Electronic Supplementary Material (ESI) for New Journal of Chemistry.

Supporting Information

Stress degradation study of bortezomib: Effect of co-solvent, isolation and characterization of degradation products by UHPLC-Q-TOF-MS/MS, NMR and evaluation of the toxicity of the degradation products

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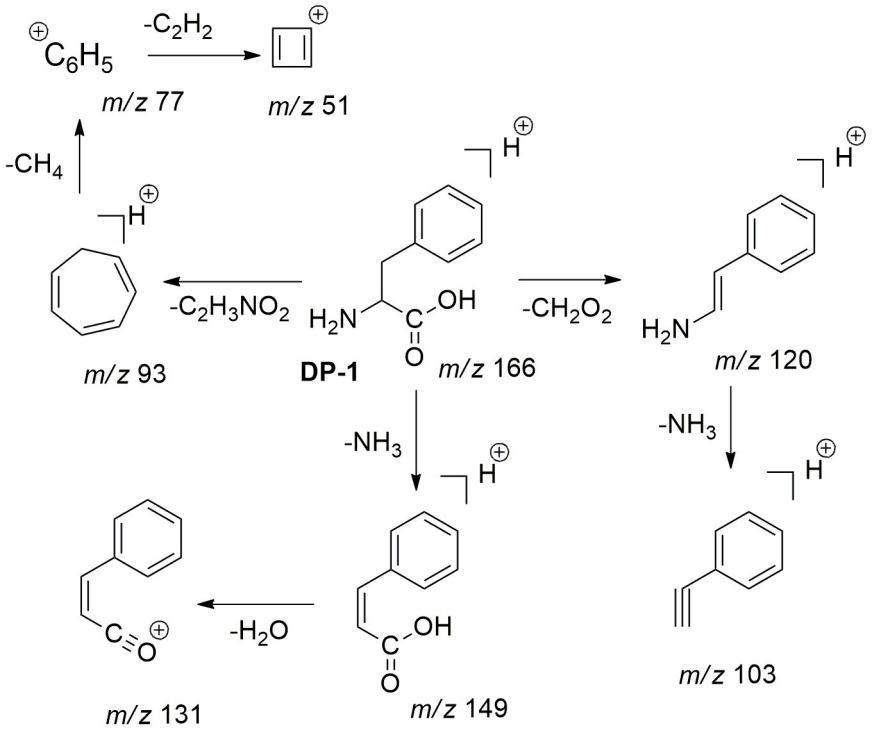
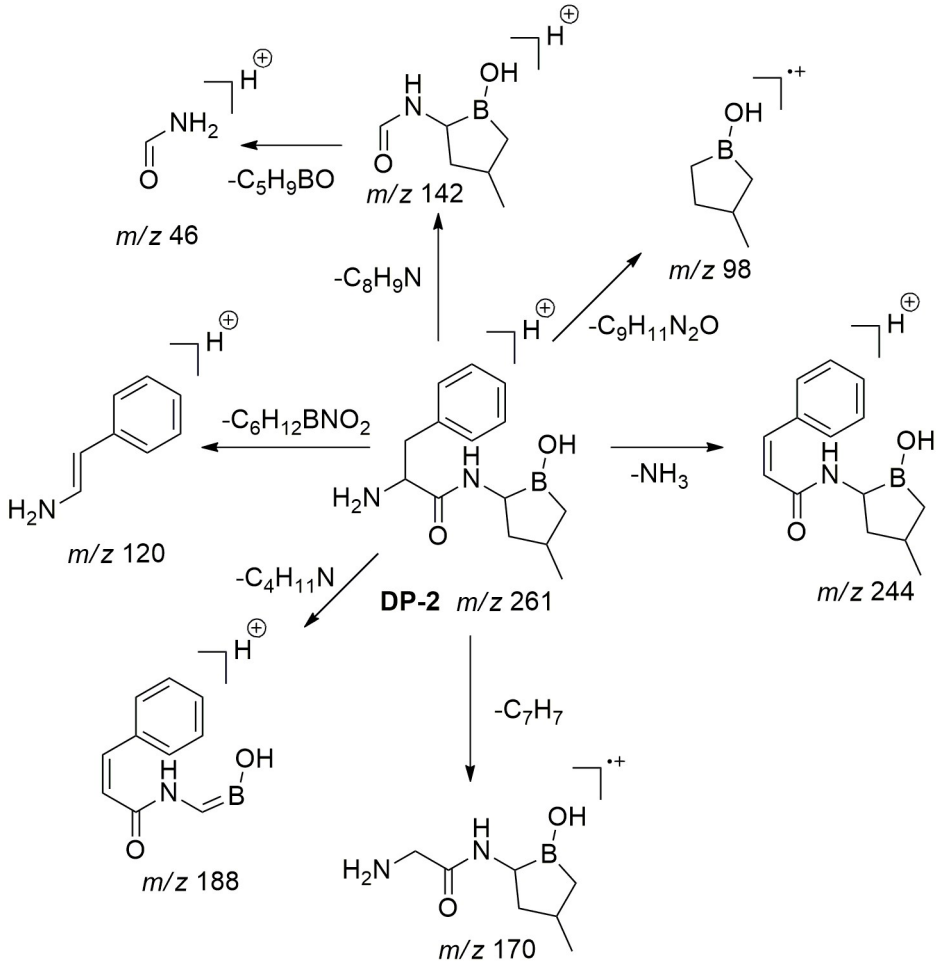
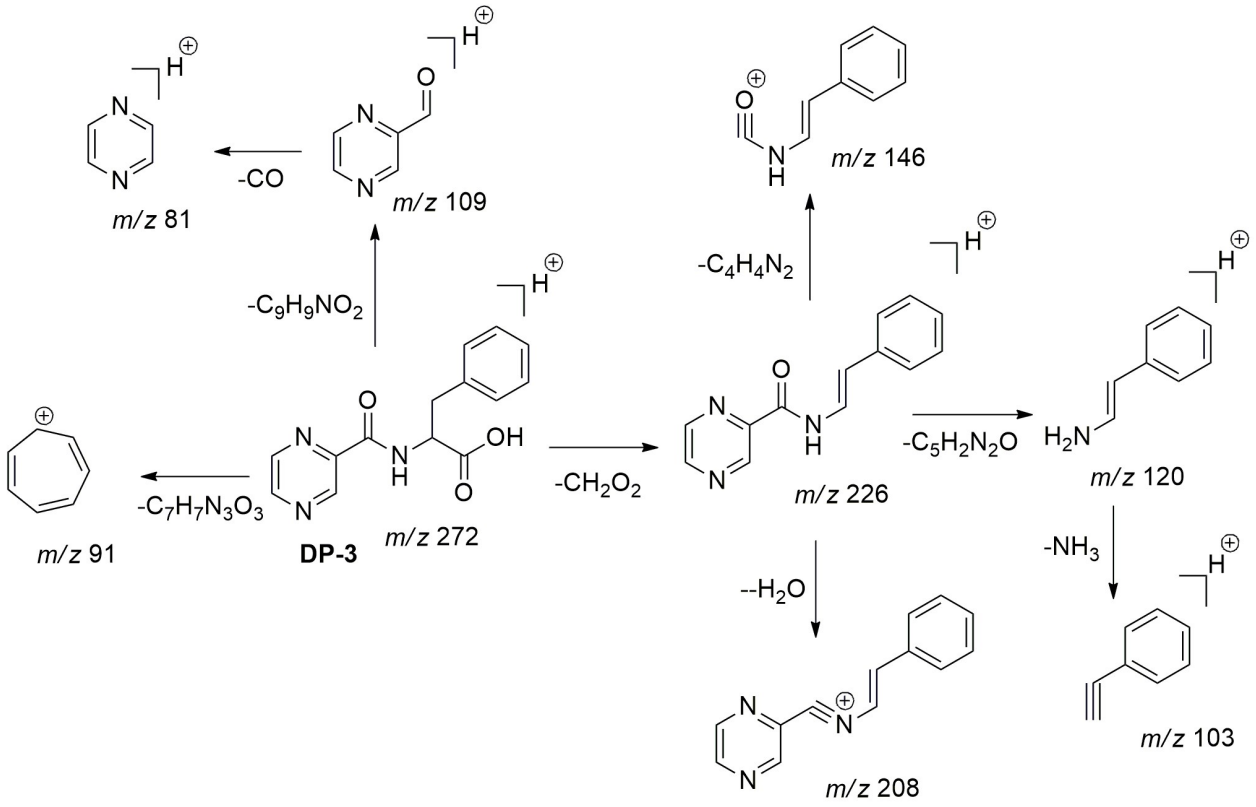


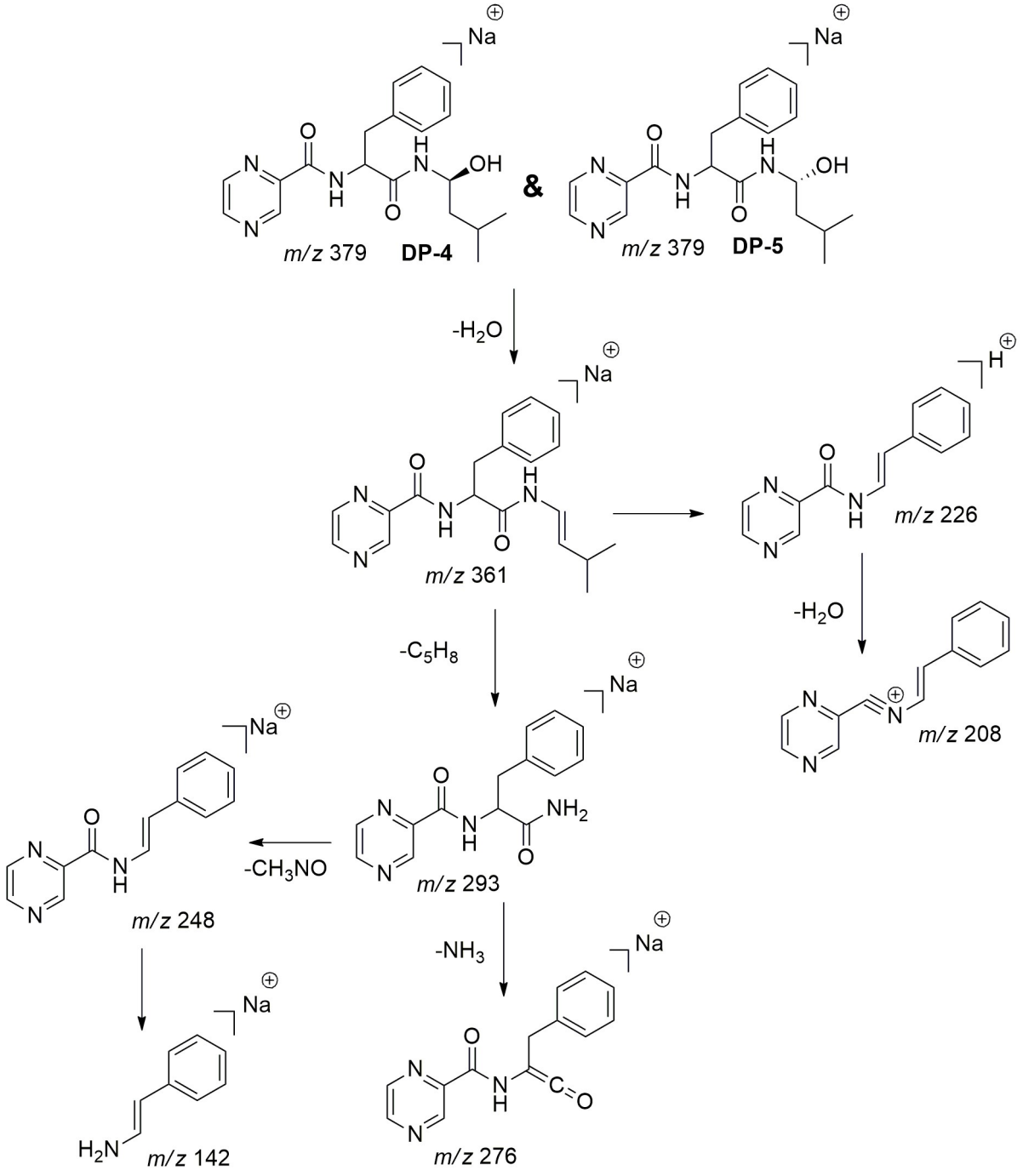
Scheme S1. Proposed fragmentation pathway of protonated **DP-1**(***m/z*** 166)



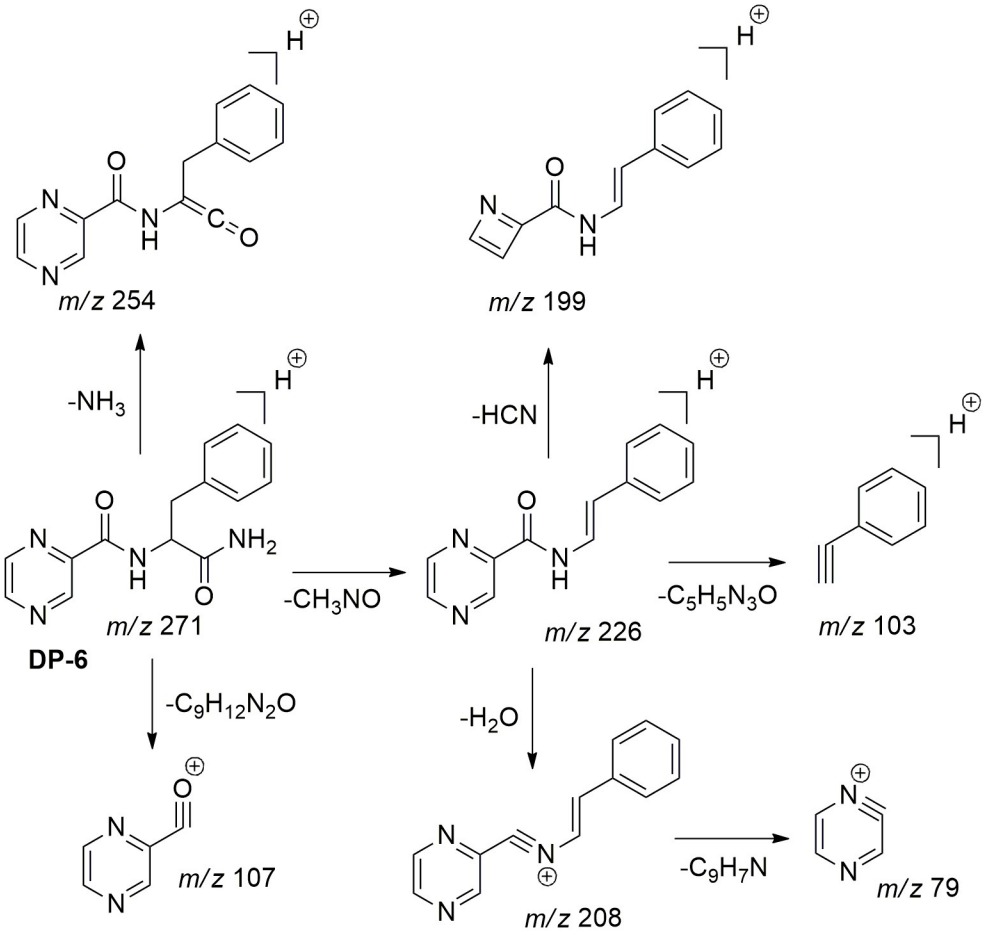
Scheme S2. Proposed fragmentation pathway of protonated **DP-2**(***m/z*** 261)



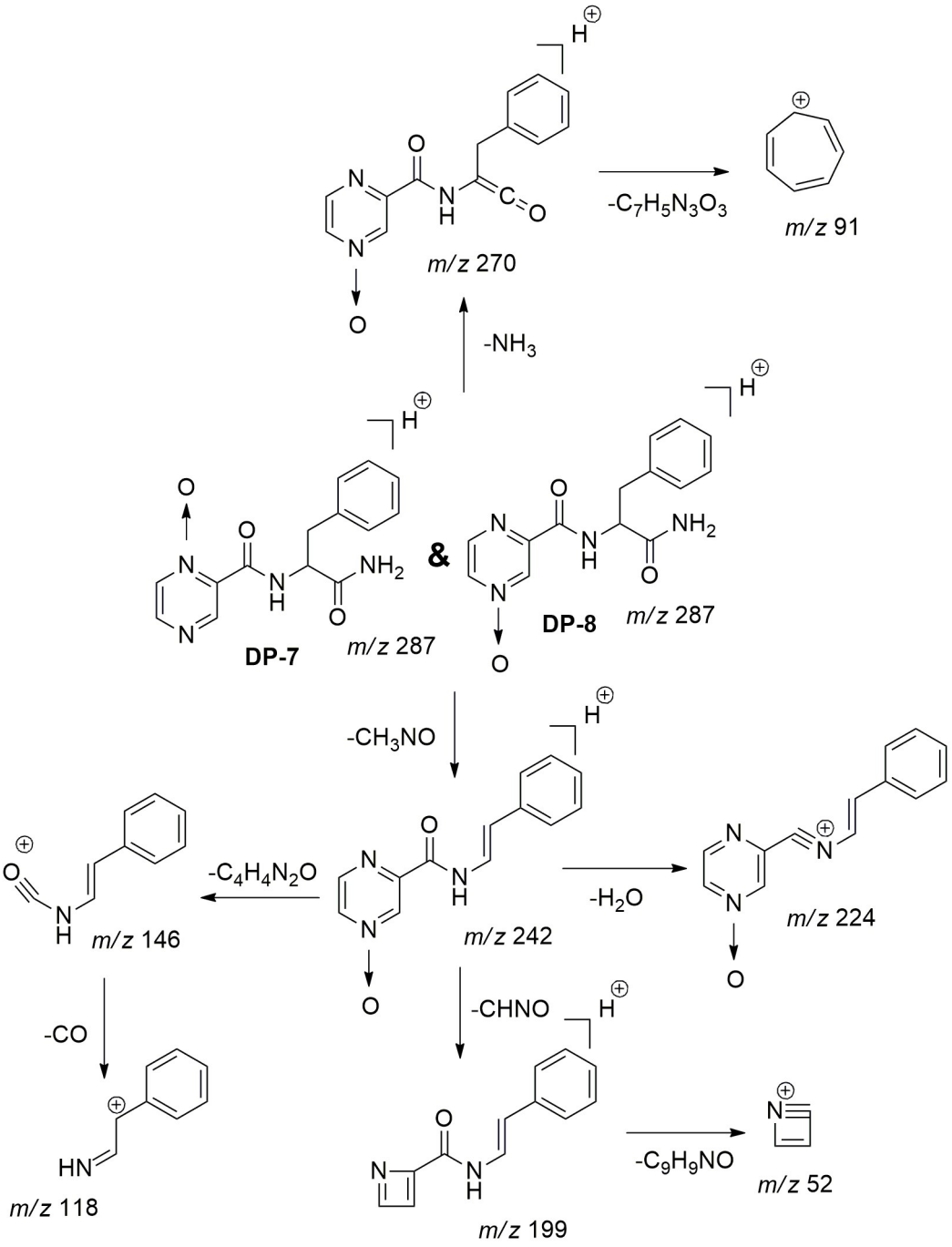
Scheme S3. Proposed fragmentation pathway of protonated **DP-3**(***m/z*** 272)



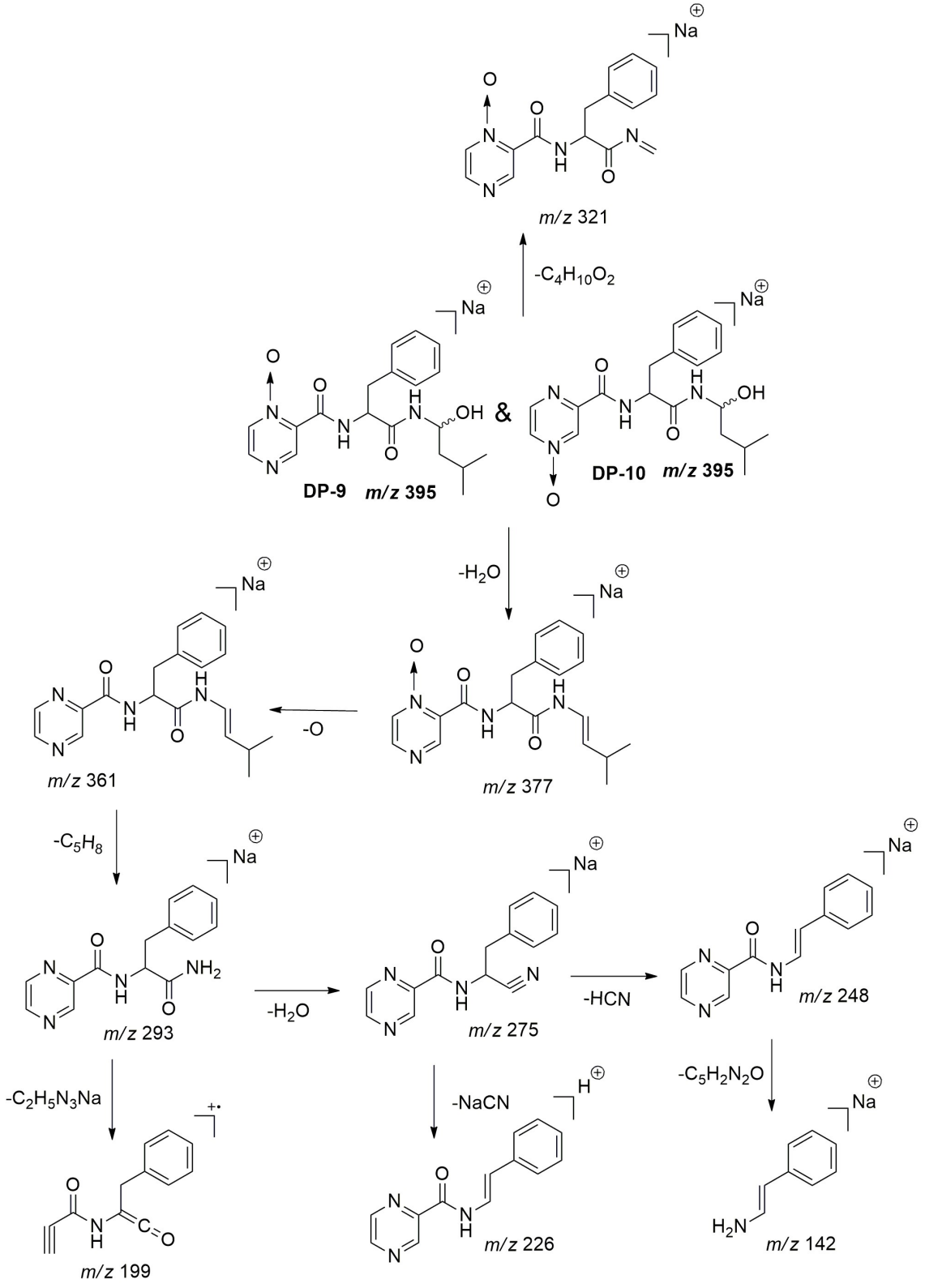
Scheme S4. Proposed fragmentation pathway of protonated **DP-4 and DP-5** (***m/z*** 379)



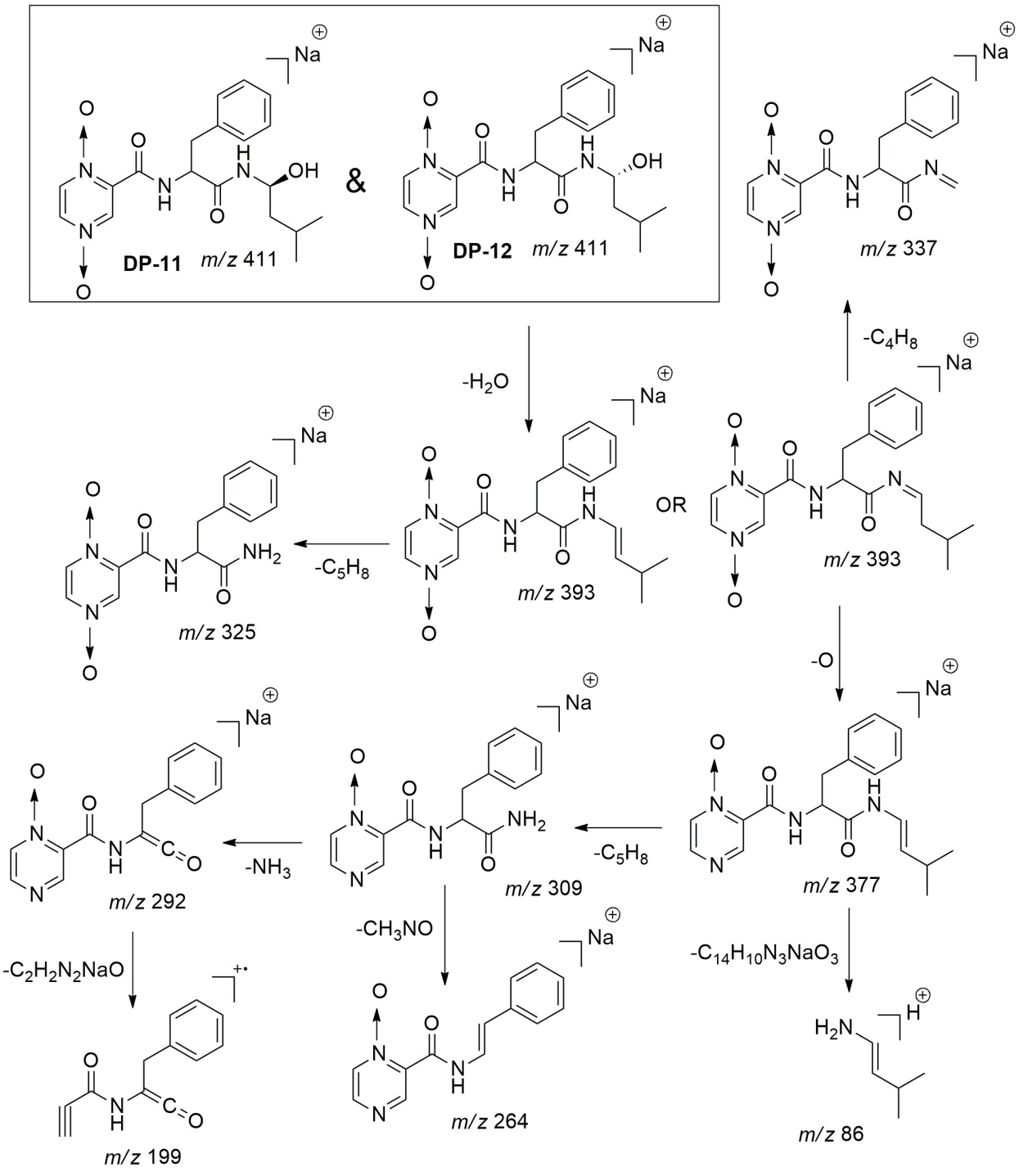
Scheme S5. Proposed fragmentation pathway of protonated **DP-6** (***m/z*** 271)



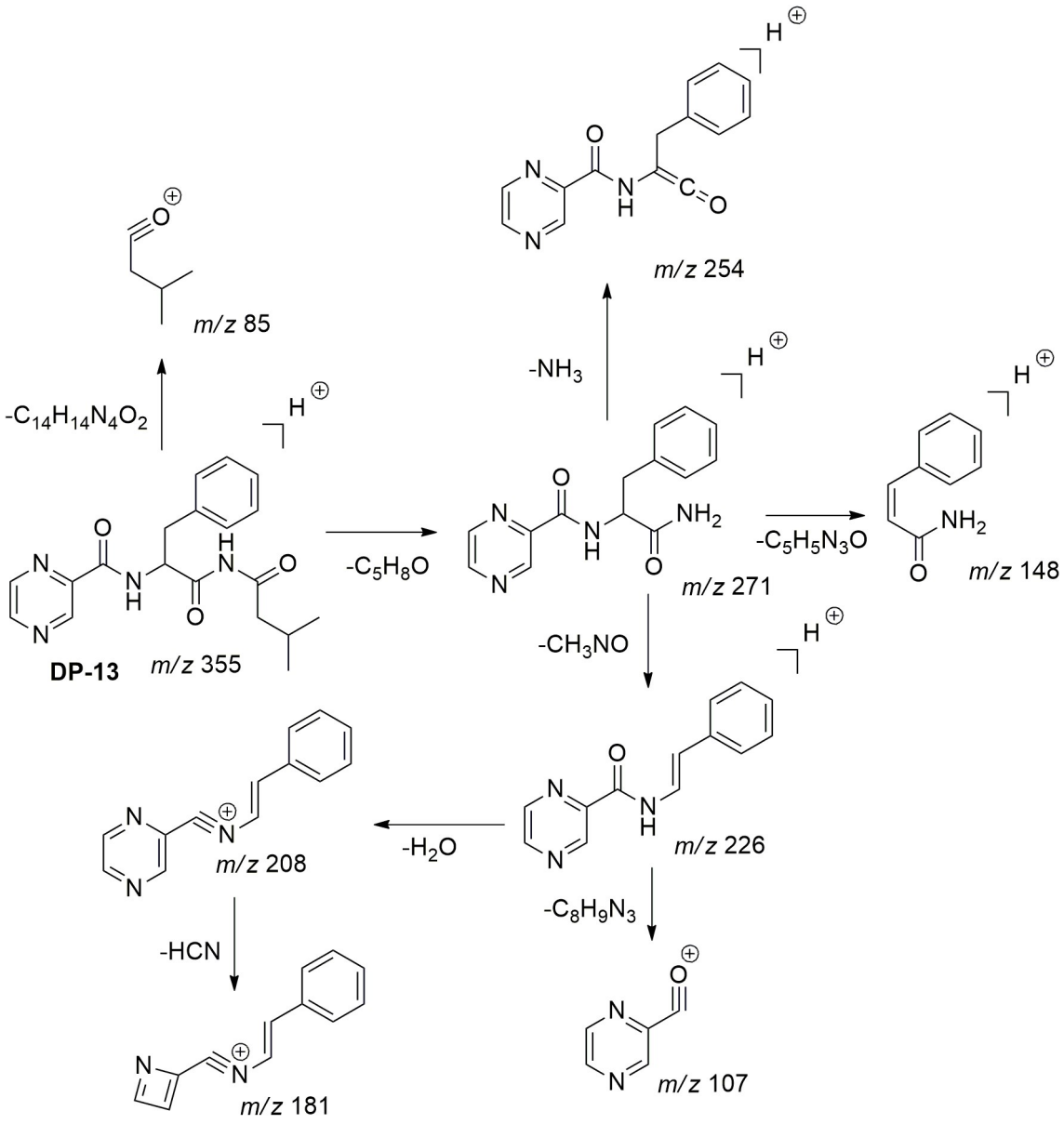
Scheme S6. Proposed fragmentation pathway of protonated **DP-7 and DP-8** (***m/z*** 287)



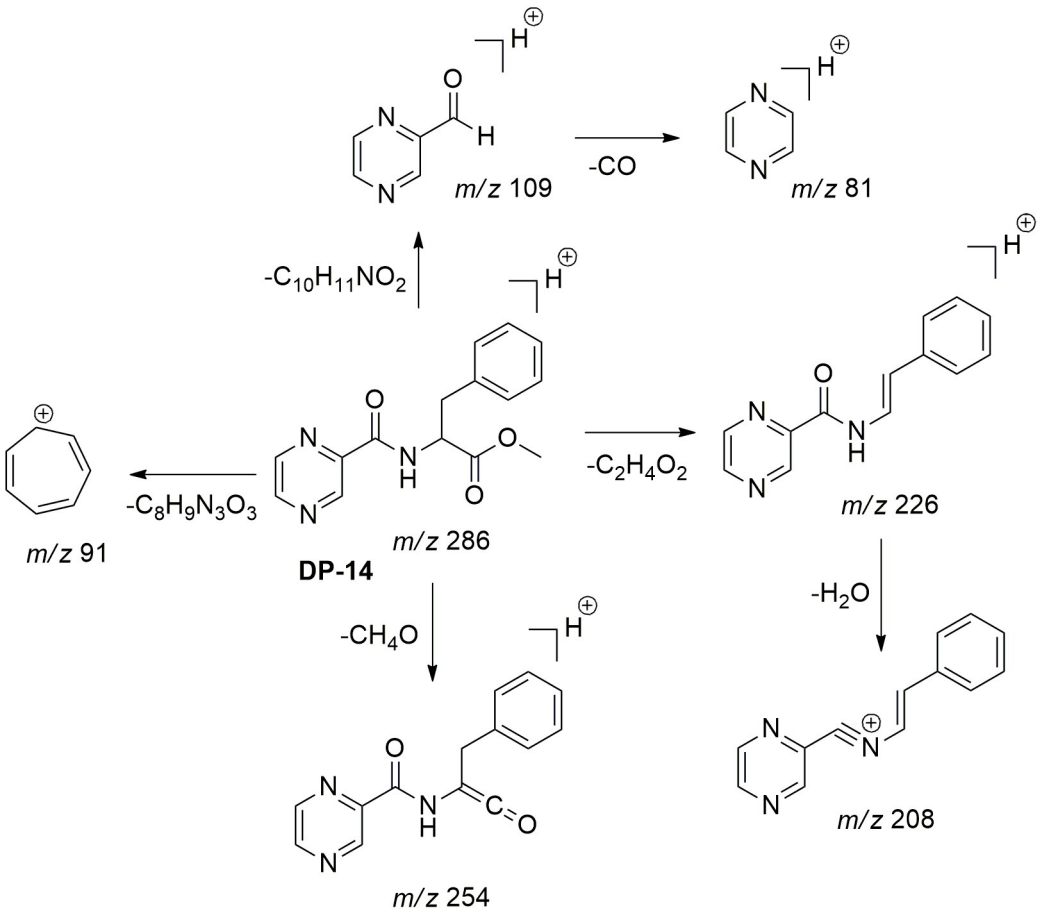
Scheme S7. Proposed fragmentation pathway of protonated **DP-9 and DP-10** (***m/z*** 395)



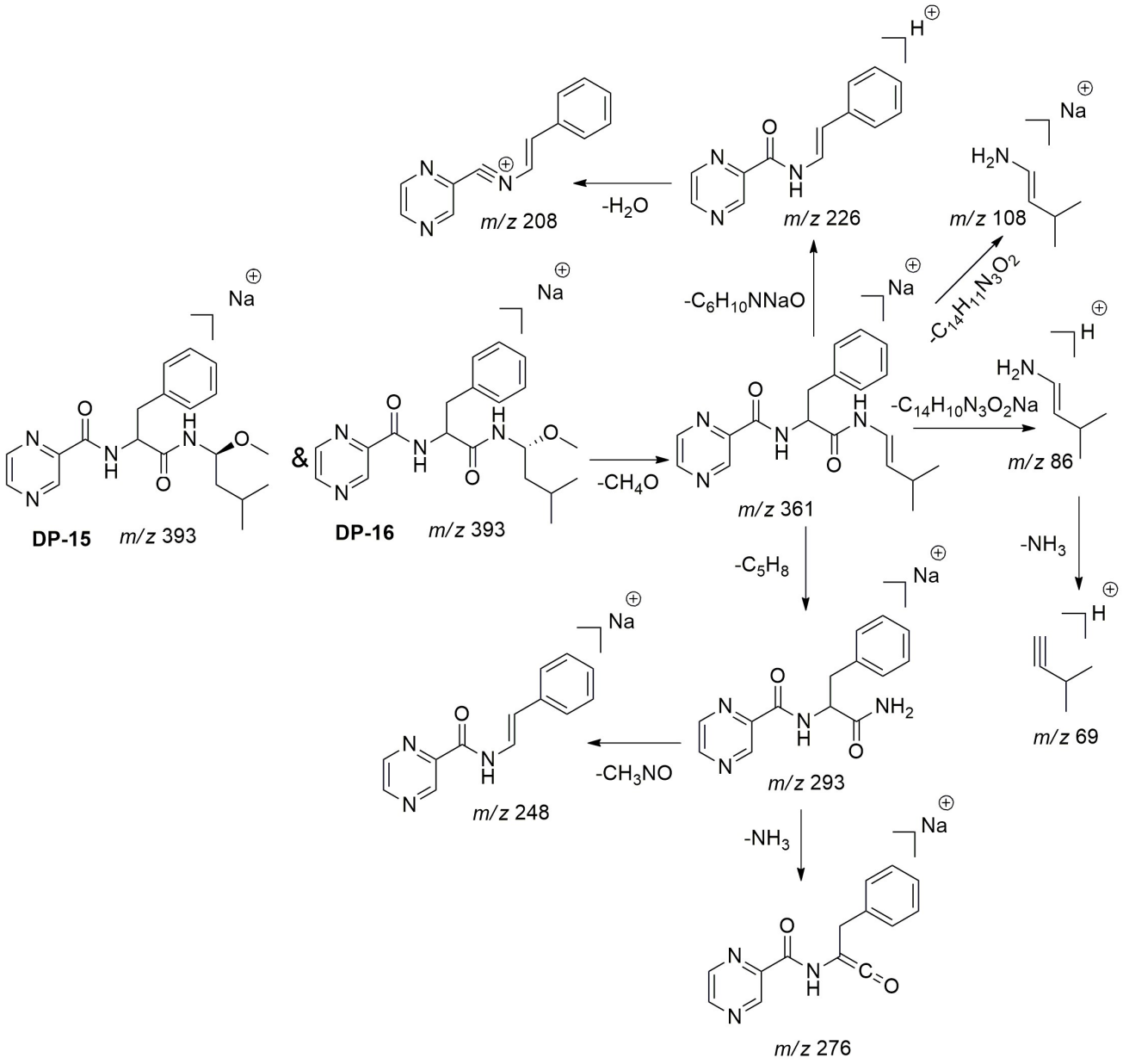
Scheme S8. Proposed fragmentation pathway of protonated **DP-11 and DP-12** (***m/z*** 411)



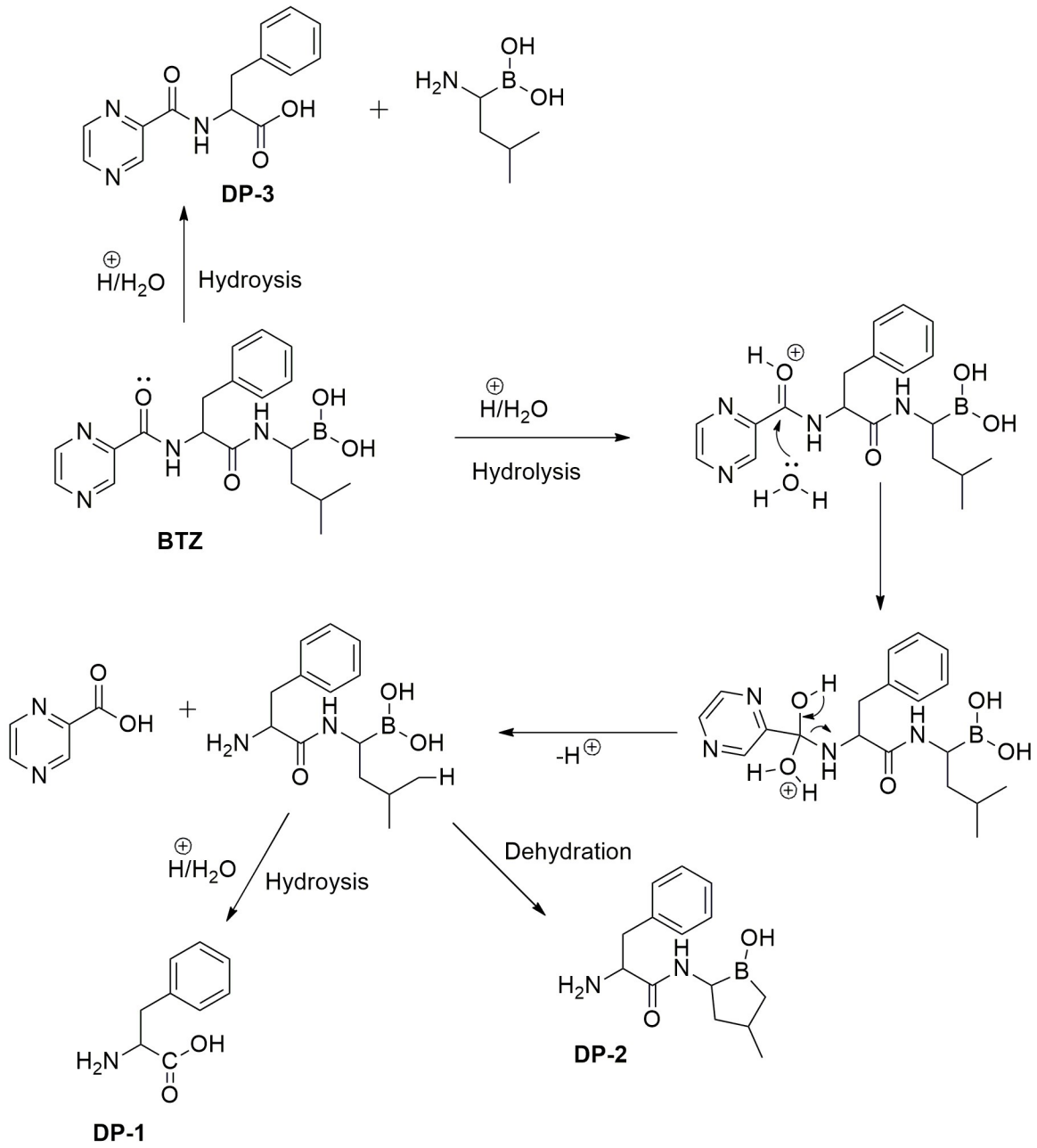
Scheme S9. Proposed fragmentation pathway of protonated **DP-13** (***m/z*** 355)



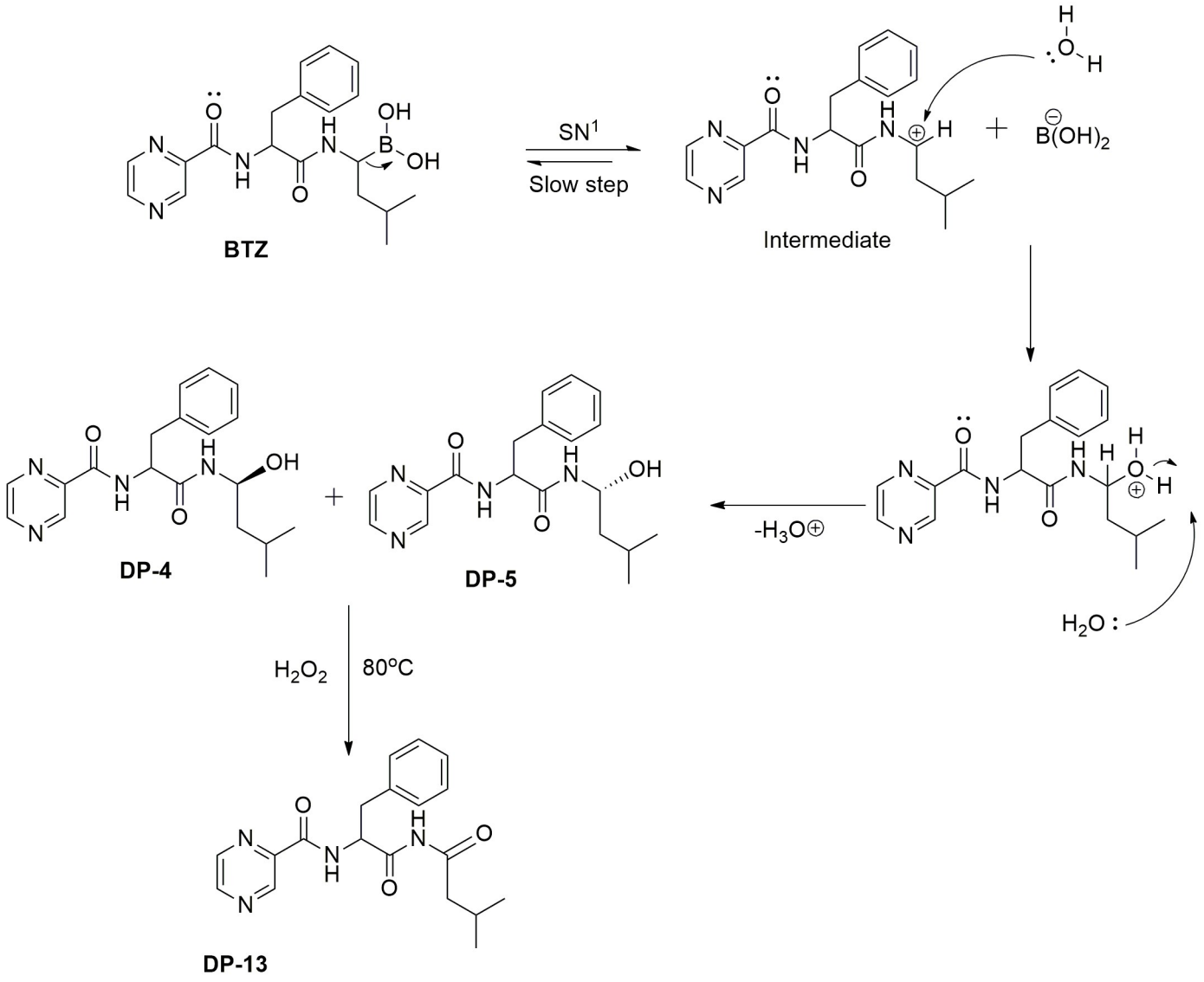
Scheme S10. Proposed fragmentation pathway of protonated **DP-14** (***m/z*** 286)



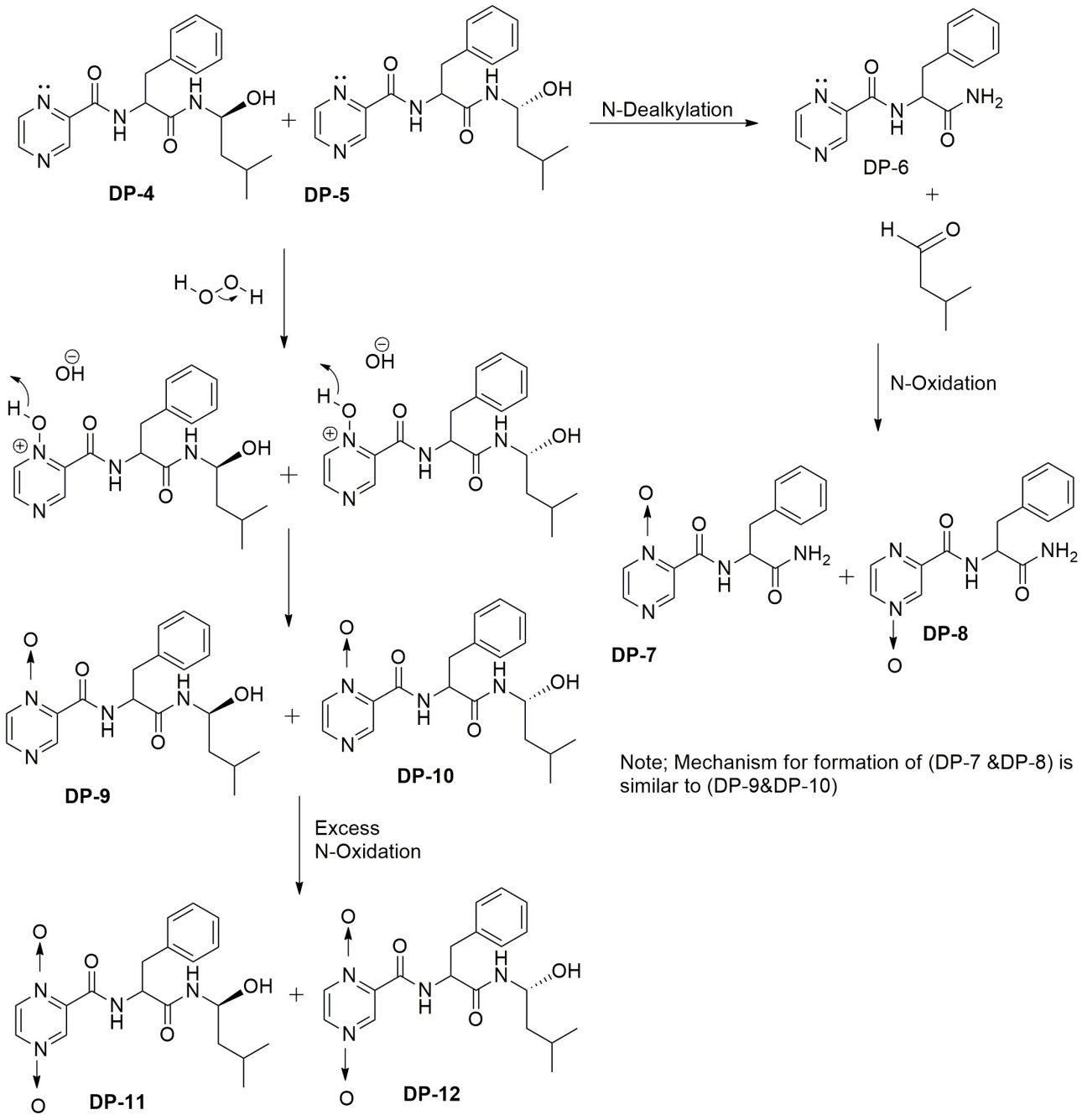
Scheme S11. Proposed fragmentation pathway of protonated **DP-15 and DP-16** (***m/z*** 393)



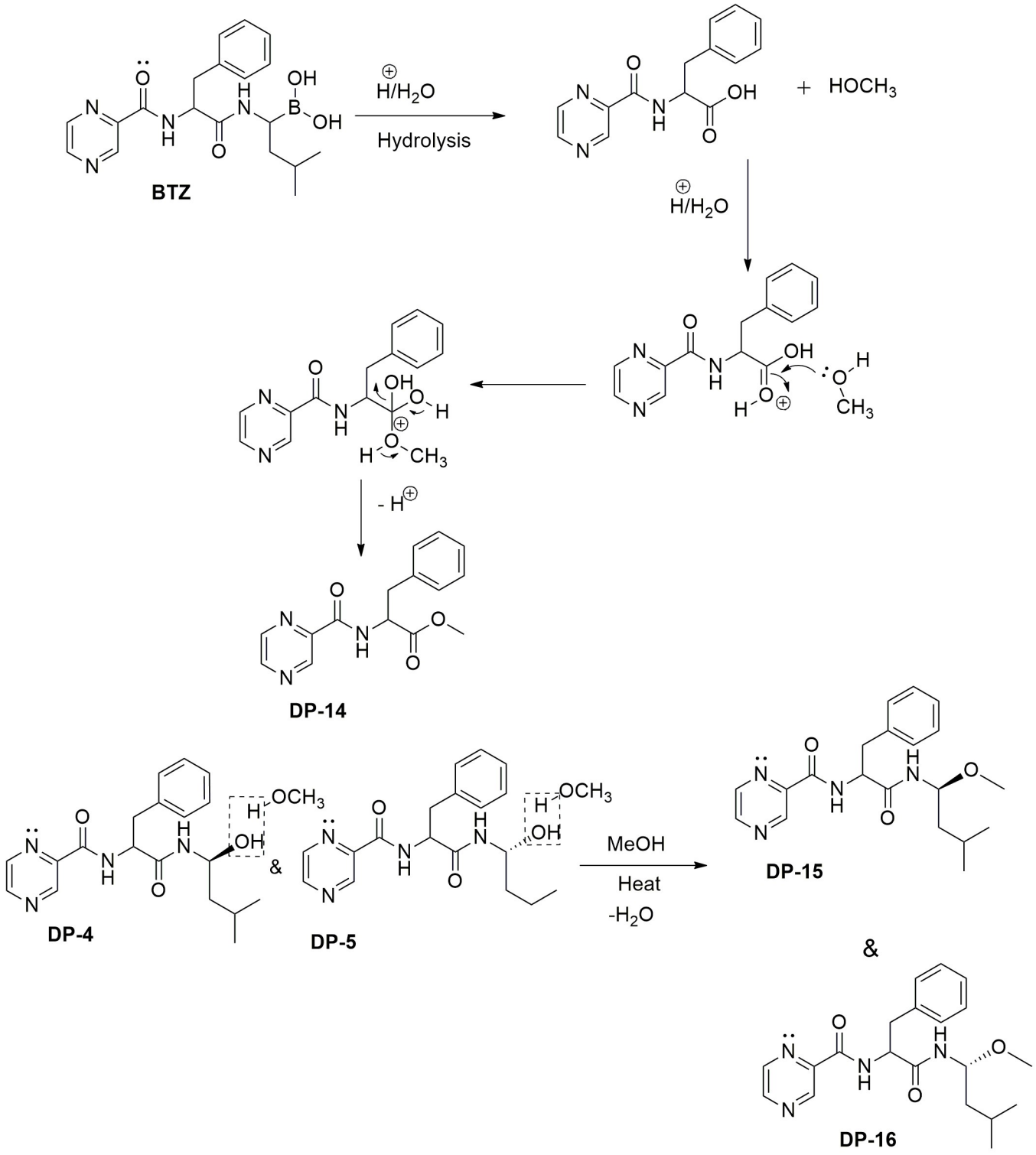
Scheme S12. Probable mechanism for formation of degradation products (DP-1, DP-2 and DP-3) under acidic hydrolysis using acetonitrile as co-solvent



Scheme S13. Probable mechanism for formation of degradation products (DP-4 and DP-5) in neutral hydrolysis and DP-13 in oxidation condition using acetonitrile as co solvent



Scheme S14. Probable mechanism for formation of degradation products (DP-7, DP-8, DP-9, DP-10, DP-11 and DP-12) under oxidation condition using acetonitrile as co-solvent



Scheme S15. Probable mechanism for formation of degradation product (DP-14) in acidic and (DP-15 / DP-16) under oxidation condition using methanol as co solvent

Table S1: Elemental composition for fragment ions of BTZ and DP-1

DRUG	Proposed molecular formula **[M+H]$^+$**	Calculated (***m/z***)	Observed (***m/z***)	Error (ppm)
BTZ	$C_{19}H_{24}BN_4O_3^+$	367.19360	367.19311	1.33
	$C_{19}H_{22}BN_4O_2^+$	349.18303	349.18353	-1.43
	$C_{12}H_{17}BN_4O_3^{+\cdot}$	276.13882	276.13789	3.36
	$C_{14}H_{13}N_4O^+$	253.10839	253.10807	1.26
	$C_{14}H_{19}BNO_2^+$	244.15034	244.15161	-5.20
	$C_{13}H_{12}N_3O^+$	226.09749	226.09714	1.54
	$C_{13}H_{10}N_3^+$	208.08692	208.08635	2.73
	$C_{12}H_{11}N_2O^+$	199.08659	199.08572	4.36
	$C_{10}H_{11}BNO_2^+$	188.08774	188.08813	2.07
	$C_5H_3N_2O^+$	107.02399	107.02338	5.69
	$C_7H_7^+$	91.05423	91.05409	1.53
	$C_4H_3N_2^+$	79.02907	79.02859	6.07
DP-1	$C_9H_{12}NO_2^+$	166.08626	166.08605	1.26
	$C_9H_9O_2^+$	149.05971	149.05954	1.14
	$C_9H_7O^+$	131.04914	131.04897	1.29
	$C_8H_{10}N^+$	120.08078	120.08081	-0.24
	$C_8H_7^+$	103.05423	103.05416	0.67
	$C_7H_9^+$	93.06988	93.06958	3.22
	$C_6H_5^+$	77.03858	77.03844	1.81
	$C_4H_3^+$	51.02293	51.02321	-5.48

Table S2: Elemental composition for fragment ions of DP-2, DP-3 and DP-4/DP-5

Degradation products	Proposed molecular formula **[M+H]$^+$**	Calculated (***m/z***)	Observed (***m/z***)	Error (ppm)
DP-2	$C_{14}H_{22}BN_2O_2^+$	261.17688	261.17653	1.34
	$C_{14}H_{19}BNO_2^+$	244.15034	244.15037	-0.12
	$C_{10}H_{11}BNO_2^+$	188.08774	188.08735	2.07
	$C_7H_{15}BN_2O_2^{+\cdot}$	170.12211	170.12189	1.29
	$C_6H_{13}BNO_2^+$	142.10339	142.10364	-1.75
	$C_8H_{10}N^+$	120.08078	120.08055	1.91
	$C_5H_{11}BO^{+\cdot}$	98.09475	98.09611	-4.8
	CH_4NO^+	46.02874	46.02836	8.25
DP-3	$C_{14}H_{14}N_3O_3^+$	272.10297	272.10268	1.06
	$C_{13}H_{12}N_3O^+$	226.09749	226.09711	1.68
	$C_{13}H_{10}N_3^+$	208.08692	208.08651	1.97
	$C_9H_8NO^+$	146.06004	146.06101	-6.64
	$C_8H_{10}N^+$	120.08078	120.08074	0.33
	$C_5H_5N_2O^+$	109.03964	109.03956	0.73
	$C_8H_7^+$	103.05423	103.05397	2.52
	$C_7H_7^+$	91.05423	91.05414	0.98
	$C_4H_5N_2^+$	81.04472	81.04471	0.12
DP-4 / DP-5	$C_{19}H_{24}N_4NaO_3^+$	379.17406	379.17326	2.10
	$C_{19}H_{22}N_4NaO_2^+$	361.16350	361.16239	3.29
	$C_{14}H_{14}N_4NaO_2^+$	293.10090	293.10274	-6.27
	$C_{14}H_{11}N_3NaO_2^+$	276.07435	276.07344	3.29
	$C_{13}H_{11}N_3NaO^+$	248.07943	248.07826	4.71
	$C_{13}H_{12}N_3O^+$	226.09749	226.09817	-3.00
	$C_{13}H_{10}N_3^+$	208.08692	208.08534	7.68
	$C_8H_9NNa^+$	142.06272	142.06218	3.09

Table S3. Elemental composition for fragment ions of DP-6 , DP-7/ DP-8 and DP-9/ DP-10

Degradation products	Proposed molecular formula **[M+H]$^+$**	Calculated (***m/z***)	Observed (***m/z***)	Error (ppm)
DP-6	$C_{14}H_{15}N_4O_2^+$	271.11895	271.11709	6.86
	$C_{14}H_{12}N_3O_2^+$	254.09240	254.09178	2.44
	$C_{13}H_{12}N_3O^+$	226.09749	226.09704	1.99
	$C_{13}H_{10}N_3^+$	208.08692	208.08675	0.81
	$C_{12}H_{11}N_2O^+$	199.08659	199.08771	-5.62
	$C_5H_3N_2O^+$	107.02399	107.02491	-8.59
	$C_8H_7^+$	103.05423	103.05461	-3.69
	$C_4H_3N_2^+$	79.02907	79.02892	1.89
DP-7/ DP-8	$C_{14}H_{15}N_4O_3^+$	287.11387	287.11364	0.80
	$C_{14}H_{12}N_3O_3^+$	270.08732	270.08726	0.22
	$C_{13}H_{12}N_3O_2^+$	242.09240	242.09251	-0.45
	$C_{13}H_{10}N_3O^+$	224.08184	224.08147	1.65
	$C_{12}H_{11}N_2O^+$	199.08659	199.08618	2.05
	$C_9H_8NO^+$	146.06004	146.05938	4.51
	$C_8H_8N^+$	118.06513	118.06476	3.13
	$C_7H_7^+$	91.05423	91.05424	-0.10
	$C_3H_2N^+$	52.01818	52.01807	2.11
DP-9/ DP-10	$C_{19}H_{24}N_4NaO_4^+$	395.16898	395.16884	0.03
	$C_{19}H_{22}N_4NaO_3^+$	377.15841	377.15798	0.11
	$C_{19}H_{22}N_4NaO_2^+$	361.16350	361.16296	0.14
	$C_{15}H_{14}N_4NaO_3^+$	321.09581	321.09555	0.08
	$C_{14}H_{14}N_4NaO_2^+$	293.10090	293.09937	0.52
	$C_{14}H_{12}N_4NaO^+$	275.09033	275.09061	-0.10
	$C_{13}H_{11}N_3NaO^+$	248.07943	248.07839	0.41
	$C_{13}H_{12}N_3O^+$	226.09749	226.09754	-0.02
	$C_{12}H_9NO_2^{+\cdot}$	199.06278	199.06287	-0.04
	$C_8H_9NNa^+$	142.06272	142.06227	0.31

Table S4: Elemental composition for fragment ions of DP-11 or DP-12, DP-13 and DP-14

Degradation products	Proposed molecular formula **[M+H]$^+$**	Calculated (***m/z***)	Observed (***m/z***)	Error (ppm)
DP-11/ DP-12	$C_{19}H_{24}N_4NaO_5^+$	411.16389	411.16521	-3.21
	$C_{19}H_{22}N_4NaO_4^+$	393.15333	393.15434	-2.56
	$C_{19}H_{22}N_4NaO_3^+$	377.15841	377.15923	-2.17
	$C_{15}H_{14}N_4NaO_4^+$	337.09073	337.09165	-2.72
	$C_{14}H_{14}N_4NaO_4^+$	325.09073	325.09271	-6.09
	$C_{14}H_{14}N_4NaO_3^+$	309.09581	309.09814	-7.53
	$C_{14}H_{11}N_3NaO_3^+$	292.06926	292.06929	-0.10
	$C_{13}H_{11}N_3NaO_2^+$	264.07435	264.07427	0.30
	$C_{12}H_9NO_2^{+\cdot}$	199.06278	199.05929	-0.45
	$C_5H_{12}N^+$	86.09643	86.09671	-3.25
DP-13	$C_{19}H_{23}N_4O_3^+$	355.17647	355.17642	0.14
	$C_{14}H_{15}N_4O_2^+$	271.11895	271.11913	-0.66
	$C_{14}H_{12}N_3O_2^+$	254.09240	254.09251	-0.43
	$C_{13}H_{12}N_3O^+$	226.09749	226.09761	-0.53
	$C_{13}H_{10}N_3^+$	208.08692	208.08688	0.19
	$C_{12}H_9N_2^+$	181.07602	181.07409	9.55
	$C_9H_{10}NO^+$	148.07569	148.07526	2.90
	$C_5H_3N_2O^+$	107.02399	107.02387	1.12
	$C_5H_9O^+$	85.06479	85.06512	-3.87
DP-14	$C_{15}H_{16}N_3O_3^+$	286.11862	286.11816	0.16
	$C_{14}H_{12}N_3O_2^+$	254.09240	254.09109	0.51
	$C_{13}H_{12}N_3O^+$	226.09749	226.09675	0.32
	$C_{13}H_{10}N_3^+$	208.08692	208.08607	0.40
	$C_5H_5N_2O^+$	109.03964	109.03928	0.33
	$C_7H_7^+$	91.05423	91.05379	0.48
	$C_4H_5N_2^+$	81.04472	81.04481	-0.11

Table S5: Elemental composition for fragment ions of degradation products DP-15 or DP-16,

Degradation products	Proposed molecular formula **[M+H]$^+$**	Calculated (***m/z***)	Observed (***m/z***)	Error (ppm)
DP-15/DP-16	$C_{20}H_{26}N_4NaO_3^+$	393.18971	393.18837	3.40
	$C_{19}H_{22}N_4NaO_2^+$	361.16350	361.16219	3.62
	$C_{14}H_{14}N_4NaO_2^+$	293.10090	293.09997	3.17
	$C_{14}H_{11}N_3NaO_2^+$	276.07435	276.07338	3.51
	$C_{13}H_{11}N_3NaO^+$	248.07943	248.07845	3.95
	$C_{13}H_{12}N_3O^+$	226.09749	226.09628	5.35
	$C_{13}H_{10}N_3^+$	208.08692	208.08629	3.02
	$C_5H_{11}NNa^+$	108.07837	108.07806	2.86
	$C_5H_{12}N^+$	86.09643	86.09711	-7.89
	$C_5H_9N^+$	69.06933	69.06925	1.15

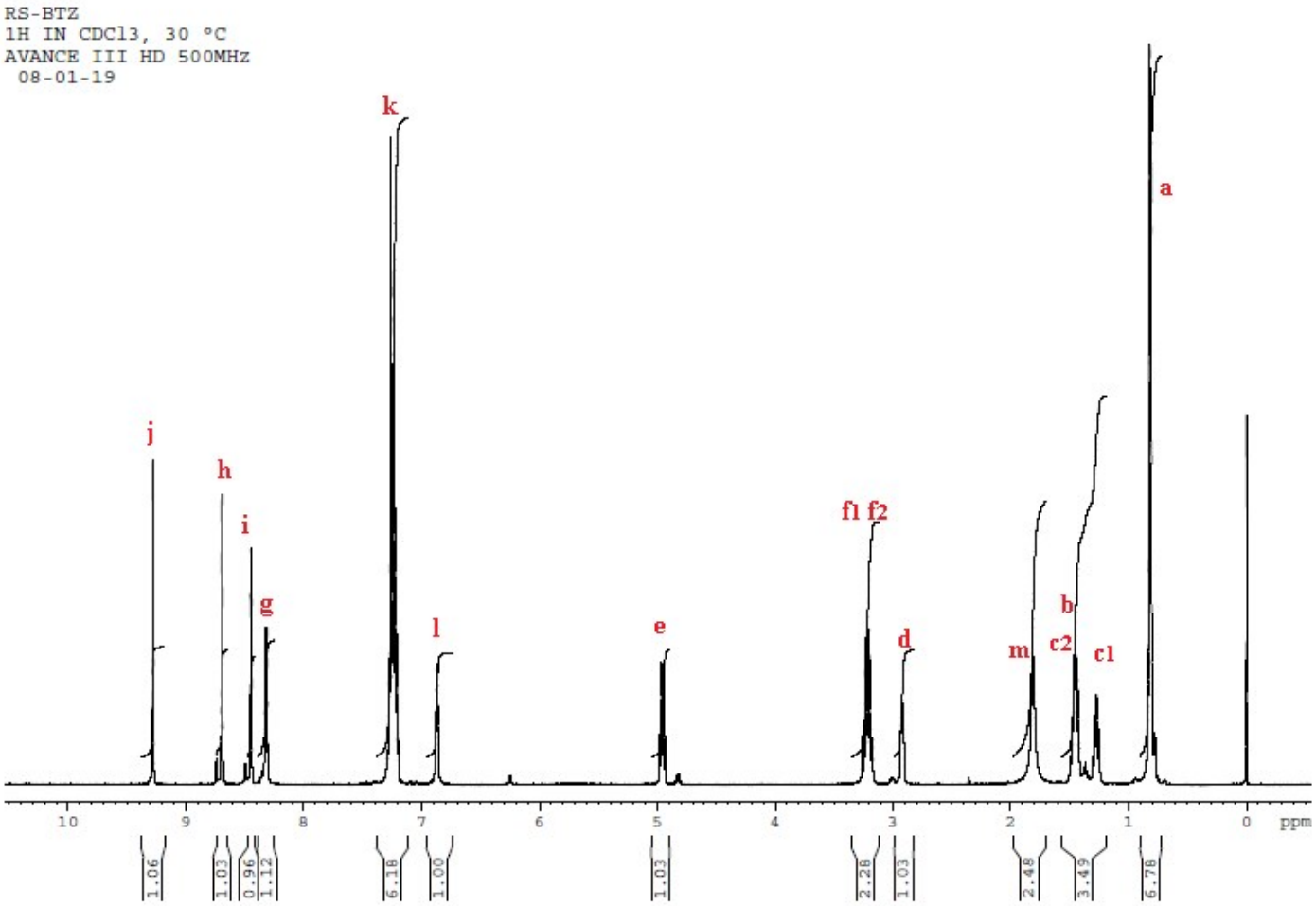


Figure S1. ^{1}H NMR spectrum of BTZ

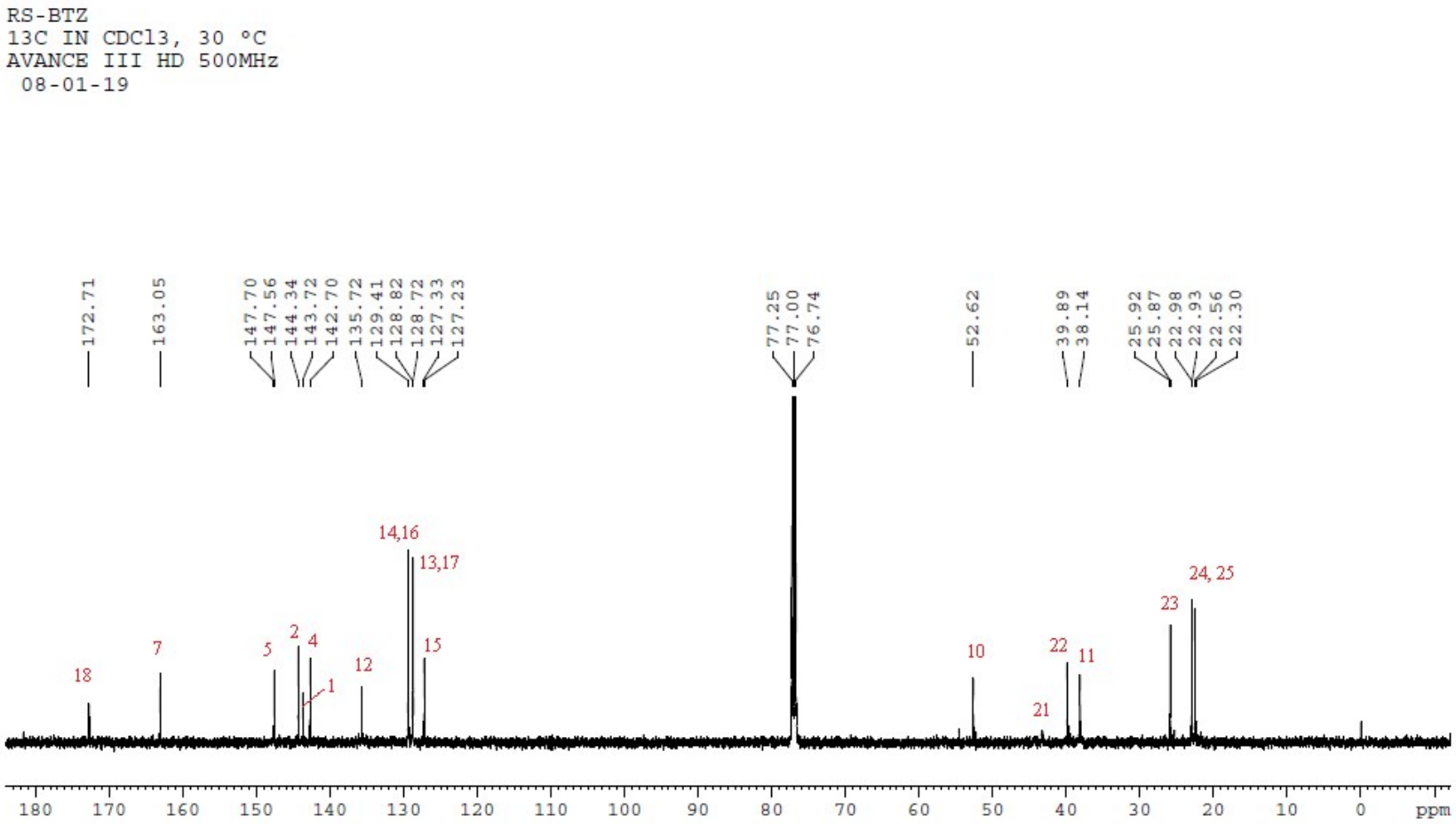


Figure S2. ^{13}C NMR spectrum of BTZ

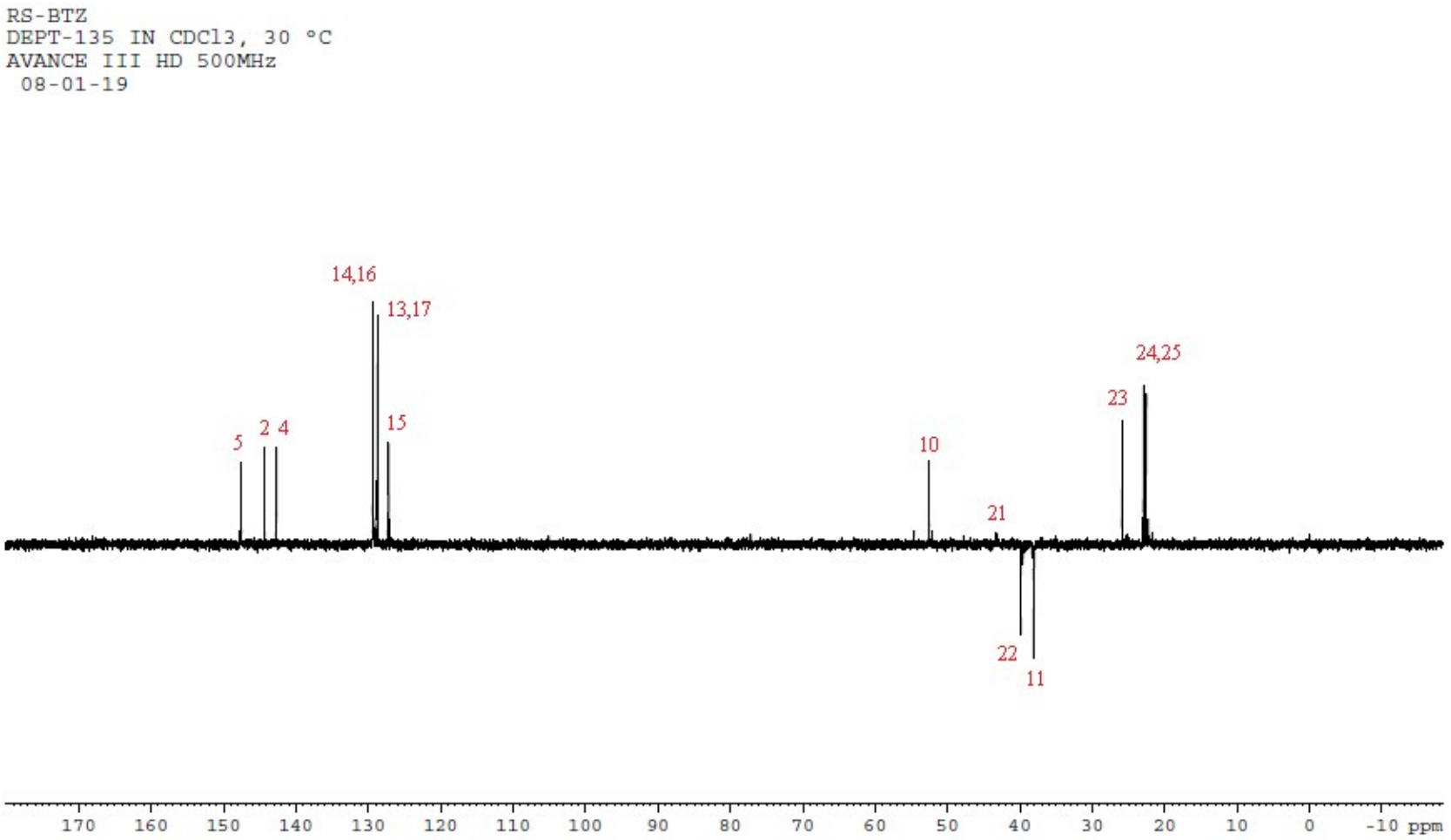


Figure S3. DEPT135 spectrum of BTZ

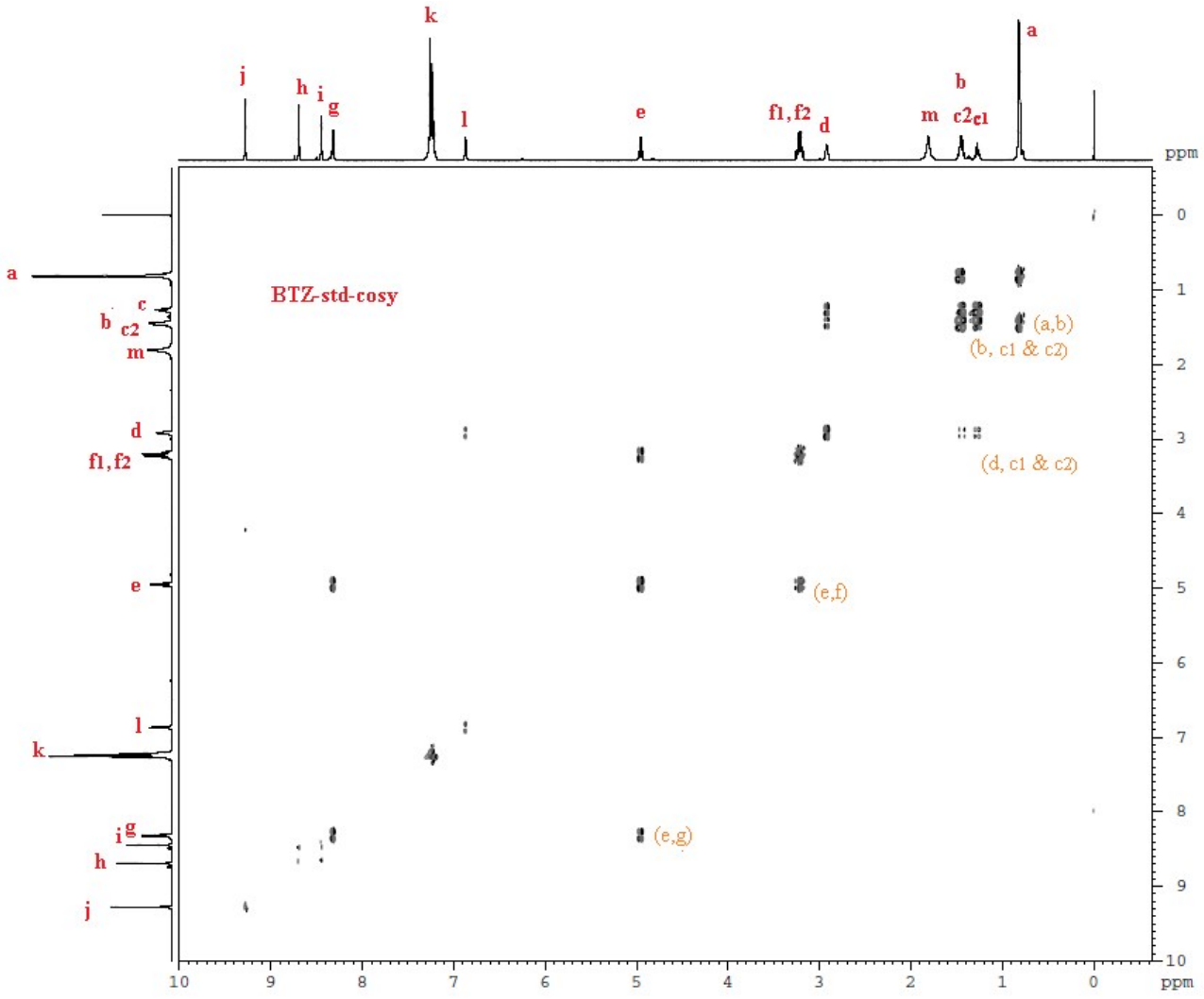


Figure S4. ^{1}H-^{1}H COSY spectrum of BTZ

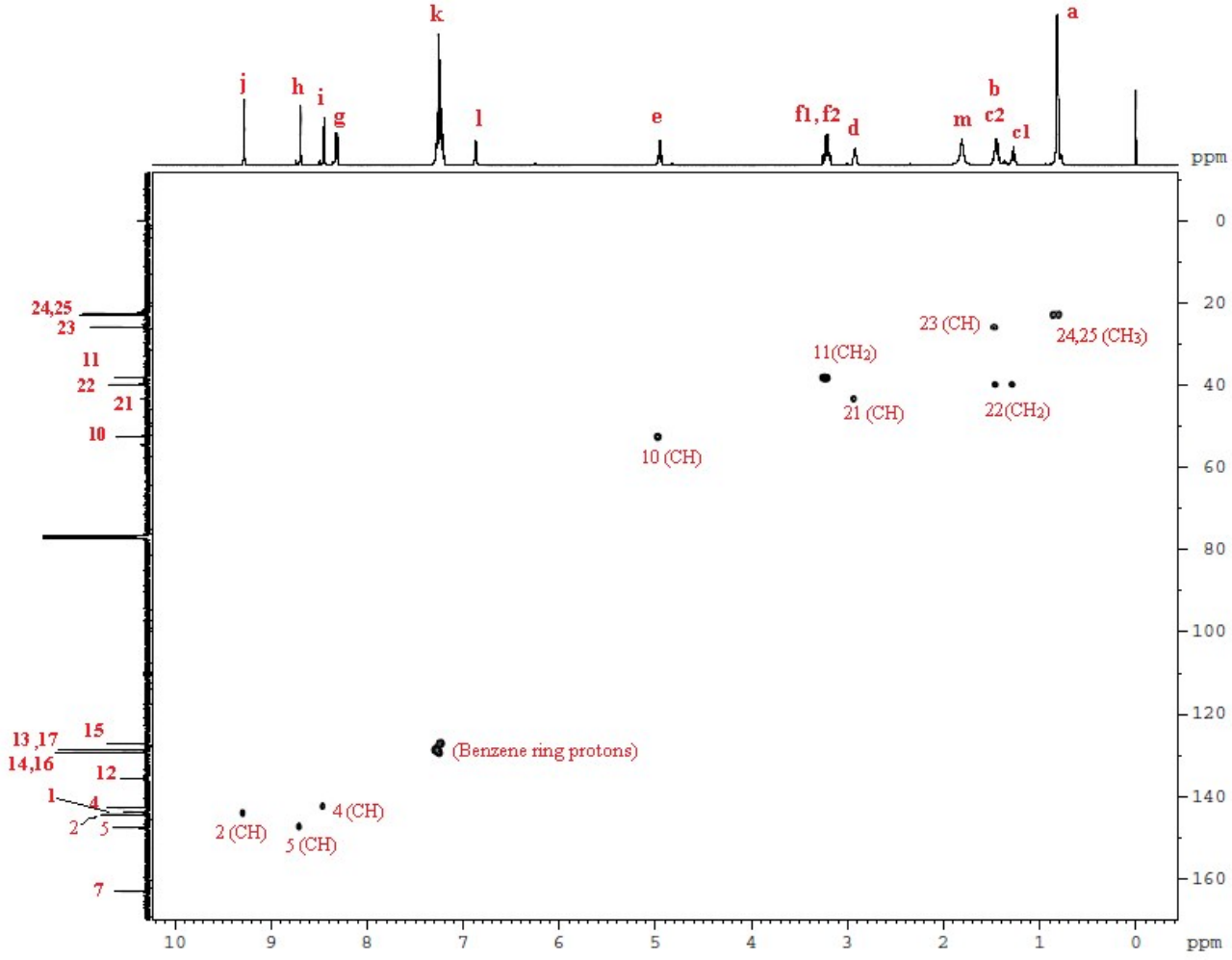


Figure S5. HSQC spectrum of BT

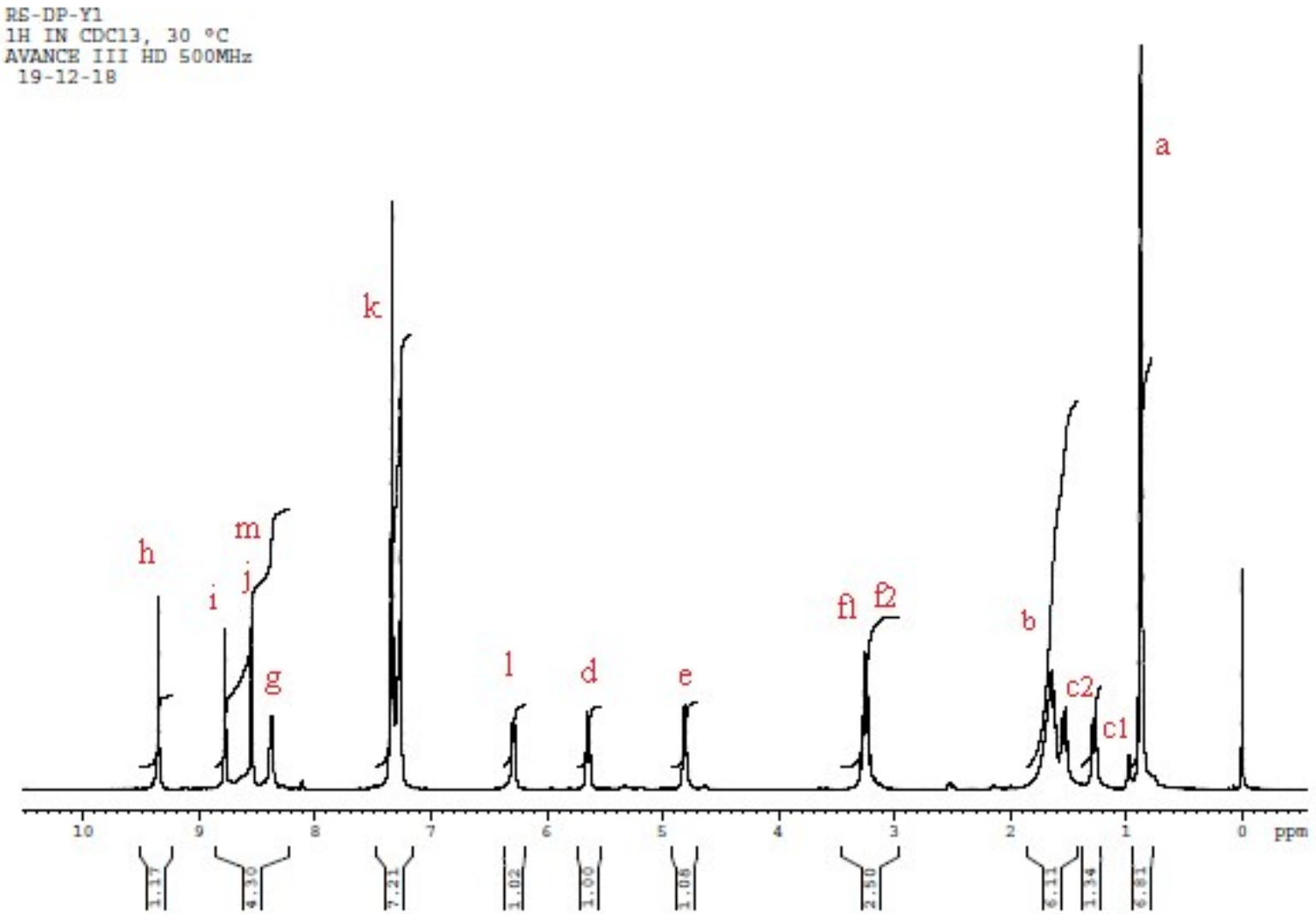


Figure S6. ^{1}H NMR spectrum of DP-9

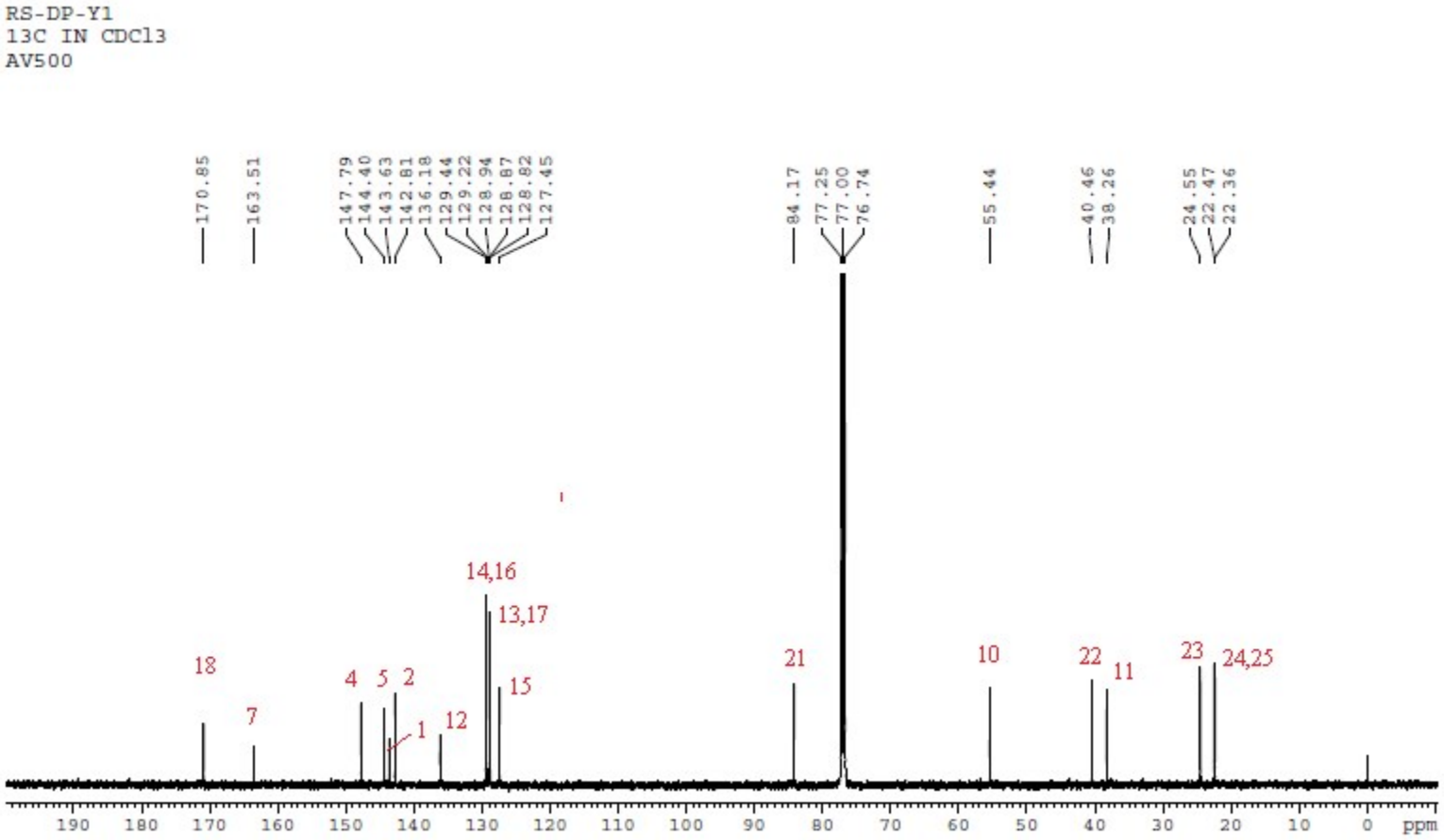


Figure S7. ^{13}C NMR spectrum of DP-9

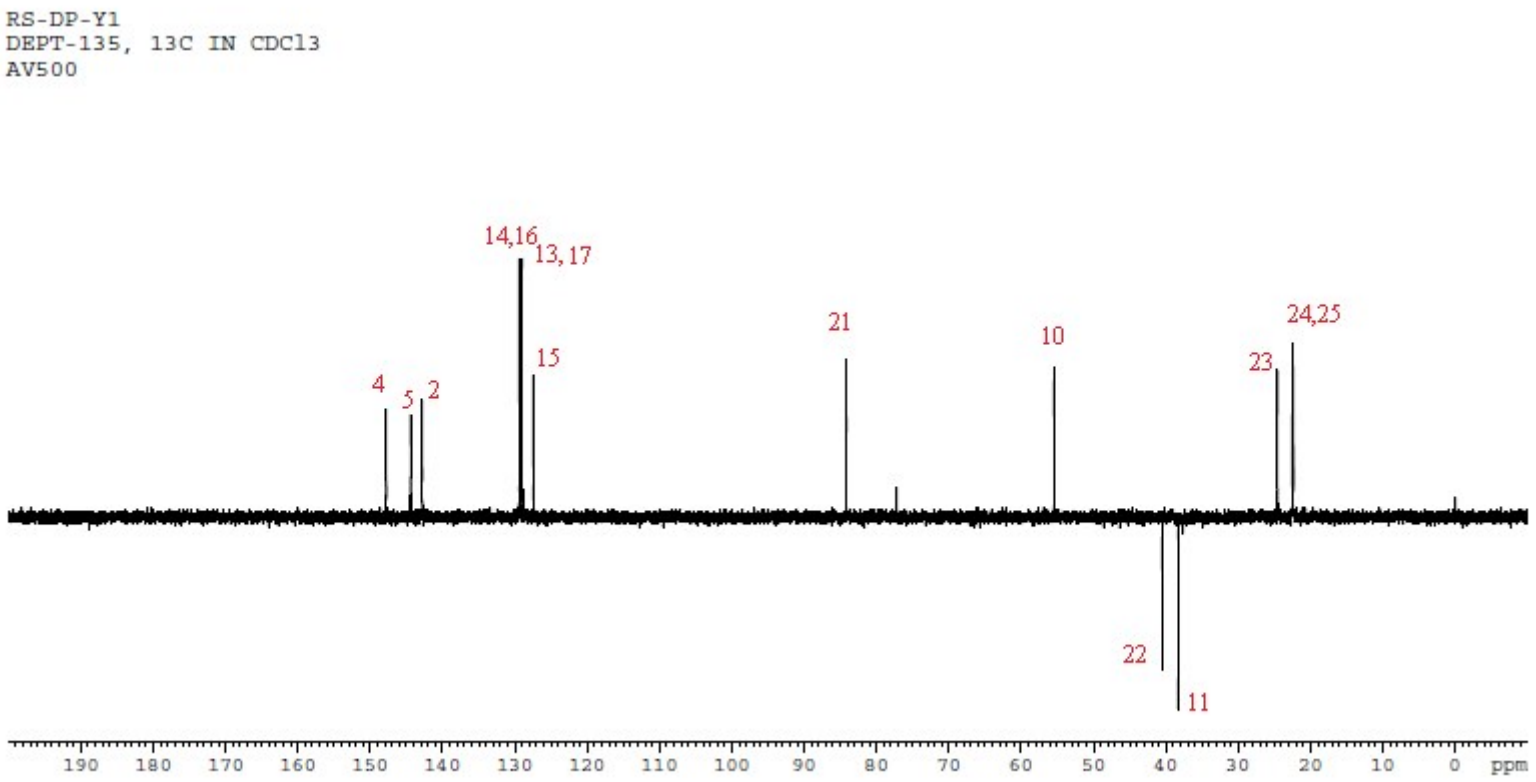


Figure S8. DEPT135 spectrum of DP-9

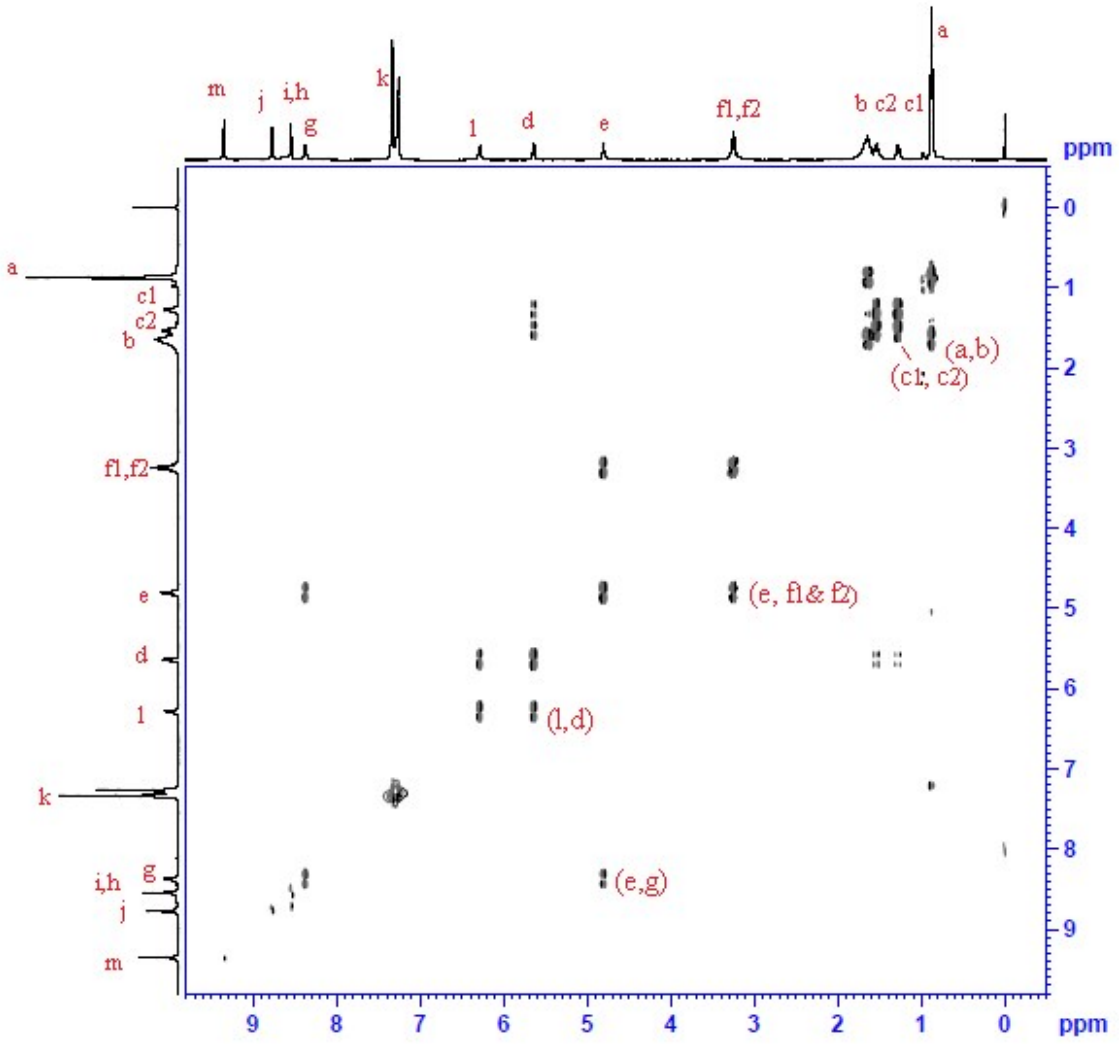


Figure S9. ^{1}H-^{1}H COSY spectrum of DP-9

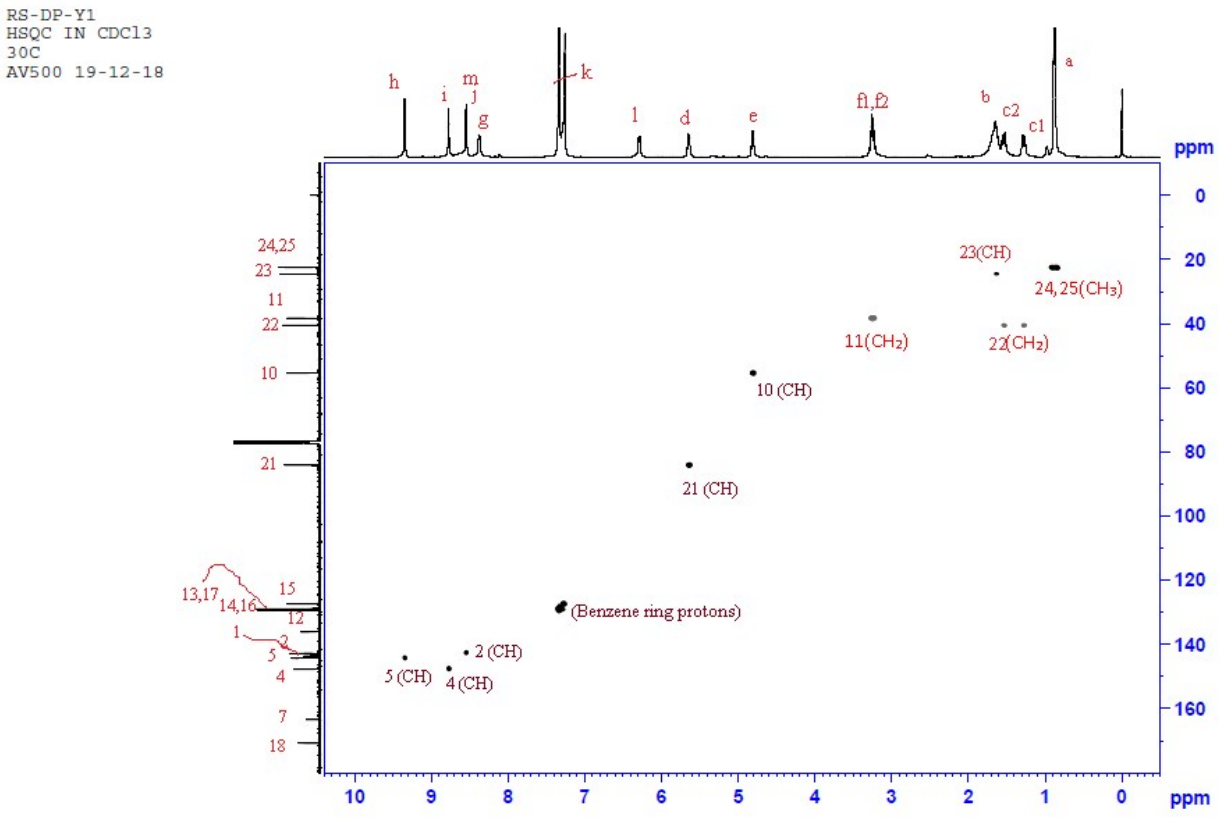


Figure S10. HSQC spectrum of DP-9

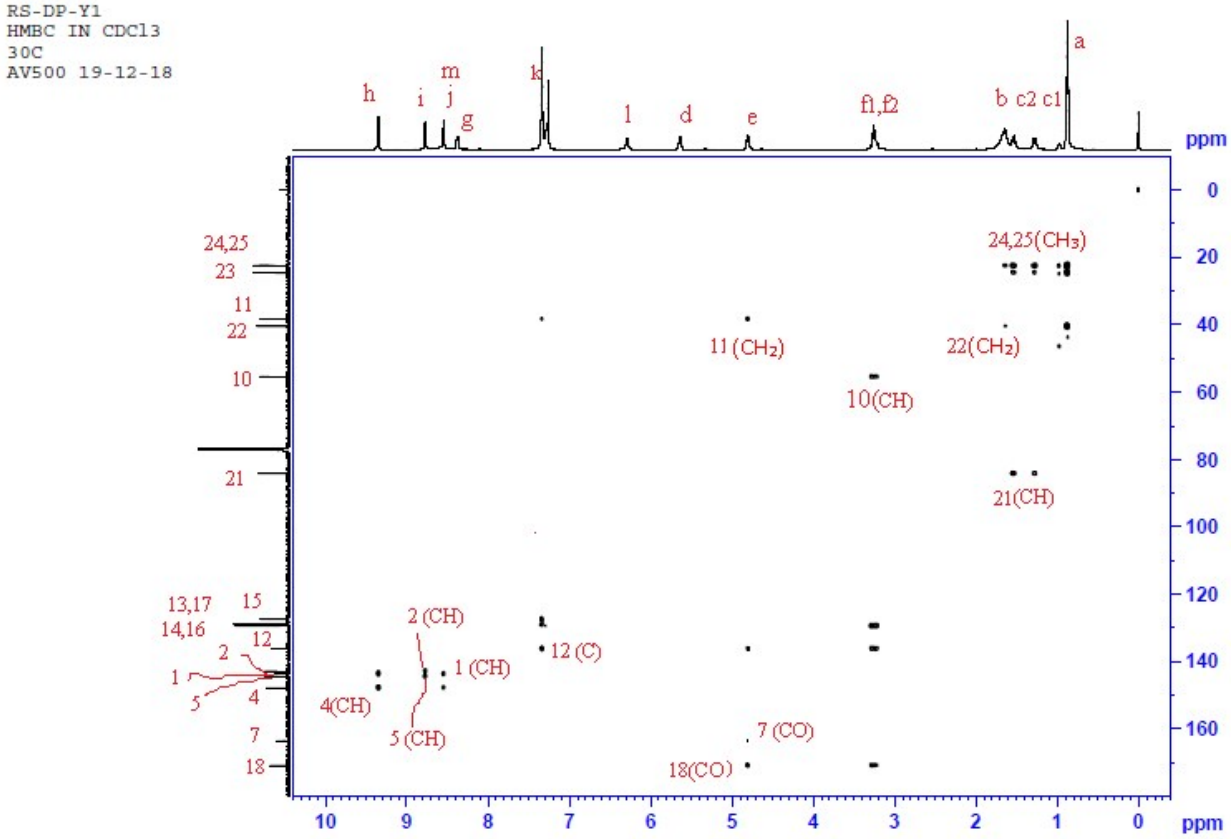


Figure S11. HMBC spectrum of DP-9

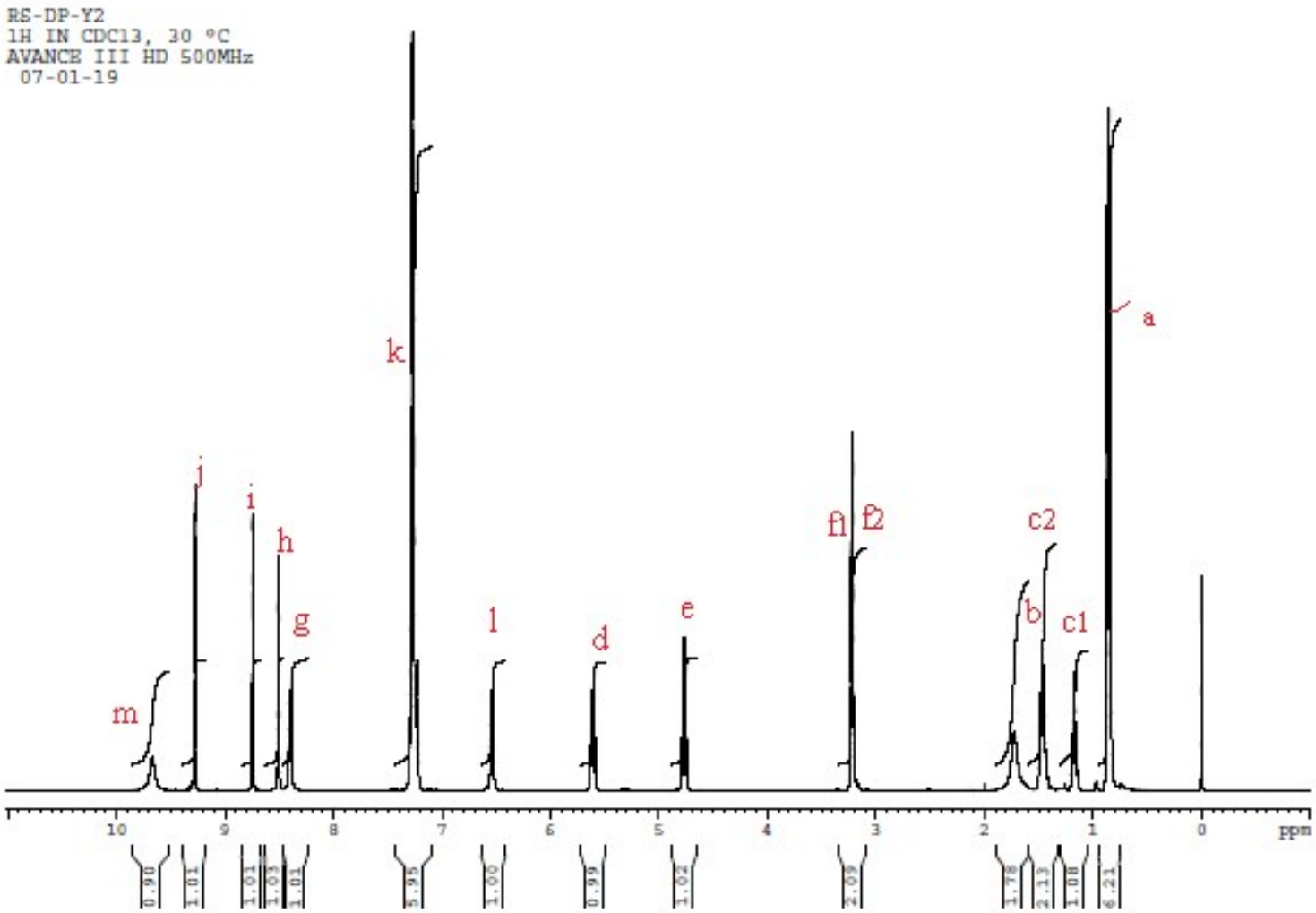


Figure S12. ^{1}H NMR spectrum of DP-10

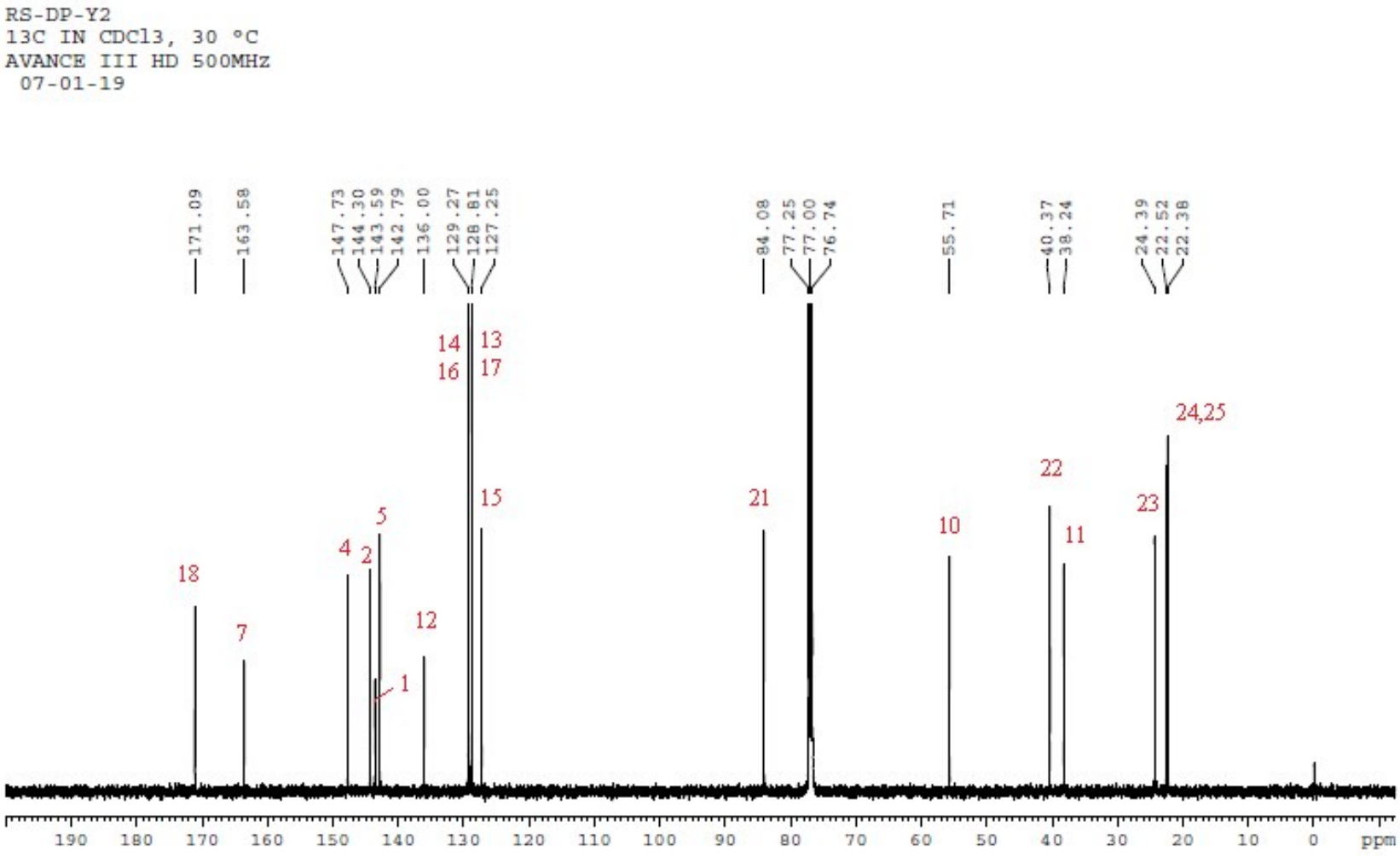


Figure S13. ^{13}C NMR spectrum of DP-10

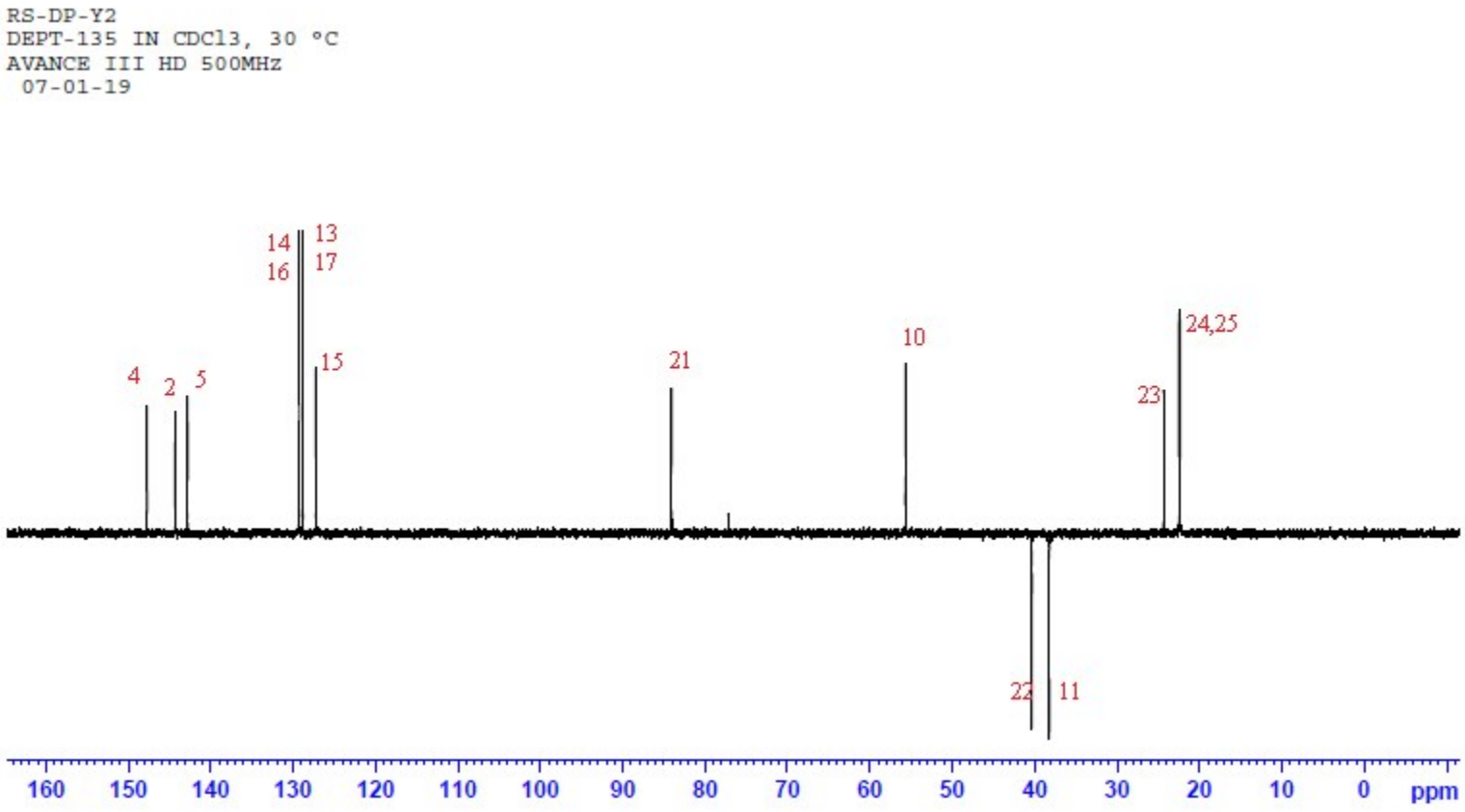


Figure S14. DEPT135 spectrum of DP-10

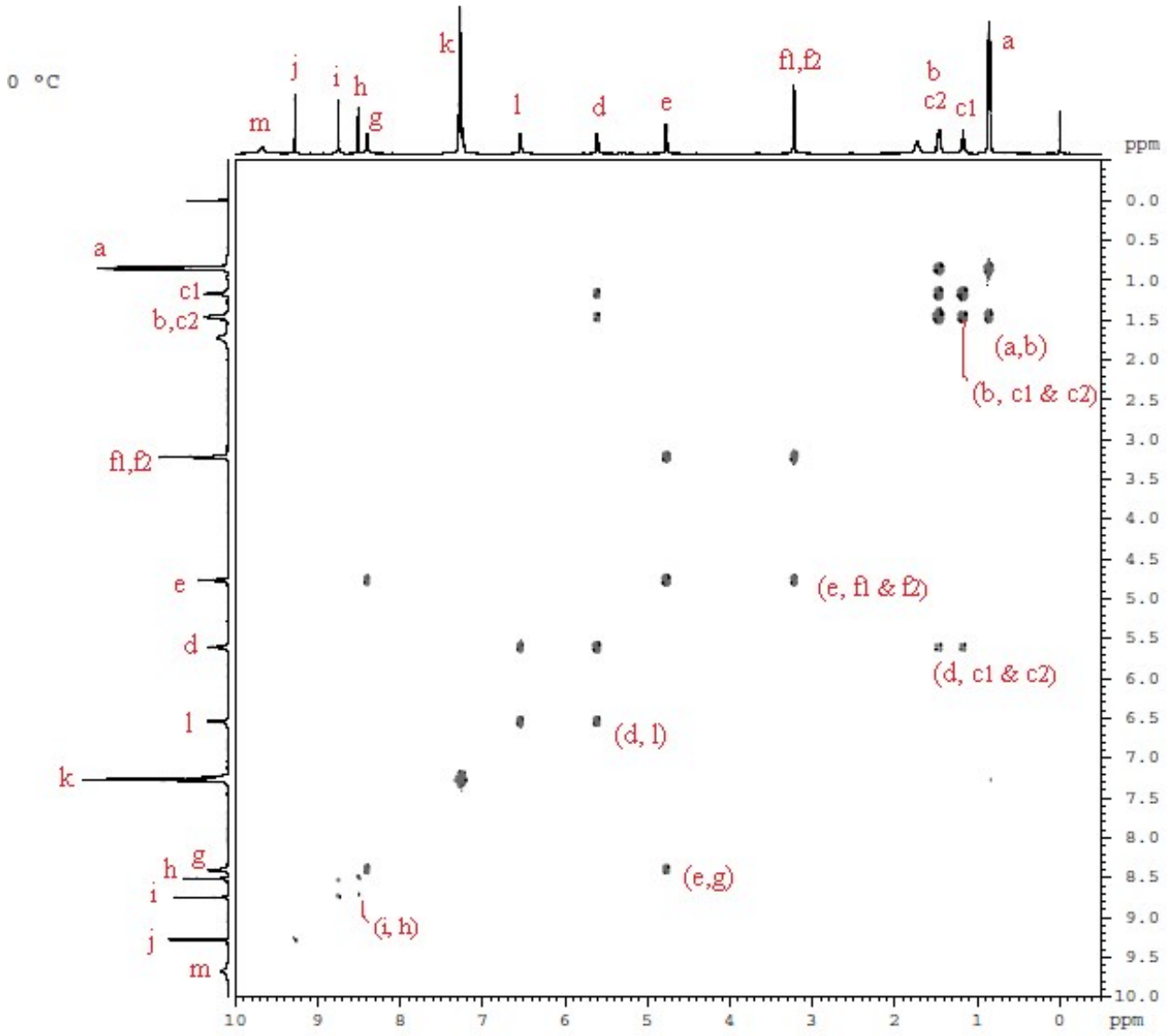


Figure S15. ^{1}H-^{1}H COSY spectrum of DP-10

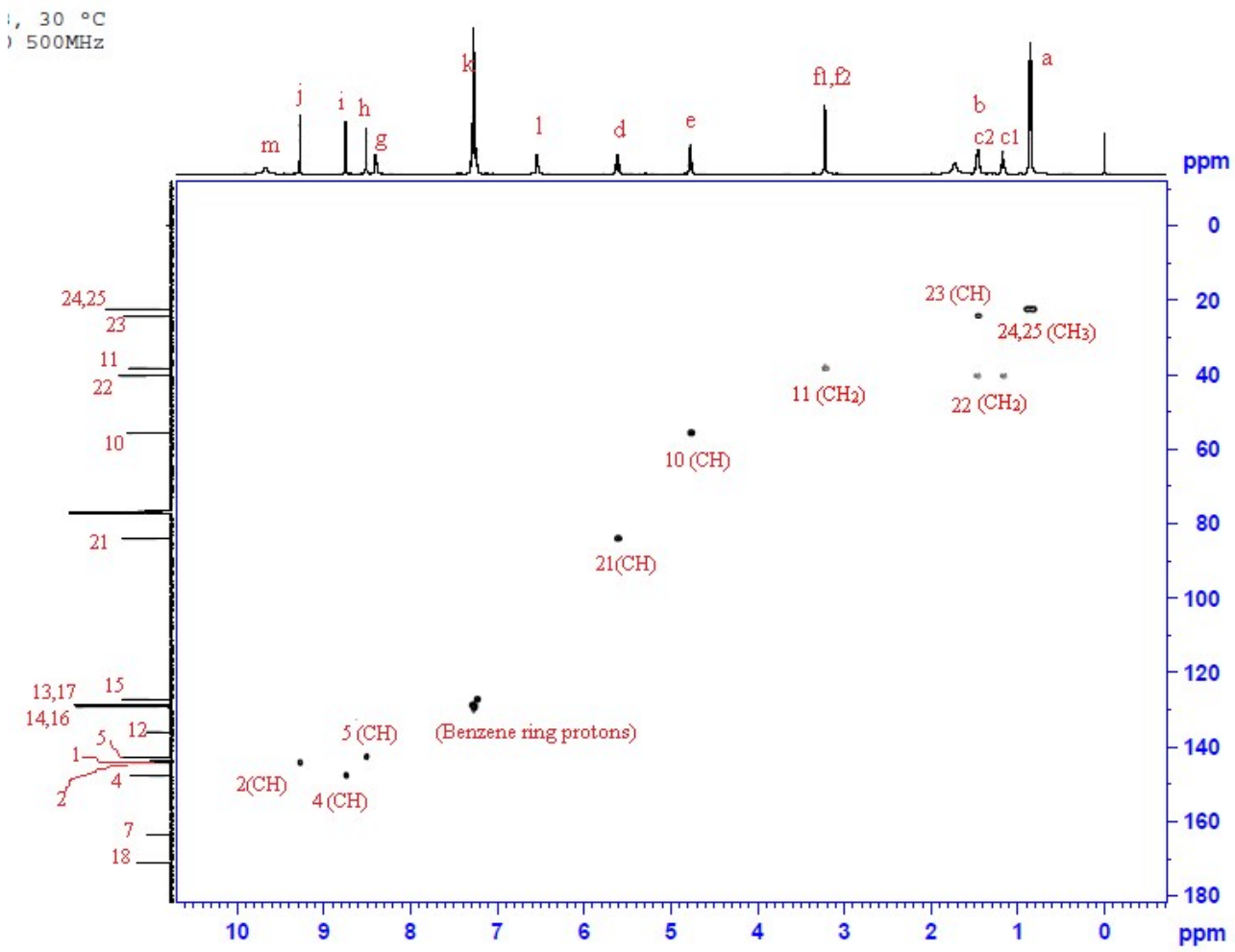


Figure S16. HSQC spectrum of DP-10

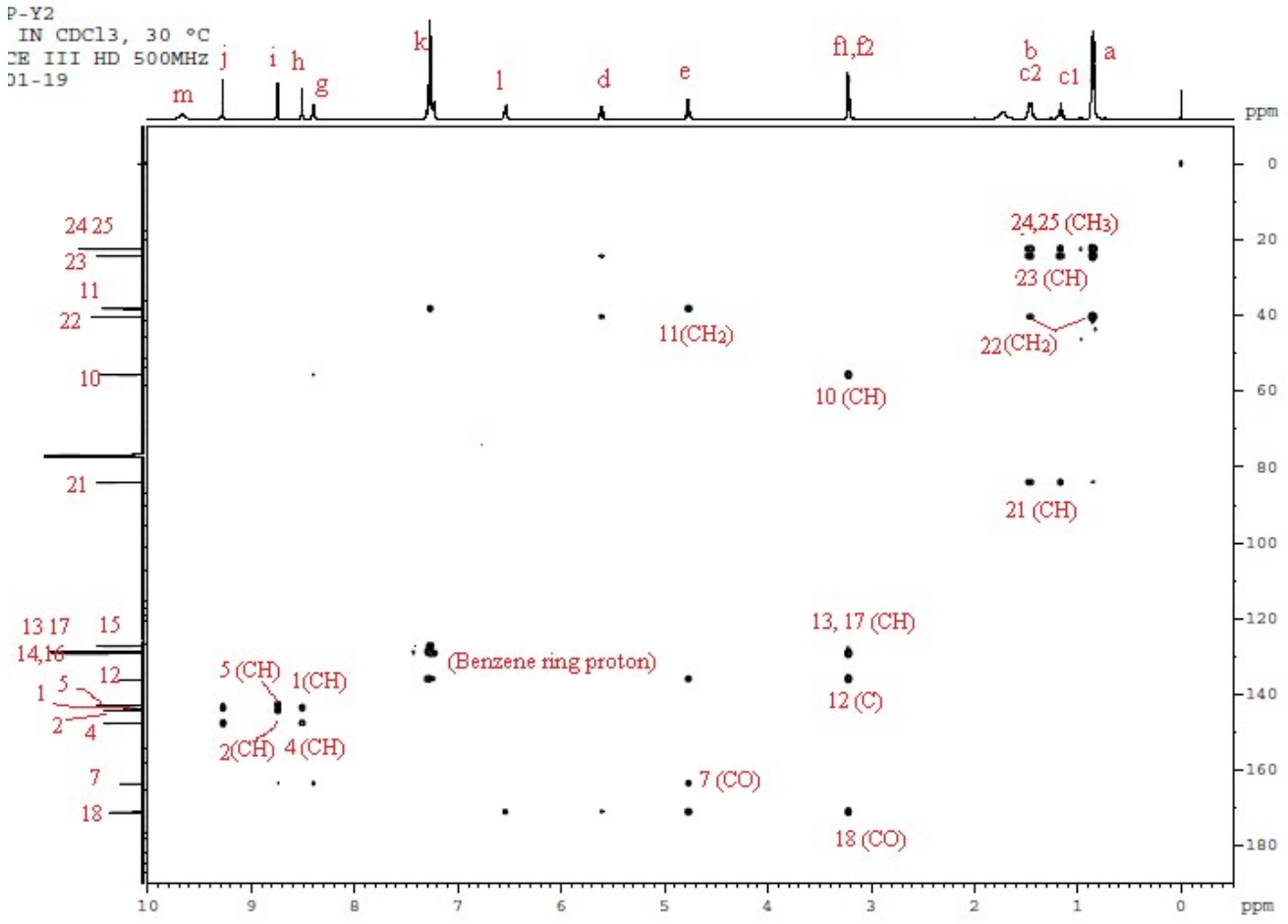


Figure S17. HMBC spectrum of DP-10

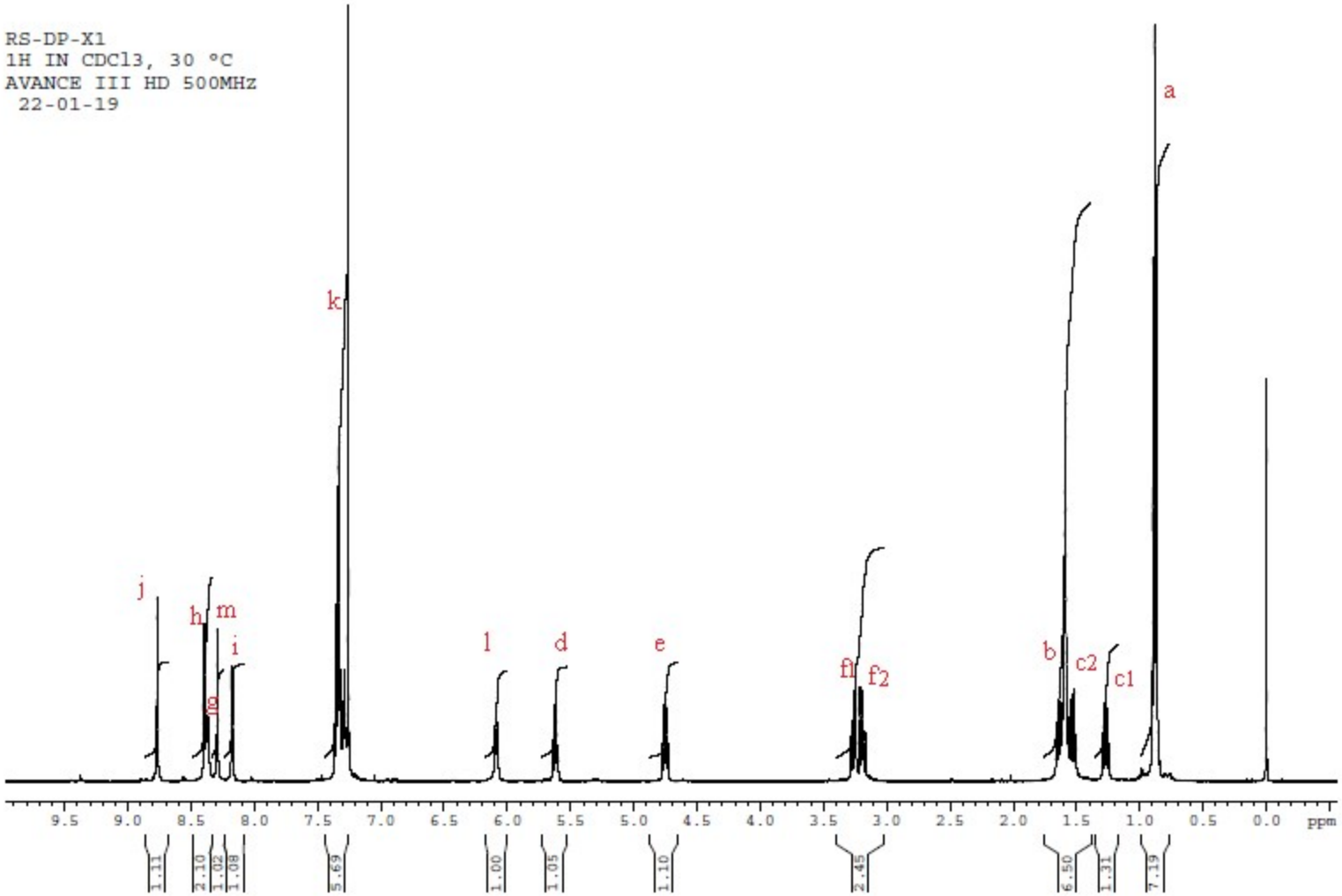


Figure S18. ^{1}H NMR spectrum of DP-11

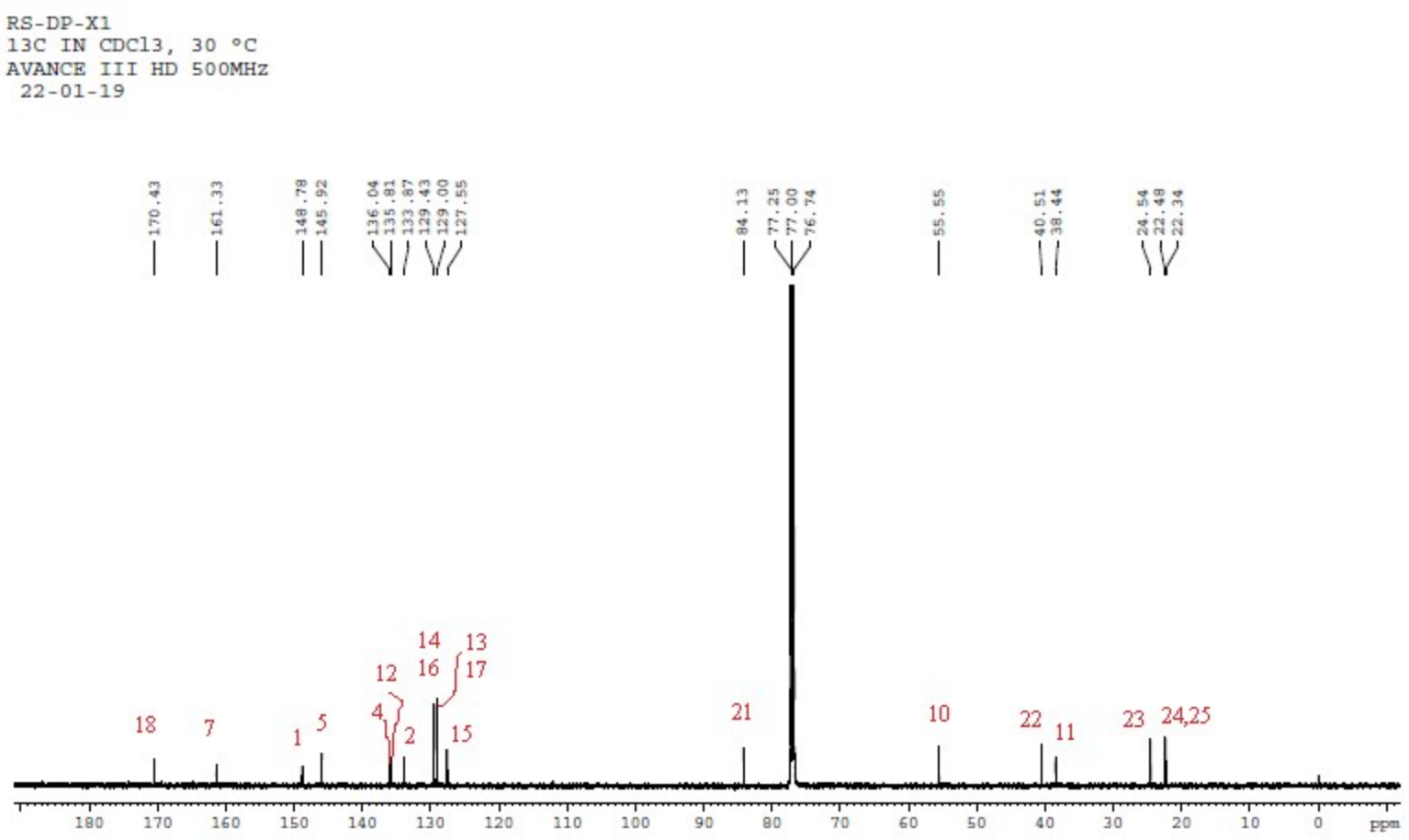


Figure S19. ^{13}C NMR spectrum of DP-11

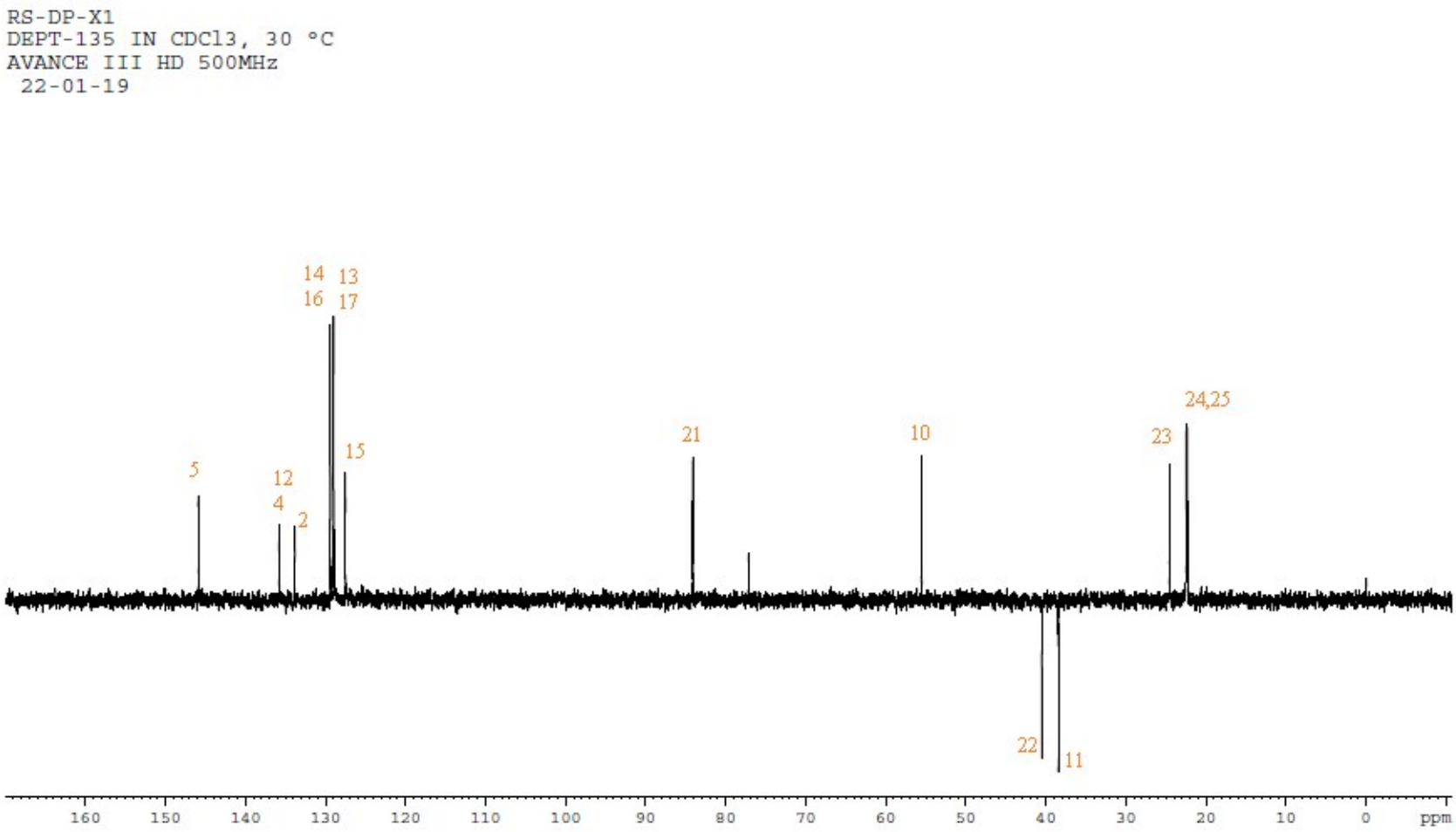


Figure S20. DEPT135 spectrum of DP-11

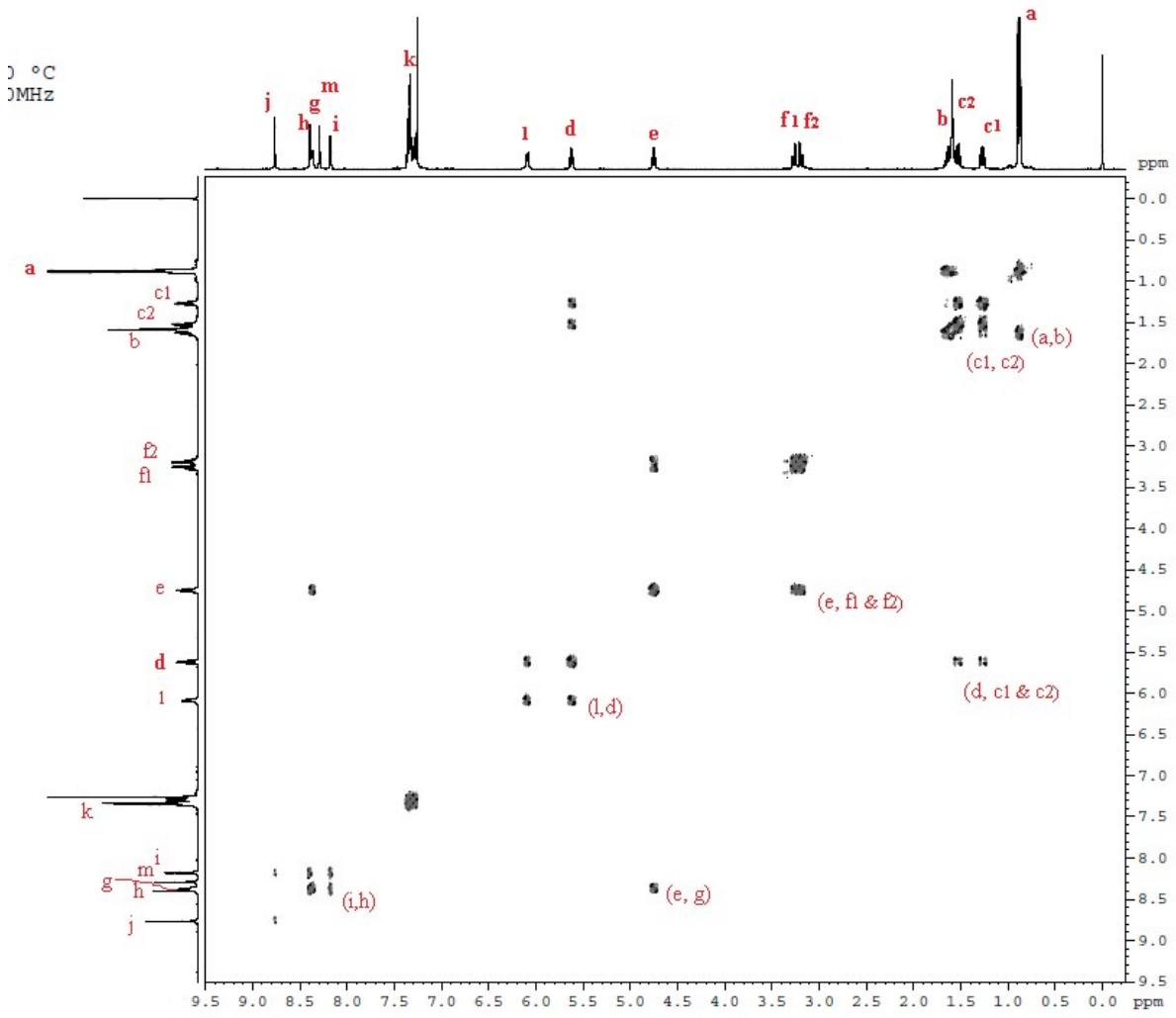


Figure S21. ^{1}H-^{1}H COSY spectrum of DP-11

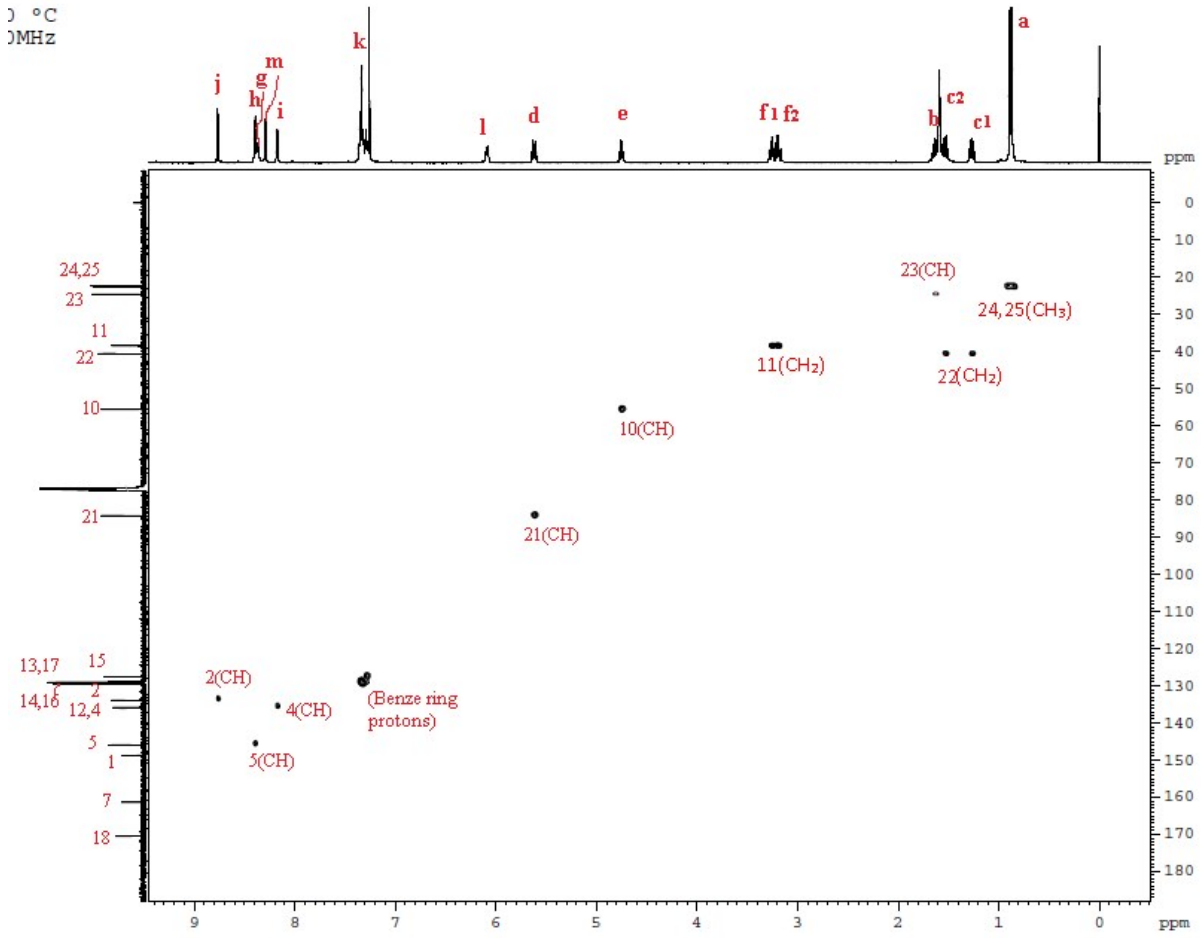


Figure S22. HSQC spectrum of DP-11

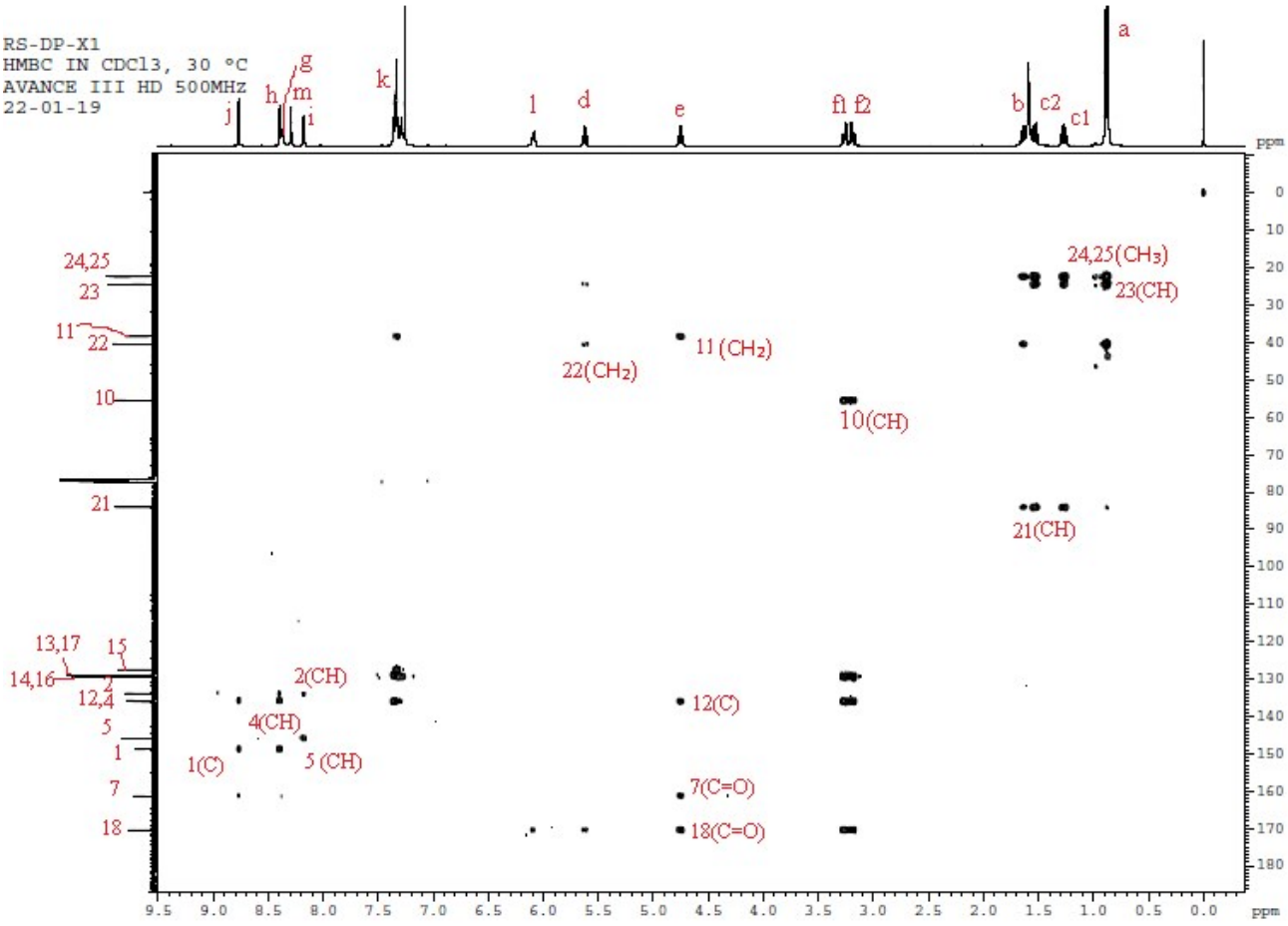


Figure S23. HMBC spectrum of DP-11

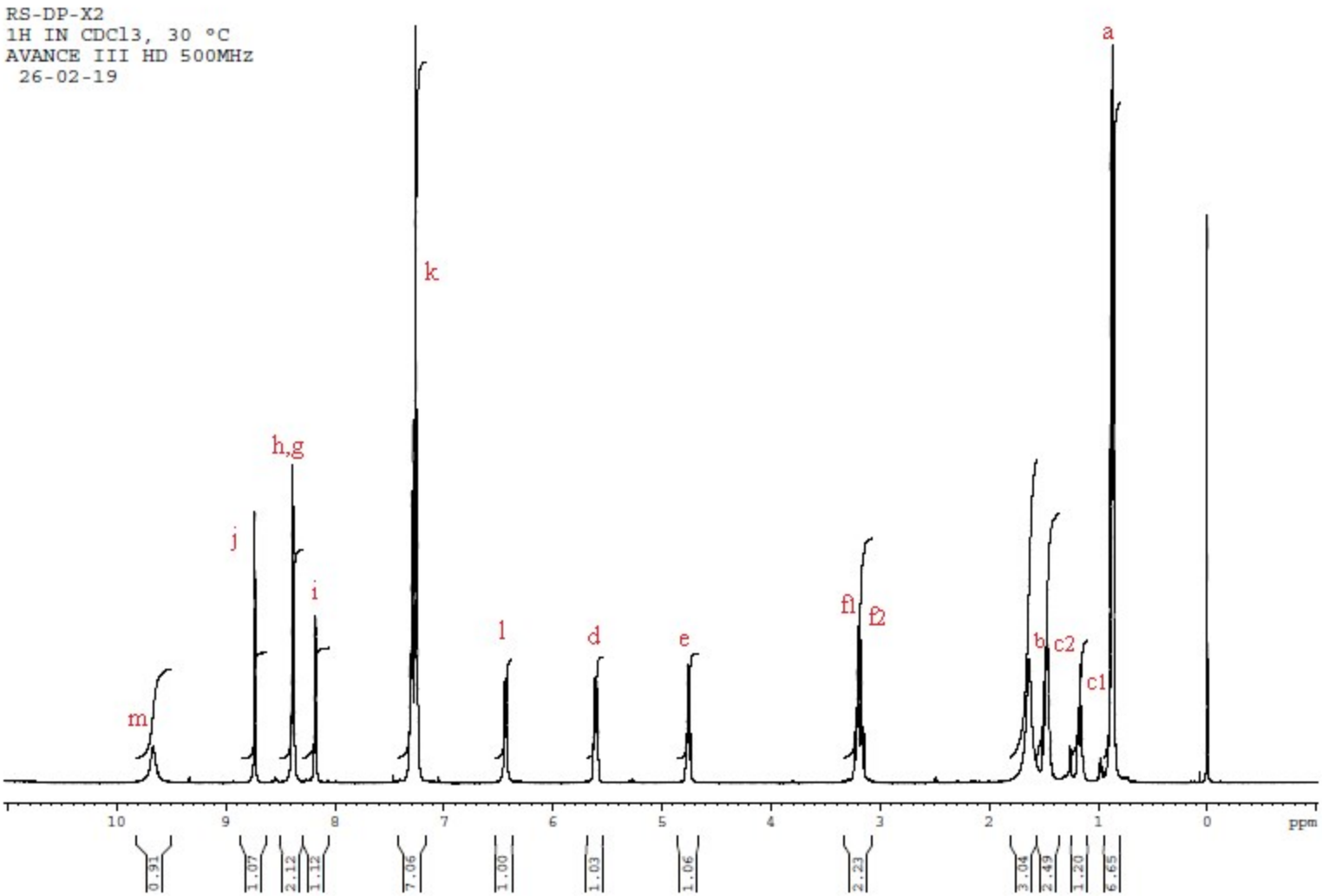


Figure S24. ^{1}H NMR spectrum of DP-12

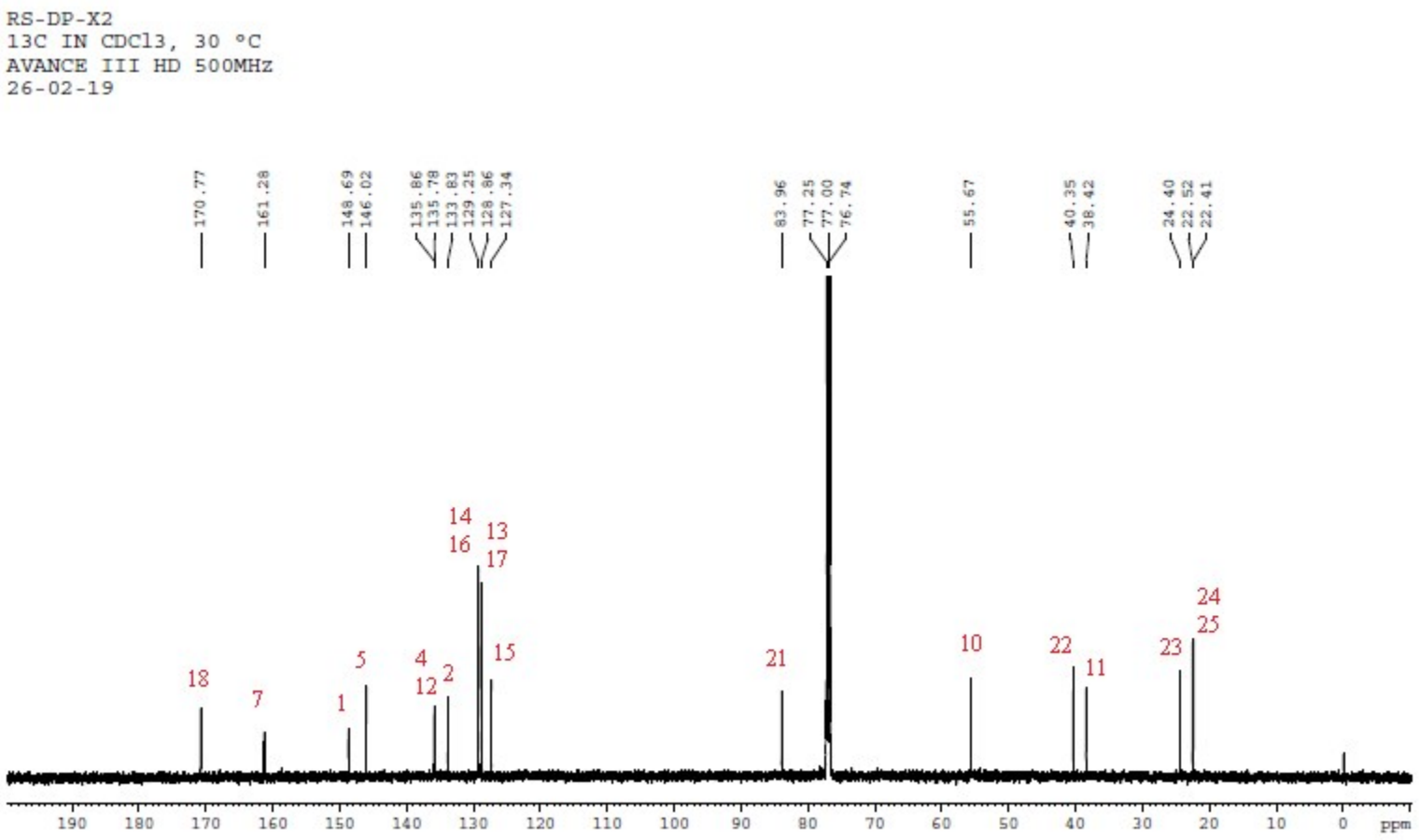


Figure S25. [13] C NMR spectrum of DP-12

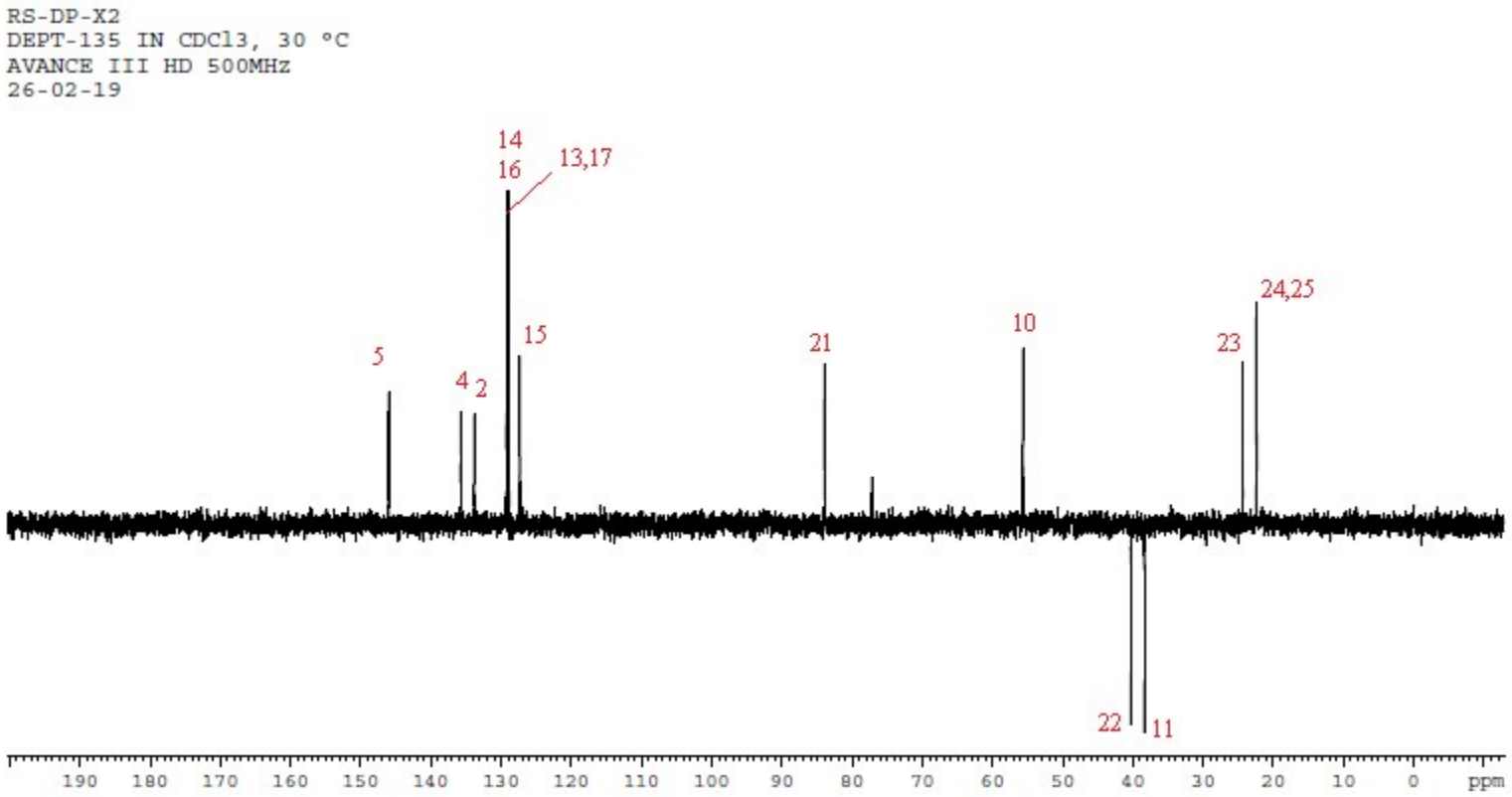


Figure S26. DEPT-135 spectrum of DP-12

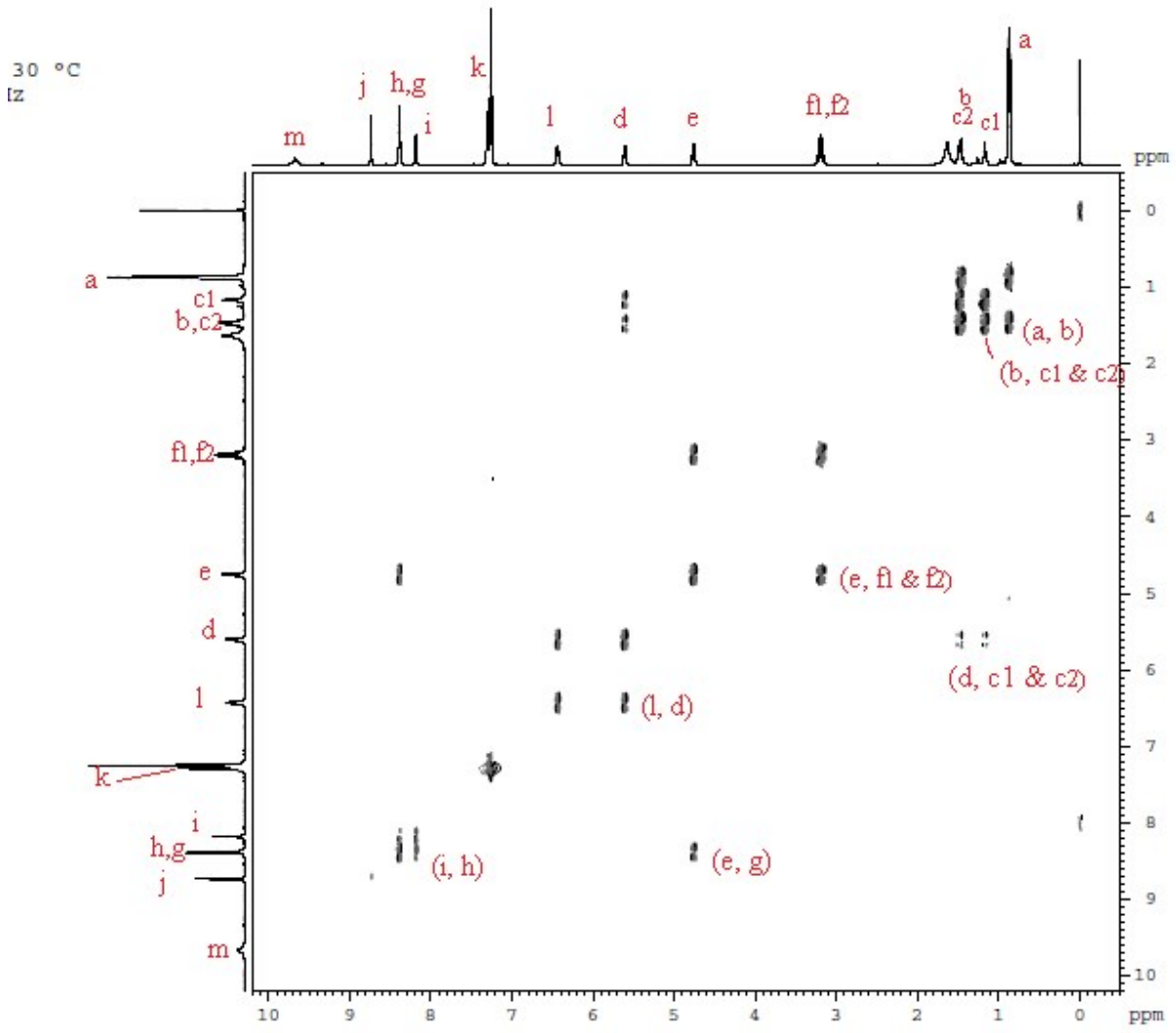


Figure S27. ^{1}H-^{1}H COSY spectrum of DP-12

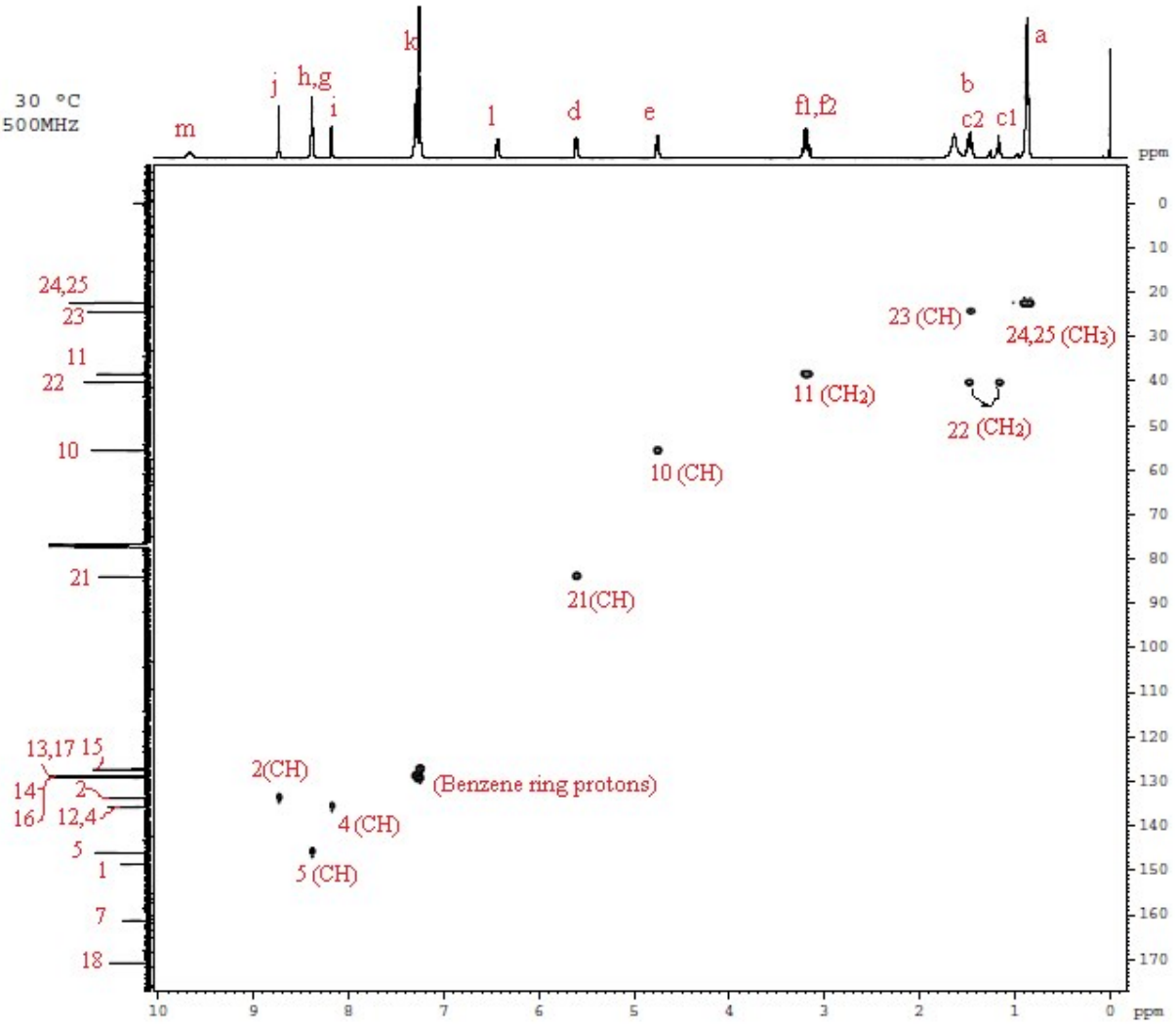


Figure S28. HSQC spectrum of DP-12

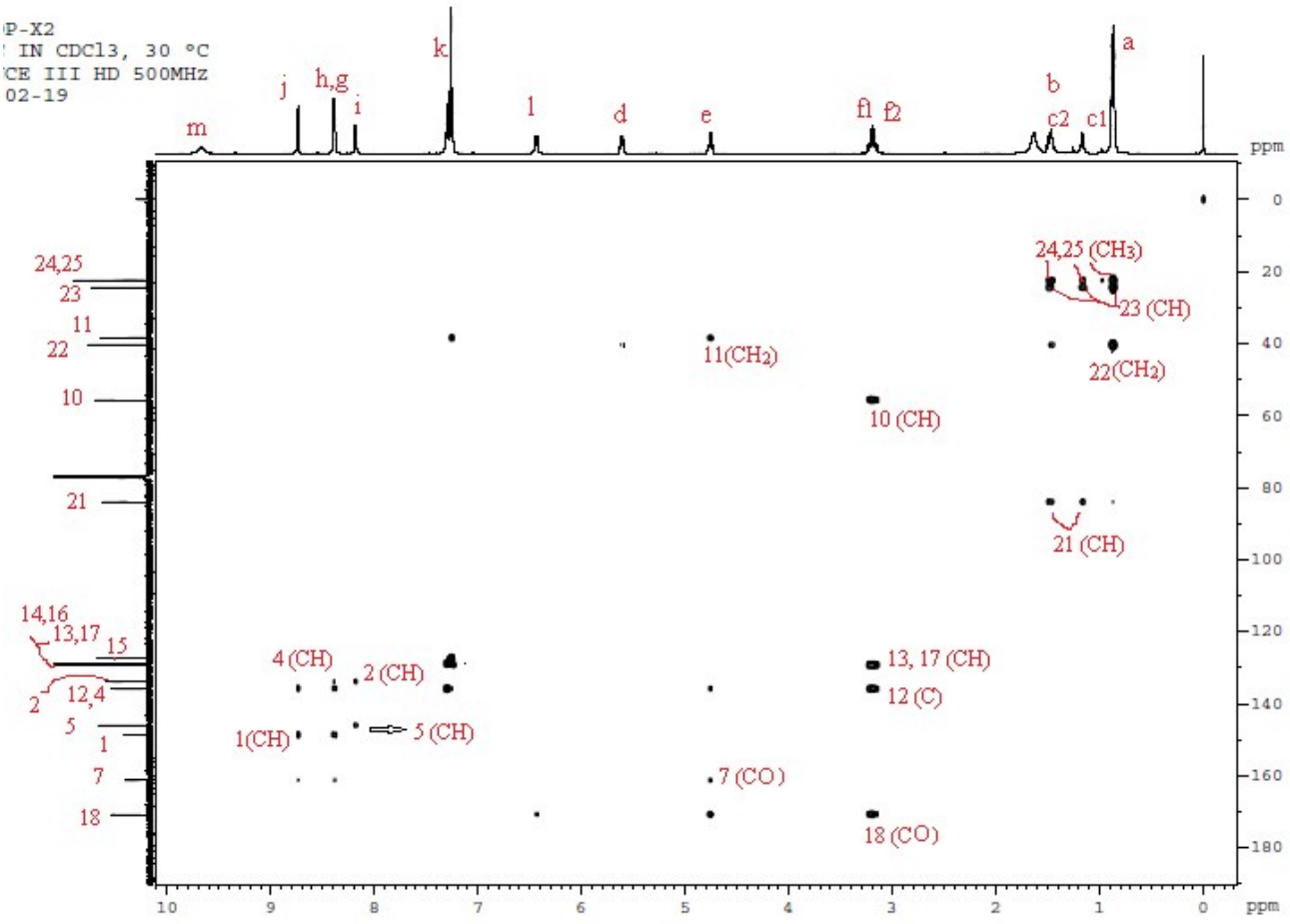


Figure S29. HMBC spectrum of DP-12

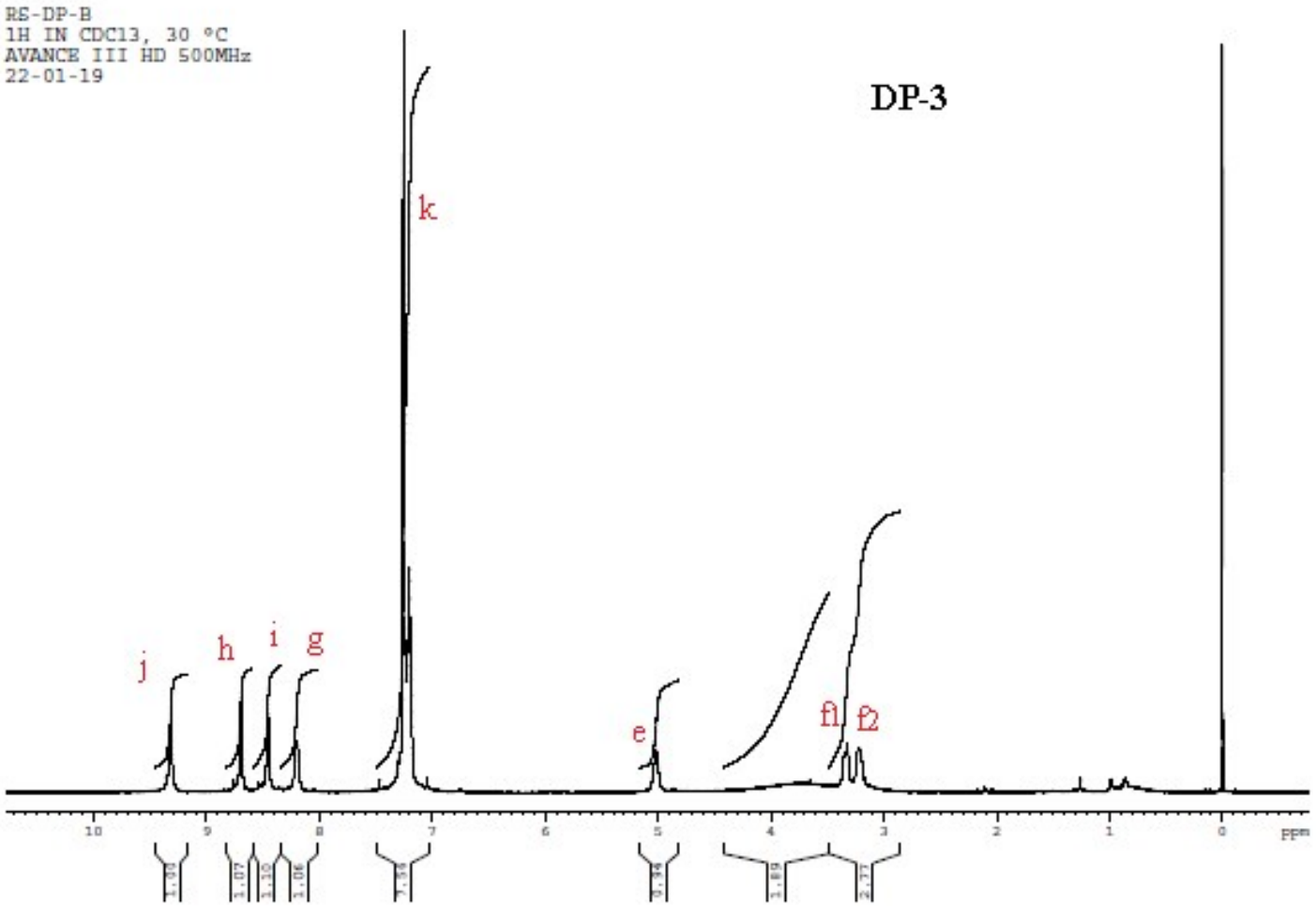


Figure S30. ^{1}H NMR spectrum of DP-3

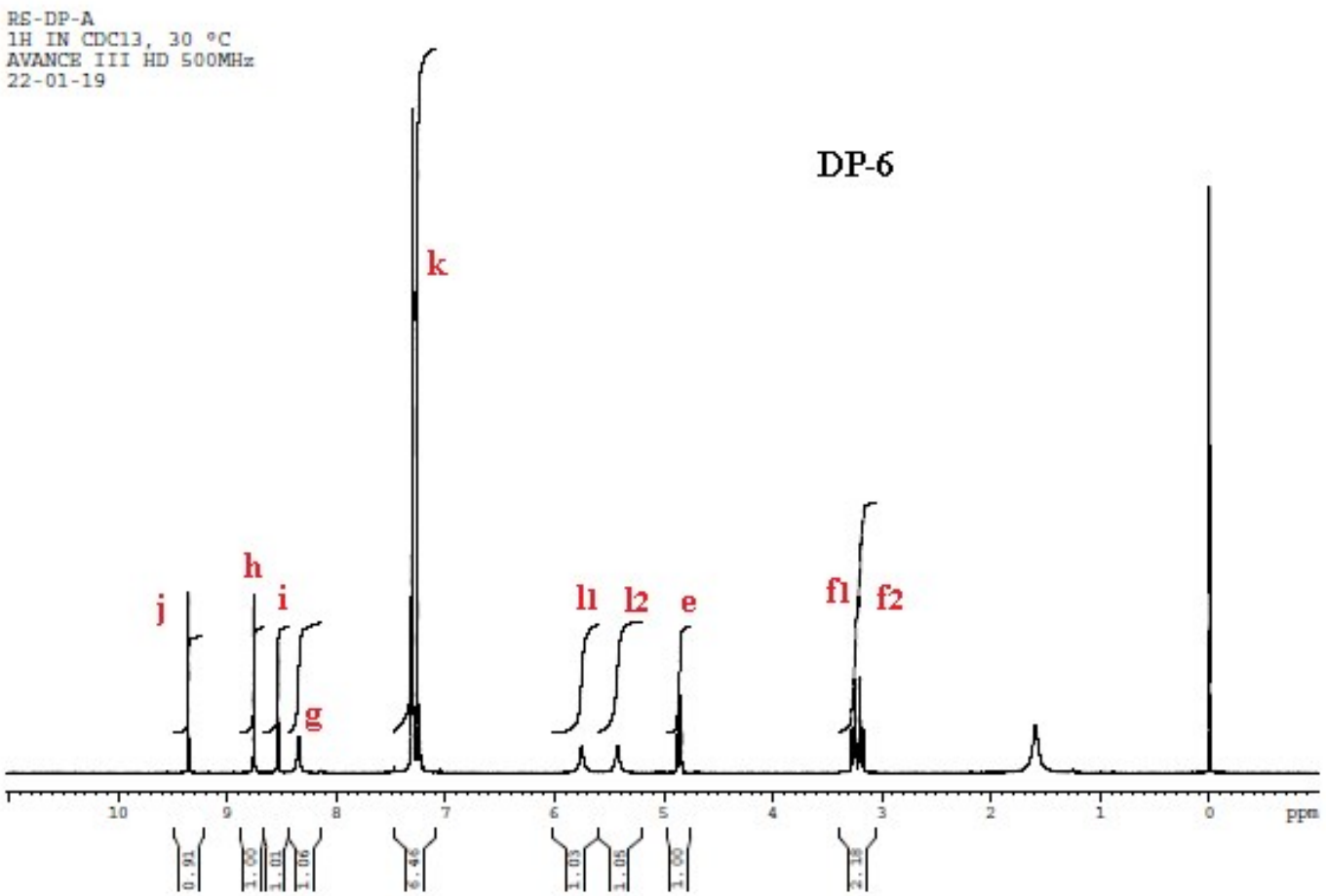


Figure S31. ^{1}H NMR spectrum of DP-6