

Supporting Information

Discovery of Potent and Brain-Penetrant GPR52 Agonist that Suppresses Psychostimulant Behavior

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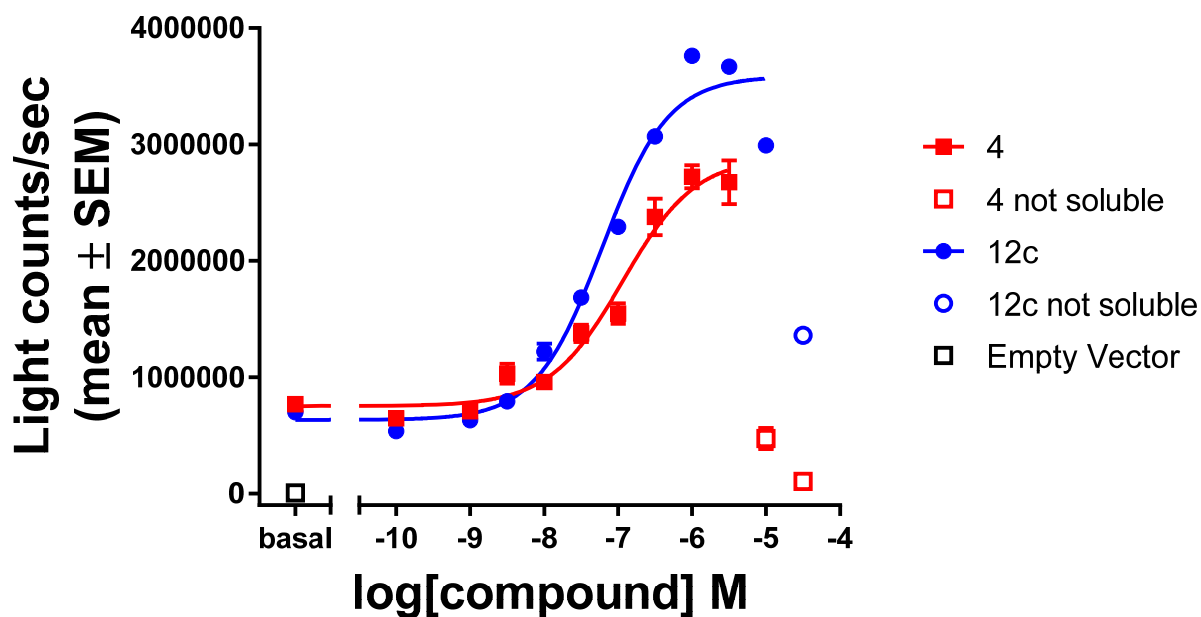


Figure S1. Representative concentration-responses of compound **4** and **12c** on cAMP signaling in HEK293 cells transiently expressing GPR52 and cAMP Glosensor reporter. Transient expression of GPR52 resulted in >100 fold light counts/sec over empty vector, indicating high constitutive receptor activity. Compound **4** (positive control) yields a robust ~3-fold increase in light counts/sec over basal values. Compounds were tested in twelve-point concentration-responses (0.1 nM – 30 μ M); however, due to poor water solubility of compound **4**, 10 and 30 μ M points were excluded for the potency and efficacy analysis. Similarly, if a severe drop in light counts was observed at high concentration points (i.e. 30 μ M for compound **12c**), these points were excluded for curve fitting analyses.

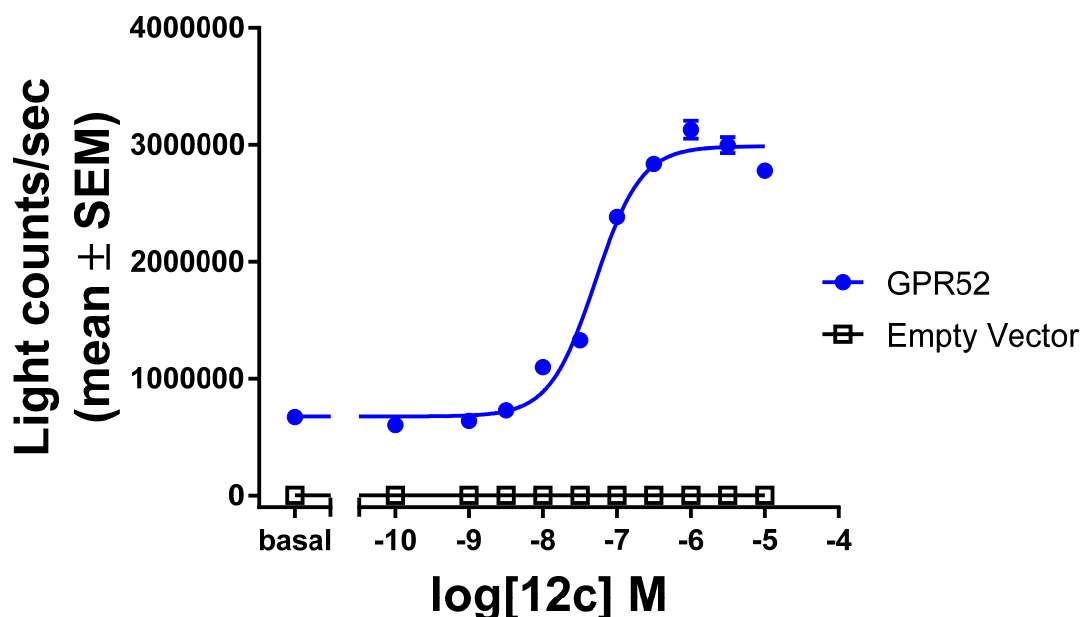
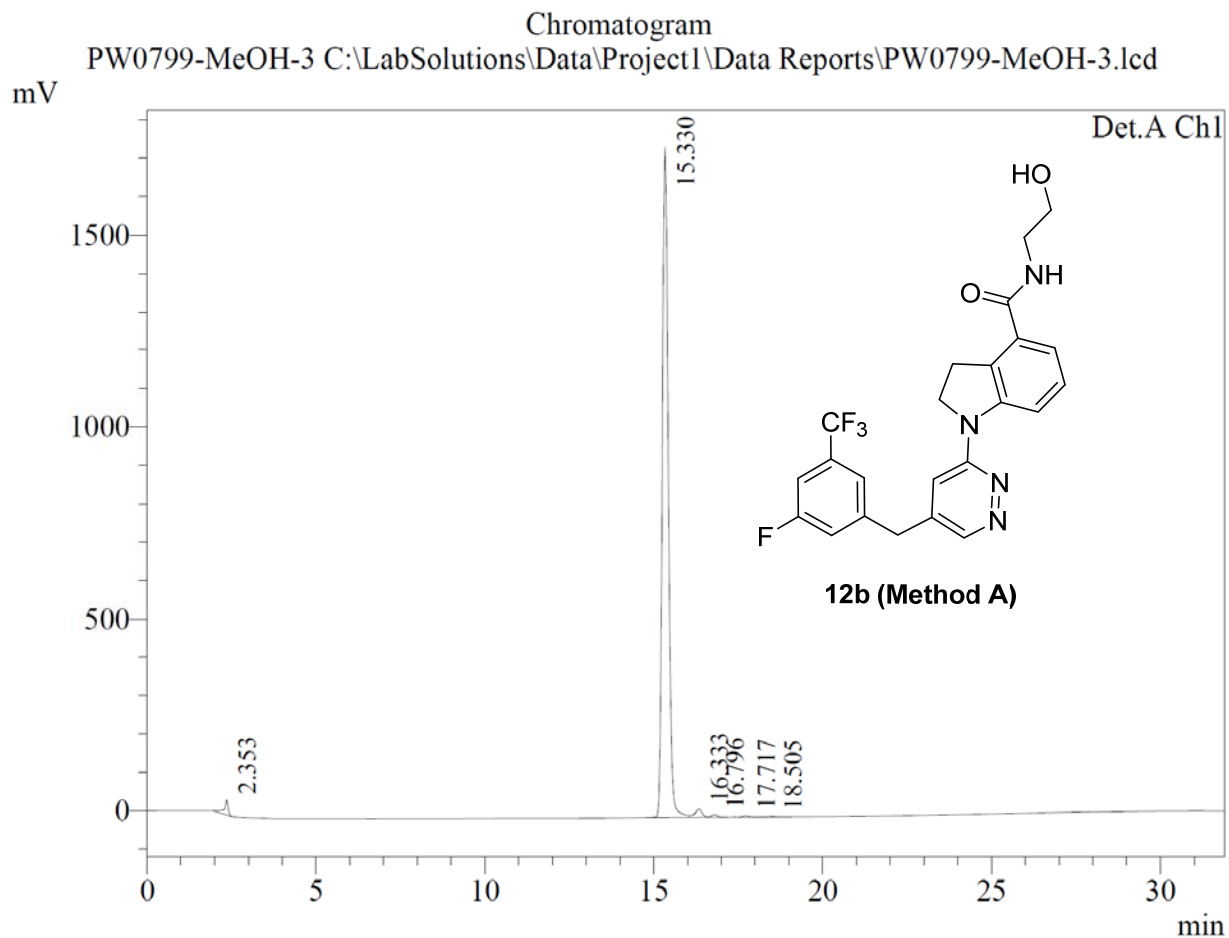


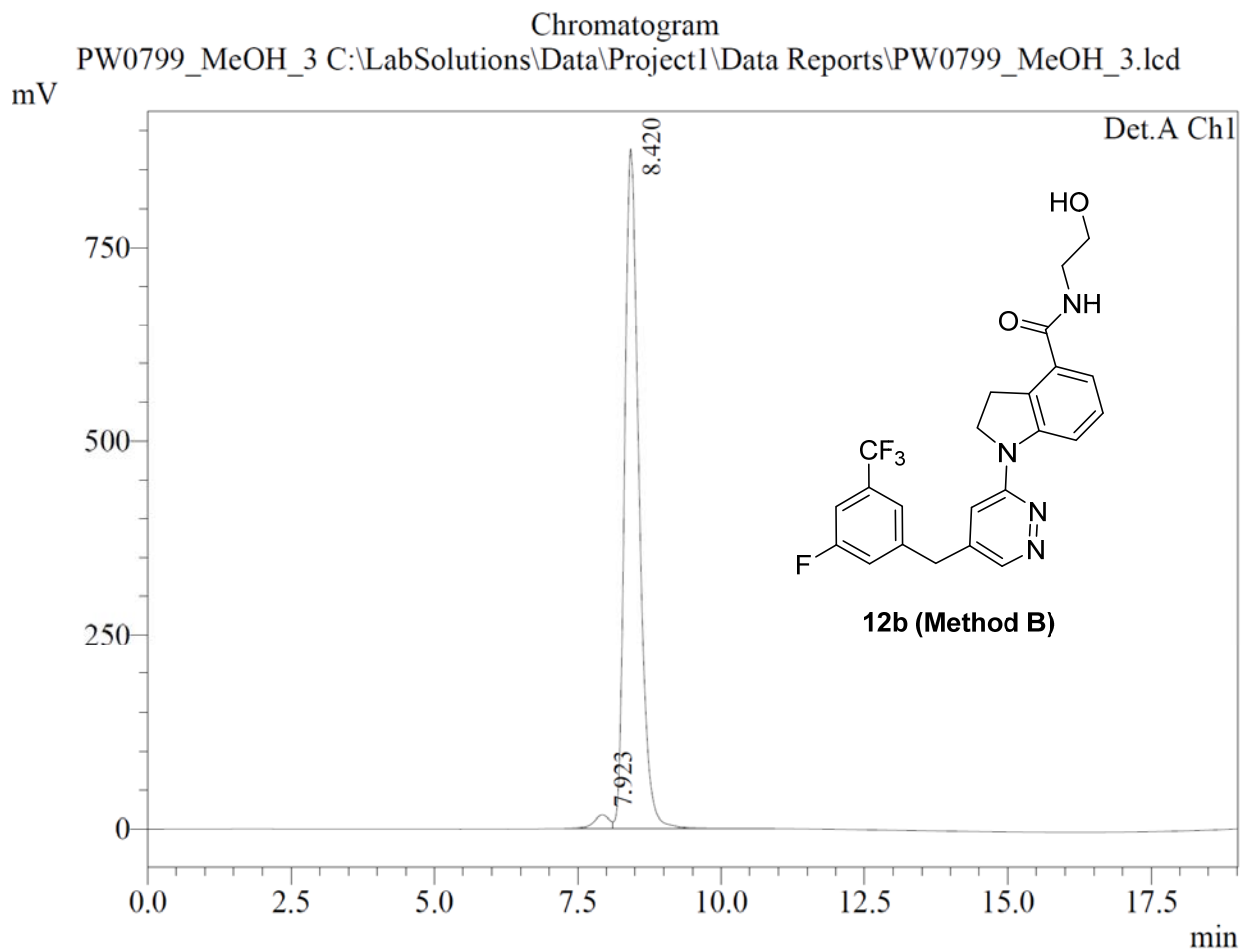
Figure S2. Representative concentration-responses of compound **12c** on cAMP signaling in HEK293 cells transiently expressing GPR52 or an empty vector (control) and cAMP Glosensor reporter. Compound **12c** was tested in twelve-point concentration-responses (0.1 nM – 10 μ M). Compound **12c** yields a robust ~3-fold increase in light counts/sec over basal values in cells expressing GPR52 (blue circles). Importantly, no increase in cAMP was observed in cells expressing empty vector (black squares), indicating that compound **12c** elevation of cAMP is due to selectively activating GPR52.



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Area %	Height %
1	2.353	323543	1.448	2.122
2	15.330	21537858	96.392	96.000
3	16.333	324207	1.451	1.206
4	16.796	85734	0.384	0.383
5	17.717	49741	0.223	0.211
6	18.505	22852	0.102	0.079
Total		22343935	100.000	100.000

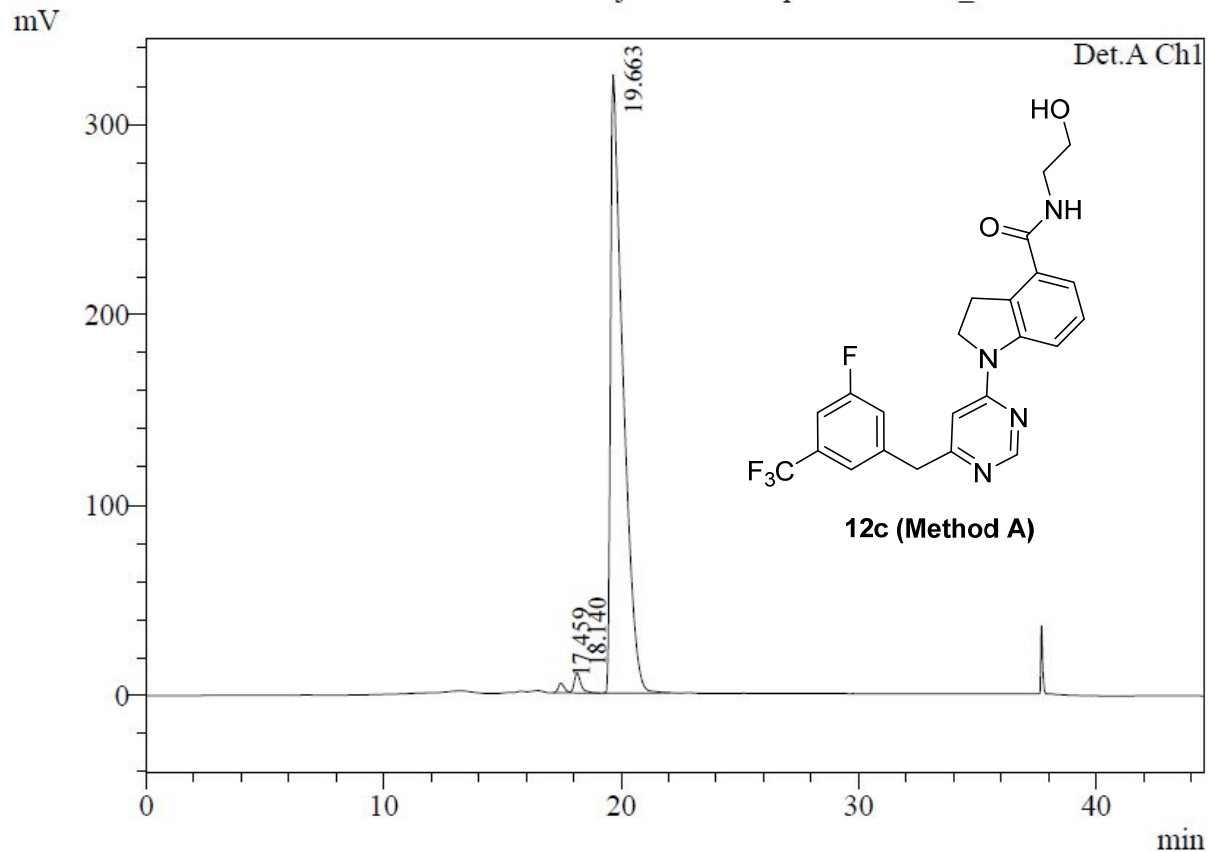


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Area %	Height %
1	7.923	311553	2.002	1.934
2	8.420	15247990	97.998	98.066
Total		15559543	100.000	100.000

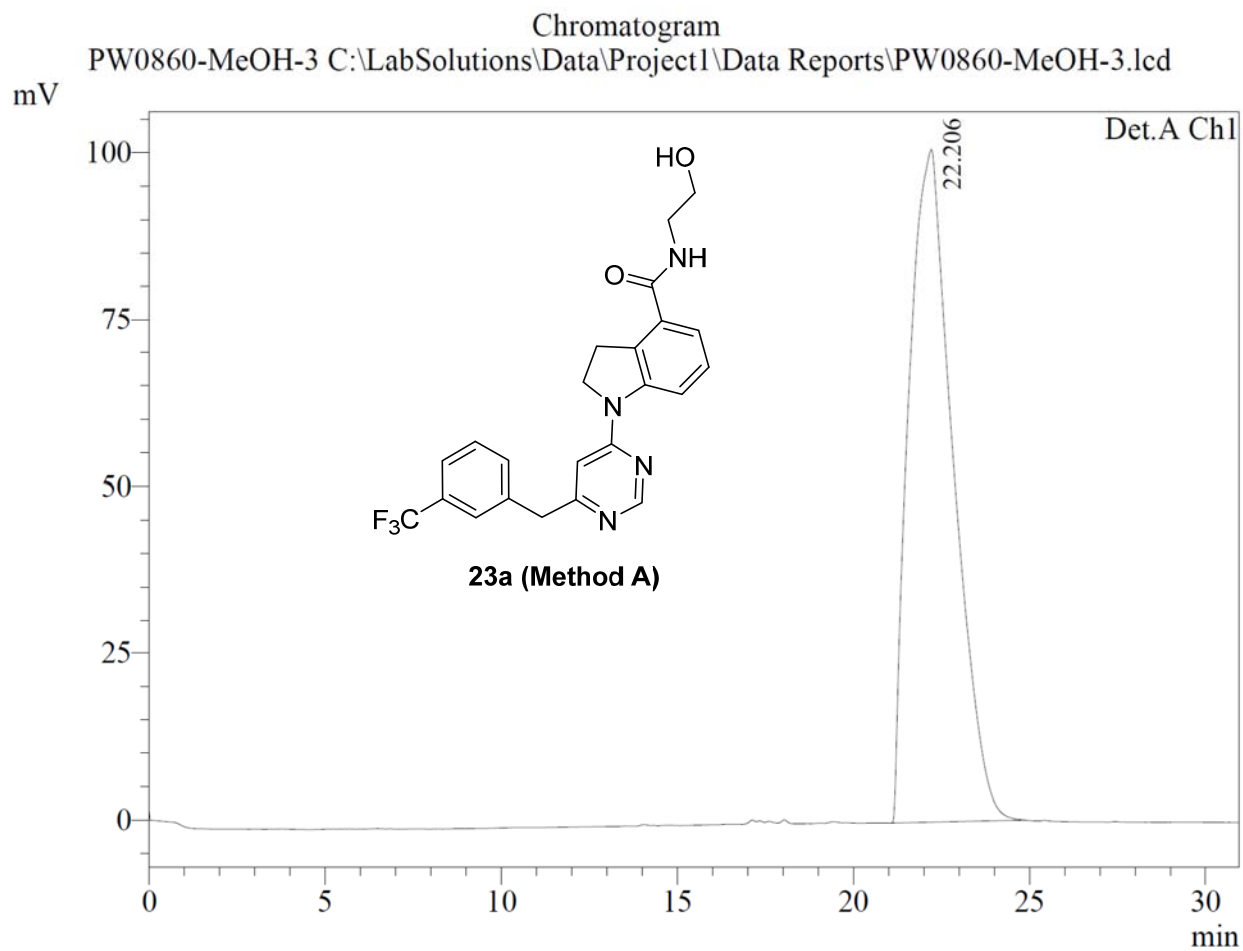
Chromatogram
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PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Area %	Height %
1	17.459	89681	0.741	1.477
2	18.140	205021	1.695	3.089
3	19.663	11804114	97.564	95.434
Total		12098816	100.000	100.000



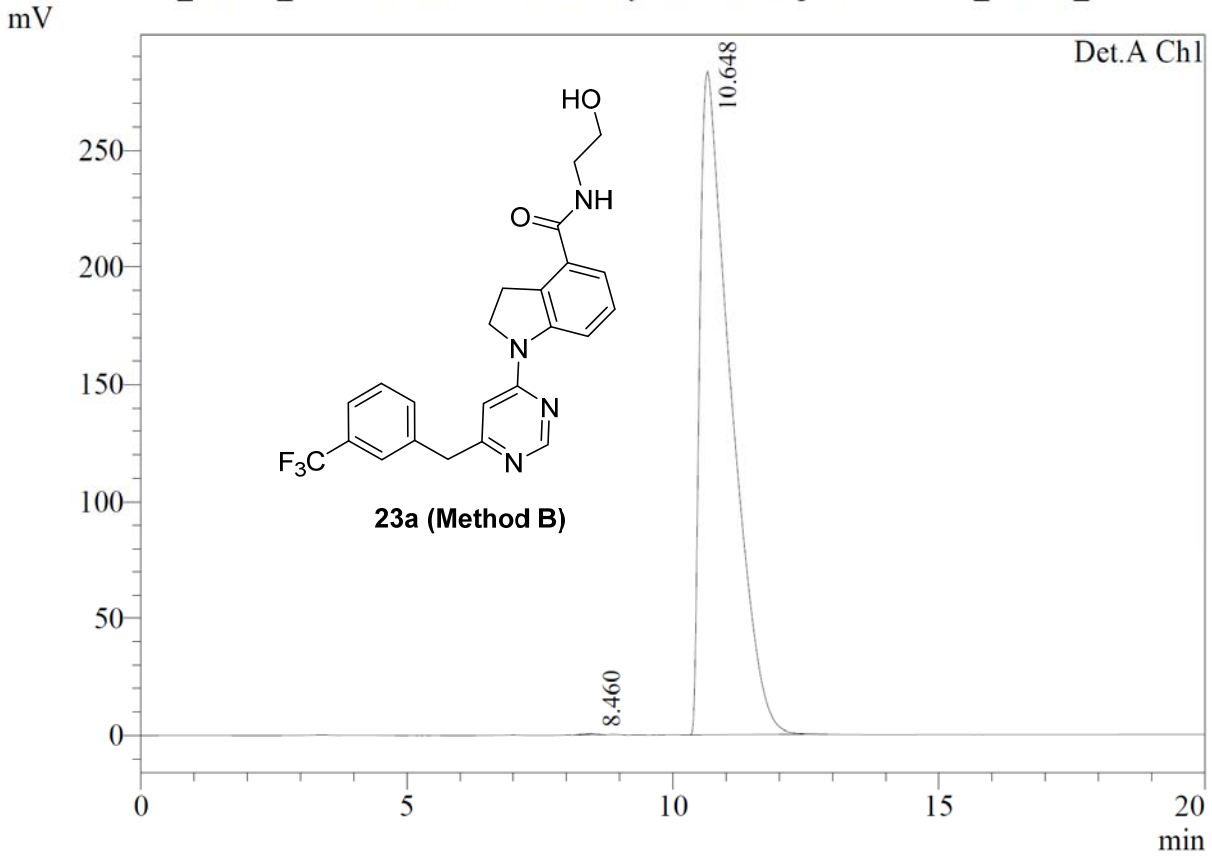
PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Area %	Height %
1	22.206	8839268	100.000	100.000
Total		8839268	100.000	100.000

Chromatogram

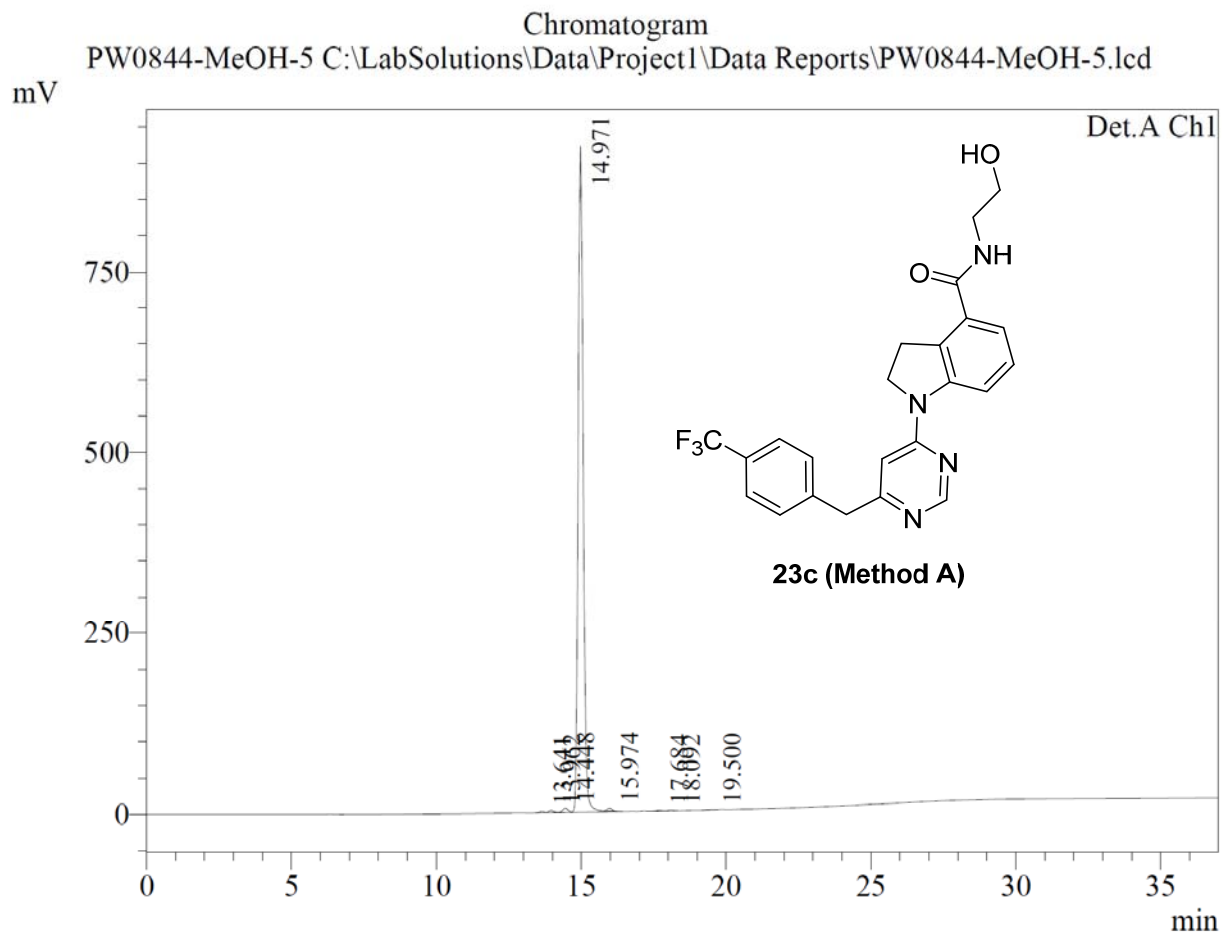
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PeakTable

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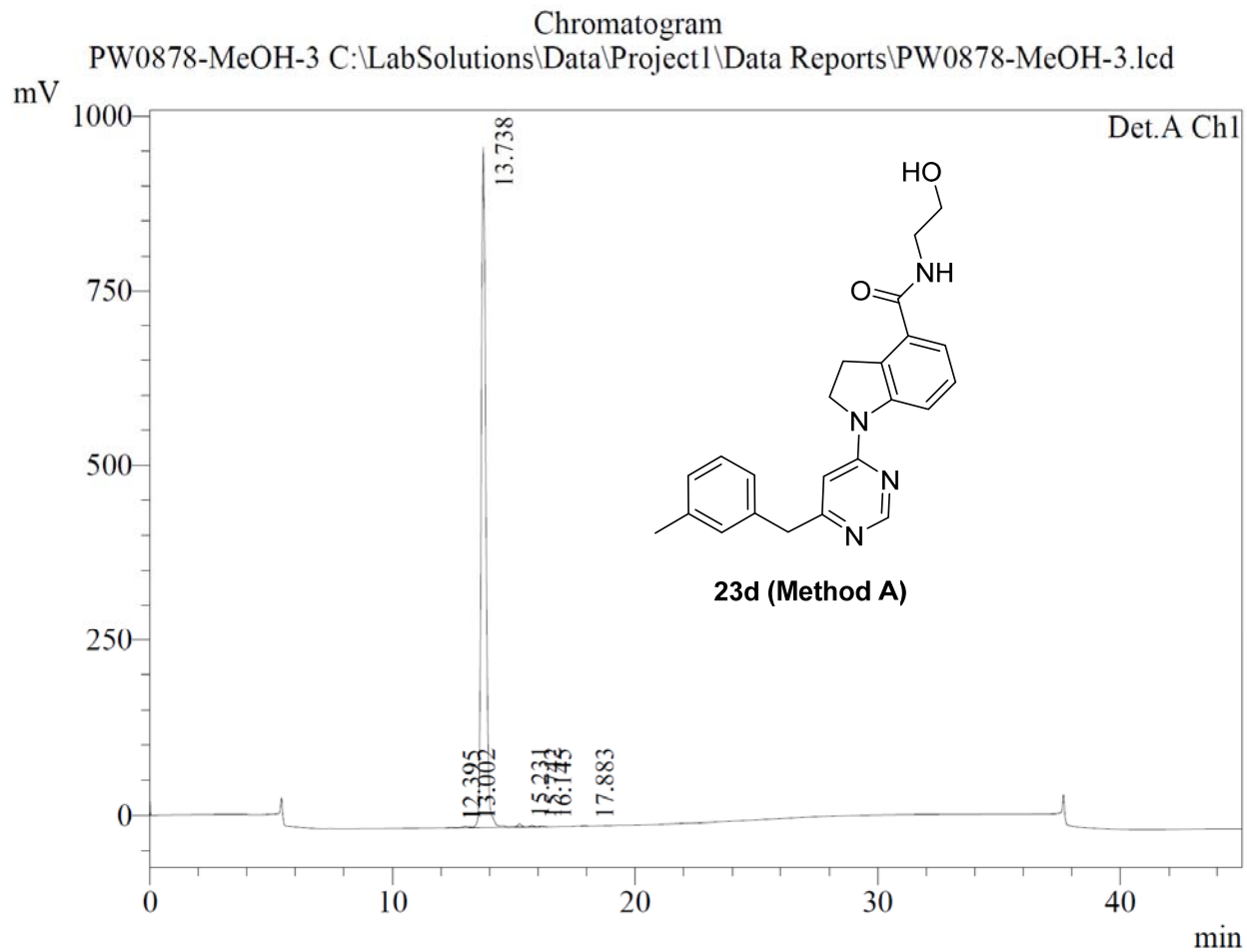
Peak#	Ret. Time	Area	Area %	Height %
1	8.460	11540	0.101	0.204
2	10.648	11409889	99.899	99.796
Total		11421429	100.000	100.000



PeakTable

Detector A Ch1 254nm

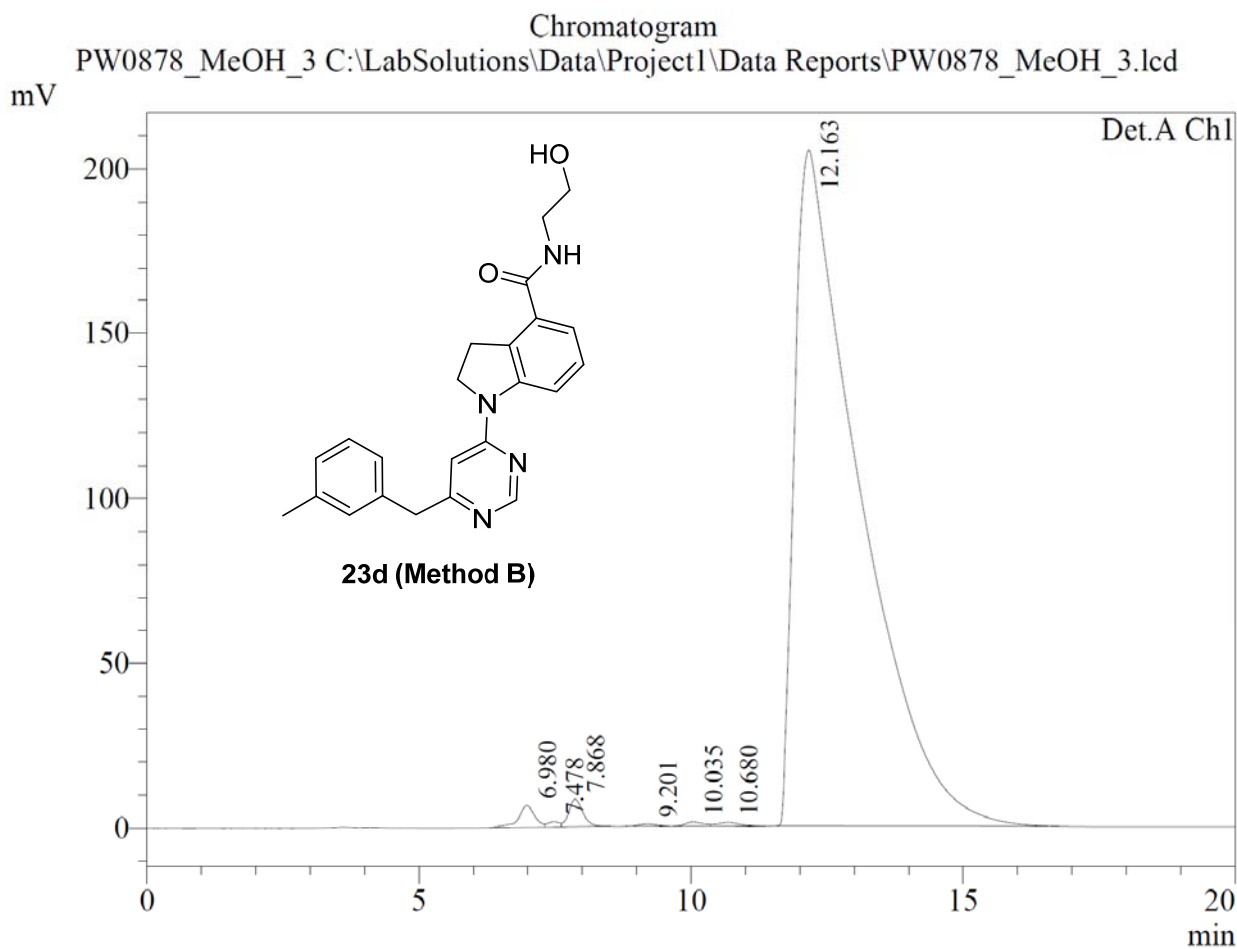
Peak#	Ret. Time	Area	Area %	Height %
1	13.641	19235	0.170	0.184
2	13.962	35710	0.315	0.311
3	14.448	74149	0.654	0.634
4	14.971	11136556	98.187	98.218
5	15.974	43812	0.386	0.419
6	17.684	11297	0.100	0.086
7	18.092	10944	0.096	0.098
8	19.500	10510	0.093	0.048
Total		11342214	100.000	100.000



PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Area %	Height %
1	12.395	12734	0.097	0.098
2	13.002	47562	0.364	0.217
3	13.738	12902679	98.776	98.791
4	15.231	49171	0.376	0.443
5	15.742	25549	0.196	0.224
6	16.145	14588	0.112	0.130
7	17.883	10326	0.079	0.098
Total		13062608	100.000	100.000

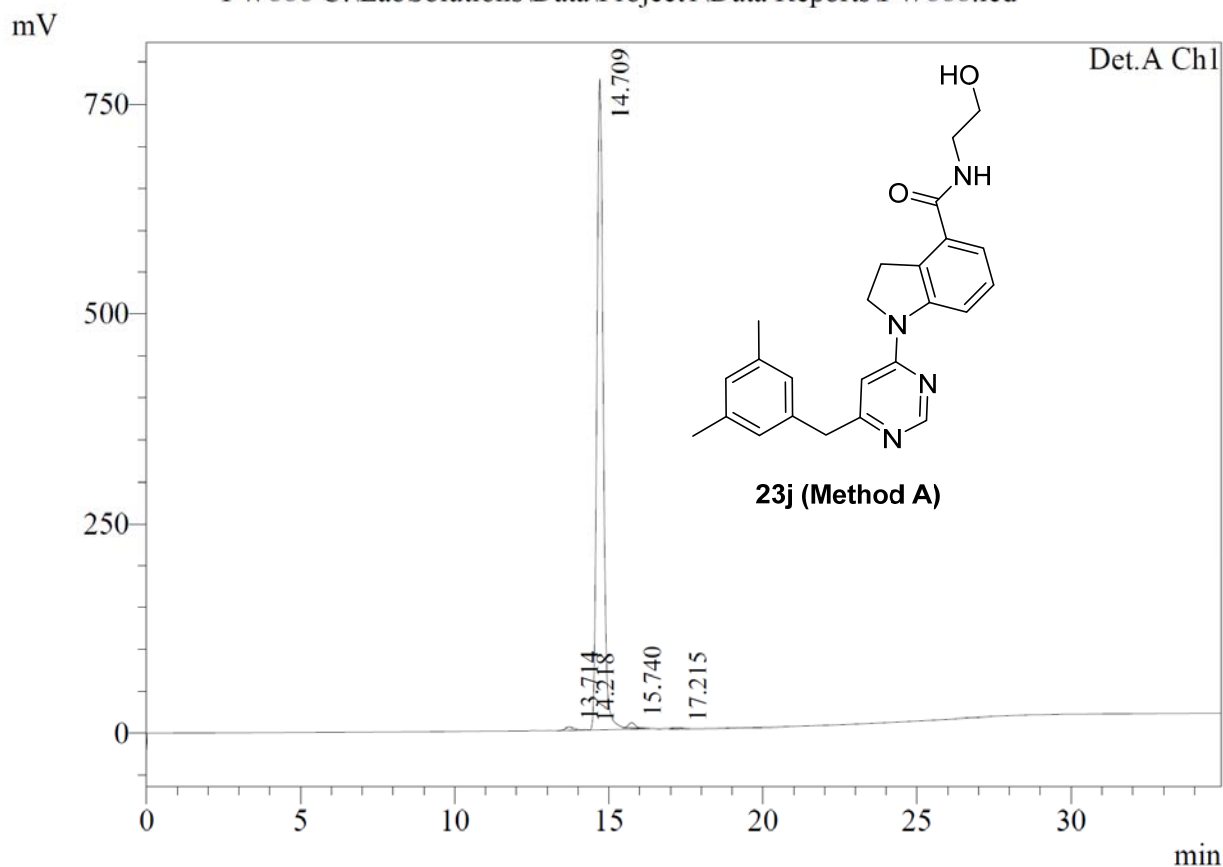


PeakTable

Detector A Ch1 254nm

Peak#	Ret. Time	Area	Area %	Height %
1	6.980	136911	0.789	2.944
2	7.478	23233	0.134	0.695
3	7.868	148134	0.854	3.707
4	9.201	12271	0.071	0.283
5	10.035	28209	0.163	0.562
6	10.680	31861	0.184	0.505
7	12.163	16970935	97.806	91.304
Total		17351553	100.000	100.000

Chromatogram
 PW888 C:\LabSolutions\Data\Project1\Data Reports\PW888.lcd

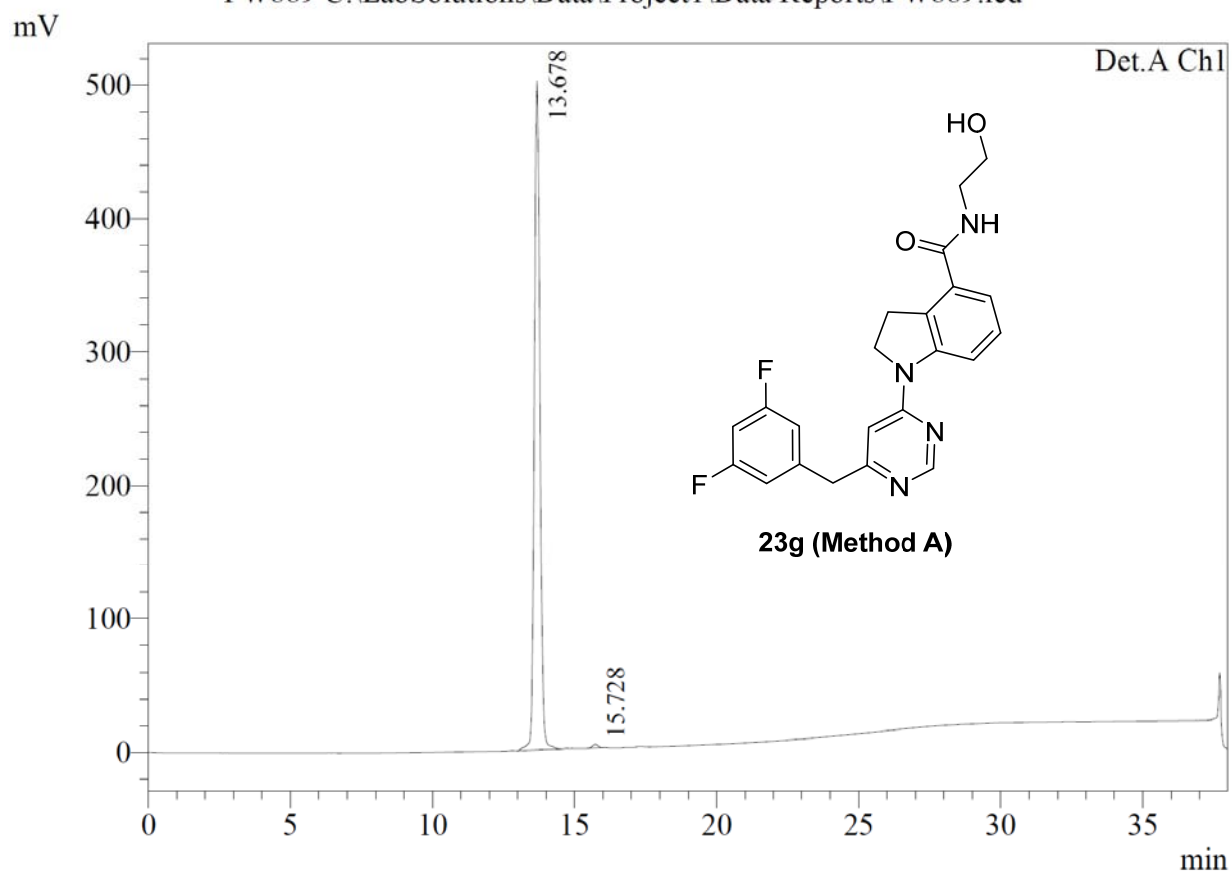


PeakTable

Detector A Chl 254nm

Peak#	Ret. Time	Area	Area %	Height %
1	13.714	80765	0.715	0.486
2	14.218	10170	0.090	0.108
3	14.709	11097346	98.247	98.477
4	15.740	81619	0.723	0.783
5	17.215	25408	0.225	0.146
Total		11295308	100.000	100.000

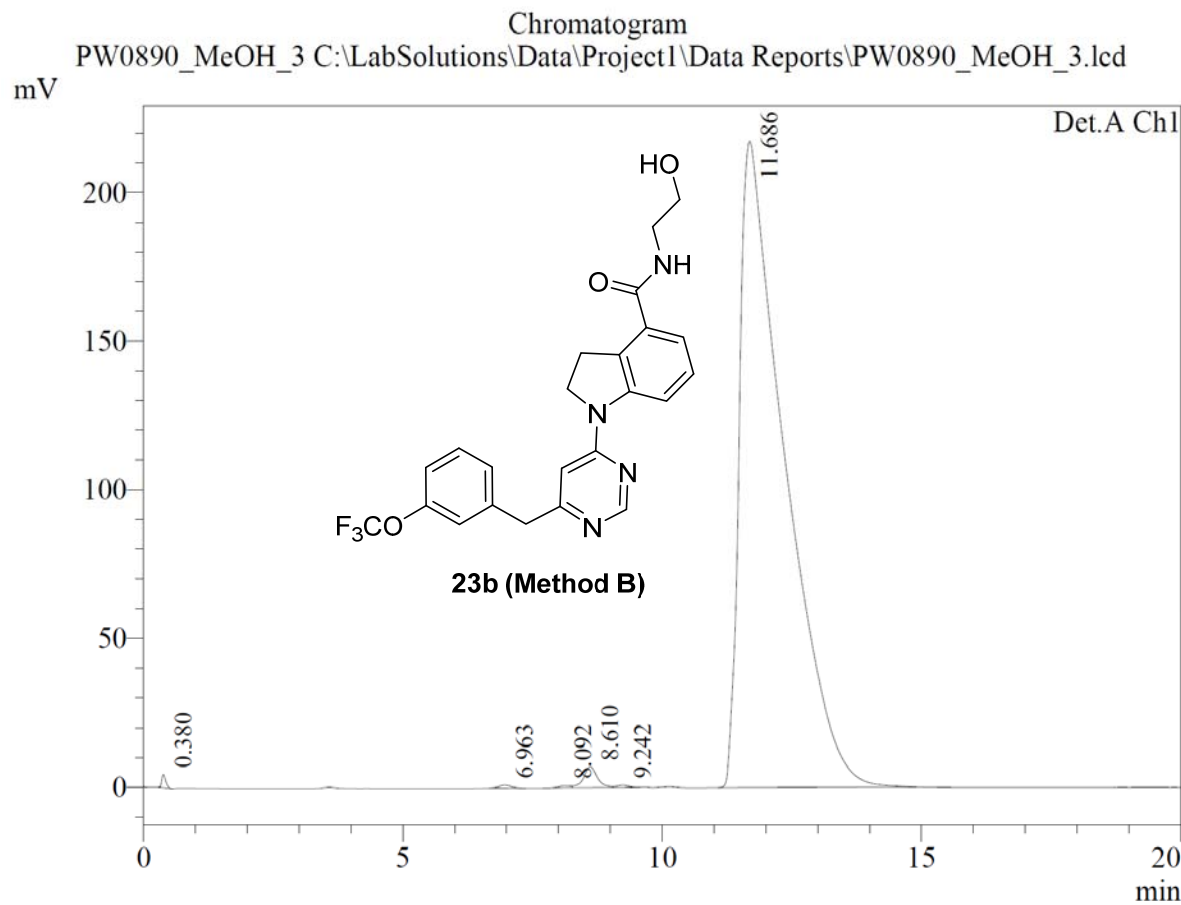
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PeakTable

Detector A Ch1 254nm

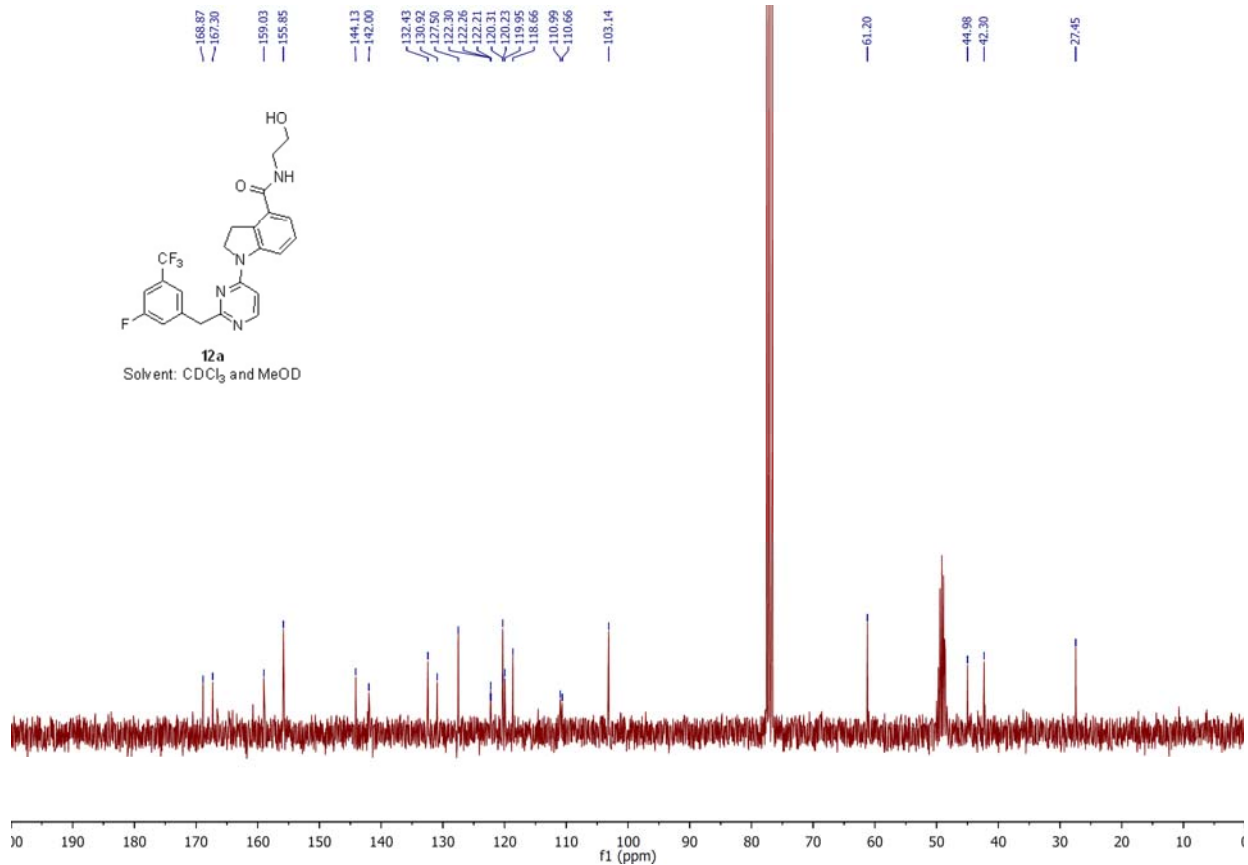
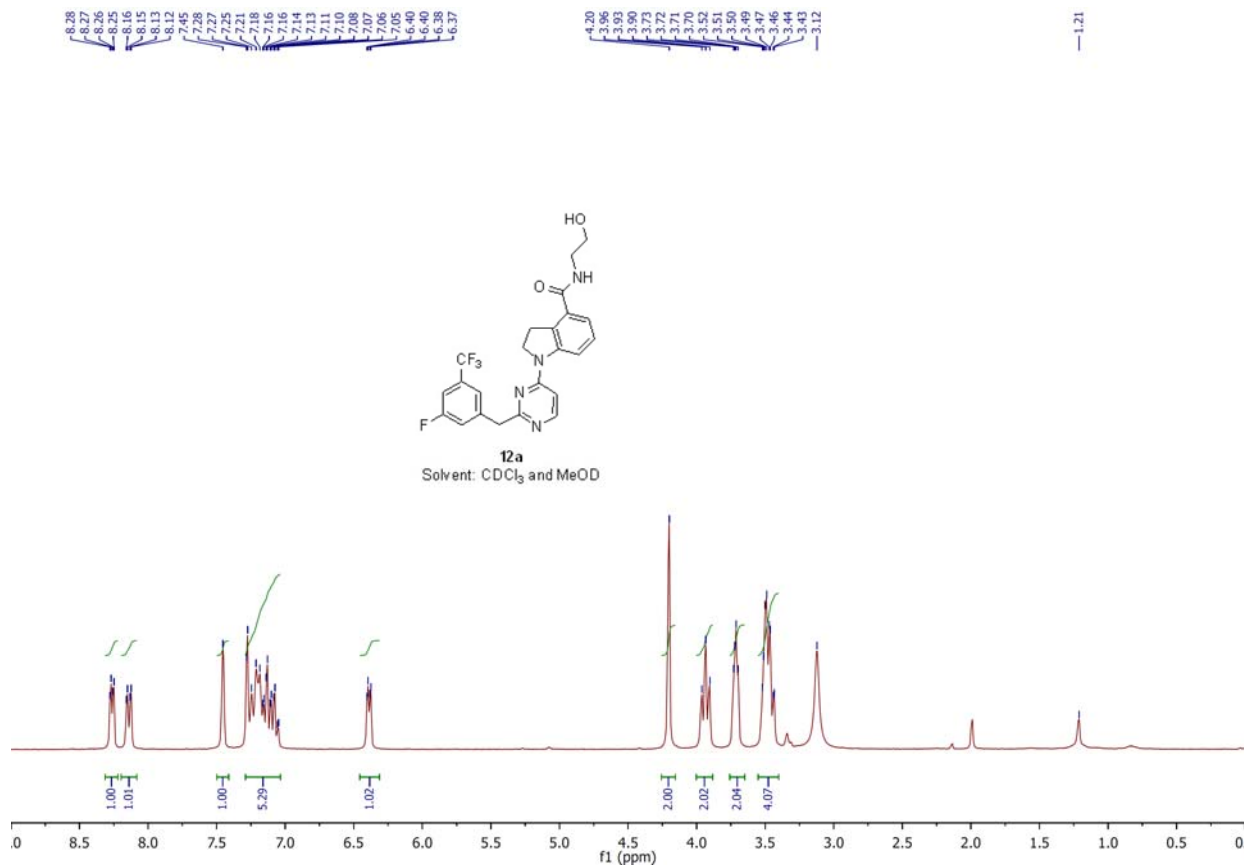
Peak#	Ret. Time	Area	Area %	Height %
1	13.678	6878546	99.478	99.452
2	15.728	36118	0.522	0.548
Total		6914664	100.000	100.000

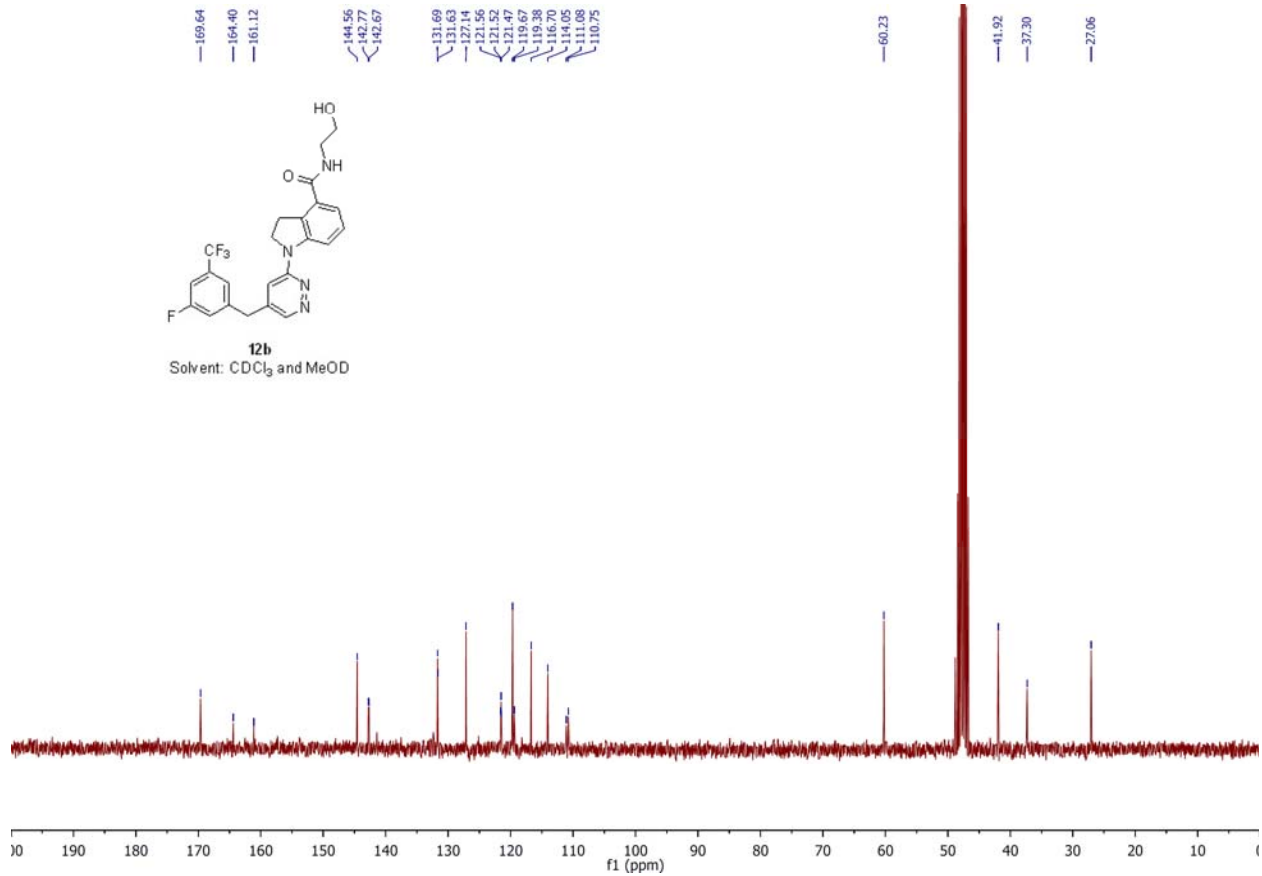
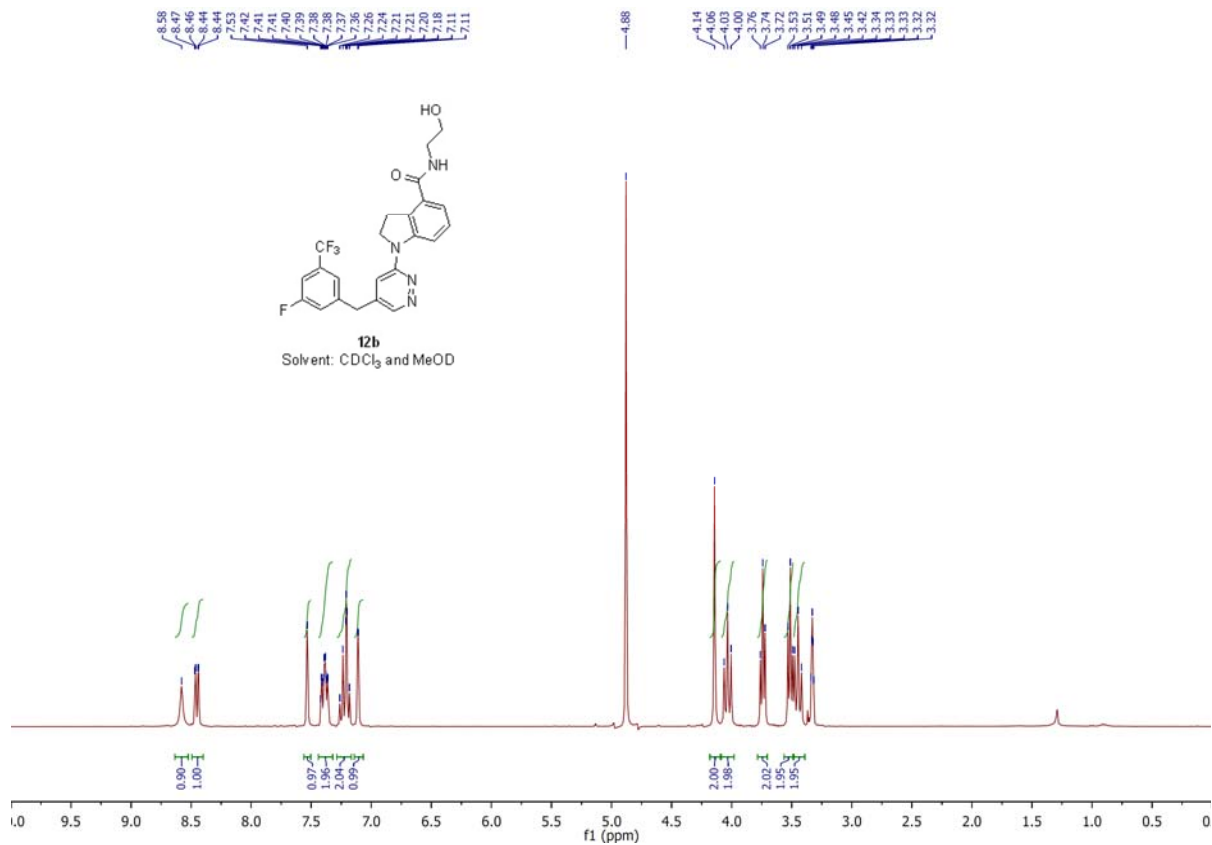


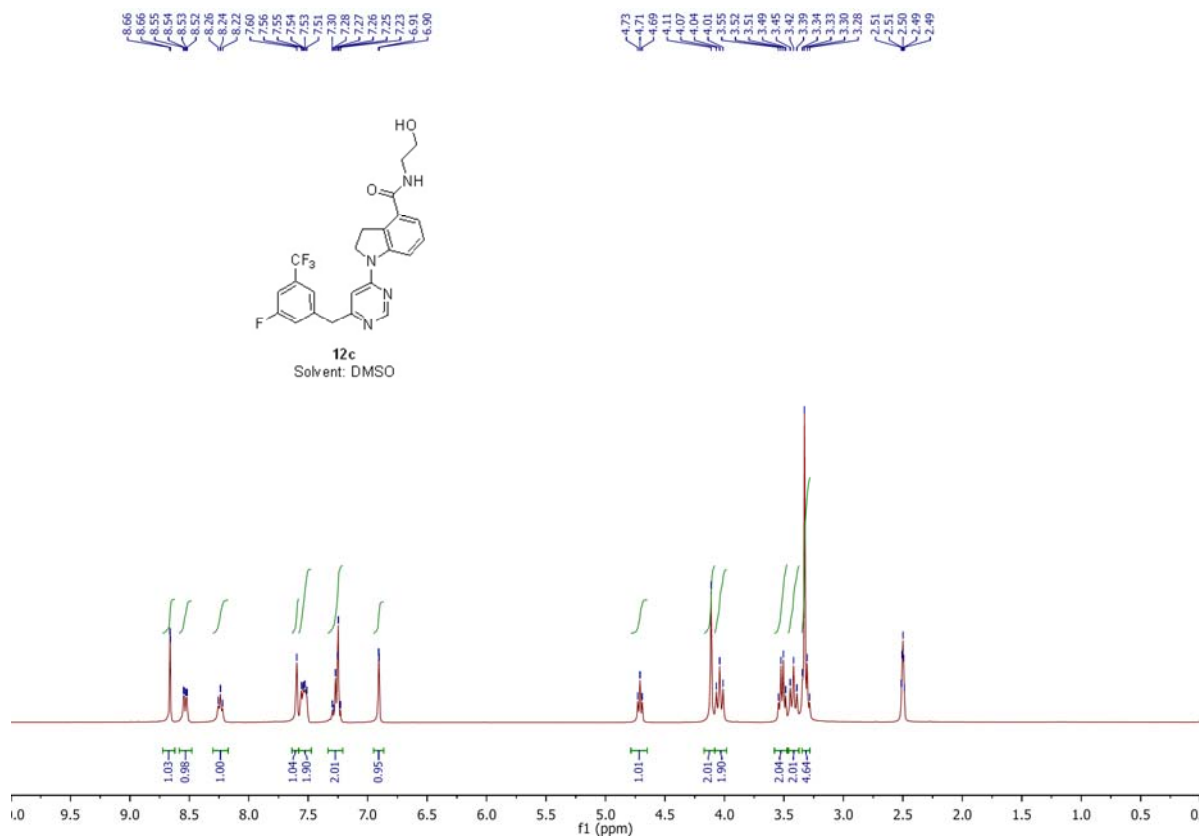
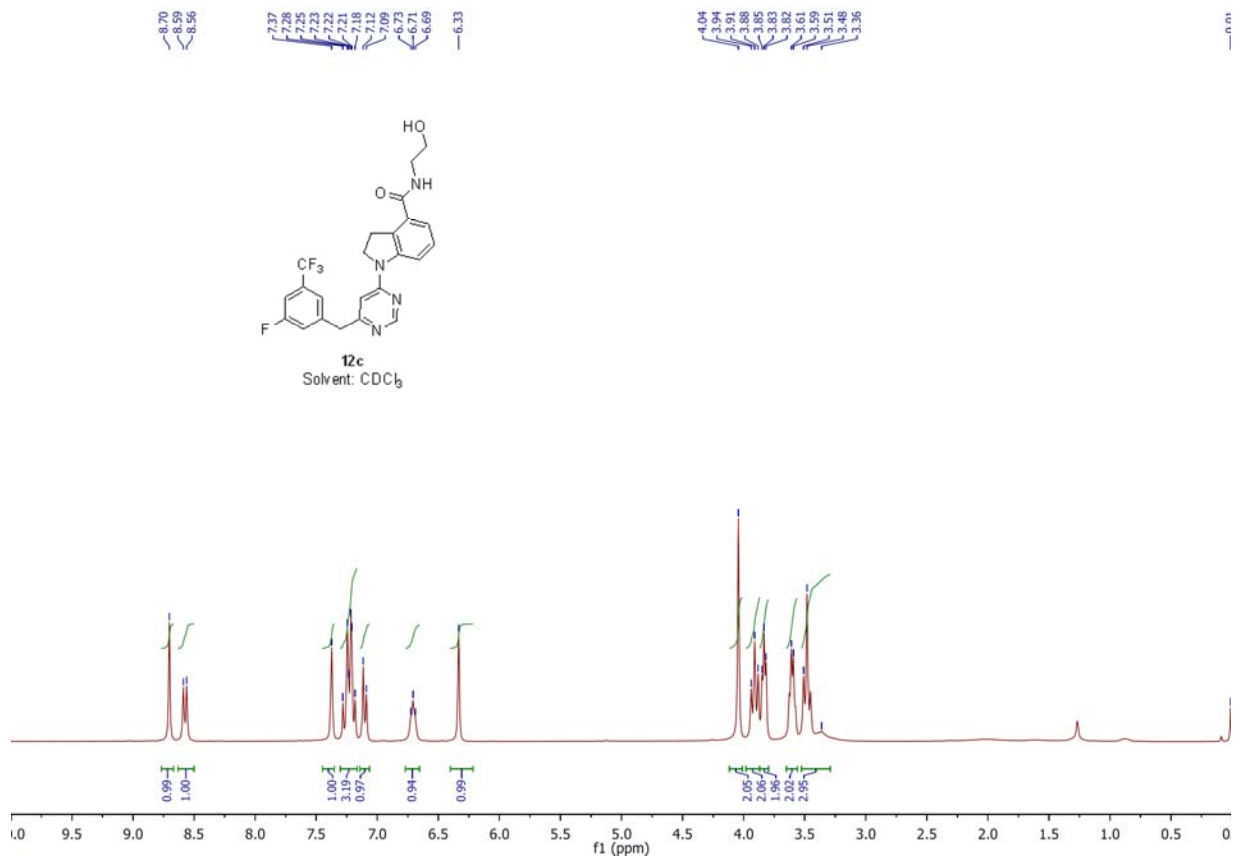
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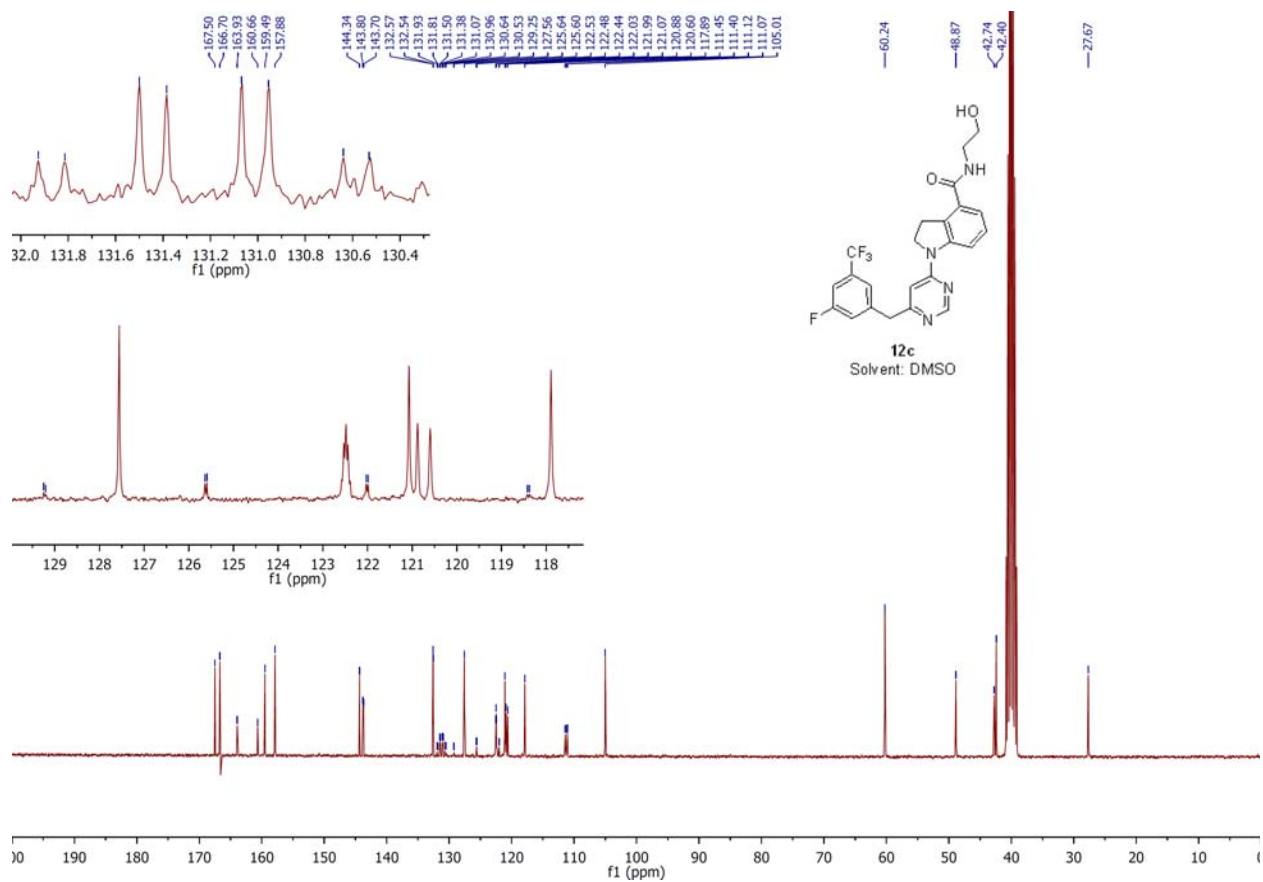
Detector A Ch1 254nm

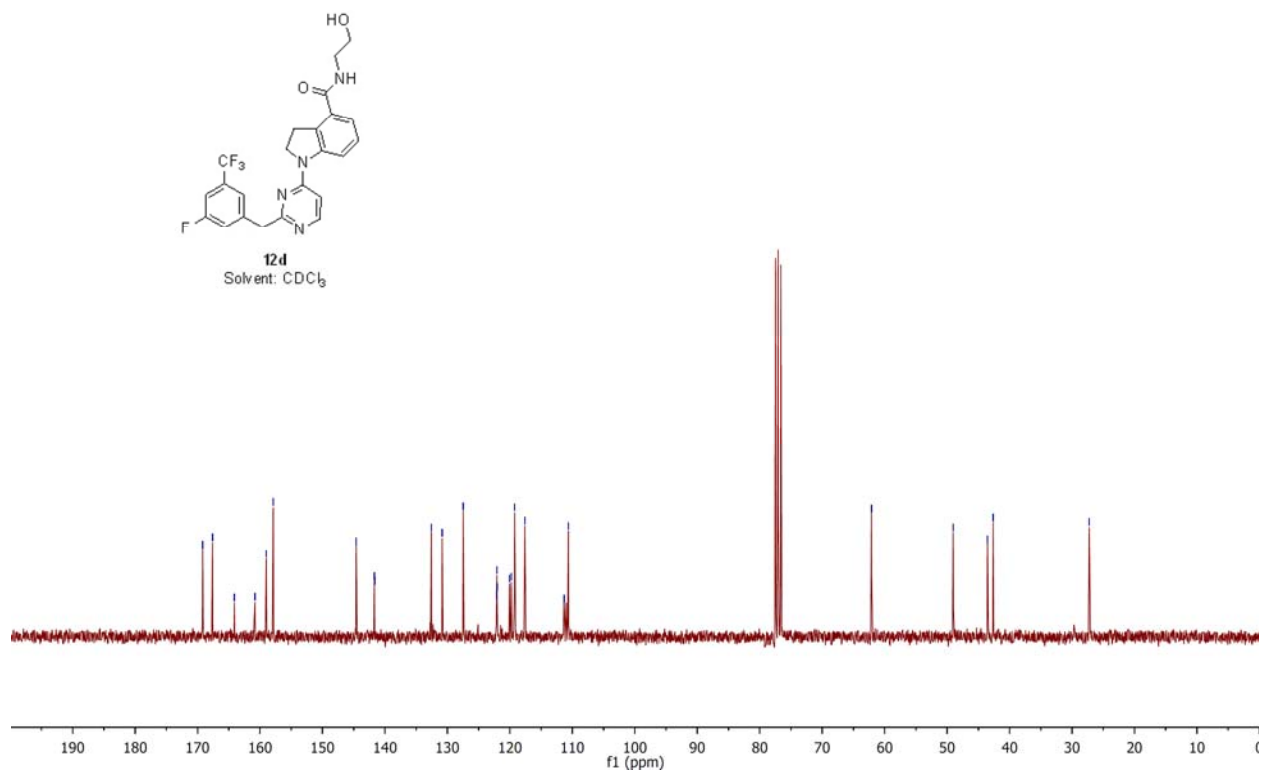
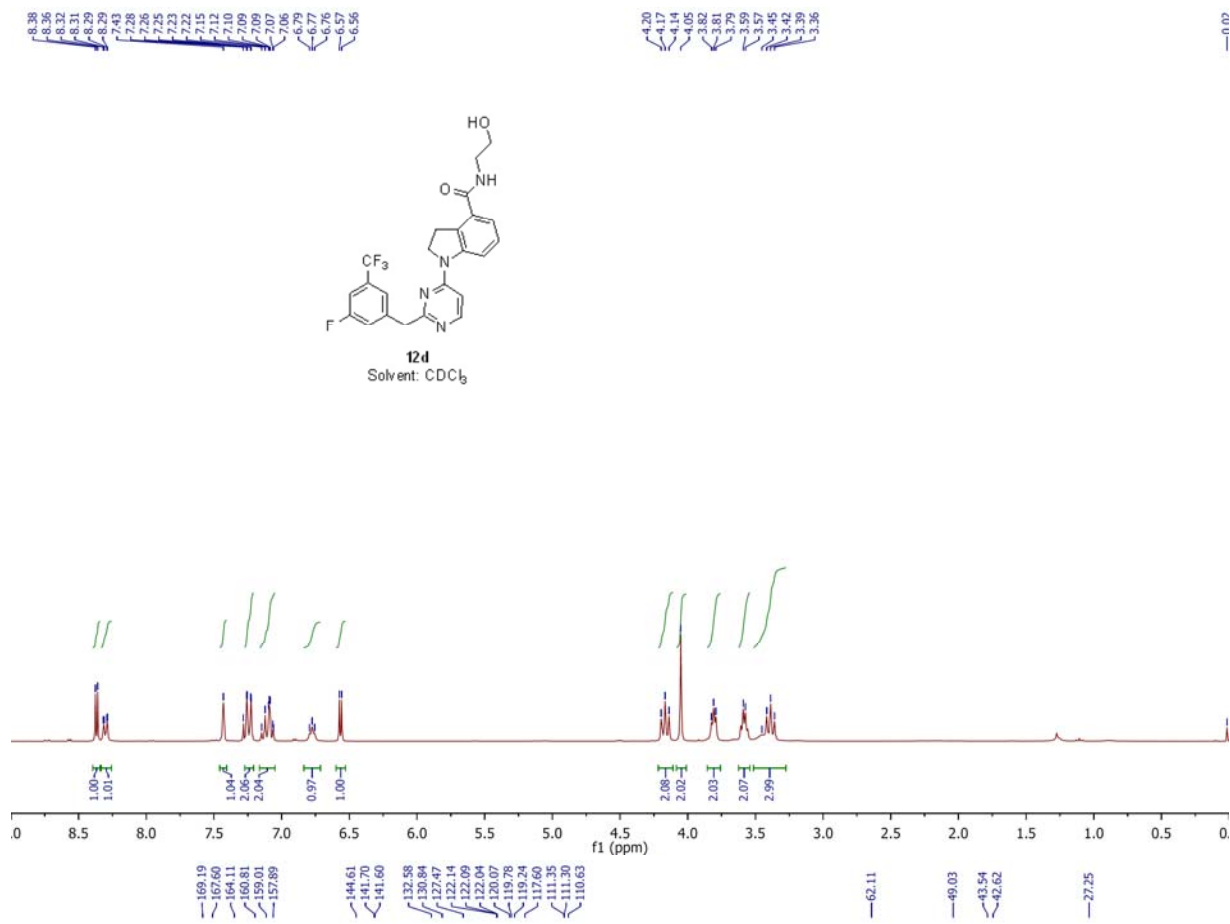
Peak#	Ret. Time	Area	Area %	Height %
1	0.380	22939	0.172	1.925
2	6.963	16339	0.123	0.429
3	8.092	10505	0.079	0.297
4	8.610	127794	0.959	3.043
5	9.242	12748	0.096	0.351
6	11.686	13130053	98.571	93.954
Total		13320377	100.000	100.000

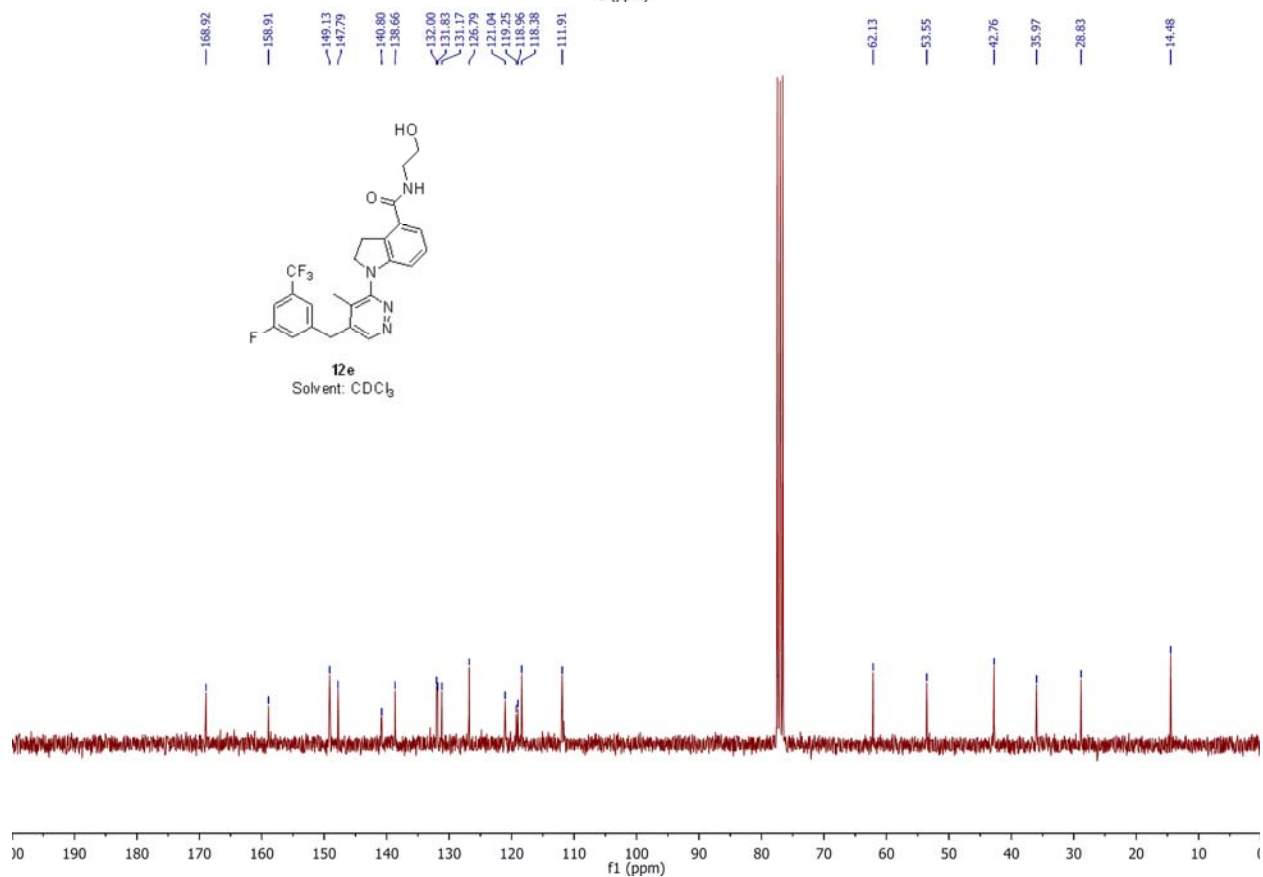
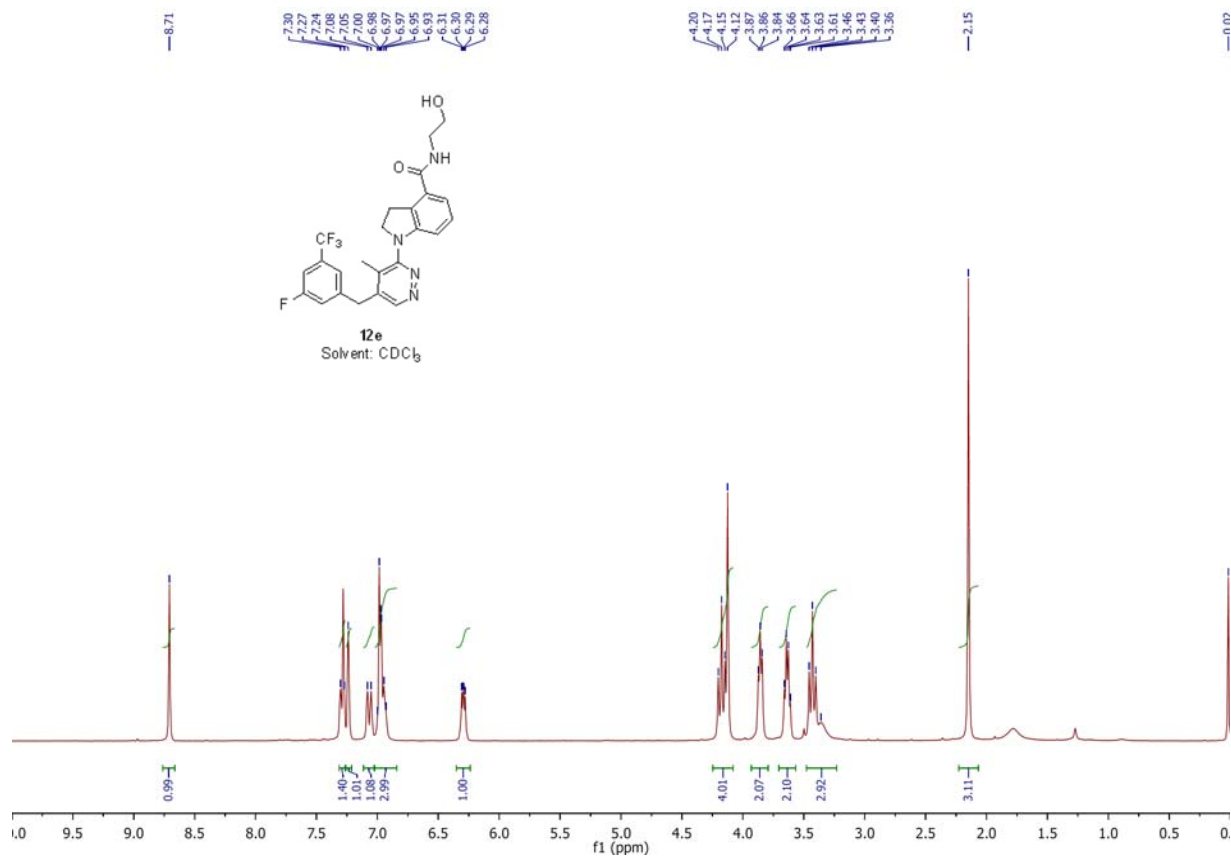


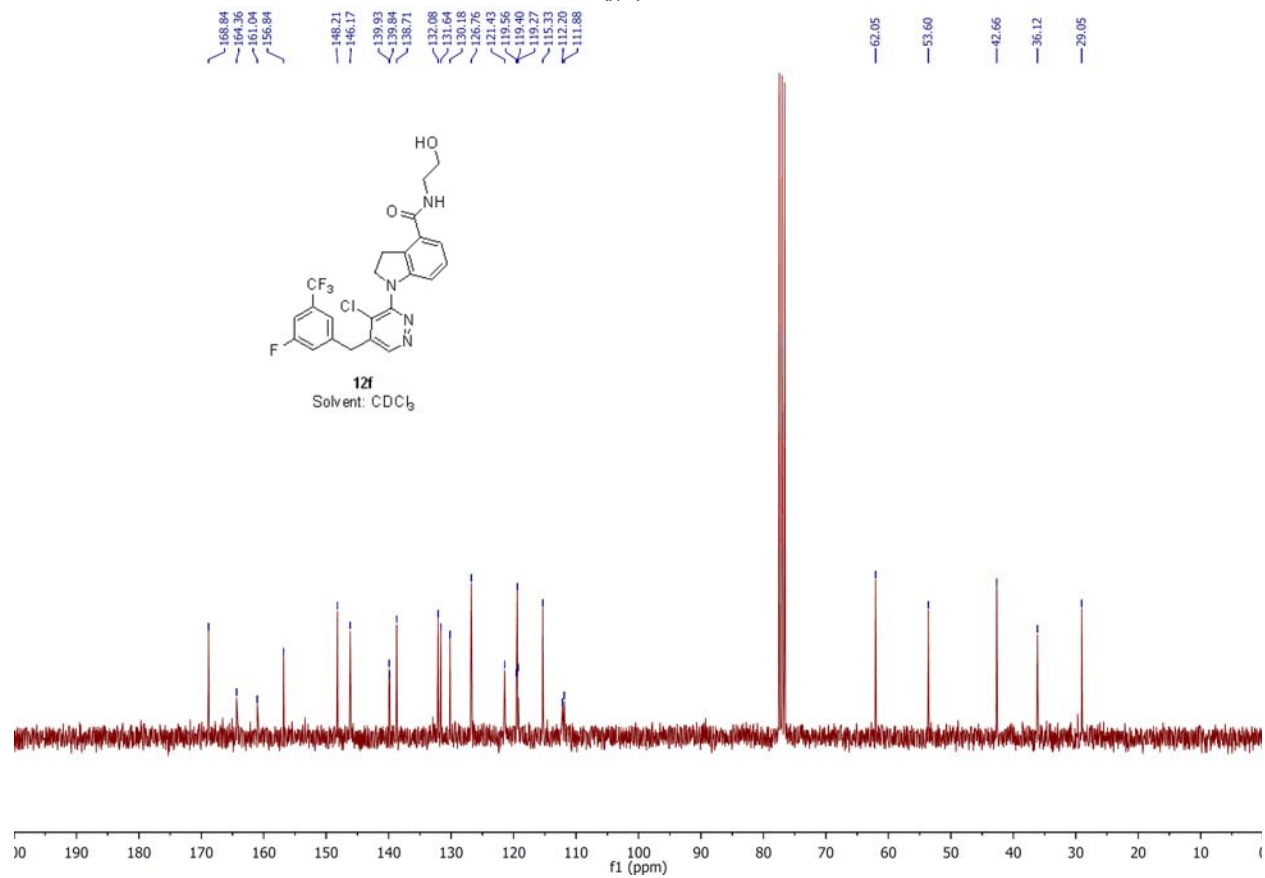
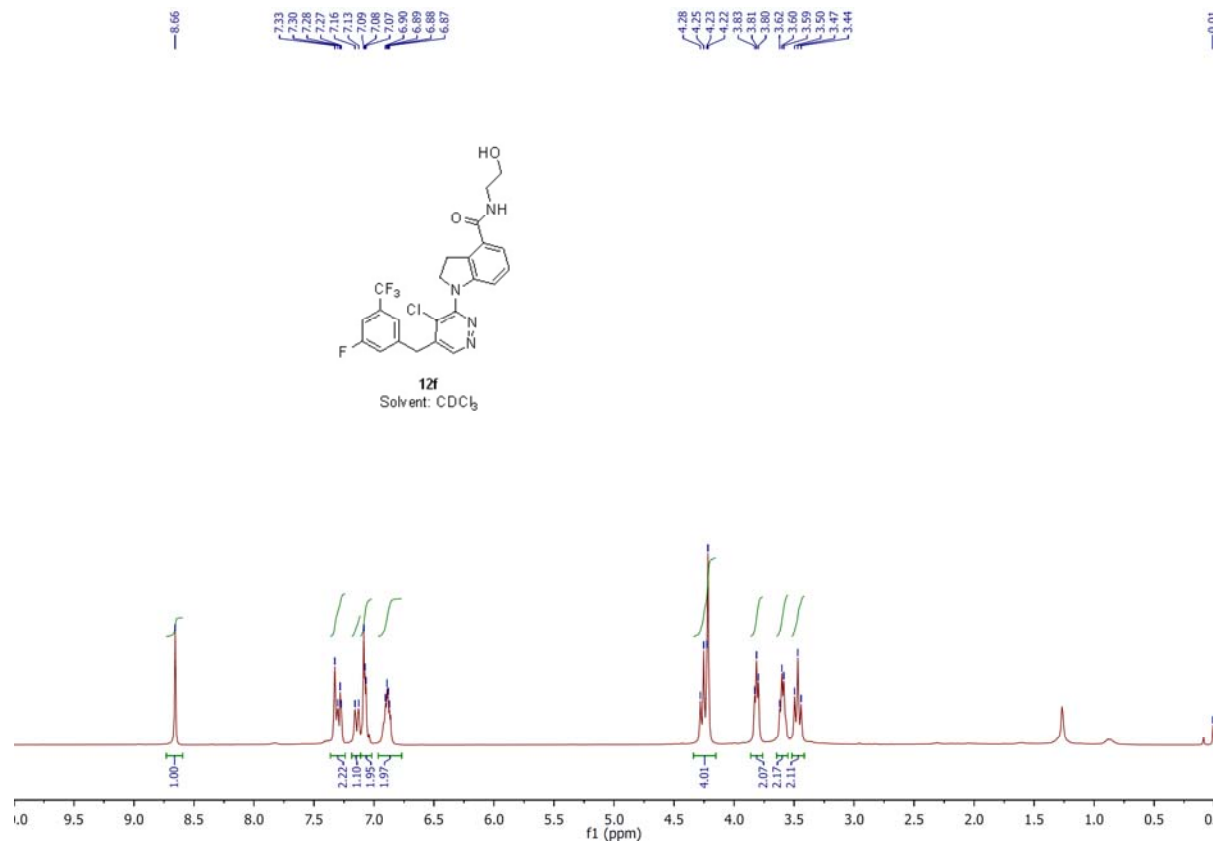










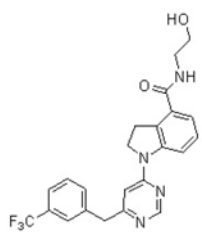


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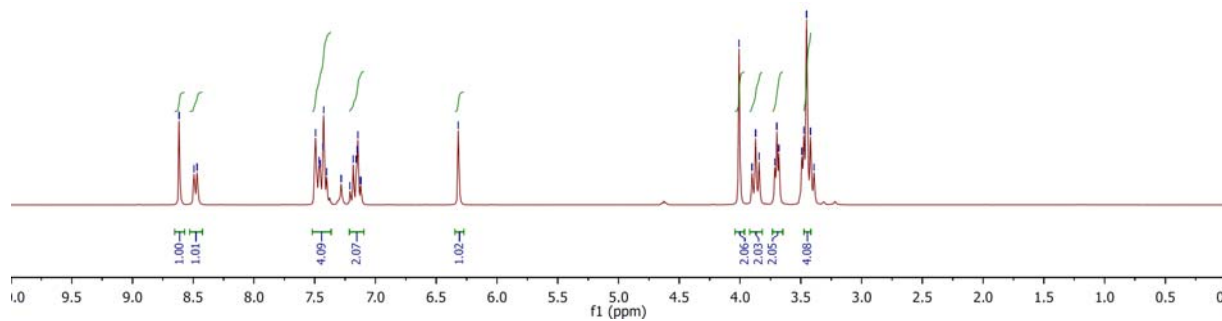
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7.12

6.32

4.01
3.90
3.87
3.84
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3.70
3.68
3.46
3.45
3.42
3.39



23a
Solvent: CDCl₃ and MeOD



168.82
166.74

159.40
157.45

144.22

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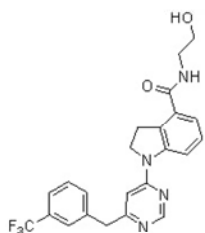
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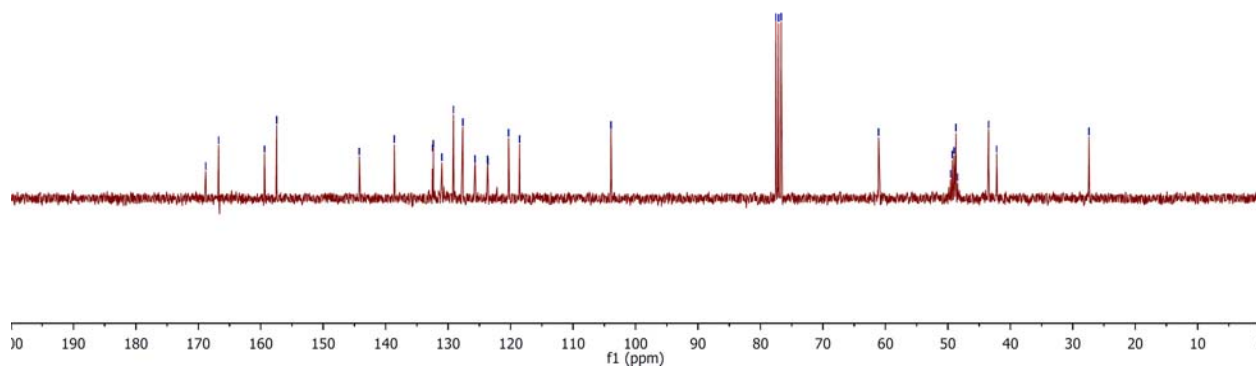
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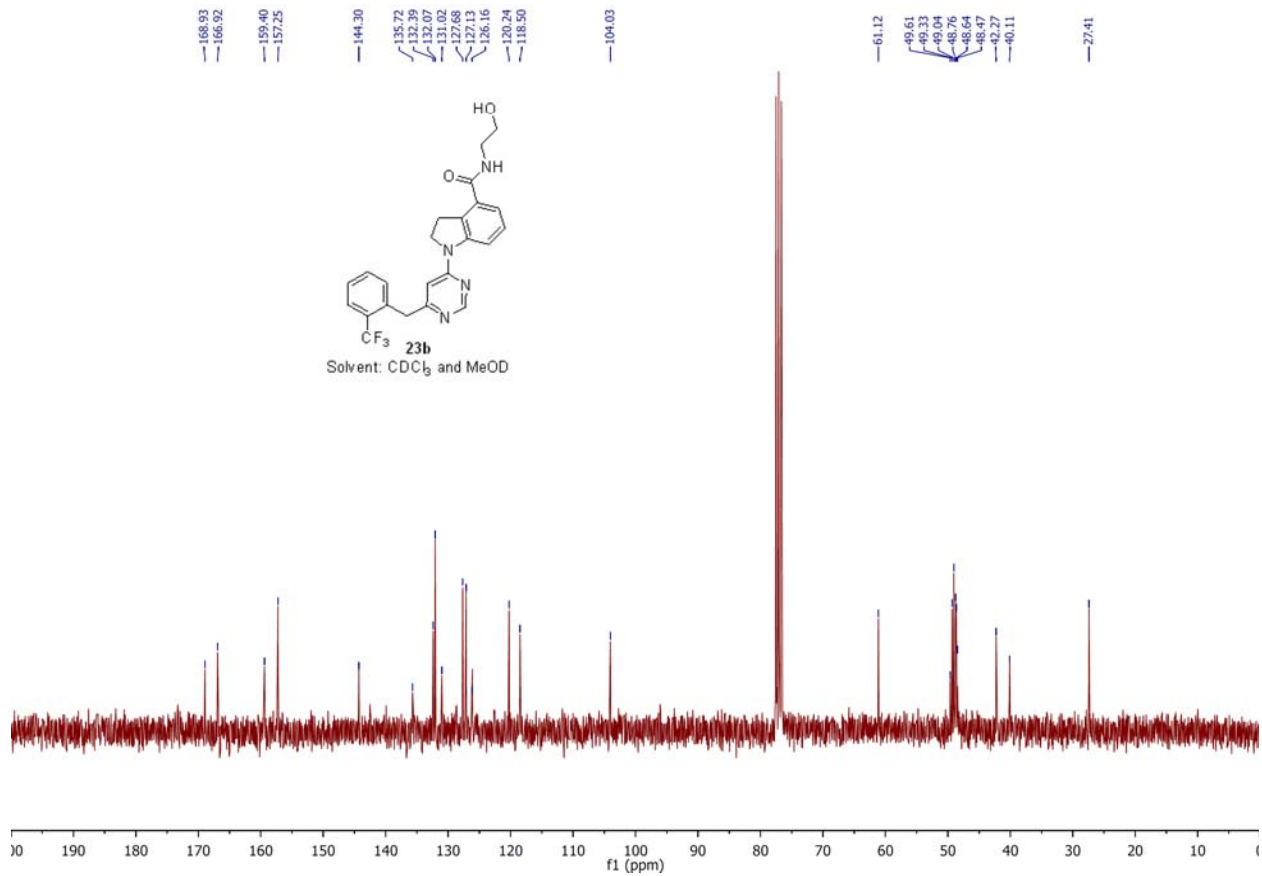
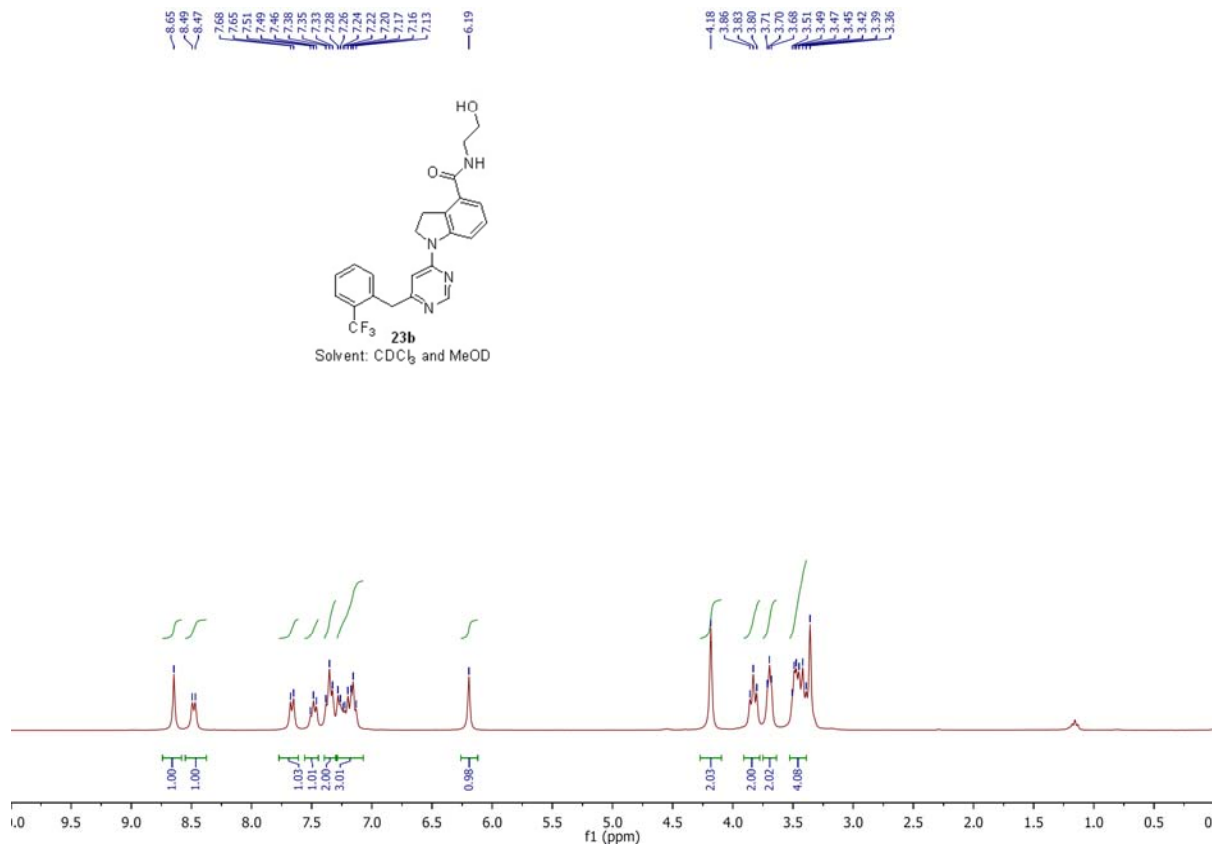
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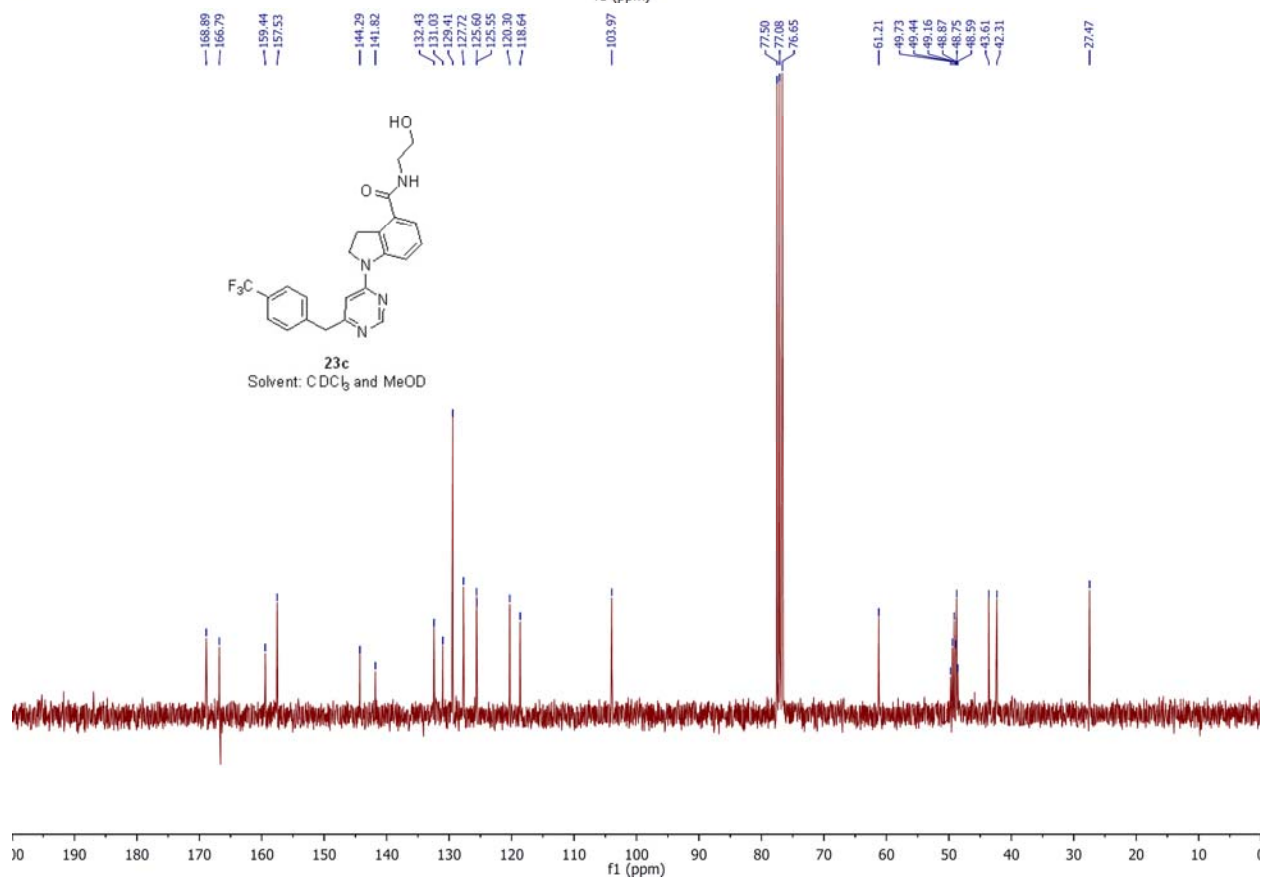
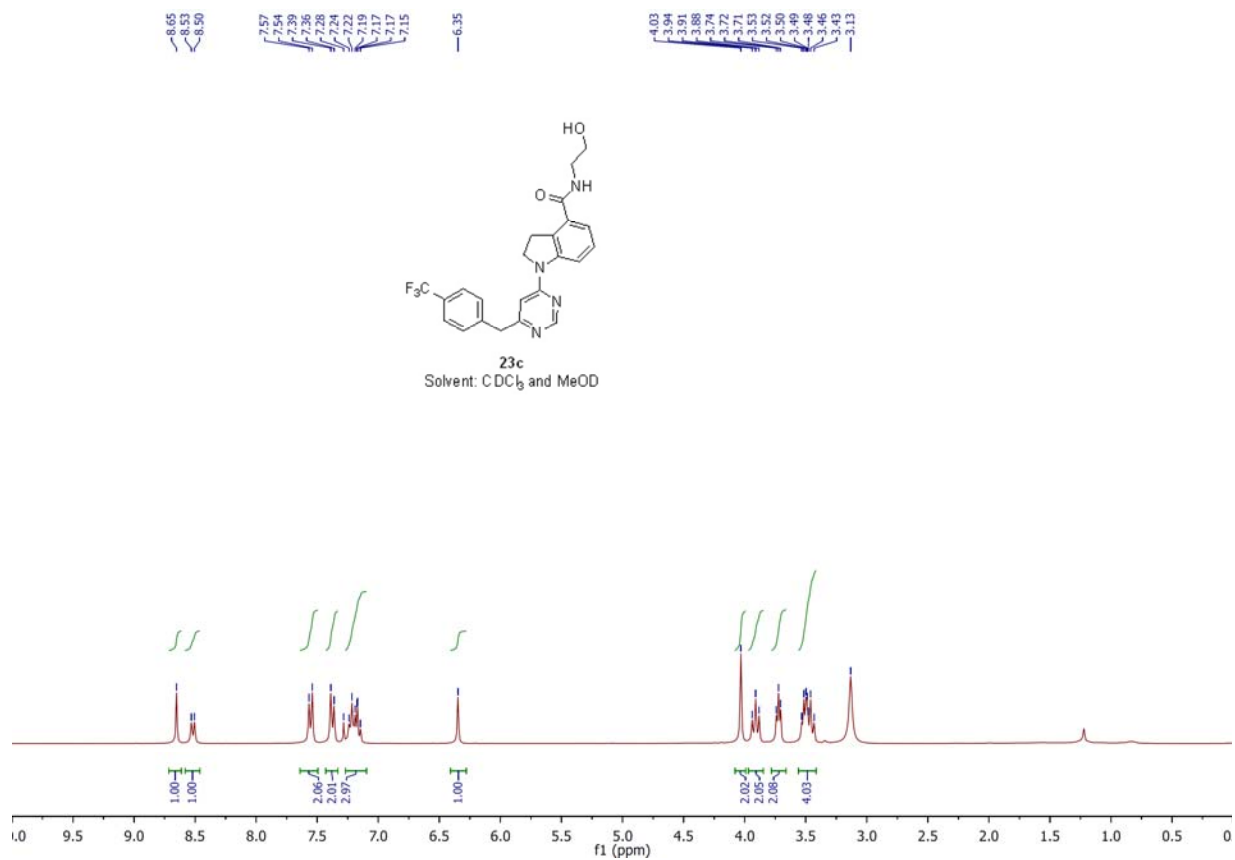
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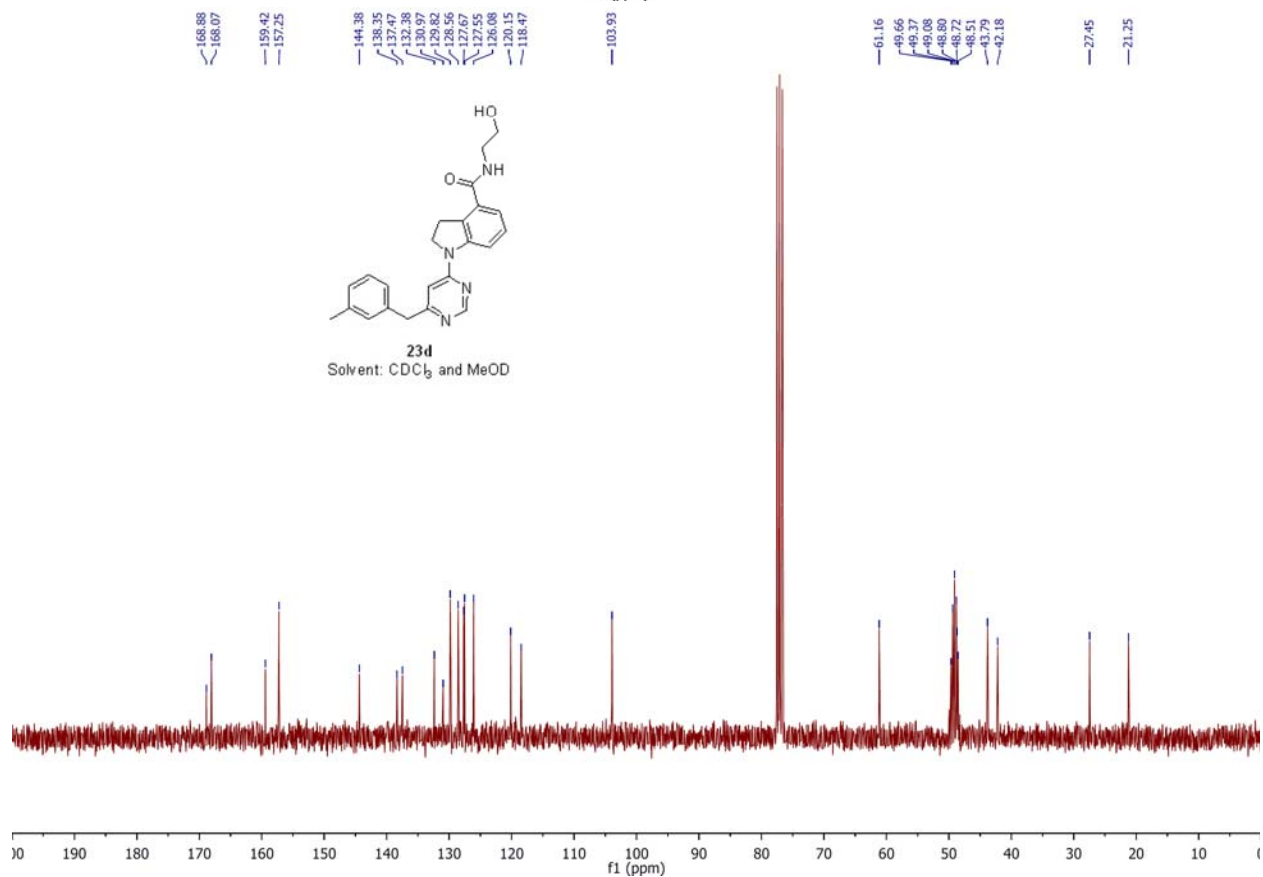
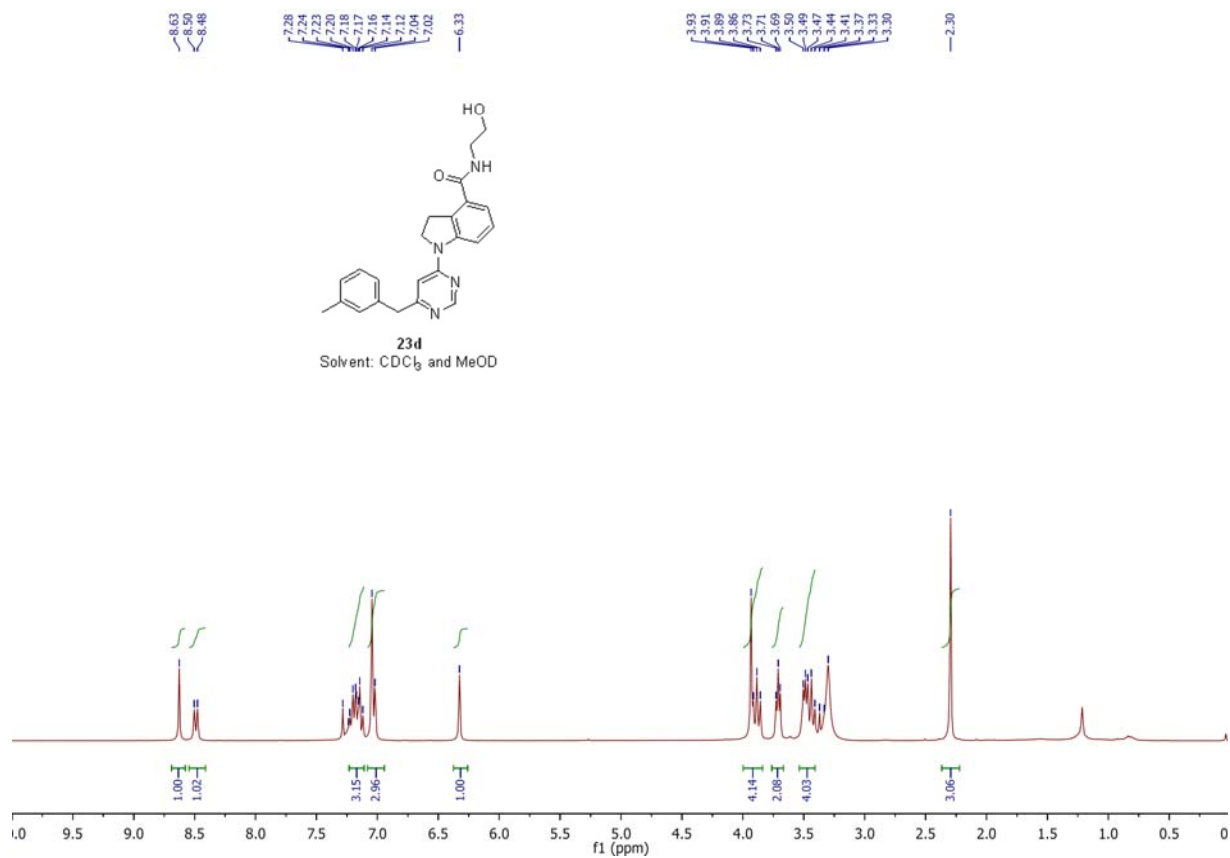


23a
Solvent: CDCl₃ and MeOD



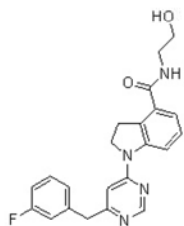




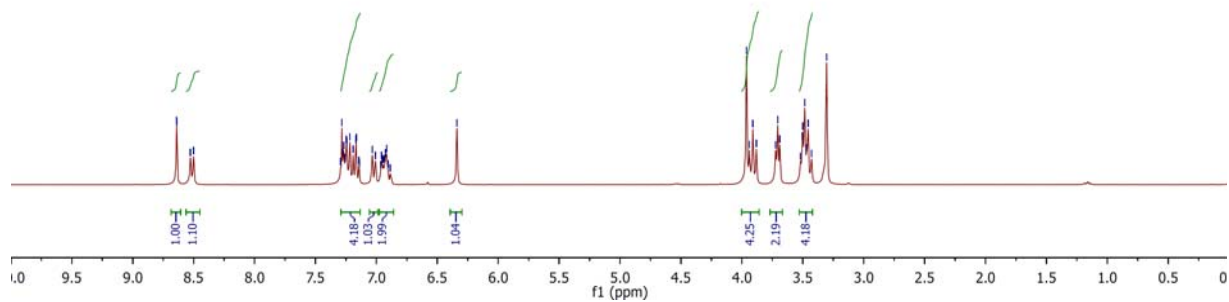


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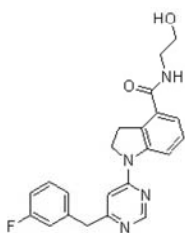
23e
Solvent: CDCl₃ and MeOD



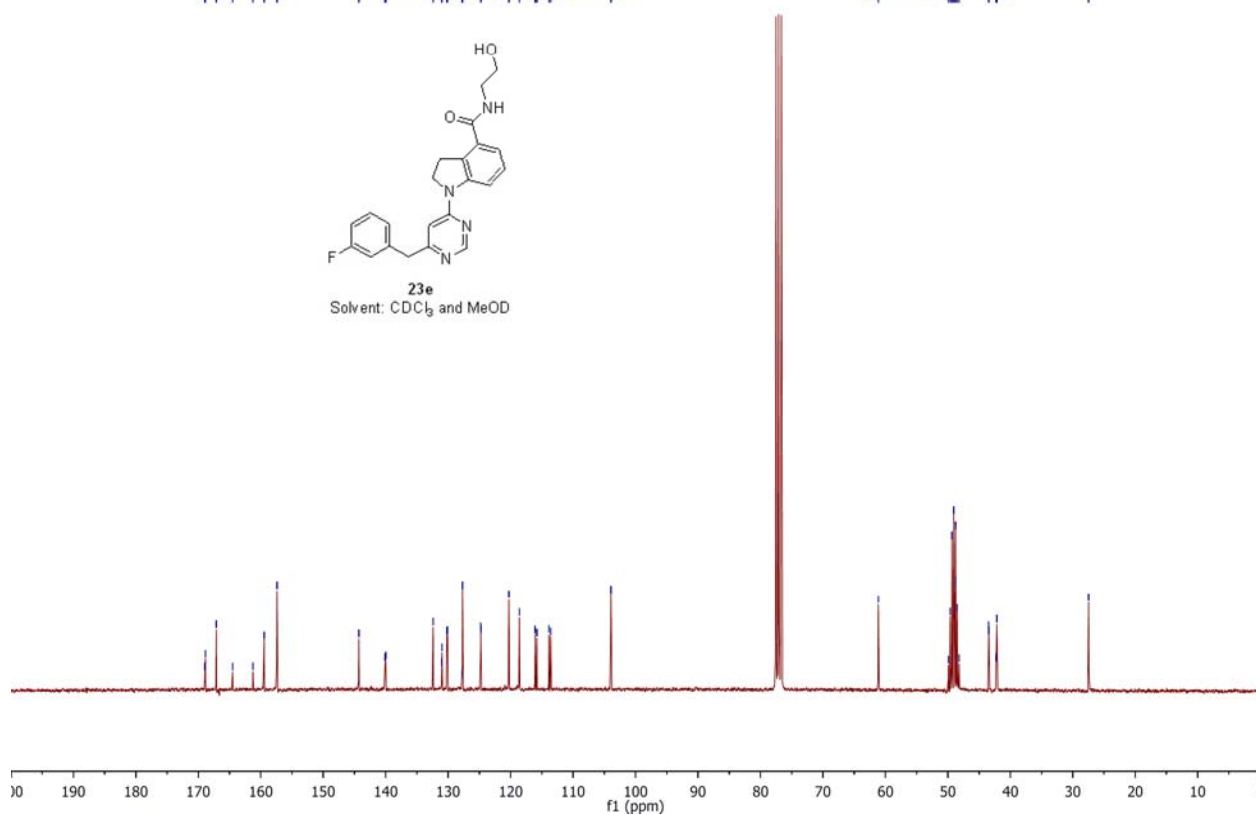
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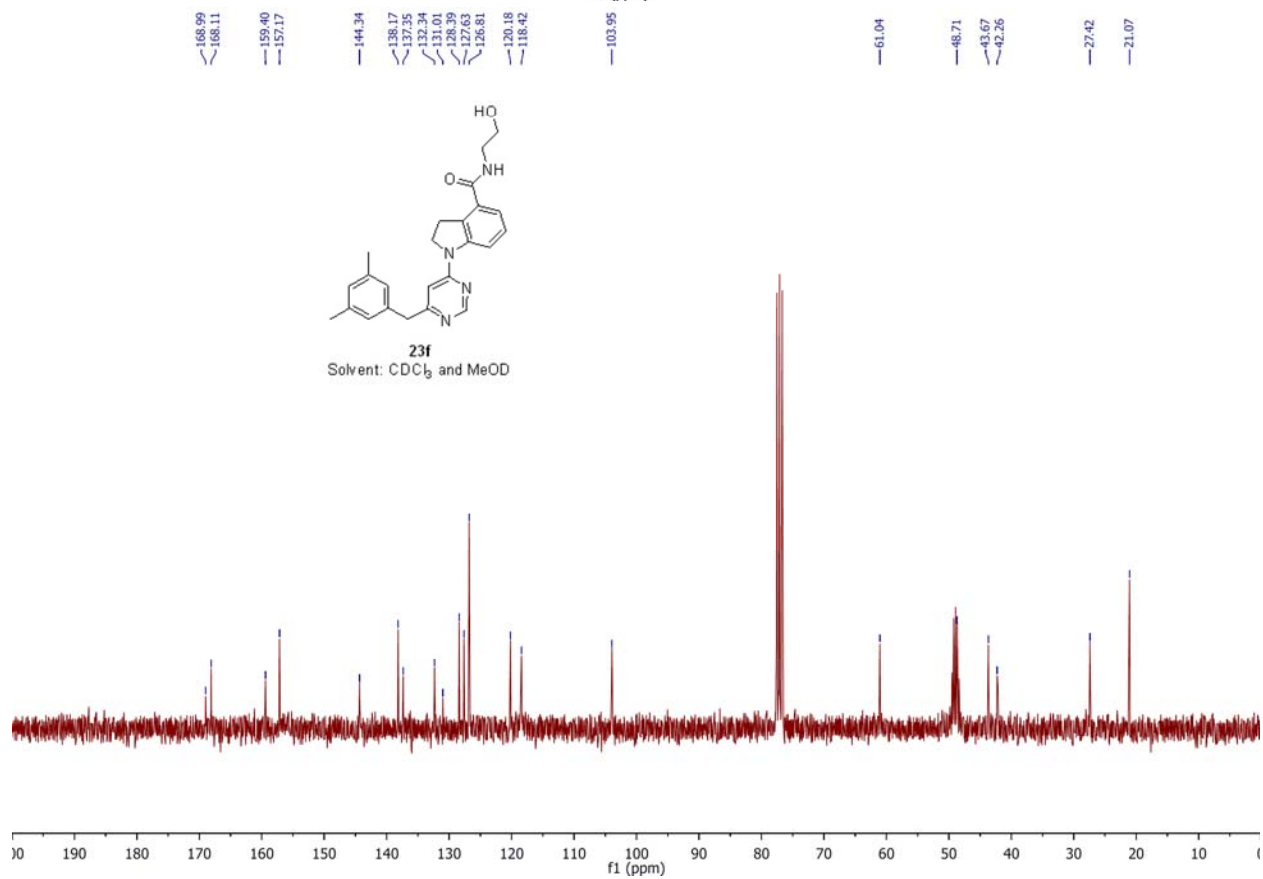
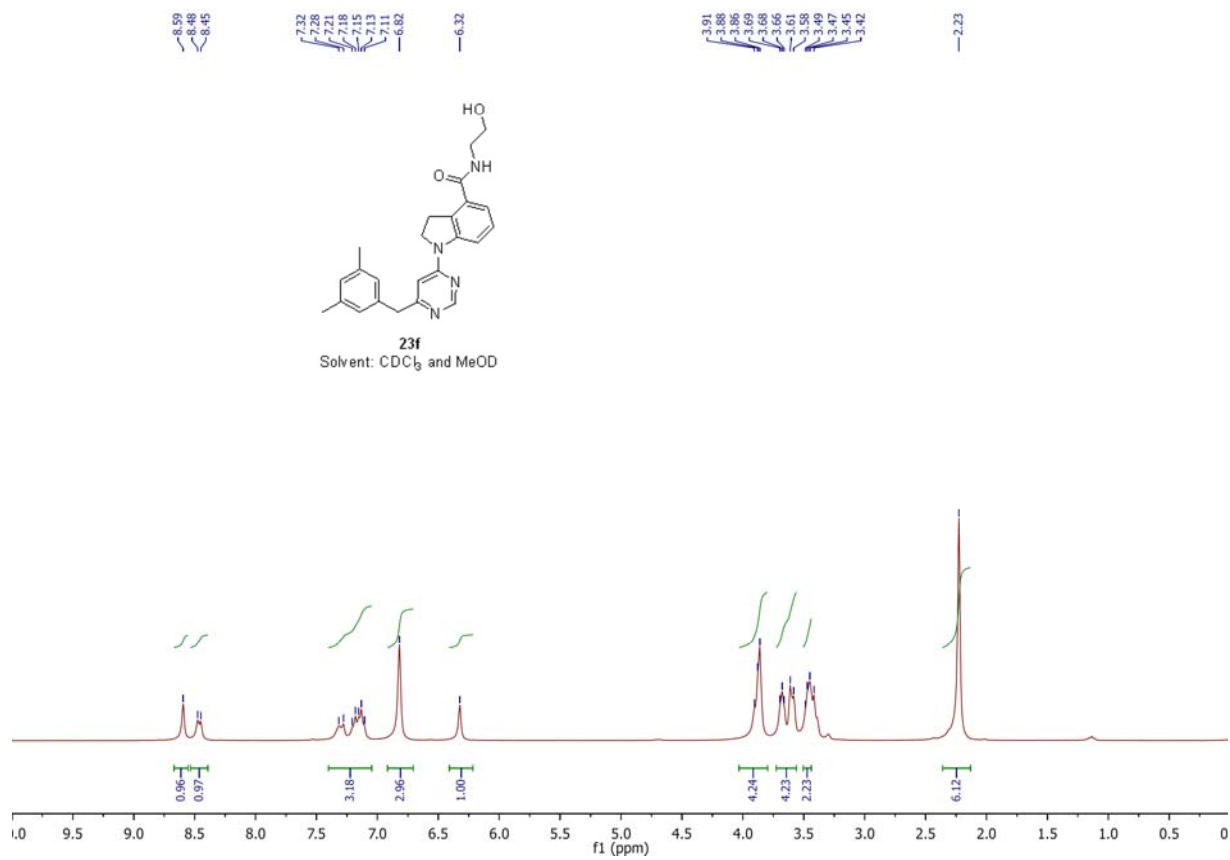
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118.59
116.99
115.89
113.87
113.59
103.94

61.14
49.91
49.63
49.34
49.06
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27.45



23e
Solvent: CDCl₃ and MeOD

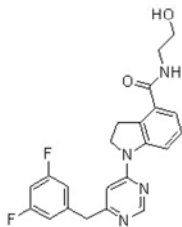




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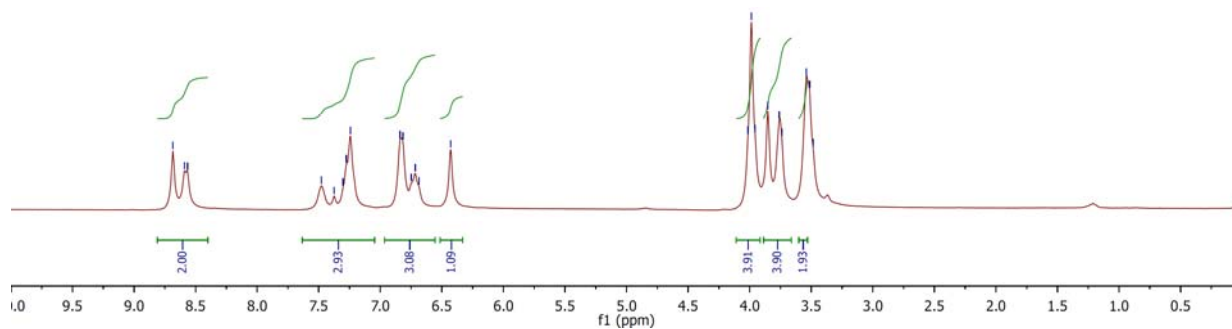
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3.74
3.54
3.51
3.48



23g

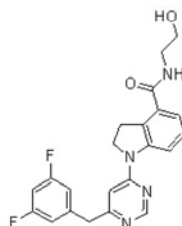
Solvent: CDCl₃ and MeOD



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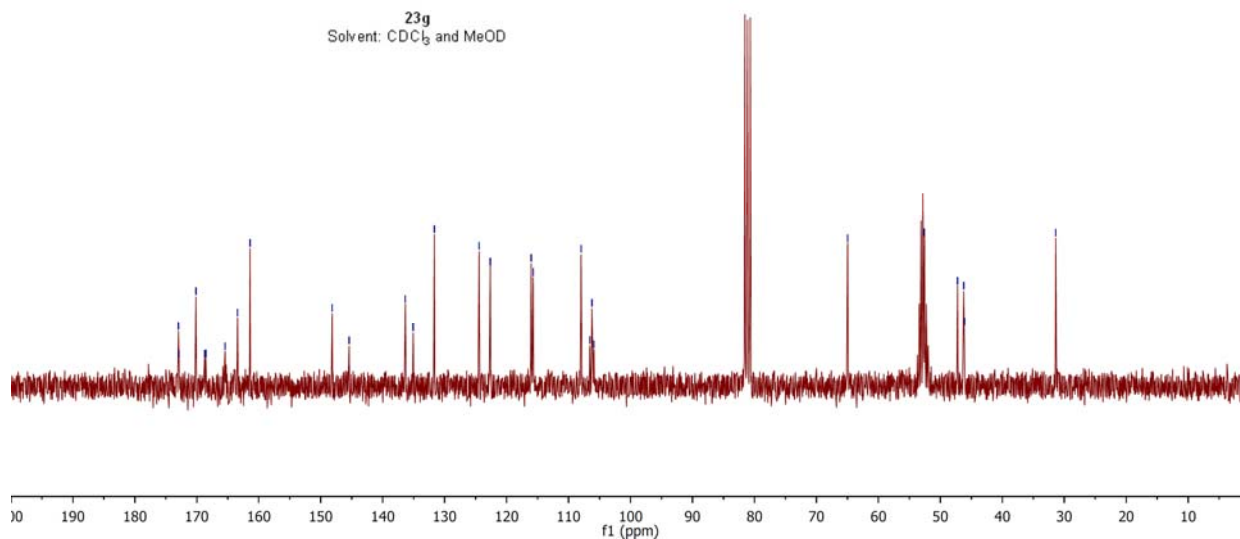
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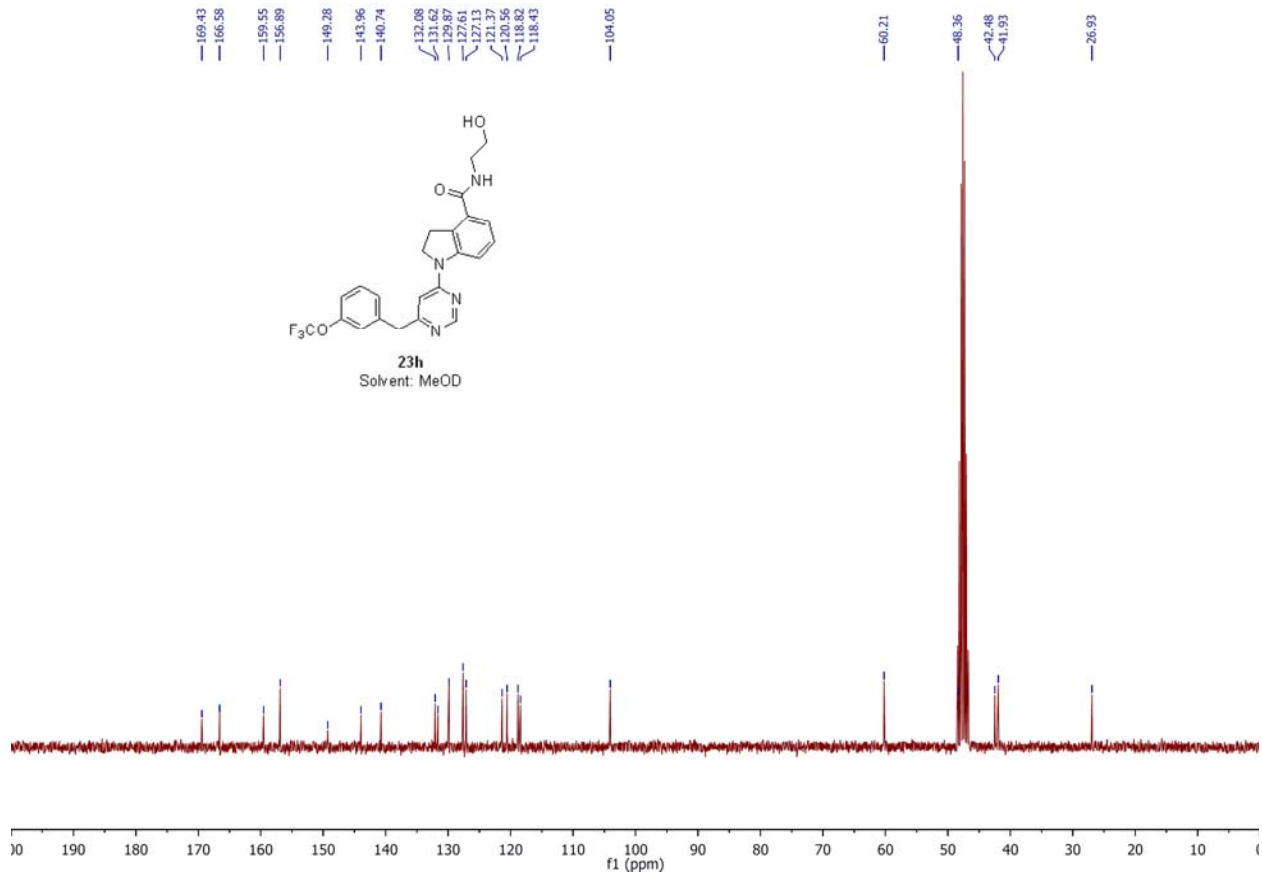
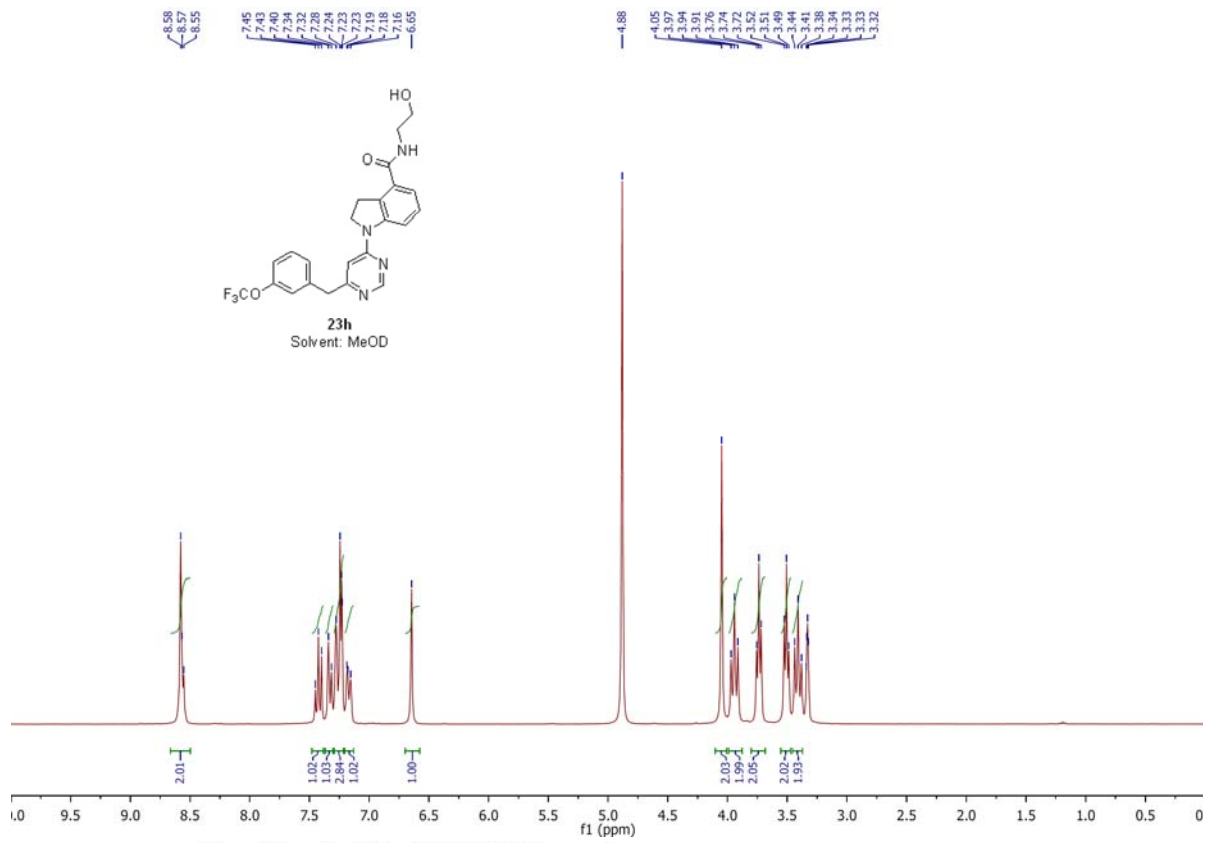
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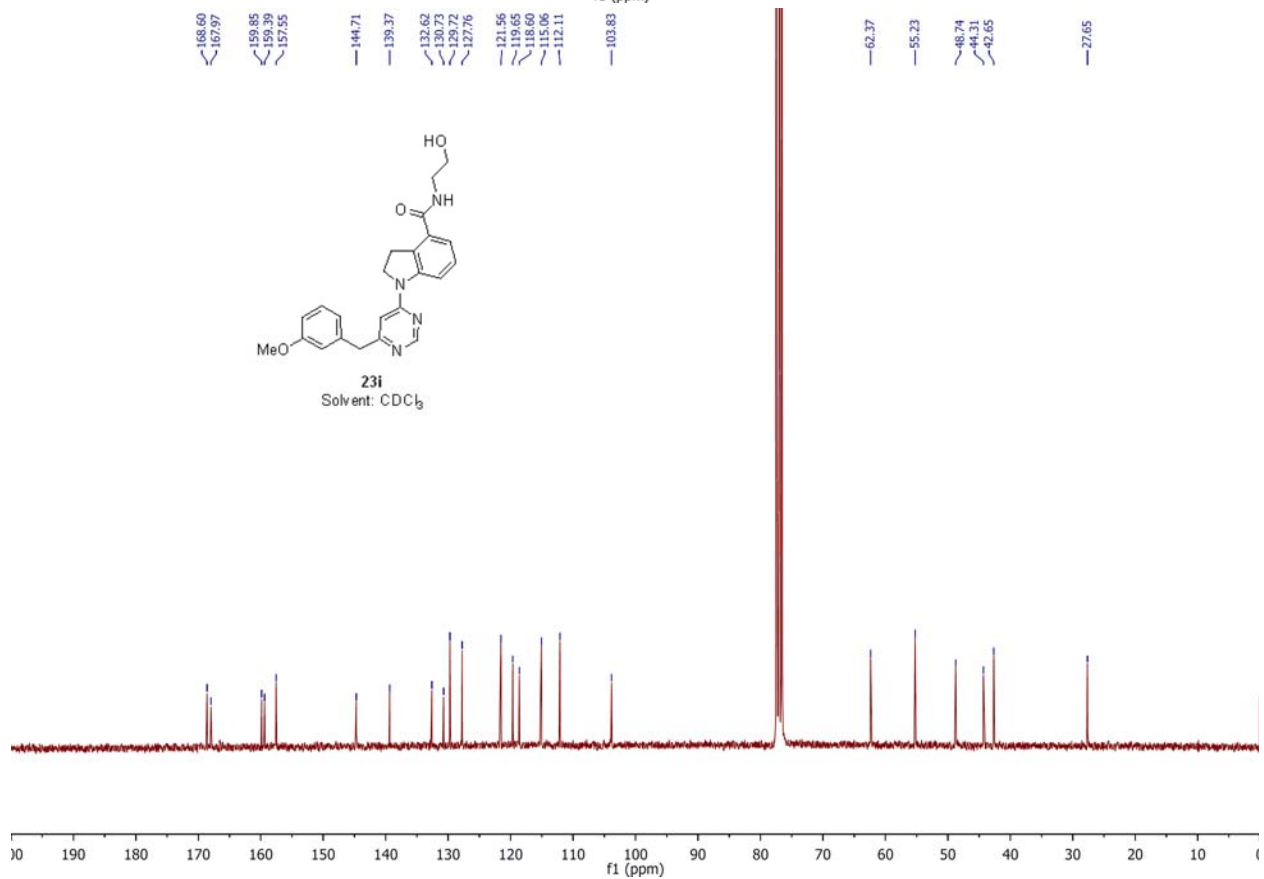
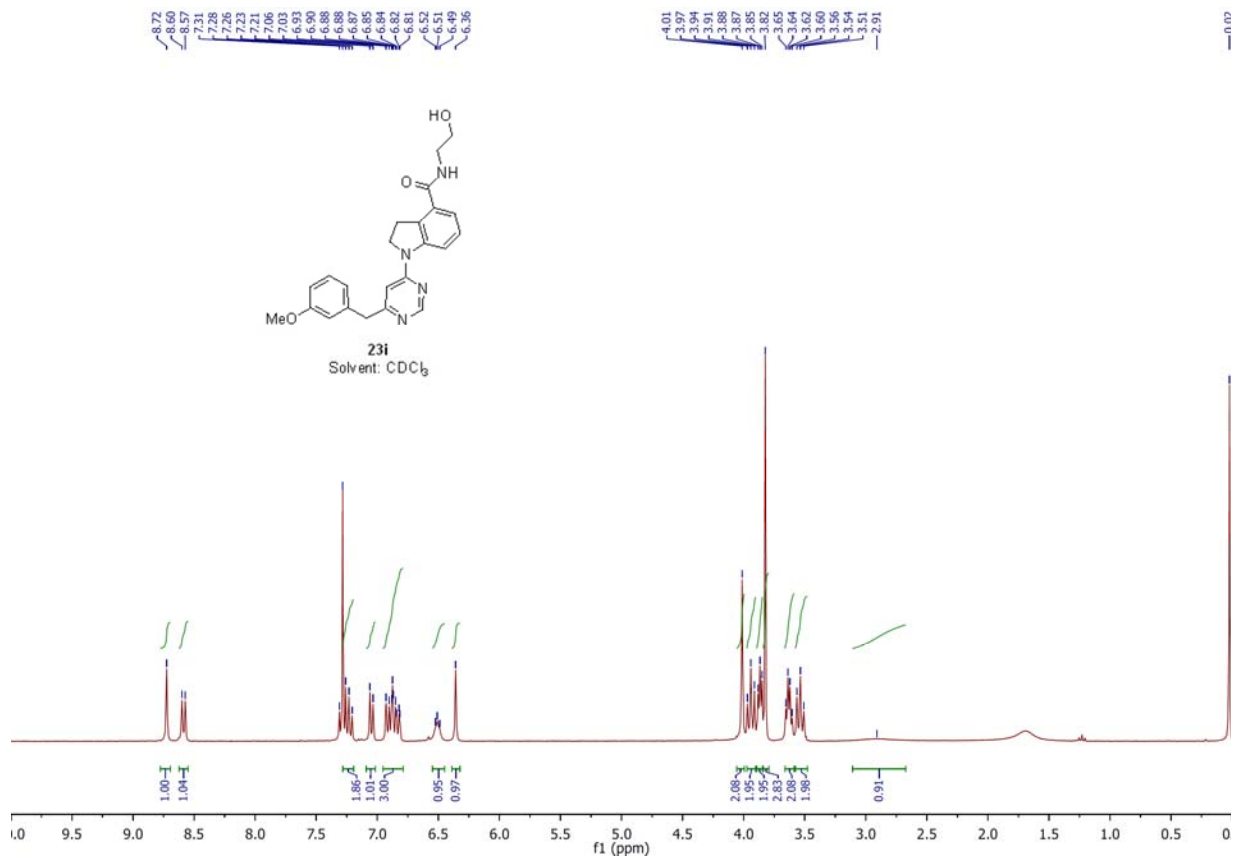


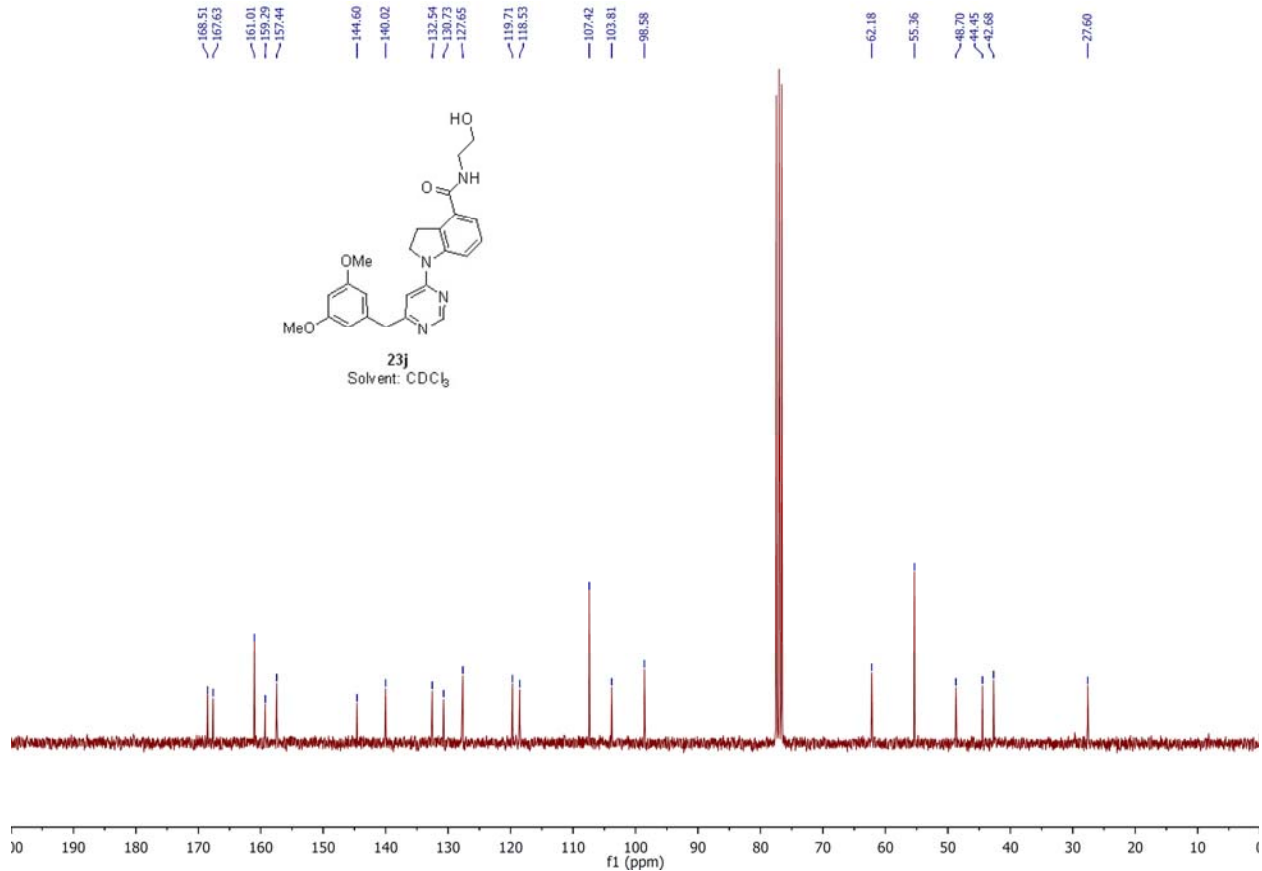
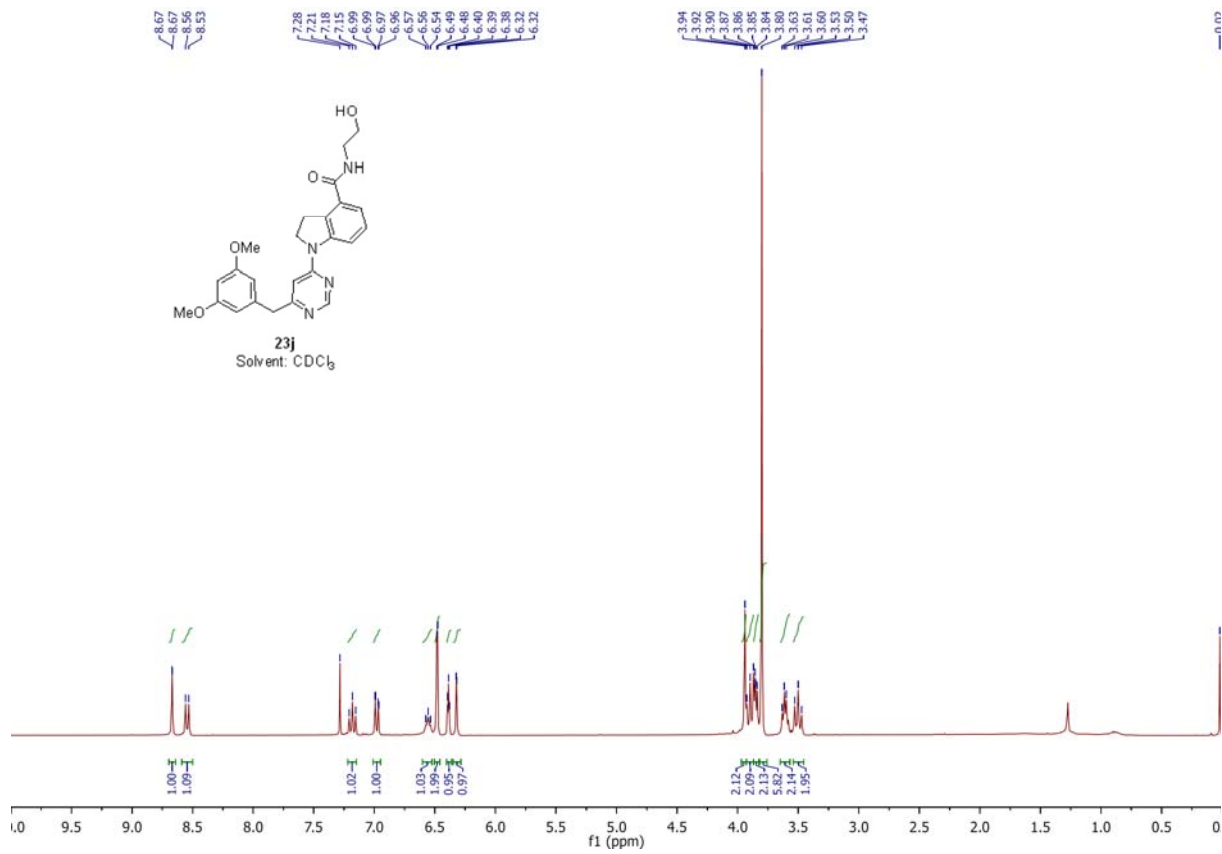
23g

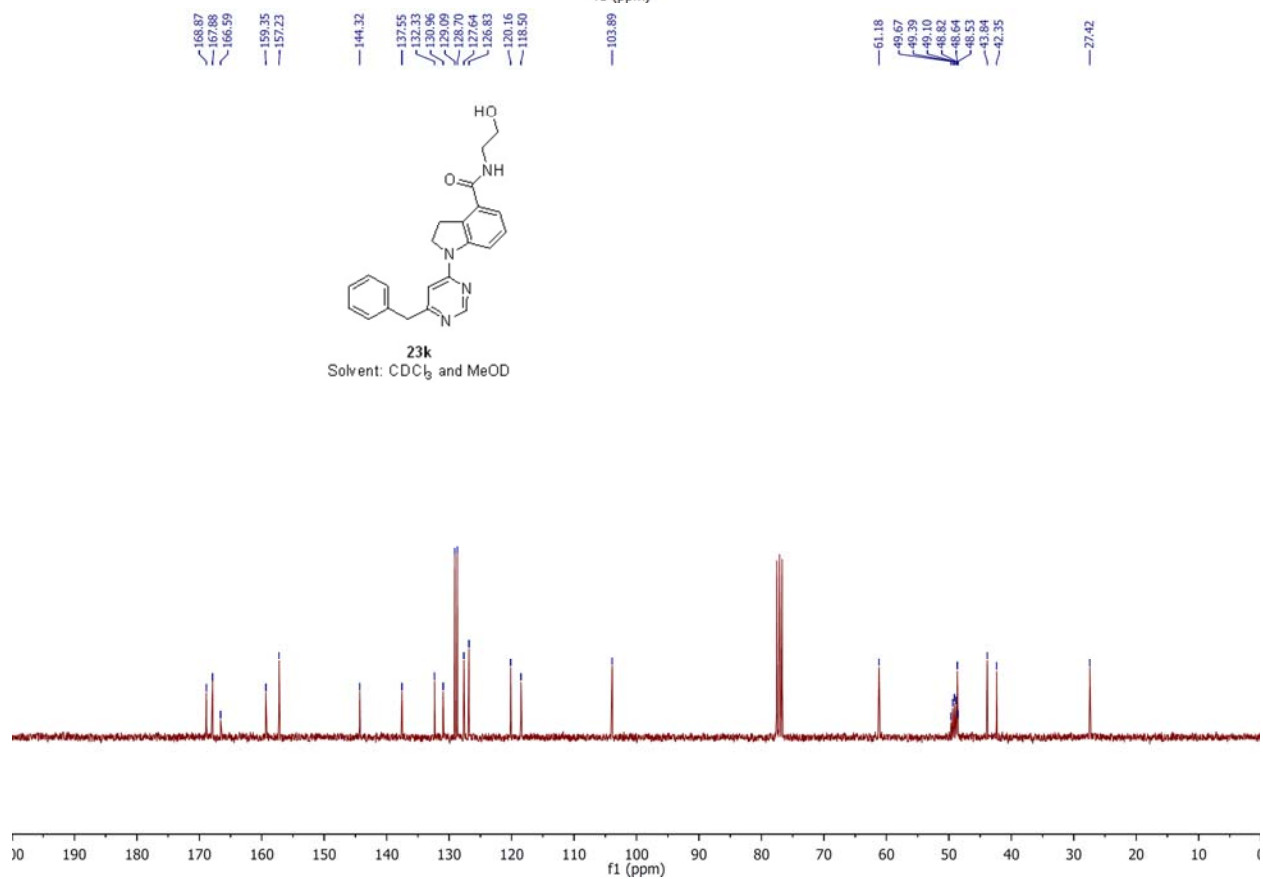
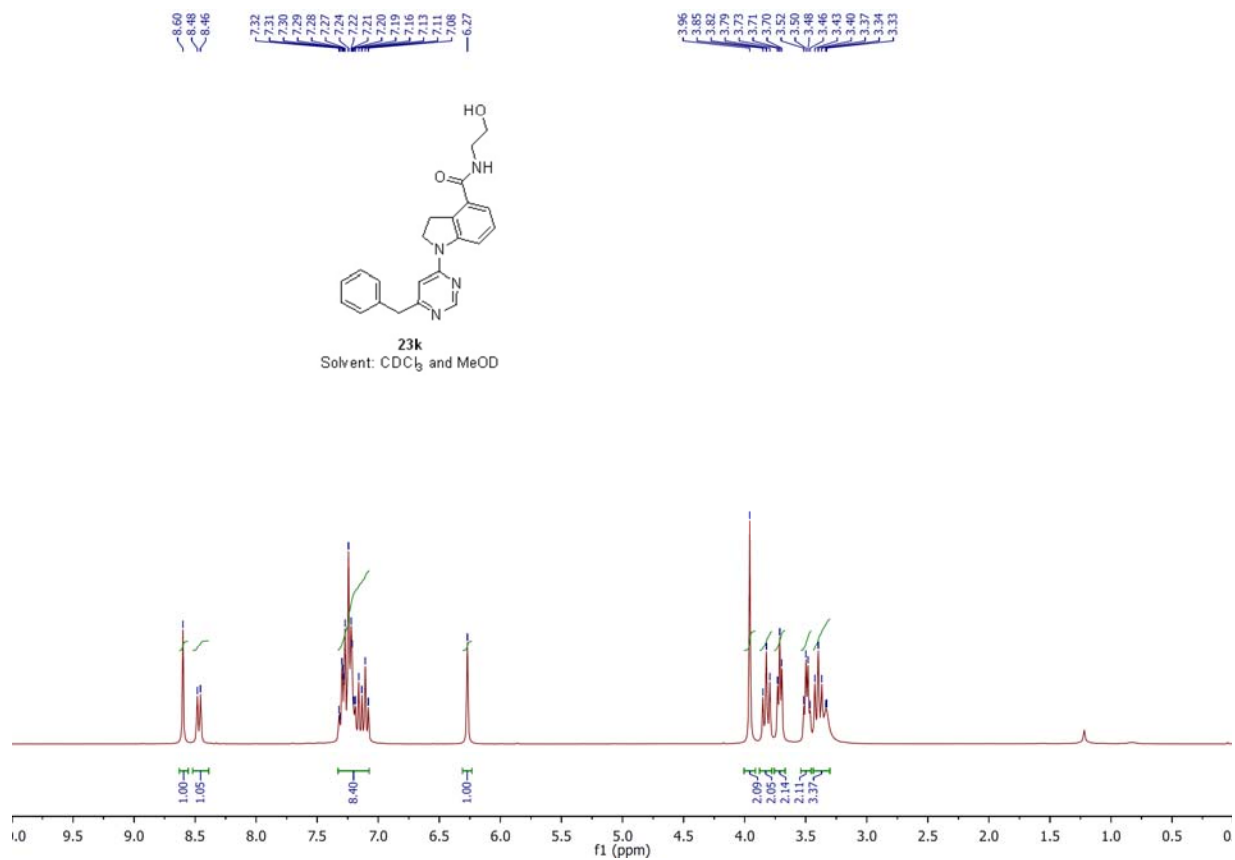
Solvent: CDCl₃ and MeOD

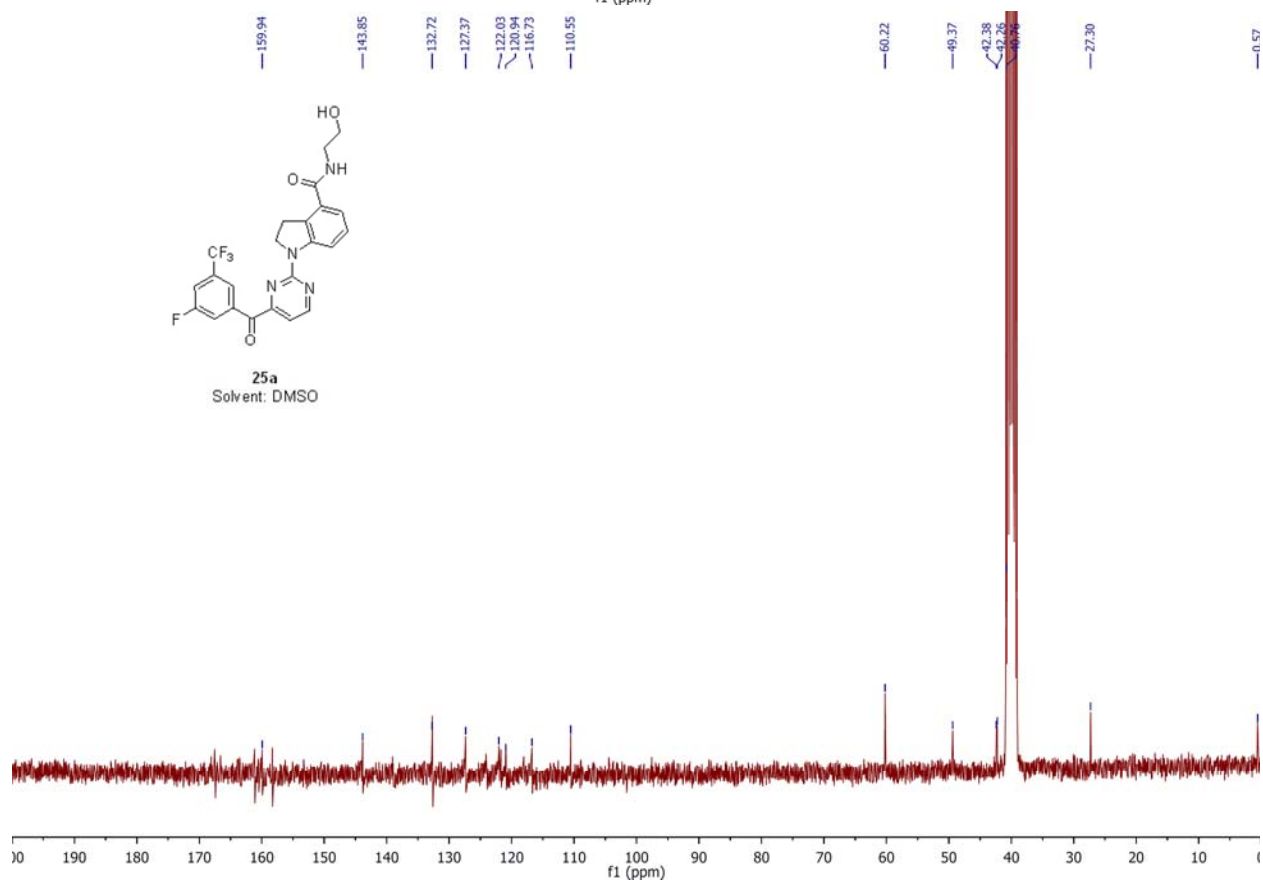
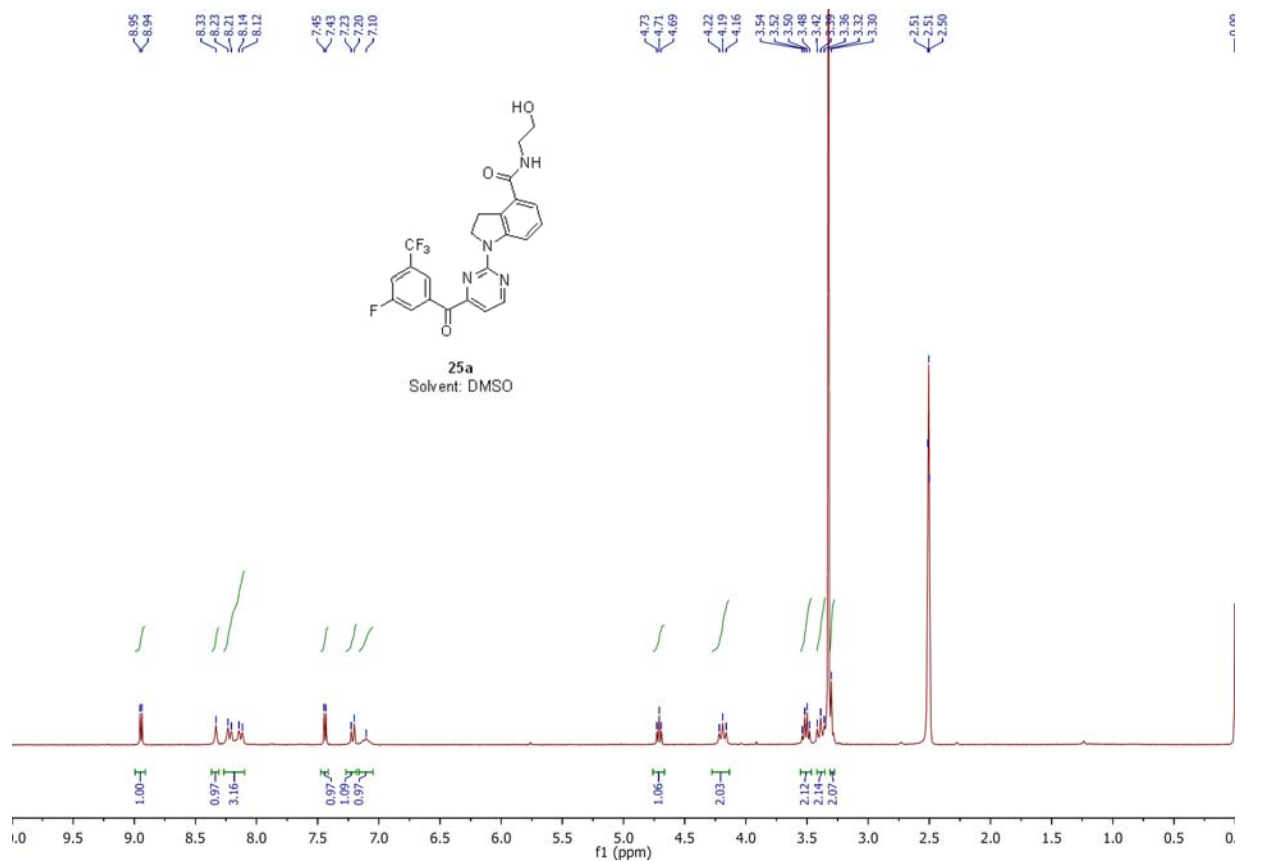


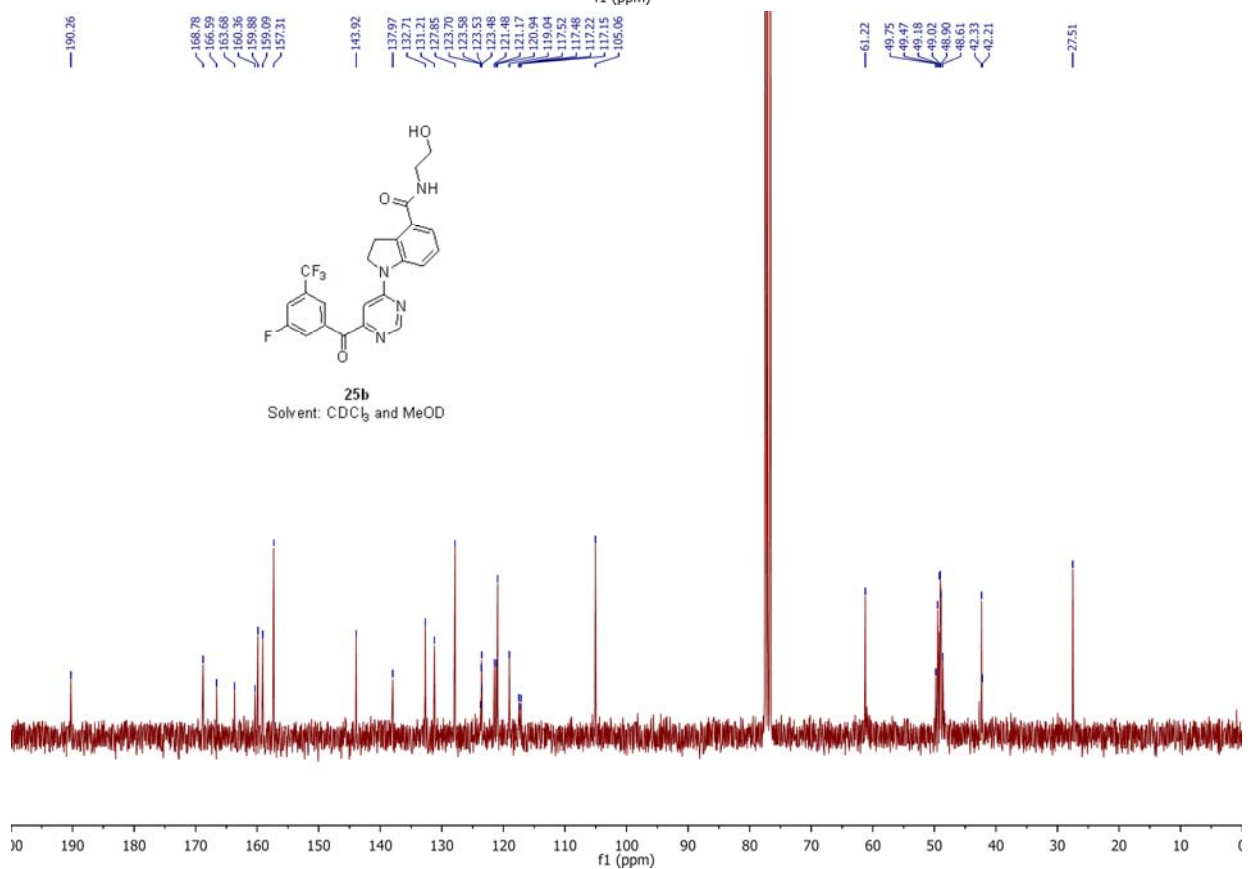
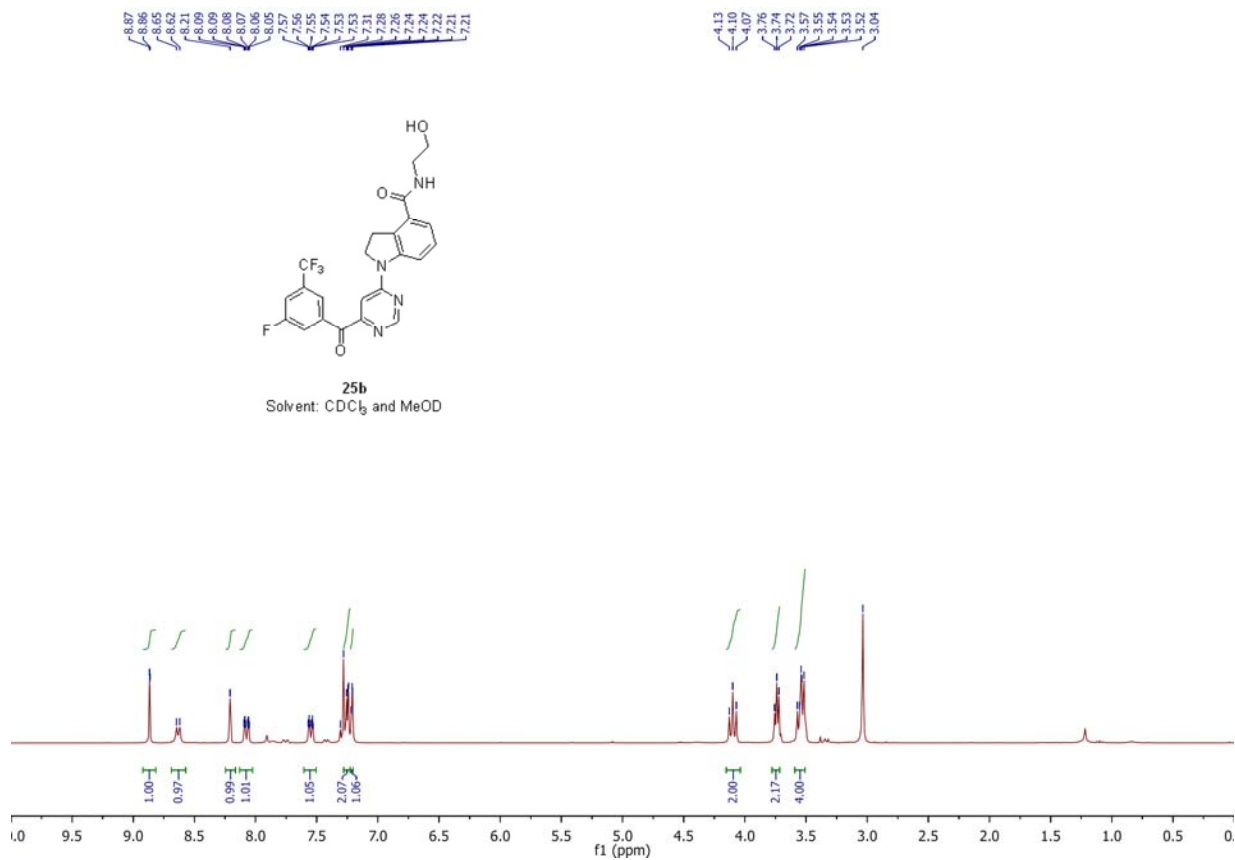


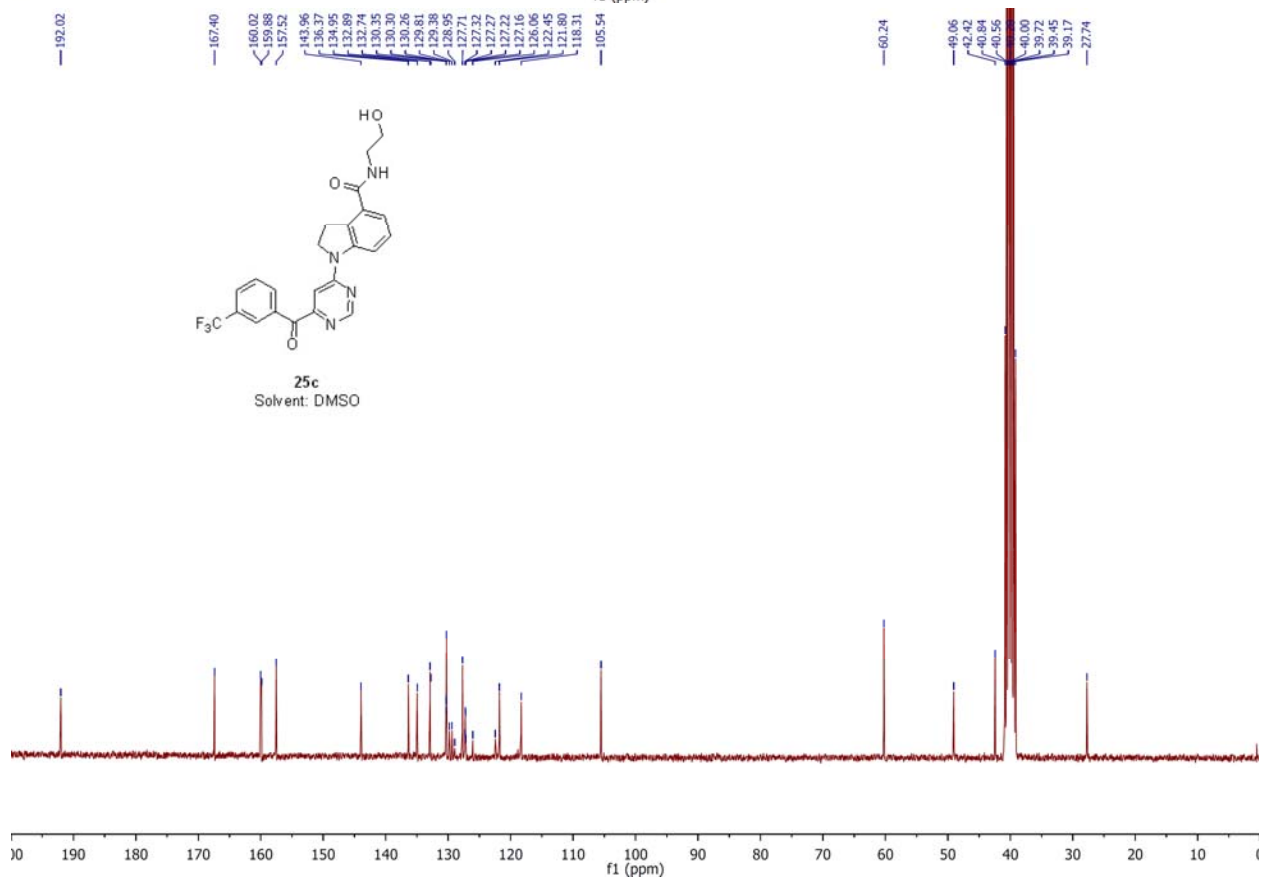
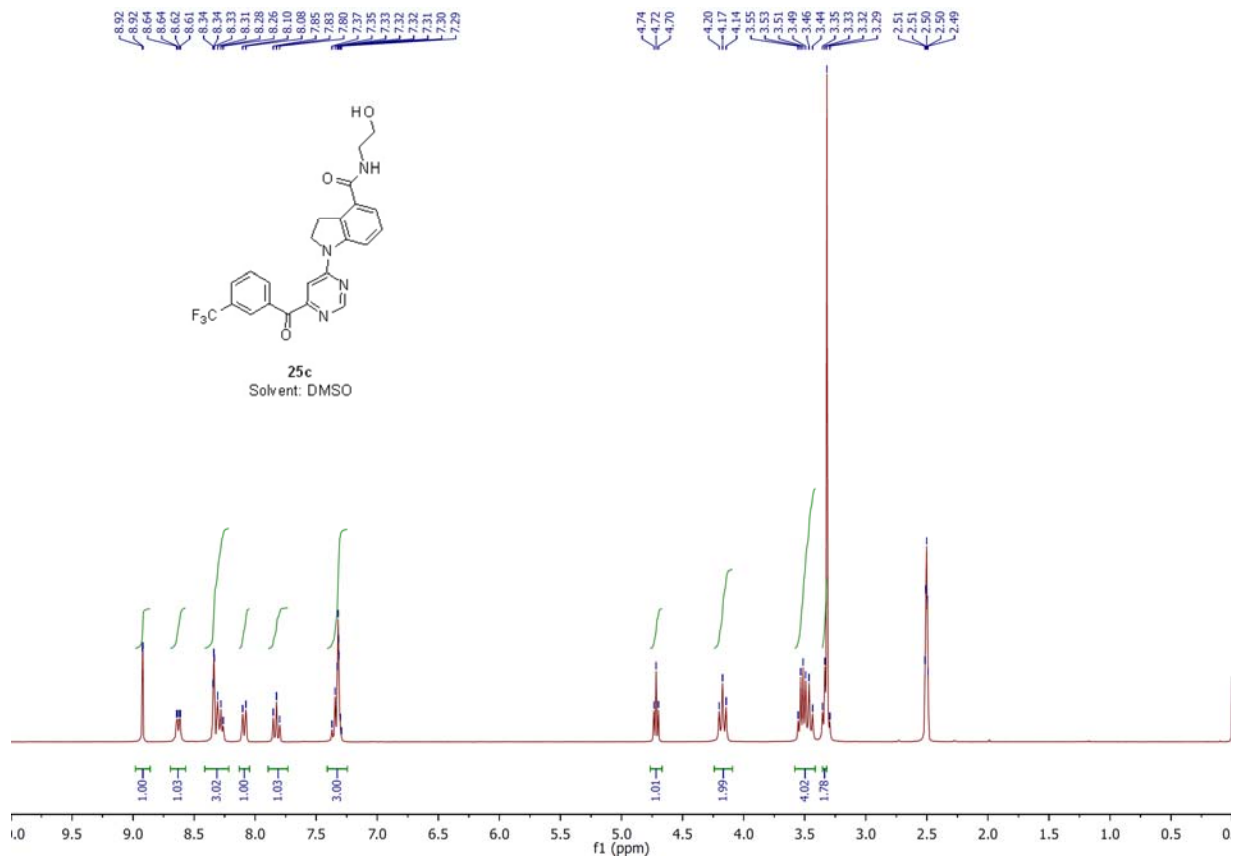


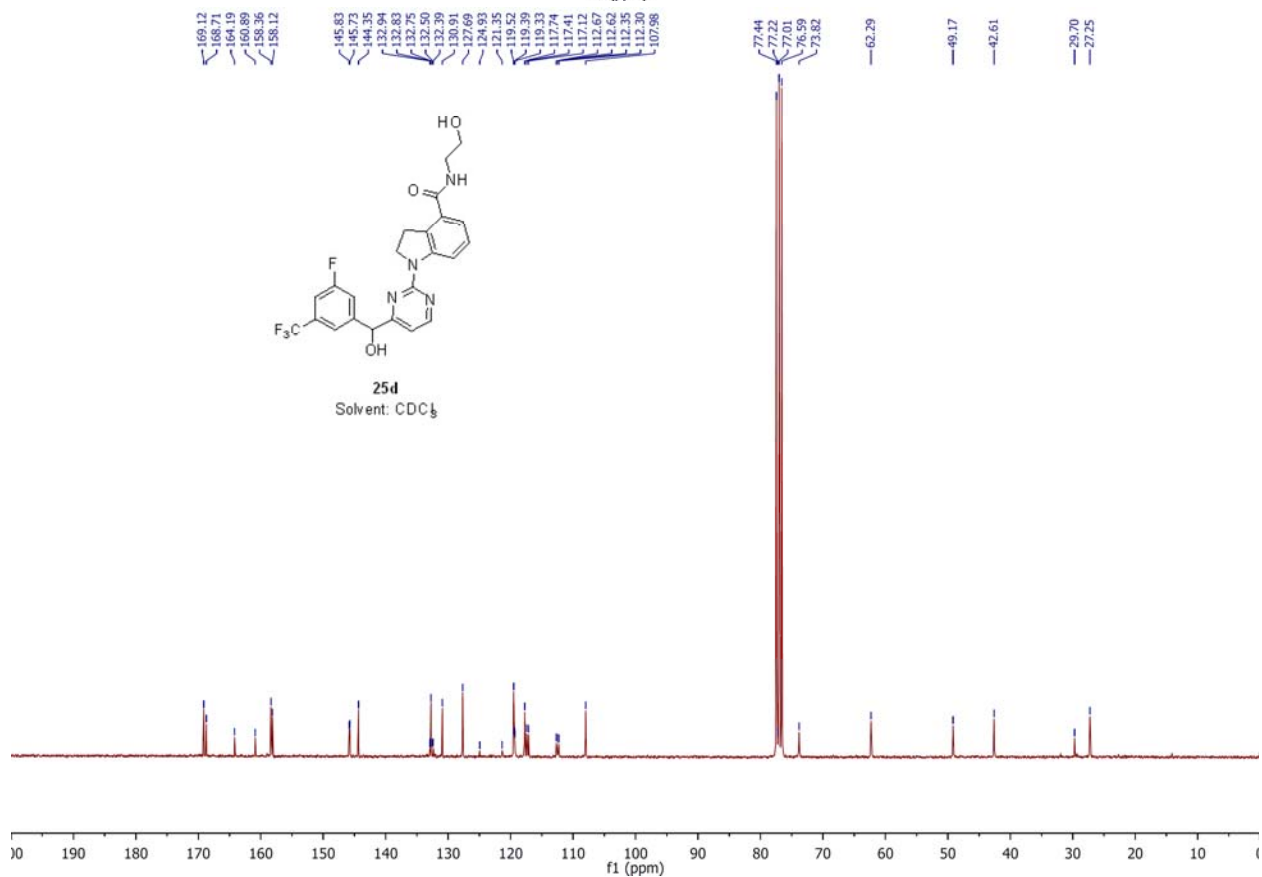
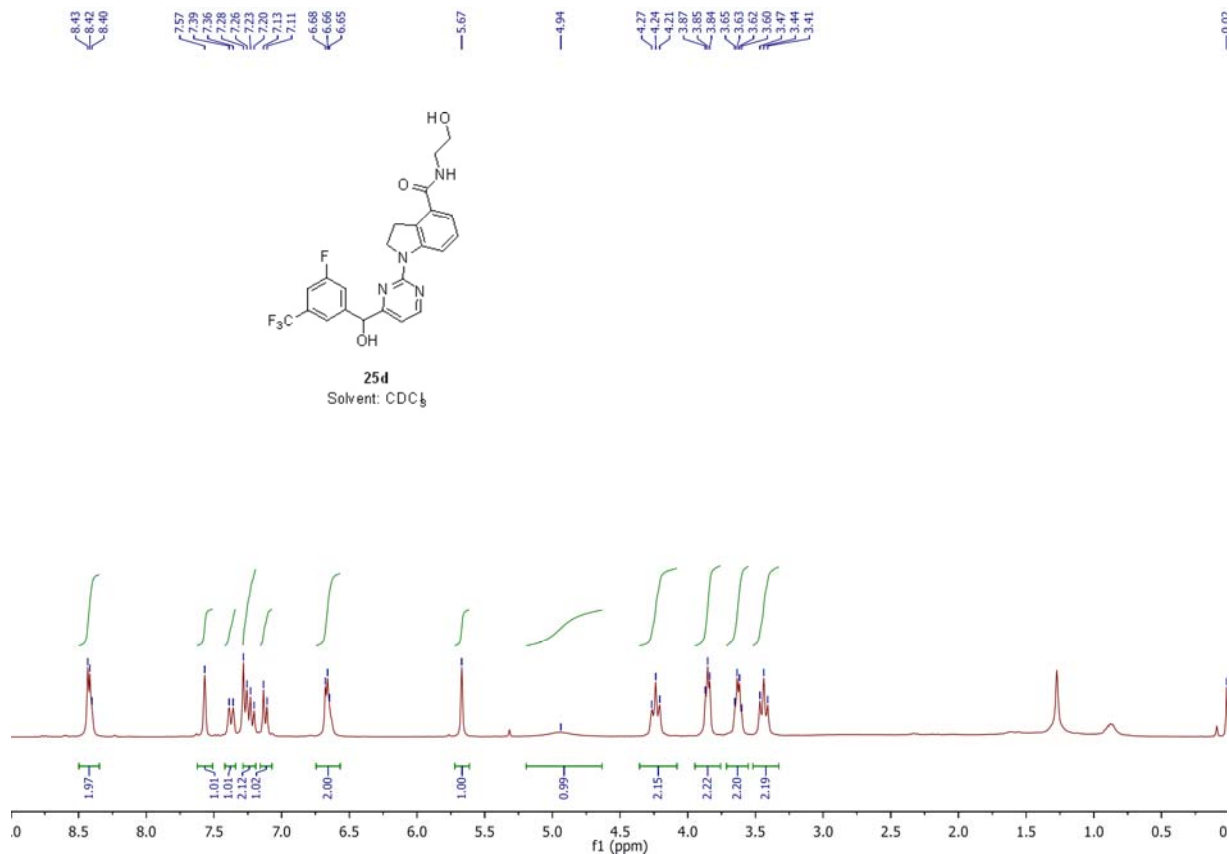


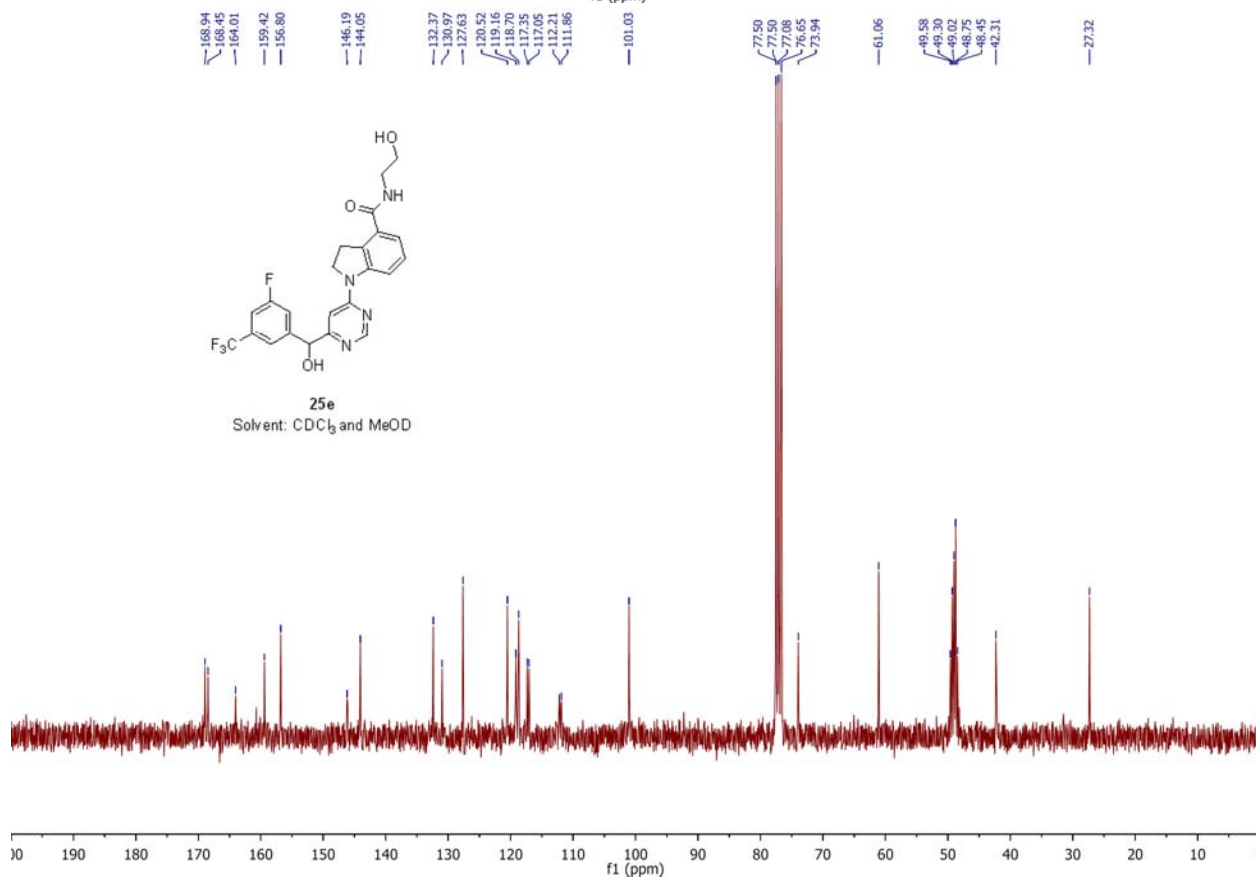
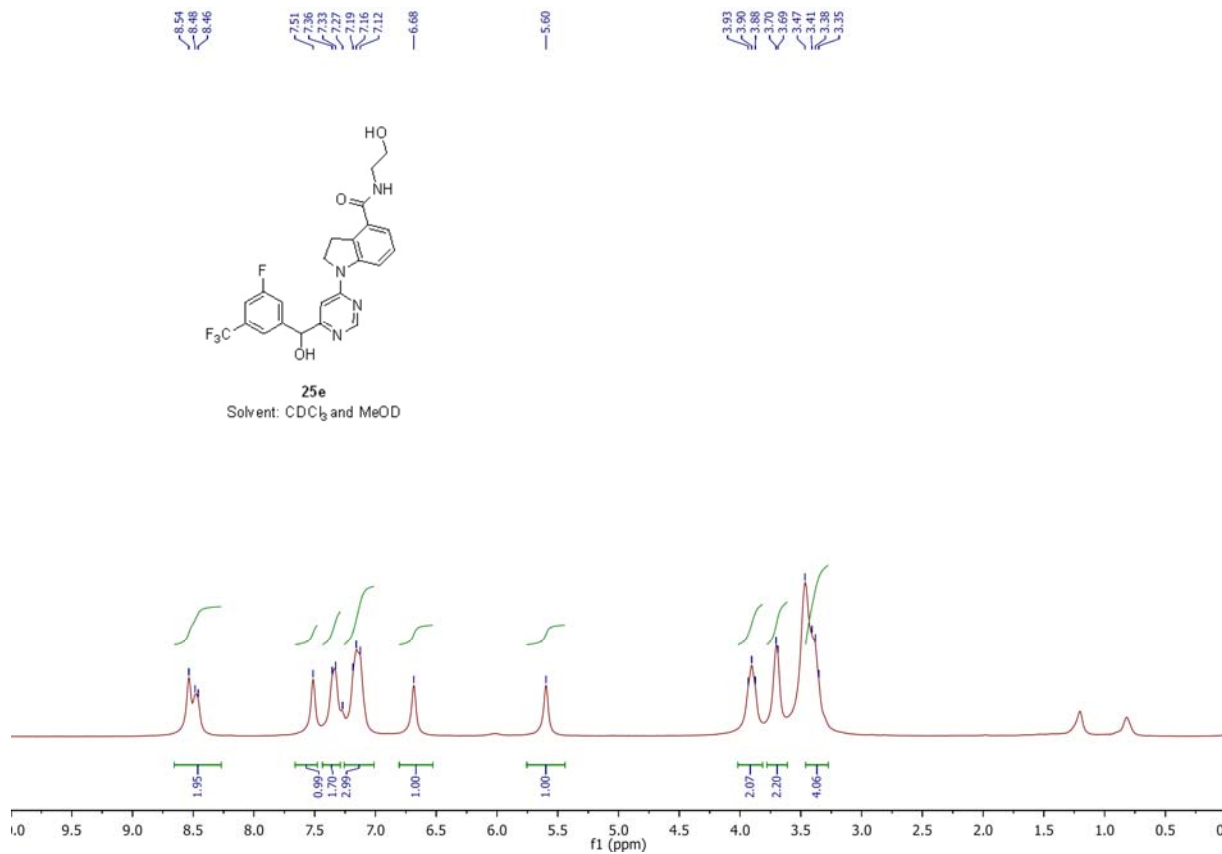


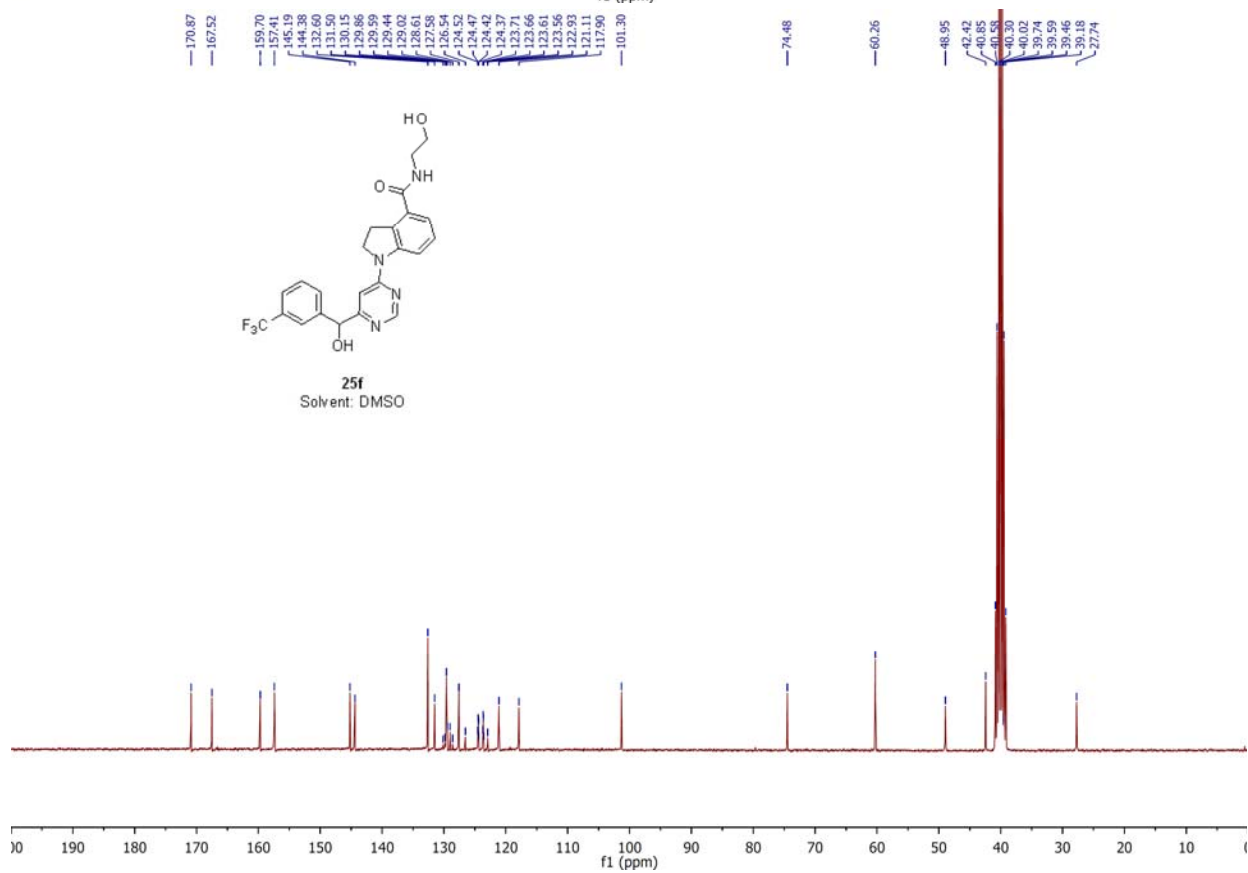
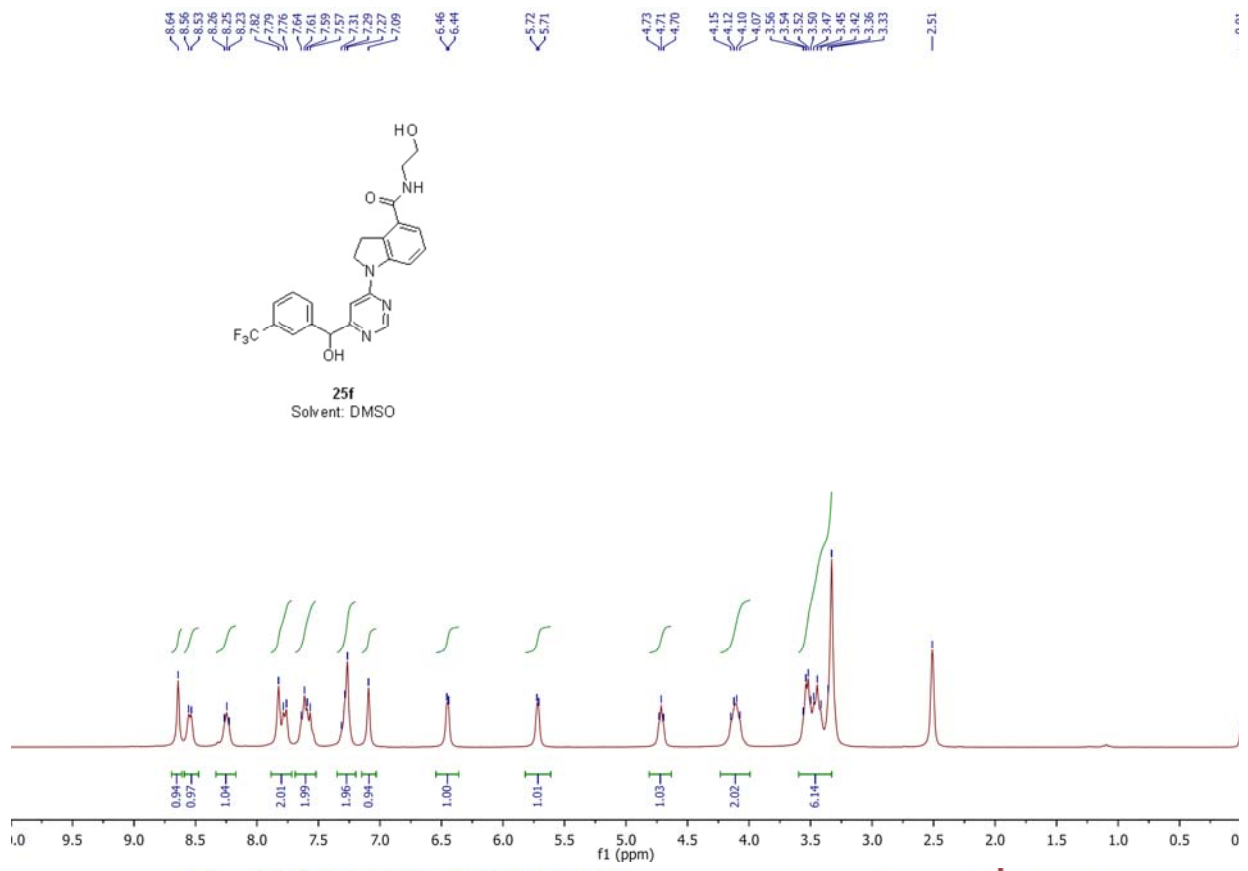




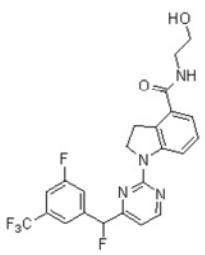




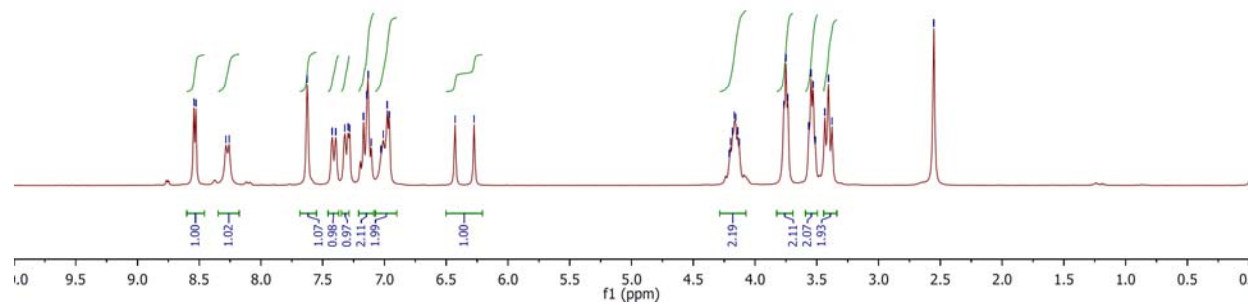




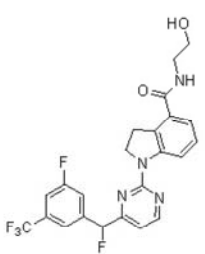
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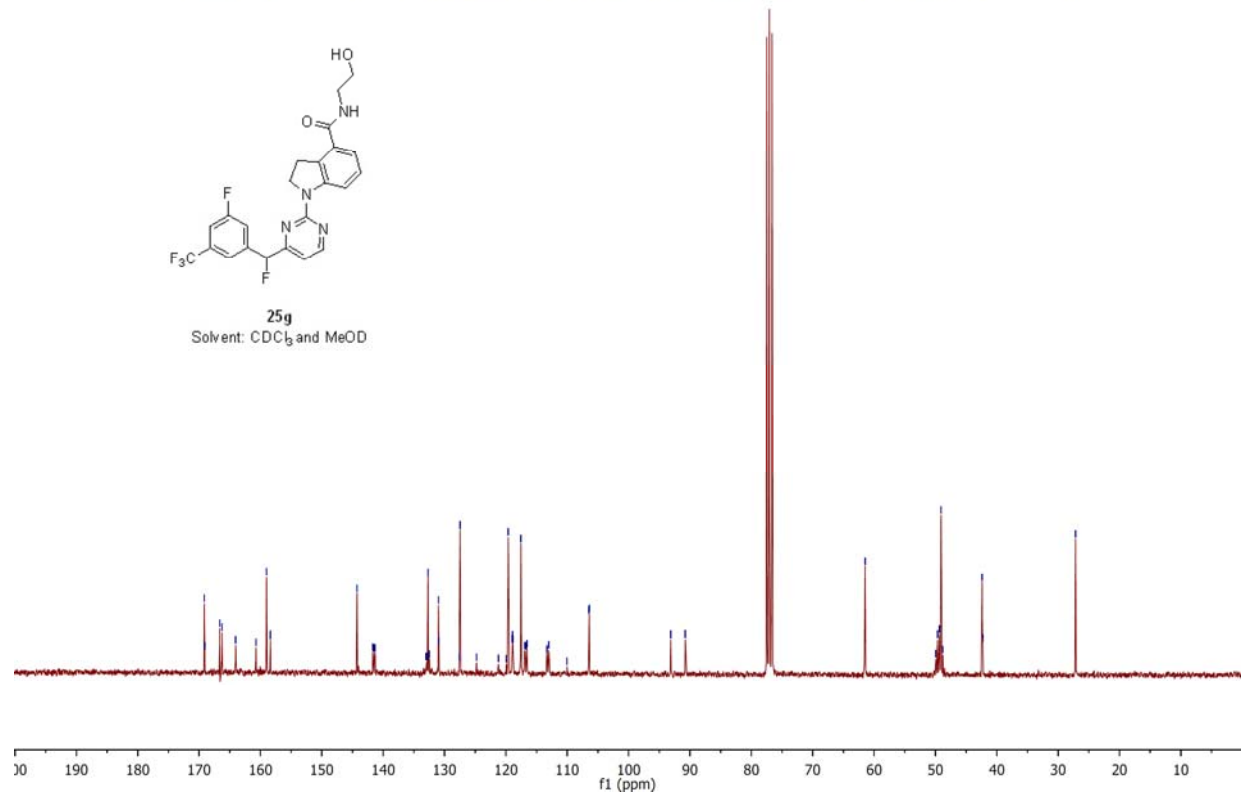
25g
Solvent: CDCl₃ and MeOD

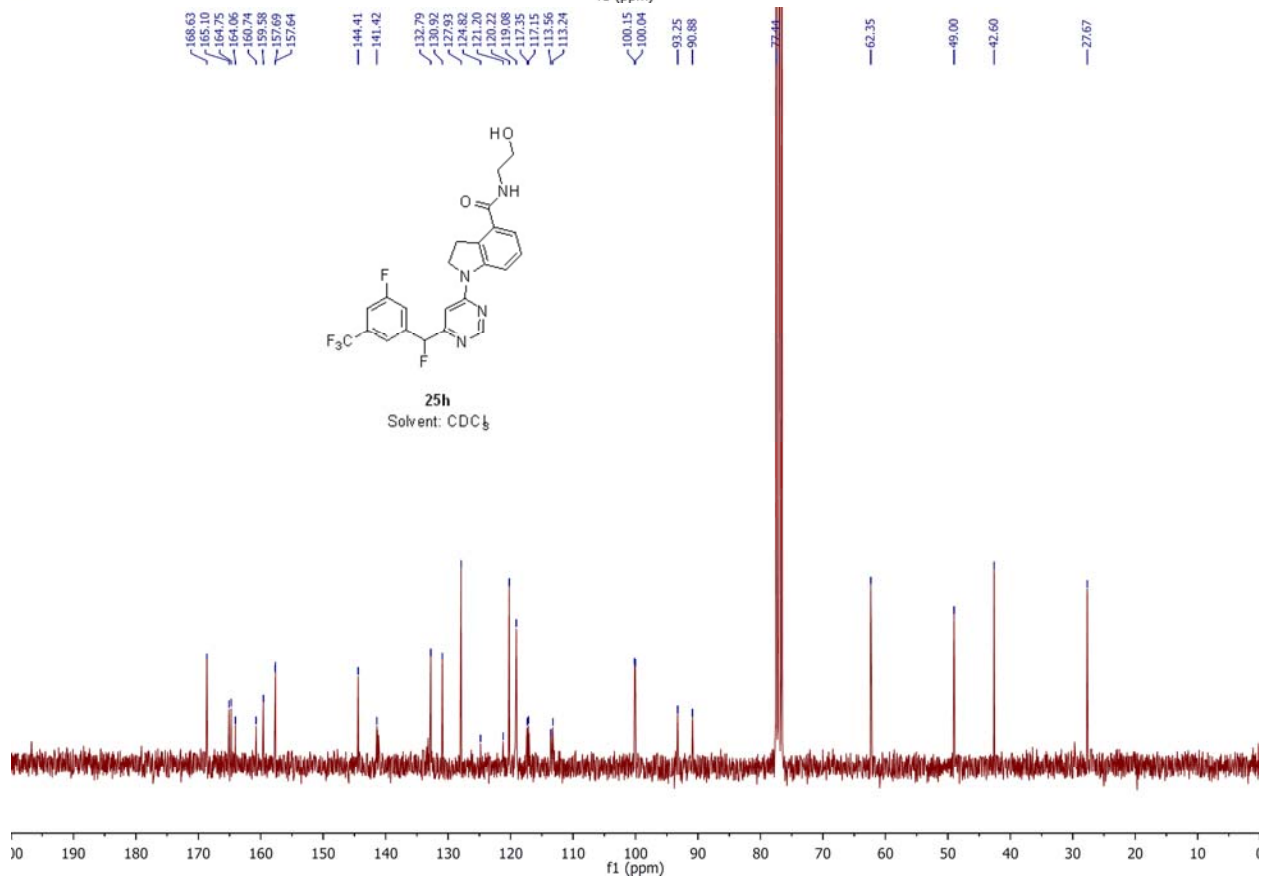
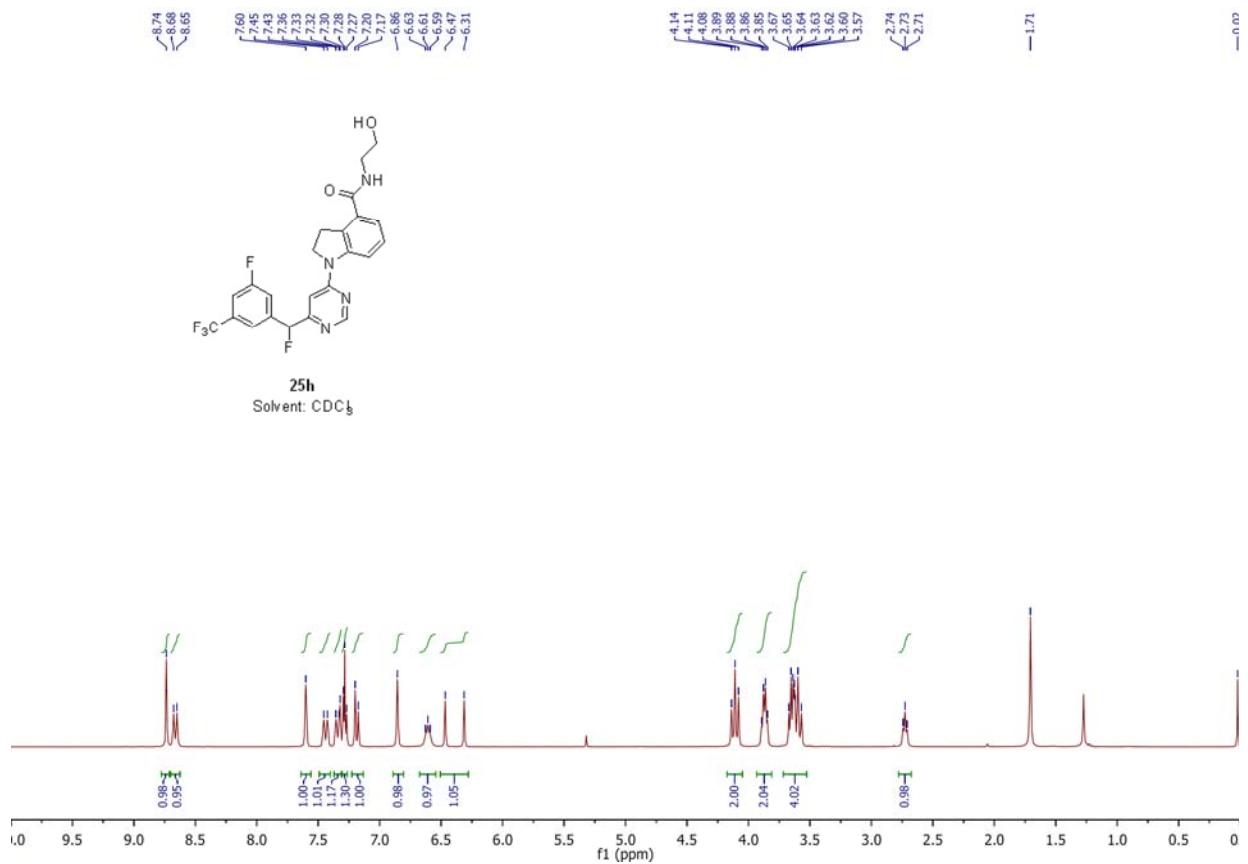


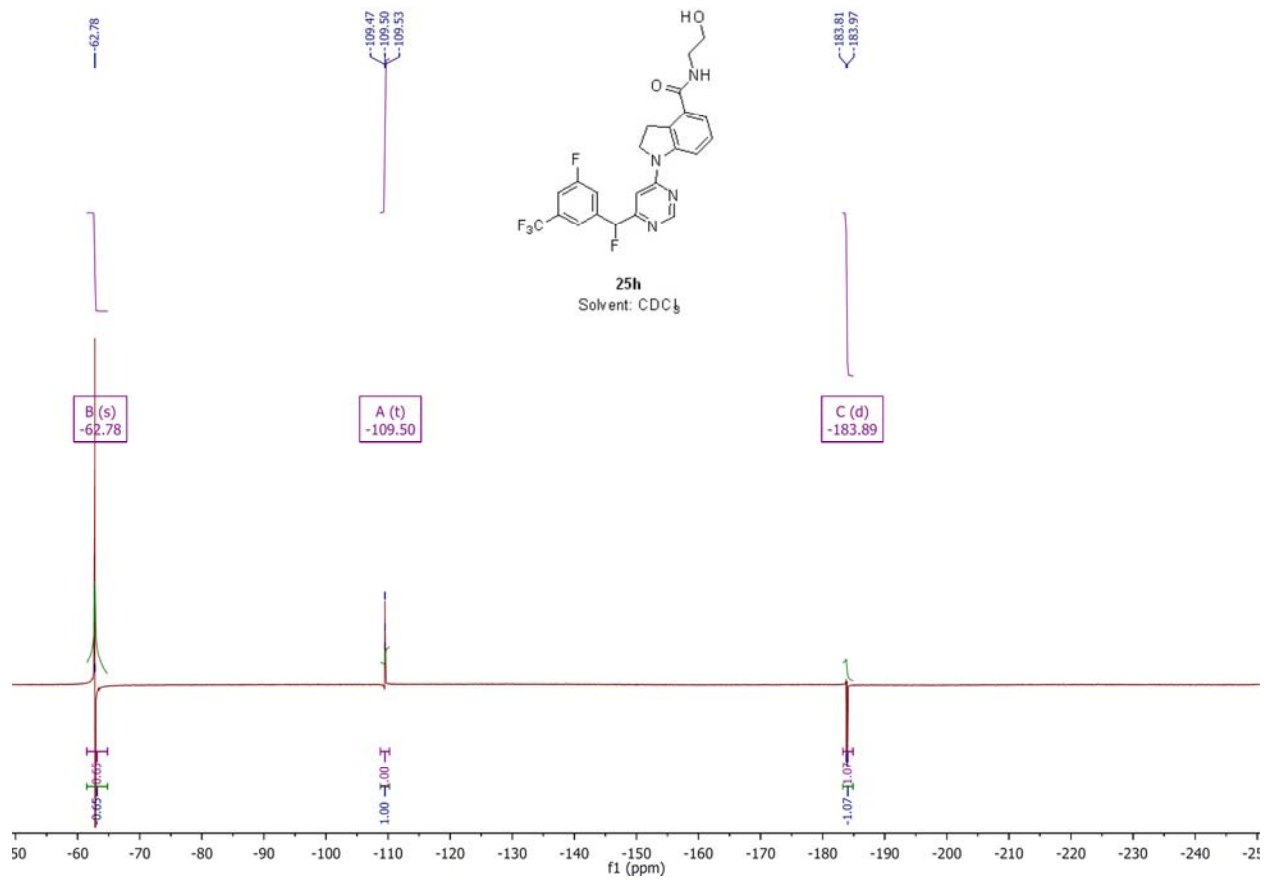
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25g
Solvent: CDCl₃ and MeOD



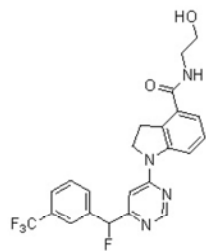




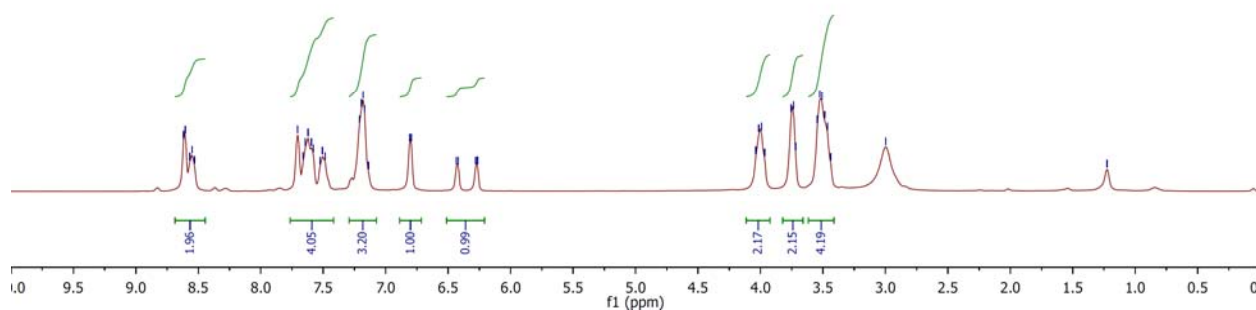
8.62
8.60
8.57
8.55
8.53
7.77
7.76
7.64
7.62
7.59
7.58
7.53
7.51
7.48
7.21
7.18
7.17
7.14
6.81
6.79
6.43
6.42
6.28
6.26

4.04
4.01
3.99
3.97
3.75
3.74
3.72
3.54
3.53
3.49
3.46
3.44
3.00

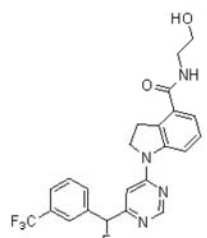
1.23



25i
Solvent: CDCl₃ and MeOD



168.83
165.43
165.08
159.46
157.41
144.14
138.49
138.22
132.51
131.24
131.06
130.80
130.29
130.21
129.70
127.74
125.89
123.51
120.54
118.87
100.28
100.17
83.84
91.48
77.51
77.08
76.66
61.29
49.54
49.25
48.89
42.38
27.46



25i
Solvent: CDCl₃ and MeOD

