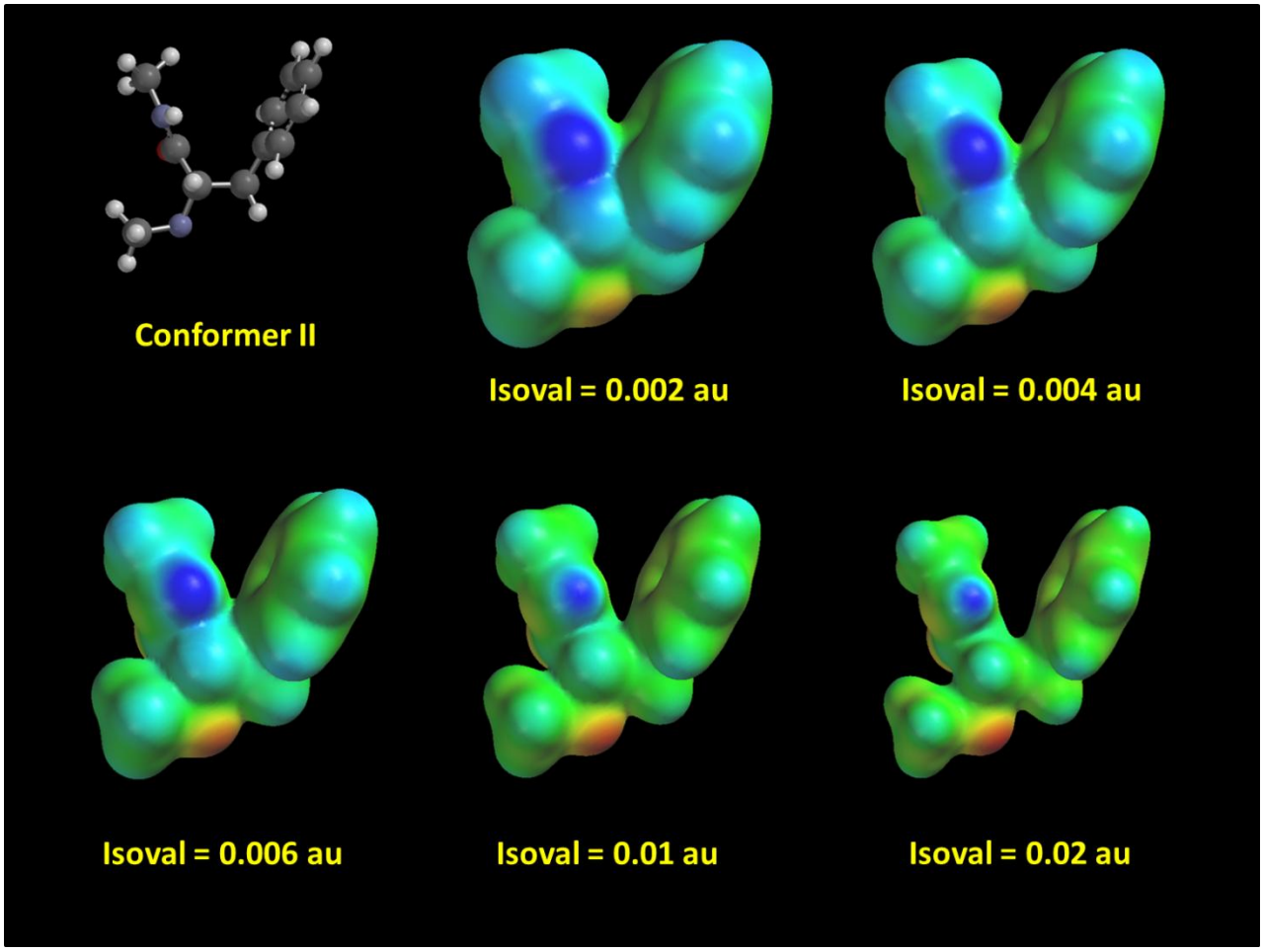
	Atom		X	Y	Z
1	C	CA	2.1812174	-0.2014817	0.3959243
2	C	C	2.4524325	1.3081303	0.1737551
3	O	O	3.5803262	1.7895006	0.0350902
4	H	HA	1.3768712	-0.2530694	1.1426305
5	C	CB	3.3938648	-0.9338558	1.0297160
6	N	N2	1.3311992	2.0750416	0.1125771
7	C	C1	1.4036799	3.5069608	-0.1234463

8	H	H2	1.9476123	4.0148475	0.6820669
9	H	H5	0.3853657	3.9012798	-0.1722193
10	H	H6	1.9222560	3.7244671	-1.0643484
11	C	C2	2.1702600	-0.4808722	-2.1058412
12	H	H3	1.6322171	-1.0417204	-2.8794044
13	H	H7	3.2268251	-0.7453619	-2.1830476
14	H	H8	2.0784257	0.5952849	-2.3361707
15	N	N1	1.6265723	-0.8680349	-0.8010310
16	H	H11	0.6158211	-0.7310658	-0.8199407
17	H	H1	3.7678835	-0.2569483	1.8109397
18	C	C3	2.9285575	-2.2340752	1.7066086
19	H	H9	2.4619461	-2.9044759	0.9749838
20	H	H10	2.1957599	-2.0372320	2.5006337
21	H	H12	3.7766964	-2.7623083	2.1604476
22	C	C4	4.5677407	-1.2220994	0.0799606
23	H	H13	4.9004847	-0.3156529	-0.4319073
24	H	H14	4.2991995	-1.9831644	-0.6629487
25	H	H15	5.4156353	-1.6166697	0.6553357
26	O	O1	-1.5229982	1.2492469	0.5477601
27	C	C5	-2.6001885	0.7260041	0.2574444
28	N	N3	-3.7811258	1.2787171	0.6410287
29	H	H18	-4.6431243	0.8611933	0.3185503
30	C	C6	-3.8452472	2.5076127	1.4220327
31	H	H17	-3.2043964	2.4269239	2.3044351
32	H	H19	-4.8782131	2.6675531	1.7394598
33	H	H20	-3.5111173	3.3702187	0.8338270
34	C	C7	-2.7272416	-0.6064311	-0.5102445
35	H	H21	-3.7041512	-0.5772833	-1.0392614
36	N	N4	-1.6315977	-0.7416090	-1.4587367
37	H	H16	-1.6066616	-1.6968753	-1.8054055
38	C	C8	-1.7027278	0.1861740	-2.5889252
39	H	H23	-1.5361342	1.2086497	-2.2355552
40	H	H24	-2.6713363	0.1541441	-3.1215385
41	H	H25	-0.9067560	-0.0533778	-3.2999312
42	C	C9	-2.8063061	-1.8022648	0.4876689
43	H	H22	-3.6340565	-1.5573596	1.1691727
44	C	C10	-1.5374693	-1.9909477	1.3328157
45	H	H26	-1.2656806	-1.0747078	1.8656931
46	H	H28	-0.6818808	-2.2835468	0.7150816
47	H	H29	-1.7019449	-2.7815664	2.0745948
48	C	C11	-3.1916072	-3.1071458	-0.2323057
49	H	H27	-4.0895013	-2.9825057	-0.8510544
50	H	H30	-3.3982492	-3.8928730	0.5035918
51	H	H31	-2.3831596	-3.4828231	-0.8727242
52	H	H32	0.4176108	1.6529926	0.2533650

ESP onto the electronic density surface for conformer I of **3c** at selected representative isovalues.



ESP onto the electronic density surface for conformer II of **3c** at selected representative isovalues.



ESP onto the electronic density surface for conformer III of **3c** at selected representative isovalues.