Conformational Study of 9-Dehydro-9-Trifluoromethyl Cinchona Alkaloids via ^{19}F NMR Spectroscopy: Emergence of Trifluoromethyl Moiety as a Conformational Stabilizer and a Probe

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Supporting Information

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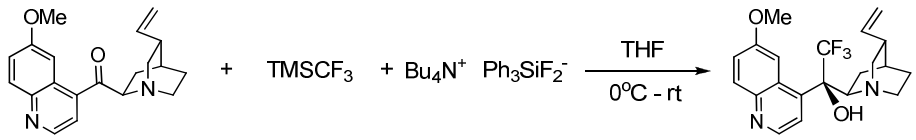
General Information

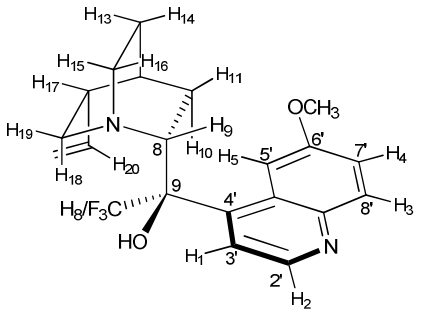
Unless otherwise mentioned, all the chemicals were purchased from commercial sources. Anhydrous DMSO-d_6 was purchased from the Sigma-Aldrich Inc. without further purification. Other deuterated solvents were purchased from the Cambridge Isotope Laboratories, Inc. The non-deuterated solvents for the NMR experiments were purchased from commercial sources and used as received. The DriSolv® solvents were purchased from EMD™ and used without further purification. Silica gel chromatography was performed to isolate the products using 60-200 mesh silica gel. One dimensional ^{1}H, ^{13}C, ^{19}F and Dynamic NMR spectra were recorded on Varian Mercury 400 MHz NMR Spectrometer or Varian VNMRS-500 NMR Spectrometer. The temperature calibration was carried by measuring the chemical-shift separation between the OH resonances and CH resonances in methanol (at low temperature) and ethylene glycol (at high temperature) to give an accuracy at ±0.1 K. COSY and NOESY spectra were performed on Varian 400-MR NMR Spectrometer or Varian VNMRS-500 NMR Spectrometer. ^{1}H-^{19}F HOESY spectra were recorded on Bruker AMX-500 NMR Spectrometer. ^{1}H NMR chemical shifts were determined relative to $CDCl_3$ and DMSO-d_6 as the internal standards at δ 7.26 ppm and 2.50 ppm, respectively. ^{13}C NMR shifts were determined relative to $CDCl_3$ and DMSO-d_6 as the internal standards at δ 77.16 ppm and 39.52 ppm, respectively. ^{19}F NMR chemical shifts were determined relative to internal standard $CFCl_3$ at δ 0.00 ppm. Mass spectra were recorded on a high resolution mass spectrometer in the ESI mode.

Procedure for the Preparation of *epi*CF_3QD (1)



Quinidinone was prepared according to the known procedures described by Woodward et al.[1] and Skarżewski et al.[2] Quinidinone (3.74 g, 11.6 mmol) and $TMSCF_3$ (4.14 g, 29.1 mmol, 2.5 eq.) were quickly dissolved in anhydrous THF (72 mL) in a Schlenk flask under argon atmosphere. Tetrabutylammonium difluorotriphenylsilicate (1.57 g, 2.9 mmol, 0.25 eq.) was added to above mentioned solution within 2 min at 0 ºC. The ice bath was removed thereafter, and the reaction mixture was warmed to room temperature and the mixture was stirred for 2h before evaporating the volatile matters. The resulting crude product was purified by column chromatography with Et_2O-Et_2O/MeOH (98:2) as the eluent affording the desired product as a yellowish amorphous solid (3.24 g, 71%).

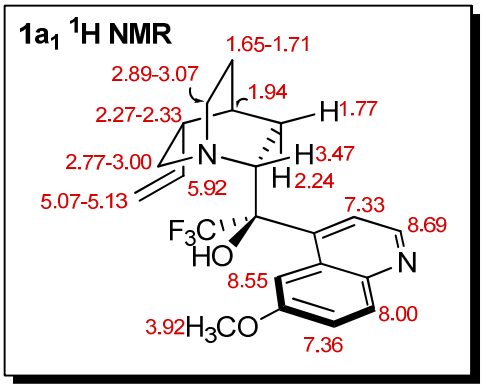
Atom numbering of Cinchona Alkaloids and *epi*CF_3QD (1)

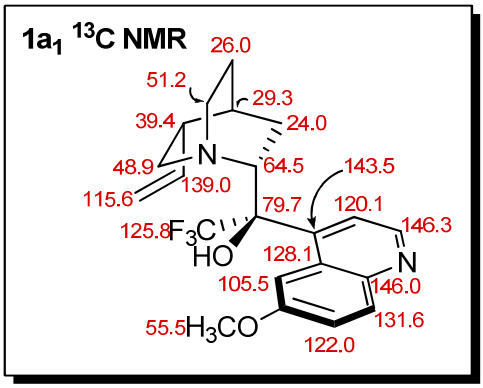


General Procedure for NMR experiments

All the NMR spectroscopic studies were performed using the 0.1M solutions of **1**, and the possible dimerization of the cinchona alkaloid can been substantially suppressed at this concentration.[3,4,5]

Characterization of 1a (in $CDCl_3$)



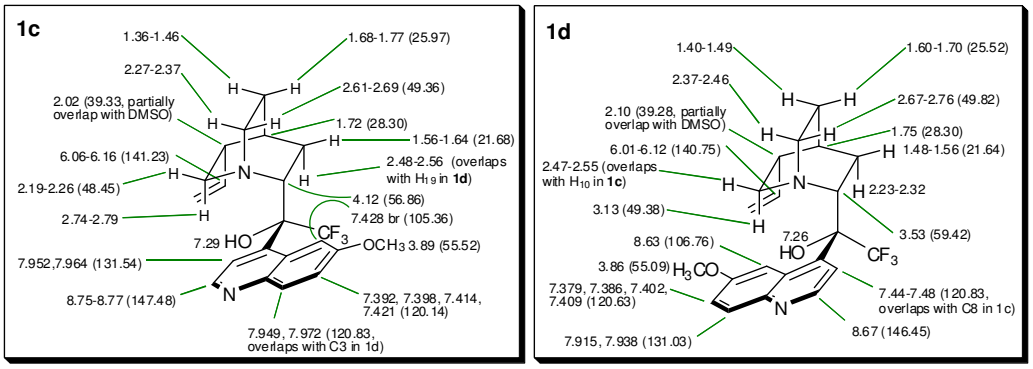


^{1}H NMR (400 MHz, $CDCl_3$, 293K) δ 1.65-1.71 (m, 2H), 1.77 (m, 1H), 1.94 (m, pseudo s, 1H), 2.19-2.25 (m, 1H), 2.26-2.33 (m, 1H), 2.77-3.00 (m, 2H), 2.89-3.07 (m, 2H), 3.47 (m, pseudo t, J = 10.2 Hz, 1H), 5.07-5.13 (m, 2H), 5.92 (ddd, J = 17.3, 10.6, 7.1 Hz, 1H), 7.05 (br s, 1H), 7.33 (d, J = 4.8 Hz, 1H), 7.36 (dd, J = 9.2, 2.8 Hz, 1H), 8.00 (d, J = 9.2 Hz, 1H), 8.54 (d, J = 2.8 Hz, 1H), 8.69 (d, J = 4.8 Hz, 1H). ^{13}C

NMR (101 MHz, $CDCl_3$, 293 K) δ 24.0, 26.0, 29.3, 39.4, 48.9 (q, J = 3.3 Hz), 51.2, 55.5, 64.5, 79.8 (q, J = 27.5 Hz), 105.5, 115.6, 120.1, 122.0, 125.8 (q, J = 288.2 Hz), 128.1, 131.6, 139.0, 143.5, 146.0, 146.3, 157.4. ^{19}F NMR (376 MHz, $CDCl_3$, 293K) δ -70.64 (s, 3F). HRMS (ESI) Exact mass calculated for $C_{21}H_{24}F_3N_2O_2$ $[M+H^+]$ 393.1784; Found 393.1788.

Characterization of 1c and 1d (in DMSO-*d_6*)

Due to the high complexity of the spectra of **1** in DMSO, several ^1H NMR resonances are indicated by the individual chemical shifts of each multiplet in order to differentiate resonances of different protons (H_1, H_3, H_4 in **1c**; H_3, H_4 in **1d**). For the severely overlapped signals such as H_{10}, the chemical shift ranges of the signals are given based on their COSY and HSQC spectra. The ^{13}C NMR signals of the critical carbon atoms are assigned, and are indicated in the parentheses.



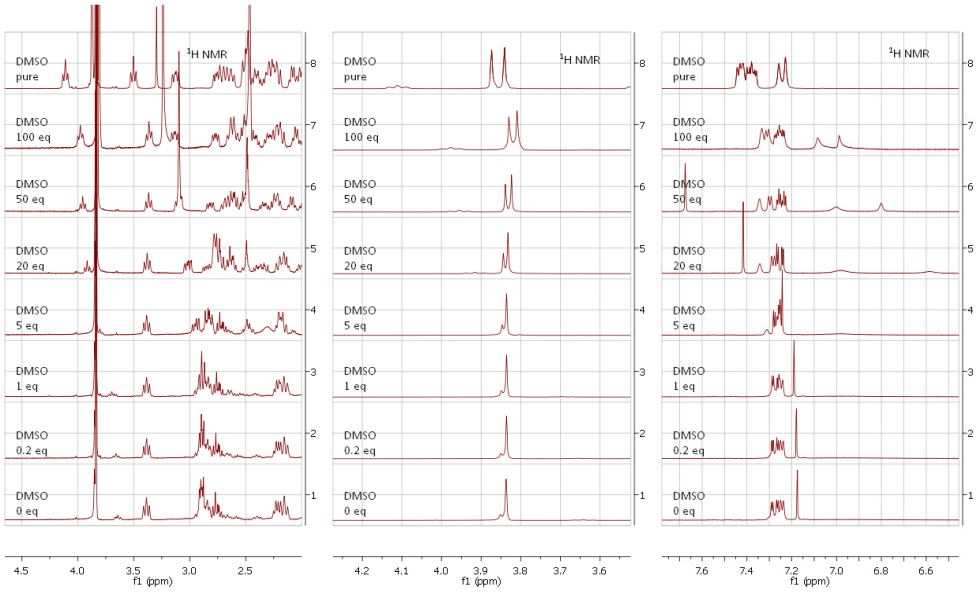
^1H NMR (400 MHz, DMSO-*d_6*, 293K) δ 1.36-1.46 (m, 1H), 1.40-1.49 (m, 1H), 1.48-1.56 (m, 1H), 1.56-1.64 (m, 1H), 1.60-1.70 (m, 1H), 1.68-1.77 (m, 1H), 1.72 (m, 1H), 1.75 (m, 1H), 2.02 (pseudo q, J = 8.5 Hz, 1H), 2.10 (pseudo q, J = 8.4 Hz, 1H), 2.19-2.26 (m, 1H), 2.23-2.32 (m, 1H), 2.27-2.32 (m, 1H), 2.37-2.46 (m, 1H),

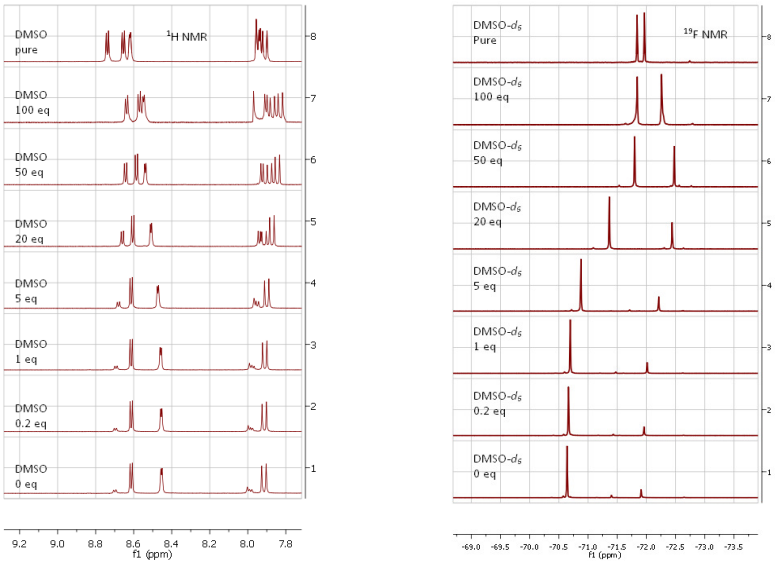
2.47-2.55 (m, 1H), 2.48-2.56 (m, 1H), 2.61-2.69 (m, 1H), 2.67-2.76(m, 1H), 2.74-2.79 (m, 1H), 3.13 (dd, J = 12.8, 8.6 Hz, 1H), 3.53 (pseudo t, J = 9.3 Hz, 1H), 3.86 (s, 3H), 3.89 (s, 3H), 4.12 (pseudo t, J = 8.8 Hz, 1H), 4.97-5.01 (m, 4H), 6.02-6.15 (m, 2H), 7.26 (s, 1H), 7.29 (s, 1H), 7.39 (dd, J = 9.2, 2.9 Hz, 1H), 7.39-7.42 (m, 1H), 7.43 (br, 1H), 7.46 (d, J = 4.9 Hz, 1H), 7.92-7.94 (d, J = 9.2 Hz, 1H), 7.95-7.96 (d, J =4.9 Hz, 1H), 7.95-7.97 (d, J = 8.9 Hz, 1H), 8.63 (d, J = 2.9 Hz, 1H), 8.67 (d, J = 4.9 Hz, 1H), 8.76 (d, J = 4.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, 293 K) δ 21.64, 21.68, 25.55, 25.97, 28.30 (2C), 39.28, 39.33, 48.45, 49.36, 49.38, 49.82, 55.09, 55.52, 56.86, 59.42, 81.45 (q, J = 26.7 Hz, 1C), 83.82 (q, J = 24.6 Hz, 1C), 105.33(q, J = 4.7 Hz, 1C), 106.76, 114.32, 114.40, 120.14, 120.63, 120.83 (2C), 125.67 (q, J = 290.1 Hz, 1C), 125.77 (q, J = 291.2 Hz, 1C), 127.38, 129.08, 131.03, 131.54, 140.75, 141.23, 141.96, 144.40, 144.42, 145.29, 146.45, 147.48, 155.97, 156.49. ^{19}F NMR (376 MHz, DMSO-d_6, 293K) δ -71.70 (s, 3F), -71.82 (s, 3F).

Characterization of Quinidinone

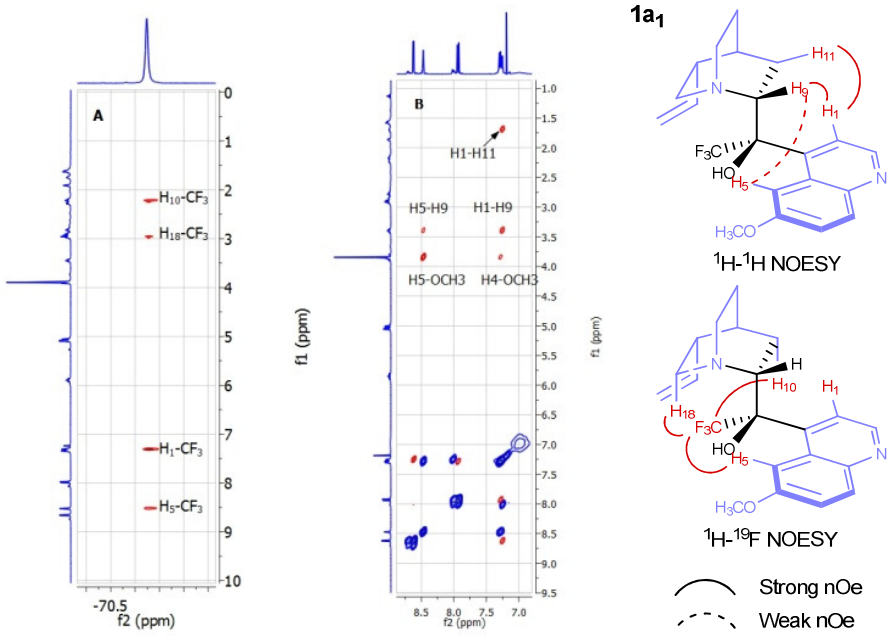
^{1}H NMR (400 MHz, DMSO-d_6, 293K) δ 1.71 – 1.43 (m, 4H), 2.36 – 2.12 (m, 4H), 1.77-1.81 (m, 1H), 2.80 – 2.62 (m, 3H), 3.05 – 2.95 (m, 1H), 4.42 (pseudo t, J = 8.8 Hz, 1H), 4.98-5.08 (m, 2H), 5.93 (ddd, J = 17.3, 10.4, 7.1 Hz, 1H), 7.47 – 7.44 (m, 2H), 7.84 (d, J = 4.5 Hz, 1H), 8.01 (dd, J = 8.8, 0.8 Hz, 1H), 8.85 (d, J = 4.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, 293K) δ17.41, 21.07, 26.41, 27.13, 47.87, 49.38, 55.39, 62.37, 102.78, 114.69, 120.32, 121.92, 124.96, 131.27, 140.72, 141.81, 144.55, 147.39, 158.25, 204.29.

The NMR Spectra of 1 in A Series of $CDCl_3$-DMSO-d_6 Systems





Determination of the Conformations of 1 in $CDCl_3$

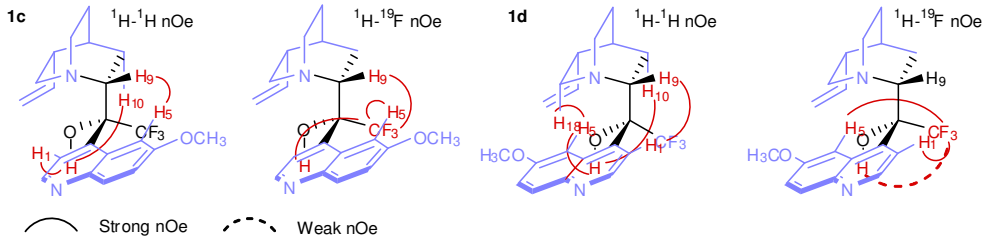


The conformational analysis of **1** in $CDCl_3$ was investigated by various NMR techniques. The signal assignments were assisted by correlation spectroscopy (COSY) and heteronuclear single quantum coherence (HSQC). The conformation of **1a** was derived from the critical interproton and proton-fluorine interactions, which were deciphered from ^{1}H-^{1}H nuclear Overhauser effect spectroscopy (NOESY) and ^{1}H{^{19}F} heteronuclear Overhauser effect spectroscopy (HOESY), respectively. The HOESY spectrum of **1a** shows the strong interactions of H_1-CF_3 and H_5-CF_3 with essentially the same intensity, indicating the CF_3-C_9 bond is roughly perpendicular to the quinoline system. H_{18}-CF_3 and H_{10}-CF_3 interactions have also been observed with similar strengths, which can be interpreted as the CF_3 group pointing towards the H_{18} and H_{10} protons. The cross-peaks corresponding to the H_9-CF_3 and H_{11}-CF_3

interactions were not found in the HOESY spectrum; thus the approximate *trans*-orientation of the CF_3-C_9 bond relative to the C_8-H_9 bond can be confirmed.

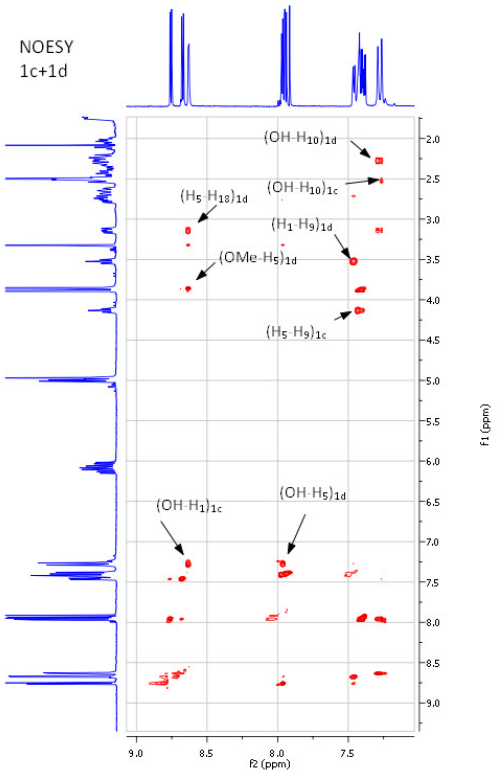
In the NOESY spectrum, the strong interactions of H_1-H_{11} and H_1-H_9 have been shown with approximately the same intensity representing a conformation in which H_9 and H_{11} are spatially close to H_1 at similar distances. In comparison, slightly weaker interaction between H_5 and H_9 was observed, which evidently indicates the *syn*-conformation. Notably, although the H_5-H_9 distance is estimated to be considerably longer than the H_1-H_9 distance in a typical *syn*-Open conformation, the cross-peaks of H_5-H_9 and H_1-H_9 were found to display similar volumes. Hence, the observed conformation of **1a** can be rationalized as a weighted average of two or more conformers generated by the partial free rotation around τ_2. In particular, the negative nOe effects in the ^{1}H-^{1}H NOESY spectrum (the blue cross peaks in the aromatic region) appear to correlate with the signals arising from the minor and the major conformations, which can be attributed the exchange processes between these species. We therefore were able to conclude that there are two NMR-distinguishable species that exist in $CDCl_3$ at room temperature as kinetically persistent conformers, **$1a_1$-$1a_2$** and **$1b_1$**.

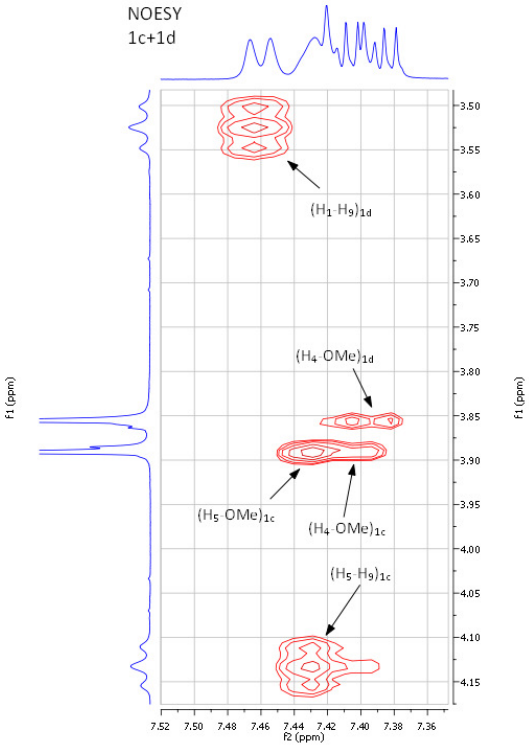
Determination of the Conformations of 1 in DMSO-d_6

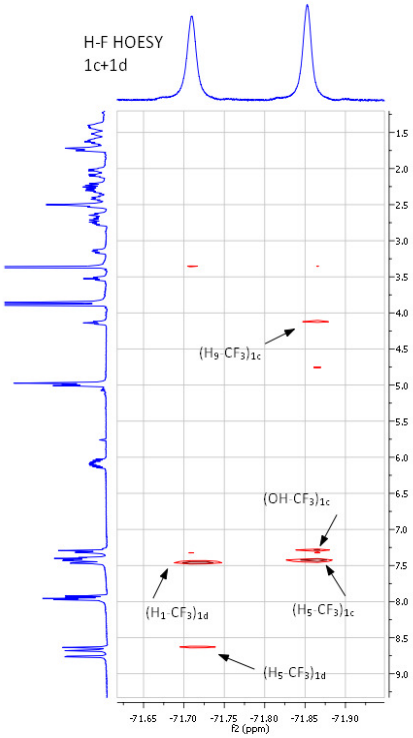


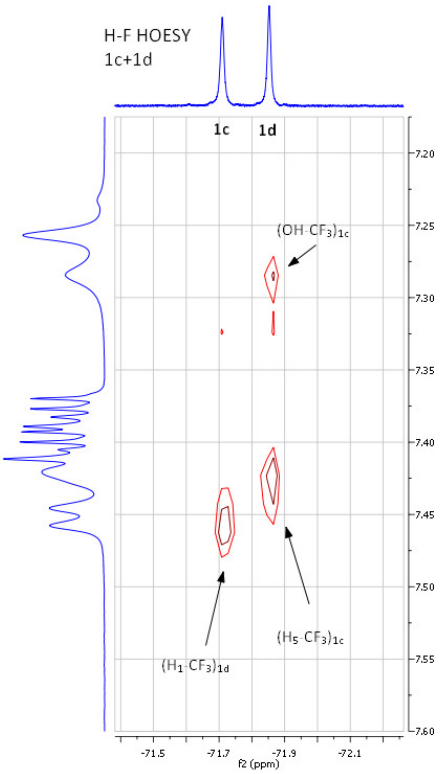
Similar to the aforementioned observations, two conformers have been found by ^{19}F NMR spectroscopy in DMSO-d_6 with equal population. Detailed 2D NMR studies were performed at room temperature to further characterize the two conformers. As depicted, the strong H_1-OH and H_5-CF_3 interactions in **1c** have been observed in the NOESY and the HOESY spectra, respectively. In contrast, the interaction between H_5 and the OH group was not detectable, which unequivocally confirms the *anti* orientation of the O-C_9-$C_{4'}$-$C_{5'}$ system. Furthermore, consistent with the nOe correlation between OH and H_{10} in **1c**, an intensive cross-peak corresponding to the CF_3-H_9 interaction has also been detected in the HOESY spectrum, and this suggests the Closed conformation.

On the other hand, the *syn* conformation adopted by **1d** was validated by the observation of the cross peaks due to the H_5-OH, H_5-H_{18}, H_1-H_9 and CF_3-H_1 interactions. In comparison with the intensive CF_3-H_1 interaction, the cross-peak corresponding to the CF_3-H_5 interaction was found to be rather weak, which further validates the proposed *syn* structure. Similar to **1c**, the strong nOe signal between OH and H_{10} has been found to indicate the Closed conformation.

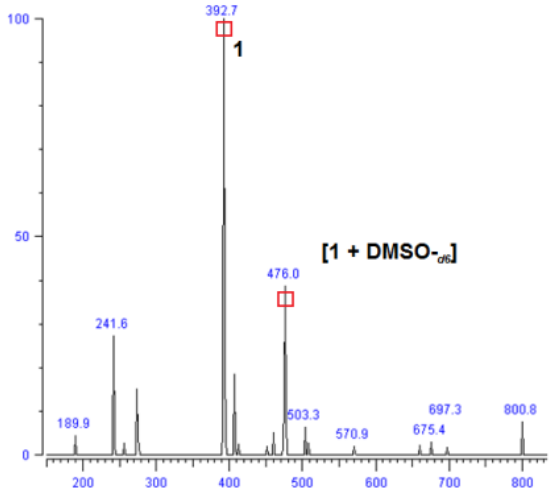

NOESY
1c+1d
(OH-H10)1d
(OH-H10)1c
(H5-H18)1d
(H1-H9)1d
(OMe-H5)1d
(H5-H9)1c
(OH-H1)1c
(OH-H5)1d
f2 (ppm)


NOESY
1c+1d
(H1-H9)1d
(H4-OMe)1d
(H5-OMe)1c
(H4-OMe)1c
(H5-H9)1c
f1 (ppm)
f2 (ppm)


H-F HOESY
1c+1d
(H9-CF3)1c
(OH-CF3)1c
(H1-CF3)1d
(H5-CF3)1c
(H5-CF3)1d
f2 (ppm)

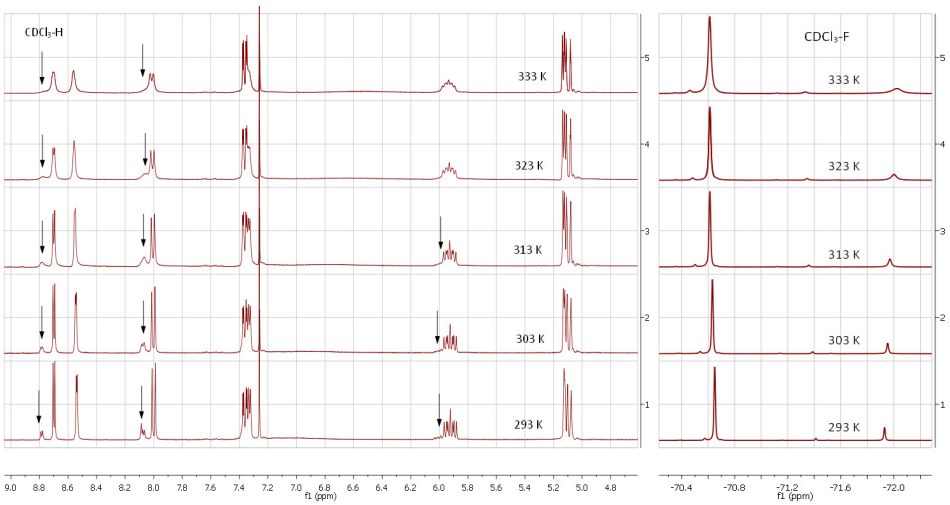

H-F HOESY
1c+1d
1c
1d
(OH-CF3)1c
(H5-CF3)1c
(H1-CF3)1d
f2 (ppm)

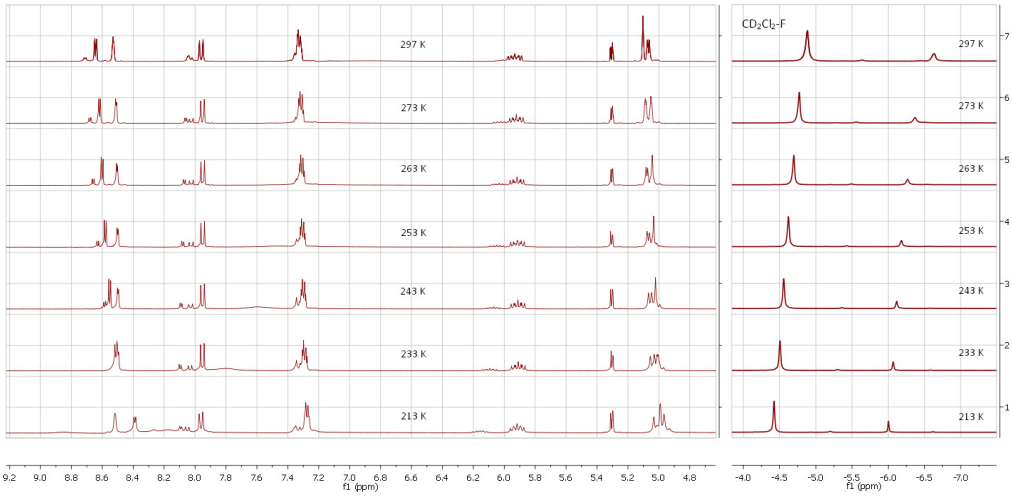
API Mass Spectrometry Data of 1 in 0.1 M DMSO-d_6 Solution



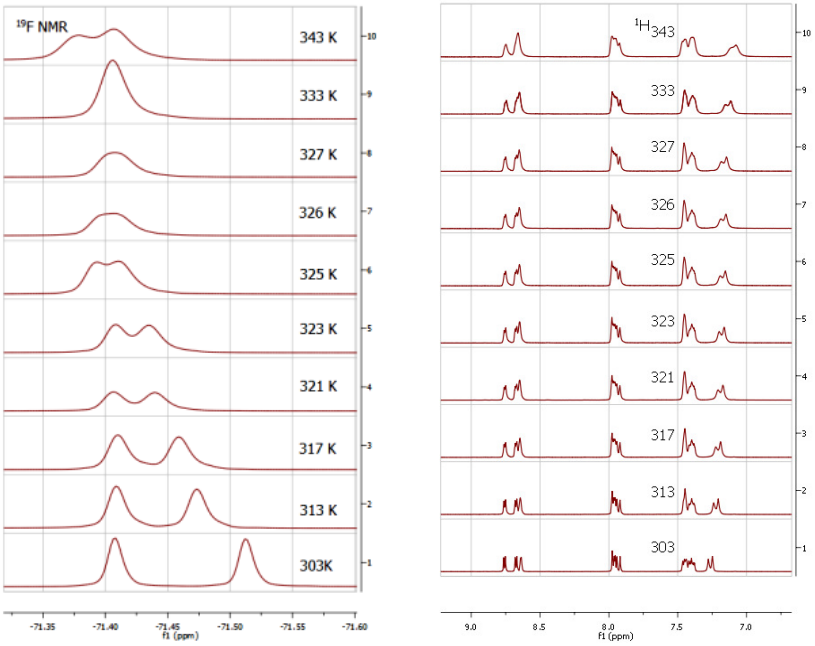
The atmospheric pressure ionization (API) mass spectrometry of the DMSO-d_6 solution of **1** has clearly shown a complex of **1** and DMSO-d_6 in a 1:1 ratio suggesting remarkably strong intermolecular interactions between the two species. Under similar conditions, the aggregation between **1** and solvent molecules in 0.1 M CD_3OD solution was not observed indicating a relatively weak hydrogen bonding interaction.

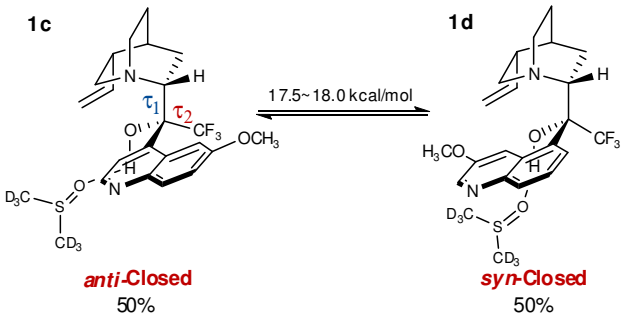
DNMR Spectra of 1 in $CDCl_3$ (293K-333K) and CD_2Cl_2 (213K-297K)





DNMR Spectra of 1 in DMSO-d_6 (303K-343K)





The frequency difference of the two signals ($\Delta\nu$) was found to be 5.75 Hz.

Applying the Eyring equation (ref. 19a):

$\Delta G^{*} = RT_c[22.96+\ln(T_c/\Delta\nu)]$ (J/mol)

The rotational barrier was determined to be 18.0 kcal/mol.

Using the modified Eyring equation described by Mannschreck (ref. 19b):

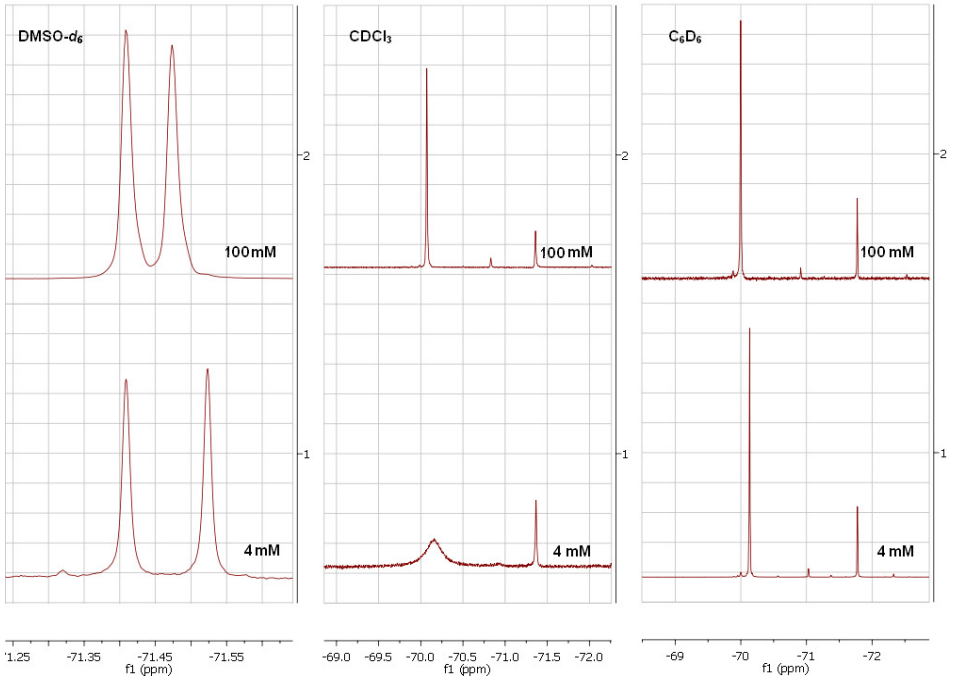
$\Delta G^{*} = 19.145\ T_c[10.32+\log(T_c/k_c)]$ (J/mol)

where $k_c = 2.22\Delta\nu$

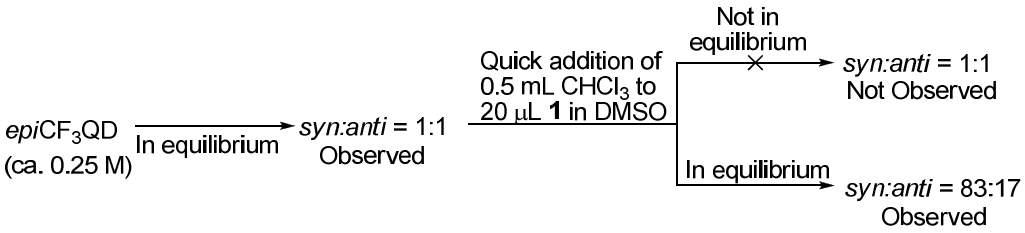
The rotational barrier was determined to be 17.5 kcal/mol.

Concentration Dependence of the NMR Spectra of 1

As illustrated, the relative populations of the two conformers have been found to be independent of the concentrations of the solutions of **1**, implying that the aggregation of **1** in different solvents is negligible even at a concentration of 0.1 M. Notably, the line shapes of **1** in $CDCl_3$ appear to be rather concentration-dependent. The line broadening of **1a** at low concentrations can be attributed to the presence of the trace amounts of moisture and HCl in $CDCl_3$, which protonate the bridge-head nitrogen of **1** and display a profound influence thereof.

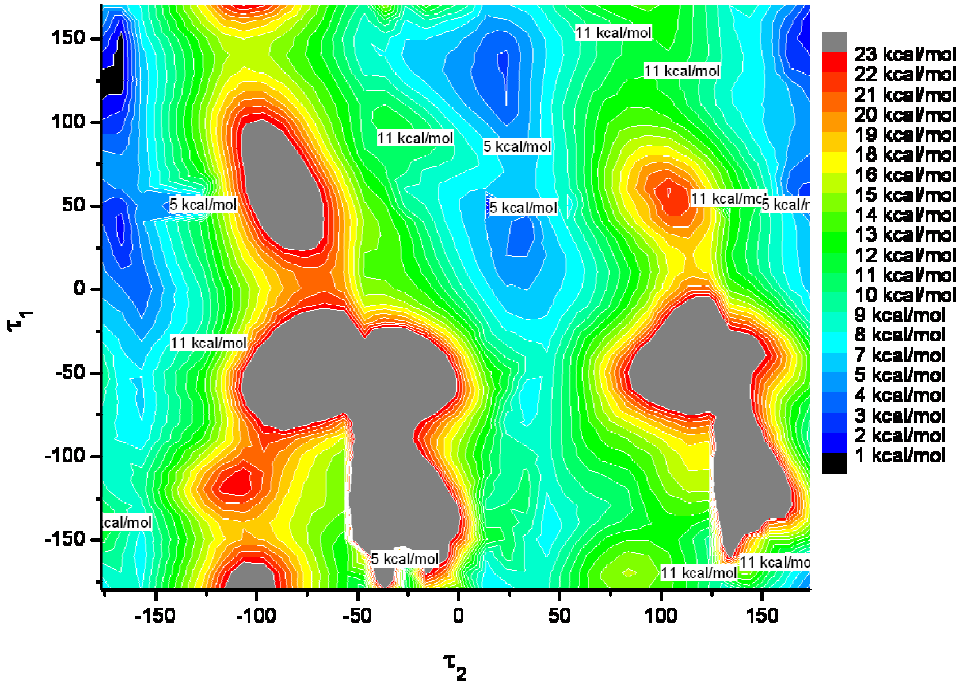


Validation of the Equilibration of 1a and 1b in $CDCl_3$ at Room Temperature.



Since a complete coalescence of the CF_3 signals of **1a** and **1b** has not been observed in $CDCl_3$ in temperature dependent ^{19}F NMR, a further experiment was performed to confirm that in the chloroform solution, **1a** and **1b** exists as an equilibration mixture at room temperature. As shown by NMR experiments, even at high concentrations (>0.1 M), **1a** and **1b** can still reach equilibrium rapidly with a ratio of 1:1 in DMSO-d_6 at room temperature. Hence, a quick addition of a large amount of chloroform into the aforementioned solution (0.25M) is anticipated to "freeze" the two conformations, **1a** and **1b**, so that no thermodynamic equilibrium is observed in the mixed solvents. As such **1a** and **1b** are supposed to be detected in a ratio of approximately 50:50. To the contrary, the experiment in fact led to the *syn* and the *anti* conformations in a ratio of 83:17, which unequivocally confirms the equilibrium between **1a** and **1b**.

Preliminary Computational Studies of the Potential Energy Surface 1.



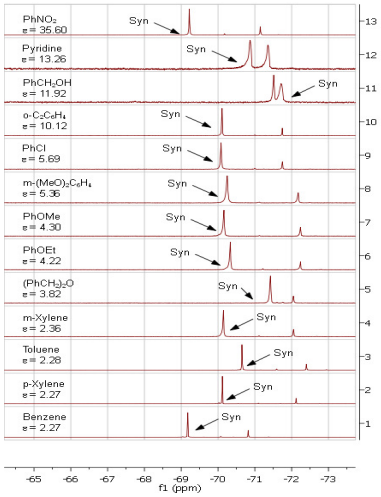
The potential energy surface (PES) of **1** was computed at the B3LYP/6-31G(d) level using the Gaussian 03 program package[6] as a function of the two characteristic rotations, τ_1 and τ_2. The dihedral angles of these two rotations were systematically varied from 0° to 360° by an increment of 10°. The formed conformations were allowed to calculate up to five optimization steps for each constrained dihedral angles, and this computational method was previously validated for the estimation of the energetic and geometric properties of conformations with satisfactory accuracy.[7] As such, the conformational profile of **1** in the gas phase was permitted to plot in a 36×36 PES with 1296 geometry optimizations. The identified local minima have been further fully optimized at the HF 6-311+G(dp)//B3LYP/6-311+G(2d,p) level, which have shown a good agreement with both the PES and the experimental outcomes (will be published separately).

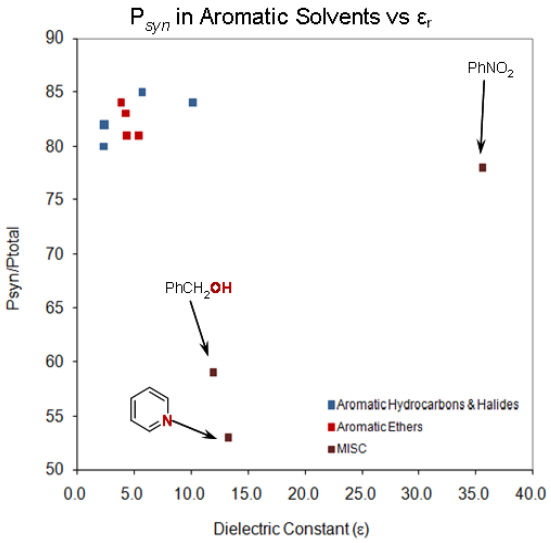
Relative Populations of the *syn*-Conformations in Various Solvents

The experiments were generally performed using solutions of **1** at concentrations of ca. 0.05 M. Saturated solutions were used for the solvents in which the solubility of **1** is essentially low.

Solvent	ε_r	P_{syn} (%)	Solvent	ε_r	P_{syn} (%)
Pentane	1.84	86	1-PrOH	20.80	52
C_6D_6	2.27	80	EtOH-d_6	25.30	54
p-Xylene	2.27	82	MeOH-d_4	33.00	58
Toluene-d_8	2.28	82	HOC_2H_4OH	40.40	65
m-Xylene	2.36	82	D_2O	80.10	71
$PhCH_2OCH_2Ph$	3.82	84	CD_3CN	36.64	55
PhOEt	4.22	83	DMF-d_7	38.25	55
Anisole	4.30	81	DMSO-d_6	47.24	50
m-Dimethoxylbenzene	5.36	81	Acetone-d_6	21.01	55
PhCl	5.69	85	THF-d_8	7.52	65
o-ClC_6H_4Cl-d_4	10.12	84	$CH_3OC_2H_4OCH_3$	7.30	62
$PhCH_2OH$	11.92	59	Et_2O	4.27	64
$PhNO_2$-d_5	35.60	78	*n*-Bu_2O	3.08	72
Pyridine-d_5	13.26	53	1,4-Dioxane	2.22	60
4-Methyl-4-heptanol	2.92	63	*t*-BuOMe	-	61
2-Octanol	8.13	52	ClC_2D_4Cl	10.42	81
1-Octanol	10.30	54	CD_2Cl_2	8.93	83
1-heptanol	10.75	55	$CDCl_3$	4.80	83
t-BuOH	12.47	51	CCl_4	2.24	82
1-Pentanol	15.13	54	Ethyl Acetate	6.08	61
sec-BuOH	17.26	51	CD_3NO_2	37.27	82
n-BuOH	17.84	55	$EtNO_2$	29.11	78
Iso-BuOH	17.93	52	1-$PrNO_2$	24.70	79
i-PrOH-d_8	20.18	50			

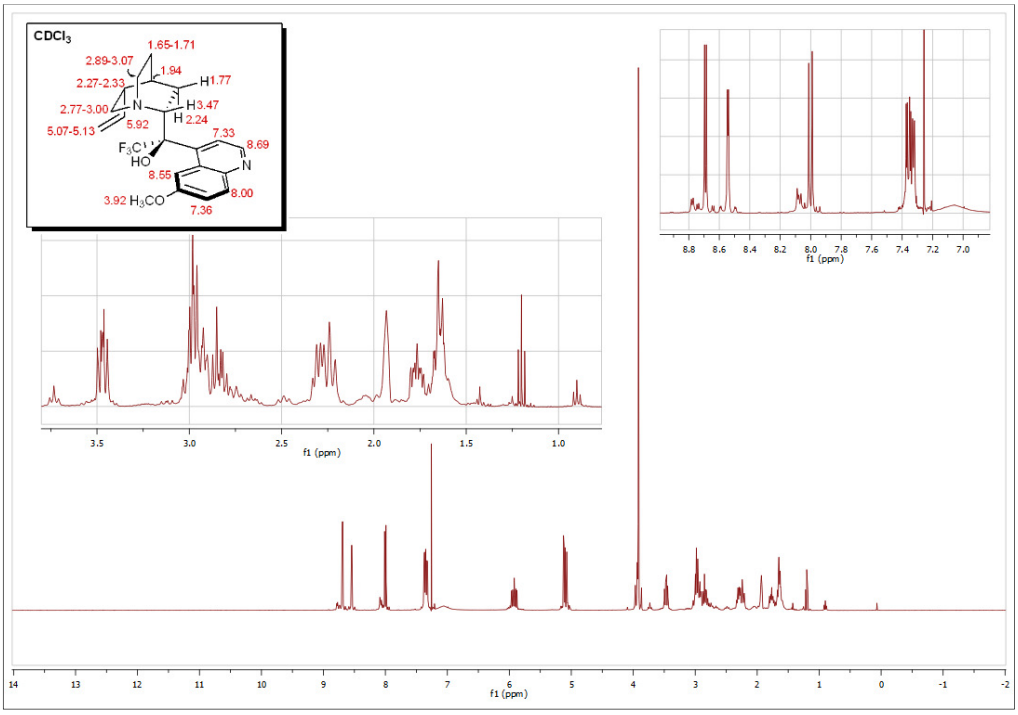
^{19}F NMR Spectra of **1** in Ethers



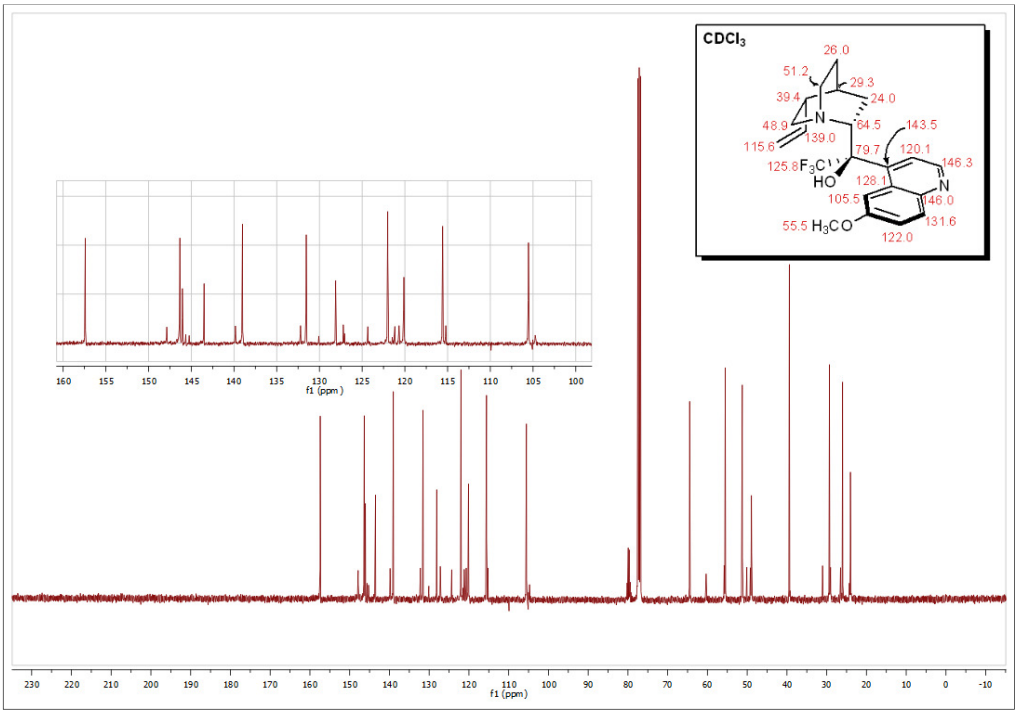


NMR Spectra of 1 in $CDCl_3$

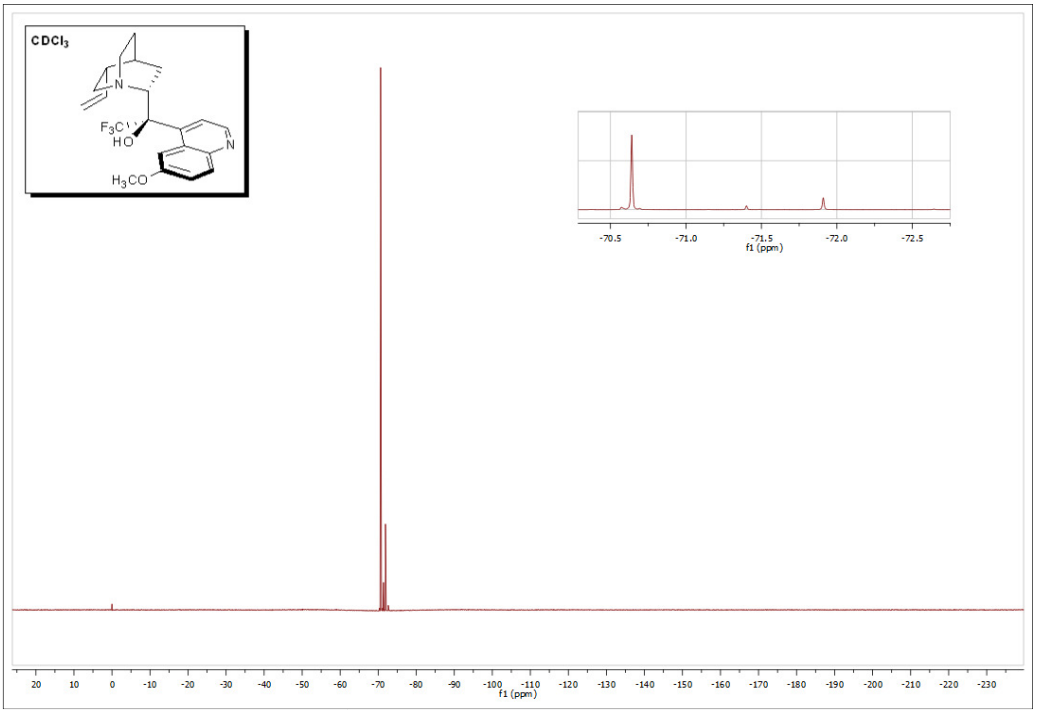
^{1}H NMR



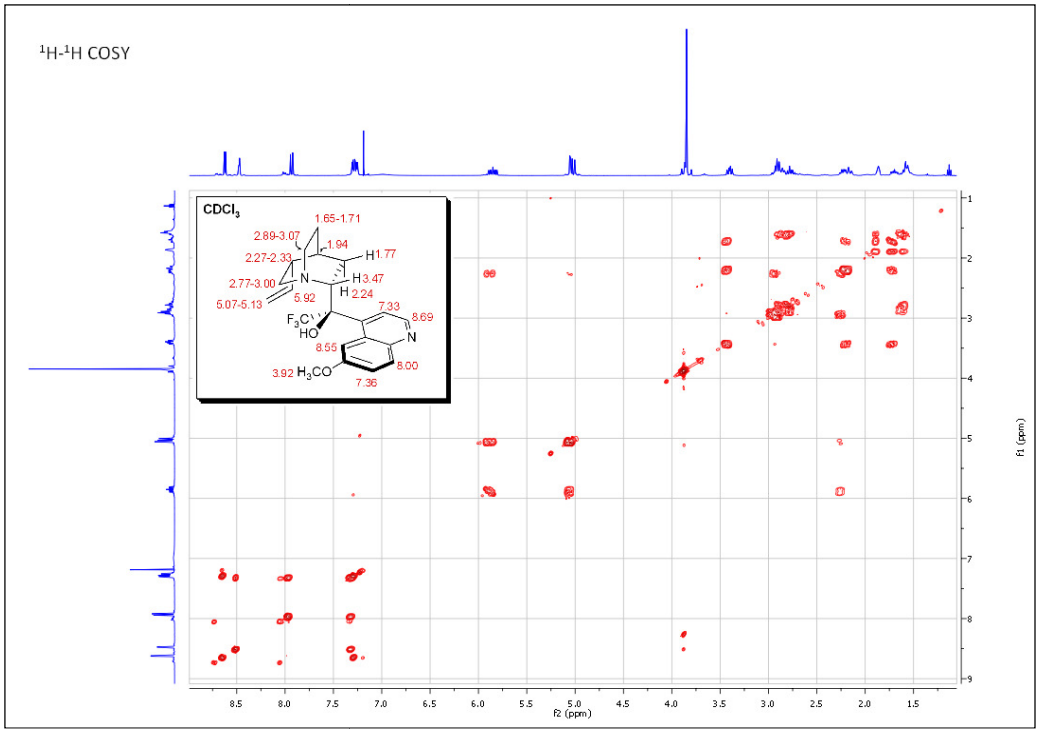
^{13}C NMR



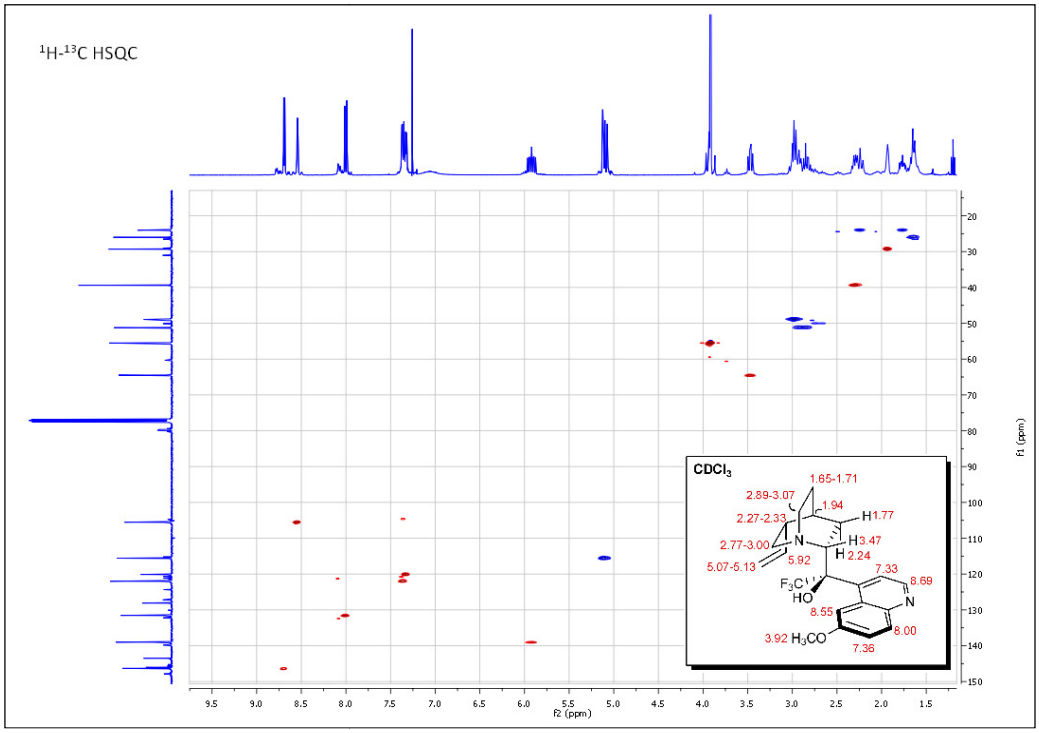
^{19}F NMR



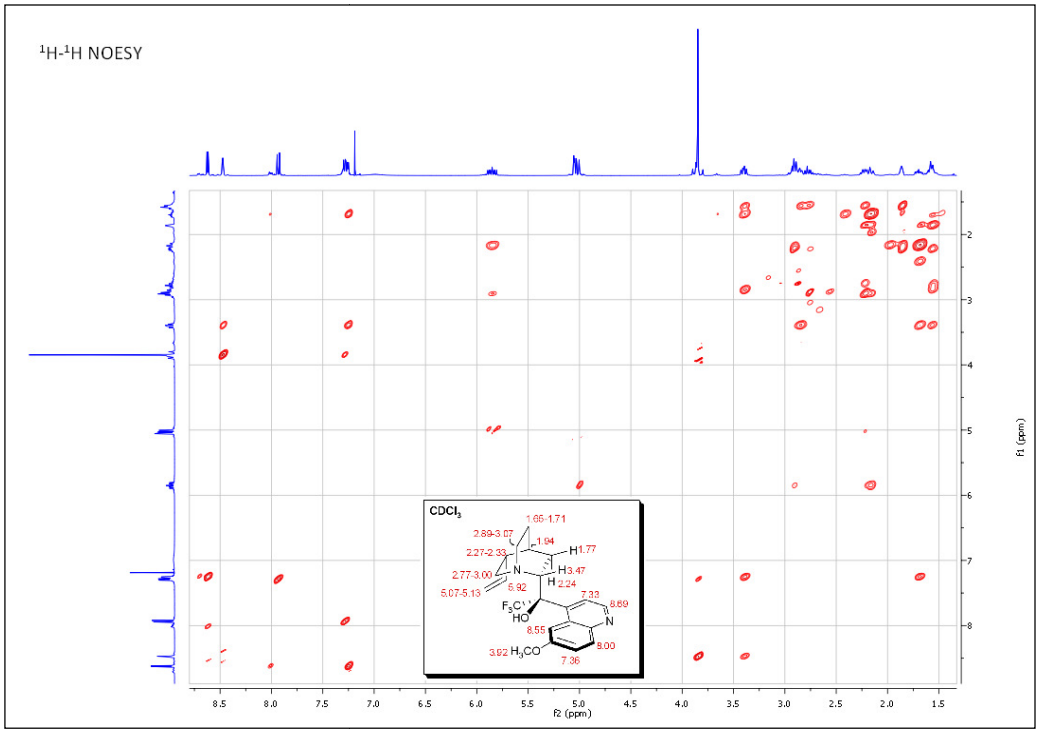
^{1}H-^{1}H COSY



^{1}H-^{13}C HSQC

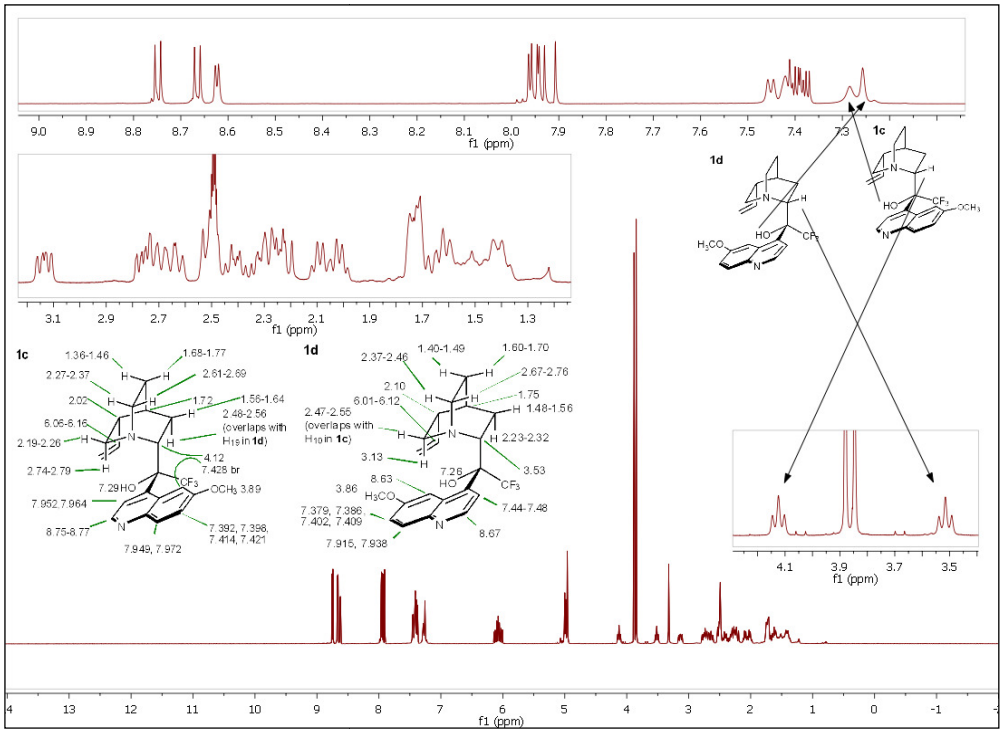


^{1}H-^{1}H NOESY (Negative signals are omitted for clarity.)

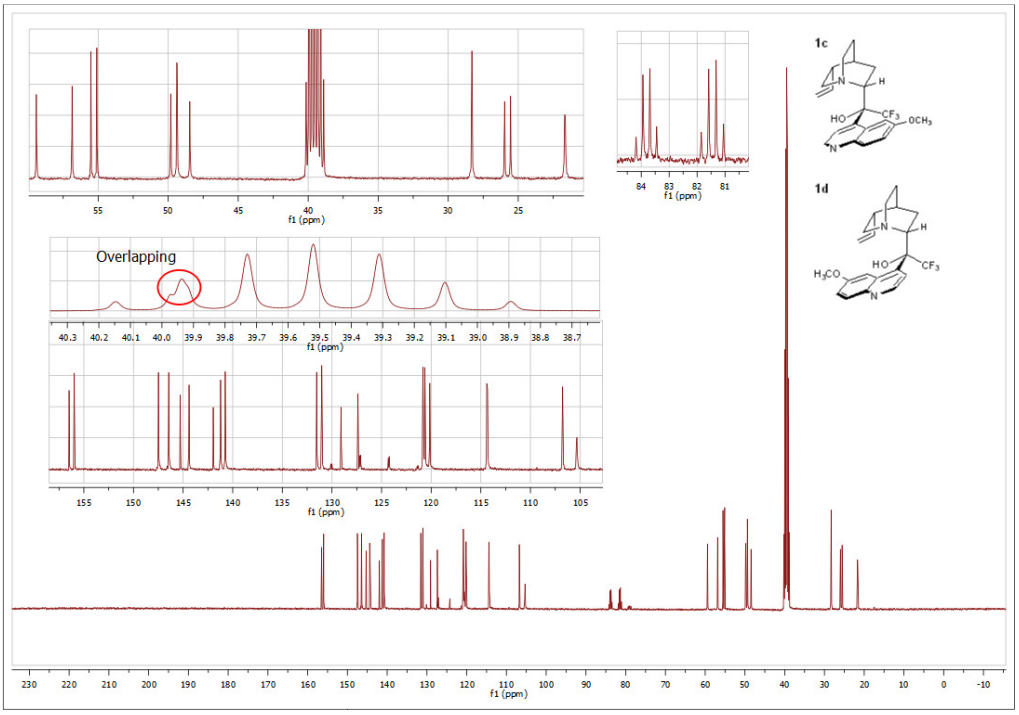


NMR Spectra of 1 in DMSO-d_6

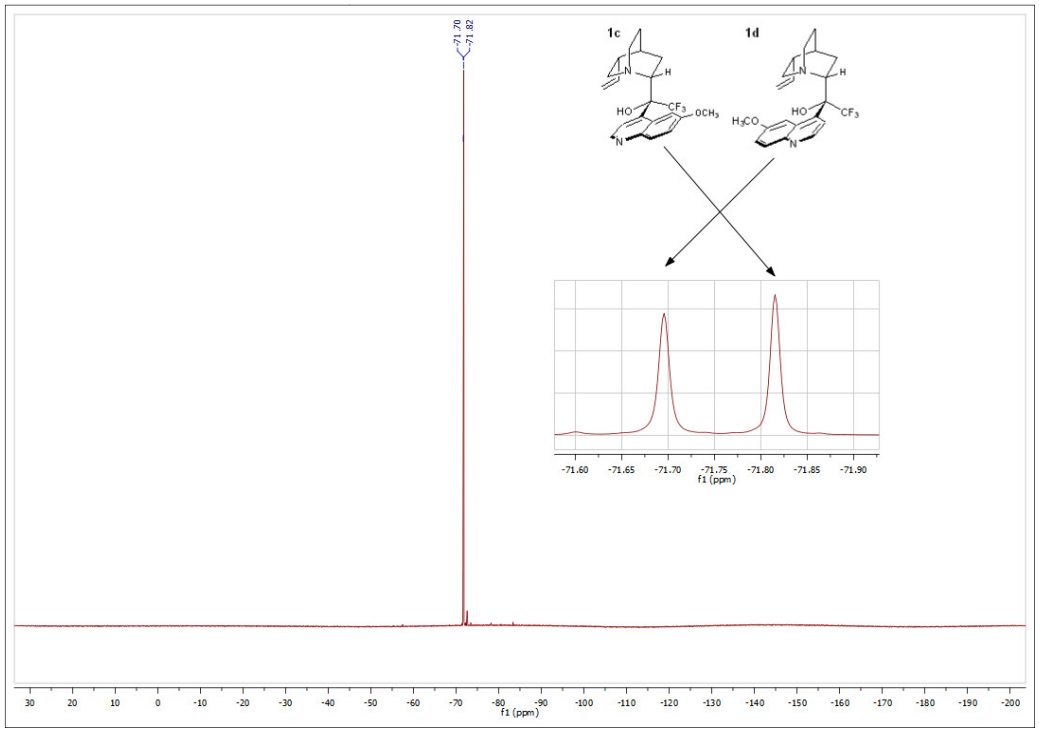
^{1}H NMR



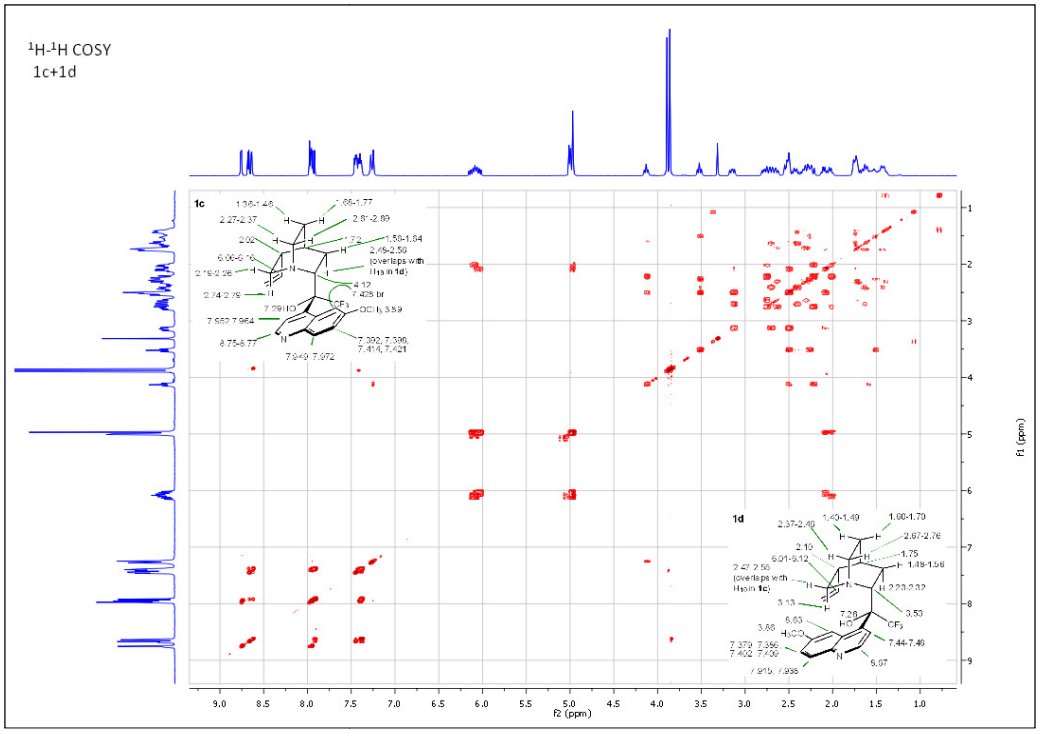
^{13}C NMR



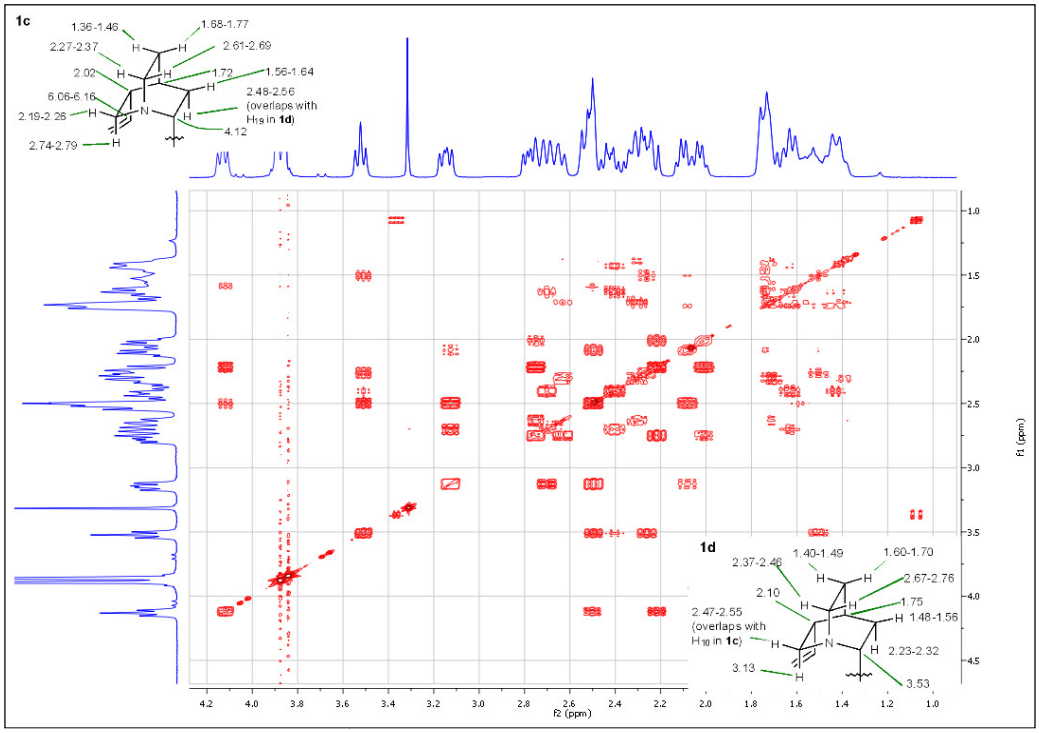
^{19}F NMR



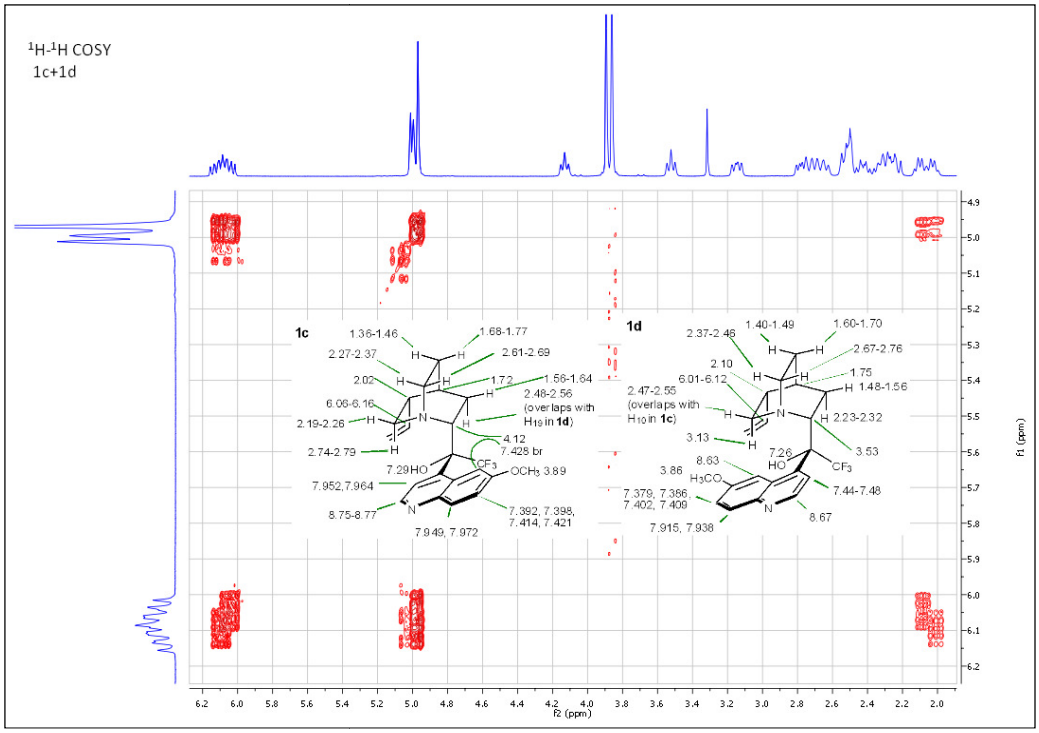
^{1}H-^{1}H COSY (1)



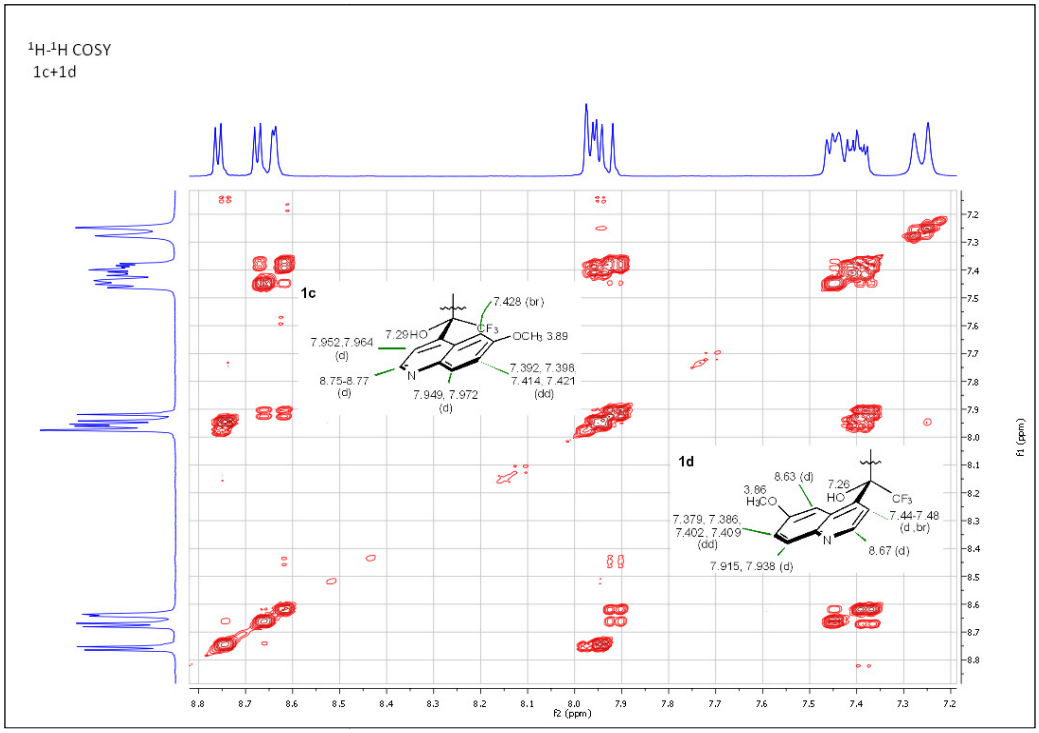
^{1}H-^{1}H COSY (2)



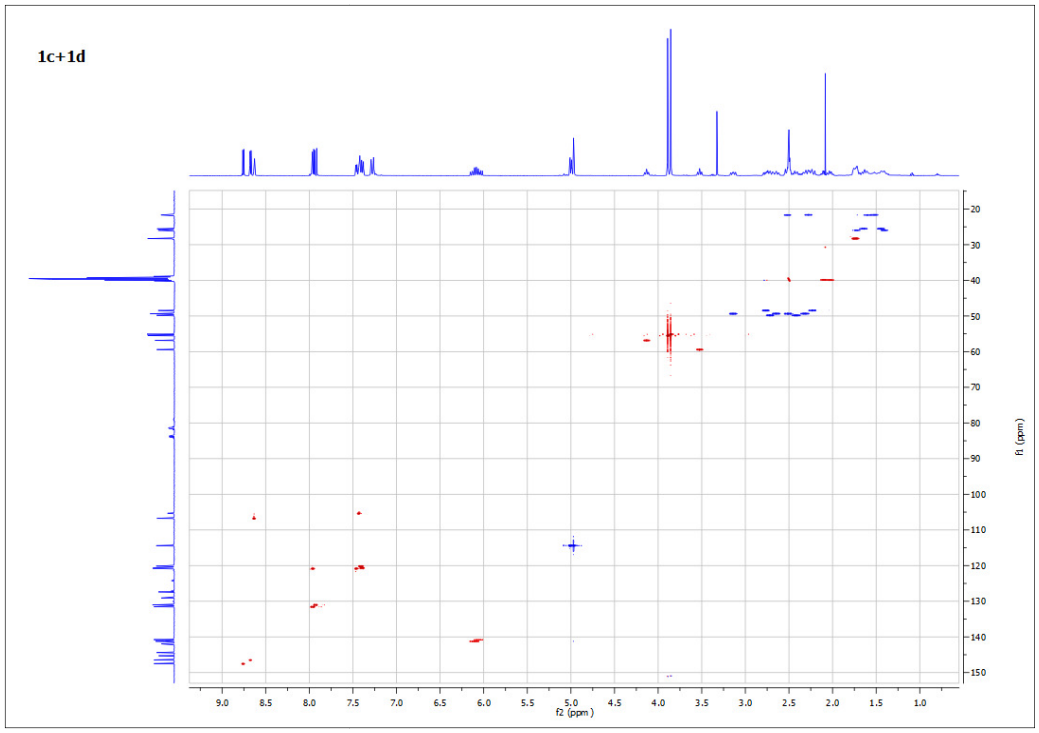
^{1}H-^{1}H COSY (3)



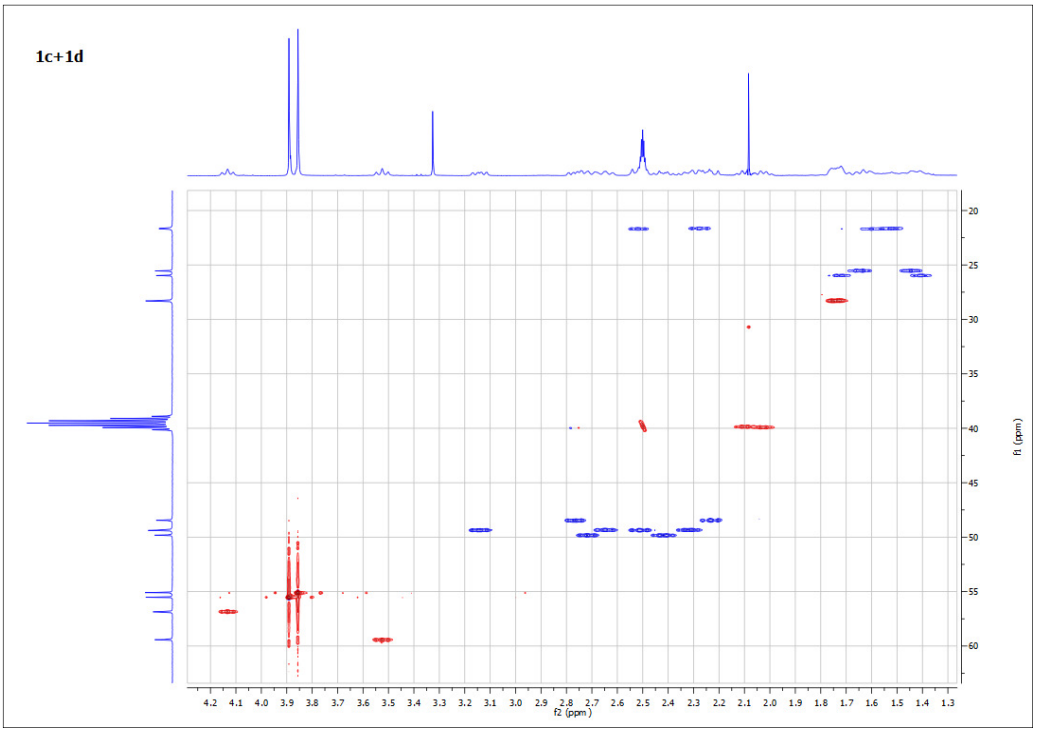
^{1}H-^{1}H COSY (4)



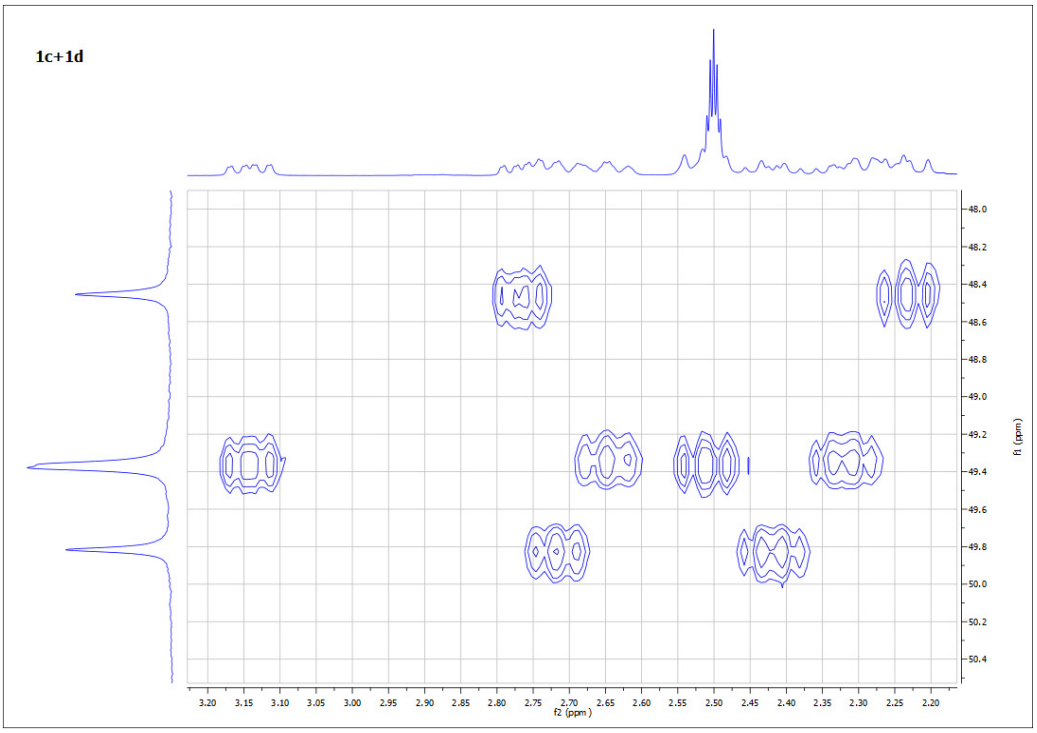
^{1}H-^{13}C HSQC (1)



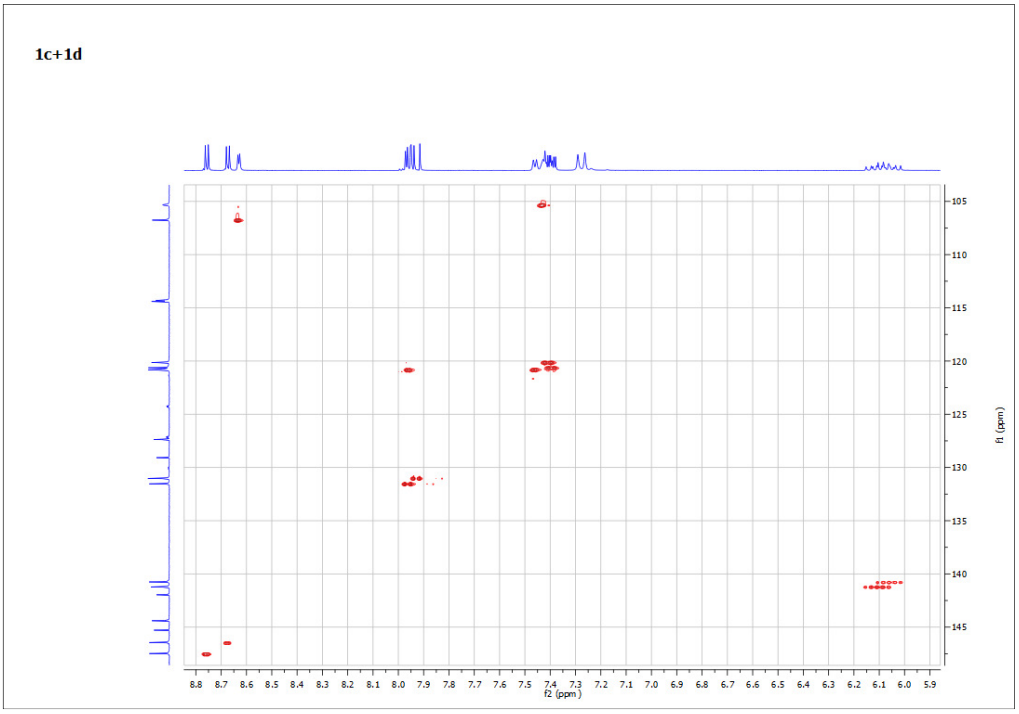
^{1}H-^{13}C HSQC (2)



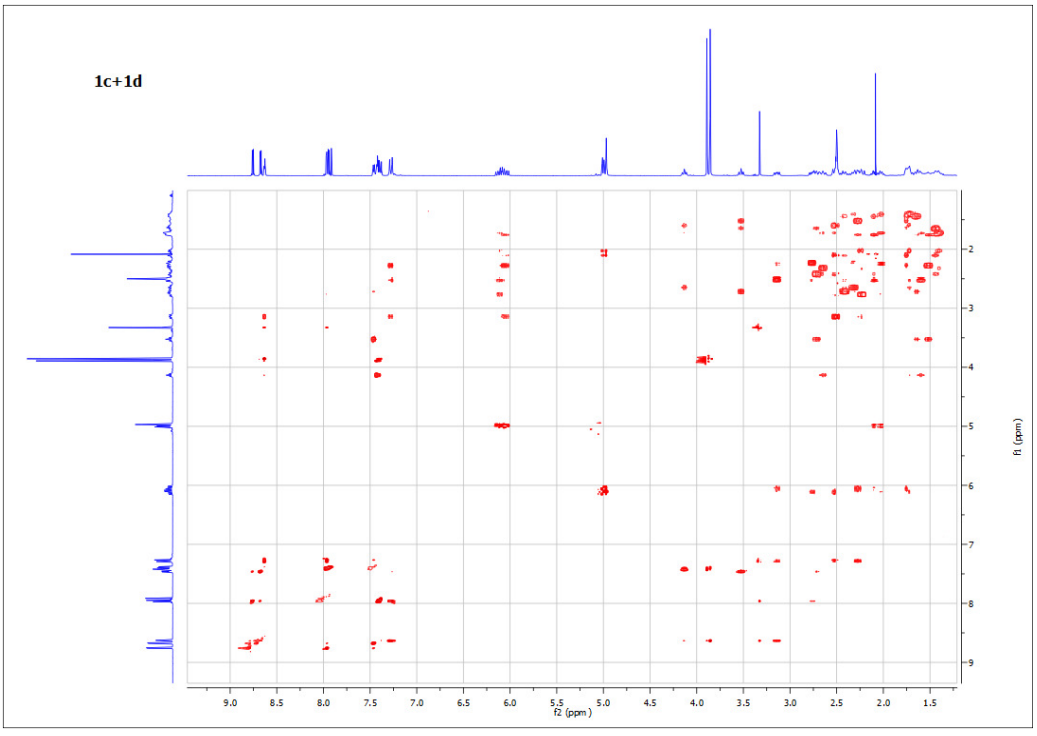
^{1}H-^{13}C HSQC (3)



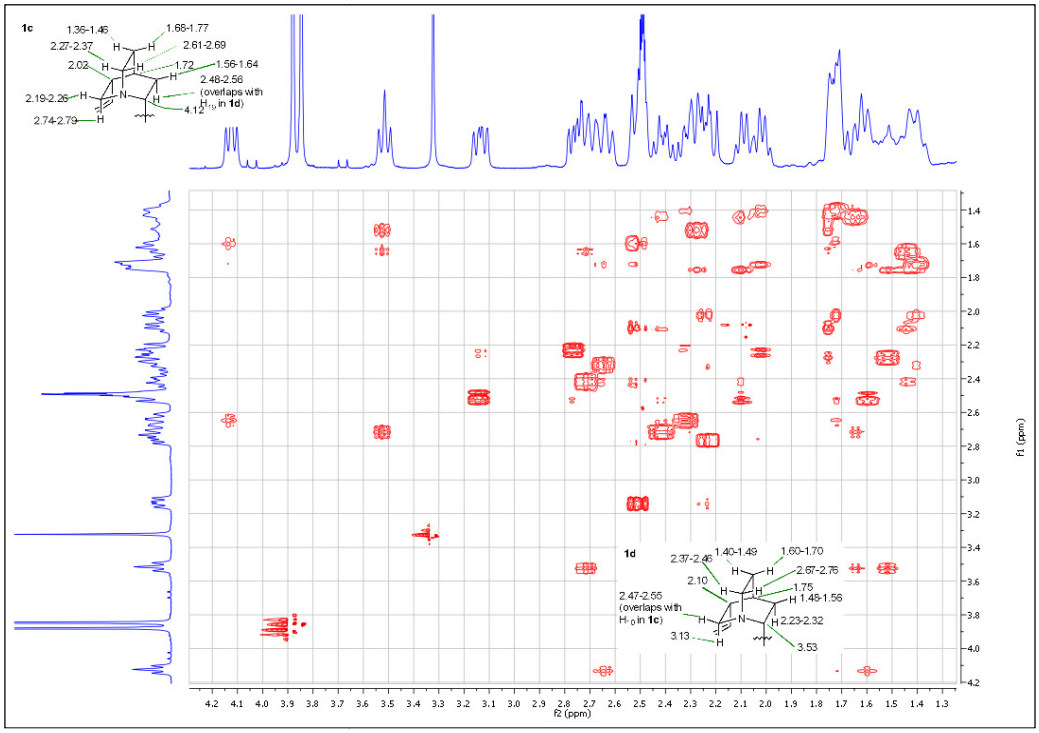
^{1}H-^{13}C HSQC (4)



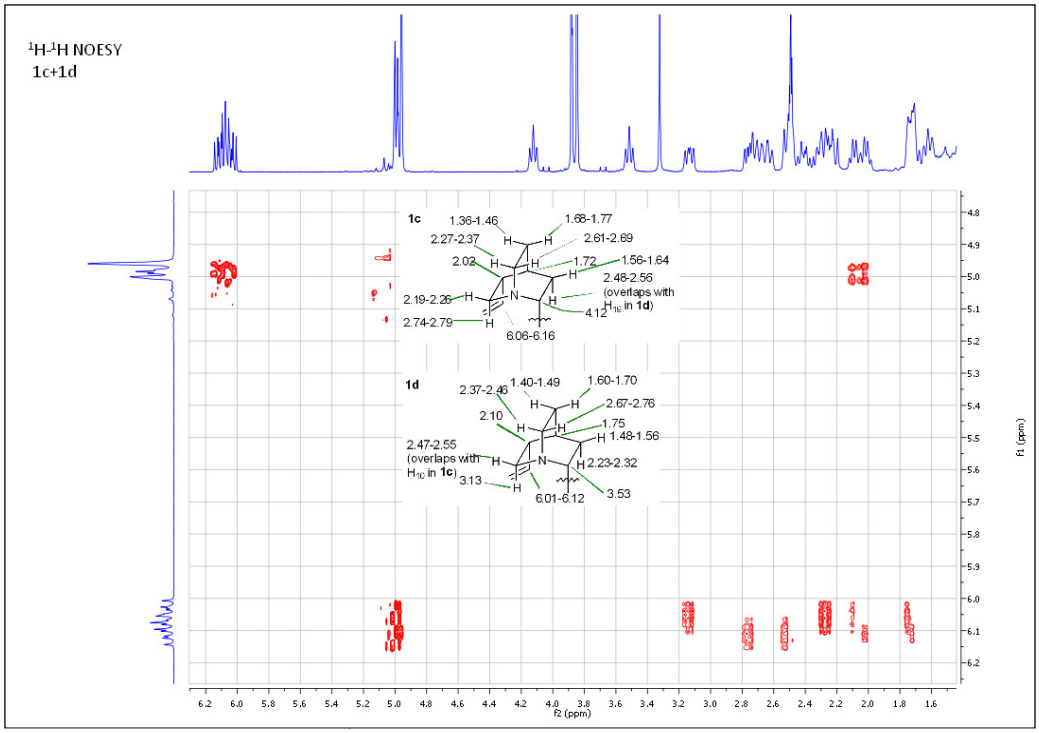
^{1}H-^{1}H NOESY (1) (Negative signals are omitted for clarity.)



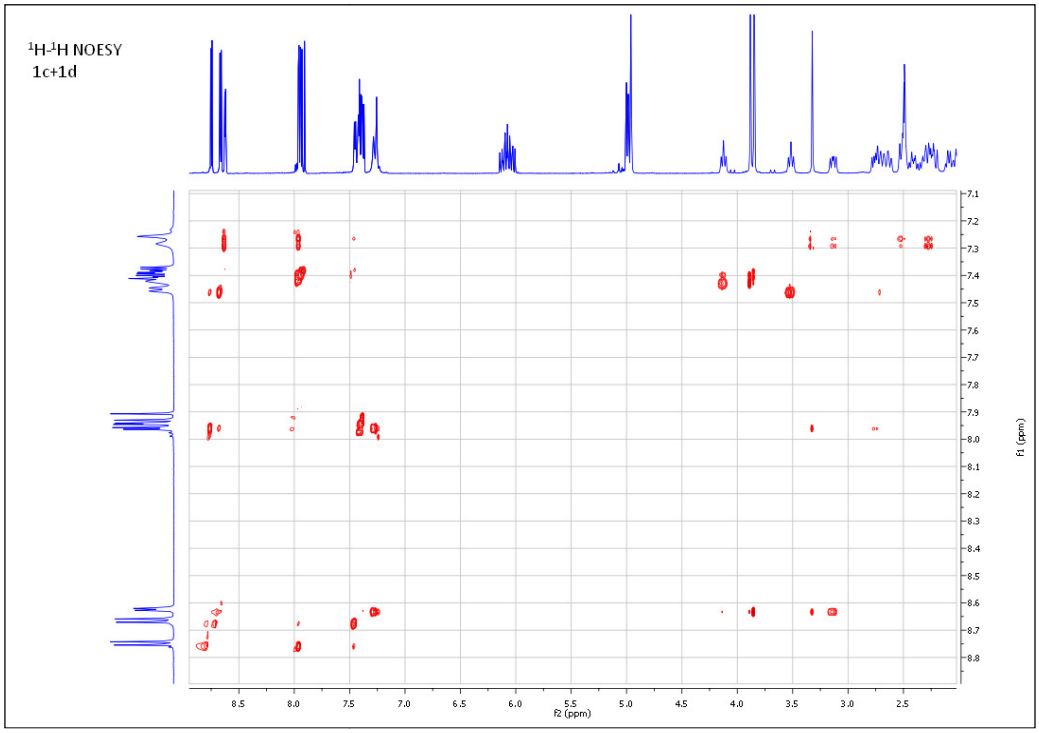
^{1}H-^{1}H NOESY (2) (Negative signals are omitted for clarity.)



^{1}H-^{1}H NOESY (3) (Negative signals are omitted for clarity.)

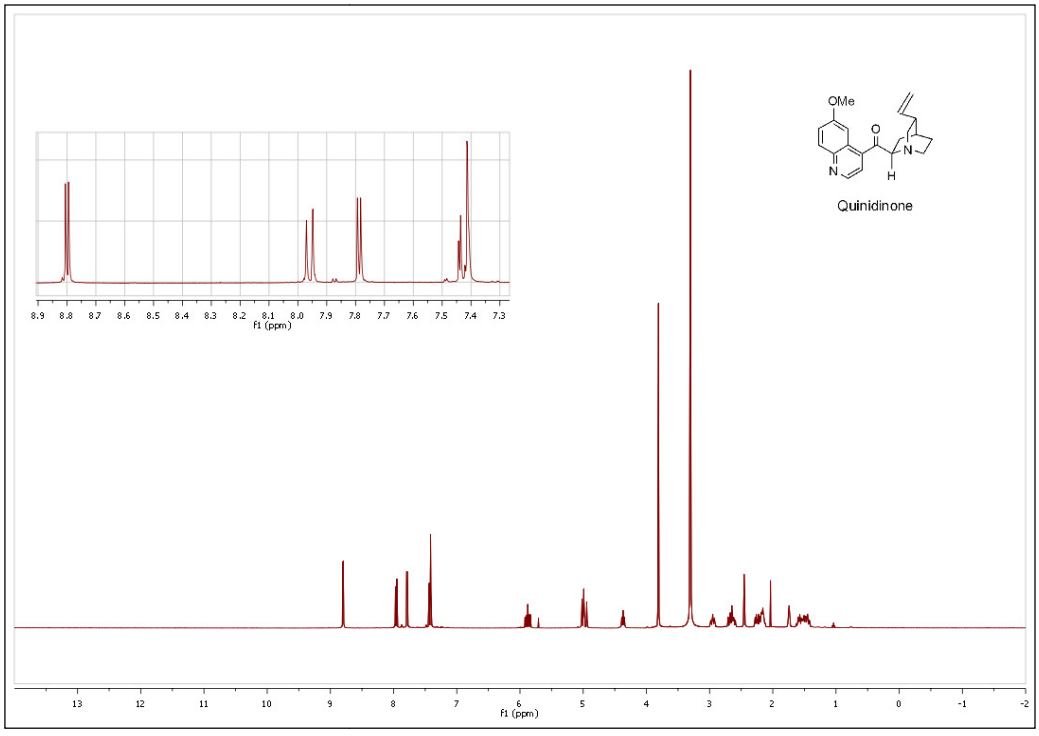


^{1}H-^{1}H NOESY (4) (Negative signals are omitted for clarity.)

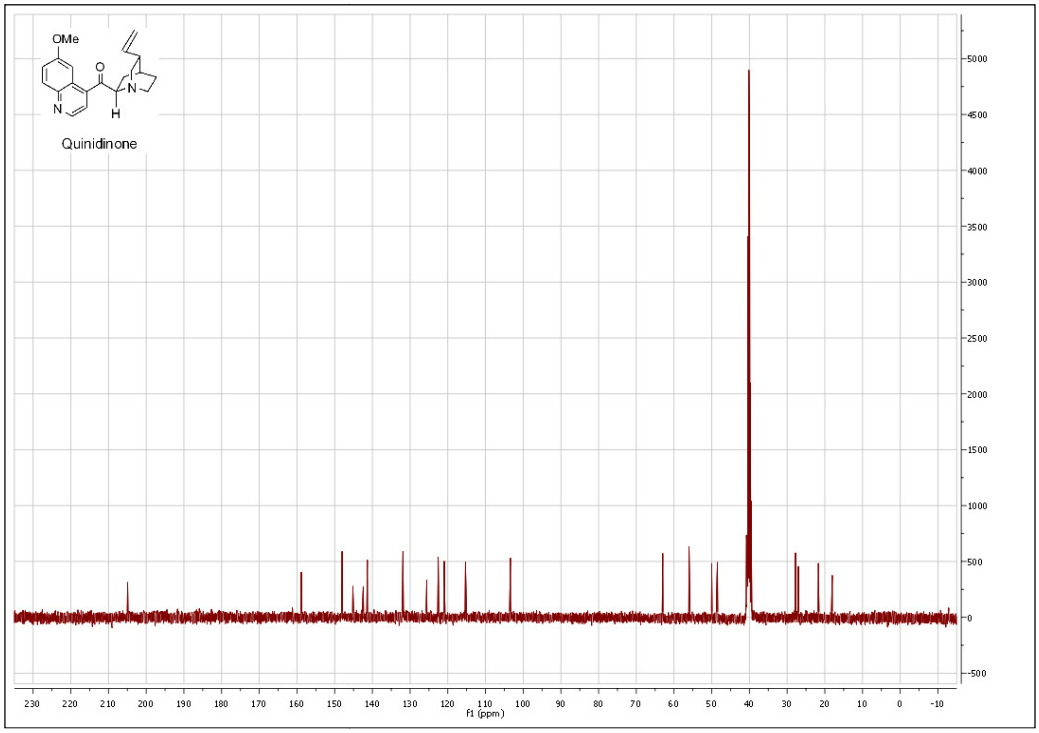


NMR Spectra of Quinidinone (DMSO-d_6)

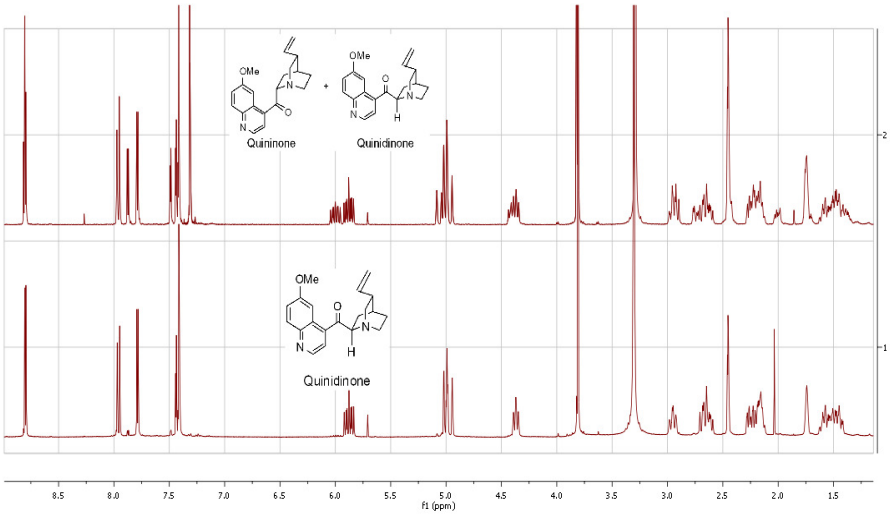
^{1}H NMR



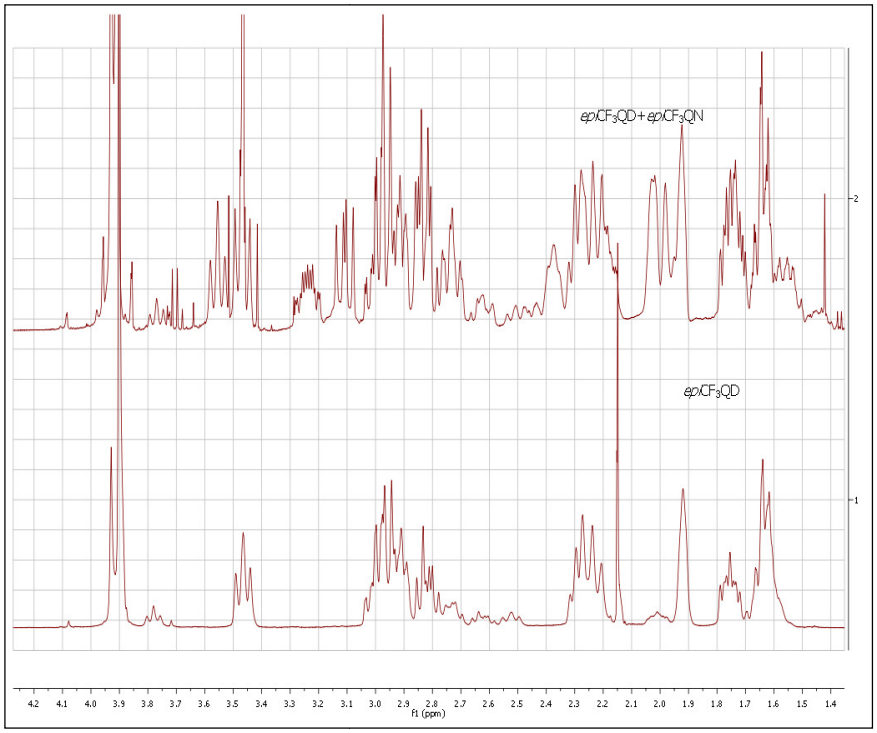
^{13}C NMR

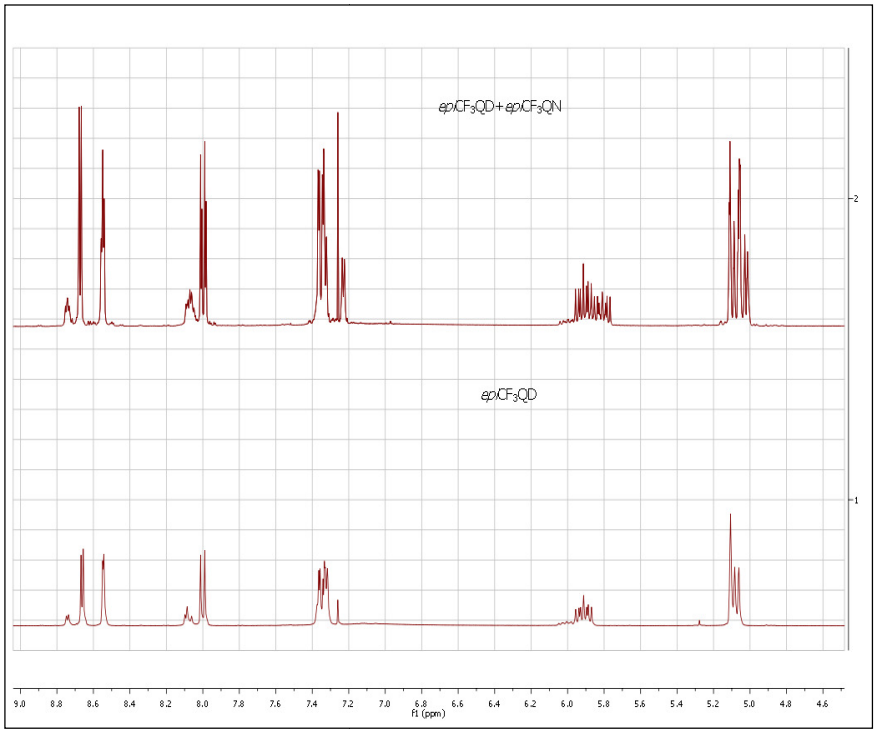


^{1}H NMR Spectra of Quinidinone and Quininone (DMSO-d_6)



^{1}H NMR Spectra of *epi*CF_3QD and *epi*CF_3QN ($CDCl_3$)





X-ray Crystal Structure of Quinidinone (Crystallized from Ether)

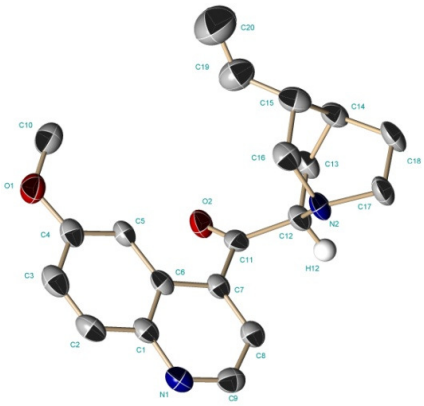


Table 1. Crystal data and structure refinement for C20 H22 N2 O2.

Identification code	fang1m	
Empirical formula	C20 H22 N2 O2	
Formula weight	322.40	
Temperature	143(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)	
Unit cell dimensions	a = 8.293(2) Å	□= 90°.
	b = 8.115(2) Å	□= 95.021(4)°.
	c = 12.531(3) Å	□ = 90°.
Volume	840.1(4) Å^3	
Z	2	
Density (calculated)	1.274 Mg/m^3	

Absorption coefficient	0.083 mm^{-1}
F(000)	344
Crystal size	0.26 x 0.15 x 0.06 mm^3
Theta range for data collection	2.47 to 27.44°.
Index ranges	-10<=h<=10, -10<=k<=10, -15<=l<=14
Reflections collected	7135
Independent reflections	3621 [R(int) = 0.0408]
Completeness to theta = 27.44°	98.6 %
Absorption correction	semi-empirical
Transmission factors	min/max: 0.746
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	3621 / 1 / 218
Goodness-of-fit on F^2	1.021
Final R indices [I>2sigma(I)]	R1 = 0.0638, wR2 = 0.1257
R indices (all data)	R1 = 0.1113, wR2 = 0.1470
Absolute structure parameter	-1(2)
Largest diff. peak and hole	0.322 and -0.214 e.$Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters (Å^{2}x 103) for C20 H22 N2 O2.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	3165(4)	10585(4)	4495(3)	34(1)
C(2)	4591(4)	11485(5)	4850(3)	43(1)
C(3)	5903(4)	11481(5)	4281(3)	46(1)
C(4)	5882(4)	10598(4)	3302(3)	37(1)
C(5)	4524(4)	9739(4)	2920(2)	33(1)
C(6)	3138(4)	9720(4)	3510(2)	31(1)
C(7)	1692(4)	8810(4)	3194(2)	31(1)
C(8)	464(4)	8815(4)	3849(2)	36(1)
C(9)	598(4)	9773(4)	4788(3)	39(1)
C(10)	7314(4)	9771(5)	1852(3)	52(1)
C(11)	1482(4)	8016(4)	2098(3)	32(1)
C(12)	700(4)	6300(4)	1973(2)	33(1)
C(13)	855(4)	5560(4)	862(3)	37(1)
C(14)	1652(4)	3861(4)	1005(3)	38(1)
C(15)	3334(4)	4037(5)	1630(3)	46(1)
C(16)	3077(4)	4874(4)	2706(3)	42(1)

C(17)	452(4)	3627(4)	2763(3)	43(1)
C(18)	587(5)	2807(4)	1655(3)	47(1)
C(19)	4530(5)	4982(6)	1037(3)	61(1)
C(20)	5911(6)	4480(9)	793(4)	102(2)
N(1)	1895(3)	10651(4)	5111(2)	39(1)
N(2)	1364(3)	5200(3)	2845(2)	35(1)
O(1)	7259(3)	10692(3)	2803(2)	46(1)
O(2)	1873(3)	8755(3)	1323(2)	38(1)

Table 3. Bond lengths [Å] and angles [°] for C20 H22 N2 O2.

C(1)-N(1)	1.360(4)
C(1)-C(6)	1.419(4)
C(1)-C(2)	1.427(5)
C(2)-C(3)	1.352(5)
C(3)-C(4)	1.419(5)
C(4)-O(1)	1.352(4)
C(4)-C(5)	1.374(4)
C(5)-C(6)	1.420(4)
C(6)-C(7)	1.434(4)
C(7)-C(8)	1.363(4)
C(7)-C(11)	1.513(4)
C(8)-C(9)	1.406(4)
C(9)-N(1)	1.324(4)
C(10)-O(1)	1.411(4)
C(11)-O(2)	1.210(4)
C(11)-C(12)	1.539(5)
C(12)-N(2)	1.479(4)
C(12)-C(13)	1.531(4)
C(13)-C(14)	1.533(5)
C(14)-C(18)	1.517(5)

C(14)-C(15)	1.545(5)
C(15)-C(19)	1.501(5)
C(15)-C(16)	1.541(4)
C(16)-N(2)	1.470(4)
C(17)-N(2)	1.482(4)
C(17)-C(18)	1.554(5)
C(19)-C(20)	1.278(6)

N(1)-C(1)-C(6)	124.0(3)
N(1)-C(1)-C(2)	117.7(3)
C(6)-C(1)-C(2)	118.2(3)
C(3)-C(2)-C(1)	121.2(3)
C(2)-C(3)-C(4)	120.5(3)
O(1)-C(4)-C(5)	124.5(3)
O(1)-C(4)-C(3)	115.1(3)
C(5)-C(4)-C(3)	120.3(3)
C(4)-C(5)-C(6)	120.0(3)
C(1)-C(6)-C(5)	119.7(3)
C(1)-C(6)-C(7)	116.3(3)
C(5)-C(6)-C(7)	123.9(3)
C(8)-C(7)-C(6)	118.9(3)
C(8)-C(7)-C(11)	121.0(3)

C(6)-C(7)-C(11)	119.8(3)
C(7)-C(8)-C(9)	119.8(3)
N(1)-C(9)-C(8)	123.8(3)
O(2)-C(11)-C(7)	120.0(3)
O(2)-C(11)-C(12)	120.5(3)
C(7)-C(11)-C(12)	119.5(3)
N(2)-C(12)-C(13)	112.3(3)
N(2)-C(12)-C(11)	110.2(2)
C(13)-C(12)-C(11)	112.3(3)
C(12)-C(13)-C(14)	108.4(3)
C(18)-C(14)-C(13)	107.7(3)
C(18)-C(14)-C(15)	108.8(3)
C(13)-C(14)-C(15)	109.7(3)
C(19)-C(15)-C(16)	110.8(3)
C(19)-C(15)-C(14)	113.8(3)
C(16)-C(15)-C(14)	107.3(3)
N(2)-C(16)-C(15)	113.0(3)
N(2)-C(17)-C(18)	110.7(3)
C(14)-C(18)-C(17)	109.2(3)
C(20)-C(19)-C(15)	126.9(5)
C(9)-N(1)-C(1)	117.0(3)
C(16)-N(2)-C(12)	108.8(2)

C(16)-N(2)-C(17)	109.2(3)
C(12)-N(2)-C(17)	108.3(3)
C(4)-O(1)-C(10)	116.9(3)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C20 H22 N2 O2.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[h^2 a^{*2} U^{11} + ... + 2 h k a^* b^* U^{12}]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	42(2)	24(2)	35(2)	2(2)	-4(1)	4(2)
C(2)	56(2)	33(2)	38(2)	-7(2)	-7(2)	6(2)
C(3)	46(2)	35(2)	54(2)	-1(2)	-14(2)	-1(2)
C(4)	42(2)	28(2)	41(2)	5(2)	-3(2)	-1(2)
C(5)	38(2)	23(2)	36(2)	-1(2)	-3(2)	-2(2)
C(6)	42(2)	19(2)	31(2)	4(1)	-2(1)	3(1)
C(7)	36(2)	23(2)	33(2)	4(2)	-1(1)	1(2)
C(8)	41(2)	28(2)	39(2)	4(2)	1(2)	1(2)
C(9)	44(2)	37(2)	38(2)	6(2)	6(2)	8(2)
C(10)	42(2)	56(3)	58(2)	7(2)	7(2)	-4(2)
C(11)	34(2)	24(2)	38(2)	2(2)	4(2)	7(1)
C(12)	35(2)	24(2)	37(2)	2(2)	-4(2)	2(1)
C(13)	49(2)	25(2)	36(2)	-1(2)	-3(2)	-3(2)
C(14)	50(2)	28(2)	37(2)	2(2)	4(2)	7(2)
C(15)	53(2)	41(2)	44(2)	-1(2)	1(2)	14(2)
C(16)	47(2)	35(2)	41(2)	5(2)	-5(2)	5(2)

C(17)	61(2)	23(2)	47(2)	0(2)	8(2)	-9(2)
C(18)	72(3)	20(2)	48(2)	-3(2)	3(2)	-6(2)
C(19)	55(2)	78(3)	50(2)	0(2)	6(2)	4(2)
C(20)	77(4)	110(5)	122(5)	1(4)	23(3)	7(3)
N(1)	48(2)	32(2)	36(2)	-2(1)	0(1)	4(1)
N(2)	47(2)	18(1)	38(2)	6(1)	0(1)	-3(1)
O(1)	37(1)	47(2)	53(2)	0(1)	3(1)	-7(1)
O(2)	51(1)	27(1)	36(1)	3(1)	5(1)	-6(1)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for C20 H22 N2 O2.

	x	y	z	U(eq)
H(2)	4618	12099	5497	52
H(3)	6846	12074	4539	56
H(5)	4513	9157	2261	39
H(8)	-479	8173	3672	43
H(9)	-294	9791	5215	47
H(10A)	7107	8607	1998	78
H(10B)	8385	9886	1587	78
H(10C)	6487	10181	1310	78
H(12)	-481	6437	2054	39
H(13A)	1523	6287	444	44
H(13B)	-229	5453	469	44
H(14)	1759	3343	290	46
H(15)	3779	2908	1782	55
H(16A)	3532	4159	3298	50
H(16B)	3680	5928	2753	50
H(17A)	-700	3840	2864	52

H(17B)	887	2869	3337	52
H(18A)	1060	1692	1753	56
H(18B)	-503	2698	1271	56
H(19)	4229	6069	821	73
H(20A)	6273	3402	990	123
H(20B)	6577	5184	414	123

X-ray Crystal Structure of *epi*CF_3QD and *epi*CF_3QN

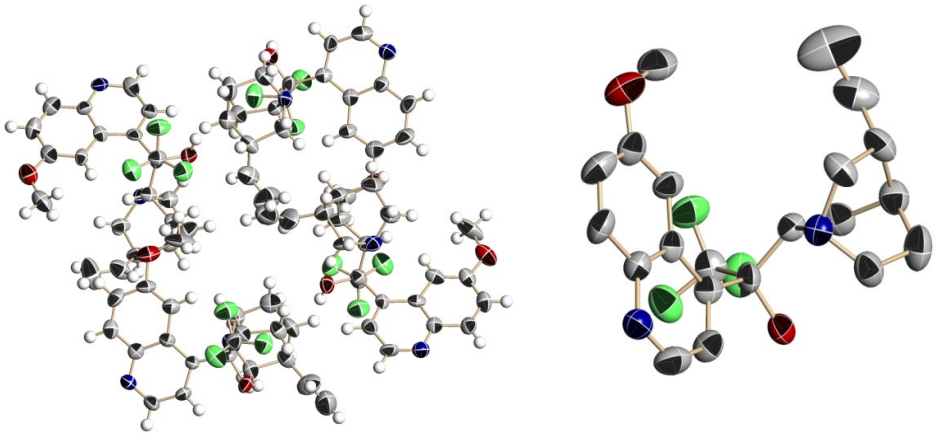


Table 1. Crystal data and structure refinement for C21 H23 F3 N2 O2

Identification code	fang4m	
Empirical formula	C21 H23 F3 N2 O2	
Formula weight	392.41	
Temperature	153(2) K	
Wavelength	0.71073 Å	
Crystal system	Monoclinic	
Space group	P2(1)/c	
Unit cell dimensions	a = 12.440(10) Å	□= 90°.
	b = 12.594(10) Å	□=

100.954(14)°.

	c = 12.697(10) Å	□ = 90°.
Volume	1953(3) $Å^3$	
Z	4	

Density (calculated)	1.334 Mg/m^3
Absorption coefficient	0.105 mm^{-1}
F(000)	824
Crystal size	0.19 x 0.14 x 0.08 mm^3
Theta range for data collection	1.62 to 28.09°.
Index ranges	-16<=h<=16, -16<=k<=16, -15<=l<=16
Reflections collected	16803
Independent reflections	13747 [R(int) = 0.0563]
Completeness to theta = 28.09°	89.5 %
Absorption correction	Multi-scan
Transmission factors	min/max: 0.743
Refinement method	Full-matrix least-squares on F^2
Data / restraints / parameters	13747 / 3 / 1017
Goodness-of-fit on F^2	0.705
Final R indices [I>2sigma(I)]	R1 = 0.0513, wR2 = 0.0878
R indices (all data)	R1 = 0.1818, wR2 = 0.1196
Absolute structure parameter	-1.4(9)
Largest diff. peak and hole	0.218 and -0.143 $e.Å^{-3}$

Table 2. Atomic coordinates (x 10^4) and equivalent isotropic displacement parameters ($Å^2$x 10^3) for C21 H23 F3 N2 O2.

U(eq) is defined as one third of the trace of the orthogonalized U^{ij} tensor.

	x	y	z	U(eq)
C(1)	9024(7)	2334(6)	2227(7)	50(2)
C(2)	9082(7)	1697(7)	1327(8)	58(3)
C(3)	9877(7)	3014(6)	500(7)	45(2)
C(4)	10285(6)	3346(7)	-398(7)	57(3)
C(5)	10667(7)	4347(8)	-484(8)	59(3)
C(6)	10643(7)	5064(7)	386(8)	55(3)
C(7)	10263(6)	4780(6)	1295(6)	42(2)
C(8)	9864(6)	3736(6)	1382(7)	39(2)
C(9)	9415(6)	3343(6)	2279(7)	42(2)
C(10)	11103(8)	6818(7)	1061(8)	82(3)
C(11)	9329(6)	3986(6)	3328(7)	43(2)
C(12)	10445(7)	4177(7)	4041(8)	51(2)
C(13)	8720(7)	5042(6)	3100(6)	43(2)
C(14)	8459(6)	5653(6)	4095(6)	51(2)
C(15)	7391(6)	6200(6)	3714(7)	51(2)
C(16)	7412(7)	6842(7)	2661(8)	58(2)

C(17)	7475(7)	6012(6)	1752(6)	53(2)
C(18)	6844(6)	4554(6)	2671(7)	51(2)
C(19)	6523(7)	5364(7)	3498(8)	70(3)
C(20)	8259(7)	7692(6)	2814(6)	74(2)
C(21)	8642(8)	8185(8)	2121(7)	119(4)
C(22)	9770(6)	10000(6)	6354(7)	42(2)
C(23)	10153(6)	8952(6)	6294(7)	49(2)
C(24)	10488(7)	8593(7)	5383(8)	52(2)
C(25)	10534(7)	9241(8)	4513(8)	60(3)
C(26)	10174(6)	10251(7)	4521(7)	53(2)
C(27)	9780(6)	10667(7)	5431(7)	43(2)
C(28)	9088(7)	12077(6)	6206(7)	50(2)
C(29)	9018(6)	11475(6)	7135(7)	43(2)
C(30)	9345(6)	10435(6)	7241(6)	36(2)
C(31)	10904(8)	6857(7)	6201(9)	97(4)
C(32)	9242(6)	9858(6)	8328(7)	41(2)
C(33)	10351(7)	9625(7)	9039(8)	56(3)
C(34)	8578(6)	8817(6)	8088(7)	50(2)
C(35)	8274(6)	8315(6)	9089(7)	56(2)
C(36)	7137(7)	7827(6)	8758(8)	59(3)
C(37)	7123(7)	7191(7)	7706(7)	68(3)
C(38)	7232(7)	7970(7)	6757(7)	66(3)

C(39)	6752(6)	9491(6)	7661(7)	52(2)
C(40)	6333(7)	8717(6)	8487(7)	56(2)
C(41)	6148(7)	9326(7)	9490(8)	92(3)
C(42)	5286(8)	9572(7)	9758(8)	113(3)
C(43)	3733(6)	-1256(6)	5555(7)	43(2)
C(44)	3334(6)	-204(6)	5662(7)	48(2)
C(45)	2930(7)	68(8)	6563(9)	57(3)
C(46)	2927(7)	-626(8)	7432(8)	64(3)
C(47)	3294(7)	-1641(7)	7358(8)	60(3)
C(48)	3714(6)	-1968(6)	6443(7)	46(2)
C(49)	4508(7)	-3298(7)	5620(8)	65(3)
C(50)	4565(7)	-2661(7)	4708(7)	50(2)
C(51)	4174(6)	-1644(6)	4632(7)	41(2)
C(52)	2500(8)	1837(7)	5892(8)	75(3)
C(53)	4281(7)	-1000(6)	3615(7)	47(2)
C(54)	3140(7)	-836(7)	2909(7)	49(2)
C(55)	4869(6)	49(6)	3847(6)	42(2)
C(56)	5132(6)	645(6)	2837(7)	56(3)
C(57)	6198(6)	1216(7)	3207(7)	55(2)
C(58)	6195(7)	1836(6)	4288(7)	57(2)
C(59)	6119(7)	1005(6)	5173(7)	55(2)
C(60)	6771(6)	-428(6)	4270(7)	59(3)

C(61)	7078(7)	376(7)	3435(8)	76(3)
C(62)	5345(7)	2673(6)	4116(6)	77(2)
C(63)	4946(8)	3194(9)	4819(7)	132(4)
C(64)	3828(6)	4983(6)	10598(7)	44(2)
C(65)	3451(6)	3923(6)	10663(8)	51(2)
C(66)	3079(7)	3571(7)	11555(8)	53(3)
C(67)	3065(7)	4229(8)	12437(8)	61(3)
C(68)	3401(6)	5250(7)	12438(7)	54(2)
C(69)	3798(6)	5635(7)	11506(7)	45(2)
C(70)	4505(7)	7052(6)	10745(7)	55(3)
C(71)	4571(6)	6459(6)	9792(7)	49(2)
C(72)	4241(6)	5418(6)	9683(6)	37(2)
C(73)	2699(8)	1844(7)	10761(9)	97(4)
C(74)	4357(7)	4848(6)	8605(7)	44(2)
C(75)	3237(7)	4620(8)	7916(8)	59(3)
C(76)	5004(7)	3816(6)	8868(7)	55(3)
C(77)	5314(6)	3326(6)	7817(7)	61(3)
C(78)	6469(7)	2833(7)	8184(7)	61(3)
C(79)	6463(7)	2164(7)	9232(8)	71(3)
C(80)	6345(8)	2964(7)	10167(8)	75(3)
C(81)	6869(7)	4477(6)	9284(7)	58(3)
C(82)	7276(7)	3725(7)	8465(7)	58(2)

C(83)	7437(7)	4295(7)	7455(9)	92(3)
C(84)	8281(10)	4563(7)	7175(8)	126(4)
F(1)	11055(4)	3305(4)	4077(4)	72(2)
F(2)	10418(4)	4400(4)	5087(4)	69(2)
F(3)	10997(4)	4956(4)	3675(4)	67(2)
F(4)	11017(4)	10442(4)	9052(4)	75(2)
F(5)	10847(4)	8781(4)	8701(5)	78(2)
F(6)	10298(4)	9413(4)	10067(4)	67(2)
F(7)	3158(4)	-597(4)	1854(4)	75(2)
F(8)	2522(4)	-1694(4)	2862(4)	70(2)
F(9)	2597(4)	-34(4)	3264(4)	70(2)
F(10)	2577(4)	5444(4)	7881(4)	72(2)
F(11)	3295(4)	4420(4)	6868(4)	74(2)
F(12)	2736(4)	3783(4)	8230(5)	78(2)
N(1)	9493(5)	2000(5)	467(6)	49(2)
N(2)	7754(5)	4933(5)	2228(5)	49(2)
N(3)	9443(6)	11683(5)	5355(6)	52(2)
N(4)	7621(6)	9005(5)	7210(6)	56(2)
N(5)	5842(5)	-66(5)	4701(5)	45(2)
N(6)	4098(5)	-3005(5)	6467(6)	52(2)
N(7)	4135(6)	6664(5)	11584(6)	55(2)
N(8)	5979(6)	4003(6)	9728(6)	54(2)

O(1)	8751(4)	3388(4)	3998(5)	54(2)
O(2)	11081(5)	6040(5)	214(6)	74(2)
O(3)	10886(5)	7580(5)	5288(5)	75(2)
O(4)	8749(4)	10534(4)	8982(5)	54(2)
O(5)	2524(5)	1059(5)	6737(6)	80(2)
O(6)	4839(4)	-1609(4)	2945(5)	55(2)
O(7)	4871(4)	5500(4)	7964(5)	54(2)
O(8)	2707(5)	2565(5)	11658(6)	79(2)

Table 3. Bond lengths [Å] and angles [°] for C21 H23 F3 N2 O2

C(1)-C(9)	1.358(10)
C(1)-C(2)	1.410(12)
C(2)-N(1)	1.346(11)
C(3)-N(1)	1.361(9)
C(3)-C(4)	1.398(11)
C(3)-C(8)	1.445(11)
C(4)-C(5)	1.360(11)
C(5)-C(6)	1.431(13)
C(6)-C(7)	1.376(12)
C(6)-O(2)	1.378(9)
C(7)-C(8)	1.418(10)
C(8)-C(9)	1.447(11)
C(9)-C(11)	1.580(11)
C(10)-O(2)	1.451(11)
C(11)-O(1)	1.427(9)
C(11)-C(12)	1.525(11)
C(11)-C(13)	1.532(10)
C(12)-F(1)	1.332(9)
C(12)-F(3)	1.331(10)
C(12)-F(2)	1.363(10)

C(13)-N(2)	1.478(9)
C(13)-C(14)	1.565(11)
C(14)-C(15)	1.493(10)
C(15)-C(19)	1.495(10)
C(15)-C(16)	1.567(12)
C(16)-C(20)	1.489(10)
C(16)-C(17)	1.571(11)
C(17)-N(2)	1.501(9)
C(18)-N(2)	1.438(9)
C(18)-C(19)	1.569(11)
C(20)-C(21)	1.244(9)
C(22)-C(23)	1.410(10)
C(22)-C(30)	1.441(11)
C(22)-C(27)	1.444(12)
C(23)-C(24)	1.378(11)
C(24)-O(3)	1.382(9)
C(24)-C(25)	1.383(12)
C(25)-C(26)	1.349(11)
C(26)-C(27)	1.437(11)
C(27)-N(3)	1.344(9)
C(28)-N(3)	1.337(10)
C(28)-C(29)	1.419(11)

C(29)-C(30)	1.371(9)
C(30)-C(32)	1.586(11)
C(31)-O(3)	1.470(12)
C(32)-O(4)	1.409(9)
C(32)-C(33)	1.527(11)
C(32)-C(34)	1.548(10)
C(33)-F(4)	1.319(9)
C(33)-F(5)	1.340(10)
C(33)-F(6)	1.347(10)
C(34)-N(4)	1.487(10)
C(34)-C(35)	1.531(11)
C(35)-C(36)	1.525(10)
C(36)-C(40)	1.498(10)
C(36)-C(37)	1.555(12)
C(37)-C(38)	1.579(11)
C(38)-N(4)	1.470(10)
C(39)-N(4)	1.451(10)
C(39)-C(40)	1.591(11)
C(40)-C(41)	1.541(12)
C(41)-C(42)	1.225(10)
C(43)-C(44)	1.431(10)
C(43)-C(48)	1.444(12)

C(43)-C(51)	1.468(11)
C(44)-C(45)	1.377(12)
C(45)-O(5)	1.380(10)
C(45)-C(46)	1.409(13)
C(46)-C(47)	1.367(11)
C(47)-C(48)	1.423(11)
C(48)-N(6)	1.389(9)
C(49)-N(6)	1.327(11)
C(49)-C(50)	1.422(12)
C(50)-C(51)	1.367(10)
C(51)-C(53)	1.552(11)
C(52)-O(5)	1.449(10)
C(53)-O(6)	1.421(9)
C(53)-C(55)	1.512(10)
C(53)-C(54)	1.542(11)
C(54)-F(8)	1.321(9)
C(54)-F(9)	1.339(10)
C(54)-F(7)	1.378(10)
C(55)-N(5)	1.471(9)
C(55)-C(56)	1.574(11)
C(56)-C(57)	1.503(10)
C(57)-C(61)	1.510(10)

C(57)-C(58)	1.580(12)
C(58)-C(62)	1.479(10)
C(58)-C(59)	1.551(11)
C(59)-N(5)	1.490(9)
C(60)-N(5)	1.443(10)
C(60)-C(61)	1.565(11)
C(62)-C(63)	1.281(9)
C(64)-C(69)	1.421(12)
C(64)-C(65)	1.423(10)
C(64)-C(72)	1.463(11)
C(65)-C(66)	1.376(12)
C(66)-O(8)	1.363(10)
C(66)-C(67)	1.396(13)
C(67)-C(68)	1.352(11)
C(68)-C(69)	1.450(11)
C(69)-N(7)	1.359(10)
C(70)-N(7)	1.331(11)
C(70)-C(71)	1.438(12)
C(71)-C(72)	1.372(9)
C(72)-C(74)	1.577(11)
C(73)-O(8)	1.455(12)
C(74)-O(7)	1.394(9)

C(74)-C(75)	1.525(11)
C(74)-C(76)	1.532(10)
C(75)-F(10)	1.319(10)
C(75)-F(12)	1.324(10)
C(75)-F(11)	1.370(11)
C(76)-N(8)	1.487(10)
C(76)-C(77)	1.583(11)
C(77)-C(78)	1.553(10)
C(78)-C(82)	1.503(10)
C(78)-C(79)	1.576(12)
C(79)-C(80)	1.585(12)
C(80)-N(8)	1.460(10)
C(81)-N(8)	1.462(10)
C(81)-C(82)	1.561(11)
C(82)-C(83)	1.516(12)
C(83)-C(84)	1.218(11)

C(9)-C(1)-C(2)	119.9(9)
N(1)-C(2)-C(1)	125.6(8)
N(1)-C(3)-C(4)	115.8(8)
N(1)-C(3)-C(8)	124.0(8)
C(4)-C(3)-C(8)	120.2(8)

C(5)-C(4)-C(3)	122.0(9)
C(4)-C(5)-C(6)	117.6(9)
C(7)-C(6)-O(2)	125.0(9)
C(7)-C(6)-C(5)	123.1(8)
O(2)-C(6)-C(5)	111.9(9)
C(6)-C(7)-C(8)	119.2(8)
C(7)-C(8)-C(3)	117.9(8)
C(7)-C(8)-C(9)	124.9(8)
C(3)-C(8)-C(9)	117.2(7)
C(1)-C(9)-C(8)	118.1(8)
C(1)-C(9)-C(11)	116.0(8)
C(8)-C(9)-C(11)	125.9(7)
O(1)-C(11)-C(12)	103.6(7)
O(1)-C(11)-C(13)	106.4(6)
C(12)-C(11)-C(13)	109.7(7)
O(1)-C(11)-C(9)	110.8(7)
C(12)-C(11)-C(9)	112.5(7)
C(13)-C(11)-C(9)	113.3(7)
F(1)-C(12)-F(3)	107.0(8)
F(1)-C(12)-F(2)	104.8(7)
F(3)-C(12)-F(2)	107.3(7)
F(1)-C(12)-C(11)	109.8(7)

F(3)-C(12)-C(11)	112.4(7)
F(2)-C(12)-C(11)	115.0(8)
N(2)-C(13)-C(11)	111.3(6)
N(2)-C(13)-C(14)	112.8(6)
C(11)-C(13)-C(14)	116.5(7)
C(15)-C(14)-C(13)	105.9(7)
C(14)-C(15)-C(19)	107.6(7)
C(14)-C(15)-C(16)	110.8(7)
C(19)-C(15)-C(16)	109.6(8)
C(20)-C(16)-C(15)	112.7(7)
C(20)-C(16)-C(17)	116.2(7)
C(15)-C(16)-C(17)	107.2(7)
N(2)-C(17)-C(16)	110.2(7)
N(2)-C(18)-C(19)	111.5(7)
C(15)-C(19)-C(18)	108.3(7)
C(21)-C(20)-C(16)	128.6(9)
C(23)-C(22)-C(30)	125.2(8)
C(23)-C(22)-C(27)	116.5(8)
C(30)-C(22)-C(27)	118.3(7)
C(24)-C(23)-C(22)	120.8(8)
C(23)-C(24)-O(3)	123.1(9)
C(23)-C(24)-C(25)	122.7(8)

O(3)-C(24)-C(25)	113.9(9)
C(26)-C(25)-C(24)	119.1(9)
C(25)-C(26)-C(27)	120.9(9)
N(3)-C(27)-C(26)	116.1(8)
N(3)-C(27)-C(22)	124.1(9)
C(26)-C(27)-C(22)	119.8(8)
N(3)-C(28)-C(29)	123.7(8)
C(30)-C(29)-C(28)	121.9(8)
C(29)-C(30)-C(22)	115.6(7)
C(29)-C(30)-C(32)	116.9(7)
C(22)-C(30)-C(32)	127.5(7)
O(4)-C(32)-C(33)	102.3(7)
O(4)-C(32)-C(34)	110.6(7)
C(33)-C(32)-C(34)	110.0(7)
O(4)-C(32)-C(30)	110.6(6)
C(33)-C(32)-C(30)	112.9(7)
C(34)-C(32)-C(30)	110.2(7)
F(4)-C(33)-F(5)	107.3(8)
F(4)-C(33)-F(6)	106.8(8)
F(5)-C(33)-F(6)	105.3(7)
F(4)-C(33)-C(32)	110.7(7)
F(5)-C(33)-C(32)	112.5(8)

F(6)-C(33)-C(32)	114.0(8)
N(4)-C(34)-C(35)	113.5(7)
N(4)-C(34)-C(32)	109.5(6)
C(35)-C(34)-C(32)	113.2(7)
C(36)-C(35)-C(34)	107.4(7)
C(40)-C(36)-C(35)	107.8(6)
C(40)-C(36)-C(37)	106.9(7)
C(35)-C(36)-C(37)	107.7(7)
C(36)-C(37)-C(38)	110.3(7)
N(4)-C(38)-C(37)	108.7(7)
N(4)-C(39)-C(40)	111.3(7)
C(36)-C(40)-C(41)	112.4(7)
C(36)-C(40)-C(39)	108.8(7)
C(41)-C(40)-C(39)	111.0(7)
C(42)-C(41)-C(40)	129.1(10)
C(44)-C(43)-C(48)	116.3(8)
C(44)-C(43)-C(51)	124.9(8)
C(48)-C(43)-C(51)	118.8(7)
C(45)-C(44)-C(43)	119.8(8)
C(44)-C(45)-O(5)	124.1(9)
C(44)-C(45)-C(46)	123.5(9)
O(5)-C(45)-C(46)	112.4(9)

C(47)-C(46)-C(45)	118.4(10)
C(46)-C(47)-C(48)	120.4(9)
N(6)-C(48)-C(47)	115.6(8)
N(6)-C(48)-C(43)	122.9(8)
C(47)-C(48)-C(43)	121.4(8)
N(6)-C(49)-C(50)	126.1(9)
C(51)-C(50)-C(49)	120.9(9)
C(50)-C(51)-C(43)	115.9(8)
C(50)-C(51)-C(53)	117.5(8)
C(43)-C(51)-C(53)	126.5(7)
O(6)-C(53)-C(55)	108.4(6)
O(6)-C(53)-C(54)	103.0(7)
C(55)-C(53)-C(54)	110.7(7)
O(6)-C(53)-C(51)	110.2(7)
C(55)-C(53)-C(51)	114.2(7)
C(54)-C(53)-C(51)	109.8(6)
F(8)-C(54)-F(9)	107.8(8)
F(8)-C(54)-F(7)	104.6(7)
F(9)-C(54)-F(7)	105.4(7)
F(8)-C(54)-C(53)	112.4(7)
F(9)-C(54)-C(53)	111.9(7)
F(7)-C(54)-C(53)	114.2(7)

N(5)-C(55)-C(53)	110.9(7)
N(5)-C(55)-C(56)	112.2(6)
C(53)-C(55)-C(56)	115.2(7)
C(57)-C(56)-C(55)	106.3(7)
C(56)-C(57)-C(61)	106.8(7)
C(56)-C(57)-C(58)	111.2(7)
C(61)-C(57)-C(58)	107.5(7)
C(62)-C(58)-C(59)	116.6(8)
C(62)-C(58)-C(57)	110.1(7)
C(59)-C(58)-C(57)	107.8(7)
N(5)-C(59)-C(58)	111.2(7)
N(5)-C(60)-C(61)	111.6(7)
C(57)-C(61)-C(60)	108.8(7)
C(63)-C(62)-C(58)	128.5(8)
C(69)-C(64)-C(65)	115.8(8)
C(69)-C(64)-C(72)	119.6(7)
C(65)-C(64)-C(72)	124.5(8)
C(66)-C(65)-C(64)	121.1(9)
O(8)-C(66)-C(65)	123.5(9)
O(8)-C(66)-C(67)	114.8(9)
C(65)-C(66)-C(67)	121.8(9)
C(68)-C(67)-C(66)	121.0(9)

C(67)-C(68)-C(69)	118.1(9)
N(7)-C(69)-C(64)	123.7(8)
N(7)-C(69)-C(68)	114.0(9)
C(64)-C(69)-C(68)	122.3(8)
N(7)-C(70)-C(71)	124.5(8)
C(72)-C(71)-C(70)	121.1(8)
C(71)-C(72)-C(64)	114.9(8)
C(71)-C(72)-C(74)	116.6(7)
C(64)-C(72)-C(74)	128.5(7)
O(7)-C(74)-C(75)	104.2(7)
O(7)-C(74)-C(76)	110.3(7)
C(75)-C(74)-C(76)	110.5(7)
O(7)-C(74)-C(72)	111.5(7)
C(75)-C(74)-C(72)	111.0(7)
C(76)-C(74)-C(72)	109.2(7)
F(10)-C(75)-F(12)	108.1(8)
F(10)-C(75)-F(11)	105.0(7)
F(12)-C(75)-F(11)	105.1(8)
F(10)-C(75)-C(74)	111.5(8)
F(12)-C(75)-C(74)	114.1(8)
F(11)-C(75)-C(74)	112.4(8)
N(8)-C(76)-C(74)	110.3(7)

N(8)-C(76)-C(77)	112.7(7)
C(74)-C(76)-C(77)	110.4(7)
C(78)-C(77)-C(76)	105.2(7)
C(82)-C(78)-C(77)	108.1(7)
C(82)-C(78)-C(79)	108.0(7)
C(77)-C(78)-C(79)	108.3(7)
C(78)-C(79)-C(80)	108.0(7)
N(8)-C(80)-C(79)	110.5(8)
N(8)-C(81)-C(82)	112.0(7)
C(78)-C(82)-C(83)	110.0(8)
C(78)-C(82)-C(81)	109.0(7)
C(83)-C(82)-C(81)	112.8(7)
C(84)-C(83)-C(82)	129.7(11)
C(2)-N(1)-C(3)	115.2(8)
C(18)-N(2)-C(13)	109.1(7)
C(18)-N(2)-C(17)	108.6(6)
C(13)-N(2)-C(17)	108.1(6)
C(28)-N(3)-C(27)	116.3(8)
C(39)-N(4)-C(38)	108.3(7)
C(39)-N(4)-C(34)	108.8(7)
C(38)-N(4)-C(34)	108.1(7)
C(60)-N(5)-C(55)	111.0(7)

C(60)-N(5)-C(59)	107.3(6)
C(55)-N(5)-C(59)	107.6(6)
C(49)-N(6)-C(48)	115.3(8)
C(70)-N(7)-C(69)	116.1(8)
C(80)-N(8)-C(81)	108.0(7)
C(80)-N(8)-C(76)	106.9(7)
C(81)-N(8)-C(76)	110.7(7)
C(6)-O(2)-C(10)	116.0(8)
C(24)-O(3)-C(31)	117.0(8)
C(45)-O(5)-C(52)	116.7(8)
C(66)-O(8)-C(73)	117.2(8)

Symmetry transformations used to generate equivalent atoms:

Table 4. Anisotropic displacement parameters ($Å^2 x\ 10^3$) for C21H23F3N2O2.

The anisotropic displacement factor exponent takes the form: $-2\pi^2[\ h^2\ a^{*2}U^{11} + ... + 2\ h\ k\ a^*\ b^*\ U^{12}\ ]$

	U^{11}	U^{22}	U^{33}	U^{23}	U^{13}	U^{12}
C(1)	62(6)	44(5)	44(6)	0(5)	7(5)	8(5)
C(2)	43(5)	63(6)	66(7)	13(5)	3(5)	-12(5)
C(3)	48(5)	44(5)	44(6)	-3(5)	11(4)	8(4)
C(4)	42(5)	76(6)	53(7)	-14(5)	7(5)	-4(5)
C(5)	40(5)	94(7)	42(6)	-4(5)	6(4)	-11(5)
C(6)	42(5)	56(6)	66(8)	5(5)	6(5)	-8(4)
C(7)	38(5)	60(6)	28(5)	9(4)	4(4)	5(4)
C(8)	30(4)	47(5)	35(6)	10(4)	-5(4)	4(4)
C(9)	43(5)	35(5)	45(6)	2(4)	2(4)	16(4)
C(10)	66(6)	72(7)	104(9)	30(6)	7(6)	-5(5)
C(11)	44(5)	49(5)	38(6)	4(4)	10(5)	-1(4)
C(12)	55(6)	50(6)	45(7)	-9(5)	-3(5)	5(5)
C(13)	50(5)	44(5)	30(5)	-6(4)	-8(4)	6(4)
C(14)	66(5)	47(5)	37(6)	9(4)	8(4)	14(4)
C(15)	55(5)	54(5)	48(6)	-11(4)	16(4)	17(4)
C(16)	48(5)	57(5)	64(7)	-5(5)	-5(4)	19(4)

C(17)	63(5)	49(5)	39(5)	-2(4)	-10(4)	24(4)
C(18)	44(5)	55(5)	50(6)	-4(4)	-1(4)	0(4)
C(19)	51(5)	84(7)	78(7)	-24(6)	18(5)	1(5)
C(20)	90(7)	65(5)	57(6)	10(4)	-12(5)	2(5)
C(21)	152(10)	138(9)	54(6)	22(6)	-16(6)	-62(7)
C(22)	41(5)	37(5)	43(6)	-3(4)	0(4)	-2(4)
C(23)	44(5)	48(5)	52(7)	-3(5)	0(5)	3(4)
C(24)	54(5)	45(5)	53(7)	-12(5)	-4(5)	18(4)
C(25)	44(5)	83(7)	56(7)	-5(6)	20(5)	9(5)
C(26)	43(5)	70(6)	41(6)	10(5)	1(4)	-1(4)
C(27)	35(5)	49(5)	41(6)	-8(5)	-2(4)	-8(4)
C(28)	57(6)	39(5)	51(7)	8(5)	7(5)	4(4)
C(29)	45(5)	44(5)	41(6)	-10(4)	8(4)	8(4)
C(30)	37(5)	34(5)	34(6)	-1(4)	2(4)	0(4)
C(31)	102(8)	54(6)	117(10)	-19(6)	-25(7)	40(6)
C(32)	33(5)	40(5)	46(6)	-7(4)	-2(4)	10(4)
C(33)	53(6)	57(6)	60(8)	-5(5)	16(6)	-6(5)
C(34)	46(5)	48(5)	55(7)	9(5)	4(5)	-3(4)
C(35)	60(6)	56(5)	49(6)	14(4)	-1(5)	-1(4)
C(36)	59(6)	49(5)	65(7)	21(5)	3(5)	-12(5)
C(37)	64(6)	68(6)	69(7)	-13(5)	1(5)	-12(5)
C(38)	70(6)	71(6)	54(7)	-6(5)	8(5)	-11(5)

C(39)	36(5)	63(5)	55(6)	14(4)	2(4)	-4(4)
C(40)	59(5)	46(5)	57(6)	5(4)	-3(5)	-11(4)
C(41)	54(6)	101(7)	126(9)	-13(6)	29(6)	7(5)
C(42)	132(10)	104(8)	110(8)	6(6)	42(8)	-14(7)
C(43)	25(4)	55(5)	47(6)	1(5)	1(4)	-2(4)
C(44)	39(5)	49(5)	54(7)	-7(5)	4(5)	8(4)
C(45)	33(5)	66(6)	70(8)	0(6)	6(5)	7(4)
C(46)	53(6)	79(7)	61(7)	-6(6)	12(5)	25(5)
C(47)	48(6)	75(7)	64(7)	2(5)	27(5)	8(5)
C(48)	42(5)	53(6)	45(6)	0(5)	10(4)	2(4)
C(49)	61(7)	55(6)	75(8)	-12(6)	4(6)	14(5)
C(50)	57(6)	61(6)	36(6)	5(5)	15(5)	6(5)
C(51)	28(4)	47(5)	43(6)	-2(4)	-7(4)	5(4)
C(52)	70(6)	71(7)	79(8)	-20(6)	6(6)	8(5)
C(53)	45(5)	51(5)	49(7)	3(5)	20(5)	-8(4)
C(54)	47(6)	61(6)	32(6)	13(5)	-7(5)	1(5)
C(55)	37(4)	50(5)	37(6)	-5(4)	2(4)	2(4)
C(56)	60(5)	53(5)	53(7)	12(4)	6(5)	3(4)
C(57)	49(5)	66(5)	50(6)	-2(5)	4(4)	-9(4)
C(58)	56(5)	46(5)	63(7)	13(4)	-3(4)	-9(4)
C(59)	67(6)	52(5)	40(6)	6(4)	-6(4)	-16(4)
C(60)	41(5)	60(5)	72(8)	11(5)	1(5)	-3(4)

C(61)	56(6)	103(8)	75(7)	30(6)	23(5)	-3(6)
C(62)	103(7)	66(6)	53(6)	-5(4)	-11(5)	2(5)
C(63)	169(11)	157(10)	58(7)	-8(7)	-6(7)	68(8)
C(64)	40(5)	35(5)	54(7)	-5(5)	-1(4)	8(4)
C(65)	41(5)	40(5)	66(7)	3(5)	-7(5)	0(4)
C(66)	45(5)	56(6)	52(7)	11(5)	-7(5)	-6(4)
C(67)	48(5)	76(7)	61(7)	16(6)	13(5)	-11(5)
C(68)	41(5)	63(6)	59(7)	8(5)	15(5)	5(4)
C(69)	31(5)	54(5)	46(6)	4(5)	1(4)	4(4)
C(70)	76(7)	36(5)	49(7)	-14(5)	2(5)	10(5)
C(71)	44(5)	47(5)	56(7)	7(5)	8(5)	3(4)
C(72)	30(5)	44(5)	34(6)	9(4)	0(4)	6(4)
C(73)	111(8)	43(6)	115(10)	14(6)	-33(7)	-27(5)
C(74)	46(5)	47(5)	36(6)	5(4)	1(4)	1(4)
C(75)	43(6)	76(7)	57(8)	13(6)	3(6)	5(5)
C(76)	54(5)	59(6)	50(7)	3(5)	5(5)	19(5)
C(77)	50(5)	62(5)	63(7)	-33(5)	-9(5)	11(4)
C(78)	58(6)	68(6)	57(7)	-10(5)	8(5)	23(5)
C(79)	72(6)	55(5)	81(8)	1(5)	4(5)	26(5)
C(80)	75(6)	67(6)	82(8)	14(6)	15(6)	20(5)
C(81)	51(5)	53(5)	67(7)	-17(5)	7(5)	17(4)
C(82)	54(5)	65(6)	52(6)	-8(5)	0(5)	13(4)

C(83)	65(6)	96(7)	128(9)	8(6)	51(6)	5(5)
C(84)	207(14)	88(8)	87(8)	13(6)	34(9)	44(9)
F(1)	55(3)	71(4)	82(5)	-14(3)	-10(3)	21(3)
F(2)	74(4)	82(4)	47(4)	-8(3)	-1(3)	0(3)
F(3)	53(3)	77(4)	65(4)	9(3)	-7(3)	-14(3)
F(4)	44(3)	80(4)	89(5)	13(3)	-12(3)	-17(3)
F(5)	63(3)	88(4)	73(4)	-12(3)	-11(3)	27(3)
F(6)	61(3)	88(4)	47(4)	8(3)	-5(3)	5(3)
F(7)	71(4)	107(4)	41(4)	10(3)	-2(3)	-5(3)
F(8)	58(3)	69(4)	77(5)	2(3)	-4(3)	-14(3)
F(9)	61(3)	70(4)	74(4)	-4(3)	2(3)	24(3)
F(10)	51(3)	79(4)	80(5)	1(3)	-4(3)	22(3)
F(11)	65(4)	108(4)	40(4)	-10(3)	-9(3)	16(3)
F(12)	67(3)	79(4)	79(5)	9(3)	-6(3)	-16(3)
N(1)	53(5)	43(4)	52(5)	-5(4)	10(4)	13(3)
N(2)	54(5)	54(4)	38(5)	1(4)	8(4)	9(4)
N(3)	58(5)	40(4)	58(5)	5(4)	14(4)	2(4)
N(4)	46(4)	54(4)	62(6)	2(4)	-2(4)	-15(4)
N(5)	47(4)	53(4)	34(5)	5(3)	6(4)	1(3)
N(6)	48(5)	50(5)	59(6)	1(4)	9(4)	0(4)
N(7)	54(5)	50(5)	61(6)	-2(4)	14(4)	1(4)
N(8)	45(4)	63(5)	51(5)	-1(4)	4(4)	18(4)

O(1)	55(4)	54(4)	56(5)	4(3)	17(3)	11(3)
O(2)	73(4)	71(4)	77(5)	6(4)	12(4)	-15(3)
O(3)	64(4)	71(4)	83(6)	-21(4)	0(4)	18(3)
O(4)	49(4)	70(4)	46(4)	4(3)	19(3)	13(3)
O(5)	78(5)	78(5)	85(5)	-3(4)	21(4)	29(4)
O(6)	50(3)	53(4)	65(5)	-11(3)	15(3)	-15(3)
O(7)	51(3)	66(4)	44(4)	15(3)	11(3)	9(3)
O(8)	69(4)	60(4)	99(6)	20(4)	-3(4)	-17(3)

Table 5. Hydrogen coordinates (x 10^4) and isotropic displacement parameters ($Å^2$x 10^3) for C21 H23 F3 N2 O2.

	x	y	z	U(eq)
H(1)	8712	2057	2797	60
H(2)	8808	993	1327	70
H(4)	10295	2857	-966	68
H(5)	10941	4563	-1100	71
H(7)	10268	5278	1858	51
H(10A)	10351	7000	1122	123
H(10B)	11483	7458	889	123
H(10C)	11488	6521	1742	123
H(13)	9234	5515	2801	52
H(14A)	8403	5153	4683	61
H(14B)	9041	6177	4359	61
H(15)	7234	6691	4284	62
H(16)	6686	7204	2464	70
H(17A)	6762	5982	1249	64
H(17B)	8040	6235	1343	64
H(18A)	7038	3865	3032	61

H(18B)	6207	4438	2084	61
H(19A)	5806	5692	3202	85
H(19B)	6463	4994	4172	85
H(20)	8545	7882	3537	89
H(21A)	8392	8033	1383	143
H(21B)	9185	8714	2331	143
H(23)	10180	8488	6888	59
H(25)	10815	8979	3918	72
H(26)	10181	10693	3916	63
H(28)	8872	12801	6187	60
H(29)	8736	11802	7699	52
H(31A)	11362	7162	6843	146
H(31B)	11205	6170	6042	146
H(31C)	10157	6759	6326	146
H(34)	9063	8299	7807	60
H(35A)	8813	7760	9381	68
H(35B)	8268	8860	9649	68
H(36)	6950	7364	9337	70
H(37A)	6430	6787	7521	82
H(37B)	7737	6678	7813	82
H(38A)	7756	7676	6336	79
H(38B)	6513	8053	6273	79

H(39A)	6134	9673	7075	62
H(39B)	7025	10158	8032	62
H(40)	5617	8408	8127	67
H(41)	6794	9542	9969	110
H(42A)	4608	9382	9318	135
H(42B)	5296	9952	10406	135
H(44)	3348	306	5113	58
H(46)	2675	-395	8055	77
H(47)	3268	-2132	7921	73
H(49)	4790	-3999	5623	78
H(50)	4880	-2945	4144	60
H(52A)	3248	1973	5787	112
H(52B)	2177	2498	6093	112
H(52C)	2060	1564	5224	112
H(55)	4355	522	4147	51
H(56A)	5200	132	2262	67
H(56B)	4544	1157	2556	67
H(57)	6349	1713	2639	67
H(58)	6920	2198	4491	68
H(59A)	6828	971	5681	66
H(59B)	5552	1228	5578	66
H(60A)	6600	-1126	3921	71

H(60B)	7406	-521	4864	71
H(61A)	7793	711	3725	92
H(61B)	7138	0	2764	92
H(62)	5058	2847	3389	93
H(63A)	5198	3058	5561	158
H(63B)	4398	3716	4598	158
H(65)	3456	3450	10080	62
H(67)	2815	3955	13045	74
H(68)	3379	5702	13032	64
H(70)	4742	7771	10778	66
H(71)	4847	6793	9228	59
H(73A)	2222	2130	10121	145
H(73B)	2426	1148	10935	145
H(73C)	3445	1768	10625	145
H(76)	4519	3296	9149	66
H(77A)	4778	2774	7509	74
H(77B)	5330	3884	7271	74
H(78)	6670	2377	7605	74
H(79A)	7153	1756	9425	85
H(79B)	5843	1658	9113	85
H(80A)	5811	2679	10581	90
H(80B)	7060	3039	10660	90

H(81A)	7487	4641	9876	69
H(81B)	6612	5152	8923	69
H(82)	7994	3415	8818	70
H(83)	6783	4469	6968	111
H(84A)	8969	4416	7621	152
H(84B)	8251	4919	6511	152
H(1A)	9146	2884	4280	81
H(4A)	8122	10306	9014	81
H(6)	4417	-2078	2629	83
H(7A)	4411	5922	7620	80

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