Molecular dynamics and NMR reveal the coexistence of H-bond-assisted and through-space J_{FH} coupling in fluorinated amino alcohols.

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Electronic Support Information

NMR Spectra

Compound 1 (*trans*-2-((2-fluorophenyl)amino)cyclohexan-1-ol)

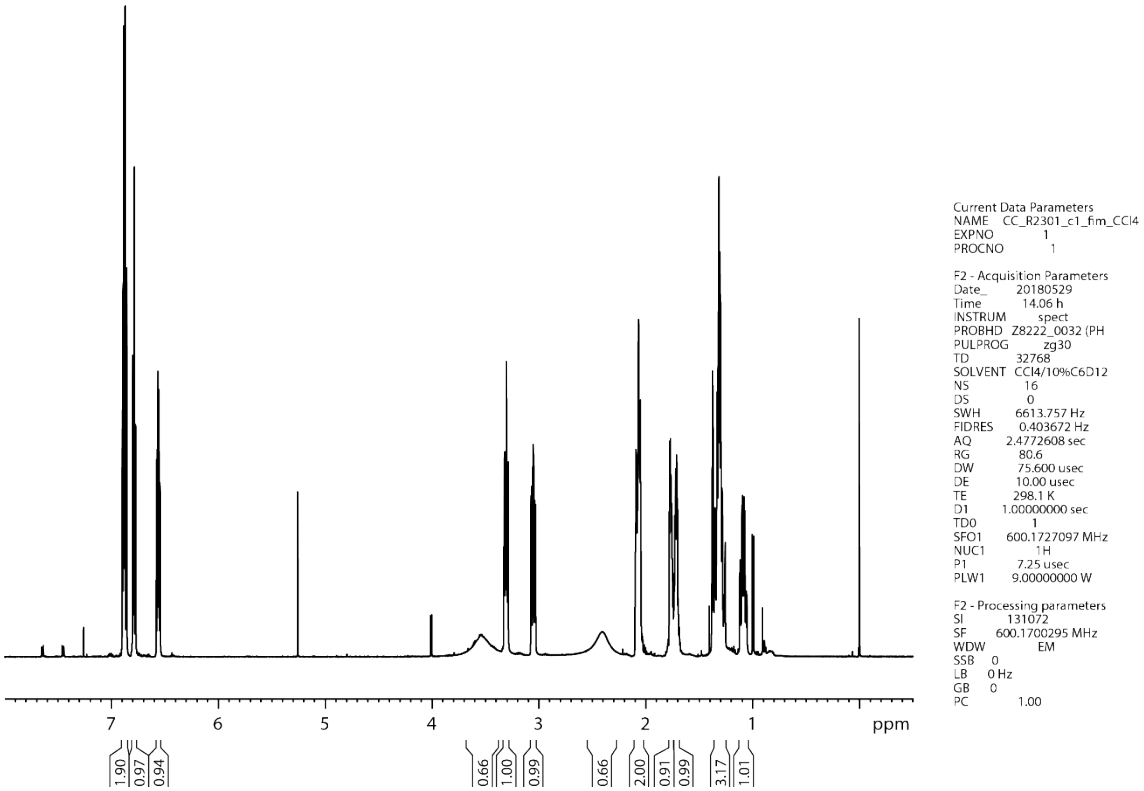

Figure S1. ^{1}H spectrum for compound 1 in CCl_4/C_6D_{12}, obtained at 600 MHz.

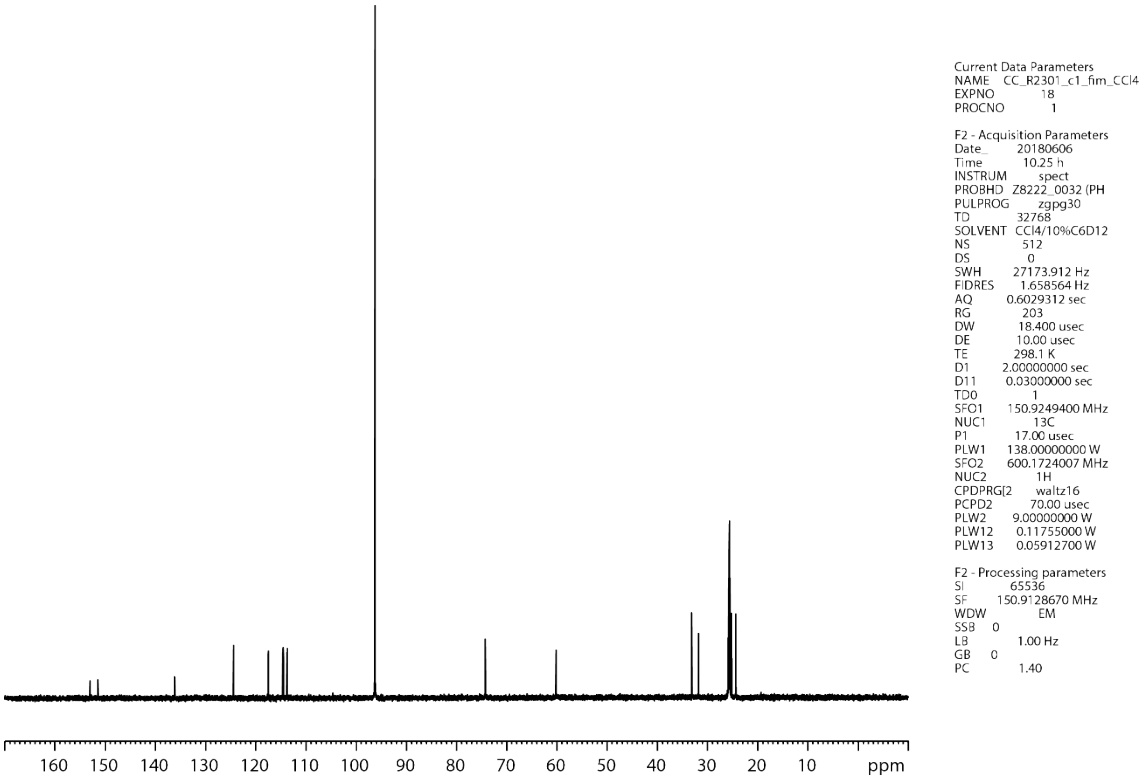

Figure S2. ^{13}C spectrum for compound 1 in CCl_4/C_6D_{12}, obtained at 150 MHz.

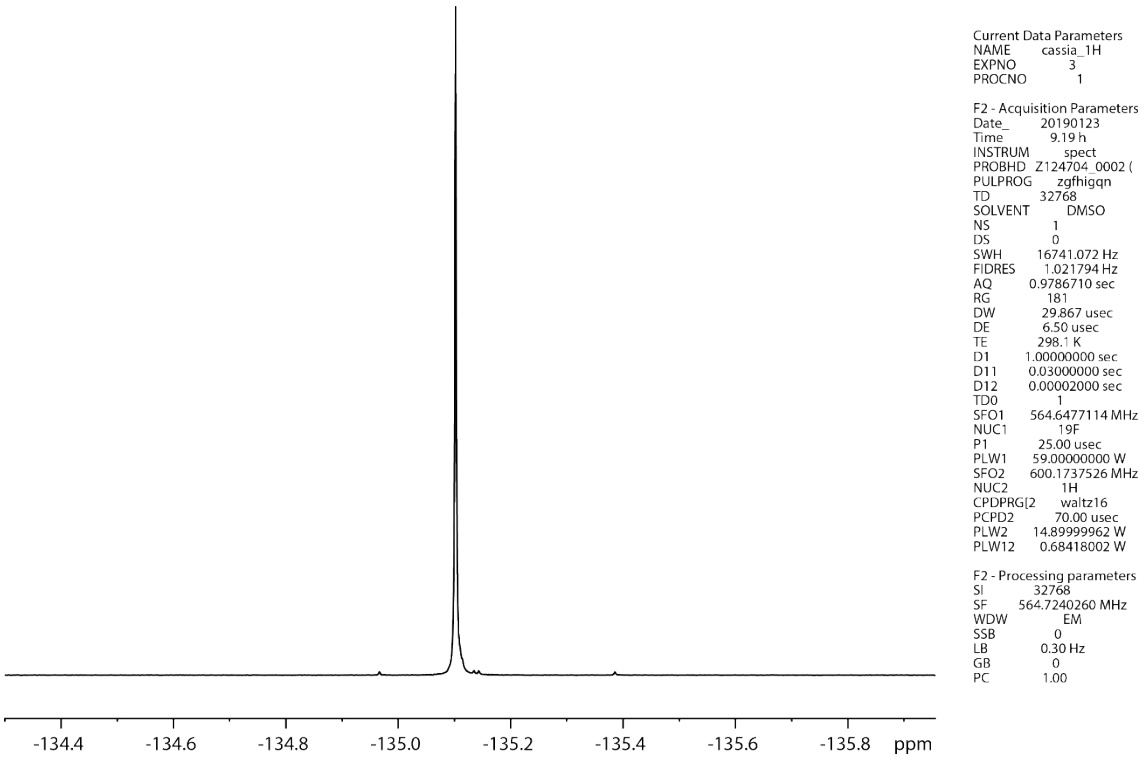

Figure S3. $^{19}F\{^1H\}$ spectrum for compound 1 in CCl_4/C_6D_{12}, obtained at 565 MHz.

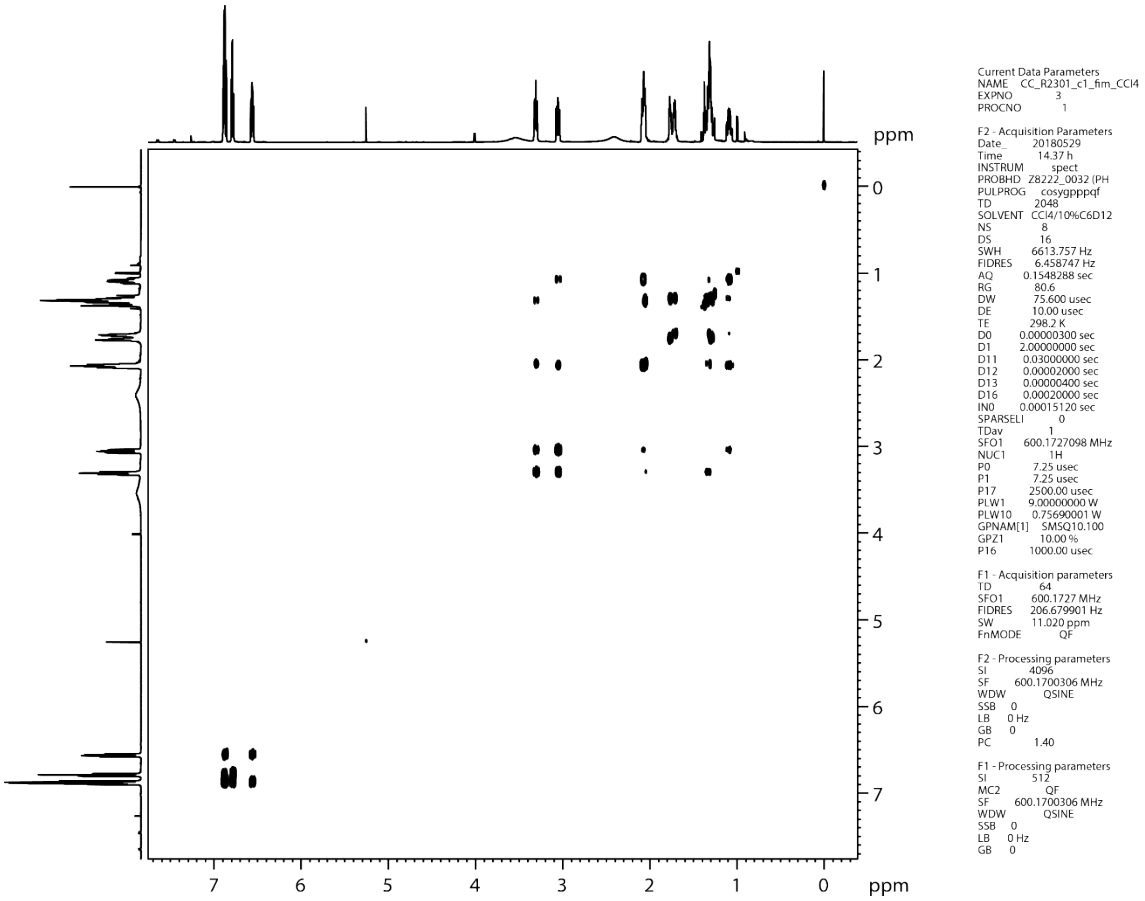

Figure S4. ^{1}H-^{1}H COSY contour map for compound 1 in CCl_4/C_6D_{12}, obtained at 600 MHz.

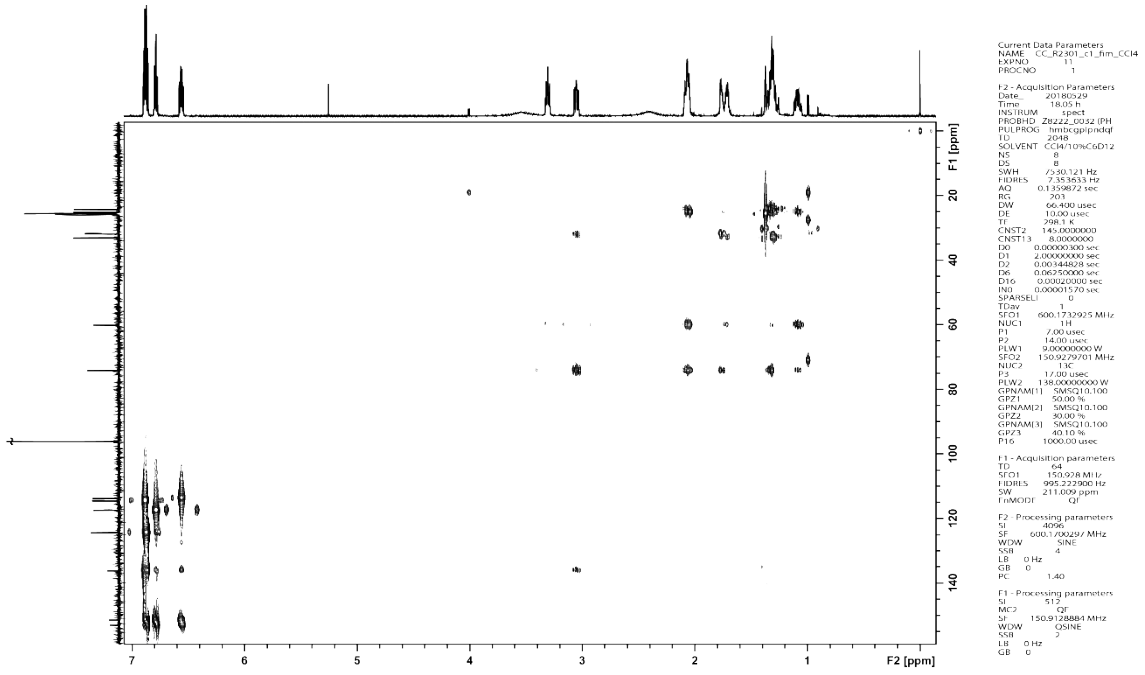

Figure S5. ^{1}H-^{13}C HMBC contour map for compound 1 in CCl_4/C_6D_{12}, obtained at 600 MHz (^{1}H).

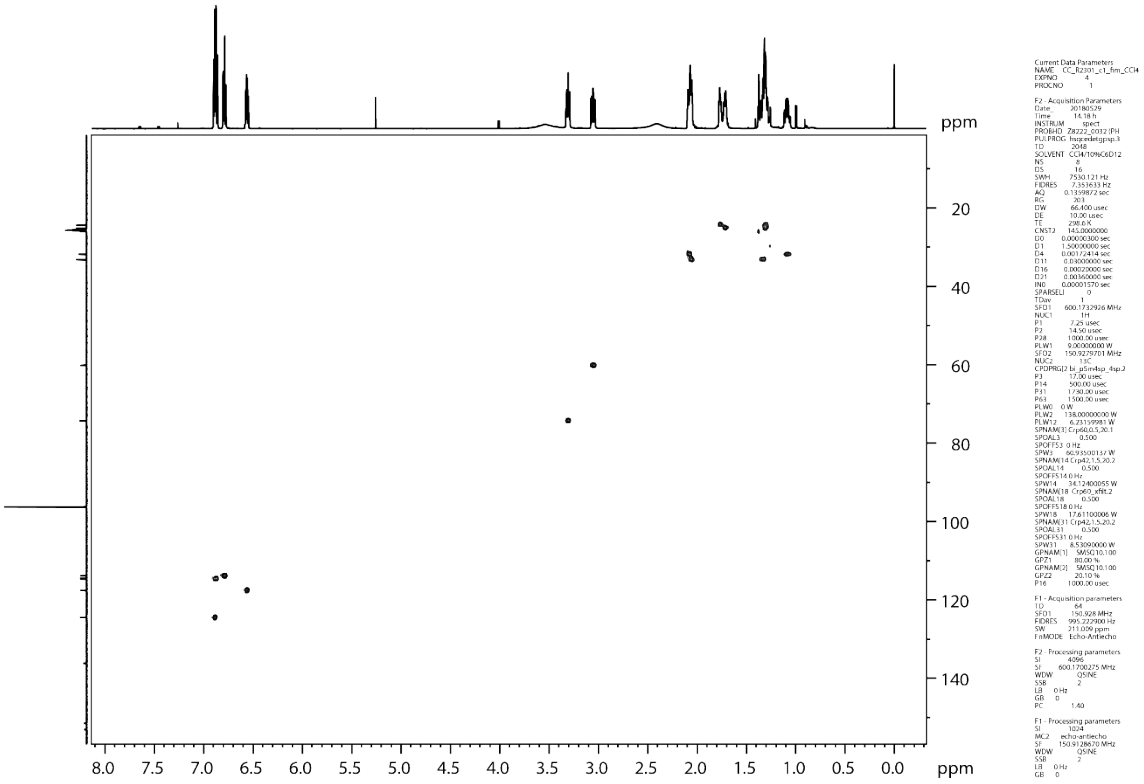

Figure S6. ^{1}H-^{13}C HSQC contour map for compound 1 in CCl_4/C_6D_{12}, obtained at 600 MHz (^{1}H).

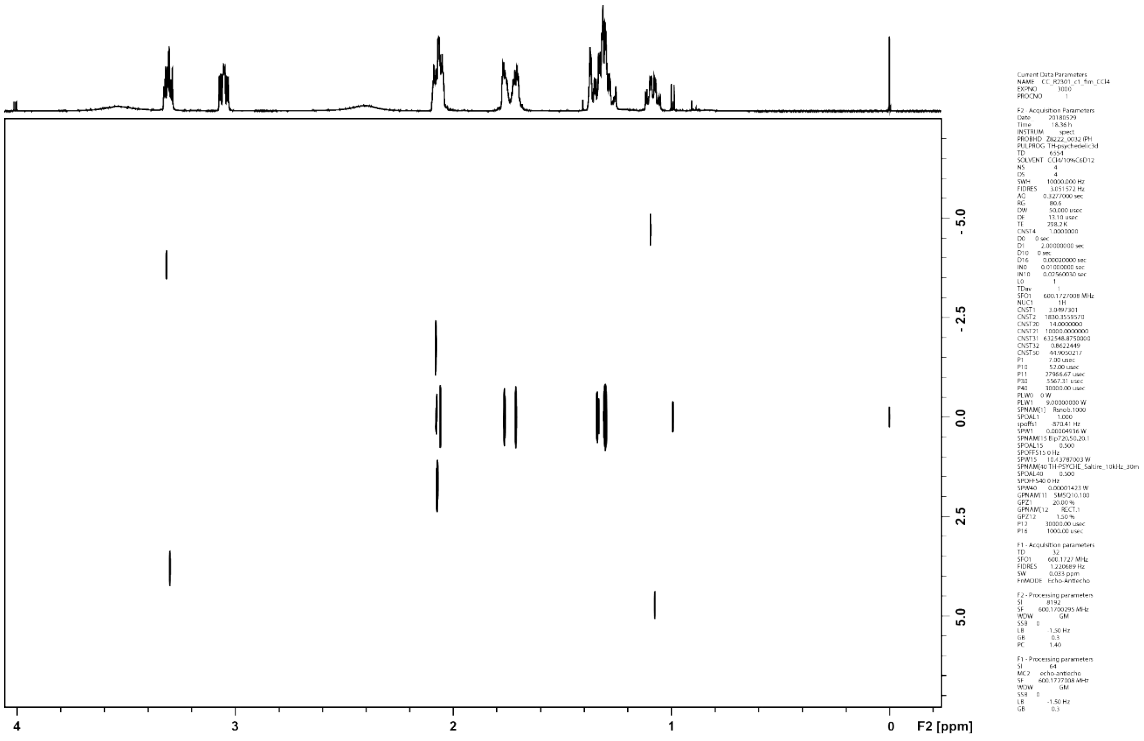

Figure S7. PSYCHEDELIC spectrum in CCl_4/C_6D_{12} with selective pulse applied to H2 of compound 1, obtained at 600 MHz (^{1}H).

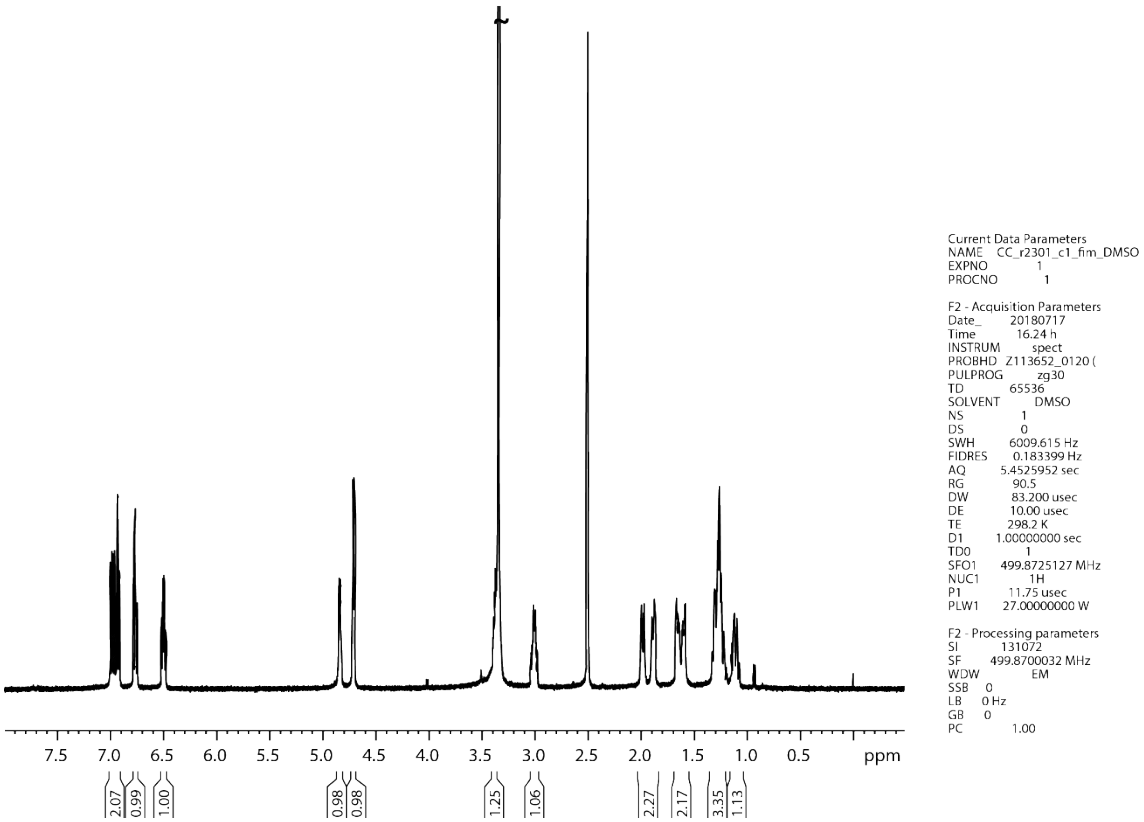

Figure S8. ^{1}H spectrum for compound 1 in DMSO-d_6, obtained at 500 MHz.

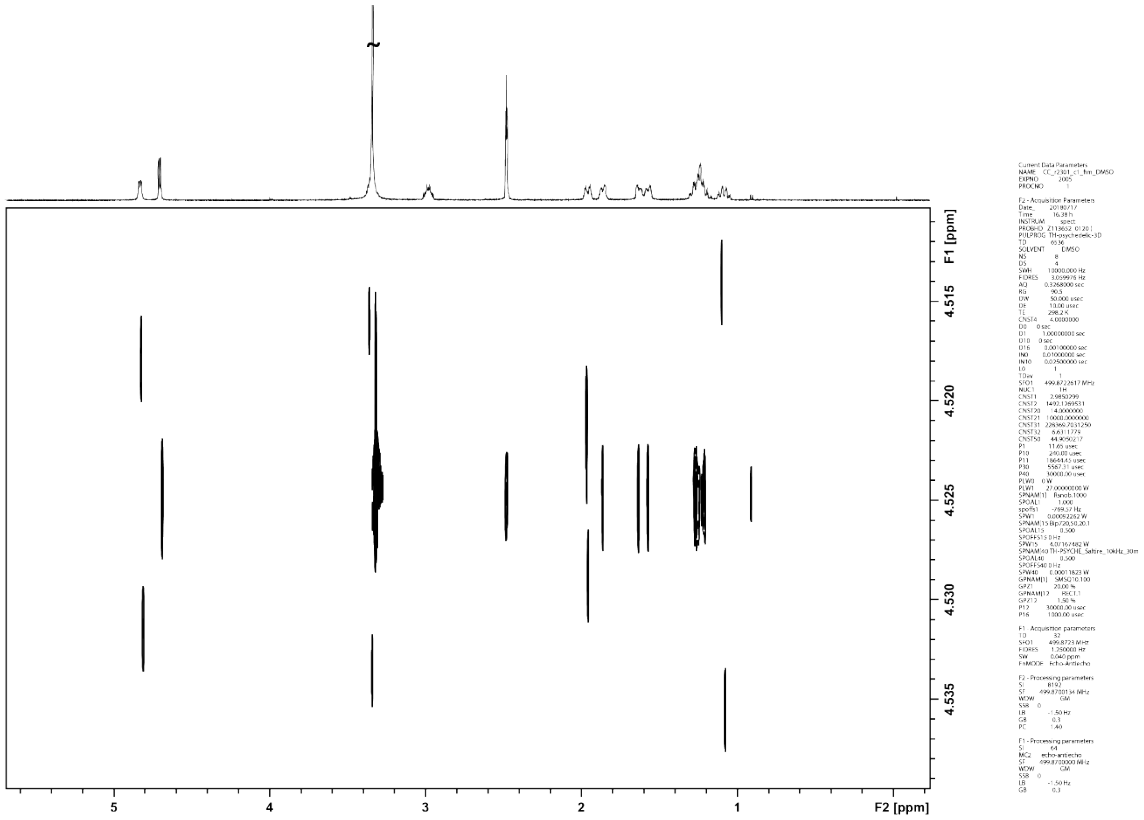

Figure S9. PSYCHEDELIC spectrum in DMSO-d_6 with selective pulse applied to H2 of compound 1, obtained at 500 MHz (^{1}H).

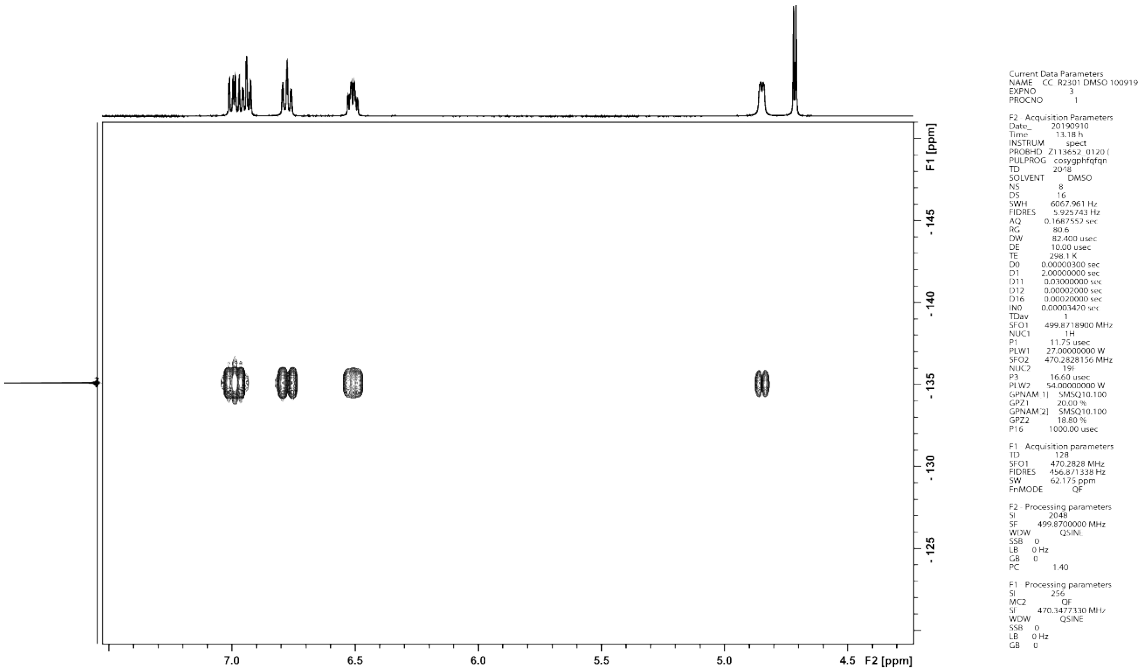

Figure S10. ^{1}H-^{19}F COSY contour map for compound 1 in DMSO-d_6, obtained at 500 MHz (^{1}H).

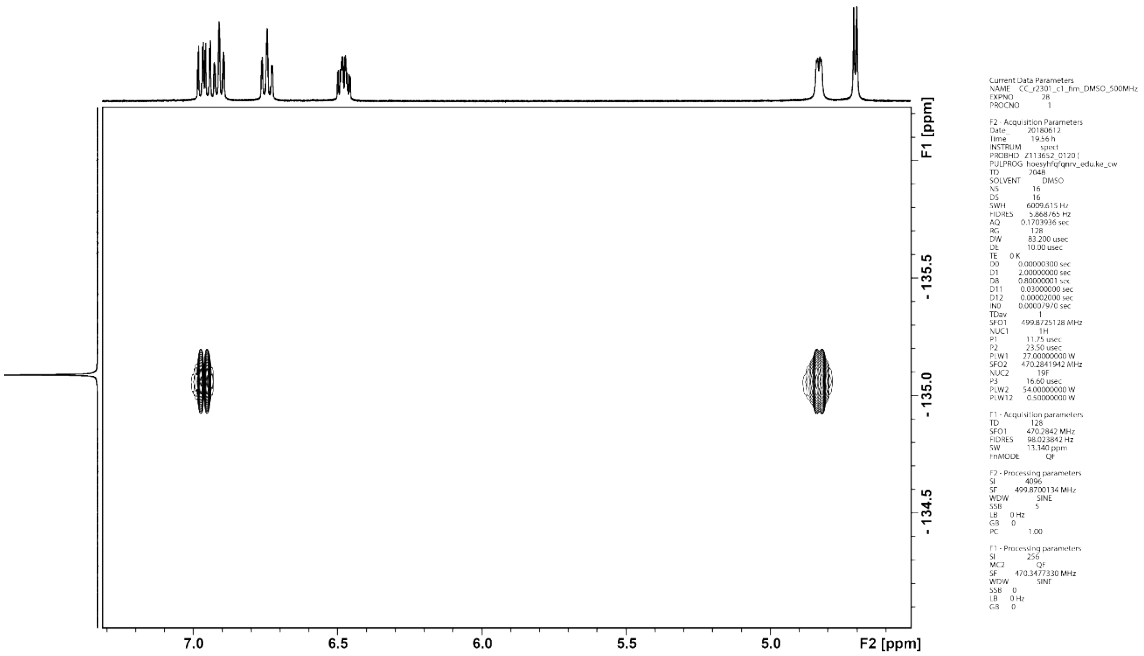

Figure S11. ^{1}H-^{19}F HOESY contour map for compound 1 in DMSO-d_6, obtained at 500 MHz (^{1}H).

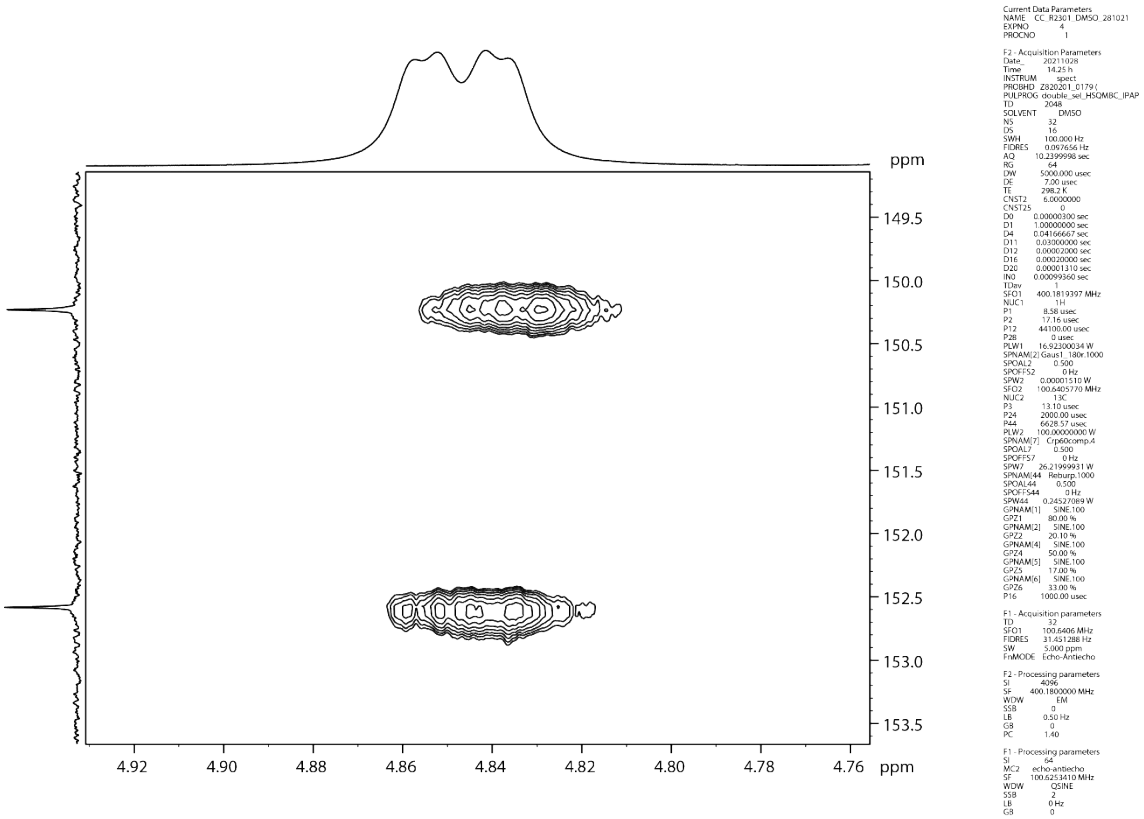

Figure S12. ^{1}H-^{13}C dsel-HSQMBC-IP contour map for compound 1 in DMSO-d_6, obtained at 400 MHz (^{1}H), with selective pulse applied to C10 and H8.

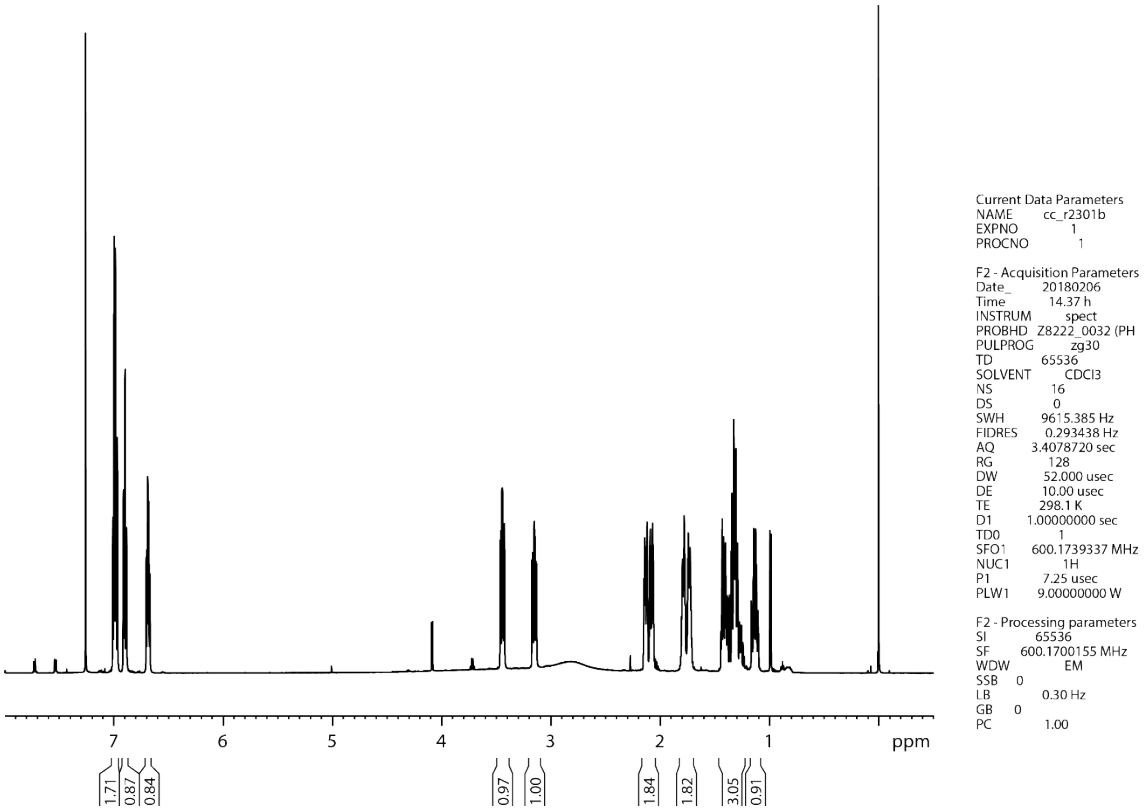

Figure S13. ^{1}H spectrum for compound 1 in $CDCl_3$, obtained at 600 MHz.

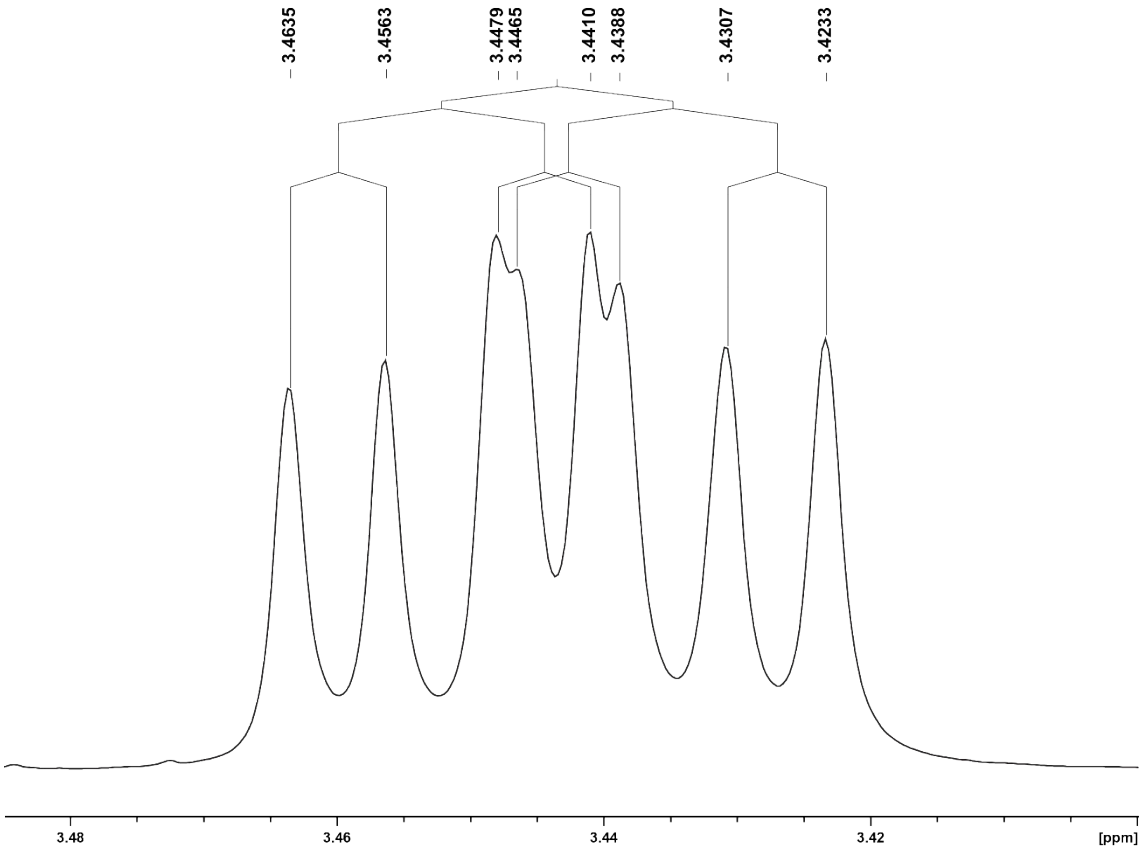

Figure S14. Expansion of ^{1}H spectrum for compound 1 in $CDCl_3$ in the region of hydrogen H1, obtained at 600 MHz.

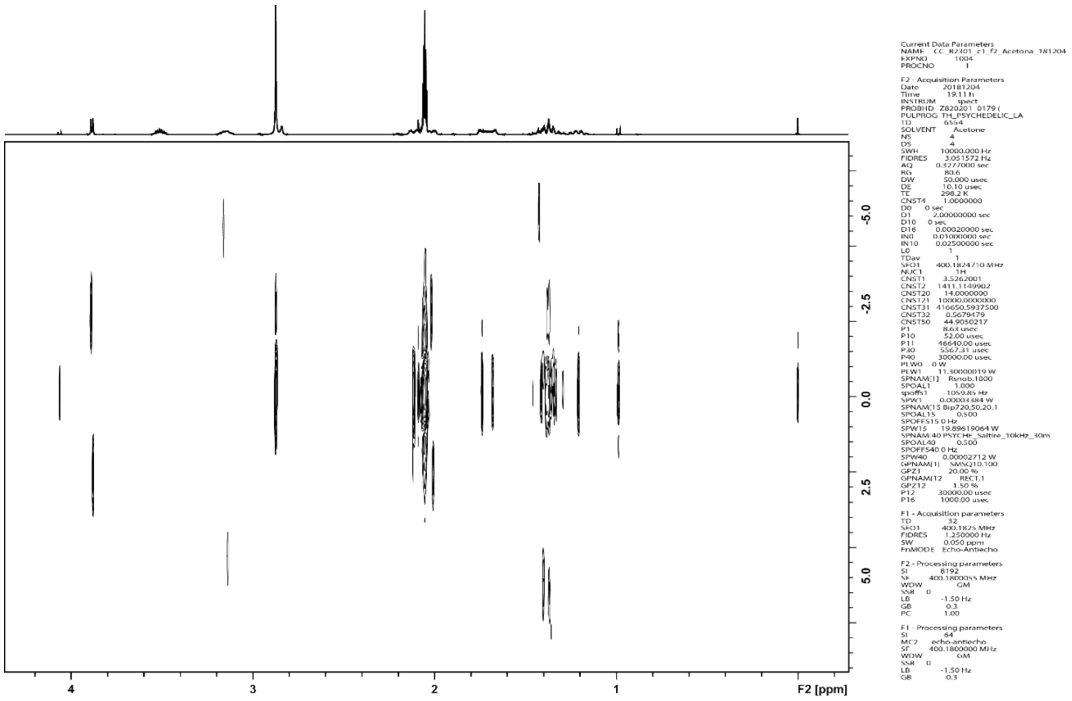

Figure S15. PSYCHEDELIC spectrum in acetone-d_6 with selective pulse applied to H1 of compound 1, obtained at 400 MHz (^{1}H).

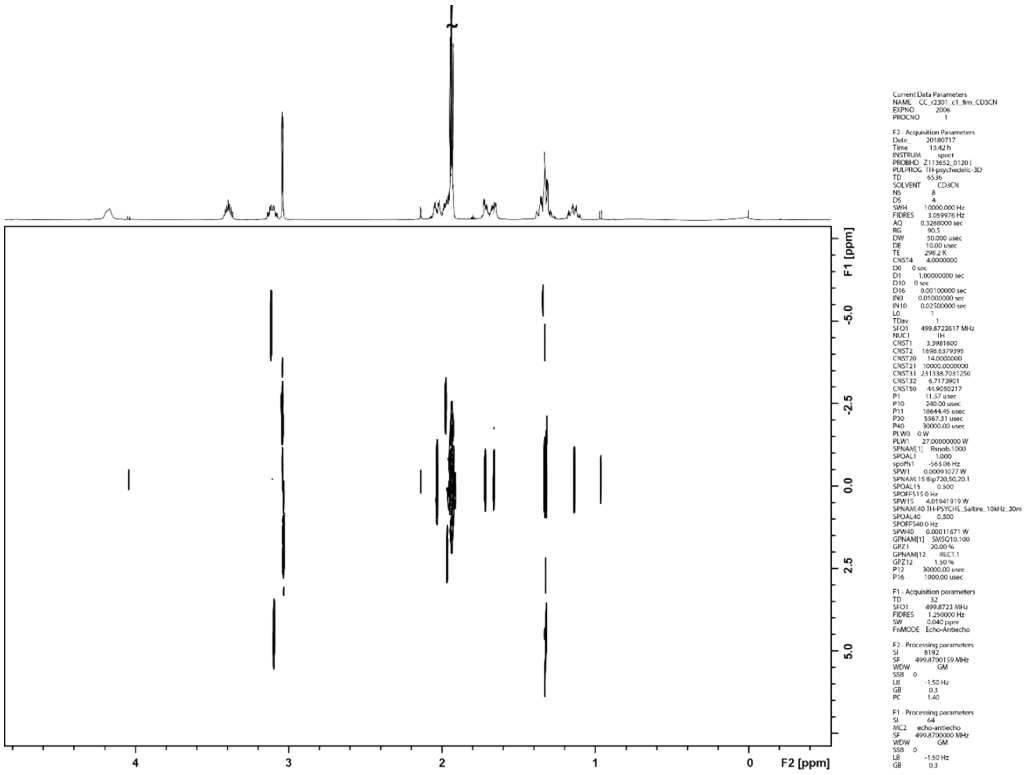

Figure S16. PSYCHEDELIC spectrum in CD_3CN with selective pulse applied to H1 of compound 1, obtained at 500 MHz (^{1}H).

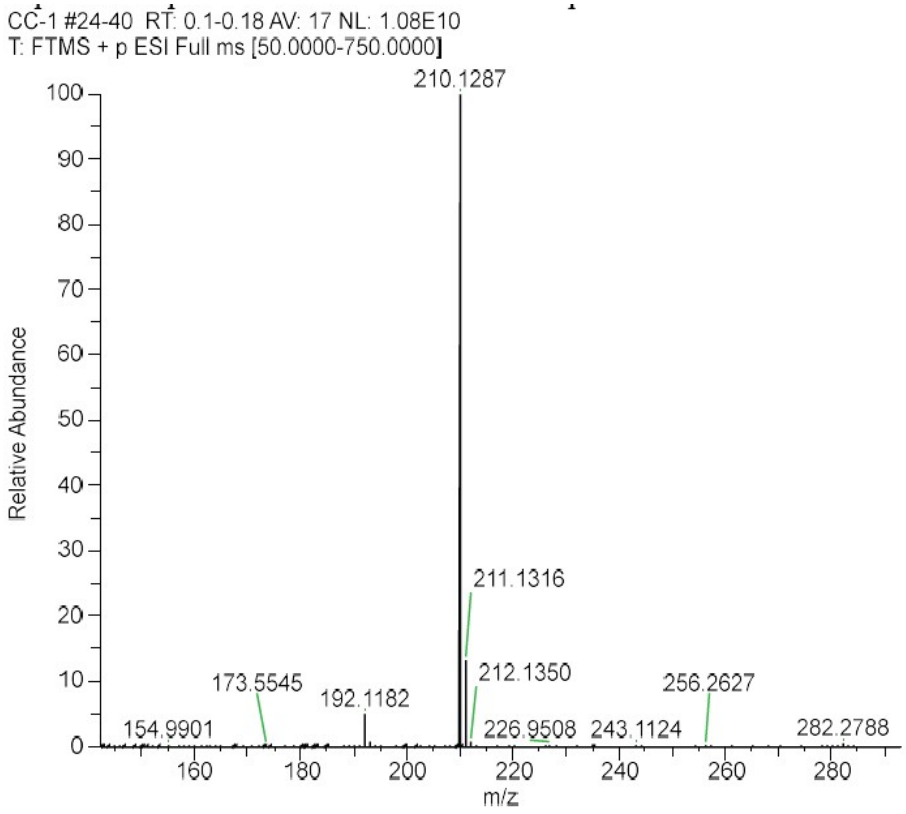

Figure S17. HRMS of compound **1**.

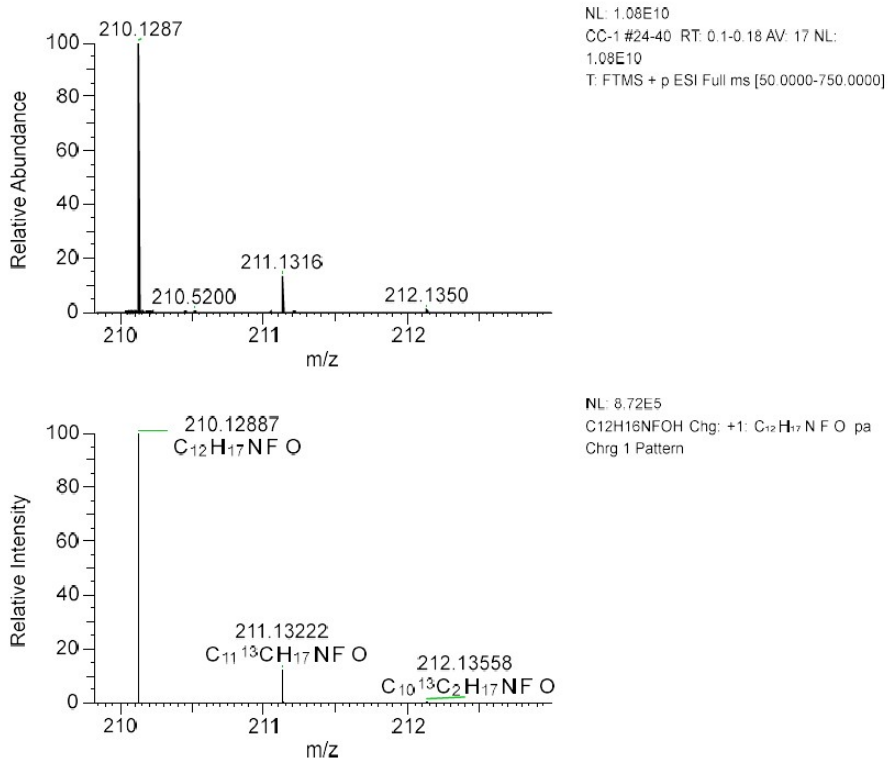

Figure S18. Comparison between experimental (top) and simulated (bottom) for $C_{12}H_{17}FNO$ $[M+H]^+$ of compound **1**.

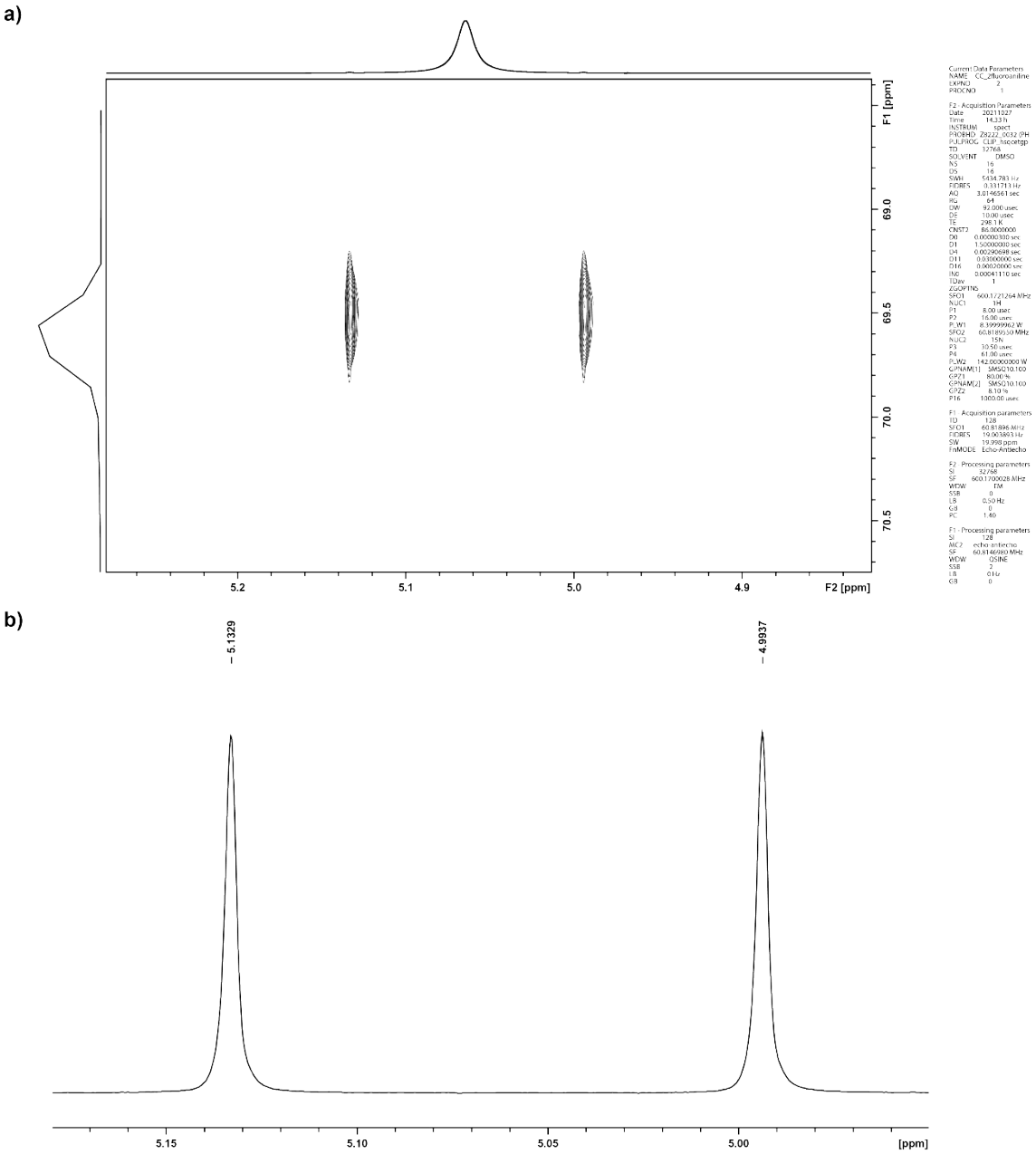

Figure S19. ^{1}H-^{15}N CLIP-HSQC contour map (**a**) and slice (**b**) for starting material 2-fluoroaniline in DMSO-d_6, obtained at 600 MHz (^{1}H).

Compound 2 (*trans*-2-((3-fluoropyridin-4-yl)amino)cyclohexan-1-ol)

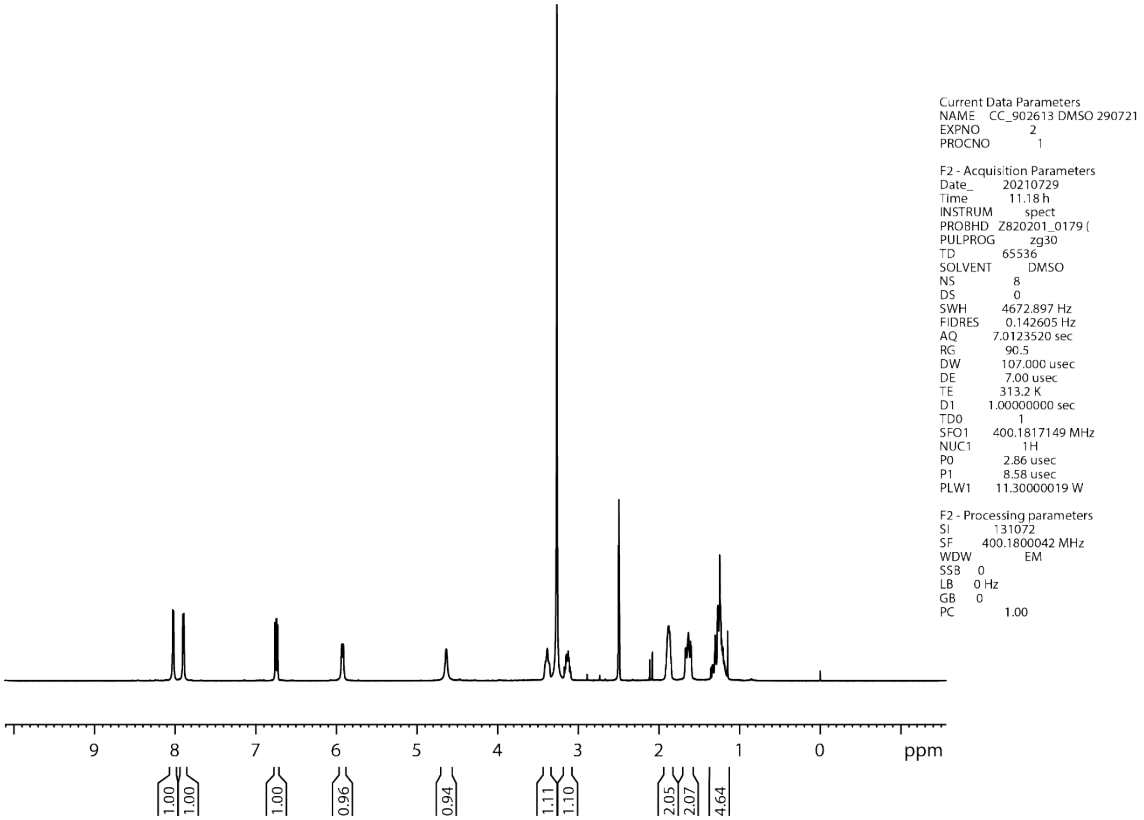

Figure S20. ^{1}H spectrum for compound 2 in DMSO-d_6 at 40 °C, obtained at 400 MHz.

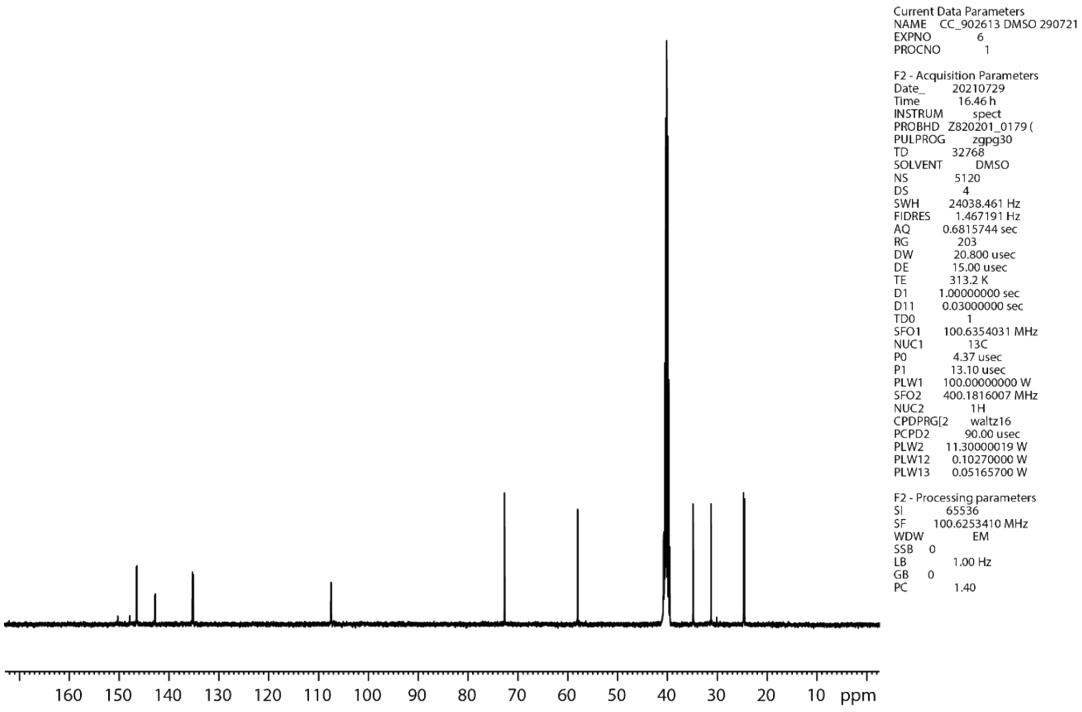

Figure S21. ^{13}C spectrum for compound 2 in DMSO-d_6 at 40 °C, obtained at 100 MHz.

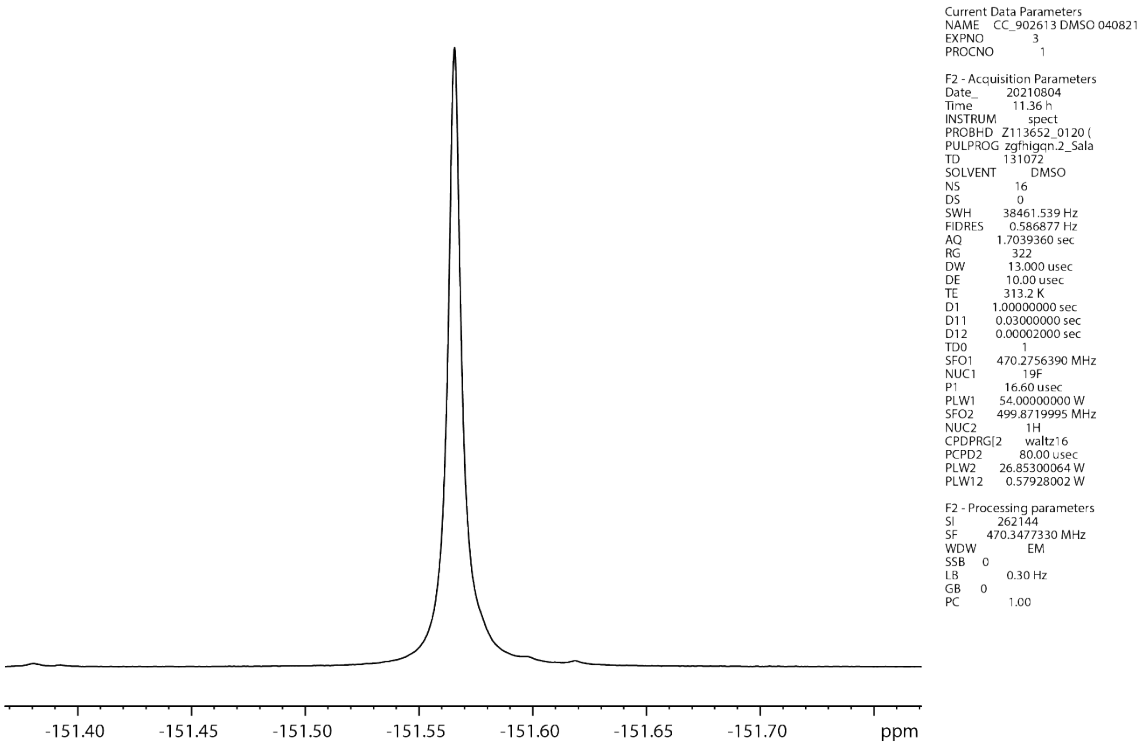

Figure S22. $^{19}F\{^{1}H\}$ spectrum for compound 2 in DMSO-d_6 at 40 °C, obtained at 470 MHz.

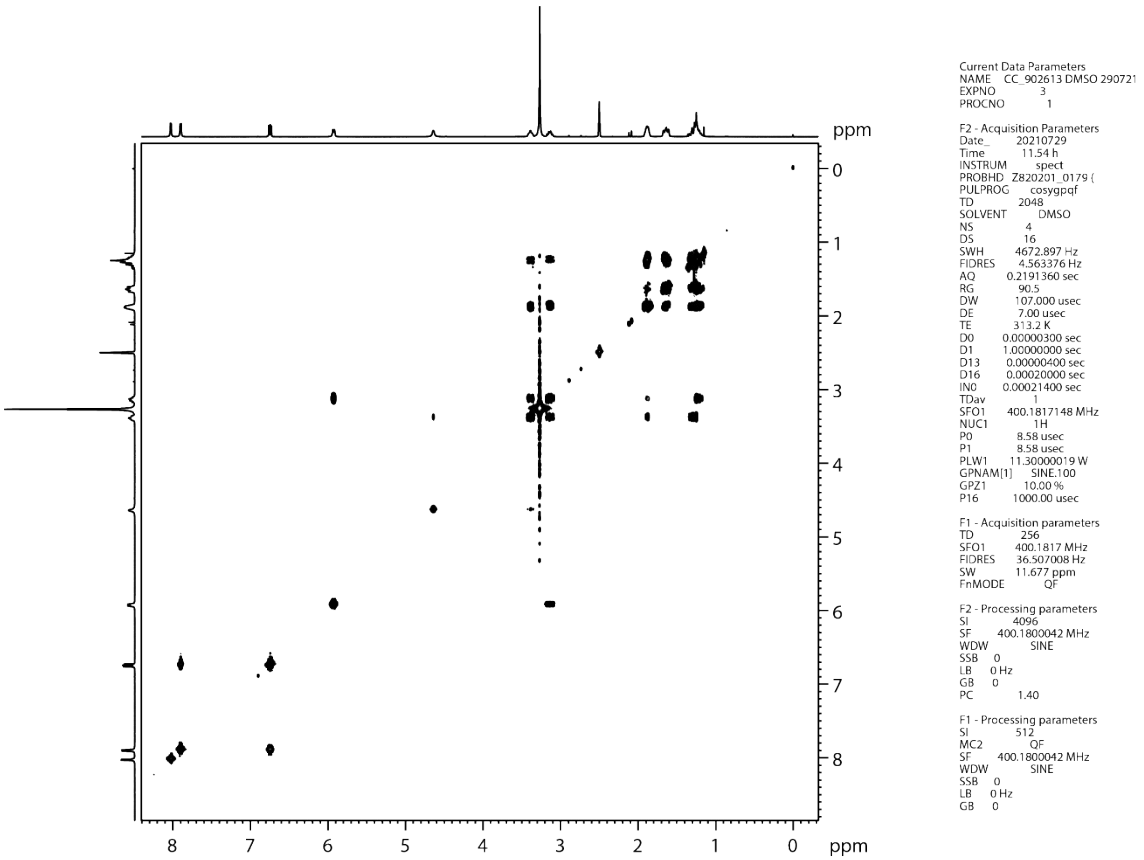

Figure S23. ^{1}H-^{1}H COSY contour map for compound 2 in DMSO-d_6 at 40 °C, obtained at 400 MHz.

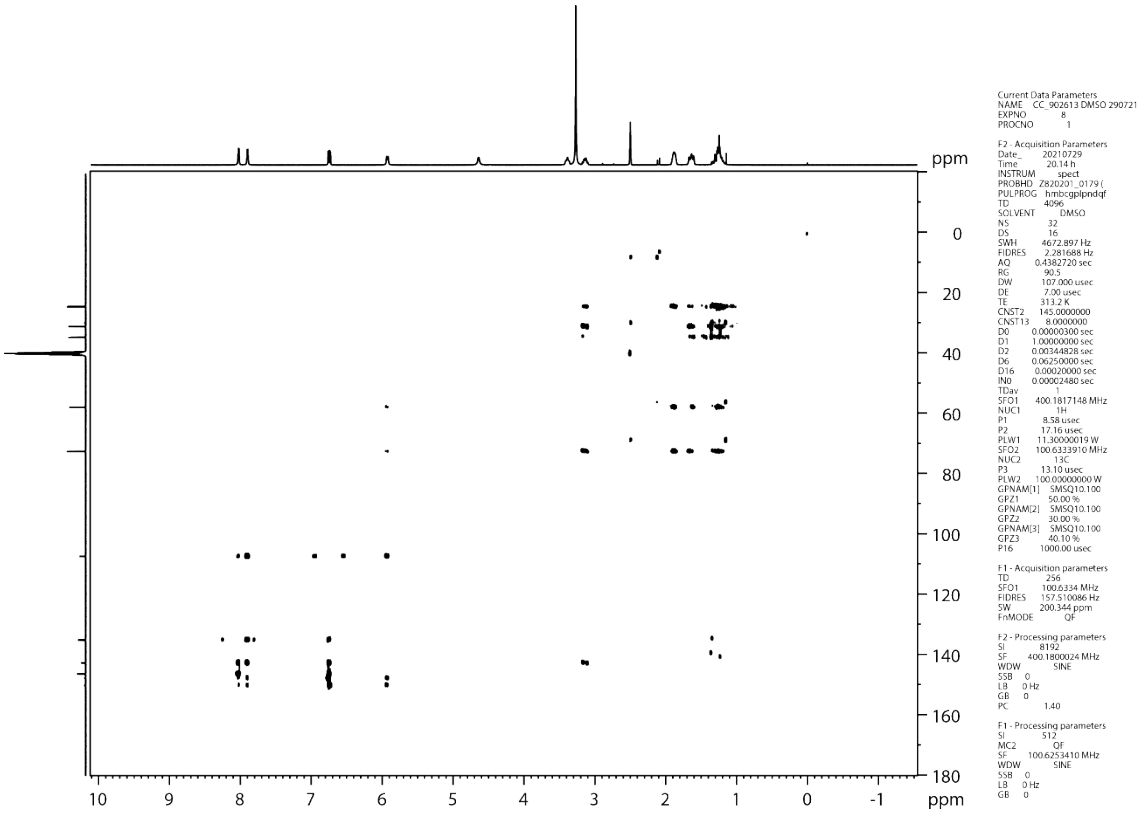

Figure S24. ^{1}H-^{13}C HMBC contour map for compound 2 in DMSO-d_6 at 40 °C, obtained at 400 MHz (^{1}H).

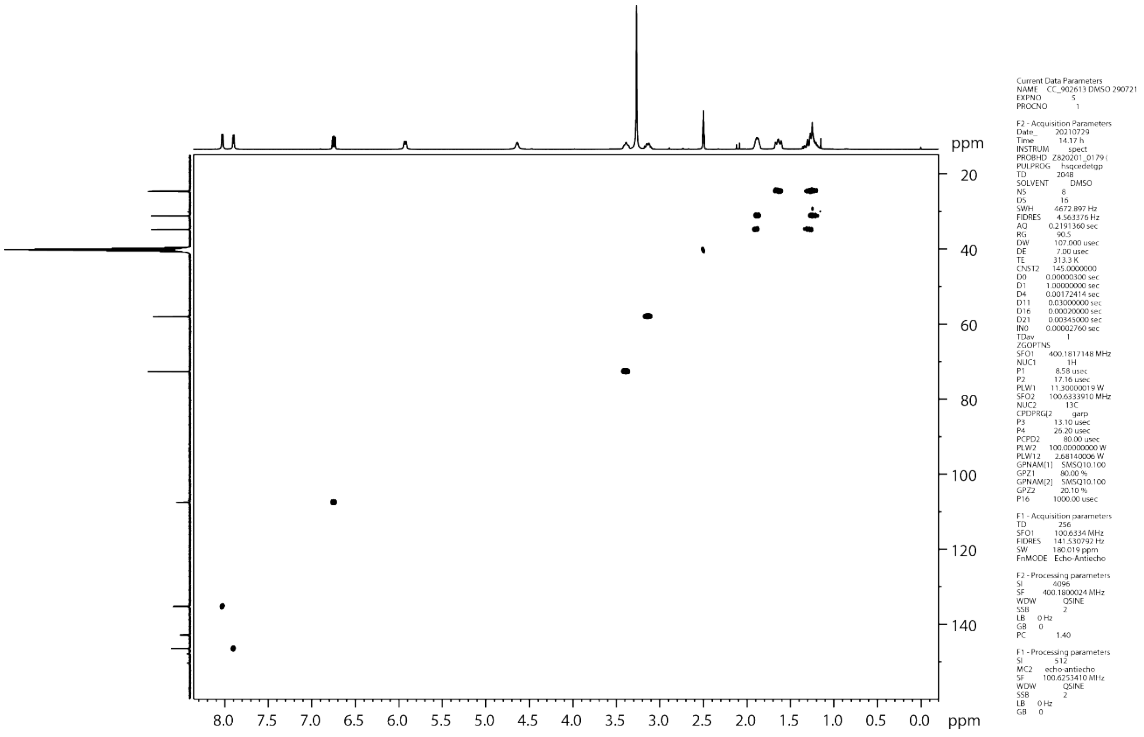

Figure S25. ^{1}H-^{13}C HSQC contour map for compound 2 in DMSO-d_6 at 40 °C, obtained at 400 MHz (^{1}H).

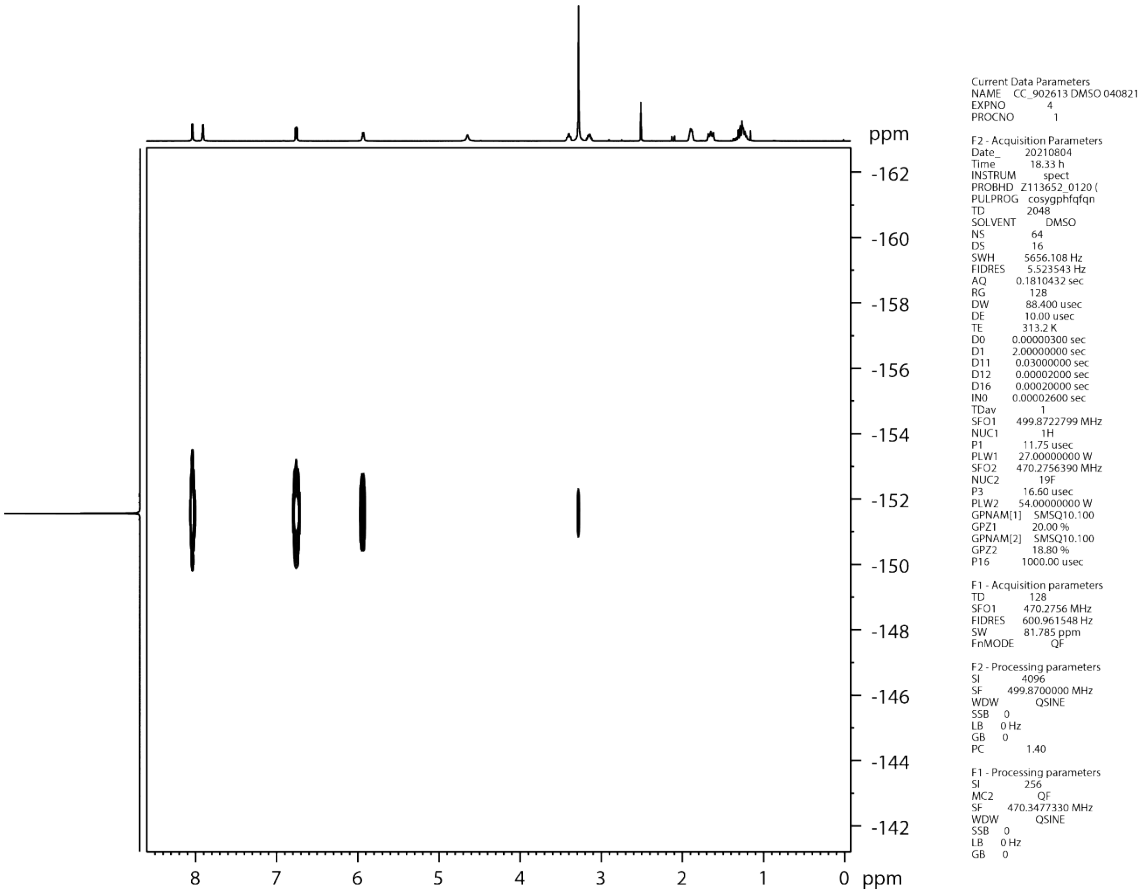

Figure S26. ^{1}H-^{19}F COSY contour map for compound 2 in DMSO-d_6 at 40 °C, obtained at 500 MHz (^{1}H).

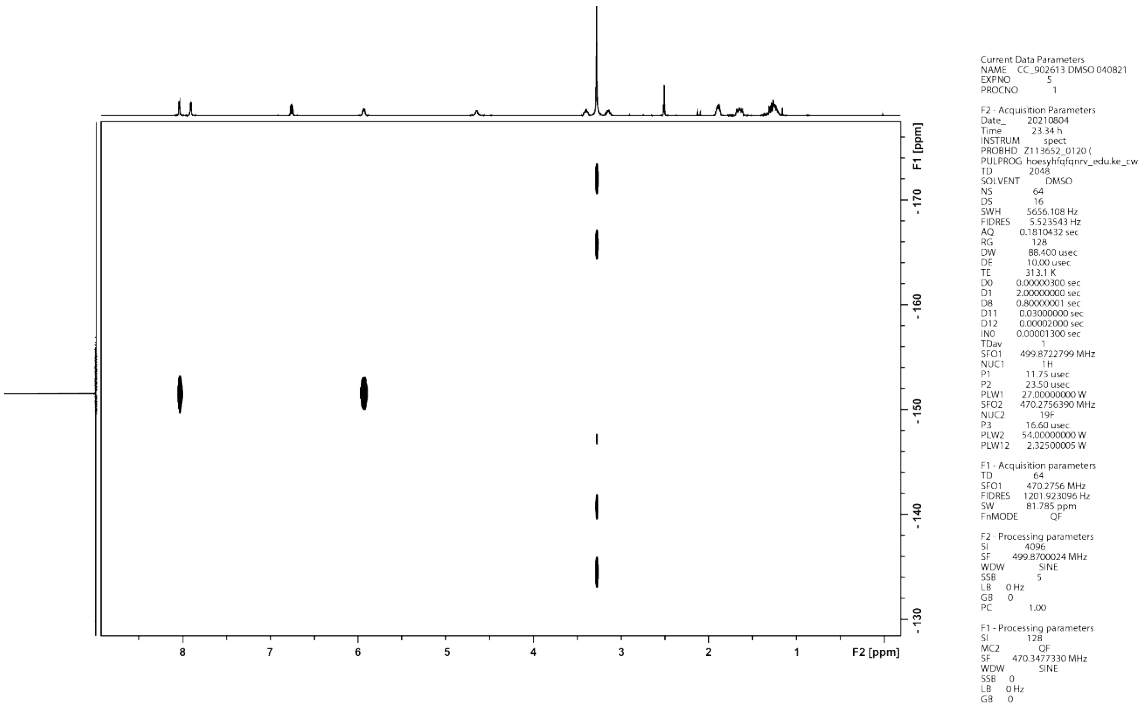

Figure S27. ^{1}H-^{19}F HOESY contour map for compound 2 in DMSO-d_6 at 40 °C, obtained at 500 MHz (^{1}H).

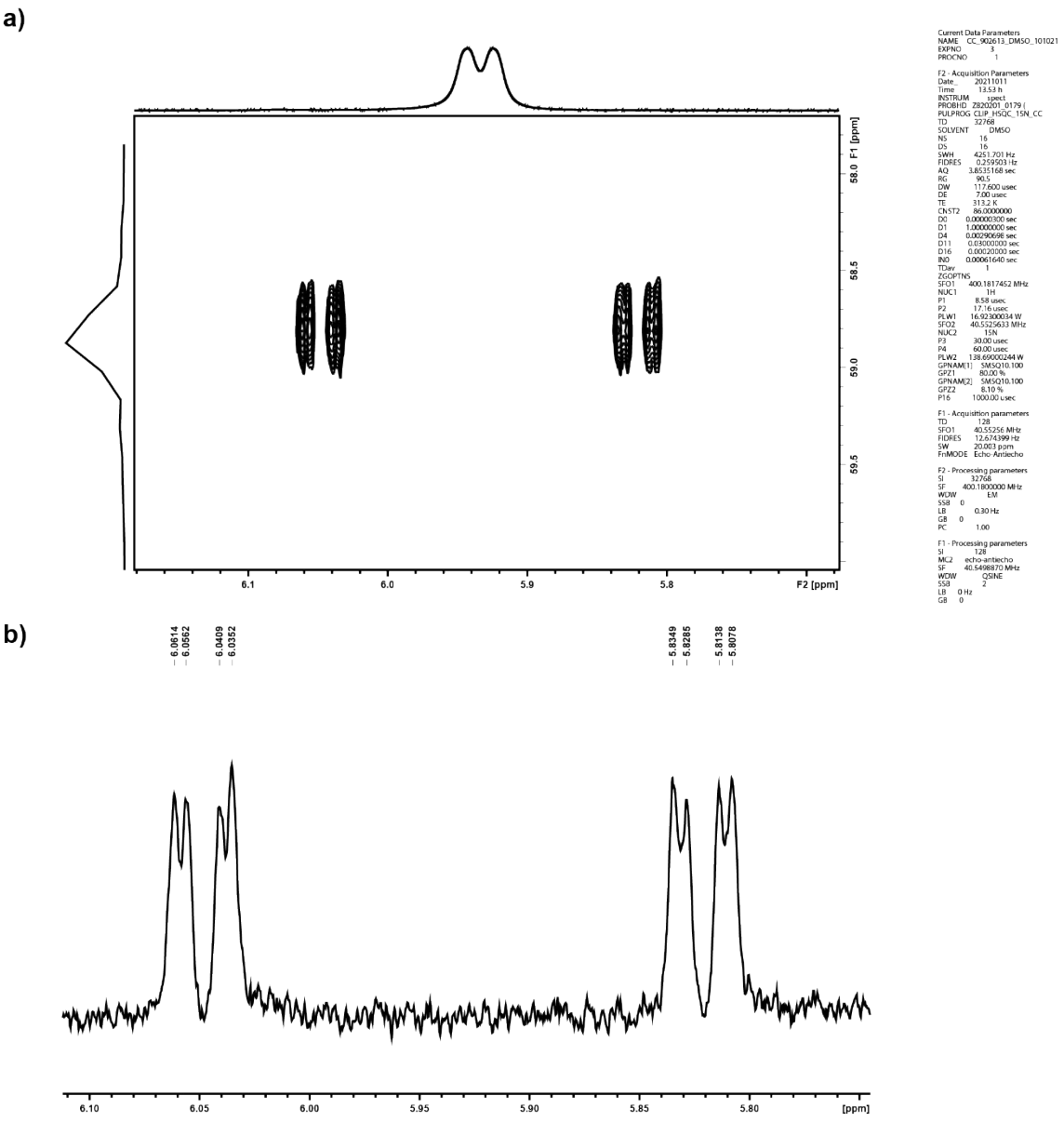

Figure S28. ^{1}H-^{15}N CLIP-HSQC contour map (**a**) and slice (**b**) for compound 2 in DMSO-d_6 at 40 °C, obtained at 400 MHz (^{1}H).

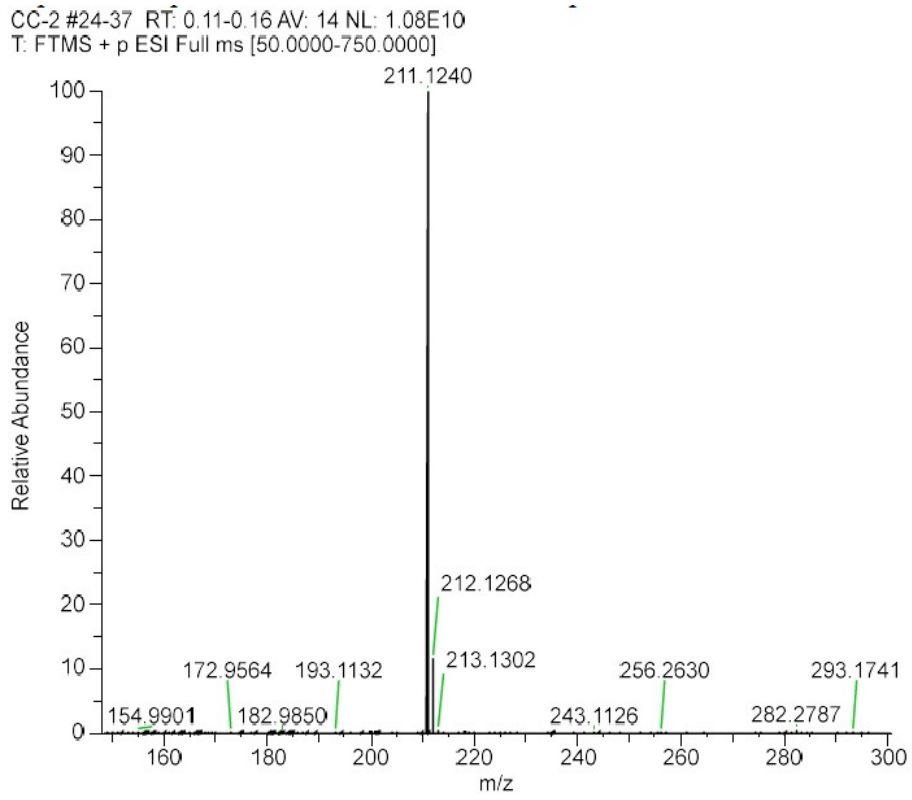

Figure S29. HRMS of compound **2**.

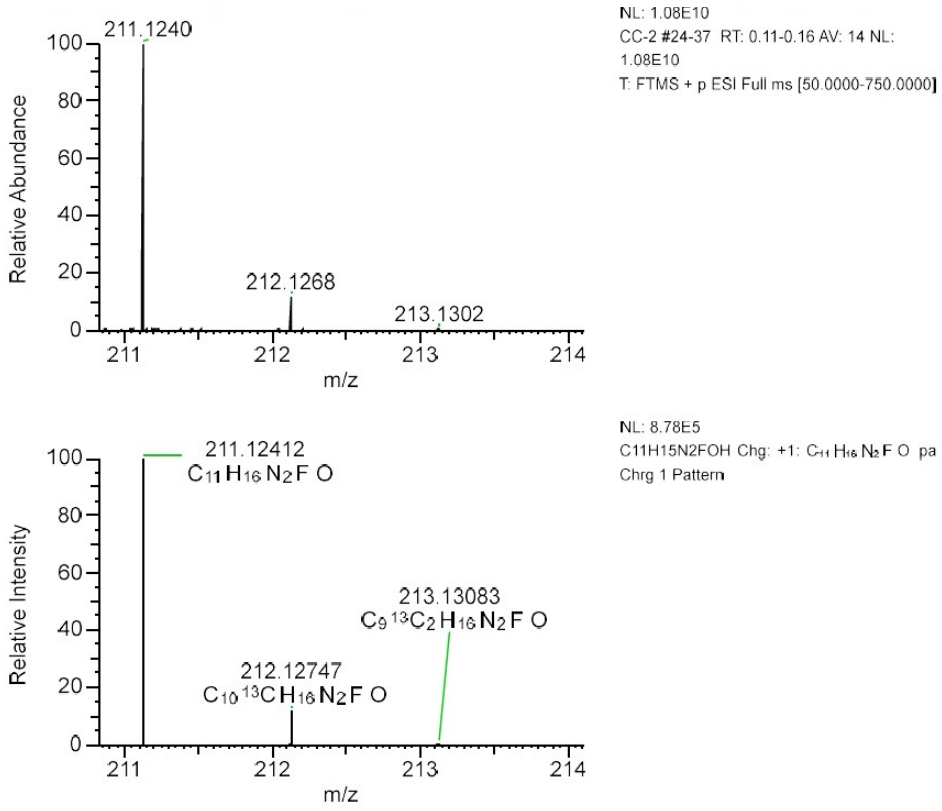

Figure S30. Comparison between experimental (top) and simulated (bottom) for $C_{11}H_{16}FN_2O$ $[M+H]^+$ of compound **2**.

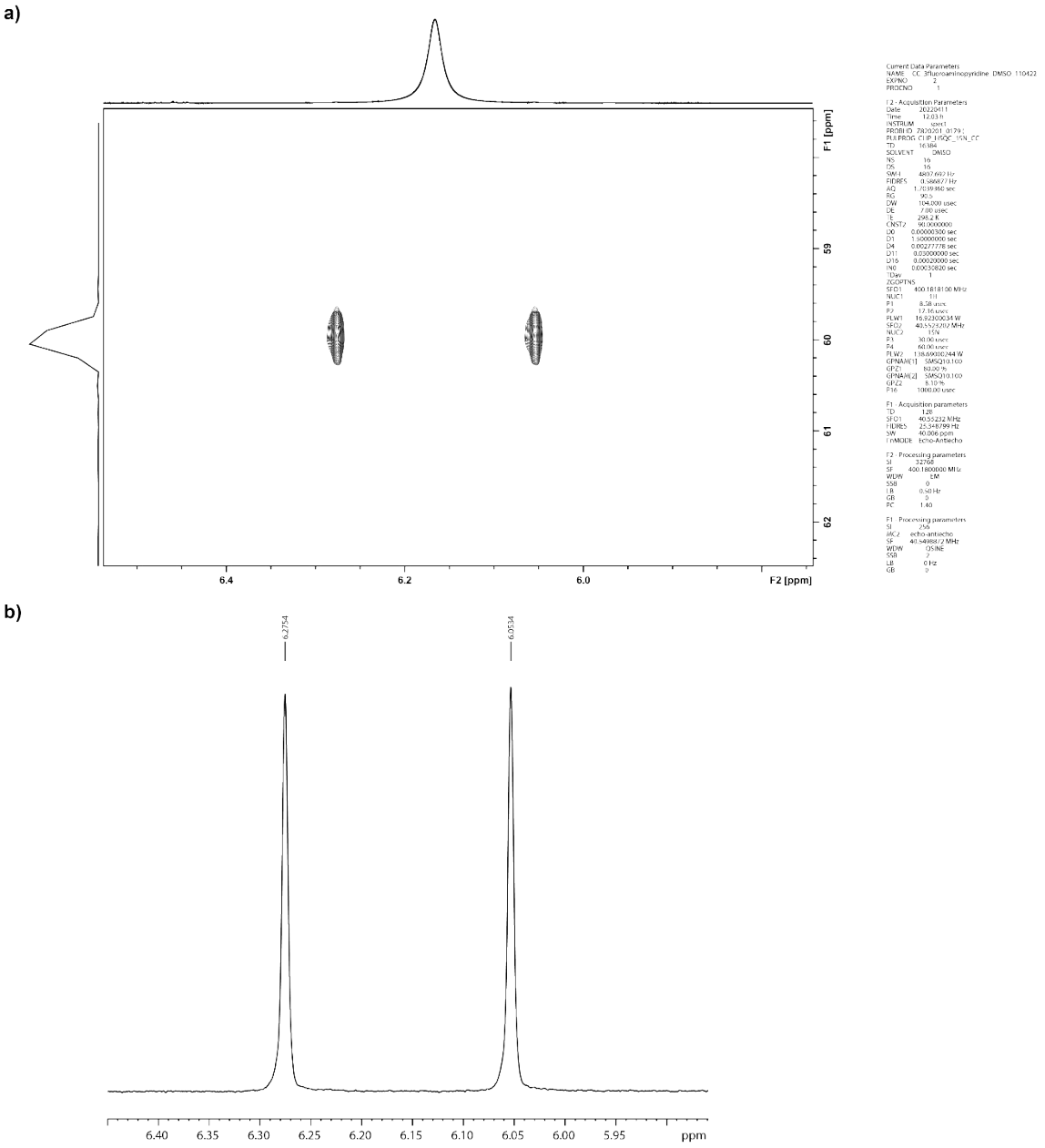

Figure S31. ^{1}H-^{15}N CLIP-HSQC contour map (**a**) and slice (**b**) for starting material 3-fluoro-4-aminopyridine in DMSO-d_6, obtained at 400 MHz (^{1}H).

Compound 3 (*trans*-2-((perfluoropyridin-4-yl)amino)cyclohexan-1-ol)

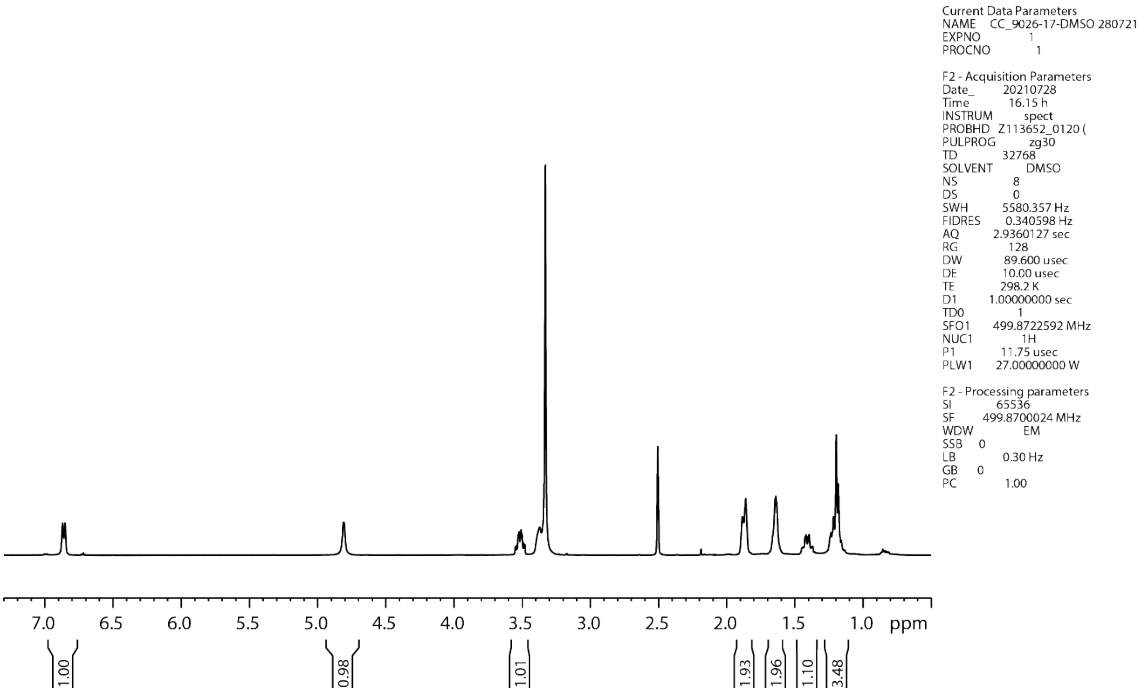

Figure S32. ^{1}H spectrum for compound 3 in DMSO-d_6, obtained at 500 MHz.

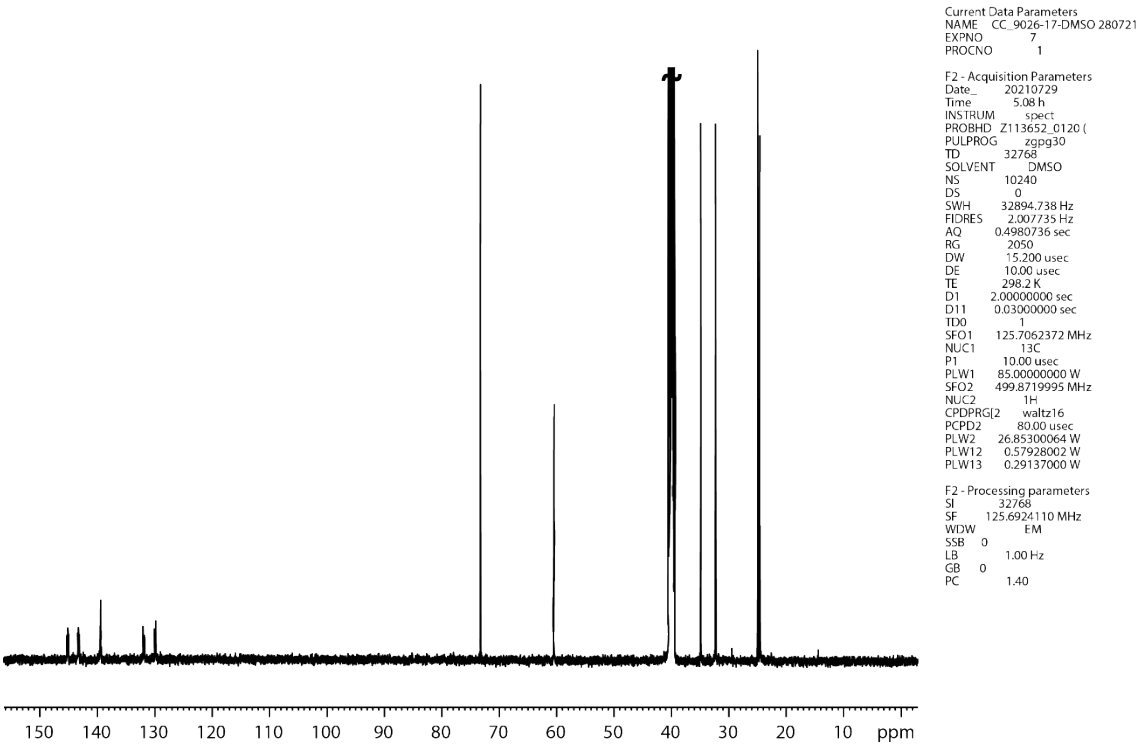

Figure S33. ^{13}C spectrum for compound 3 in DMSO-d_6, obtained at 125 MHz.

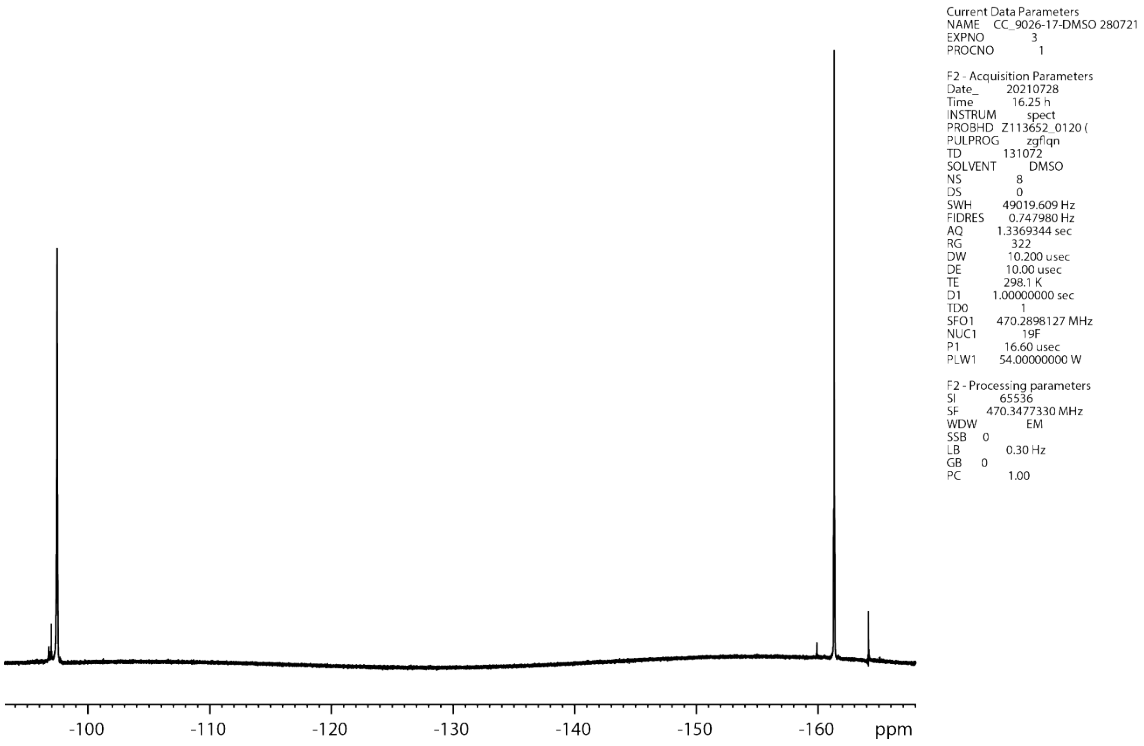

Figure S34. $^{19}F\{^{1}H\}$ spectrum for compound 3 in DMSO-d_6, obtained at 470 MHz.

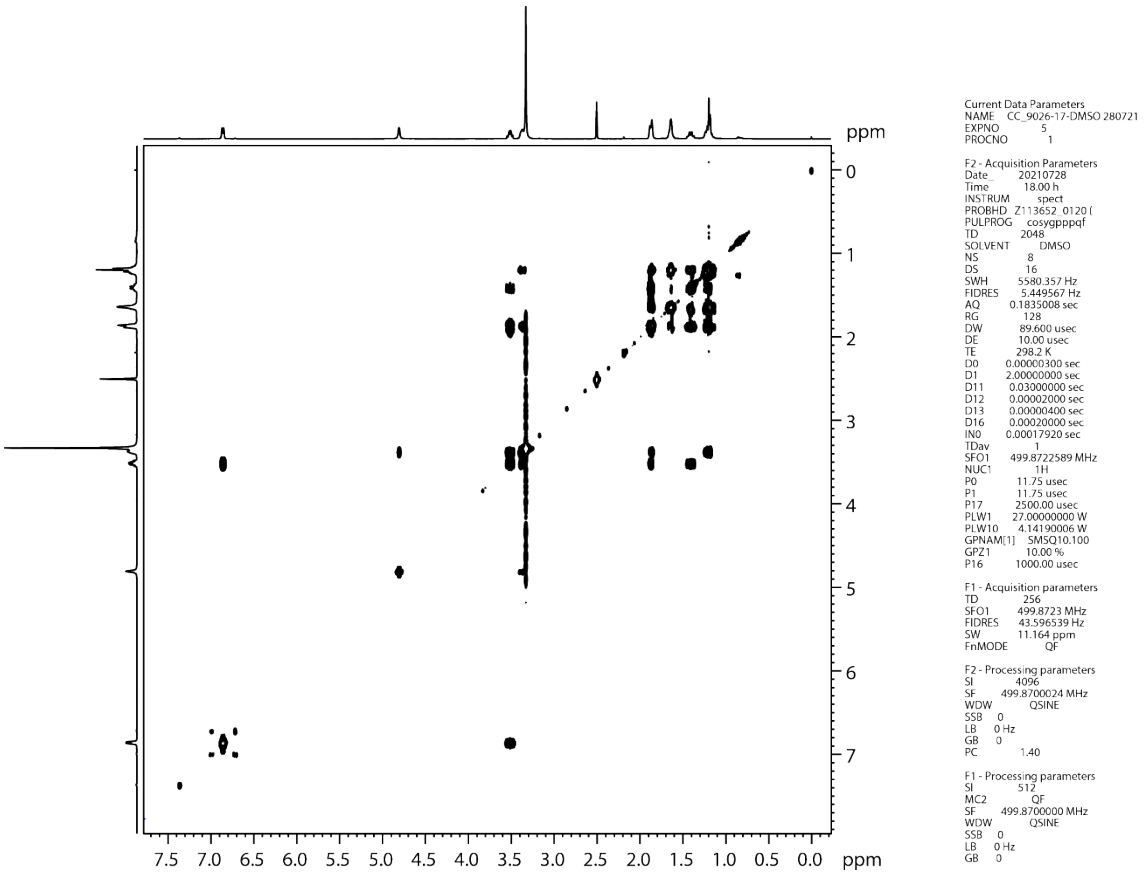

Figure S35. ^{1}H-^{1}H COSY contour map for compound 3 in DMSO-d_6, obtained at 500 MHz.

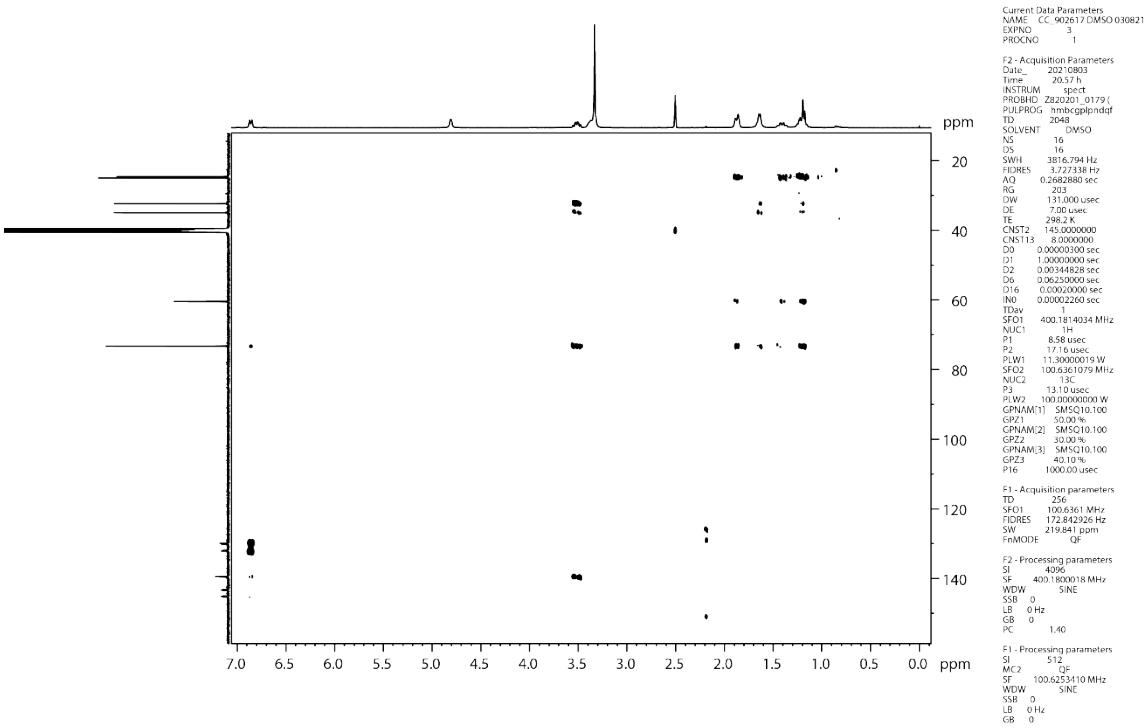

Figure S36. ^{1}H-^{13}C HMBC contour map for compound 3 in DMSO-d_6, obtained at 400 MHz (^{1}H).

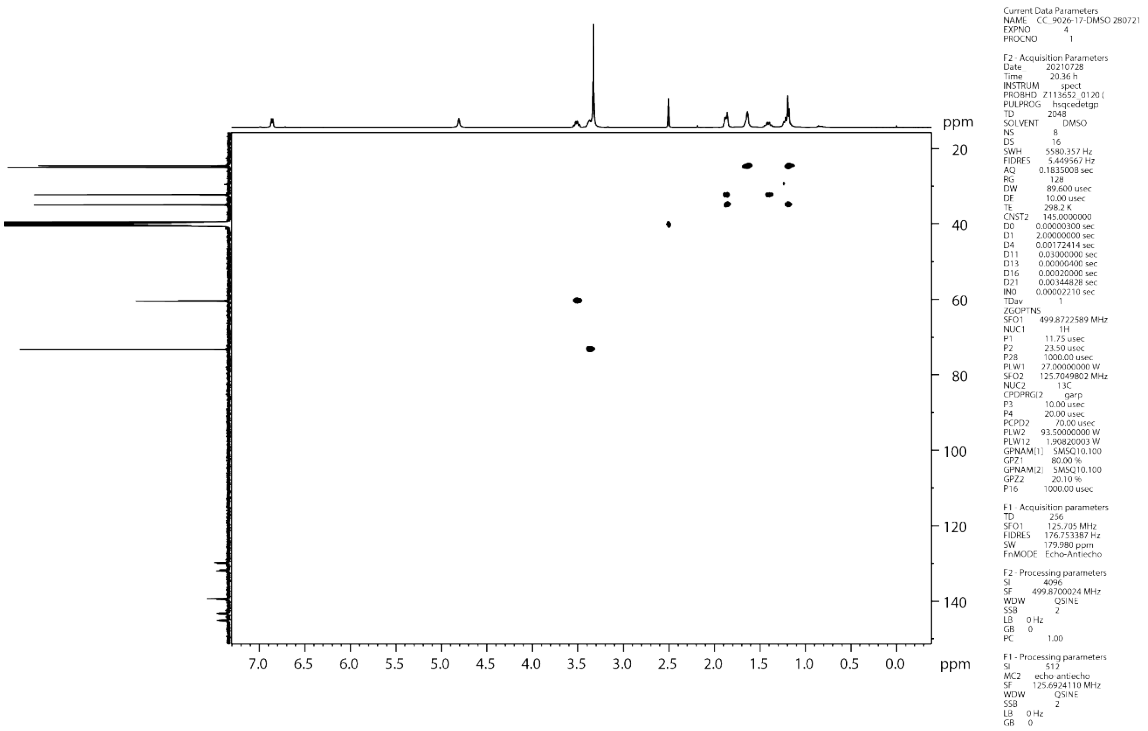

Figure S37. ^{1}H-^{13}C HSQC contour map for compound 3 in DMSO-d_6, obtained at 500 MHz (^{1}H).

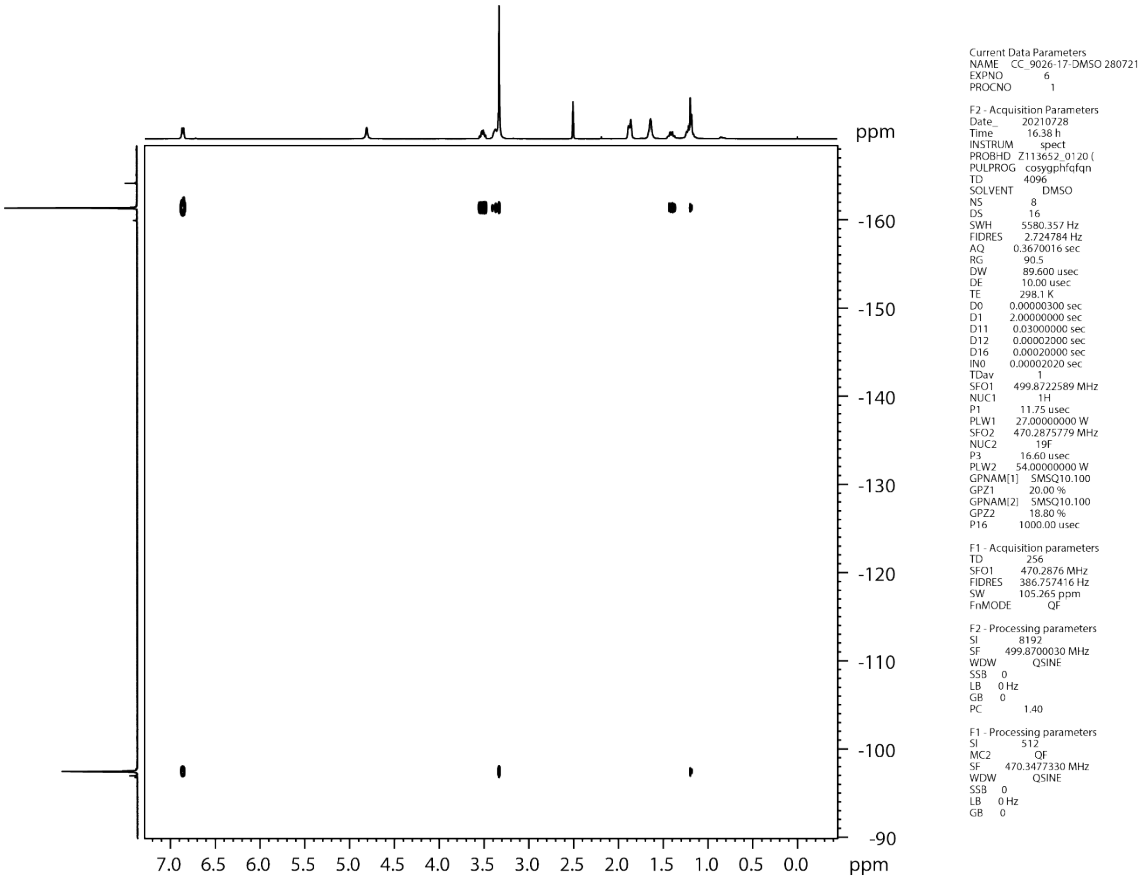

Figure S38. ^{1}H-^{19}F COSY contour map for compound 3 in DMSO-d_6, obtained at 500 MHz (^{1}H).

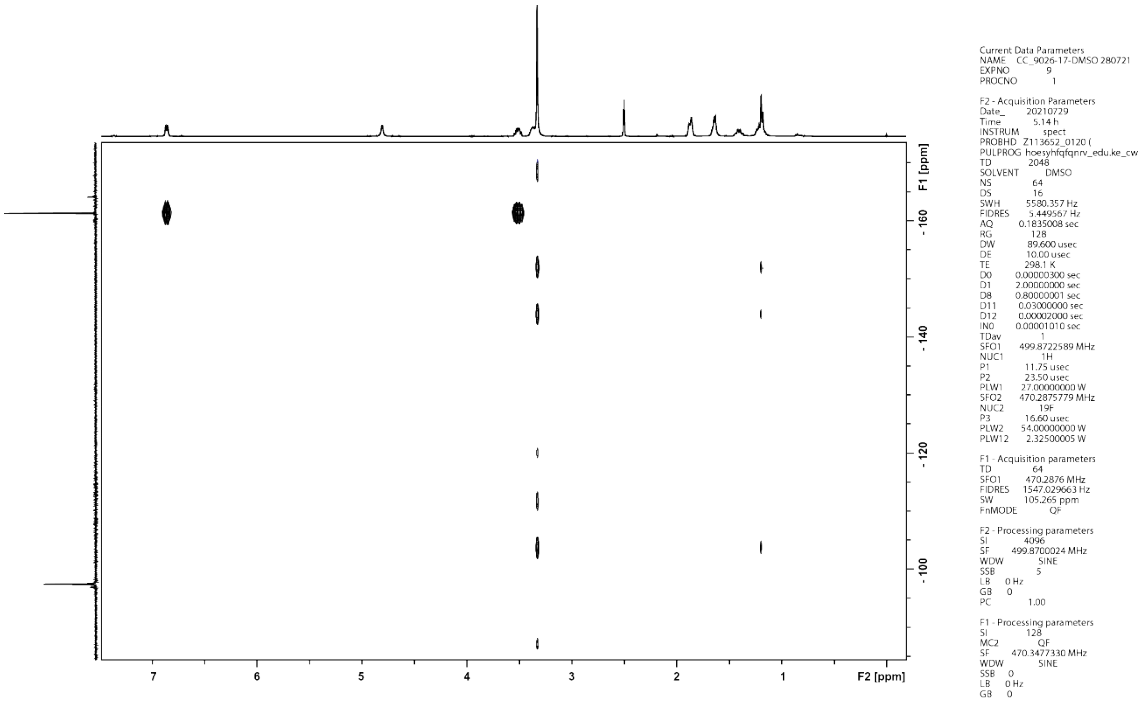

Figure S39. ^{1}H-^{19}F HOESY contour map for compound 3 in DMSO-d_6, obtained at 500 MHz (^{1}H).

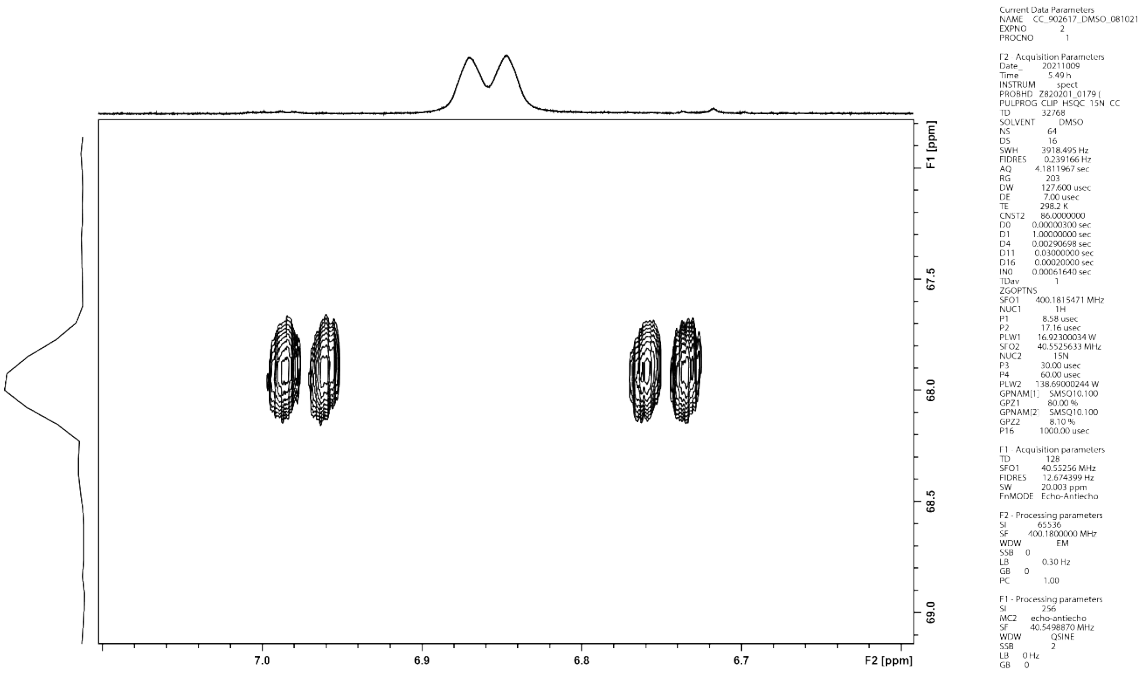

Figure S40. ^{1}H-^{15}N CLIP-HSQC contour map for compound 3 in DMSO-d_6, obtained at 400 MHz (^{1}H).

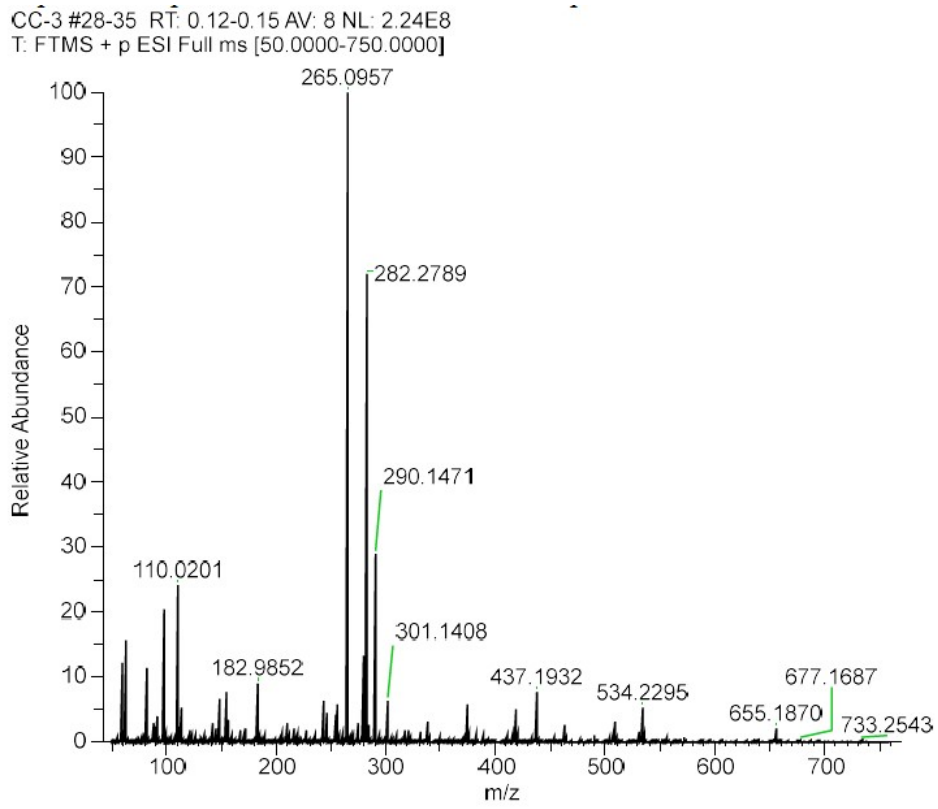

Figure S41. HRMS of compound **3**.

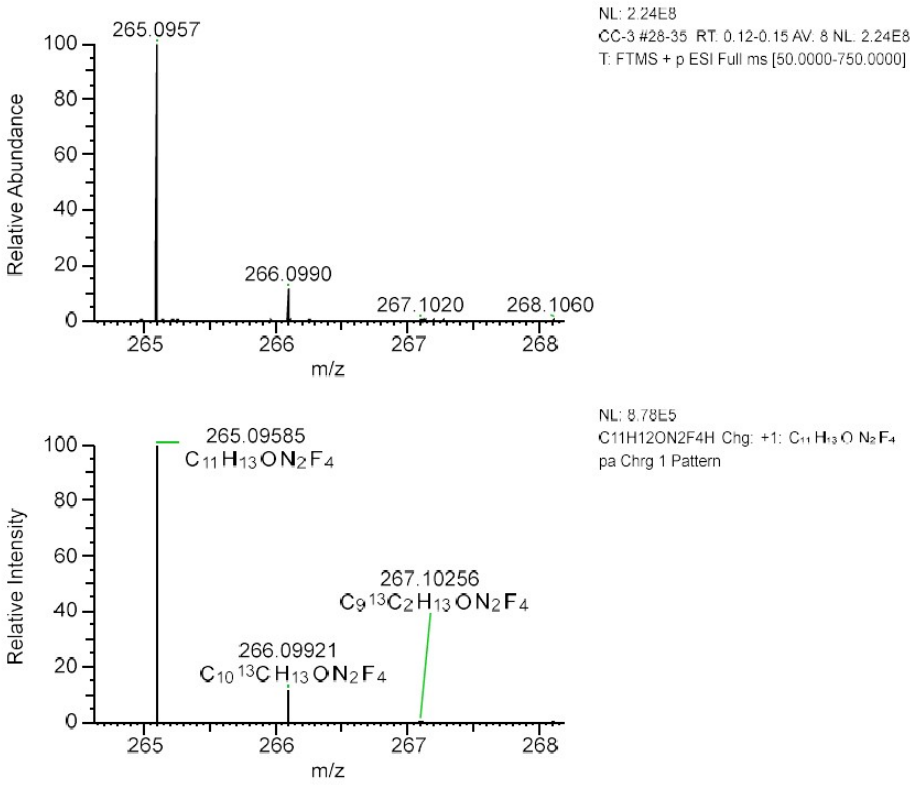

Figure S42. Comparison between experimental (top) and simulated (bottom) for $C_{11}H_{13}F_4N_2O$ $[M+H]^+$ of compound **3**.

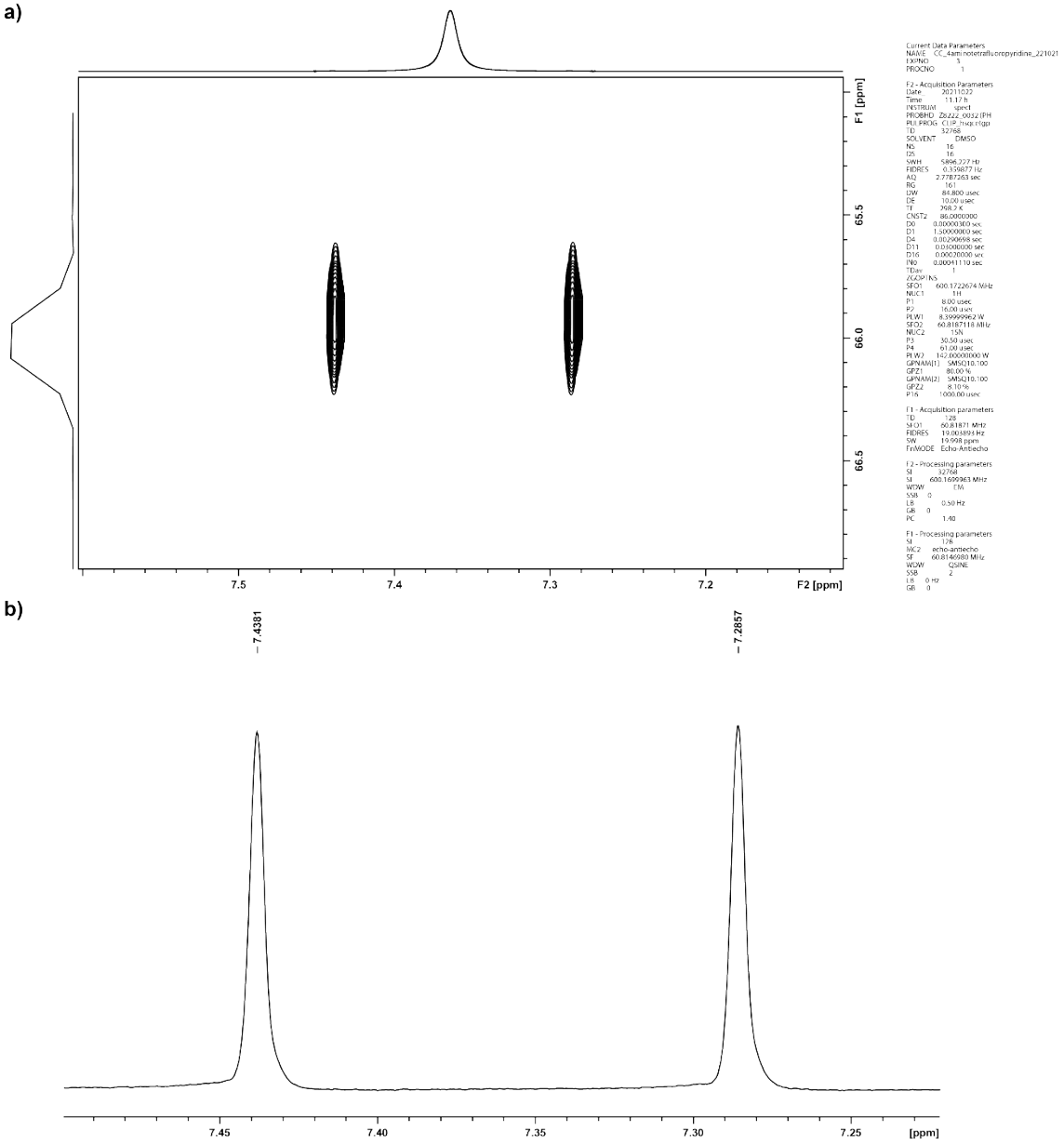

Figure S43. ^{1}H-^{15}N CLIP-HSQC contour map (**a**) and slice (**b**) for starting material 2,3,5,6-fluoro-4-aminopyridine in DMSO-d_6, obtained at 600 MHz (^{1}H).

Computational details – implicit solvation

Table S1. Theoretical *J* coupling values (Hz) calculated at PBE0(40%HF)/EPR-III level of theory with geometries optimised at M06-2X/aug-cc-pVDZ level of theory, and corresponding energies and population at the conformational equilibrium.

Confor.	ΔG (kcal mol^{-1})	Population	$^{3}J_{H1H2}$	$^{3}J_{H1H7}$	$^{3}J_{H2H8}$	J_{H8F10}	J_{H8F14}
A1	0.00	46%	9.3	1.2	6.3	-3.9	-
A2	0.37	25%	9.6	14.7	0.7	-1.4	-
A3	0.63	16%	9.5	1.1	0.7	-1.4	-
A4	0.73	13%	9.4	-0.2	12.5	-2.6	-
B1	0.00	52%	9.1	0.2	11.4	-2.6	-
B2	0.67	17%	9.3	1.6	8.5	-3.5	-
B3	0.97	10%	9.6	0.9	3.7	-2.7	-
B4	1.04	9%	9.7	14.8	3.2	-2.6	-
B5	1.17	7%	9.6	14.7	11.2	-3.5	-
B6	1.40	5%	9.5	1.1	9.0	-3.6	-
C1	0.00	25%	9.1	0.5	10.9	-2.3	-3.4
C2	0.01	25%	9.5	0.7	8.3	-3.7	-2.8
C3	0.15	20%	9.6	14.7	8.0	-2.8	-3.7
C4	0.20	18%	9.6	14.5	10.5	-2.4	-4.1
C5	0.46	12%	9.4	1.4	11.2	-4.1	-2.4

Table S2. Contributions from spin-dipole (SD), paramagnetic spin-orbital (PSO), diamagnetic spin-orbital (DSO) and Fermi contact (FC) mechanisms to J_{H8F} coupling. The values are averaged over 32 MD configurations.

***J*-coupling**	**1**	**2**	**3**
$^{SD}J_{H8F}$	-0.5	-0.3	-0.3
$^{PSO}J_{H8F}$[a]	-2.6	-3.2	-1.6
$^{DSO}J_{H8F}$[a]	2.1	2.6	1.0
$^{FC}J_{H8F}$	-0.9	-1.1	-1.1
$^{Total}J_{H8F}$[b]	-1.9	-2.0	-2.0

[a]Only the sum PSO+DSO is physically meaningful.

[b] $^{Total}J_{H8F} = {}^{SD}J_{H8F} + {}^{PSO}J_{H8F} + {}^{DSO}J_{H8F} + {}^{FC}J_{H8F}$

Table S3. *J*-coupling values calculated at PBE0(40%HF)/EPR-III level of theory for minimised geometries with OPLS force field.

J	[a]OPLS[bare]			[b]OPLS[impl]			[c]OPLS[full]			[d]Exp.		
	1	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**	**1**	**2**	**3**
H_1H_2	7.4	8.0	7.9	7.5	8.1	8.0	7.8	8.6	8.4	8.8	9.2	9.3
H_1H_7	4.3	0.1	-0.3	4.3	0.1	-0.3	4.5	0.2	*	5.1	6.0	*
H_2H_8	11.0	9.8	12.1	10.7	9.5	11.5	10.4	8.5	10.0	6.4	7.1	9.2
H_8F	-1.7	-1.7	-0.1	-1.8	-1.7	-0.4	-1.6	-0.7	*	–2.3	–2.2	*

[a]All solvent molecules were removed and without implicit solvation.

[b]Soluto embedded by implicit solvation model (SMD) using DMSO as solvent and all solvent molecules were removed.

[c]Solute solvated by the three explicit smallest number nearest-neighbour solvent molecules embedded by implicit solvation model (SMD) using DMSO as solvent to treat bulk effects.

[d]Experimental data measured in DMSO-d_6.

*Values could not be measured due to signal's linewidth.

Compound 1 (*trans*-2-((2-fluorophenyl)amino)cyclohexan-1-ol)

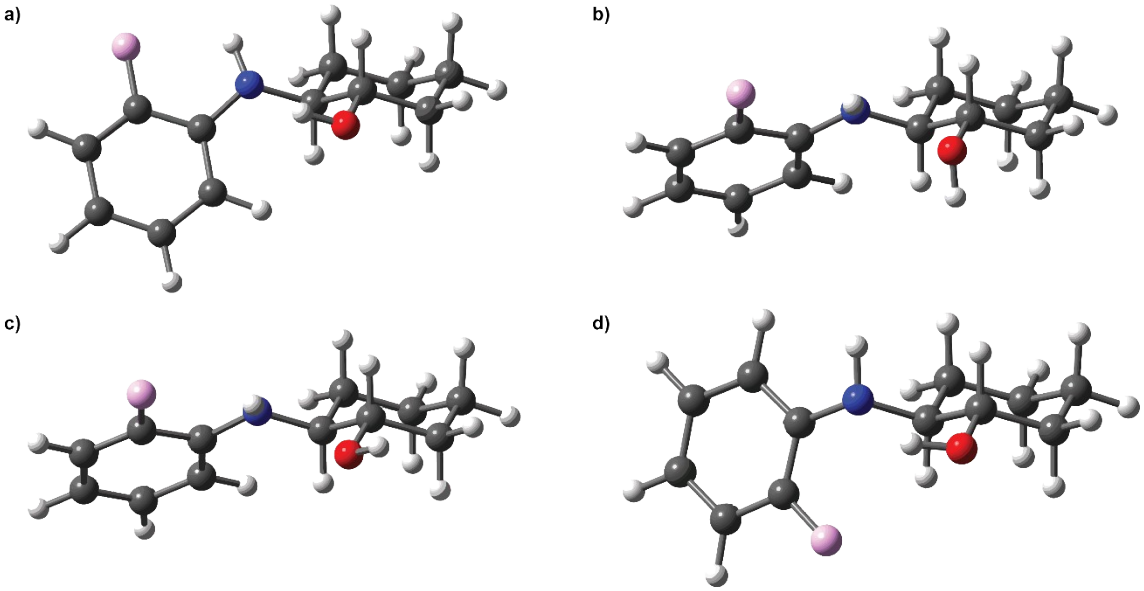

Figure S44. Geometry of conformers optimised at M06-2X/aug-cc-pVDZ level for compound 1: A1 (**a**), A2 (**b**), A3 (**c**) and A4 (**d**).

Geometry A1

0 1

H	0.68379	-1.77028	0.76648
C	1.55060	-1.14534	0.56477
C	3.81636	0.40176	0.01465
C	1.37494	0.11314	-0.03643
C	2.82714	-1.61067	0.88899
C	3.96393	-0.85094	0.62071
C	2.54741	0.84344	-0.29354
H	2.92677	-2.59016	1.35525
H	4.95590	-1.22032	0.87314
H	4.67122	1.03557	-0.21749
N	0.15507	0.63454	-0.42397
H	0.18921	1.61325	-0.68445
F	2.39269	2.06290	-0.88337
C	-1.11631	0.20971	0.15975
C	-3.28114	0.98416	1.18882
C	-3.22932	-1.08689	-0.24900
C	-4.06238	0.11304	0.20372
C	-1.91049	-0.62667	-0.84601
C	-1.93834	1.42009	0.60099
H	-3.10004	0.41358	2.11222
H	-3.01256	-1.74067	0.60969
H	-4.33590	0.71614	-0.67521
H	-2.11023	0.01183	-1.72487
H	-2.10667	2.06761	-0.27405
H	-0.91198	-0.41744	1.03902
H	-3.86908	1.86885	1.46421
H	-3.77235	-1.68334	-0.99305
H	-4.99717	-0.23284	0.66247
H	-1.36052	1.99769	1.33373
O	-1.17416	-1.77548	-1.25307
H	-0.33119	-1.46254	-1.60885

Geometry A2

0 1

H	-0.70802	-1.90091	0.64580
C	-1.57407	-1.27940	0.43128
C	-3.83905	0.28069	-0.08490
C	-1.39551	0.01026	-0.09615
C	-2.85514	-1.77722	0.68603
C	-3.99045	-1.01192	0.43131
C	-2.56679	0.74971	-0.33144
H	-2.95776	-2.78248	1.09299
H	-4.98559	-1.40490	0.63039
H	-4.69370	0.92195	-0.29631
N	-0.17121	0.56858	-0.41993
H	-0.17091	1.58176	-0.37074
F	-2.40694	2.00772	-0.83021
C	1.07208	-0.03504	0.04494
C	2.85339	-1.76486	-0.39348
C	3.47245	0.46610	0.59982
C	3.93451	-0.68938	-0.28941
C	2.14762	1.05000	0.12332

C	1.54125	-1.15732	-0.88596	H	3.17363	-2.56332	-1.07449
H	2.69536	-2.22383	0.59456	H	4.22125	1.26785	0.62081
H	3.33975	0.10715	1.63322	H	4.86522	-1.11380	0.10769
H	4.15591	-0.30387	-1.29609	H	0.76290	-1.92464	-0.97299
H	2.27291	1.48290	-0.88044	O	1.72581	2.13870	0.94211
H	1.68317	-0.72499	-1.88783	H	1.66112	1.81391	1.85115
H	0.93744	-0.44162	1.06466				

Geometry A3

0 1

H	0.71222	-1.89991	-0.65133
C	1.57726	-1.27779	-0.43473
C	3.83998	0.28443	0.08467
C	1.39657	0.01151	0.09298
C	2.85915	-1.77436	-0.68758
C	3.99343	-1.00807	-0.43119
C	2.56689	0.75212	0.32949
H	2.96324	-2.77944	-1.09464
H	4.98921	-1.40012	-0.62889
H	4.69366	0.92667	0.29702
N	0.17156	0.56837	0.41618
H	0.17009	1.58129	0.36605
F	2.40525	2.01009	0.82804
C	-1.07040	-0.03899	-0.05167
C	-2.85133	-1.77079	0.39657
C	-3.46739	0.44971	-0.61164
C	-3.93278	-0.69562	0.28844
C	-2.14709	1.03669	-0.12701
C	-1.53645	-1.16151	0.88078
H	-2.69734	-2.23623	-0.58901
H	-3.32305	0.08586	-1.63988
H	-4.15239	-0.30315	1.29283
H	-2.28085	1.45835	0.88462
H	-1.67220	-0.73113	1.88416
H	-0.93425	-0.44009	-1.07154
H	-3.16906	-2.56455	1.08423
H	-4.22097	1.24896	-0.64317
H	-4.86426	-1.12211	-0.10442
H	-0.75749	-1.92863	0.96193
O	-1.66638	2.05578	-1.00380
H	-2.34073	2.74466	-1.05775

Geometry A4

0 1

H	1.90716	-1.59203	1.91517
C	2.29149	-0.98326	1.09620
C	3.25465	0.57038	-1.00938
C	1.44715	-0.01441	0.53758
C	3.59109	-1.17046	0.62540
C	4.07454	-0.40311	-0.43431
C	1.97684	0.74932	-0.50955
H	4.22355	-1.92933	1.08408
H	5.08455	-0.55213	-0.81206
H	3.59876	1.20213	-1.82709
N	0.15328	0.23518	1.02997
H	0.00496	-0.30913	1.87874
F	1.20813	1.73599	-1.04002
C	-0.97442	-0.00403	0.10727
C	-2.46889	-1.68593	-1.02702
C	-3.40981	0.50965	-0.22169
C	-3.69594	-0.97482	-0.45347
C	-2.20178	0.69677	0.68190
C	-1.25254	-1.48948	-0.12098
H	-2.24627	-1.27643	-2.02414
H	-3.20006	1.00430	-1.18211
H	-3.97390	-1.44605	0.50156
H	-2.41494	0.24584	1.66958
H	-1.43742	-1.96272	0.85652
H	-0.73222	0.47792	-0.84840
H	-2.67230	-2.75689	-1.15390
H	-4.27658	1.01078	0.22818
H	-4.55236	-1.08713	-1.13028
H	-0.36146	-1.96469	-0.55251
O	-1.95476	2.08808	0.84077
H	-1.05391	2.15694	1.18915

Compound 2 (*trans*-2-((3-fluoropyridin-4-yl)amino)cyclohexan-1-ol)

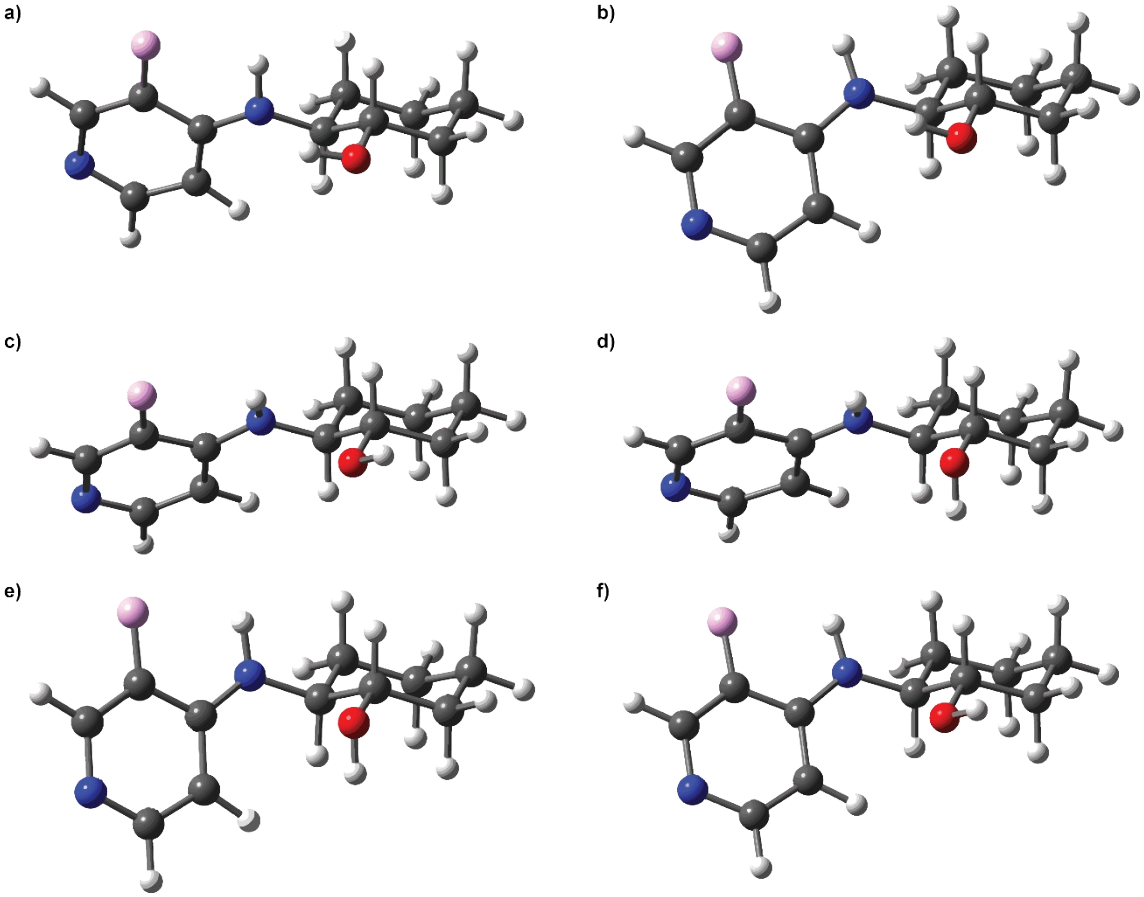

Figure S45. Geometry of conformers optimised at M06-2X/aug-cc-pVDZ level for compound 2: B1 (**a**), B2 (**b**), B3 (**c**), B4 (**d**), B5 (**e**) and B6 (**f**).

Geometry B1

0 1

C	2.19536	1.00382	0.28425
C	3.86915	-0.68035	-0.55614
C	1.41467	-1.05165	-0.95056
C	2.76020	-1.72508	-0.68519
C	1.08374	-0.03416	0.14324
C	3.53590	0.33345	0.53878
H	3.98665	-0.15654	-1.51693
H	1.44741	-0.51998	-1.91386
H	2.69758	-2.30685	0.24707
H	0.99095	-0.54057	1.11330
H	3.48367	-0.17419	1.51361
H	2.24735	1.57585	-0.66051
H	4.82759	-1.16504	-0.33211
H	0.60719	-1.79286	-1.01125
H	2.98961	-2.43000	-1.49426
H	4.31089	1.10717	0.60785
N	-0.16796	0.67519	-0.11266
H	-0.12851	1.34025	-0.88032
O	1.93164	1.89124	1.36488
H	1.01253	2.17965	1.28116
C	-1.38931	0.08723	0.06462
N	-4.01684	-0.95647	0.41896
C	-1.63096	-1.08412	0.80368
C	-2.54012	0.67980	-0.48098
C	-3.80046	0.15864	-0.29651
C	-2.93710	-1.54371	0.94758
H	-0.81654	-1.63818	1.26296
H	-4.65806	0.66198	-0.74494
H	-3.11624	-2.45153	1.52510
F	-2.37866	1.80964	-1.21517

Geometry B2

0 1

C	-1.84142	-0.60860	-0.85003
C	-4.07234	0.07090	0.07776
C	-2.00570	1.39687	0.65416
C	-3.37391	0.91980	1.14049
C	-1.13309	0.21613	0.22890
C	-3.19029	-1.10125	-0.35329
H	-4.29567	0.69844	-0.79824
H	-2.13036	2.06851	-0.20982
H	-3.24193	0.32142	2.05454
H	-0.95950	-0.43183	1.09859
H	-3.01936	-1.77683	0.49872
H	-1.99022	0.04535	-1.72719
H	-5.02995	-0.30446	0.45978
H	-1.48587	1.96035	1.43891
H	-3.99328	1.78588	1.40561
H	-3.67254	-1.68345	-1.14858
N	0.15696	0.69857	-0.24895
H	0.16956	1.62445	-0.65992
O	-1.06578	-1.74195	-1.22603
H	-0.22230	-1.42189	-1.57249
C	1.36353	0.14916	0.04352
N	3.97871	-0.86941	0.56502
C	1.56989	-1.09521	0.67096
C	2.54820	0.82538	-0.30433
C	3.79782	0.31536	-0.04201
C	2.86900	-1.53756	0.90125
H	0.73120	-1.72055	0.96451
H	4.67927	0.88880	-0.33245
H	3.01653	-2.50200	1.38929
F	2.42566	2.03038	-0.91887

Geometry B3

0 1

C	-2.13937	1.03881	-0.15445
C	-3.93511	-0.66454	0.34116
C	-1.53299	-1.15392	0.88895
C	-2.86648	-1.75263	0.44476
C	-1.07648	-0.04935	-0.06994
C	-3.47595	0.45334	-0.59542
H	-4.12437	-0.24757	1.34180
H	-1.63580	-0.71181	1.89103
H	-2.74015	-2.23649	-0.53582
H	-0.94905	-0.46739	-1.08174
H	-3.35688	0.06291	-1.61714
H	-2.24877	1.48844	0.84856
H	-4.88166	-1.08581	-0.01977
H	-0.75848	-1.92788	0.95249
H	-3.17871	-2.53009	1.15314
H	-4.22070	1.26055	-0.63133
N	0.18252	0.54828	0.35502
H	0.16942	1.53330	0.58919
O	-1.66595	2.02571	-1.06865
H	-2.34618	2.70646	-1.14798
C	1.39412	0.01286	0.06757
N	4.01320	-0.99734	-0.44522
C	1.60667	-1.25264	-0.51384
C	2.57414	0.72139	0.36176
C	3.82601	0.21412	0.10618
C	2.90794	-1.69140	-0.74002
H	0.77118	-1.89192	-0.78707
H	4.70465	0.81062	0.35585
H	3.06136	-2.67300	-1.19084
F	2.44408	1.95459	0.91554

Geometry B4

0 1

C	2.14406	1.05151	0.13820
C	3.93449	-0.67022	-0.33253
C	1.53313	-1.15439	-0.88541
C	2.86108	-1.75411	-0.42704
C	1.07807	-0.04337	0.06646
C	3.48156	0.46958	0.58118
H	4.13141	-0.27002	-1.33854
H	1.64569	-0.71510	-1.88784
H	2.72679	-2.22517	0.55875
H	0.95638	-0.46043	1.08139
H	3.37042	0.09619	1.61203
H	2.24765	1.49497	-0.86365
H	4.87677	-1.09153	0.03956
H	0.75740	-1.92667	-0.95368
H	3.17367	-2.54202	-1.12358
H	4.22454	1.27665	0.59880
N	-0.18170	0.55266	-0.35538
H	-0.17166	1.54643	-0.54994
O	1.73130	2.12715	0.97564
H	1.67603	1.79041	1.88090
C	-1.39286	0.01231	-0.06866
N	-4.00952	-1.00724	0.43402
C	-1.60273	-1.25937	0.49905
C	-2.57362	0.72338	-0.35233
C	-3.82477	0.21127	-0.10221
C	-2.90336	-1.70301	0.72060
H	-0.76618	-1.89985	0.76614
H	-4.70448	0.80936	-0.34408
H	-3.05519	-2.68998	1.16004
F	-2.44570	1.96337	-0.89064

Geometry B5

0 1

C	1.71191	-0.50908	0.88549
C	4.06031	-0.02740	0.10174
C	2.12421	1.29639	-0.81781
C	3.50151	0.70649	-1.11657
C	1.14813	0.21930	-0.34187
C	3.08410	-1.10096	0.58298
H	4.23152	0.69547	0.91376
H	2.21030	2.05978	-0.02840
H	3.41737	0.00196	-1.95776
H	1.01326	-0.51261	-1.14988
H	2.96599	-1.87084	-0.19723
H	1.79889	0.22526	1.70049
H	5.02945	-0.48304	-0.13696
H	1.70619	1.78630	-1.70577
H	4.18563	1.50529	-1.42912
H	3.45939	-1.59881	1.48606
N	-0.14274	0.82492	-0.05760
H	-0.12394	1.65316	0.52680
O	0.80600	-1.49381	1.37133
H	0.73925	-2.19027	0.70364
C	-1.34405	0.20831	-0.18335
N	-3.97023	-0.89365	-0.43066
C	-1.58406	-1.02190	-0.82795
C	-2.50420	0.82779	0.31860
C	-3.75824	0.27842	0.19000
C	-2.88458	-1.50521	-0.92135
H	-0.77244	-1.60300	-1.25726
H	-4.61695	0.80812	0.60513
H	-3.05555	-2.45738	-1.42571
F	-2.35287	2.01993	0.95333

Geometry B6

0 1

C	-1.78690	-0.62919	-0.81277
C	-4.07310	0.06612	-0.01785
C	-2.04141	1.39432	0.65299
C	-3.43198	0.92234	1.07349
C	-1.13250	0.22313	0.27355
C	-3.16470	-1.11055	-0.37202
H	-4.23925	0.68238	-0.91434
H	-2.12588	2.06303	-0.21826
H	-3.34941	0.33065	1.99761
H	-0.97566	-0.41033	1.15767
H	-3.03713	-1.76329	0.50503
H	-1.88737	-0.00223	-1.71607
H	-5.05318	-0.30210	0.31026
H	-1.56151	1.96332	1.45866
H	-4.06154	1.79227	1.29915
H	-3.60474	-1.71628	-1.17665
N	0.15743	0.74481	-0.14849
H	0.15680	1.64442	-0.61344
O	-0.90972	-1.71943	-1.08226
H	-1.32345	-2.27266	-1.75682
C	1.36189	0.16965	0.07288
N	3.98895	-0.86779	0.50540
C	1.58232	-1.07677	0.69254
C	2.54038	0.83601	-0.31483
C	3.79489	0.31740	-0.09646
C	2.88449	-1.52704	0.87959
H	0.74799	-1.69767	1.00432
H	4.66935	0.88492	-0.41826
H	3.04190	-2.49275	1.36247
F	2.40621	2.04446	-0.92313

Compound 3 (*trans*-2-((perfluoropyridin-4-yl)amino)cyclohexan-1-ol)

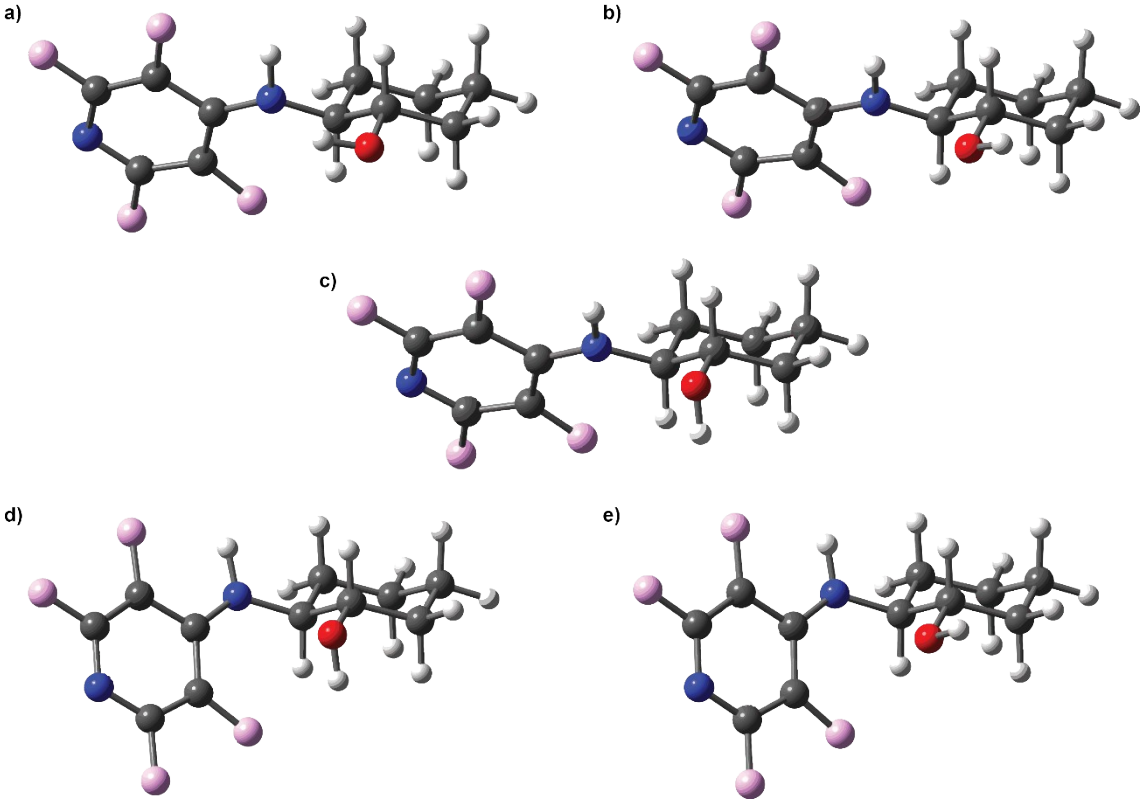

Figure S46. Geometry of conformers optimised at M06-2X/aug-cc-pVDZ level for compound 3: C1 (**a**), C2 (**b**), C3 (**c**), C4 (**d**) and C5 (**e**).

Geometry C1

0 1

C	-1.63169	-0.04545	0.11804
C	-3.21883	1.31573	-1.28337
C	-4.10251	-0.22724	0.49783
C	-4.36439	0.38888	-0.87638
C	-2.77508	-0.96857	0.53497
C	-1.88806	0.56609	-1.25969
H	-3.16935	2.16429	-0.58433
H	-4.07057	0.56426	1.26146
H	-4.46561	-0.41202	-1.62425
H	-2.80825	-1.81554	-0.17464
H	-1.90372	-0.24800	-2.00033
H	-1.55592	0.73998	0.87730
H	-3.39425	1.72776	-2.28497
H	-4.90248	-0.92484	0.77529
H	-5.31346	0.93891	-0.85921
H	-1.05566	1.23271	-1.52123
O	-2.58754	-1.45782	1.85794
H	-1.69647	-1.82771	1.91520
N	-0.39349	-0.83472	0.14641
C	0.85891	-0.31897	0.08356
N	3.56518	0.56774	-0.01133
C	1.94260	-1.16128	-0.24148
C	1.23641	1.01043	0.35197
C	2.56990	1.37031	0.28679
C	3.22966	-0.67944	-0.26972
F	0.33310	1.95270	0.67561
H	-0.47654	-1.75433	-0.28055
F	1.68947	-2.45090	-0.52641
F	4.22277	-1.51964	-0.58250
F	2.88459	2.64485	0.54841

Geometry C2

0 1

C	-1.62703	-0.06951	0.14267
C	-3.18429	1.46909	-1.10811
C	-4.10222	-0.27554	0.44977
C	-4.34698	0.51544	-0.83509
C	-2.77818	-1.03119	0.40612
C	-1.86449	0.70246	-1.15834
H	-3.13503	2.22507	-0.30969
H	-4.07395	0.40814	1.31138
H	-4.44991	-0.18162	-1.68029
H	-2.80334	-1.77084	-0.41453
H	-1.88274	-0.02178	-1.98658
H	-1.57686	0.62342	0.99095
H	-3.33877	2.00289	-2.05407
H	-4.91290	-0.99662	0.62317
H	-5.28974	1.07074	-0.75447
H	-1.02242	1.38292	-1.33535
O	-2.51092	-1.69322	1.63876
H	-3.26837	-2.25743	1.84014
N	-0.38249	-0.83868	0.09303
C	0.86175	-0.32889	0.06453
N	3.56773	0.57787	0.00883
C	1.23157	1.00167	0.35279
C	1.95874	-1.16206	-0.25006
C	3.24106	-0.67051	-0.26009
C	2.56187	1.37002	0.30366
F	1.71677	-2.45267	-0.54466
H	-0.46501	-1.80877	-0.19120
F	0.31746	1.93006	0.69271
F	2.86599	2.64407	0.58443
F	4.24409	-1.50263	-0.56688

Geometry C3

0 1

C	-1.62853	-0.07817	0.14376
C	-3.17621	1.48219	-1.08501
C	-4.10763	-0.29418	0.43724
C	-4.34411	0.53066	-0.82832
C	-2.78394	-1.05056	0.38750
C	-1.86093	0.70924	-1.14908
H	-3.12159	2.22464	-0.27427
H	-4.08845	0.37251	1.31460
H	-4.45221	-0.14783	-1.68789
H	-2.80354	-1.77641	-0.43979
H	-1.88666	-0.00778	-1.98353
H	-1.58673	0.61095	0.99775
H	-3.32891	2.03273	-2.02162
H	-4.91596	-1.01977	0.59006
H	-5.28327	1.09031	-0.73569
H	-1.01594	1.38674	-1.32339
O	-2.58079	-1.83023	1.55984
H	-2.61434	-1.23330	2.32029
N	-0.38172	-0.84197	0.09734
C	0.86167	-0.33000	0.06729
N	3.56468	0.58362	0.00355
C	1.96019	-1.16196	-0.24471
C	1.22827	1.00228	0.35092
C	2.55740	1.37432	0.29727
C	3.24116	-0.66695	-0.25900
F	0.31198	1.92786	0.69283
H	-0.46074	-1.81696	-0.16986
F	1.72109	-2.45443	-0.53304
F	4.24598	-1.49765	-0.56349
F	2.85872	2.65014	0.57273

Geometry C4

0 1

C	-1.70014	-0.25444	-0.40962
C	-4.11260	-0.53369	-1.08395
C	-3.51718	0.83059	0.94564
C	-4.55675	-0.09308	0.31039
C	-2.14597	0.16681	0.99636
C	-2.73240	-1.18748	-1.04096
H	-4.07658	0.34248	-1.74853
H	-3.43378	1.75738	0.35441
H	-4.68812	-0.98080	0.94733
H	-2.19514	-0.73920	1.61808
H	-2.77747	-2.11190	-0.44356
H	-1.59980	0.64011	-1.03445
H	-4.83790	-1.23682	-1.51185
H	-3.81002	1.11200	1.96496
H	-5.52689	0.41658	0.25855
H	-2.39658	-1.46097	-2.04883
O	-1.17390	0.99628	1.62293
H	-1.16982	1.84600	1.16098
N	-0.41286	-0.94629	-0.37206
C	0.81121	-0.39918	-0.23635
N	3.49362	0.55028	0.00769
C	1.91209	-1.23160	0.06582
C	1.16593	0.95414	-0.41080
C	2.48353	1.34272	-0.27411
C	3.18245	-0.71950	0.17066
F	0.24941	1.89296	-0.71562
H	-0.46668	-1.93243	-0.13678
F	1.68675	-2.54556	0.25310
F	4.18814	-1.55447	0.46110
F	2.77166	2.64013	-0.44432

Geometry C5

0 1

C	-1.70264	-0.19570	-0.43709
C	-4.13293	-0.37720	-1.08998
C	-3.48315	0.74710	1.06099
C	-4.54380	-0.09800	0.35565
C	-2.12149	0.06450	1.00871
C	-2.75630	-1.03771	-1.15440
H	-4.10552	0.57031	-1.64852
H	-3.39631	1.72897	0.57164
H	-4.66458	-1.05203	0.89072
H	-2.17975	-0.91104	1.52257
H	-2.79778	-2.02804	-0.67424
H	-1.59490	0.76549	-0.94869
H	-4.87215	-1.02281	-1.58015
H	-3.75565	0.92023	2.11141
H	-5.51236	0.41636	0.38484
H	-2.44242	-1.18771	-2.19457
O	-1.09963	0.85832	1.60481
H	-1.33879	1.01017	2.52775
N	-0.42307	-0.90458	-0.49469
C	0.80508	-0.37671	-0.29817
N	3.48497	0.53456	0.06140
C	1.17721	0.97631	-0.42938
C	1.88436	-1.22948	0.01764
C	3.15661	-0.73490	0.17921
C	2.49354	1.34538	-0.23678
F	1.63973	-2.54544	0.16334
H	-0.48941	-1.89645	-0.28596
F	0.28714	1.92555	-0.76104
F	2.80313	2.64291	-0.36811
F	4.14272	-1.58872	0.48352

Computational details – implicit and explicit solvation

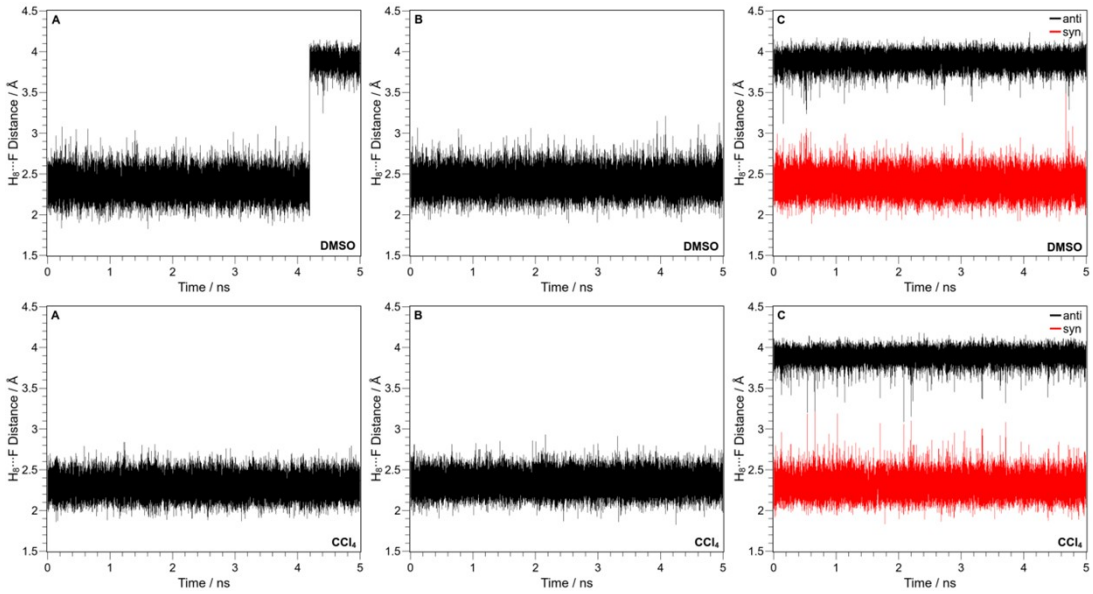

Figure S47. Time development of the H8···F distance throughout the MD production trajectory. For compound 3, the distances from H8 to both F10 (syn) and F14 (anti) were measured separately to show that in both solvents there is no variation of the dihedral angles, which would lead to a change in the positions of the F atoms.

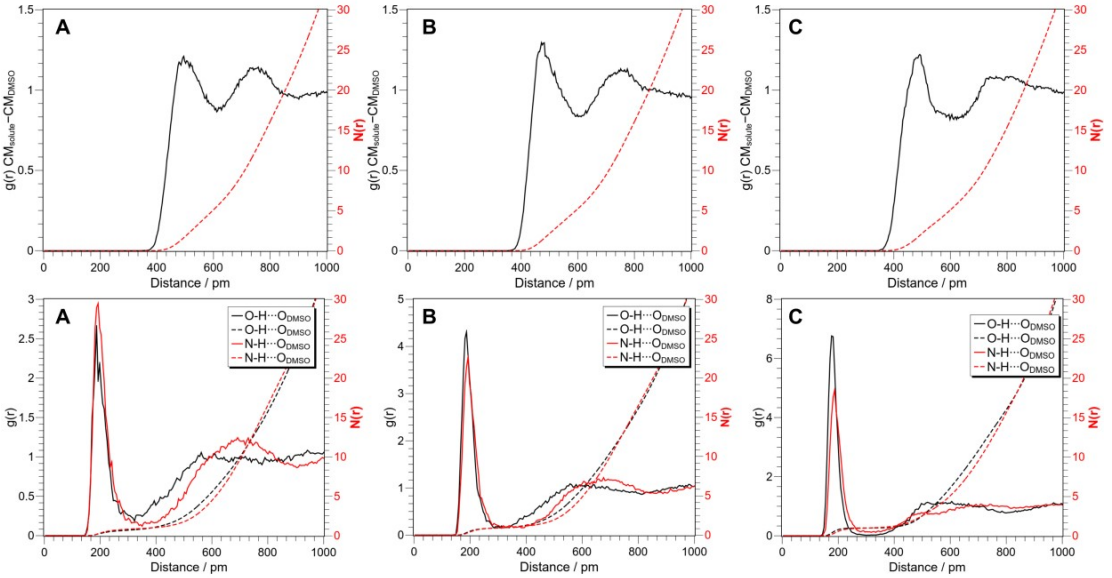

Figure S48. Top: Radial distribution function, g(r), between centres of mass of compounds A, B, and C and solvent showing the first (peak starting at 3.5 Å) and second (peak starting at 6.0 Å) solvation shells; Bottom: Radial distribution functions, g(r), and their integrations, N(r), between hydrogens H7 and H8 of compounds A, B, and C and oxygen of solvent.

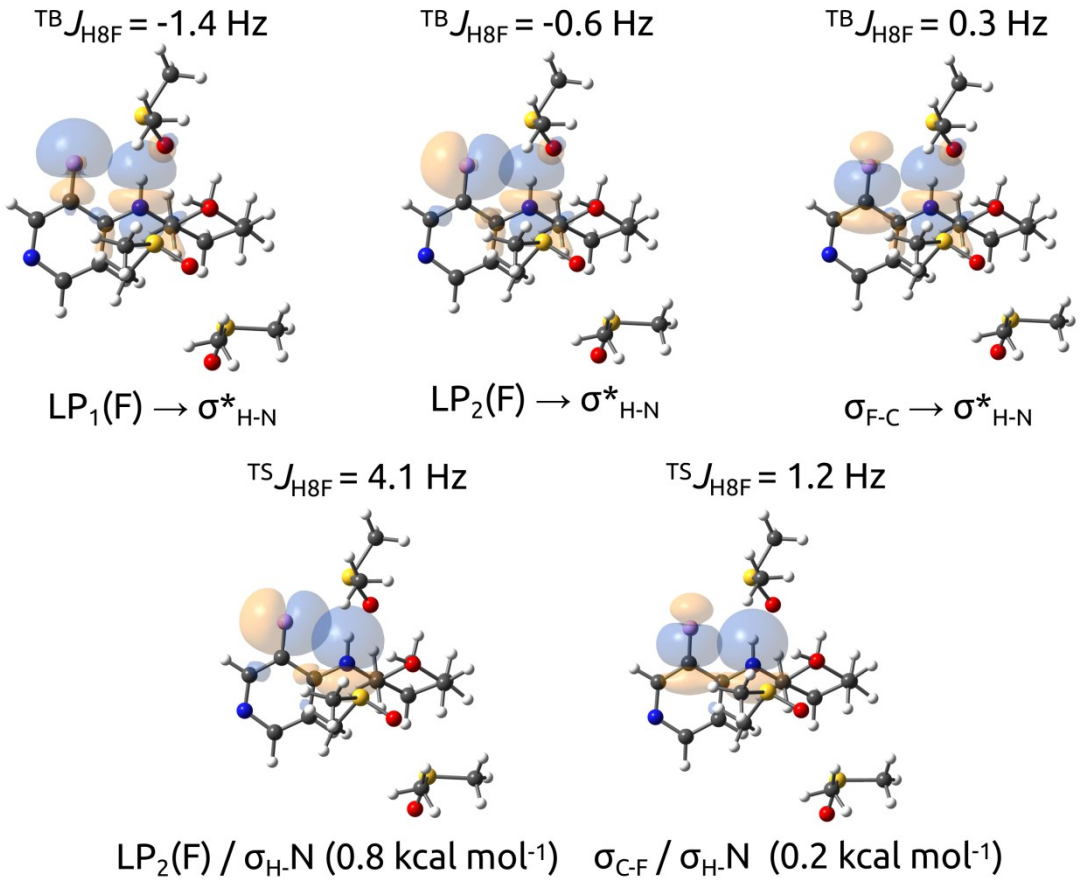

Figure S49. Main NJC interactions for the transmission pathway through-space ($^{TS}J_{H8F}$) and through-bond ($^{TS}J_{H8F}$) for compound **2,** where red=O; blue=N; grey=C; yellow=S; light blue=F; white=H.

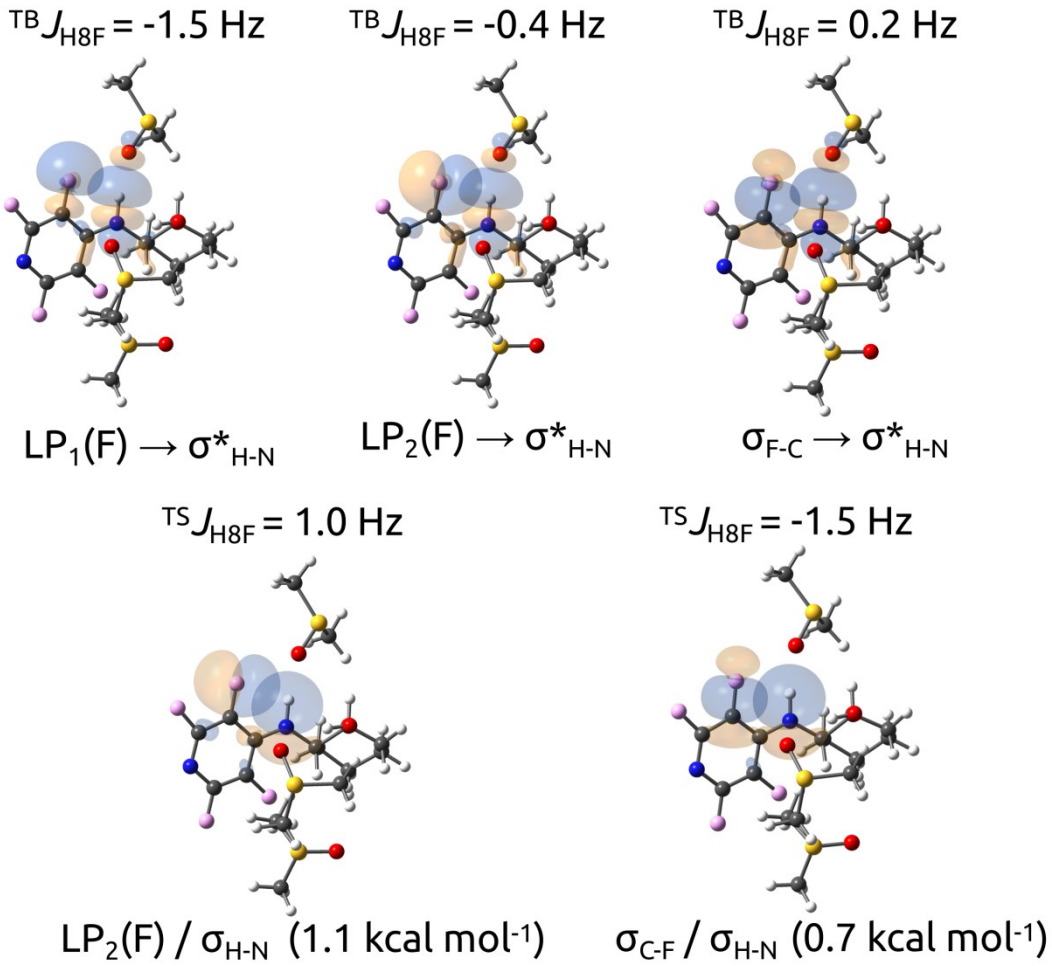

Figure S50. Main NJC interactions for the transmission pathway through-space ($^{TS}J_{H8F}$) and through-bond ($^{TS}J_{H8F}$) for compound **3,** where red=O; blue=N; grey=C; yellow=S; light blue=F; white=H.

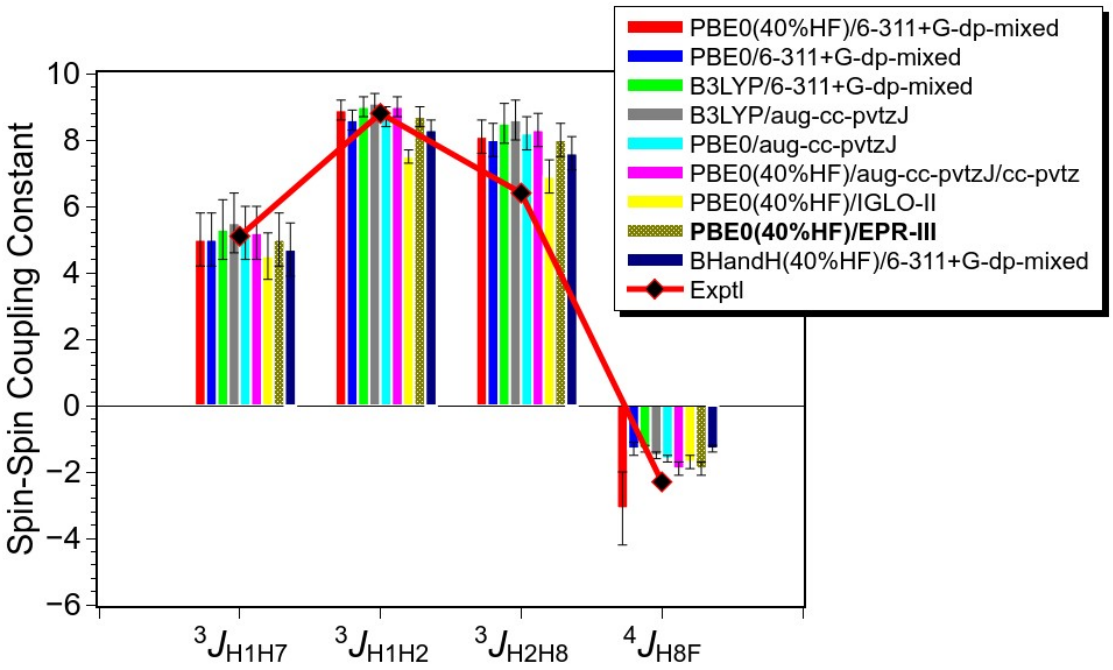

Figure S51. Levels of theory tested to calculate the *J*-couplings averaged over 32 MD configurations from production trajectory of compound 1, taking into account the implicit (SMD) and explicit (3 DMSO solvent molecules) solvation.

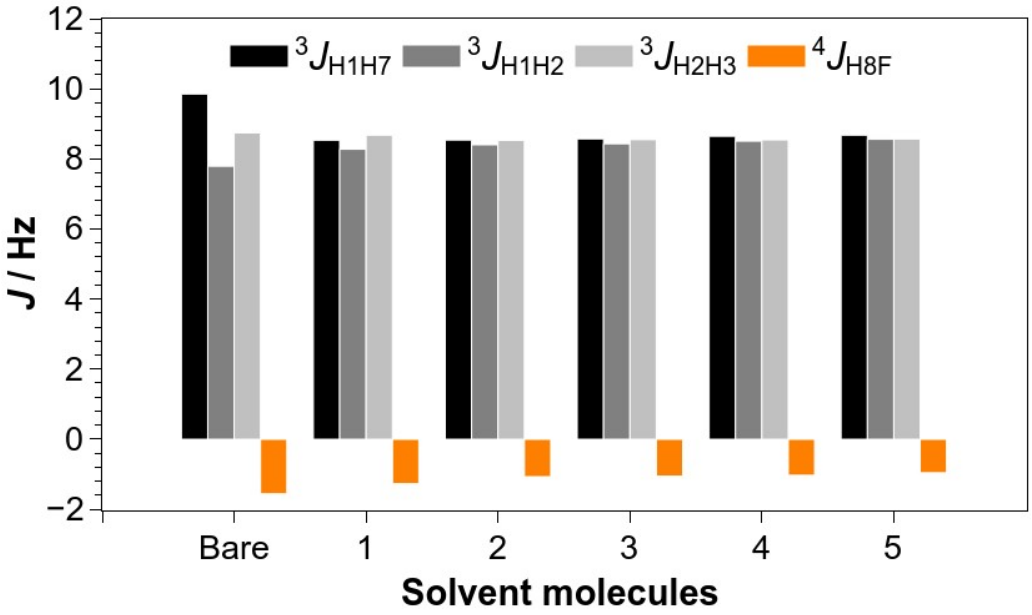

Figure S52. *J*-coupling dependence on the explicit nearest neighbouring (NN) solvent count for compound 1**.** All data are means corresponding to trajectory averages (32 configurations). The 'Bare' corresponds to structures wherein all solvent molecules were stripped and without implicit solvation, while the remaining counts (1–5) correspond to structures including the NN given number of explicit solvent molecules and implicit solvation via SMD.

Averaged *J*-coupling over MD configurations solvated by 3 DMSO molecules

Compound 1 (*trans*-2-((2-fluorophenyl)amino)cyclohexan-1-ol)

#Configuration JH1H7 JH1H2 JH2H8 JH8F#
0001 -0.490494 9.210510 10.545600 -3.728410
0002 14.777400 9.877320 7.400380 -1.751440
0003 8.936610 7.248510 12.281700 -1.932490
0004 2.719440 8.096620 5.880380 -0.772849
0005 3.816270 6.860520 9.710680 -1.280280
0006 3.396030 9.678050 6.823810 -1.614630
0007 -0.009980 6.804460 8.688640 -3.916140
0008 2.103380 11.504900 10.999100 -1.876540
0009 2.096640 9.897330 8.972120 1.159850
0010 0.475454 10.603500 12.724200 -1.538880
0011 11.976400 8.619730 4.789580 -2.047750
0012 6.190280 8.510260 7.320780 -3.589050
0013 0.470093 11.432100 11.254900 -1.823050
0014 3.619550 8.405570 9.377660 -2.283710
0015 1.357060 7.133460 5.178230 -1.257440
0016 7.919010 10.104900 5.394460 -1.620720
0017 3.467690 7.190400 3.395010 -0.657158
0018 11.902600 8.594780 7.206120 -1.476220
0019 2.526670 7.518270 0.789334 -1.781270
0020 4.390510 8.863280 9.391840 -0.798363
0021 4.977270 7.482860 1.510590 -1.391690
0022 1.163230 9.443340 8.469920 -1.899840
0023 2.622160 11.474900 8.472040 -2.037720
0024 6.321940 7.759200 6.005070 -1.936790
0025 9.127340 8.618580 10.445400 -1.536750
0026 3.197530 9.545390 8.135900 -1.666190
0027 2.181980 8.737810 5.484550 -2.700910
0028 14.417500 8.849720 13.031300 -2.271110
0029 -0.077980 5.217260 7.061860 -2.711580
0030 0.049605 10.188300 9.673170 -1.201990
0031 11.566800 6.382010 9.919190 -3.044660
0032 13.478200 9.212730 10.366600 -3.025540

== JH1H7 ==

```
##################################
#     Statistic Parameters     #
##################################
N = 32
sum = 160.666
mean = 5.020818
mean error = 0.807625
std = 4.56861
variance = 20.8722

== JH1H2 ==

##################################
#     Statistic Parameters     #
##################################
N = 32
sum = 279.067
mean = 8.720830
mean error = 0.26524
std = 1.50042
variance = 2.25127

== JH2H8 ==

##################################
#     Statistic Parameters     #
##################################
N = 32
sum = 256.7
mean = 8.021879
mean error = 0.520676
std = 2.94539
variance = 8.67531

== JH8F ==

##################################
#     Statistic Parameters     #
##################################
N = 32
sum = -60.0113
mean = -1.875353
mean error = 0.17139
std = 0.969526
variance = 0.93998
```

Compound 2 (*trans*-2-((3-fluoropyridin-4-yl)amino)cyclohexan-1-ol)

#Configuration JH1H7 JH1H2 JH2H8 JH8F#
0001 14.187200 6.379480 11.104500 -1.262520
0002 8.553420 6.176030 2.106370 -0.688670
0003 3.041640 8.151020 4.214440 -1.249630
0004 3.281580 10.362100 3.564680 -0.318929
0005 5.635310 9.157680 12.832100 -7.272320
0006 -0.179171 8.246270 6.048730 -1.383590
0007 8.685500 7.306900 5.960620 -1.771960
0008 0.471405 8.421220 6.899680 -0.580591
0009 11.159000 7.795550 13.486100 -2.433300
0010 6.211810 10.147900 12.180200 -0.651525
0011 15.420600 8.092850 12.477400 -3.194550
0012 2.064390 11.333800 6.530750 -0.998028
0013 -0.559975 12.368100 8.822900 -2.346760
0014 0.189940 8.456030 11.387400 -2.014890
0015 4.113320 9.106220 7.404100 -2.591680
0016 0.110255 7.229720 4.995530 -3.254470
0017 3.035480 4.950330 12.760700 -1.860780
0018 4.217070 8.799670 8.328520 -1.419750
0019 6.558520 9.766790 10.460200 -1.945080
0020 5.738570 10.687400 9.644980 -0.457803
0021 3.064540 9.373370 9.893440 -2.337870
0022 14.384100 9.679390 10.000100 -1.218980
0023 -0.309235 7.245510 11.021500 -1.727680
0024 11.566100 8.083630 9.149170 -1.590180
0025 5.252600 9.977360 5.351980 -1.288640
0026 0.704359 7.869410 9.581020 -4.337140
0027 1.154710 7.308420 7.592980 -2.849960
0028 8.905080 8.650610 2.291170 -0.848150
0029 14.166600 6.934530 13.664000 -2.646870
0030 11.712700 6.311770 8.022450 -1.287700
0031 18.553800 8.123600 11.937600 -3.296760
0032 11.109300 7.531720 8.959740 -3.256580

== JH1H7 ==

##################################
Statistic Parameters
##################################
N = 32
sum = 202.201
mean = 6.318766

mean error = 0.944796
std = 5.34458
variance = 28.5645

== JH1H2 ==

##################################
Statistic Parameters
##################################
N = 32
sum = 270.024
mean = 8.438262
mean error = 0.277696
std = 1.57089
variance = 2.46768

== JH2H8 ==

##################################
Statistic Parameters
##################################
N = 32
sum = 278.675
mean = 8.708595
mean error = 0.564654
std = 3.19417
variance = 10.2027

== JH8F ==

##################################
Statistic Parameters
##################################
N = 32
sum = -64.3833
mean = -2.011979
mean error = 0.238568
std = 1.34955
variance = 1.82128

Compound 3 (*trans*-2-((perfluoropyridin-4-yl)amino)cyclohexan-1-ol)

#Configuration JH1H7 JH1H2 JH2H8 JH8F10 JH8F14#
0001 4.060660 5.971540 4.732060 -2.188360 -2.263230

0002 -0.293406 7.759830 12.092500 -3.112940 -2.087670
0003 0.464467 8.790290 9.682200 -1.424530 -2.401430
0004 14.417500 8.053830 9.822940 -1.449540 -2.807440
0005 -0.265573 9.479780 11.099100 -1.803220 -2.268090
0006 15.276500 6.579460 10.392300 -2.999710 -2.622560
0007 0.779608 10.726800 9.514050 -0.843970 -2.631760
0008 11.449500 8.193530 13.627500 -2.484320 -2.323410
0009 11.288600 7.884840 10.708100 -0.006170 -0.409293
0010 13.913500 9.050390 5.267730 -1.898800 -3.523920
0011 2.532310 7.413580 3.775670 -1.395440 -2.901760
0012 -0.023744 7.562580 11.975100 -2.996120 -2.539830
0013 4.741970 10.999100 6.749650 0.479245 -1.549950
0014 7.954840 9.408710 7.443940 -0.903361 -2.609880
0015 8.518420 6.831640 7.139630 0.299230 -0.904565
0016 12.894100 10.178500 6.696280 -1.801600 -2.856650
0017 5.025420 8.466300 8.578360 -1.380120 -3.031260
0018 9.113410 10.243000 8.655890 -1.473920 -2.605480
0019 4.969120 7.381170 9.261920 -0.864282 -2.714040
0020 2.458980 9.743350 5.671690 -6.306400 -2.085400
0021 2.910400 5.447110 7.035240 -0.578356 -1.951640
0022 4.695130 7.920130 0.434320 2.932020 2.272620
0023 1.048080 7.307140 5.737600 -2.405180 -2.829620
0024 -0.259280 8.358220 9.052940 -4.942140 -2.111900
0025 1.400680 9.545140 4.539260 -3.066700 -2.155070
0026 0.512825 7.554150 8.299340 -1.959790 -2.116820
0027 3.090610 8.177660 11.469100 -3.390030 -2.739570
0028 -0.859410 8.805010 11.400000 -2.666760 -2.536740
0029 0.948714 6.040500 10.325100 0.427512 -0.119022
0030 10.499800 7.723780 9.636110 -3.046040 -2.227490
0031 4.562250 8.626310 8.526660 -2.434650 -2.760880
0032 2.178540 7.143980 10.432600 -3.296620 -2.947750

== JH1H7 ==

##################################
Statistic Parameters
##################################
N = 32
sum = 160.005
mean = 5.000141
variance = 23.8037
std = 4.8789
mean error = 0.862476

== JH1H2 ==

```
###################################
#     Statistic Parameters     #
###################################
N = 32
sum = 263.367
mean = 8.230230
variance = 1.80111
std = 1.34205
mean error = 0.237244

== JH2H8 ==

###################################
#     Statistic Parameters     #
###################################
N = 32
sum = 269.775
mean = 8.430465
variance = 7.86913
std = 2.8052
mean error = 0.495894

== JH8F10 ==

###################################
#     Statistic Parameters     #
###################################
N = 32
sum = -58.9811
mean = -1.843158
variance = 2.80576
std = 1.67504
mean error = 0.296108

== JH8F14 ==

###################################
#     Statistic Parameters     #
###################################
N = 32
sum = -69.3615
mean = -2.167547
variance = 1.13331
std = 1.06457
```

mean error = 0.188191