Supplementary data for

First total synthesis of antrocamphin A and its analogs as anti-inflammatory and anti-platelet aggregation agents

Chia-Lin Lee,[ahi] Chi-Huan Huang,[ai] Hui-Chun Wang,[a] Da-Wei Chuang,[a] Ming-Jung Wu,[b] Sheng-Yang Wang,[c] Tsong-Long Hwang,[d] Chin-Chung Wu,[a] Yeh-Long Chen,[e] Fang-Rong Chang*[af] and Yang-Chang Wu*[gh]

[a] *Graduate Institute of Natural Products, Kaohsiung Medical University, Kaohsiung 807, Taiwan. E-mail: aaronfrc@kmu.edu.tw; Fax, +886 7 311 4773; Tel: +886 7 312 1101 ext. 2162*

[b] *Department of Chemistry, National Sun Yant-sen University, Kaohsiung 804, Taiwan*

[c] *Department of Forestry, National Chung-Hsing University, Taichung 402, Taiwan*

[d] *Graduate Institute of Natural Products, Chang Gung University, Tao-Yuan 333, Taiwan*

[e] *Department of Medicinal and Applied Chemistry, Kaohsiung Medical University, Kaohsiung 807, Taiwan*

[f] *Department of Marine Biotechnology and Resources, National Sun Yat-sen University, Kaohsiung 804, Taiwan*

[g] *Graduate Institute of Integrated Medicine, College of Chinese Medicine, China Medical University, Taichung 40402, Taiwan E-mail: yachwu@mail.cmu.edu.tw; Fax, +886 4 220 60248; Tel: +886 4 220 57153*

[h] *Natural Medicinal Products Research Center, China Medical University Hospital, Taichung 40402, Taiwan*

[i] *Equal contributions as first author*

Contents

Experimental Section

Chemicals and reagents. 2-Hydroxy-3-methoxybenzaldehyde, triethylamine (Et_3N), 2-iodoanisole, 3-iodoanisole, 4-iodotoluene, 4-iodobenzonitrile, 1,2,4-trimethoxybenzene, 1-iodo-4-nitrobenzene, and 1-iodo-2,4-dimethoxybenzene were purchased from Alfa Aesar. Palladium on carbon (extent of label: 10wt% loading, matrix activated carbon), iodine (99.999% trace metals basis) and 2-methyl-1-buten-3-yne were obtained from commercial company, ALDRICH. 50-75% Potassium nitrosodisulfonate (remainder water and methanol), titanium (III) chloride 20% w/w solution in 2N hydrochloric acid, copper (I) iodide, 4-iodoanisole, and 3,5-dimethoxytoluene were purchased from ACROS. Tetrakis(triphenylphosphine) palladium (0) and iodobenzene were bought from TCI company. Anhydrous potassium carbonate, potassium dihydrogenphosphat, 98% silver trifluoroacetate, acetic acid glacial, tetrahydrofuran, and 99.9% anhydrous dichloromethane were purchased from J.T.Baker, SHOWA, Strem Chemicals, Scharlau, ECHO, and Scharlau, respectively.

General. IR spectra were measured on PERKIN ELMER System 2000 FT-IR spectrophotometer. NMR spectra were recorded on Varian Unity-plus 400 MHz FT-NMR and Varian GErmini-2000 200 MHz FT-NMR instruments. Chemical shift (δ) values are in ppm (parts per million) with $CDCl_3$ as the internal standard, and coupling constants (*J*) are in Hz. HRESI-MS, ESI-MS, HREI-MS and EI-MS measurements were performed on a Bruker Daltonics APEX II 30e, THERMO TRACE GC ULTRA DSQ II, C400 , A. JEOL JMS-700 and B. SHIMADZU QP2010 mass spectrometers, respectively. TLC was performed on Kieselgel 60, F 254 (0.20 nm, Merck), and spots were viewed under ultraviolet light

at 254 and 356 nm. For column chromatography, silica gel (Kieselgel 60, 70–230, and 230–400 mesh, Merck) and a Biotage® SP system apparatus were used.

Characterization of all compounds

2-Hydroxy-3-methoxytoluene (4).[1] *o*-Vanillin (**5**) (2.00 g, 13.2 mmol) and 10% Pd/C (1.00 g) were placed under H_2 in the mixture solvent consisting of EtOAc (40 mL) and acetic acid (10 mL) and reacted at room temperature for 3 days. The mixture was filtered with celite® 545 to remove 10% Pd/C and the solvent was evaporated. The crude product was chromatographed on silica gel eluting with EtOAc/*n*-hexane (1:10) to yield **4** (1.43 g). Milky crystal; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.27 (3H, s, CH_3), 3.88 (3H, s, OCH_3), 5.70 (1H, s, OH), 6.75 (3H, brs); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 15.4, 56.0, 108.2, 119.1, 123.2, 123.9, 143.7, 146.2.

2-Methoxy-6-methyl-1,4-benzoquinone (6).[1] Potassium nitrosodisulfonate [fremy's salt, $(KSO_3)_2NO$] (4.90 g, 18.1 mmol) and KH_2PO_4 (0.82 g, 6.0 mmol) were added in the 250 mL of water. Then, the mixture solution was treated in portions with a solution of compound **4** (1.00 g, 7.2 mmol) in 25 mL of ether. The reaction mixture was stirred for 1 h, during which time a yellow precipitate formed little by little. Finally, the mixture was extracted with CH_2Cl_2 (100 mL × 3) and dried with $MgSO_4$ to afford compound **6** (771.40 mg). Yellow solid; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.06 (3H, d, J = 1.6 Hz, CH_3), 3.81 (3H, s, OCH_3), 5.87 (1H, d, J = 2.4 Hz), 6.53 (1H, m); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 55.5, 104.7, 121.2, 142.7, 158.0, 177.6, 179.2.

2,5-Dihydroxy-3-methoxytoluene (7).[1] Titanium trichloride (11.73 g) was added dropwise into the solution of **6** (771.40 mg, 5.1 mmol) in 15 mL of acetone. The 50 mL brine was poured into the reaction mixture after reacting at room temperature for 10-20 min. The mixture was extracted with ether (50 mL) to afford compound **7** (783.90 mg). White solid; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.11 (3H, s, CH_3), 3.76 (3H, s, OCH_3), 6.20 (1H, d, J = 2.6 Hz), 6.31 (1H, d, J = 2.6 Hz), 6.66 (1H, s, OH), 7.58 (1H, s, OH); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 14.8, 55.1, 97.3, 108.3, 123.6, 137.1, 147.1, 149.6.

2,3,5-Trimethoxytoluene (8).[1] The hydroquinone **7** (767.60 mg, 4.9 mmol) and K_2CO_3 (6.88 g, 49.8 mmol) were dissolved in acetone (10 mL) and then dimethyl sulfate (1.57 g, 14.9 mmol) was added. The mixture was stirred at 67 ^{o}C for 15 h, and the K_2CO_3 was then removed. The crude product was chromatographed on silica gel and eluted with EtOAc/*n*-hexane (1:10) to yield **8** (795.95 mg). Pale yellow oil; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.29 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 3.79 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 6.30 (1H, d, J = 2.6 Hz), 6.38 (1H, d, J = 2.6 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 16.2, 55.6, 55.9, 60.4, 98.0, 106.1, 132.1, 141.6, 153.4, 155.9.

2-Iodo-3,5,6-trimethoxytoluene (2). Iodine (1.30 g, 5.2 mmol) and CF_3COOAg (1.20 g, 5.2 mmol) were dissolved in CH_2Cl_2 (10 mL) and then compound **8** (788.00 mg, 4.3 mmol) was added into the mixture solution. The reaction mixture was filtered after stirring at 0 ^{o}C for 8 h and the saturated $Na_2SO_{3(aq)}$ was added into the filtrate. The mixture was dried with $MgSO_4$ to afford compound **2** (986.00 mg) after chromatography with EtOAc/*n*-hexane (1:8). White solid; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.43 (3H, s, CH_3), 3.72 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.87 (3H, s, OCH_3), 6.41 (1H, s); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 21.7, 56.0, 56.8, 60.6, 82.1, 94.8, 136.1, 141.3, 153.2, 154.6.

Antrocamphin A (1).[2] $Pd(PPh_3)_4$ (57.80 mg, 5 mol%) and CuI (19.10 mg, 10 mol%) were dissolved in Et_3N/THF (1:1, 10 mL) and then compound **2** (308.11 mg, 1.0 mmol) and 2-methylbut-1-en-3yne (**3**) (0.11 mL, 1.2 mmol) were added. The mixture was stirred under N_2 at room temperature for 12 h and then extract with EtOAc (50 mL) and dried with $MgSO_4$ to afford **1** (25.00 mg) after chromatography with EtOAc/*n*-hexane (1:4). Yellow oil; IR (neat) ν_{max} 2193 (C≡C), 1594, 1487, 1453 (aromatic C=C stretch) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.01 (3H, dd, J = 0.8, 1.2 Hz, CH_3), 2.35 (3H, s, CH_3), 3.72 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 5.25 (1H, q, J = 0.8 Hz), 5.37 (1H, q, J = 1.2 Hz), 6.33 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 14.1, 23.7, 55.8, 56.3, 60.4, 83.6, 94.3, 97.5, 104.8, 120.7, 127.3, 135.3, 141.1, 153.4, 157.2; EI-MS m/z 246.10 $[M]^+$.

Compound 9. The commercial iodobenzene (0.11 mL, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.11 mL, 1.0 mmol) and Et_3N/THF (1:1, 10 mL) were used with the method described for **1** to yield **9** (132.21 mg) after chromatography with *n*-hexane. Pale yellow oil; IR (neat) ν_{max} 2199 (C≡C), 1487, 1443 (aromatic C=C stretch) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.99 (3H, t, J = 1.2 Hz, CH_3), 5.30 (1H, m), 5.39 (1H, m), 7.31 (3H, m), 7.44 (2H, m); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.5, 88.3, 90.5, 121.9, 123.2, 126.8, 128.1, 128.3 (2C), 131.6 (2C); EI-MS m/z 142.10 $[M]^+$.

Compound 10. The commercial 4-iodoanisole (234.16 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.11 mL, 1.2 mmol) and Et_3N/THF (1:1, 10 mL) were used with the method described for **1** to afford **10** (149.71 mg) after chromatography with

n-hexane. Yellow oil; IR (neat) ν_{max} 2199 (C≡C), 1601, 1509, 1454 (aromatic C=C stretch) cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz): δ 1.98 (3H, m, CH_3), 3.81 (3H, s, OCH_3), 5.26 (1H, m), 5.35 (1H, m), 6.83 (2H, d, *J* = 9.0 Hz), 7.38 (2H, d, *J* = 9.0 Hz); ^{13}C NMR ($CDCl_3$, 50 MHz): δ 23.6, 55.3, 88.4, 89.3, 113.9 (2C), 115.4, 121.2, 127.0, 133.0 (2C), 159.5; EI-MS *m*/*z* 172.20 $[M]^+$.

Compound 11. The commercial 2-iodoanisole (0.13 mL, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.11 mL, 1.2 mmol) and Et_3N/THF (1:1, 10 mL) were used with the method described for **1** to yield **11** (125.15 mg) after chromatography with *n*-hexane. Pale yellow oil; IR (neat) ν_{max} 2199 (C≡C), 1594, 1491, 1458 (aromatic C=C stretch) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.0 (s, CH_3), 3.87 (s, OCH_3), 5.28 (1H, m), 5.41 (1H, m), 6.85 (2H, m), 7.27 (1H, td, *J* = 7.4, 1.6 Hz), 7.40 (1H, dd, *J* = 7.4, 1.6 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 23.5, 55.8, 84.6, 94.6, 110.6, 112.4, 120.4, 121.8, 127.0, 129.6, 133.5, 159.8; EI-MS *m*/*z* 172.10 $[M]^+$.

Compound 12. The commercial 3-iodoanisole (0.12 mL, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.11 mL, 1.0 mmol) and Et_3N/THF (1:1, 10 mL) were used with the method described for **1** to afford **12** (93.95 mg) after chromatography with *n*-hexane. Pale yellow oil; IR (neat) ν_{max} 2191 (C≡C), 1594, 1480 (aromatic C=C stretch) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.99 (3H, t, *J* = 1.2 Hz, CH_3), 3.80 (3H, s, OCH_3), 5.31 (1H, m), 5.40 (1H, m), 6.87 (1H, ddd, *J* = 8.4, 5.2, 1.2 Hz), 6.98 (1H, dd, *J* = 5.2, 1.2 Hz), 7.05 (1H, dt, *J* = 7.6, 1.2 Hz), 7.22 (1H, t, *J* = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.5, 55.2, 88.3, 90.3, 114.8, 116.2, 122.1, 124.1, 124.2, 126.8, 129.3, 159.3; EI-MS *m*/*z* 172.10 $[M]^+$.

Compound 13. The commercial 4-iodotoluene (218.11 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.11 mL, 1.2 mmol) and Et_3N/THF (1:1, 10 mL) were used with the method described for **1** to yield **13** (138.56 mg) after chromatography with *n*-hexane. Pale yellow oil; IR (neat) ν_{max} 2197 (C≡C), 1610, 1509, 1461 (aromatic C=C stretch) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.99 (3H, m, CH_3), 2.35 (3H, s, OCH_3), 5.28 (1H, m), 5.37 (1H, m), 7.27 (2H, d, J = 8.0 Hz), 7.34 (2H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.5, 23.5, 88.5, 89.9, 120.2, 121.5, 127.0, 129.0 (2C), 131.5 (2C), 138.2; EI-MS m/z 156.10 $[M]^+$.

Compound 14. The commercial 4-iodo-benzonitrile (229.09 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.11 mL, 1.2 mmol) and Et_3N/THF (1:1, 10 mL) were used with the method described for **1** to yield **14** (138.50 mg) after chromatography with EtOAc/*n*-hexane (1:10). Milky white crystal; IR (neat) ν_{max} 2214 (C≡C), 2236 (C≡N), 1605, 1498, 1432 (aromatic C=C stretch) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 1.94 (3H, s, CH_3), 5.38 (1H, brs), 5.46 (1H, brs), 7.51 (2H, d, J = 8.4 Hz), 7.60 (2H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.2, 86.6, 94.9, 112.0, 118.5, 123.7, 126.2, 128.2 (2C), 131.9, 132.0 (2C); EI-MS m/z 167.10 $[M]^+$.

Compound 15. The commercial 1,2,4-trimethoxybenzene (0.15 mL, 1.0 mmol), iodine (328.90 mg, 1.3 mmol) and CF_3COOAg (287.14 mg, 1.3 mmol) were used with the method described for **2** to offer 1-iodo-2,4,5-trimethoxybenzene (298.00 mg, 100%). ^1H NMR ($CDCl_3$, 200 MHz): δ 3.83 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.56 (1H, s), 7.03 (1H, s). 1-Iodo-2,4,5-trimethoxybenzene (294.01 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.11 mL, 1.2 mmol) and Et_3N/THF (1:1, 10 mL) were used with the

method described for **1** to offer **15** (188.03 mg) after chromatography with EtOAc/*n*-hexane (1:8). Milky white solid; IR (neat) ν_{max} 2199 (C≡C), 1605, 1513, 1458 (aromatic C=C stretch) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.00 (3H, m, CH_3), 3.84 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.26 (1H, m), 5.38 (1H, m), 6.47 (1H, s), 6.90 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.6, 56.0, 56.4, 56.8, 84.7, 93.5, 97.3, 103.3, 115.8, 121.3, 127.0, 142.8, 150.2, 155.2; ESI-MS *m*/*z* 255 $[M + Na]^+$; HRESI-MS *m*/*z* 255.0995 $[M + Na]^+$ (calculated for $C_{14}H_{16}O_3Na$ 255.0997).

Compound 16. The commercial 1-iodo-4-nitrobenzene (249.01 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.11 mL, 1.2 mmol) and Et_3N/THF (1:1, 10 mL) were used with the method described for **1** to yield **16** (155.28 mg) after chromatography with EtOAc/*n*-hexane (1:10). White crystal; IR (neat) ν_{max} 2202 (C≡C), 1592 ($ArNO_2$), 1515, 1503 (aromatic C=C stretch) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.01 (3H, m, CH_3), 5.41 (1H, m), 5.49 (1H, m), 7.57 (2H, d, *J* = 9.2 Hz), 8.18 (2H, d, *J* = 9.2 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.1, 86.5, 95.8, 123.6, 124.0 (2C), 126.1, 130.3, 132.3 (2C), 146.9; ESI-MS *m*/*z* 210 $[M + Na]^+$; HRESI-MS *m*/*z* 210.0530 $[M + Na]^+$ (calculated for $C_{11}H_9NO_2Na$ 210.0531).

Compound 17. The commercial 2-iodotoluene (0.13 mL, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.11 mL, 1.2 mmol) and Et_3N/THF (1:1, 10 mL) were used with the method described for **1** to yield **17** (120.13 mg) after chromatography with *n*-hexane. Pale yellow oil; IR (neat) ν_{max} 2198 (C≡C), 1611, 1481, 1450 (aromatic C=C stretch) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.02 (3H, s, CH_3), 2.45 (3H, s, CH_3), 5.30 (1H, brs), 5.40 (1H, brs), 7.15 (1H, m),

7.21 (2H, m), 7.42 (1H, d, J = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 20.6 (s, CH_3), 23.6 (s, CH_3), 87.3, 94.5, 121.5, 122.9, 125.5, 127.0, 128.2, 129.4, 131.8, 140.1; EI-MS m/z 156.20 $[M]^+$.

Compound 18. The commercial 2,5-diiodo-*p*-xylene (357.96 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.24 mL, 2.4 mmol) and Et_3N/THF (1:1, 10 mL) were used with the method described for **1** to yield **18** (72.58 mg) after chromatography with EtOAc/*n*-hexane (1:10). White amorphous powder; IR (neat) ν_{max} 2197 (C≡C), 1610, 1485, 1452 (aromatic C=C stretch) cm-1; 1H NMR (CDCl3, 400 MHz): δ 2.00 (6H, m, CH3), 2.36 (6H, s, CH3), 5.29 (2H, m), 5.38 (2H, m), 7.25(2H, s); 13C NMR (CDCl3, 100 MHz): δ 19.9, 23.5, 87.3, 95.6, 121.8, 122.8, 126.9, 132.5, 137.1; EI-MS m/z 234.20 [M]+; HREI-MS m/z 234.2409 $[M]^+$ (calculated for $C_{18}H_{18}$ 234.3355).

Compound 19. The commercial 2,3-dimethoxytoluene (0.15 mL, 1.0 mmol), iodine (279.19 mg, 1.1 mmol) and CF_3COOAg (242.97 mg, 1.1 mmol) were used with the method described for **2** to offer 2-iodo-5,6-dimethoxytoluene (270.8 mg, 97%). ^{1}H NMR ($CDCl_3$, 200 MHz): δ 2.38 (3H, s, CH_3), 3.77 (3H, s, OCH_3), 3.83 (3H, s, OCH_3), 6.54 (1H, d, J = 8.8 Hz), 7.51 (1H, d, J = 8.8 Hz). 2-Iodo-5,6-dimethoxytoluene (292.07 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.11 mL, 1.2 mmol) and Et_3N/THF (1:1, 10 mL) were used with the method described for **1** to offer **19** (157.80 mg) after chromatography with EtOAc/*n*-hexane (1:8). Pale yellow oil; IR (neat) ν_{max} 2191 (C≡C), 1590, 1483, 1450 (aromatic C=C stretch) cm^{-1}; ^{1}H NMR ($CDCl_3$, 400 MHz): δ 2.00 (3H, m, CH_3), 2.37 (3H, s), 3.78 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.25 (1H, m), 5.35 (1H, m), 6.70 (1H, d, J = 8.4 Hz), 7.16 (1H, d, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz):

δ 13.9, 23.6, 55.7, 60.2, 87.3, 92.9, 109.5, 116.3, 120.9, 127.1, 128.0, 134.3, 147.1, 153.1; EI-MS *m*/*z* 216.06 $[M]^+$; HREI-MS *m*/*z* 216.1151 $[M]^+$ (calculated for $C_{14}H_{16}O_2$ 216.1150).

Compound 20. 1-Iodo-2,4-dimethoxybenzene (264.06 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.11 mL, 1.2 mmol) and Et_3N/THF (1:1, 10 mL) were used with the method described for **1** to offer **20** (127.26 mg) after chromatography with EtOAc/*n*-hexane (1:8). Pale yellow oil; IR (neat) ν_{max} 2191 (C≡C), 1601, 1502, 1461 (aromatic C=C stretch) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.00 (3H, t, *J* = 1.2 Hz, CH_3), 3.81 (3H, s, OCH_3), 3.86 (3H, s, OCH_3), 5.25 (1H, q, *J* = 1.2 Hz), 5.37 (1H, q, *J* = 1.2 Hz), 6.43 (2H, m), 7.33 (1H, d, *J* = 8.0 Hz); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.7, 55.4, 55.8, 84.7, 93.3, 98.4, 104.7, 104.9, 121.1, 127.2, 134.3, 161.0, 161.1; EI-MS *m*/*z* 202.05 $[M]^+$; HREI-MS *m*/*z* 202.0992 $[M]^+$ (calculated for $C_{13}H_{14}O_2$ 202.0994).

Compound 21. The commercial 3,5-dimethoxytoluene (0.15 mL, 1.0 mmol), iodine (279.19 mg, 1.1 mmol) and CF_3COOAg (242.97 mg, 1.1 mmol) were used with the method described for **2** to offer 2-iodo-3,5-dimethoxytoluene (225.30 mg, 81%); ^1H NMR ($CDCl_3$, 200 MHz): δ 2.47 (3H, s, CH_3), 3.82 (3H, s, OCH_3), 3.88 (3H, s, OCH_3), 6.30 (1H, d, *J* = 2.6 Hz), 6.51 (1H, d, *J* = 2.6 Hz) and 2,6-diiodo-3,5-dimethoxytoluene (28.60 mg, 7%); ^1H NMR ($CDCl_3$, 200 MHz): δ 2.86 (3H, s, CH_3), 3.90 (6H, s, OCH_3), 6.29 (1H, s). 1-Iodo-2,4-dimethoxytoluene (278.09 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.11 mL, 1.2 mmol) and Et_3N/THF (1:1, 10 mL) were used with the method described for **1** to offer **21** (36.76 mg) after chromatography with EtOAc/*n*-hexane (1:4). Pale yellow solid; IR (neat) ν_{max} 2191 (C≡C), 1601, 1487,

1461 (aromatic C=C stretch) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.02 (3H, s, CH_3), 2.40 (3H, s, CH_3), 3.80 (3H, s, OCH_3), 3.84 (3H, s, OCH_3), 5.24 (1H, brs), 5.37 (1H, brs), 6.28 (1H, d, J = 2.4 Hz), 6.37 (1H, d, J = 2.4 Hz);^{13}C NMR ($CDCl_3$, 100 MHz): δ 21.1, 23.8, 55.3, 55.9, 83.6, 95.7, 97.7, 104.0, 106.2, 120.5, 127.4, 143.3, 160.3, 161.2; EI-MS *m*/*z* 216.20 $[M]^+$; HREI-MS *m*/*z* 216.1147 $[M]^+$ (calculated for $C_{14}H_{16}O_2$ 216.1150).

Compound 22. 2,6-Diiodo-3,5--dimethoxytoluene (403.98 mg, 1.0 mmol), $Pd(PPh_3)_4$ (57.78 mg, 5 mol%), CuI (19.05 mg, 10 mol%), 2-methylbut-1-en-3-yne (**3**) (0.11 mL, 1.2 mmol) and Et_3N/THF (1:1, 10 mL) were used with the method described for **1** to offer **22** (44.30 mg) after chromatography with EtOAc/*n*-hexane (1:4). Transparent crystal; IR (neat) ν_{max} 2199 (C≡C), 1576, 1458 (aromatic C=C stretch) cm^{-1}; ^1H NMR ($CDCl_3$, 400 MHz): δ 2.01 (3H, m), 2.64 (3H, s, CH_3), 3.89 (3H, s, OCH_3), 3.90 (3H, s, OCH_3), 5.26 (1H, m), 5.38 (1H, m), 6.29 (1H, s); ^{13}C NMR ($CDCl_3$, 100 MHz): δ 23.6, 27.3, 56.1, 56.5, 82.3, 83.7, 92.5, 97.9, 105.8, 121.1, 127.1, 145.5, 158.7, 161.6; EI-MS *m*/*z* 342.00 $[M]^+$; HREI-MS *m*/*z* 342.0117 $[M]^+$ (calculated for $C_{14}H_{15}O_2I$ 342.0117).

Nitric oxide inhibitory assay.[3] Effects of all compounds on NO production were measured indirectly by analysis of nitrite levels using the Greiss reaction. This assay was carried out according to established protocols.

Measurement of superoxide generation and elastase release.[4,5] The method of preparation of human neutrophils approved by the institutional review board at Chang Gung Memorial Hospital was used. All compounds were tested on the superoxide generation and elastase release.

Measurement of platelet aggregation.[6] Platelet aggregation was measured with a light-transmission aggregometer (Chrono-Log Co., U.S.A.). The platelet suspension was incubated with DMSO (vehicle) or tested compounds at 37 ^{o}C for 3 min with a stirrer (1200 rpm) prior to the addition of the platelet aggregation inducers. The extent of platelet aggregation was measured as the maximal increase of light transmission within 5 min after the addition of inducers.

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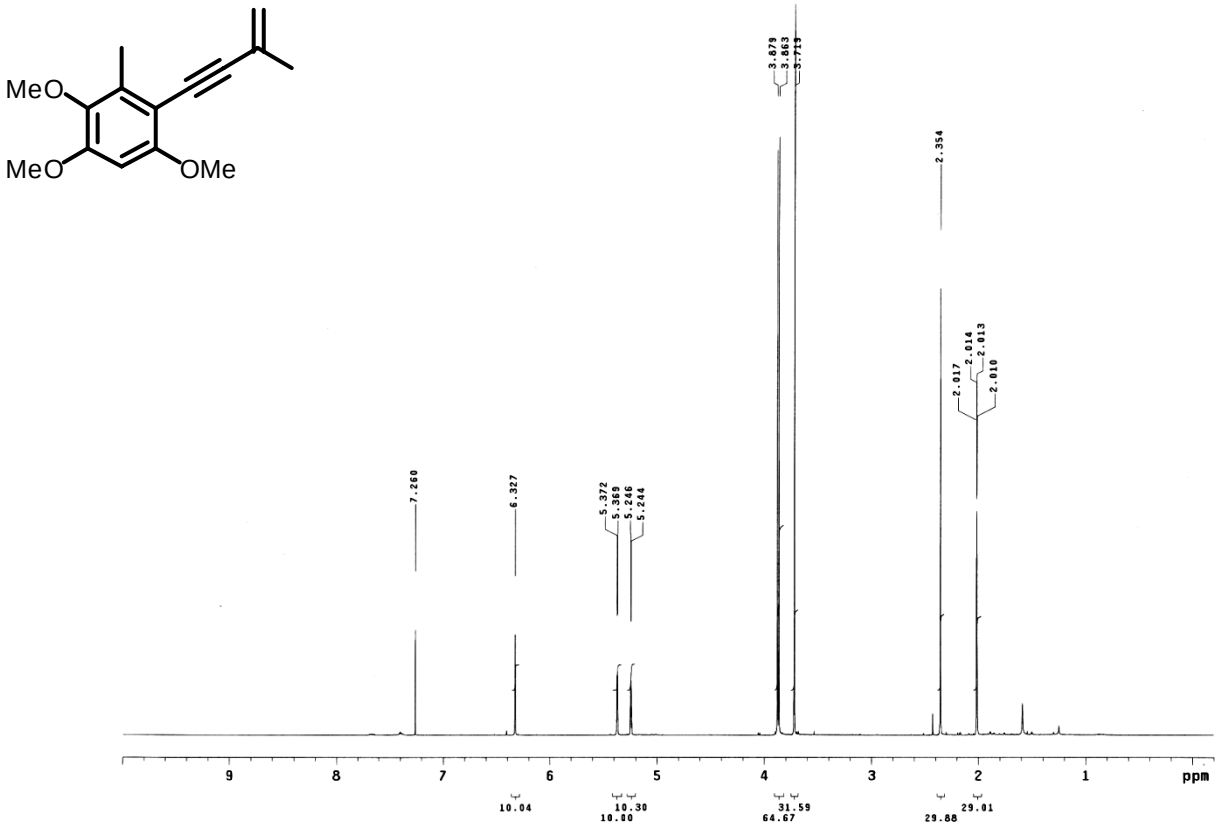

Fig. S1 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **1**

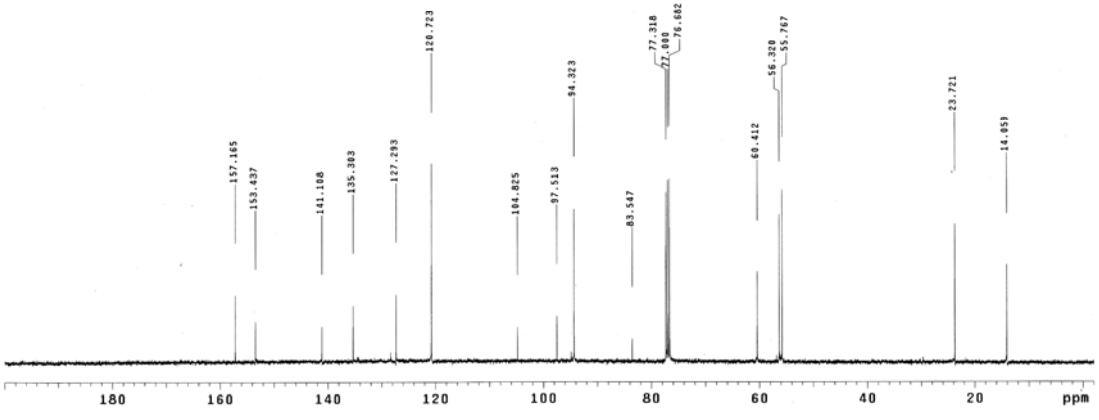

Fig. S2 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **1**

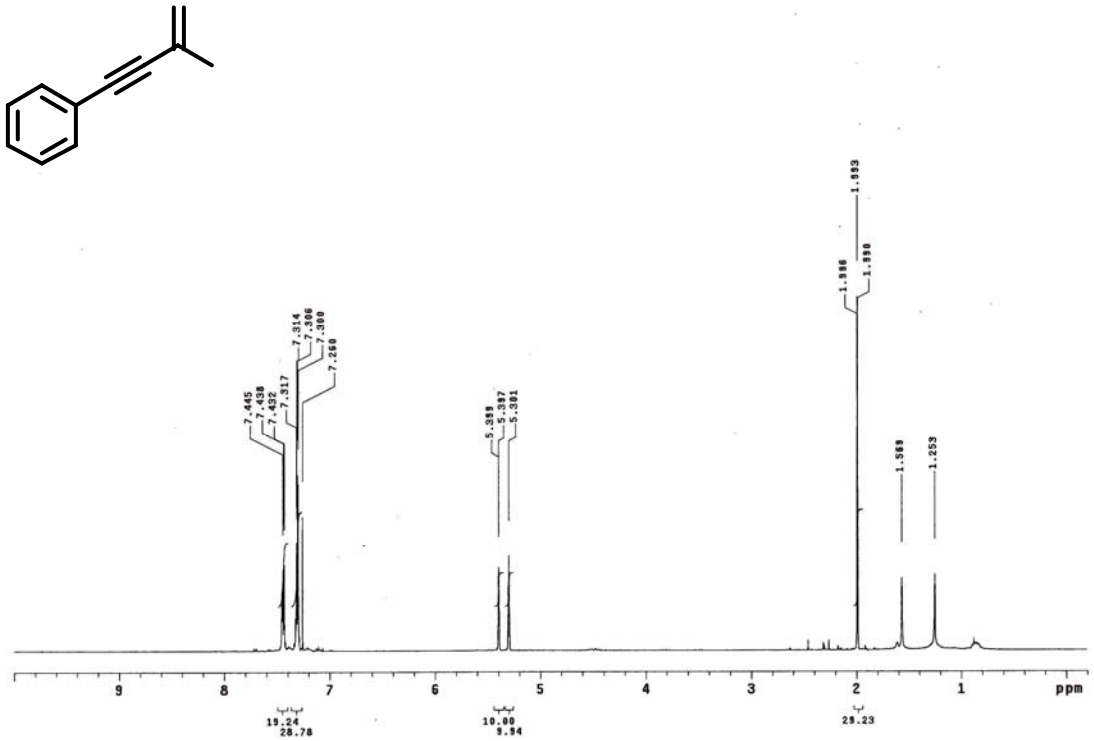

Fig. S3 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **9**

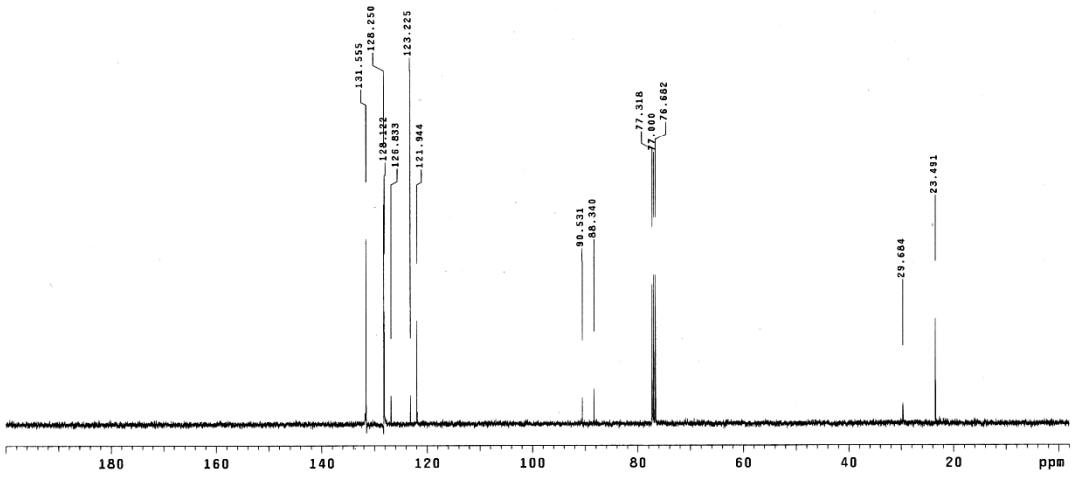

Fig. S4 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **9**

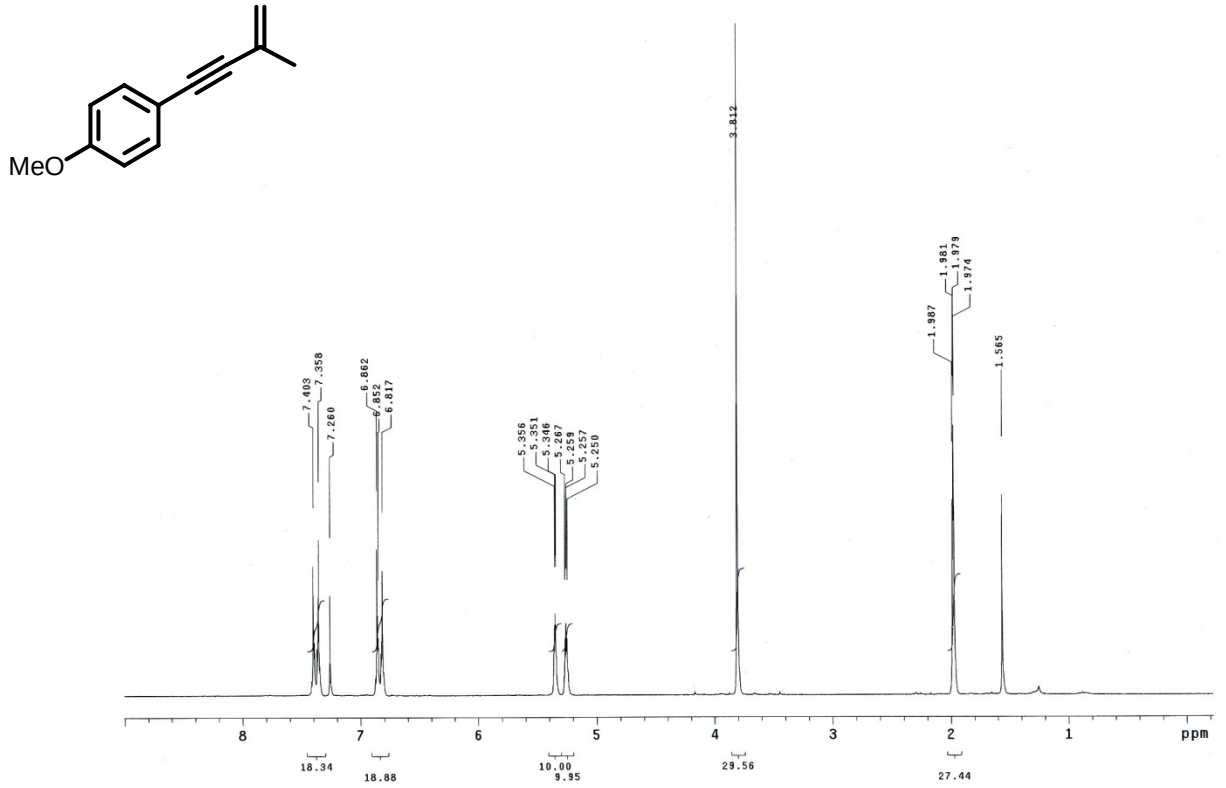

Fig. S5 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **10**

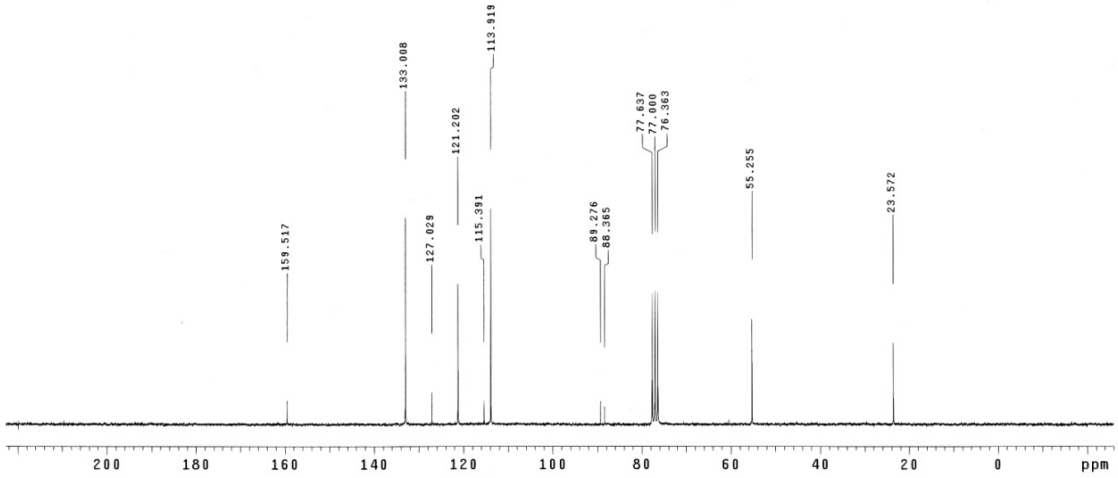

Fig. S6 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **10**

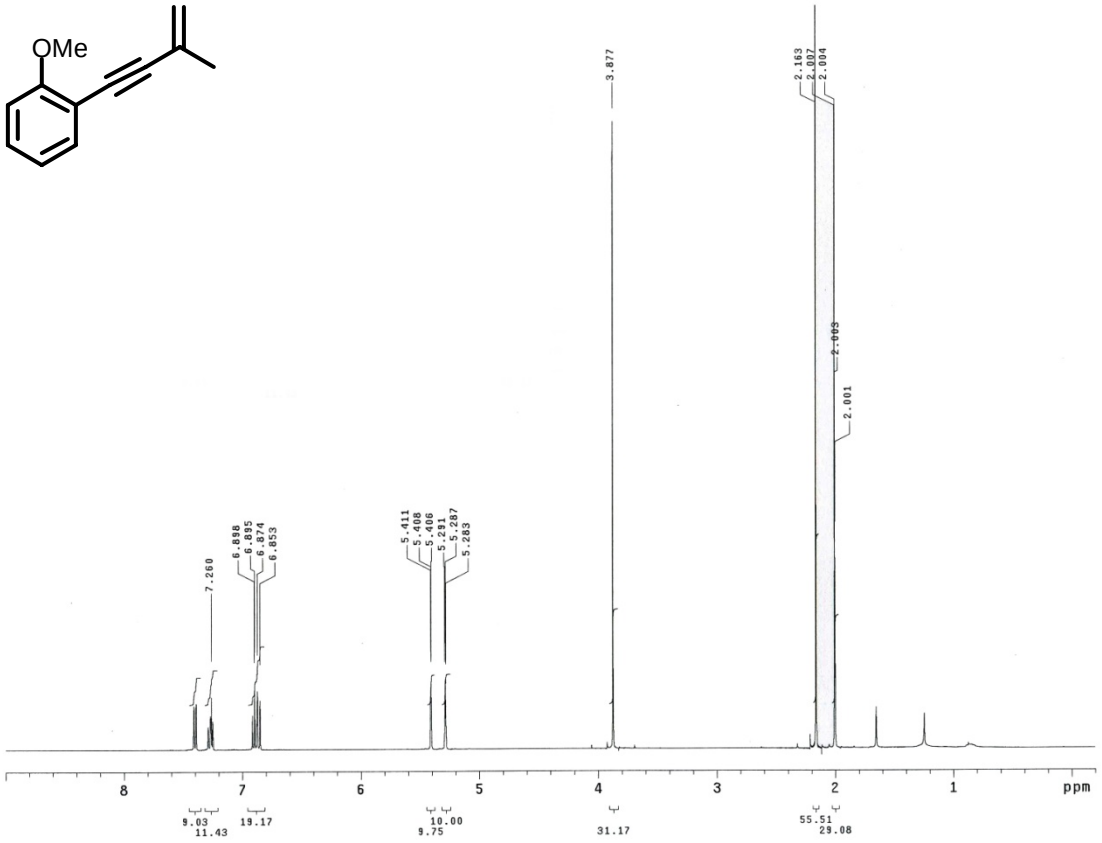

Fig. S7 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **11**

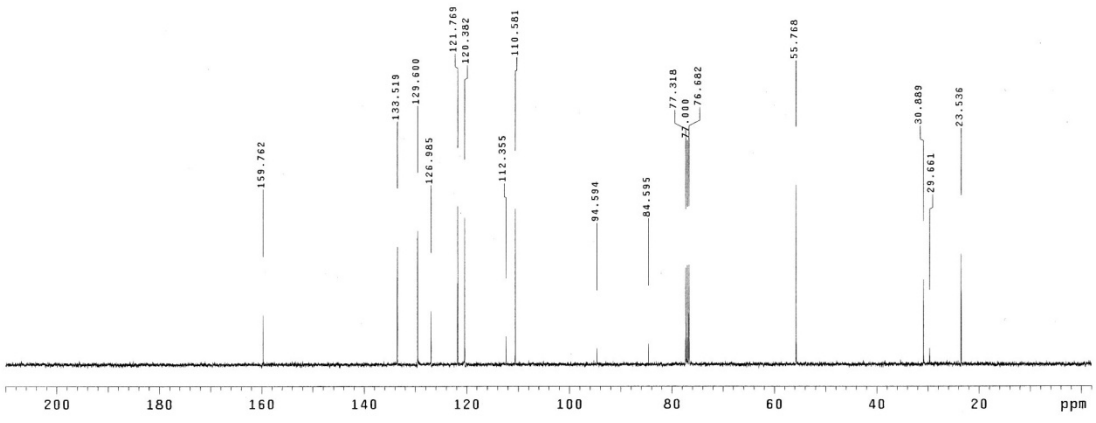

Fig. S8 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **11**

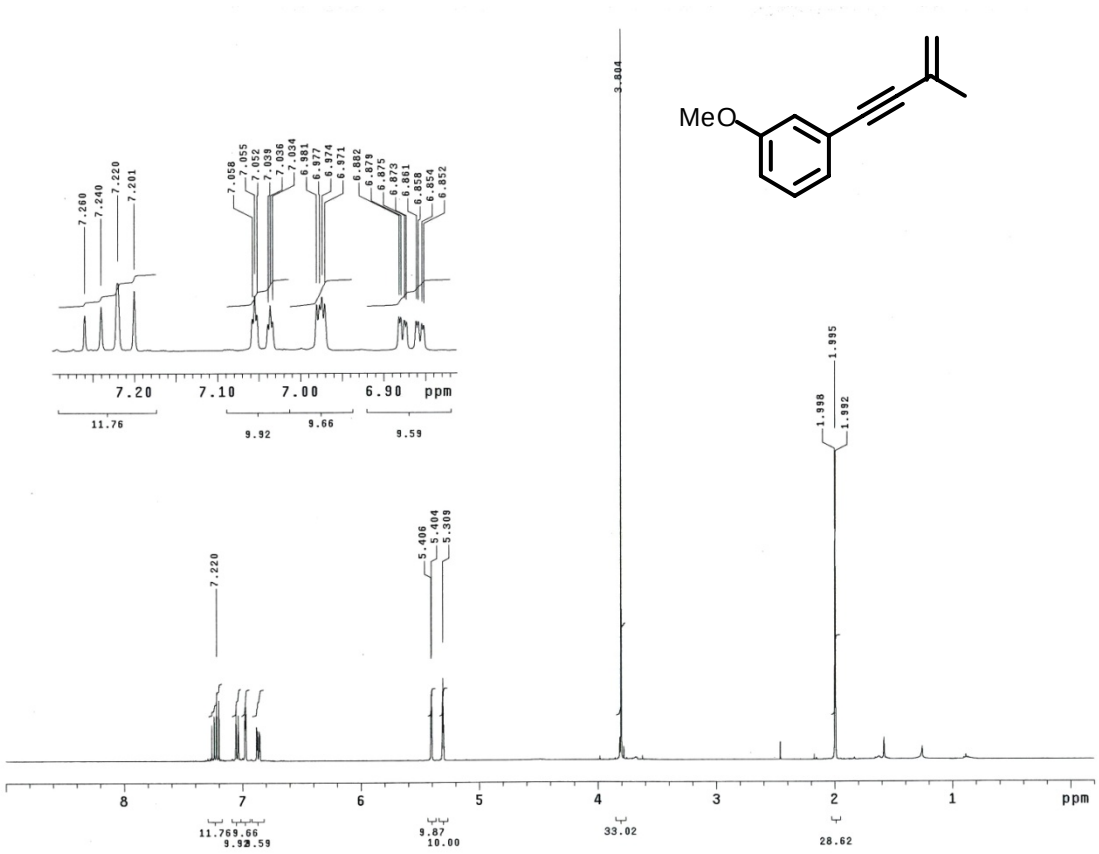

Fig. S9 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **12**

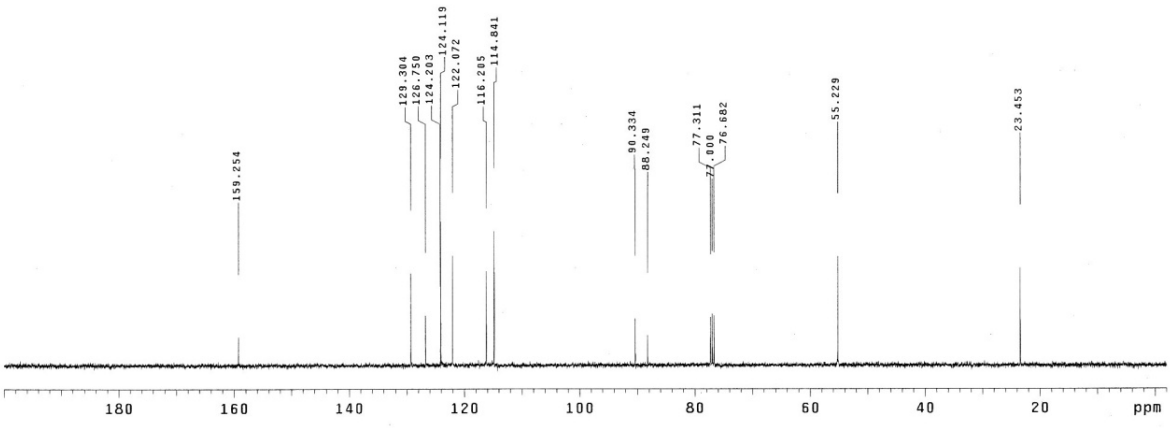

Fig. S10 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **12**

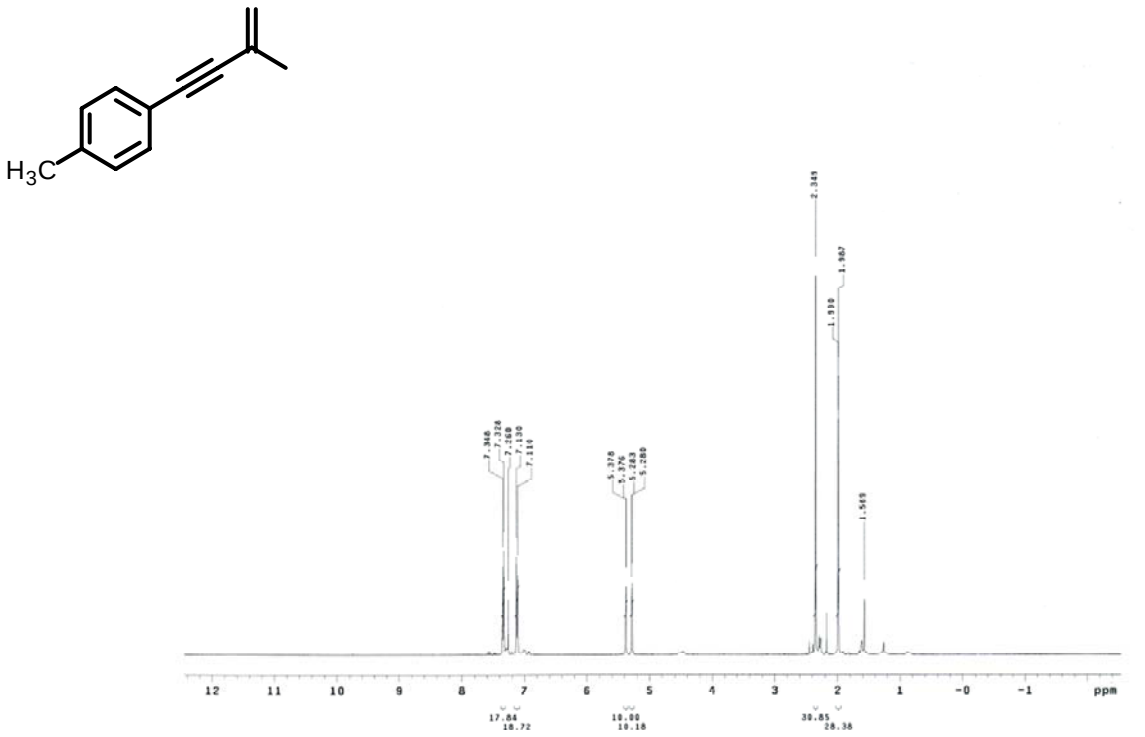

Fig. S11 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **13**

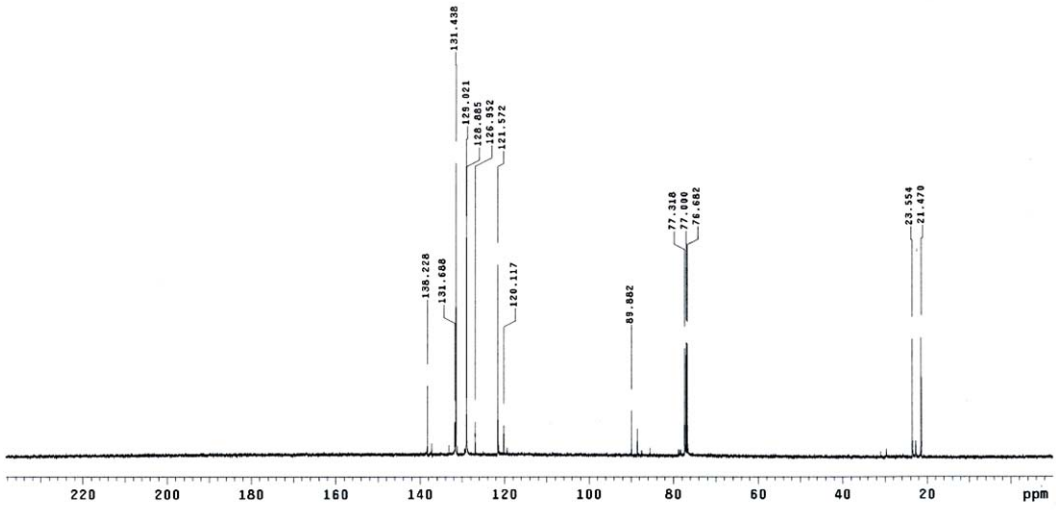

Fig. S12 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **13**

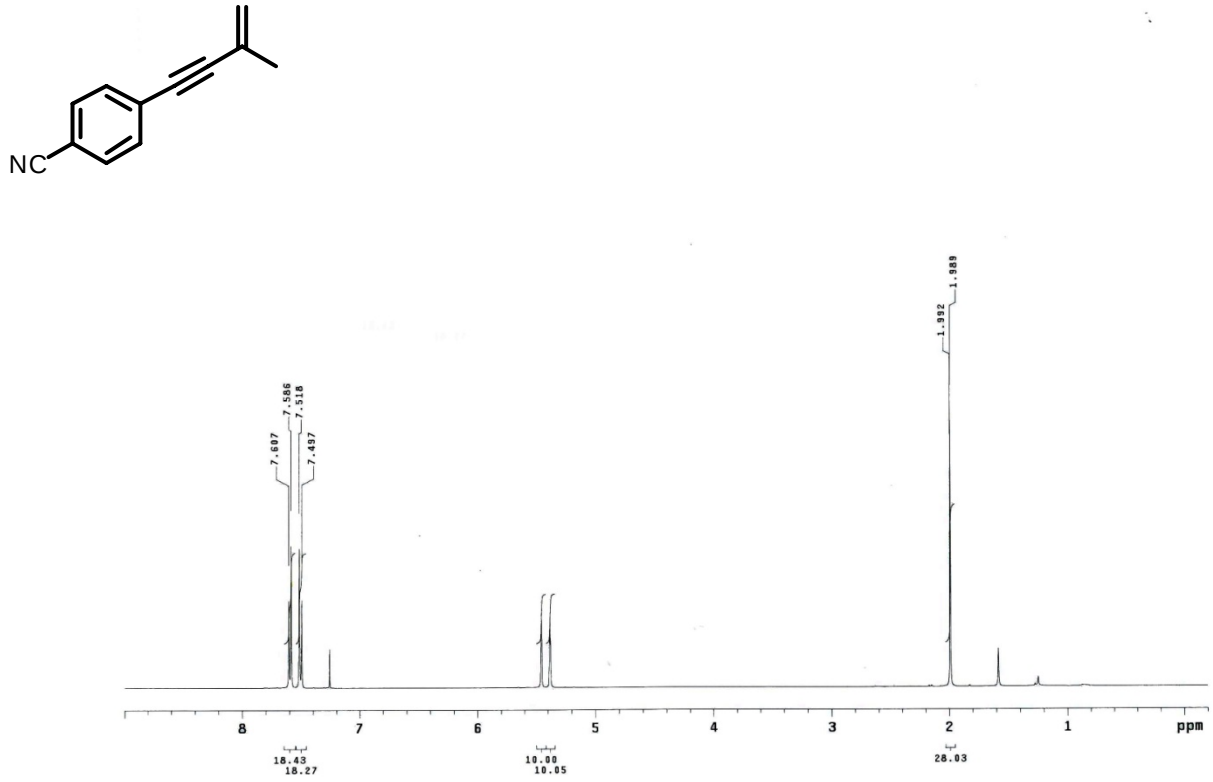

Fig. S13 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **14**

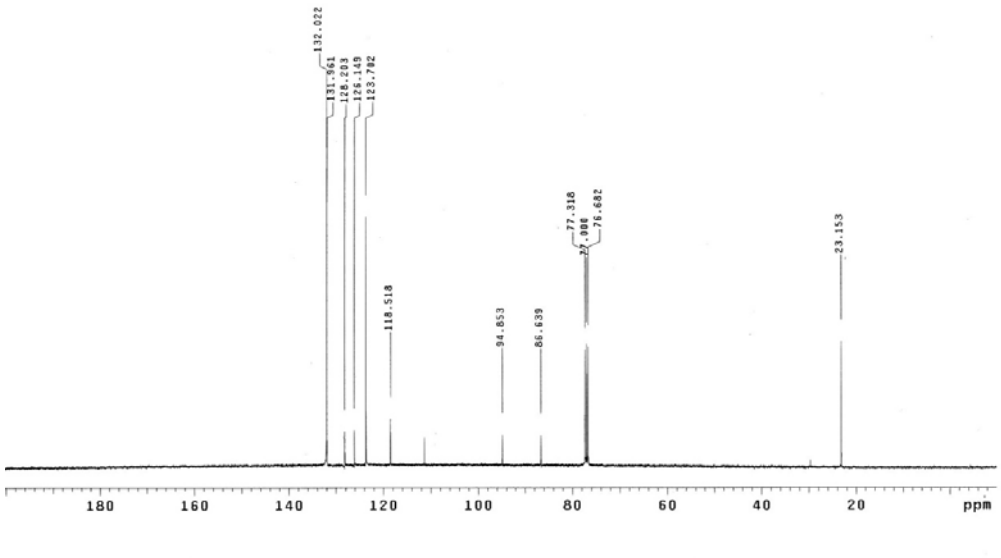

Fig. S14 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **14**

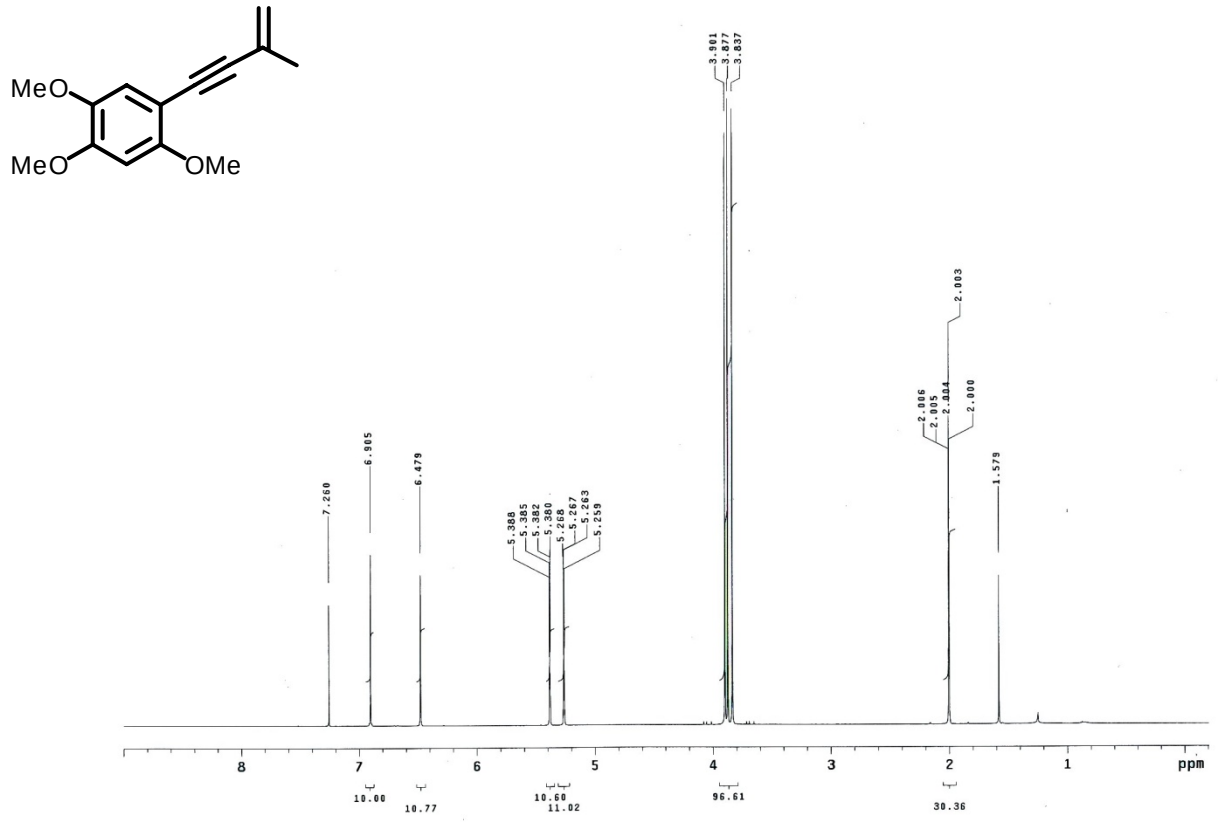

Fig. S15 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **15**

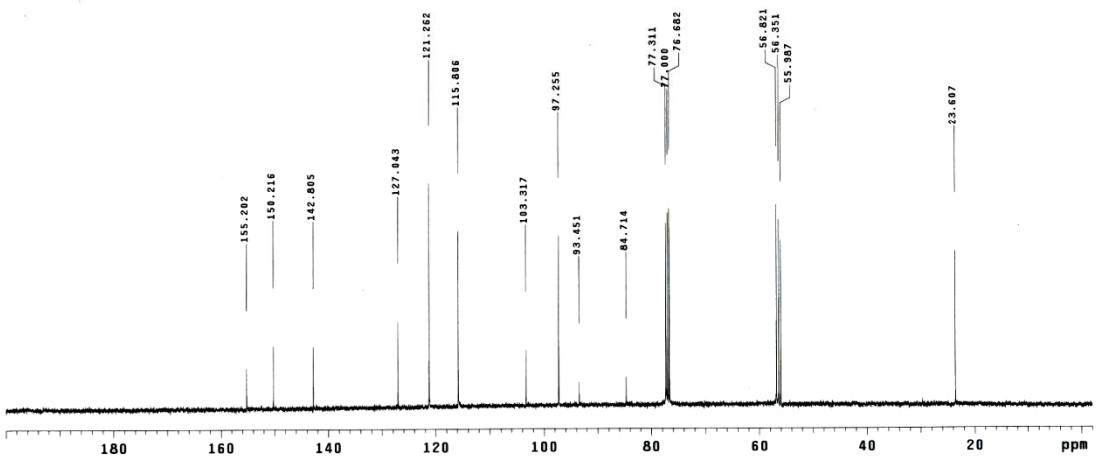

Fig. S16 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **15**

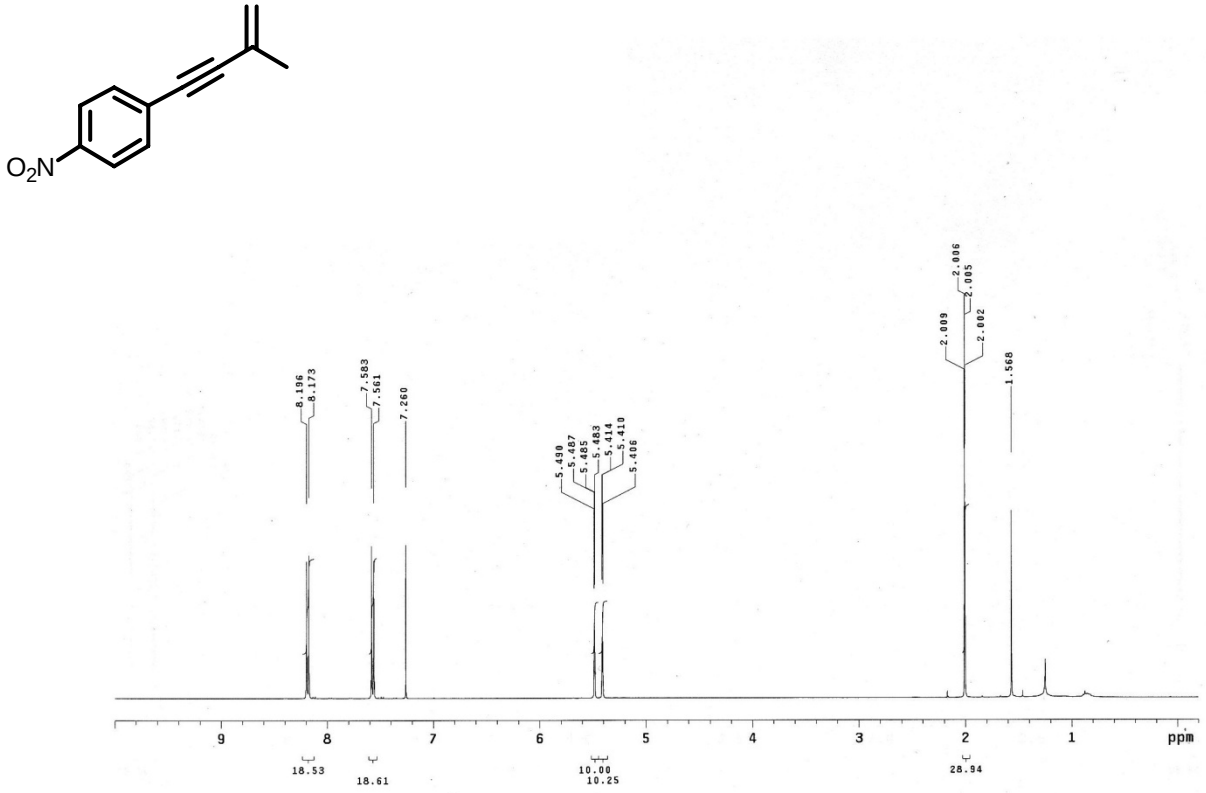

Fig. S17 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **16**

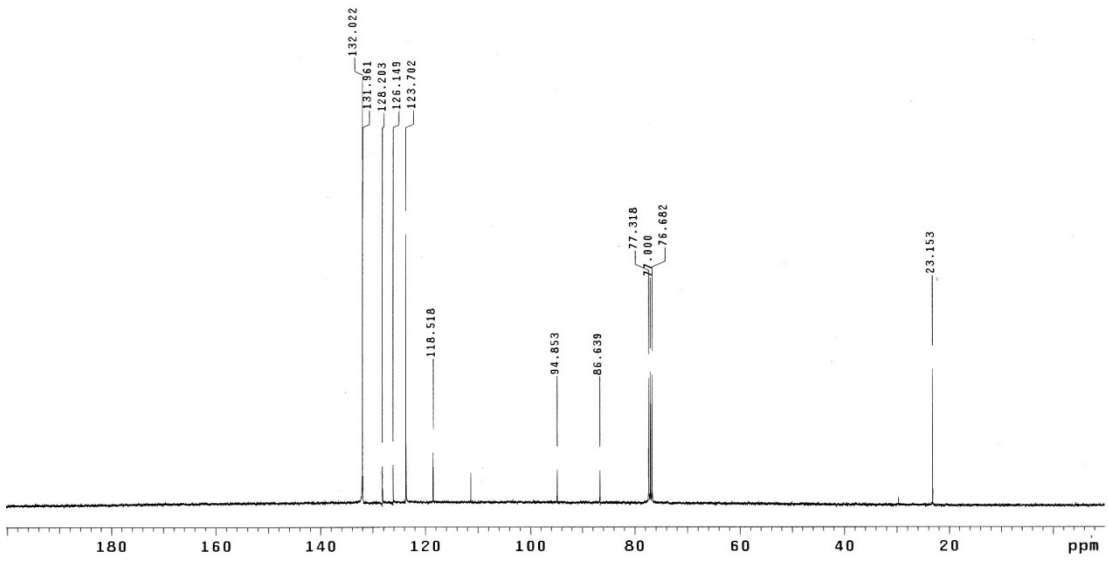

Fig. S18 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **16**

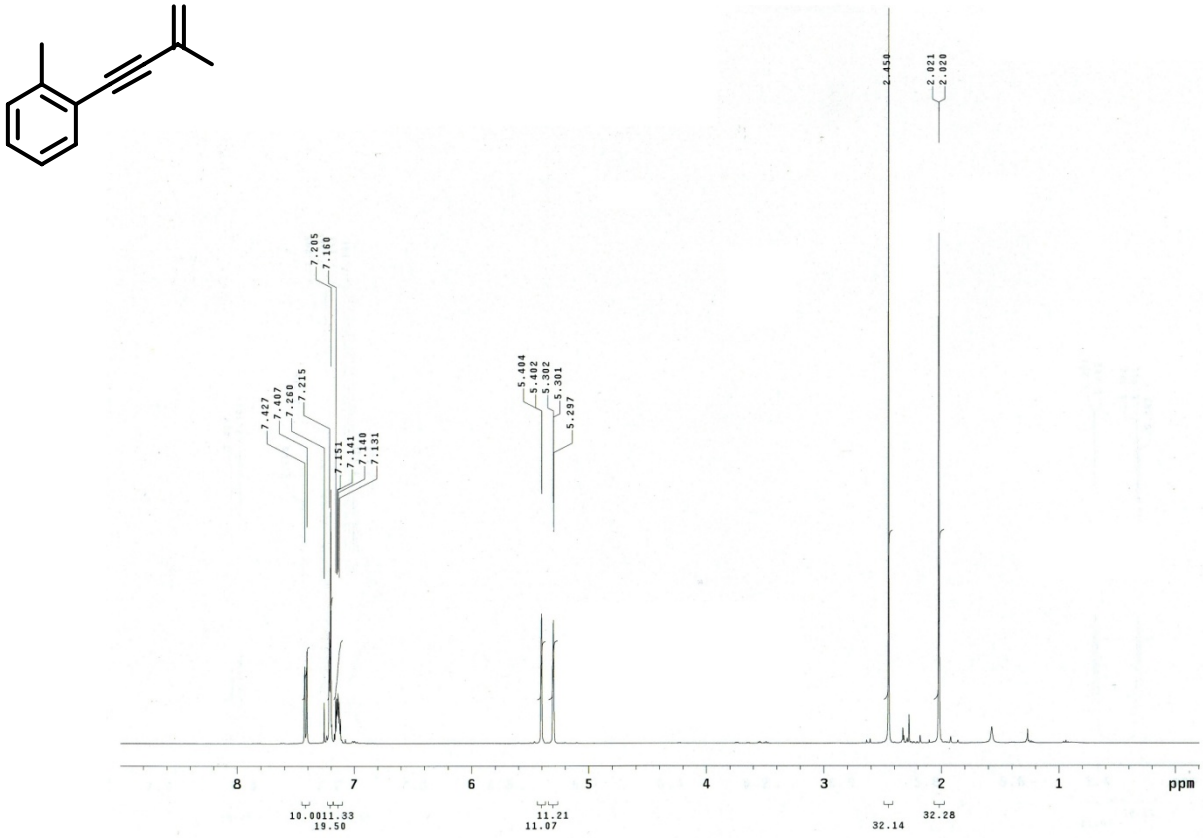

Fig. S19 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **17**

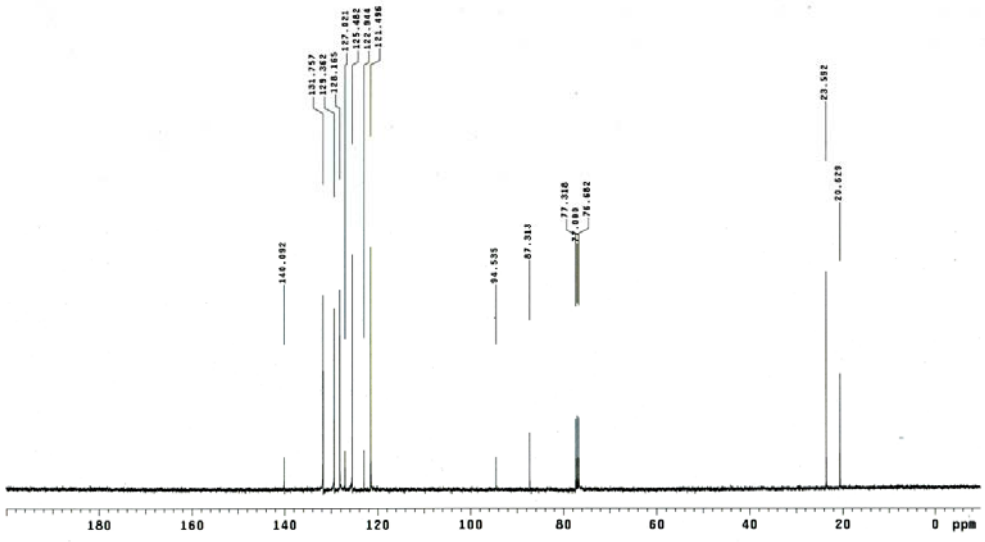

Fig. S20 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **17**

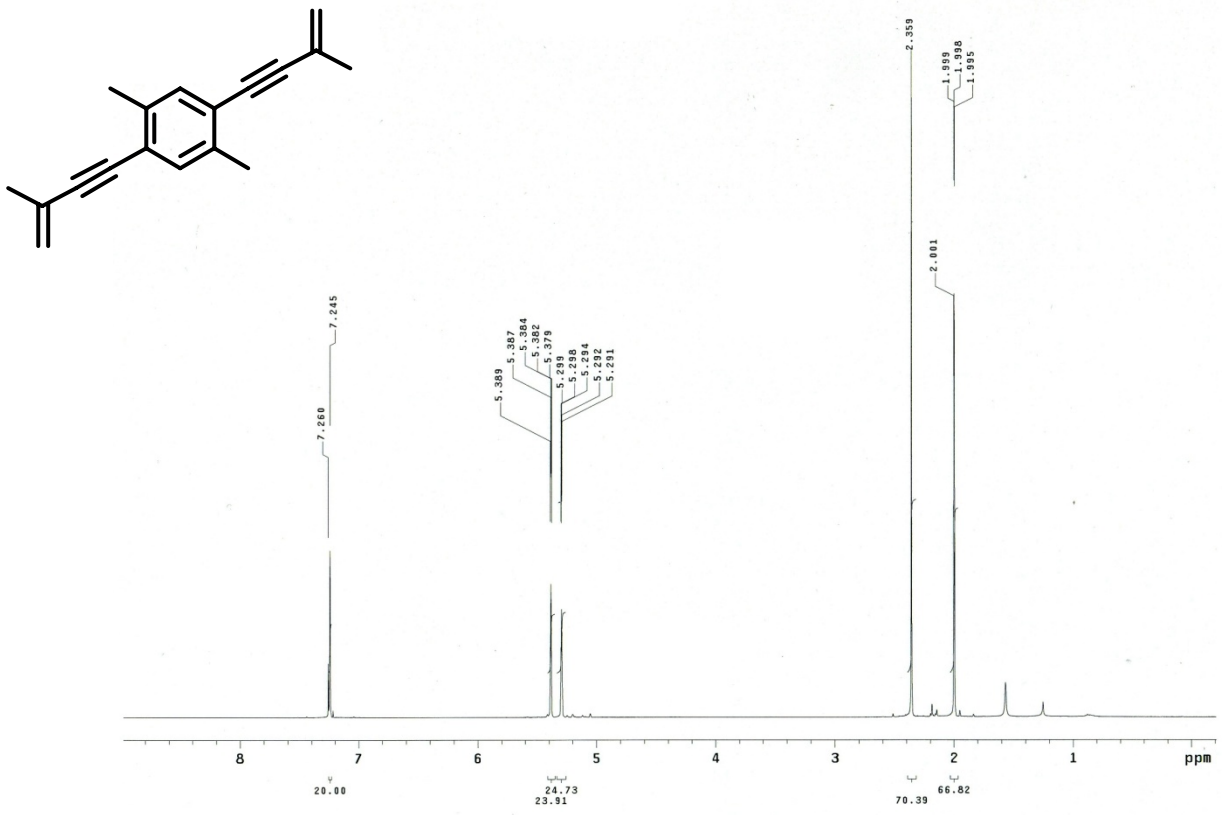

Fig. S21 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **18**

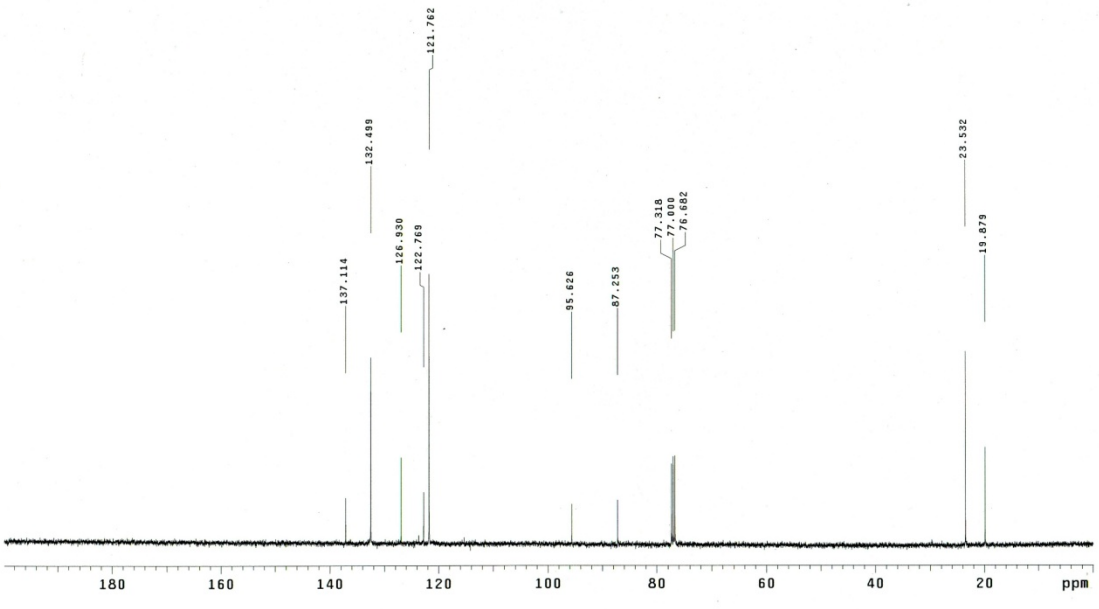

Fig. S22 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **18**

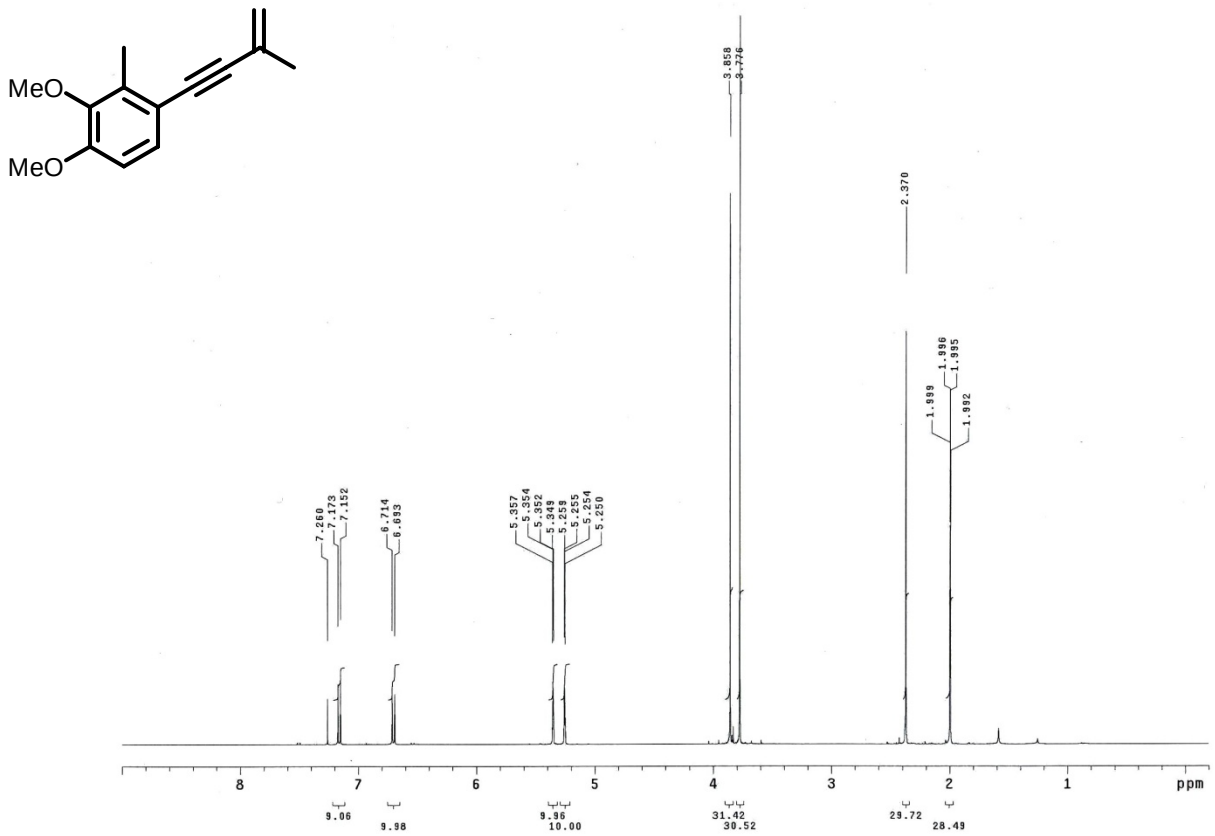

Fig. S23 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **19**

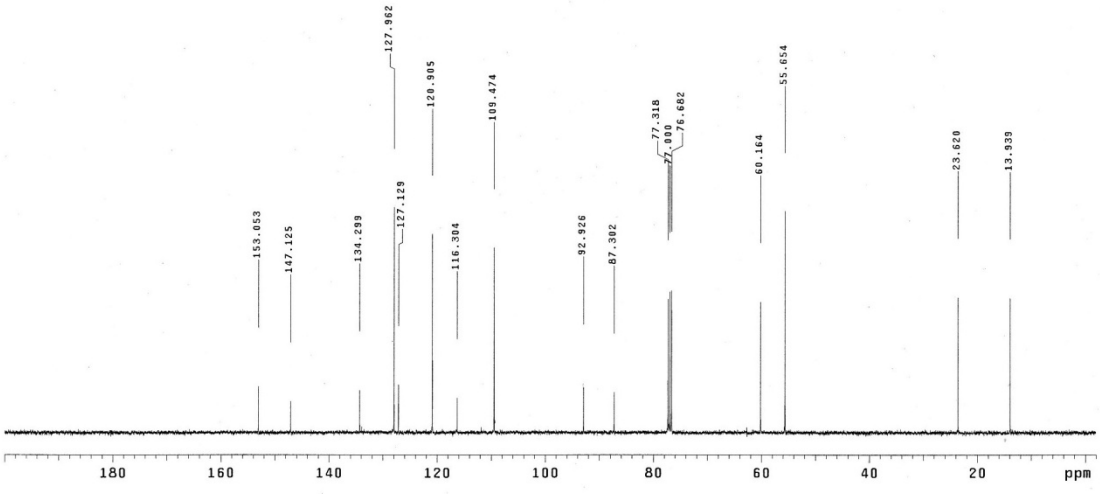

Fig. S24 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **19**

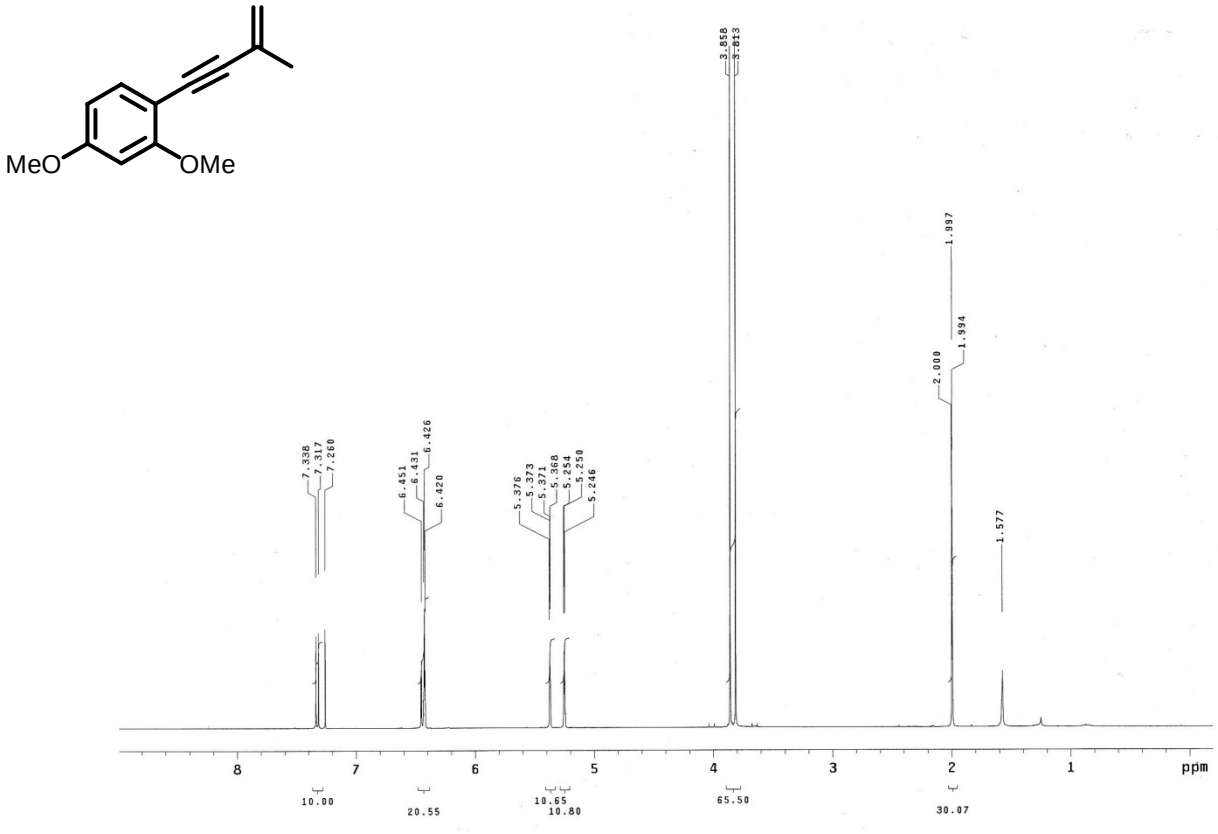

Fig. S25 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **20**

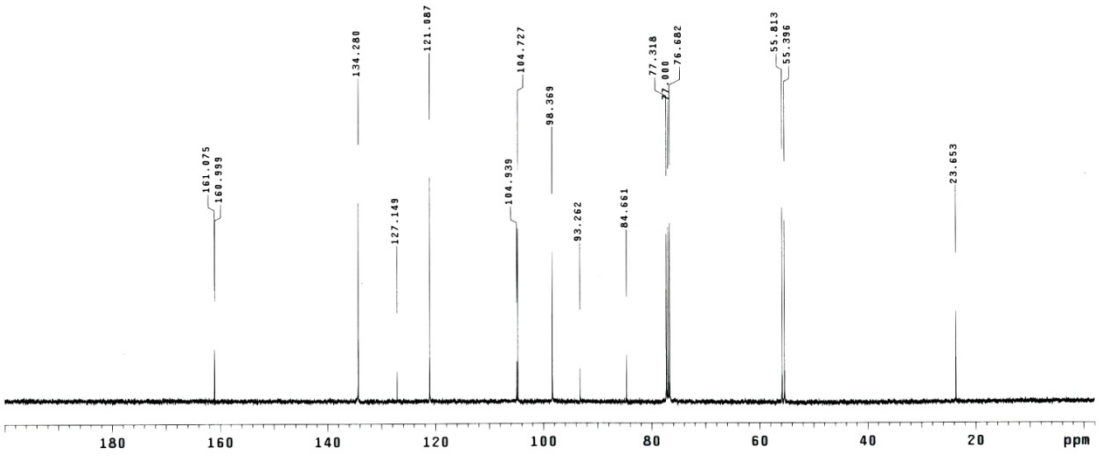

Fig. S26 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **20**

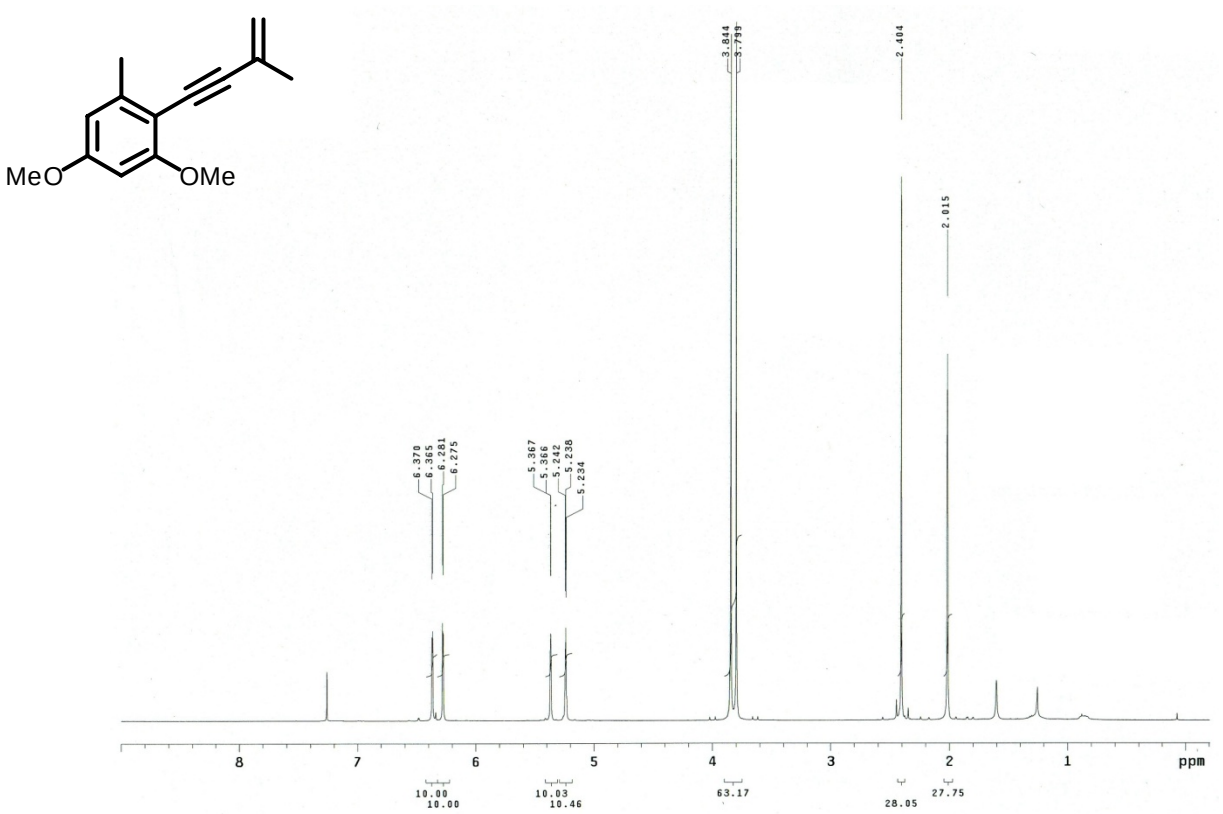

Fig. S27 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **21**

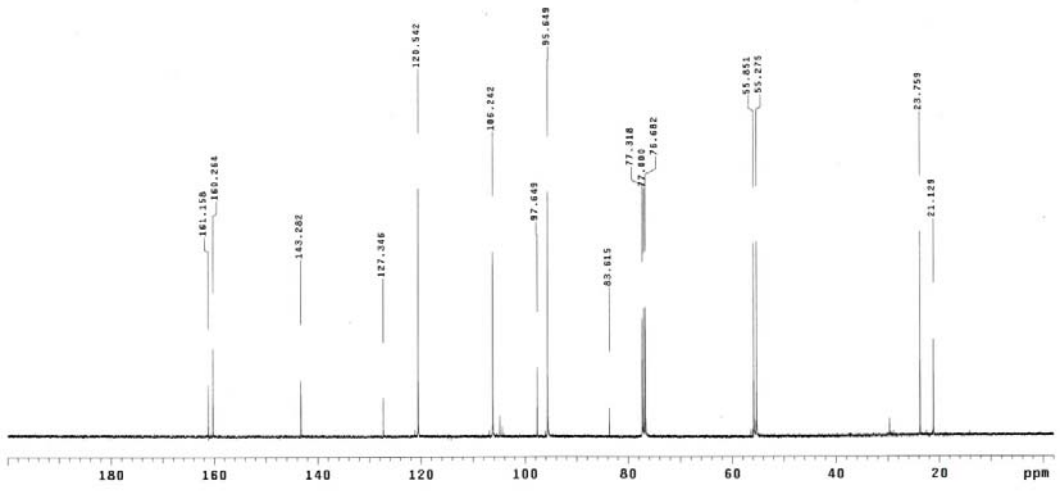

Fig. S28 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **21**

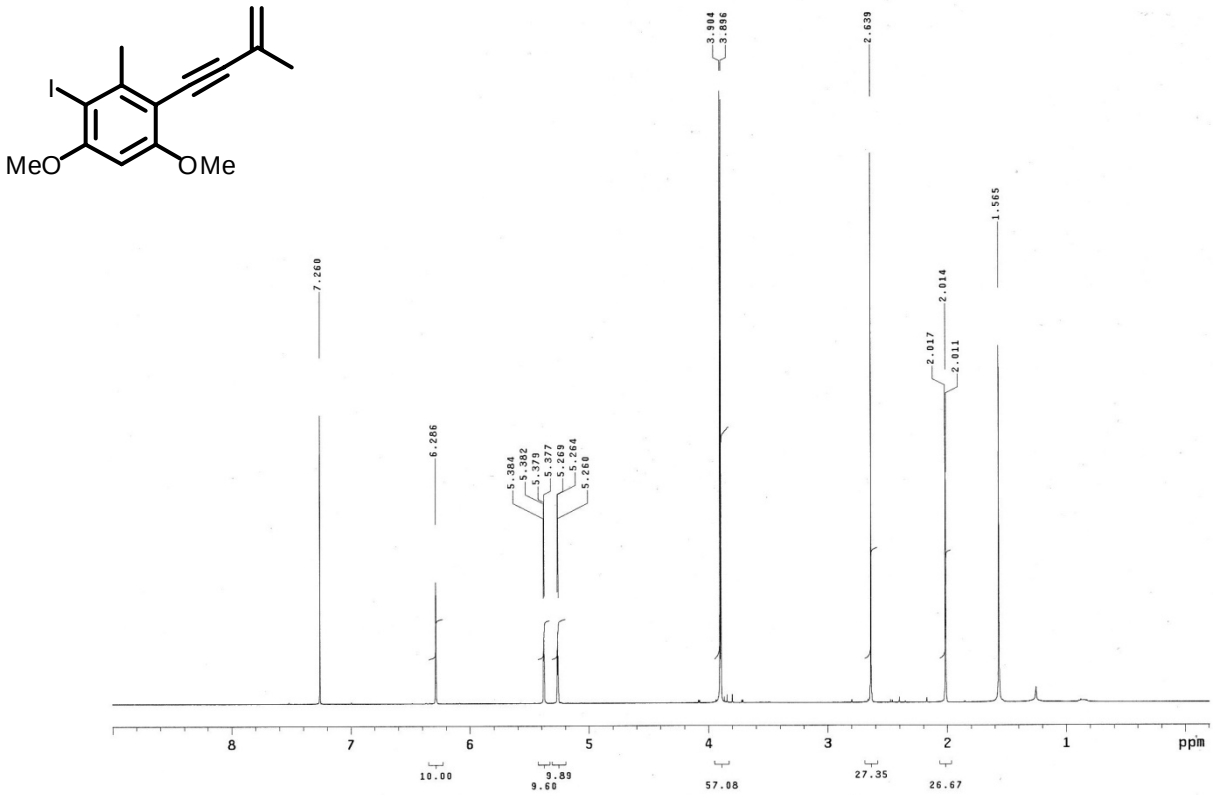

Fig. S29 ^{1}H NMR (400 MHz, $CDCl_3$) of compound **22**

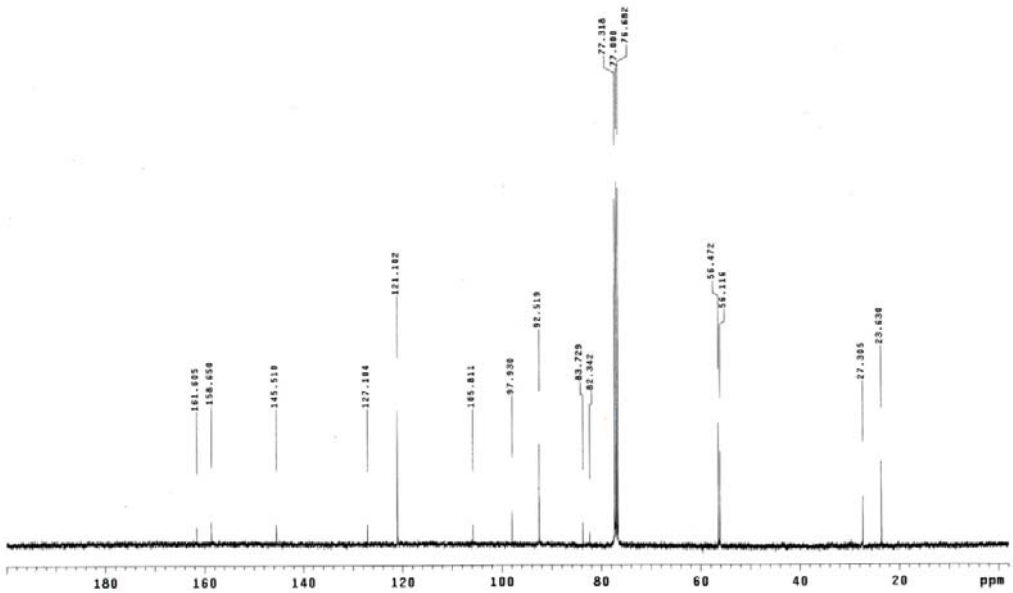

Fig. S30 ^{13}C NMR (100 MHz, $CDCl_3$) of compound **22**