Supporting Information

New inhibitors of Bcr-Abl based on 2,6,9-trisubstituted purine scaffold elicited cytotoxicity in chronic myeloid leukaemia-derived cell lines sensitive and resistant to TKIs

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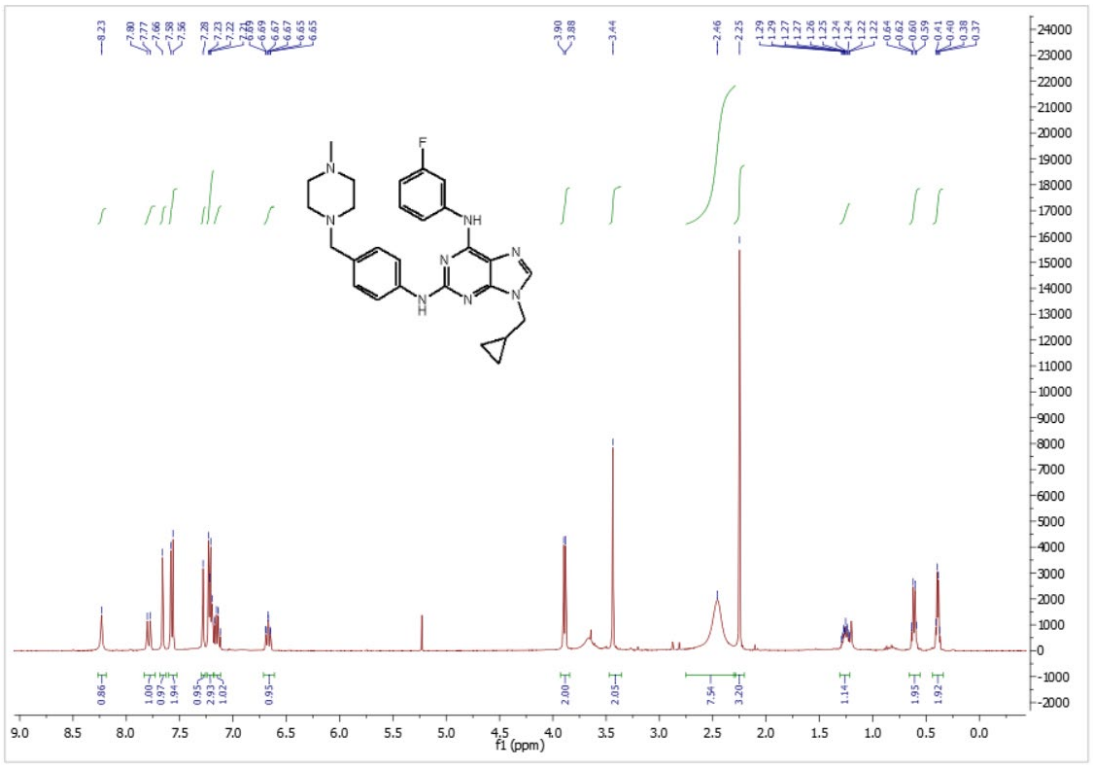
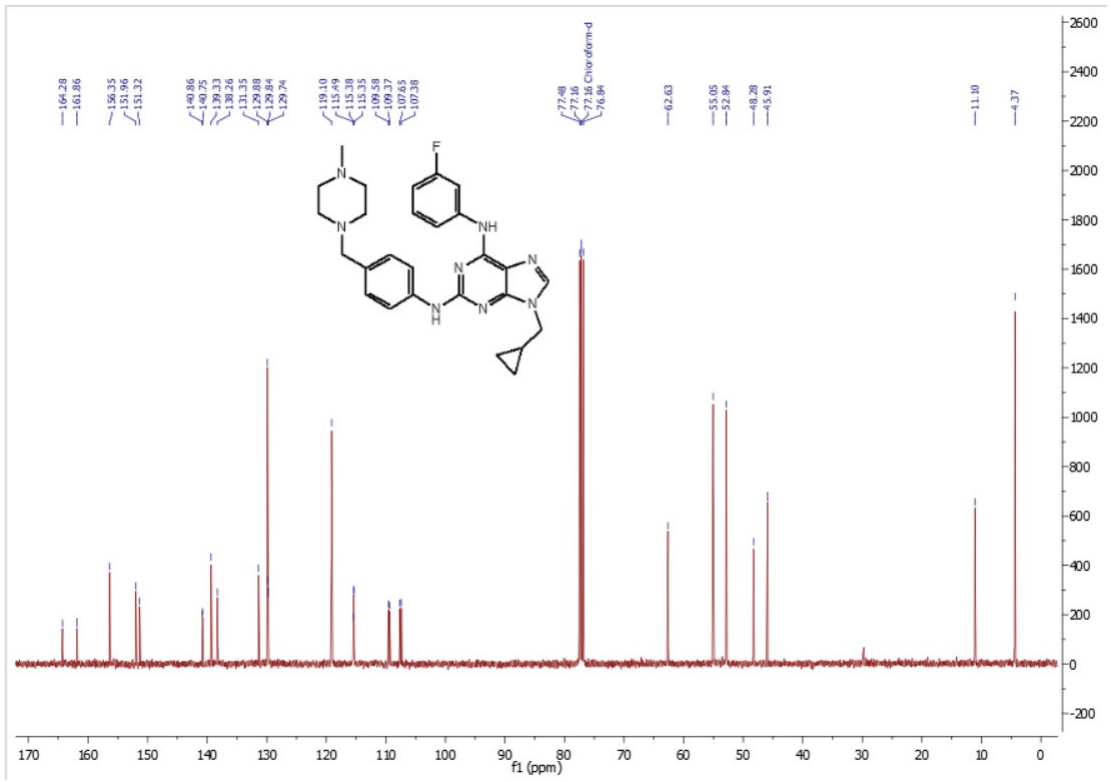
^{1}H NMR spectra of compound **7a**



^{13}C NMR spectra of compound **7a**



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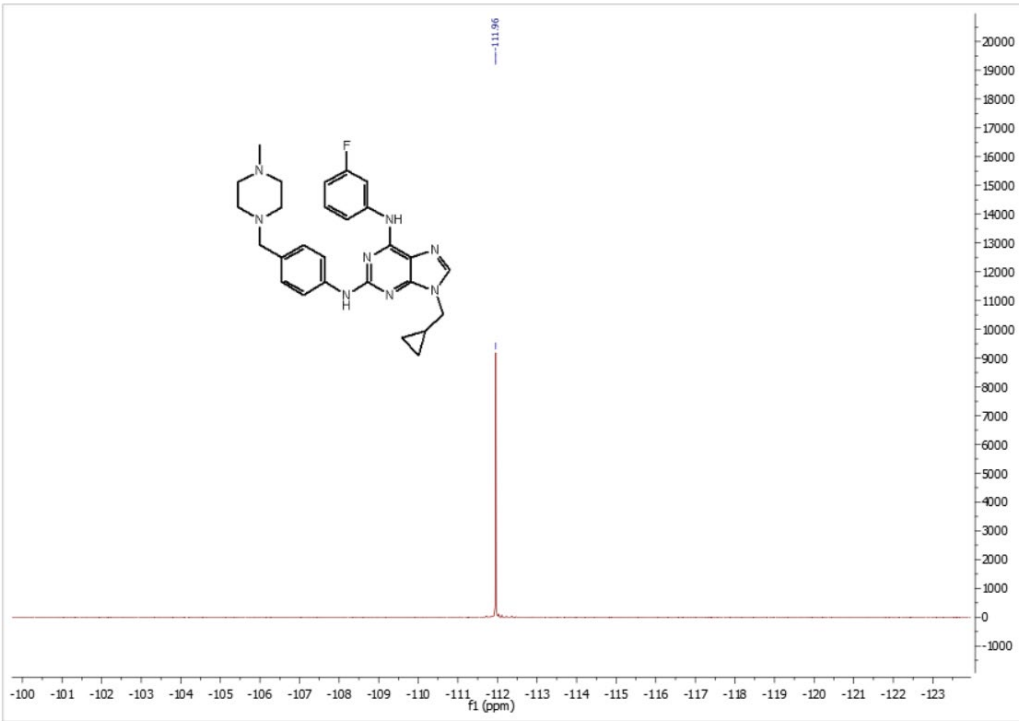

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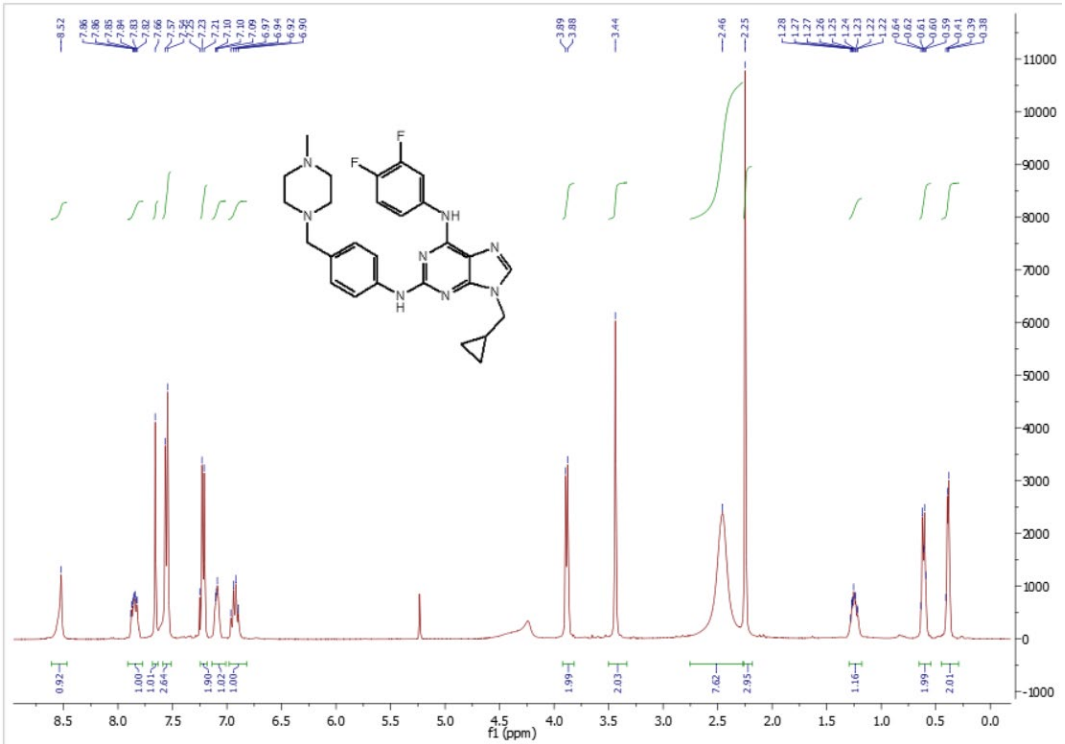

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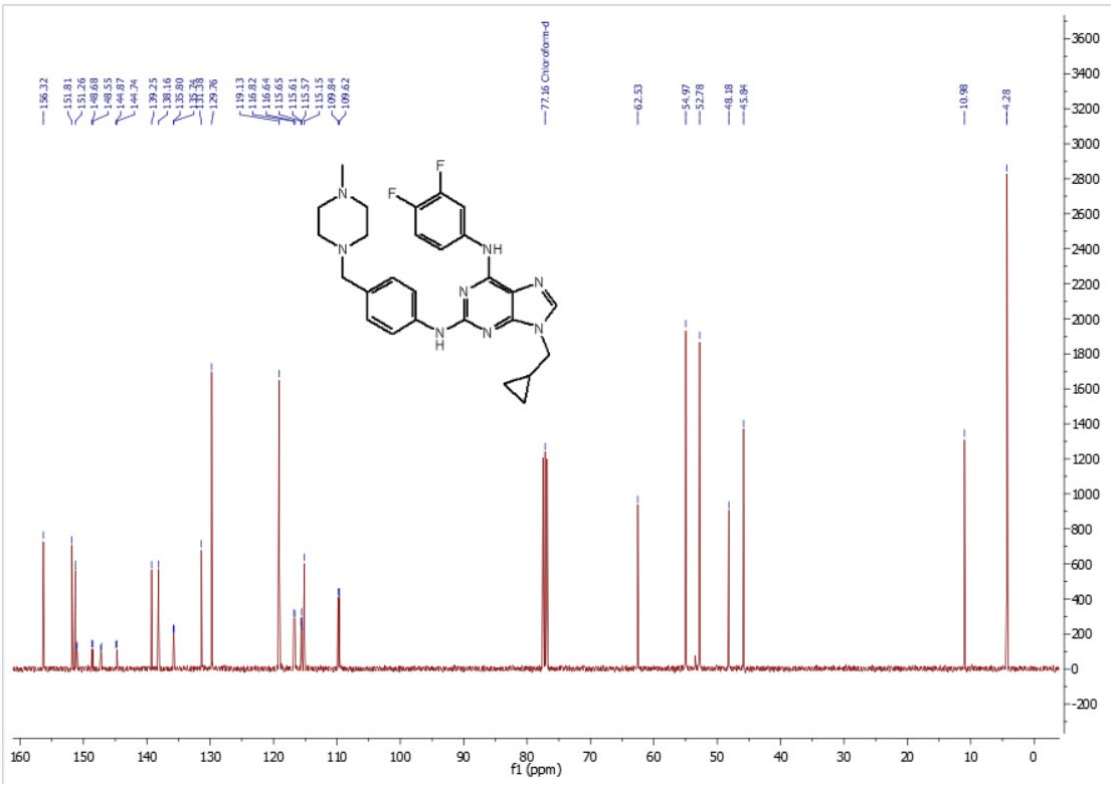

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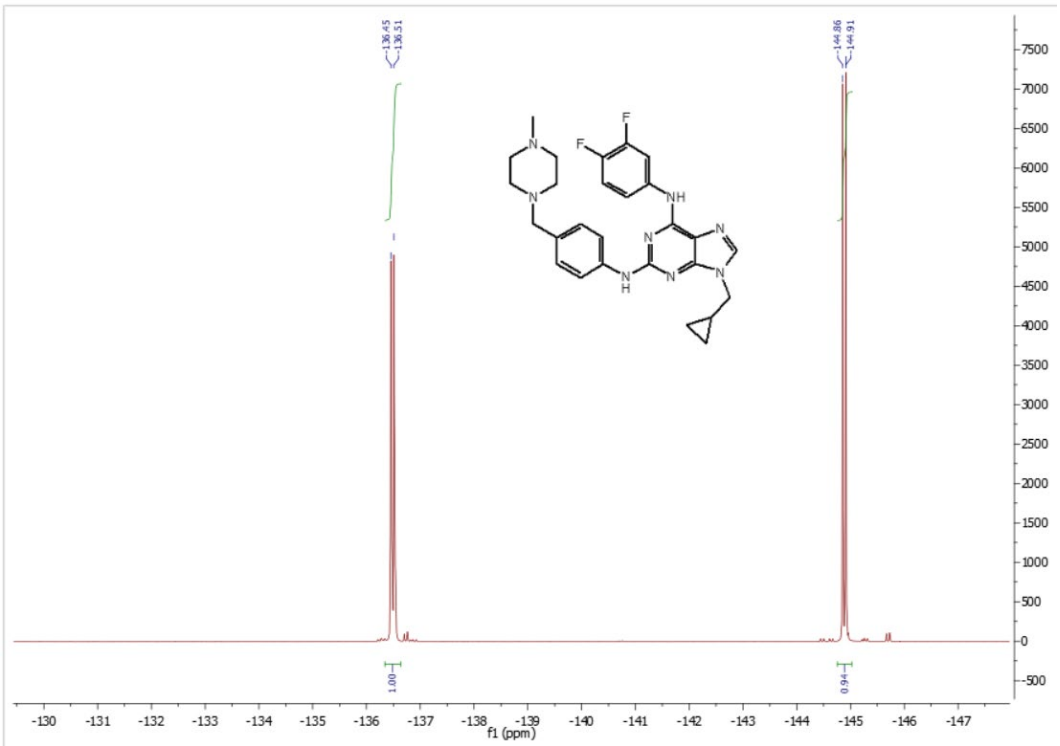
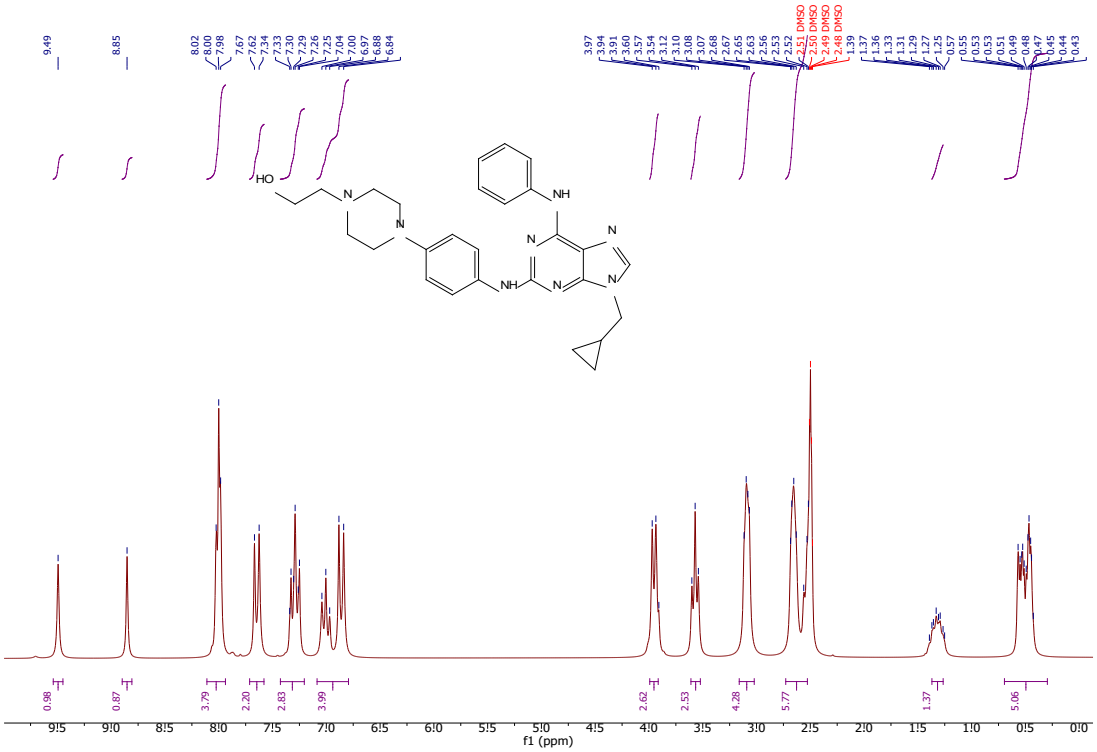


^{1}H NMR spectra of compound **11a**



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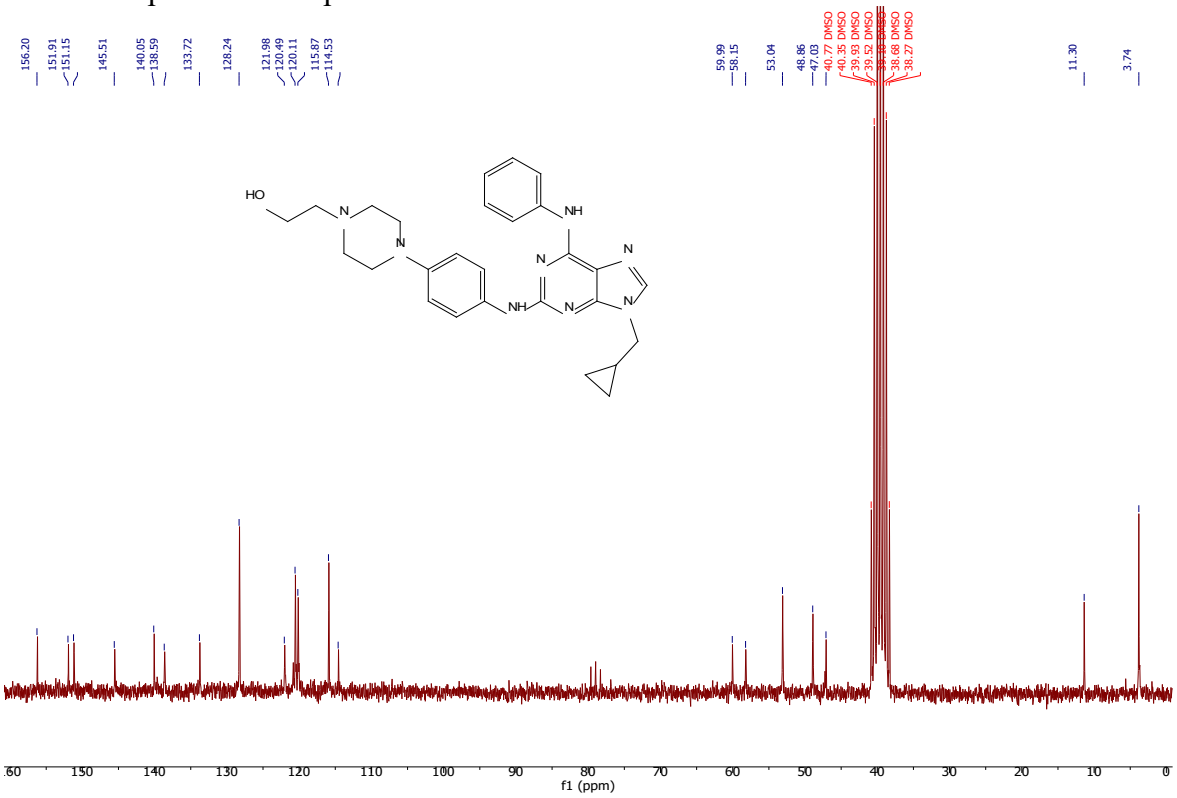

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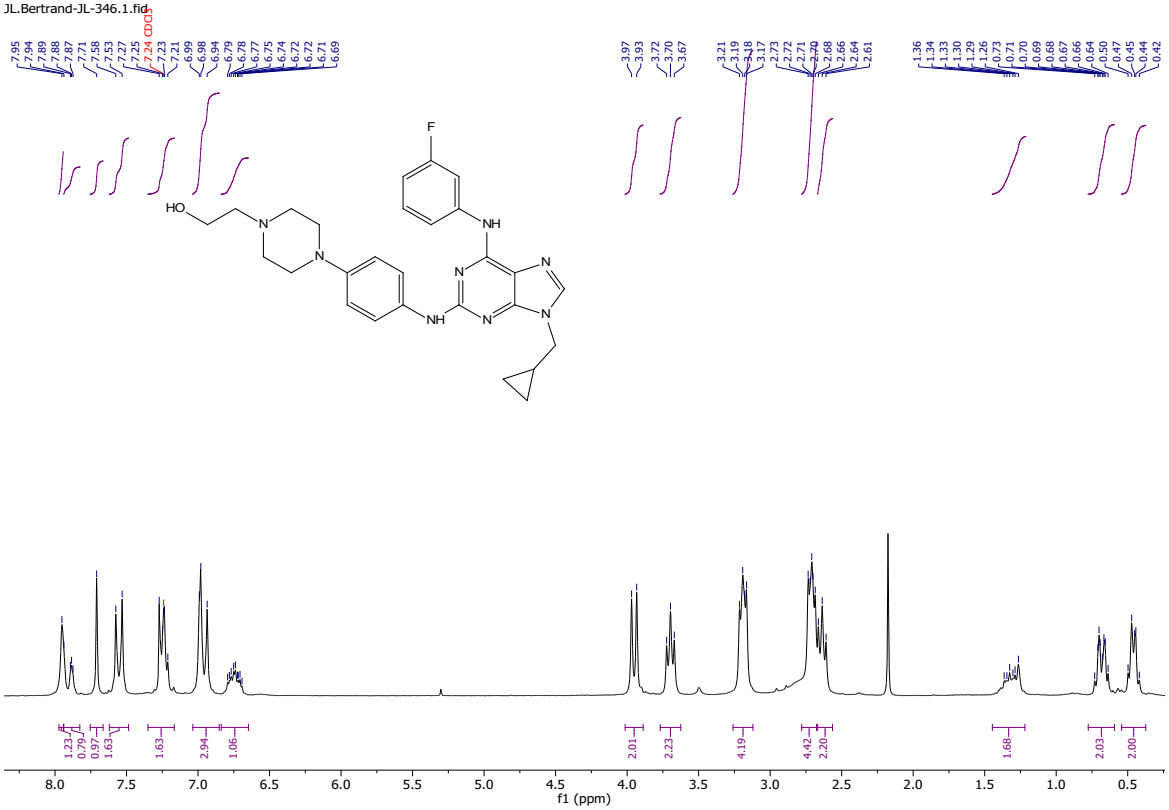

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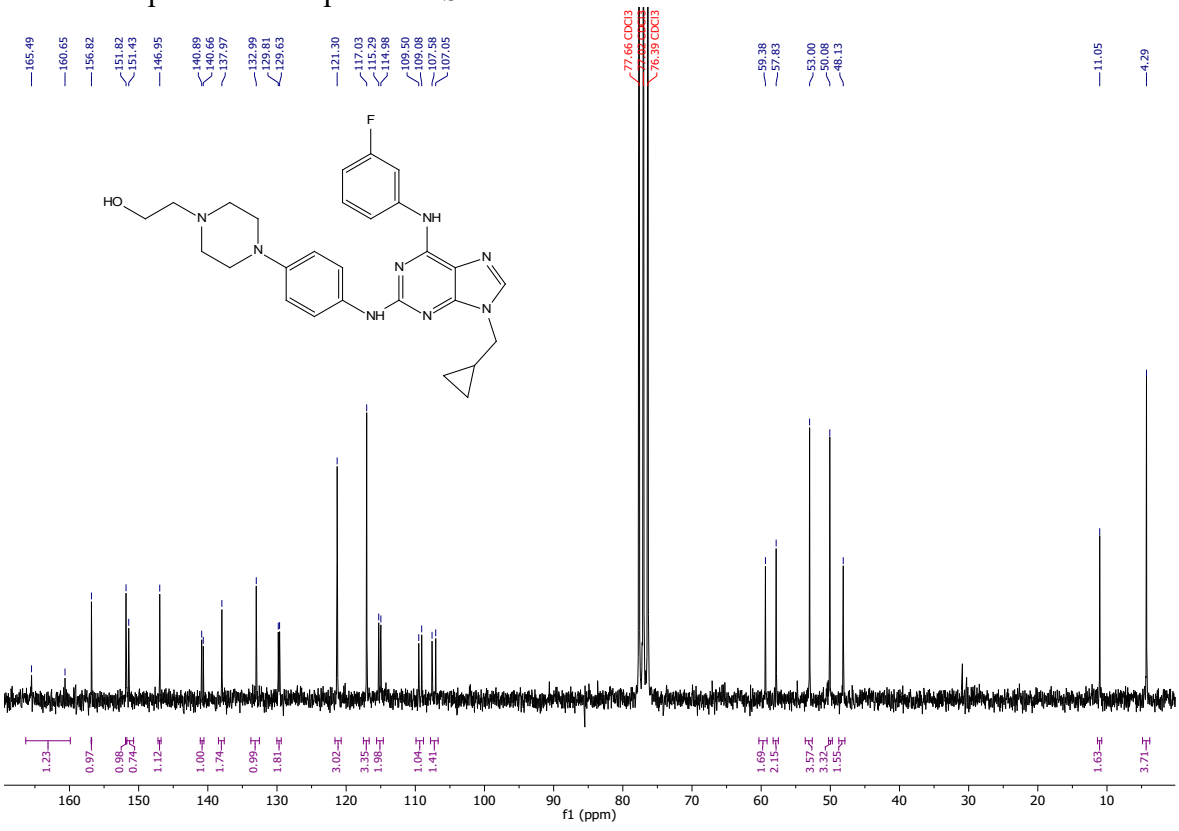

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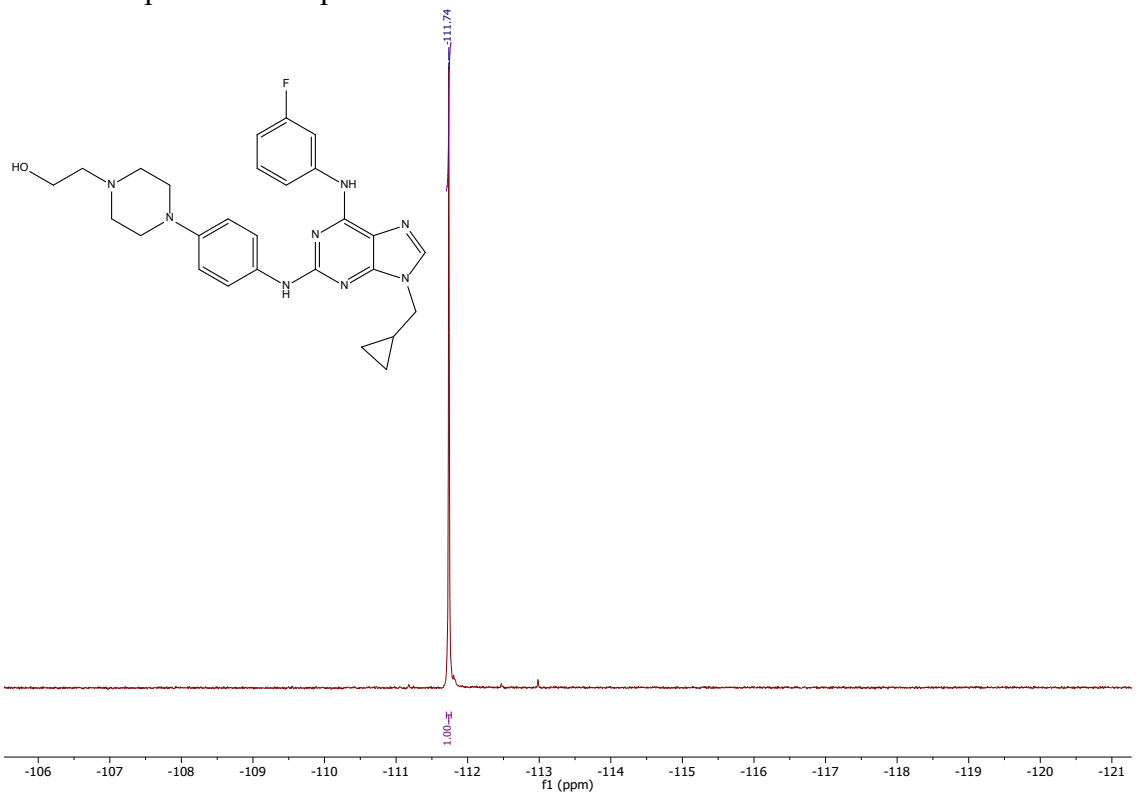

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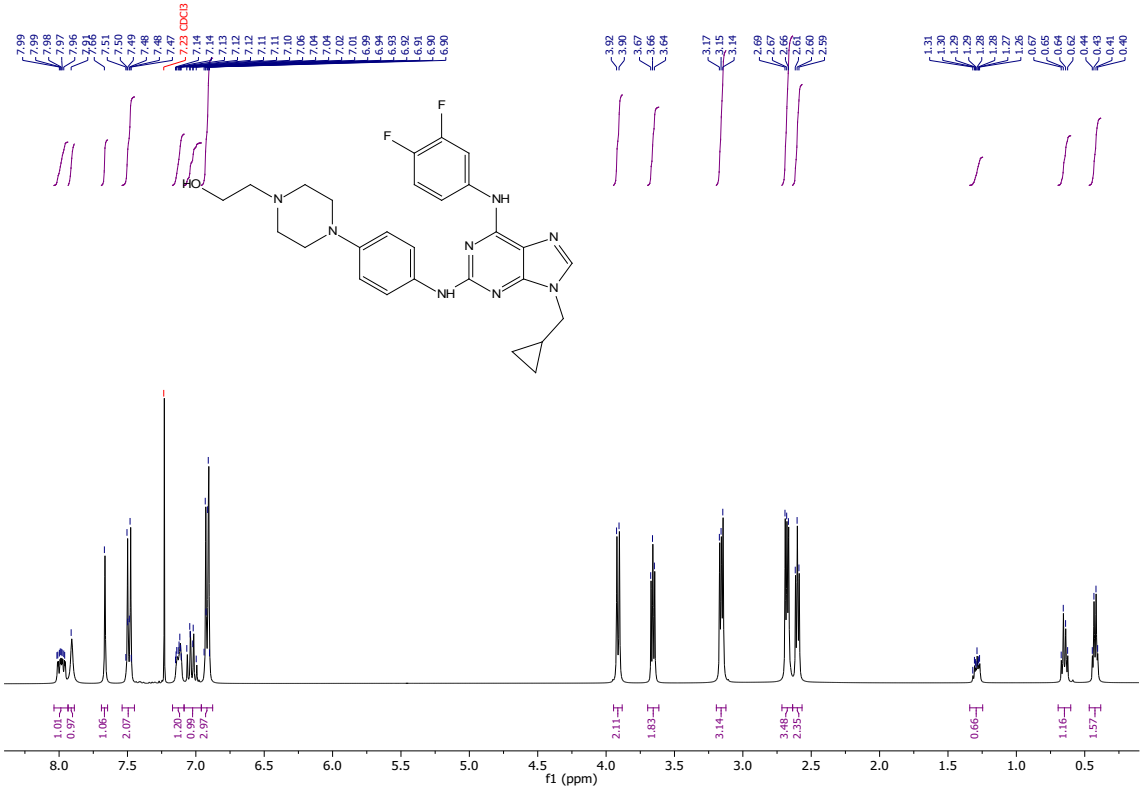

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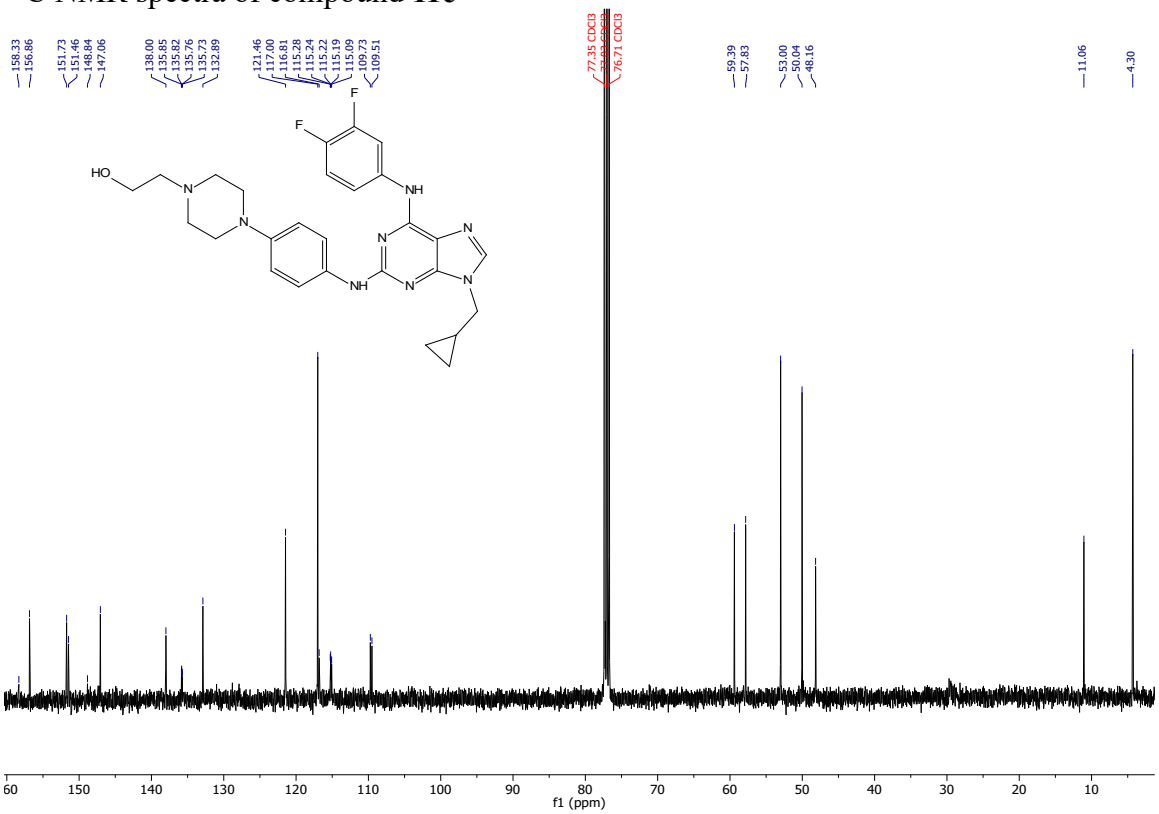

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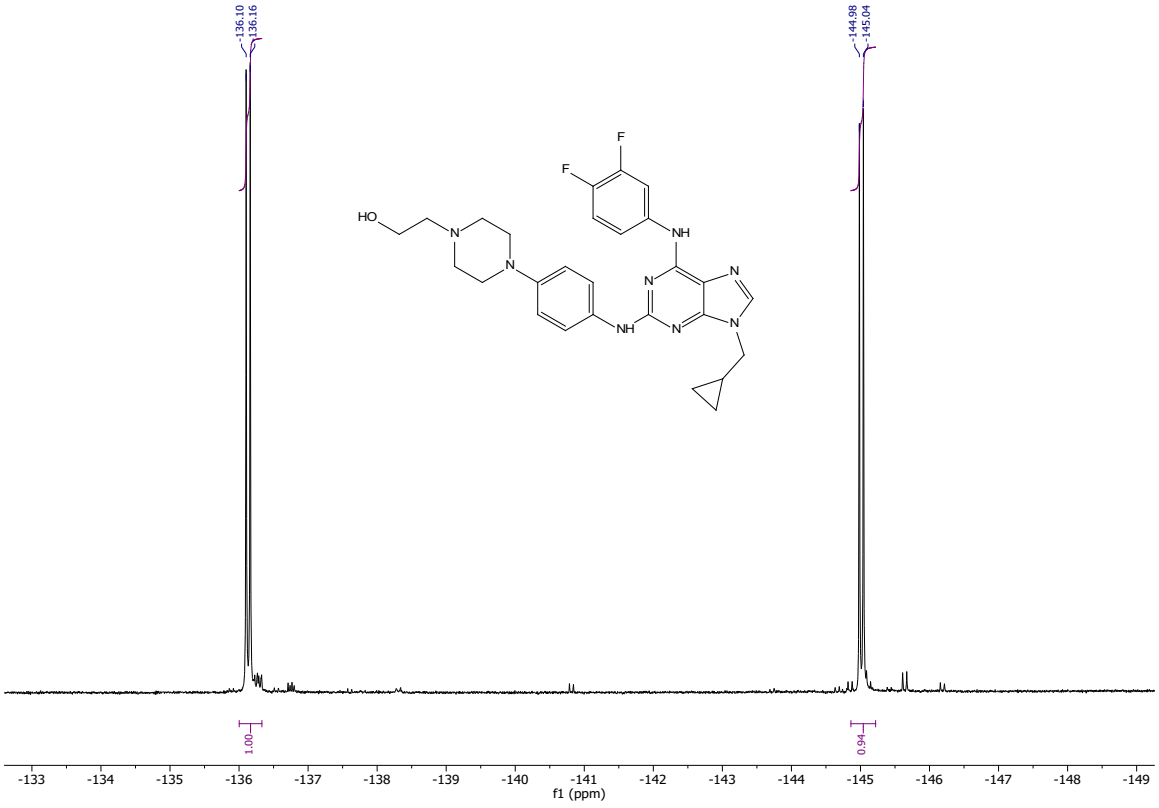

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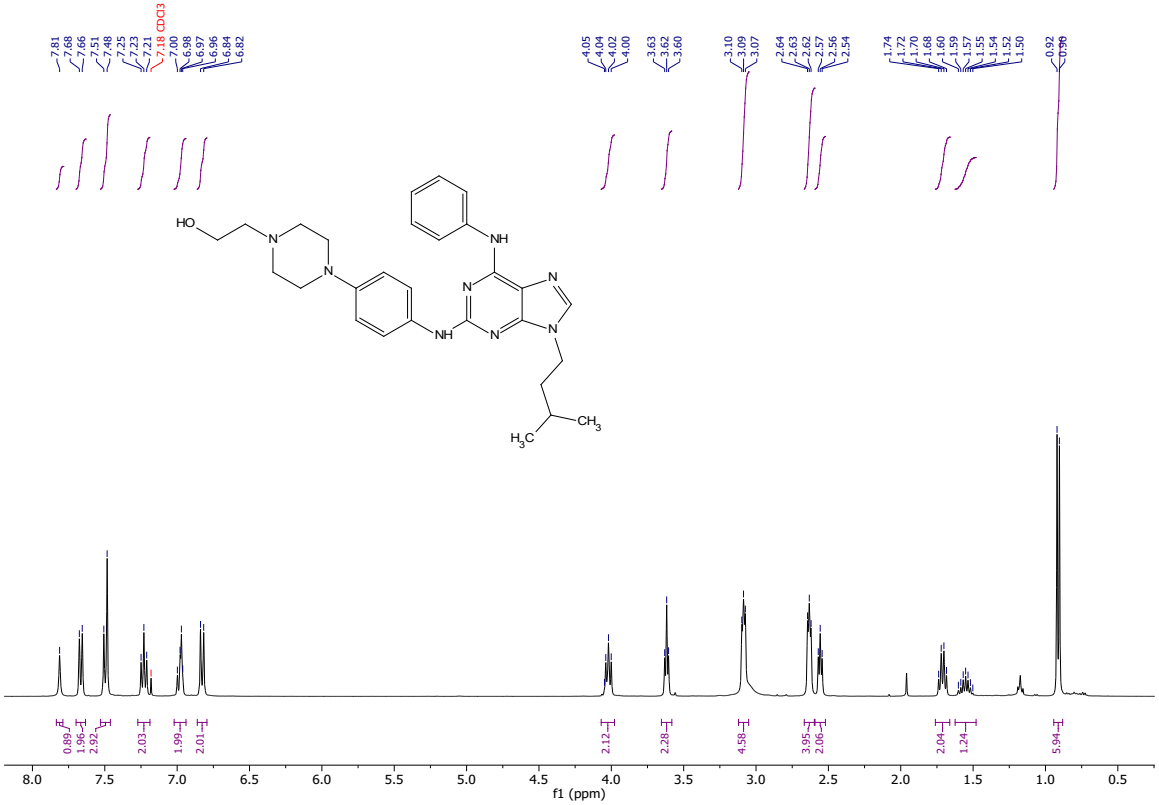

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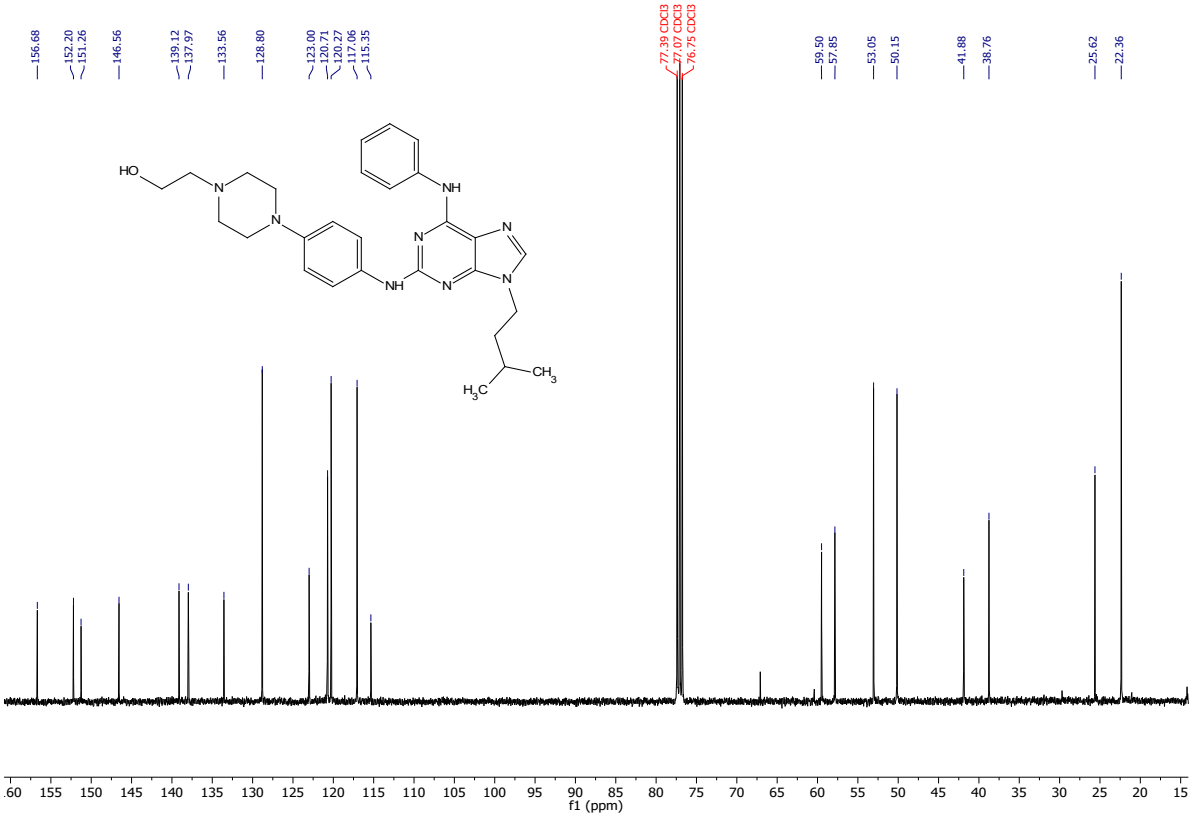

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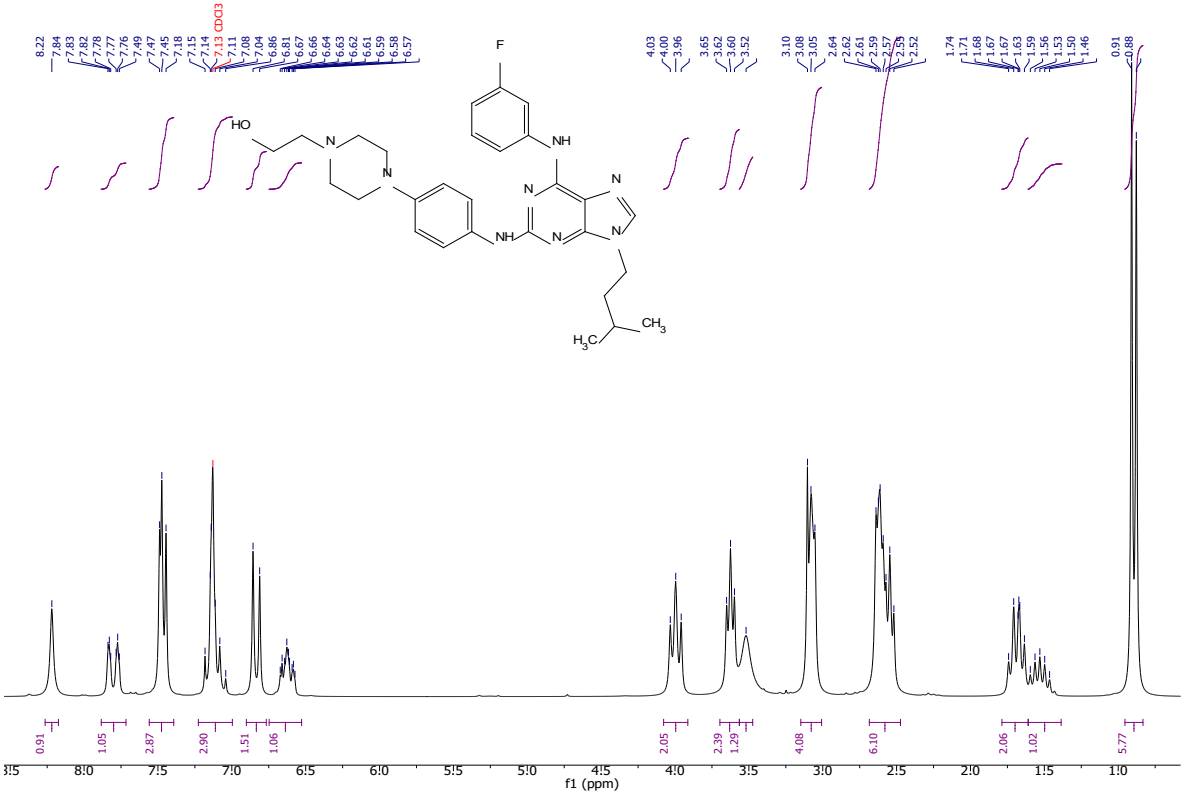

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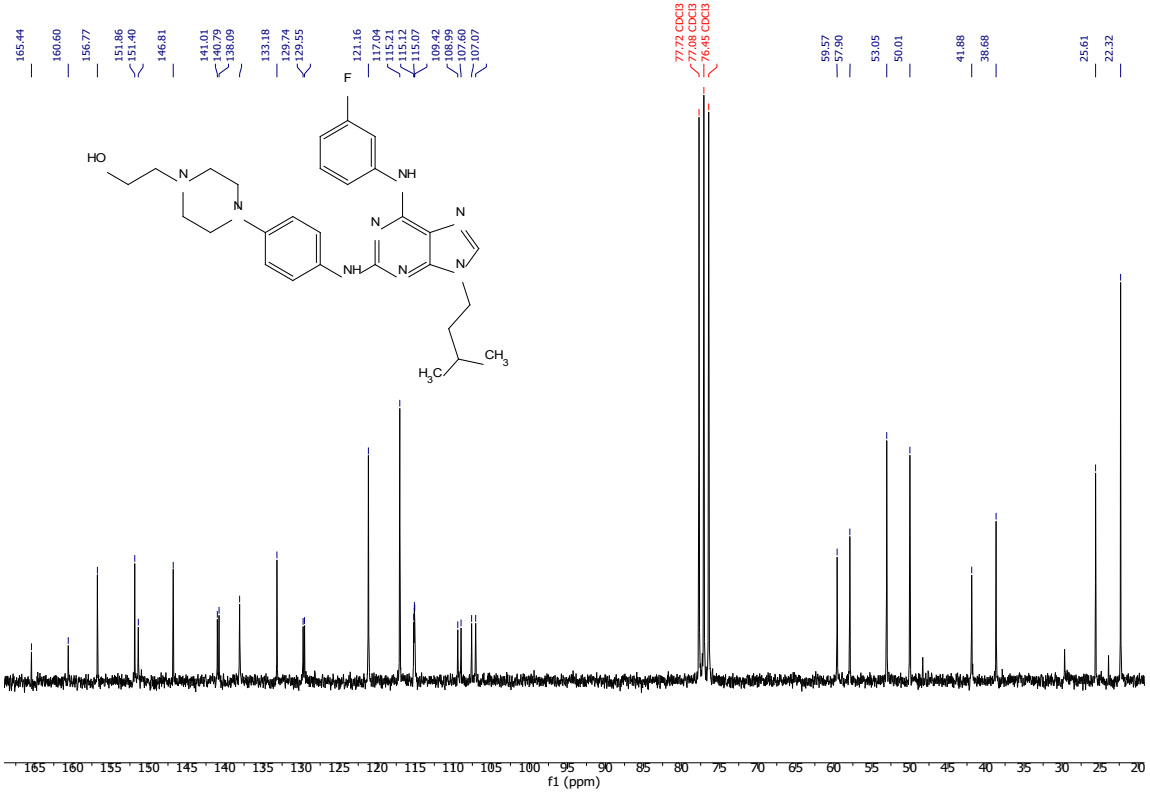

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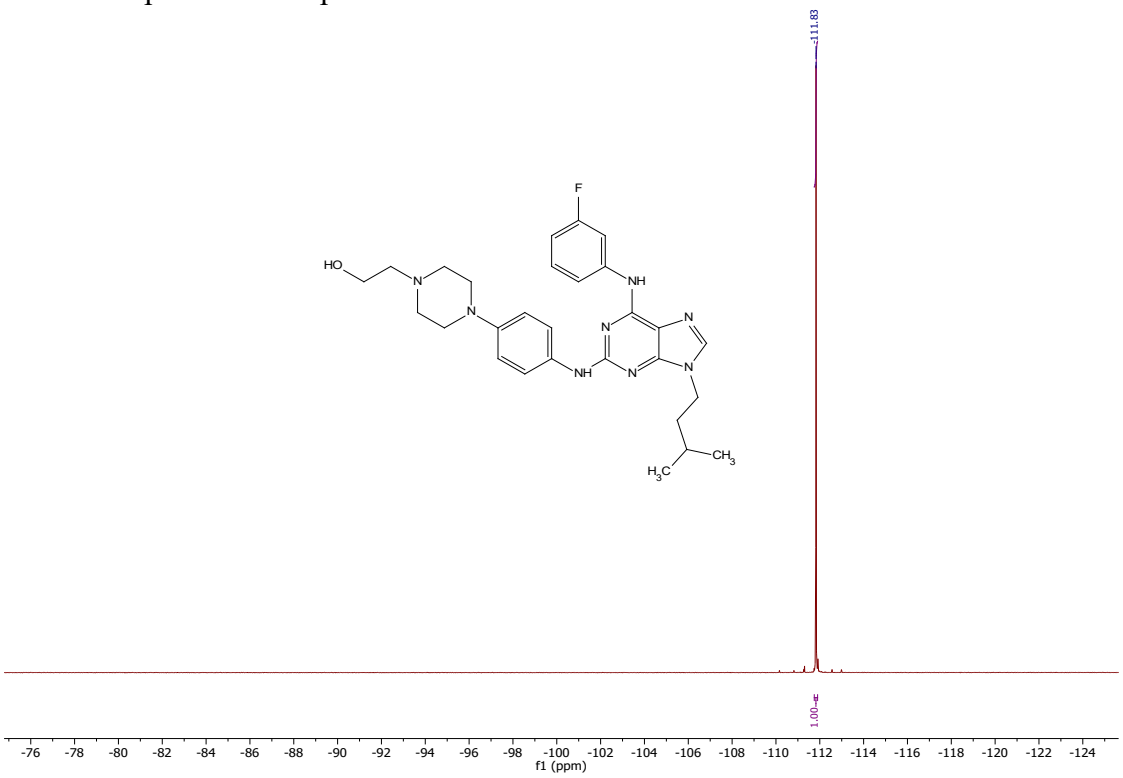

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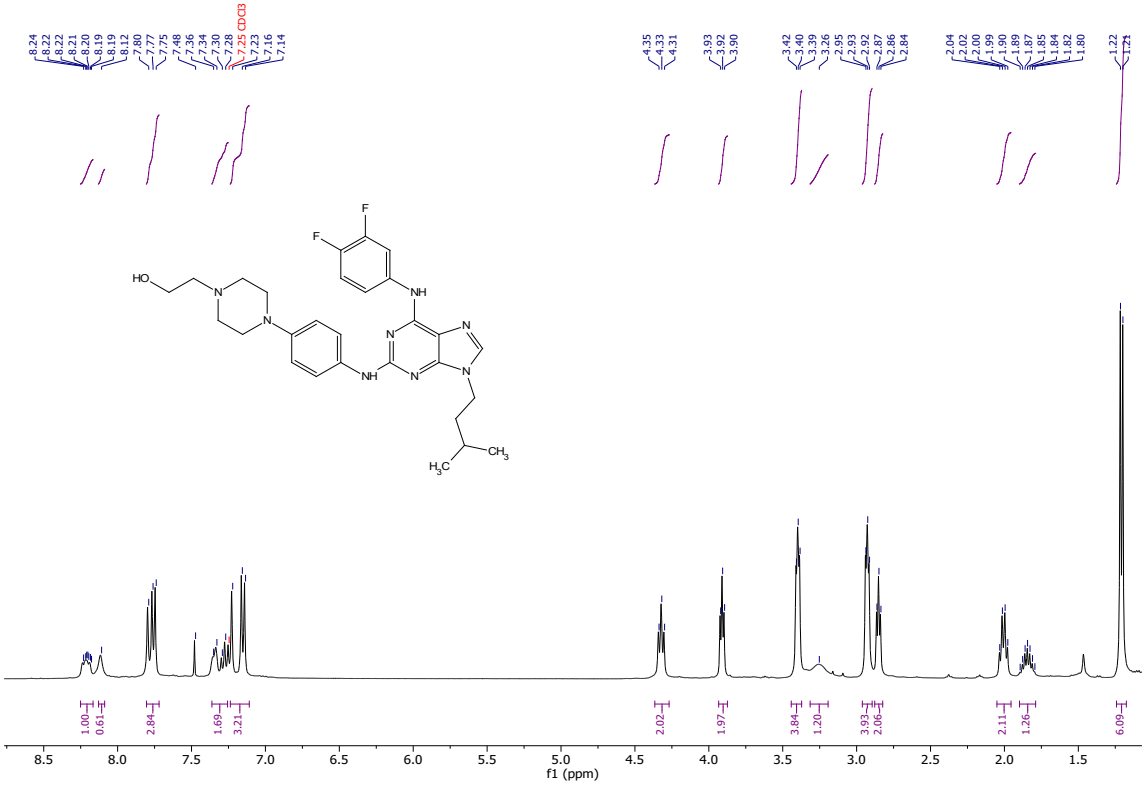

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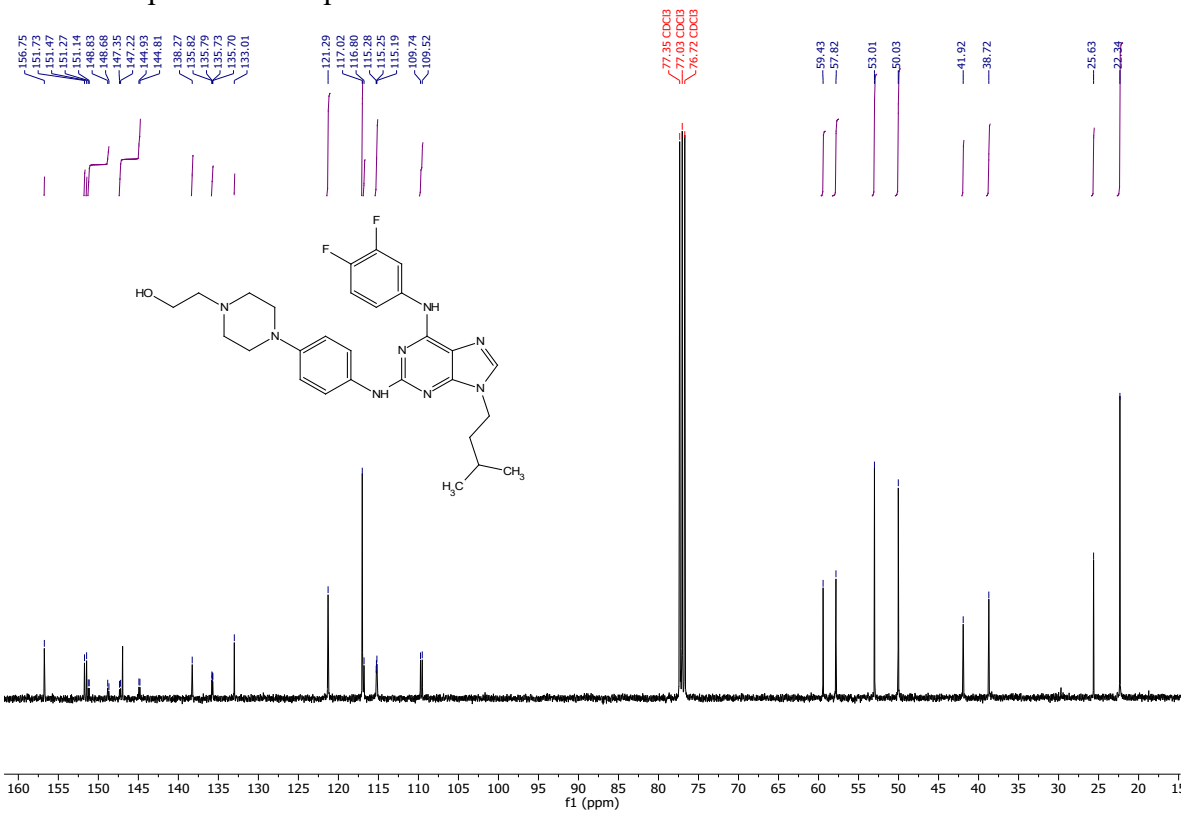

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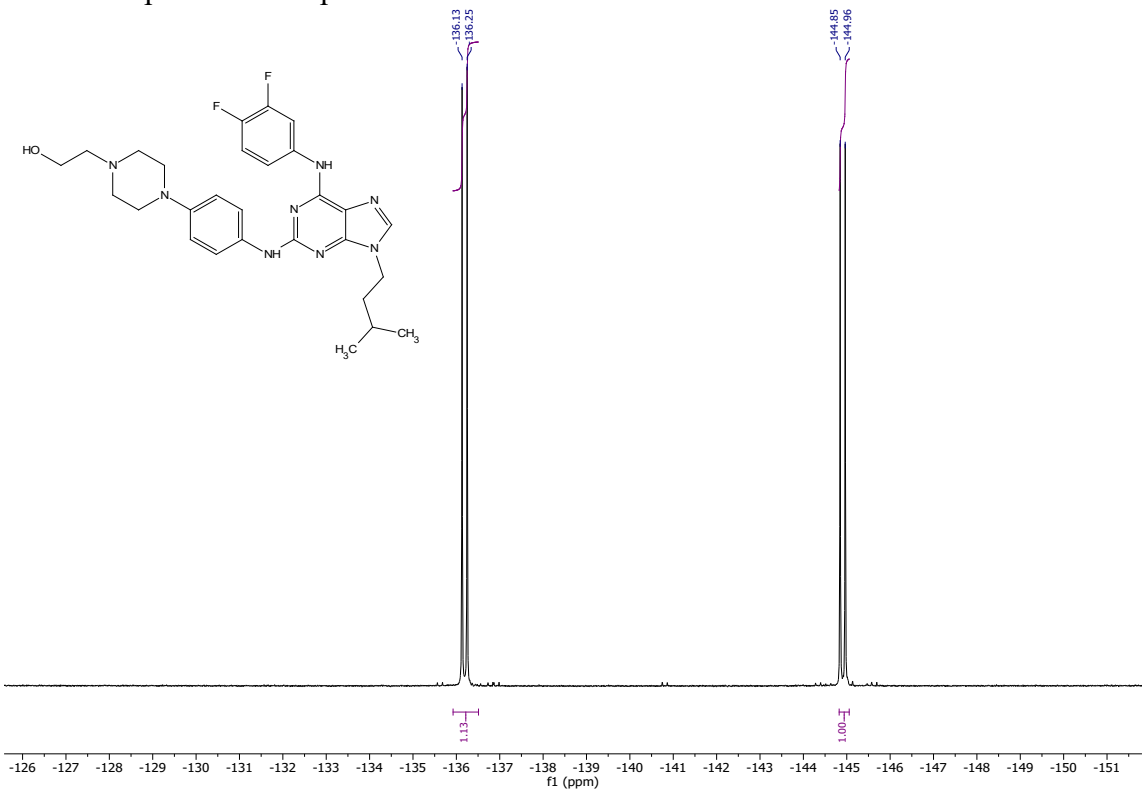
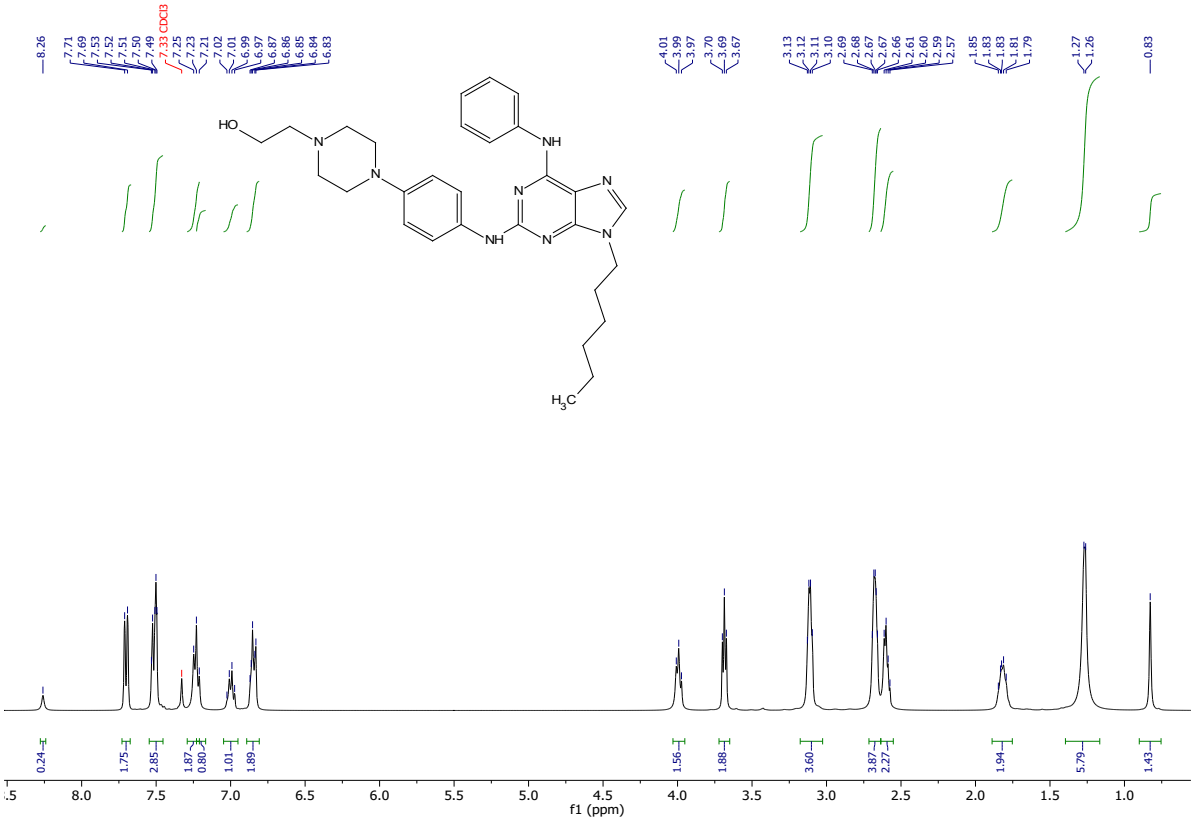
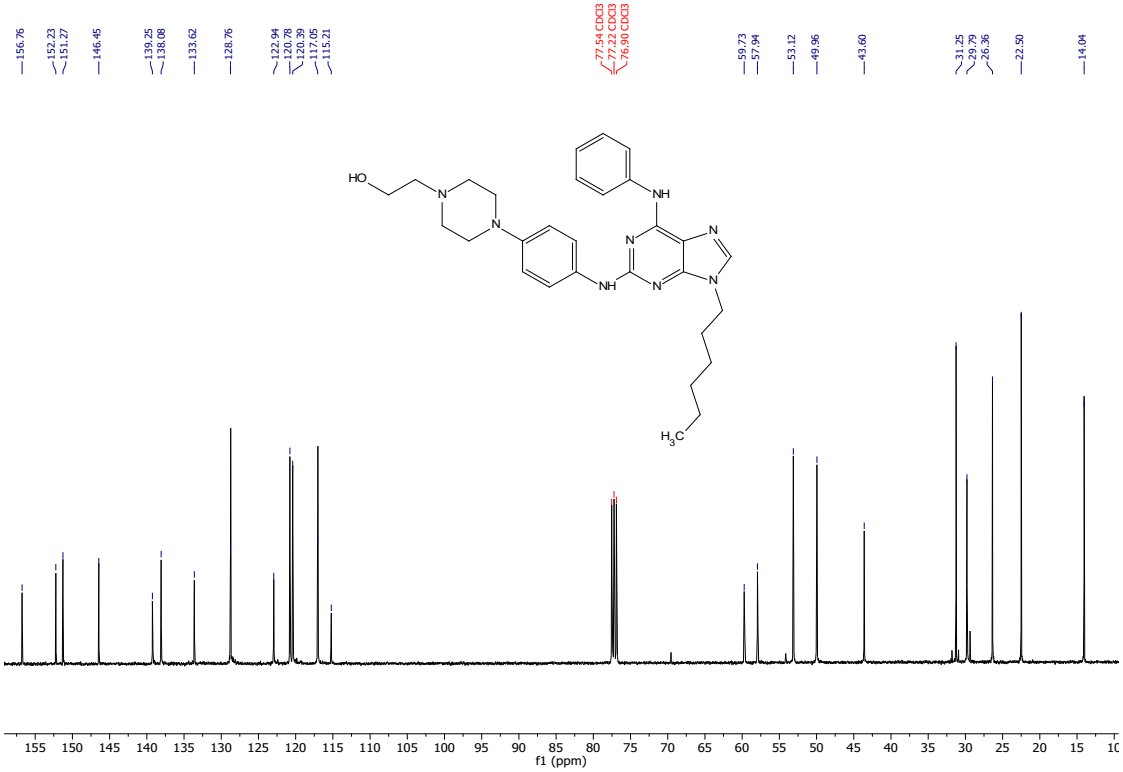


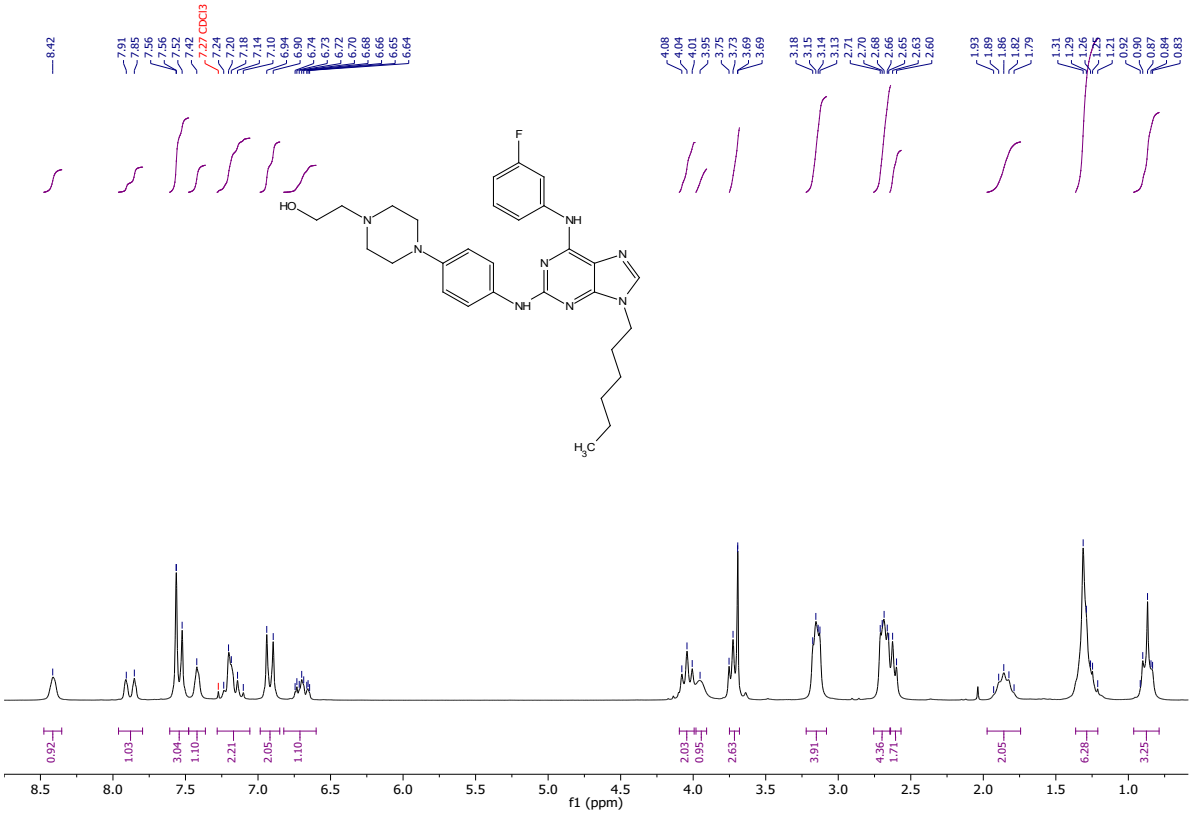
^{1}H NMR spectra of compound **11g**



^{13}C NMR spectra of compound **11g**



^{1}H NMR spectra of compound **11h**



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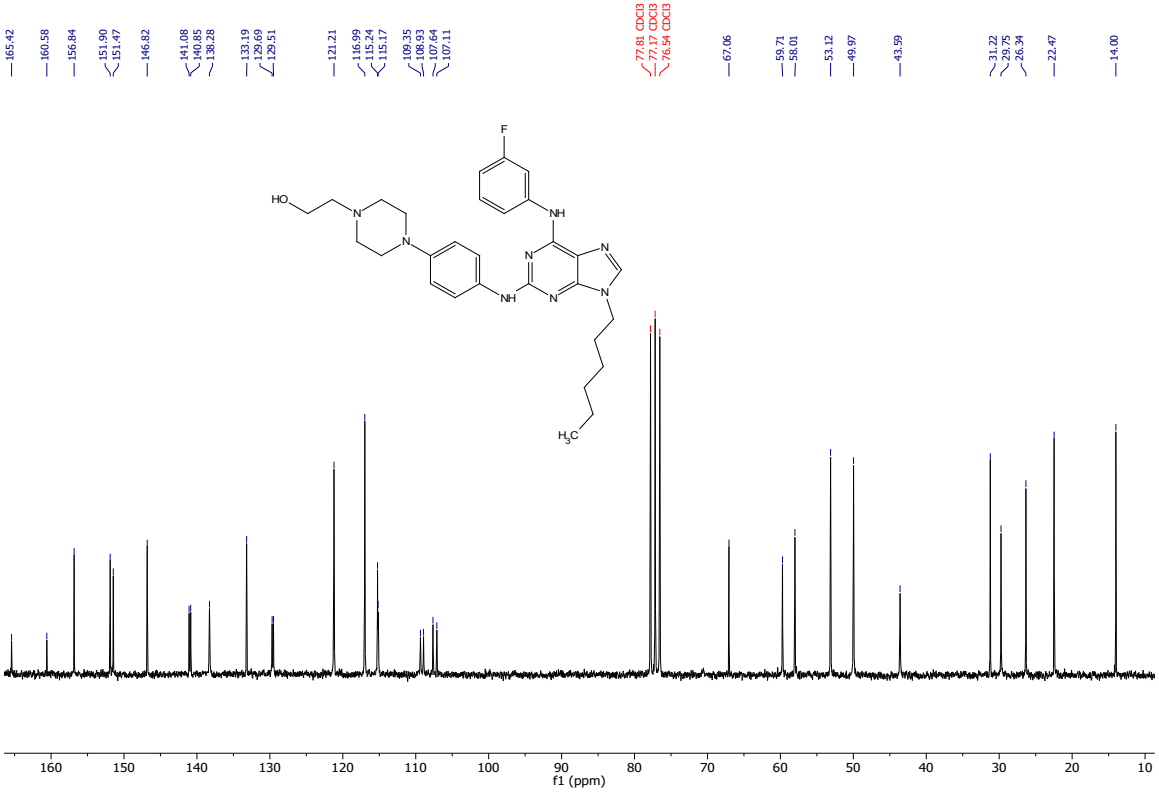

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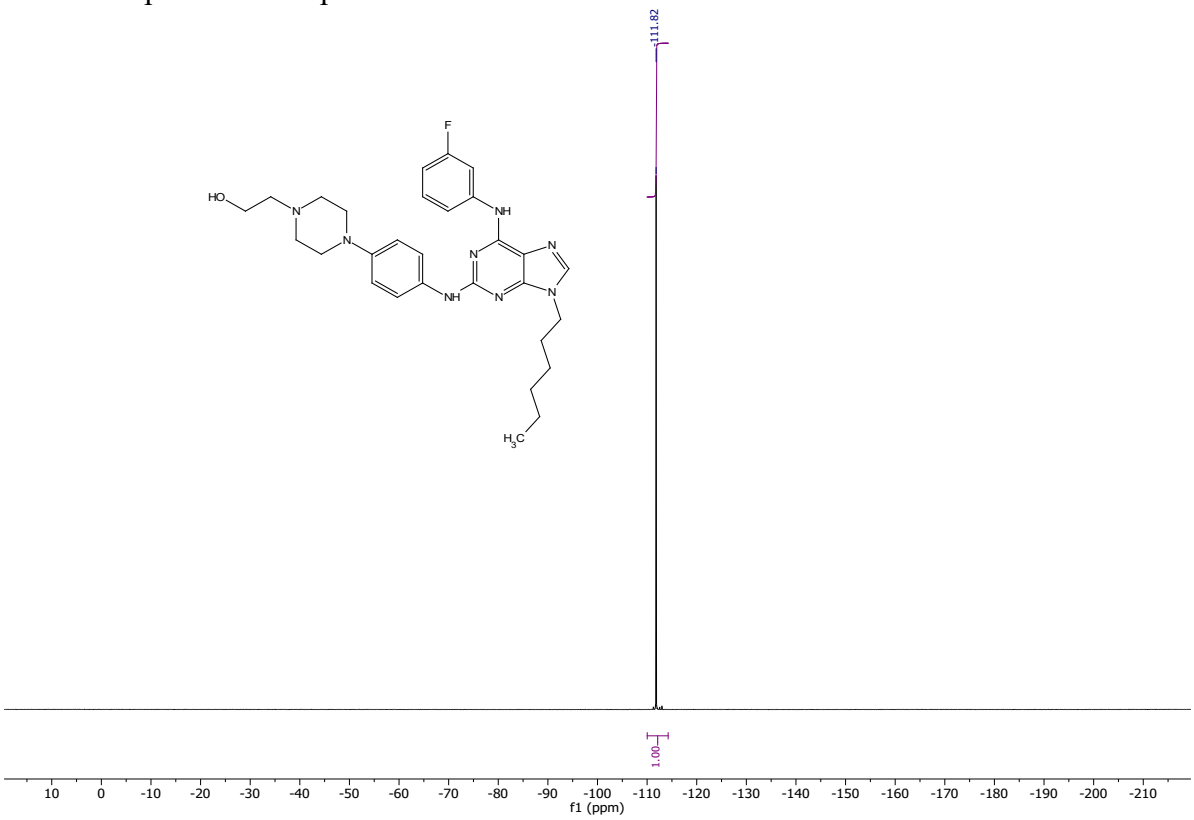
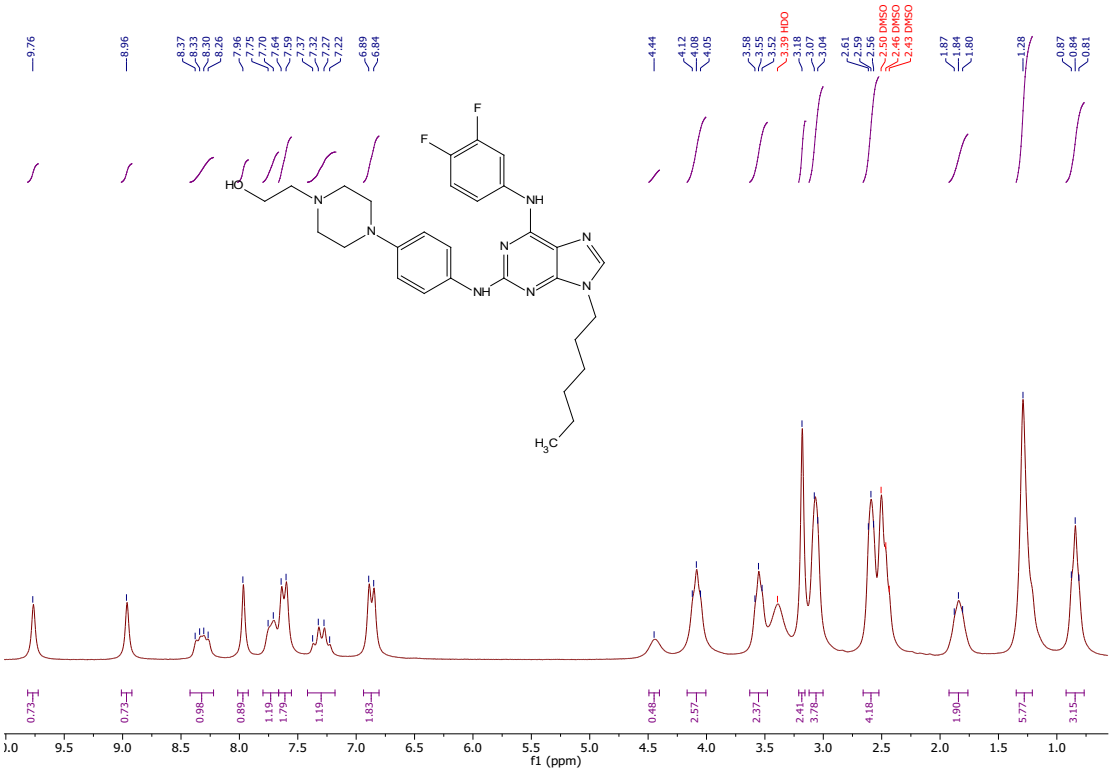


^{1}H NMR spectra of compound **11i**



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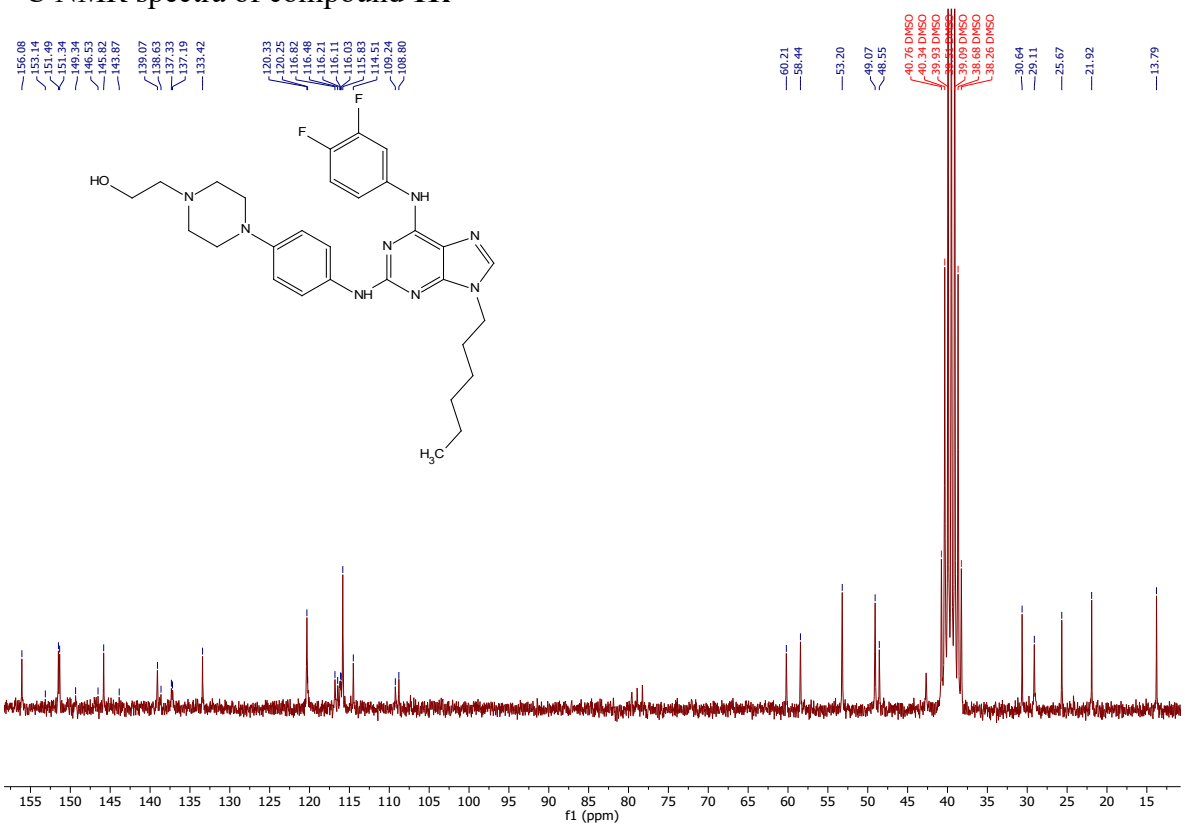

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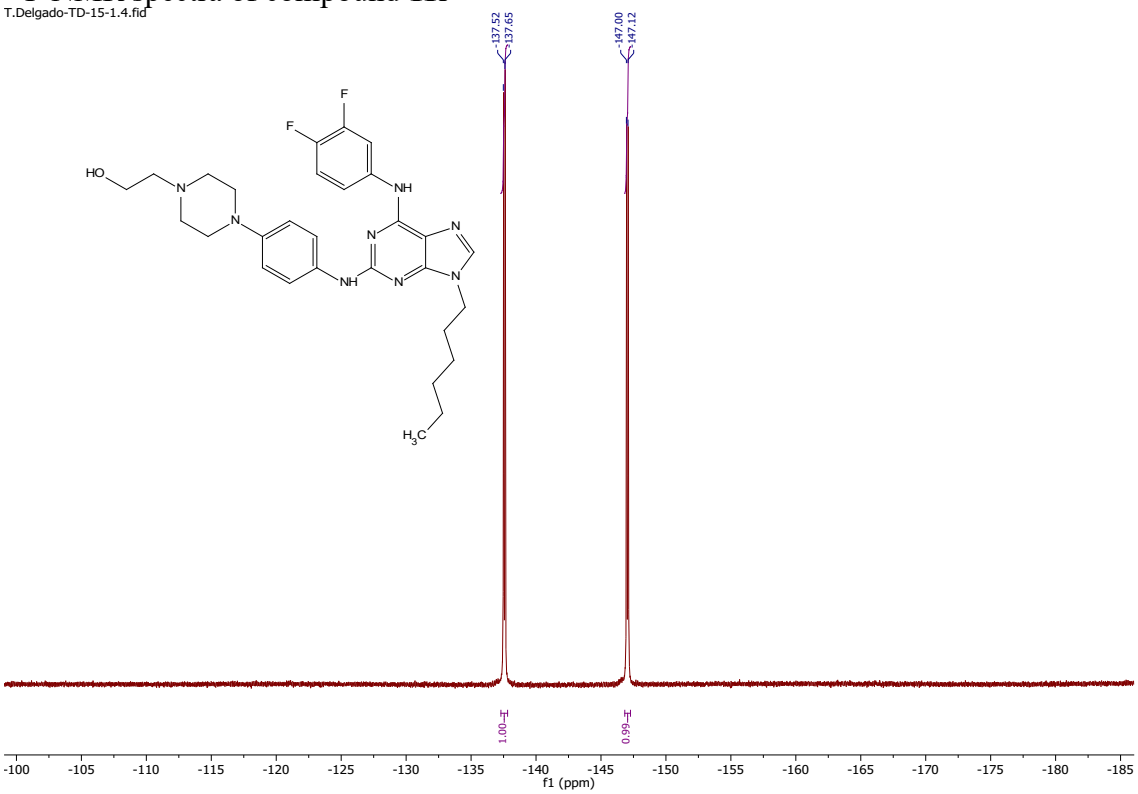
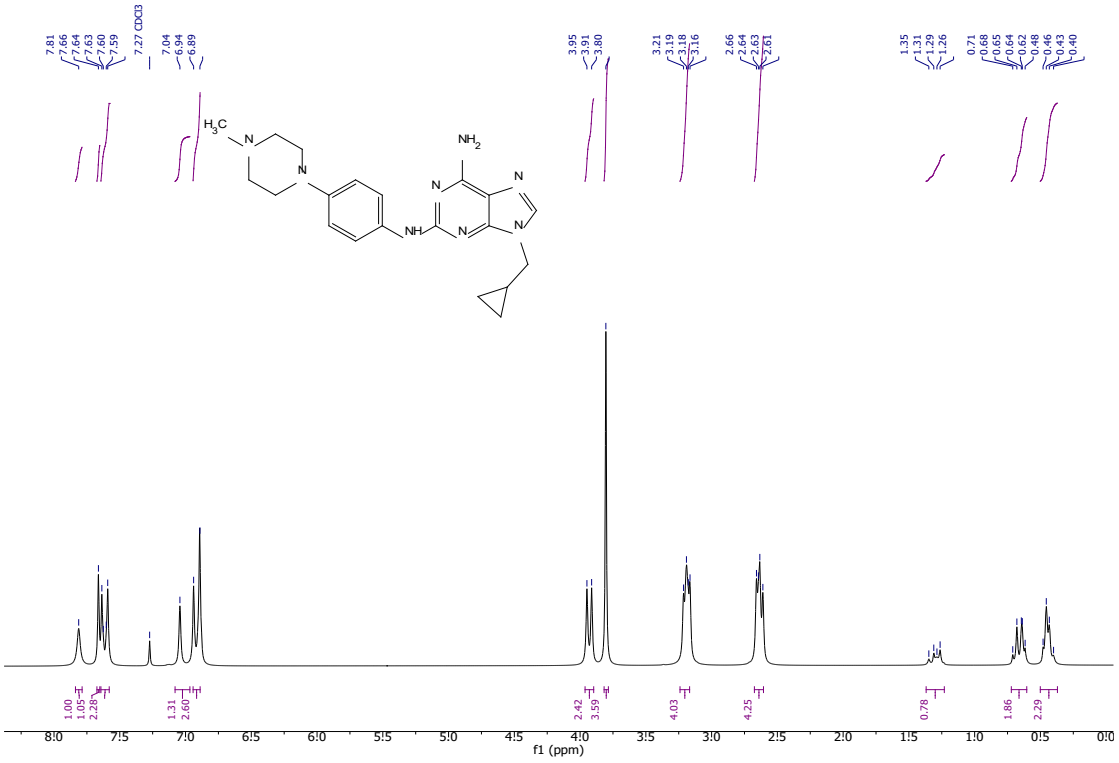
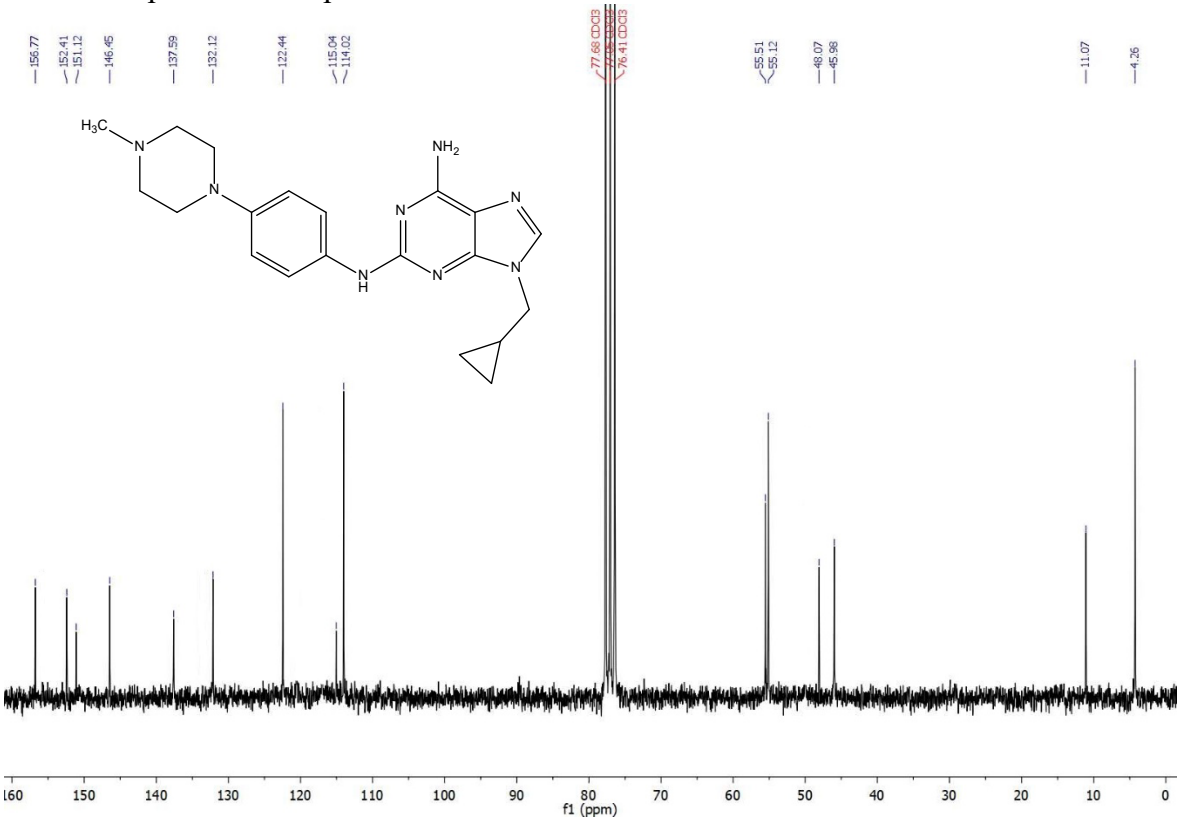


^{1}H NMR spectra of compound **13a**



^{13}C NMR spectra of compound **13b**



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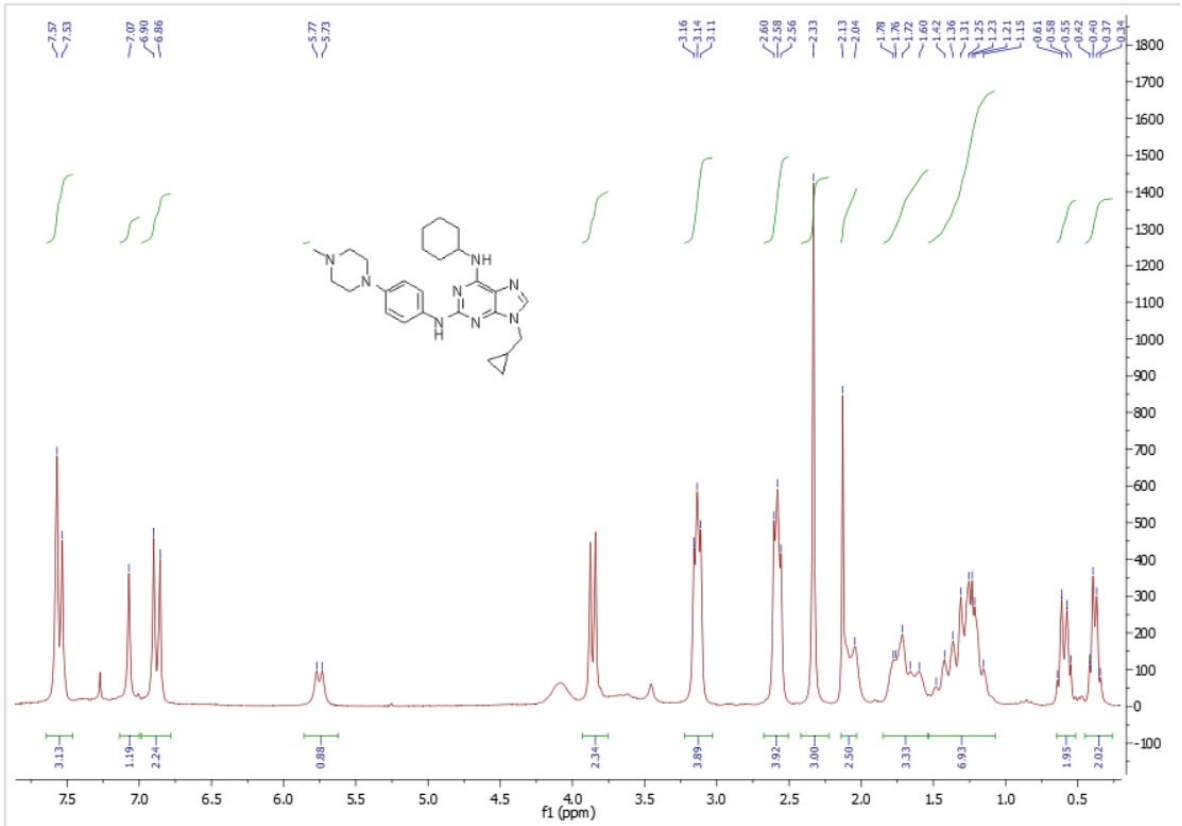

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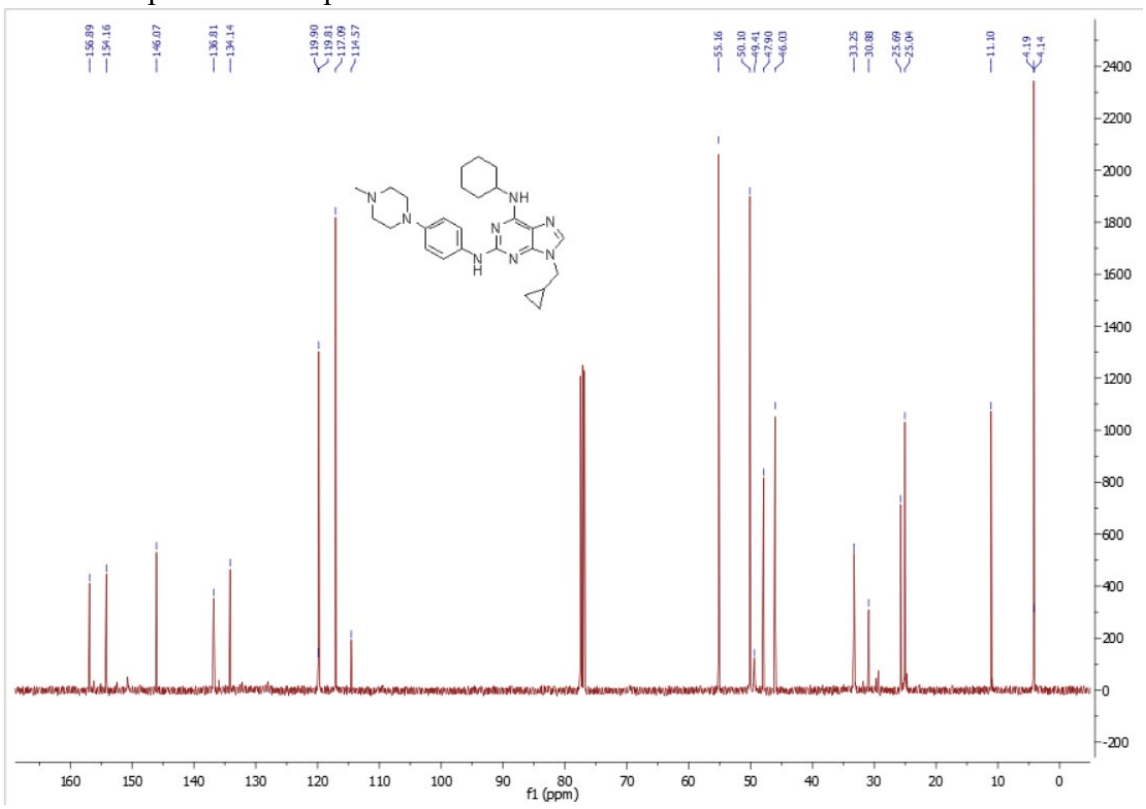

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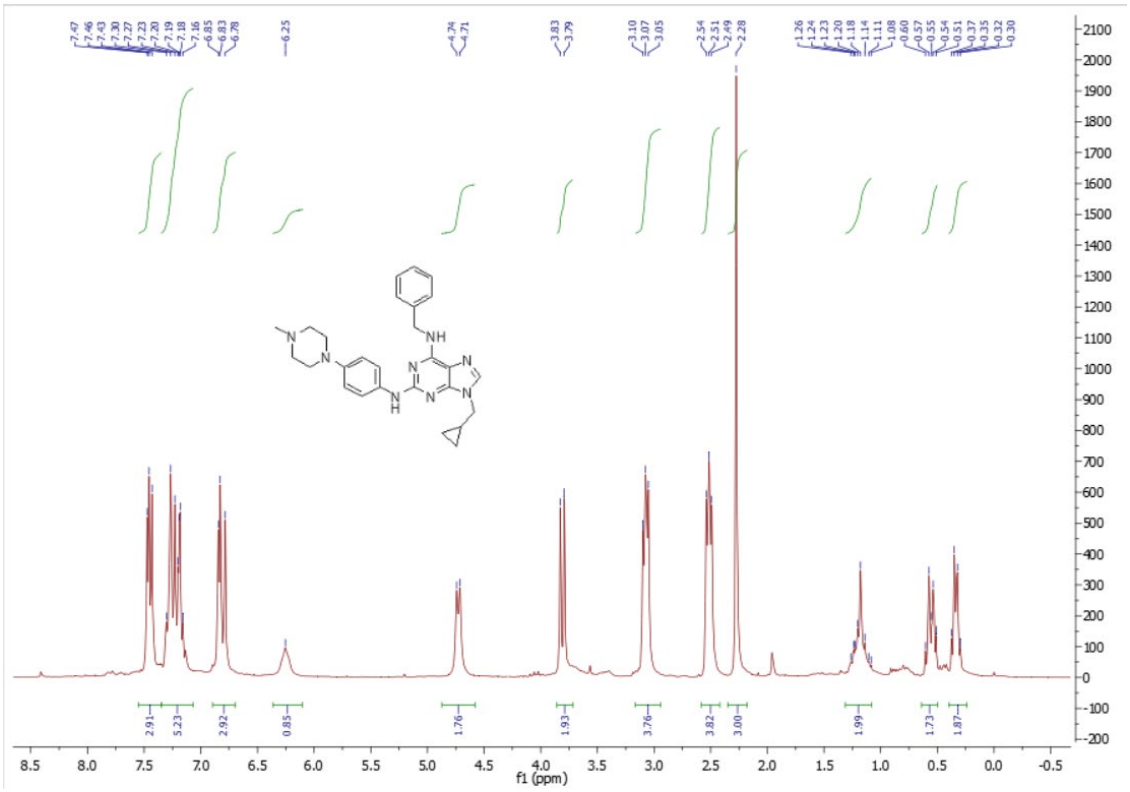

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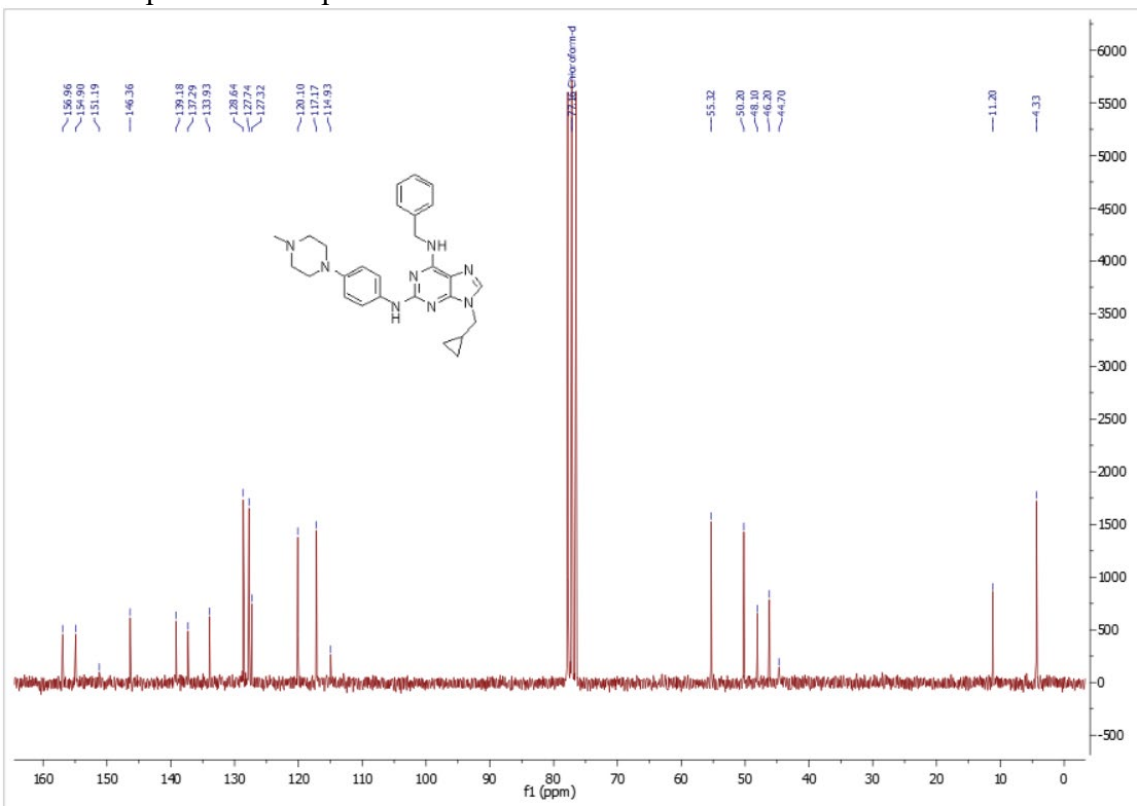

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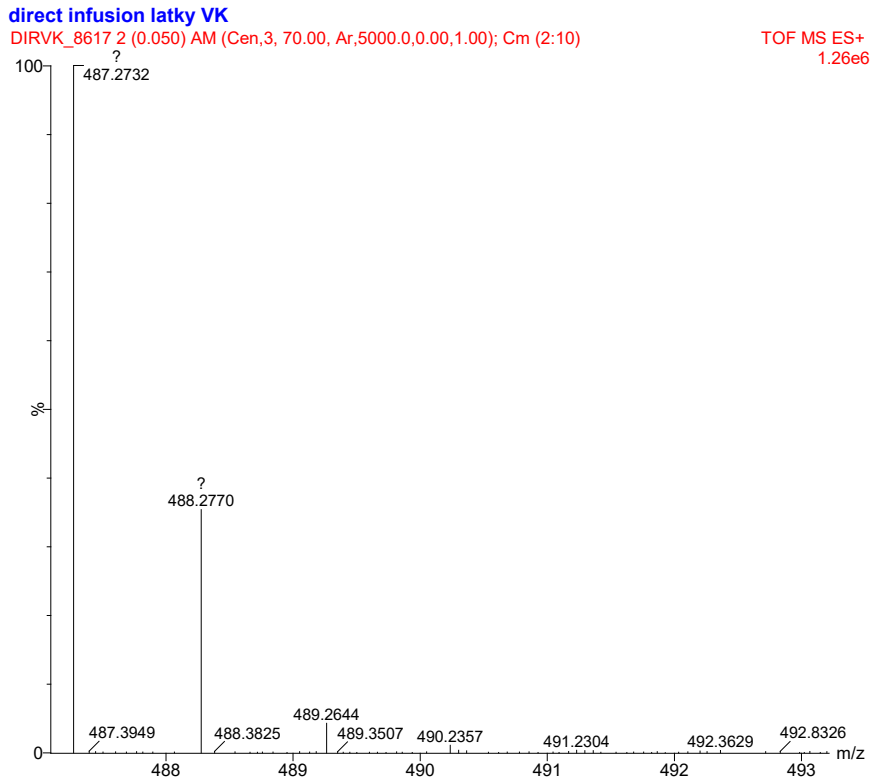

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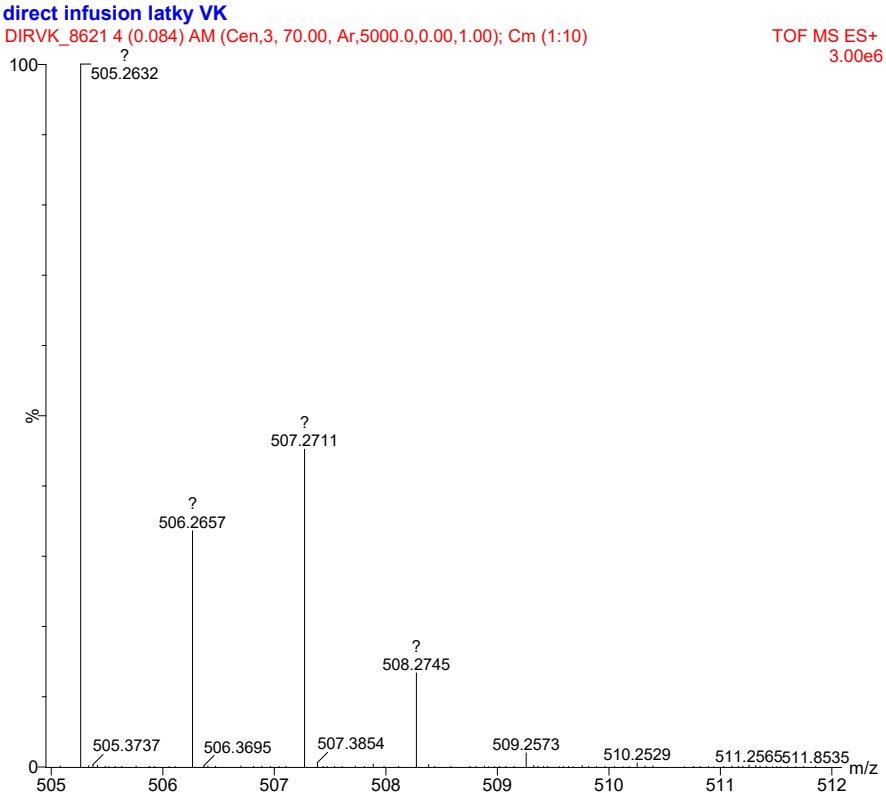

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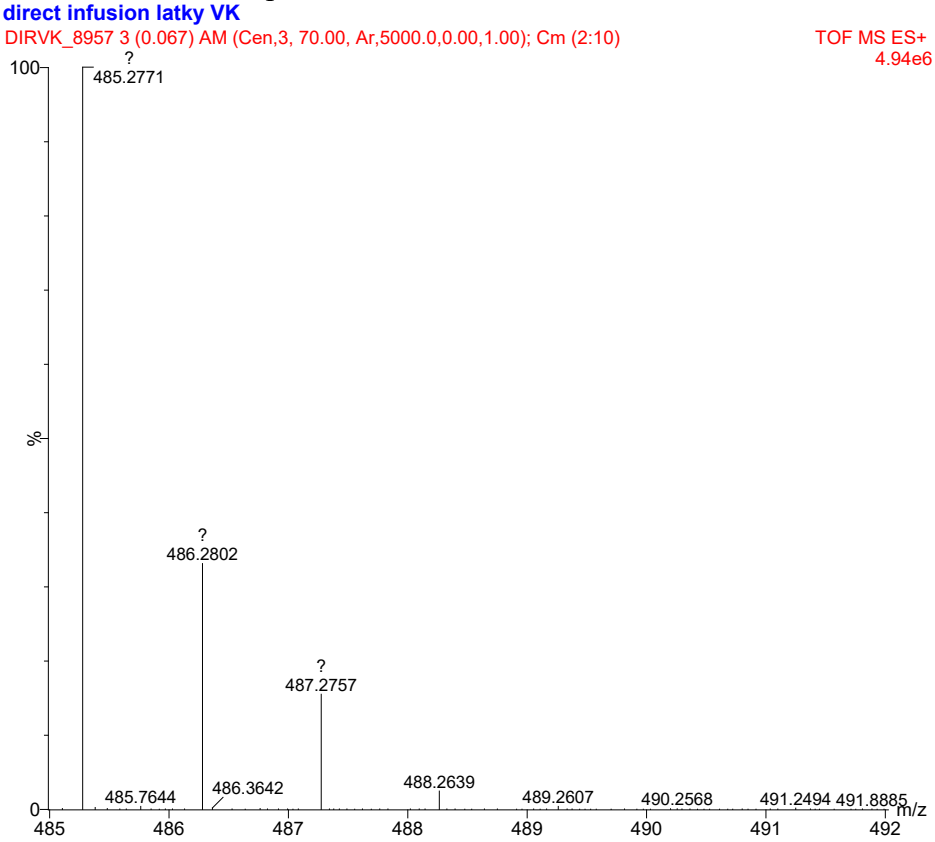

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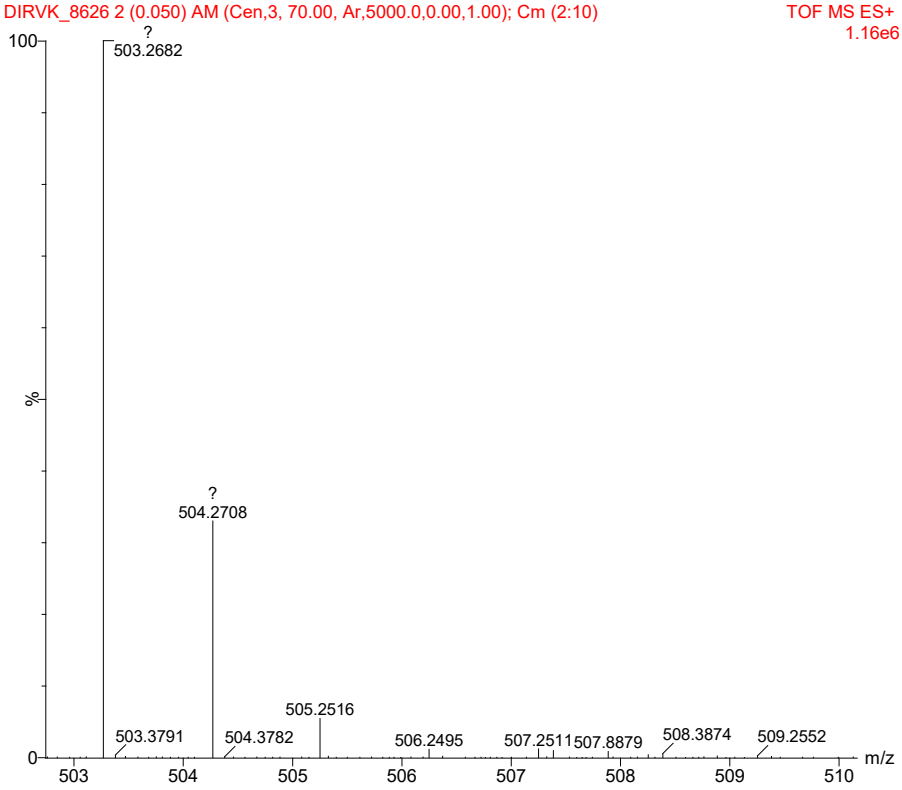
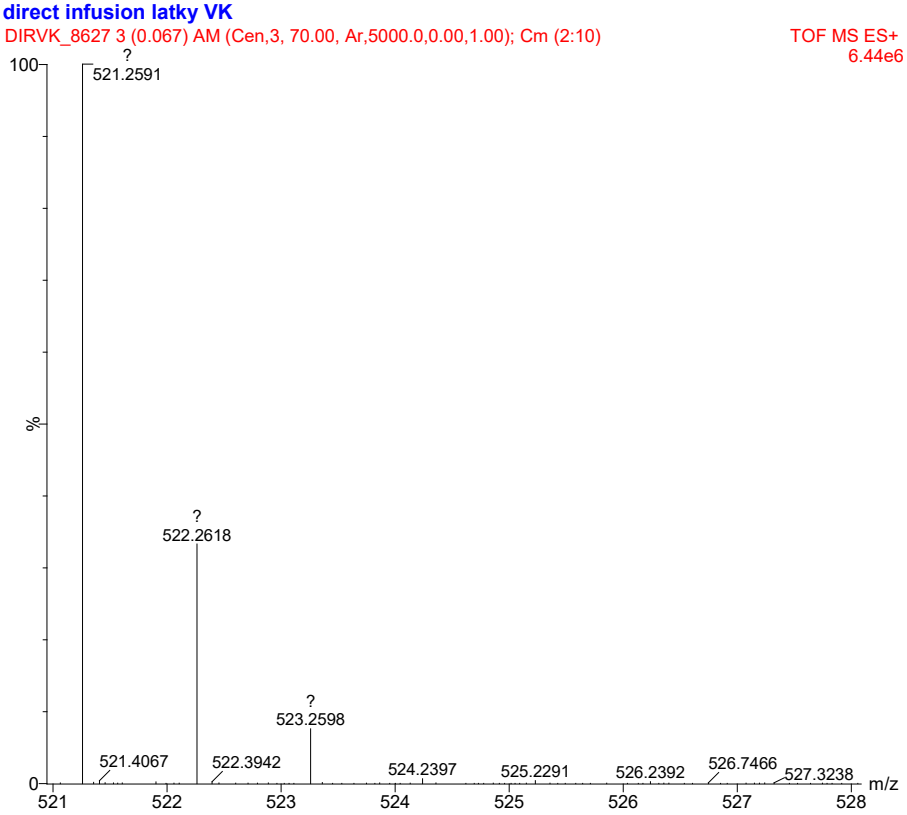
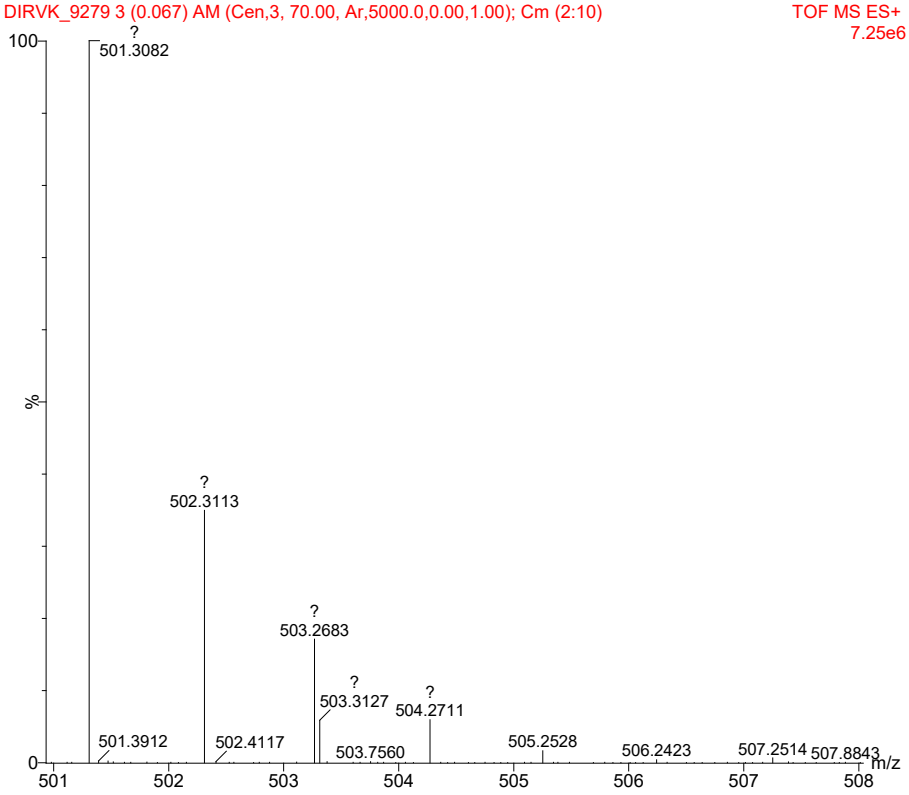


Mass spectra of compound **11c**



Mass spectra of compound **11d**



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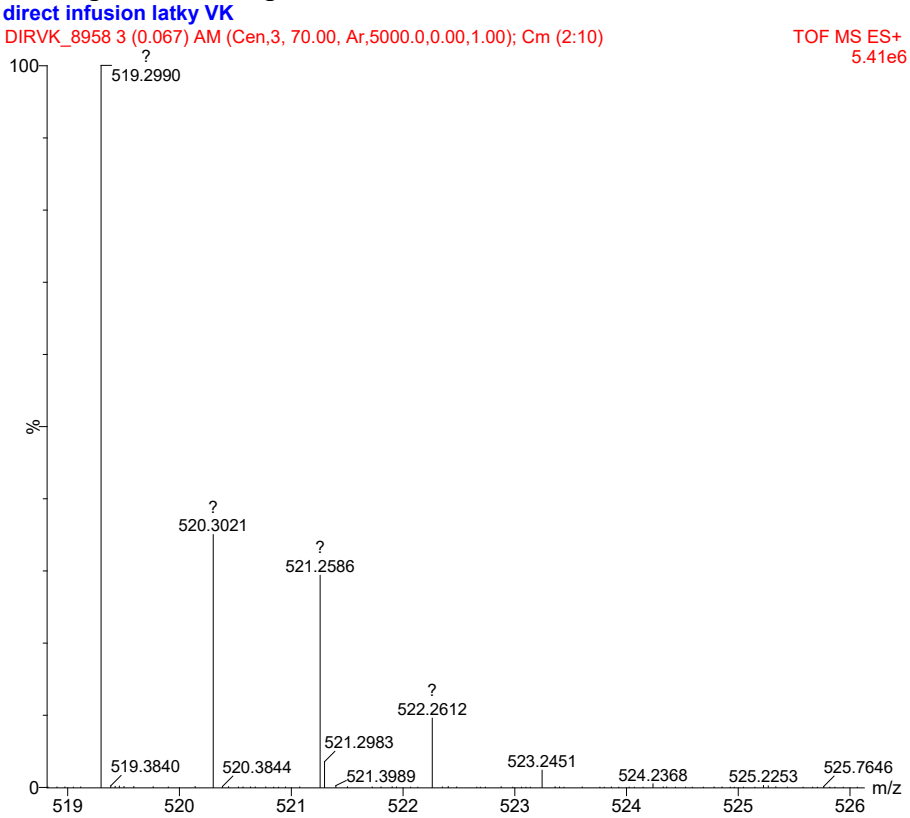
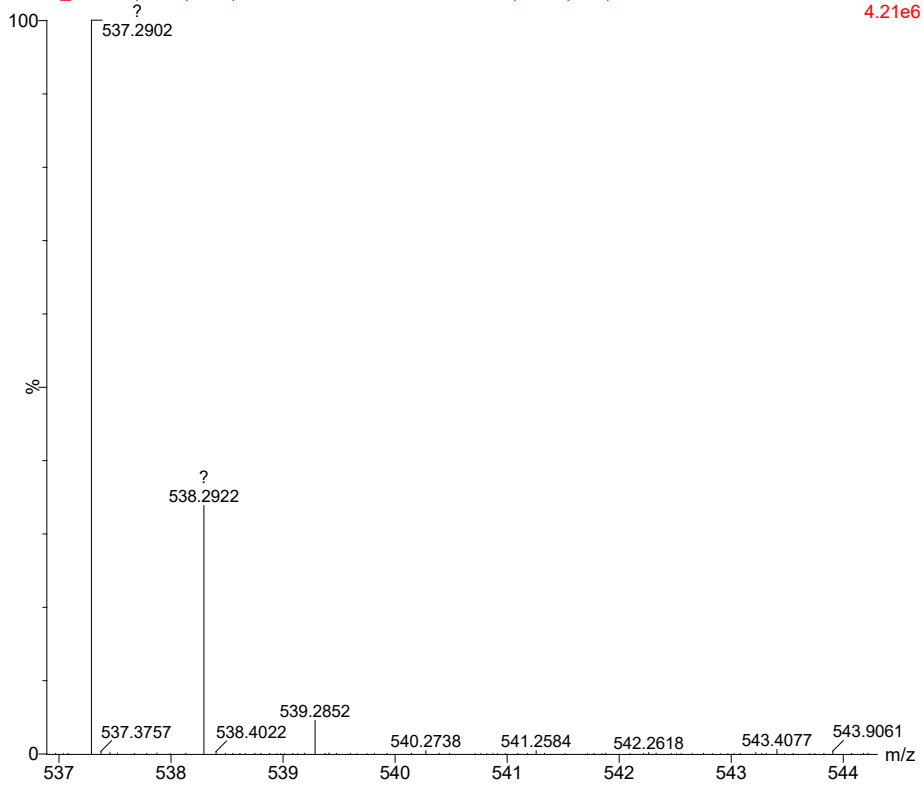


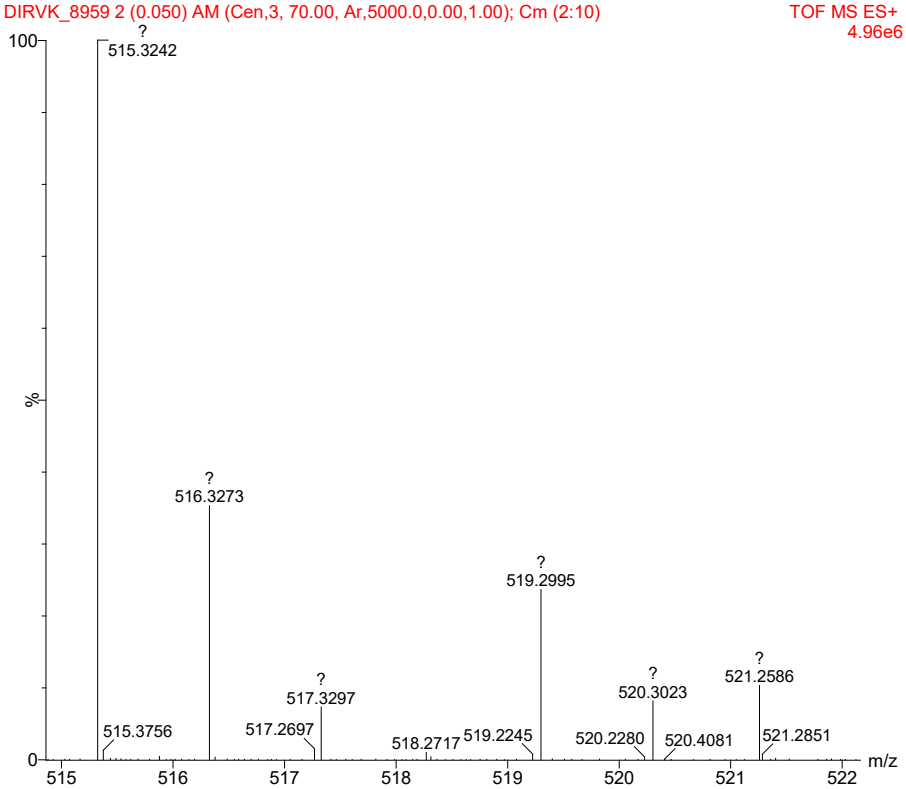
Mass spectra of compound **11f**



Mass spectra of compound **11g**

direct infusion latky VK

DIRVK_8959 2 (0.050) AM (Cen,3, 70.00, Ar,5000.0,0.00,1.00); Cm (2:10) TOF MS ES+ 4.96e6



Mass spectra of compound **11h**

direct infusion latky VK

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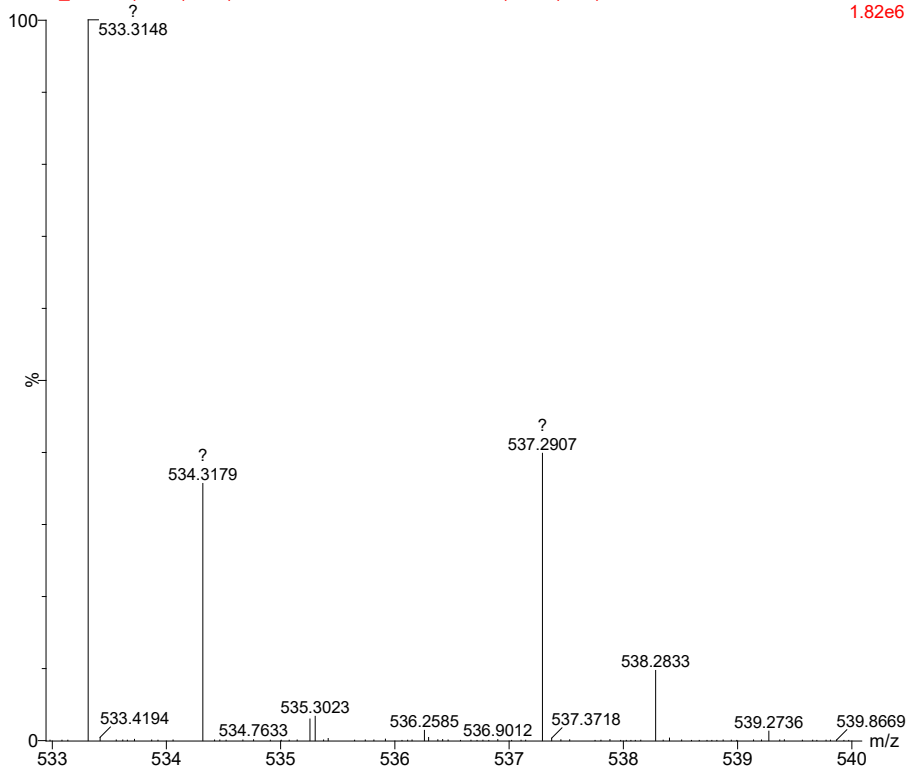
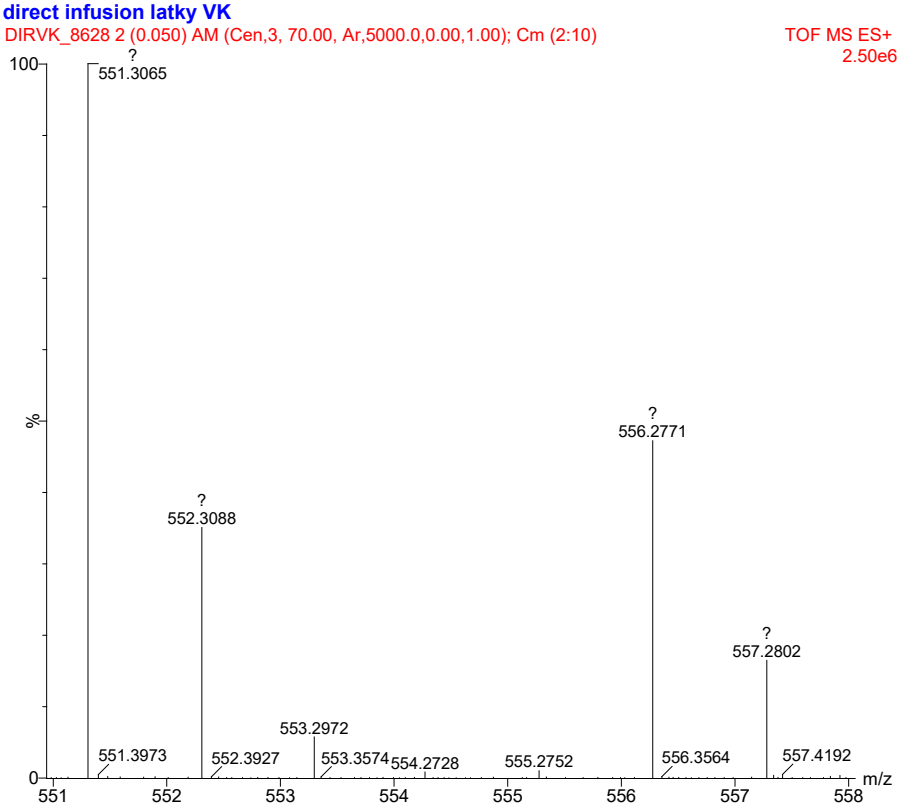
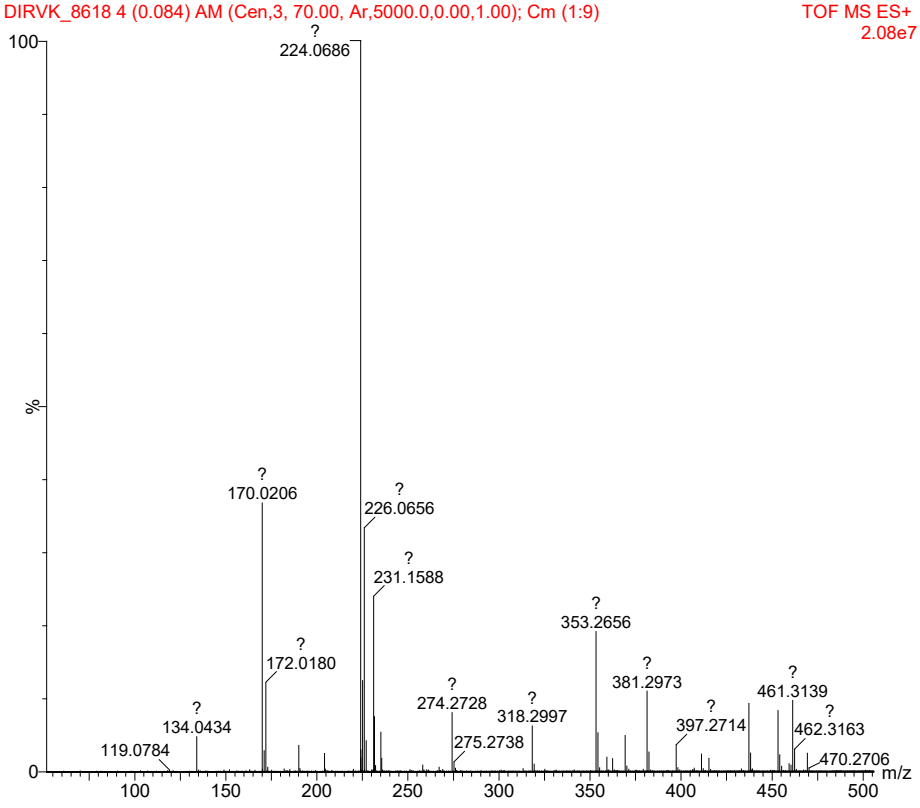


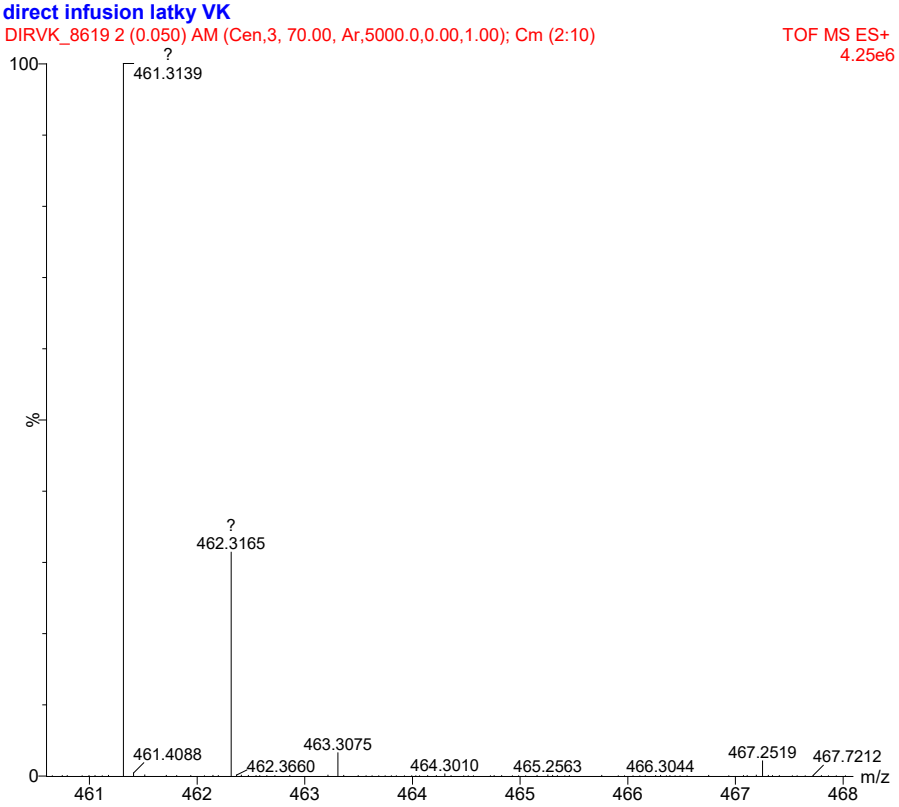
Mass spectra of compound **11i**



Mass spectra of compound **13a**



Mass spectra of compound **13b**



Mass spectra of compound **13c**

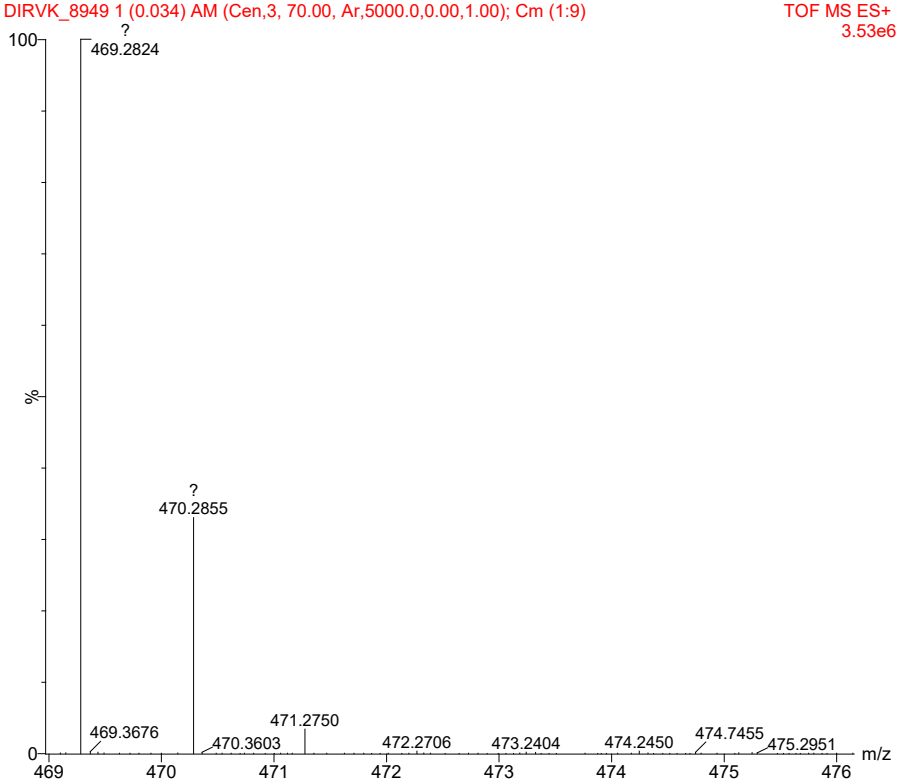


Table S1. Binding affinity scores (kcal/mol) of the purine derivatives with RDOCK, XP Score and MM-GBSA (ΔG_{bind} and their respective energy contributions) in the Bcr-Abl^{WT}.

Compd.	IC_{50}	pIC_{50}	RDOCK	XP Score	ΔG_{Bind}	$\Delta G_{Coul.}$	ΔG_{Hbond}	ΔG_{Lipo}	$\Delta G_{Packing}$	ΔG_{Solv_GB}	ΔG_{vdW}
7b	0.220	6.658	-15.66	-8.51	-64.21	-15.29	-1.16	-22.94	-0.79	26.87	-56.66
7a	0.180	6.745	-14.38	-9.16	-59.92	-40.76	-1.37	-21.14	-1.48	51.6	-59.46
13c	0.840	6.076	-15.31	-7.74	-50.43	-15.57	-1.69	-19.3	-1.05	26.14	-51.97
13b	11.050	4.957	-14.22	-7.57	-51.13	-41.41	-1.76	-17.41	-1.07	47.1	-45.27
13a	3.950	5.403	-13.94	-7.51	-48.57	-8.79	-1.3	-16.44	-0.59	15.37	-47.62
11i	1.680	5.775	-15.15	-6.91	-55.34	-3.88	-2.29	-29.12	-0.66	19.24	-51.52
11h	0.670	6.174	-15.39	-7.33	-53.75	-10.36	-1.54	-20.23	-0.75	20.36	-50.32
11g	0.830	6.081	-13.19	-7.25	-52.36	-9.56	-1.47	-19.50	-0.70	20.50	-49.50
11f	1.760	5.754	-17.66	-8.57	-66.75	-18.34	-2.44	-24.09	-1.59	31.97	-53.41
11e	0.130	6.886	-17.33	-8.40	-65.32	-17.65	-2.30	-23.31	-1.47	30.23	-52.14
11d	1.240	5.907	-16.84	-8.20	-60.11	-16.48	-2.01	-22.32	-1.40	28.06	-51.04
11c	0.019	7.721	-19.04	-9.11	-74.32	-23.49	-2.7	-20.95	-0.89	24.31	-54.69
11b	0.014	7.854	-20.69	-9.36	-73.34	-24.39	-2.69	-20.92	-0.89	26.22	-54.71
11a	0.037	7.432	-17.49	-9.23	-71.06	-26.33	-3.07	-21.6	-1.16	29.25	-57.85
I	0.090	7.046	-15.19	-8.54	-57.16	-43.55	-1.24	-20.24	-1.23	48.37	-47.55
II	0.040	7.398	-16.91	-8.83	-60.04	-37.06	-0.83	-21.32	-1.53	45.94	-55.10
III	0.040	7.398	-16.54	-9.57	-59.74	-39.82	-1.19	-20.50	-1.24	42.57	-49.56
Purvalanol*	—	—	-31.45	-9.60	-69.69	-18.25	-1.90	-18.51	-1.46	15.06	-46.15
Dasatinib**	0.00014	9.854	—	-13.91	-87.55	-36.72	-2.12	-25.85	0.92	43.96	-58.09

ΔG_{Bind} = Binding free energy

ΔG_{Coul} = Coulomb energy

ΔG_{Hbond} = Hydrogen bonding correction

ΔG_{Lipo} = Lipophilic energy

$\Delta G_{Packing}$ = Pi-pi packing correction

$\Delta G_{Solv\ GB}$ = Generalized Born electrostatic solvation energy

ΔG_{vdW} = van der Waals energy

ΔGBind = Binding free energy

*Docking score calculated with RDOCK, PDB: 6BL8

**Docking score calculated with PDB 2GQG

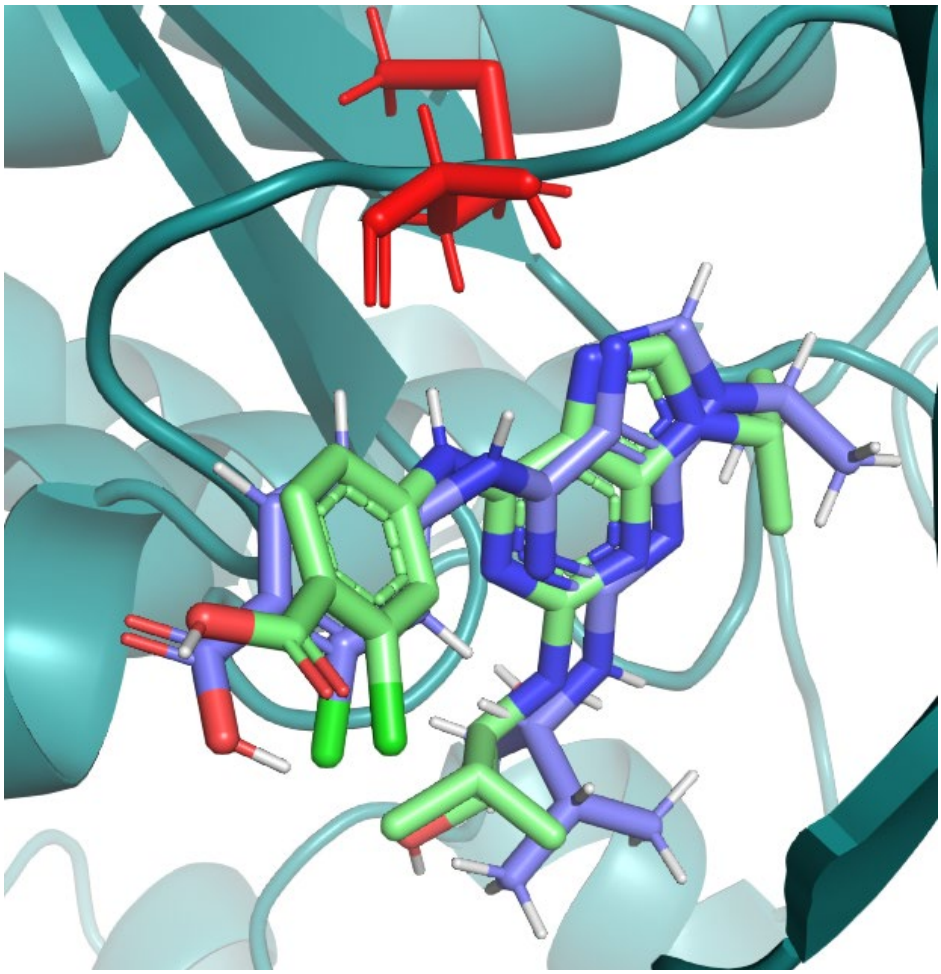


Figure S1. Co-crystallized ligand, purvalanol, in the Bcr-Abl binding site. Its experimentally determined binding mode is shown in blue, while the docking pose of purvalanol from our self-docking protocol is shown in green.

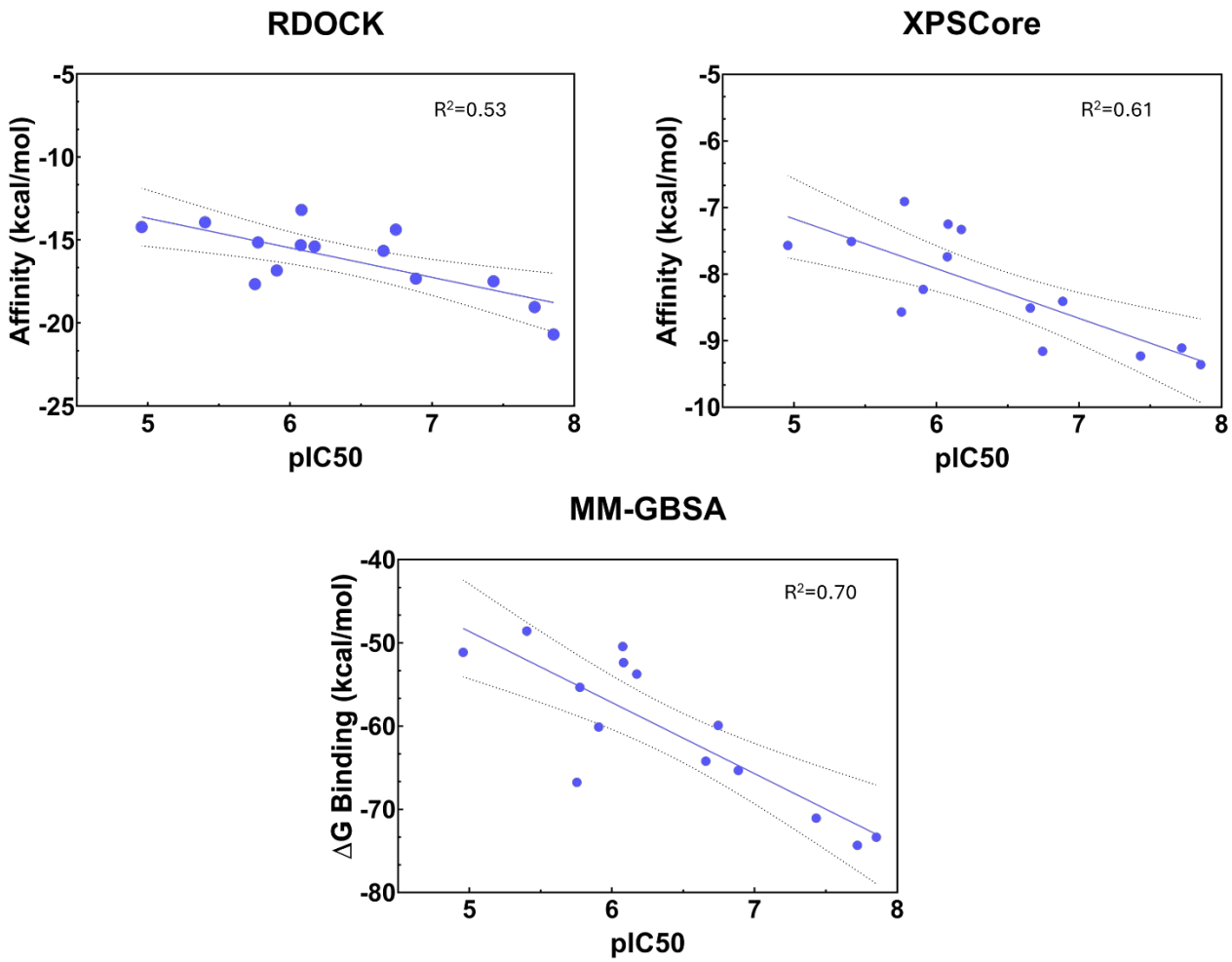


Figure S2. Correlation plot between biological activity in pIC_{50} and affinity energies achieved with RDOCK, Glide (XP Score) and MM-GBSA of the synthesised compounds.

Comp.	T315I (100%) KCL22B8 GI50 (uM)	SP Score	MM-GBSA
11c	9.06	-11.14	-65.17
11d	7.83	-11.48	-69.82
11e	6.91	-12.18	-71.67
11f	7.20	-12.12	-70.14

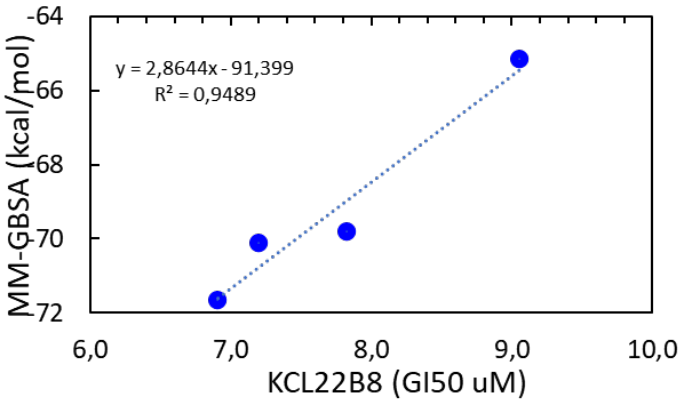
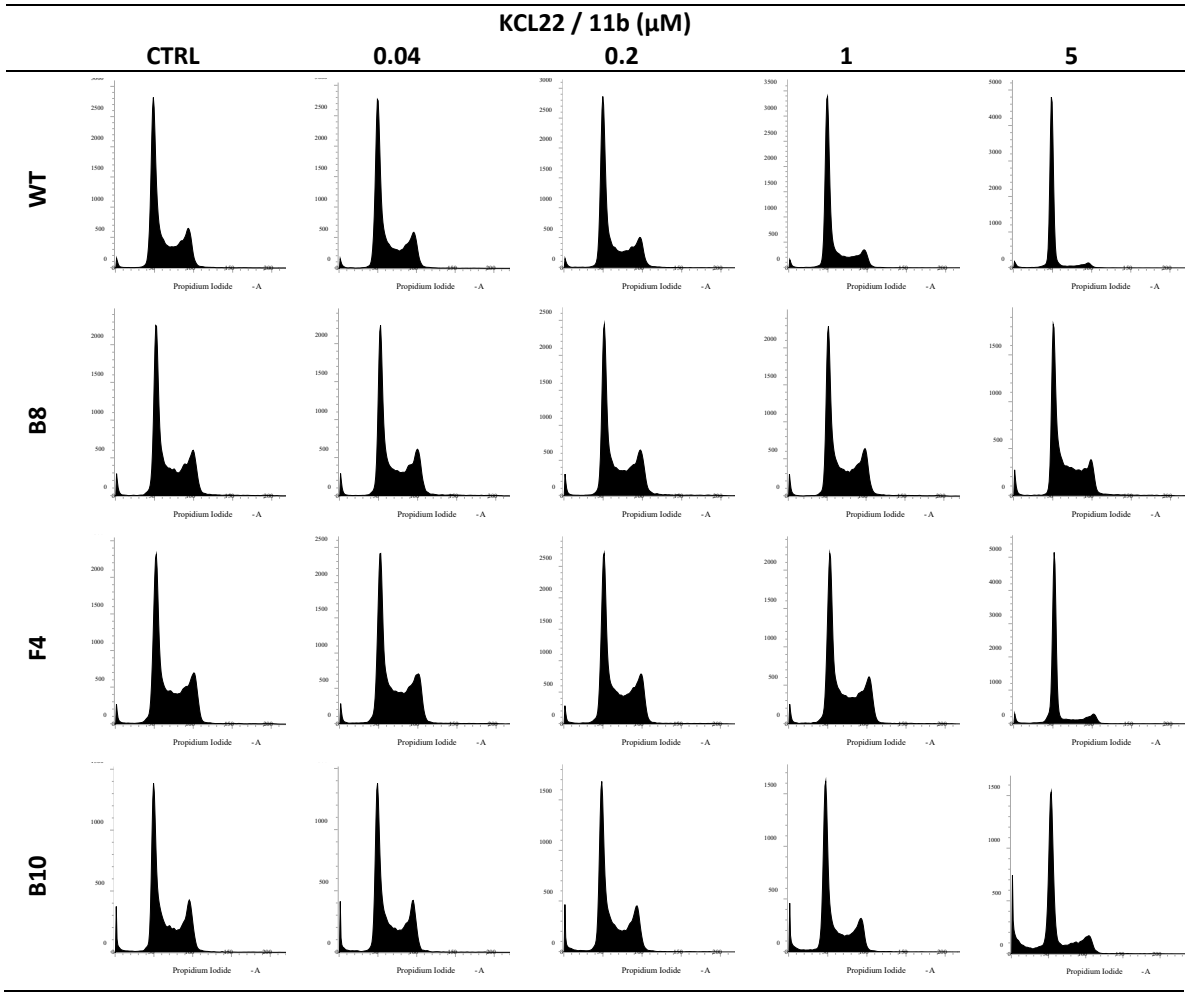
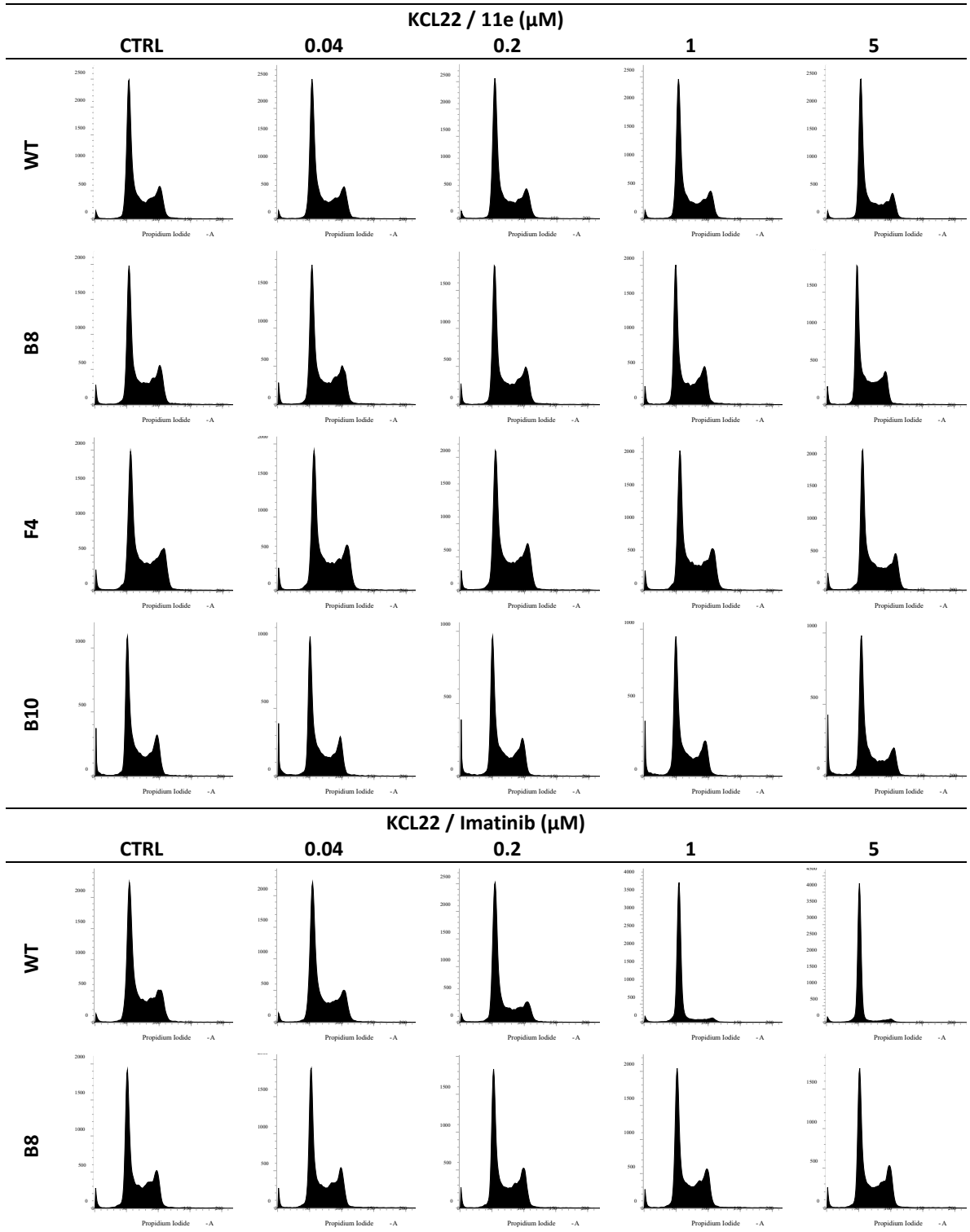
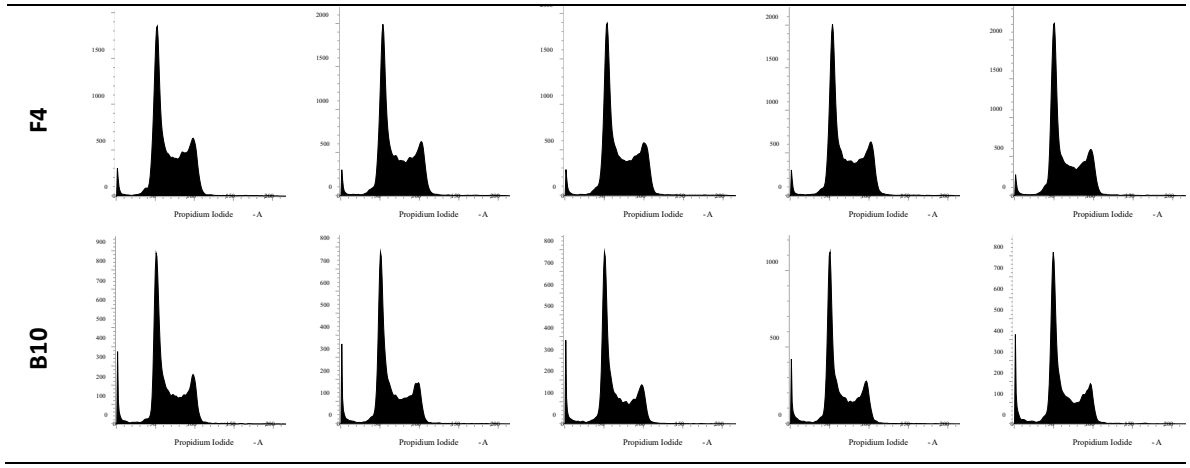


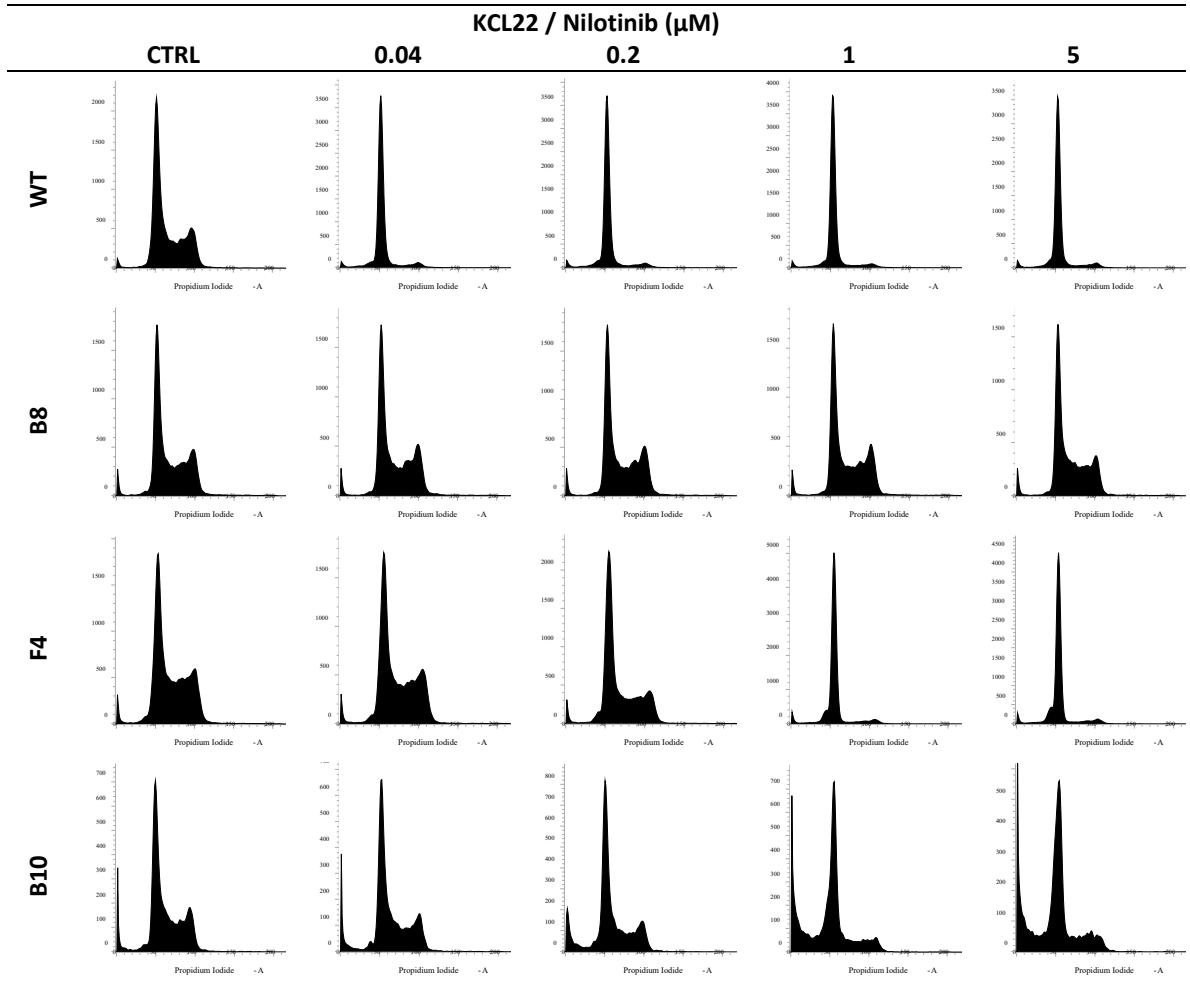
Figure S3. Correlation plot between biological activity in pGI_{50} values on B8 cells and affinity energies achieved with MM-GBSA of the selected compounds.

Figure S4. Histograms of flow cytometry of selected compounds on KCL cells and their subclones.




KCL22 / 11e (µM)
CTRL
0.04
0.2
1
5
WT
B8
F4
B10
Propidium Iodide - A
KCL22 / Imatinib (µM)
CTRL
0.04
0.2
1
5
WT
B8
Propidium Iodide - A


F4
B10
Propidium Iodide -A


KCL22 / Nilotinib (µM)
CTRL
0.04
0.2
1
5
WT
B8
F4
B10
Propidium Iodide -A