

Supporting Information

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Synthesis of *Ortho*-carboxamidostilbene Analogues and their Antidiabetic Activity Through *in vitro* and *in silico* Approaches

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General Procedure for the synthesis of methoxy styrenes

A stirred solution of methyl triphenyl phosphonium bromide (1.5 equiv) in dry THF (60 mL) under an argon gas atmosphere at -75 °C, *ter*-buOK (1.5 equiv), and 2,4-dimethoxybenzaldehyde (1 equiv) were added. The dry ice (ice bath) was removed after 40 min and the resulting mixture was stirred at room temperature for 24 hours and quenched with NH₄Cl (10 mL sat. eq.). The mixture was extracted with

ethyl acetate (3 x 20 mL). The organic layers were combined and dried by addition of anhydrous Na₂SO₄, filtered and evaporated under reduced pressure to give the crude product. Chromatography on silica gel eluted with 100 % hexane gave the desired product.

3,4,5-trimethoxystyrene (2a): Colourless oil, Yield: 98%; $R_f \approx 0.63$ [UV-active, Hexane/EtOAc (Purple spot)]. IR ν_{\max} : 2940 (C-H), 2835, 1730 (C-H bend), 1585 (C=C), 1404 (C-H bend), 1325, 1229 (C-O str), 1119, 995 (C=C), 835. ¹H NMR (500 MHz, CDCl₃) δ ppm: 6.62 (s, H-2, H-6, 2H), 6.59 (t, $J = 10.8$ Hz, H-7, 1H), 5.64 (d, $J = 17.5$ Hz, H-8b, 1H), 5.18 (d, $J = 10.8$ Hz, H-8a 1H), 3.84 (s, H-10, 6H), 3.82 (s, H-10, 3H). ¹³C NMR (125 MHz, CDCl₃) δ ppm: 153.2 (C-3, C-5), 137.9 (C-4), 136.7 (C-7), 133.3 (C-1), 113.2 (C-8), 103.2 (C-2, C-6), 60.8 (C-10), 56.0 (C-9).

2,4-dimethoxystyrene (2b): Colorless oil. Yield: 89%; $R_f \approx 0.80$ [UV-active, Hexane/EtOAc (Purple spot)]. IR ν_{\max} : 2950 (C-H), 2835, 1735 (C-H aromatic), 1600 (C=C str), 1499, 1455, 1270, 1200, 1025, 894, 820. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.24 (d, $J = 8.4$ Hz, H-6, 1H), 6.84 (m, H-7, 1H), 6.32 (dd, $J = 8.4, 2.5$ Hz, H-5, 1H), 6.28 (s, H-3, 1H), 5.51 (dd, $J = 7.9, 1.7$ Hz, H-8b, 1H), 5.02 (dd, $J = 11.1, 1.6$ Hz, H-8a, 1H), 3.64 (s, H-9, 3H), 3.63 (s, H-10, 3H). ¹³C NMR (125 MHz, CDCl₃) δ ppm: 160.7 (C-4), 157.9 (C-2), 131.3 (C-7), 127.3 (C-6), 119.8 (C-8), 112.2 (C-1), 104.7 (C-5), 98.3 (C-3), 55.4 (C-9), 55.3 (C-10).

2,5-dimethoxystyrene (2c): Colourless oil, Yield: 98%; $R_f \approx 0.9$ [UV-active, Hexane/EtOAc (Purple spot)]. IR ν_{\max} : 2945 (C-H), 2830, 1580 (C=C), 1494, 1215, 1030, 905, 800, 704. ¹H NMR (500 MHz, CDCl₃) δ ppm: 7.06 (d, $J = 8.5$ Hz, H-7, 1H), 7.03 (d, $J = 11.1$ Hz, H-3, 1H), 6.82 (s, H-6, 1H), 6.78 (d, $J = 8.5$ Hz, H-4, 1H), 5.75 (dd, $J = 17.7, 1.4$ Hz, H-8b, 1H), 5.29 (dd, $J = 11.1, 1.5$ Hz, H-8a, 1H), 3.80 (s, H-10, 3H), 3.79 (s, H-9, 3H). ¹³C NMR (125 MHz, CDCl₃): δ ppm: 153.7 (C-5), 151.2 (C-2), 131.5 (C-7), 127.6 (C-1), 114.6 (C-3), 113.8 (C-8), 112.3 (C-4), 111.9 (C-6), 56.2 (C-10), 55.7 (C-9).

General procedure for the synthesis of *N*-(2-iodophenyl)acylamides

To a stirred, cooled (0-5 °C) solution of 2-iodoaniline (2.0 equiv) in 40 mL THF and Et₃N (3.0 equiv) was added acyl chloride (3.0 equiv) in 5 mL THF dropwise and the ice bath was removed. The resulting mixture was stirred vigorously for 6 h at room temperature. The solid Et₃N.HCl was filtered and the resulting filtrate was washed with THF (3 x 5 mL). The organic layers were combined and THF was removed and concentrated under reduced pressure to give the corresponding amide as a white solid.

***N*-(2-iodophenyl)acetamide (4a):** White solid. Yield: 87%; m.p. 103–105 °C; $R_f \approx 0.62$ [UV-active, Hexane/EtOAc (Purple spot)]. IR ν_{\max} : 3270 (N-H), 1654 (C=O), 1570 (C=C), 1425, 1279, 1004, 745 (C-N), 660 (C-I). ¹H NMR (500 MHz, Acetone-*d*) δ ppm: 8.39 (s, N-H, 1H), 7.86 (d, $J = 8.0$ Hz, H-6, 1H), 7.84 (d, $J = 8.0$ Hz, H-3, 1H), 7.37 (t, $J = 7.8$ Hz, H-5, 1H), 6.93 (t, $J = 7.8$ Hz, H-4, 1H), 2.16 (s, H-8, 3H). ¹³C NMR (125 MHz, CDCl₃) δ ppm: 168.3 (C-7), 138.8 (C-1), 138.2 (C-3), 129.2 (C-5), 126.0 (C-4), 122.2 (C-6), 90.1 (C-2), 24.8 (C-8).

***N*-(2-iodophenyl)butyramide (4b):** White solid. Yield: 74%; m.p. 81–83 °C; $R_f \approx 0.56$ [UV-active, Hexane/EtOAc (Purple spot)]. IR ν_{\max} : 3264 (N-H), 2955 (C-H), 1650 (C=O), 1580 (C=C), 1520 (C=C aromatic), 1430, 1279, 1190, 1009 (C-O), 750 (C-N). ¹H NMR (500 MHz, CDCl₃) δ ppm: 8.24 (d, $J = 8.0$ Hz, H-6, 1H), 7.77 (dd, $J = 8.0, 1.0$ Hz, H-3, 1H), 7.47 (br s, N-H, 1H), 7.33 (dd, $J = 8.0, 1.0$ Hz, H-5, 1H), 6.83 (t, $J = 8.0$ Hz, H-4, 1H), 2.41 (t, $J = 7.5$ Hz, H-8, 2H), 1.80 (m, $J = 7.5$ Hz, H-9, 2H), 1.04 (t, $J = 7.5$ Hz, H-10, 3H). ¹³C NMR (125 MHz, CDCl₃) δ ppm: 171.2 (C-7), 138.7 (C-2), 138.2 (C-6), 129.3 (C-4), 125.8 (C-5), 122.0 (C-3), 89.2 (C-1) 39.9 (C-8), 19.1 (C-9), 13.7 (C-10).

***N*-(2-iodophenyl)isobutyramide (4c):** White solid. Yield: 76%; m.p. 112–114 °C; $R_f \approx 0.86$ [UV-active, Hexane/EtOAc (Purple spot)]. IR ν_{\max} : 3254 (N-H), 2960 (C-H), 1654 (C=O), 1525 (C=C), 1425, 1279, 1200, 1009, 745 (C-N), 650 (C-I). ¹H NMR (500 MHz, CDCl₃) δ ppm: 8.25 (d, $J = 8.0$ Hz, H-6, 1H), 7.93 (d, $J = 8.0$ Hz, H-3, 1H), 7.52 (br s, N-H, 1H), 7.33 (t, $J = 8.5$ Hz, H-5, 1H), 6.82 (t, $J = 8.0$ Hz, H-4, 1H), 2.64–2.56 (m, H-8, 1H), 1.31 (d, $J = 6.5$

Hz, H-9, 6H). ^{13}C NMR (125 MHz, CDCl_3) δ ppm: 175.1 (C-7), 138.7 (C-1), 138.1 (C-3), 129.2 (C-5), 125.8 (C-4), 121.9 (C-6), 90.0 (C-2), 37.0 (C-8), 19.6 (C-9).

N-(2-iodophenyl)furan-2-carboxamide (**4d**): White solid. Yield: 67%; m.p. 79 – 81 °C; $R_f \approx 0.8$ [UV-active, Hexane/EtOAc (Purple spot)]. IR ν_{max} : 3349 (N-H), 3110, 1664 (C=O), 1585 (C=C), 1426, 1284, 1160 (C-N), 1004 (C-O), 740 (C-N). ^1H NMR (500 MHz, CDCl_3) δ ppm: 8.81 (s, N-H, 1H), 8.17 (dd, $J = 8.0, 1.5$ Hz, H-6, 1H), 7.93 (dd, $J = 8.0, 1.5$ Hz, H-3, 1H), 7.65 (s, H-4', 1H), 7.46 (td, $J = 7.1$ Hz, H-5, 1H), 7.28 (dd, $J = 3.5$ Hz, H-2, 1H), 6.98 (dd, $J = 8.0, 1.5$ Hz, H-4, 1H), 6.72 (m, H-3', 1H). ^{13}C NMR (125 MHz, CDCl_3) δ ppm: 161.5 (C-7), 156.1 (C-1'), 147.6 (C-2), 144.2 (C-4'), 138.9 (C-6), 129.4 (C-4), 126.1 (C-5), 121.7 (C-3), 115.7 (C-2'), 112. (C-3'), 89.82 (C-1).

N-(2-iodophenyl)cyclohexane carboxamide (**4e**): White solid. Yield: 87%; m.p. 134–136 °C; $R_f \approx 0.9$ [UV-active, Hexane/EtOAc (Purple spot)]. IR ν_{max} : 3264 (N-H), 2919 (C-H), 2845, 1654 (C=O), 1575 (C=C), 1515, 1430, 1274, 1174, 1015 (C-O), 740 (C-N). ^1H NMR (500 MHz, CDCl_3) δ ppm: 8.27 (br s, NH), 7.87 (d, $J = 8.0, 1.5$ Hz, H-6, 1H), 7.86 (d, $J = 8.0$ Hz, H-3, 1H), 7.37 (td, 8.5, 1.5 Hz, H-5, 1H), 6.90 (td, $J = 8.0, 1.5$ Hz, H-4, 1H), 2.50 (t, $J = 3.5$ Hz, H-1', 1H), 2.04 – 1.81 (m, H-4', 2H), 1.79 – 1.54 (m, H-2', H-6', 4H), 1.34 – 1.28 (m, H-3', H-5', 2H). ^{13}C NMR (125 MHz, CDCl_3) δ ppm: 174.3 (C-7), 138.7 (C-6), 138.2 (C-2), 129.2 (C-5), 125.7 (C-4), 121.9 (C-3), 90.1 (C-1), 46.6 (C-1'), 29.7 (C-2', C-6'), 25.7 (C-3', C-5'), 25.7 (C-4')

N-(2-Iodophenyl)benzamide (**4f**): White solid. Yield: 86%; m.p. 137–139 °C; $R_f \approx 0.9$ [UV-active, Hexane/EtOAc (Purple spot)]. IR ν_{max} : 3204 (N-H), 1640 (C=O), 1515 (C=C), 1455, 1290, 1009, 740 (C-N), 709 (C-I). ^1H NMR (500 MHz, CDCl_3) δ ppm: 8.47 (dd, $J = 8.0, 1.5$ Hz, H-6, 1H), 8.30 (br s, N-H, 1H), 7.98 (d, $J = 7.5, 1.5$ Hz, H-2', H-6', 2H), 7.83 (dd, $J = 8.0, 1.5$ Hz, H-3, 1H), 7.59 (t, $J = 7.5$ Hz, H-5, 1H), 7.53 (t, $J = 8.0$ Hz, H-3', H-5', 2H), 7.41 (t, $J = 8.0$ Hz, H-4', 1H), 6.88 (td, $J = 7.5, 1.5$ Hz, H-4, 1H). ^{13}C NMR (125 MHz, CDCl_3) δ ppm: 165.4 (C-7), 138.8 (C-1), 138.3 (C-3), 134.5 (C-1'), 132.2 (C-4'), 129.5 (C-3', C-5'), 129.0 (C-5), 127.2 (C-2', C-4'), 126.1 (C-4), 121.8 (C-6), 90.4 (C-2).

General Procedure for Heck Reactions

In a two neck round bottom flask, *N*-(2-iodophenyl) acylamide (1.0 equiv) was dissolved in 12 mL of dry DMF and stirred under nitrogen gas (N_2). The solution was heated to 120 °C and reflux for 15 minutes, palladium (II) acetate (1.0 equiv) and trimethylamine (5.0 equiv) were added into the reaction flask, and then followed by Styrene (1.2 equiv). The mixture was stirred and heated at 120 °C under nitrogen gas (N_2) until all the amides had been consumed. The reaction was stopped, allowed to cool, and quenched with aqueous ammonium chloride. The mixture was then extracted with 40 mL ethyl acetate, concentrated and the crude residue was purified by column chromatography (silica gel, hexane-ethyl acetate mixture) afforded the coupling products.

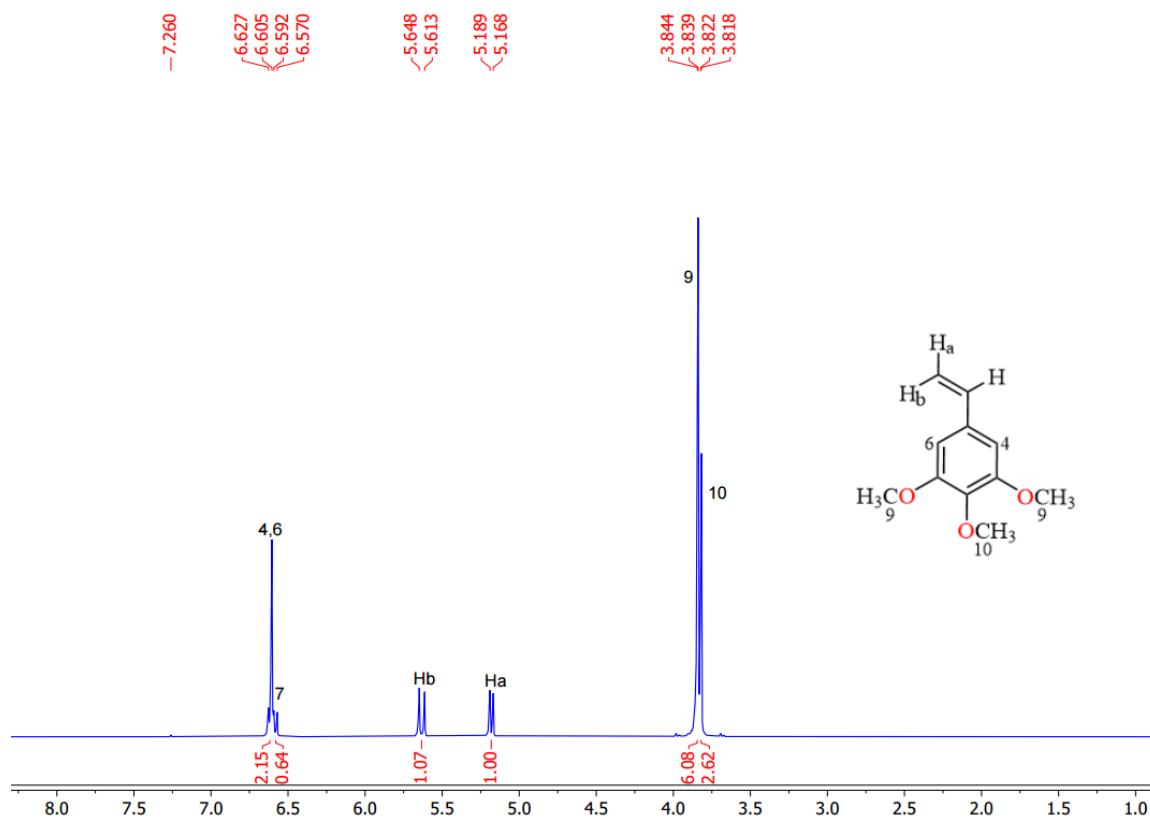


Figure S1: 1H NMR (500 MHz, $CDCl_3$) spectrum of **2a**

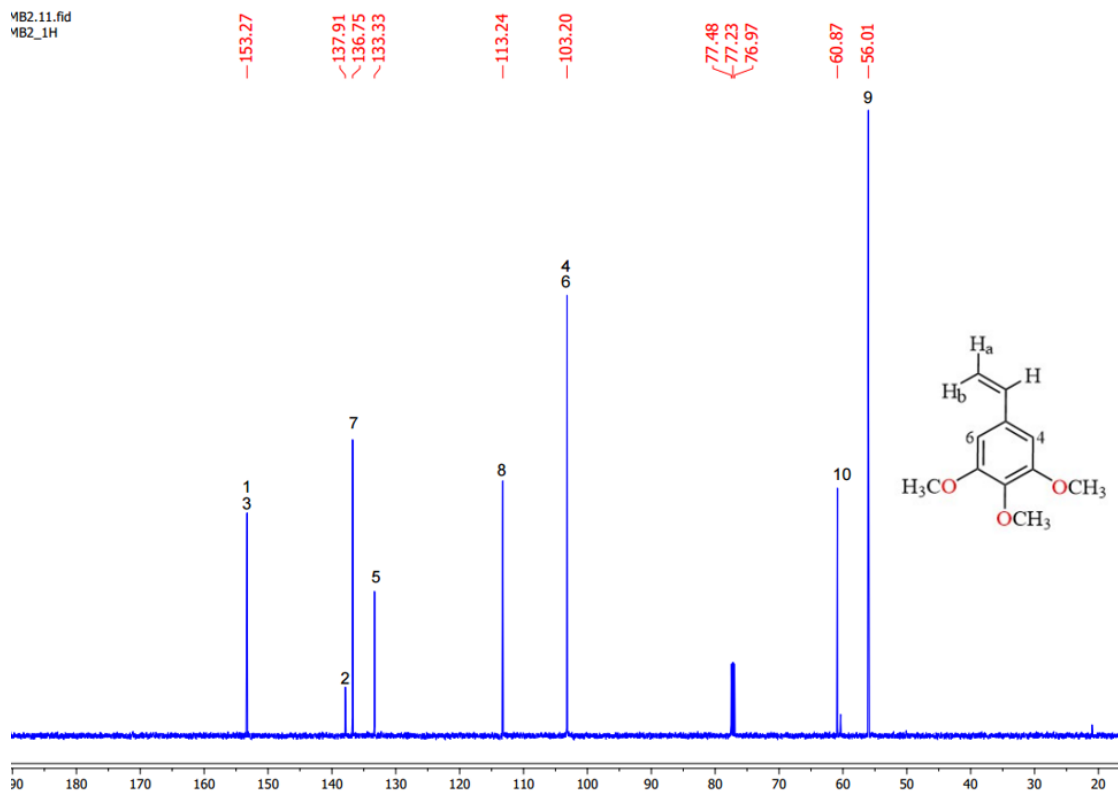


Figure S2: ^{13}C -NMR (125 MHz, $CDCl_3$) Spectrum of **2a**

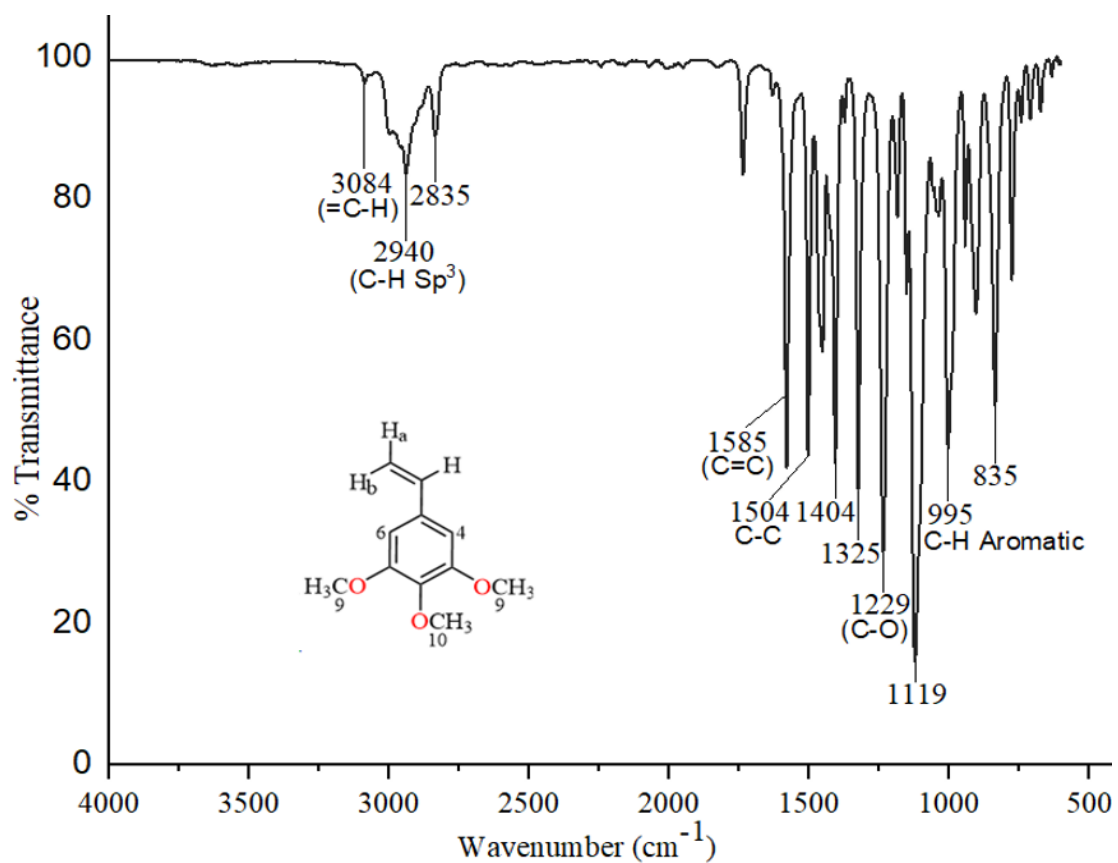


Figure S3: FT-IR Spectrum of **2a**

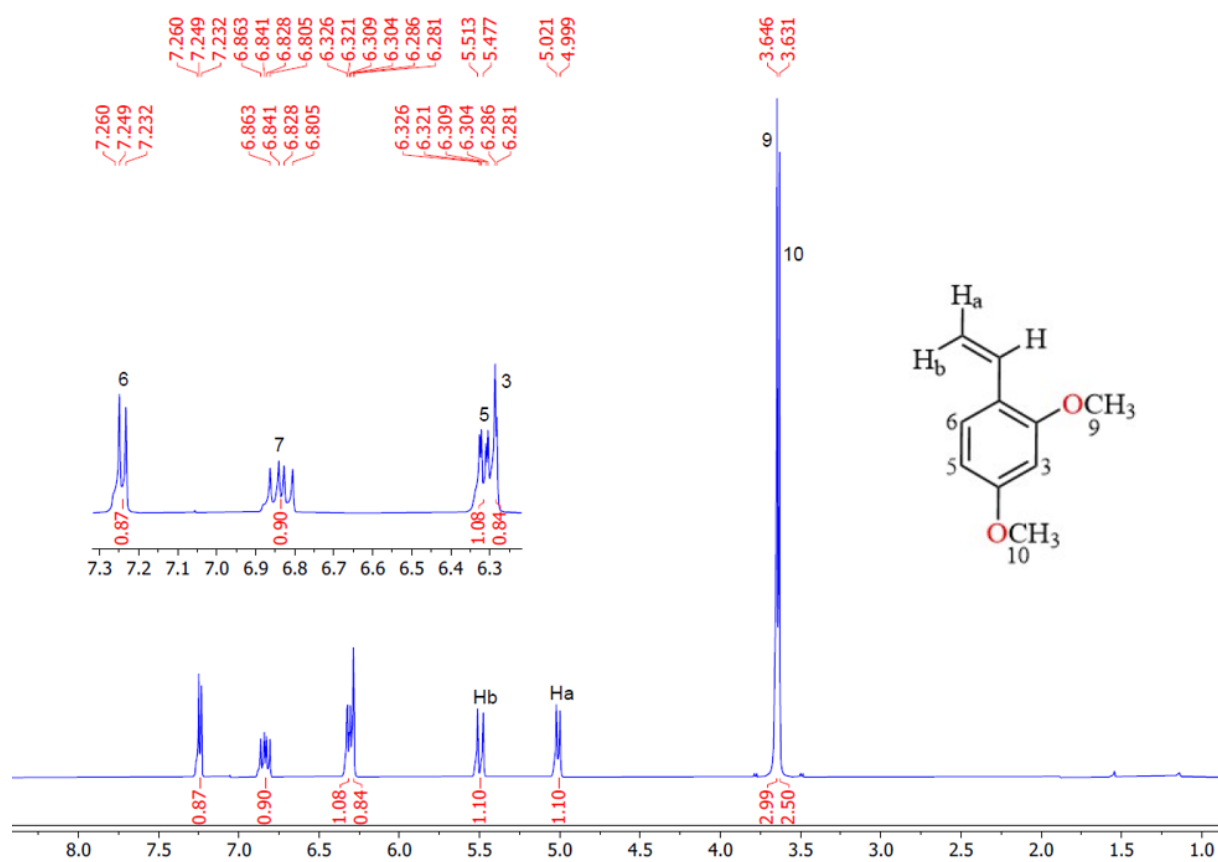
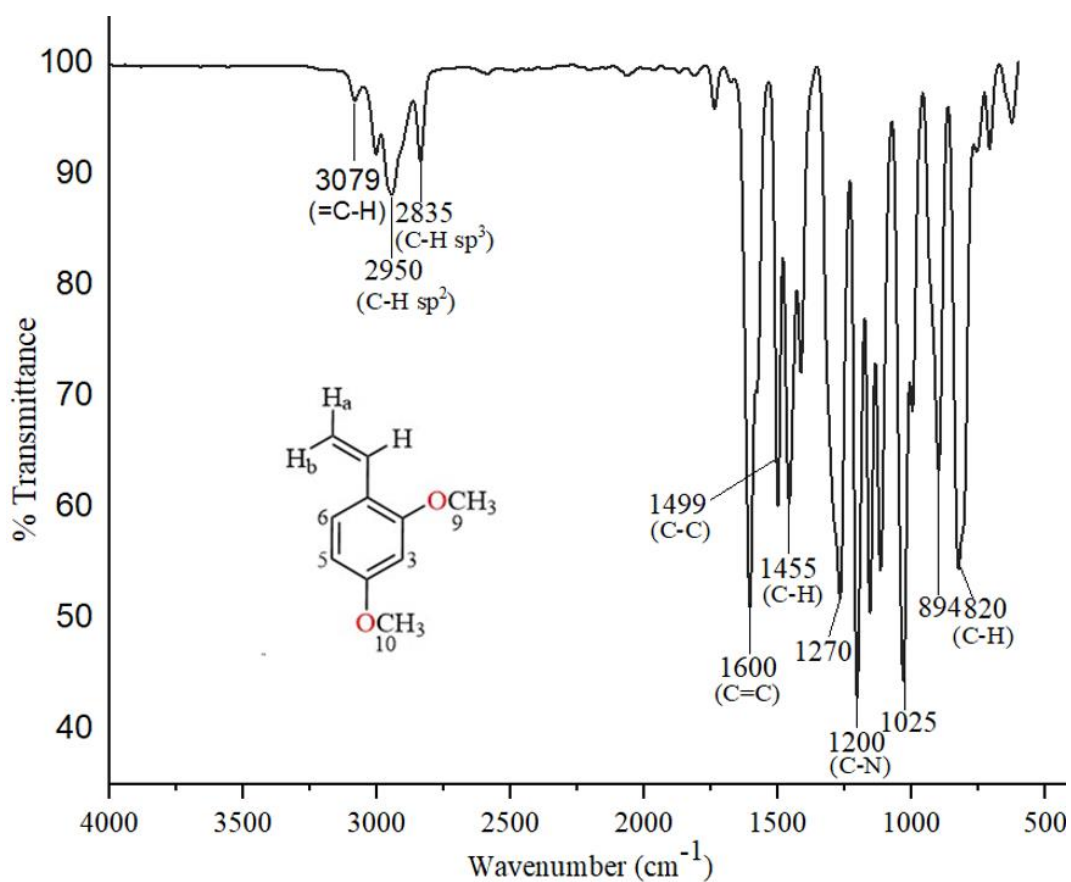
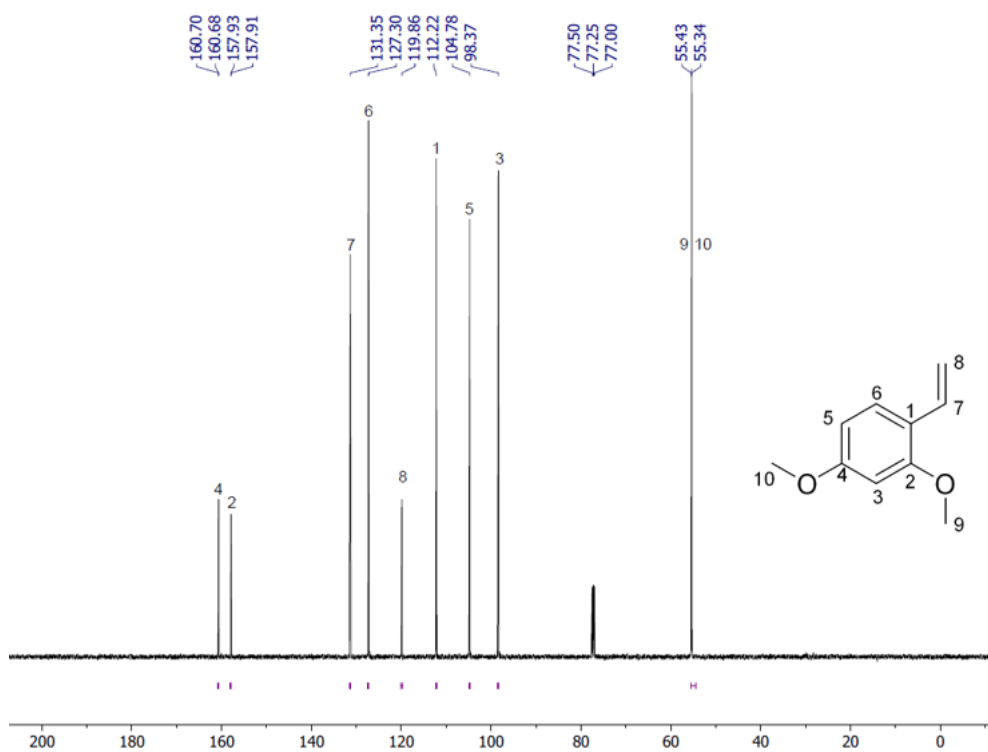


Figure S4: $^1\text{H NMR}$ (500 MHz, CDCl_3) spectrum of **2b**



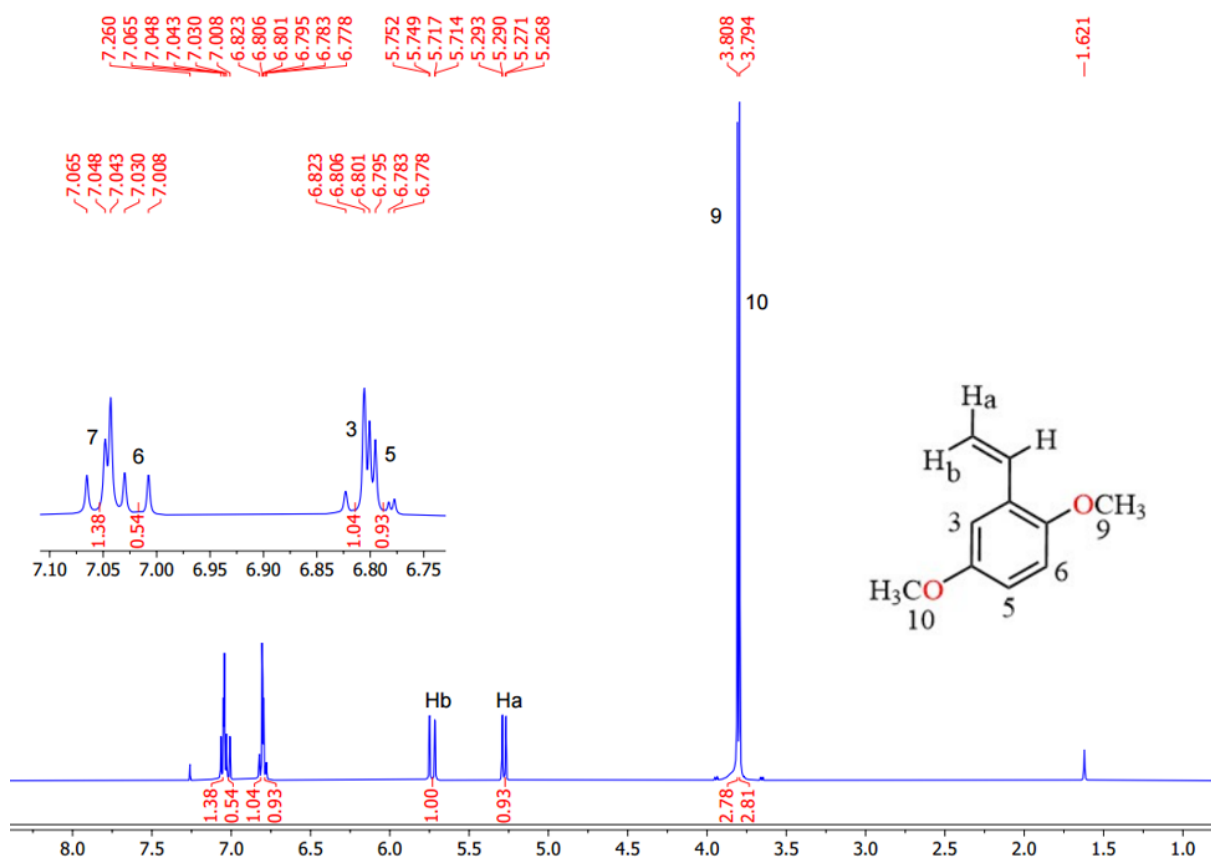


Figure S7: ¹H NMR (500 MHz, CDCl₃) spectrum of **2c**

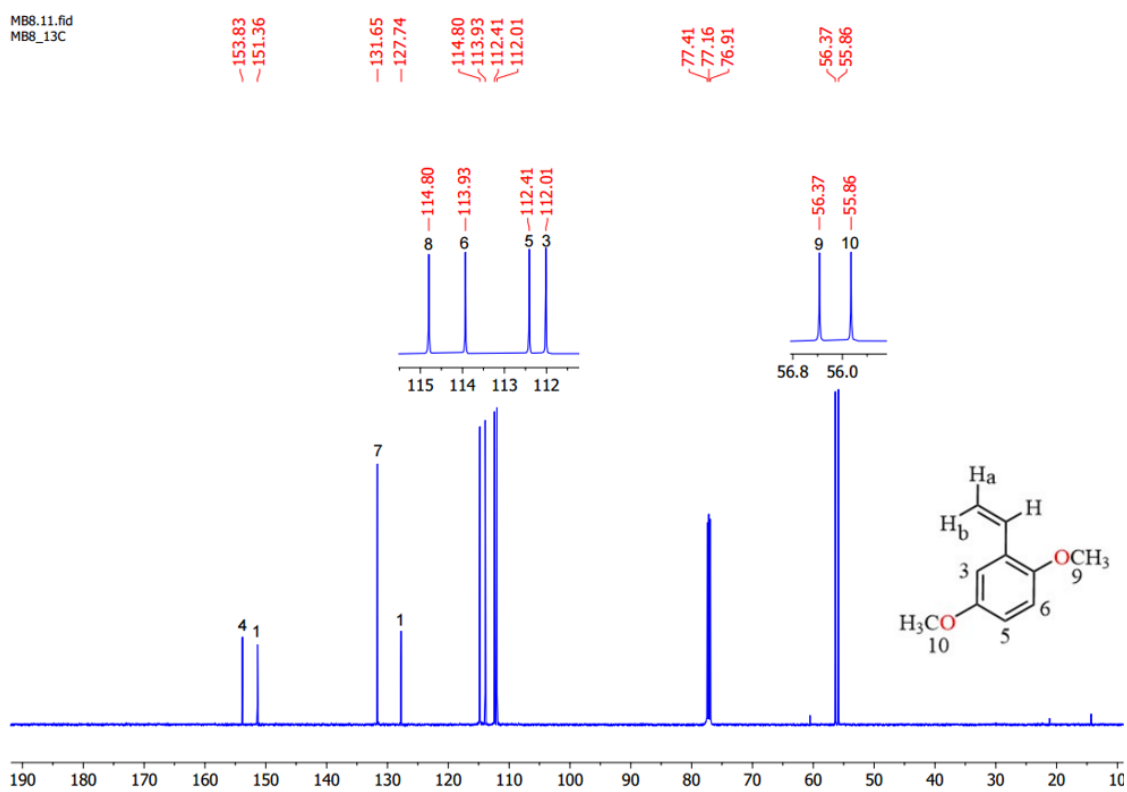


Figure S8: ¹³C-NMR (125 MHz, CDCl₃) Spectrum of **2c**

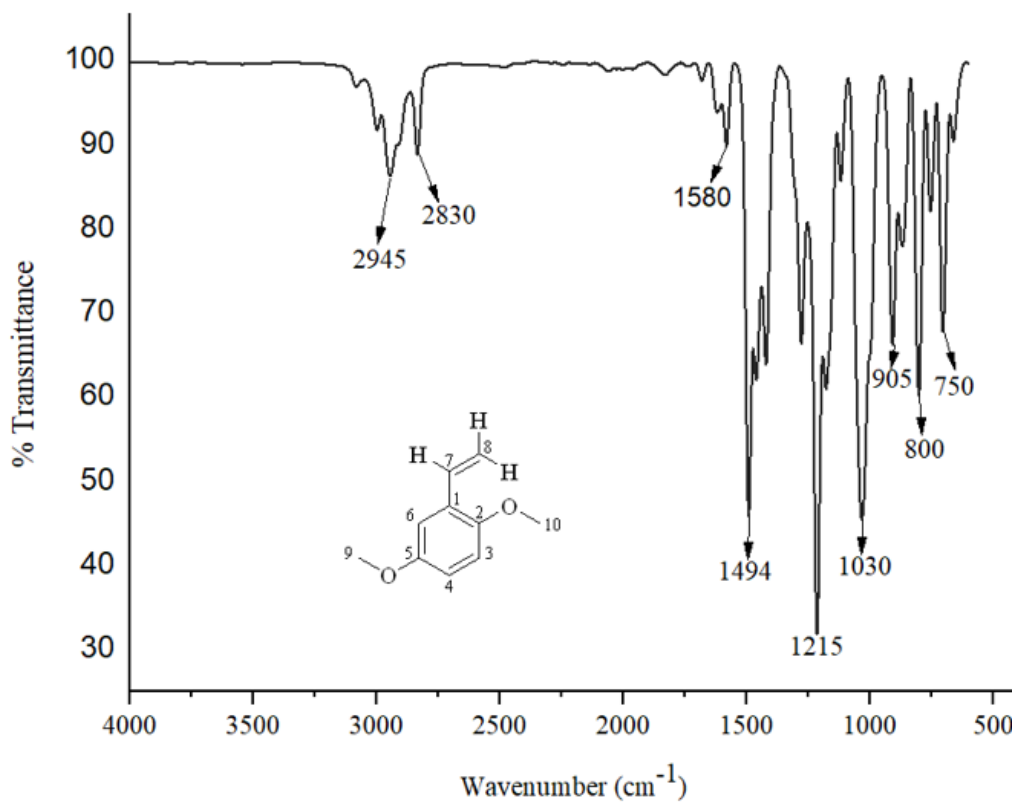


Figure S9: FT-IR Spectrum of **2c**

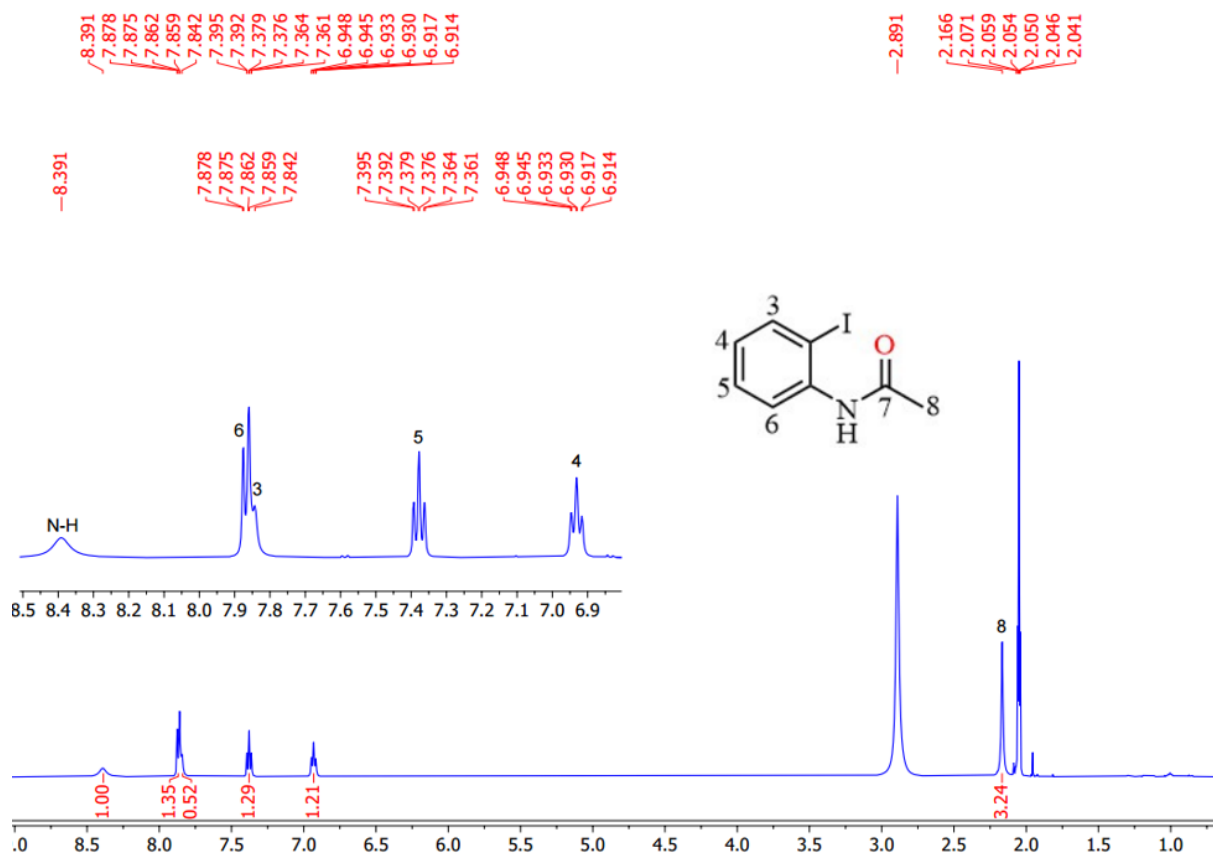


Figure S10: ¹H NMR (500 MHz, CDCl₃) spectrum of **4a**

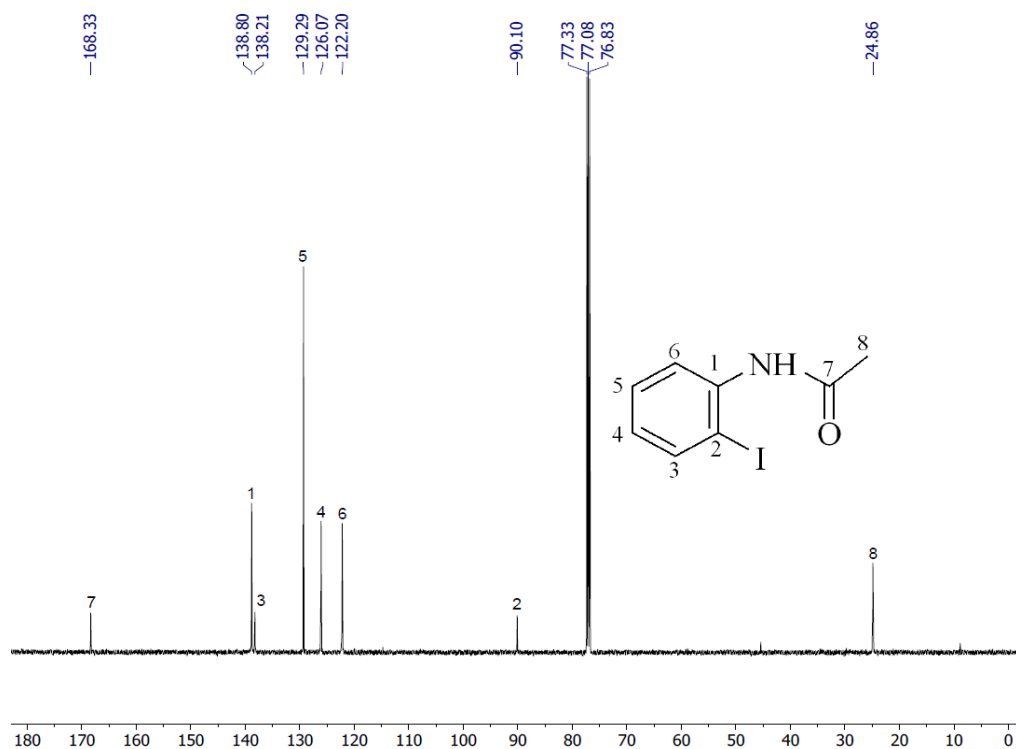


Figure S11: ^{13}C -NMR (125 MHz, CDCl_3) Spectrum of 4a

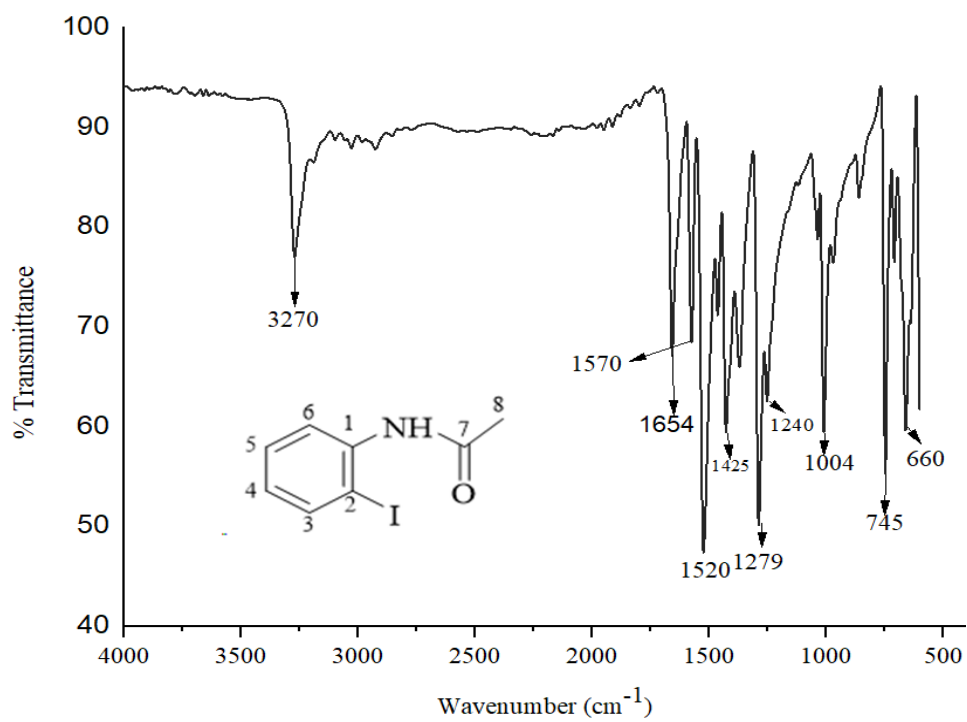


Figure S12: FT-IR Spectrum of 4a

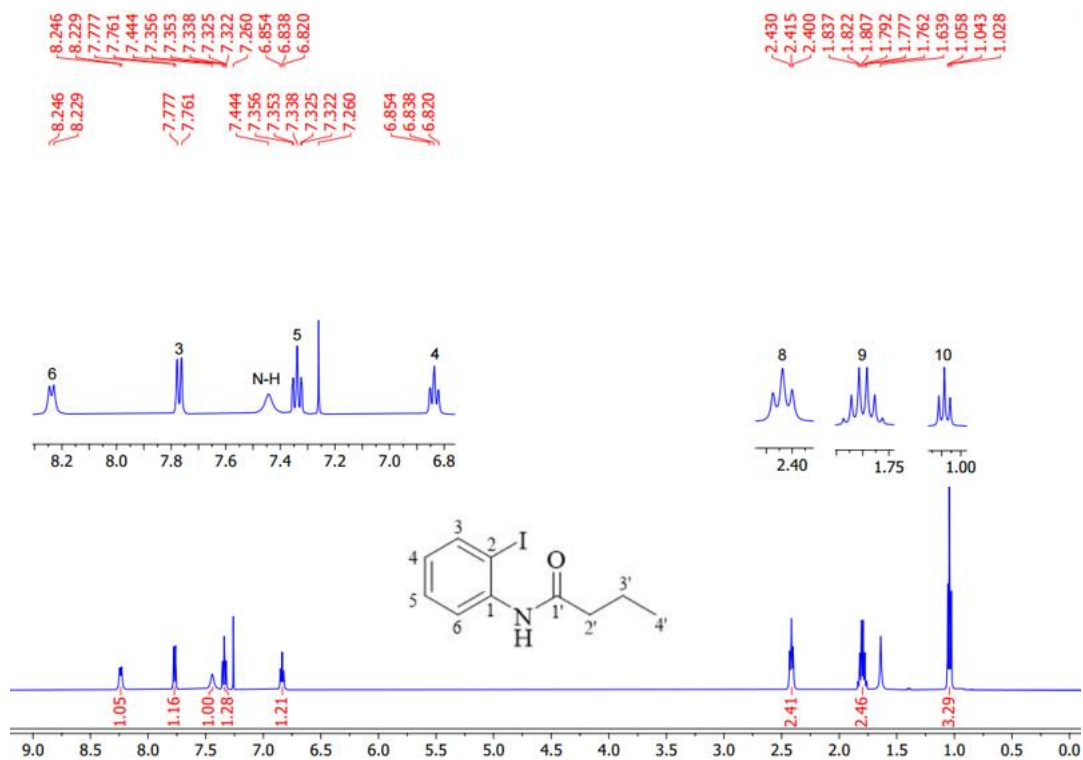


Figure S13: ¹H NMR (500 MHz, CDCl₃) spectrum of **4b**

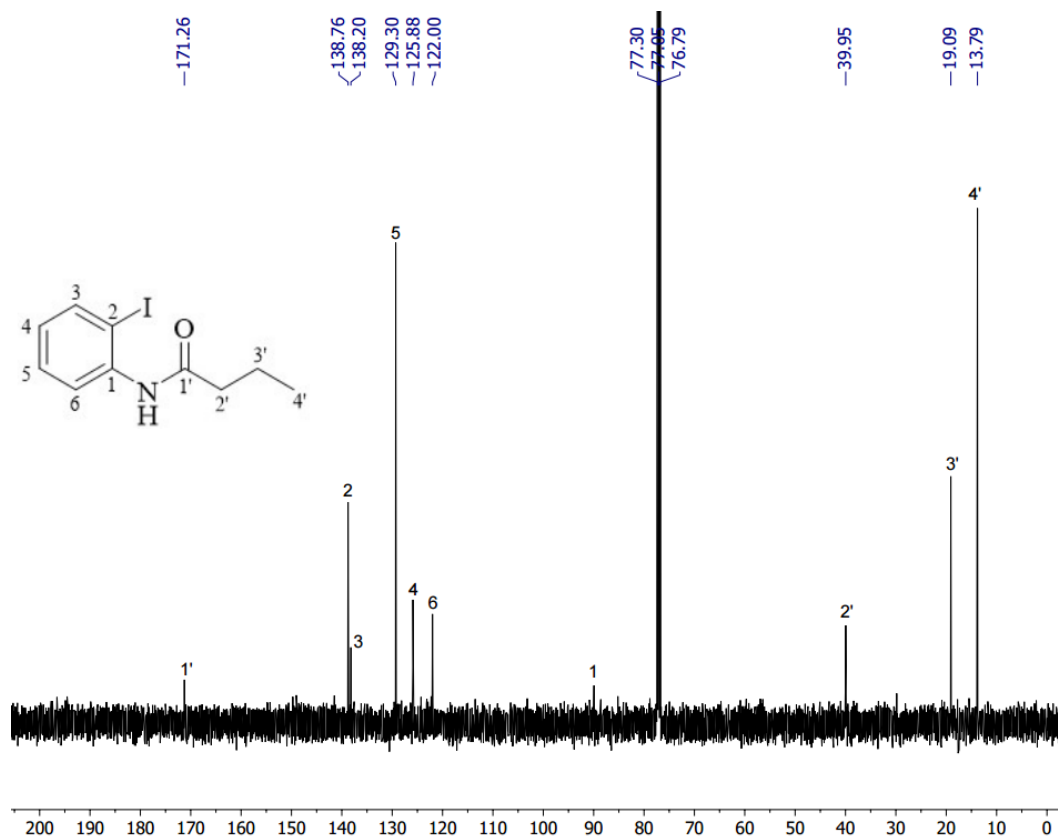


Figure S14: ¹³C-NMR (125 MHz, CDCl₃) Spectrum of **4b**

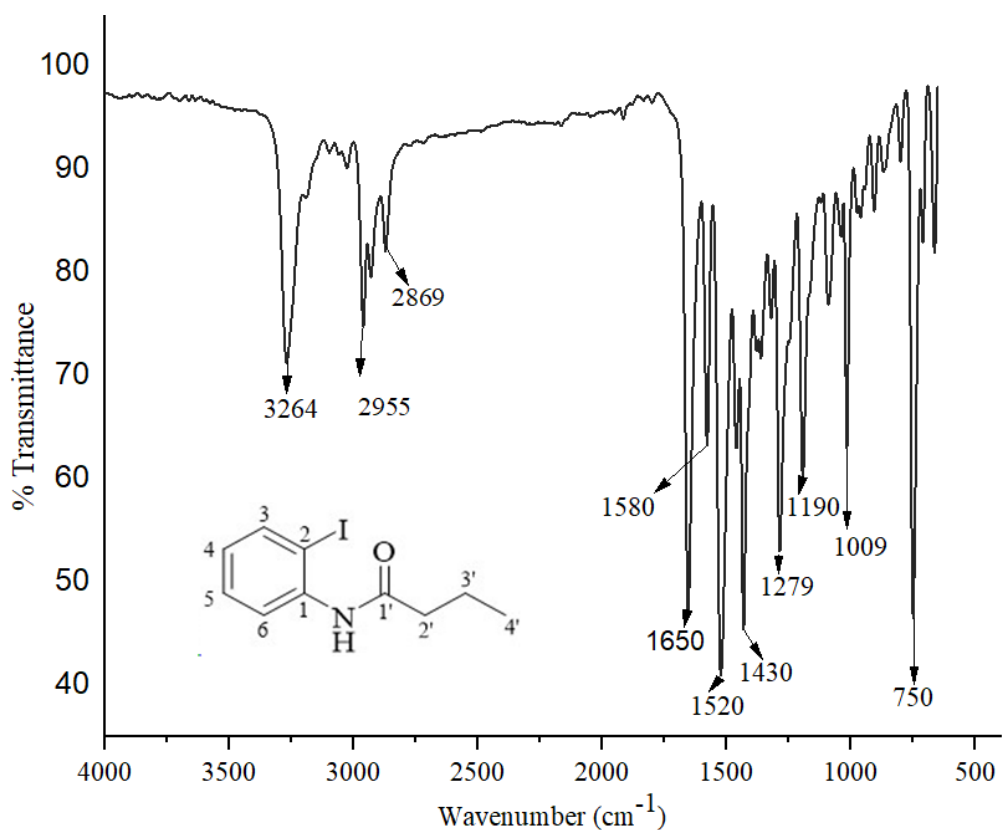


Figure S15: FT-IR Spectrum of **4b**

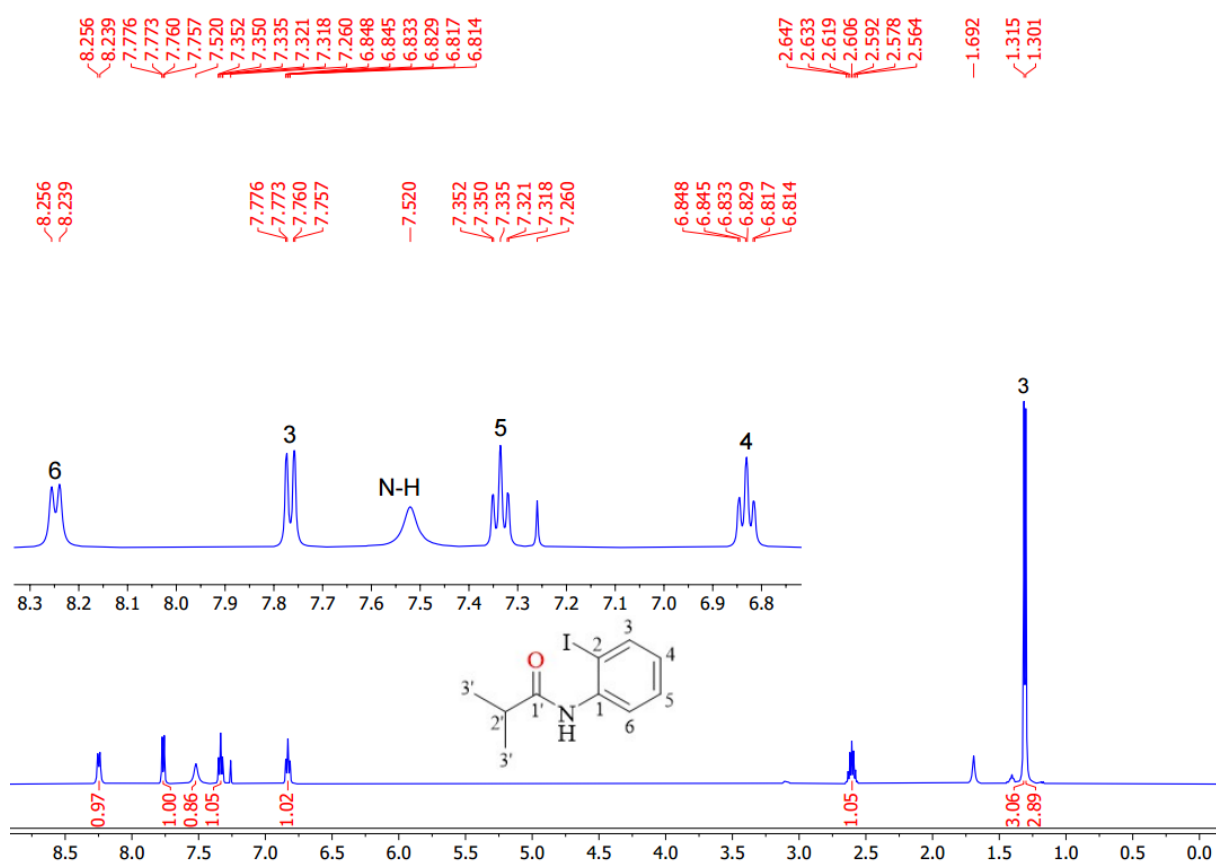


Figure S16: ¹H NMR (500 MHz, CDCl₃) spectrum of **4c**

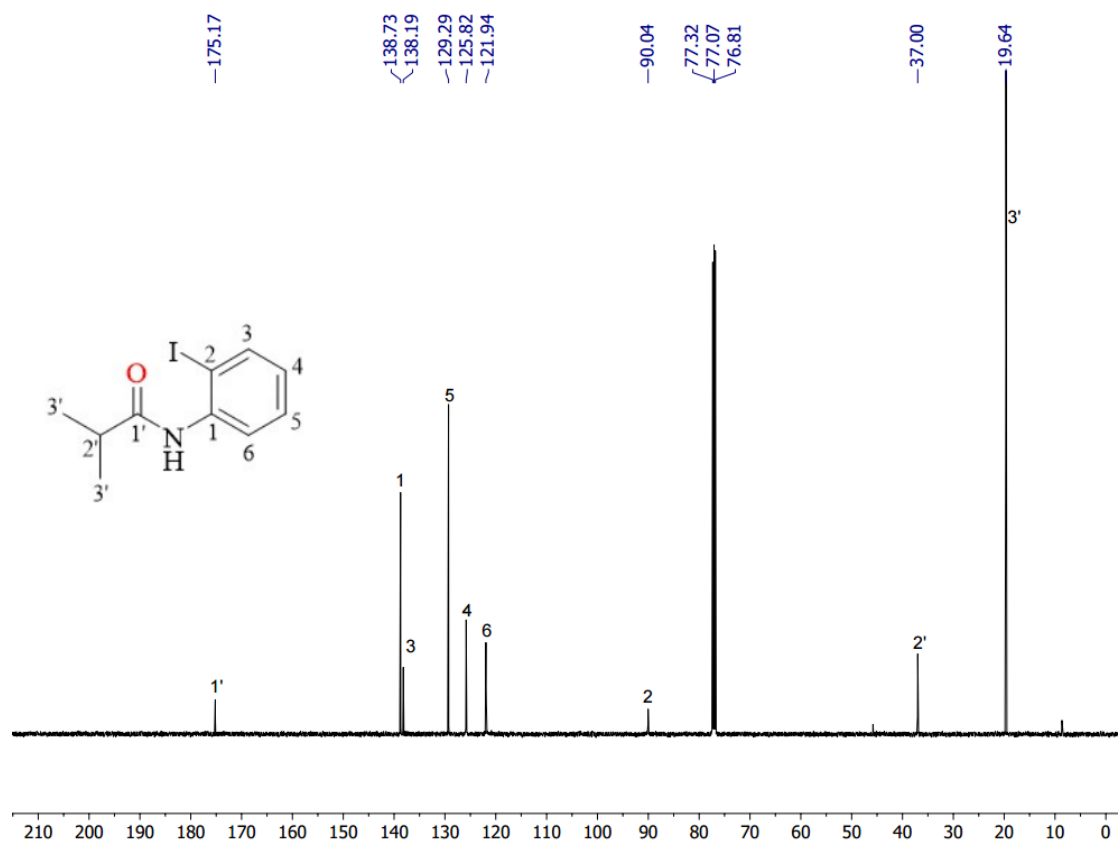


Figure S17: ^{13}C -NMR (125 MHz, CDCl_3) Spectrum of **4c**

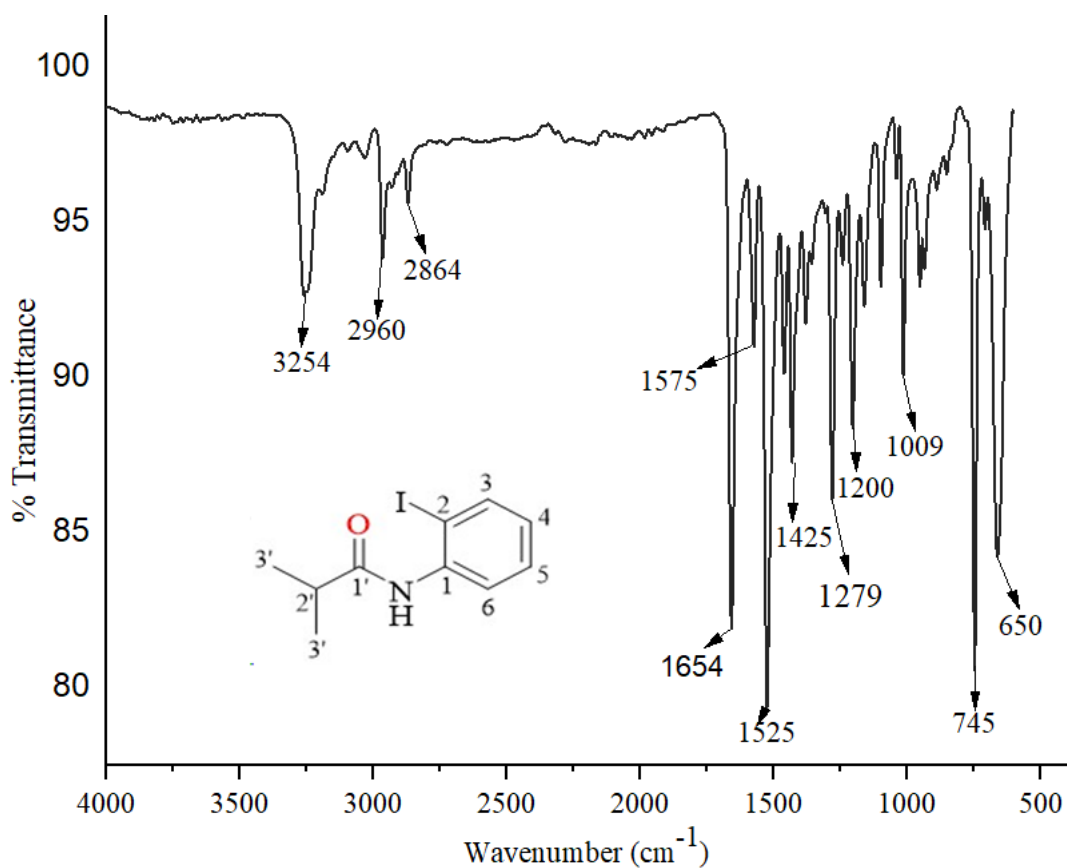


Figure S18: FT-IR Spectrum of **4c**

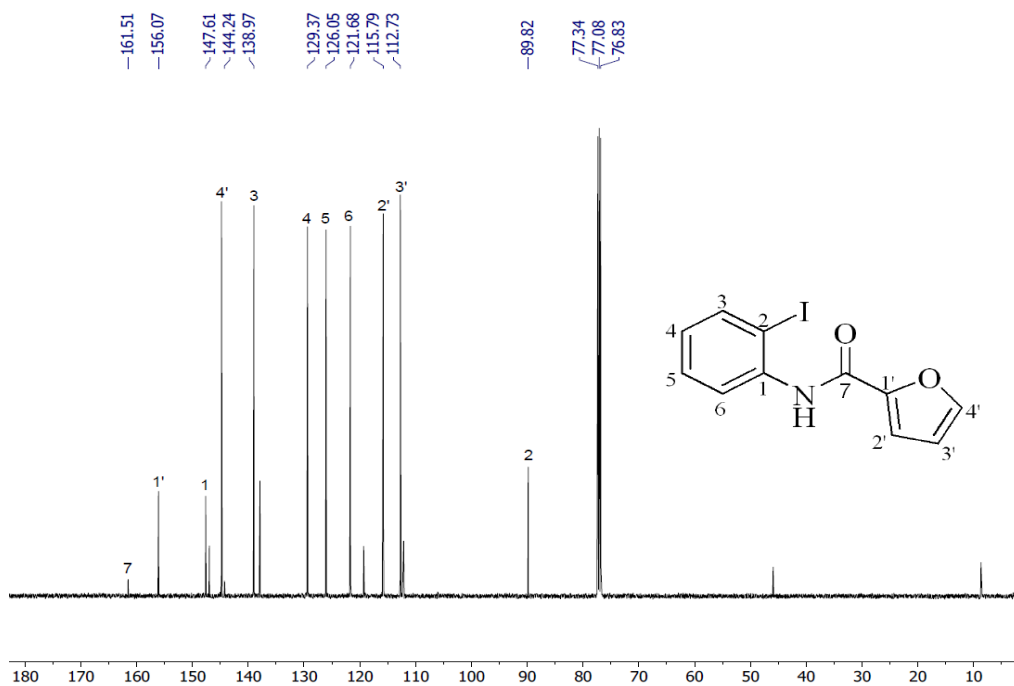
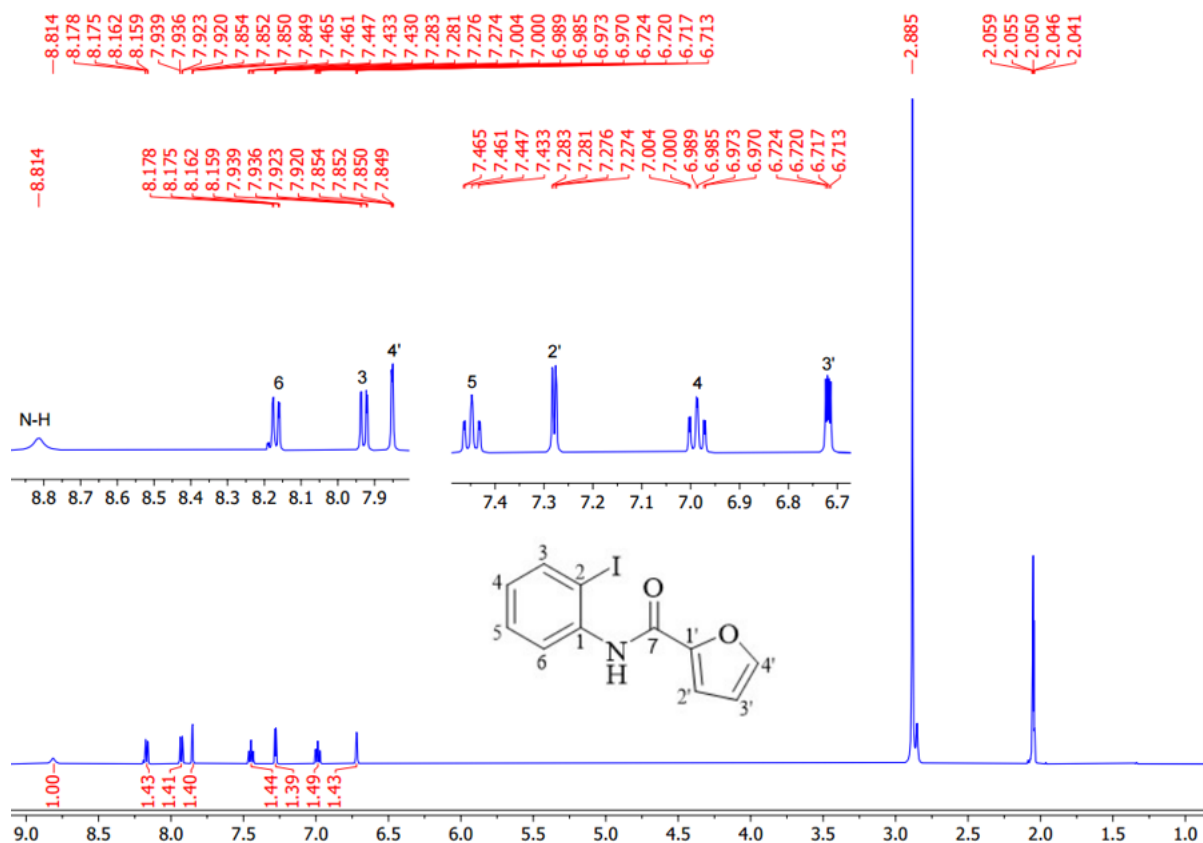


Figure S20: ^{13}C -NMR (125 MHz, CDCl_3) Spectrum of **4d**

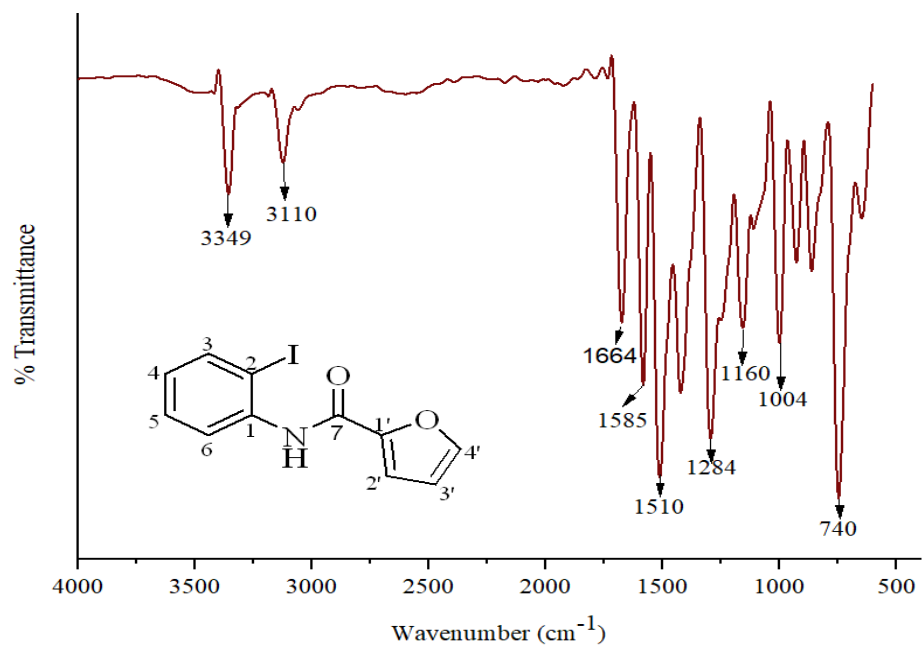


Figure S21: FT-IR Spectrum of **4d**

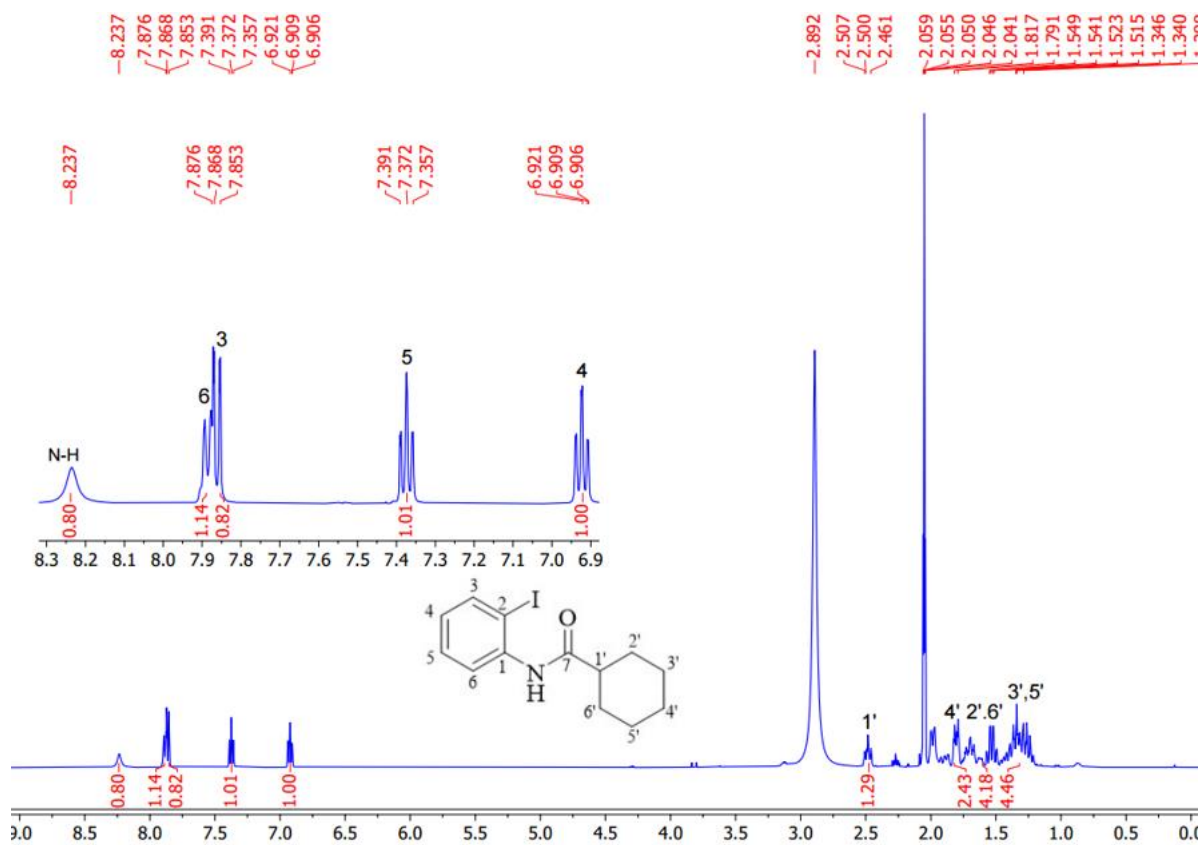


Figure S22: ^1H NMR (500 MHz, CDCl_3) spectrum of **4e**

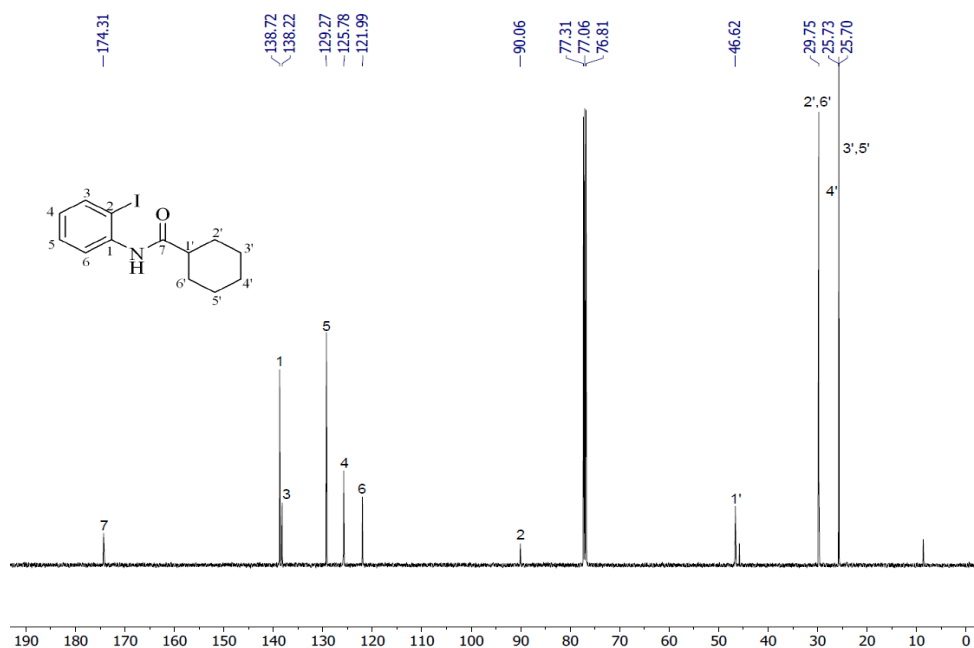


Figure S23: ^{13}C -NMR (125 MHz, CDCl_3) Spectrum of **4e**

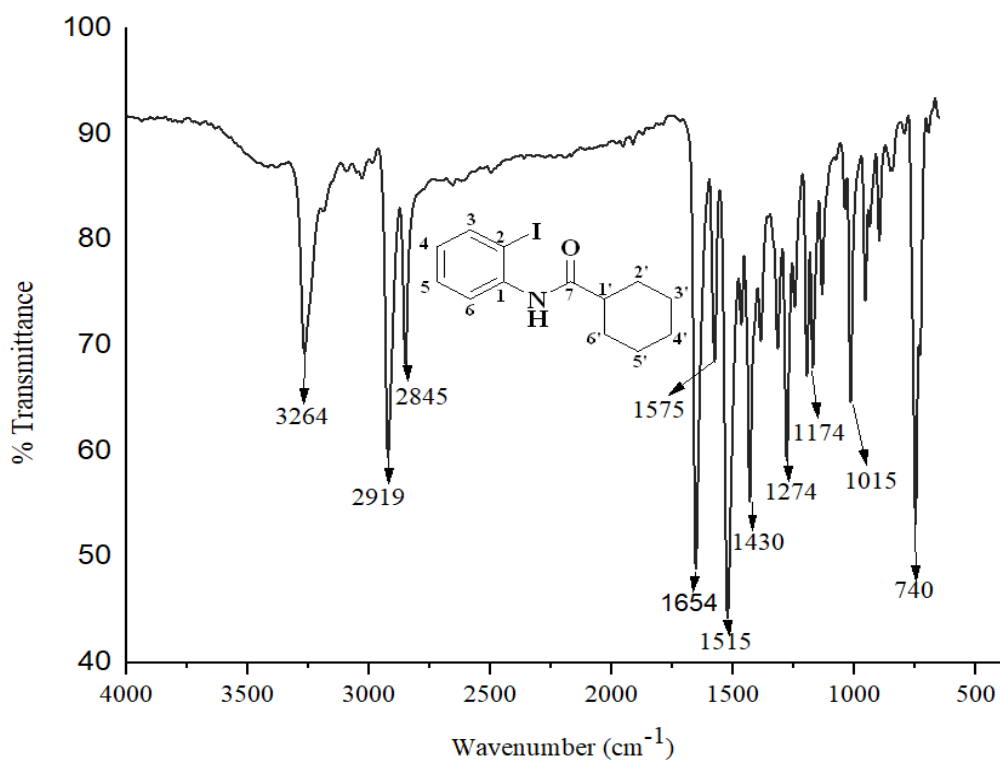


Figure S24: FT-IR Spectrum of **4e**

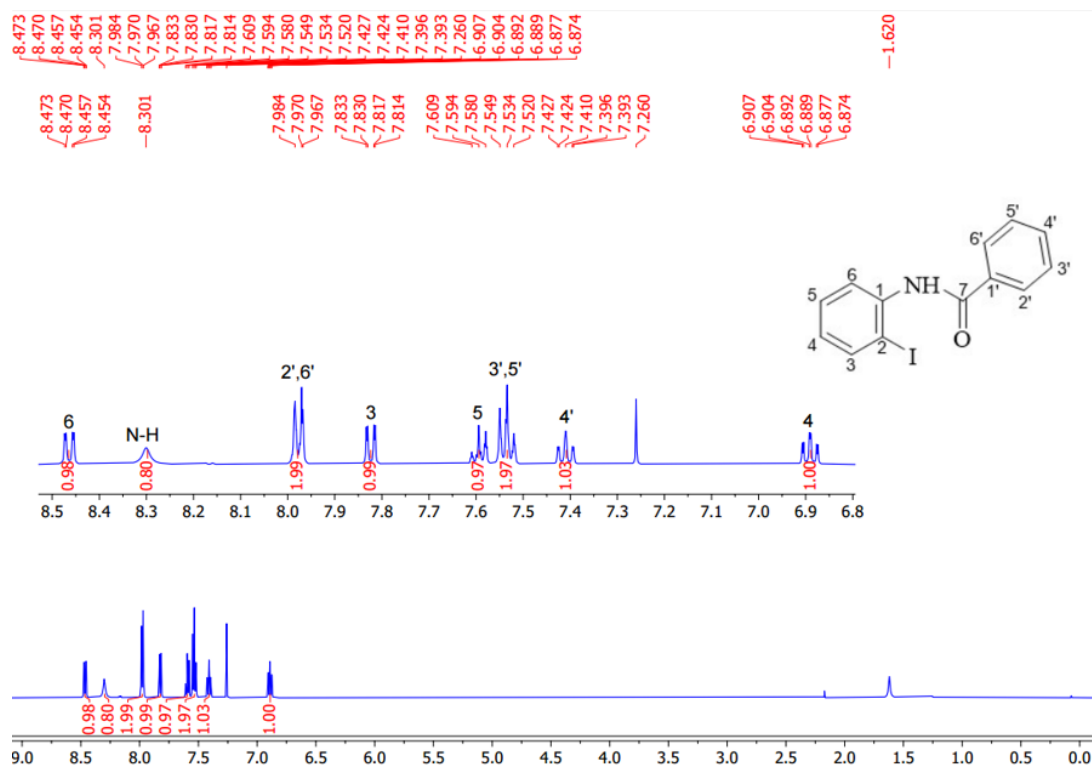


Figure S25: ^1H NMR (500 MHz, CDCl_3) spectrum of **4f**

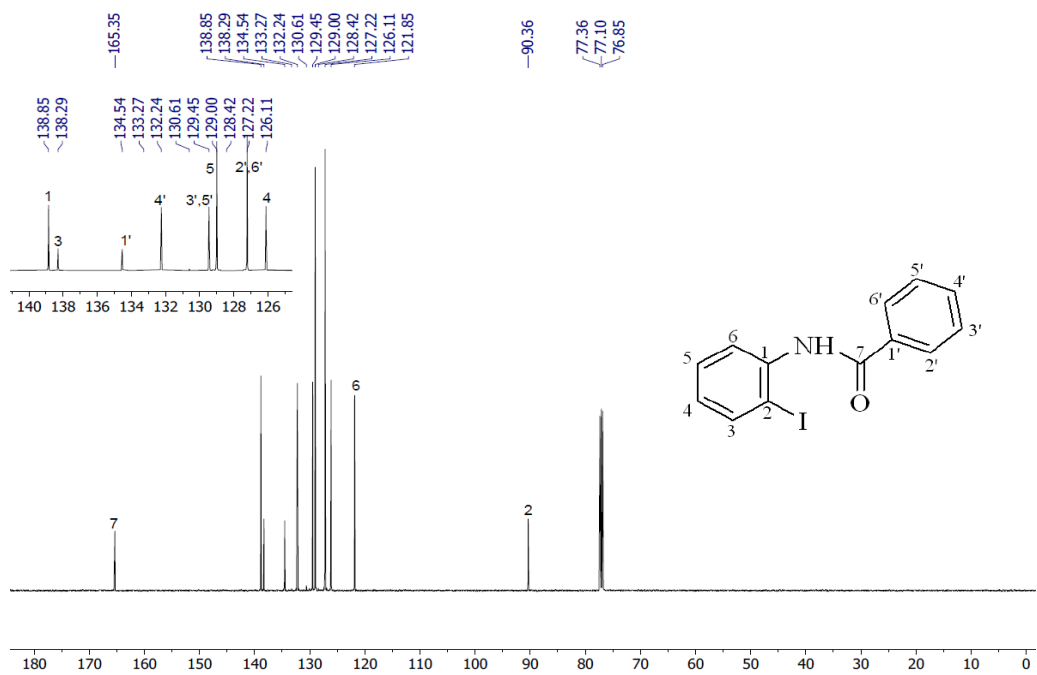


Figure S26: ^{13}C -NMR (125 MHz, CDCl_3) Spectrum of **4f**

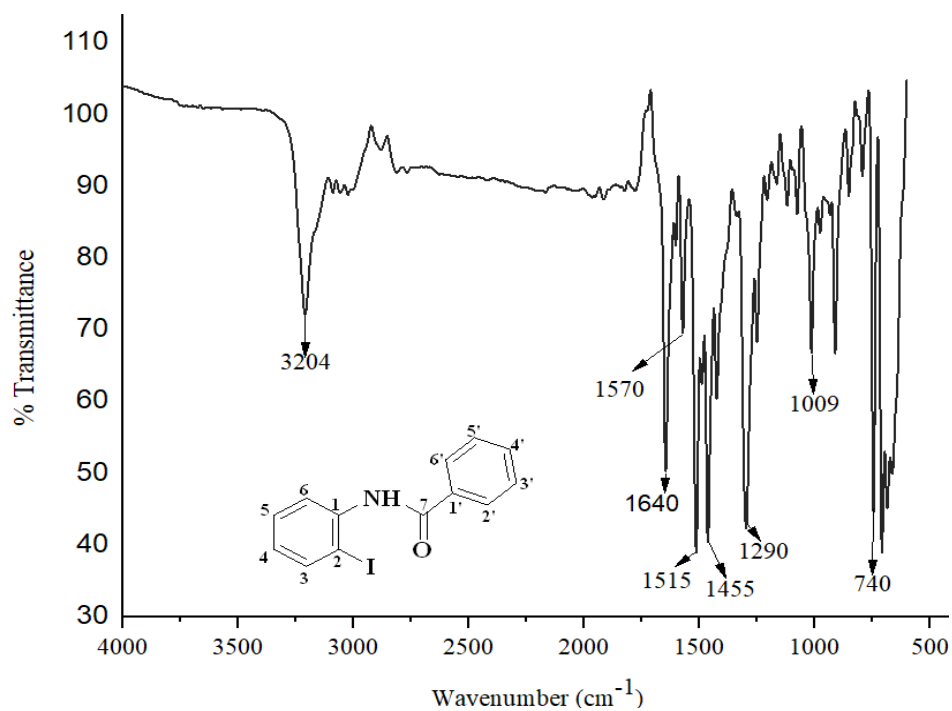


Figure S27: FT-IR Spectrum of **4f**

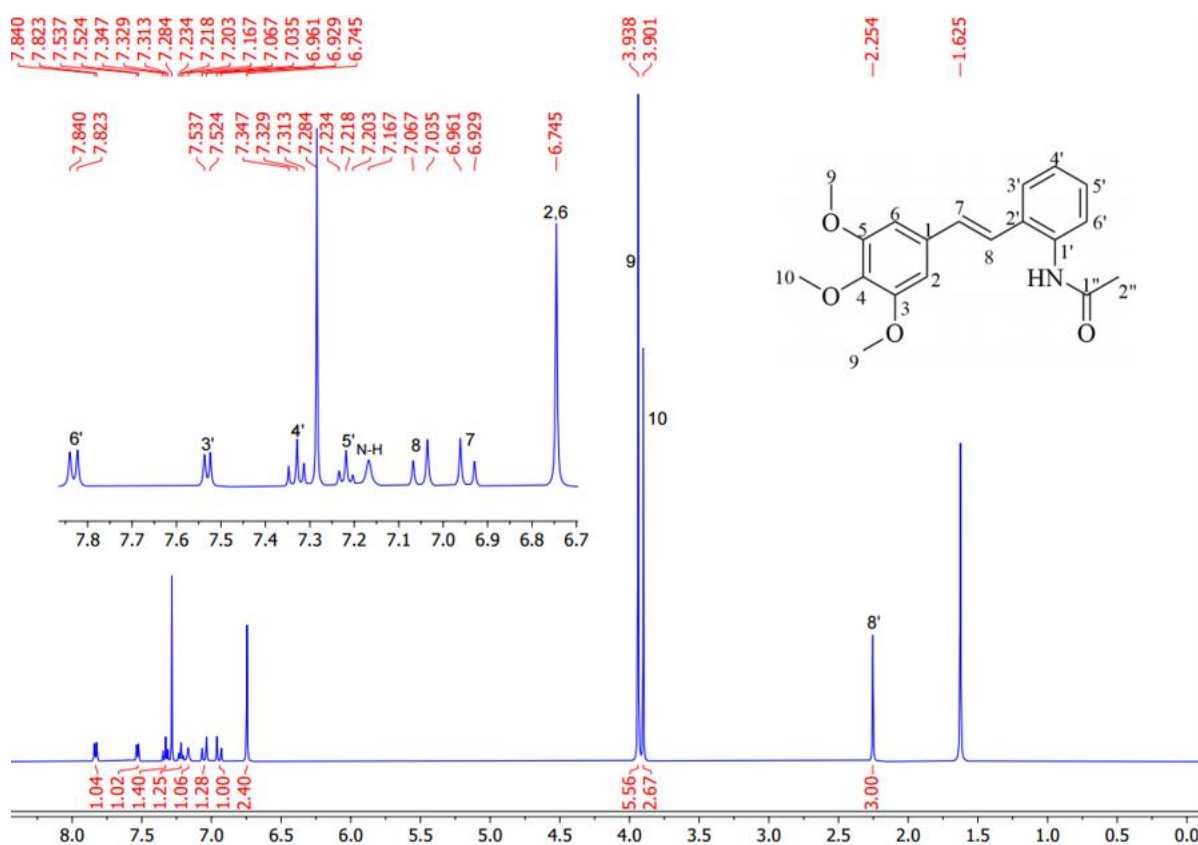


Figure S28: ^1H NMR (500 MHz, CDCl_3) spectrum of **5a**

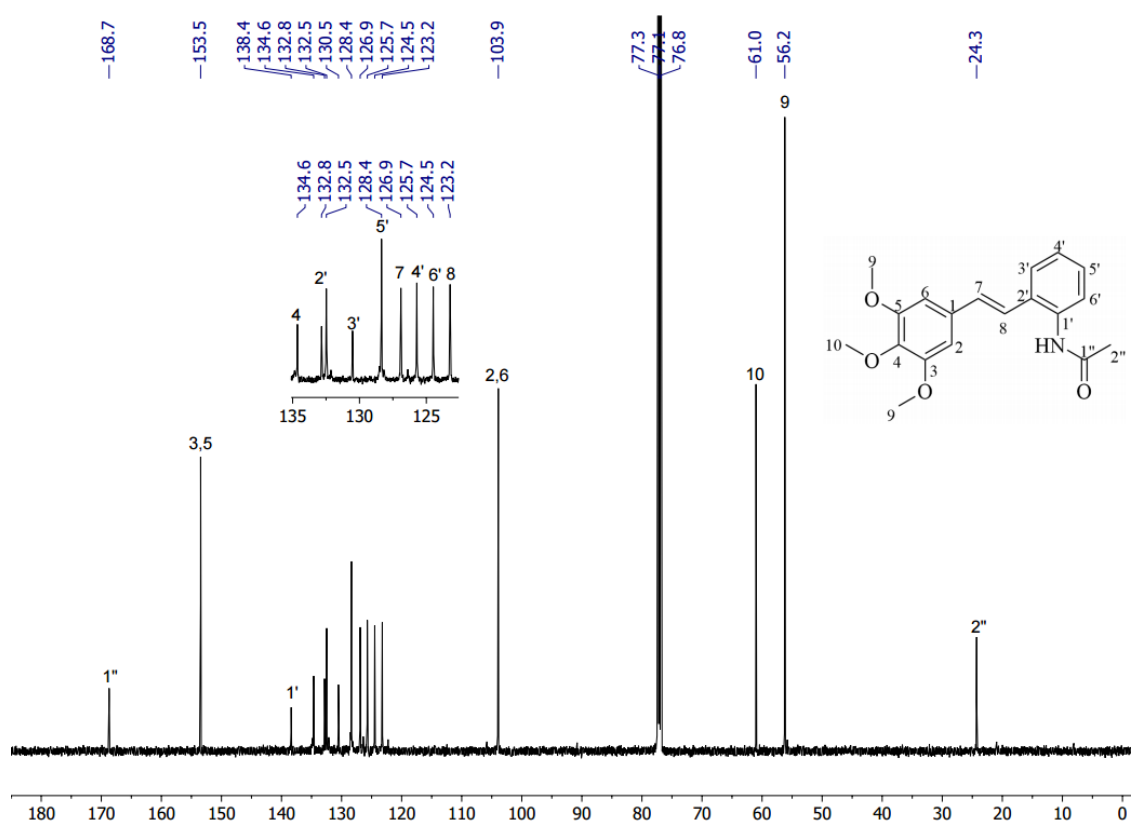


Figure S29: ^{13}C -NMR (125 MHz, CDCl_3) Spectrum of **5a**

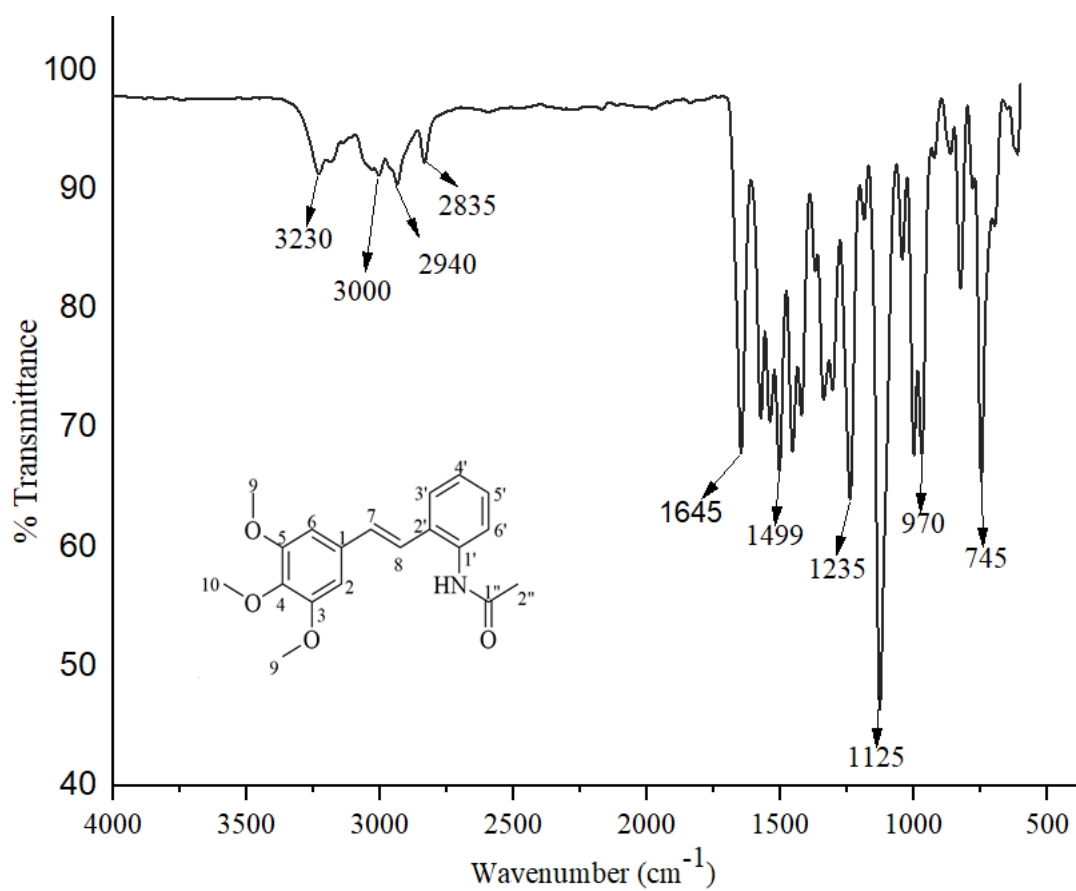


Figure S30: FT-IR Spectrum of **5a**

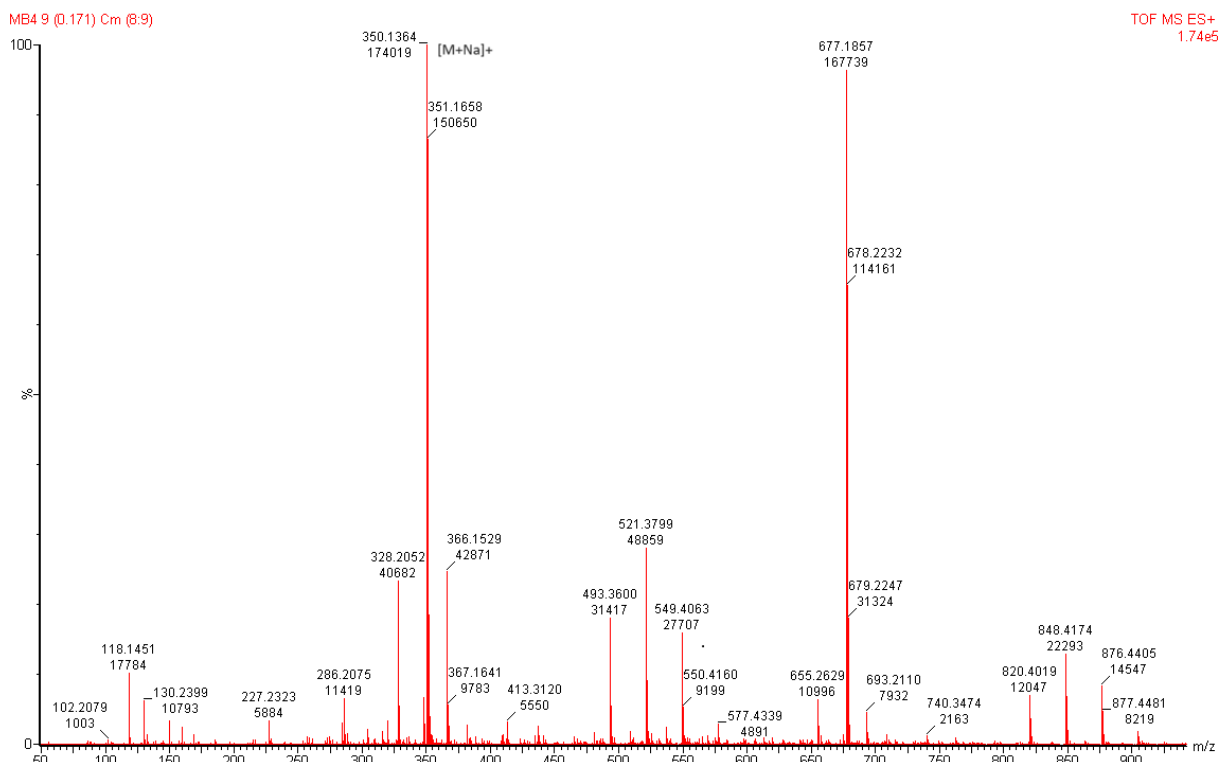


Figure S31: HRMS (+ESI) $[M+Na]^+$ for Compound 5a

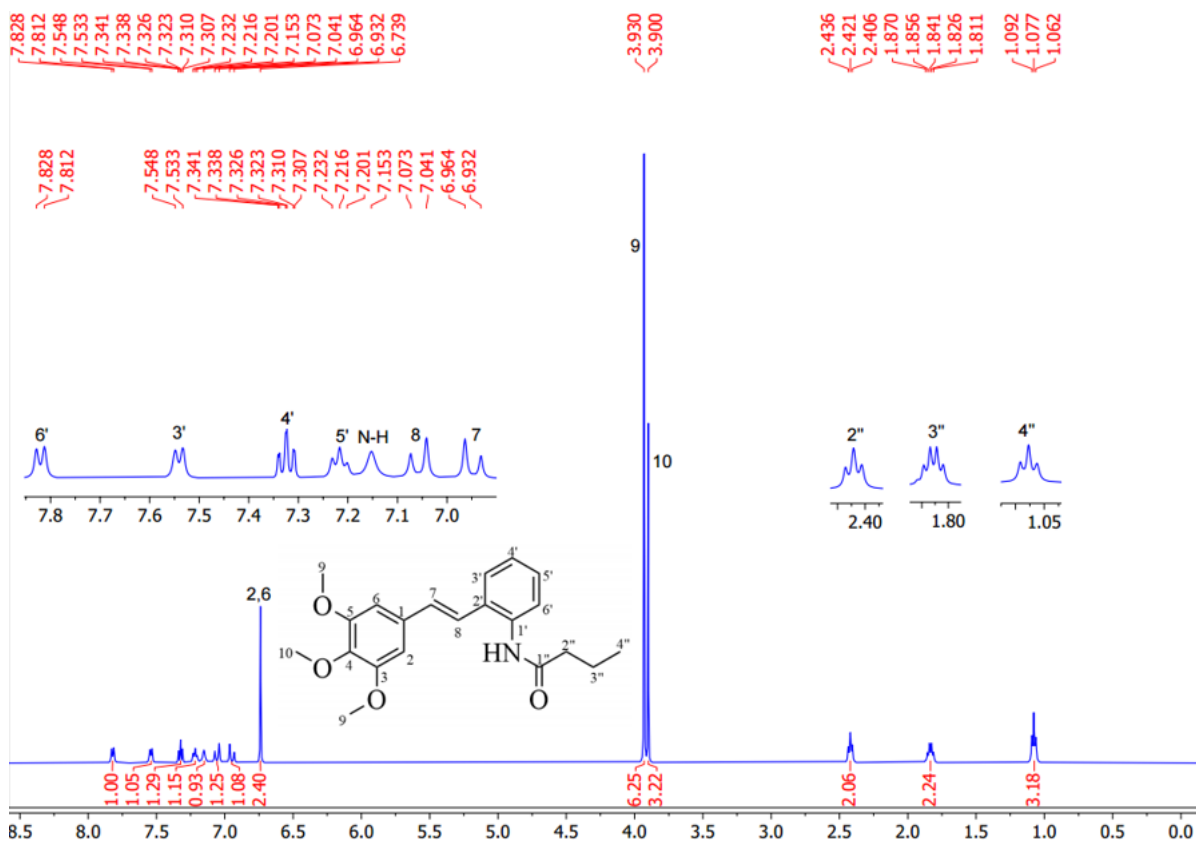


Figure S32: ^1H NMR (500 MHz, CDCl_3) spectrum of 5b

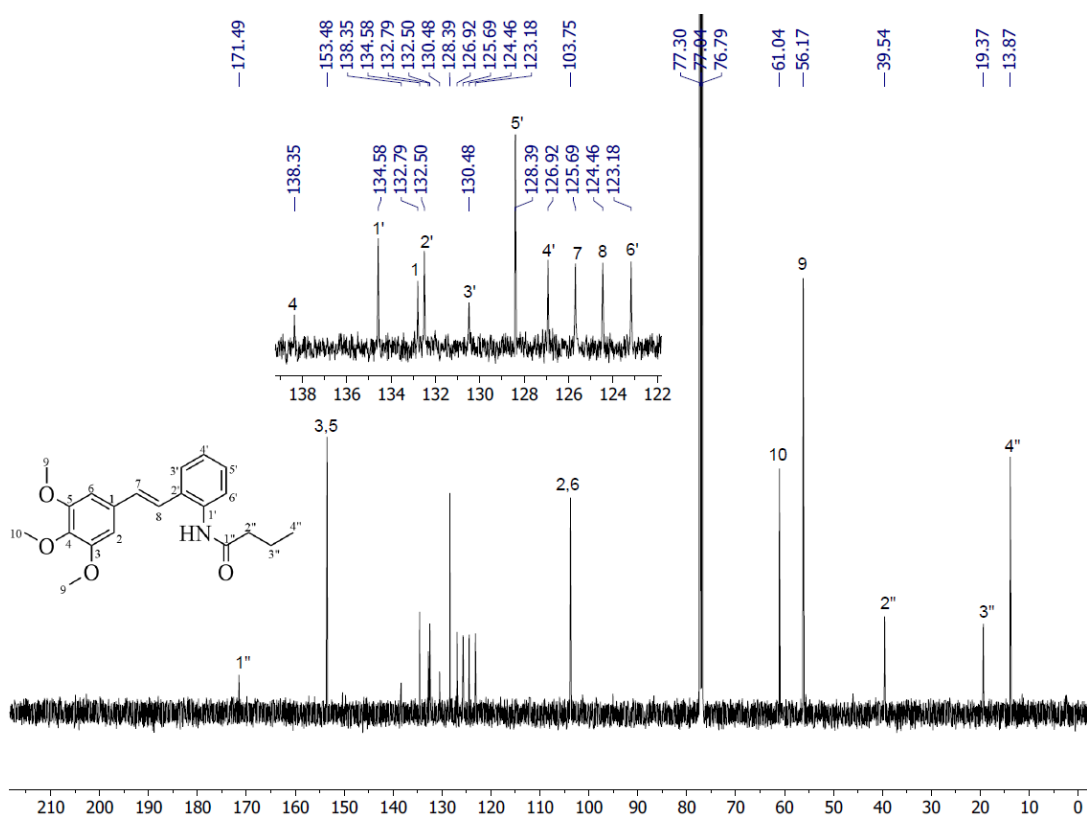


Figure S33: ^{13}C -NMR (125 MHz, CDCl_3) Spectrum of **5b**

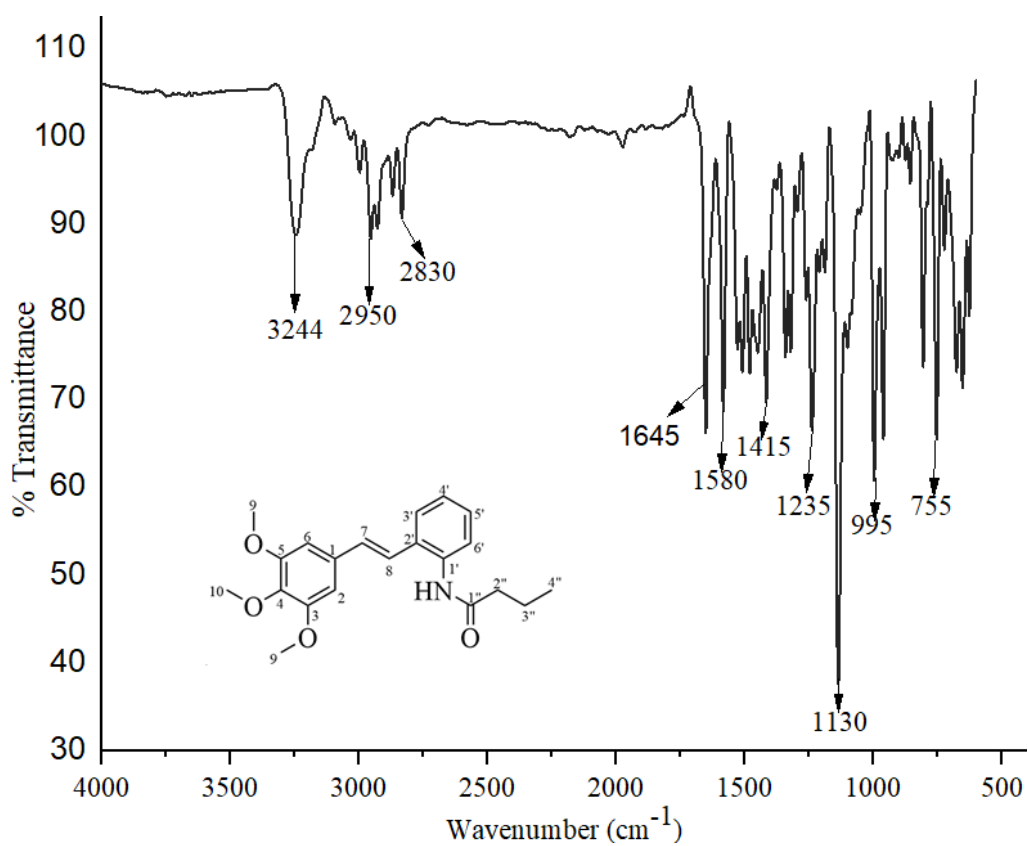


Figure S34: FT-IR Spectrum of **5b**

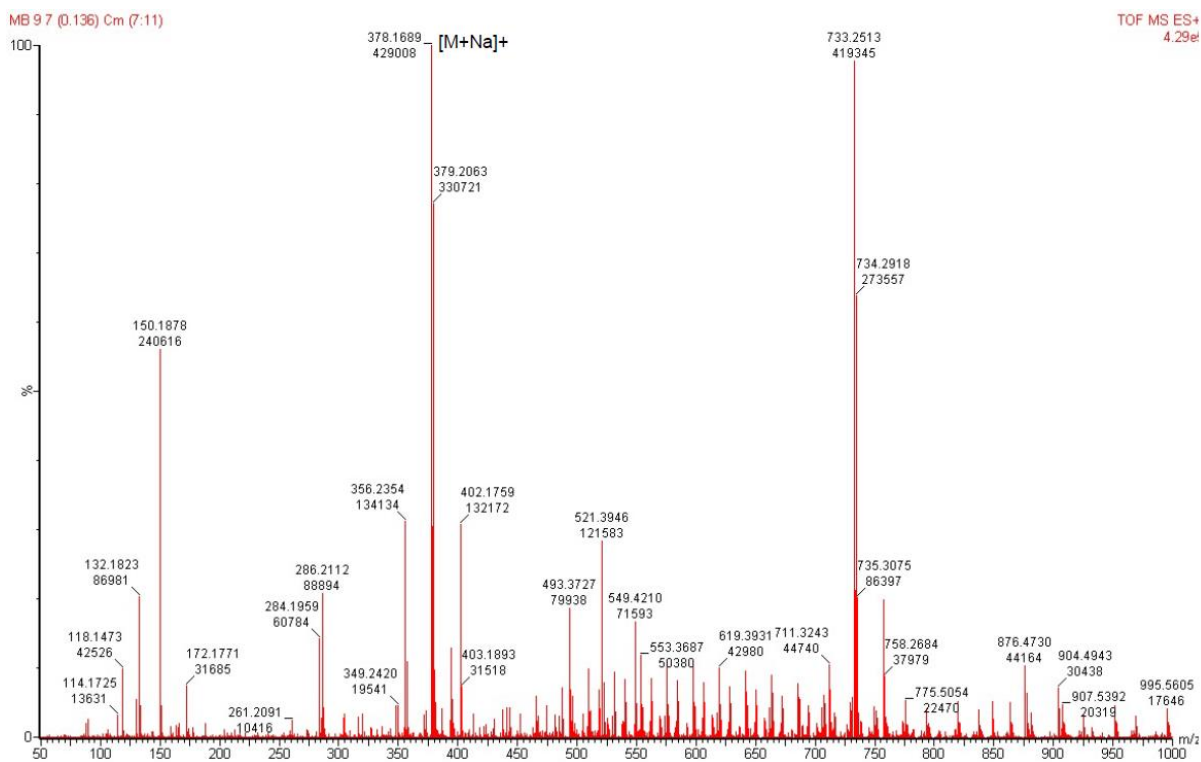


Figure S35: HRMS (+ESI) [M+Na]⁺ of **5b**

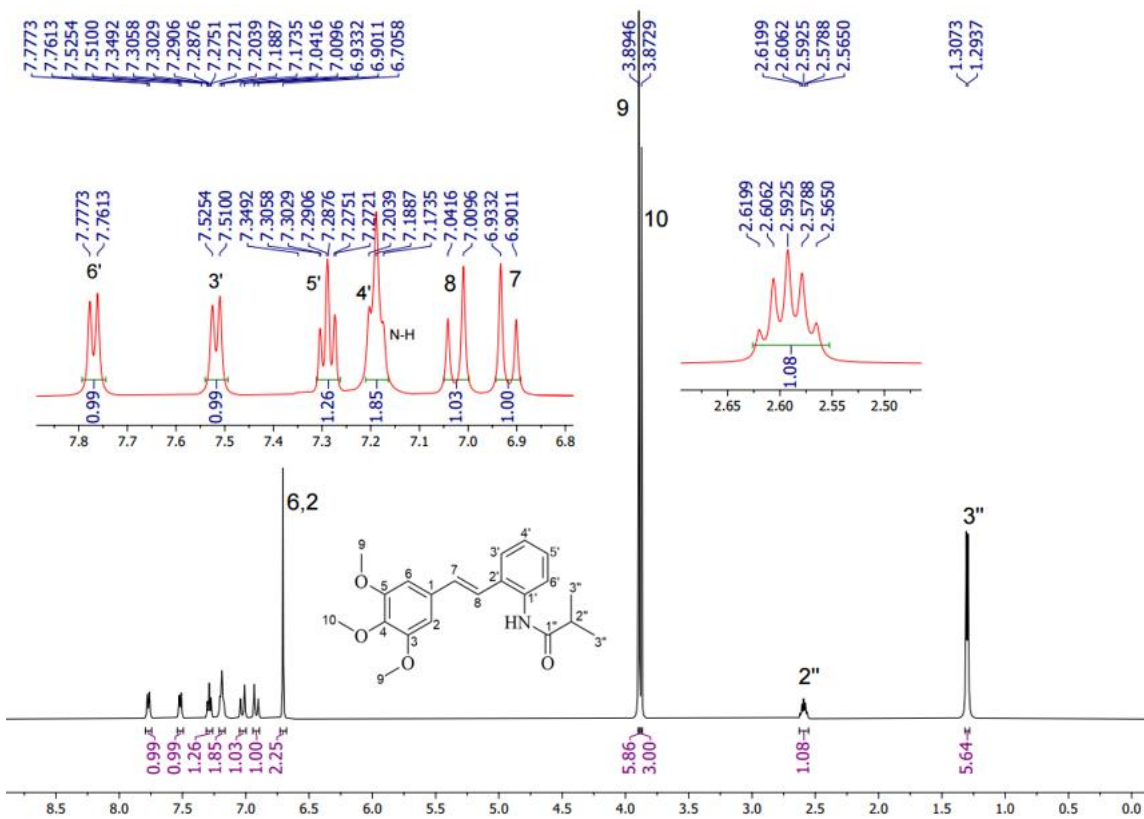


Figure S36: ¹H NMR (500 MHz, CDCl₃) spectrum of **5c**

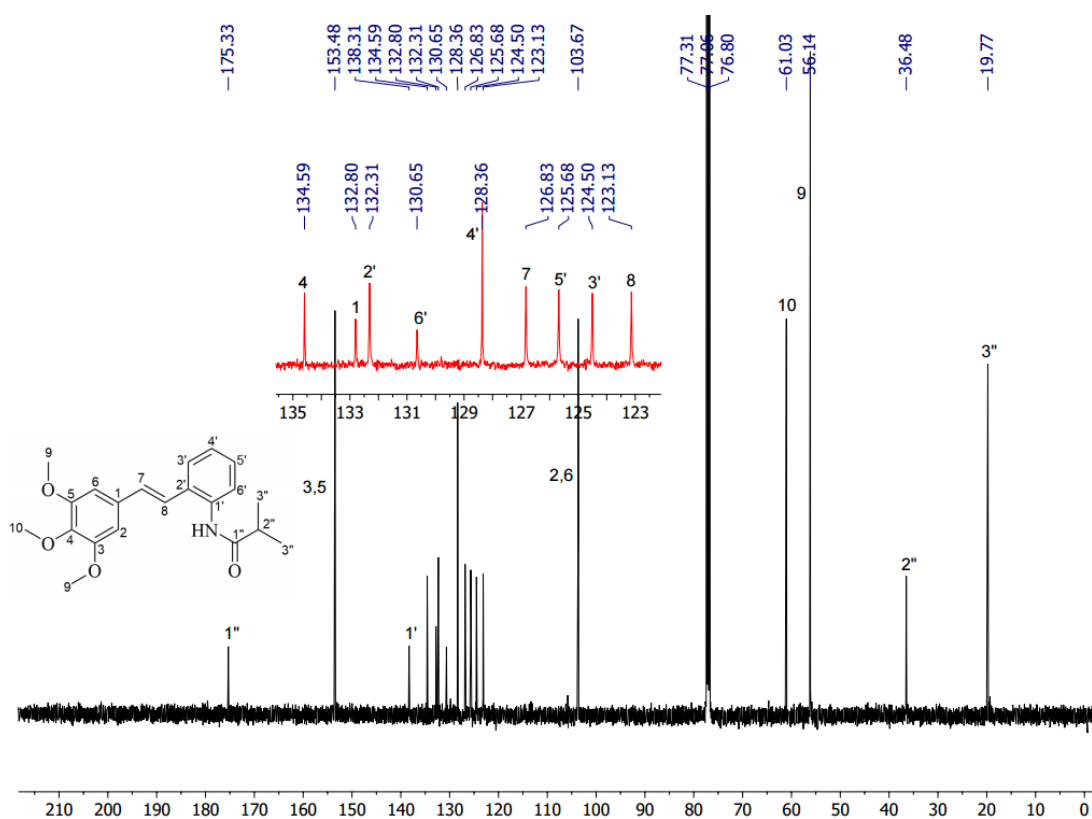


Figure S37: ^{13}C -NMR (125 MHz, CDCl_3) Spectrum of **5c**

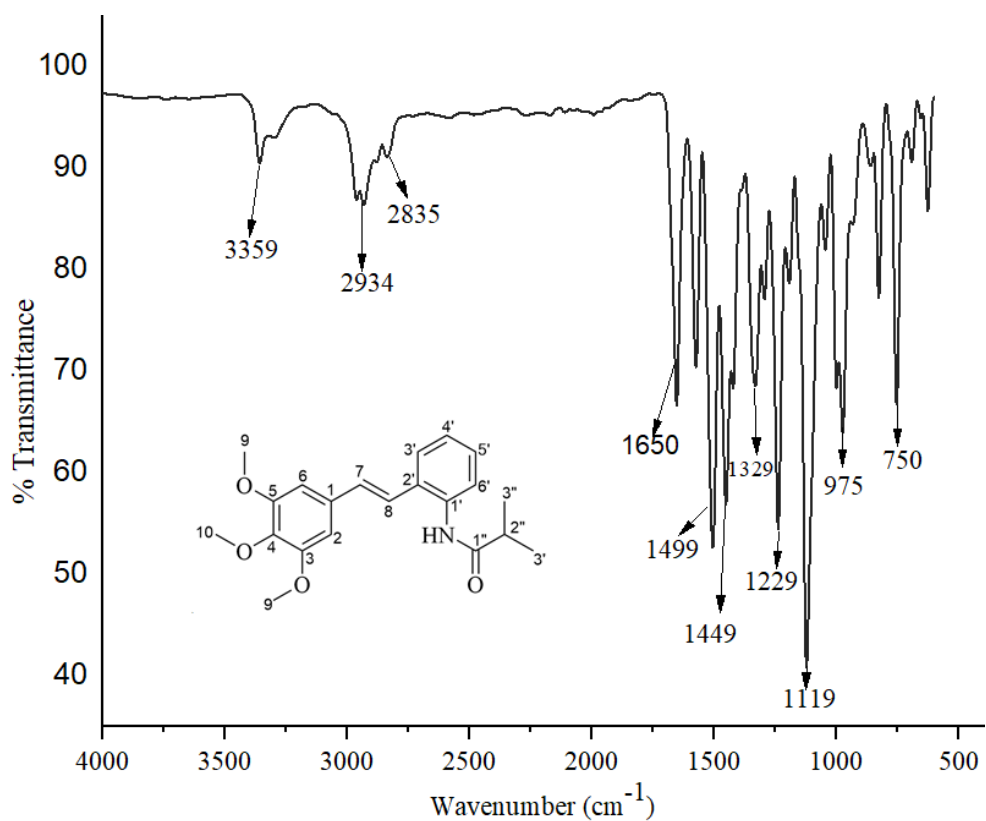


Figure S38: FT-IR Spectrum of **5c**

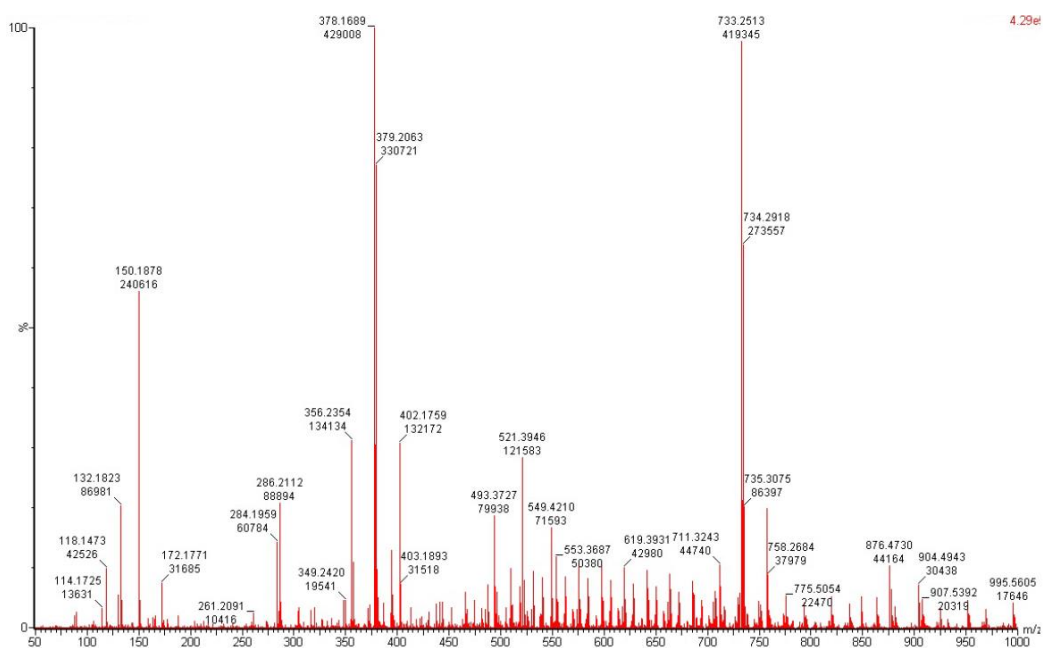


Figure S39: HRMS (+ESI) [M+Na]⁺ of **5c**

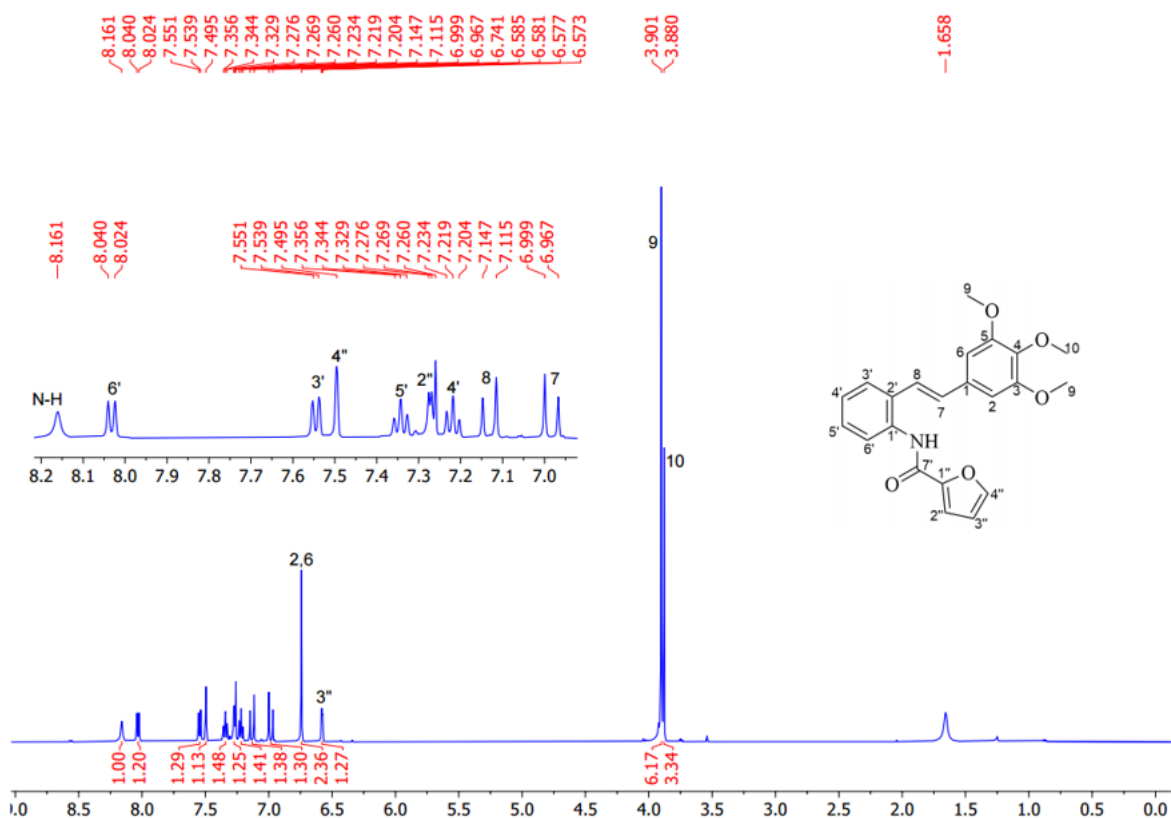


Figure S40: ¹H NMR (500 MHz, CDCl₃) spectrum of **5d**

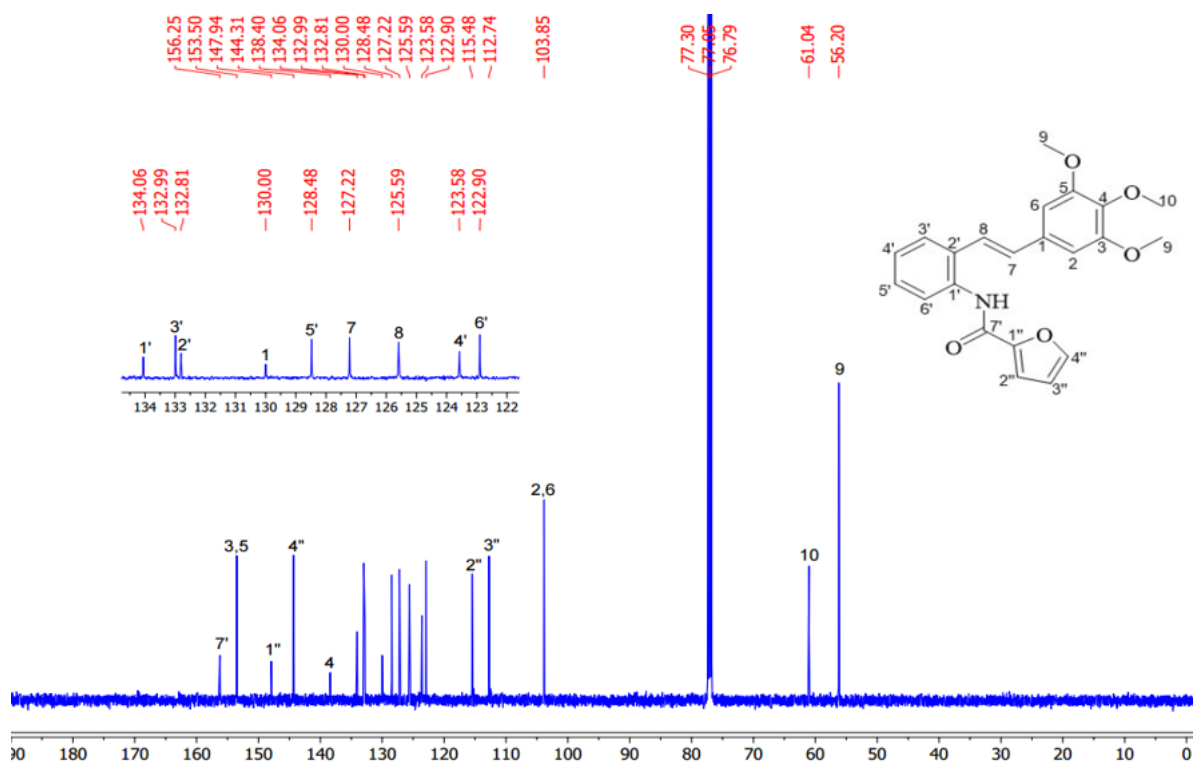


Figure S41: ¹³C-NMR (125 MHz, CDCl₃) Spectrum of **5d**

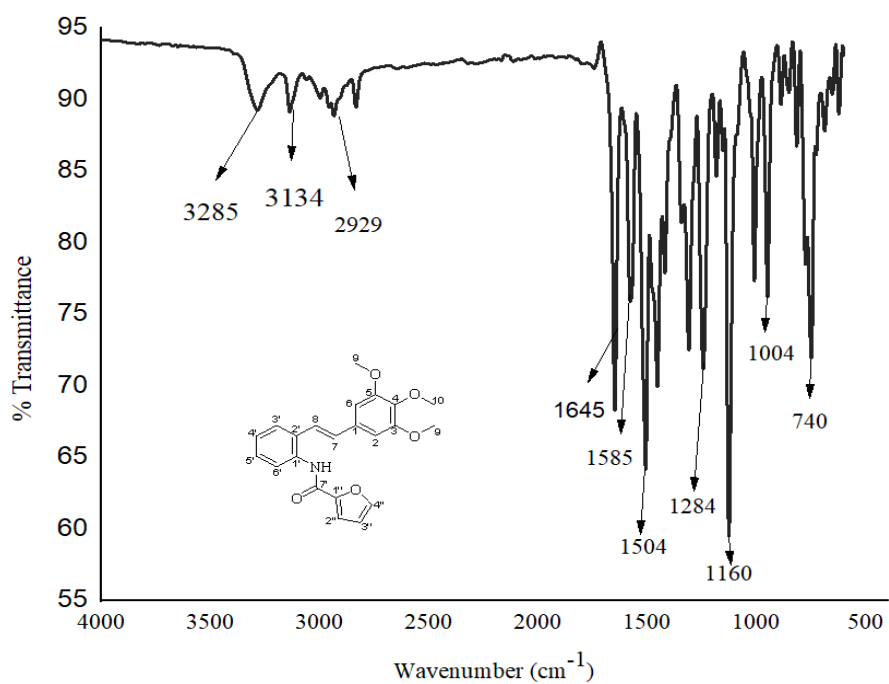


Figure S42: FT-IR Spectrum of **5d**

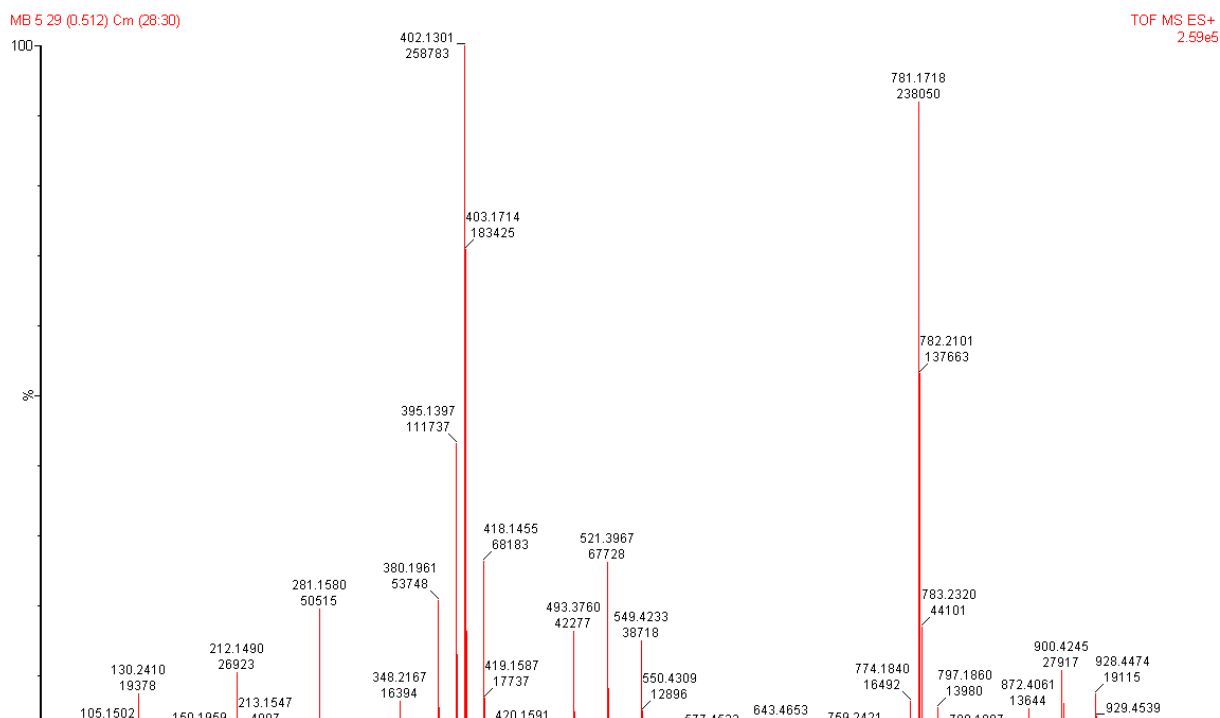


Figure S43: HRMS (+ESI) $[M+Na]^+$ of **5d**

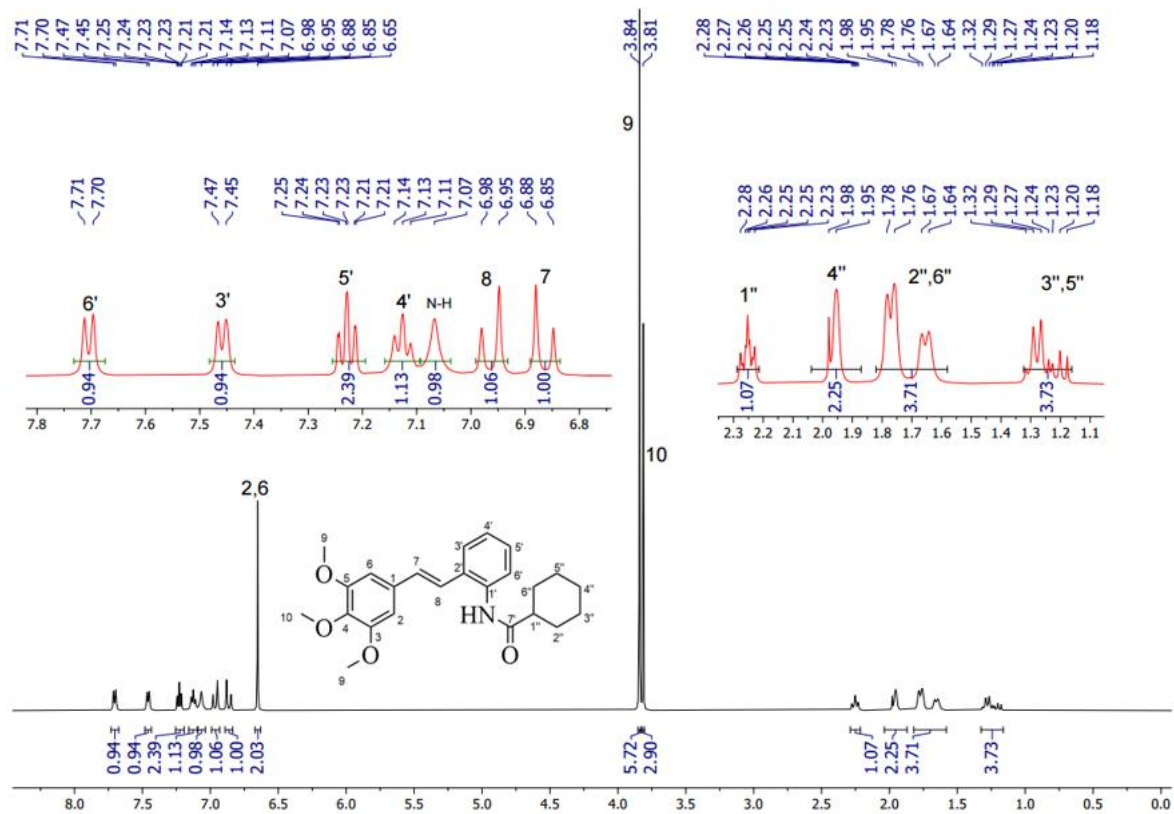


Figure S44: ^1H NMR (500 MHz, CDCl_3) spectrum of **5e**

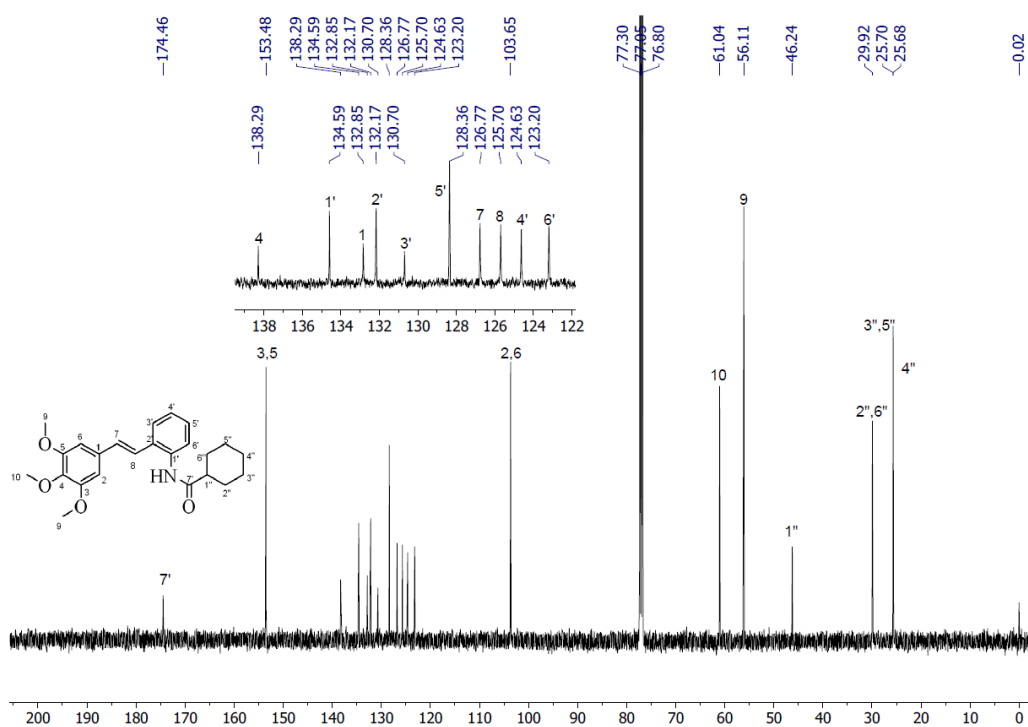


Figure S45: ^{13}C -NMR (125 MHz, CDCl_3) spectrum of **5e**

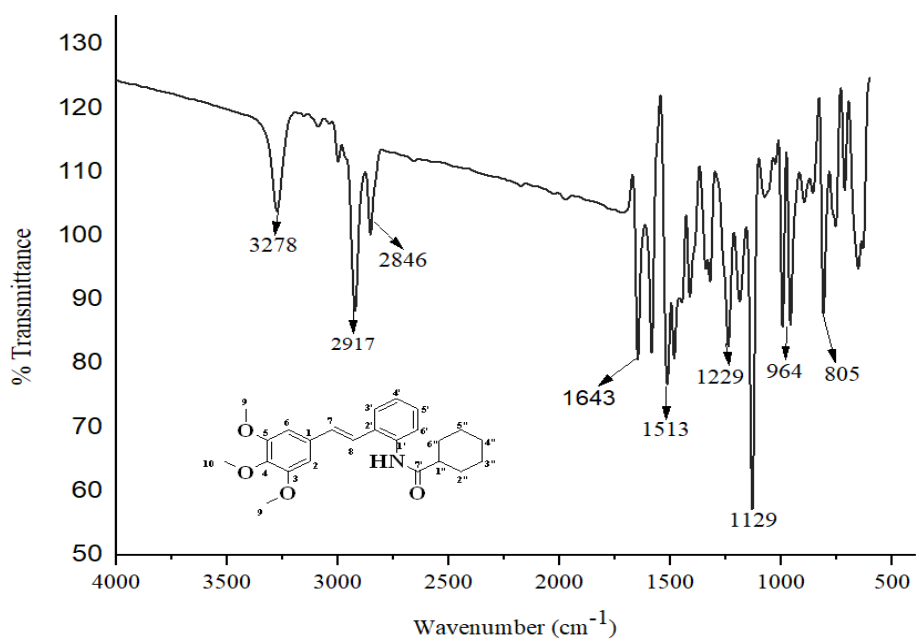


Figure S46: FT-IR Spectrum of **5e**

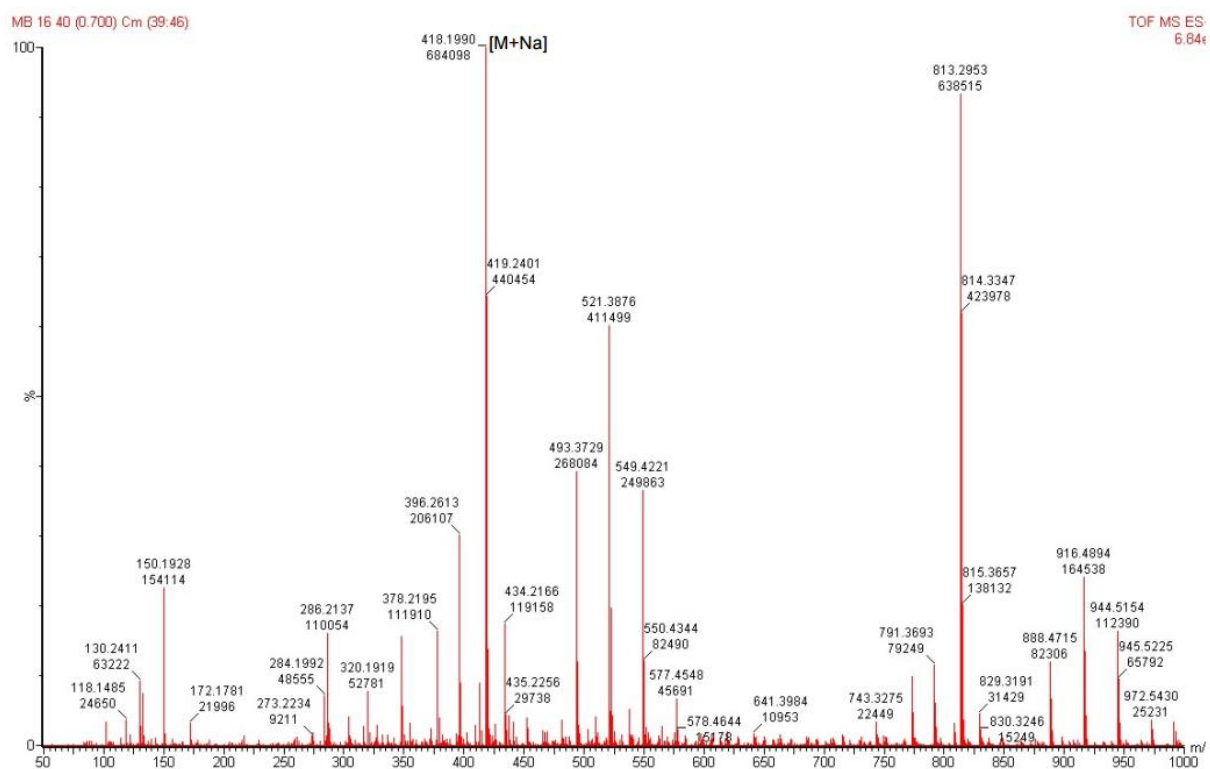


Figure S47: HRMS (+ESI) $[M+Na]^+$ of **5e**

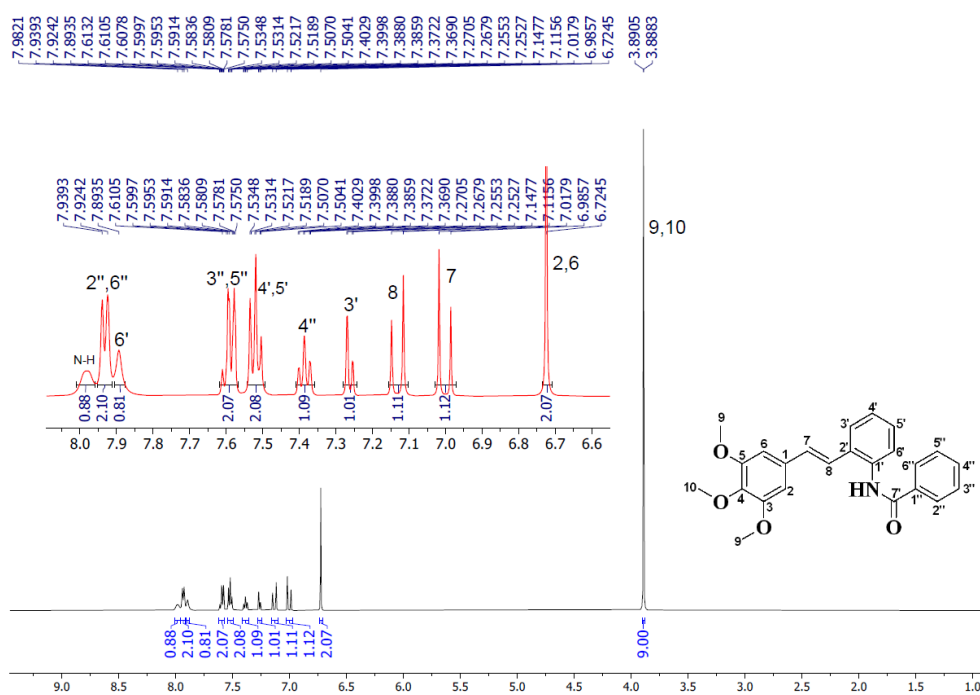


Figure S48: ^1H NMR (500 MHz, CDCl_3) spectrum of **5f**

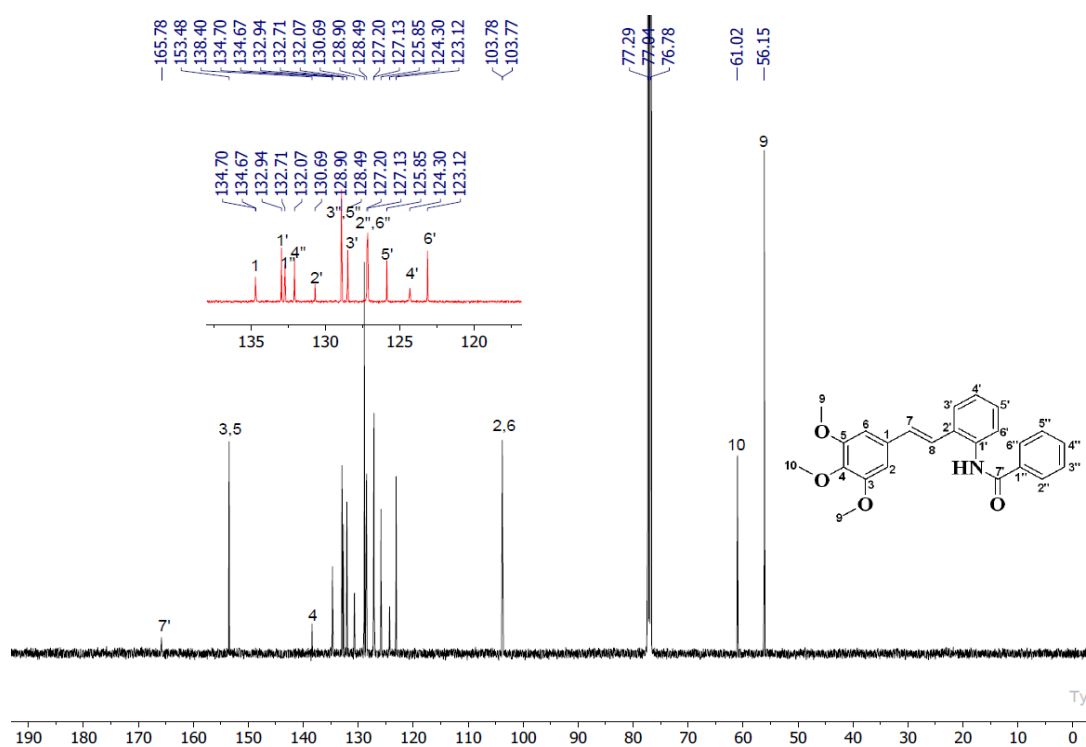


Figure S49: ^{13}C -NMR (125 MHz, CDCl_3) spectrum of **5f**

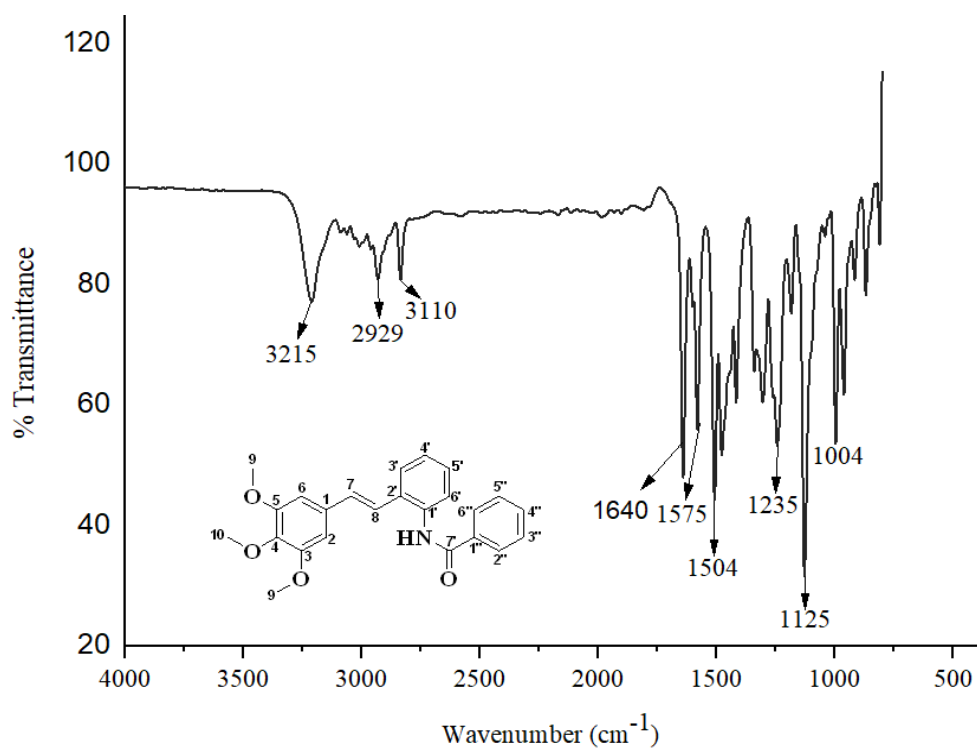


Figure S50: FT-IR spectrum of **5f**

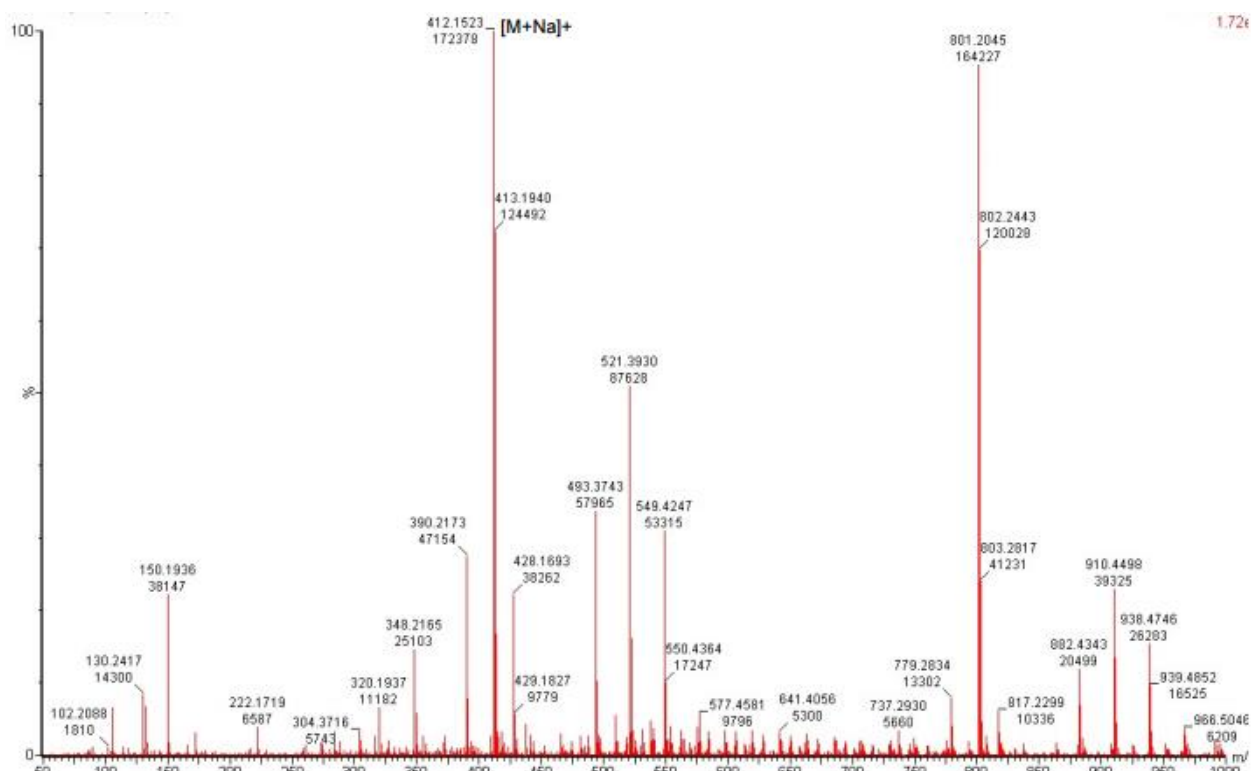


Figure S51: HRMS (+ESI) $[M+Na]^+$ 5f

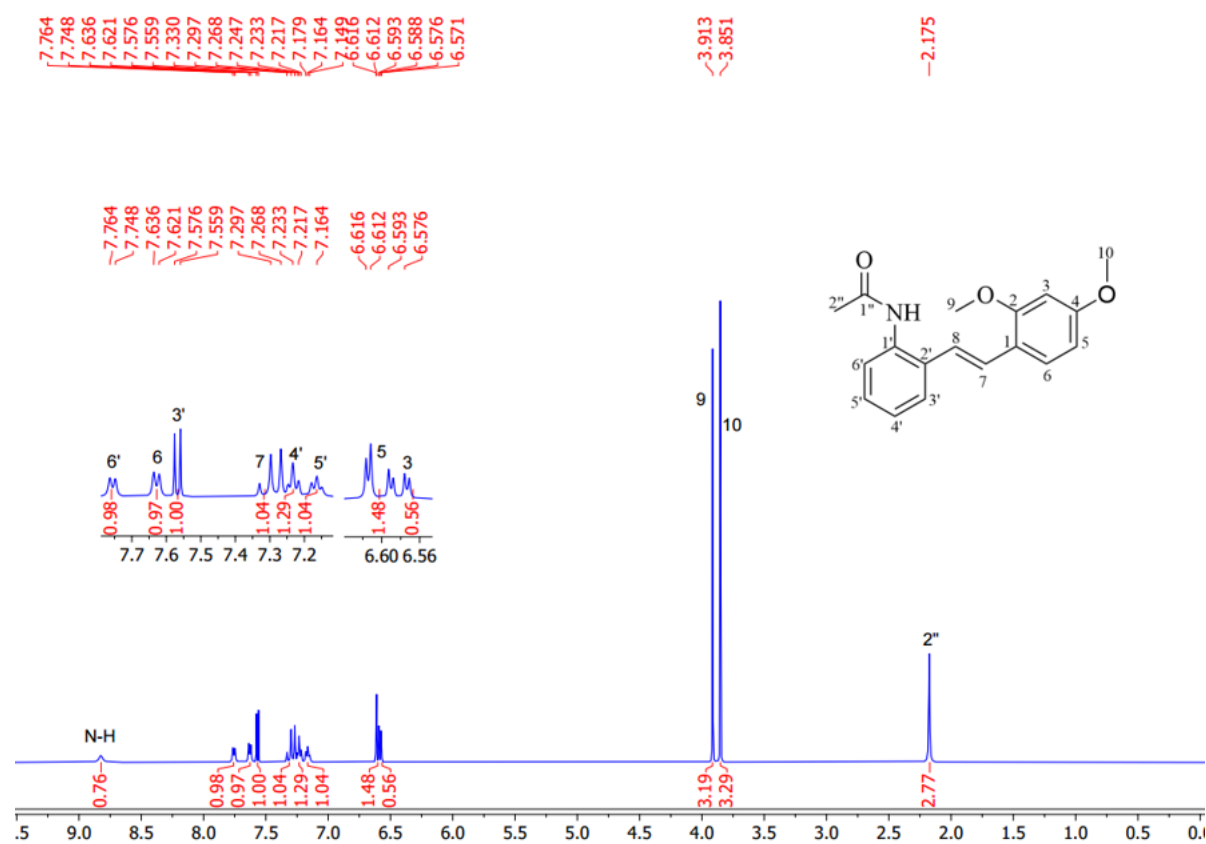


Figure S52: 1H NMR (500 MHz, $CDCl_3$) spectrum of 6a

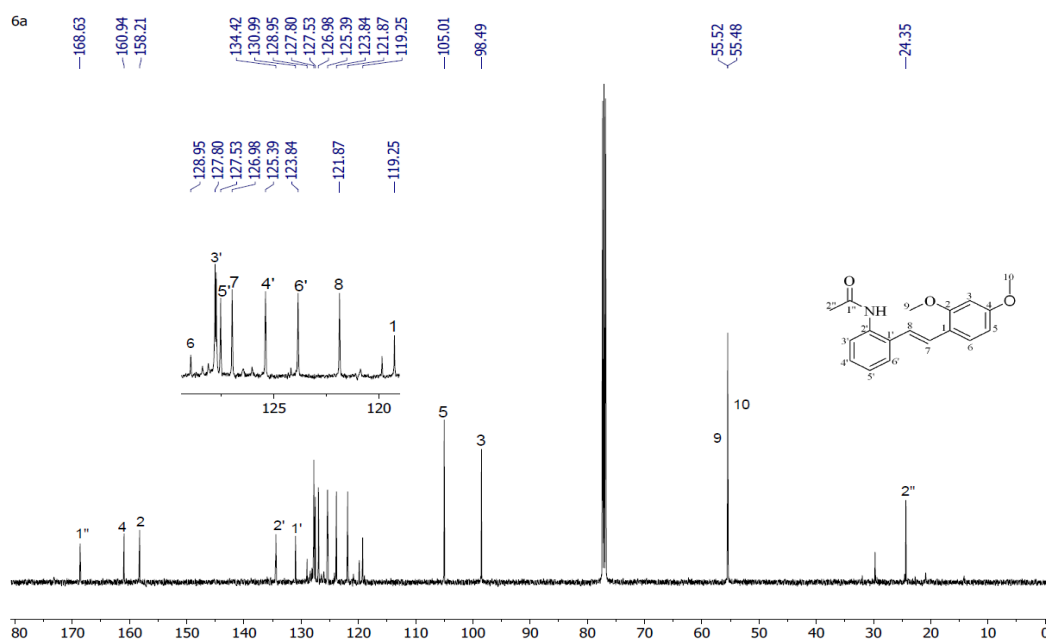


Figure S53: ^{13}C -NMR (125 MHz, CDCl_3) spectrum of **6a**

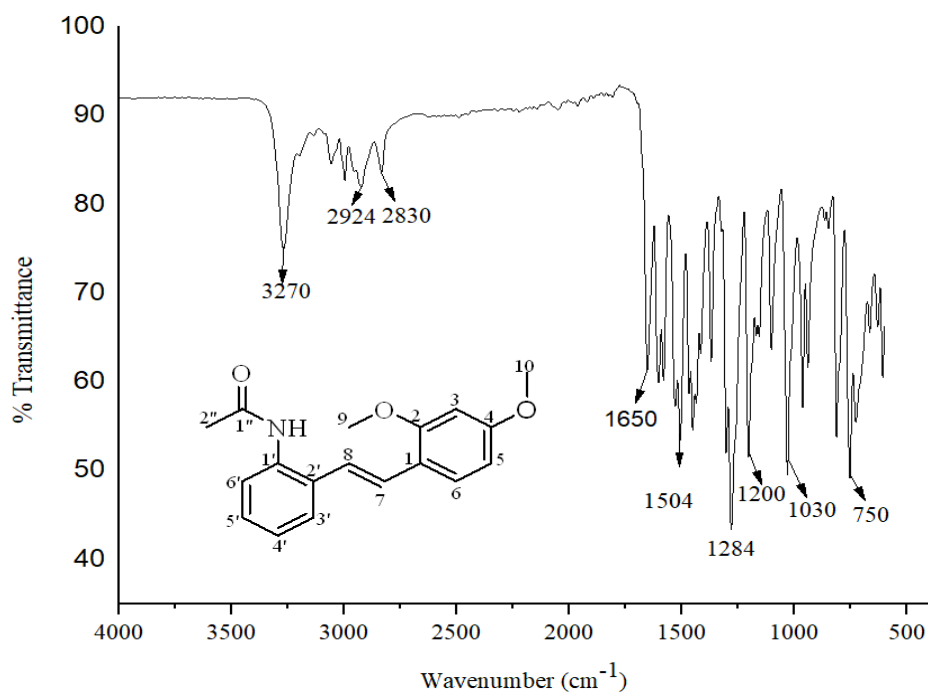


Figure S54: FT-IR spectrum of **6a**

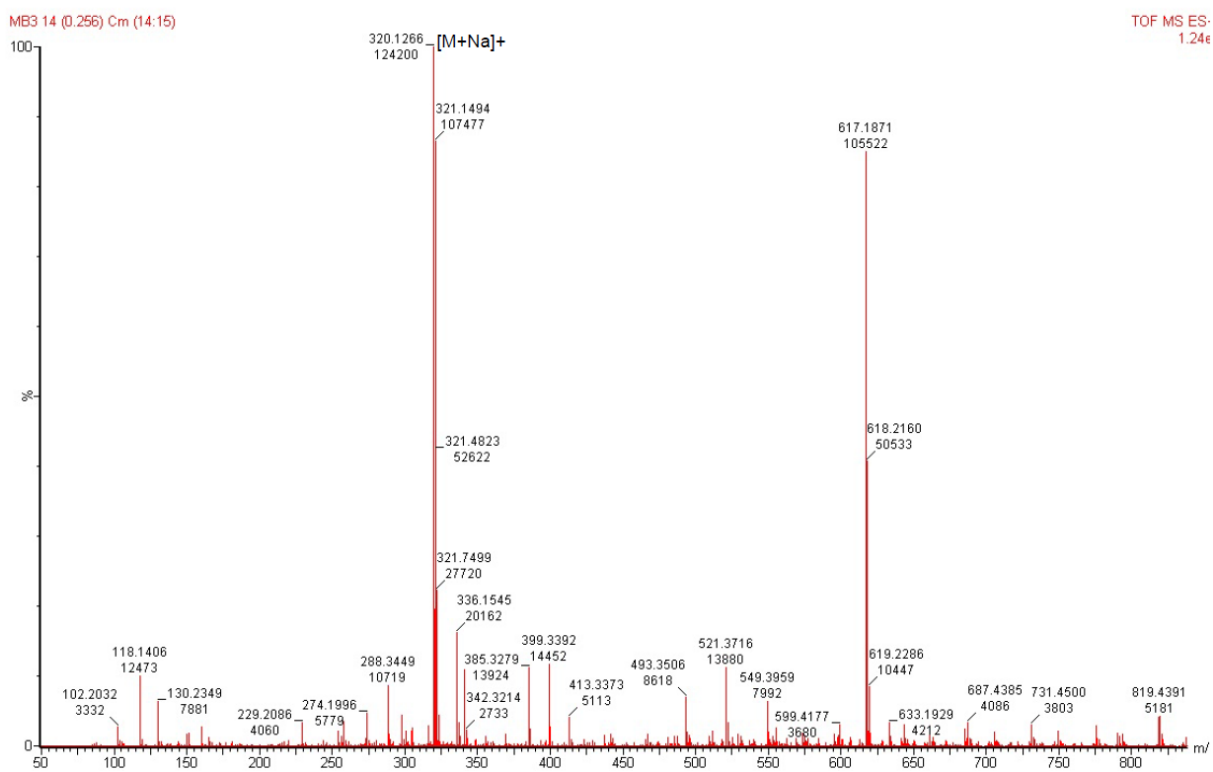


Figure S55: HRMS (+ESI) [M+Na]⁺ of 6a

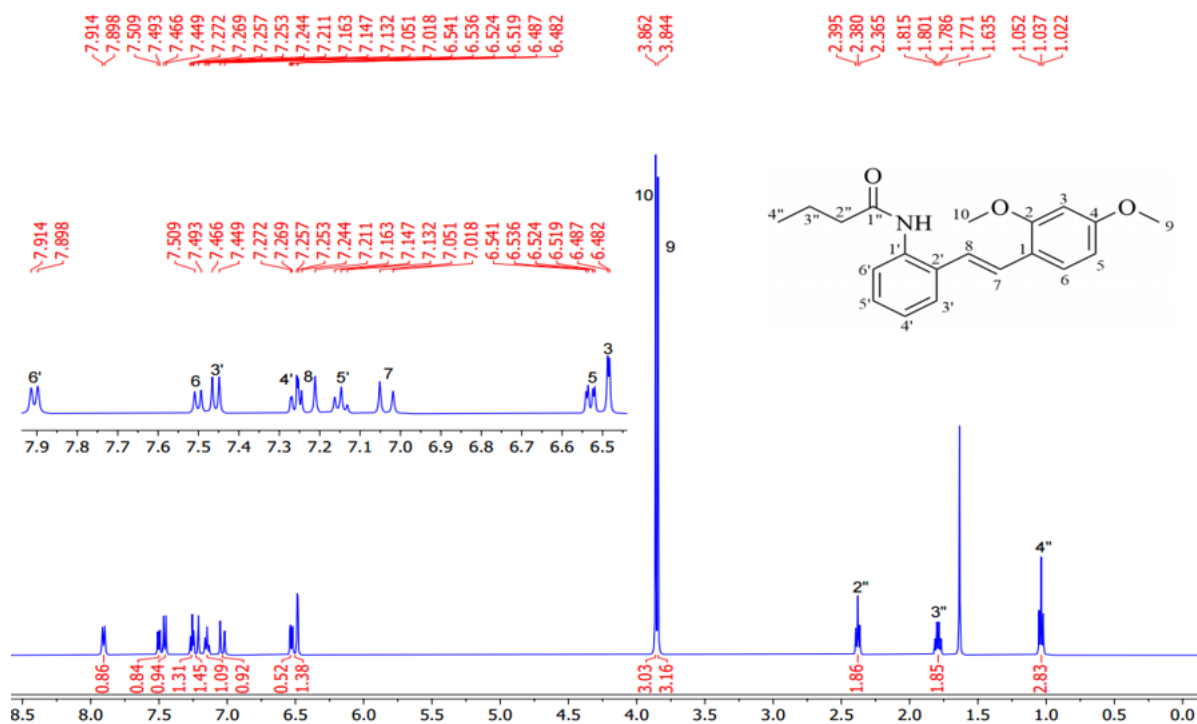


Figure S56: ¹H NMR (500 MHz, CDCl₃) spectrum of 6b

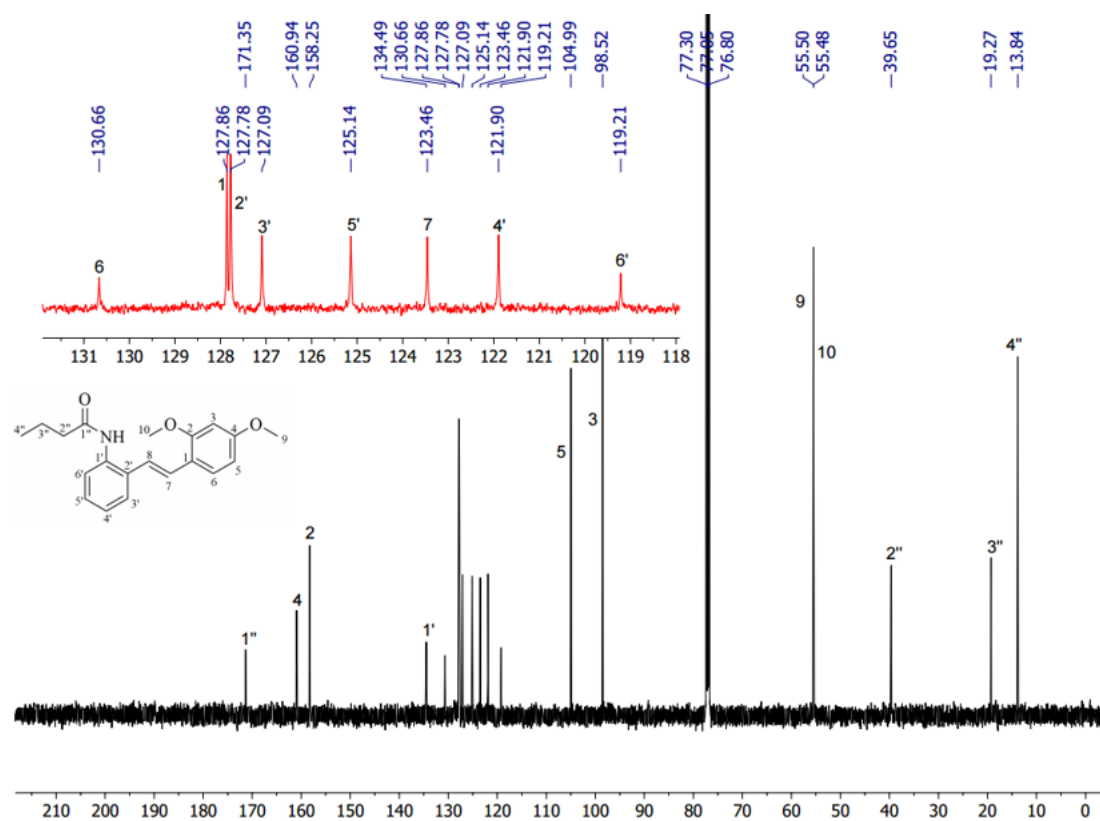


Figure S57: ¹³C-NMR (125 MHz, CDCl₃) spectrum of 6b

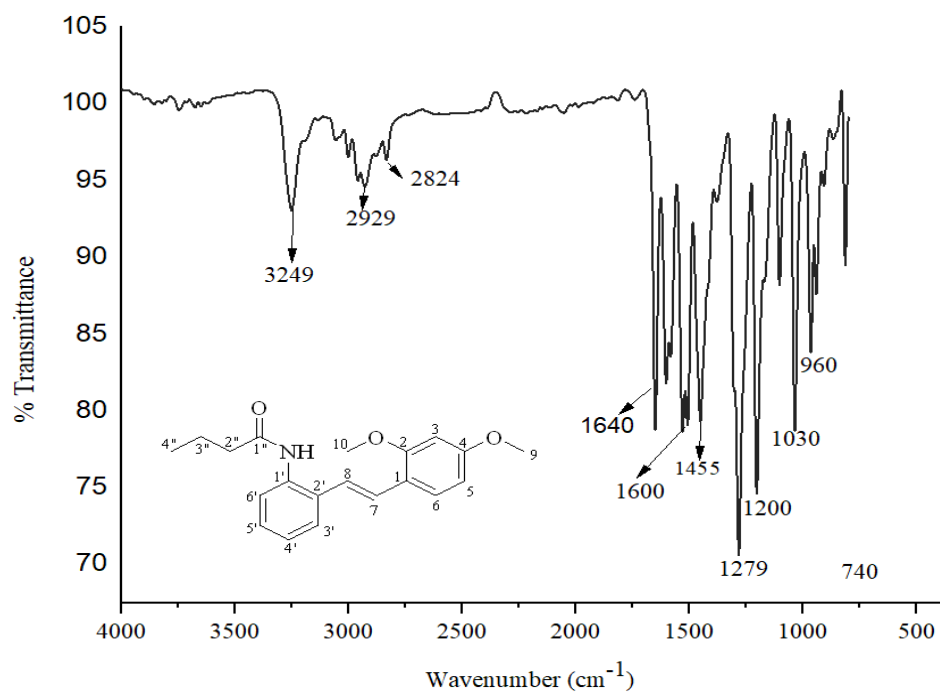


Figure S58: FT-IR spectrum of 6b

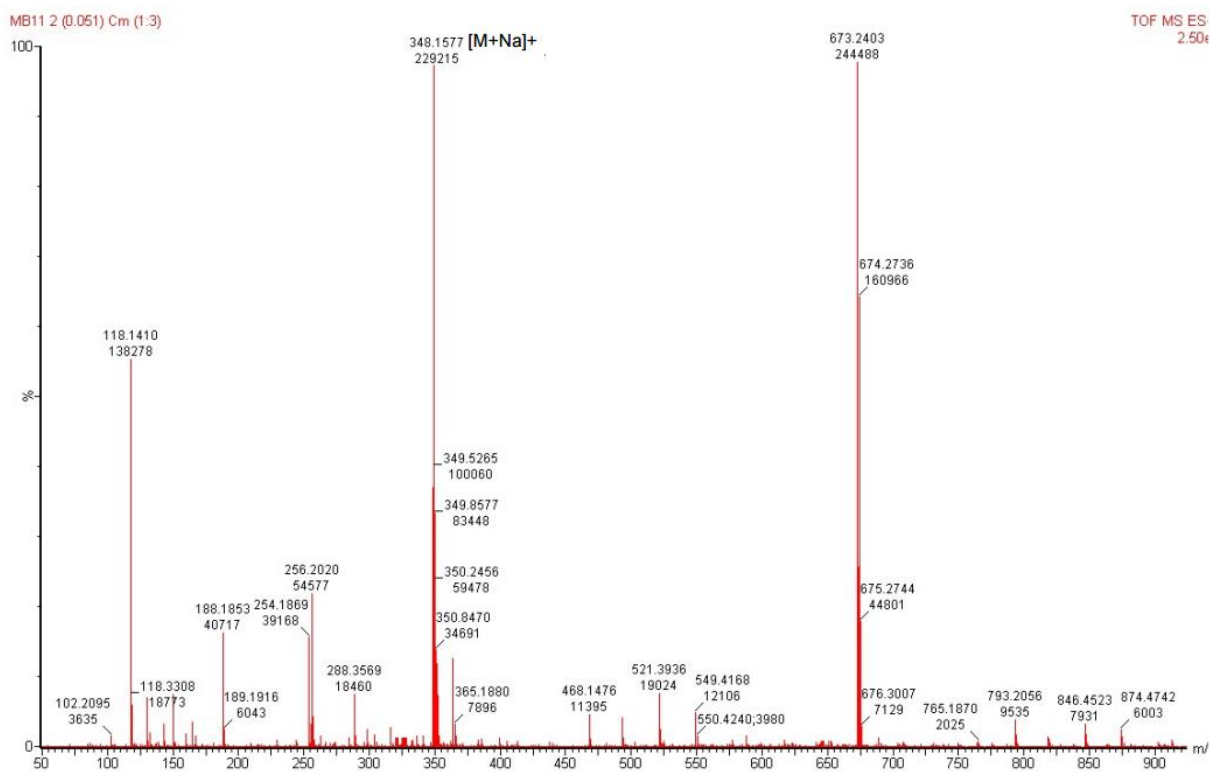


Figure S59: HRMS (+ESI) [M+Na]⁺ of **6b**

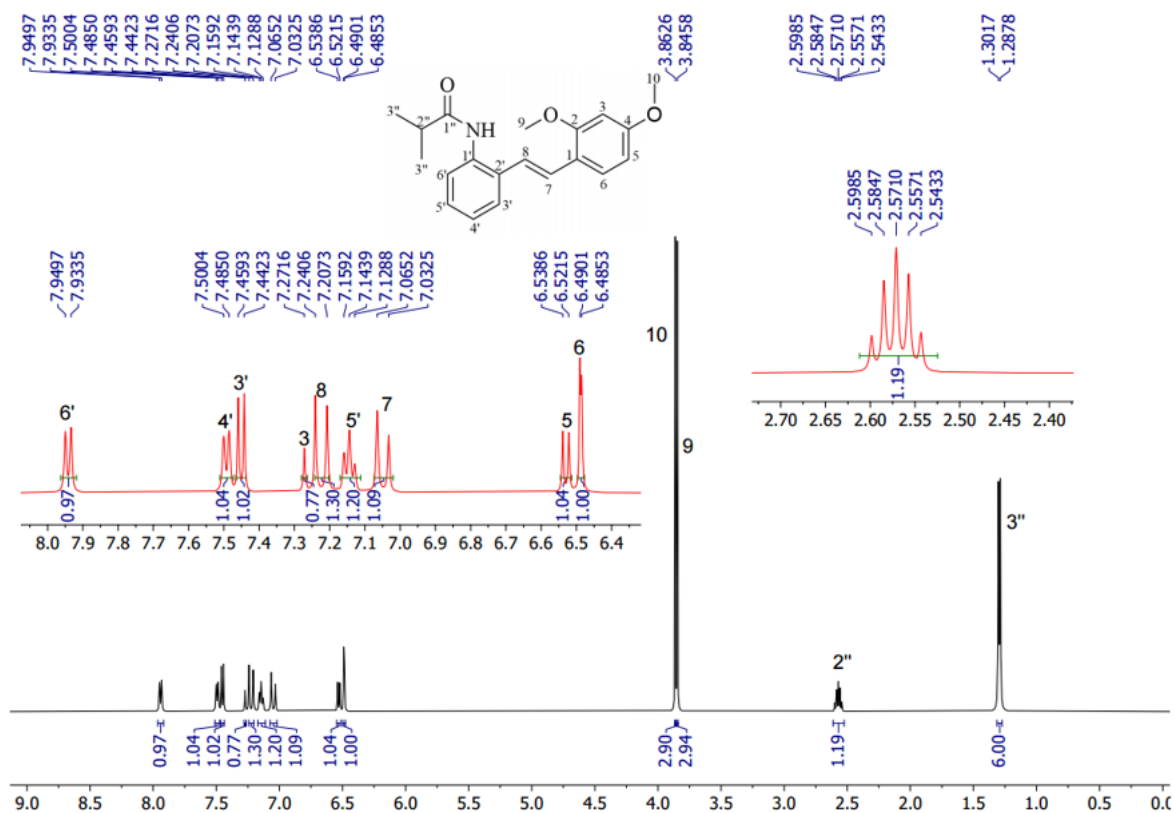


Figure S60: ¹H NMR (500 MHz, CDCl₃) spectrum of **6c**

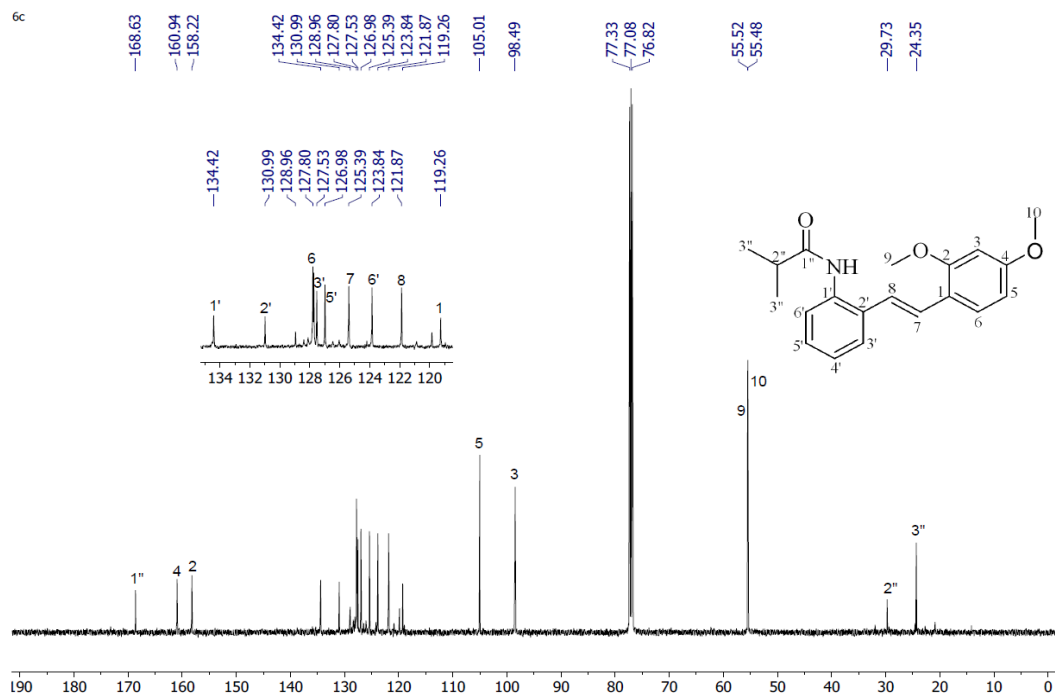


Figure S61: ^{13}C -NMR (125 MHz, CDCl_3) spectrum of 6c

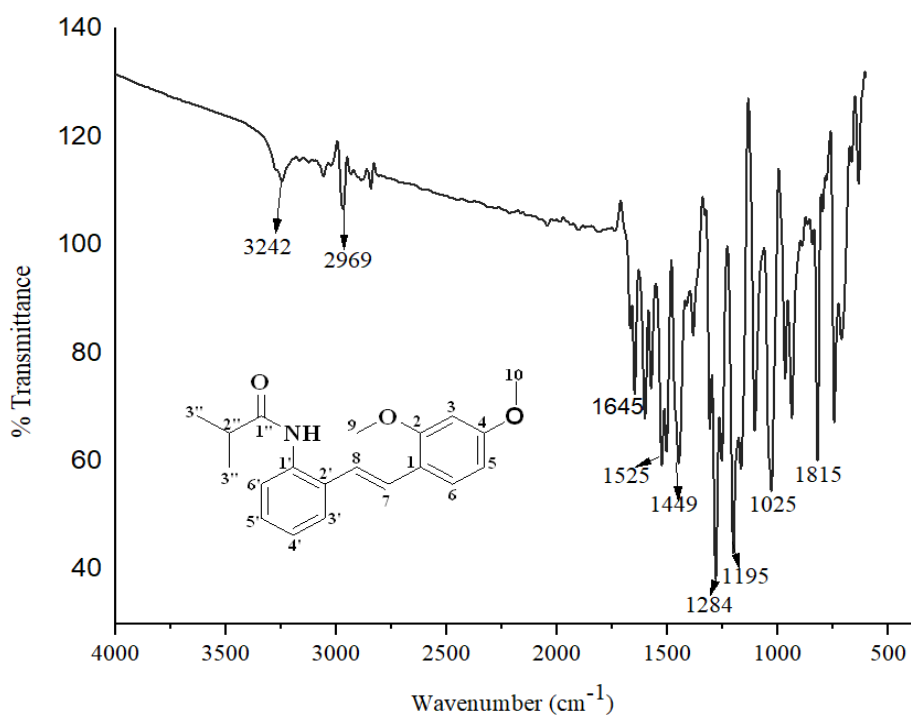


Figure S62: FT-IR spectrum of 6c

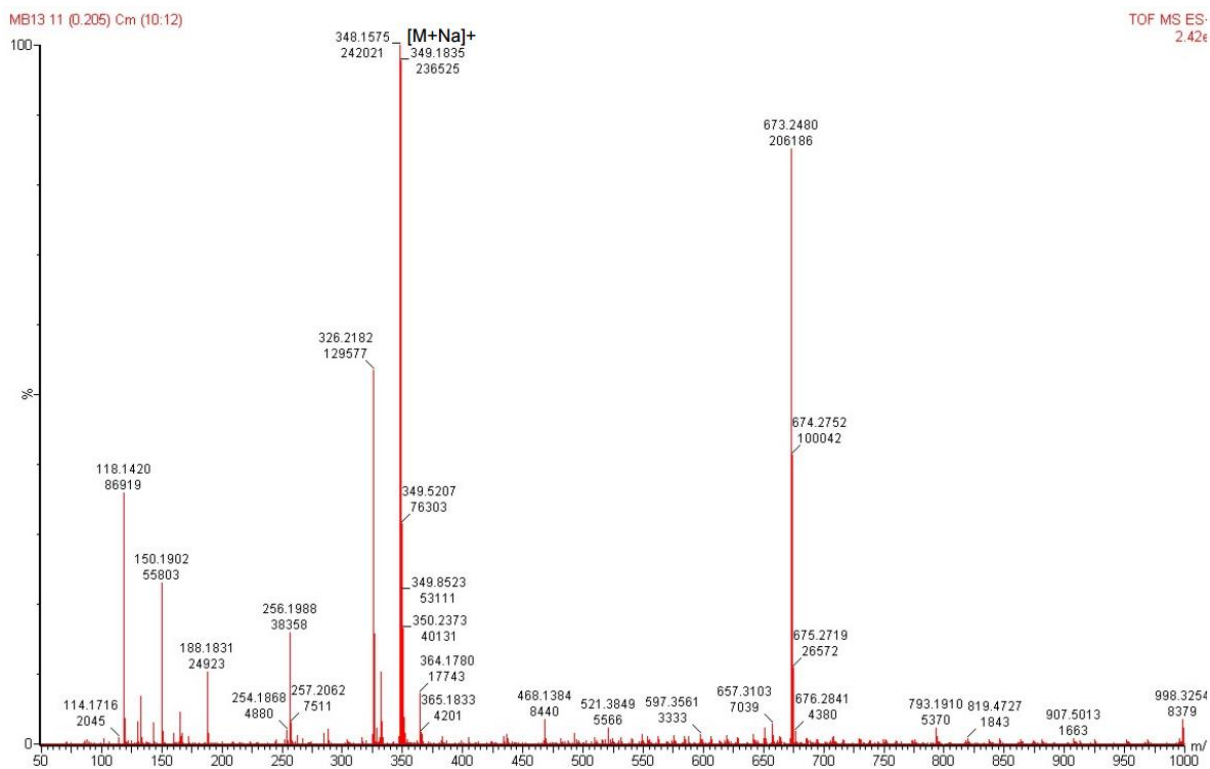


Figure S63: HRMS (+ESI) [M+Na]⁺ of 6c

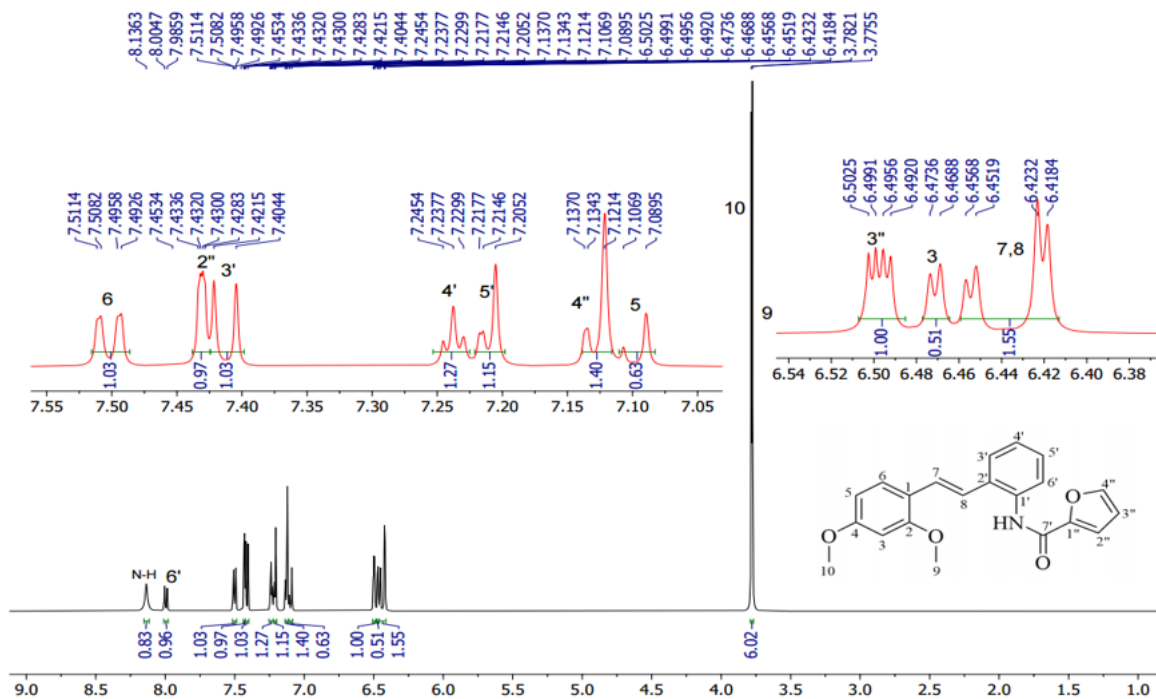


Figure S64: ¹H NMR (500 MHz, CDCl₃) spectrum of 6d

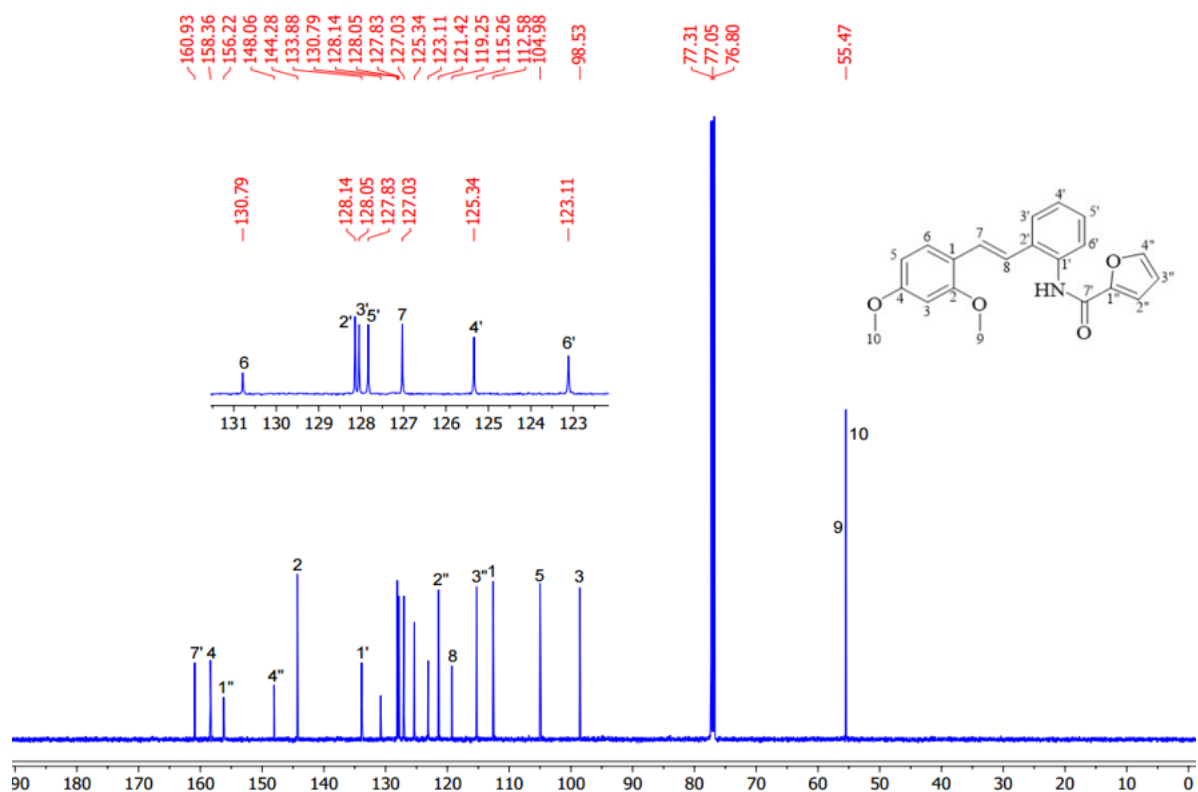


Figure S65: ¹³C-NMR (125 MHz, CDCl₃) spectrum of 6d

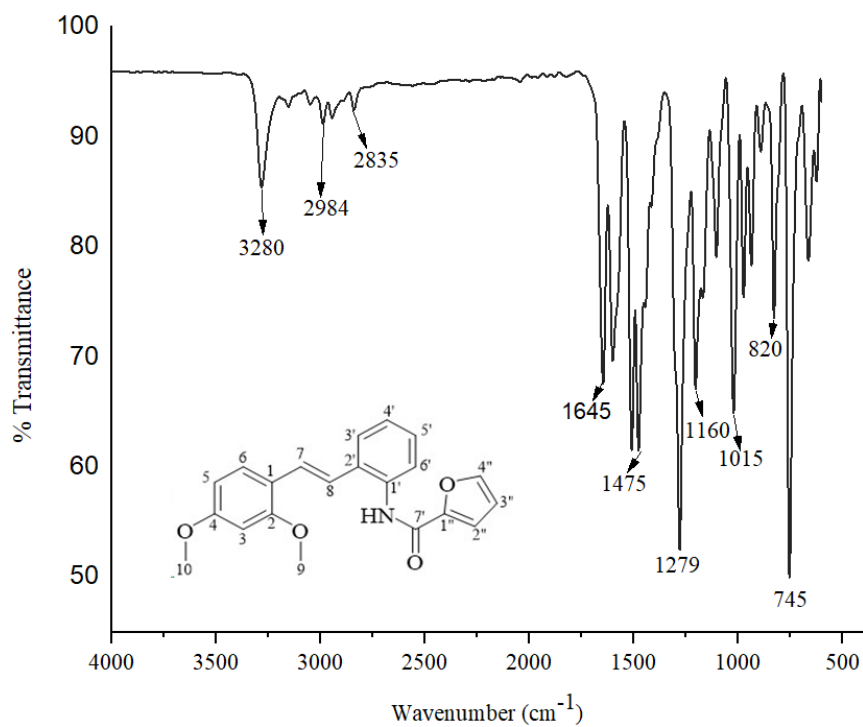


Figure S66: FT-IR spectrum of 6d

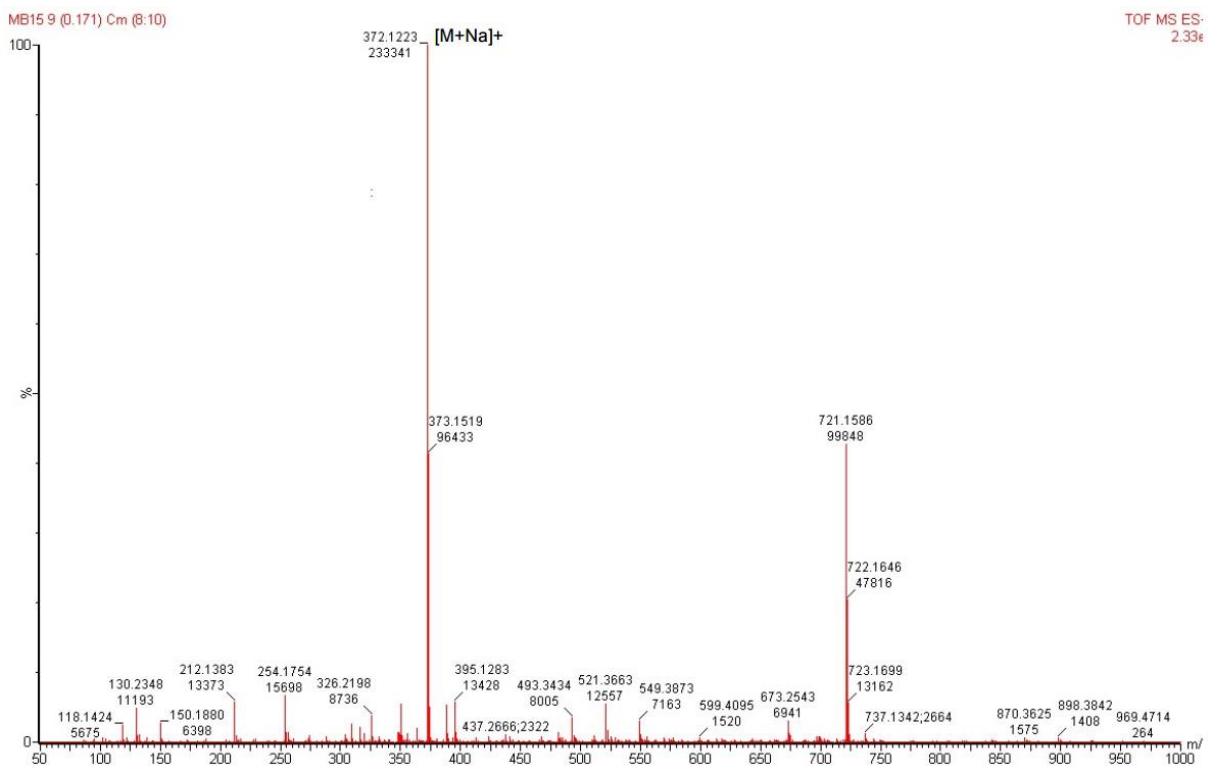


Figure S67: HRMS (+ESI) [M+Na]⁺ of 6d

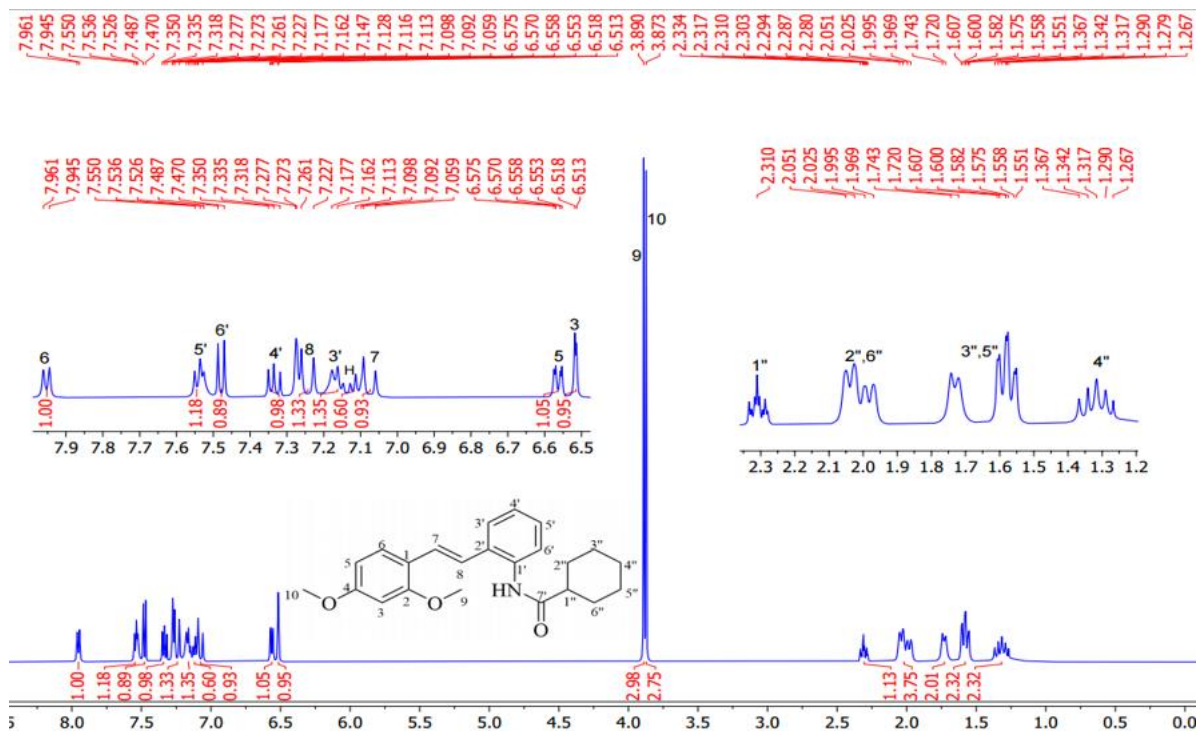


Figure S68: ¹H NMR (500 MHz, CDCl₃) spectrum of 6e

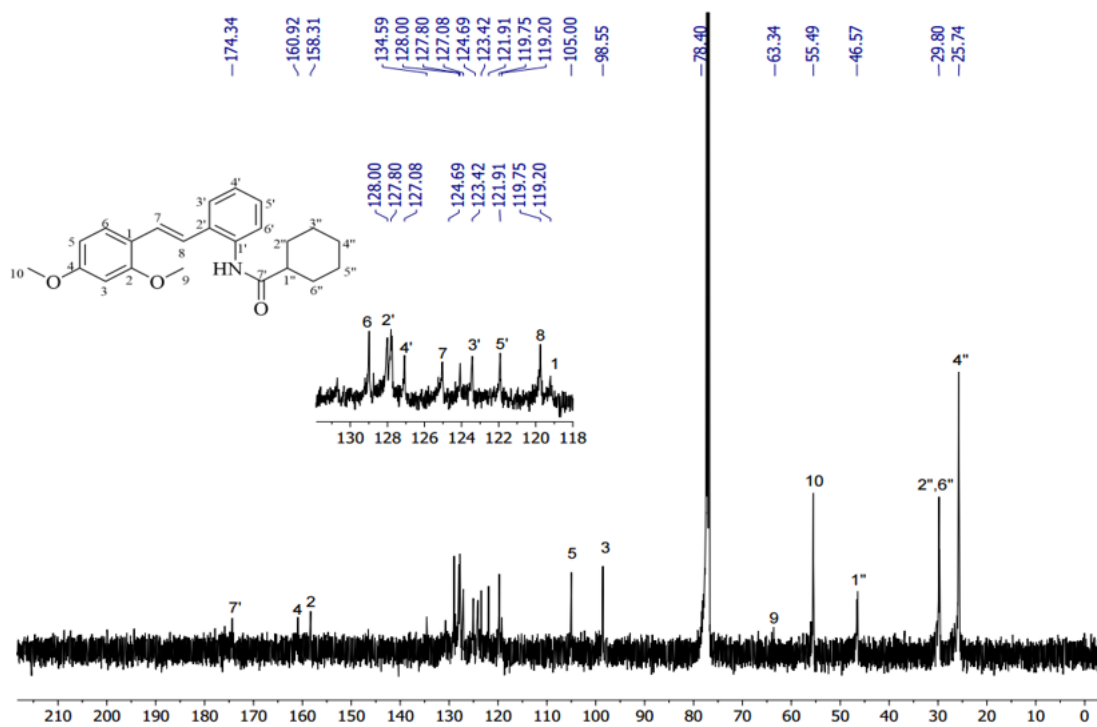


Figure S69: ^{13}C -NMR (125 MHz, CDCl_3) spectrum of **6e**

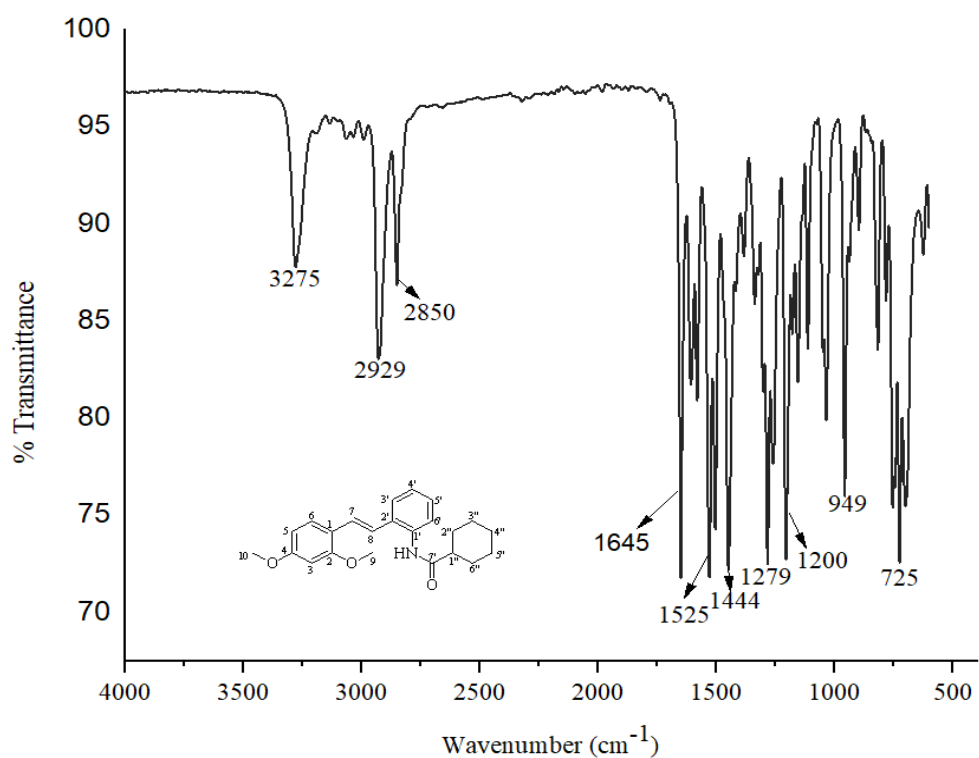


Figure S70: FT-IR spectrum of **6e**

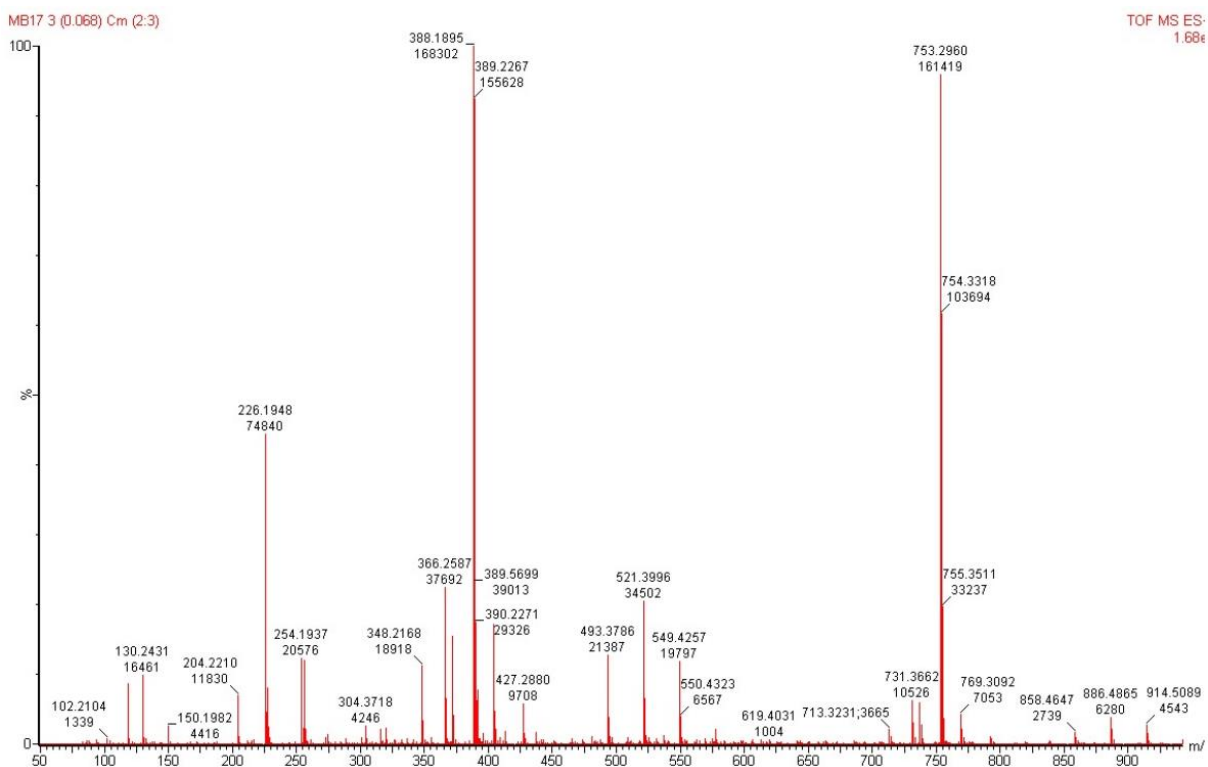


Figure S71: HRMS (+ESI) $[M+Na]^+$ of **6e**

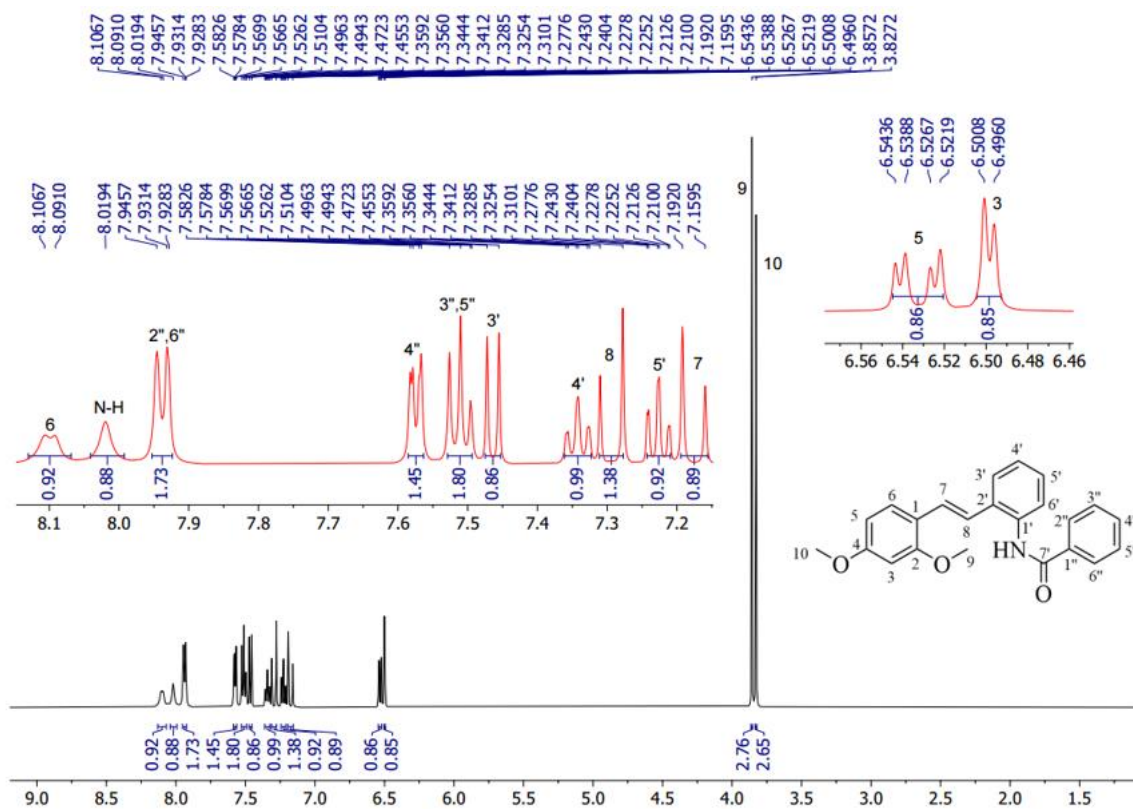


Figure S72: ^1H NMR (500 MHz, CDCl_3) spectrum of **6f**

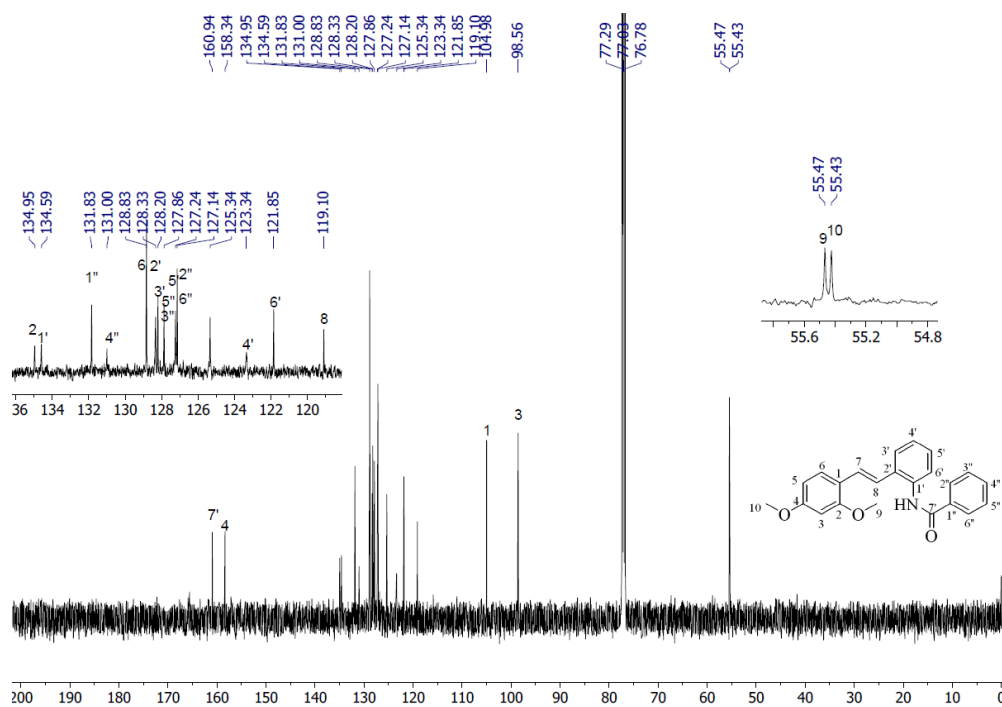


Figure S73: ^{13}C -NMR (125 MHz, CDCl_3) spectrum of 6f

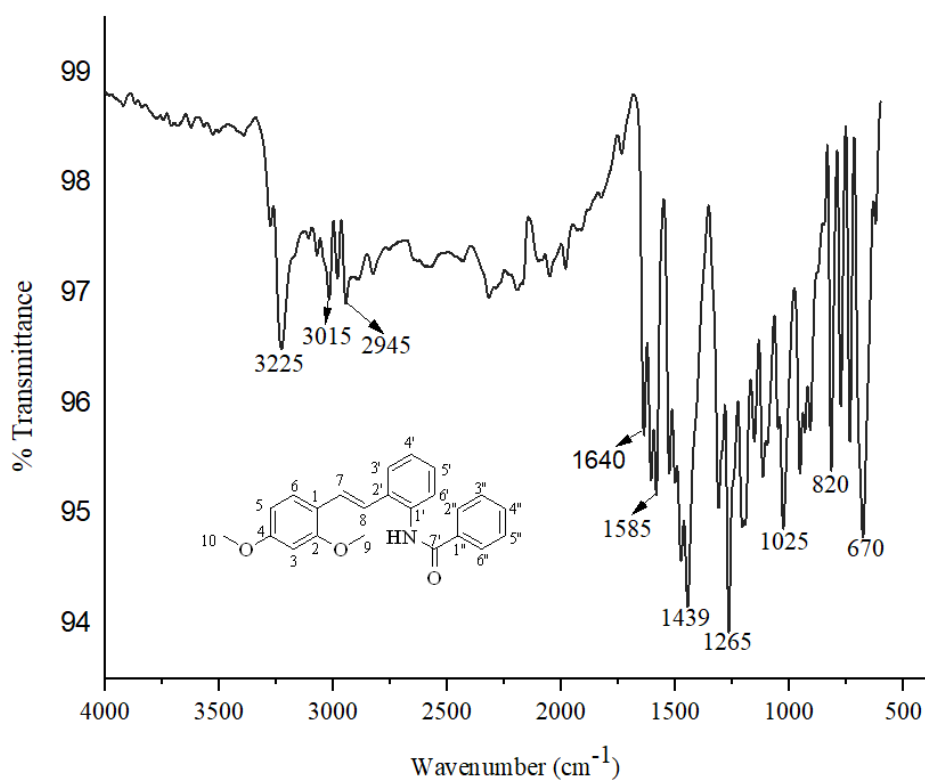


Figure S74: FT-IR spectrum of 6f

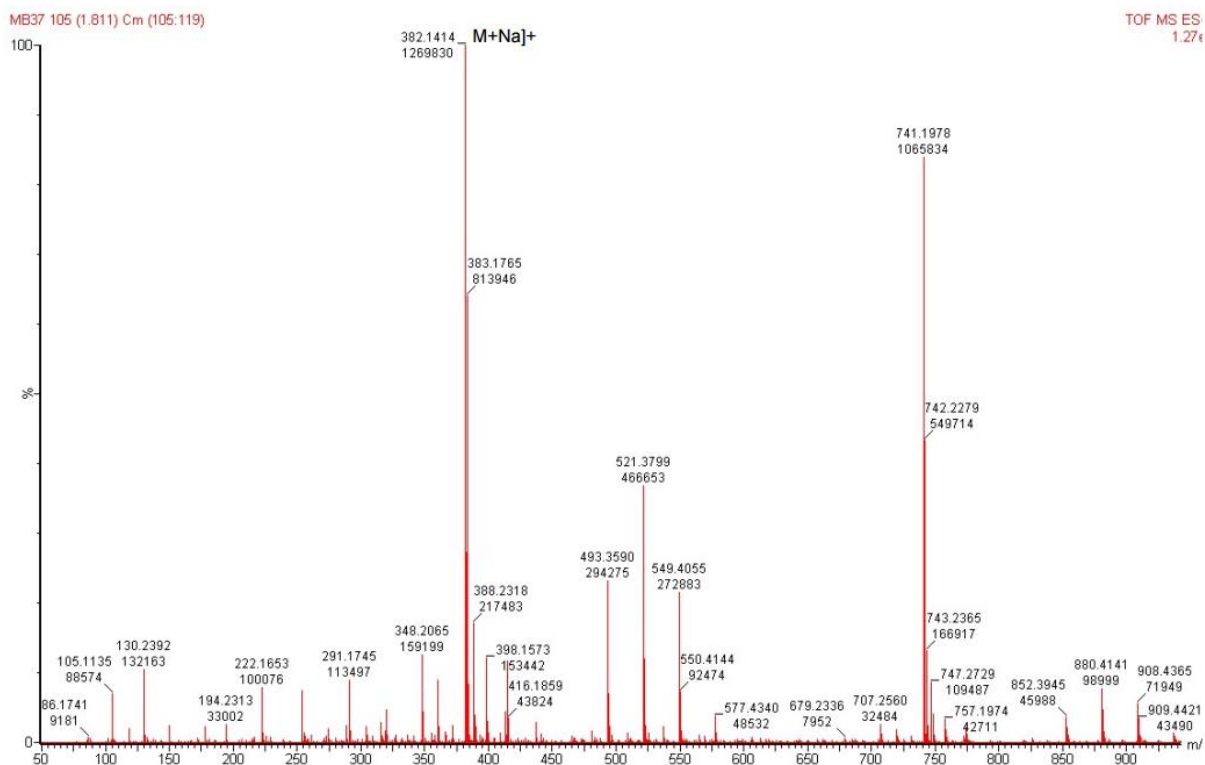


Figure S75: HRMS (+ESI) [M+Na]⁺ of 6f

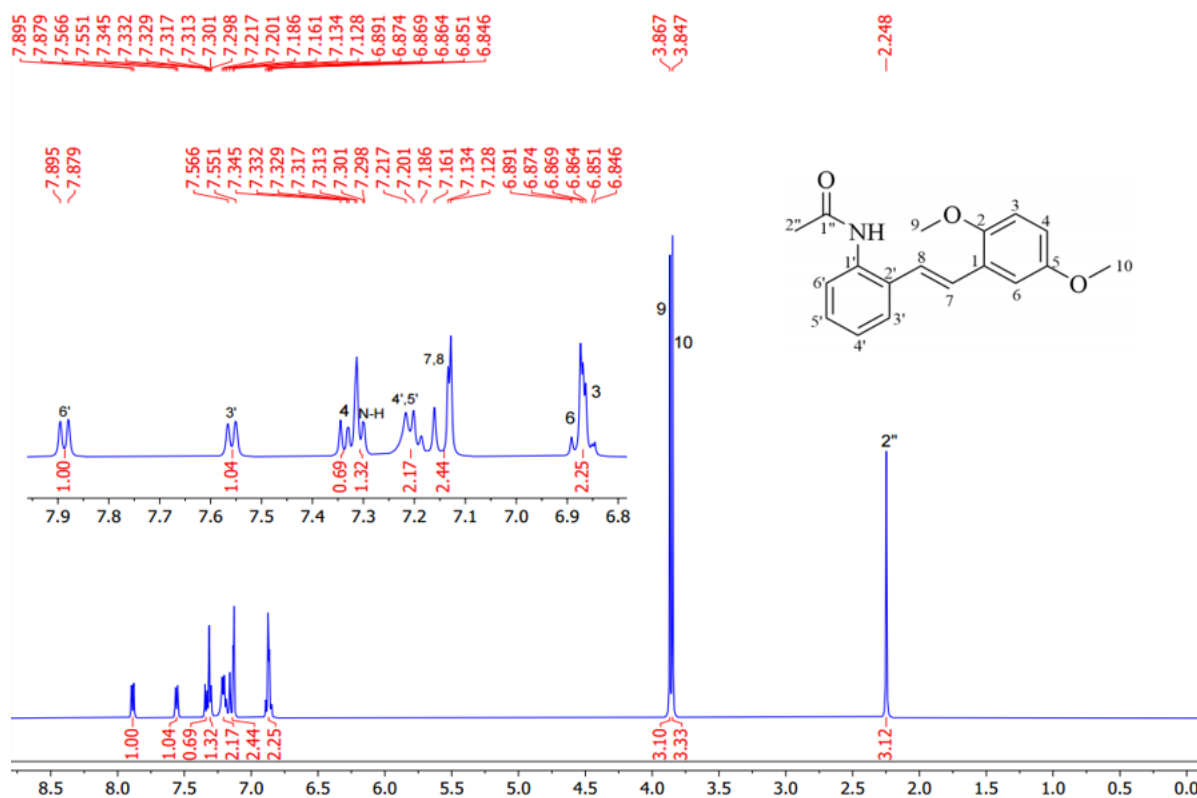


Figure S76: ¹H NMR (500 MHz, CDCl₃) spectrum of 7a

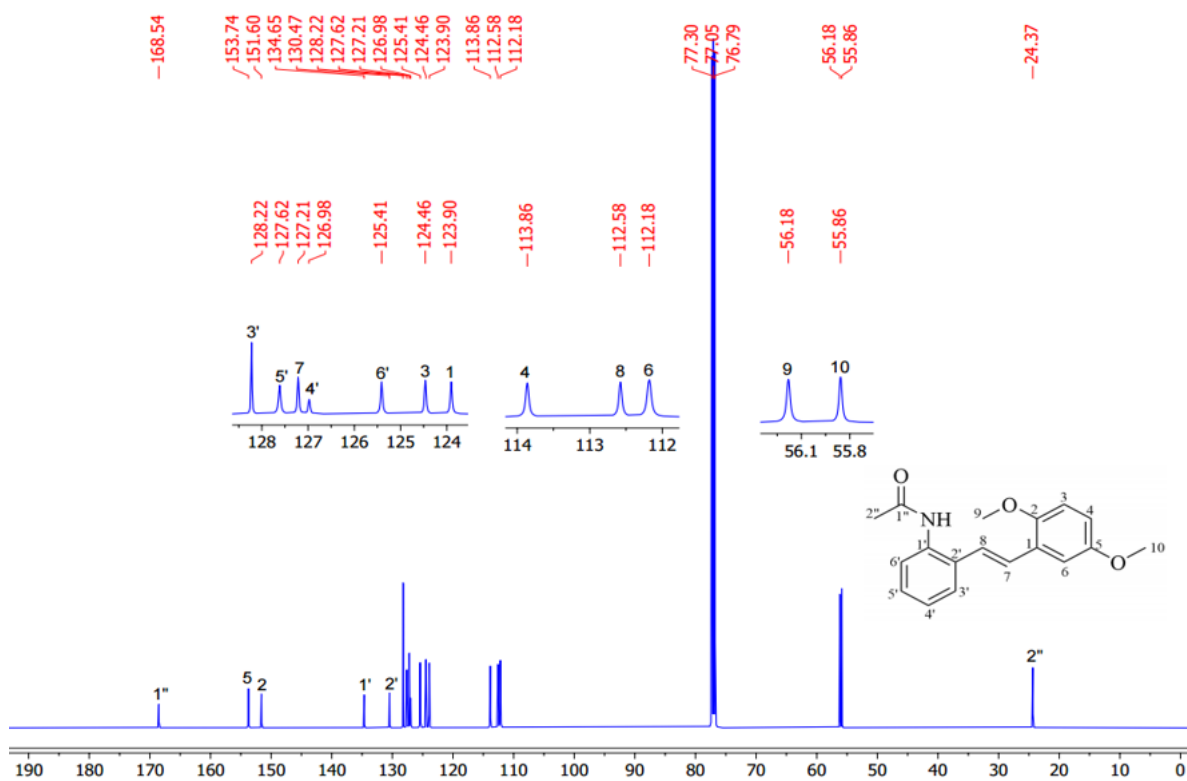


Figure S77: ^{13}C -NMR (125 MHz, CDCl_3) spectrum of 7a

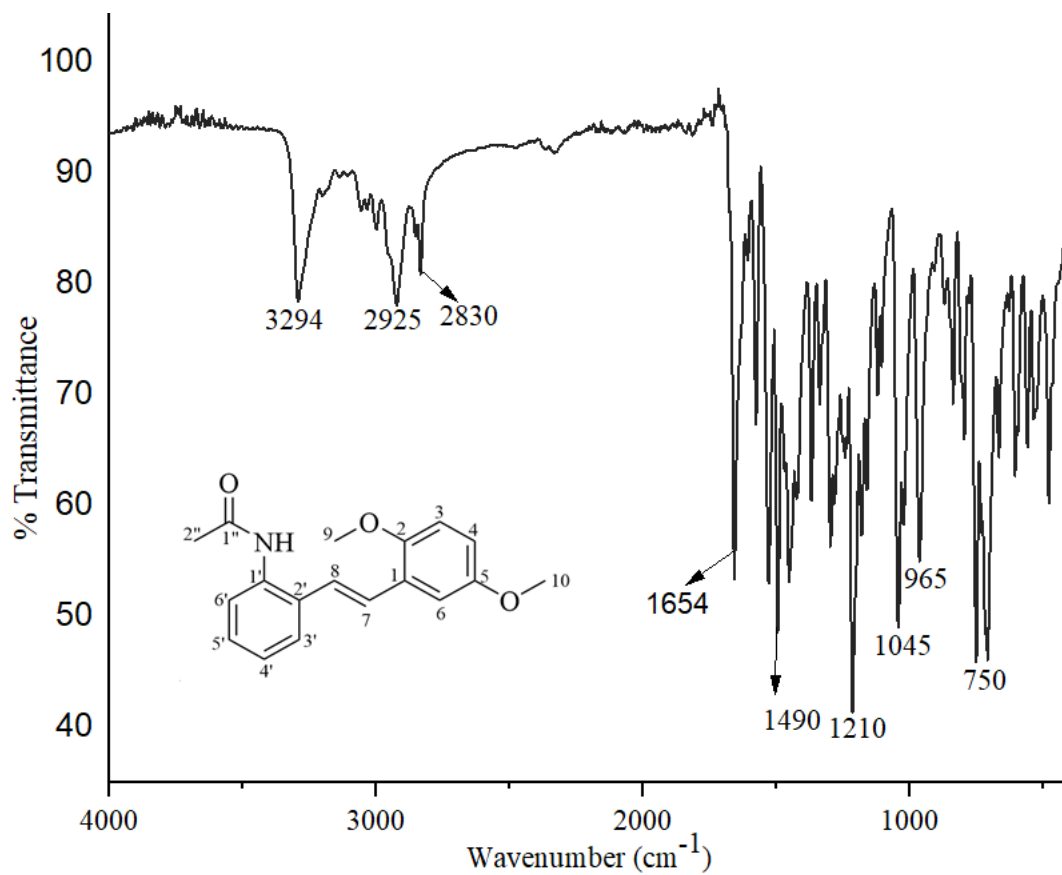


Figure S78: FT-IR spectrum of 7a

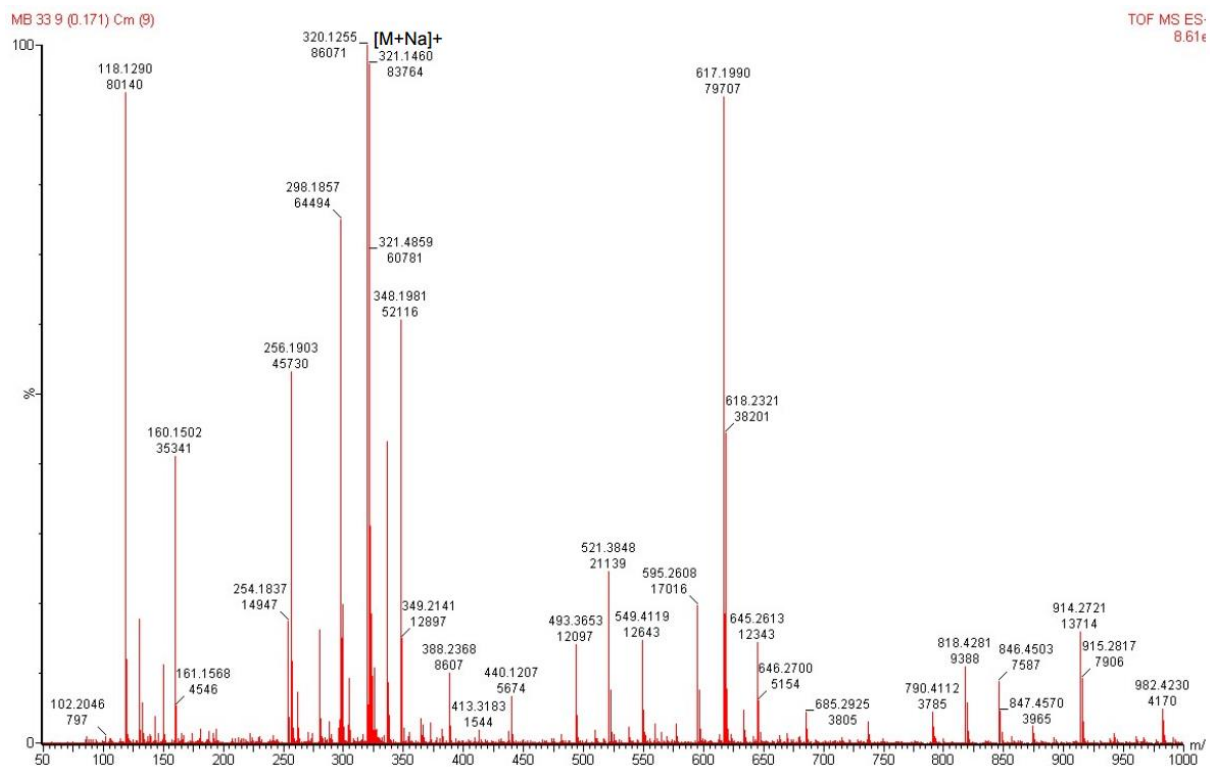


Figure S79: HRMS (+ESI) $[M+Na]^+$ of **7a**

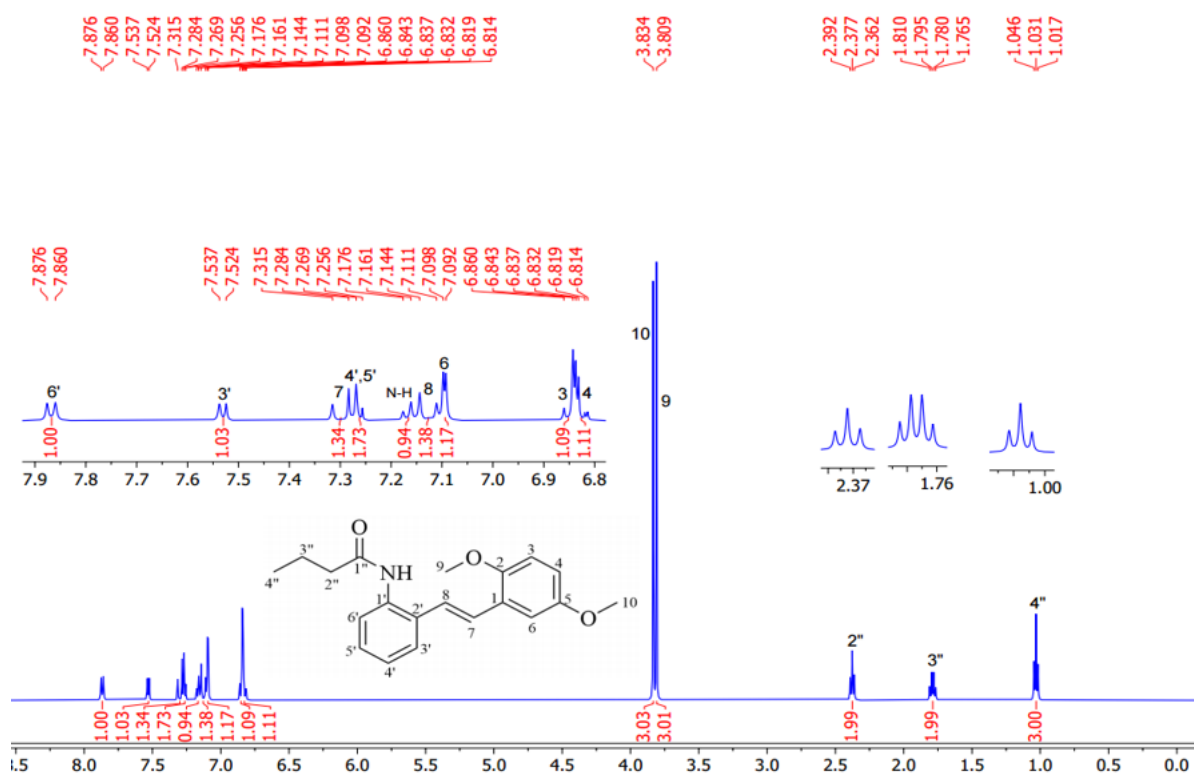


Figure S80: ^1H NMR (500 MHz, CDCl_3) spectrum of **7b**

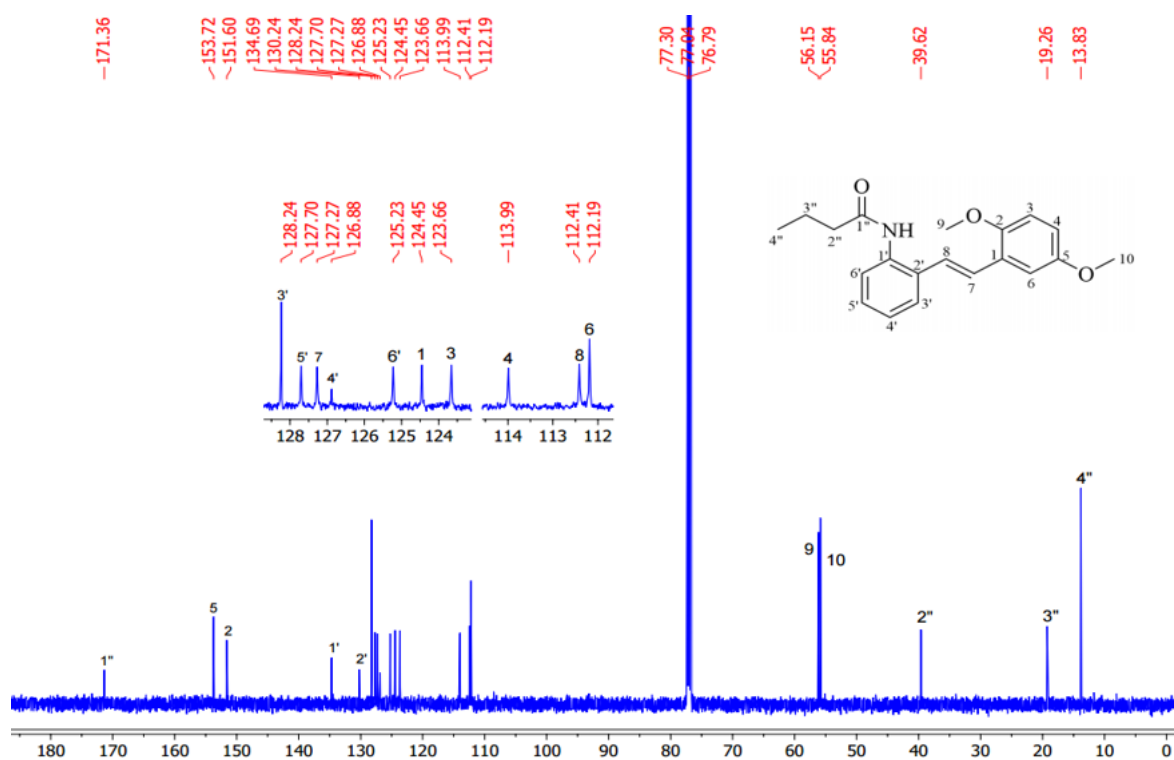


Figure S81: ^{13}C -NMR (125 MHz, CDCl_3) spectrum of **7b**

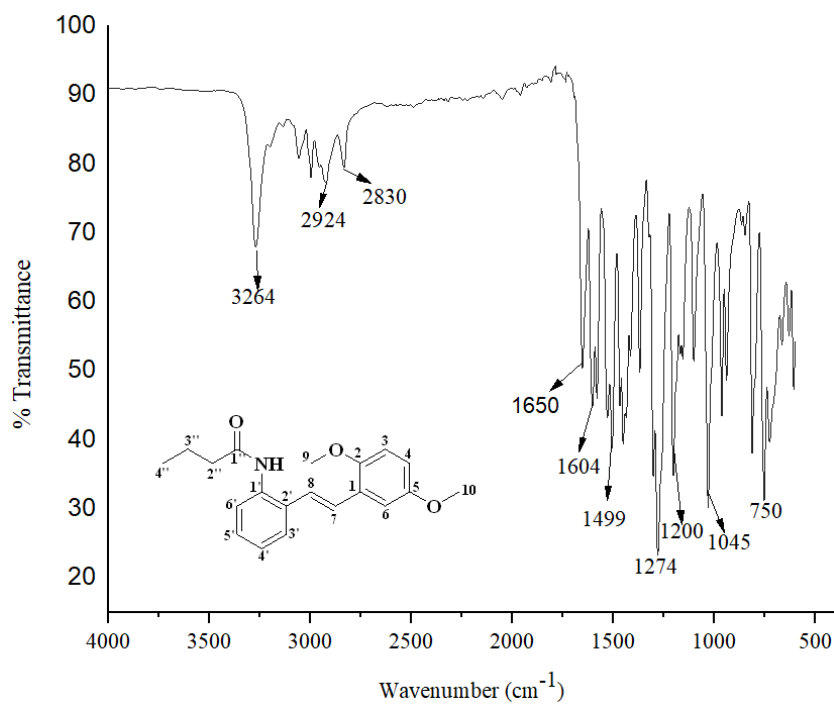


Figure S82: FT-IR spectrum of **7b**

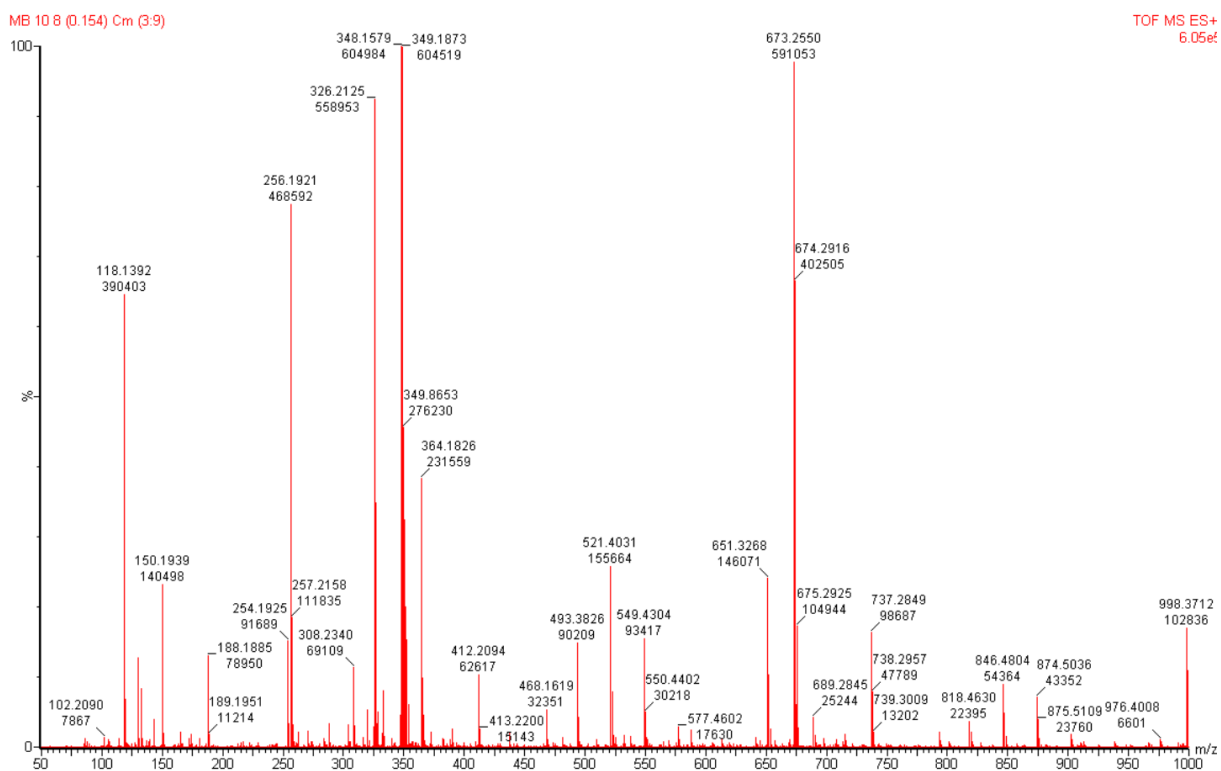


Figure S83: HRMS (+ESI) $[M+Na]^+$ of 7b

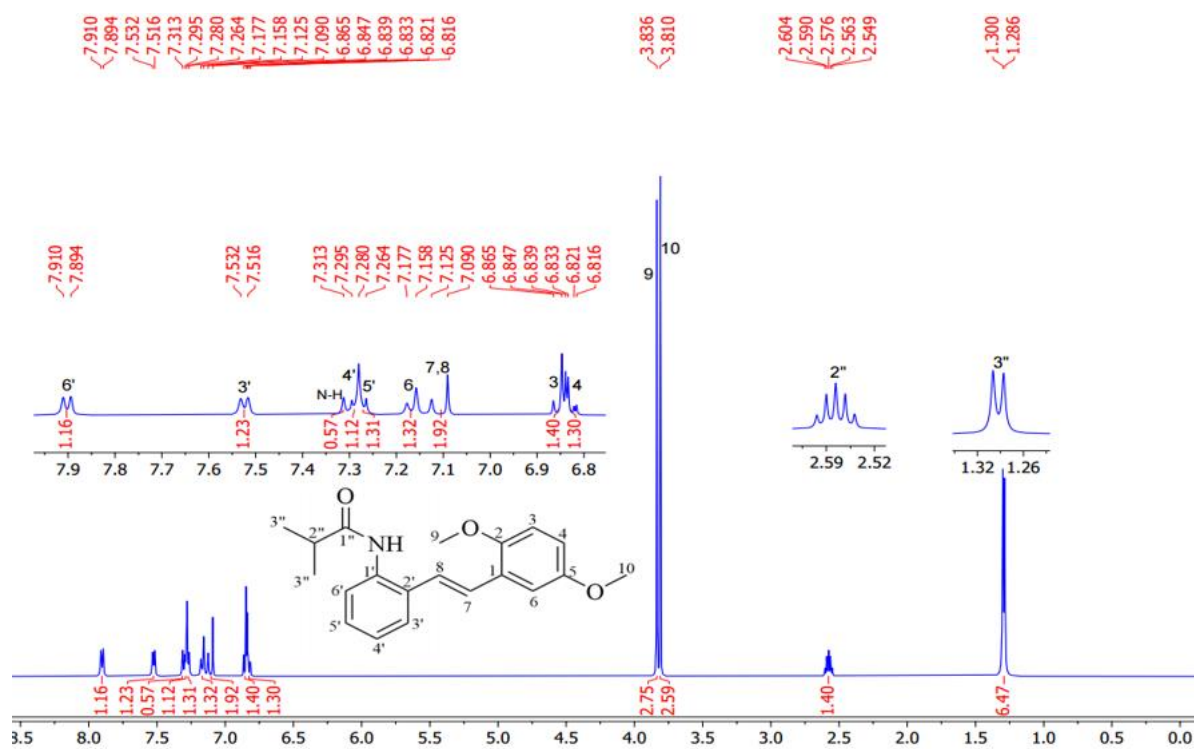


Figure S84: ^1H NMR (500 MHz, CDCl_3) spectrum of 7c

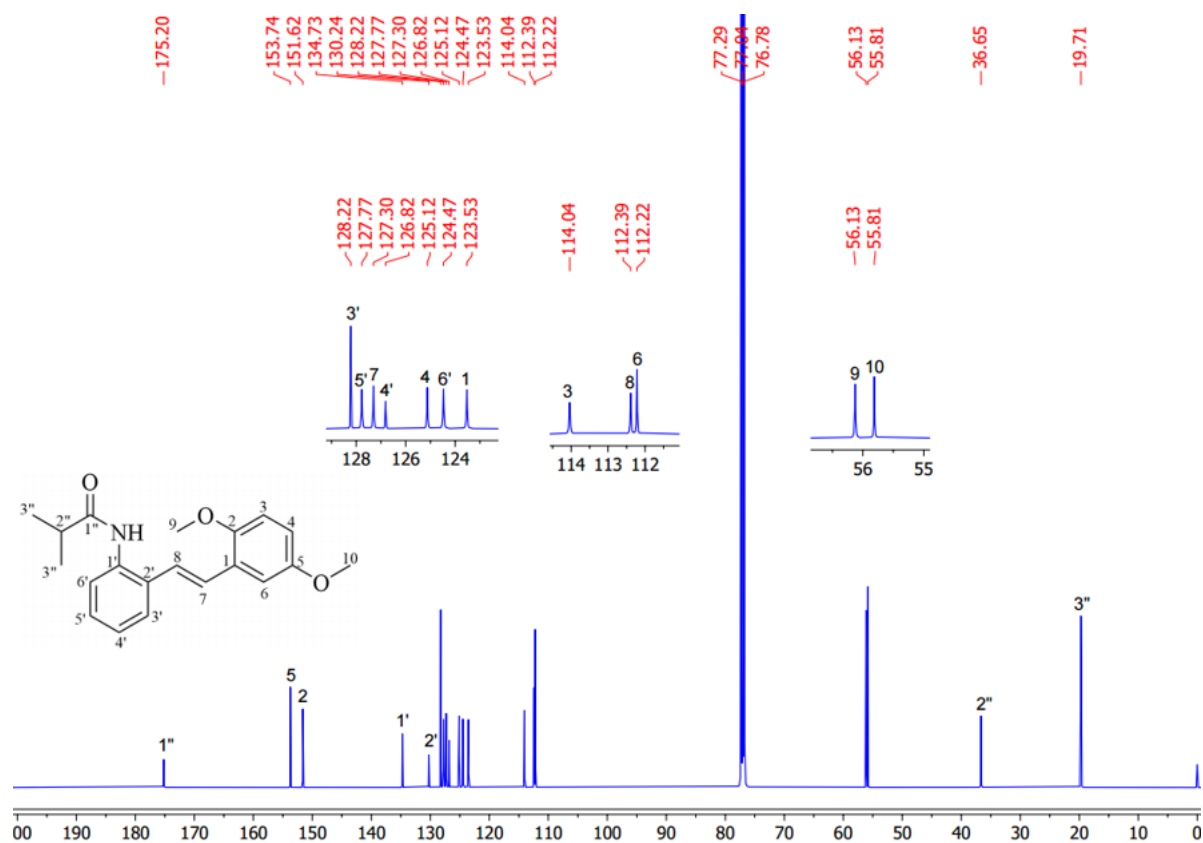


Figure S85: ^{13}C -NMR (125 MHz, CDCl_3) spectrum of 7c

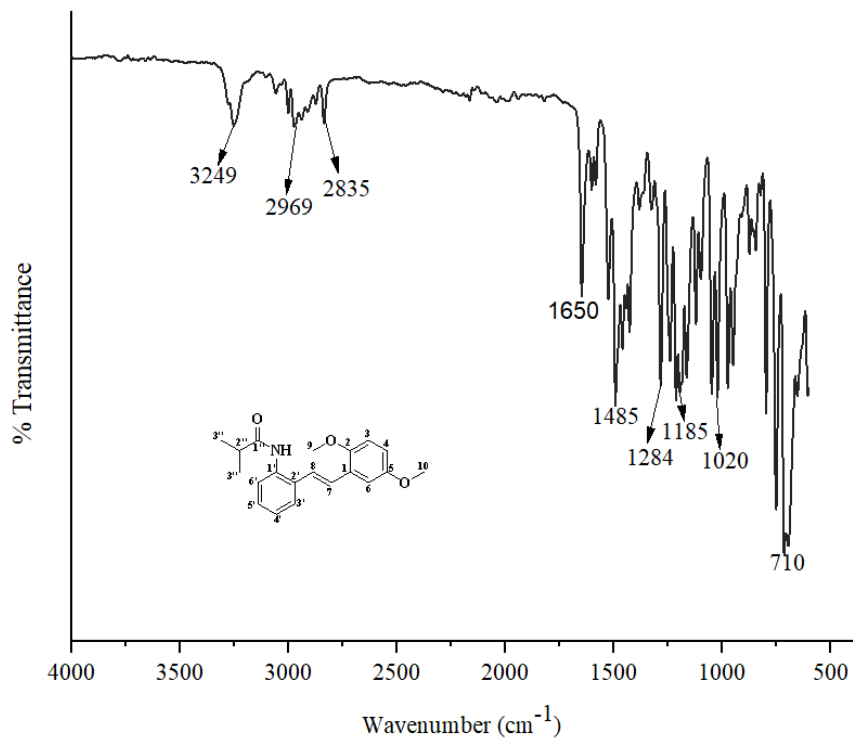


Figure S86: FT-IR spectrum of 7c

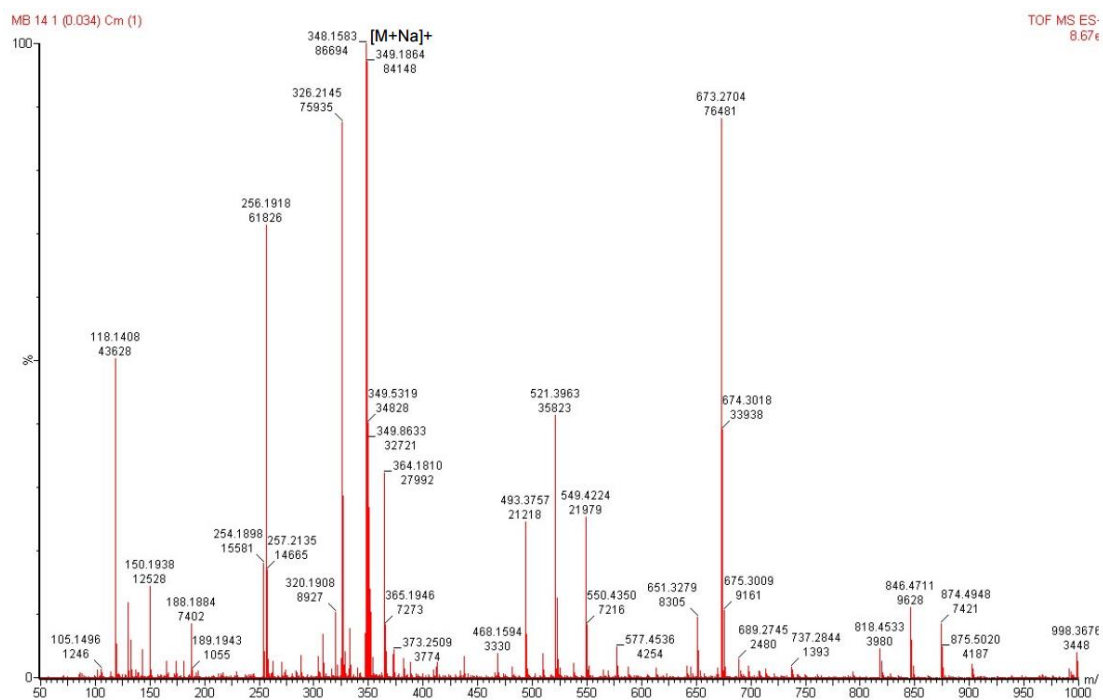


Figure S87: HRMS (+ESI) [M+Na]⁺ of 7c

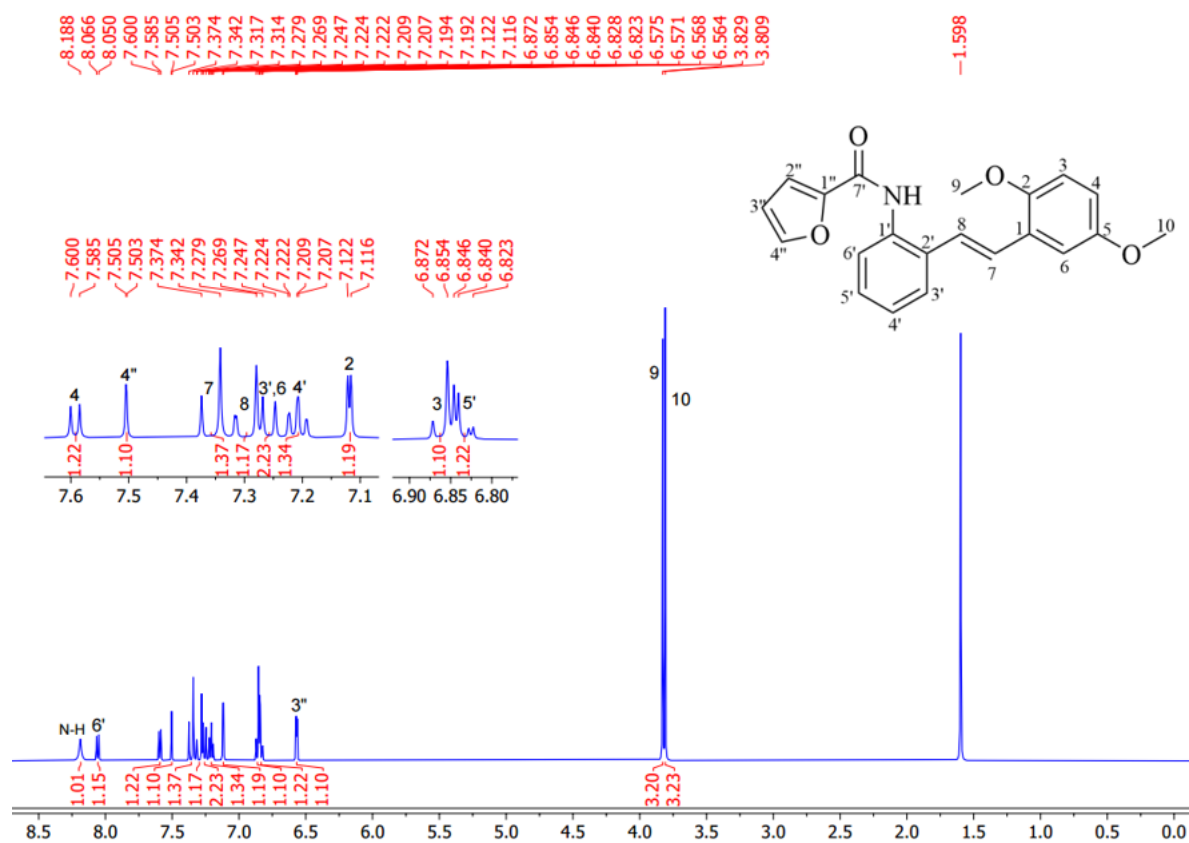


Figure S88: ¹H NMR (500 MHz, CDCl₃) spectrum of 7d

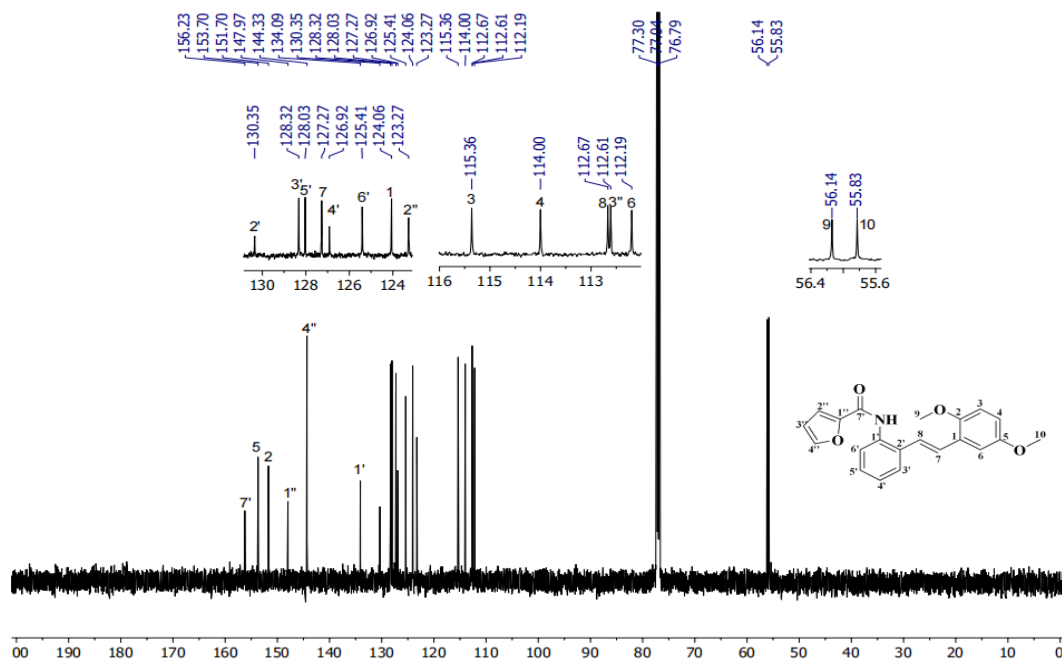


Figure S89: ^{13}C -NMR (125 MHz, CDCl_3) spectrum of **7d**

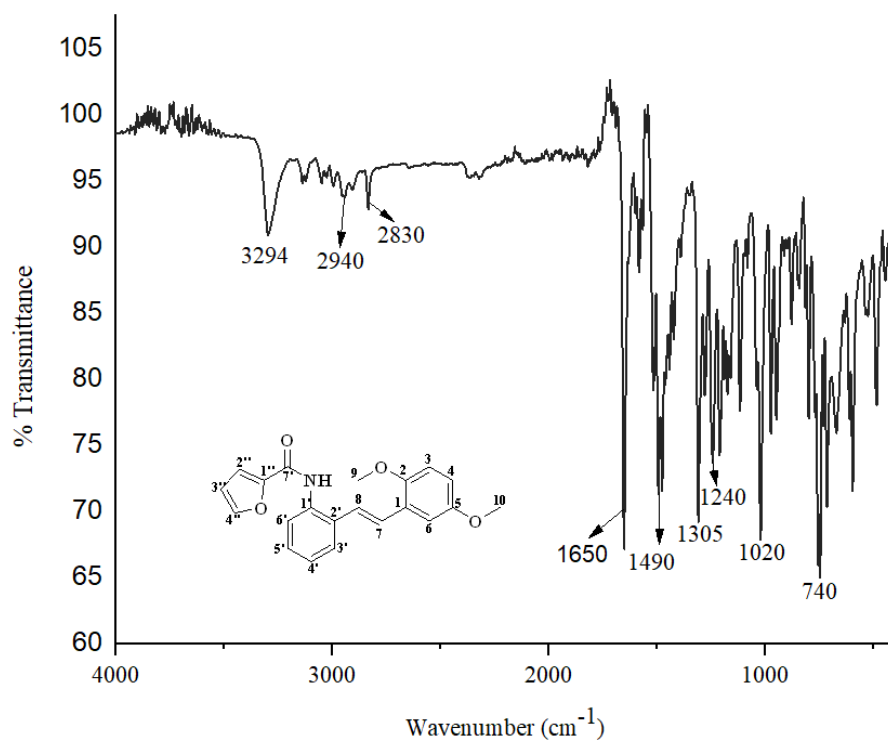


Figure S90: FT-IR spectrum of **7d**

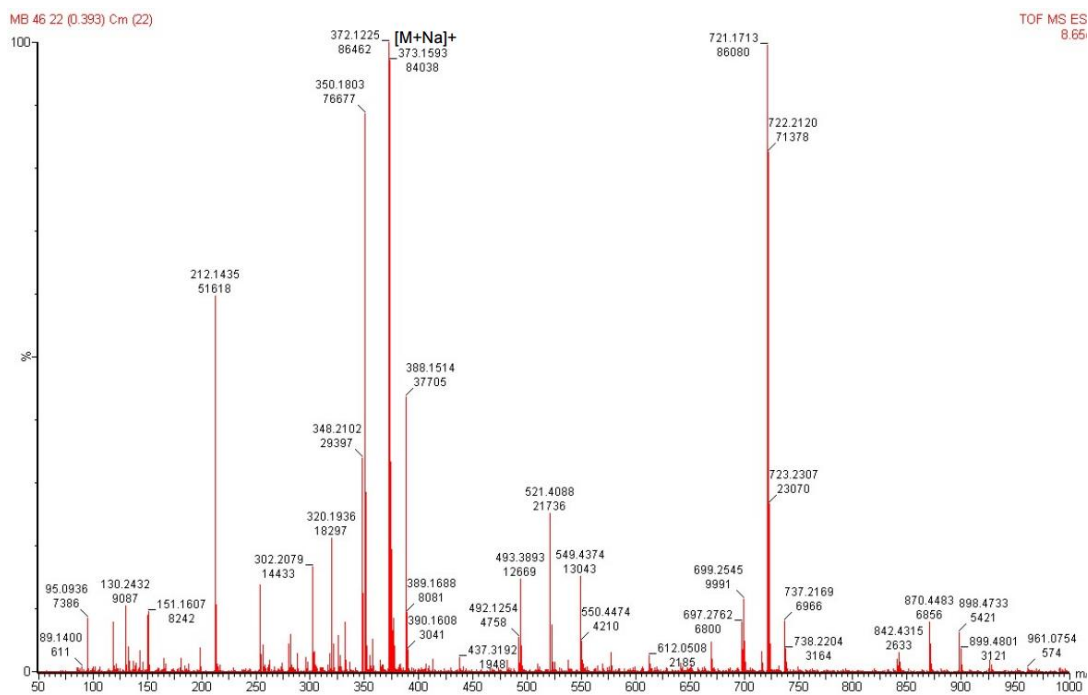


Figure S91: HRMS (+ESI) [M+Na]⁺ of 7d

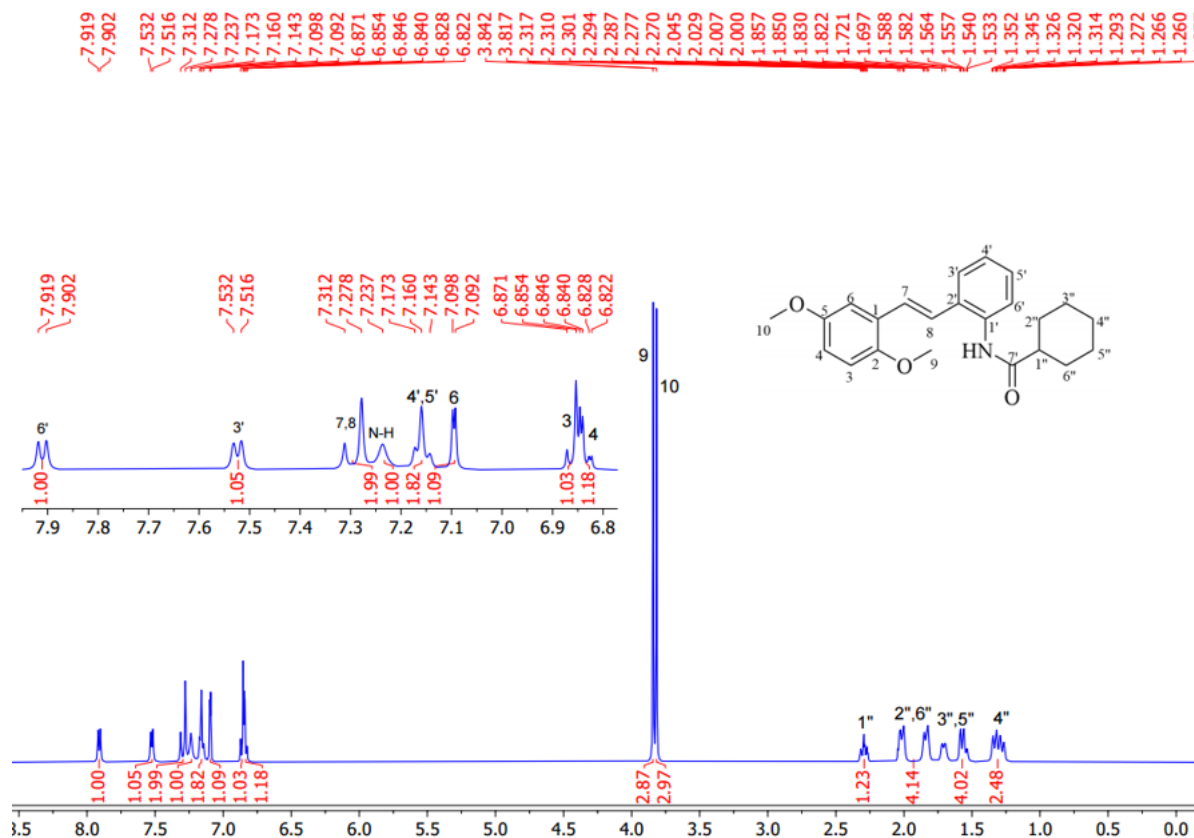
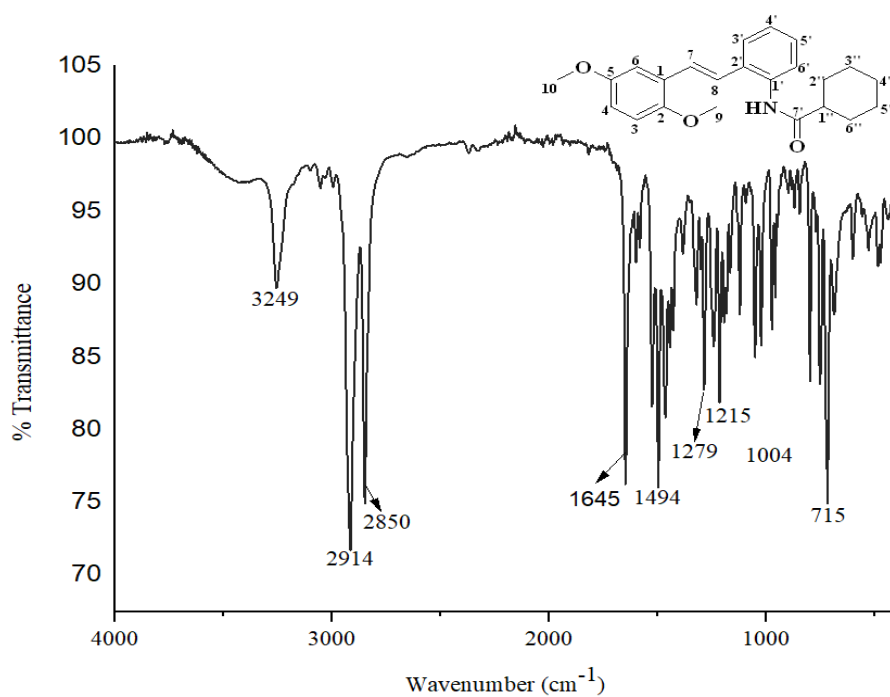
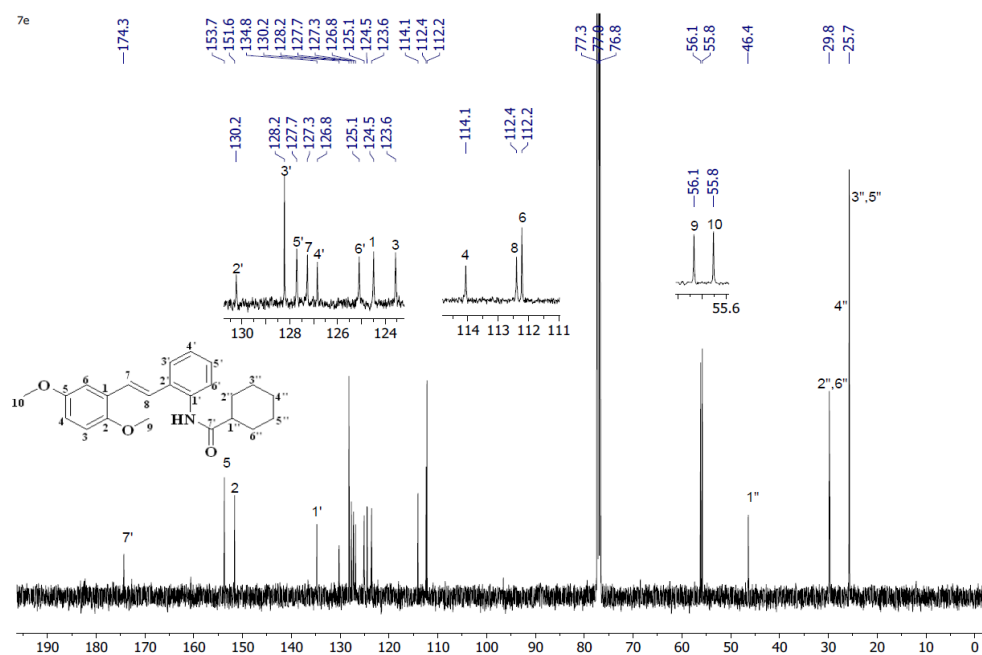


Figure S92: ¹H NMR (500 MHz, CDCl₃) spectrum 7e



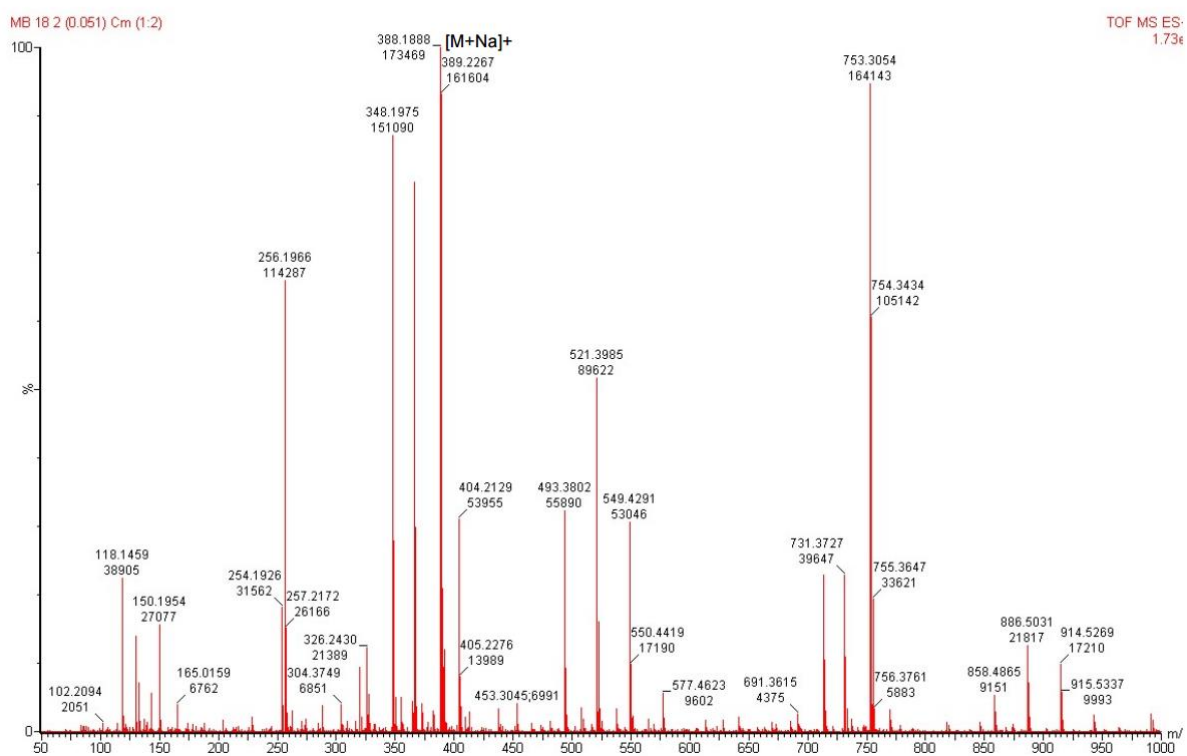


Figure S95: HRMS (+ESI) $[M+Na]^+$ of **7e**

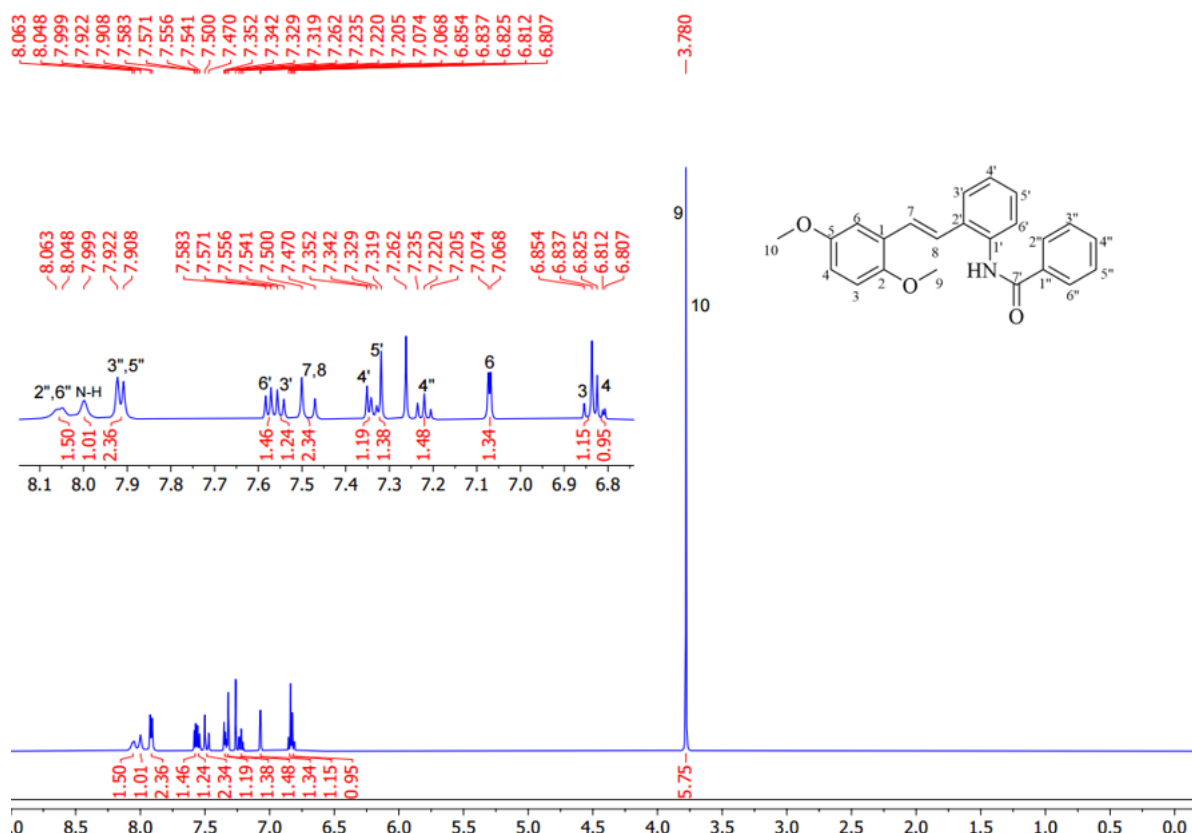


Figure S96: ^1H NMR (500 MHz, CDCl_3) spectrum of **7f**

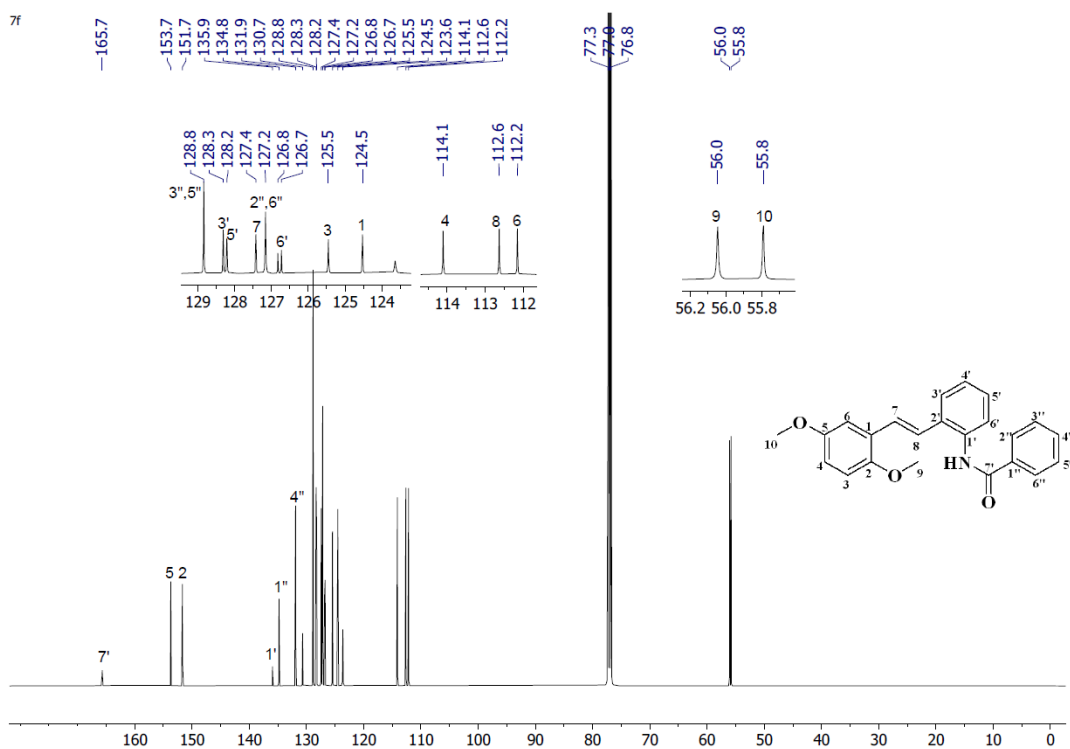


Figure S97: ^{13}C -NMR (125 MHz, CDCl_3) spectrum of **7f**

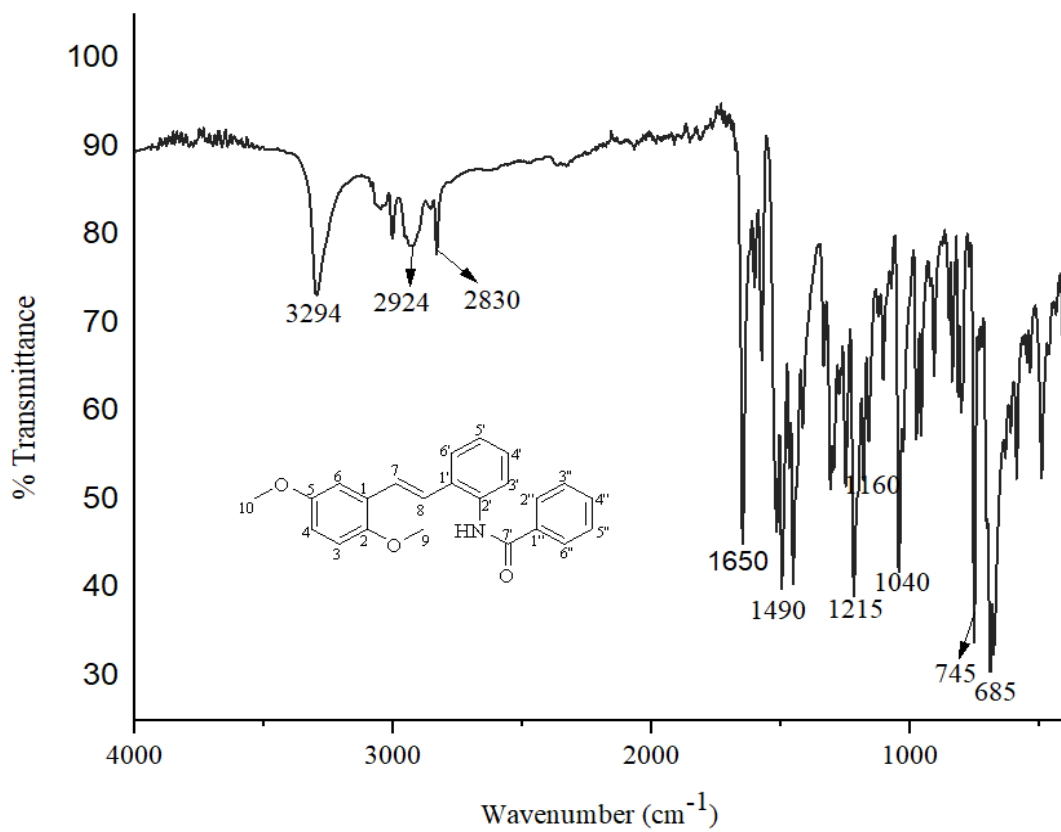


Figure S98: FT-IR spectrum of **7f**

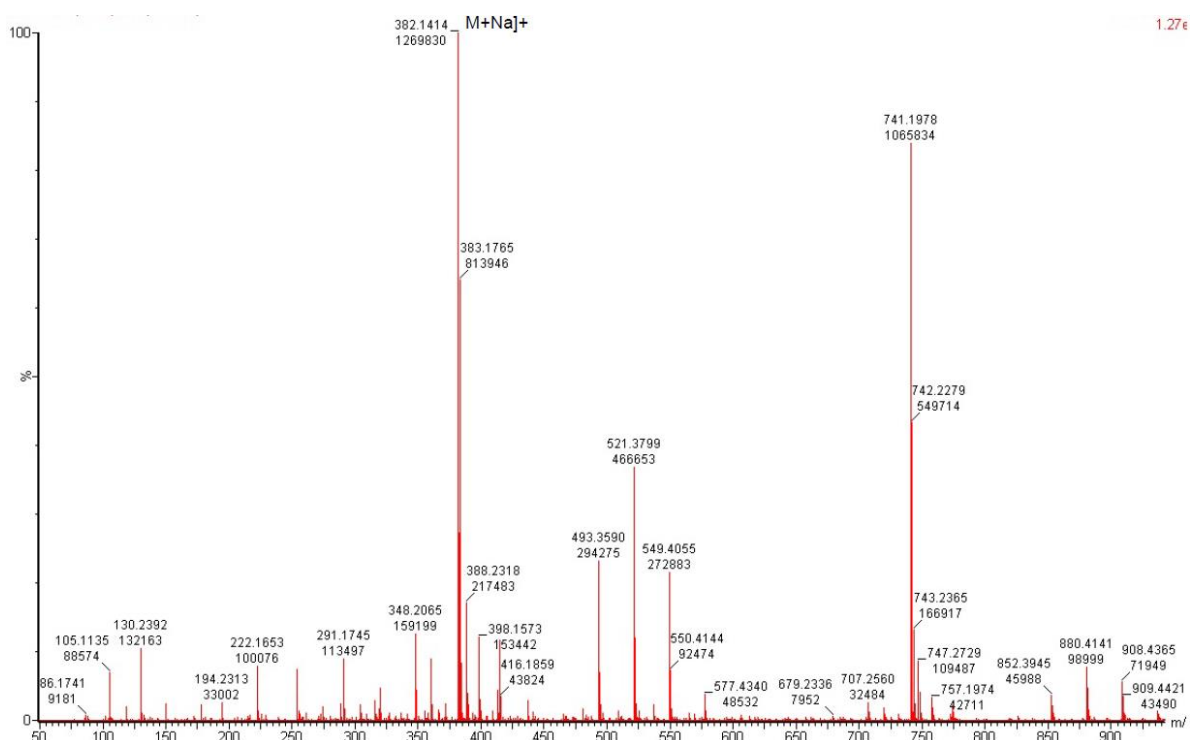


Figure S99: HRMS (+ESI) $[M+Na]^+$ of **7f**

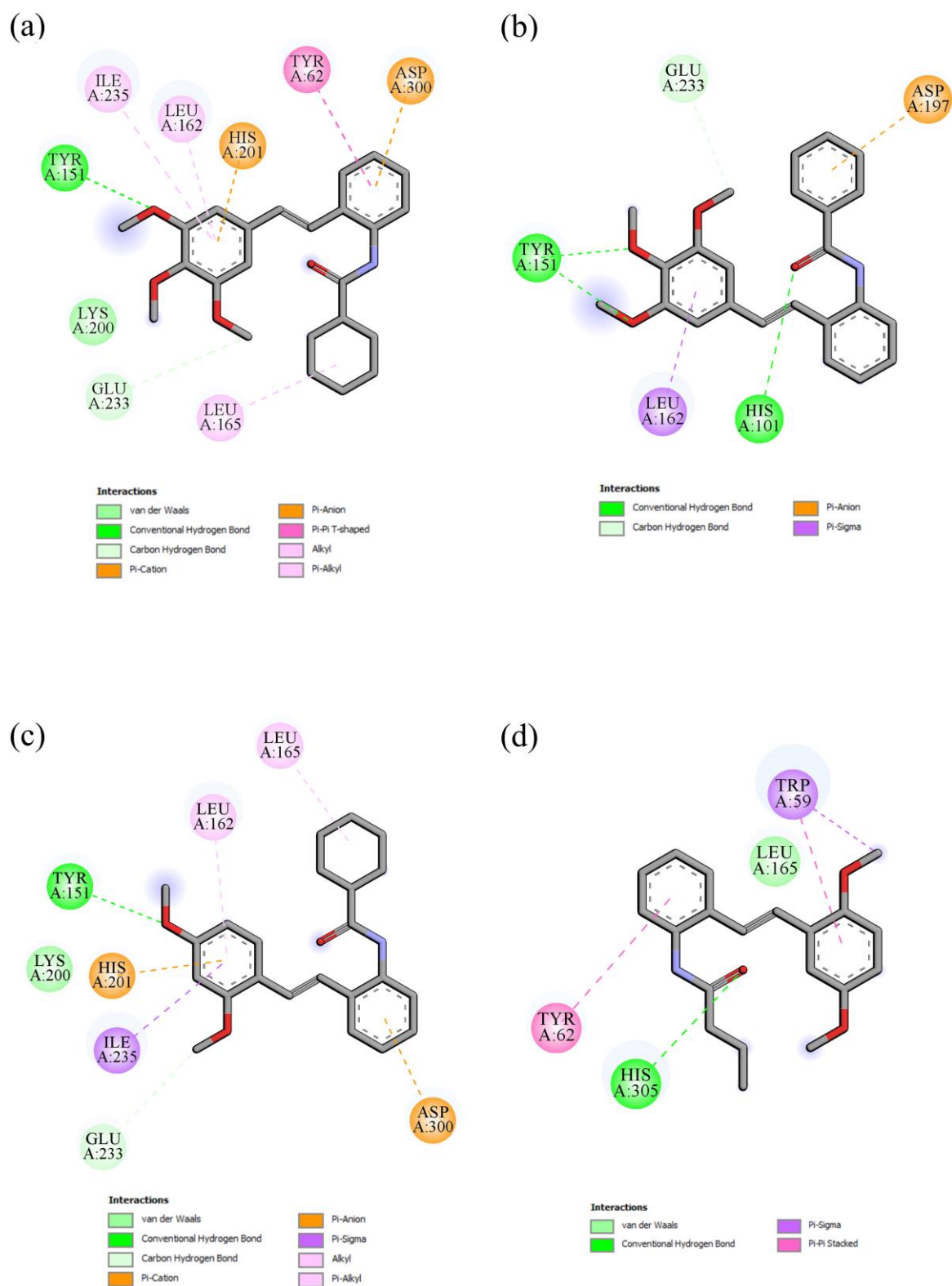


Figure S100: 2D structure of Docking poses of compounds **5e**, **5f**, **6e** and **7b** (a, b, c and d) docked within the human pancreatic α -amylase binding site