Synthesis of novel 2,9-disubstituted-6-morpholinopurine derivatives assisted by Virtual Screening and modelling of Class I PI3K isoforms

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Supporting Information

Table S1. Grid Box centre axial coordinates (x,y,z) for the 4 targets under study.

Table S2. $\Delta G_{binding}$ of synthetic precursors **25** for the 4 targets under study.

Figure S3. Interaction-binding mode of docked ligands in the active site of PI3Kα.

Table S4. General procedure for the synthesis of starting reagents 23

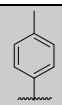
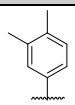
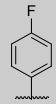
Table S5. ^{1}H NMR (DMSO-d6, 400 MHz) and ^{13}C NMR (DMSO-d6, 100 MHz) spectra of representative synthesised compounds.

Table S6 MS spectra of representative synthesised inhibitors

Table S1. Grid Box centre axial coordinates (x,y,z) for the 4 targets under study.

	PI3Kα	**PI3Kβ**	**PI3Kγ**	**PI3Kδ**
x center	-18.53	-26.22	17.04	-8.60
y center	11.64	21.24	-5.37	-30.25
z center	25.60	27.38	18.23	23.87

Table S2. $\Delta G_{binding}$ of synthetic precursors **25** for the 4 targets under study.

R1	$\Delta G_{binding}$ (kcal/mol)			
	PI3Kα	**PI3Kβ**	**PI3Kγ**	**PI3Kδ**
	-8.6	-8.4	-8.3	-8.0
	-10.0	-8.3	-9.1	-8.8
	-10.0	-8.5	-9.3	-8.7
	-10.4	-8.7	-9.8	-8.9
	-9.8	-8.4	-9.2	-9.2
	-10.2	-8.5	-9.3	-9.2

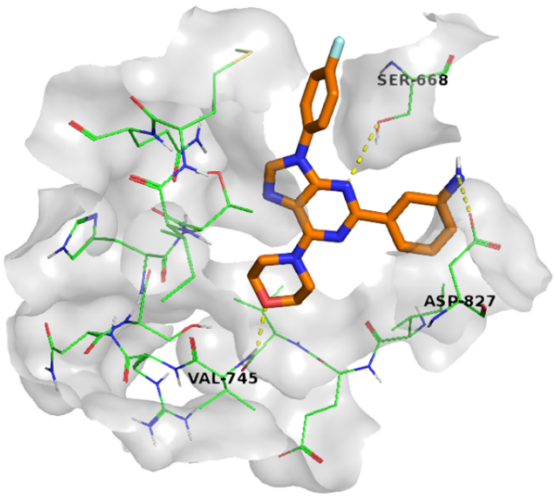


Figure S3. Interaction-binding mode of docked ligands in the active site of PI3Kα.

Table S4. General procedure for the synthesis of starting reagents 23

Morpholine (5 equivalent) was added to a suspension of 5-amino-4-cyanoformimidoylimidazole **22a-h** in acetonitrile. The mixture was stirred at room temperature until all the starting material was consumed (evidence by TLC). The obtained solid that precipitated from the reaction mixture was filtered and washed with acetonitrile and diethyl ether.

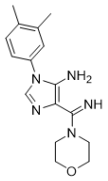
2.2.2.1. 4-[Imino(morpholin-4-yl)methyl]-1-(3,4-dimethylphenyl)-1H-imidazol-5-amine (23e)

Compound **23e** (4.84 g, 16.17 mmol, 87%), was obtained as a grey solid from the reaction of [5-amino-1-(3,4-dimethylphenyl)-1H-imidazol-4-yl](imino)acetonitrile **22e** (4.43 g, 18.49 mmol) with morpholine (6.45 mL, 73.97 mmol, 4 eq.) in acetonitrile (30 mL) after 21 hours. M.p. 175 – 177 °C. IR (nujol) νmax: 3377, 3119, 1624, 1595, 1586, 1548, 1515 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.31 (s, 1H), 7.29 (d, 1H, J^3 = 8.0 Hz), 7.25 (t, 1H, J^4 = 2.0 Hz), 7.17 (dd, 1H, J^3 = 8.0 Hz, J^4 = 2.0 Hz), 6.7 – 4.7 (br.s, 2H, NH_2, exchangeable by D_2O), 3.67 (t, 4H, J^3 = 4.8 Hz), 3.33 (t, 4H, J^3 = 4.8 Hz), 2.27 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.23, 139.41, 137.90, 136.33, 132.45, 130.47, 129.86, 125.66, 122.02, 114.27, 66.07, 47.13, 19.33, 18.93. MS (ESI) 300 [M^+ + 1]. HRMS (ESI): *m*/*z* [M^+ + 1] calcd for $C_{16}H_{22}N_5O$: 300.1824; Found: 300.1829.

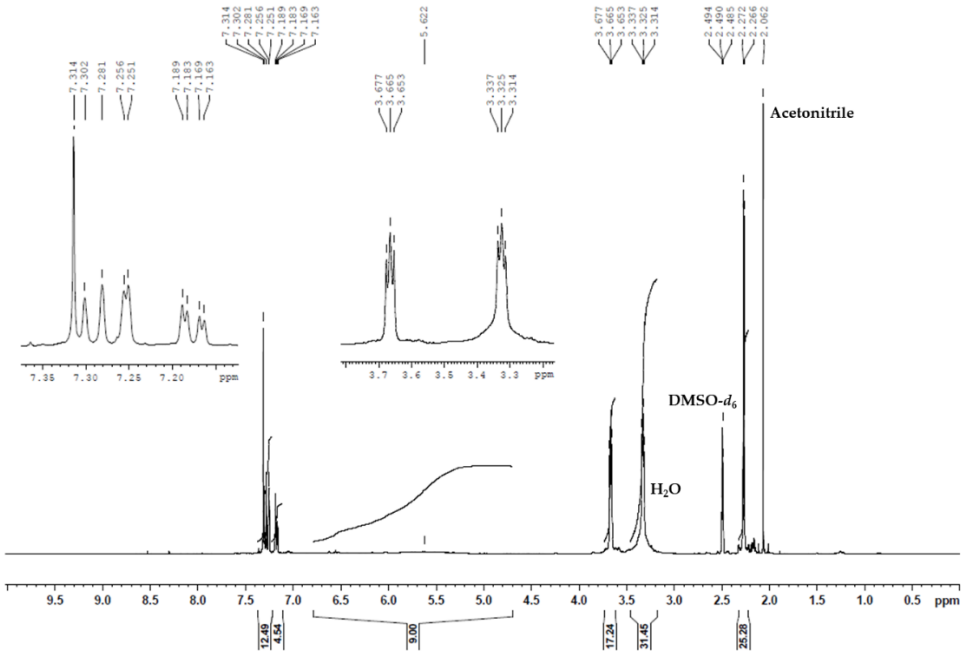
2.2.2.2. 4-[Imino(morpholin-4-yl)methyl]-1-(4-aminophenyl)-1H-imidazol-5-amine (23h)

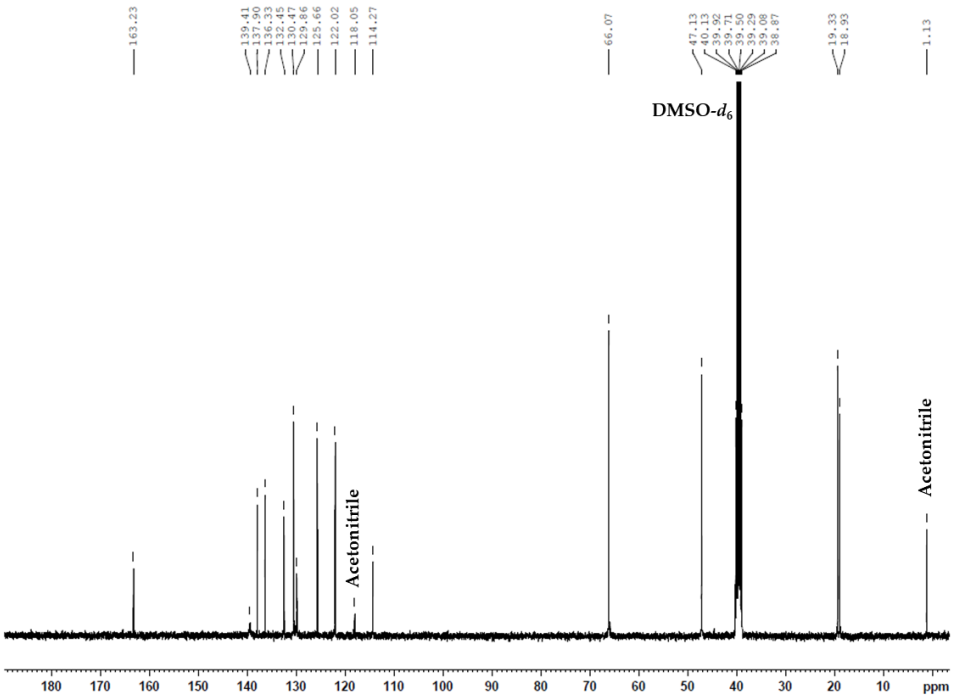
Compound **23h** (3.64 g, 12.72 mmol, 95%), was obtained as an off-white solid from the reaction of [5-amino-1-(4-aminophenyl)-1H-imidazol-4-yl](imino)acetonitrile **22h** (3.04 g, 13.43 mmol) with morpholine (5.86 mL, 67.14 mmol, 5 eq.) in acetonitrile (23 mL) after 16 hours. M.p. 178 – 180 °C. IR (nujol) νmax: 3322, 3288, 3196, 3113, 1626, 1609, 1586, 1550, 1521 cm^{-1}. ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.18 (s, 1H), 7.04 (d, 2H, J^3 = 8.4 Hz), 6.66 (d, 2H, J^3 = 8.4 Hz), 6.0 – 4.7 (br s, 4H, NH_2, exchangeable by D_2O), 3.66 (t, 4H, J^3 = 4.4 Hz), 3.30 (t, 4H, J^3 = 4.4 Hz); ^{13}C NMR (100 MHz, DMSO-d_6) δ: 163.55, 148.99, 139.51, 130.31, 126.13, 122.66, 114.10, 113.76, 66.12, 47.25. MS (ESI) 287 [M^+ + 1]. HRMS (ESI): *m*/*z* [M^+ + 1] calcd for $C_{14}H_{19}N_6O$: 287.1620; Found: 287.1625.

Table S5. ^{1}H NMR (DMSO-d6, 400 MHz) and ^{13}C NMR (DMSO-d6, 100 MHz) spectra of representative synthesised compounds.



23e





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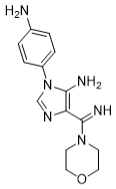

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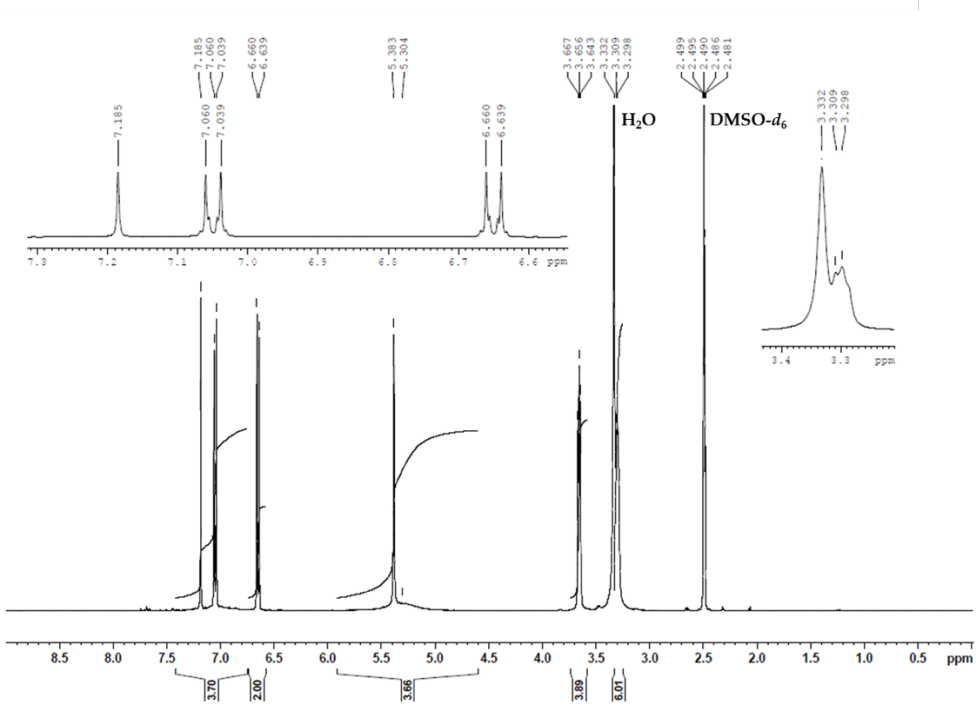

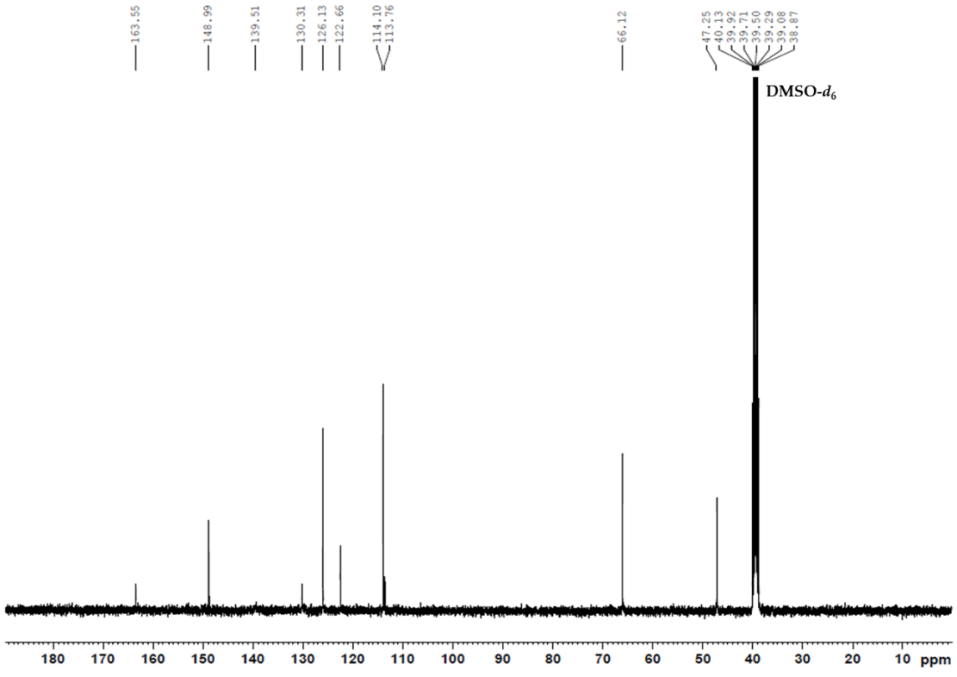

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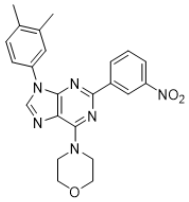

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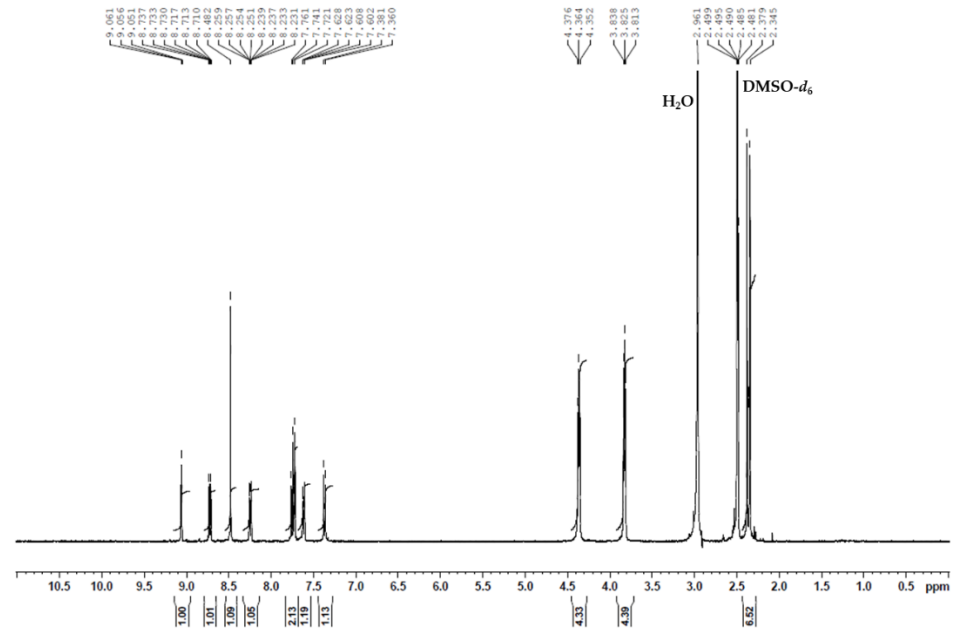

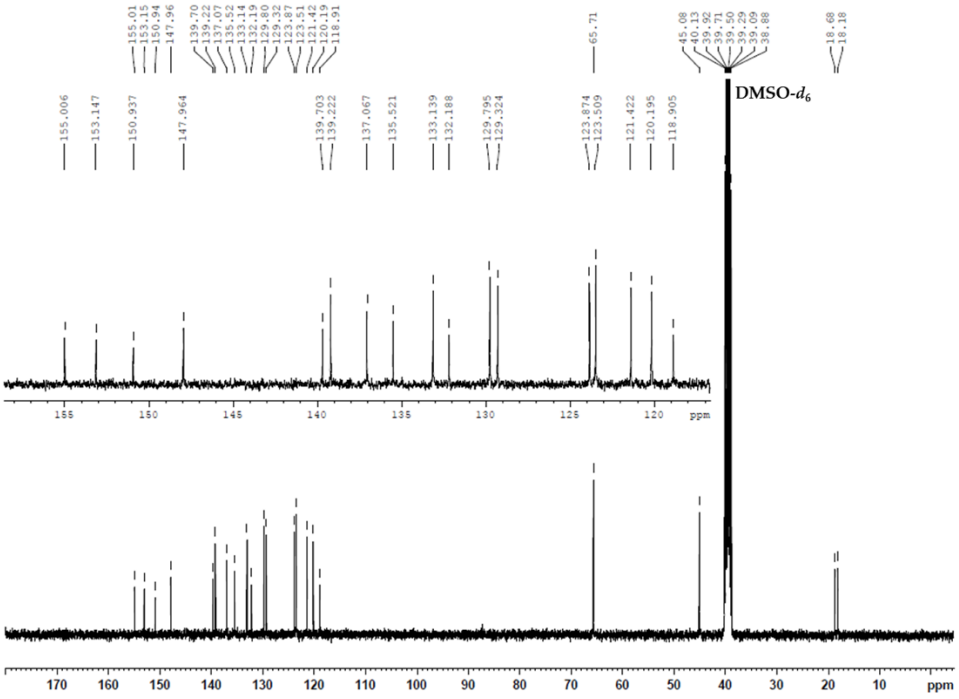

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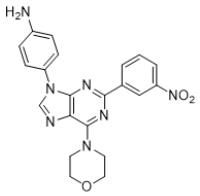

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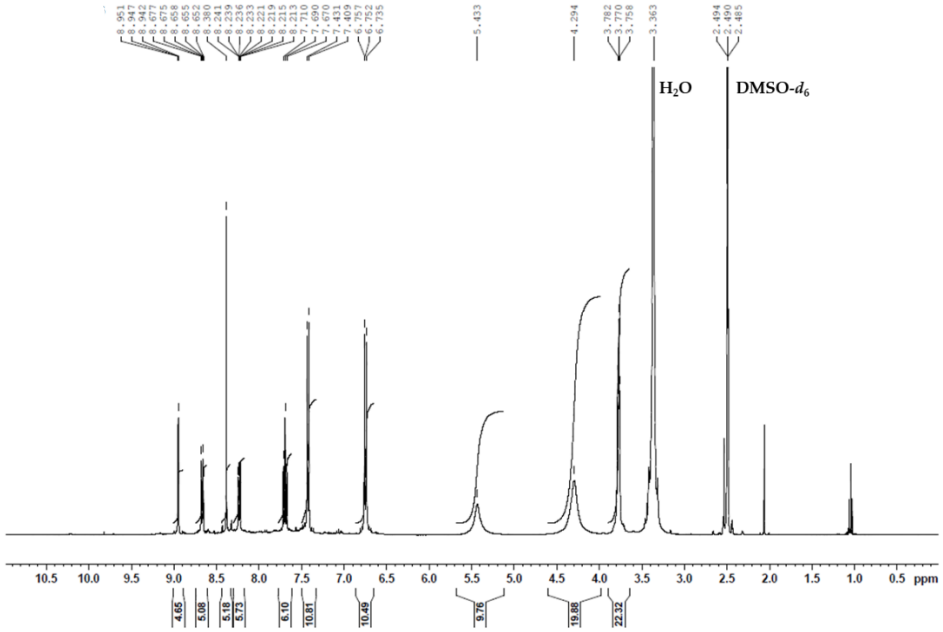

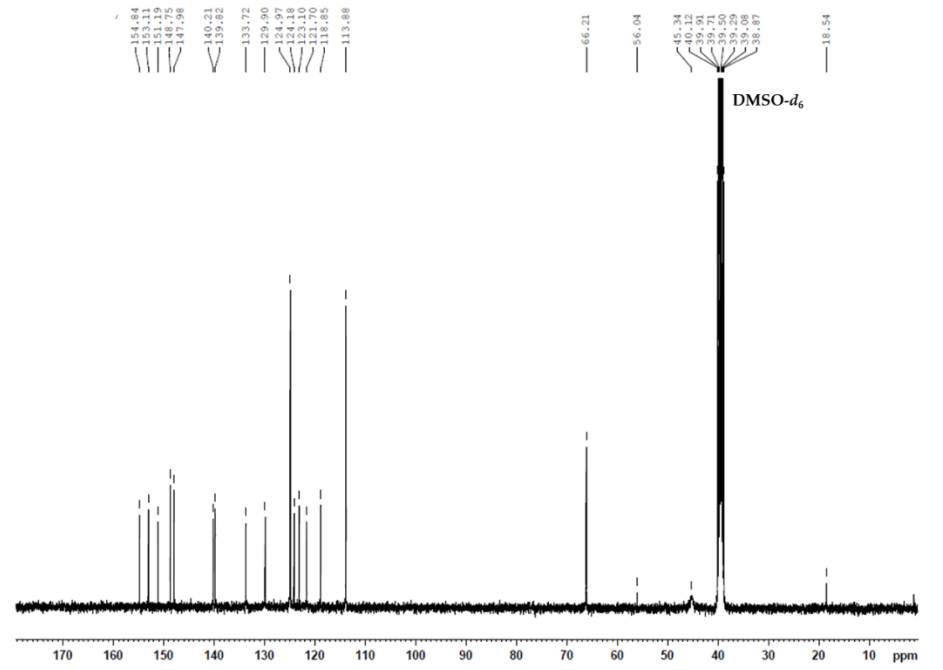

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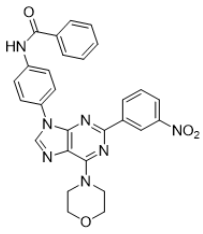

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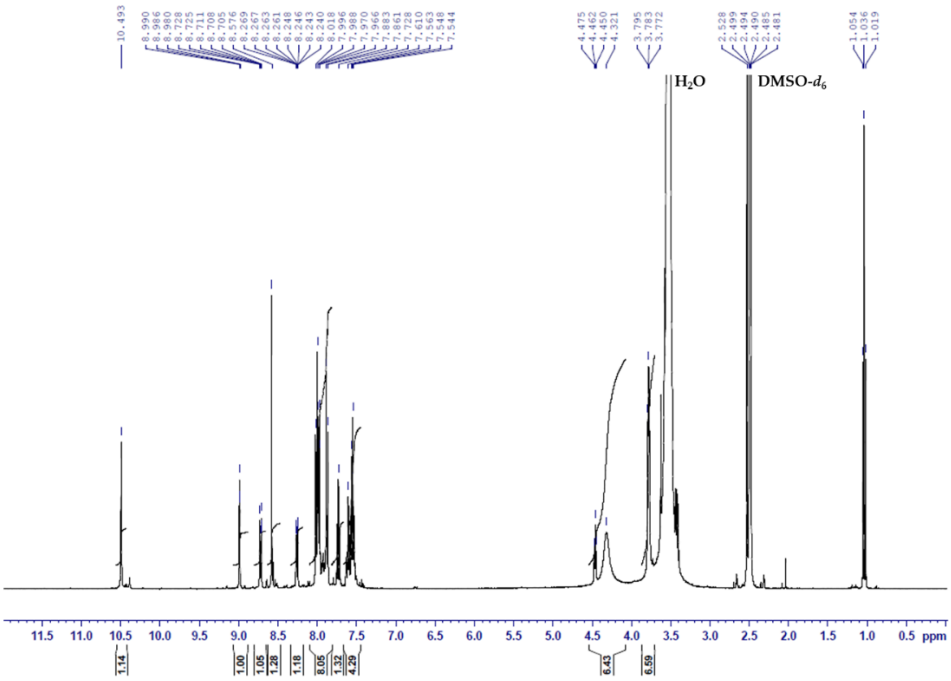

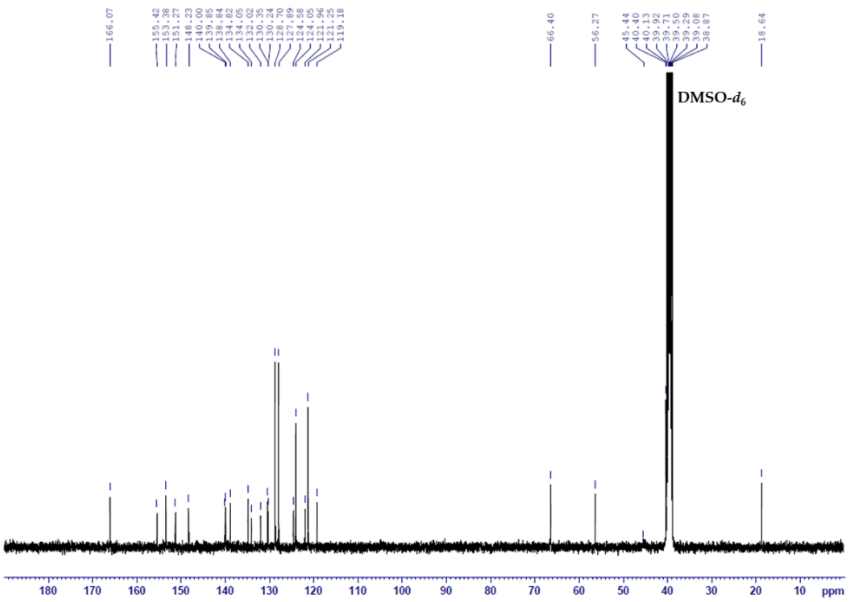

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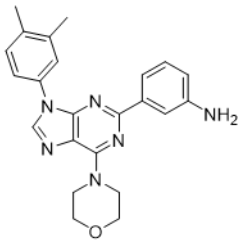

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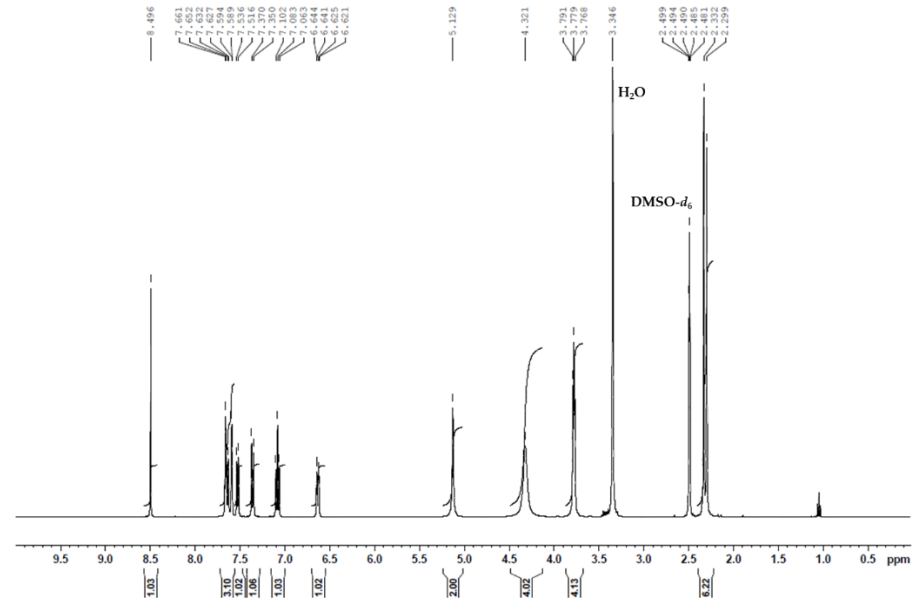

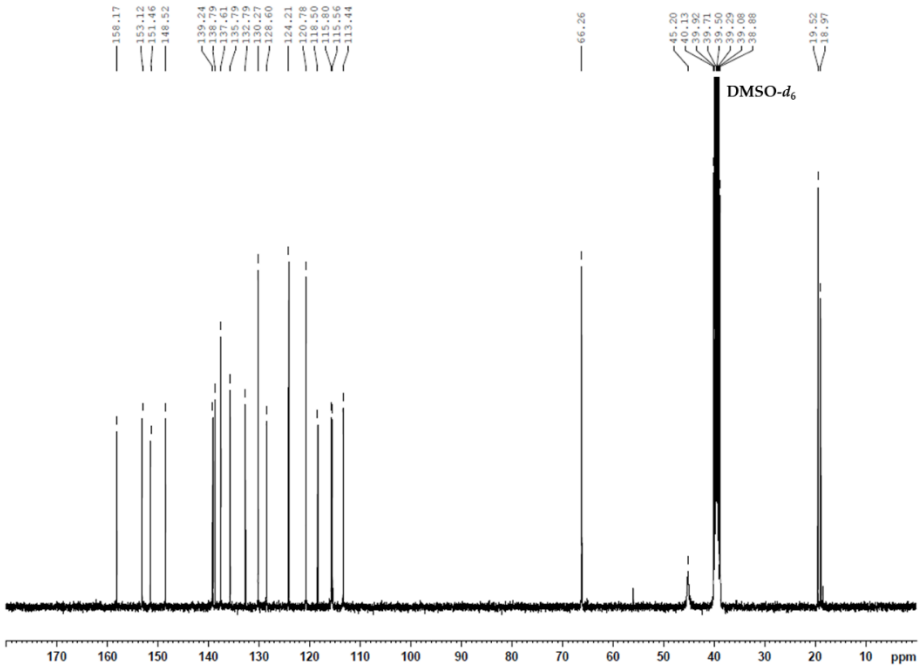

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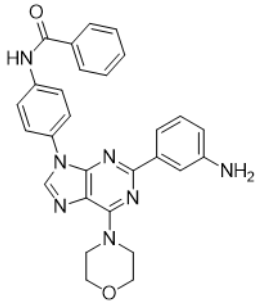

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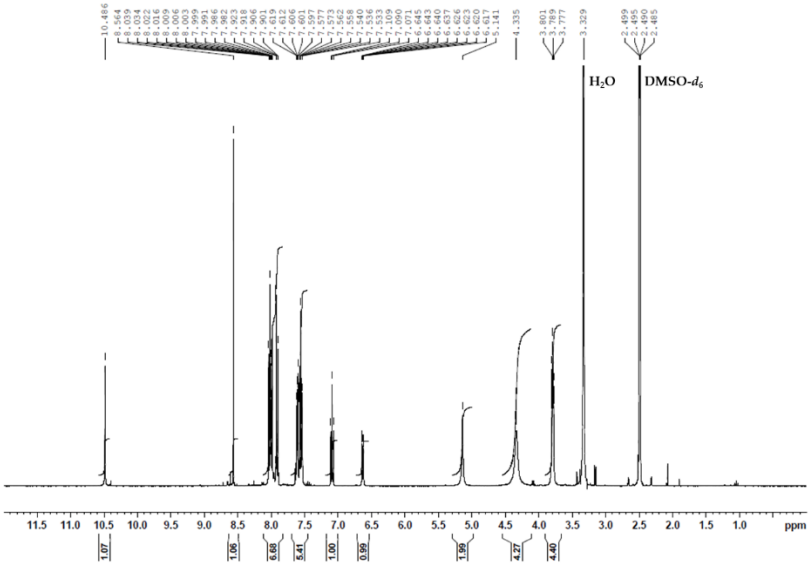

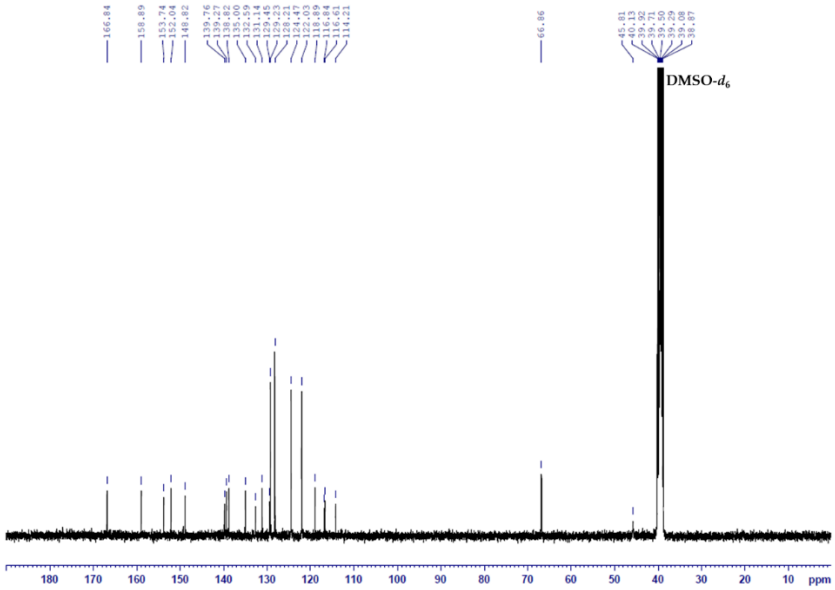

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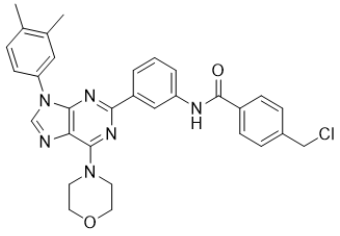

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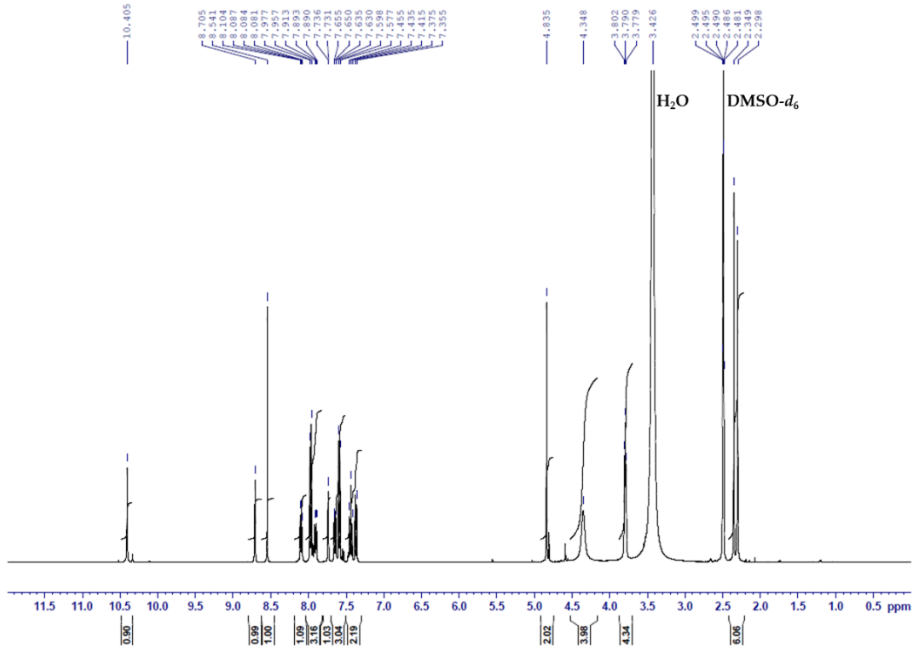

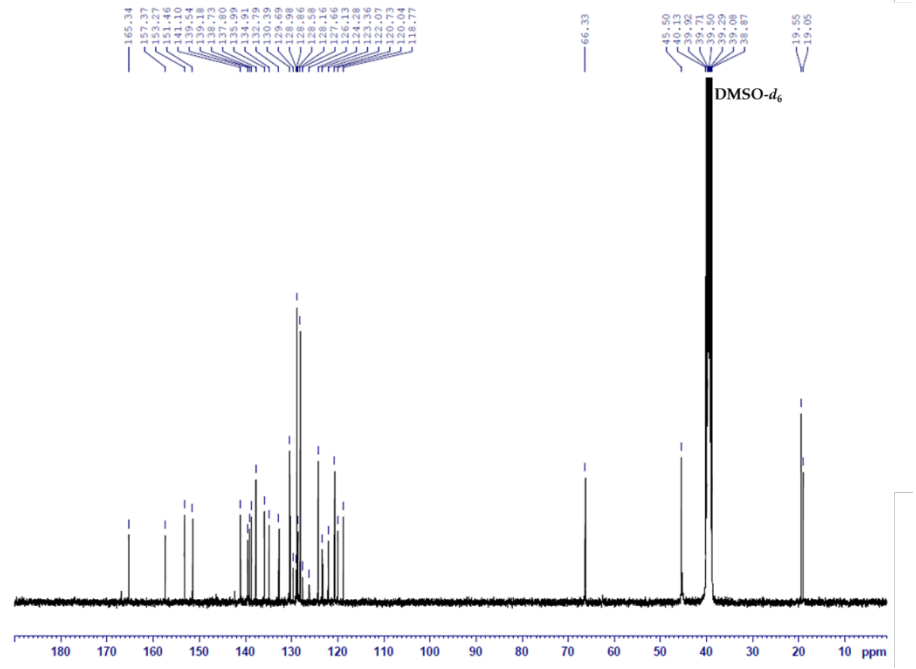

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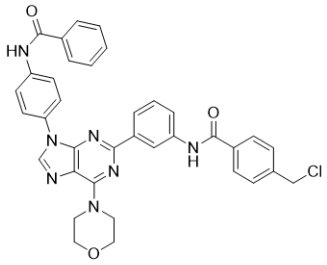

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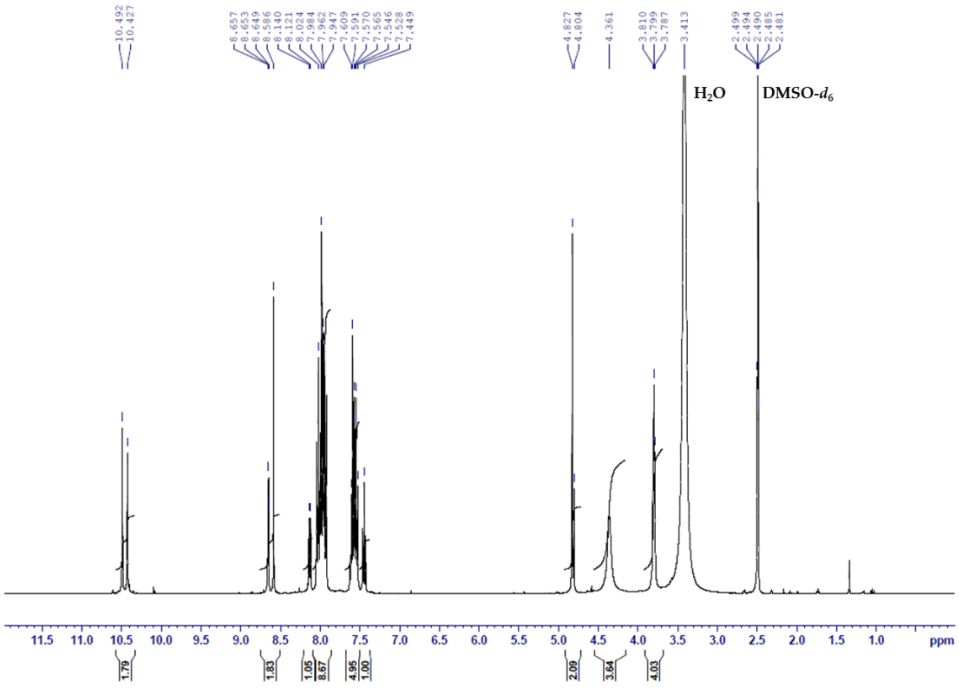

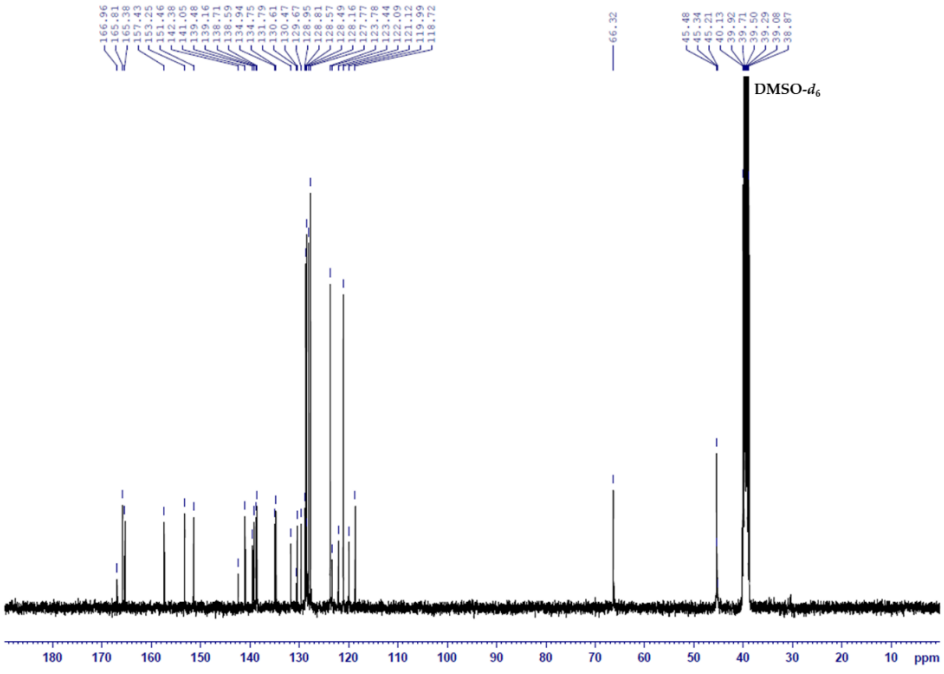

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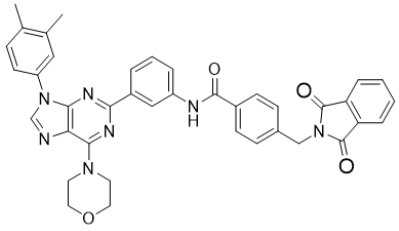

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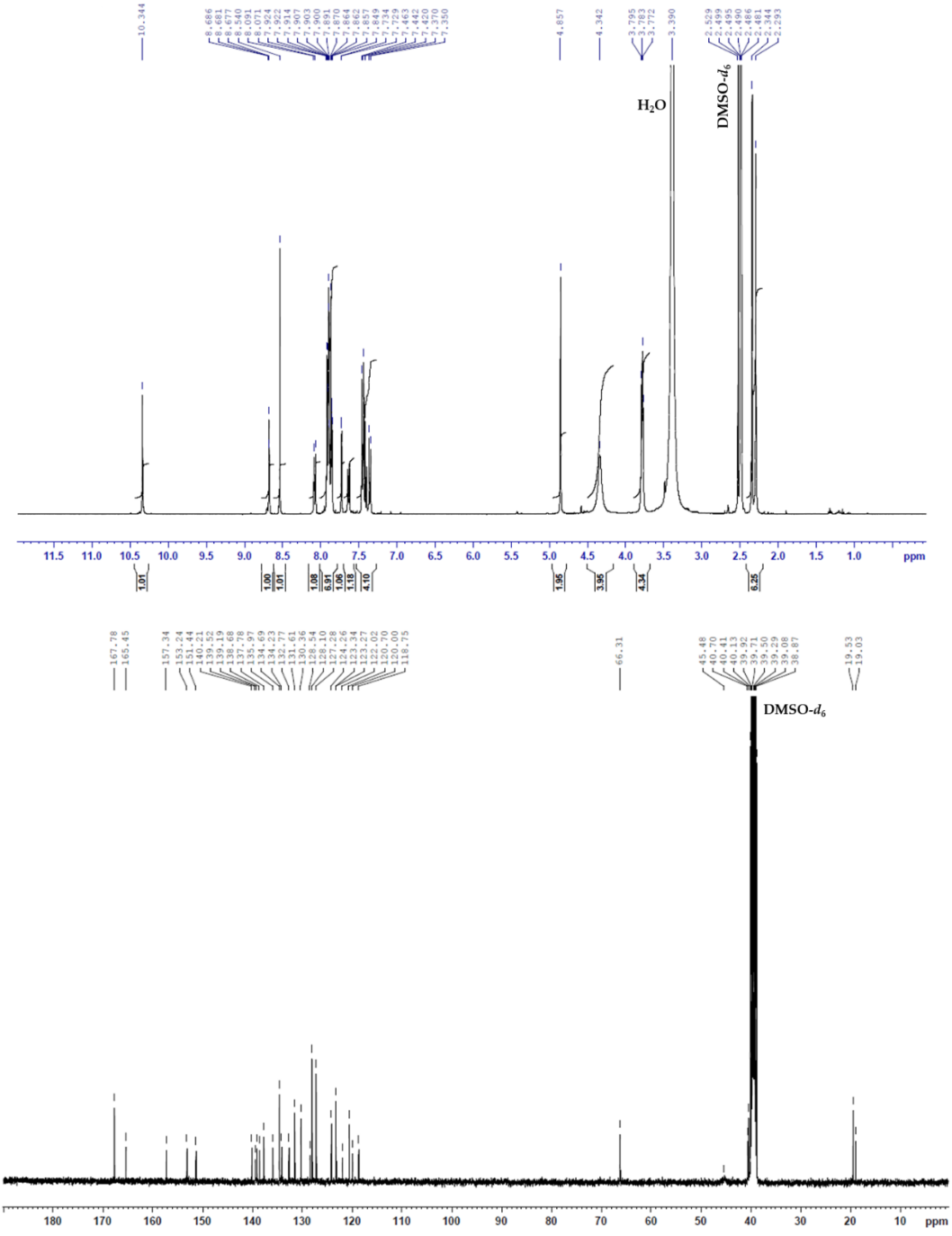

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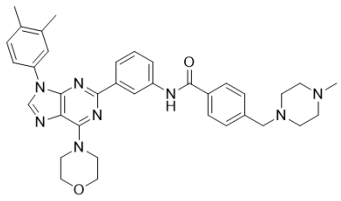

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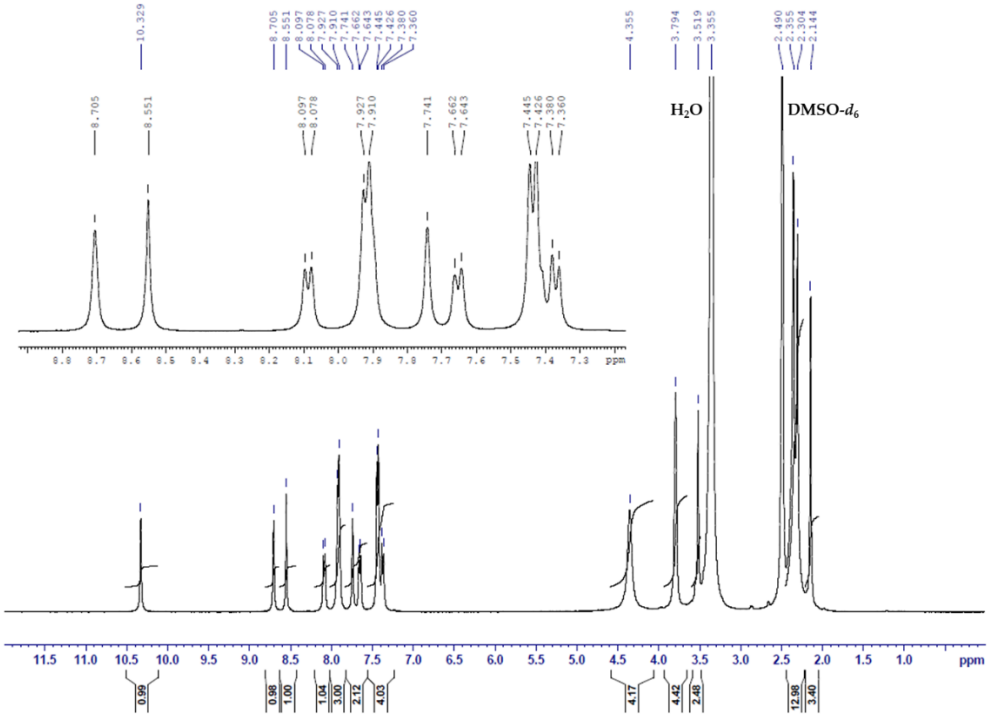

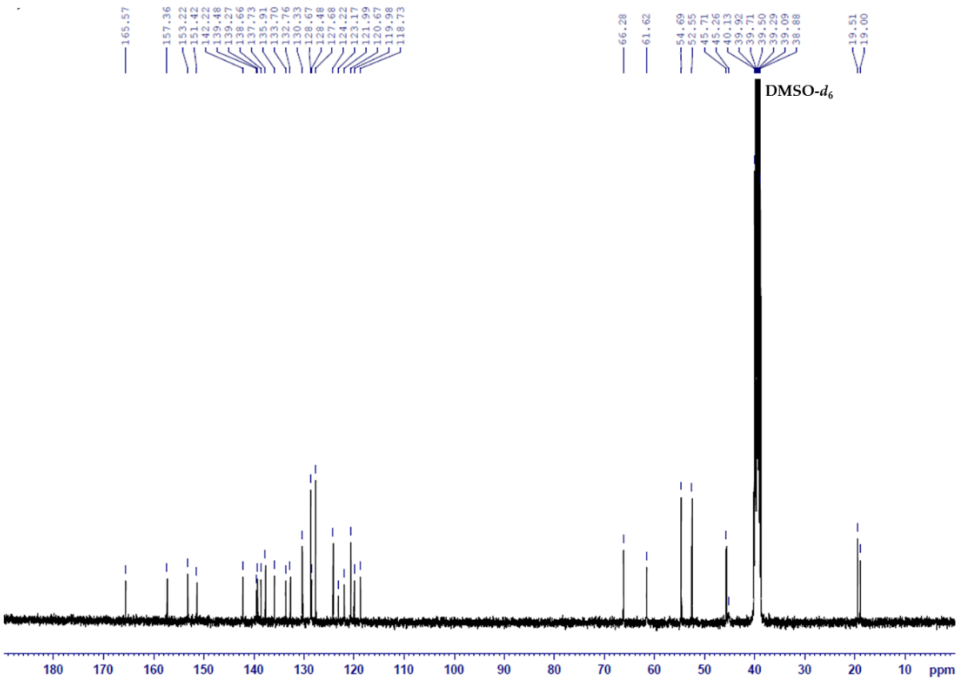

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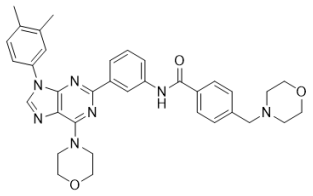

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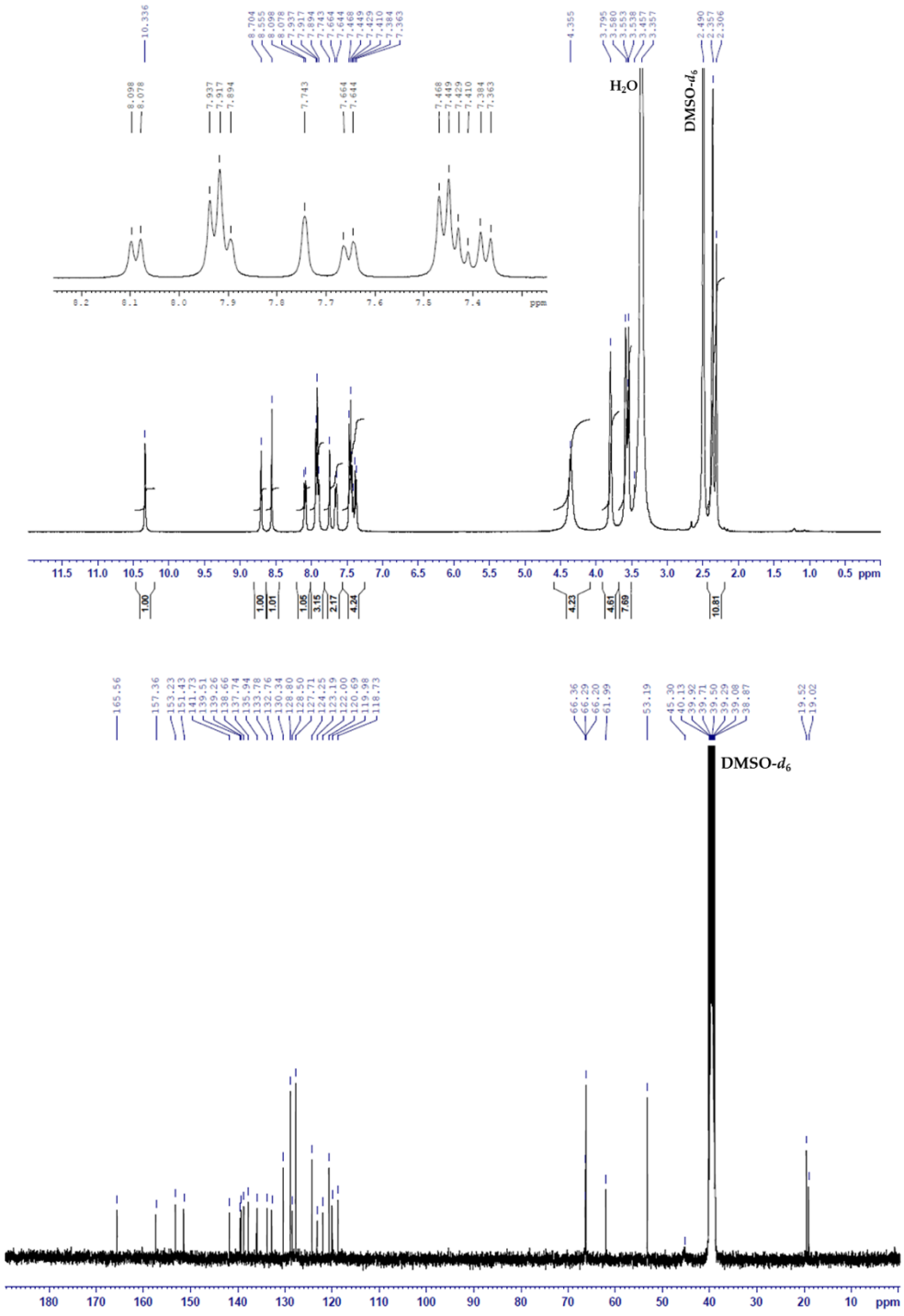

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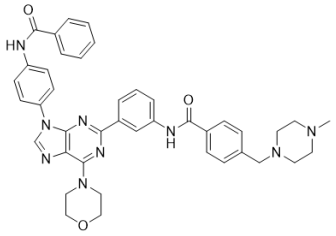

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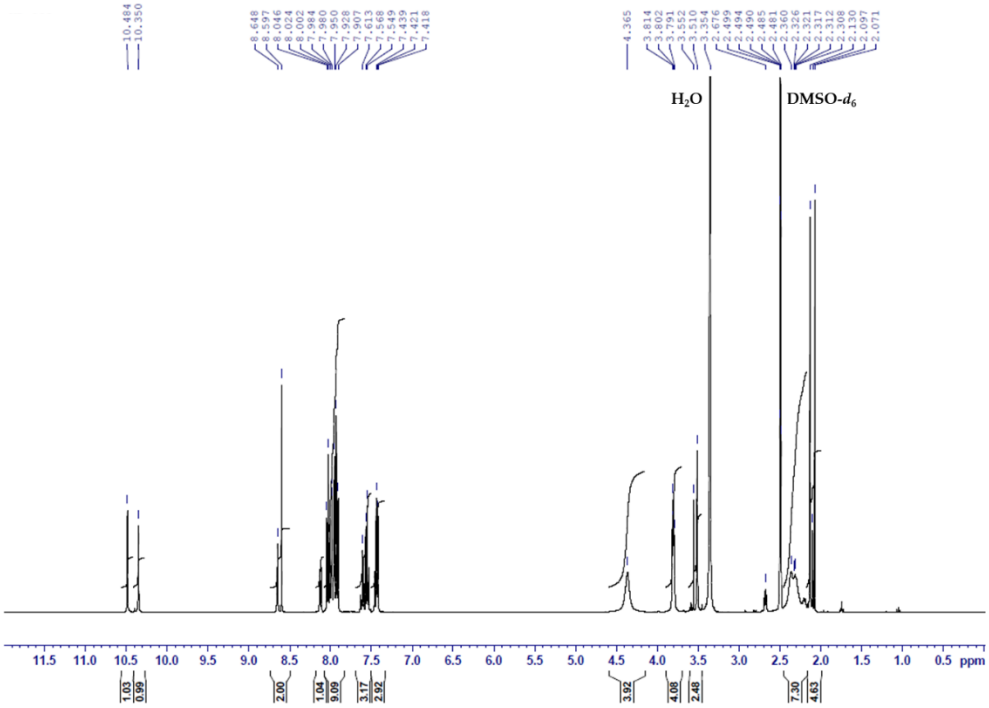

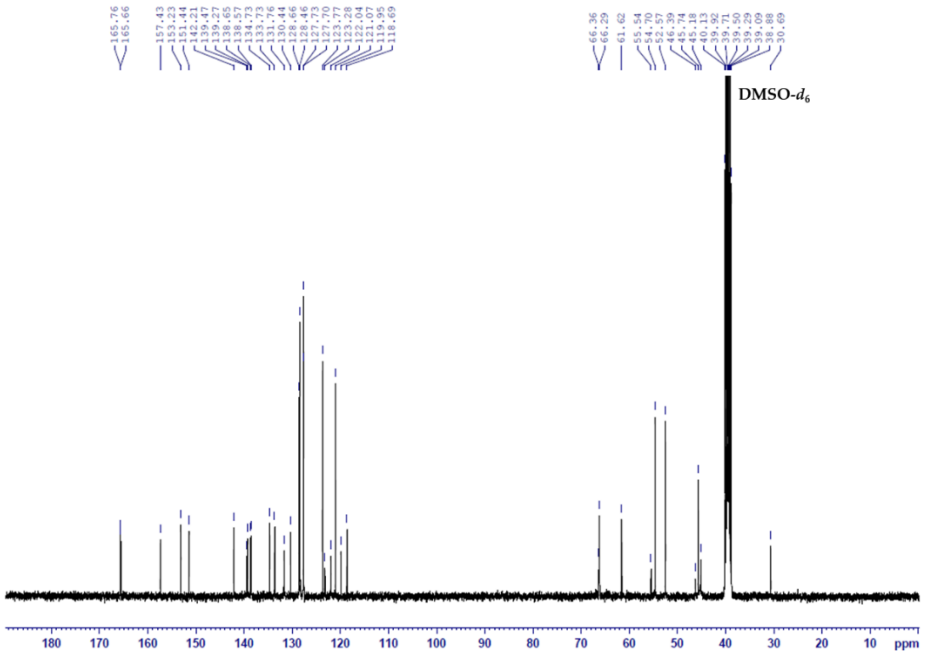

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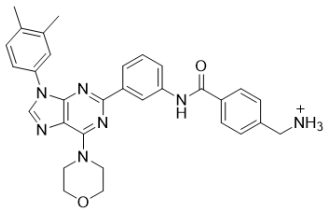

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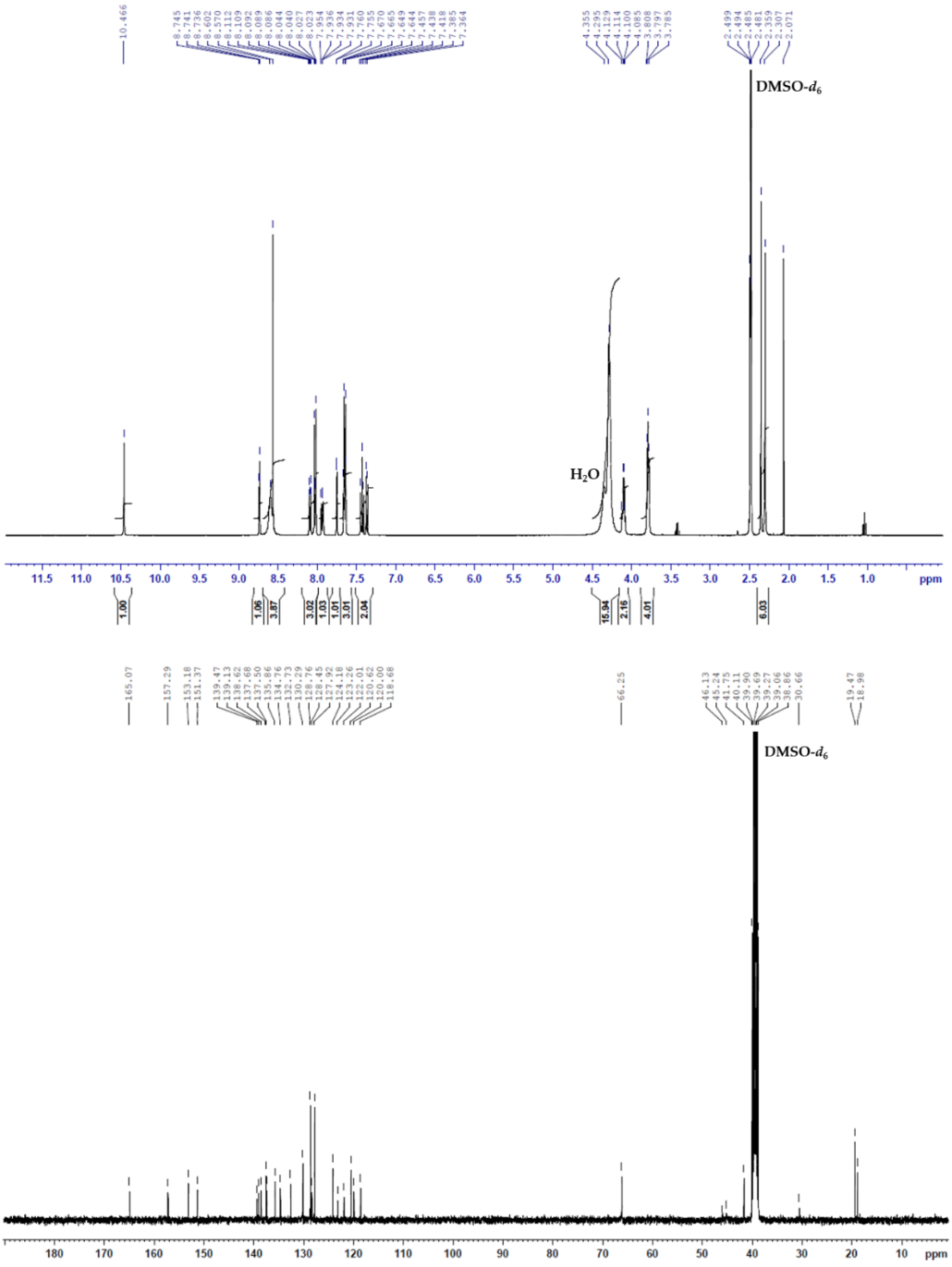

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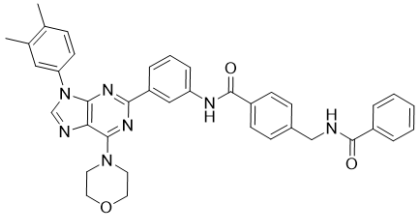

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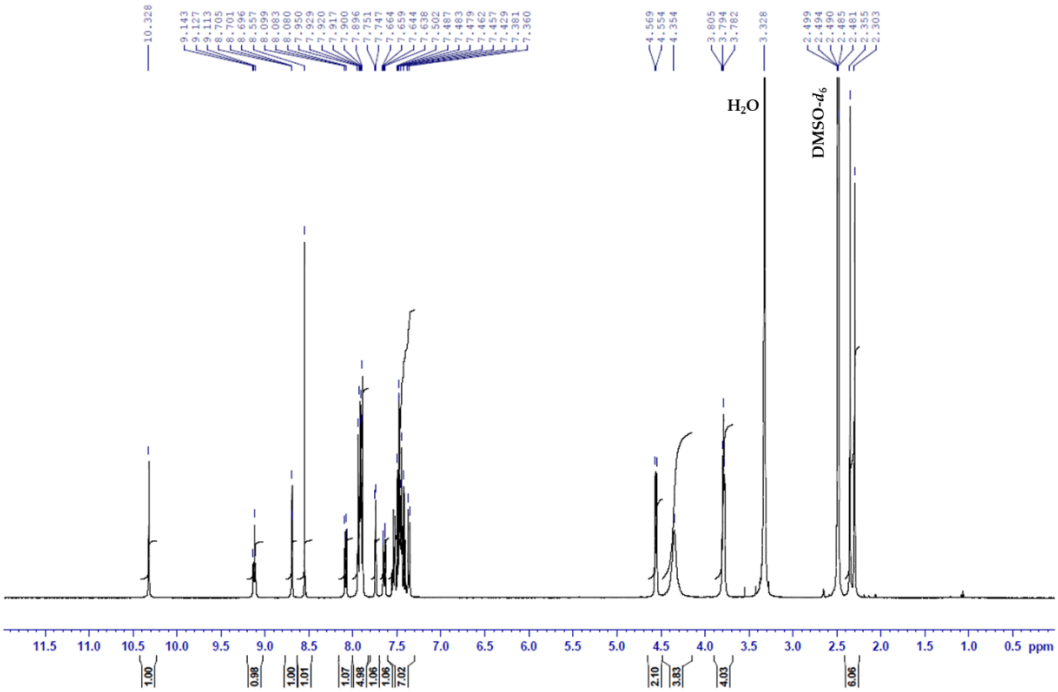


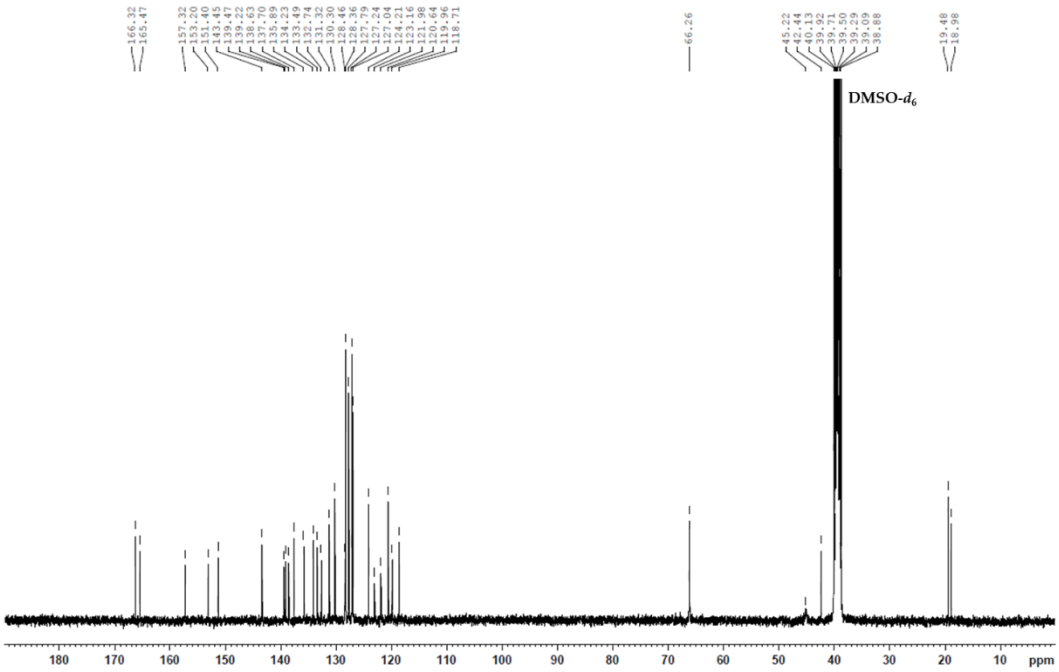
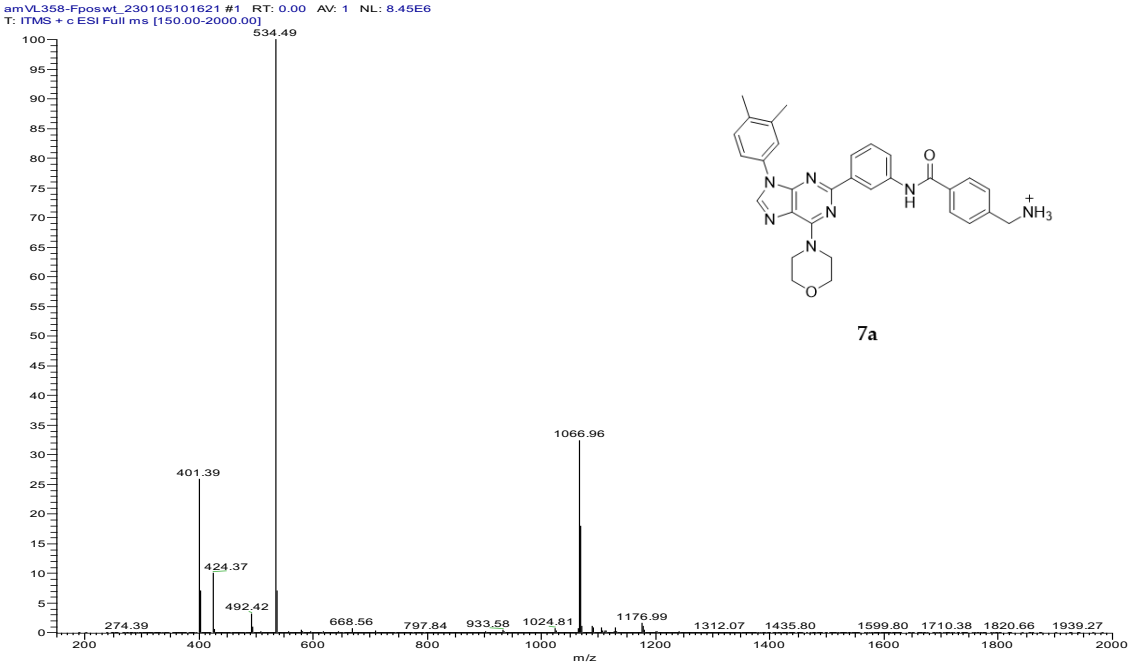


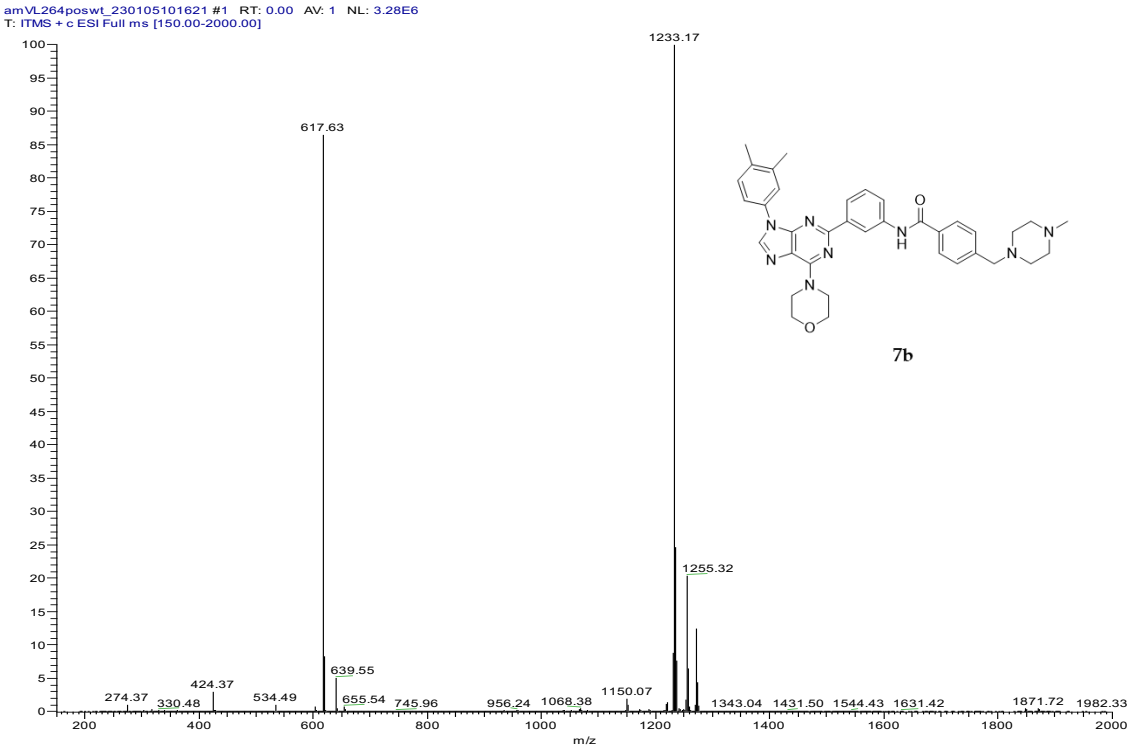
Table S6. MS spectra of representative synthesised inhibitors

Compound 7a



7a

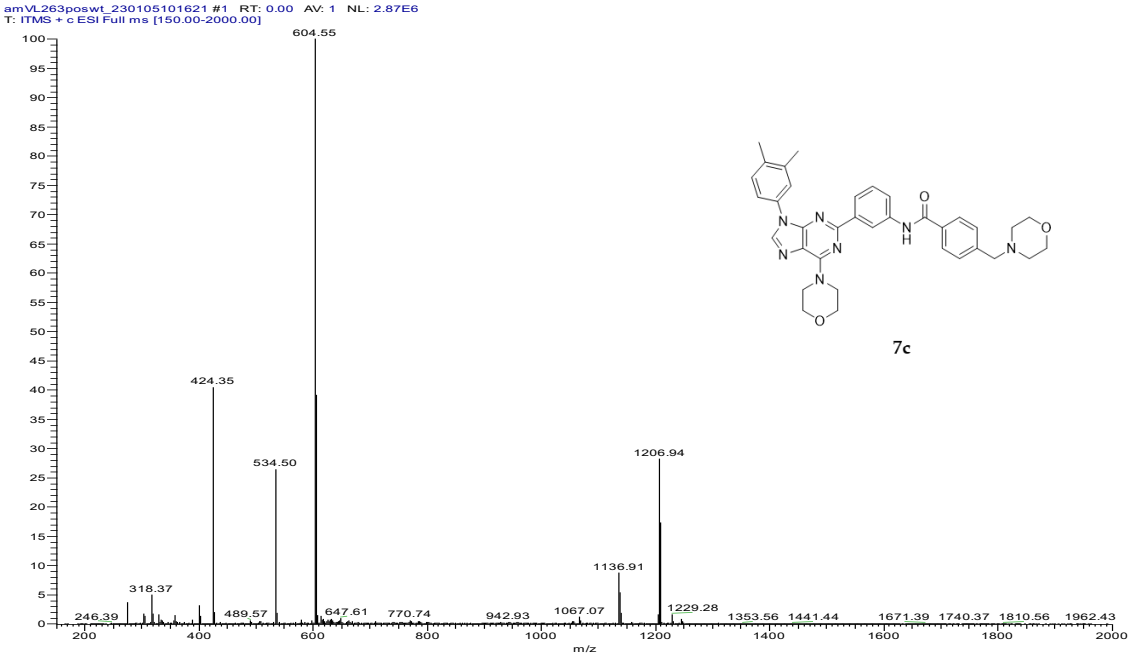
Compound 7b



7b

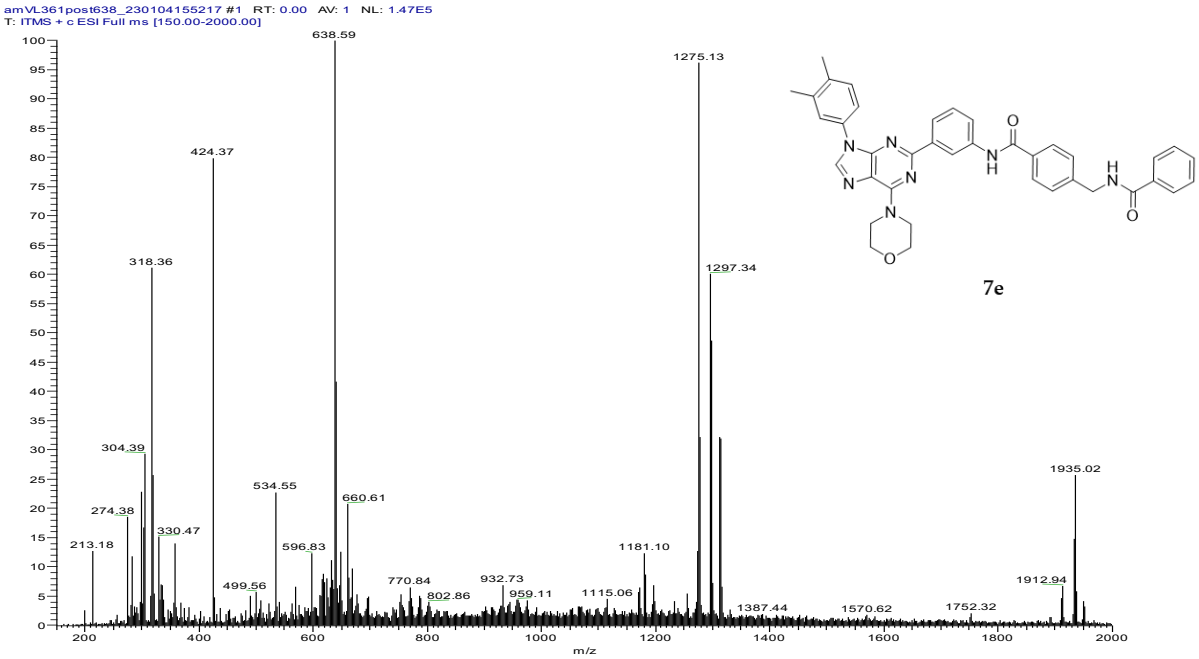
Table S6. cont.

Compound 7c



7c

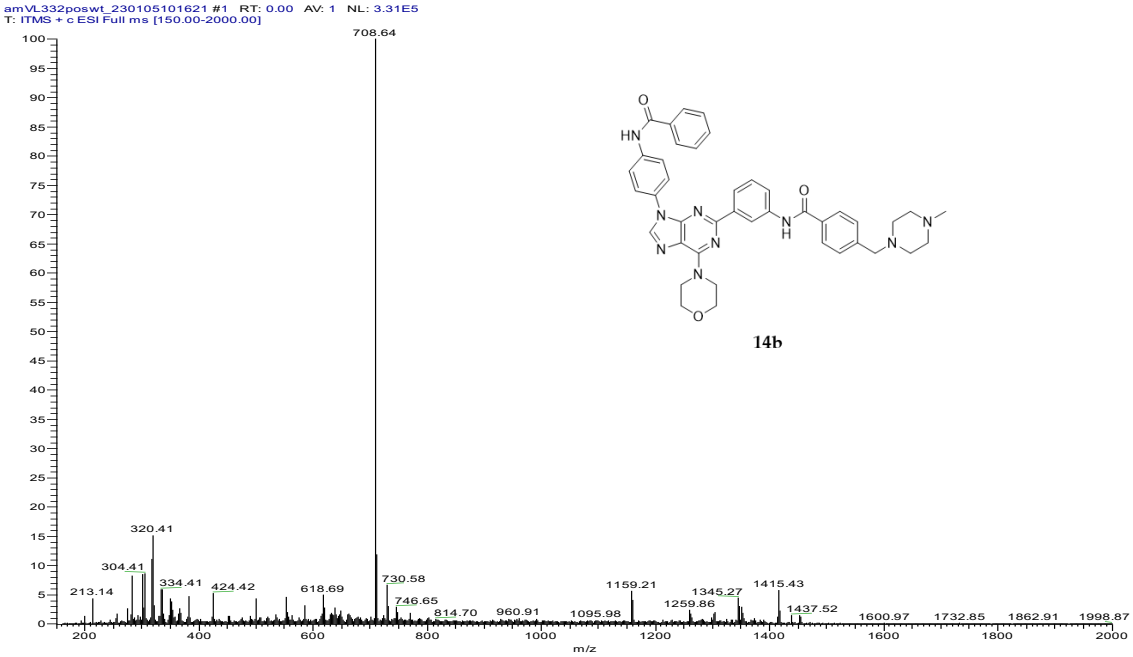
Compound 7e



7e

Table S6. cont.

Compound 14b



14b