Supporting Information

The conjugates of 5'-deoxy-5-fluorocytidine and hydroxycinnamic acids - synthesis, anti-pancreatic cancer activity and molecular docking studies

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Table S1. Predicted selected ADMET properties of the tested compounds.

compound	MW[a]	dipole[b]	vol[c]	SASA[d]	dHB[e]	aHB[f]	logP[g]	logS[h]	metab[i]	P[j]	Ro3[k]	Ro5[l]
1	517.5	2.54	1540.4	857.6	1	14.2	1.6	-5.3	1	68.8	0	2
2	517.5	7.06	1539.8	853.2	1	14.2	1.8	-5.3	1	97.3	0	2
3	517.5	4.88	1541.0	863.3	1	14.2	1.6	-5.4	1	69.3	0	2
4	575.5	4.88	1683.2	928.9	1	16.7	1.1	-5.3	1	29.8	0	2
5	575.5	4.61	1687.0	928.8	1	16.7	1.1	-5.3	1	31.1	0	2
6	491.4	5.21	1423.3	792.5	3	13.2	1.0	-4.9	3	25.5	0	1
30	491.4	9.36	1441.2	811.6	3	16.1	-0.1	-4.3	3	23.8	0	1
31	407.4	9.58	1178.2	678.8	5	12.6	-0.5	-3.5	5	16.9	1	0
32	633.5	4.79	1832.0	997.0	1	19.2	0.7	-5.3	1	16.9	1	2
33	507.4	6.92	1470.2	832.5	4	14.0	0.3	-5.1	4	5.6	1	2
34	423.4	6.09	1199.7	694.7	6	13.4	-1.2	-3.4	6	5.1	1	2
5-dFCR	245.2	5.85	691.2	416.1	4	9.1	-1.4	-1.8	3	80.6	0	0
benazepril	424.5	3.78	1360.8	744.9	2	8.5	1.7	-4.7	7	30.8	1	0
capecitabine	373.4	7.50	1107.9	635.8	3	11.1	0.3	-3.2	3	93.3	0	0
cis-ermethrin	391.3	2.61	1150.2	611.5	0	2.5	6.0	-5.9	2	5009	1	1
irinotecan	586.7	13.88	1780.8	952.1	1	12.8	3.4	-6.7	4	50.6	1	1

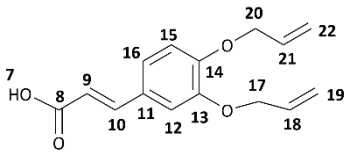
[a]MW – molecular weight (Da); [b]dipole – dipole moment (D); [c]vol – total molecular volume (Å^3); [d]SASA – solvent accessible surface (Å^2); [e]dHB – estimated number of hydrogen bonds that would be donated by the solute to water molecules in an aqueous solution; [f]aHB – estimated number of hydrogen bonds that would be accepted by the solute from water molecules in an aqueous solution; [g]logP – octanol/water partition coefficient; [g]logS – predicted aqueous solubility (mol/dm^3); [i]metab – number of likely metabolic reactions; [j]P – apparent Caco-2 permeability (nm/sec); [k]Ro3 – number of violations of Jorgensen's rule of three; [l]Ro5 – number of violations of Lipinski's rule of five.

Table S2. Predicted selected ADMET properties of the tested compounds, cont.

compound	FOSA[a]		FISA[b]	PISA[c]	glob[d]	HERG[e]	BB[f]	MDCK[g]	Kp[h]	HSA[i]	Jm[j]	LD_{50}[k]
1	406.9		227.6	191.2	0.75	-6.5	-2.5	41.0	-4.4	-0.5	0.000	5000
2	388.6		211.7	210.9	0.76	-6.5	-2.2	67.7	-4.0	-0.5	0.000	5000
3	415.2		227.3	187.5	0.75	-6.5	-2.5	42.1	-4.4	-0.5	0.000	5000
4	488.2		265.9	142.9	0.74	-6.5	-3.1	16.6	-5.1	-0.7	0.000	5000
5	486.5		264.0	146.5	0.74	-6.5	-3.1	17.3	-5.1	-0.7	0.000	5000
6	296.6		273.0	181.0	0.77	-6.1	-2.9	15.9	-5.1	-0.4	0.000	5000
30	339.4		276.3	153.9	0.76	-6.1	-3.0	14.7	-5.3	-0.9	0.000	1000
31	162.5		291.8	182.5	0.79	-5.7	-2.9	10.2	-5.5	-0.8	0.000	1000
32	558.8		292.0	113.3	0.73	-6.5	-3.6	9.1	-5.6	-0.9	0.000	5000
33	308.1		342.4	149.0	0.75	-6.3	-3.9	2.8	-6.4	-0.5	0.000	5000
34	161.8		346.3	153.5	0.79	-5.7	-3.6	2.5	-6.5	-0.9	0.000	1000
5-dFCR	122.9		220.3	28.6	0.91	-3.1	-1.3	56.8	-5.2	-0.8	0.025	3390
benazepril	282.7		137.9	324.4	0.80	-5.3	-1.0	16.2	-4.1	0.1	0.001	4019
capecitabine	350.6		213.6	27.3	0.81	-4.7	-2.0	66.5	-4.6	-0.7	0.007	1000
cis-permethrin	201.9		31.2	293.7	0.87	-5.1	0.1	8214.0	-0.5	1.0	0.166	85
irinotecan	638.0		178.0	136.1	0.75	-7.0	-1.4	21.8	-6.0	0.6	0.000	765

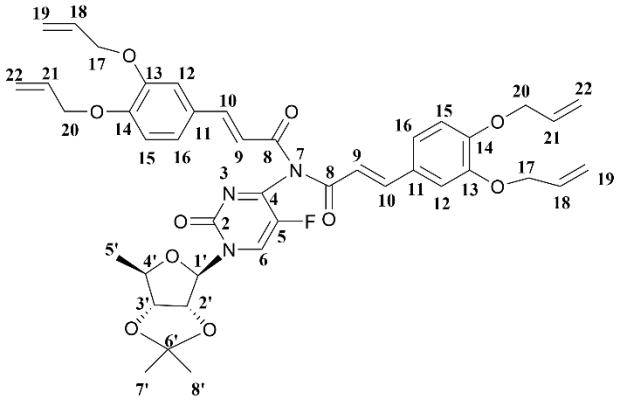
[a]FOSA – hydrophobic component of the SASA; [b]FISA – hydrophilic component of the SASA; [c]PISA – π (carbon and attached hydrogen) component of the SASA; [d]glob – globularity descriptor; [e]HERG – predicted IC_{50} value for blockage of HERG K^+ channels; [f]BB – predicted brain/blood partition coefficient; [g]MDCK – predicted apparent MDCK cell permeability (nm/sec); [g]K_p – predicted skin permeability; [i]HSA – prediction of binding to human serum albumin; [j]J_m – Predicted maximum transdermal transport rate (μg cm^{-2} hr^{-1}); [k]LD_{50} – predicted value of median lethal dose (mg/kg).

(3,4-diallyloxy)cinnamic acid (**18**)



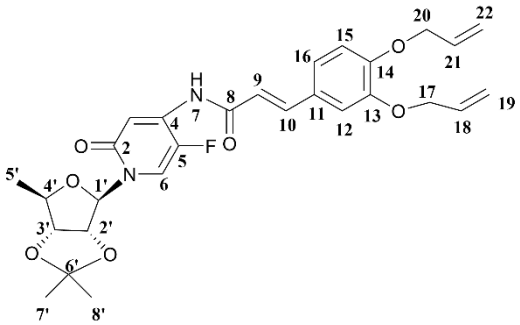
Methyl ester **12** [1] (1.00 g, 5.15 mM) was dissolved in acetone (30 mL), then K_2CO_3 (2.84, 20.60 mM) and allyl bromide (2.49 g, 20.60 mM) were added. The mixture was stirred overnight at ambient temperature. The inorganic salts were filtered off, and solvents were evaporated to oily residue. Then, methanol (10 mL) was added, followed by the addition of a NaOH (0.41 g, 10.30 mM) solution in water (5 mL). After stirring in r.t. for 1 h, the mixture was diluted with water (100 mL) and washed twice with methylene chloride. The aqueous layer was acidified to pH 1 with conc. HCl aq. The product was extracted with methylene chloride (3x30 mL). The combined organic layers were dried under anhydrous $MgSO_4$, evaporated, and dried *in vacuo* to give **18** as white solid. Yield 1.19 g (89%); m.p. 161.7°C (159-160°C [2]); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.71 (d, 1H, J = 15.8 Hz, H-10), 7.13-7.08 (m, 2H, H-12, H-16), 6.88 (d, 1H, *J* = 8.1 Hz, H-15), 6.28 (d, 1H, *J* = 15.8 Hz, H-9), 6.14-6.02 (m, 2H, H-18, H-21), 5.47-5.40 (m, 2H, H-19, H-22), 5.34-5.28 (m, 2H, H-19, H-22), 4.67-4.62 (m, 4H, H-17, H-20). ^{13}C NMR (125 MHz, $CDCl_3$) δ 172.6 (C-8), 151.0 (C-14), 148.6 (C-13), 146.9 (C-10), 133.0 (C-18), 132.8 (C-21), 127.1 C-11), 123.1 (C-16), 118.0 (C-22), 117.9 (C-19), 114.9 (C-9), 113.3 (C-12), 112.8 (C-15), 69.9 (C-17), 69.7 (C-20); HRMS (ESI, m/z): calculated for $C_{15}H_{17}O_4$ $[M + H]^+$ 261.1127; found 261.1139, calculated for $C_{15}H_{16}O_4Na$ $[M + Na]^+$ 283.0946; found 283.0951.

5'-deoxy-5-fluoro-2',3'-O-isopropylidene-N^4, N^4-(bis(3,4-diallyloxy)cinnamoyl)cytidine (**26**)



5'-deoxy-5-fluoro-2',3'-O-isopropylidenocytidine (**27**) (0.110 g, 0.386 mM) and 3,4-di-O-allycaffeic acid (**17**) (0,100 g, 0.39 mM) were dissolved in dry pyridine (2 mL) and cooled to -25°C. To the stirred on an ice-salt bath solution the $POCl_3$ (0.04 mL) was added dropwise over a period of 5 min. with the temperature kept below -20°C. The reaction was stirred 4 hours at -20°C, then it was allowed to reach ambient temperature and stirred overnight. After extraction by water/methylene chloride system, the separated organic layer was dried over anhydrous $MgSO_4$, and the solvent was distilled off under reduced pressure. The crude oil was purified using flash column chromatography on a silica gel with hexanes: ethyl acetate 3:1 to 1:1 (v/v), to give two main products: monosubstituted **28** with the yield of 0.067 g (33%) as a yellow solid and disubstituted **26** as a yellow solid**.** Yield of **26** 0.016 g (5.4%); m.p. 83°C (dec.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.87 (d, 1H, *J* = 4.9 Hz, H-6, double bound in flucytosine ring), 7.78 (d, 2H, *J* = 15.4 Hz, H-10, double bond), 7.12 (dd, 2H, J_1 = 8.4 Hz, J_2 = 1.9 Hz, H-16, aromatic CA), 7.05 (d, 2H, *J* = 1.9 Hz, H-12, aromatic CA), 6.86 (d, 2H, *J* = 8.4 Hz, H-15, aromatic CA), 6.61 (d, 2H, *J* = 15.4 Hz, H-9, double bond), 6.11-6.00 (m, 4H, H-18, H-21, allyl C*H*), 5.78 (d, 1H, *J* = 1.6 Hz, H-1', deoxyribose), 5.46-5.39 (m, 4H, H-19, H-22, allyl CH_2), 5.33-5.25 (m, 4H, H-19, H-22, allyl CH_2), 4.96 (dd, 1H, J_1 = 6.3 Hz, J_2 = 1.8 Hz, H-2', deoxyribose), 4.64 (m, 4H, H-20, CH_2), 4.59 (m, 4H, H-17, CH_2), 4.51 (dd, 1H, J_1 = 6.3 Hz, J_2 = 4.1 Hz, H-3', deoxyribose), 4,42 (dq, 1H, J_1 = 6.6 Hz, J_2 = 4.1 Hz, H-4', deoxyribose), 1.58 (s, 3H, H-7' or H-8', isopropylidene CH_3), 1.43 (d, *J* = 6,6 Hz, 3H, H-5', deoxyribose CH_3), 1.36 (s, 3H, H-7' or H-8', isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3 (C-8, C=O CA), 157.3 (d, J_{CF} = 13.4 Hz, C-4, flucytosine ring), 152.4 (C-2, C=O flucytosine ring), 151.4 (C-14, aromatic CA), 148.5 (C-13, aromatic CA), 146.7 (C-10, double bond), 140.4 (d, J_{CF} = 247.7 Hz, C-5, flucytosine ring), 133.0 (C-18, allyl *C*H), 132.7 (C-21, allyl *C*H), 130.6 (d, J_{CF} = 34.1 Hz, C-6, flucytosine ring), 127.3 (C-11, aromatic CA), 123.5 (C-16, aromatic CA), 118.1 (C-22, allyl *C*H_2), 118.1 (C-19, allyl *C*H_2), 117.3 (C-9, double bond), 114.6 (C-6', isopropylidene), 113.5 (C-12, aromatic CA), 113.3 (C-15, aromatic CA), 94.7 (C-1', deoxyribose), 85.6 (C-2', deoxyribose), 84.6 (C-3', deoxyribose), 84.3 (C-4', deoxyribose), 70.1 (C-17, *C*H_2), 69.7 (C-20 , *C*H_2), 27.1 (C-7' or C-8', isopropylidene *C*H_3), 25.3 (C-7' or C-8', isopropylidene *C*H_3), 19.3 (C-5', deoxyribose CH_3); HRMS (ESI, m/z): calculated for $C_{42}H_{45}N_3O_{10}F$ $[M + H]^+$ 770.3089; found 770.3081, calculated for $C_{42}H_{44}N_3O_{10}FNa$ $[M + Na]^+$ 792.2908; found 792.2902.

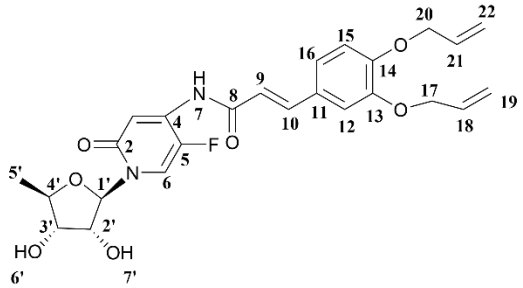
5'-deoxy-5-fluoro-2',3'-O-isopropylidene-N^4-(3,4-diallyloxy)cinnamoyl)cytidine (**28**)



To 5'-deoxy-5-fluoro-2',3'-O-isopropylidenocytidine (**27**) (1.10 g, 3.86 mmol) in methylene chloride (4 mL), 50% NaOH (0.925 g; 11.57 mM) was added. Then, after 1 min. stirring in ambient temperature, the solution (3,4-diallyloxy)cinnamoyl chloride (**24**) (1.08, 3.86 mM) in methylene chloride (6 mL) was added dropwise. The reaction mixture was heated with stirring for 1 h at 50°C. After cooling, it was extracted with water/methylene chloride. The separated organic layer was dried over anhydrous $MgSO_4$, and the solvent was distilled off under reduced pressure. The crude product **28** was purified by flash column chromatography on a silica gel with hexanes: ethyl acetate 4:1to 1:1 (v/v). Yield 1,85 g (91%); m.p. 85°C (dec.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.82 (d, 1H, *J* = 15.6 Hz, H-10, double bond), 7.56 (bs, 1H, H-7, NH), 7.22-7.12 (m, 2H, H-12, H-16, aromatic CA), 6.87 (d, 1H, *J* = 8.3 Hz, H-15, aromatic CA), 6.15-6.00 (m, 2H, H-18, H-21, allyl C*H*), 5.67 (s, 1H, H-1', C*H*N deoxyribose), 5.55-5.38 (d, 2H, *J* = 15.3 Hz, H-19, H-22, allyl CH_2), 5.30 (d, 2H, *J* = 10.5 Hz, H-19, H-22, allyl CH_2), 4.92 (d, 1H, *J*

= 5.5 Hz, H-2', deoxyribose), 4.65 (d, 4H, *J* = 4.5 Hz, H-17, H-20, CH_2), 4.51 (dd, 1H, $J_1 = J_2$ = 4.6 Hz, H-3', deoxyribose), 4.31 (m, 1H, H-4', deoxyribose), 1.57 (s, 3H, H-7' or H-8', isopropylidene CH_3), 1.41 (d, 3H, *J* = 6.5 Hz, H-5', deoxyribose CH_3), 1.34 (s, 3H, H-7' or H-8', isopropylidene CH_3); ^{13}C NMR (125 MHz, $CDCl_3$) δ 150.9 (C-14, aromatic CA), 148.5 (C-13, aromatic CA), 146.0 (C-10, double bound), 133.0 (C-18, allyl CH), 132.9 (C-21, allyl CH), 127.8 (C-11, aromatic CA), 123.3 (C-16, aromatic CA), 118.0 (C-19, C-22, allyl CH_2), 114.7 (C-6', isopropylidene), 113.3 (C-15, aromatic CA), 113.1 (C-12, aromatic CA), 93.9 (C-1', deoxyribose), 85.3 (C-2', deoxyribose), 84.7 (C-3', deoxyribose), 83.5 (C-4', deoxyribose), 69.9 (C-17, CH_2), 69.7 (C-20, CH_2), 27.1 (C-7' or C-8', isopropylidene CH_3), 25.3 (C-7' or C-8', isopropylidene CH_3), 19.1 (C-5', deoxyribose CH_3); HRMS (ESI, m/z): calculated for $C_{27}H_{31}N_3O_7F$ $[M + H]^+$ 528.2146; found 528.2145, calculated for $C_{27}H_{30}N_3O_7FNa$ $[M + Na]^+$ 550.1965; found 550.1964.

5'-deoxy-5-fluoro-N^4-(3,4-diallyloxy)cinnamoyl)cytidine (**29**)



To 5'-deoxy-5-fluoro-2',3'-O-isopropylidenocytidine (**27**) (0.48 g, 1.68 mmol) in methylene chloride (2 mL), 50% NaOH (0.27 g, 3.37 mM) was added. Then, after 1 min. stirring in ambient temperature, the solution of (3,4-diallyloxy)cinnamoyl chloride (**24**) (0.47 g, 1.69 mM) in methylene chloride (3 mL) was added dropwise. The reaction mixture was heated with stirring for 1 h at 50°C. After cooling, 5 M HCl aq. (2.5 mL) and methanol (2 mL) were added to reaction mixture and stirred 20 min. in ambient temperature. Due to the lack of progress, methylene chloride was distilled off and another portion of methanol (10 mL) and conc. HCl aq. (1.5 mL) were added to reaction mixture. After additional 1 h stirring, it was diluted with an aqueous saturated sodium bicarbonate solution, then extracted with methylene chloride. The organic layer was dried over anhydrous $MgSO_4$, and the solvent was distilled off under reduced pressure. The crude product **29** was purified by flash column chromatography on a silica gel with methylene chloride: methanol 50:1 to 25:1. Yield 0.19 g (23%); m.p. 59°C (dec.); ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.75 (d, 1H, *J* = 15.6 Hz, H-10, double bond), 7.16 (d, 1H, *J* = 8.2 Hz, H-16, aromatic CA), 7.13 (d, 1H, *J* = 1.5 Hz, H-12, aromatic CA), 6.84 (d, 1H, *J* = 8.4 Hz, H-15, aromatic CA), 6.11-6.01 (m, 2H, H-18, H-21, allyl CH), 5.72 (d, 1H, *J* = 3.7 Hz, H-1', CHN deoxyribose), 5.47-4.38 (m, 2H, H-19, H-22, allyl CH_2), 5.32-5.27 (m, 2H, H-19, H-22, allyl CH_2), 4.63 (m, 2H, H-17, CH_2), 4.61 (m, 2H, H-20, CH_2), 4.30 (bs, 1H, H-4', deoxyribose), 4.27 (m, 1H, H-2', deoxyribose), 3.86 (bs, 1H, H-3', deoxyribose), 3.56 (bs, 1H, deoxyribose OH), 1.38 (d, 3H, *J* = 6,5 Hz, H-5', CH_3 deoxyribose), ^{13}C NMR (125 MHz, $CDCl_3$) δ 151.1 (C-14, aromatic CA), 148.4 (C-13, aromatic CA), 146.6 (C-10, double bond), 133.0 (C-18, allyl CH), 132.8 (C-21, allyl CH), 127.5 (C-11, aromatic CA), 123.2 (C-16, aromatic CA), 118.0 (C-19, C-22, allyl CH_2), 113.7 (C-12, aromatic CA), 113.3 (C-15, aromatic CA), 92.9 (C-1', deoxyribose), 81.9 (C-4', deoxyribose), 76.2 (C-2', deoxyribose), 75.3 (C-3', deoxyribose), 70.0 (C-17, CH_2), 69.6 (C-20, CH_2), 18.8 (C-5', deoxyribose CH_3); HRMS (ESI, m/z): calculated for $C_{24}H_{27}N_3O_7F$ $[M + H]^+$ 488.1833; found 488.1830.

[1] N. Bukowski, J. Pandey, L. Doyle, T. Richard, C .Anderson and Y. Zhu*, Bioconjug Chem.* 2014, **25(12)**, 2189.
[2] H. Tozuka, M. Ota, H. Kofujita and K. Takahashi, *J. Wood Sci.* 2005, **51**, 48.

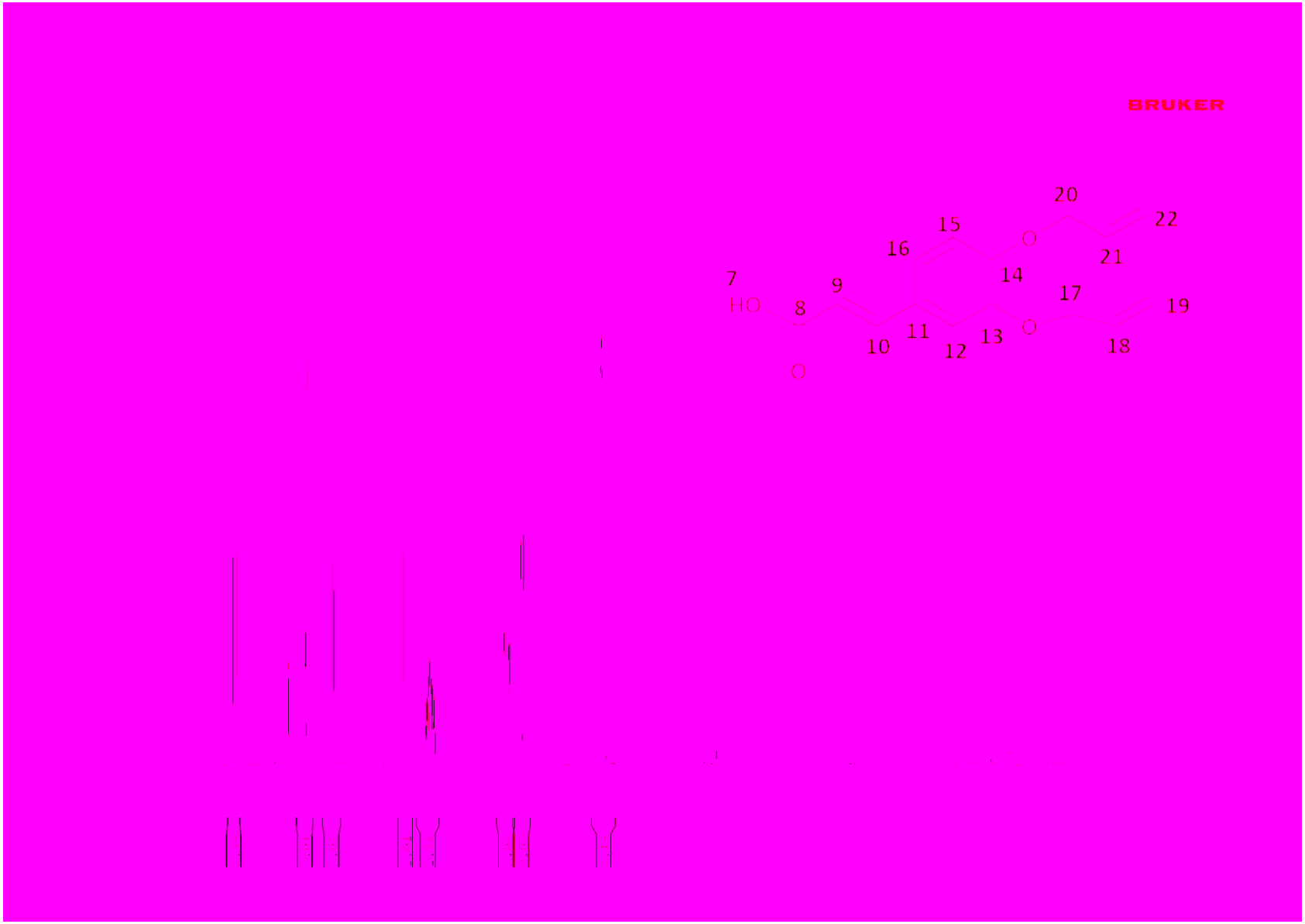


Figure S1. ^{1}H NMR spectrum of compound **18** ($CDCl_3$)

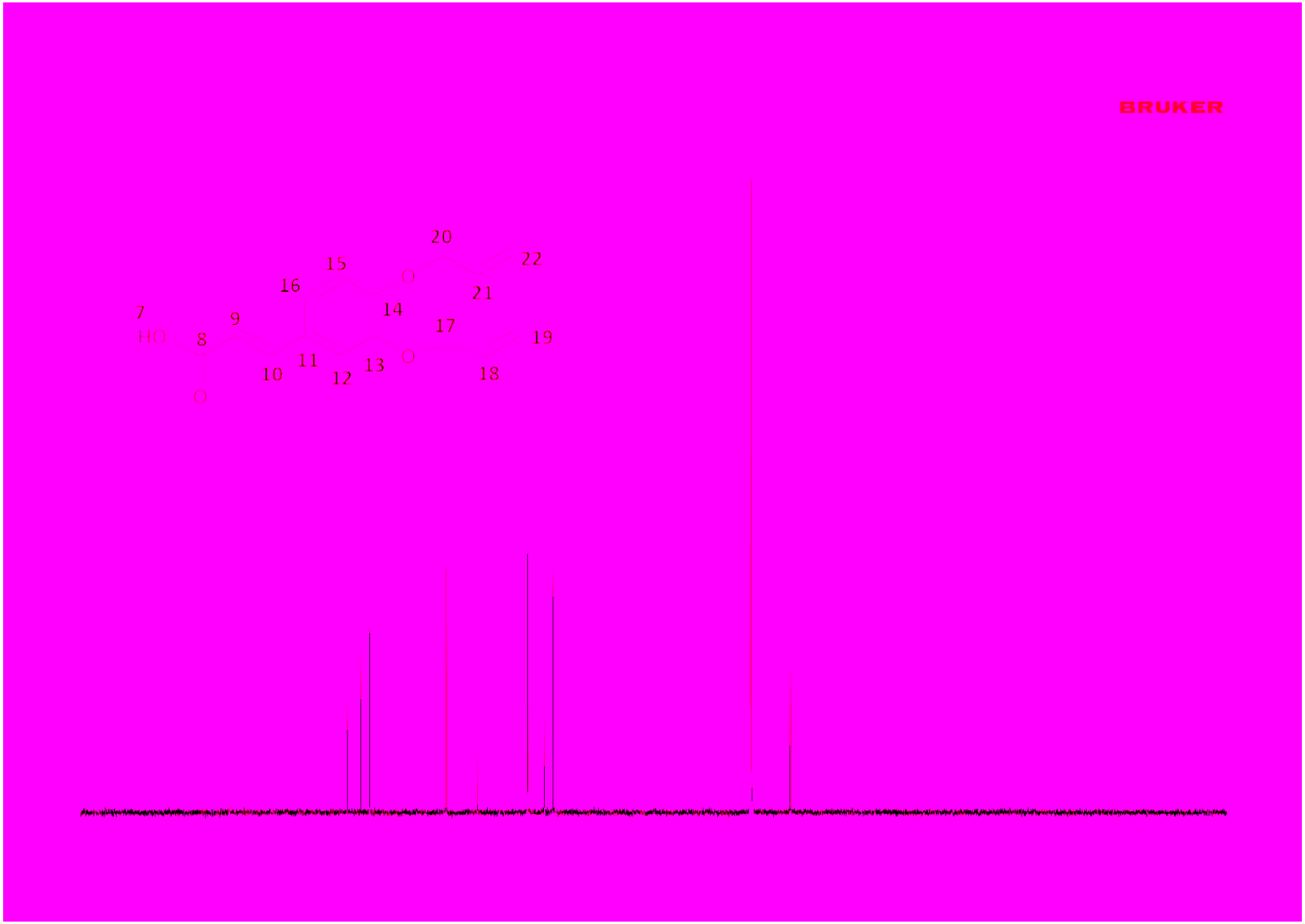


Figure S2. ^{13}C NMR spectrum of compound **18** ($CDCl_3$)

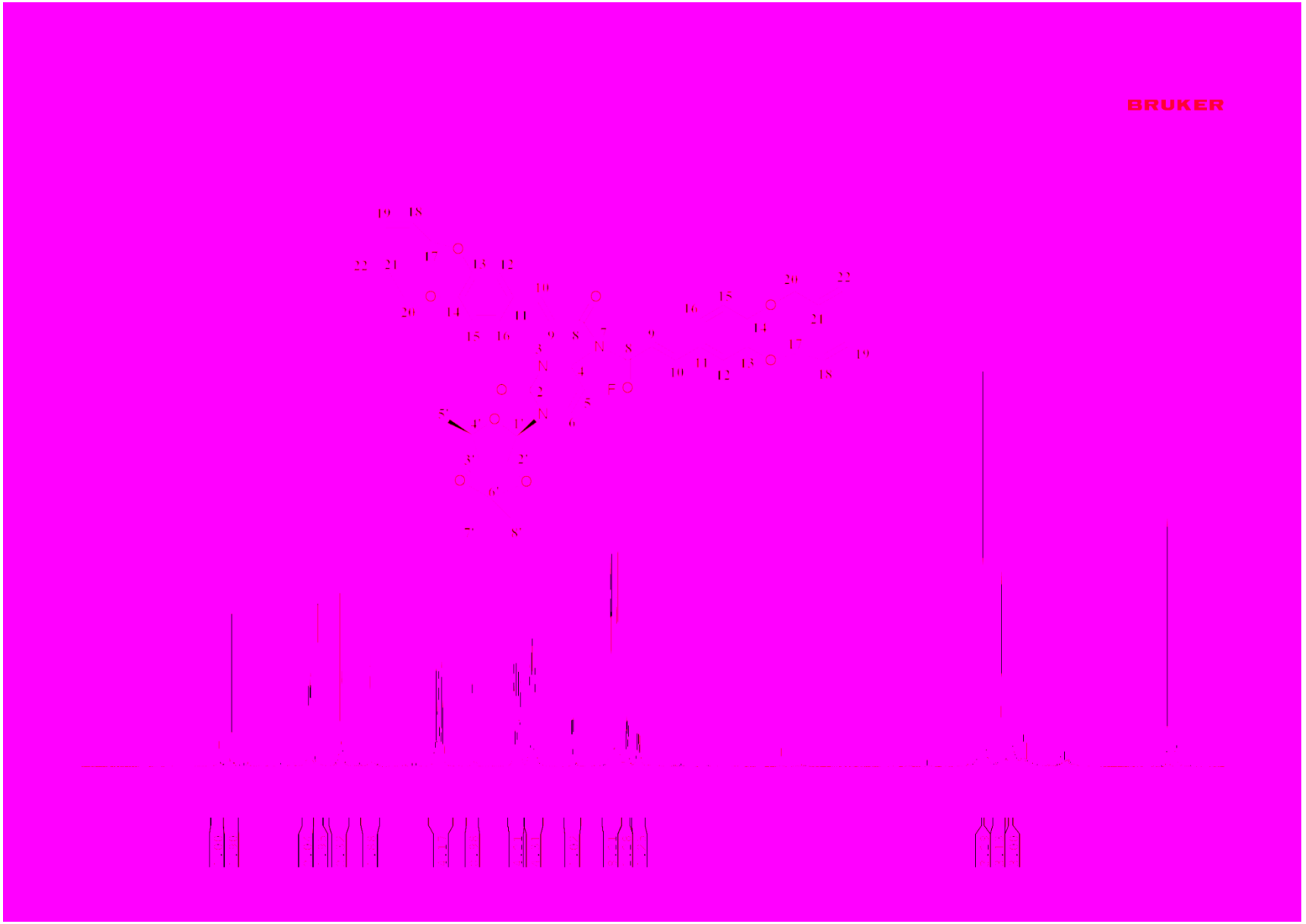


Figure S3. ^{1}H NMR spectrum of compound **26** ($CDCl_3$)

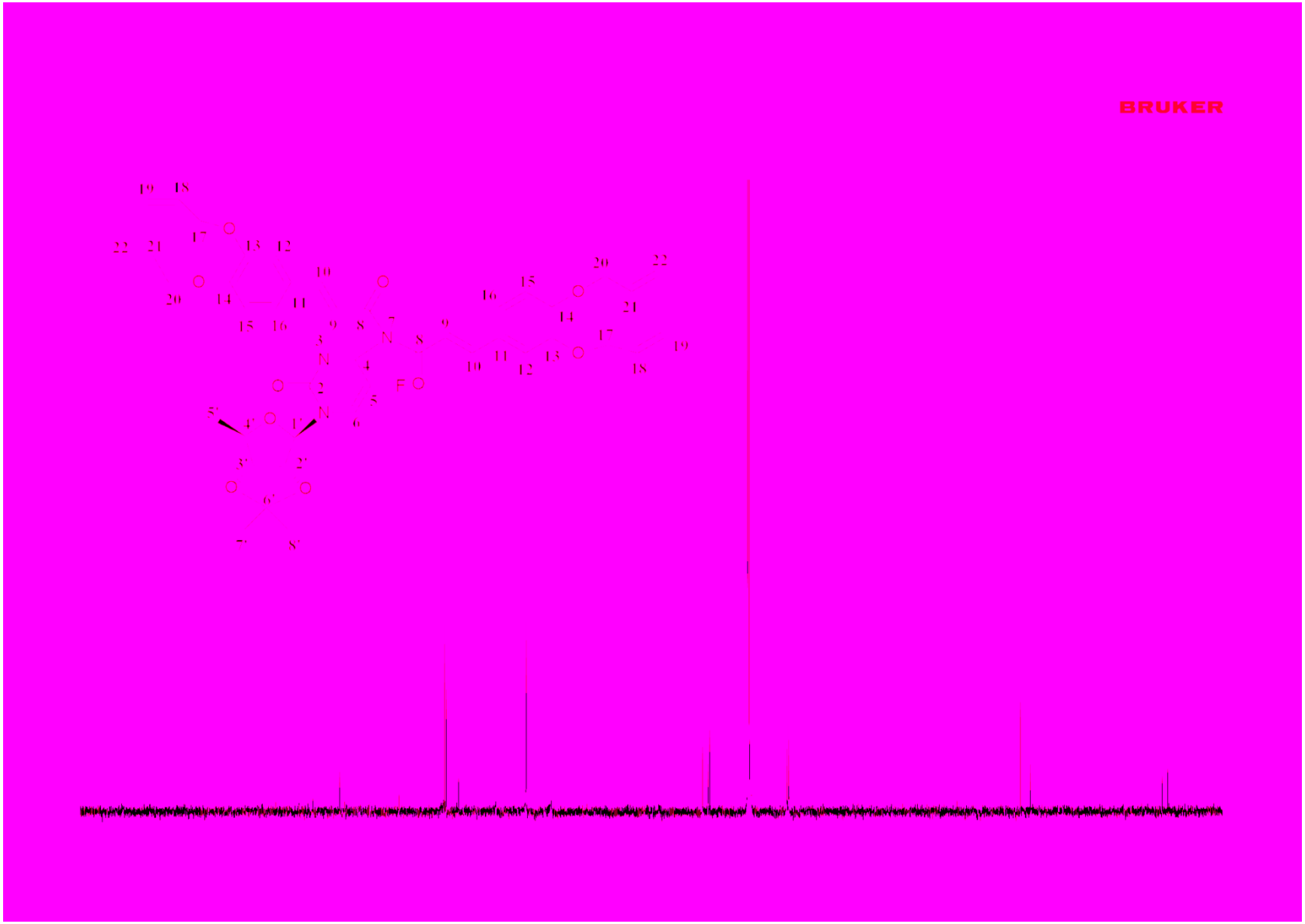


Figure S4. ^{13}C NMR spectrum of compound **26** ($CDCl_3$)

Figure S5. ^{1}H NMR spectrum of compound **28** ($CDCl_3$)

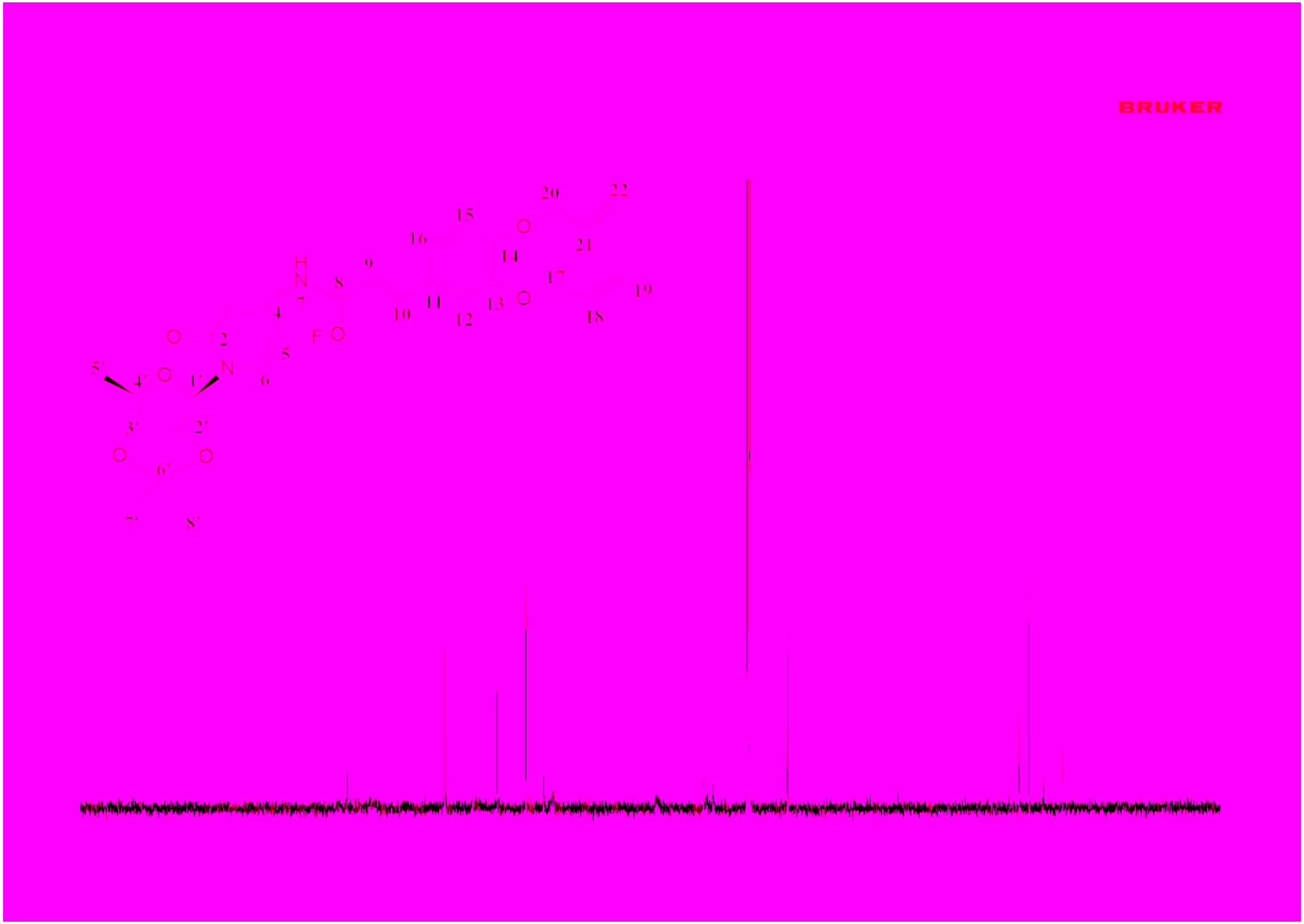


Figure S6. ^{13}C NMR spectrum of compound **28** ($CDCl_3$)

Figure S7. ^{1}H NMR spectrum of compound **29** ($CDCl_3$)

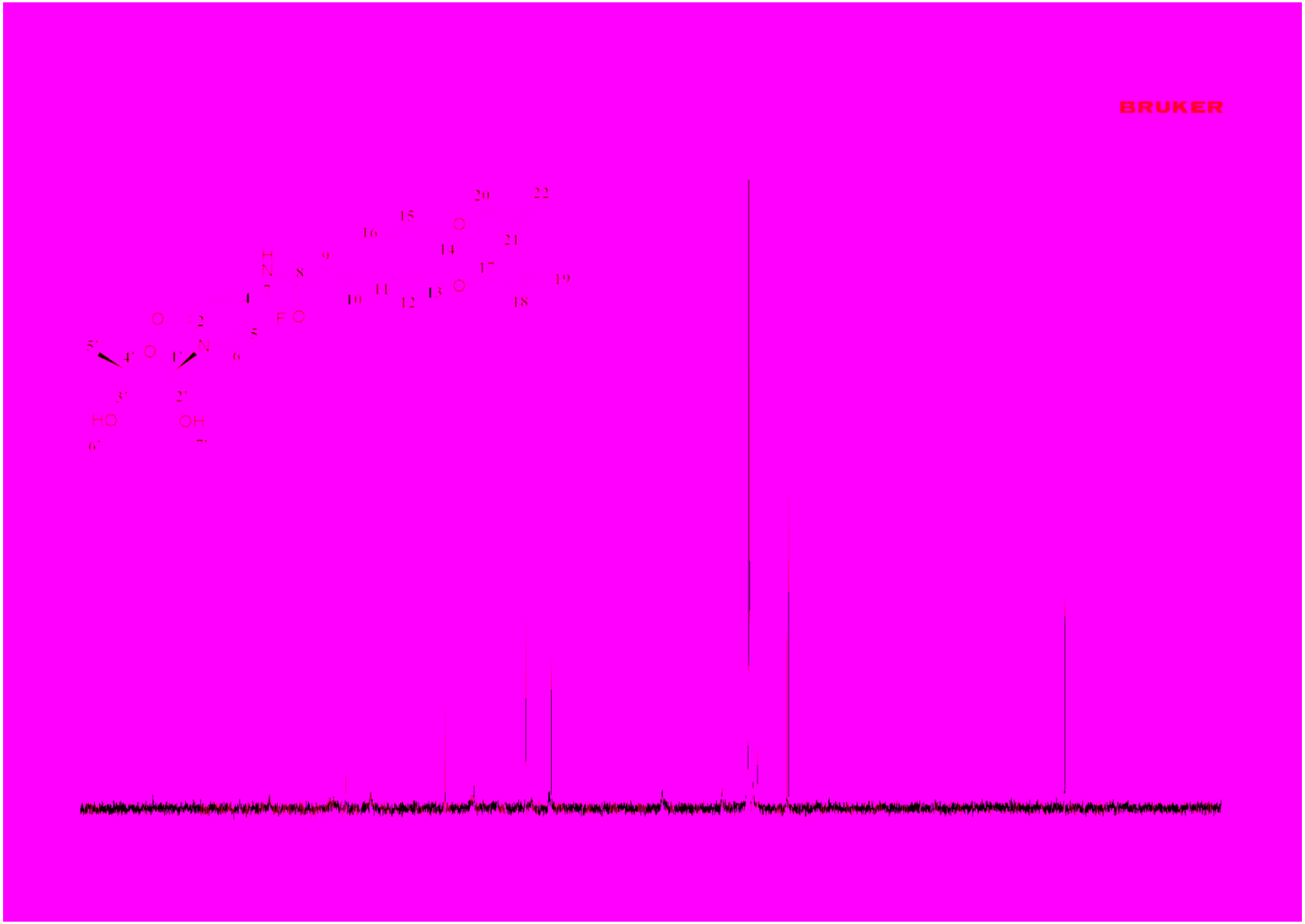


Figure S8. ^{13}C NMR spectrum of compound **29** ($CDCl_3$)

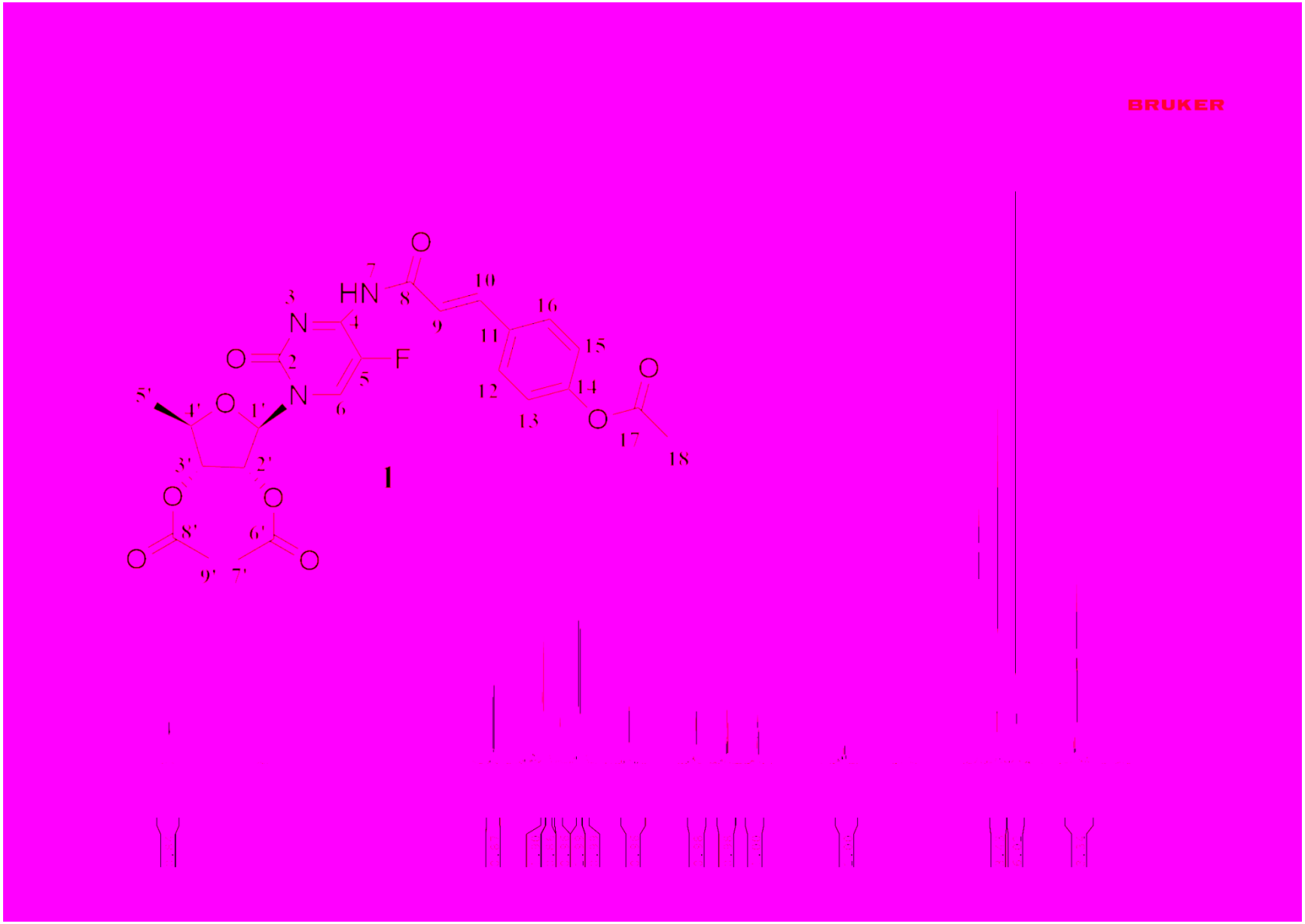


Figure S9. ^{1}H NMR spectrum of compound **1** (DMSO-d_6)

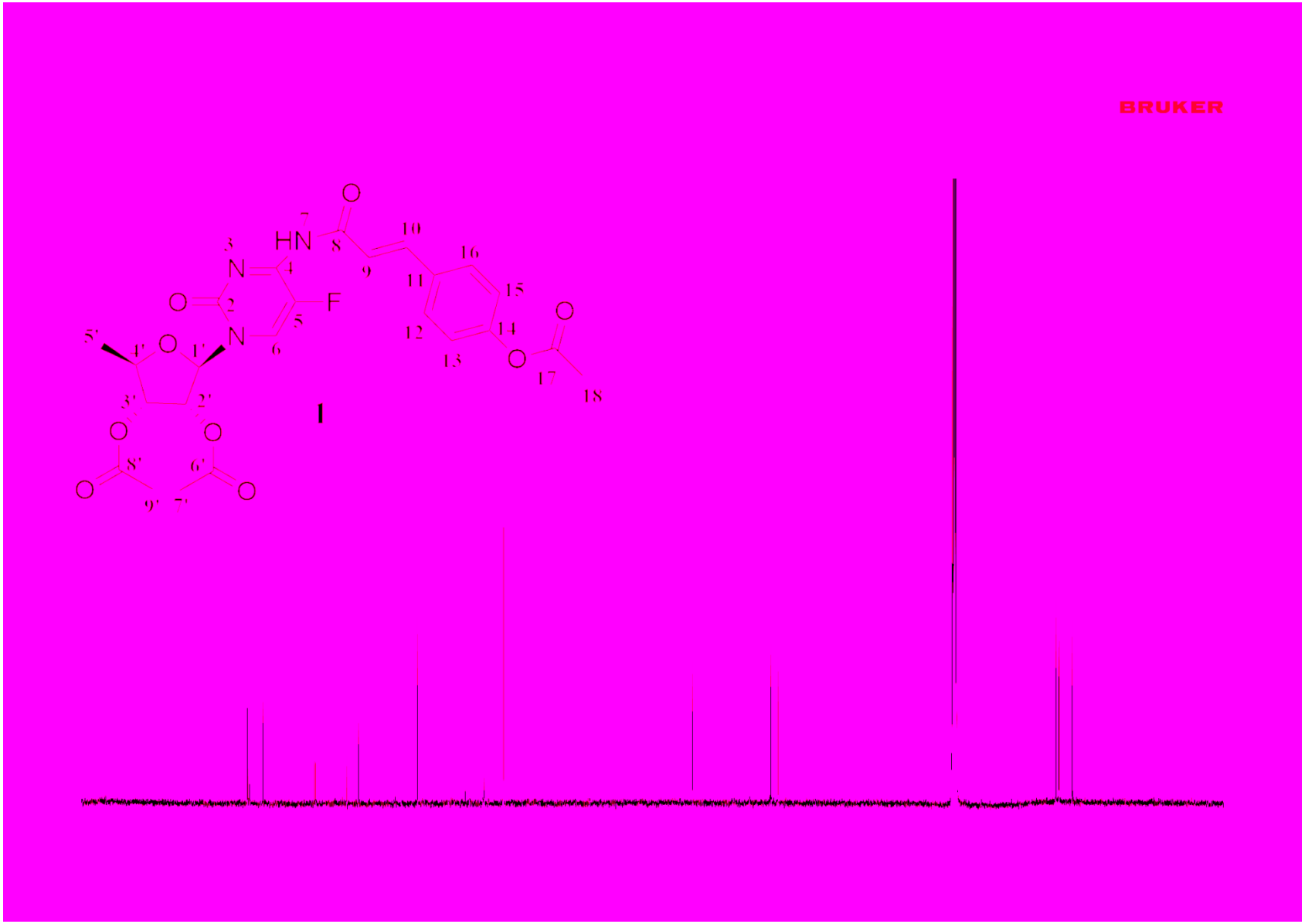


Figure S10. ^{13}C NMR spectrum of compound **1** (DMSO-d_6)

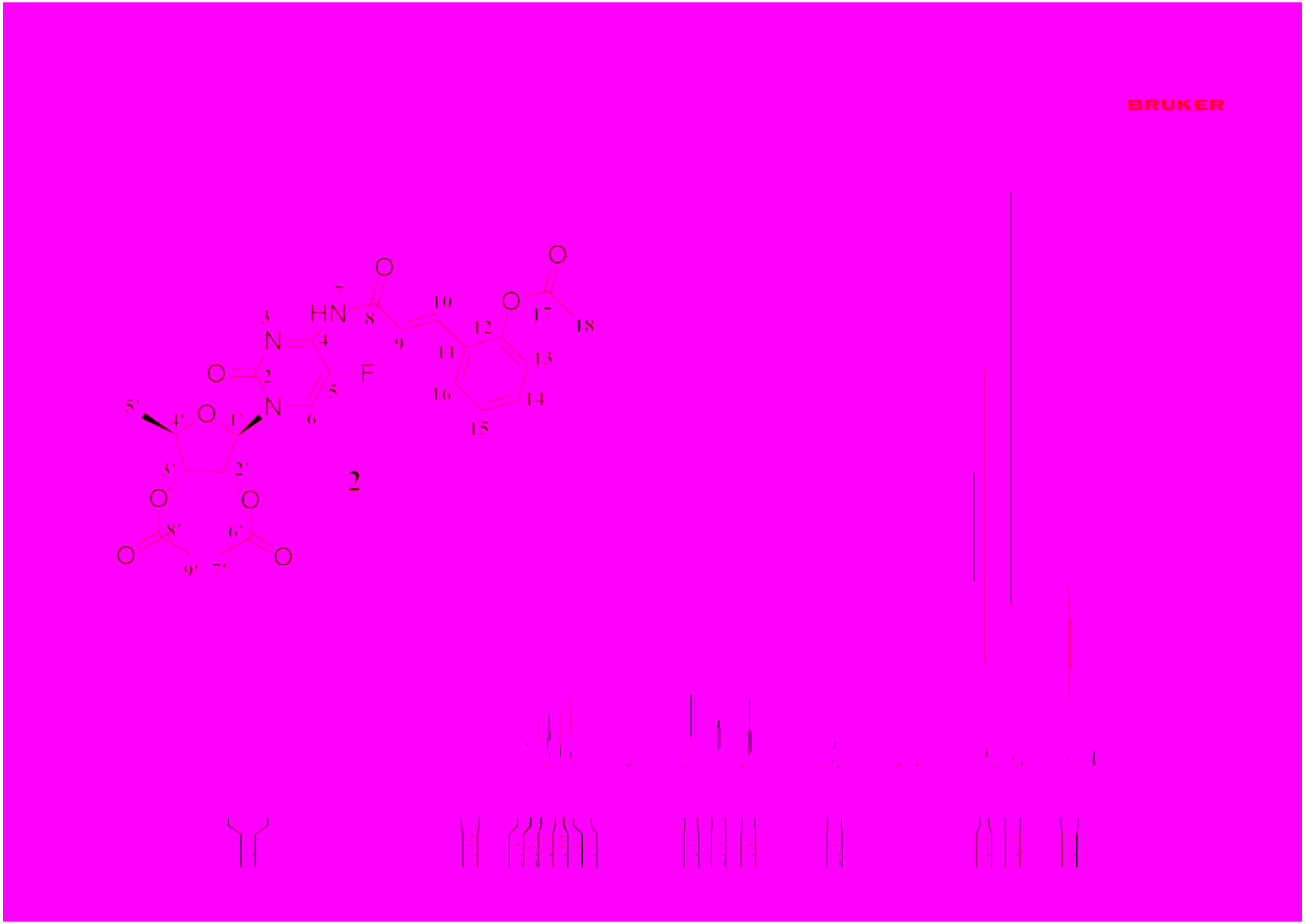


Figure S11. ^{1}H NMR spectrum of compound **2** (DMSO-d_6)

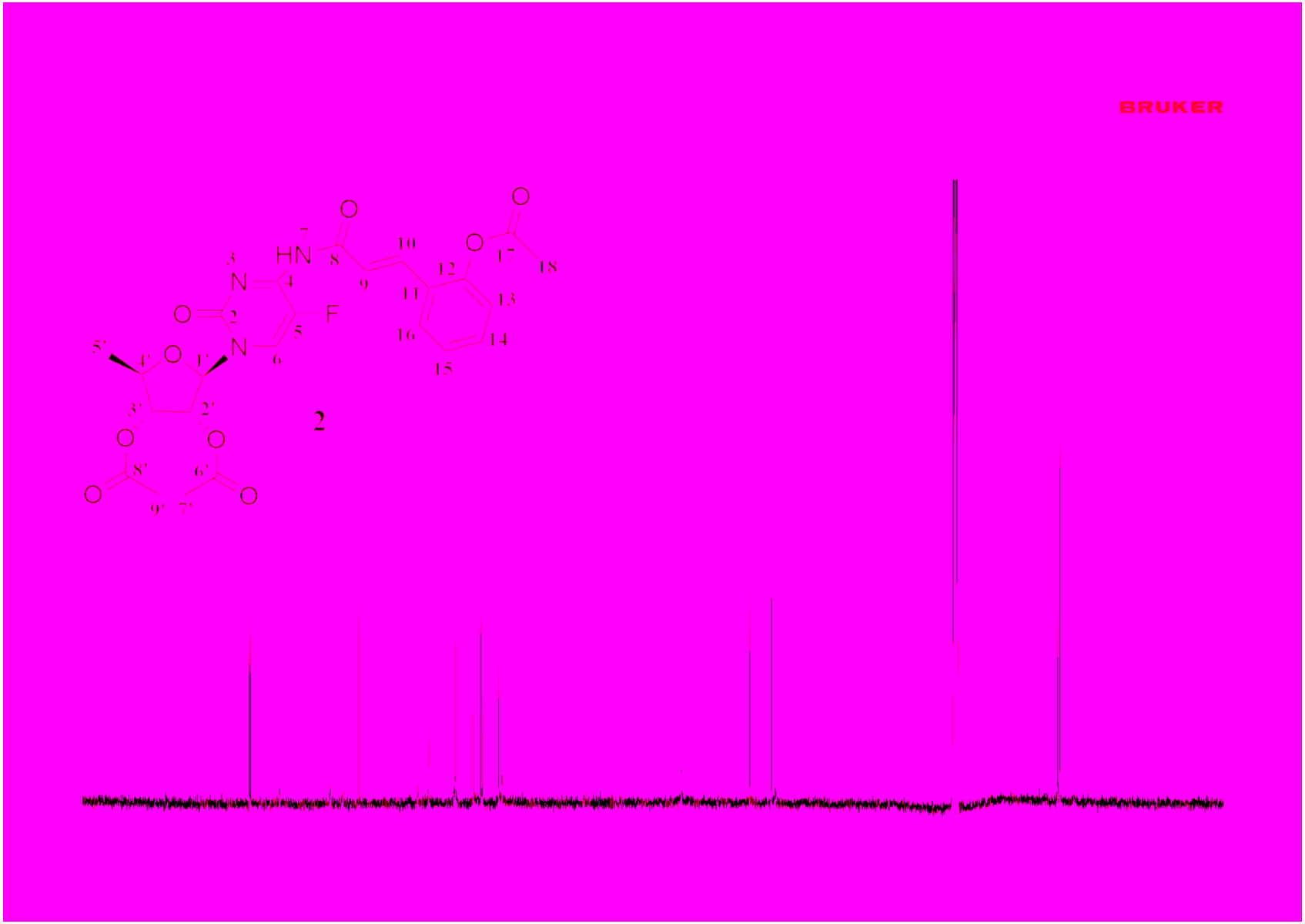


Figure S12. ^{13}C NMR spectrum of compound **2** (DMSO-d_6)

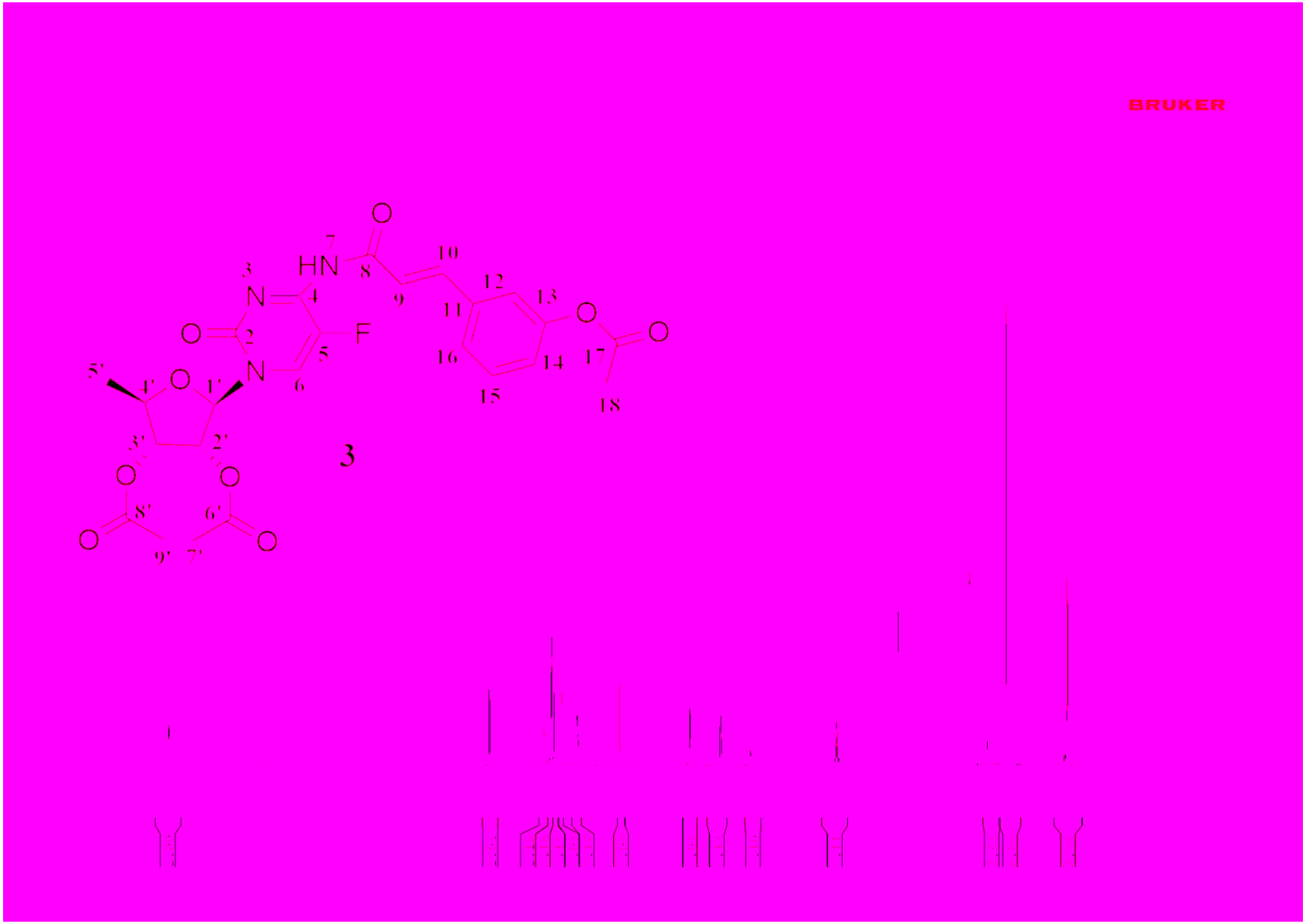


Figure S13. ^{1}H NMR spectrum of compound **3** (DMSO-d_6)

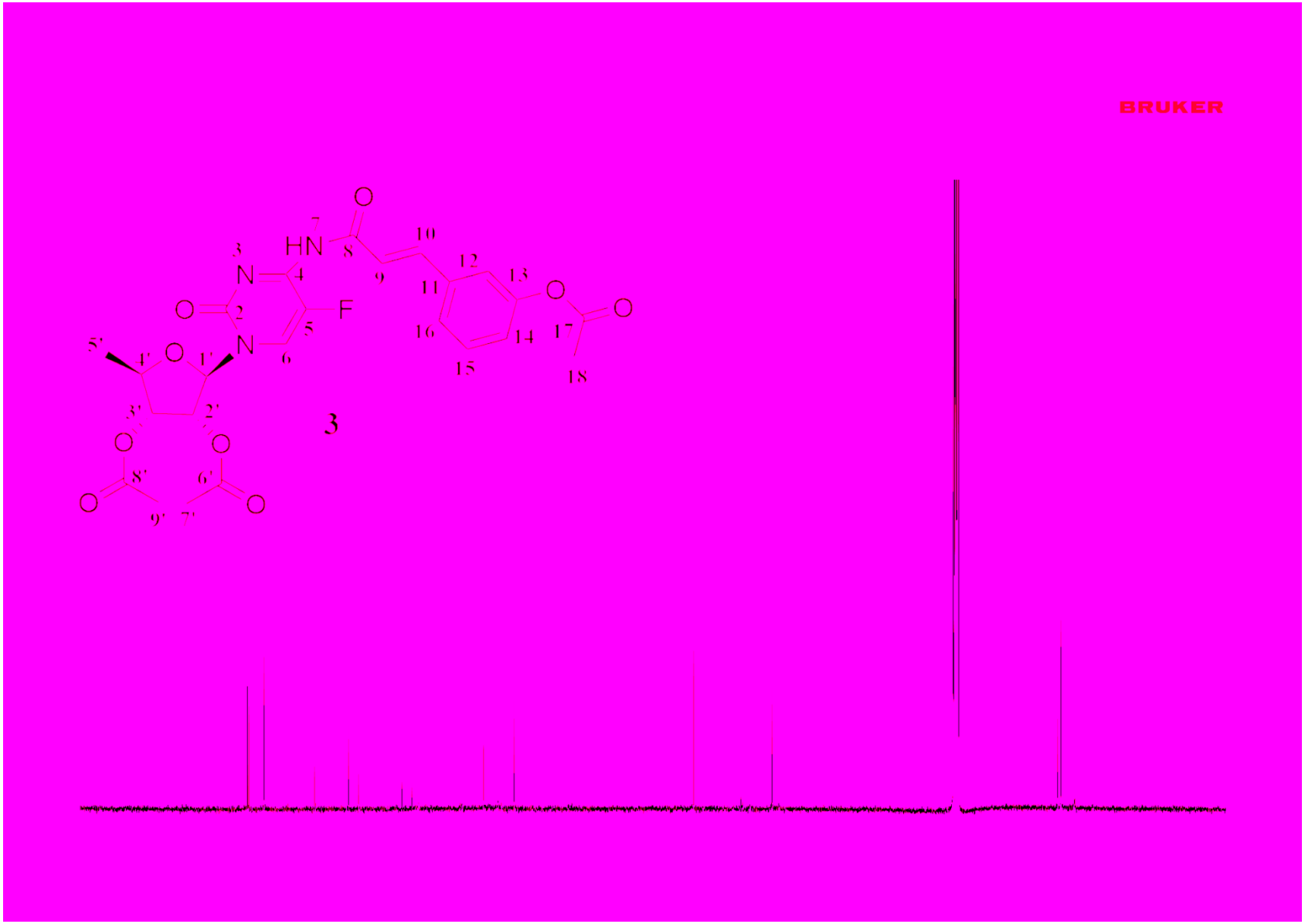


Figure S14. ^{13}C NMR spectrum of compound **3** (DMSO-d_6)

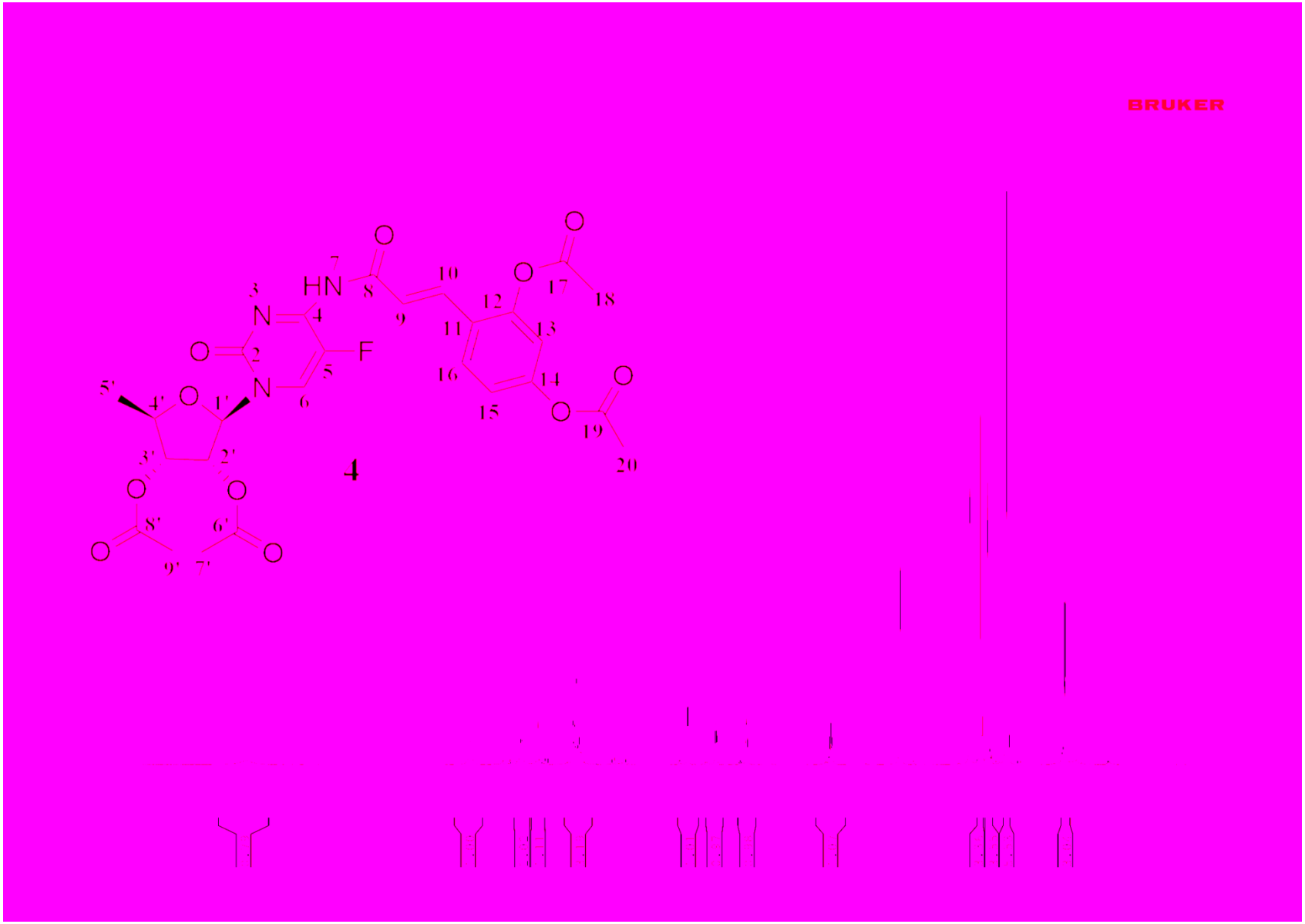


Figure S15. ^{1}H NMR spectrum of compound **4** (DMSO-d_6)

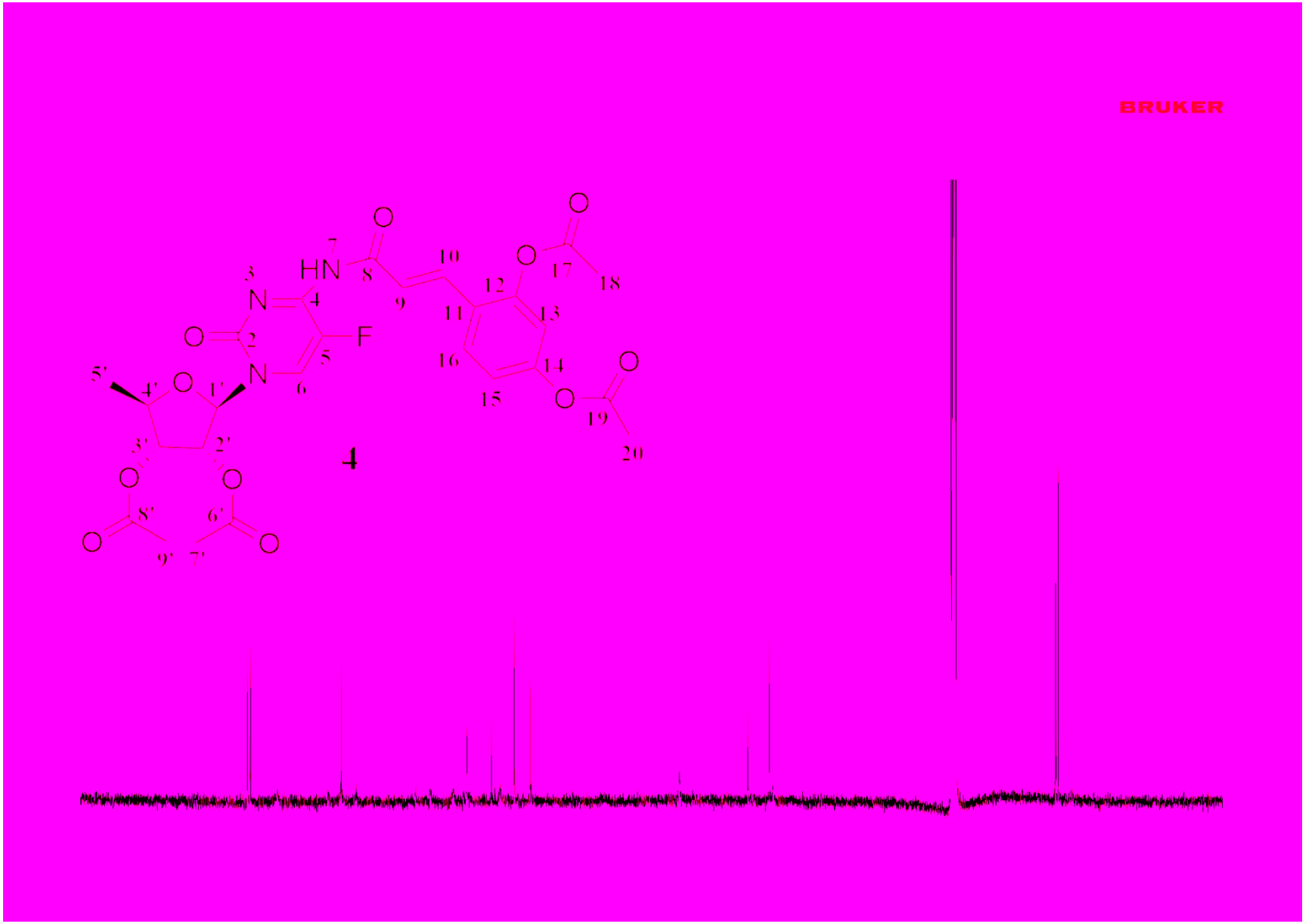


Figure S16. ^{13}C NMR spectrum of compound **4** (DMSO-d_6)

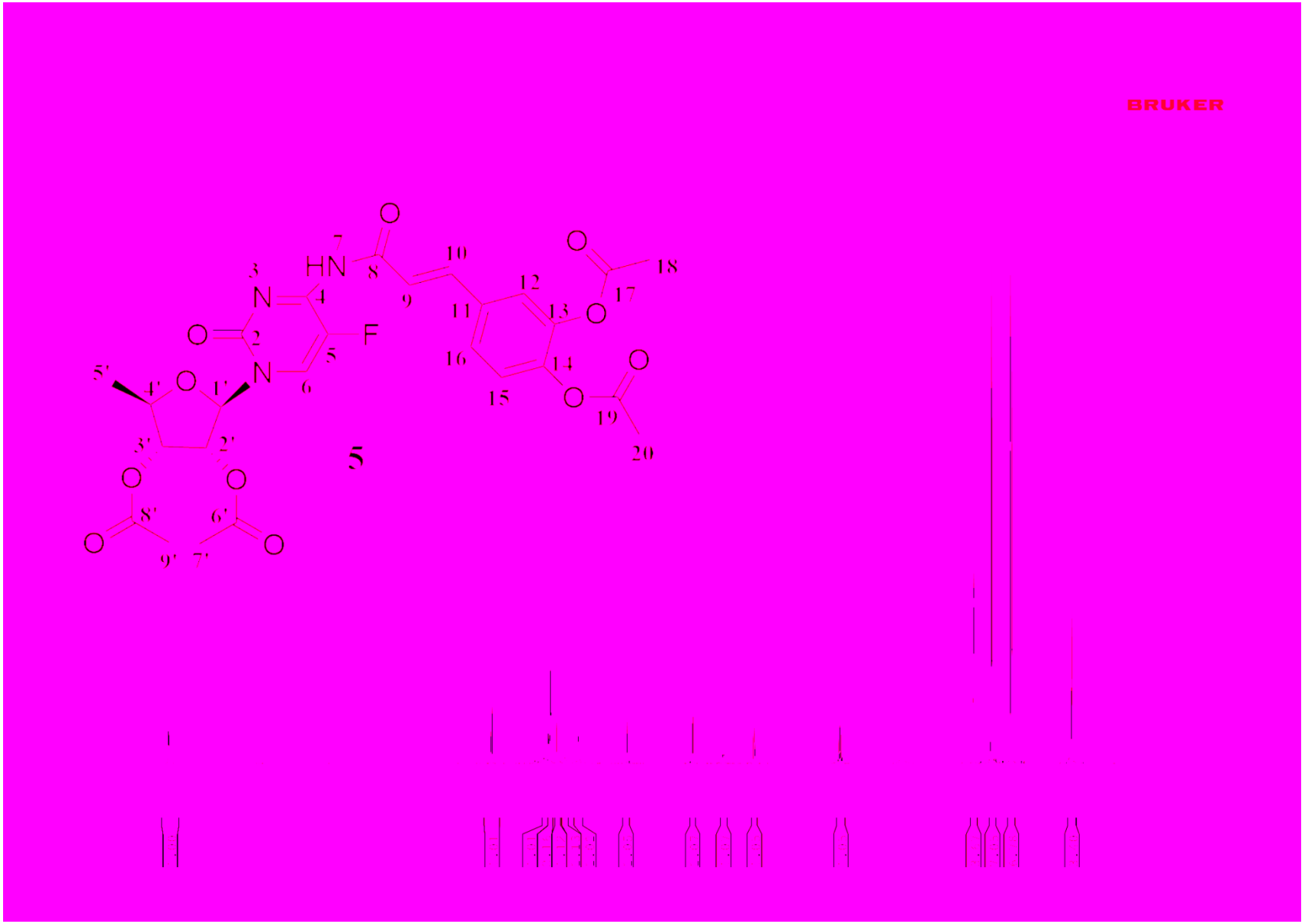


Figure S17. ^{1}H NMR spectrum of compound **5** (DMSO-d_6)

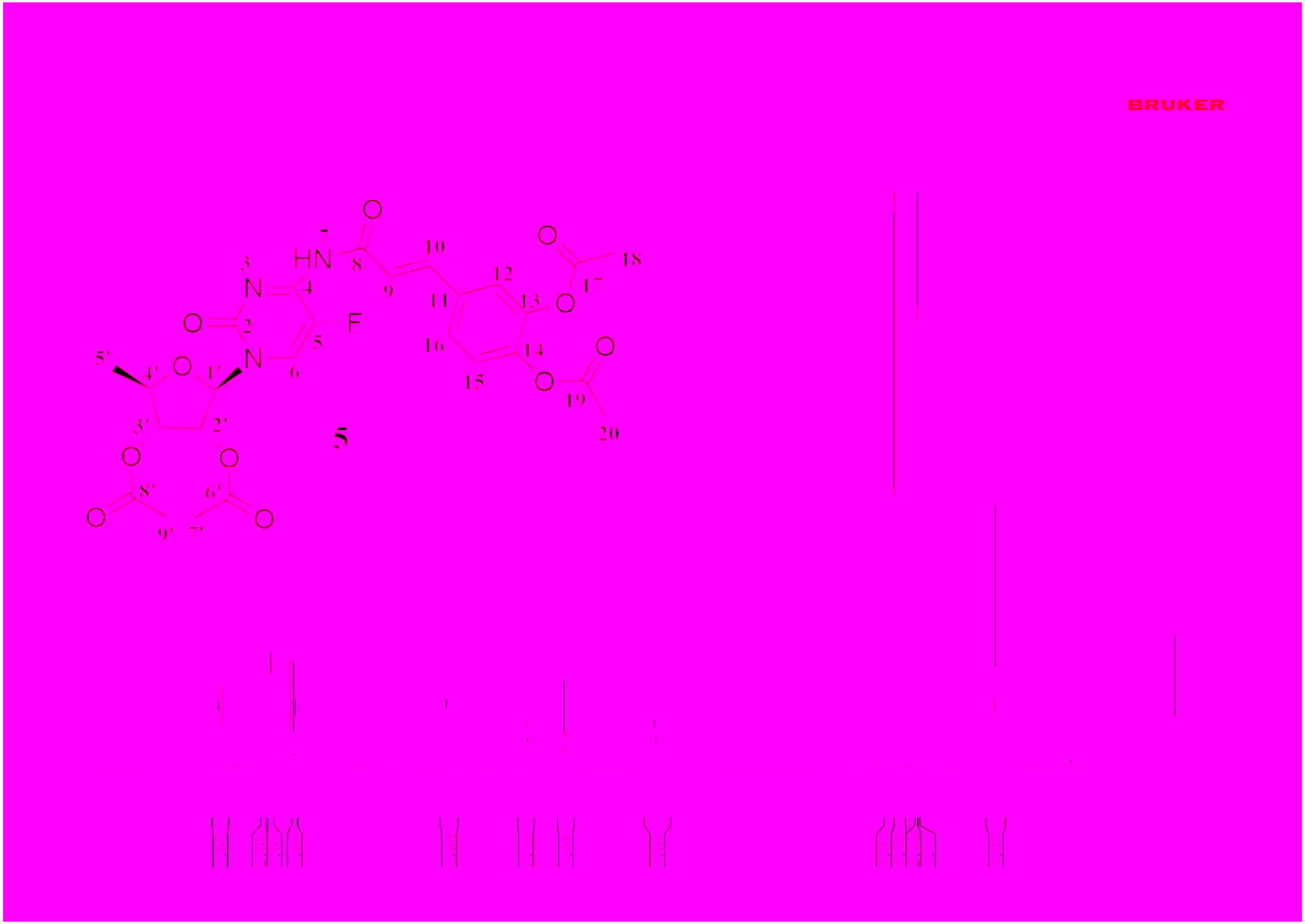


Figure S18. ^{1}H NMR spectrum of compound **5** ($CDCl_3$)

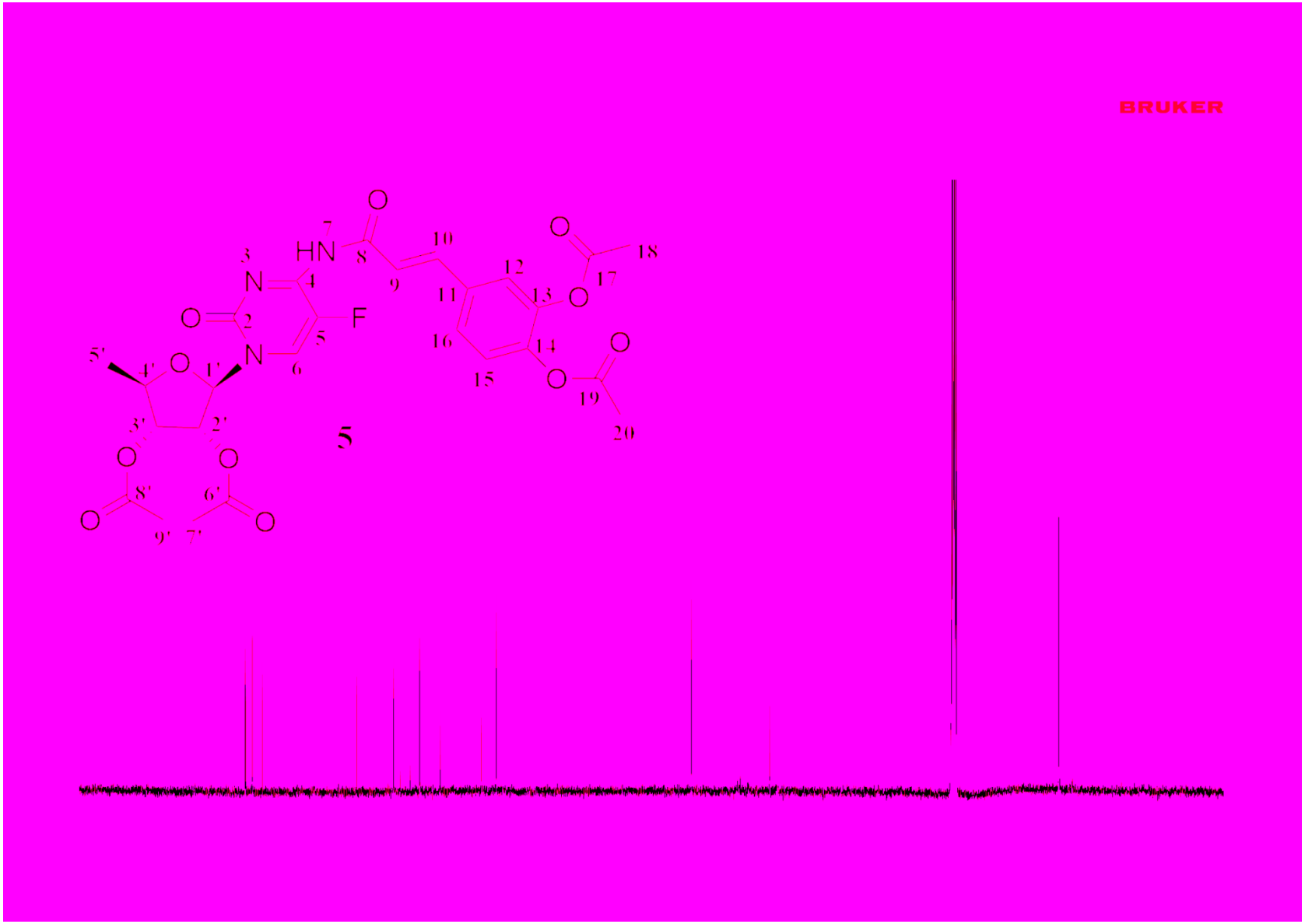


Figure S19. ^{13}C NMR spectrum of compound (DMSO-d_6)

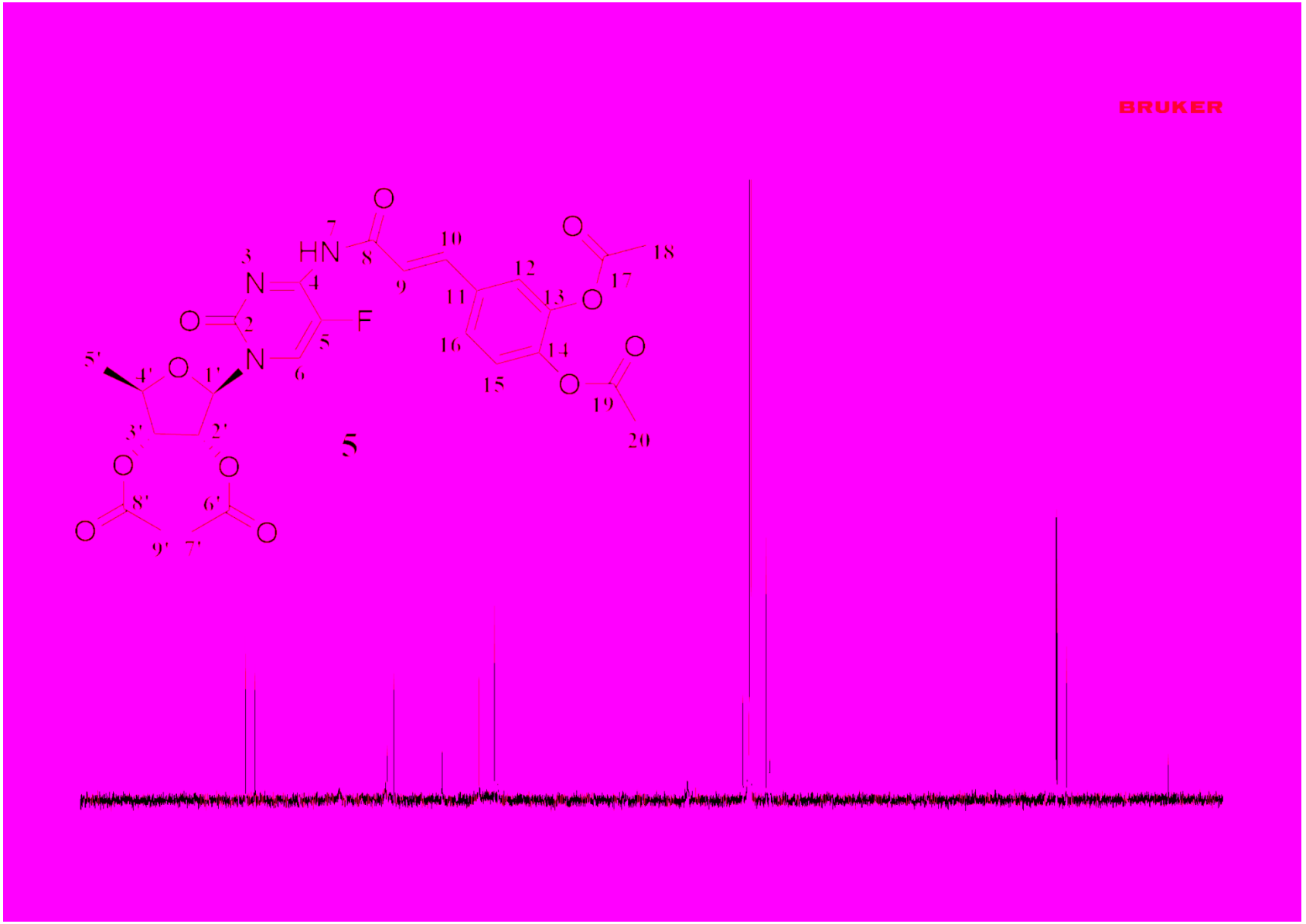


Figure S20. ^{13}C NMR spectrum of compound **5** ($CDCl_3$)

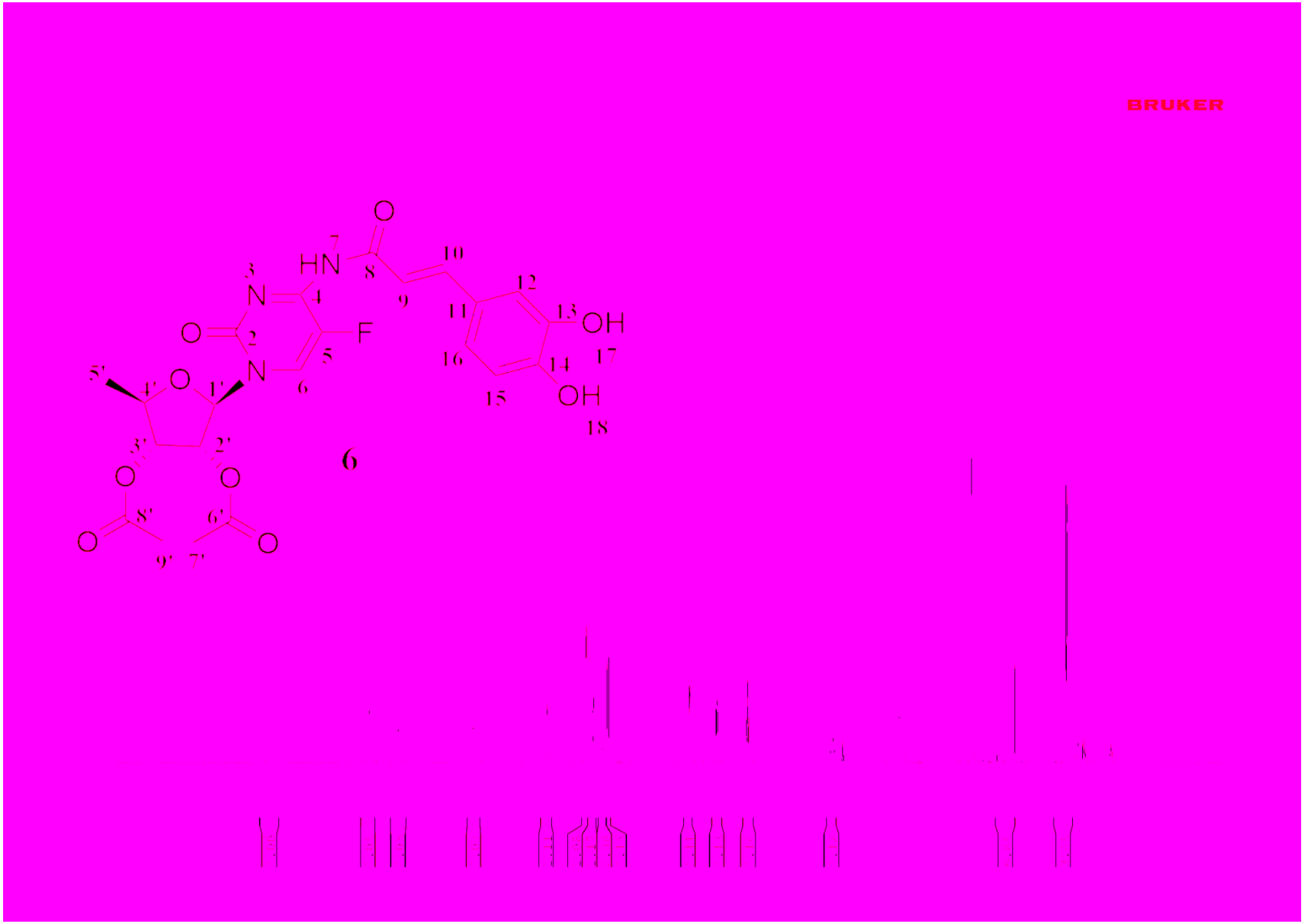


Figure S21. ^{1}H NMR spectrum of compound **6** (DMSO-d_6)

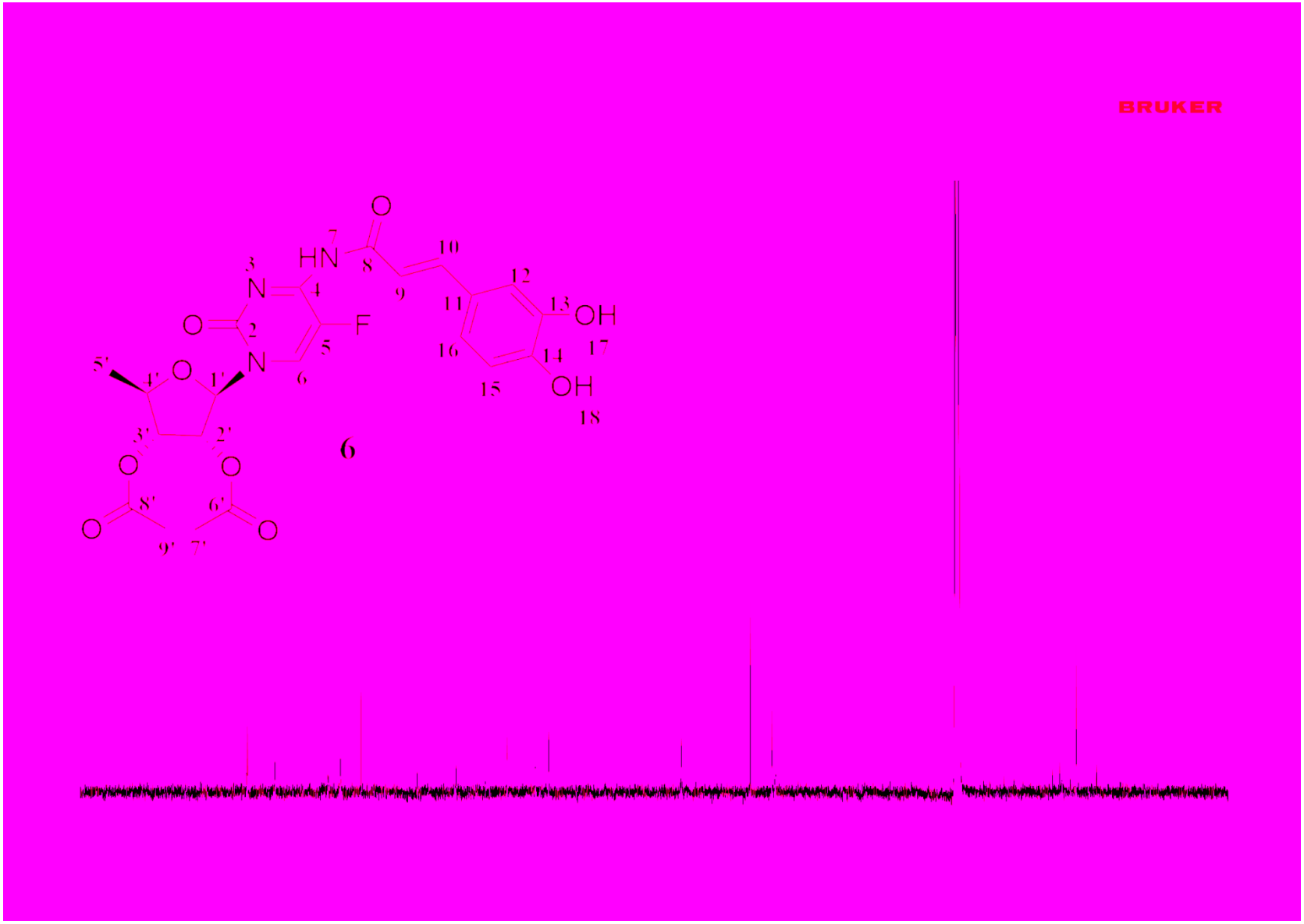


Figure S22. ^{13}C NMR spectrum of compound **6** (DMSO-d_6)

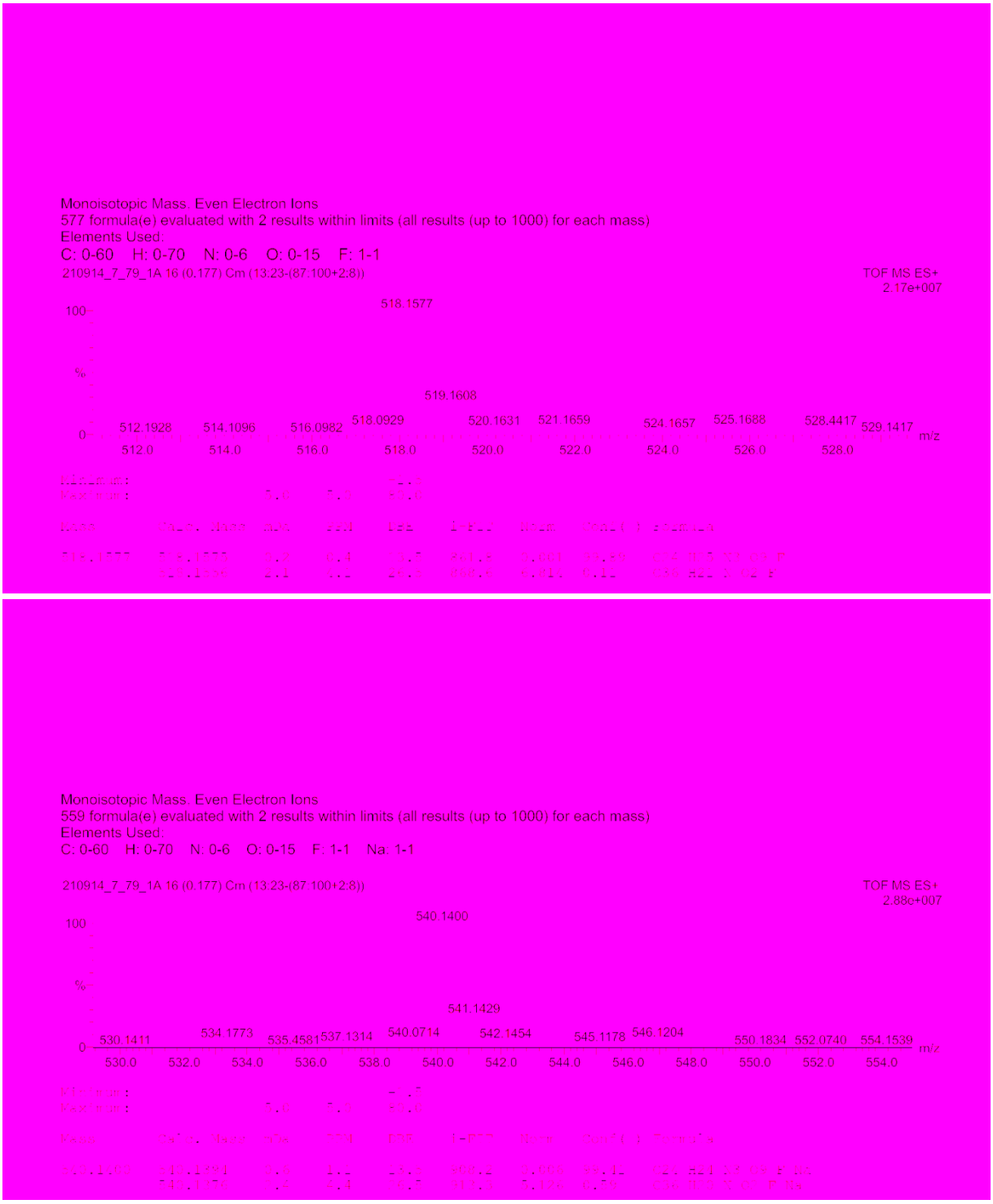


Figure S23. HRMS data of compound **1**

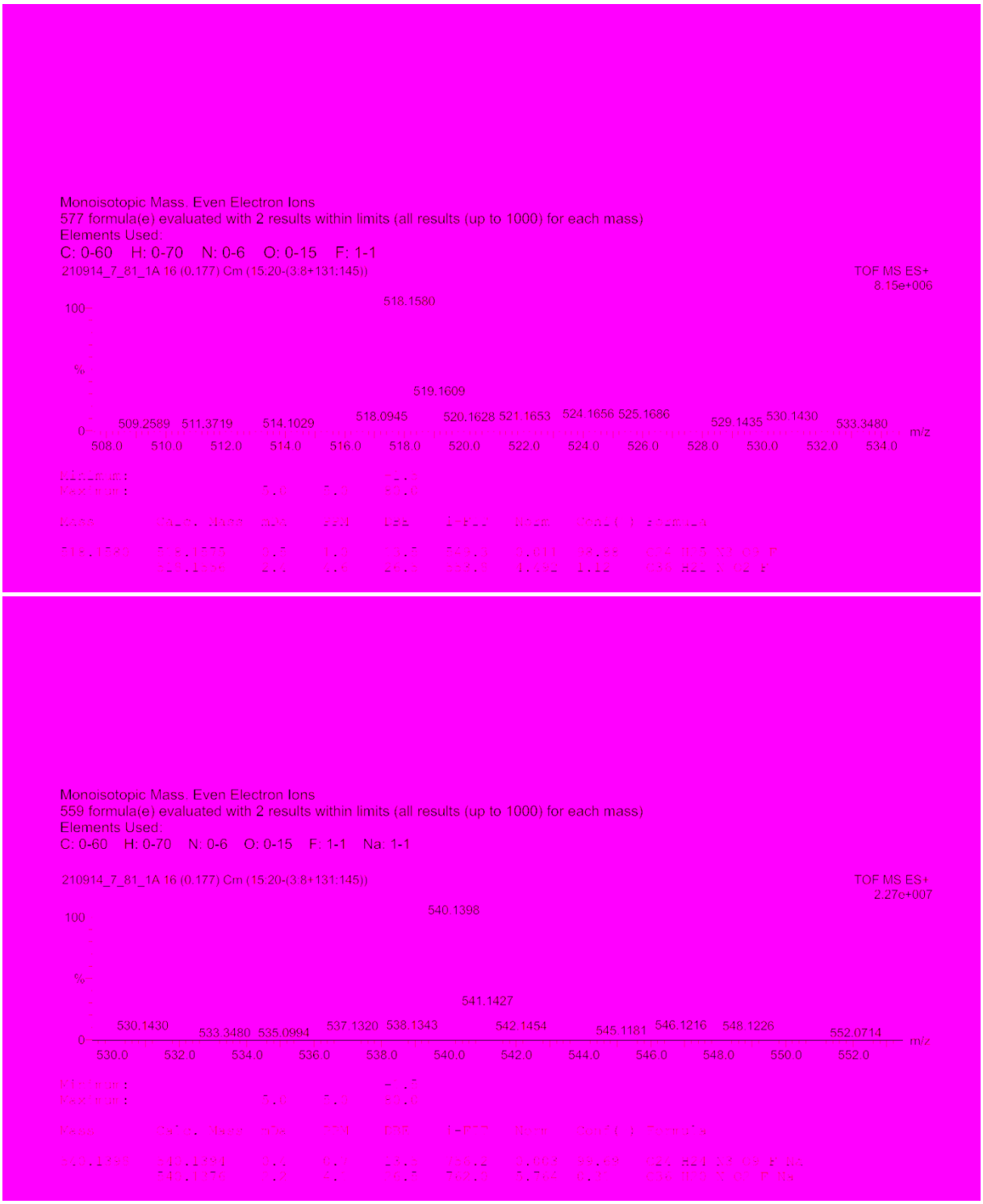


Figure S24. HRMS data of compound **2**

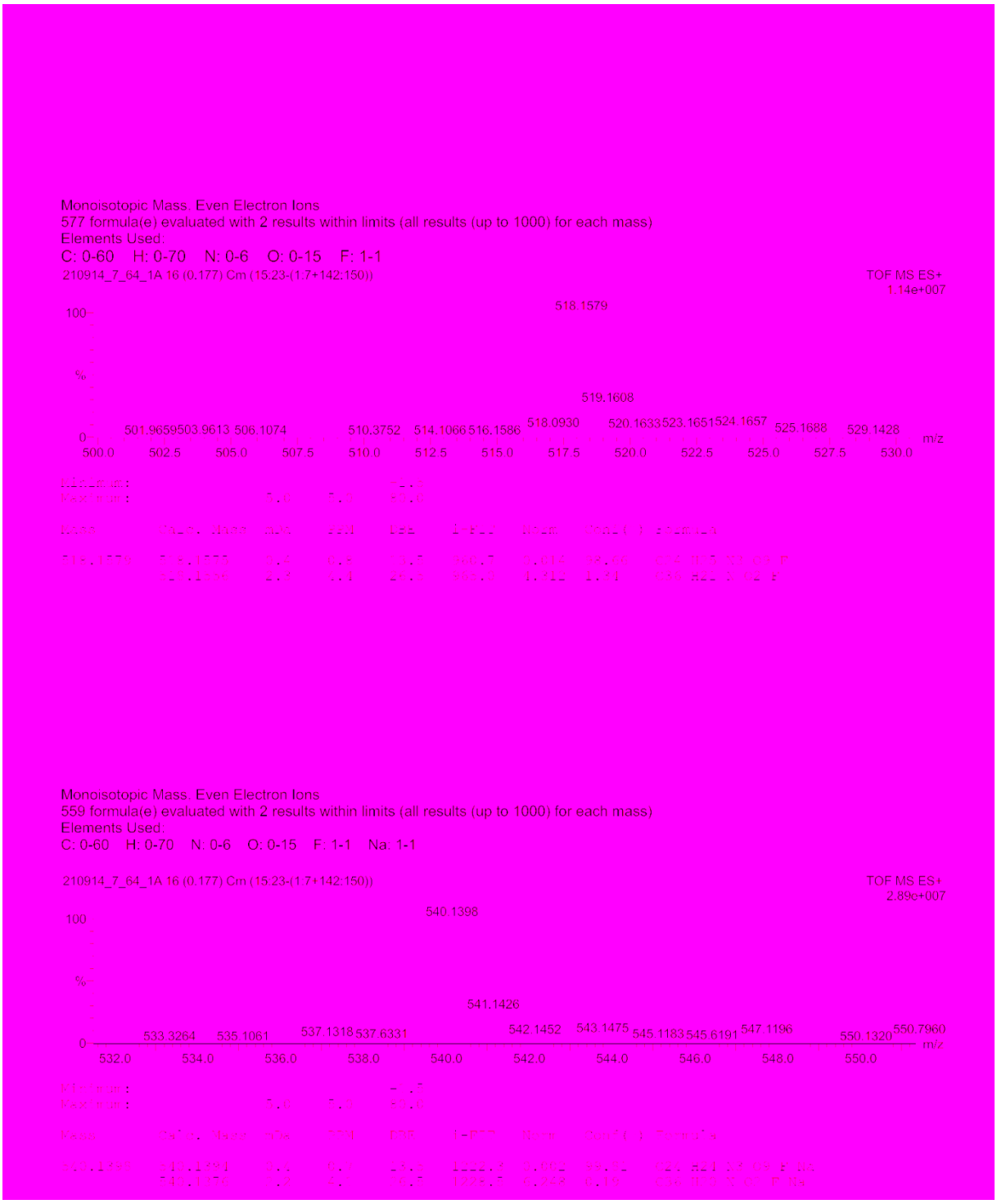


Figure S25. HRMS data of compound **3**

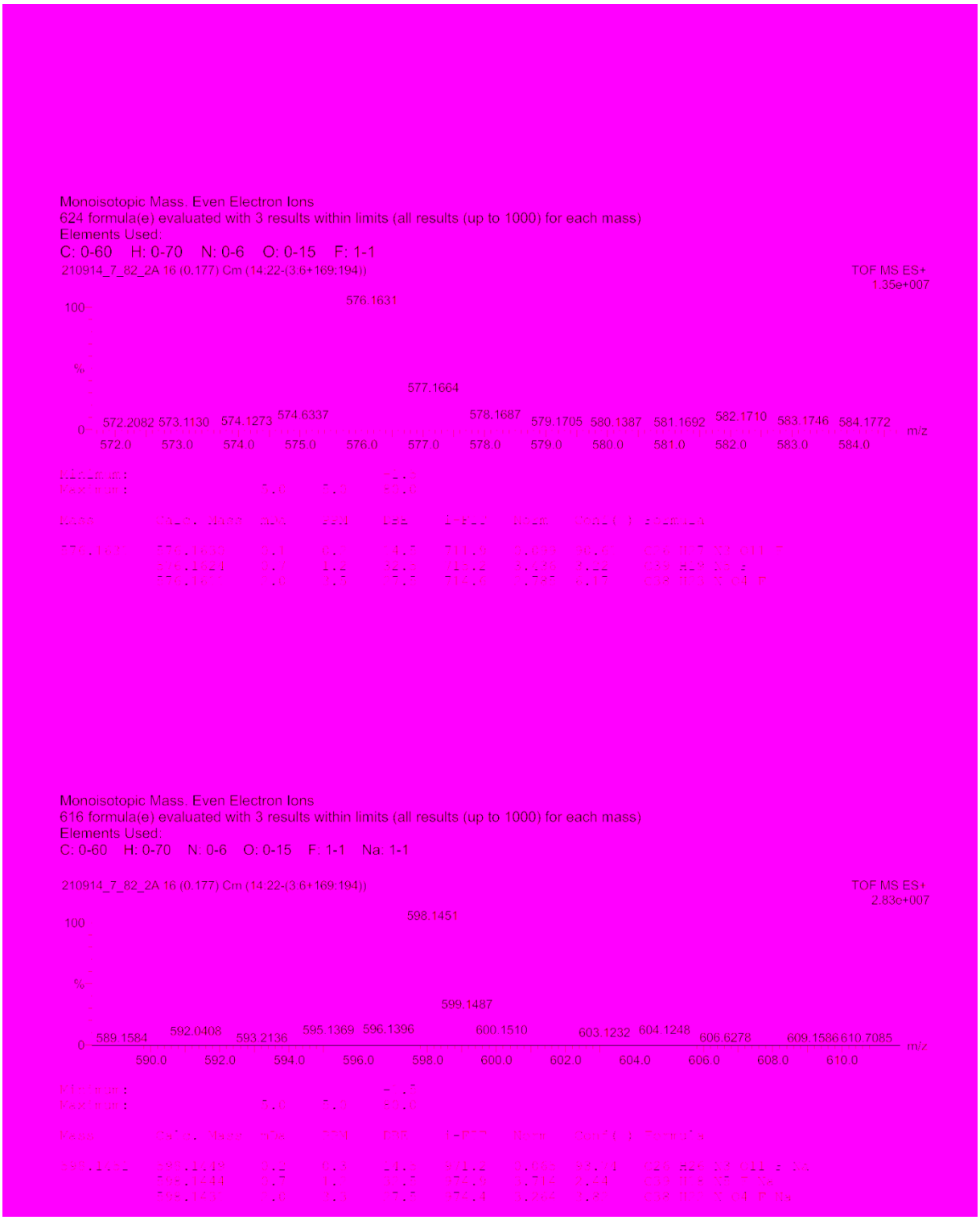


Figure S26. HRMS data of compound **4**

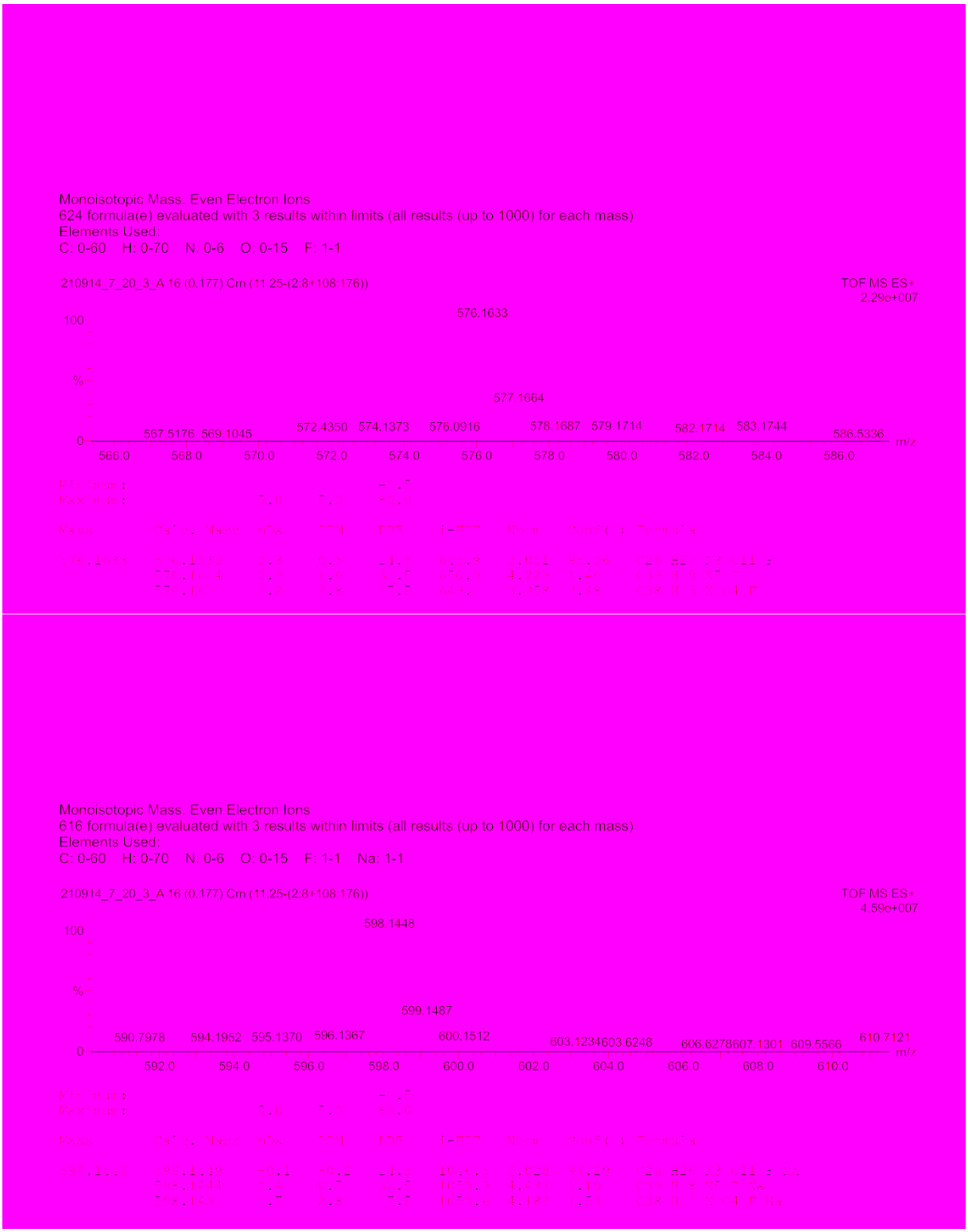


Figure S27. HRMS data of compound **5**

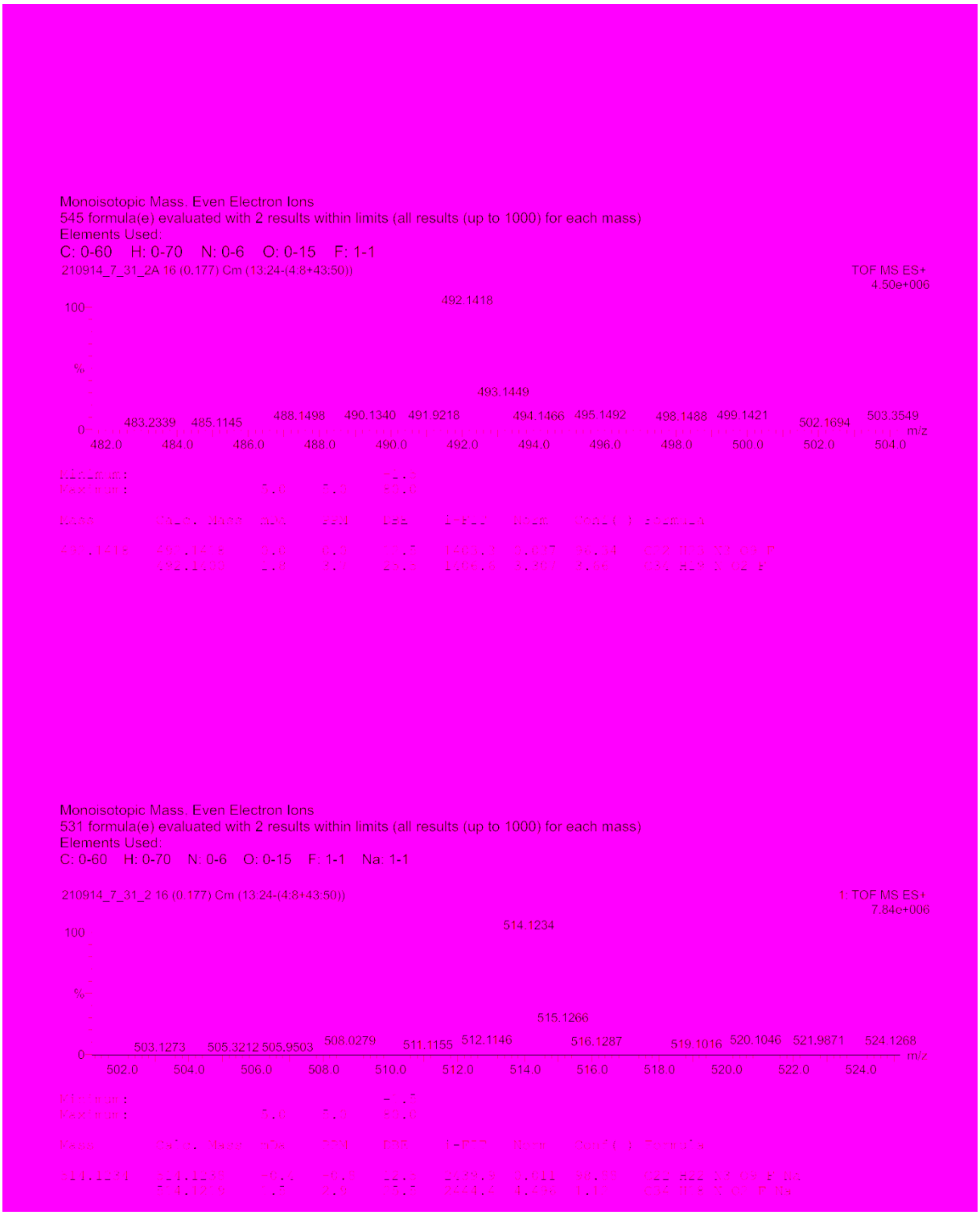


Figure S28. HRMS data of compound **6**