Supporting Information

4-Fluoro-Threonine: From Diastereoselective Synthesis to pH-Dependent Conformational Equilibrium in Aqueous Solution

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Optimization of the reaction conditions

Table S1. Tested conditions for diastereoselective formation of oxazoline **2**.[a]

Entry	Solvent	Base[b]	Additive[c]	Notes	Yield (%)[d]	2:3[e]	d. r.[f]
1	THF	TEA	none	-	63	70:30	76:24
2	THF	TEA	none	TEA-deactivated silica for chromatographic purification	71	90:10	85:15
3	DCM	DIPEA	PPh_3	-	73	85:15	>99:1
4	DCM	DIPEA	PPh_3	TEA-deactivated silica for chromatographic purification	77	100:0	>99:1

[a] Typical general conditions: 1 equiv. of ethyl isocyanoacetate, 1 equiv. of **1**, CuCl 5 mol %. [b] TEA 5 mol %, DIPEA 10 mol %. [c] 10 mol %. [d] Sum of **2** and **3** after chromatographic purification. [e] Determined after flash chromatography of the crude by ^{1}H NMR. [f] *trans*:*cis* ratio, determined upon conversion to **4**, either after chromatographic separation of diastereoisomers (entries 1-2) or through 1H NMR analysis of crude **4** (entries 3-4).

Table S2. Tested conditions for fluorination of **5**.[a]

Entry	Fluorinating Agent	Equiv.	Additive (equiv.)	Addition order[b]	T (°C)[c]	Scale (mmol)	Reaction Time[d]	Yield[e]
1	XtalFluor-E®	1.5	DBU (1.5)	A	-78 to r.t.	0.1	4 h	traces
2	XtalFluor-E®	1.5	DBU (1.5)	A	-78 to r.t.	0.1	overnight	traces
3[f]	PyFluor	1.1	DBU (2)	A	r.t.	0.1	48 h	n. d.[g]
4	DAST	5	None	A	-78 to 0	0.2	overnight	38 %
5	DAST	5	None	A	-78 to 0	0.5	overnight	42 %
6	DAST	5	None	A	-78 to 0	0.5	3 h	25 %
7	DAST	1.1 + 1.1	None	A	-78 to 0	0.15	overnight	17 %
8	DAST	1.5 + 1	None	A	0 to r.t.	0.15	2 h + 2 h	35 %
9[h]	DAST	1.5 + 1	Na_2CO_3 (1.2)	A	0 to r.t.	0.15	2 h + 2 h	27 %
10	DAST	2.5	None	A	0 to r.t.	0.15	1 h	16 %
11	DAST	2	None	B	0 to r.t.	0.15	1.5 h	46 %
12	DAST	2	None	B	0 to r.t.	1	1.5 h	29 %
13	DAST	1.5	None	C	0 to r.t.	1	1.5 h	10 %
14	DAST	2	None	C	-78 to r.t.	0.15	3 h	58 %
15	DAST	2	None	C	-78 to r.t.	3.75	1 h	32 %
16	DAST	2	None	C	-78 to r.t.	3.75	3 h	25 %
17	DAST	2	None	C	-78 to 0	2	3 h	29 %

[a] Typical general condition: under inert atmosphere (N_2), anhydrous DCM as the solvent, quenched (for entries 1-3 the volatiles were simply removed under reduced pressure) with saturated aqueous $NaHCO_3$ added either at 0 °C (entries 4-13) or at -78 °C (entries 14-17). [b] A: neat fluorinating agent was added to a DCM solution of the alcohol; B: alcohol added to the fluorinating agent (both in DCM); C: a DCM solution of fluorinating agent was added to a DCM solution of the alcohol. [c] Room temperature (r.t.) was reached by simple removal of either -78 °C or ice bath, whilst 0 °C was reached by simple switch to ice bath. [d] Starting from removal/switch of bath. [e] Determined either by ^{1}H NMR and ^{19}F NMR analysis on the crude mixture (entries 1-3) or after flash chromatography (entries 4-17). [f] Performed in toluene with non-anhydrous conditions. [g] Not detected. [h] Performed in dry THF.

Table S3.
Titration data

4-Fluoro-threonine						Threonine			
V (μL)	pH	V (μL)	pH	V (μL)	pH	V (μL)	pH	V (μL)	pH
0	1.47	0	1.42	0	1.36	0	1.29	0	1.7
50	1.52	50	1.48	50	1.39	50	1.3	50	1.8
100	1.61	100	1.52	100	1.47	100	1.34	100	1.98
150	1.76	150	1.63	150	1.58	150	1.42	150	2.16
200	1.96	200	1.77	200	1.72	200	1.53	200	2.43
250	2.22	250	1.95	250	1.93	250	1.65	210	2.5
270	2.37	300	2.19	300	2.21	300	1.82	220	2.58
290	2.57	350	2.54	350	2.68	350	2.05	230	2.66
310	2.85	360	2.65	360	2.85	400	2.35	240	2.76
320	3.07	370	2.77	370	3.13	410	2.44	250	2.87
330	3.43	380	2.96	380	3.76	420	2.54	260	3.02
340	4.14	390	3.22	390	6.82	430	2.64	270	3.2
350	4.98	400	3.76	400	7.43	440	2.76	280	3.52
360	6.48	410	4.56	410	7.72	450	2.89	290	4.3
370	7.32	420	5.37	420	7.93	460	3.07	300	6.91
380	7.64	430	6.8	430	8.09	470	3.32	310	7.74
390	7.85	440	7.45	440	8.24	480	3.86	320	8.07
400	8.02	450	7.73	450	8.35	490	7.14	330	8.27
410	8.15	460	7.92	460	8.47	500	7.87	340	8.42
420	8.28	470	8.08	470	8.58	510	8.12	350	8.55
430	8.39	480	8.2	480	8.7	520	8.33	360	8.66
440	8.49	490	8.32	490	8.81	530	8.48	370	8.75
450	8.59	500	8.43	500	8.93	540	8.63	380	8.84
460	8.7	510	8.52	510	9.09	550	8.72	390	8.92
470	8.8	520	8.62	520	9.24	560	8.83	400	9.02
480	8.91	530	8.71	530	9.44	570	8.93	410	9.1
490	9.04	540	8.8	540	9.71	580	9.04	420	9.19
500	9.17	550	8.91	550	10.1	590	9.12	430	9.26
510	9.33	560	9.03	560	10.79	600	9.19	440	9.37
520	9.55	570	9.16	570	11.15	610	9.31	450	9.47
530	9.85	580	9.34	580	11.33	620	9.41	460	9.59
540	10.38	590	9.53	590	11.47	630	9.53	470	9.72
550	10.91	600	9.79	600	11.57	640	9.67	480	9.87
560	11.21	610	10.15	610	11.64	650	9.85	490	10,08
570	11.38	620	10,65	620	11.72	660	10,09	500	10,34
580	11.5	630	11.03	630	11.77	670	10,48	510	10,7
590	11.59	640	11.23	640	11.82	680	10,94	520	11.03
600	11.66	650	11.37	650	11.86	690	11.21	530	11.25
650	11.88	700	11.72	700	12	700	11.39	540	11.38
700	11.99	750	11.88	750	12.1	710	11.5	550	11.49
750	12.08	800	12.01	800	12.17	720	11.6	560	11.57
800	12.15	850	12.09	850	12.22	730	11.67	570	11.63
		900	12.17	900	12.27	740	11.73	580	11.68
						800	11.95	600	11.79
						850	12.05	650	11.93
						900	12.14	700	12.04
								750	12.11
								800	12.17

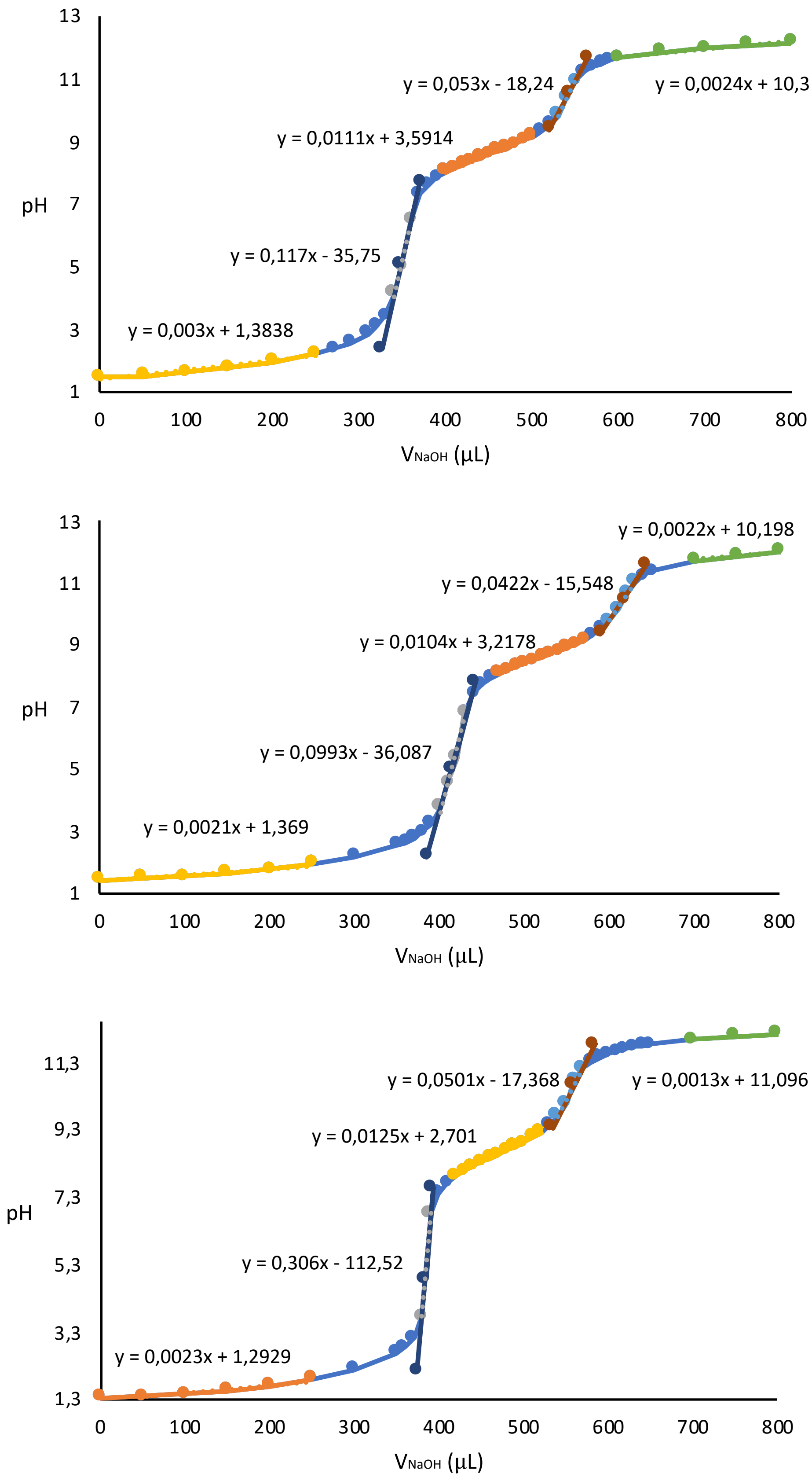


Figure S1. Titration curves of 4F-Thr.

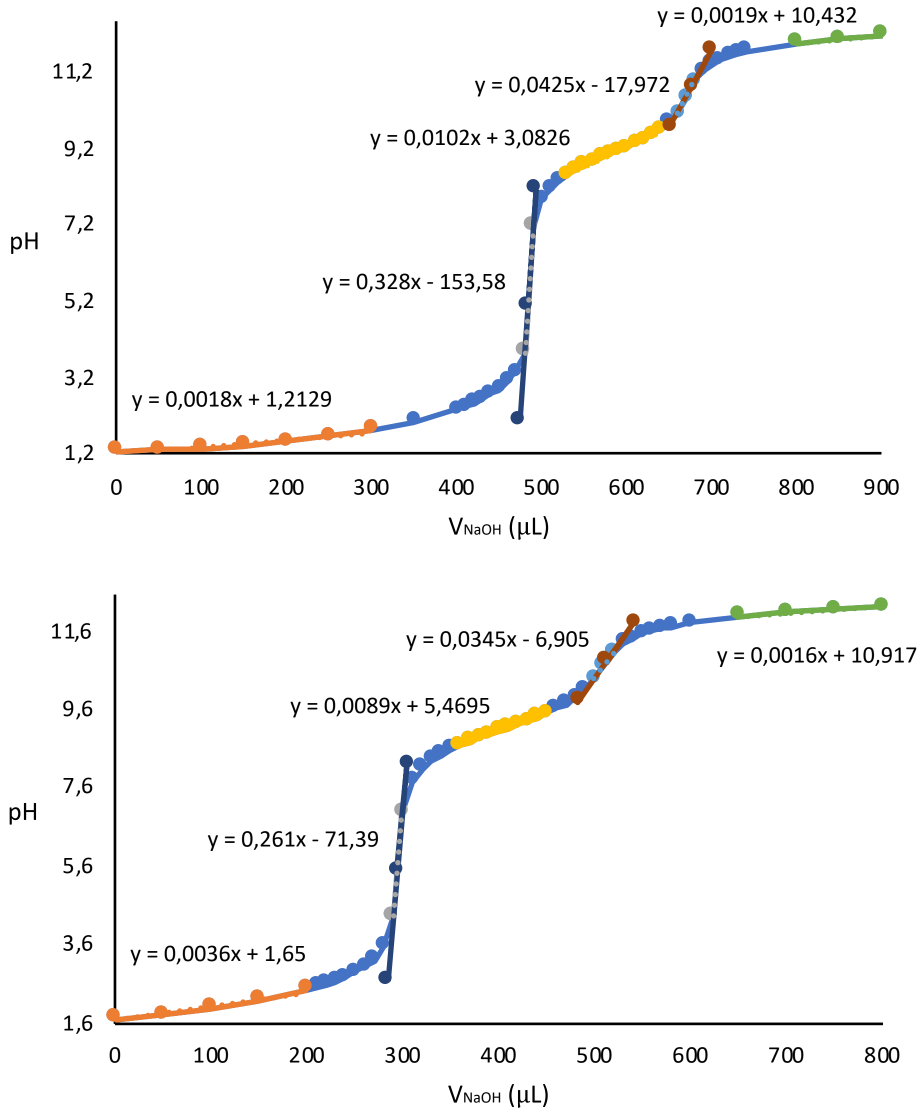


Figure S2. Titration curves of Thr.

Conformational Analysis

Table S4. ΔE and ΔG values (in kJ mol^{-1}) of different conformers of 4F-Thr, at the B2 (B2PLYP-D3(BJ)/jun-cc-pVTZ) level of theory, with respect to the most stable conformer for each form.[a]

Conf.	*ΔE*	*ΔG*	Conf.	*ΔE*	*ΔG*	Conf.	*ΔE*	*ΔG*
4FT-A-1	0.0	0.0	4FT-Z-1	0.0	0.0	4FT-C-1	0.0	0.0
4FT-A-2	4.4	3.7	4FT-Z-2	1.8	0.8	4FT-C-2	5.3	5.9
4FT-A-3	13.2	10.2	4FT-Z-3	4.5	2.8	4FT-C-3	9.2	11.2
4FT-A-4	15.9	11.9	4FT-Z-4	5.8	4.5	4FT-C-4	17.4	14.1
4FT-A-5	17.7	14.4	4FT-Z-5	6.1	6.0	4FT-C-5	15.4	14.7
4FT-A-6	20.2	16.3	4FT-Z-6	5.1	6.1	4FT-C-6	26.2	24.1
4FT-A-7	31.7	29.1	4FT-Z-7	23.3	21.6			

[a] A stands for anionic, Z for zwitterionic, and C for cationic.

Table S5. Root mean square displacements in Å between the zwitterionic and cationic forms of 4F-Thr. The hydroxy hydrogen of the cationic form was excluded in the rms calculations.

	4FT-Z-1	4FT-Z-2	4FT-Z-3	4FT-Z-4	4FT-Z-5	4FT-Z-6	4FT-Z-7
4FT-C-1	0.3305	0.7908	0.7257	0.7619	1.2391	1.3498	1.3442
4FT-C-2	0.7299	0.2203	0.785	0.7291	0.8571	1.1194	1.1143
4FT-C-3	1.2503	0.8701	1.1683	1.11	0.2242	1.1839	0.9013
4FT-C-4	0.365	0.8069	0.7489	0.7785	1.4223	1.3207	1.3065
4FT-C-5	0.7744	0.3773	0.7371	0.759	0.9183	1.1777	1.135
4FT-C-6	1.319	1.1185	1.4021	1.3783	0.9734	0.5765	0.2866

Table S6. Root mean square displacements in Å between the zwitterionic and anionic forms of the 4F-Thr. The hydrogen atoms of NH_2 and NH_3 groups were excluded in the rms calculations.

	4FT-Z-1	4FT-Z-2	4FT-Z-3	4FT-Z-4	4FT-Z-5	4FT-Z-6	4FT-Z-7
4FT-A-1	1.4481	1.374	1.6204	1.5612	1.3404	0.8464	1.0339
4FT-A-2	0.9323	0.5178	0.9052	0.9095	0.8723	1.2346	1.1479
4FT-A-3	0.8012	1.0979	1.0343	1.1094	1.3651	1.4092	1.4374
4FT-A-4	0.8346	0.3293	0.8822	0.8259	0.9293	1.1058	1.173
4FT-A-5	1.3828	0.9984	1.2633	1.2566	0.4025	1.0645	0.9785
4FT-A-6	1.2886	1.296	1.0475	1.0547	0.9149	1.3064	1.2219
4FT-A-7	1.6059	1.3952	1.4538	1.435	0.8469	1.3562	1.2294

Table S7. Root mean square displacements in Å between the anionic forms of the 4F-Thr and Thr. The hydrogen and fluorine atoms of the methyl groups were excluded in the rms calculations.

	4FT-A-1	4FT-A-2	4FT-A-3	4FT-A-4	4FT-A-5	4FT-A-6	4FT-A-7
T-A-1	1.3008	0.6015	0.4272	1.0917	1.1286	1.0113	1.252
T-A-2	1.2305	0.7113	0.1362	0.6507	1.0425	1.0641	1.1408
T-A-3	1.0479	0.0894	0.727	0.5521	0.9092	0.9334	1.0986
T-A-4	1.0609	0.5422	0.7106	0.0917	1.0056	1.0365	1.1657

Table S8. Root mean square displacements in Å between the zwitterionic forms of the 4F-Thr and Thr. The hydrogen and fluorine atoms of the methyl groups were excluded in the rms calculations.

	4FT-Z-1	4FT-Z-2	4FT-Z-3	4FT-Z-4	4FT-Z-5	4FT-Z-6	4FT-Z-7
T-Z-1	0.3302	0.3606	0.1142	0.9803	0.8641	1.0767	1.2937
T-Z-2	0.099	0.0859	0.2944	0.1001	0.8458	1.0904	1.0682
T-Z-3	0.8358	0.8176	0.8208	0.8251	0.0838	1.2072	0.8882
T-Z-4	1.2526	1.0596	1.0737	1.0588	0.9583	0.4517	0.3315
T-Z-5	1.3026	1.0731	1.1099	1.0806	0.9189	0.4941	0.1056

Table S9. Root mean square displacements in Å between the cationic forms of the 4F-Thr and Thr. The hydrogen and fluorine atoms of the methyl groups were excluded in the rms calculations.

	4FT-C-1	4FT-C-2	4FT-C-3	4FT-C-4	4FT-C-5	4FT-C-6
T-C-1	0.2727	0.1064	0.9103	0.489	0.5023	1.1482
T-C-2	0.4797	0.5487	1.0299	0.737	0.1177	1.2047
T-C-3	0.3915	0.4664	0.8873	0.2064	0.7305	1.0967

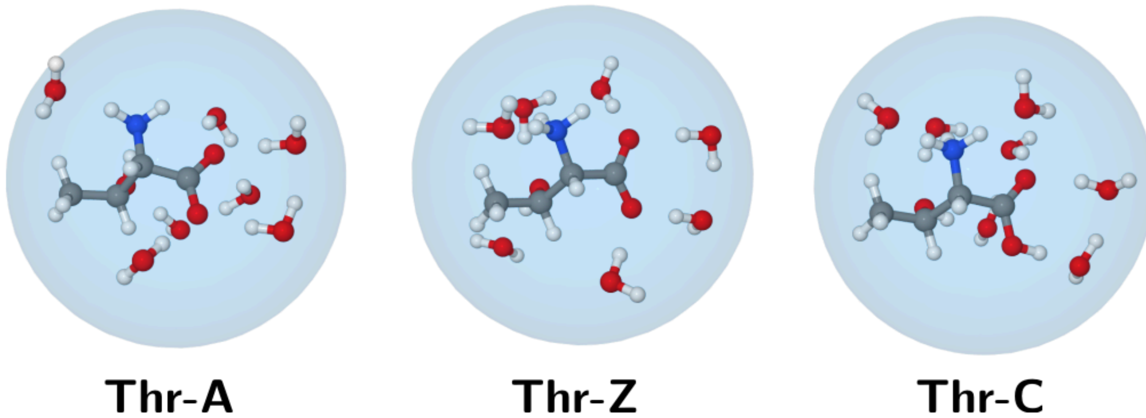


Figure S3. Clusters containing the water molecules of the first-solvation shell for the anionic (left), zwitterionic (middle), and cationic (right) forms of Thr.

Simulated NMR Chemical Shifts and J spin-spin coupling constants

Threonine

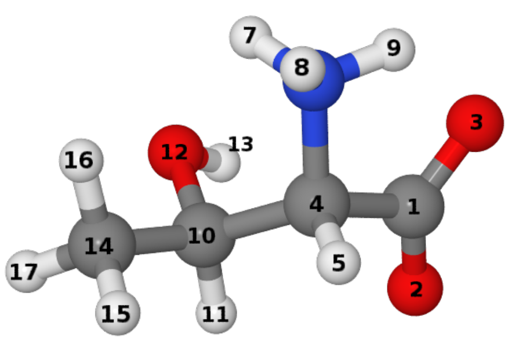


Table S10. Experimental and Boltzmann averaged chemical shifts in ppm of Thr in zwitterionic form. B3 stands for B3LYP-D3(BJ), juldz for jul-cc-pVDZ, juntz for jun-cc-pVTZ.

Nucleus	Index	Exp.	B3juldz	B3juntz
^{13}C	1-C	173.4	167.68	171.17
^{13}C	4-C	61.0	59.87	60.80
^{13}C	10-C	66.5	66.86	67.66
^{13}C	14-C	20.1	17.53	16.55
^{1}H	5-H	3.57	3.10	3.19
^{1}H	11-H	4.24	4.37	4.47
^{1}H	CH_3	1.32	0.88	0.97

Table S11. Experimental and absolute values of the Boltzmann averaged simulated J spin-spin coupling constants (Hz) of Thr in zwitterionic form. B3 stands for B3LYP-D3(BJ), juldz for jul-cc-pVDZ, juntz for jun-cc-pVTZ.

				Exp.	B3juldz		B3juntz	
Index	Nucleus	Index	Nucleus		spinspin	mixed	spinspin	mixed
5	^{1}H	11	^{1}H	4.9	2.04	2.46	2.19	2.59
11	^{1}H	CH_3	^{1}H	6.6	5.06	6.92	6.09	7.21

4-Fluoro-threonine

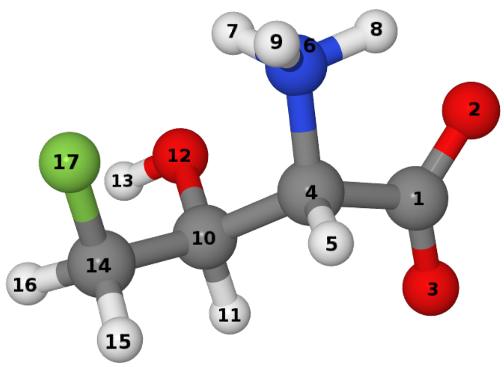


Table S12. Experimental and Boltzmann averaged chemical shifts in ppm of 4F-Thr in zwitterionic form. B3 stands for B3LYP-D3(BJ), juldz for jul-cc-pVDZ, juntz for jun-cc-pVTZ.

Nucleus	Index	Exp.	B3juldz	B3juntz
^{13}C	1-C	172.5	166.88	170.29
^{13}C	4-C	56.8	54.58	55.15
^{13}C	10-C	68.4	68.46	69.31
^{13}C	14-C	85.6	84.76	87.54
^{1}H	5-H	3.87	3.26	3.37
^{1}H	11-H	4.35	4.60	4.70
^{1}H	15-H	4.72	4.37	4.40
^{1}H	16-H	4.60	4.39	4.42
^{19}F	17-F	-232	-238.26	-245.23

Table S13. Experimental and absolute values of the Boltzmann averaged simulated J spin-spin coupling constants (Hz) of 4F-Thr in zwitterionic form. B3 stands for B3LYP-D3(BJ), juldz for jul-cc-pVDZ, juntz for jun-cc-pVTZ.

				Exp.	B3juldz		B3juntz	
Index	Nucleus	Index	Nucleus		spinspin	mixed	spinspin	mixed
4	^{13}C	17	^{19}F	4.4	2.25	1.57	1.14	1.61
10	^{13}C	17	^{19}F	19.1	16.88	17.58	15.14	18.14
14	^{13}C	17	^{19}F	163.3	162.01	220.90	206.60	215.26
5	^{1}H	11	^{1}H	4.7	1.25	1.40	1.24	1.46
11	^{1}H	15	^{1}H	3.7	4.31	5.92	5.24	6.17
11	^{1}H	16	^{1}H	3.1	3.01	3.98	3.53	4.14
15	^{1}H	16	^{1}H	10.8	9.51	11.07	9.12	11.16
11	^{1}H	17	^{19}F	24.9	17.66	21.28	17.87	21.80
15	^{1}H	17	^{19}F	46.6	31.88	52.04	41.25	52.93
16	^{1}H	17	^{19}F	47.0	31.81	51.85	41.25	52.75

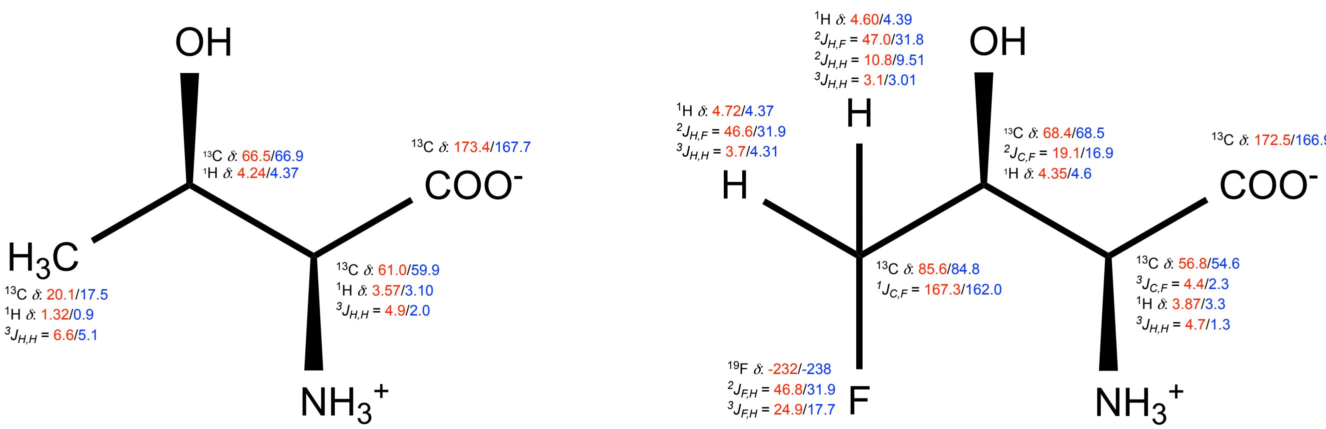
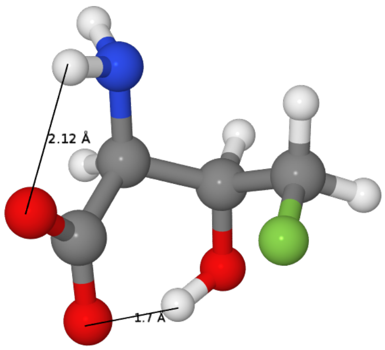
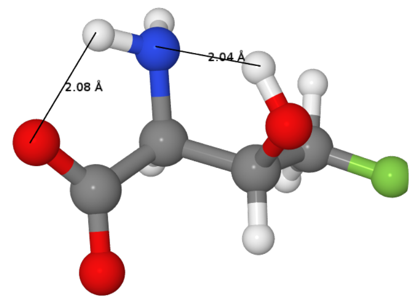
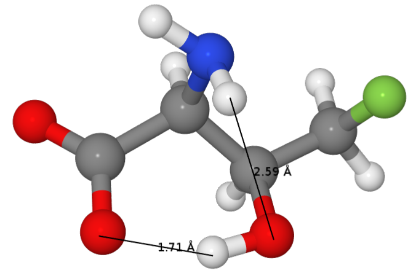


Figure S4. Experimental (red values) and simulated (blue values) chemical shifts (δ in ppm) and coupling constants (J in Hz) of the zwitterionic form of Thr (left) and 4F-Thr (right) in D_2O. Simulated values taken at the B3/jul-cc-pVDZ (spin-spin) level.

Molecular Structures

Table S14. Molecular structures and key atomic distances of Anionic 4F-Thr.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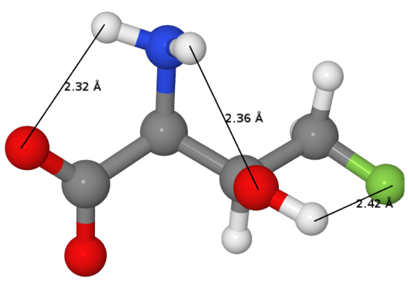
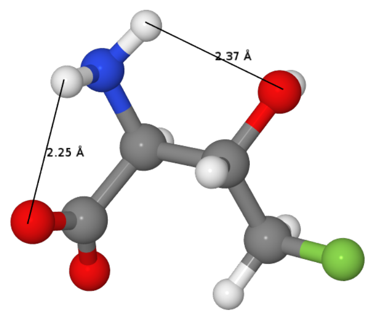
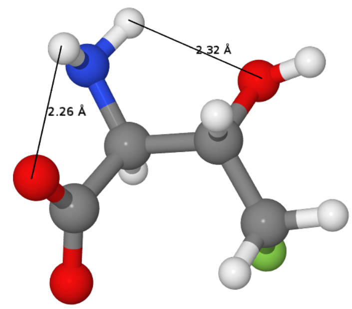
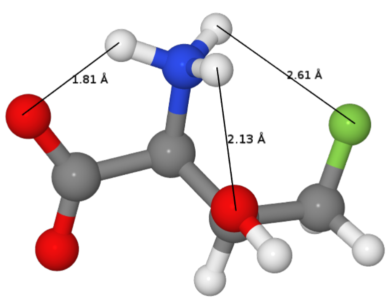
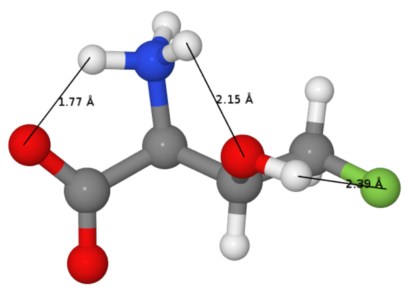
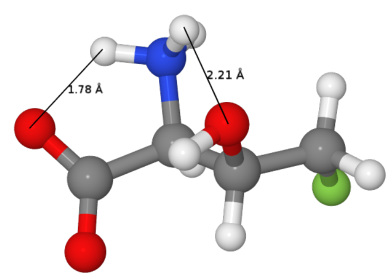
		
4F-Thr-A-4	**4F-Thr-A-5**	**4F-Thr-A-6**

Table S15. Molecular structures and key atomic distances of Zwitterionic 4F-Thr.

		
4F-Thr-Z-1	**4F-Thr-Z-2**	**4F-Thr-Z-3**

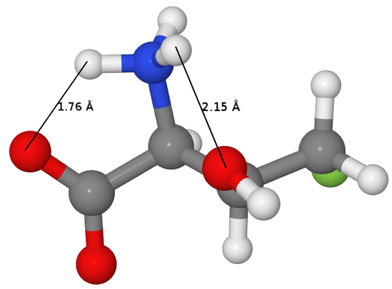
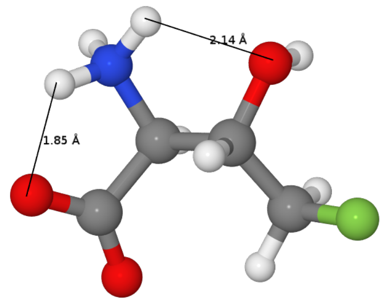
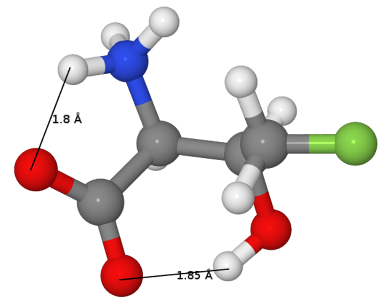
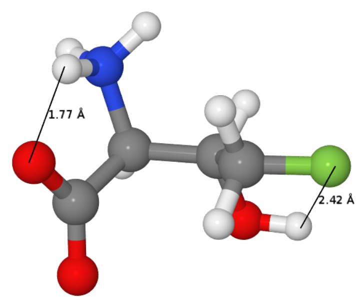
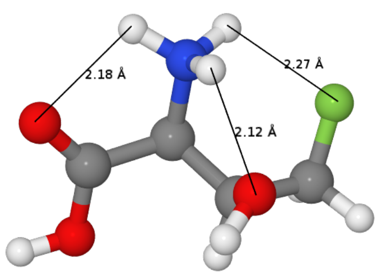
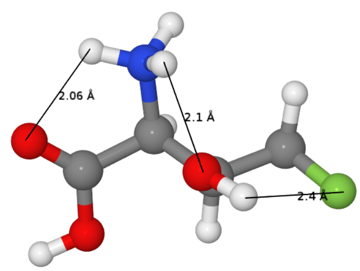
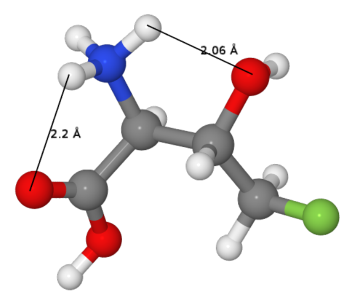
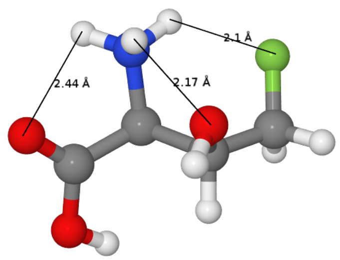
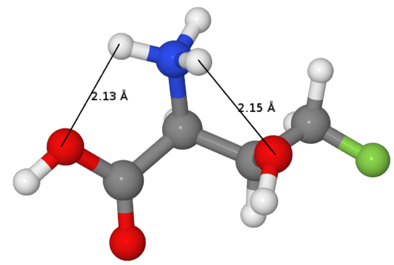
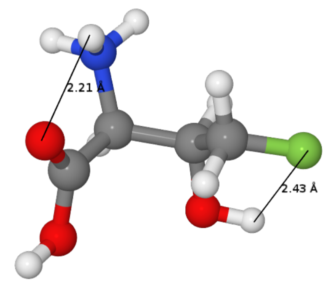
		
4F-Thr-Z-4	**4F-Thr-Z-5**	**4F-Thr-Z-6**
		
	4F-Thr-Z-7	

Table S16. Molecular structures and key atomic distances of Cationic 4F-Thr.

		
4F-Thr-C-1	**4F-Thr-C-2**	**4F-Thr-C-3**

		
4F-Thr-C-4	**4F-Thr-C-5**	**4F-Thr-C-6**

Cartesian coordinates in XYZ format

In the following, the number of imaginary frequencies (IF), the electronic energy (EE) and the sum of electronic and thermal Free Energies (TE) in Hartree at B2 level of theory are reported in the comment line of xyz format (Angstrom).

Anionic 4F-Thr

```
16
4FT-A-1,IF=0,EE= -536.92677542,TE= -536.83976342
C          1.26098       -0.51731       -0.04743
O          2.16146       -0.09942       -0.80835
O          0.95337       -1.73317        0.15831
C          0.45946        0.52082        0.77842
H          0.73803        0.32235        1.81769
N          0.78399        1.89145        0.38882
H          1.63386        1.84710       -0.16344
H          0.97347        2.46085        1.20191
C         -1.06409        0.27820        0.70946
H         -1.53532        0.97014        1.41457
O         -1.38300       -1.04440        1.12173
H         -0.60723       -1.57550        0.81568
C         -1.68254        0.60741       -0.63128
H         -1.50527        1.64654       -0.89204
H         -2.74881        0.39258       -0.61200
F         -1.12602       -0.18035       -1.65918

16
4FT-A-2,IF=0,EE= -536.92511668,TE= -536.83837168
C          1.78452       -0.45865        0.11228
O          2.74053        0.24978       -0.29877
O          1.75639       -1.71011        0.22115
C          0.50039        0.28949        0.56976
H          0.41290        0.10378        1.64335
N          0.58886        1.71929        0.26073
H          1.56711        1.92057        0.08168
H          0.27418        2.29358        1.03006
C         -0.74067       -0.28905       -0.13291
H         -0.65357       -1.37188       -0.17759
O         -0.79180        0.19761       -1.47026
H         -0.42983        1.09949       -1.38968
C         -1.99726        0.07829        0.62340
H         -2.16206        1.15452        0.62674
H         -1.96161       -0.29905        1.64401
F         -3.12133       -0.50608        0.00713

16
4FT-A-3,IF=0,EE= -536.92172954,TE= -536.83586554
C         -1.78970       -0.01683       -0.15070
O         -2.73861        0.63147       -0.64985
O         -1.89094       -1.11157        0.49295
C         -0.36964        0.59533       -0.26649
H         -0.37247        1.27412       -1.11896
N         -0.03380        1.37727        0.93523
H          0.09285        0.74211        1.71496
H         -0.82088        1.96956        1.17375
C          0.66769       -0.49953       -0.53883
H          0.36105       -0.97488       -1.48223
O          0.69436       -1.46391        0.50448
H         -0.26723       -1.59117        0.69858
```

C	2.07855	-0.02887	-0.80987
H	2.07958	0.75664	-1.56341
H	2.68340	-0.86699	-1.15126
F	2.71560	0.47791	0.33297

16
4FT-A-4,IF=0,EE= -536.92073512,TE= -536.83524012

C	-1.80858	-0.38250	-0.15117
O	-2.74240	0.27186	0.37945
O	-1.81269	-1.60488	-0.45336
C	-0.51916	0.40651	-0.53412
H	-0.47716	0.36830	-1.62620
N	-0.50303	1.81092	-0.11598
H	-0.25261	1.83854	0.86689
H	-1.46452	2.13268	-0.13953
C	0.72290	-0.31205	-0.02596
H	0.66685	-1.35064	-0.35187
O	0.71183	-0.25243	1.40589
H	1.50877	-0.68981	1.72392
C	1.99050	0.30522	-0.56578
H	2.12646	1.32479	-0.21851
H	2.01940	0.26292	-1.65213
F	3.09179	-0.44253	-0.08715

16
4FT-A-5,IF=0,EE= -536.92002636,TE= -536.83429636

C	-1.55590	-0.60267	-0.03171
O	-2.16236	-0.45914	1.06215
O	-1.59381	-1.60116	-0.79712
C	-0.63151	0.56359	-0.45690
H	-0.50709	0.51802	-1.54058
N	-1.24605	1.84095	-0.09677
H	-0.52918	2.55397	-0.02651
H	-1.65424	1.72188	0.82456
C	0.75906	0.39369	0.18698
H	0.64473	0.40815	1.27105
O	1.59623	1.51857	-0.10648
H	1.74059	1.54967	-1.05973
C	1.43190	-0.89750	-0.21995
H	1.67636	-0.90097	-1.28193
H	0.81300	-1.75757	0.01433
F	2.64404	-1.04319	0.48192

16
4FT-A-6,IF=0,EE= -536.9190892,TE= -536.8336592

C	1.49130	-0.51585	0.00835
O	1.45847	-1.67981	0.48492
O	2.29883	-0.07091	-0.85077
C	0.40468	0.47414	0.49465
H	0.03449	0.13550	1.46070
N	0.98866	1.80873	0.64319
H	0.25103	2.50258	0.61586
H	1.58646	1.96258	-0.16201
C	-0.77066	0.46322	-0.49386
H	-0.38795	0.74471	-1.48019
O	-1.70871	1.44650	-0.03599
H	-2.31414	1.65310	-0.75515
C	-1.44013	-0.88497	-0.65032
H	-0.73222	-1.63215	-0.99926

```
H          -2.28273       -0.81920       -1.33685
F          -1.95283       -1.33264        0.57959

16
4FT-A-7,IF=0,EE= -536.91471083,TE= -536.82866783
C           1.39344       -0.22537        0.20652
O           2.04836       -0.21834       -0.87030
O           1.54965       -1.00096        1.18585
C           0.27531        0.84321        0.33880
H           0.12368        1.03498        1.40036
N           0.61224        2.10741       -0.33025
H           1.17098        1.85688       -1.14138
H           1.23347        2.63982        0.26723
C          -1.05894        0.33349       -0.20983
H          -1.03794        0.40476       -1.30079
O          -2.07848        1.18678        0.32580
H          -2.87694        1.07764       -0.20131
C          -1.40935       -1.09925        0.16756
H          -2.47524       -1.26708        0.02721
H          -1.12262       -1.33102        1.18997
F          -0.74000       -2.00225       -0.67540
```

Zwitterionic 4F-Thr

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17
4FT-Z-1,IF=0,EE= -537.38539075,TE= -537.28463175
C          -1.79915       -0.16323       -0.21578
O          -2.49882        0.77869        0.24614
O          -2.13133       -1.32554       -0.50591
C          -0.31037        0.21147       -0.49726
H          -0.18623        0.29920       -1.57269
N          -0.09452        1.56092        0.11349
H           0.39568        1.46364        1.00278
H          -1.06631        1.88209        0.30020
H           0.41683        2.20621       -0.47916
C           0.67820       -0.79630        0.06973
H           0.30700       -1.78678       -0.19671
O           0.65140       -0.59750        1.48221
H           1.21021       -1.25322        1.91182
C           2.07132       -0.65472       -0.50143
H           2.07380       -0.87992       -1.56549
H           2.77677       -1.30035        0.01658
F           2.52487        0.66824       -0.34697

17
4FT-Z-2,IF=0,EE= -537.3846941,TE= -537.2843401
C          -1.79796       -0.48571       -0.11633
O          -2.71011        0.27665        0.30591
O          -1.79353       -1.72100       -0.24180
C          -0.50136        0.25518       -0.57893
H          -0.45678        0.20189       -1.66282
N          -0.67984        1.68637       -0.17805
H          -1.68881        1.70197        0.09676
H          -0.48306        2.35902       -0.91221
H          -0.11540        1.89528        0.64630
C           0.76168       -0.32514        0.03670
H           0.68181       -1.40970       -0.03545
O           0.76603        0.09049        1.40024
H           1.58823       -0.20348        1.80795
```

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C          2.01859        0.12968       -0.67278
H          2.15056        1.20933       -0.63401
H          2.03484       -0.21743       -1.70300
F          3.11807       -0.43940       -0.00933

17
4FT-Z-3,IF=0,EE= -537.38368053,TE= -537.28354753
C         -1.67954       -0.45819       -0.18319
O         -2.61102        0.39067       -0.24284
O         -1.73516       -1.67549        0.06360
C         -0.26044        0.11338       -0.48851
H          0.03646       -0.22884       -1.47579
N         -0.41436        1.60068       -0.52456
H          0.03438        2.05705       -1.31228
H         -0.08175        2.00977        0.34983
H         -1.45218        1.70815       -0.55958
C          0.78203       -0.29319        0.54700
H          0.67388       -1.36391        0.70452
O          0.58541        0.43664        1.75623
H         -0.06911       -0.01711        2.29782
C          2.20845        0.01580        0.12681
H          2.90686       -0.36446        0.86664
H          2.36929        1.08383       -0.01137
F          2.47397       -0.61896       -1.09072

17
4FT-Z-4,IF=0,EE= -537.38318281,TE= -537.28291781
C          1.66945        0.51991       -0.07221
O          2.62469       -0.29001       -0.23047
O          1.68775        1.68952        0.34597
C          0.27416       -0.03371       -0.49884
H         -0.03047        0.47473       -1.40871
N          0.48478       -1.48441       -0.80829
H          0.11801       -2.07134       -0.05898
H          1.52921       -1.54724       -0.79717
H          0.10396       -1.78702       -1.69869
C         -0.78744        0.13898        0.57362
H         -0.69080        1.15474        0.95347
O         -0.49324       -0.82729        1.57938
H         -1.01002       -0.64285        2.37033
C         -2.20357       -0.08096        0.06389
H         -2.92138        0.03217        0.87322
H         -2.32639       -1.05975       -0.39643
F         -2.49275        0.88826       -0.90409

17
4FT-Z-5,IF=0,EE= -537.38307705,TE= -537.28235705
C          1.53706       -0.74313        0.00936
O          1.30021       -1.88253        0.45058
O          2.41464       -0.36887       -0.81354
C          0.59670        0.39414        0.50695
H          0.47315        0.35355        1.58488
N          1.25844        1.68468        0.14721
H          0.57486        2.36906       -0.17925
H          1.93604        1.40843       -0.58901
H          1.77321        2.08549        0.92610
C         -0.76914        0.35632       -0.20182
H         -0.61082        0.21364       -1.27075
O         -1.42513        1.61799       -0.09753
```

```
H          -1.76680        1.72786        0.79881
C          -1.61850       -0.77666        0.32707
H          -1.93447       -0.58197        1.35174
H          -1.07866       -1.71649        0.27744
F          -2.77444       -0.88545       -0.45511
17
4FT-Z-6,IF=0,EE= -537.38346062,TE= -537.28228962
C           1.43797       -0.54597       -0.26319
O           2.28175        0.05423       -0.97060
O           1.13373       -1.76116       -0.25226
C           0.64802        0.34263        0.73955
H           0.94560        0.07491        1.74827
N           1.08442        1.75498        0.49197
H           0.34829        2.36440        0.14511
H           1.81797        1.63726       -0.24175
H           1.48505        2.19302        1.31688
C          -0.86983        0.12946        0.63614
H          -1.38018        0.81649        1.31198
O          -1.15844       -1.18329        1.07856
H          -0.47538       -1.74468        0.65546
C          -1.39549        0.35900       -0.77111
H          -1.05828       -0.42527       -1.44510
H          -1.11573        1.33212       -1.17320
F          -2.79319        0.31977       -0.73947

17
4FT-Z-7,IF=0,EE= -537.37653087,TE= -537.27638887
C          -1.44330       -0.61723        0.19209
O          -1.37536       -1.82332       -0.09015
O          -2.04255       -0.05188        1.15082
C          -0.65957        0.36671       -0.73515
H          -0.87585        0.15987       -1.77689
N          -1.17988        1.73213       -0.39356
H          -1.68283        1.55303        0.50669
H          -1.85083        2.06406       -1.08109
H          -0.46454        2.44736       -0.28736
C           0.86349        0.31227       -0.54997
H           1.28482        1.26712       -0.88162
O           1.34324       -0.72919       -1.38315
H           2.29801       -0.78619       -1.26194
C           1.27364        0.08926        0.89211
H           0.95752       -0.88992        1.24230
H           0.89978        0.86829        1.55282
F           2.67609        0.12449        0.94747
```

Cationic 4F-Thr

```
18
4FT-C-1,IF=0,EE= -537.82552094,TE= -537.71179494
C           1.73858        0.01422       -0.19586
O           2.47560       -0.83015        0.25579
O           2.08282        1.25335       -0.52416
H           3.03068        1.37746       -0.35381
C           0.26733       -0.24439       -0.48923
H           0.14441       -0.27798       -1.56918
N          -0.04961       -1.59036        0.06874
H          -0.31924       -1.47548        1.05104
H           0.77915       -2.18771        0.03477
H          -0.82351       -2.03098       -0.42435
```

```
C         -0.68145        0.79697        0.13857
H         -0.27539        1.78712       -0.05670
O         -0.78031        0.53202        1.53194
H         -0.18690        1.11025        2.02274
C         -2.06074        0.74646       -0.47615
H         -2.03037        1.03395       -1.52370
H         -2.74222        1.38380        0.07816
F         -2.55963       -0.56770       -0.41252

18
4FT-C-2,IF=0,EE= -537.82350108,TE= -537.70952708
C         -1.76457       -0.32776       -0.10955
O         -2.67516        0.31423        0.35939
O         -1.75449       -1.63702       -0.30799
H         -2.60129       -2.01198       -0.01616
C         -0.46782        0.31916       -0.58918
H         -0.44209        0.25449       -1.67353
N         -0.55090        1.75786       -0.18899
H         -0.05019        1.88565        0.69592
H         -1.53662        1.98867       -0.02081
H         -0.17423        2.39449       -0.88755
C          0.77319       -0.32519        0.02806
H          0.66971       -1.40544       -0.06734
O          0.75099        0.06982        1.39136
H          1.54994       -0.25061        1.82586
C          2.05634        0.10119       -0.65837
H          2.22602        1.17398       -0.59782
H          2.07768       -0.23036       -1.69334
F          3.10931       -0.52050        0.02109

18
4FT-C-3,IF=0,EE= -537.8220353,TE= -537.7075483
C          1.57346       -0.55388       -0.03327
O          2.39204       -0.28276       -0.87964
O          1.41383       -1.73697        0.54664
H          2.04860       -2.36744        0.16800
C          0.56296        0.46102        0.47659
H          0.45561        0.38972        1.55486
N          1.09954        1.81303        0.15170
H          1.61435        1.77515       -0.73271
H          1.73792        2.15485        0.86786
H          0.31092        2.46327        0.06905
C         -0.82159        0.33600       -0.21635
H         -0.67180        0.24087       -1.29125
O         -1.53442        1.54827       -0.04057
H         -1.96779        1.55563        0.82281
C         -1.59066       -0.86705        0.28865
H         -1.87303       -0.74027        1.33311
H         -1.02122       -1.78354        0.17100
F         -2.76077       -0.98493       -0.45886

18
4FT-C-4,IF=0,EE= -537.81889397,TE= -537.70642097
C         -1.74532       -0.03725       -0.16651
O         -2.35883        0.80366        0.44173
O         -2.31518       -1.18802       -0.52395
H         -1.74729       -1.74770       -1.07187
C         -0.27936        0.15336       -0.54051
H         -0.14014       -0.00749       -1.60648
```

N	0.06278	1.57197	-0.23342
H	0.12469	1.67635	0.78309
H	-0.64915	2.21502	-0.57622
H	0.97039	1.81577	-0.63054
C	0.66183	-0.75744	0.28594
H	0.25890	-1.76954	0.28740
O	0.74876	-0.22987	1.59993
H	0.21711	-0.75462	2.20708
C	2.04432	-0.84191	-0.32348
H	2.01040	-1.31406	-1.30147
H	2.71252	-1.37922	0.34162
F	2.56848	0.45277	-0.49700

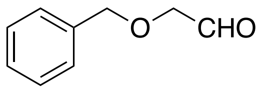
18
4FT-C-5,IF=0,EE= -537.81965132,TE= -537.70618732

C	-1.68454	-0.50811	-0.19987
O	-1.67765	-1.71049	-0.22592
O	-2.74213	0.25760	0.08216
H	-3.51282	-0.30436	0.26237
C	-0.45357	0.32753	-0.54318
H	-0.39942	0.37397	-1.62901
N	-0.60545	1.72443	-0.02433
H	-0.31735	1.73846	0.95966
H	-1.57650	2.03332	-0.07886
H	-0.03347	2.39137	-0.53977
C	0.81642	-0.29734	0.05541
H	0.75645	-1.37048	-0.11049
O	0.86597	0.01473	1.44109
H	0.54495	-0.73084	1.95900
C	2.07237	0.22891	-0.60475
H	2.25852	1.27168	-0.35267
H	2.02149	0.10689	-1.68406
F	3.15808	-0.50908	-0.13780

18
4FT-C-6,IF=0,EE= -537.81552574,TE= -537.70260574

C	1.44977	-0.36940	-0.27983
O	1.85303	0.16750	-1.28702
O	1.62764	-1.63719	0.05260
H	2.11929	-2.08464	-0.65617
C	0.62567	0.38460	0.75654
H	0.90679	0.08765	1.76142
N	0.96116	1.83177	0.58322
H	0.24684	2.44665	0.97326
H	1.08695	2.04447	-0.41081
H	1.84095	2.06020	1.04692
C	-0.88918	0.15103	0.60476
H	-1.39984	0.91131	1.20293
O	-1.12484	-1.13396	1.13867
H	-2.06940	-1.31719	1.07255
C	-1.38587	0.25328	-0.82692
H	-0.97002	-0.53417	-1.45144
H	-1.19453	1.22840	-1.27028
F	-2.77157	0.07190	-0.79024

Copies of NMR spectra



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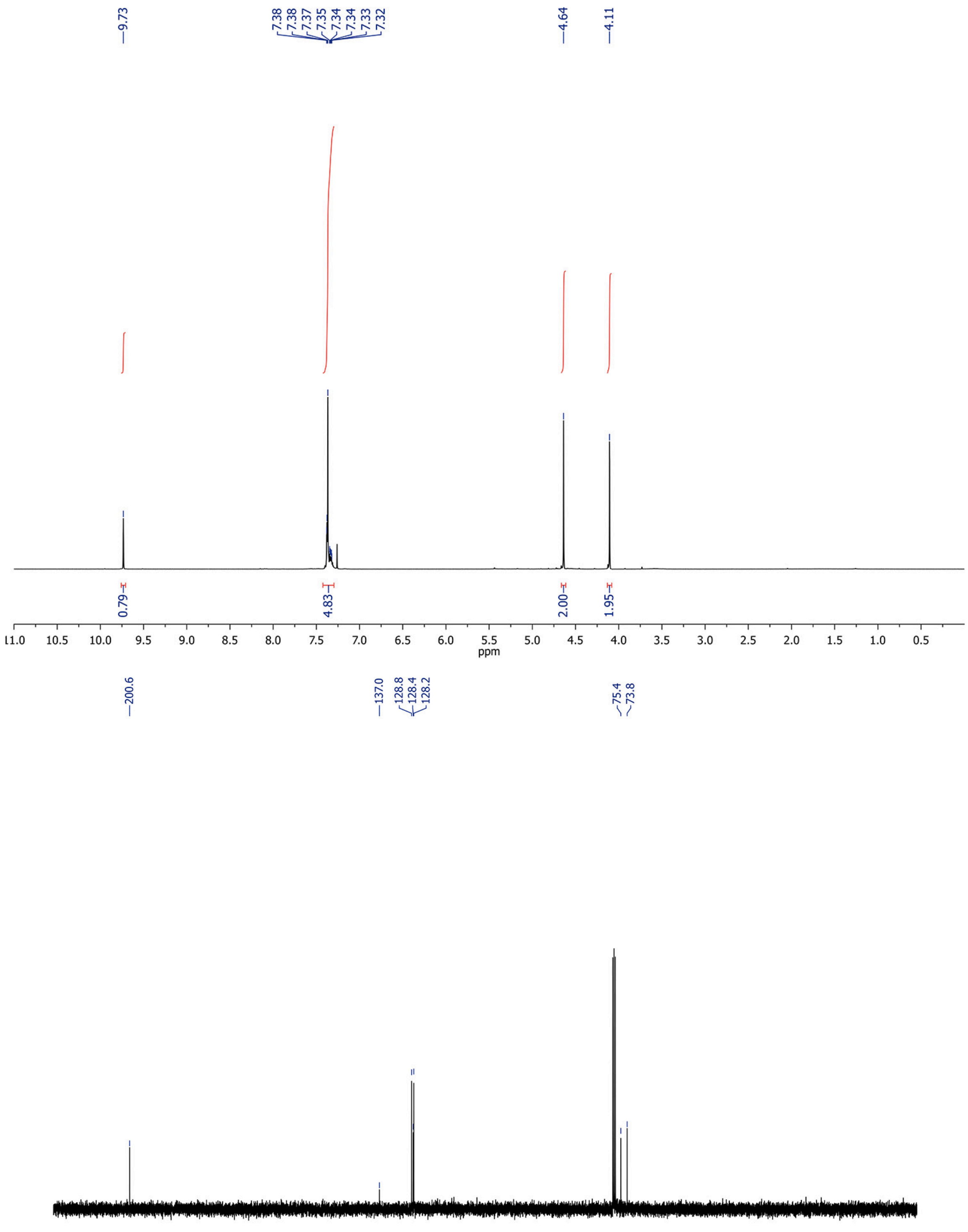
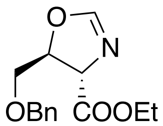


Figure S5. ^{1}H (top) and ^{13}C (bottom) NMR spectra of **1** ($CDCl_3$, 400 and 101 MHz, respectively).



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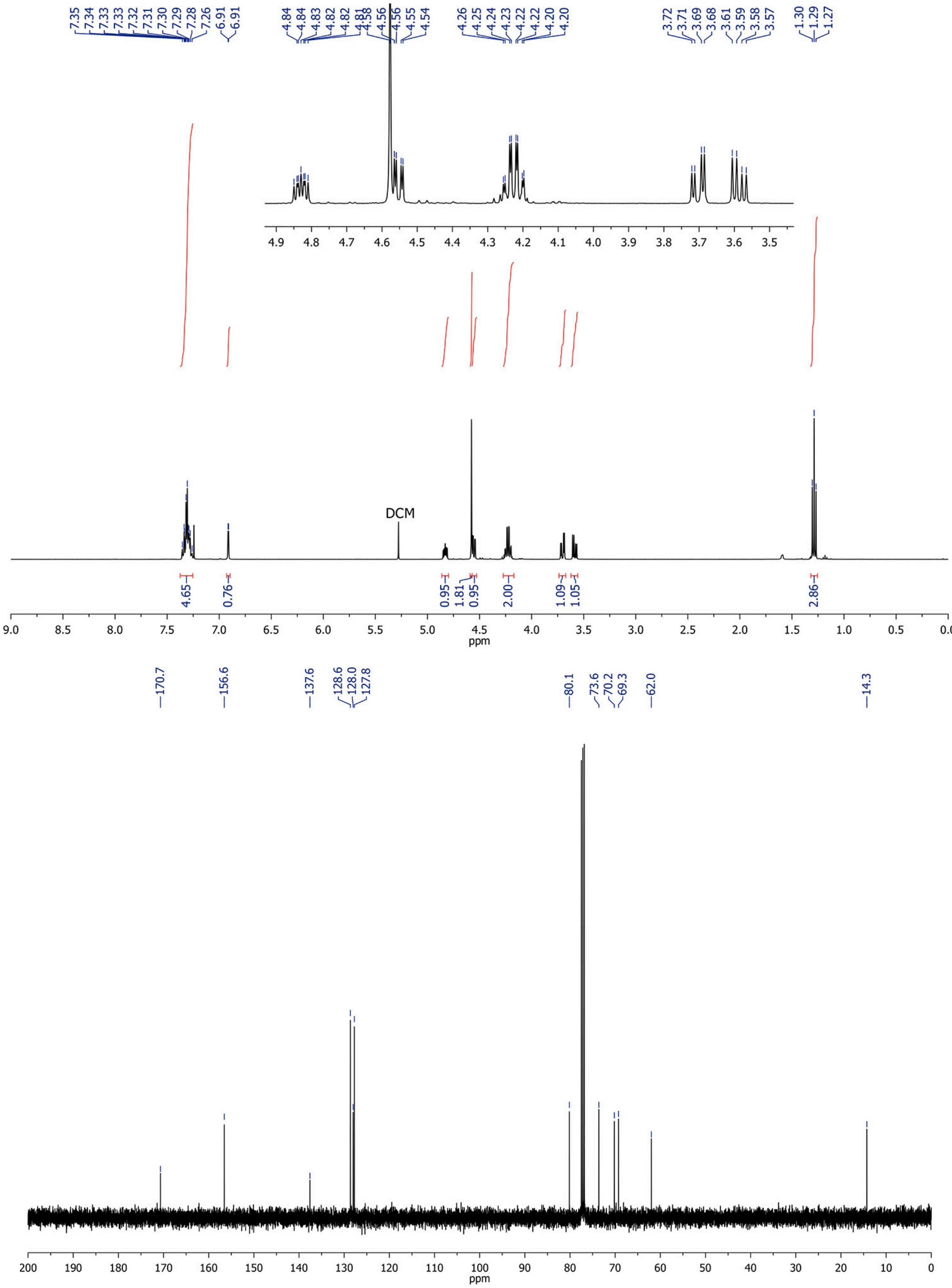
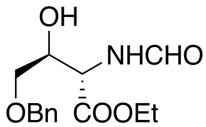


Figure S6. ^{1}H (top) and ^{13}C (bottom) NMR spectra of **2** ($CDCl_3$, 400 and 101 MHz, respectively).



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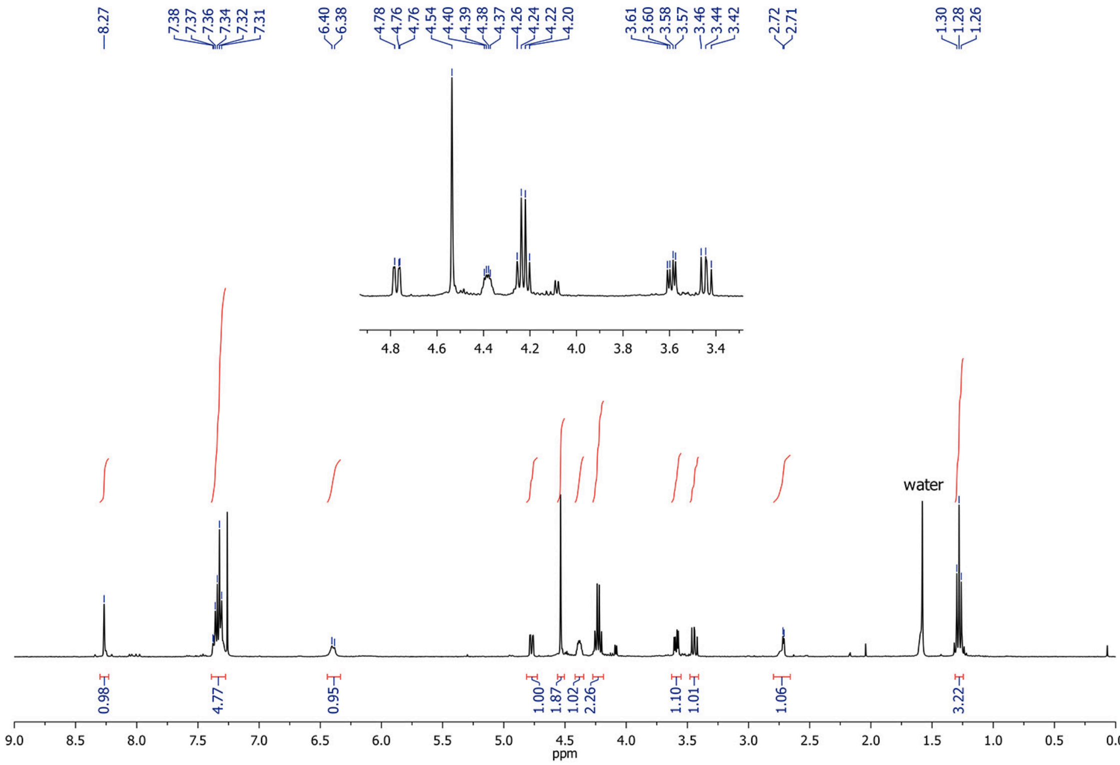
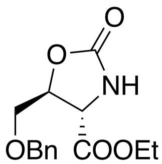
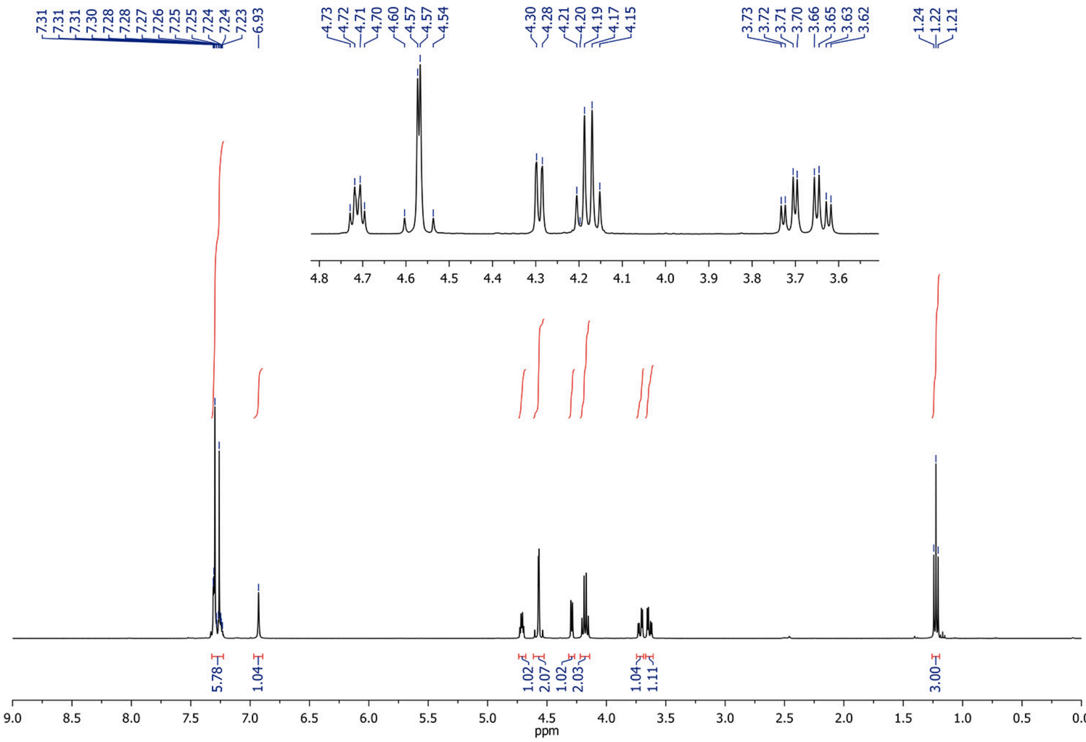


Figure S7. ^{1}H NMR spectrum of **3** ($CDCl_3$, 400 MHz).



trans-**4**



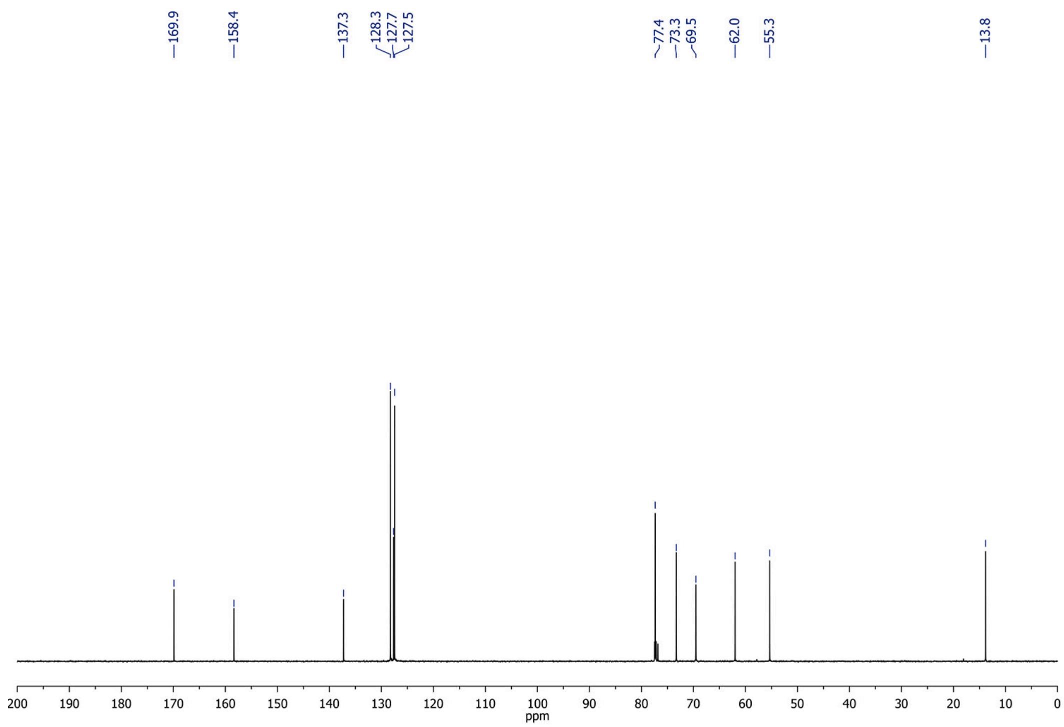
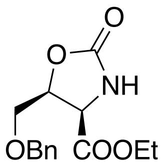
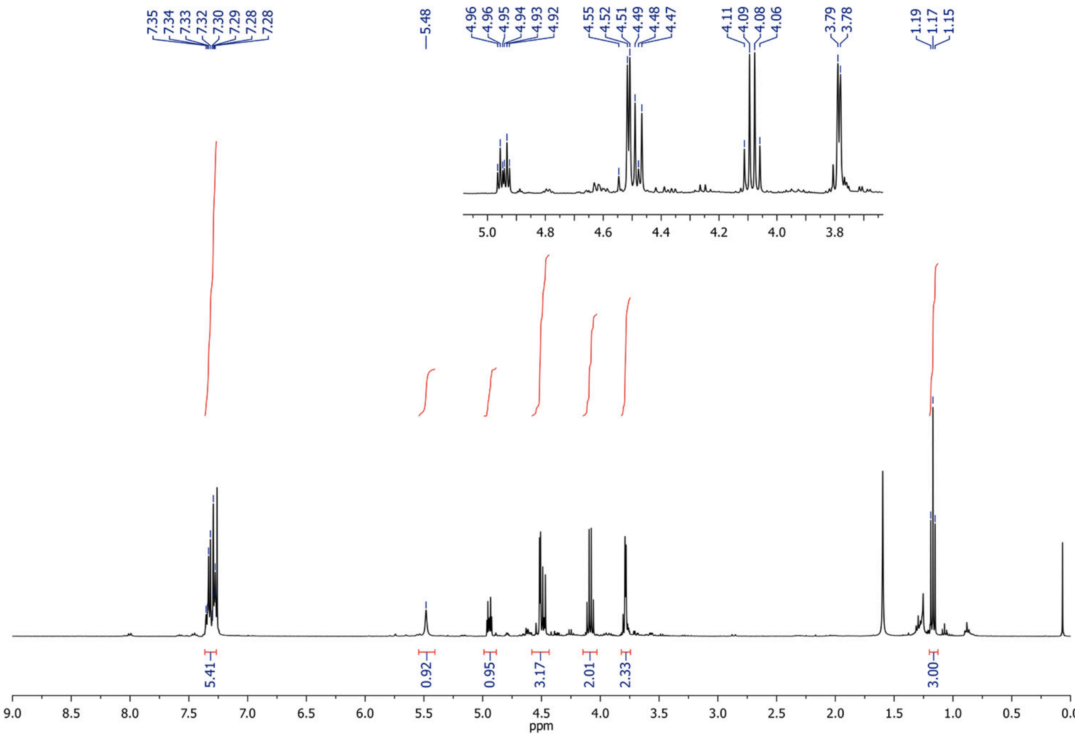


Figure S8. ^{1}H (top) and ^{13}C (bottom) NMR spectra of *trans*-**4** ($CDCl_3$, 400 and 101 MHz, respectively).



cis-**4**



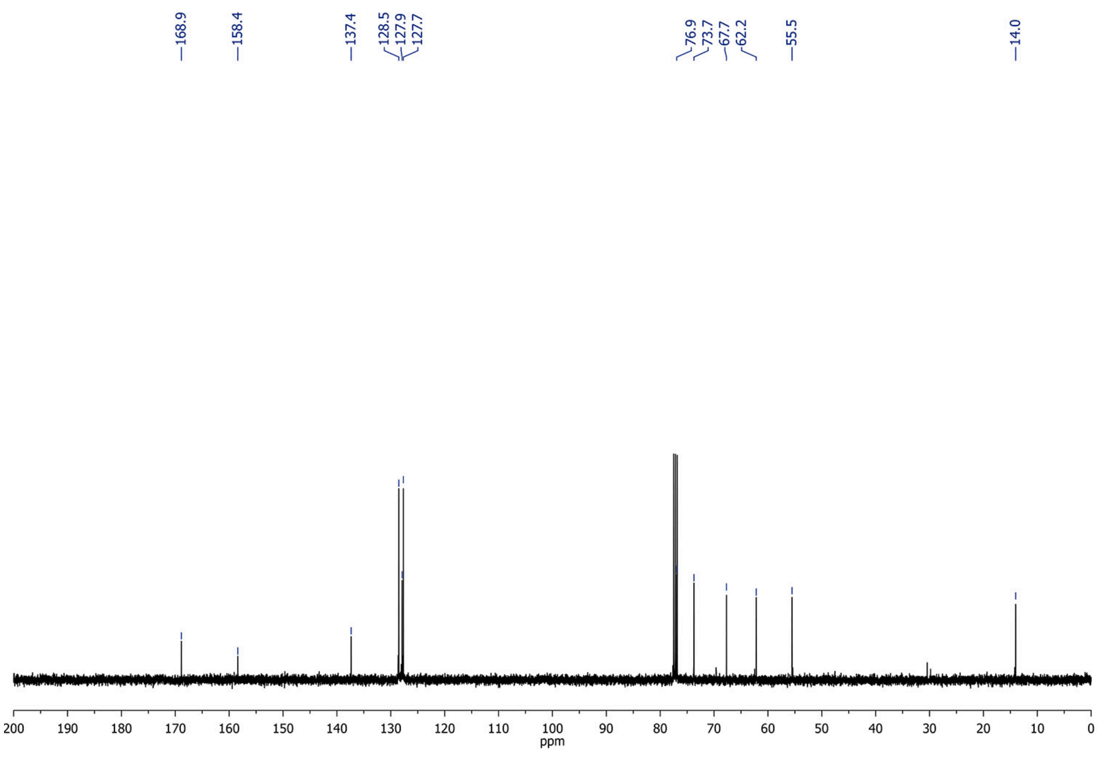
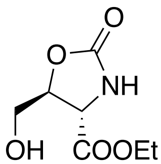


Figure S9. ^{1}H (top) and ^{13}C (bottom) NMR spectra of *cis*-**4** ($CDCl_3$, 400 and 101 MHz, respectively).



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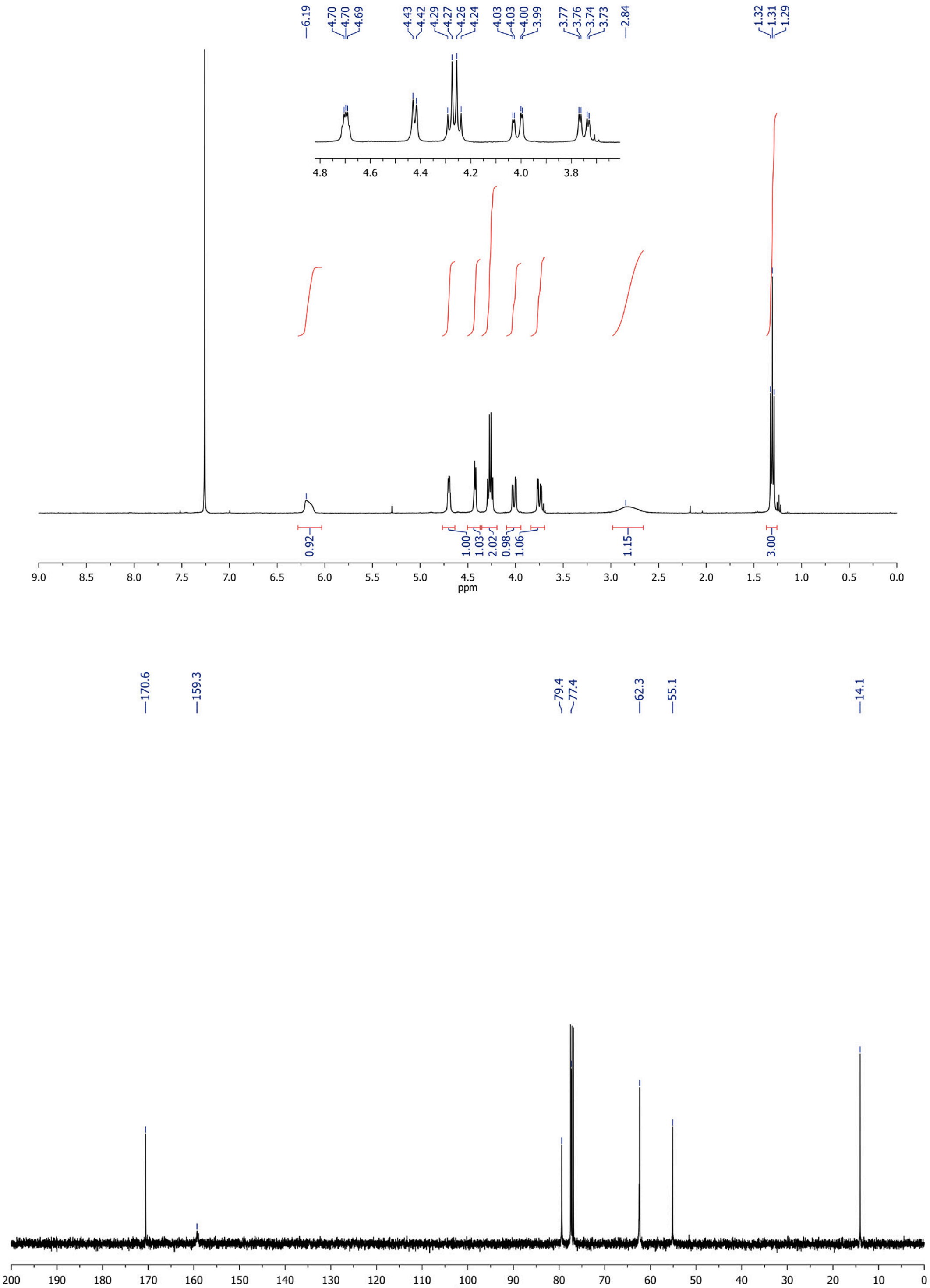
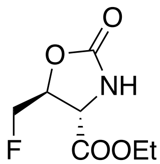


Figure S10. ^{1}H (top) and ^{13}C (bottom) NMR spectra of **5** ($CDCl_3$, 400 and 101 MHz, respectively).



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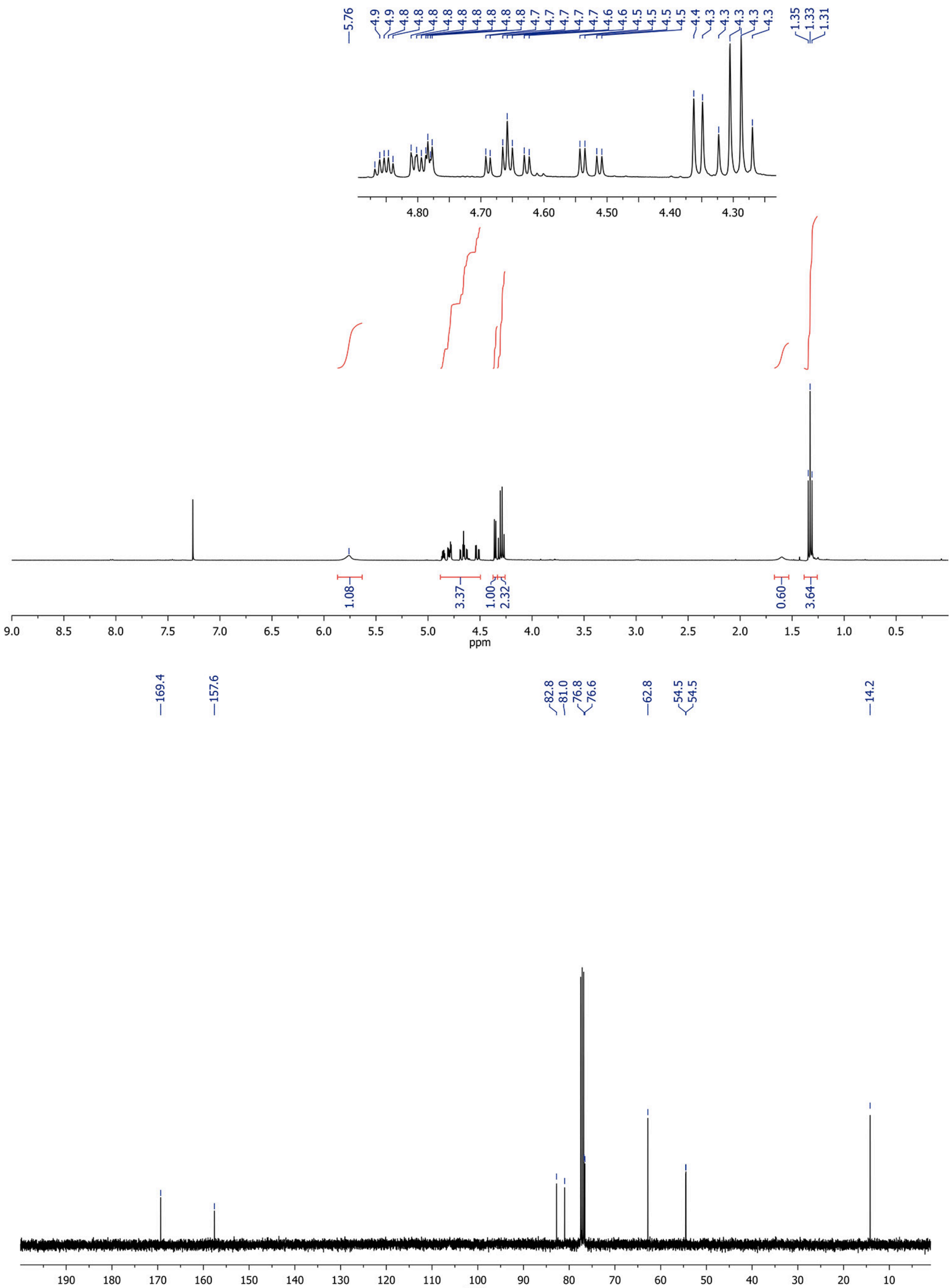


Figure S11. ^{1}H (top) and ^{13}C (bottom) NMR spectra of **6** ($CDCl_3$, 400 and 101 MHz, respectively).

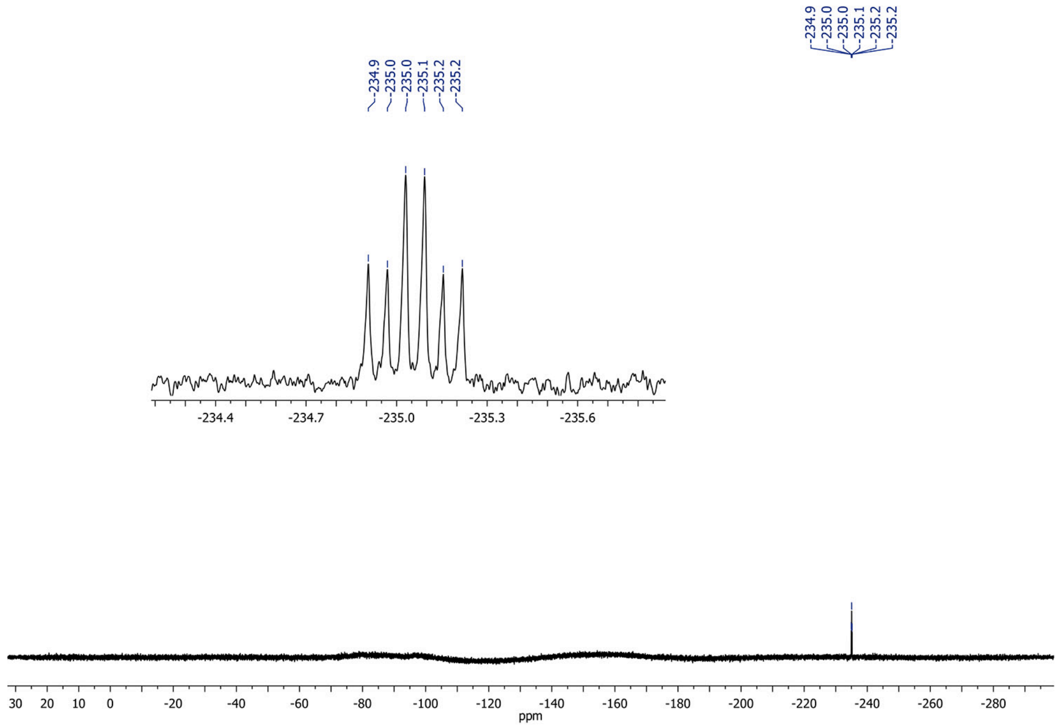
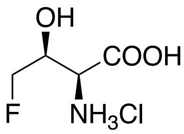


Figure S12. ^{19}F NMR spectrum of **6** ($CDCl_3$, 376.5 MHz).



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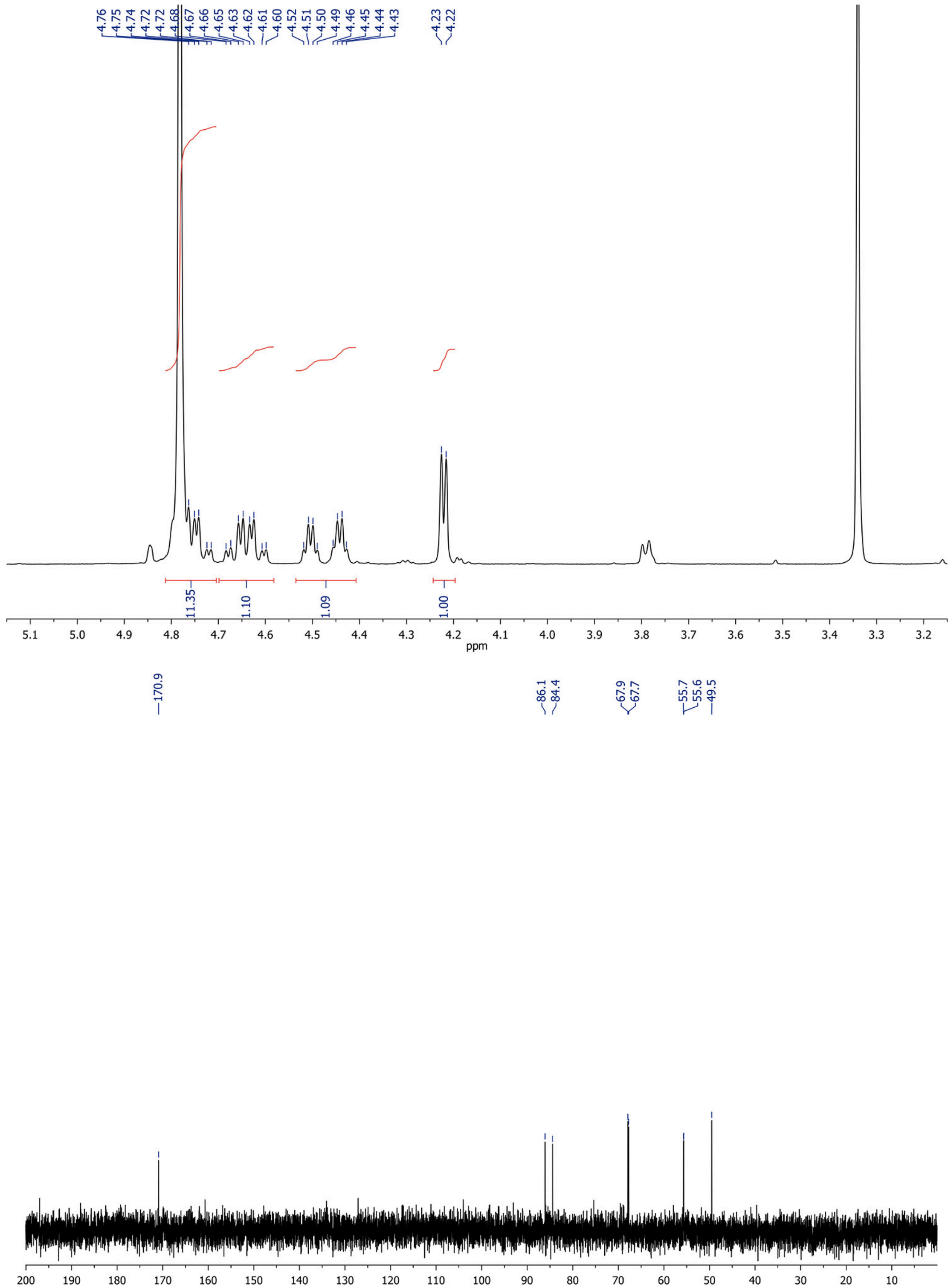


Figure S13. ^{1}H (top) and ^{13}C (bottom) NMR spectra of **7** (D_2O, 400 and 101 MHz, respectively). Methanol was added as a reference (far-right signals, 3.34 ppm for ^{1}H NMR and 49.5 ppm for ^{13}C NMR).

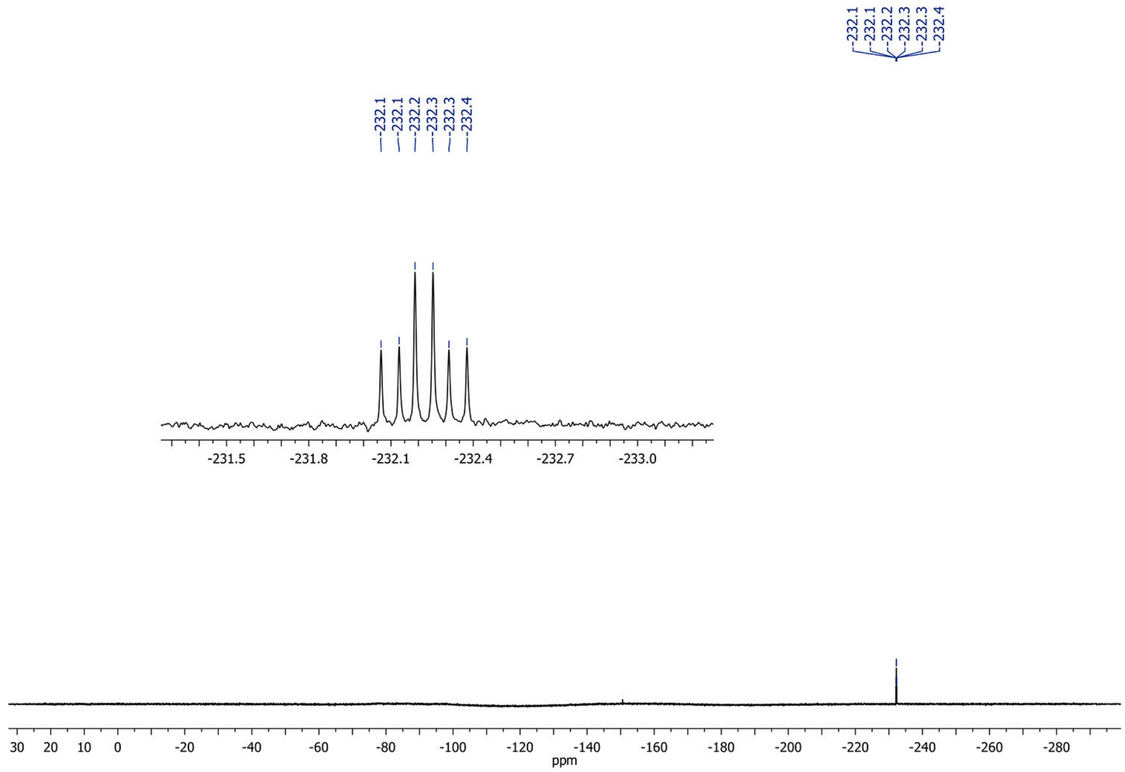
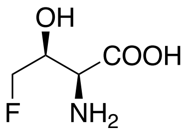


Figure S14. ^{19}F NMR spectrum of **7** (D_2O, 376.5 MHz).



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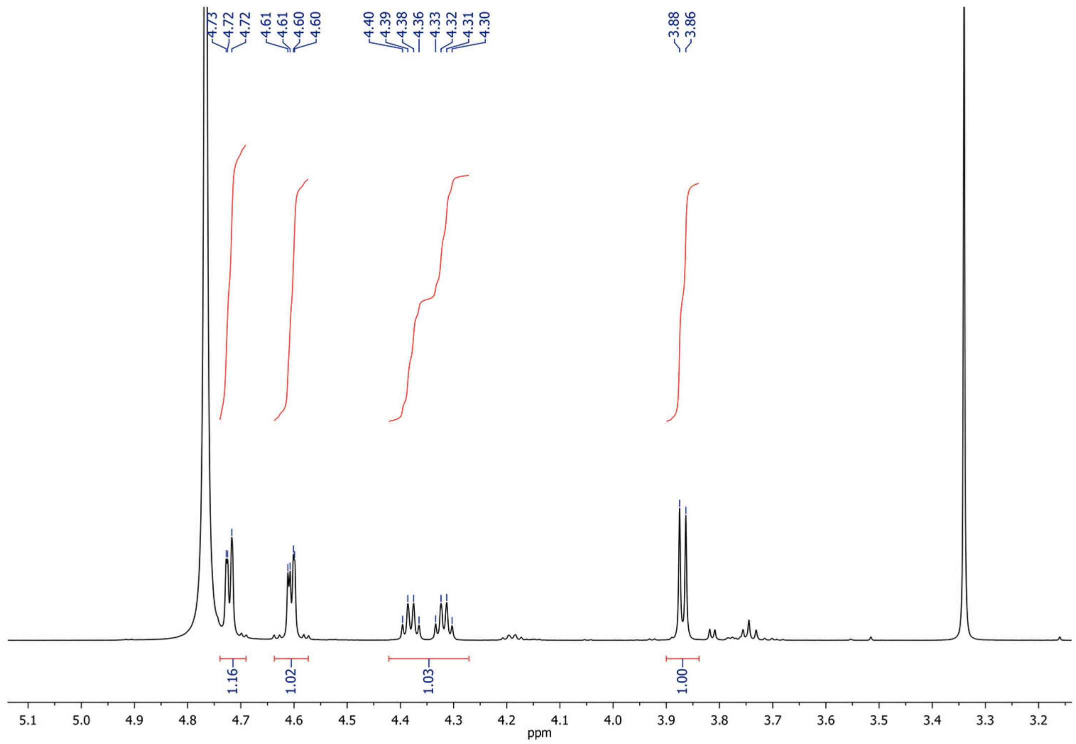


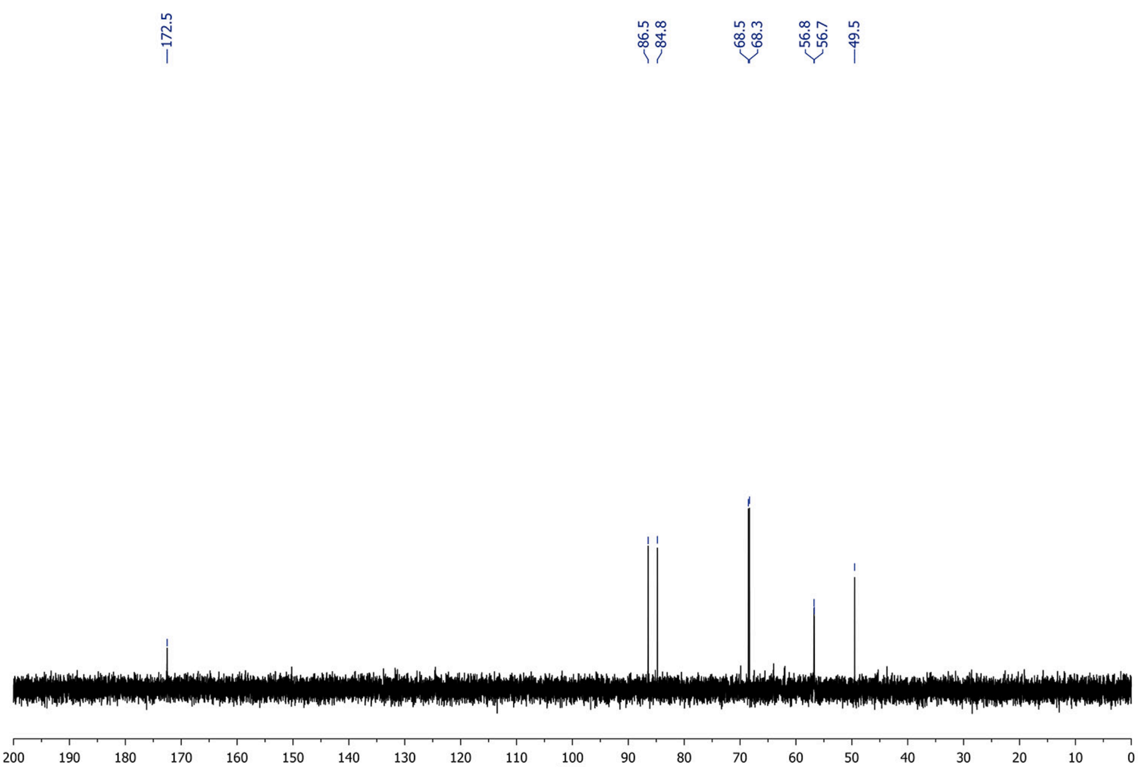


Figure S15. ^{1}H (top) and ^{13}C (bottom) NMR spectra of **8** (D_2O, 400 and 101 MHz, respectively). Methanol was added as a reference (far-right signals, 3.34 ppm for ^{1}H NMR and 49.5 ppm for ^{13}C NMR).

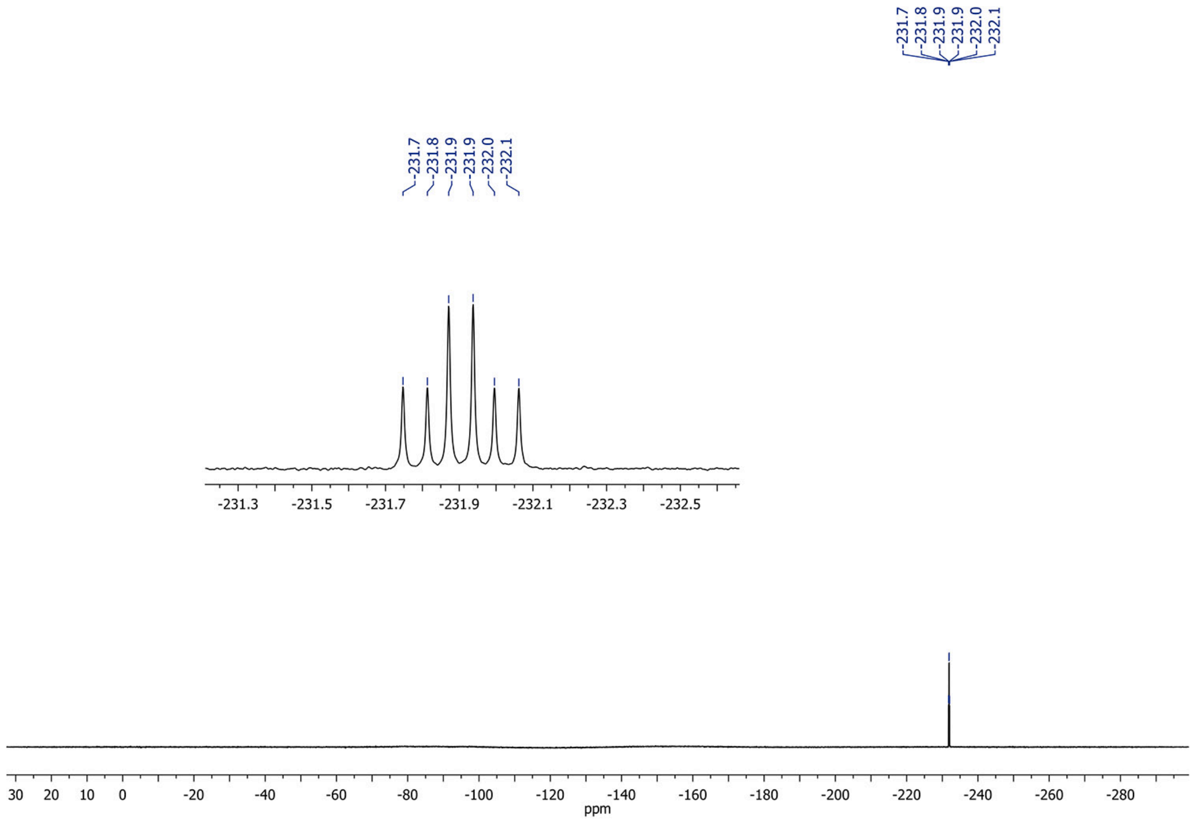
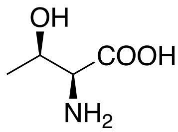


Figure S16. ^{19}F NMR spectrum of **8** (D_2O, 376.5 MHz).



Thr

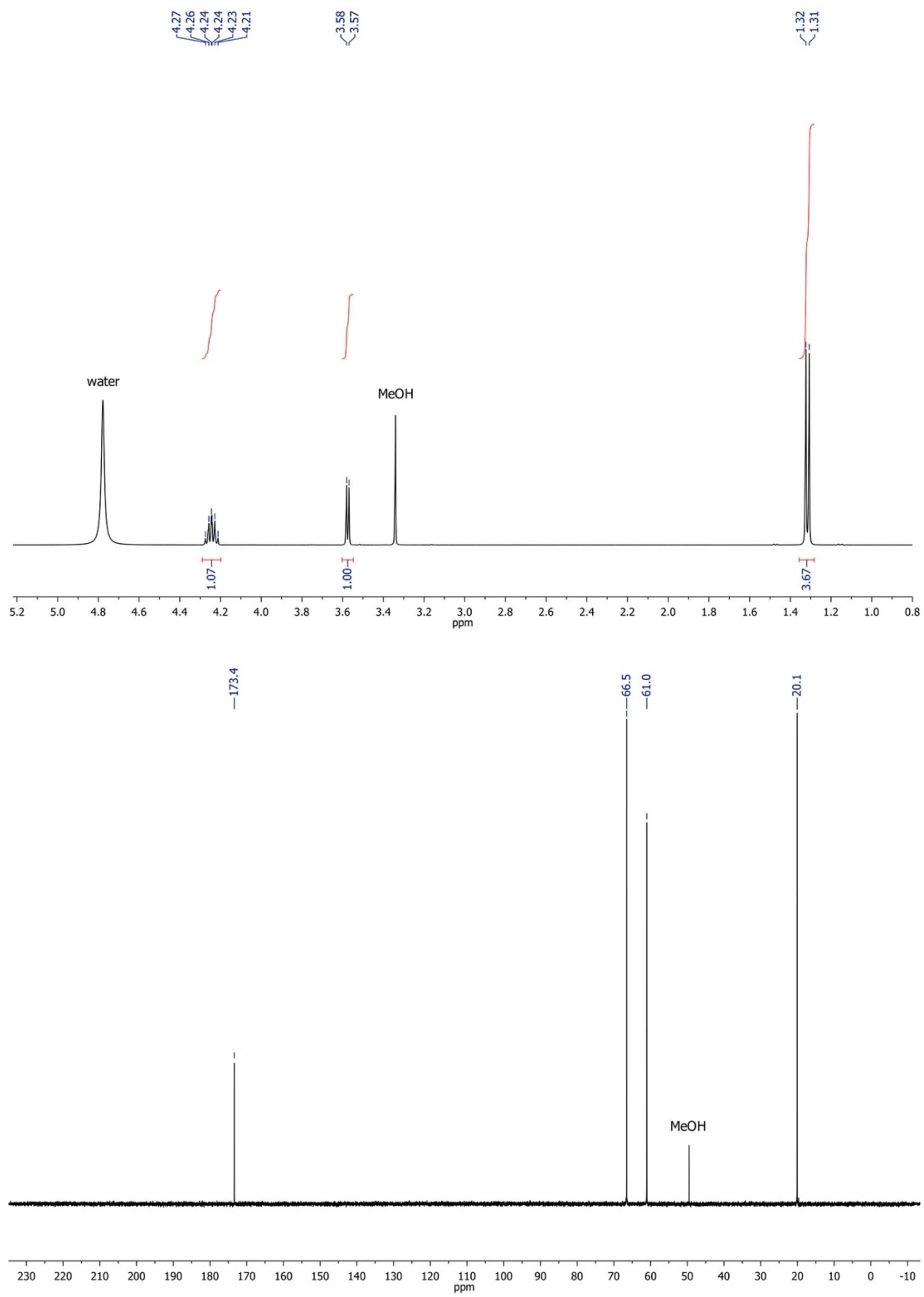
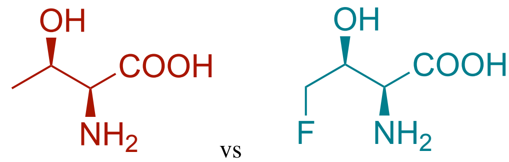
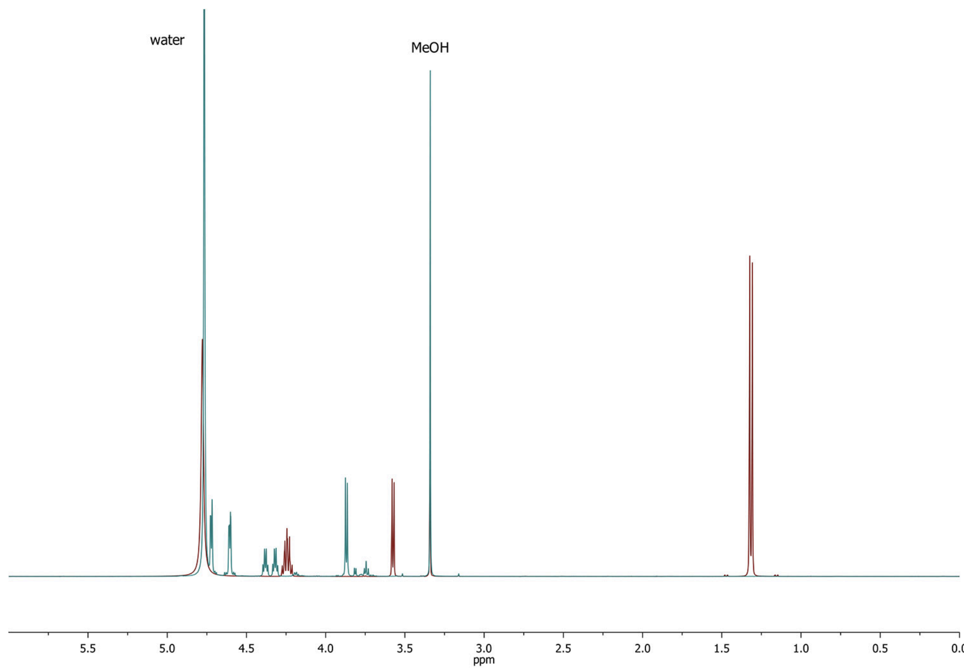


Figure S17. ^{1}H (top) and ^{13}C (bottom) NMR spectra of Thr (D_2O, 400 and 101 MHz, respectively). Methanol was added as a reference (3.34 ppm for ^{1}H NMR and 49.5 ppm for ^{13}C NMR). Thr, ^{1}H NMR δ: 4.24 (1H, dq, J = 6.6, 4.9 Hz), 3.57 (1H, d, J = 4.9 Hz), 1.32 (3H, d, J = 6.6 Hz). ^{13}C NMR δ: 173.4, 66.5, 61.0, 20.1.





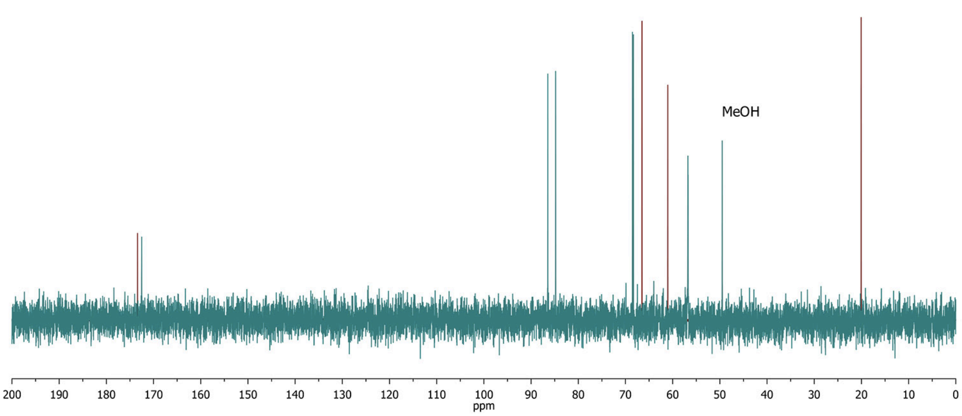


Figure S18. Stacked ^{1}H (top) and ^{13}C (bottom) NMR spectra (D_2O, 400 and 101 MHz, respectively) of Thr (red) and 4F-Thr (green). Methanol was added as a reference (3.34 ppm for ^{1}H NMR and 49.5 ppm for ^{13}C NMR).