

# Cytotoxic Cyclolignans Obtained by the Enlargement of the Cyclolignan Skeleton of Podophyllic Aldehyde, a Selective Podophyllotoxin-Derived Cyclolignan

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**Table S1.** Cytotoxicity data (GI<sub>50</sub> in  $\mu$ M) for the synthesized cyclolignans

<b>Compound</b>	<b>A-549</b>	<b>HT-29</b>	<b>MEL-28</b>
<b>1</b>	0.012	0.012	-
<b>2</b>	0.12	0.012	0.23
<b>3</b>	0.27	0.27	0.27
<b>4</b>	0.22	0.22	0.22
<b>5</b>	0.27	0.27	0.27
<b>6</b>	10	2.1	12
<b>7</b>	2.6	2.6	2.6
<b>8</b>	2.3	2.3	2.3
<b>9</b>	0.061	0.061	0.061
<b>9a</b>	0.024	0.024	0.024
<b>9b</b>	0.024	0.024	0.024
<b>10</b>	9.7	12	9.7
<b>11</b>	2.5	2.5	2.5
<b>12</b>	1.9	1.9	1.9
<b>13</b>	0.92	0.92	0.92
<b>14</b>	9.2	9.2	9.2
<b>15</b>	1.7	1.7	-
<b>16</b>	>9.7	>9.7	>9.7
<b>17</b>	>9.5	>9.5	>9.5
<b>18</b>	>9.1	>9.1	>9.1
<b>19</b>	>9.4	>9.4	9.4
<b>20</b>	>8.4	>8.4	8.4
<b>21</b>	1.0	0.50	1.0
<b>22</b>	>9.7	>9.7	>9.7
<b>28</b>	4.7	0.95	-
<b>29</b>	0.92	0.92	-
<b>30</b>	0.92	0.92	-
<b>31</b>	0.87	0.09	-
<b>32</b>	>8.3	0.83	-

**Table S2:** Swissadme results for compounds synthesized in this work.

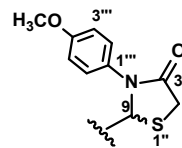
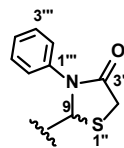
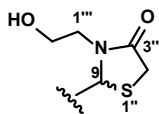
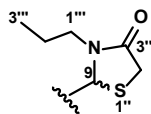
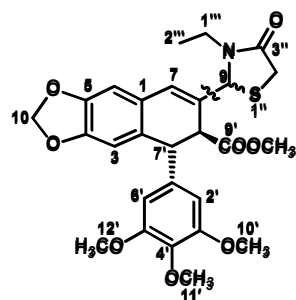
Compound	MW	Lipinski #violations	#Rotatable bonds	#H-bond acceptors	#H-bond donors	TPSA	Log P
<b>1</b>	414.41	0	4	8	1	92.68	2.28
<b>2</b>	426.42	0	7	8	0	89.52	2.93
<b>3</b>	469.44	0	8	9	0	118.27	2.81
<b>4</b>	452.45	0	8	8	0	89.52	3.31
<b>5</b>	466.48	0	8	8	0	89.52	3.59
<b>6</b>	482.48	0	9	9	0	98.75	3.52
<b>7</b>	454.47	0	8	8	1	92.68	3.24
<b>8</b>	426.46	0	7	7	2	86.61	3.02
<b>9</b>	410.42	0	4	7	0	72.45	3.34
<b>9a</b>	410.42	0	4	7	0	72.45	3.37
<b>9b</b>	410.42	0	4	7	0	72.45	3.37
<b>10</b>	502.46	1	7	10	0	89.52	4.19
<b>11</b>	514.53	1	7	8	1	101.13	4.17
<b>12</b>	528.55	1	8	8	1	101.13	4.49
<b>13</b>	542.58	1	7	8	1	101.13	4.81
<b>14</b>	528.55	1	7	8	1	101.13	4.49
<b>15</b>	583.42	1	7	8	1	101.13	5.24
<b>16</b>	515.51	1	7	9	0	98.48	4.42
<b>17</b>	529.54	1	7	9	0	98.48	4.74
<b>18</b>	549.96	1	7	9	0	98.48	4.93
<b>19</b>	531.58	1	7	8	0	113.58	4.92
<b>20</b>	599.57	1	8	11	0	113.58	5.94
<b>21</b>	515.51	1	7	9	1	114.02	3.53
<b>22</b>	516.50	2	7	10	1	126.91	3.00
<b>28</b>	527.59	1	8	8	0	118.06	3.41
<b>29</b>	541.61	1	9	8	0	118.06	3.72
<b>30</b>	543.59	1	9	9	1	138.29	2.64
<b>31</b>	575.63	1	8	8	0	118.06	4.17
<b>32</b>	605.65	1	9	9	0	127.29	4.14



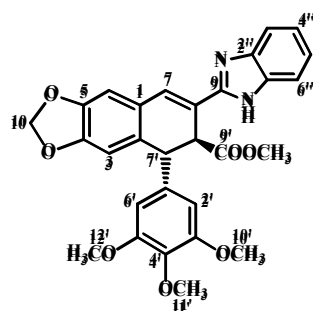
**Table S3:** Additional Swissadme results for compounds synthesized in this work.

<b>Compound</b>	<b>GI absorption</b>	<b>BBB permeant</b>	<b>Pgp substrate</b>	<b>CYP1A2 inhibitor</b>	<b>CYP2C19 inhibitor</b>	<b>CYP2C9 inhibitor</b>	<b>CYP2D6 inhibitor</b>
<b>1</b>	High	No	No	No	No	No	Yes
<b>2</b>	High	No	No	No	Yes	Yes	Yes
<b>3</b>	High	No	No	No	Yes	Yes	Yes
<b>4</b>	High	No	No	No	Yes	Yes	Yes
<b>5</b>	High	No	No	No	Yes	Yes	Yes
<b>6</b>	High	No	No	No	Yes	Yes	Yes
<b>7</b>	High	No	No	No	Yes	Yes	Yes
<b>8</b>	High	No	Yes	No	No	Yes	Yes
<b>9</b>	High	Yes	No	No	Yes	Yes	Yes
<b>9a</b>	High	Yes	No	No	Yes	Yes	Yes
<b>9b</b>	High	Yes	No	No	Yes	Yes	Yes
<b>10</b>	High	No	No	No	Yes	Yes	Yes
<b>11</b>	High	No	Yes	No	No	Yes	Yes
<b>12</b>	High	No	Yes	No	No	Yes	Yes
<b>13</b>	High	No	Yes	No	No	Yes	Yes
<b>14</b>	High	No	Yes	No	No	Yes	Yes
<b>15</b>	Low	No	Yes	No	No	Yes	Yes
<b>16</b>	High	No	Yes	No	No	Yes	Yes
<b>17</b>	High	No	Yes	No	No	Yes	Yes
<b>18</b>	High	No	Yes	No	No	Yes	Yes
<b>19</b>	Low	No	Yes	No	No	Yes	Yes
<b>20</b>	Low	No	Yes	No	No	Yes	No
<b>21</b>	High	No	Yes	No	No	Yes	Yes
<b>22</b>	High	No	Yes	No	No	Yes	Yes
<b>28</b>	High	No	No	No	Yes	Yes	Yes
<b>29</b>	High	No	No	No	Yes	Yes	Yes
<b>30</b>	High	No	No	No	No	Yes	Yes
<b>31</b>	High	No	Yes	No	Yes	Yes	Yes
<b>32</b>	Low	No	Yes	No	No	Yes	Yes

**Table S4.**  $^{13}\text{C}$  NMR data for thiazolidines **28-32**

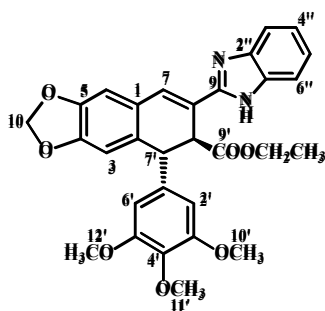


C	28	29	30	31	32
1	126.4/125.6	127.6 / 126.5	126.5 / 125.7	126.0	126.0
2	128.6/129.2	128.5	128.2 / 128.5	128.9	128.7
3	109.7/109.4	109.7 / 109.4	109.7 / 109.5	109.6	109.6
4	148.0	148.0	148.0	148.0	148.0
5	147.0/146.9	147.0 / 146.9	147.1	146.9	146.9
6	107.4/107.6	107.4 / 107.6	107.5	107.5	107.5
7	127.5/129.5	127.6 / 129.5	128.5 / 130.3	126.1	126.9 / 128.7
8	129.2/129.5	129.5 / 129.7	129.5 / 129.4	128.9	129.2
9	63.6/64.7	64.1 / 65.1	65.4 / 66.6	66.4	66.7
10	101.2	101.2	101.3	101.2	101.2
1'	137.8/138.0	137.8	137.8	137.8 / 138.0	138.1
2'. 6'	105.1/105.0	104.9	104.9	104.9	104.9
3'. 5'	153.1	153.1	153.1	153.0	153.0
4'	137.2	137.1	137.1	136.9	136.9
7'	46.9/47.6	46.8 / 47.5	46.9 / 47.6	46.5	46.8 / 47.7
8'	48.0/47.2	47.8 / 47.5	48.0 / 47.3	48.9	48.6 / 49.2
9'	172.3/172.0	172.3 / 172.0	172.4	172.3	172.6 / 171.9
10'. 12'	56.1	56.1	56.2	56.0	55.9 / 56.0
11'	60.8	60.8 / 60.3	60.8	60.8	60.8
9'-	52.4	52.4	52.5	52.4	52.4
2''	32.2/32.9	32.1 / 32.8	31.9 / 32.7	32.7	32.7 / 33.1
3''	170.9/170.4	171.1 / 170.7	172.1	171.1 / 170.9	170.9
1'''	36.7/37.3	43.4 / 44.0	44.7	137.8	130.1 / 130.9
2'''	11.8	19.7 / 19.8	60.8	123.0	125.1
3'''		11.0 / 14.1		128.9	114.1
4'''				125.8	157.7
5'''				128.9	114.1
6'''				123.0	125.1
4'''-					55.3 / 55.4

**Table S5.** Correlations and assignments for compound **11** ( $\delta$  in ppm).

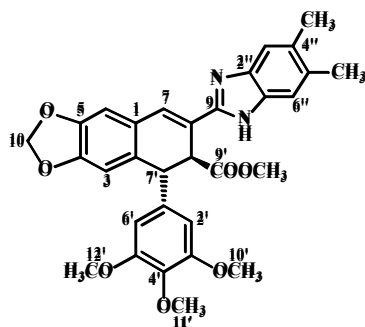
$\delta$ $^{13}\text{C}$	TYPE*	HMQC, $\delta$ $^1\text{H}$ ( <i>J</i> in Hz)	HMBC, $\delta$ $^1\text{H}$	Assigned
46,1	CH	4,65 d	6,70 s, 6,35 s, 4,50 sa	7'
47,7	CH	4,50 sa	7,38 sa, 4,65 d	8'
52,7	CH <sub>3</sub>	3,65 s		9'-OCH <sub>3</sub>
56,0	CH <sub>3</sub>	3,69 s		3', 5'-OCH <sub>3</sub>
60,7	CH <sub>3</sub>	3,74 s		4'-OCH <sub>3</sub>
101,3	CH <sub>2</sub>	5,95 d, 5,93 d		10
104,8	CH	6,35 s	6,35 s, 4,65 d	2', 5'
107,9	CH	6,61 sa	7,38 sa	6
109,6	CH	6,70 s	4,65 d	3
122,0	C		4,65 d, 4,50 sa	8
122,7	CH	7,15 m		4'', 5''
126,0	C		6,70 s, 4,65 d	1
129,2	CH	7,38 sa	6,61 sa, 4,50 sa	7
130,1	C		7,38 sa, 4,65 d	2
136,7	C		6,35 s, 3,74 s	4'
138,0	C		4,65 d, 4,50 sa	1'
147,0	C		6,70 s, 6,61 sa, 5,95 d, 5,93 d	5
148,3	C		6,70 s, 6,61 sa, 5,95 d, 5,93 d	4
151,5	C		7,38 sa, 4,50 sa	9
153,0	C		6,35 s, 3,69 s	3', 5'
173,2	C		4,65 d, 4,50 sa, 3,65 s	9'

\* Carbon type according to DEPT experiment

**Table S6.** Correlations and assignments for compound **12** ( $\delta$  in ppm):

$\delta$ $^{13}\text{C}$	TYPE*	HMQC, $\delta$ $^1\text{H}$ ( $J$ in Hz)	HMBC, $\delta$ $^1\text{H}$	Assigned
14,0	CH <sub>3</sub>	1,14 t	(4,13 dc)	9'-OCH <sub>2</sub> CH <sub>3</sub>
46,0	CH	4,64 sa	6,70 s, 6,36 s	7'
48,2	CH	4,39 sa	4,64 sa	8'
56,1	CH <sub>3</sub>	3,71 s		3', 5'-OCH <sub>3</sub>
60,7	CH <sub>3</sub>	3,73 s		4'-OCH <sub>3</sub>
61,7	CH <sub>2</sub>	4,13 dc	1,14 t	9'-OCH <sub>2</sub> CH <sub>3</sub>
101,4	CH <sub>2</sub>	5,98 s, 5,97 s		10
104,7	CH	6,36 s	6,36 s, 4,64 sa	2', 6'
108,2	CH	6,76 s		6
109,6	CH	6,70 s		3
123,1	CH / CH	7,16 m		7 / 4'', 5''
125,8	C		6,70 s, (4,64 sa)	1
130,6	C		6,76 s, (4,64 sa), 4,39 sa	2
136,9	C		6,36 s, 3,73 s	4'
137,7	C		4,64 sa	1'
147,0	C		6,76 s, 6,70 s, 5,98 s, 5,97 s	5
148,6	C		6,76 s, 6,70 s, 5,98 s, 5,97 s	4
151,2	CH			9
153,1	C		6,36 s, 3,71 s	3', 5'
172,4	C		(4,39 sa), (4,13 dc)	9'

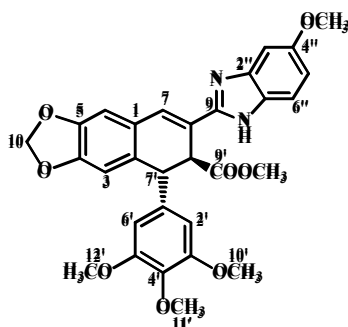
\* Carbon type according to DEPT experiment

**Table S7.** Correlations and assignments for compound **13** ( $\delta$  in ppm):

$\delta^{13}\text{C}$	TYPE*	HMQC, $\delta^1\text{H}$ ( <i>J</i> in Hz)	HMBC, $\delta^1\text{H}$	Assigned
20,3	CH <sub>3</sub>	2,30 s		4'', 5''-CH <sub>3</sub>
46,2	CH	4,63 d	6,70 s, 6,36 s, 4,48 d	7'
47,7	CH	4,48 d	7,31 s, 4,63 d	8'
52,7	CH <sub>3</sub>	3,67 s		9'-OCH <sub>3</sub>
56,1	CH <sub>3</sub>	3,69 s		3', 5'-OCH <sub>3</sub>
60,7	CH <sub>3</sub>	3,73 s		4'-OCH <sub>3</sub>
101,3	CH <sub>2</sub>	5,96 d, 5,95 d		10
104,7	CH	6,36 s	6,36 s, 4,63 d	2', 6'
108,0	CH	6,65 s	7,31 s	6
109,6	CH	6,70 s	4,63 d	3
110,7 <sup>#</sup>	CH		2,30 s	3''
119,2 <sup>#</sup>	CH		2,30 s	6''
122,2	C		4,63 d, 4,48 d	8
126,1	C		6,70 s	1
128,3	CH	7,31 s	6,65 s, 4,48 d	7
130,3	C		7,31 s, 6,65 s, 4,63 d, 4,48 d	2
131,1 <sup>§</sup>	C		2,30 s	4''
132,3 <sup>§</sup>	C		2,30 s	5''
136,8	C		6,36 s, 3,73 s	4'
137,9	C		4,63 d, 4,48 d	1'
146,9	C		6,70 s, 5,96 d, 5,95 d	5
148,2	C		6,65 s, 5,96 d, 5,95 d	4
150,5	C		7,31 s, 4,48 d	9
153,0	C		6,36 s, 3,69 s	3', 5'
173,3	C		4,63 d, 4,48 d, 3,67 s	9'

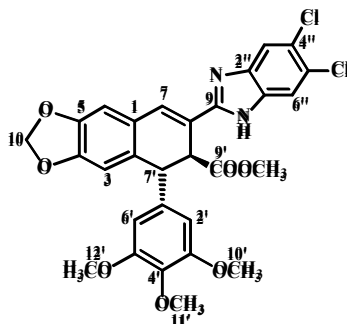
\* Carbon type according to DEPT experiment

#, § Interchangeable signals

**Table S8.** Correlations and assignments for compound **14** ( $\delta$  in ppm):

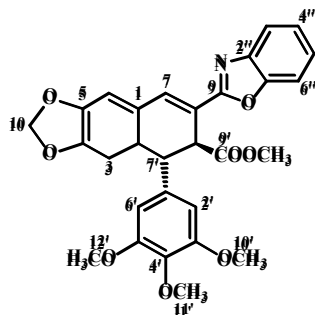
$\delta$ <sup>13</sup> C	TYPE*	HMQC, $\delta$ <sup>1</sup> H ( <i>J</i> in Hz)	HMBC, $\delta$ <sup>1</sup> H	Assigned
46,1	CH	4,65 d	6,70 s, 6,34 s, 4,46 d	7'
47,7	CH	4,46 d	(7,37 s), 4,65 d	8'
52,8	CH <sub>3</sub>	3,69 s		9'-OCH <sub>3</sub>
55,6	CH <sub>3</sub>	3,81 s		4''-OCH <sub>3</sub>
56,1	CH <sub>3</sub>	3,71 s		3', 5'-OCH <sub>3</sub>
60,7	CH <sub>3</sub>	3,73 s		4'-OCH <sub>3</sub>
101,4	CH <sub>2</sub>	5,97 d, 5,96 d		10
104,8	CH	6,34 s	6,34 s, 4,65 d	2', 6'
108,1	CH	6,66 s		6
109,6	CH	6,70 s	4,65 d	3
112,6	CH	6,78 d		3'', 6''
121,4	C		4,65 d, (4,46 d)	8
126,0	C		6,70 s, 4,65 d	1
129,0	CH			7
130,2	C		6,66 s, 4,65 d, 4,46 d	2
136,9	C		6,34 s, 3,73 s	4'
137,9	C		4,65 d, 4,46 d	1'
147,1	C		6,70 s, 5,97 d, 5,96 d	5
148,4	C		6,66 s, 5,97 d, 5,96 d	4
150,8	C		(4,46 d)	9
153,0	C		6,34 s, 3,71 s	3', 5'
156,7	C		(6,78 d), 3,81 s	4''
173,4	C		4,65 d, 4,46 d	4

\* Carbon type according to DEPT experiment

**Table S9.** Correlations and assignments for compound **15** ( $\delta$  in ppm):

$\delta^{13}\text{C}$	TYPE*	HMQC, $\delta^1\text{H}$ ( <i>J</i> in Hz)	HMBC, $\delta^1\text{H}$	Assigned
46,3	CH	4,68 d	6,69 s, 6,33 s, 4,66 d	7'
47,6	CH	4,66 d	7,15 s, 4,68 d	8'
53,2	CH <sub>3</sub>	3,82 s		9'-OCH <sub>3</sub>
56,2	CH <sub>3</sub>	3,71 s		3', 5'-OCH <sub>3</sub>
60,7	CH <sub>3</sub>	3,74 s		4'-OCH <sub>3</sub>
101,5	CH <sub>2</sub>	5,97 d, 5,94 d		10
105,1	CH	6,33 s	6,33 s, 4,68 d	2', 6'
108,2	CH	6,24 s	7,15 s	6
109,6	CH	6,69 s	4,68 d	3
121,3	C		4,68 d, 4,66 d	8
125,6	C		7,15 s, 6,69 s, 4,68 d	1
130,1	C		7,15 s, 6,24 s, 4,68 d	2
130,2	CH	7,15 s	6,24 s, 4,66 d	7
137,1	C		6,33 s, 3,74 s	4'
137,7	C		4,68 d, 4,66 d	1'
147,0	C		6,69 s, 6,24 s, 5,97 d, 5,94 d	5
148,6	C		6,69 s, 6,24 s, 5,97 d, 5,94 d	4
152,9	C		7,15 s, 4,66 d	9
153,1	C		6,33 s, 3,71 s	3', 5'
174,7	C		7,15 s, 4,68 d, 4,66 d	9'

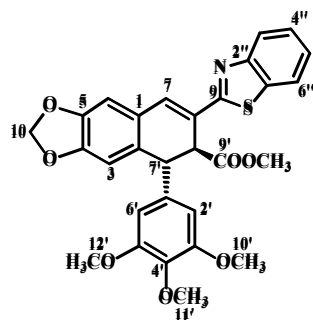
\* Carbon type according to DEPT experiment

**Table S10.** Correlations and assignments for compound **16** ( $\delta$  in ppm):

$\delta^{13}\text{C}$	TYPE*	HMQC, $\delta^1\text{H}$ ( <i>J</i> in Hz)	HMBC, $\delta^1\text{H}$	Assigned
46,2	CH	4,72 d	(6,72 s), 6,30 s, 4,40 d	7'
47,4	CH	4,40 d	7,73 s, 4,72 d	8'
52,7	CH <sub>3</sub>	3,65 s		9'-OCH <sub>3</sub>
56,0	CH <sub>3</sub>	3,72 s		3', 5'-OCH <sub>3</sub>
60,7	CH <sub>3</sub>	3,75 s		4'-OCH <sub>3</sub>
101,5	CH <sub>2</sub>	6,01 d, 5,99 d		10
104,8	CH	6,30 s	6,30 s, 4,72 d	2', 6'
108,4	CH	6,90 s	(7,73 s)	6
110,0	CH	6,72 s	4,72 d	3
110,2	CH	(7,49 m)		6''
119,4	C		4,72 d, 4,40 d	8
119,8	CH	(7,67 m)		3''
124,4	CH		7,49 m	4''
126,0	C		6,72 s, (4,72 d)	1
131,0	C		7,73 s, 6,90 s, 4,72 d, 4, 40 d	2
132,7	CH	7,73 s	6,90 s, 4,40 d	7
137,0	C		6,30 s, 3,75 s	4'
137,6	C		4,72 d, 4,40 d	1'
142,1	C		(7,49 m)	2''
147,2	C		(6,90 s), 6,72 s, (6,01 s, 5,99 s)	5
149,0	C		6,90 s, (6,72 s), (6,01 s, 5,99 s)	4
150,5	C		(7,67 m)	1''
153,1	C		6,30 s, 3,72 s	3', 5'
163,0	C		7,73 s, (4,40 d)	9
172,2	C		4,72 d, 4,40 d, 3,65 s	9'

\* Carbon type according to DEPT experiment

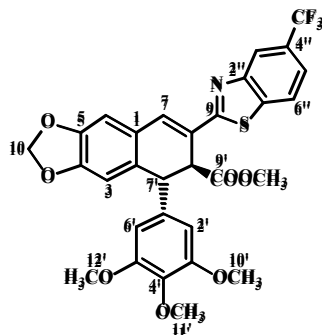


**Table S11.** Correlations and assignments for compound **19** ( $\delta$  in ppm):

$\delta^{13}\text{C}$	TYPE*	HMQC, $\delta^1\text{H}$ ( <i>J</i> in Hz)	HMBC, $\delta^1\text{H}$	Assigned
46,5	CH	4,67 d	6,73 s, 6,38 s, 4,61 d	7'
48,3	CH	4,61 d	7,40 s, 4,67 d	8'
52,5	CH <sub>3</sub>	3,62 s		9'-OCH <sub>3</sub>
56,0	CH <sub>3</sub>	3,71 s		3', 5'-OCH <sub>3</sub>
60,7	CH <sub>3</sub>	3,75 s		4'-OCH <sub>3</sub>
101,4	CH <sub>2</sub>	5,99 s, 5,98 s		10
104,6	CH	6,38 s	6,38 s, 4,67 d	2', 6'
108,2	CH	6,86 s	7,40 s	6
109,8	CH	6,73 s	4,67 d	3
121,3	CH	7,82 m	7,42 m	6''
123,0	CH	7,92 m	7,34 m	3''
125,2	CH	7,34 m	7,92 m	5''
126,0	CH	7,42 m	7,82 m	4''
126,1	C		6,73 s, 4,67 d	1
127,4	C		4,67 d, 4,61 d	8
131,3	C		7,40 s, 6,86 s, 4,67 d, 4,61 d	2
131,8	CH	7,40 s	6,86 s	7
134,4	C		7,92 m, 7,34 m	2''
136,8	C		6,38 s, 3,75 s	4'
137,8	C		4,67 d, 4,61 d	1'
147,1	C		6,86 s, 6,73 s, 5,99 s, 5,98 s	5
148,7	C		6,86 s, 6,73 s, 5,99 s, 5,98 s	4
153,0	C		6,38 s, 3,71 s	3', 5'
153,7	C		7,82 m, 7,42 m	1''
167,8	C		7,40 s, 4,61 d	9
172,5	C		4,67 d, 4,61 d, 3,62 s	9'

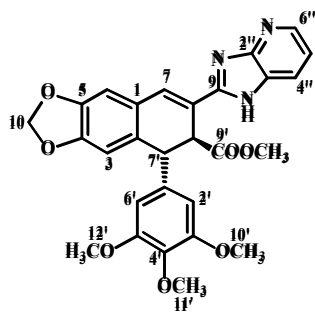
\* Carbon type according to DEPT experiment

**Table S12.** Correlations and assignments for compound **20** ( $\delta$  in ppm):



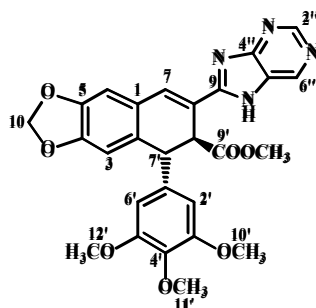
$\delta^{13}\text{C}$	TYPE*	HMQC, $\delta^1\text{H}$ ( <i>J</i> in Hz)	HMBC, $\delta^1\text{H}$	Assigned
46,5	CH	4,69 d	6,73 s, 6,36 s, 4,58 d	7'
48,4	CH	4,58 d	7,43 s, 4,69 d	8'
52,6	CH <sub>3</sub>	3,64 s		9'-OCH <sub>3</sub>
56,1	CH <sub>3</sub>	3,72 s		3', 5'-OCH <sub>3</sub>
60,7	CH <sub>3</sub>	3,75 s		4'-OCH <sub>3</sub>
101,5	CH <sub>2</sub>	6,01 d, 5,99 d		10
104,6	CH	6,36 s	6,36 s, 4,69 d	2', 6'
108,3	CH	6,87 s	7,43 s	6
109,9	CH	6,73 s	4,69 d	3
120,1	CH	8,19 s	7,56 dd	3''
121,5	CH	7,56 dd	8,19 s	5''
121,9	CH	7,92 d		6''
125,5	C		8,19 s, 7,56 dd	4''-CF <sub>3</sub>
125,8	C		7,43 s, 6,73 s	1
127,0	C		4,69 d, 4,58 d	8
129,1	C		7,92 d	2''
131,5	C		7,43 s, 6,87 s, 4,69 d, 4,58 d	2
133,1	CH	7,43 s	6,87 s, 4,58 d	7
137,0	C		6,36 s, 3,75 s	4'
137,7	C		4,69 d, 4,58 d	1'
137,8	C		8,19 s, 7,56 dd	1''
147,2	C		6,87 s, 6,73 s, 6,01 s, 5,99 s	5
149,0	C		6,87 s, 6,73 s, 6,01 s, 5,99 s	4
153,1	C		6,36 s, 3,72 s	3', 5'
153,3	C		7,92 d	4''
169,8	C		7,43 s, 4,58 d	9
172,3	C		4,69 d, 4,58 d, 3,64 s	9'

\* Carbon type according to DEPT experiment

**Table S13.** Correlations and assignments for compound **21** ( $\delta$  in ppm):

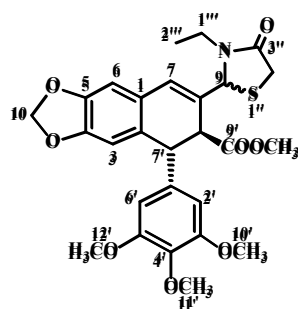
$\delta^{13}\text{C}$	TYPE*	HMQC, $\delta^1\text{H}$ ( <i>J</i> in Hz)	HMBC, $\delta^1\text{H}$	Assigned
46,2	CH	4,75 d	6,75 s, 6,36 s, 4,61 d	7'
47,5	CH	4,61 d	7,65 s, 4,75 d	8'
52,6	CH <sub>3</sub>	3,63 d		9'-OCH <sub>3</sub>
55,9	CH <sub>3</sub>	3,67 s		3', 5'-OCH <sub>3</sub>
60,6	CH <sub>3</sub>	3,72 s		4'-OCH <sub>3</sub>
101,5	CH <sub>2</sub>	6,02 s, 6,00 s		10
104,6	CH	6,36 s	6,36 s, 4,75 d	2', 6'
107,9	CH	6,84 s	7,65 s	6
109,9	CH	6,75 s	4,75 d	3
118,2	CH	7,26 m		5''
122,4	C		4,75 d, 4,61 d	8
126,0	C		6,75 s, 4,75 d	1
130,6	C		7,65 s, 6,84 s, 4,75 d, 4,61 d	2
130,8	CH	7,65 s	6,84 s, 4,61 d	7
136,7	C		6,36 s, 3,72 s	4'
137,7	C		4,75 d, 4,61 d	1'
142,4	CH	8,35 d		4''
147,2	C		(6,84 s), 6,75 s, 6,02 s, 6,00 s	5
148,7	C		6,84 s, 6,75 s, 6,02 s, 6,00 s	9
153,0	C		6,36 s, 3,67 s	3', 5'
153,8	C		7,65 s, 4,61 d	9
172,6	C		4,75 d, 4,61 d, 3,63 s	9'

\* Carbon type according to DEPT experiment

**Table S14.** Correlations and assignments for compound **22** ( $\delta$  in ppm):

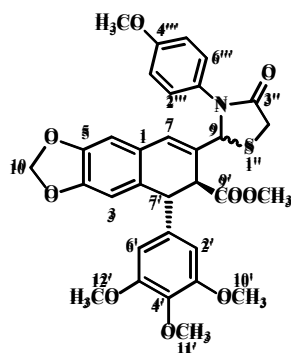
$\delta^{13}\text{C}$	TYPE*	HMQC, $\delta^1\text{H}$ ( <i>J</i> in Hz)	HMBC, $\delta^1\text{H}$	Assigned
46,1	CH	4,74 d	6,73 s, 6,31 s, 4,55 d	7'
47,6	CH	4,55 d	7,58 s, 4,74 d	8'
52,8	CH <sub>3</sub>	3,69 s		9'-OCH <sub>3</sub>
56,1	CH <sub>3</sub>	3,70 s		3', 5'-OCH <sub>3</sub>
60,7	CH <sub>3</sub>	3,73 s		4'-OCH <sub>3</sub>
101,6	CH <sub>2</sub>	6,01 s, 6,00 s		10
104,8	CH	6,31 s	6,31 s, 4,74 d	2', 6'
108,2	CH	6,75 s	7,58 s	6
110,0	CH	6,73 s	4,74 d	3
121,4	C		4,74 d, 4,55 d	8
125,4	C		6,73 s, 4,74 d	1
131,0	C		7,58 s, 6,75 s	2
132,3	CH	7,58 s	6,75 s, 4,55 d	7
135,2	C		9,04 s	5''
137,1	C		6,31 s, 3,73 s	4'
137,5	C		4,74 d, 4,55 d	1'
147,2	CH	9,04 s	8,95 s	6''
147,3	C		6,73 s, 6,01 s, 6,00 s	5
149,3	C		6,73 s, 6,01 s, 6,00 s	4
151,5	CH	8,95 s	9,04 s	2''
153,1	C		6,31 s, 3,70 s	9
153,2	C		9,04 s, 8,95 s	4''
154,4	C		7,58 s, 4,55 d	9
172,5	C		4,74 d, 4,55 d, 3,69 s	9'

\* Carbon type according to DEPT experiment

**Table S15.** Correlations and assignments for compound **28** ( $\delta$  in ppm):

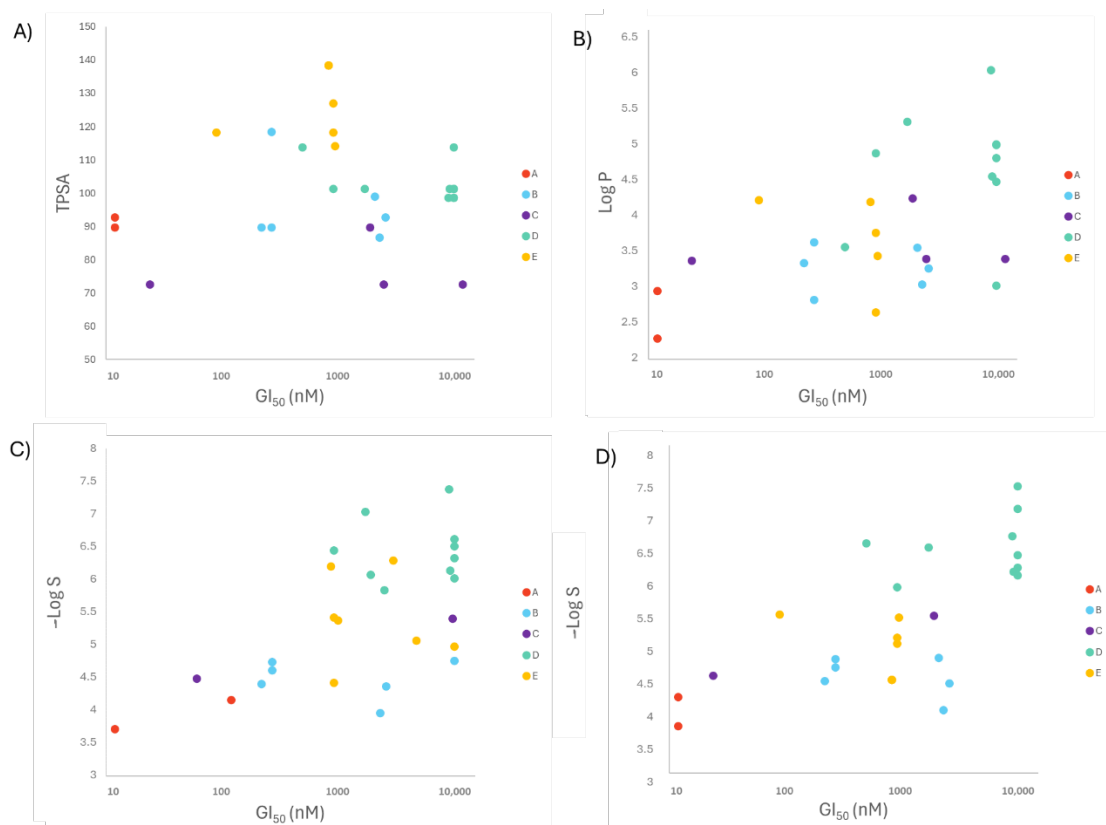
$\delta^{13}\text{C}$	TYPE*	HMQC, $\delta^1\text{H}$ ( <i>J</i> in Hz)	HMBC, $\delta^1\text{H}$	Assigned
11,8 / 11,8	CH <sub>3</sub>	0,95 t / 1,05 t		2'''
32,2 / 32,9	CH <sub>2</sub>	3,48 d, 3,45 s / 3,61 d, 3,41 s		2''
36,7 / 37,3	CH <sub>2</sub>		0,95 t / 1,05 t	1'''
46,9 / 47,6	CH	4,41 d / 4,32 d	6,18 s / 6,28 s	7'
48,0 / 47,2	CH	3,23 d / 3,63 d	6,47 s / 6,55 s	8'
52,4 / 52,4	CH <sub>3</sub>	3,66 s / 3,61 s		9'-OCH <sub>3</sub>
56,1 / 56,1	CH <sub>3</sub>	3,73 s / 3,76 s		3', 5'-OCH <sub>3</sub>
60,8 / 60,8	CH <sub>3</sub>	3,77 s / 3,80 s		4'-OCH <sub>3</sub>
63,6 / 64,7	CH	5,27 d / 5,25 d	6,47 s / 6,55 s	9
101,2 / 101,2	CH <sub>2</sub>	5,97 d, 5,96 d / 5,94 d, 5,93d		10
105,1 / 105,0	CH	6,18 s / 6,28 s	6,18 s, 4,41 d / 6,28 s, 4,32 d	2', 6'
107,4 / 107,6	CH	6,73 s / 6,71 s	6,47 s / 6,55 s	6
109,7 / 109,4	CH	6,60 s / 6,56 s	4,41 d / (4,32 d)	3
126,4 / 125,6	C		6,60 s, 4,41 d / 6,56 s, (4,32 d)	1
127,5 / 129,5	CH	6,47 s / 6,55 s	6,73 s, 5,27 d / 6,71 s, (5,25 d)	7
128,6 / 129,2	C		6,73 s, 6,47 s / 6,71 s, 6,55 s	2
129,2 / 129,5	C		4,41 d, 3,23 d / 4,32 d, 3,63 d	8
137,2 / 137,2	C		6,18 s, 3,77 s / 6,28 s	4'
137,8 / 138,0	C		4,41 d, 3,23 d / 4,32 d	1'
147,0 / 146,9	C		6,60 s, 5,97 d, 5,96 d / 6,56 s	5
148,0 / 148,0	C		6,73 s / 6,71 s	4
153,1 / 153,1	C		6,18 s, 3,73 s / 6,28 s, 3,76 s	3', 5'
170,9 / 170,4	C		3,48 d, 3,45 s / 3,61 d, 3,41 s	3''
172,3 / 172,0	C		3,66 s, 3,23 d / 3,61 s, 3,63 d	9'

\* Carbon type according to DEPT experiment

**Table S16.** Correlations and assignments for compound **32** ( $\delta$  in ppm):

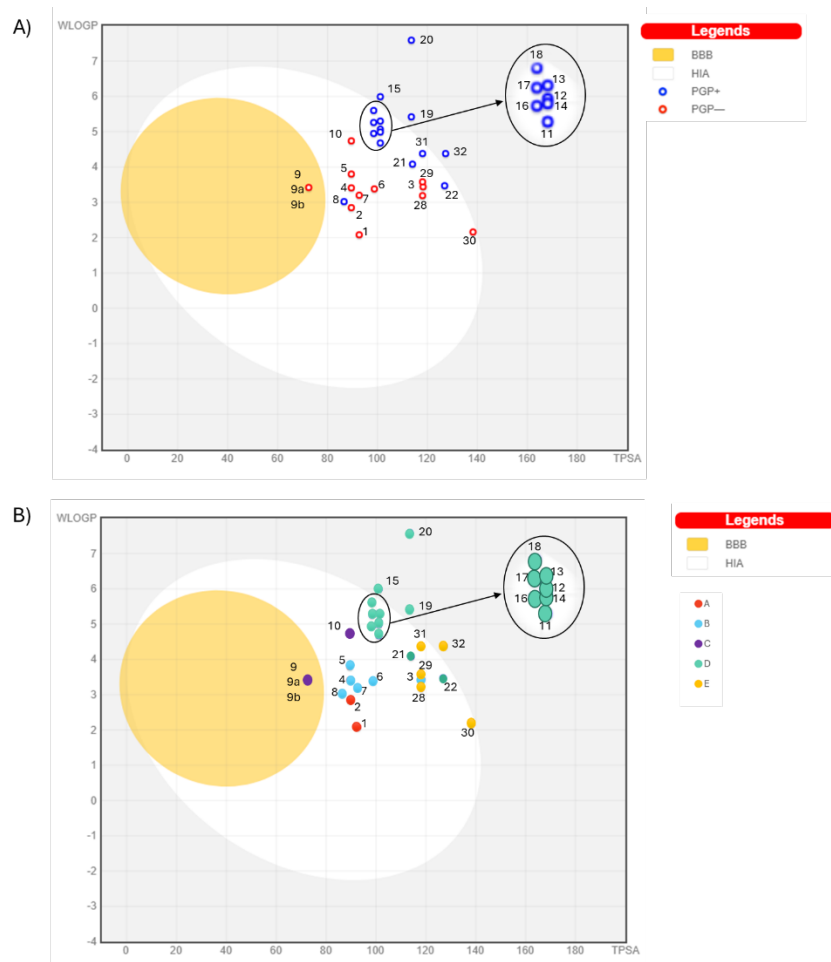
$\delta^{13}\text{C}$	TYPE*	HMQC, $\delta^1\text{H}$ ( <i>J</i> in Hz)	HMBC, $\delta^1\text{H}$	Assigned
32,7 / 33,1	CH <sub>2</sub>	3,60 s / 3,48 s		2''
46,8 / 47,7	CH	4,42 d / 4,31 d	6,55 s, 6,07 s, 3,43 d / 6,18 s	7'
48,6 / 49,2	CH	3,43 d / 3,52 sa	6,40 s, 5,65 s, 4,42 d / 6,52 s	8'
52,4 / 52,4	CH <sub>3</sub>	3,65 s / 3,53 s		9'-OCH <sub>3</sub>
55,3 / 55,4	CH <sub>3</sub>	3,79 s / 3,80 s		4'''-OCH <sub>3</sub>
55,9 / 56,0	CH <sub>3</sub>	3,66 s / 3,71 s		3', 5'-OCH <sub>3</sub>
60,8 / 60,8	CH <sub>3</sub>	3,80 s / 3,81 s		4'-OCH <sub>3</sub>
66,7 / 66,7	CH	5,65 s / 5, 53 s	6,40 s / 6,52 s	9
101,2 / 101,2	CH <sub>2</sub>	5,93 d, 5,92 d / 5,93 d, 5,92 d		10
104,9 / 104,9	CH	6,07 s / 6,18 s	6,07 s, 4,42 d / 6,18 s, (4,31 d)	2', 6'
107,5 / 107,5	CH	6,64 s / 6,66s	6,40 s / (6,52 s)	6
109,6 / 109,6	CH	6,55 s / 6,51 s	4,42 d	3
114,1 / 114,1	CH	6,75 d / 6,86 d	6,75 d / 6,86 d	3''', 5'''
125,1 / 125,1	CH	6,99 d / 7,12 d	6,99 d / 7,12 d	2''', 6'''
126,0 / 126,0	C		6,55 s, 4,42 d	1
126,9 / 128,7	CH	6,40 s / 6,52 s	6,64 s, 5,65 s, 3,43 d / 6,66 s	7
128,7 / 128,7	C		6,40 s, 3,43 d / 6,52 s	2
129,2 / 129,2	C		4,42 d, 3,43 d	8
130,1 / 130,9	C		6,75 d / 6,86 d	1'''
136,9 / 136,9	C		6,07 s, 3,80 s / 6,18 s, (3,81 s)	4'
138,1 / 138,1	C		4,42 d, 3,43 d / 4,31 d	1'
146,9 / 146,9	C		6,55 s / 6,51s	5
148,0 / 148,0	C		6,64 s, 5,93 d, 5,92 d	4
153,0 / 153,0	C		6,07 s, 3,66 s / 6,18 s, 3,71 s	3', 5'
157,7 / 157,7	C		6,99 d, 6,75 d, 3,79 s / 7,12 d, 6,86 d, 3,80 s	4'''
170,9 / 170,9	C		5,65 s	3''
172,6 / 171,9	C		4,42 d, 3,65 s, 3,43 d / 3,53 s, 3,52 sa	9'

\* Carbon type according to DEPT experiment



**Figure S1:** Graphical representation of the Log P, TPSA and Log S values of the synthesized compounds, calculated by Swissadme.

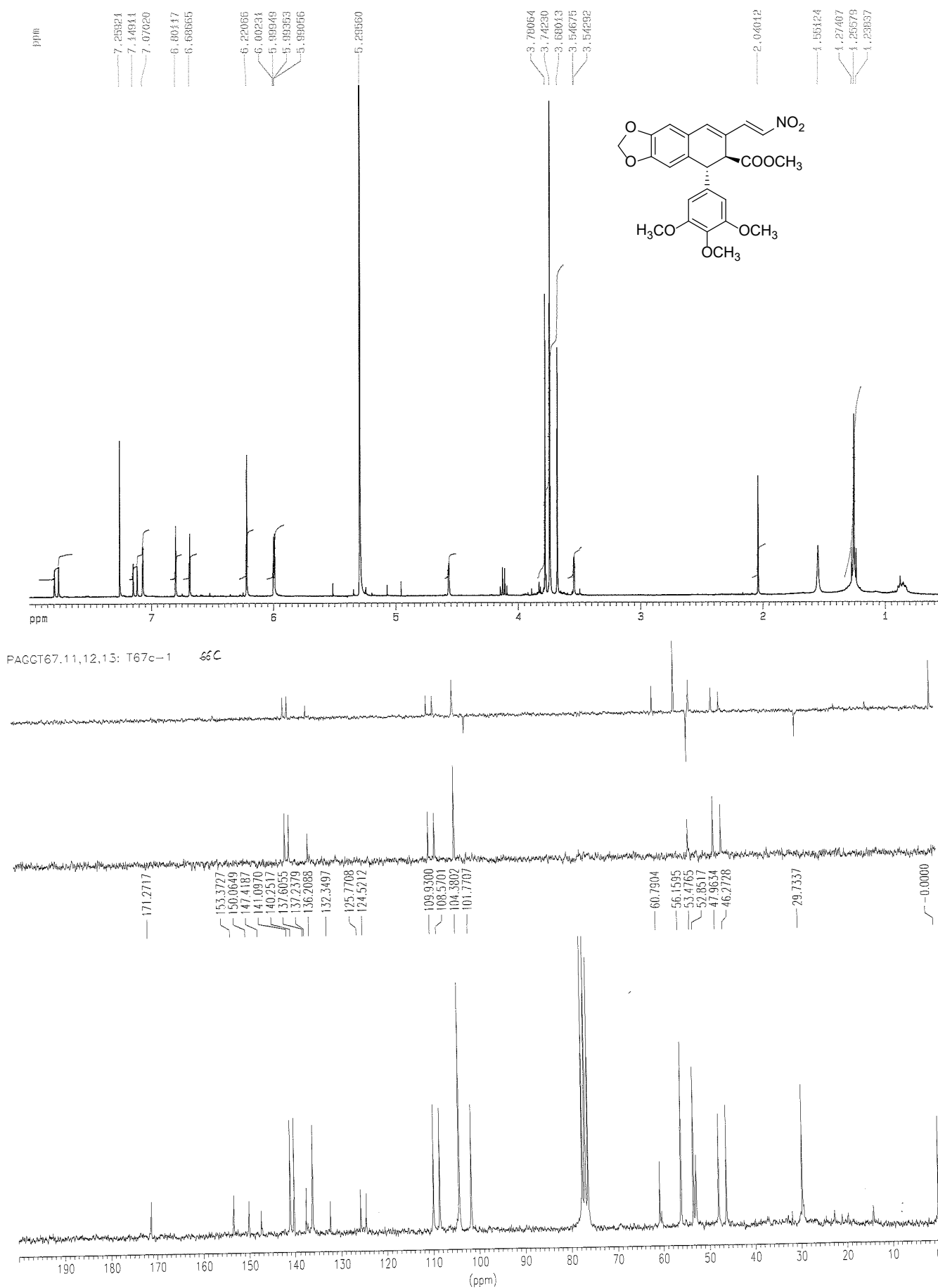
A) and B) TPSA and Log P values respectively, plotted with the cytotoxicity values of the compounds in A549 (expressed in nanomolar). C) and D) Log S plotted with the cytotoxicity values of the compounds in A549 and HT-29 respectively (expressed in nanomolar). Color code for the different subfamilies of compounds synthesized in this work as it is in the manuscript.



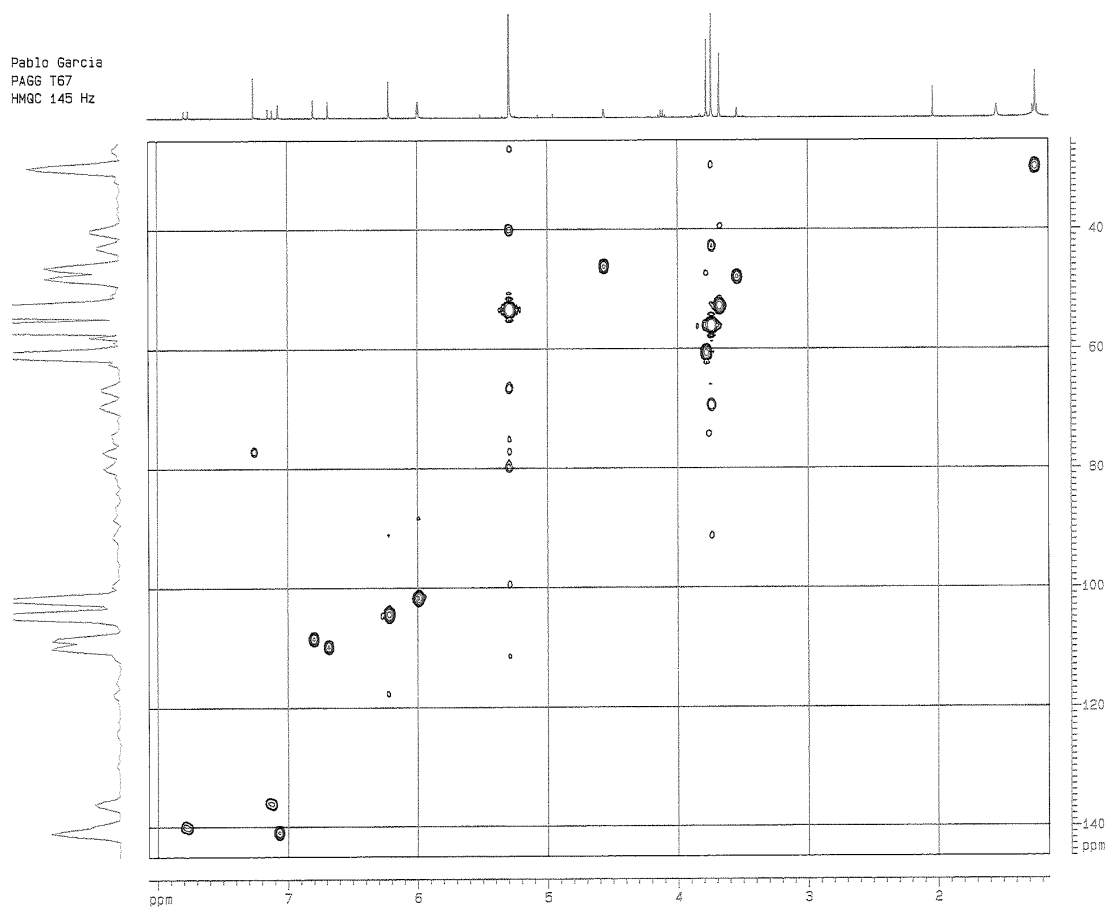
**Figure S2:** BOILED-Egg model obtained in Swissadme.

Yellow region indicates the compounds that are predicted to passively permeate through the blood-brain barrier (BBB). White region indicates a high intestinal absorption (HIA). In panel A, red points refer to compounds that are not predicted to be substrate of P-glycoprotein and blue points compound predicted to be substrate of P-glycoprotein. In panel B, color code for the different subfamilies of compounds synthesized in this work as it is in the manuscript.

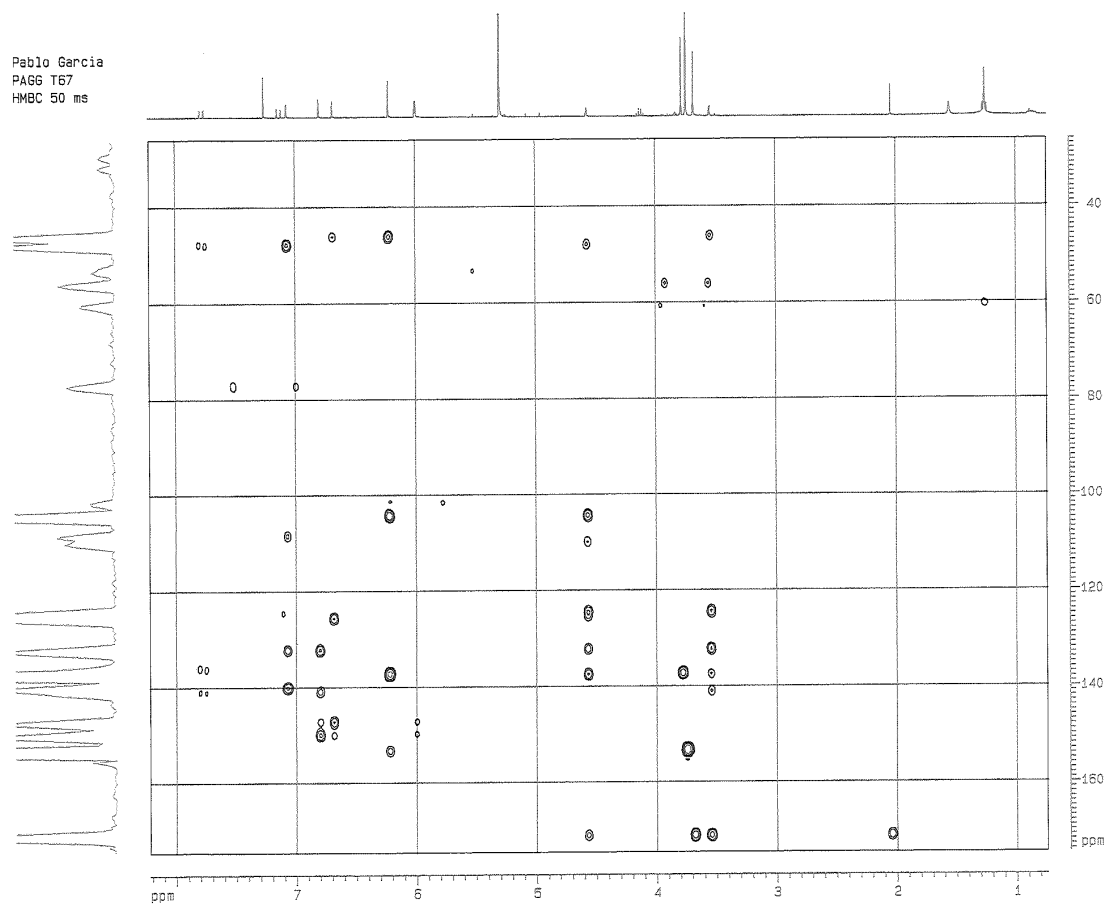




Pablo Garcia  
PAGG T67  
HMQC 145 Hz



Pablo Garcia  
PAGG T67  
HMBC 50 ms



**Figure S4.** HMQC and HMBC for compound **3**.

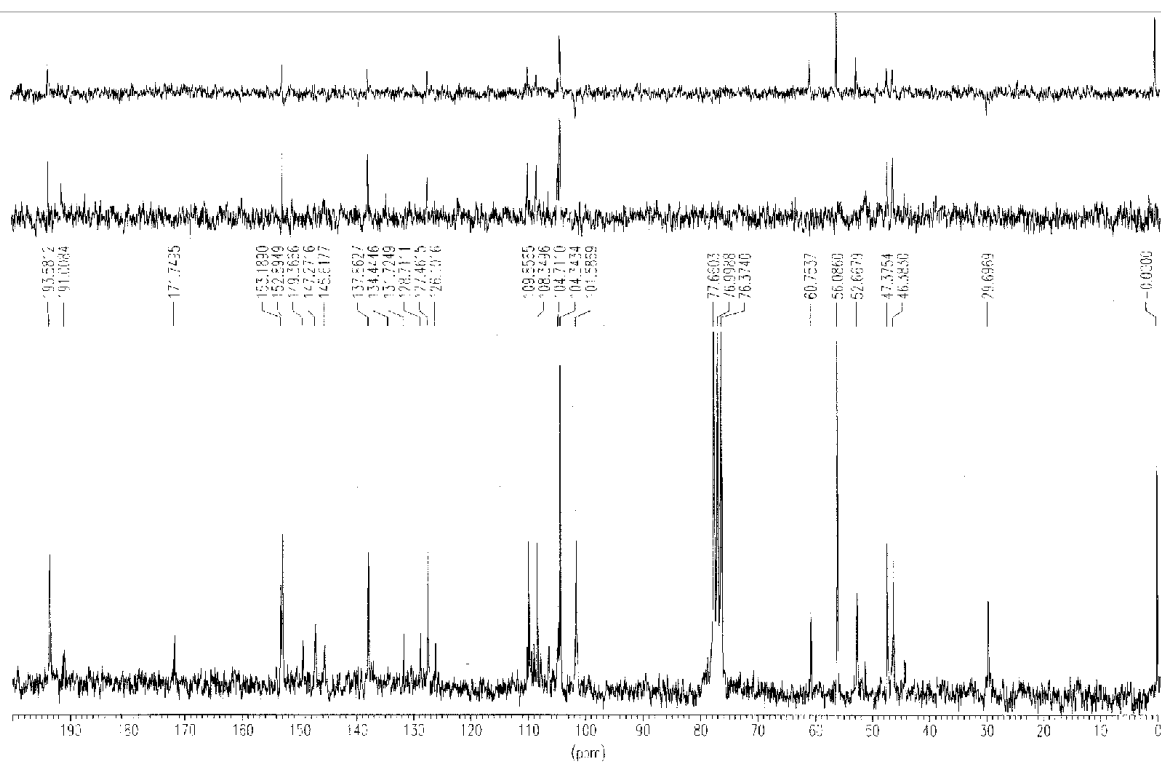
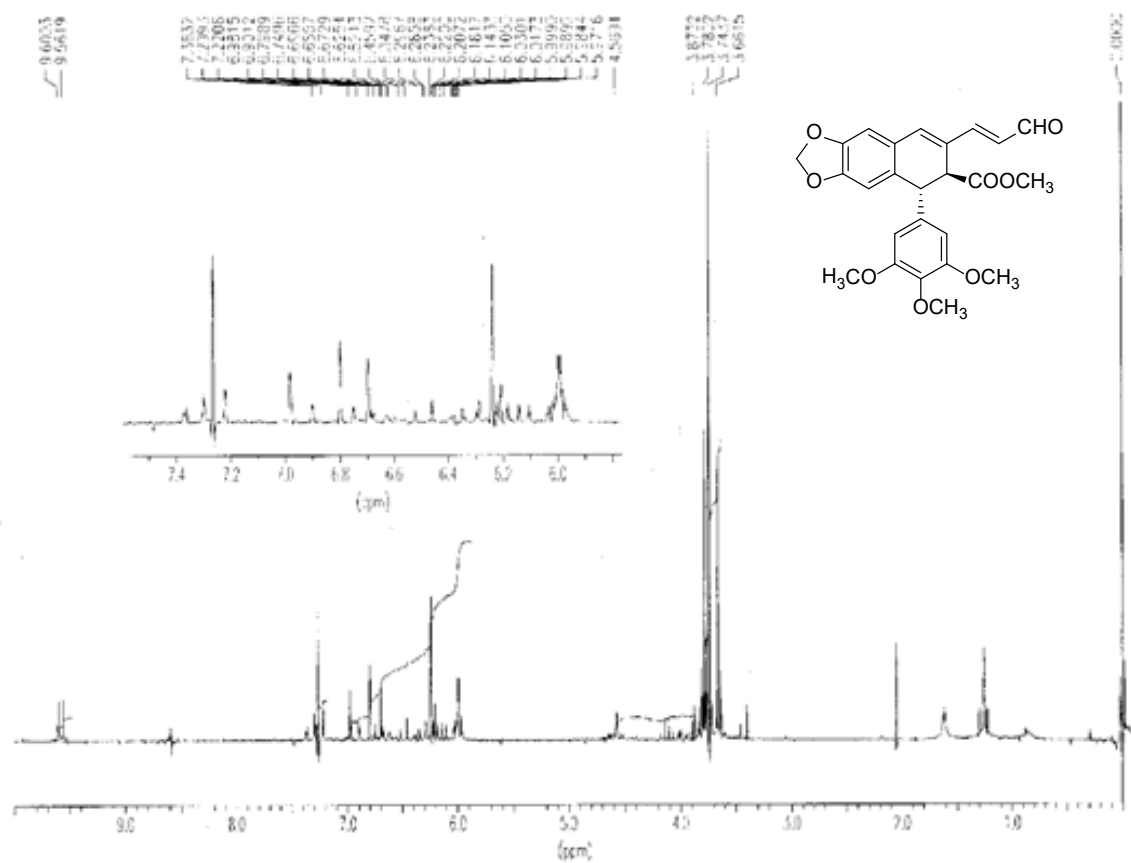
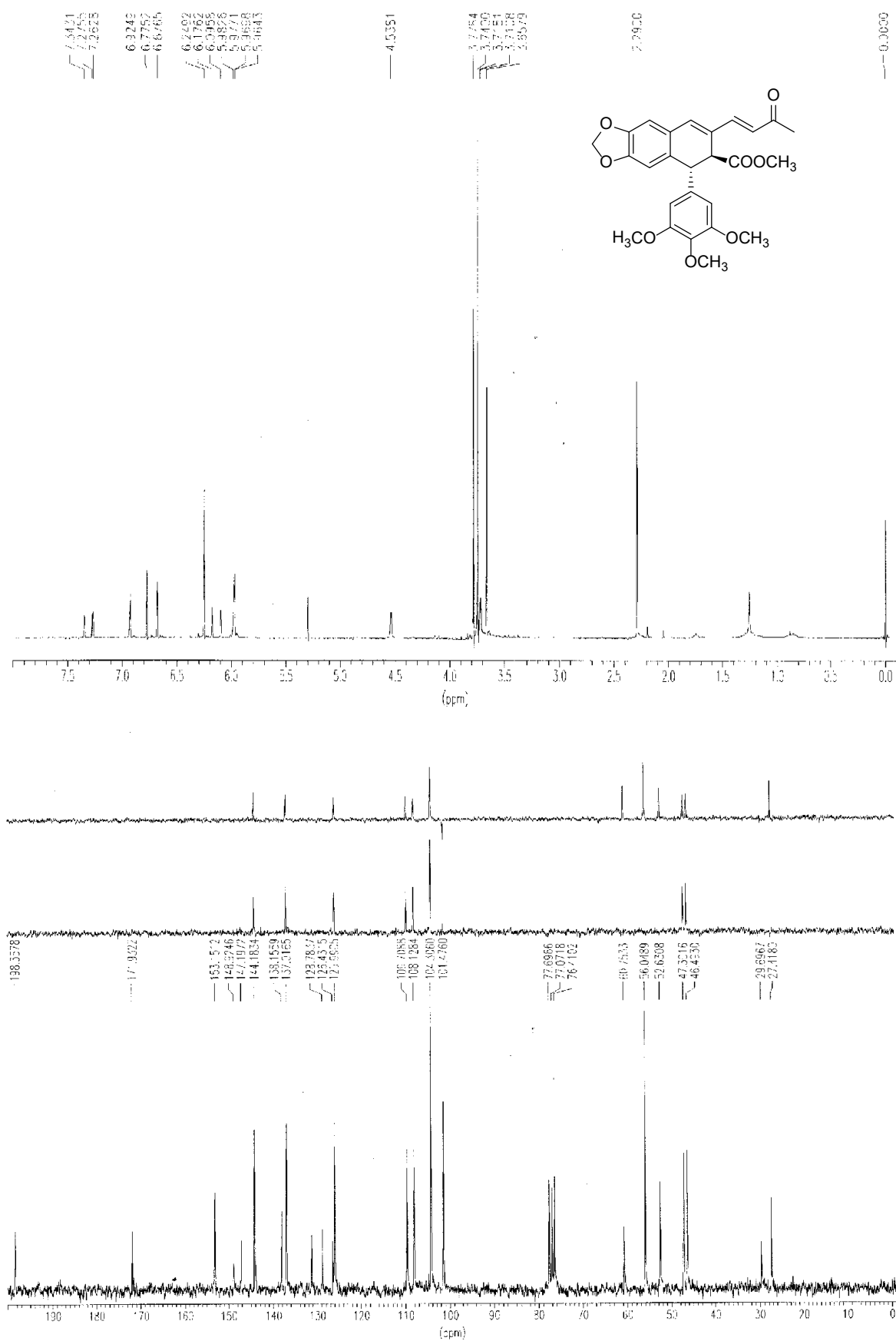


Figure S5. <sup>1</sup>H and <sup>13</sup>C for compound 4.



**Figure S6.** <sup>1</sup>H and <sup>13</sup>C for compound **5**.

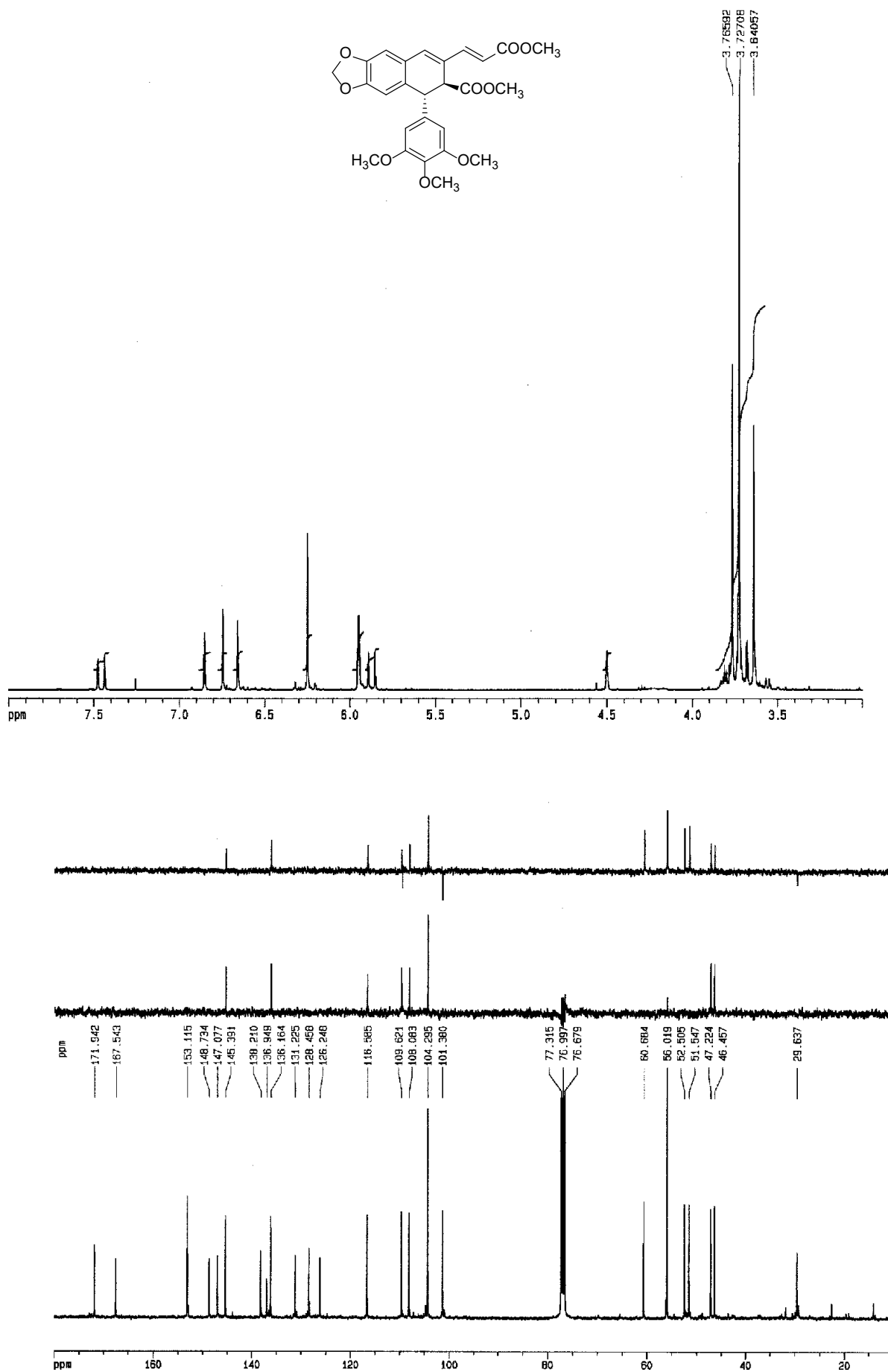


Figure S7.  $^1\text{H}$  and  $^{13}\text{C}$  for compound 6.

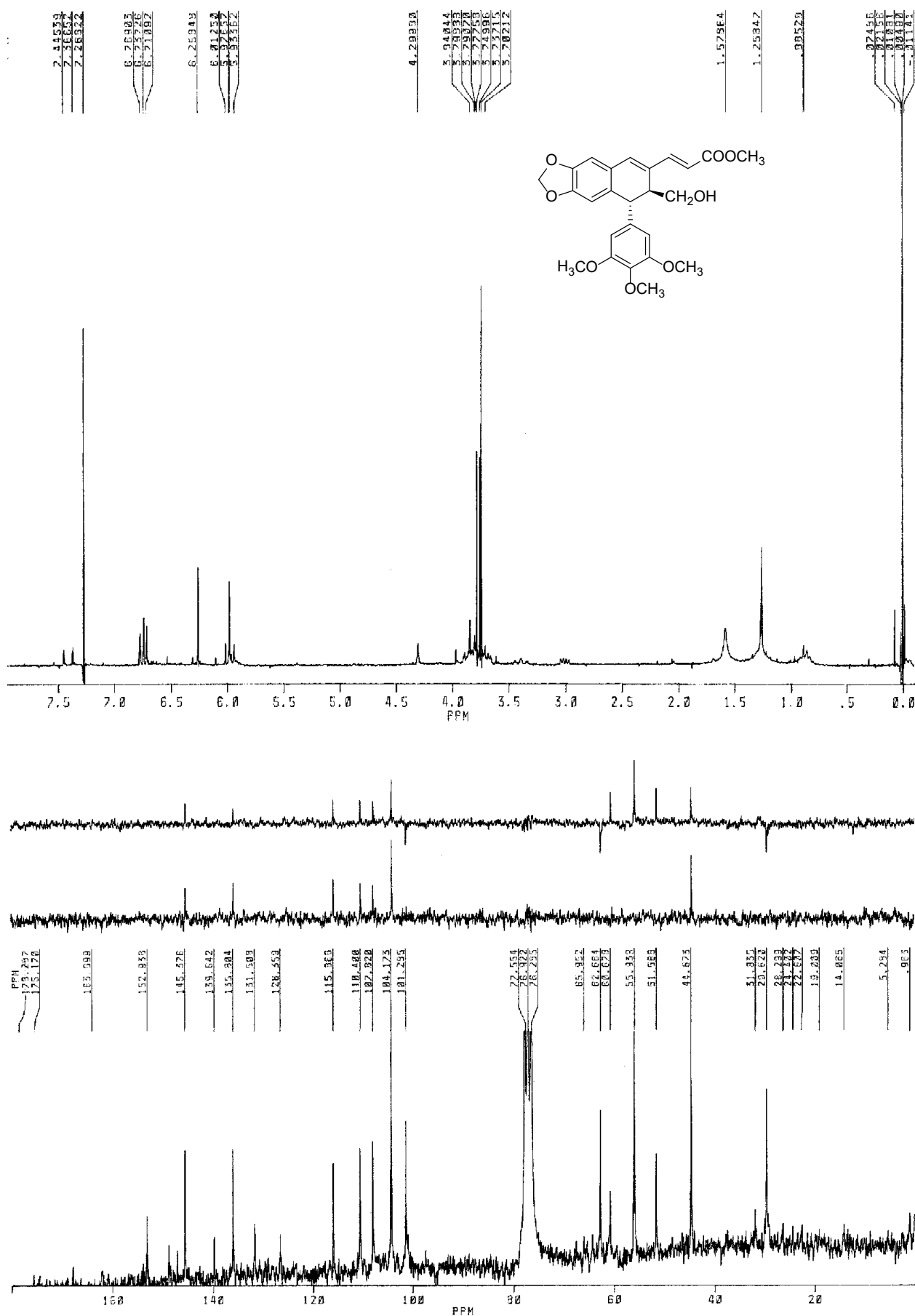


Figure S8. <sup>1</sup>H and <sup>13</sup>C for compound 7.

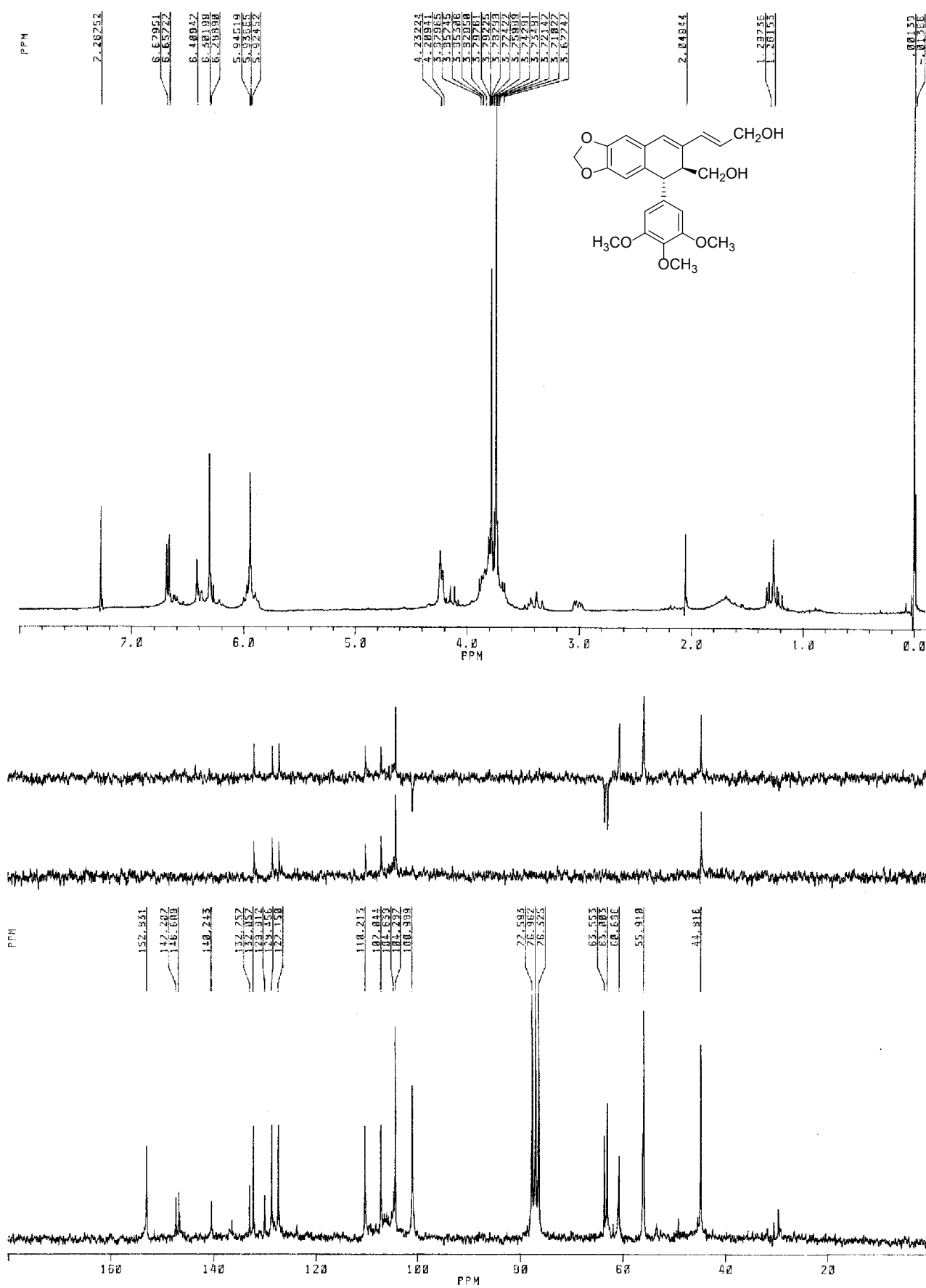
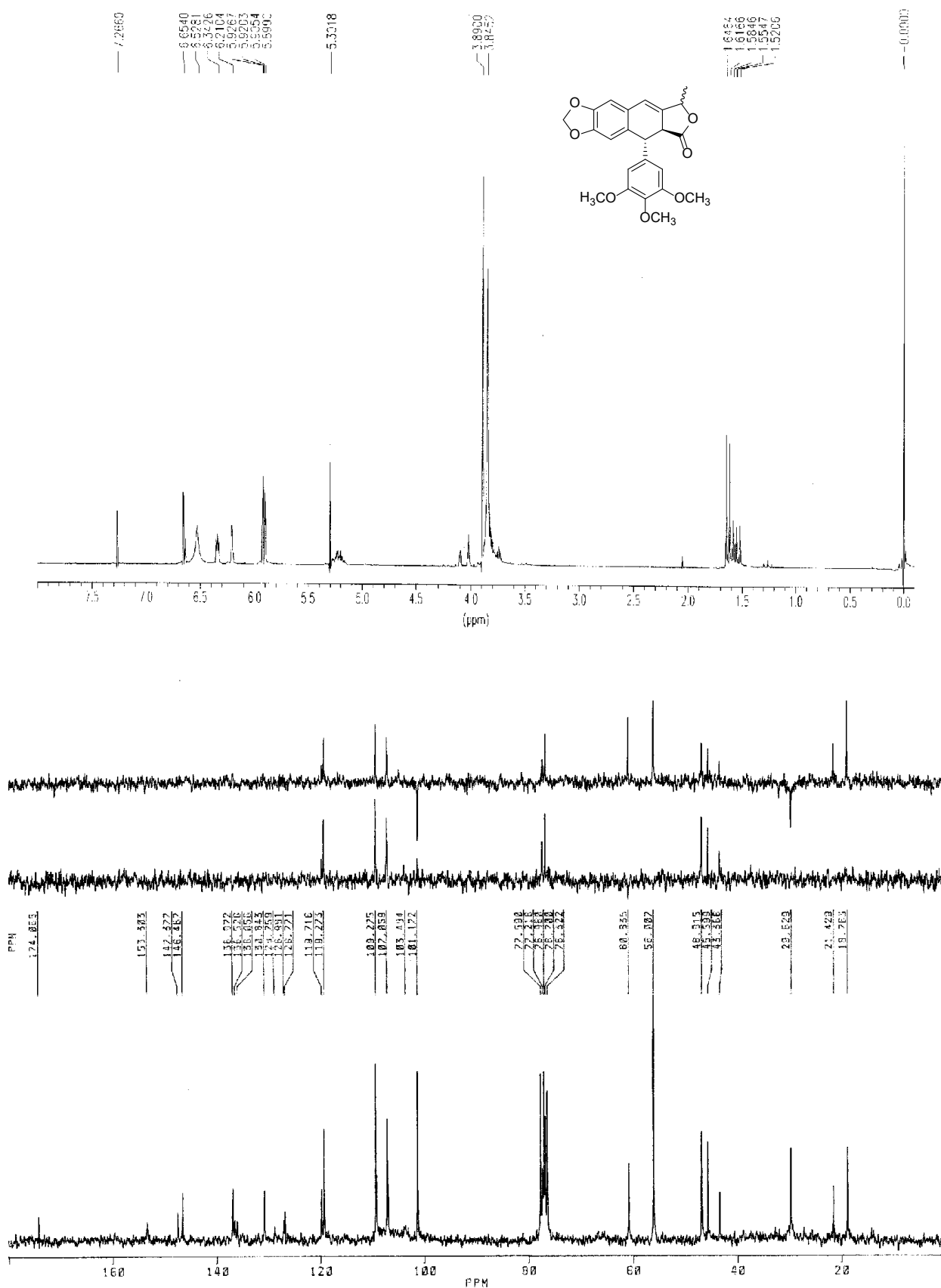


Figure S9. <sup>1</sup>H and <sup>13</sup>C for compound 8.



**Figure S10.**  $^1\text{H}$  and  $^{13}\text{C}$  for compound **9**



JOPAGA20.14: T20-C (0)

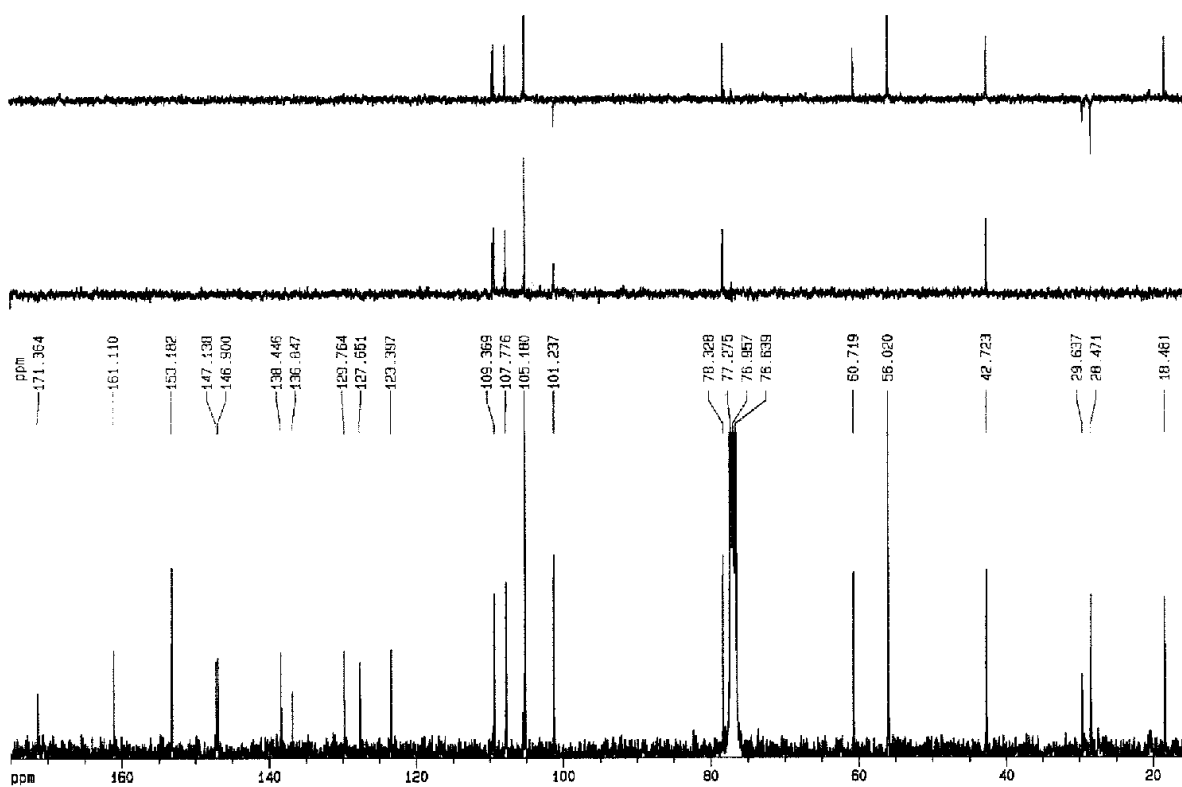
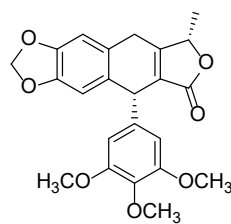
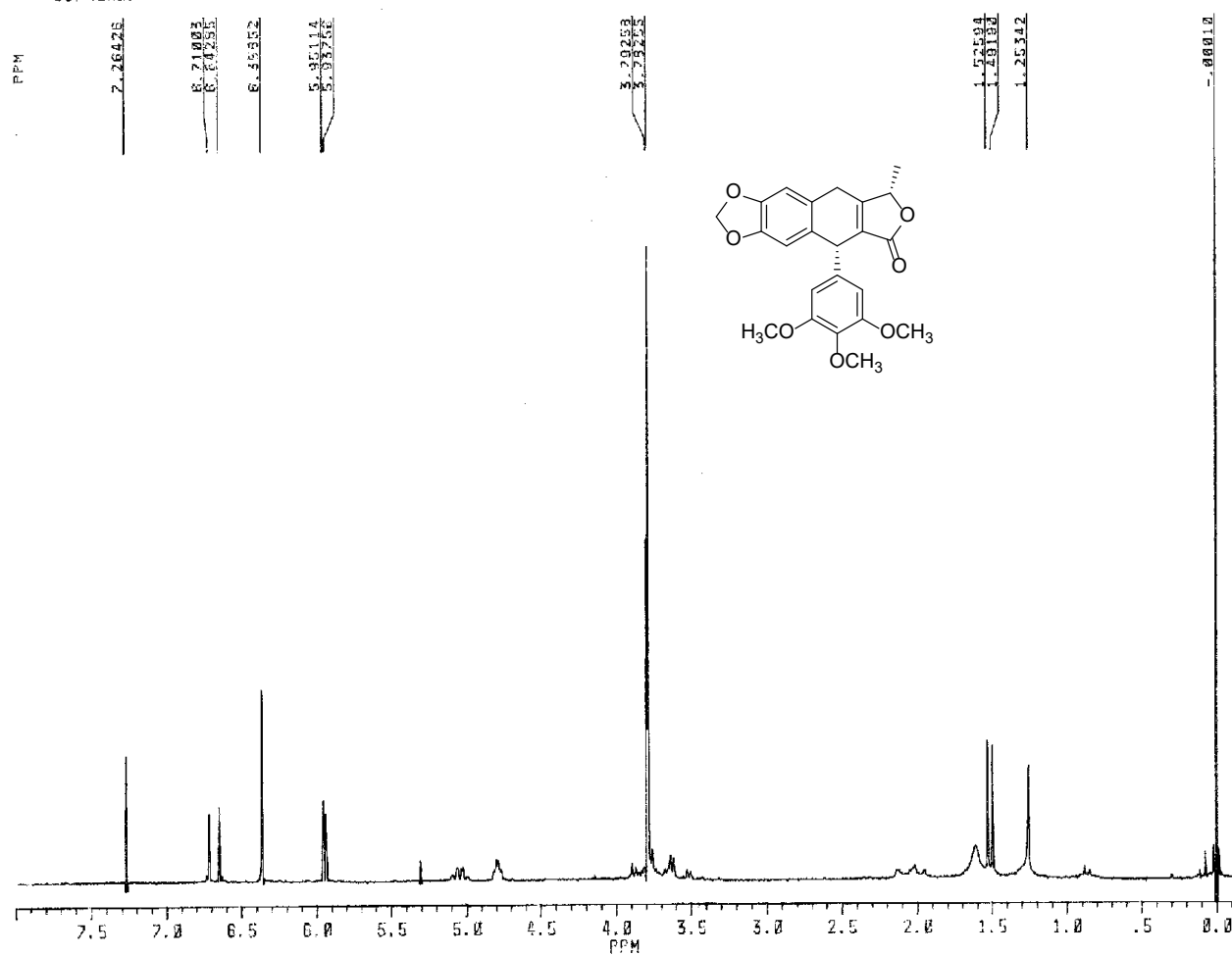


Figure S11. <sup>1</sup>H and <sup>13</sup>C for compound 9a

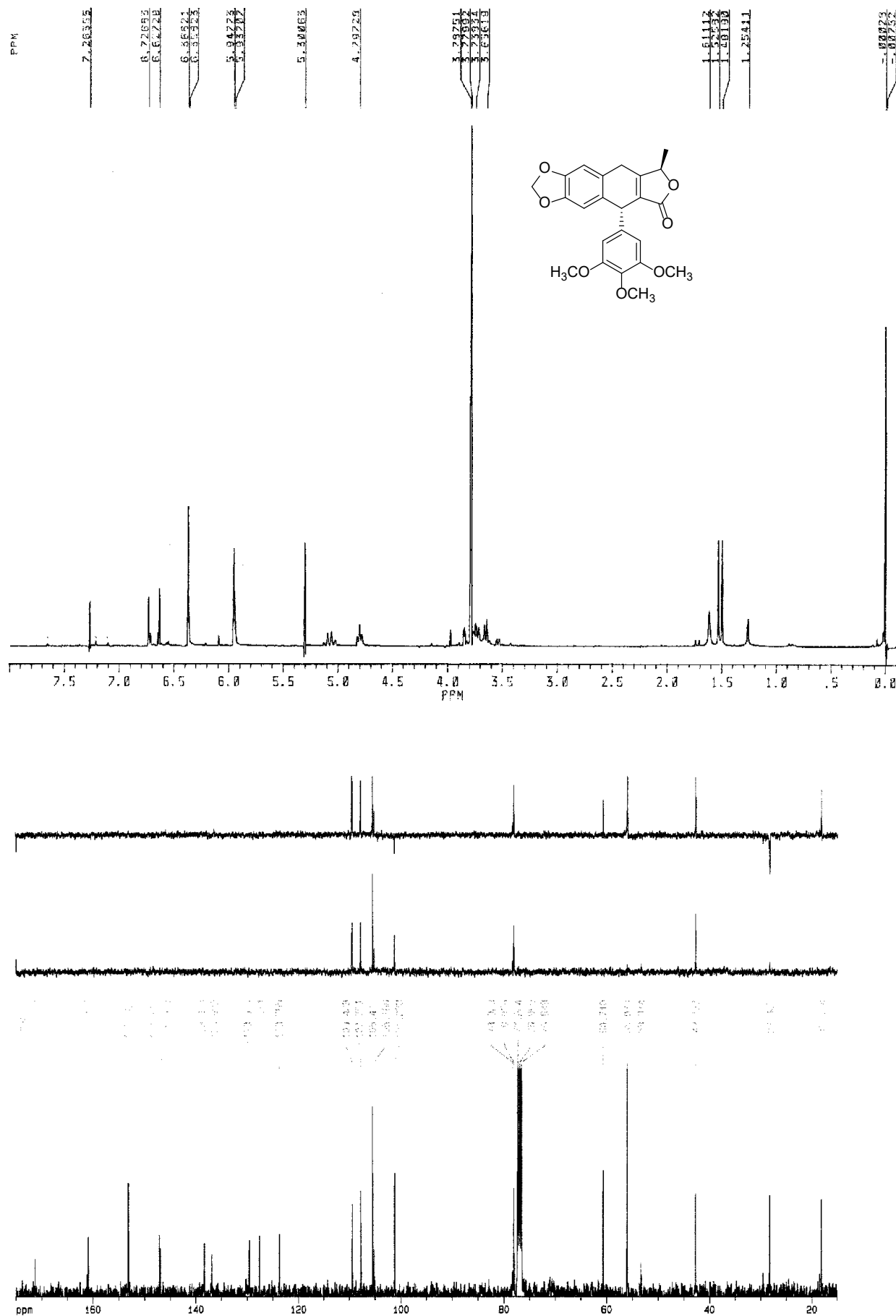
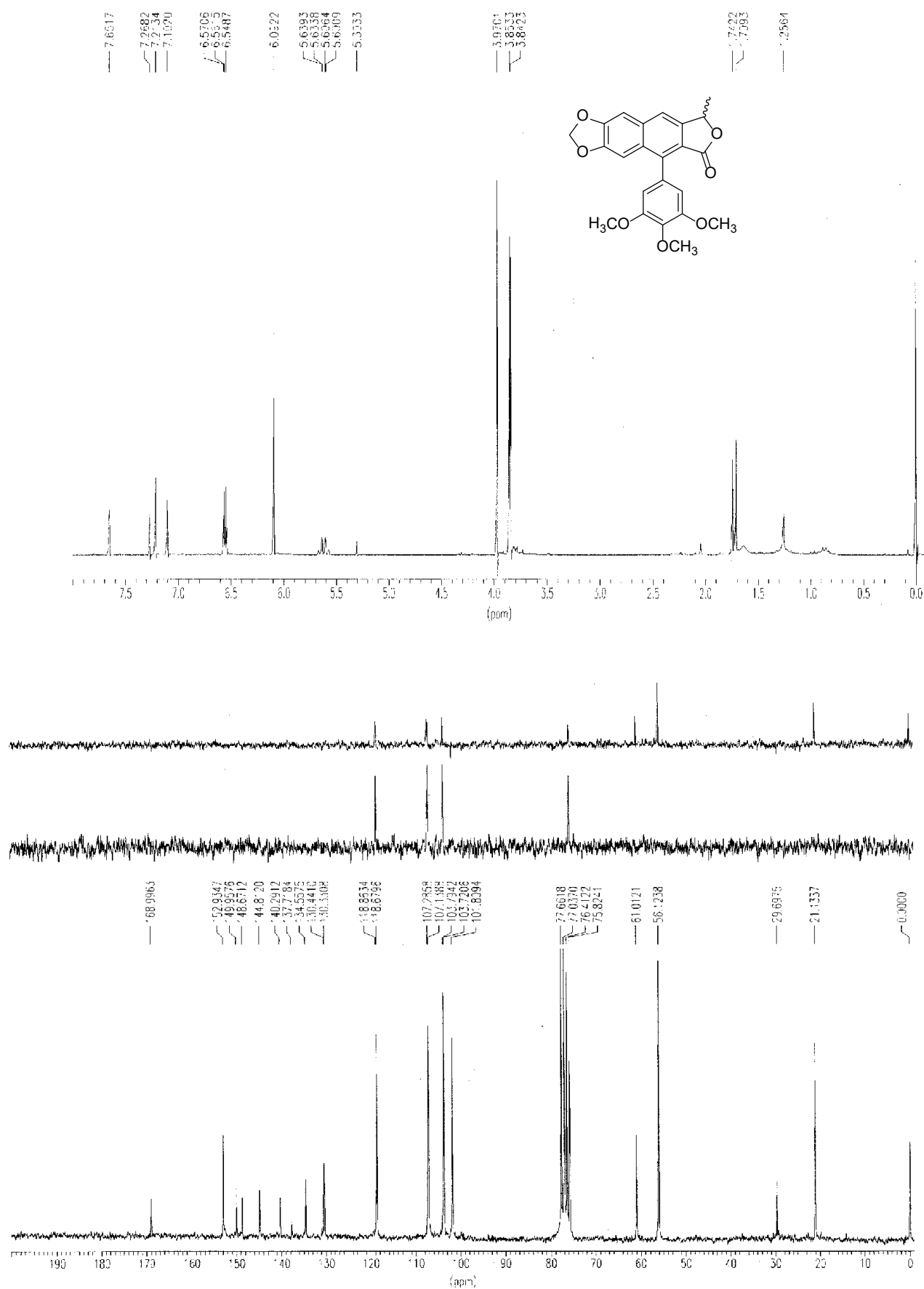
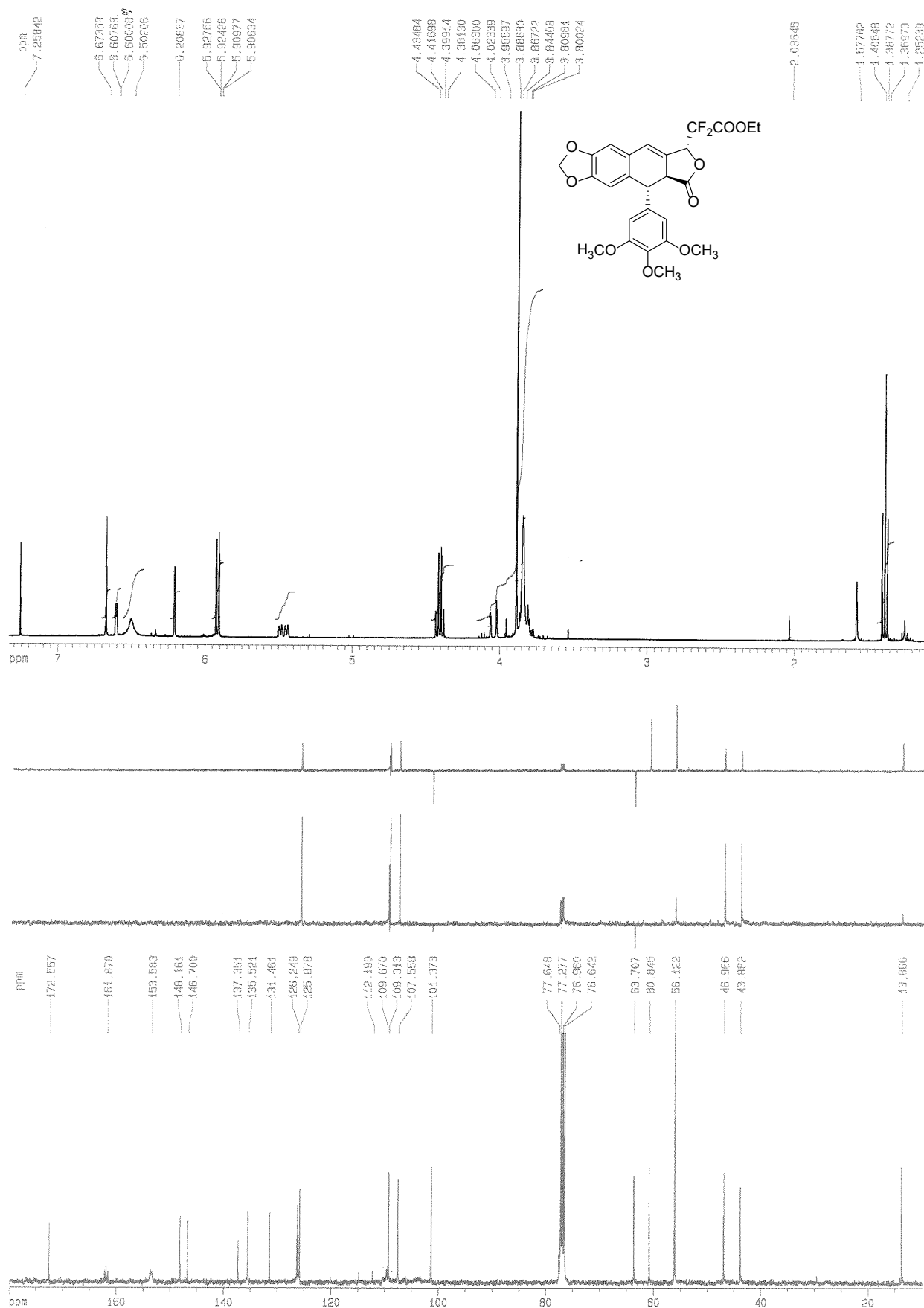


Figure S12. <sup>1</sup>H and <sup>13</sup>C for compound 9b

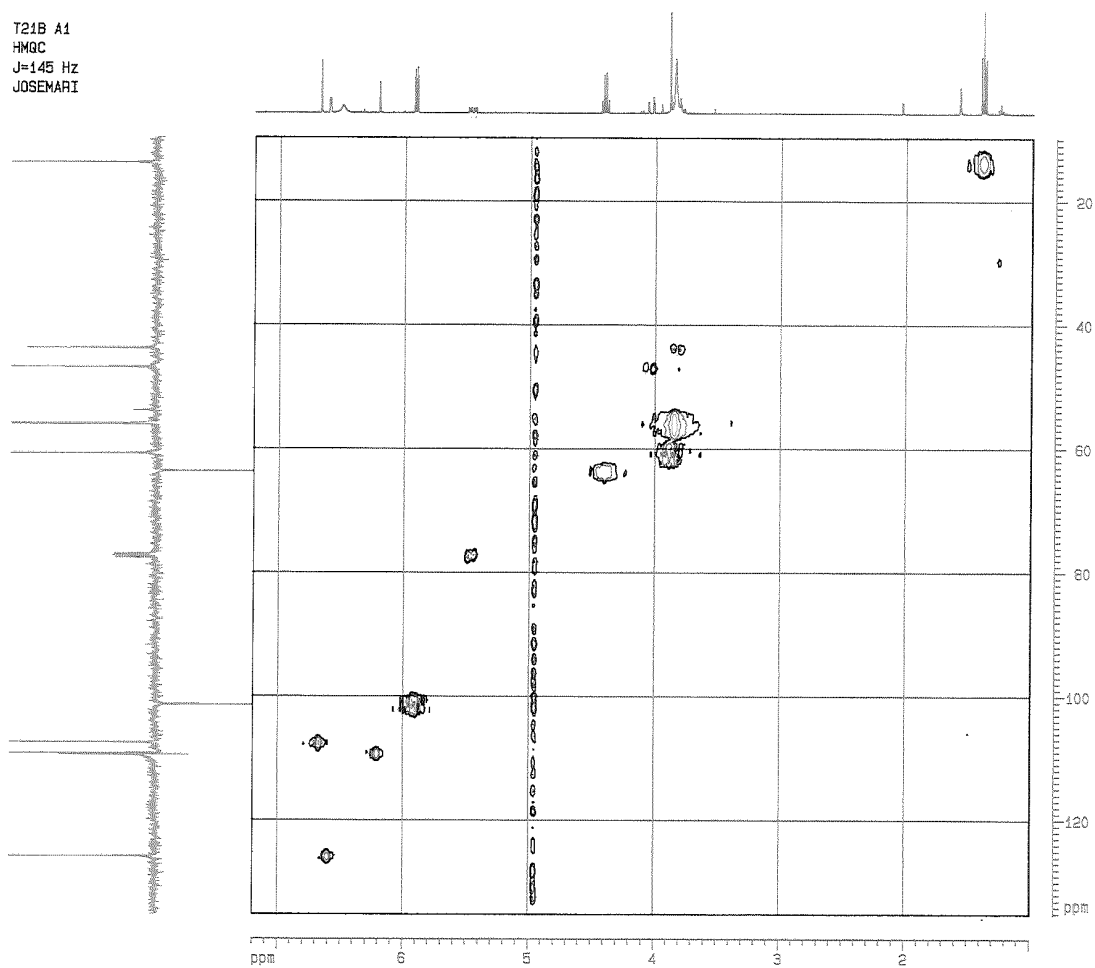


**Figure S13.** <sup>1</sup>H and <sup>13</sup>C for compound **9c**

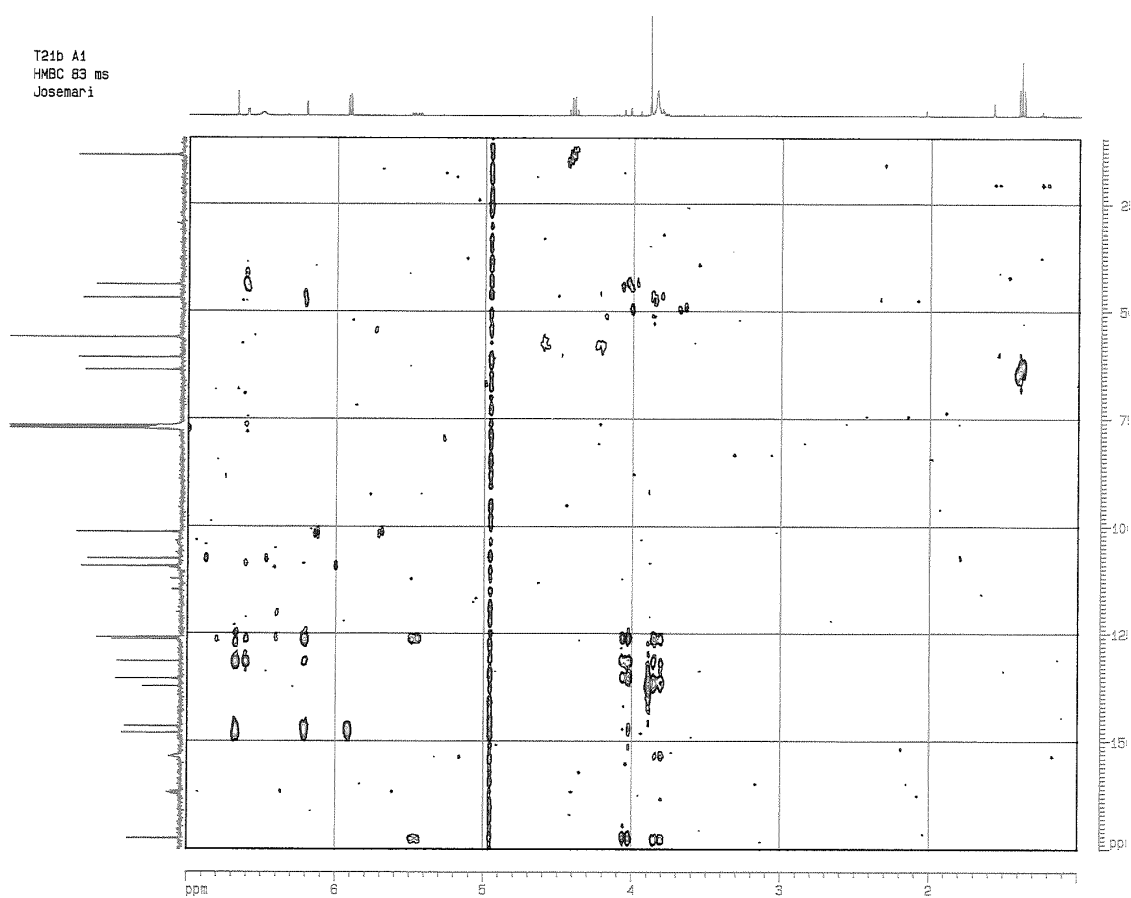


**Figure S14.** <sup>1</sup>H and <sup>13</sup>C for compound 10

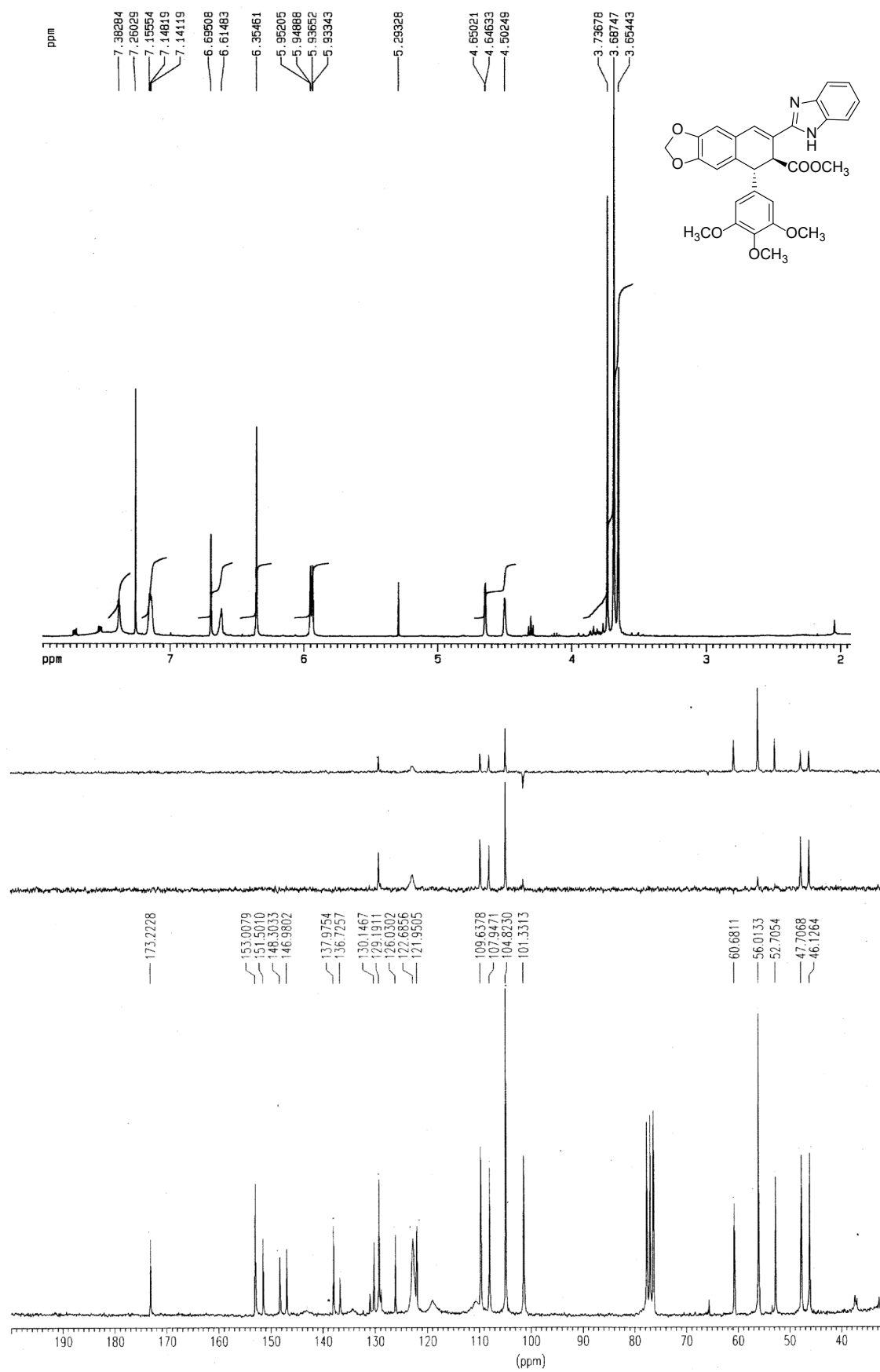
T21B A1  
HMQC  
J=145 Hz  
JOSEMAR1



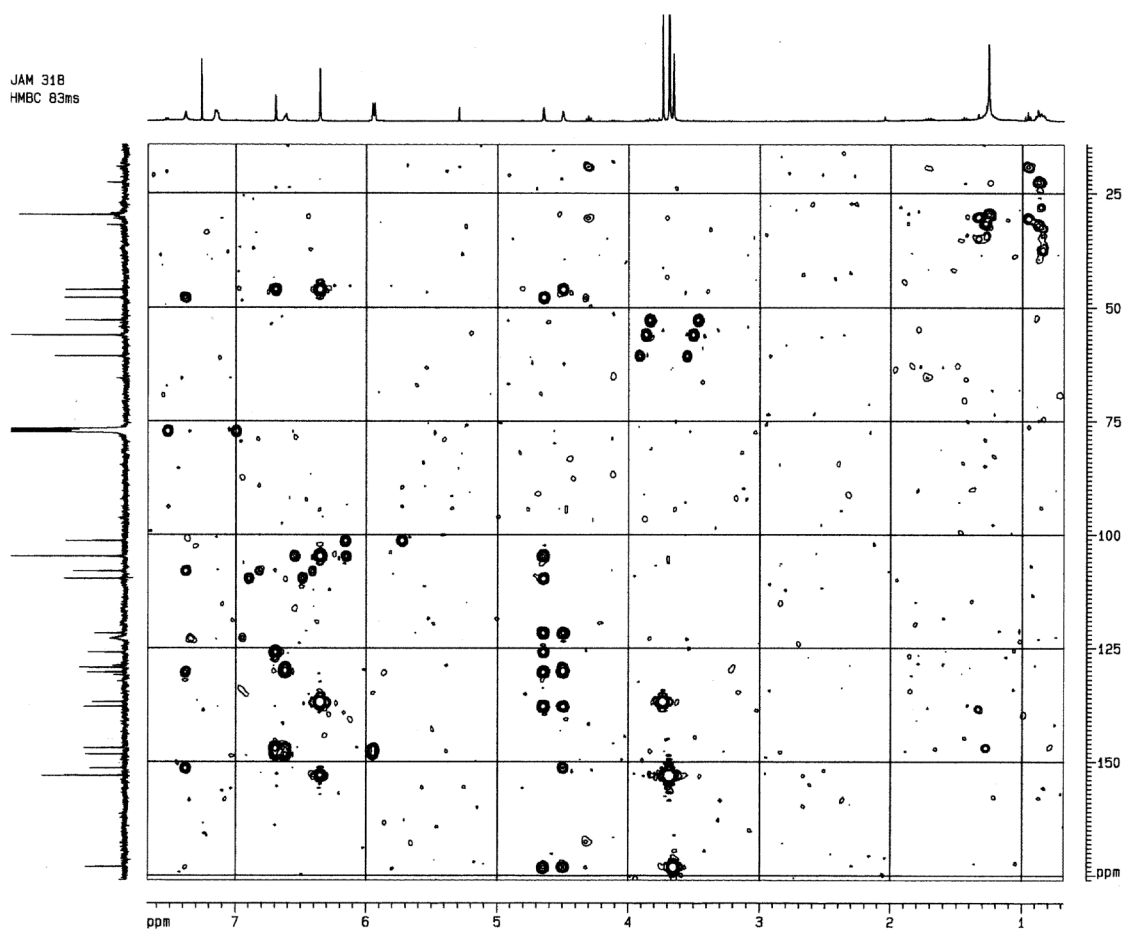
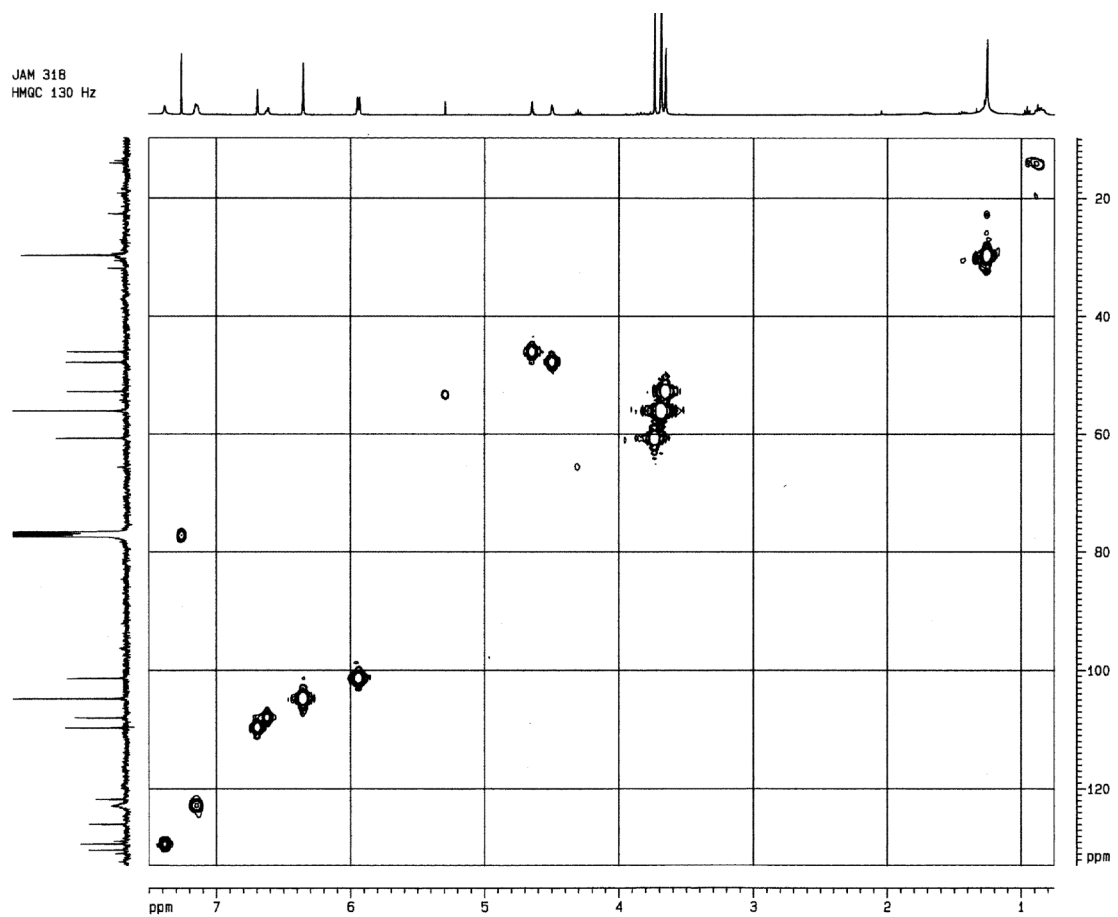
T21b A1  
HMBC 63 ms  
Josemari



**Figure S15.** HMQC and HMBC for compound **10**



**Figure S16.** <sup>1</sup>H and <sup>13</sup>C for compound 11



**Figure S17.** HMQC and HMBC for compound **11**

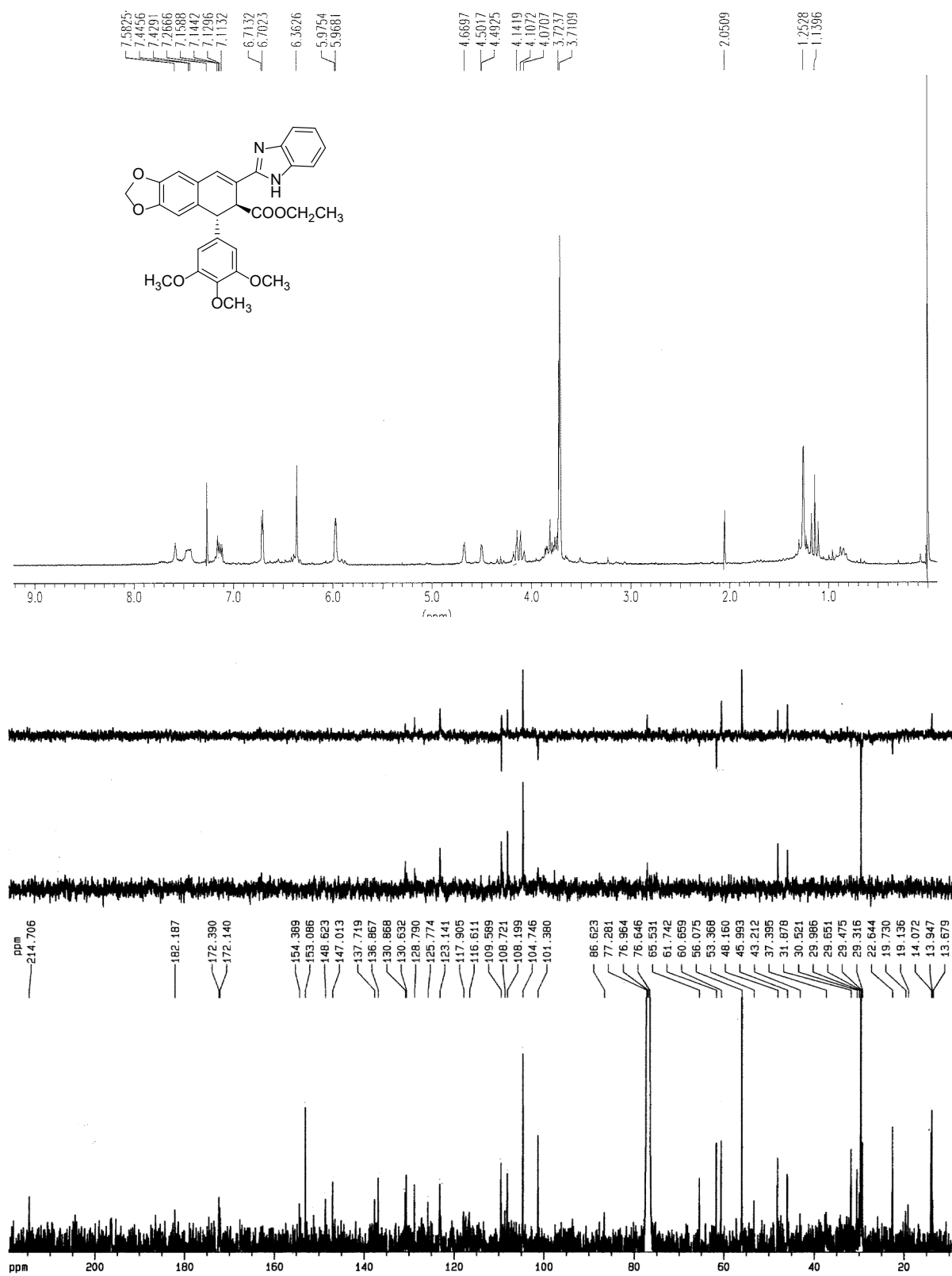
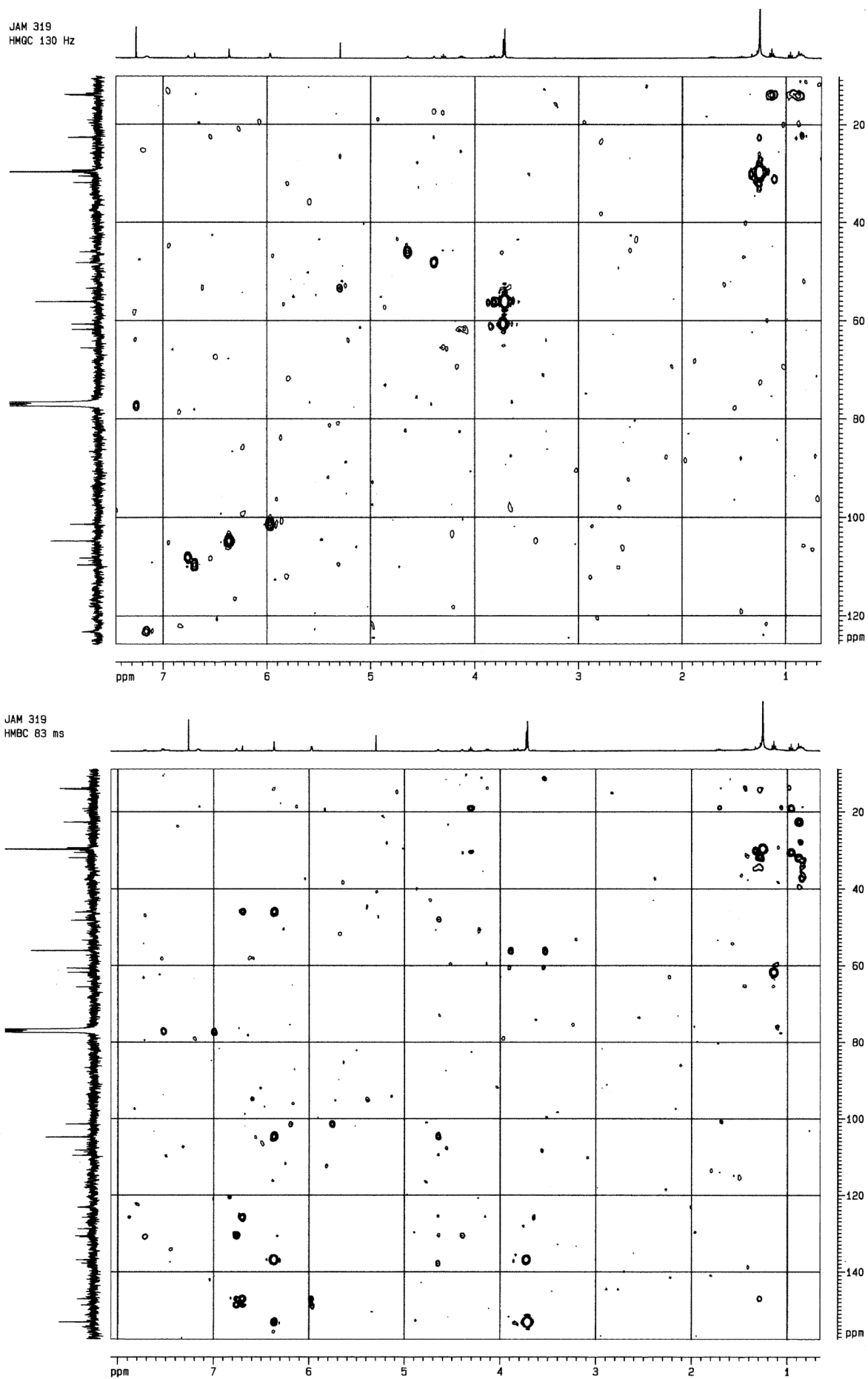


Figure S18. <sup>1</sup>H and <sup>13</sup>C for compound 12





**Figure S19.** HMQC and HMBC for compound **12**

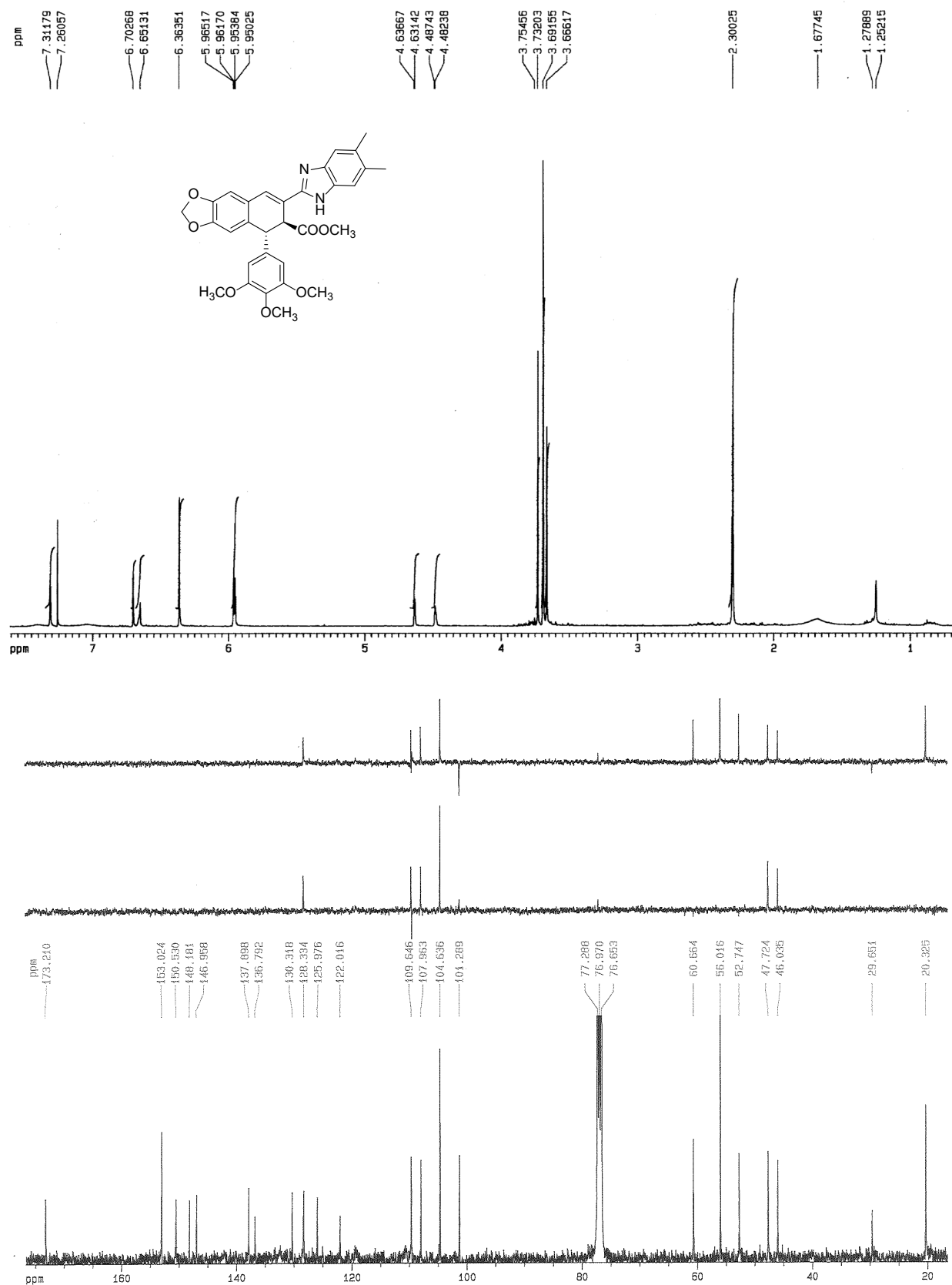
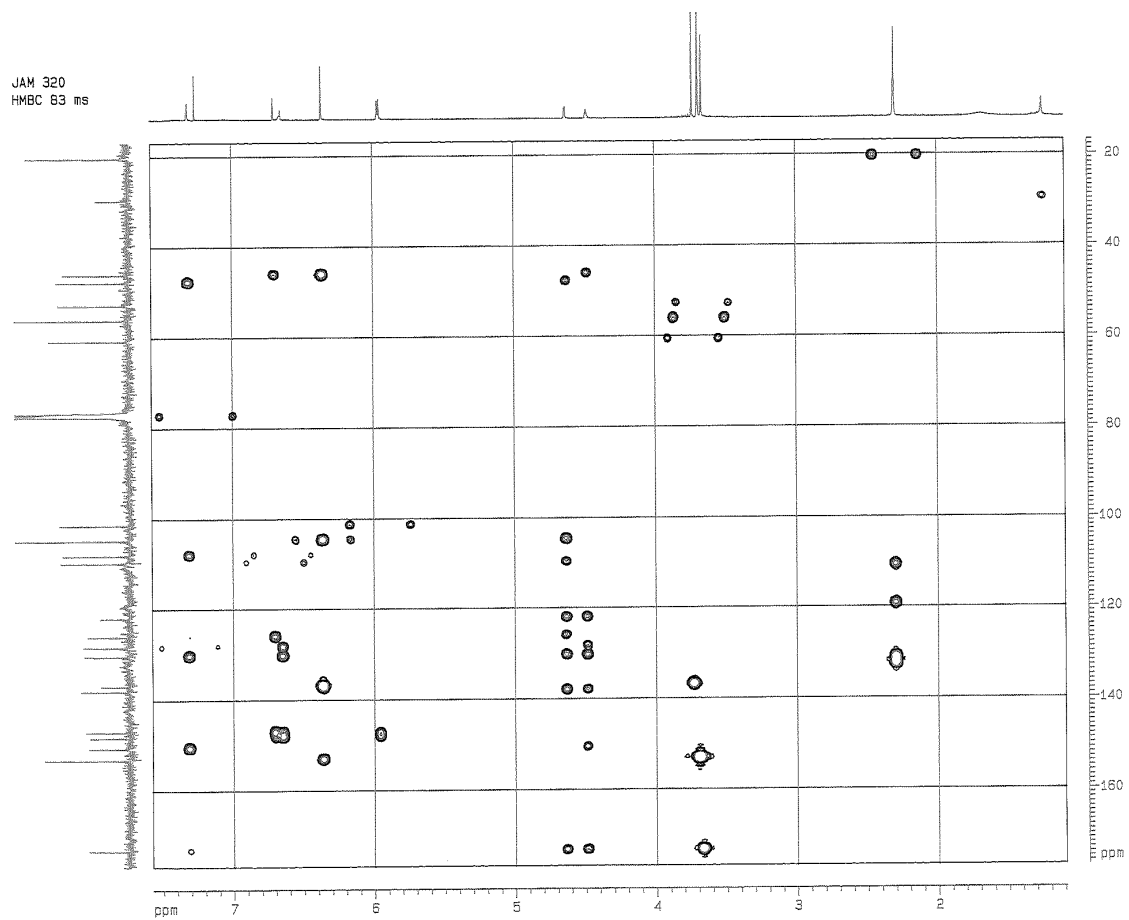
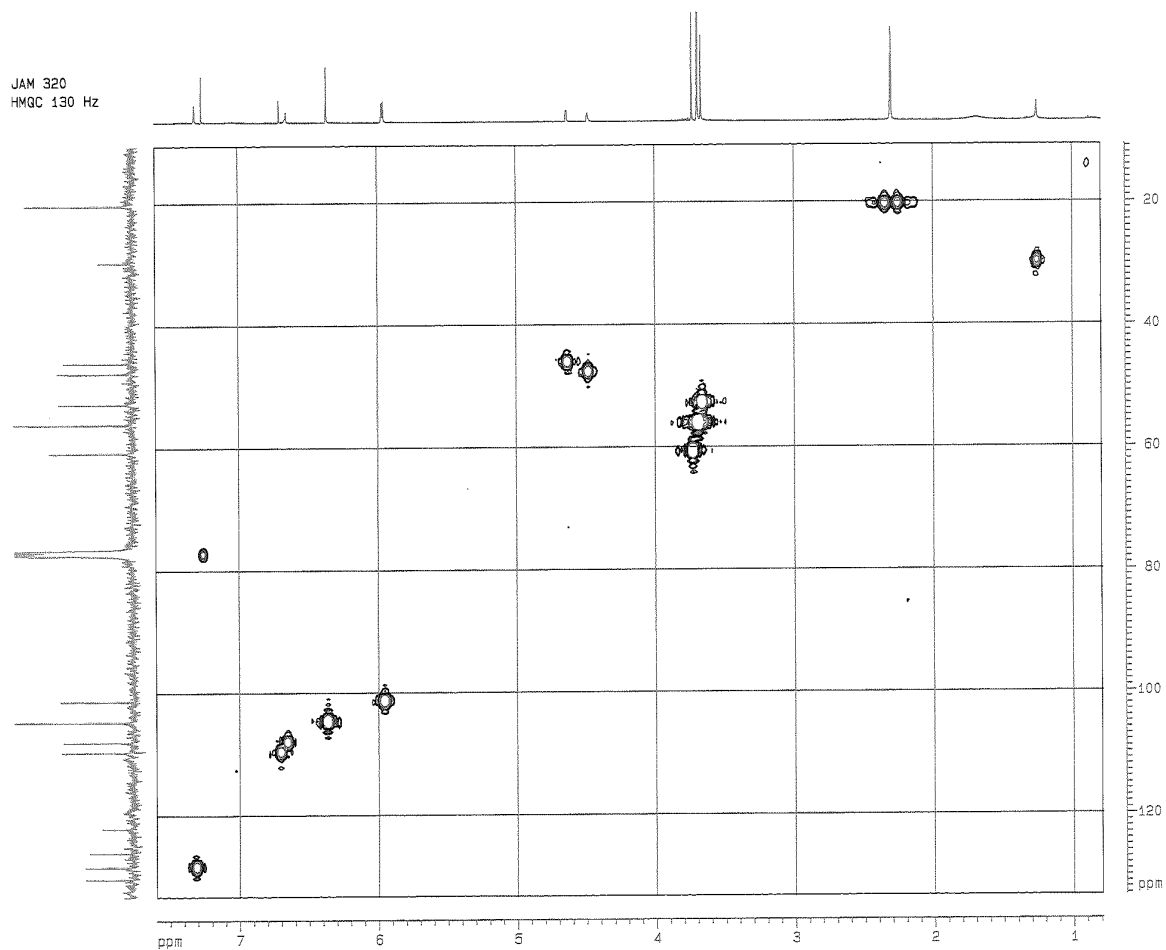
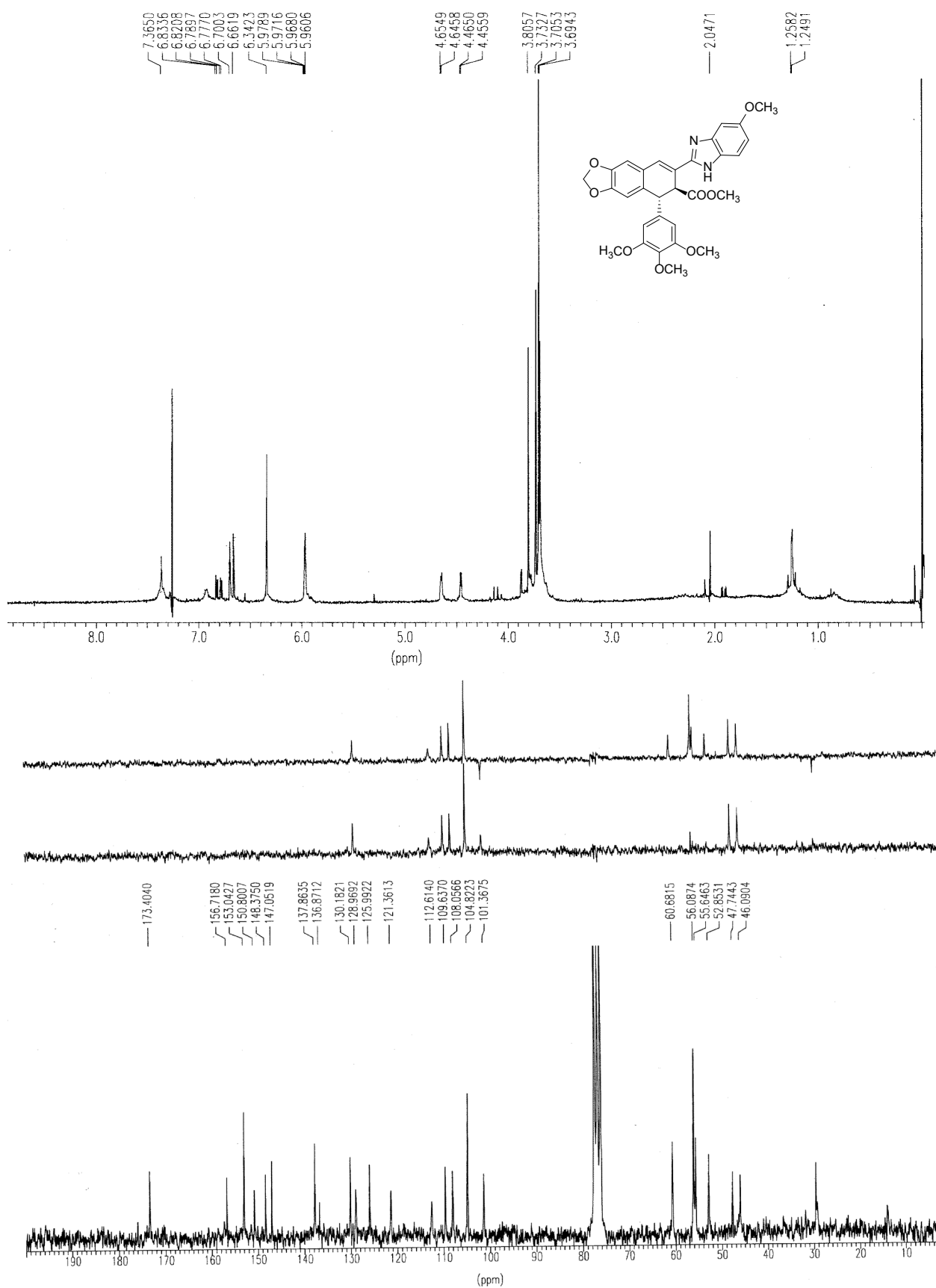


Figure S20. <sup>1</sup>H and <sup>13</sup>C for compound 13



**Figure S21.** HMQC and HMBC for compound **13**



**Figure S22.** <sup>1</sup>H and <sup>13</sup>C for compound **14**

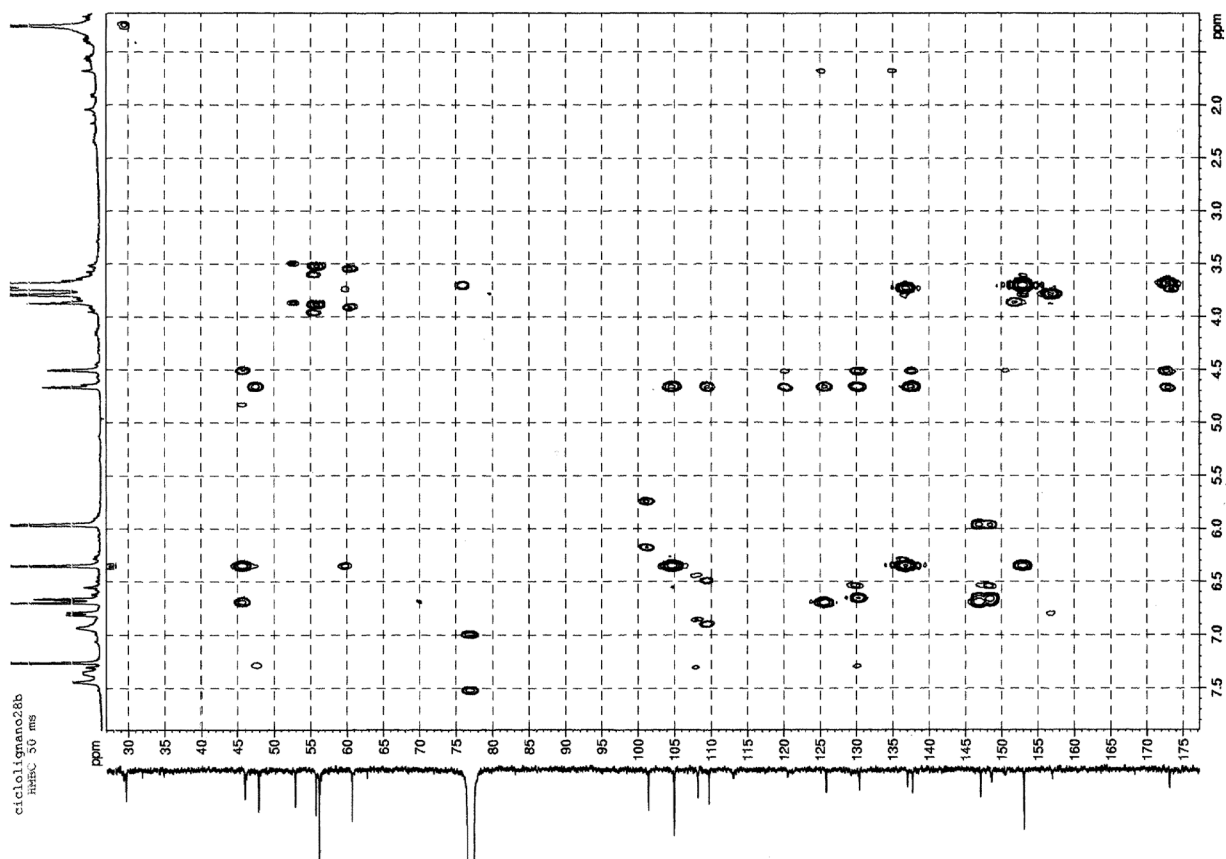
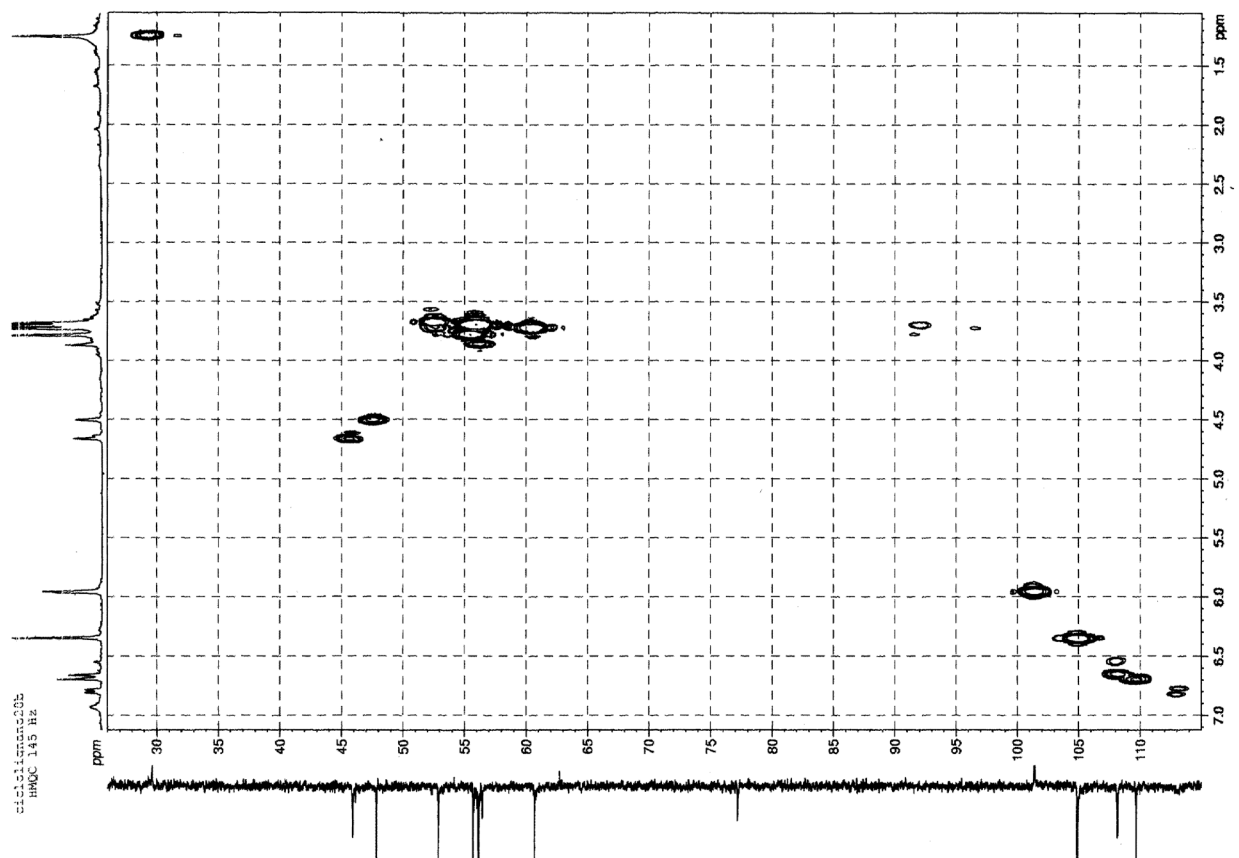
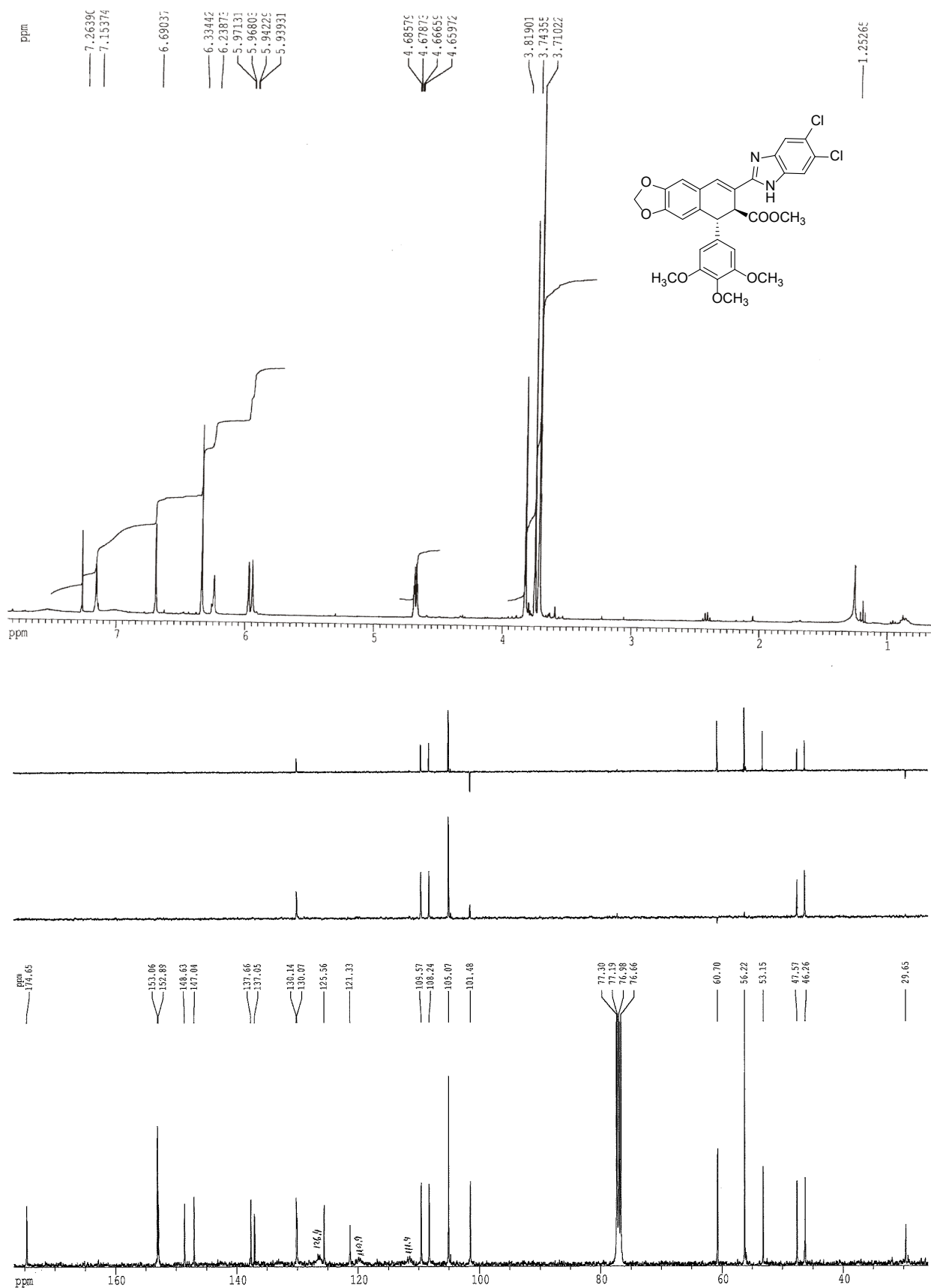
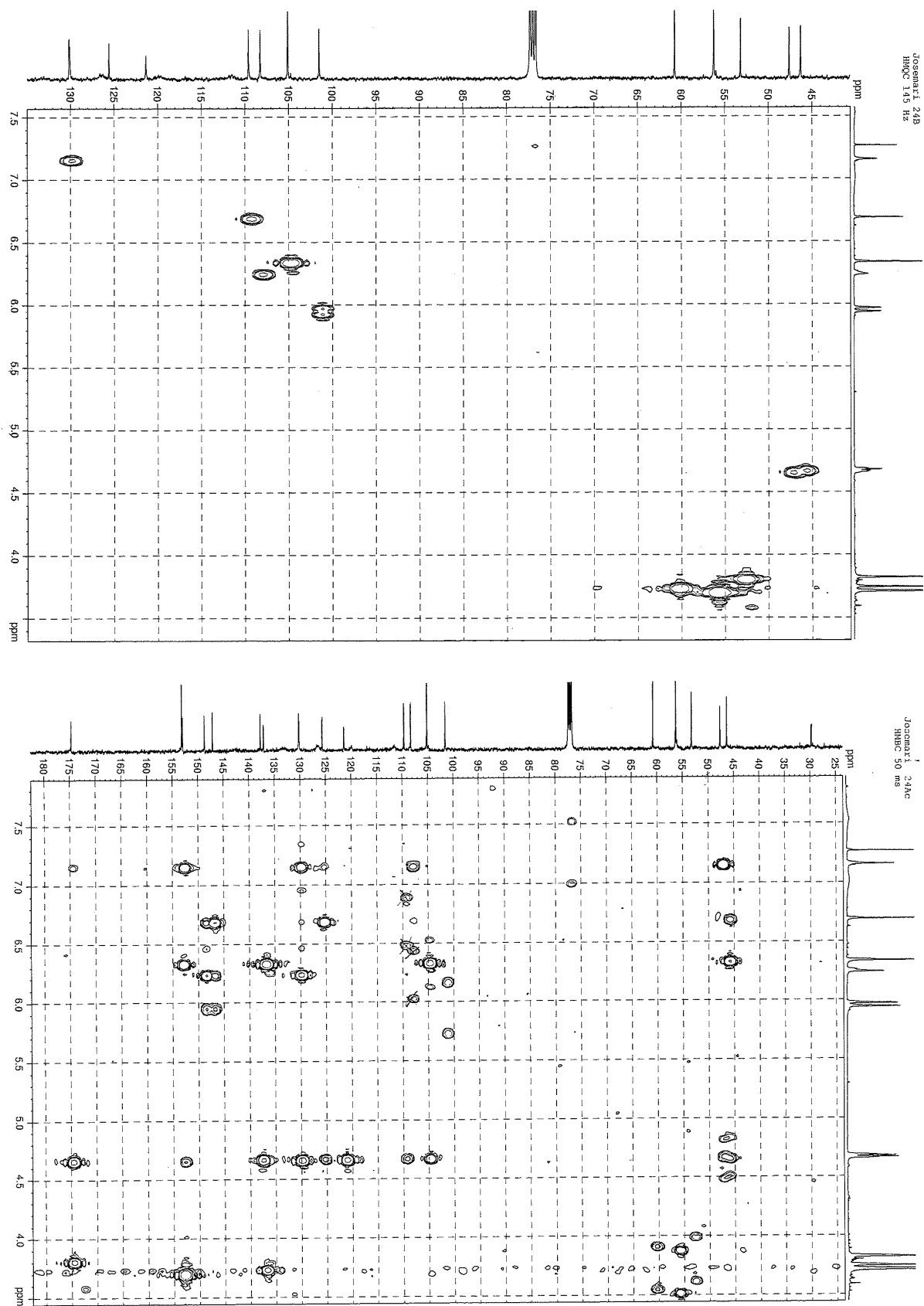


Figure S23. HMQC and HMBC for compound 14



**Figure S24.** <sup>1</sup>H and <sup>13</sup>C for compound **15**



**Figure S25.** HMQC and HMBC for compound 15

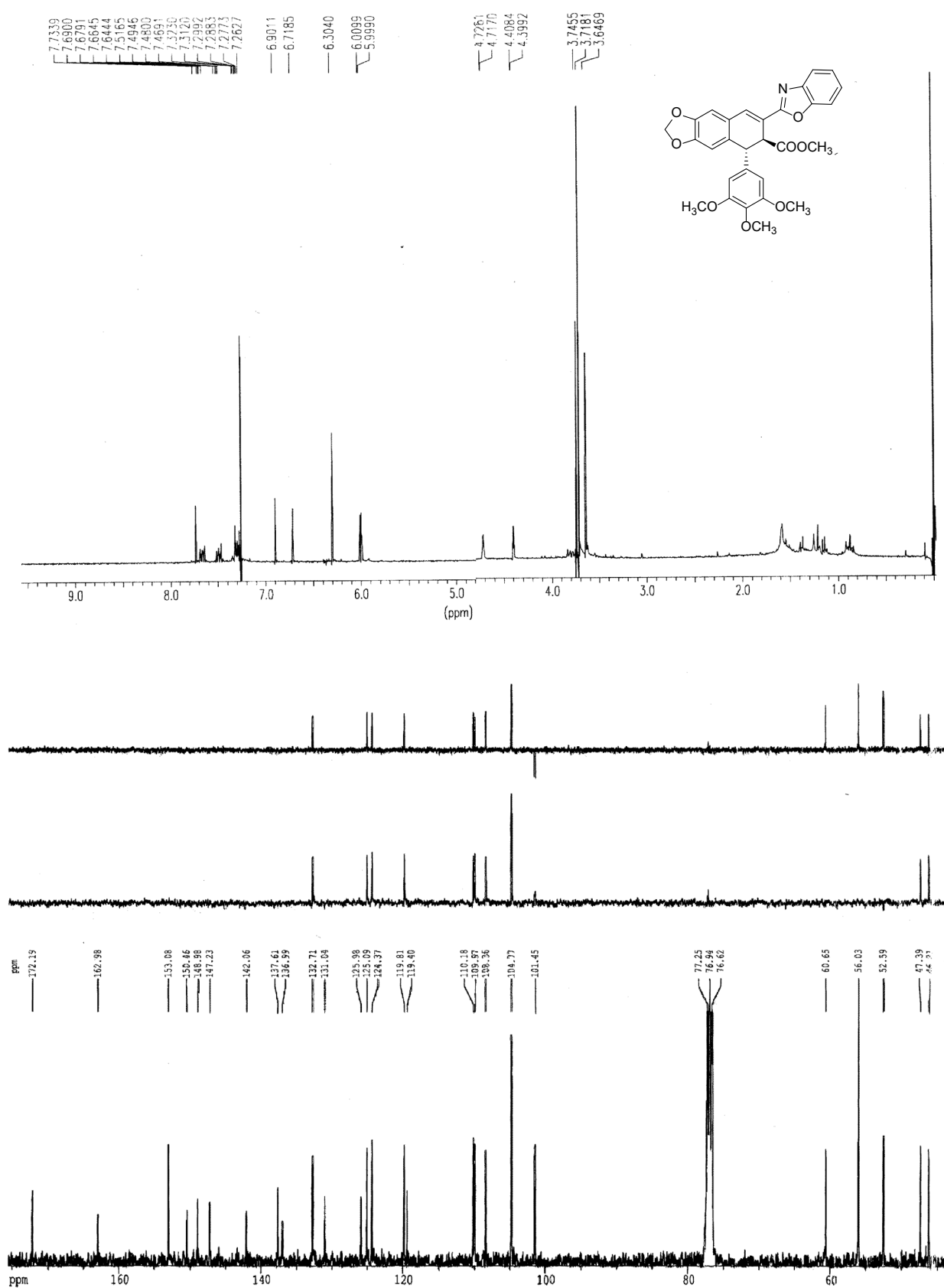


Figure S26. <sup>1</sup>H and <sup>13</sup>C for compound 16



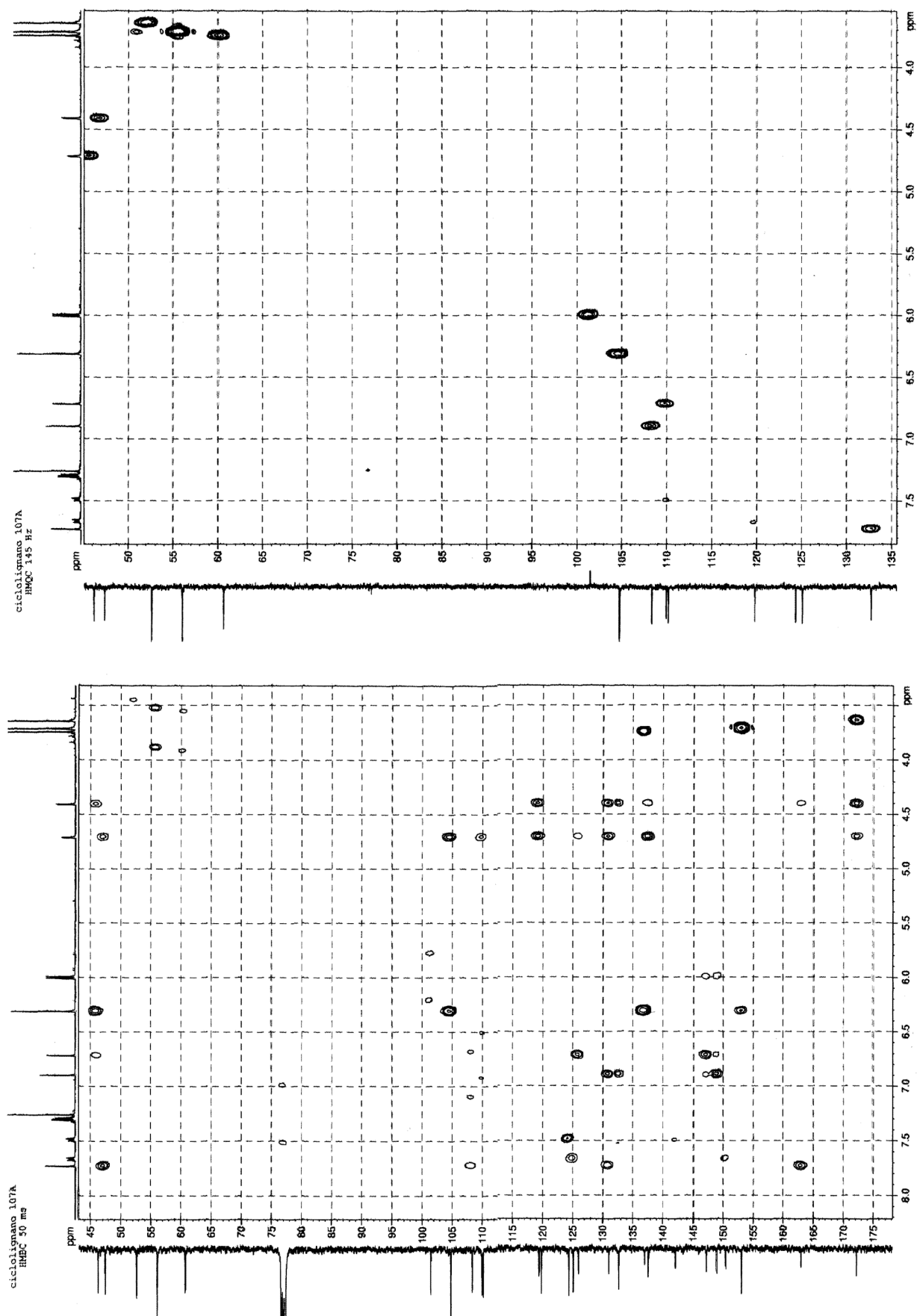
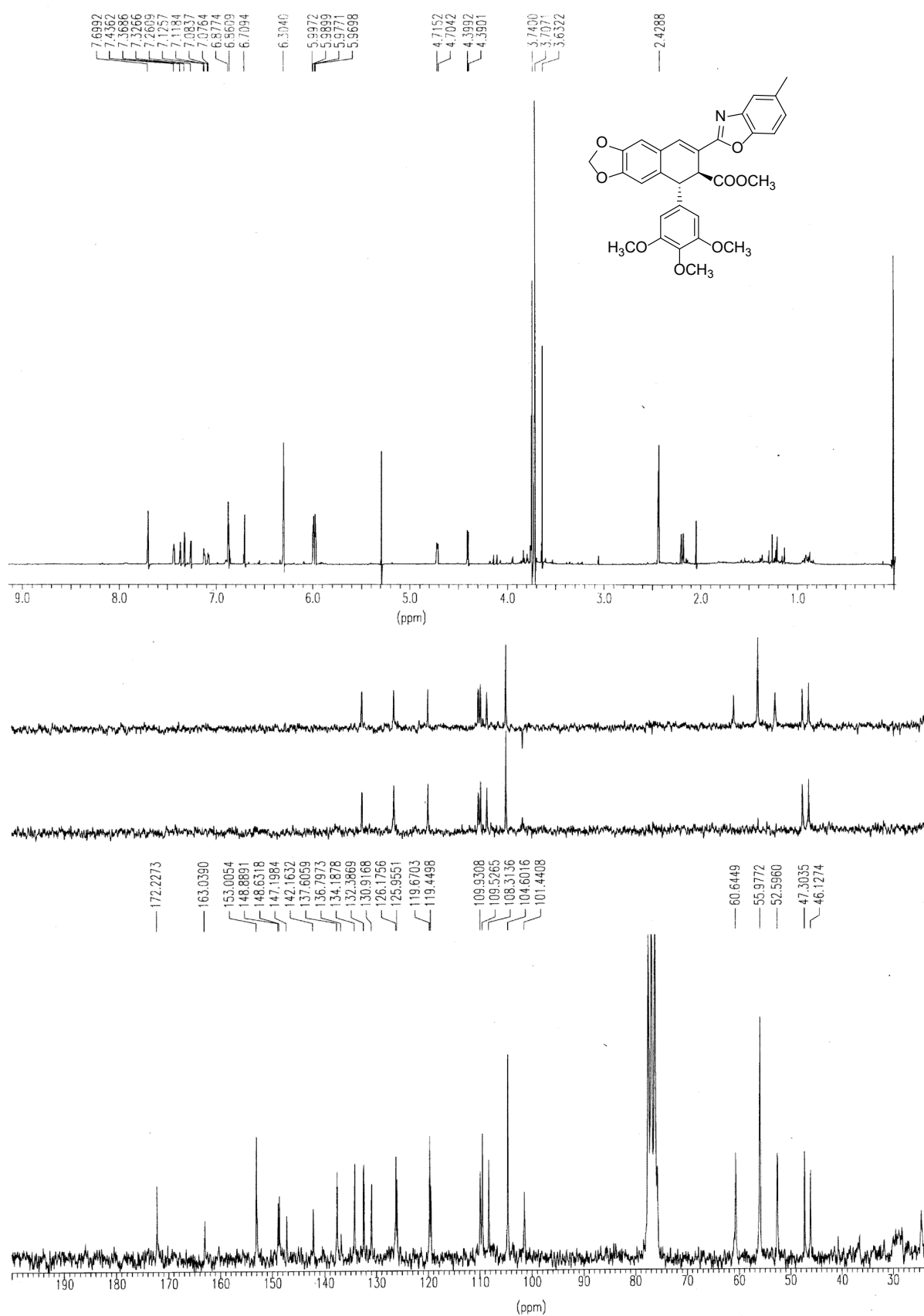
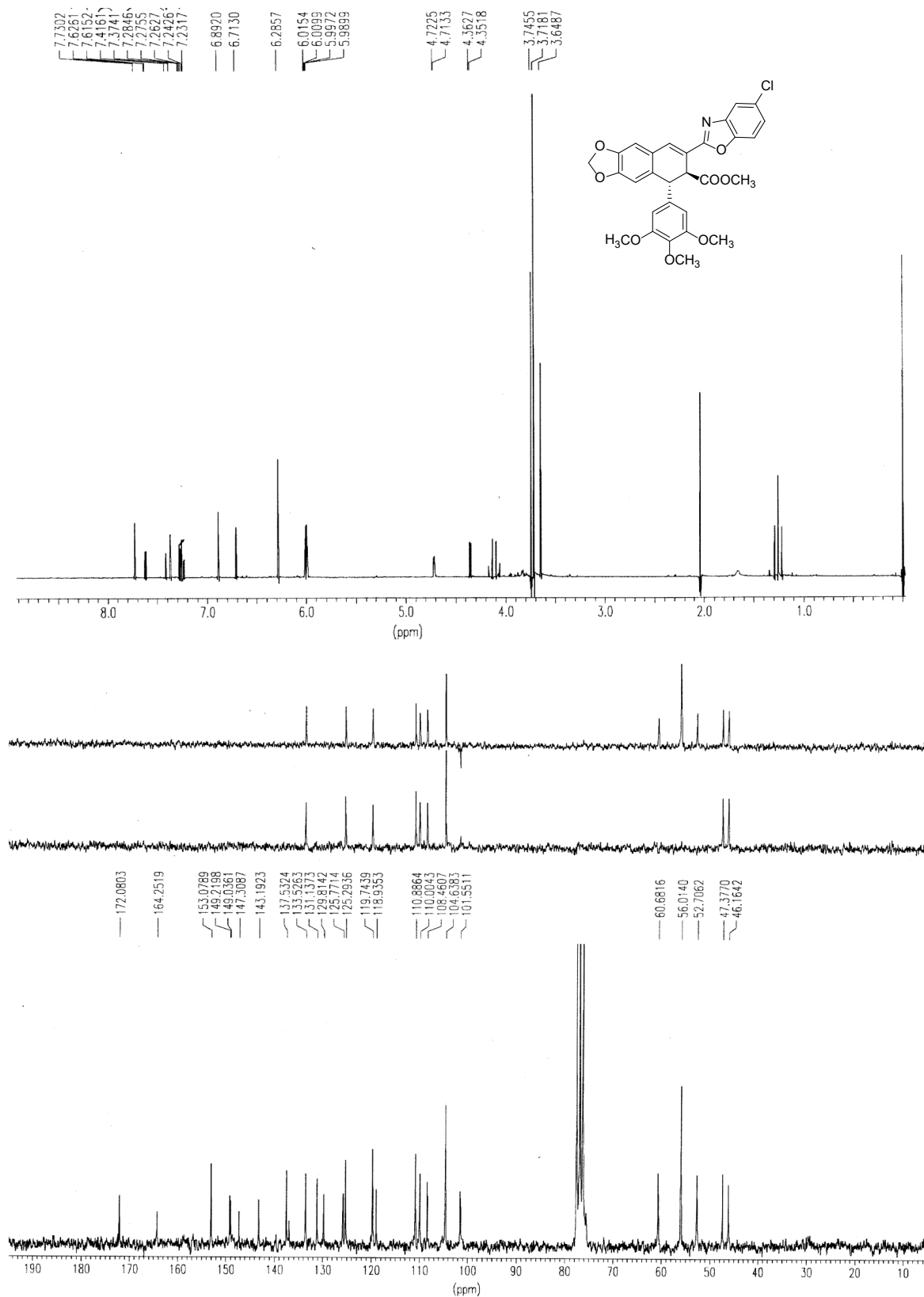


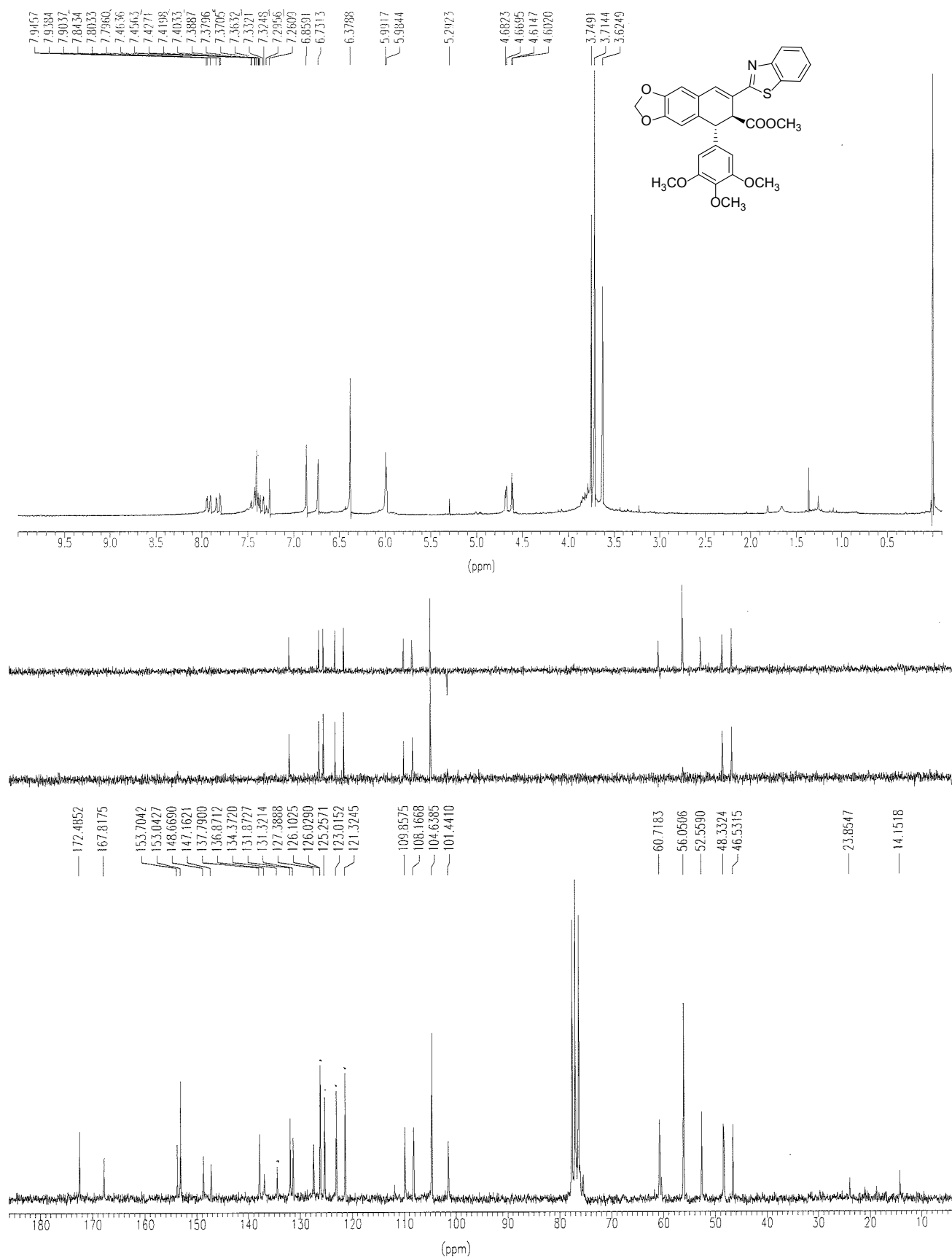
Figure S27. HMQC and HMBC for compound 16



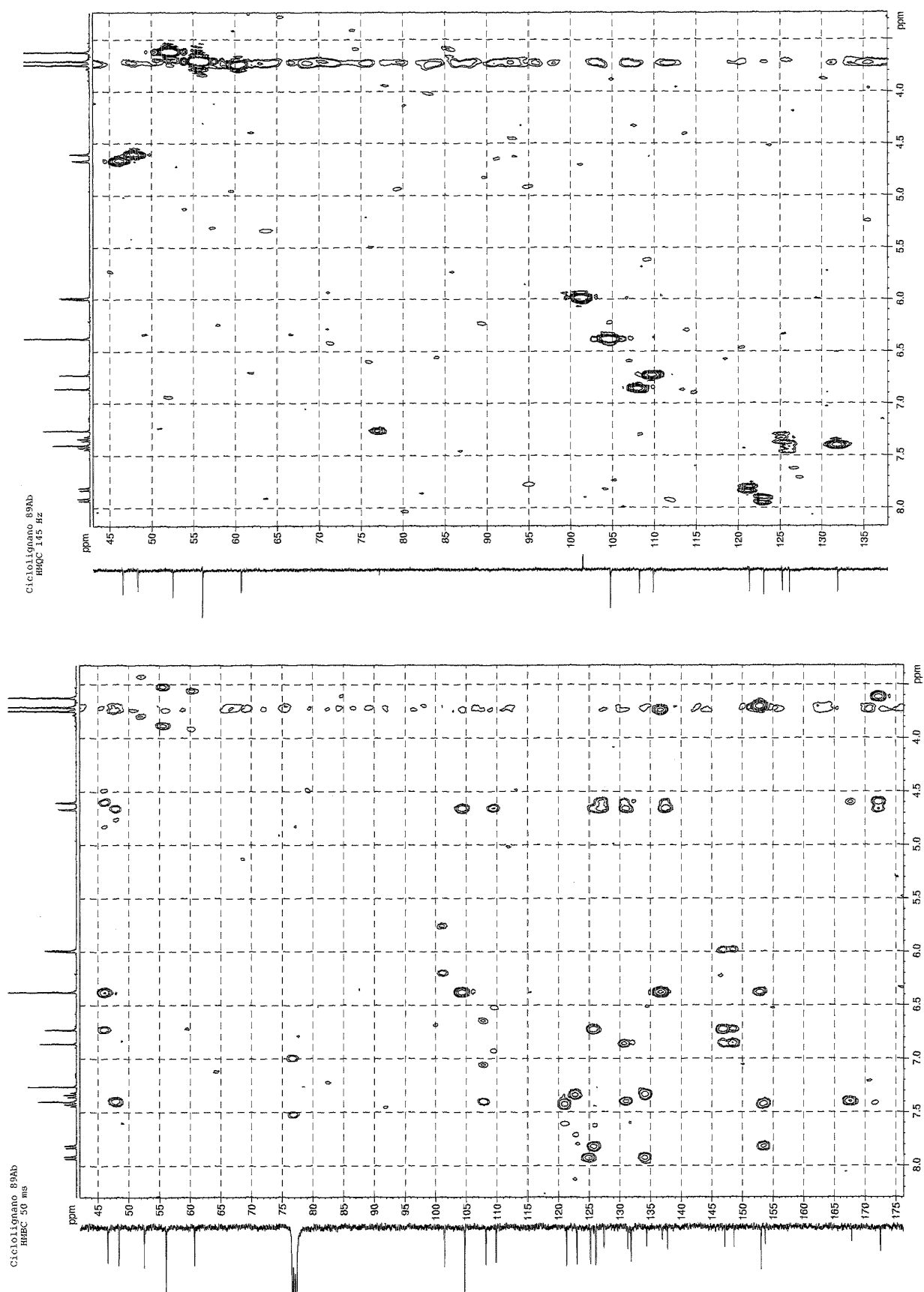
**Figure S28.** <sup>1</sup>H and <sup>13</sup>C for compound **17**



**Figure S29.** <sup>1</sup>H and <sup>13</sup>C for compound **18**



**Figure S30.** <sup>1</sup>H and <sup>13</sup>C for compound **19**



**Figure S31.** HMBC and HMQC for compound 19

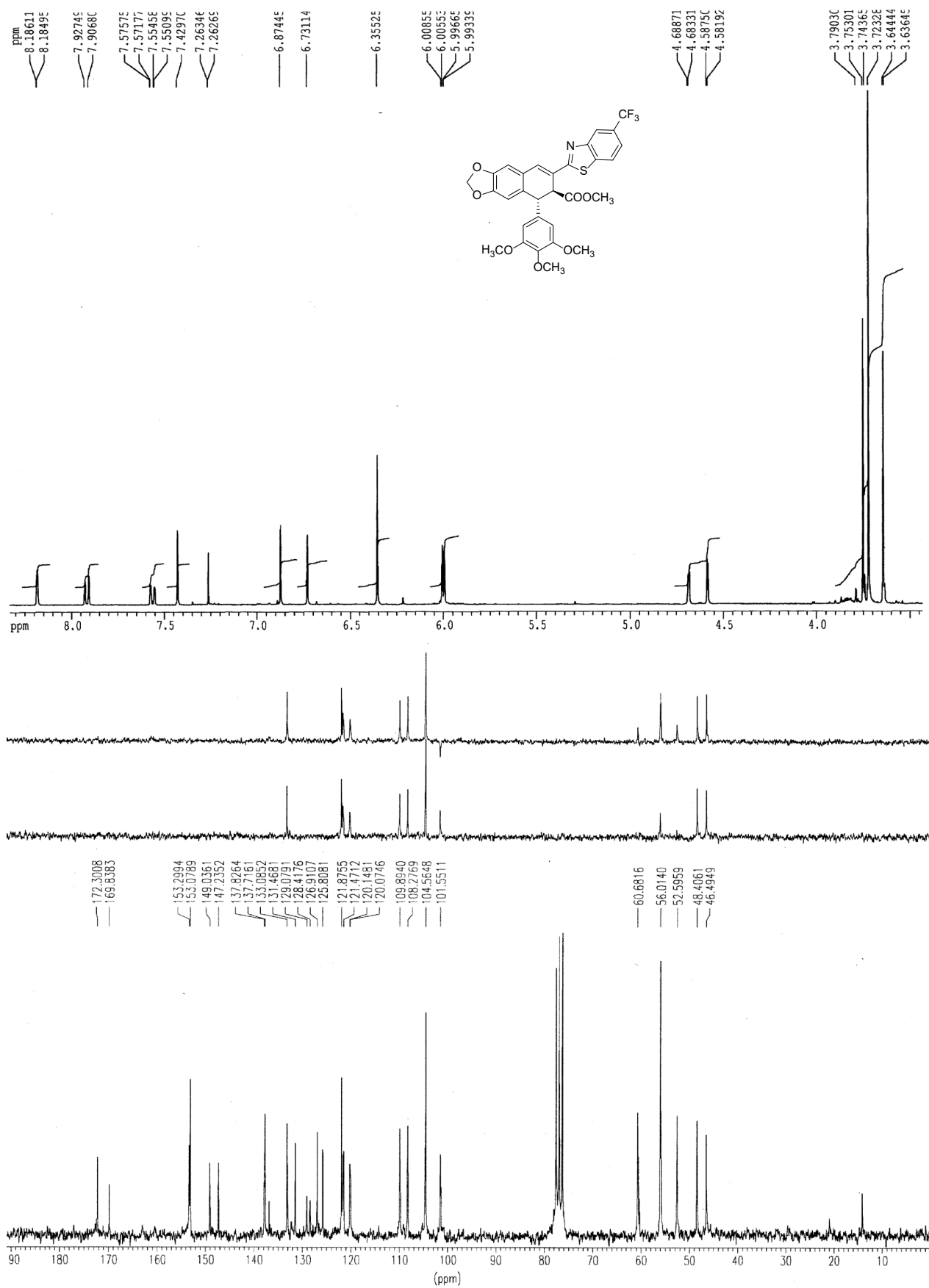


Figure S32. <sup>1</sup>H and <sup>13</sup>C for compound 20

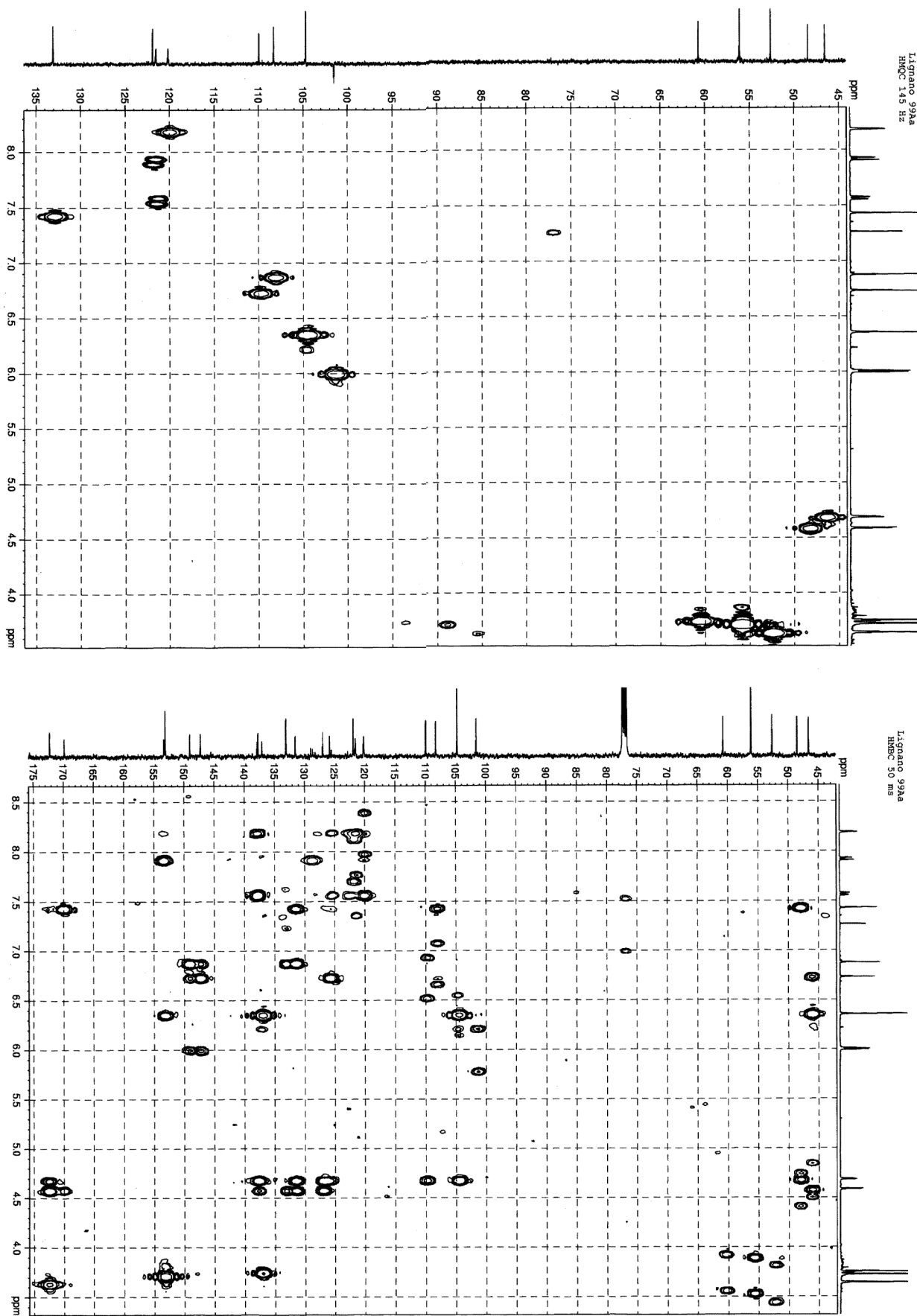
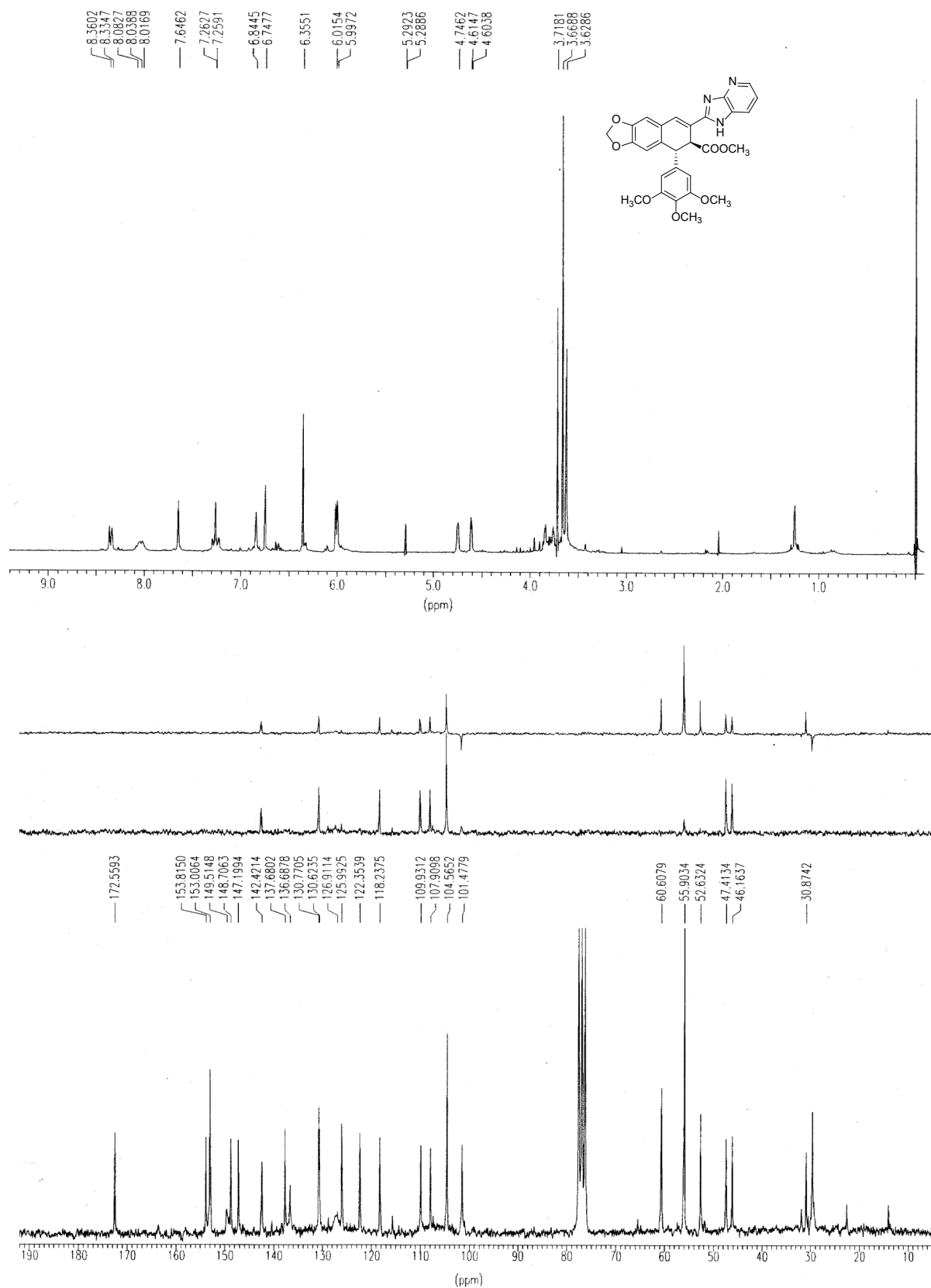


Figure S33. HMQC and HMBC for compound 20



**Figure S34.** <sup>1</sup>H and <sup>13</sup>C for compound **21**



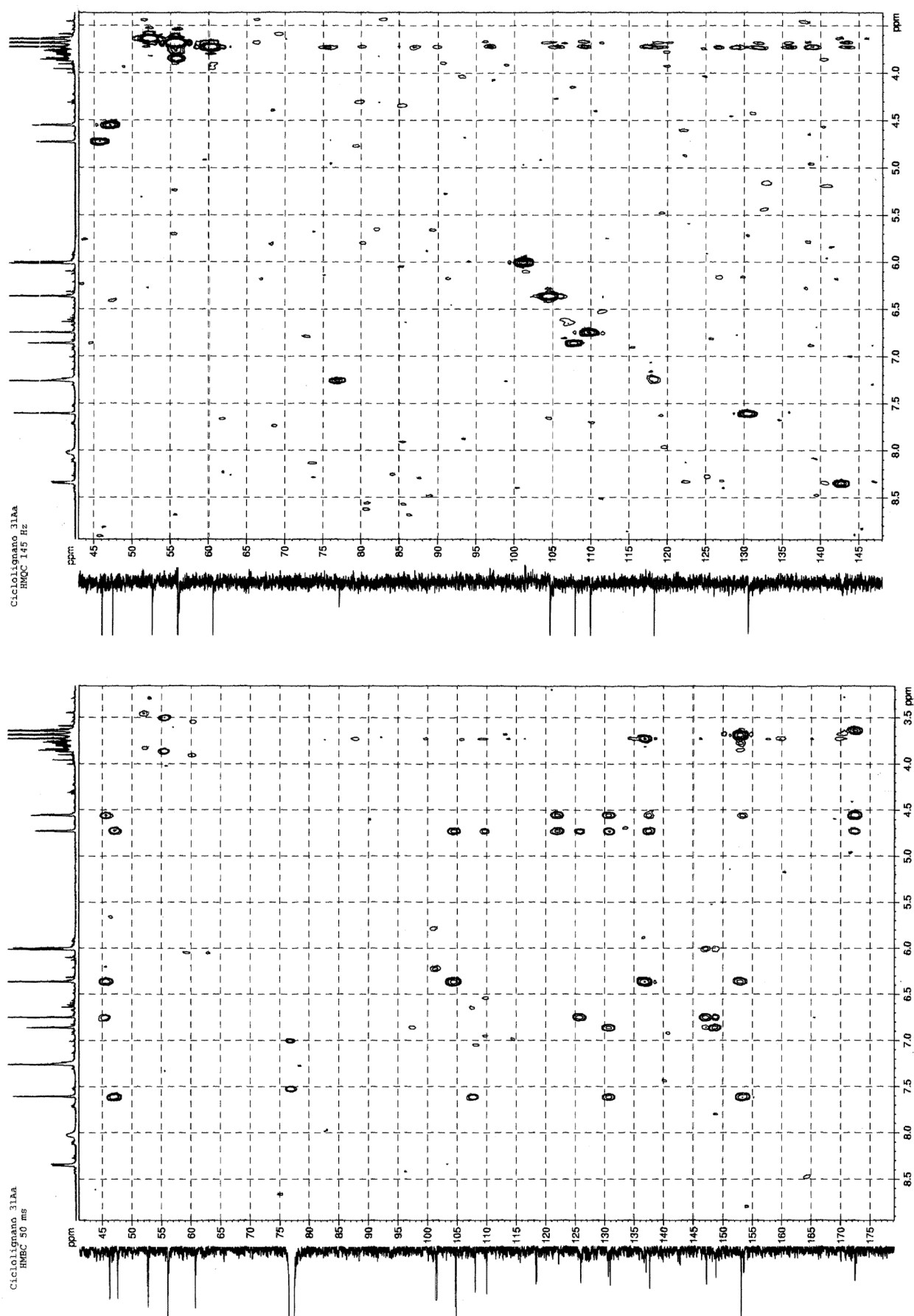
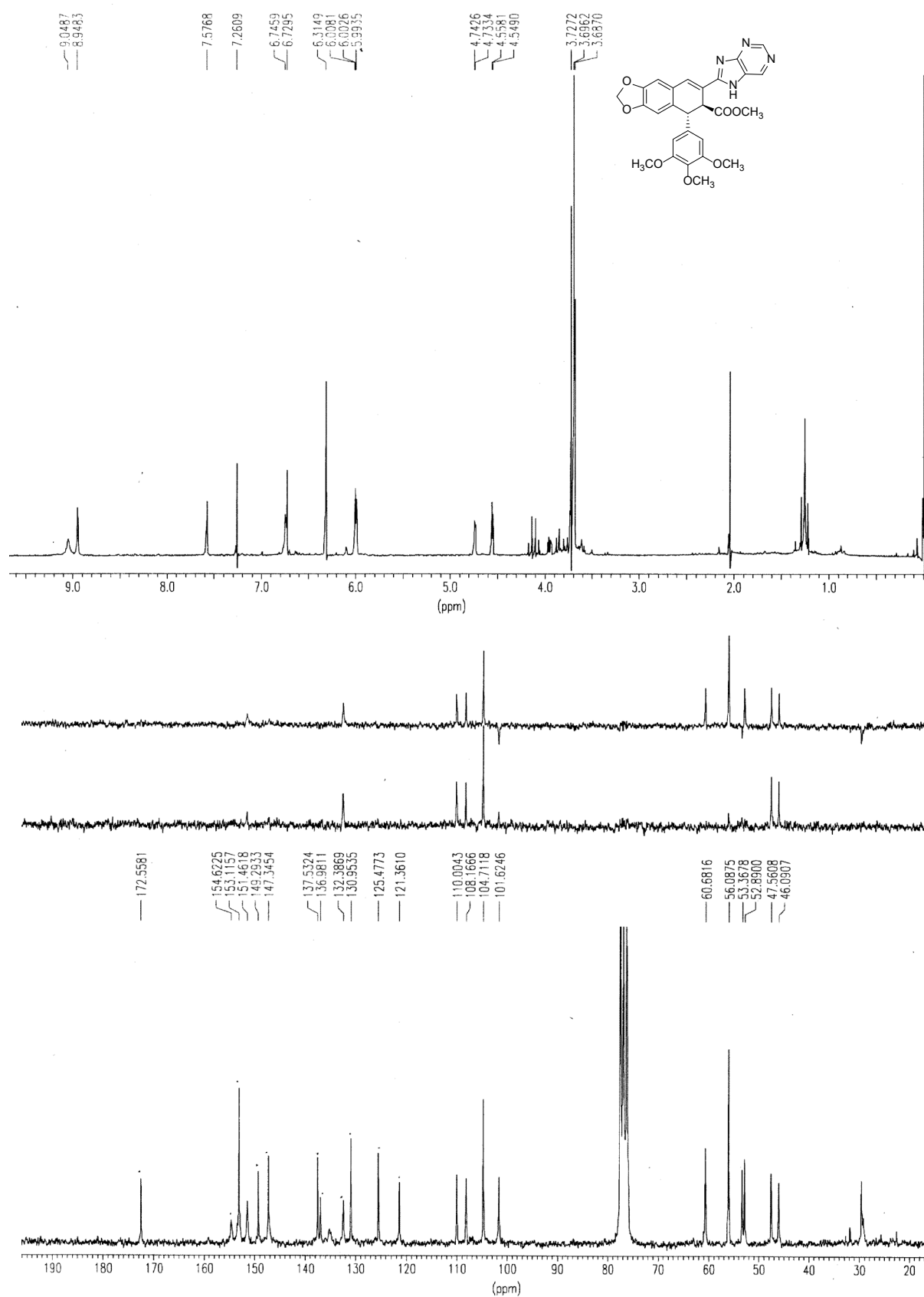


Figure S35. HMBC and HMQC for compound 21



**Figure S36.** <sup>1</sup>H and <sup>13</sup>C for compound **22**

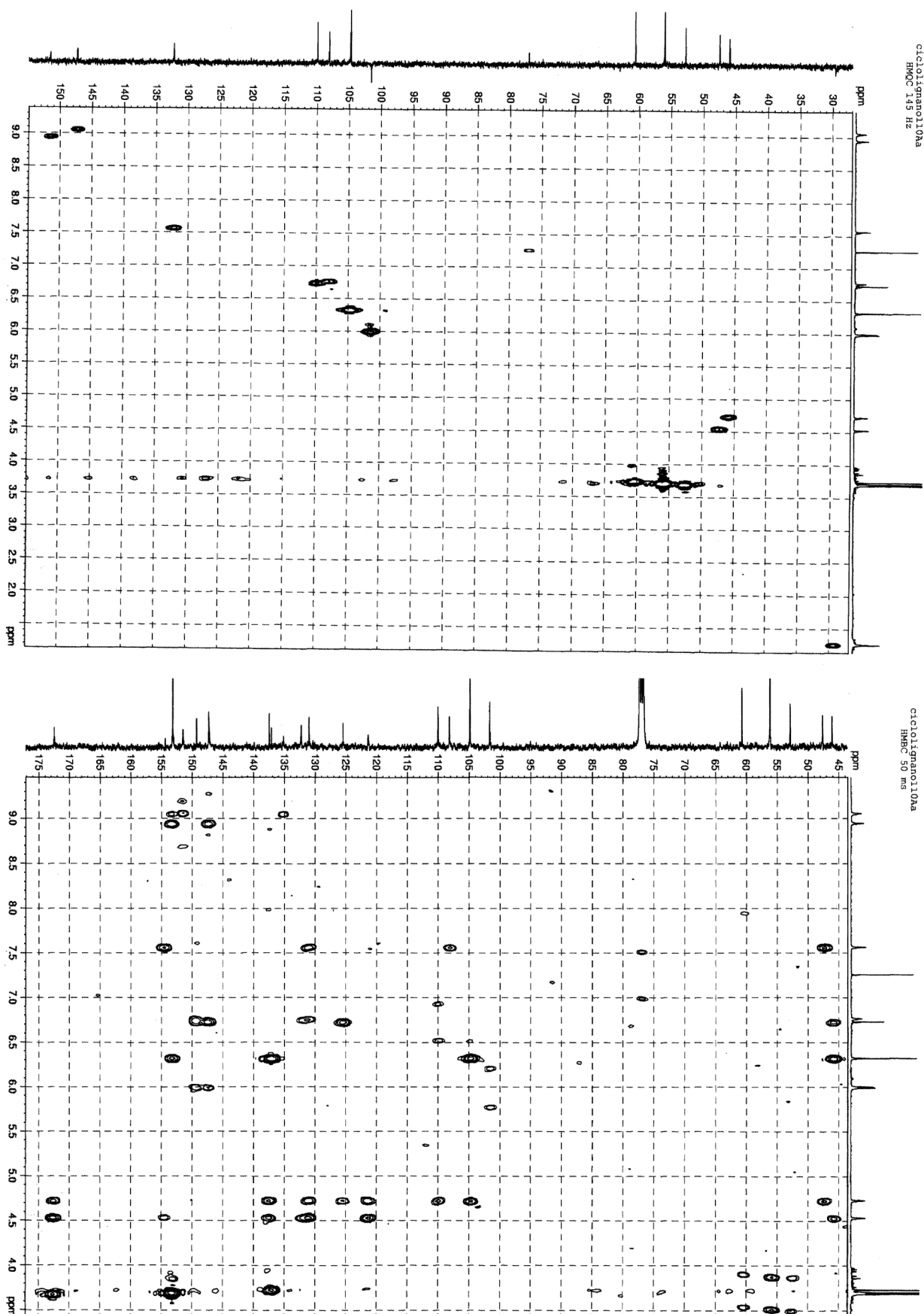


Figure S37. HMQC and HMBC for compound 22

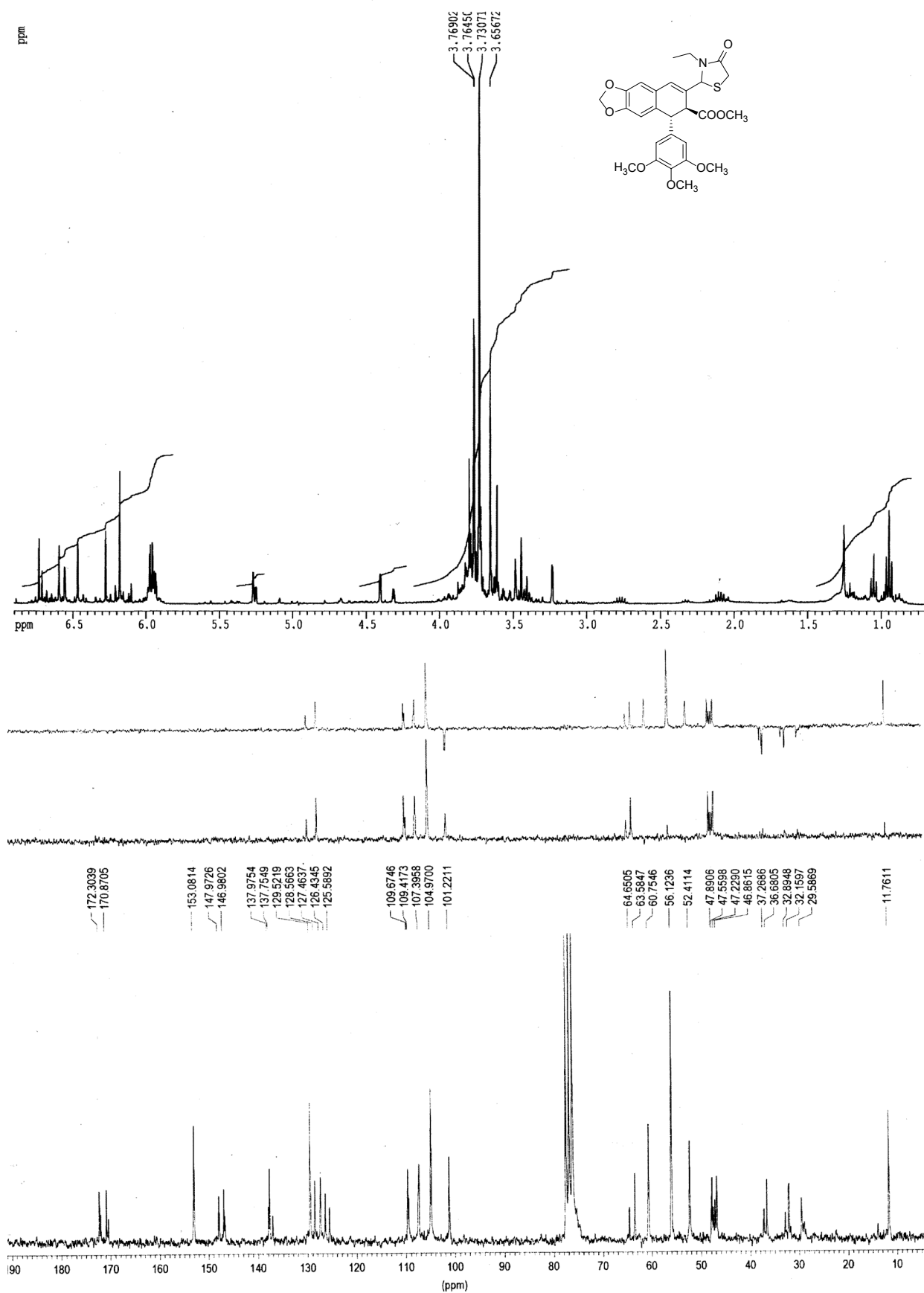


Figure S38.  $^1\text{H}$  and  $^{13}\text{C}$  for compound 28

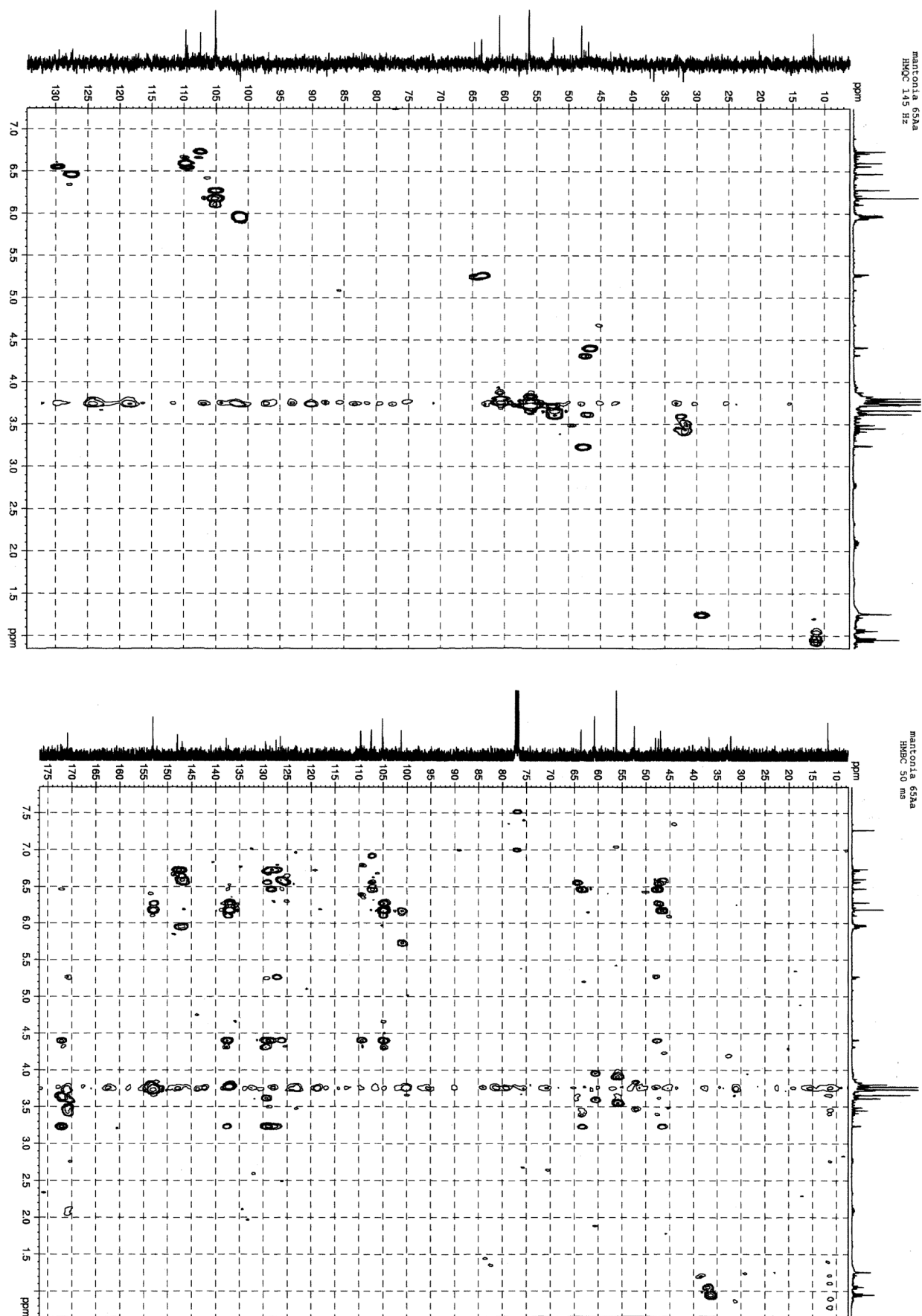


Figure S39. HMQC and HMBC for compound 28

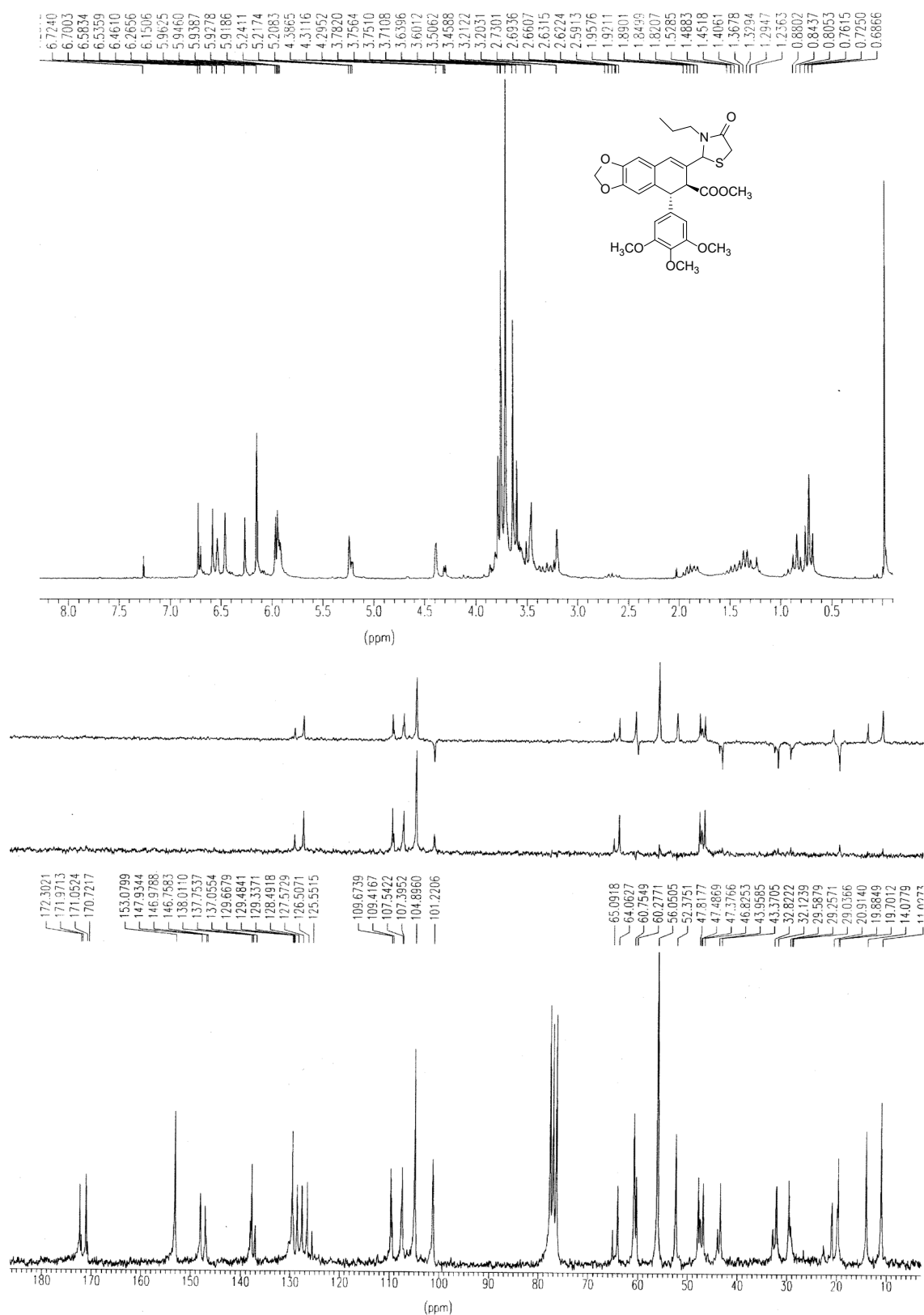
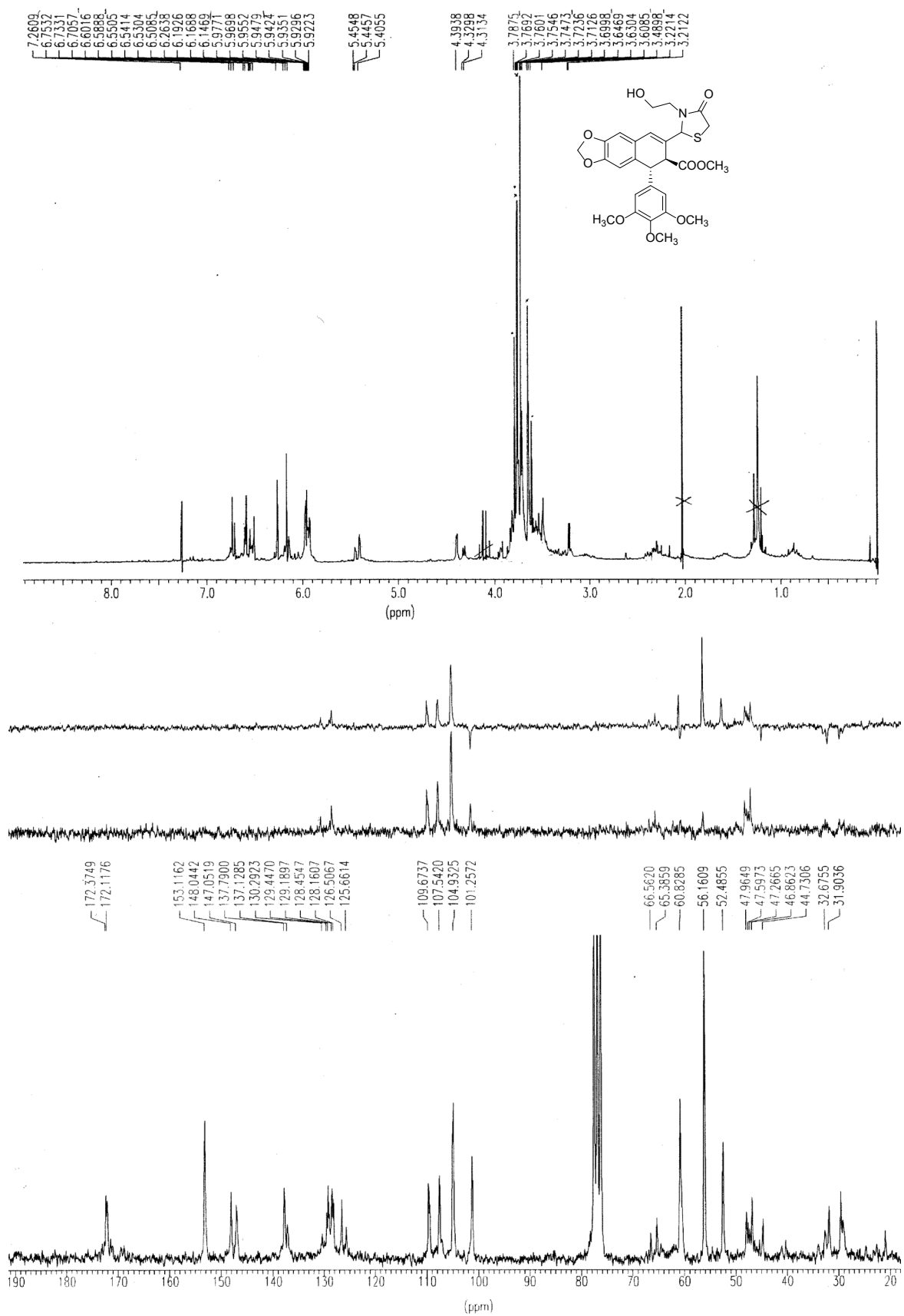


Figure S40. <sup>1</sup>H and <sup>13</sup>C for compound 29



**Figure S41.** <sup>1</sup>H and <sup>13</sup>C for compound **30**

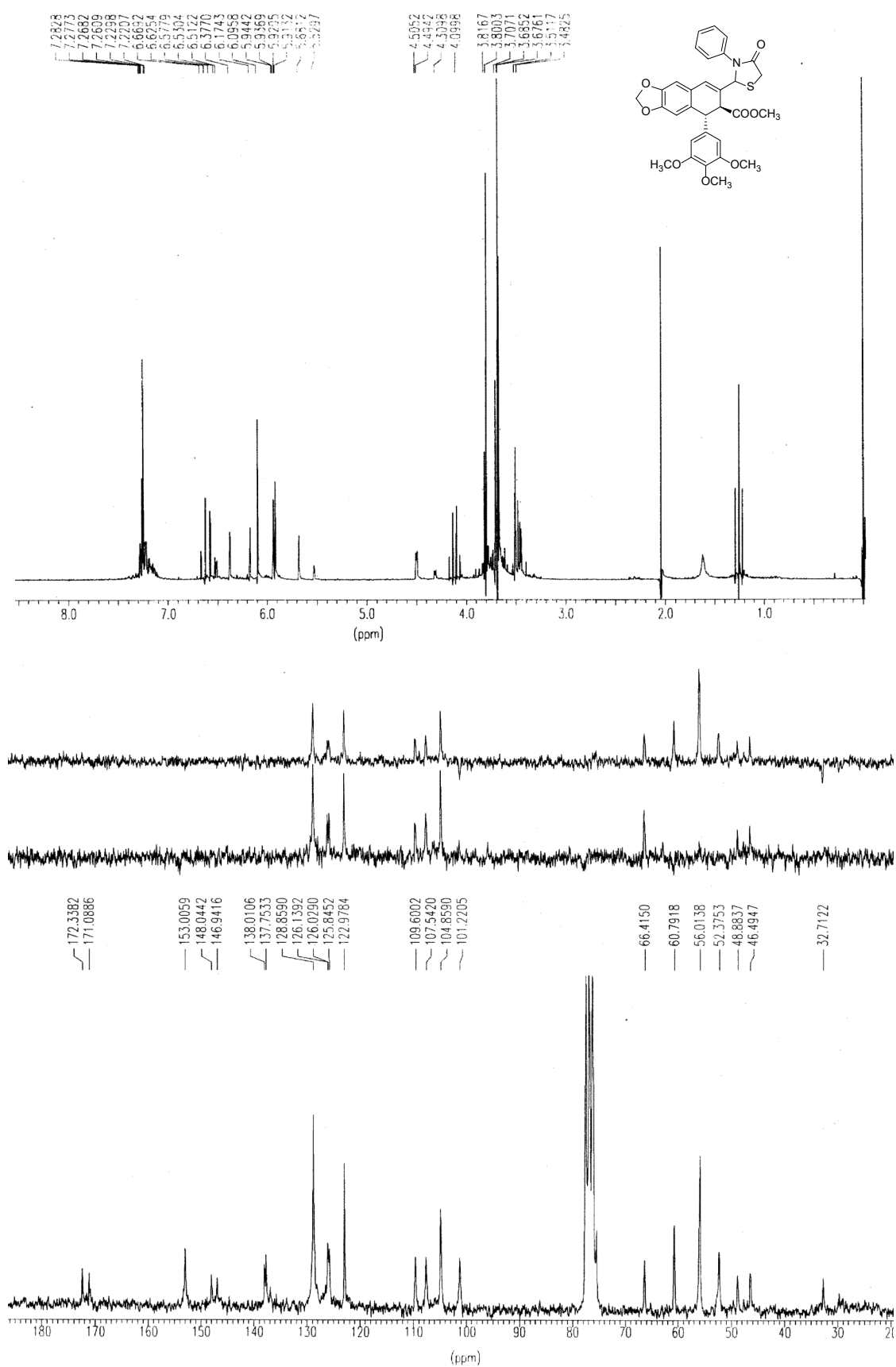


Figure S42. <sup>1</sup>H and <sup>13</sup>C for compound **31**



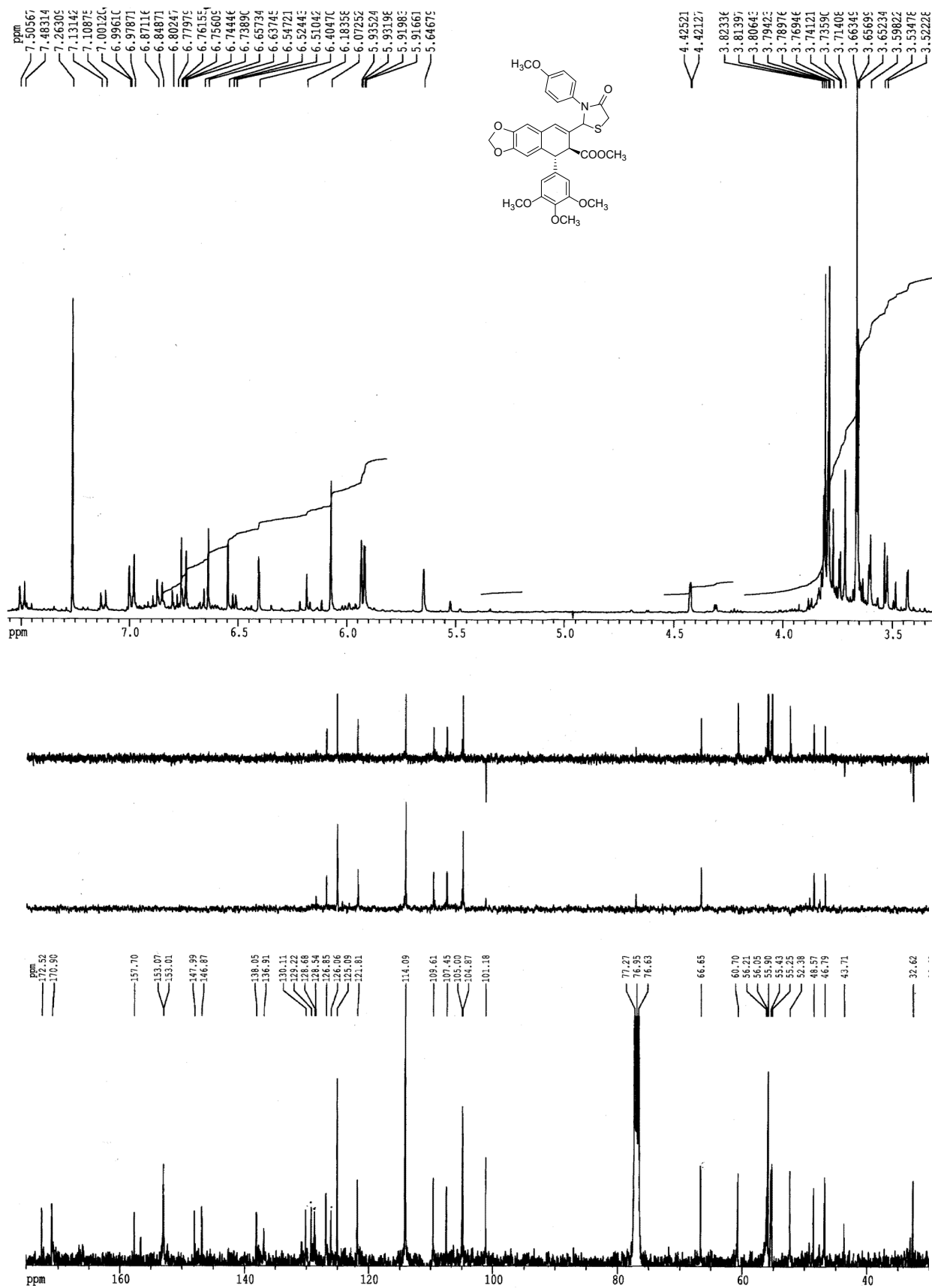
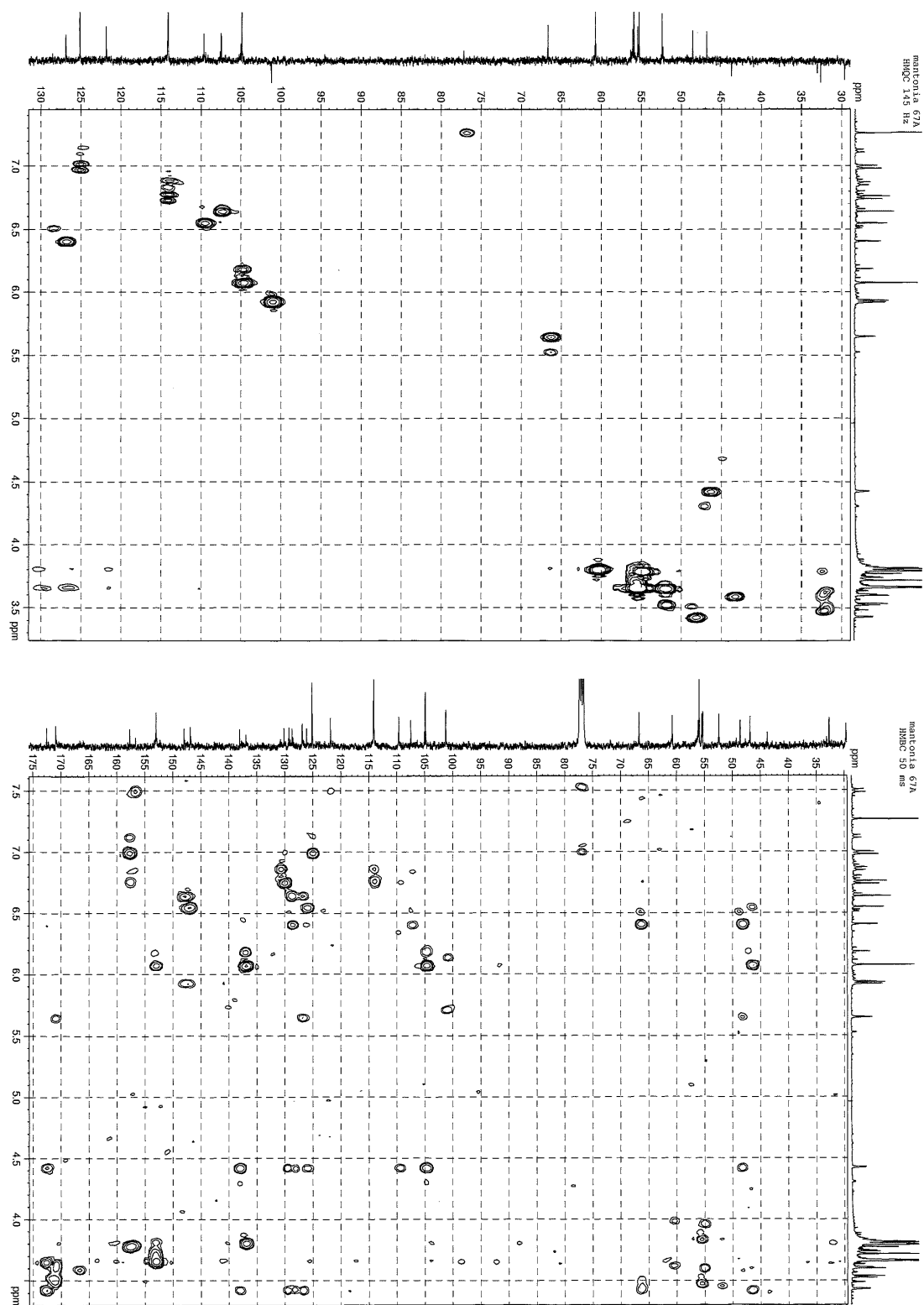


Figure S43. <sup>1</sup>H and <sup>13</sup>C for compound 32



**Figure S44.** HMQC and HMBC for compound **32**