Electronic Supplementary Material (ESI) for Green Chemistry

"On Water" Direct Pd-Catalysed C-H Arylation of Thiazolo[5,4-*d*]pyrimidine Derivatives

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General Information: The reactions were monitored by TLC carried out on silica gel (F_{254}) by using UV light as visualizant agent. ^{1}H and ^{13}C NMR spectra were collected on BRUKER AV-300 (300MHz) spectrometer using $CDCl_3$ or DMSO as solvent. Chemical shifts of 1H NMR were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ = 0.00 ppm) with the solvent resonance as an internal standard ($CDCl_3$: δ = 7.26 ppm; DMSO-d_6: δ = 2.50 ppm). Data are reported as follows: chemical shift in ppm (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constant (Hz), and integration. Chemical shifts of ^{13}C NMR were reported in ppm with the solvent as the internal standard ($CDCl_3$: δ = 77.0 ppm; DMSO-d_6: δ = 40.5 ppm). Infrared spectra (IR) were taken on a Thermo Scientific iS10 FT/IR spectrometer using potassium bromide as pellets; absorptions are reported in reciprocal centimeters. High Resolution Mass measurement was performed on Agilent QTOF 6520 mass spectrometer with electron spray ionization (ESI) as the ion source. ESI mass spectrometry was carried out on Waters Q-Tof micro™. $Pd(PPh_3)_4$ was stored in refrigerator. Reactions were performed in 10 ml microwave tube. 5-methyl-N-phenylthiazolo[5,4-d]pyrimidin-7-amine, 5-methyl-7-phenylthiazolo[5,4-d]pyrimidin, 7-(4-methoxyphenyl)-5-methylthiazolo[5,4-d]pyrimidine were synthesized according to literature procedure.

Materials: $Pd(PPh_3)_4$, $Pd(dppf)Cl_2$, $PdCl_2$ and $PdOAc_2$ were used as received. All aryl iodides, silver carbonate and triphenylphosphine were stored in sealed, cool and dry condition. Powdered K_3PO_4, K_2CO_3, Cs_2CO_3 and CuI were kept in desiccators. Solvents were dried by refluxing for at least 24 h over CaH_2 (DMF), or phosphorus pentoxide (acetonitrile), and freshly distilled prior to use.

The following starting materials were obtained from commercial sources and were used without further purification: Iodobenzene, 4-iodotoluene, 1-chloro-4-iodobenzene, 4-iodobenzotrifluoride, 4-iodofluorobenzene, 4-iodoanisole, 2-iodothiophene, paraiodoaniline, benzoboric acid, 4-methoxybenzeneboronic acid, aniline.

Synthesis of starting materials

5-methyl-N-phenylthiazolo[5,4-*d*]pyrimidin-7-amine 3. A solution of

7-chloro-2-methylthiazolo[5,4-*d*]pyrimidine **1** (74.3 mg, 0.4mmol) in isopropanol and water (0.5ml+0.5ml) was added ith aniline (40μl, 0.44mmol)and concentrated hydrochloric acid (50μl)[1]. The resulting suspension was heated to 85 ^{o}C for seven hours, diluted with saturated sodium bicarbonate (10ml), and extracted with ethyl acetate (3 × 10 mL). Organic phase was dried over $MgSO_4$ and filtrate was concentrated under vacuum. The residue was washed with mixture of light petroleum and dichloromethane (6ml, V/V = 2:1). The target compound (100mg, 52%) was obtained when the resulting residue was dried. This compound is known[2]. ^{1}H NMR (300MHz, DMSO-d_6, ppm) δ 13.13 (s, 1H), 8.32 (s, 1H), 7.60 (d, *J* = 7.77 Hz, 2H), 7.30 (t, *J* = 8.1 Hz, 2H), 7.00 (t, *J* = 7.29 Hz, 1H), 2.31 (s, 3H).

General procedure for synthesis of 4-(5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)morpholine 6. Morpholine (0.81 ml) was added to the ethanol (10 ml) solution of 7-chloro-2-methylthiazolo[5,4-*d*]pyrimidine **1** (853mg, 4.59mmol)[3]. The resulting solution was stirred for 12 h under room temperature. When reaction was completed, the solution was evaporated and extracted with ethyl acetate and water, and then the residual was chromatographed on a silica gel column (ethyl acetate light petroleum 1:8). Evaporation and drying of the product containing fractions afforded the 4-(5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)morpholine **6** as white solid. ^{1}H NMR (300MHz, $CDCl_3$, ppm) δ 8.32 (s, 1H), 8.66 (s, 1H), 4.38 (s, 4H), 3.84 (s, 4H), 2.59 (s, 3H).

General procedure for synthesis of 7-arylsubstituted thiazolo[5,4-*d*]pyrimidine (8). Toluene (10 mL) was added to an nitrogen-purged two-neck flask containing 7-chloro-2-methylthiazolo[5,4-*d*]pyrimidine **1** (1 mmol), K_2CO_3 (1.5 mmol), substituted phenylboronic acid (1.5 mmol) and $Pd(PPh_3)_4$ (0.05 mmol) and the mixture was stirred under nitrogen at 100 °C for 5 h[4]. After being cooled to ambient temperature the mixture was filtered, washed with dichloromethane and evaporated in vacuo and the residue was chromatographed on a silica gel column (ethyl acetate light petroleum 1:20). Evaporation and drying of the product containing fractions afforded the 7-phenylthiazolo[5,4-*d*]pyrimidines 8a,8b as white solid.

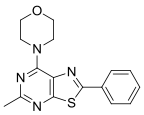
5-methyl-7-phenylthiazolo[5,4-*d*]pyrimidine (8a): benzoboric acid (385 mg, 3 mmol), $Pd(PPh_3)_4$

(120 mg, 0.1 mmol), 5-methyl-7-phenylthiazolo[5,4-*d*]pyrimidine (372 mg, 2 mmol), K_2CO_3 (414.6 mg, 3 mmol). Product 430 mg (94.6 %) was obtained as a white solid. ^{1}H NMR (300MHz, $CDCl_3$, ppm) δ 9.07 (s, 1H), 8.61-8.64 (m, 2H), 7.55-7.58 (m, 4H), 2.93 (s, 3H).

7-(4-methoxyphenyl)-5-methylthiazolo[5,4-*d*]pyrimidine (8b): $Pd(PPh_3)_4$ (174 mg, 0.15 mmol), 5-methyl-7-phenylthiazolo[5,4-*d*]pyrimidine (567mg, 3mmol), K_2CO_3 (622 mg, 4.5 mmol), 4-methoxybenzeneboronic acid (705 mg, 4.5 mmol). Product 760 mg (98.5 %) was obtained as a white solid. ^{1}H NMR (300MHz, $CDCl_3$, ppm) δ 9.04 (s, 1H), 8.72 (d, *J* = 8.97 Hz, 2H), 7.07 (d, *J* = 8.97 Hz, 2H), 3.91 (s, 3H), 2.90 (s, 3H).

General Procedure for Direct Arylation of Iodoarenes with 4-(5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)morpholine (6). A 10ml microwave tube equipped with a magnetic stir bar was changed with premixed $Pd(PPh_3)_4$ (12 mg, 0.01 mmol), Ag_2CO_3 (110.3 mg, 0.4 mmol), 4-(5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)morpholine (47.3 mg, 0.2 mmol), iodoarenes (2 equiv), and deionized water (1 ml). The tube was placed in a preheated oil bath (60 ^{o}C) for 24 h. The reaction mixture was allowed to be cooled to room temperature and filtrated, washed the filter cake with dichloromethane (3 ml). The resulting suspension was extracted with dichloromethane (3 × 5 ml) and brine (5 ml). The combined organic layer was dried with anhydrous Na_2CO_3 (3 g) and filtered. The filtrate was concentrated under vacuum. The crude product was purified by column chromatography (dichloromethane).

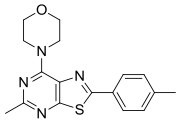
4-(5-methyl-2-phenylthiazolo[5,4-*d*]pyrimidin-7-yl)morpholine (7a)



Yield: 58.5 mg (94%) white solid. mp 188-189 ^{o}C. FT-IR (KBr, cm^{-1}) υ 3008, 2954, 2921, 2850, 1652, 1560, 1534, 1405, 1269, 1115, 996, 763, 688. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ7.94-7.98 (m, 2H), 7.48 (m, 3H), 4.44 (s, 4H), 3.87 (t, *J* = 4.71, 4.95 Hz, 4H), 2.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 166.2, 163.1, 160.2, 154.3, 133.4, 130.8, 129.6, 129.0, 127.0, 67.1, 46.3, 25.9. MS (ESI) *m/z* 313.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{16}H_{16}N_4OS$ (M^+) 312.1045,

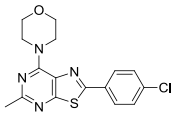
Found 312.1049.

4-(5-methyl-2-(p-tolyl)thiazolo[5,4-*d*]pyrimidin-7-yl)morpholine (7b)



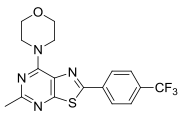
Yield: 61.6mg (95%) white solid. mp 218-219 ^{o}C. FT-IR (KBr, cm^{-1}) υ 3008, 2957, 2855, 1611, 1558, 1532, 1402, 1266, 1117, 997, 822, 635. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.84 (d, *J* = 8.13 Hz, 2H), 7.29 (s, 2H), 4.44 (s, 4H), 3.87 (t, *J* = 4.89, 4.71 Hz, 4H), 2.59 (s, 3H), 2.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 166.0, 162.9, 160.4, 154.2, 141.3, 130.7, 129.7, 129.5, 126.9, 67.1, 46.3, 25.9, 21.5. MS (ESI) *m/z* 327.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{17}H_{18}N_4OS$ (M^+) 326.1201, Found 326.1205.

4-(2-(4-chlorophenyl)-5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)morpholine (7c)



Yield: 63.3 mg (92 %) white solid. mp 232-233 ^{o}C. FT-IR (KBr, cm^{-1}) υ 3008, 2962, 2850, 1643, 1549, 1448, 1400, 1262, 1117, 1084, 996, 846, 637. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.89 (d, *J* = 8.58 Hz, 2H), 7.44 (d, *J* = 8.58 Hz, 2H), 4.43 (s, 4H), 3.87 (t, *J* = 4.68 Hz, 4H), 2.59 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 166.3, 163.3, 158.7, 154.3, 136.9, 131.9, 129.5, 129.2, 128.1, 67.1, 46.3, 25.9. MS (ESI) *m/z* 347.0 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{16}H_{15}ClN_4OS$ (M^+) 346.0655, Found 346.0658.

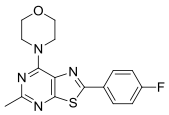
4-(5-methyl-2-(4-(trifluoromethyl)phenyl)thiazolo[5,4-*d*]pyrimidin-7-yl)morpholine (7d)



Yield: 30 mg (39 %) white solid. mp 254-255 ^{o}C. FT-IR (KBr, cm^{-1}) υ 3008, 2973, 2856, 1614, 1552, 1449, 1407, 1324, 1265, 1159, 1113, 1066, 998, 856, 639. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.07 (d, *J* = 8.10 Hz, 2H), 7.73 (d, *J* = 8.28 Hz, 2H), 4.44 (s, 4H), 3.88 (t, *J* = 4.89 Hz, 4H), 2.60

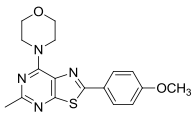
(s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 166.6, 163.7, 158.1, 154.5, 136.5, 134.5, 129.6, 128.0, 127.2, 126.0, 67.1, 46.4, 25.9. MS (ESI) *m/z* 381.0 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{17}H_{15}F_3N_4OS$ (M^+) 380.0919, Found 380.0925.

4-(2-(4-fluorophenyl)-5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)morpholine (7e)



Yield: 65 mg (98 %) white solid. mp 230-231 °C. FT-IR (KBr, cm^{-1}) υ 3003, 2920, 2861, 1599, 1557, 1516, 1451, 1403, 1266, 1161, 1118, 997, 849, 636. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.97 (dd, *J* = 5.22, 8.85 Hz, 2H), 7.18 (t, *J* = 8.52 Hz, 2H), 4.44 (s, 4H), 3.89 (t, *J* = 4.71 Hz, 4H), 2.60 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 166.3, 166.0, 163.1, 162.6, 158.9, 154.3, 129.5, 128.9, 128.8, 116.3, 116.0, 67.1, 46.3, 25.9. MS (ESI) *m/z* 331.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{16}H_{15}FN_4OS$ (M^+) 330.0951, Found 330.0953.

4-(2-(4-methoxyphenyl)-5-methylthiazolo[5,4-*d*]pyrimidin-7-yl)morpholine (7f)

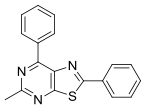


Yield: 55.4 mg (81 %) white solid. mp 206-207 °C. FT-IR (KBr, cm^{-1}) υ 3009, 2968, 2867, 1605, 1558, 1518, 1447, 1260, 1173, 1117, 1012, 835, 618. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 7.90 (d, *J* = 8.85 Hz, 2H), 6.98 (d, *J* = 8.85 Hz, 2H), 4.42 (s, 4H), 3.84-3.88 (m, 7H), 2.58 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 166.0, 162.7, 161.9, 160.1, 154.1, 146.5, 128.5, 126.3, 114.3, 67.1, 55.5, 46.3, 25.8. MS (ESI) *m/z* 343.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{17}H_{18}N_4O_2S$ (M^+) 342.1150, Found 342.1154.

General Procedure for Direct Arylation of Iodoarenes with 7-phenyl-5-methylthiazolo[5,4-*d*]pyrimidine (8a) and 7-(4-methoxyphenyl)-5-methylthiazolo[5,4-*d*]pyrimidine (8b). $Pd(PPh_3)_4$ (12 mg, 0.01 mmol), Ag_2CO_3 (110.3 mg, 0.4 mmol), 7-substituted-5-methylthiazolo[5,4-*d*]pyrimidine (0.2 mmol),

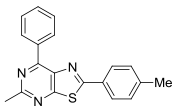
iodoarenes (0.4 mmol) were combined and thoroughly mixed in the bottom of microwave tube. Deionized water (1 ml) was added, and the suspension heated to 60 ^{o}C for 48 h. The reaction mixture was allowed to cool to room temperature and filtrated, washed the filter cake with dichloromethane (3 ml). The resulting suspension was extracted with dichloromethane (3 × 5 ml) and brine (5 ml). The combined organic layer was dried with anhydrous Na_2CO_3 (3 g) and filtered. The filtrate was concentrated under vacuum. The crude product was purified by column chromatography (ethyl acetate/petroleum ethyl 1/30).

5-methyl-2,7-diphenylthiazolo[5,4-*d*]pyrimidine (9a)



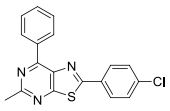
Yield: 20.7 mg (69 %) white solid. mp 172-173 ^{o}C. FT-IR (KBr, cm^{-1}) υ 2926, 2849, 1542, 1490, 1405, 1349, 1256, 974, 917, 750, 683, 642. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.75-8.78 (m, 2H), 8.14 (m, 2H), 7.52-7.59 (m, 6H), 2.92 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 167.9, 166.3, 163.4, 156.4, 140.3, 135.9, 133.1, 131.8, 131.0, 130.4, 129.1, 128.5, 127.8, 26.1. MS (ESI) *m/z* 304.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{18}H_{13}N_3S$ (M^+) 303.0830, Found 303.0822.

5-methyl-7-phenyl-2-(p-tolyl)thiazolo[5,4-*d*]pyrimidine (9b)



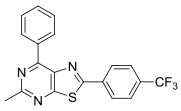
Yield: 49.3 mg (78 %) white solid. mp 151-152 ^{o}C. FT-IR (KBr, cm^{-1}) υ 2920, 2849, 1609, 1542, 1512, 1399, 1349, 1254, 969, 815, 754, 688, 643. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.75 (m, 2H), 8.02 (d, *J* = 7.86 Hz, 2H), 7.57 (d, *J* = 6.51 Hz, 3H), 7.32 (d, *J* = 7.98 Hz, 2H), 2.91 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 167.9, 166.5, 163.2, 156.1, 142.5, 140.3, 135.9, 131.0, 130.4, 129.8, 128.5, 127.8, 26.1, 21.6. MS (ESI) *m/z* 318.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{19}H_{15}N_3S$ (M^+) 317.0987, Found 317.0980.

2-(4-chlorophenyl)-5-methyl-7-phenylthiazolo[5,4-*d*]pyrimidine (9c)



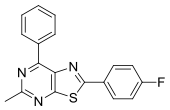
Yield: 46.2 mg (68.34 %) white solid. mp 171-172 ^{o}C. FT-IR (KBr, cm^{-1}) υ 2926, 1595, 1540, 1500, 1402, 1255, 1091, 973, 831, 750, 680, 646. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.72-8.75 (m, 2H), 8.06 (d, *J* = 8.55 Hz, 2H), 7.58 (m, 3H), 7.50 (d, *J* = 8.52 Hz, 2H), 2.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 167.9, 164.9, 163.7, 156.6, 140.2, 138.0, 135.7, 131.5, 131.1, 130.4, 129.4, 128.9, 128.5, 26.1. MS (ESI) *m/z* 338.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{18}H_{12}ClN_3S$ (M^+) 337.0440, Found 337.0426.

5-methyl-7-phenyl-2-(4-(trifluoromethyl)phenyl)thiazolo[5,4-*d*]pyrimidine (9d)



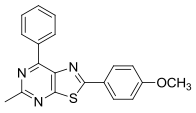
Yield: 47.8 mg (65 %) white solid. mp 197-198 ^{o}C. FT-IR (KBr, cm^{-1}) υ 2920, 2849, 1540, 1491, 1407, 1325, 1163, 1122, 1067, 853, 822, 749, 688, 643. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.74 (dd, *J* = 7.56, 3.99 Hz, 2H), 8.25 (d, *J* = 8.16 Hz, 2H), 7.80 (d, *J* = 8.25 Hz, 2H), 7.58-7.60 (m, 3H), 2.93 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 167.9, 164.4, 164.1, 157.1, 140.4, 136.2, 135.6, 133.4, 133.0, 131.3, 130.4, 128.6, 128.1, 126.1, 26.1. MS (ESI) *m/z* 372.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{19}H_{12}F_3N_3S$ (M^+) 371.0704, Found 371.0697.

2-(4-fluorophenyl)-5-methyl-7-phenylthiazolo[5,4-*d*]pyrimidine (9e)



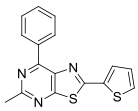
Yield: 18.7 mg (59 %) white solid. mp 167-168 ^{o}C. FT-IR (KBr, cm^{-1}) υ 2920, 2849, 1599, 1546, 1513, 1480, 1412, 1236, 1163, 1100, 975, 839, 750, 683. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.72-8.75 (m, 2H), 8.13 (dd, *J* = 8.82, 5.25 Hz, 2H), 7.58 (m, 3H), 7.19-7.26 (m, 2H), 2.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 167.9, 166.6, 165.0, 163.6, 163.2, 156.5, 140.3, 135.8, 131.1, 130.4, 129.9, 129.8, 128.5, 116.5, 116.2, 26.1. MS (ESI) *m/z* 322.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{18}H_{12}FN_3S$ (M^+) 321.0736, Found 321.0734.

2-(4-methoxyphenyl)-5-methyl-7-phenylthiazolo[5,4-*d*]pyrimidine (9f)



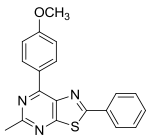
Yield: 36.1 mg (55 %) white solid. mp 164-165 ^{o}C. FT-IR (KBr, cm^{-1}) υ 2920, 2843, 1604, 1518, 1481, 1403, 1256, 1172, 1030, 972, 833, 747, 680, 628. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.74-8.77 (m, 2H), 8.08 (d, *J* = 8.79 Hz, 2H), 7.57 (m, 3H), 7.02 (d, *J* = 8.79 Hz, 2H), 3.9 (s, 3H), 2.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 168.0, 166.1, 163.0, 162.6, 155.8, 140.4, 136.0, 130.9, 130.4, 129.5, 128.5, 125.9, 55.5, 26.0. MS (ESI) *m/z* 334.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{19}H_{15}N_3OS$ (M^+) 333.0936, Found 333.0935.

5-methyl-7-phenyl-2-(thiophen-2-yl)thiazolo[5,4-*d*]pyrimidine (9h)



Yield: 21.2 mg (35 %) white solid. mp 129-130 ^{o}C. FT-IR (KBr, cm^{-1}) υ 2920, 2843, 1556, 1521, 1471, 1403, 753, 714, 684, 642. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.73 (dd, *J* = 6.48, 2.58 Hz, 2H), 7.73 (m, 1H), 7.55-7.59 (m, 4H), 7.18 (t, *J* = 5.22 Hz, 1H), 2.90 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 168.0, 163.4, 159.7, 155.9, 140.0, 137.2, 135.8, 131.0, 130.6, 130.4, 129.8, 128.5, 128.3, 26.1. MS (ESI) *m/z* 310.0 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{16}H_{11}N_3S_2$ (M^+) 309.0394, Found 309.0386.

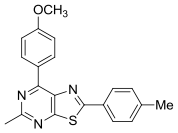
7-(4-methoxyphenyl)-5-methyl-2-phenylthiazolo[5,4-*d*]pyrimidine (9i)



Yield: 49.6 mg (75 %) white solid. mp 162-163 ^{o}C. FT-IR (KBr, cm^{-1}) υ 2920, 2850, 1609, 1507, 1402, 1256, 1181, 1034, 836, 759, 685, 588. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.85 (d, *J* = 8.85 Hz, 2H), 8.13 (m, 3H), 7.54 (m, 3H), 7.10 (d, *J* = 8.88 Hz, 2H), 3.93 (s, 3H), 2.89 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 167.7, 165.7, 163.3, 162.1, 155.9, 139.7, 133.2, 132.2, 131.6,

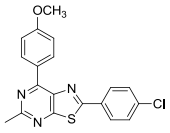
129.1, 128.4, 127.7, 113.9, 55.4, 26.1. MS (ESI) *m/z* 334.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{19}H_{15}N_3OS$ (M^+) 333.0936, Found 333.0937.

7-(4-methoxyphenyl)-5-methyl-2-(p-tolyl)thiazolo[5,4-*d*]pyrimidine (9j)



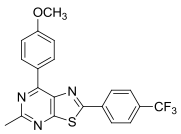
Yield: 60.4 mg (88 %) white solid. mp 155-156 ^oC. FT-IR (KBr, cm^{-1}) υ 2920, 2850, 1607, 1505, 1401, 1255, 1179, 1102, 1032, 836, 787, 629, 579. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 8.84 (d, *J* = 9.00 Hz, 2H), 8.02 (d, *J* = 8.13 Hz, 2H), 7.32 (d, *J* = 7.95 Hz, 2H), 7.10 (d, *J* = 8.97 Hz, 2H), 3.92 (s, 3H), 2.87 (s, 3H), 2.45 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 167.7, 165.9, 163.0, 162.1, 155.6, 142.3, 139.7, 132.2, 130.6, 129.8, 128.5, 127.7, 113.9, 55.4, 26.1, 21.6. MS (ESI) *m/z* 348.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{20}H_{17}N_3OS$ (M^+) 347.1092, Found 347.1085.

2-(4-chlorophenyl)-7-(4-methoxyphenyl)-5-methylthiazolo[5,4-*d*]pyrimidine (9k)



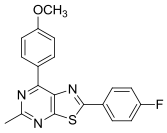
Yield: 70.9 mg (97 %) white solid. mp 160-161 ^oC. FT-IR (KBr, cm^{-1}) υ 2920, 2850, 1606, 1508, 1403, 1305, 1253, 1174, 1090, 1029, 834, 786. ^1H NMR (300 MHz, $CDCl_3$, ppm) δ 8.82 (d, *J* = 8.61 Hz, 2H), 8.06 (d, *J* = 8.25 Hz, 2H), 7.50 (d, *J* = 8.31 Hz, 2H), 7.09 (d, *J* = 8.64 Hz, 2H), 3.93 (s, 3H), 2.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 167.7, 164.4, 163.5, 162.2, 156.1, 137.8, 132.2, 131.7, 129.4, 128.9, 128.3, 114.0, 55.4, 26.1. MS (ESI) *m/z* 368.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{19}H_{14}ClN_3OS$ (M^+) 367.0546, Found 367.0544.

2-(4-(trifluoromethyl)phenyl)-7-(4-methoxyphenyl)-5-methylthiazolo[5,4-*d*]pyrimidine (9l)



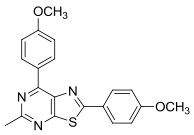
Yield: 71.2 mg (89 %) white solid. mp 157-158 ^{o}C. FT-IR (KBr, cm^{-1}) υ 2920, 2850, 1604, 1505, 1404, 1325, 1253, 1170, 1111, 1066, 1027, 844, 791, 629. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.82 (d, *J* = 8.91 Hz, 2H), 8.23 (d, *J* = 8.25 Hz, 2H), 7.79 (d, *J* = 8.28 Hz, 2H), 7.10 (d, *J* = 8.94 Hz, 2H), 3.93 (s, 3H), 2.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 167.6, 163.9, 162.3, 156.5, 139.6, 136.3, 133.3, 132.8, 132.3, 128.1, 128.0, 126.1, 121.9, 114.0, 55.4, 26.1. MS (ESI) *m/z* 402.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{20}H_{14}F_3N_3OS$ (M^+) 401.0810, Found 401.0808.

2-(4-fluorophenyl)-7-(4-methoxyphenyl)-5-methylthiazolo[5,4-*d*]pyrimidine (9m)



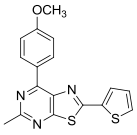
Yield: 71.2 mg (89 %) white solid. mp 178-179 ^{o}C. FT-IR (KBr, cm^{-1}) υ 2920, 2850, 1604, 1505, 1402, 1258, 1181, 1099, 1030, 834, 786, 629, 600, 576. ^{1}H NMR (300 MHz, DMSO-d_6, ppm) δ 8.82 (d, *J* = 8.88 Hz, 2H), 8.13 (dd, *J* = 8.61, 5.34 Hz, 2H), 7.21 (d, *J* = 8.52 Hz, 2H), 7.09 (d, *J* = 8.88 Hz, 2H), 3.89 (s, 3H), 2.76 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 167.7, 166.5, 164.4, 163.3, 163.1, 162.1, 155.9, 139.7, 132.2, 129.8, 129.7, 128.4, 116.5, 116.2, 113.9, 55.4, 26.1. MS (ESI) *m/z* 352.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{19}H_{14}FN_3OS$ (M^+) 351.0842, Found 351.0838.

2,7-bis(4-methoxyphenyl)-5-methylthiazolo[5,4-*d*]pyrimidine (9n)



Yield: 52.4 mg (73 %) white solid. mp 189-190 ^{o}C. FT-IR (KBr, cm^{-1}) υ 2926, 2830, 1603, 1505, 1400, 1304, 1256, 1171, 1031, 833, 786, 626, 585. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.83 (d, *J* = 8.88 Hz, 2H), 8.07 (d, *J* = 8.76 Hz, 2H), 7.09 (d, *J* = 8.85 Hz, 2H), 7.02 (d, *J* = 8.76 Hz, 2H), 3.92 (s, 3H), 3.90 (s, 3H), 2.87 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 167.7, 165.4, 162.8, 162.4, 162.0, 155.2, 139.8, 132.2, 129.4, 128.6, 126.0, 114.4, 113.9, 55.5, 55.4, 26.0. MS (ESI) *m/z* 364.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{20}H_{17}N_3O_2S$ (M^+) 363.1041, Found 363.1038.

5-methyl-7-(4-methoxyphenyl)-2-(thiophen-2-yl)thiazolo[5,4-*d*]pyrimidine (9p)



Yield: 23.4 mg (35 %) white solid. mp 157-158 ^{o}C. FT-IR (KBr, cm^{-1}) υ 2920, 2850, 1605, 1555, 1504, 1401, 1253, 1176, 1028, 840, 784, 713, 629. ^{1}H NMR (300 MHz, $CDCl_3$, ppm) δ 8.81 (d, *J* = 8.88 Hz, 2H), 7.71 (m, 2H), 7.57 (m, 2H), 7.17 (t, *J* = 4.77 Hz,1H), 7.08 (d, *J* = 8.85 Hz, 2H), 3.92 (s, 3H), 2.88 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$, ppm) δ 167.7, 163.3, 162.1, 159.1, 155.3, 139.3, 137.3, 132.2, 130.4, 129.6, 128.4, 128.2, 113.9, 55.4, 26.1. MS (ESI) *m/z* 340.1 $(M+H)^+$. HRMS (ESI-TOF) calcd for $C_{17}H_{13}N_3OS_2$ (M^+) 339.0500, Found 339.0493.

Experimental References

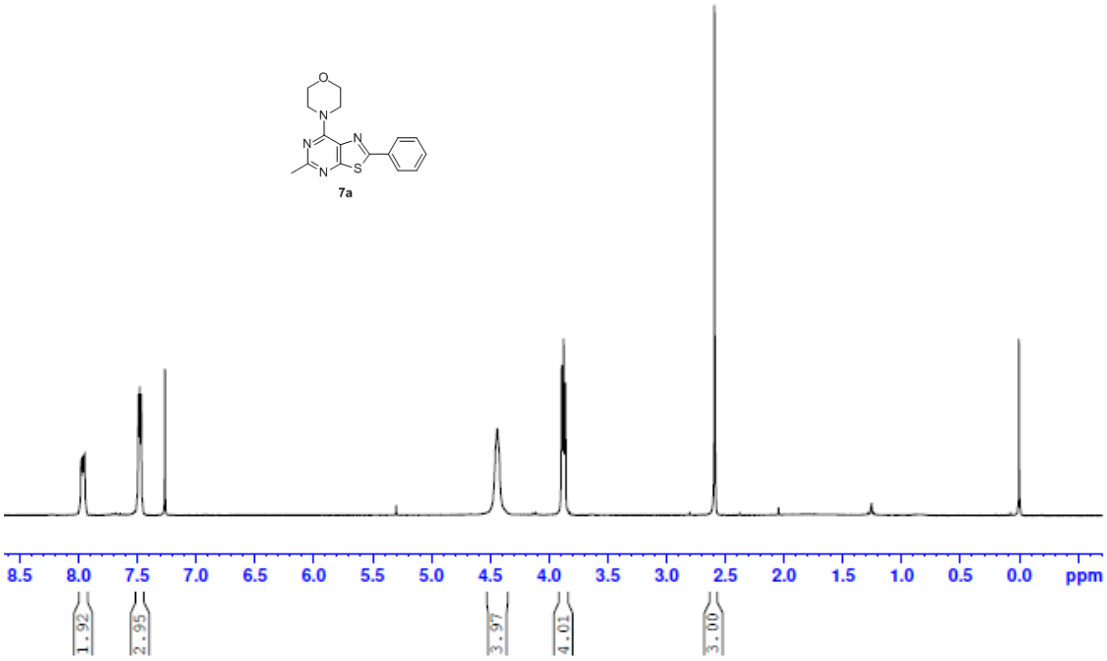
(1) Cai, S. X., Kemnitzer, W. E., Sirisoma, N. S., Zhang, H. Z. Patent Application WO 2008057402, 2008.

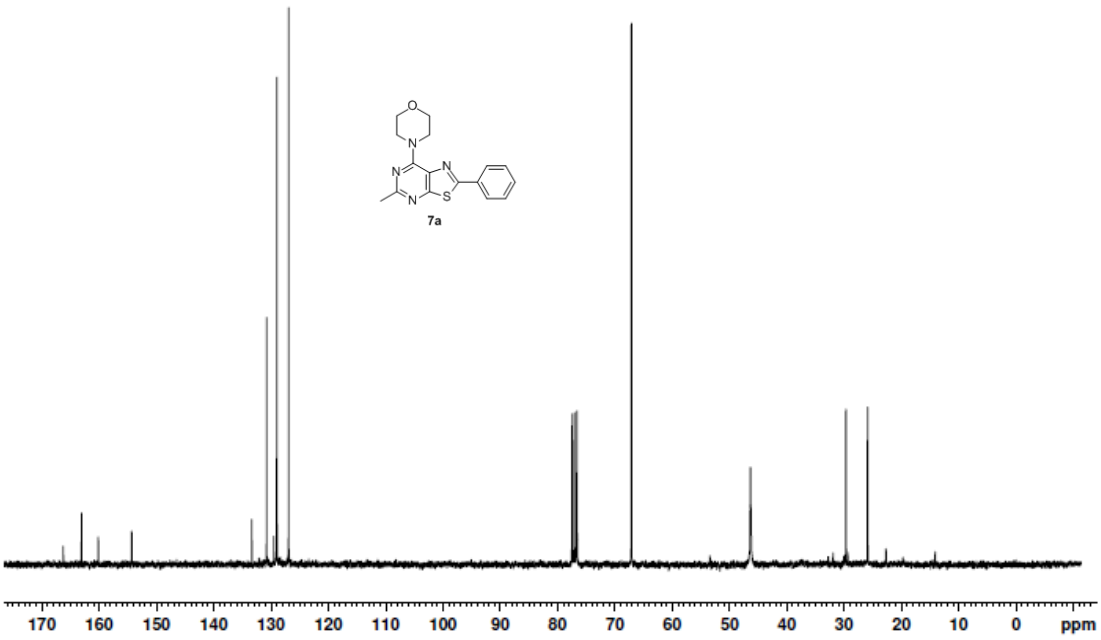
(2) Andersen, K. E.; Hammad, M.; Hilmy, K. M. H.; Pedersen, E. B. *Acta Chemica Scandinavica*, 1987, **B 41**, 708.

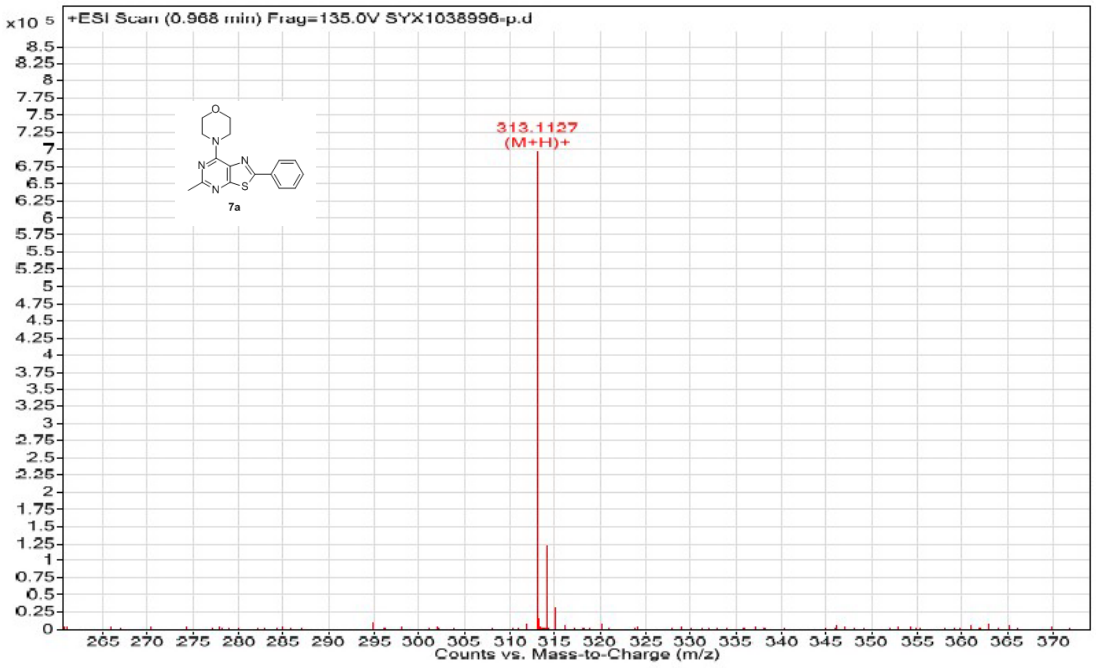
(3) Venkatesan, A. M.; Dehnhardt, C. M.; Chen, Z.; Santos, E. D.; Dos Santos, O.; Bursavich, M.; Gilbert, A. M.; Ellingboe, J. W.; Ayral-Kaloustian, S.; Khafizova, G.; Brooijmans, N.; Mallon, R.; Hollander, I.; Feldberg, L.; Lucas, J.; Yu, K.; Gibbons, J.; Abraham, R.; Mansour, T. S. *Bioorganic & Medicinal Chemistry Letters* 2010, **20**, 653.

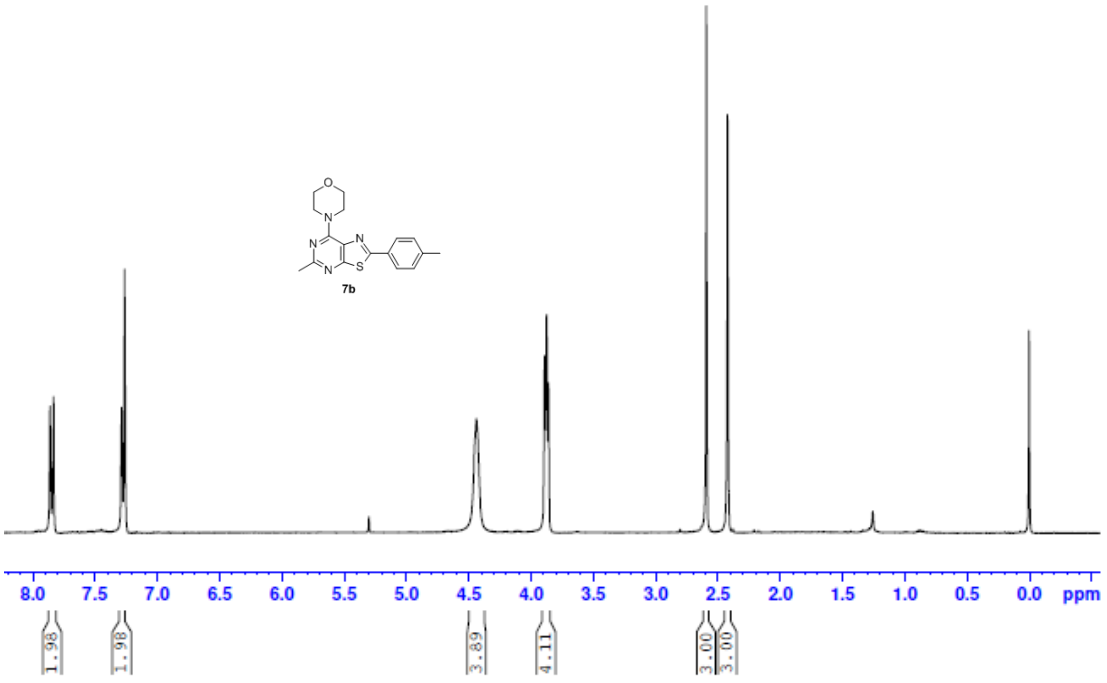
(4) (a) Hocek, M.; Holý, a.; Votruba, I.; Dvoráková, H. *J. Med. Chem.* 2000, **43**, 1817. (b) Chang, L. C. W.; Spanjersberg, R. F.; Krieger, T. M. *J. Med. Chem.* 2006, **49**, 2867.

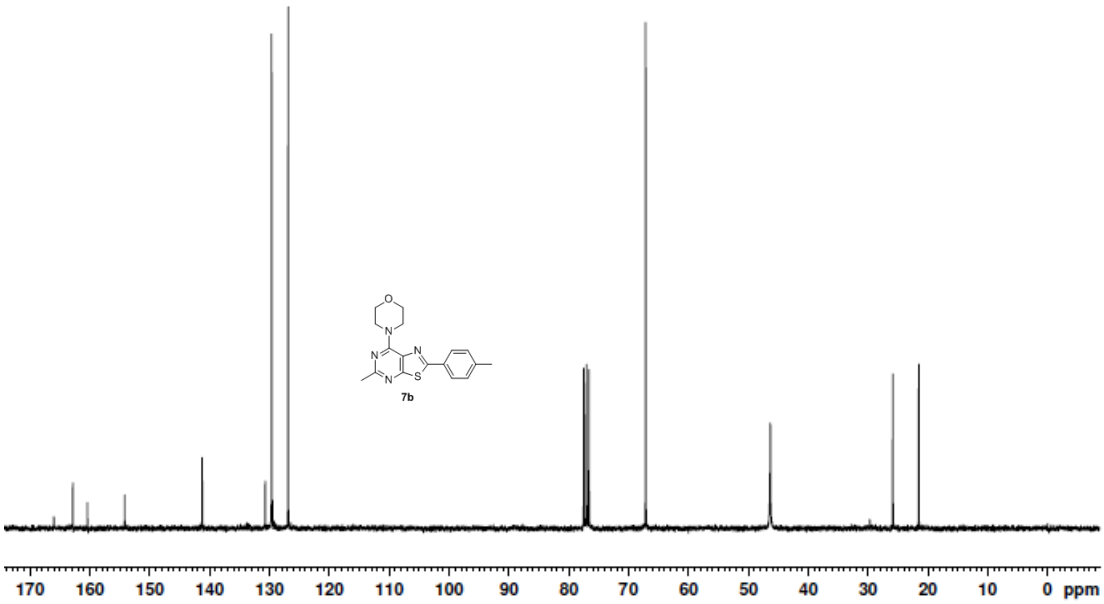
SPECTRA

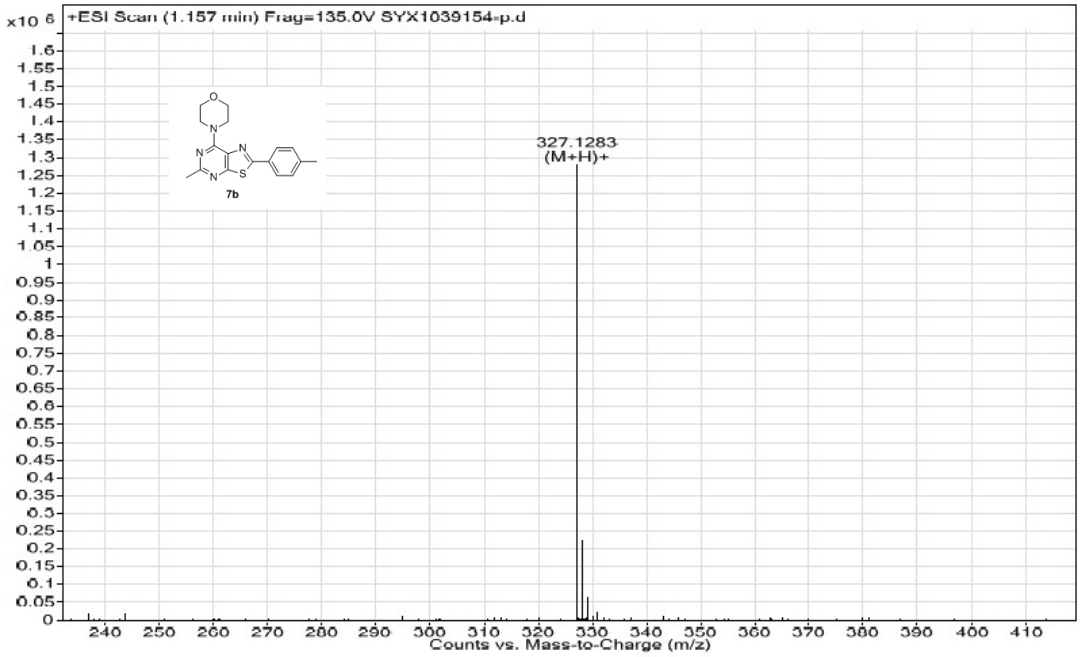


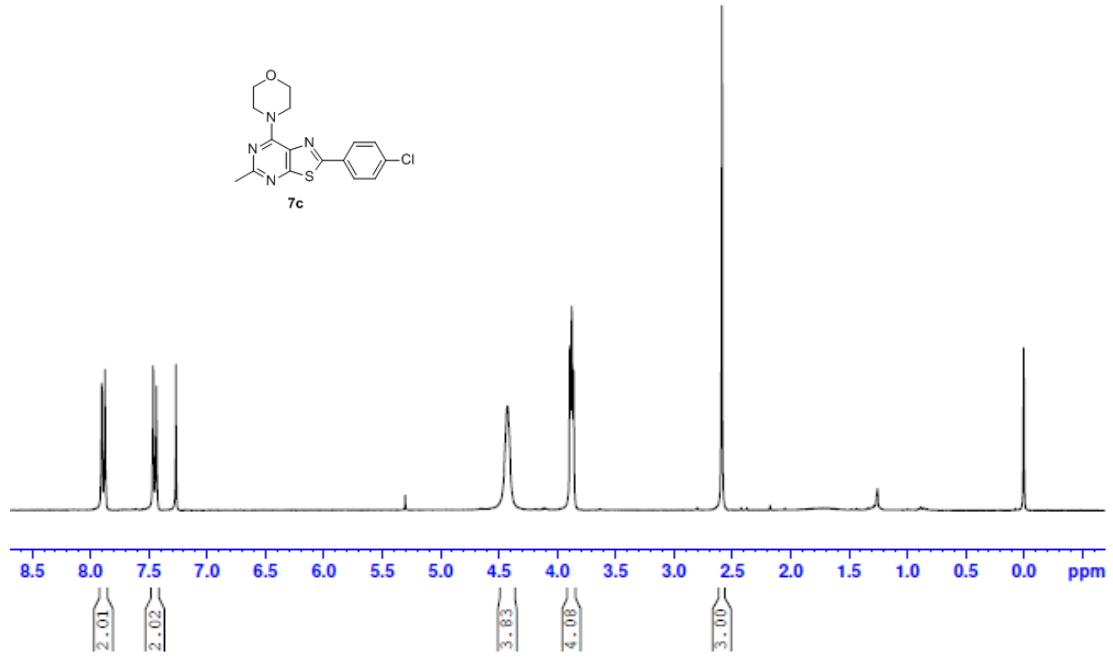


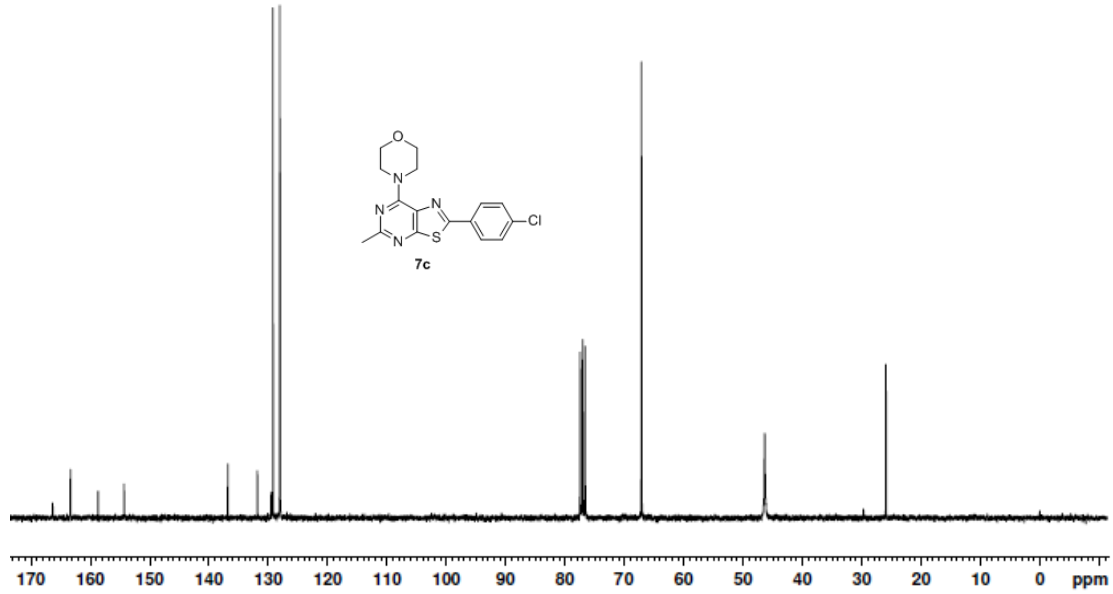

x10 5
+ESI Scan (0.968 min) Frag=135.0V SYX1038996-p.d
313.1127
(M+H)+
7a
Counts vs. Mass-to-Charge (m/z)

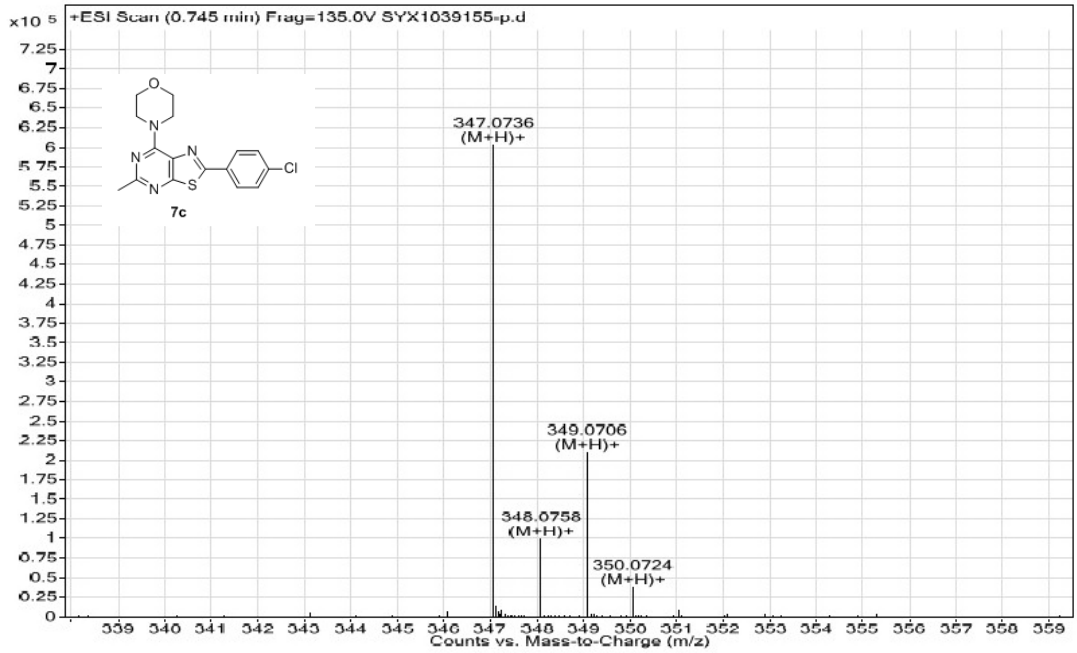

7b
ppm
1.98
1.98
3.89
4.11
3.00
3.00


7b
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


x10 6
+ESI Scan (1.157 min) Frag=135.0V SYX1039154-p.d
7b
327.1283
(M+H)+
Counts vs. Mass-to-Charge (m/z)



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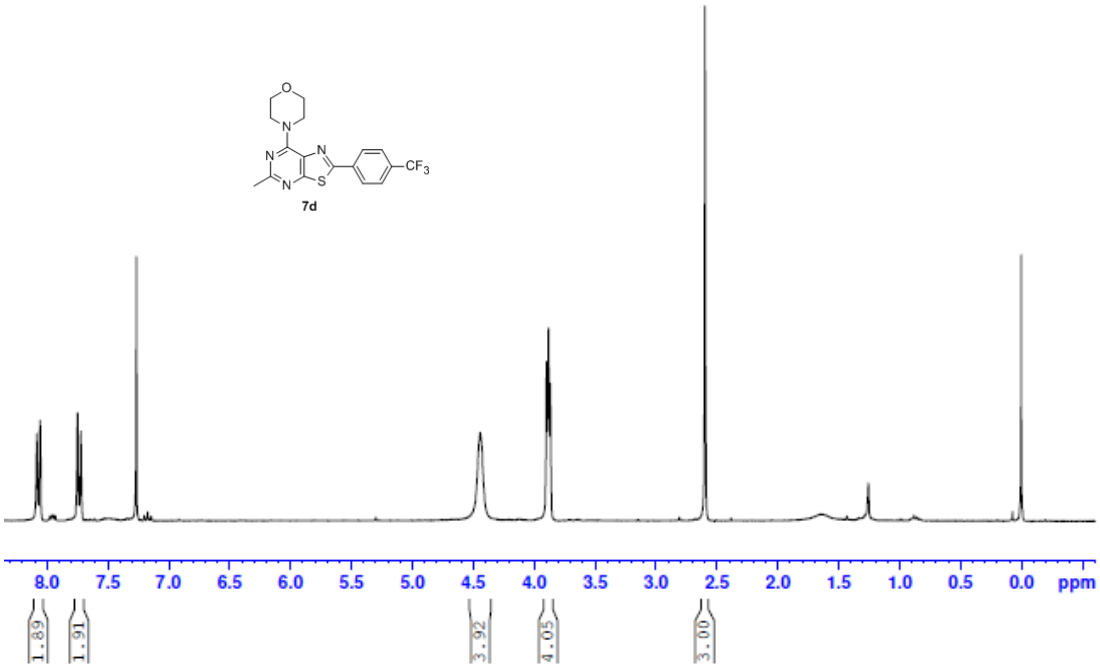
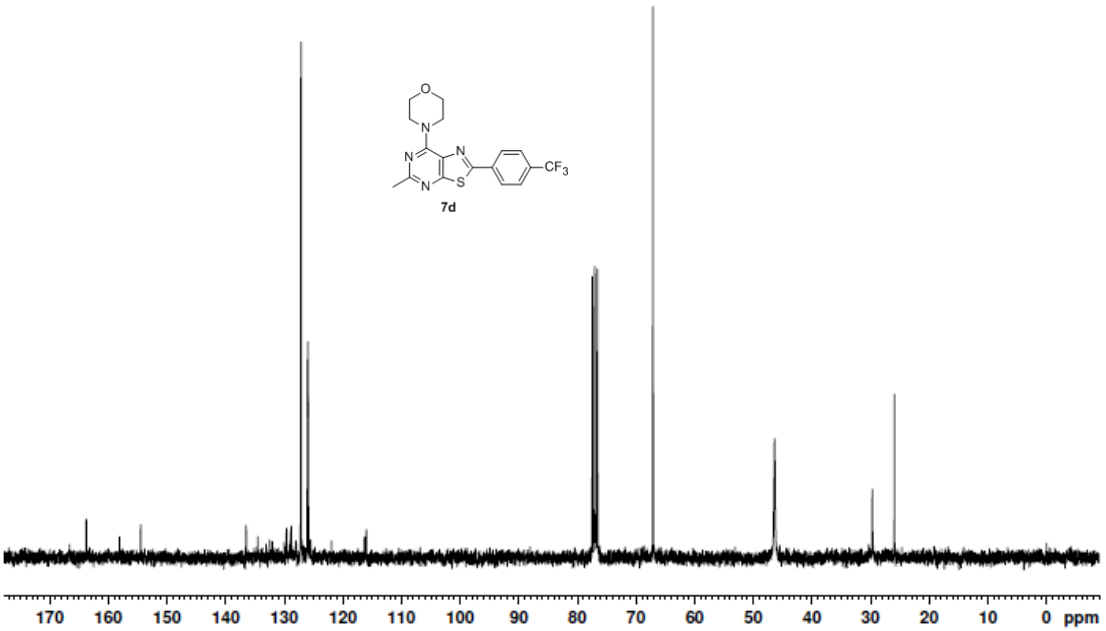
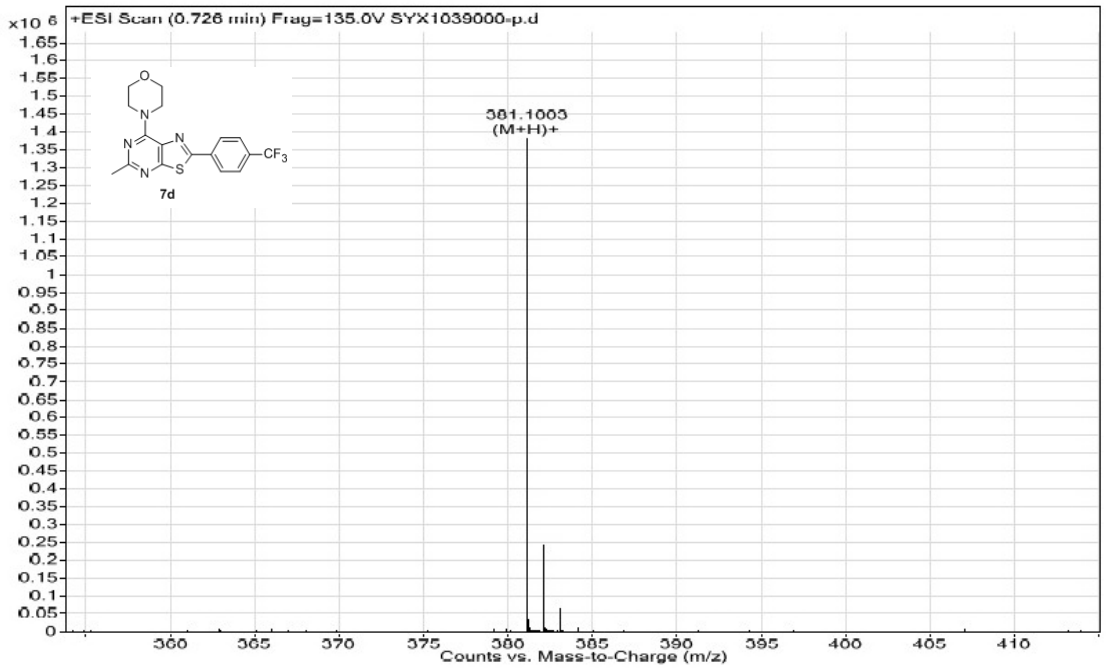
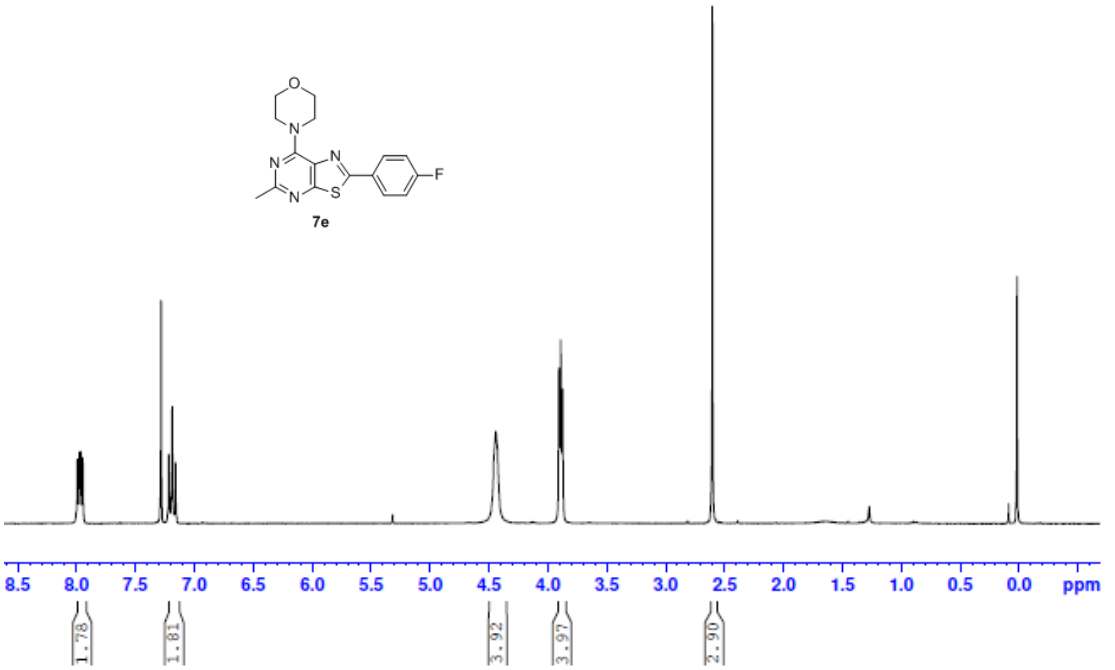
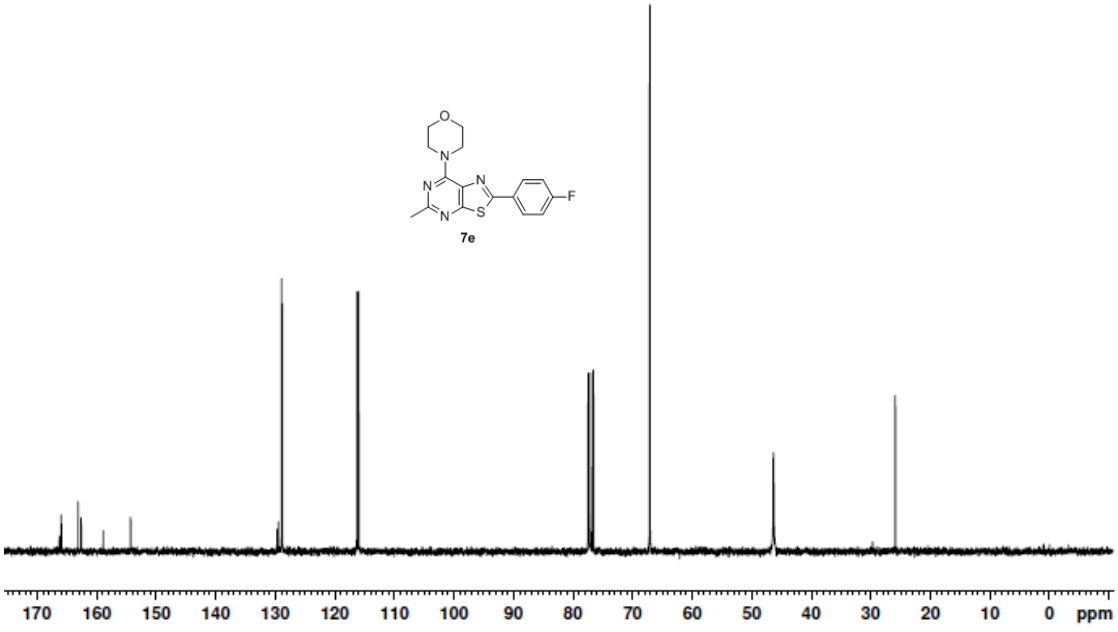
x10 5
347.0736
(M+H)+
349.0706
(M+H)+
348.0758
(M+H)+
350.0724
(M+H)+
Counts vs. Mass-to-Charge (m/z)
7c

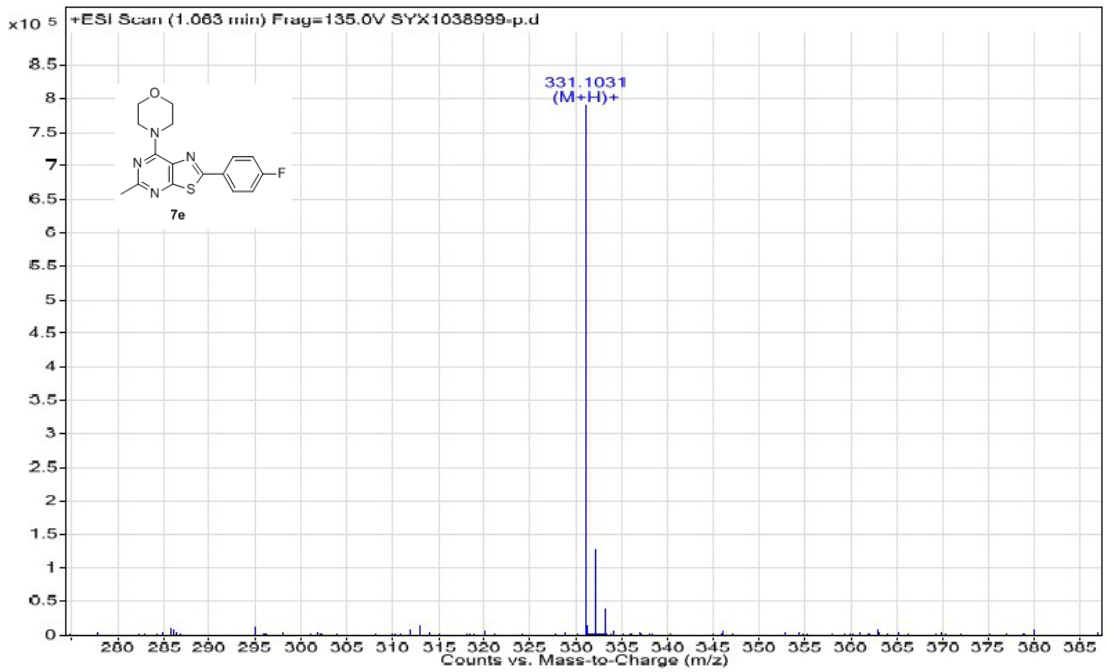

7d
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.89
1.91
3.92
4.05
3.00

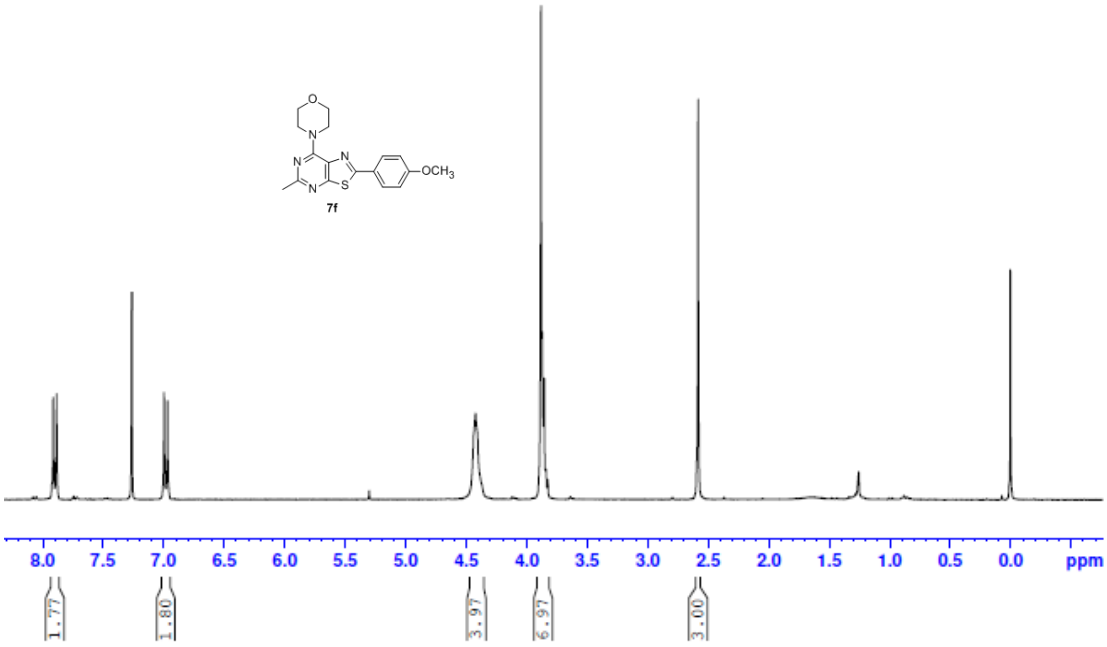


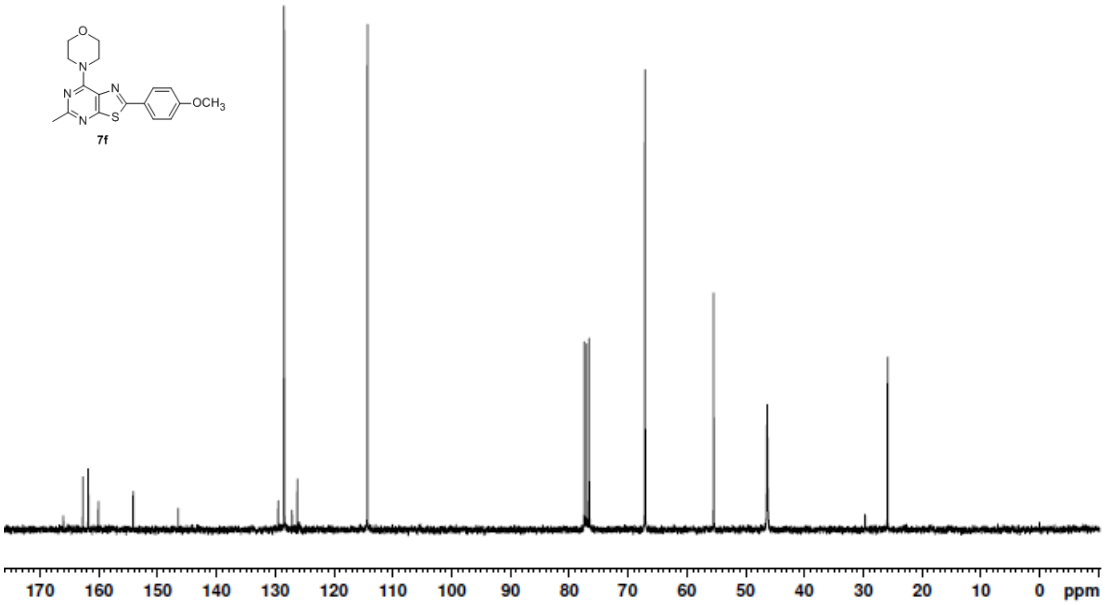


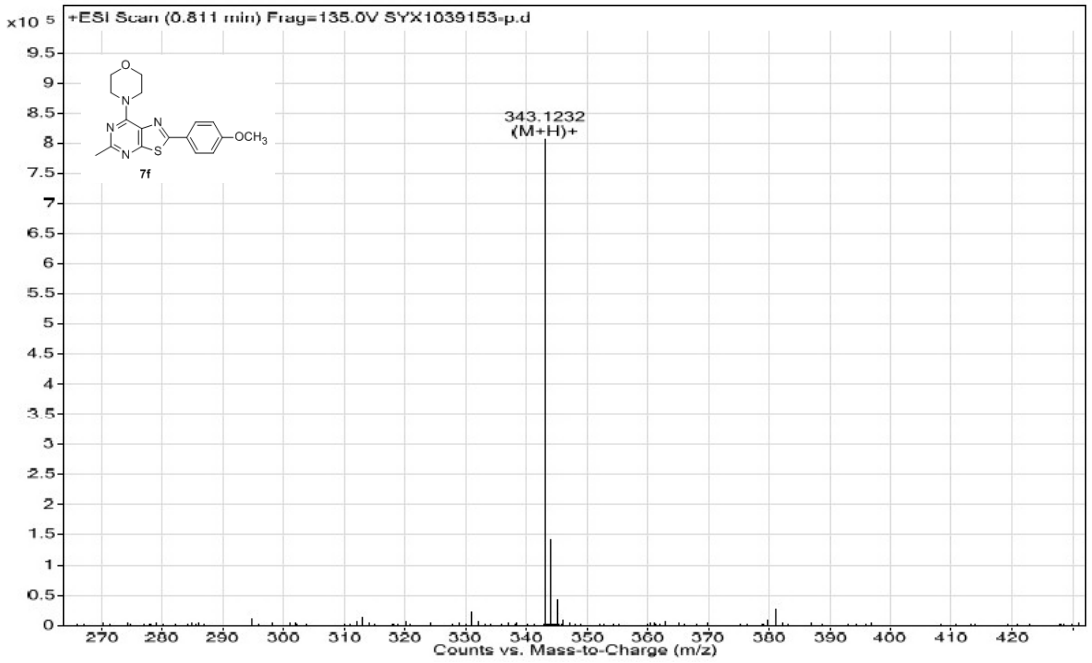


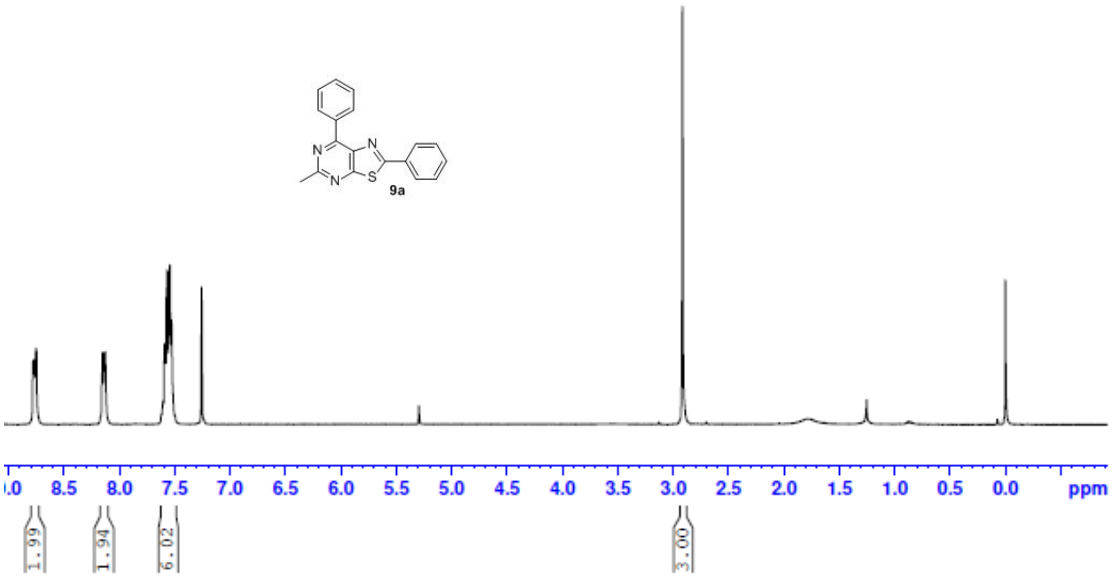


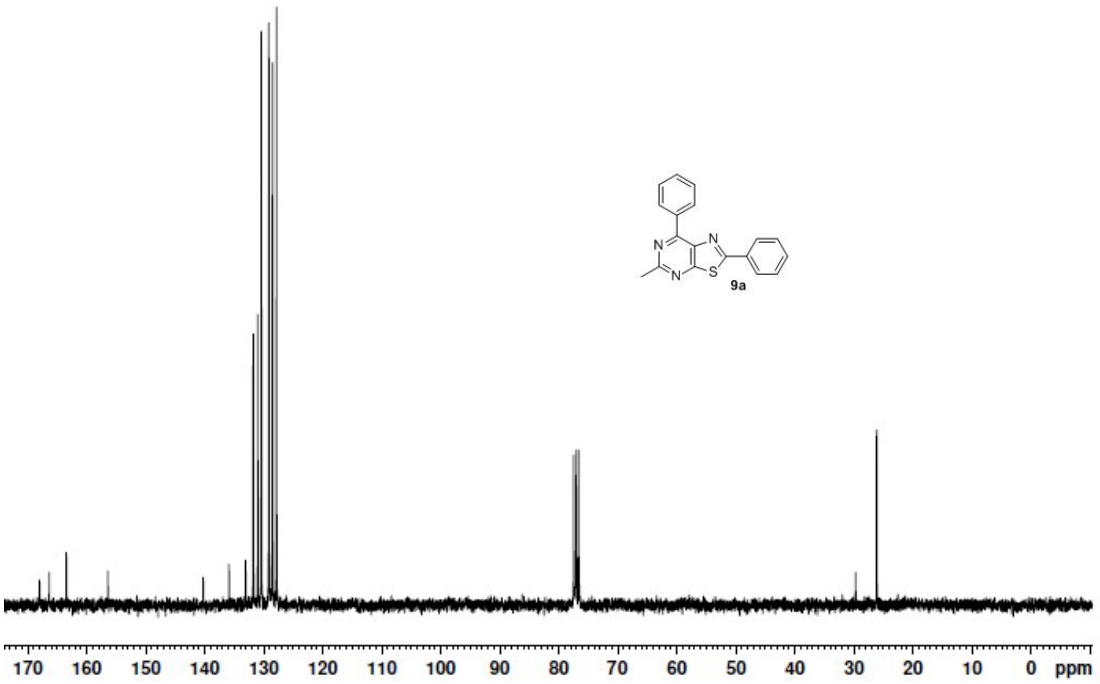

+ESI Scan (1.083 min) Frag=135.0V SYX1038999-p.d
x10 5
331.1031
(M+H)+
7e
Counts vs. Mass-to-Charge (m/z)

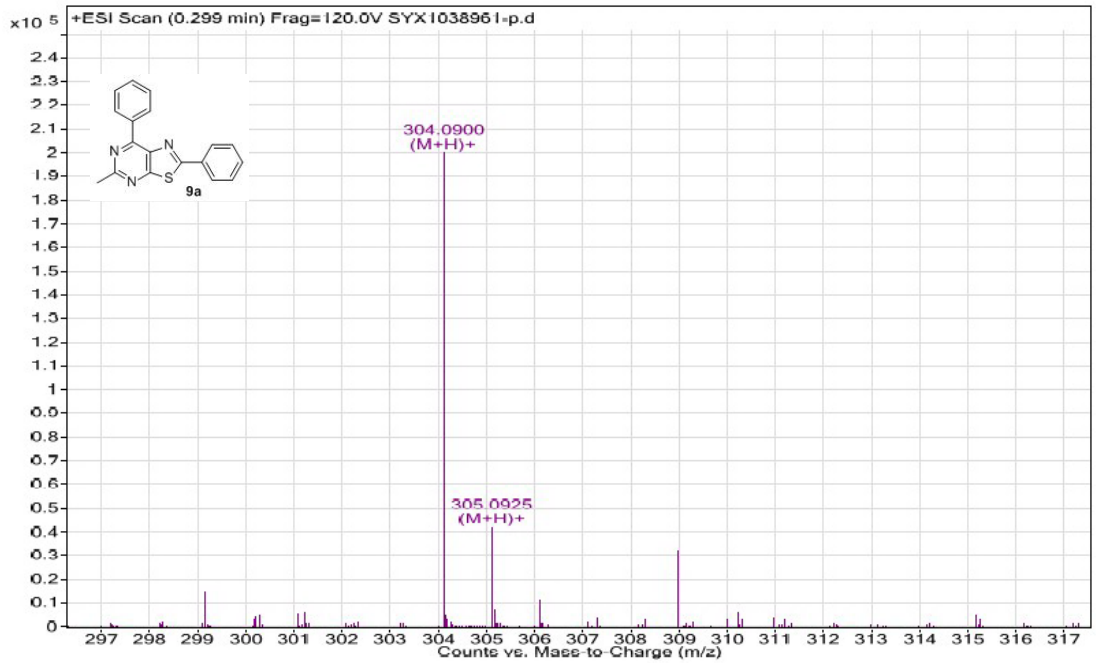

7f
ppm
1.77
1.80
3.97
6.97
3.00

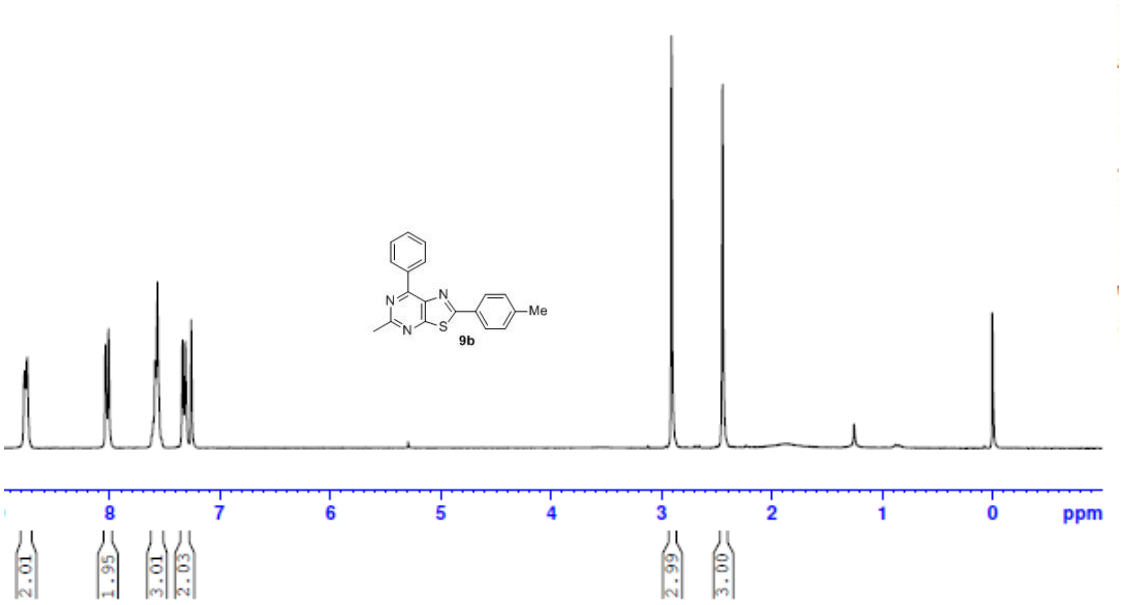

7f
OCH3
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

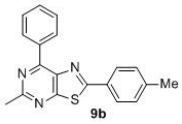

x10 5
+ESI Scan (0.811 min) Frag=135.0V SYX1039153-p.d
343.1232
(M+H)+
7f
OCH3
Counts vs. Mass-to-Charge (m/z)

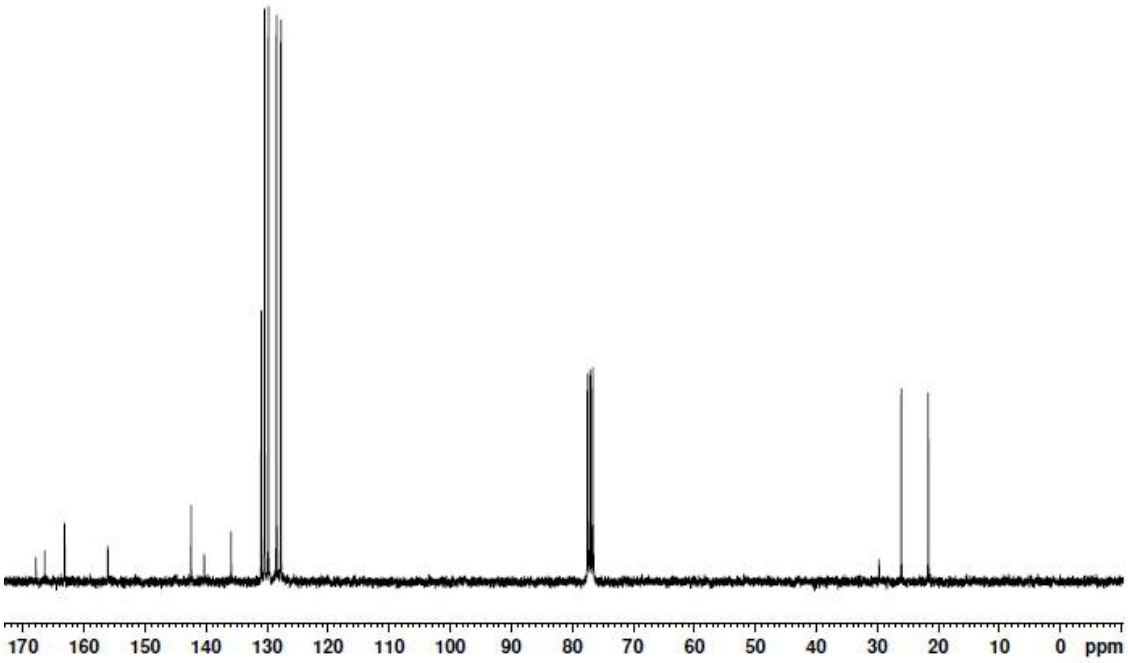

9a
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
ppm
1.99
1.94
6.02
3.00

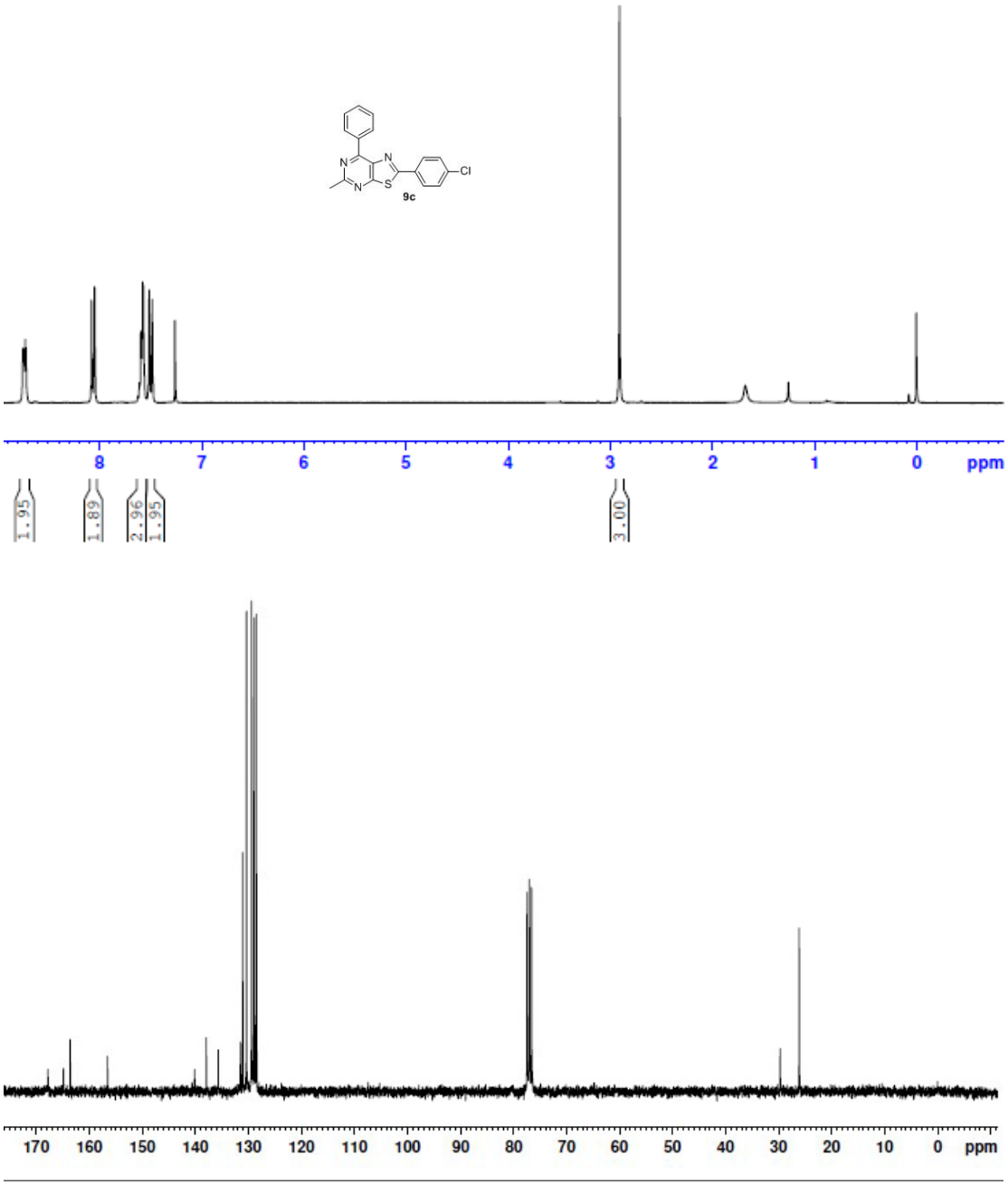

9a
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

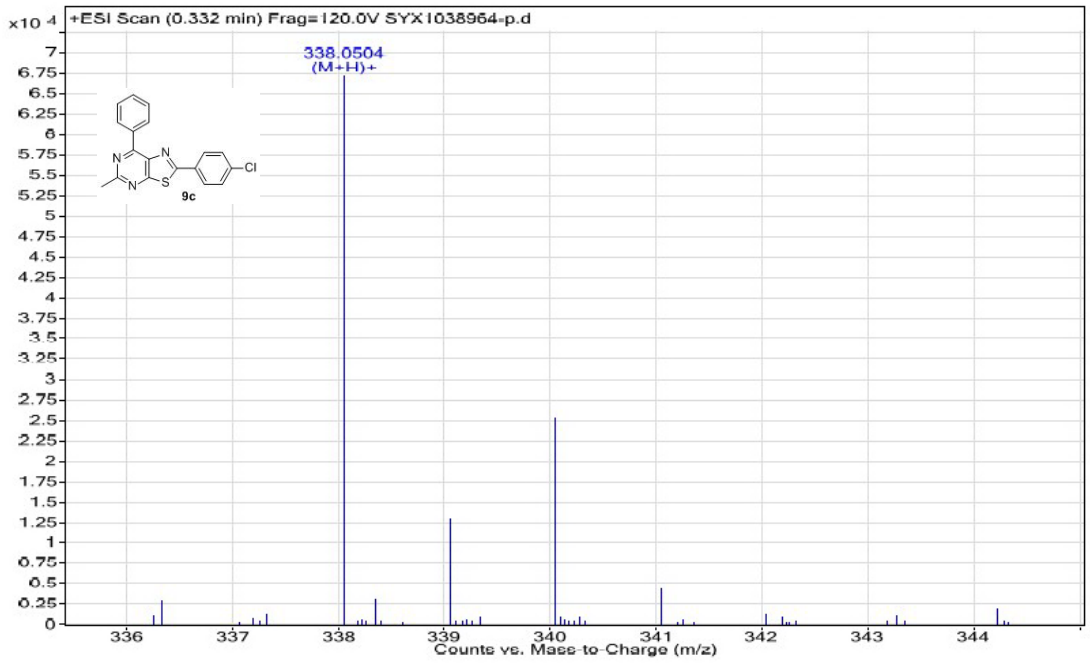


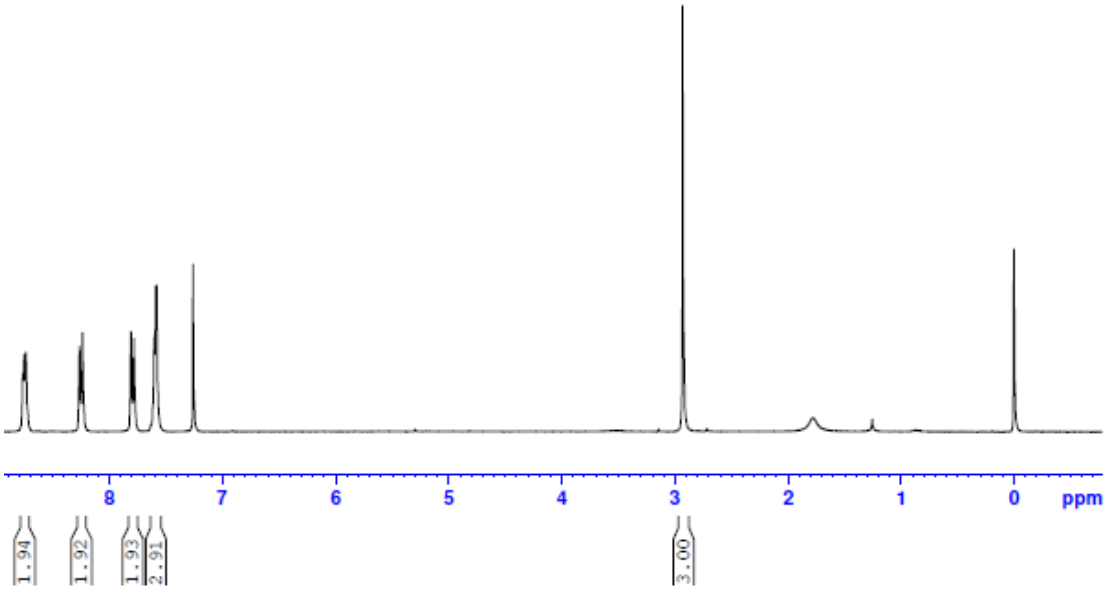


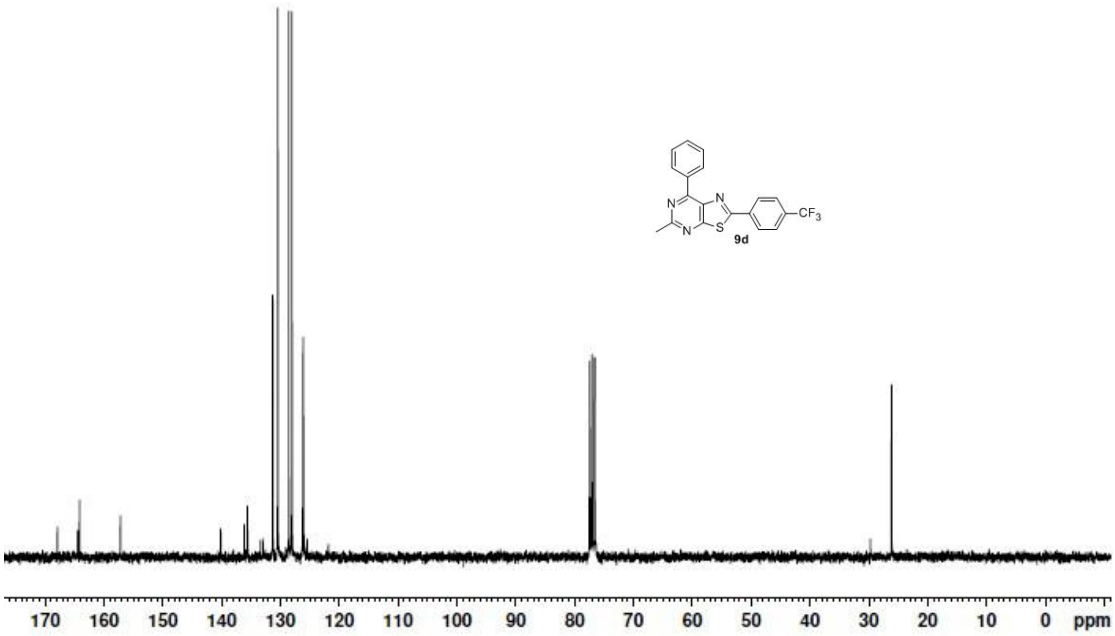


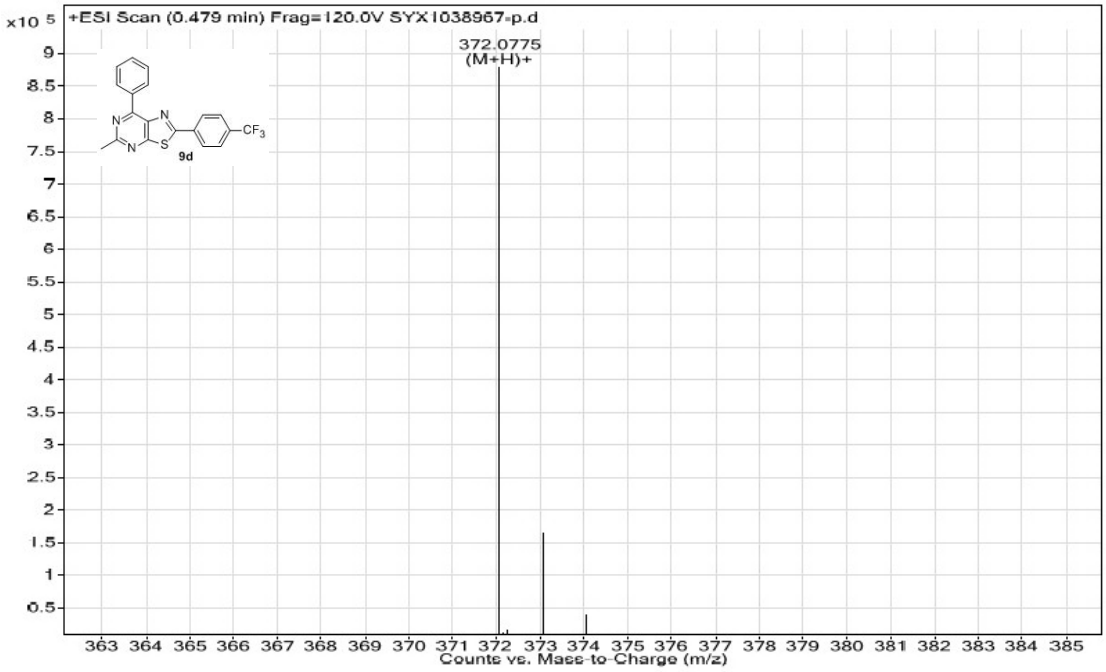


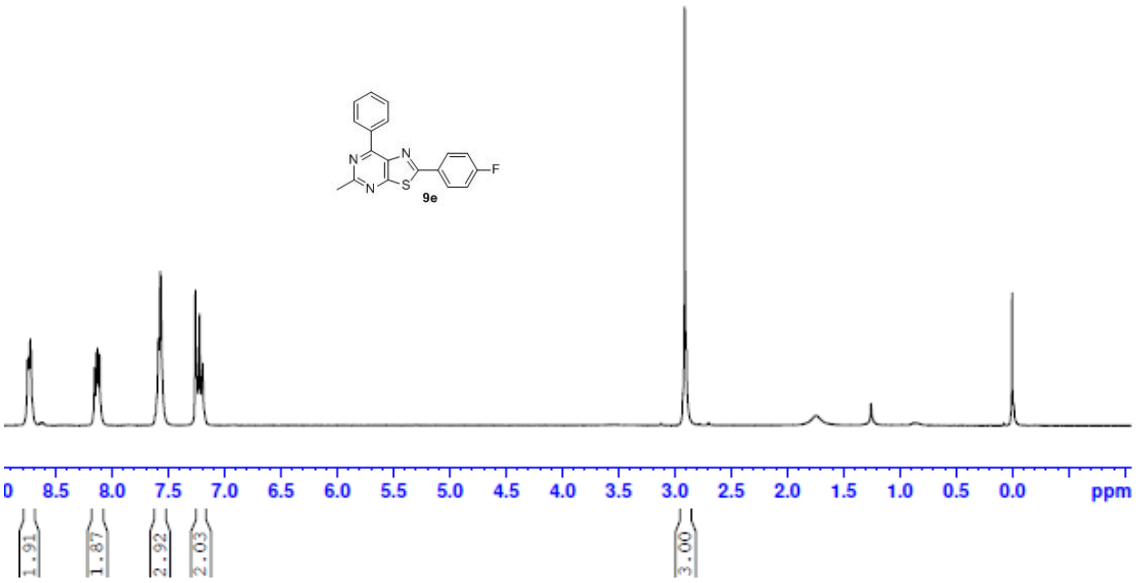

Cl
9c
8
7
6
5
4
3
2
1
0
ppm
1.95
1.89
2.96
1.95
3.00
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
ppm

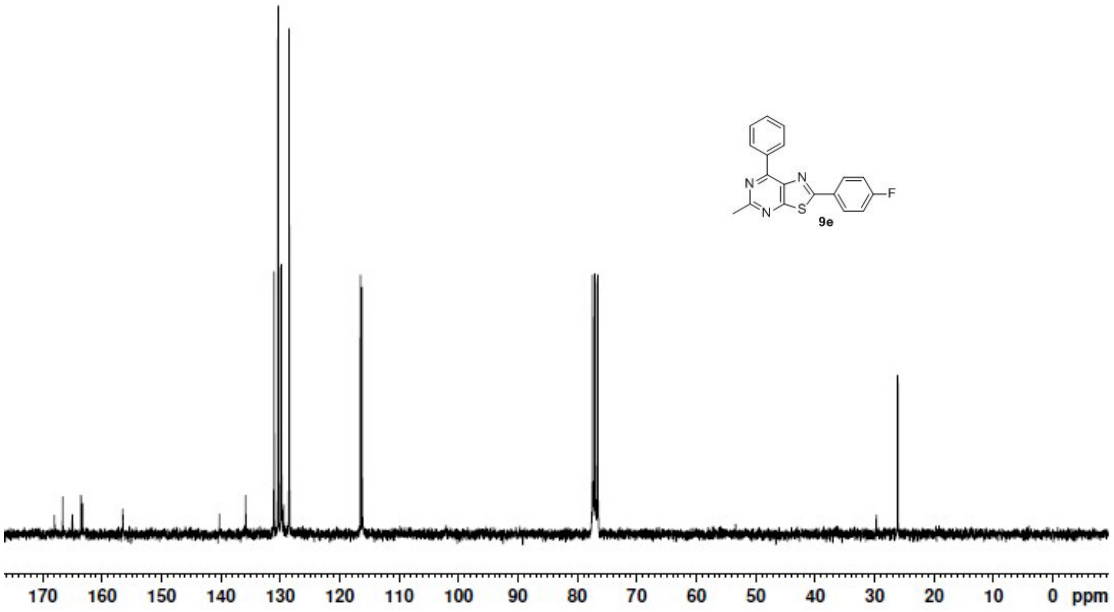


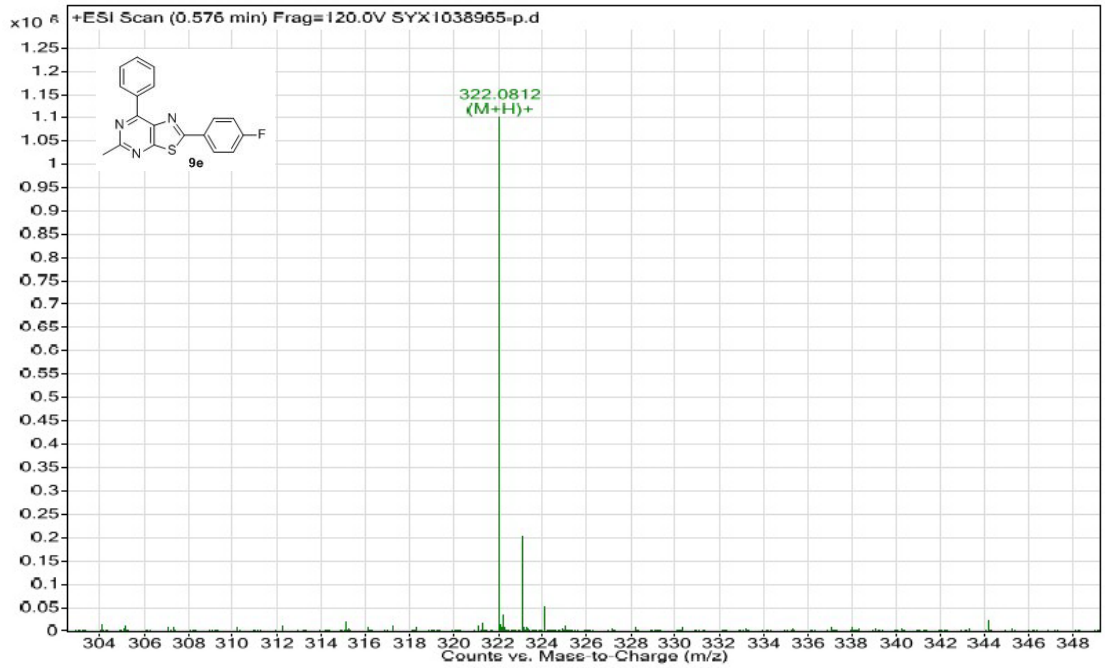


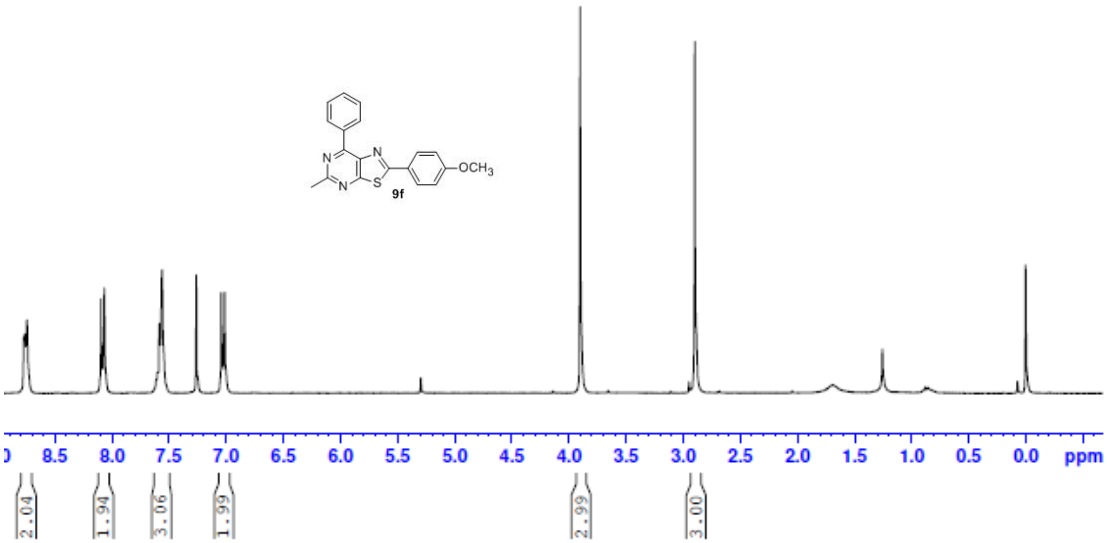

9d
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

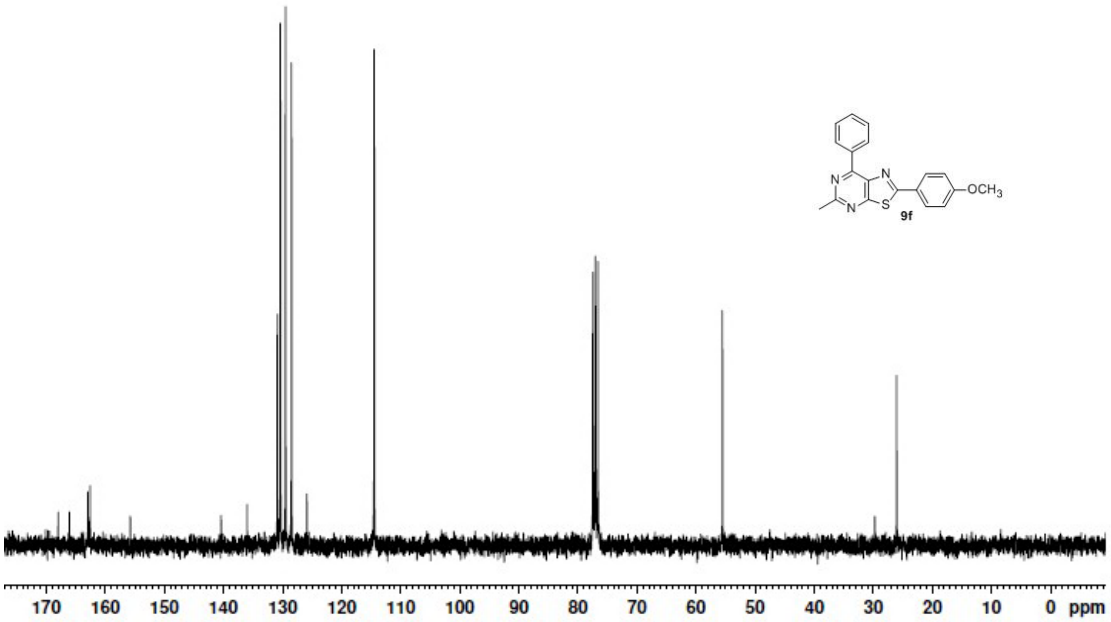

+ESI Scan (0.479 min) Frag=120.0V SYX1038967-p.d
372.0775
(M+H)+
9d
x10 5
9
8.5
8
7.5
7
6.5
6
5.5
5
4.5
4
3.5
3
2.5
2
1.5
1
0.5
363 364 365 366 367 368 369 370 371 372 373 374 375 376 377 378 379 380 381 382 383 384 385
Counts vs. Mass-to-Charge (m/z)

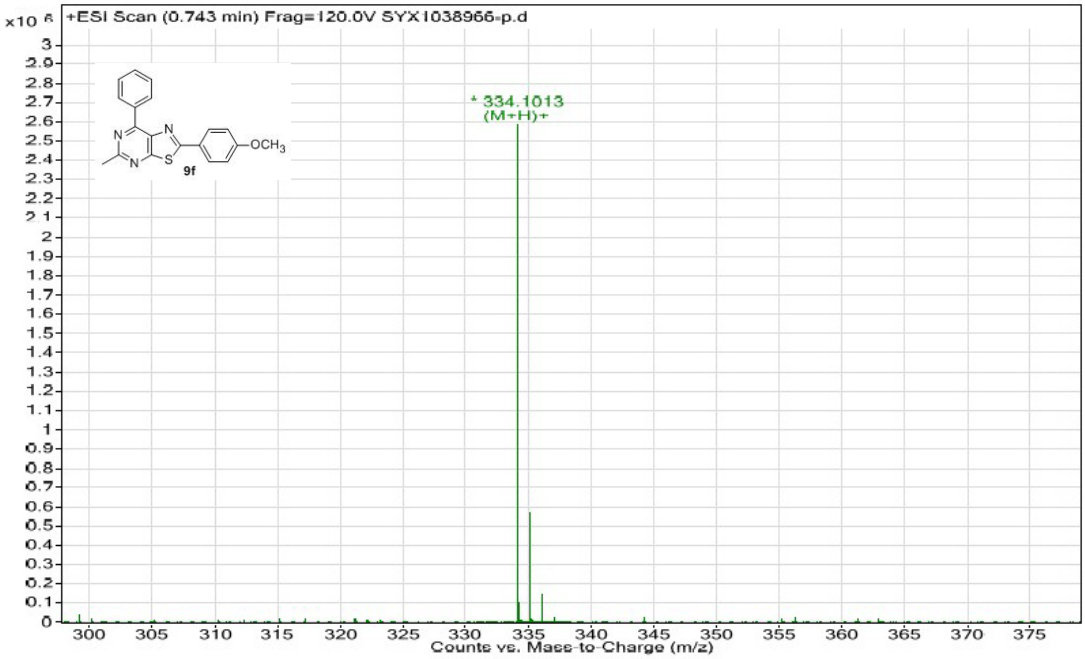


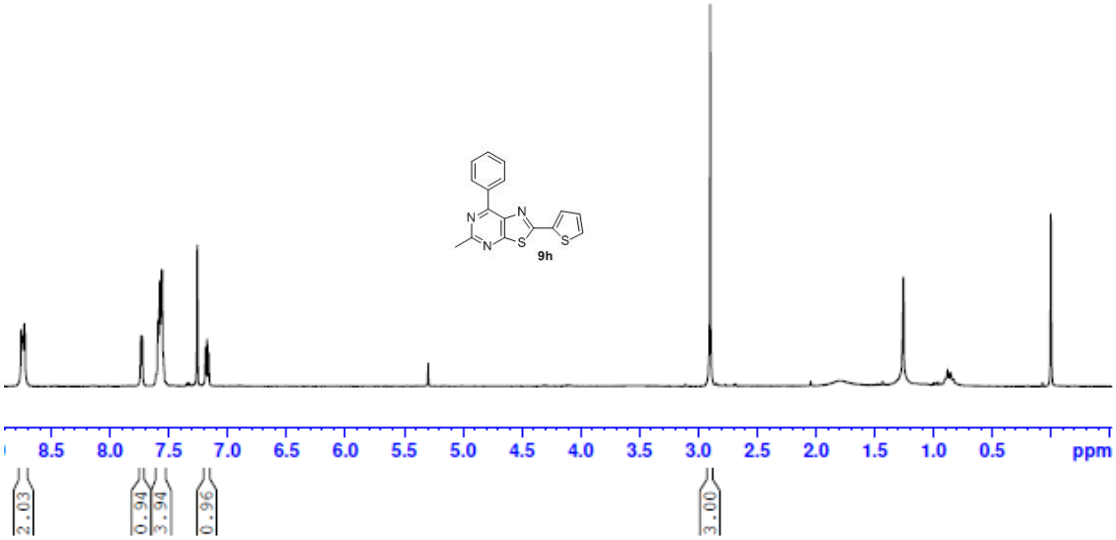


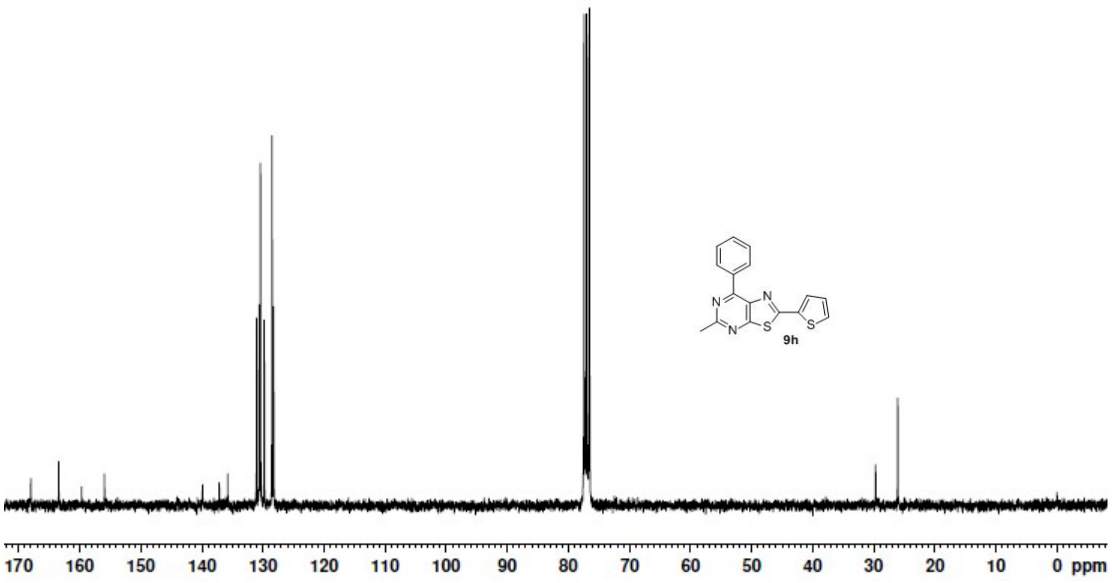

+ESI Scan (0.576 min) Frag=120.0V SYX1038965-p.d
322.0812
(M+H)+
9e
Counts vs. Mass-to-Charge (m/z)

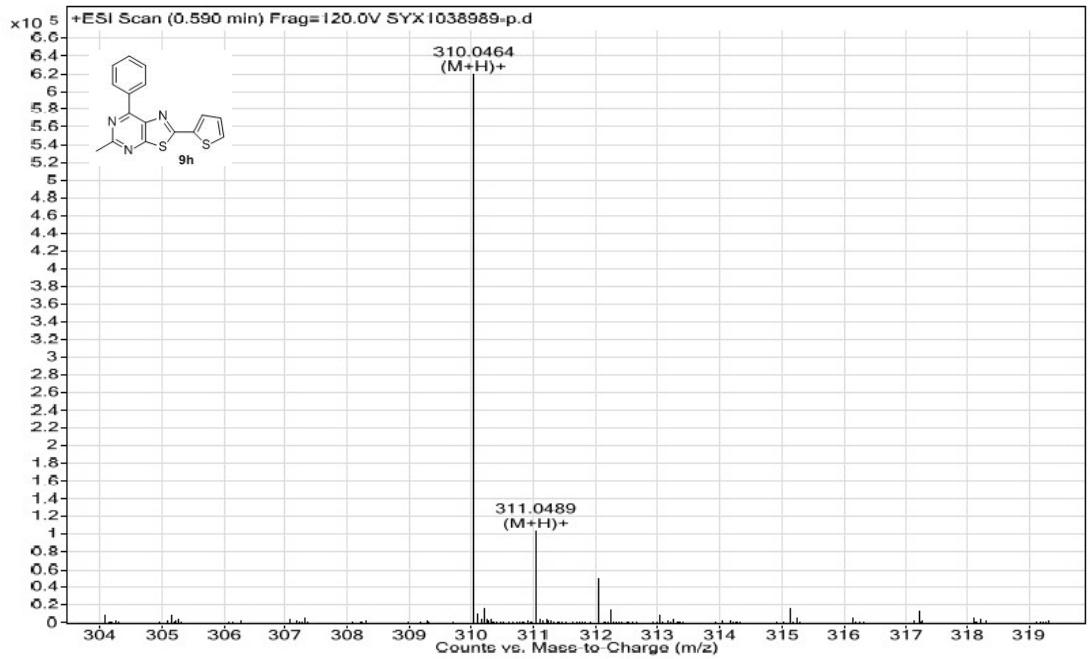

9f
ppm
2.04
1.94
3.06
1.99
2.99
3.00

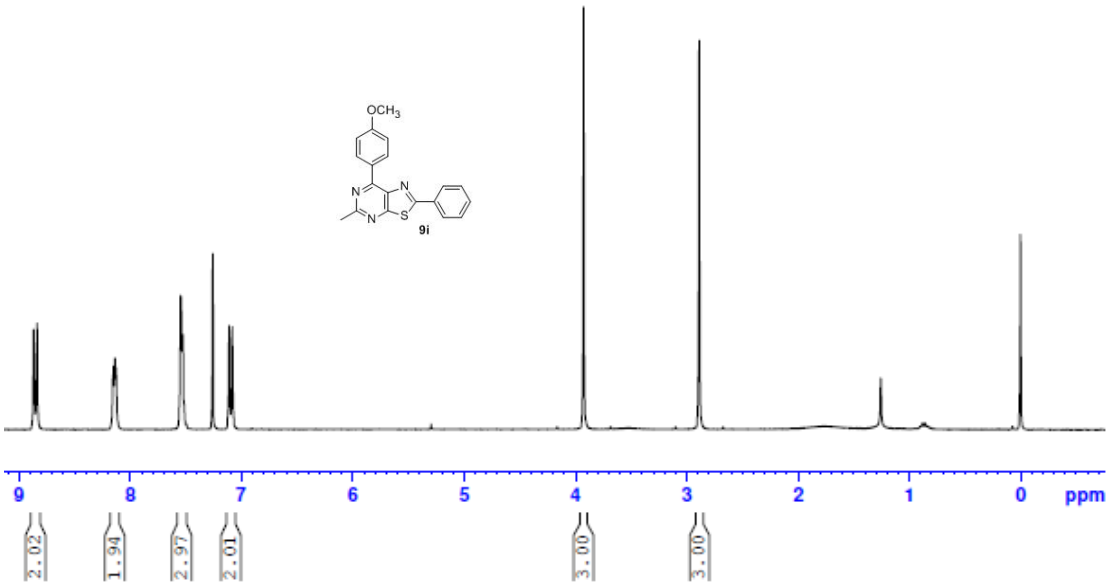


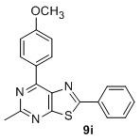


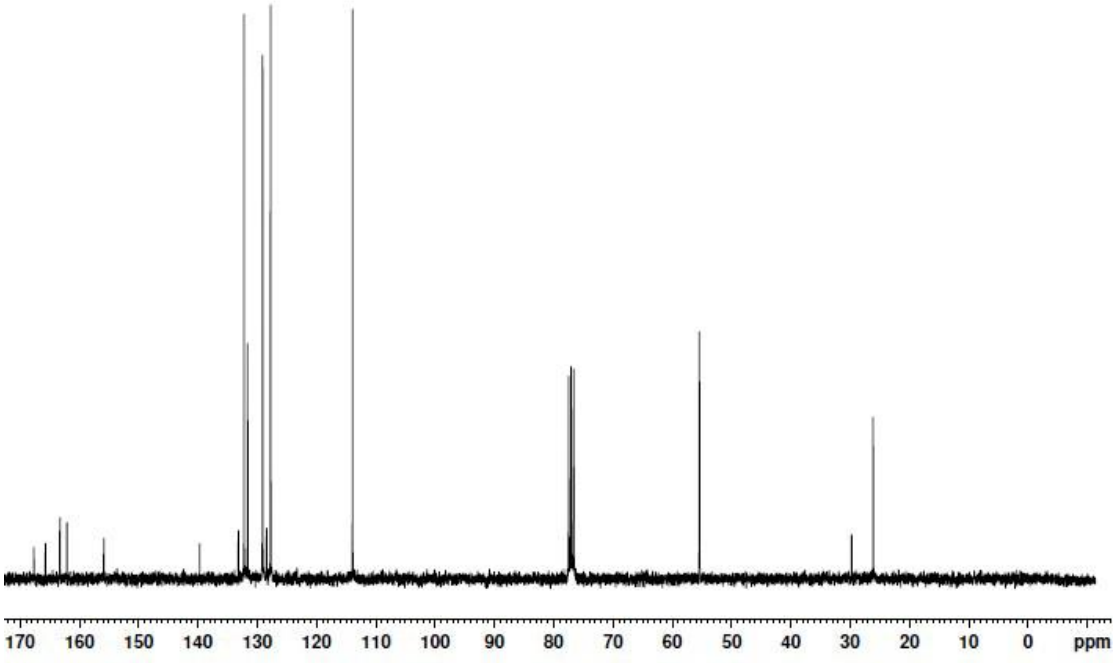


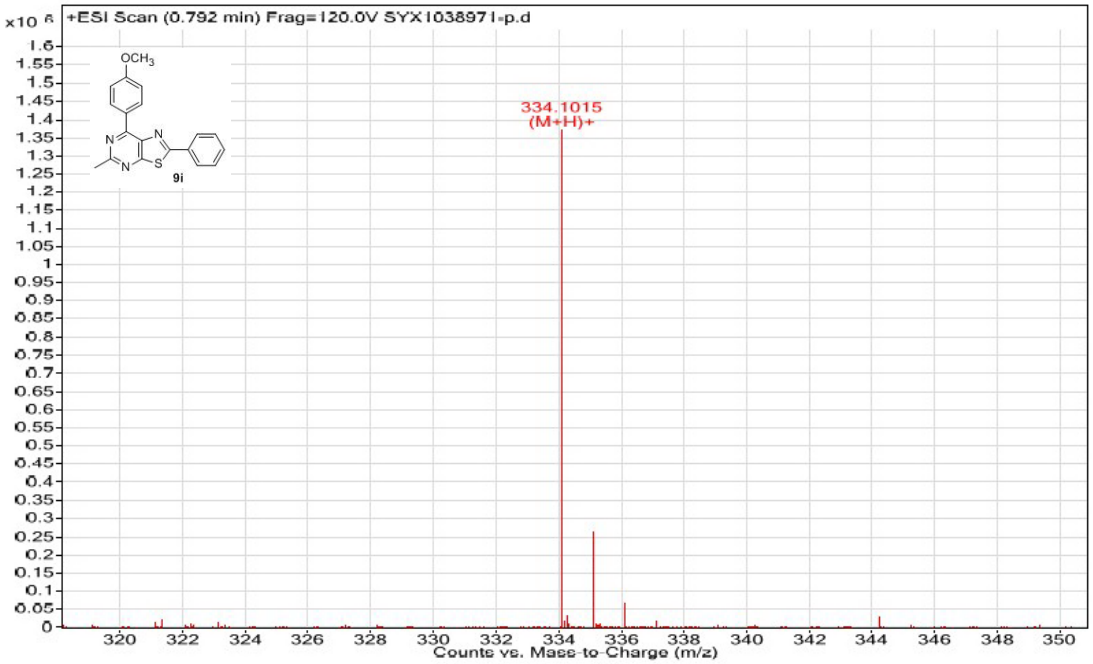


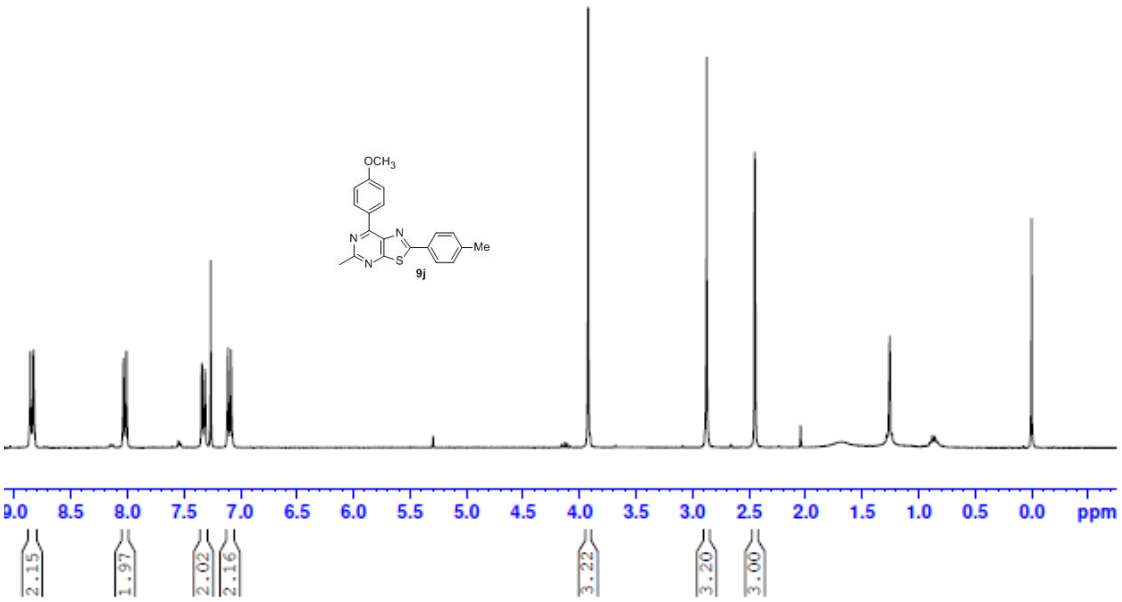


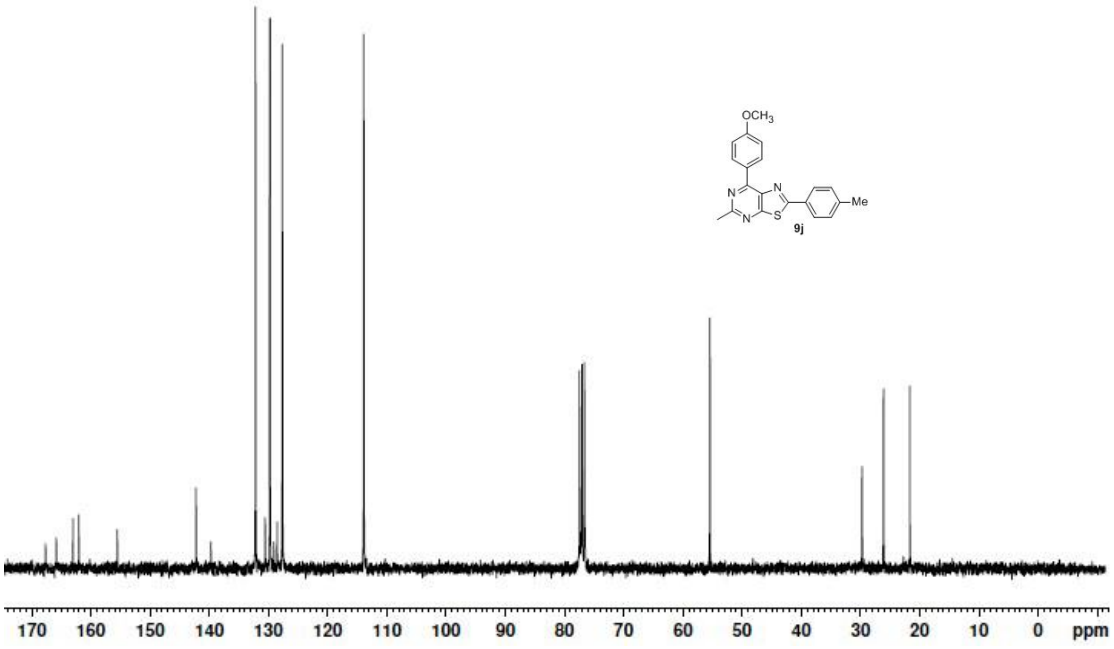


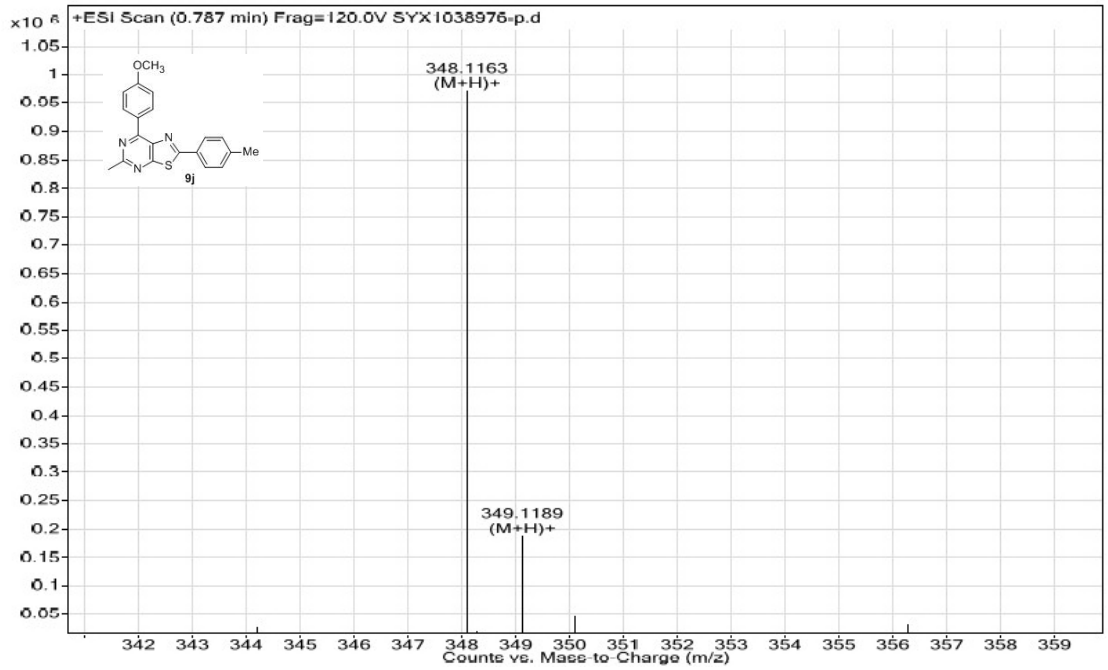


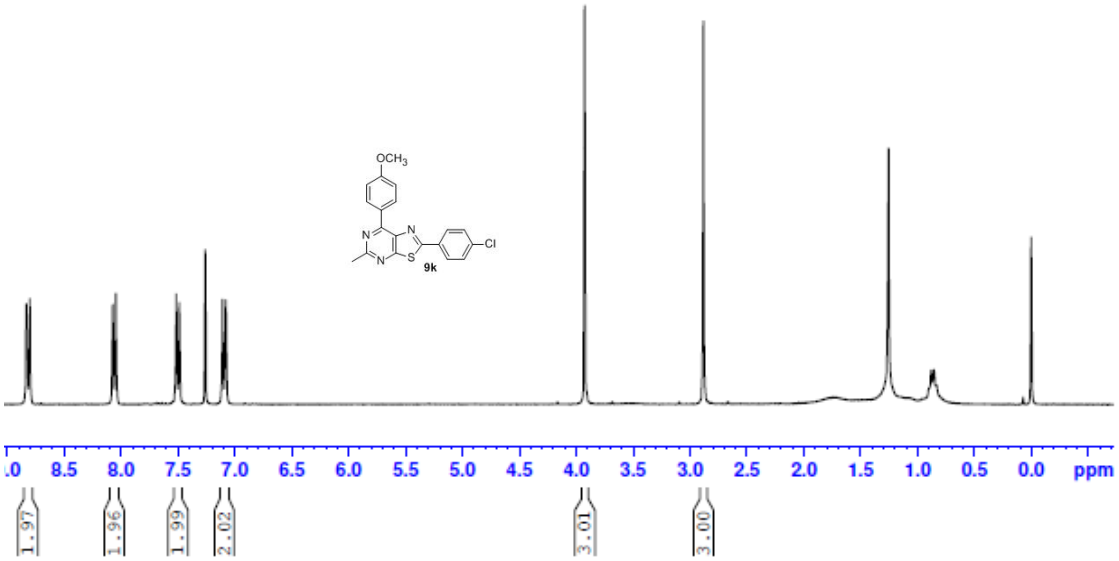


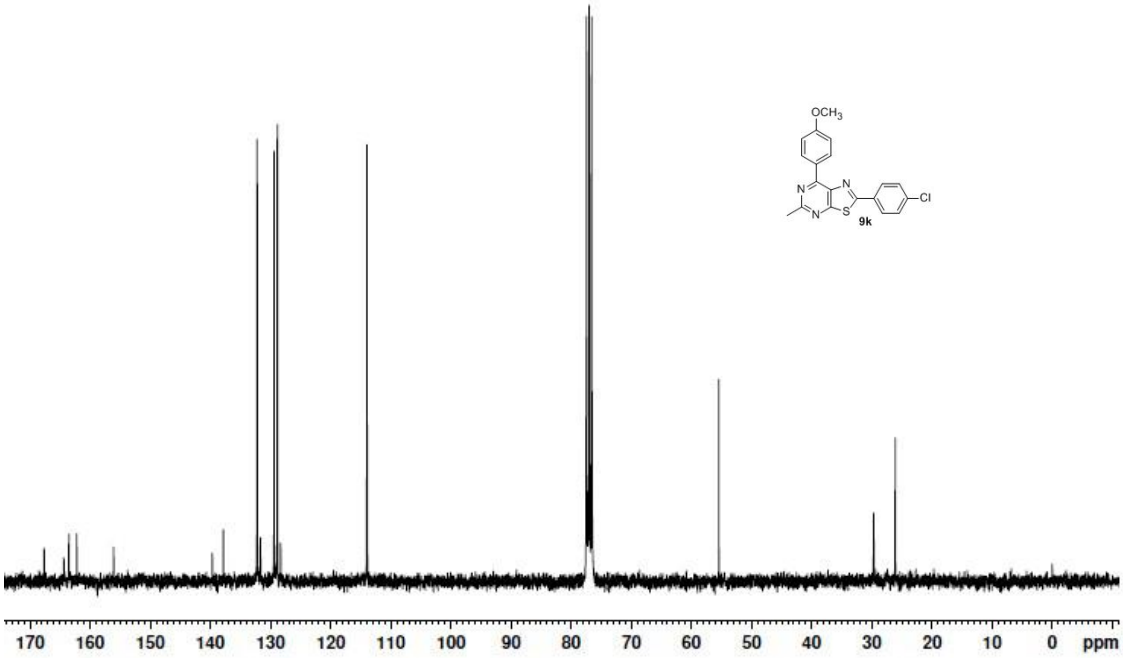


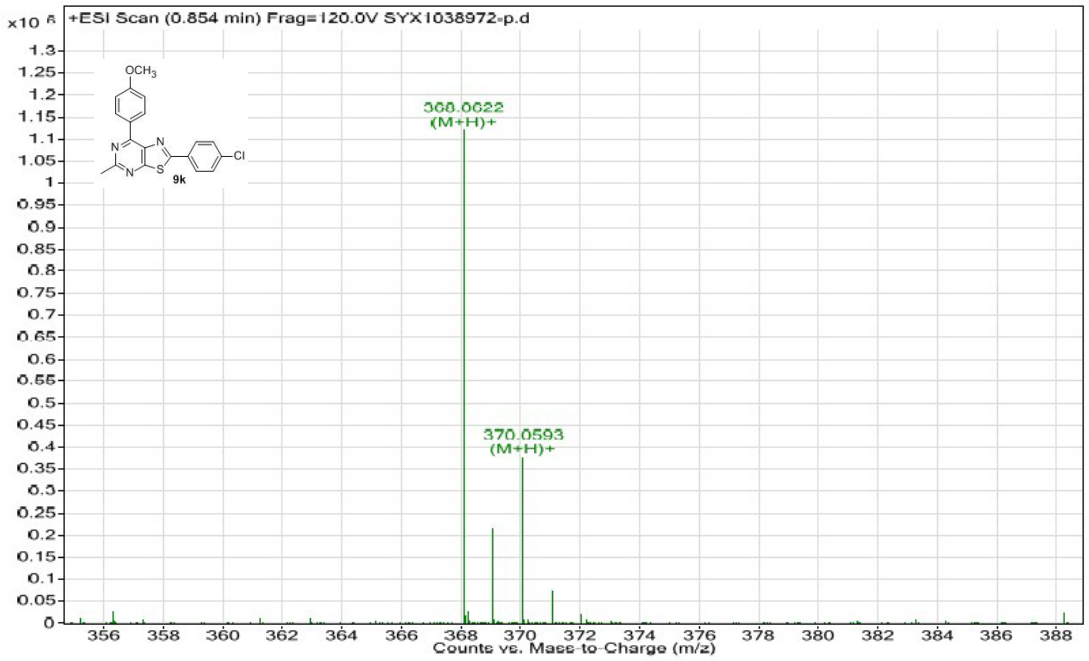


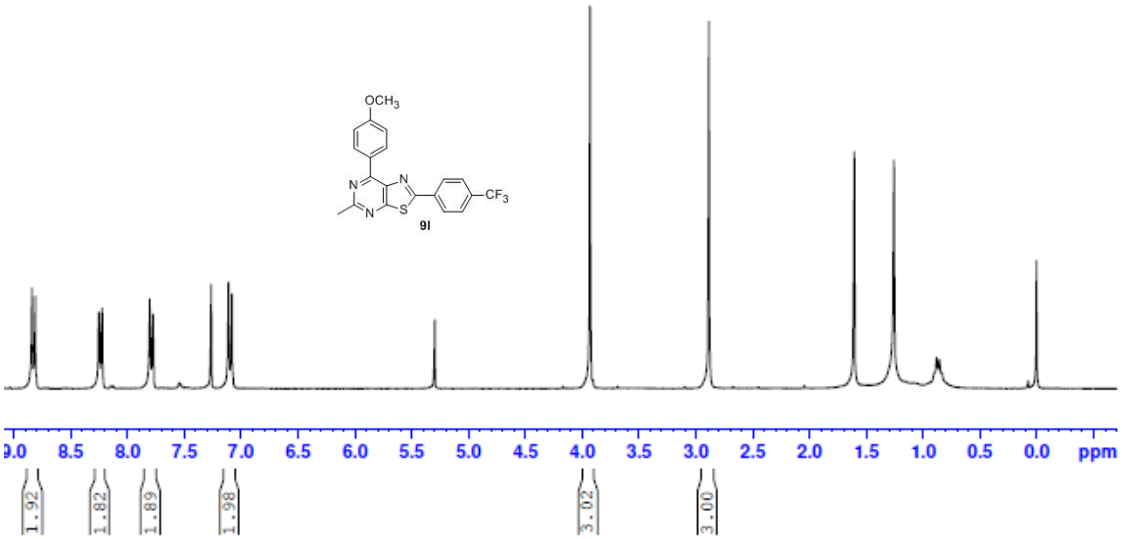


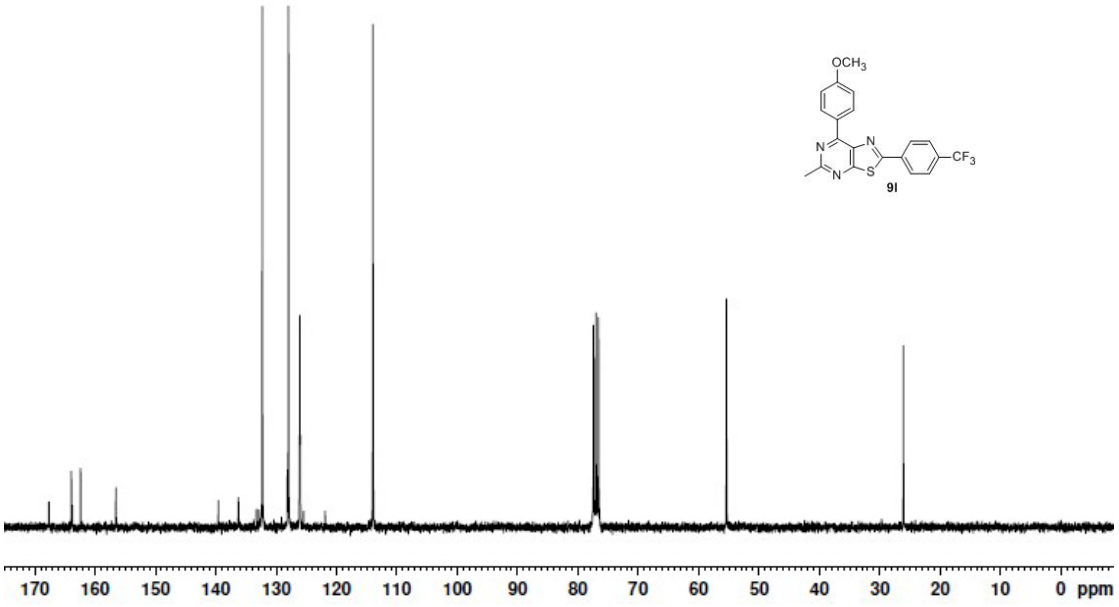

+ESI Scan (0.787 min) Frag=120.0V SYX1038976-p.d
348.1163
(M+H)+
349.1189
(M+H)+
OCH3
Me
9j
Counts vs. Mass-to-Charge (m/z)

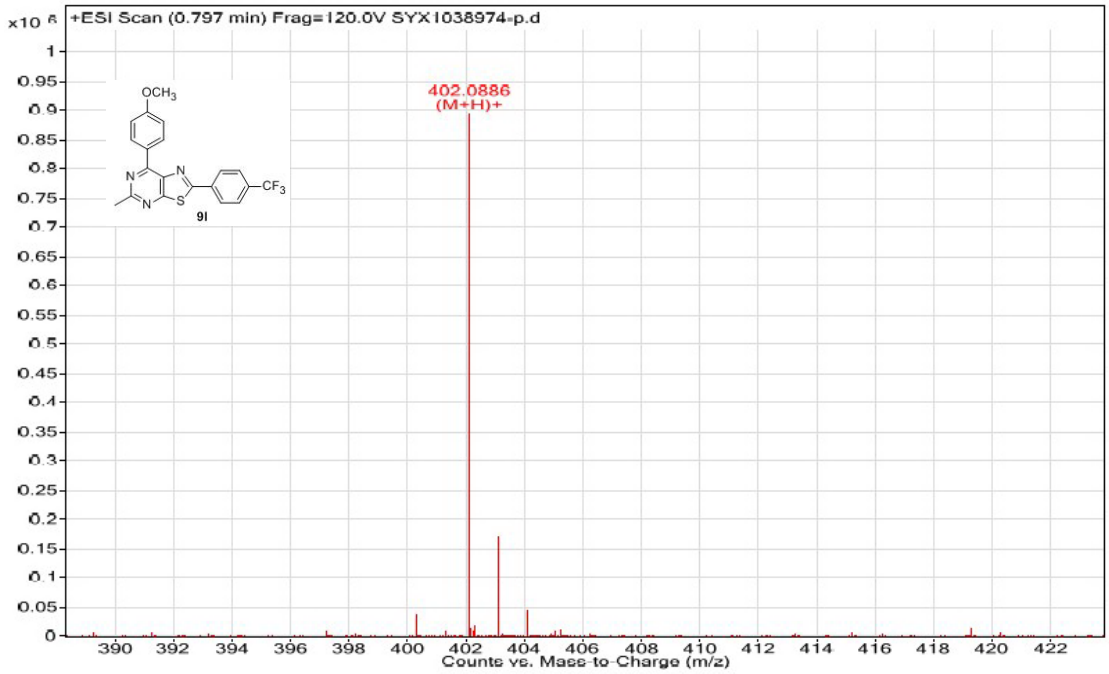

OCH3
Cl
9k
ppm
1.97
1.96
1.99
2.02
3.01
3.00

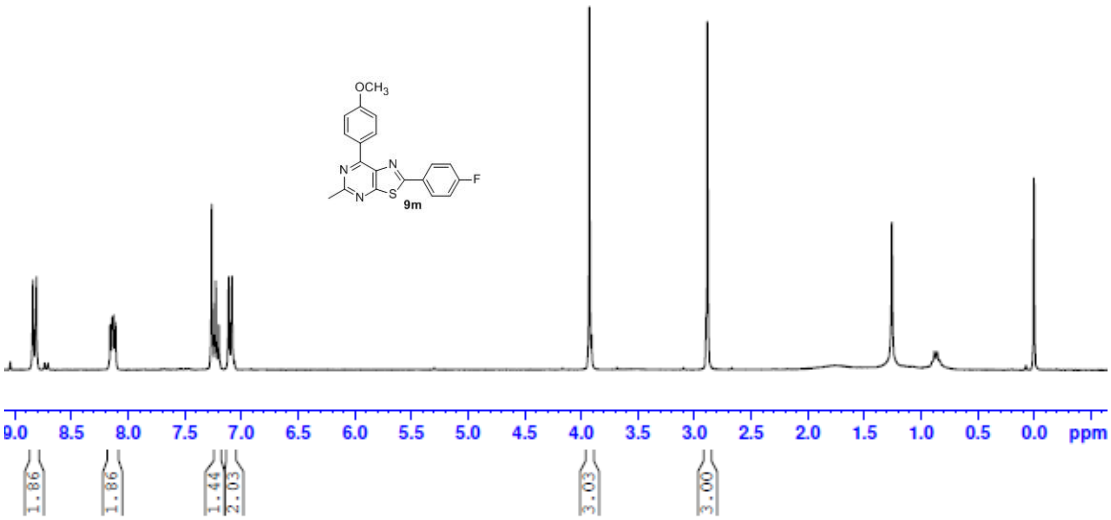

OCH3
N
N
S
N
Cl
9k
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

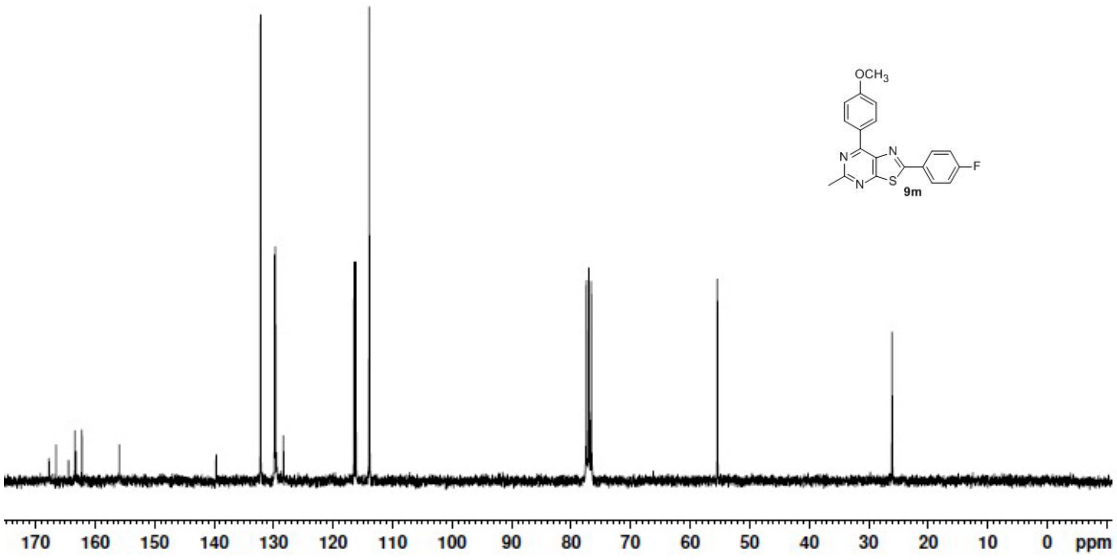

x10 6
+ESI Scan (0.854 min) Frag=120.0V SYX1038972-p.d
OCH3
N
N
S
N
Cl
9k
368.0622
(M+H)+
370.0593
(M+H)+
1.3
1.25
1.2
1.15
1.1
1.05
1
0.95
0.9
0.85
0.8
0.75
0.7
0.65
0.6
0.55
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
0
356 358 360 362 364 366 368 370 372 374 376 378 380 382 384 386 388
Counts vs. Mass-to-Charge (m/z)

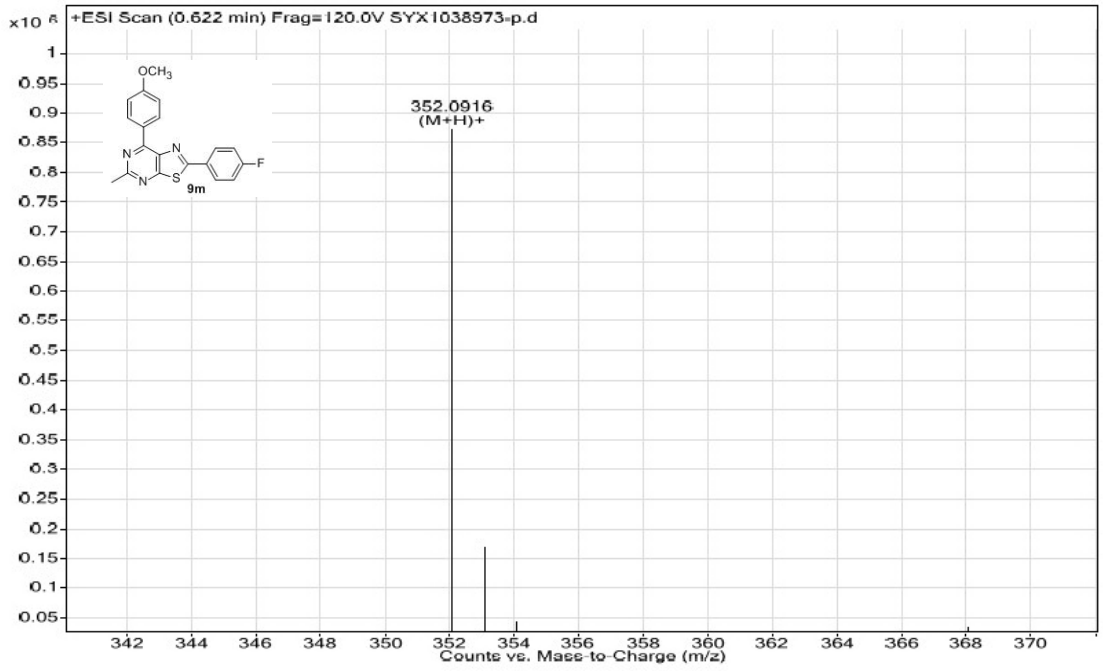

OCH3
N
N
S
N
CF3
9l
9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 ppm
1.92
1.82
1.89
1.98
3.02
3.00

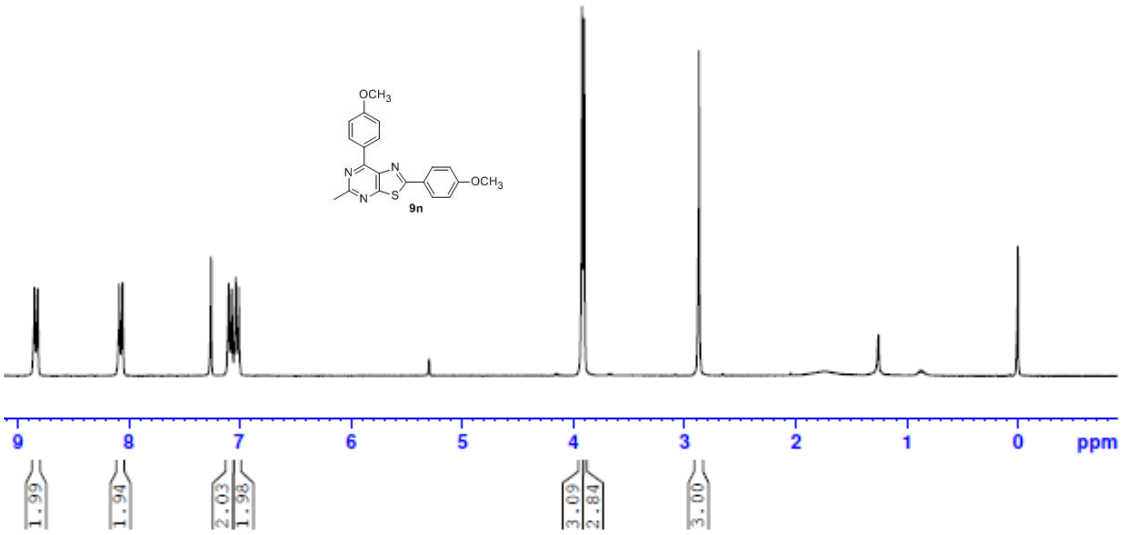

OCH3
N
N
S
N
CF3
9l
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm

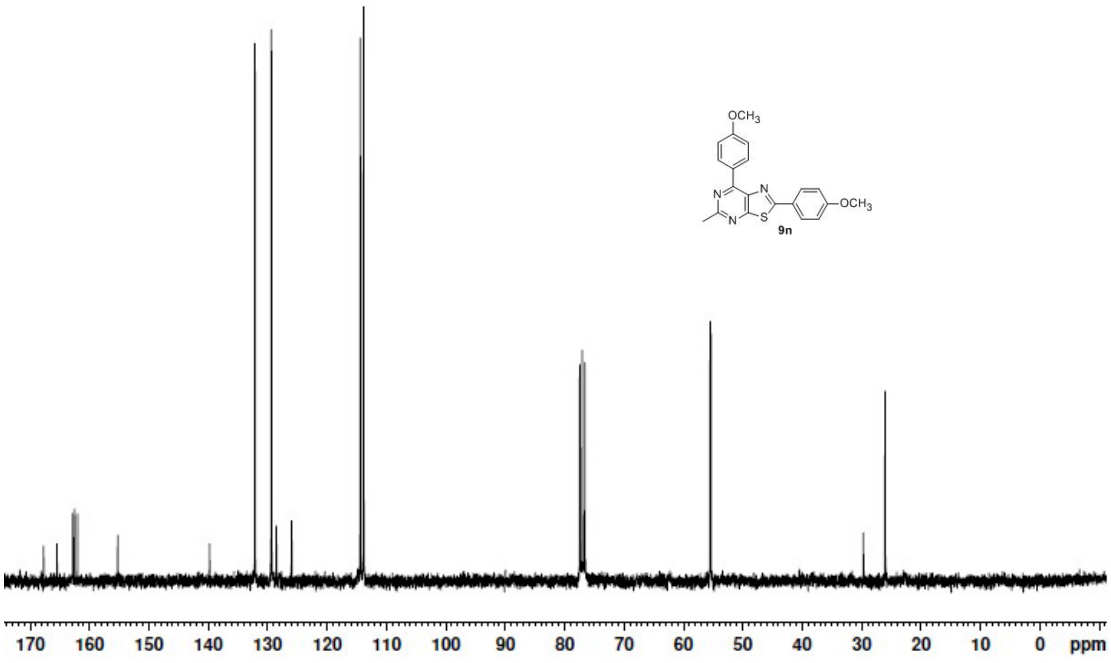

+ESI Scan (0.797 min) Frag=120.0V SYX1038974-p.d
402.0886
(M+H)+
OCH3
CF3
9l
Counts vs. Mass-to-Charge (m/z)

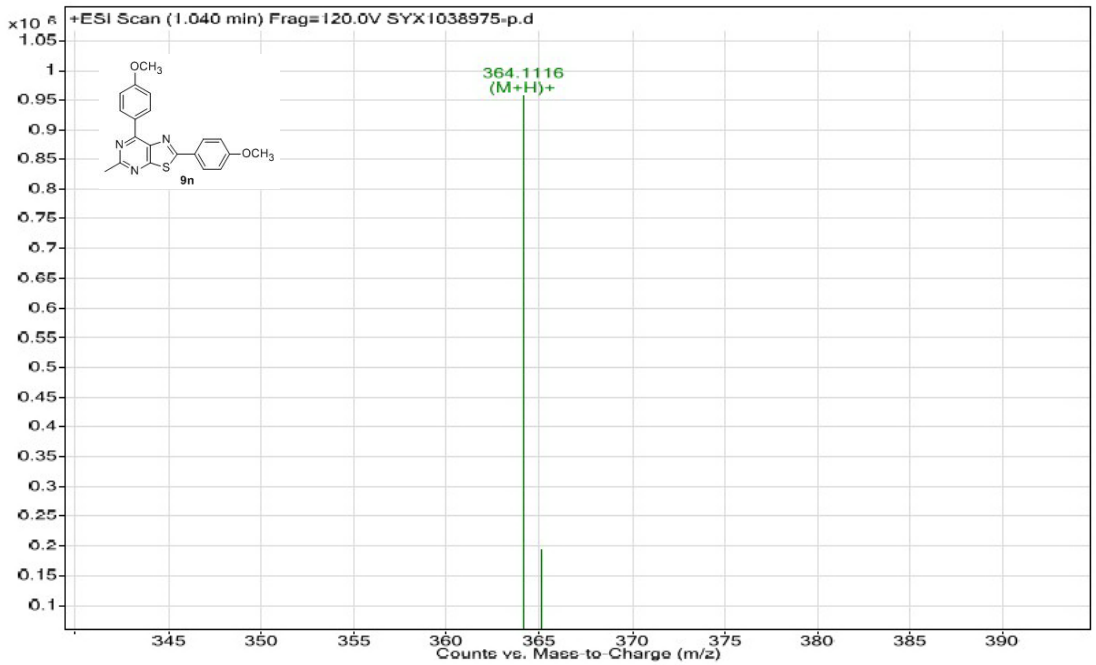

OCH3
F
9m
ppm
1.86
1.86
1.44
2.03
3.03
3.00

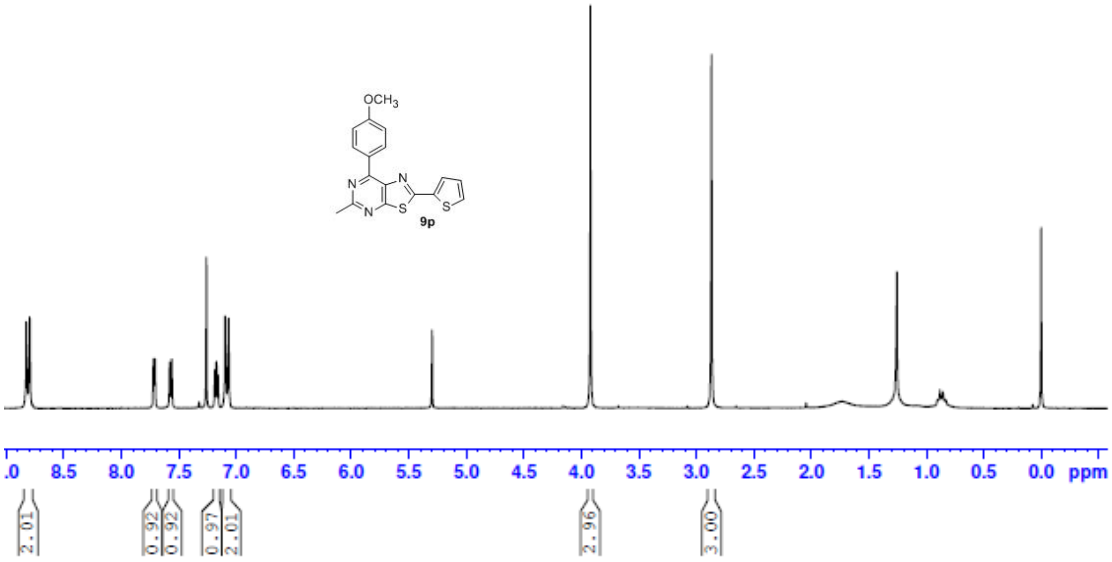

OCH3
N
N
S
F
9m
170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 ppm


x10 6
+ESI Scan (0.622 min) Frag=120.0V SYX1038973-p.d
OCH3
N
N
S
F
9m
352.0916
(M+H)+
1
0.95
0.9
0.85
0.8
0.75
0.7
0.65
0.6
0.55
0.5
0.45
0.4
0.35
0.3
0.25
0.2
0.15
0.1
0.05
342 344 346 348 350 352 354 356 358 360 362 364 366 368 370
Counts vs. Mass-to-Charge (m/z)






+ESI Scan (1.040 min) Frag=120.0V SYX1038975-p.d
364.1116
(M+H)+
9n
Counts vs. Mass-to-Charge (m/z)


9p
ppm