Electronic Supplementary Material (ESI) for RSC Advances.

Supporting information

Theophylline-based hybrids as acetylcholinesterase inhibitors endowed with anti-inflammatory activity: Synthesis, bioevaluation, in silico and preliminary kinetic studies

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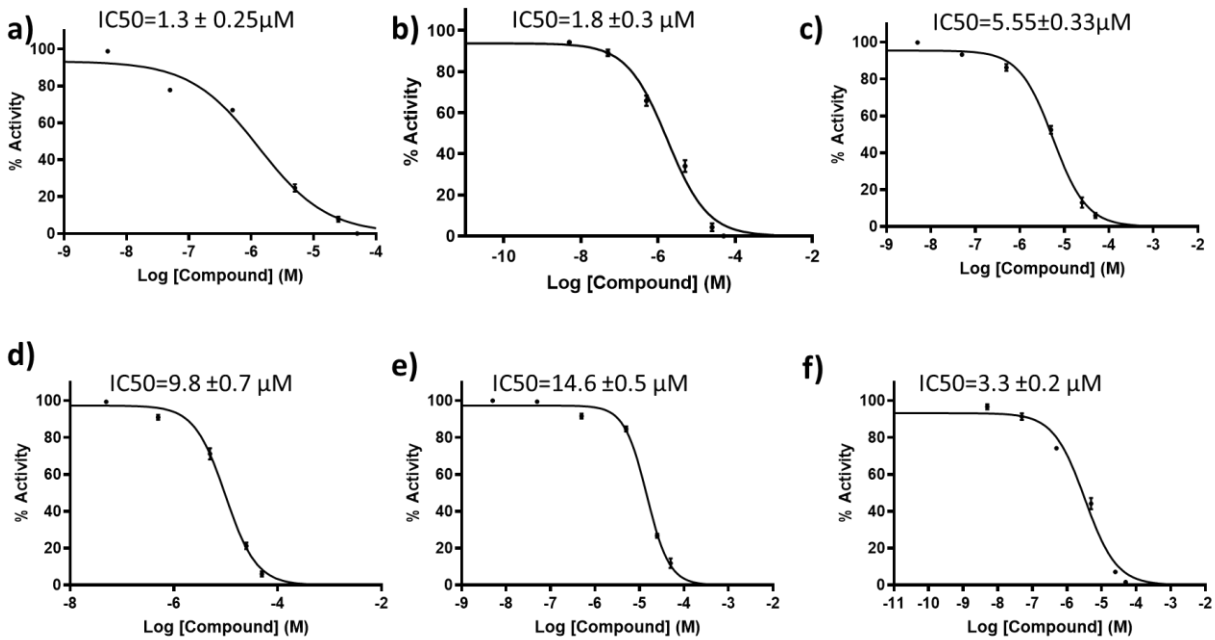


Figure S1: IC_{50} of the most active hybrid against Acetylcholinesterase (AChE). a) Galantamine b) **6d** c) **9c** d) **15c** e) **18j** F)**19**

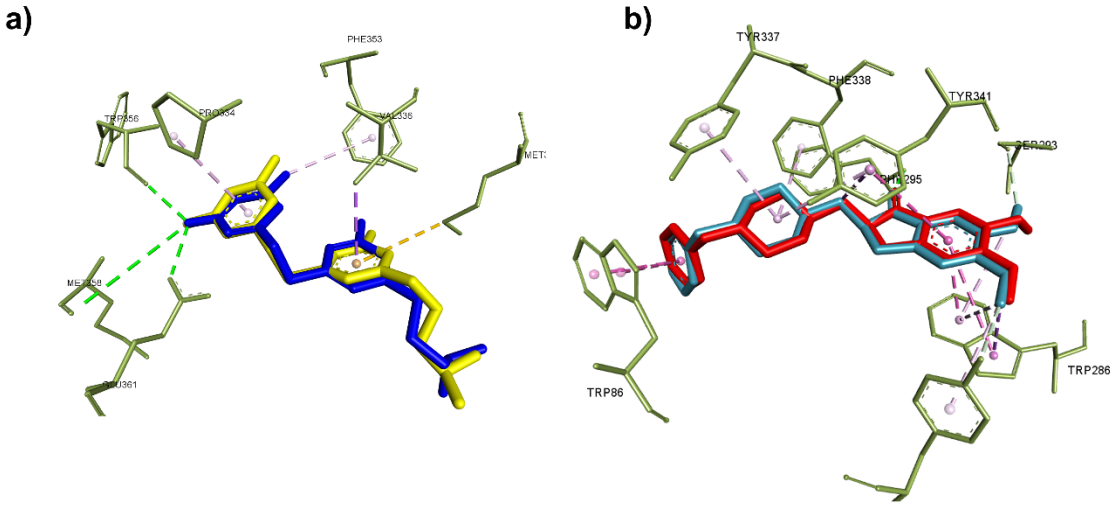
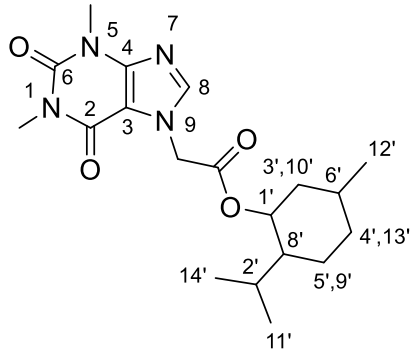
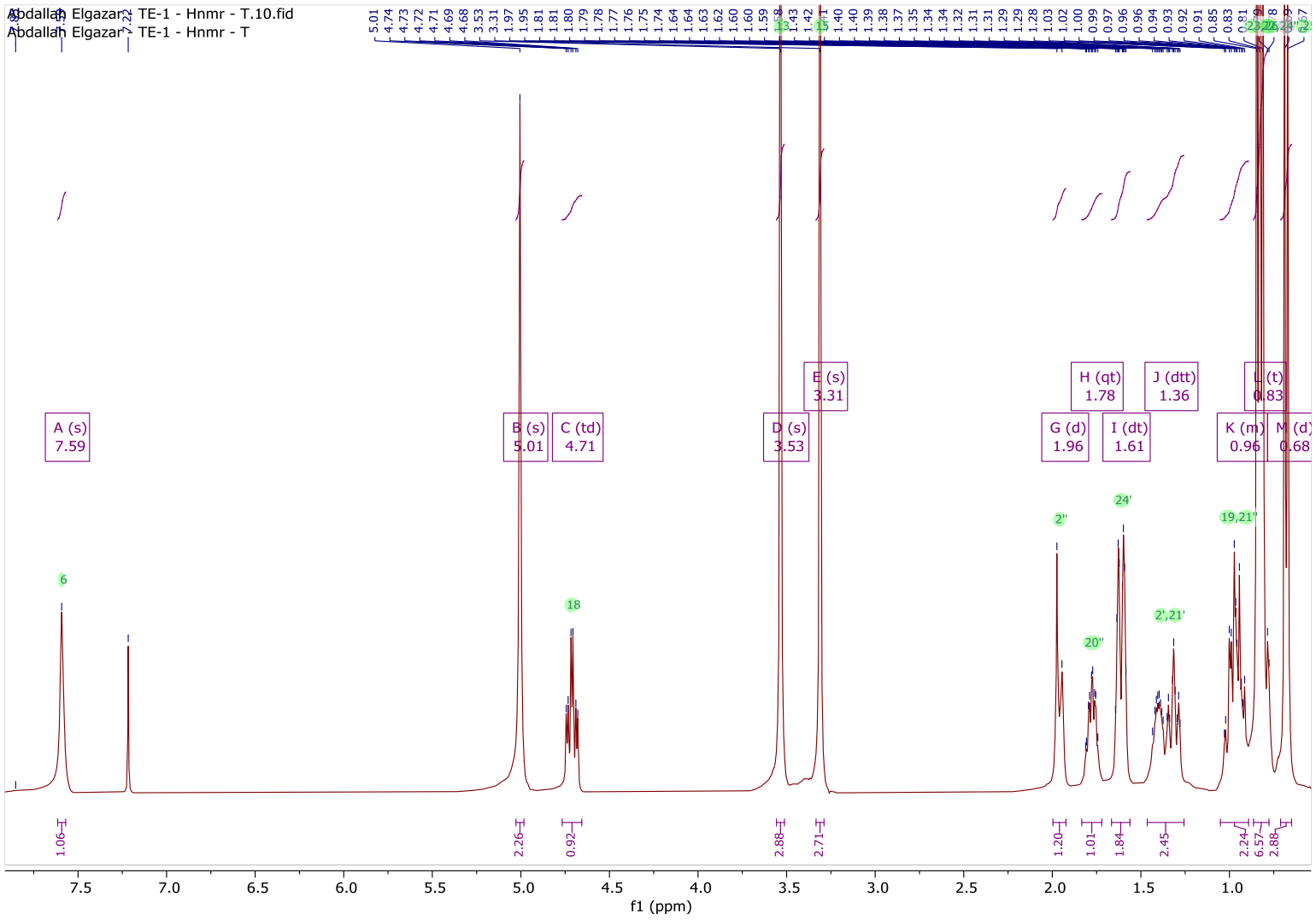


Figure S2: a)Redocking the co-crystallized ligand W69 in the active site of nitric oxide synthase, PDB: 6AV7 where the redocked pose represented as blue sticks and the experimental pose as yellow sticks. B) Redocking the co-crystallized ligand E20 in the active site of acetylcholinesterase, PDB: 4ey7 where the redocked pose represented as cyan sticks and the experimental pose as red sticks

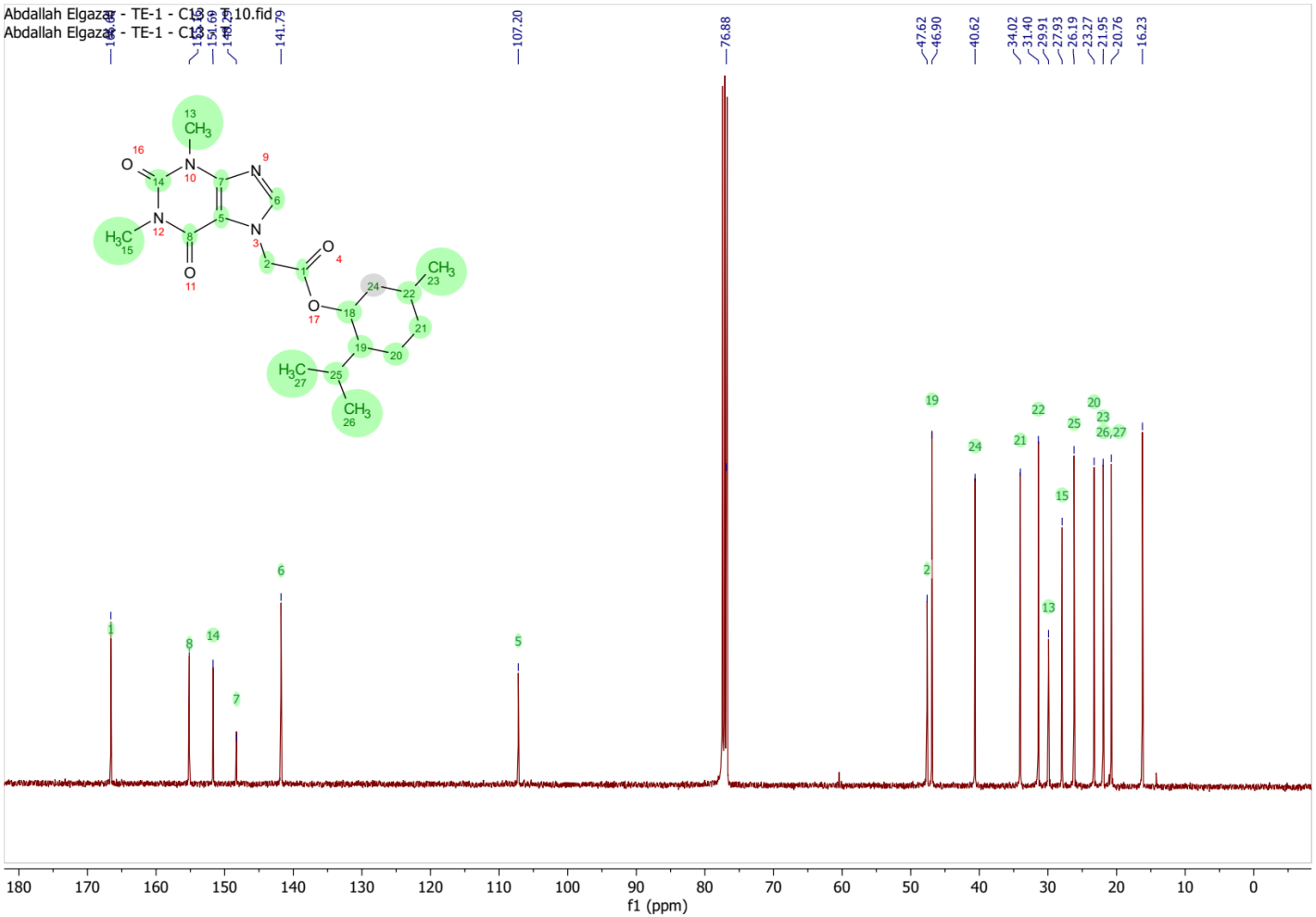
Table.s1 NMR assignment of ACEFYLLINE-menthol hybrid 4a



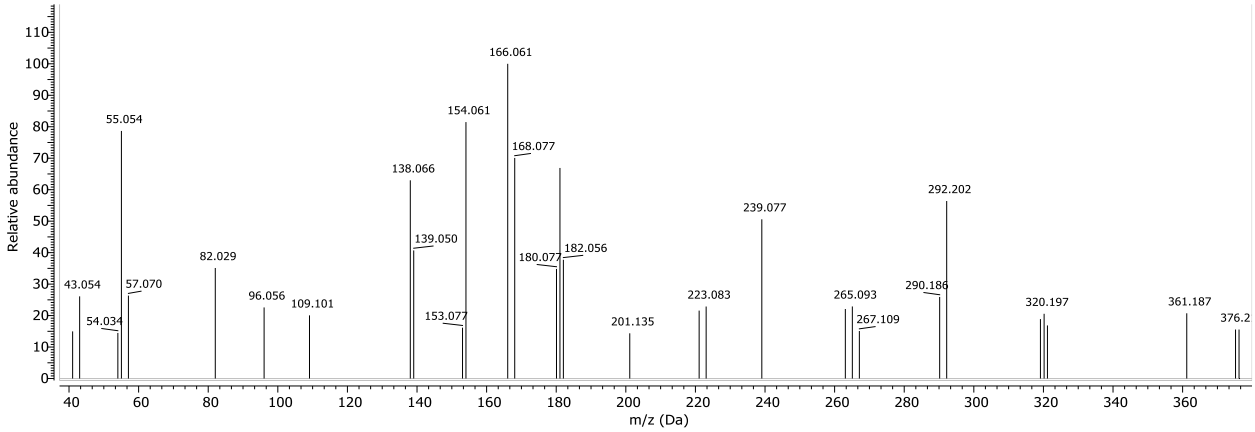
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ, ppm) (J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H (δ, ppm) (J,Hz)	^{13}C (δ, ppm)
COOH		169.48	C	---	166.60
1	-	154.3	C	--	155.16
2	--	151.13	C	--	151.69
3	--	148.36	C	--	148.29
4	8.04	143.63	CH	7.59 (s, 1H)	141.79
5	--	106.83	C	--	107.20
1’	3.4 td,(j=10.4,4.3)	71.5	CH	4.71 (td, *J* = 10.9, 4.4 Hz, 1H)	76.88
8’	1.1	50.12	CH	1.36 (dtt, *J* = 38.3, 11.3, 3.0 Hz, 1H)	47.62
CH2CO	5.07	47.6	CH2	5.01 (s, 2H)	46.90
3’	1.9	45	CH	1.78 (qt, *J* = 7.2, 3.2 Hz, 1H)	40.62
10’	0.95	45	CH	1.05 – 0.89 (m, 1H)	40.62
13’	0.84	34.52	CH	0.83 (t, *J* = 7.0 Hz, 1H)	34.02
4’	1.66	34.5	CH	1.61 (dt, *J* = 12.1, 2.8 Hz, 1H)	34.02
6’	1.43	31.6	CH	1.61 (dt, *J* = 12.1, 2.8 Hz, 1H)	31.40
6	3.44	29.92	CH3	3.53 (s, 3H)	29.91
7	3.20	27.9	CH3	3.31 (s, 3H)	27.93
2’	2.17	25.8	CH	1.96 (d, *J* = 11.5 Hz, 1H)	26.19
5’	0.97	23.1	CH	1.36 (dtt, *J* = 38.3, 11.3, 3.0 Hz, 1H)	23.27
9’	0.97	23.1	CH	1.05 – 0.89 (m, 1H)	23.27
12’	0.91	22.2	CH3	0.83 (t, *J* = 7.0 Hz, 3H)	21.95
11’	0.92	21	CH3	0.83 (t, *J* = 7.0 Hz, 3H)	20.76
14’	0.8	16	CH3	0.68 (d, *J* = 6.9 Hz, 3H)	16.23
7’	1.35	--	--	--	



^{1}H NMR spectrum of compound 4a

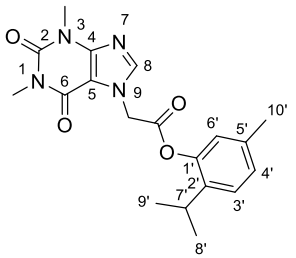


^{13}C NMR spectrum of compound 4a

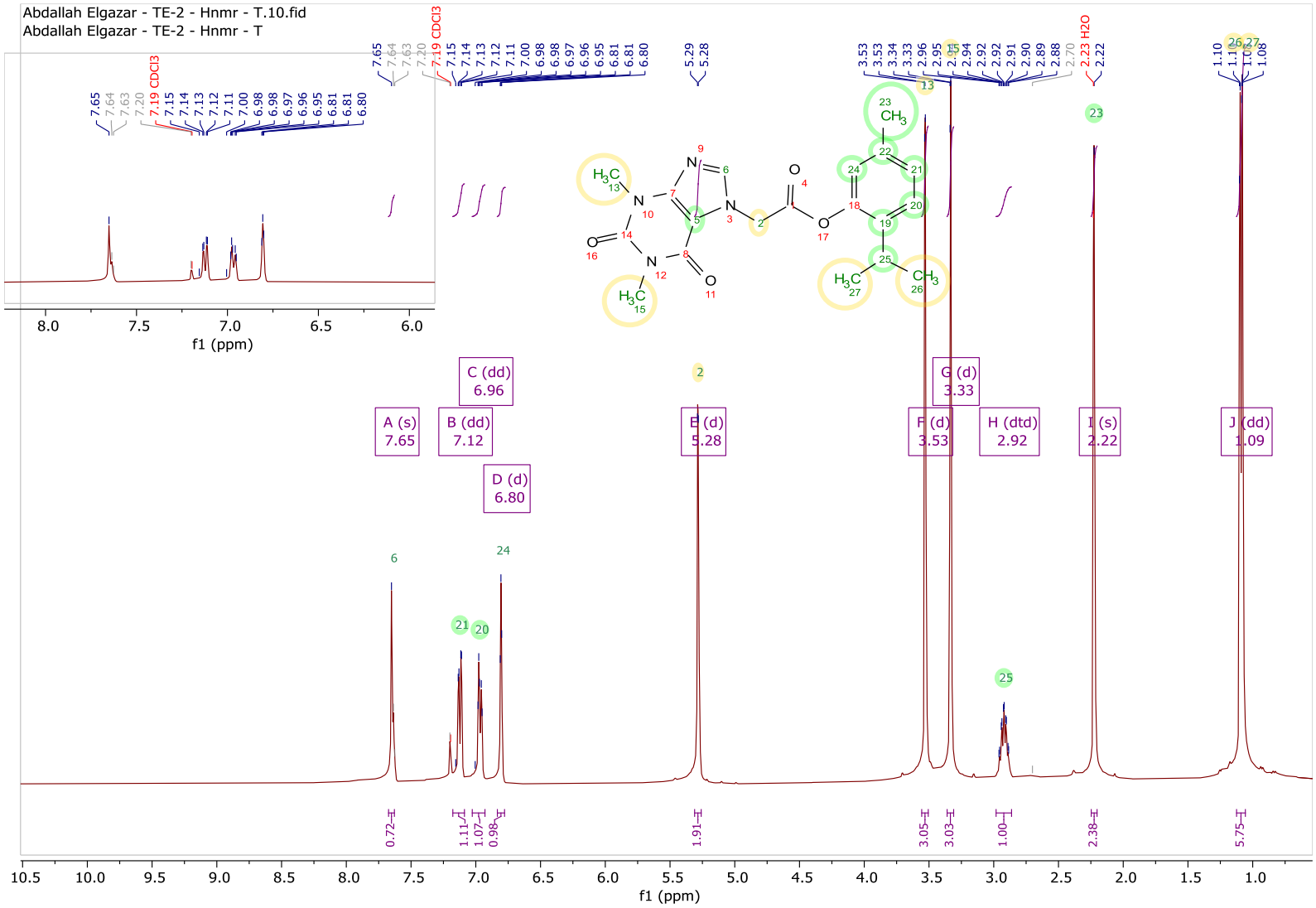


Mass spectrum of compound 4a

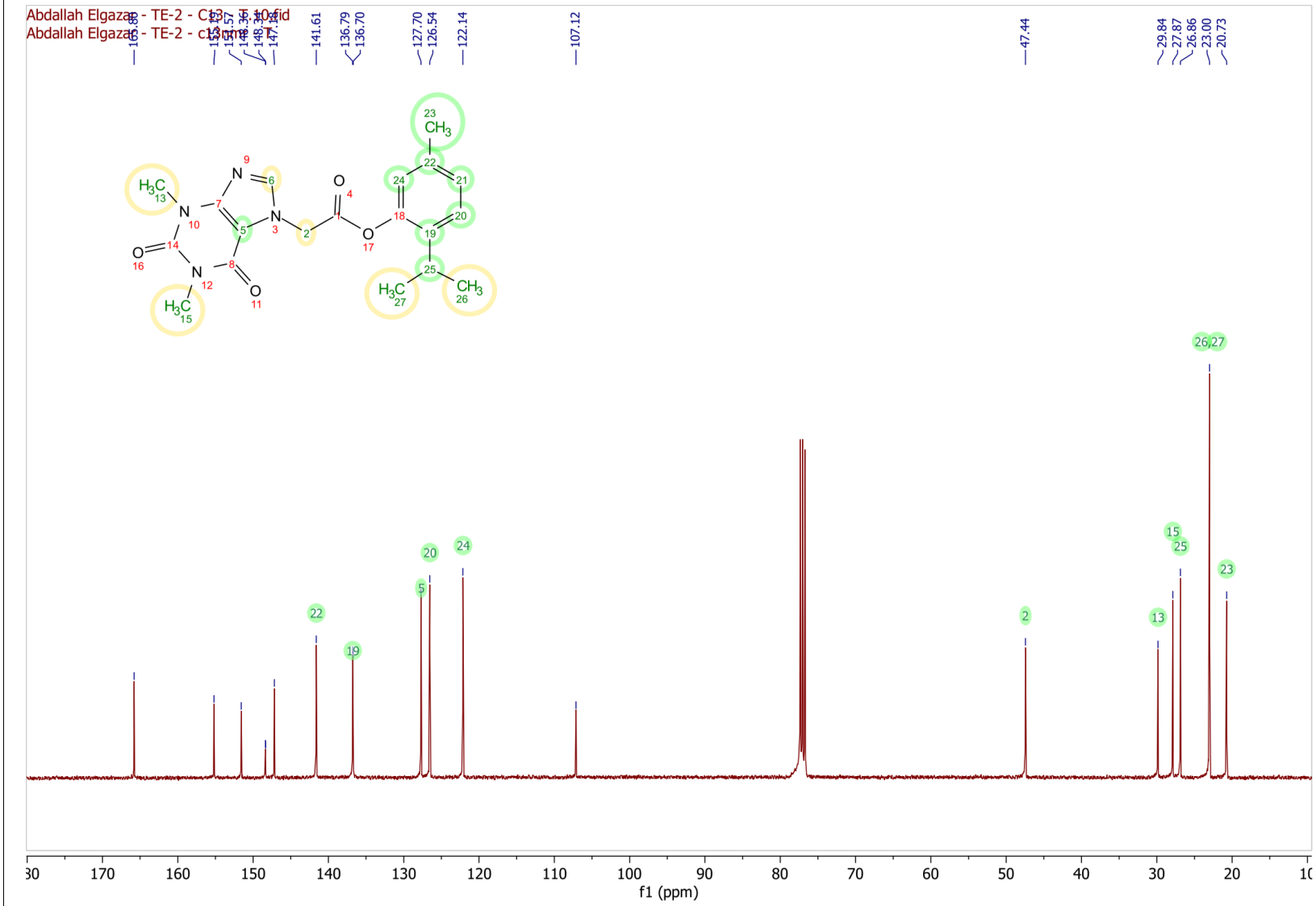
Table.S2 NMR assignment of ACEFYLLINE-thymol hybrid 4b



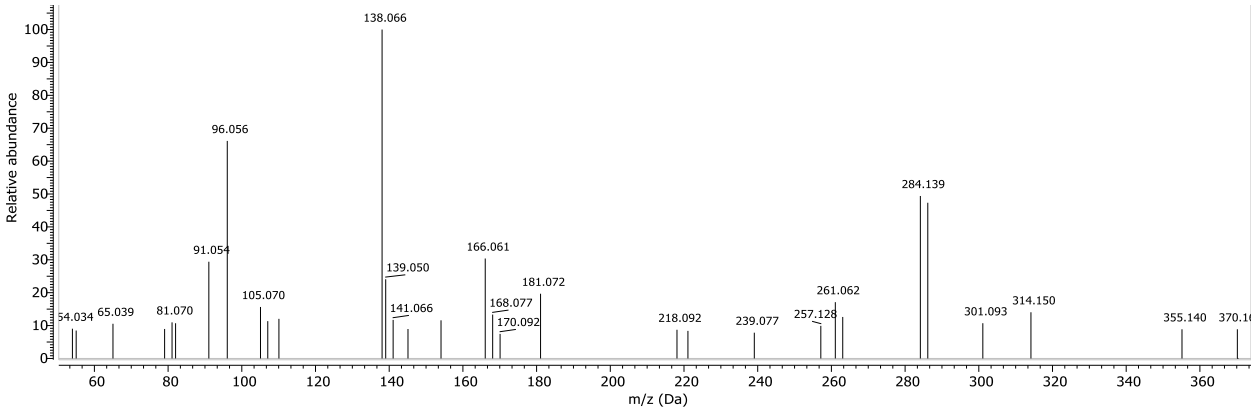
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ, ppm) (J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
COOH	10	169.48	C	--	165.80
1	-	154.3	C	--	155.19
2	--	151.13	C	--	151.57
1[1]	-	150.2	C	--	148.36
3	--	148.36	C	--	147.18
4	8.04	143.63	CH	7.64 (d, *J* = 6.2 Hz, 1H)	141.61
3’	-	138.4	C	--	136.79
6’	--	131.7	C	--	136.70
4’	7.08	126.3	CH	7.12 (dd, *J* = 8.0, 2.2 Hz, 1H)	127.70
5’	7.08	126.3	CH	7.00 – 6.93 (m, 1H)	126.54
2’	5.4	116.9	CH	6.80 (d, *J* = 2.2 Hz, 1H)	122.14
5	--	106.83	C	--	107.12
CH2CO	5.07	47.6	CH2	5.28 (d, *J* = 2.3 Hz, 2H)	47.44
6	3.44	29.92	CH3	3.53 (d, *J* = 2.2 Hz, 3H)	29.84
7	3.20	27.9	CH3	3.33 (d, *J* = 2.2 Hz, 3H)	27.87
8’	1.05	26.1	CH3	1.09 (dd, *J* = 6.9, 2.2 Hz, 3H)	26.86
9’	1.05	26.1	CH3	1.09 (dd, *J* = 6.9, 2.2 Hz, 3H)	26.86
7’	3.38	25.5	CH	2.98 – 2.86 (m, 1H)	23.00
10’	2.2	18.7	CH3	2.22 (s, 3H)	20.73



^{1}H NMR spectrum of compound 4b

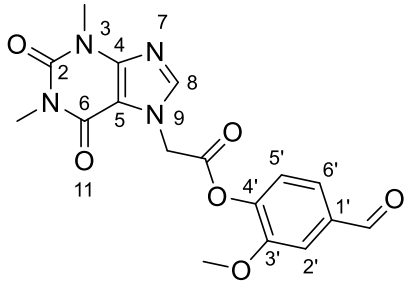


^{13}C NMR spectrum of compound 4b

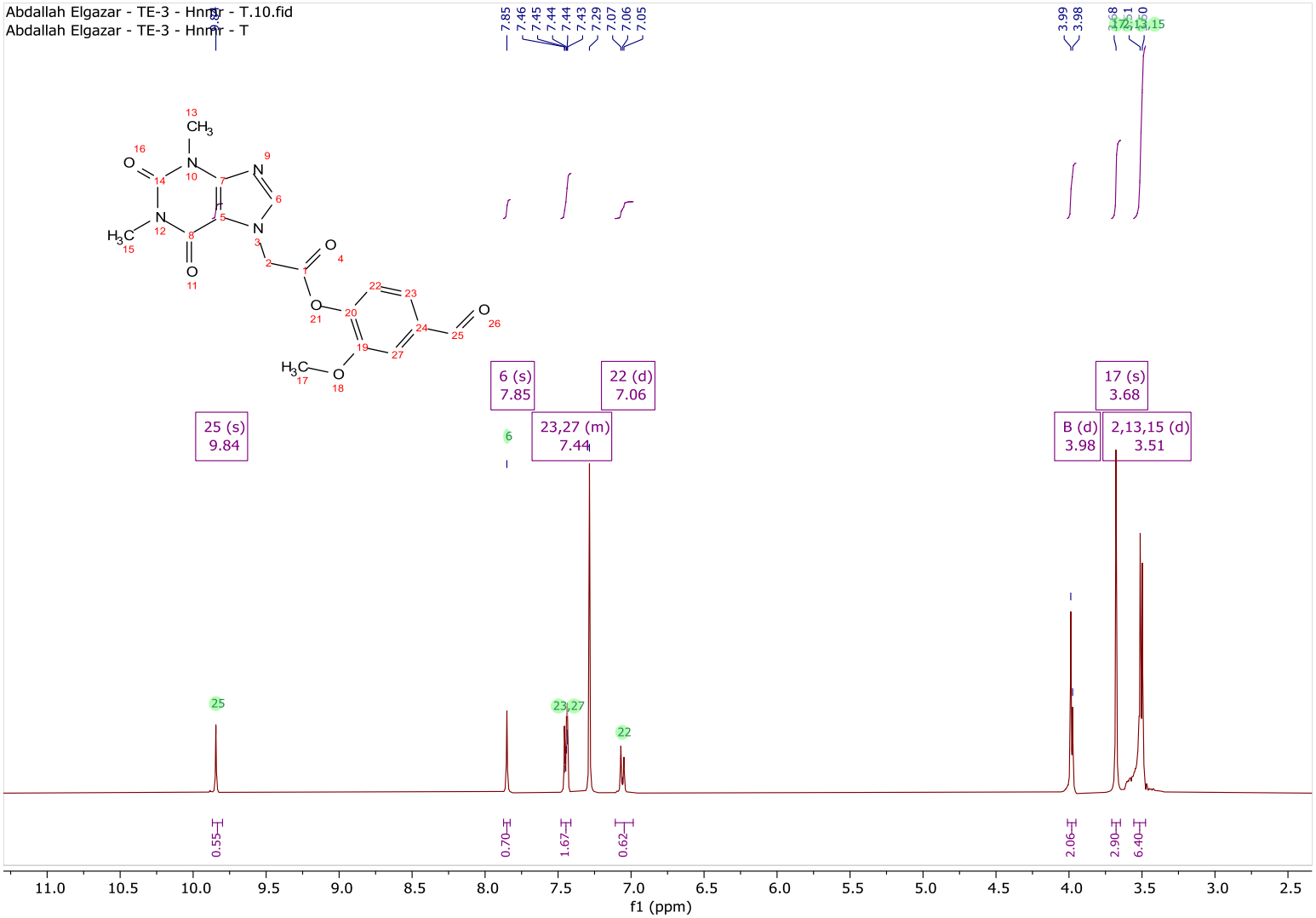


Mass spectrum of compound 4b

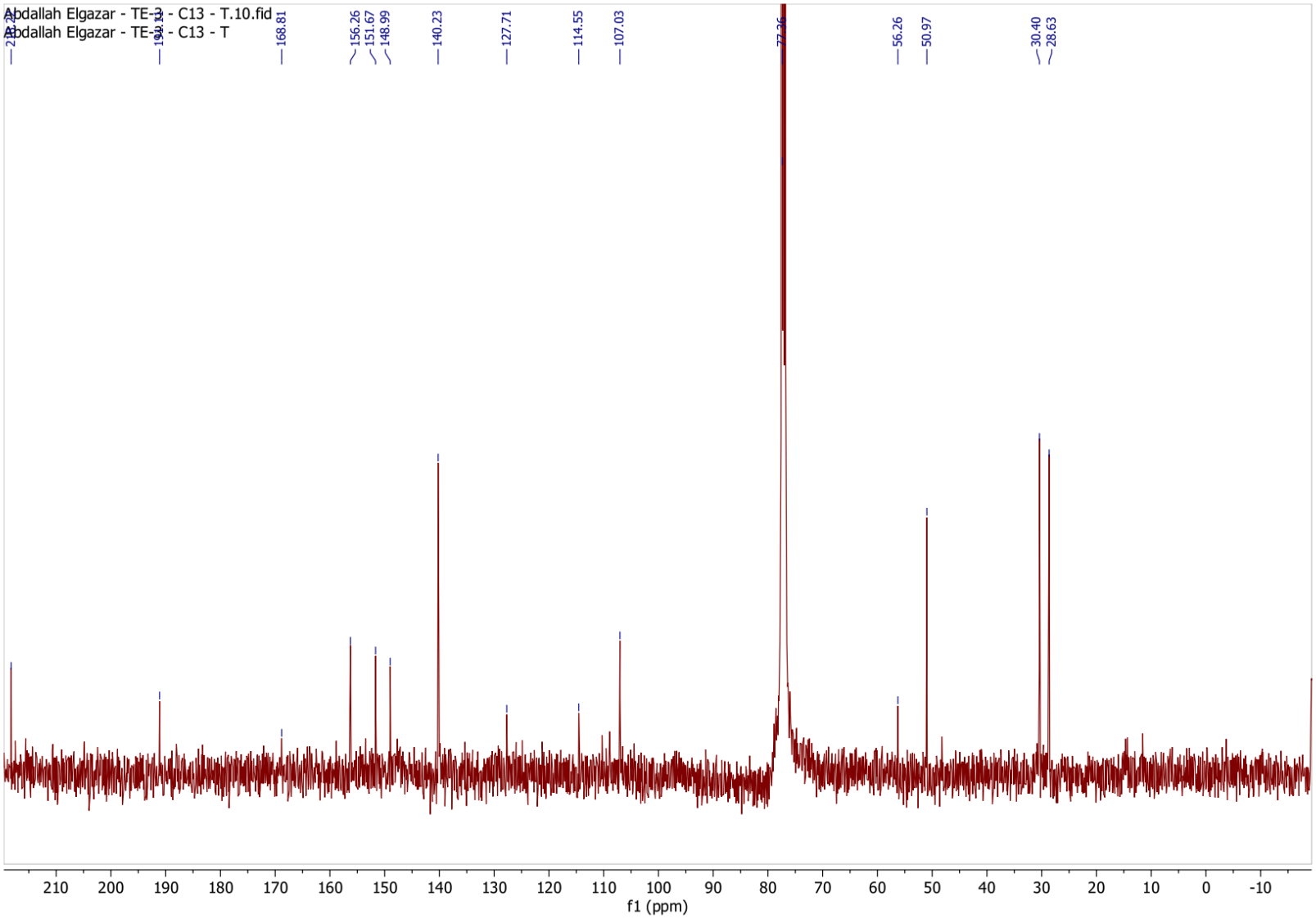
Table.S3 NMR assignment of ACEFYLLINE-vanillin hybrid **4c**



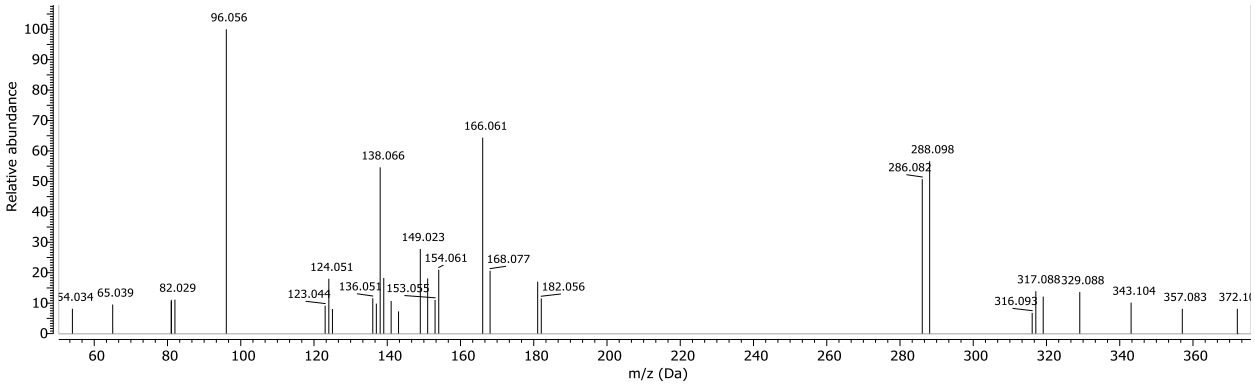
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ, ppm) (J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
HC=O	10.11	191.2	CH	9.84 (s, 1H)	191.11
COOH	10	169.48	C	-	168.80
1	-	154.3	C	-	156.26
4’	-	152.18	C	--	151.67
2	--	151.13	C	--	151.67
3	--	148.36	C	--	148.99
3’	--	147.5	C	--	148.99
4	8.04	143.63	CH	7.85 (s, 1H)	140.23
1[1]	--	129.77	C	--	140.23
6’	6.9 d(J=7.5)	127.49	CH	7.06 (d, *J* = 8.5 Hz, 1H)	127.70
5’	7.2	114.75	CH	7.48 – 7.41 (m, 1H)	114.55
2’	7.3 d(J=1.50)	109.14	CH	7.48 – 7.41 (m, 1H)	107.03
5	--	106.83	C	--	107.03
-OCH3 vanillin	3.84	56.2	CH3	3.68 (s, 3H)	56.26
CH2CO	5.07	47.6	CH2	3.98 (d, *J* = 5.1 Hz, 2H)	50.97
6	3.44	29.92	CH3	3.51 (d, *J* = 5.9 Hz, 3H)	30.40
7	3.20	27.9	CH3	3.51 (d, *J* = 5.9 Hz, 3H)	28.63



^{1}H NMR spectrum of compound 4c

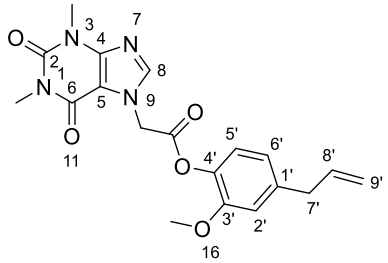


^{13}C NMR spectrum of compound 4c

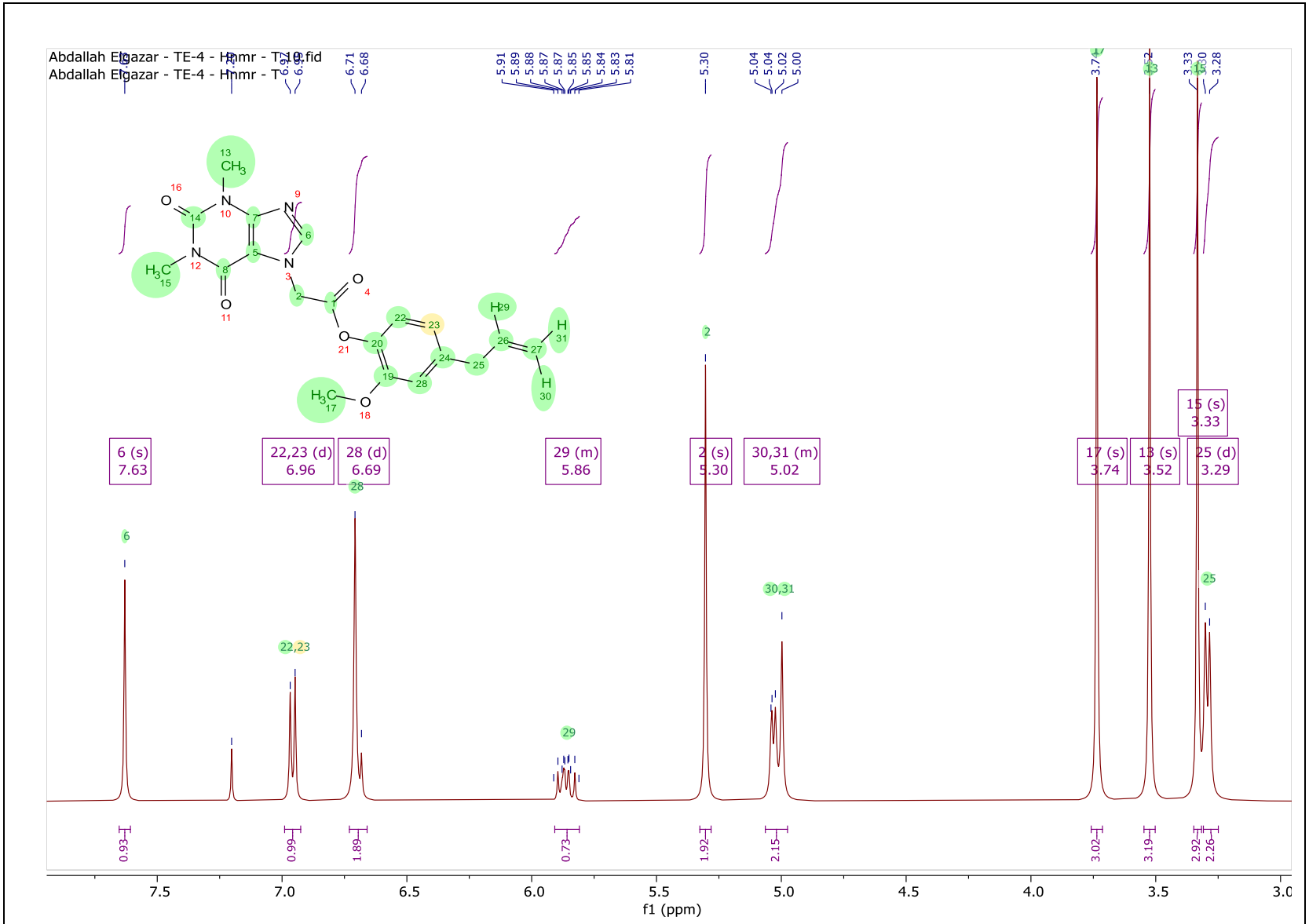


Mass spectrum of compound 4c

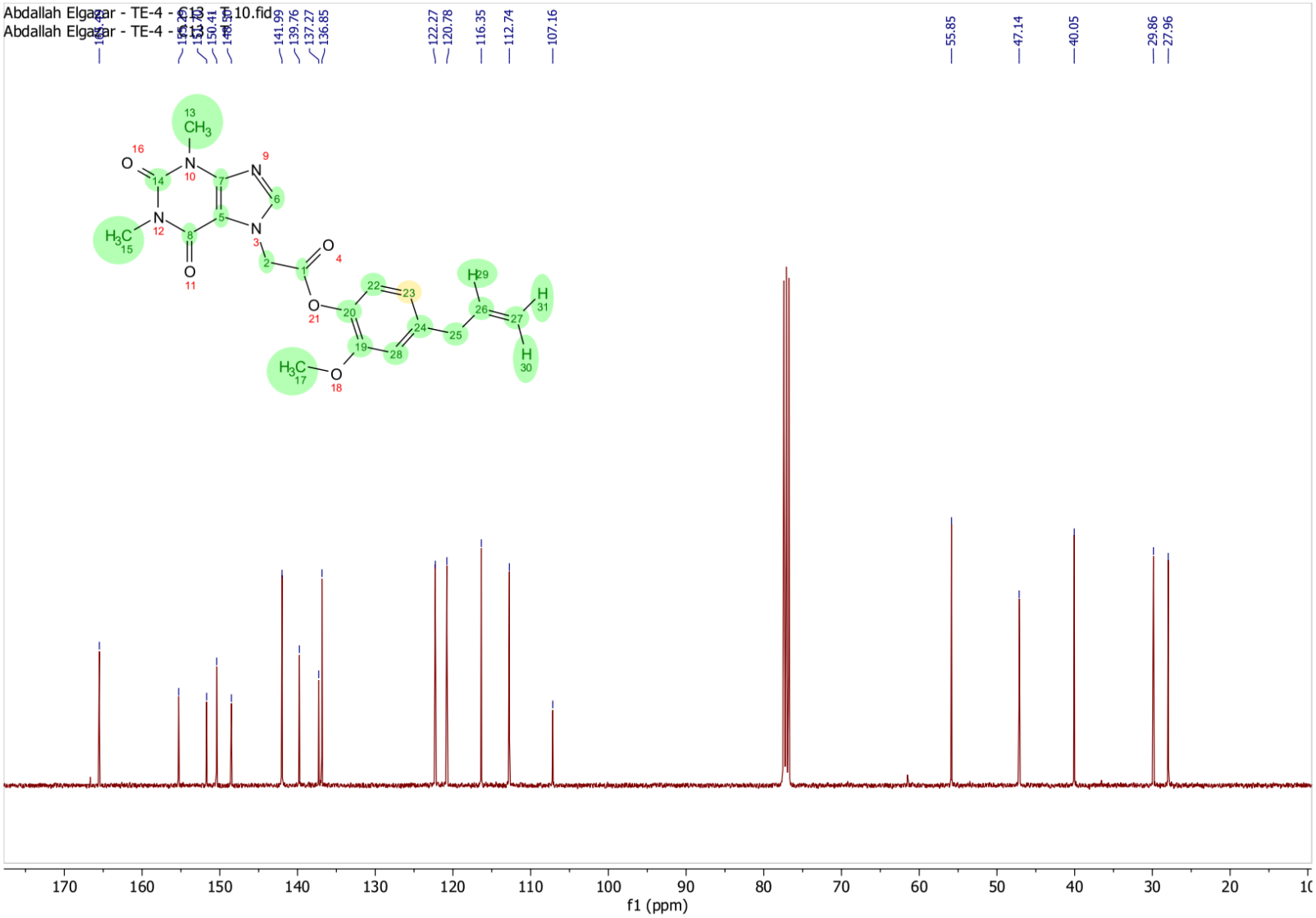
Table.S4 NMR assignment of ACEFYLLINE-menthol hybrid **4d**



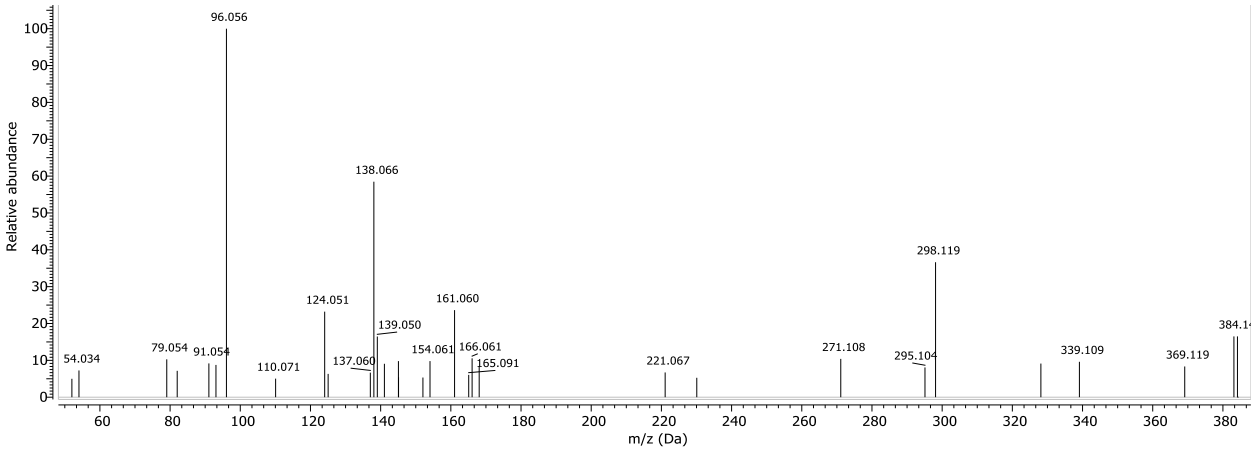
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ, ppm) (J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
COOH	10	169.48	C	--	165.49
1	-	154.3	C		155.29
2	--	151.13	C	--	151.70
3	--	148.36	C	--	150.41
1[1]	--	146.6	C	--	148.50
2’	--	144.03	C	--	141.99
4	8.04	143.63	CH	7.63 (s, 1H)	139.76
-CH= eugenol	5.9	137.9	CH	5.91 – 5.81 (m, 1H)	137.27
5’	--	131.94	C	--	136.85
4’	6.67	121.2	CH	6.69 (d, *J* = 10.4 Hz, 1H)	122.27
3’	6.82	115.49	CH	6.96 (d, *J* = 7.8 Hz, 1H)	120.78
6’	6.66	114.46	CH	6.69 (d, *J* = 10.4 Hz, 1H)	116.35
EugenolCH=CH2-	5.06, 5.04	111.8	CH2	5.06 – 4.98 (m, 2H)	112.74
5	--	106.83	C	--	107.16
-OCH3 Eugenol	3.8	55.8	CH3	3.74 (s, 3H)	55.85
CH2CO	5.07	47.6	CH2	5.30 (s, 2H)	47.14
CH2-CH= eugenol	3.29	39.9	CH2	3.29 (d, *J* = 6.9 Hz, 2H)	40.05
6	3.44	29.92	CH3	3.52 (s, 3H)	29.86
7	3.20	27.9	CH3	3.33 (s, 3H)	27.96



^{1}H NMR spectrum of compound 4d

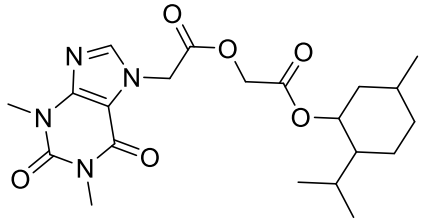


^{13}C NMR spectrum of compound 4d

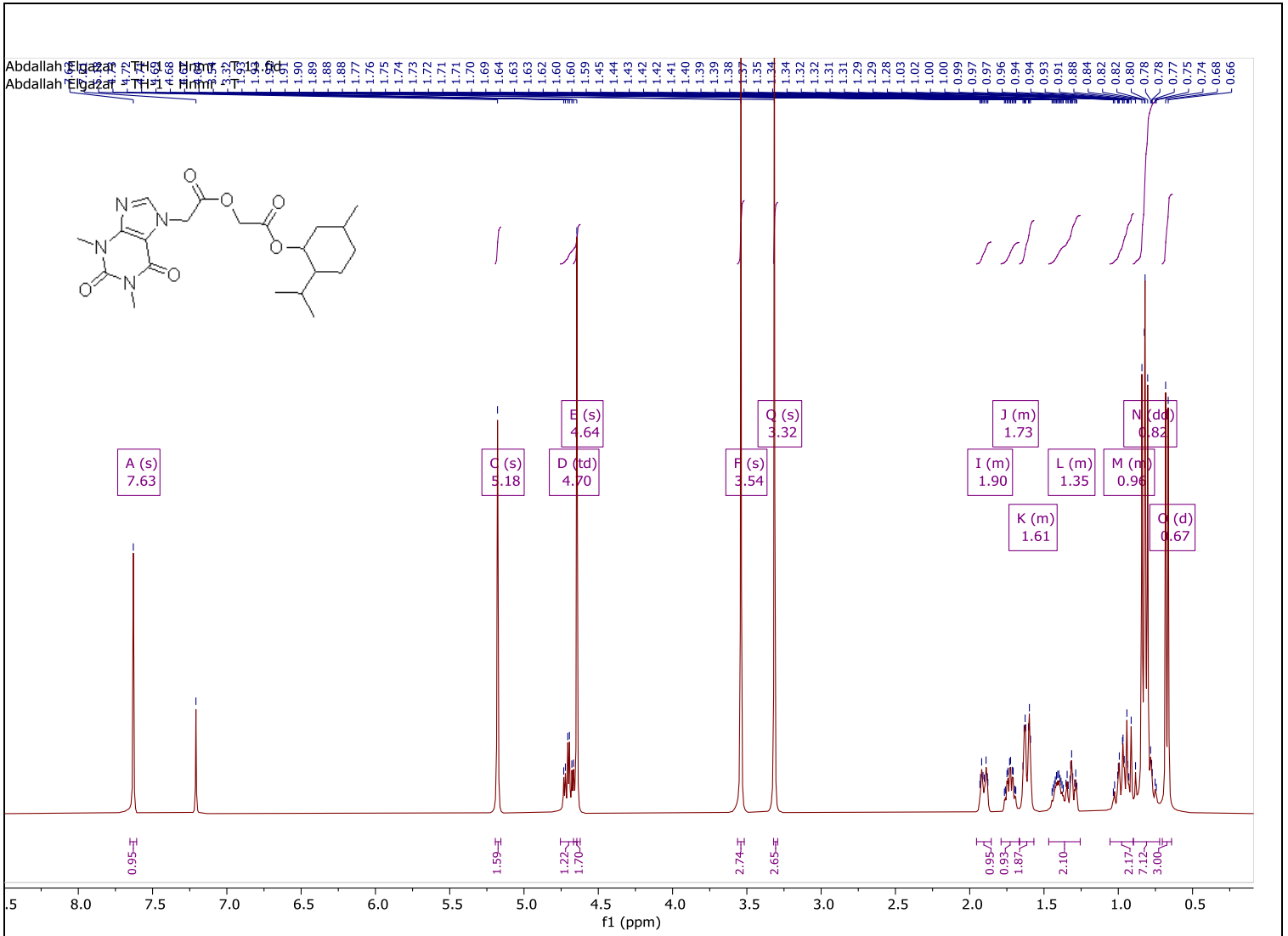


Mass spectrum of compound 4d

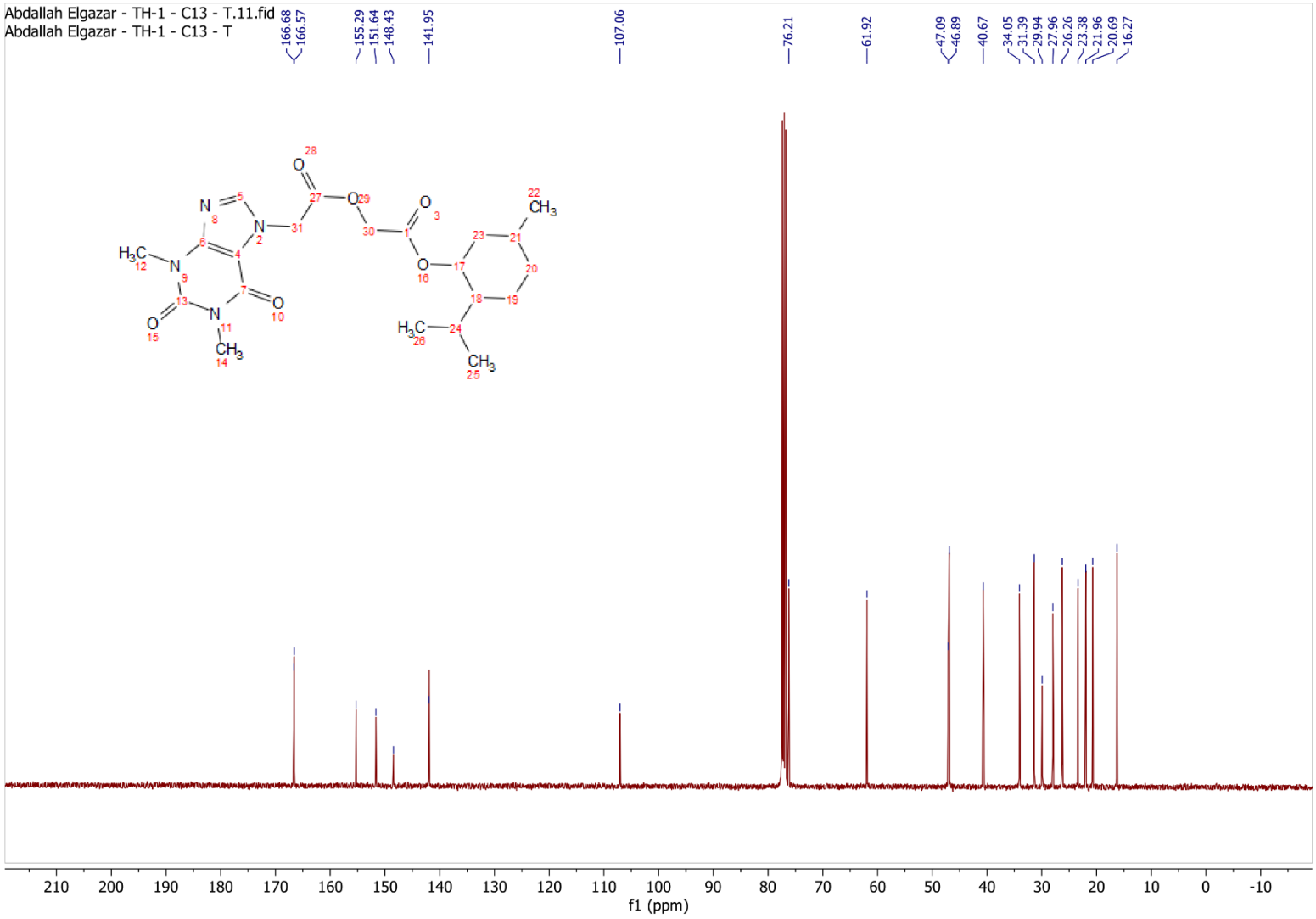
Table.S5 NMR assignment of ACEFYLLINE-acetyl-menthol hybrid 6a



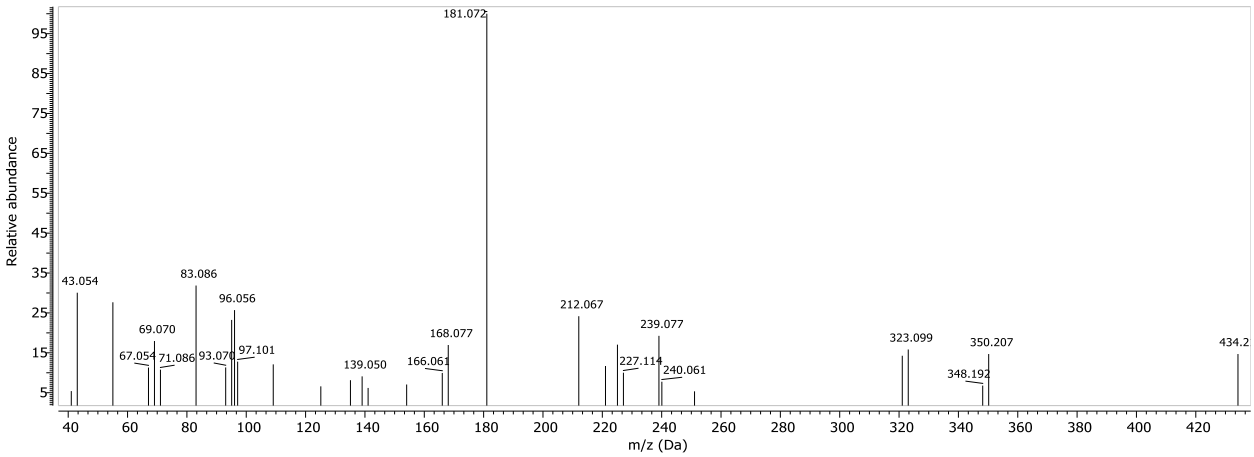
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ, ppm) (J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
COOH	--	169.48	C	---	166.68
C=O-Linker	--	165.6	C		166.57
1	-	154.3	C	--	155.29
2	--	151.13	C	--	151.64
3	--	148.36	C	--	148.43
4	8.04	143.63	CH	7.63 (s, 1H)	141.95
5	--	106.83	C	--	107.06
1’	3.4td(j=10.4,4.3)	71.5	CH	4.70 (td, *J* = 11.0, 4.5 Hz, 1H)	76.21
CH2LINKER	4.9	60	CH2	4.64 (s, 2H)	61.92
8’	1.1	50.12	CH	1.47 – 1.26 (m, 1H)	47.09
CH2CO	5.07	47.6	CH2	5.18 (s, 2H)	46.89
3’	1.9	45	CH	1.79 – 1.67 (m, 1H)	40.67
10’	0.95	45	CH	1.06 – 0.90 (m, 1H)	40.67
13’	0.84	34.52	CH	0.82 (t, *J* = 7.0 Hz, 1H)	34.05
4’	1.66	34.5	CH	1.66 – 1.57 (m, 1H)	34.05
6’	1.43	31.6	CH	1.66 – 1.57 (m, 1H)	31.39
6	3.44	29.92	CH3	3.54 (s, 3H)	29.94
7	3.20	27.9	CH3	3.32 (s, 3H)	27.96
2’	2.17	25.8	CH	1.95 – 1.86 (m, 1H)	26.26
5’	1.6	23.1	CH	1.47 – 1.26 (m, 1H)	23.27
9’	0.97	23.1	CH	1.06 – 0.90 (m, 1H)	23.38
12’	0.91	22.2	CH3	0.82 (t, *J* = 7.0 Hz, 3H)	21.96
11’	0.92	21	CH3	0.82 (t, *J* = 7.0 Hz, 3H)	20.69
14’	0.8	16	CH3	0.67 (d, *J* = 7.0 Hz, 3H)	16.27
7’	1.35	--	--	--	--



^{1}H NMR spectrum of compound 6a

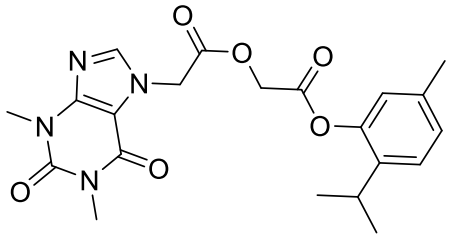


^{13}C NMR spectrum of compound 6a

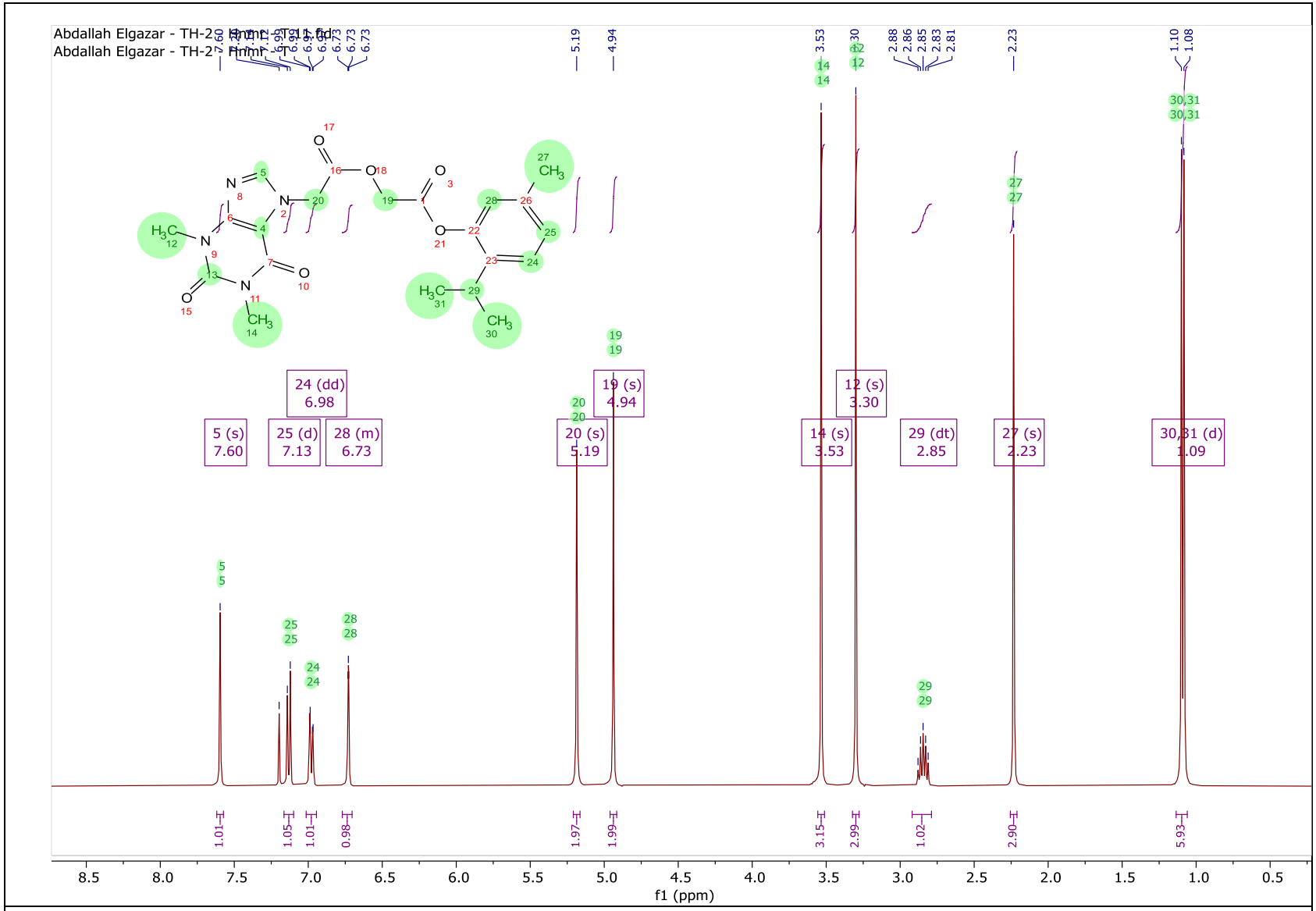


Mass spectrum of compound 6a

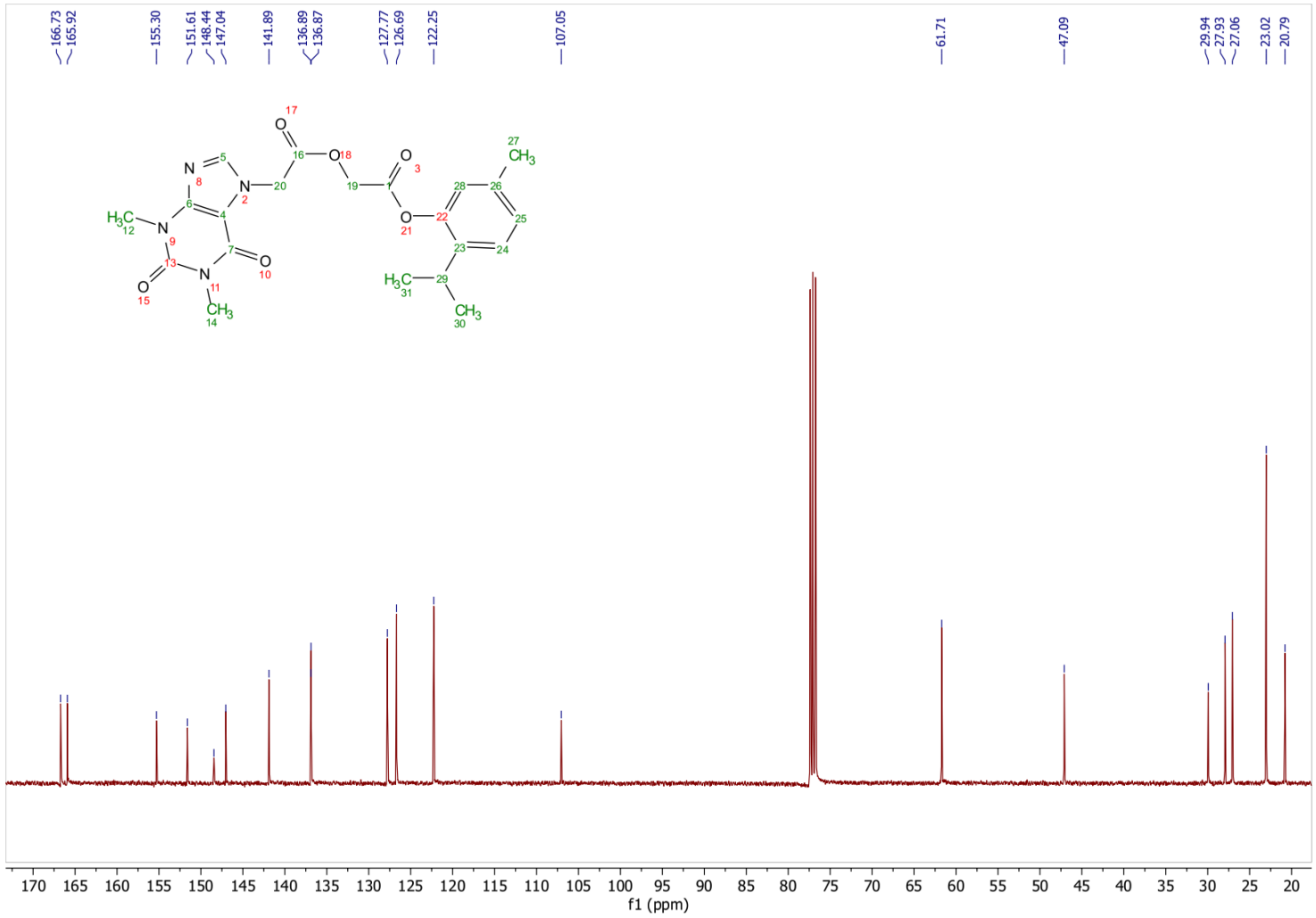
Table.S6 NMR assignment of ACEFYLLINE-acetyl-thymyl hybrid 6b



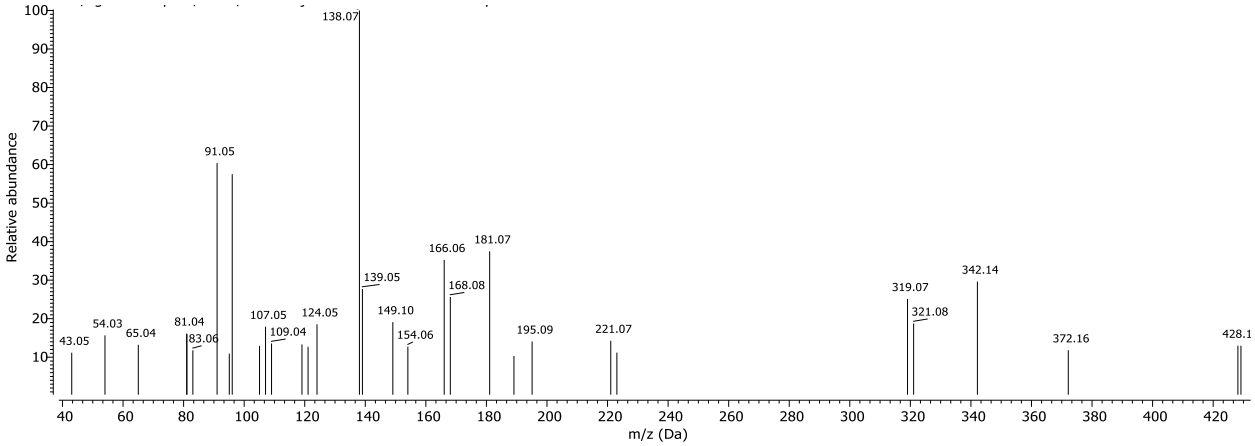
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ, ppm) (J,Hz)	^{13}C(δ, ppm)	DEPT	^{1}H(δ, ppm) (J,Hz)	^{13}C(δ, ppm)
COOH	10	169.48	C	--	166.73
4	8.04	143.63	CH	7.60 (s, 1H)	141.89
4’	7.08	126.3	CH	7.13 (d, *J* = 7.9 Hz, 1H)	127.77
5’	7.08	126.3	CH	6.98 (dd, *J* = 8.0, 1.8 Hz, 1H)	126.69
2’	5.4	116.9	CH	6.77 – 6.70 (m, 1H)	122.25
CH2CO	5.07	47.6	CH2	5.19 (s, 2H)	47.09
CH2LINKER	4.9	60	CH2	4.94 (s, 2H)	61.71
6	3.44	29.92	CH3	3.53 (s, 3H)	29.94
7’	3.38	25.5	CH	2.85 (dt, *J* = 13.7, 6.8 Hz, 1H)	23.02
7	3.20	27.9	CH3	3.33 (d, *J* = 2.2 Hz, 3H)	27.93
10’	2.2	18.7	CH3	2.23 (s, 3H)	20.79
8’	1.05	26.1	CH3	1.09 (d, *J* = 6.9 Hz, 3H)	27.06
9’	1.05	26.1	CH3	1.09 (d, *J* = 6.9 Hz, 3H)	27.06
CO-LINKER	--	165.6	C	--	165.92
1	-	154.3	C	--	155.30
2	--	151.13	C	--	151.61
1[1]	-	150.2	C	--	148.44
3	--	148.36	C	--	147.04
3’	-	138.4	C	--	136.89
6’	--	131.7	C	--	136.87
5	--	106.83	C	--	107.5



^{1}H NMR spectrum of compound 6b

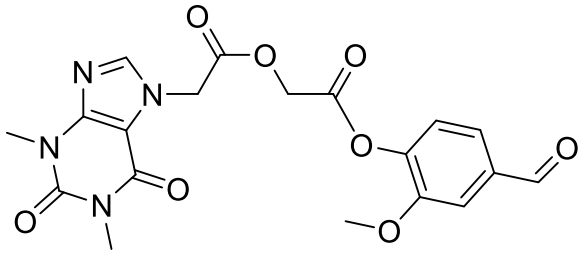


^{13}C NMR spectrum of compound 6b

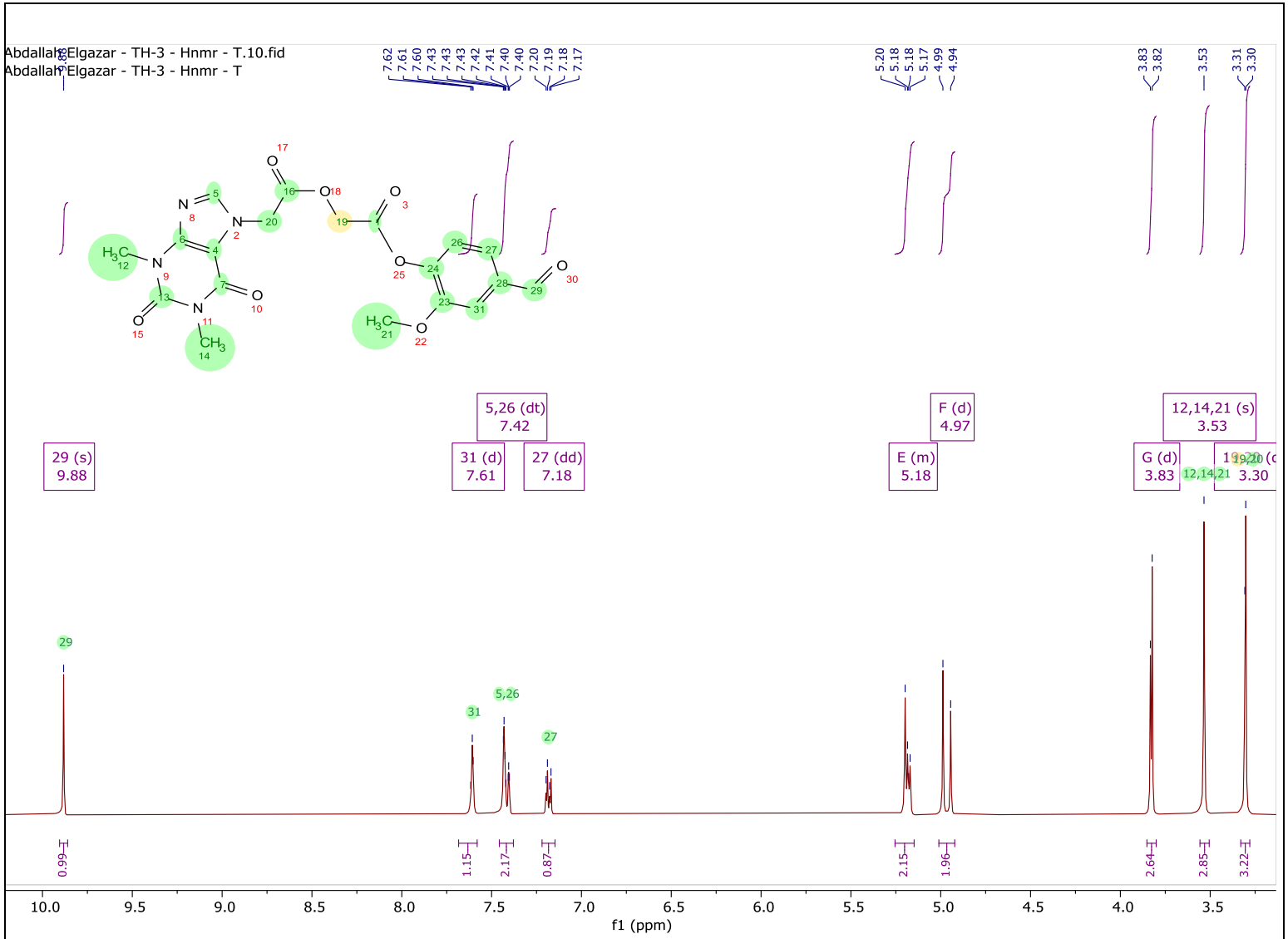


Mass spectrum of compound 6b

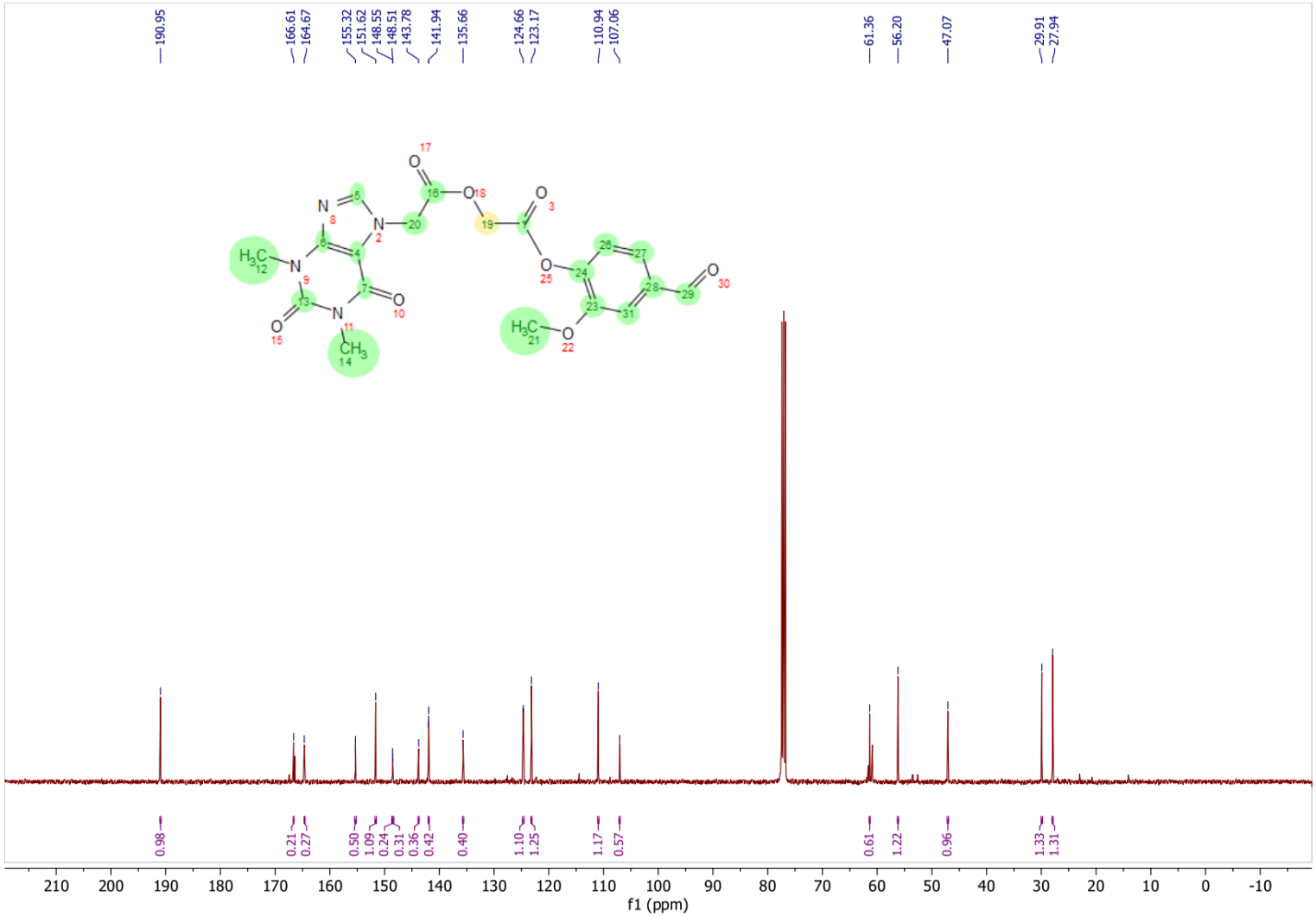
Table.S7 NMR assignment of ACEFYLLINE-acetyl-vanillin hybrid 6c



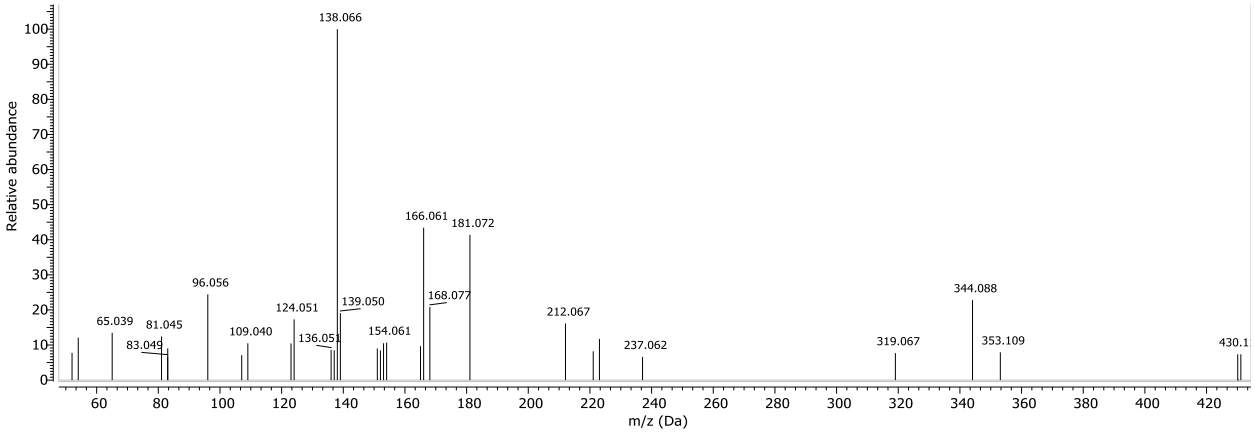
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ, ppm) (J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
HC=O	10.11	191.2	CH	9.88 (s, 1H)	190.95
COOH	10	169.48	C	-	166.61
CO-LINKER	--	165.6	C	--	164.67
1	-	154.3	C	-	155.32
4’	-	152.18	C	--	151.62
2	--	151.13	C	--	148.55
3	--	148.36	C	--	148.51
3’	--	147.5	C	--	143.78
4	8.04	143.63	CH	7.61 (d, *J* = 1.8 Hz, 1H)	141.94
1[1]	--	129.77	C	--	135.66
6’	6.9d(J=7.5)	127.49	CH	7.18 (dd, *J* = 7.9, 3.0 Hz, 1H)	124.66
5’	7.2	114.75	CH	7.42 (dt, *J* = 9.7, 1.6 Hz, 1H)	123.17
2’	7.3 d(J=1.50)	109.14	CH	7.42 (dt, *J* = 9.7, 1.6 Hz, 2H)	110.94
5	--	106.83	C	--	107.06
CH2-LINKER	4.9	60	CH2	4.97 (d, *J* = 17.3 Hz, 2H)	61.36
-OCH3vanillin	3.84	56.2	CH3	3.83 (d, *J* = 3.9 Hz, 3H)	56.20
CH2CO	5.07	47.6	CH2	5.25 – 5.15 (m, 2H)	47.07
6	3.44	29.92	CH3	3.53 (s, 3H)	29.91
7	3.20	27.9	CH3	3.30 (d, *J* = 2.1 Hz, 3H)	27.94



^{1}H NMR spectrum of compound 6c

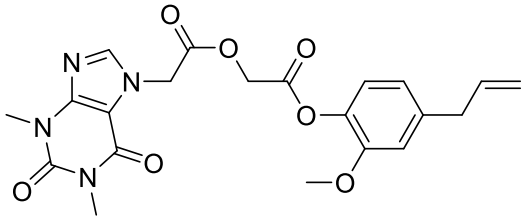


^{3}C NMR spectrum of compound 6c

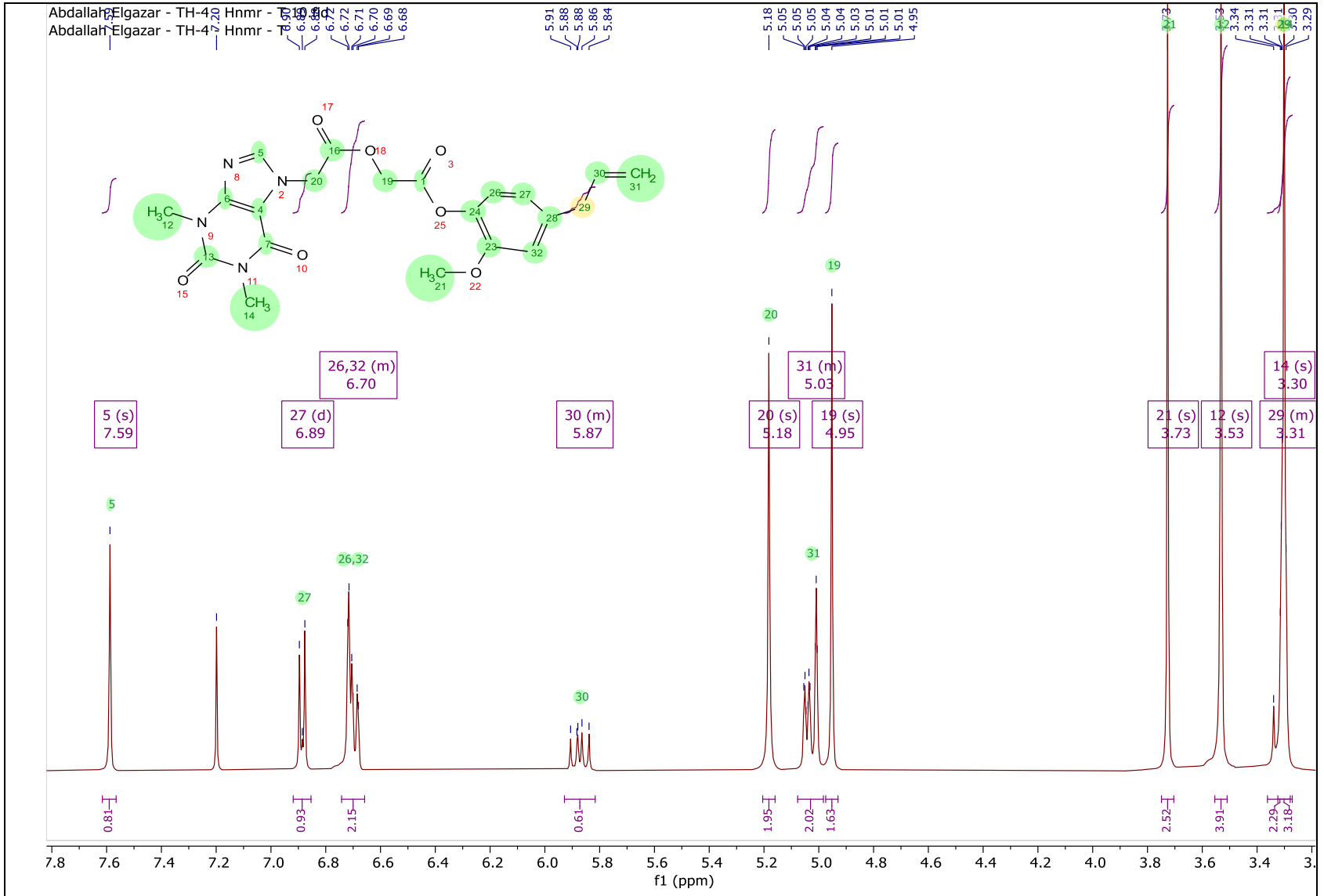


Mass spectrum of compound 6c

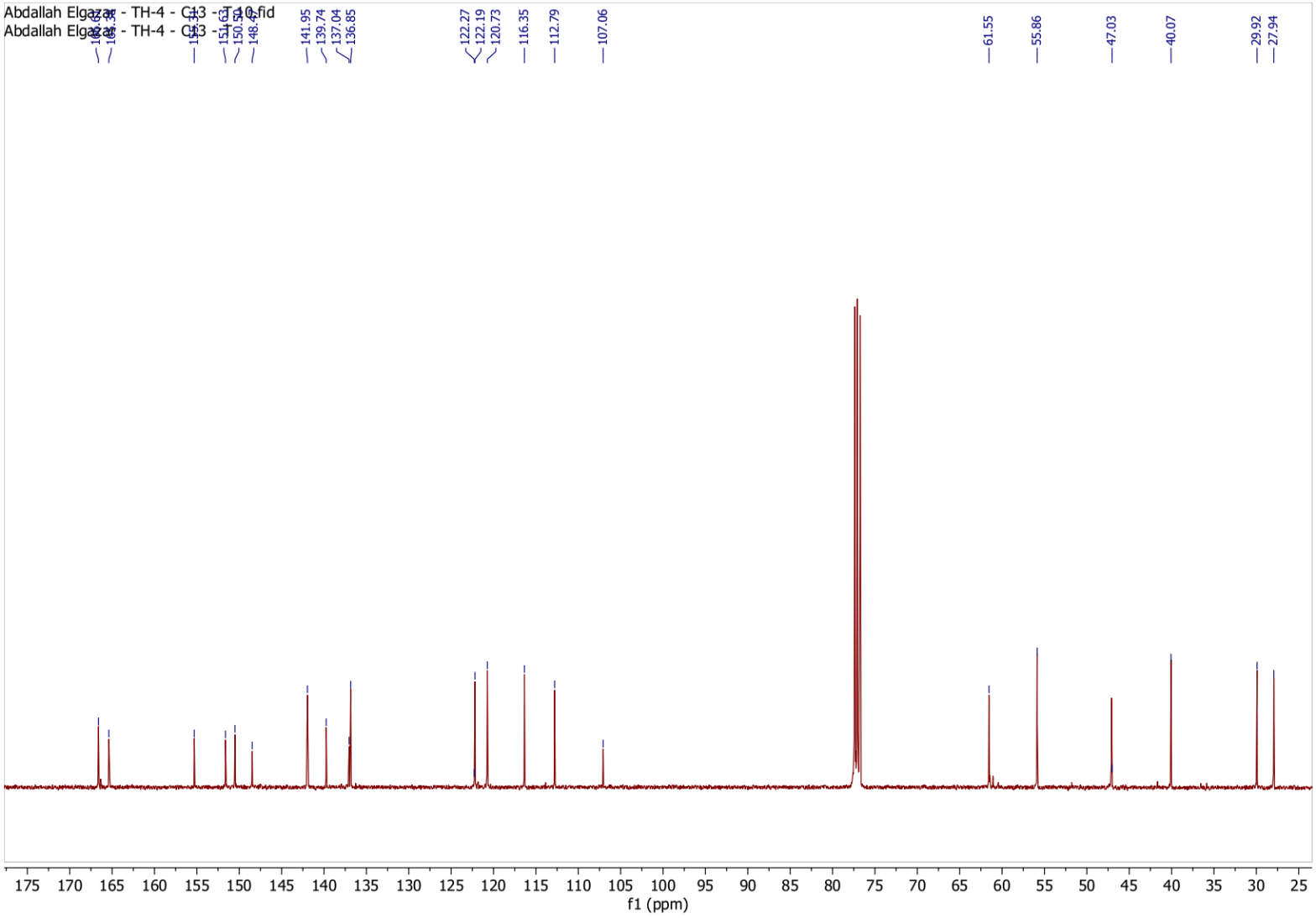
Table.s8 NMR assignment of acefylline-acetyl-eugenol hybrid 6d



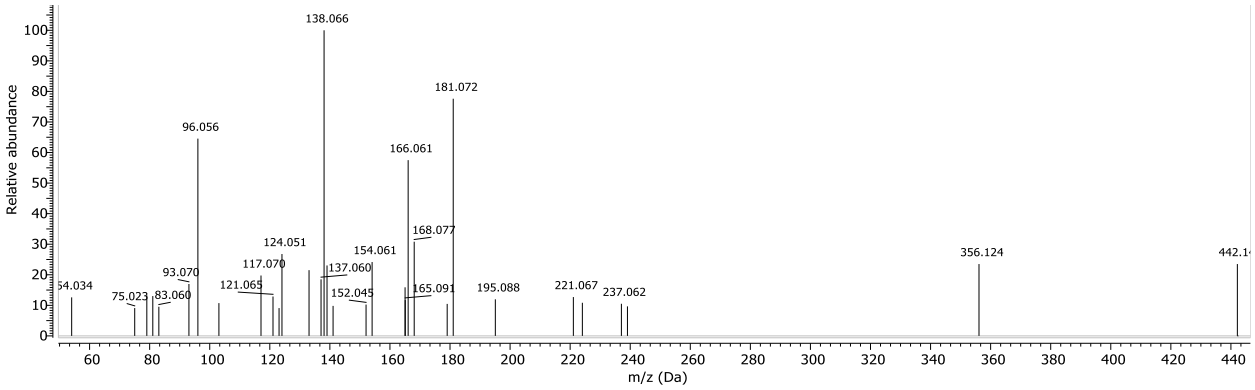
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ, ppm) (J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
COOH	10	169.48	C	--	166.61
4	8.04	143.63	CH	7.59 (s, 1H)	139.74
3’	6.82	115.49	CH	6.89 (d, *J* = 8.0 Hz, 1H)	120.73
4’	6.67	121.2	CH	6.74 – 6.66 (m, 1H)	122.19
6’	6.66	114.46	CH	6.74 – 6.66 (m, 1H)	116.35
-CH=eugenol	5.9	137.9	CH	5.93 – 5.82 (m, 1H)	137.04
CH2CO	5.07	47.6	CH2	5.18 (s, 2H)	47.03
Eugeno-CH=CH2	5.06, 5.04	111.8	CH2	5.08 – 4.98 (m, 2H)	112.79
CH2-LINKER	4.9	60	CH2	4.95 (s, 2H)	61.55
OCH3Eugenol	3.8	55.8	CH3	3.73 (s, 3H)	55.85
6	3.44	29.92	CH3	3.53 (s, 3H)	29.92
CH2-CH=eugenol	3.29	39.9	CH2	3.36 – 3.27 (m, 2H)	40.07
7	3.20	27.9	CH3	3.30 (s, 3H)	27.94
CO-LINKER	--	165.6	C	--	165.38
1	-	154.3	C	--	155.31
2	--	151.13	C	--	151.63
3	--	148.36	C	--	150.50
1[1]	--	146.6	C	--	148.47
2’	--	144.03	C	--	141.95
5’	--	131.94	C	--	136.85
5	--	106.83	C	--	107.06



^{1}H NMR spectrum of compound 6d

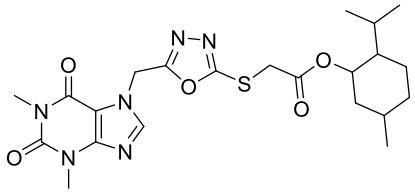


^{13}C NMR spectrum of compound 6d

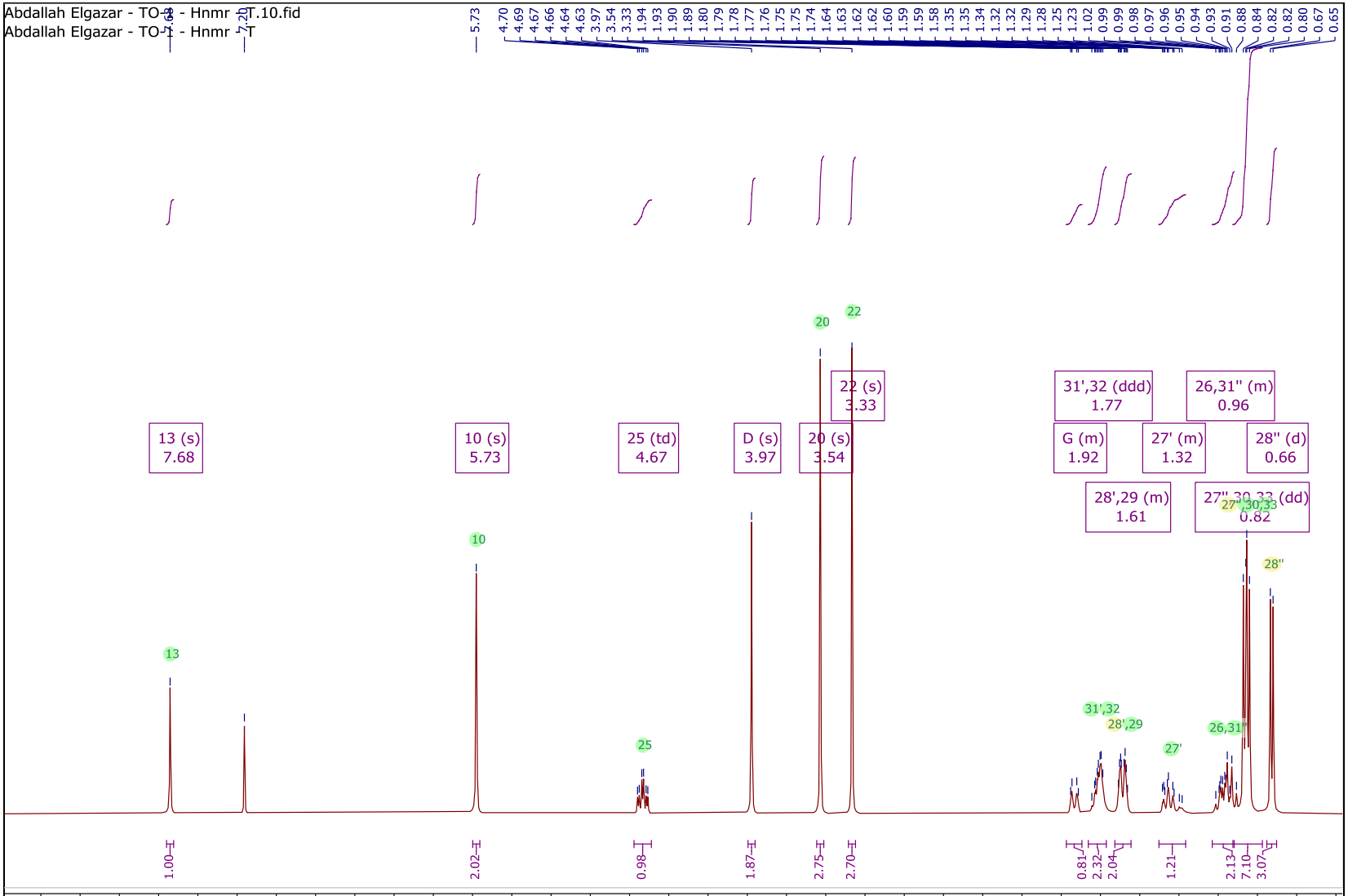


Mass spectrum of compound 6d

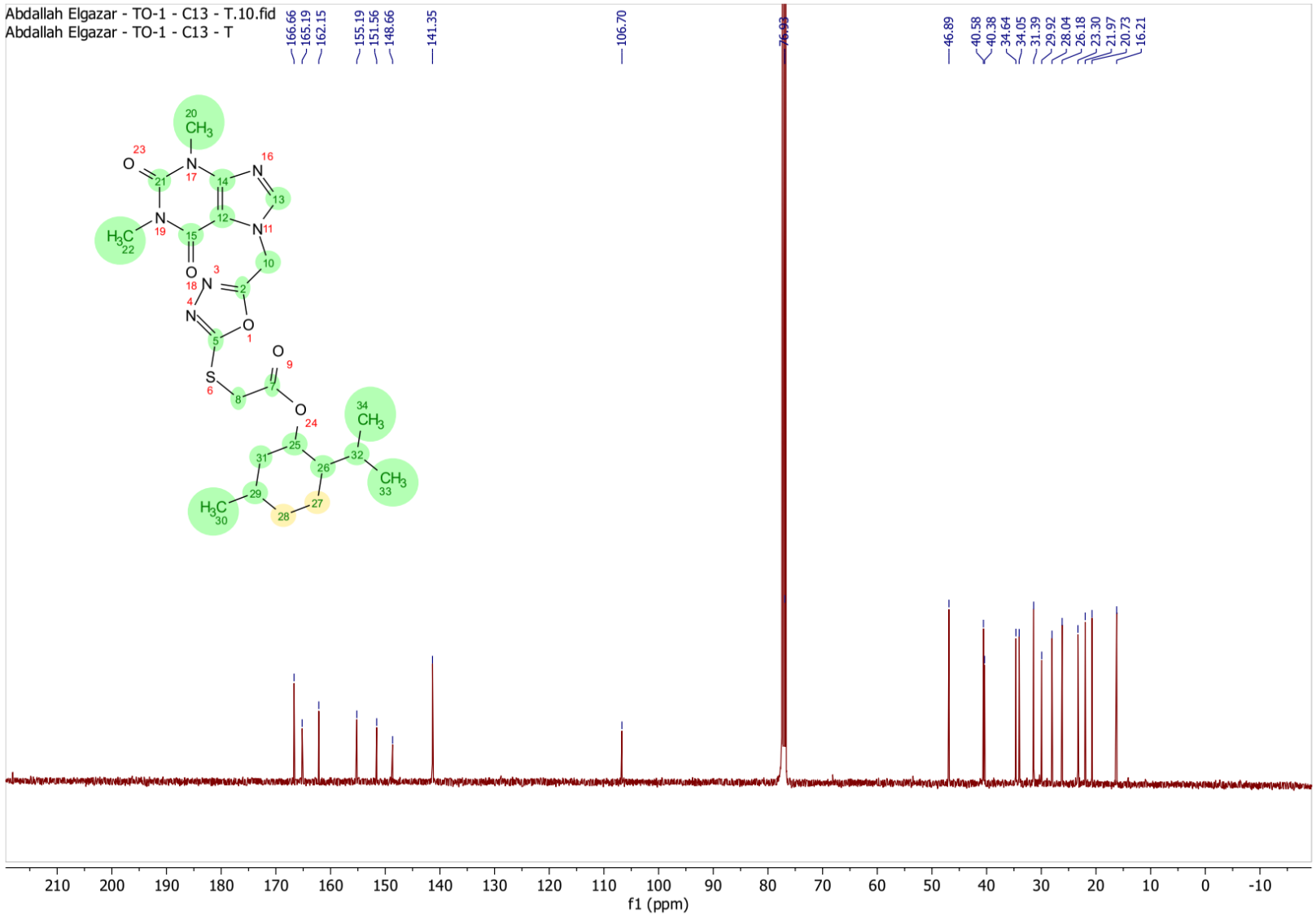
Table.s9 NMR assignment of acefylline-oxadiazole-menthol hybrid 9a



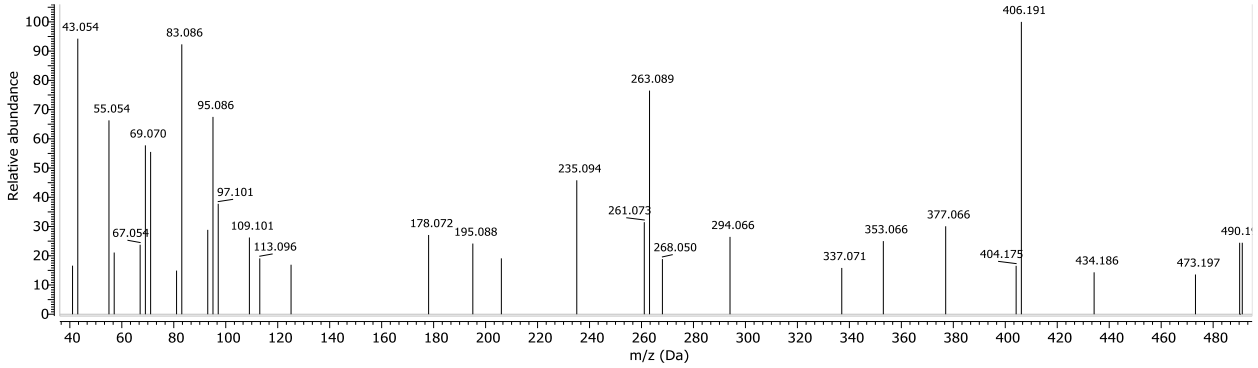
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ, ppm) (J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
7’	1.35	--	--	--	--
14’	0.8	16	CH3	0.66 (d, *J* = 6.9 Hz, 3H)	16.21
11’	0.92	21	CH3	0.82 (dd, *J* = 9.0, 6.7 Hz, 3H)	20.73
12’	0.91	22.2	CH3	0.82 (dd, *J* = 9.0, 6.7 Hz, 3H)	21.97
5’	1.61	23.1	CH	1.66 – 1.56 (m, 1H)	23.30
9’	0.97	23.1	CH	1.04 – 0.90 (m, 1H)	23.30
2’	2.17	25.8	CH	1.97 – 1.87 (m, 1H)	26.18
7	3.20	27.9	CH3	3.33 (s, 3H)	28.04
6	3.44	29.92	CH3	3.54 (s, 3H)	29.92
6’	1.43	31.6	CH	1.66 – 1.56 (m, 1H)	31.39
4’	1.66	34.5	CH	1.77 (ddd, *J* = 11.3, 8.4, 5.7 Hz, 1H)	34.05
13’	0.84	34.52	CH	0.82 (dd, *J* = 9.0, 6.7 Hz, 1H)	34.05
CH2LINKER	4.9	38	CH2	3.97 (s, 2H)	34.64
3’	1.9	45	CH	1.77 (ddd, *J* = 11.3, 8.4, 5.7 Hz, 1H)	40.38
10’	0.95	45	CH	1.04 – 0.90 (m, 1H)	40.38
CH2CO	5.07	43	CH2	5.73 (s, 2H)	40.58
8’	1.1	50.12	CH	1.38 – 1.21 (m, 1H)	46.89
1’	3.4 td, (j=10.4,4.3)	71.5	CH	4.67 (td, *J* = 10.9, 4.4 Hz, 1H)	76.93
5	--	106.83	C	--	106.70
4	8.04	143.63	CH	7.68 (s, 1H)	141.35
3	--	148.36	C	--	148.66
2	--	151.13	C	--	151.56
1	-	154.3	C	--	155.19
S-C=N	--	164	C	--	162.15
C=O-Linker	--	165.6	C		165.19
CH2-C=N	--	163	C	---	166.68



^{1}H NMR spectrum of compound 9a

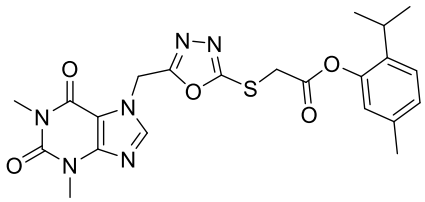


^{13}C NMR spectrum of compound 9a

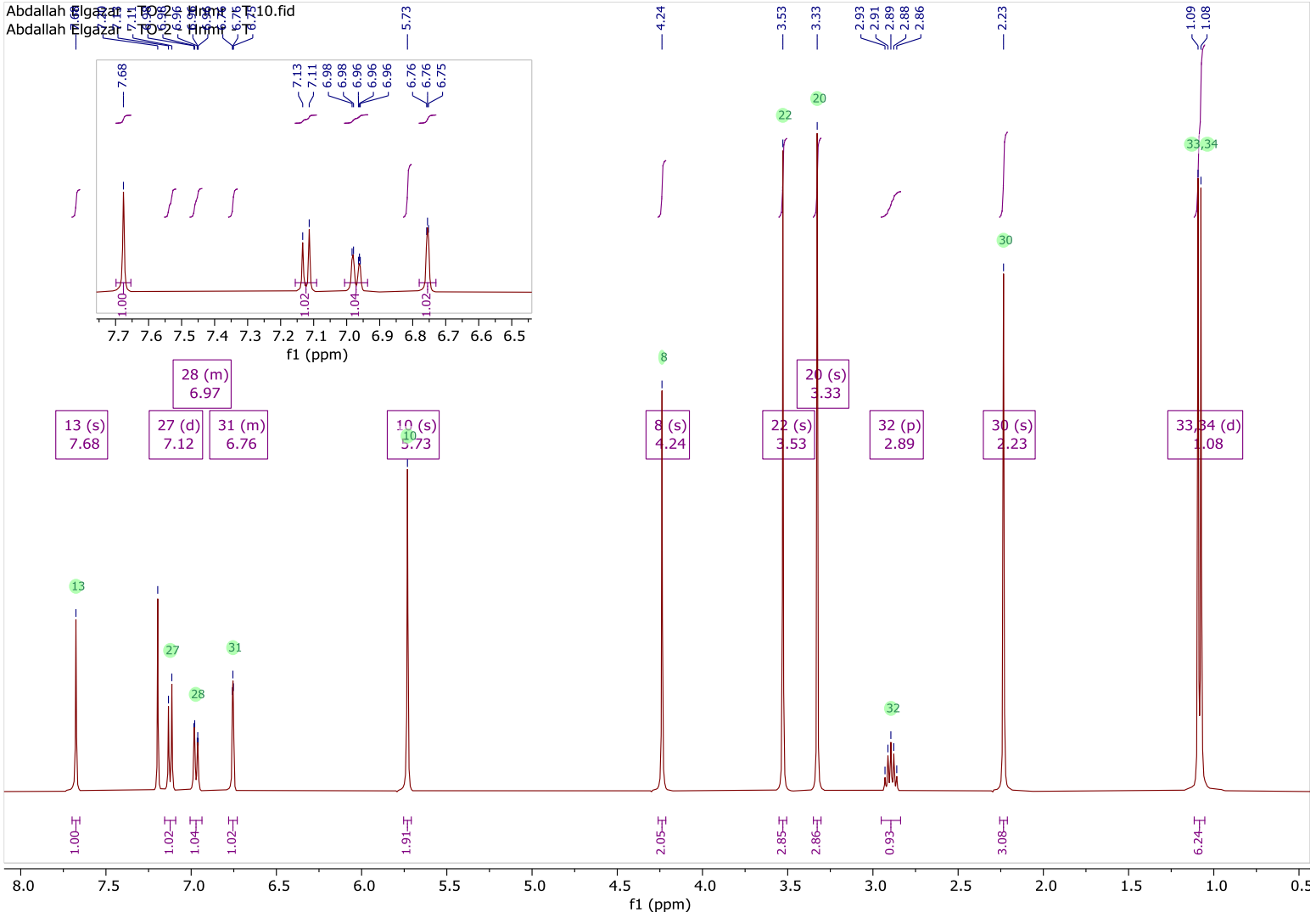


Mass spectrum of compound 9a

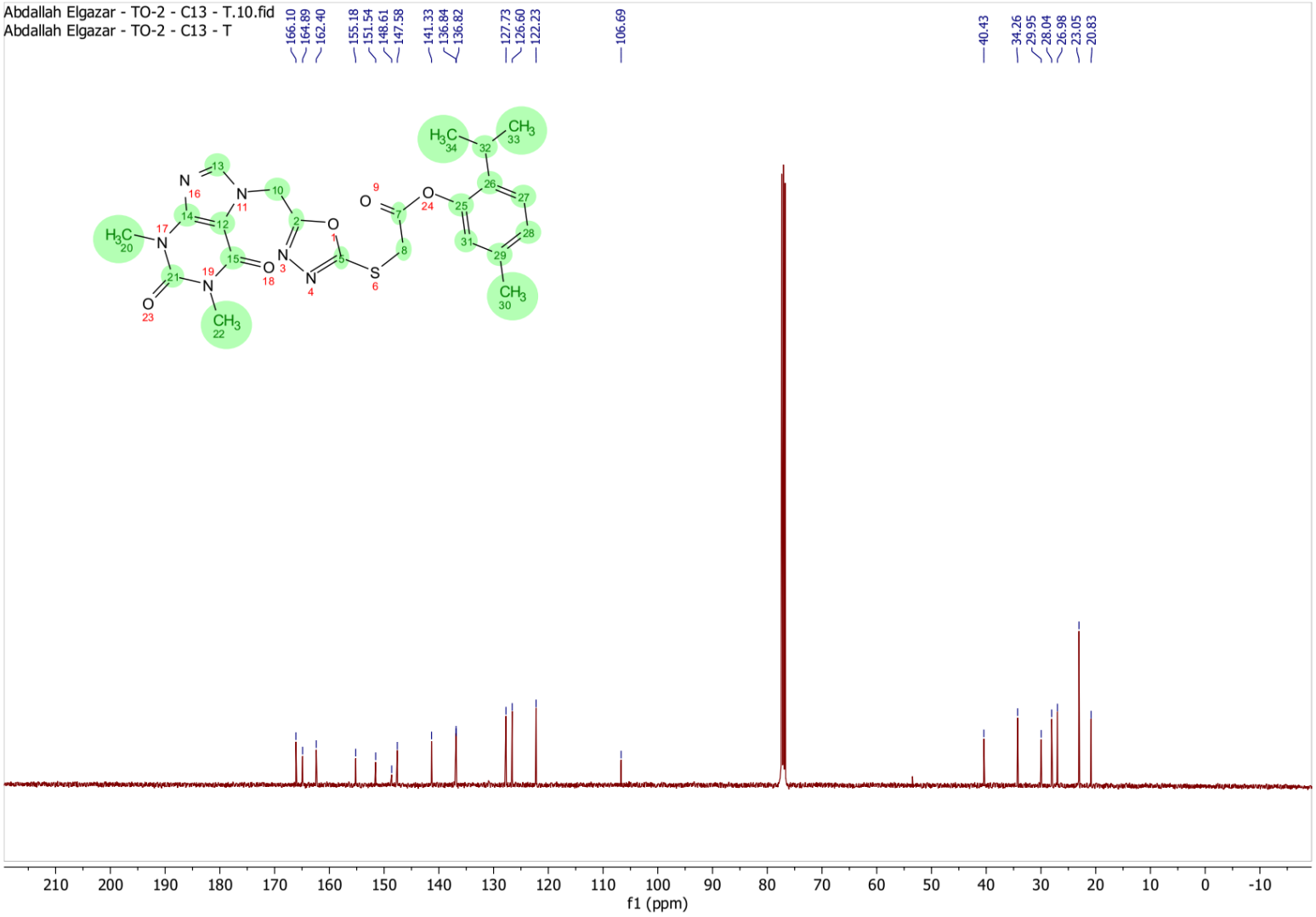
Table.s10 NMR assignment of acefylline-oxadiazole-thymol hybrid 9b



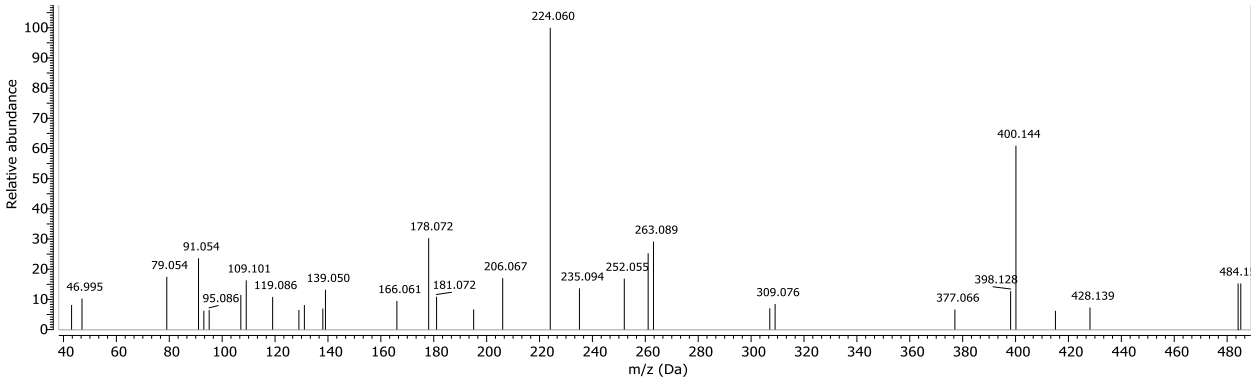
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ, ppm) (J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
C=N	--	164	C	--	166.10
CO-LINKER	--	165.6	C	--	164.89
C=N-S	--	163	C	--	162.40
1	-	154.3	C	--	155.18
2	--	151.13	C	--	151.54
1[1]	-	150.2	C	--	148.61
3	--	148.36	C	--	147.58
4	8.04	143.63	CH	7.68 (s, 1H)	141.33
3’	-	138.4	C	--	136.84
6’	--	131.7	C	--	136.82
4’	7.08	126.3	CH	7.12 (d, *J* = 7.9 Hz, 1H)	127.73
5’	7.08	126.3	CH	7.01 – 6.94 (m, 1H)	126.60
2’	5.4	116.9	CH	6.78 – 6.73 (m, 1H)	122.23
5	--	106.83	C	--	106.69
CH2-LINKER	4.9	43	CH2	4.24 (s, 2H)	40.43
CH2CO	5.07	38	CH2	5.73 (s, 2H)	34.26
6	3.44	29.92	CH3	3.53 (s, 3H)	29.95
7	3.20	27.9	CH3	3.33 (s, 3H)	28.04
8’	1.05	26.1	CH3	1.08 (d, *J* = 6.9 Hz, 3H)	26.98
9’	1.05	26.1	CH3	1.08 (d, *J* = 6.9 Hz, 3H)	26.98
7’	3.38	25.5	CH	2.89 (p, *J* = 6.9 Hz, 1H)	23.05
10’	2.2	18.7	CH3	2.23 (s, 3H)	20.83



^{1}H NMR spectrum of compound 9b

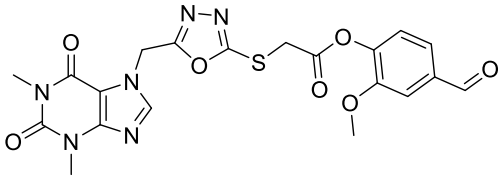


^{13}C NMR spectrum of compound 9b

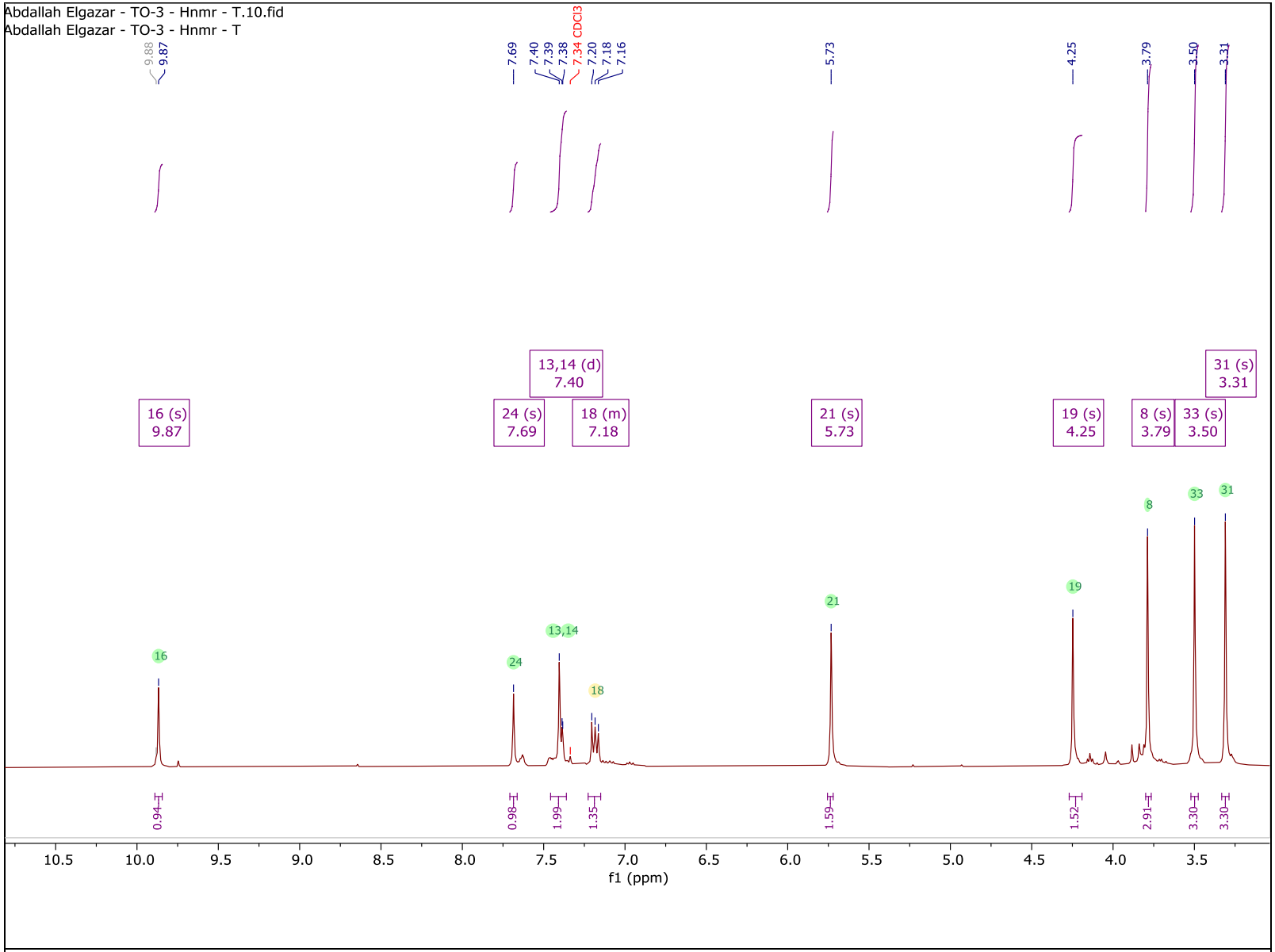


Mass spectrum of compound 9b

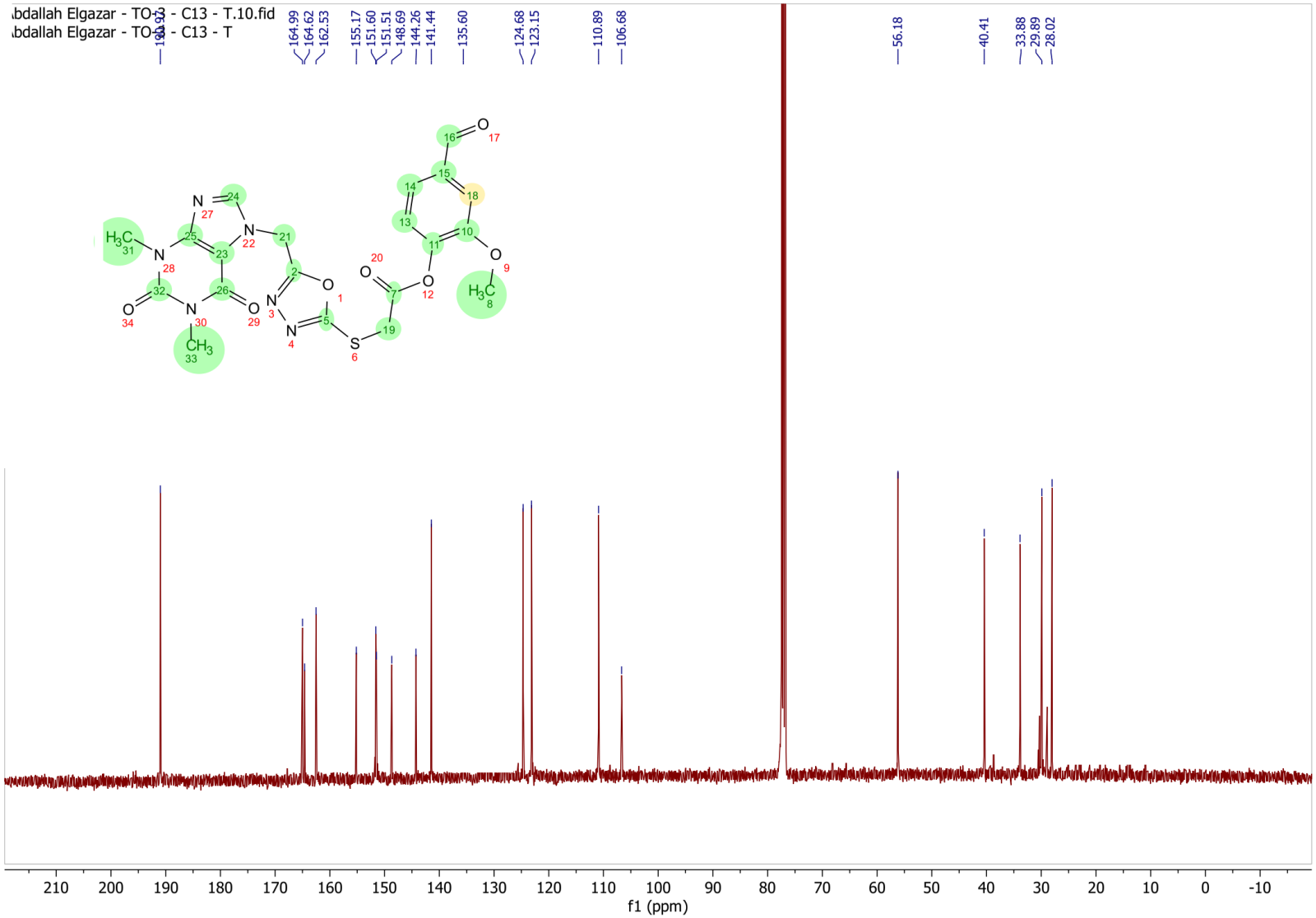
Table.s11 NMR assignment of acefylline-oxadiazole-vanillin hybrid 9c



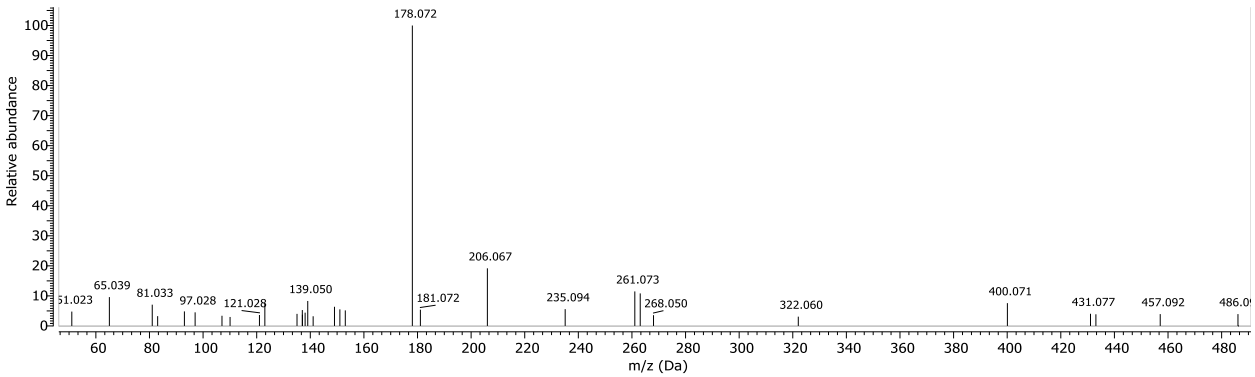
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ, ppm) (J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
HC=O	10.11	191.2	CH	9.87 (s, 1H)	190.97
CO-LINKER	--	165.6	C	--	164.99
C=N	--	164	C	--	164.62
C=N-S	--	163	C	--	162.53
1	-	154.3	C	-	155.17
4’	-	152.18	C	--	151.60
2	--	151.13	C	--	151.51
3	--	148.36	C	--	148.69
3’	--	147.5	C	--	144.26
4	8.04	143.63	CH	7.69 (s, 1H)	141.44
1[1]	--	129.77	C	--	135.60
6’	6.9d(J=7.5)	127.49	CH	7.23 – 7.15 (m, 1H)	124.68
2’	7.3 d(J=1.50)	109.14	CH	7.40 (d, *J* = 6.9 Hz, 1H)	110.89
5’	7.2	114.75	CH	7.40 (d, *J* = 6.9 Hz, 1H)	123.15
5	--	106.83	C	--	106.68
OCH3vanillin	3.84	56.2	CH3	3.79 (s, 3H)	56.18
CH2CO	5.07	43	CH2	5.73 (s, 2H)	40.41
CH2LINKER	4.9	38	CH2	4.25 (s, 2H)	33.88
6	3.44	29.92	CH3	3.50 (s, 3H)	29.89
7	3.20	27.9	CH3	3.31 (s, 3H)	28.02



^{1}H NMR spectrum of compound 9c

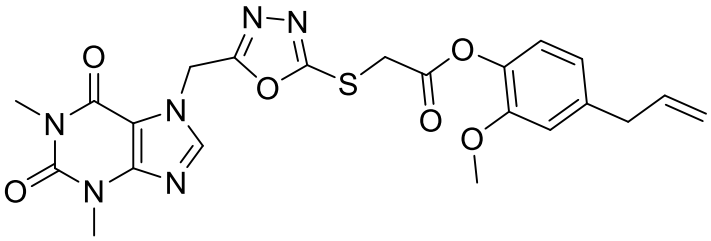


^{13}C NMR spectrum of compound 9c

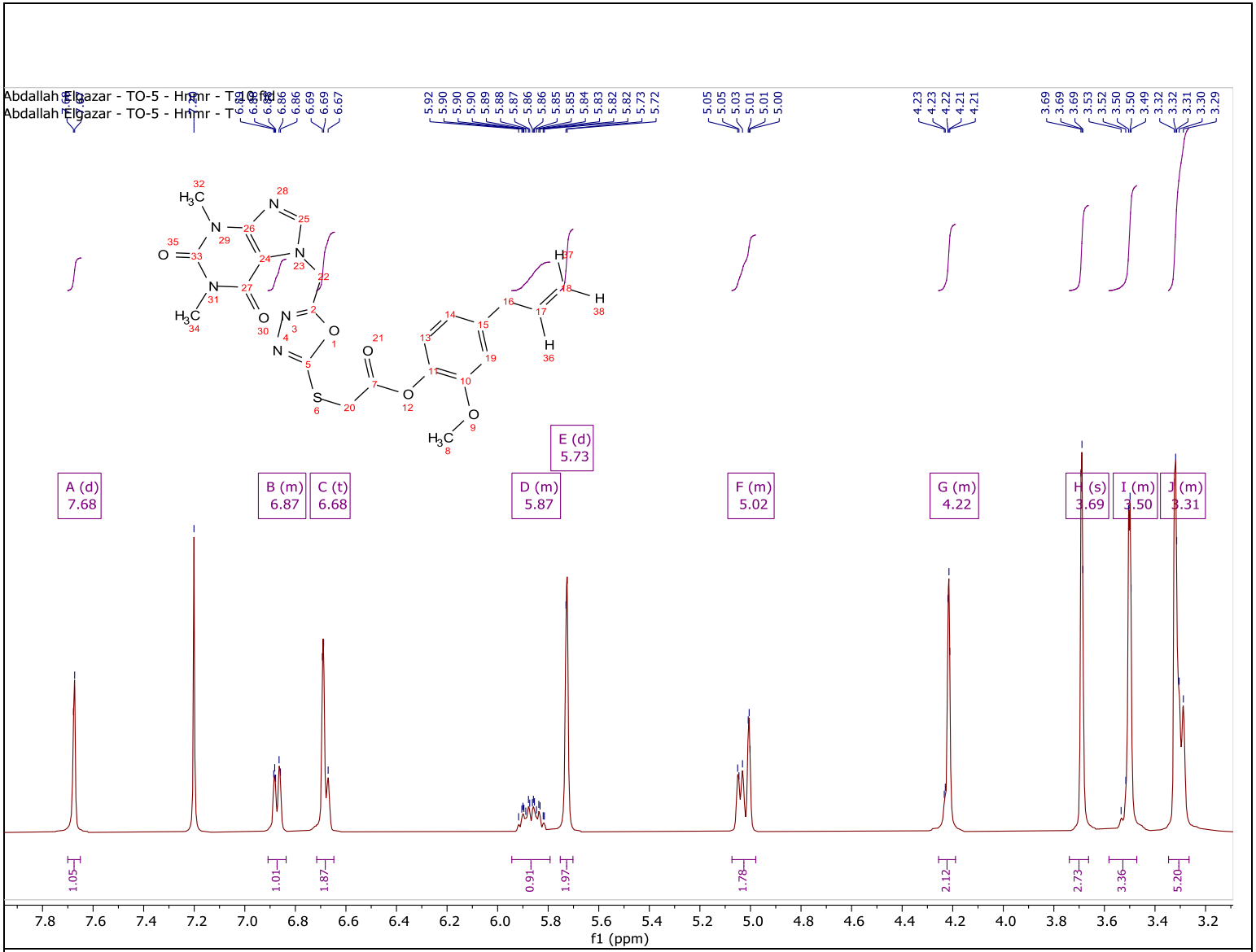


Mass spectrum of compound 9c

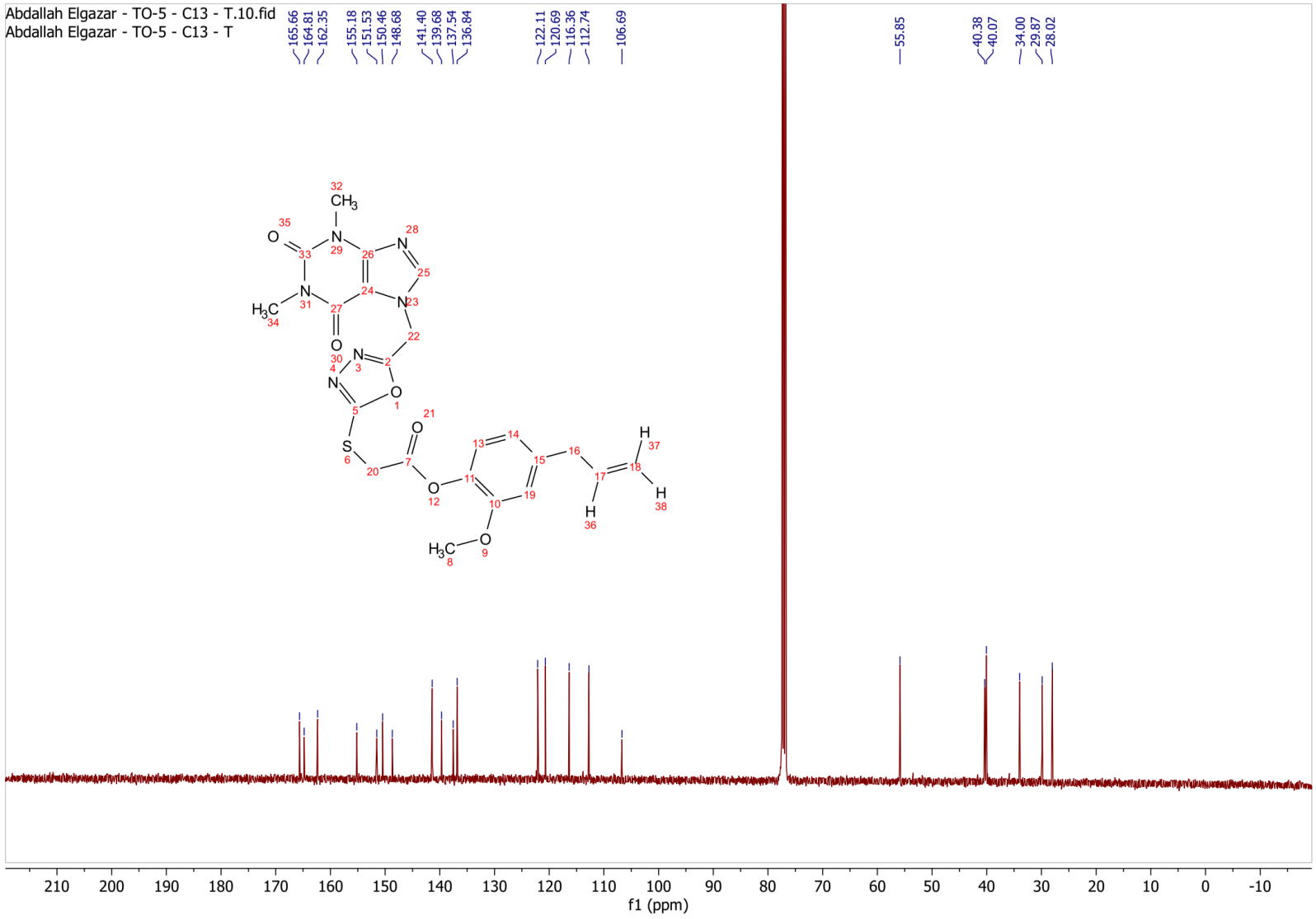
Table.s12 NMR assignment of ACEFYLLINE-oxadiazole-eugenol hybrid 9d



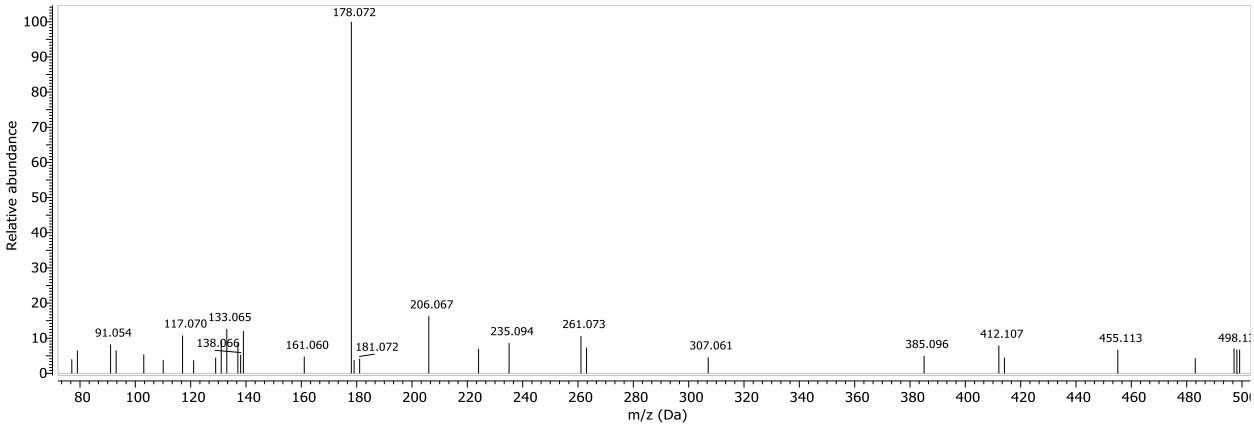
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ, ppm) (J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
CO-LINKER	--	165.6	C	--	165.66
C=N	--	164	C	--	164.81
C=N-S	--	163	C	--	162.35
1	-	154.3	C	--	155.18
2	--	151.13	C	--	151.53
3	--	148.36	C	--	150.46
1[1]	--	146.6	C	--	148.68
2’	--	144.03	C	--	141.40
4	8.04	143.63	CH	7.68 (d, *J* = 1.9 Hz, 1H)	139.68
-CH=eugenol	5.9	137.9	CH	5.94 – 5.79 (m, 1H)	137.54
5’	--	131.94	C	--	136.84
4’	6.67	121.2	CH	6.68 (t, *J* = 4.6 Hz, 1H)	122.11
3’	6.82	115.49	CH	6.91 – 6.84 (m, 1H)	120.69
6’	6.66	114.46	CH	6.68 (t, *J* = 4.6 Hz, 1H)	116.36
EugenolCH=CH2	5.06, 5.04	111.8	CH2	5.07 – 4.98 (m, 2H)	112.74
5	--	106.83	C	--	106.69
OCH3Eugenol	3.8	55.8	CH3	3.69 (s, 3H)	55.85
CH2CO	5.07	43	CH2	5.73 (d, *J* = 2.1 Hz, 2H)	40.38
CH2-CH= eugenol	3.29	39.9	CH2	3.35 – 3.27 (m, 2H)	40.07
CH2-LINKER	4.9	38	CH2	4.26 – 4.19 (m, 2H)	34.00
6	3.44	29.92	CH3	3.58 – 3.47 (m, 3H)	29.87
7	3.20	27.9	CH3	3.35 – 3.27 (m, 3H)	28.02



^{1}H NMR spectrum of compound 9d

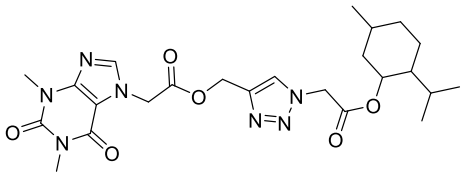


^{13}C NMR spectrum of compound 9d

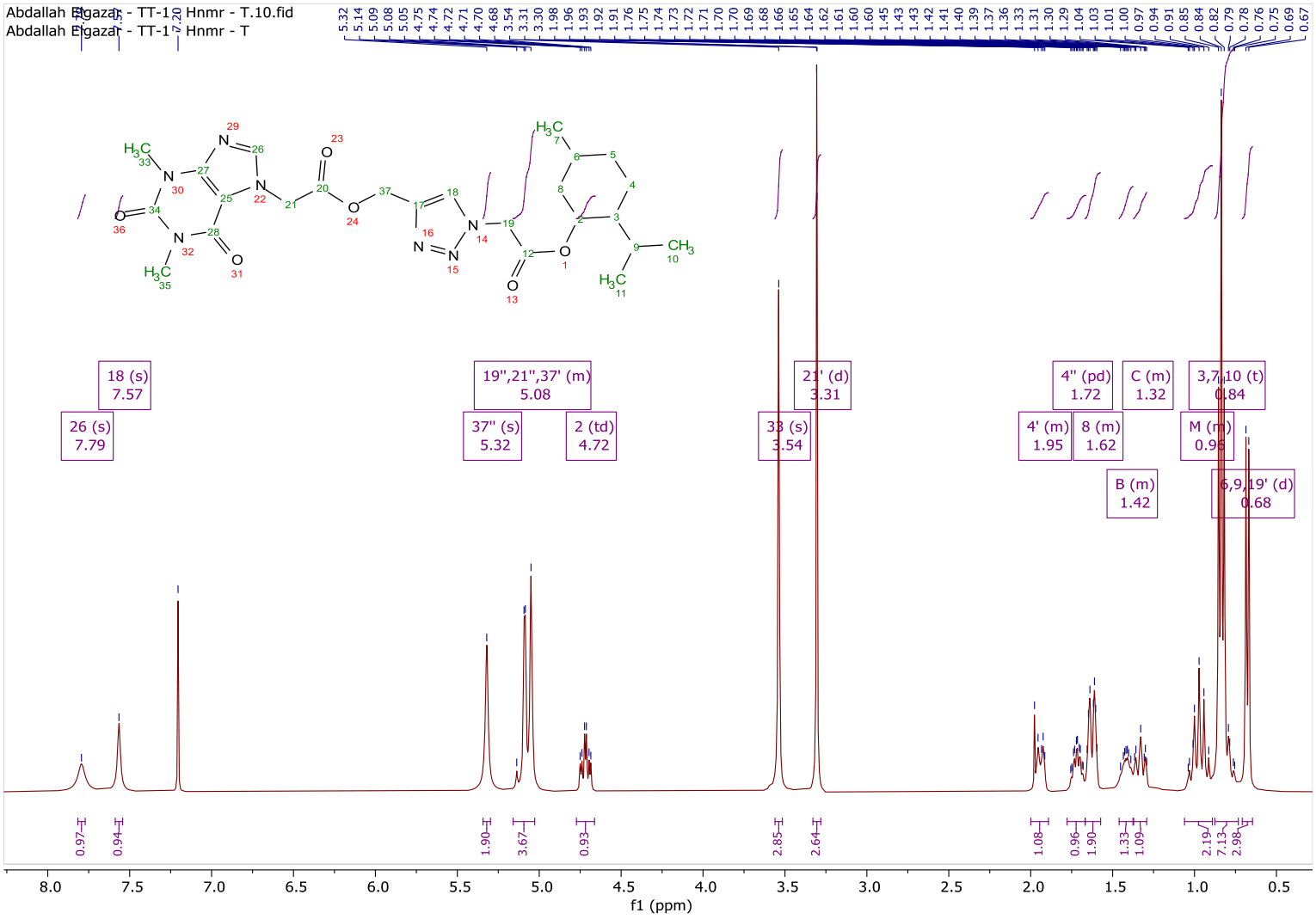


Mass spectrum of compound 9d

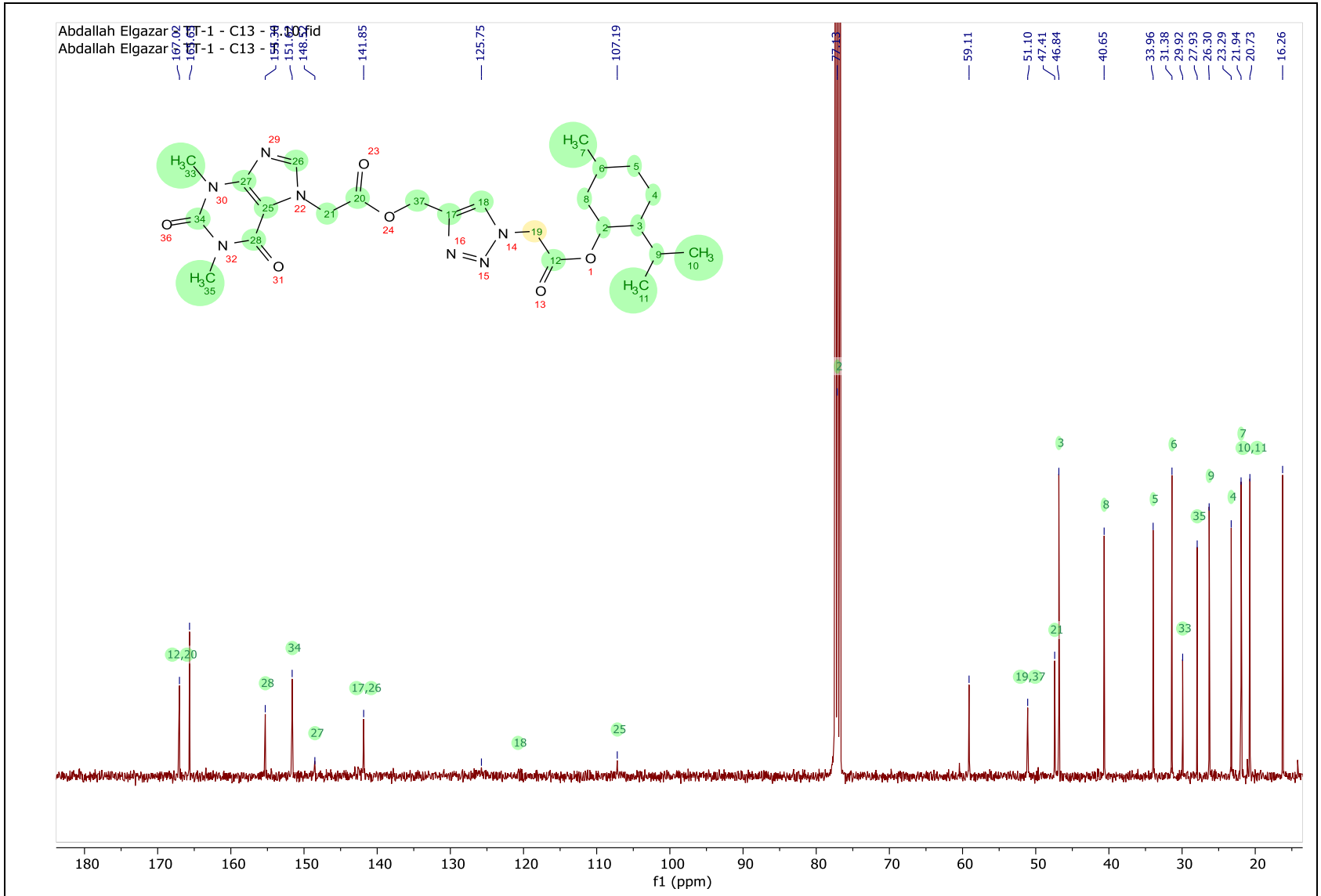
Table.s13 NMR assignment of acefylline-triazole-menthol hybrid 15a



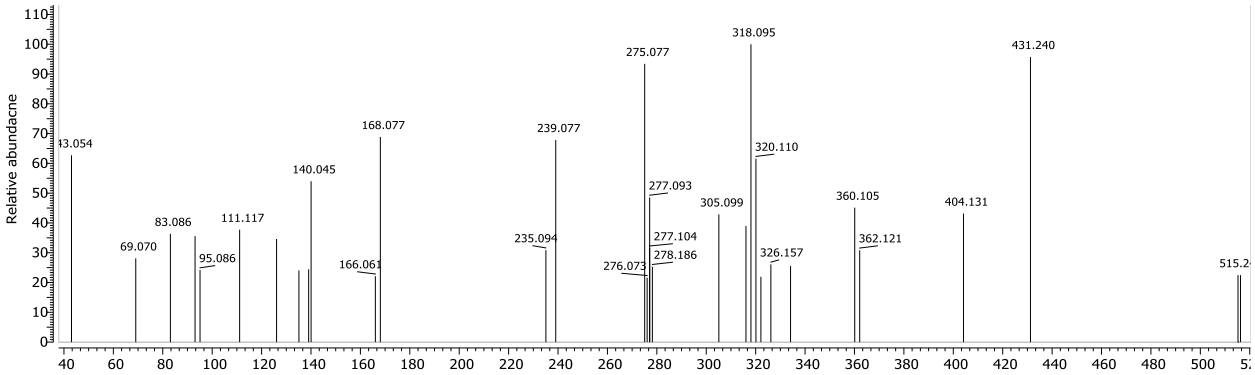
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
COO	--	169.48	C	--	167.02
C=O-Linker	--	165.6	C	--	165.65
1	-	154.3	C	--	155.30
2	--	151.13	C	--	151.62
3	--	148.36	C	--	148.52
4	8.04	143.63	CH	7.57 (s, 1H)	141.85
C=C TRIAZOLE	--	142	C	--	141.85
CH=C-TRIAZOLE	8	122	CH	7.79 (s, 1H)	125.75
5	--	106.83	C	--	107.19
1’	3.4,td,(j=10.4,4.3)	71.5	CH	4.72 (td, *J* = 10.9, 4.4 Hz, 1H)	77.13
CH2-C=	5.23	60	CH2	5.32 (s, 2H)	59.11
8’	1.1	50.12	CH	1.37 – 1.29 (m, 1H)	51.10
CH2CO	5.07	47.6	CH2	5.16 – 5.03 (m, 2H)	47.41
CH2-LINKER	4.9	50	CH2	5.16 – 5.03 (m, 2H)	46.84
3’	1.9	45	CH	1.72 (pd, *J* = 6.9, 2.5 Hz, 1H)	40.65
10’	0.95	45	CH	1.06 – 0.89 (m, 1H)	40.65
4’	1.66	34.5	CH	1.67 – 1.57 (m, 1H)	33.96
13’	0.84	34.52	CH	0.84 (t, *J* = 7.0 Hz, 1H)	33.96
6’	1.43	31.6	CH	1.46 – 1.38 (m, 1H)	31.38
6	3.44	29.92	CH3	3.54 (s, 3H)	29.92
7	3.20	27.9	CH3	3.31 (d, *J* = 1.1 Hz, 3H)	27.93
2’	2.17	25.8	CH	2.00 – 1.89 (m, 1H)	26.30
5’	1.6	23.1	CH	1.67 – 1.57 (m, 1H)	23.29
9’	0.97	23.1	CH	1.06 – 0.89 (m, 1H)	23.29
12’	0.91	22.2	CH3	0.84 (t, *J* = 7.0 Hz, 3H)	21.94
11’	0.92	21	CH3	0.84 (t, *J* = 7.0 Hz, 3H)	20.73
14’	0.8	16	CH3	0.68 (d, *J* = 6.9 Hz, 3H)	16.26
7’	1.35	--	--	--	--



^{1}H NMR spectrum of compound 15a

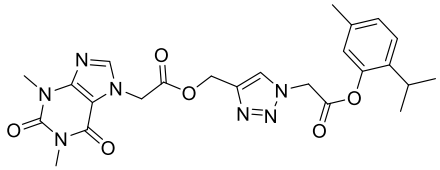


^{13}C NMR spectrum of compound 15a

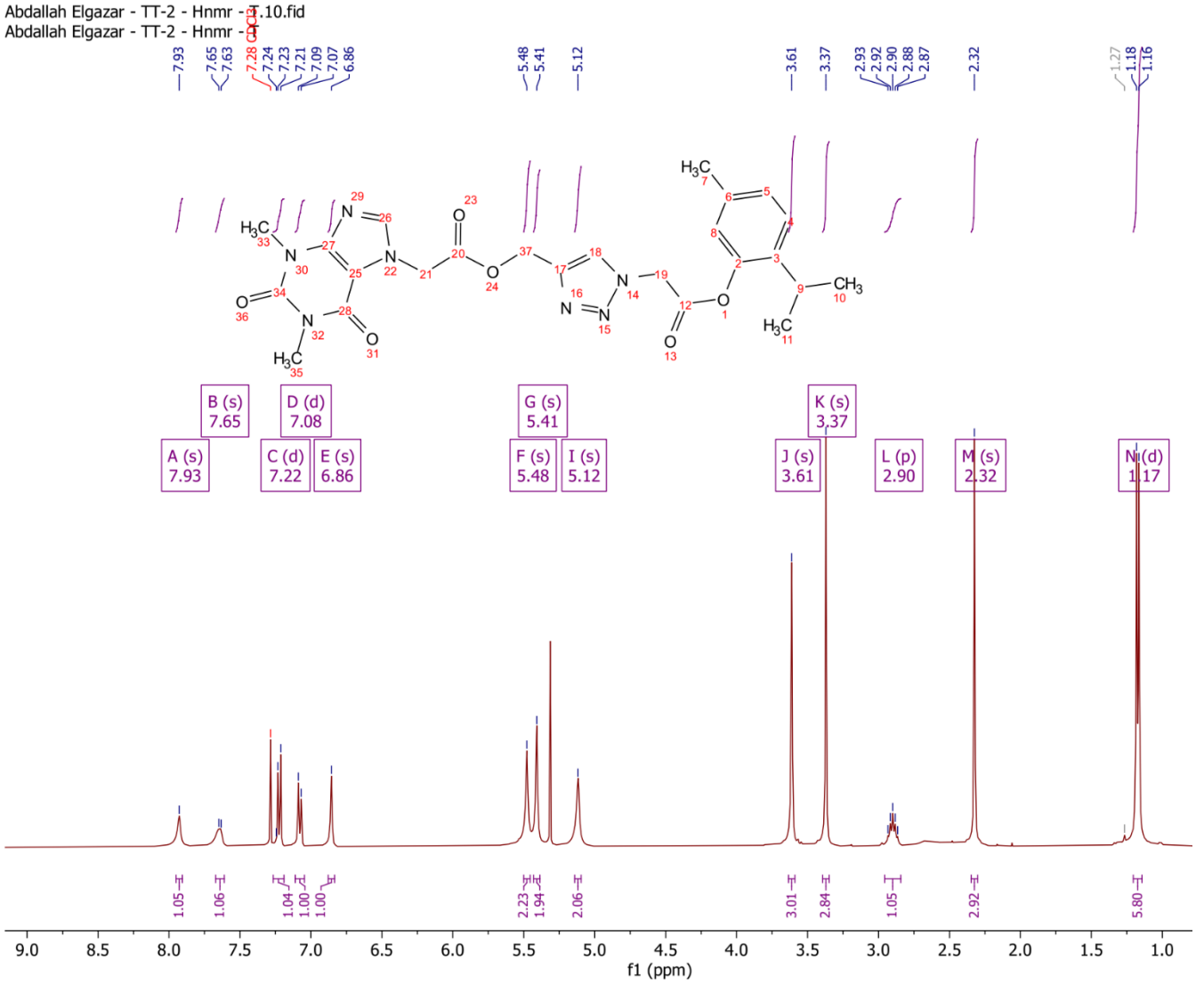


Mass spectrum of compound 15a

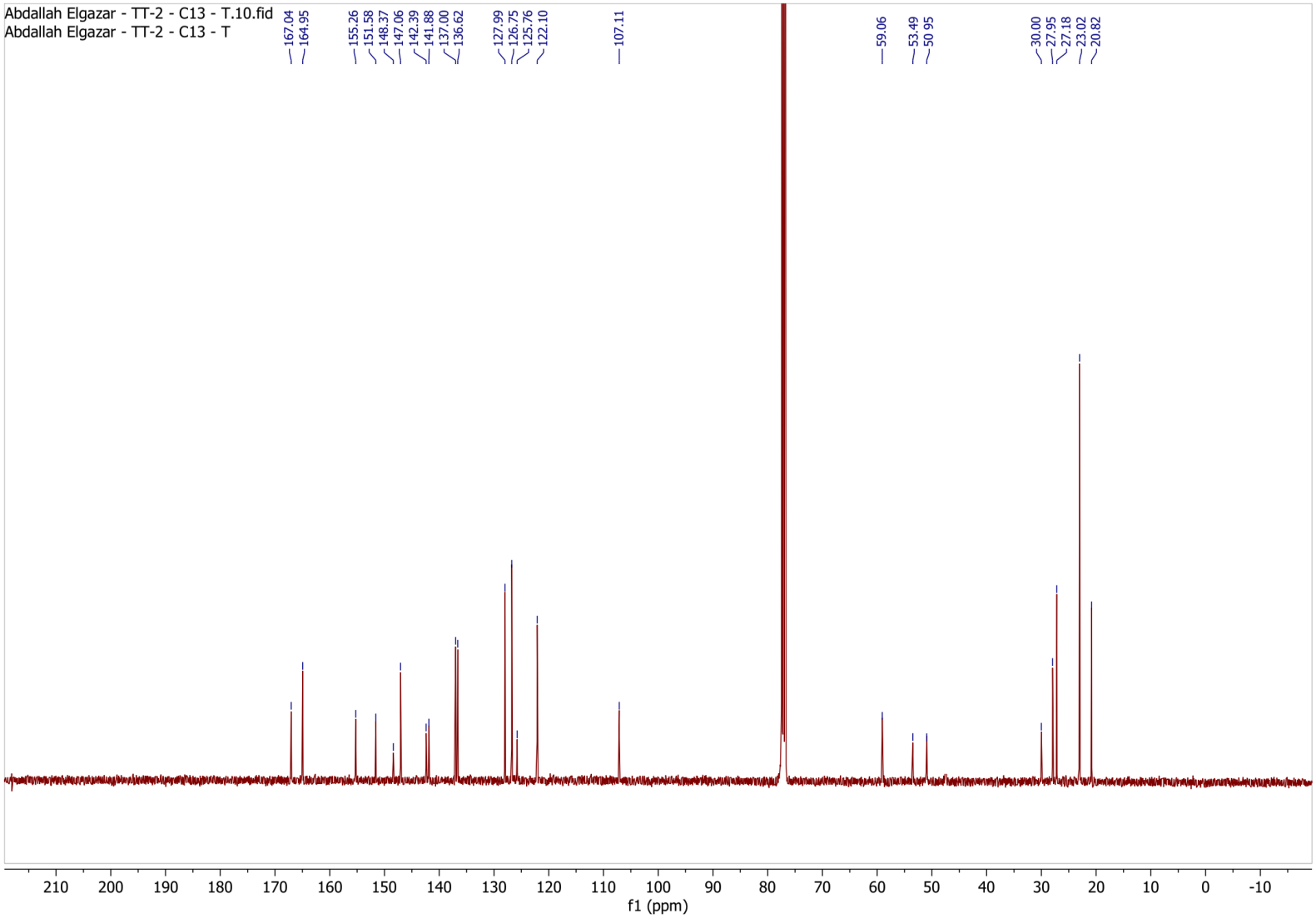
Table.s14 NMR assignment of acefylline-triazole-thymol hybrid 15b



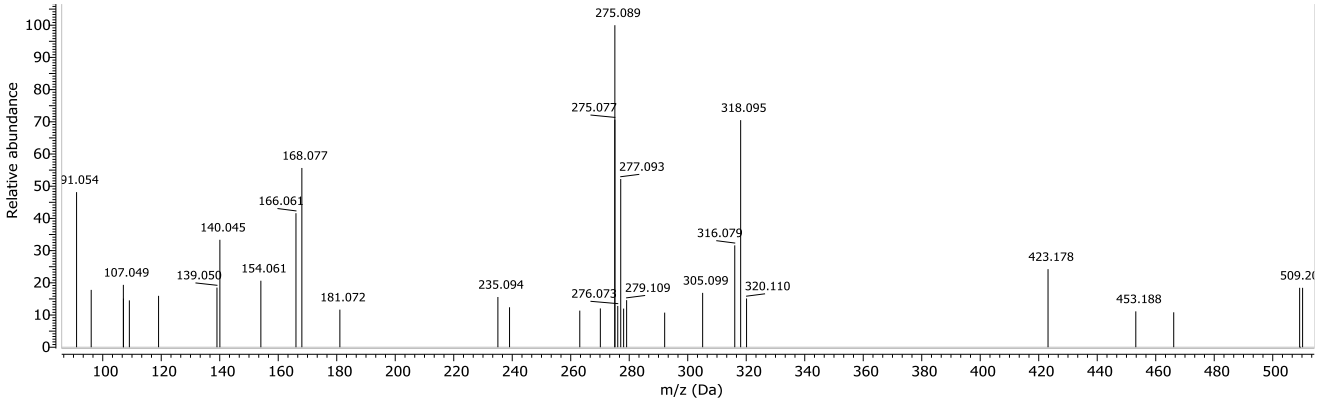
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
COO	10	169.48	C	--	167.04
CO-LINKER	--	165.6	C	--	164.95
1	-	154.3	C	--	155.26
2	--	151.13	C	--	151.58
1[1]	-	150.2	C	--	148.37
3	--	148.36	C	--	147.06
4	8.04	143.63	CH	7.65 (s, 1H)	142.39
C=CTRIAZOLE	--	142	C	--	141.88
3’	-	138.4	C	--	137.00
6’	--	131.7	C	--	136.62
4’	7.08	126.3	CH	7.22 (d, *J* = 7.9 Hz, 1H)	127.99
5’	7.08	126.3	CH	7.08 (d, *J* = 7.9 Hz, 1H)	126.75
CH=CTRIAZOLE	8	122	CH	7.93 (s, 1H)	125.76
2’	5.4	116.9	CH	6.86 (s, 1H)	122.10
5	--	106.83	C	--	107.11
CH2-C=	5.23	60	CH2	5.48 (s, 2H)	59.06
CH2-LINKER	4.9	50	CH2	5.12 (s, 2H)	53.49
CH2CO	5.07	47.6	CH2	5.41 (s, 2H)	50.95
6	3.44	29.92	CH3	3.61 (s, 3H)	30.00
7	3.20	27.9	CH3	3.37 (s, 3H)	27.95
7’	3.38	25.5	CH	2.90 (p, *J* = 6.9 Hz, 1H)	27.18
8’	1.05	26.1	CH3	1.17 (d, *J* = 6.8 Hz, 3H)	23.02
9’	1.05	26.1	CH3	1.17 (d, *J* = 6.8 Hz, 3H)	23.02
10’	2.2	18.7	CH3	2.32 (s, 3H)	20.82



^{1}H NMR spectrum of compound 15b

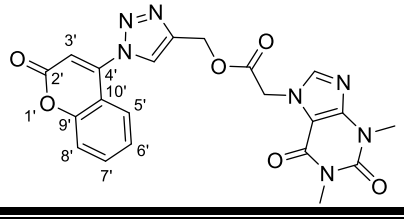


^{13}C NMR spectrum of compound 15b

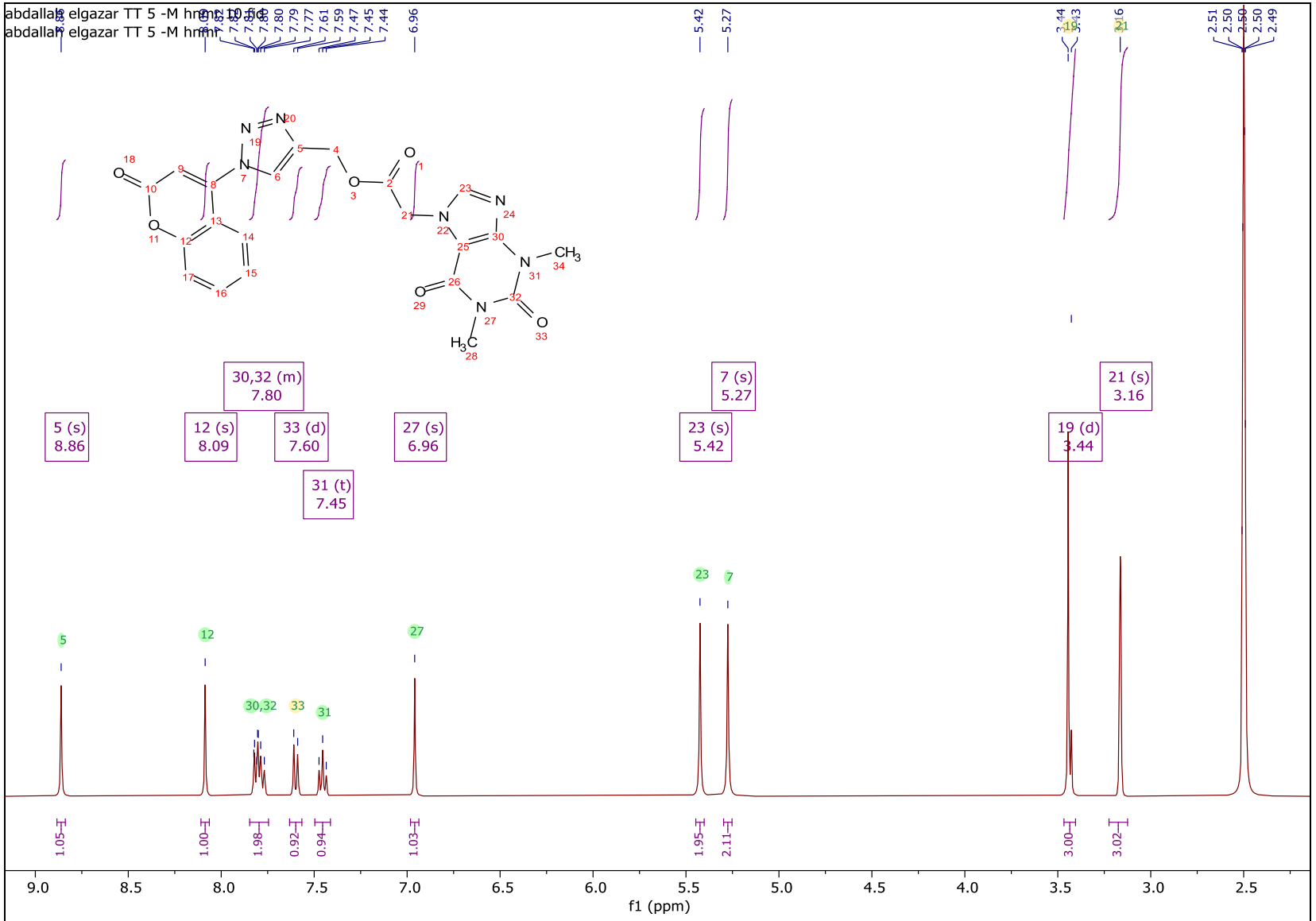


Mass spectrum of compound 15c

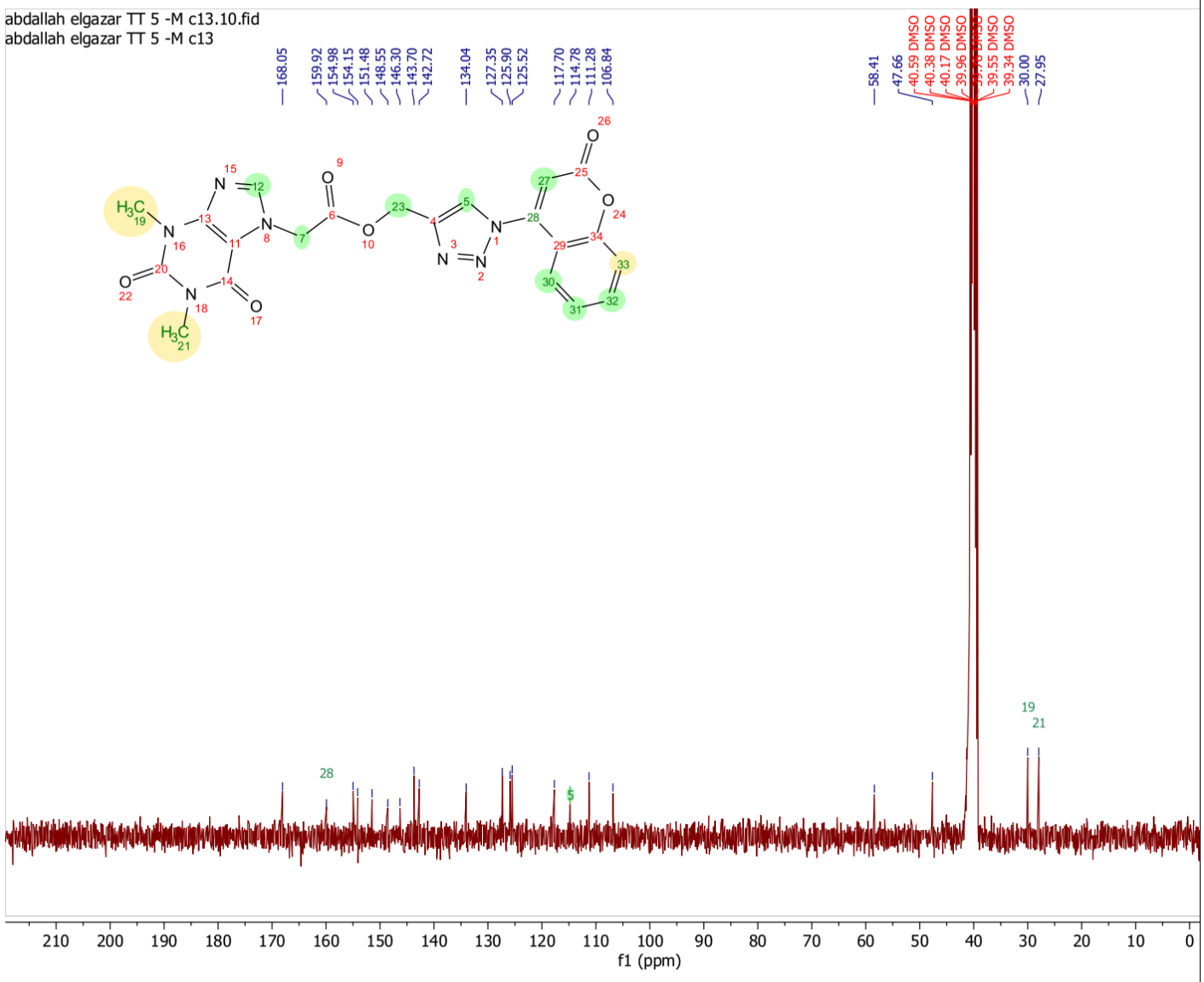
Table.s15 NMR assignment of acefylline-triazole-coumarin hybrid 15c



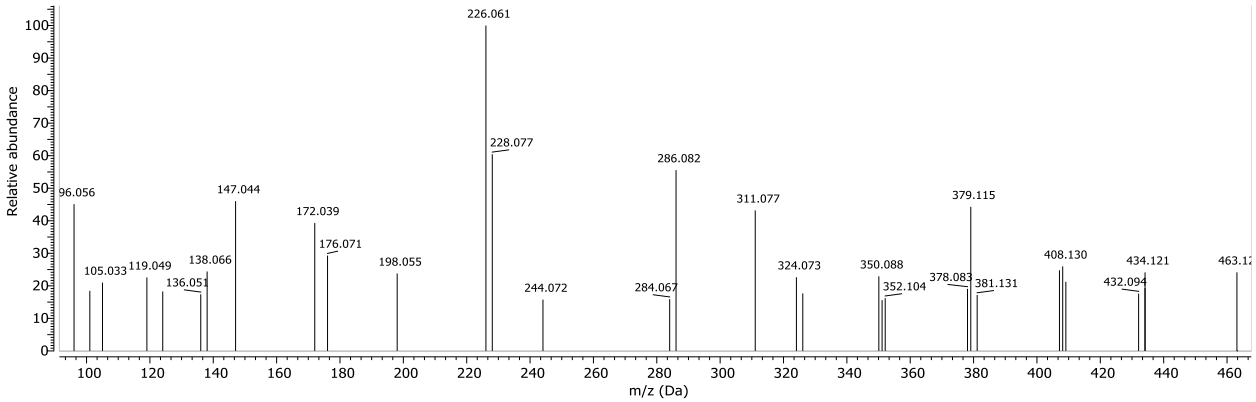
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
COOH	10	169.48	C	--	168.05
2’	--	166.1	C	--	159.92
4’	--	162.32	C	--	154.98
9’	--	153.98	C	--	151.48
2	--	151.13	C	--	148.55
3	--	148.36	C	--	146.30
4	8.04	143.63	CH	8.09 (s, 1H)	143.70
C=CTRIAOLE	--	142	C	--	142.72
7’	7.65 (d, *J* = 7.8 Hz, 1H)	133.17	CH	7.85 – 7.75 (m, 1H)	134.04
6’	7.38 7.34 (m, 1H)	124.39	CH	7.60 (d, *J* = 8.4 Hz, 1H)	127.35
5’	7.83 (d, *J* = 7.2 Hz, 1H)	123.66	CH	7.85 – 7.75 (m, 1H)	125.90
C=CHTRIAZOLE	8	122	CH	8.86 (s, 1H)	125.52
8’	7.38 7.34 (m, 1H)	116.7	CH	7.45 (t, *J* = 7.8 Hz, 1H)	117.70
10’	--	116.27	C	--	114.78
5	--	106.83	C	--	111.28
3’	5.60 (s, 1H)	91.46	CH	6.96 (s, 1H)	106.84
CH2-TRIAZOLE	5.23	60	CH2	5.42 (s, 2H)	58.41
CH2CO	5.07	47.6	CH2	5.27 (s, 2H)	47.68
6	3.44	29.92	CH3	3.44 (d, *J* = 6.8 Hz, 3H)	30.00
7	3.20	27.9	CH3	3.16 (s, 3H)	27.95



^{1}H NMR spectrum of compound 15c

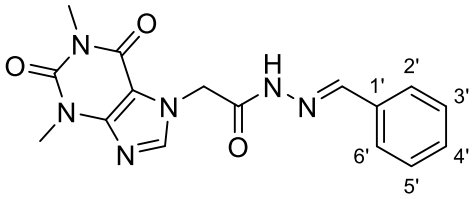


^{13}C NMR spectrum of compound 15c

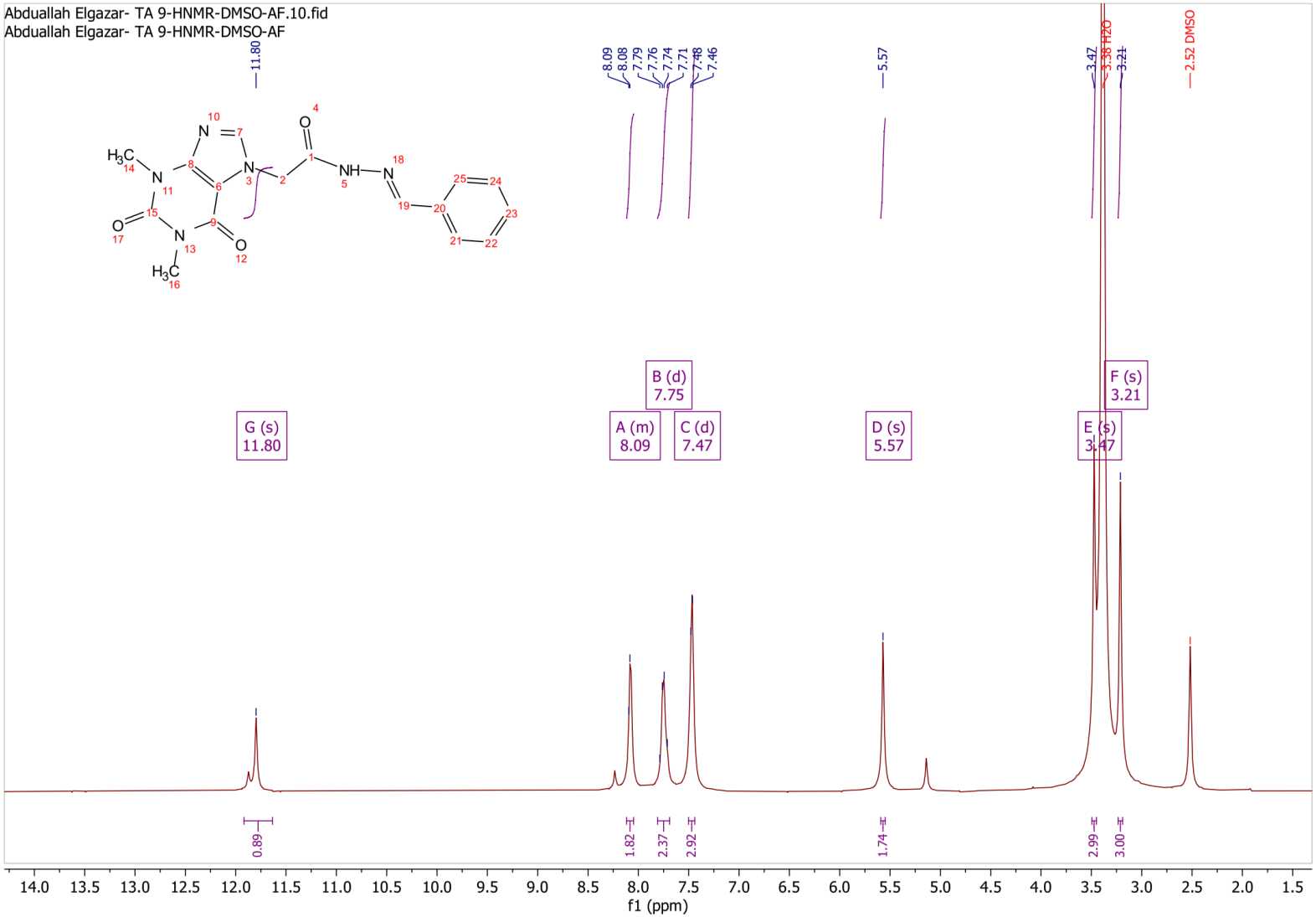


Mass spectrum of compound 15

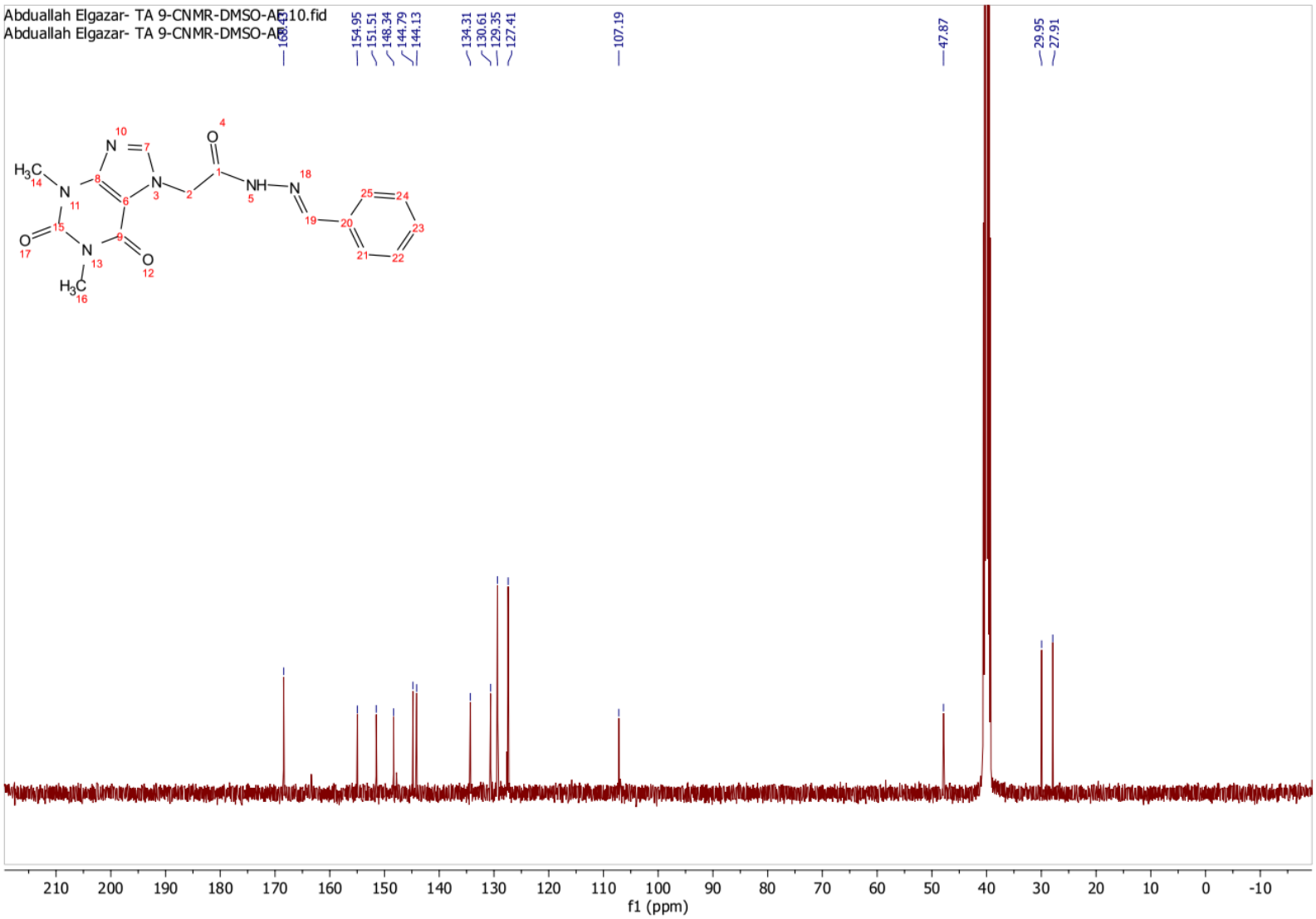
Table s16. NMR assignment of acefylline-hydrazone-benzaldehyde hybrid 18a



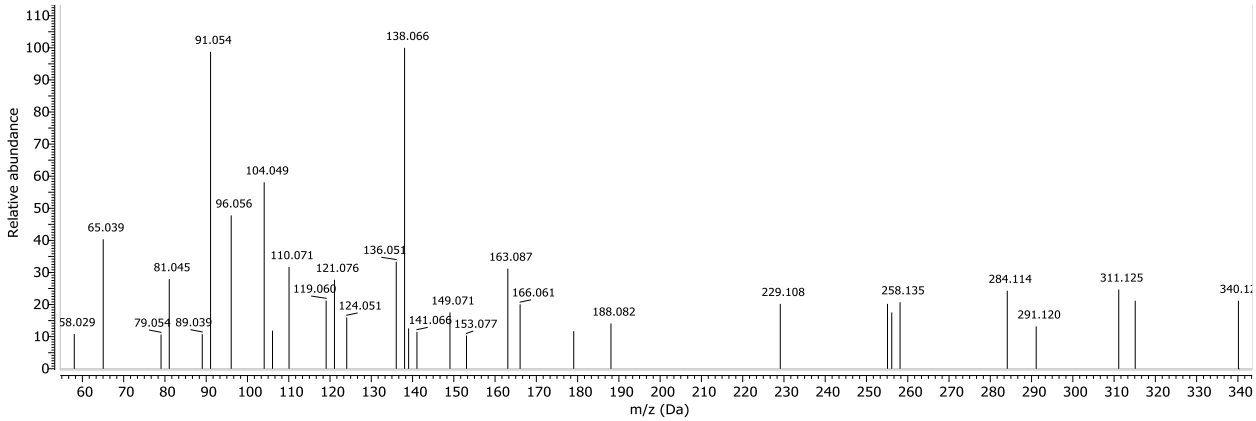
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
COOH	--	169.48	C	--	168.43
1	-	154.3	C	--	154.95
2	--	151.13	C	--	151.51
3	--	148.36	C	--	148.34
4	8.04	143.63	CH	8.12 – 8.05 (m, 1H)	144.79
CH=N	10.2	192.28	CH	8.12 – 8.05 (m, 1H)	144.13
1’	--	136.47	C	--	134.31
4’	7.64	134.43	CH	7.47 (d, *J* = 6.3 Hz, 1H)	130.61
2’	7.87	129.68	CH	7.75 (d, *J* = 7.0 Hz, 1H)	129.35
6’	7.87	129.68	CH	7.75 (d, *J* = 7.0 Hz, 1H)	129.35
5’	7.56	129.68	CH	7.47 (d, *J* = 6.3 Hz, 1H)	127.41
3’	7.56	128.98	CH	7.47 (d, *J* = 6.3 Hz, 1H)	127.41
5	--	106.83	C	--	107.19
CH2CO	5.07	47.6	CH2	5.57 (s, 2H)	47.87
6	3.44	29.92	CH3	3.47 (s, 3H)	29.95
7	3.20	27.9	CH3	3.21 (s, 3H)	27.91
NH	11.25	--	NH	11.80 (s, 1H)	--



^{1}H NMR spectrum of compound 18a

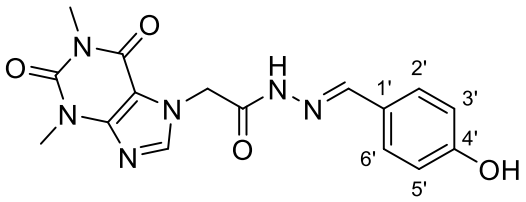


^{13}C NMR spectrum of compound 18a

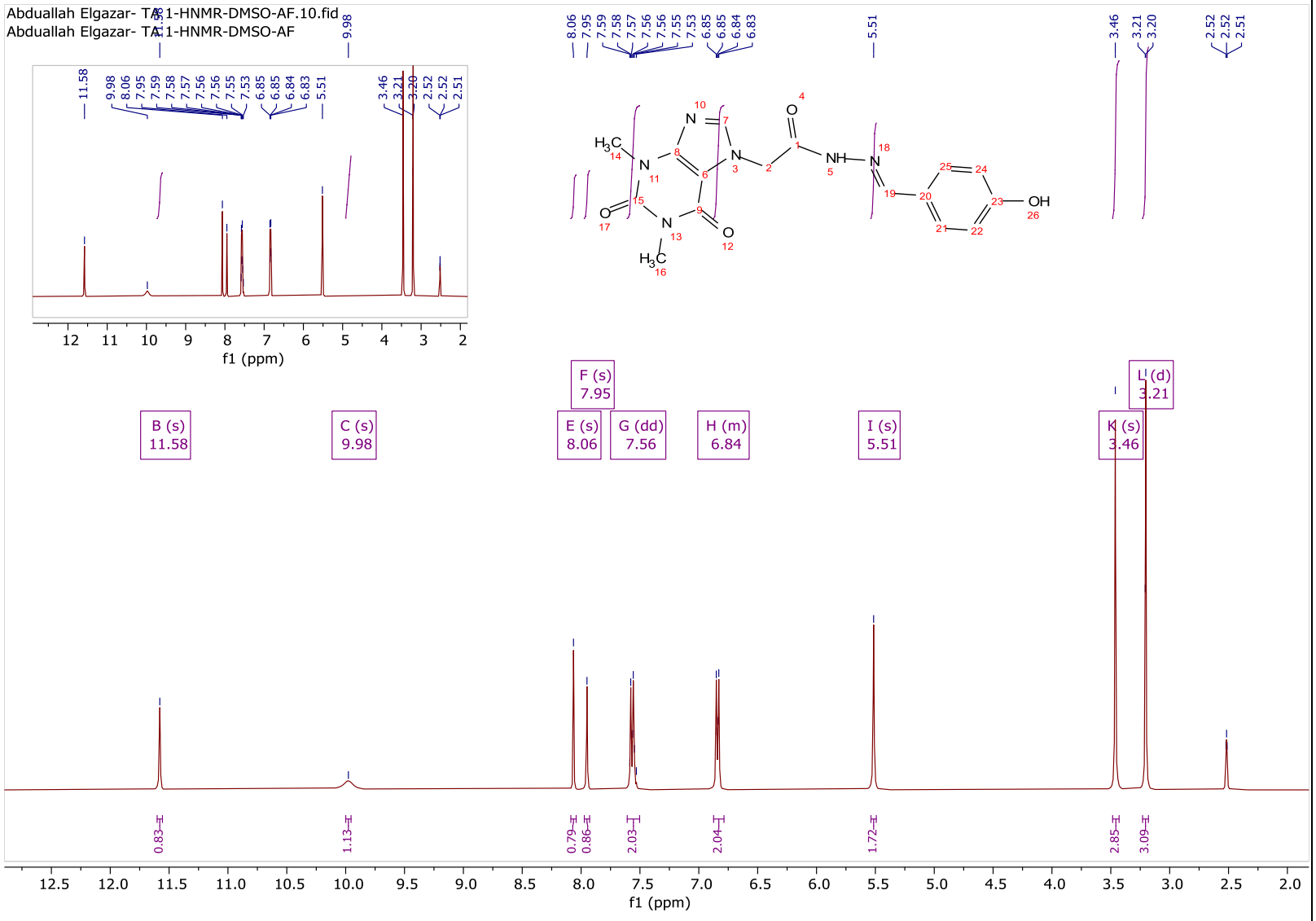


Mass spectrum of compound 18a

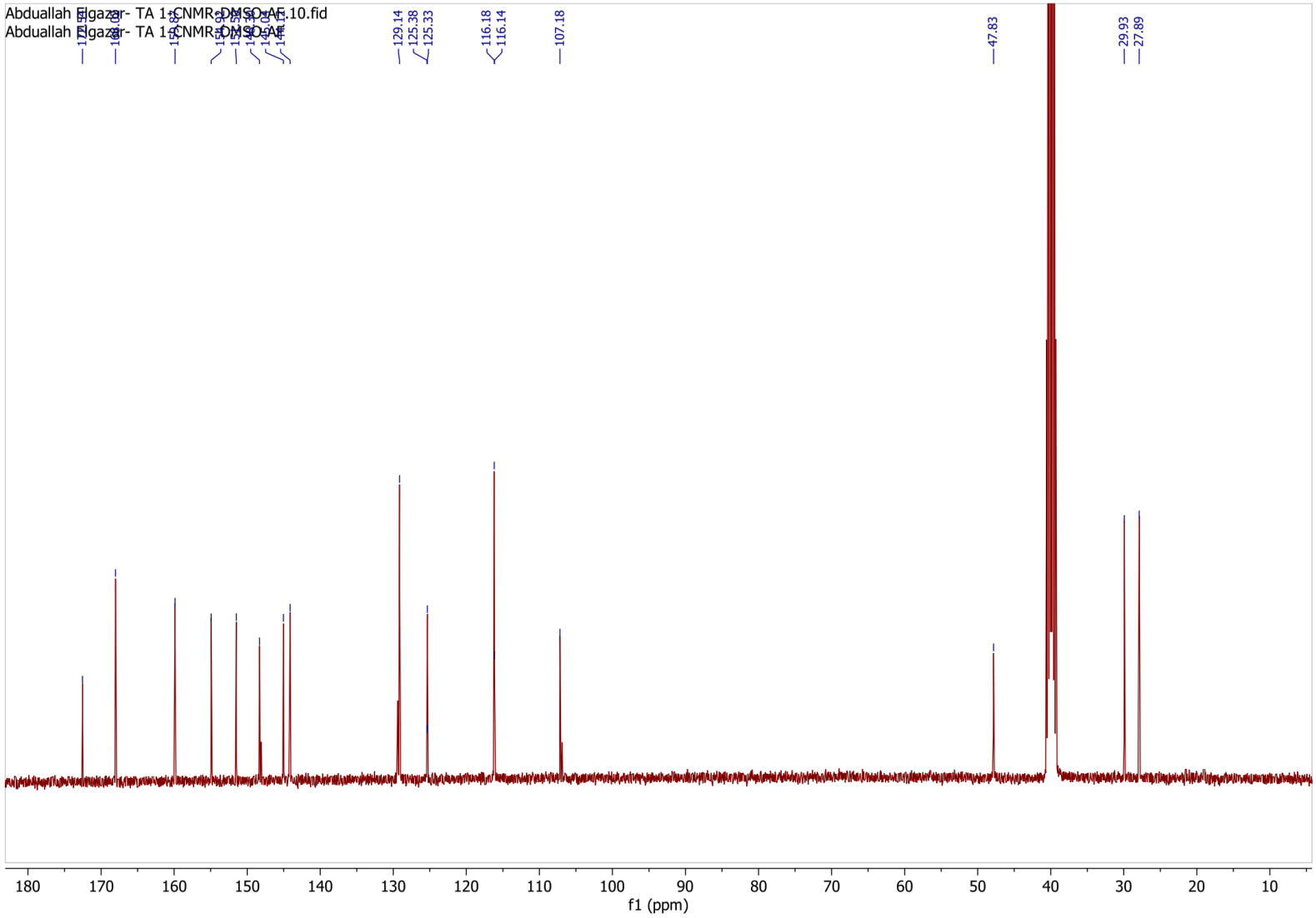
Table.s17 NMR assignment of acefylline-hydrazone-hydroxy benzaldehyde hybrid 18b



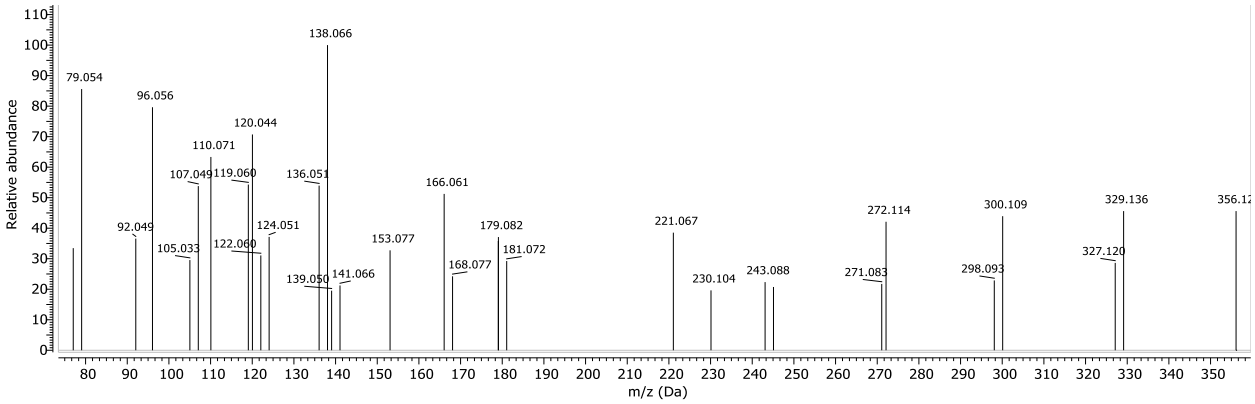
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)
CH=N	10.6	191.26	CH	8.06 (s, 1H)	145.04
COOH	--	169.48	C	--	168.02
4’	--	161.65	C	--	159.87
1	-	154.3	C	-	154.92
2	--	151.13	C	--	151.50
3	--	148.36	C	--	148.30
4	8.04	143.63	CH	7.95 (s, 1H)	144.12
2’	7.78	132.56	CH	7.56 (dd, *J* = 9.6, 2.9 Hz, 1H)	129.14
6’	7.78	132.56	CH	7.56 (dd, *J* = 9.6, 2.9 Hz, 1H)	129.14
1’	--	129.94	C	--	125.33
3’	6.9	116.06	CH	6.87 – 6.79 (m, 1H)	116.18
5’	6.9	116.06	CH	6.87 – 6.79 (m, 1H)	116.14
5	--	106.83	C	--	107.18
CH2CO	5.07	47.6	CH2	5.51 (s, 2H)	47.83
6	3.44	29.92	CH3	3.46 (s, 3H)	29.93
7	3.20	27.9	CH3	3.21 (d, *J* = 1.7 Hz, 3H)	27.89
NH	11	--	NH	11.58 (s, 1H)	--
OH	9	--	OH	9.98 (s, 1H)	--



^{1}H NMR spectrum of compound 18b

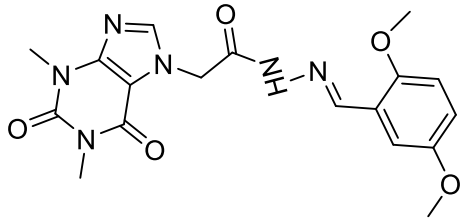


^{13}C NMR spectrum of compound 18b

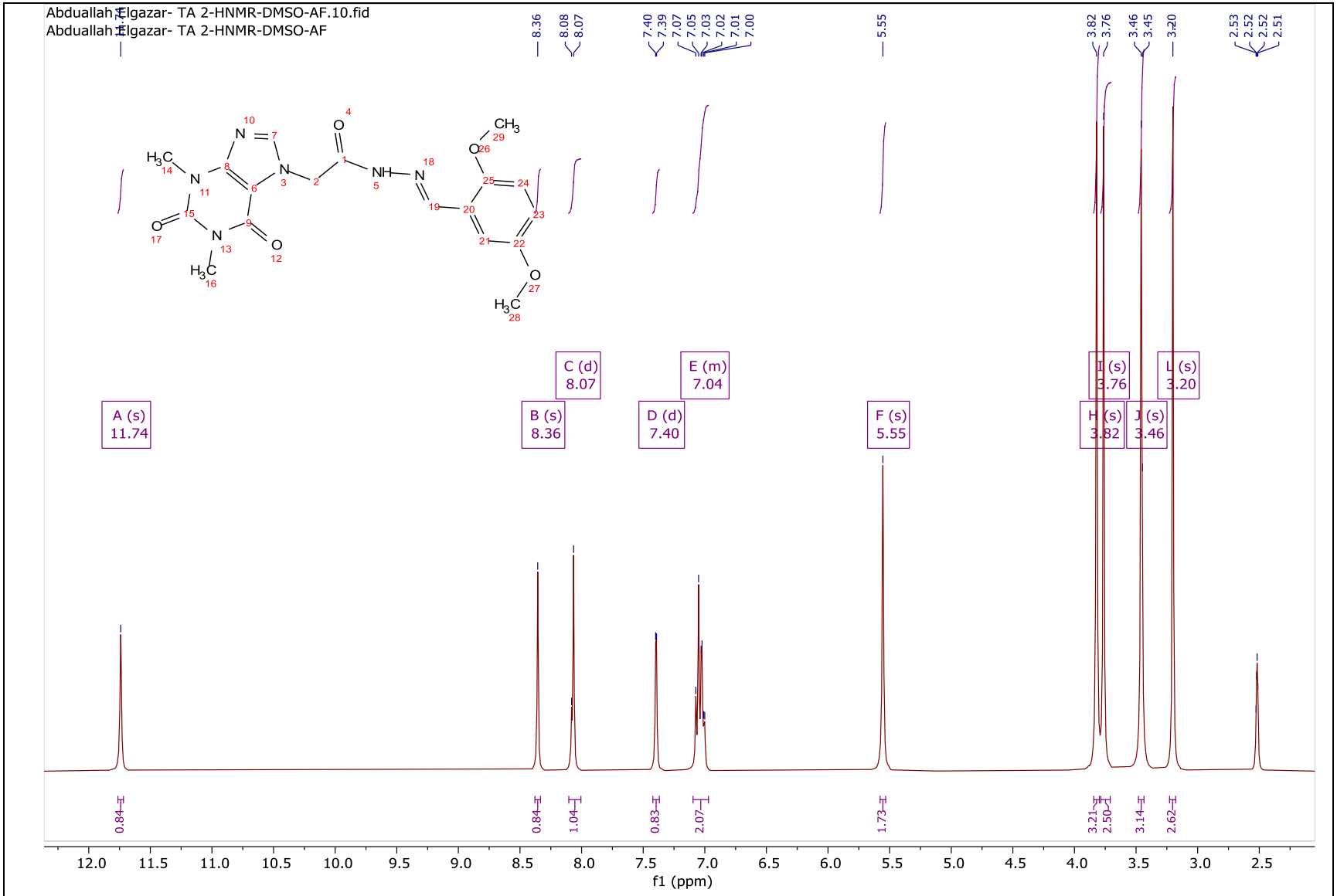


Mass spectrum of compound 18b

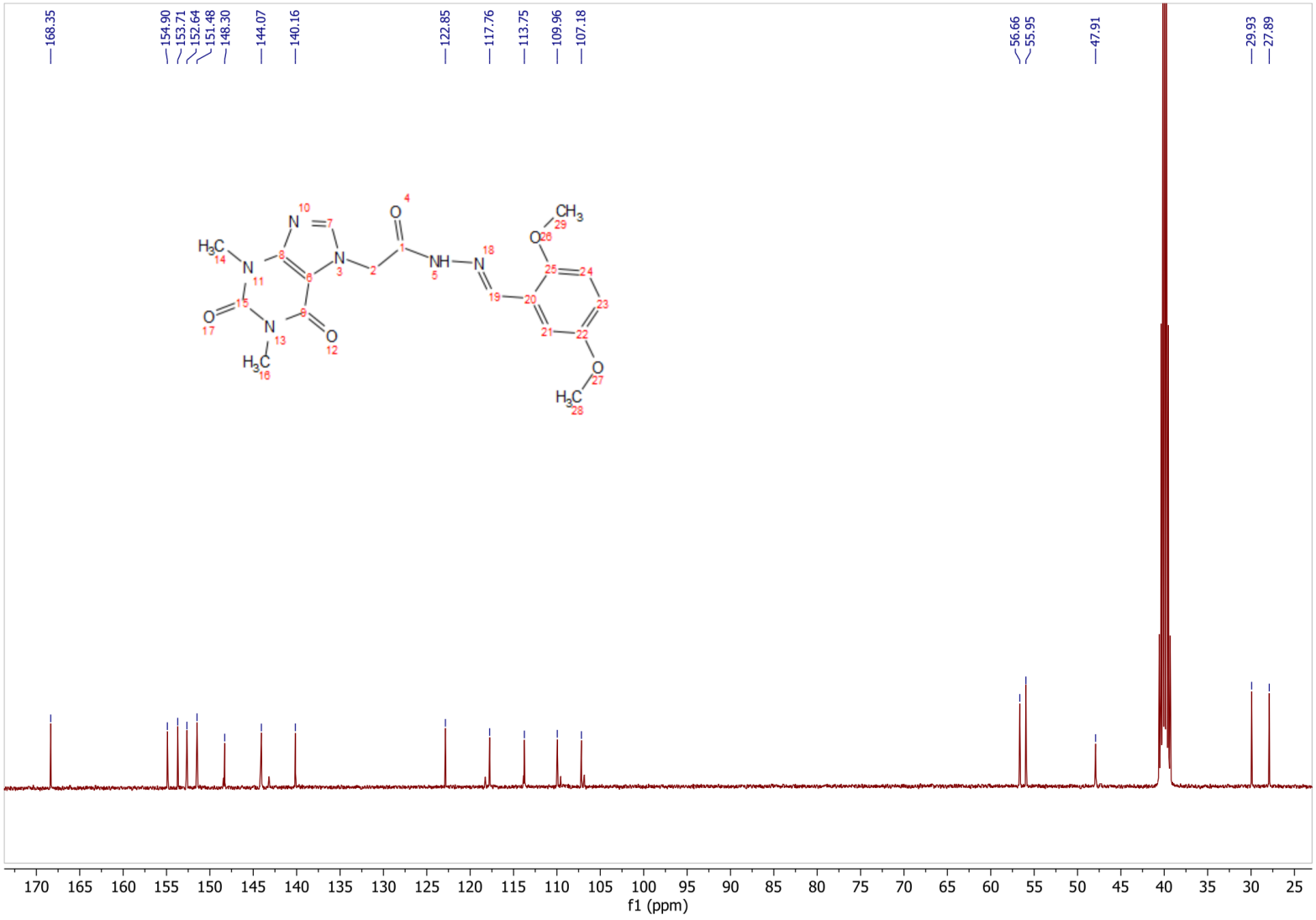
Table.s18 NMR assignment of acefylline-hydrazone-2,5 dimethoxy benzaldehyde hybrid 18c



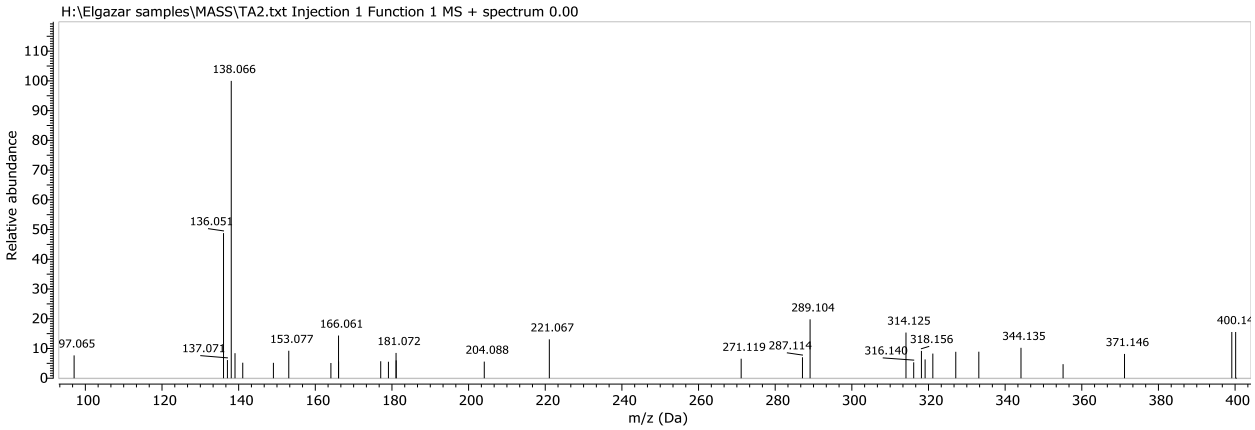
Parent compound			Hybrid compound		
Atom C/H	^{1}-H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C(δ, ppm)
COOH	--	169.48	C	--	168.35
2’	--	156.73	C	--	154.90
1	-	154.3	C	-	153.71
5’	--	153.69	C	--	152.64
2	--	151.13	C	--	151.48
3	--	148.36	C	--	148.30
CH=N	10.2	189.37	CH	8.36 (s, 1H)	144.06
4	8.04	143.63	CH	8.07 (d, *J* = 6.5 Hz, 1H)	140.16
1’	--	125.03	C	--	122.85
4’	7.78	123.29	CH	7.40 (d, *J* = 3.0 Hz, 1H)	117.76
6’	6.4	113.38	CH	7.10 – 6.97 (m, 1H)	113.75
3’	6.5	110.60	CH	7.10 – 6.97 (m, 1H)	109.96
5	--	106.83	C	--	107.18
OCH3	3.8	56.17	CH_3	3.82 (s, 3H)	56.66
OCH3	3.8	56.16	CH_3	3.76 (s, 3H)	55.95
CH2CO	5.07	47.6	CH2	5.55 (s, 2H)	47.91
6	3.44	29.92	CH3	3.46 (s, 3H)	29.93
7	3.20	27.9	CH3	3.20 (s, 3H)	27.89
NH	11	--	NH	11.74 (s, 1H)	--



^{1}H NMR spectrum of compound 18c

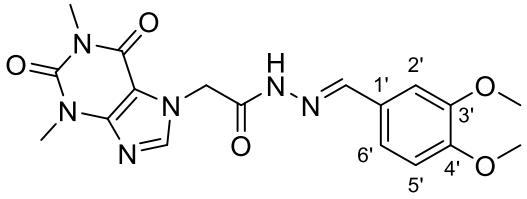


^{13}C NMR spectrum of compound 18c

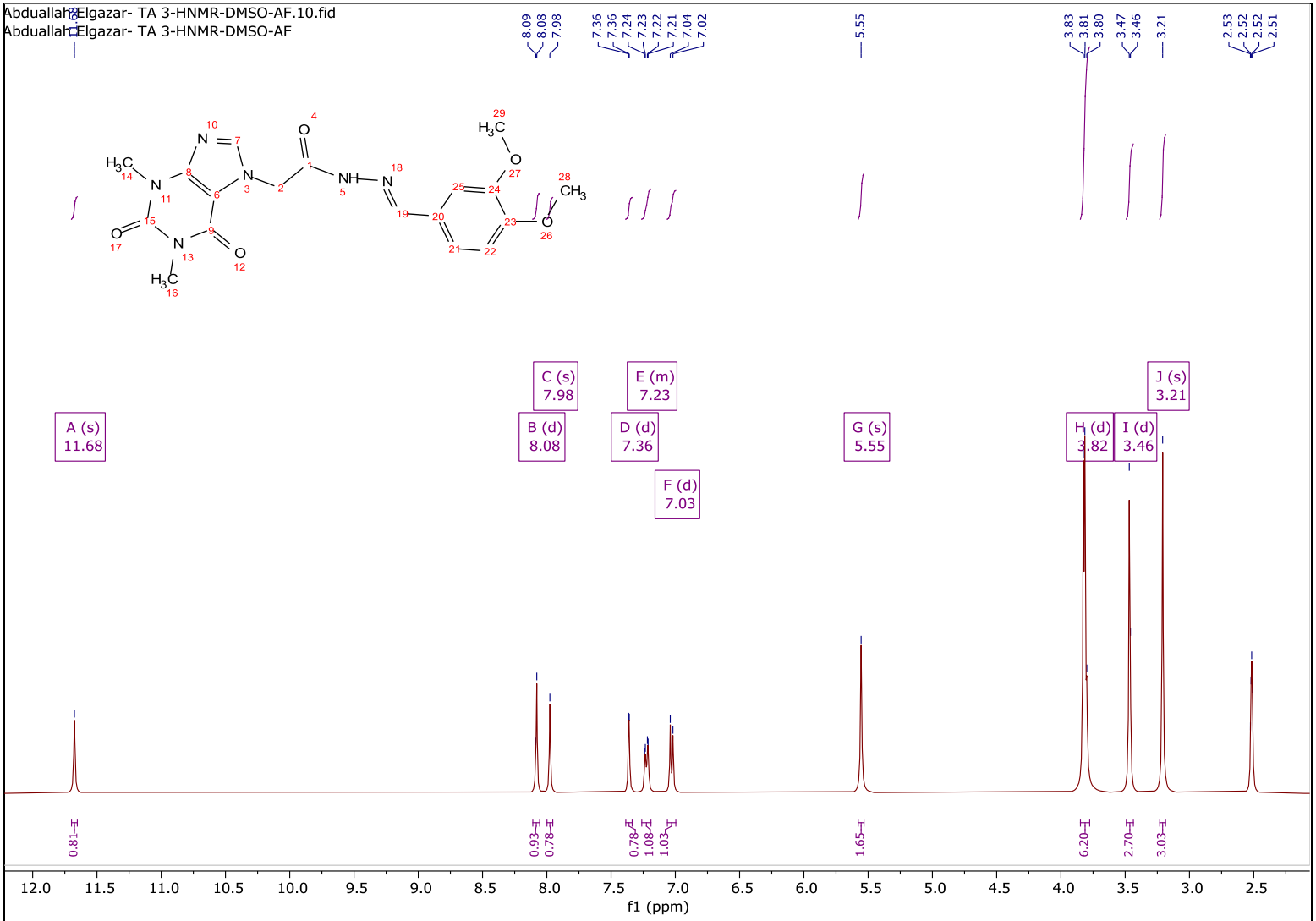


Mass spectrum of compound 18c

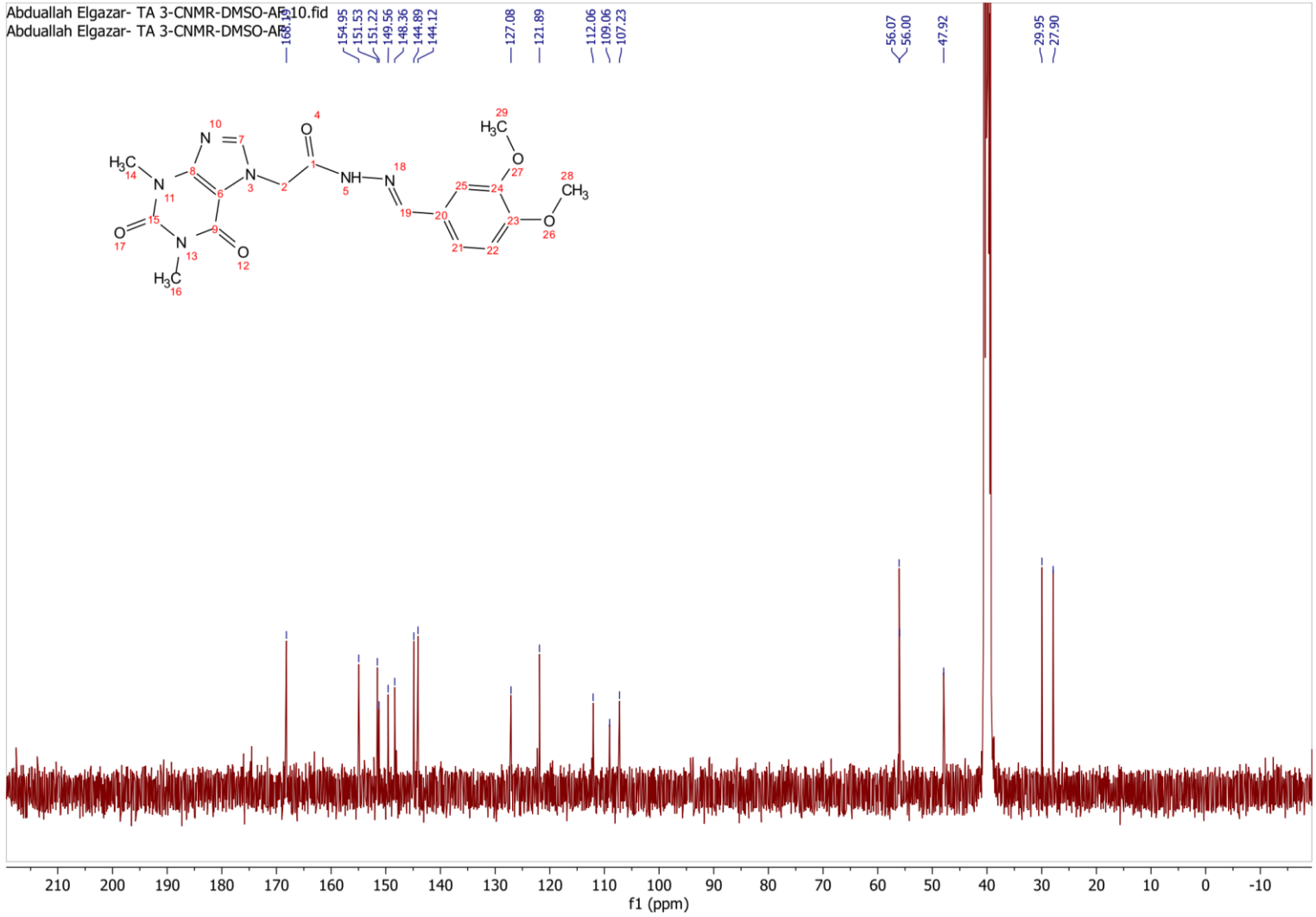
Table.s19 NMR assignment of acefylline-hydrazone-3,4 dimethoxy benzaldehyde hybrid 18d



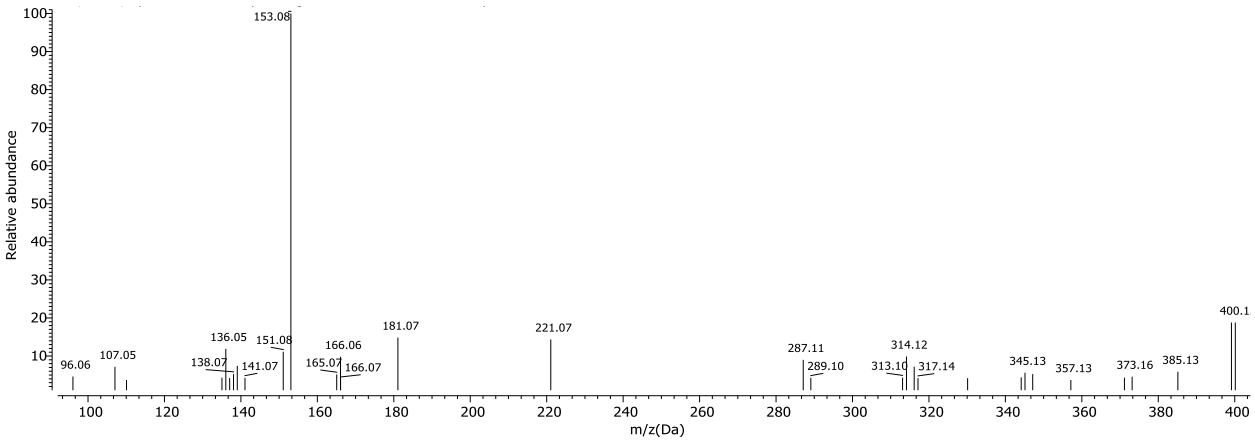
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C(δ, ppm)
COOH	--	169.48	C	--	168.19
1	-	154.3	C	--	154.95
4’	--	154.61	C	--	151.53
2	--	151.13	C	--	151.22
3’	--	149.73	C	--	149.56
3	--	148.36	C	--	148.36
4	8.04	143.63	CH	7.98 (s, 1H)	144.89
CH=N	10.6	191.26	CH	8.08 (d, *J* = 3.3 Hz, 1H)	144.12
1’	--	130.27	C	--	127.08
6’	7.47	126.59	CH	7.36 (d, *J* = 1.9 Hz, 1H)	121.89
2’	7.41	110.62	CH	7.26 – 7.19 (m, 1H)	112.06
5’	6.99	109.29	CH	7.03 (d, *J* = 8.3 Hz, 1H)	109.06
5	--	106.83	C	--	107.23
OCH3	3.8	56.16	CH_3	3.82 (d, *J* = 4.7 Hz, 3H)	56.07
OCH3	3.8	56.17	CH_3	3.82 (d, *J* = 4.7 Hz, 3H)	56.00
CH2CO	5.07	47.6	CH2	5.55 (s, 2H)	47.92
6	3.44	29.92	CH3	3.46 (d, *J* = 3.7 Hz, 3H)	29.95
7	3.20	27.9	CH3	3.21 (d, *J* = 1.7 Hz, 3H)	27.90
NH	11	--	NH	11.68 (s, 1H)	--



^{1}H NMR spectrum of compound 18d

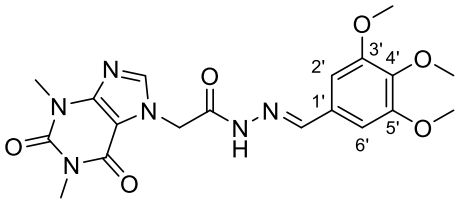


^{13}C NMR spectrum of compound 18d

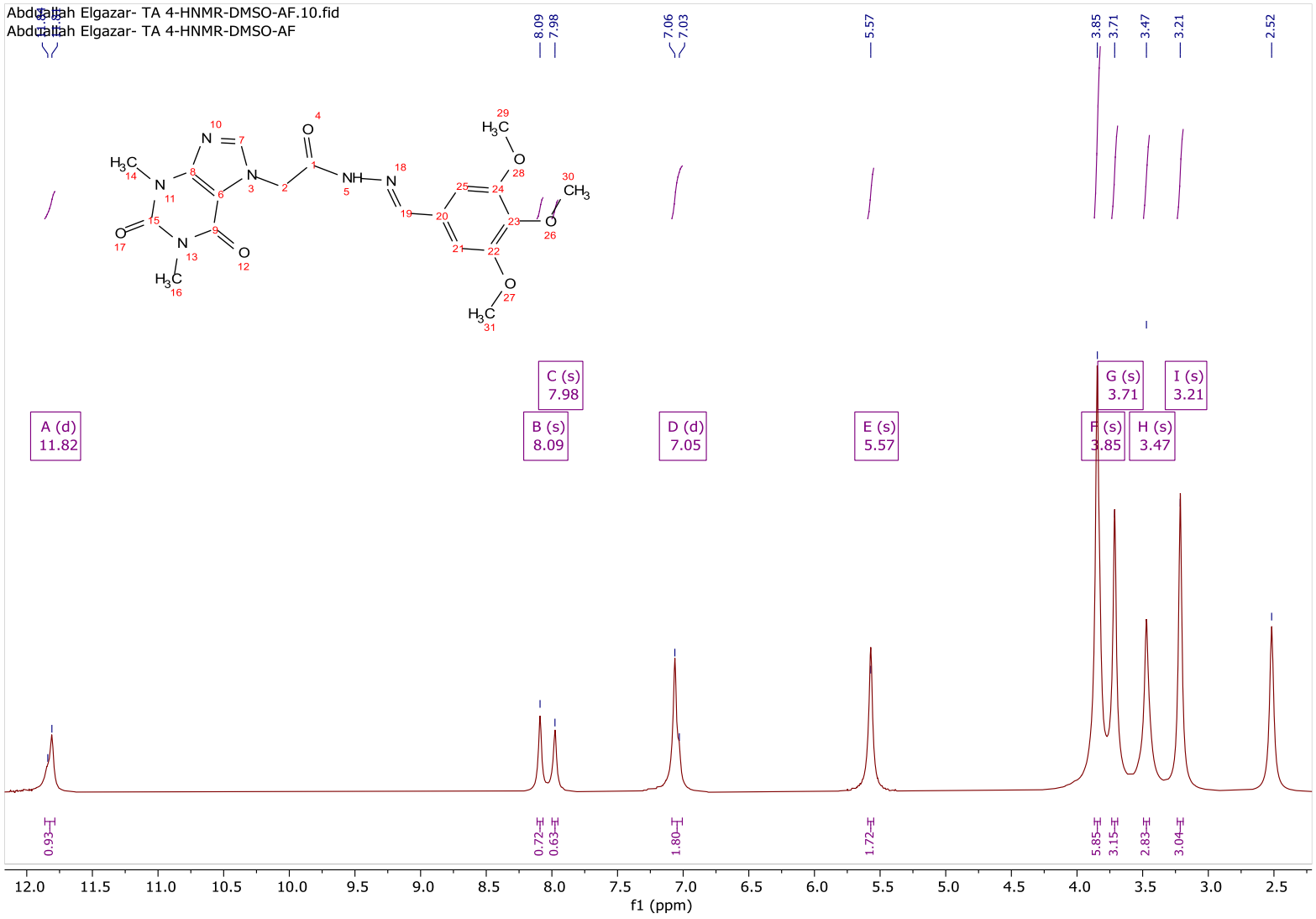


Mass spectrum of compound 18d

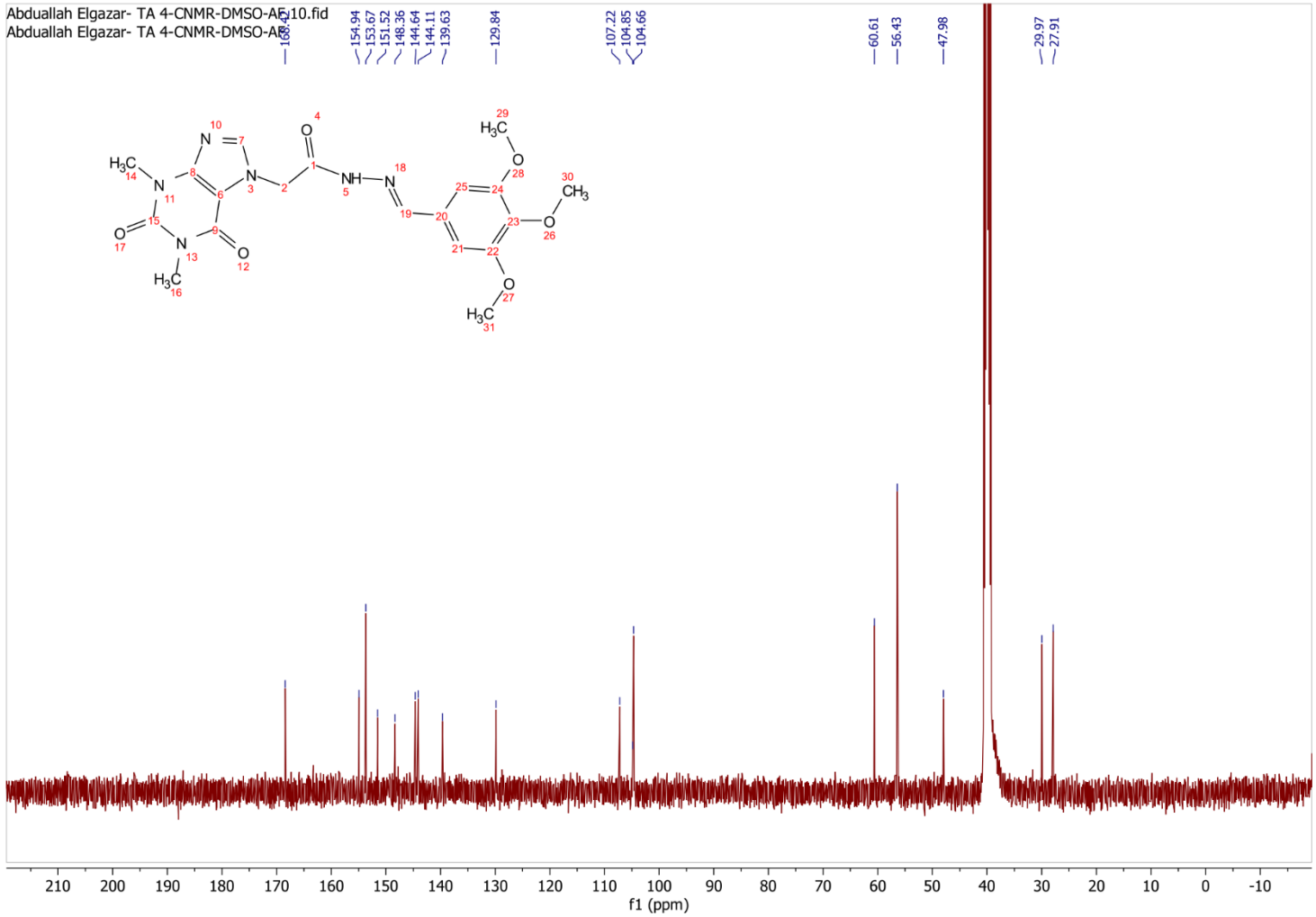
Table.s20 NMR assignment of acefylline-hydrazone-3,4,5 trimethoxy benzaldehyde hybrid 18e.



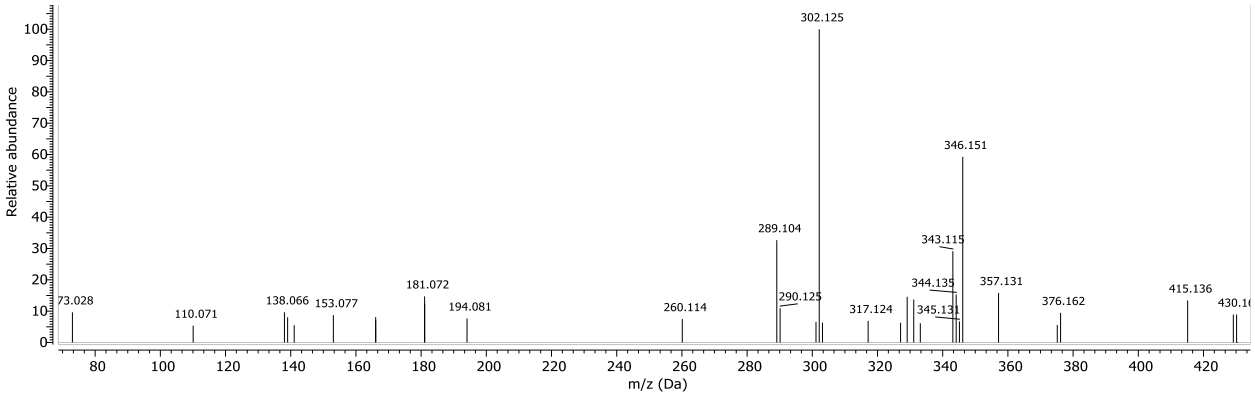
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C(δ, ppm)
COOH	--	169.48	C	--	168.42
1	-	154.3	C		154.94
3’	--	153.72	C	--	153.67
5’	--	153.72	C	--	153.67
2	--	151.13	C	--	151.52
3	--	148.36	C	--	148.36
4’	--	143.72	C	--	144.64
CH=N	10.6	191.26	CH	8.09 (s, 1H)	144.11
4	8.04	143.63	CH	7.98 (s, 1H)	139.63
1’	--	131.84	C	--	129.84
5	--	106.83	C	--	107.22
2’	7.13	106.81	CH	7.05 (d, *J* = 13.7 Hz, 1H)	104.85
6’	7.13	106	CH	7.05 (d, *J* = 13.7 Hz, 1H)	104.66
OCH3	3.93	60.93	CH_3	3.85 (s, 3H)	60.61
OCH3	3.93	60.93	CH_3	3.85 (s, 3H)	56.43
OCH3	3.93	60.93	CH_3	3.71 (s, 3H)	56.43
CH2CO	5.07	47.6	CH2	5.57 (s, 2H)	47.98
6	3.44	29.92	CH3	3.47 (s, 3H)	29.97
7	3.20	27.9	CH3	3.21 (s, 3H)	27.91
NH	11	--	NH	11.82 (d, *J* = 12.5 Hz, 1H)	--



H NMR spectrum of compound 18e

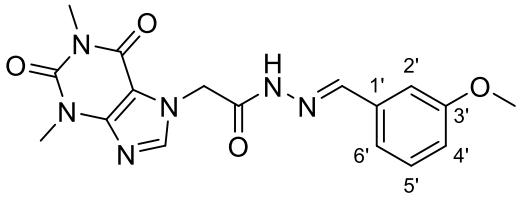


^{13}C NMR spectrum of compound 18e

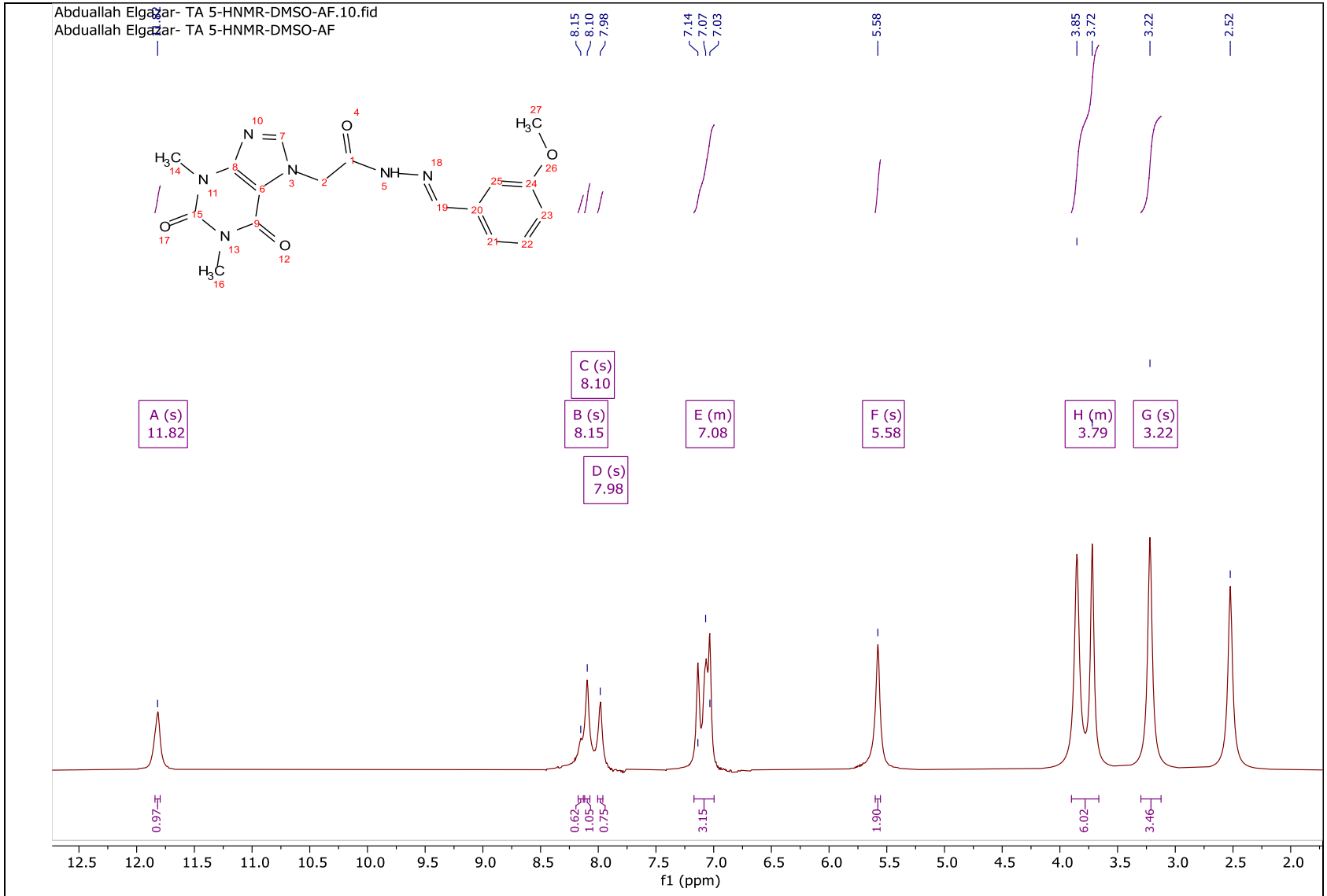


Mass spectrum of compound 18e

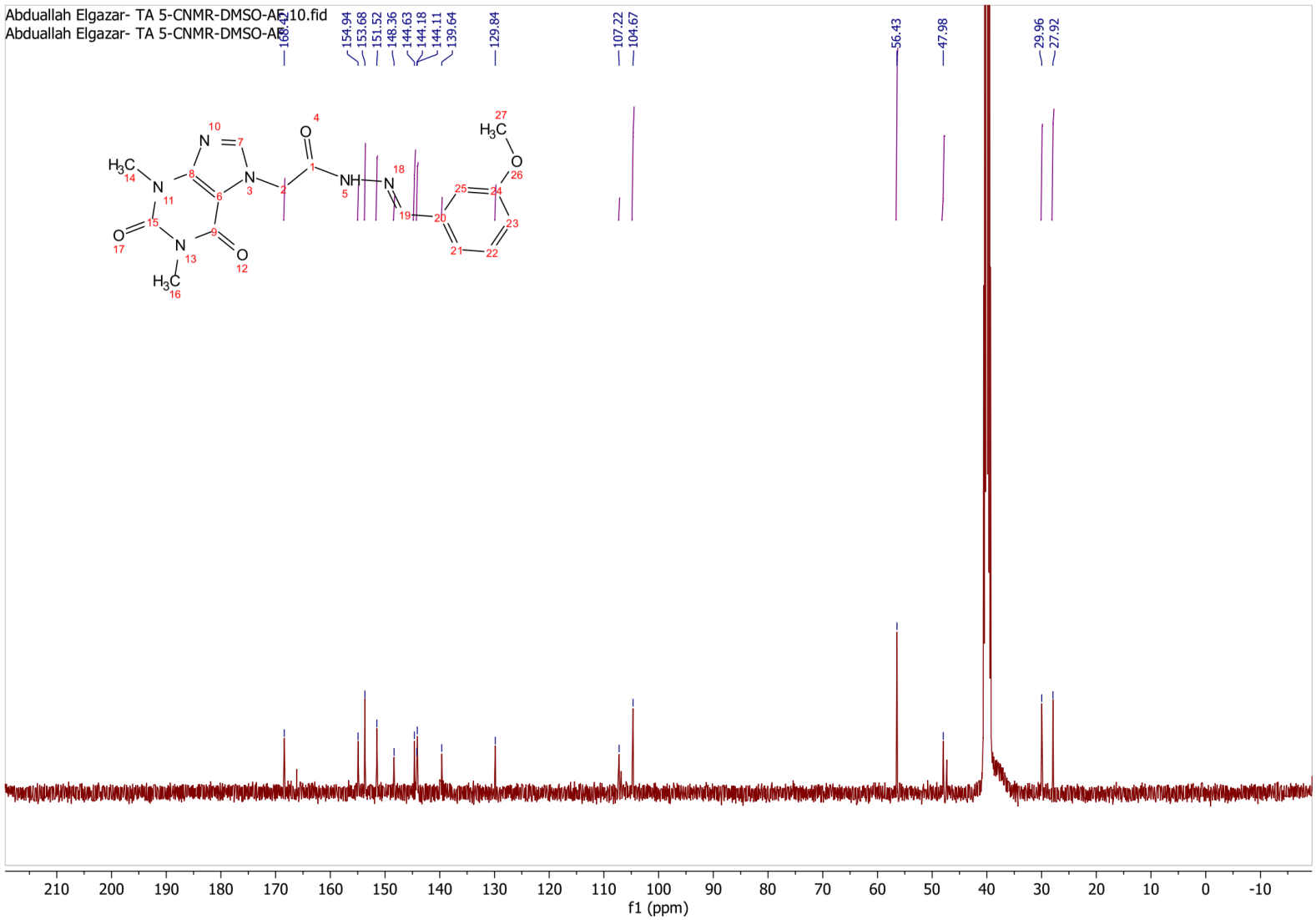
Table.s21 NMR assignment of acefylline-hydrazone 3 -methoxy benzaldehyde hybrid 18f



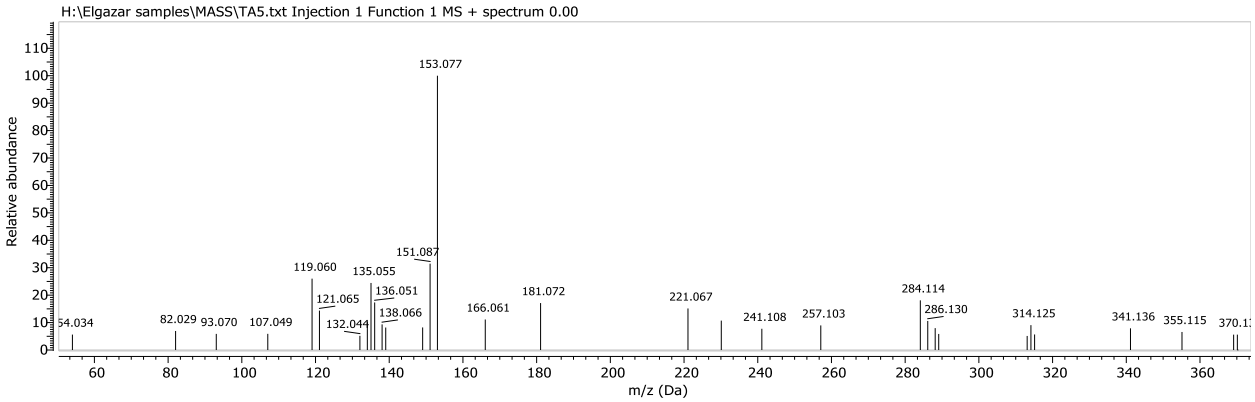
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C(δ, ppm)
COOH	--	169.48	C	--	168.42
1	-	154.3	C	--	154.94
5’	7.44	130.05	CH	7.17 – 7.00 (m, 1H)	153.67
3’	--	160.15	C	---	153.67
2	--	151.13	C	--	151.52
3	--	148.36	C	--	148.36
4’	7.18	121.25	CH	7.17 – 7.00 (m, 1H)	144.64
CH=N	10.6	191.26	CH	8.15 (s, 1H)	144.11
4	8.04	143.63	CH	8.10 (s, 1H)	139.63
1’	--	137.79	C	--	129.84
5	--	106.83	C	--	107.22
2’	7.37	112.05	CH	7.98 (s, 1H)	104.85
6’	7.44	123.57	CH	7.17 – 7.00 (m, 1H)	104.66
OCH3	3.93	60.93	CH_3	3.79 (d, J = 53.2 Hz, 3H)	56.43
CH2CO	5.07	47.6	CH2	5.58 (s, 2H)	47.98
6	3.44	29.92	CH3	3.79 (d, J = 53.2 Hz, 3H)	29.97
7	3.20	27.9	CH3	3.22 (s, 3H)	27.91
NH	11	--	NH	11.82 (d, *J* = 12.5 Hz, 1H)	--



^{1}H NMR spectrum of compound 18f

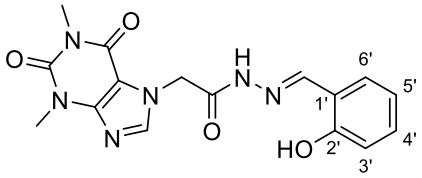


^{13}C NMR spectrum of compound 18f

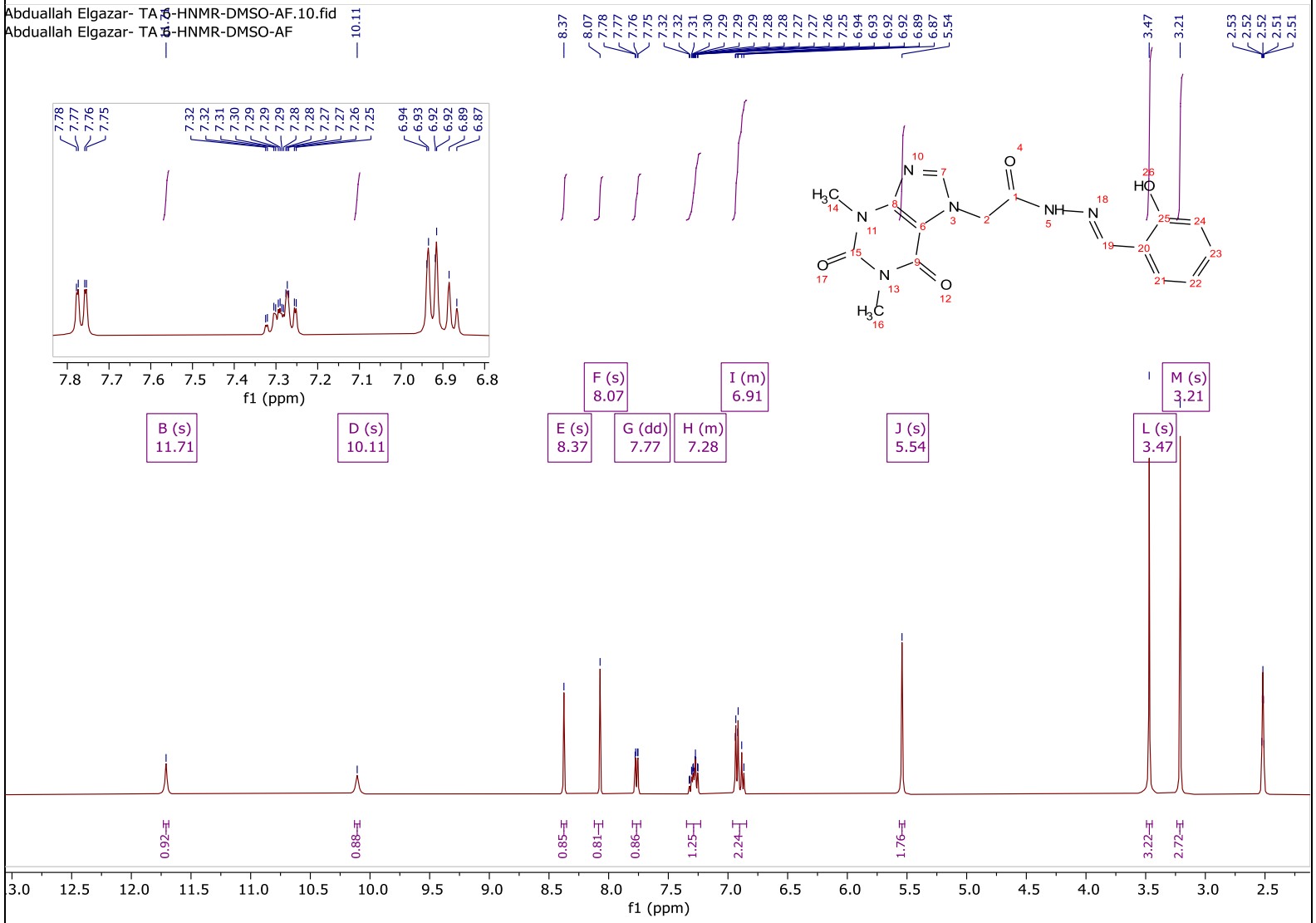


Mass spectrum of compound 18f

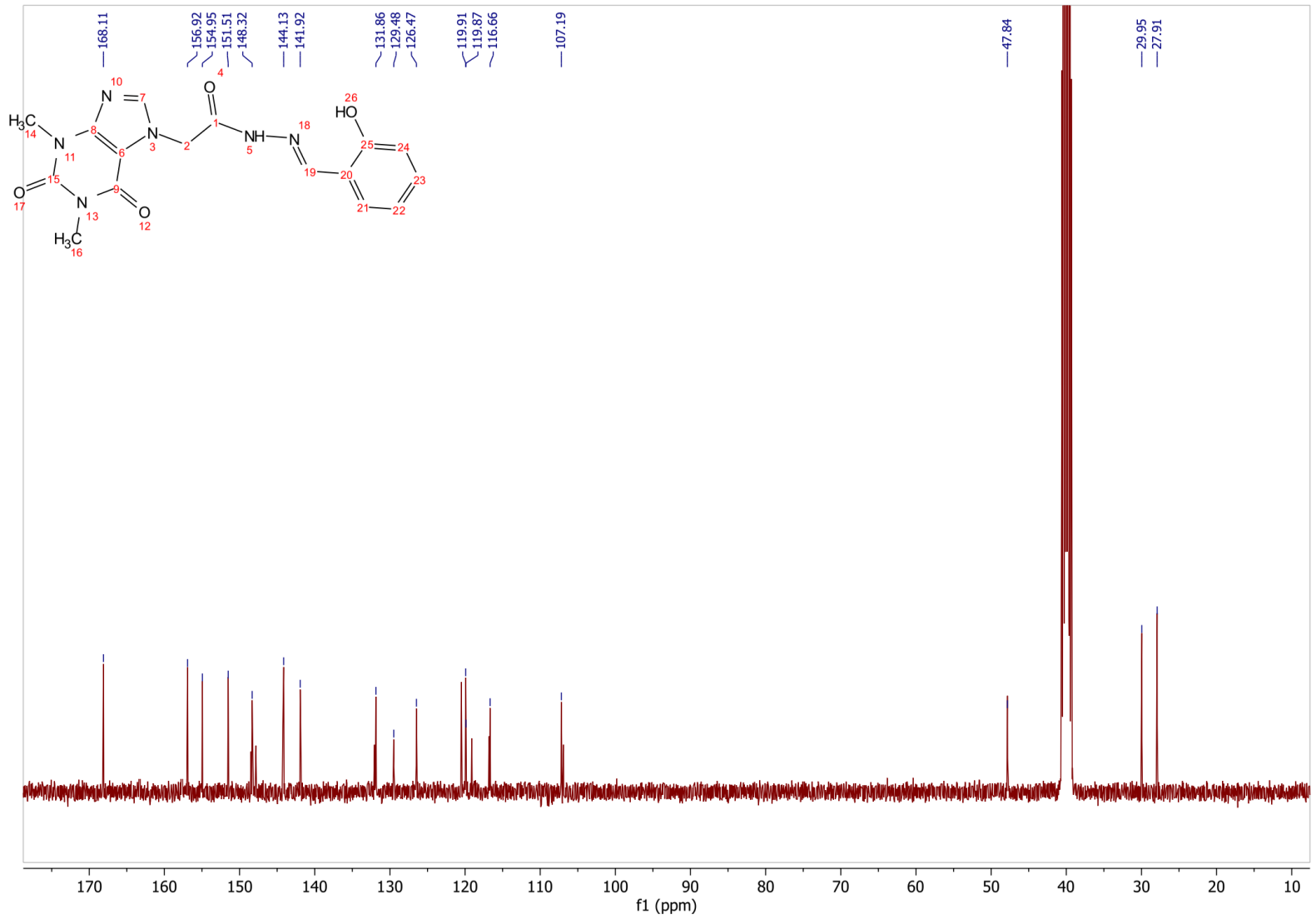
Table.s22 NMR assignment of ACEFYLLINE-hydrazone 2 -hydroxy benzaldehyde hybrid 18g



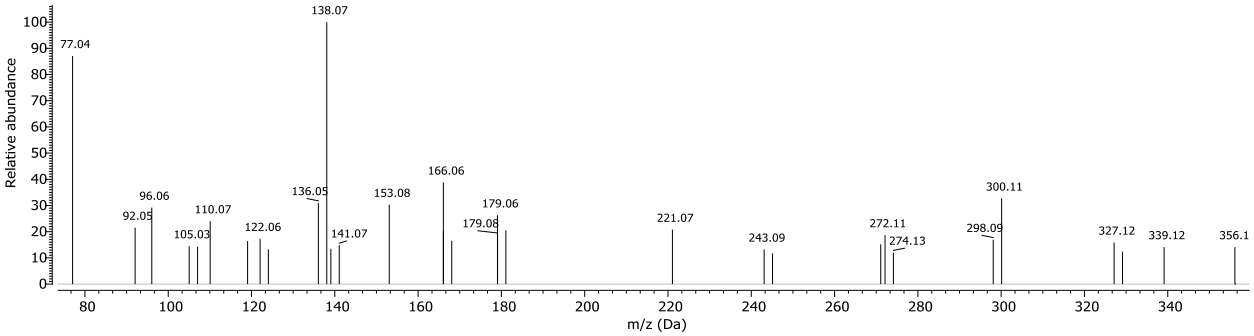
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C(δ, ppm)
COOH	--	169.48	C	--	168.11
2’	--	162	C	--	156.92
1	-	154.3	C	--	154.95
2	--	151.13	C	--	151.51
3	--	148.36	C	--	148.32
CH=N	10.6	191.26	CH	8.37 (s, 1H)	144.13
4	8.04	143.63	CH	8.07 (s, 1H)	141.92
4’	6.9	136.68	CH	7.77 (dd, *J* = 7.9, 1.7 Hz, 1H)	131.86
6’	6.7	133.69	CH	7.35 – 7.23 (m, 1H)	129.48
1’	--	120.926	C	--	126.47
5’	6.45	120.5	CH	6.96 – 6.84 (m, 1H)	119.89
3’	6.69	117.69	CH	6.96 – 6.84 (m, 1H)	116.66
5	--	106.83	C	--	107.19
CH2CO	5.07	47.6	CH2	5.54 (s, 2H)	47.84
6	3.44	29.92	CH3	3.47 (s, 3H)	29.95
7	3.20	27.9	CH3	3.21 (s, 3H)	27.91
OH	9.1	--	--	10.11	--
NH	11	--	NH	11.71 (s, 1H)	--



^{1}H NMR spectrum of compound 18g

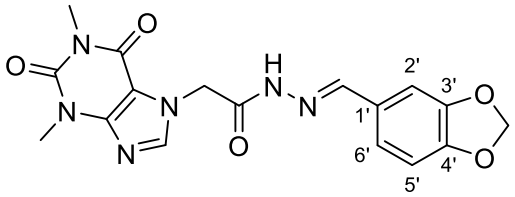


^{13}C NMR spectrum of compound 18g



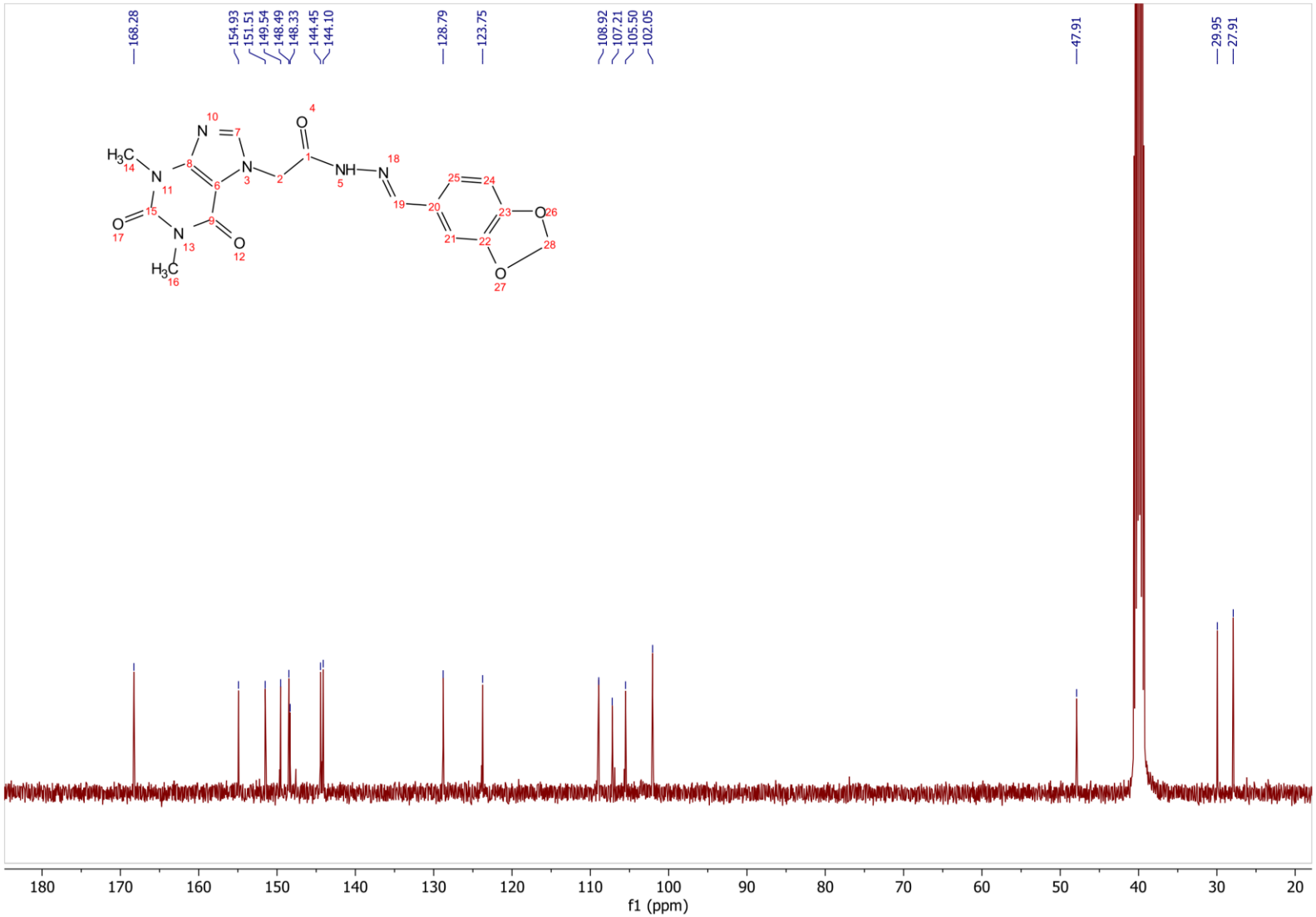
Mass spectrum of compound 18g

Table.s23 NMR assignment of acefylline-hydrazone piperonal hybrid 18h

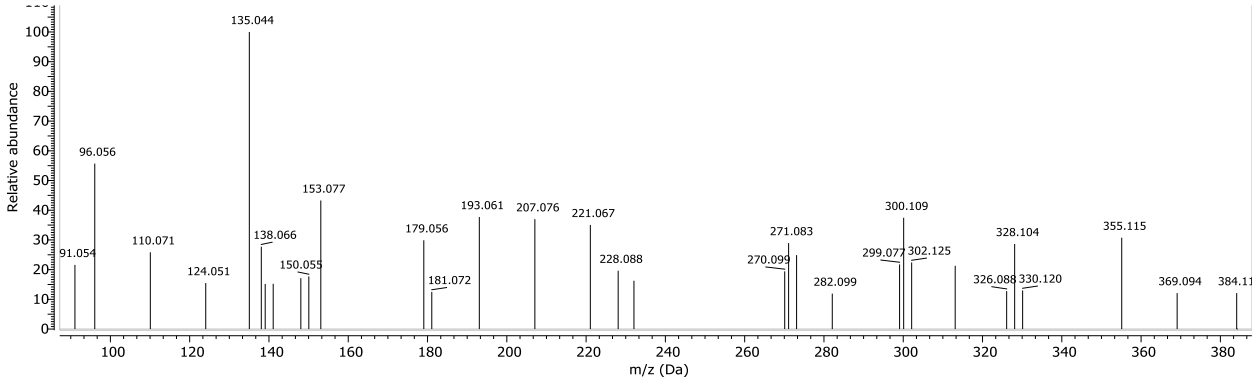


Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C(δ, ppm)
COOH	--	169.48	C	168.28	--
1	-	154.3	C	154.93	--
4’	--	153.1	CH	151.51	--
2	--	151.13	C	149.54	--
3’	--	148.7	CH	148.49	7.00 (d, *J* = 8.0 Hz, 1H)
3	--	148.36	C	148.33	
CH=N	10.6	191.26	CH	144.45	8.07 (s, 1H)
4	8.04	143.63	CH	144.10	7.96 (s, 1H)
1’	--	131.9	C	128.79	--
5’	6.92	128.6	CH	123.75	--
6’	7.23	108.3	CH	108.92	7.37 (s, 1H)
2’	7.2	106.9	CH	107.21	7.17 (d, *J* = 8.1 Hz, 1H)
5	--	106.83	C	105.50	--
O-CH2-O	6.06	102.1	CH2	102.05	6.10 (s, 2H)
CH2CO	5.07	47.6	CH2	47.91	5.54 (s, 2H)
6	3.44	29.92	CH3	29.95	3.47 (s, 3H)
7	3.20	27.9	CH3	27.91	3.21 (s, 3H)
NH	11	--	NH	--	11.68 (s, 1H)

^{1}H NMR spectrum of compound 18h

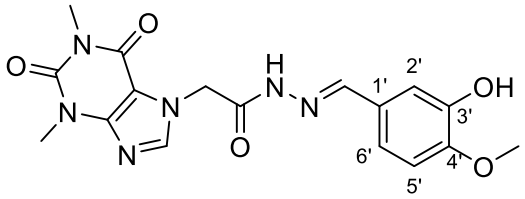


^{13}C NMR spectrum of compound 18h



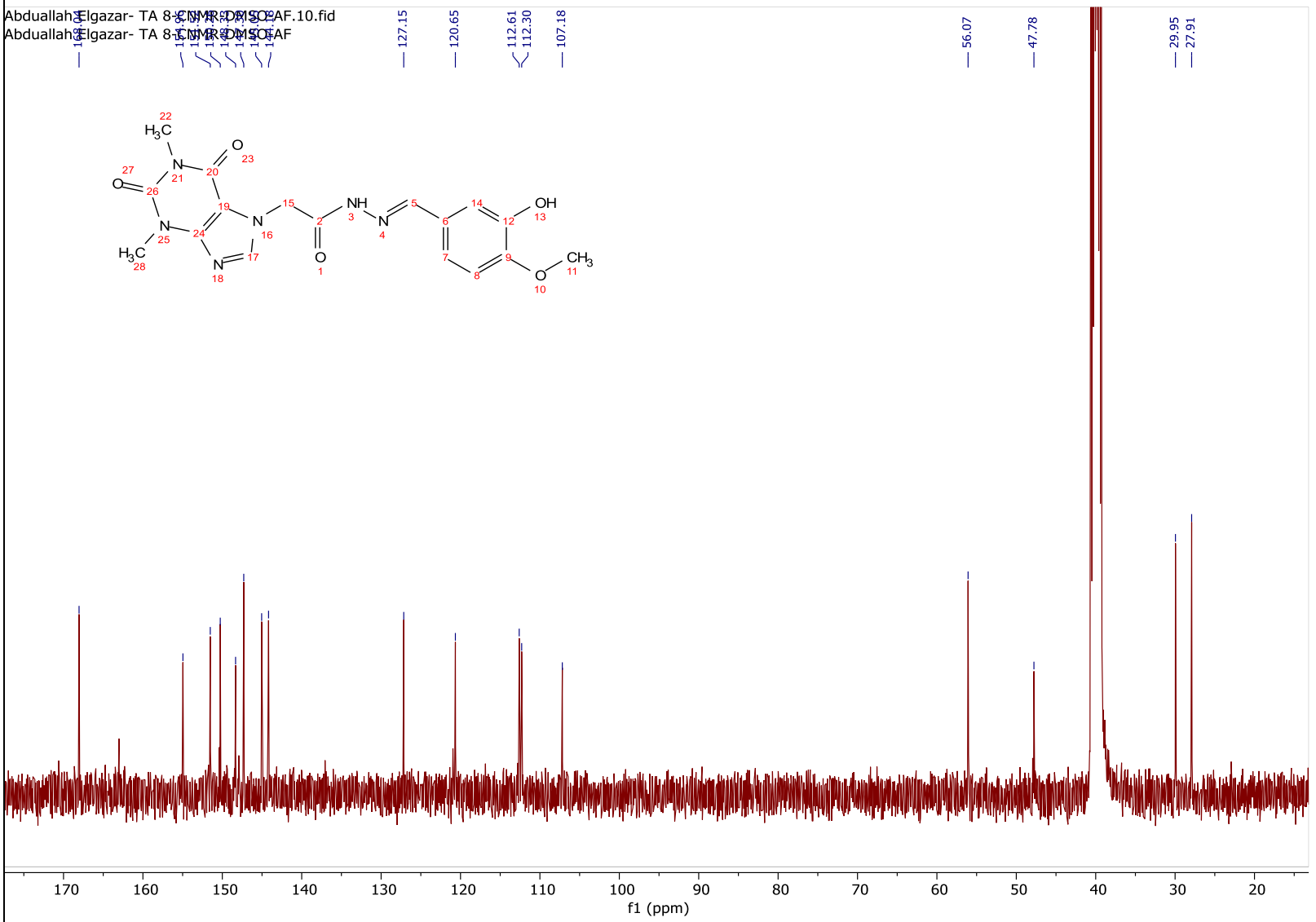
Mass spectrum of compound 18h

Table.s24 NMR assignment of acefylline-hydrazone isovanillin hybrid 18i.

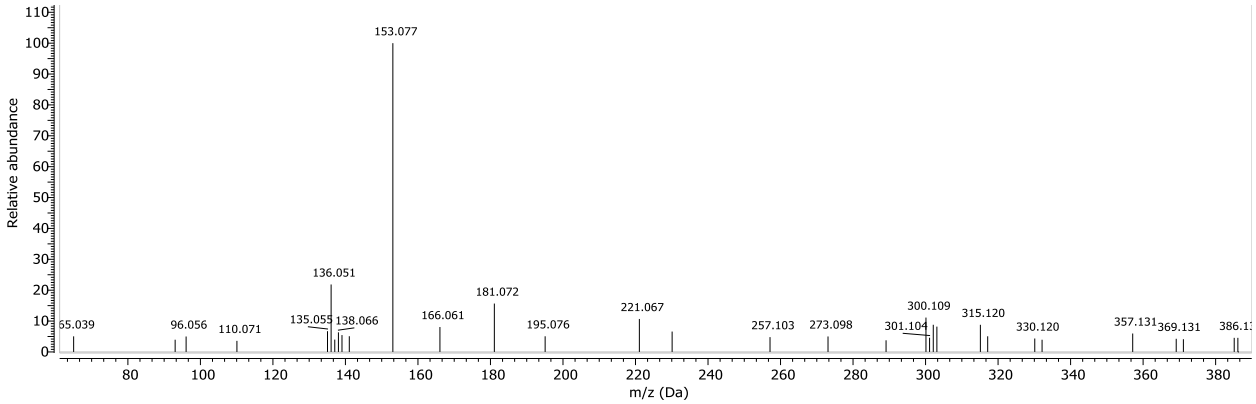


Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C(δ, ppm)
OH	9	--	OH	9.30 (s, 1H)	--
CH=N	10.6	191.26	CH	8.07 (s, 1H)	144.18
4	8.04	143.63	CH	7.92 (s, 1H)	145.05
2’	7.3 d(J=1.50)	109.14	CH	7.24 (t, *J* = 3.0 Hz, 1H)	112.30
5’	7.2	114.75	CH	7.11 – 7.04 (m, 1H)	112.61
6’	6.9 d(J=7.5)	127.49	CH	6.98 (dd, *J* = 8.4, 4.9 Hz, 1H)	120.65
CH2CO	5.07	47.6	CH2	5.53 (s, 2H)	47.78
OCH3	3.8	56	CH3-	3.82 (d, *J* = 5.2 Hz, 3H)	56.07
6	3.44	29.92	CH3	3.47 (s, 3H)	29.95
7	3.20	27.9	CH3	3.21 (s, 3H)	27.91
NH	11	--	NH	11.61 (s, 1H)	--
COOH	--	169.48	C	--	168.04
1	-	154.3	C	--	154.96
3’	--	152.14	C	--	151.52
2	--	151.13	C	--	150.26
3	--	148.36	C	--	148.33
4’	--	147.5	C	--	147.30
1’	--	129.77	C	--	127.15
5	--	106.83	C	--	107.18

^{1}H NMR spectrum of compound 18i

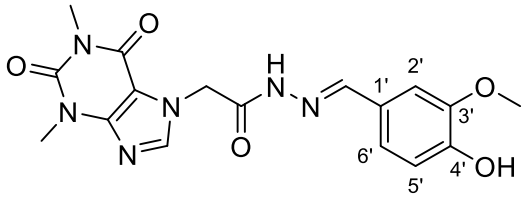


^{13}C NMR spectrum of compound 18i

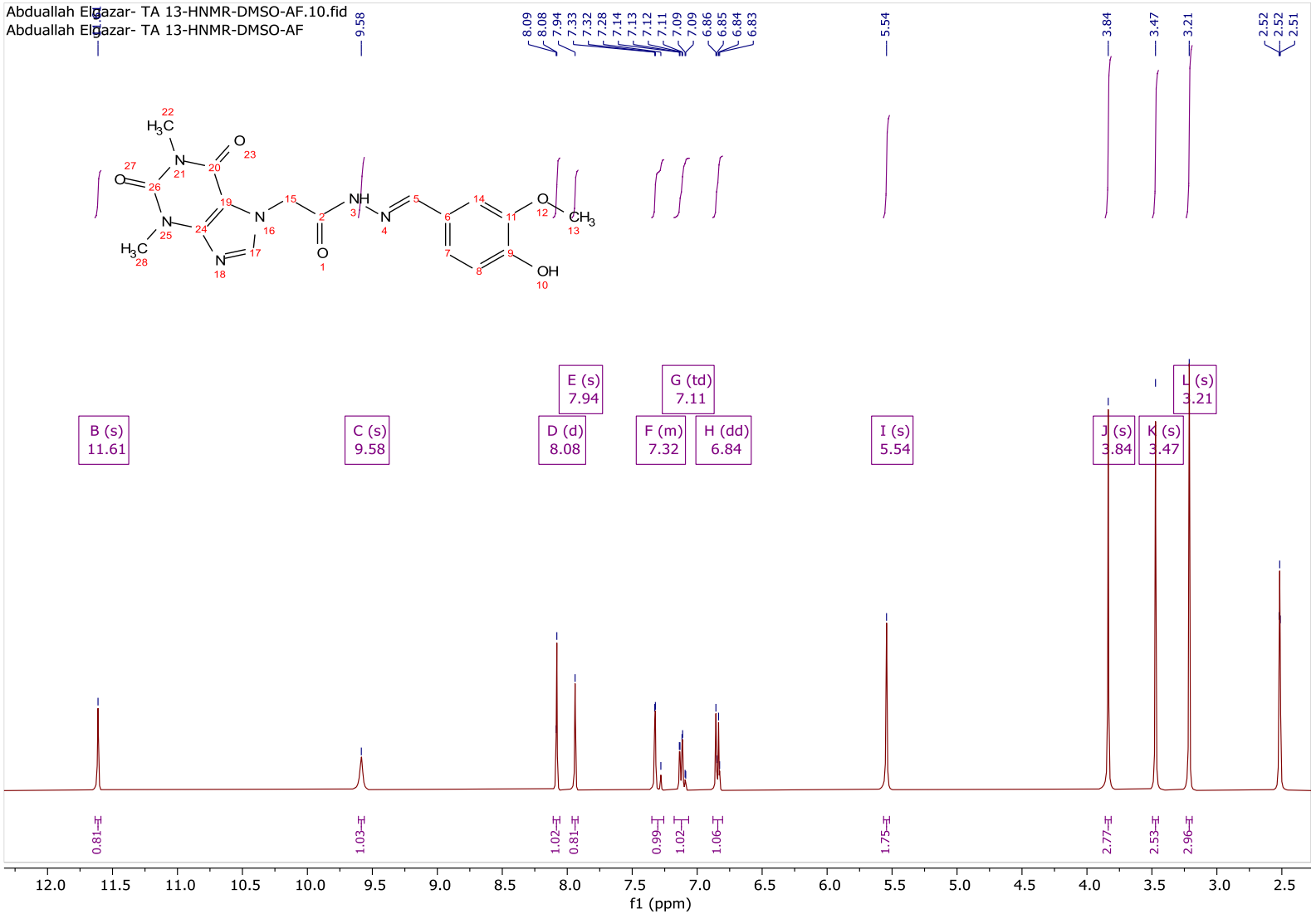


Mass spectrum of compound 18i

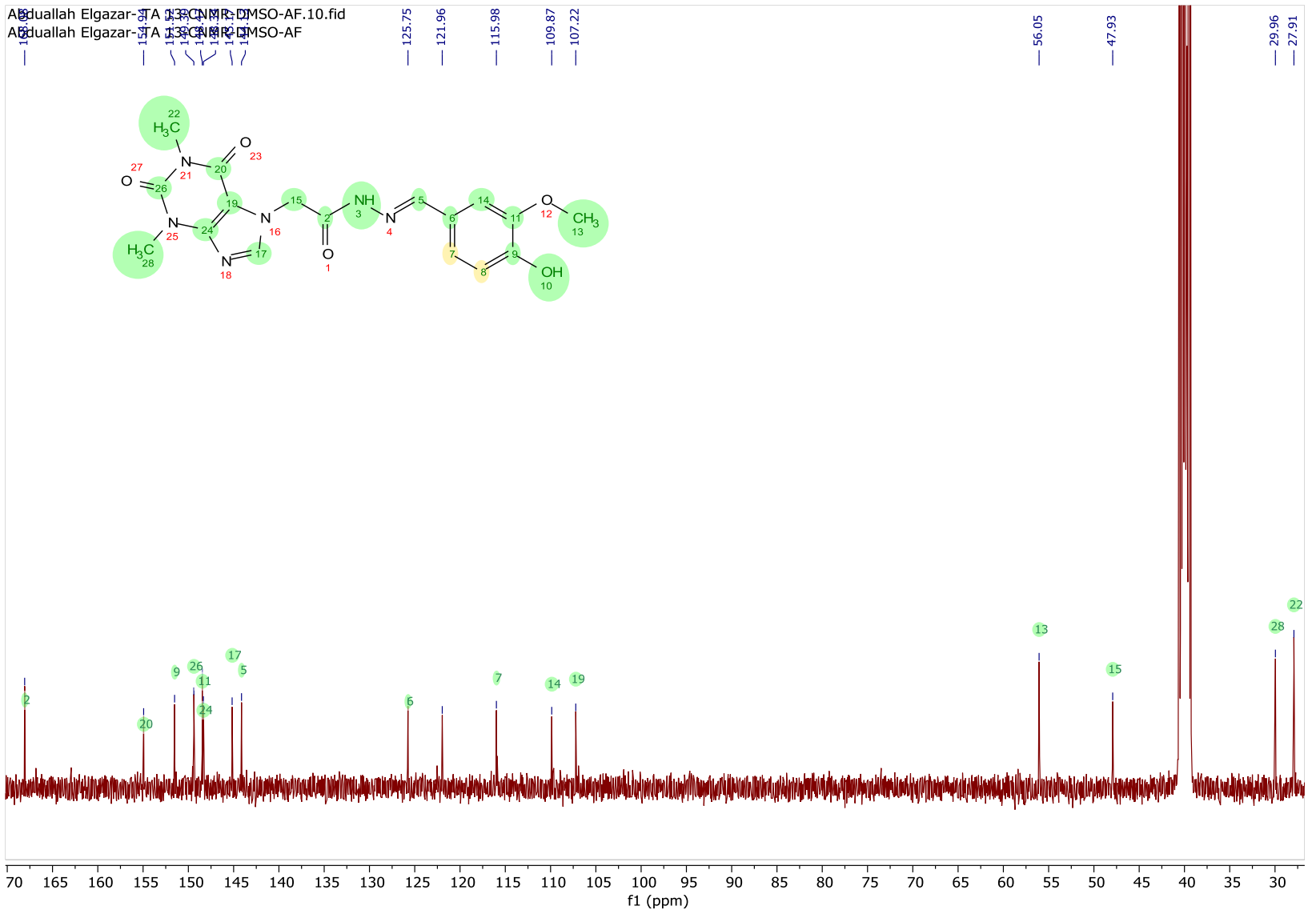
Table.s25 NMR assignment of acefylline-hydrazone vanillin hybrid 18j



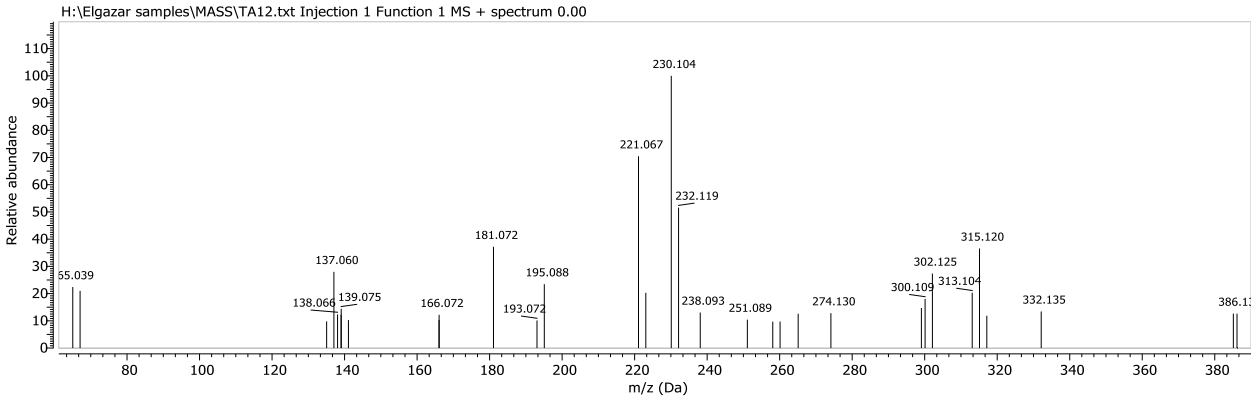
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C(δ, ppm)
OH	9	--	OH	9.58 (s, 1H)	--
CH=N	10.6	191.26	CH	8.08 (d, *J* = 2.2 Hz, 1H)	144.13
4	8.04	143.63	CH	7.94 (s, 1H)	145.17
2’	7.3 d(J=1.50)	109.14	CH	7.35 – 7.26 (m, 1H)	109.87
5’	7.2	114.75	CH	7.11 (td, *J* = 8.9, 1.9 Hz, 1H)	115.98
6’	6.9 d(J=7.5)	127.49	CH	6.84 (dd, *J* = 8.1, 3.4 Hz, 1H)	121.96
CH2CO	5.07	47.6	CH2	5.54 (s, 2H)	47.93
OCH3	3.8	56	CH3	3.84 (s, 3H)	56.05
6	3.44	29.92	CH3	3.47 (s, 3H)	29.96
7	3.20	27.9	CH3	3.21 (s, 3H)	27.91
NH	11	--	NH	11.61 (s, 1H)	--
COOH	--	169.48	C	--	168.08
4’	--	152.14	C	--	151.52
2	--	151.13	C	--	149.39
3	--	148.36	C	--	148.47
3’	--	147.5	C	--	148.34
1’	--	129.77	C	--	125.75
5	--	106.83	C	--	107.22
1	-	154.3	C	-	154.94



^{1}H NMR spectrum of compound 18j

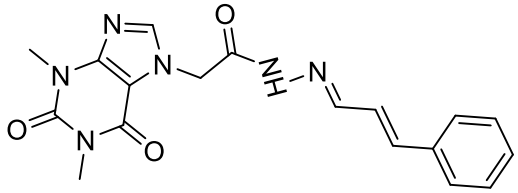


^{13}C NMR spectrum of compound 18j

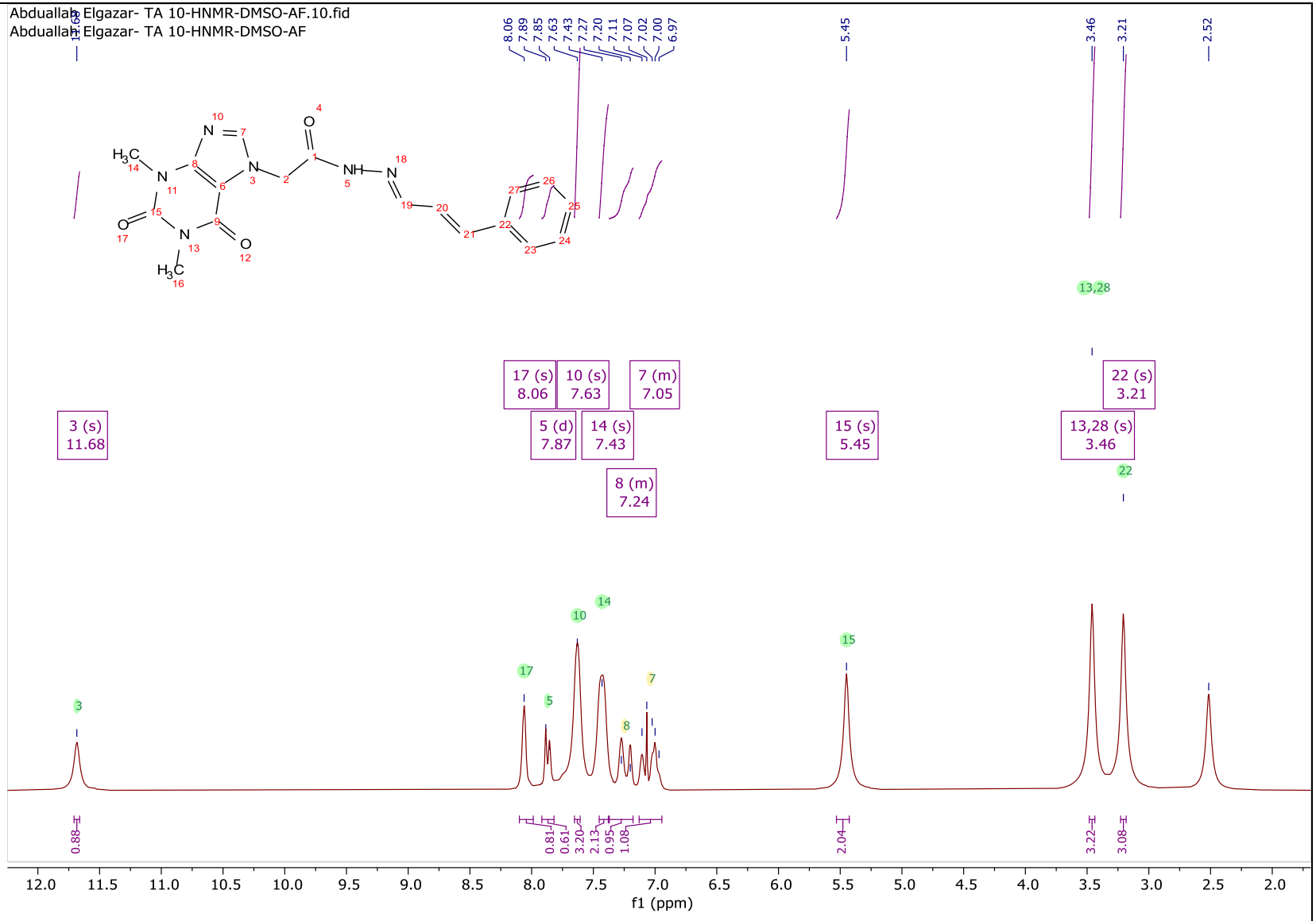


Mass spectrum of compound 18j

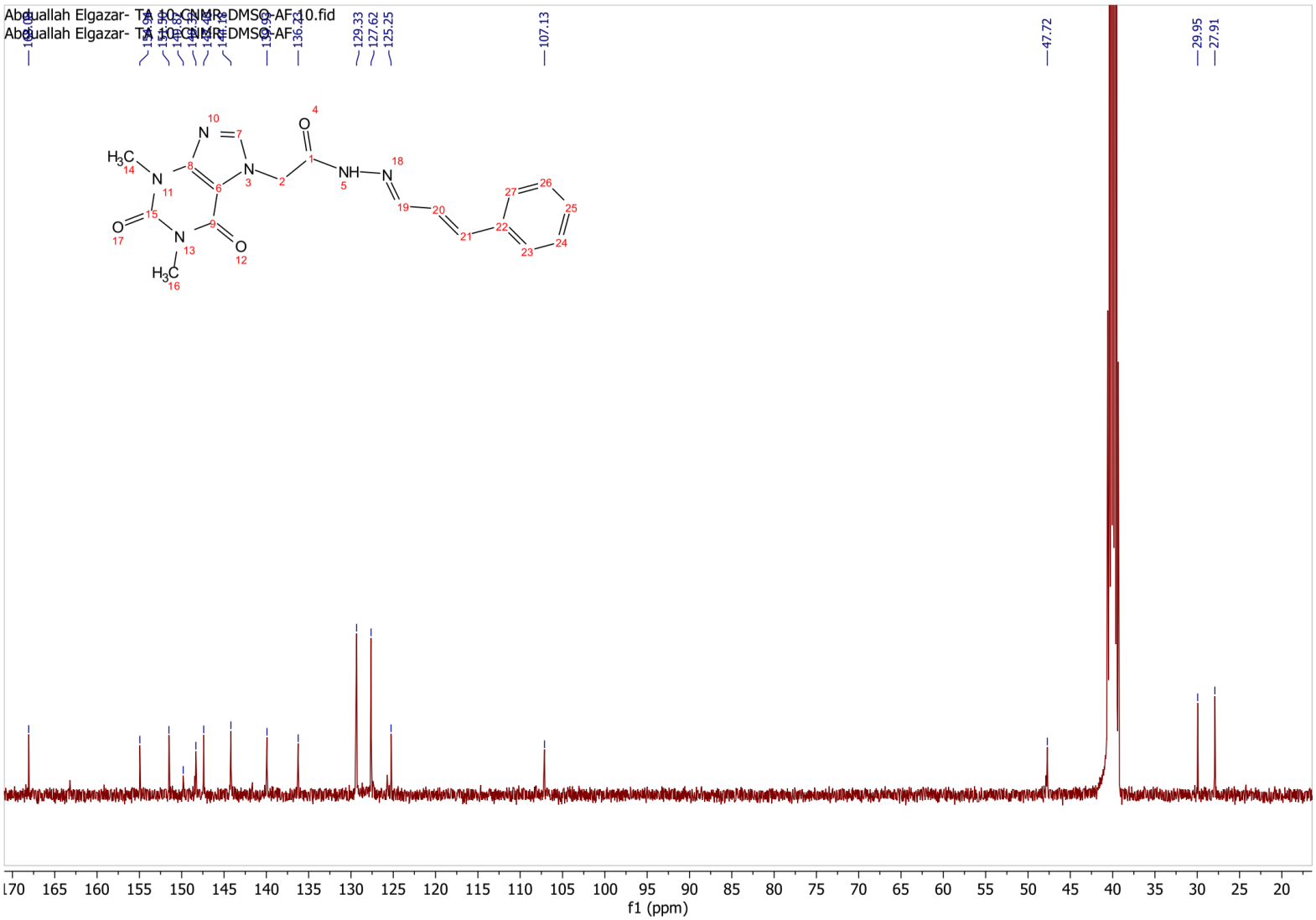
Table.s26 NMR assignment of acefylline-hydrazone cinnamaldehyde hybrid **18k**



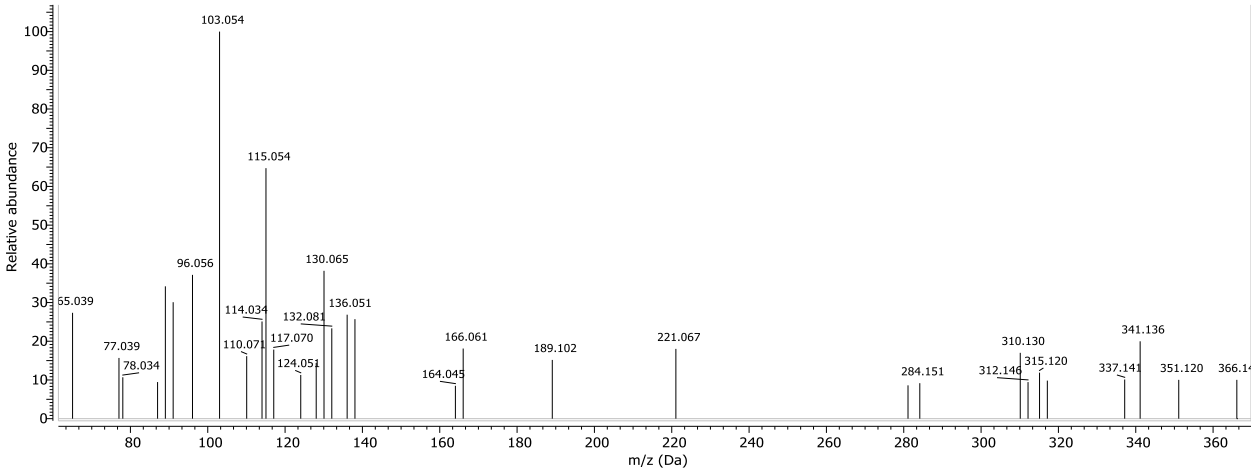
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C(δ, ppm)
COOH	--	169.48	C	--	168.08
1	-	154.3	C	--	154.94
Ph-CH	7.48	152.46	CH	7.24 (d, *J* = 28.9 Hz, 1H)	151.50
2	--	151.13	C	--	149.82
3	--	148.36	C	--	148.32
4	8.04	143.63	CH	7.87 (d, *J* = 12.3 Hz, 1H)	147.40
CH=N	10.2	192.28	CH	8.06 (s, 1H)	144.18
1’	--	136.47	C	--	139.93
4’	7.64	134.43	CH	7.65 – 7.61 (m, 1H)	136.23
CH=CH	6.6	131.17	CH	7.05 (dd, *J* = 29.9, 12.6 Hz, 1H)	129.33
2’	7.87	129.68	CH	7.65 – 7.61 (m, 1H)	127.62
6’	7.87	129.68	CH	7.65 – 7.61 (m, 1H)	127.62
5’	7.56	129.68	CH	7.45 – 7.38 (m, 1H)	125.25
3’	7.56	128.98	CH	7.45 – 7.38 (m, 1H)	125.25
5	--	106.83	C	--	107.13
CH2CO	5.07	47.6	CH2	5.45 (s, 2H)	47.72
6	3.44	29.92	CH3	3.46 (s, 3H)	29.95
7	3.20	27.9	CH3	3.21 (s, 3H)	27.91
NH	11.25	--	NH	11.68 (s, 1H)	--



^{1}H NMR spectrum of compound 18k

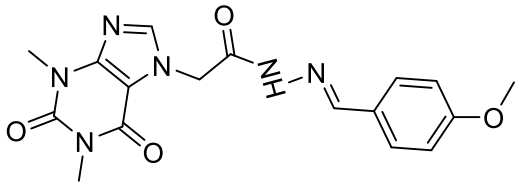


^{13}C NMR spectrum of compound 18k

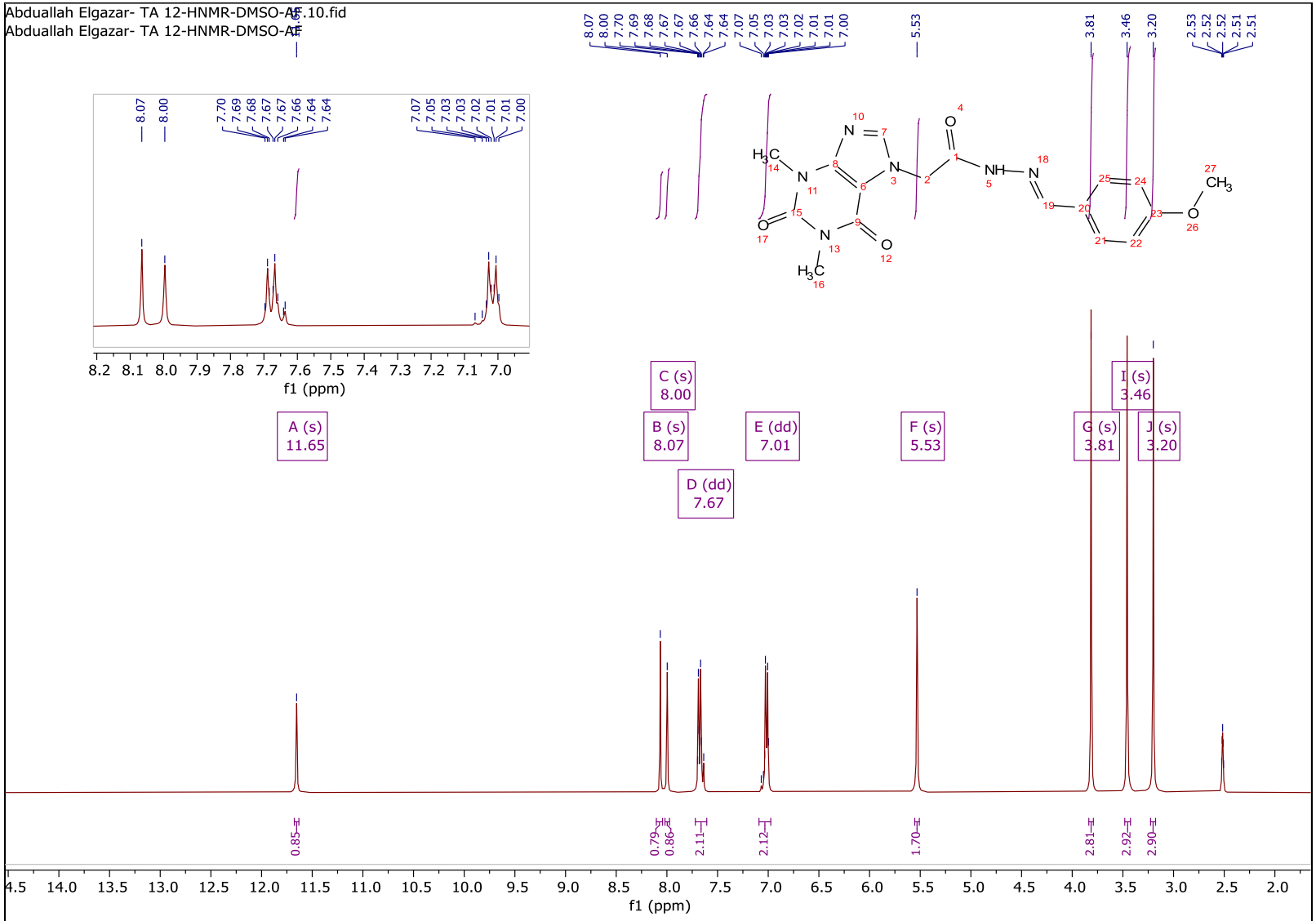


Mass spectrum of compound 18k

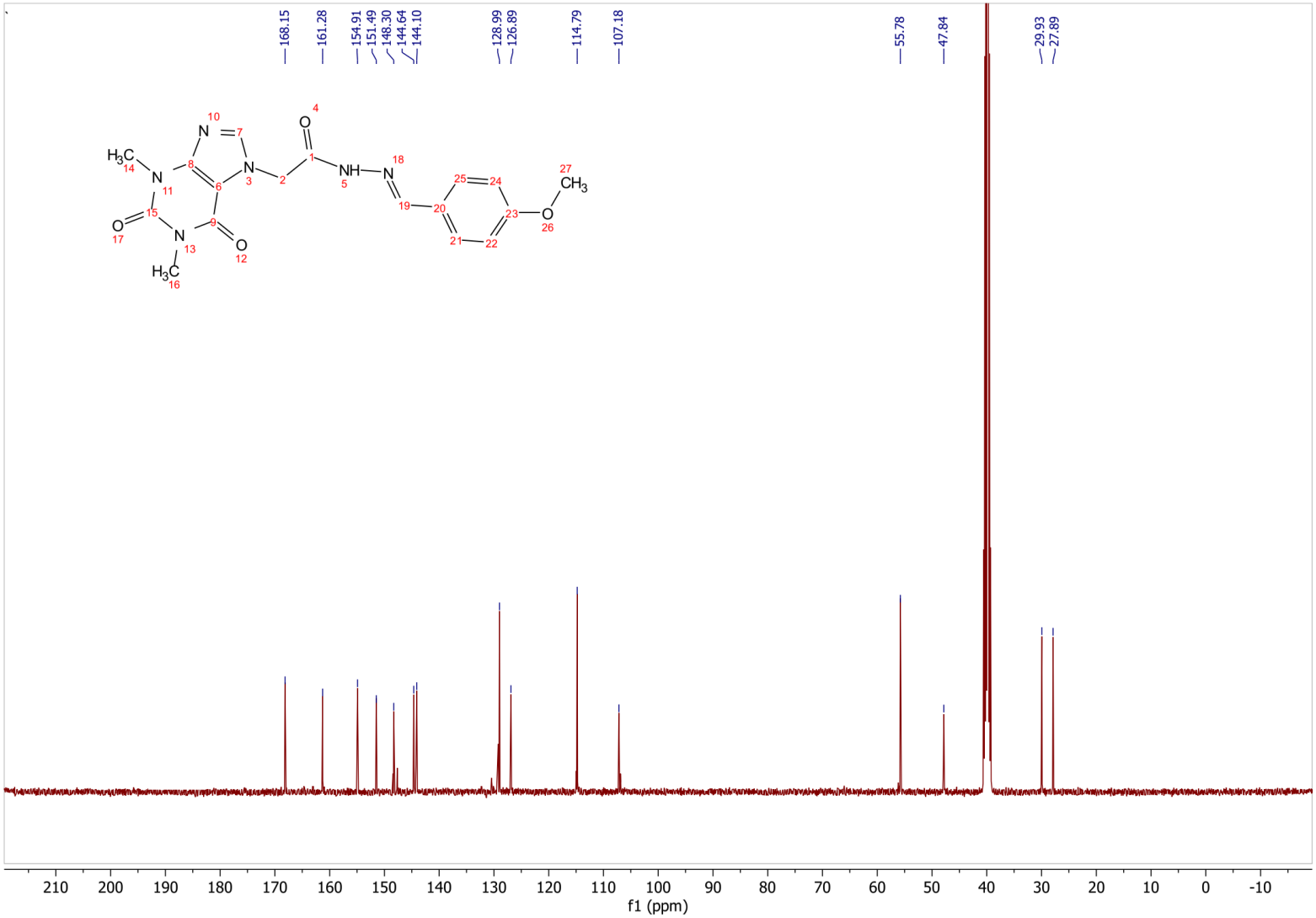
Table.s27 NMR assignment of acefylline-hydrazone anisaldehyde hybrid **18l**



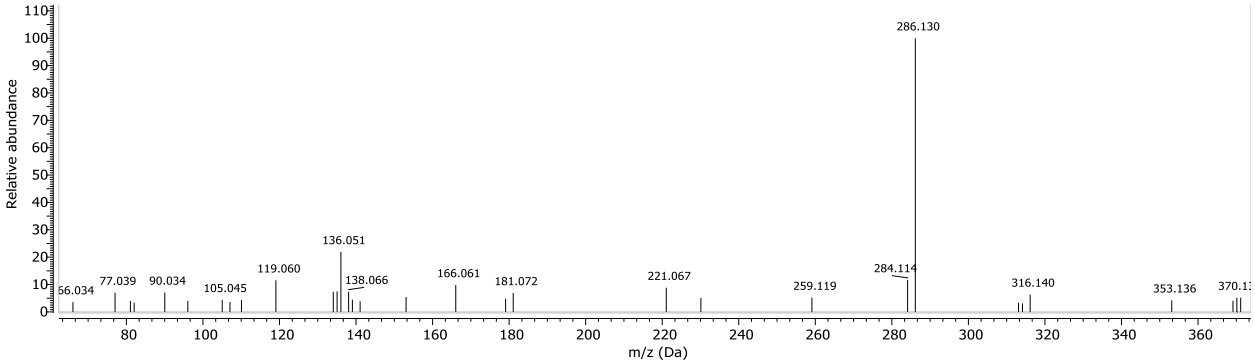
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C(δ, ppm)
CH=N	10.6	191.26	CH	8.07 (s, 1H)	144.10
4	8.04	143.63	CH	8.00 (s, 1H)	144.64
2’	7.78	132.56	CH	7.67 (dd, *J* = 7.2, 5.1 Hz, 1H)	128.99
6’	7.78	132.56	CH	7.67 (dd, *J* = 7.2, 5.1 Hz, 1H)	128.99
3’	6.9	116.06	CH	7.01 (dd, *J* = 9.0, 3.1 Hz, 1H)	114.79
5’	6.9	116.06	CH	7.01 (dd, *J* = 9.0, 3.1 Hz, 1H)	114.79
CH2CO	5.07	47.6	CH2	5.53 (s, 2H)	47.84
OCH3	3.85	56	CH_3	3.81 (s, 3H)	55.78
6	3.44	29.92	CH3	3.46 (s, 3H)	29.93
7	3.20	27.9	CH3	3.20 (s, 3H)	27.89
NH	11	--	NH	11.65 (s, 1H)	--
COOH	--	169.48	C	--	168.15
4’	--	161.65	C	--	161.28
2	--	151.13	C	--	151.49
3	--	148.36	C	--	148.30
1’	--	129.94	C	--	126.89
5	--	106.83	C	--	107.18
1	-	154.3	C	-	154.91



^{1}H NMR spectrum of compound 18l

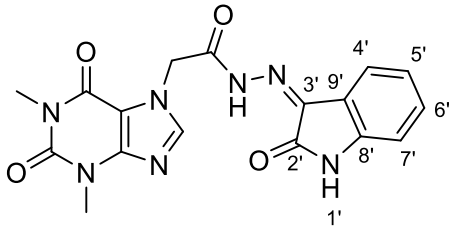


^{13}C NMR spectrum of compound 18l

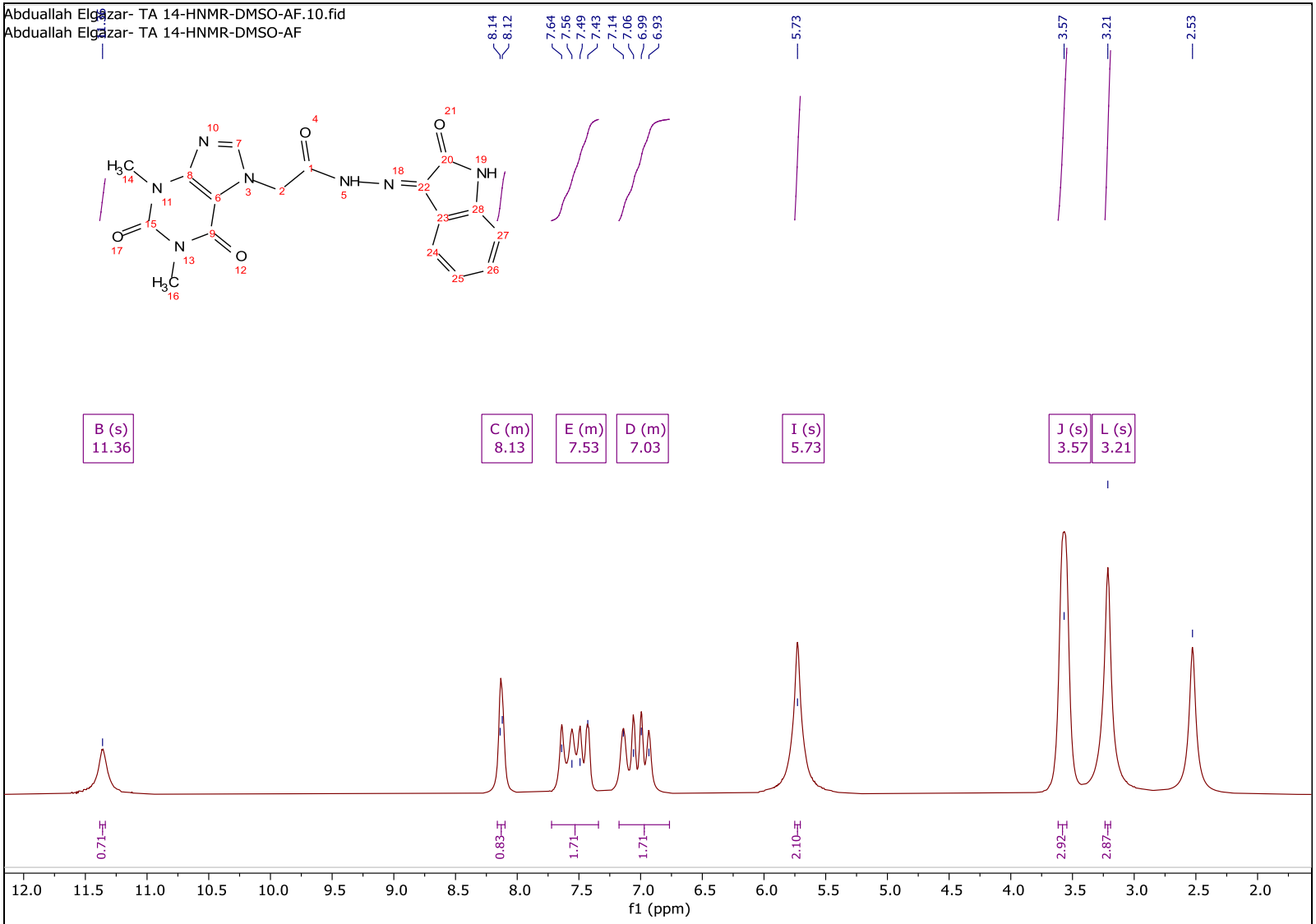


Mass spectrum of compound 18l

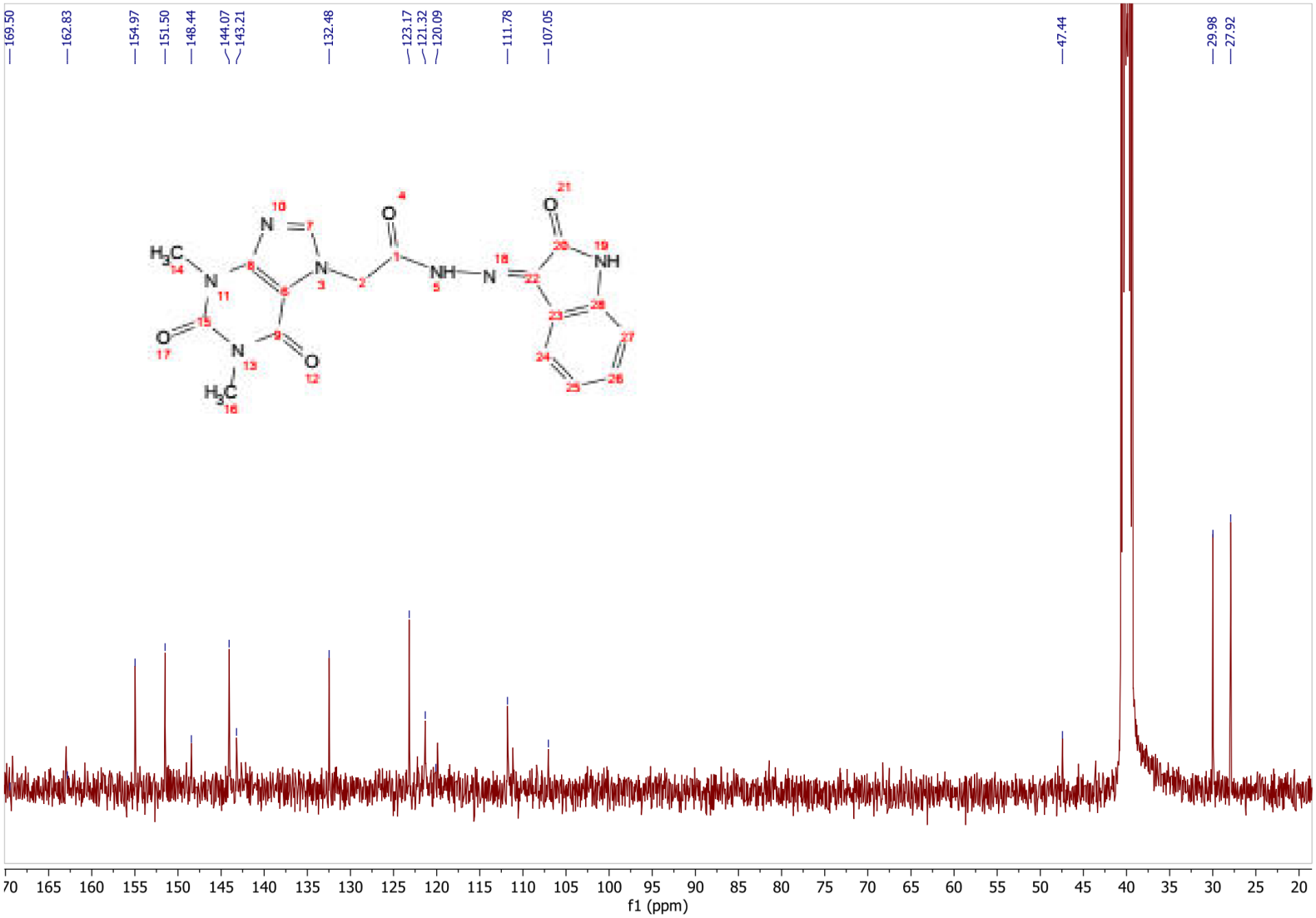
Table.s28 NMR assignment of acefylline-hydrazone isatin hybrid 19



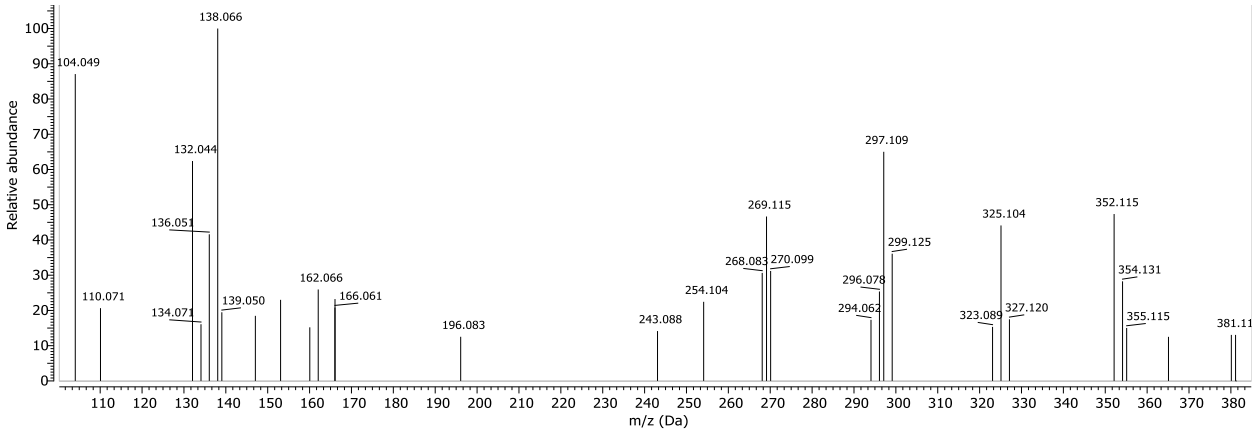
Parent compound			Hybrid compound		
Atom C/H	^{1}H(δ,ppm)(J,Hz)	^{13}C (δ, ppm)	DEPT	^{1}H(δ,ppm)(J,Hz)	^{13}C(δ, ppm)
4	8.04	143.63	CH	8.16 – 8.10 (m, 1H)	144.07
4’	7.50	124.59	CH	7.72 – 7.34 (m, 1H)	132.48
6’	7.58	117.73	CH	7.72 – 7.34 (m, 1H)	121.32
5’	7.07	122.68	CH	7.17 – 6.77 (m, 1H)	123.17
7’	6.9	112.12	CH	7.17 – 6.77 (m, 1H)	111.78
NH ISATIN	11.023	--	--	12.72 (s, 1H)	--
NH-HYDRAZIDE	11	--	--	11.36 (s, 1H)	--
CH2CO	5.07	47.6	CH2	5.73 (s, 2H)	47.44
6	3.44	29.92	CH3	3.57 (s, 3H)	29. 98
7	3.20	27.9	CH3	3.21 (s, 3H)	27.92
COOH	--	169.48	C	--	162.83
2’	--	159.26	C	--	154.97
1	-	154.3	C	--	154.97
2	--	151.13	C	--	151.50
8’	--	150.64	C	--	151.50
3	--	148.36	C	--	148.44
C=O/C=N	10.6	184.3	C	--	143.21
9’	--	117.73	C	-	119.89
5	--	106.83	C	--	107.05



^{1}H NMR spectrum of compound 19



^{13}C NMR spectrum of compound 19



Mass spectrum of compound 19