

Electronic Supplementary Information

Design and synthesis of cenocladamide analogues and their evaluation against breast cancer cell lines

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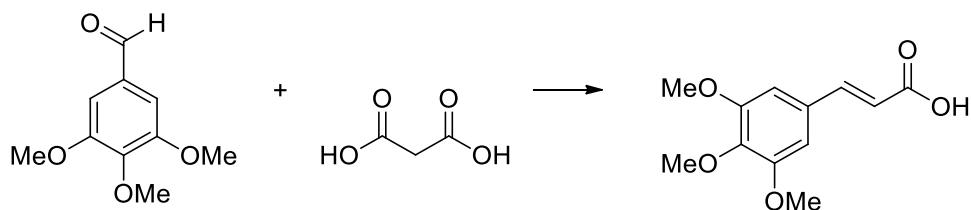
*E-mail: Sandra.dias@lnbio.cnpem.br

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1. Experimental section - Chemistry

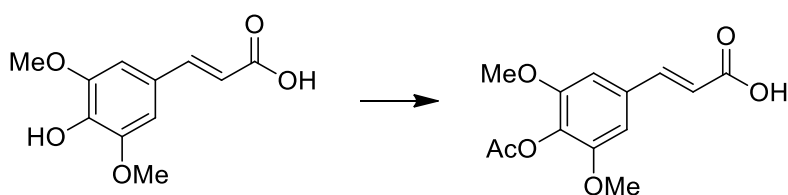
Synthesis of methoxylated carboxylic acids



(E)-3-(3,4,5-trimethoxyphenyl)acrylic acid

A mixture of 3,4,5-trimethoxybenzaldehyde (1.00 g, 5.0 mmol, 1 eq.), malonic acid (1.15 g, 11.0 mmol, 2.2 eq.) and piperidine (98.8 μ L, 1 mmol, 0.2 eq.) in anhydrous pyridine (2.31 mL, 28.5 mmol, 5.7 eq.) was heated at reflux for 2 h. After cooling to room temperature, an aqueous solution of HCl (5% v/v, 50 mL) was added to the reaction. The solvent was removed and the precipitate was dissolved in ethyl acetate (35 mL) and washed with water (2 x 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to yield the carboxylic acid.

Yield: 1.15 g, 96% as a white solid; R_f = 0.33, hexanes/ethyl acetate (50:50); mp 102-104 $^{\circ}$ C; δ_H (250 MHz; CDCl₃) 3.90 (9H, s), 6.36 (1H, d, J = 15.8 Hz), 6.78 (2H, s), 7.61 (1H, d, J = 15.9 Hz), 11.43 (1H, br. s); δ_C (62.9 MHz; CDCl₃) 56.1 (CH₃), 60.9 (CH₃), 105.5 (CH), 116.4 (CH), 129.4 (C), 140.5 (C), 147 (CH), 153.4 (C), 172.4 (C).



(E)-3-(4-acetoxy-3,5-dihydroxyphenyl)acrylic acid

To sinapic acid (229 mg, 1 mmol, 1 eq.) were added pyridine (1.0 mL, 12.5 mmol, 12.5 eq.) and acetic anhydride (1.0 mL, 11 mmol, 11 eq.) at room temperature. The mixture was stirred overnight. The mixture was diluted with cold HCl (1 M, 20 mL) and ethyl acetate (30 mL). The organic phase was washed with cold H₂O (10 mL), and dried (Na₂SO₄). The crude was further purified by flash chromatography, eluting with hexanes/ethyl acetate (75:25 to 50:50).

Yield: 187 mg, 70 % as a white solid; R_f = 0.20, hexanes/ethyl acetate (50:50); mp 199-201 °C; δ_{H} (250 MHz) 2.36 (3H, s), 3.87 (6H, s), 6.40 (1H, d, J = 15.9 Hz), 6.81 (2H, s), 7.73 (1H, d, J = 15.9 Hz); δ_{C} (62.9 MHz; CDCl₃) 20.4 (CH₃), 56.2 (CH₃), 104.9 (CH), 117.5 (CH), 130.8 (C), 132.3 (C), 146.7 (CH), 152.5 (C), 168.5 (C), 171.9 (C)

2. NMR Spectra

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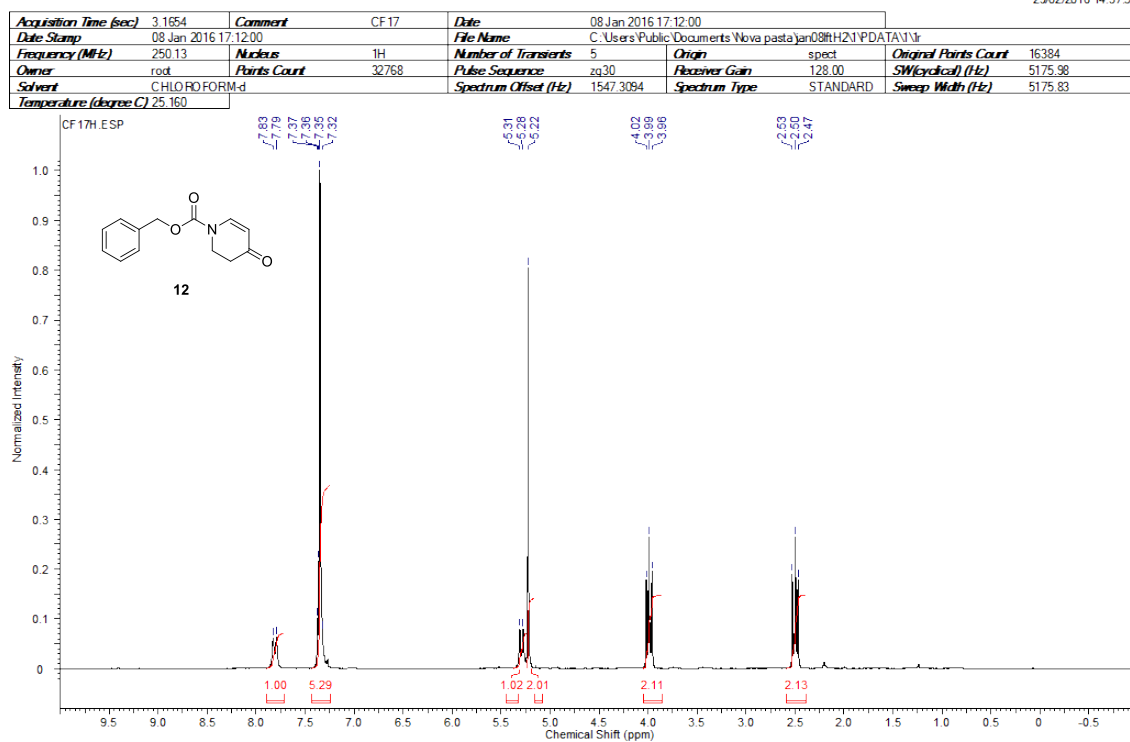


Figure S1. ¹H NMR spectrum of **12** (CDCl₃, 250 MHz)

18/02/2016 14:49:25

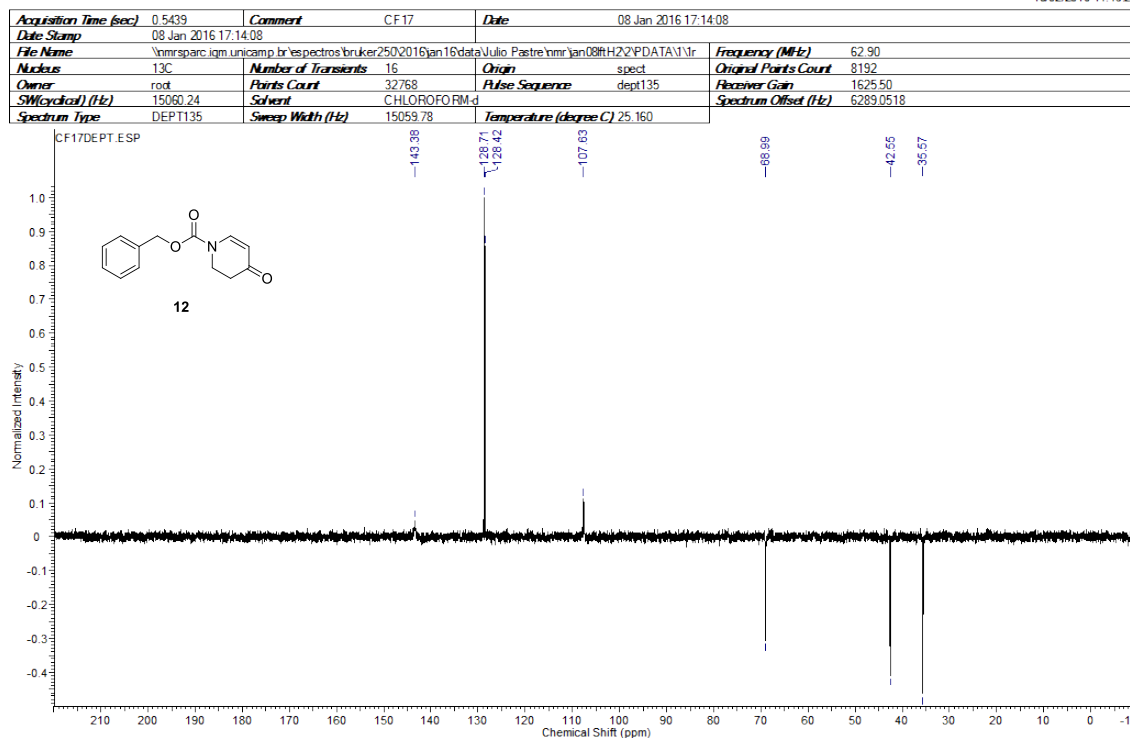
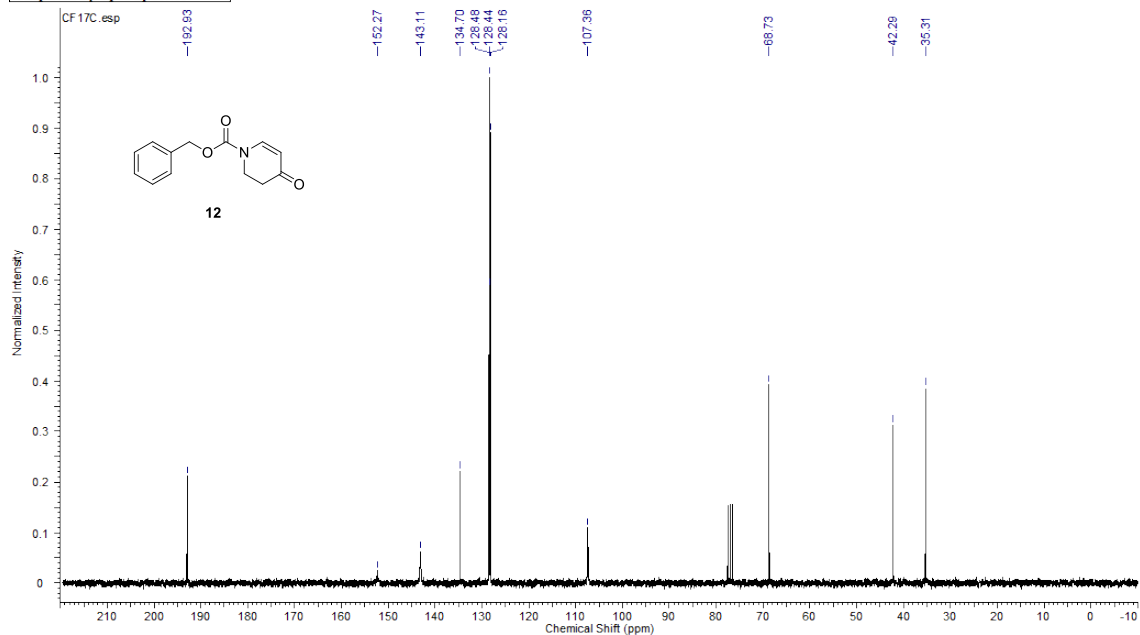
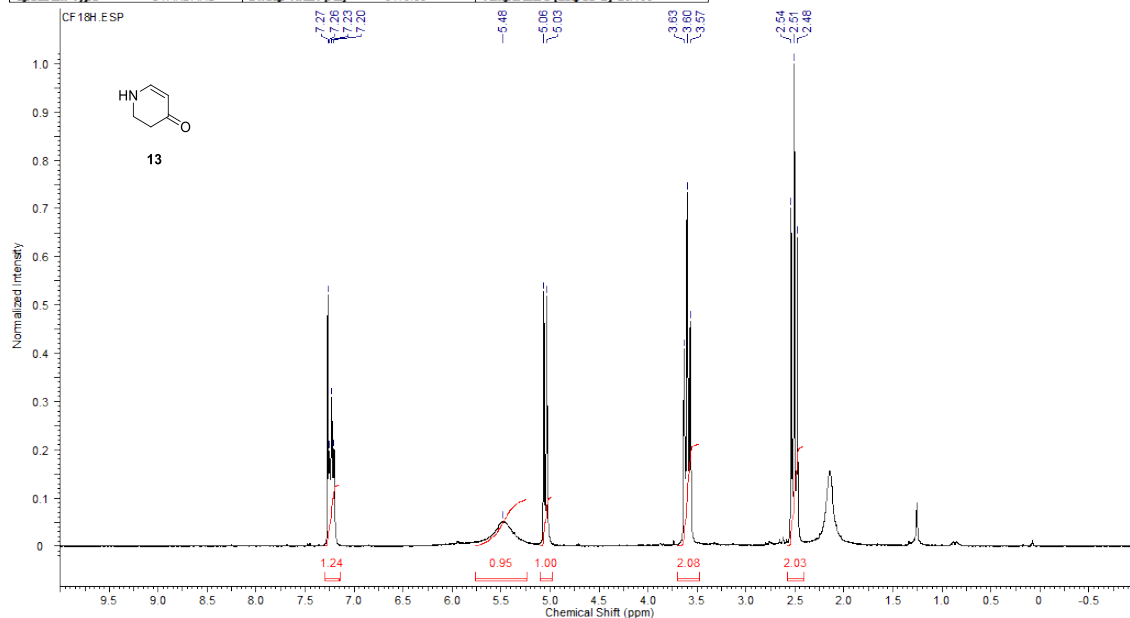


Figure S2. DEPT135 spectrum of **12** (CDCl₃, 62.9 MHz)

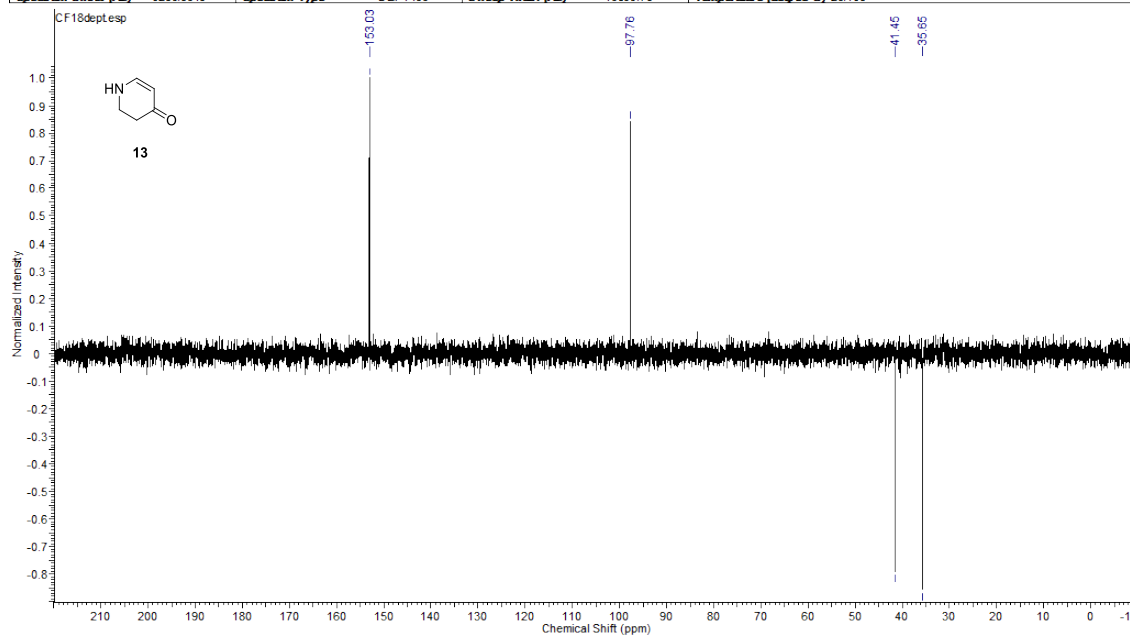
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Figure S3. ¹³C NMR spectrum of **12** (CDCl₃, 62.9 MHz)

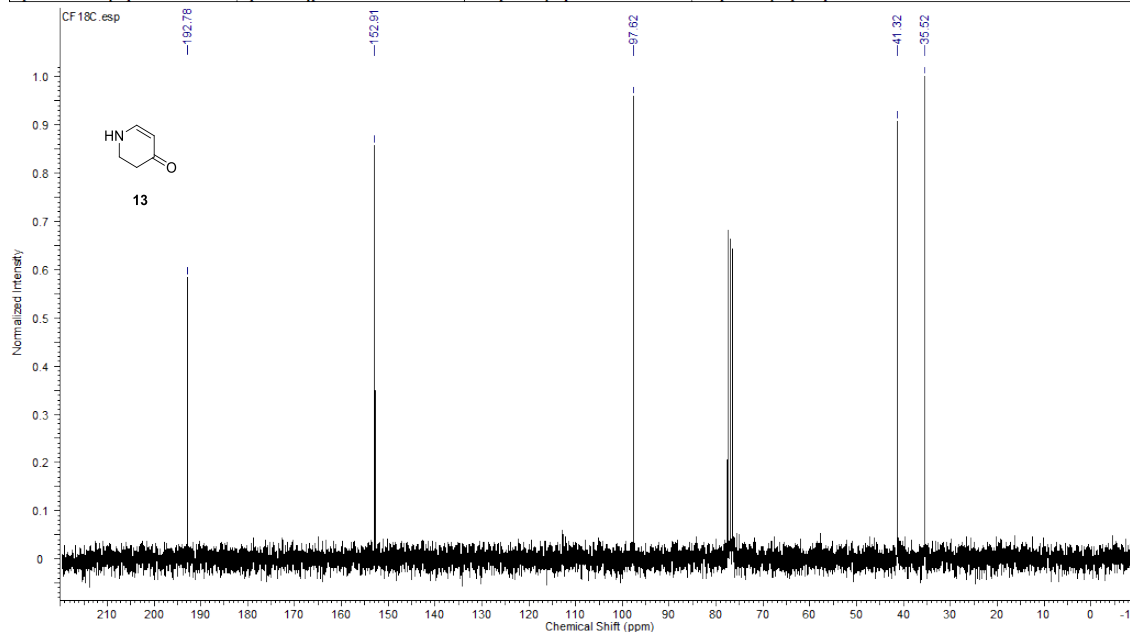
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Solvent	CHLOROFORM-d			Receiver Gain	1625.50
Spectrum Type	STANDARD	Sweep Width (Hz)	5175.83	Temperature (degree C)	25.160

Figure S4. ¹H NMR spectrum of **13** (CDCl₃, 250 MHz)

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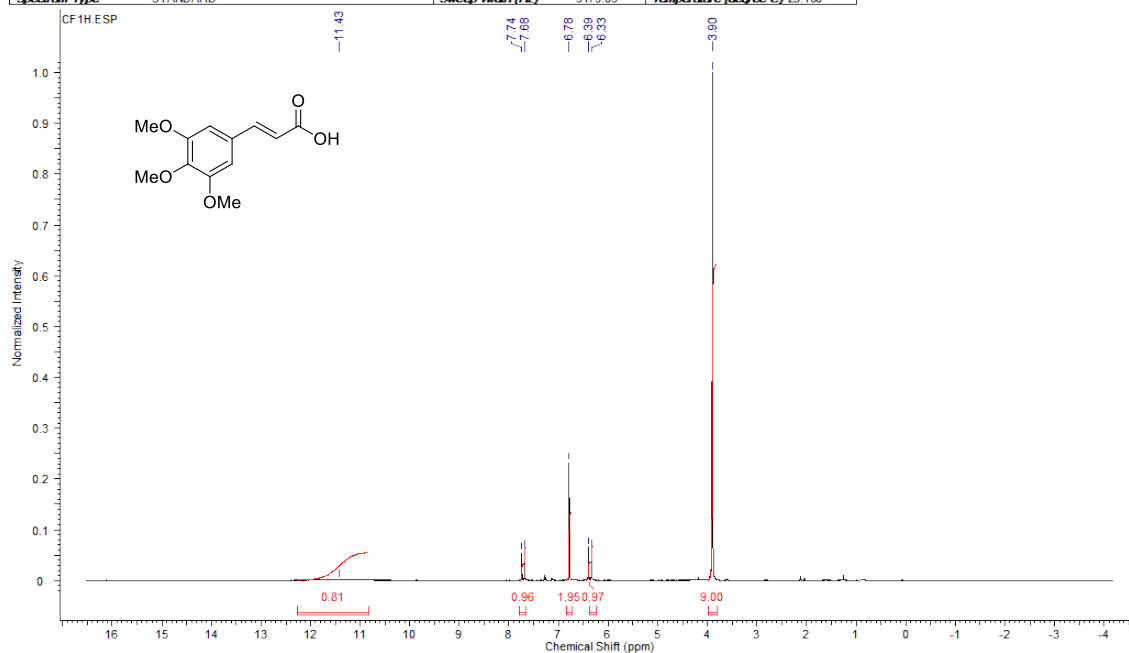
Figure S5. DEPT135 spectrum of **13** (CDCl₃, 62.9 MHz)

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Original Points Count	16384	Owner	root	Points Count	32768
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Spectrum Offset (Hz)	6280.7988	Spectrum Type	STANDARD	Sweep Width (Hz)	15059.78
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Figure S6. ¹³C NMR spectrum of **13** (CDCl₃, 62.9 MHz)

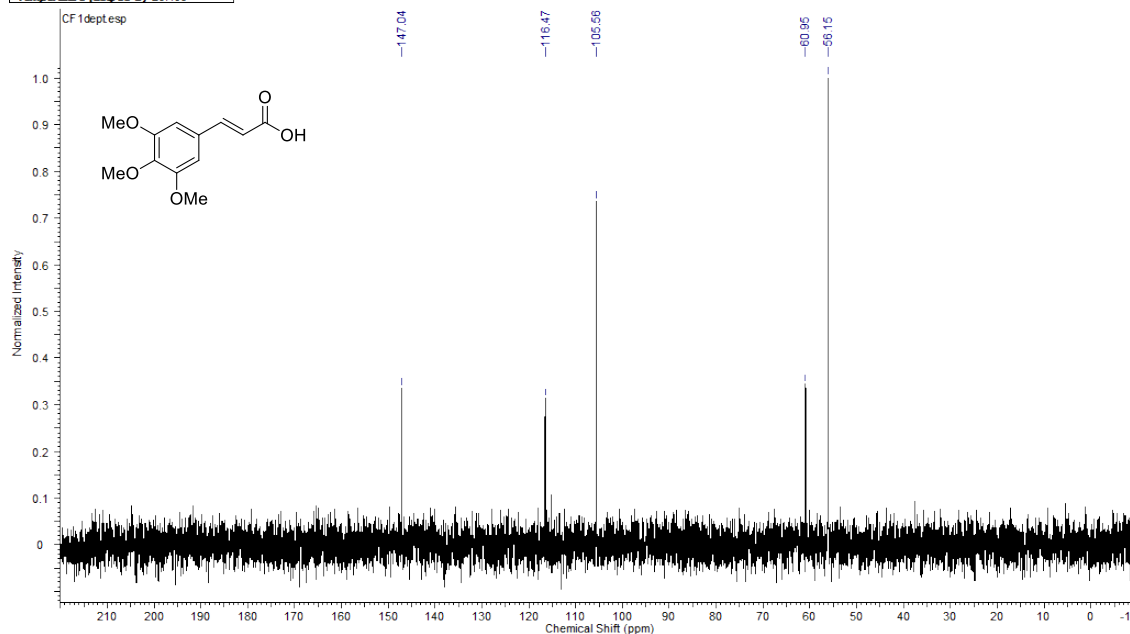
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Receiver Gain	456.10	SW(cyclical) (Hz)	5175.98	Solvent	CHLOROFORM-d	Pulse Sequence	zg30
Spectrum Type	STANDARD	Sweep Width (Hz)	5175.83	Temperature (degree C)	25.160	Spectrum Offset (Hz)	1546.8354

Figure S7. ¹H NMR spectrum of 3,4,5-trimethoxycinnamic acid (CDCl₃, 250 MHz)

16/02/2016 14:43:10

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Receiver Gain	724.10	SW(cyclical) (Hz)	15060.24	Solvent	CHLOROFORM-d	Pulse Sequence	dept135
Spectrum Type	DEPT135	Sweep Width (Hz)	15069.78	Temperature (degree C)	25.160	Spectrum Offset (Hz)	6289.0518

Figure S8. DEPT135 spectrum of 3,4,5-trimethoxycinnamic acid (CDCl₃, 62.9 MHz)

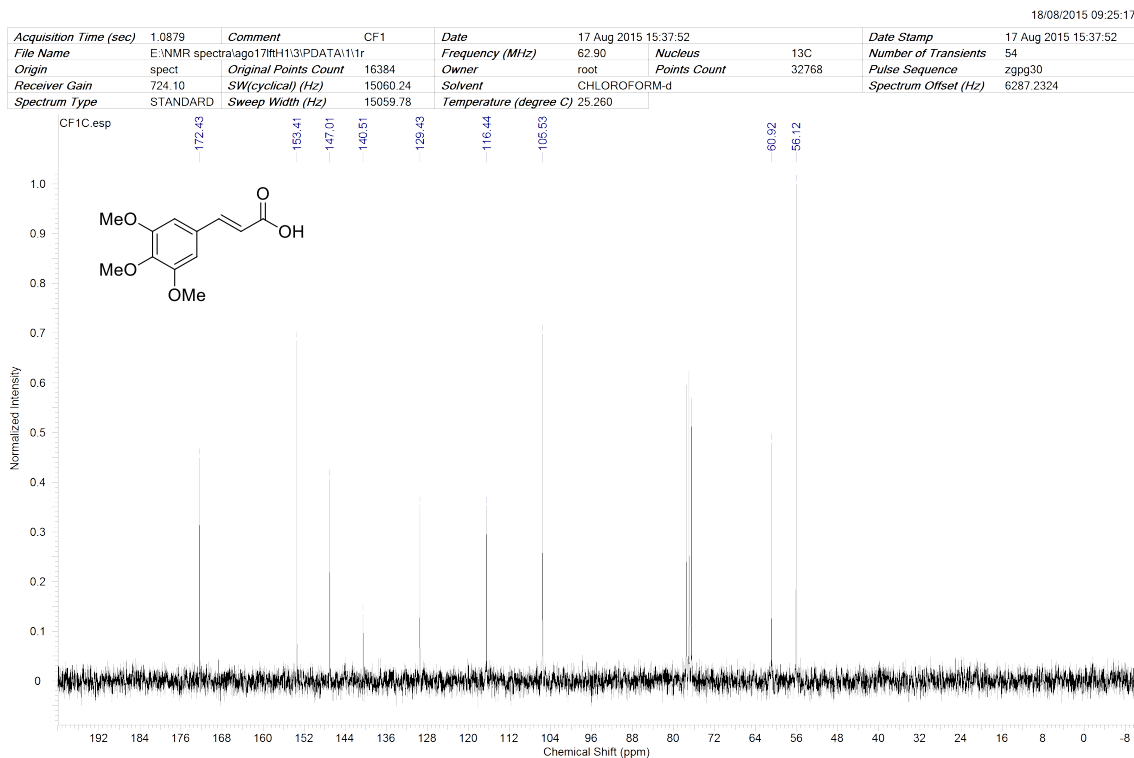


Figure S9. ^{13}C NMR spectrum of 3,4,5-trimethoxycinnamic acid (CDCl_3 , 62.9 MHz)

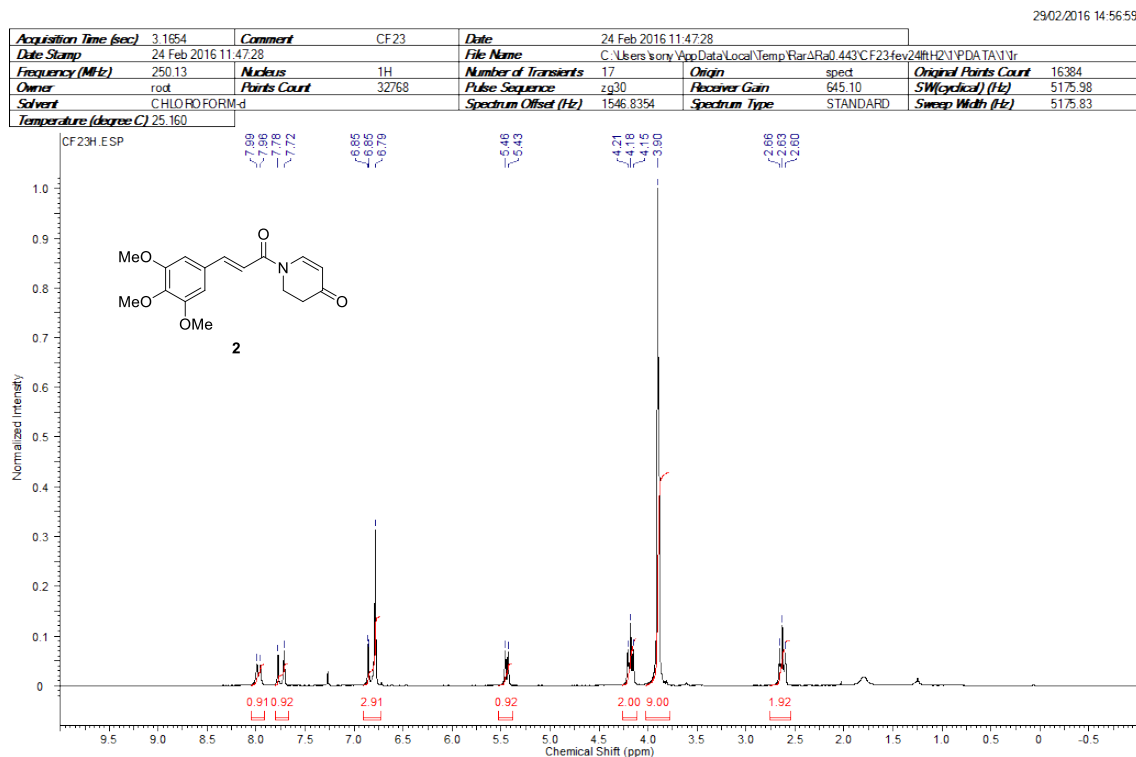
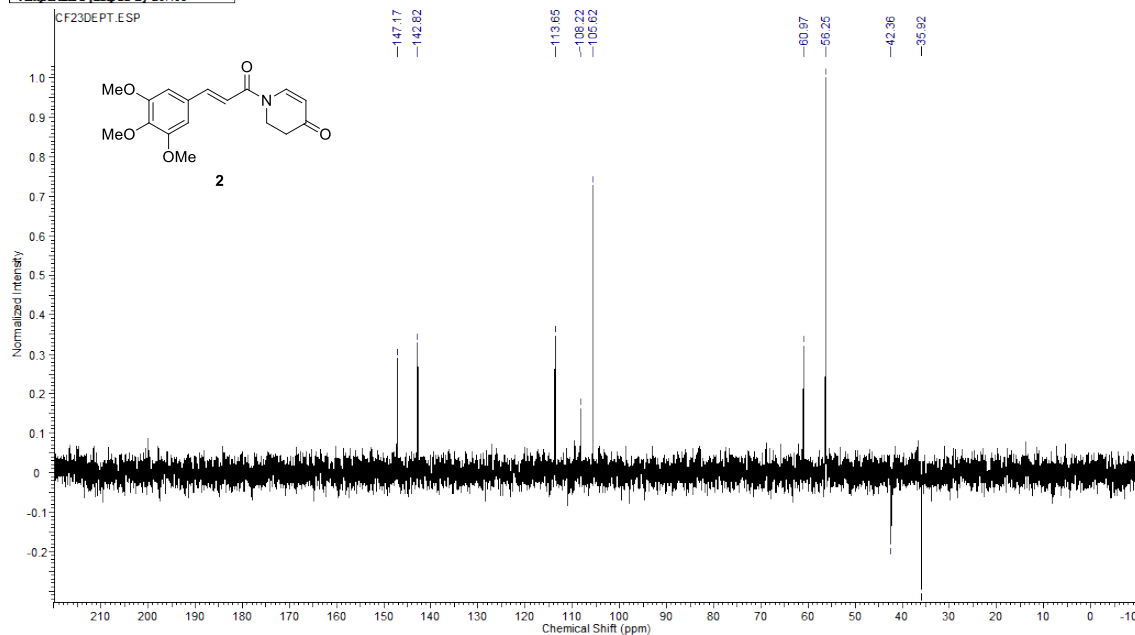
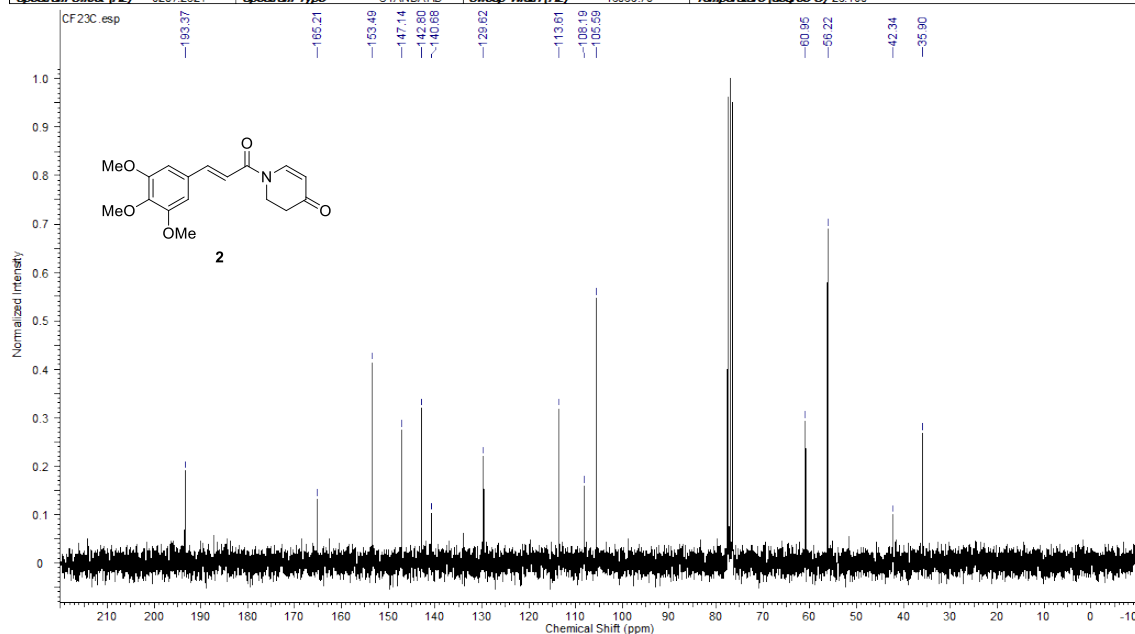


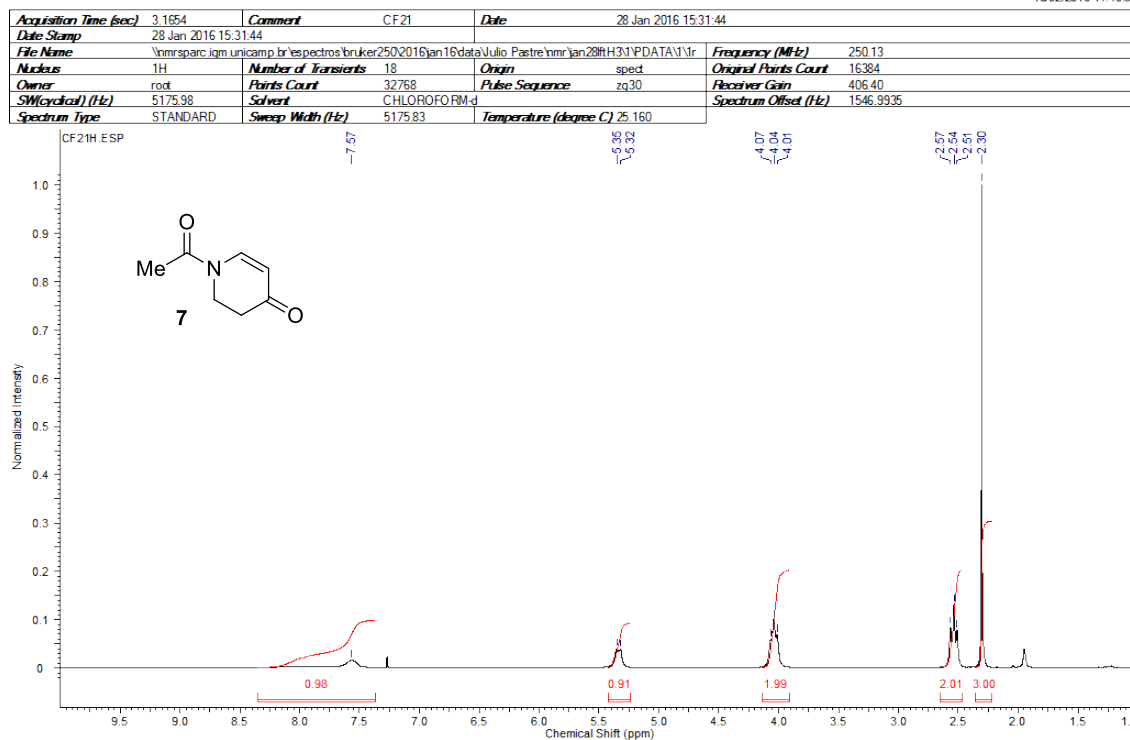
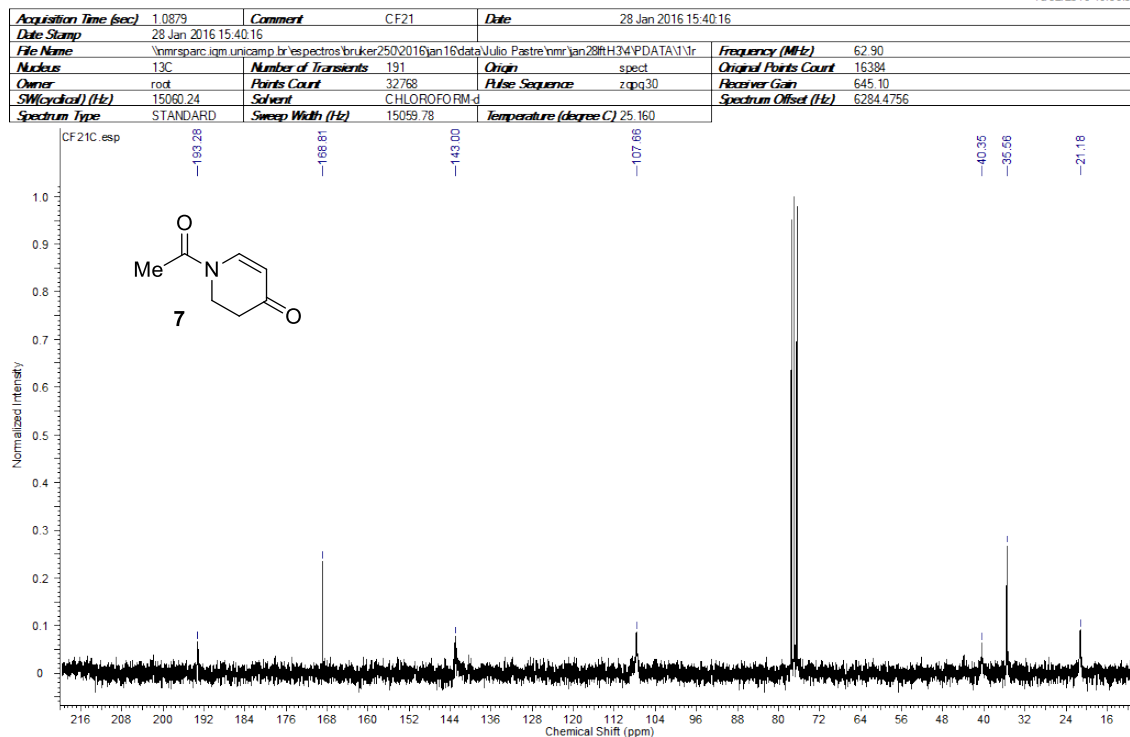
Figure S10. ^1H NMR spectrum of **2** (CDCl_3 , 250 MHz)

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Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	6289.0518	Receiver Gain	1824.60
Temperature (degree C)	25.160	Spectrum Type	DEPT135	Original Points Count	8192
				SW(cyclical) (Hz)	15060.24
				Sweep Width (Hz)	15059.78

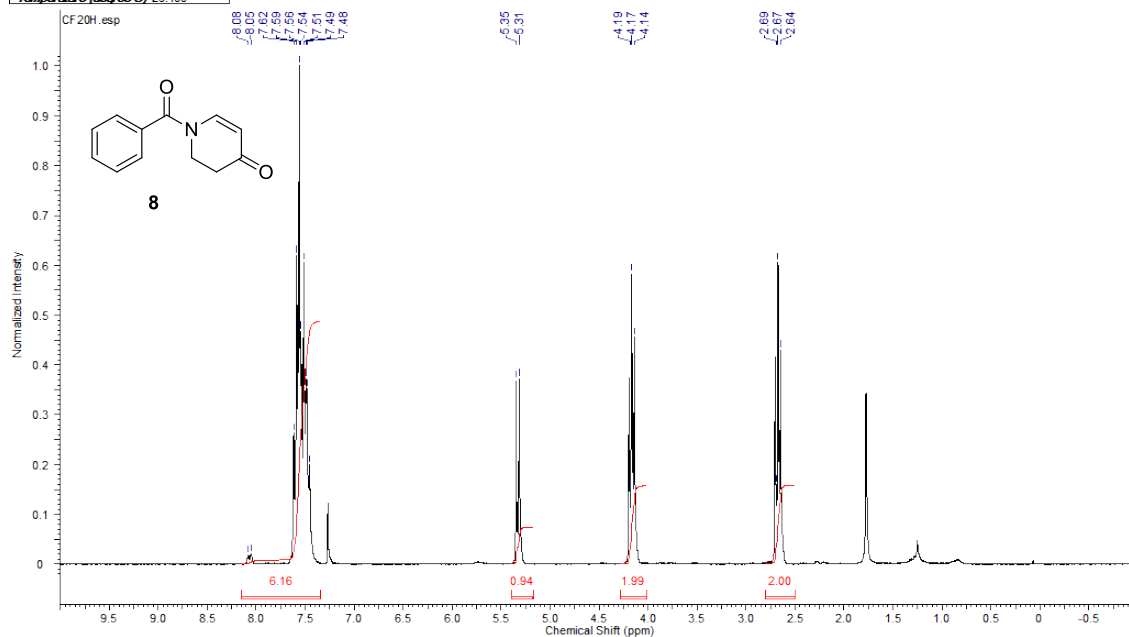
Figure S11. DEPT135 spectrum of **2** (CDCl₃, 62.9 MHz)

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Original Points Count	16384	Owner	root	Points Count	32768
Receiver Gain	724.10	SW(cyclical) (Hz)	15060.24	Pulse Sequence	zgpg30
Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	6287.2324	Solvent	CHLOROFORM-d
Temperature (degree C)	25.160	Spectrum Type	STANDARD	Sweep Width (Hz)	15059.78

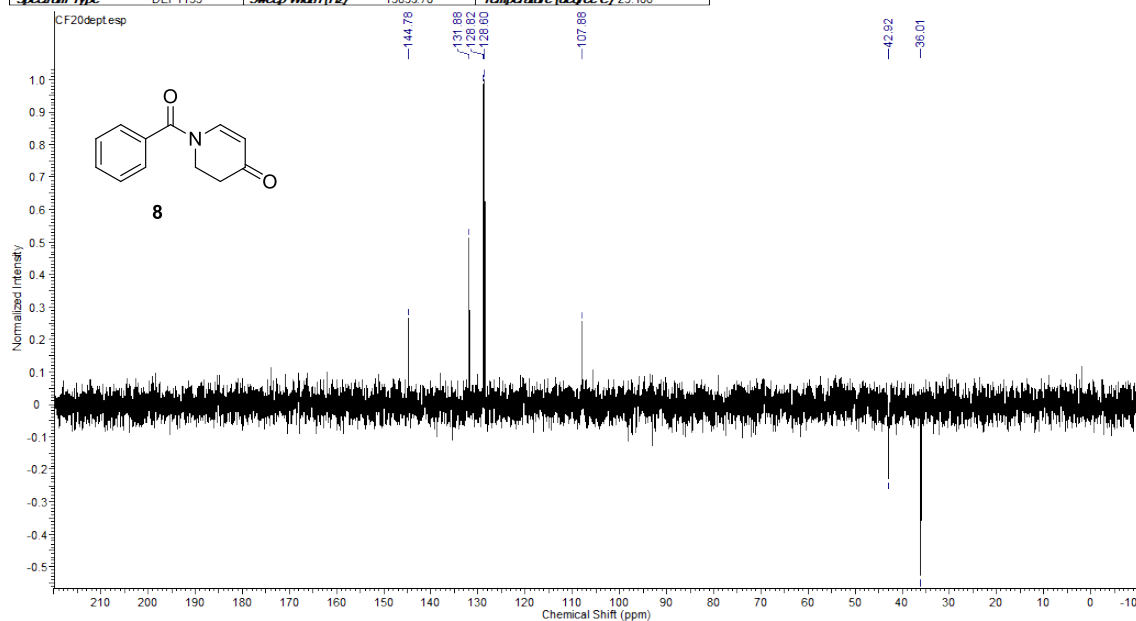
Figure S12. ¹³C NMR spectrum of **2** (CDCl₃, 62.9 MHz)

Figure S13. ¹H NMR spectrum of **7** (CDCl₃, 250 MHz)Figure S14. ¹³C NMR spectrum of **7** (CDCl₃, 62.9 MHz)

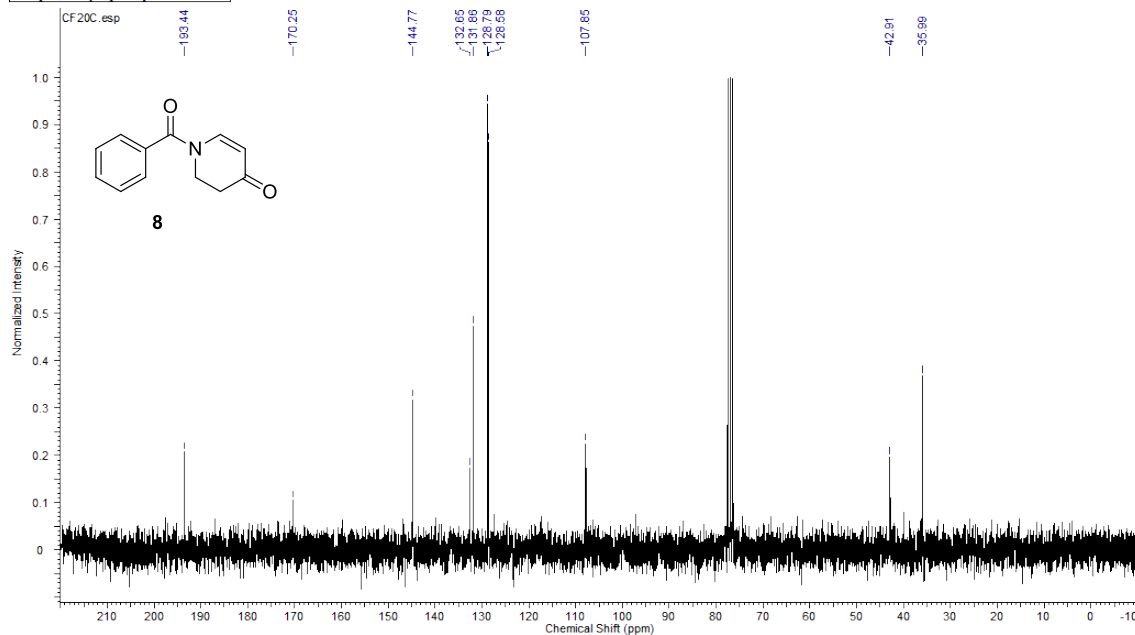
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Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	1546.6775	Receiver Gain	724.10
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				Sweep Width (Hz)	5175.83



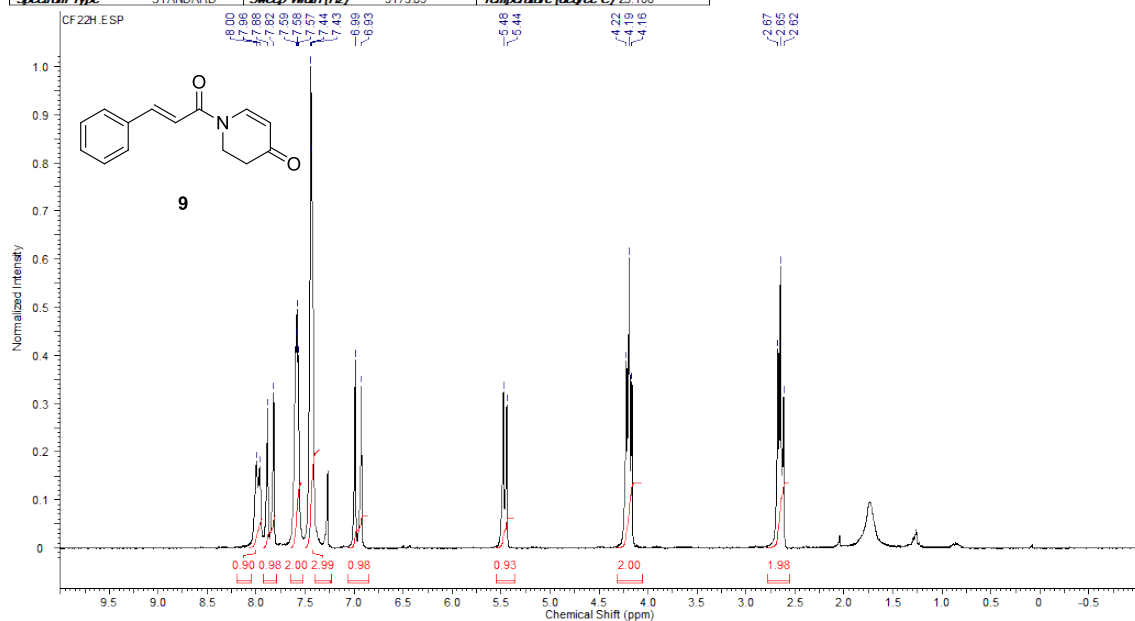
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Frequency (MHz)	62.90	Nucleus	^{13}C	Number of Transients	33
Owner	root	Points Count	32768	Origin	spect
SWH (Hz)	15060.24	Pulse Sequence	dept135	Receiver Gain	1824.60
Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	15059.78	Original Points Count	8192
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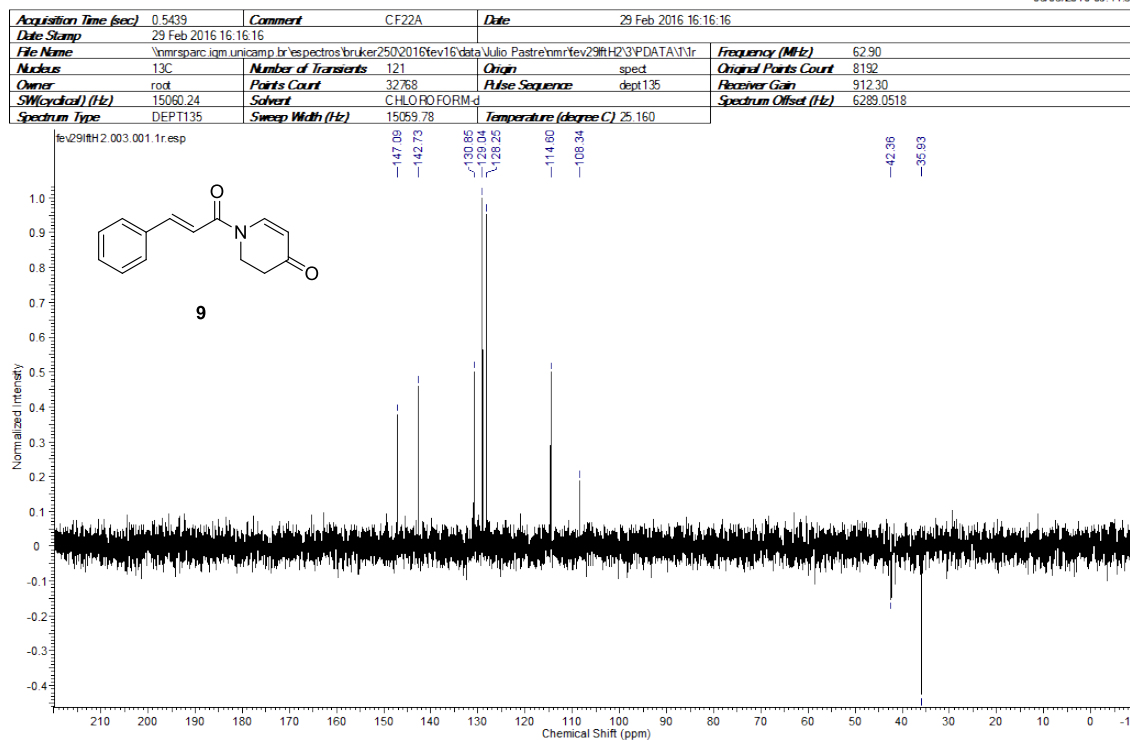
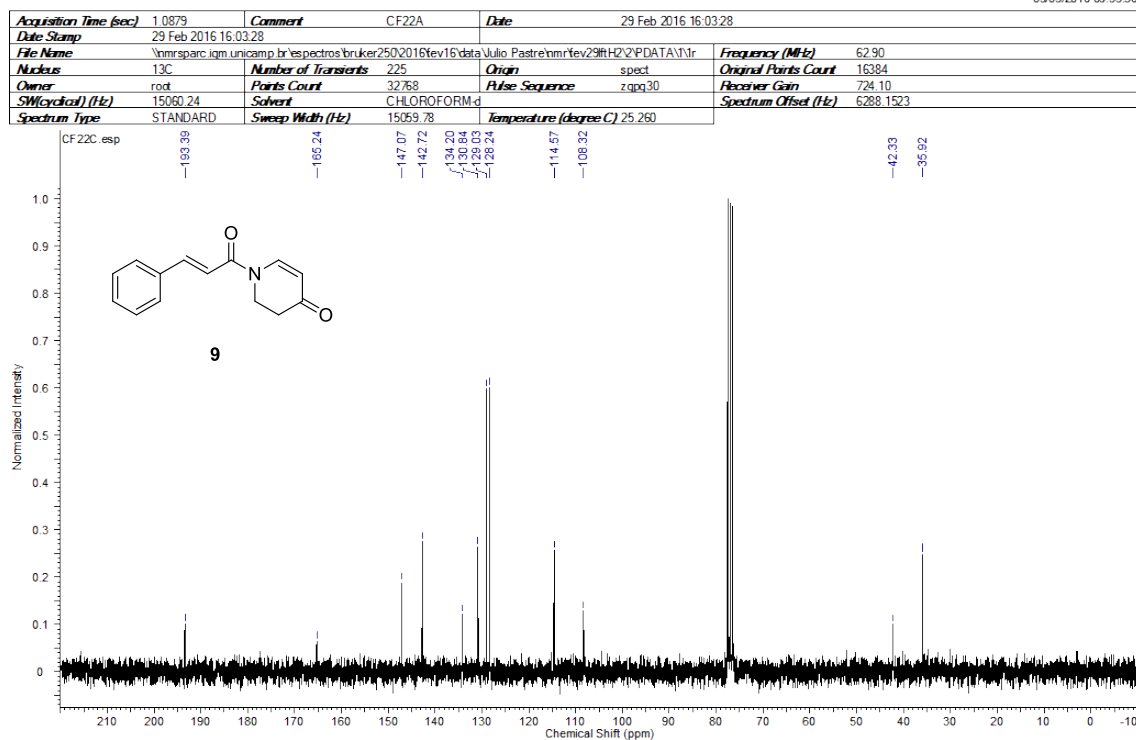


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Owner	root	Points Count	32768	Pulse Sequence	zgpg30	Receiver Gain	645.10
Solvent	CHLOROFORM-d			Spectrum Offset (Hz)	6287.2324	SW (cyclical) (Hz)	15060.24
Temperature (degree C)	25.160			Spectrum Type	STANDARD	Sweep Width (Hz)	15059.78

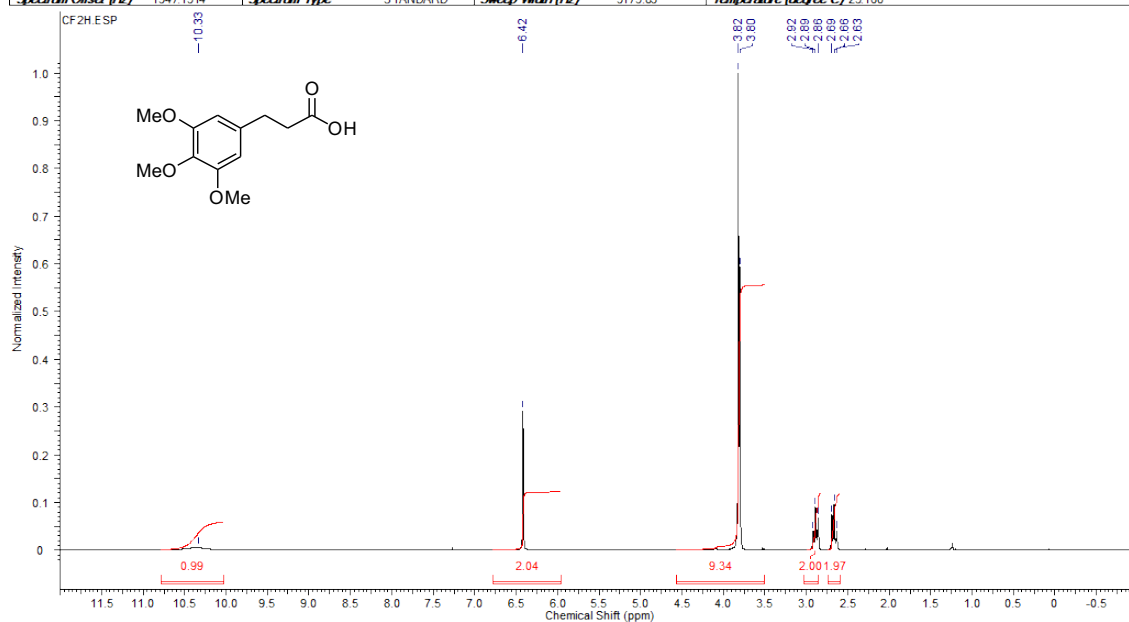
Figure S17. ¹³C NMR spectrum of **8** (CDCl₃, 62.9 MHz)

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Owner	root	Points Count	32768	Pulse Sequence	zg30
SWH (Hz)	5175.98	Solvent	CHLOROFORM-d	Receiver Gain	1024.00
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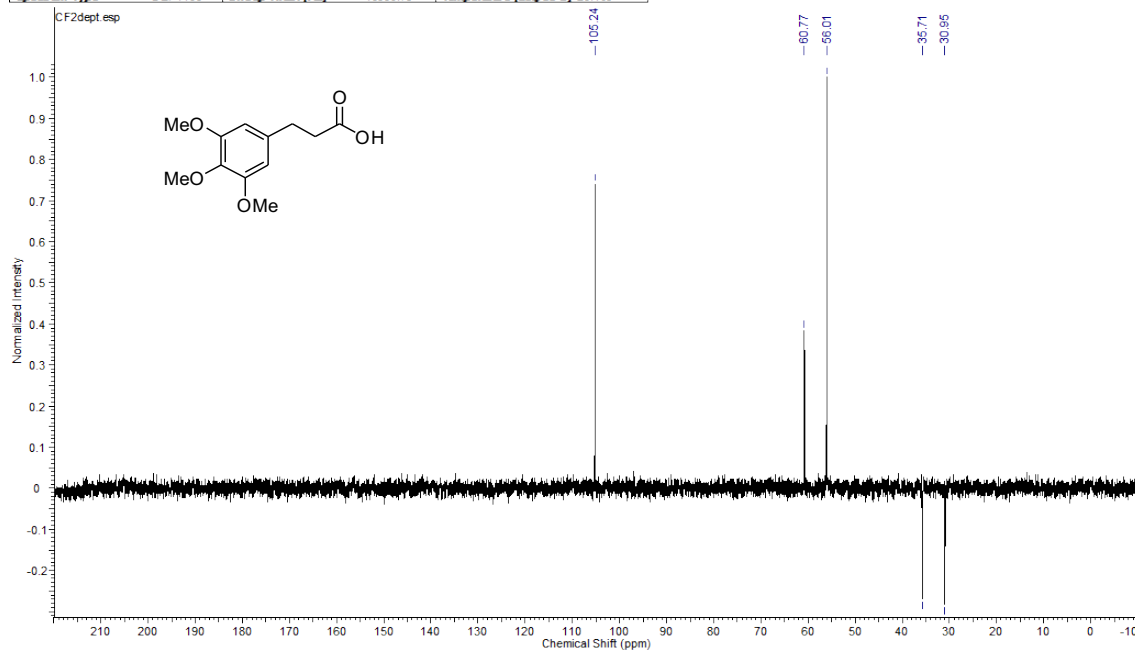
Figure S18. ¹H NMR spectrum of **9** (CDCl₃, 250 MHz)

Figure S19. DEPT135 spectrum of **9** (CDCl₃, 62.9 MHz)Figure S20. ¹³C NMR spectrum of **9** (CDCl₃, 62.9 MHz)

Acquisition Time (sec)	3.1654	Comment	CF2	Date	21 Aug 2015 14:27:28
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Receiver Gain	143.70	SW (cycles) (Hz)	5175.98	Solvent	CHLOROFORM-d
Spectrum Offset (Hz)	1547.1514	Spectrum Type	STANDARD	Sweep Width (Hz)	5175.83
				Temperature (degree C)	25.160

Figure S21. ¹H NMR spectrum of 3-(3,4,5-trimethoxyphenyl)propanoic acid (CDCl₃, 250 MHz)

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Spectrum Type	DEPT135	Sweep Width (Hz)	15059.78	Points Count	32768
				Solvent	CHLOROFORM-d
				Temperature (degree C)	25.160

Figure S22. DEPT135 spectrum of 3-(3,4,5-trimethoxyphenyl)propanoic acid (CDCl₃, 62.9 MHz)

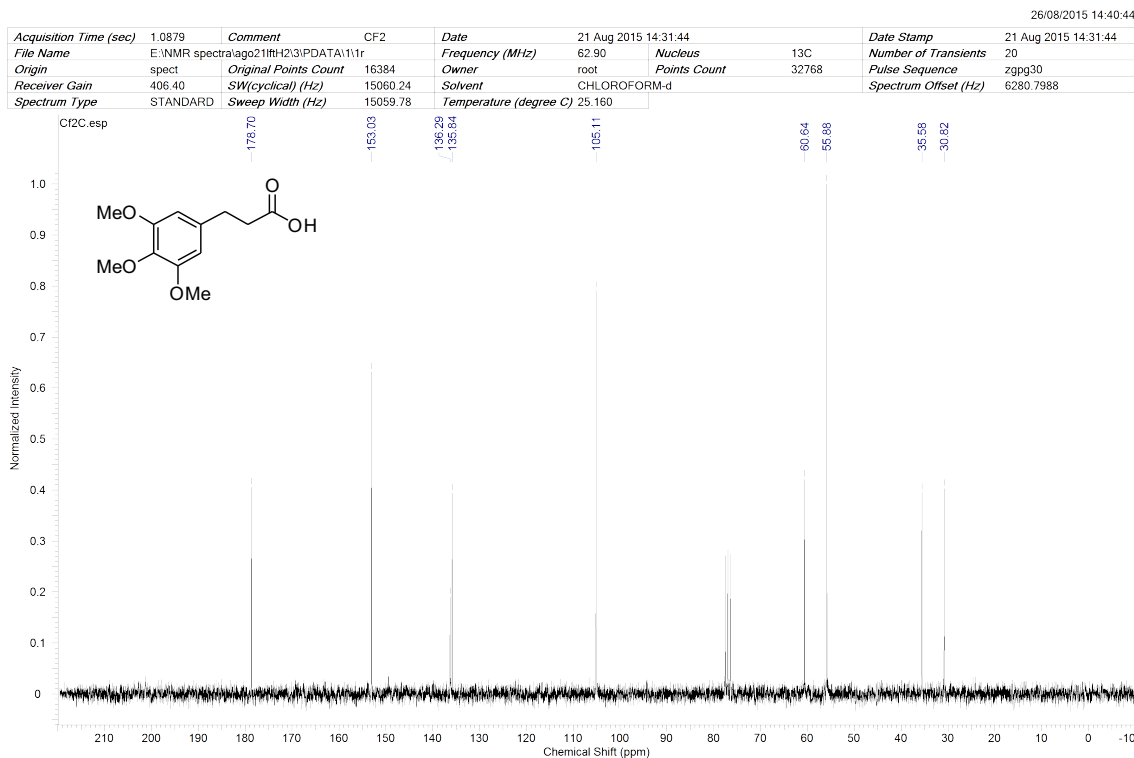


Figure S23. ¹³C NMR spectrum of 3-(3,4,5-trimethoxyphenyl)propanoic acid (CDCl₃, 62.9 MHz)

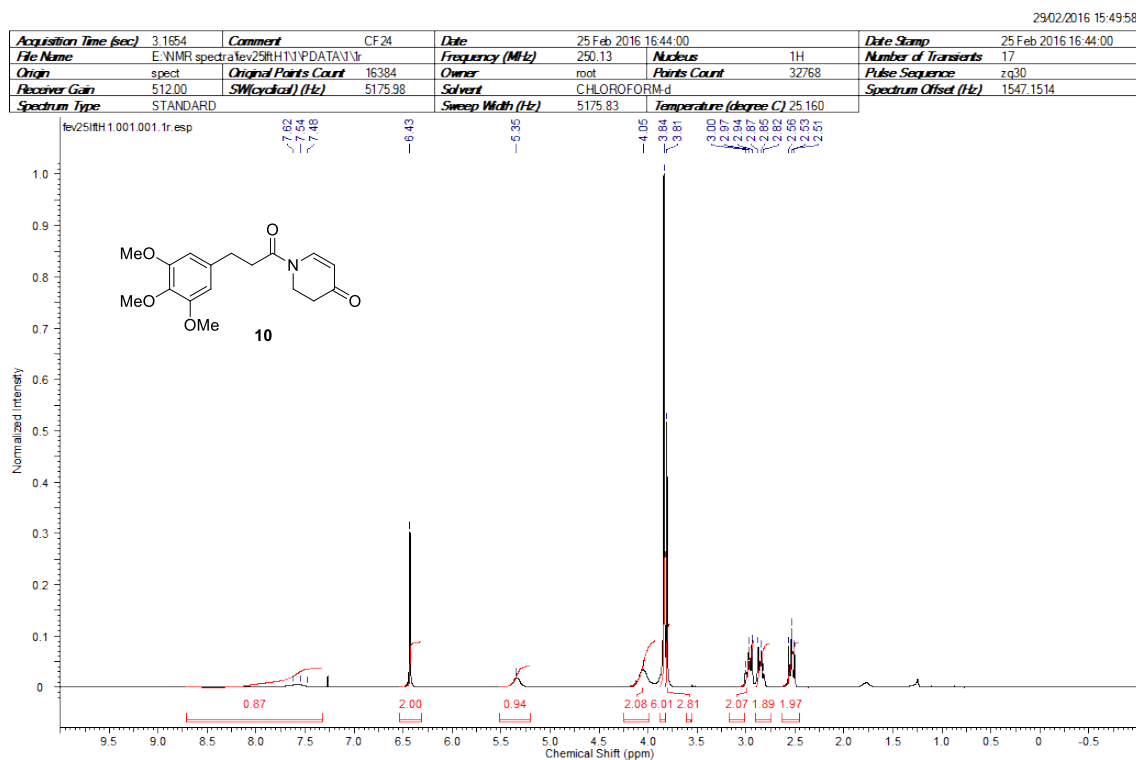
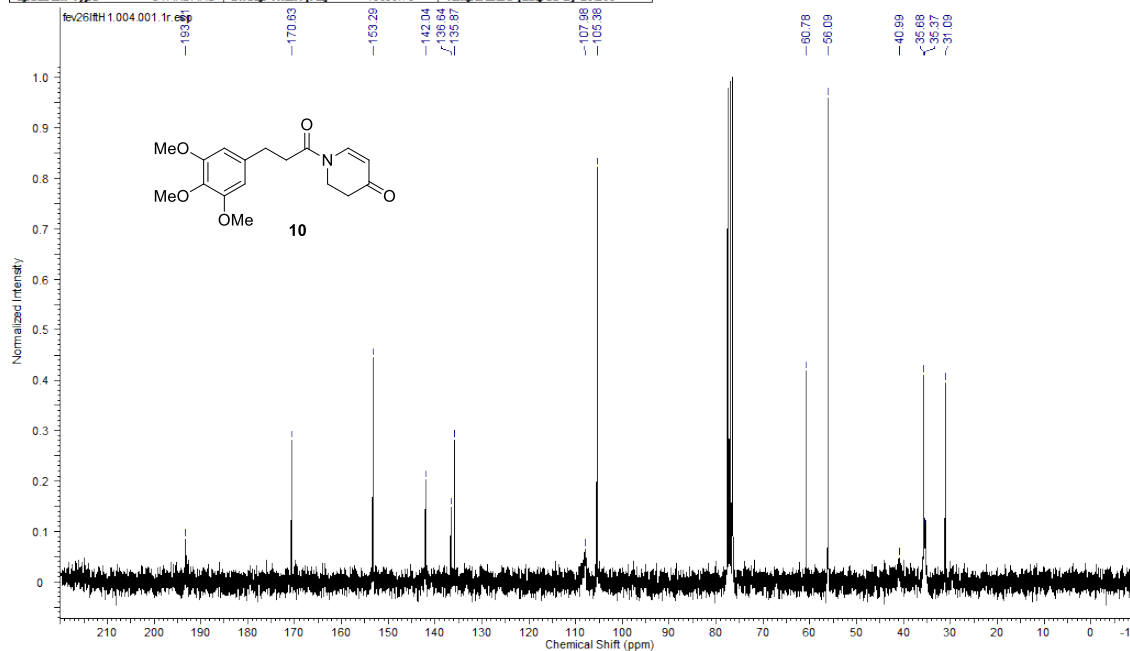


Figure S24. ¹H NMR spectrum of **10** (CDCl₃, 250 MHz)

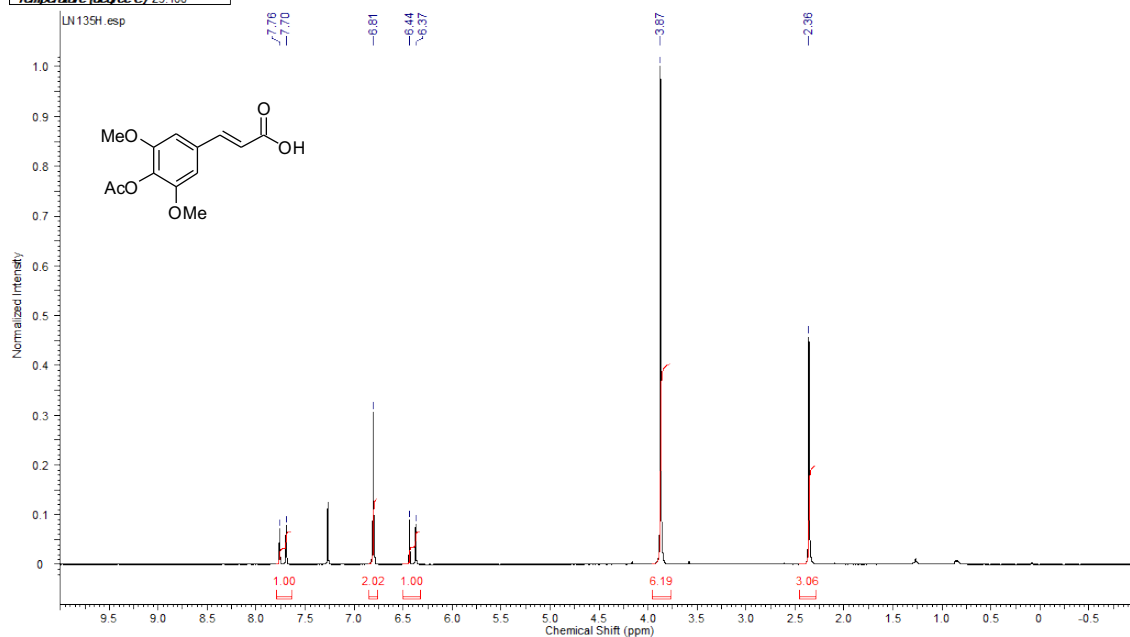
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Receiver Gain	645.10	SW (cycles) (Hz)	15060.24	Solvent	CHLOROFORM-d	Pulse Sequence	zgpg30
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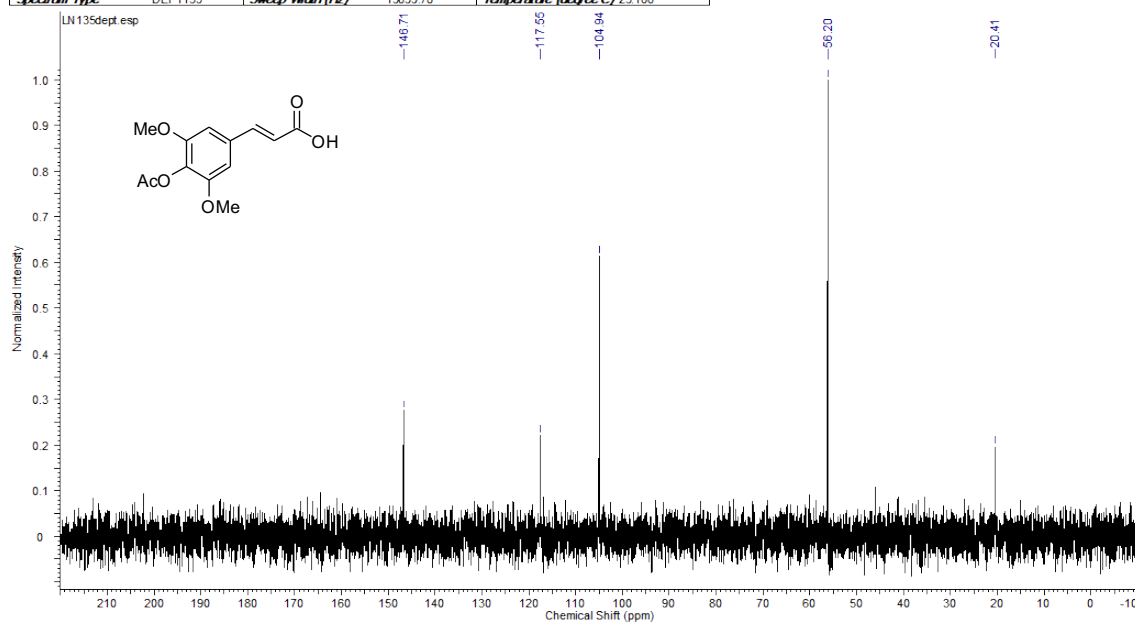
Figure S25. ¹³C NMR spectrum of **10** (CDCl₃, 62.9 MHz)

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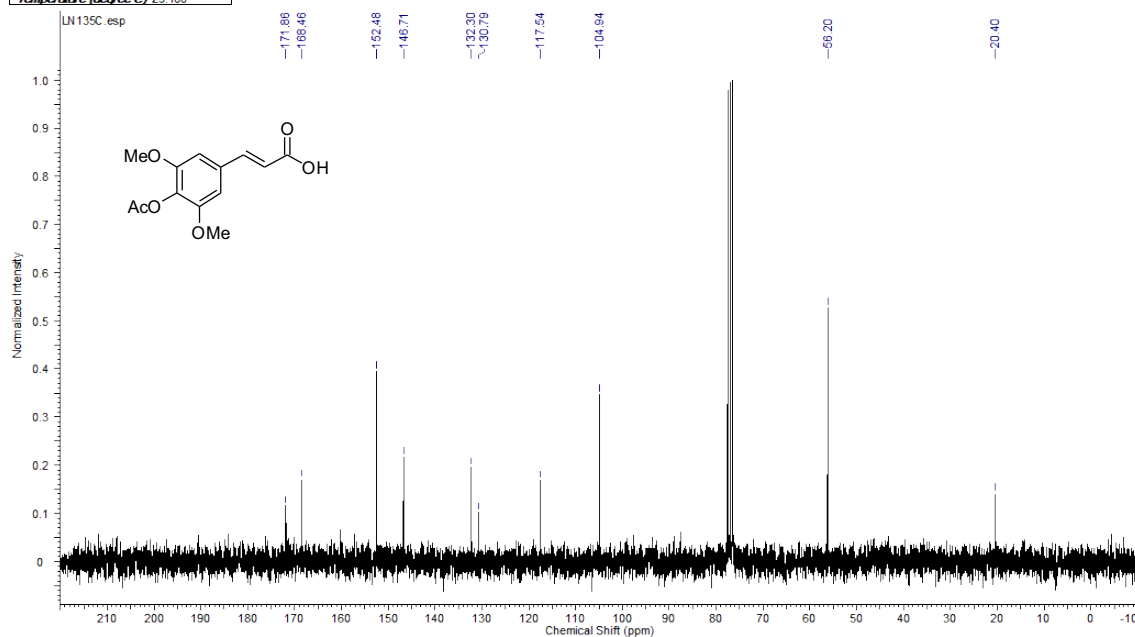
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Receiver Gain	2048.00	SW (cycles) (Hz)	5175.38	Solvent	CHLOROFORM-d	Pulse Sequence	zg30
Spectrum Type	STANDARD	Sweep Width (Hz)	5175.83	Temperature (degree C)	25.160	Spectrum Offset (Hz)	1546.8354

Figure S26. ¹H NMR spectrum of 3,5-dimethoxy-4-acetoxycinnamic acid (CDCl₃, 250 MHz)

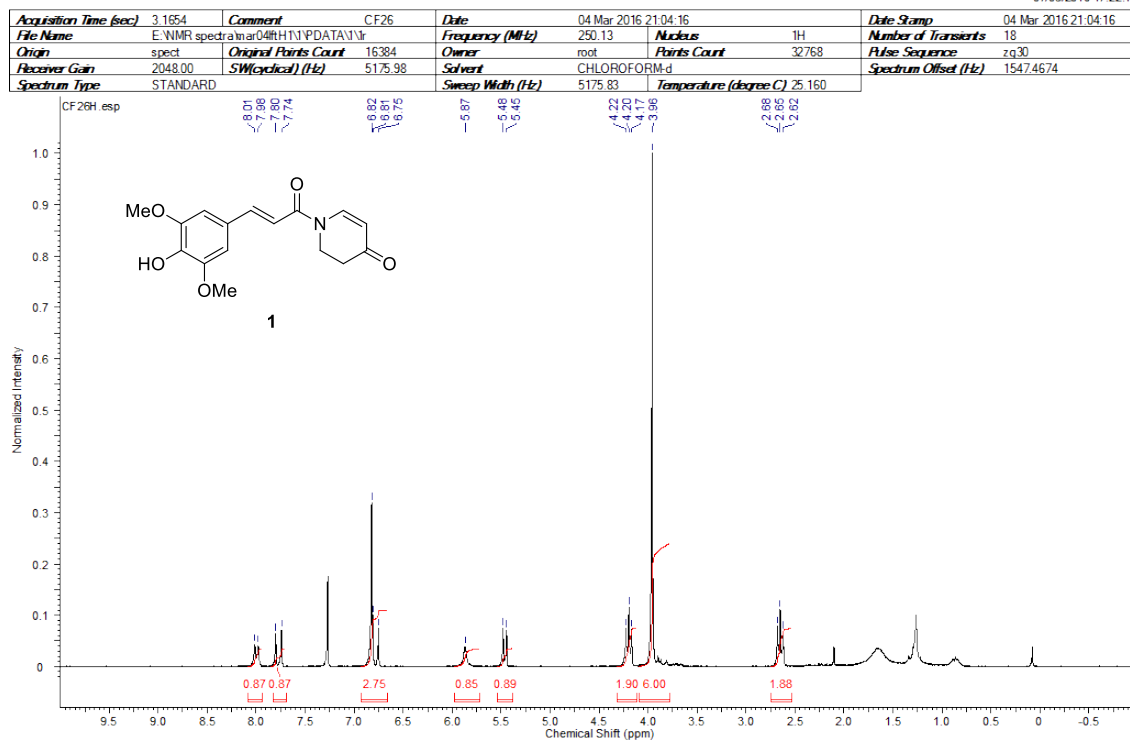
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Owner	root	Points Count	32768	Pulse Sequence	dept135
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Spectrum Type	DEPT135	Sweep Width (Hz)	15059.78	Temperature (degree C)	25.160
				Spectrum Offset (Hz)	6289.0518

Figure S27. DEPT135 spectrum of 3,5-dimethoxy-4-acetoxycinnamic acid (CDCl₃, 62.9 MHz)

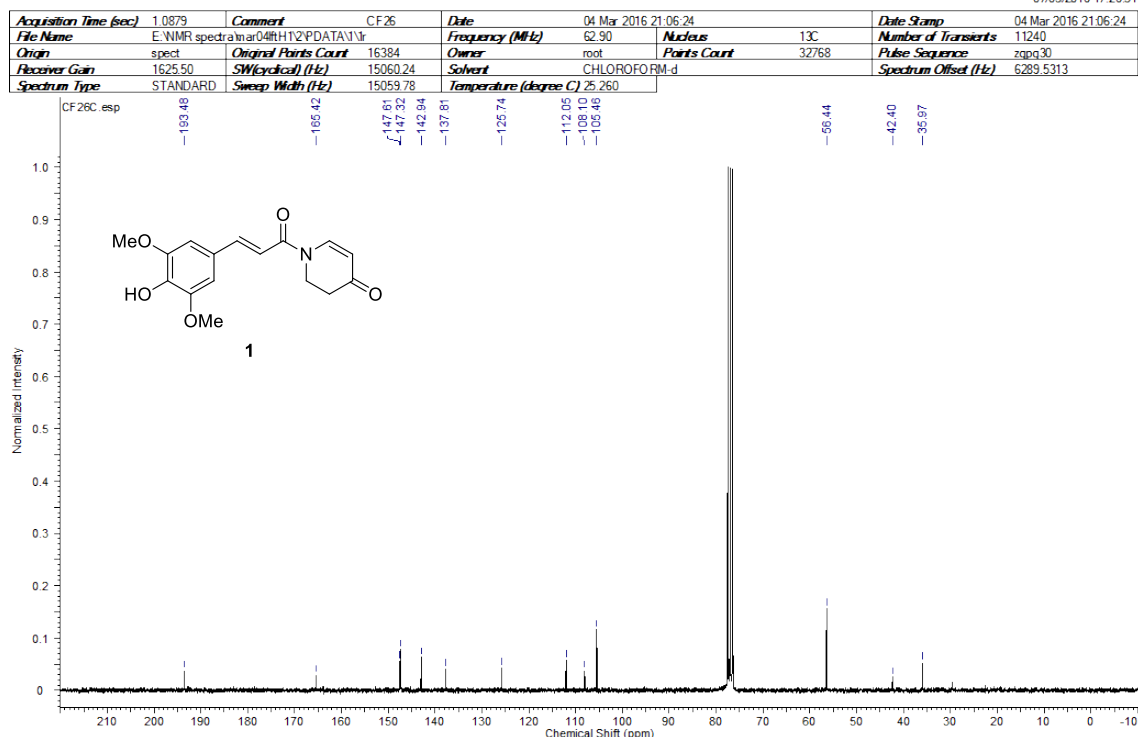
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Frequency (MHz)	62.90	Nucleus	¹³ C	Number of Transients	83
Owner	root	Points Count	32768	Origin	spect
Solvent	CHLOROFORM-d			Pulse Sequence	zgpg30
Temperature (degree C)	25.160			Receiver Gain	574.70
				Spectrum Offset (Hz)	6289.0713
				Spectrum Type	STANDARD
				Sweep Width (Hz)	15059.78

Figure S28. ¹³C NMR spectrum of 3,5-dimethoxy-4-acetoxycinnamic acid (CDCl₃, 62.9 MHz)

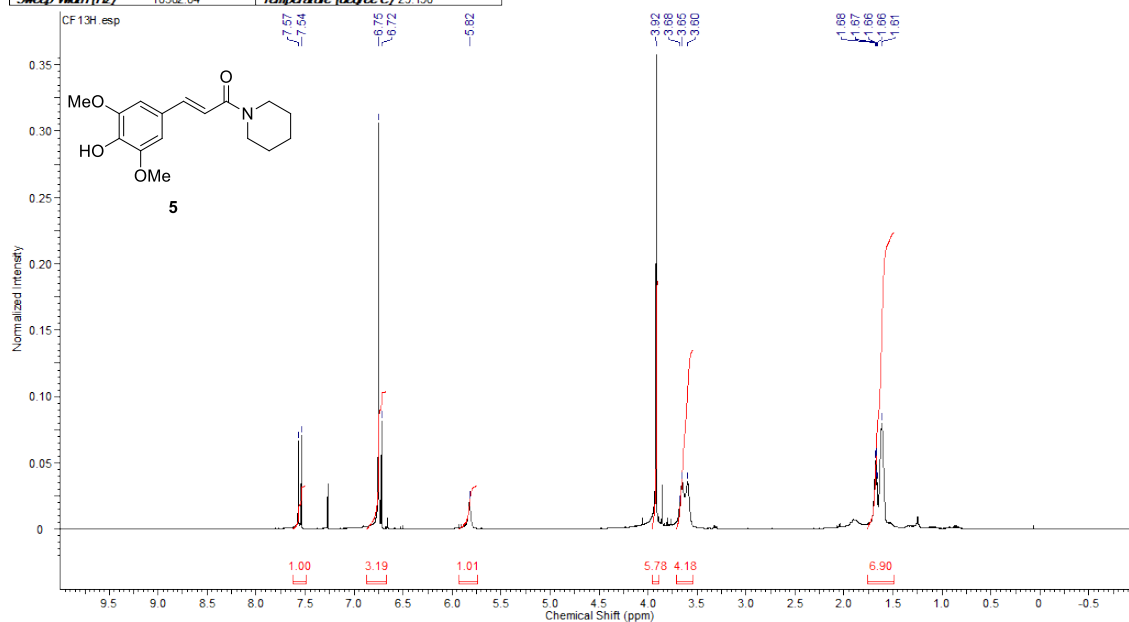
07/03/2016 17:22:12

Figure S29. ¹H NMR spectrum of **1** (CDCl₃, 250 MHz)

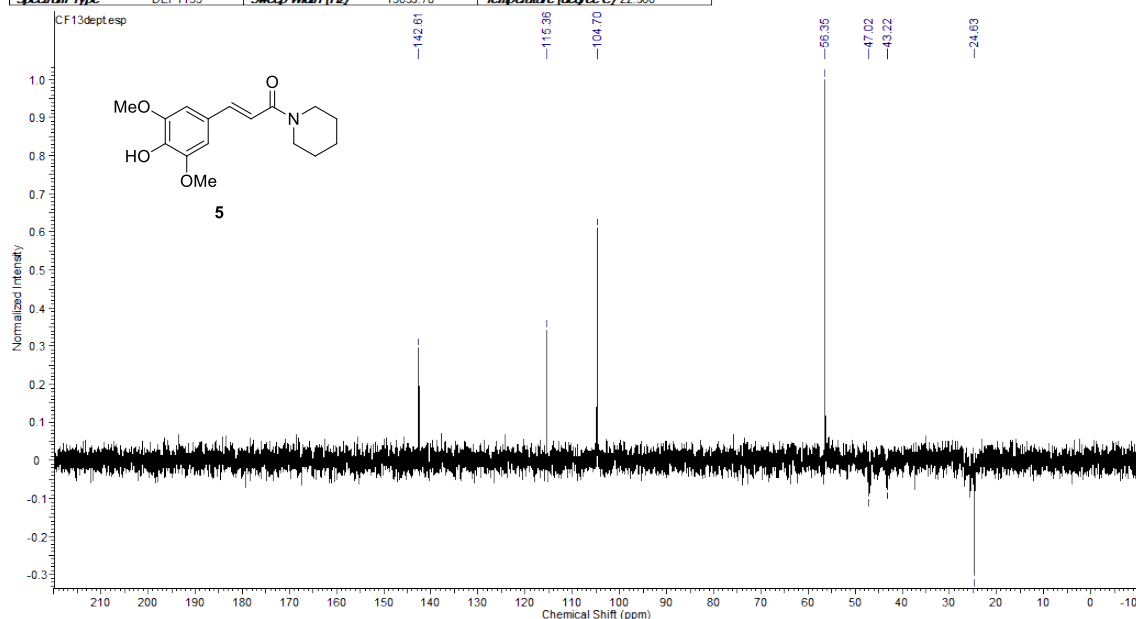
07/03/2016 17:26:31

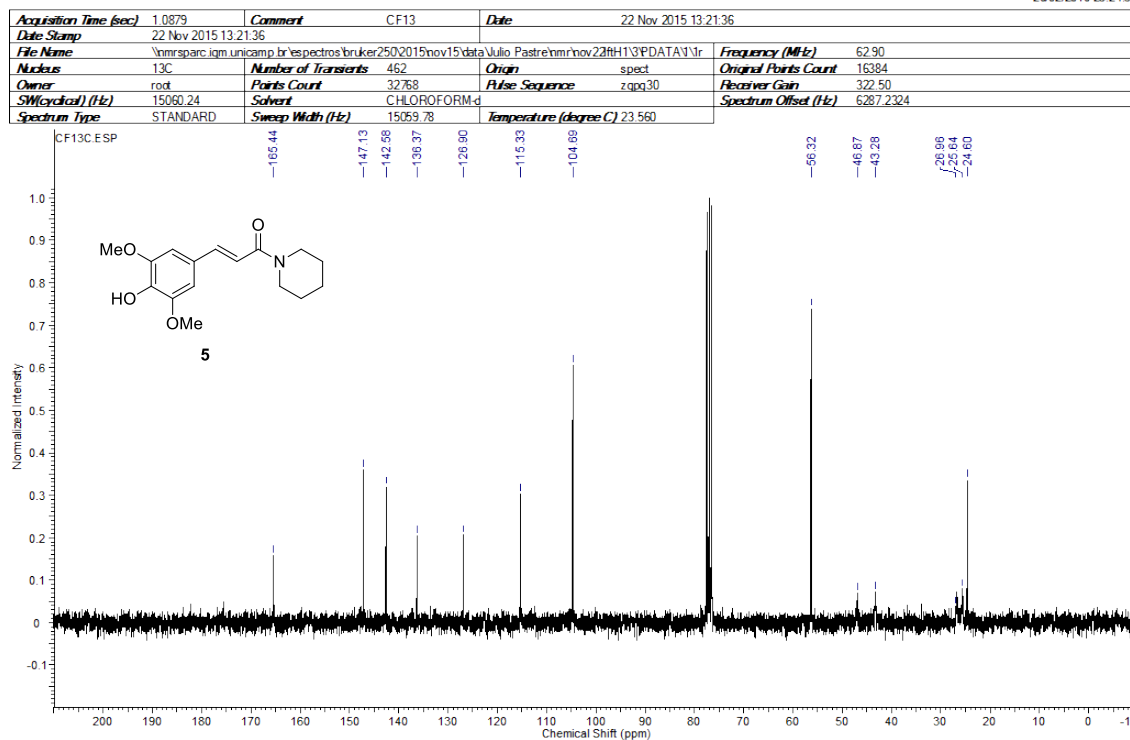
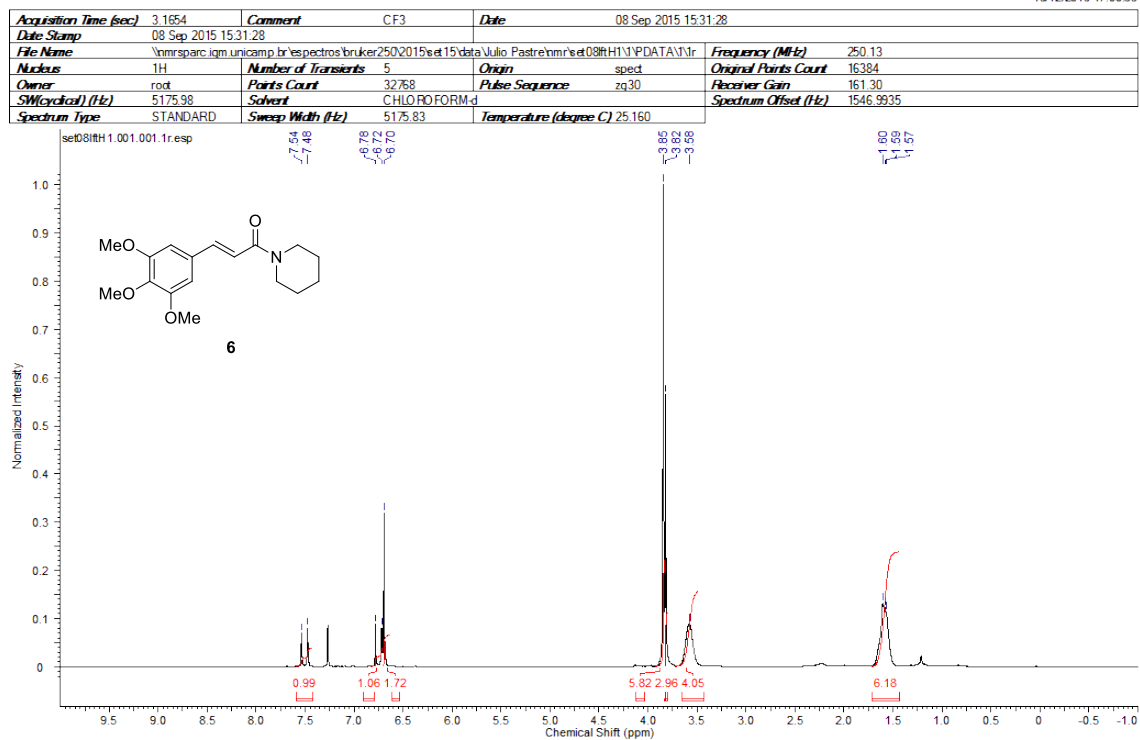
Figure S30. ¹³C NMR spectrum of **1** (CDCl₃, 62.9 MHz)

Acquisition Time (sec)	1.5903	Comment	Luiz - CF 13 - CDCl ₃ - Avance 500 MHz - nov23dH1	Date	23 Nov 2015 11:09:20
Date Stamp	23 Nov 2015 11:09:20				
File Name	\nmr\sparc\igim\unicamp.br\espectros\avance500\2015\nov15\Julio_Pastre\nov23ftH1\1\PDATA\1\lr				
Nucleus	¹ H	Number of Transients	16	Origin	spect
Owner	nmrsu	Points Count	65536	Pulse Sequence	zg30
SW (Hz)	10302.20	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	3074.9763
Sweep Width (Hz)	10302.04	Temperature (degree C)	25.150	Receiver Gain	90.50
				Spectrum Type	STANDARD

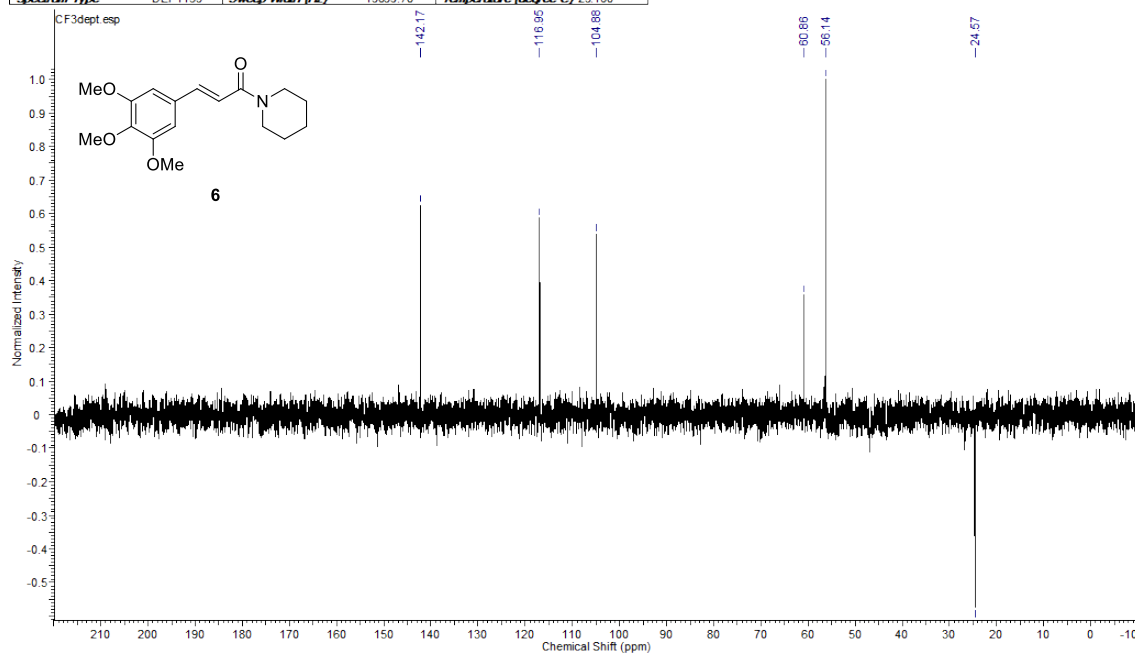
Figure S31. ¹H NMR spectrum of **5** (CDCl₃, 250 MHz)

Acquisition Time (sec)	0.5439	Comment	CF13	Date	22 Nov 2015 13:13:04
Date Stamp	22 Nov 2015 13:13:04				
File Name	\nmr\sparc\igim\unicamp.br\espectros\bruker250\2015\nov15\data\Julio_Pastre\nov23ftH1\2\PDATA\1\lr				
Nucleus	¹³ C	Number of Transients	127	Origin	spect
Owner	root	Points Count	32768	Pulse Sequence	dept135
SW (Hz)	15060.24	Solvent	CHLOROFORM-d	Receiver Gain	2896.30
Spectrum Type	DEPT135	Sweep Width (Hz)	15059.78	Temperature (degree C)	22.960
				Spectrum Offset (Hz)	6289.0518

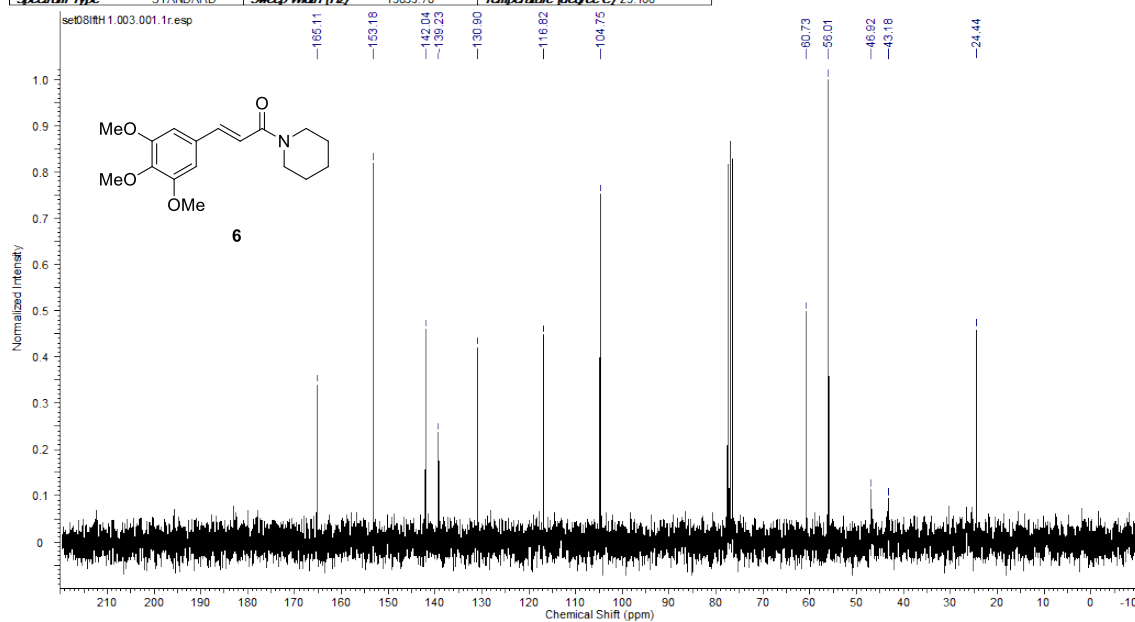
Figure S32. DEPT135 spectrum of **5** (CDCl₃, 62.9 MHz)

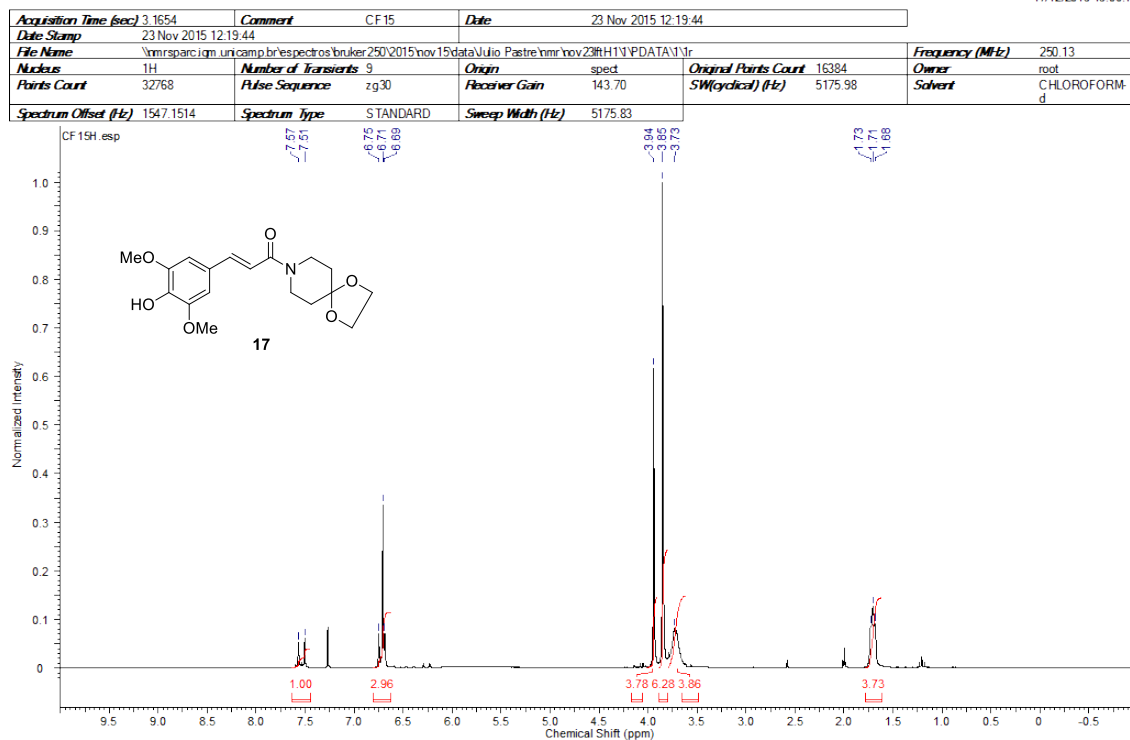
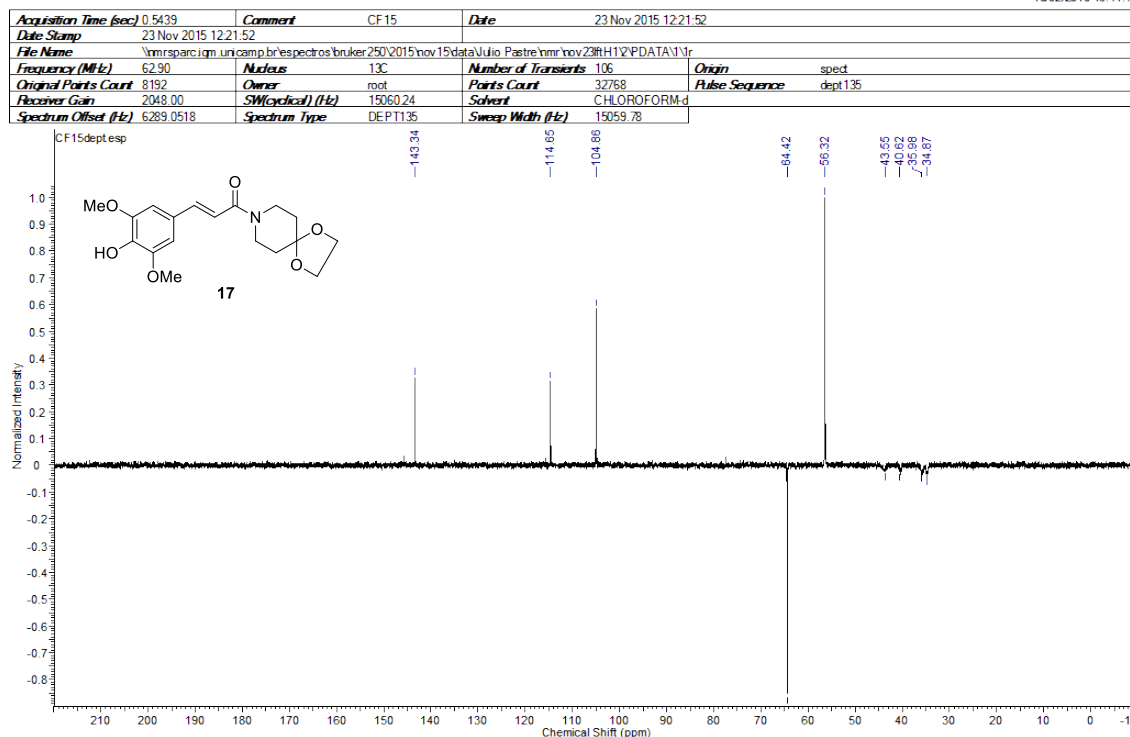
Figure S33. ¹³C NMR spectrum of 5 (CDCl₃, 62.9 MHz)Figure S34. ¹H NMR spectrum of 6 (CDCl₃, 250 MHz)

Acquisition Time (sec)	0.5439	Comment	CF3	Date	08 Sep 2015 15:33:36	Date Stamp	08 Sep 2015 15:33:36
File Name	E:\NMR spectra\set08\H1\2\PDATA\1\1r	Frequency (MHz)	62.90	Nucleus	¹³ C	Number of Transients	50
Origin	spect	Original Points Count	8192	Owner	root	Points Count	32768
Receiver Gain	1290.20	SW (cycles) (Hz)	15060.24	Solvent	CHLOROFORM-d	Pulse Sequence	dept135
Spectrum Type	DEPT135	Sweep Width (Hz)	15069.78	Temperature (degree C)	25.160	Spectrum Offset (Hz)	6289.0518

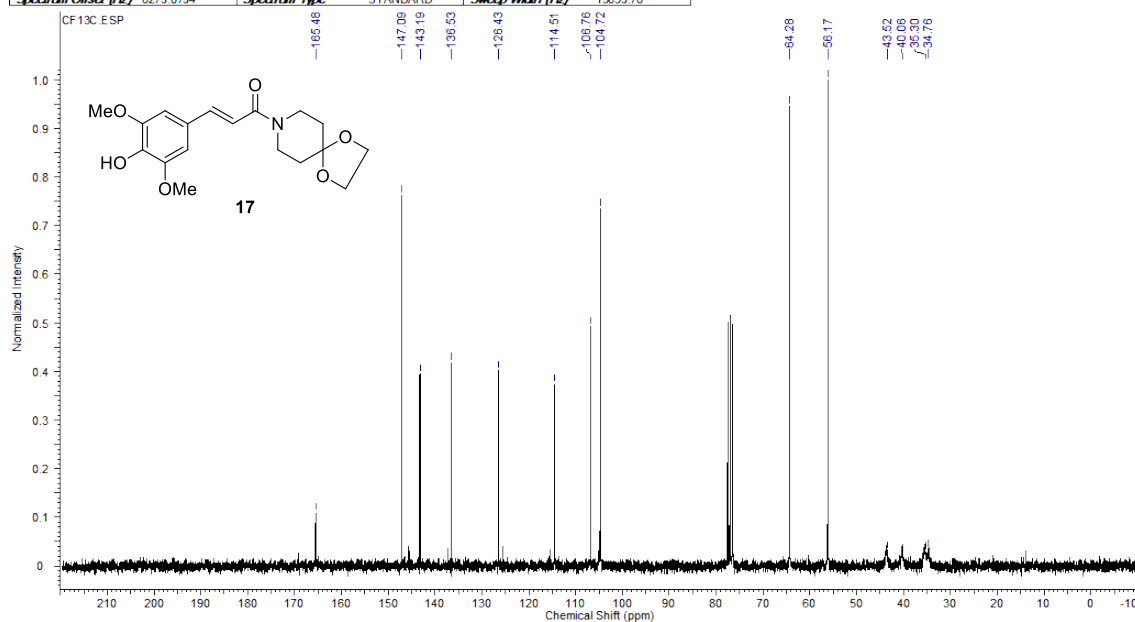
Figure S35. DEPT135 spectrum of **6** (CDCl₃, 62.9 MHz)

Acquisition Time (sec)	1.0879	Comment	CF3	Date	08 Sep 2015 15:35:44	Frequency (MHz)	62.90
Date Stamp	08 Sep 2015 15:35:44	Original Points Count	100	Origin	spect	Original Points Count	16384
File Name	\nmr\spc\igm\unicamp.br\espectros\bruker250\2015\set15\data\Julio_Pastre\nmr\set08\H1\3\PDATA\1\1r	Points Count	32768	Pulse Sequence	zpgg30	Receiver Gain	812.70
Nucleus	¹³ C	SW (cycles) (Hz)	15060.24	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	6280.7988
Owner	root	Spectrum Type	STANDARD	Sweep Width (Hz)	15069.78	Temperature (degree C)	25.160

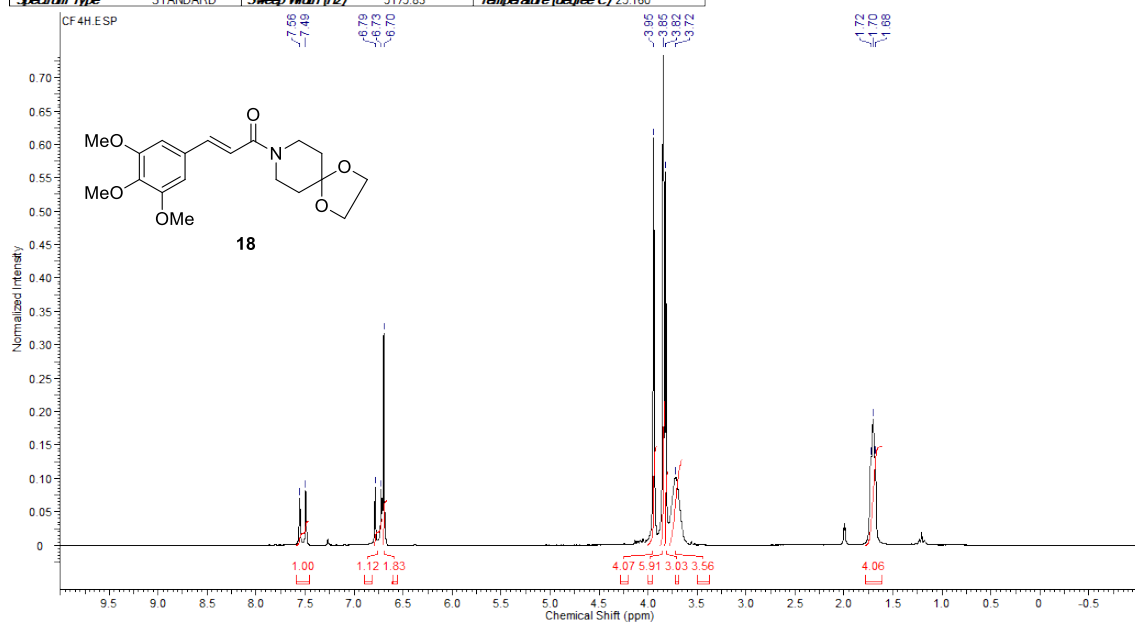
Figure S36. ¹³C NMR spectrum of **6** (CDCl₃, 62.9 MHz)

Figure S37. ¹H NMR spectrum of **17** (CDCl₃, 250 MHz)Figure S38. DEPT135 spectrum of **17** (CDCl₃, 62.9 MHz)

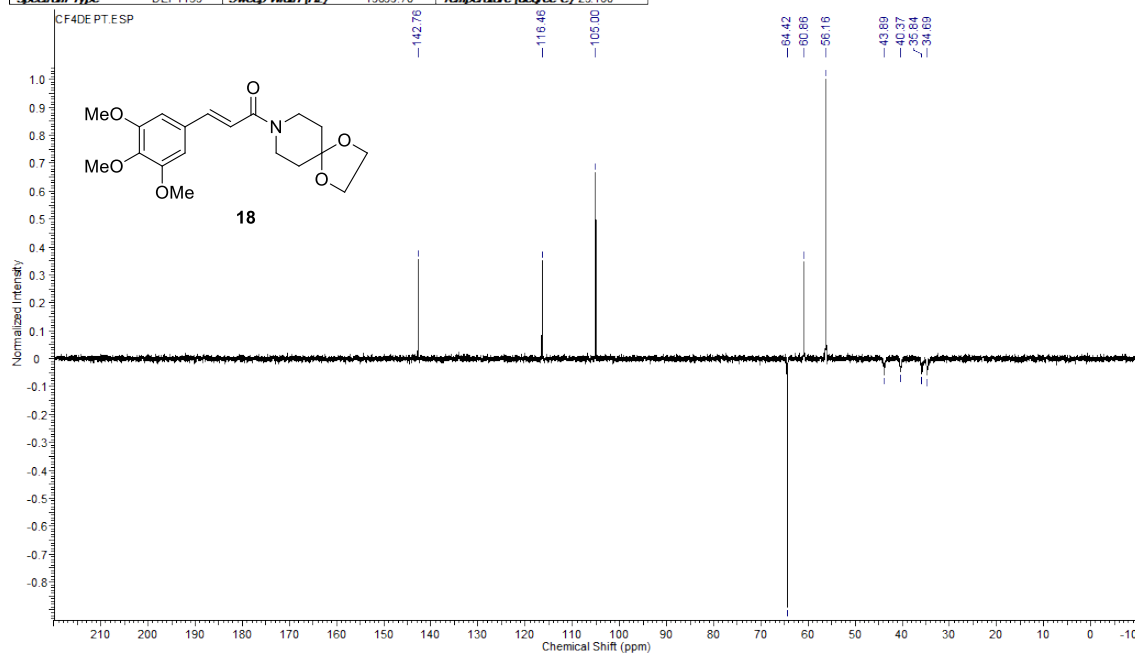
Acquisition Time (sec)	1.0879	Comment	CF15	Date	23 Nov 2015 12:28:16
Date Stamp	23 Nov 2015 12:28:16				
File Name	\nmr\sparc\igmp\unicamp.br\espectros\bruker250\2015\nov15\data\Julio_Pastre\nmr\nov23\ftH13\PDATA\1\				
Frequency (MHz)	62.90	Nucleus	13C	Number of Transients	200
Original Points Count	16384	Owner	root	Points Count	32768
Receiver Gain	406.40	SW (Hz)	15060.24	Solvent	CHLOROFORM-d
Spectrum Offset (Hz)	6279.8794	Spectrum Type	STANDARD	Sweep Width (Hz)	15059.78

Figure S39. ^{13}C NMR spectrum of **17** (CDCl_3 , 62.9 MHz)

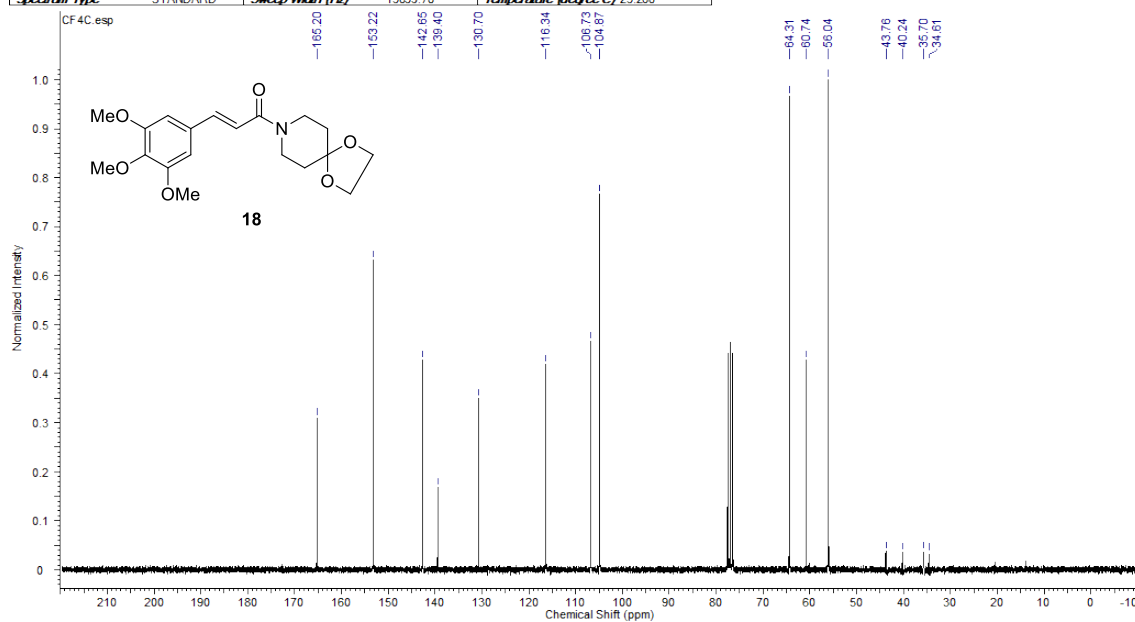
Acquisition Time (sec)	3.1654	Comment	CF4	Date	17 Sep 2015 08:01:20
Date Stamp	17 Sep 2015 08:01:20				
File Name	\nmr\sparc\igmp\unicamp.br\espectros\bruker250\2015\nov15\data\Julio_Pastre\nmr\nov17\ftH2\1\PDATA\1\				
Nucleus	1H	Number of Transients	9	Origin	spect
Owner	root	Points Count	32768	Pulse Sequence	zg30
SW (Hz)	5175.98	Solvent	CHLOROFORM-d	Receiver Gain	181.00
Spectrum Type	STANDARD	Sweep Width (Hz)	5175.83	Temperature (degree C)	25.160

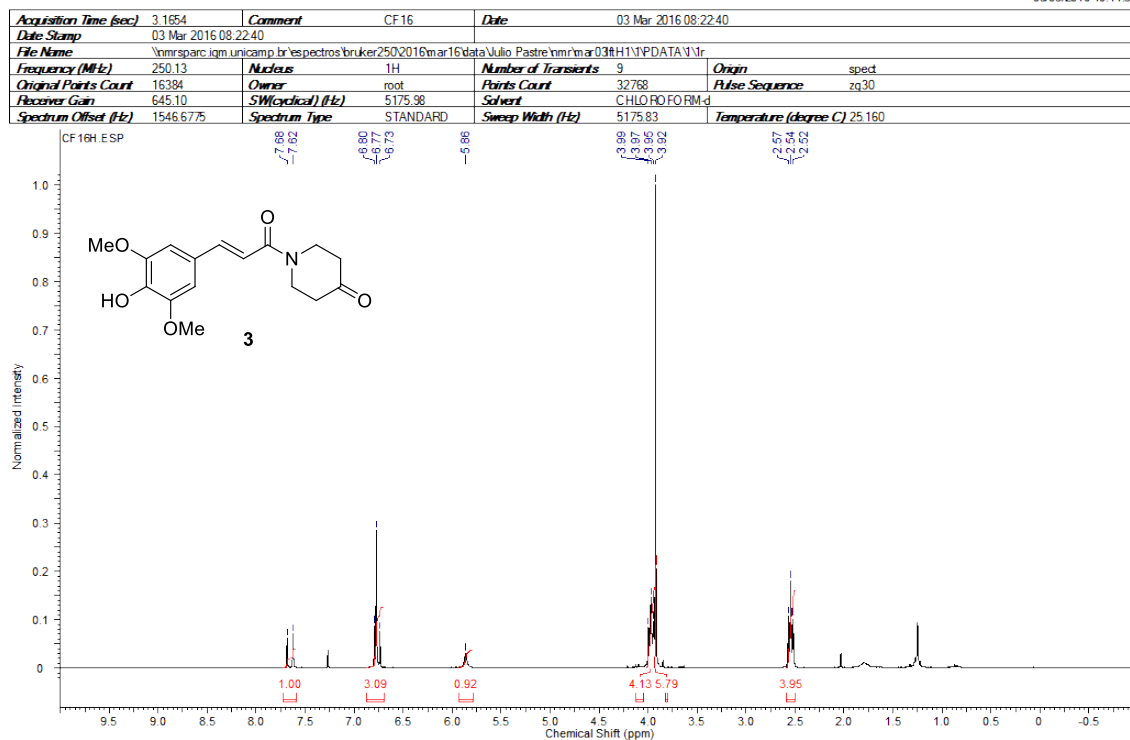
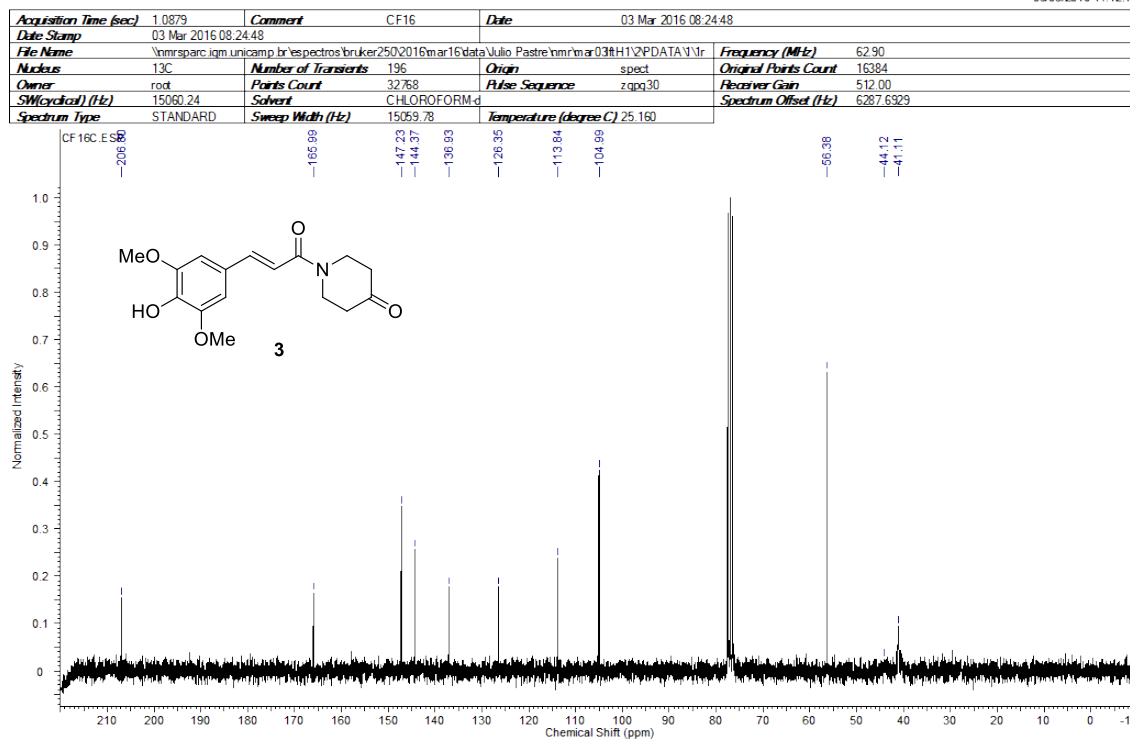
Figure S40. ^1H NMR spectrum of **18** (CDCl_3 , 250 MHz)

Acquisition Time (sec)	0.5439	Comment	CF4	Date	17 Sep 2015 08:05:36	Date Stamp	17 Sep 2015 08:05:36
File Name	E:\NMR spectra\et17\H2\2\PDATA\1\1r	Frequency (MHz)	62.90	Nucleus	¹³ C	Number of Transients	89
Origin	spect	Original Points Count	8192	Owner	root	Points Count	32768
Receiver Gain	1625.50	SW (cycles) (Hz)	15060.24	Solvent	CHLOROFORM-d	Pulse Sequence	dept135
Spectrum Type	DEPT135	Sweep Width (Hz)	15059.78	Temperature (degree C)	25.160	Spectrum Offset (Hz)	6289.0518

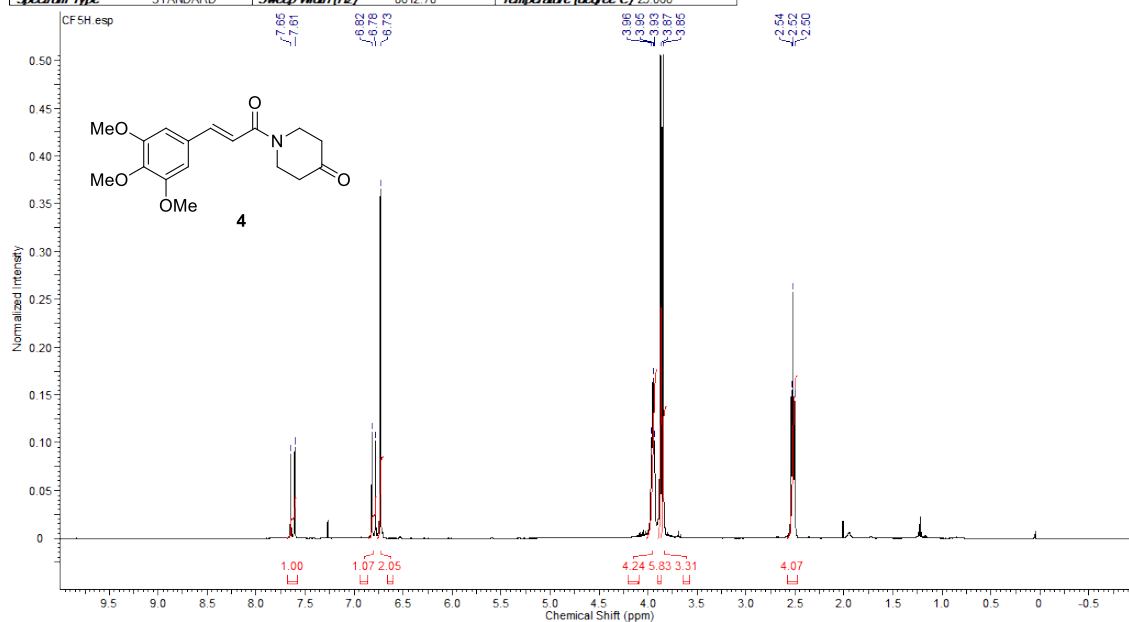
Figure S41. DEPT135 spectrum of **18** (CDCl₃, 62.9 MHz)

Acquisition Time (sec)	1.0879	Comment	CF4	Date	17 Sep 2015 08:09:52	Frequency (MHz)	62.90
Date Stamp	17 Sep 2015 08:09:52	Number of Transients	773	Origin	spect	Original Points Count	16384
File Name	\nmr\sparc\igm\unicamp.br\spectros\bruker250\2015\et15\data\Julio Pastre\nmr\et17\H2\3\PDATA\1\1r	Points Count	32768	Pulse Sequence	zpgg30	Receiver Gain	574.70
Nucleus	¹³ C	Solvent	CHLOROFORM-d	Temperature (degree C)	25.260	Spectrum Offset (Hz)	6281.7178
Owner	root	Sweep Width (Hz)	15059.78				
SW (cycles) (Hz)	15060.24						
Spectrum Type	STANDARD						

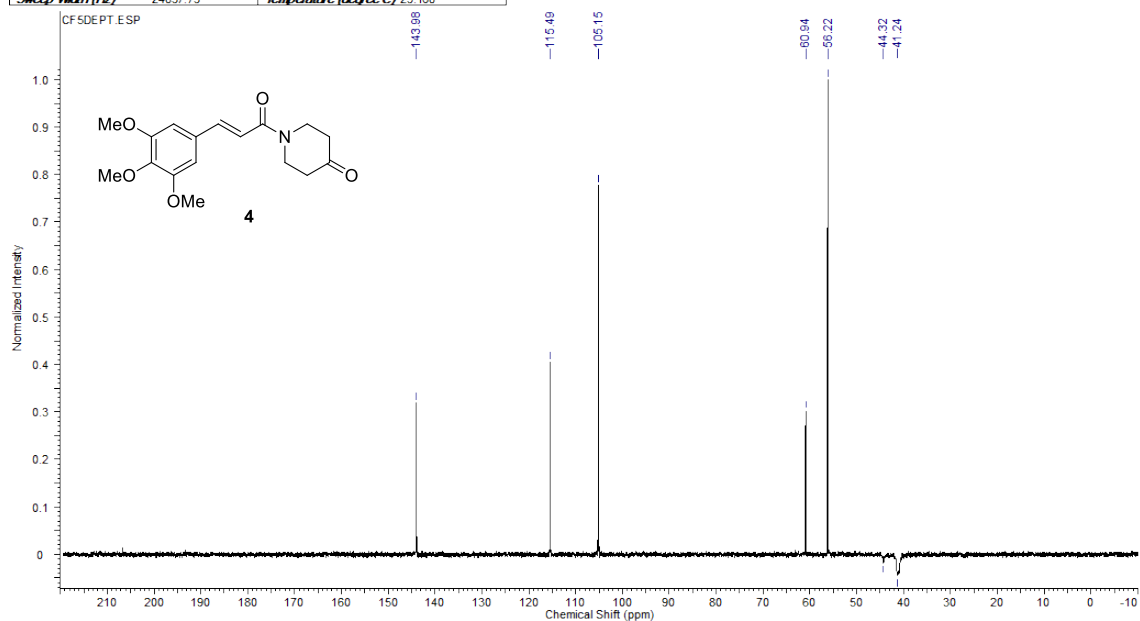
Figure S42. ¹³C NMR spectrum of **18** (CDCl₃, 62.9 MHz)

Figure S43. ¹H NMR spectrum of **3** (CDCl₃, 250 MHz)Figure S44. ¹³C NMR spectrum of **3** (CDCl₃, 62.9 MHz)

Acquisition Time (sec)	2.0447	Comment	Luiz - CF5 - CDCl3 - Av 400MHz - set23RH1	Date	23 Sep 2015 12:55:44
Date Stamp	23 Sep 2015 12:55:44				
File Name	Nmrsparc.igim.unicamp.br/espectros/avance400/2015/set15/Julio Pastre/set23RH1/3/PDATA/1/1r			Frequency (MHz)	400.18
Nucleus	¹ H	Number of Transients	16	Origin	spect
Owner	avance	Points Count	65536	Pulse Sequence	zg30
SWH (kHz)	8012.82	Solvent	CHLOROFORM-d	Receiver Gain	32.00
Spectrum Type	STANDARD	Sweep Width (Hz)	8012.70	Temperature (degree C)	25.060
				Spectrum Offset (Hz)	2466.2778

Figure S45. ¹H NMR spectrum of **4** (CDCl₃, 400 MHz)

Acquisition Time (sec)	0.6816	Comment	Luiz - CF5 - CDCl3 - Av 400MHz - set23RH1 dept135	Date	23 Sep 2015 14:04:00
Date Stamp	23 Sep 2015 14:04:00				
File Name	Nmrsparc.igim.unicamp.br/espectros/avance400/2015/set15/Julio Pastre/set23RH1/3/PDATA/1/1r			Frequency (MHz)	100.63
Nucleus	¹³ C	Number of Transients	512	Origin	spect
Owner	avance	Points Count	32768	Pulse Sequence	deptsp135
SWH (kHz)	24038.46	Solvent	CHLOROFORM-d	Spectrum Offset (Hz)	10062.1055
Sweep Width (Hz)	24037.73	Temperature (degree C)	25.160		

Figure S46. DEPT135 spectrum of **4** (CDCl₃, 100 MHz)

Acquisition Time (sec)	0.6816	Comment	Luiz - CF5 - CDCl3 - Av 400MHz - set23rH1.13C	Date	23 Sep 2015 13:57:36
Date Stamp	23 Sep 2015 13:57:36			File Name	E:\NMR spectra\set23rH1\2\pdata\1\1r
Frequency (MHz)	100.63	Nucleus	¹³ C	Number of Transients	2048
Original Points Count	16384	Owner	avance	Points Count	65536
Receiver Gain	203.00	SW (cycles) (Hz)	24038.46	Solvent	CHLOROFORM-d
Spectrum Offset (Hz)	10082.6357	Spectrum Type	STANDARD	Sweep Width (Hz)	24038.08
				Temperature (degree C)	25.260

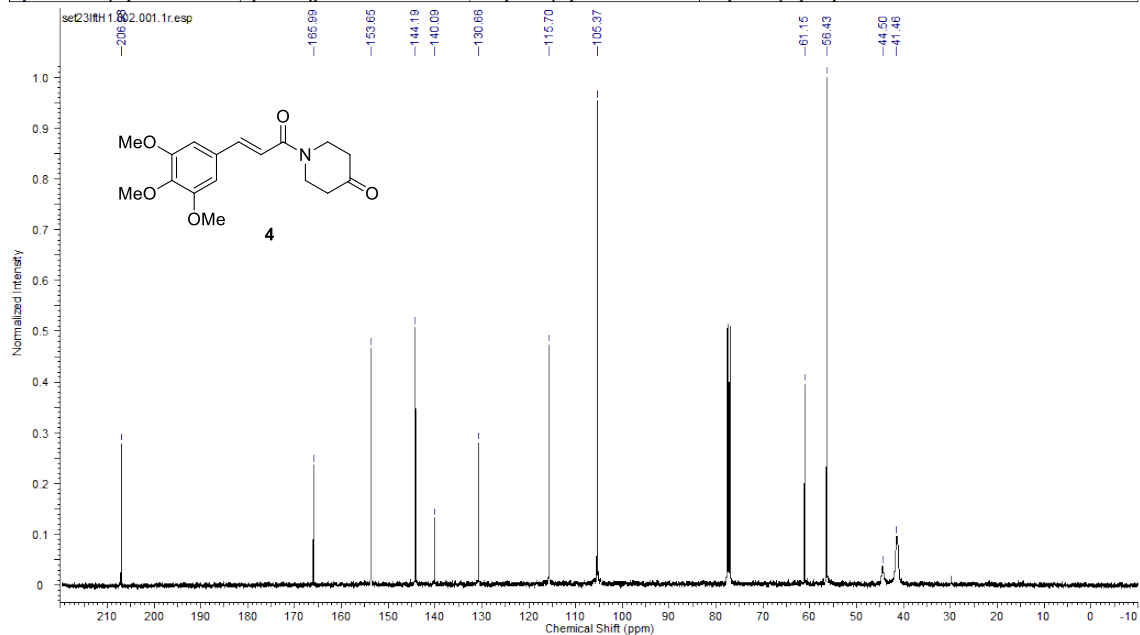


Figure S47. ¹³C NMR spectrum of **4** (CDCl₃, 100 MHz)

3. Experimental section - Biology

Proliferation assay

Table 1: Growth inhibitory effects of the cenocladamide derivatives on MDA-MB-231.

Compound	Cell loss/proliferation (%)
3	- 54,9 ± 10,8
2	43,3 ± 5,9
9	43,9 ± 8,8
1	82,9 ± 4,1
4	85,6 ± 5,7
8	94,8 ± 8,8
7	98,3 ± 7,4
6	98,7 ± 10,5
5	103,0 ± 10,9
10	103,0 ± 5,6

Table 2: Growth inhibitory effects of analogue **3** on several human breast cancer cell lines.

	Cell loss/proliferation (%)		
	3	5	Doxo
SKBR3	- 86,7 ± 5,9	105,6 ± 8,2	1,9 ± 10,0
Hs578T	- 79,6 ± 4,8	104,9 ± 6,3	15,5 ± 3,3
HCC38	- 78,0 ± 1,9	98,1 ± 6,2	0,2 ± 1,6
MDA-MB-468	- 74,1 ± 5,9	96,0 ± 4,6	5,5 ± 1,5
BT549	- 69,0 ± 5,6	98,2 ± 3,9	13,3 ± 0,6
MDA-MB-231	- 66,9 ± 6,15	101,8 ± 1,9	10,5 ± 1,7
MCF-10A	- 51,3 ± 2,4	113,5 ± 10,5	9,4 ± 1,7
T47D	- 50,5 ± 5,0	98,0 ± 14,0	0,2 ± 2,6
iHMEC	- 39,9 ± 8,9	77,6 ± 9,6	-23,9 ± 6,8
MCF7	- 9,3 ± 7,3	103,3 ± 10,1	49,4 ± 6,7