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Metal-free direct *C*-arylation of 1,3-dicarbonyl compounds and ethyl cyanoacetate: A platform to access diverse array of *meta*-functionalized phenols

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SUPPORTING INFORMATION

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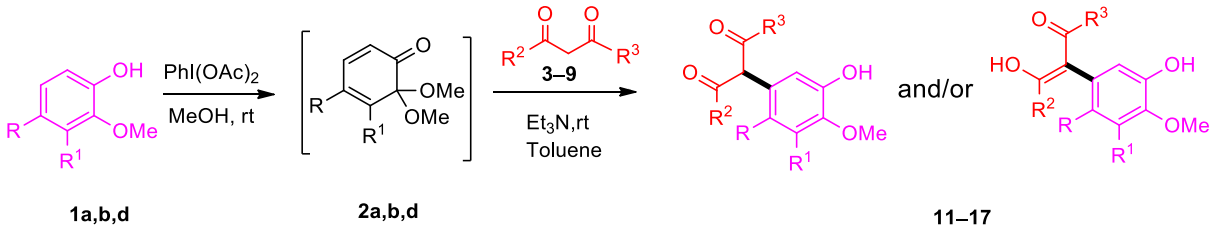
General information:

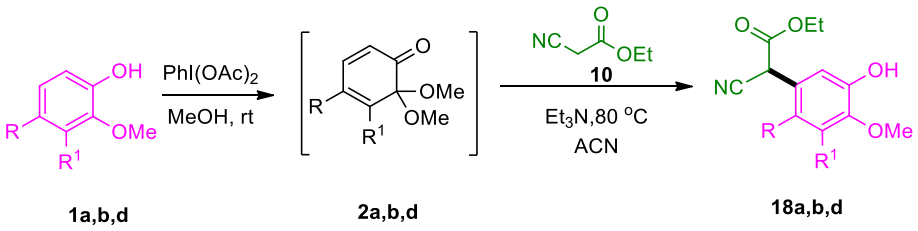
Unless otherwise noted, chemicals were purchased from the highest purity grade available and were used without further purification. Thin layer chromatography was performed on Merck pre-coated 0.25 mm silica gel plates (60F-254) using UV light as visualizing agent. Silica gel (100–200 mesh) was used for column chromatography. NMR spectra were recorded in $CDCl_3$ and DMSO-d_6 using TMS as an internal standard on JEOL (400 MHz) instrument. Chemical shifts (δ) were reported as parts per million (ppm) in δ scale downfield from TMS. ^1H NMR spectra were referenced to $CDCl_3$ (7.26 ppm) or DMSO-d_6 (2.50 ppm), and ^{13}C NMR spectra were referenced to $CDCl_3$ (77.0 ppm, the middle peak) or DMSO-d_6 (39.5 ppm, the middle peak). Coupling constants were expressed in Hz. The following abbreviations were used to explain the multiplicities: s = singlet, d = doublet, dd = doublet of doublet, t = triplet, q = quartet, m = multiplet. Melting points were recorded on Opti Melt Automated Melting Point System and are uncorrected. High-resolution mass spectra (HRMS) were obtained on a Brüker micrOTOF™-Q II mass spectrometer (ESI-MS).

General procedure for α-arylation of 1,3-dicarbonyl compounds:



To a solution of guaiacol derivative (**1**, 0.3 mmol) in dry MeOH (3 mL) was added solid $PhI(OAc)_2$ (0.36 mmol) at room temperature and stirred for 5 min. After complete conversion of guaiacol derivative into its MOB **2**, MeOH was removed under reduced pressure. The residue was dissolved in toluene (3 mL) and was added Et_3N (0.67 mmol) followed by the addition of 1,3-dieneones **3**–**9** (0.45 mmol) and reaction mixture kept for stirring at rt. After the completion of the reaction checked by the TLC, the mixture was extracted with DCM (3×10 mL) and then the combined organic extracts were washed with brine (10 mL), dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate = 3:1) to give the corresponding *m*-substituted phenols.

General procedure for α-arylation of ethyl cyanoacetate:

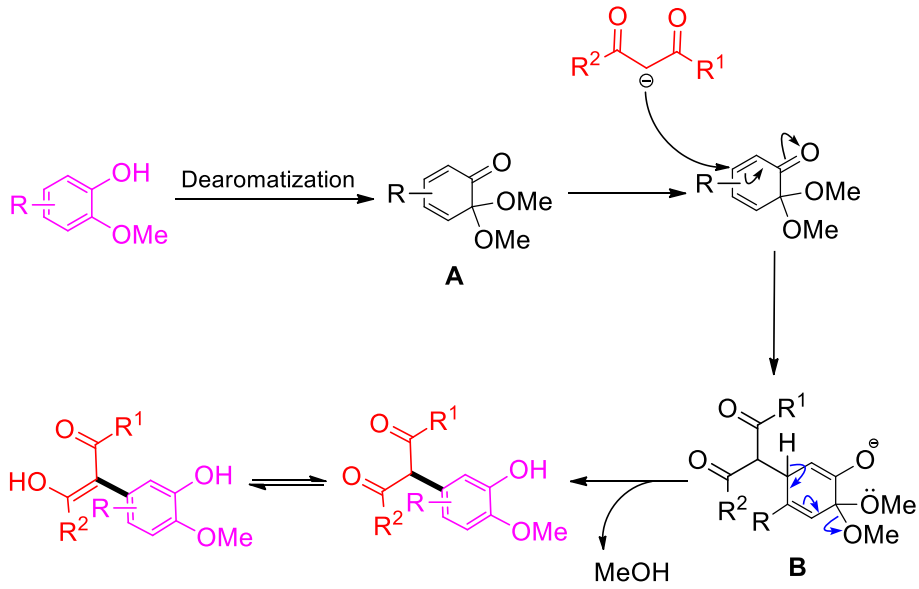


1a,b,d **2a,b,d** **18a,b,d**

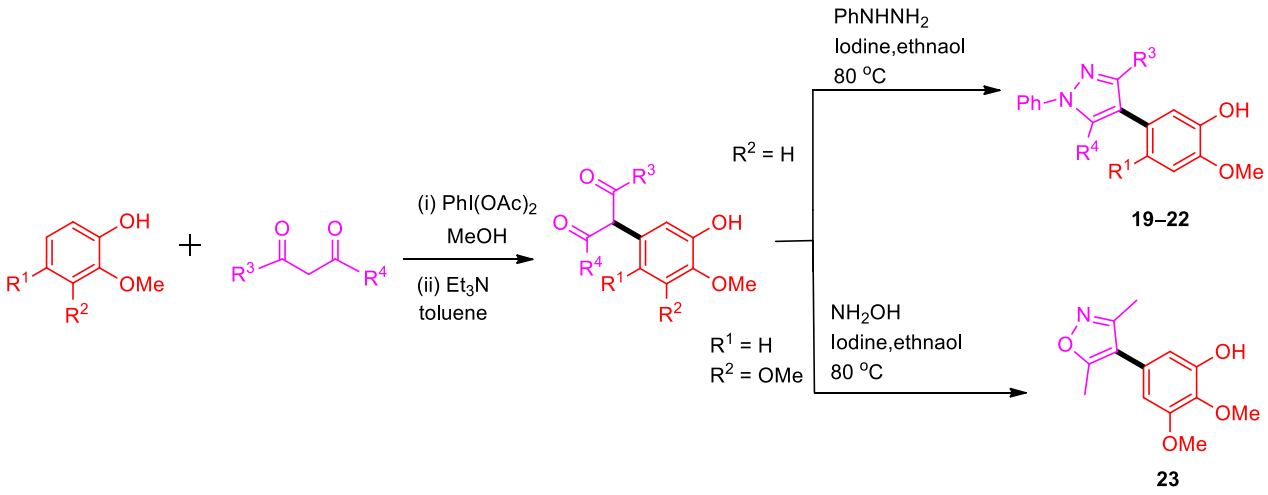
To a solution of guaiacol derivative (**1**, 0.3 mmol) in dry MeOH (3 mL) was added solid $PhI(OAc)_2$ (0.36 mmol) at room temperature and stirred for 5 min. After complete conversion of guaiacol derivative into its MOB **2**, MeOH was removed under reduced pressure. The residue was dissolved in acetonitrile (3 mL) and was added Et_3N (0.67 mmol) followed by addition of ethyl cyanoacetate (**10**, 0.45 mmol) and reaction mixture kept for stirring at 80 °C. After the completion of the reaction checked by the TLC, the mixture was extracted with DCM (3×10 mL) and then the combined organic extracts were washed with brine (10 mL), dried over sodium sulfate, and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate = 3:1) to afford the corresponding *m*-substituted phenols.

General Mechanism for α-arylation of C-H activated pronucleophiles

The proposed reaction mechanism for α-arylation is depicted below. Intially, 2-methoxyphenol gets dearomatized to the intermediate MOB **A** which undergoes Michael attack by the base-generated nucleophile to generate species **B**. The subsequent rearomatization of **B** releases α-arylated product.

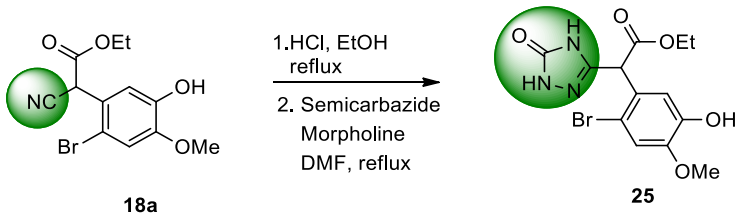


General procedure for the synthesis of pyrazoles and isoxazoles:



To a solution of guaiacol derivative **1** (0.3 mmol) in dry MeOH (3 mL) was added solid $PhI(OAc)_2$ (0.36 mmol) at room temperature and stirred for 5 min. After complete conversion of guaiacol derivative into its MOB **2**, MeOH was removed under reduced pressure. The residue was dissolved in Toluene (3 mL) and was added Et_3N followed by addition of 1,3-dieneone (0.45 mmol) and reaction mixture kept for stirring at rt**.** After the completion of the reaction checked by the TLC toluene evaporated under vacuo followed by the dilution with ethanol, hydrazine hydrate (36%) (0.75 mmol)/ hydroxylamine (0.75 mmol for isoxazoles) and molecular iodine (20 mol%) were added sequentially and the mixture were stirred for 2–3 h. The whole was quenched with 1 M HCl, and extracted with DCM (3×10 mL) and then the combined organic extracts were washed with brine (10 mL), dried over anhyd. sodium sulfate, and filtered. The solvent was removed under reduced pressure and the residue was purified by flash column chromatography (hexane/ethyl acetate = 3:1) to give the desired pyrazoles **19**–**22** or isoxazole **23**.

General procedure for the synthesis of triazolene derivative 25:

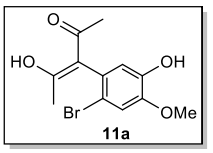


To a solution of ethyl cyanoacetate derivative **18**, (0.163 mg, 0.5 mmol) in dry EtOH (5 mL) was added 4 equivalent of conc. HCl dropwise at room temperature and reaction kept for refluxing for 7 h. After complete conversion of nitrile group to ester group EtOH was removed under reduced pressure. The mixture was quenched with saturated solution of bicarbonate and then extracted with DCM (3×15 mL). The obtained diester was directly used for the further conversion by dissolving it in DMF followed by the subsequent addition of semicarbazide

(1.5 equiv) and morpholine (2 equiv). The reaction kept for refluxing and monitored by TLC. The whole was quenched with 0.1 M HCl, and extracted with DCM (3×10 mL) and then the combined organic extracts were washed with brine (10 mL), dried over anhyd. sodium sulfate. The residue was purified by flash column chromatography (hexane/ethyl acetate = 3:1) to give the desired triazolene **25**.

Characterization data

(*Z*)-3-(2-Bromo-5-hydroxy-4-methoxyphenyl)-4-hydroxypent-3-en-2-one (**11a**):



11a

Reaction time: 3 h.

Yield: 64 mg (72%) as colourless solid.

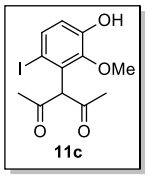
Mp: 120–122 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.10 (s, 1H), 6.79 (s, 1H), 5.70 (br, OH), 3.92 (s, 3H), 1.85 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.1, 146.8, 145.1, 129.9, 118.0, 115.9, 114.8, 114.4, 56.2, 23.7 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{12}H_{13}O_4BrNa$ calcd: 322.9889, found: 322.9881.

3-(3-Hydroxy-6-iodo-2-methoxyphenyl)pentane2,4-dione (**11c**):



11c

Reaction time: 3 h.

Yield: 74 mg (71%) as colourless solid.

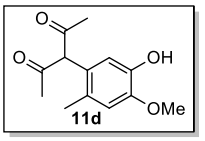
Mp: 129–130 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.39 (d, *J* = 8.4 Hz, 1H), 6.94 (d, *J* = 8.8 Hz, 1H), 5.73 (s, 1H), 3.95 (s, 3H), 2.77 (s, 3H), 2.61 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.2, 162.8, 144.0, 141.5, 130.8, 121.9, 117.6, 111.4, 108.7, 77.2, 57.1, 31.0, 15.4 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{12}H_{13}O_4INa$ calcd: 370.9750, found: 370.9752.

3-(5-Hydroxy-4-methoxy-2-methylphenyl)pentane-2,4-dione (**11d**):



11d

Reaction time: 50 min.

Yield: 55 mg (78%) as colourless solid.

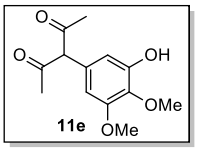
Mp: 109–110 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.74 (s, 1H), 6.66 (s, 1H), 5.49 (s, 1H), 3.90 (s, 3H), 2.09 (s, 3H), 1.82 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 146.0, 143.6, 129.2, 128.5, 117.1, 113.1, 112.4, 90.6, 55.8, 23.7, 23.6, 19.4 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{13}H_{16}O_4Na$ calcd: 259.0940, found: 259.0946.

3-(3-Hydroxy-4,5-dimethoxyphenyl)pentane-2,4-dione (**11e**):



11e

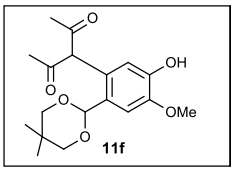
Reaction time: 4 h.

Yield: 45 mg (60%) as colourless solid.

Mp: 144–145 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (s, 1H), 6.26 (s, 1H), 5.87 (s, 1H), 3.93 (s, 3H), 3.84 (s, 3H), 1.92 (s, 6H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ 191.0, 152.4, 149.3, 134.8, 132.8, 115.0, 110.9, 106.9, 61.0, 55.9, 29.6, 23.9 ppm.
HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{13}H_{16}O_5Na$ calcd: 275.0998, found: 275.0988.

3-(2-(5,5-Dimethyl-1,3-dioxan-2-yl)-5-hydroxy-4-methoxyphenyl)pentane-2,4-dione (**11f**):



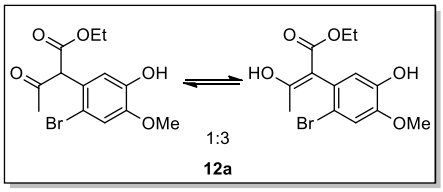
11f

Reaction time: 4 h.

Yield: 81 mg (81%).

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.23 (s, 1H), 6.637 (s, 1H), 5.18 (s, 1H), 3.97 (s, 3H), 3.70–3.52 (m, 1H), 1.85 (s, 6H), 1.29 (s, 3H), 0.75 (s, 3H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ 191.3, 146.5, 146.1, 130.1, 128.0, 116.8, 111.5, 108.5, 99.9, 55.8, 30.1, 24.1, 23.1, 21.7 ppm.

Ethyl 2-(2-bromo-5-hydroxy-4-methoxyphenyl)-3-hydroxybut-2-enoate (**12a**):



12a

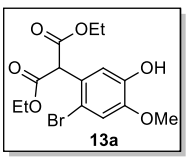
Reaction time: 3 h.

Yield: 70 mg (71%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.03 (br, enol OH), 7.06 (s, 1H), 6.77 (s, 1H), 5.17 (s, 0.3H keto), 4.25–4.18 (m, 2H), 3.89 (s, 3H), 1.78 (s, 3H), 1.18 (t, J = 6.8 Hz, 3H) ppm.
^{13}C NMR (100 MHz, $CDCl_3$): δ 201.2, 174.4, 171.7, 168.2, 146.4, 144.7, 128.6, 126.8, 125.1, 118.1, 115.8, 114.8, 114.5, 103.7, 63.5, 60.5, 56.0, 19.8, 14.3 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{13}H_{16}BrO_5Na$ calcd: 352.9995, found: 352.9994.

Diethyl 2-(2-bromo-5-hydroxy-4-methoxyphenyl)malonate (**13a**):



13a

Reaction time: 5 h.

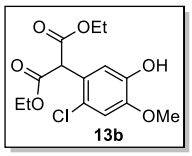
Yield: 74 mg (68%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (s, 1H), 7.02 (s, 1H), 5.59 (br, 1H), 5.08 (s, 1H), 4.27–4.20 (m, 4H), 3.87 (s, 3H), 1.27 (t, *J* = 6.8 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.8, 147.0, 145.0, 125.4, 115.9, 114.6, 114.1, 61.9, 56.7, 56.1, 14.0 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{14}H_{17}O_6BrNa$ calcd: 383.0100, found: 383.0100.

Diethyl 2-(2-chloro-5-hydroxy-4-methoxyphenyl)malonate (**13b**):



Reaction time: 6 h.

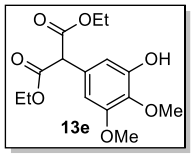
Yield: 61 mg (65%) as colourless liquid.

^{1}H NMR (400MHz, $CDCl_3$): δ 7.04 (s, 1H), 6.87 (s, 1H), 5.55 (br, 1H), 5.08 (s, 1H), 4.28–4.19 (m, 4H), 3.88 (s, 3H), 1.27 (t, *J* = 6.8 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.7, 147.0, 145.1, 125.6, 115.9, 114.7, 114.2, 61.9, 56.8, 56.2, 14.0 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{14}H_{17}O_6ClNa$ calcd: 339.0605, found: 339.060.

Diethyl 2-(3-hydroxy-4,5-dimethoxyphenyl)malonate (**13e**):



Reaction time: 7 h.

Yield: 57 mg (61%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.63 (s, 1H), 6.55 (s, 1H), 5.80 (s, 1H), 4.26–4.15 (m, 4H), 3.89 (s, 3H), 3.86 (s, 3H), 1.27 (t, *J* = 6.8 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 168.0, 152.2, 149.2, 135.4, 128.5, 109.4, 105.1, 61.8, 60.8, 57.6, 55.8, 13.9 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{15}H_{20}O_7Na$ calcd: 335.1101, found: 335.1102.

Ethyl-3-ethoxy-3-hydroxy-2-(4-hydroxy-5-methoxy-[1,1'-biphenyl]-2-yl)acrylate (13g):

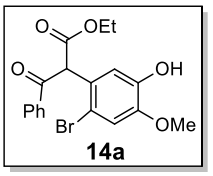
Reaction time: 6 h.

Yield: 55 mg (52%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 12.57 (enolic, -OH), 7.95–7.92 (m, 2H), 7.61–7.57 (m, 1H), 7.49–7.45 (m, 2H), 4.26–4.13 (m, 4H), 3.98 (s, 3H), 1.25 (t, *J* = 7.6 Hz, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 192.6, 167.6, 135.9, 133.7, 131.2, 128.7, 128.4, 125.9, 87.3, 61.4, 45.9, 14.0 ppm.

Ethyl 2-(2-bromo-5-hydroxy-4-methoxyphenyl)-3-oxo-3-phenylpropanoate (**14a**):



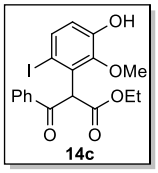
Reaction time: 4 h.

Yield: 83 mg (80%) colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03–8.01 (m, 2H), 7.54–7.52 (m, 1H), 7.47–7.45 (m, 2H), 6.99 (s, 1H), 6.97 (s, 1H), 5.73 (s, 1H), (4.39 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.7, 168.4, 147.0, 145.2, 133.6, 128.8, 128.7, 125.7, 116.5, 114.8, 113.7, 61.8, 59.3, 56.1, 14.0 ppm.

Ethyl 2-(3-hydroxy-6-iodo-2-methoxyphenyl)-3-oxo-3-phenylpropanoate (**14c**):



Reaction time: 5 h.

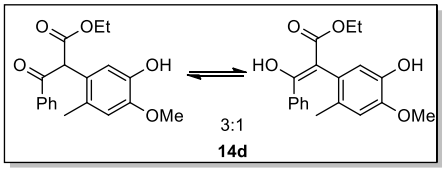
Yield: 100 mg (76%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.04–8.01 (m, 2H), 7.53 (d, *J* = 8.8 Hz, 1H), 7.48–7.45 (m, 3H), 6.98 (d, *J* = 8.4 Hz, 1H), 5.73 (s, 1H), 4.39 (q, *J* = 7.2 Hz, 2H), 3.97 (s, 3H), 1.39 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.0, 160.8, 144.5, 141.9, 130.9, 130.1, 129.5, 127.9, 122.9, 112.7, 109.1, 76.7, 60.6, 57.2, 29.7, 14.2 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{18}H_{17}O_5INa$ calcd: 463.0012, found: 463.0012

Ethyl 2-(5-hydroxy-4-methoxy-2-methylphenyl)-3-oxo-3-phenylpropanoate (**14d**):



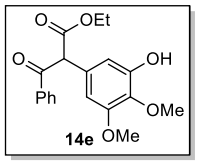
Reaction time: 2 h.

Yield: 78 mg (80%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 13.6 (br, 0.35 OH), 7.86–7.84 (m, 2H), 7.53–7.49 (m, 1H), 7.41–7.37 (m, 2H), 6.79 (s, 1H), 6.70 (s, 1H), 5.61 (s, 1H), 5.38 (s, 1H), 4.28–4.19 (m, 2H), 3.85 (s, 3H), 2.34 (s, 3H), 1.27–1.23 (m, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 170.5, 169.1, 146.0, 143.8, 135.7, 133.3, 129.6, 128.7, 128.6, 128.5, 127.6, 115.5, 113.0, 76.7, 61.6, 60.9, 57.3, 19.5, 14.1 ppm.

Ethyl 2-(3-hydroxy-4,5-dimethoxyphenyl)-3-oxo-3-phenylpropanoate (**14e**):



Reaction time: 6 h.

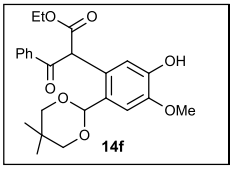
Yield: 64 mg (62%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97–7.95 (m, 2H), 7.57–7.53 (m, 1H), 7.45–7.42 (m, 2H), 6.63 (s, 1H), 6.52 (s, 1H), 5.75 (br, 1H), 5.47 (s, 1H), 4.25–4.19 (m, 2H), 3.87 (s, 3H), 3.83 (s, 3H), 1.25 (t, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 193.1, 168.8, 152.5, 149.3, 135.7, 135.4, 133.5, 128.9, 128.8, 128.7, 109.6, 105.4, 61.7, 60.2, 55.9, 29.7, 14.1 ppm .

HRMS (ESI-TOF): m/z $[M]^+$ $C_{19}H_{20}O_6$ calcd: 344.1254, found: 344.1254.

Ethyl 2-(2-(5,5-dimethyl-1,3-dioxan-2-yl)-5-hydroxy-4-methoxyphenyl)-3-oxo-3-phenylpropanoate (**14f**):



14f

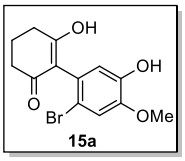
Reaction time: 5 h.

Yield: 94 mg (74%)

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03–8.01 (m, 2H), 7.49–7.45 (m, 1H), 7.38–7.34 (m, 2H), 7.05 (s, 1H), 6.77 (s, 1H), 6.21 (s, 1H), 5.44 (s, 1H), 4.31–4.16 (m, 2H), 3.87 (s, 3H), 3.83–3.63 (m, 4H), 1.33 (s, 3H), 1.25 (t, *J* = 7.2 Hz, 3H), 0.80 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 195.0, 169.4, 145.9, 145.7, 135.6, 133.3, 129.2, 128.4, 127.7, 124.9, 116.4, 110.6, 102.5, 78.2, 61.2, 57.0, 55.8, 30.2, 23.6, 22.1, 14.2 ppm.

2-(2-Bromo-5-hydroxy-4-methoxyphenyl) cyclohexane-1,3-dione (**15a**):



15a

Reaction time: 3 h.

Yield: 76 mg (82%) as colourless solid.

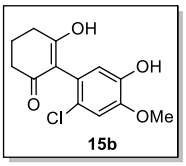
Mp: 178–179 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.00 (s, 1H), 3.94 (s, 3H), 2.99 (t, *J* = 6.4 Hz, 2H), 2.57 (t, *J* = 7.2 Hz, 2H), 2.28–2.21 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.7, 169.7, 148.7, 145.4, 143.8, 116.5, 105.9, 99.9, 94.5, 56.4, 37.8, 23.9, 22.6 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{13}H_{13}O_4Br$ calcd: 313.0069, found: 313.0054.

2'-Chloro-5',6-dihydroxy-4'-methox-4,5-dihydro-[1,1'-biphenyl]-2(3*H*)-one (**15b**):



15b

Reaction time: 2 h.

Yield: 64 mg (80%) as colourless solid.

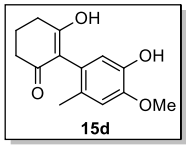
Mp: 186–189 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.38 (s, 1H), 6.88 (s, 1H), 3.79 (s, 3H), 2.86 (t, *J* = 6.0 Hz, 2H), 2.43 (t, *J* = 6.4 Hz, 2H), 2.15–2.08 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.6, 169.5, 148.1, 145.8, 143.9, 116.2, 115.7, 105.7, 94.6, 55.9, 37.4, 29.2, 23.4, 22.2 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{13}H_{13}O_4Cl$ calcd: 269.0575, found: 269.0575.

2-(5-Hydroxy-4-methoxy-2-methylphenyl)cyclohexane-1,3-dione (**15d**):



Reaction time: 3 h.

Yield: 63 mg (85%) as colourless solid.

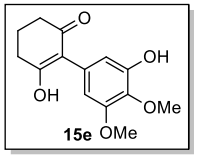
Mp: 272–273 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.79 (s, 1H), 6.62 (s, 1H), 5.69 (br, 1H), 3.88 (s, 3H), 2.57–2.52 (m, 4H), 2.12–2.08 (m, 2H), 2.04 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 146.3, 143.5, 128.9, 123.6, 117.4, 112.8, 77.3, 55.4, 39.6, 20.4, 18.7 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{14}H_{16}O_4$ calcd: 249.1121, found: 249.1103.

3',6-Dihydroxy-4',5'-dimethoxyphenyl-4,5-dihydro-[1,1'-biphenyl]-2(3*H*)-one (**15e**):



Reaction time: 5 h.

Yield: 55 mg (70%) as colourless solid.

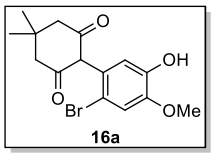
Mp: 117–118 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.42 (s, 1H), 6.29 (s, 1H), 3.90 (s, 3H), 3.83 (s, 1H), 2.55 (t, *J* = 6.0 Hz, 4H), 2.11–2.04 (m, 2H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 153.2, 150.0, 135.2, 126.5, 117.8, 110.0, 106.6, 60.9, 60.8, 55.9, 55.8, 20.4 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{14}H_{16}O_5Na$ calcd: 287.0867, found: 287.0889.

2-(2-Bromo-5-hydroxy-4-methoxyphenyl)-5,5-dimethylcyclohexane-1,3-dione (16a):



Reaction time: 4 h.

Yield: 87 mg (86%) as colourless solid.

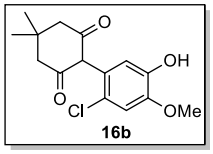
Mp: 144–145 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.57 (s, 1H), 6.99 (s, 1H), 5.83 (s, 1H), 3.93 (s, 3H), 2.85 (s, 2H), 2.16 (s, 2H), 1.18 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 169.0, 145.3, 143.8, 116.2, 115.4, 105.7, 94.1, 56.2, 52.2, 37.8, 35.3, 29.7, 28.6 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{15}H_{17}O_4BrNa$ calcd: 363.0202, found: 363.0205.

2-(2-Chloro-5-hydroxy-4-methoxyphenyl)-5,5-dimethylcyclohexane-1,3-dione (16b):



16b

Reaction time: 3 h.

Yield: 75 mg (85%) as colourless solid.

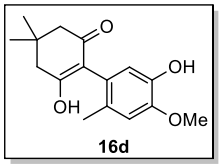
Mp: 145–146 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.56 (s, 1H), 7.00 (s, 1H), 5.75 (s, 1H), 3.93 (s, 3H), 2.85 (s, 2H), 2.45 (s, 2H), 1.18 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 194.3, 168.9, 148.9, 145.3, 143.7, 116.3, 115.4, 105.6, 94.6, 56.3, 52.1, 37.8, 35.3, 28.6 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{15}H_{17}O_4ClNa$ calcd: 319.0707, found: 319.0739.

3-Hydroxy-2-(5-hydroxy-4-methoxy-2-methylphenyl)-5,5-dimethylcyclohex-2-enone (16d):



16d

Reaction time: 4 h.

Yield: 71 mg (86%) as colourless solid.

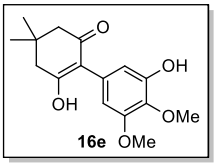
Mp: 235–236 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.56 (s, 1H), 6.38 (s, 1H), 3.68 (s, 3H), 2.43–2.40 (m, 1H), 2.21–2.20 (m, 3H), 1.86 (s, 3H), 0.98 (s, 3H), 0.97 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 196.4, 146.0, 143.2, 128.5, 123.9, 117.5, 115.1, 112.6, 55.2, 31.3, 28.3, 27.8, 27.5, 18.8 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{16}H_{20}O_4Na$ calcd: 299.1253, found: 299.1256.

3-Hydroxy-2-(3-hydroxy-4,5-dimethoxyphenyl)-5,5-dimethylcyclohex-2-enone (16e):



16e

Reaction time: 5 h.

Yield: 66 mg (76%) as colourless solid.

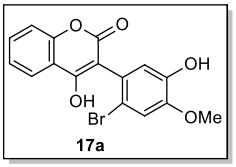
Mp: 225–226 ºC.

^{1}H NMR (400MHz, $CDCl_3$): δ 6.33 (s, 1H), 6.21 (s, 1H), 3.76 (s, 3H), 3.73 (s, 3H), 2.30–2.29 (m, 4H), 1.04 (s, 6H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 204.6, 152.6, 149.7, 134.9, 127.7, 116.2, 111.0, 106.2, 60.4, 60.3, 55.5, 52.1, 31.4, 28.1 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{16}H_{20}O_5Na$ calcd: 315.1202, found: 315.1202.

3-(2-Bromo-5-hydroxy-4-methoxyphenyl)-4-hydroxy-2H-chromen-2-one (**17a**):



17a

Reaction time: 4 h.

Yield: 84 mg (78%) as colourless solid.

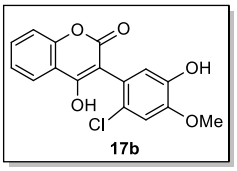
Mp: 208–210 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98–7.95 (m, 1H), 7.62–7.48 (m, 2H), 7.41–7.37 (m, 1H), 7.27 (s, 1H), 7.20 (s, 1H), 5.75 (br, 1H), 4.01 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.7, 152.8, 149.7, 147.5, 144.8, 130.8, 124.4, 121.2, 121.1, 117.1, 115.7, 112.7, 105.6, 105.5, 95.0, 56.2 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{16}H_{11}O_5BrNa$ calcd: 384.9682, found: 384.9684**.**

3-(2-Chloro-5-hydroxy-4-methoxyphenyl)-4-hydroxy-2H-chromen-2-one (17b):



17b

Reaction time: 4 h.

Yield: 71 mg (75%) as colourless solid.

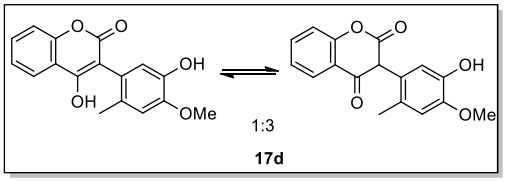
Mp: 118–220 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.97–7.96 (m, 1H), 7.62 (s, 1H), 7.58–7.55 (m, 1H), 7.50–7.48 (m, 1H), 7.41–7.38 (m, 1H), 7.20 (s, 1H), 5.72 (br, 1H), 4.01 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 158.0, 157.5, 152.1, 149.1, 147.6, 144.7, 130.4, 123.9, 120.5, 116.4, 114.8, 112.1, 104.9, 94.8, 55.6 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{16}H_{11}O_5ClNa$ calcd: 341.0187, found: 341.0188.

3-(5-hydroxy-4-methoxy-2-methylphenyl)chroman-2,4-dione (17d):



17d

Reaction time: 3 h.

Yield: 78 mg (88%) as colourless solid.

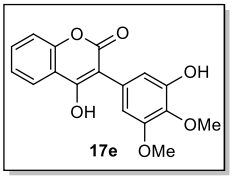
Mp: 119–200 ^oC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.84–7.82 (m, 1H), 7.74–7.72 (m, 2H), 7.44–7.38 (m, 3H), 7.21–7.11 (m, 3H) 6.69 (s, 1H), 6.67 (s, 1H), 5.62 (s, 1.5H), 5.19 (s, 0.5H), 3.76 (s, 3H), 2.03 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 167.2, 163.8, 153.7, 146.7, 143.6, 131.6, 131.1, 123.3, 123.1, 116.7, 116.0, 115.8, 113.0, 90.8, 45.5, 8.2 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{17}H_{14}O_5Na$ calcd: 321.0733, found: 321.0733.

4-Hydroxy-3-(3-hydroxy-4,5-dimethoxyphenyl)-2H-chromen-2-one (17e):



Reaction time: 5 h.

Yield: 70 mg (75%) as colourless solid.

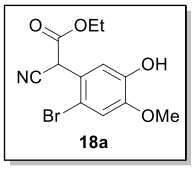
Mp: 248–249 ºC.

^{1}H NMR (400MHz, $CDCl_3$): δ 9.33 (br, 1H), 7.88–7.86 (d, *J* = 7.6 Hz, 1H), 7.48–7.45 (m, 1H), 7.23–7.18 (m, 2H), 6.60 (s, 1H), 6.46 (s, 1H), 3.82 (s, 3H), 3.78 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 162.4, 160.1, 152.8, 152.3, 131.4, 126.1, 123.5, 123.3, 115.9, 115.8, 111.5, 111.4, 105.84, 105.82, 105.6, 60.1, 55.4 ppm.

HRMS (ESI-TOF): m/z $[M +H]^+$ $C_{17}H_{14}O_6$ calcd: 315.0872, found: 315.0863.

Ethyl 2-(2-bromo-5-hydroxy-4-methoxyphenyl)-2-cyanoacetate (18a):



Reaction time: 4 h.

Yield: 73 mg (78%) as colourless solid.

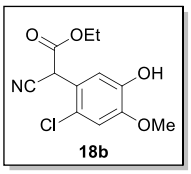
Mp: 122–123 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (s, 1H), 7.05 (s, 1H), 5.66 (br, 1H), 5.10 (s, 1H), 4.31–4.25 (m, 2H), 3.91 (s, 3H), 1.31 (t, *J* = 8.0 Hz, 3H,) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.2, 147.8, 145.7, 122.7, 115.5, 115.2, 115.1, 113.1, 63.4, 56.3, 42.8, 13.9 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{12}H_{12}NO_4BrNa$ calcd: 335.9841, found: 335.9844.

Ethyl 2-(2-chloro-5-hydroxy-4-methoxyphenyl)-2-cyanoacetate (18b):



Reaction time: 5 h.

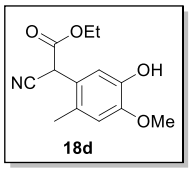
Yield: 64 mg (80%) as colourless liquid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.09 (s, 1H), 6.89 (s, 1H), 5.07 (s, 1H), 4.31–4.25 (m, 2H), 3.91 (s, 3H), 1.31 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 164.3, 147.7, 145.1, 124.1, 120.8, 115.4, 115.2, 112.1, 63.3, 55.7, 40.3, 13.9 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{12}H_{12}NO_4ClNa$ calcd: 292.0347, found: 292.0342.

Ethyl 2-cyano-2-(5-hydroxy-4-methoxy-2-methylphenyl)acetate (18d):



18d

Reaction time: 3 h.

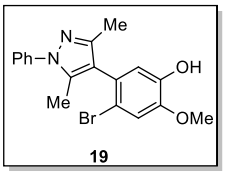
Yield: 65 mg (88%) as colourless solid.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00 (s, 1H), 6.68 (s, 1H), 5.54 (s, 1H), 4.76 (s, 1H), 4.28–4.20 (m, 2H), 3.88 (s, 3H), 2.32 (s, 3H), 1.29 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 146.9, 144.3, 127.9, 121.2, 115.8, 114.7, 113.2, 63.1, 55.9, 40.6, 19.0, 13.9 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{13}H_{15}NO_4Na$ calcd: 272.0893, found: 272.0860.

4-Bromo-5-(3,5-dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-2-methoxyphenol (**19**):



19

Yield: 87 mg (78%) as colourless solid.

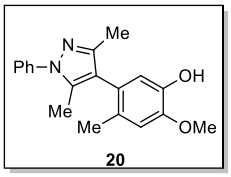
Mp:.157–158 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.50–7.42 (m, 5H), 7.13 (s, 1H), 6.81 (s, 1H), 3.91 (s, 3H), 2.18 (s, 3H), 2.15 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.6, 146.7, 144.8, 139.7, 137.3, 128.9, 127.3, 127.1, 124.7, 120.5, 118.1, 114.9, 114.5, 56.1, 12.3, 11.7 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{18}H_{17}BrN_2O_2$ calcd: 373.0546, found: 373.0546.

5-(3,5-Dimethyl-1-phenyl-1*H*-pyrazol-4-yl)-2-methoxy-4-methylphenol (**20**):



20

Yield: 73 mg (80%) as colourless solid.

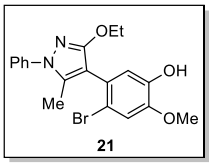
Mp: 160–162 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51–7.43 (m, 4H), 7.35–7.32 (m, 1H), 6.79 (s, 1H), 6.73 (s, 1H), 3.91 (s, 3H), 2.14 (s, 3H), 2.12 (s, 3H), 2.10 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 147.7, 145.8, 143.2, 140.0, 136.7, 129.2, 128.9, 125.4, 124.6, 120.3, 117.1, 112.2, 55.8, 19.5, 12.3, 11.5 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{19}H_{20}N_2O_2$ calcd: 309.1597, found: 309.1560.

4-Bromo-5-(3-methoxy-5-methyl-1-phenyl-1*H*-pyrazol-4-yl)-2 methoxyphenol (**21**):



21

Yield: 86 mg (72%) as colourless solid.

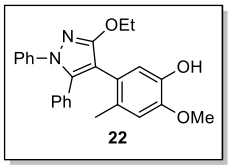
Mp: 160–161 ºC.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.75–7.73 (m, 2H), 7.44–7.39 (m, 2H), 7.27 (s, 1H), 7.12 (s, 1H), 6.92 (s, 1H), 5.70 (br, 1H), 3.94 (s, 3H), 3.89–3.82 (m, 2H), 2.12 (s, 3H), 1.15 (t, *J* = 6.8 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 150.3, 148.1, 146.7, 144.7, 138.7, 128.7, 126.3, 126.0, 122.2, 121.3, 119.6, 119.1, 118.2, 115.2, 114.7, 110.2, 69.0, 56.2, 15.2, 13.2 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{19}H_{19}BrN_2O_3$ calcd: 403.0651, found: 403.0641.

5-(3-Ethoxy-1,5-diphenyl-1*H*-pyrazol-4-yl)-2-methoxy-4-methylphenol (**22**):



22

Yield: 90 mg (75%) as colourless solid.

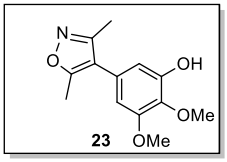
Mp: 217–218 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 8.03–8.01 (m, 1H), 7.95–7.93 (m, 1H), 7.50–7.48 (m, 1H), 7.43–7.41 (m, 2H), 7.24–7.23 (m, 2H), 6.76 (s, 1H), 6.71 (s, 1H), 5.05 (br, 1H), 3.87 (s, 3H), 2.51 (q, *J* = 7.2 Hz, 2H), 2.02 (s, 3H), 0.98 (t, *J* = 7.6 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 148.8, 145.9, 143.3, 130.4, 129.8, 128.8, 128.7, 128.6, 128.2, 127.9, 126.8, 126.6, 125.2, 119.0, 117.6, 112.7, 55.8, 44.6, 19.6, 8.3 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{25}H_{24}N_2O_3$ calcd: 401.1859, found: 401.1857.

5-(3,5-Dimethylisoxazol-4-yl)-2,3-dimethoxyphenol (**23**):



23

Yield: 60 mg (81%) as colourless solid.

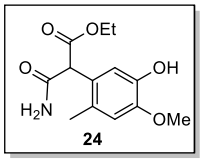
Mp: 152–153 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.48 (s, 1H), 6.32 (s, 1H), 5.95 (s, 1H), 3.94 (s, 3H), 3.87 (s, 3H), 2.40 (s, 3H), 2.27 (s, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 165.1, 158.6, 152.4, 149.5, 134.9, 126.4, 116.6, 109.0, 105.2, 61.0, 55.9, 11.5, 10.8 ppm.

HRMS (ESI-TOF): m/z $[M + Na]^+$ $C_{13}H_{15}NO_4Na$ calcd: 272.0893, found: 272.0897.

Ethyl 3-amino-2-(2-bromo-5-hydroxy-4-methoxy-2-methylphenyl)-3-oxopropanoate (**24**):



24

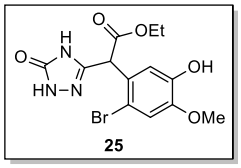
Yield: 54 mg (68%) as colourless solid.

Mp: 154–156 °C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 6.97 (s, 1H), 6.69 (s, 1H), 5.72 (s, 1H), 4.65 (s, 1H), 4.25–4.14 (m, 2H), 3.86 (s, 3H), 2.34 (s, 3H), 1.24 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.7, 170.2, 146.1, 144.0, 128.7, 125.0, 113.4, 113.3, 61.8, 55.9, 54.3, 29.7, 14.1 ppm.

Ethyl 2-bromo-5-hydroxy-4-methoxyphenyl)-2-(5-oxo-4,5-dihydro-1*H*-1,2,4-triazol-3-yl)acetate (25):



25

Yield: 99 mg (55%) as colourless solid.

Mp: 136–138 ^{o}C.

^{1}H NMR (400 MHz, $CDCl_3$): δ 7.13 (s, 1H), 7.05 (s, 1H), 5.61 (br,1H), 5.10 (s, 1H), 4.32–4.26 (m, 2H), 3.91 (s, 3H), 3.73 (s, 1H), 1.31 (t, *J* = 7.2 Hz, 3H) ppm.

^{13}C NMR (100 MHz, $CDCl_3$): δ 170.6, 147.1, 146.3, 145.6, 145.9, 128.5, 117.1, 115.6, 114.9, 113.8, 60.9, 56.2, 41.1, 14.1 ppm.

HRMS (ESI-TOF): m/z $[M + H]^+$ $C_{13}H_{14}BrN_3O_4$ calcd: 372.0189, found: 372.0185.

Copies of ^{1}H and ^{13}C NMR spectra

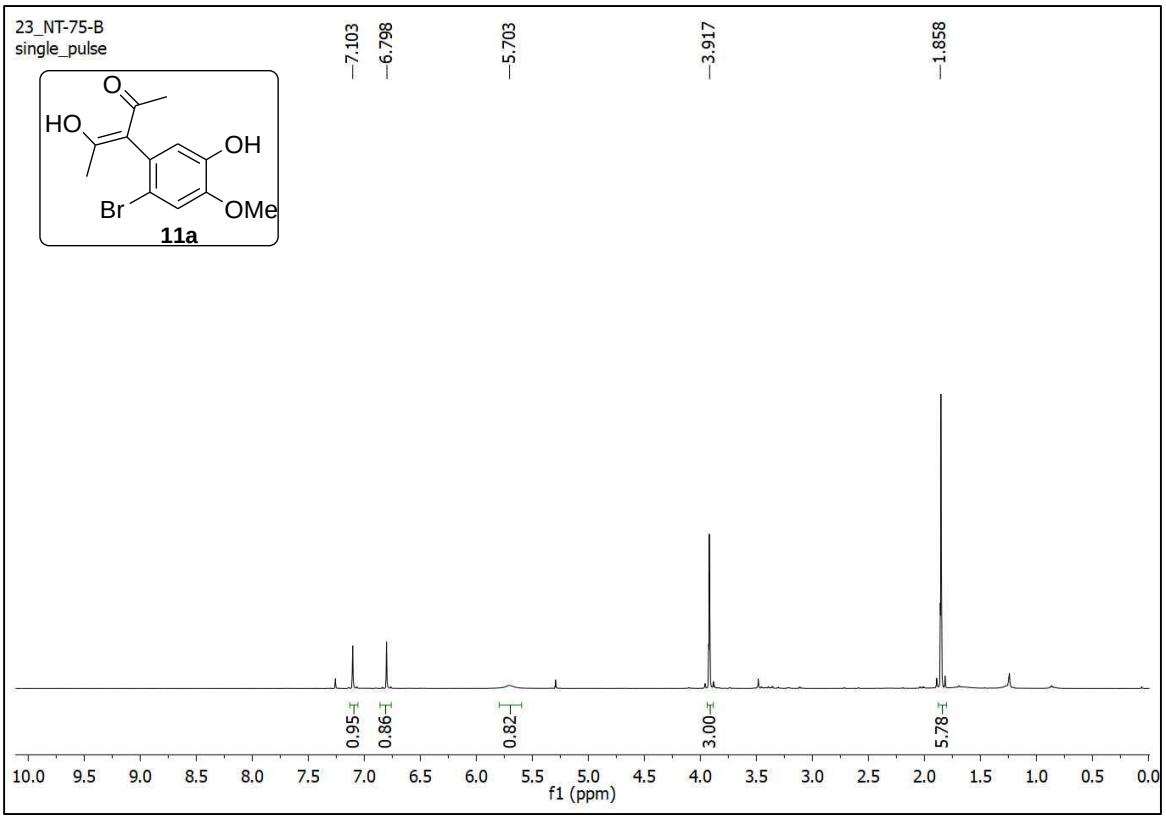


Fig S1: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **11a**.

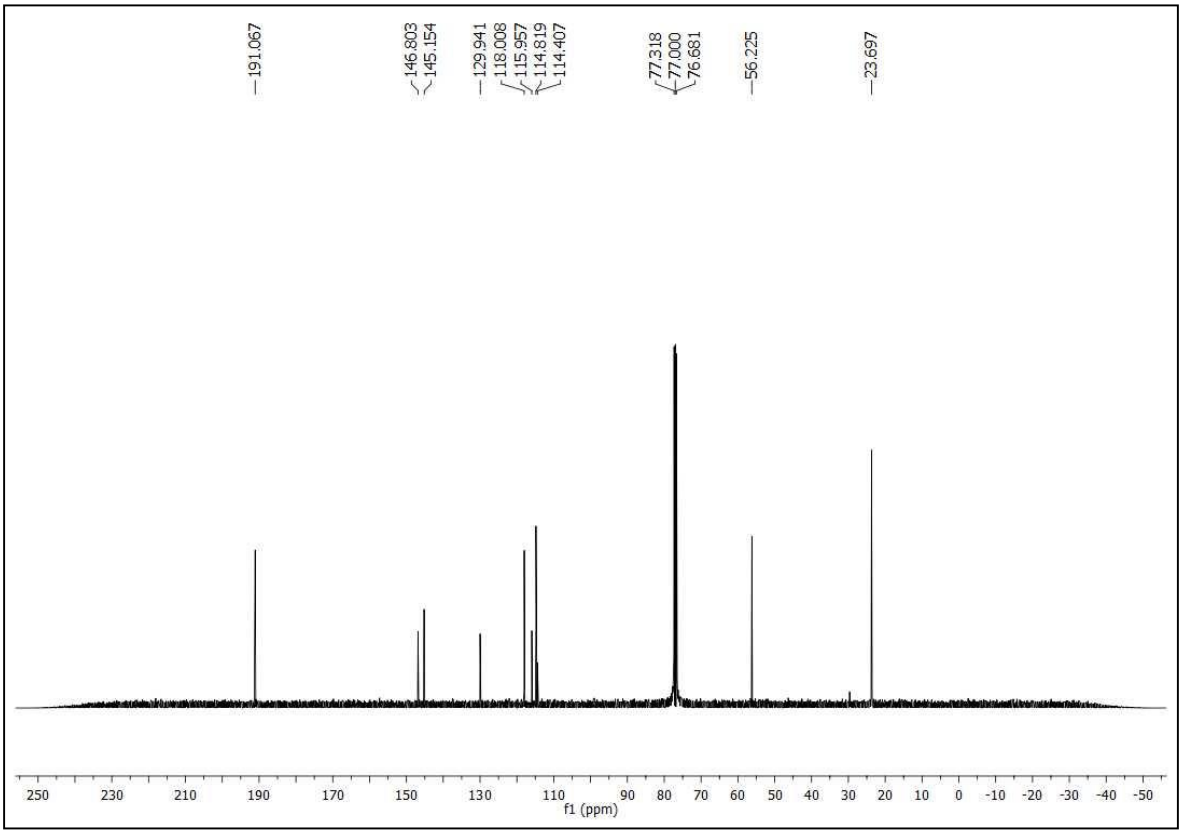


Fig S2: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **11a**.

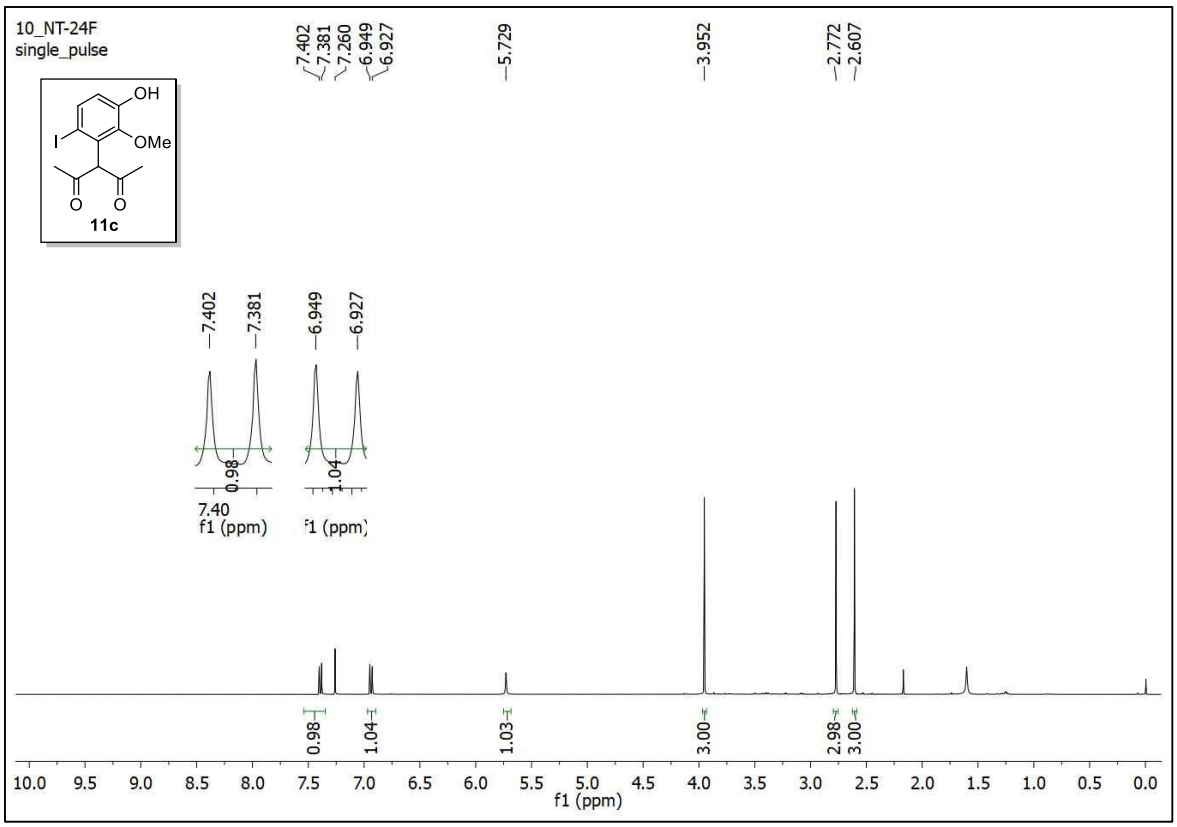


Fig S3: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **11c**.

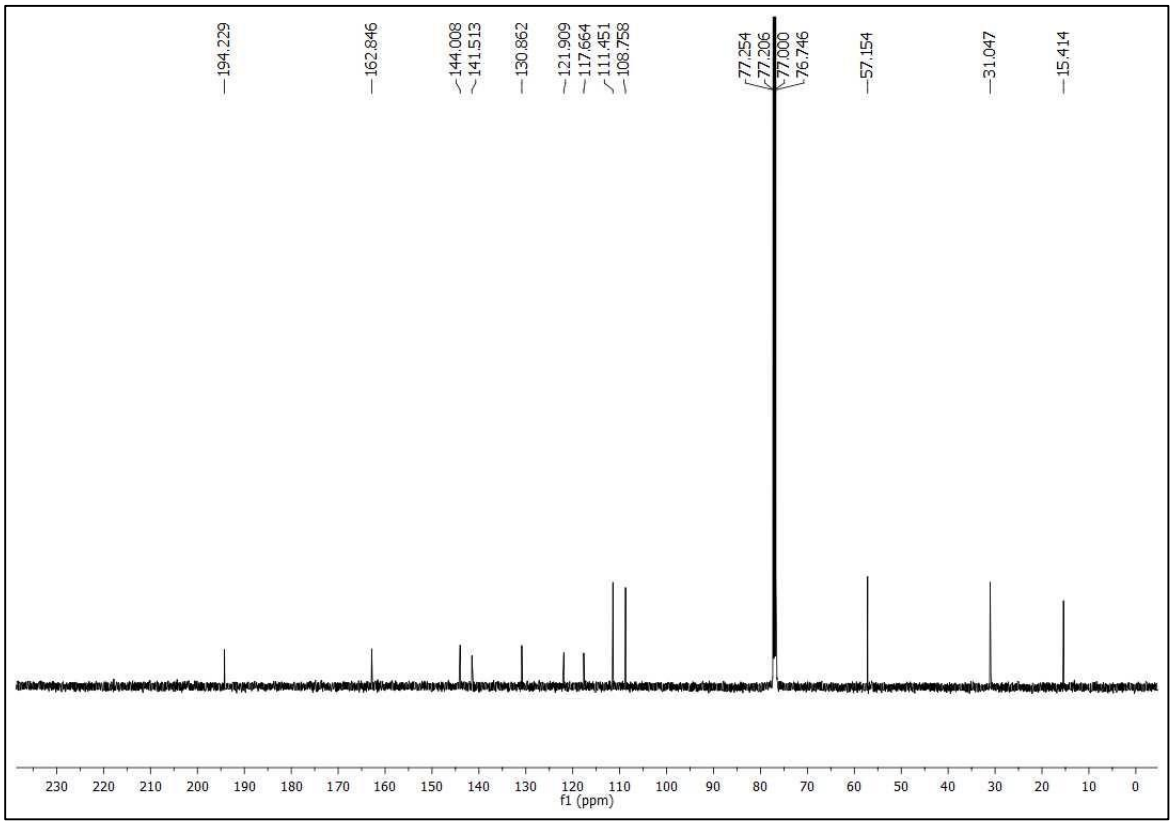


Fig S4: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **11c**.

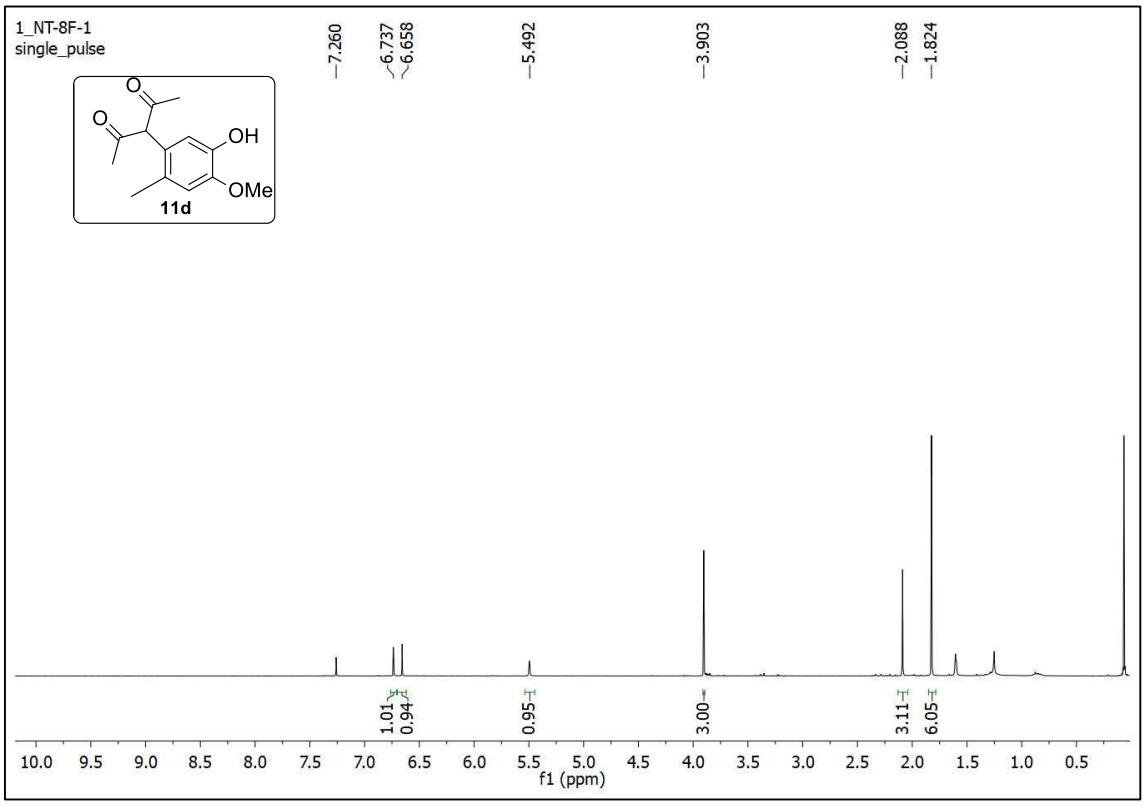


Fig S5: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **11d.**

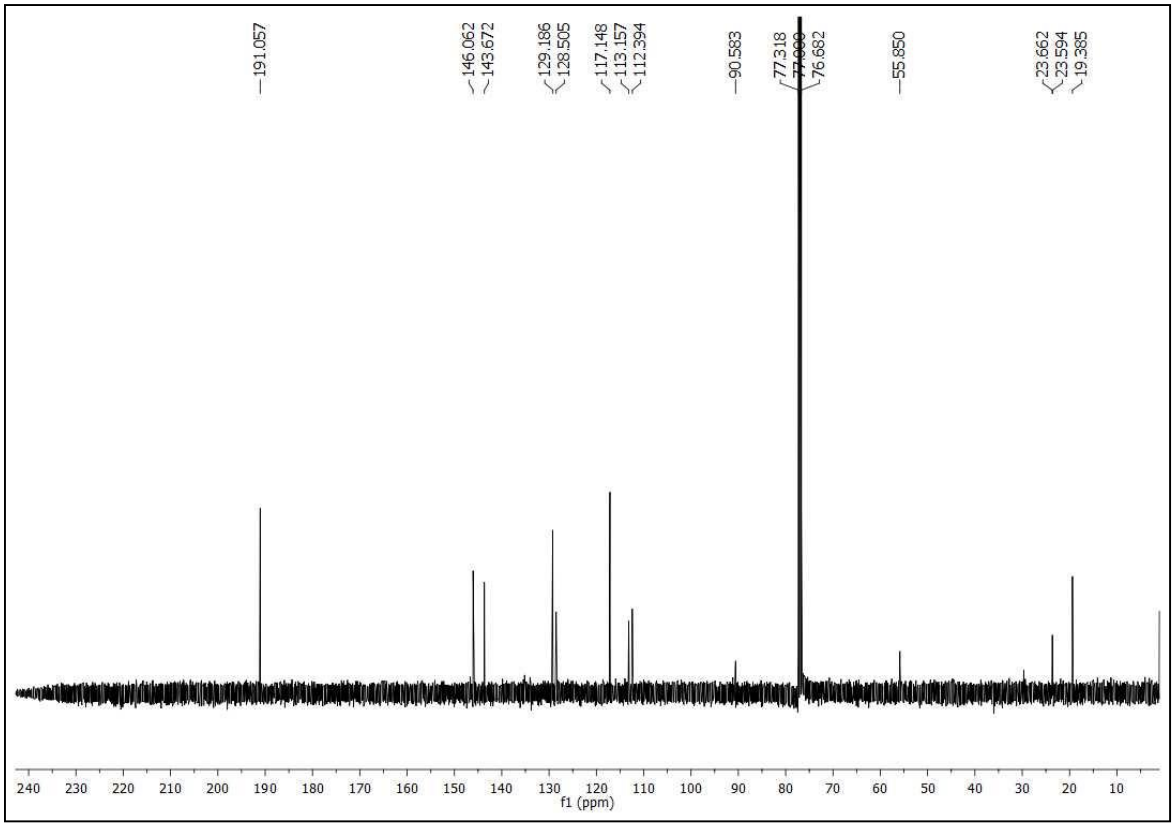


Fig S6: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **11d.**

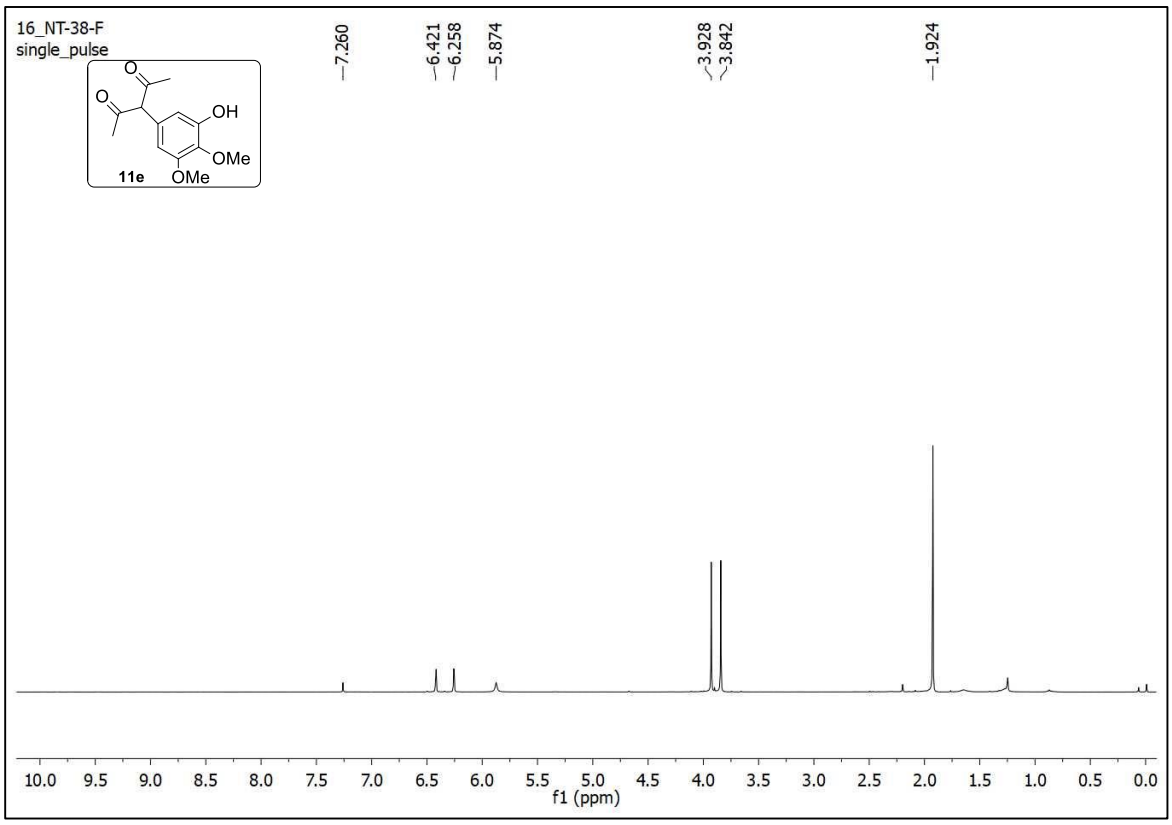


Fig S7: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **11e.**

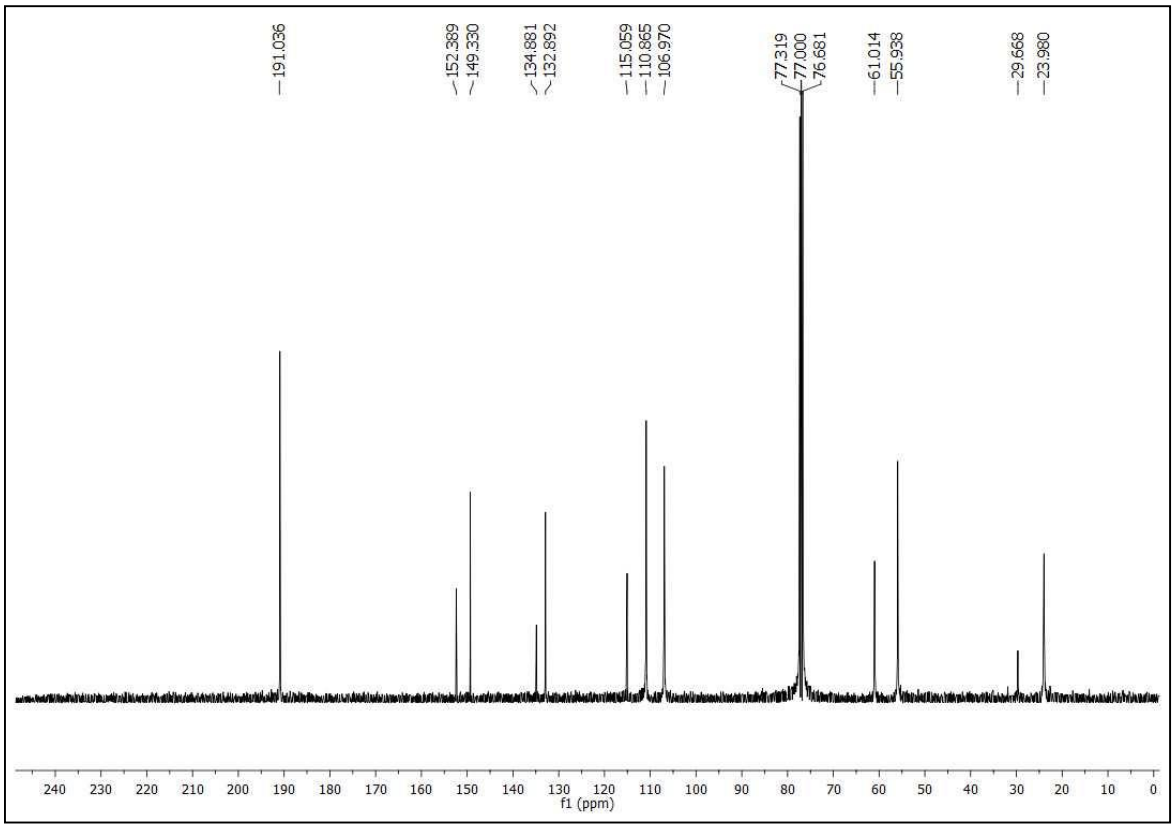


Fig S8: ^{1}H NMR (125 MHz, $CDCl_3$) spectrum of **11e**.

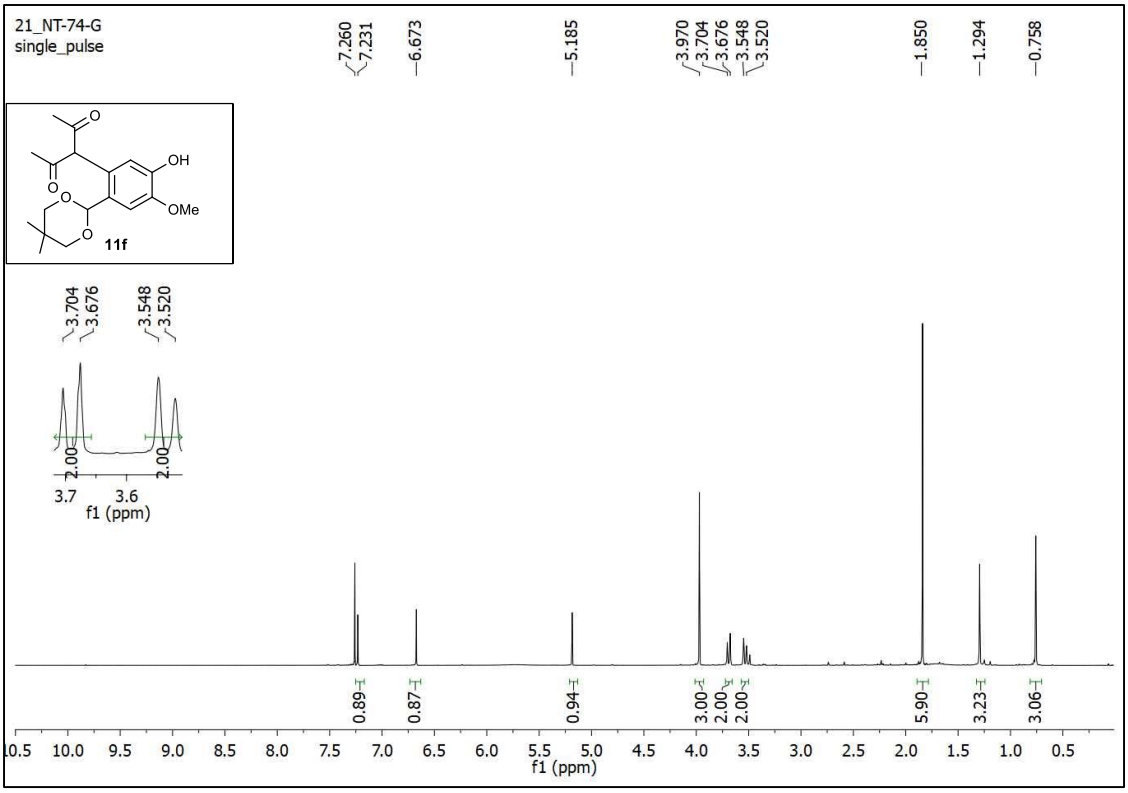


Fig S25: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **11f**

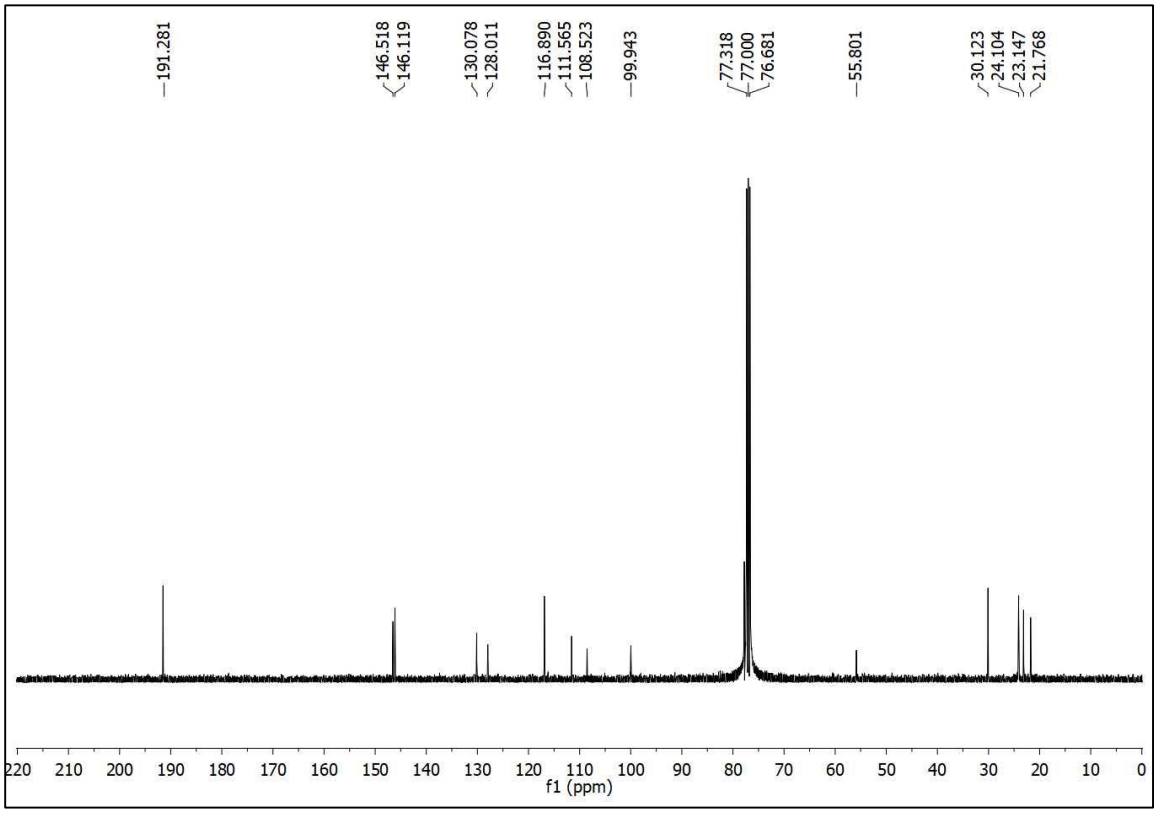


Fig S26: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **11f**.

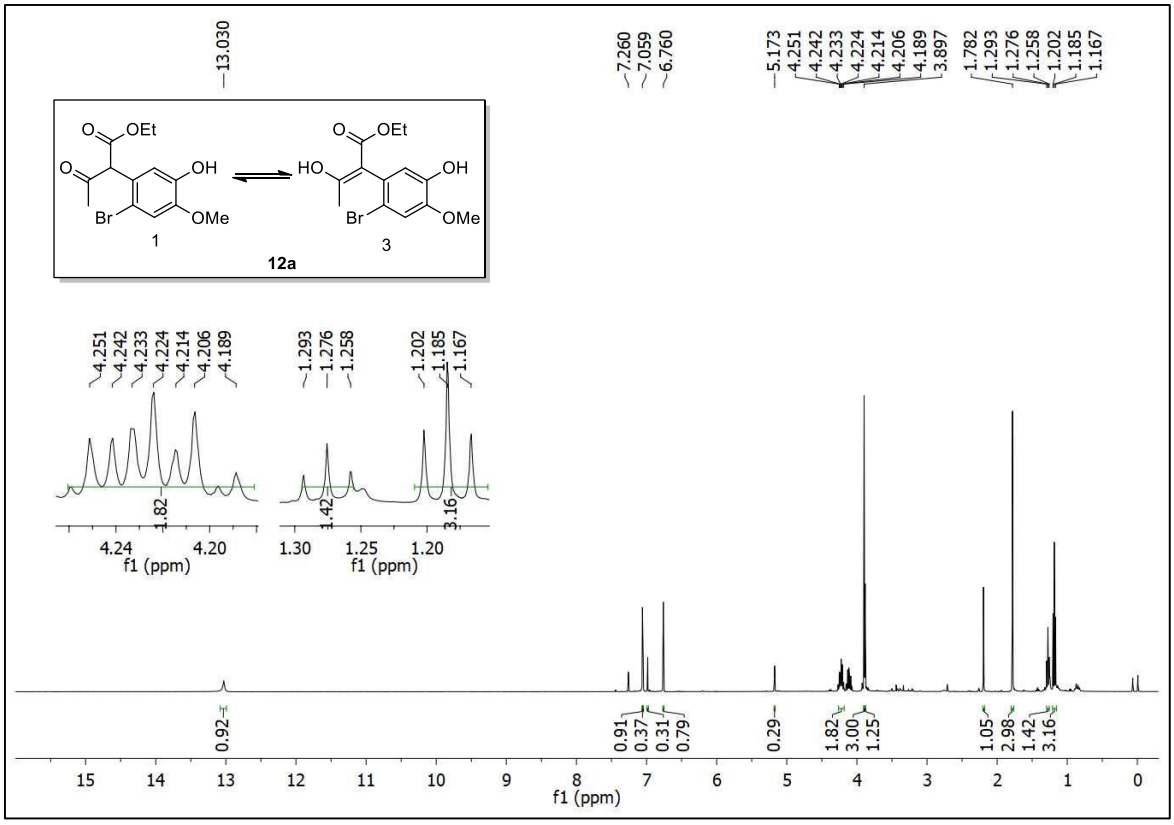


Fig S9: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **12a**.

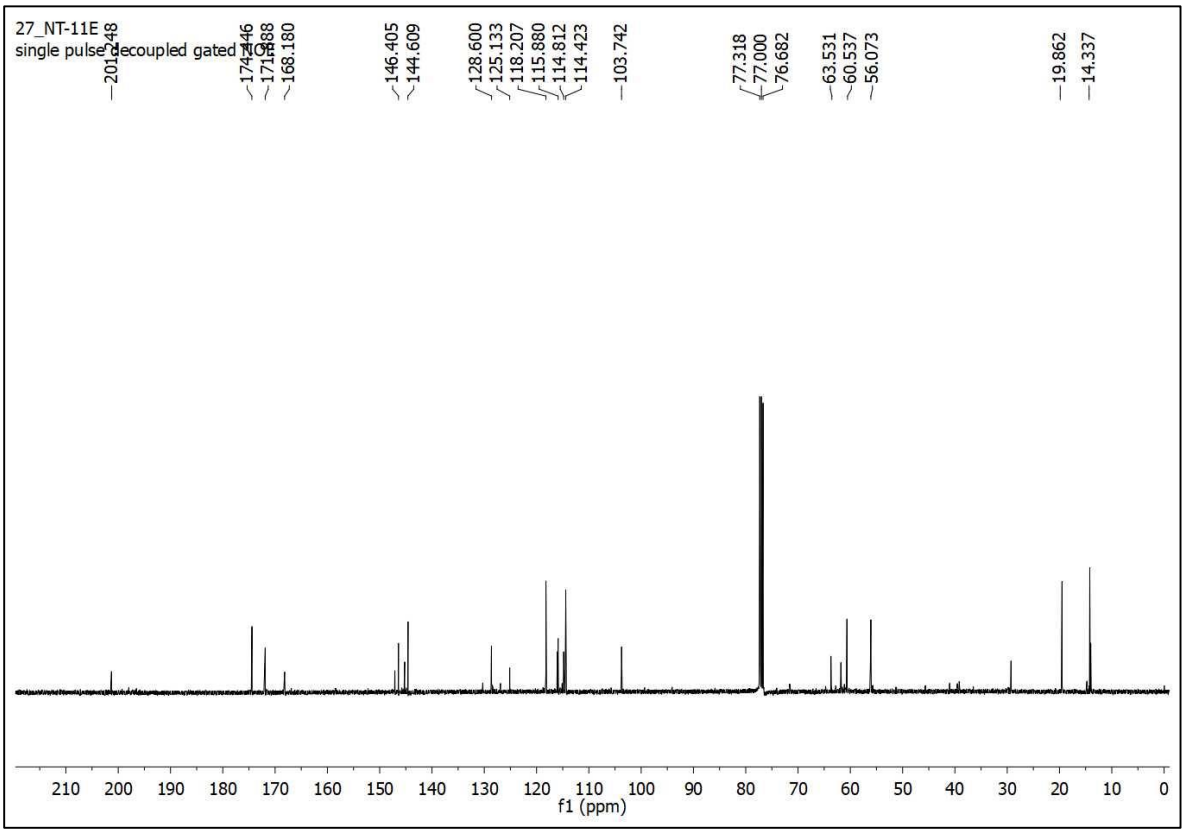


Fig S10: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **12a**.

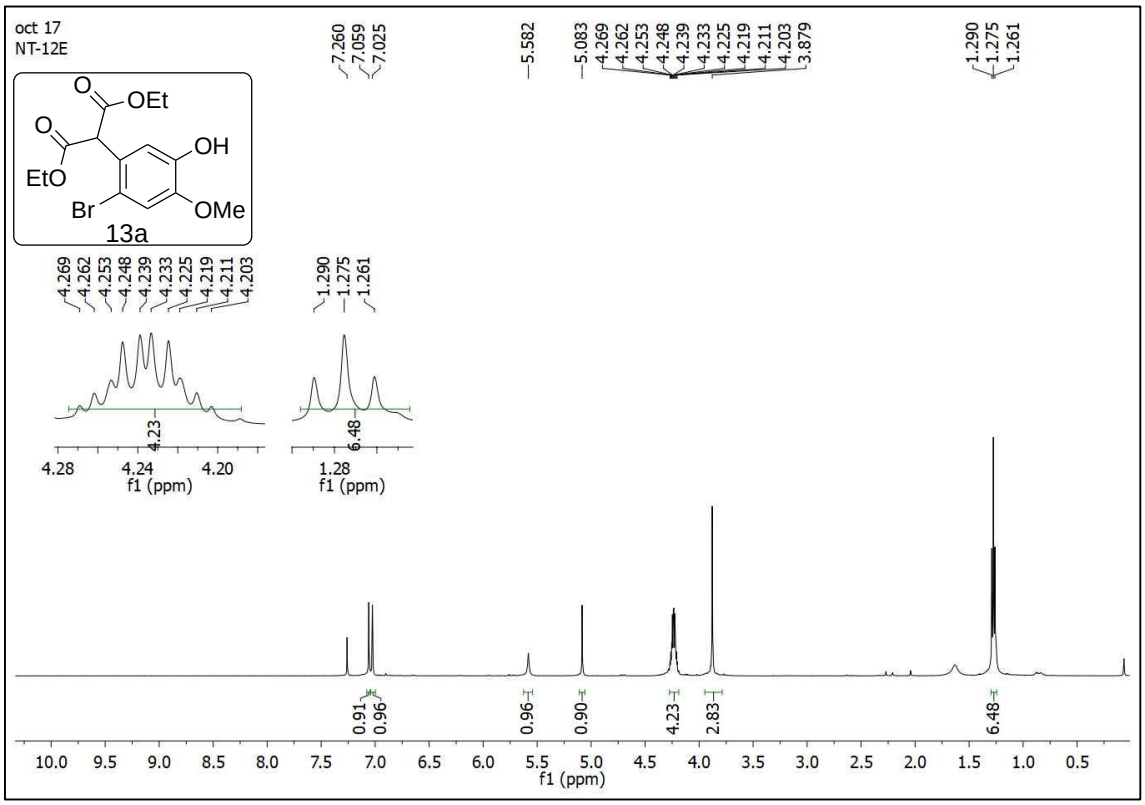


Fig S11: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **13a**.

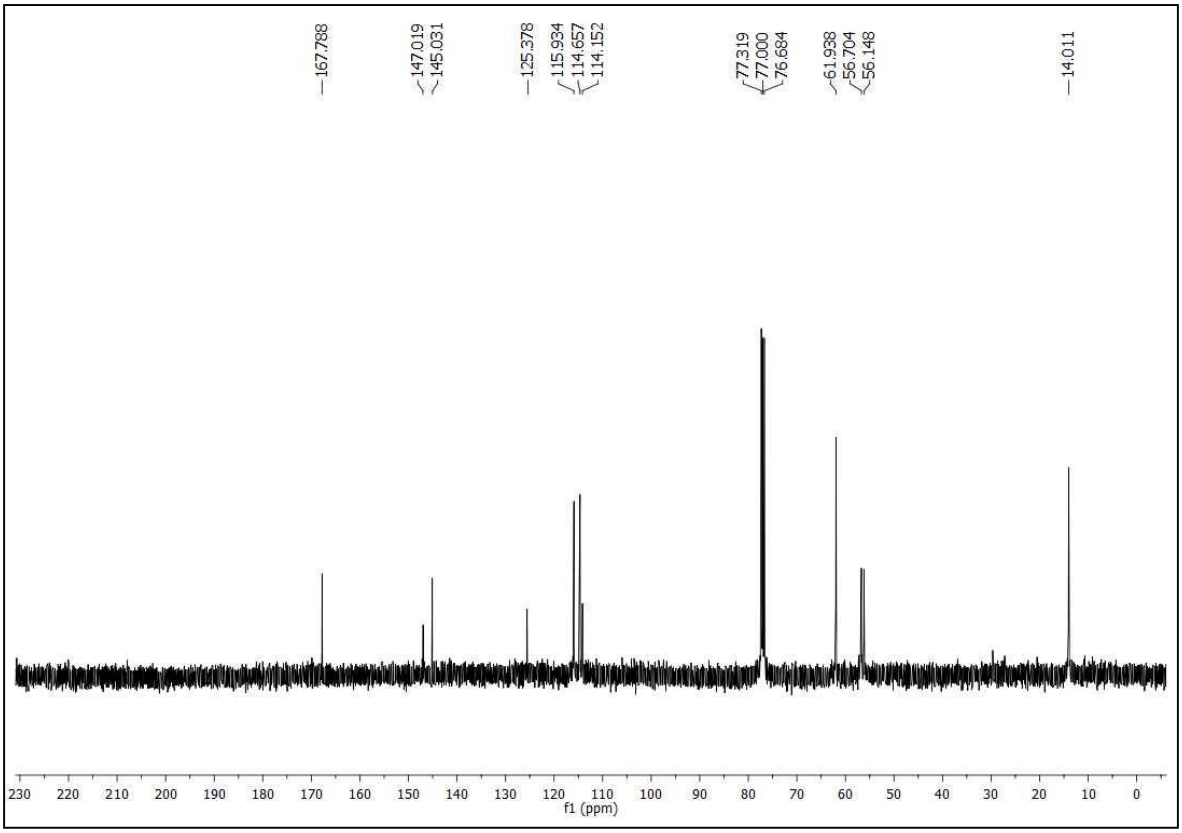


Fig S12: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **13a**.

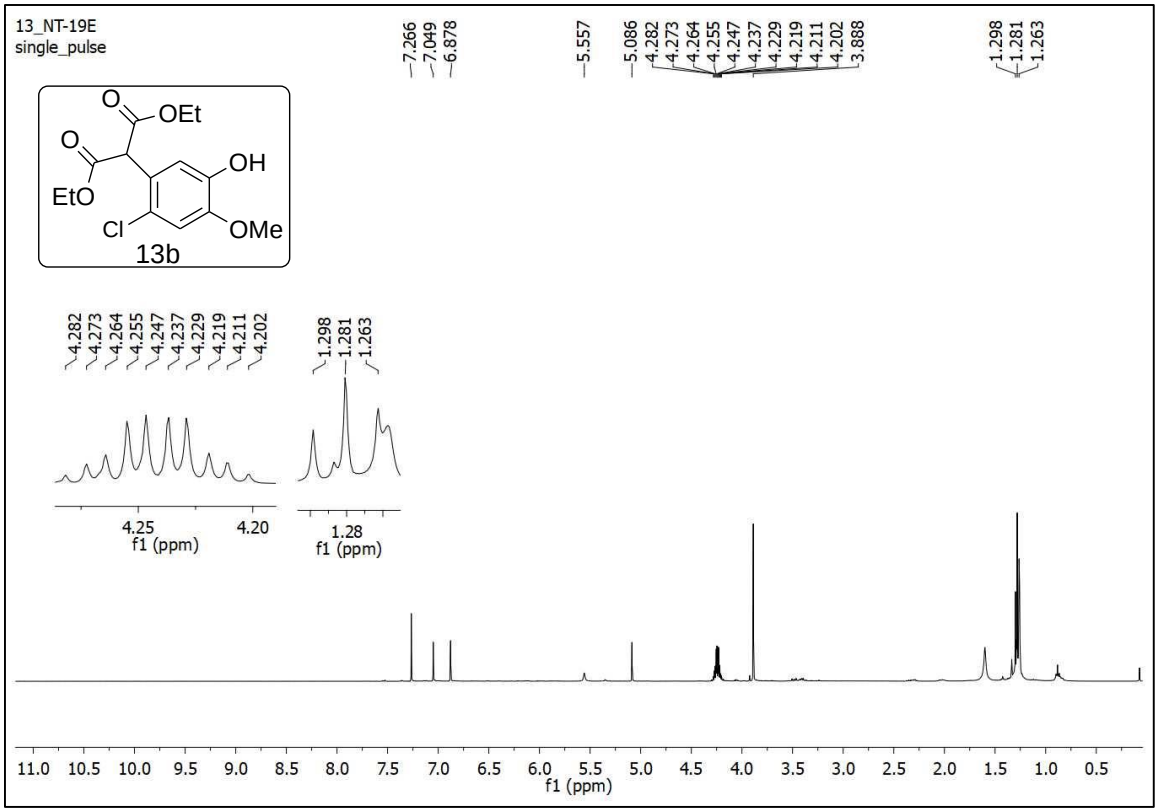


Fig S13: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **13b**.

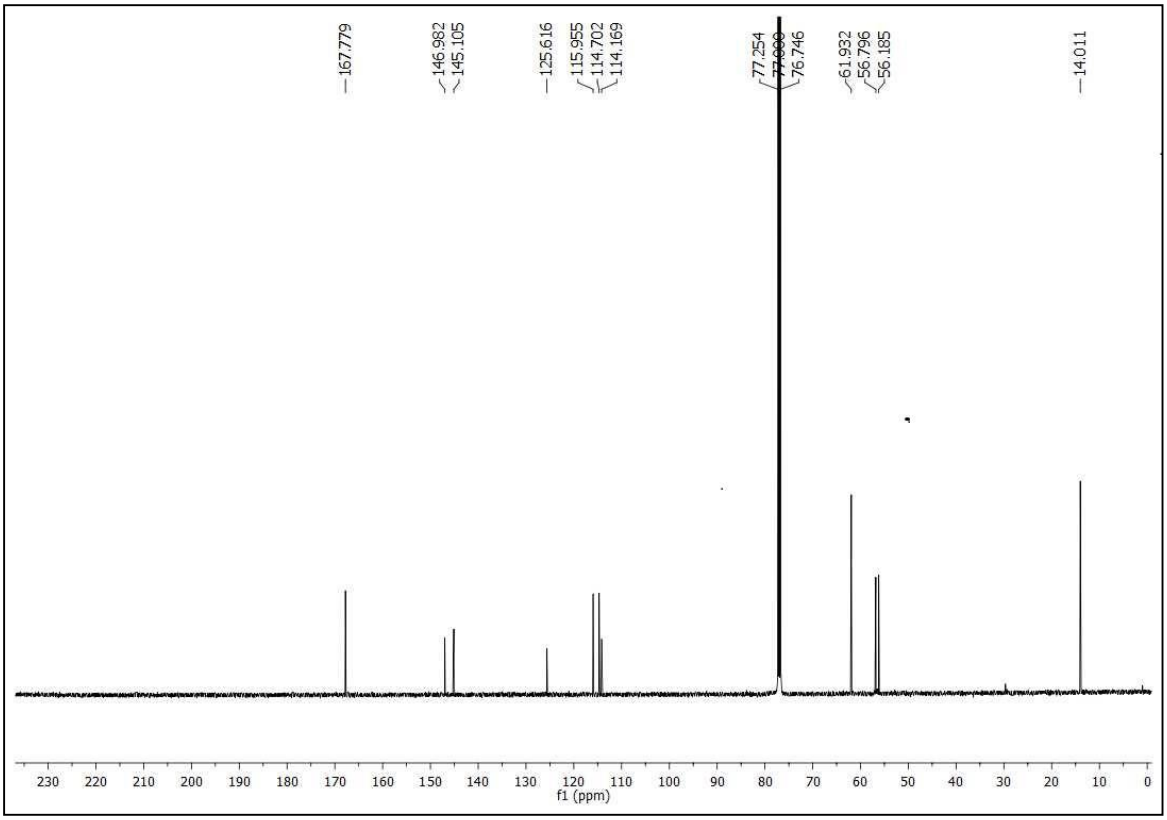


Fig S14: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **13b**.

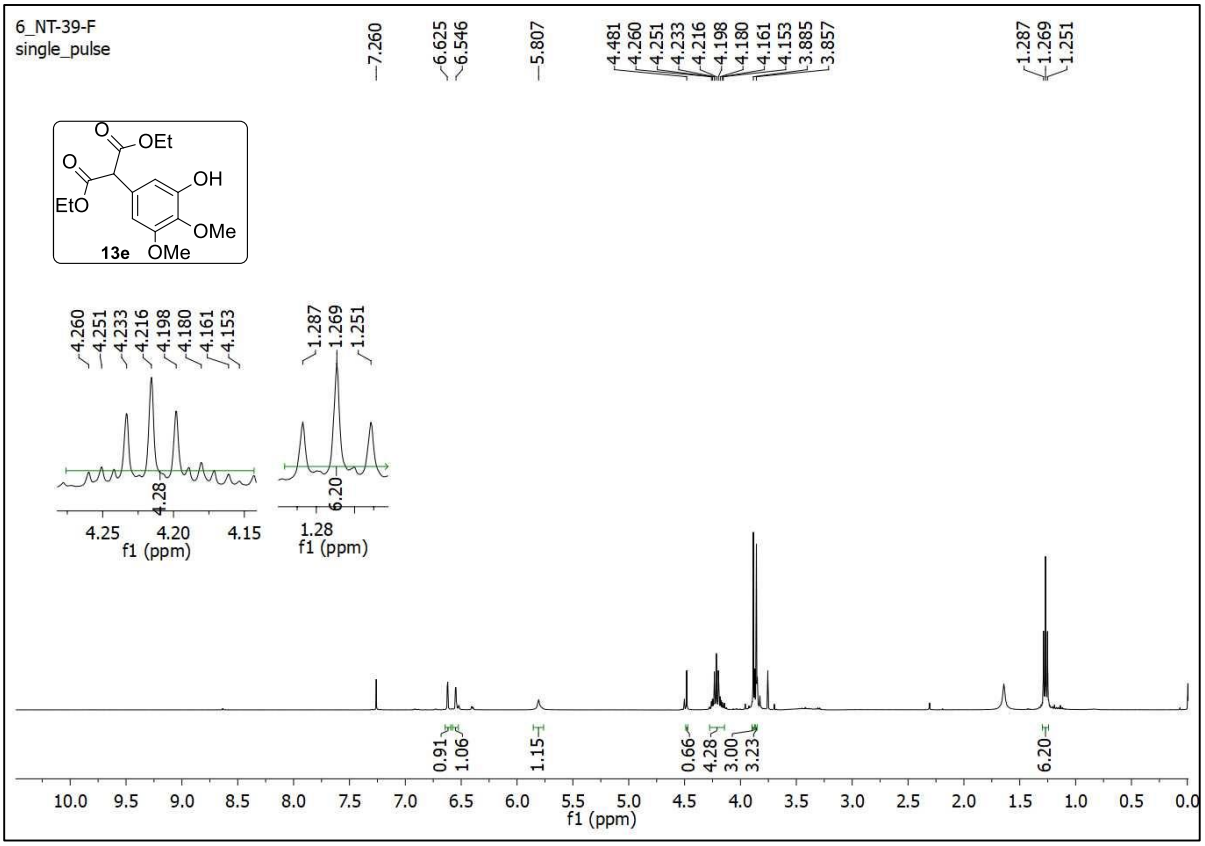


Fig S15: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **13e**.

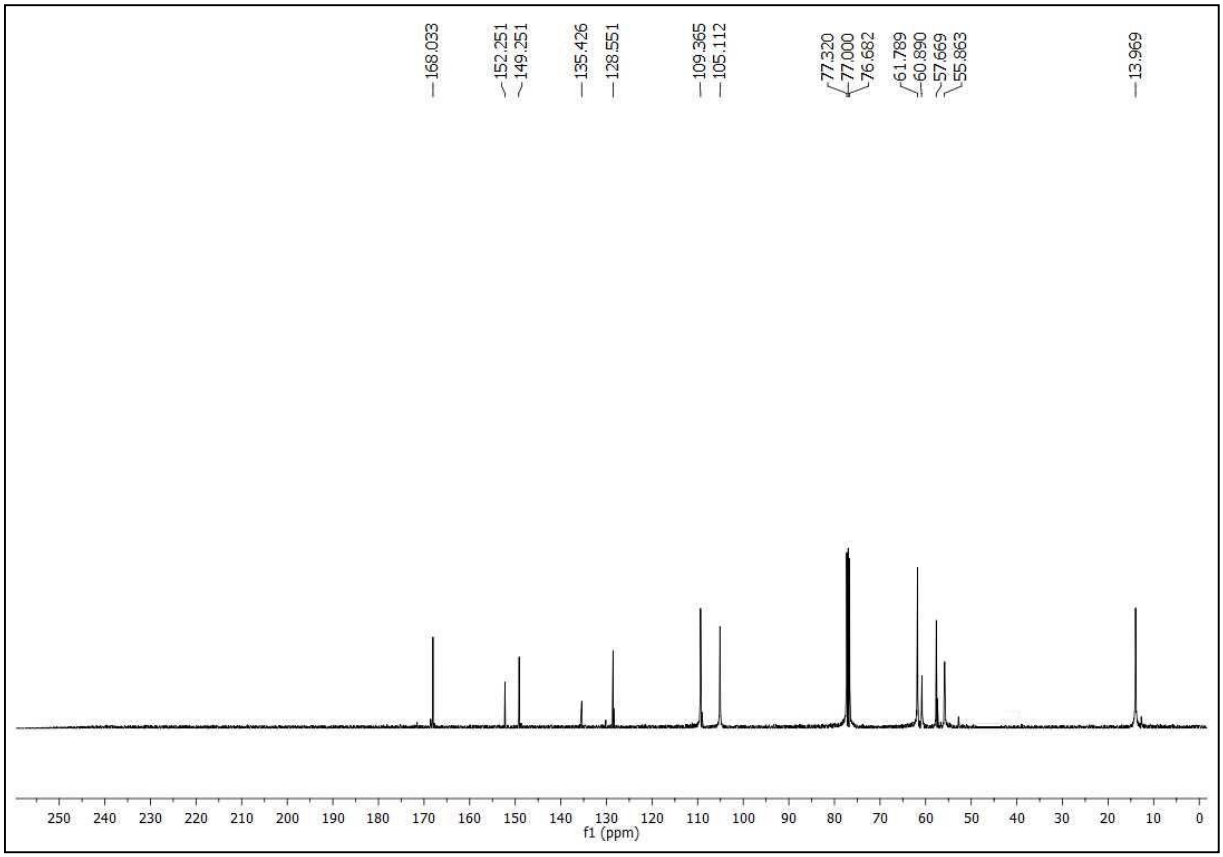


Fig S16: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **13e**.

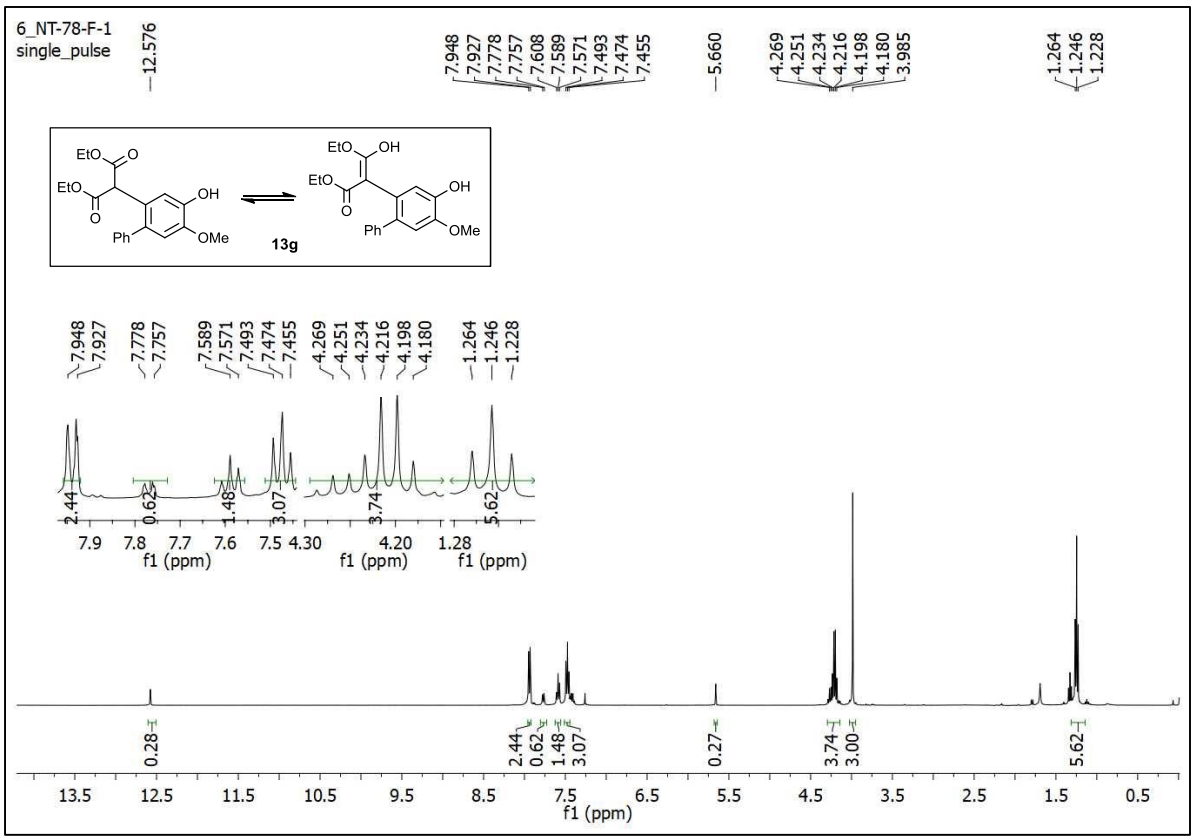


Fig S29: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **13g**

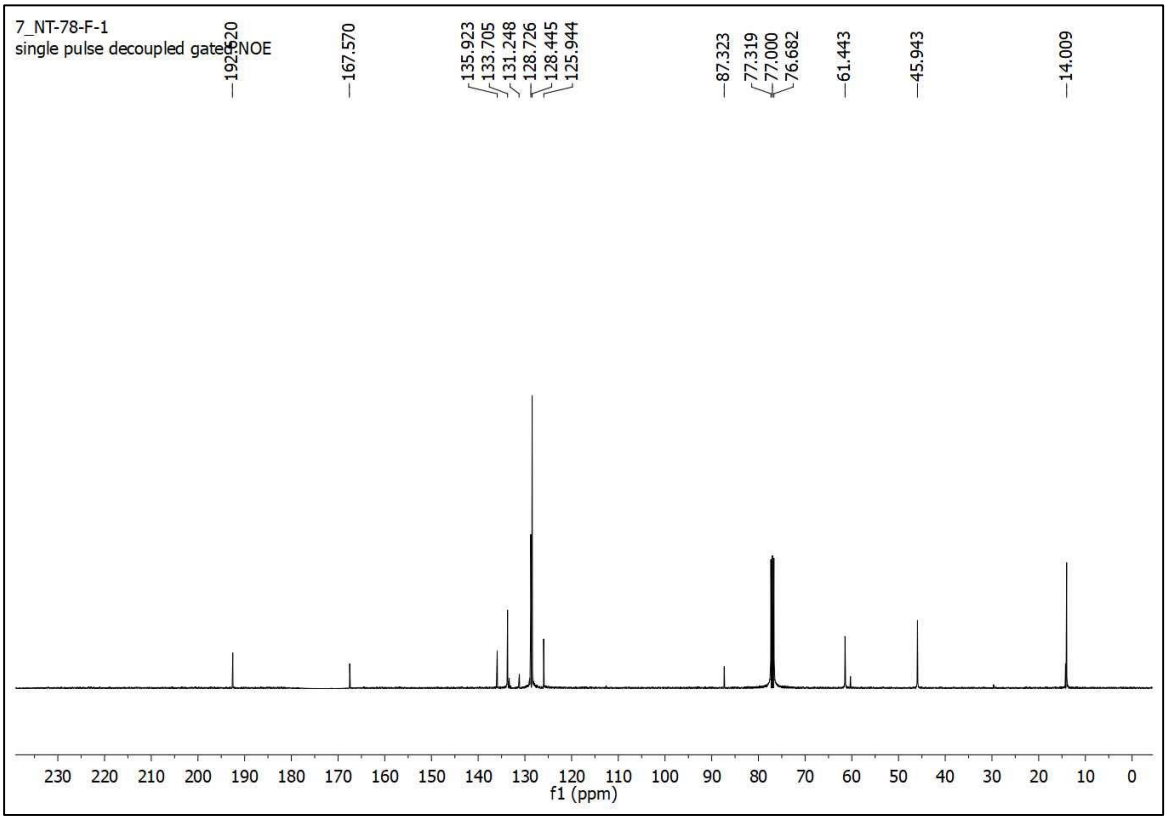


Fig S30: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **13g**.

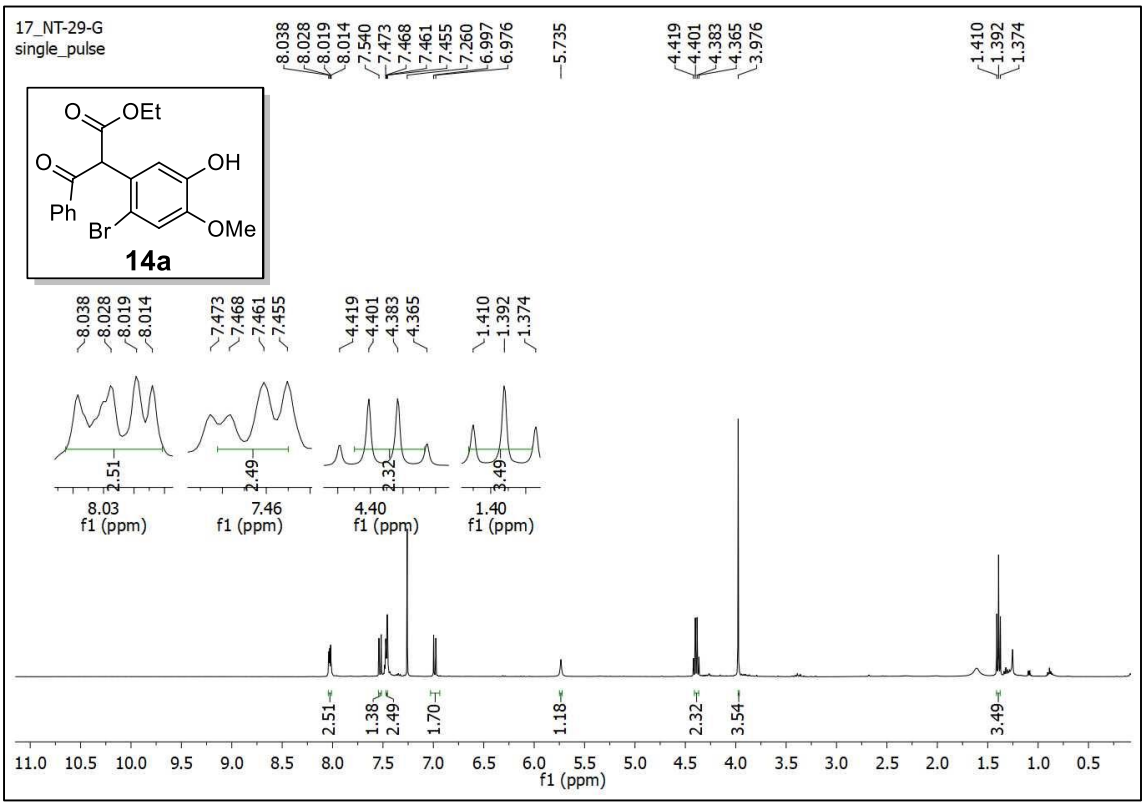


Fig S17: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **14a**.

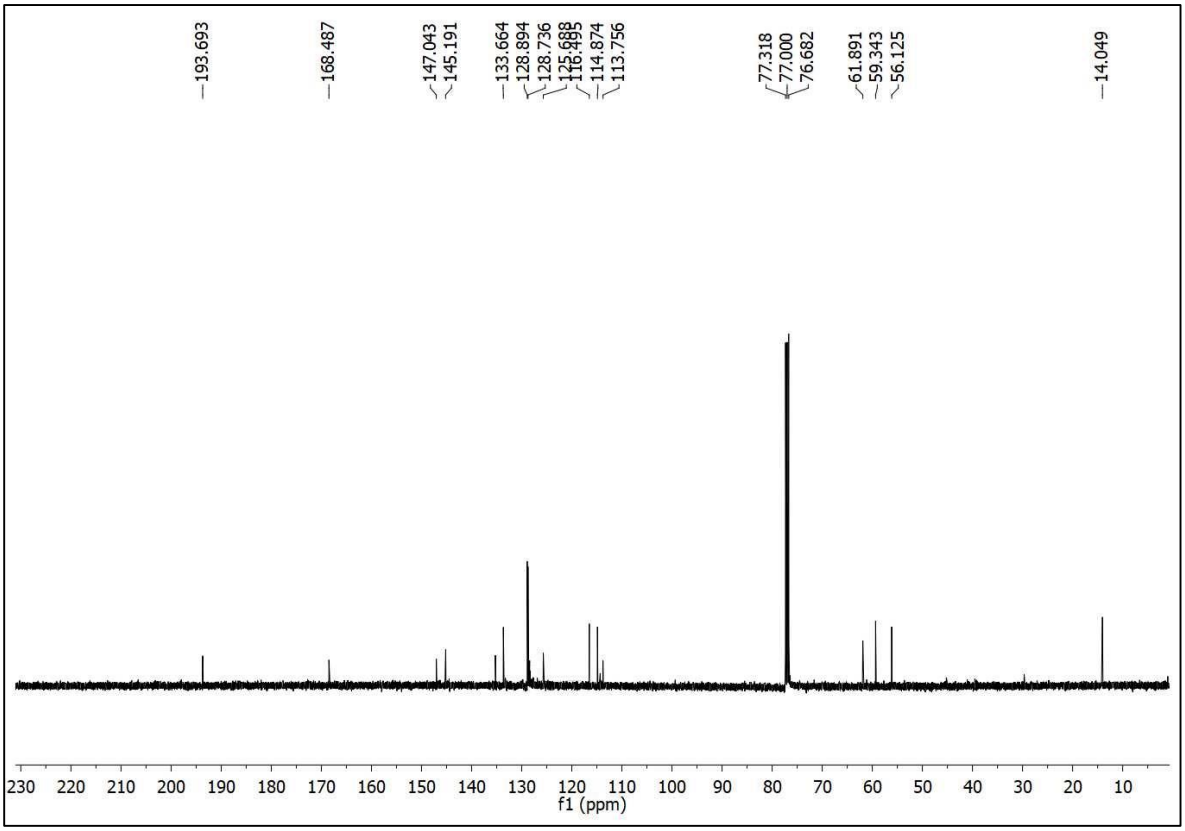


Fig S18: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **14a**.

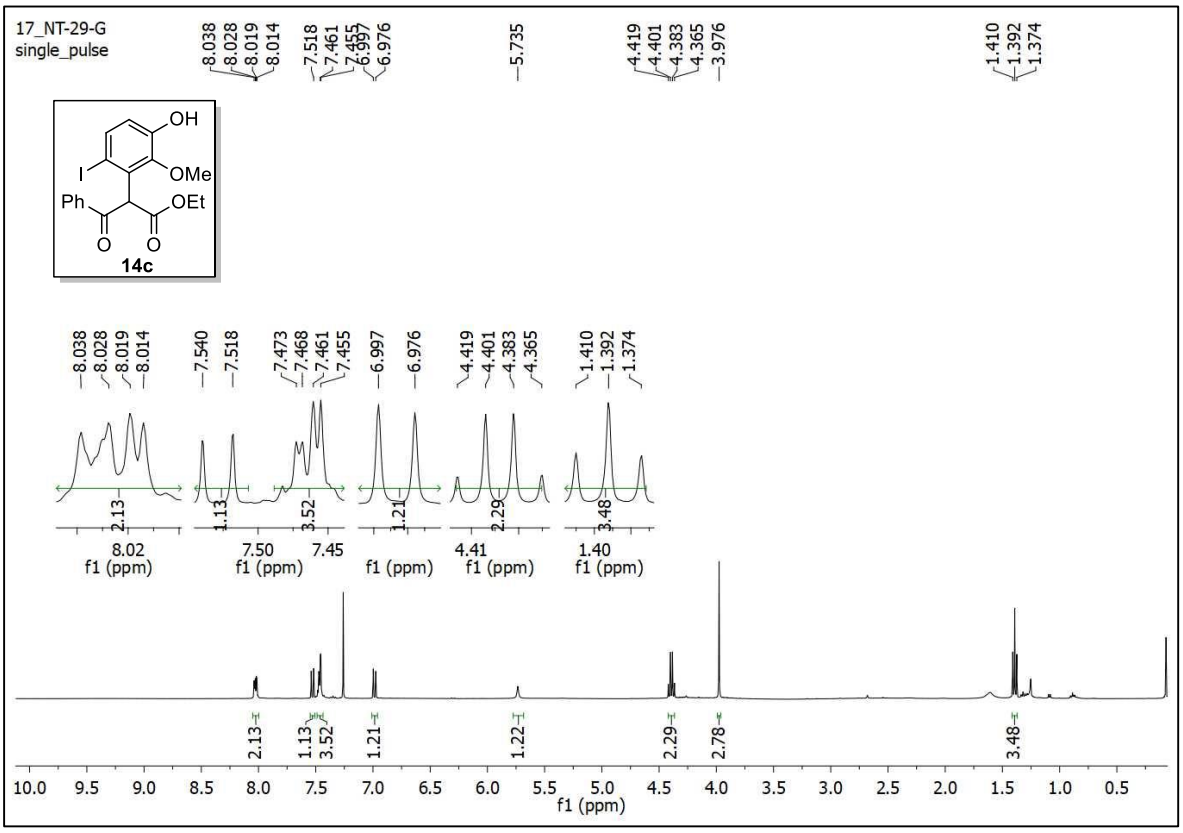


Fig S19: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **14c**.

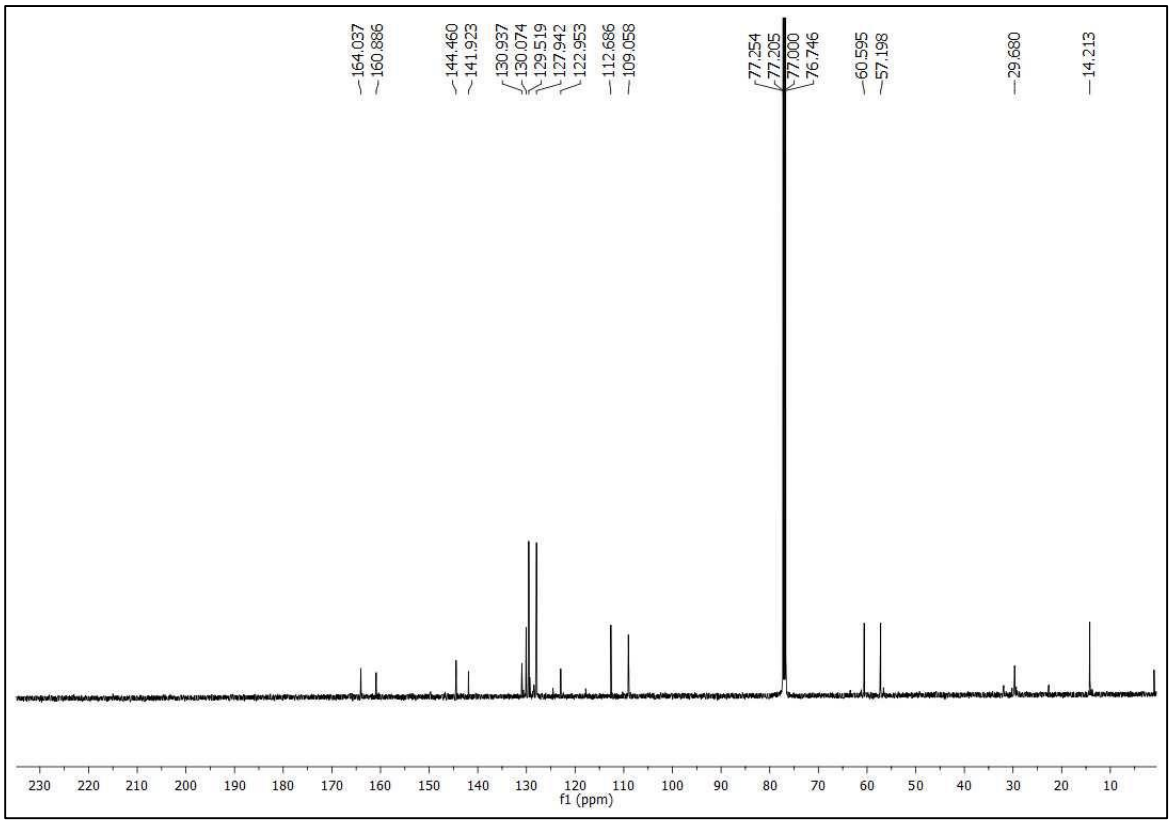


Fig S20: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **14c**.

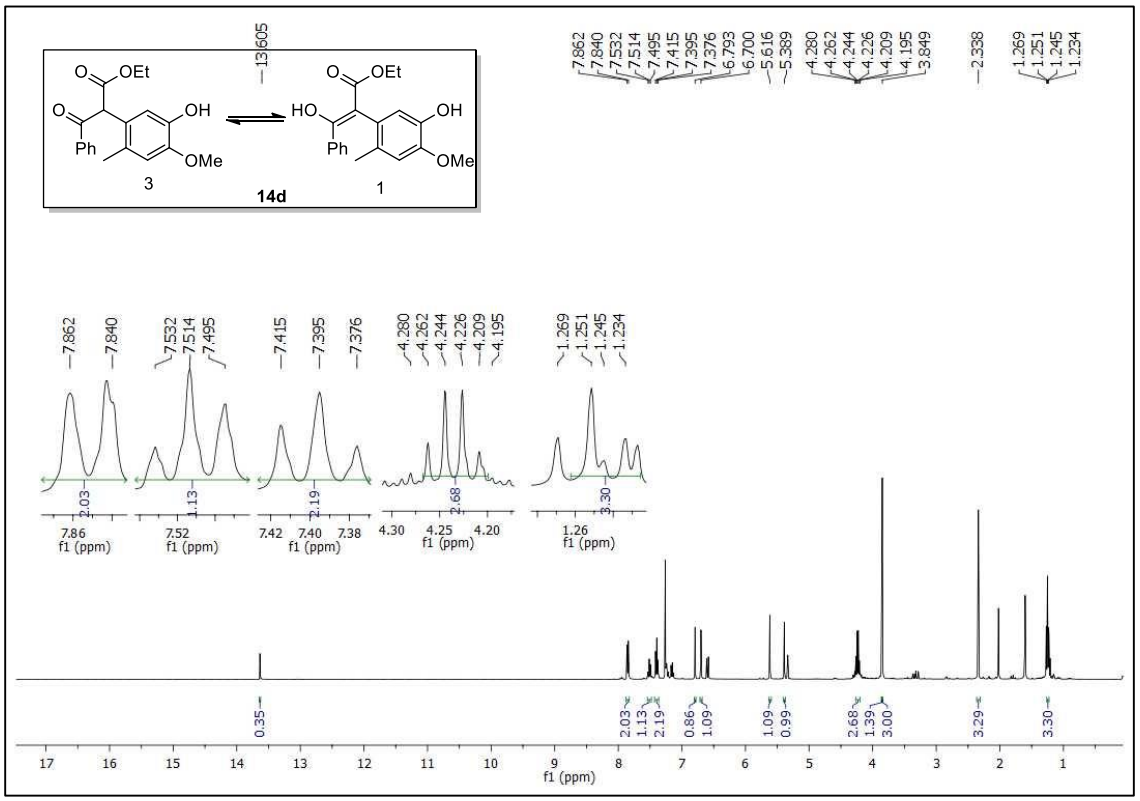


Fig S21: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **14d**.

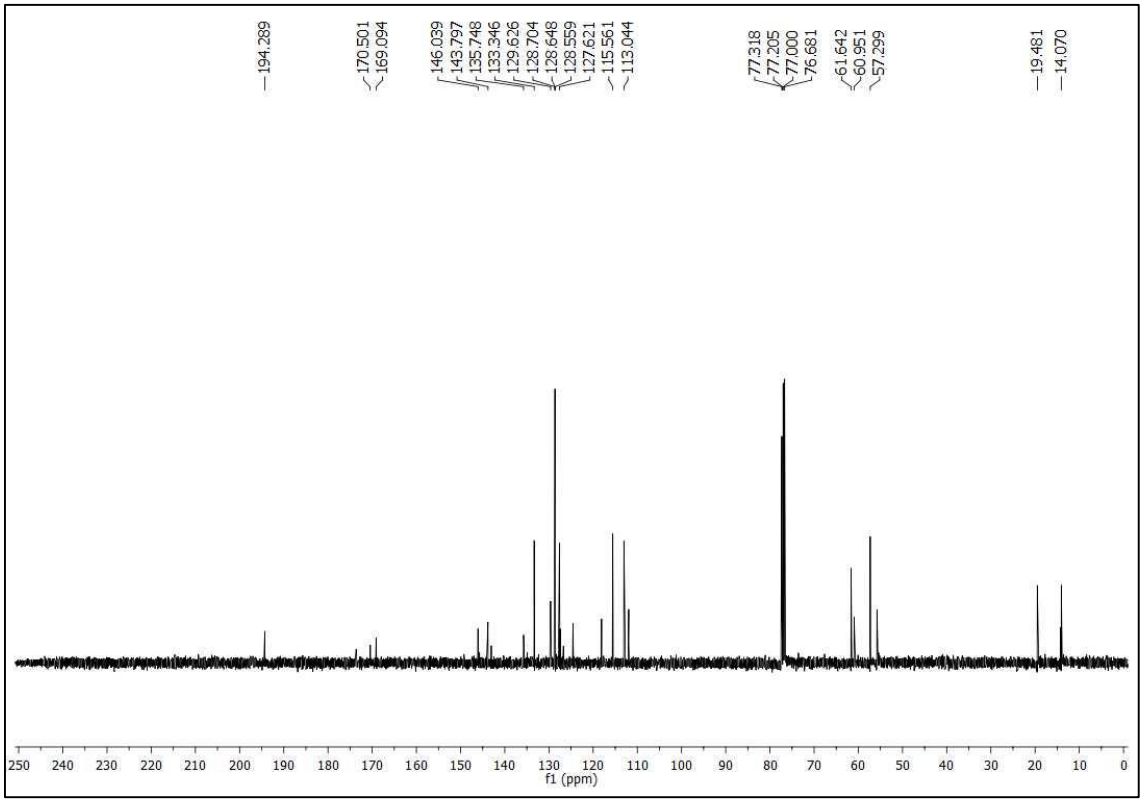


Fig S22: ^{13}C NMR (125MHz, $CDCl_3$) spectrum of **14d**.

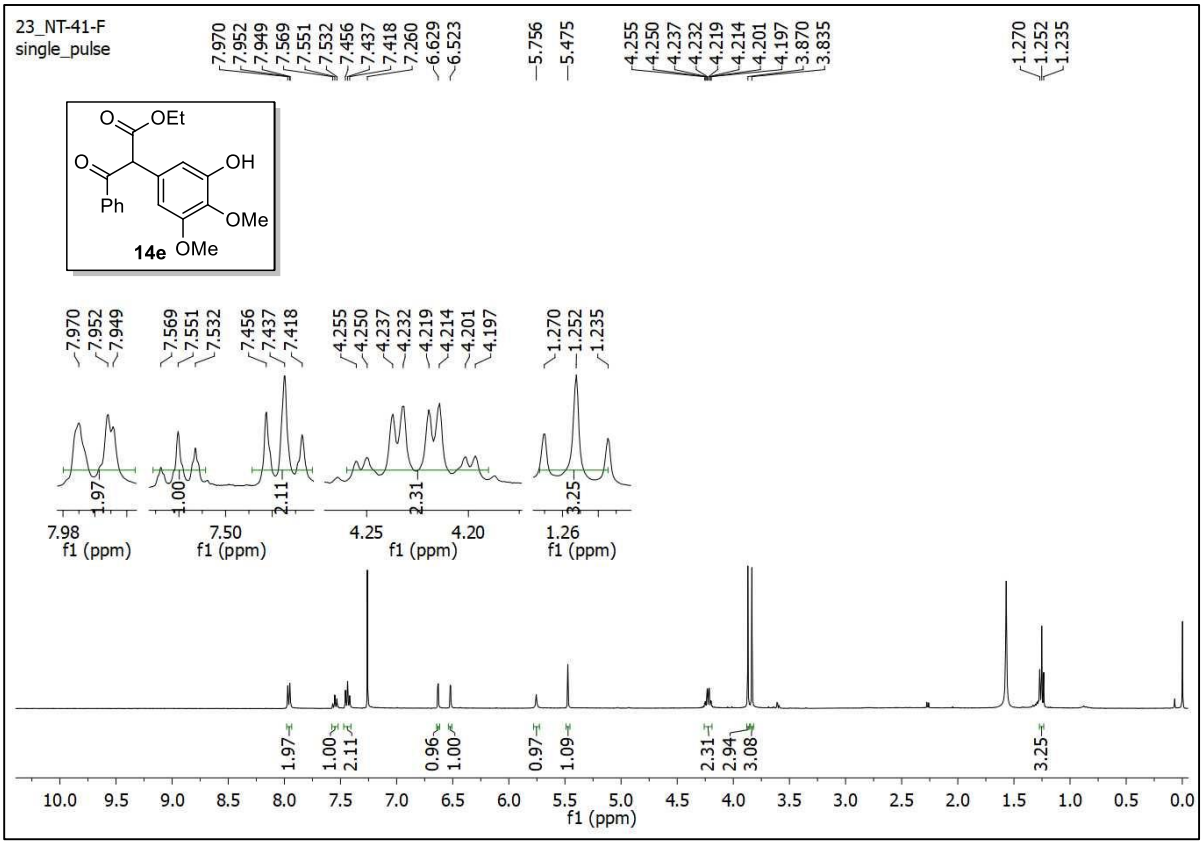


Fig S23: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **14e**.

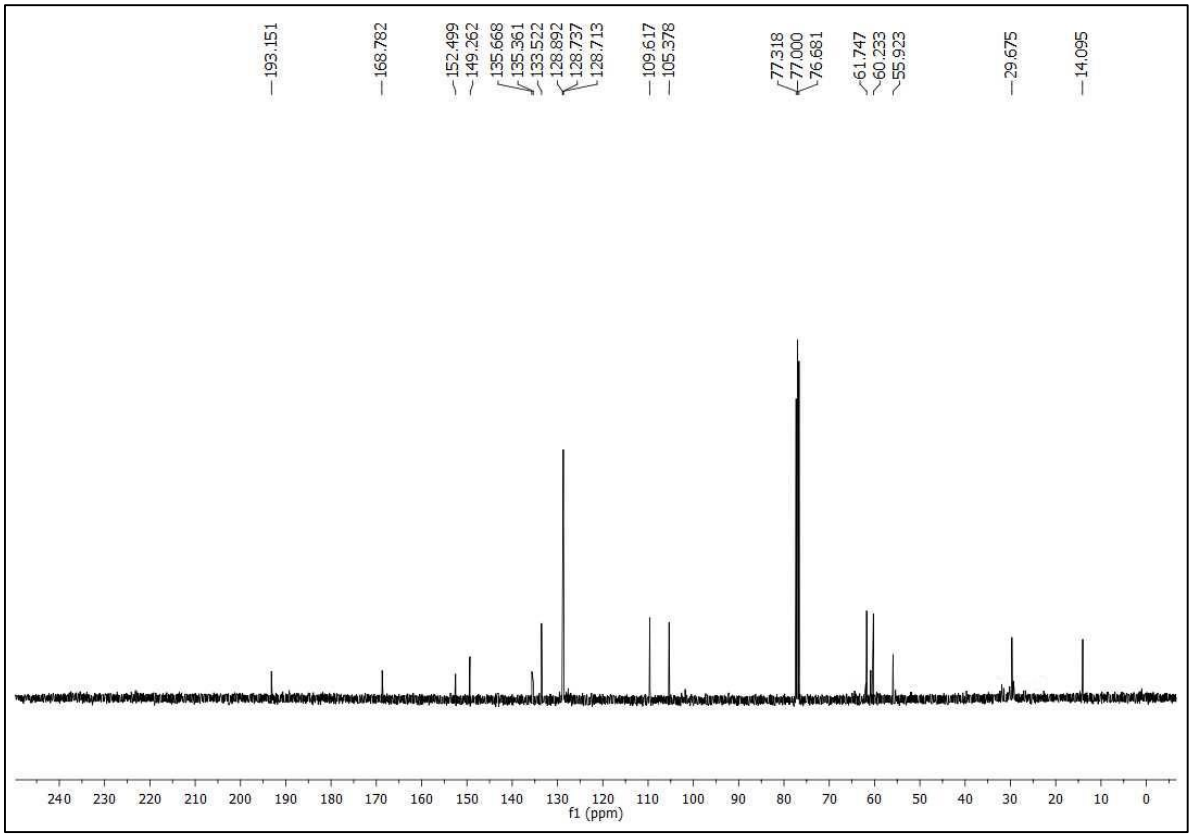


Fig S24: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **14e**

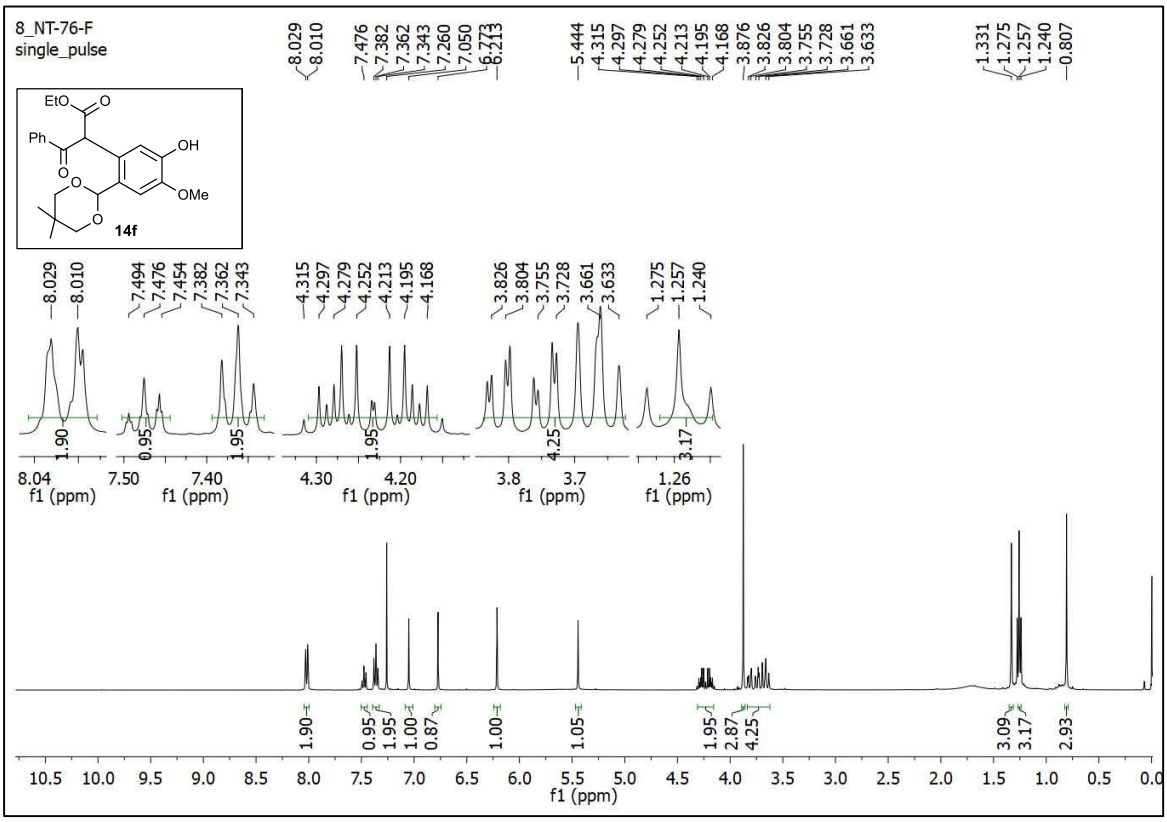


Fig S27: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **14f**.

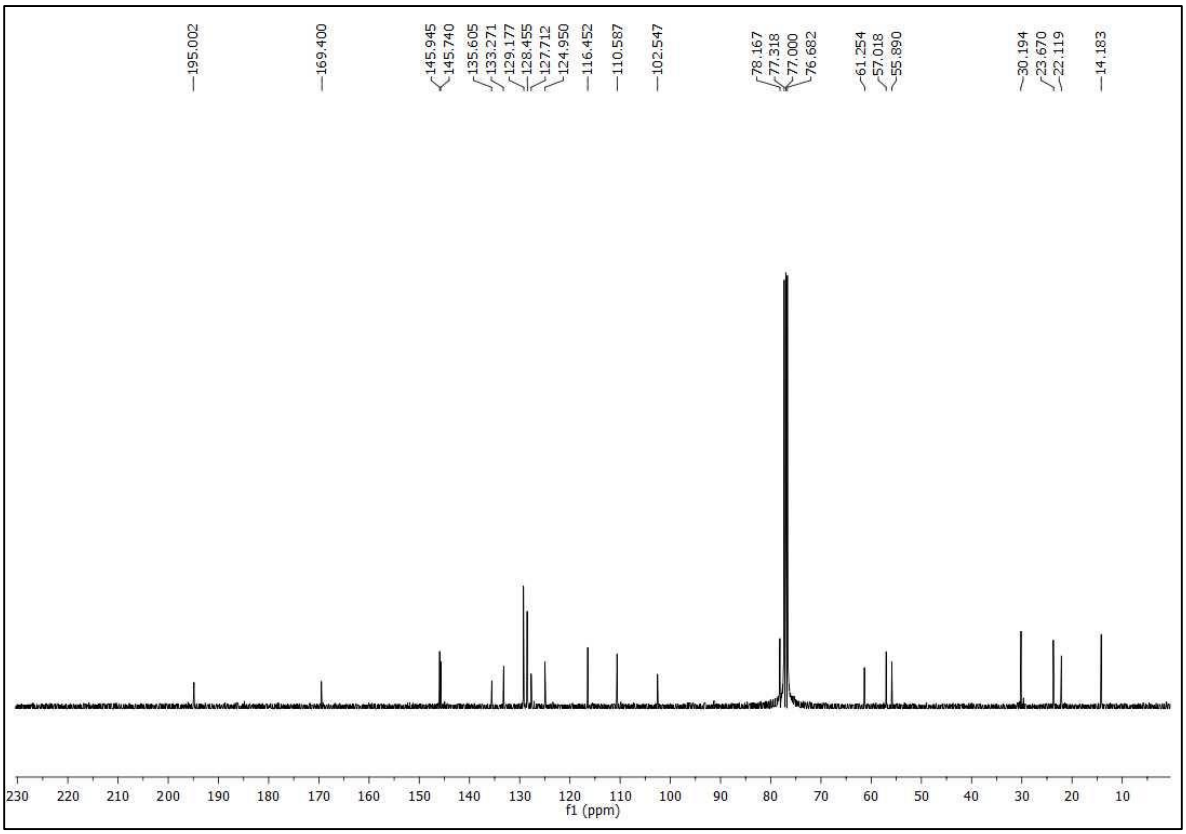


Fig S28: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **14f**.

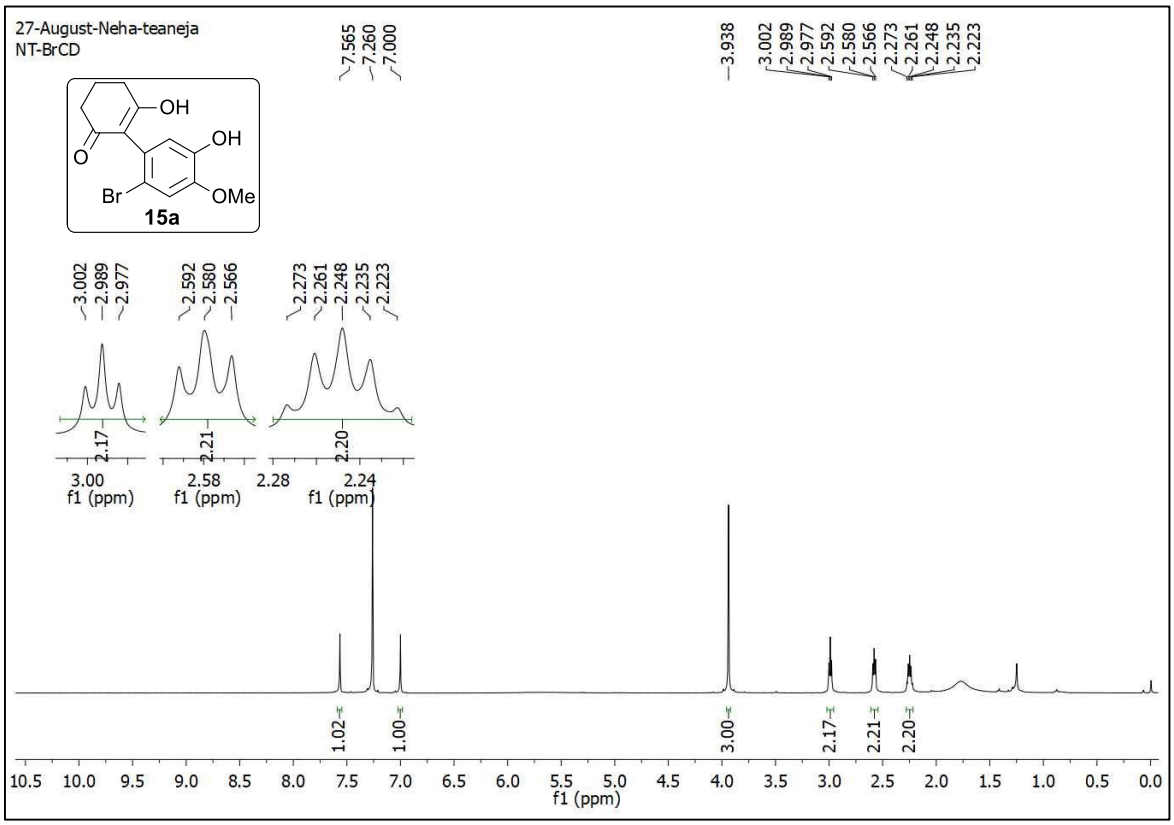


Fig S31: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **15a.**

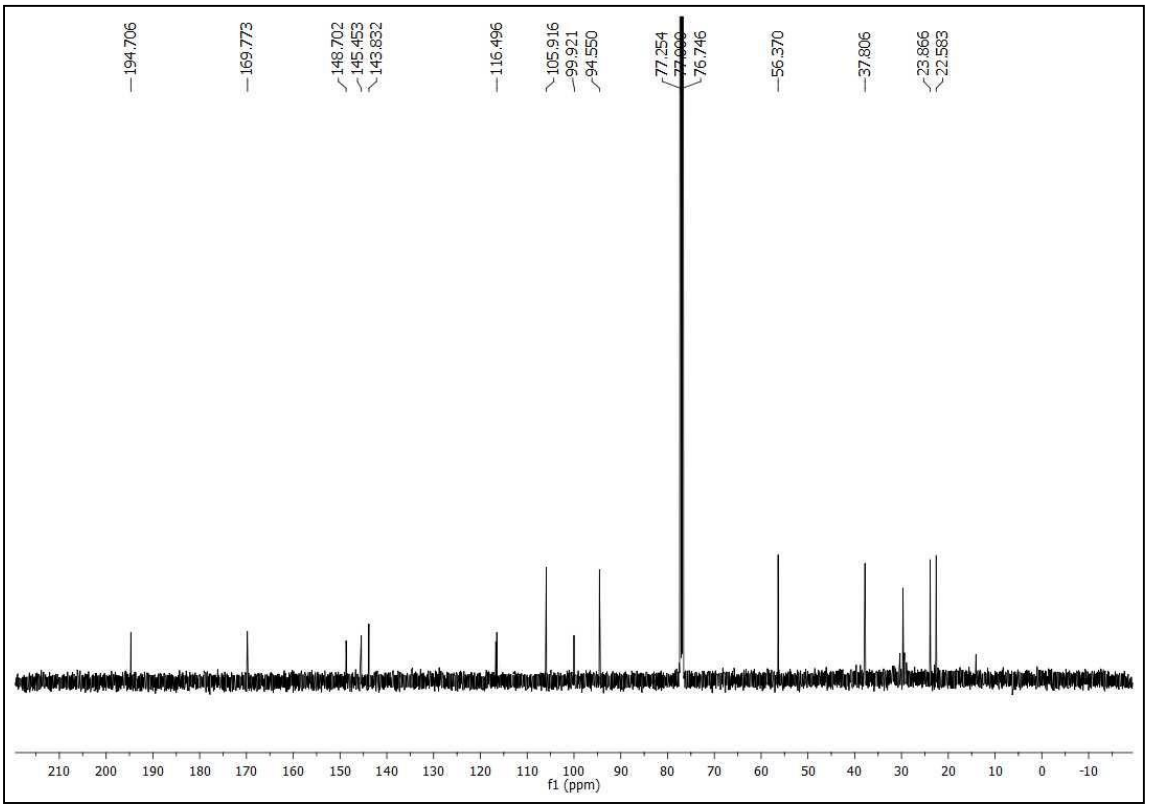


Fig S32: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **15a.**

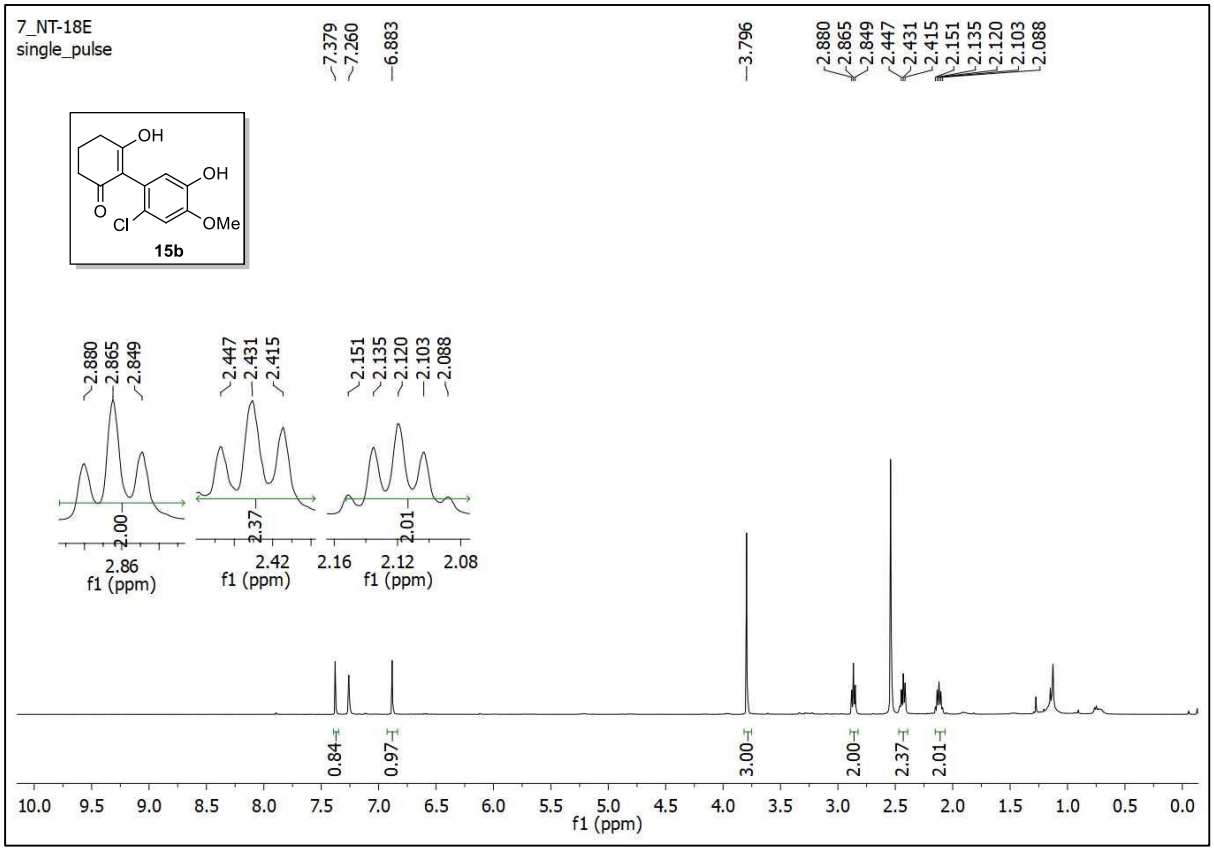


Fig S33: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **15b**.

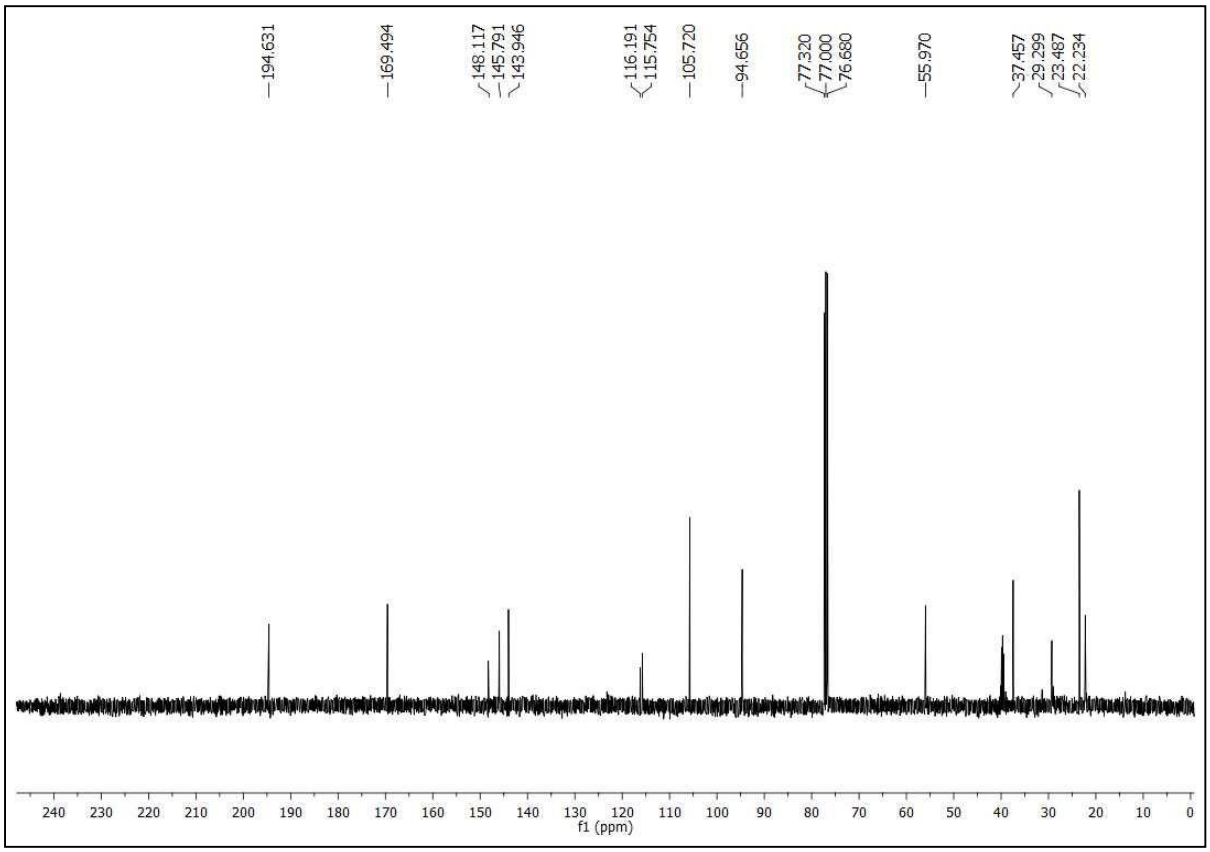


Fig S34: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **15b**.

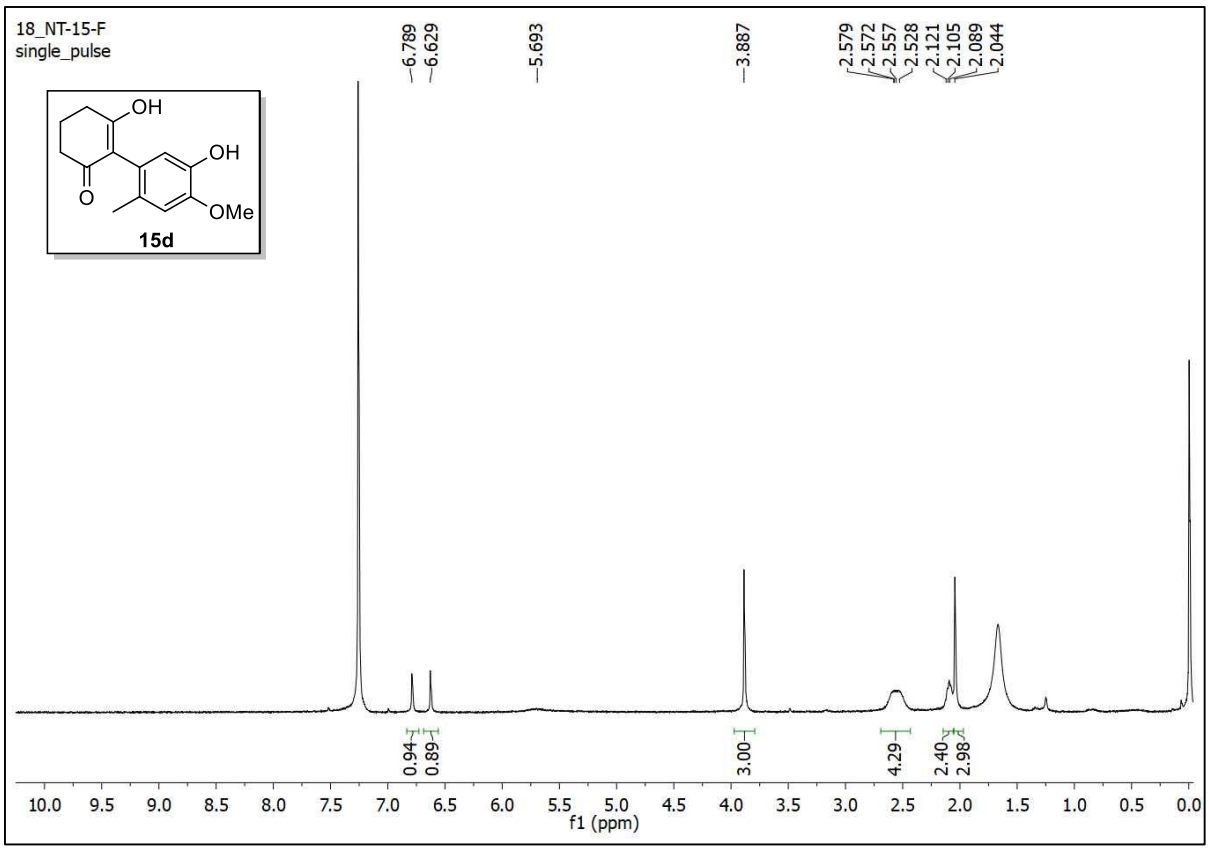


Fig S35: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **15d**.

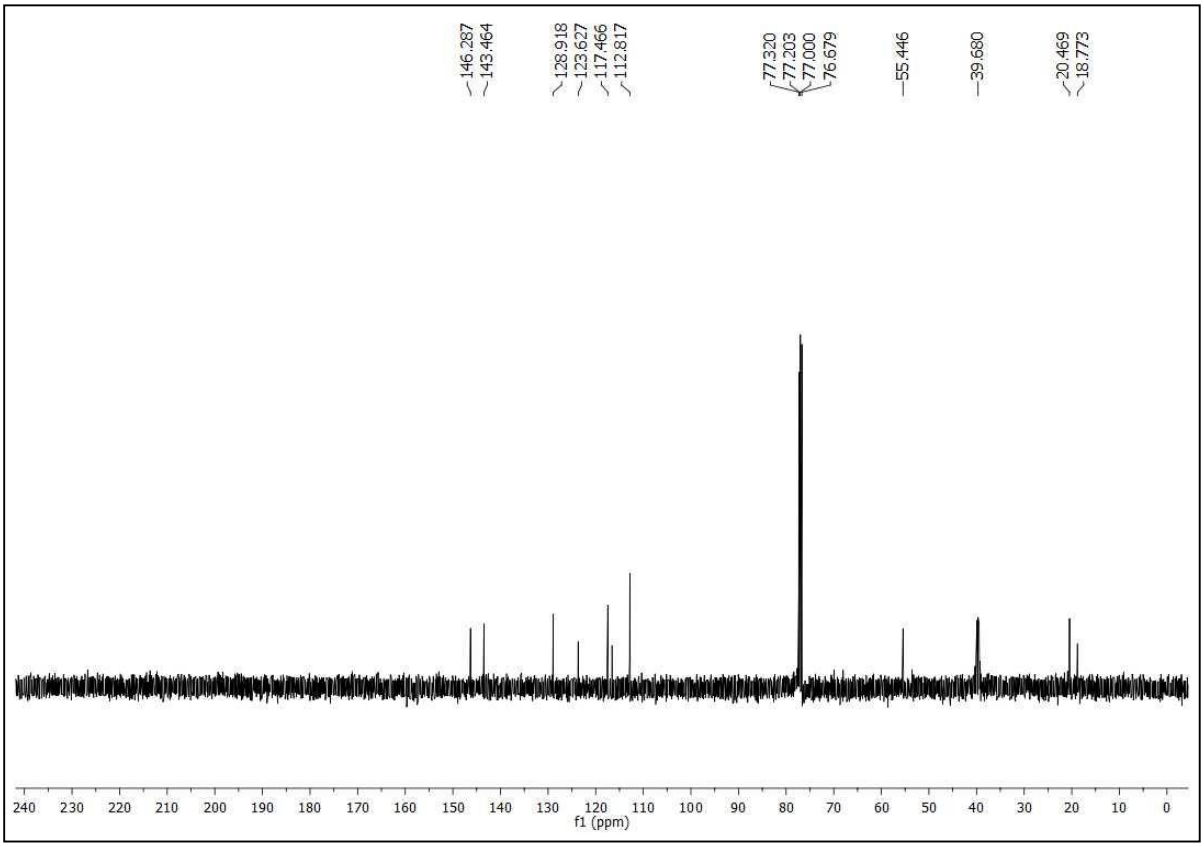


Fig S36: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **15d**.

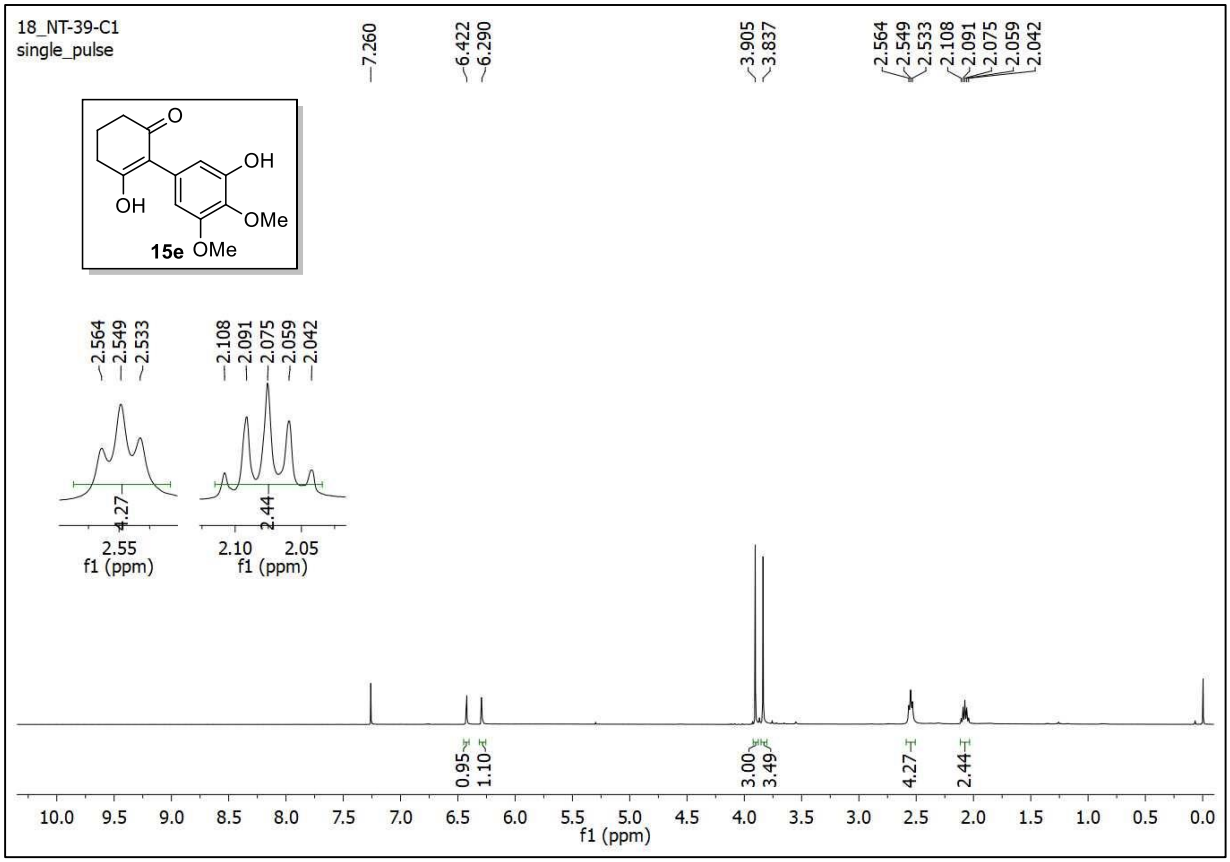


Fig S37: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **15e.**

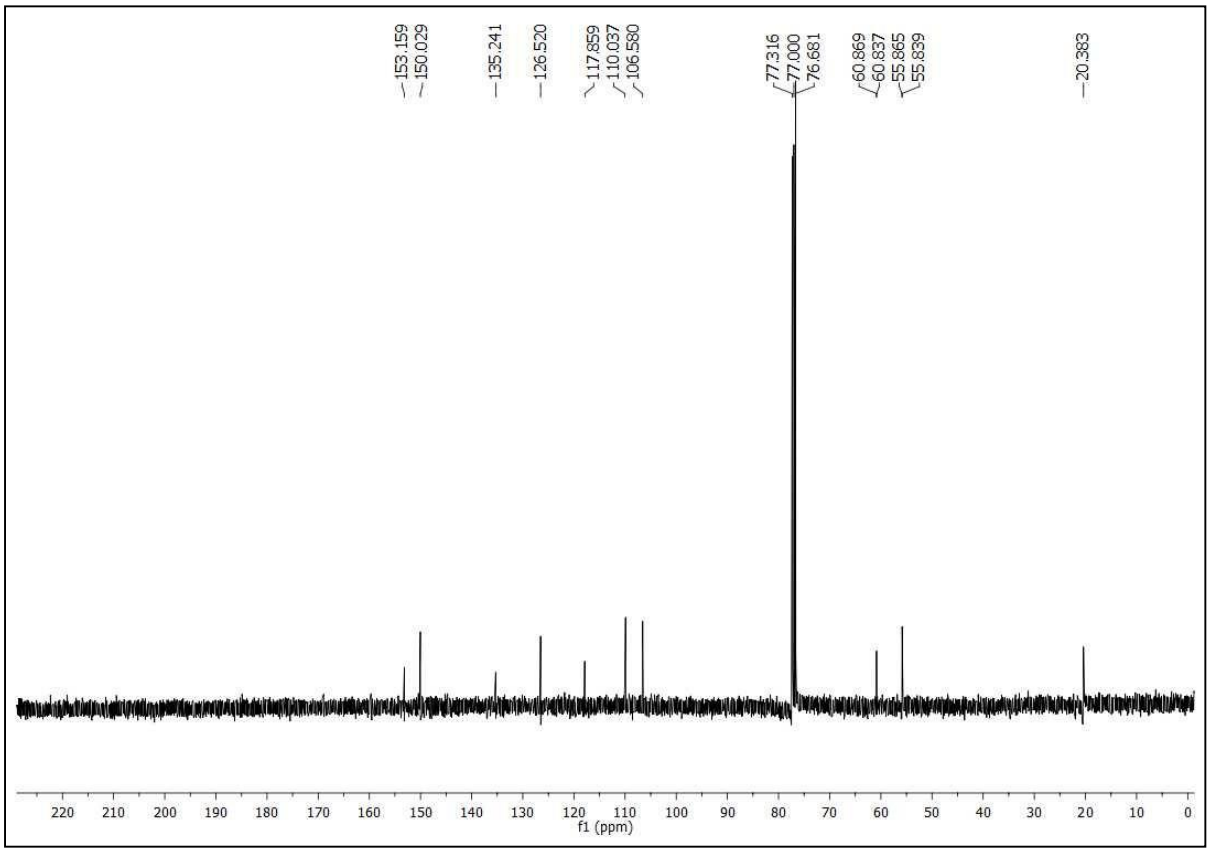


Fig S38: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **15e.**

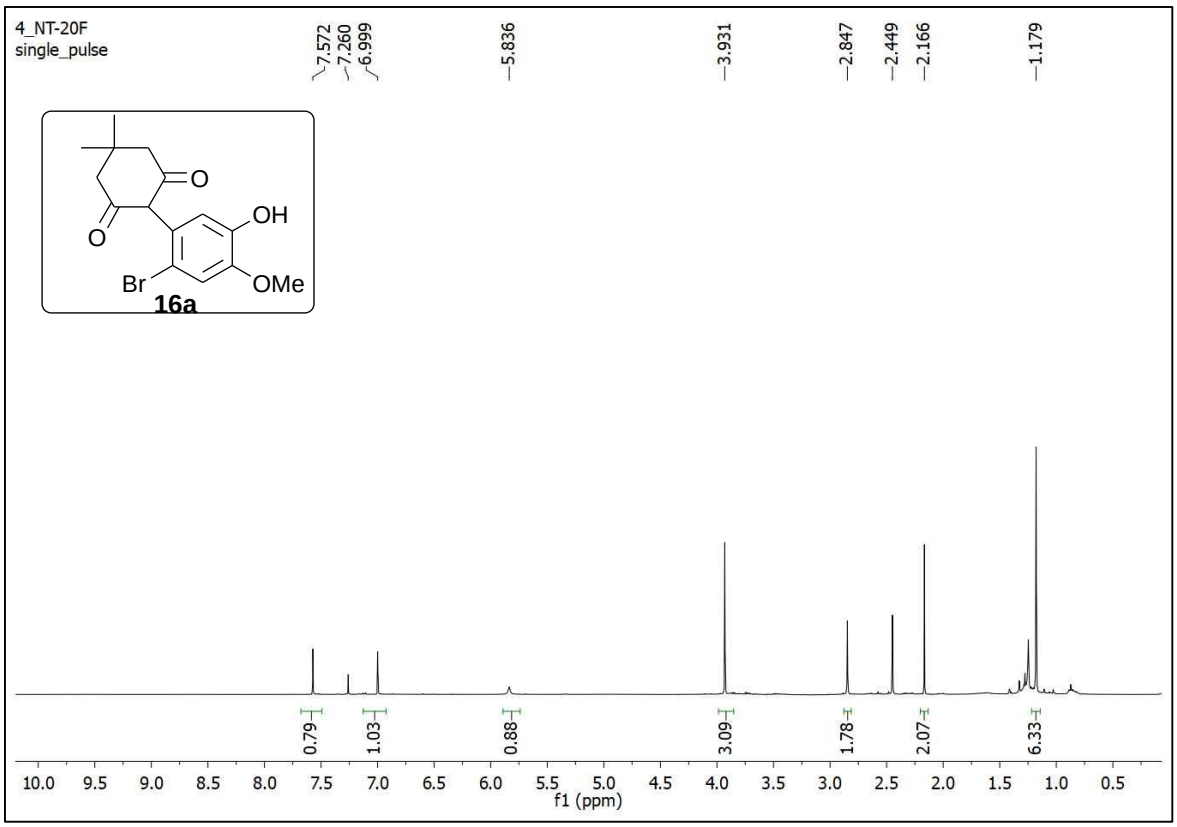


Fig S39: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **16a**.

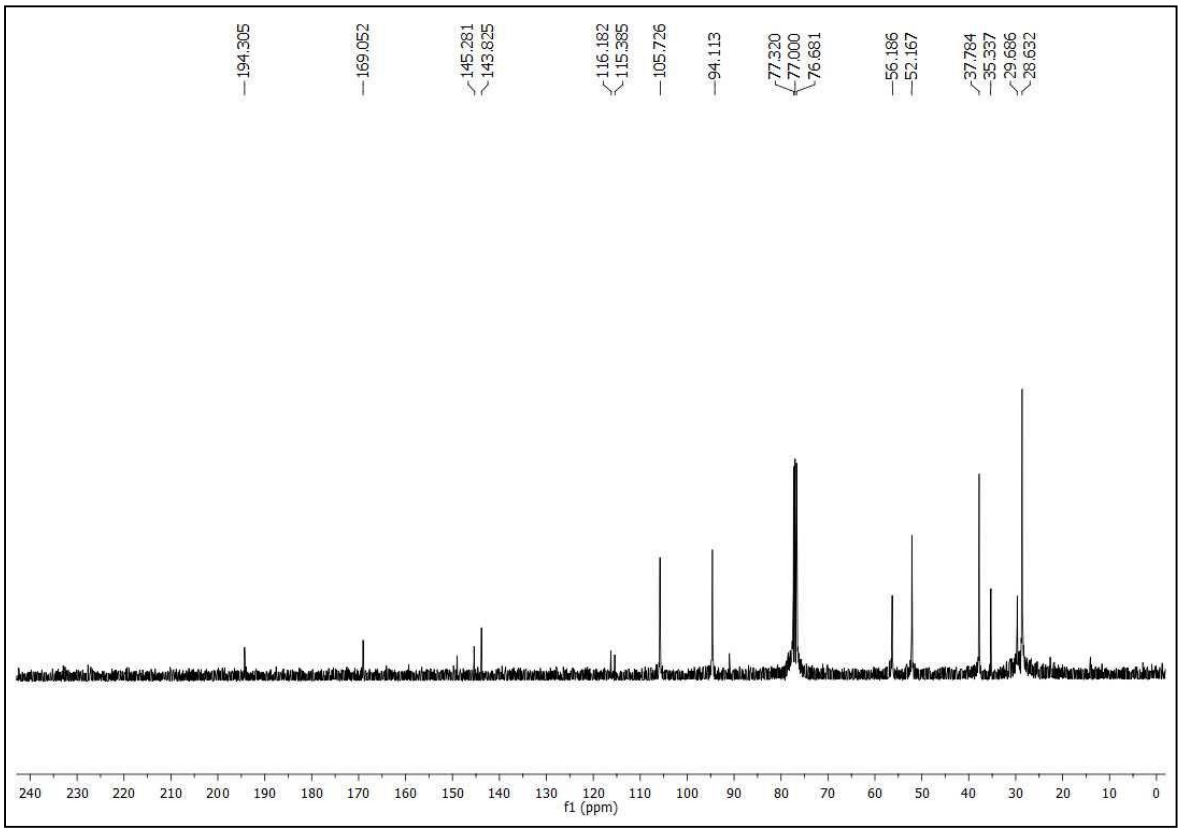


Fig S40: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **16a**.

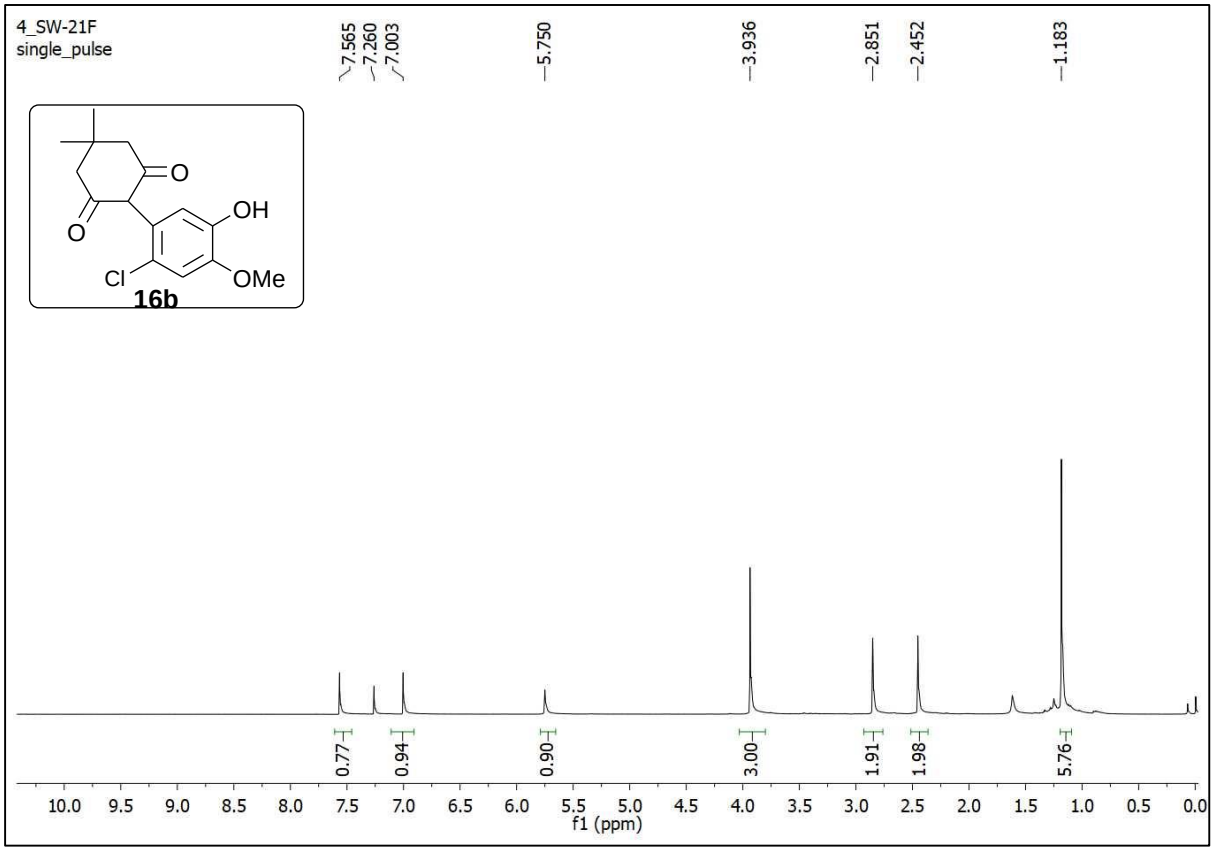


Fig S41: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **16b**.

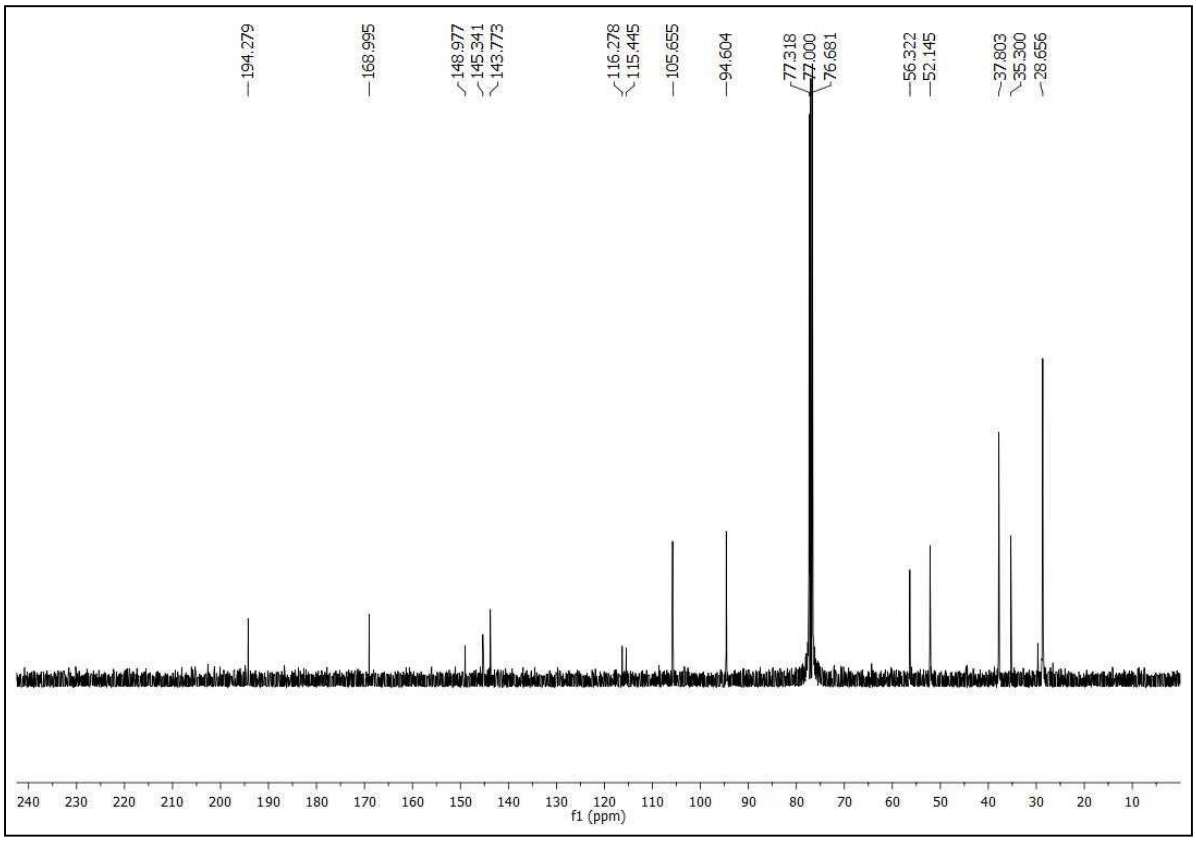


Fig S42: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **16b**.

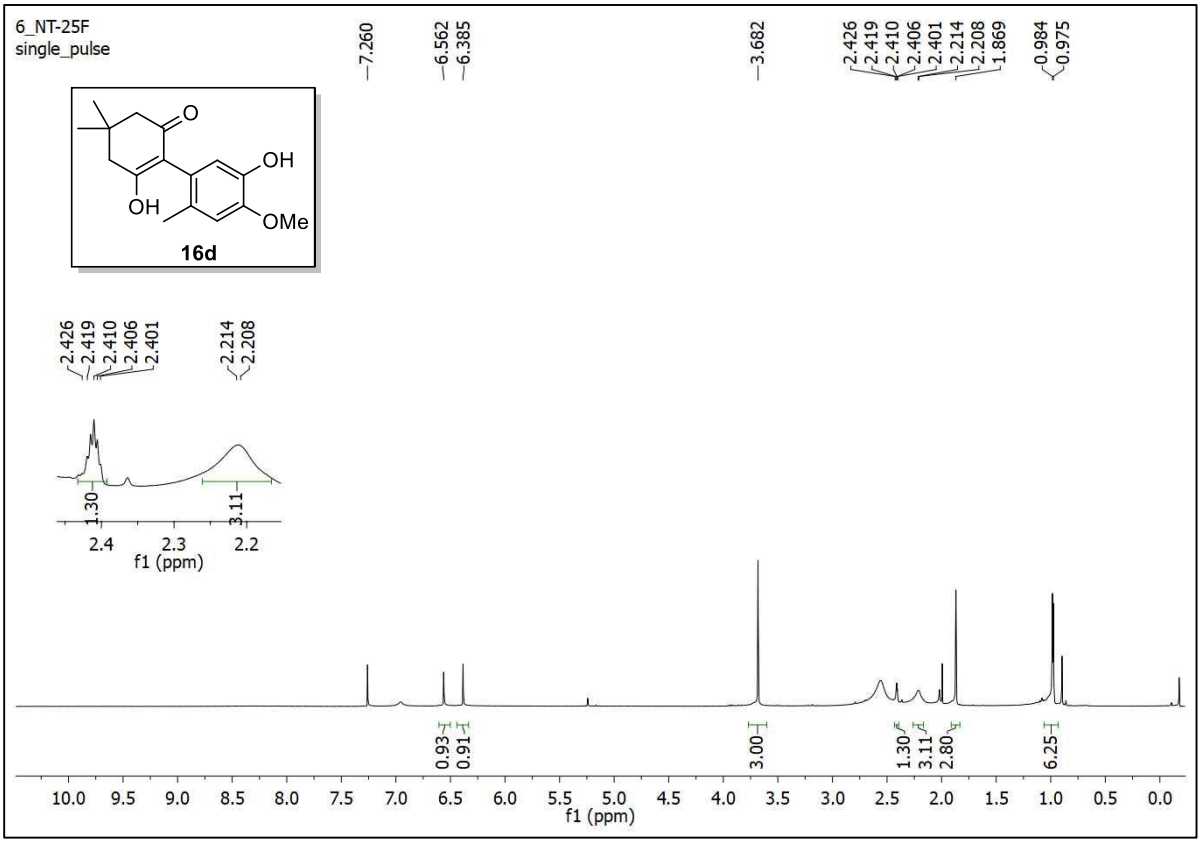


Fig S43: ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO) spectrum of **16d**.

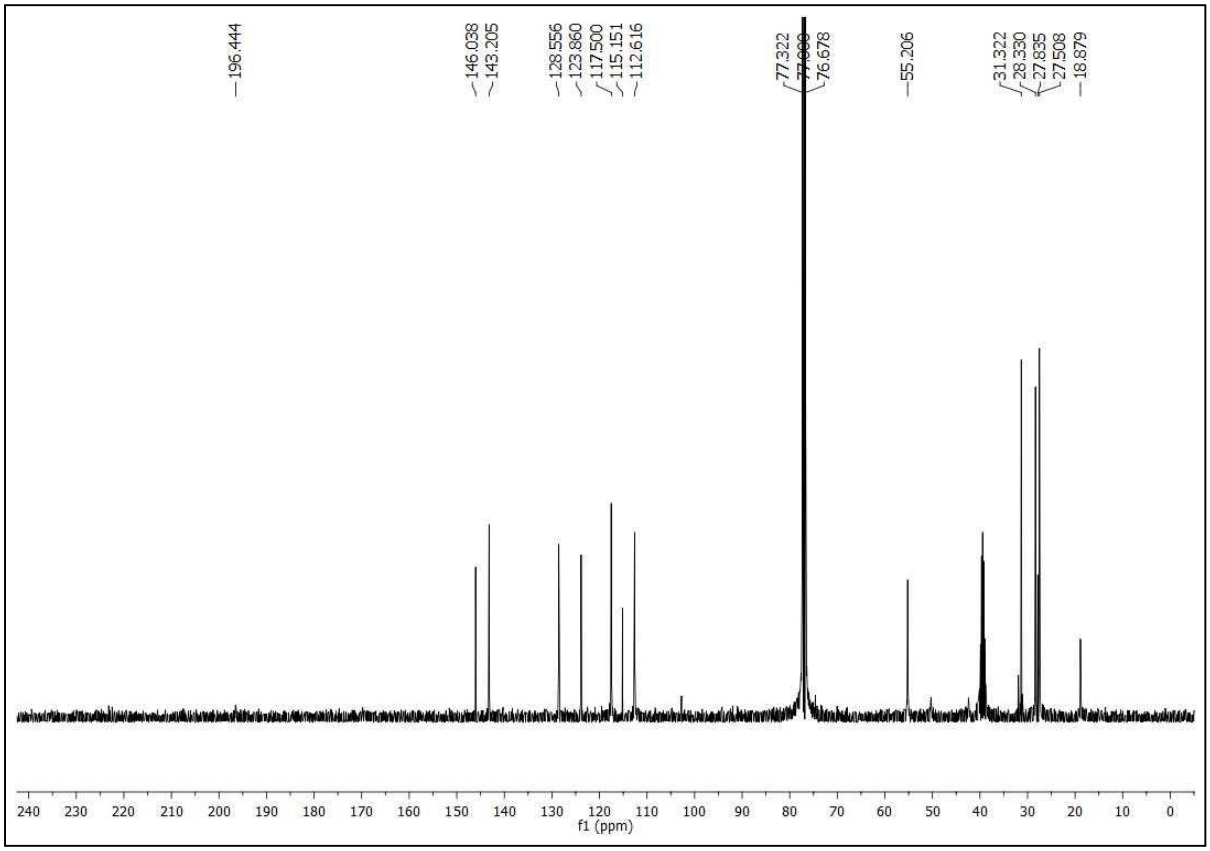


Fig S44: ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO) spectrum of **16d**.

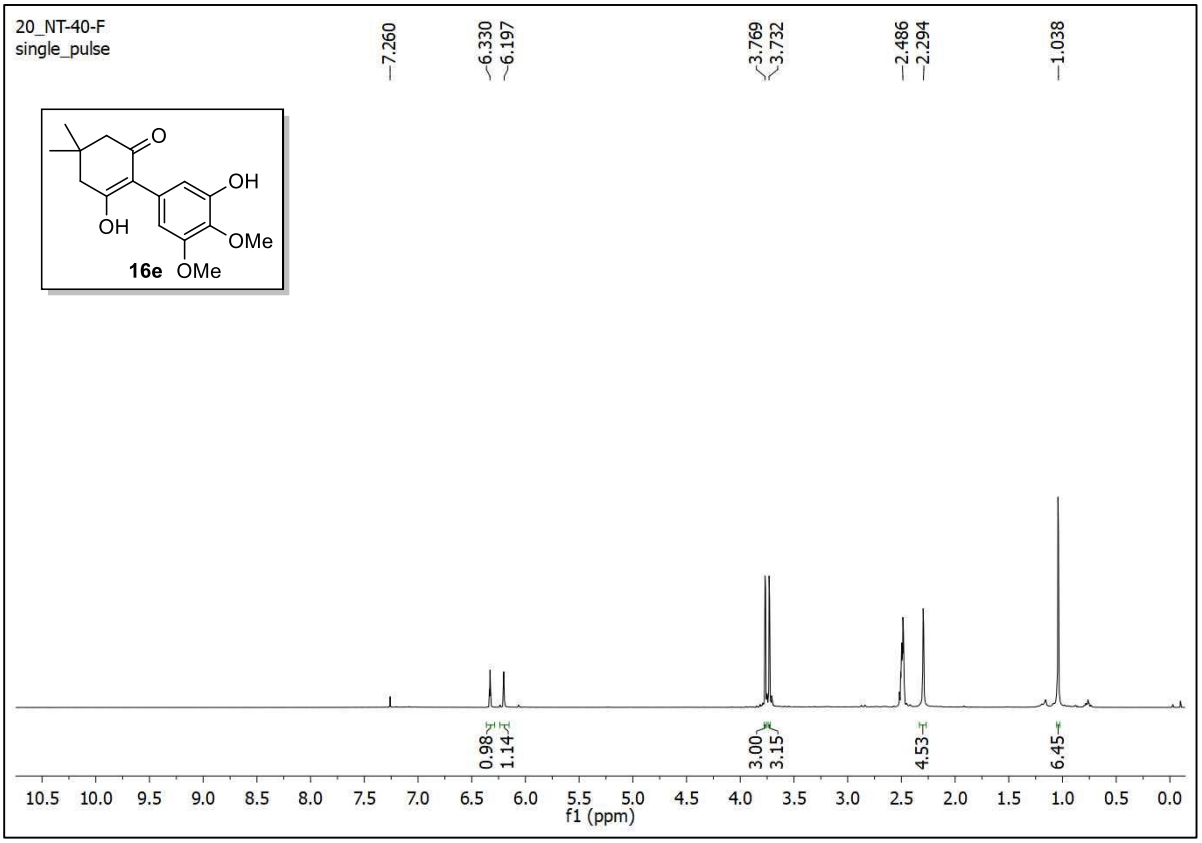


Fig S45: ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO) spectrum of **16e**.

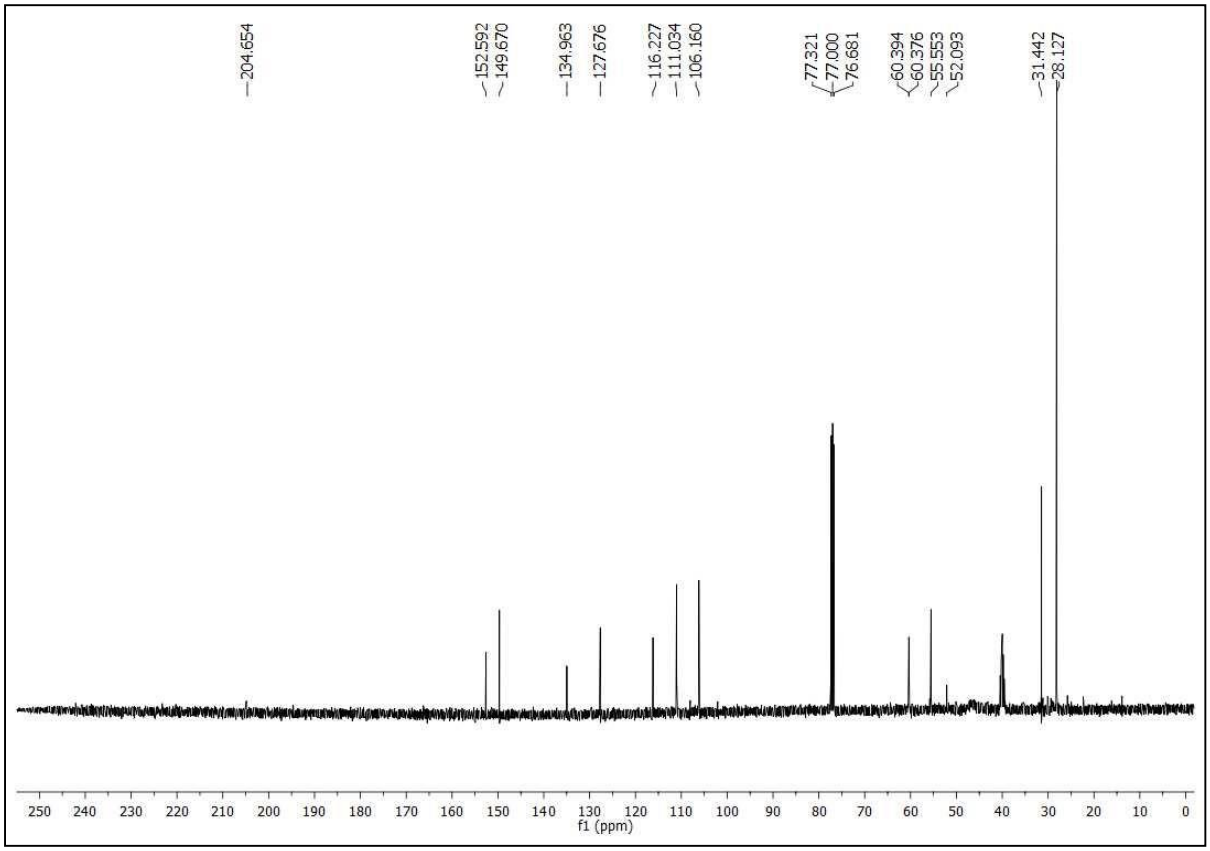


Fig S46: ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO) spectrum of **16e**.

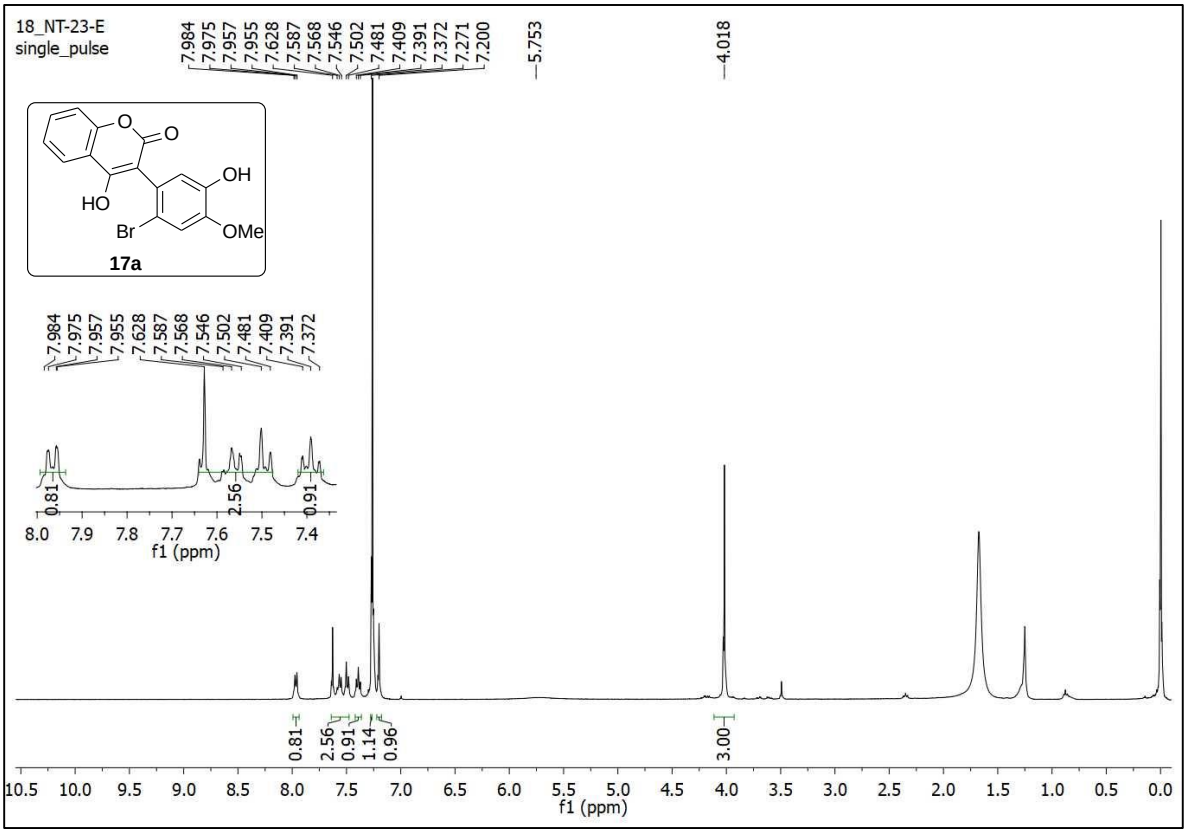


Fig S47: ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO) spectrum of **17a**.

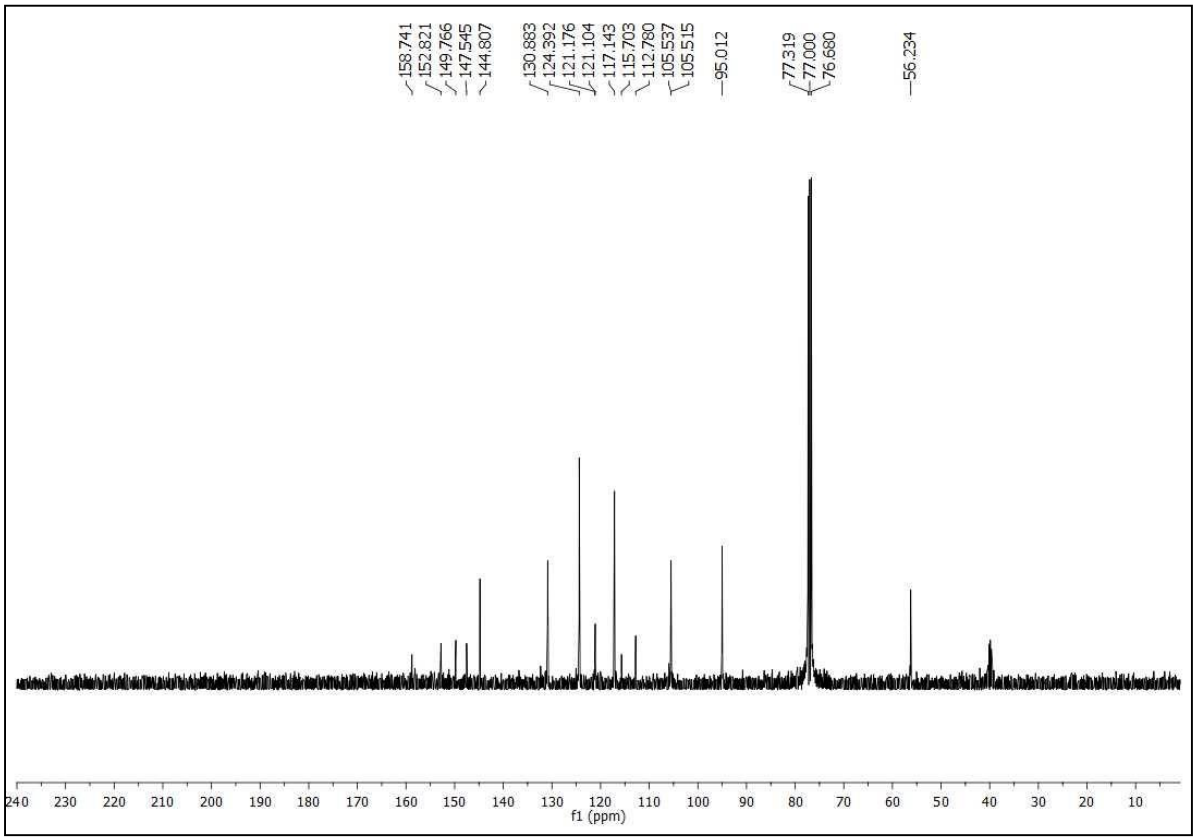


Fig S48: ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO) spectrum of **17a**.

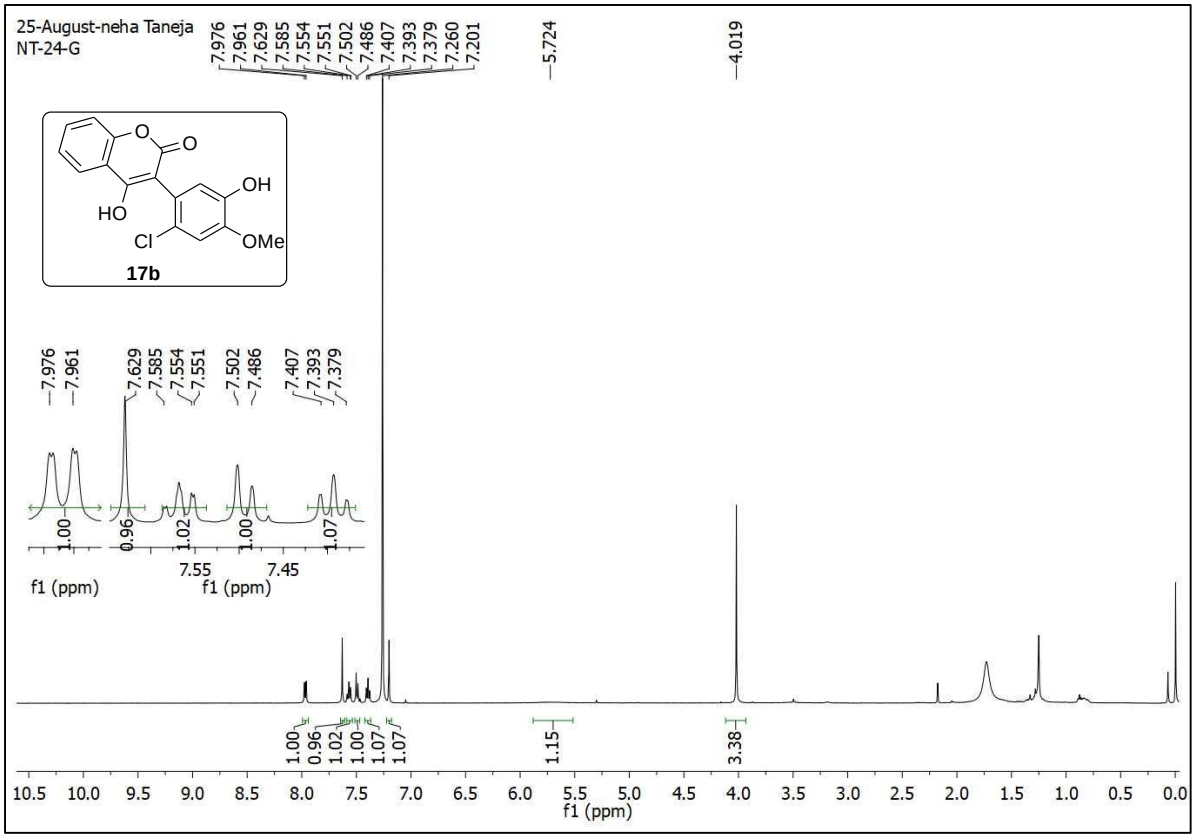


Fig S49: ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO) spectrum of **17b**.

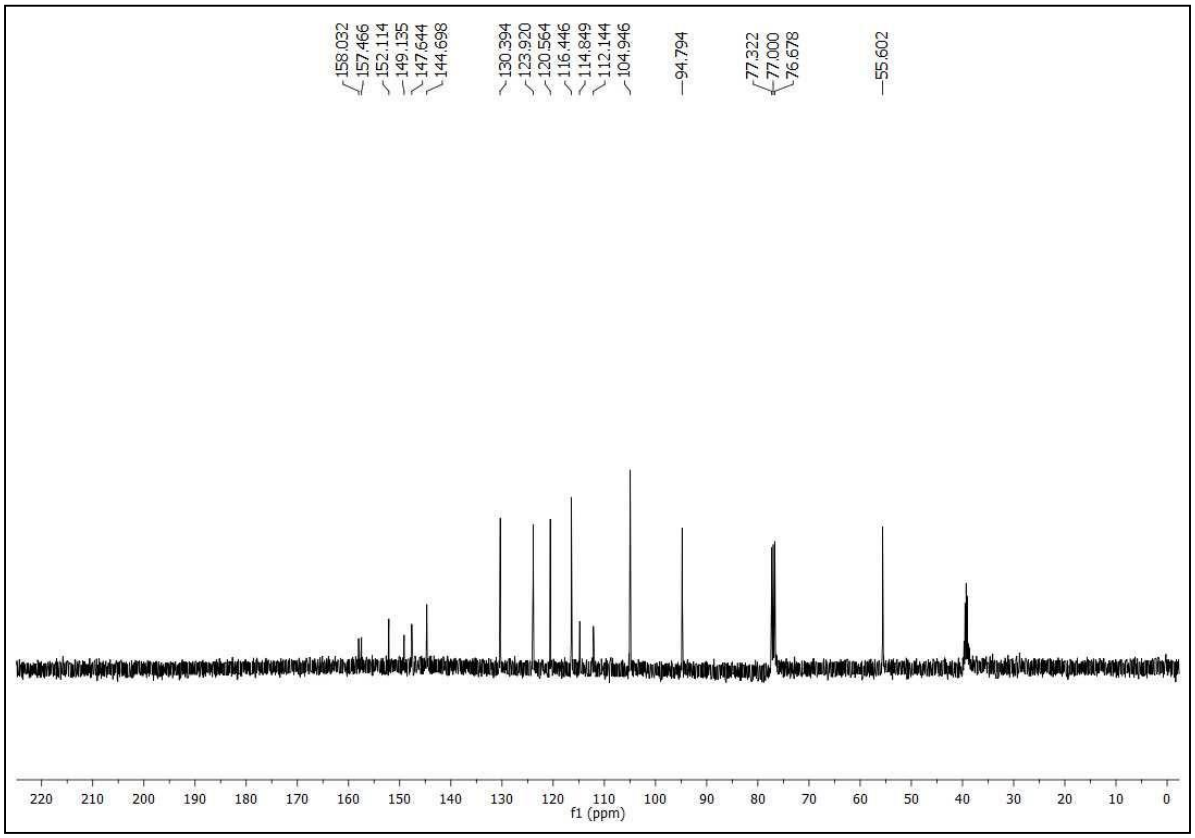


Fig S50: ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO) spectrum of **17b**.

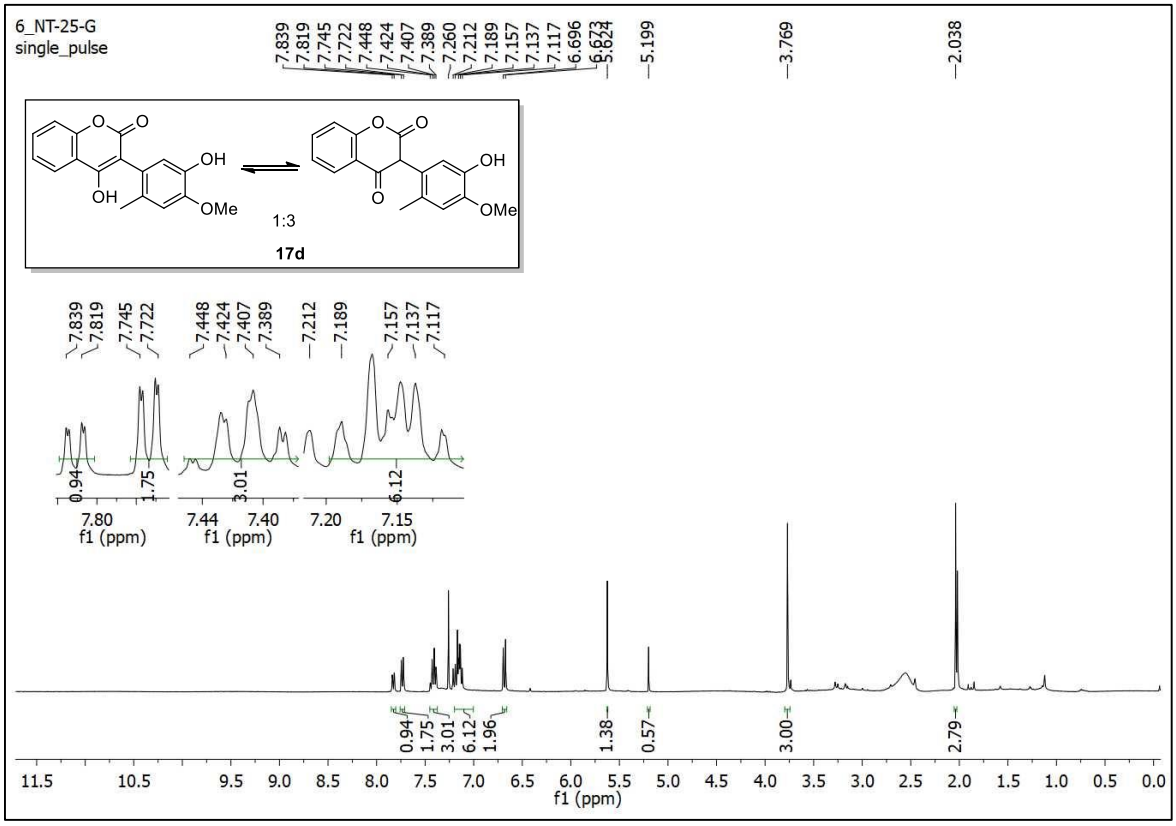


Fig S51: ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO) spectrum of **17d**.

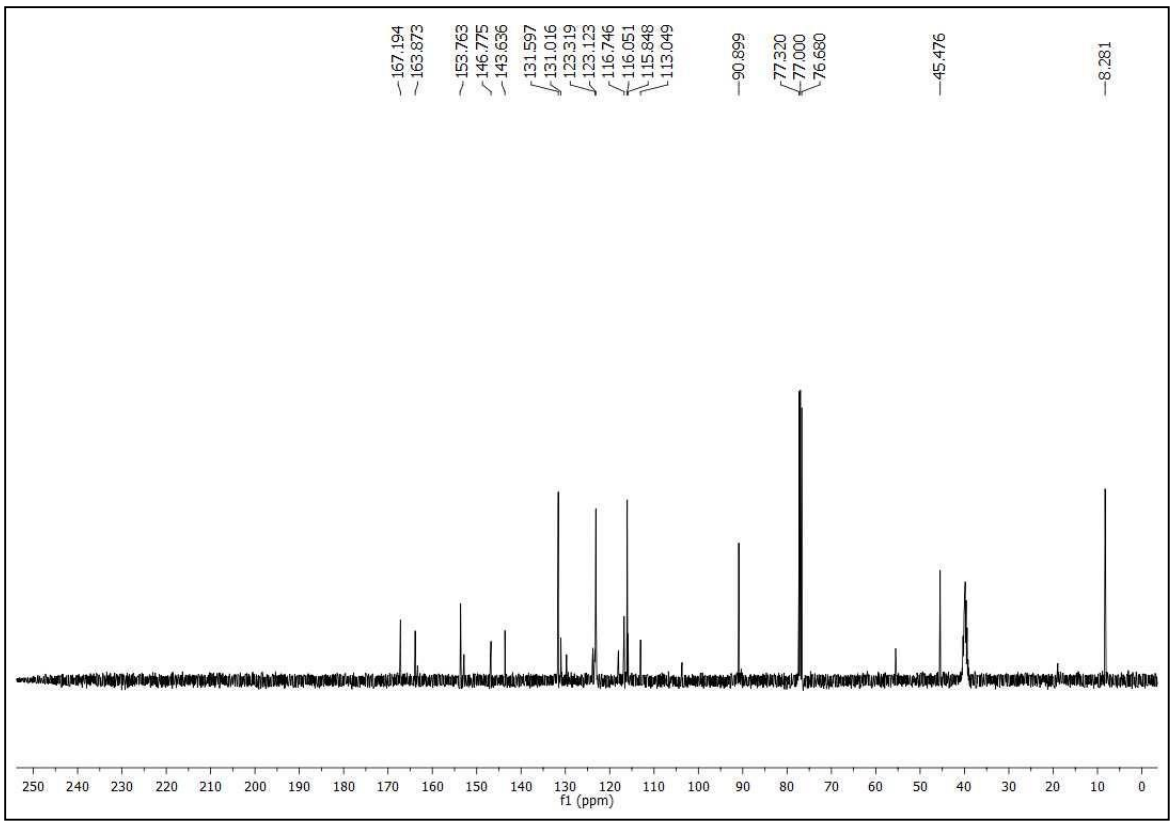


Fig S52: ^{13}C NMR (125 MHz, $CDCl_3$ + DMSO) spectrum of **17d**.

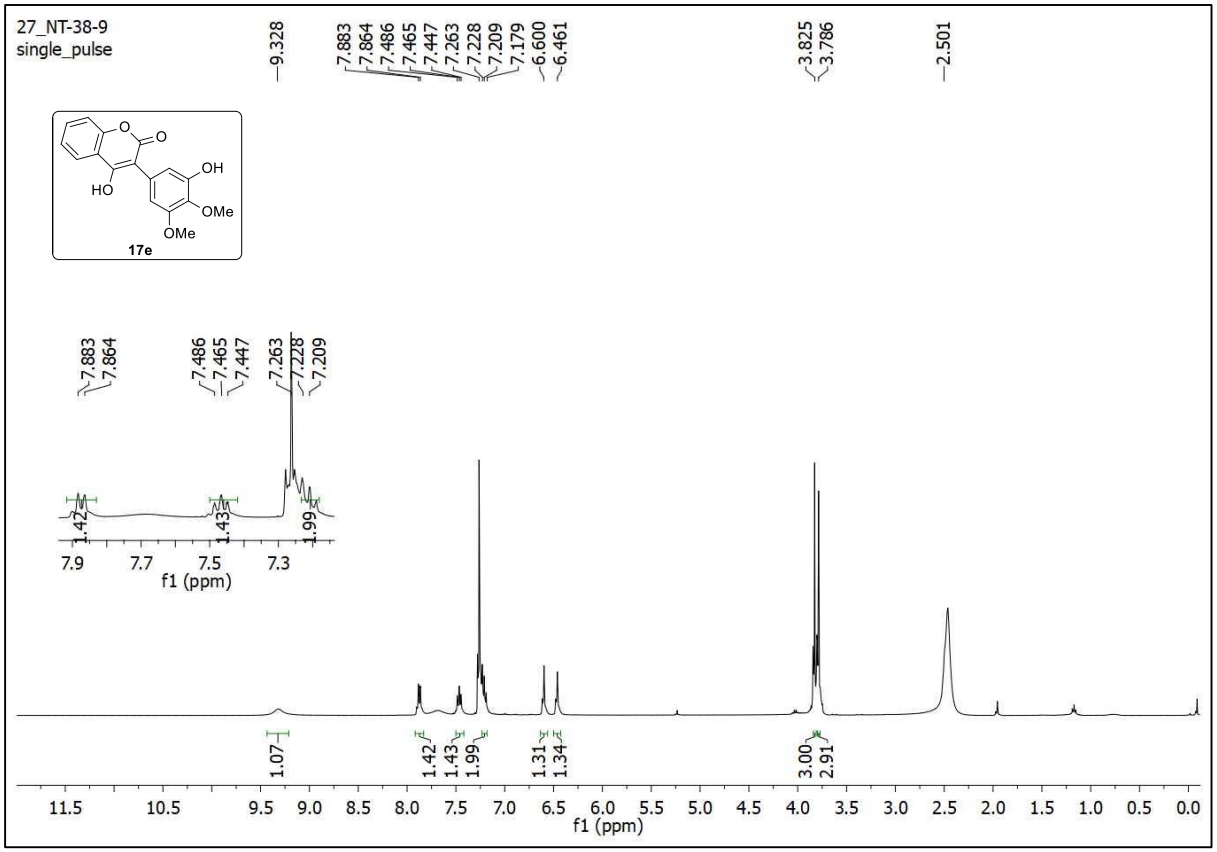


Fig S53: ^{1}H NMR (400 MHz, $CDCl_3$ + DMSO) spectrum of **17e**.

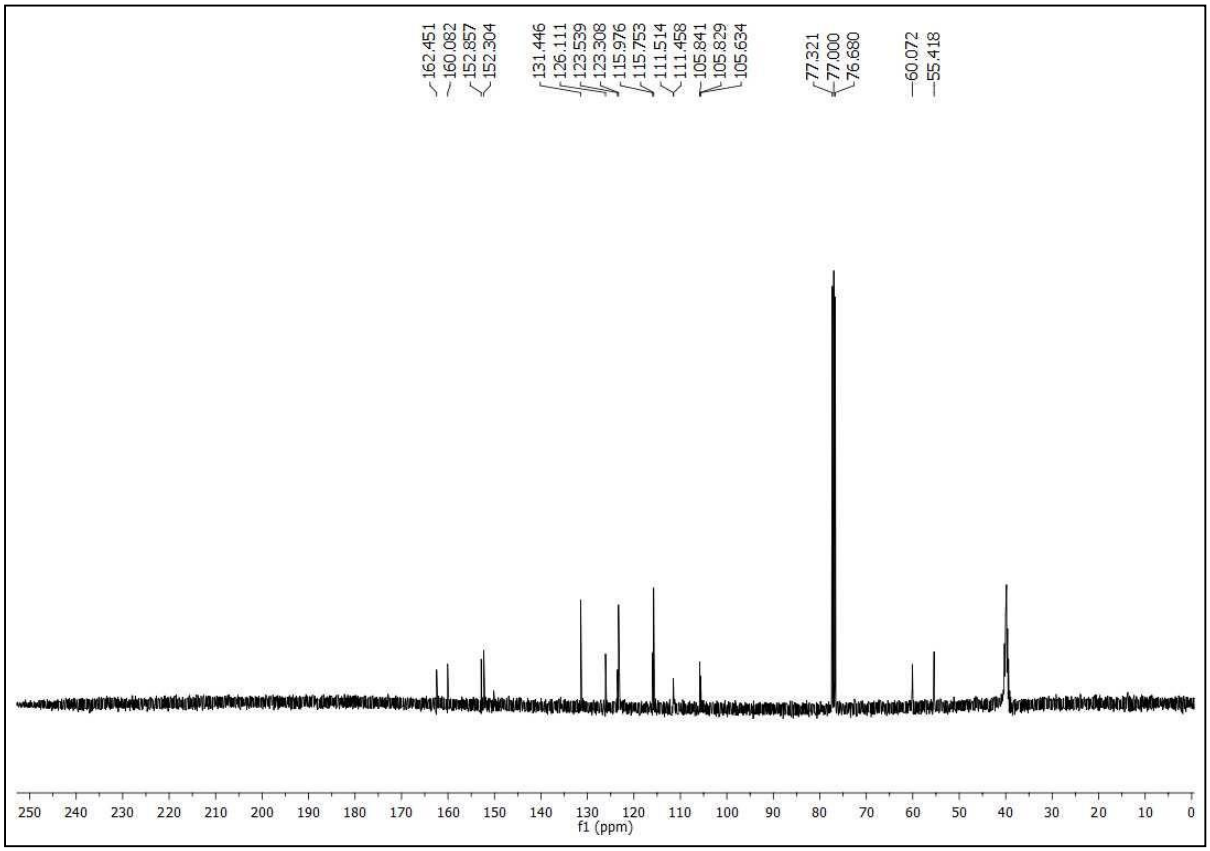


Fig S54: ^{13}C NMR (125MHz, $CDCl_3$ + DMSO) spectrum of **17e.**

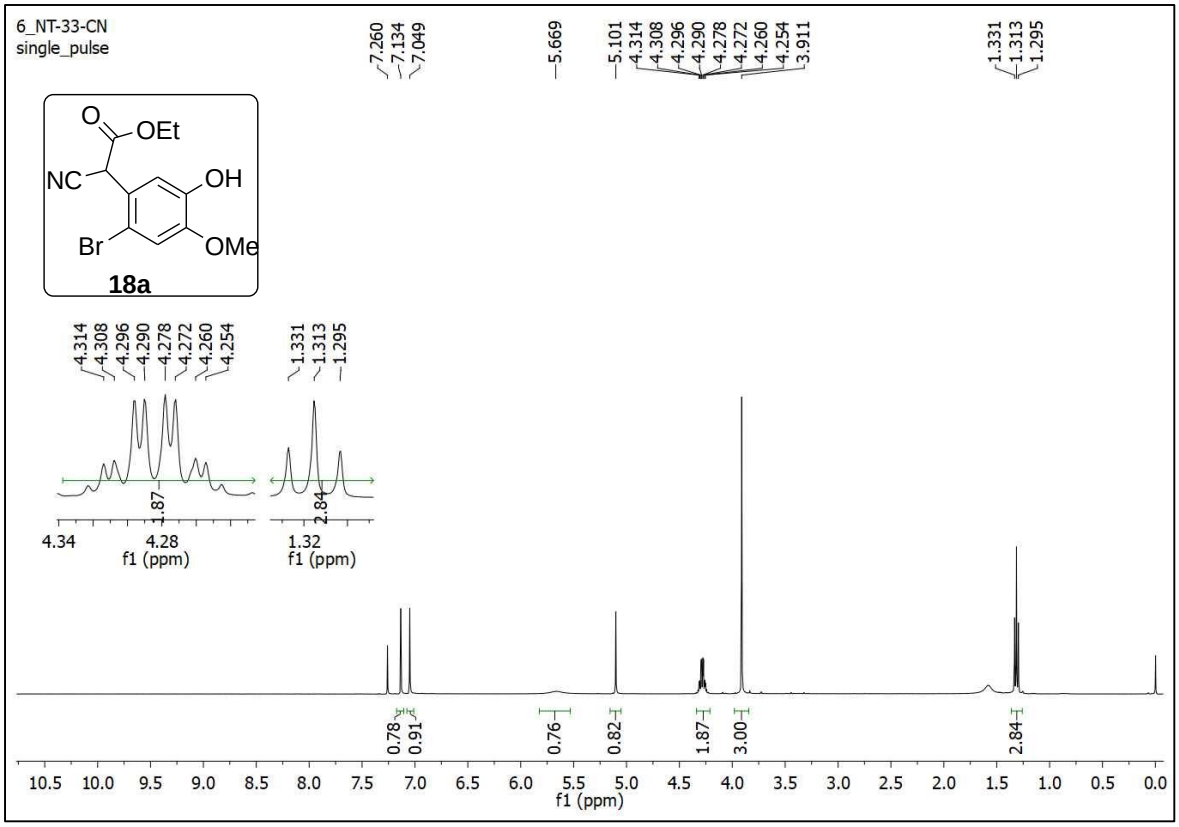


Fig S55: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **18a**.

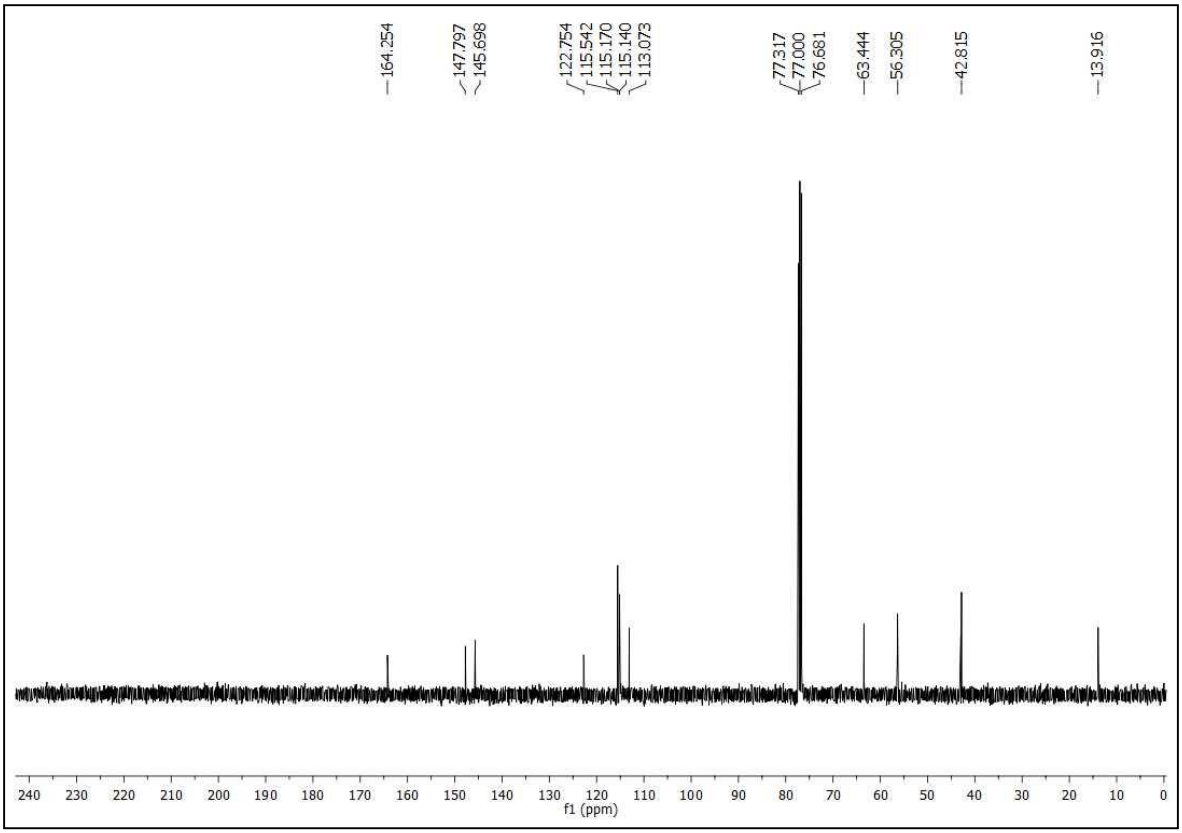


Fig S56: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **18a**.

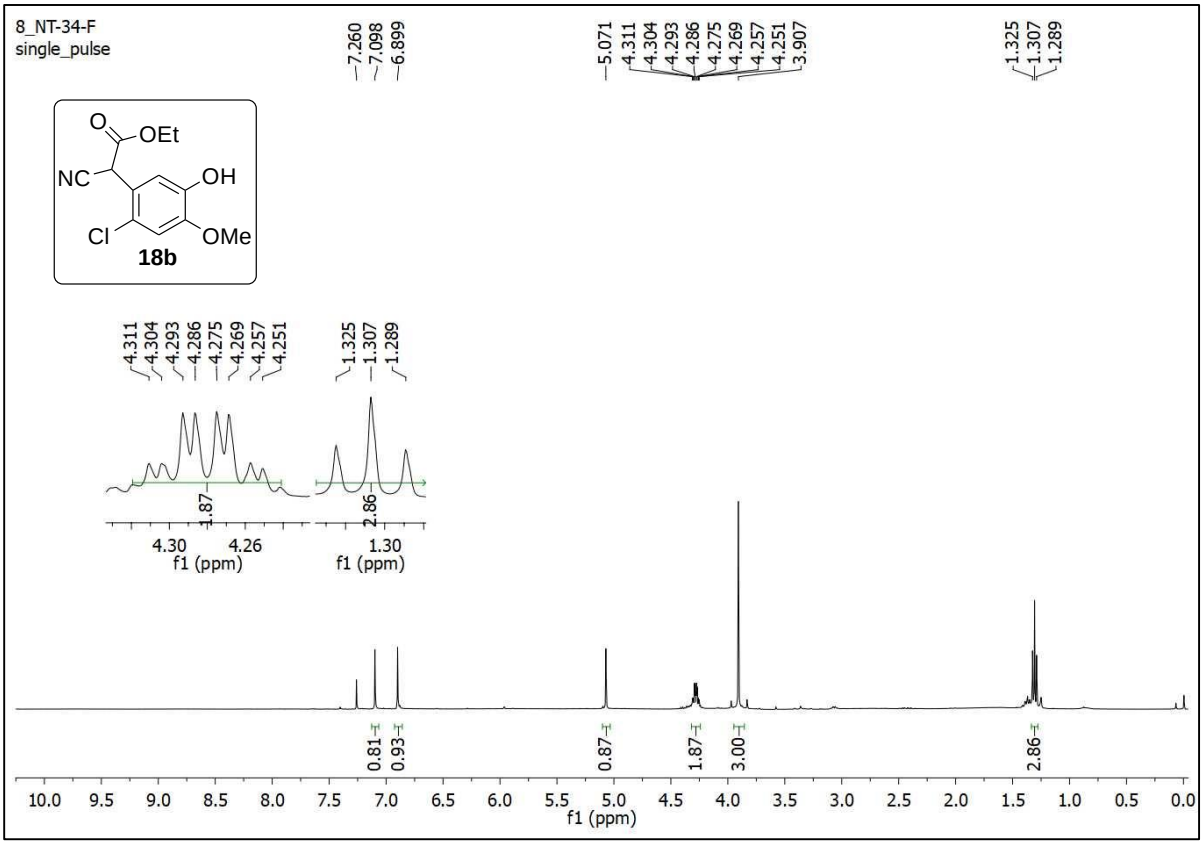


Fig S57: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **18b**.

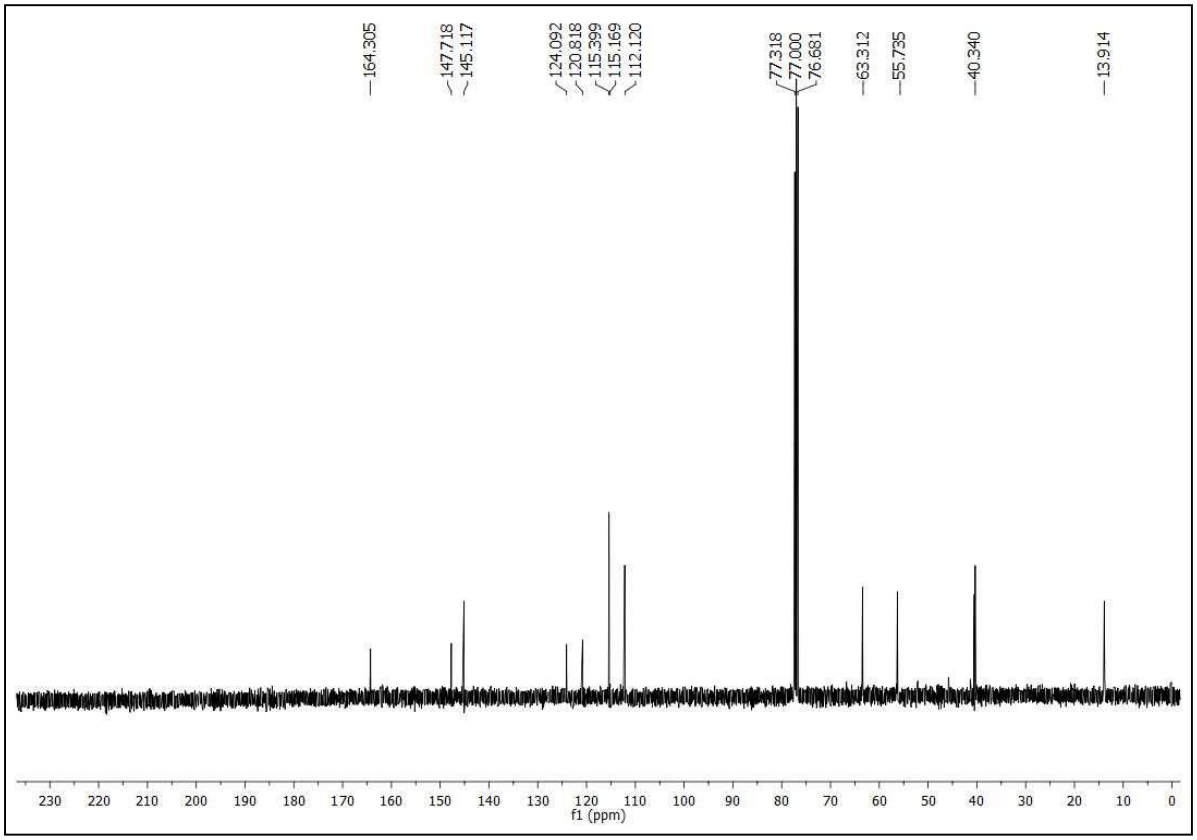


Fig S58: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **18b**.

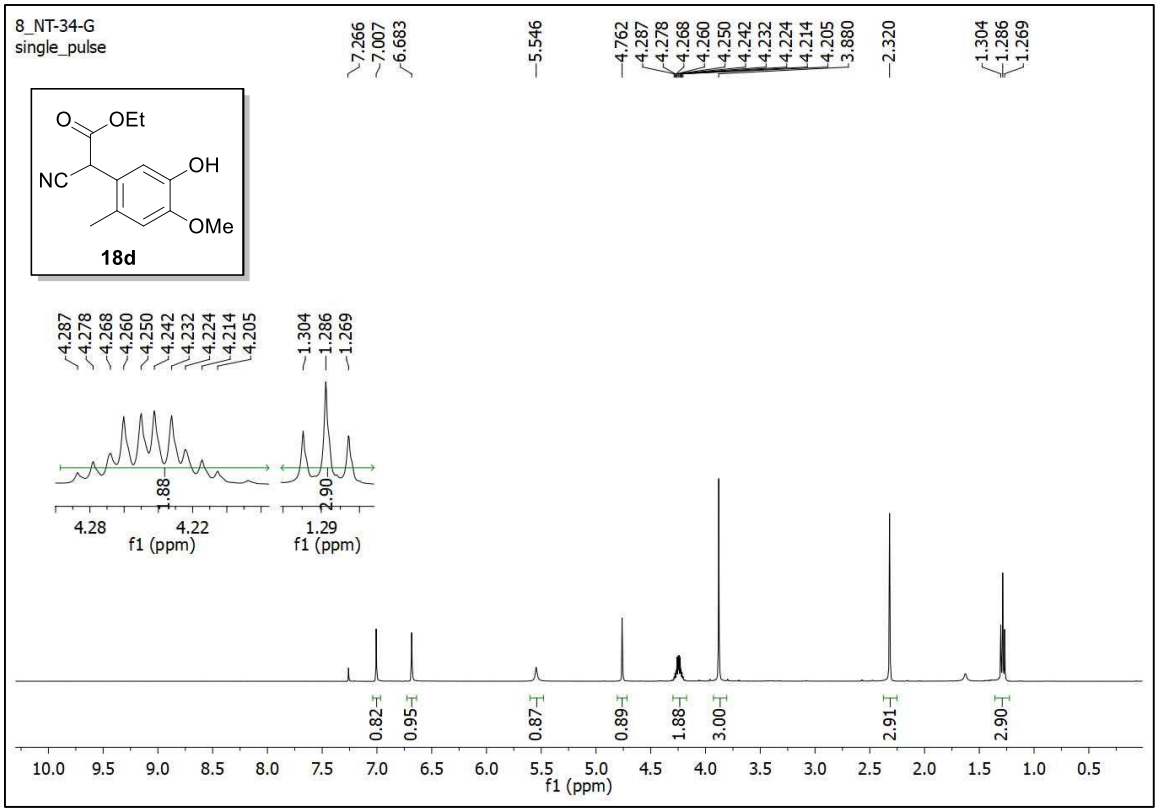


Fig S59: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **18d**.

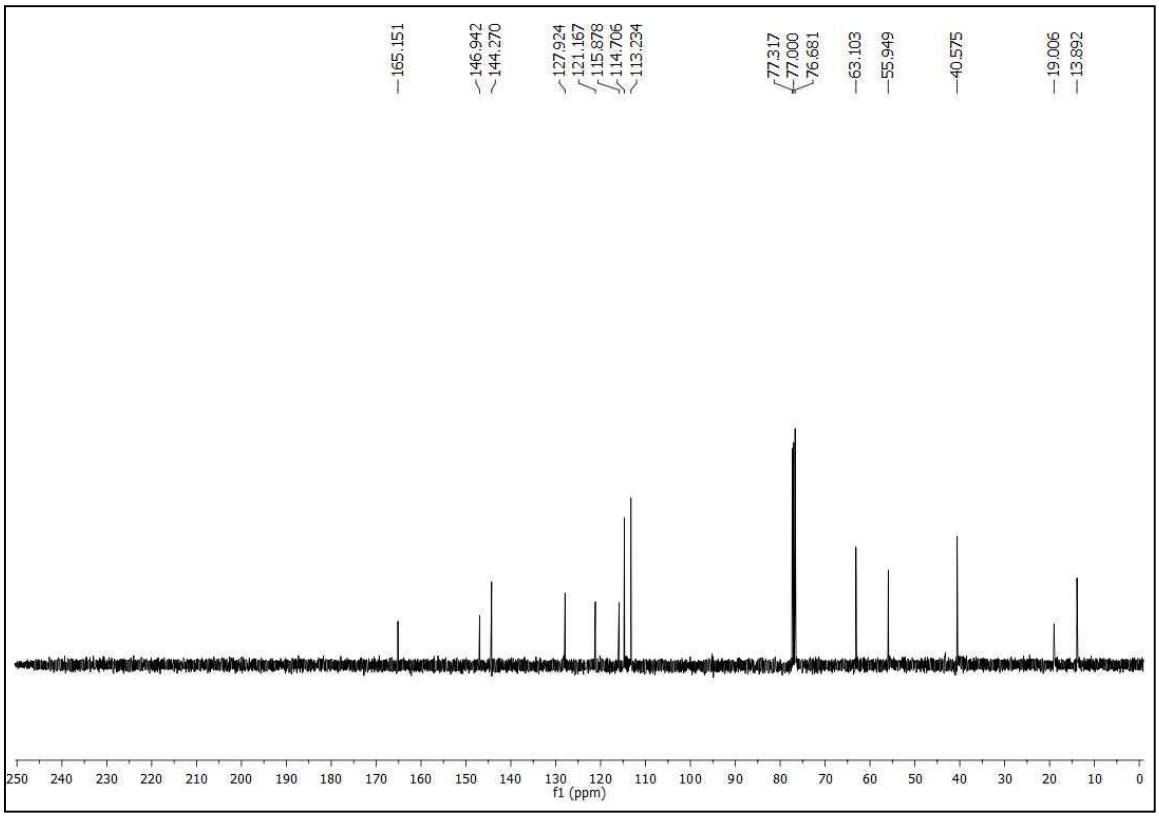


Fig S60: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **18d**.

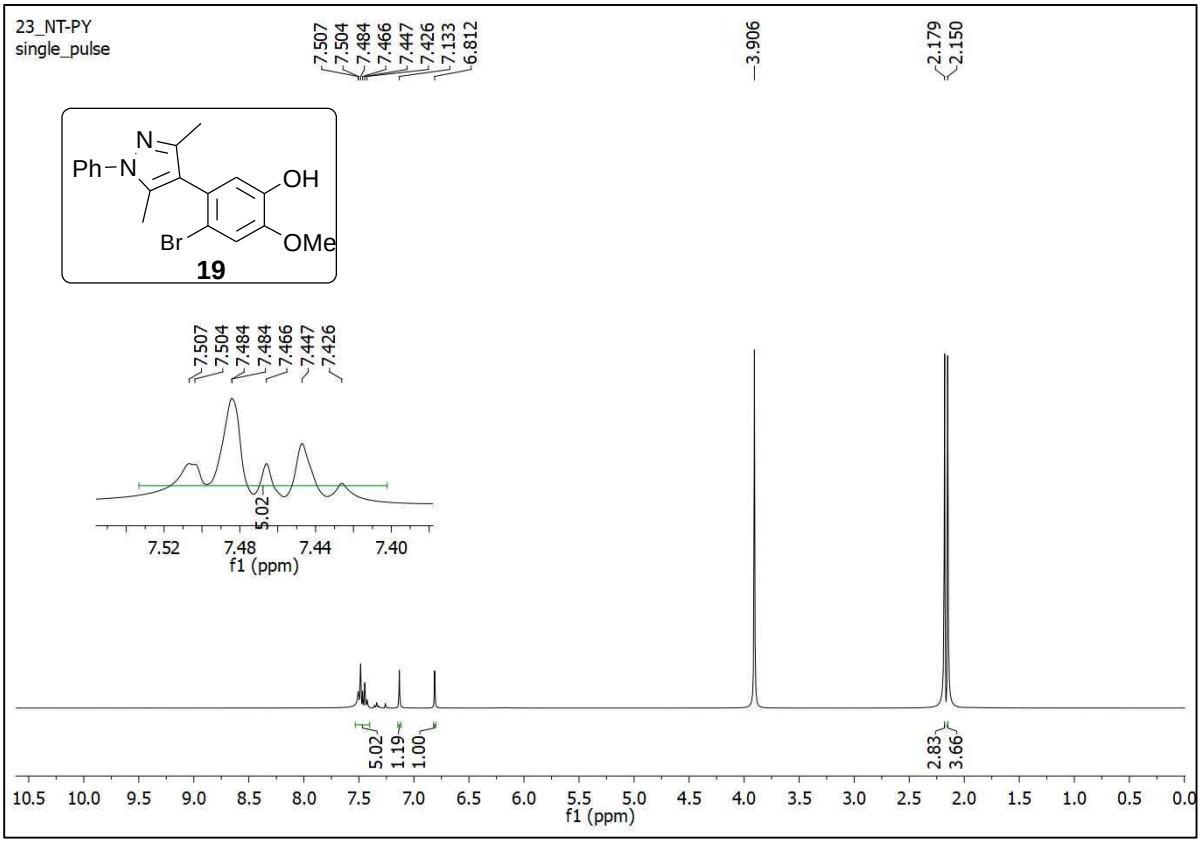


Fig S61: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **19**.

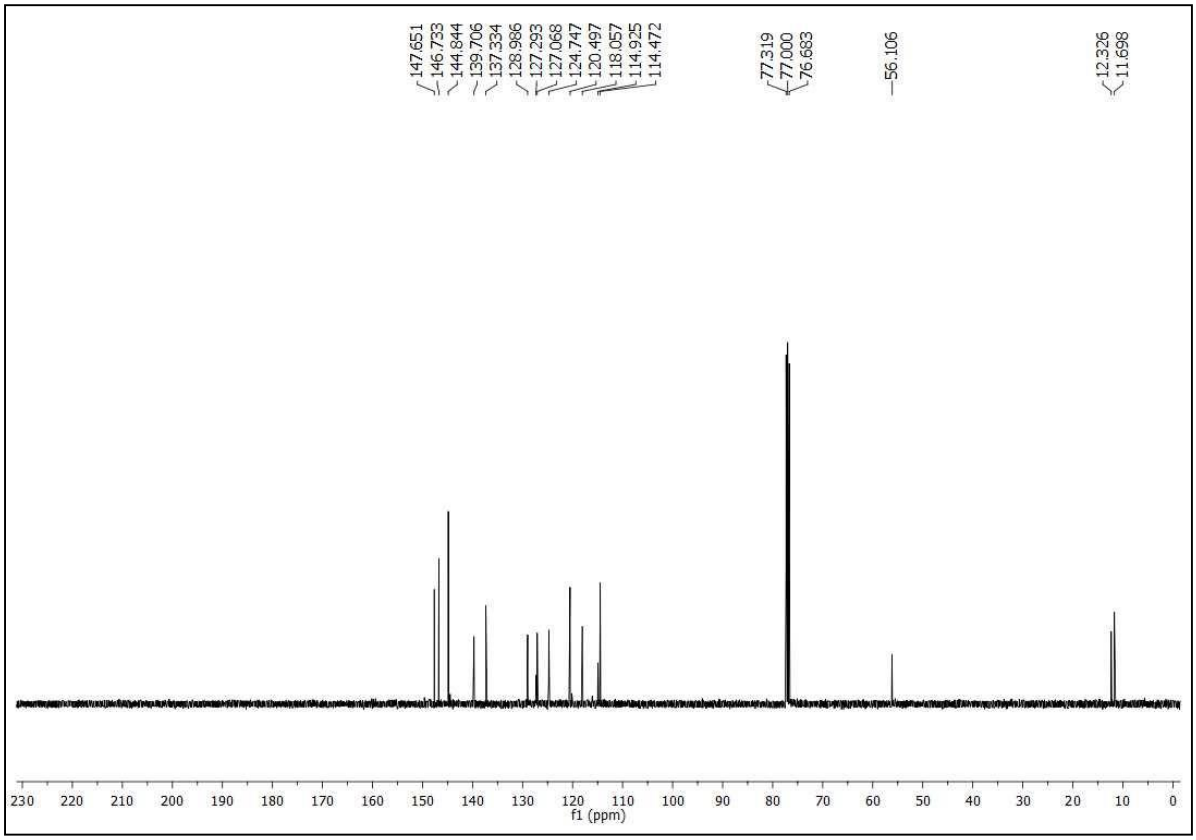


Fig S62: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **19**.

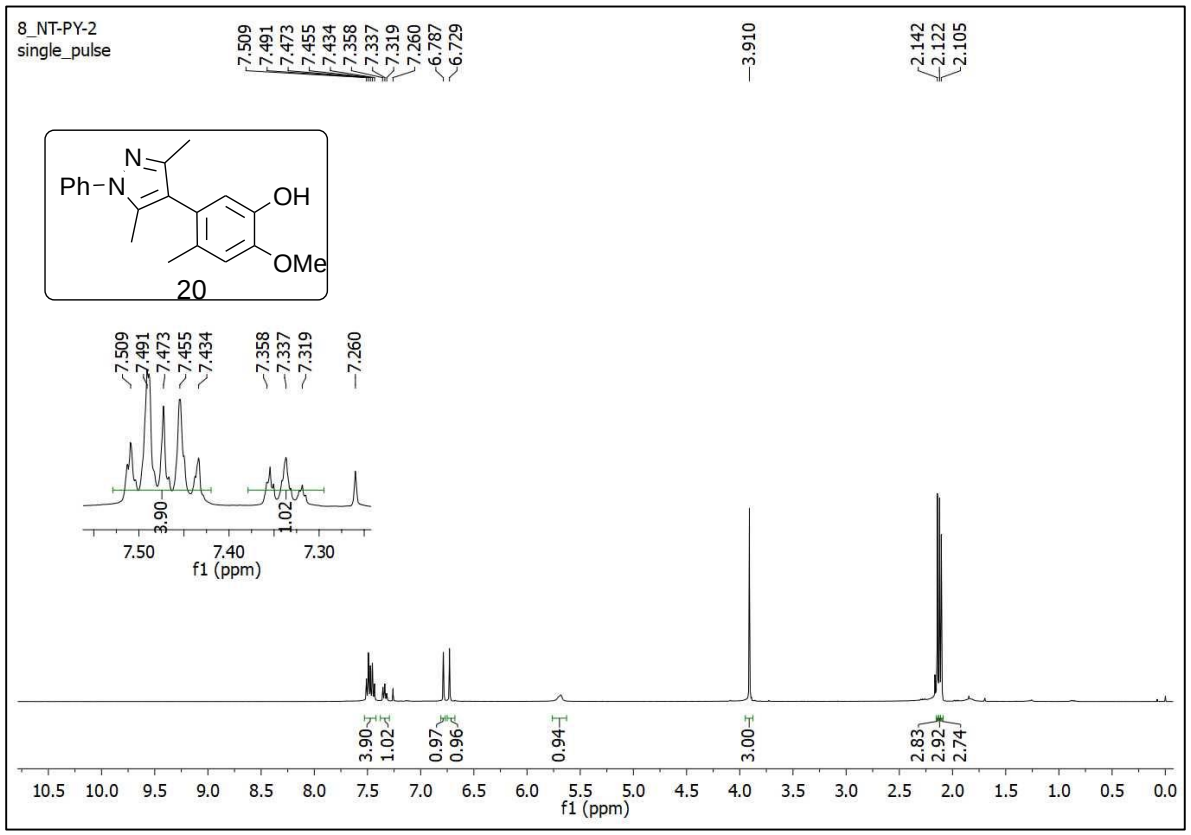


Fig S63: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **20**.

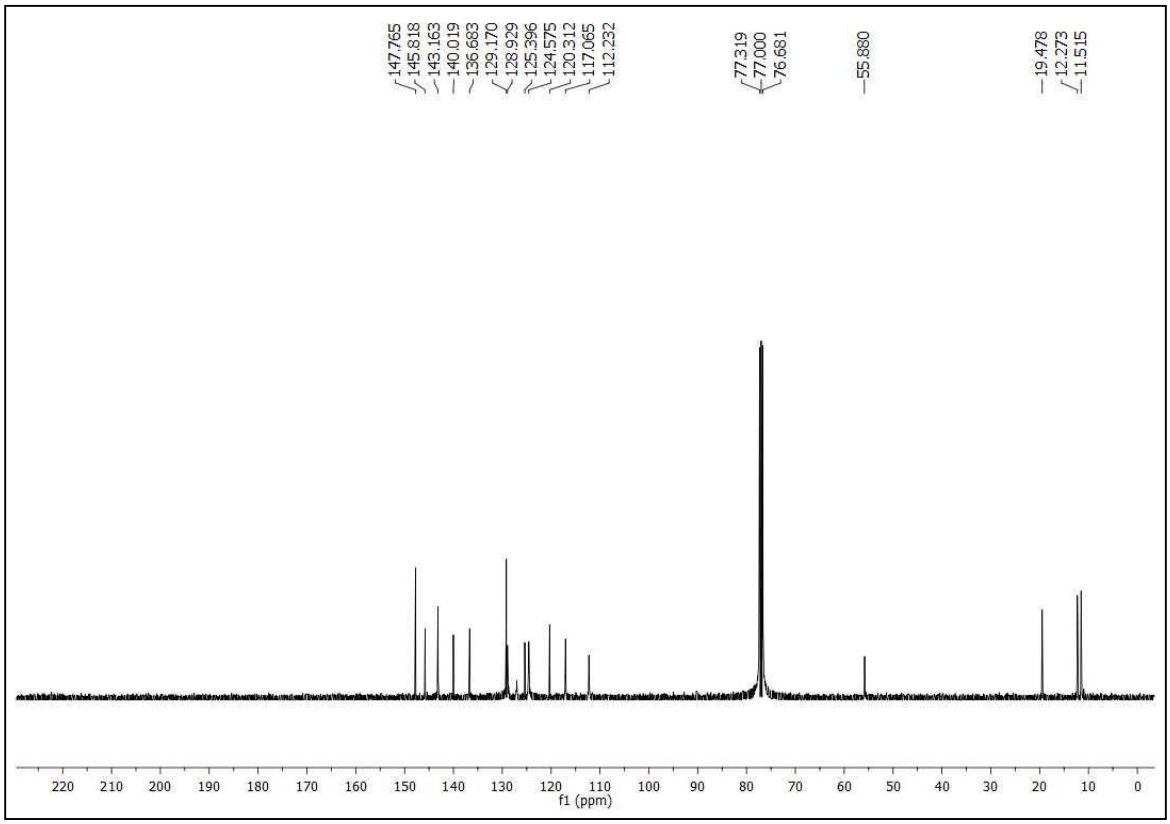


Fig S64: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **20**.

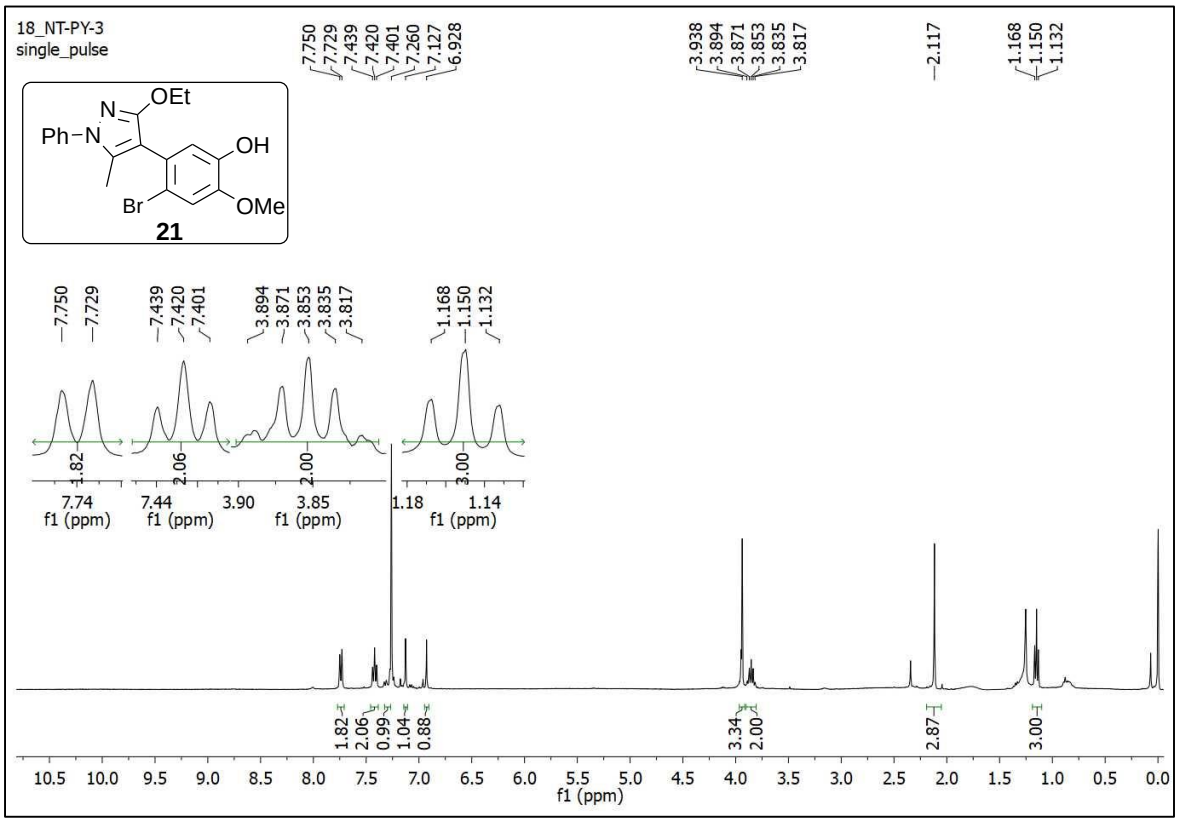


Fig S65: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **21**.

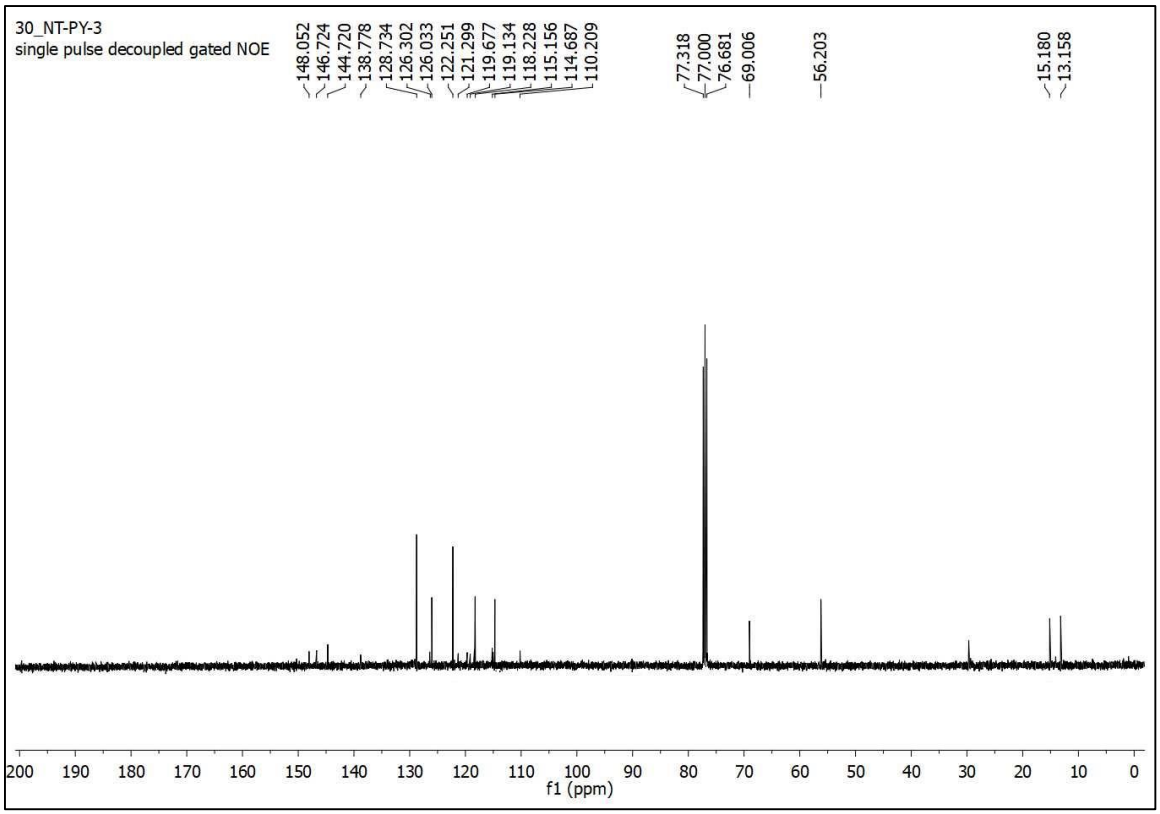


Fig S66: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **21**.

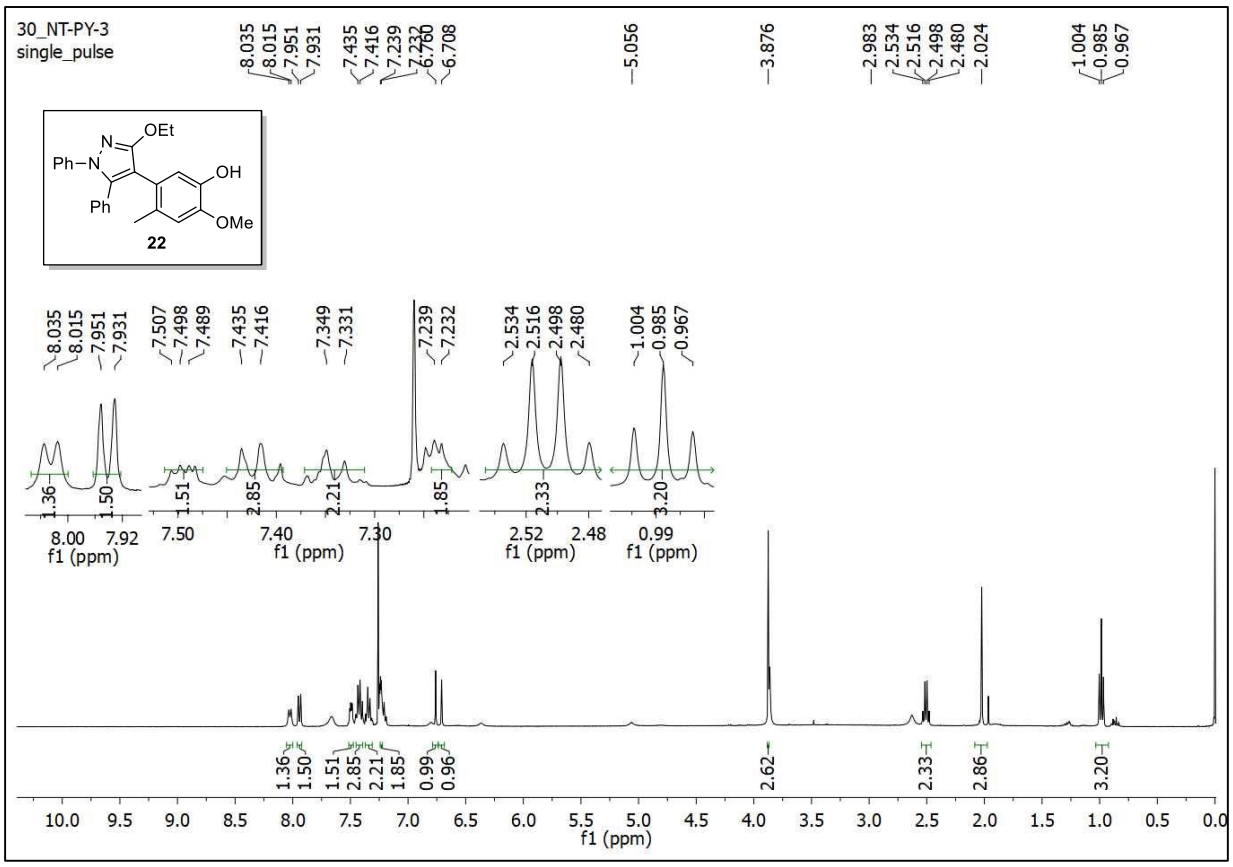


Fig S67: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **22**.

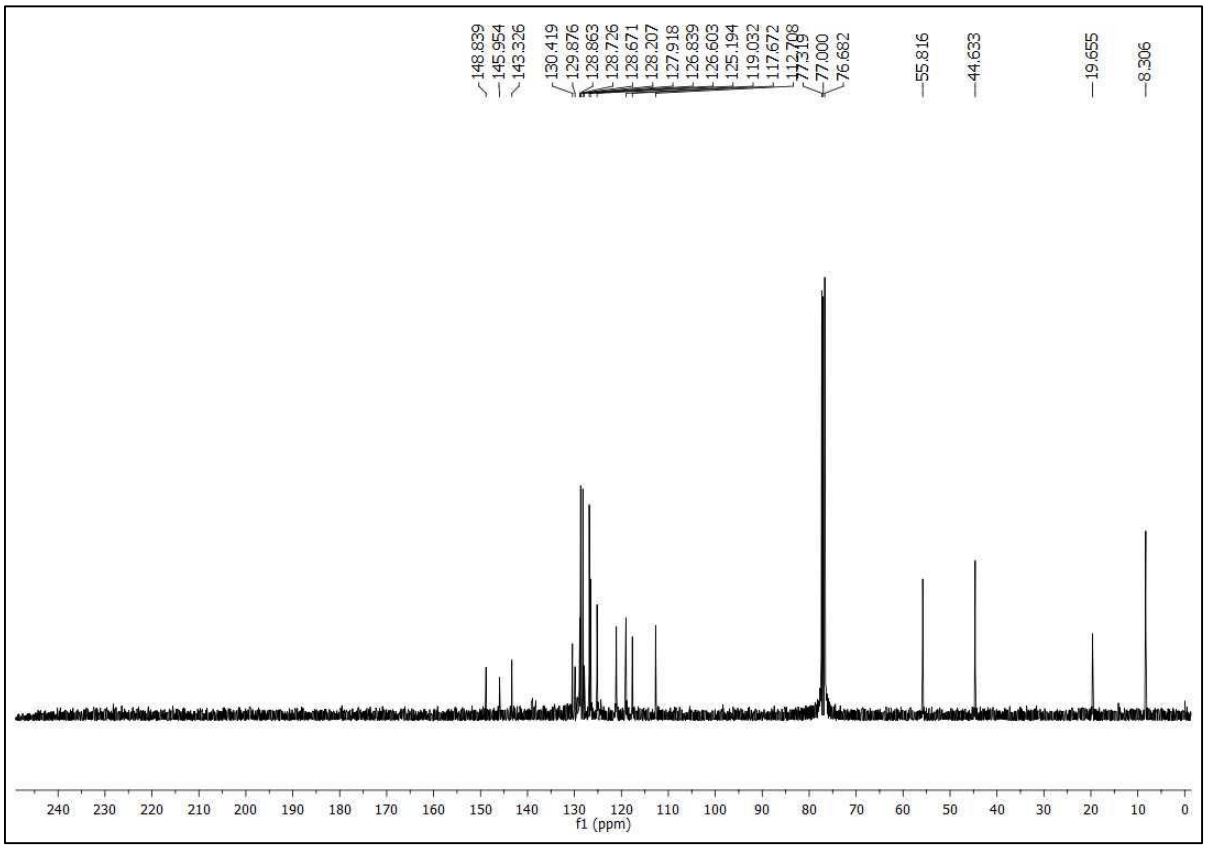


Fig S68: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **22**.

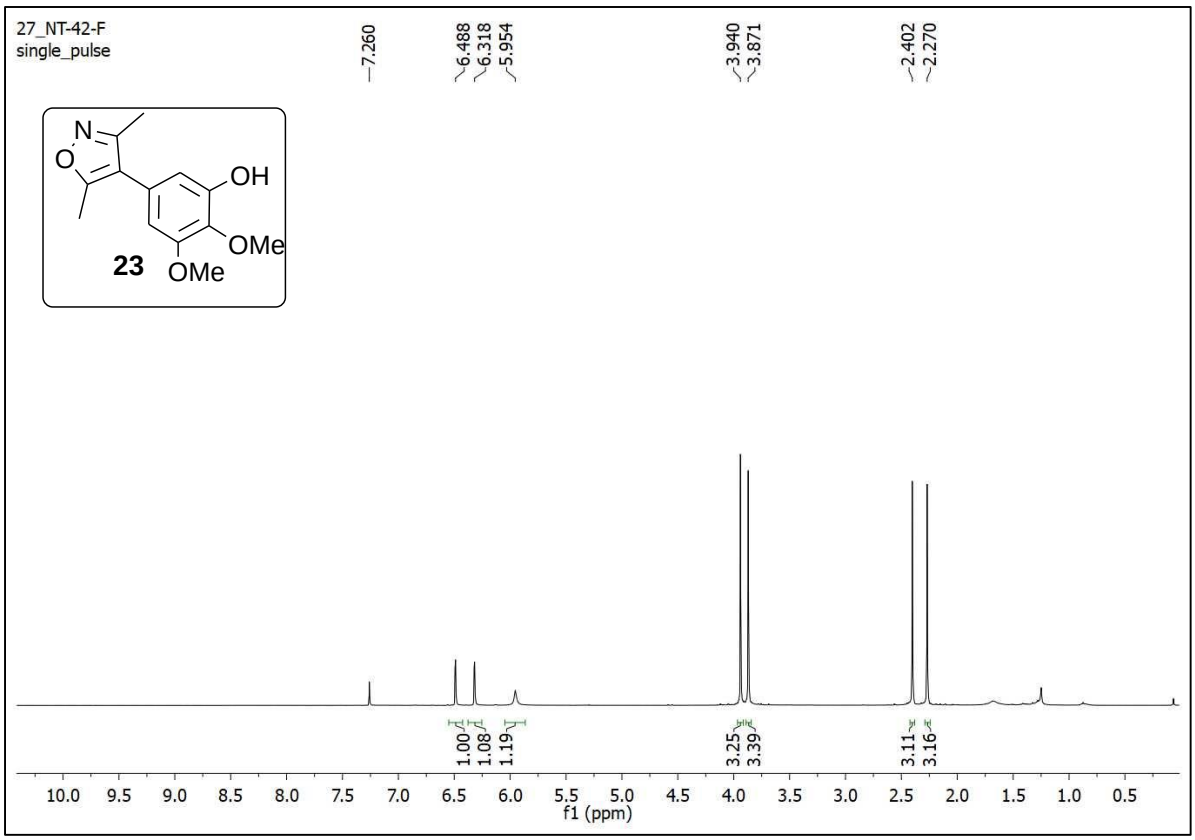


Fig S69: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **23**.

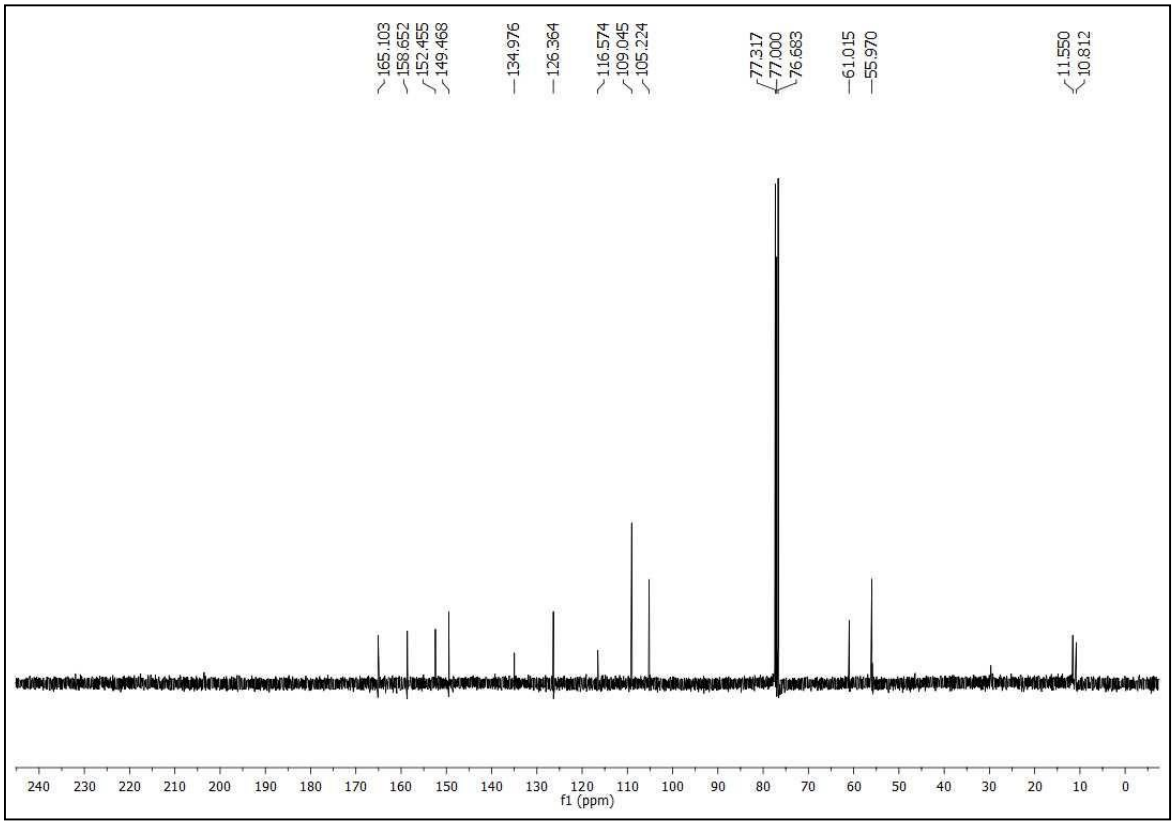


Fig S70: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **23**.

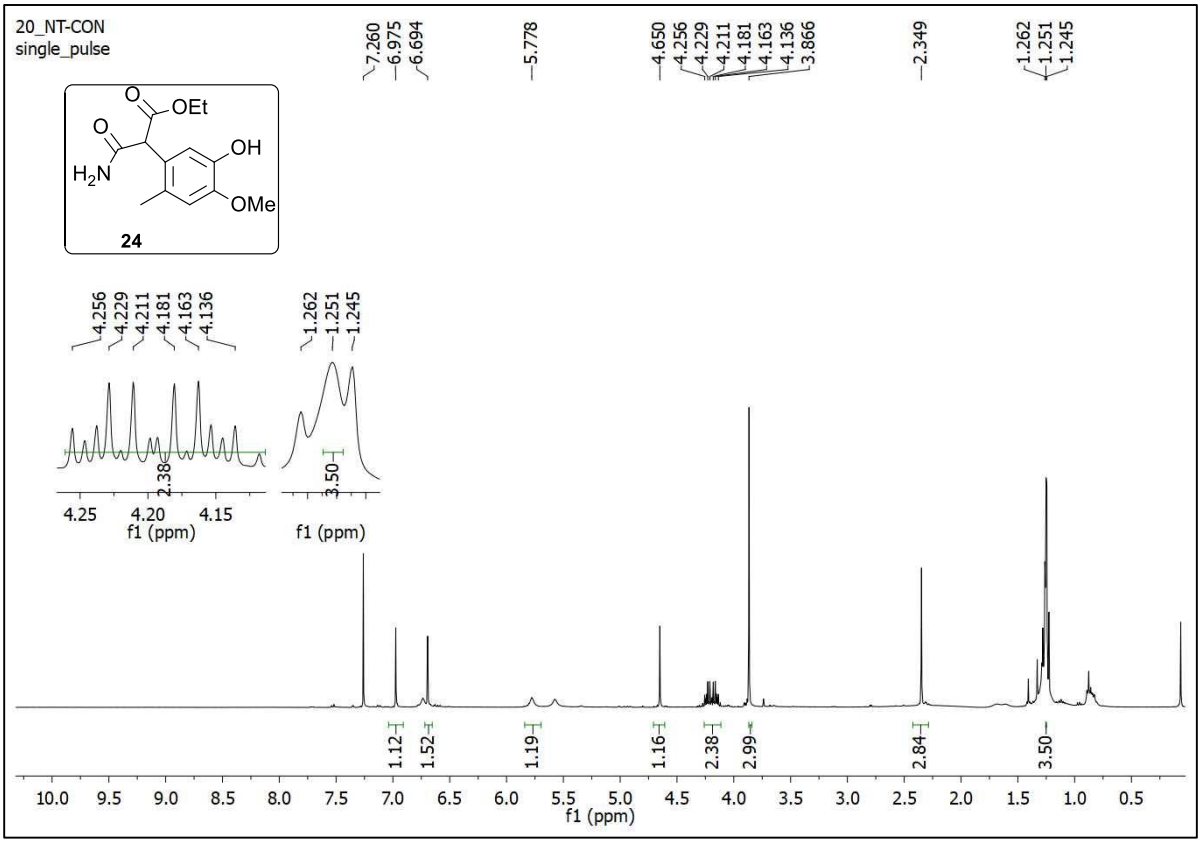


Fig S71: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **24**.

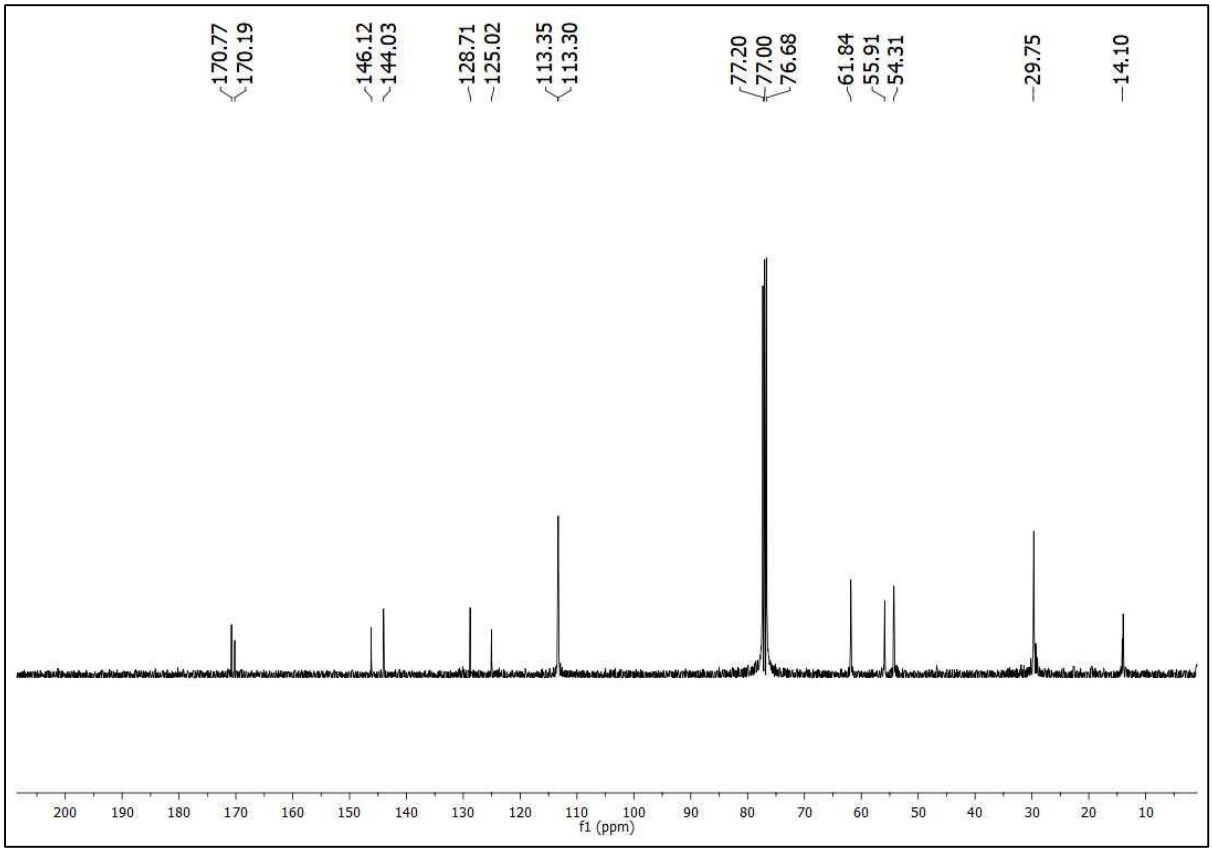


Fig S72: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **24**.

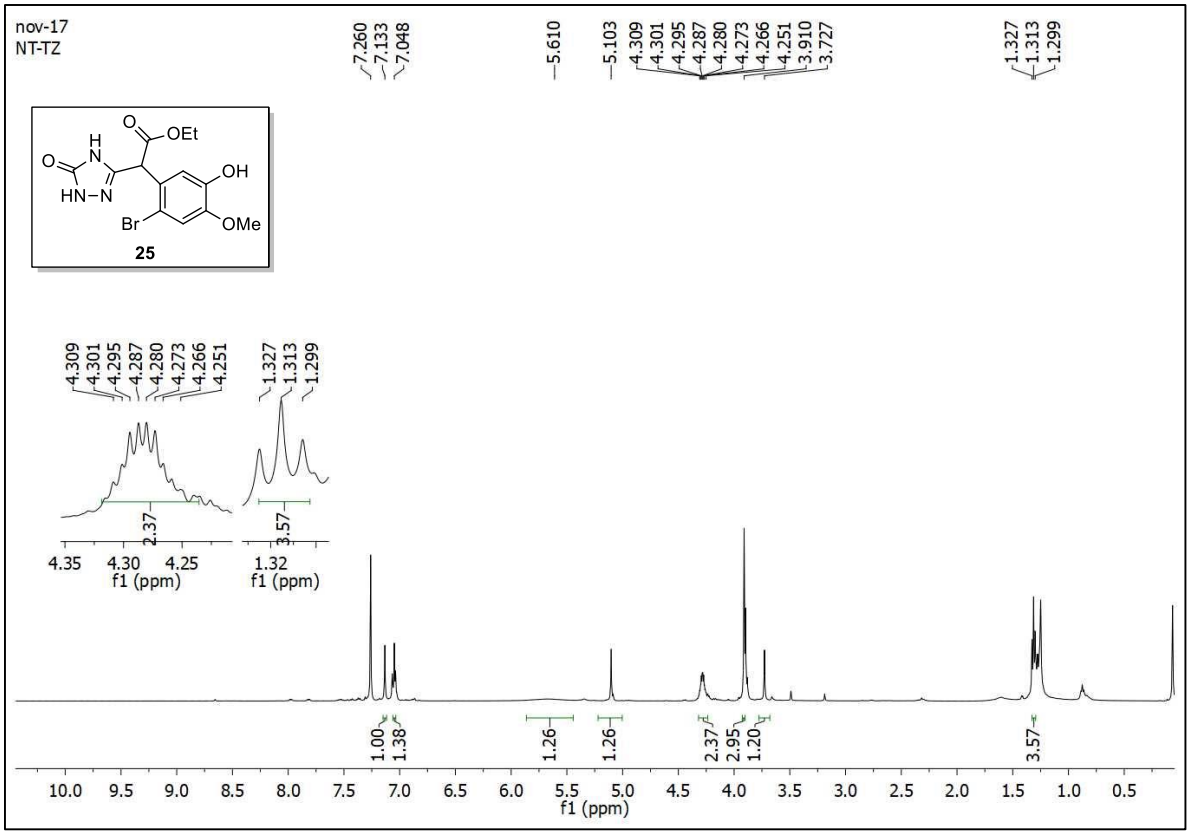


Fig S73: ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **25**.

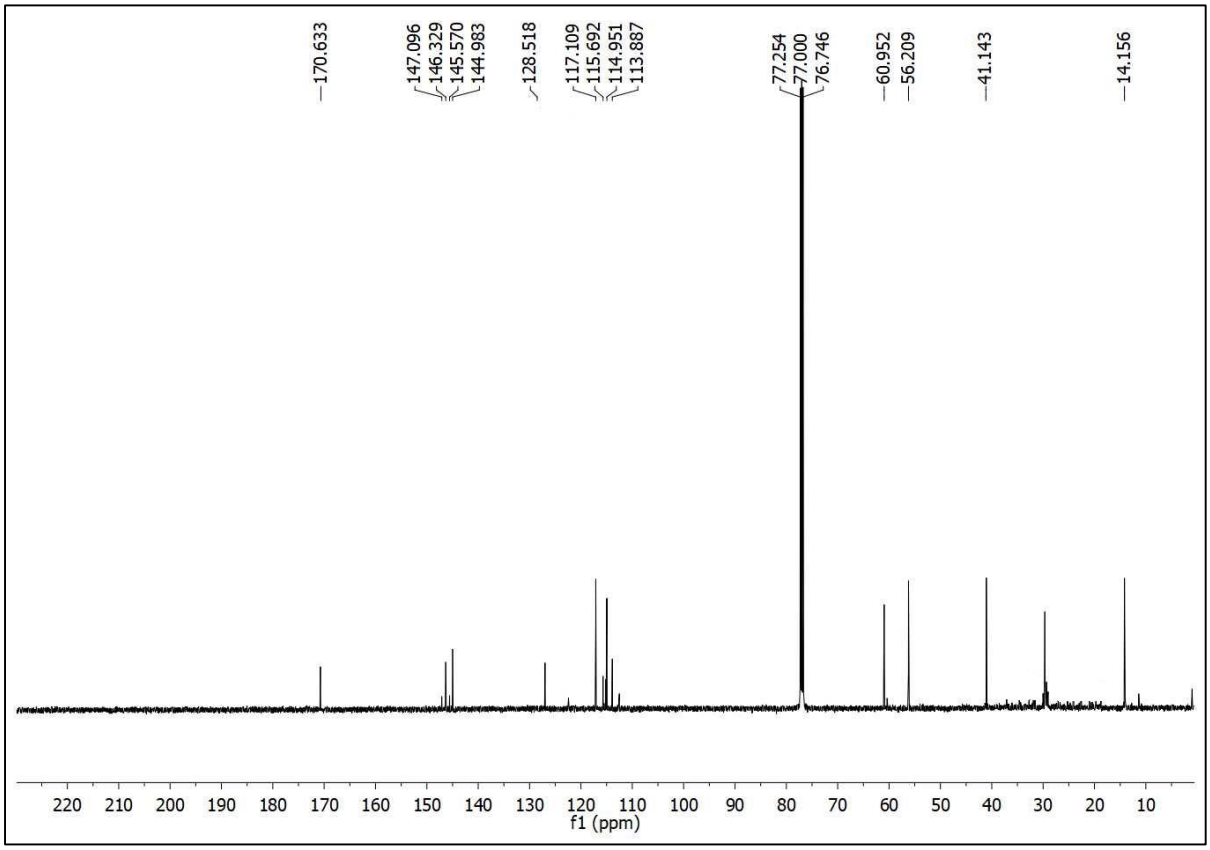


Fig S74: ^{13}C NMR (125 MHz, $CDCl_3$) spectrum of **25**.

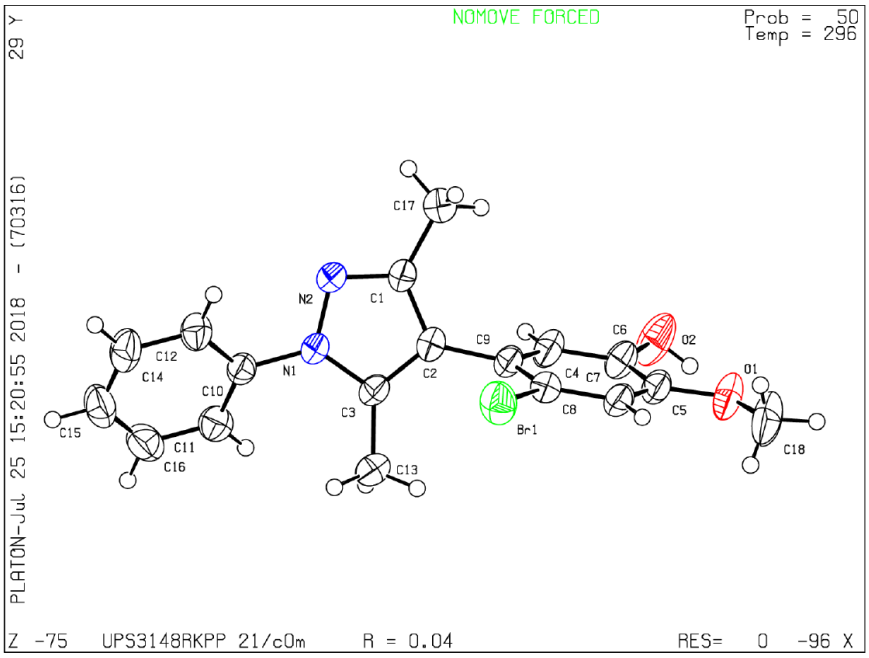


Fig S75: ORTEP diagram of compound **19**.

Table S1: Crystal data of compound **19**.

Formula	$C_{18}H_{17}BrN_2O_2$
Formula Wt.	373.24
Crystal color	Brown
Crystal system	Monoclinic
Space group	P 21/c
a (Å)	12.5690(3)
b (Å)	7.6182(2)
c (Å)	17.8411(4)
α (deg)	90
β (deg)	104.1610(1)
γ (deg)	90
V (Å^3)	1656.43(7)