SUPPLEMENTARY MATERIAL TO

Determination of enol form of asymmetric 1,3-dicarbonyl compounds: 2D NMR data and DFT calculations

MELTEM TAN, İSHAK BİLDİRİCİ and NURETTİN MENGES

Faculty of Pharmacy, Yüzüncü Yil University, 65080, Van, Turkey

Table of Contents

Experimental Section

General Methods: NMR spectra were recorded on a 400 MHz spectrometer. Infrared (IR) spectra were recorded in the range 4000-600 cm^{-1} via ATR diamond. Melting points were determined using a melting point apparatus and were uncorrected. Mass spectra were recorded by LC-MS TOF electrospray ionization technique. Column chromatography was performed on silica gel (60-mesh), TLC was carried out on 0.2 mm silica gel 60 F254 analytical aluminium plates. Evaporation of solvents was performed at reduced pressure, using a rotary vacuum evaporator.

Syntheses:

General procedure for synthesis of the compounds 1-10:

Acetyl ketone (1 equiv) was added to dry 1,4-dioxane and NaH (60% oil suspension, 5 equiv) was added by pieces to the mixture at ice-bath. It was stirred at room temperature for 1 h. Related ester (5 equiv) was added to the mixture and refluxed for 1 h. After cooling 10% HCl solution was added to the reaction mixture and extracted with CH_2Cl_2 (3×20 mL). Crude product dried on $MgSO_4$. Recrystallization or column chromatography gave the product, which was dried *in vacuo* (25 °C, 0.5 mbar), affording spectroscopically pure product.[1]

Synthesis of 1-(2,6-dimethoxyphenyl)-3-phenylpropane-1,3-dione (1)

1-(2,6- dimethoxphenyl)ethanone (0.72 g, 4 mmol) and ethyl benzoate (2,8 mL, 20 mmol) reacted according to general procedure. Column chromatography heksan/ethyl acetate (5:1) gave the product as a white crystals in 95% yield (1,113 g). Mp: 85-88 ^oC.[2]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 16.13 (bs, 1H, OH), 7.92-7.90 (m, 2H, Ar-H), 7.53-7.49 (m, 1H, Ar-H), 7.47-7.42 (m, 2H, Ar-H), 7.33 (t, $J_{5,4}$=8.4 Hz, 1H, H-5), 6.61 (d, $J_{4,5}$=8.4 Hz, 2H, H-4 and H-6), 6.4 (s, 1H, H-13), 3.83 (s, 6H, H-8 and H-12); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 189.4, 181.5, 157.7, 135.0, 132.1, 131.2, 128.5, 127.1, 117.2, 104.2, 100.6, 56.1; IR (ATR, cm^{-1}) 2921, 2989, 1681, 1598, 1582, 1495, 1469, 1453, 1424, 1323, 1287, 1247, 1176, 1111, 1071; HR-MS m/z $(M+H)^+$ ($C_{17}H_{17}O_4$) theoretical: 285.1121; experimental: 285.1119.

Synthesis of 1-phenyl-3-(2,4,6-trimethoxyphenyl)propane-1,3-dione (2)

1-(2,4,6-trimethoxyphenyl)ethanone (0.84 g, 4 mmol) and ethyl benzoate (2,8 mL, 20 mmol) reacted according to general procedure. Column chromatography heksan/ethyl acetate (5:1) gave the product as a honey yellow crystals in 87% yield (1,09 g). Mp: 95-98 ^oC.[3]

^{1}H-NMR (400 MHz, CDCl3) δ 16.23 (bs, 1H, OH), 7.91-7.89 (m, 2H, Ar-H), 7.52-7.48 (m, 1H, Ar-H), 7.46-7.42 (m, 2H, Ar-H), 6.41 (s, 1H, H-15), 6.16 (s, 2H, H-4 and H-6), 3.85 (s, 3H, H-

14), 3.82 (s, 6H, H-8 and H-12); ^{13}C-NMR (100 MHz, CDCl3) δ 188.7, 181.3, 162.8, 159.1, 135.3, 131.9, 128.5, 127.0, 110.3, 101.0, 90.8, 56.1, 55.5; IR (ATR, cm-1) 2969, 2940, 2838, 1698, 1682, 1585, 1490, 1452, 1411, 1331, 1274, 1226, 1203, 1185, 1154, 1123; HR-MS m/z $(M+H)^+$ ($C_{18}H_{19}O_5$) theoretical: 315.1227; experimental: 315.1224.

Synthesis of 1-(2,6-dimethoxyphenyl)butane-1,3-dione (3)

1-(2,6-dimethoxyphenyl)ethanone (0.54 g, 3 mmol) and ethyl acetate (1,47 mL, 15 mmol) reacted according to general procedure. Column chromatography heksan/ethyl acetate (5:1) gave the product as a bright gel-like in 54% yield (0,852 g).[4]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 15.54 (bs, 0.8 H, OH), 7.32-7.27 (m, 1.75 H, keto and enol H-5), 6.59-6.55 (m, 3H, keto and enol H-4 ve H-6), 5.71 (s, 0.8 H, enol H-13), 3.88 (s, 0.8 H, keto H-13), 3.81 (s, 8.5 H, keto and enol H-8 and H-12), 2.29 (s, 1H, keto H-16), 2.12 (s, 3H, H-16); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 189.5, 186.8, 157.6, 131.1, 116.4, 104.1, 104.0, 56.0, 24.6 (enol form), 201.8, 197.3, 157.0, 131.7, 119.2, 104.1, 60.1, 55.8, 30.2 (keto form); HR-MS m/z $(M+H)^+$ ($C_{12}H_{15}O_4$) theoretical: 223.0965; experimental: 223.0964.

Synthesis of 1-(2,4,6-trimethoxyphenyl)butane-1,3-dione (4)

1-(2,4,6-trimethoxyphenyl)ethanone (0.63 g, 3 mmol) and ethyl acetate (1,47 mL, 15 mmol) reacted according to general procedure. Column chromatography heksan/ethyl acetate (5:1) gave the product as a light yellow solid in 86% yield (0,653 g). Mp: 99-102 ^{o}C.[5]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 15.65 (bs, 1H, OH), 6.12 (s, 2H,enol H-4 ve H-6), 6.09 (s, 1H, keto H-4 and H-6), 5.71 (s, 1H, enol H-15), 3.85 (s, 1H, keto H-15), 3.83 (s, 5 H, keto and enol H-14), 3.80 (s, 10H, keto and enol H-8 ve H-12), 2.26 (s, 1.5H, keto H-18), 2.10 (s, 3H, enol H-18); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 189.5, 186.0, 162.6, 159.0, 104.3, 90.8, 90.6, 56.0, 55.8, 24.8 (enol form), 202.4, 195.9, 163.3, 159.1, 112.4, 109.6, 60.5, 55.5, 55.4, 30.1 (keto form); HRMS m/z $(M+H)^+$ ($C_{13}H_{17}O_5$) theoretical: 253.1071; experimental: 253.1064.

Synthesis of 1,3-di(naphthalen-1-yl)propane-1,3-dione (5)

1-acetyl naphthalene (0.3 mL, 2 mmol) and ethyl-1-naftoat (1,8 mL, 10 mmol) reacted according to general procedure. Column chromatography heksan/ethyl acetate (8:1) gave the product as a light yellow crystal in 89% yield (0,58 g). Mp: 104-108 ^{o}C.[6]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.61 (d, 2H, Ar-H), 8.00 (d, 2H, Ar-H), 7.92 (d, 2H, Ar-H), 7.84 (dd, 2H, Ar-H), 7.64-7.58 (m, 3H, Ar-H), 7.56-7.53 (m, 3H, Ar-H), 6.60 (s, 1H, H-13); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 188.2, 133.4, 132.9, 130.9, 129.2, 127.6, 126.4, 126.3, 125.4, 124.6, 123.8,

102.1; IR (ATR, cm^{-1}) 3041, 1708, 1673, 1593, 1574, 1527, 1506, 1459, 1423, 1384, 1364, 1338, 1290, 1278, 1243, 1194, 1123, 1065; HRMS m/z $(M+H)^+$ ($C_{23}H_{17}O_2$) theoretical: 325.1223; experimental: 325.1219.

Synthesis of 1-(naphthalen-1-yl)butane-1,3-dione (6)

1-acetyl naphthalene (0.75 mL, 5 mmol) and ethyl acetate (2.45 mL, 25 mmol) reacted according to general procedure. Column chromatography heksan/ethyl acetate (5:1) gave the product in 81% yield (0,766 g).[7]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 16.12 (bs, 1H, OH), 8.46 (m, 1H, Ar-H), 7.96 (m, 1H, Ar-H), 7.89 (m, 1H, Ar-H), 7.72 (m, 1H, Ar-H), 7.59-7.48 (m, 3H, Ar-H), 6.04 (s, 1H, H-13), 2.22 (s, 3H, H-16); ^{13}C-NMR (100 MHz, CDCl3) δ 191.4, 187.3, 133.3, 132.8, 130.6, 129.1, 127.5, 126.2, 125,9, 125.3, 124.5, 123.7, 100.7, 24.4; IR (ATR, cm-1) 3048, 1717, 1575, 1508, 1418, 1392, 1363, 1339, 1280, 1244, 1210, 1173, 1123, 1068; HRMS m/z (M+H)+ (C14H13O2) theoretical: 213.0910; experimental: 213.0905.

Synthesis of 1-(naphthalen-1-yl)-3-phenylpropane-1,3-dione (7)

Acetophenone (0.58 mL, 5 mmol) and ethyl-1-naftoate (4.5 mL, 25 mmol) reacted according to general procedure. Column chromatography heksan/ethyl acetate (8:1) gave the product as a yellow crystal in 80% yield (1 g). Mp: 60-63 ^{o}C.[8]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 8.53 (m, 1H, Naf-H), 8.01-7.98 (m, 3H, Ar-H, Naf-H), 7.92 (m, 1H, Naf-H), 7.83 (m, 1H, Naf-H), 7.62-7.54 (m, 4H, Ar-H, Naf-H), 7.52-7.48 (m, 2H, Ar-H), 6.73 (s, 1H, H-13); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 188.5, 182.4, 133.1, 133.0, 131.8, 130.5, 129.7, 128.1, 126.7, 126.5, 125.3, 125.2, 125.0, 124.4, 123.6, 122.8, 96.2; IR (ATR, cm^{-1}) 3045, 2952, 2922, 2853, 1722, 1603, 1590, 1542, 1508, 1462, 1420, 1388, 1287, 1256, 1229, 1210, 1178, 1157, 1123, 1086, 1066; HRMS m/z $(M+H)^+$ ($C_{19}H_{15}O_2$) for theoretical: 275.1067; experimental: 275. 1064.

Synthesis of 1-(3-bromothiophene-2-yl)butane-1,3-dione (8)

3-bromo-2-acetyl thiophene (1.025 g, 5 mmol) and ethyl acetate (2.45 mL, 25 mmol) reacted according to general procedure. Column chromatography heksan/ethyl acetate (4:1) gave the product as a yellow solid in 53% yield (0.65 g). Mp: 55-58 ^{o}C.

^{1}H-NMR (400 MHz, $CDCl_3$) δ 15.88 (bs, 1H, OH), 7.51 (d, $J_{2,3}$=5.2 Hz, 1H, H-2), 7.10 (d, $J_{3,2}$=5.2 Hz, 1H, H-3), 6.56 (s, 1H, H-9), 2.19 (s, 3H, H-12); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 190.9, 178.8, 135.4, 133.5, 130.8, 112.6, 97.9, 24.9; IR (ATR, cm^{-1}) 3101, 2915, 1716, 1698, 1559, 1540, 1499,

1458, 1398, 1363, 1350, 1255, 1179, 1151; HRMS m/z $(M+Na)^+$ ($C_8H_7BrNaO_2S$) theoretical: 268.9242; experimental: 268.9242.

Synthesis of 1,3-di(thiophen-2-yl)propane-1,3-dione (9)

1-(thiophen-2-yl)ethanone (0.43 mL, 4 mmol) and ethyl thiophene-2-carboxylate (2.7 mL, 20 mmol) reacted according to general procedure. Column chromatography heksan/ethyl acetate (5:1) gave the product as a lemon yellow solid in 78% yield (0.736 g). Mp: 99-101 ^oC.[9]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 16.18 (bs, 1H, OH), 7.78 (dd, $J_{4,2}$=1.2 Hz, $J_{4,3}$=3.8 Hz, 2H, H-4), 7.62 (dd, $J_{2,3}$=4.9 Hz, $J_{2,4}$=1.2 Hz, 2H, H-2), 7.17 (t, $J_{3,2}$=4.9 Hz, $J_{3,4}$=3.8 Hz, 2H, H-3), 6.54 (s, 1H, H-8); ^{13}C-NMR (100 MHz) δ 176.3, 138.2, 129.5, 127.5, 125.8, 90.2; IR (ATR, cm^{-1}) 3102, 3080, 1526, 1406, 1336, 1276, 1228; HR-MS m/z $(M+H)^+$ ($C_{11}H_9O_2S_2$) theoretical: 237.0038; experimental: 237.0037.

Synthesis of 1-(thiophen-2-yl)butane-1,3-dione (10)

2-acetyl thiophene (0.54 mL, 5 mmol) and ethyl acetate (2.45 mL, 25 mmol) reacted according to general procedure. Column chromatography heksan/ethyl acetate (5:1) gave the product as a brick red solid in 90% yield (0.80 g). Mp: 44-48 ^oC.[10]

^{1}H-NMR (400 MHz, $CDCl_3$) δ 15.65 (bs, 1H, OH) 7.69 (dd, $J_{4,2}$=1.2 Hz, $J_{4,3}$=3.8 Hz, 1H, H-4), 7.60 (dd, $J_{2,3}$=4.9 Hz, $J_{2,4}$=1.2 Hz, 1H, H-2), 7.13 (t, $J_{3,2}$=4.9 Hz, $J_{3,4}$=3.8 Hz, 1H, H-3), 6.03 (s, 1H, H-8), 2.14 (s, 3H, H-11); ^{13}C-NMR (100 MHz, $CDCl_3$) δ 187.3, 181.7, 141.7, 132.3, 130.2, 128.2, 96.5, 23.9; IR (ATR, cm^{-1}) 3105, 1698, 1558, 1515, 1425, 1404, 1368, 1354, 1268, 1236; HRMS m/z $(M+Na)^+$ ($C_8H_8NaO_2S$) theoretical: 191.0137; experimental: 191.0137.

REFERENCES

1. J. Berger, L. A. Flippin, R. Greenhouse, S. Jaime-Figueroa, Y. Liu, A. K. Miller, D. G. Putman, K. K. Weinhardt, S.H. Zhao, United States Patent, 5.863.924 (1999).
2. J. Zawadiak, M. Mrzyczek, *Spectrochim Acta A*. **96** (2012) 815
3. T. Emilewicz, S. Kostanecki, J. Tambor, *Chem. Ber*. **32** (1899) 2448.
4. K. Ahluwalia, *Indian J. Chem. B* **15** (1977) 514.
5. E. Jochum, S. Kostanecki, *Chem. Ber*. **37** (1904) 2099.
6. N.V. Dubrovina, V.L. Tararov, A. Monsees, R. Kadyrov, C. Fischer, A. Börner, *Tetrahedron-Asymmetr*. **14** (2003) 2739.

7. A.M. El-Metwally, *Egypt. J. Chem*. **54** (2011) 129.
8. E.V. Gukhman, V.A. Reutov, Russ. *J. Gen. Chem*. **69** (1999) 1608.
9. S.R. Harris, R. Levine, *J. Am. Chem. Soc*. **70** (1948) 3360.
10. G. Rai, C.J. Thomas, W. Leister, D.J. Maloney, *Tetrahedron Lett*. **50** (2009) 1710.

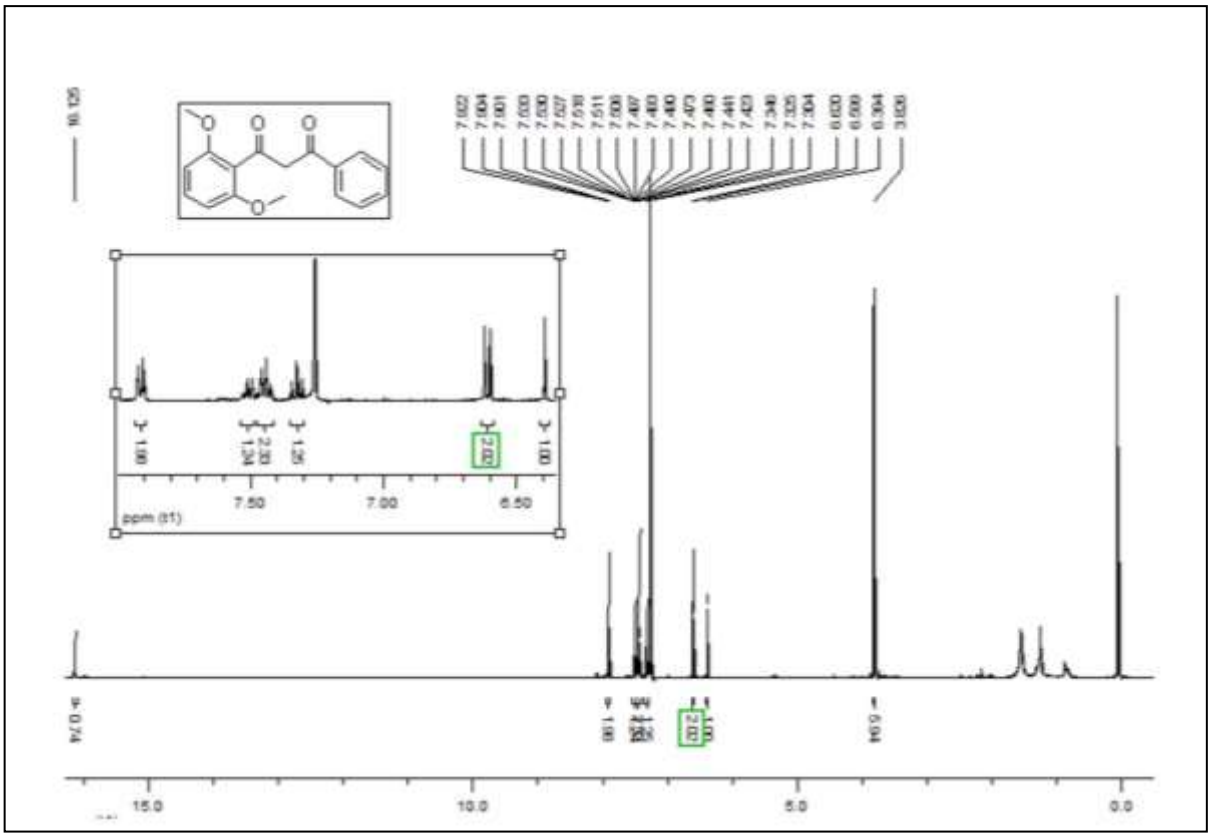


Fig. S1. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **1.**

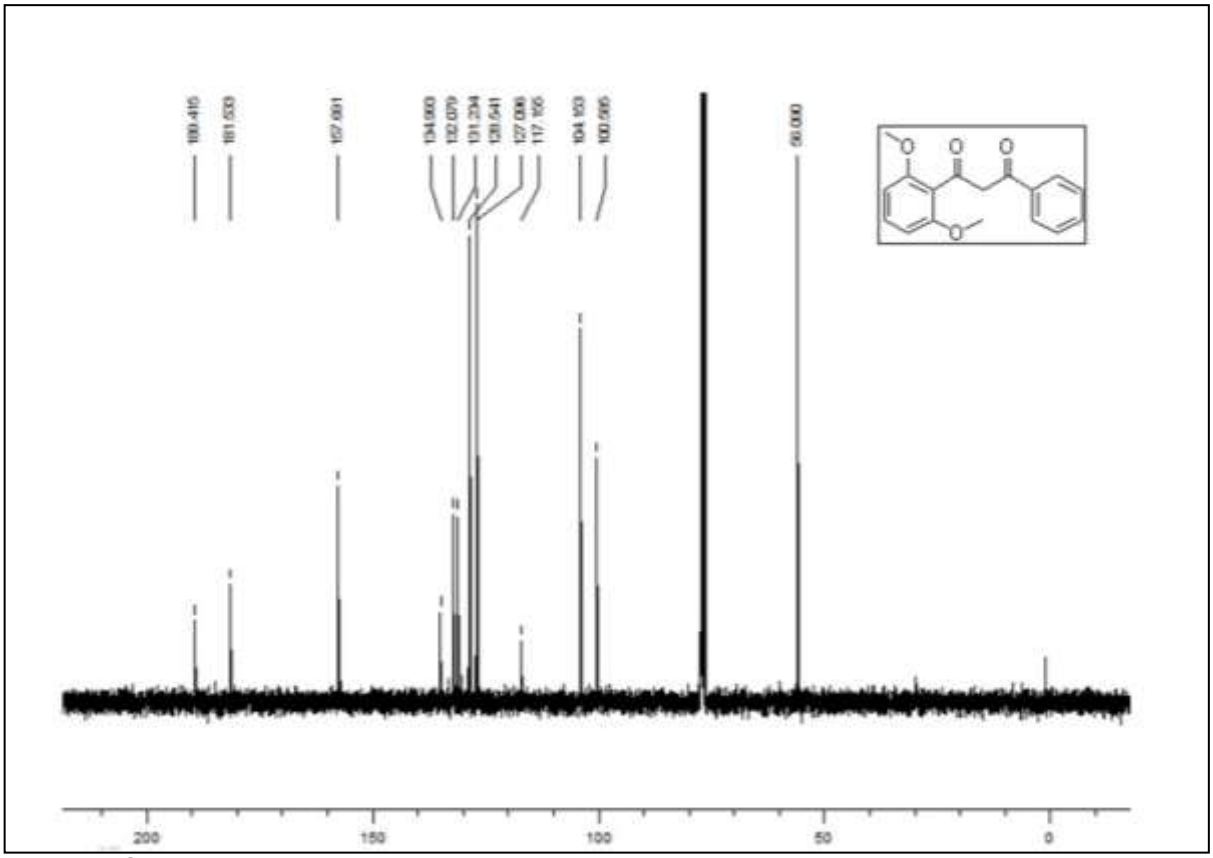
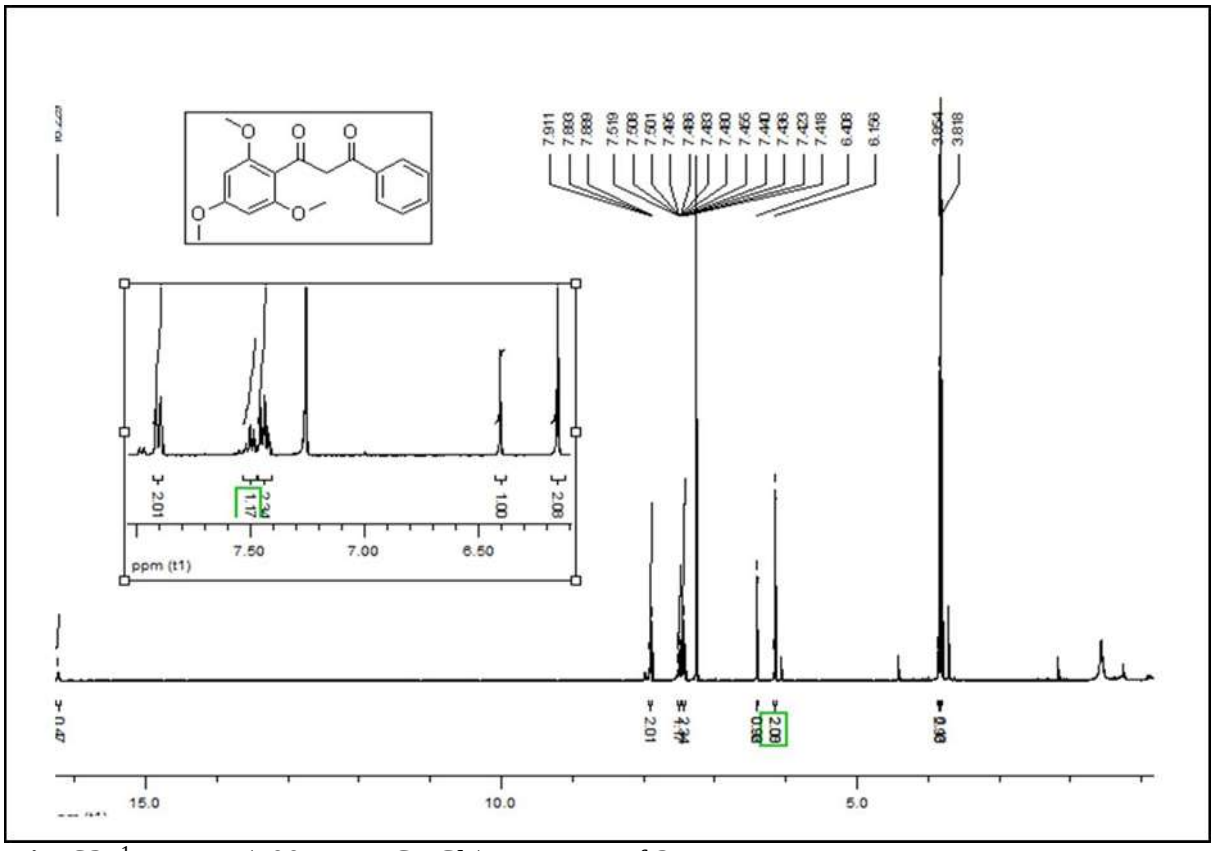
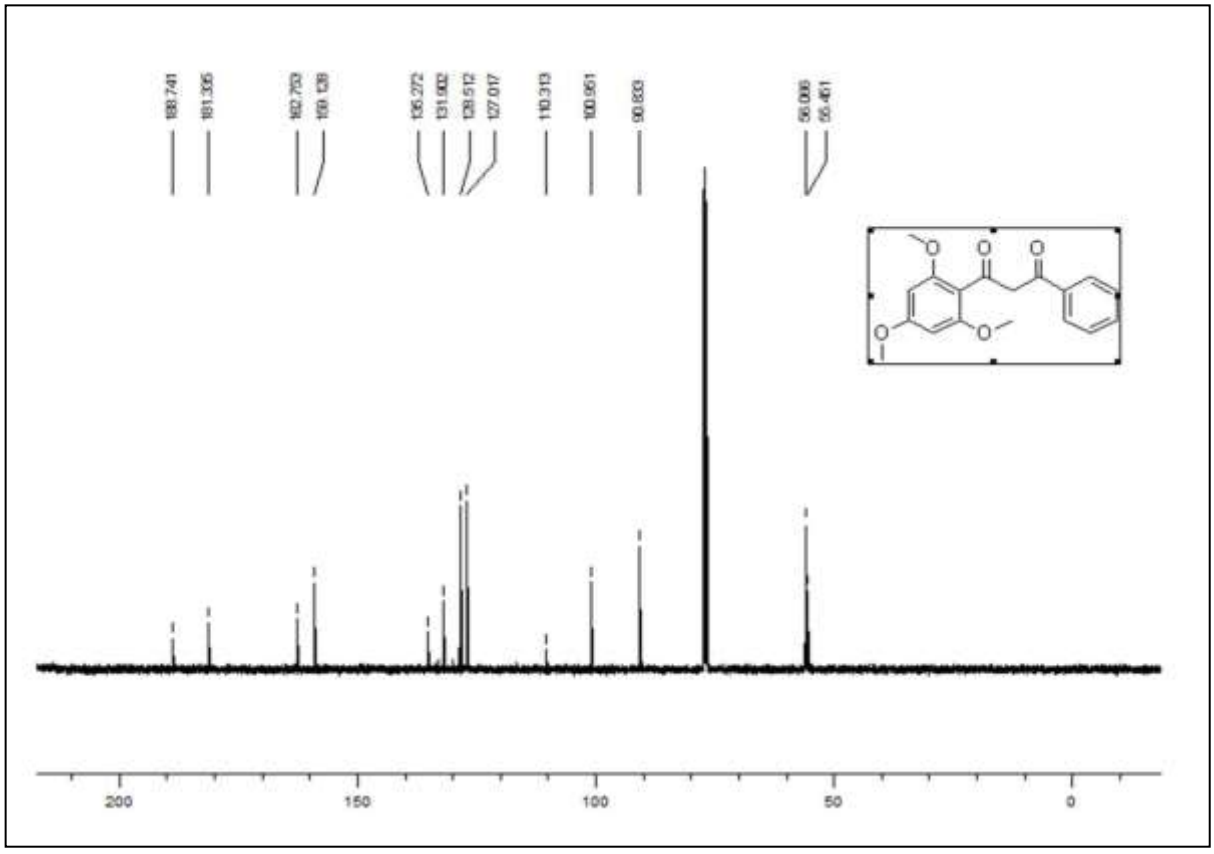


Fig. S2. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **1.**



230 **Fig. S3.** ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **2.**

231



232 **Fig. S4**. ^{13}C NMR (400 MHz, $CDCl_3$) spectrum of **2**

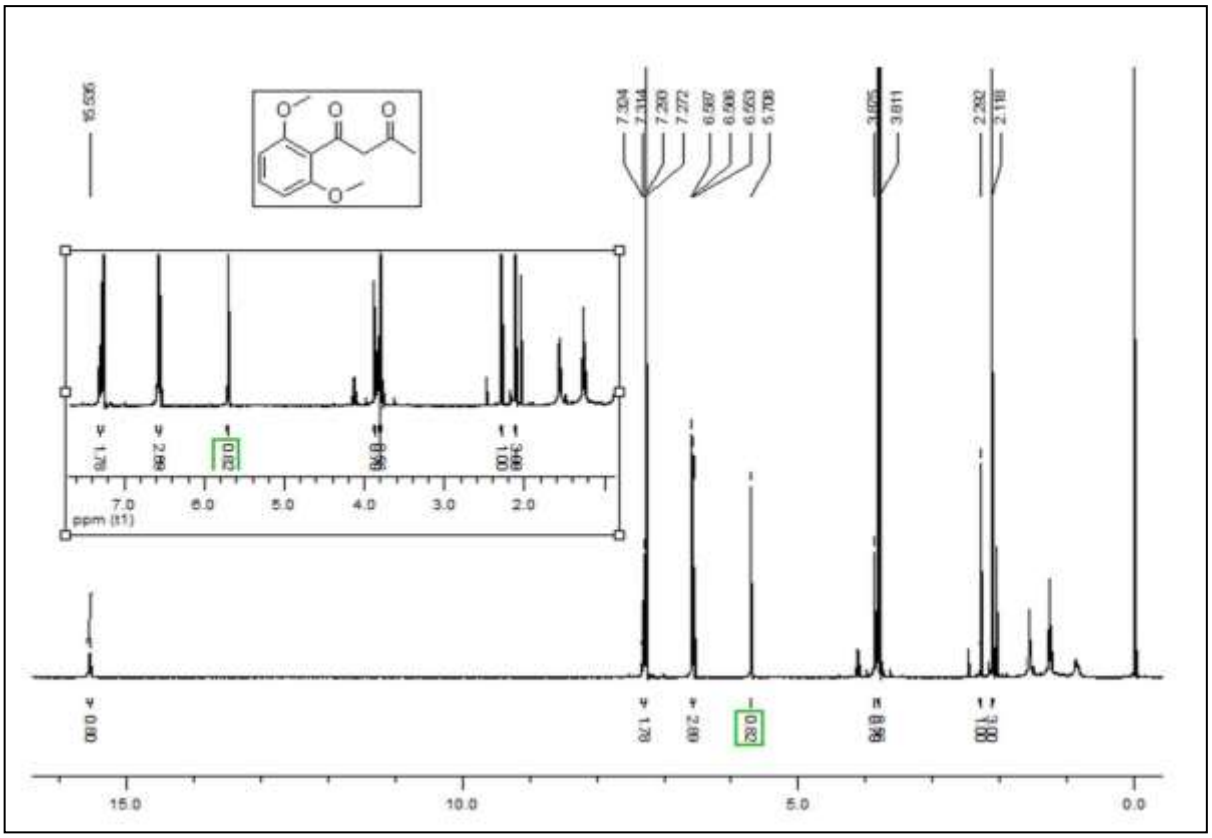


Fig. S5. 1H NMR (400 MHz, $CDCl_3$) spectrum of **3.**

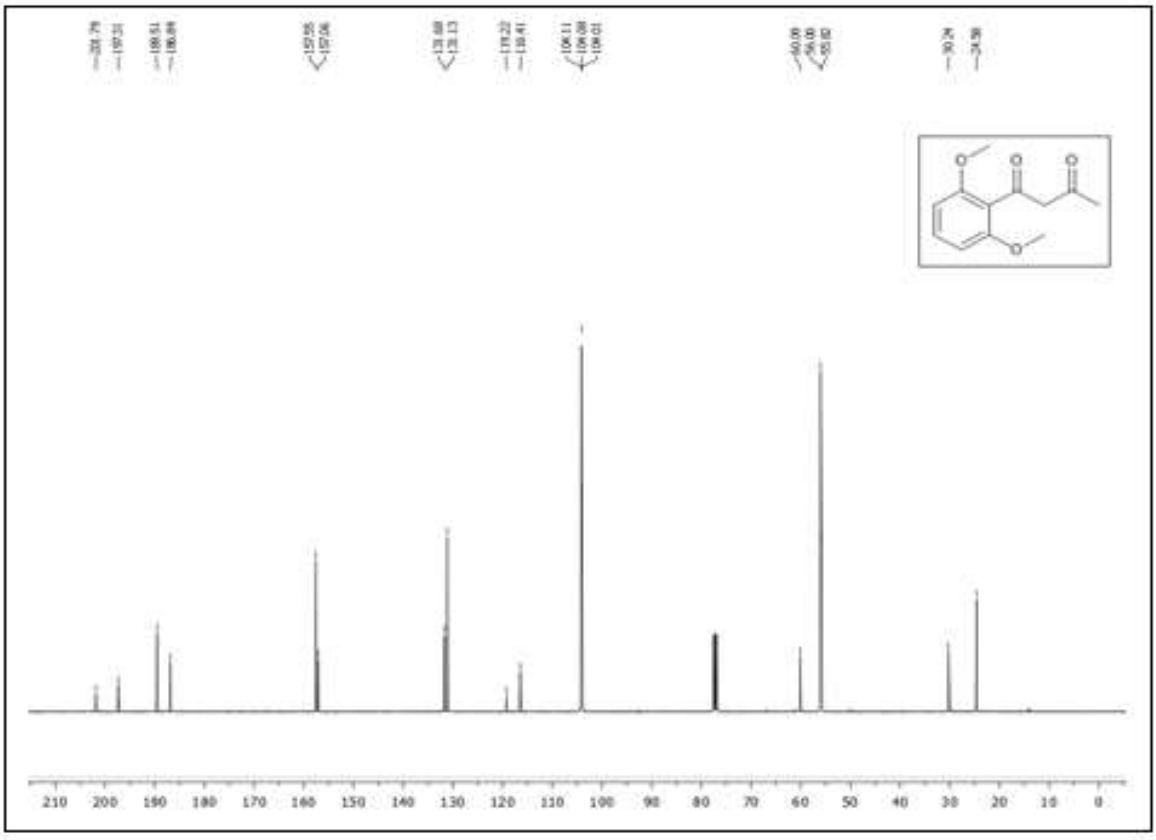
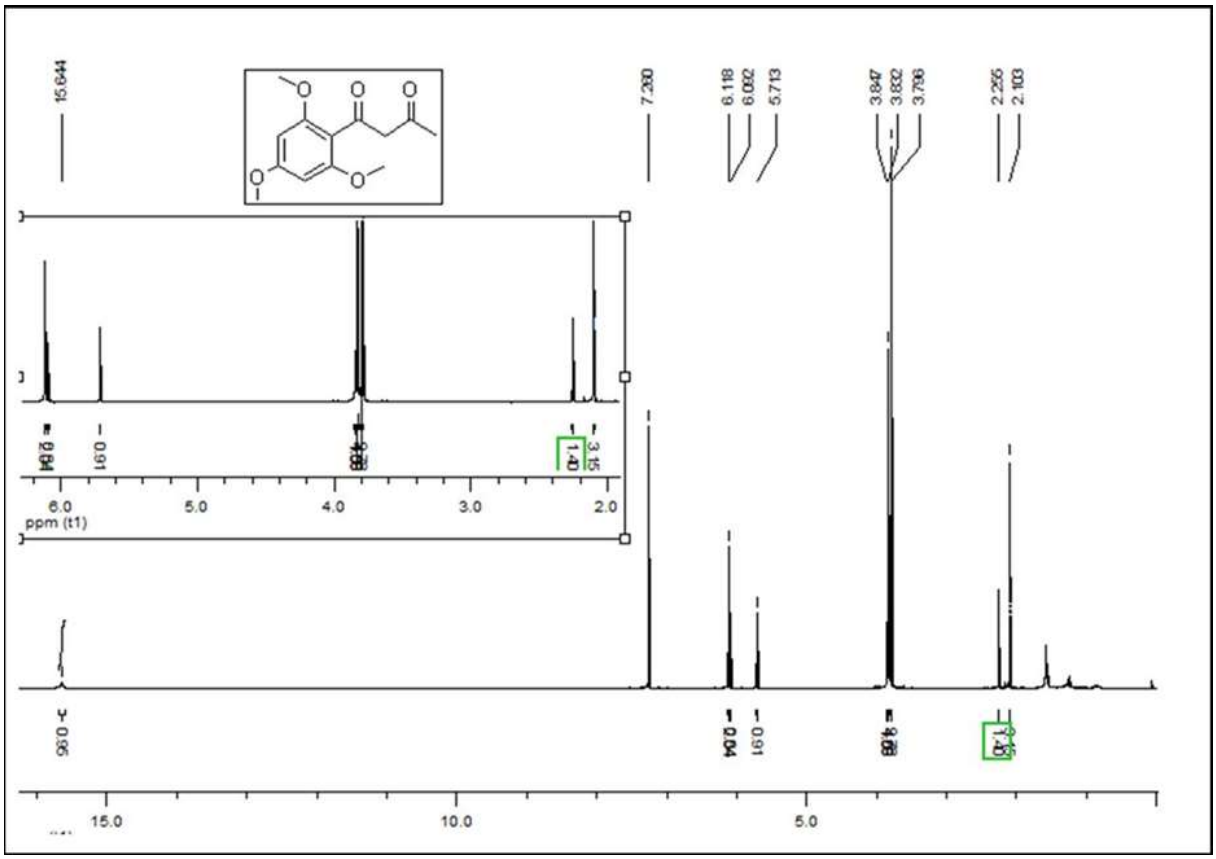
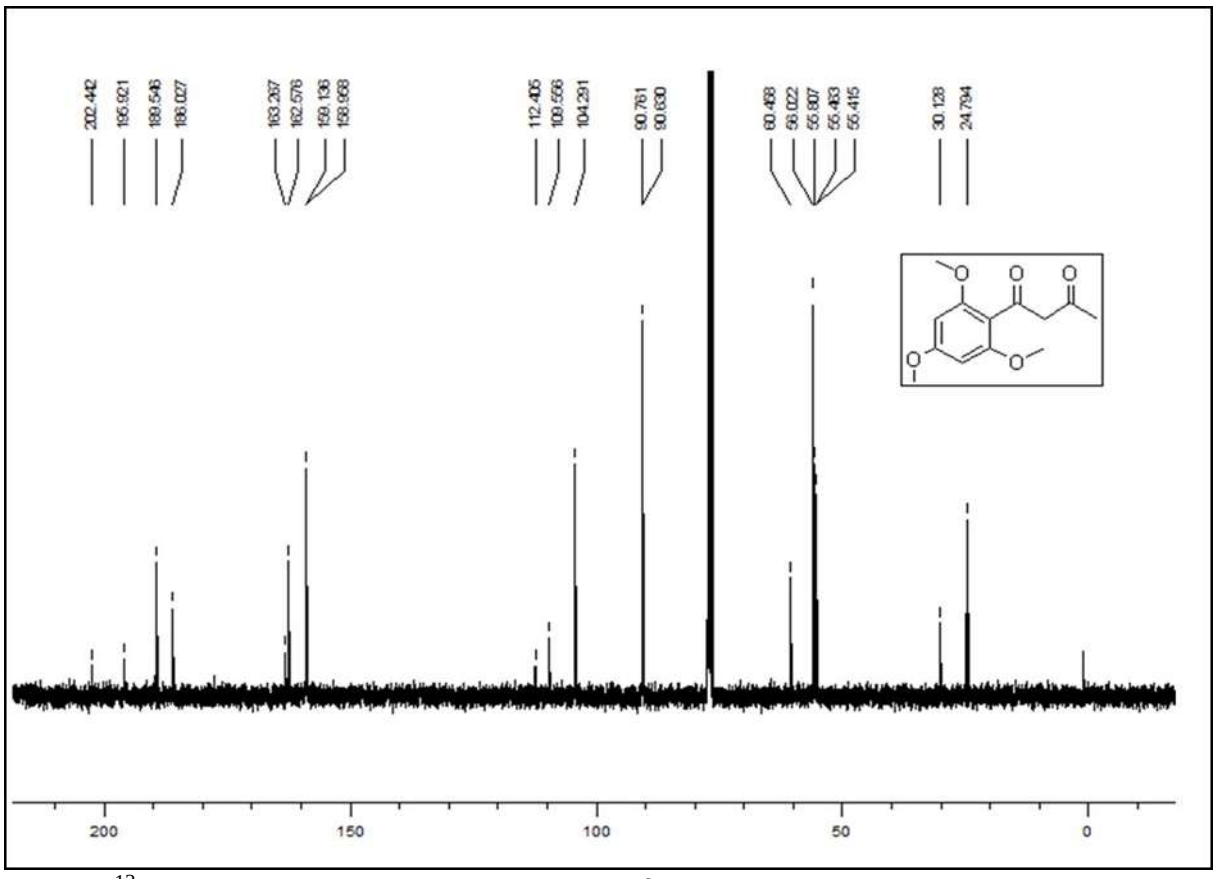


Fig. S6. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **3.**

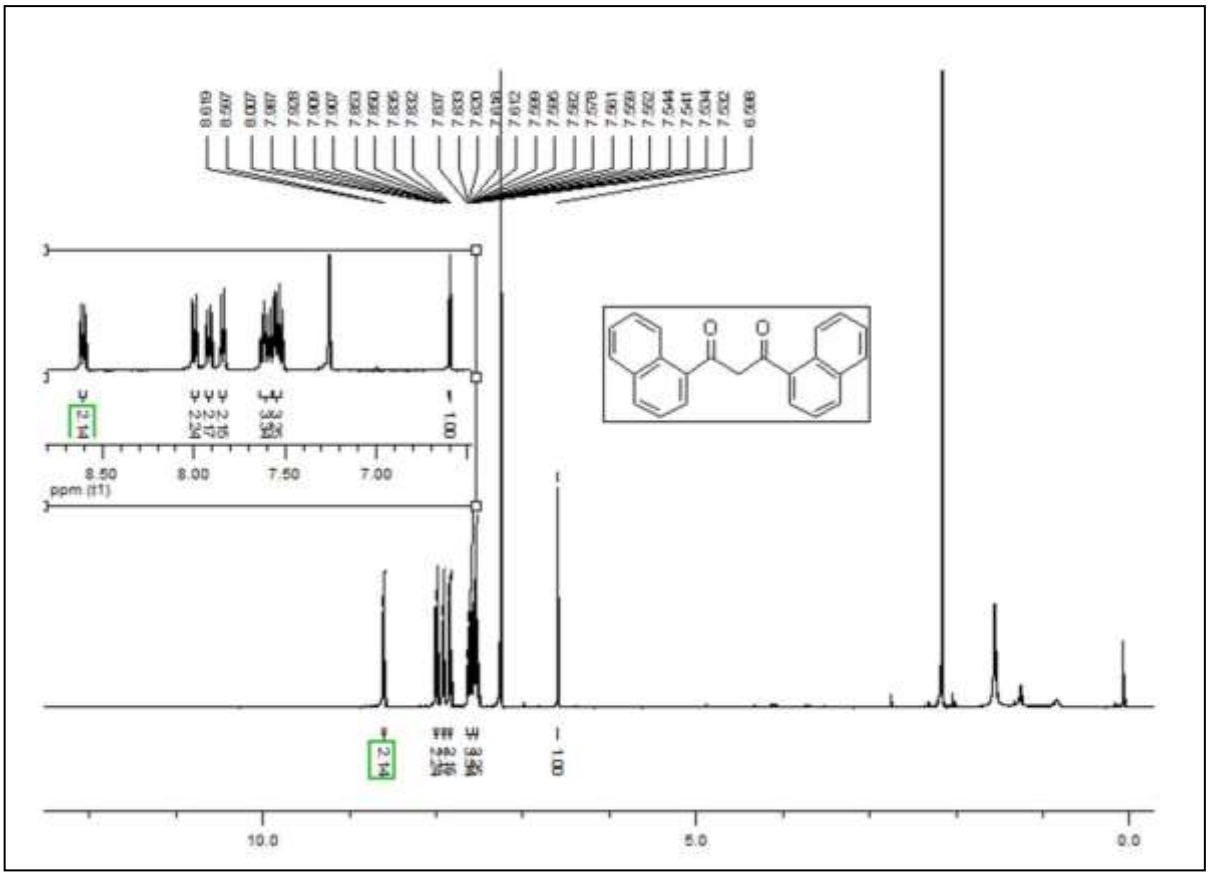


236 **Fig. S7.** ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **4.**

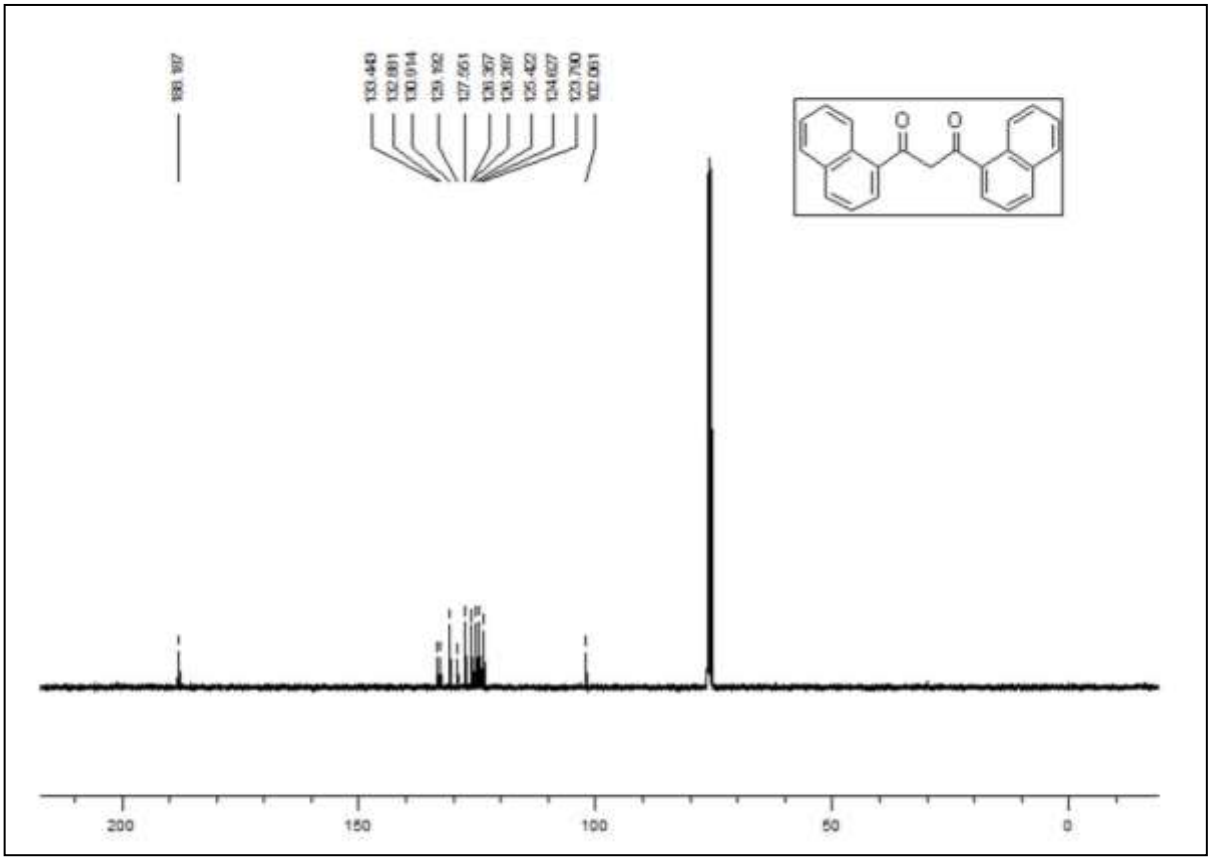
237



238 **Fig. S8**. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **4.**



239 **Fig. S9.** ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **5.**



240 **Fig. S10**. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **5.**

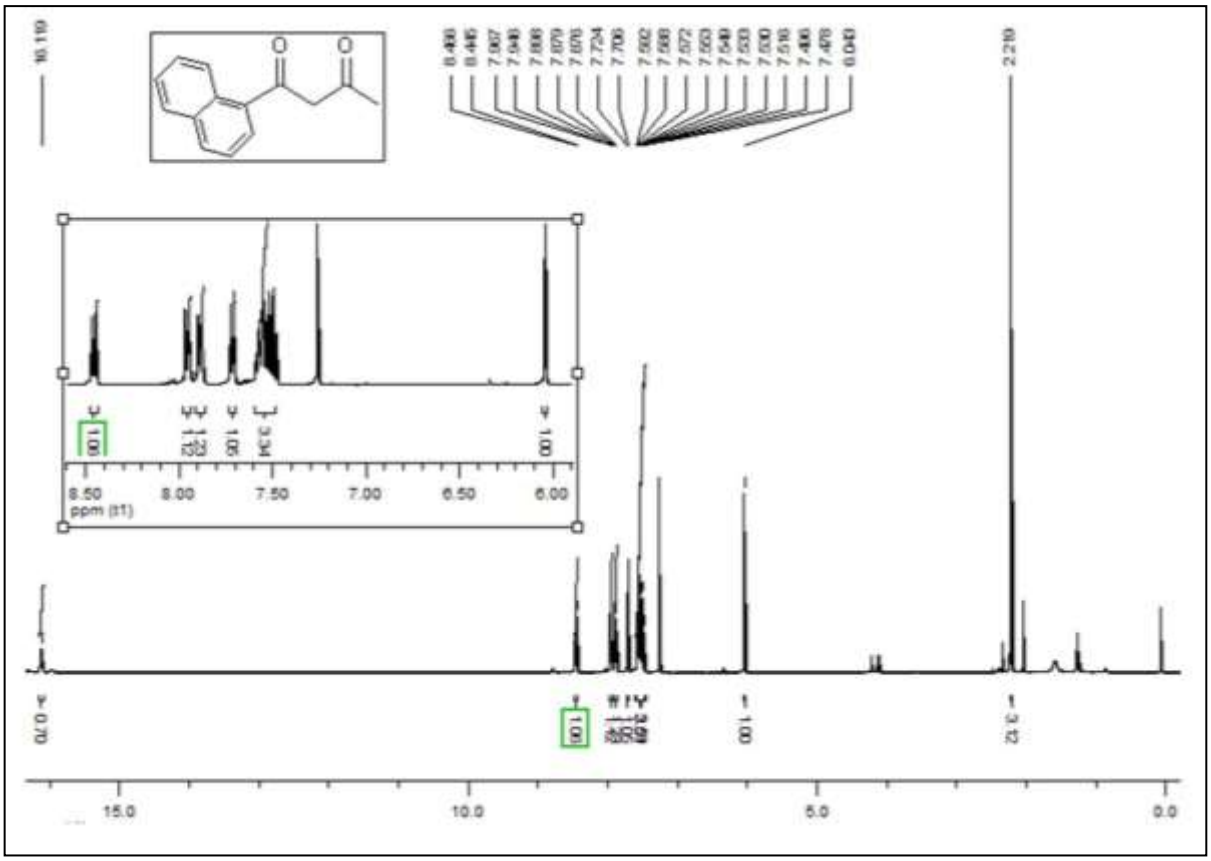


Fig. S11. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **6.**

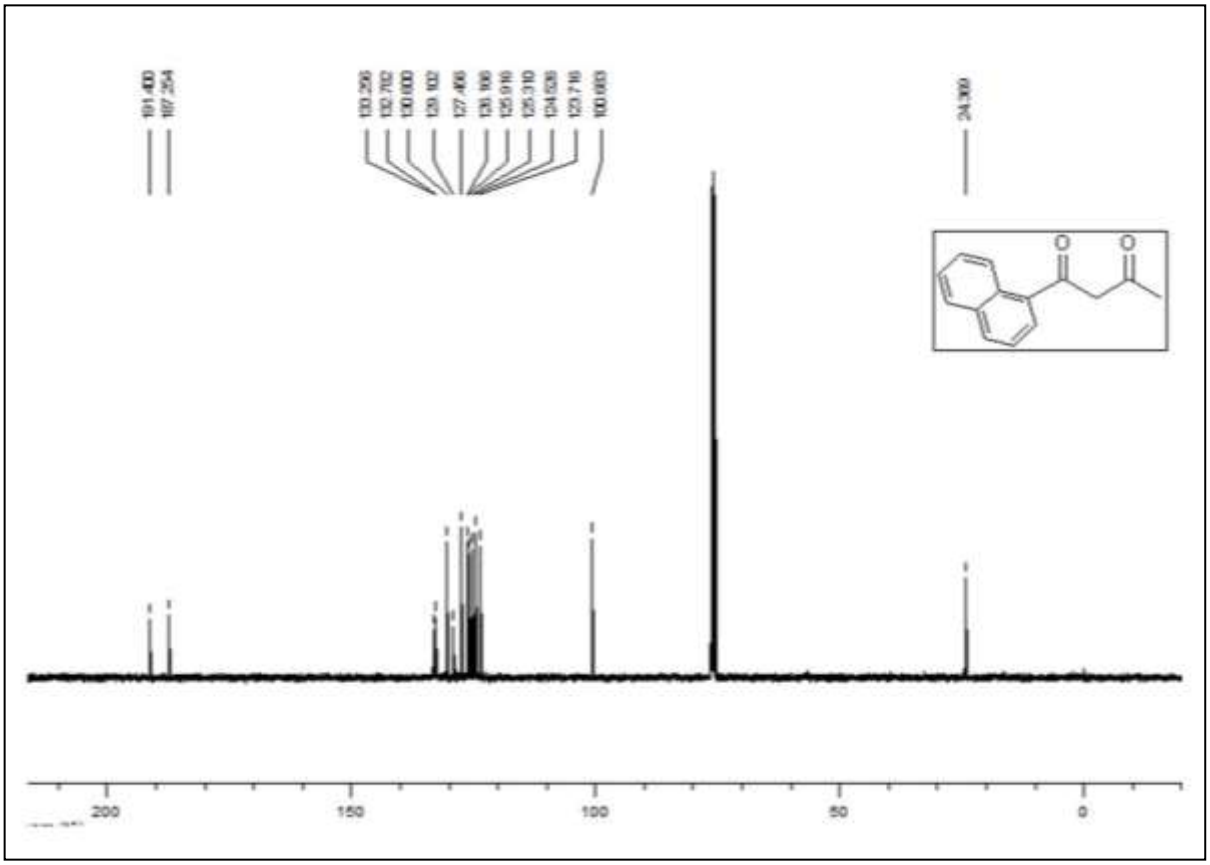


Fig. S12. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **6.**

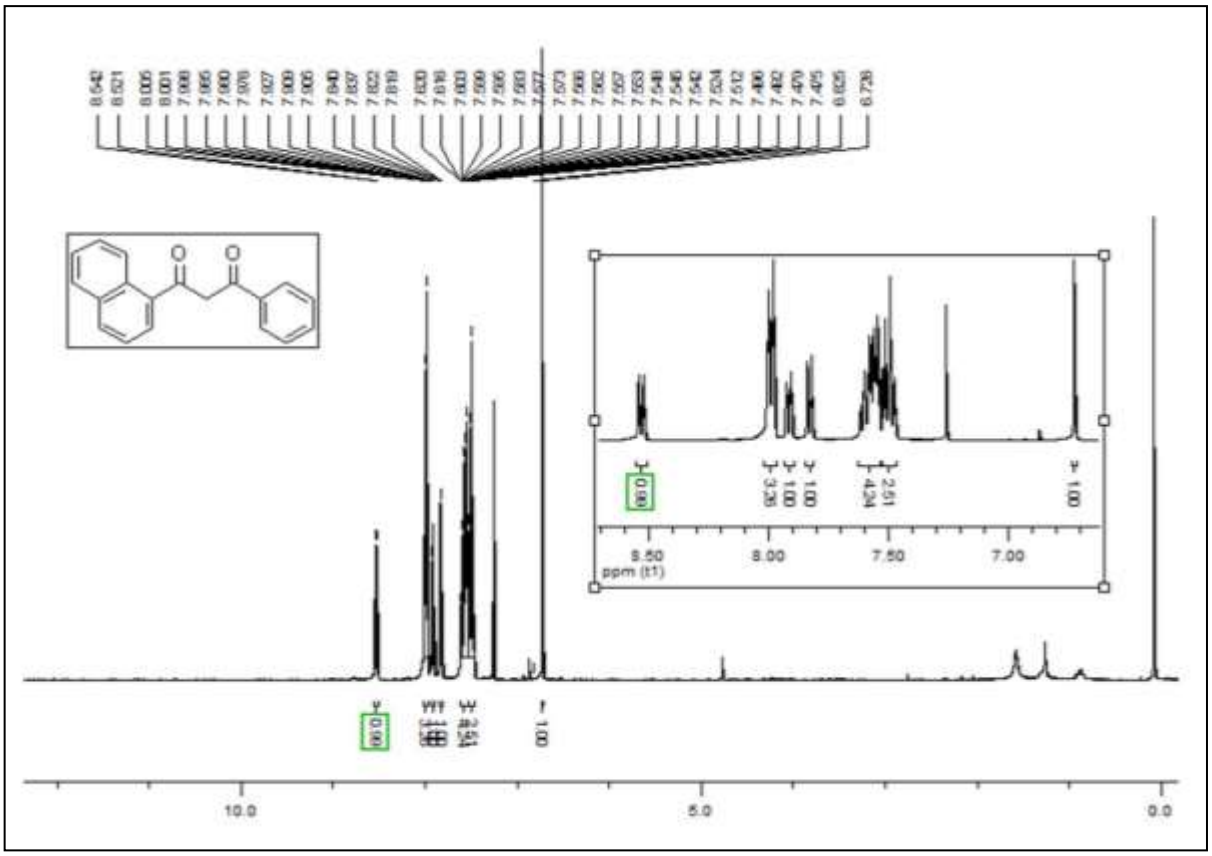


Fig. S13. ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **7.**

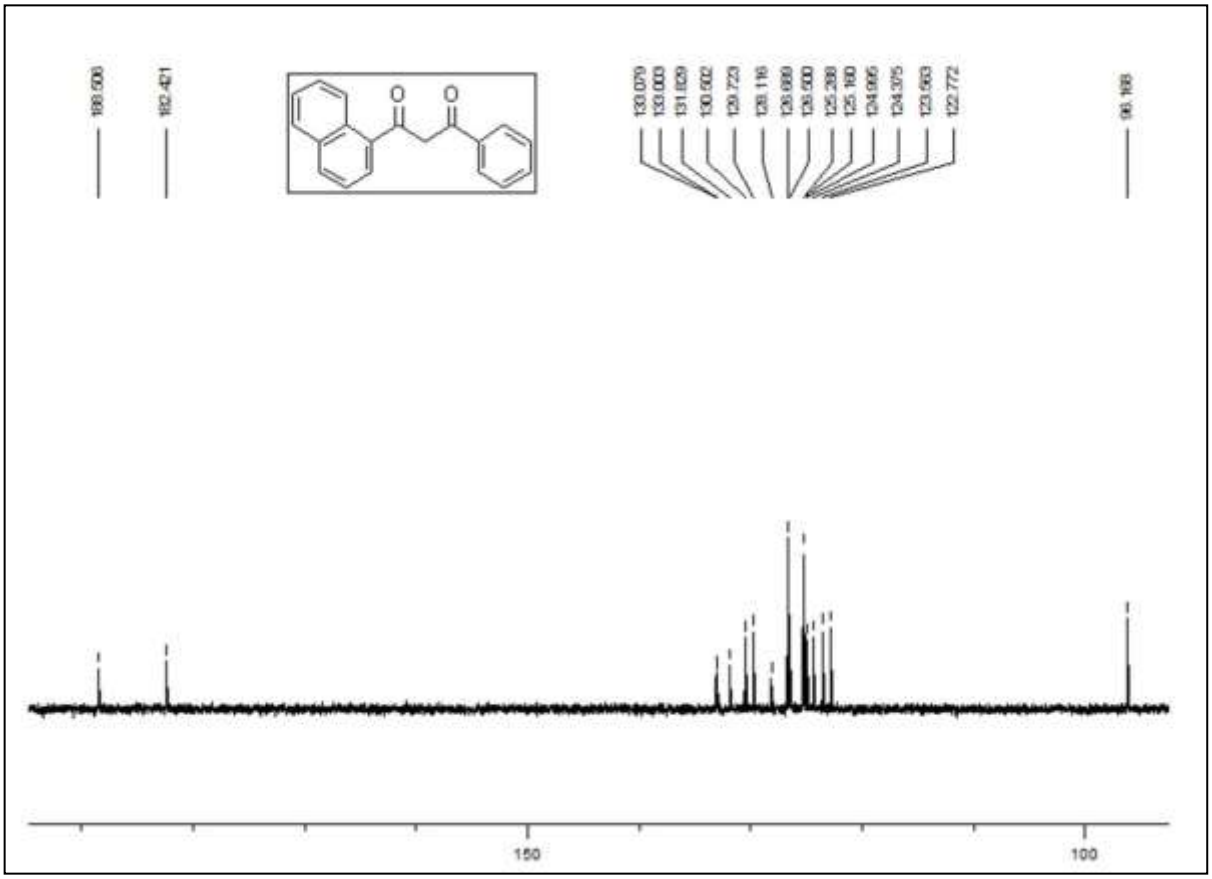
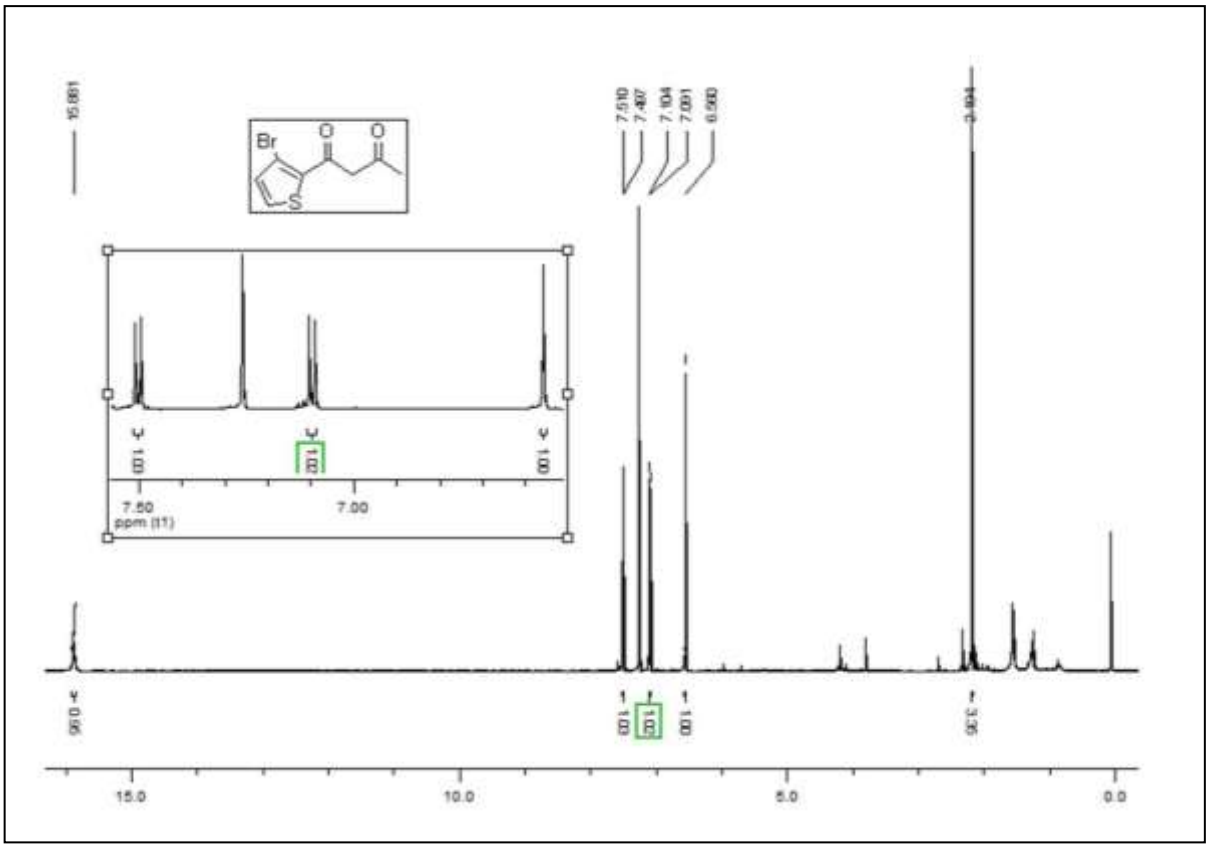
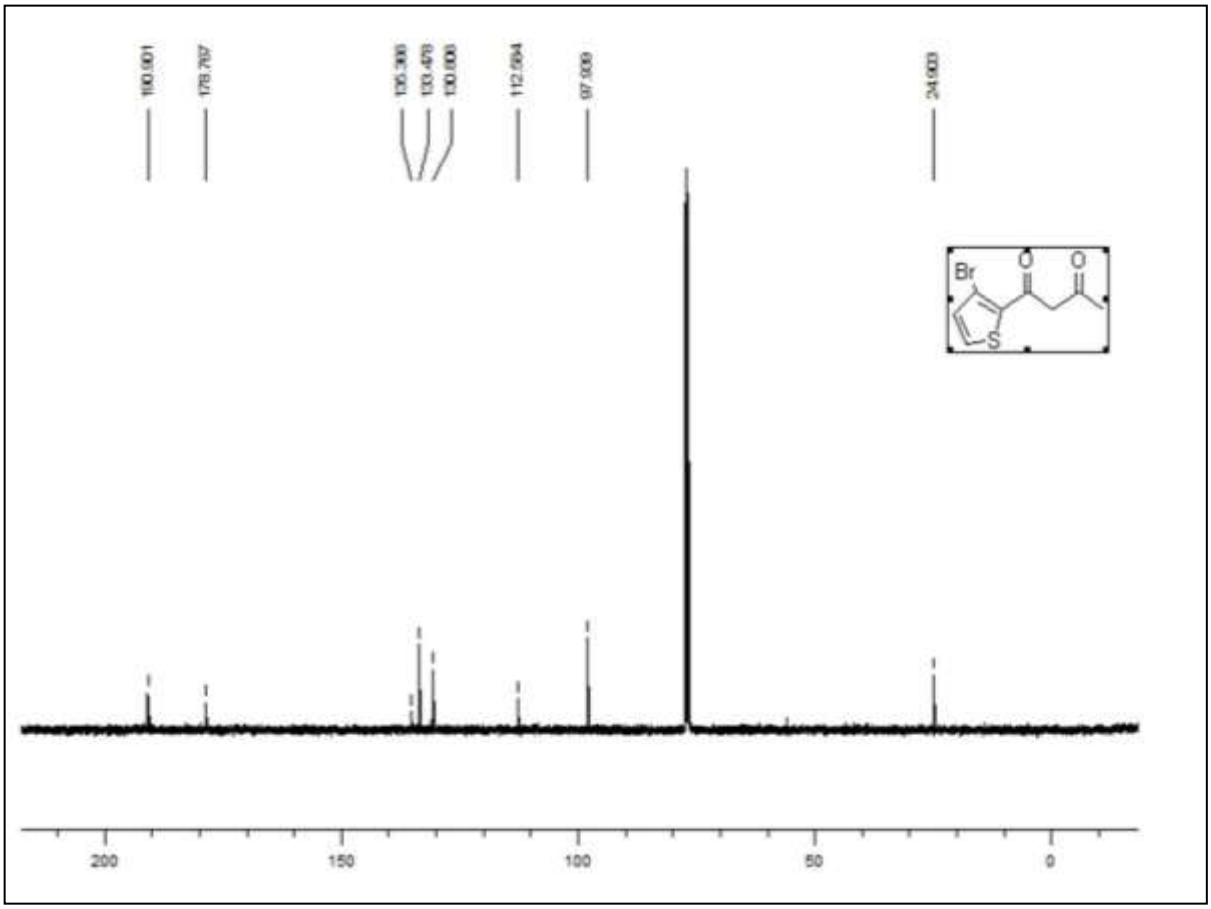


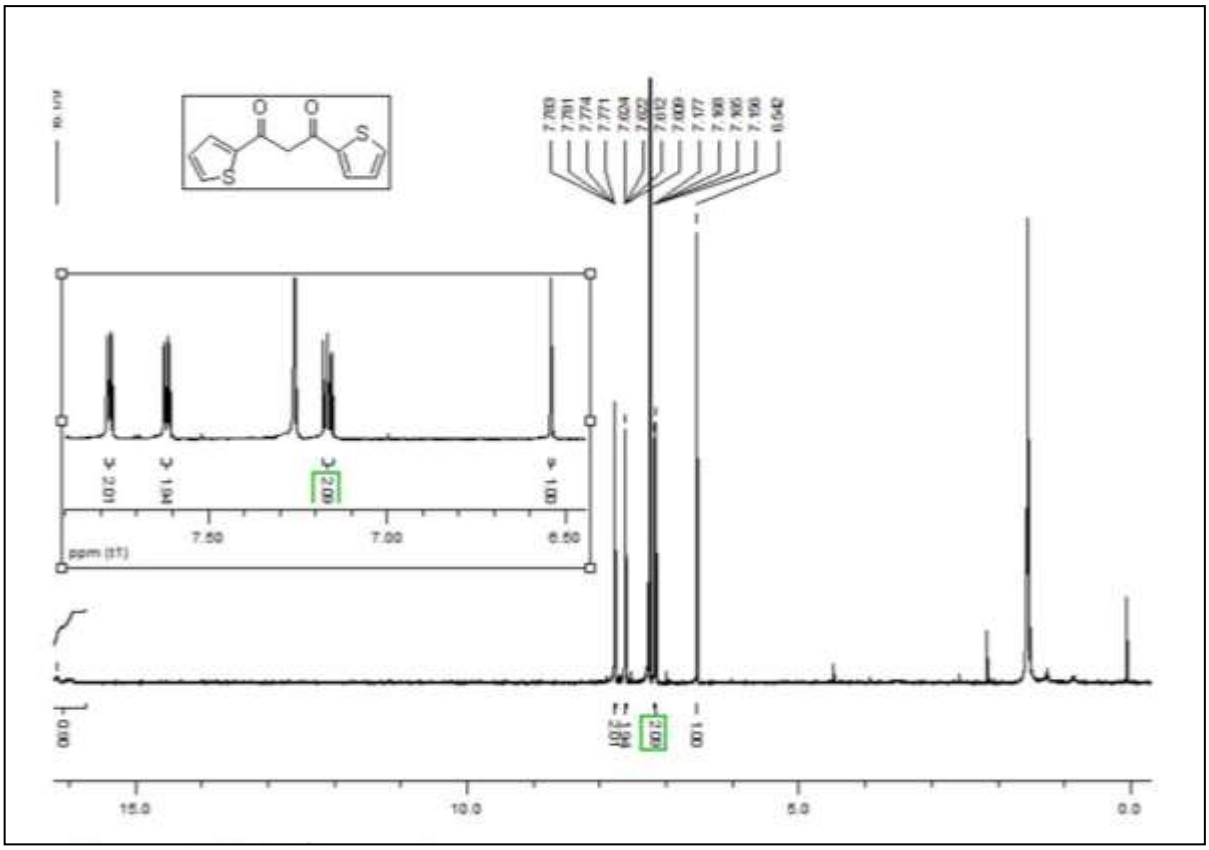
Fig. S14. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **7.**



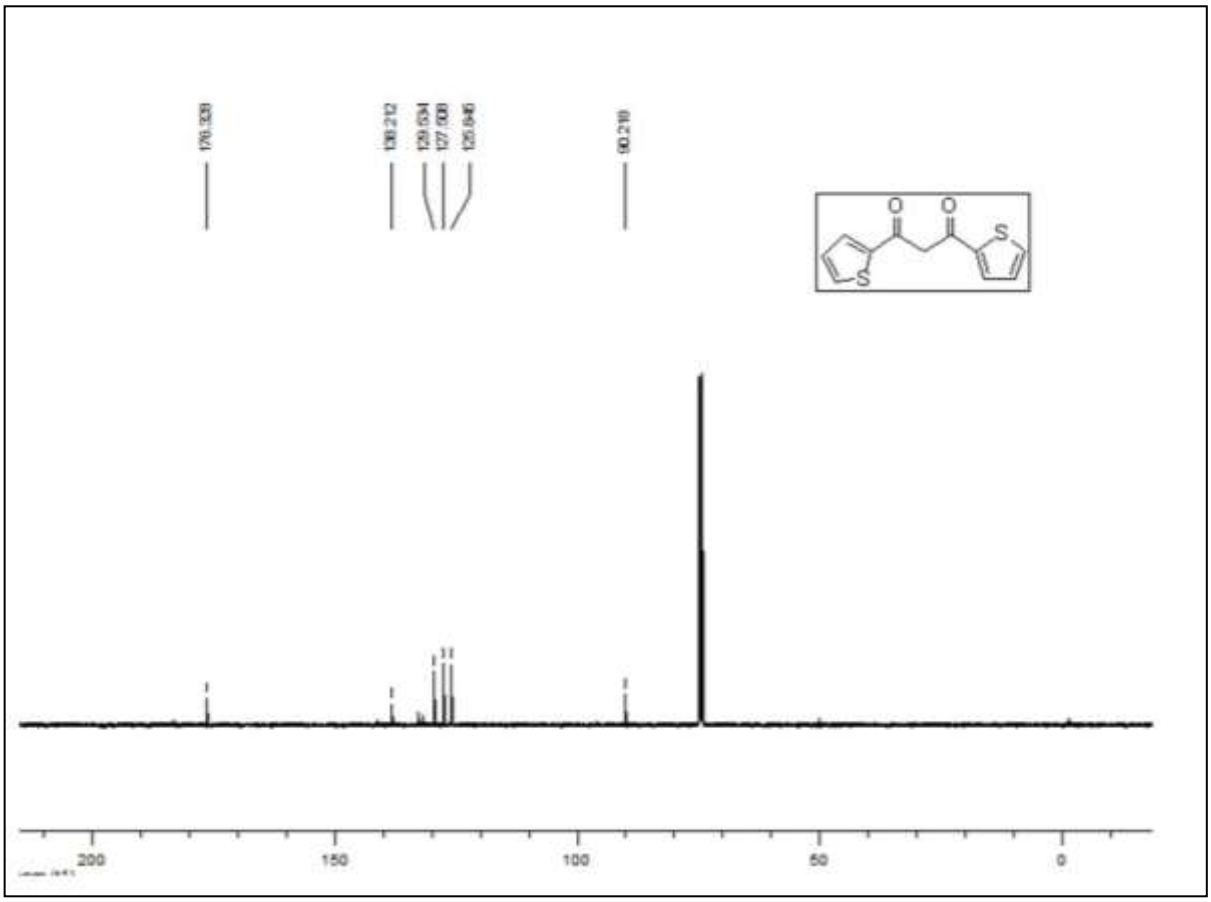
246 **Fig. S15.** ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **8.**



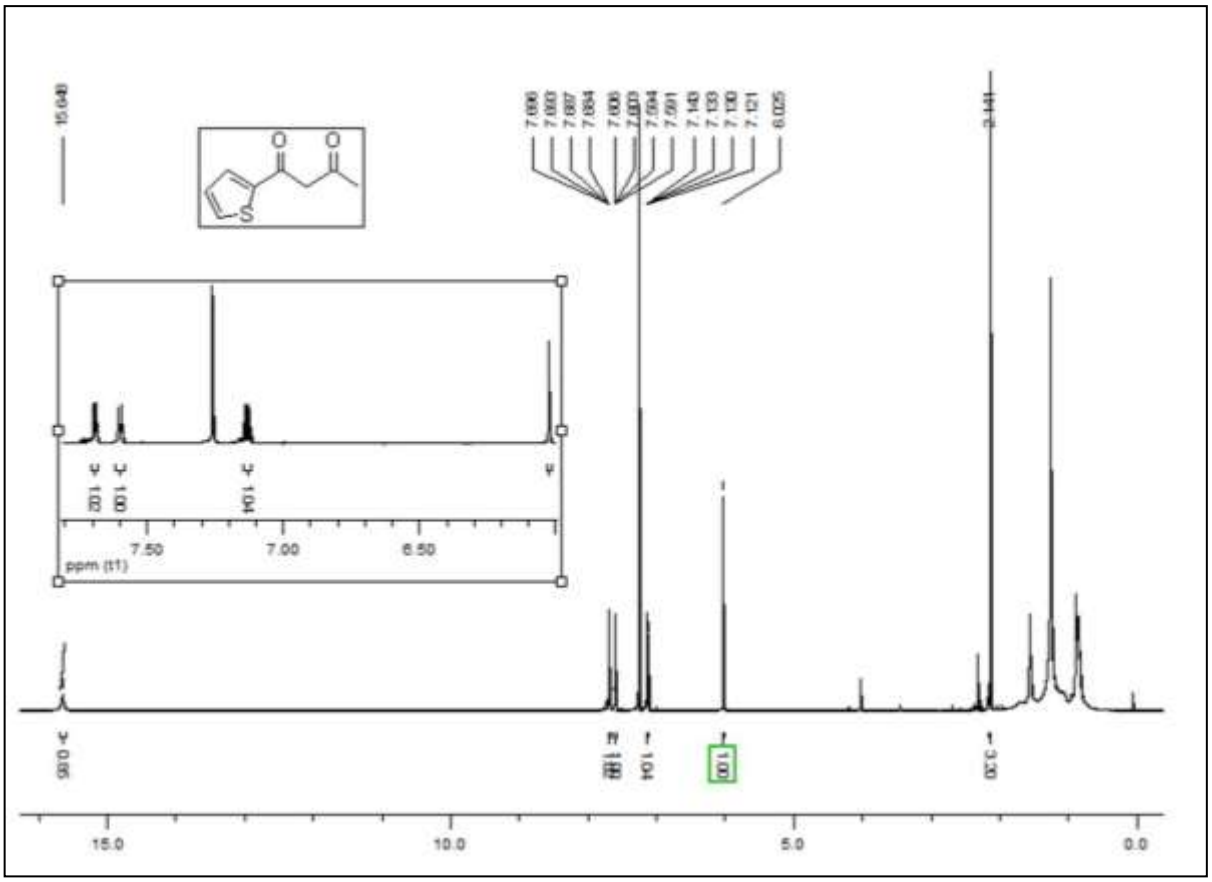
247 **Fig. S16**. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **8**



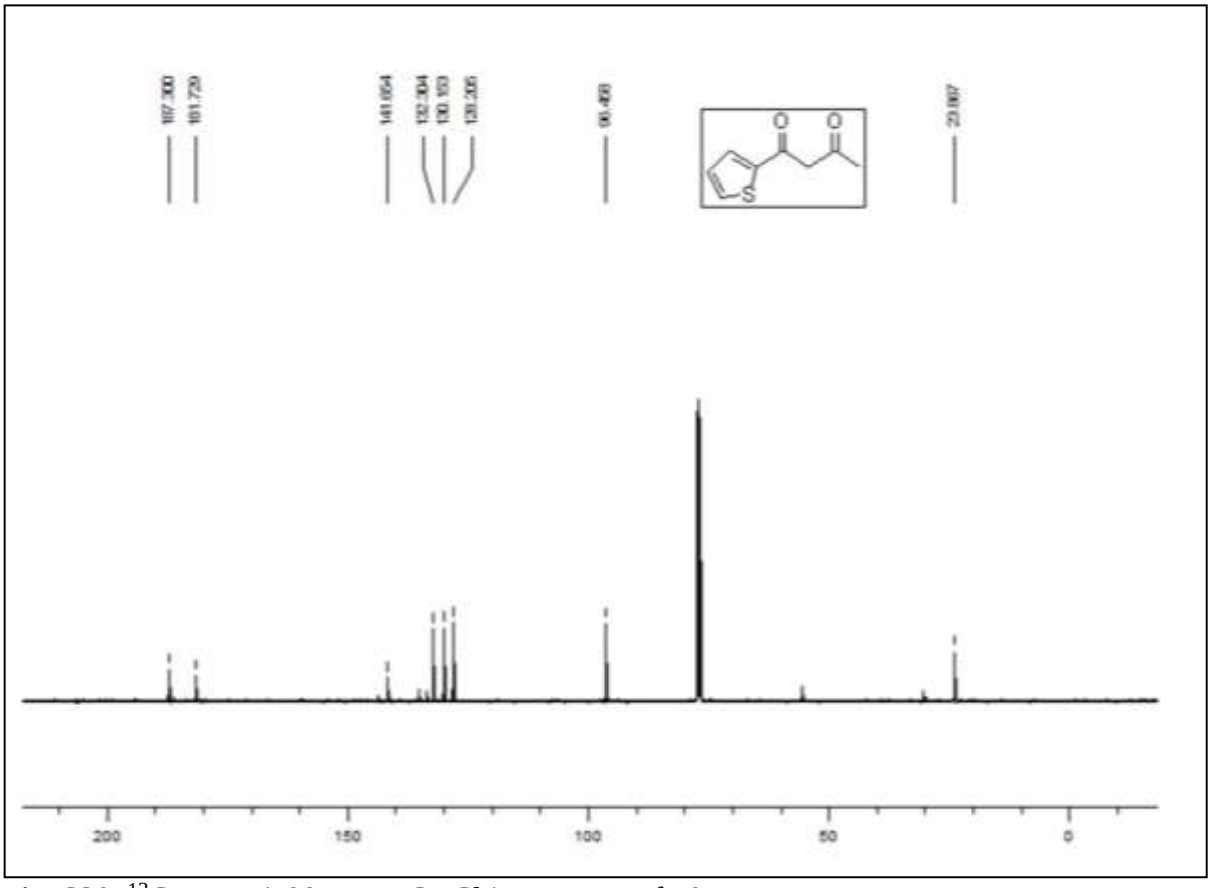
248 **Fig. S17.** ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **9.**



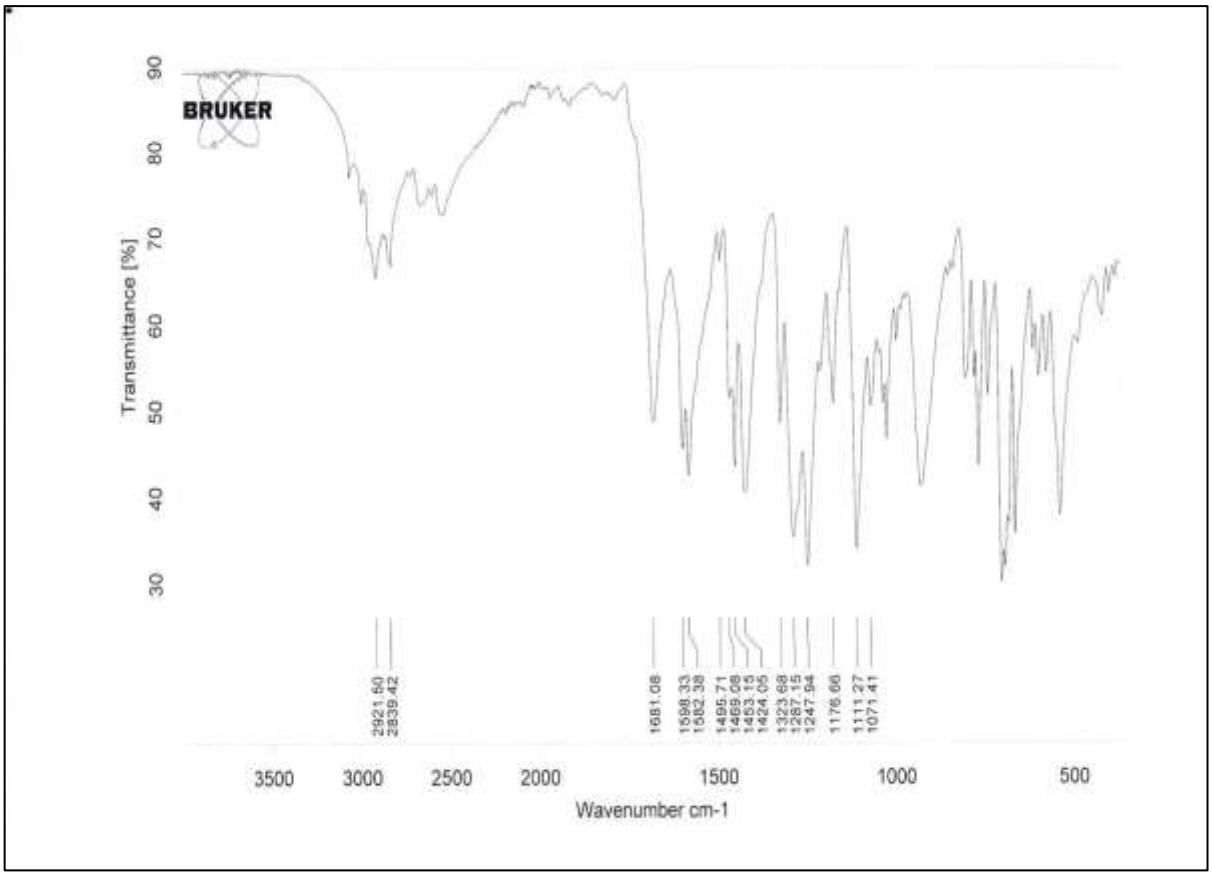
249 **Fig. S18**. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **9.**



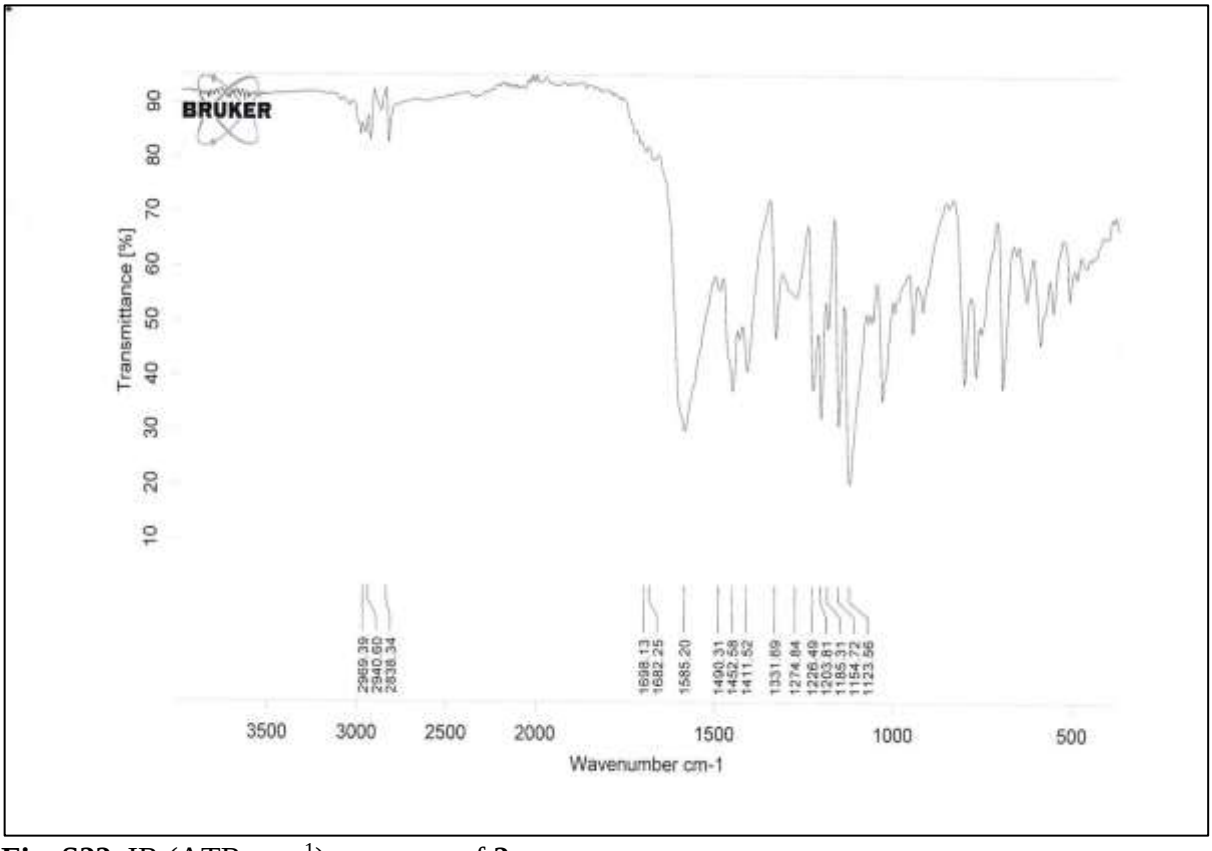
250 **Fig. S19.** ^{1}H NMR (400 MHz, $CDCl_3$) spectrum of **10.**



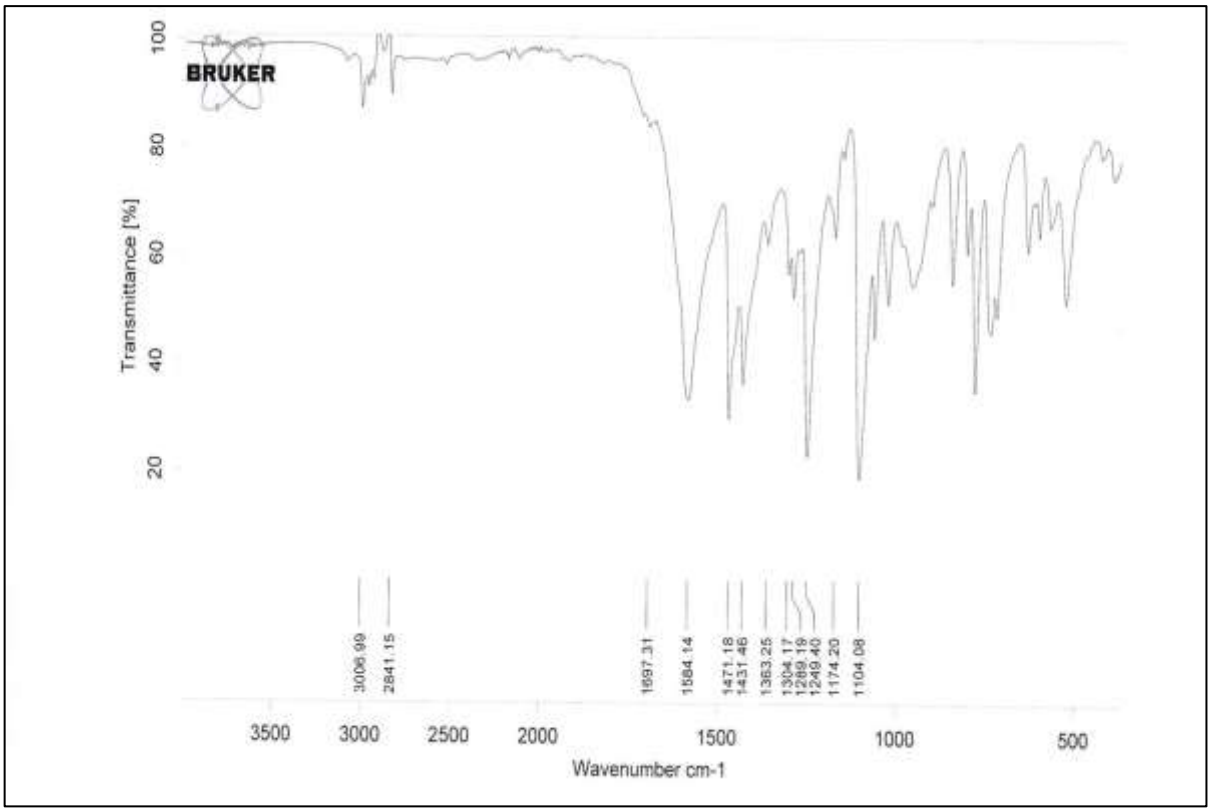
251 **Fig. S20**. ^{13}C NMR (100 MHz, $CDCl_3$) spectrum of **10**



252 **Fig. S21.** IR (ATR, cm^{-1}) spectrum of **1.**

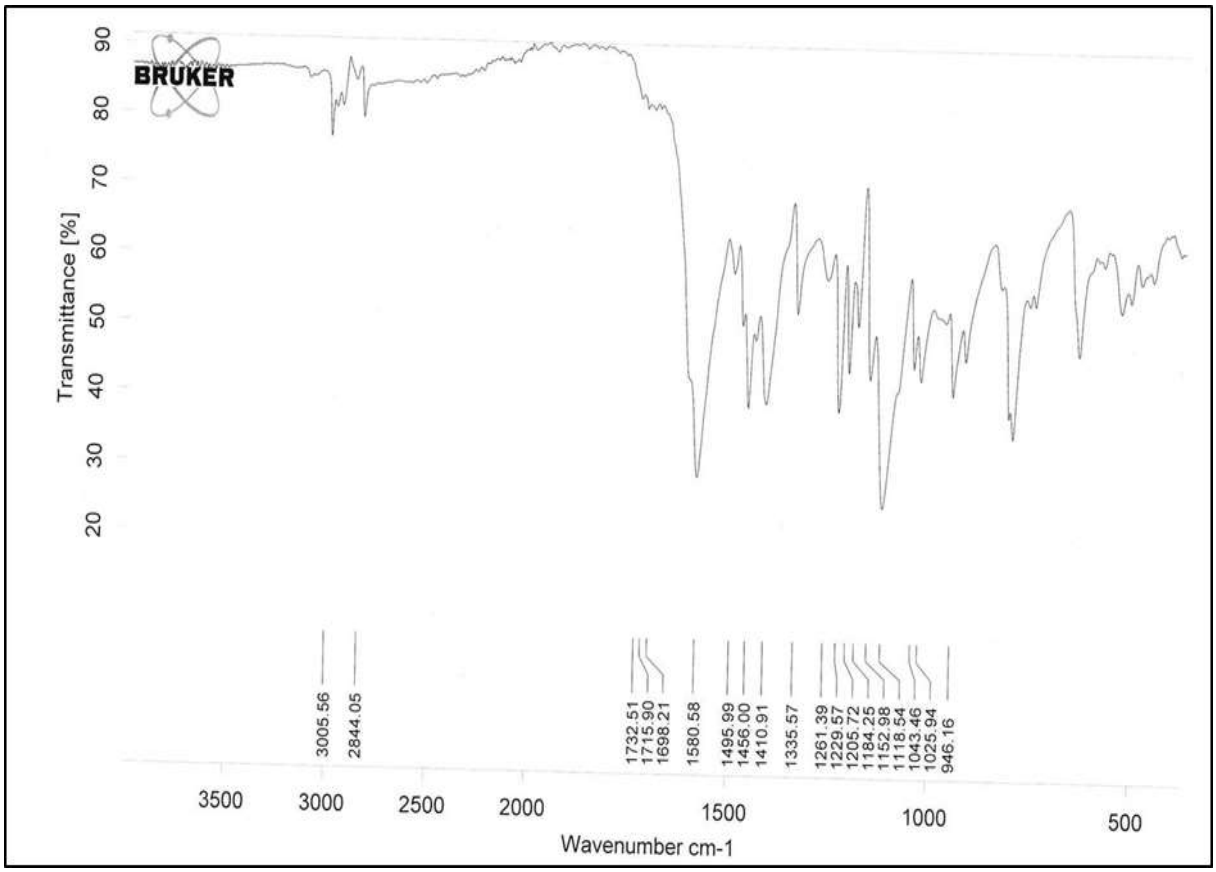


253 **Fig. S22.** IR (ATR, cm^{-1}) spectrum of **2.**

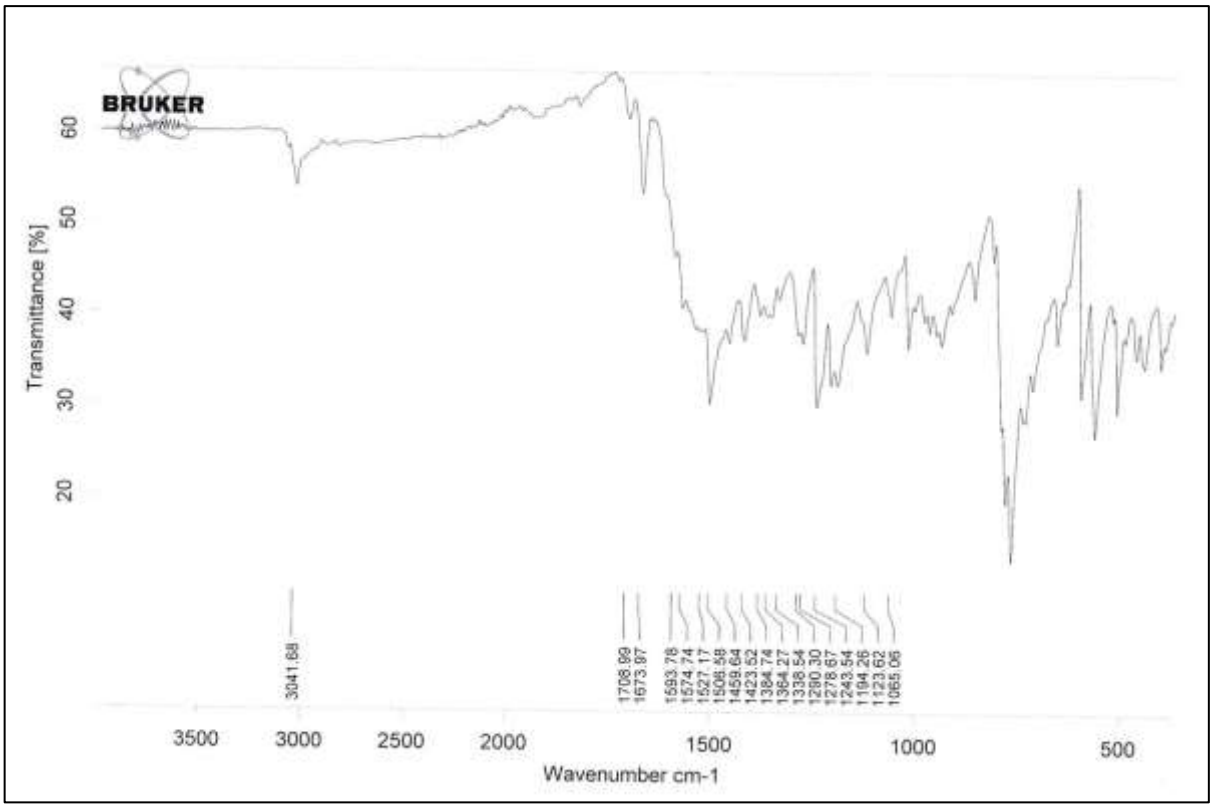


254 **Fig. S23.** IR (ATR, cm^{-1}) spectrum of **3.**

255

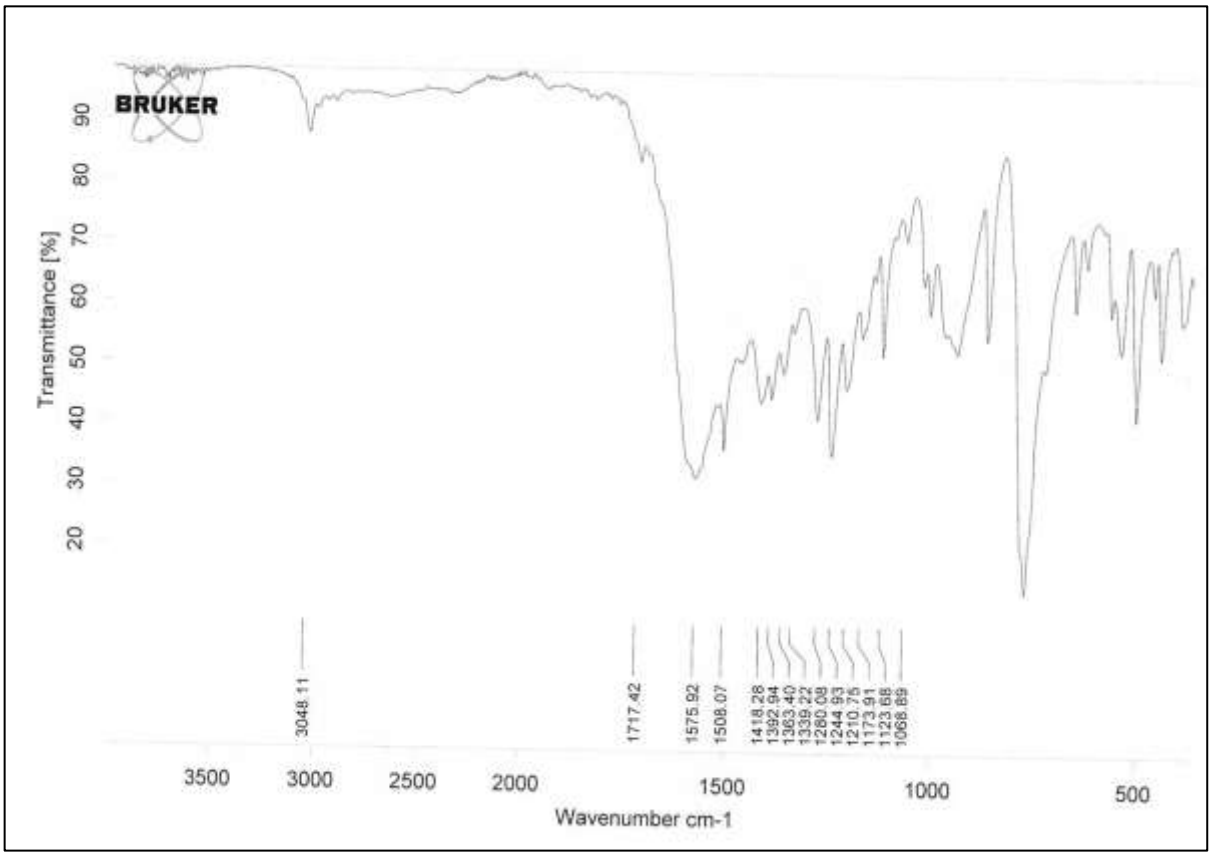


256 **Fig. S24.** IR (ATR, cm^{-1}) spectrum of **4.**

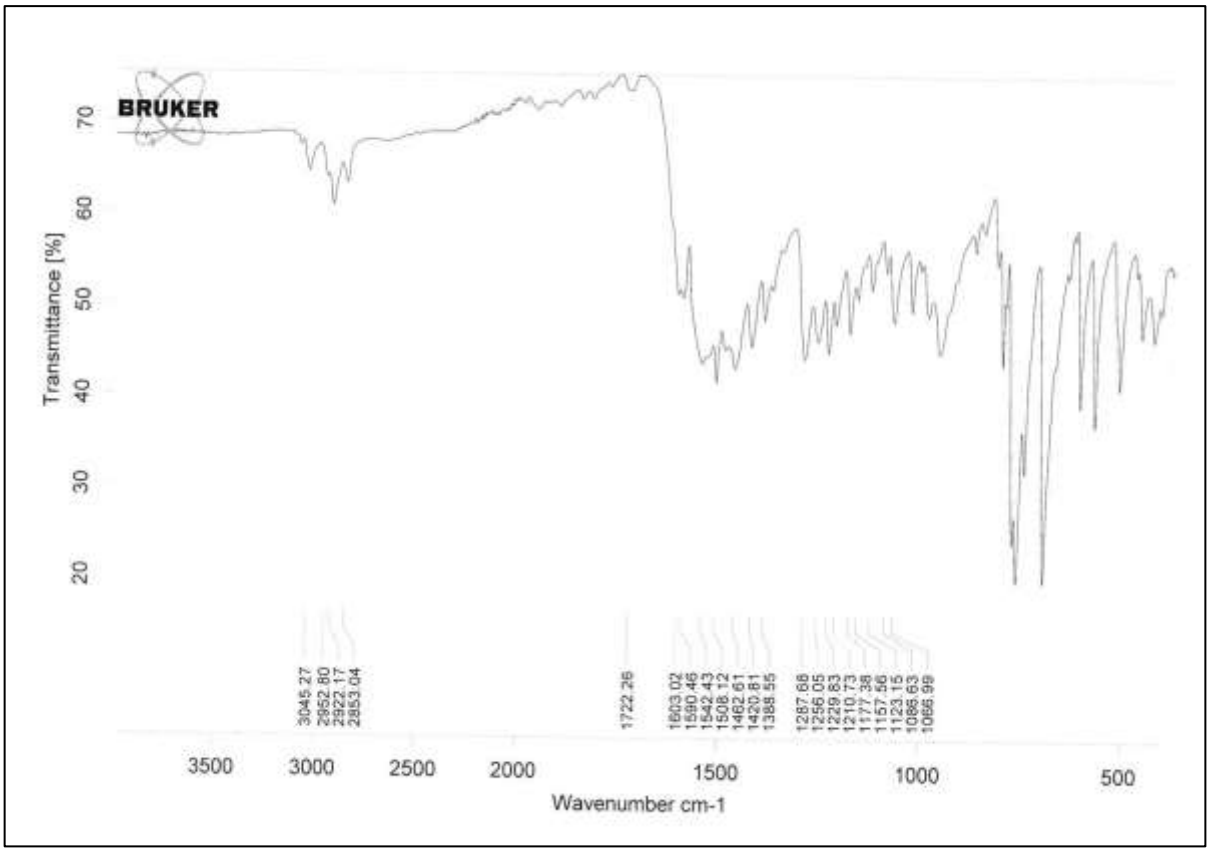


257

258 **Fig. S25.** IR (ATR, cm^{-1}) spectrum of **5.**

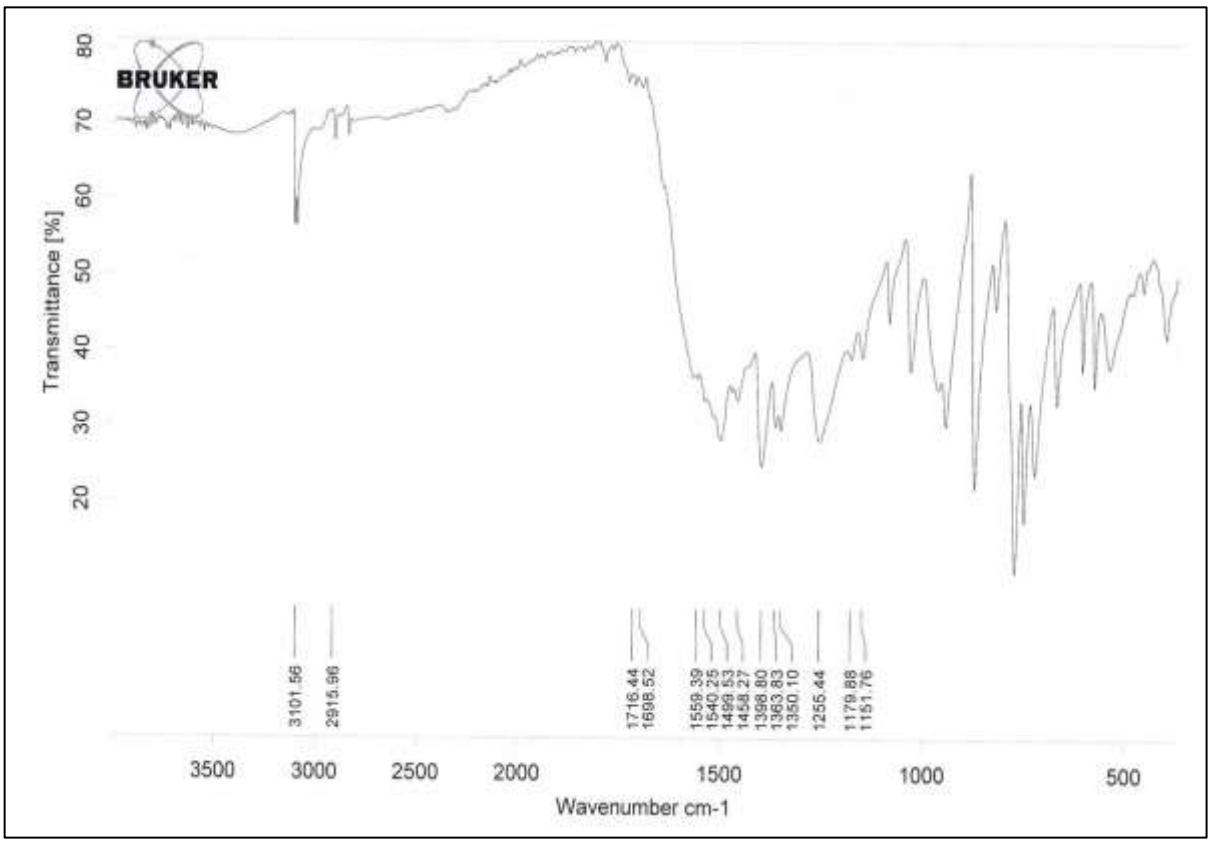


259 **Fig. S26.** IR (ATR, cm^{-1}) spectrum of **6.**

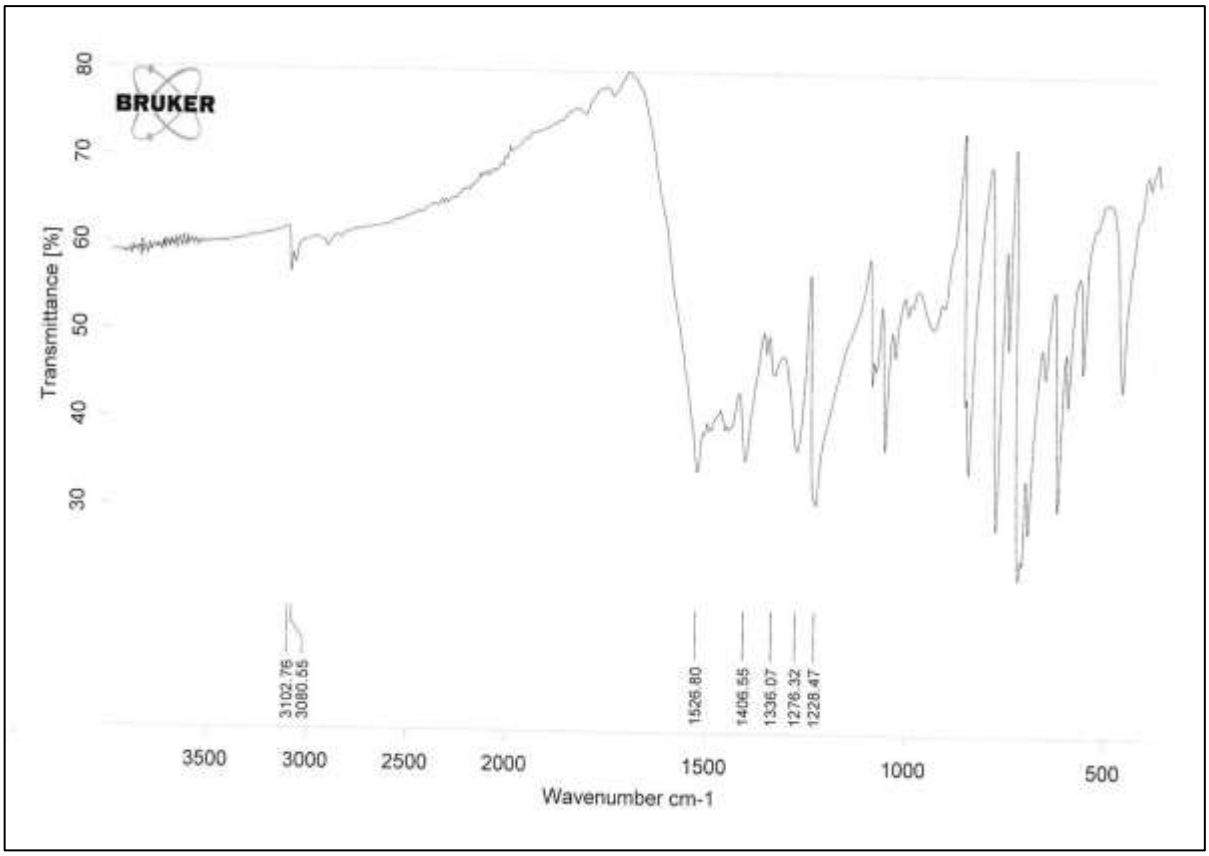


260 **Fig. S27.** IR (ATR, cm^{-1}) spectrum of **7.**

261

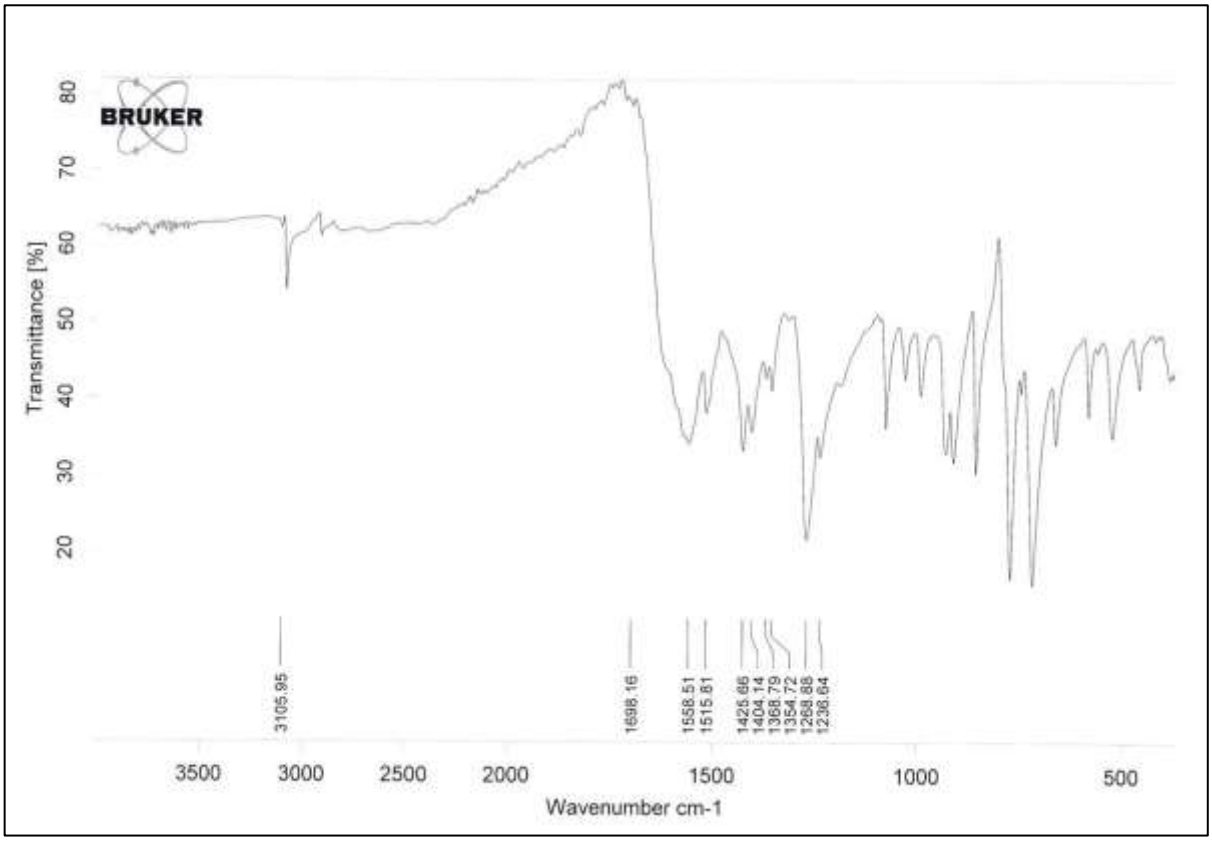


262 **Fig. S28.** IR (ATR, cm^{-1}) spectrum of **8.**



263 **Fig. S29.** IR (ATR, cm^{-1}) spectrum of **9.**

264



265 **Fig. S30.** IR (ATR, cm^{-1}) spectrum of **10.**

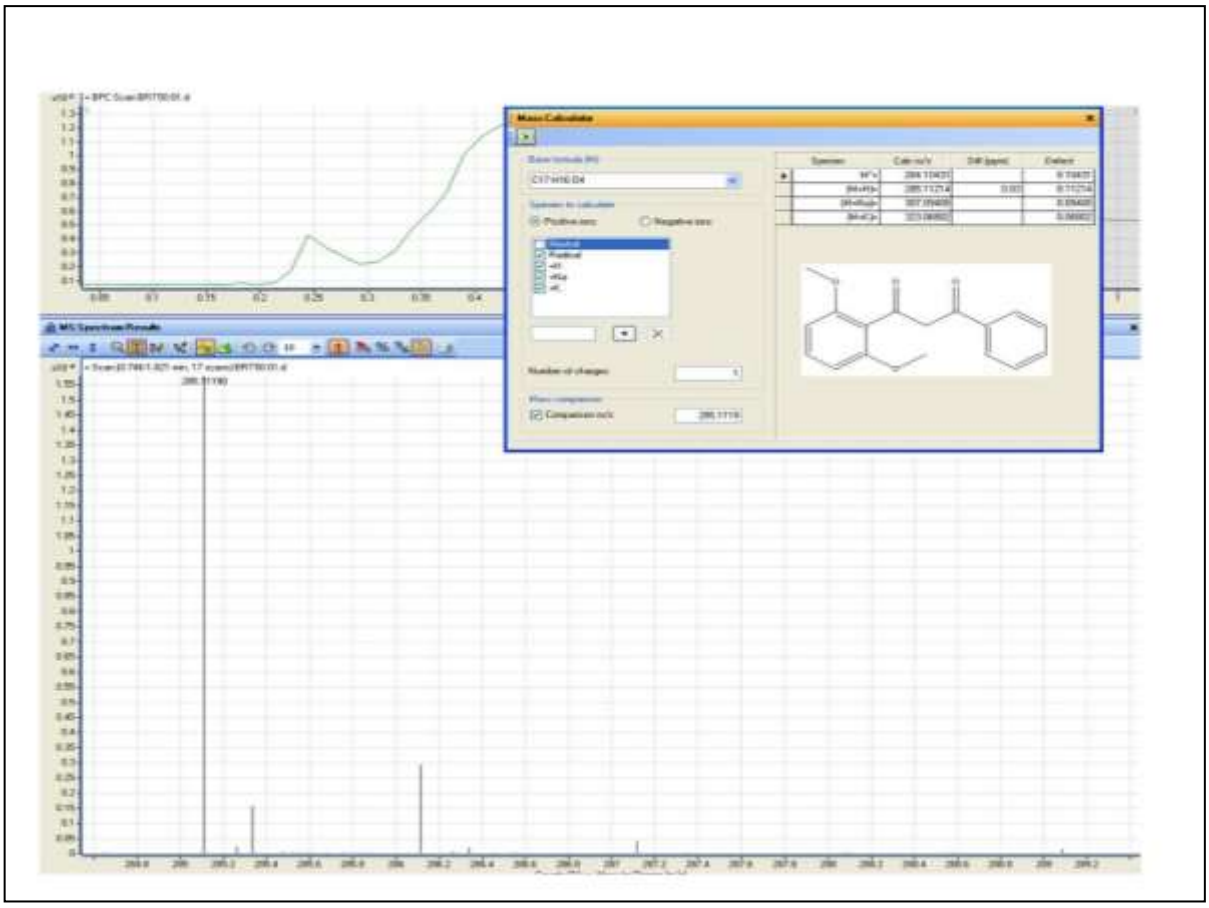


Fig. S31. HR-MS (m/z $(M+H)^+$) spectrum of **1**.

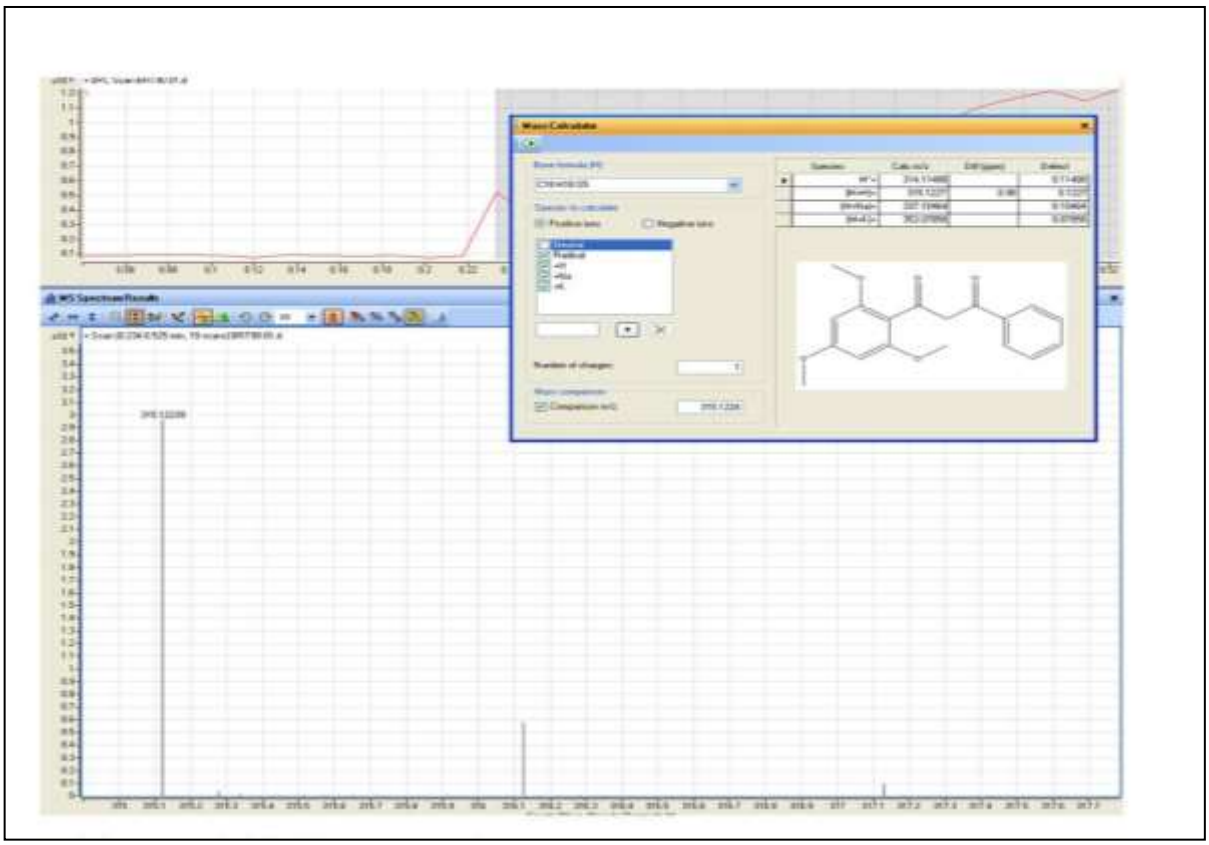


Fig. S32. HR-MS (m/z $(M+H)^+$) spectrum of **2**.

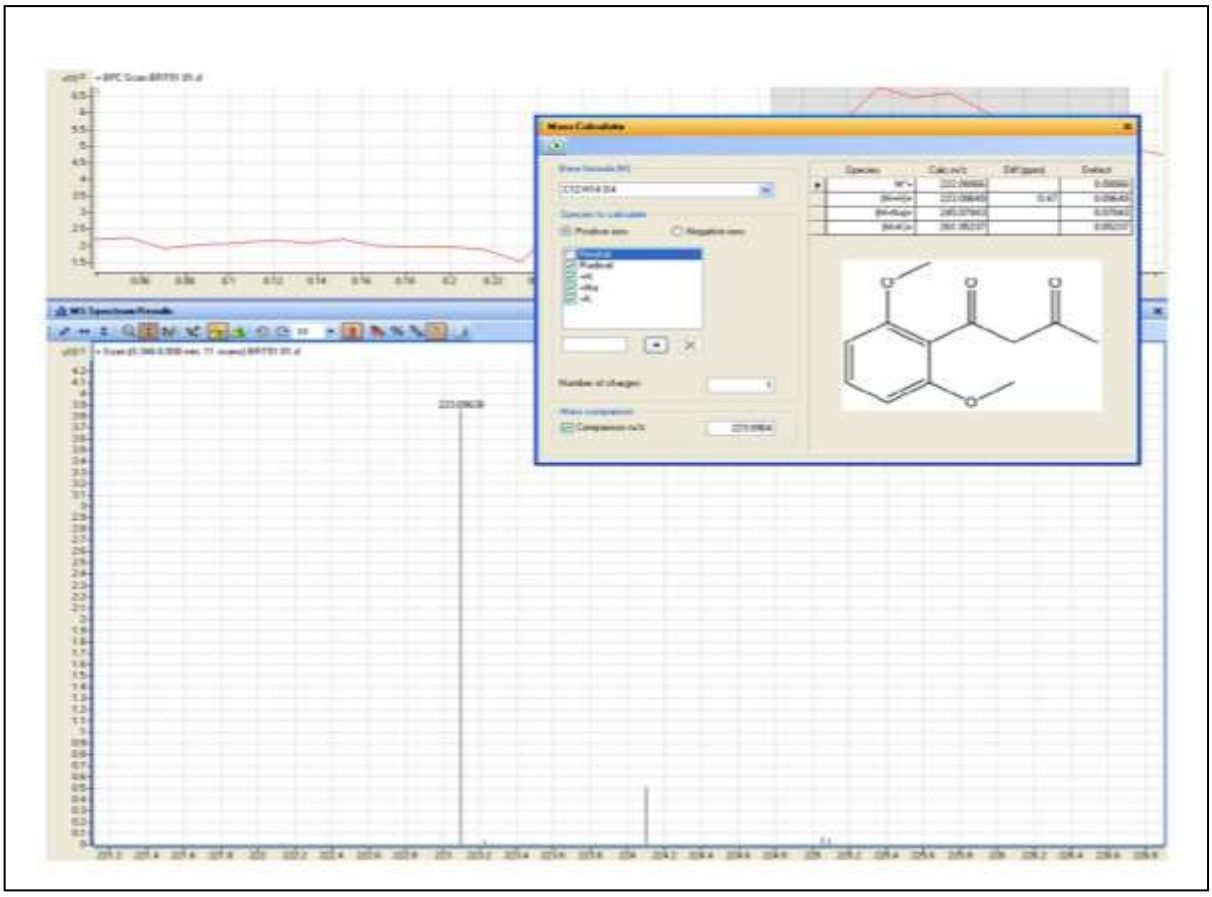


Fig. S33. HR-MS (m/z $(M+H)^+$) spectrum of **3**.

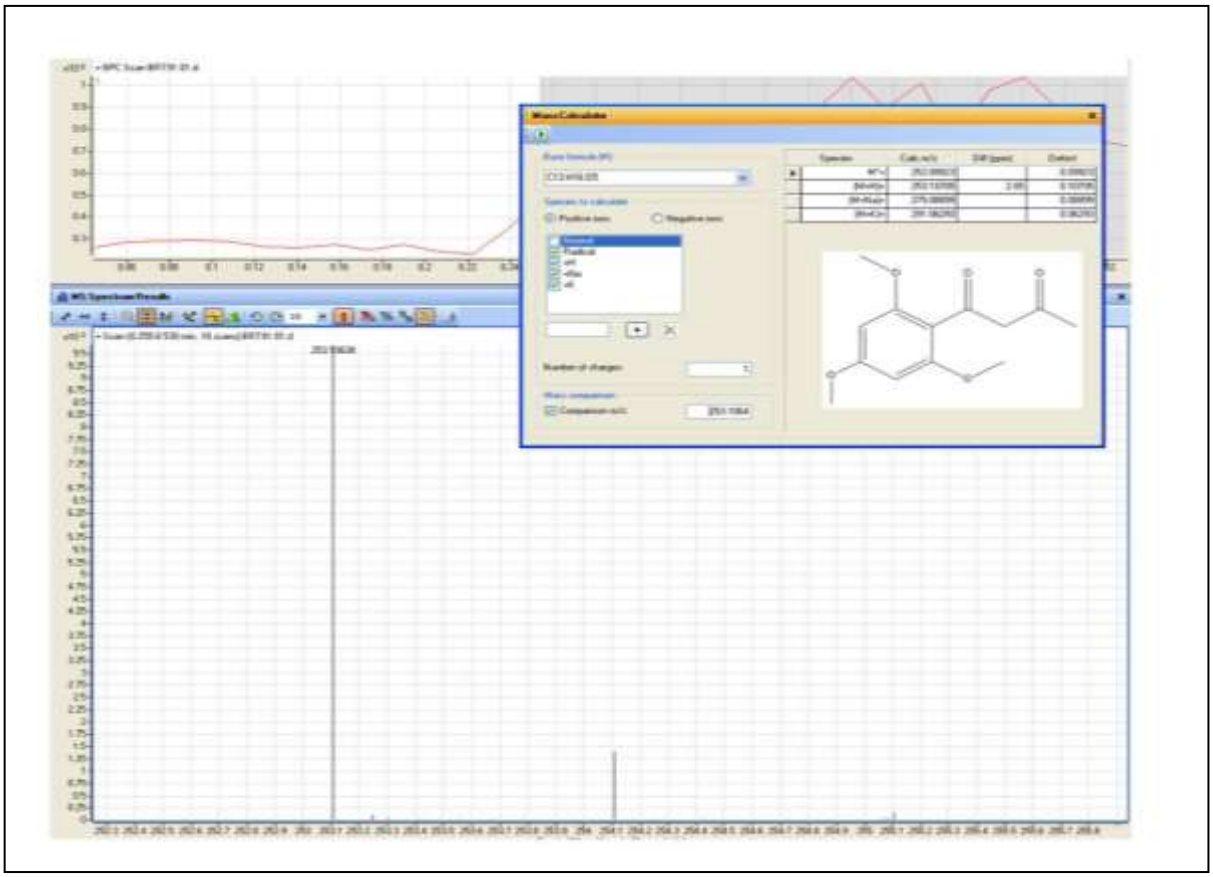


Fig. S34. HR-MS (m/z $(M+H)^+$) spectrum of **4**.

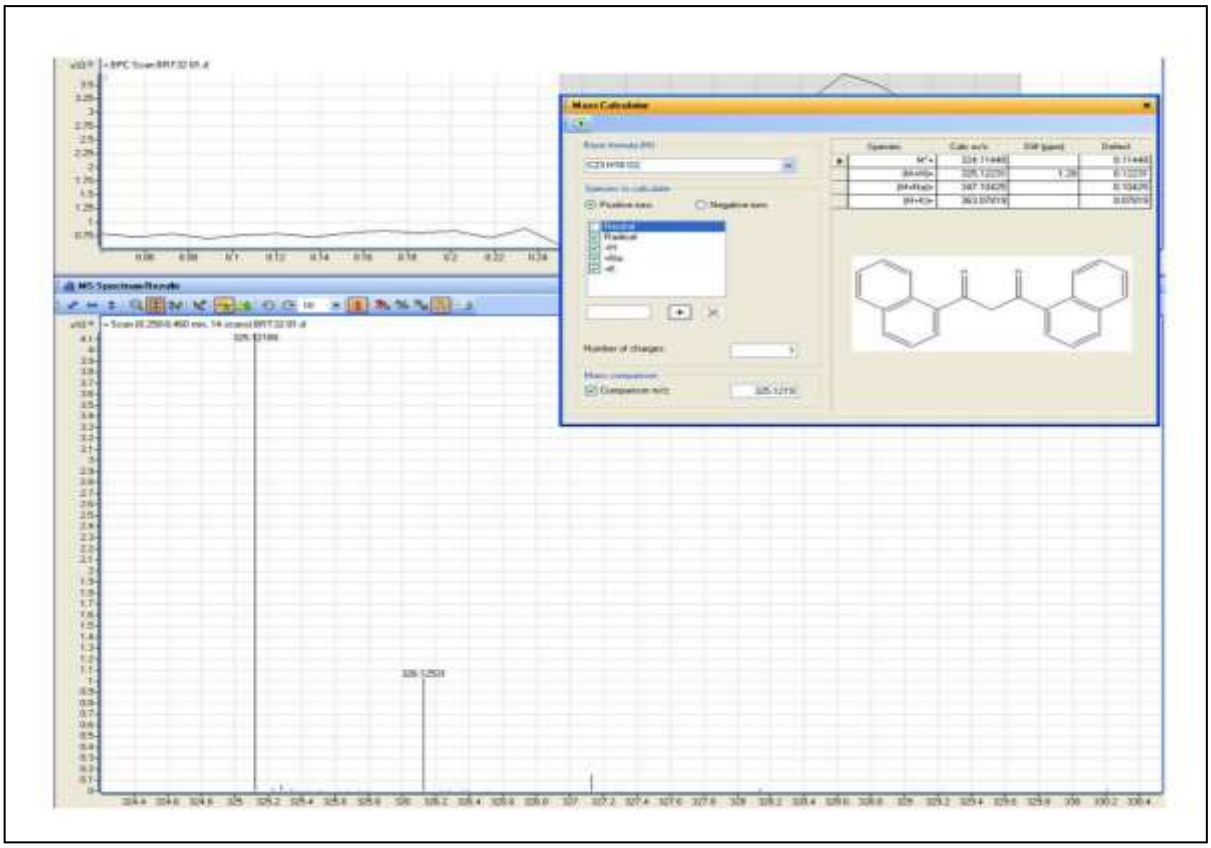


Fig. S35. HR-MS (m/z $(M+H)^+$) spectrum of **5**.

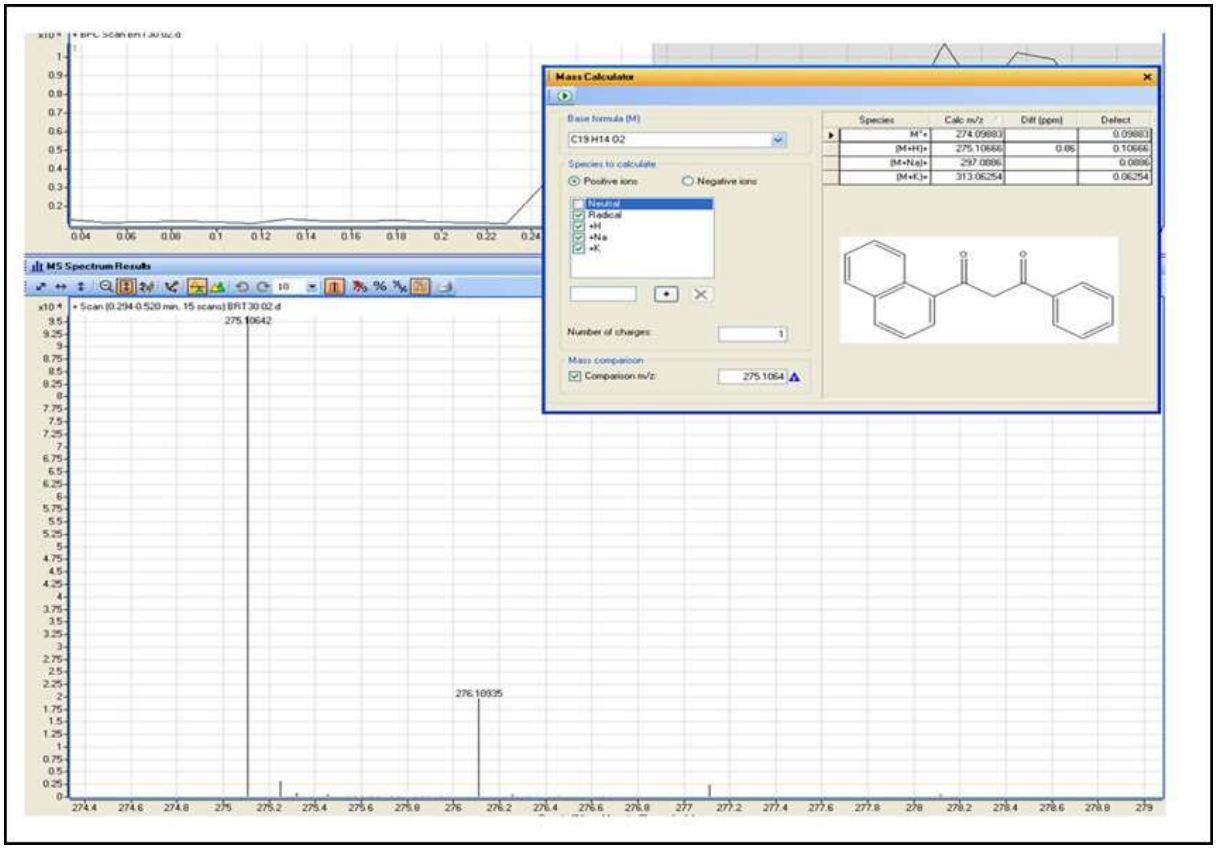


Fig. S36. HR-MS (m/z $(M+H)^+$) spectrum of **6**.

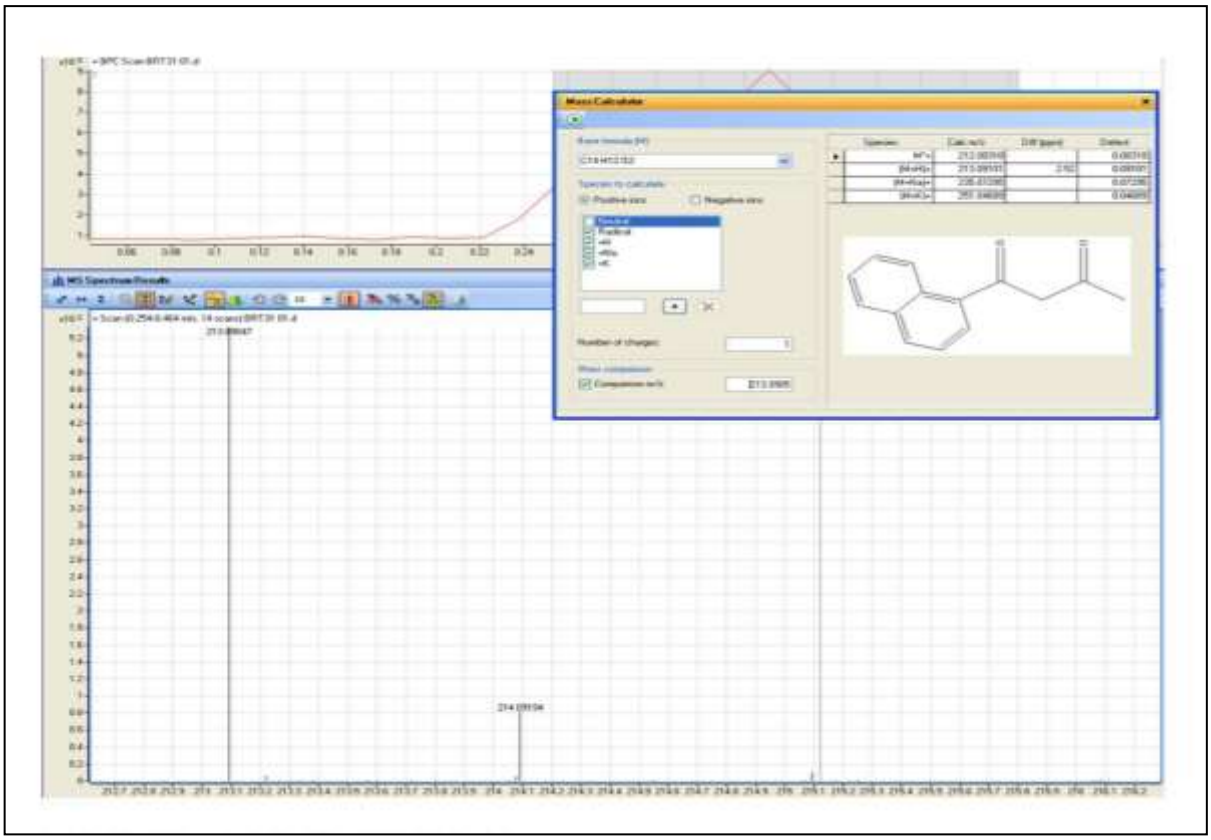


Fig. S37. HR-MS (m/z $(M+H)^+$) spectrum of **7**.

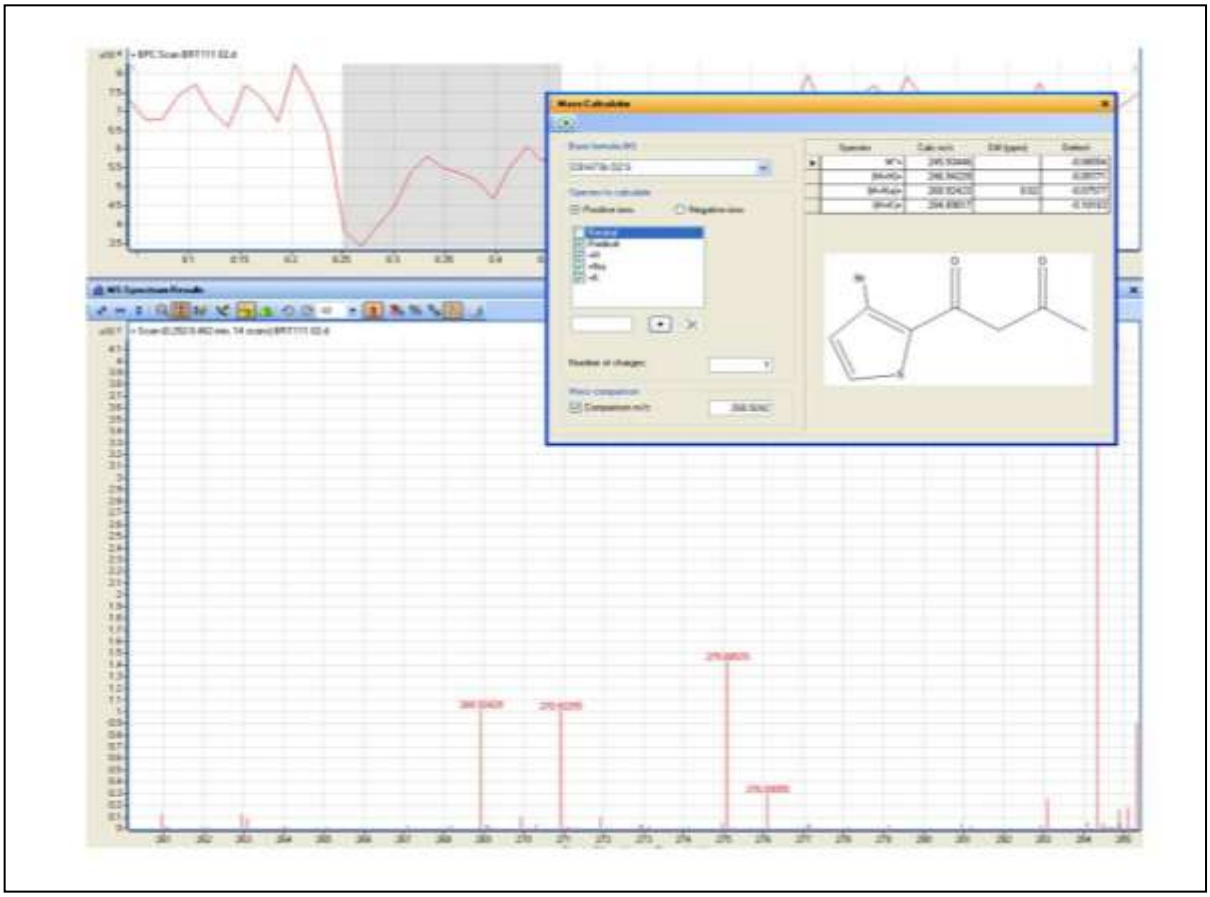


Fig. S38. HR-MS (m/z $(M+Na)^+$) spectrum of **8**.

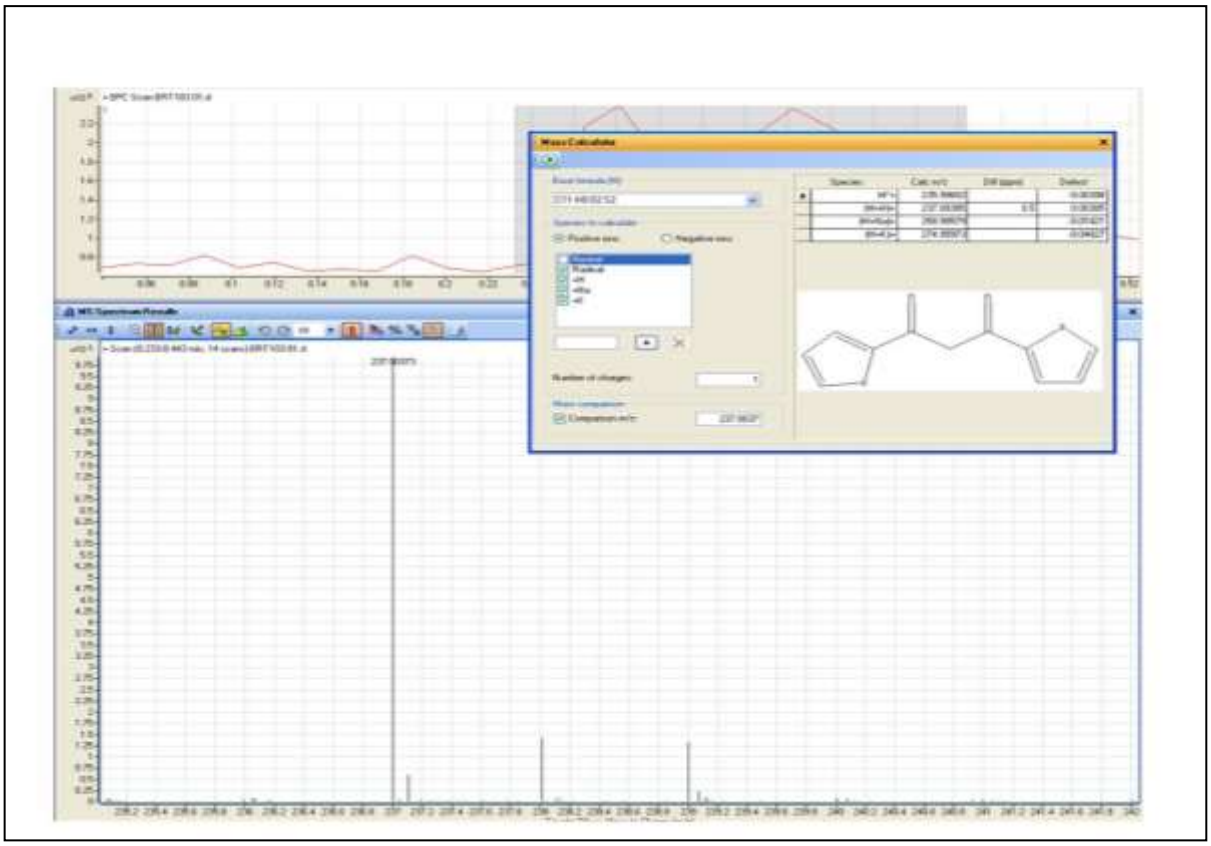


Fig. S39. HR-MS (m/z $(M+H)^+$) spectrum of **9**.

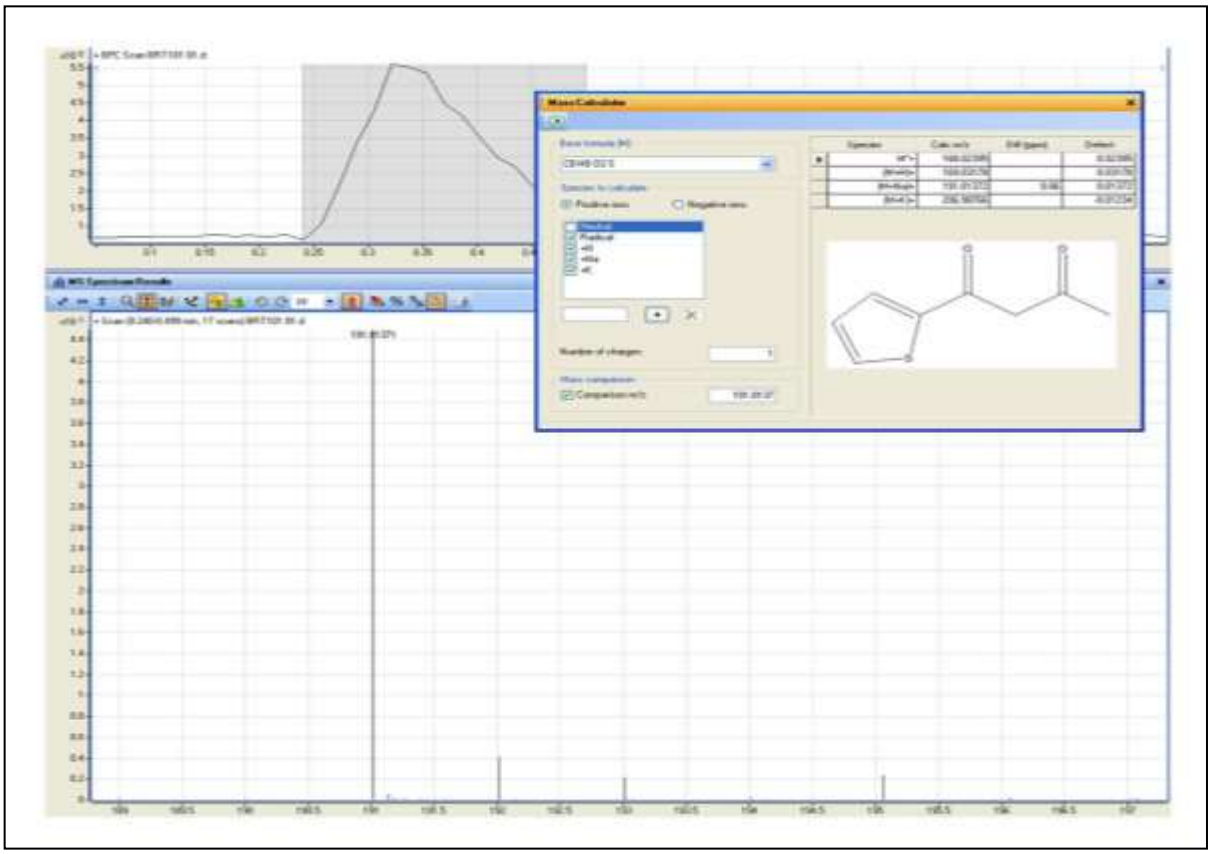
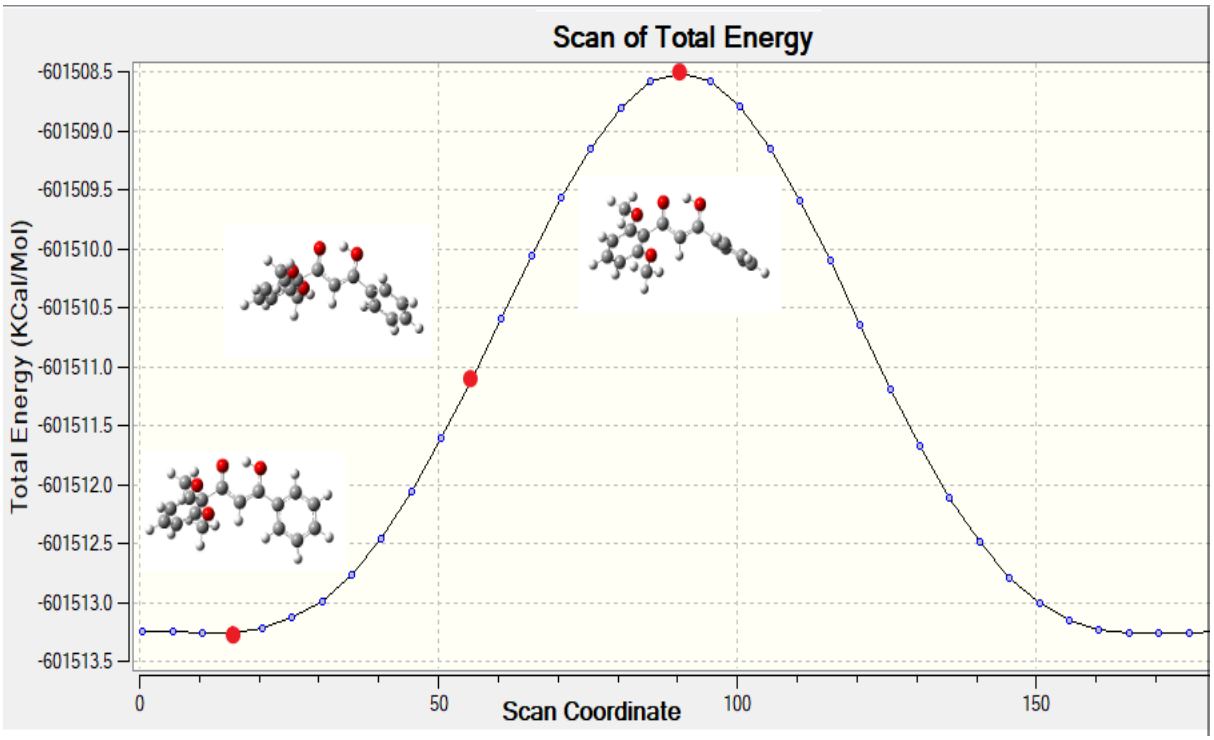
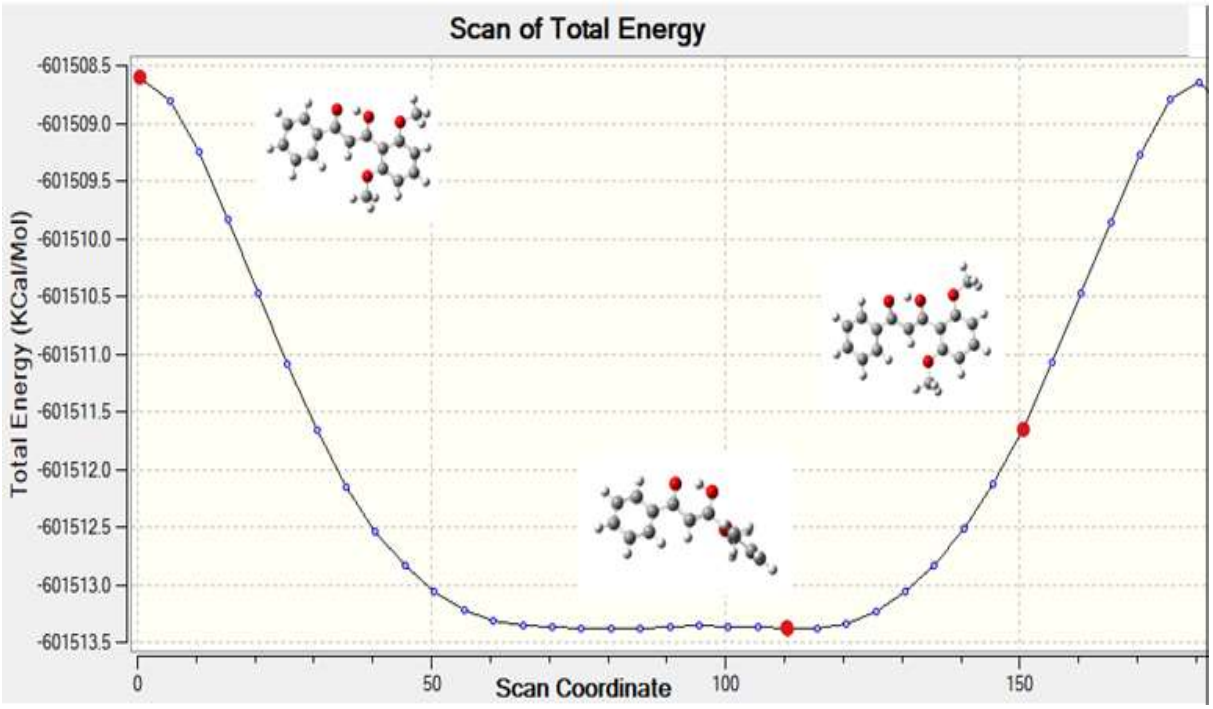


Fig. S40. HR-MS (m/z $(M+Na)^+$) spectrum of **10**.

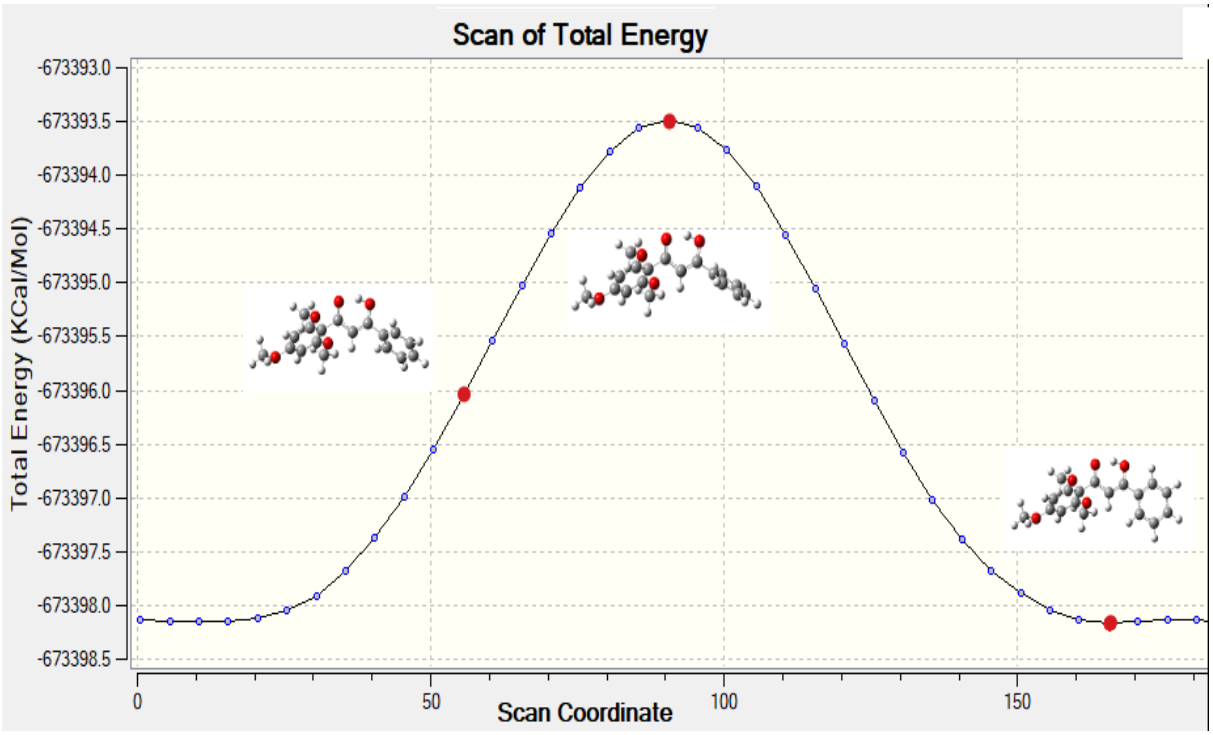


a.

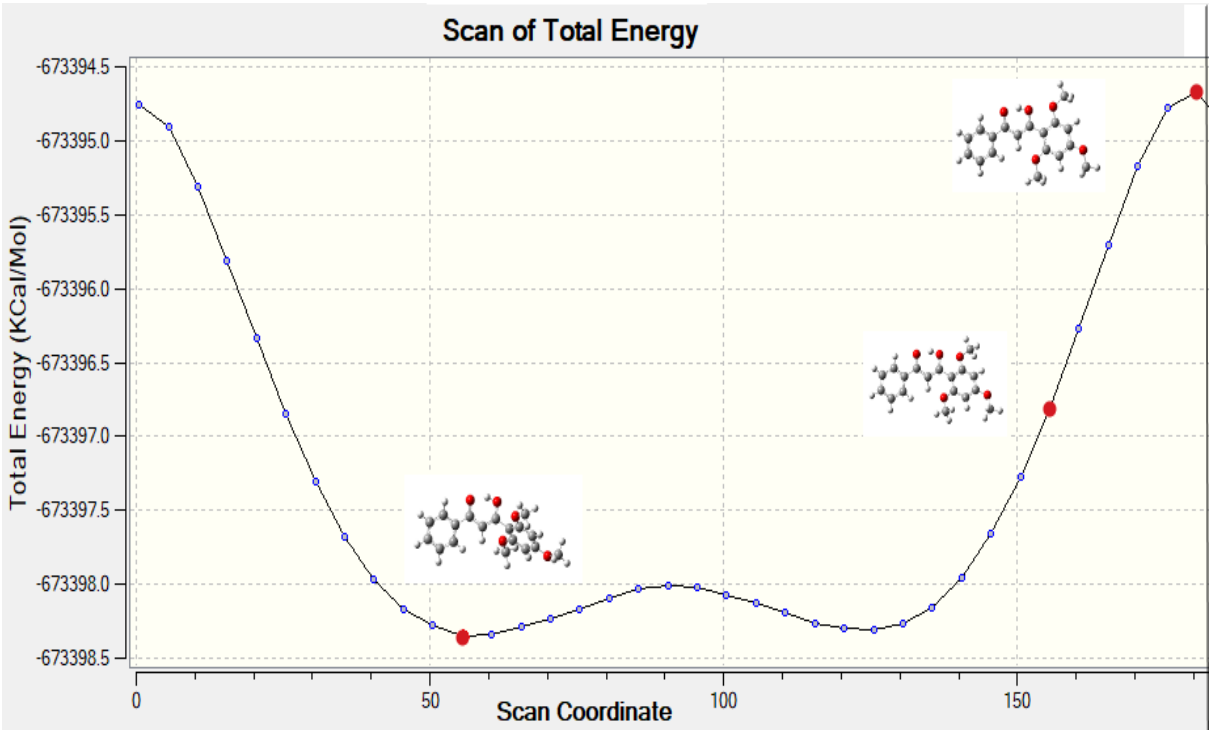


b.

Fig. S41. a. Dihedral angle scanning of the enol form **1a** (most and least stable conformers)**; b.** Dihedral angle scanning of the enol form **1b** (most and least stable conformers).

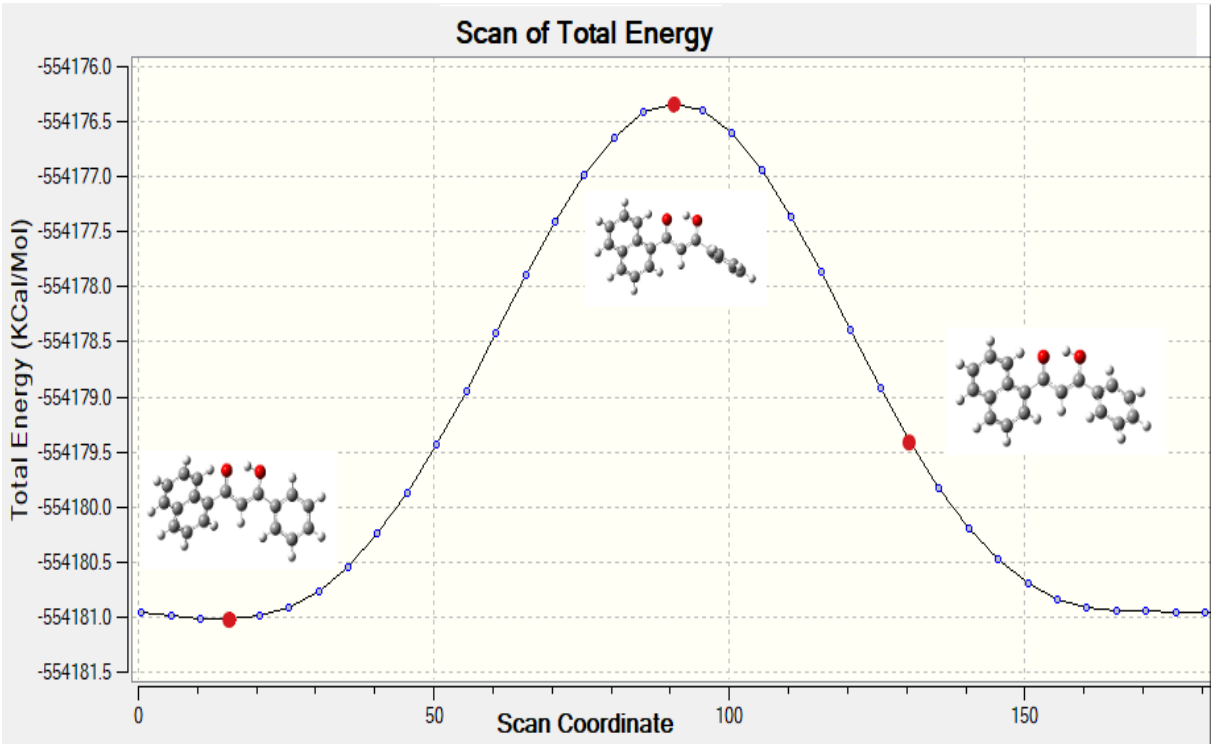


a.

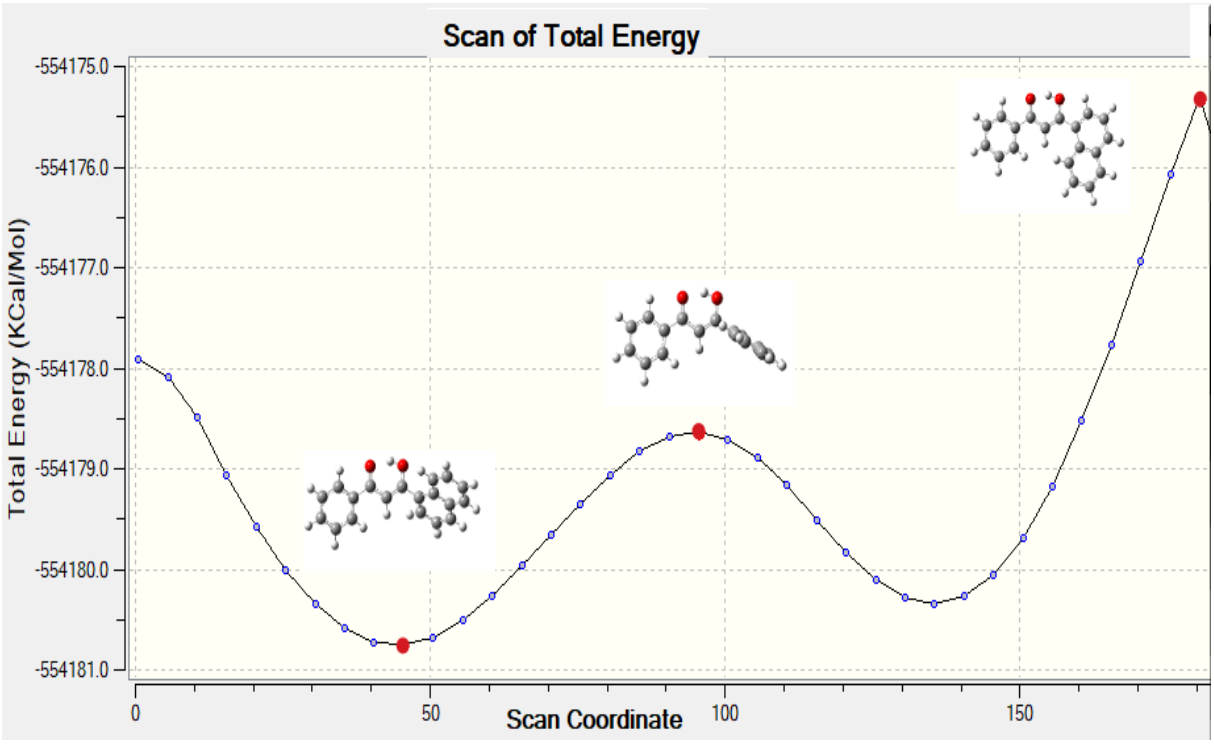


b.

Fig. S42. a. Dihedral angle scanning of the enol form **2a** (most and least stable conformers)**; b.** Dihedral angle scanning of the enol form **2b** (most and least stable conformers).

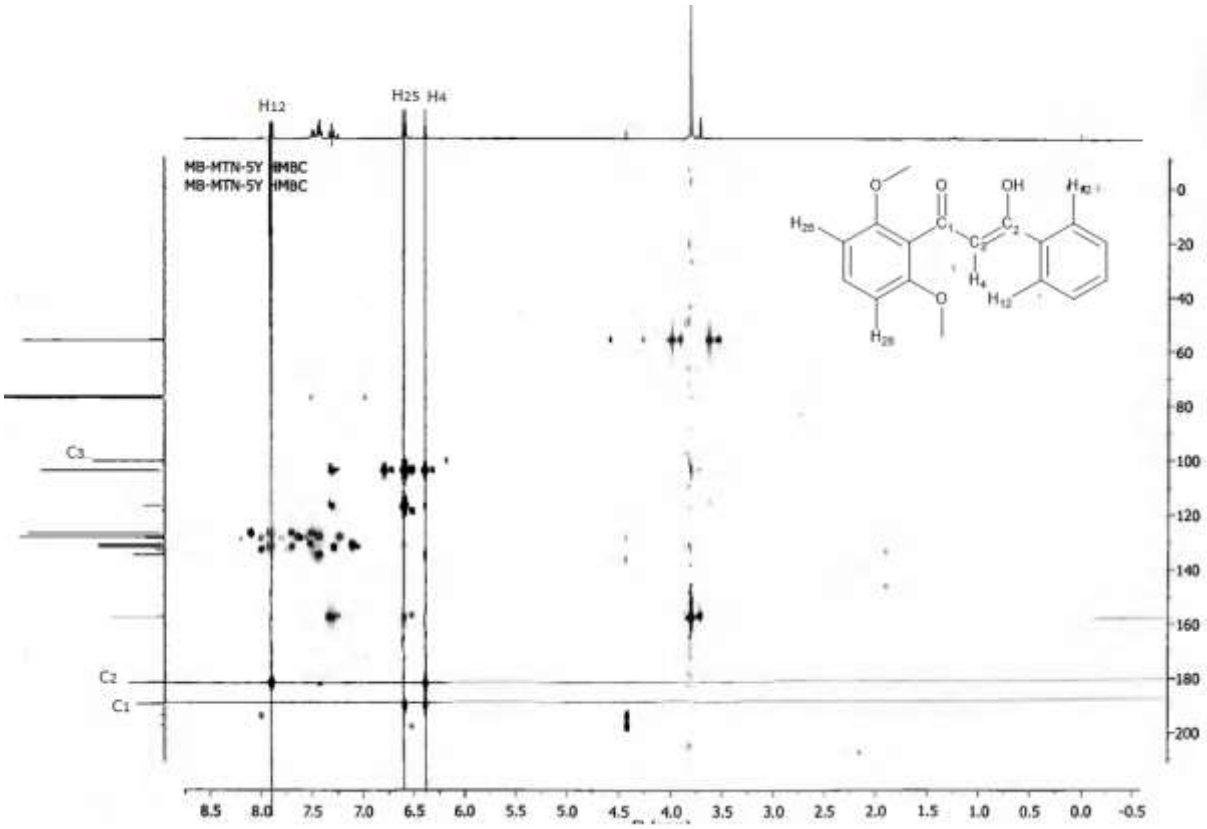


a.



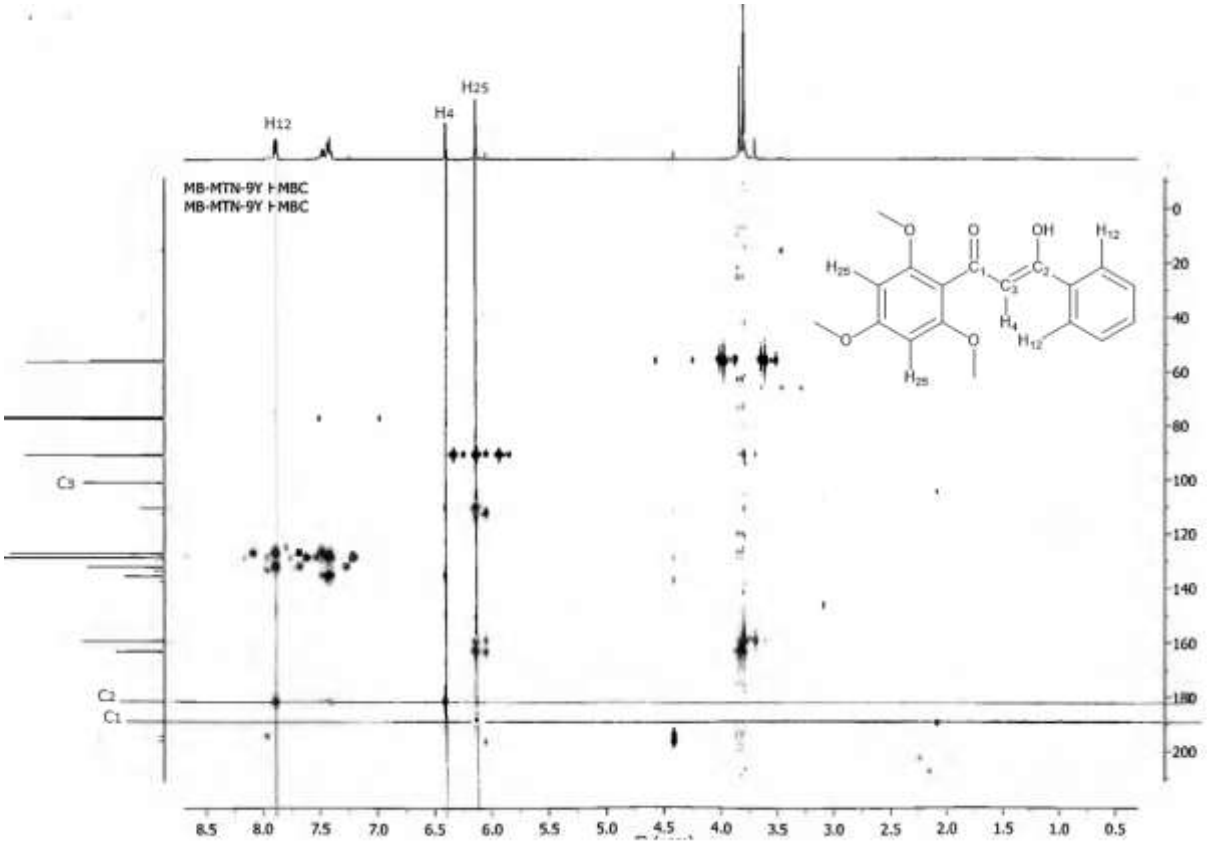
b.

Fig. S43. a. Dihedral angle scanning of the enol form **7a** (most and least stable conformers)**; b.** Dihedral angle scanning of the enol form **7b** (most and least stable conformers).

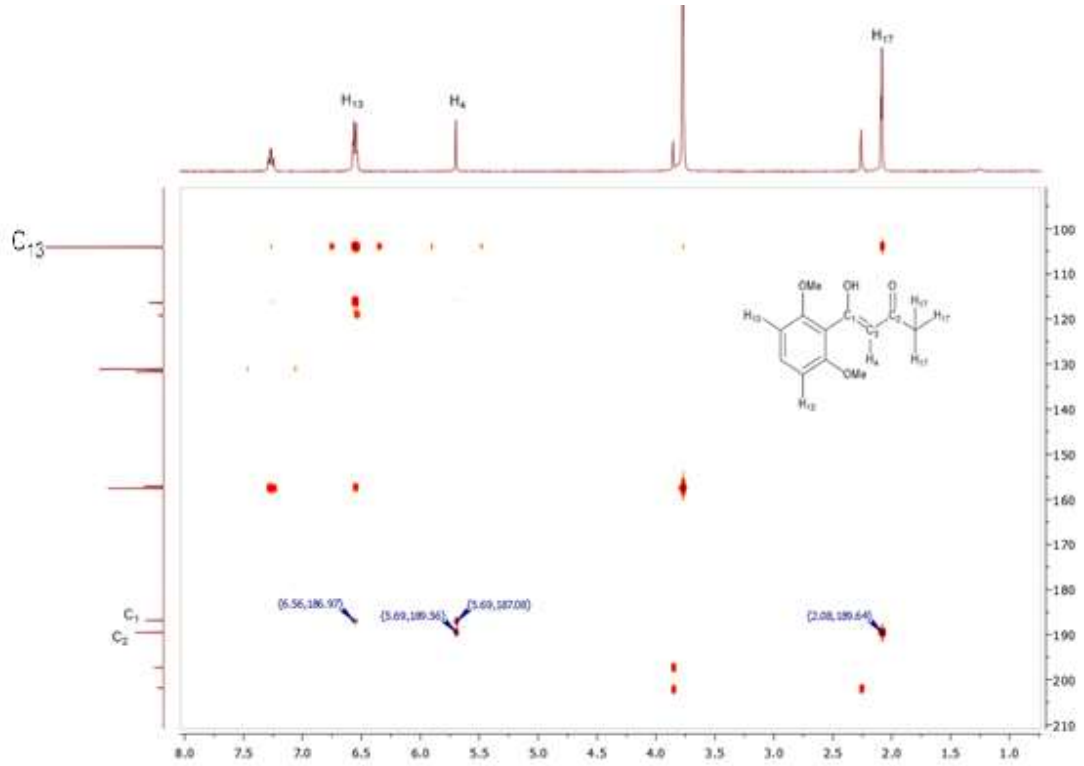


299

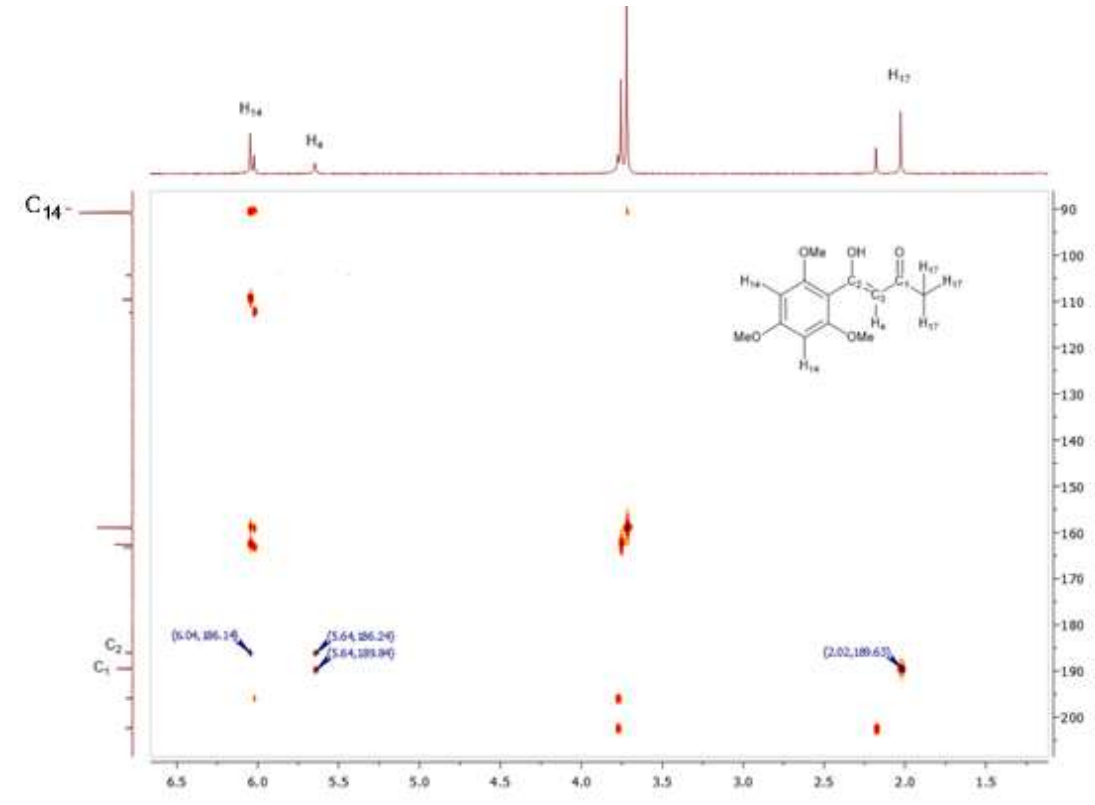
300 **Fig. S44.** HMBC spectrum of the compound **1.**



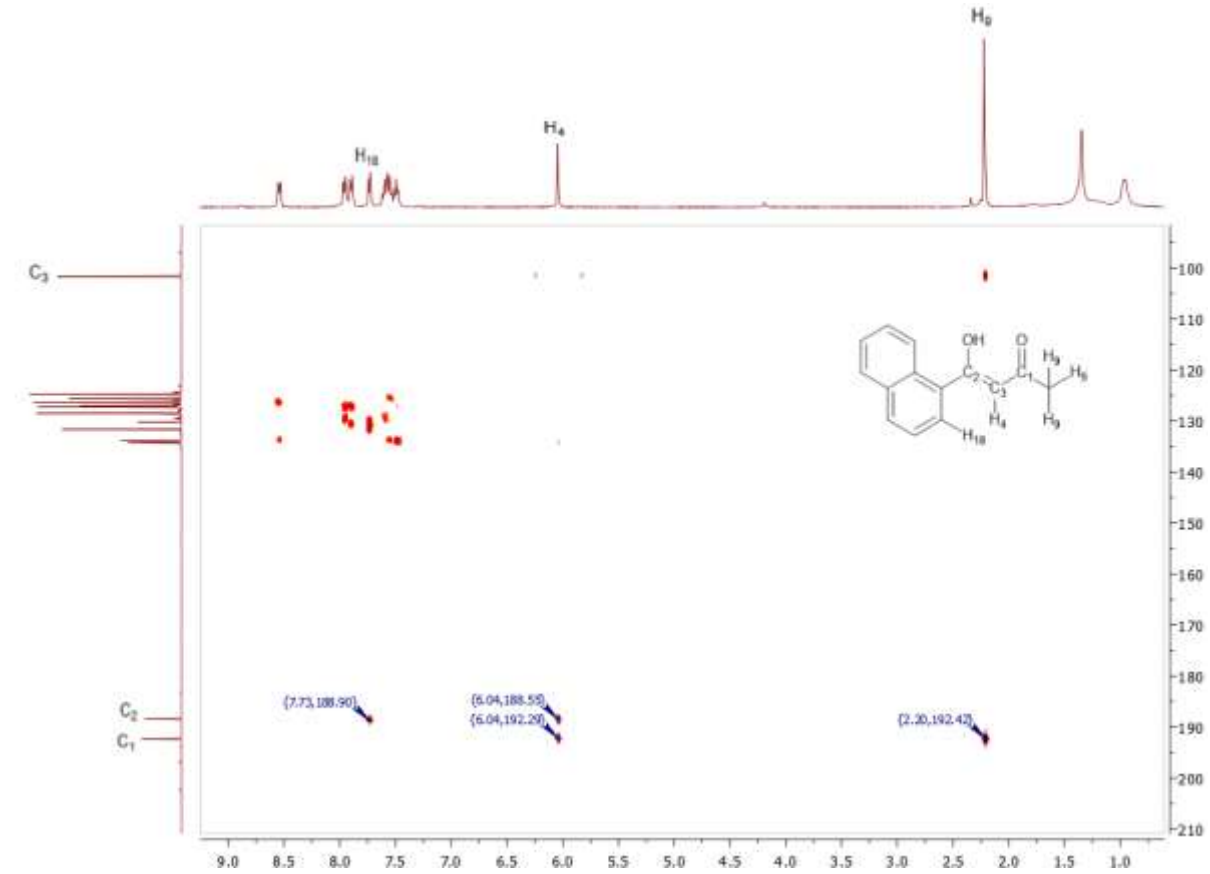
301 **Fig. S45.** HMBC spectrum of the compound **2.**



302 **Fig. S46.** HMBC spectrum of the compound **3.**

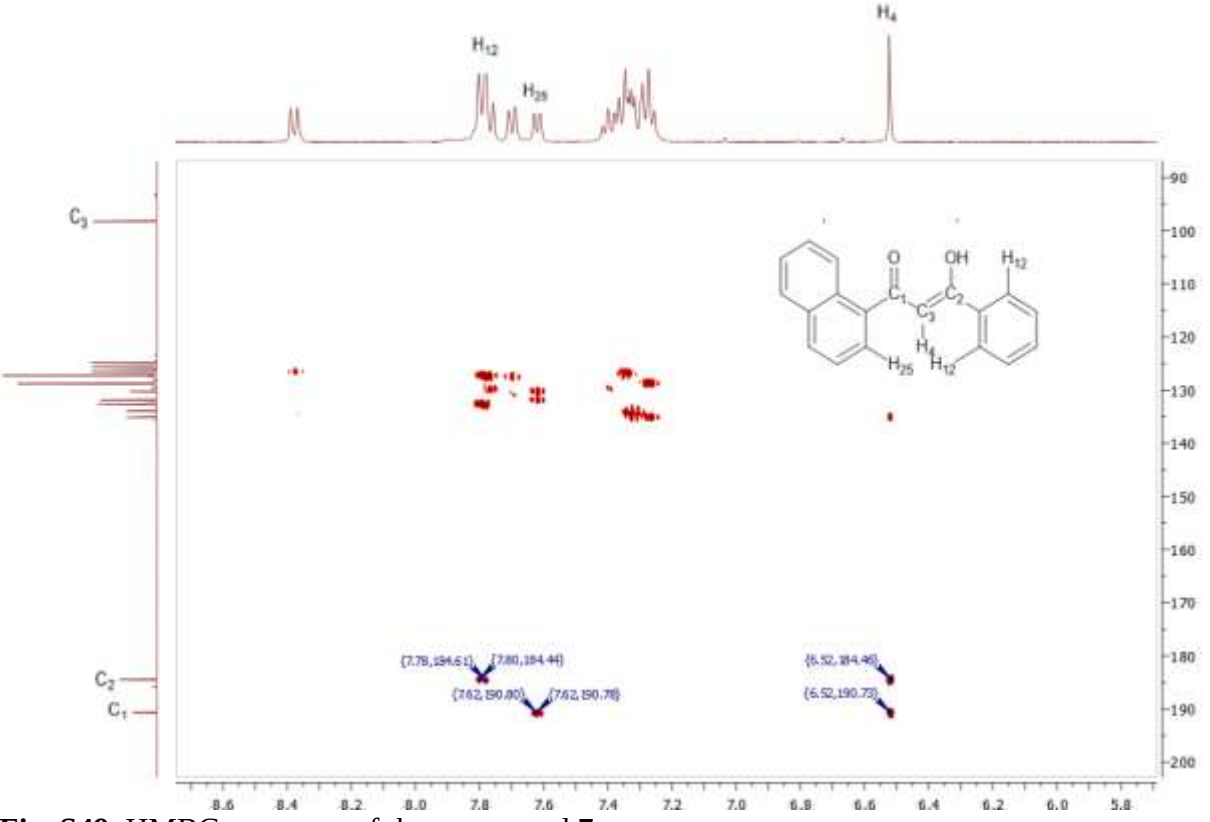


303 **Fig. S47.** HMBC spectrum of the compound **4.**



304

305 **Fig. S48.** HMBC spectrum of the compound **6.**



306 **Fig. S49.** HMBC spectrum of the compound **7.**