Novel *N*-Arylsulfonylindoles targeted as ligands of the 5-HT$_6$ Receptor. Insights on the Influence of C-5 substitution on ligand affinity.

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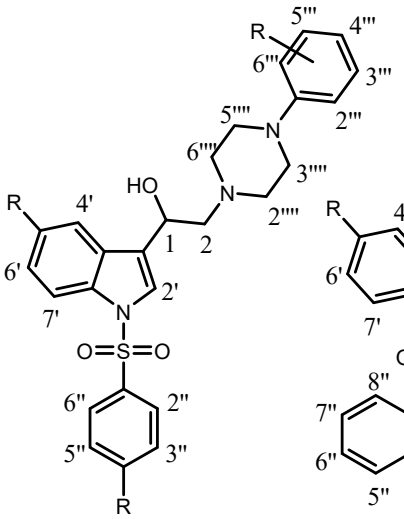
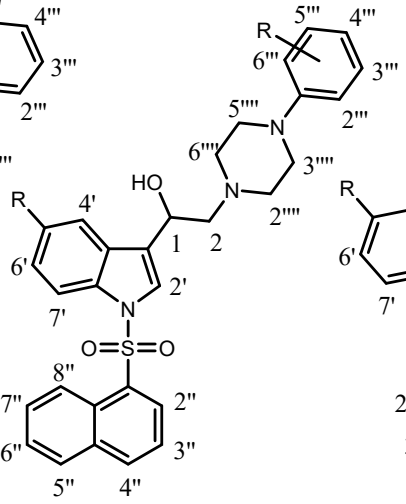
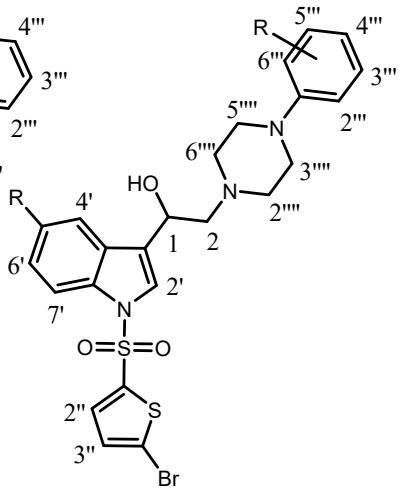
1. Atom numbering for the final compounds.



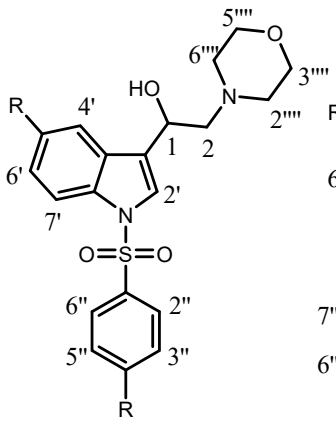
4a-b, 4h, 4j, 4o-p, 4u-v



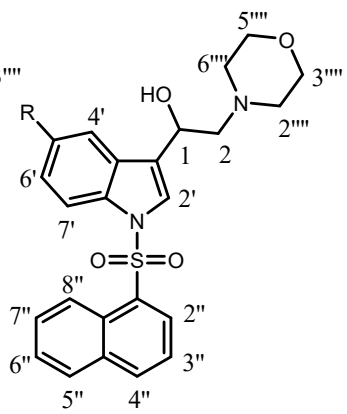
4d-e, 4g, 4l, 4n



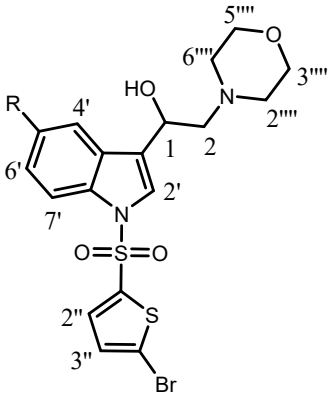
4i, 4r



4c, 4k, 4q, 4t



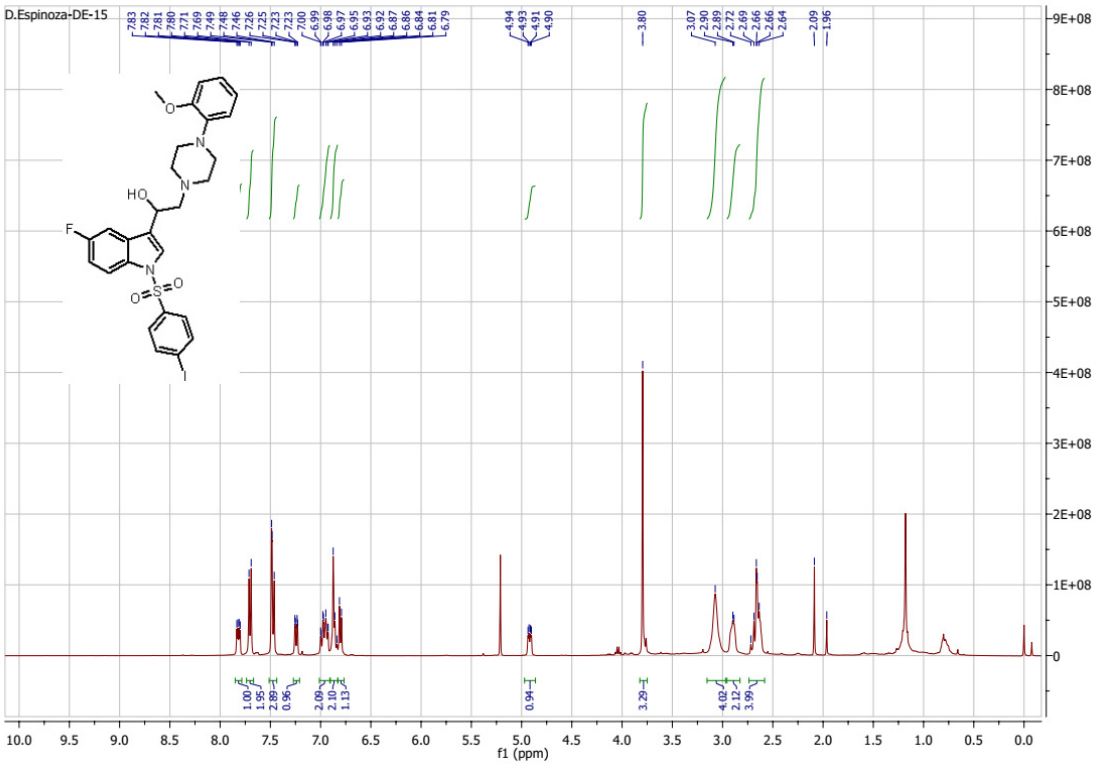
4f, 4m



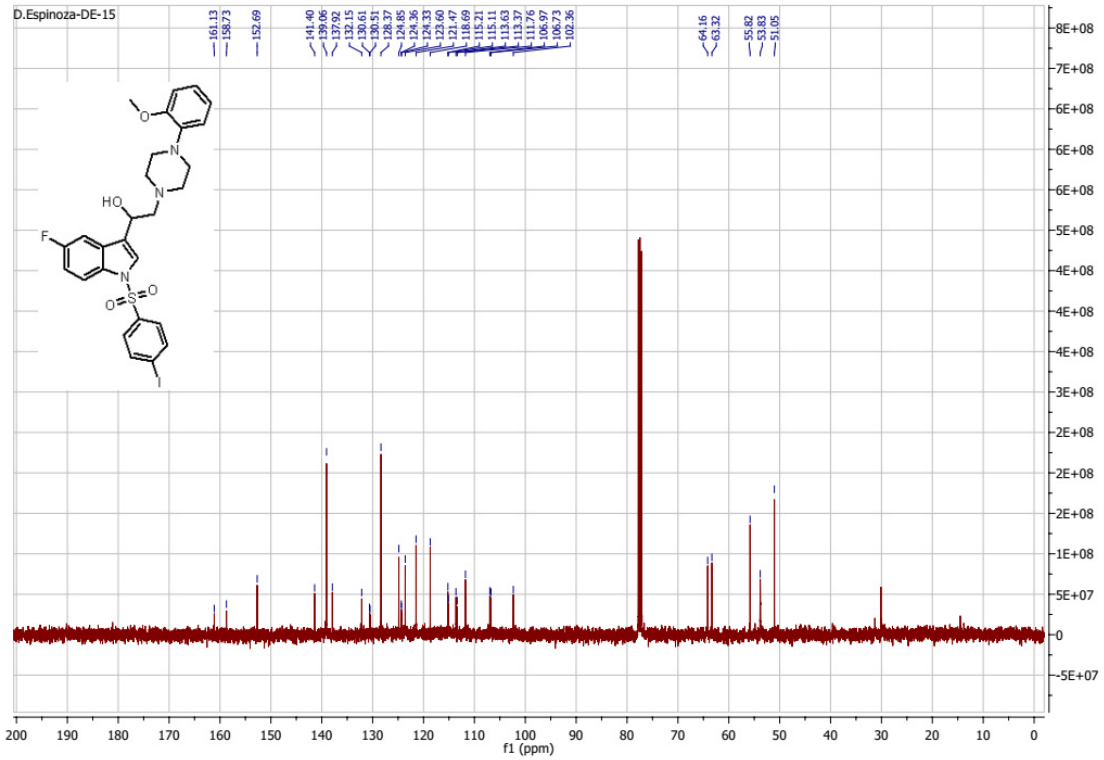
4s

2. ^{1}H-NMR and ^{13}C-NMR spectra of final compounds.

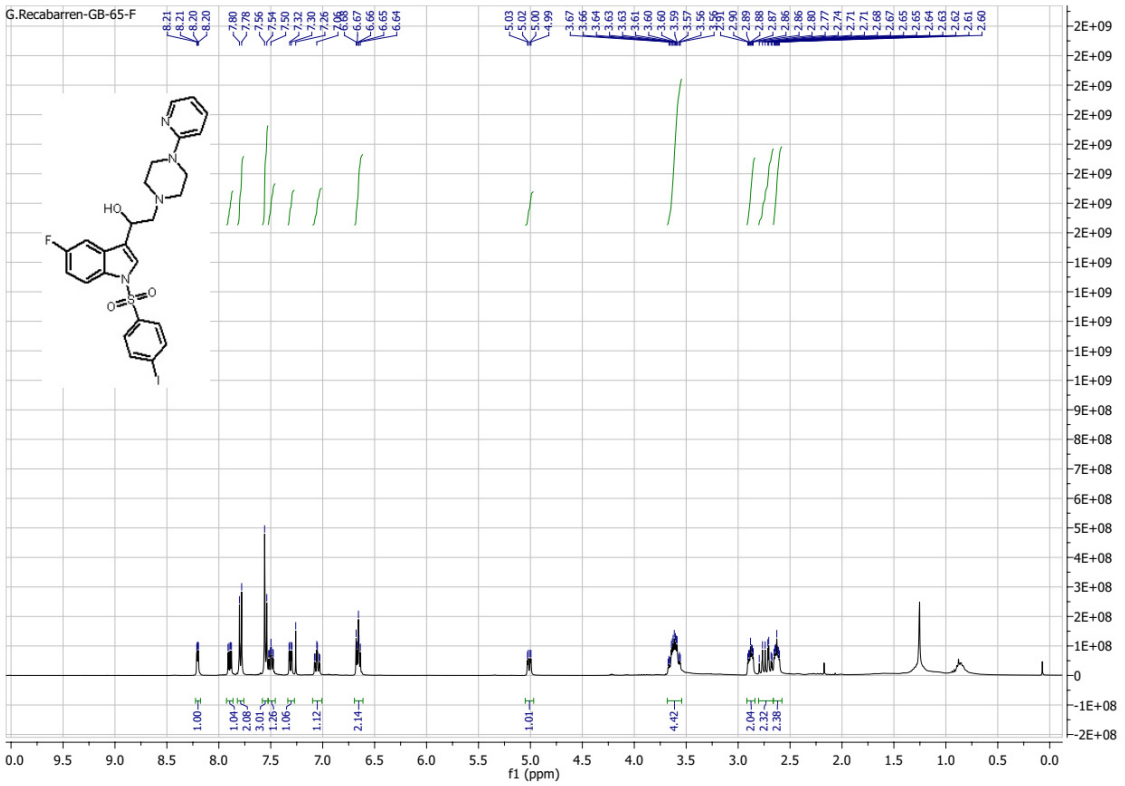
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4a**



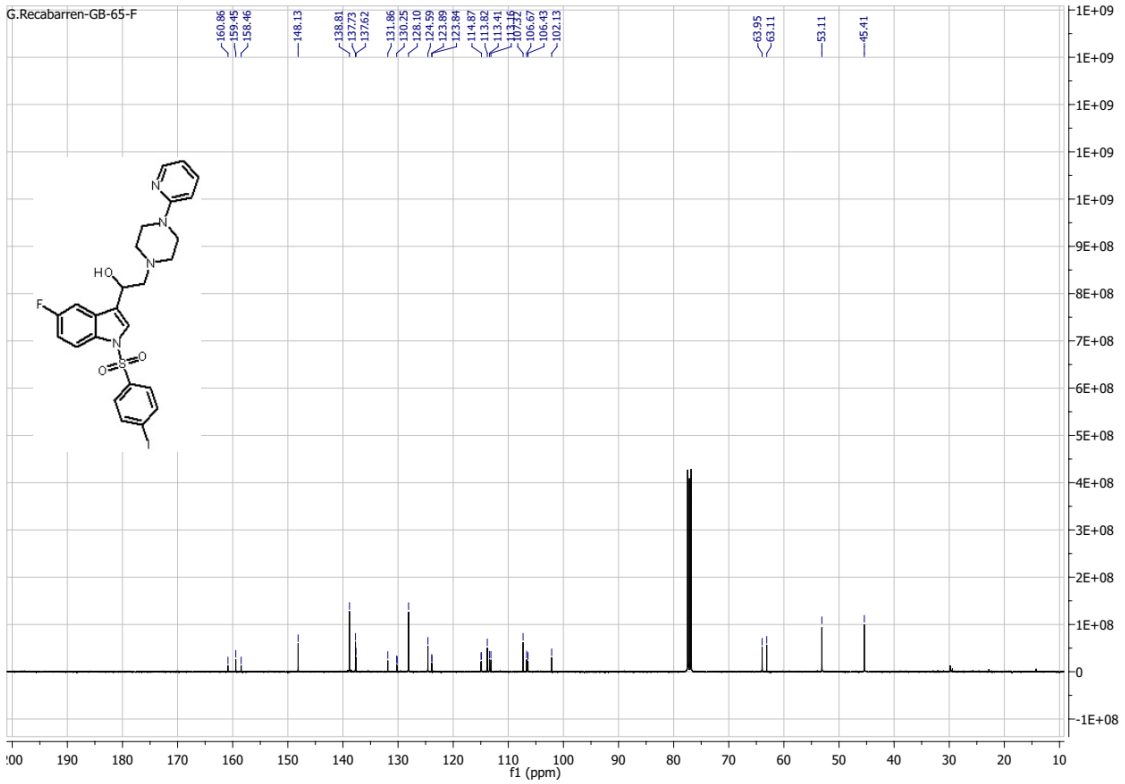
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4a**



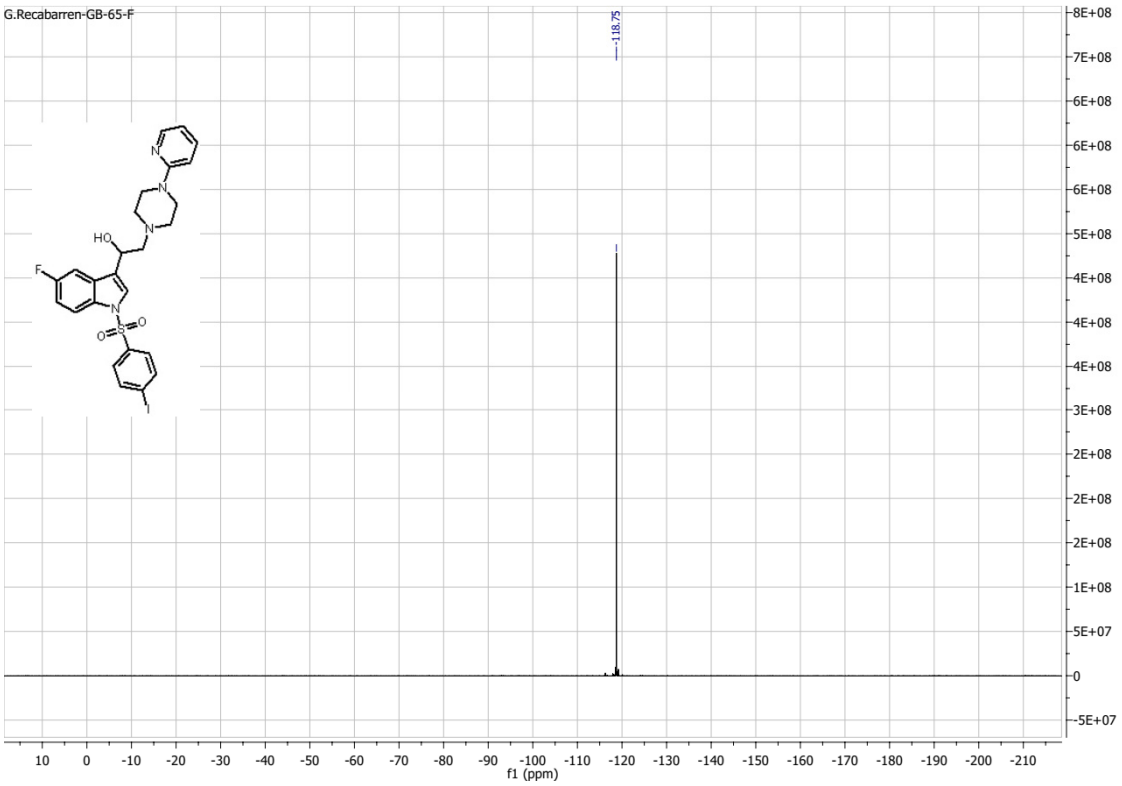
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4b**



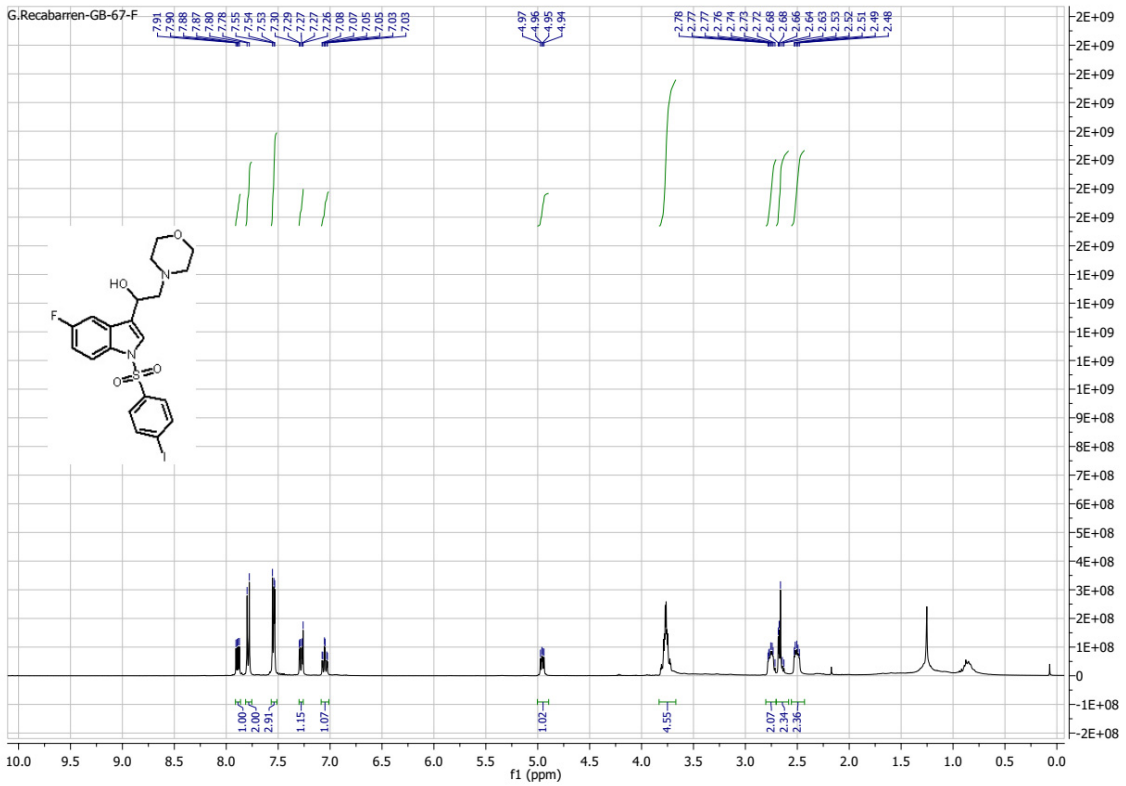
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4b**



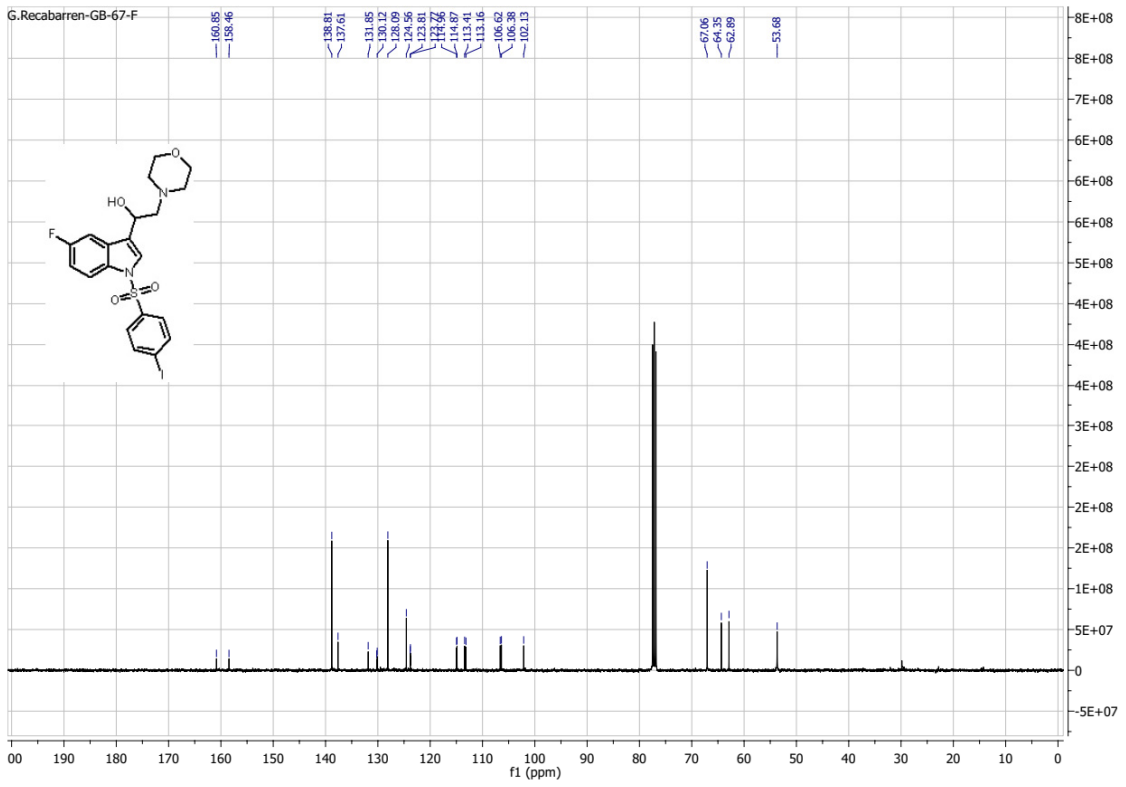
^{19}F-NMR (376.5 MHz, $CDCl_3$) for **4b**



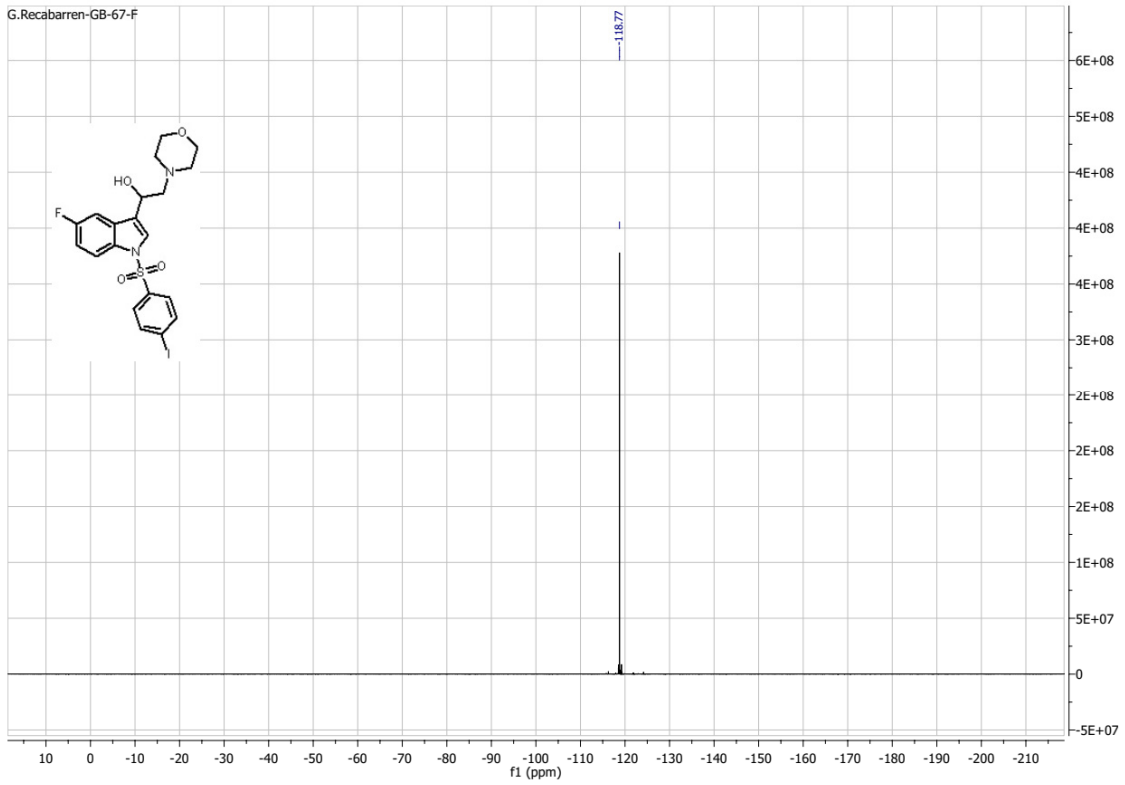
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4c**



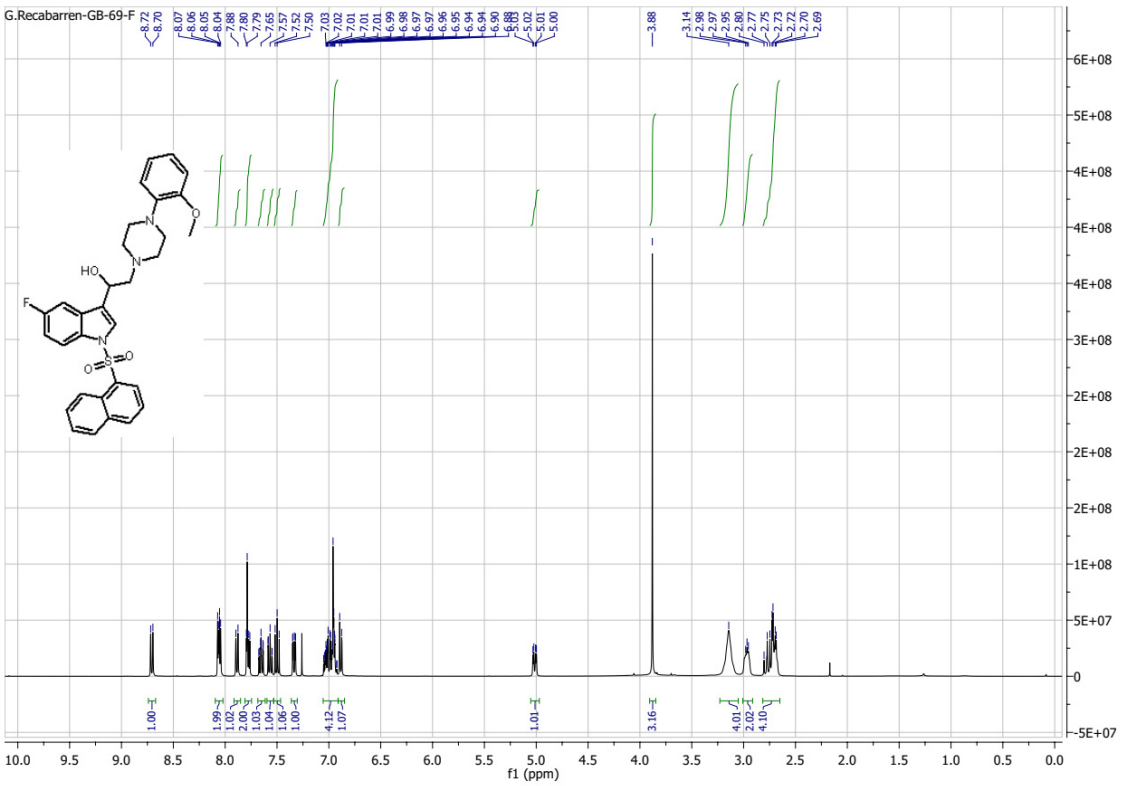
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4c**



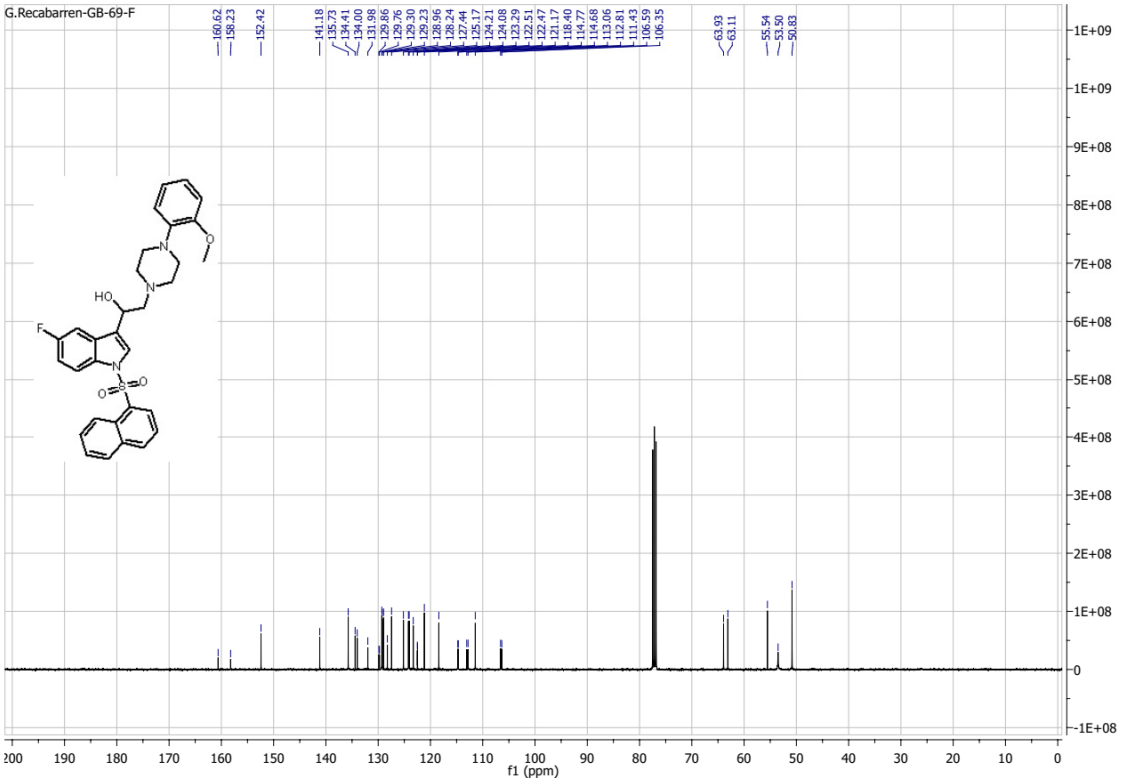
^{19}F-NMR (376.5 MHz, $CDCl_3$) for **4c**



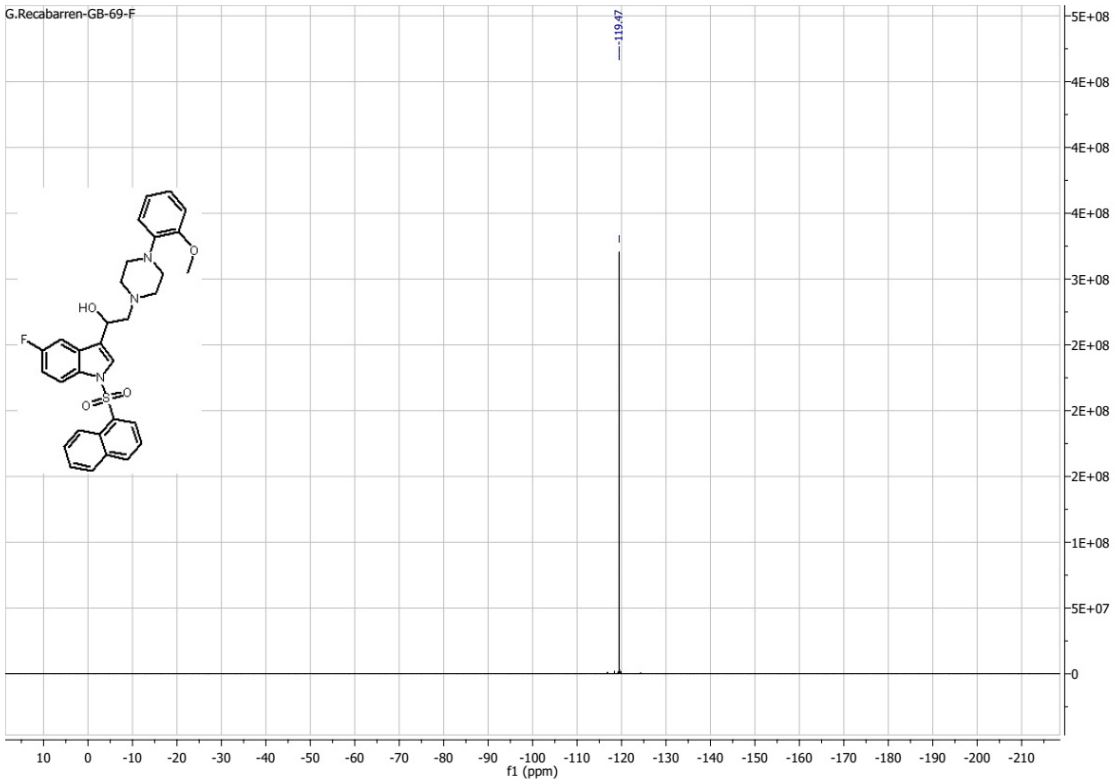
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4d**



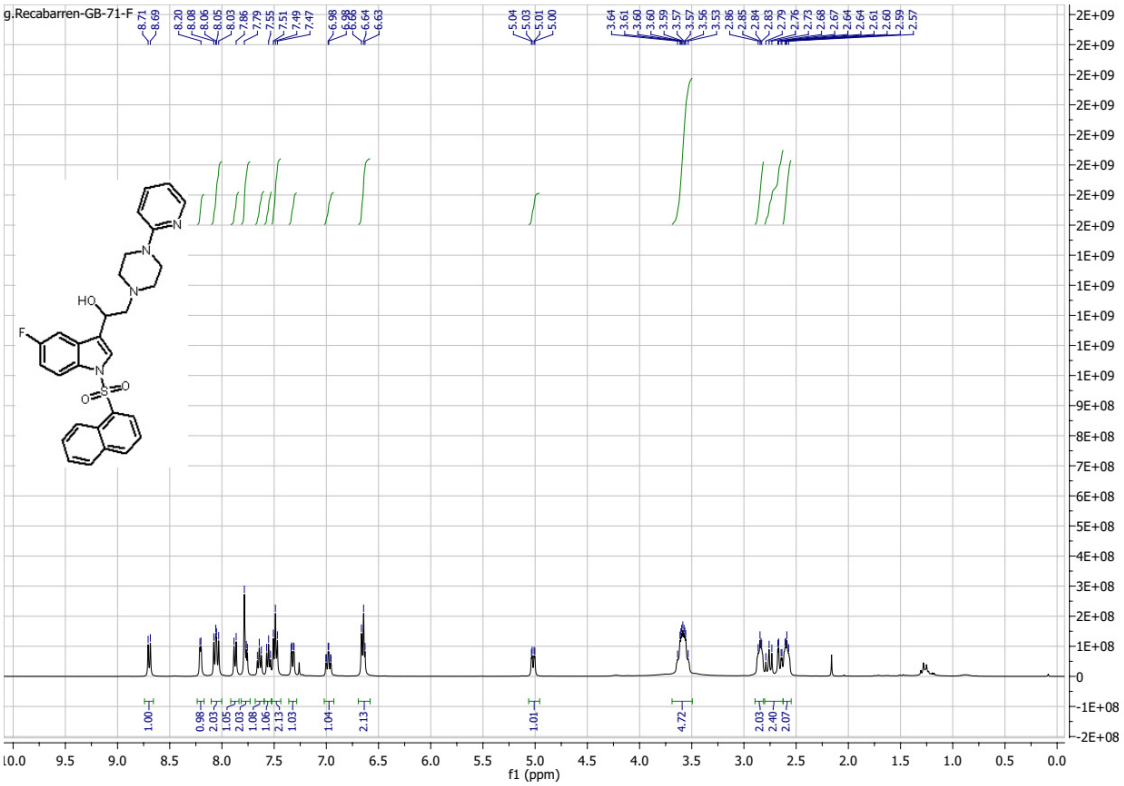
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4d**



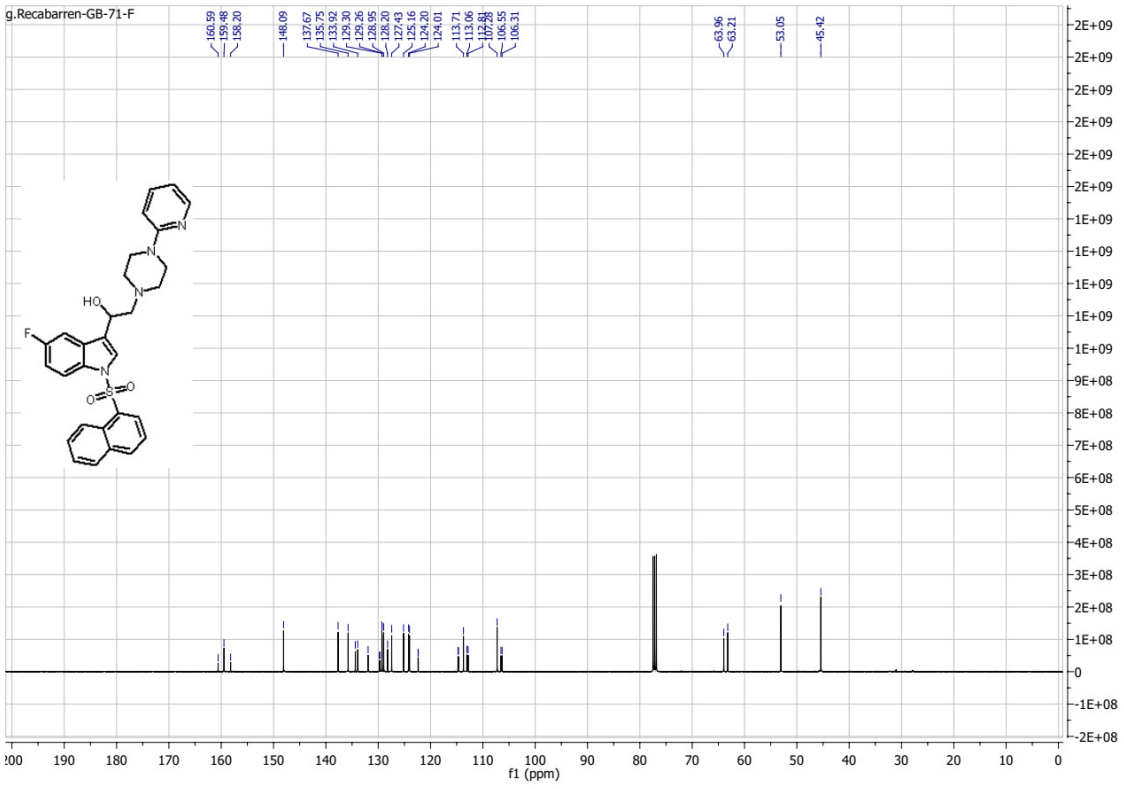
^{19}F-NMR (376.5 MHz, $CDCl_3$) for **4d**



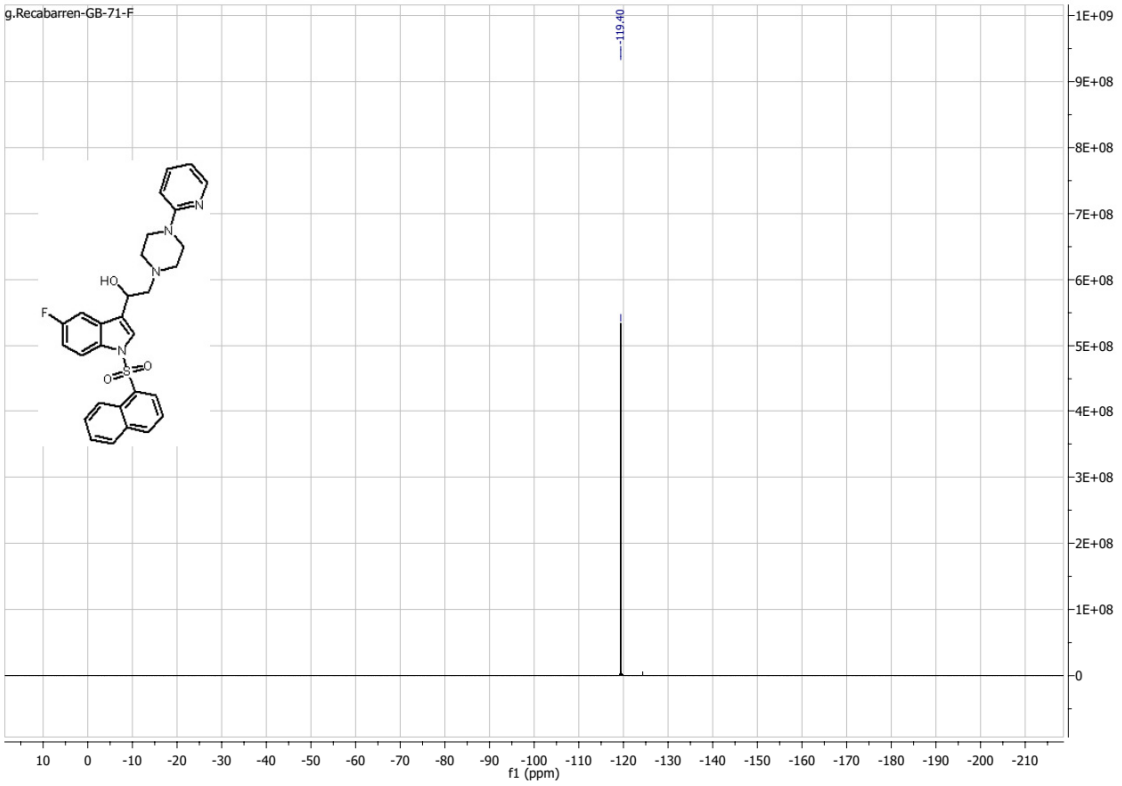
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4e**



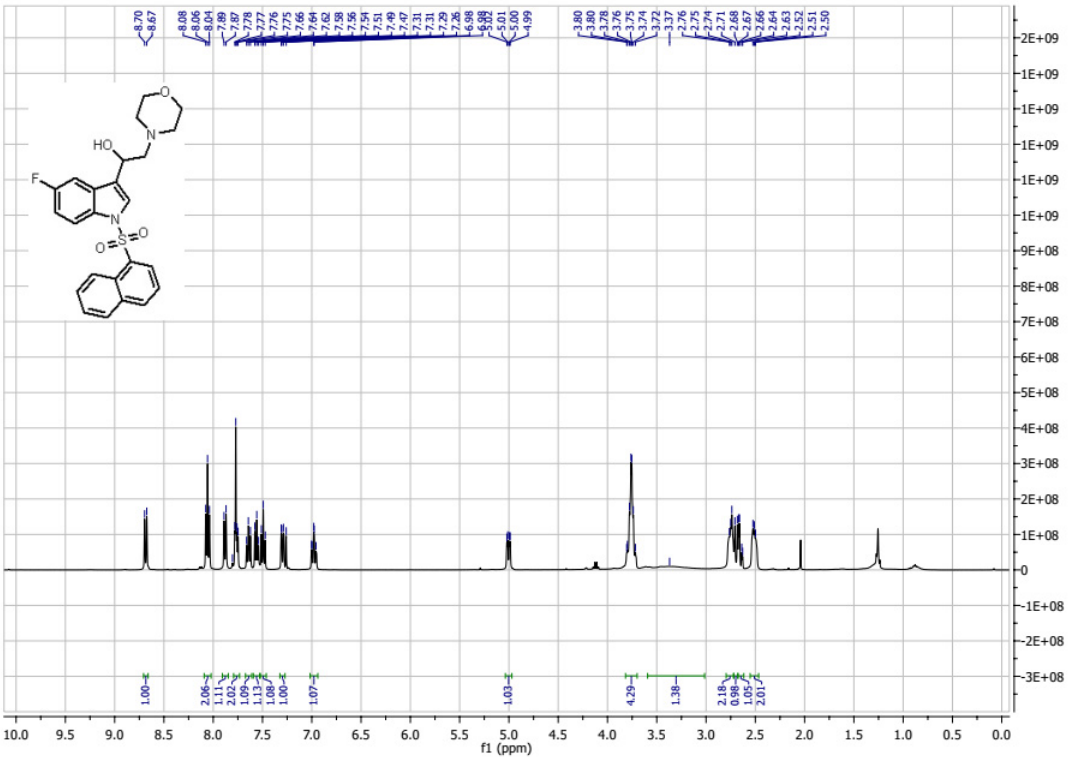
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4e**



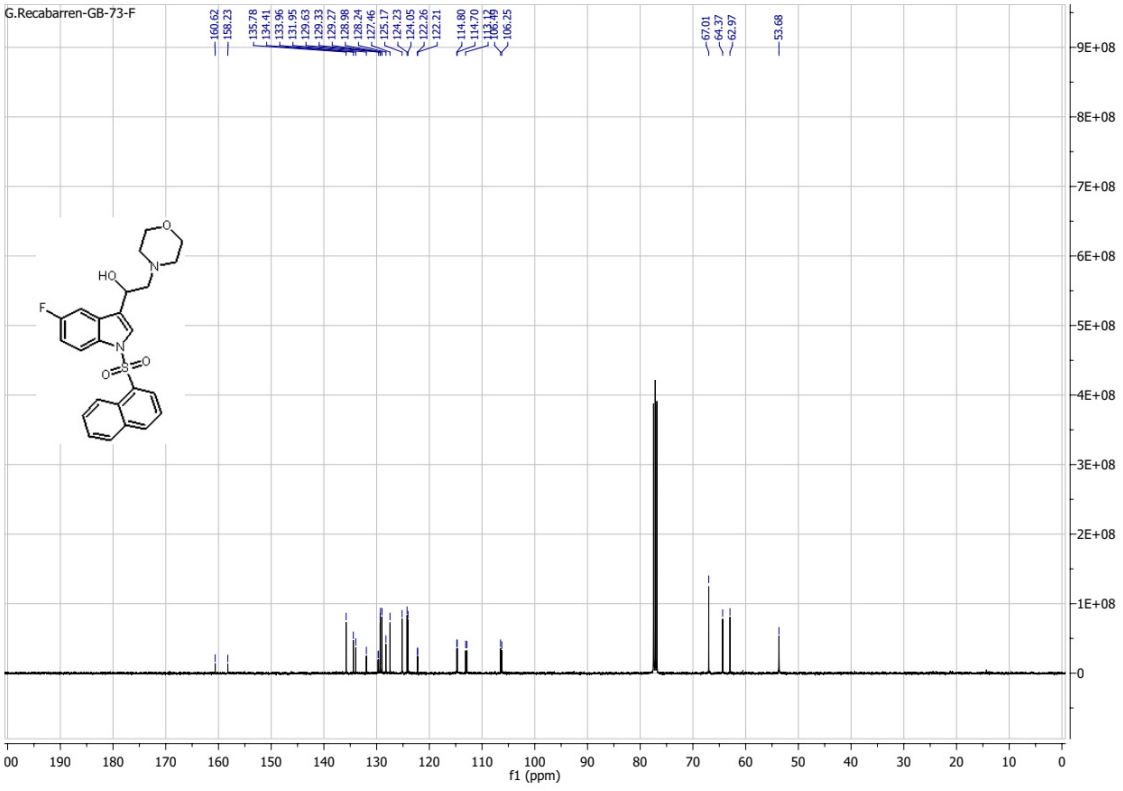
^{19}F-NMR (376.5 MHz, $CDCl_3$) for **4e**



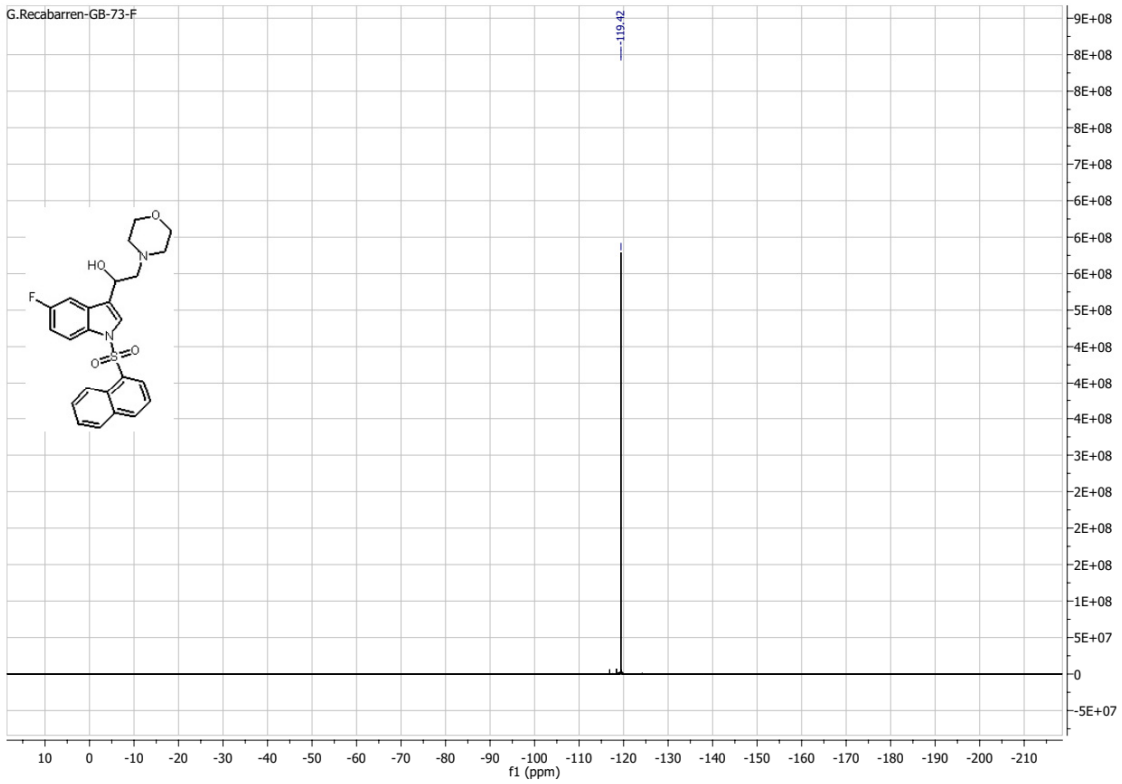
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4f**



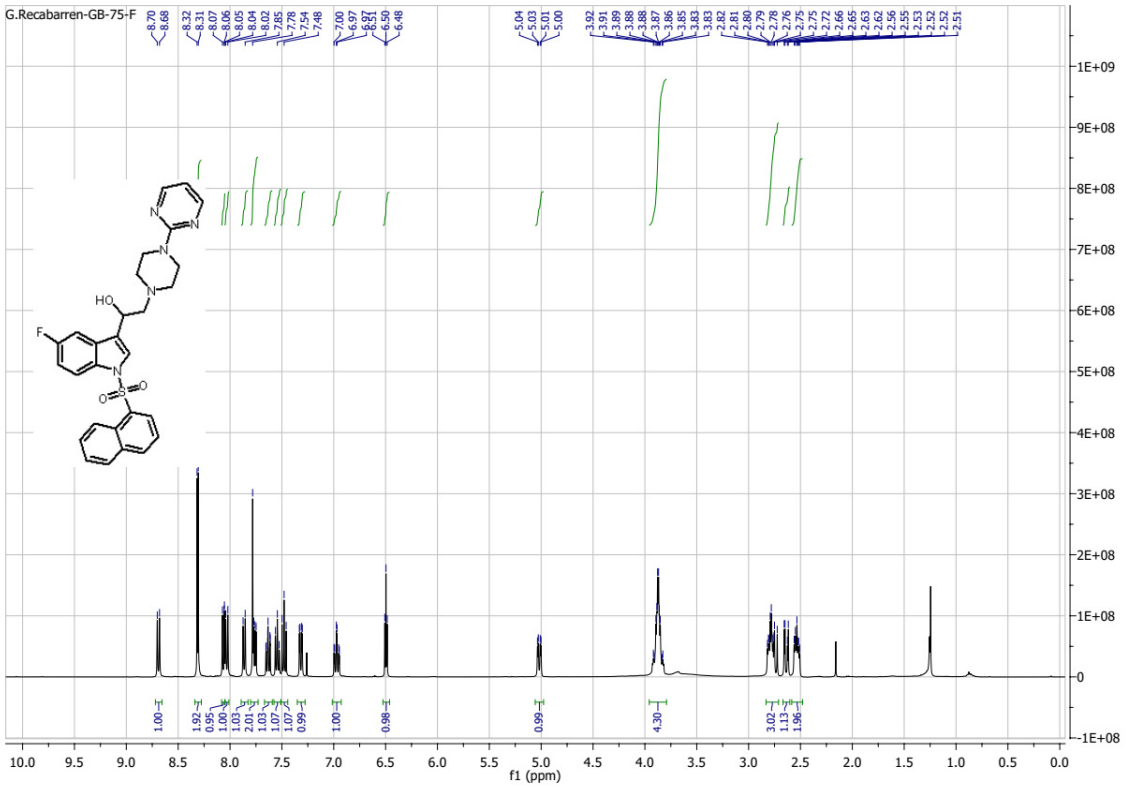
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4f**



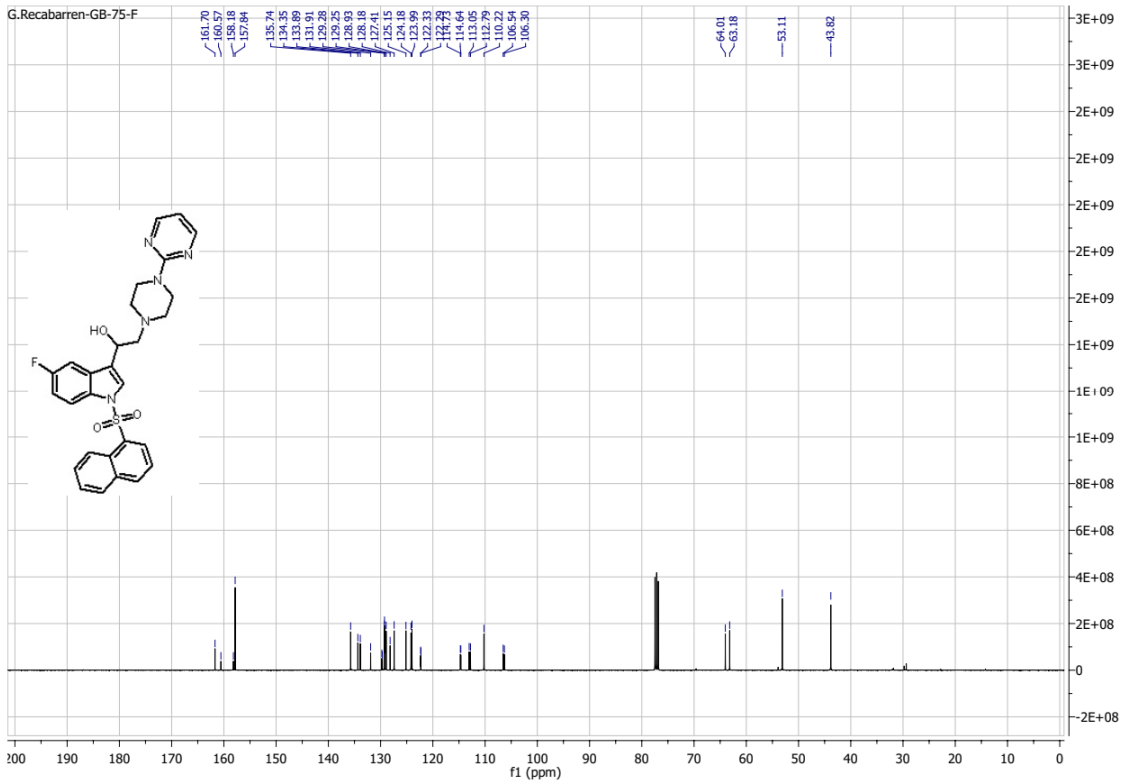
^{19}F-NMR (376.5 MHz, $CDCl_3$) for **4f**



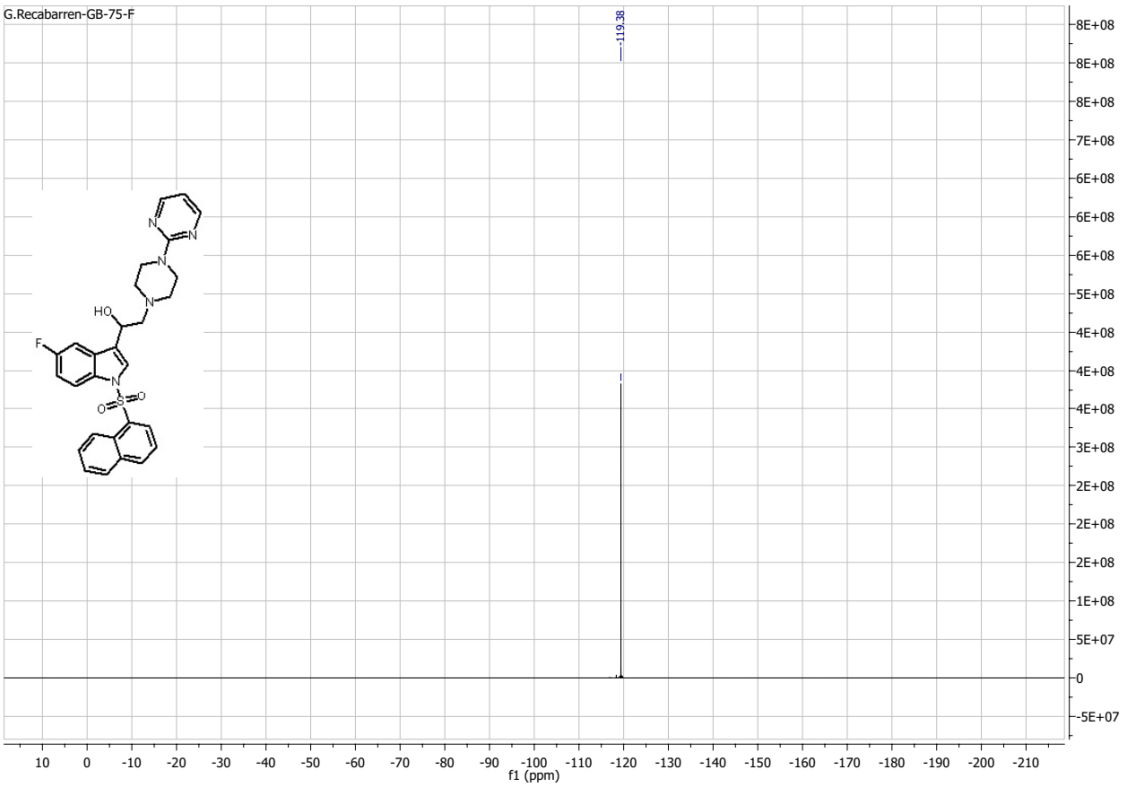
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4g**



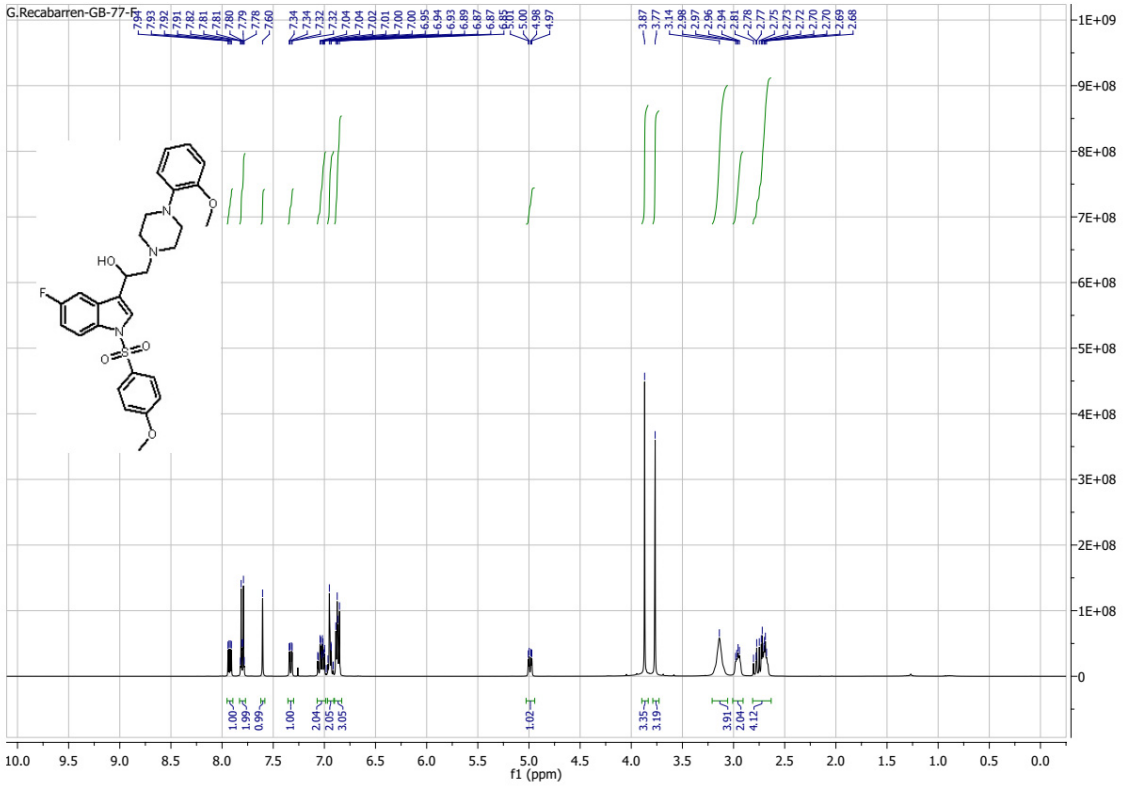
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4g**



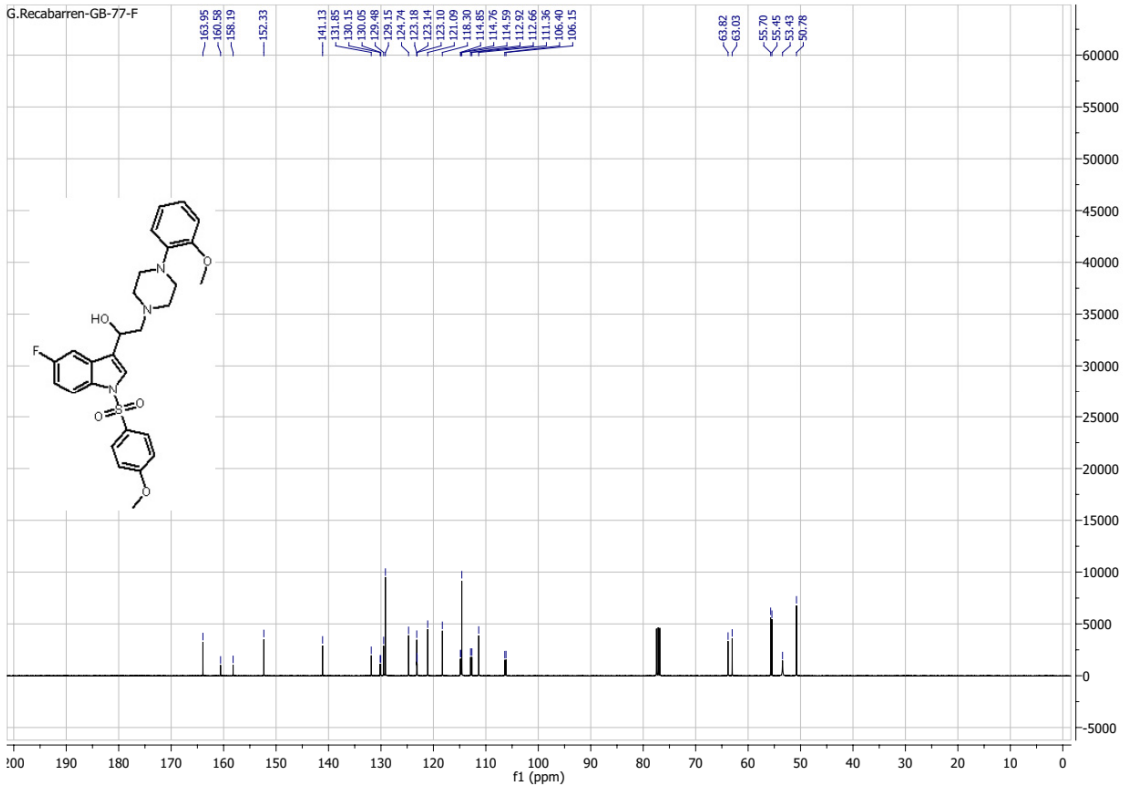
^{19}F-NMR (376.5 MHz, $CDCl_3$) for **4g**



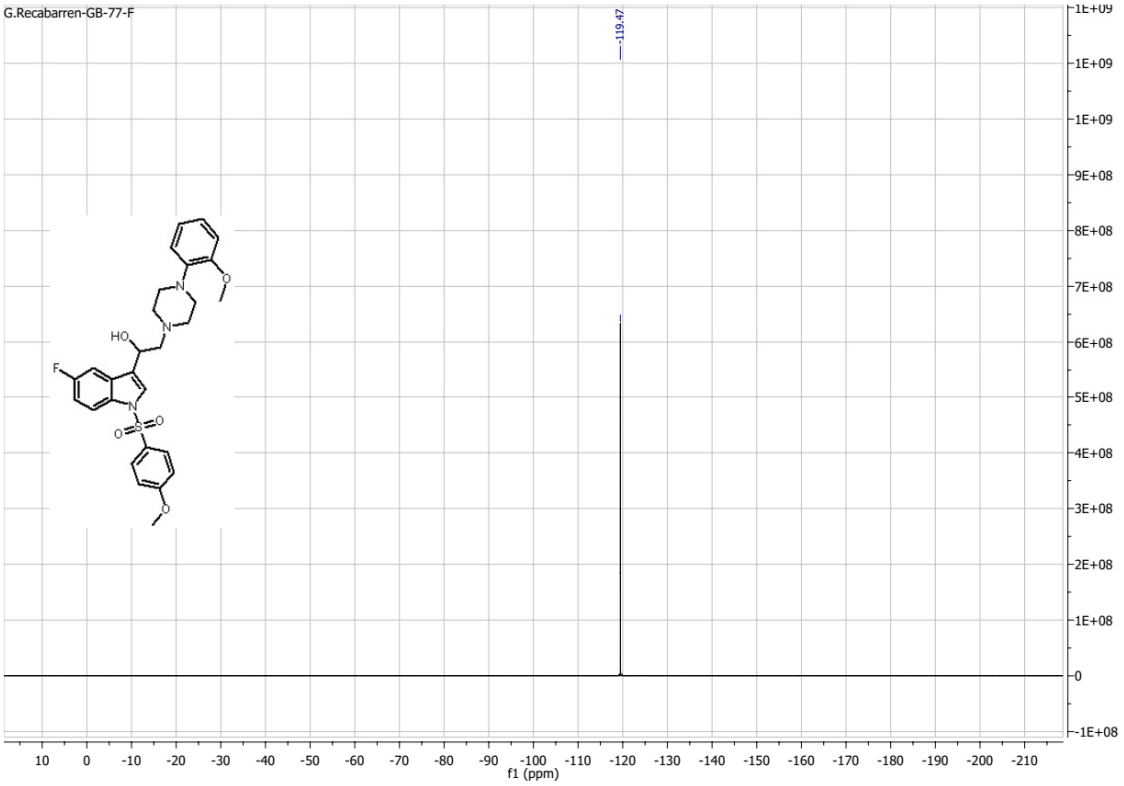
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4h**



^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4h**



^{19}F-NMR (376.5 MHz, $CDCl_3$) for **4h**



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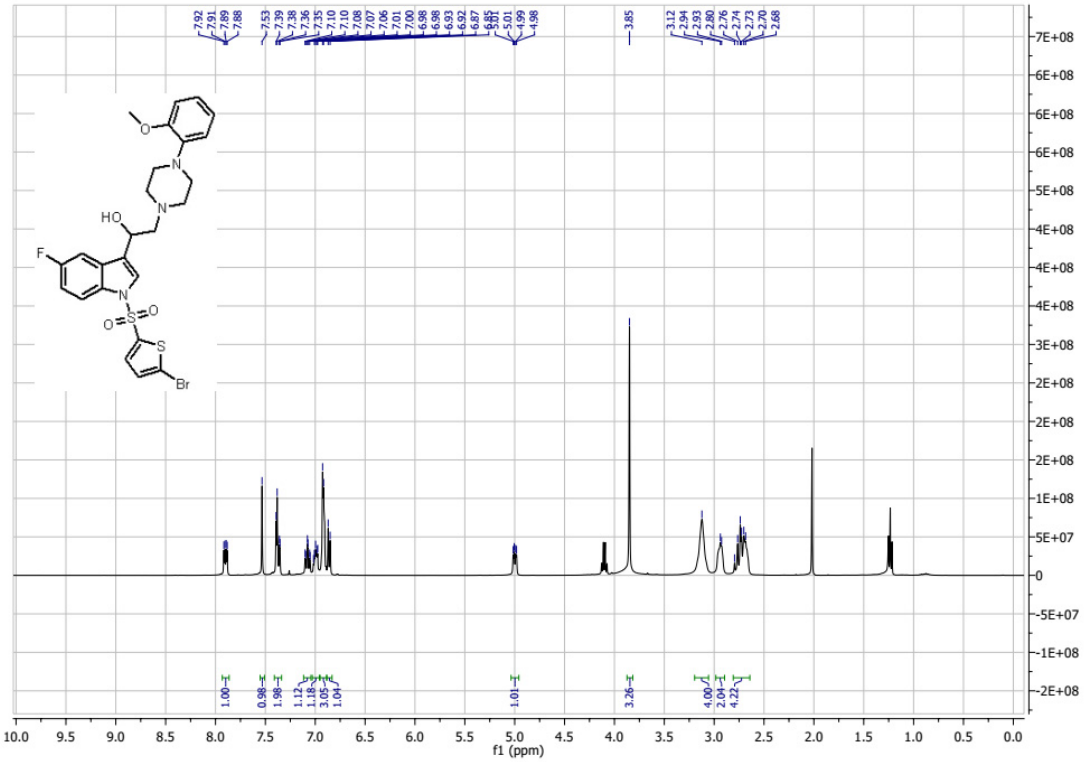
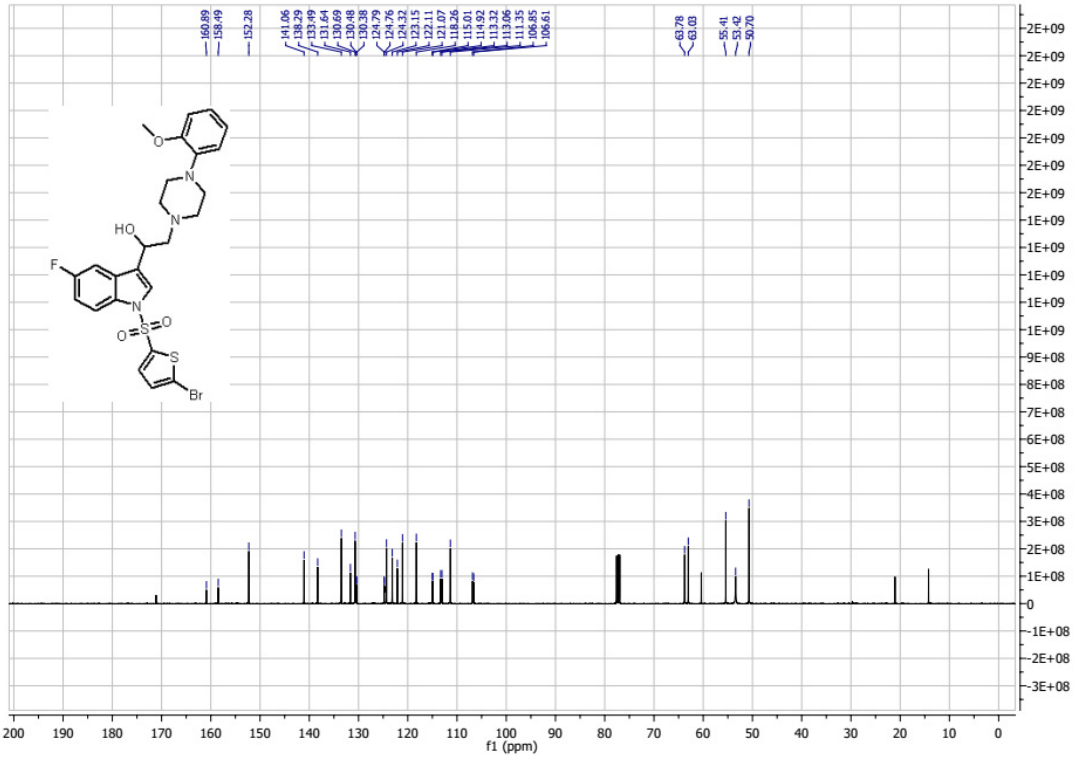
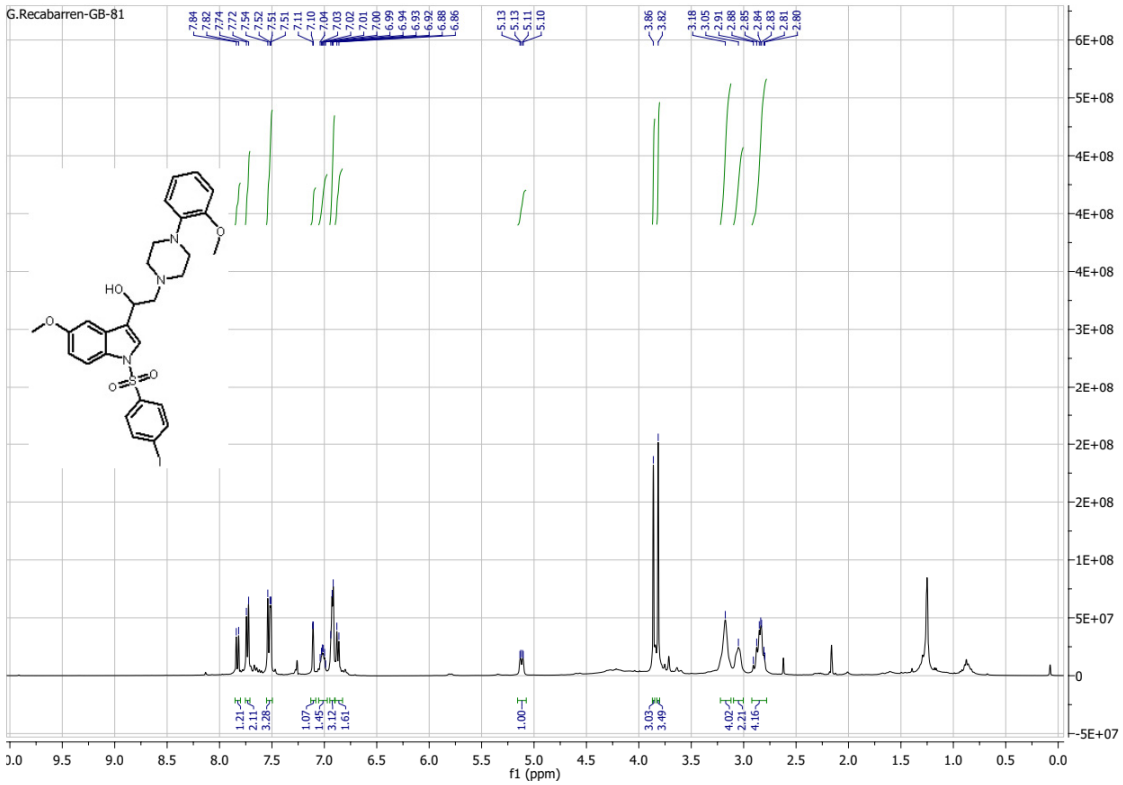


^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4i**



^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4j**



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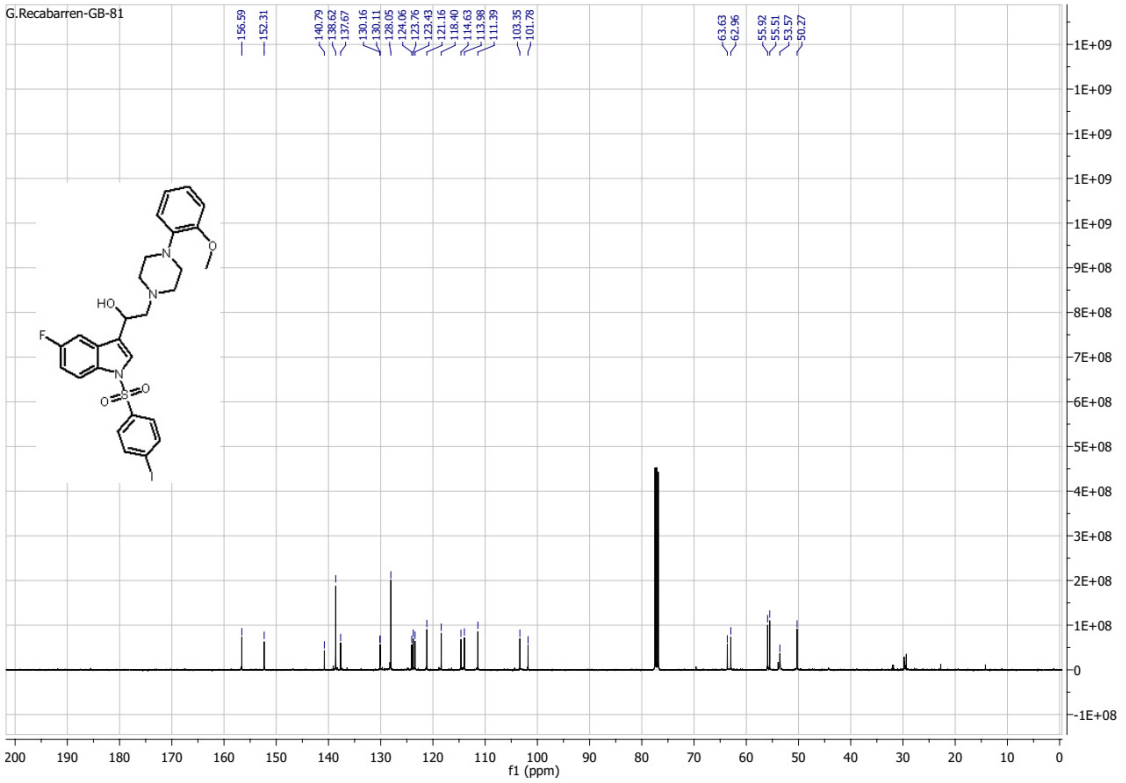
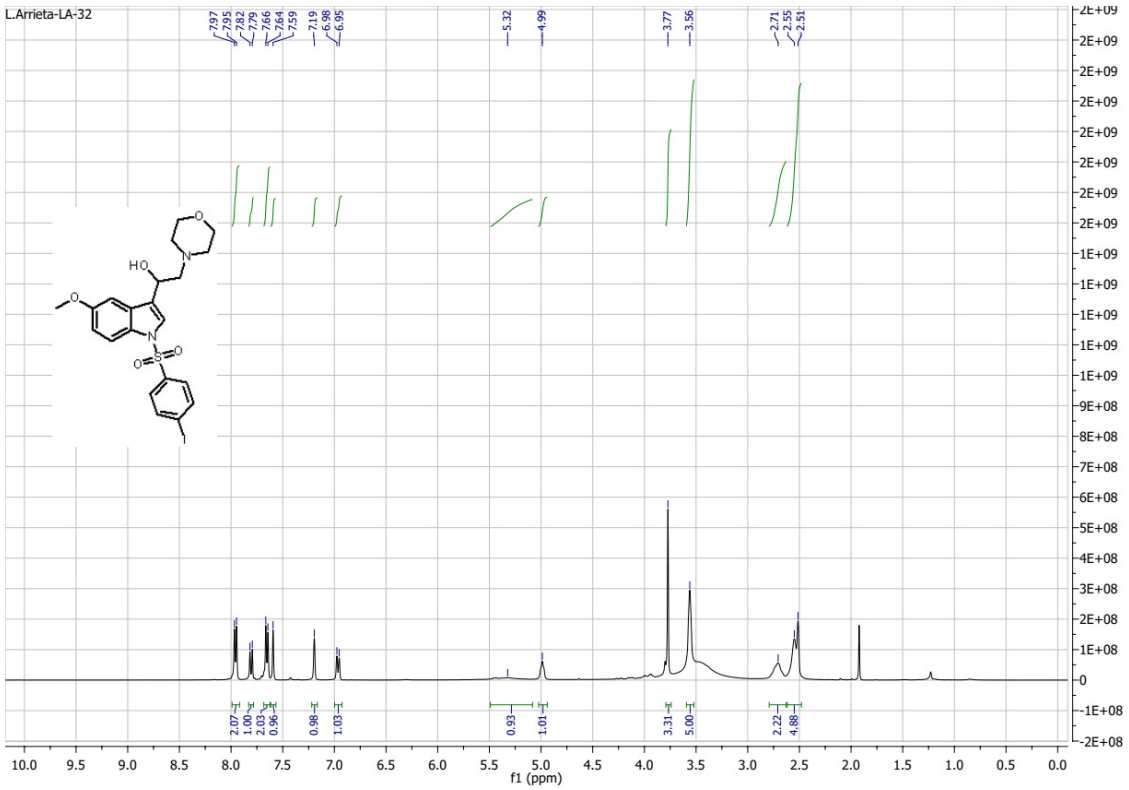
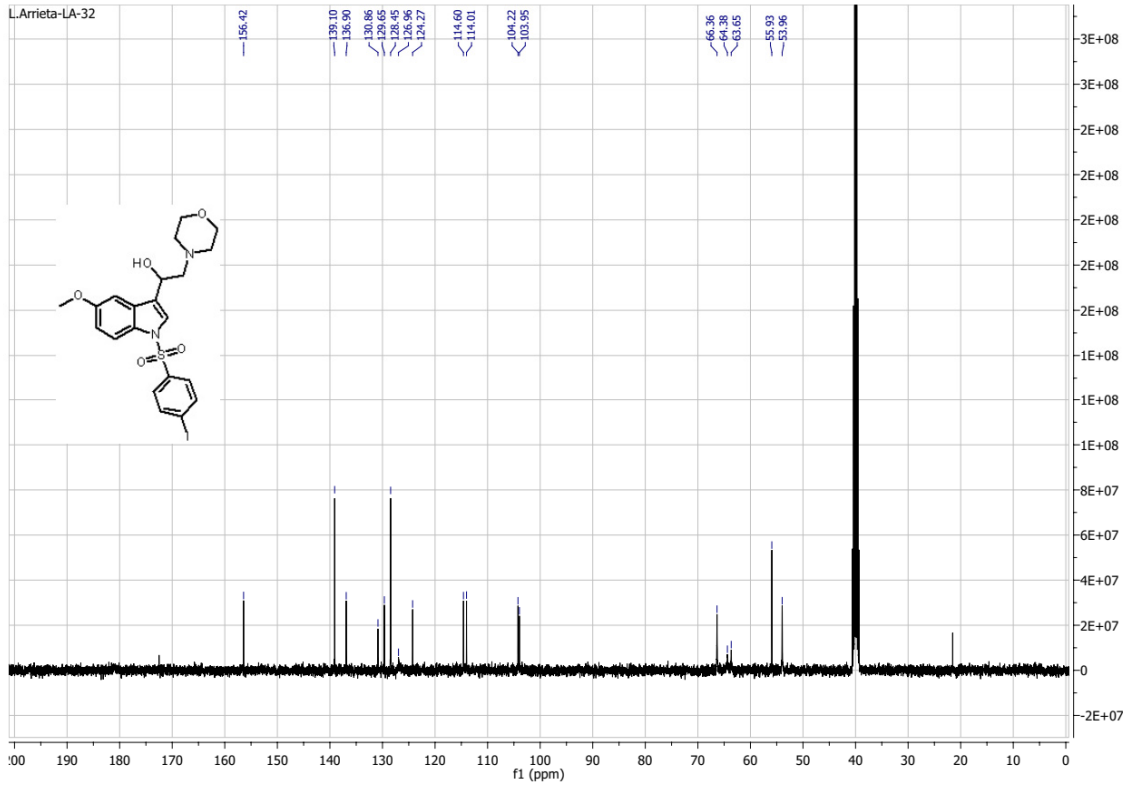


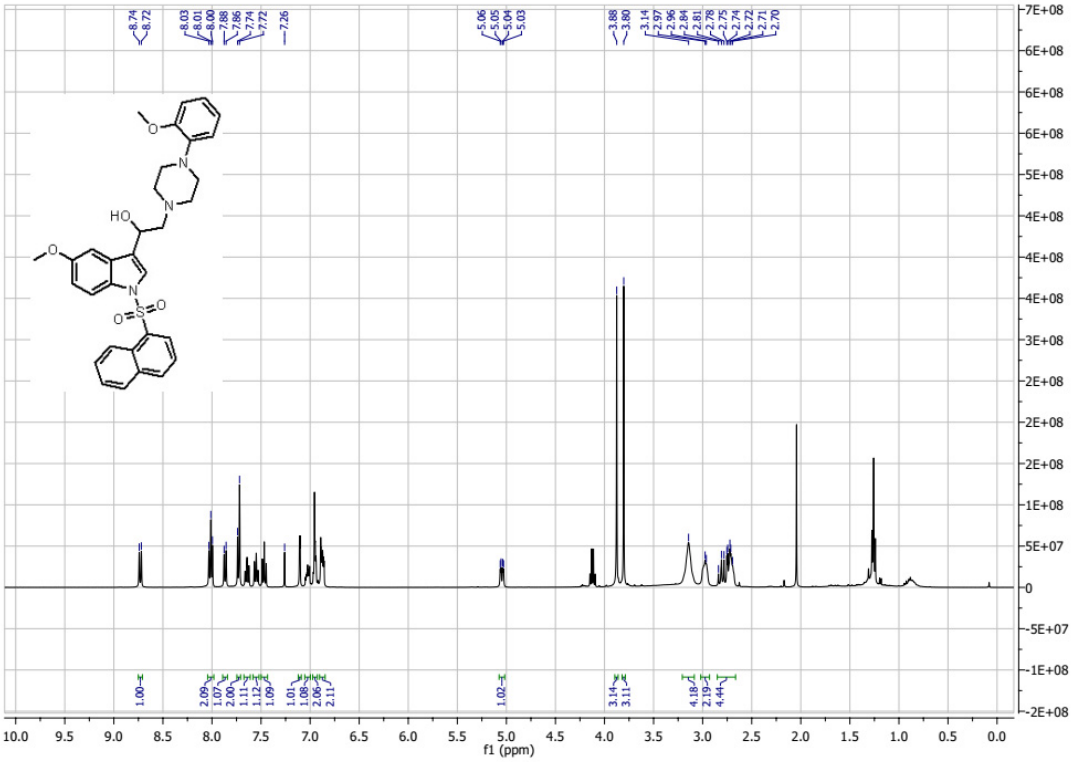
^{1}H-NMR (400.1 MHz, DMSO-d$_6$) for **4k**



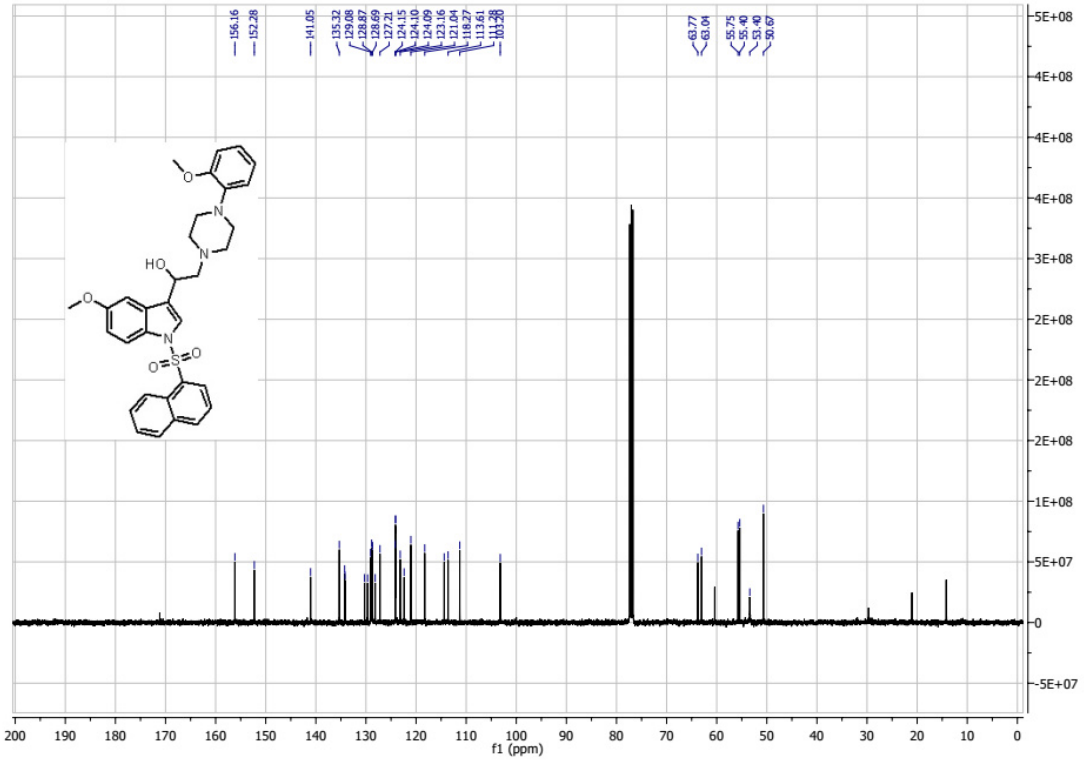
^{13}C-NMR (100.6 MHz, DMSO-d$_6$) for **4k**



^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4l**



^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4l**



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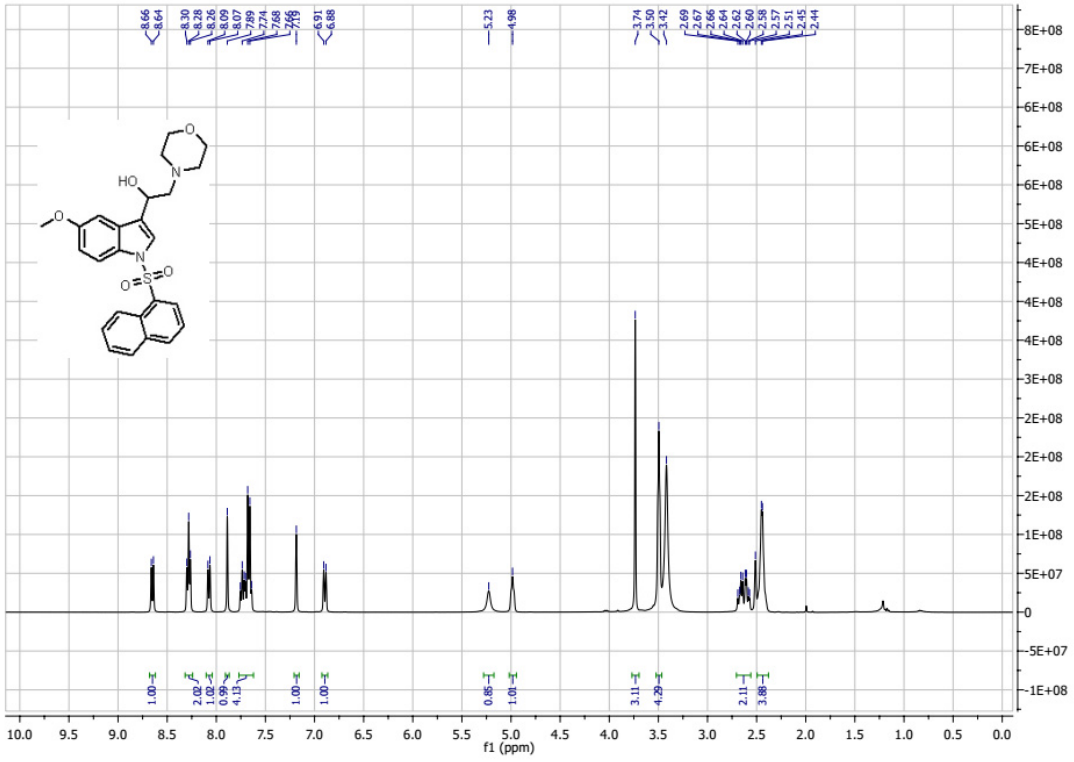
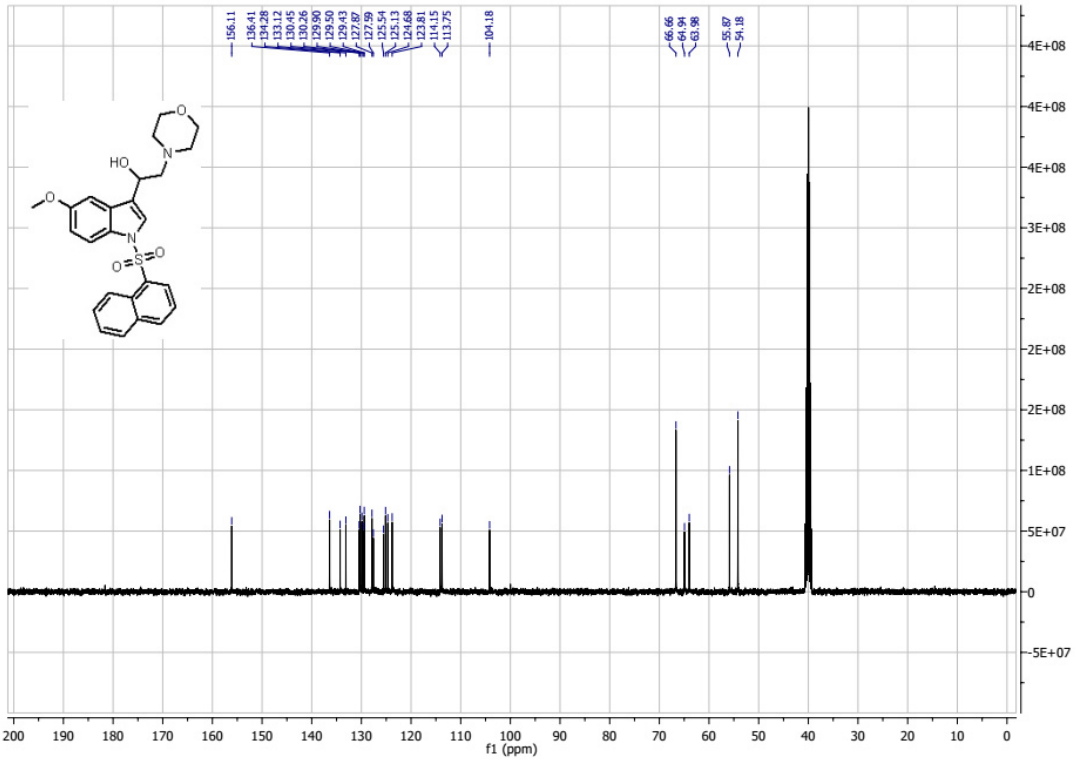
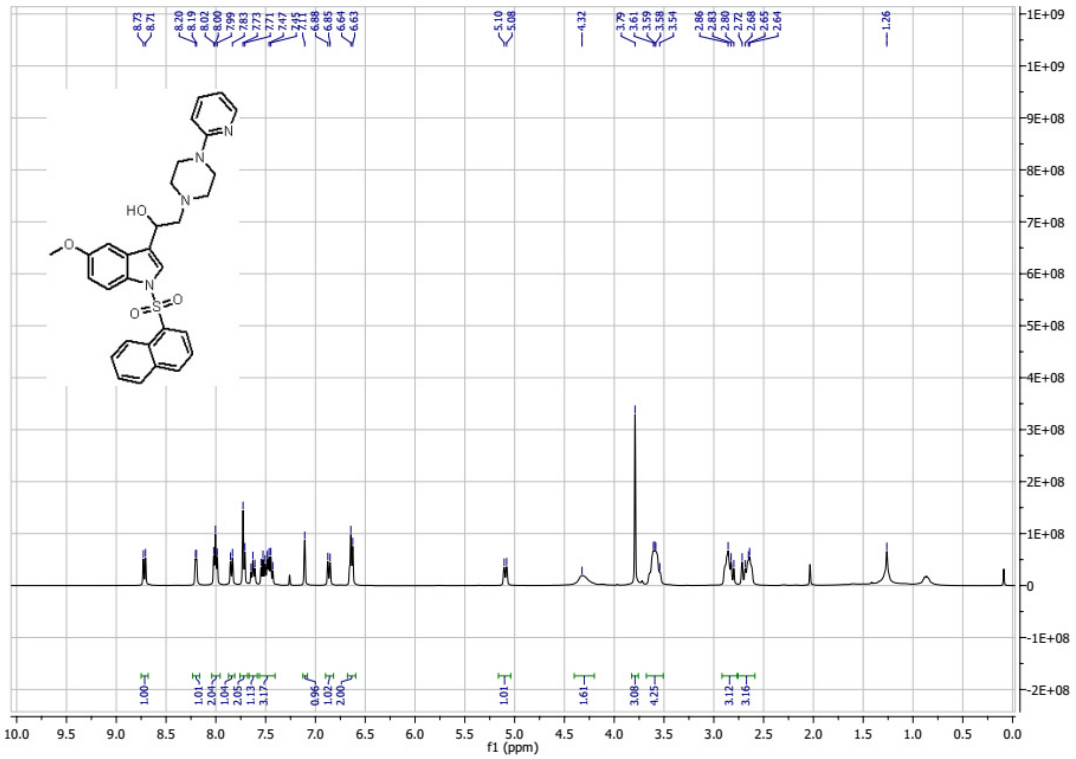


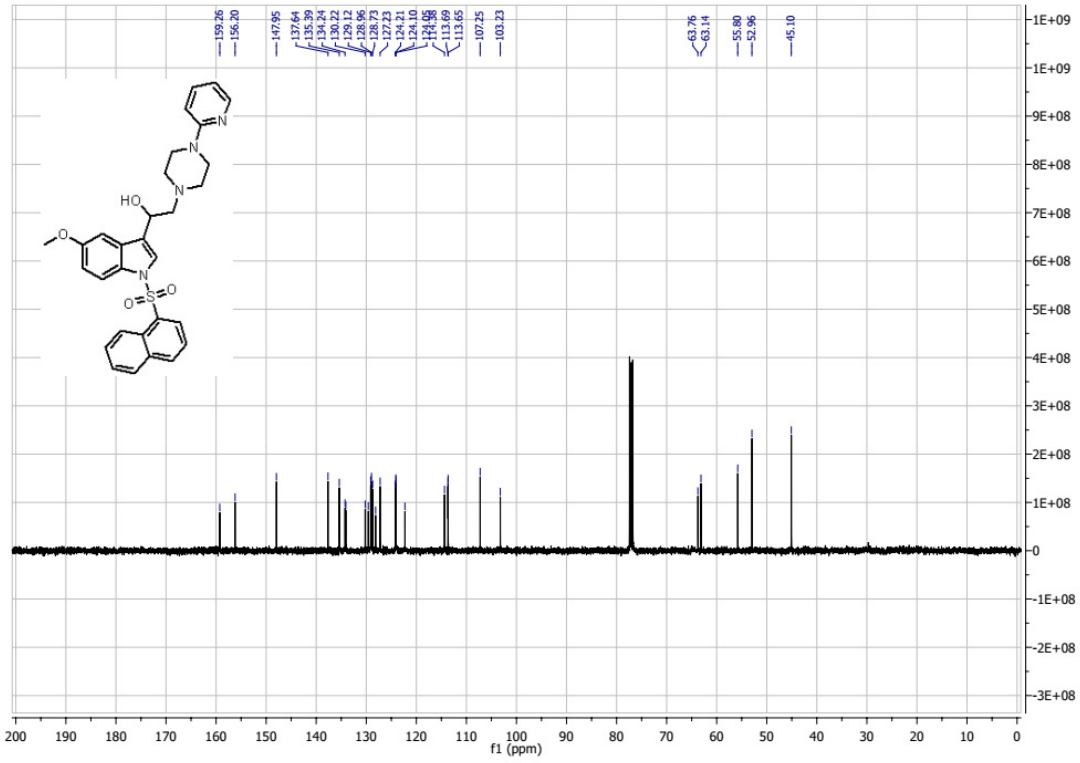
^{13}C-NMR (100.6 MHz, DMSO-d_6) for **4m**



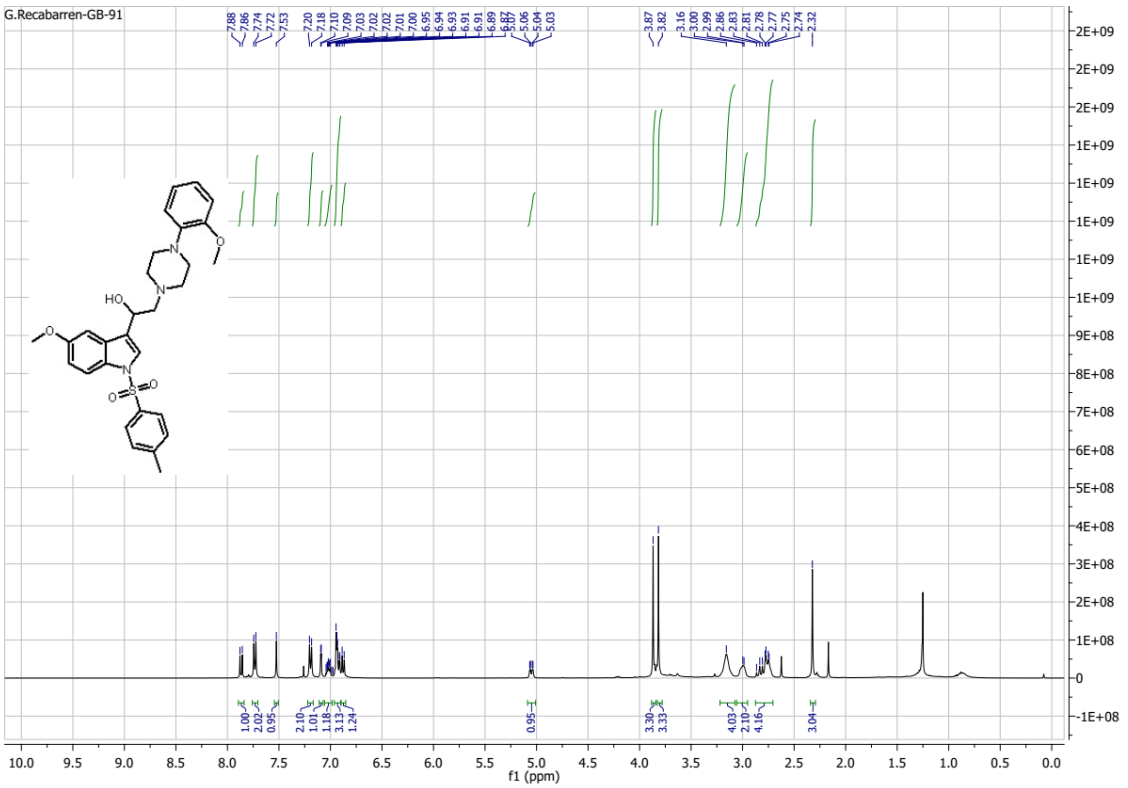
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4n**



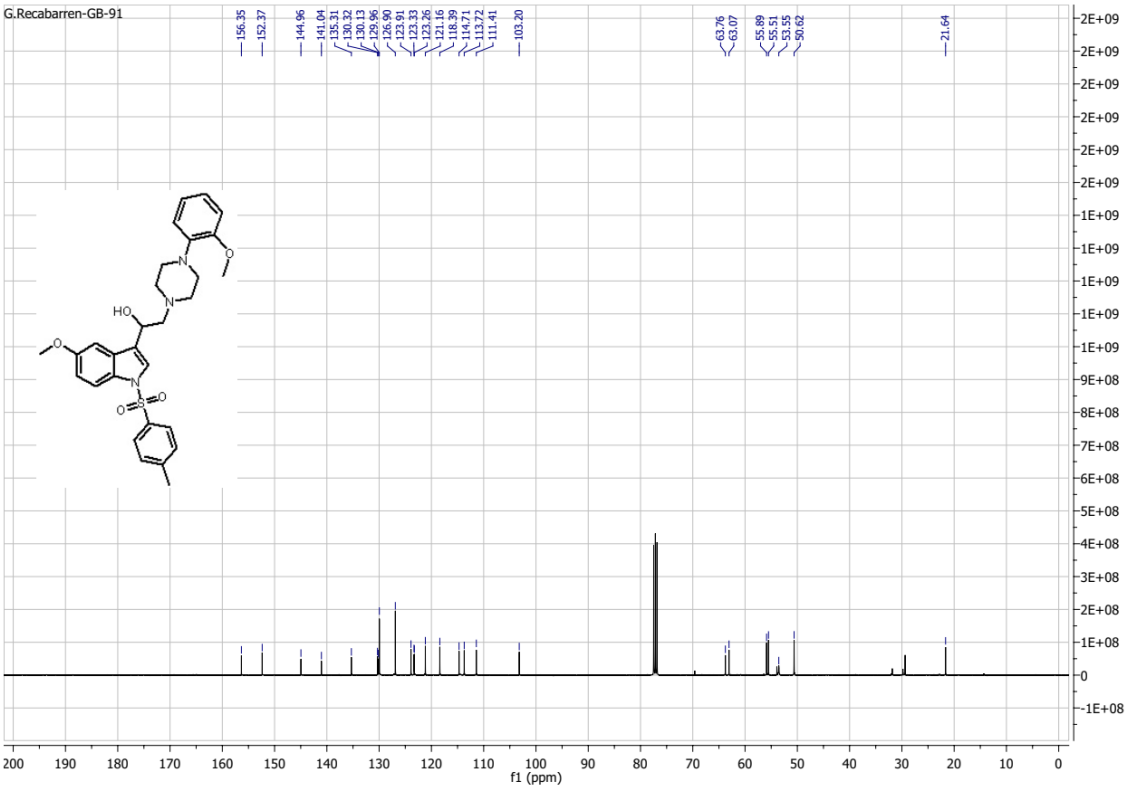
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4n**



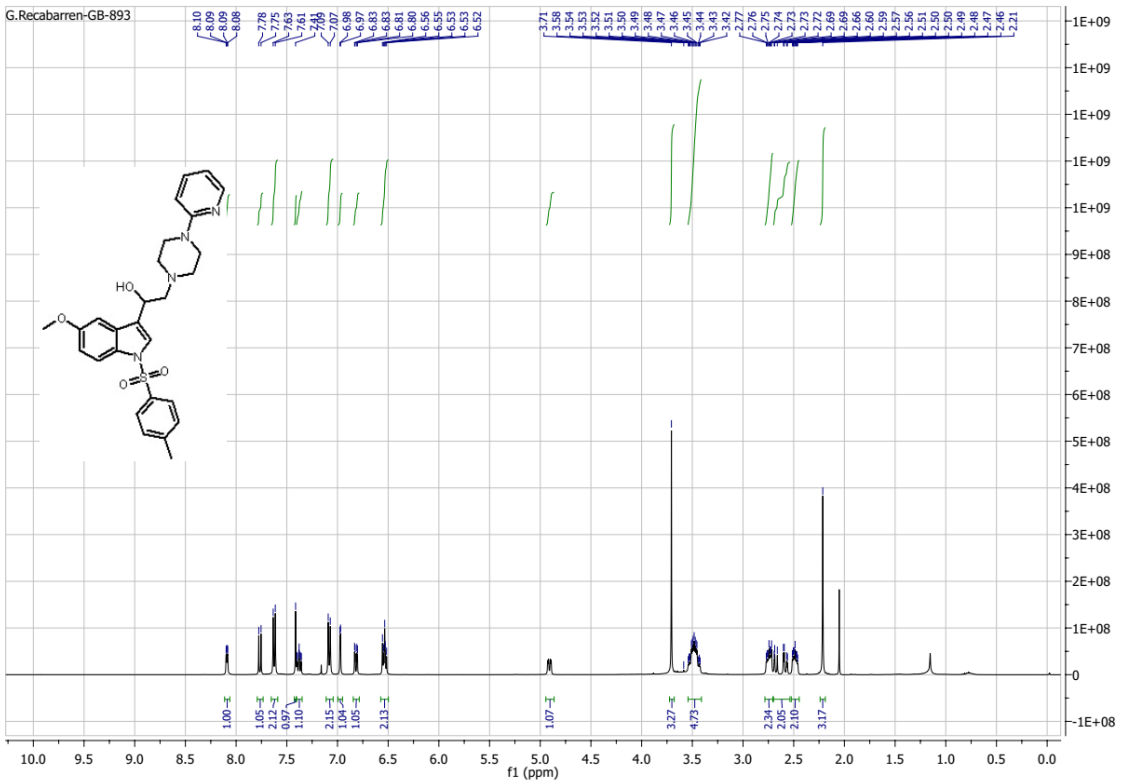
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4o**



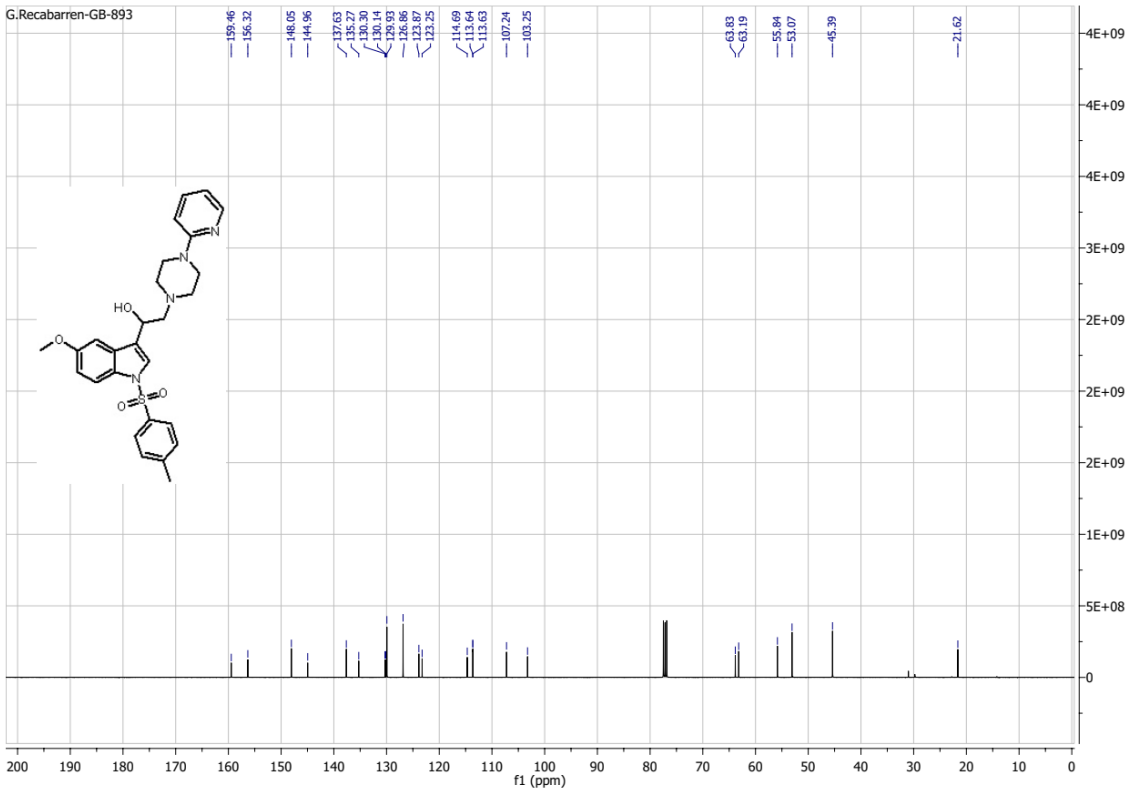
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4o**



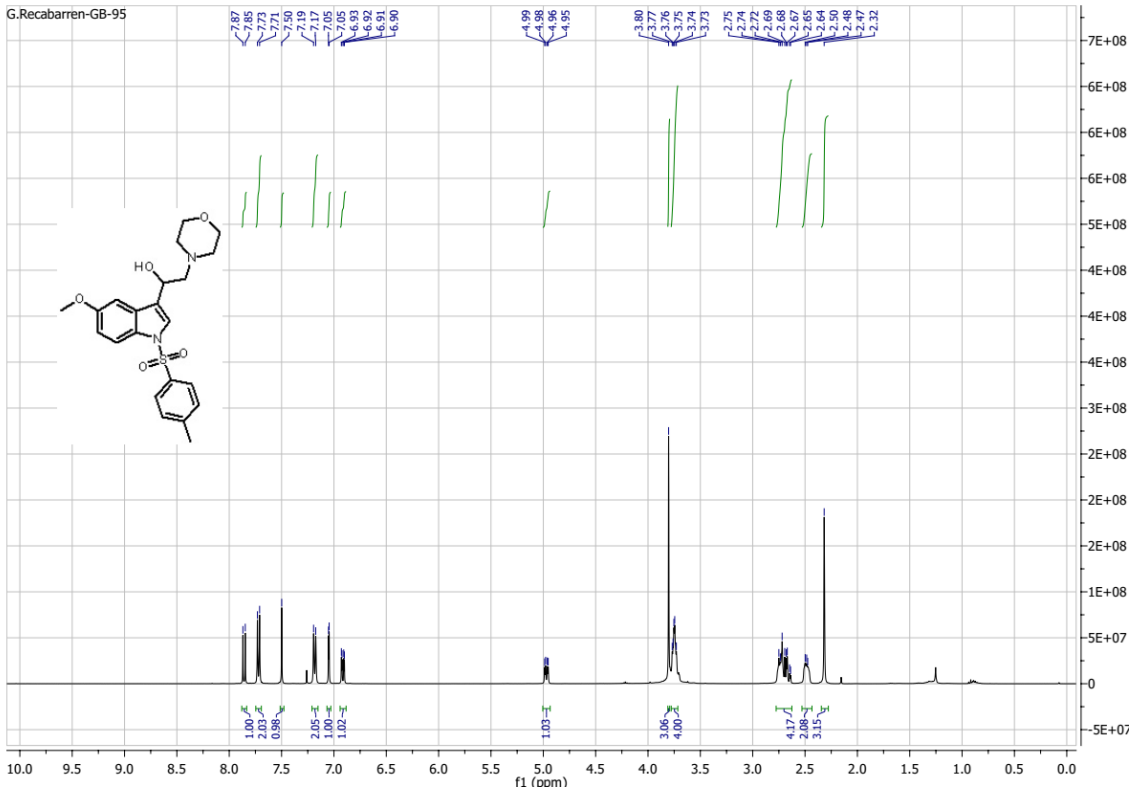
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4p**



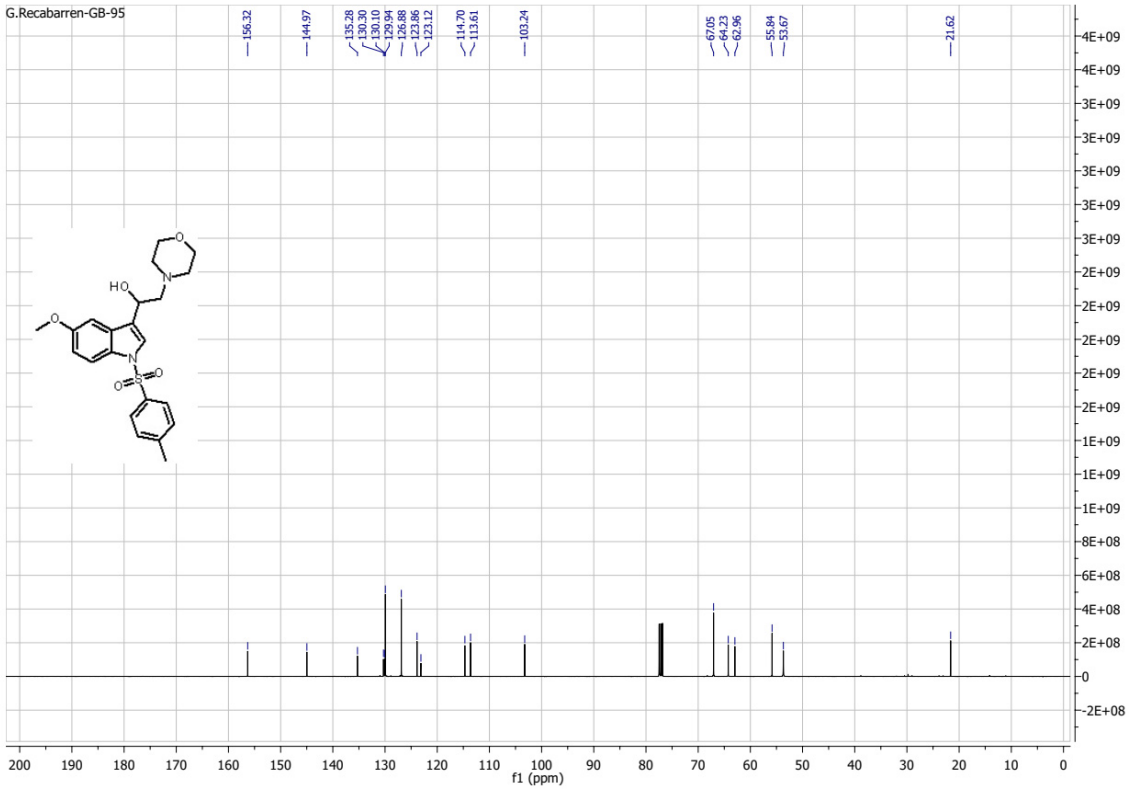
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4p**



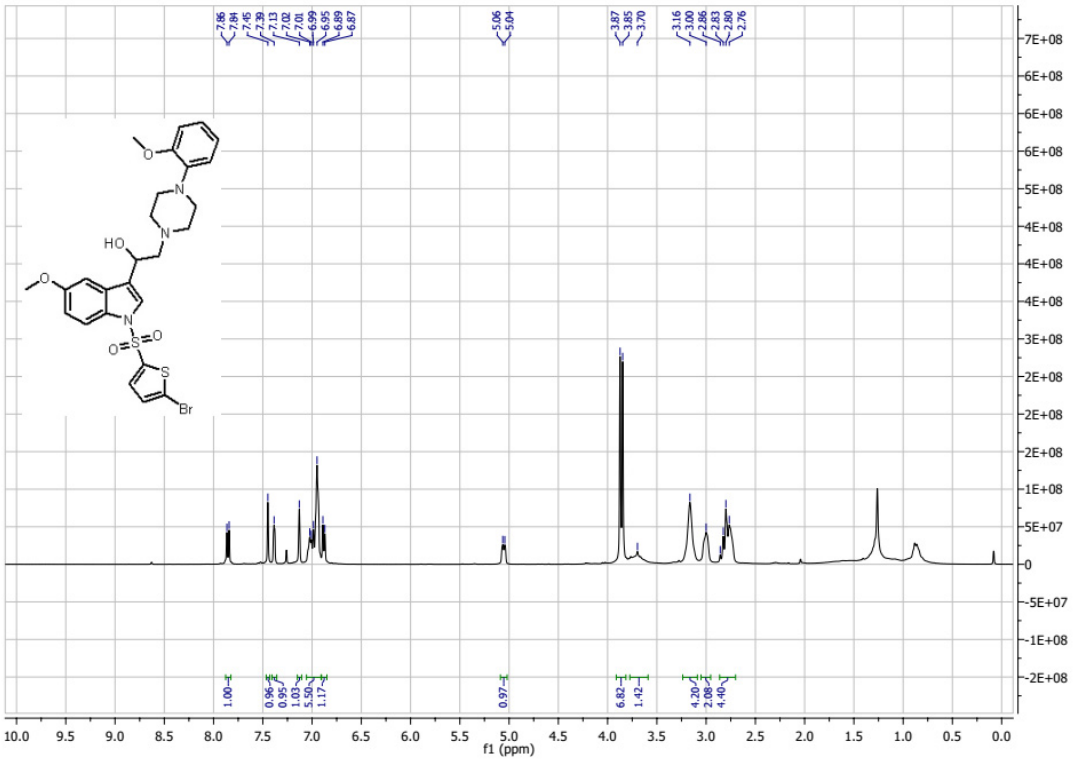
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4q**



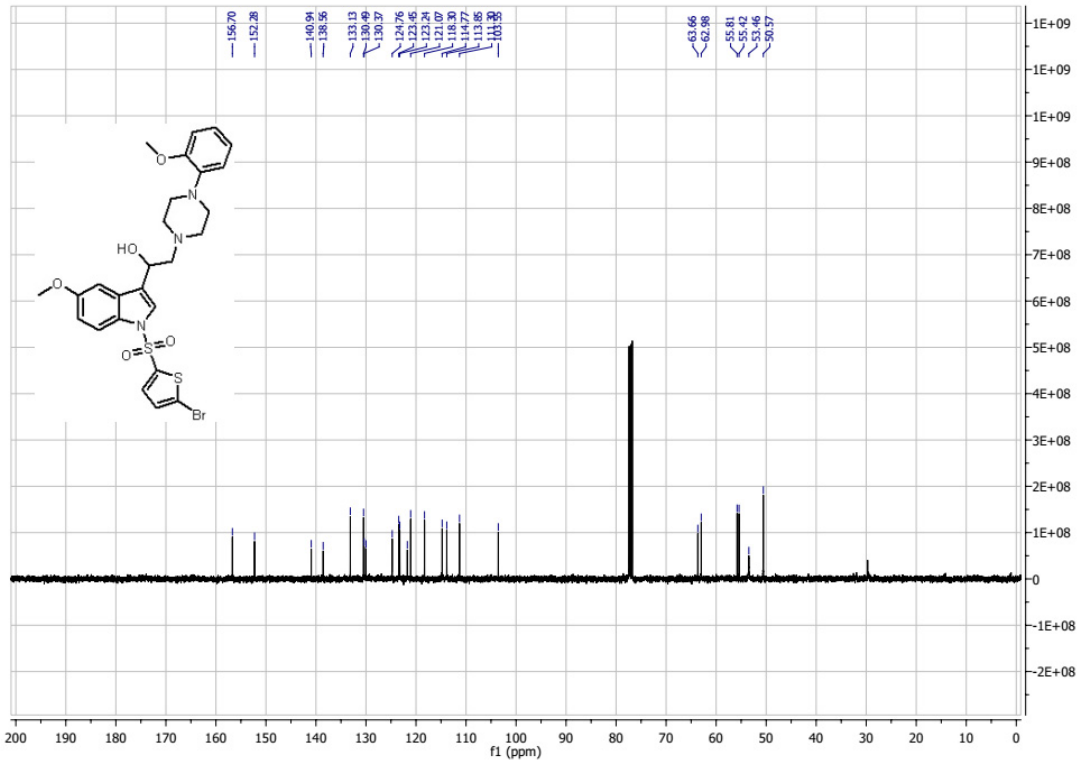
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4q**



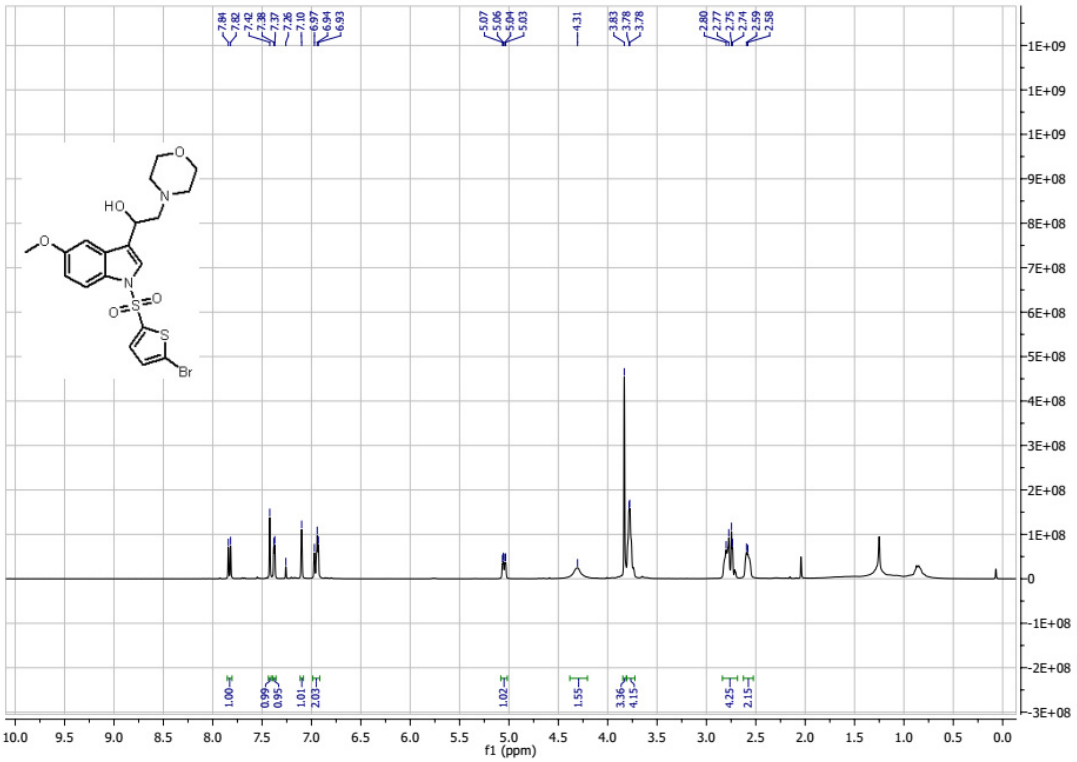
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4r**



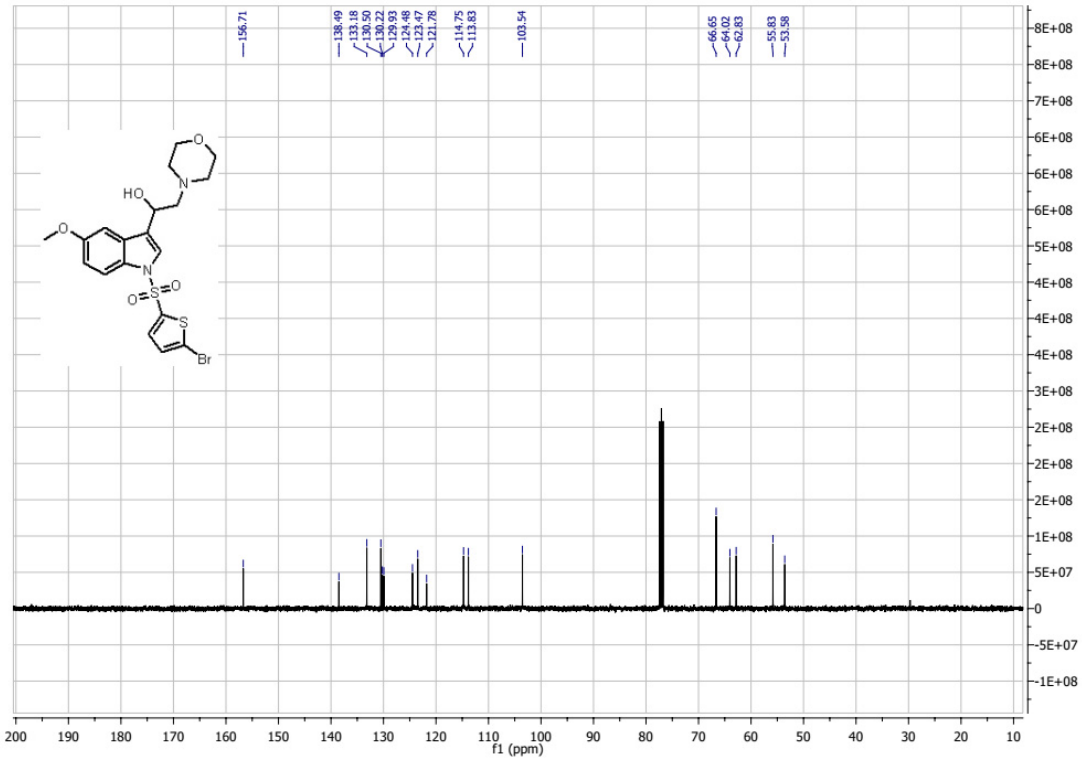
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4r**



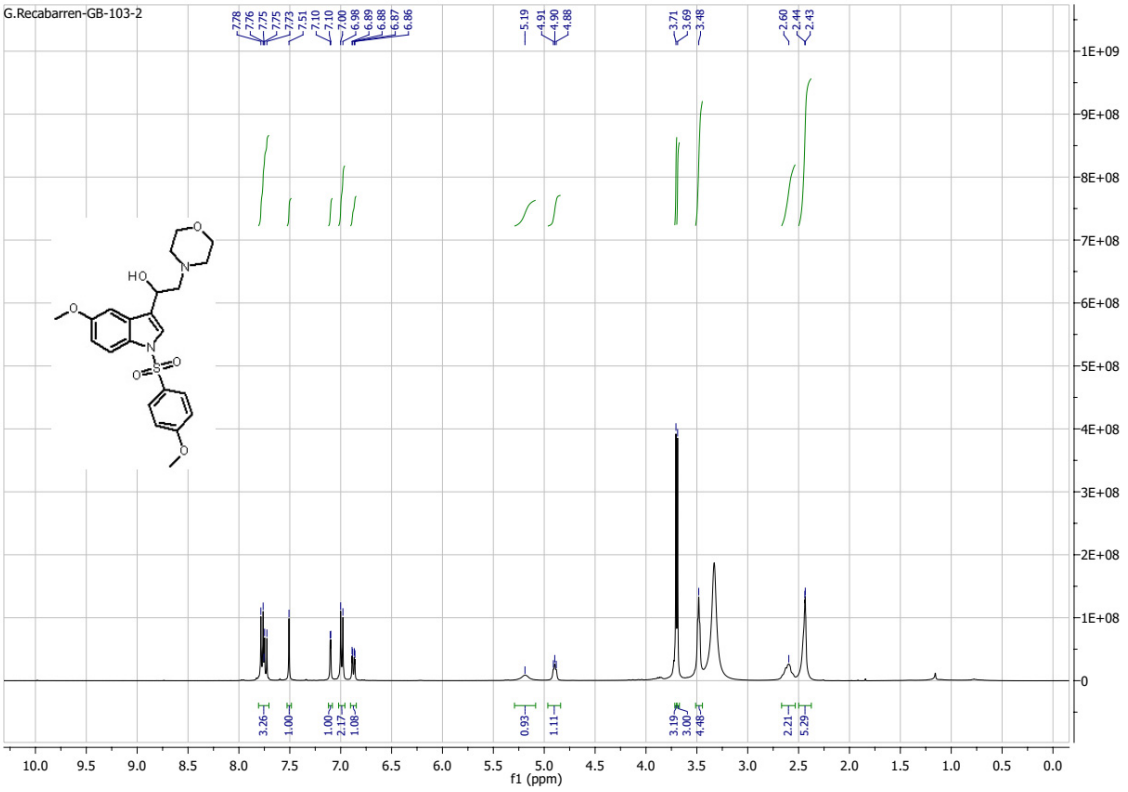
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4s**



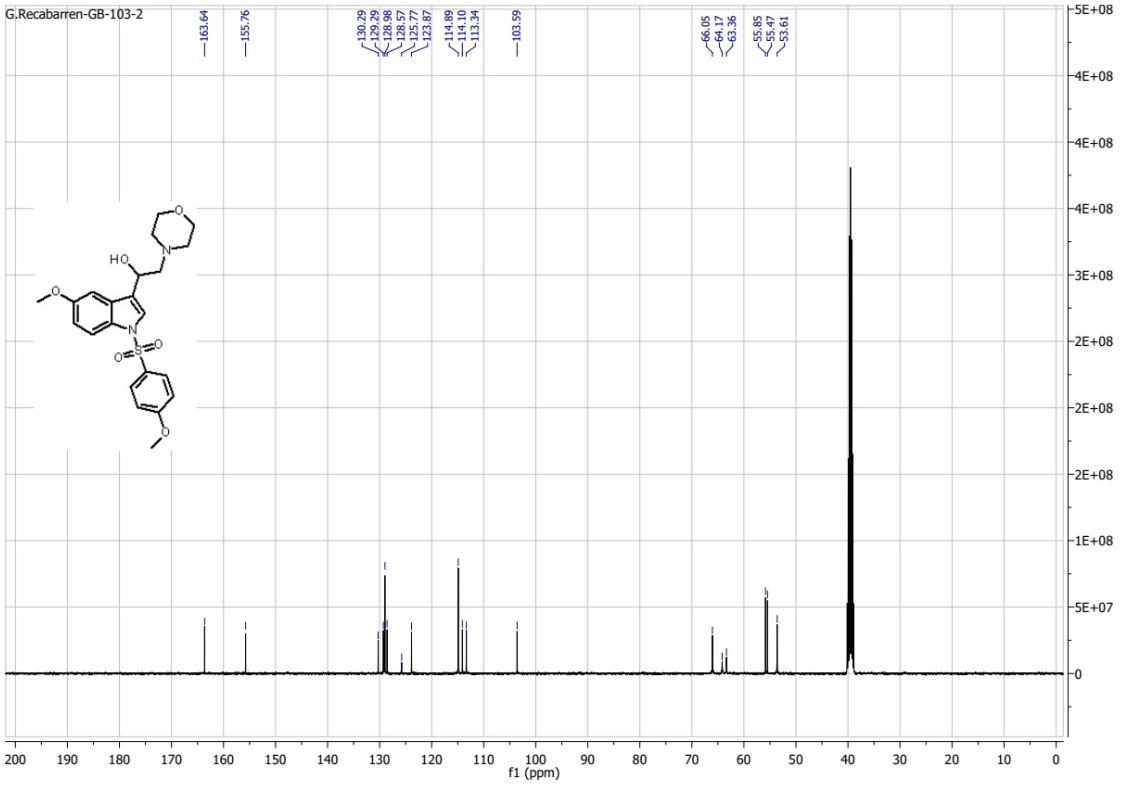
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4s**



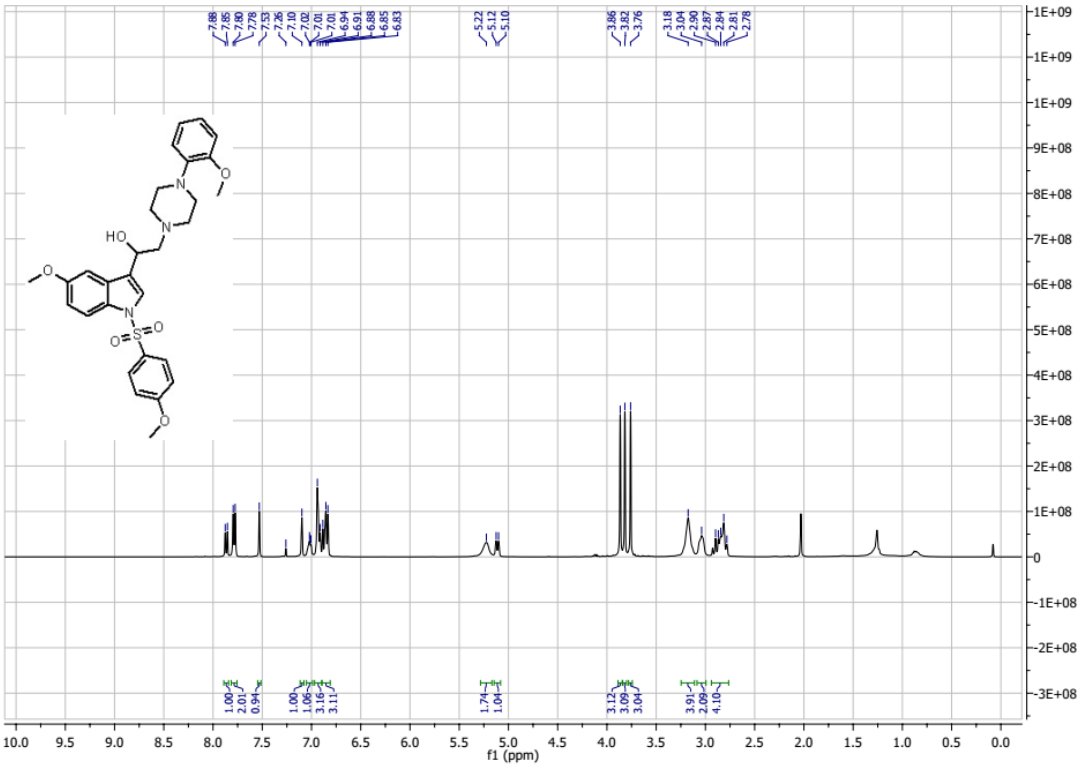
^{1}H-NMR (400.1 MHz, DMSO-d$_6$) for **4t**



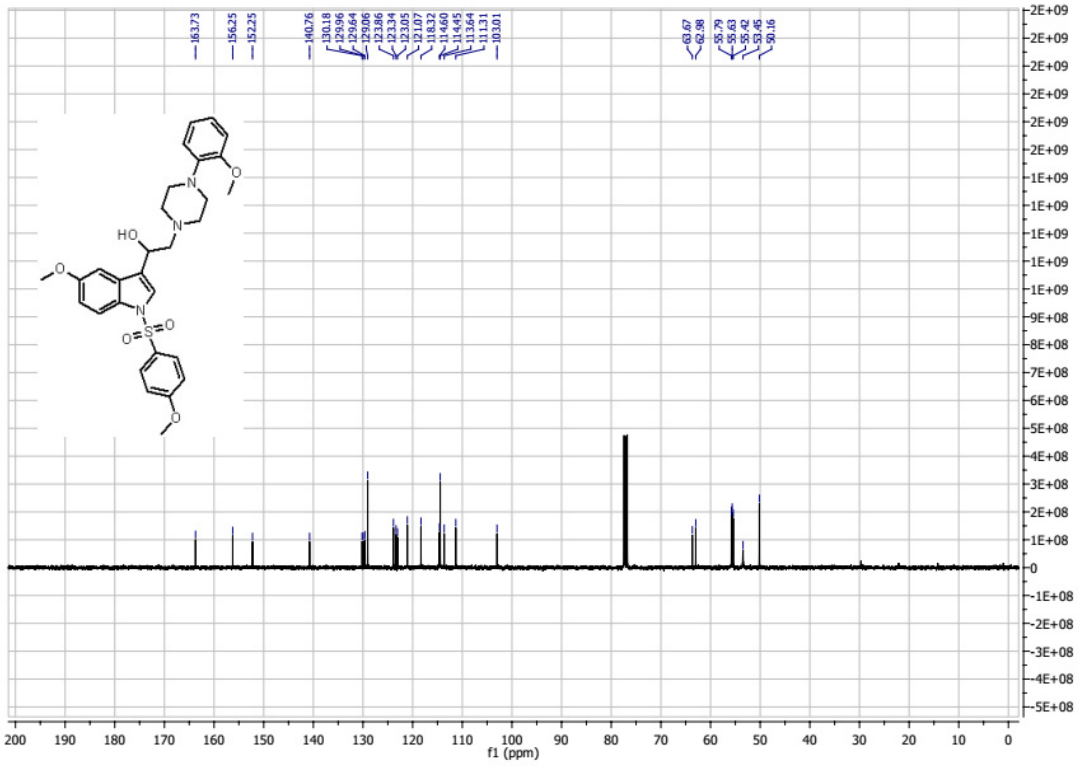
^{13}C-NMR (100.6 MHz, DMSO-d$_6$) for **4t**



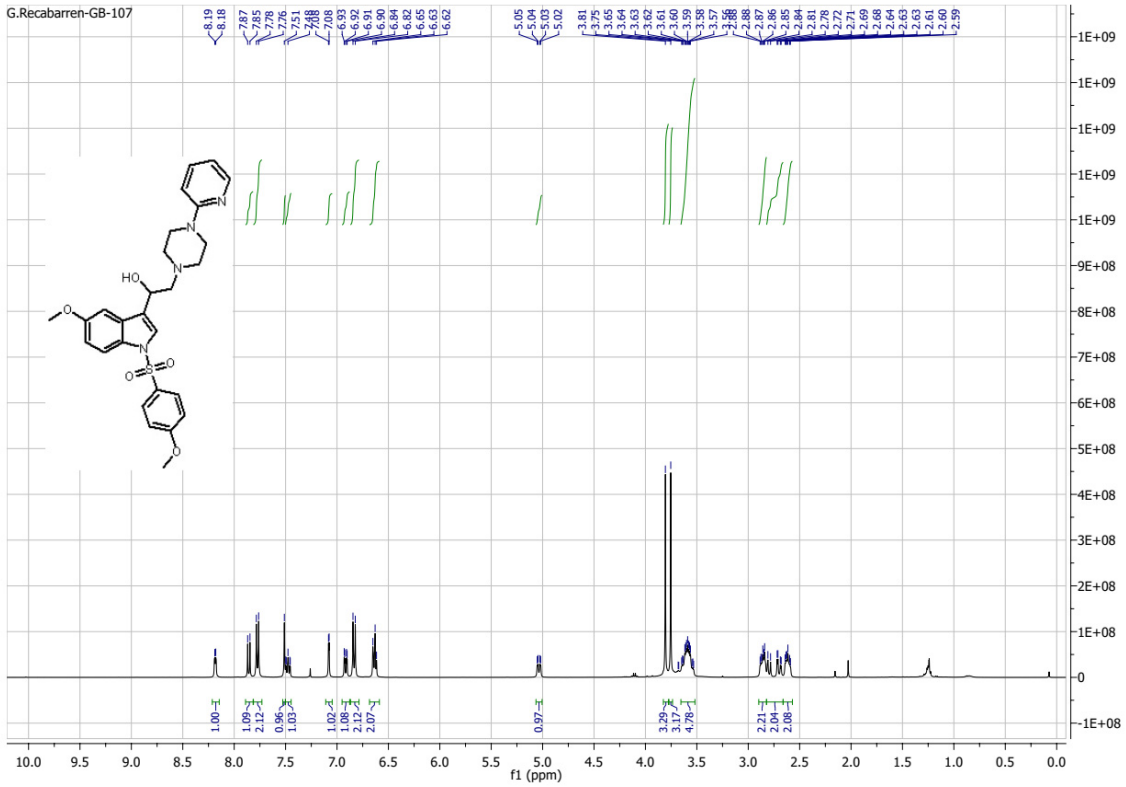
^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4u**



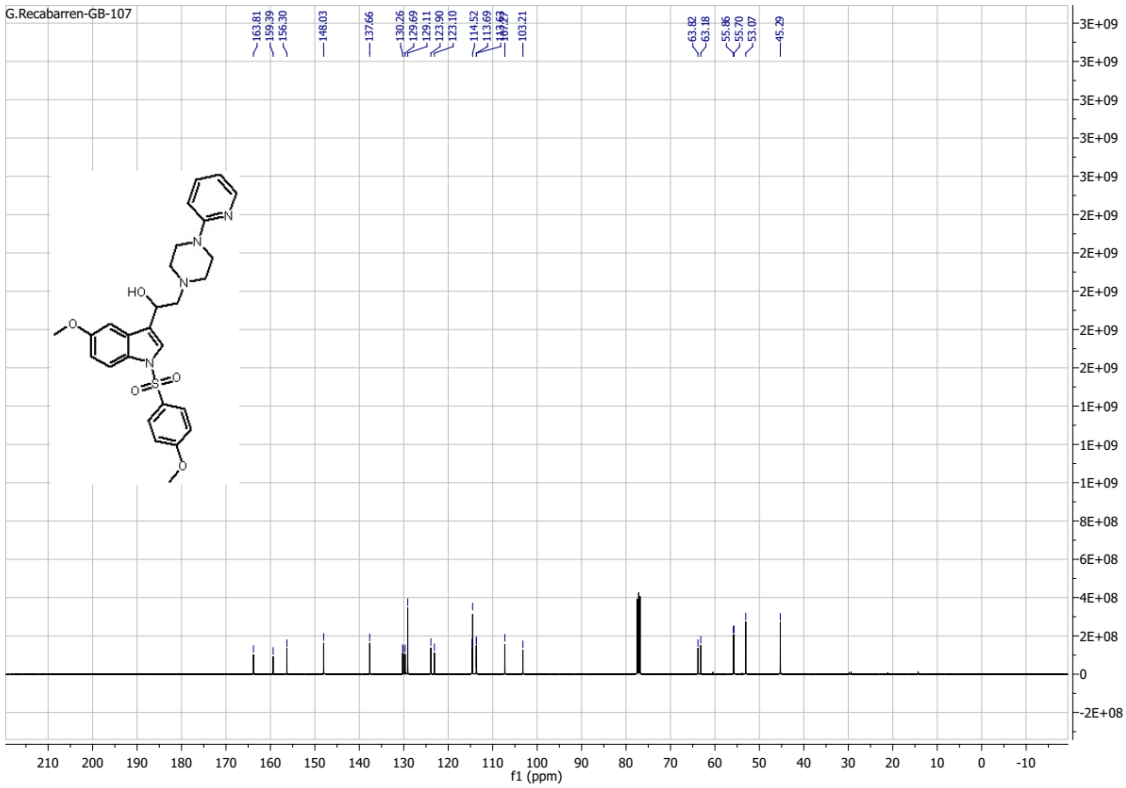
^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4u**



^{1}H-NMR (400.1 MHz, $CDCl_3$) for **4v**

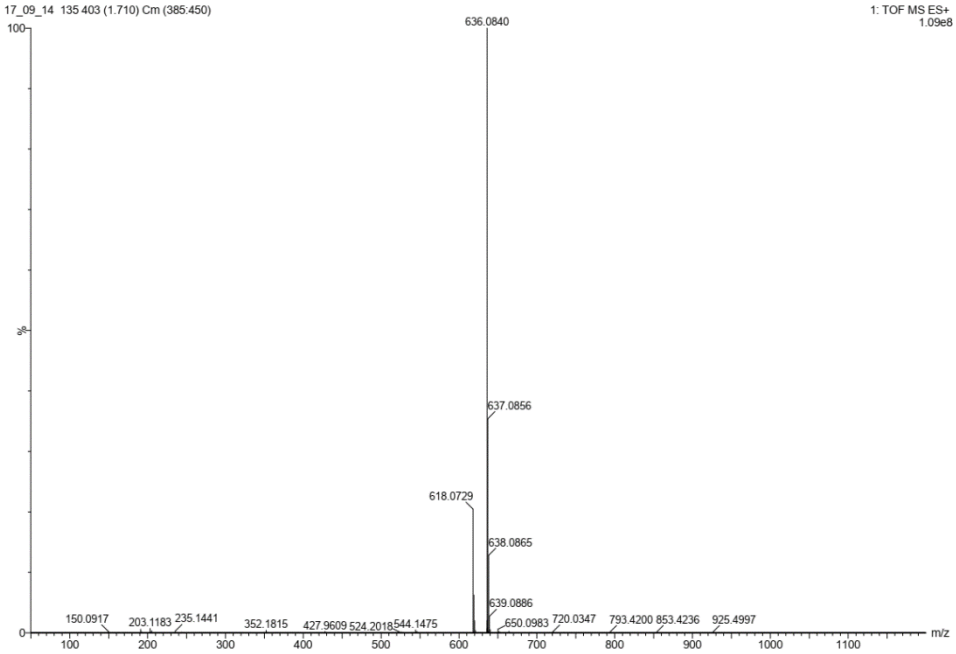


^{13}C-NMR (100.6 MHz, $CDCl_3$) for **4v**

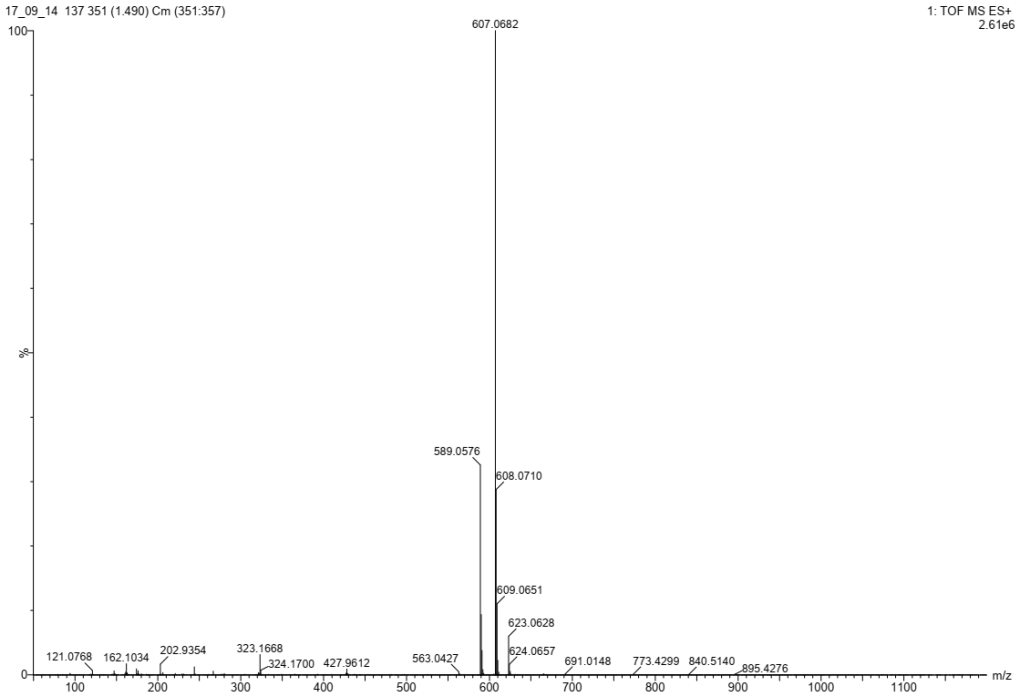


3. High resolution mass spectra of final compounds.

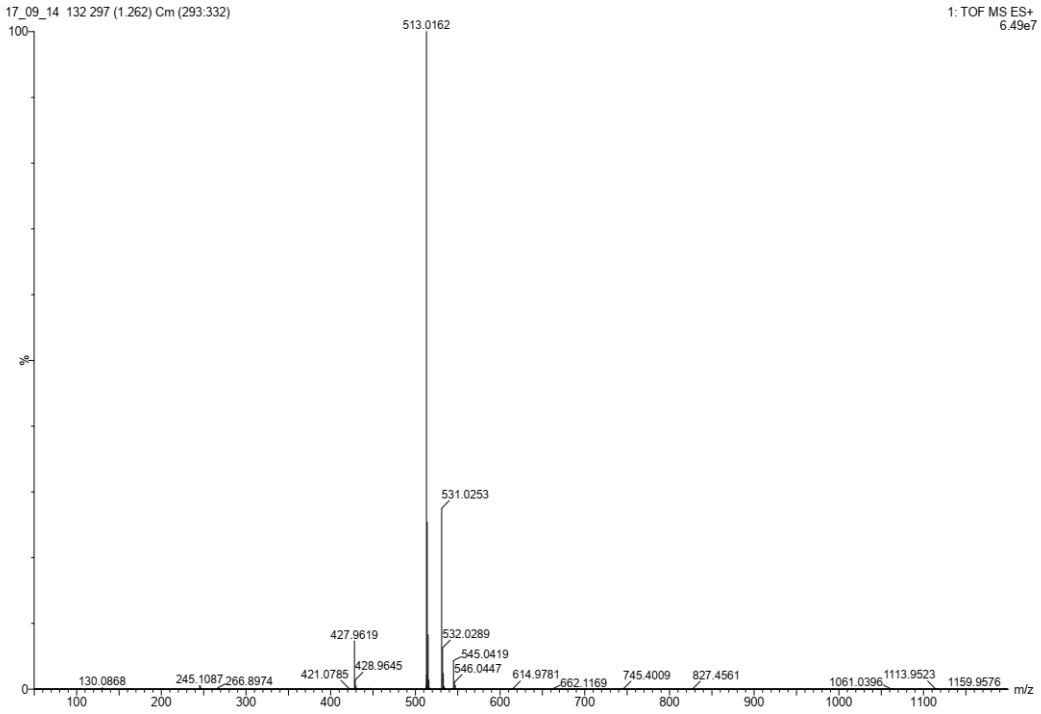
HRMS for **4a**



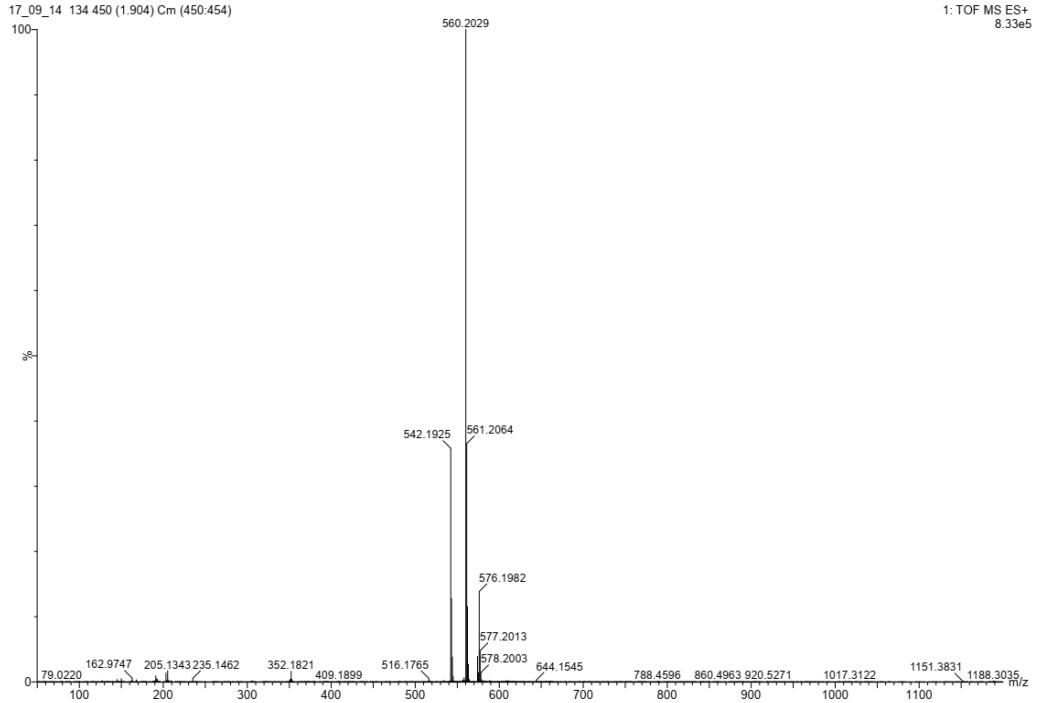
HRMS for **4b**



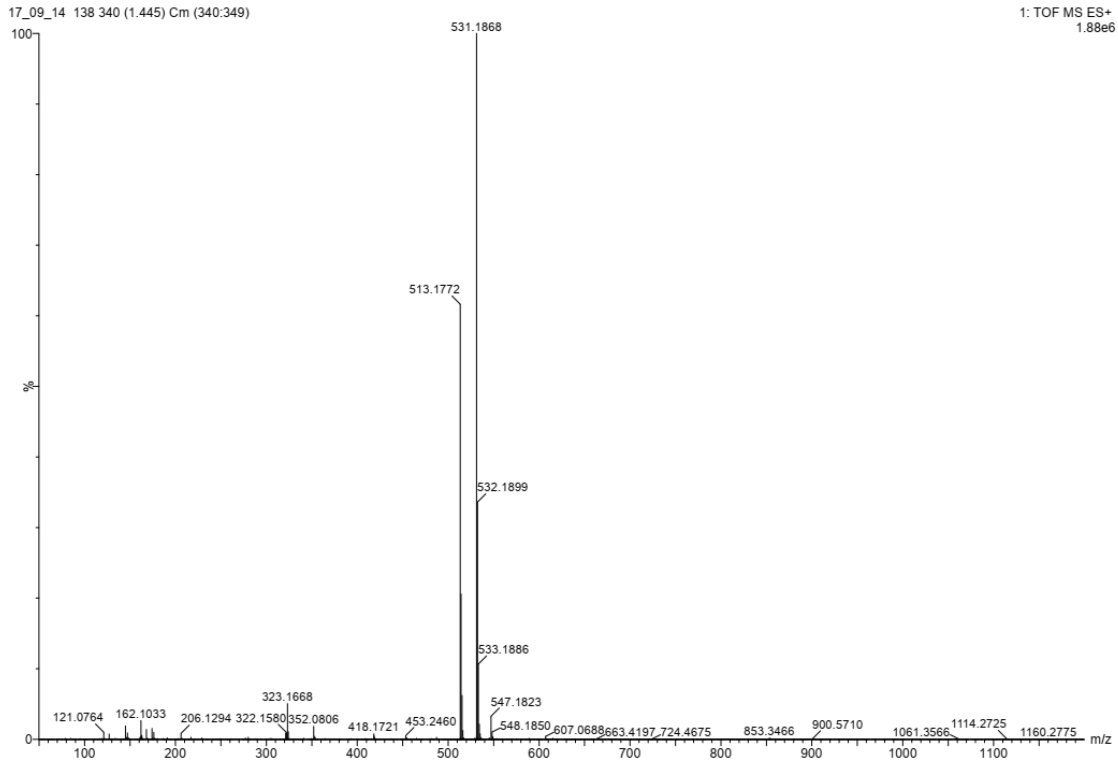
HRMS for **4c**



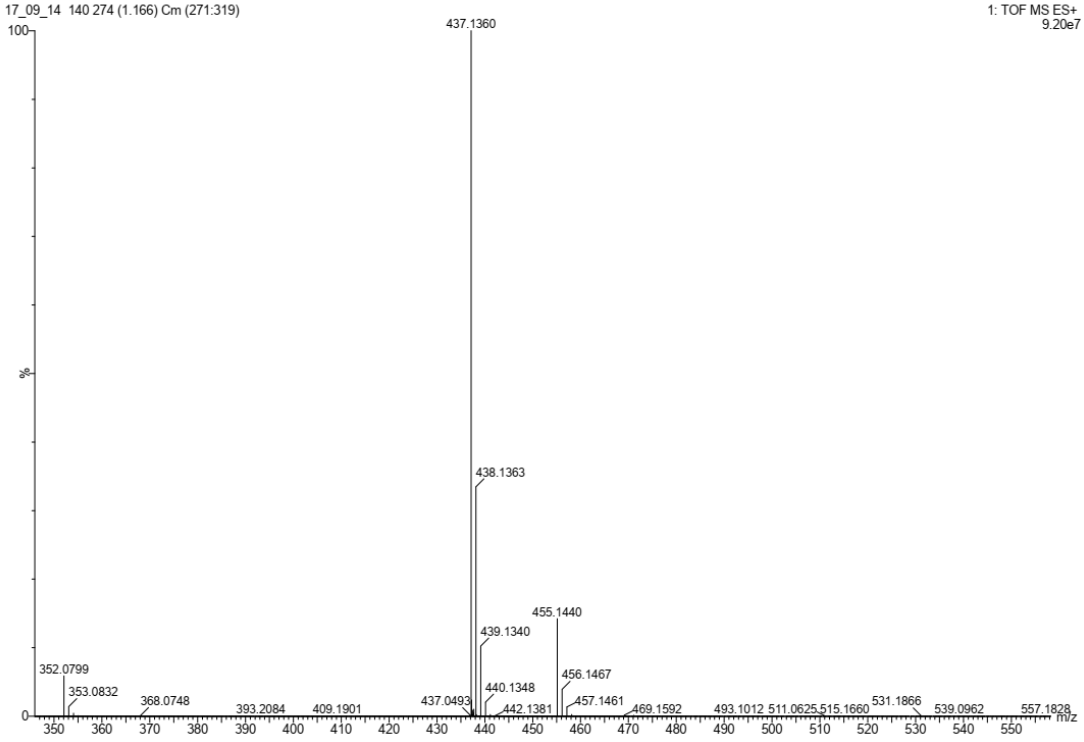
HRMS for **4d**



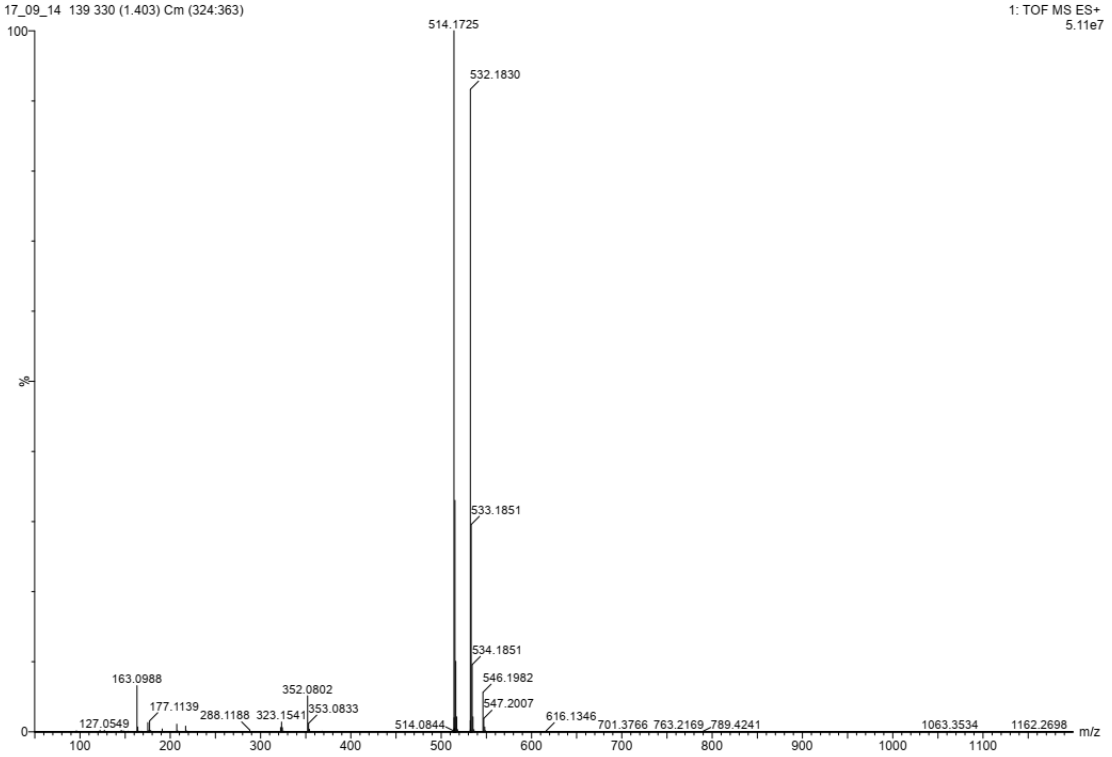
HRMS for **4e**



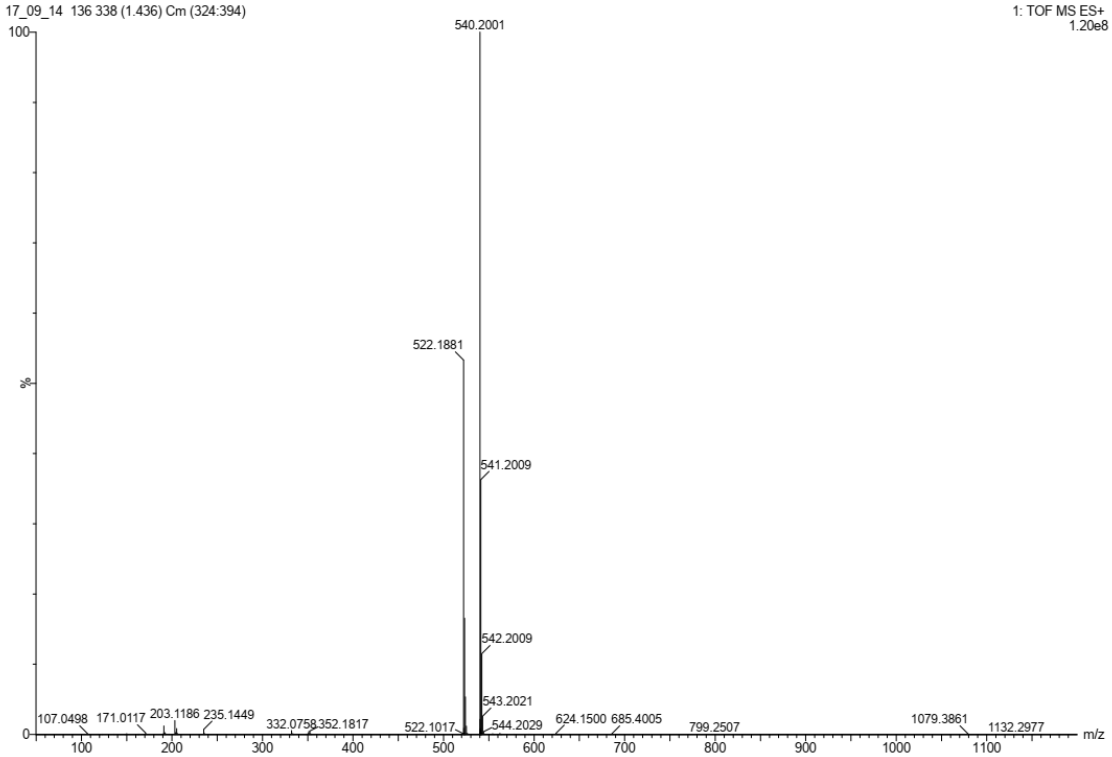
HRMS for **4f**



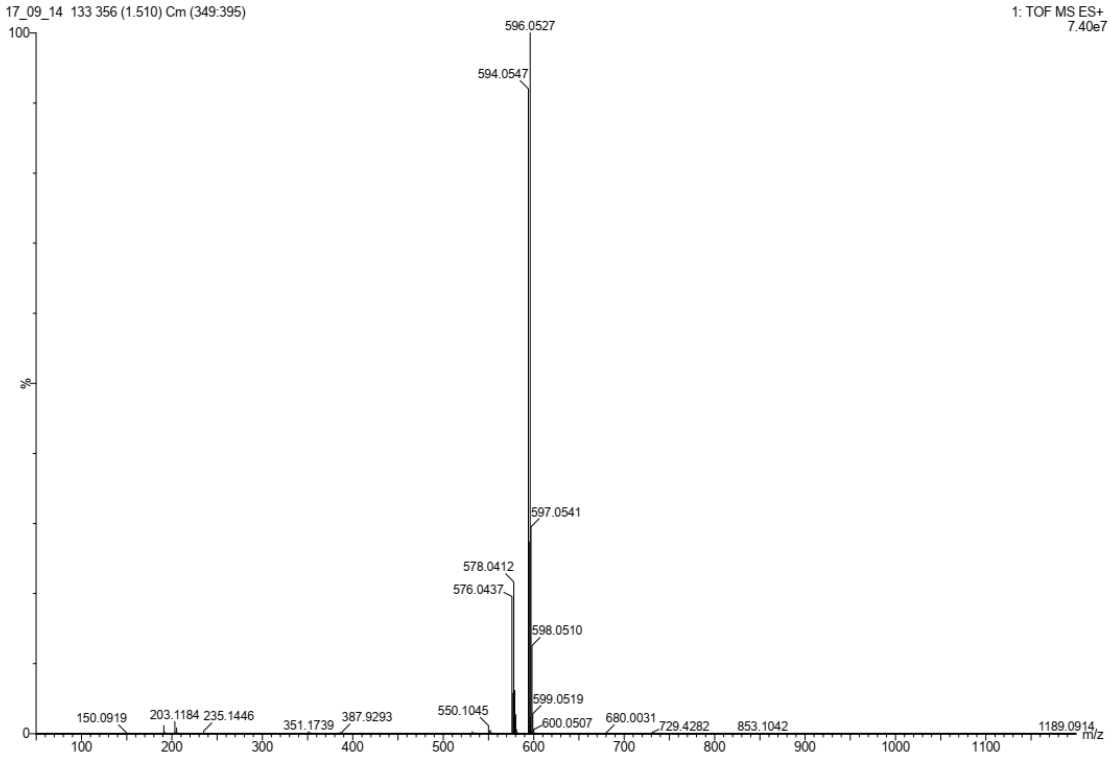
HRMS for **4g**



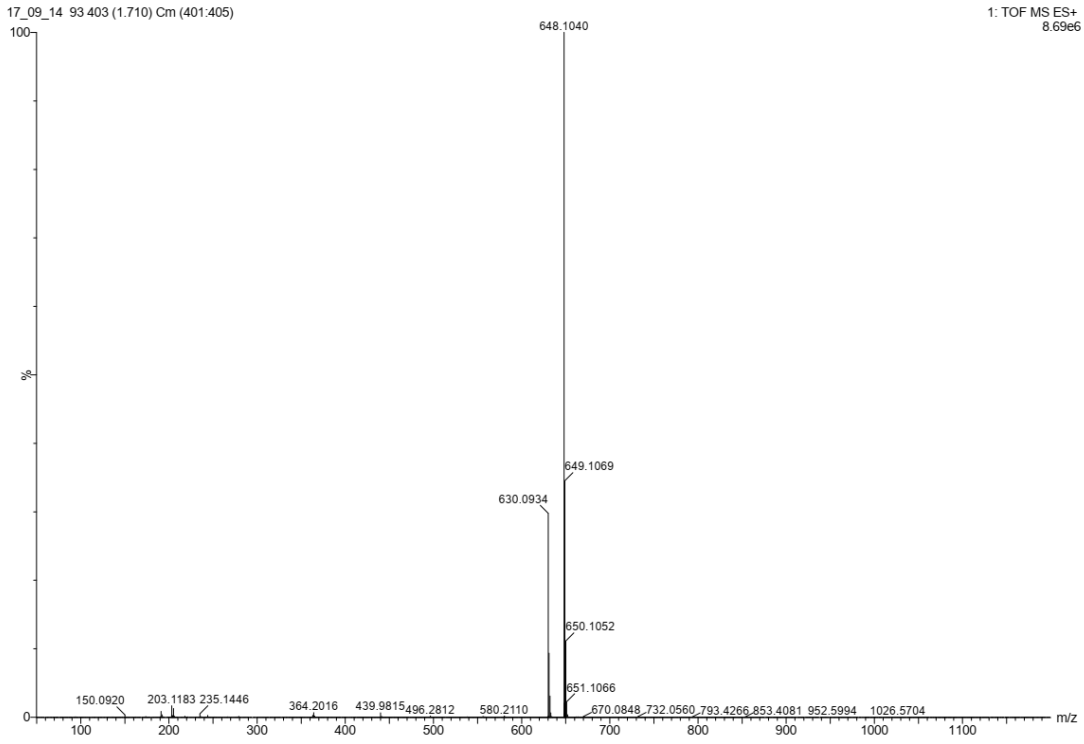
HRMS for **4h**



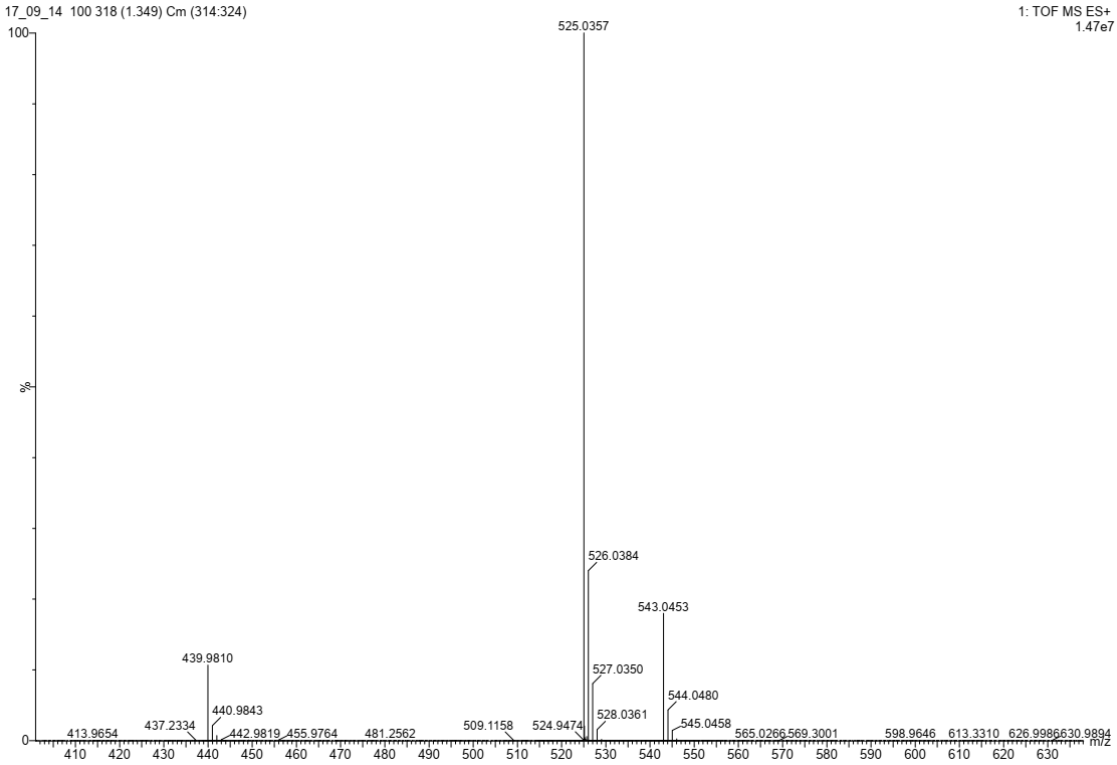
HRMS for **4i**



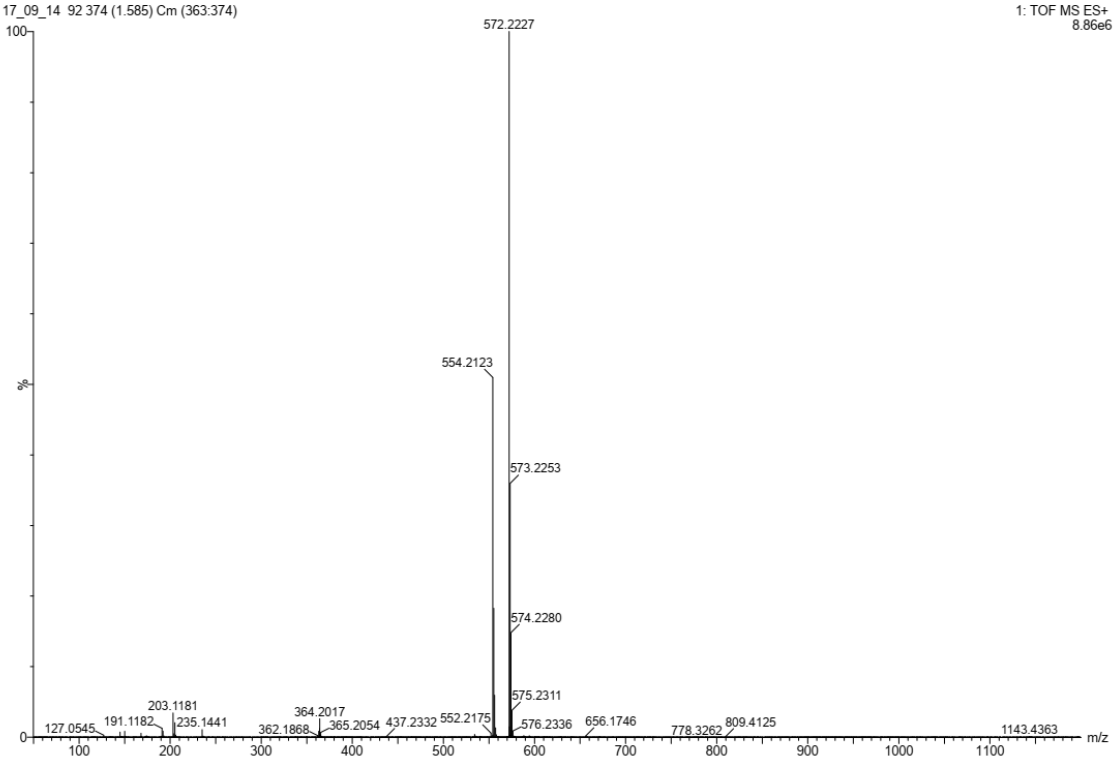
HRMS for **4j**



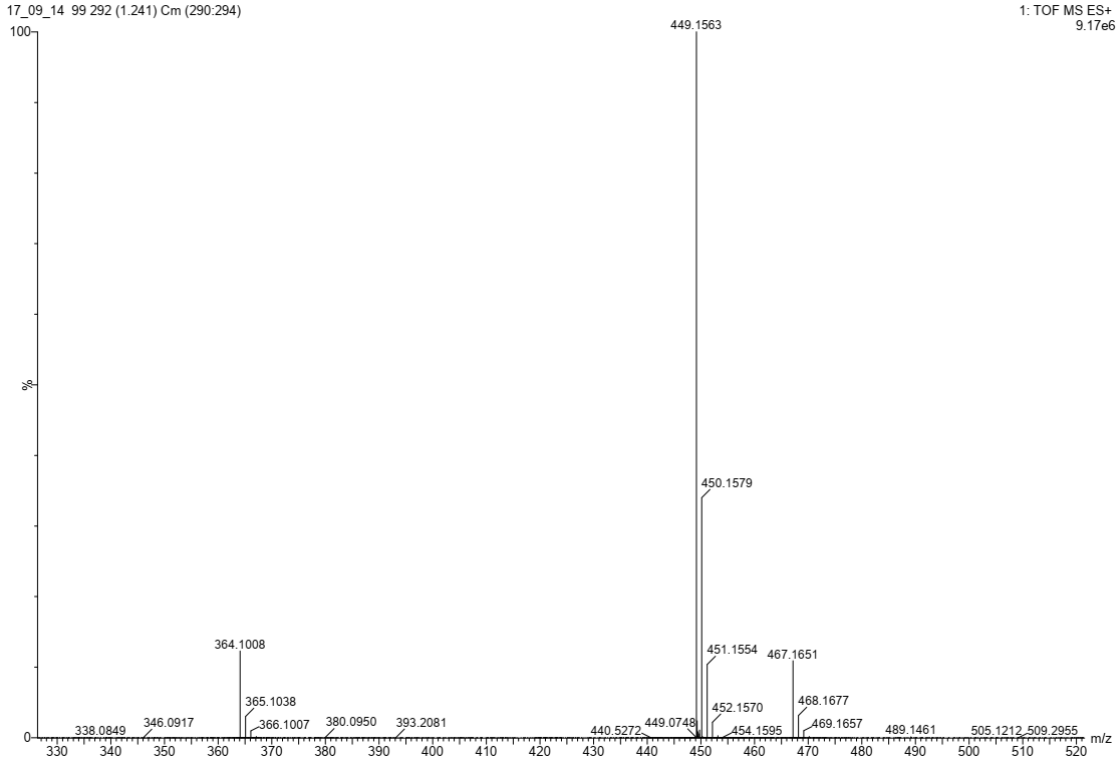
HRMS for **4k**



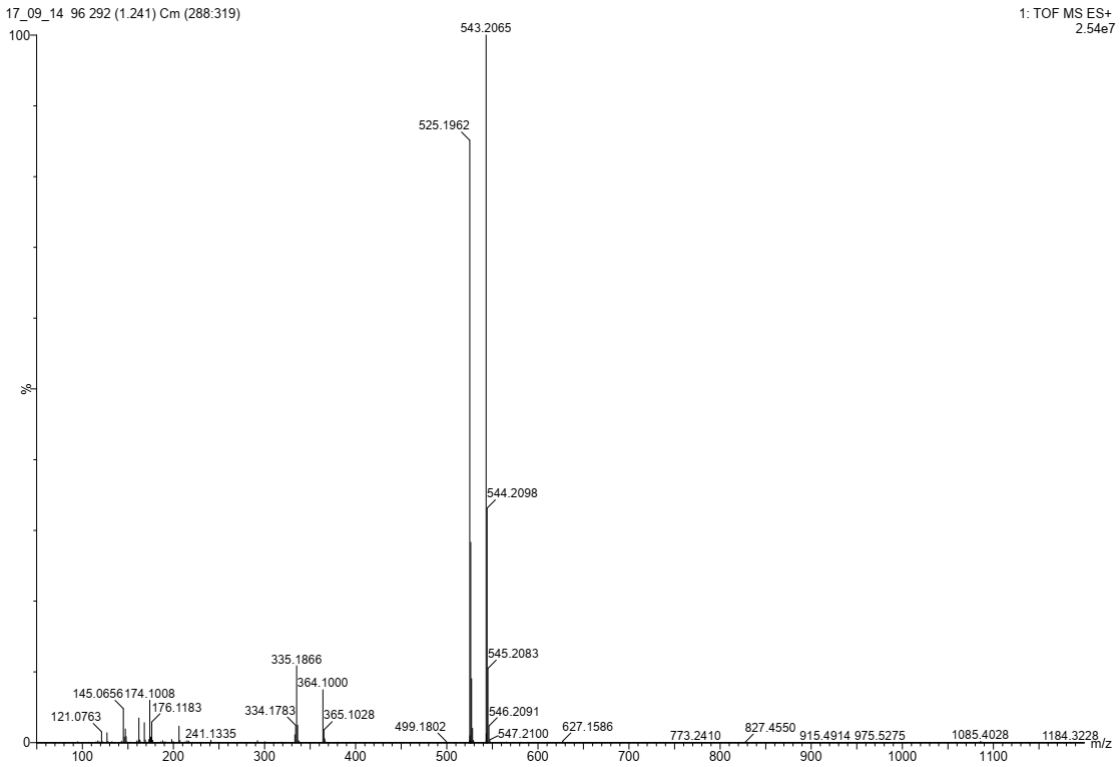
HRMS for **4l**



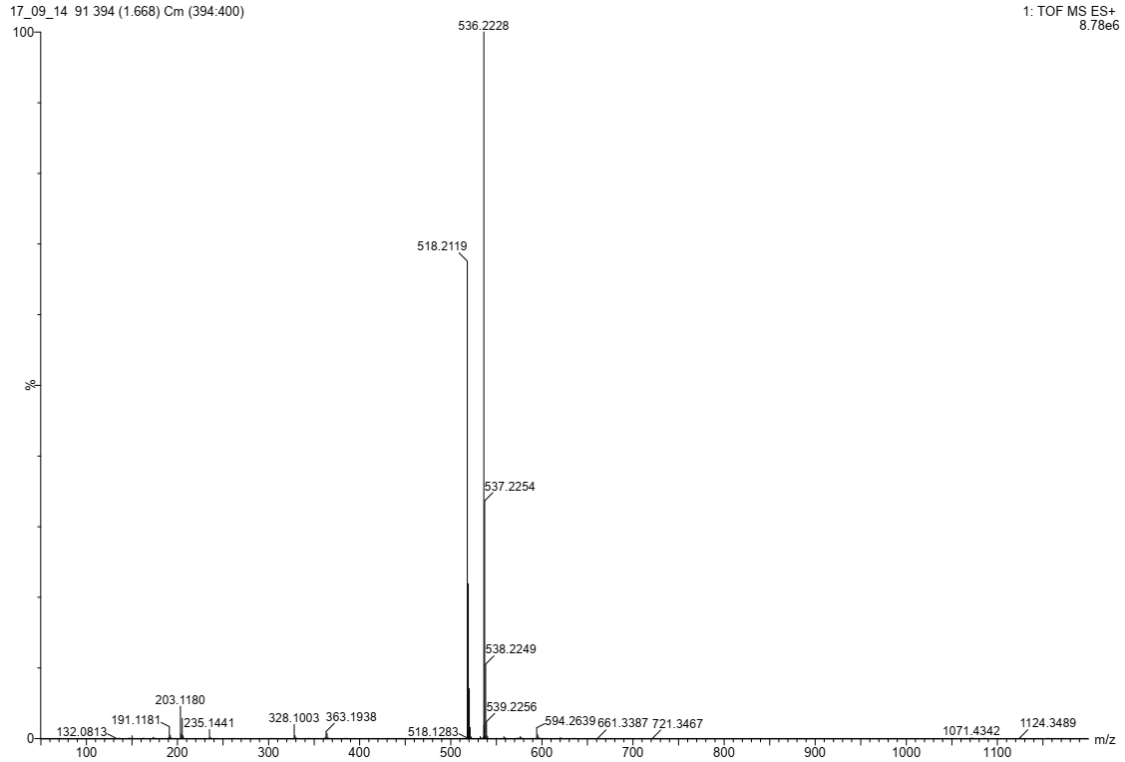
HRMS for **4m**



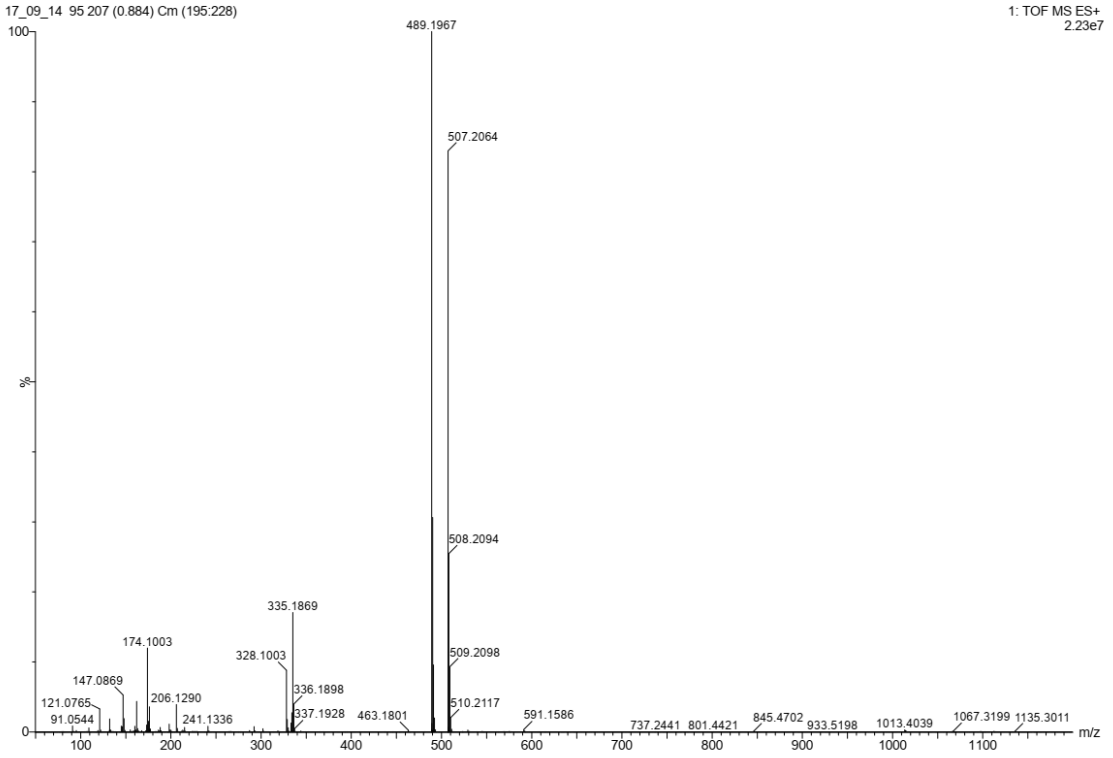
HRMS for **4n**



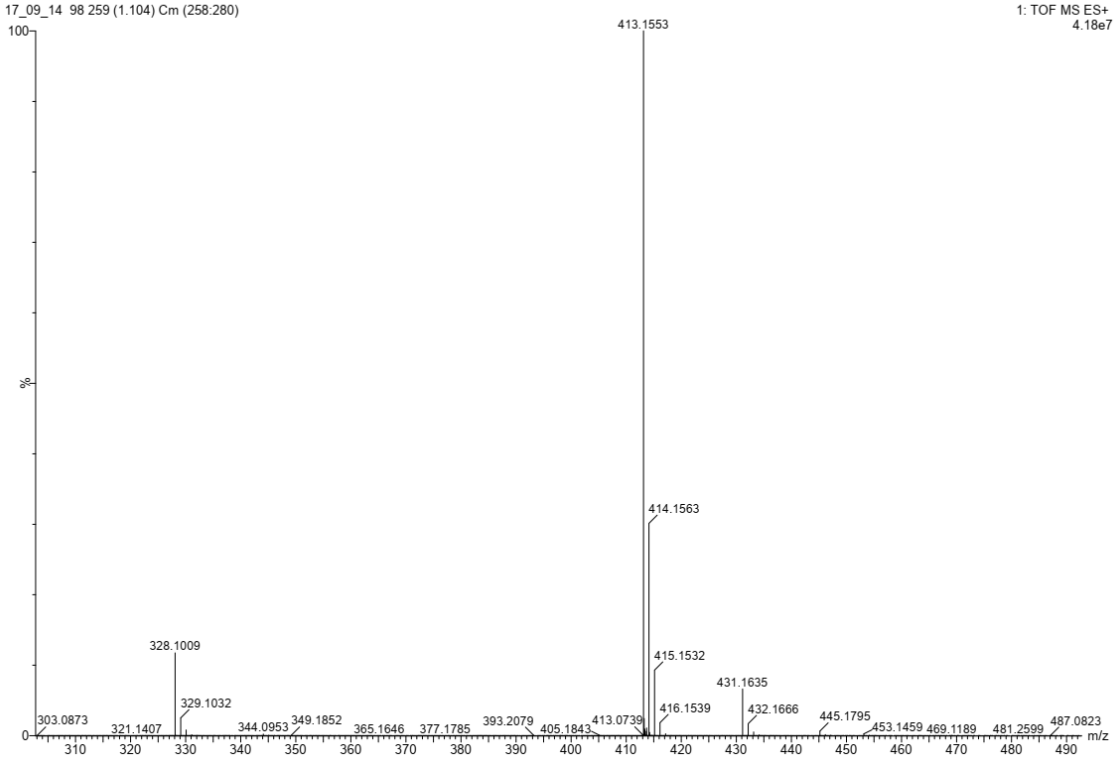
HRMS for **4o**



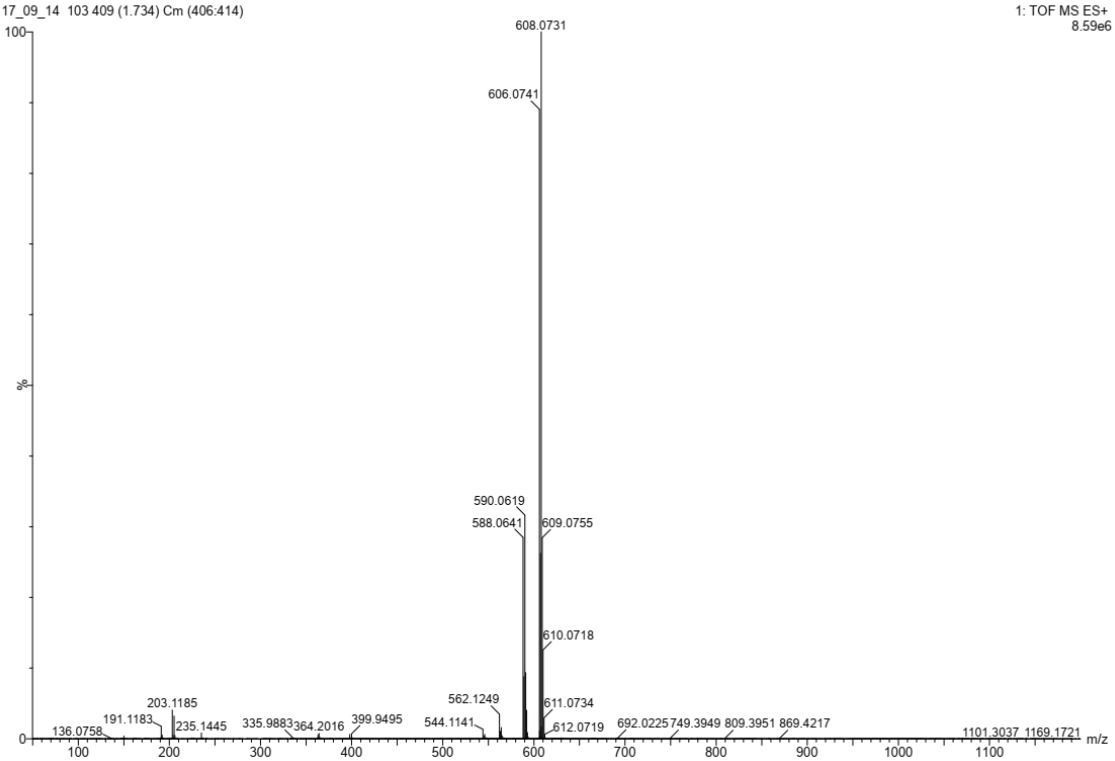
HRMS for **4p**



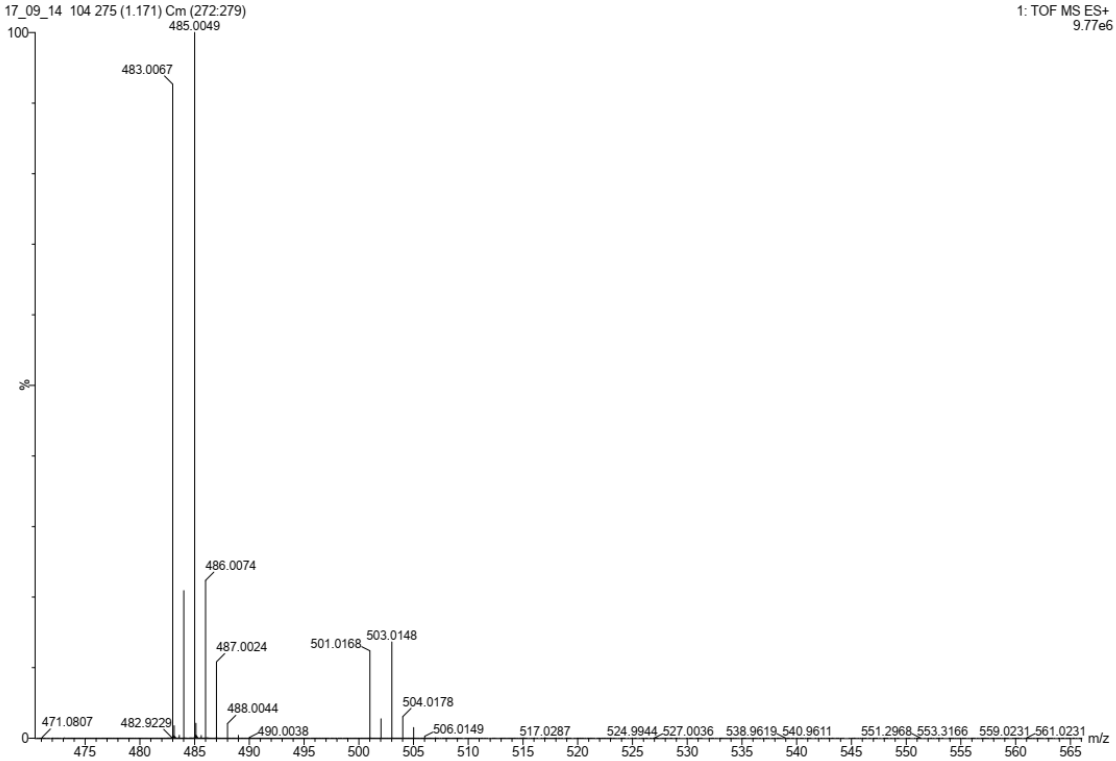
HRMS for **4q**



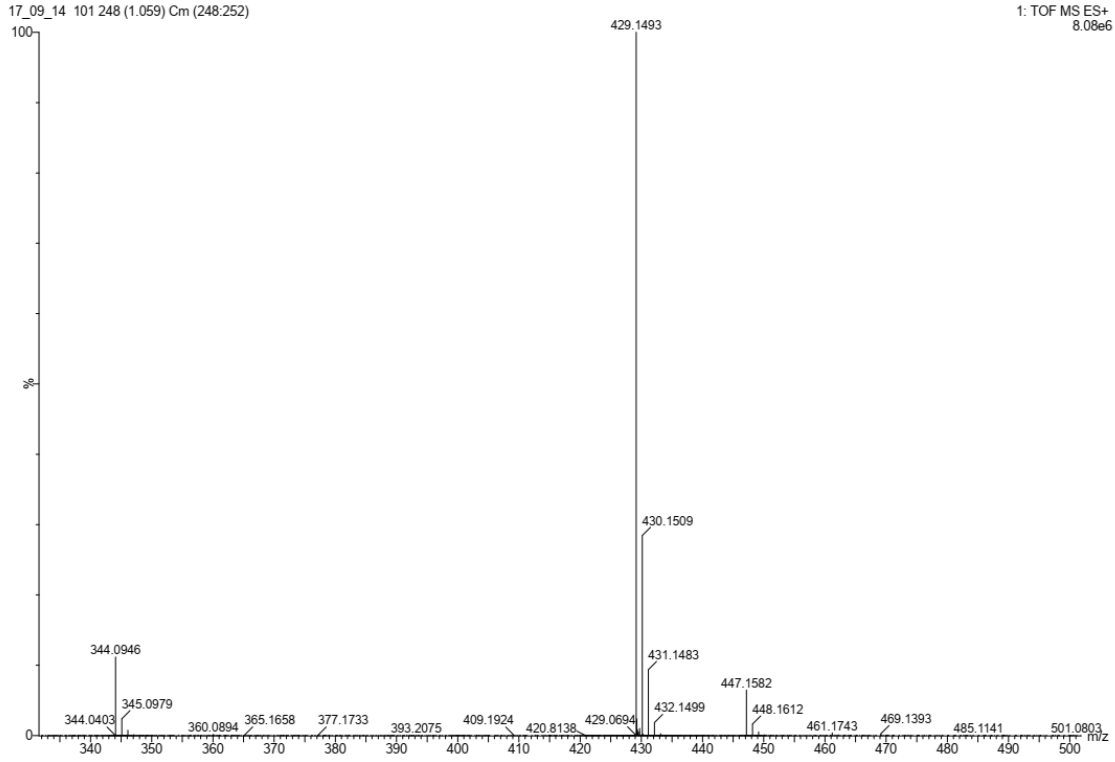
HRMS for **4r**



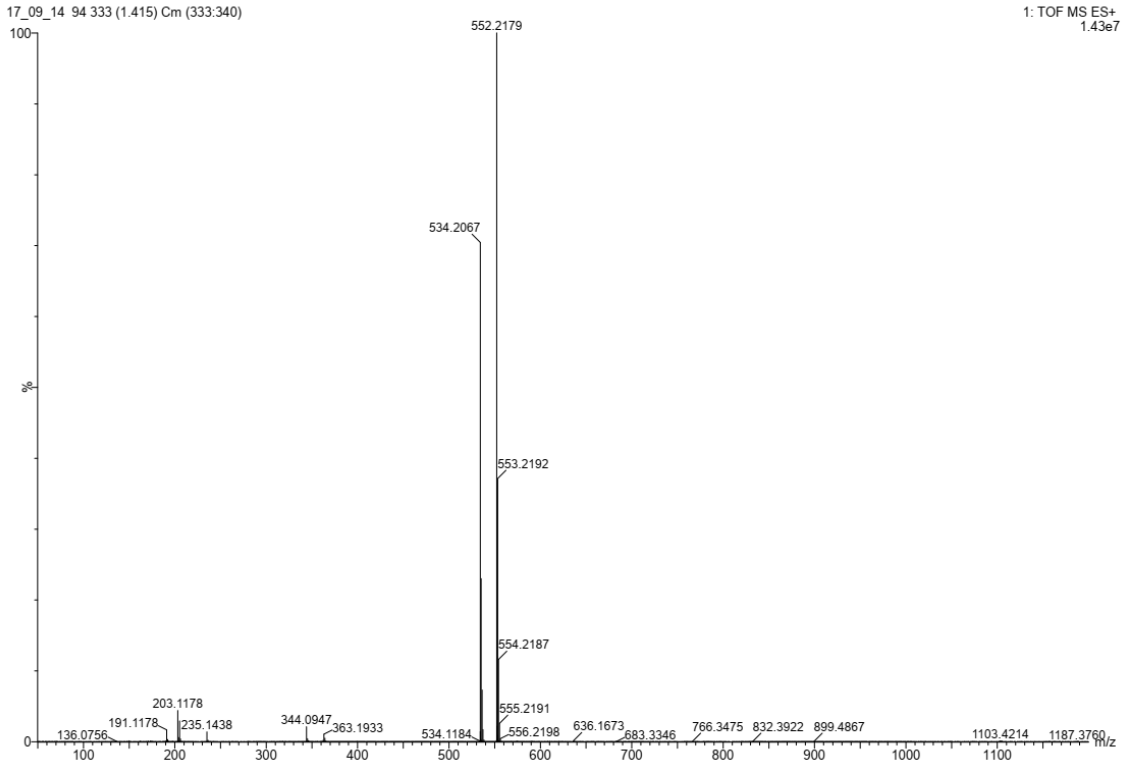
HRMS for **4s**



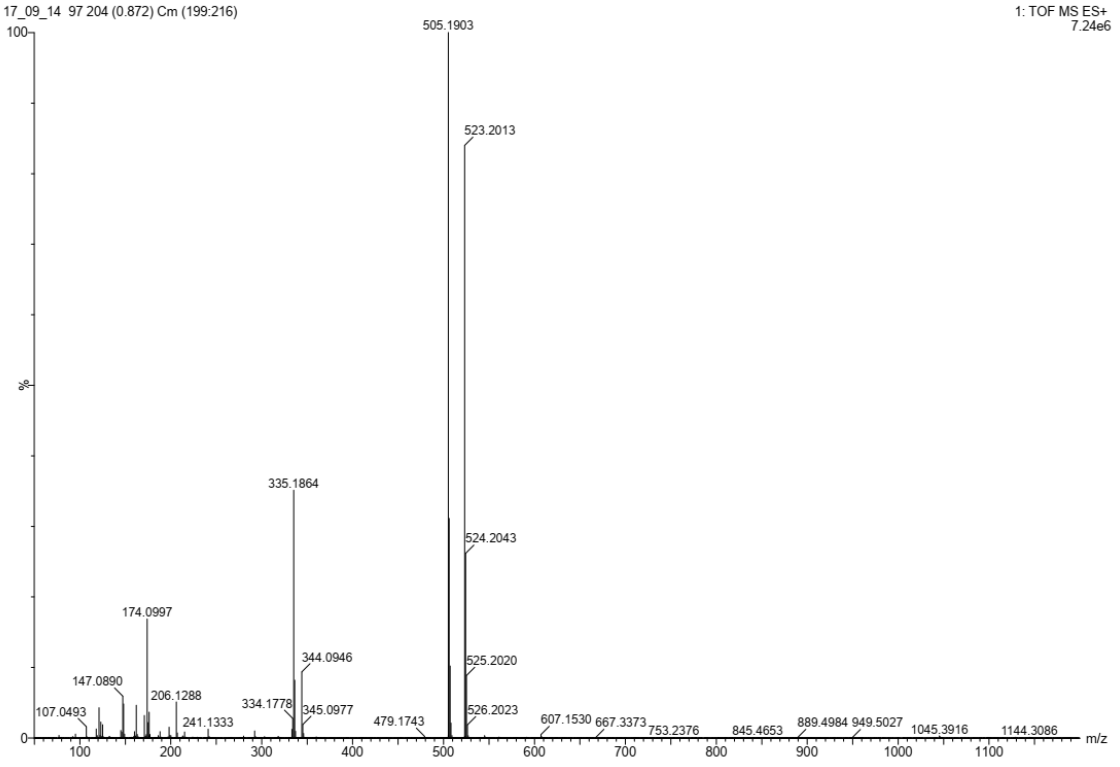
HRMS for **4t**



HRMS for **4u**

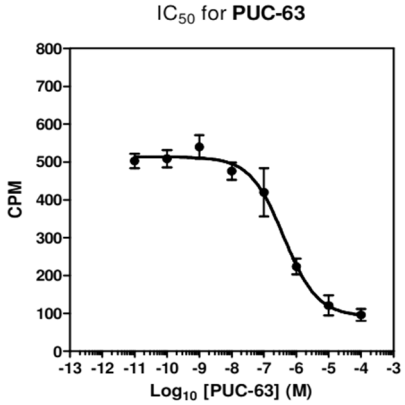


HRMS for **4v**

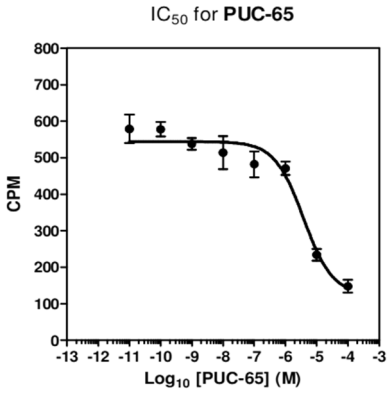


4. IC_{50} graphs for compounds 4a-4v and clozapine in 5-HT_6 radioligand binding assay.

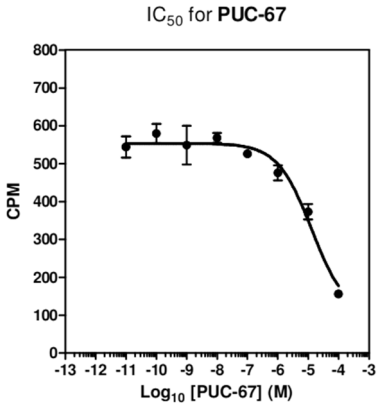
IC_{50} graph for **4a**



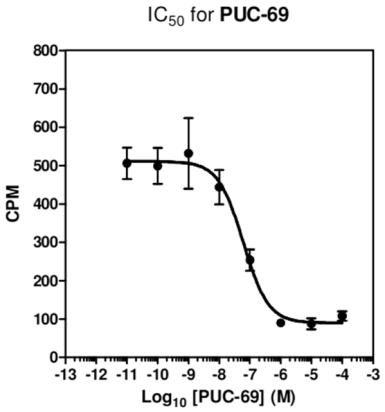
IC_{50} graph for **4b**



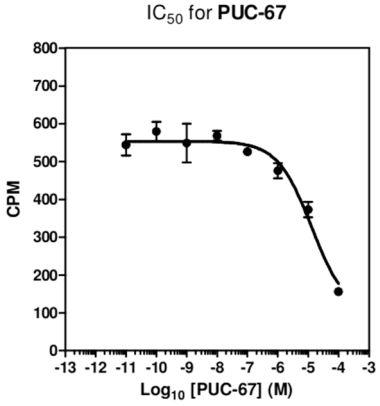
IC_{50} graph for **4c**



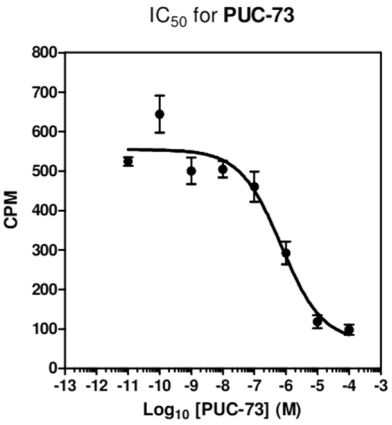
IC_{50} graph for **4d**



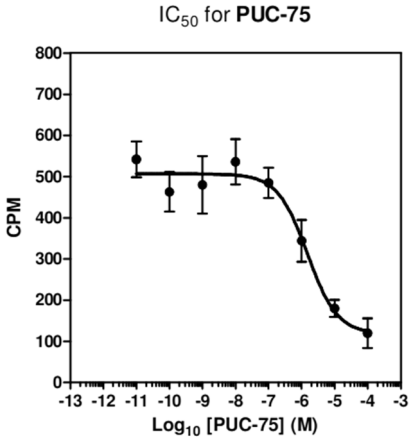
IC_{50} graph for **4e**



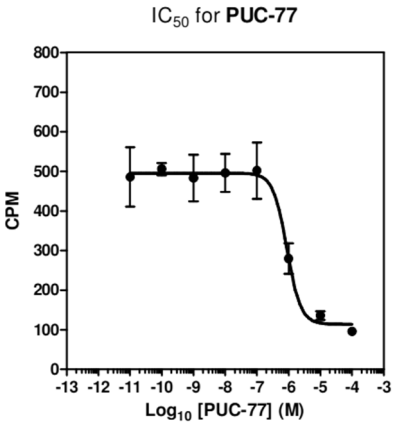
IC_{50} graph for **4f**



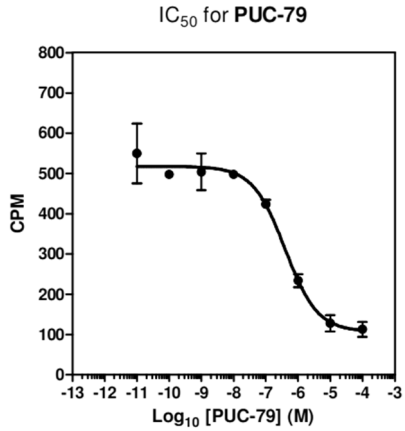
IC50 graph for **4g**



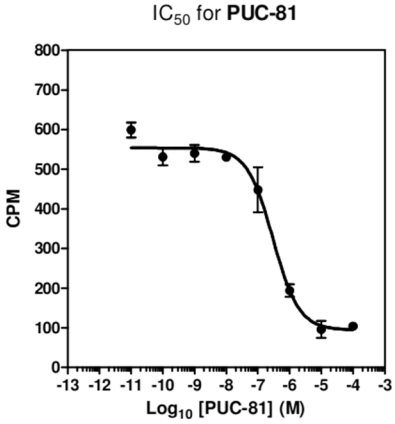
IC50 graph for **4h**



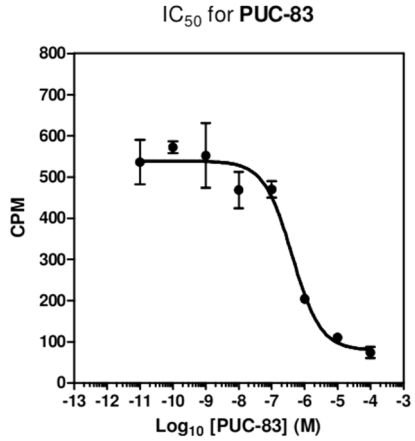
IC50 graph for **4i**



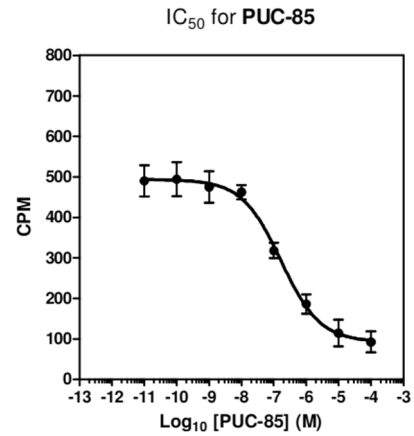
IC50 graph for **4j**



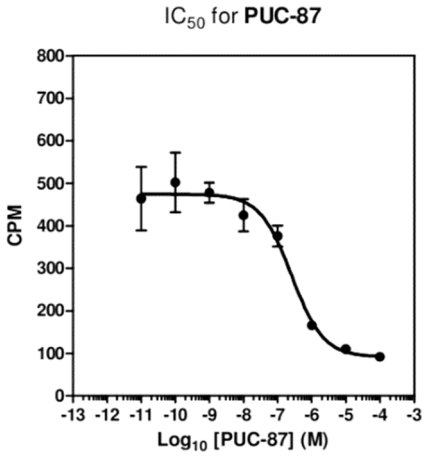
IC50 graph for **4k**



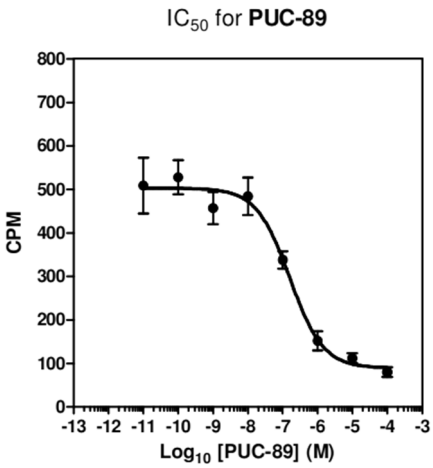
IC50 graph for **4l**



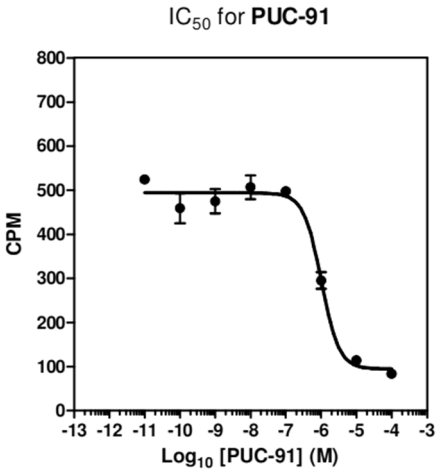
IC50 graph for **4m**



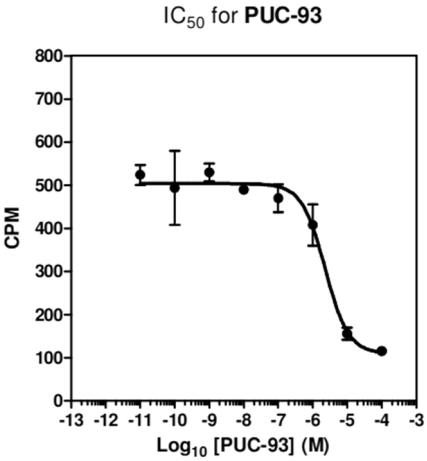
IC50 graph for **4n**



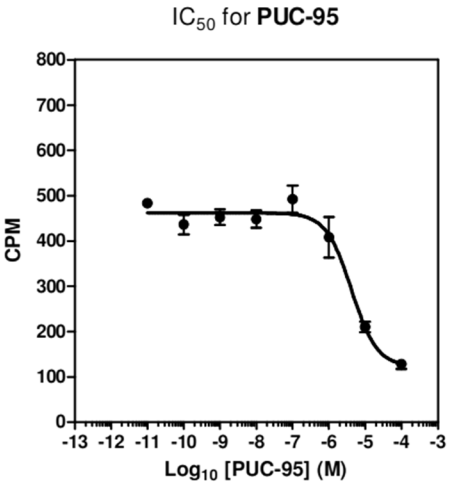
IC50 graph for **4o**



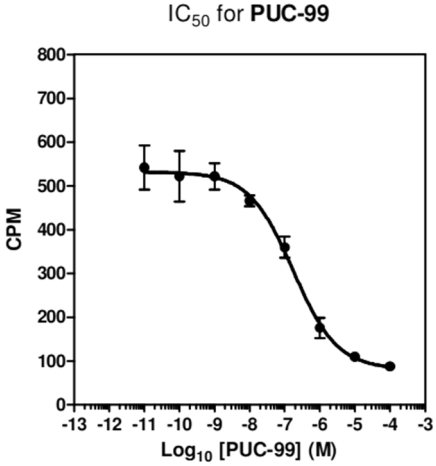
IC50 graph for **4p**



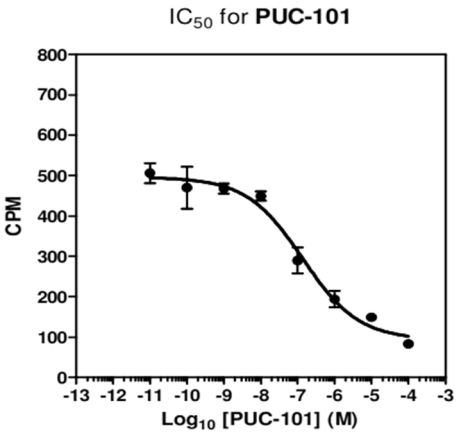
IC50 graph for **4q**



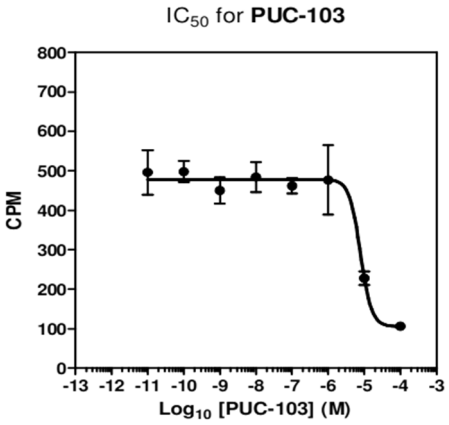
IC50 graph for **4r**



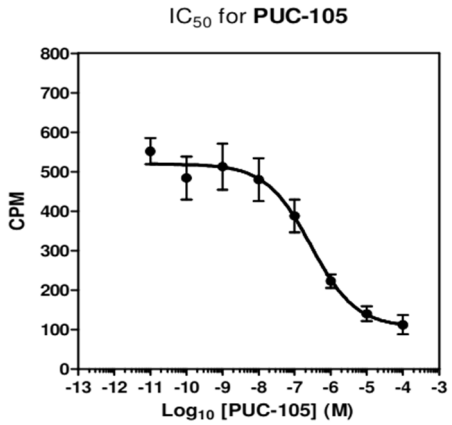
IC50 graph for **4s**



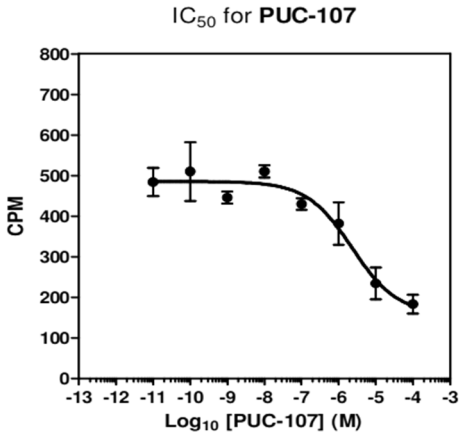
IC50 graph for **4t**



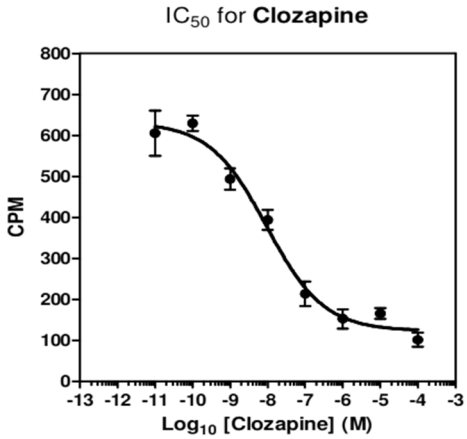
IC50 graph for **4u**



IC50 graph for **4v**



IC50 graph for Clozapine



5. 3D-QSAR

Table S1. Statistical parameters and Field combinations for CoMFA and CoMSIA.

Model	q^2	N	SEP	SEE	r^2	F	Field Contributions				
							S	E	H	D	A
CoMFA-S	0.665	3	0.410	0.224	0.900	81.432	1				
CoMFA-E	0.64	2	0.418	0.222	0.898	123.484		1			
CoMFA-SE	0.653	2	0.41	0.243	0.879	101.243	0.449	0.551			
CoMSIA-S	0.679	3	0.402	0.283	0.841	47.618	1				
CoMSIA-E	0.643	4	0.431	0.179	0.939	99.431		1			
CoMSIA-H	0.523	1	0.472	0.371	0.706	69.64			1		
CoMSIA-D	0.384	7	0.603	0.213	0.923	39.279				1	
CoMSIA-A	0.512	5	0.515	0.249	0.885	38.650					1
CoMSIA-SE	0.692	5	0.409	0.128	0.97	161.624	0.392	0.608			
CoMSIA-SEH	0.617	3	0.439	0.233	0.892	74.036	0.248	0.375	0.377		
CoMSIA-SEHD	0.578	4	0.469	0.202	0.922	76.661	0.2	0.303	0.296	0.2	
CoMSIA-SEHA	0.596	3	0.45	0.254	0.871	61.03	0.191	0.293	0.304		0.212
CoMSIA-SED	0.657	7	0.45	0.099	0.983	194.743	0.28	0.449		0.271	
CoMSIA-SEA	0.65	5	0.442	0.147	0.96	120.809	0.28	0.426			0.293
CoMSIA-SEDA	0.613	5	0.458	0.167	0.949	92.828	0.219	0.338		0.217	0.226
CoMSIA-SH	0.577	2	0.453	0.312	0.799	55.626	0.376		0.624		
CoMSIA-SD	0.558	5	0.49	0.193	0.931	67.834	0.542			0.458	
CoMSIA-SA	0.597	4	0.459	0.245	0.885	50.031	0.465				0.535
CoMSIA-SHD	0.541	2	0.472	0.334	0.769	46.684	0.251		0.402	0.347	
CoMSIA-SHA	0.562	3	0.469	0.273	0.852	51.754	0.271		0.426		0.303
CoMSIA-SDA	0.53	5	0.505	0.206	0.922	58.858	0.337			0.303	0.36
CoMSIA-SHDA	0.524	3	0.489	0.292	0.83	43.979	0.204		0.321	0.248	0.227
CoMSIA-EH	0.575	4	0.471	0.163	0.949	120.591		0.52	0.48		
CoMSIA-ED	0.616	7	0.476	0.121	0.975	129.339		0.63		0.37	
CoMSIA-EA	0.605	5	0.463	0.168	0.948	91.456		0.587			0.413
CoMSIA-EHD	0.549	2	0.468	0.3	0.814	61.186		0.342	0.362	0.296	
CoMSIA-EHA	0.561	5	0.488	0.141	0.963	131.673		0.374	0.358		0.268
CoMSIA-EDA	0.588	7	0.493	0.12	0.976	131.854		0.44		0.276	0.283
CoMSIA-EHDA	0.531	5	0.504	0.153	0.957	111.34		0.301	0.291	0.198	0.21
CoMSIA-HD	0.476	2	0.504	0.336	0.767	46.047			0.549	0.451	
CoMSIA-HA	0.504	2	0.49	0.333	0.771	47.145			0.588		0.412
CoMSIA-HDA	0.474	2	0.505	0.349	0.749	41.769			0.392	0.336	0.272
CoMSIA-DA	0.453	7	0.568	0.18	0.945	56.843				0.457	0.543
CoMSIA-ALL	0.566	3	0.467	0.27	0.855	52.887	0.155	0.238	0.246	0.19	0.171

[a] q^2 = the square of the LOO cross-validation (CV) coefficient; N = the optimum number of components; SEP = standard error of prediction; SEE is the standard error of estimation of non CV analysis; r^2_{ncv} is the square of the non CV coefficient; F is the F-test value; S, E, H, D and A are the steric, electrostatic, hydrophobic, hydrogen-bond donor, and hydrogen-bond acceptor contributions respectively.

External validation

The models were subjected to external validation criteria according to the proposed test by Golbraikh and Tropsha [1,2], which considers a QSAR model predictive, if some of the following conditions are satisfied:

$$q^2 > 0.5 \quad (2)$$

$$r^2 > 0.6 \quad (3)$$

$$\frac{|r^2 - r_0^2|}{r^2} < 0.1 \text{ or } \frac{|r^2 - r'^2_0|}{r^2} < 0.1 \quad (4)$$

$$0.85 \leq k \leq 1.15 \text{ or } 0.85 \leq k' \leq 1.15 \quad (5)$$

$$|r_0^2 - r'^2_0| < 0.3 \quad (6)$$

$$r_m^2 = r^2 \left(1 - \left|\sqrt{r^2 - r_0^2}\right|\right) \quad (7)$$

Where r^2 and r_0^2 are the squared correlation coefficients between the observed and predicted activities of the test set with and without the (0,0) intercept, respectively [1,3].

Table S2. Summary of external validation parameters for CoMFA and CoMSIA.

Condition	Parameters	Threshold value	CoMFA	CoMSIA
1	q^2	>0.5	0.653	0.692
2	r_{test}^2	>0.6	0.786	0.726
3a	r_0^2	Close to value of r_{test}^2	0.999	0.999
3b	r'^2_0	Close to value of r_{test}^2	0.999	0.999
4a	k	$0.85 < k < 1.15$	0.995	1.004
4b	k'	$0.85 < k' < 1.15$	1.004	0.995
5a	$\|(r^2 - r_0^2)\|/r^2$	<0.1	0.271	0.376
5b	$\|(r^2 - r'^2_0)\|/r^2$	<0.1	0.271	0.376
6	$\|r_0^2 - r'^2_0\|$	<0.3	0.000	0.000
7	r_m^2	>0.5	0.423	0.347

q^2 and r^2_{test} are the same parameters as listed in table 1; r_0^2 and k are the correlation coefficient between the actual and predicted activities for test set and the respective slope of regression; and $r_0'^2$ and k′ are the correlation coefficient between the predicted and actual activities for test set and the respective slope of regression. r^2_m is the r^2 metric.

Table S3. Experimental and predicted pIC_{50} and residual values for analyzed compounds according to CoMFA and CoMSIA.

Molecule	Exp. pKi(M)	CoMFA		CoMSIA	
		Predicted pKi (M)	Residual	Predicted pKi (M)	Residual
4aR	6.409	6.459	-0.05	6.500	-0.09
4aS	6.409	6.534	-0.13	6.548	-0.14
4bR	5.440	5.762	-0.32	5.546	-0.11
4bS	5.440	5.668	-0.23	5.442	0.00
4cR	4.902	4.960	-0.06	5.046	-0.14
4cS	4.902	5.089	-0.19	4.928	-0.03
4dR	7.234	7.115	0.12	7.381	-0.15
4dS	7.234	6.699	0.54	6.921	0.31
4eR*	6.096	6.083	0.01	6.215	-0.12
4eS	6.096	6.093	0.00	6.022	0.07
4fR	6.165	5.965	0.20	6.211	-0.05
4fS	6.165	6.179	-0.01	6.034	0.13
4gR*	5.840	5.912	-0.07	6.008	-0.17
4gS	5.840	6.157	-0.32	5.718	0.12
4hR*	6.071	5.950	0.12	6.134	-0.06
4hS*	6.071	5.861	0.21	6.192	-0.12
4iR	6.419	6.674	-0.25	6.517	-0.10
4iS	6.419	6.567	-0.15	6.561	-0.14
4jR	6.539	6.471	0.07	6.694	-0.15
4jS	6.539	6.602	-0.06	6.551	-0.01
4kR*	6.395	5.767	0.63	5.567	0.83
4kS	6.395	6.241	0.15	6.468	-0.07
4lR*	6.796	6.779	0.02	6.965	-0.17
4lS*	6.796	6.829	-0.03	6.486	0.31
4mR	6.607	6.510	0.10	6.533	0.07
4mS*	6.607	6.270	0.34	6.575	0.03
4nR	6.815	6.273	0.54	6.565	0.25
4nS	6.815	6.973	-0.16	6.793	0.02
4oR*	6.012	6.083	-0.07	6.327	-0.32
4oS	6.012	6.275	-0.26	6.044	-0.03
4pR*	5.659	5.920	-0.26	5.780	-0.12
4pS*	5.659	5.998	-0.34	5.693	-0.03
4qR	5.395	5.040	0.36	5.310	0.09
4qS	5.395	5.534	-0.14	5.415	-0.02
4rR	6.775	6.655	0.12	6.835	-0.06
4rS	6.775	6.922	-0.15	6.659	0.12
4sR	6.886	5.322	1.56	5.449	1.44
4sS	6.886	6.579	0.31	6.805	0.08
4tR	5.125	4.840	0.29	5.034	0.09
4tS	5.125	5.155	-0.03	5.088	0.04
4uR*	6.567	6.333	0.23	6.637	-0.07

4uS*	6.567	6.456	0.11	6.083	0.48
4vR	5.660	5.863	-0.20	5.602	0.06
4vS	5.660	5.896	-0.24	5.730	-0.07

* test set compounds.

Applicability domain calculation

The AD was evaluated based on the simple standardization method reported by Roy et al. [4]. First, each descriptor "i" for each compound "k" is standardized (S_{ik}). Every compound must have a maximum value $[S_i]_{max(k)} \leq 3$. In the case that $[S_i]_{max(k)} > 3$ and its minimum value $[s_i]_{min(k)} < 3$, then the $S_{new(k)}$ parameter must be calculated and has to fulfill the condition: $S_{new(k)} = \bar{S}_k + 1.28 * \sigma_{S_k}$, where $\bar{S}_k$ is the mean of *Sik* values for compound *k* and σ_{S_k} is the standard deviation for such values. The software is available free of charge on the authors' website: http://dtclab.webs.com/software-tools and http://teqip.jdvu.ac.in/QSAR_Tools/.

6. References

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