Electronic Supplementary Material (ESI) for ChemComm.

Supporting Information

Synergistic n→π* and n_N→π^*_{Ar} interactions in C-terminal modified prolines: Effect on Xaa-Pro cis/trans equilibrium

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1. General Experimental Information

All reagents were purchased from commercial sources (Sigma-Aldrich, Alfa Aesar, Spectrochem, CDH and TCI) and were used without further purification. Anhydrous solvents for reaction purposes were purchased from commercial sources (Chemlabs, Finar and Rankem) and were used without further purification. Column chromatography was performed on silica gel (100-200 mesh particle size) as a stationary phase using commercial solvents as mobile phase (hexane, ethylacetate and methanol). The reactions were monitored by thin layer chromatography (TLC) on silica gel 60 F_{254} (Merck). The NMR spectra were recorded in $CDCl_3$, $[CD_3]_2SO$ and D_2O or as stated deuterated solvents. ^1H (400 MHz), ^{13}C (100 and 150 MHz) and ^{19}F (564 MHz) NMR were obtained on Bruker 400 MHz and Jeol 600 MHz NMR spectrometer using tetramethylsilane (TMS) as an internal standard. ^1H, ^{13}C and ^{19}F NMR spectra were recorded at ambient temperature in $CDCl_3$, $[CD_3]_2SO$, and D_2O. Chemical shifts (δ) are reported in part per million (ppm) relative to residual undeuterated solvent as an internal reference (^1H: δ 7.26 for $CDCl_3$, δ 2.50 for $[CD_3]_2SO$, and δ 4.79 for D_2O; ^{13}C: δ 77.16 for $CDCl_3$). Chemical shifts for fluorine are reported in parts per million from $CFCl_3$ (δ 0 ppm) as the external standard. Abbreviations of NMR peak multiplicities were explained as s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad signal and dd = doublet of doublets. NMR data were processed by using MestReNova and Delta software. HRMS data were obtained using Electron Spray Ionization (ESI) "G6538A UHD Accurate-Mass Quadrupole Time-of-Flight (Q-TOF) LC/MS system (Agilent Technologies, Santa Clara, CA, USA) equipped with Agilent 1290 UPLC system". In case of isotopic pattern, we reported the highest intensity peak mass.

2. X-ray crystal structure determination method

The compounds were crystallized by slow evaporation method. The compounds (2-3 mg) were dissolved in 1 mL solvent (Table S4) in 10 mL Borosil beaker. The beaker was covered with either parafilm or Aluminium foil depending upon the volatility of the solvents used. Aluminium foil was used for volatile solvents. One or two pinholes were made on the parafilm, or aluminium foil and the beakers were kept at ambient temperature. Solvents were allowed to slowly evaporate to dryness. The crystals obtained were observed through a microscope and the best of the crystals were mounted for data collection.

Single crystal structures of the compounds were determined by measuring x-ray intensity data on a D8 venture *APEX* 3[1] X-ray diffractometer equipped with monochromatised micro-focus sources of Mo Kα radiation (λ= 0.71073 Å). Data collections were done in phi (ϕ) and omega

(ω) scan strategy at low and room temperature (297 K-300 K). Data was processed by SAINT[2] and absorption correction was done using SADABS[3] implemented in APEX 3. The structures were solved by using XSHELL program based on SHELX[4] program implemented in APEX 3 and Olex2 1.5 (Bourhis et al., 2015) (Dolomanov et al., 2009) (compiled 2022.04.07 svn.rca3783a0 for OlexSys, GUI svn.r6498). The non-hydrogen atoms were refined anisotropically and all the hydrogen atoms were assigned in idealized locations. All the structures were deposited in the CCDC[5] (CCDC No: **2239865-2239866, 2240713** and **2240910**) database.

3. Computational Studies

All the calculations were performed by using Gaussian09/16 suite quantum chemistry program.[6] We optimized each conformer using the hybrid Minnesota functional (M06-2X)/6-311+G(2d,p) level of theory.[7] Frequency calculations were also done at the same level of theory. To keep the overall environment water, we also used implicit solvent model SMD (solvent = water) developed by Truhlar and co-workers.[8] The stabilization energies due to the orbital interactions were evaluated using Natural Bond Orbital (NBO)[9] analyses. As the default amide configuration in NBO analysis is a C=O double bond with an unconjugated nitrogen lone pair, n_N(amide) → π^*_{Ar} interaction energies are likely to be overestimated. Therefore, we also carried out NBO analysis for the resonance structure [$^{(+)}$N=C─O$^{(-)}$] of the donor amide (NHCO), which, as expected, showed no n_N(amide) → π^*_{Ar} interaction as the nitrogen lone pair is completely in conjugation with the CO group in such a structure. Previous studies have indicated that the non-delocalized structure having C=O double bond with an unconjugated nitrogen lone pair contributes ~60% and the delocalized structure with N→CO delocalization contributes ~30% to the resonance hybrid of acetamide.[10] Therefore, we have presented the NBO energies as a weighted average by using 60% contribution for non-delocalized structure, which should provide a more accurate representation of the NBO n_N(amide) → π^*_{Ar} interaction energies.

4. 2D-NOESY studies

2D gradient Nuclear Overhauser Effect Spectroscopy (NOESY) ^{1}H-^{1}H Correlation (spin-lattice relaxation) NMR experiments were performed on a Bruker 400 MHz spectrometer using the following parameters – 5 mm PABBO BB/ probe or 5 mm DUL 13C-1, noesygpphpp pulse sequence, NS = 4, 8 and 32 (number of scans, 8*n), DS = 4 or 32 (numbers of dummy scans were run prior to acquisition), D1= 1.98976004 sec (relaxation delay or mixing time between 1- 5 sec) and P1= 12.85 or 13.26 usec (^{1}H 90° pulse).

5. Calculation of hydrogen bond acidity parameter A

The hydrogen bond acidity parameter A is calculated with the following equations by using chemical shift difference of a proton in DMSO-d_6 and $CDCl_3$.[11]

$$\delta\Delta = \delta(\text{DMSO-}d_6) - \delta(CDCl_3) \quad (1)$$

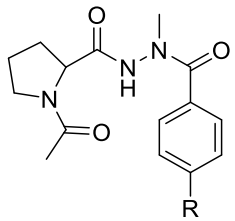
$$A = 0.0065 + 0.133\ \delta\Delta \quad (2)$$

6. Concentration-dependent ^{1}H-NMR studies

A 100 mM stock solution of the compounds was prepared in 0.6 mL (600 µL) of deuterated $CDCl_3$. After that serial dilution was done to make the solution of required concentration between 100 to 1 mM by diluting with deuterated $CDCl_3$.

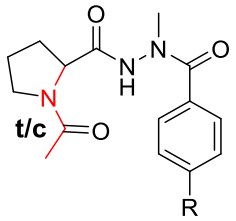
7. Supplementary Figures and Tables

Table S1. Amidic NH chemical shift values (ppm) and hydrogen bond acidity parameter A of Pro-DAH **1-6**.



Comp	R	$CDCl_3$ (NH peak)	$(CD_3)_2SO$ (NH peak)	δΔ t-t-c	A t-t-c
1	NMe_2	9.67	10.34	0.67	0.096
2	OMe	9.62	10.37	0.75	0.106
3	H	9.65	10.39	0.74	0.105
4	CF_3	9.78	10.44	0.66	0.094
5	CN	9.71	10.45	0.74	0.105
6	NO_2	9.75	10.48	0.73	0.104

Table S2: Table showing the equilibrium constant $K_{t/c}$ and Hammett parameter (σ_P)[12] for the para-substituents of Pro-DAH **1-6** in D_2O (20 mM).



Comp	R	σ_P	Rotamers % in D_2O		$K_{t/c}$ D_2O	Rotamers % in $[CD_3]_2SO$		$K_{t/c}$ $[CD_3]_2SO$
			trans	cis		trans	cis	
1	NMe_2	-0.83	73	27	2.7	67	33	2.0
2	OMe	-0.27	75	25	3.0	68	32	2.1
3	H	0.0	77	23	3.4	69	31	2.2
4	CF_3	0.54	79	21	3.8	70	30	2.3
5	CN	0.66	80	20	4.0	72	28	2.6
6	NO_2	0.78	81	19	4.3	74	26	2.8

Table S3. Concentration-dependent amidic NH proton chemical shifts of trans-trans-cis (t-t-c) conformer of Pro-DAH **2-4** & **6** in $CDCl_3$.

Concentration (mM)	**2** (R = OMe)	**3** (R = H)	**4** (R = CF_3)	**6** (R = NO_2)
100	9.62	9.68	9.77	9.73
90	9.62	9.68	9.77	9.73
80	9.62	9.68	9.77	9.73
70	9.62	9.68	9.77	9.73
60	9.62	9.68	9.77	9.73
50	9.62	9.67	9.77	9.74
40	9.61	9.67	9.78	9.74
30	9.61	9.67	9.78	9.74
20	9.61	9.67	9.78	9.74
10	9.61	9.67	9.78	9.74
1	9.61	9.67	9.78	9.74

Table S4. Structural parameters and NBO data of Pro-DAH molecules obtained from geometry optimizations (in water) and NBO analyses carried out at M06-2X/6-311+G(2d,p) level of theory.

Comp.	**R**	$\mathbf{d_{O\cdots C}}$ (Å) $\mathbf{CO_{NH}\cdots CO_{NMe}}$	$\mathbf{n_O \rightarrow \pi^*_{C=O}}$ *(kcal·mol^{-1})* $\mathbf{CO_{NH}\cdots CO_{NMe}}$
1	NMe_2	2.886	0.82
2	OMe	2.896	0.82
3	H	2.914	0.76
5	CN	2.909	0.81
6	NO_2	2.911	0.81

Table S5. Details of Crystallization conditions and their CCDC number. All compounds were crystallized at room temperature (RT).

Comp	Crystallization Solvents	CCDC	Resolution (Å)
2	Dichloromethane-Methanol (3:1), RT	2240713	0.70
3	Acetone, RT	2239866	0.80
4	Ethyl acetate-Methanol (1:1), RT	2239865	0.81
5	Acetone, RT	2240910	0.70

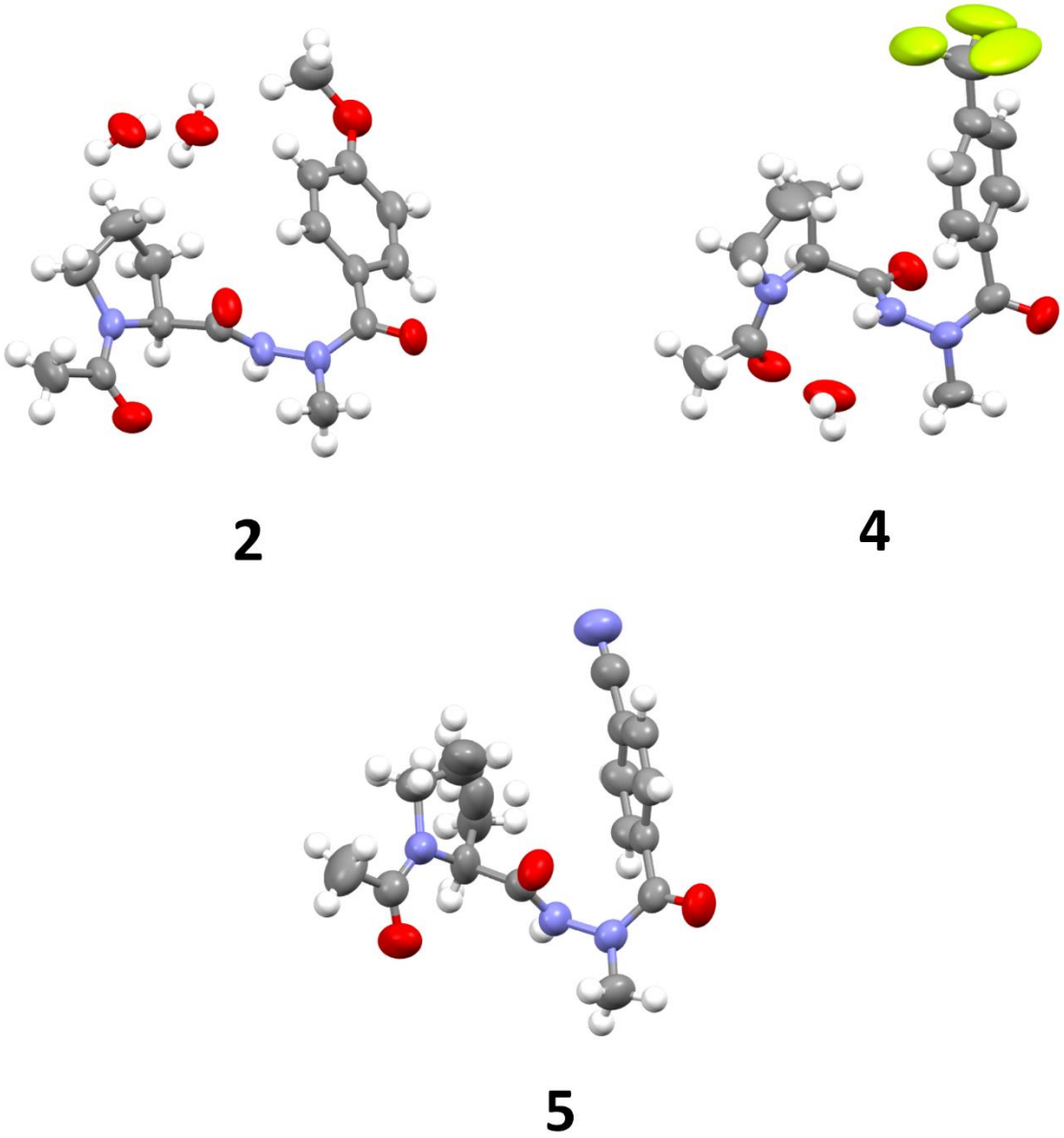


Figure S1. Crystal Structures of **2** and **4**-**5** showing 50 % ellipsoid probability.

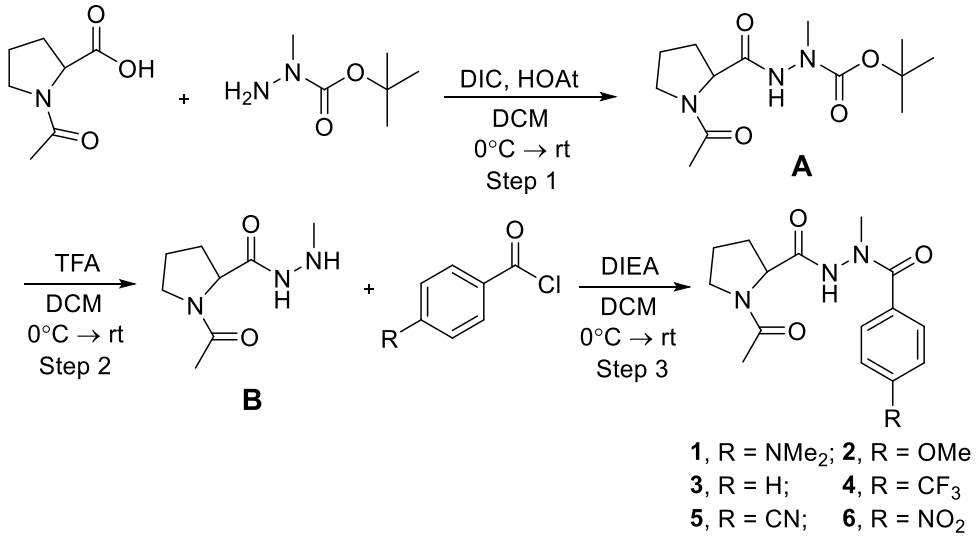
Table S6. Details of Crystal Structures for **2-4** and **5**.

	2	**3**
Empirical formula	$C_{16}H_{25}N_3O_6$	$C_{15}H_{19}N_3O_3$
Formula weight	355.39	289.34
Temperature	299 K	300 K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Orthorhombic
Space group	P 1 21 1	P 21 21 21
Unit cell dimensions	a = 9.5736 (9), α = 90º;	a = 8.3640 (3), α = 90º;
	b = 8.7880 (7), β = 106.122º (4);	b = 10.6149 (5), β = 90º;
	c = 11.6294 (11), γ = 90º;	c = 17.5618 (9), γ = 90º;
Volume	939.94 (15)	1559.19 (12)
Z	2	4
Density	1.256 g/cm^3	1.233 g/cm^3
Absorption coefficient	0.096	0.087
F (000)	380	616
Crystal size	0.05 x 0.25 x 0.30	0.057 x 0.097 x 0.310
Theta max.	27.84	21.48
Theta min.	2.21	2.24
Reflections collected	16661	16192
Independent reflections	3717	3136
Absorption correction	Multi-scan with SADABS	Multi-scan with SADABS
Max. and min. Transmission	0.7461 and 0.6748	0.9705 and 0.8947
Goodness-of-fit on F^2	1.021	1.12
R1 (I> 2σ (I))	0.0393	0.0401
wR2 (I > 2σ (I))	0.0867	0.0904
R1 (all data)	0.0763	0.0761
wR2 (all data)	0.1053	0.1141
R_{int} (all data)	0.0299	0.0480

	4	**5**
Empirical formula	$C_{16}H_{20}F_3N_3O_4$	$C_{16}H_{18}N_4O_3$
Formula weight	375.35	314.35
Temperature	300 K	297 K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Monoclinic	Orthorhombic
Space group	C 1 2 1	P 21 21 21
Unit cell dimensions	a = 16.380 (3), α = 90º;	a = 6.8839 (4), α = 90º;
	b = 6.0768 (12), β = 93.389º (9);	b = 14.6506 (11), β = 90º;
	c = 18.447 (4), γ = 90º;	c = 16.5975 (12), γ = 90º;
Volume	1833.0 (6)	1673.9 (2)
Z	4	4
Density	1.360 g/cm^3	1.247 g/cm^3
Absorption coefficient	0.118	0.089
F (000)	784	664
Crystal size	0.078 x 0.098 x 0.135	0.023 x 0.120 x 0.168
Theta max.	23.38	21.10
Theta min.	2.21	2.78
Reflections collected	10302	19160
Independent reflections	2345	3151
Absorption correction	Multi-scan with SADABS	Multi-scan with SADABS
Max. and min. Transmission	0.745 and 0.582	0.7461 and 0.6740
Goodness-of-fit on F^2	0.997	1.144
R1 (I> 2σ (I))	0.0596	0.0495
wR2 (I > 2σ (I))	0.1572	0.1235
R1 (all data)	0.1229	0.1563
wR2 (all data)	0.1950	0.1990
R_{int} (all data)	0.0407	0.0492

8. Synthetic protocols and characterization.

6.1. General scheme for the synthesis of Proline-diacylhydrazines (Pro-DAH) **1-6**.

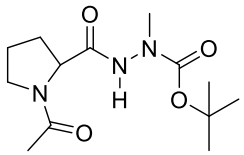


Procedure:

Step 1: In a two-neck Rb flask, x = 1.00 gm of N-acetyl-L-proline [y = 6.36 mmol (1 eqv.)] were activated by using coupling reagents, x´ = 1.18 mL of *N*,*N*´-diisopropylcarbodiimide (DIC) [y´ = 7.64 mmol (1.2 eqv.)] and x´´ = 1.04 gm of 1-Hydroxy-7-azabenzotriazole (HOAt) [y´´ = 7.64 mmol (1.2 eqv.)] at 0ºC and stirred for 15 minutes. Then x´´´ = 0.94 mL of tert-butyl 2-methylcarbazate [y´´´ = 6.36 mmol (1 eqv.)] were added slowly into the reaction mixture at 0ºC. Then the reaction mixture was warmed to room temperature and stirred for another 1 h. The solvent was evaporated to dryness by using the rotary evaporator. The reaction mixture was dissolved in CH_2Cl_2 and washed twice with water, then a 10% citric acid solution followed by a saturated sodium bicarbonate ($NaHCO_3$) solution and finally with brine solution. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The final residue was then purified by the column chromatography using silica gel (100-200 Mesh) and gradient of hexane and ethyl acetate as an eluent.

Step 2: x = 2.68 mL of trifluoroacetic acid (TFA) [y = 35.0 mmol (10 eqv.)] were added slowly to a solution of x' = 1.00 gm **A** [y' = 3.50 mmol (1 eqv.)] in CH_2Cl_2 (3-5 mL) at 0 °C over a period of 15 minutes. The reaction mixture was allowed to warm to room temperature and stirred for another 2 h 45 minutes. The solvent was evaporated to dryness under reduced pressure and purged with Nitrogen or Argon for 15 minutes to remove the TFA completely. The final residue was used for the next step directly.

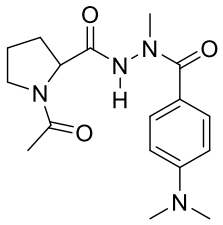
Step 3: x = 100 mg of compound **B** [y = 0.54 mmol (1 eqv.)] was dissolved in 15 mL of CH_2Cl_2 and neutralised with a x´ = 185 µL of *N*,*N*-diisopropylethylamine [DIEA-y´ = 1.08 mmol (2 eqv.)] at 0 °C. Then x´´ mg/µL of acyl chloride [y´´ mmol (1.5 eqv.)] were added slowly into the reaction mixture at 0 °C. The reaction mixture was warmed to room temperature and stirred for 1 h. The solvent was evaporated to dryness by using the rotary evaporator. The reaction mixture was dissolved in CH_2Cl_2 and washed twice with water, then a 10% citric acid solution followed by a saturated sodium bicarbonate ($NaHCO_3$) solution and finally with brine solution. The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure. The final residue was then purified by the column chromatography using Silica Gel (100-200 Mesh) as the stationary phase and a gradient of hexane/ethyl acetate/methanol as eluent.



Compound **A**: tert-butyl 2-(acetylprolyl)-1-methylhydrazine-1-carboxylate.

Step 1. Yield (%): 85 % as a white solid.

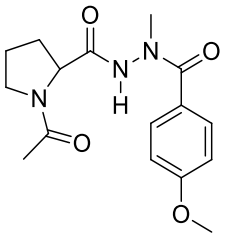
^{1}H NMR 400 MHz (20 mM, $CDCl_3$) δ ppm: 9.08 (brs, 1H, NH), 4.55 (brd, *J* = 8.0 Hz, 1H, α-CH), 3.60-3.55 (m, 1H, δ-CH_2), 3.47-3.40 (m, 1H, δ-CH_2), 3.09 (s, 3H, NCH_3), 2.52-2.48 (m, 1H, β-CH_2), 2.12 [s, 3H, C(O)-CH_3], 2.03-1.96 [m, 1H, β-CH_2], 1.84-1.77 (m, 2H, γ-CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm: 171.3, 169.6, 155.2, 80.7, 57.9, 48.5, 37.0, 28.3, 26.8, 25.2, 22.6; HRMS $[M + H]^+$ calcd. for, $C_8H_{16}N_3O_2$, m/z: 186.1243; found m/z: 186.1234 (without Boc).



Compound **1**: 1-acetyl-*N´*-[4-(dimethylamino)benzoyl]-*N´*-methylpyrrolidine-2-carbohydrazide.

Step 3. x´´ = 149 mg of 4-(dimethylamino)benzoyl chloride [y´´ = 0.810 mmol (1.5 eqv.)]. Yield (%): 65 % as a white solid.

^{1}H NMR 400 MHz (20 mM, $CDCl_3$) δ ppm [t-t-c rotamer: ~100 %]: 9.67 (s, 1H, NH), 7.37 (d, 2H, *J* = 8.0 Hz, Ph-NMe_2), 6.58 (d, 2H, *J* = 8.0 Hz, Ph-NMe_2), 4.45 (brd, *J* = 4.0 Hz, 1H, α-CH), 3.31-3.20 (m, 2H, δ-CH_2), 3.25 (s, 3H, NCH_3), 2.97 [s, 6H, N-$(CH_3)_2$], 2.39-2.36 (m, 1H, β-CH_2), 1.97 [s, 3H, C(O)-CH_3], 1.89 [brs, 1H, β-CH_2], 1.89 (brs, 1H, γ-CH_2), 1.74-1.72 (m, 1H, γ-CH_2); ^{1}H NMR 400 MHz [20 mM, $(CD_3)_2SO$] δ ppm [t-t-c rotamer: 67 %]: 10.34 (brs, 1H, NH), 7.35 (d, 2H, *J* = 8.0 Hz, Ph-NMe_2), 6.63 (d, 2H, *J* = 8.0 Hz, Ph-NMe_2), 4.08 (dd, *J* = 10.0 Hz, *J* = 4.0 Hz, 1H, α-CH), 3.45-3.22 (m, 2H, δ-CH_2), 3.01 (s, 3H, NCH_3), 2.92 [s, 6H, $N(CH_3)_2$], 1.95 [s, 3H, C(O)-CH_3], 1.81-1.55 (m, 4H, β, γ-CH_2); [c-t-c rotamer: 33 %]: 10.66 (s, 1H, NH), 7.34 (d, 2H, *J* = 8.0 Hz, Ph-NMe_2), 6.63 (d, 2H, *J* = 8.0 Hz, Ph-NMe_2), 4.18 (brd, *J* = 8.0 Hz, 1H, α-CH), 3.45-3.22 (m, 2H, δ-CH_2), 3.04 (s, 3H, NCH_3), 2.92 [s, 6H, $N(CH_3)_2$], 1.32 [s, 3H, C(O)-CH_3], 1.81-1.23 (m, 4H, β, γ-CH_2); ^{1}H NMR 400 MHz (20 mM, D_2O) δ ppm [t-t-c rotamer: 73 %]: 7.35 (d, 2H, *J* = 8.0 Hz, Ph-NMe_2), 6.83 (d, 2H, *J* = 8.0 Hz, Ph- NMe_2), 4.20 (brs, 1H, α-CH), 3.46 (brs, 2H, δ-CH_2), 3.18 (s, 3H, NCH_3), 2.89 [brs, 6H, $N(CH_3)_2$], 2.05 [s, 3H, C(O)-CH_3], 1.89 (brs, 1H, β-CH_2), 1.75 (brs, 1H, β-CH_2), 1.52 (brs, 1H, γ-CH_2), 1.20-1.18 (m, 1H, γ-CH_2); [c-t-c rotamer: 27 %]: 7.35 (d, 2H, *J* = 8.0 Hz, Ph-NMe_2), 6.81 (d, 2H, *J* = 8.0 Hz, Ph-NMe_2), 4.33 (brs, 1H, α-CH), 3.39-3.32 (m, 2H, δ-CH_2), 3.20 (s, 3H, NCH_3), 2.88 [brs, 6H, $N(CH_3)_2$], 2.12 [brs, 3H, C(O)-CH_3], 1.92 (brs, 2H, β-CH_2), 1.53 (brs, 1H, γ-CH_2), 1.13 (brs, 1H, γ-CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm: 173.2, 171.1, 169.4, 151.6, 129.1, 121.6, 110.5, 63.7, 57.8, 47.9, 40.1, 37.0, 26.5, 24.7, 22.3; $[M + H]^+$ calcd. for, $C_{17}H_{25}N_4O_3$, m/z: 333.1927; found m/z: 333.1915.

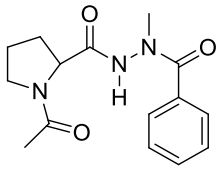


Compound **2**: 1-acetyl-*N´*-[4-methoxybenzoyl]-*N´*-methylpyrrolidine-2-carbohydrazide.

Step 3. x´´ = 109 µL of 4-methoxybenzoyl chloride [y´´ = 0.810 mmol (1.5 eqv.)]. Yield (%): 78 % as a white solid.

^{1}H NMR 400 MHz (20 mM, $CDCl_3$) δ ppm [t-t-c rotamer: ~100 %]: 9.62 (s, 1H, NH), 7.39 (d, 2H, *J* = 8.0 Hz, Ph-OMe), 6.82 (d, 2H, *J* = 8.0 Hz, Ph-OMe), 4.41 (brd, *J* = 4.0 Hz, 1H, α-CH), 3.81 (s, 3H, O-CH_3), 3.25 (s, 3H, NCH_3), 3.22-3.20 (m, 1H, δ-CH_2), 3.07 (brs, 1H, δ-CH_2), 2.41-2.40 (m, 1H, β-CH_2), 1.95 [s, 3H, C(O)-CH_3], 1.89-1.86 [brs, 1H, β-CH_2], 1.82-1.79 (m, 1H, γ-CH_2), 1.68-1.63 (m, 1H, γ-CH_2); ^{1}H NMR 400 MHz [20 mM, $(CD_3)_2SO$] δ ppm [t-t-c

rotamer: 68 %]: 10.37 (brs, 1H, NH), 7.40 (d, 2H, *J* = 8.0 Hz, Ph-OMe), 6.91 (d, 2H, *J* = 8.0 Hz, Ph-OMe), 4.06 (brd, *J* = 4.0 Hz, 1H, α-CH), 3.77 (s, 3H, OCH_3), 3.42-3.21 (m, 2H, δ-CH_2), 3.03 (s, 3H, NCH_3), 1.94 [s, 3H, C(O)-CH_3], 1.78-1.17 (m, 4H, β, γ-CH_2); [c-t-c rotamer: 32 %]: 10.70 (s, 1H, NH), 7.40 (d, 2H, *J* = 8.0 Hz, Ph-OMe), 6.91 (d, 2H, *J* = 8.0 Hz, Ph-OMe), 4.17 (brd, *J* = 8.0 Hz, 1H, α-CH), 3.76 (s, 3H, OCH_3), 3.42-3.21 (m, 2H, δ-CH_2), 3.07 (s, 3H, NCH_3), 1.35 [s, 3H, C(O)-CH_3], 1.78-1.17 (m, 4H, β, γ-CH_2); ^{1}H NMR 400 MHz (20 mM, D_2O) δ ppm [t-t-c rotamer: 75 %]: 7.43 (d, 2H, *J* = 8.0 Hz, Ph-OMe), 7.05 (d, 2H, *J* = 8.0 Hz, Ph-OMe), 4.21 (brs, 1H, α-CH), 3.87 (s, 3H, OCH_3), 3.50 (t, 2H, *J* = 8.0 Hz, δ-CH_2), 3.23 (s, 3H, NCH_3), 2.08 [s, 3H, C(O)-CH_3], 1.85-1.77 (m, 2H, β-CH_2), 1.53 (brs, 1H, γ-CH_2), 1.13 (brs, 1H, γ-CH_2); [c-t-c rotamer: 25 %]: 7.45 (d, 2H, *J* = 8.0 Hz, Ph-OMe), 7.05 (d, 2H, *J* = 8.0 Hz, Ph-OMe), 4.39 (brd, *J* = 8.0 Hz, 1H, α-CH), 3.87 (s, 3H, OCH_3), 3.43-3.32 (m, 2H, δ-CH_2), 3.26 (s, 3H, NCH_3), 2.07 [brs, 3H, C(O)-CH_3], 1.92 (brs, 2H, β-CH_2), 1.53 (brs, 1H, γ-CH_2), 1.13 (brs, 1H, γ-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm: 173.0, 171.5, 169.4, 160.9, 129.1, 127.5, 113.0, 57.9, 55.5, 48.1, 36.7, 26.3, 24.9, 22.5; HRMS $[M + H]^+$ calcd. for, $C_{16}H_{22}N_3O_4$, m/z: 320.1610; found m/z: 320.1605.

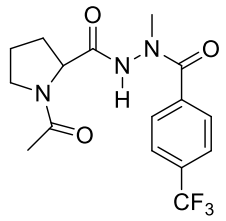


Compound **3**: 1-acetyl-*N´*-benzoyl-*N´*-methylpyrrolidine-2-carbohydrazide.

Step 3. x´´ = 94 µL of Benzoyl chloride [y´´ = 0.810 mmol (1.5 eqv.)]. Yield (%): 75 % as a white solid.

^{1}H NMR 400 MHz (20 mM, $CDCl_3$) δ ppm [t-t-c rotamer: ~100 %]: 9.65 (s, 1H, NH), 7.40-7.29 (m, 5H, Ph), 4.36 (brs, 1H, α-CH), 3.27 (s, 3H, NCH_3), 3.15 (brs, 1H, δ-CH_2), 2.92 (brs, 1H, δ-CH_2), 2.35 (brs, 1H, β-CH_2), 1.99 [s, 3H, C(O)-CH_3], 1.99 [brs, 1H, β-CH_2], 1.63-1.62 (m, 2H, γ-CH_2); ^{1}H NMR 400 MHz [20 mM, $(CD_3)_2SO$] δ ppm [t-t-c rotamer: 69 %]: 10.49-10.28 (brs, 1H, NH), 7.44-7.38 (m, 5H, Ph), 4.00 (brs, 1H, α-CH), 3.38-3.19 (m, 2H, δ-CH_2), 3.06 (s, 3H, NCH_3), 1.93 [s, 3H, C(O)-CH_3], 1.59-1.30 (m, 4H, β, γ-CH_2); [c-t-c rotamer: 31 %]: 10.72 (s, 1H, NH), 7.44-7.38 (m, 5H, Ph), 4.14 (brd, *J* = 8.0 Hz, 1H, α-CH), 3.38-3.19 (m, 2H, δ-CH_2), 3.09 (s, 3H, NCH_3), 1.59-1.30 (m, 4H, β, γ-CH_2), 1.35 [s, 3H, C(O)-CH_3]; ^{1}H NMR 400 MHz (20 mM, D_2O) δ ppm [t-t-c rotamer: 77 %]: 7.57-7.41 (m, 5H, Ph), 4.18 (brs, 1H, α-CH), 3.48 (t, 2H, *J* = 8.0 Hz, δ-CH_2), 3.26 (brs, 3H, NCH_3), 2.07 [s, 3H, C(O)-CH_3], 1.80-1.73 (m, 2H, β-CH_2), 1.52-1.30 (m, 1H, γ-CH_2), 1.02 (brs, 1H, γ-CH_2); [c-t-c rotamer: 23

%]: 7.57-7.41 (m, 5H, Ph), 4.37 (dd, *J* = 8.0 Hz, *J* = 4.0 Hz, 1H, α-CH), 3.40-3.34 (m, 2H, δ-CH_2), 3.29 (brs, 3H, NCH_3), 2.16 [s, 3H, C(O)-CH_3], 1.85 (brs, 2H, β-CH_2), 1.52-1.30 (m, 1H, γ-CH_2), 1.02 (brs, 1H, γ-CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm [t-t-c rotamer: ~100 %]: 173.5, 171.4, 169.3, 135.7, 129.6, 127.7, 126.8, 57.8, 47.9, 36.2, 26.2, 24.7, 22.5; HRMS [M + H]$^+$ calcd. for, $C_{15}H_{20}N_3O_3$, m/z: 290.1505; found m/z: 290.1500.

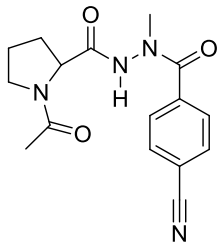


Compound **4**: 1-acetyl-*N´*-methyl-*N´*-[4-(trifluoromethyl) benzoyl] pyrrolidine-2-carbo-hydrazide.

Step 3. x´´ = 120 µL of 4-(trifluoromethyl)benzoyl chloride [y´´ = 0.810 mmol (1.5 eqv.)]. Yield (%): 80 % as a white solid.

^{1}H NMR 400 MHz (20 mM, $CDCl_3$) δ ppm [t-t-c rotamer: ~100 %]: 9.78 (s, 1H, NH), 7.58 (d, 2H, *J* = 8.0 Hz, Ph-CF_3), 7.51 (d, 2H, *J* = 8.0 Hz, Ph-CF_3), 4.34 (brd, *J* = 4.0 Hz, 1H, α-CH), 3.28 (s, 3H, NCH_3), 3.16-3.12 (m, 1H, δ-CH_2), 2.85 (brs, 1H, δ-CH_2), 2.40-2.38 (m, 1H, β-CH_2), 1.86 [s, 3H, C(O)-CH_3], 1.86 [brs, 1H, β-CH_2], 1.64-1.61 (m, 2H, γ-CH_2); ^{19}F NMR 564 MHz (20 mM, $CDCl_3$) δ ppm [t-t-c rotamer: ~100 %]: -62.6 (s, 3F, $PhCF_3$); ^{1}H NMR 400 MHz [20 mM, $(CD_3)_2SO$] δ ppm [t-t-c rotamer: 70 %]: 10.44 (brd, *J* = 128 Hz, 1H, NH), 7.76 (d, 2H, *J* = 8.0 Hz, Ph-CF_3), 7.56 (d, 2H, *J* = 8.0 Hz, Ph-CF_3), 4.00 (brs, 1H, α-CH), 3.32-3.19 (m, 2H, δ-CH_2), 3.08 (s, 3H, NCH_3), 1.92 [s, 3H, C(O)-CH_3], 1.59-1.10 (m, 4H, β, γ-CH_2); [c-t-c rotamer: 30 %]: 10.79 (s, 1H, NH), 7.76 (d, 2H, *J* = 8.0 Hz, Ph-CF_3), 7.59 (d, 2H, *J* = 8.0 Hz, Ph-CF_3), 4.15 (brd, *J* = 8.0 Hz, 1H, α-CH), 3.32-3.19 (m, 2H, δ-CH_2), 3.11 (s, 3H, NCH_3), 1.59-1.10 (m, 4H, β, γ-CH_2), 1.34 [s, 3H, C(O)-CH_3]; ^{19}F NMR 564 MHz [20 mM, $(CD_3)_2SO$] δ ppm [t-t-c rotamer: 70 %]: -61.3 (s, 3F, $PhCF_3$); [c-t-c rotamer: 30 %]: -61.4 (s, 3F, $PhCF_3$); ^{1}H NMR 400 MHz (20 mM, D_2O) δ ppm [t-t-c rotamer: 79 %]: 7.82 (d, 2H, *J* = 8.0 Hz, $PhCF_3$), 7.58 (d, 2H, *J* = 8.0 Hz, $PhCF_3$), 4.18 (brs, 1H, α-CH), 3.47 (t, 2H, *J* = 8.0 Hz, δ-CH_2), 3.27 (brs, 3H, NCH_3), 2.05 [s, 3H, C(O)-CH_3], 1.79-1.71 (m, 1H, β-CH_2), 1.52 (brs, 1H, β-CH_2), 1.37-1.25 (m, 1H, γ-CH_2), 0.83 (brs, 1H, γ-CH_2); [c-t-c rotamer: 21 %]: 7.82 (d, 2H, *J* = 8.0 Hz, $PhCF_3$), 7.61 (d, 2H, *J* = 8.0 Hz, $PhCF_3$), 4.36 (d, *J* = 8.0 Hz, 1H, α-CH), 3.38-3.32 (m, 2H, δ-CH_2), 3.30 (s, 3H, NCH_3), 2.16 [s, 3H, C(O)-CH_3], 1.79-1.71 (m, 1H, β-CH_2), 1.52 (brs, 1H, β-CH_2), 1.37-1.25 (m, 1H, γ-CH_2), 0.83 (brs, 1H, γ-CH_2); ^{19}F NMR 564 MHz (20 mM,

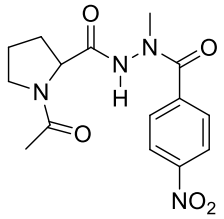
D_2O) δ ppm [t-t-c rotamer: 79 %]: -62.8 (s, 3F, $PhCF_3$); [c-t-c rotamer: 21 %]: -62.9 (s, 3F, $PhCF_3$); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm [t-t-c rotamer: ~100 %]: 172.1, 171.6, 169.2, 139.5, 131.5 (q, $^2J_{CF}$ = 32.0 Hz), 127.3, 124.6 (brs), 123.9 (q, $^1J_{CF}$ = 271.0 Hz), 57.7, 48.1, 36.3, 26.0, 24.9, 22.3; HRMS $[M + H]^+$ calcd. for, $C_{16}H_{19}F_3N_3O_3$, m/z: 358.1379; found m/z: 358.1375.



Compound **5**: 1-acetyl-*N´*-(4-cyanobenzoyl)-*N´*-methylpyrrolidine-2-carbohydrazide.

Step 3. x´´ = 134 mg of 4-cyanobenzoyl chloride [y´´ = 0.810 mmol (1.5 eqv.)]. Yield (%): 65 % as a white solid.

^1H NMR 400 MHz (20 mM, $CDCl_3$) δ ppm [t-t-c rotamer: ~100 %]: 9.71 (s, 1H, NH), 7.62 (d, 2H, *J* = 8.0 Hz, Ph-CN), 7.52 (d, 2H, *J* = 8.0 Hz, Ph-CN), 4.32 (brs, 1H, α-CH), 3.26 (s, 3H, NCH_3), 3.26 (brs, 1H, δ-CH_2), 3.01 (brs, 1H, δ-CH_2), 2.34 (brs, 1H, β-CH_2), 1.94 [s, 3H, C(O)-CH_3], 1.94 [brs, 1H, β-CH_2], 1.75-1.62 (m, 2H, γ-CH_2); ^1H NMR 400 MHz [20 mM, $(CD_3)_2SO$] δ ppm [t-t-c rotamer: 72 %]: 10.44 (brd, *J* = 108 Hz, 1H, NH), 7.87 (d, 2H, *J* = 8.0 Hz, Ph-CN), 7.52 (d, 2H, *J* = 8.0 Hz, Ph-CN), 4.00 (brs, 1H, α-CH), 3.36-3.18 (m, 2H, δ-CH_2), 3.07 (s, 3H, NCH_3), 1.93 [s, 3H, C(O)-CH_3], 1.67-1.30 (m, 4H, β, γ-CH_2); [c-t-c rotamer: 28 %]: 10.79 (s, 1H, NH), 7.89 (d, 2H, *J* = 8.0 Hz, Ph-CN), 7.55 (d, 2H, *J* = 8.0 Hz, Ph-CN), 4.17 (brd, *J* = 8.0 Hz, 1H, α-CH), 3.36-3.18 (m, 2H, δ-CH_2), 3.11 (s, 3H, NCH_3), 1.67-1.30 (m, 4H, β, γ-CH_2), 1.35 [s, 3H, C(O)-CH_3]; ^1H NMR 400 MHz (20 mM, D_2O) δ ppm [t-t-c rotamer: 80 %]: 7.89 (d, 2H, *J* = 12.0 Hz, PhCN), 7.58 (d, 2H, *J* = 8.0 Hz, PhCN), 4.18 (brs, 1H, α-CH), 3.51 (t, 2H, *J* = 4.0 Hz, δ-CH_2), 3.27 (brs, 3H, NCH_3), 2.07 [s, 3H, C(O)-CH_3], 1.87-1.79 (m, 2H, β-CH_2), 1.37-1.28 (m, 2H, γ-CH_2); [c-t-c rotamer: 20 %]: 7.90 (d, 2H, *J* = 8.0 Hz, PhCN), 7.62 (d, 2H, *J* = 8.0 Hz, PhCN), 4.40 (dd, *J* = 8.0 Hz, 1H, α-CH), 3.41-3.35 (m, 2H, δ-CH_2), 3.30 (s, 3H, NCH_3), 2.17 [s, 3H, C(O)-CH_3], 1.64 (m, 2H, β-CH_2), 0.88 (m, 2H, γ-CH_2); ^{13}C NMR (150 MHz, $CDCl_3$) δ ppm [t-t-c rotamer: ~100 %]: 171.6, 171.3, 169.4, 140.2, 131.5, 127.8, 118.2, 113.4, 57.8, 48.3, 36.3, 26.2, 25.0, 22.5; HRMS $[M + H]^+$ calcd. for, $C_{16}H_{19}N_4O_3$, m/z: 315.1457; found m/z: 315.1447.

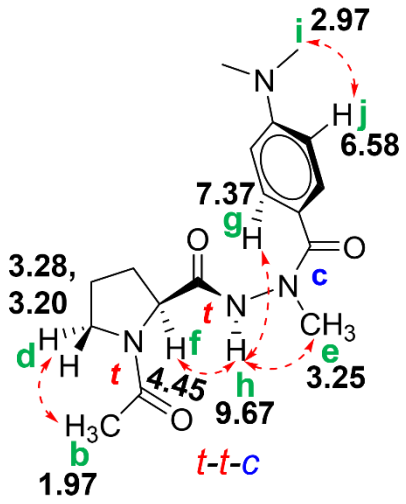


Compound **6**: 1-acetyl-*N´*-methyl-*N´*-(4-nitrobenzoyl)pyrrolidine-2-carbohydrazide.

Step 3. x´´ = 150 mg of 4-nitrobenzoyl chloride [y´´ = 0.810 mmol (1.5 eqv.)]. Yield (%): 72 % as a white solid.

^{1}H NMR 400 MHz (20 mM, $CDCl_3$) δ ppm [t-t-c rotamer: ~100 %]: 9.75 (s, 1H, NH), 8.17 (d, 2H, *J* = 12.0 Hz, Ph-NO_2), 7.59 (d, 2H, *J* = 8.0 Hz, Ph-NO_2), 4.31 (brd, *J* = 8.0 Hz, 1H, α-CH), 3.27 (s, 3H, NCH_3), 3.22-3.18 (m, 1H, δ-CH_2), 2.97 (brs, 1H, δ-CH_2), 2.34-2.32 (m, 1H, β-CH_2), 1.91 [s, 3H, C(O)-CH_3], 1.91 [brs, 1H, β-CH_2], 1.76-1.65 (m, 2H, γ-CH_2); ^{1}H NMR 400 MHz [20 mM, $(CD_3)_2SO$] δ ppm: [t-t-c rotamer: 74 %]: 10.48 (brd, *J* = 112 Hz, 1H, NH), 8.24 (d, 2H, *J* = 12.0 Hz, Ph-NO_2), 7.61 (d, 2H, *J* = 12.0 Hz, Ph-NO_2), 3.99 (brs, 1H, α-CH), 3.42-3.16 (m, 2H, δ-CH_2), 3.09 (s, 3H, NCH_3), 1.91 [s, 3H, C(O)-CH_3], 1.65-1.23 (m, 4H, β, γ-CH_2); [c-t-c rotamer: 26 %]: 10.82 (s, 1H, NH), 8.25 (d, 2H, *J* = 8.0 Hz, Ph-NO_2), 7.64 (d, 2H, *J* = 8.0 Hz, Ph-NO_2), 4.17 (dd, *J* = 10.0 Hz, *J* = 4.0 Hz, 1H, α-CH), 3.42-3.16 (m, 2H, δ-CH_2), 3.12 (s, 3H, NCH_3), 1.65-1.33 (m, 4H, β, γ-CH_2), 1.34 [s, 3H, C(O)-CH_3]; ^{1}H NMR 400 MHz (20 mM, D_2O) δ ppm: [t-t-c rotamer: 81 %]: 8.36 (d, 2H, *J* = 8.0 Hz, PhNO_2), 7.67 (d, 2H, *J* = 8.0 Hz, PhNO_2), 4.19 (brs, 1H, α-CH), 3.51 (t, 2H, *J* = 4.0 Hz, δ-CH_2), 3.30 (brs, 3H, NCH_3), 2.07 [s, 3H, C(O)-CH_3], 1.91-1.78 (m, 2H, β-CH_2), 1.63-1.32 (m, 2H, γ-CH_2); [c-t-c rotamer: 19 %]: 8.37 (d, 2H, *J* = 4.0 Hz, PhNO_2), 7.71 (d, 2H, *J* = 12.0 Hz, PhNO_2), 4.41 (dd, *J* = 8.0 Hz, *J* = 4.0 Hz, 1H, α-CH), 3.41-3.35 (m, 2H, δ-CH_2), 3.33 (s, 3H, NCH_3), 2.18 [s, 3H, C(O)-CH_3], 1.91-1.78 (m, 2H, β-CH_2), 1.09 (m, 2H, γ-CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ ppm [t-t-c rotamer: ~100 %]: 171.6, 171.1, 169.5, 148.5, 141.9, 128.2, 122.9, 57.8, 48.3, 36.3, 26.2, 25.0, 22.4; HRMS $[M + H]^+$ calcd. for, $C_{15}H_{19}N_4O_5$, m/z: 335.1355; found m/z: 335.1347.

9. 2D-NOESY Spectra of a newly synthesized compounds 1-6



Compound **1**

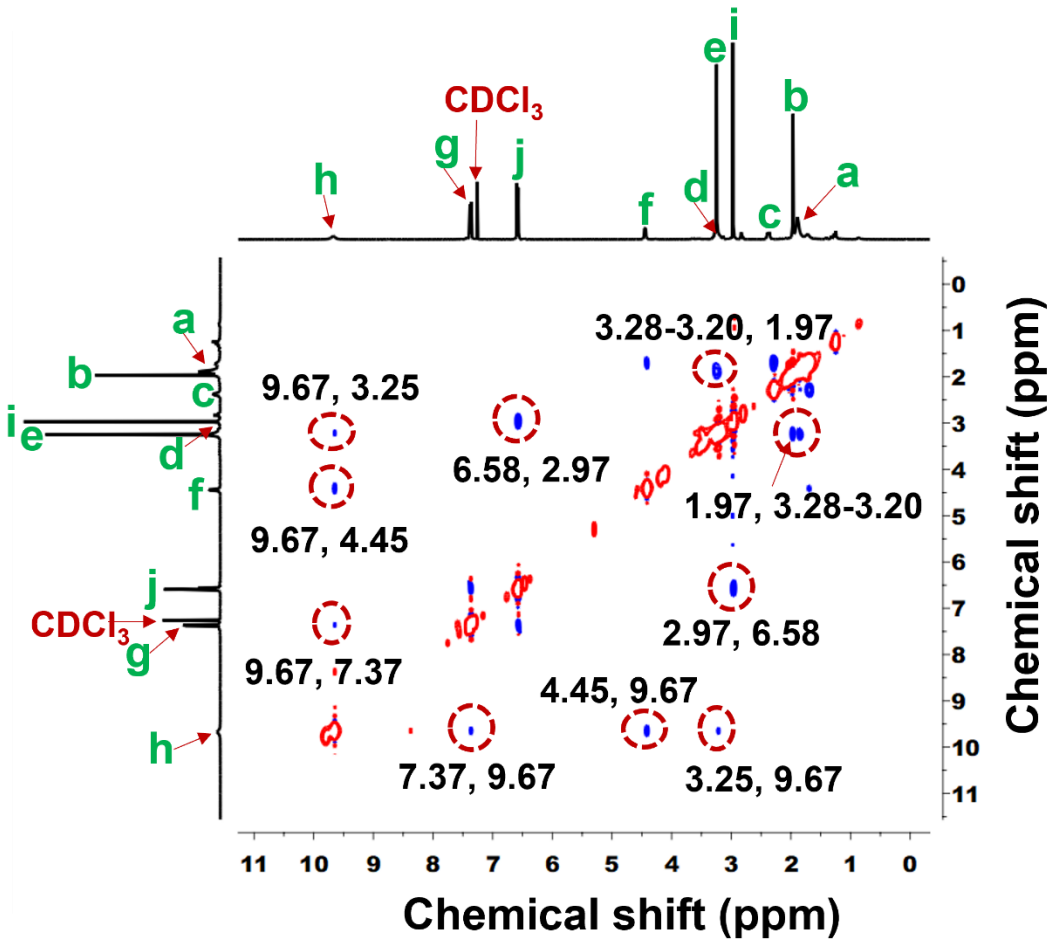
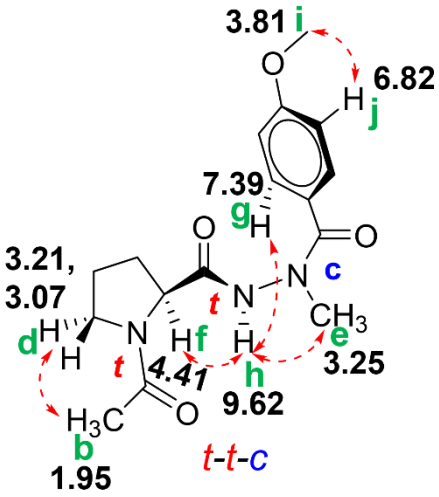


Figure S2. 2D-NOESY Spectrum of **1** [1-acetyl-*N´*-[4-(dimethylamino)benzoyl]-*N´*-methyl pyrrolidine-2-carbohydrazide] in $CDCl_3$.



Compound **2**

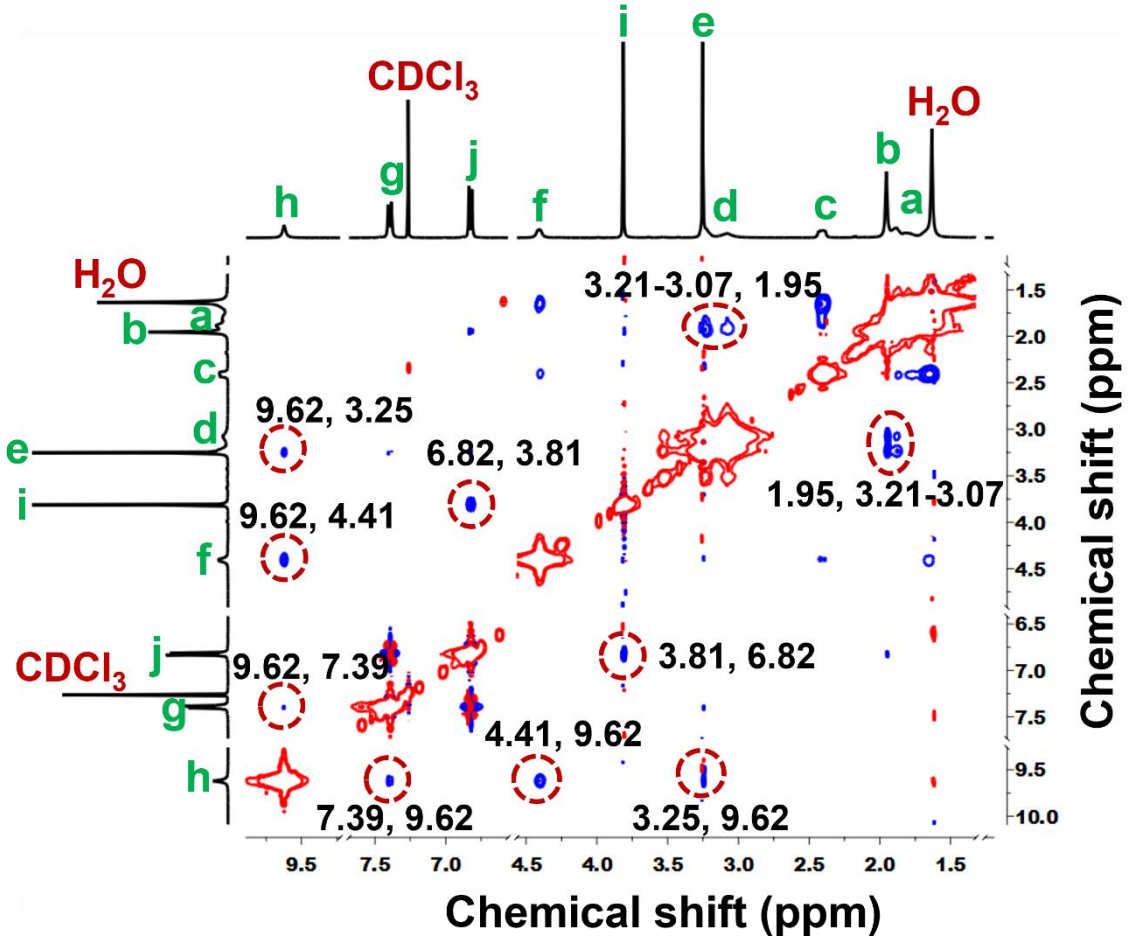
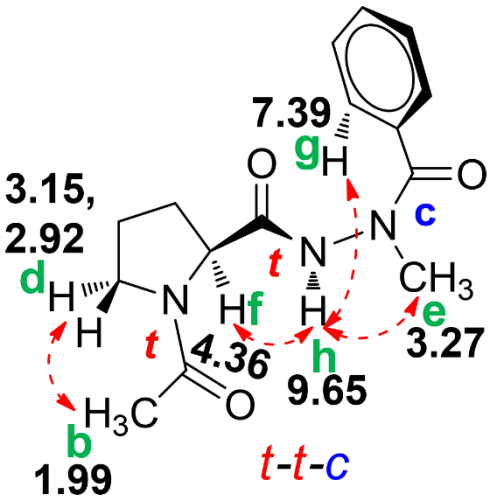


Figure S3. 2D-NOESY Spectrum of **2** [1-acetyl-*N´*-[4-methoxybenzoyl]-*N´*-methyl pyrrolidine-2-carbohydrazide] in $CDCl_3$.



Compound **3**

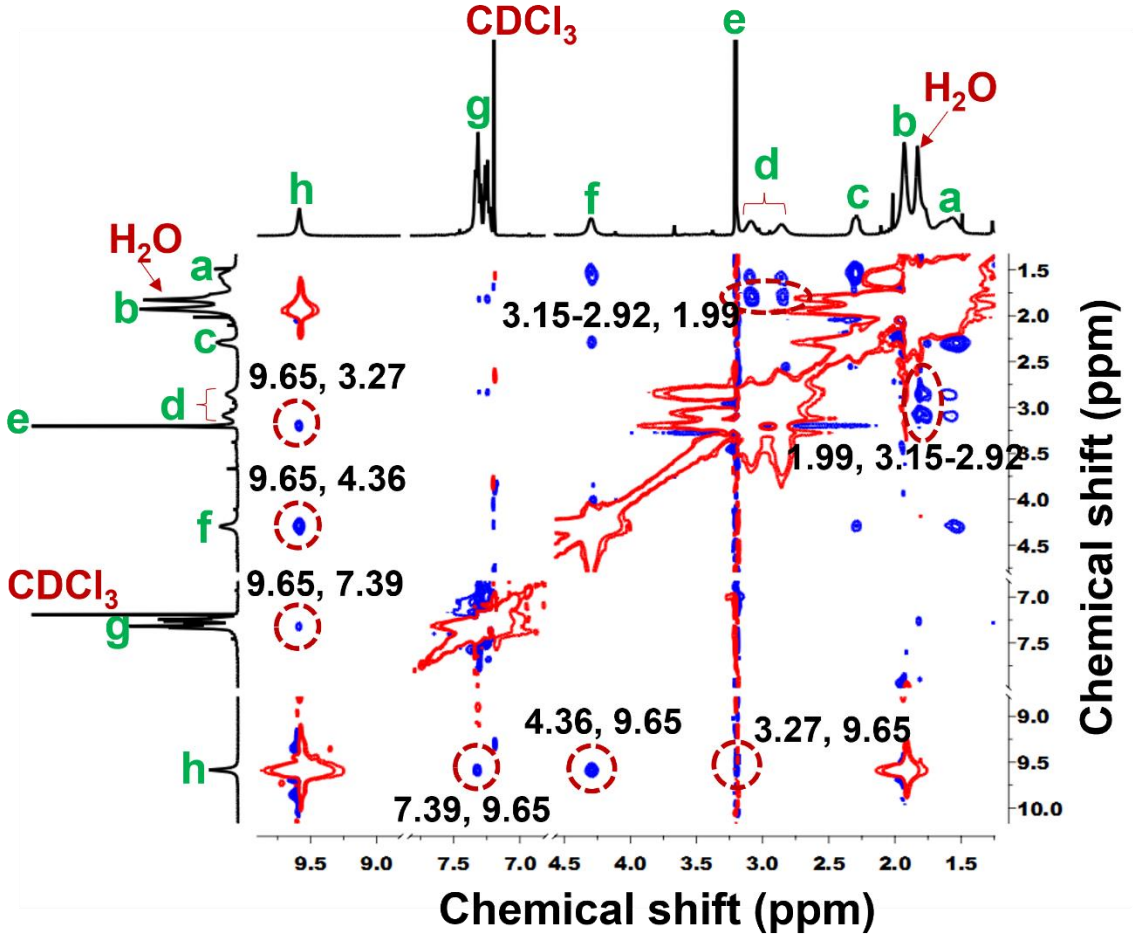
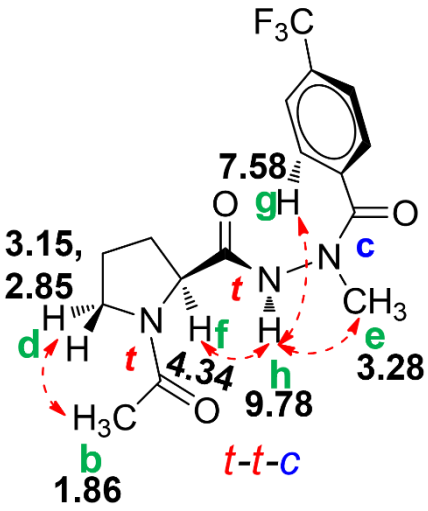


Figure S4. 2D-NOESY Spectrum of **3** [1-acetyl-*N´*-benzoyl-*N´*-methylpyrrolidine-2-carbo hydrazide] in $CDCl_3$.



Compound **4**

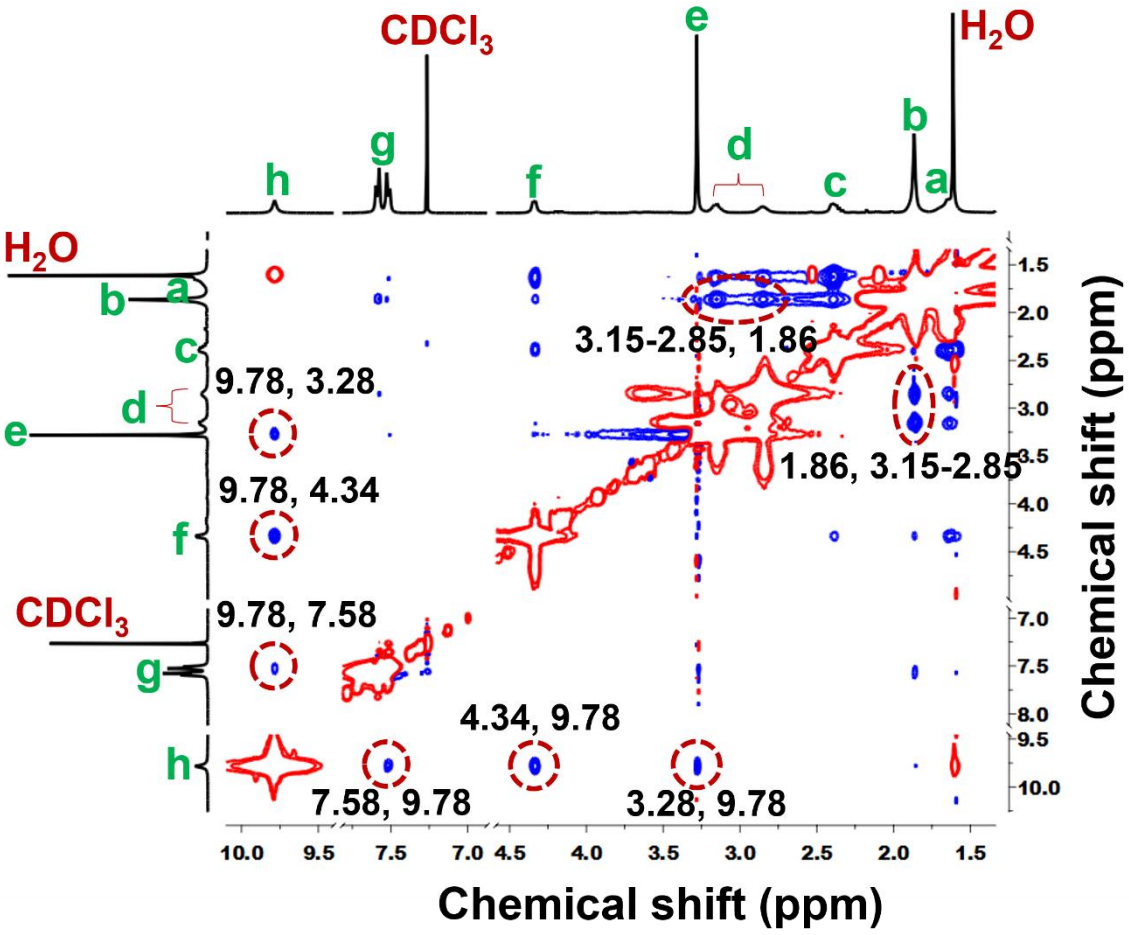
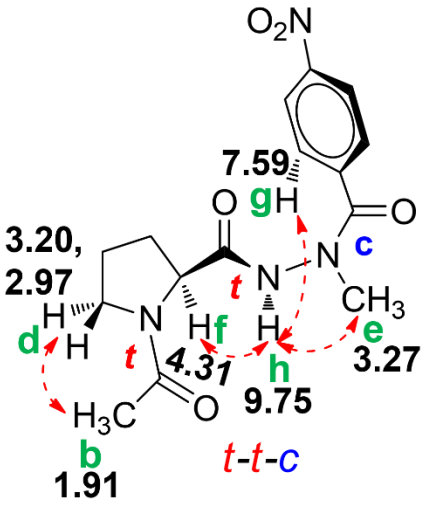


Figure S5. 2D-NOESY Spectrum of **4** [1-acetyl-*N´*-methyl-*N´*-[4-(trifluoromethyl)benzoyl] pyrrolidine-2-carbohydrazide] in $CDCl_3$.



Compound **6**

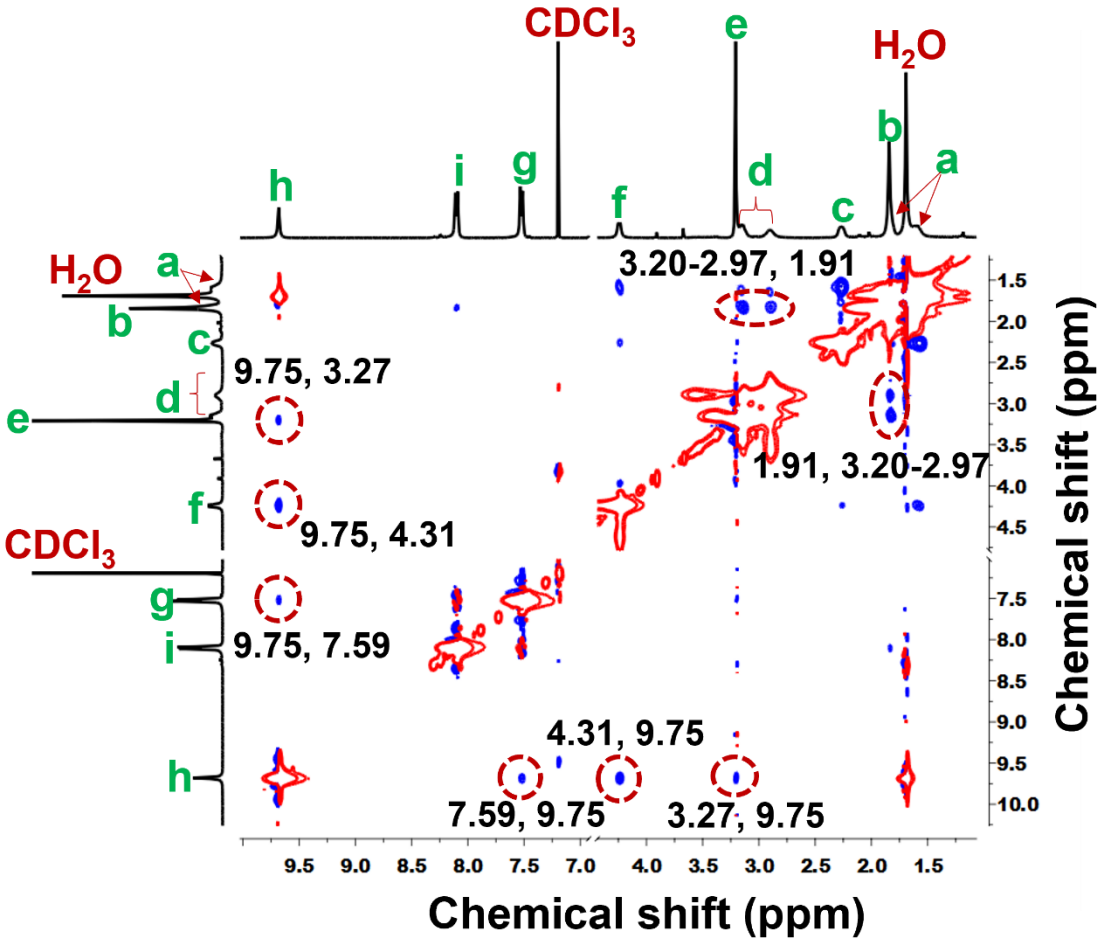
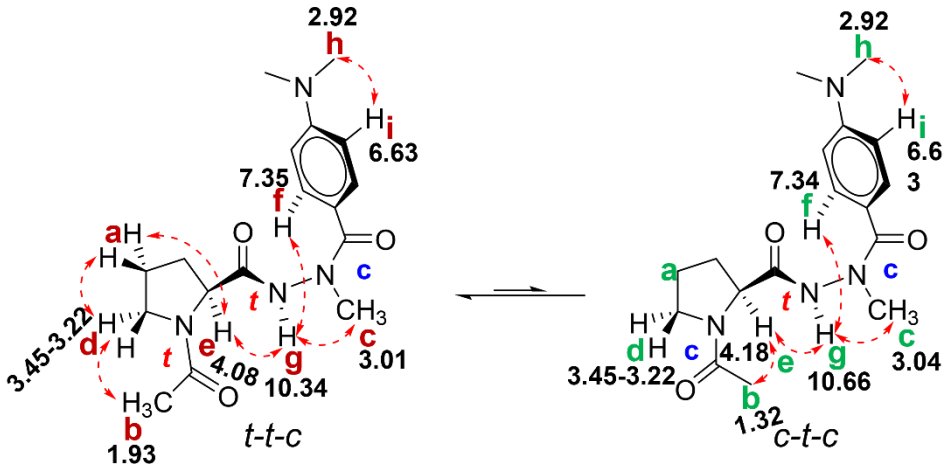


Figure S6. 2D-NOESY Spectrum of **6** [1-acetyl-*N´*-methyl-*N´*-(4-nitrobenzoyl)pyrrolidine-2-carbohydrazide] in $CDCl_3$.



Compound **1**

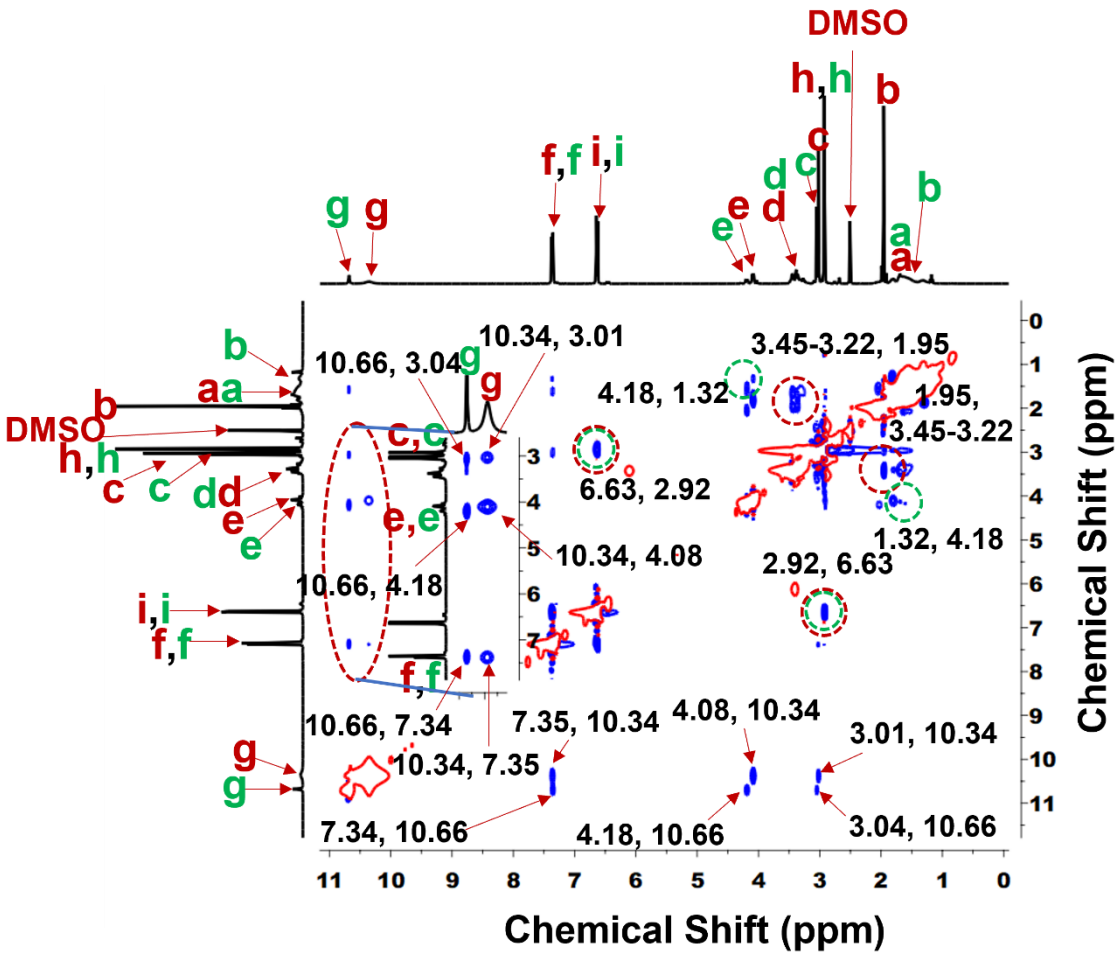
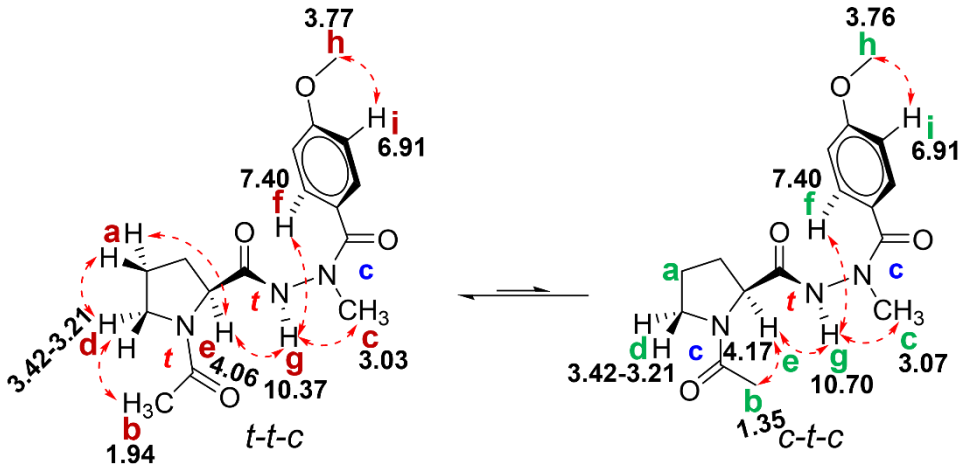


Figure S7. 2D-NOESY Spectrum of **1** [1-acetyl-*N´*-[4-(dimethylamino)benzoyl]-*N´*-methyl pyrrolidine-2-carbohydrazide] in $[CD_3]_2SO$.



Compound **2**

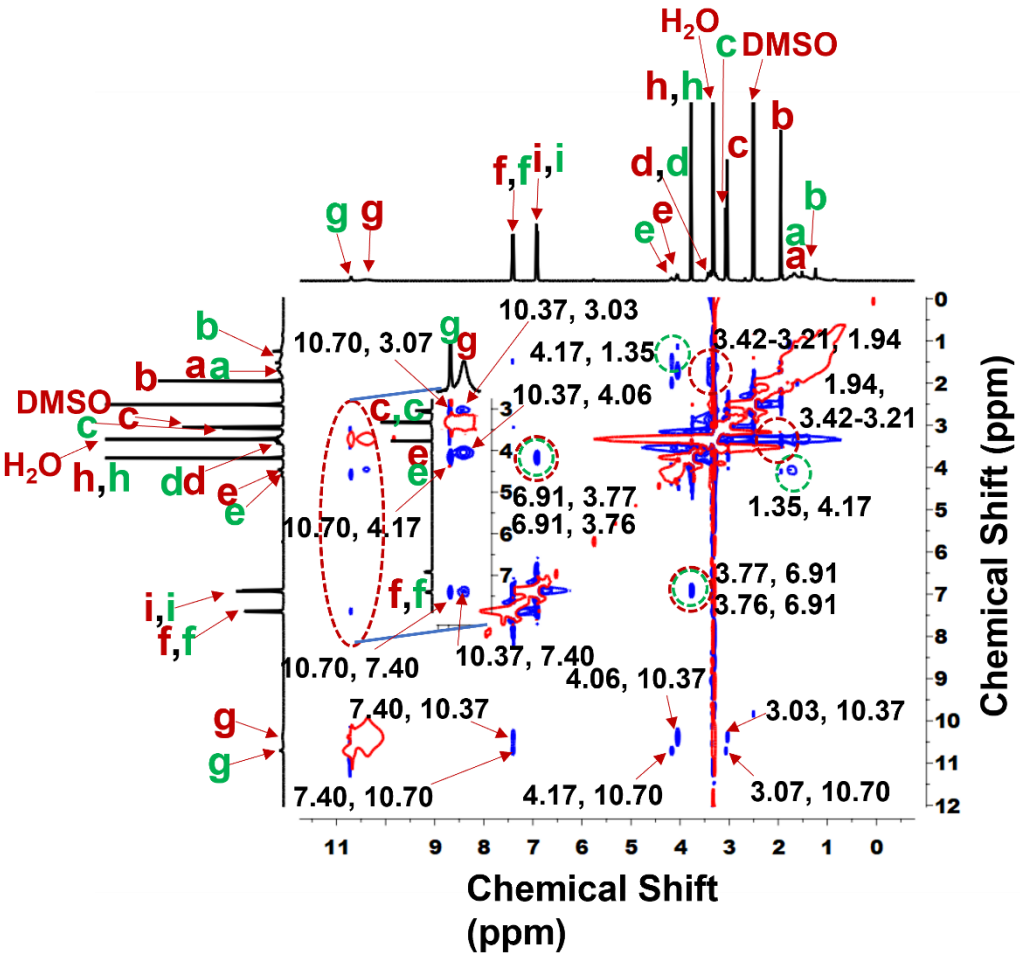
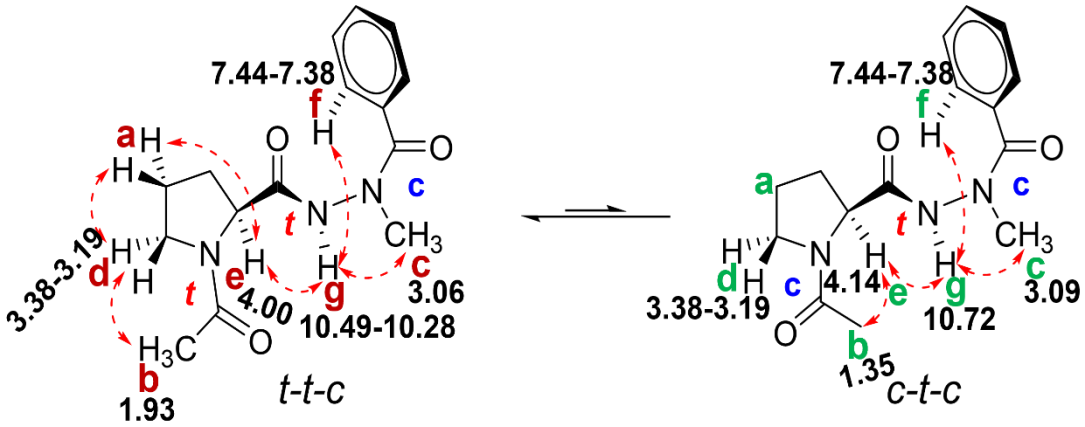


Figure S8. 2D-NOESY Spectrum of **2** [1-acetyl-*N´*-[4-methoxybenzoyl]-*N´*-methyl pyrrolidine-2-carbohydrazide] in $[CD_3]_2SO$.



Compound **3**

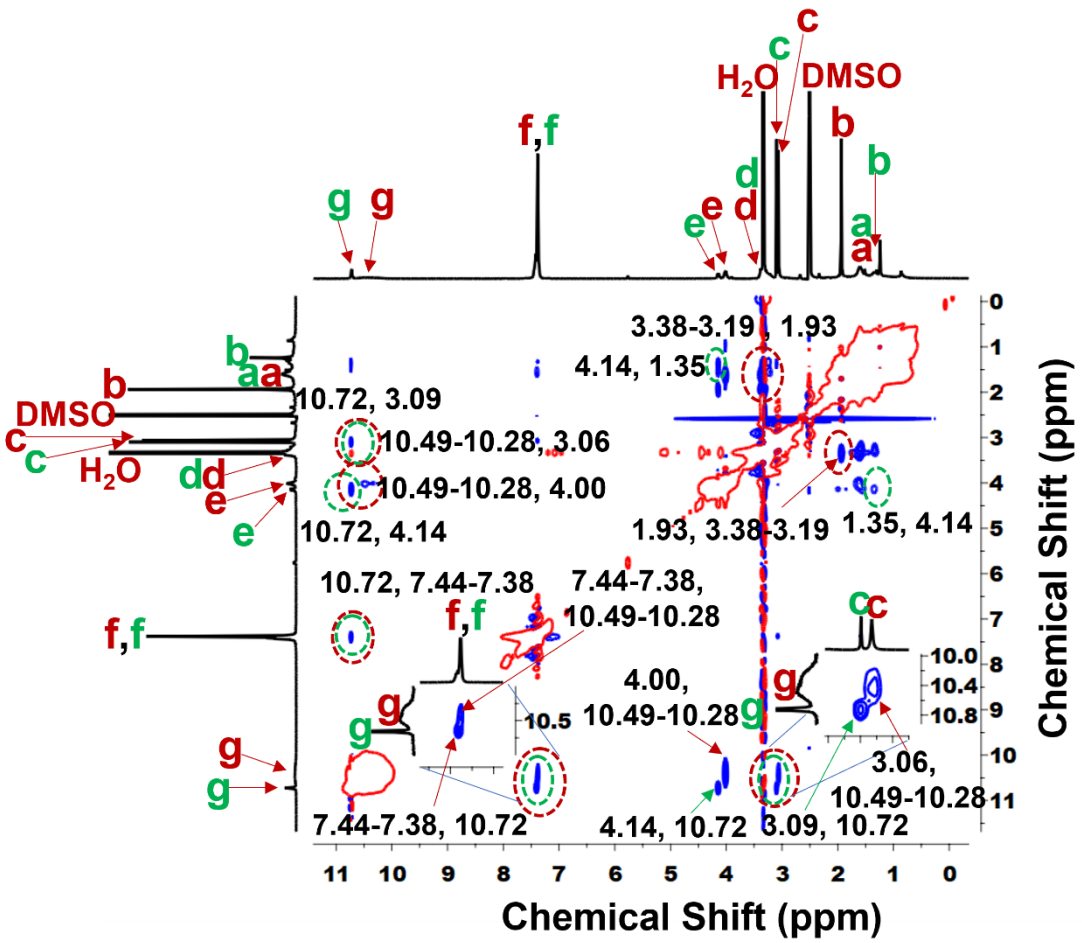
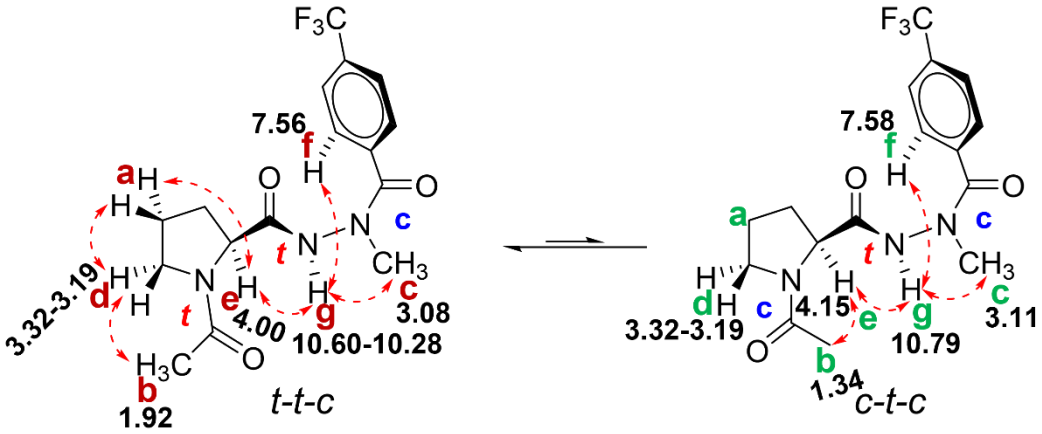


Figure S9. 2D-NOESY Spectrum of **3** [1-acetyl-*N´*-benzoyl-*N´*-methylpyrrolidine-2-carbo hydrazide] in $[CD_3]_2SO$.



Compound **4**

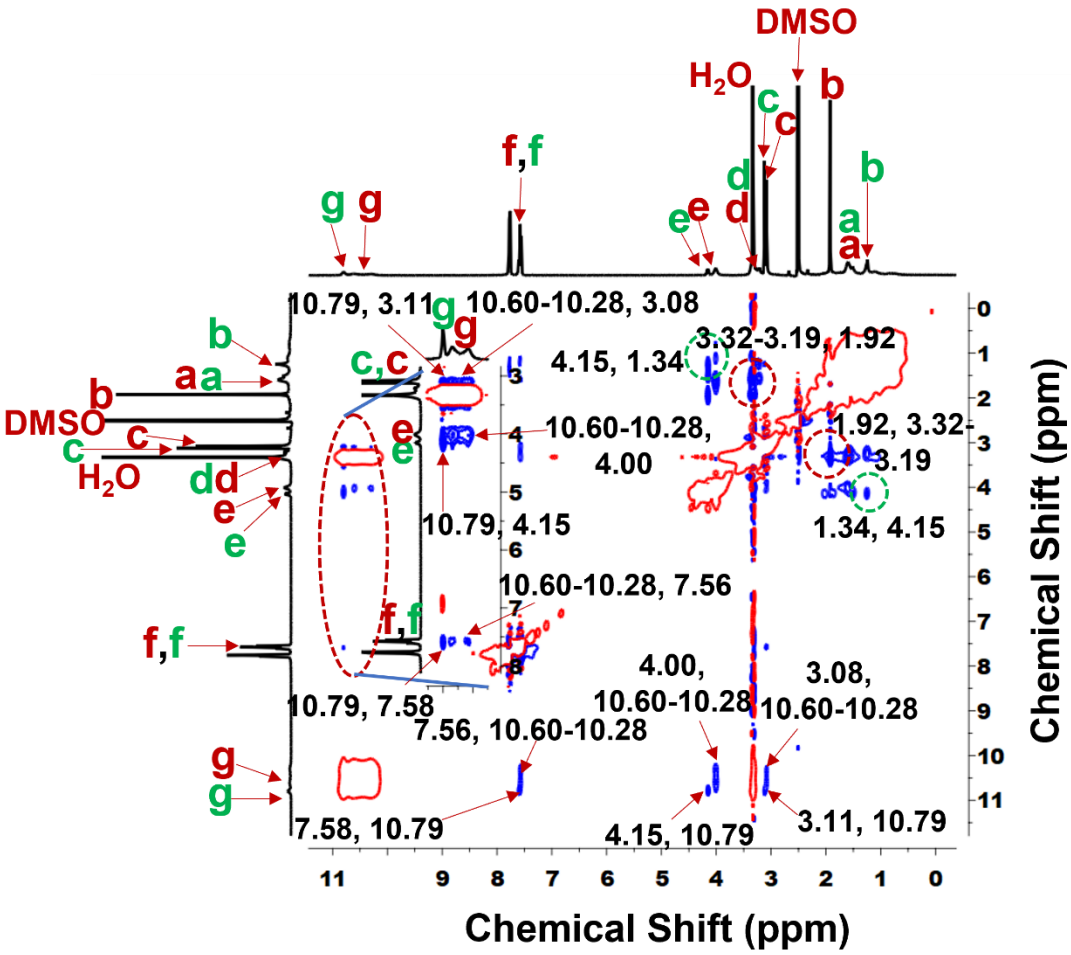
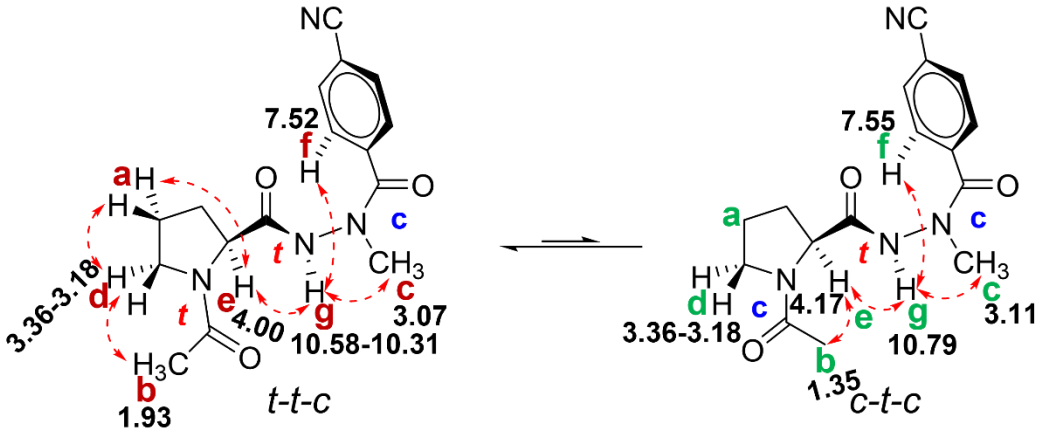


Figure S10. 2D-NOESY Spectrum of **4** [1-acetyl-*N´*-methyl-*N´*-[4-(trifluoromethyl)benzoyl] pyrrolidine-2-carbohydrazide] in $[CD_3]_2SO$.



Compound **5**

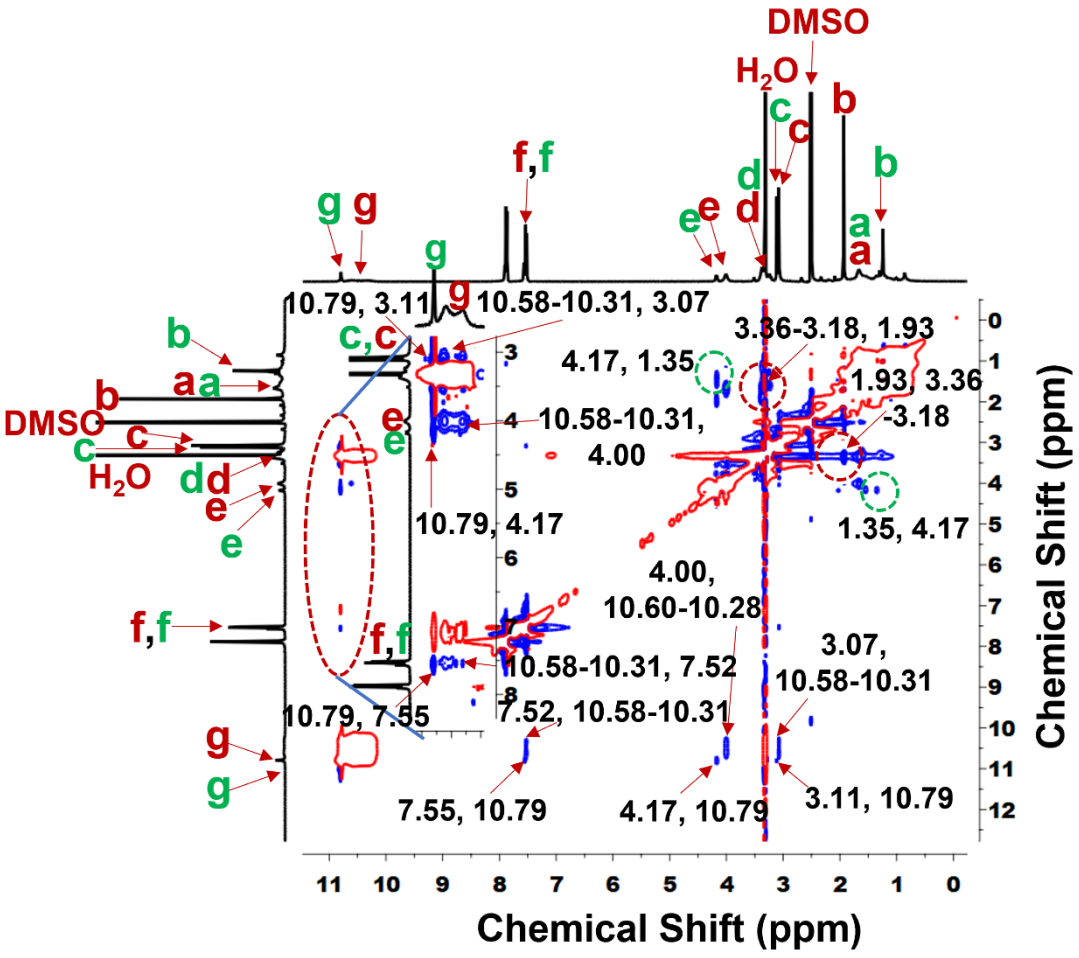
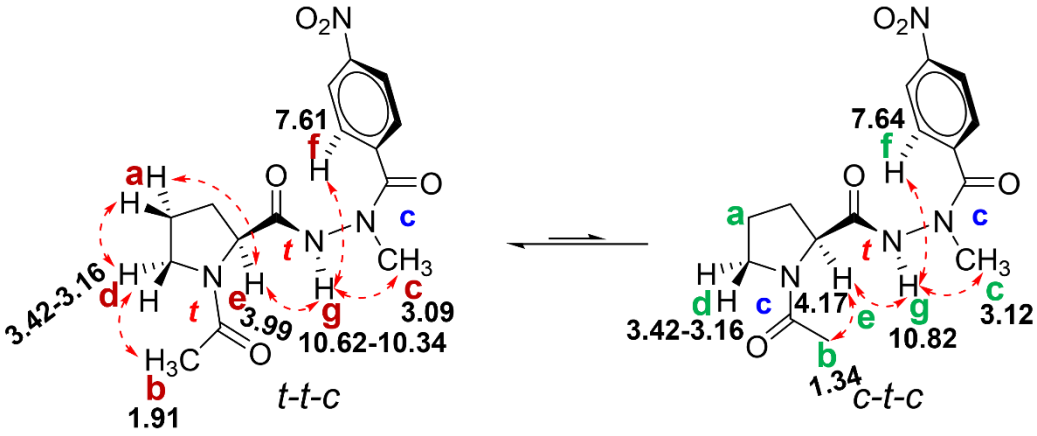


Figure S11. 2D-NOESY Spectrum of **5** [1-acetyl-*N´*-(4-cyanobenzoyl)-*N´*-methyl pyrrolidine-2-carbohydrazide] in $[CD_3]_2SO$.



Compound **6**

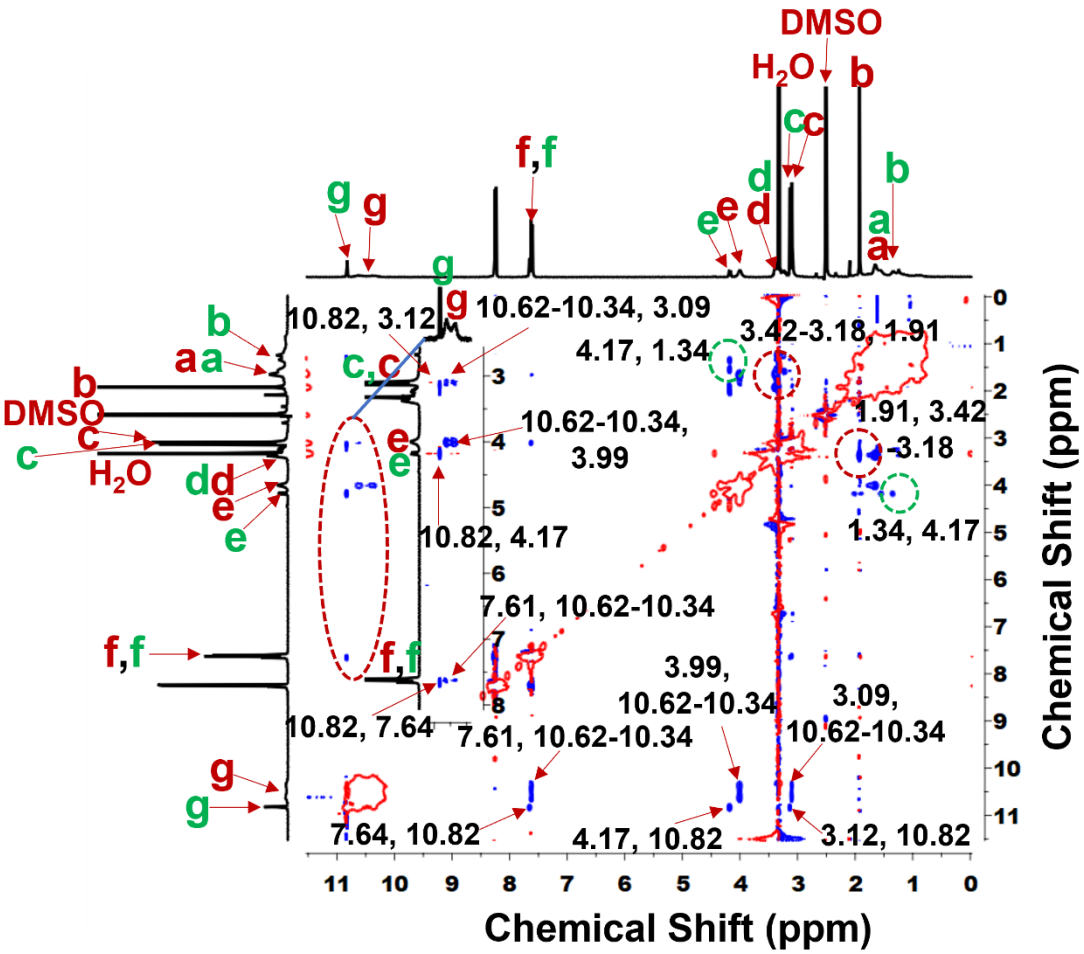
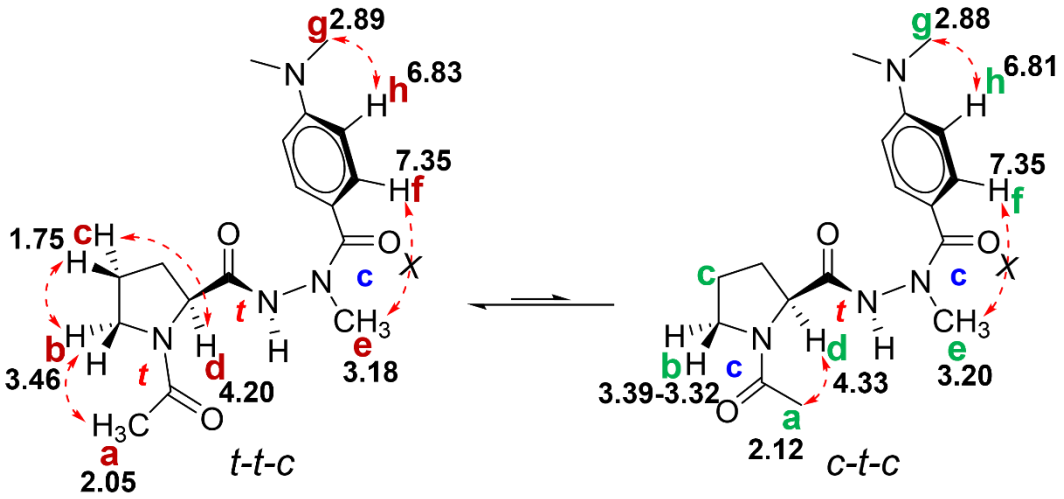


Figure S12. 2D-NOESY Spectrum of **6** [1-acetyl-*N´*-methyl-*N´*-(4-nitrobenzoyl)pyrrolidine-2-carbohydrazide] in $[CD_3]_2SO$.



Compound **1**

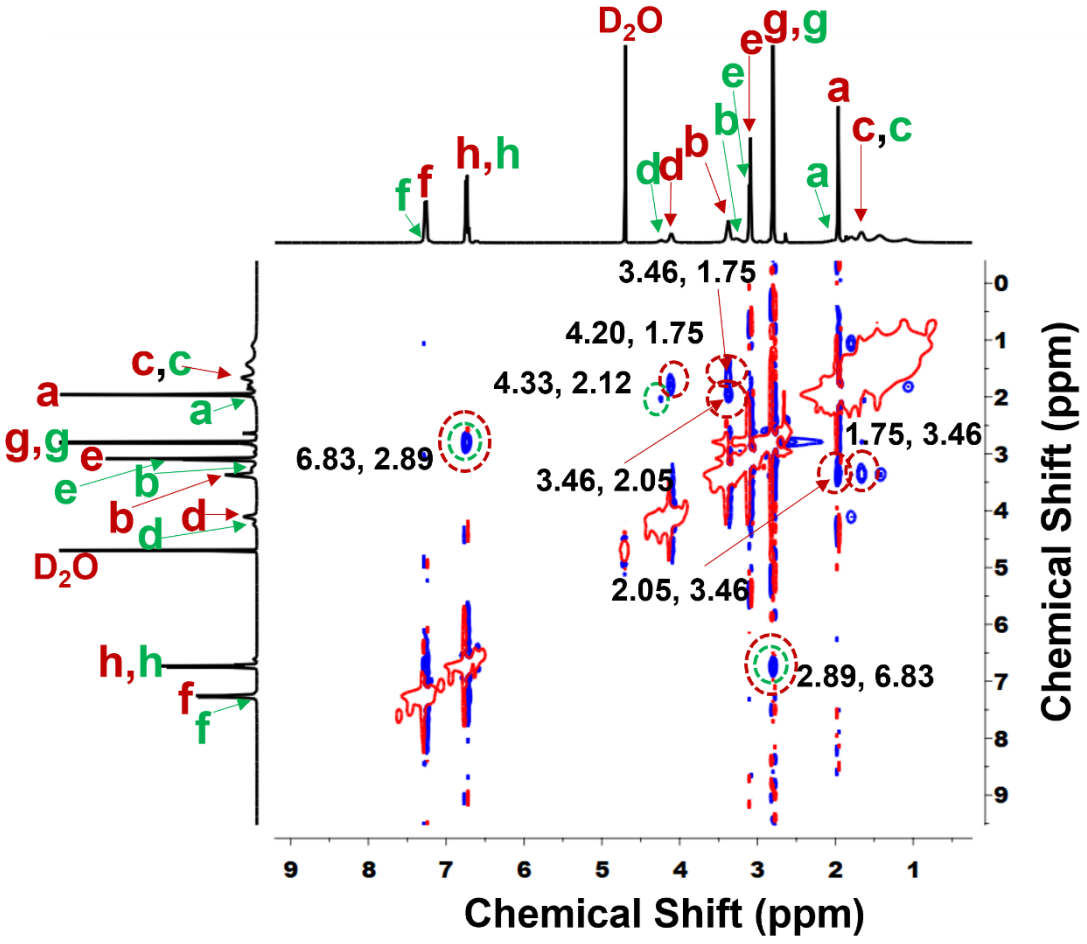
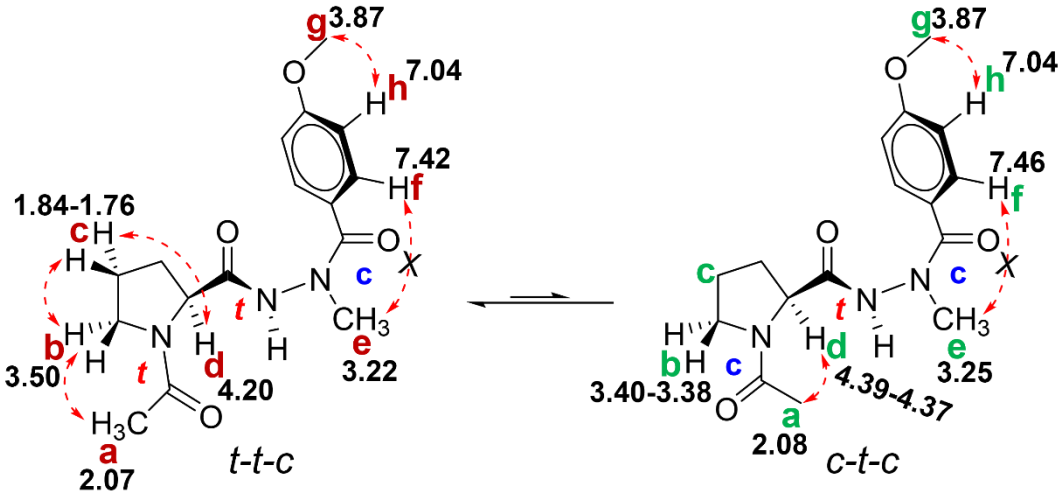


Figure S13. 2D-NOESY Spectrum of **1** [1-acetyl-*N´*-[4-(dimethylamino)benzoyl]-*N´*-methyl pyrrolidine-2-carbohydrazide] in D_2O.



Compound **2**

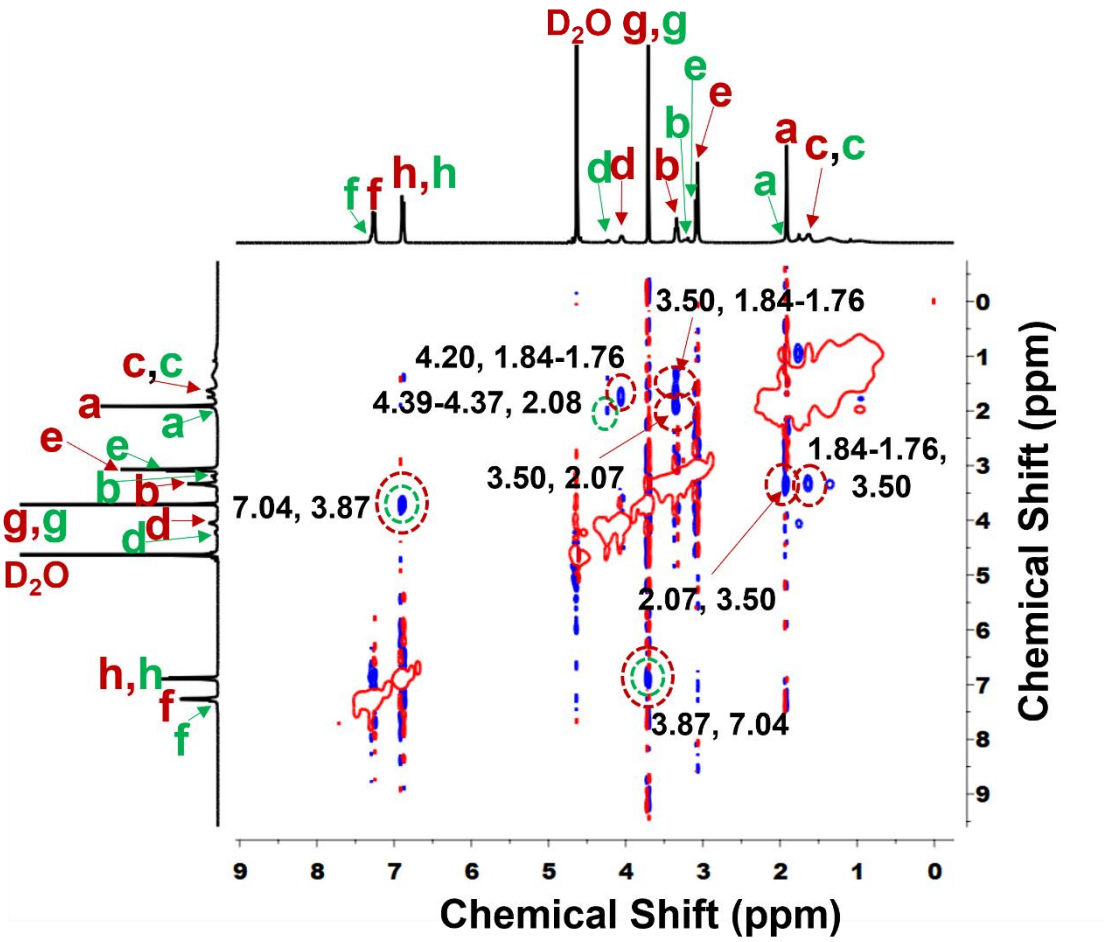
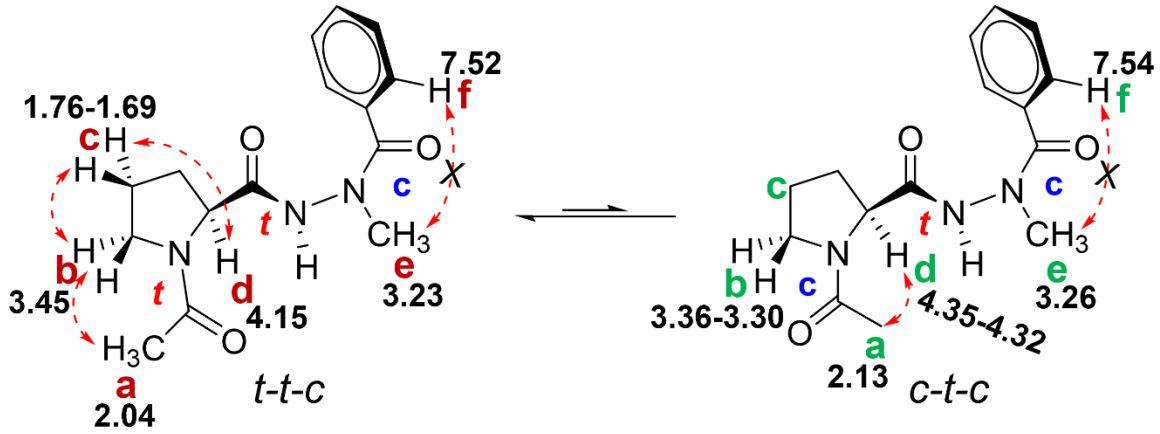


Figure S14. 2D-NOESY Spectrum of **2** [1-acetyl-*N´*-[4-methoxybenzoyl]-*N´*-methyl pyrrolidine-2-carbohydrazide] in D_2O.



Compound **3**

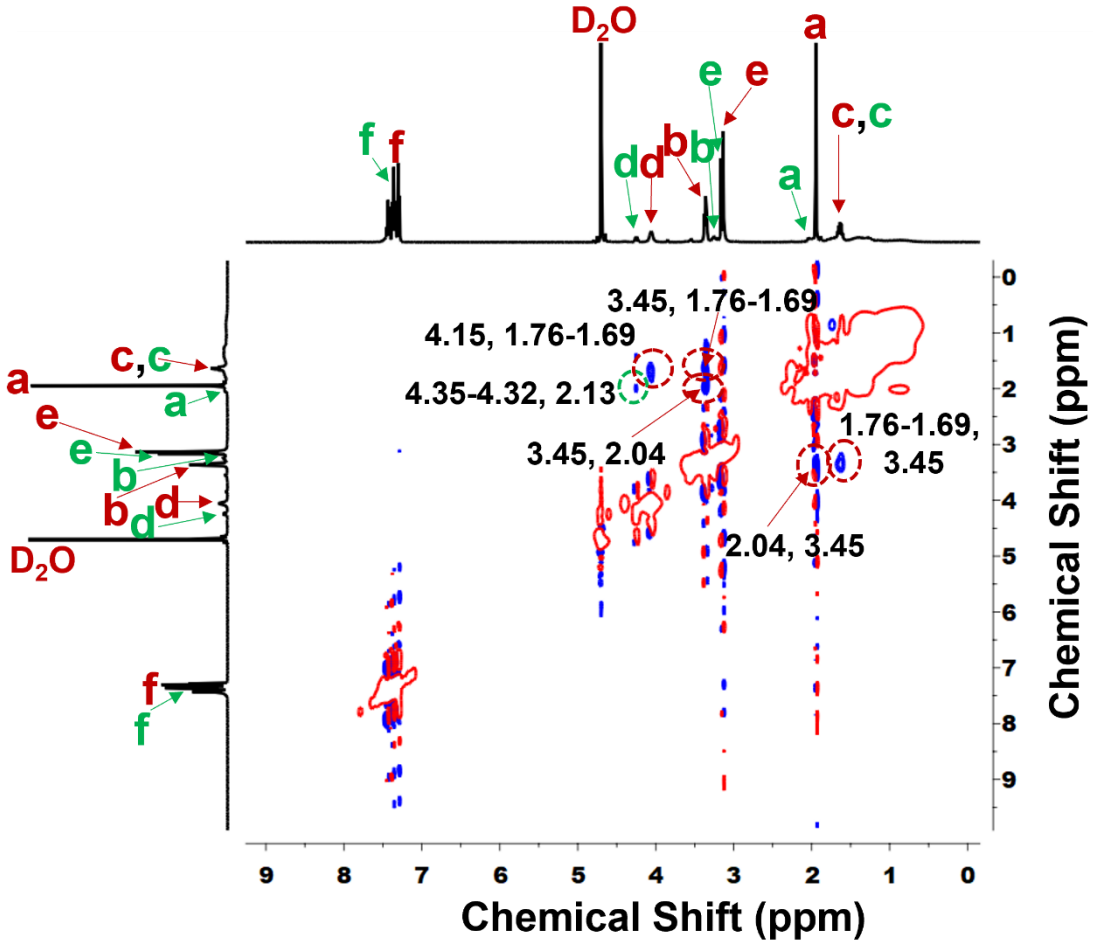
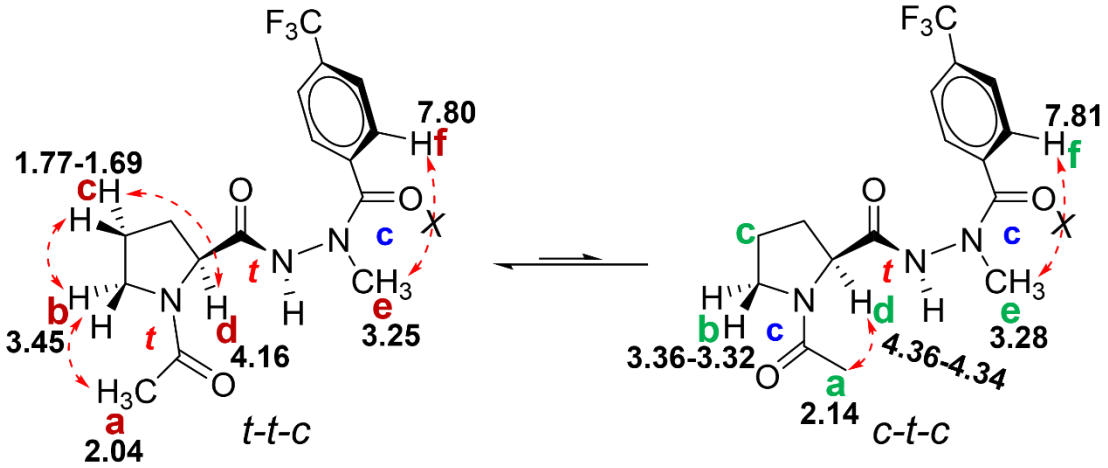


Figure S15. 2D-NOESY Spectrum of **3** [1-acetyl-*N´*-benzoyl-*N´*-methylpyrrolidine-2-carbo hydrazide] in D_2O.



Compound **4**

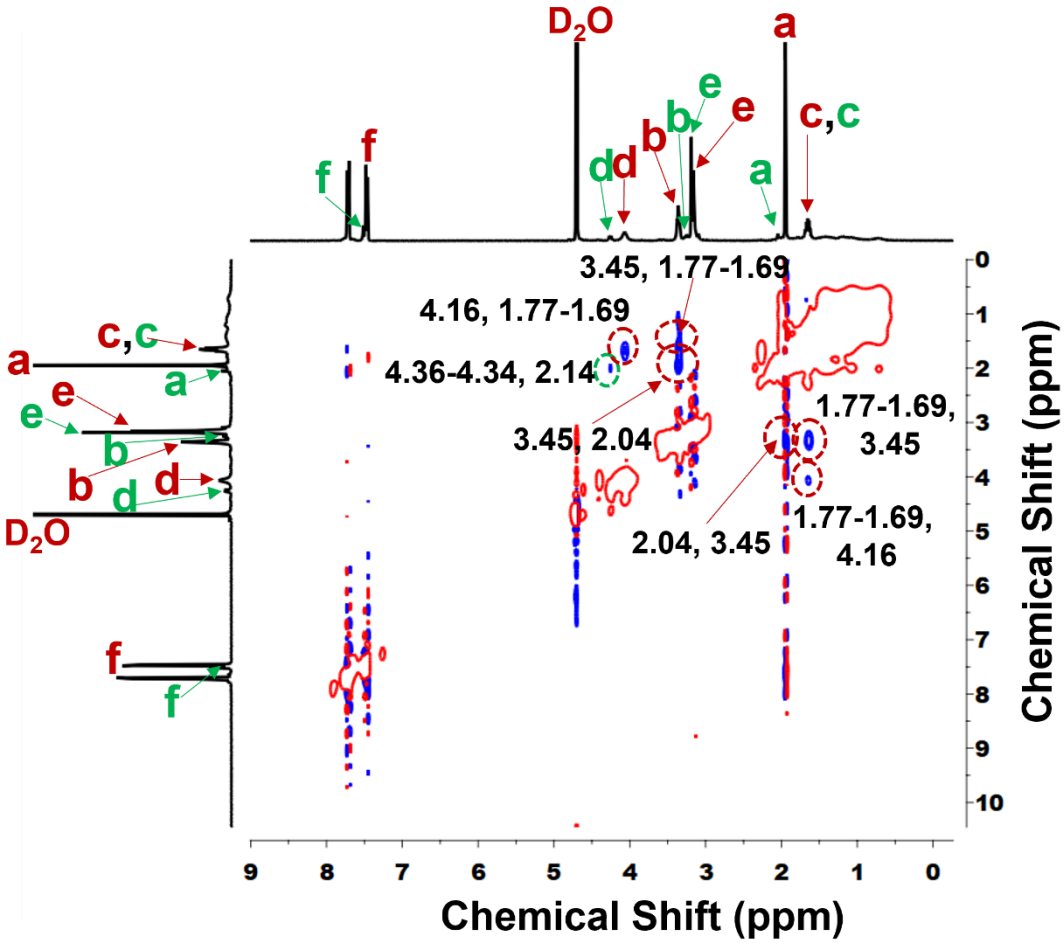
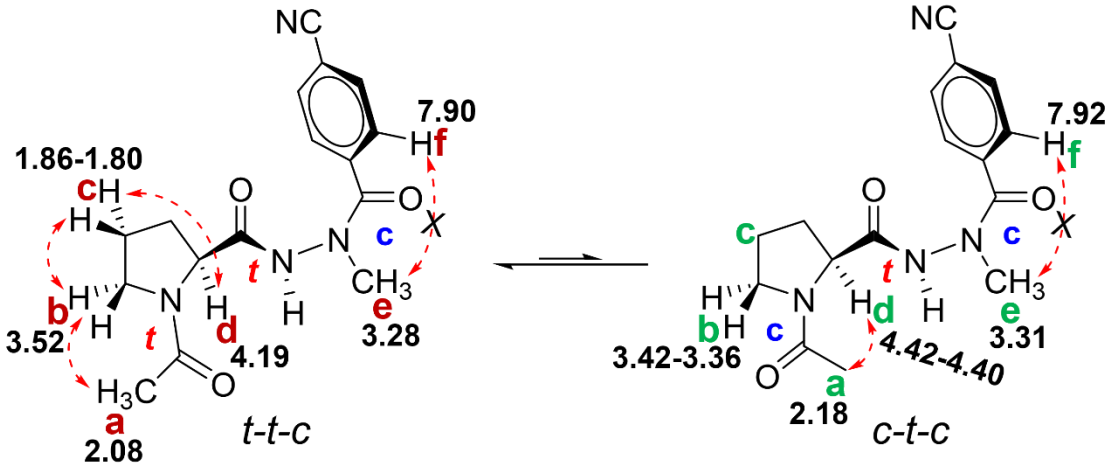


Figure S16. 2D-NOESY Spectrum of **4** [1-acetyl-*N´*-methyl-*N´*-[4-(trifluoromethyl)benzoyl] pyrrolidine-2-carbohydrazide] in D_2O.



Compound **5**

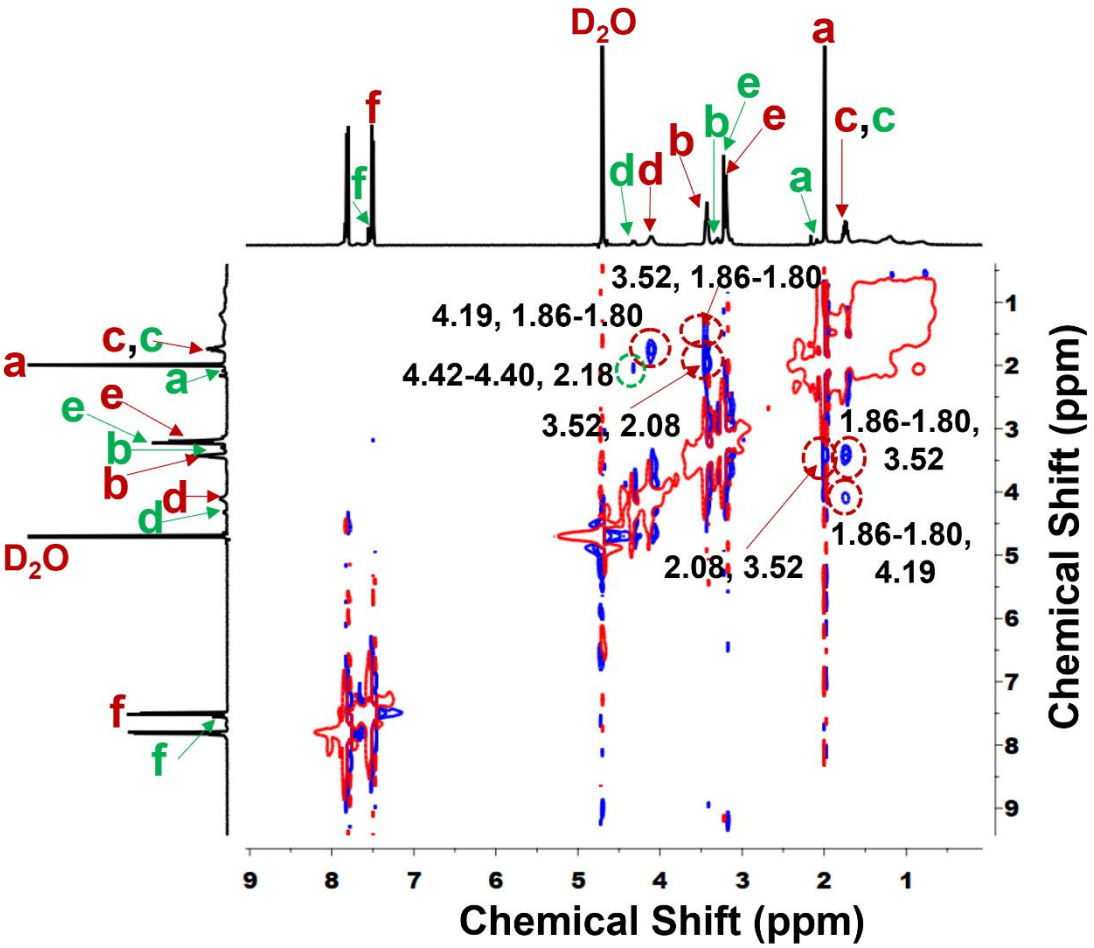
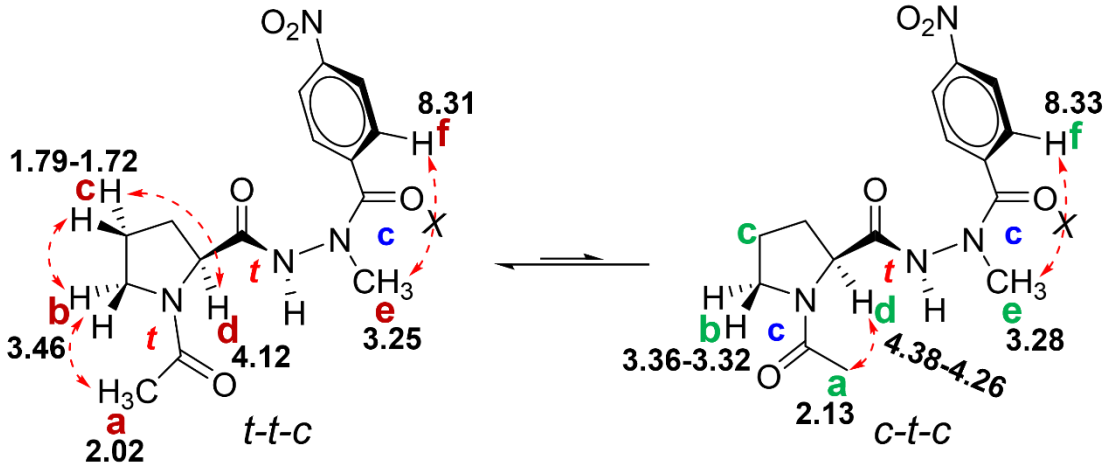


Figure S17. 2D-NOESY Spectrum of **5** [1-acetyl-*N´*-(4-cyanobenzoyl)-*N´*-methyl pyrrolidine-2-carbohydrazide] in D_2O.



Compound **6**

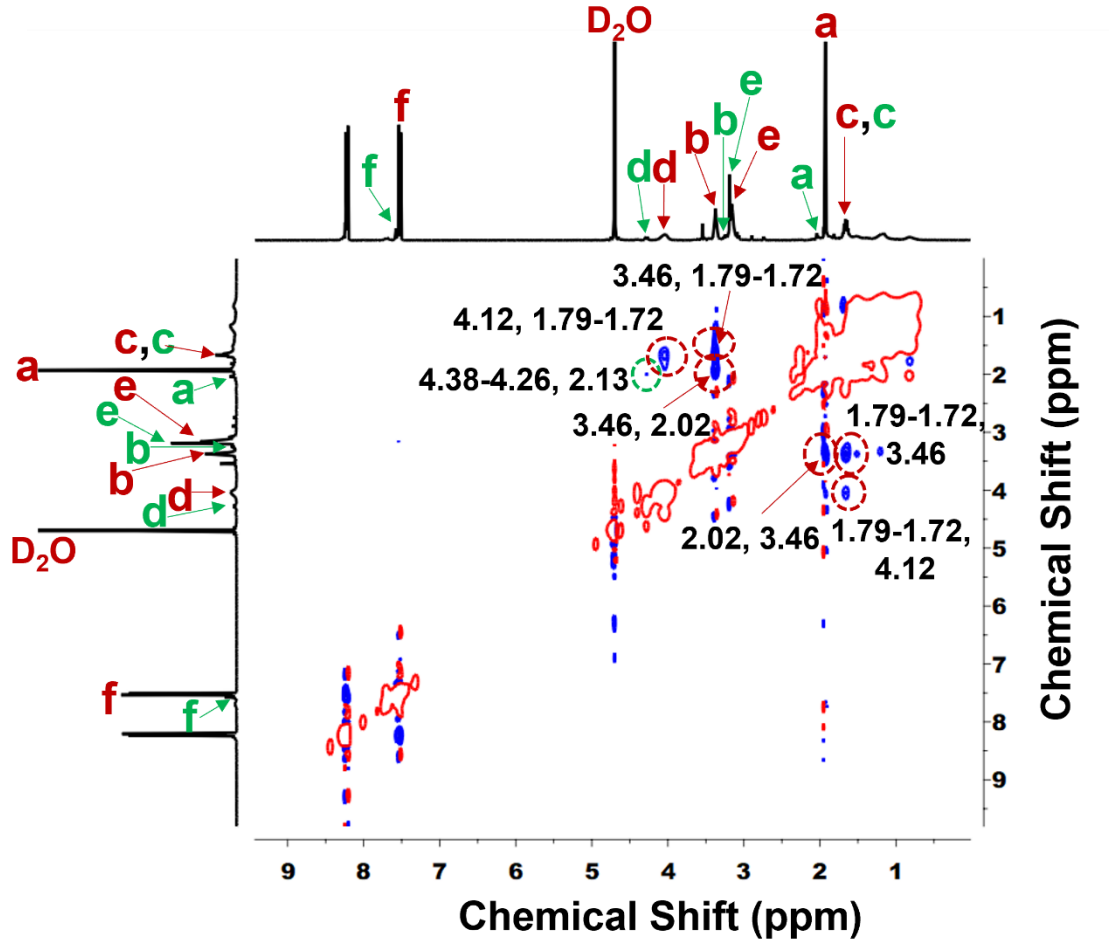
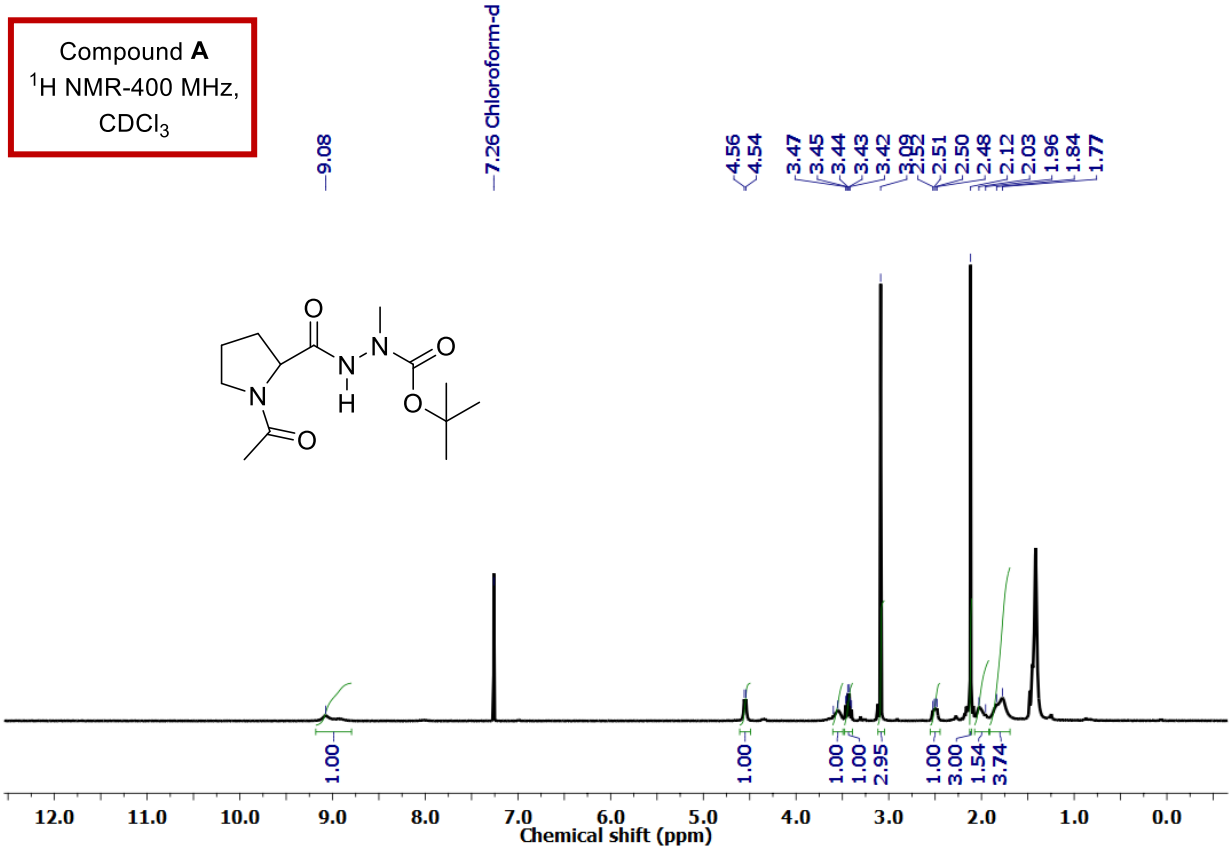


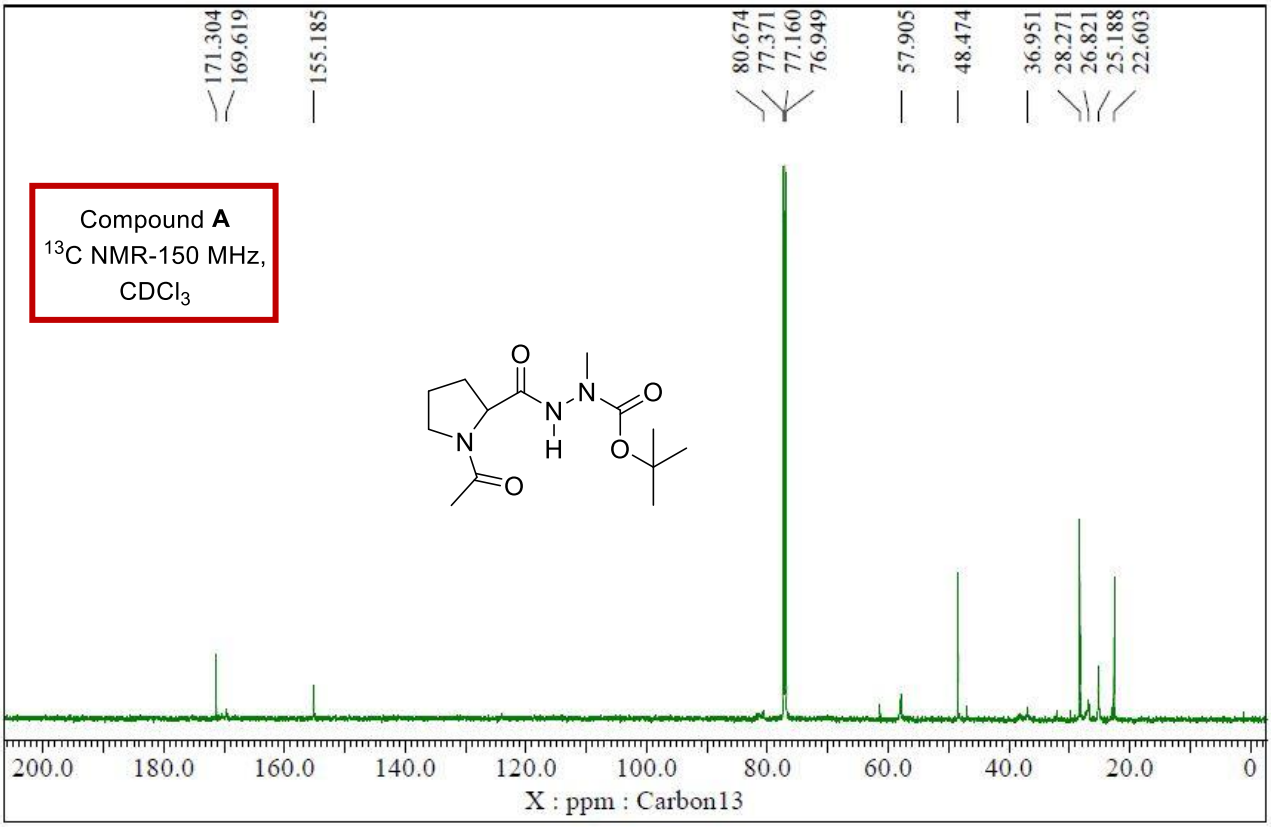
Figure S18. 2D-NOESY Spectrum of **6** [1-acetyl-*N´*-methyl-*N´*-(4-nitrobenzoyl)pyrrolidine-2-carbohydrazide] in D_2O.

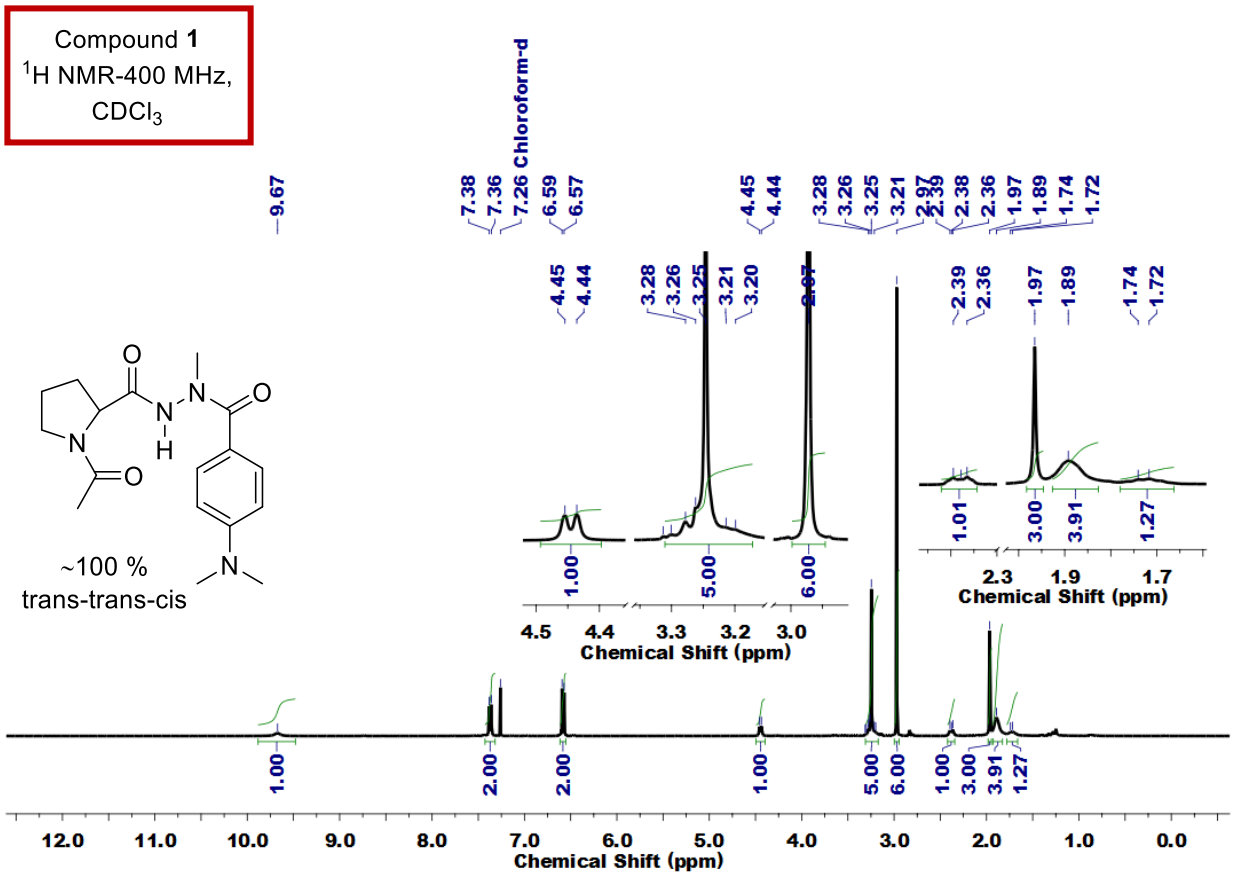
10. ^{1}H, ^{13}C and ^{19}F NMR spectra of all reported compounds

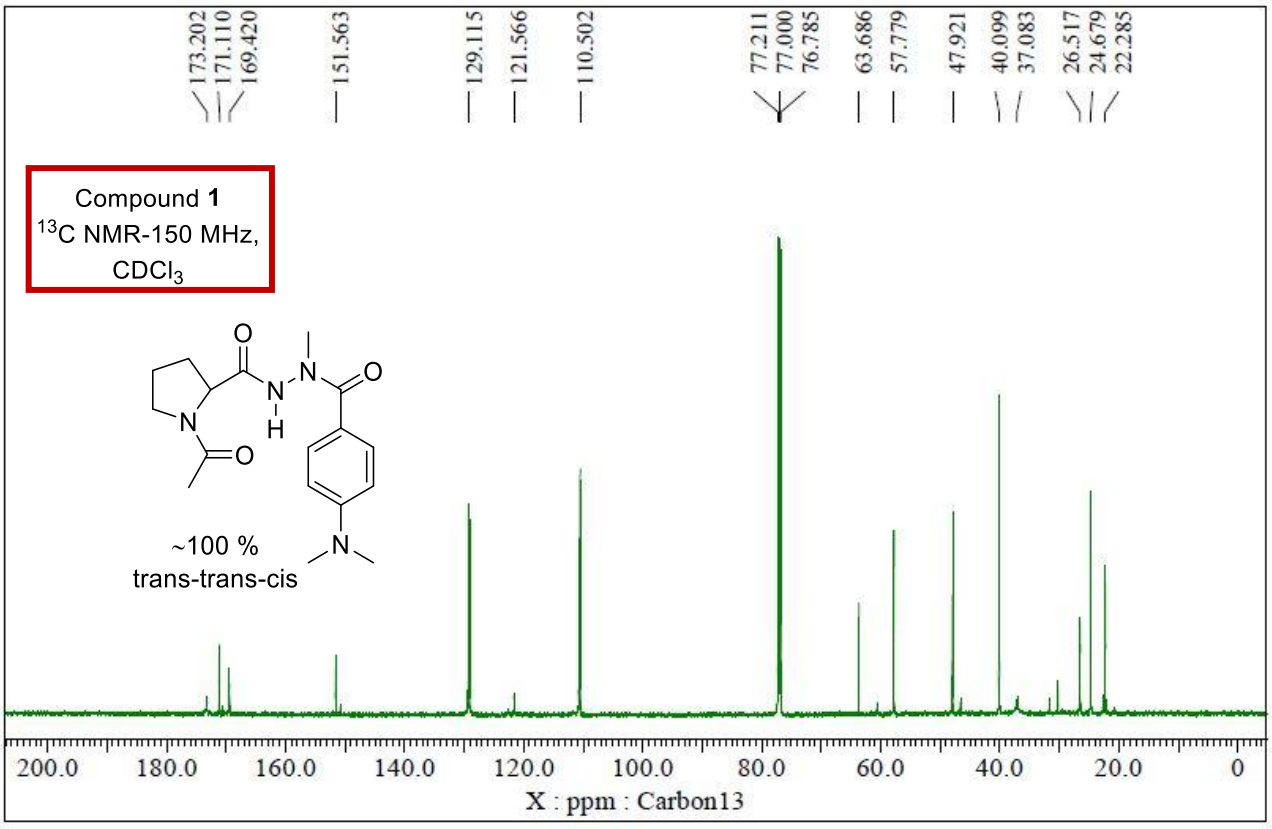
Compound **A**
^{1}H NMR-400 MHz,
$CDCl_3$

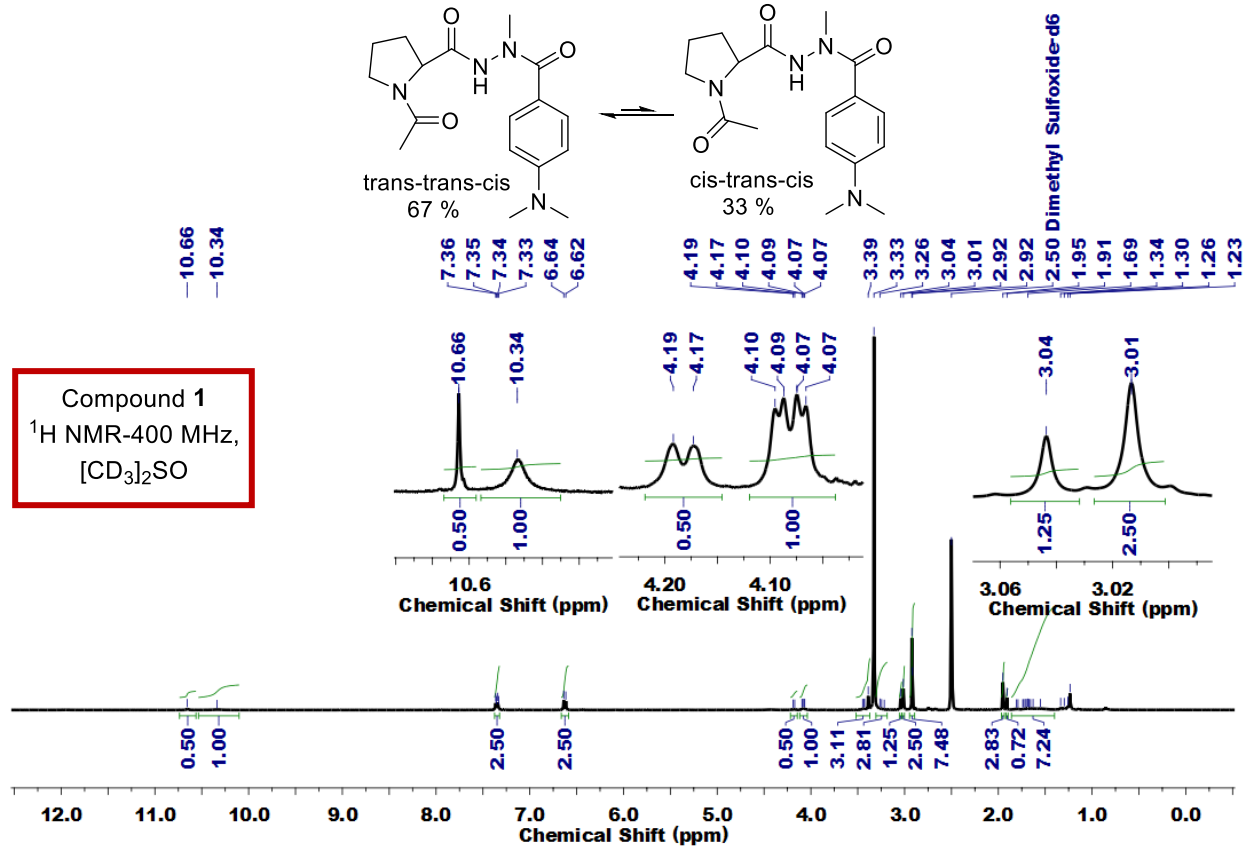


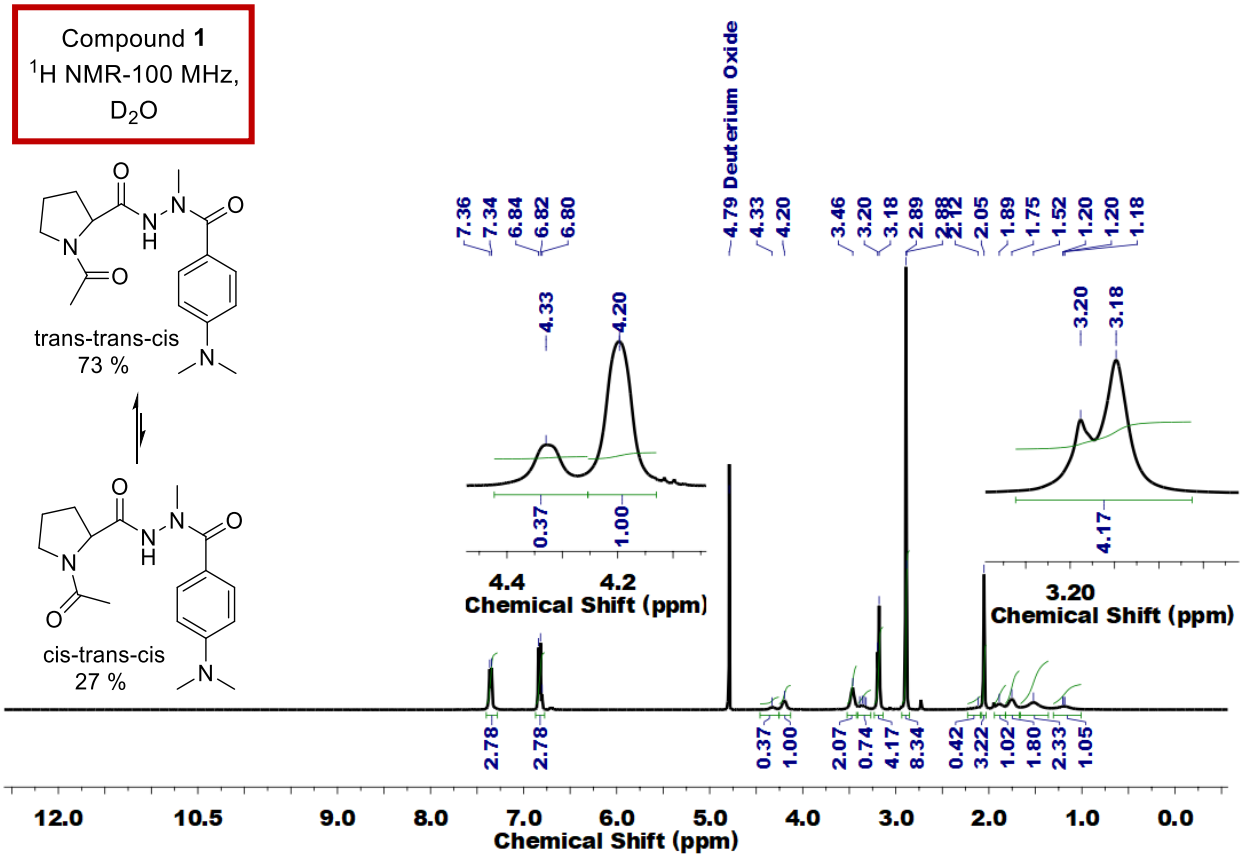
Compound **A**
^{13}C NMR-150 MHz,
$CDCl_3$



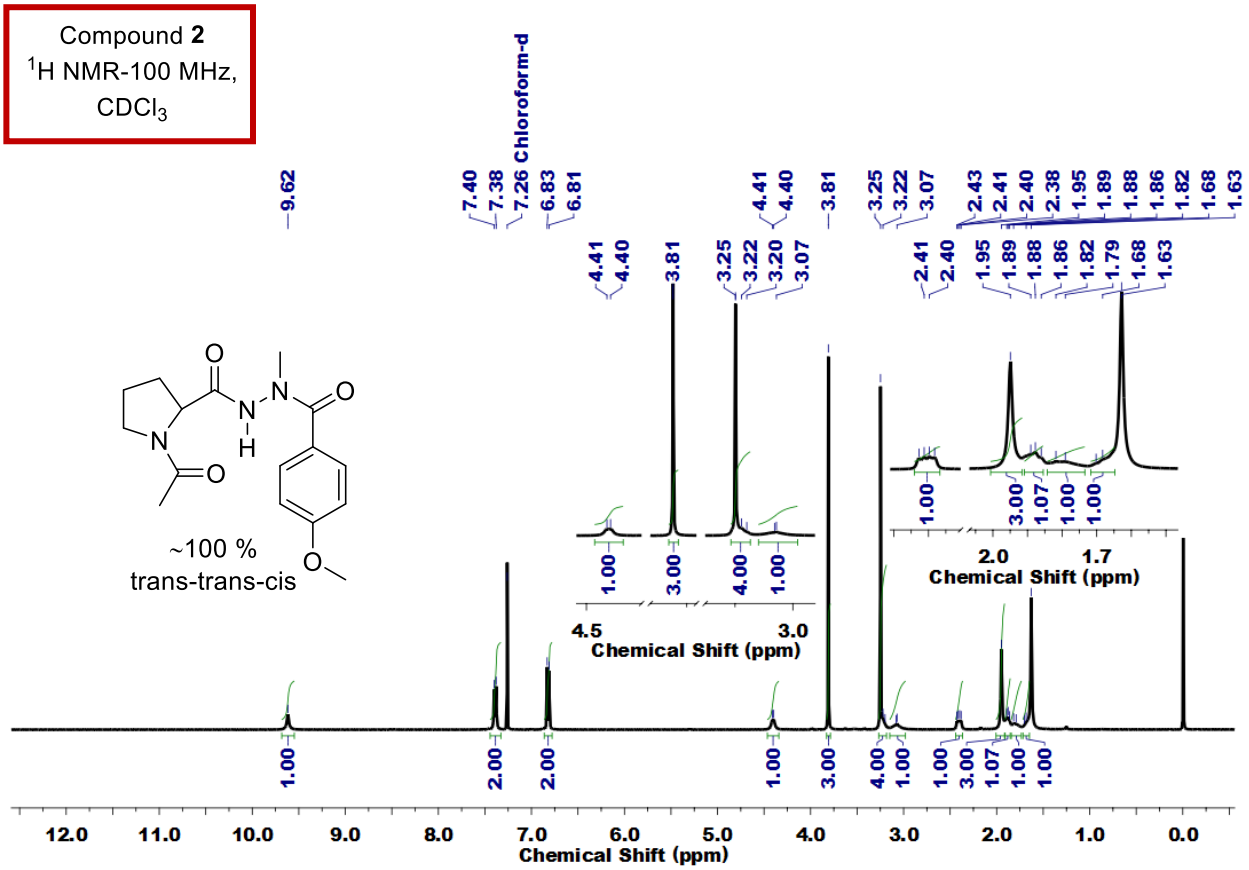

Compound 1
1H NMR-400 MHz,
CDCl3
~100 %
trans-trans-cis
Chloroform-d
Chemical Shift (ppm)


Compound 1
13C NMR-150 MHz,
CDCl3
~100 %
trans-trans-cis
X : ppm : Carbon13

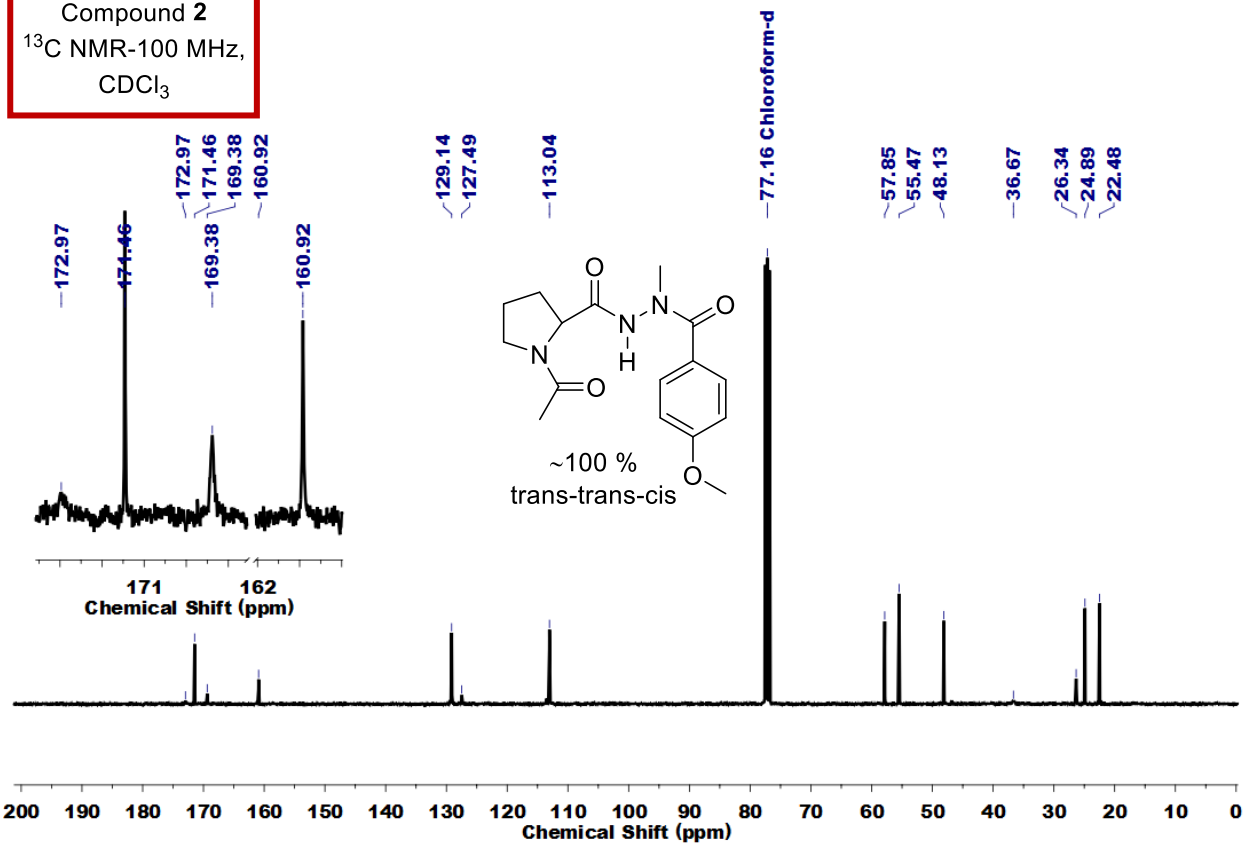

trans-trans-cis
67 %
cis-trans-cis
33 %
Dimethyl Sulfoxide-d6
Compound 1
1H NMR-400 MHz,
[CD3]2SO
Chemical Shift (ppm)

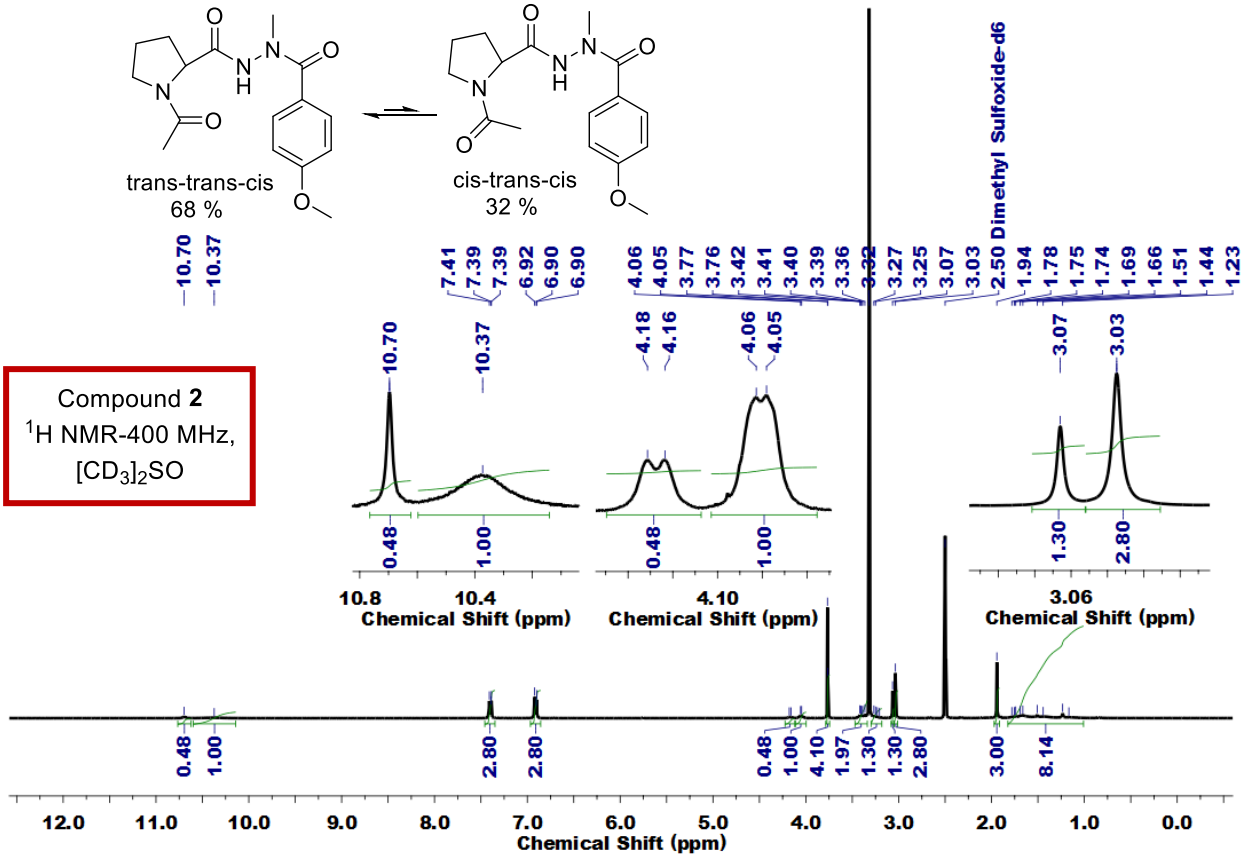

Compound 1
1H NMR-100 MHz,
D2O
trans-trans-cis
73 %
cis-trans-cis
27 %
Deuterium Oxide
Chemical Shift (ppm)

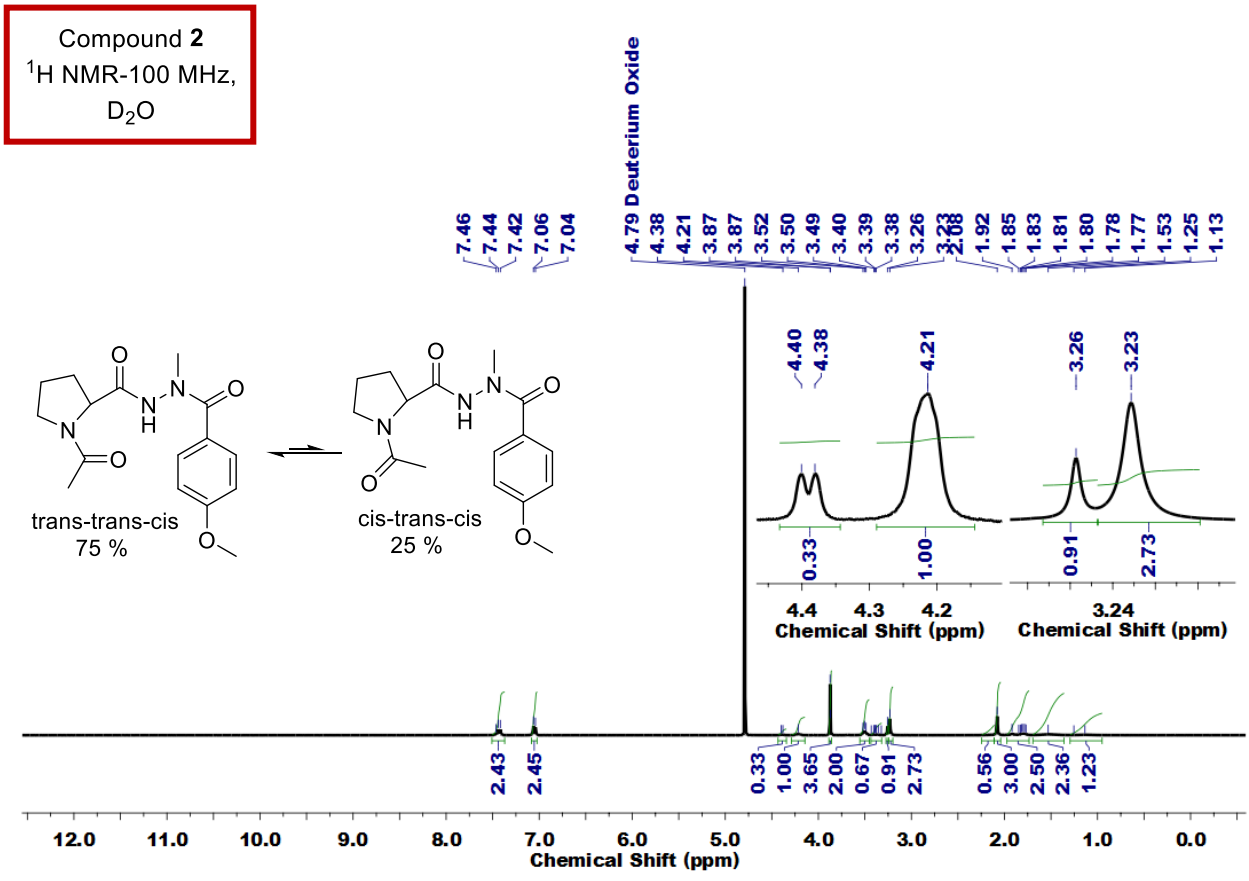
Compound **2**
^{1}H NMR-100 MHz,
$CDCl_3$



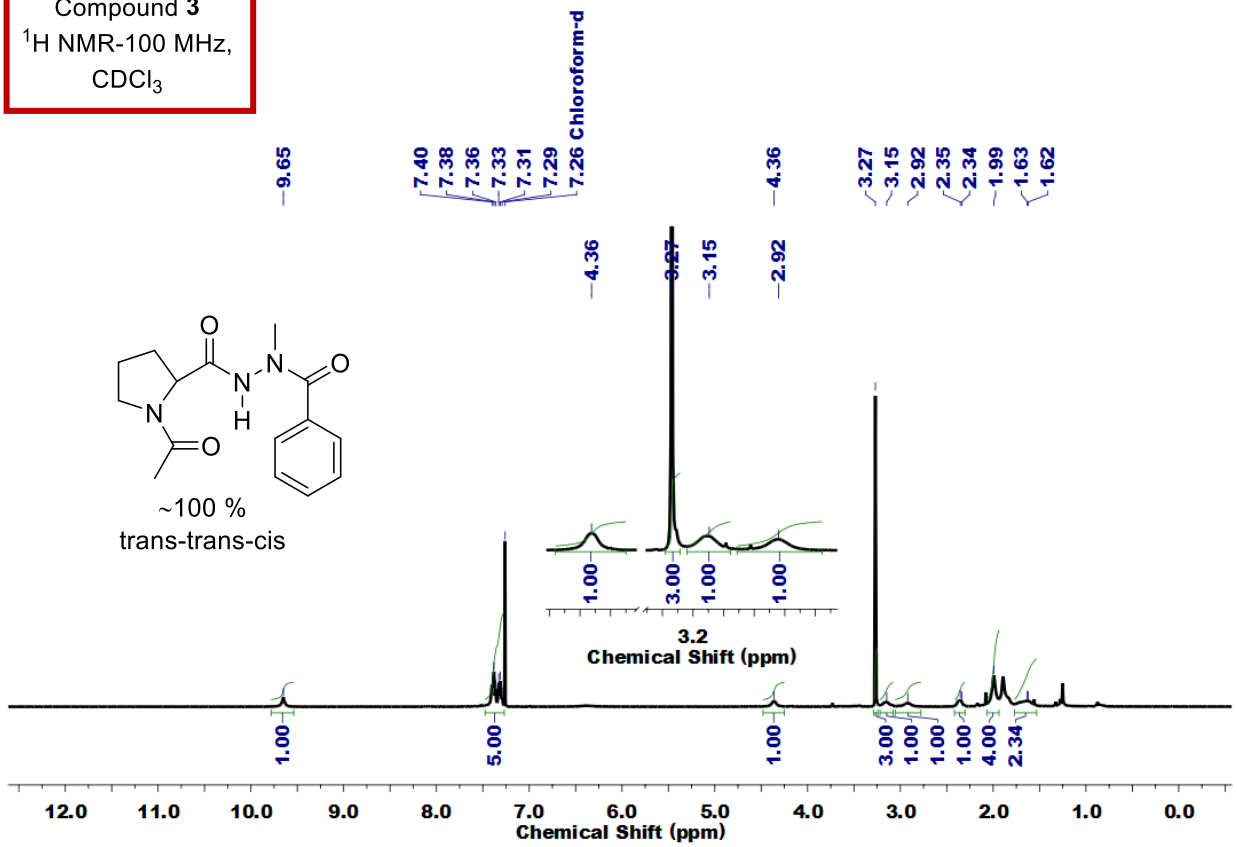
Compound **2**
^{13}C NMR-100 MHz,
$CDCl_3$



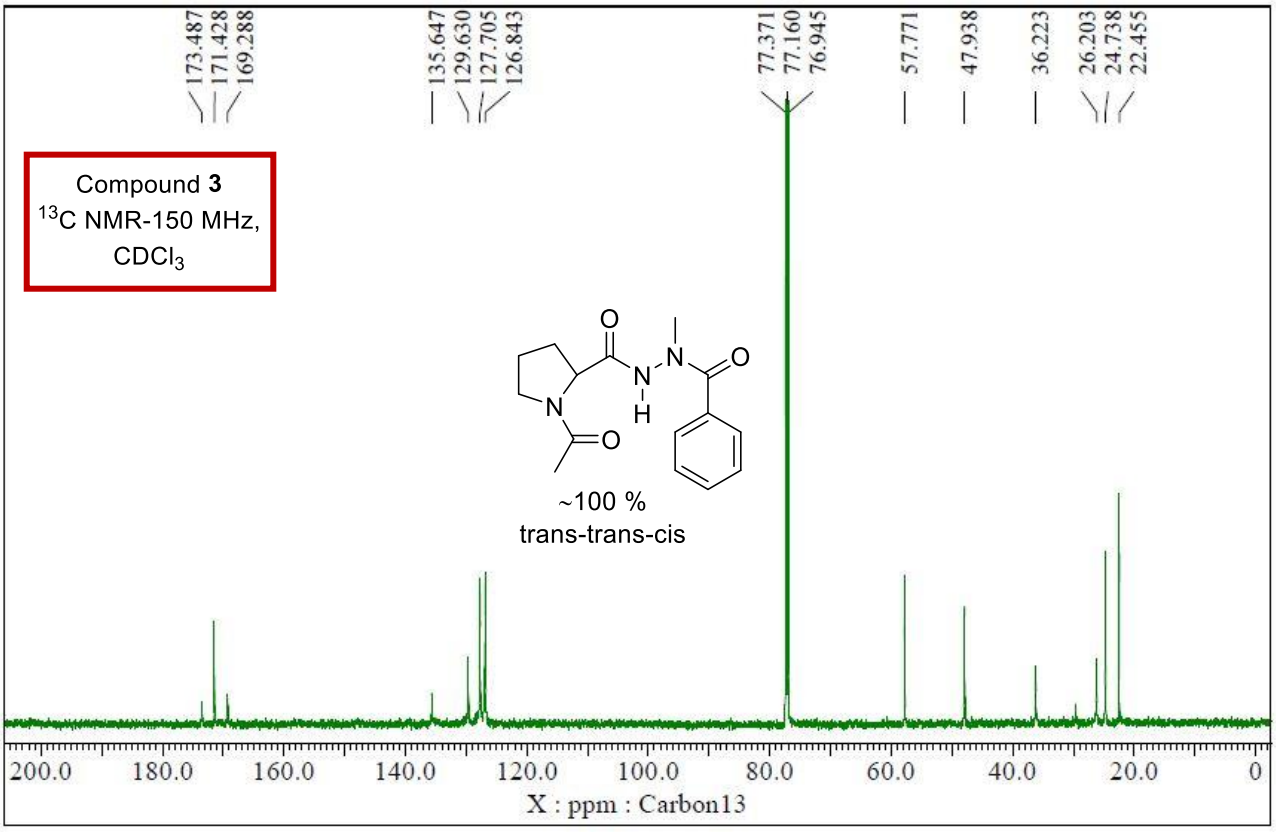

Compound 2
1H NMR-400 MHz,
[CD3]2SO
trans-trans-cis
68 %
cis-trans-cis
32 %
Dimethyl Sulfoxide-d6
Chemical Shift (ppm)

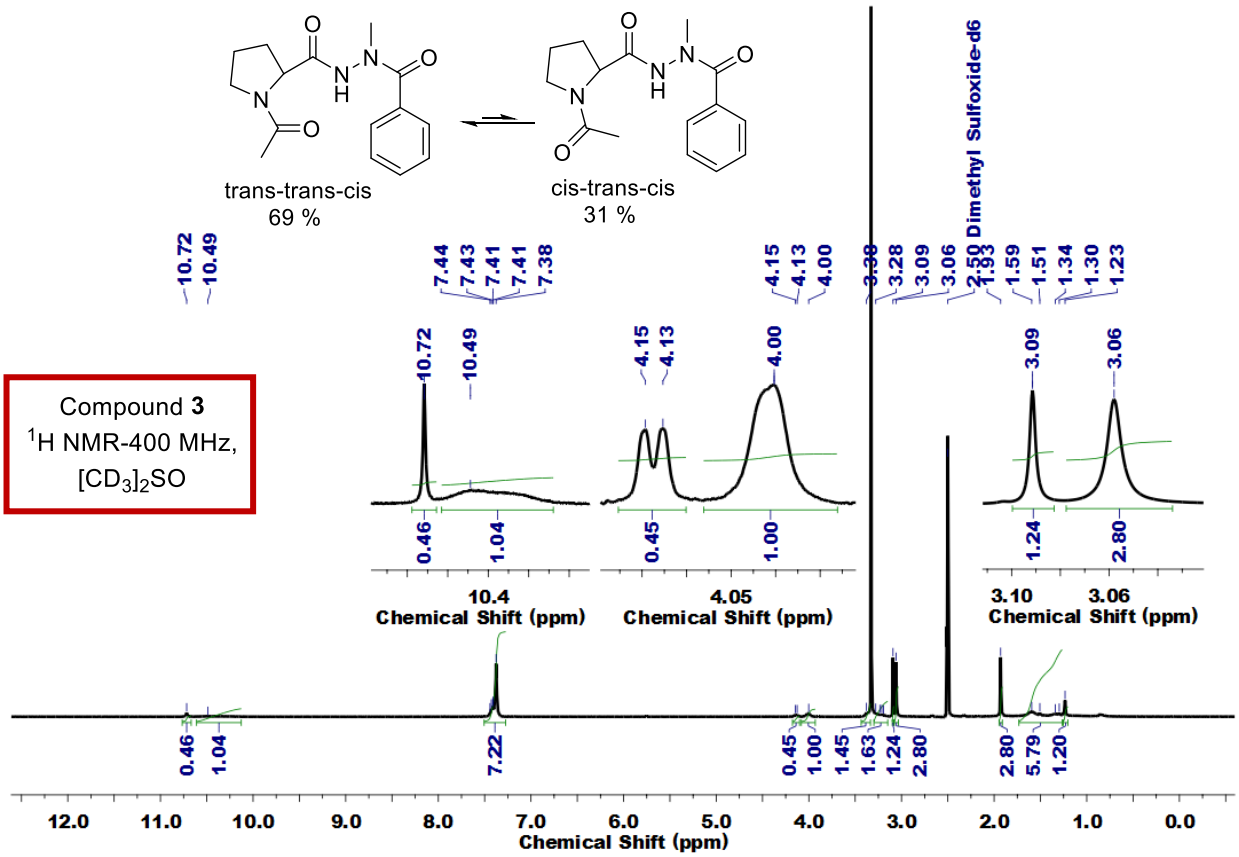

Compound 2
1H NMR-100 MHz,
D2O
trans-trans-cis
75 %
cis-trans-cis
25 %
Deuterium Oxide
Chemical Shift (ppm)

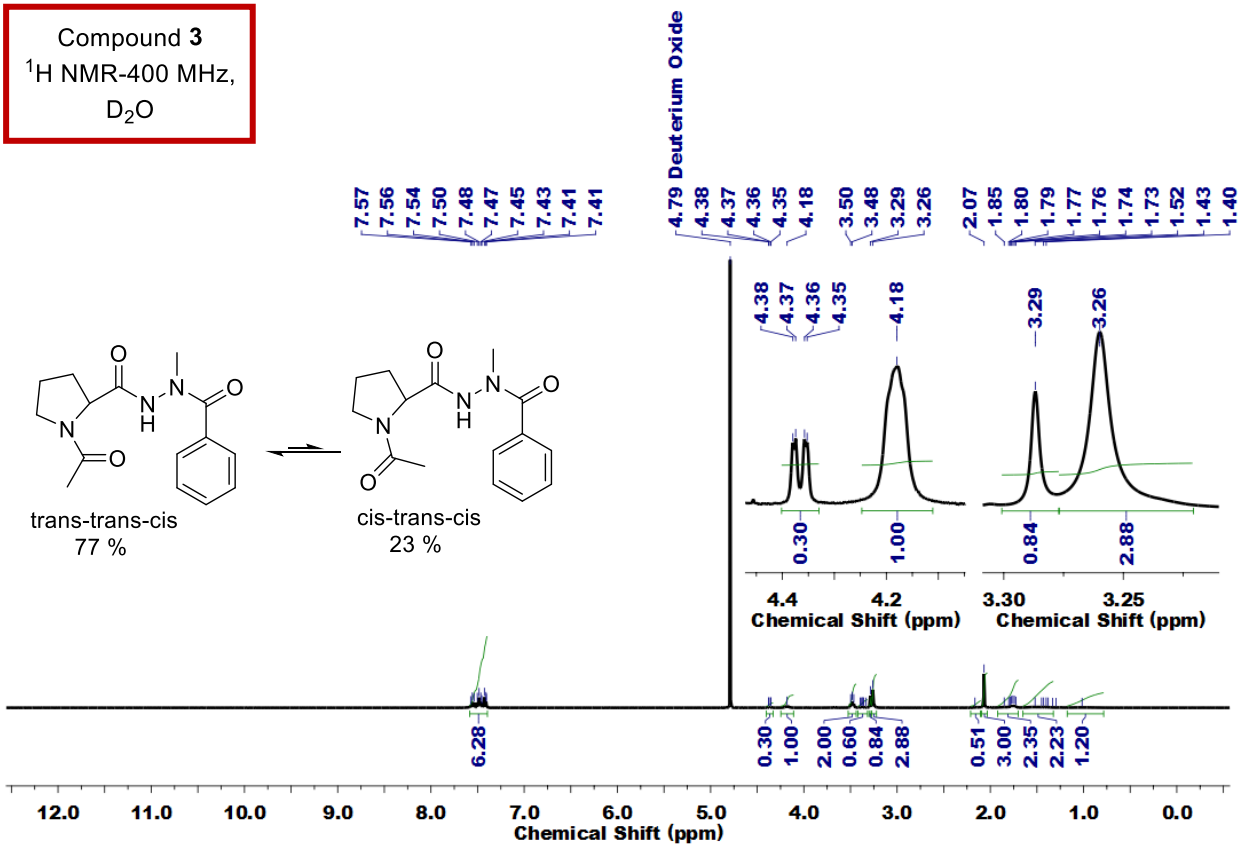
Compound **3**
^{1}H NMR-100 MHz,
$CDCl_3$



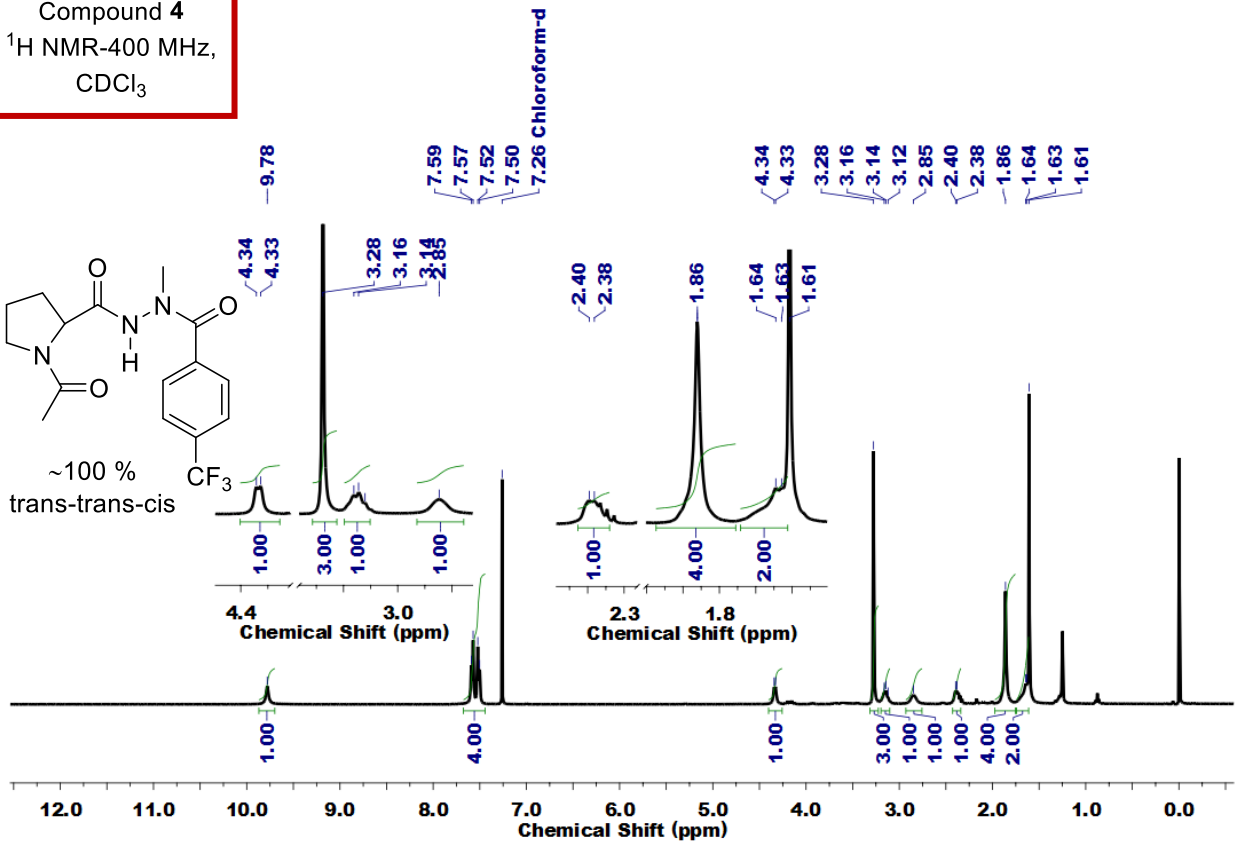
Compound **3**
^{13}C NMR-150 MHz,
$CDCl_3$



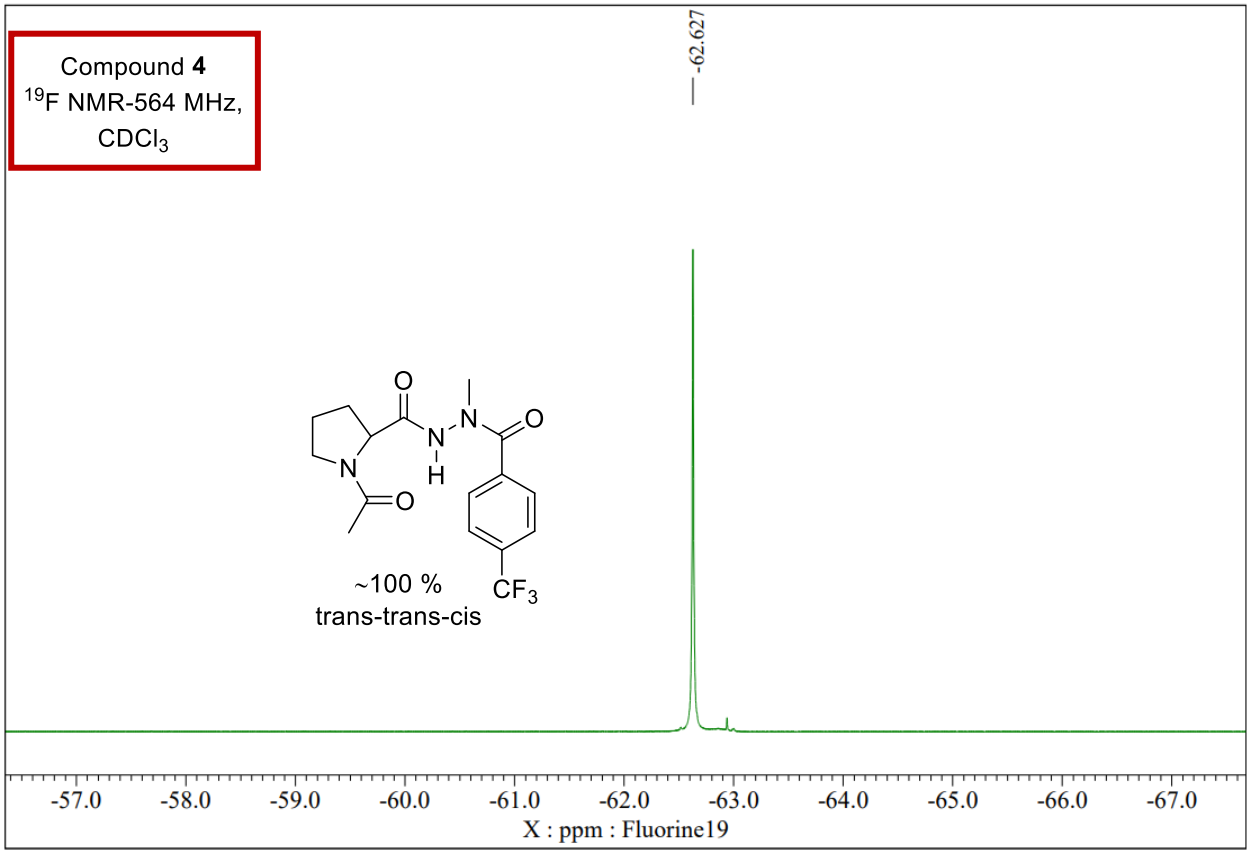

Compound 3
1H NMR-400 MHz,
[CD3]2SO
trans-trans-cis
69 %
cis-trans-cis
31 %
Dimethyl Sulfoxide-d6
Chemical Shift (ppm)

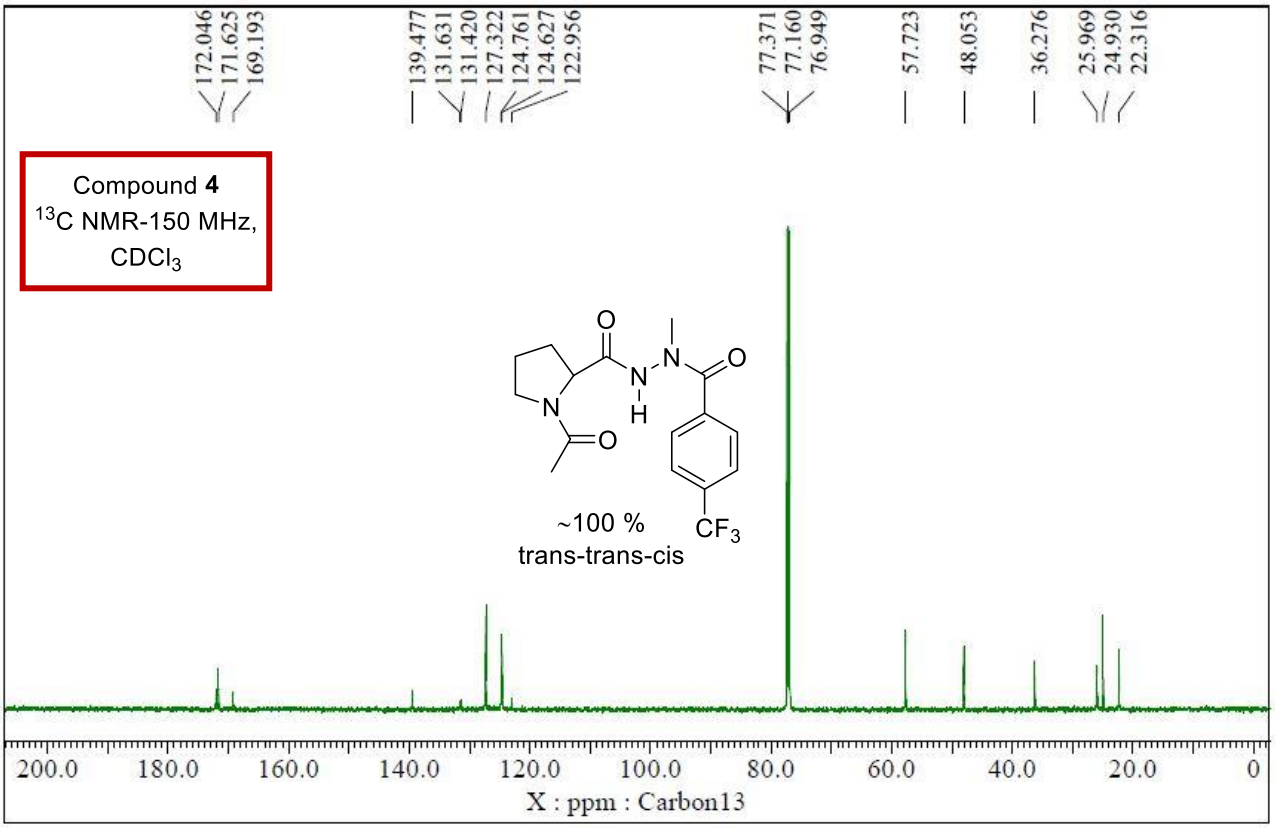

Compound 3
1H NMR-400 MHz,
D2O
Deuterium Oxide
trans-trans-cis
77 %
cis-trans-cis
23 %
Chemical Shift (ppm)

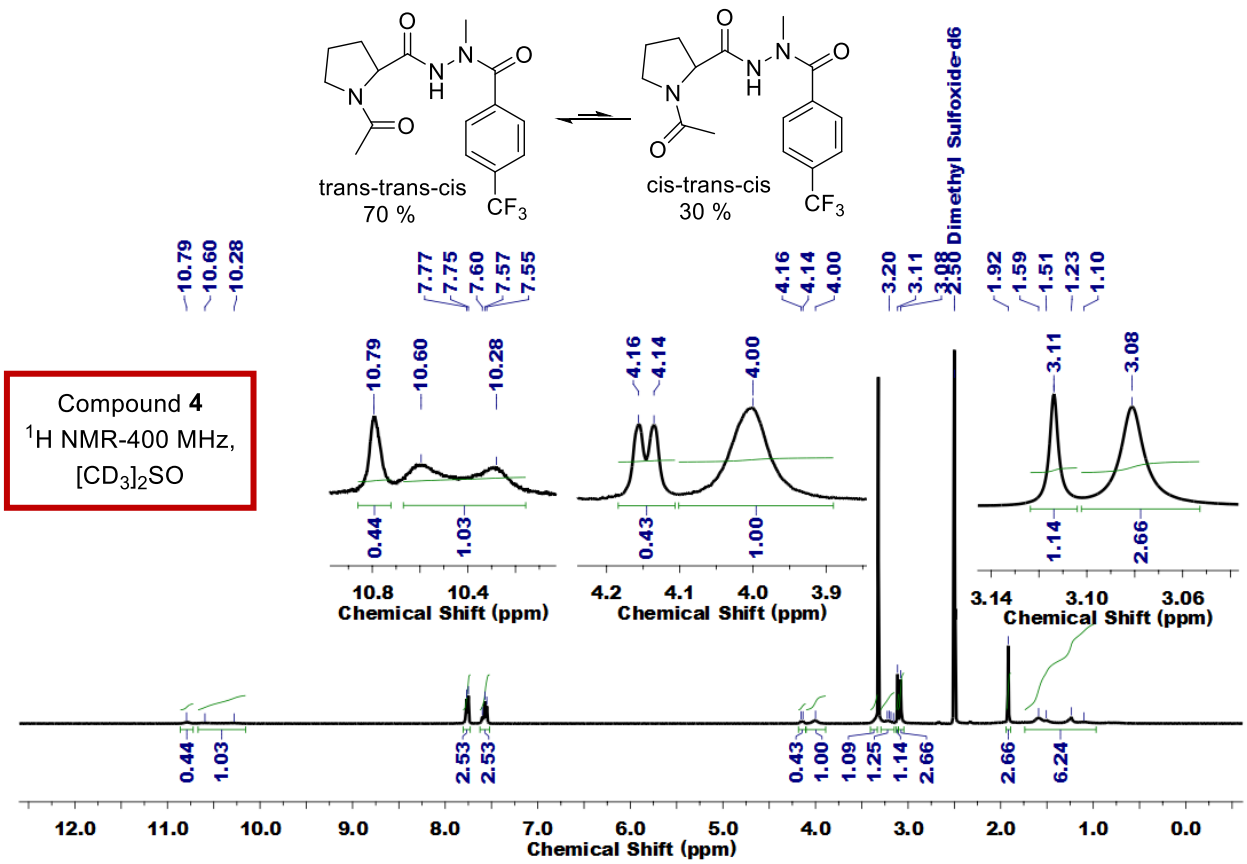
Compound **4**
^{1}H NMR-400 MHz,
$CDCl_3$

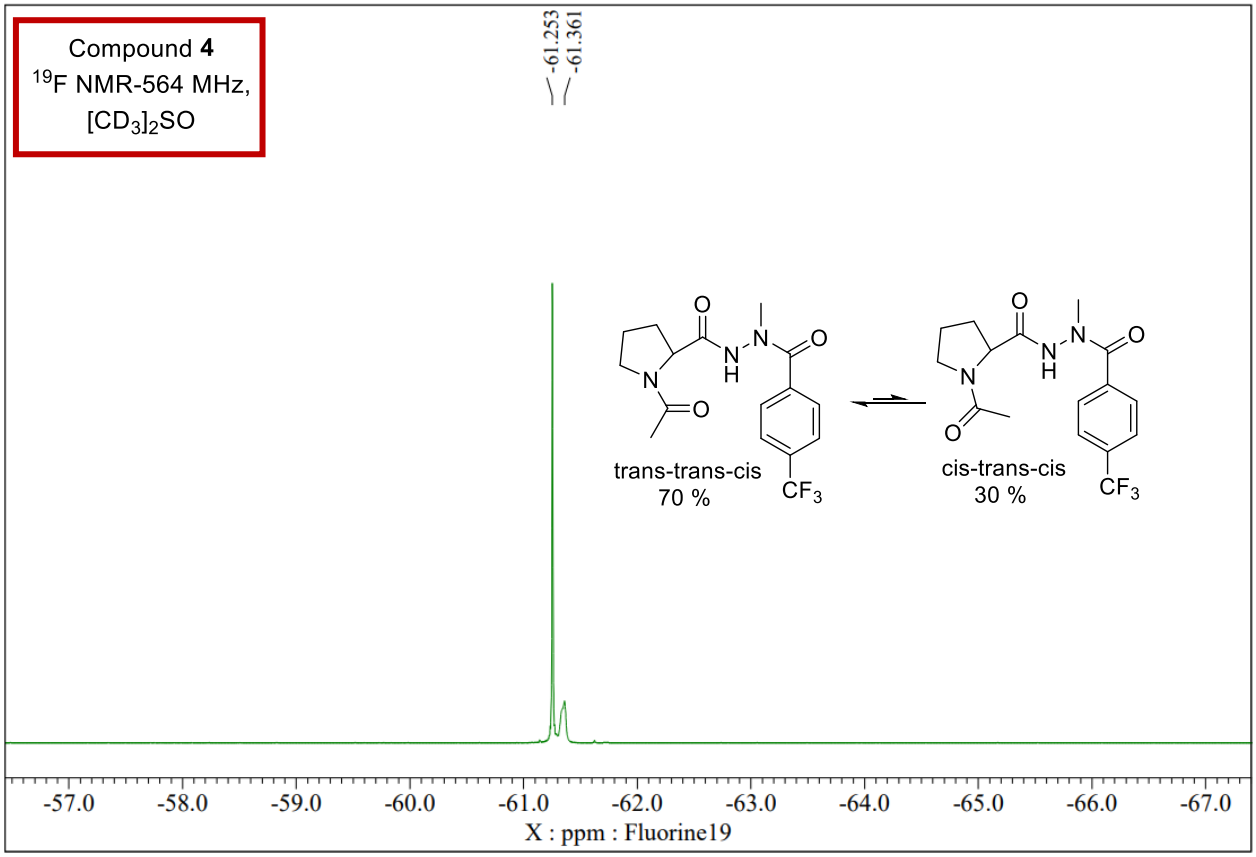


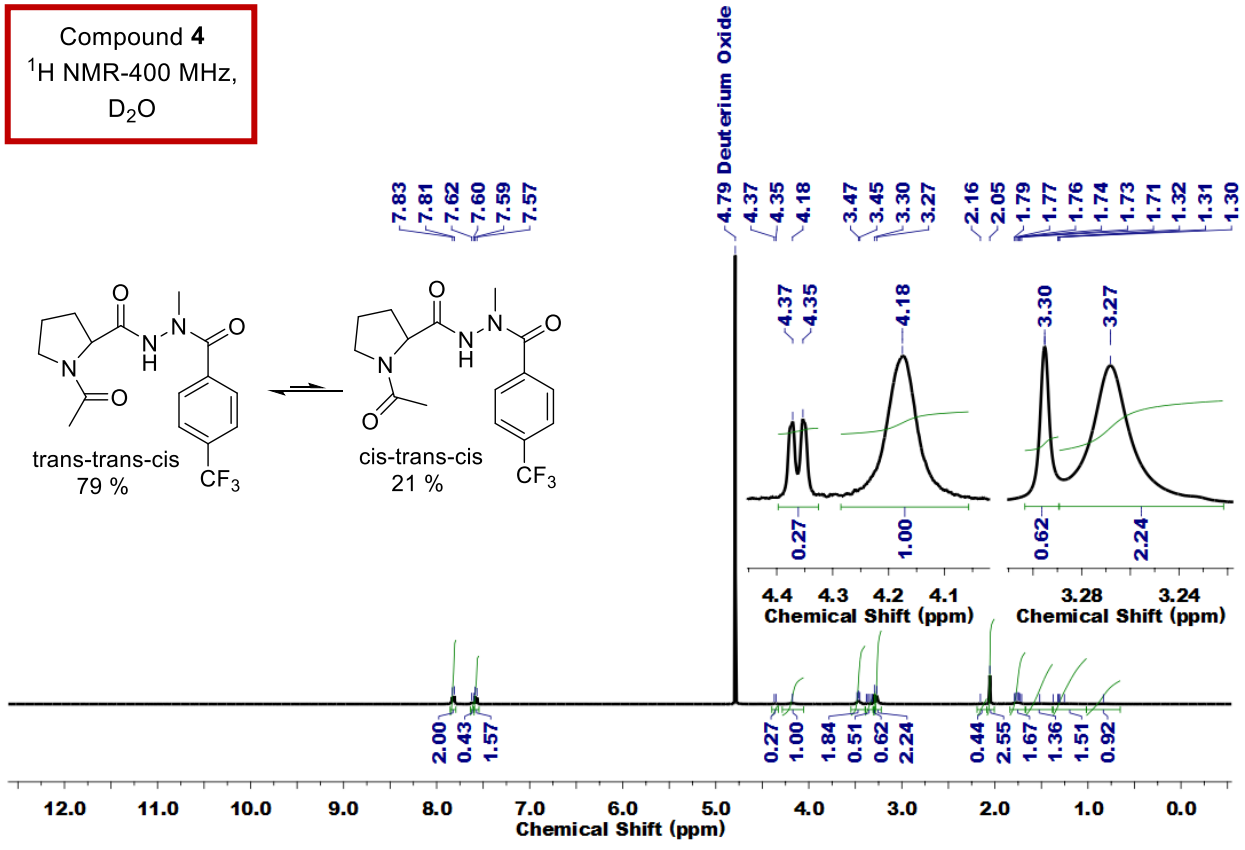
Compound **4**
^{19}F NMR-564 MHz,
$CDCl_3$



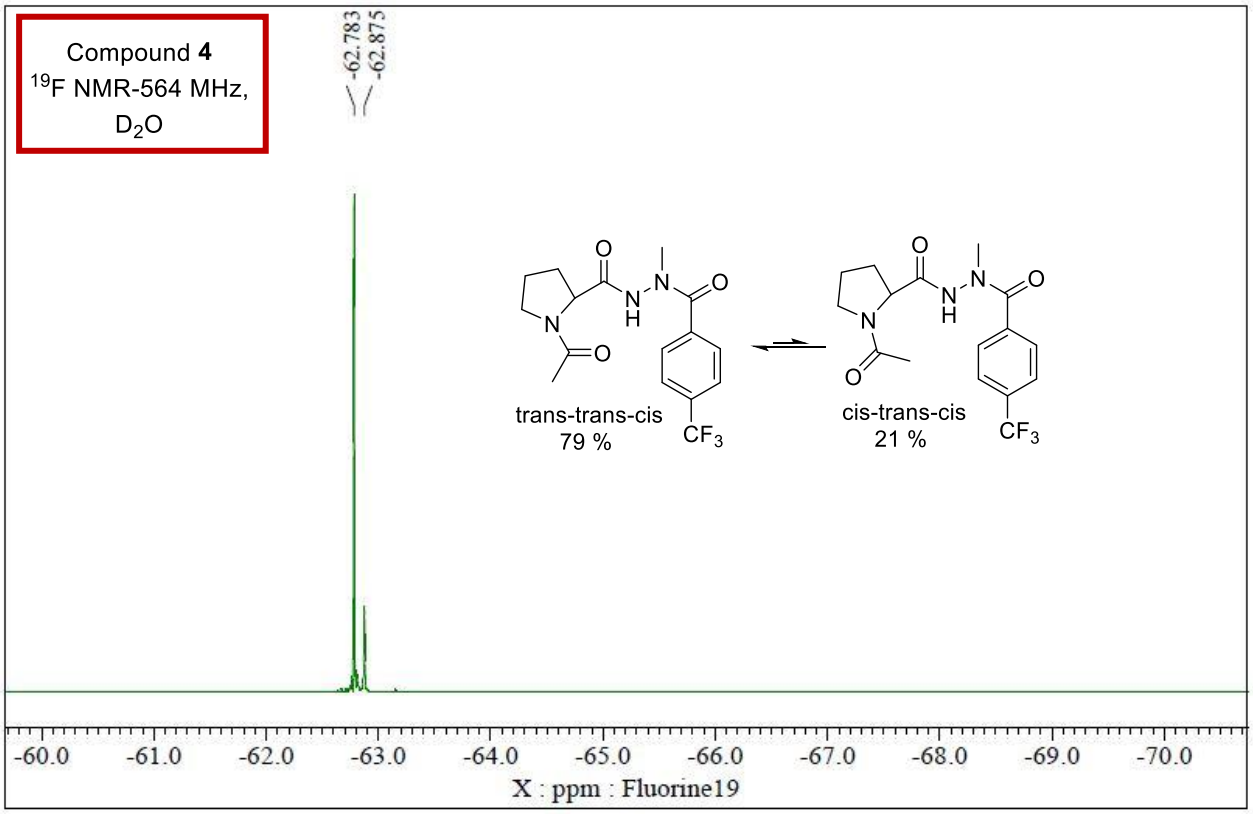

Compound 4
13C NMR-150 MHz,
CDCl3
172.046
171.625
169.193
139.477
131.631
131.420
127.322
124.761
124.627
122.956
77.371
77.160
76.949
57.723
48.053
36.276
25.969
24.930
22.316
~100 %
trans-trans-cis
CF3
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0
X : ppm : Carbon13


trans-trans-cis
70 %
cis-trans-cis
30 %
CF3
Compound 4
1H NMR-400 MHz,
[CD3]2SO
Dimethyl Sulfoxide-d6
10.79
10.60
10.28
7.77
7.75
7.60
7.57
7.55
4.16
4.14
4.00
3.20
3.11
3.08
2.50
1.92
1.59
1.51
1.23
1.10
0.44
1.03
2.53
2.53
0.43
1.00
1.09
1.25
1.14
2.66
2.66
6.24
Chemical Shift (ppm)

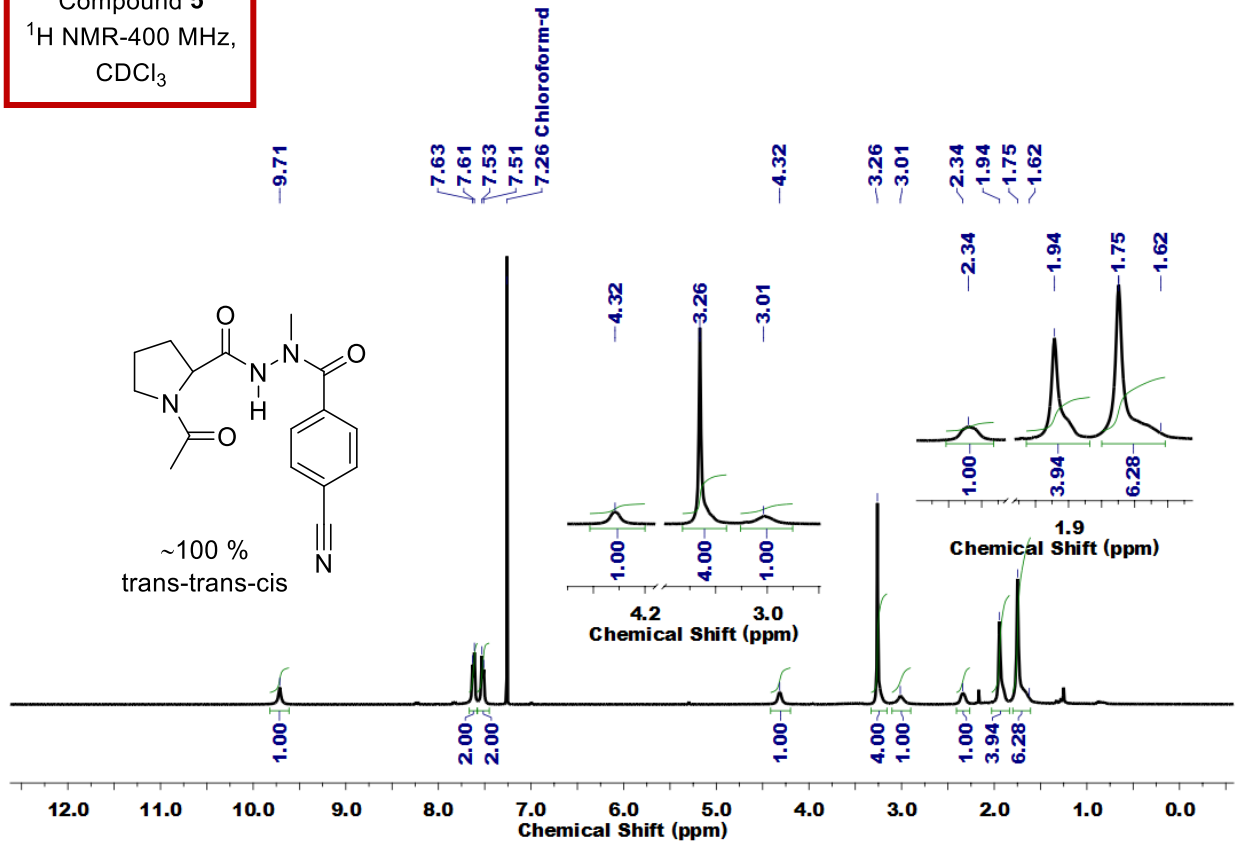

Compound 4
19F NMR-564 MHz,
[CD3]2SO
-61.253
-61.361
trans-trans-cis
70 %
cis-trans-cis
30 %
CF3
-57.0
-58.0
-59.0
-60.0
-61.0
-62.0
-63.0
-64.0
-65.0
-66.0
-67.0
X : ppm : Fluorine19

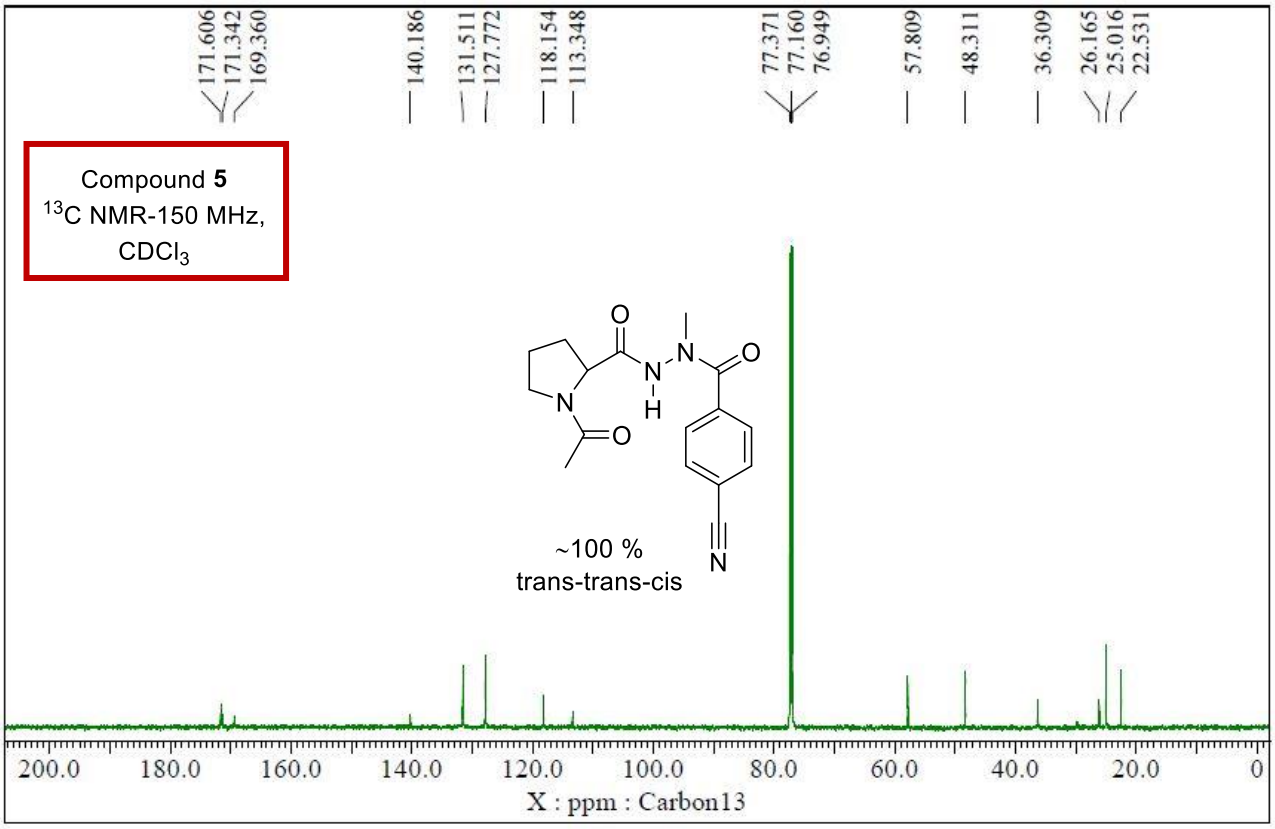

Compound 4
1H NMR-400 MHz,
D2O
7.83
7.81
7.62
7.60
7.59
7.57
4.79 Deuterium Oxide
4.37
4.35
4.18
3.47
3.45
3.30
3.27
2.16
2.05
1.79
1.77
1.76
1.74
1.73
1.71
1.32
1.31
1.30
trans-trans-cis
79 %
cis-trans-cis
21 %
CF3
0.27
1.00
0.62
2.24
4.4 4.3 4.2 4.1
Chemical Shift (ppm)
3.28 3.24
Chemical Shift (ppm)
2.00
0.43
1.57
0.27
1.00
1.84
0.51
0.62
2.24
0.44
2.55
1.67
1.36
1.51
0.92
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0
Chemical Shift (ppm)

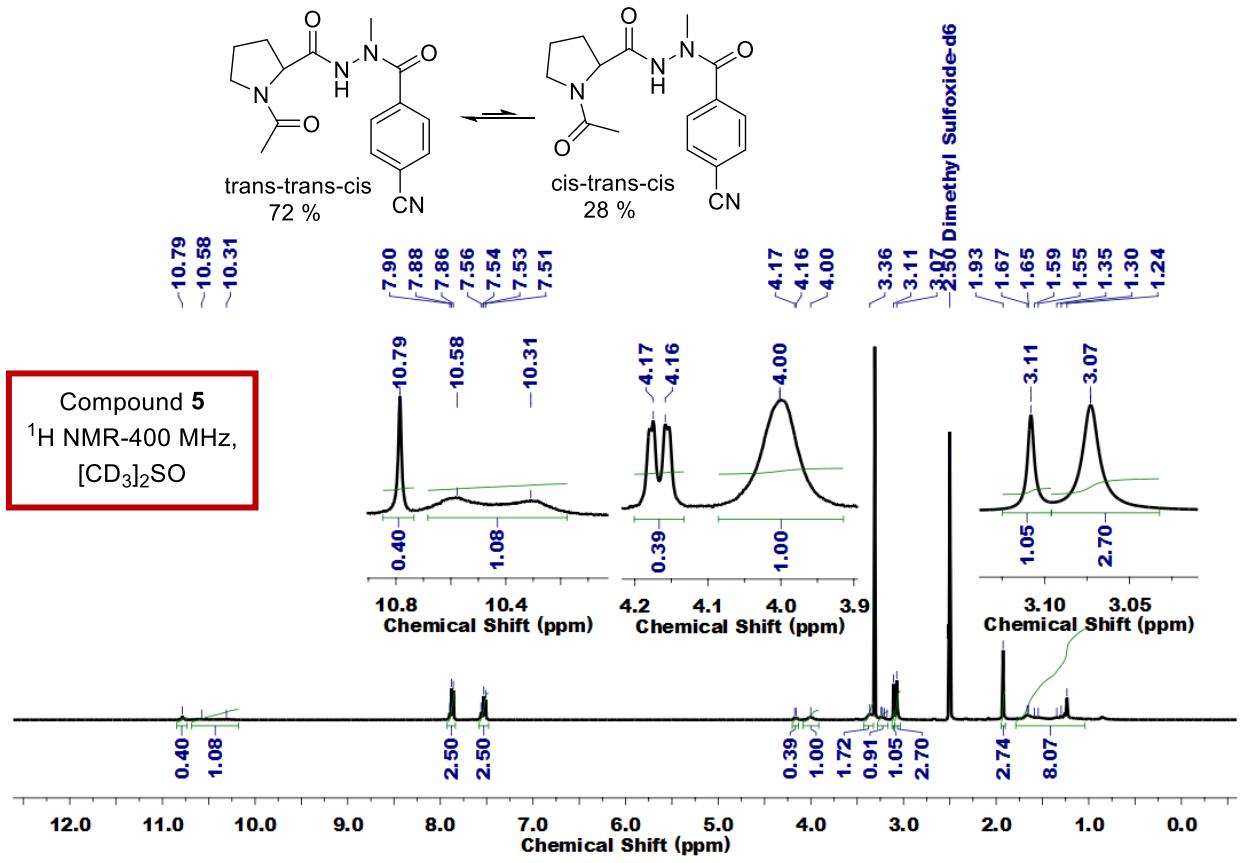
Compound **4**
^{19}F NMR-564 MHz,
D_2O



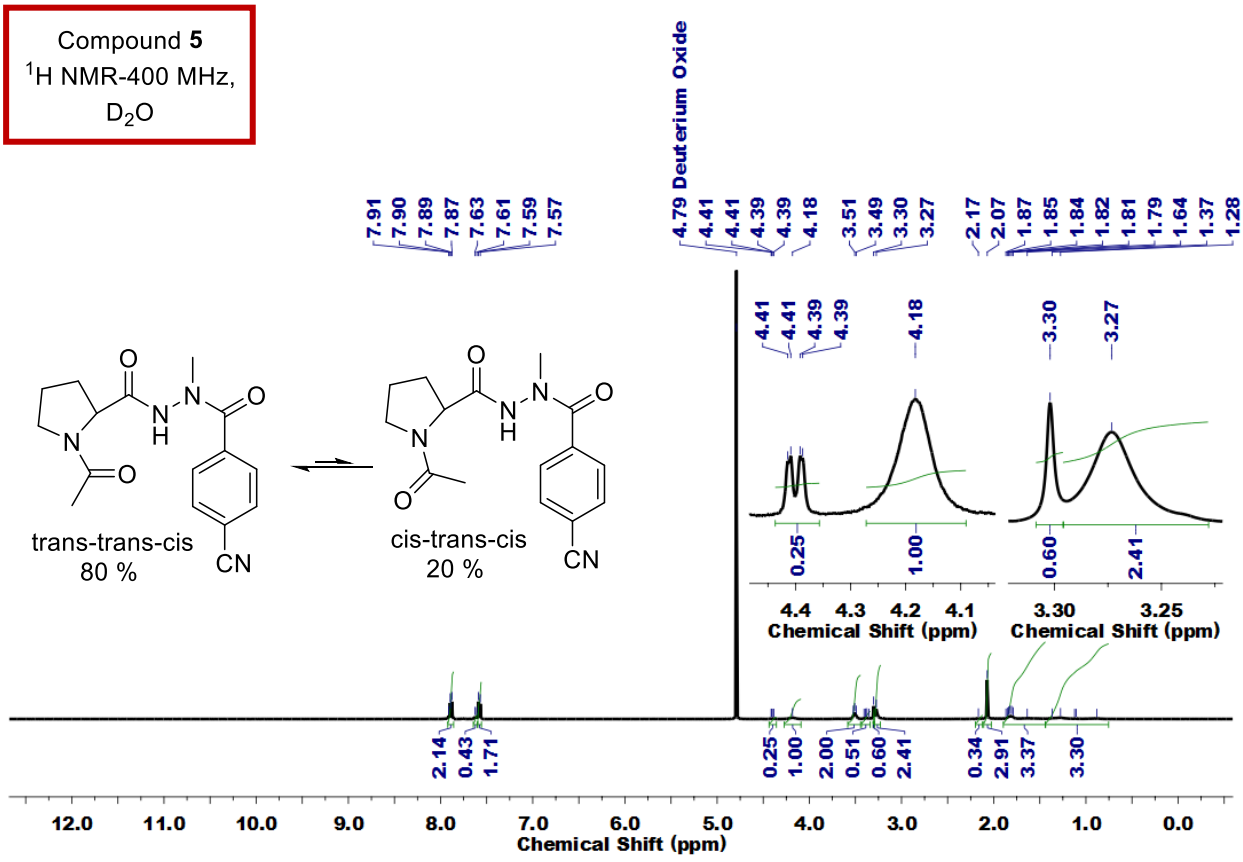
Compound **5**
^{1}H NMR-400 MHz,
$CDCl_3$



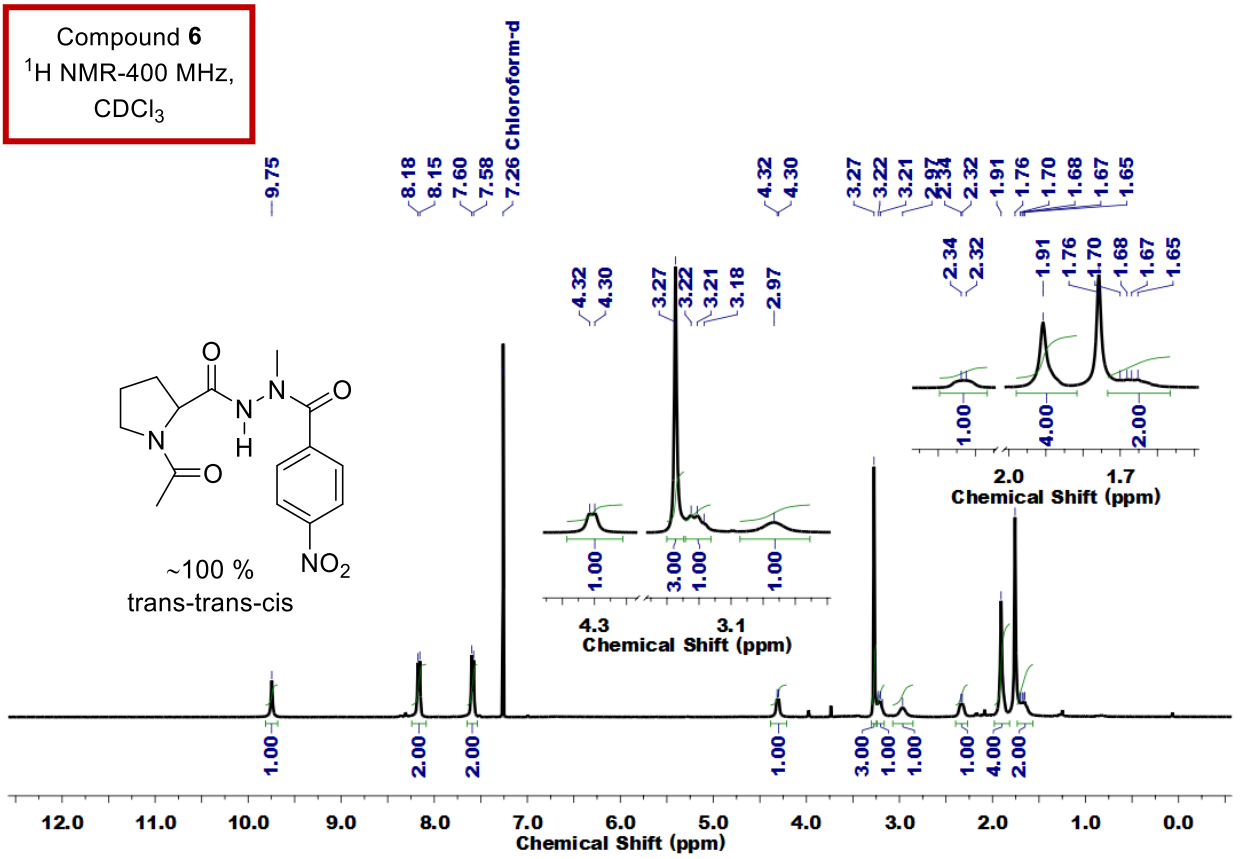

Compound 5
13C NMR-150 MHz,
CDCl3
171.606
171.342
169.360
140.186
131.511
127.772
118.154
113.348
77.371
77.160
76.949
57.809
48.311
36.309
26.165
25.016
22.531
~100 %
trans-trans-cis
200.0
180.0
160.0
140.0
120.0
100.0
80.0
60.0
40.0
20.0
0
X : ppm : Carbon13


trans-trans-cis
72 %
cis-trans-cis
28 %
Dimethyl Sulfoxide-d6
Compound 5
1H NMR-400 MHz,
[CD3]2SO
10.79
10.58
10.31
7.90
7.88
7.86
7.56
7.54
7.53
7.51
4.17
4.16
4.00
3.36
3.11
3.07
2.50
1.93
1.67
1.65
1.59
1.55
1.35
1.30
1.24
0.40
1.08
0.39
1.00
1.05
2.70
10.8
10.4
4.2
4.1
4.0
3.9
3.10
3.05
Chemical Shift (ppm)
2.50
2.50
0.91
1.72
2.74
8.07
12.0
11.0
10.0
9.0
8.0
7.0
6.0
5.0
4.0
3.0
2.0
1.0
0.0

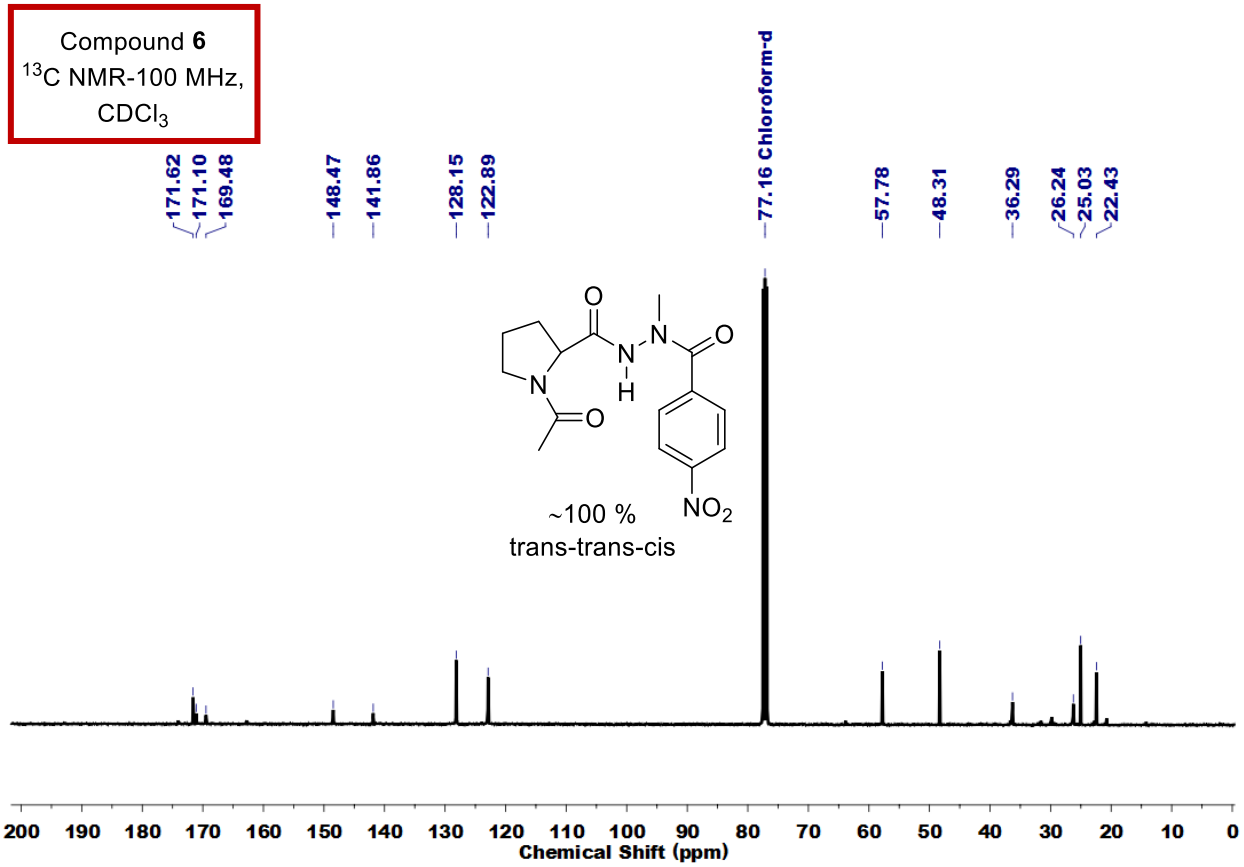
Compound **5**
^{1}H NMR-400 MHz,
D_2O

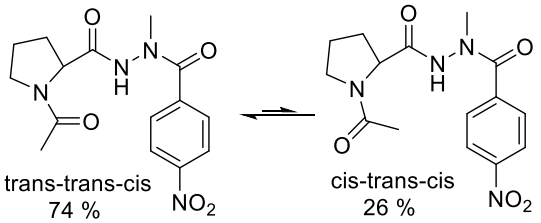


Compound **6**
^{1}H NMR-400 MHz,
$CDCl_3$

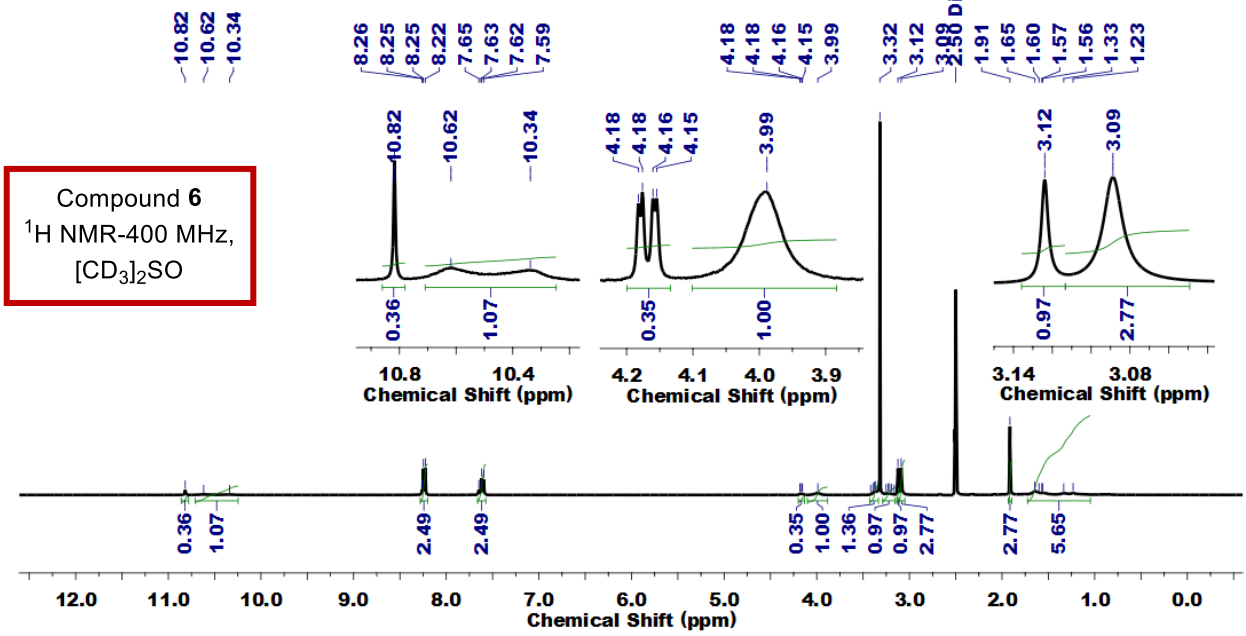


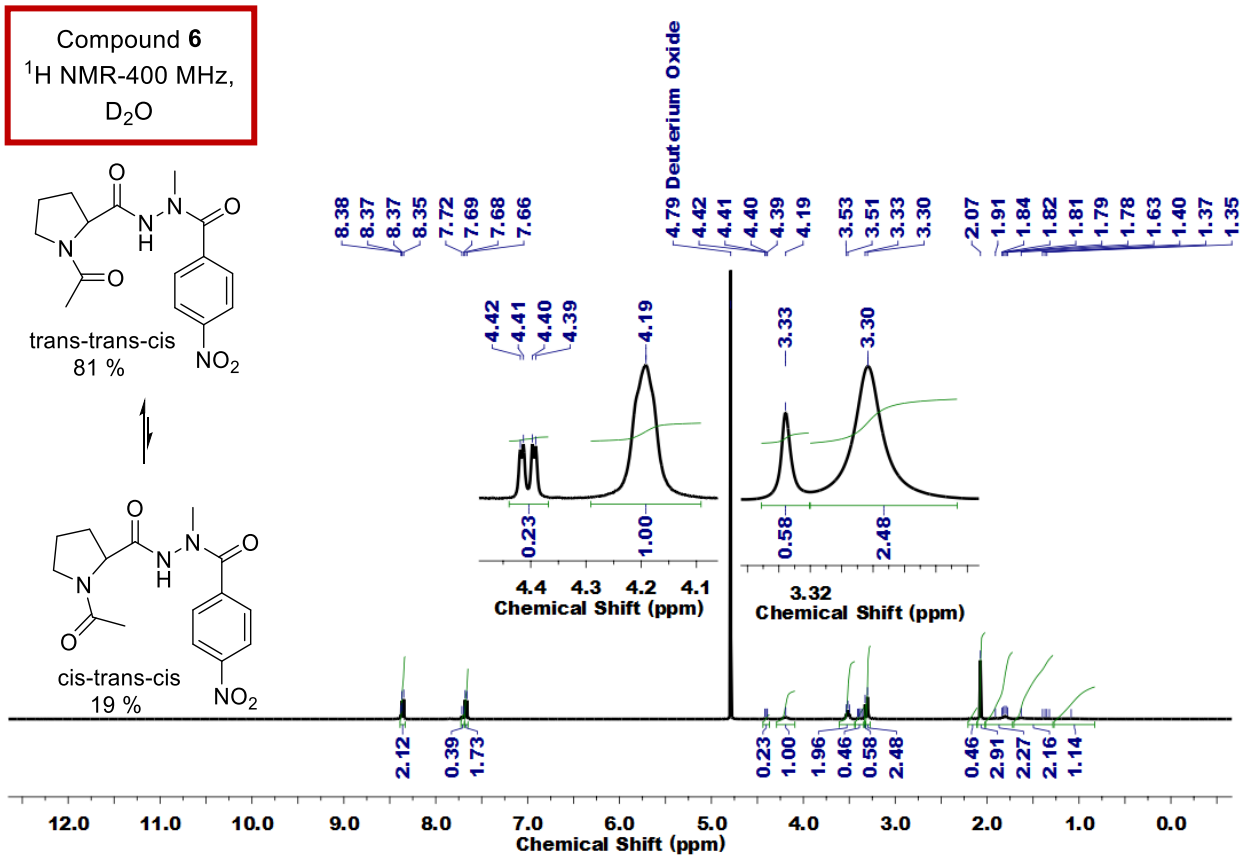
Compound **6**
^{13}C NMR-100 MHz,
$CDCl_3$



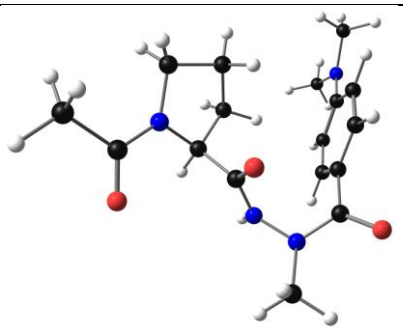


Compound **6**
^{1}H NMR-400 MHz,
$[CD_3]_2SO$




Compound 6
1H NMR-400 MHz,
D2O
trans-trans-cis
81 %
cis-trans-cis
19 %
NO2
Deuterium Oxide
Chemical Shift (ppm)

11. Cartesian Coordinates of 1-6



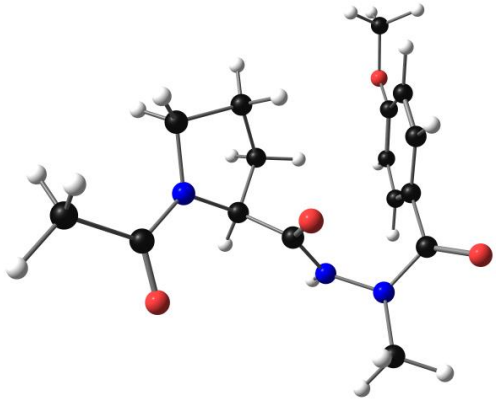
1

E = -1106.85331389 a.u.

Level of theory: M062X/6-311+G(2d,p)

Solvent: Water

8	1.724943000	0.687074000	1.000644000
8	-0.273923000	3.566611000	1.355201000
7	1.155899000	1.535027000	-1.012404000
7	0.787374000	2.756527000	-0.474439000
8	4.317192000	-0.406299000	-0.858075000
7	2.599780000	-1.687163000	-0.192016000
6	1.549087000	0.522638000	-0.190166000
6	-0.233725000	2.738695000	0.463291000
6	-1.282021000	1.699127000	0.281916000
6	1.638064000	-0.838041000	-0.868502000
1	1.906662000	-0.709281000	-1.917709000
6	3.912101000	-1.383083000	-0.229985000
6	-2.882711000	0.517262000	-1.091308000
1	-3.328206000	0.373797000	-2.064466000
6	-1.885633000	1.463951000	-0.951794000
1	-1.578772000	2.036683000	-1.819958000
6	-2.671623000	-0.023851000	1.251273000
1	-2.941619000	-0.603046000	2.121828000
6	-1.699318000	0.951026000	1.378385000
1	-1.233715000	1.118835000	2.342488000
6	-3.301085000	-0.260614000	0.010500000
6	1.883302000	3.700596000	-0.281263000
1	2.452612000	3.751083000	-1.206192000
1	2.531486000	3.383307000	0.538585000
1	1.464694000	4.676967000	-0.055268000
6	0.307920000	-1.592651000	-0.685050000
1	-0.552583000	-0.923907000	-0.689485000
1	0.196276000	-2.308677000	-1.500639000
6	4.839297000	-2.292273000	0.534837000
1	5.863487000	-2.065685000	0.252889000
1	4.620403000	-3.341513000	0.336114000
1	4.717533000	-2.122105000	1.606581000
6	0.501597000	-2.317424000	0.648700000
1	0.340840000	-1.620719000	1.472549000
1	-0.170970000	-3.164517000	0.770238000
6	1.968639000	-2.745038000	0.607827000
1	2.416258000	-2.800265000	1.598980000
1	2.088168000	-3.712990000	0.113854000
1	0.939473000	1.370301000	-1.985001000
7	-4.285142000	-1.207765000	-0.119686000
6	-4.720401000	-1.590576000	-1.451571000
1	-3.895170000	-1.981412000	-2.058272000
1	-5.483294000	-2.359249000	-1.364901000
1	-5.161417000	-0.741204000	-1.975179000
6	-4.497934000	-2.151107000	0.964110000
1	-4.812645000	-1.635138000	1.872380000
1	-5.289777000	-2.839130000	0.681502000
1	-3.594139000	-2.729427000	1.189550000



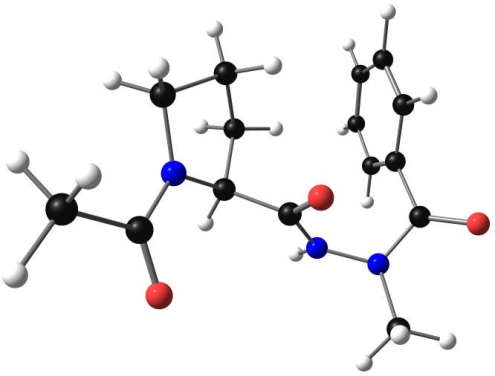
2

E = -1087.42196102

Level of theory: M062X/6-311+G(2d,p)

Solvent: Water

8	-1.347816000	0.728773000	-1.037316000
8	1.044942000	3.338439000	-1.385036000
7	-0.780307000	1.612171000	0.960001000
7	-0.238932000	2.747371000	0.384040000
8	-4.170990000	0.086060000	0.657931000
7	-2.590502000	-1.441683000	0.209295000
6	-1.265905000	0.614643000	0.169169000
6	0.825599000	2.559699000	-0.476778000
6	1.709018000	1.389396000	-0.192989000
6	-1.580179000	-0.676395000	0.913574000
1	-1.906439000	-0.444306000	1.928139000
6	-3.851225000	-0.973049000	0.120908000
6	3.103010000	0.111968000	1.299579000
1	3.543026000	-0.058082000	2.273755000
6	2.255409000	1.177628000	1.074836000
1	2.021824000	1.857806000	1.885774000
6	2.849124000	-0.581386000	-1.002219000
1	3.058156000	-1.259768000	-1.816518000
6	2.020855000	0.514034000	-1.221926000
1	1.597856000	0.676541000	-2.205893000
6	3.395049000	-0.781730000	0.264016000
6	-1.192567000	3.811746000	0.087821000
1	-1.794946000	3.982560000	0.976617000
1	-1.834948000	3.534571000	-0.750770000
1	-0.640247000	4.713396000	-0.160019000
6	-0.349797000	-1.602060000	0.883984000
1	0.587511000	-1.047619000	0.925242000
1	-0.394747000	-2.271722000	1.743971000
6	-4.828883000	-1.806310000	-0.667011000
1	-5.832922000	-1.434839000	-0.483511000
1	-4.764398000	-2.859599000	-0.393691000
1	-4.606060000	-1.722728000	-1.732727000
6	-0.534530000	-2.382058000	-0.419485000
1	-0.224661000	-1.765998000	-1.264795000
1	0.030636000	-3.312053000	-0.438706000
6	-2.043541000	-2.620192000	-0.475794000
1	-2.418879000	-2.684154000	-1.495938000
1	-2.323700000	-3.531284000	0.059511000
1	-0.662562000	1.491438000	1.955782000
8	4.212952000	-1.810176000	0.585789000
6	4.510596000	-2.757849000	-0.429327000
1	5.027884000	-2.283727000	-1.265628000
1	5.161220000	-3.495519000	0.030917000
1	3.599689000	-3.243203000	-0.785953000



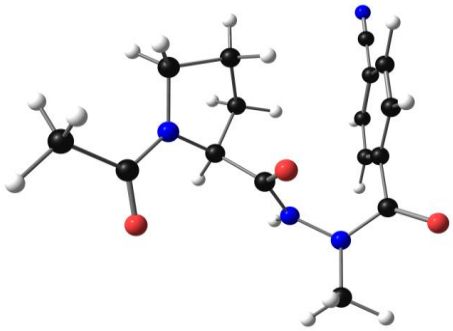
3

E = -972.902950764

Level of theory: M062X/6-311+G(2d,p)

Solvent: Water

8	-0.597506000	0.814041000	-1.033240000
8	2.723012000	2.175217000	-1.325096000
7	0.293245000	1.348273000	0.970226000
7	1.263415000	2.154657000	0.405548000
8	-3.413518000	1.443416000	0.669627000
1	3.267751000	-3.629476000	0.359767000
7	-2.656948000	-0.616285000	0.204831000
6	-0.574246000	0.665229000	0.171815000
6	2.160681000	1.549390000	-0.447334000
6	2.445835000	0.100122000	-0.195033000
6	-1.413526000	-0.370128000	0.908367000
1	-1.605190000	-0.028344000	1.926376000
6	-3.588256000	0.354886000	0.124835000
6	3.189045000	-1.676183000	1.247804000
1	3.537889000	-2.014038000	2.215238000
6	2.880114000	-0.336741000	1.054054000
1	2.983026000	0.371148000	1.868410000
6	2.598682000	-2.146234000	-1.040492000
1	2.478470000	-2.851998000	-1.852613000
6	2.313622000	-0.802001000	-1.244845000
1	1.973197000	-0.449630000	-2.210870000
6	3.039877000	-2.582660000	0.203368000
6	0.860300000	3.531564000	0.138600000
1	0.393182000	3.927379000	1.036996000
1	0.157934000	3.573689000	-0.696502000
1	1.746473000	4.111807000	-0.100591000
6	-0.703618000	-1.736057000	0.864496000
1	0.381700000	-1.641435000	0.902372000
1	-1.030289000	-2.328228000	1.720430000
6	-4.832926000	0.036382000	-0.662687000
1	-5.577595000	0.801957000	-0.464691000
1	-5.228103000	-0.945729000	-0.402951000
1	-4.600069000	0.032307000	-1.729568000
6	-1.212274000	-2.347898000	-0.442824000
1	-0.669456000	-1.919056000	-1.286382000
1	-1.105254000	-3.430510000	-0.471843000
6	-2.675989000	-1.909513000	-0.490887000
1	-3.044970000	-1.796072000	-1.509032000
1	-3.321186000	-2.614074000	0.040467000
1	0.344683000	1.181457000	1.964992000



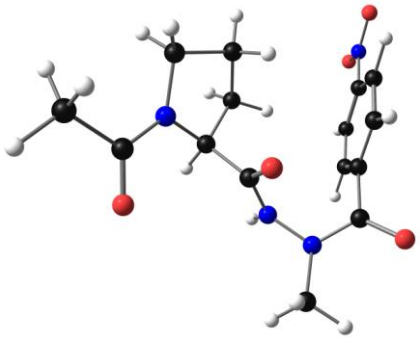
5

E = -1065.14749362

Level of theory: M062X/6-311+G(2d,p)

Solvent: Water

8	1.196232000	0.761165000	1.008822000
8	-1.362998000	3.305639000	1.268917000
7	0.538158000	1.542314000	-1.002124000
7	-0.032840000	2.674164000	-0.453890000
8	4.036638000	0.310161000	-0.699259000
7	2.596979000	-1.335584000	-0.201057000
6	1.116228000	0.609604000	-0.193269000
6	-1.073129000	2.484560000	0.422246000
6	-1.873238000	1.225931000	0.241494000
6	1.521477000	-0.671302000	-0.910087000
1	1.816421000	-0.439931000	-1.934379000
6	3.814814000	-0.760414000	-0.136772000
6	-3.279443000	-0.188372000	-1.100605000
1	-3.779841000	-0.409647000	-2.033604000
6	-2.502503000	0.949915000	-0.969388000
1	-2.387778000	1.625760000	-1.807886000
6	-2.769870000	-0.788854000	1.196053000
1	-2.872118000	-1.475625000	2.025569000
6	-2.013661000	0.364778000	1.324020000
1	-1.517137000	0.592320000	2.258473000
6	-3.402494000	-1.059448000	-0.017218000
6	0.865141000	3.807020000	-0.251903000
1	1.407387000	3.978535000	-1.178463000
1	1.566737000	3.601010000	0.558940000
1	0.268932000	4.680948000	-0.007395000
6	0.368548000	-1.689817000	-0.840291000
1	-0.609969000	-1.211140000	-0.884009000
1	0.454161000	-2.374853000	-1.684702000
6	4.867623000	-1.491292000	0.655328000
1	5.834827000	-1.041580000	0.450276000
1	4.888196000	-2.552131000	0.405452000
1	4.650961000	-1.402432000	1.721895000
6	0.631003000	-2.420410000	0.478758000
1	0.287469000	-1.810161000	1.315264000
1	0.140818000	-3.390724000	0.528603000
6	2.154694000	-2.538141000	0.516786000
1	2.547679000	-2.549554000	1.532144000
1	2.498196000	-3.436018000	-0.003475000
1	0.459576000	1.415071000	-2.001162000
6	-4.190754000	-2.254197000	-0.154689000
7	-4.819457000	-3.208455000	-0.264669000



6

E = -1177.40269234

Level of theory: M062X/6-311+G(2d,p)

Solvent: Water

8	1.546159000	0.675476000	1.008447000
8	-0.628195000	3.565265000	1.291280000
7	0.994030000	1.555616000	-0.993320000
7	0.596094000	2.754622000	-0.435428000
8	4.288269000	-0.142381000	-0.703827000
7	2.639868000	-1.585337000	-0.224854000
6	1.442654000	0.546095000	-0.194363000
6	-0.456261000	2.712553000	0.444068000
6	-1.424031000	1.575668000	0.269003000
6	1.664257000	-0.772369000	-0.923336000
1	1.984609000	-0.575030000	-1.947111000
6	3.924437000	-1.181141000	-0.155899000
6	-3.034836000	0.380971000	-1.058628000
1	-3.582809000	0.228157000	-1.976700000
6	-2.106827000	1.401397000	-0.932004000
1	-1.916056000	2.062921000	-1.767735000
6	-2.568916000	-0.308397000	1.227975000
1	-2.758202000	-0.989168000	2.045032000
6	-1.660114000	0.731011000	1.348478000
1	-1.119751000	0.878348000	2.274360000
6	-3.238189000	-0.457888000	0.025046000
6	1.647050000	3.747940000	-0.236364000
1	2.201597000	3.845371000	-1.166358000
1	2.317903000	3.440364000	0.568249000
1	1.182198000	4.696260000	0.015645000
6	0.381715000	-1.622459000	-0.858113000
1	-0.521110000	-1.012214000	-0.890611000
1	0.367362000	-2.301770000	-1.711239000
6	4.869372000	-2.058958000	0.622912000
1	5.888078000	-1.737718000	0.425955000
1	4.749755000	-3.108471000	0.353532000
1	4.663933000	-1.961733000	1.690924000
6	0.546408000	-2.399701000	0.449977000
1	0.295622000	-1.759005000	1.296668000
1	-0.073492000	-3.293168000	0.491036000
6	2.039206000	-2.727721000	0.475928000
1	2.431074000	-2.810723000	1.488337000
1	2.253007000	-3.655206000	-0.061607000
1	0.907317000	1.453894000	-1.994573000
7	-4.205166000	-1.558841000	-0.109529000
8	-4.356945000	-2.301046000	0.839609000
8	-4.799335000	-1.668007000	-1.163006000

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