Supporting Information

Rapid Access to Kinase Inhibitor Pharmacophore by Regioselective C–H Arylation of Thieno[2,3-*d*]pyrimidine

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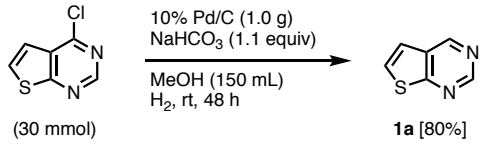
1. General

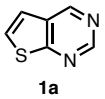
Unless otherwise noted, all reactants or reagents including dry solvents were obtained from commercial suppliers and used as received. (2,2'-bipyridyl)PhPdI complex **4** in Table 1 was synthesized according to a procedure reported in the literature.[S1] All work-up and purification procedures were carried out with reagent-grade solvents under air.

Analytical thin-layer chromatography (TLC) was performed using E. Merck silica gel 60 F254 precoated plates (0.25 mm). The developed chromatogram was analyzed by UV lamp (254 nm) or phosphomolybdic acid/sulfuric acid solution. Flash column chromatography was performed with E. Merck silica gel 60 (230–400 mesh) for material synthesis, on a Biotage Isolera® Spektra instrument equipped with a Biotage SNAP Ultra 10 g cartridge for the standard scale catalysis, or with a Biotage SNAP Ultra 50 g cartridge for the 1.0 mmol scale catalysis. Preparative thin-layer chromatography (PTLC) was performed using Wakogel B5-F silica coated plates (0.75 mm) prepared in our laboratory. Preparative recycling gel permeation chromatography (GPC) was performed with a JAI LC-9204 instrument equipped with JAIGEL-1/JAIGEL-2H columns using chloroform as eluent. Nuclear magnetic resonance (NMR) spectra were recorded on a JEOL ECA-500 (^{19}F 470 MHz) and a JEOL ECA-600II with Ultra COOL™ probe (^{1}H 600 MHz, ^{13}C 150 MHz) spectrometer. Chemical shifts for ^{1}H NMR are expressed in parts per million (ppm) relative to tetramethylsilane (δ 0.00 ppm) or $(CD_3)_2SO$ (δ 2.50 ppm). Chemical shifts for ^{13}C NMR are expressed in parts per million (ppm) relative to $CDCl_3$ (δ 77.2 ppm) or $(CD_3)_2SO$ (δ 39.5 ppm). Chemical shifts for ^{19}F NMR are expressed in parts per million (ppm) relative to hexafluorobenzene (δ –164.9 ppm) as an external standard. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, dd = doublet of doublets, t = triplet, q = quartet, sept = septet, m = multiplet, brs = broad singlet, brd = broad doublet), coupling constant (Hz), and integration. Infrared spectra were recorded on a JASCO FTIR-6100 spectrometer.

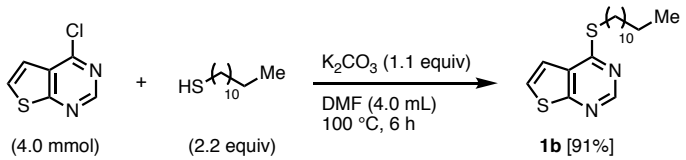
2. Synthesis of Thieno[2,3-*d*]pyrimidine Derivatives 1



A two-neck round bottom flask containing a magnetic stirring bar was dried with a heat gun under reduced pressure. To this flask were added 4-chlorothieno[2,3-*d*]pyrimidine (5.12 g, 30 mmol, 1.0 equiv), $NaHCO_3$ (2.93 g, 1.1 equiv) and 10% palladium on charcoal (1.00 g). The vessel was evacuated and back-filled with hydrogen gas, which was repeated three times. To this reaction mixture was added MeOH (150 mL), and the reaction mixture was stirred at room temperature for 2 days. The reaction mixture was passed through a pad of Celite® eluting with MeOH and the filtrate was concentrated *in vacuo* to give the crude product. Purification was carried out by flash column chromatography on silica-gel (hexane/EtOAc = 5:1) to give the corresponding compound **1a** as a white solid (3.25 g, 80%).

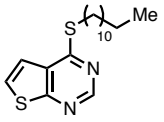


thieno[2,3-*d*]pyrimidine (1a): (3.25 g, 80%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 (d, J = 6.0 Hz, 1H), 7.58 (d, J = 6.0 Hz, 1H), 9.11 (s, 1H), 9.18 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 120.2, 128.1, 130.9, 151.9, 153.6, 168.8; FT-IR (neat, cm^{-1}): 3073, 3022, 1528, 1423, 1372, 1103, 936, 873, 795, 700; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_6H_5N_2S$ 137.0168; Found 137.0169.



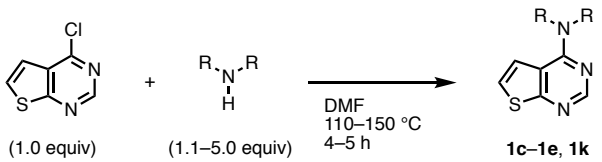
To a 20-mL round bottom flask containing a magnetic stirring bar were added 4-chlorothieno[2,3-*d*]pyrimidine (682 mg, 4.0 mmol, 1.0 equiv), K_2CO_3 (608 mg, 1.1 equiv), 1-dodecanethiol (1.22 mL, 2.2 equiv) and DMF (4.0 mL). The reaction mixture was stirred at 100 °C in an oil bath for 6 h. After cooling to ambient temperature, to the reaction mixture was added H_2O and the aqueous phase was extracted with EtOAc (repeated three times). The combined organic phases were washed with brine and dried over Na_2SO_4 successively.

Following filtration of Na_2SO_4 and removal of the solvent *in vacuo* afforded the crude mixture (2.28 g), which was purified by flash column chromatography on silica-gel (hexane/EtOAc = 30:1 → 20:1) to give the corresponding compound **1b** as a white solid (1.23 g, 91%).



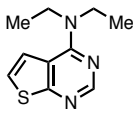
1b

4-(dodecylsulfanyl)thieno[2,3-*d*]pyrimidine (1b): (1.23 g, 91%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, J = 7.2 Hz, 3H), 1.26–1.36 (m, 16H), 1.45–1.49 (m, 2H), 1.75–1.80 (m, 2H), 3.36 (t, J = 7.2 Hz, 2H) 7.33 (d, J = 6.0 Hz, 1H), 7.45 (d, J = 6.0 Hz, 1H), 8.80 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.3, 22.9, 29.1, 29.4, 29.4, 29.5, 29.5, 29.7, 29.8, 29.8, 29.8, 32.1, 119.4, 126.2, 128.2, 152.7, 165.1, 165.8; FT-IR (neat, cm^{-1}): 2911, 2848, 1537, 1513, 1470, 1406, 1357, 1277, 1134, 880, 843, 700; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{29}N_2S_2$ 337.1767; Found 337.1767.



(1.0 equiv) (1.1–5.0 equiv) **1c–1e**, **1k**

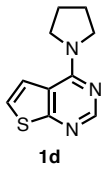
Typical Procedure for Amination: To a 50-mL round bottom flask containing a magnetic stirring bar were added 4-chlorothieno[2,3-*d*]pyrimidine (1.0 equiv), amine (1.1–5.0 equiv) and DMF. The reaction mixture was stirred at the corresponding temperature for 4–5 h in an oil bath. After cooling to ambient temperature, the crude mixture was obtained by concentration *in vacuo*. The purification was carried out by flash column chromatography on silica-gel to provide the corresponding amino-substituted thieno[2,3-*d*]pyrimidines **1c**–**1e**, **1k**.



1c

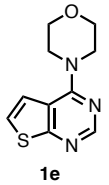
***N*,*N*-diethylthieno[2,3-*d*]pyrimidin-4-amine (1c)**: reaction scale: 2.0 mmol, amine: 5.0 equiv., DMF: 10 mL, reaction temperature: 110 °C, reaction time: 5 h. Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) afforded **1c** as a white solid (388 mg, 94%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.33 (t, J = 7.2 Hz, 6H), 3.76 (q, J = 7.2 Hz, 4H), 7.19 (d, J = 6.0 Hz, 1H), 7.32 (d, J = 6.0 Hz, 1H), 8.43 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.5, 44.3,

115.0, 120.7, 121.5, 153.3, 157.3, 169.3; FT-IR (neat, cm^{-1}): 3092, 2974, 2925, 2862, 1550, 1500, 1455, 1339, 1075, 1026, 872, 828, 693;HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{14}N_3S$ 208.0903; Found 208.0899.



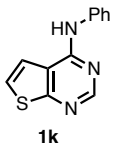
1d

4-(pyrrolidin-1-yl)thieno[2,3-*d*]pyrimidine (1d): reaction scale: 2.0 mmol, amine: 5.0 equiv., DMF: 10 mL, reaction temperature: 110 °C, reaction time: 5 h. Purification by flash column chromatography for 2 times (1^{st}: $CHCl_3$/MeOH = 20:1, 2^{nd}: hexane/EtOAc = 95:5 → 75:25) afforded **1d** as a white solid (363 mg, 88%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.07 (brs, 4H), 3.84 (brs, 4H), 7.17 (d, *J* = 6.0 Hz, 1H), 7.47 (d, *J* = 6.0 Hz, 1H), 8.44 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 25.7, 49.1, 116.3, 120.4, 121.3, 153.7, 156.3, 168.6; FT-IR (neat, cm^{-1}): 3064, 2940, 2871, 1550, 1496, 1317, 1059, 1018, 879, 799, 693;HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{12}N_3S$ 206.0746; Found 206.0742.



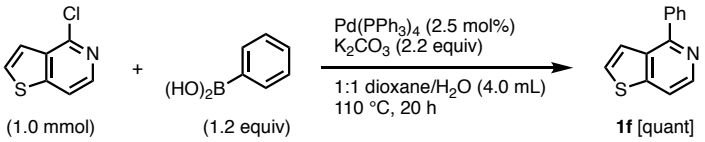
1e

4-(thieno[2,3-*d*]pyrimidin-4-yl)morpholine (1e): reaction scale: 4.0 mmol, amine: 5.0 equiv., DMF: 15 mL, reaction temperature: 110 °C, reaction time: 4 h. Purification by flash column chromatography (hexane/EtOAc = 90:10 → 50:50) and recrystallization from hexane/$CHCl_3$ afforded **1e** as a white solid (794 mg, quantitative). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.85 (t, *J* = 4.2 Hz, 4H), 3.93 (t, *J* = 4.2 Hz, 4H), 7.30 (d, *J* = 6.0 Hz, 1H), 7.34 (d, *J* = 6.0 Hz, 1H), 8.52 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 47.5, 66.9, 116.7, 120.4, 122.4, 153.1, 159.1, 169.8; FT-IR (neat, cm^{-1}): 3072, 2948, 1540, 1435, 1342, 1216, 1110, 980, 705; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{10}H_{12}N_3OS$ 222.0696; Found 222.0692.



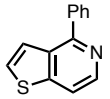
1k

***N*-phenylthieno[2,3-*d*]pyrimidin-4-amine (1k)**: reaction scale: 3.0 mmol, amine: 1.1 equiv., DMF: 1.0 mL, reaction temperature: 150 °C, reaction time: 4 h. Purification by flash column chromatography (hexane/EtOAc = 90:10 → 50:50) afforded **1k** as a pale yellow solid (566 mg, 66%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.06 (brs, 1H), 7.13 (d, *J* = 6.0 Hz, 1H), 7.19 (t, *J* = 7.8 Hz, 1H), 7.35 (d, *J* = 6.0 Hz, 1H), 7.41 (t, *J* = 7.8 Hz, 2H), 7.64 (d, *J* = 7.8 Hz, 2H), 8.62 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 116.8, 117.4, 122.3, 124.1, 125.0, 129.4, 138.4, 153.9, 155.4, 167.9; FT-IR (neat, cm^{-1}): 3262, 3073, 3016, 1610, 1536, 1495, 1446, 1353, 1206, 976, 879, 742, 693; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_{10}N_3S$ 228.0590; Found 228.0588.



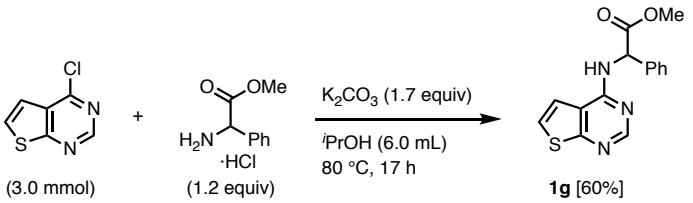
(1.0 mmol) (1.2 equiv) **1f** [quant]

To a well-dried Schlenk tube containing a magnetic stirring bar were added $Pd(PPh_3)_4$ (29.2 mg, 2.5 mol%), 4-chlorothieno[3,2-*c*]pyridine (171 mg, 1.0 mmol, 1.0 equiv), phenylboronic acid (147 mg, 1.2 equiv) and K_2CO_3 (309 mg, 2.2 equiv). The Schlenk tube was evacuated and back-filled with argon gas, which was repeated three times. Then, under a stream of argon gas, to it were added degassed 1,4-dioxane (2.0 mL) and H_2O (2.0 mL). The tube was sealed and then stirred at 110 °C in an oil bath for 20 h. Upon cooling to ambient temperature, the reaction mixture was washed with H_2O and the aqueous phase was extracted with EtOAc (repeated three times). The combined organic layers were treated with brine and Na_2SO_4 successively. Following filtration of Na_2SO_4 and removal of the solvent *in vacuo* afforded the crude mixture, which was purified by flash column chromatography on silica-gel (hexane/EtOAc = 97:3 → 90:10) to give **1f** as a white solid (234 mg, quantitative).

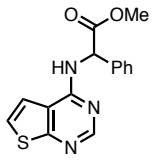


1f

4-phenylthieno[3,2-*c*]pyridine (1f): (234 mg, quantitative, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46–7.50 (m, 2H), 7.53 (t, *J* = 7.8 Hz, 2H), 7.62 (d, *J* = 6.0 Hz, 1H), 7.79 (d, *J* = 5.4 Hz, 1H), 7.84 (d, *J* = 7.8 Hz, 2H), 8.56 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 116.2, 123.6, 126.9, 128.6, 128.9, 129.2, 133.7, 140.1, 142.5, 148.4, 155.5; FT-IR (neat, cm^{-1}): 3110, 3056, 1420, 1232, 1065, 869, 835, 799, 757, 717, 694; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{10}NS$ 212.0528; Found 212.0524.

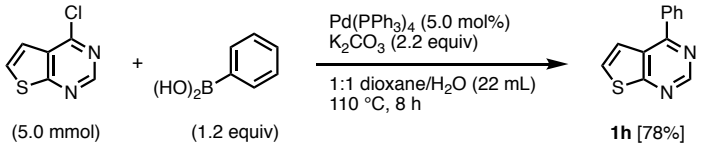


To a well-dried screw cap glass tube containing a magnetic stirring bar were added 4-chlorothieno[2,3-*d*]pyrimidine (512 mg, 3.0 mmol, 1.0 equiv), 2-phenylglycine methyl ester hydrochloride (726 mg, 1.2 equiv), K_2CO_3 (705 mg, 1.7 equiv) and ^{i}PrOH (6.0 mL). The reaction mixture was stirred at 80 °C in an oil bath for 17 h. After cooling to ambient temperature, the crude mixture was obtained by concentration *in vacuo*. The purification was carried out by flash column chromatography on silica-gel (hexane/EtOAc = 95:5 → 75:25 → 20:80) to provide **1g** as a pale yellow solid (537 mg, 60%).

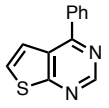


1g

methyl 2-phenyl-2-(thieno[2,3-*d*]pyrimidin-4-ylamino)acetate (1g): (537 mg, 60%, pale yellow solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.79 (s, 3H), 5.99 (d, *J* = 6.6 Hz, 1H), 6.11 (d, *J* = 6.6 Hz, 1H), 7.25 (d, *J* = 6.0 Hz, 1H), 7.33 (d, *J* = 6.0 Hz, 1H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 7.2 Hz, 2H), 7.51 (d, *J* = 7.2 Hz, 2H), 8.49 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 53.1, 57.6, 116.6, 117.2, 123.8, 127.7, 128.9, 129.2, 136.8, 153.9, 155.8, 167.1, 172.1; FT-IR (neat, cm^{-1}): 3355, 1734, 1578, 1167, 704; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{15}H_{14}N_3O_2S$ 300.0801; Found 300.0799.

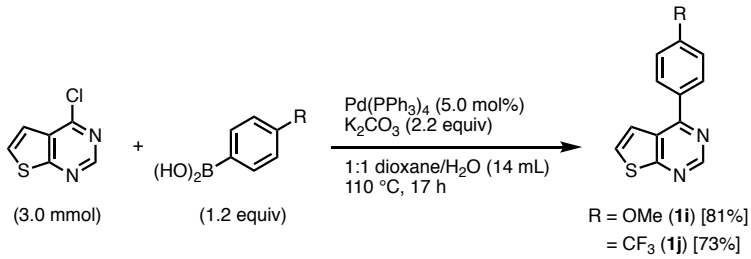


To a two-neck round bottom flask containing a magnetic stirring bar were added $Pd(PPh_3)_4$ (289 mg, 5.0 mol%), 4-chlorothieno[2,3-*d*]pyrimidine (853 mg, 5.0 mmol, 1.0 equiv), phenylboronic acid (732 mg, 1.2 equiv) and K_2CO_3 (1.52 g, 2.2 equiv). The vessel was evacuated and back-filled with argon gas, which was repeated three times. Then, under a stream of argon gas, to it were added degassed 1,4-dioxane (11 mL) and H_2O (11 mL). The vessel was sealed and then stirred at 110 °C in an oil bath for 8 h. Upon cooling to ambient temperature, the reaction mixture was washed with H_2O and the aqueous phase was extracted with EtOAc (repeated three times). The combined organic layers were treated with brine and Na_2SO_4 successively. Following filtration of Na_2SO_4 and removal of the solvent *in vacuo* afforded the crude mixture, which was purified by flash column chromatography on silica-gel (hexane/EtOAc = 98:2 → 90:10) to give **1h** as a pale yellow solid (828 mg, 78%).



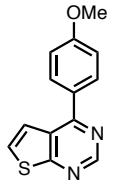
1h

4-phenylthieno[2,3-*d*]pyrimidine (1h): (828 mg, 78%, pale yellow solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.55–7.62 (m, 5H), 7.95–7.96 (m, 2H), 9.17 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 121.2, 127.3, 128.1, 129.1, 129.4, 130.6, 137.9, 153.6, 161.1, 170.0; FT-IR (neat, cm^{-1}): 3100, 1514, 1425, 1350, 1071, 871, 845, 756, 720, 690; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_9N_2S$ 213.0481; Found 213.0479.



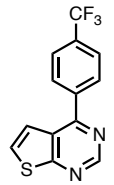
To a two-neck round bottom flask containing a magnetic stirring bar were added $Pd(PPh_3)_4$ (170 mg, 5.0 mol%), 4-chlorothieno[2,3-*d*]pyrimidine (512 mg, 3.0 mmol, 1.0 equiv), arylboronic acid (1.2 equiv) and K_2CO_3 (912 mg, 2.2 equiv). The vessel was evacuated and

back-filled with argon gas, which was repeated three times. Then, under a stream of argon gas, to it were added degassed 1,4-dioxane (7.0 mL) and H_2O (7.0 mL). The vessel was sealed and then stirred at 110 °C in an oil bath for 17 h. Upon cooling to ambient temperature, the reaction mixture was washed with H_2O and the aqueous phase was extracted with EtOAc (repeated three times). The combined organic layers were treated with brine and Na_2SO_4 successively. Following filtration of Na_2SO_4 and removal of the solvent *in vacuo* afforded the crude mixture, which was purified by flash column chromatography on silica-gel to give **1i** or **1j**.



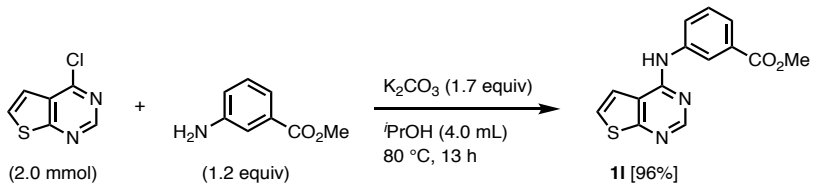
1i

4-(4-methoxyphenyl)thieno[2,3-*d*]pyrimidine (1i): Purification by flash column chromatography (hexane/EtOAc = 98:2 → 80:20) and recrystallization from hexane/$CHCl_3$ afforded **1i** as a colorless solid (588 mg, 81%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.91 (s, 3H), 7.09 (d, J = 9.0 Hz, 2H), 7.56 (d, J = 6.0 Hz, 1H), 7.63 (d, J = 6.0 Hz, 1H), 7.96 (d, J = 9.0 Hz, 2H), 9.12 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.7, 114.5, 121.3, 126.9, 127.7, 130.4, 131.0, 153.5, 160.7, 161.8, 169.9; FT-IR (neat, cm^{-1}): 3081, 2970, 1509, 1353, 1231, 1022, 714; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{11}N_2OS$ 243.0592; Found 243.0588.

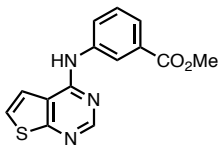


1j

4-(4-(trifluoromethyl)phenyl)thieno[2,3-*d*]pyrimidine (1j): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 85:15) and recrystallization from hexane/$CHCl_3$ afforded **1j** as a pale yellow solid (615 mg, 73%). ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.57 (d, J = 6.0 Hz, 1H), 7.64 (d, J = 6.0 Hz, 1H), 7.84 (d, J = 8.4 Hz, 2H), 8.08 (d, J = 8.4 Hz, 2H), 9.20 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 120.4, 124.0 (q, $^1J_{C–F}$ = 270 Hz), 126.0 (d, $^3J_{C–F}$ = 2.9 Hz), 128.0, 128.1, 129.6, 132.3 (q, $^2J_{C–F}$ = 32 Hz), 141.1, 153.4, 159.4, 170.2; ^{19}F NMR (470 MHz, $CDCl_3$): δ –62.68; FT-IR (neat, cm^{-1}): 3121, 3054, 1518, 1325, 1164, 1099, 1060, 846, 718; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_8F_3N_2S$ 281.0355; Found 281.0354.



To a well-dried screw cap glass tube containing a magnetic stirring bar were added 4-chlorothieno[2,3-*d*]pyrimidine (341 mg, 2.0 mmol, 1.0 equiv), methyl 3-aminobenzoate (363 mg, 1.2 equiv), K_2CO_3 (470 mg, 1.7 equiv) and ^{i}PrOH (4.0 mL). The reaction mixture was stirred at 80 °C in an oil bath for 13 h. After cooling to ambient temperature, the crude mixture was obtained by concentration *in vacuo*. The purification was carried out by flash column chromatography on silica-gel (hexane/EtOAc = 95:5 → 75:25 → 20:80) to provide **1l** as a white solid (546 mg, 96%).



1l

methyl 3-(thieno[2,3-*d*]pyrimidin-4-ylamino)benzoate (1l): (546 mg, 96%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.95 (s, 3H), 7.07 (brs, 1H), 7.23 (d, J = 6.0 Hz, 1H), 7.42 (d, J = 6.0 Hz, 1H), 7.49 (t, J = 8.4 Hz, 1H), 7.84 (dd, J = 8.4, 1.2 Hz, 1H), 8.08 (dd, J = 8.4, 1.2 Hz, 1H), 8.22 (d, J = 1.2 Hz, 1H), 8.66 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 52.5, 116.9, 117.0, 122.5, 124.7, 125.6, 126.1, 129.5, 131.3, 138.8, 153.7, 155.0, 166.9, 167.9; FT-IR (neat, cm^{-1}): 3377, 3081, 1719, 1702, 1617, 1577, 1538, 1515, 1490, 1431, 1283, 1210, 1106, 1013, 885, 799, 747, 694; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{12}N_3O_2S$ 286.0645; Found 286.0647.

3. Investigation on Reactivity Difference between Benzo[*b*]thiophene and Thieno[2,3-*d*]pyrimidine

At first, we investigated the difference in the reactivity between benzo[*b*]thiophene and thieno[2,3-*d*]pyrimidine. Since there are versatile arylation reactions of benzo[*b*]thiophene, we applied them for the arylation of thieno[2,3-*d*]pyrimidine. Overall, the reactivity of thieno[2,3-*d*]pyrimidine is lower than that of benzo[*b*]thiophene. This can be attributed to the electron-withdrawing and coordinating azine substructure of thieno[2,3-*d*]pyrimidine. All reactions were carried out in 0.20 mmol reaction scale according to the reported procedures.

Thieno[2,3-*d*]pyrimidine Arylation by Benzo[*b*]thiophene Arylation Conditions

We attempted arylations of **1a** by applying the reported α-selective benzo[*b*]thiophene arylation conditions. The rhodium and iridium catalysts developed in our group gave no arylated products (entries 1 and 2). Employing our palladium/2,2'-bipyridyl catalyst or Fagnou's palladium/phosphine catalyst slightly produced the desired products albeit unsatisfying C6-selectivity (entries 3 and 4). The recent example of near-room temperature α-arylation reaction failed to arylate thieno[2,3-*d*]pyrimidine (entry 5).

Table S1. α-Selective Benzo[*b*]thiophene Arylation Catalysis for **1a**

Entry	X	*conditions*	**2a/3a** (%)[a]	C6/C5	Recov. **1a** (%)
1[S2]	I	$RhCl(CO)\{P[OCH(CF_3)_2]_3\}_2$ (3.0 mol%) Ag_2CO_3 (1.0 equiv), 1,2-dimethoxyethane (1.0 equiv) *m*-xylene (1.0 mL), 150 °C	0/0	–	–
2[S3]	I	$[Ir(cod)(py)PCy_3]PF_6$ (5.0 mol%) Ag_2CO_3 (1.05 equiv) *m*-xylene (1.0 mL), 160 °C	0/0	–	76
3[S4]	I	$PdCl_2$ (5.0 mol%), 2,2'-bipyridyl (10 mol%) Ag_2CO_3 (1.0 equiv) *m*-xylene (0.80 mL), 120 °C	18/4	82:18	–
4[S5]	Br	$Pd(OAc)_2$ (2.0 mol%) $PCy_3 \cdot HBF_4$ (4.0 mol%) PivOH (30 mol%), K_2CO_3 (1.5 equiv) DMAc (0.67 mL), 100 °C	17/4	81:19	74
5[S6]	I	$Pd(OAc)_2$ (0.40 mol%) Ag_2O (1.0 equiv) NaOAc (0.50 equiv) HFIP (0.20 mL), 30 °C	0/0	–	–

[a] Determined by GC using dodecane as the internal standard.

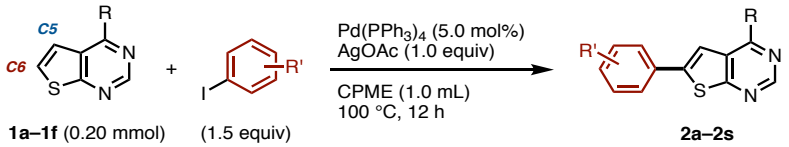
The investigation on arylation of **1a** under the reported *β*-selective conditions was performed. We applied our palladium/P[OCH(CF$_3$)$_2$]$_3$ catalyst for arylation of **1a** but the product was obtained in low yield in moderate C5-selectivity (entry 1). Other reaction conditions, which are optimized for the arylation of benzo[*b*]thiophene, were also not applicable. The palladium-catalyzed cross-coupling with iodobenzene was not applicable to convert **1a** and 92% of **1a** was recovered (entry 2). The reaction with chlorobenzene by using heterogeneous palladium on charcoal catalyst did not yield the target products (entry 3). The oxidative coupling conditions with phenylboronic acid was then tested, however, a trace amount of product was obtained (entry 4).

Table S2. *β*-Selective Arylation Catalysis

Entry	X	*conditions*	**2a**/**3a** (%)[a]	C6/C5	Recov. **1a** (%)
1[S4]	I	PdCl$_2$ (5.0 mol%) P[OCH(CF$_3$)$_2$]$_3$ (10 mol%) Ag$_2$CO$_3$ (1.0 equiv) *m*-xylene (1.0 mL), 120 °C	4/7	36:64	–
2[S7]	I	Pd$_2$(dba)$_3$·CHCl$_3$ (2.5 mol%) Ag$_2$CO$_3$ (0.75 equiv) HFIP (0.20 mL), rt	0/0	–	76
3[S8]	I	5% Pd/C (9.4 mol%) CuCl (10 mol%) Cs$_2$CO$_3$ (1.1 equiv) 1,4-dioxane (1.0 mL), 150 °C	0/0	–	–
4[S9]	Br	Pd(OAc)$_2$ (10 mol%) 2,2'-bipyridyl (10 mol%) TEMPO (4.0 equiv) PhCF$_3$ (80 µL), 80 °C	0/3	>99% C5	74

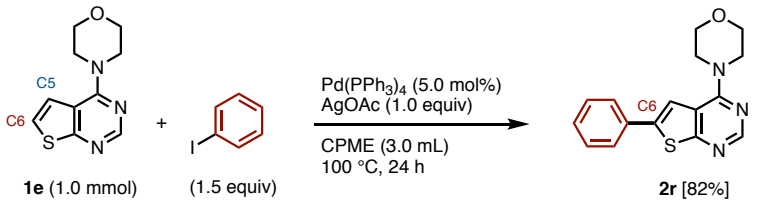
[a] Determined by GC using dodecane as the internal standard.

4. Typical Procedure for the Pd-Catalyzed C6-Selective Arylation of Thieno[2,3-*d*]pyrimidine 1



1a–1f (0.20 mmol) (1.5 equiv) **2a–2s**

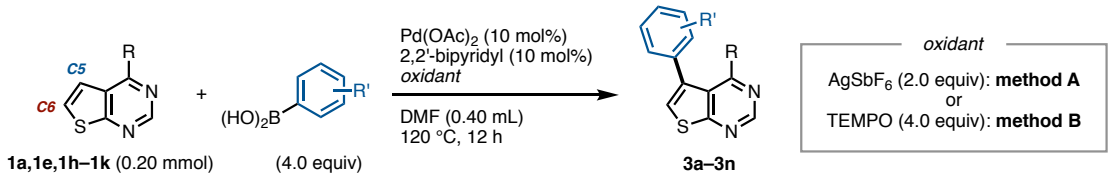
To a dried screw-capped glass tube containing a magnetic stirring bar were added thieno[2,3-*d*]pyrimidine **1** (0.20 mmol), AgOAc (33.4 mg, 1.0 equiv) and aryl iodide (1.5 equiv, when aryl iodide is solid). The tube was introduced into an argon atmosphere glovebox. In the glovebox, to this tube was added $Pd(PPh_3)_4$ (11.6 mg, 5.0 mol%). The tube was sealed with a rubber-fitted cap and taken out from the glovebox. After addition of cyclopentyl methyl ether (1.0 mL) under argon atmosphere (when aryl iodide is liquid, it was added at this time), the reaction mixture was stirred at 100 °C for 12 h in an 8-well reaction heat block. Upon cooling to ambient temperature, the mixture was passed through a short pad of Celite® with EtOAc as eluent. The filtrate was concentrated *in vacuo* and the residue was subjected to flash column chromatography on silica-gel and in some cases GPC purification to give the corresponding aryl thieno[2,3-*d*]pyrimidine **2**.



1e (1.0 mmol) (1.5 equiv) **2r** [82%]

1.0 mmol scale reaction of 1e: To a dried Schlenk tube containing a magnetic stirring bar were added **1e** (222 mg, 1.0 mmol) and AgOAc (167 mg, 1.0 equiv). The tube was introduced into an argon atmosphere glovebox. In the glovebox, to this tube was added $Pd(PPh_3)_4$ (57.8 mg, 5.0 mol%). The tube was sealed with a rubber-fitted cap and taken out from the glovebox. After addition of cyclopentyl methyl ether (3.0 mL) and iodobenzene (167 µL, 1.5 equiv) under argon atmosphere, the reaction mixture was stirred at 100 °C for 24 h in an oil bath. Upon cooling to ambient temperature, the mixture was passed through a short pad of Celite® with EtOAc as eluent. The filtrate was concentrated *in vacuo* and the residue was subjected to flash column chromatography on silica-gel (hexane/EtOAc = 95:5 → 75:25) to give the product **2r** (245 mg, 82%) as a white solid.

5. Typical Procedure for the Pd-Catalyzed C5-Selective Arylation of Thieno[2,3-*d*]pyrimidine 1

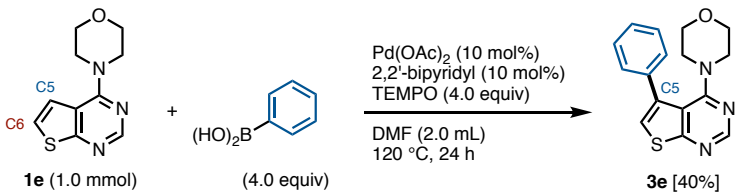


1a,1e,1h–1k (0.20 mmol) (4.0 equiv) **3a–3n**

Method A: To a dried screw-capped glass tube containing a magnetic stirring bar were added thieno[2,3-*d*]pyrimidine **1** (0.20 mmol), arylboronic acid (4.0 equiv), $Pd(OAc)_2$ (4.5 mg, 10 mol%) and 2,2'-bipyridyl (3.1 mg, 10 mol%). The tube was introduced into an argon atmosphere glovebox. In the glovebox, to this tube was added $AgSbF_6$ (137 mg, 2.0 equiv). The tube was sealed with a screw cap and taken out from the glovebox. To this mixture, DMF (0.40 mL) was added and the tube was sealed under air. The reaction mixture was stirred at 120 °C for 12 h in an 8-well reaction heat block.

Method B: To a dried screw-capped glass tube containing a magnetic stirring bar were added thieno[2,3-*d*]pyrimidine **1** (0.20 mmol), arylboronic acid (4.0 equiv), $Pd(OAc)_2$ (4.5 mg, 10 mol%), 2,2'-bipyridyl (3.1 mg, 10 mol%) and TEMPO (125 mg, 4.0 equiv). To this mixture, DMF (0.40 mL) was added and the tube was sealed under air. The reaction mixture was stirred at 120 °C for 12 h in an 8-well reaction heat block.

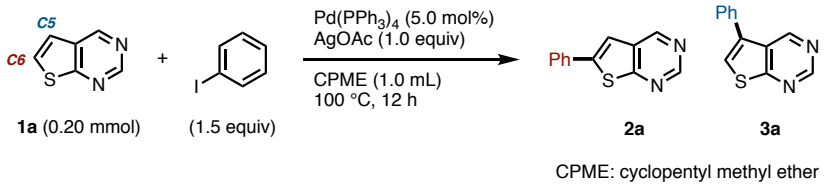
Work-up: Upon cooling to ambient temperature, the mixture was passed through a short pad of Celite® with EtOAc as eluent. The filtrate was concentrated *in vacuo* and the residue was subjected to flash column chromatography on silica-gel and in some cases GPC purification to give the corresponding aryl thieno[2,3-*d*]pyrimidine **3**.



1.0 mmol scale reaction of 1e: To a dried Schlenk tube containing a magnetic stirring bar were added **1e** (222 mg, 1.0 mmol), phenylboronic acid (488 mg, 4.0 equiv), $Pd(OAc)_2$ (22.5 mg, 10 mol%), 2,2'-bipyridyl (15.6 mg, 10 mol%) and TEMPO (625 mg, 4.0 equiv). To this mixture, DMF (2.0 mL) was added and the tube was sealed under air. The reaction mixture was stirred at 120 °C for 24 h in an oil bath. Upon cooling to ambient temperature, the mixture was passed through a short pad of Celite® with EtOAc as eluent. The filtrate was concentrated *in vacuo* and the residue was subjected to flash column chromatography on silica-gel (hexane/EtOAc = 95:5 → 80:20) and GPC purification to give the product **3e** (120 mg, 40%) as a white solid.

6. Effect of the Reaction Parameters

Table S3. Effect of Reaction Parameters on the Pd-Catalyzed C6-Selective Arylation of **1a**



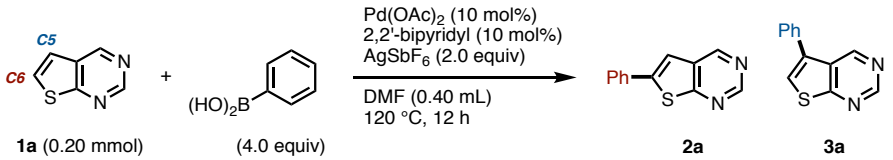
1a (0.20 mmol) (1.5 equiv) **2a** **3a**

CPME: cyclopentyl methyl ether

entry	Deviation from the standard conditions	**2a** (%)[a]	**3a** (%)[a]	C6/C5
1	none	74[b] (75)	trace[b]	>99% C6
2	PhBr instead of PhI	0	0	n.d.
3	PhOTf instead of PhI	0	0	n.d.
4	$Pd(dba)_2$ instead of $Pd(PPh_3)_4$	0	0	n.d.
5	$PdCl_2(PPh_3)_2$ instead of $Pd(PPh_3)_4$	16	4	80:20
6	$Pd(OAc)_2$ instead of $Pd(PPh_3)_4$	0	0	n.d.
7	PEPPSI-IPr instead of $Pd(PPh_3)_4$	0	0	n.d.
8	AgOPiv instead of AgOAc	8	0	>99% C6
9	$AgSbF_6$ instead of AgOAc	0	0	n.d.
10	0.50 equiv Ag_2CO_3 instead of AgOAc	45	1	98:2
11	0.50 equiv Ag_2O instead of AgOAc	34	2	94:6
12	NaOAc instead of AgOAc	0	0	n.d.
13	KOAc instead of AgOAc	0	0	n.d.
14	$^nBu_4NOAc$ instead of AgOAc	10	1	91:9
15	1,2-dichloroethane instead of CPME	22	0	>99% C6
16	toluene instead of CPME	61	0	>99% C6
17	DMF instead of CPME	19	1	95:5
18	DMSO instead of CPME	0	0	n.d.
19	HFIP instead of CPME	2	2	50:50
20	80 °C	9	0	>99% C6
21	120 °C	52	1	98:2

[a] GC yield using dodecane as the internal standard. [b] NMR yield using 1,1,2,2-tetrachloroethane as the internal standard. Yield shown in parenthesis is isolated yield. n.d.: not determined. DMSO: dimethyl sulfoxide, HFIP: hexafluoro-2-propanol

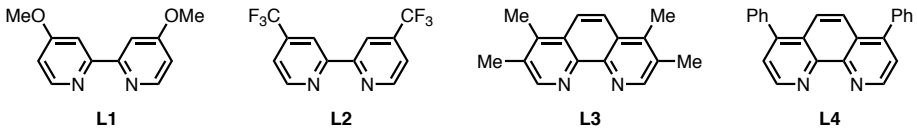
Table S4. Effect of Reaction Parameters on the Pd-Catalyzed C5-Selective Arylation of **1a**



1a (0.20 mmol) (4.0 equiv) **2a** **3a**

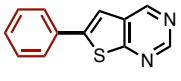
entry	Deviation from the standard conditions	**2a** (%)[a]	**3a** (%)[a]	C6/C5
1	none	0	56 (51)	>99% C5
2	PhBpin instead of $PhB(OH)_2$	0	10	>99% C5
3	1.0 equiv $(PhBO)_3$ instead of $PhB(OH)_2$	0	48	>99% C5
4	$PhBF_3K$ instead of $PhB(OH)_2$	0	0	n.d.
5	$PdCl_2$ instead of $Pd(OAc)_2$	0	42	>99% C5
6	$Pd(OPiv)_2$ instead of $Pd(OAc)_2$	0	50	>99% C5
7	$Pd(CH_3CN)_4(BF_4)_2$ instead of $Pd(OAc)_2$	0	1	>99% C5
8	without 2,2'-bipyridyl	0	22	>99% C5
9	dtbpy instead of 2,2'-bipyridyl	0	40	>99% C5
10	**L1** instead of 2,2'-bipyridyl	0	35	>99% C5
11	**L2** instead of 2,2'-bipyridyl	0	37	>99% C5
12	1,10-phenanthroline instead of 2,2'-bipyridyl	0	48	>99% C5
13	**L3** instead of 2,2'-bipyridyl	0	48	>99% C5
14	**L4** instead of 2,2'-bipyridyl	0	51	>99% C5
15	toluene instead of DMF	3	16	16:84
16	1,2-dichloroethane instead of DMF	0	5	>99% C5
17	EtOAc instead of DMF	0	17	>99% C5
18	THF instead of DMF	0	0	n.d.
19	NMP instead of DMF	0	49	>99% C5
20[b]	NMP instead of DMF	0	44 (37)	>99% C5
21	140 °C	0	42	>99% C5
22	100 °C	0	35	>99% C5
23	80 °C	0	4	>99% C5

[a] GC yield using dodecane as the internal standard. [b] TEMPO (4.0 equiv) was used instead of $AgSbF_6$. Yields shown in parenthesis are isolated yields. n.d.: not determined, dtbpy: 4,4'-di-*tert*-butyl-2,2'-bipyridyl, NMP: *N*-methylpyrrolidone



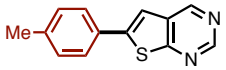
7. Characterization Data for C6-Selective Arylation Reactions

Product **2p**[S10] is a known compound and showed identical spectra according to the literature.



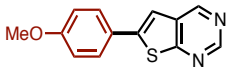
2a

6-phenylthieno[2,3-*d*]pyrimidine (**2a**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) afforded **2a** (31.7 mg, 75%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.43 (t, *J* = 7.8 Hz, 1H), 7.48 (t, *J* = 7.8 Hz, 2H), 7.51 (s, 1H), 7.73 (d, *J* = 7.8 Hz, 2H), 9.06 (s, 1H), 9.10 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 114.8, 127.1, 129.5, 129.7, 132.7, 133.2, 146.0, 151.3, 153.4, 168.5; FT-IR (neat, cm^{-1}): 3053, 2930, 2847, 1561, 1483, 1445, 1378, 1190, 827, 768, 749, 725, 688; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_9N_2S$ 213.0481; Found 213.0481.



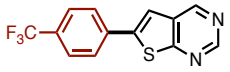
2b

6-(4-methylphenyl)thieno[2,3-*d*]pyrimidine (**2b**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) afforded **2b** (30.1 mg, 67%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.41 (s, 3H), 7.28 (d, *J* = 7.8 Hz, 2H), 7.46 (s, 1H), 7.62 (d, *J* = 7.8 Hz, 2H), 9.04 (s, 1H), 9.07 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.5, 114.1, 126.9, 130.1, 130.4, 132.8, 140.0, 146.1, 151.0, 153.3, 168.4; FT-IR (neat, cm^{-1}): 2916, 2849, 1518, 1491, 1433, 1375, 1102, 927, 854, 805, 756, 728; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{11}N_2S$ 227.0637; Found 227.0634.



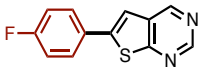
2c

6-(4-methoxyphenyl)thieno[2,3-*d*]pyrimidine (**2c**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) afforded **2c** (24.9 mg, 51%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.87 (s, 3H), 6.99 (d, *J* = 9.0 Hz, 2H), 7.38 (s, 1H), 7.66 (d, *J* = 9.0 Hz, 2H), 9.02 (s, 1H), 9.05 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.7, 113.4, 114.9, 125.9, 128.4, 133.0, 145.9, 150.8, 153.1, 161.0, 168.4; FT-IR (neat, cm^{-1}): 2965, 2924, 2853, 1605, 1493, 1375, 1253, 1178, 1028, 814, 755; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{11}N_2OS$ 243.0587; Found 243.0583.



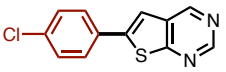
2d

6-[4-(trifluoromethyl)phenyl]thieno[2,3-*d*]pyrimidine (**2d**): Purification by PTLC (hexane/EtOAc = 2:1) afforded **2d** (38.7 mg, 69%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.61 (s, 1H), 7.74 (d, J = 8.4 Hz, 2H), 7.84 (d, J = 8.4 Hz, 2H), 9.10 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 116.6, 124.0 (q, $^{1}J_{C–F}$ = 272 Hz), 126.5 (d, $^{3}J_{C–F}$ = 2.9 Hz), 127.3, 131.5 (q, $^{2}J_{C–F}$ = 33 Hz), 132.4, 136.6, 144.0, 151.9, 153.9, 168.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ –65.84; FT-IR (neat, cm^{-1}): 2926, 1560, 1375, 1317, 1170, 1111, 1066, 1013, 829, 759; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_8F_3N_2S$ 281.0354; Found 281.0356.



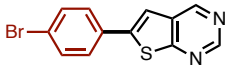
2e

6-(4-fluorophenyl)thieno[2,3-*d*]pyrimidine (**2e**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and GPC afforded **2e** (25.9 mg, 56%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.18 (t, J = 7.8 Hz, 2H), 7.44 (s, 1H), 7.69–7.72 (m, 2H), 9.06 (s, 1H), 9.10 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 114.9, 116.6 (d, $^{2}J_{C–F}$ = 22 Hz), 128.9 (d, $^{3}J_{C–F}$ = 7.2 Hz), 129.5, 132.7, 144.8, 151.3, 153.5, 163.7 (d, $^{1}J_{C–F}$ = 248 Hz), 168.5; ^{19}F NMR (470 MHz, $CDCl_3$): δ –114.02; FT-IR (neat, cm^{-1}): 3049, 2924, 2039, 1967, 1870, 1606, 1518, 1493, 1375, 1240, 1158, 1096, 860, 817, 754. 728, 647; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_8FN_2S$ 231.0387; Found 231.0384.



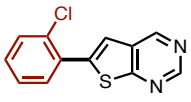
2f

6-(4-chlorophenyl)thieno[2,3-*d*]pyrimidine (**2f**): Purification by TLC (hexane/EtOAc =2:1) afforded **2f** (38.7 mg, 78%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.46 (d, J = 8.4 Hz, 2H), 7.49 (s, 1H), 7.66 (d, J = 8.4 Hz, 2H), 9.07 (s, 1H), 9.11 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 115.3, 128.2, 129.7, 131.7, 132.6, 135.8, 144.6, 151.4, 153.6, 168.5; FT-IR (neat, cm^{-1}): 3019, 2926, 2856, 1480, 1376, 1098, 809, 754, 731, 681; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_8ClN_2S$ 247.0091; Found 247.0089.



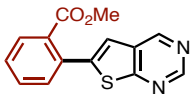
2g

6-(4-bromophenyl)thieno[2,3-*d*]pyrimidine (**2g**): Purification by PTLC (hexane/EtOAc = 2:1) afforded **2g** (46.9 mg, 81%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.51 (s, 1H), 7.58–7.62 (m, 4H), 9.07 (s, 1H), 9.11 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 115.4, 124.0, 128.5, 132.2, 132.6, 132.7, 144.6, 151.5, 153.7, 168.5; FT-IR (neat, cm^{-1}): 3059, 3020, 2930, 1509, 1376, 1076, 1008, 807, 754, 730; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_8BrN_2S$ 290.9586; Found 290.9582.



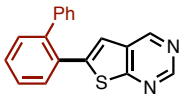
2h

6-(2-chlorophenyl)thieno[2,3-*d*]pyrimidine (**2h**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) afforded **2h** (36.4 mg, 74%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.38 (dd, J = 6.0, 1.2 Hz, 2H), 7.54–7.55 (m, 2H), 7.59 (dd, J = 6.0, 1.2 Hz, 1H), 9.10 (s, 1H), 9.16 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 120.2, 127.5, 130.5, 131.0, 131.7, 132.1, 133.2, 142.1, 151.8, 153.7, 169.0. (One sp^2 signal was not observed because of overlapping.); FT-IR (neat, cm^{-1}): 3061, 3044, 2927, 1508, 1375, 1038, 834, 745, 729, 650; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_8ClN_2S$ 247.0091; Found 247.0091.



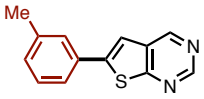
2i

methyl 2-(thieno[2,3-*d*]pyrimidin-6-yl)benzoate (**2i**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) afforded **2i** (43.5 mg, 80%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.76 (s, 3H), 7.24 (s, 1H), 7.52–7.55 (m, 2H), 7.60 (dd, J = 7.8, 7.2 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 9.09 (s, 1H), 9.12 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 52.6, 118.5, 129.5, 130.5, 131.7, 131.8, 131.9, 133.7, 144.6, 151.6, 153.4, 167.9, 169.2. (One sp^2 signal was not observed because of overlapping.); FT-IR (neat, cm^{-1}): 1729, 1378, 1260, 1088, 748, 708, 675; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{11}N_2O_2S$ 271.0536; Found 271.0533.



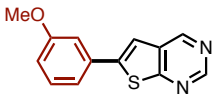
2j

6-([1,1'-biphenyl]-2-yl)thieno[2,3-*d*]pyrimidine (**2j**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) afforded **2j** (39.1 mg, 68%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.93 (s, 1H), 7.27–7.28 (m, 2H), 7.29–7.32 (m, 3H), 7.44–7.48 (m, 2H), 7.48–7.51 (m, 1H), 7.63 (dd, *J* = 7.2, 1.2 Hz, 1H), 8.94 (s, 1H), 8.99 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 119.0, 127.8, 128.0, 128.6, 129.5, 129.8, 131.1, 131.3, 131.8, 132.1, 140.6, 141.8, 145.6, 151.2, 153.2, 169.1; FT-IR (neat, cm^{-1}): 3021, 2921, 2853, 1509, 1466, 1372, 913, 840, 767, 748, 698; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_2S$ 289.0794; Found 289.0793.



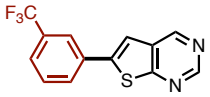
2k

6-(3-methylphenyl)thieno[2,3-*d*]pyrimidine (**2k**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) afforded **2k** (37.8 mg, 79%, pale orange solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.44 (s, 3H), 7.24 (d, *J* = 7.8 Hz, 1H), 7.36 (t, *J* = 7.8 Hz, 1H), 7.50 (s, 1H), 7.52–7.53 (m, 2H), 9.05 (s, 1H), 9.08 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.6, 114.7, 124.2, 127.7, 129.3, 130.5, 132.7, 133.1, 139.3, 146.2, 151.2, 153.4, 168.5; FT-IR (neat, cm^{-1}): 3019, 2914, 2852, 1509, 1375, 834, 773, 754, 727, 688; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{11}N_2S$ 227.0637; Found 227.0638.



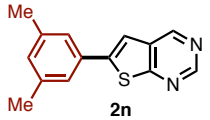
2l

6-(3-methoxyphenyl)thieno[2,3-*d*]pyrimidine (**2l**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and GPC afforded **2l** (28.2 mg, 52%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.89 (s, 3H), 6.97 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.24 (s, 1H), 7.32 (dd, *J* = 7.8, 1.2 Hz, 1H), 7.39 (t, *J* = 7.8 Hz, 1H), 7.50 (s, 1H), 9.06 (s, 1H), 9.09 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.7, 112.8, 115.1, 115.1, 119.6, 130.5, 132.6, 134.5, 145.8, 151.3, 153.5, 160.4, 168.5; FT-IR (neat, cm^{-1}): 3046, 3020, 1589, 1489, 1376, 1264, 1177, 1036, 815, 773, 754, 729, 676; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{13}H_{11}N_2OS$ 243.0587; Found 243.0585.



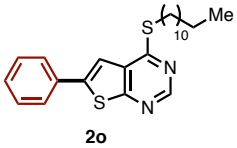
2m

6-[3-(trifluoromethyl)phenyl]thieno[2,3-*d*]pyrimidine (**2m**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and GPC afforded **2m** (31.2 mg, 54%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.60 (s, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.69 (d, J = 7.8 Hz, 1H), 7.90 (d, J = 7.8 Hz, 1H), 7.97 (s, 1H), 9.10 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 116.3, 123.7 (d, $^{3}J_{C–F}$ = 2.9 Hz), 123.9 (q, $^{1}J_{C–F}$ = 272 Hz), 126.2 (d, $^{3}J_{C–F}$ = 4.2 Hz), 130.1, 130.3, 132.1 (q, $^{2}J_{C–F}$ = 32 Hz), 132.5, 134.1, 144.0, 151.8, 153.9, 168.6; ^{19}F NMR (470 MHz, $CDCl_3$): δ –65.84; FT-IR (neat, cm^{-1}): 3045, 1509, 1416, 1416, 1377, 1325, 1180, 1123, 1073, 967, 794, 755, 688; HRMS (ESI, positive) *m/z*: [M + H]$^{+}$ Calcd for $C_{13}H_8F_3N_2S$ 281.0355; Found 281.0356.



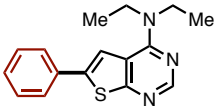
2n

6-(3,5-dimethylphenyl)thieno[2,3-*d*]pyrimidine (**2n**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) afforded **2n** (30.0 mg, 62%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.40 (s, 6H), 7.06 (s, 1H), 7.34 (s, 2H), 7.48 (s, 1H), 9.04 (s, 1H), 9.07 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.5, 114.5, 124.9, 131.5, 132.7, 133.0, 139.1, 146.4, 151.1, 153.3, 168.5; FT-IR (neat, cm^{-1}): 3021, 2912, 2853, 1513, 1372, 841, 810, 753, 723, 681; HRMS (ESI, positive) *m/z*: [M + H]$^{+}$ Calcd for $C_{14}H_{13}N_2S$ 241.0794; Found 241.0793.



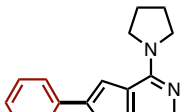
2o

4-(dodecylsulfanyl)-6-phenylthieno[2,3-*d*]pyrimidine (**2o**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and GPC afforded **2o** (41.9 mg, 51%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 0.88 (t, J = 7.2 Hz, 3H), 1.26–1.36 (m, 16H), 1.46–1.50 (m, 2H), 1.76–1.80 (m, 2H), 3.36 (t, J = 7.2 Hz, 2H) 7.39 (d, J = 7.2 Hz, 1H), 7.45 (t, J = 7.2 Hz, 2H), 7.48 (s, 1H), 7.71 (d, J = 7.2 Hz, 2H), 8.76 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 14.3, 22.9, 29.1, 29.4, 29.5, 29.5, 29.7, 29.8, 29.8, 29.9, 32.1, 114.2, 126.9, 129.4, 129.8, 133.4, 144.1, 152.6, 164.2, 165.4. (One sp^3 signal and one sp^2 signal are not observed because of overlapping.); FT-IR (neat, cm^{-1}): 2919, 2847, 1502, 1411, 1355, 1235, 828, 749, 724, 683; HRMS (ESI, positive) *m/z*: [M + H]$^{+}$ Calcd for $C_{24}H_{33}N_2S_2$ 413.2080; Found 413.2076.



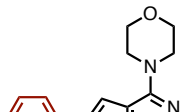
2p

***N*,*N*-diethyl-6-phenylthieno[2,3-*d*]pyrimidin-4-amine** (**2p**): Purification by flash column chromatography (hexane/EtOAc = 98:2 → 85:15) and GPC afforded **2p** (42.7 mg, 75%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.37 (t, *J* = 7.2 Hz, 6H), 3.80 (q, *J* = 7.2 Hz, 4H), 7.35 (t, *J* = 7.8 Hz, 1H), 7.43 (d, *J* = 7.8 Hz, 2H), 7.48 (s, 1H), 7.64 (d, *J* = 7.8 Hz, 2H), 8.42 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 13.6, 44.4, 116.5, 116.8, 126.4, 128.5, 129.3, 134.2, 138.2, 153.3, 157.0, 169.0; FT-IR (neat, cm^{-1}): 2983, 2969, 2923, 1550, 1325, 1032, 750, 681; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{13}N_3S$ 284.1216; Found 284.1213.



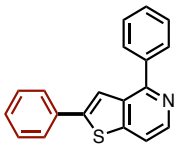
2q

6-phenyl-4-(pyrrolidin-1-yl)thieno[2,3-*d*]pyrimidine (**2q**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and GPC afforded **2q** (37.2 mg, 66%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.09 (brs, 4H), 3.89 (brs, 4H), 7.34 (t, *J* = 7.2 Hz, 1H), 7.42 (dd, *J* = 7.8, 7.2 Hz, 2H), 7.64 (s, 1H), 7.65 (d, *J* = 7.8 Hz, 2H), 8.43 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 25.7, 49.2, 116.6, 117.7, 126.4, 128.4, 129.2, 134.2, 138.1, 153.6, 156.0, 168.3; FT-IR (neat, cm^{-1}): 2960, 2880, 2861, 1550, 1480, 1313, 1124, 1029, 854, 749, 684; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{16}N_3S$ 282.1059; Found 282.1057.



2r

4-(6-phenylthieno[2,3-*d*]pyrimidin-4-yl)morpholine (**2r**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) afforded **2r** (0.20 mmol scale: 48.7 mg, 82%, white solid; 1.0 mmol scale: 245 mg, 82%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.87 (t, *J* = 4.8 Hz, 4H), 3.95 (t, *J* = 4.8 Hz, 4H), 7.37 (t, *J* = 7.2 Hz, 1H), 7.44 (dd, *J* = 7.8, 7.2 Hz, 2H), 7.46 (s, 1H), 7.66 (d, *J* = 7.8 Hz, 2H), 8.50 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 47.6, 66.9, 115.5, 118.3, 126.6, 128.9, 129.3, 133.7, 140.1, 153.0, 158.7, 169.4; FT-IR (neat, cm^{-1}): 3028, 2958, 2854, 1509, 1104, 971, 753; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{16}N_3OS$ 298.1009; Found 298.1005.

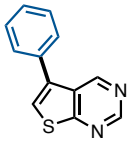


2s

2,4-diphenylthieno[3,2-*c*]pyridine (**2s**): Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and PTLC (hexane/EtOAc = 5:1) afforded **2s** (28.8 mg, 50%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.37 (t, *J* = 7.2 Hz, 1H), 7.44 (dd, *J* = 7.8, 7.2 Hz, 2H), 7.50 (t, *J* = 7.8 Hz, 1H), 7.55 (dd, *J* = 7.8, 7.2 Hz, 2H), 7.70 (d, *J* = 7.8 Hz, 2H), 7.74 (d, *J* = 5.4 Hz, 1H), 7.78 (s, 1H), 7.87 (d, *J* = 7.2 Hz, 1H), 8.54 (d, *J* = 5.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 116.1, 118.8, 126.9, 128.8, 129.0, 129.1, 129.3, 133.7, 135.0, 140.3, 142.8, 145.2, 148.2, 155.3. (One sp^2 signal was not observed because of overlapping.); FT-IR (neat, cm^{-1}): 3056, 3026, 1484, 1429, 947, 817, 763, 745, 725, 686; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{14}NS$ 288.0841; Found 288.0838.

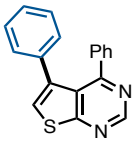
8. Characterization Data for C5-selective Arylation Reactions

Product **3e**[S11] is a known compound and showed identical spectra according to the literature.



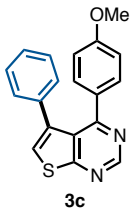
3a

5-diphenylthieno[2,3-*d*]pyrimidine (**3a**): Method A, Purification by flash column chromatography (hexane/EtOAc = 95:5 → 85:15) and GPC afforded **3a** (21.6 mg, 51%, white solid): ^{1}H NMR (600 MHz, $CDCl_3$): δ 7.47 (t, J = 7.8 Hz, 1H), 7.52 (s, 1H), 7.53 (t, J = 7.8 Hz, 2H), 7.59 (d, J = 7.8 Hz, 2H), 9.15 (s, 1H), 9.27 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 123.7, 128.5, 128.7, 129.4, 134.1, 135.4, 151.8, 153.8, 169.7. (One sp^2 signal was not observed because of overlapping.); FT-IR (neat, cm^{-1}): 3014, 1374, 1205, 943, 830, 783, 752, 698; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{12}H_9N_2S$ 213.0481; Found 213.0479.



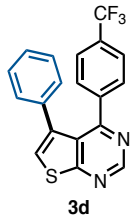
3b

4,5-diphenylthieno[2,3-*d*]pyrimidine (**3b**): Method A, Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and GPC afforded **3b** (23.6 mg, 41%, white solid): ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.95 (d, J = 7.8 Hz, 2H), 7.02–7.06 (m, 4H), 7.11 (t, J = 7.2 Hz, 1H), 7.18 (t, J = 7.2 Hz, 1H), 7.22 (d, J = 7.8 Hz, 2H), 7.48 (s, 1H), 9.19 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 125.1, 126.2, 127.3, 127.6, 127.9, 128.9, 129.2, 129.6, 136.0, 136.9, 137.3, 153.0, 162.8, 170.8; FT-IR (neat, cm^{-1}): 3091, 3025, 2970, 1354, 749, 693; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_2S$ 289.0794; Found 289.0790.



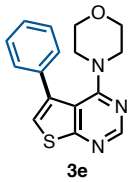
3c

4-(4-methoxyphenyl)-5-phenylthieno[2,3-*d*]pyrimidine (**3c**): Method A, Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and GPC afforded **3c** (27.1 mg, 43%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.73 (s, 3H), 6.56 (d, J = 8.4 Hz, 2H), 6.98 (d, J = 7.8 Hz, 2H), 7.07 (t, J = 7.8 Hz, 2H), 7.15 (t, J = 7.8 Hz, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.47 (s, 1H), 9.15 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 55.5, 113.1, 124.7, 125.9, 127.3, 127.9, 129.0, 129.8, 131.2, 136.2, 136.9, 153.0, 160.7, 162.3, 170.7; FT-IR (neat, cm^{-1}): 3004, 2923, 1606, 1505, 1428, 1348, 1252, 1029, 828, 750, 693; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{15}N_2OS$ 319.0900; Found 319.0897.



3d

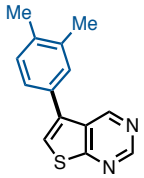
5-phenyl-4-[4-(trifluoromethyl)phenyl]thieno[2,3-*d*]pyrimidine (**3d**): Method A, Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and GPC afforded **3d** (35.9 mg, 50%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.90 (d, J = 6.6 Hz, 2H), 7.03 (t, J = 7.8 Hz, 2H), 7.14 (t, J = 7.8 Hz, 1H), 7.28–7.31 (m, 4H), 7.53 (s, 1H), 9.22 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 124.0 (q, $^{1}J_{C–F}$ = 272 Hz), 124.5 (d, $^{3}J_{C–F}$ = 4.4 Hz), 125.6, 126.5, 127.7, 128.1, 129.0, 129.8, 131.0 (q, $^{2}J_{C–F}$ = 33 Hz), 135.5, 136.4, 140.6, 153.0, 161.2, 170.8; ^{19}F NMR (470 MHz, $CDCl_3$): δ –62.87; FT-IR (neat, cm^{-1}): 3047, 1320, 1168, 1114, 1059, 838, 753, 697; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{12}N_2F_3S$ 357.0668; Found 357.0667.



3e

4-(5-phenylthieno[2,3-*d*]pyrimidin-4-yl)morpholine (**3e**): Method B, Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and PTLC (hexane/EtOAc = 2:1) afforded **3e** (0.20 mmol scale: 25.8 mg, 43%, white solid; 1.0 mmol scale: 120 mg, 40%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.21 (t, *J* = 4.8 Hz,4H), 3.30 (t, *J* = 4.8 Hz,4H), 7.40–7.42 (m, 1H), 7.44–7.47 (m, 5H), 8.63 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 50.1, 66.0, 116.0, 122.1, 128.1, 128.6, 128.8, 136.1, 136.6, 152.5, 161.6, 170.5; FT-IR (neat, cm^{-1}): 3090, 2966, 2926, 2839, 1530, 1498, 1444, 1348, 1262, 1109, 1066, 979, 794, 757, 701; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{16}H_{16}N_3OS$ 298.1009; Found 298.1008.

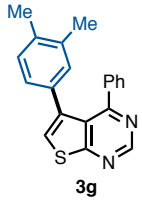
Note: Method A ($AgSbF_6$) did not afford product **3e** (0%).



3f

5-(3,4-dimethylphenyl)thieno[2,3-*d*]pyrimidine (**3f**): Method A, Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and GPC afforded **3f** (14.6 mg, 30%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.35 (s, 3H), 2.36 (s, 3H), 7.29 (d, *J* = 7.2 Hz, 1H), 7.32 (d, *J* = 7.2 Hz, 1H), 7.36 (s, 1H), 7.47 (s, 1H), 9.13 (s, 1H), 9.27 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.8, 20.1, 123.0, 125.8, 129.6, 129.6, 130.6, 131.6, 135.5, 137.4, 137.8, 151.9, 153.7, 169.7; FT-IR (neat, cm^{-1}): 3065, 3017, 2969, 1371, 1215, 864, 810, 762; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{14}H_{13}N_2S$ 241.0794; Found 241.0791.

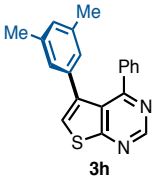
Note: Method B (TEMPO) afforded product **3f** in 22% NMR yield.



3g

5-(3,4-dimethylphenyl)-4-phenylthieno[2,3-*d*]pyrimidine (**3g**): Method B, 18 h, 3.3 equiv. of arylboronic acid was used. Purification by flash column chromatography (hexane/EtOAc = 98:2 → 90:10) and GPC afforded **3g** (31.3 mg, 49%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.95 (s, 3H), 2.16 (s, 3H), 6.56 (s, 1H), 6.81 (d, J = 7.2 Hz, 1H), 6.87 (d, J = 7.2 Hz, 1H), 7.04 (t, J = 7.8 Hz, 2H), 7.18 (t, J = 7.8 Hz, 1H), 7.22 (d, J = 7.8 Hz, 2H), 7.43 (s, 1H), 9.18 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 19.5, 19.6, 124.3, 126.2, 126.5, 127.4, 128.9, 129.2, 129.5, 130.7, 133.3, 135.8, 136.0, 137.0, 137.6, 152.9, 162.9, 170.7; FT-IR (neat, cm^{-1}): 3056, 3017, 2968, 1505, 1431, 1 355, 1215, 793, 753, 694; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{17}N_2S$ 317.1107; Found 317.1104.

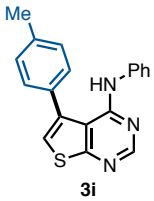
Note: Method A ($AgSbF_6$) gave **3g** (26.8 mg, 42%) as a white solid.



3h

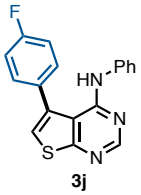
5-(3,5-dimethylphenyl)-4-phenylthieno[2,3-*d*]pyrimidine (**3h**): Method B, 18 h, Purification by flash column chromatography (hexane/EtOAc = 98:2 → 90:10) and GPC afforded **3h** (43.0 mg, 68%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.08 (s, 6H), 6.57 (s, 2H), 6.75 (s, 1H), 7.07 (t, J = 7.2 Hz, 2H), 7.20 (t, J = 7.2 Hz, 1H), 7.24 (d, J = 7.2 Hz, 2H), 7.45 (s, 1H), 9.18 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.1, 124.5, 126.4, 127.1, 127.5, 128.9, 129.2, 129.4, 135.6, 137.1, 137.5, 137.6, 152.9, 162.9, 170.8; FT-IR (neat, cm^{-1}): 3039, 2969, 1492, 1354, 1216, 842, 757, 697, 658; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{17}N_2S$ 317.1107; Found 317.1103.

Note: Method A ($AgSbF_6$) gave **3h** (20.0 mg, 32%) as a white solid.



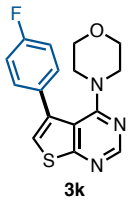
3i

***N*-phenyl-5-(*p*-tolyl)thieno[2,3-*d*]pyrimidin-4-amine** (**3i**): Method B, Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) afforded **3i** (29.7 mg, 47%, pale yellow solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 2.49 (s, 3H), 7.00 (brs, 1H), 7.05 (t, J = 7.8 Hz, 1H), 7.16 (s, 1H), 7.28 (t, J = 7.8 Hz, 2H), 7.36–7.38 (m, 4H), 7.43 (d, J = 7.8 Hz, 2H), 8.62 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 21.5, 114.9, 120.7, 121.2, 123.9, 129.1, 129.6, 130.1, 133.2, 134.5, 138.6, 139.4, 153.9, 155.5, 167.8; FT-IR (neat, cm^{-1}): 3393, 2969, 1494, 1443, 1366, 1216, 777, 747, 689; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{16}N_3S$ 318.1059; Found 318.1058.



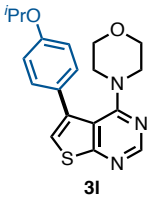
3j

5-(4-fluorophenyl)-*N*-phenylthieno[2,3-*d*]pyrimidin-4-amine (**3j**): Method B, Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and GPC afforded **3j** (35.8 mg, 56%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.81 (brs, 1H), 7.07 (t, J = 7.2 Hz, 1H), 7.19 (s, 1H), 7.27–7.31 (m, 4H), 7.38 (d, J = 7.8 Hz, 2H), 7.54 (dd, J = 7.8, 7.2 Hz, 2H), 8.63 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 114.8, 116.6 (d, $^{2}J_{C–F}$ = 21 Hz), 120.6, 121.9, 124.1, 129.2, 131.5 (d, $^{3}J_{C–F}$ = 7.2 Hz), 132.1, 133.2, 138.4, 154.0, 155.4, 163.3 (d, $^{1}J_{C–F}$ = 248 Hz), 167.9; ^{19}F NMR (470 MHz, $CDCl_3$): δ –111.19; FT-IR (neat, cm^{-1}): 3404, 3093, 2919, 1598, 1566, 1494, 1445, 1226, 980, 774, 749, 688; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{18}H_{13}N_3FS$ 322.0809; Found 322.0807.



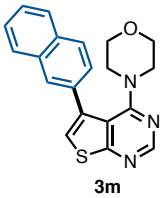
3k

4-[5-(4-fluorophenyl)thieno[2,3-*d*]pyrimidin-4-yl]morpholine (**3k**): Method B, Purification by flash column chromatography (hexane/EtOAc = 95:5 → 85:15 → 75:25) and GPC afforded **3k** (34.7 mg, 55%, pale gray solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.21 (t, J = 4.8 Hz, 4H), 3.35 (t, J = 4.8 Hz, 4H), 7.16 (t, J = 9.0 Hz, 2H), 7.24 (s, 1H), 7.42–7.44 (m, 2H), 8.63 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 50.1, 66.0, 115.7 (d, $^{2}J_{C–F}$ = 22 Hz), 116.0, 122.2, 130.3 (d, $^{3}J_{C–F}$ = 7.2 Hz), 132.7, 134.9, 152.6, 161.6, 162.7 (d, $^{1}J_{C–F}$ = 247 Hz), 170.4; ^{19}F NMR (470 MHz, $CDCl_3$): δ –113.44; FT-IR (neat, cm^{-1}): 3092, 2924, 2863, 1505, 1442, 1350, 1260, 1220, 1164, 1114, 1066, 984, 830, 766, 616; HRMS (ESI, positive) *m/z*: [M + H]$^{+}$ Calcd for $C_{16}H_{15}N_3OFS$ 316.0914; Found 316.0912.



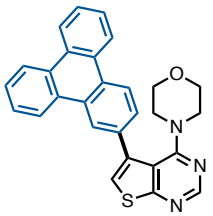
3l

4-[5-(4-isopropoxyphenyl)thieno[2,3-*d*]pyrimidin-4-yl]morpholine (**3l**): Method B, 18 h, Purification by flash column chromatography (hexane/EtOAc = 95:5 → 90:10 → 75:25) afforded **3l** (30.9 mg, 43%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 1.39 (d, J = 6.0 Hz, 6H), 3.23 (t, J = 4.8 Hz, 4H), 3.36 (t, J = 4.8 Hz, 4H), 4.62 (sept, J = 6.0 Hz, 1H), 6.96 (d, J = 6.6 Hz, 2H), 7.19 (s, 1H), 7.35 (d, J = 6.6 Hz, 2H), 8.61 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 22.2, 50.1, 66.1, 70.3, 116.1, 116.2, 121.2, 129.0, 129.8, 135.8, 152.4, 157.9, 161.7, 170.3; FT-IR (neat, cm^{-1}): 3080, 2974, 2822, 1508, 1430, 1239, 1183, 1110, 981, 956, 864, 826, 787, 618; HRMS (ESI, positive) *m/z*: [M + H]$^{+}$ Calcd for $C_{19}H_{22}N_3O_2S$ 356.1427; Found 356.1424.



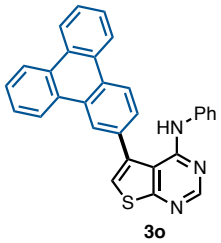
3m

4-[5-(naphthalen-2-yl)thieno[2,3-*d*]pyrimidin-4-yl]morpholine (**3m**): Method B, 18 h, Purification by flash column chromatography (hexane/EtOAc = 95:5 → 85:15) and GPC afforded **3m** (34.8 mg, 50%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.16 (t, *J* = 4.8 Hz, 4H), 3.21 (t, *J* = 4.8 Hz, 4H), 7.37 (s, 1H), 7.54–7.59 (m, 3H), 7.87–7.93 (m, 4H), 8.66 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 50.0, 65.9, 116.1, 122.4, 126.6, 126.7, 127.1, 127.3, 128.4, 128.1, 128.4, 132.8, 133.4, 133.8, 136.0, 152.6, 161.7, 170.6; FT-IR (neat, cm^{-1}): 3073, 2922, 2849, 1529, 1429, 1257, 1109, 980, 858, 818, 787, 752, 667; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{18}N_3OS$ 348.1165; Found 348.1165.



3n

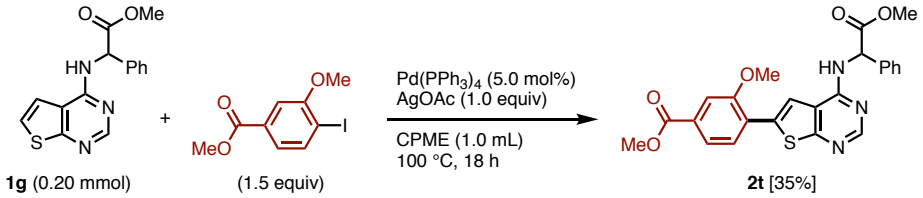
4-(5-(triphenylen-2-yl)thieno[2,3-*d*]pyrimidin-4-yl)morpholine (**3n**): Method B, 18 h, Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and GPC afforded **3n** (20.7 mg, 23%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.15 (t, *J* = 4.8 Hz, 4H), 3.25 (t, *J* = 4.8 Hz, 4H), 7.49 (s, 1H), 7.66–7.73 (m, 4H), 7.81 (dd, *J* = 8.4, 1.8 Hz, 1H), 8.64 (d, *J* = 7.8 Hz, 1H), 8.69– 8.72 (m, 5H), 8.75 (d, *J* = 8.4 Hz, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 50.1, 65.9, 116.1, 122.6, 123.3, 123.5, 123.6, 123.7, 123.8, 123.9, 127.0, 127.6, 127.7, 127.8, 127.9, 129.4, 129.5, 129.6, 129.9, 130.2, 130.5, 134.9, 136.0, 152.6, 161.8, 170.7; FT-IR (neat, cm^{-1}): 3055, 2839, 1533, 1265, 1114, 985, 753, 723, 634; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{28}H_{22}N_3OS$ 448.1478; Found 448.1477.



3o

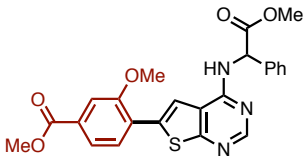
***N*-phenyl-5-(triphenylen-2-yl)thieno[2,3-*d*]pyrimidin-4-amine** (**3o**): Method B, 18 h, Purification by flash column chromatography (hexane/EtOAc = 95:5 → 75:25) and GPC afforded **3o** (37.0 mg, 41%, colorless solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 6.95 (t, J = 7.8 Hz, 1H), 7.11–7.14 (m, 3H), 7.26 (d, J = 7.2 Hz, 2H, overlapped with $CHCl_3$ peak), 7.37 (s, 1H), 7.66 (t, J = 7.8 Hz, 1H), 7.71–7.77 (m, 3H), 7.83 (dd, J = 8.4, 1.2 Hz, 1H), 8.66 (d, J = 8.4 Hz, 1H), 8.68 (s, 1H), 8.71–8.85 (m, 3H), 8.84–8.85 (m, 2H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 114.9, 120.7, 122.0, 123.6, 123.7, 123.8, 124.0, 124.5, 124.6, 127.8, 127.9, 128.0, 128.2, 128.3, 129.1, 129.2, 129.3, 130.4, 130.4, 130.5, 134.5, 134.7, 138.3, 154.0, 155.5, 168.1. (Two sp^2 signals were not observed because of overlapping.); FT-IR (neat, cm^{-1}): 3391, 3090, 1565, 1489, 1446, 954, 833, 788, 754, 717, 686, 665; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{30}H_{20}N_3S$ 454.1372; Found 454.1370.

9. Synthesis of EGFR-TK inhibitor 2u



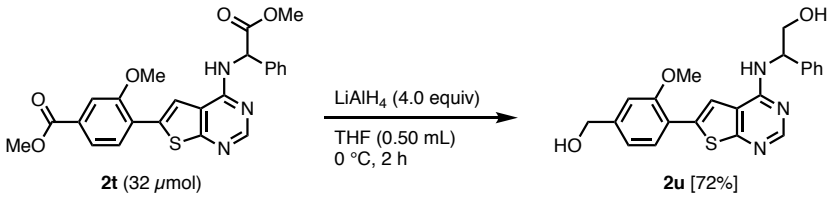
1g (0.20 mmol) (1.5 equiv) **2t** [35%]

To a dried screw-capped glass tube containing a magnetic stirring bar were added thieno[2,3-*d*]pyrimidine **1g** (59.9 mg, 0.20 mmol, 1.0 equiv), AgOAc (33.4 mg, 1.0 equiv) and methyl 4-iodo-3-methoxybenzoate (87.6 mg, 1.5 equiv, synthesized according to the literature[S12]). The tube was introduced into an argon atmosphere glovebox. In the glovebox, to this tube was added $Pd(PPh_3)_4$ (11.6 mg, 5.0 mol%). The tube was sealed with a rubber-fitted cap and taken out from the glovebox. After addition of cyclopentyl methyl ether (1.0 mL) under argon atmosphere, the reaction mixture was stirred at 100 °C for 12 h in an 8-well reaction heat block. Upon cooling to ambient temperature, the mixture was passed through a short pad of Celite® with EtOAc as eluent. The filtrate was concentrated *in vacuo* and the residue was subjected to flash column chromatography on silica-gel (hexane/EtOAc = 95:5 → 75:25) to give the aryl thieno[2,3-*d*]pyrimidine **2t** as a pale-yellow solid (32.3 mg, 35%). Note that the starting material remained after the reaction because of poor reactivity of substrate **1g** toward the C6-selective conditions.



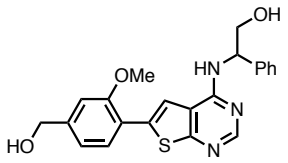
2t

2t: (32.3 mg, 35%, pale yellow solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.80 (s, 3H), 3.95 (s, 3H), 4.04 (s, 3H), 6.02 (d, J = 7.2 Hz, 1H), 6.17 (brd, J = 7.2 Hz, 1H), 7.36 (t, J = 7.2 Hz, 1H), 7.40 (t, J = 7.2 Hz, 2H), 7.52 (d, J = 7.2 Hz, 2H), 7.68 (s, 1H), 7.70–7.75 (m, 3H), 8.48 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 52.6, 53.2, 56.2, 57.7, 112.8, 116.3, 117.1, 122.5, 126.9, 127.7, 128.9, 129.0, 129.3, 131.1, 136.2, 136.8, 154.1, 155.5, 156.2, 166.7, 167.2, 172.1; FT-IR (neat, cm^{-1}): 3357, 1746, 1697, 1580, 1493, 1299, 1238, 1123, 763, 700; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{24}H_{22}N_3O_5S$ 464.1275; Found 464.1274.



2t (32 μmol) **2u** [72%]

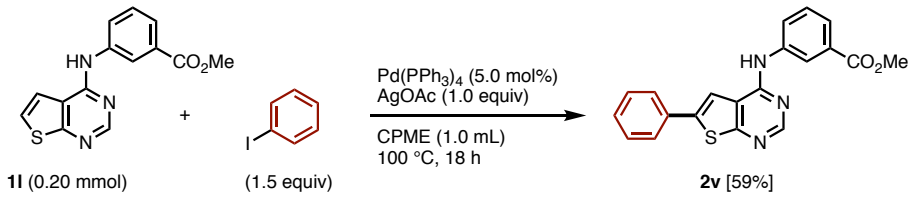
To a dried screw-capped glass tube containing a magnetic stirring bar were added $LiAlH_4$ (4.9 mg, 4.0 equiv) and THF (0.10 mL) under argon atmosphere. To the suspension of $LiAlH_4$ was added a solution of **2t** (14.8 mg, 32 µmol, 1.0 equiv) in THF (0.40 mL) dropwise at 0 °C with stirring. The reaction mixture was stirred at 0 °C for 2 h. Afterward, the reaction was quenched by slow addition of distilled water (1.0 mL) at 0 °C, and the aqueous phase was extracted with EtOAc. The combined organic layers were treated with brine and Na_2SO_4 successively. Following filtration of Na_2SO_4 and removal of the solvent *in vacuo* afforded the crude mixture, which was purified by PTLC ($CHCl_3$/MeOH = 10:1, R_f = 0.2) to yield **2u** as a white solid (9.4 mg, 72%).



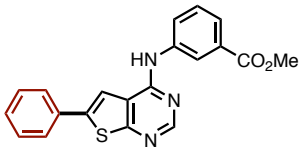
2u

2u: (9.4 mg, 72%, white solid) ^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ 3.75–3.79 (m, 2H), 3.95 (s, 3H), 4.56 (d, J = 4.2 Hz, 2H), 5.05 (brs, 1H), 5.31 (t, J = 4.2 Hz, 1H), 5.46 (m, 1H), 7.06 (d, J = 7.8 Hz, 1H), 7.16 (s, 1H), 7.23 (t, J = 7.2 Hz, 1H), 7.32 (dd, J = 7.8, 7.2 Hz, 2H), 7.44 (d, J = 7.8 Hz, 2H), 7.73 (d, J = 7.8 Hz, 1H), 8.16 (d, J = 7.8 Hz, 1H), 8.25–8.26 (m, 2H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$): δ 55.8, 56.3, 62.5, 64.6, 110.2, 116.3, 116.5, 118.9, 120.1, 126.8, 127.0, 127.6, 128.1, 134.0, 141.2, 144.8, 153.4, 155.4, 156.2, 165.4; FT-IR (neat, cm^{-1}): 3255, 2916, 2853, 1579, 1491, 1451, 1350, 1260, 1125, 1068, 1032, 777, 698; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{22}H_{22}N_3O_3S$ 408.1376; Found 408.1372.

10. Divergent synthesis of CK2 inhibitors 2w and 3p

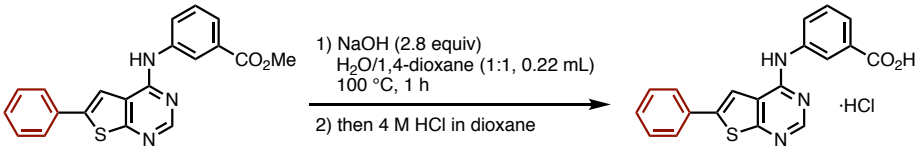


To a dried screw-capped glass tube containing a magnetic stirring bar were added thieno[2,3-*d*]pyrimidine **1l** (57.2 mg, 0.20 mmol, 1.0 equiv), AgOAc (33.4 mg, 1.0 equiv) and iodobenzene (33 µL, 1.5 equiv). The tube was introduced into an argon atmosphere glovebox. In the glovebox, to this tube was added $Pd(PPh_3)_4$ (11.6 mg, 5.0 mol%). The tube was sealed with a rubber-fitted cap and taken out from the glovebox. After addition of cyclopentyl methyl ether (1.0 mL) under argon atmosphere (when aryl iodide was liquid state, it was added at this time), the reaction mixture was stirred at 100 °C for 18 h in an 8-well reaction heat block. Upon cooling to ambient temperature, the mixture was passed through a short pad of Celite® with EtOAc as eluent. The filtrate was concentrated *in vacuo* and the residue was subjected to flash column chromatography on silica-gel (hexane/EtOAc = 95:5 → 75:25) to give **2v** as a white solid (42.4 mg, 59%).



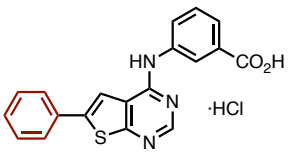
2v

2v: (42.4 mg, 59%, white solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.95 (s, 3H), 7.04 (brs, 1H), 7.37 (s, 1H), 7.39 (t, J = 7.8 Hz, 1H), 7.45 (t, J = 7.8 Hz, 2H), 7.49 (t, J = 7.8 Hz, 1H), 7.68 (d, J = 7.8 Hz, 2H), 7.84 (d, J = 7.8 Hz, 1H), 8.09 (d, J = 7.8 Hz, 1H), 8.24 (s, 1H), 8.63 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 52.5, 111.9, 118.5, 122.4, 125.5, 126.0, 126.7, 129.2, 129.4, 129.5, 131.3, 133.5, 138.9, 142.6, 153.6, 154.5, 166.9, 167.4; FT-IR (neat, cm^{-1}): 3519, 3113, 1706, 1573, 1486, 1434, 1287, 1017, 745, 674; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{16}N_3O_2S$ 362.0958; Found 362.0955.



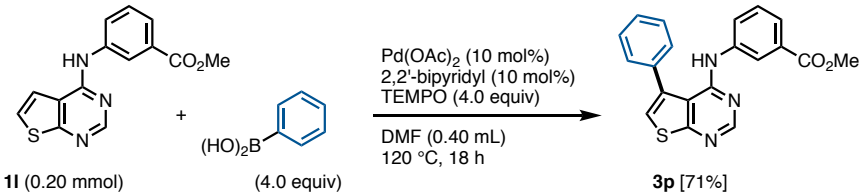
2v (80 μmol) **2w·HCl** [83%]

To a dried screw-capped glass tube containing a magnetic stirring bar were added **2v** (28.9 mg, 80 µmol, 1.0 equiv), 1,4-dioxane (0.11 mL) and 2 M NaOH solution in H_2O (0.11 mL) under air. The reaction mixture was stirred at 100 °C in an oil bath for 1 h. Upon cooling to ambient temperature, to the reaction was added 2 drops of 4 M HCl solution in 1,4-dioxane. The resulting white precipitate was collected by filter suction, washed with H_2O and Et_2O, then dried *in vacuo*, which provided hydrogen chloride adduct of **2w** as a white solid (26.0 mg), which contained 0.68 mg of Et_2O. The yield of **2w·HCl** was calculated as 83%. Note: the ratio of **2w·HCl** and Et_2O was determined by ^{1}H NMR since Et_2O was not completely removed after drying *in vacuo* for 12 h.



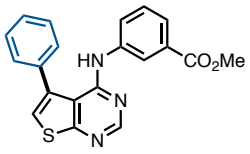
2w·HCl

2w·HCl: (26.0 mg, 83%, white solid) ^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ 7.45 (t, J = 7.2 Hz, 1H), 7.52–7.56 (m, 3H), 7.68 (d, J = 7.8 Hz, 1H), 7.76 (d, J = 7.2 Hz, 2H), 8.27 (d, J = 7.2 Hz, 1H), 8.33 (s, 1H), 8.43 (s, 1H), 8.56 (s, 1H), 9.84 (s, 1H), 12.99 (brs, 1H); ^{13}C NMR (150 MHz, DMSO): δ 115.3, 118.5, 121.6, 123.9, 125.0, 125.8, 128.9, 129.5, 131.2, 132.9, 139.4, 139.6, 153.2, 154.2, 165.9, 167.2. (One sp^2 signal was not observed because of overlapping); FT-IR (neat, cm^{-1}): 3346, 2967, 1747, 1572, 1482, 1267, 751, 682; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{14}N_3O_2S$ 348.0801; Found 348.0799.



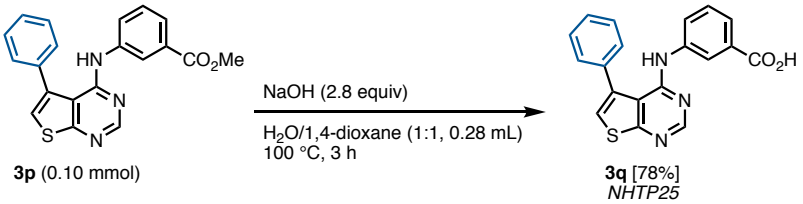
1l (0.20 mmol) (4.0 equiv) **3p** [71%]

To a dried screw-capped glass tube containing a magnetic stirring bar were added thieno[2,3-*d*]pyrimidine **1l** (57.2 mg, 0.20 mmol, 1.0 equiv), phenylboronic acid (97.5 mg, 4.0 equiv), $Pd(OAc)_2$ (4.5 mg, 10 mol%), 2,2'-bipyridyl (3.1 mg, 10 mol%) and TEMPO (125.0 mg, 4.0 equiv). To this mixture, DMF (0.40 mL) was added and the tube was sealed under air. The reaction mixture was stirred at 120 °C for 18 h in an 8-well reaction heat block. Upon cooling to ambient temperature, the mixture was passed through a short pad of Celite® with EtOAc as eluent. The filtrate was concentrated *in vacuo* and the residue was subjected to flash column chromatography on silica-gel (hexane/EtOAc = 95:5 → 75:25) to give **3p** as a pale-yellow solid (51.1 mg, 71%).

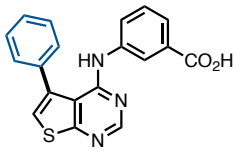


3p

3p: (51.1 mg, 71%, pale yellow solid) ^{1}H NMR (600 MHz, $CDCl_3$): δ 3.91 (s, 3H), 6.97 (brs, 1H), 7.23 (s, 1H), 7.34 (t, J = 7.8 Hz, 1H), 7.55–7.57 (m, 2H), 7.60–7.61 (m, 3H), 7.63 (d, J = 7.8 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.95 (d, J = 1.2 Hz, 1H), 8.67 (s, 1H); ^{13}C NMR (150 MHz, $CDCl_3$): δ 52.4, 115.0, 121.4, 121.7, 124.8, 129.2, 129.5, 129.6, 129.7, 131.1, 134.3, 136.1, 138.8, 153.8, 155.2, 166.9, 168.0. (One sp^2 signal was not observed because of overlapping); FT-IR (neat, cm^{-1}): 3400, 3114, 1717, 1487, 1192, 749, 711; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{20}H_{16}N_3O_2S$ 362.0958; Found 362.0956.



To a dried screw-capped glass tube containing a magnetic stirring bar were added **3o** (36.1 mg, 0.10 mmol, 1.0 equiv), 1,4-dioxane (0.14 mL) and 2 M NaOH solution in H_2O (0.14 mL) under air. The reaction mixture was stirred at 100 °C in an oil bath for 3 h. Upon cooling to ambient temperature, the reaction mixture was dried *in vacuo*. The residue was subjected to flash column chromatography on silica-gel ($CHCl_3$/MeOH = 99:1 → 90:10) to give **3p** as a white solid (26.3 mg, 78%).



3q

3q: (26.3 mg, 78%, white solid) ^{1}H NMR (600 MHz, $(CD_3)_2SO$): δ 7.39–7.42 (m, 2H), 7.54–7.56 (m, 1H), 7.57–7.61 (m, 4H), 7.64 (dd, J = 7.8, 1.8 Hz, 2H), 7.72 (s, 1H), 8.01 (s, 1H), 8.63 (s, 1H), 13.01 (brs, 1H); ^{13}C NMR (150 MHz, $(CD_3)_2SO$): δ 114.4, 120.8, 122.6, 124.0, 124.2, 128.8, 128.9, 129.0, 129.3, 131.6, 134.2, 135.3, 138.6, 153.0, 154.6, 167.0, 167.3; FT-IR (neat, cm^{-1}): 3372, 3075, 2926, 1695, 1617, 1577, 1537, 1490, 1356, 1274, 1017, 749, 650; HRMS (ESI, positive) *m/z*: $[M + H]^+$ Calcd for $C_{19}H_{14}N_3O_2S$ 348.0801; Found 348.0798.

11. Mechanistic Investigation on the C6-selective Arylation

Regarding the reaction mechanism for the C6-selective arylation of thieno[2,3-*d*]pyrimidine **1**, two possible pathways can be considered. Path A consists of oxidative addition of iodoarene (**A**→**B**), ligand exchange with AgOAc (**B**→**C**), C–H palladation (**C**→**D**), and reductive elimination (**D**→**A** and **2**). Another proposed reaction mechanism path B is based on the α-arylation of benzo[*b*]thiophene developed by the group of Larrosa,[S6] where AgOAc facilitates C–H bond cleavage of **1** to give **Ag-TP** intermediate. In path B, **Ag-TP** could take part in transmetalation step with aryl palladium **B** to generate the common intermediate **D** and AgI followed by reductive elimination (**D**→**A** and **2**). To evaluate the involvement of intermediate **Ag-TP** in the catalytic system, we carried out H/D exchange experiments.

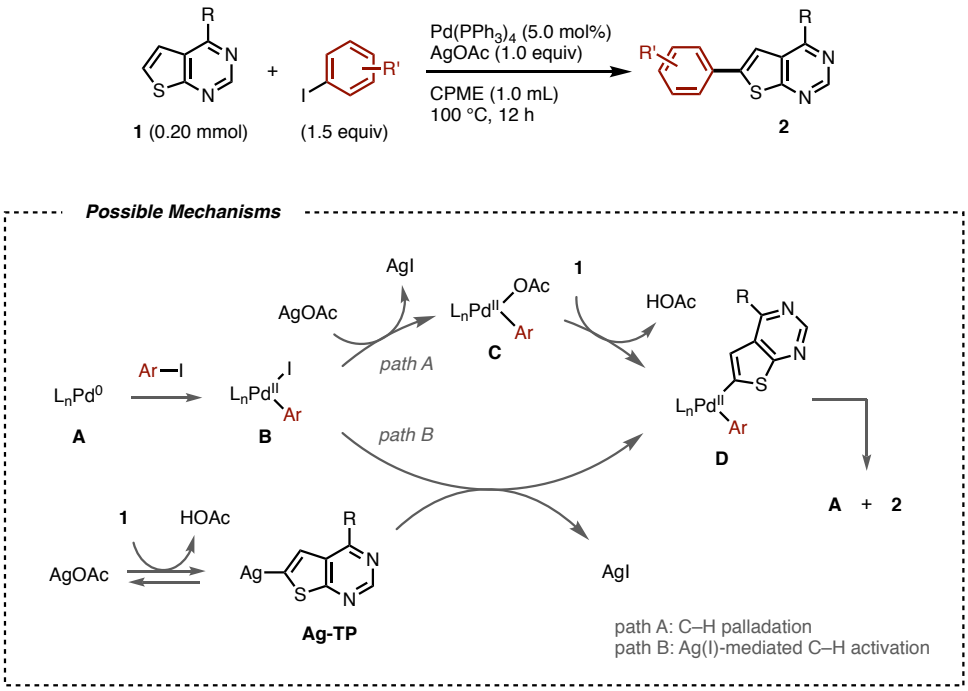
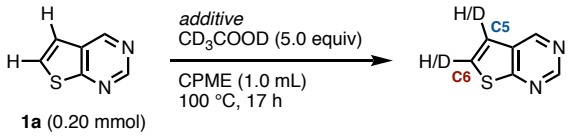


Figure S1. Possible reaction pathways in the C6-selective arylation

H/D exchange of **1a** was surveyed in the presence of CD_3COOD as the deuterium source. When the catalytic amount of $Pd(OAc)_2$ was added, deuterium incorporation slightly proceeded at both C6 and C5 positions (entry 1). The combination with catalytic PPh_3 did not affect the deuterium incorporation efficiency (entry 2). 10% H/D exchange at C6 position was observed upon the addition of AgOAc (entry 3), which significantly increased to 61% with PPh_3 while the ratio of H/D exchange at C5 was low (entry 4). A negative control experiment in the absence of any additives proved the positive effect of palladium or silver additives for the observed H/D exchanges (entry 5).

Table S4. H/D exchange experiments



entry	additive	C6[a]	C5[a]
1	$Pd(OAc)_2$ (5.0 mol%)	6% D	5% D
2	$Pd(OAc)_2$ (5.0 mol%), PPh_3 (20 mol%)	3% D	6% D
3	AgOAc (1.0 equiv)	10% D	4% D
4	AgOAc (1.0 equiv), PPh_3 (20 mol%)	61% D	11% D
5	none	0% D	0% D

[a] determined by ^1H NMR spectra of the crude product using 1,1,2,2-tetrachloroethane as the internal standard.

Considering the results in the H/D exchange experiments, the Ag(I)-mediated C–H activation step (path B) could be the major pathway in the C6-selective arylation. Moreover, the enhancement in H/D exchange with phosphine ligand was in accordance with the results reported in the literatures.[S13] However, we could not completely rule out the possibility of path A (C–H palladation) since we observed the product **2a** without the addition of silver acetate (entry 14, Table S3).

12. References

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13. ^{1}H, ^{13}C and ^{19}F NMR Spectra

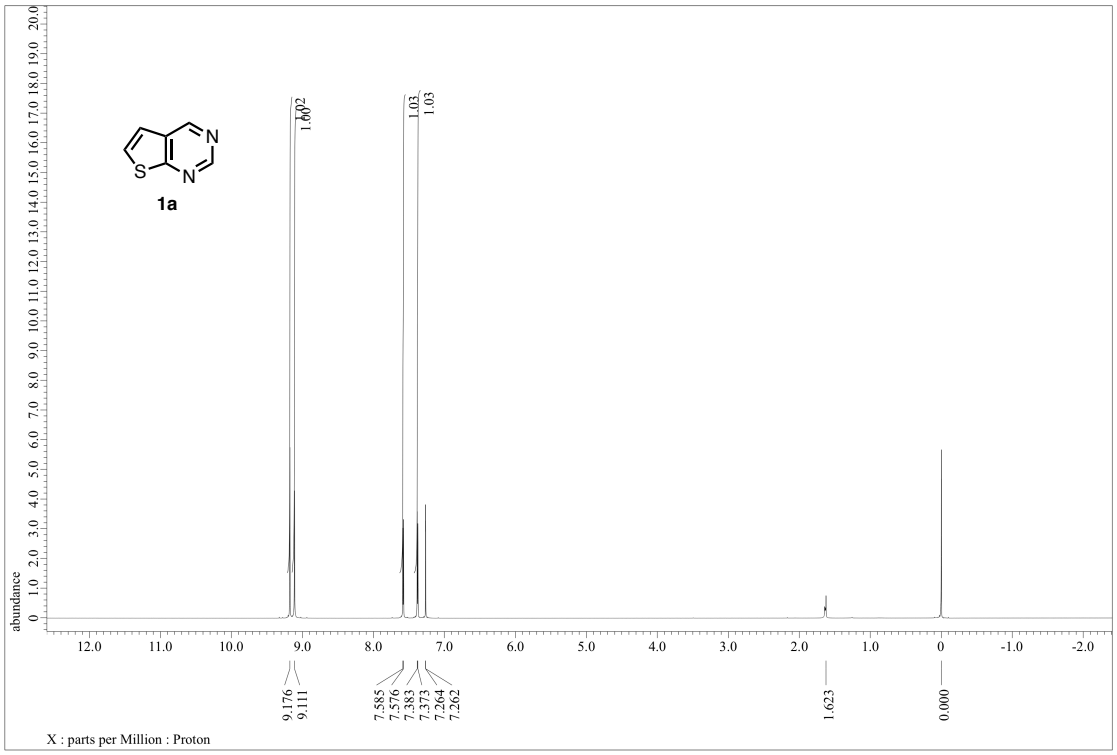

Figure S2. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **1a**.

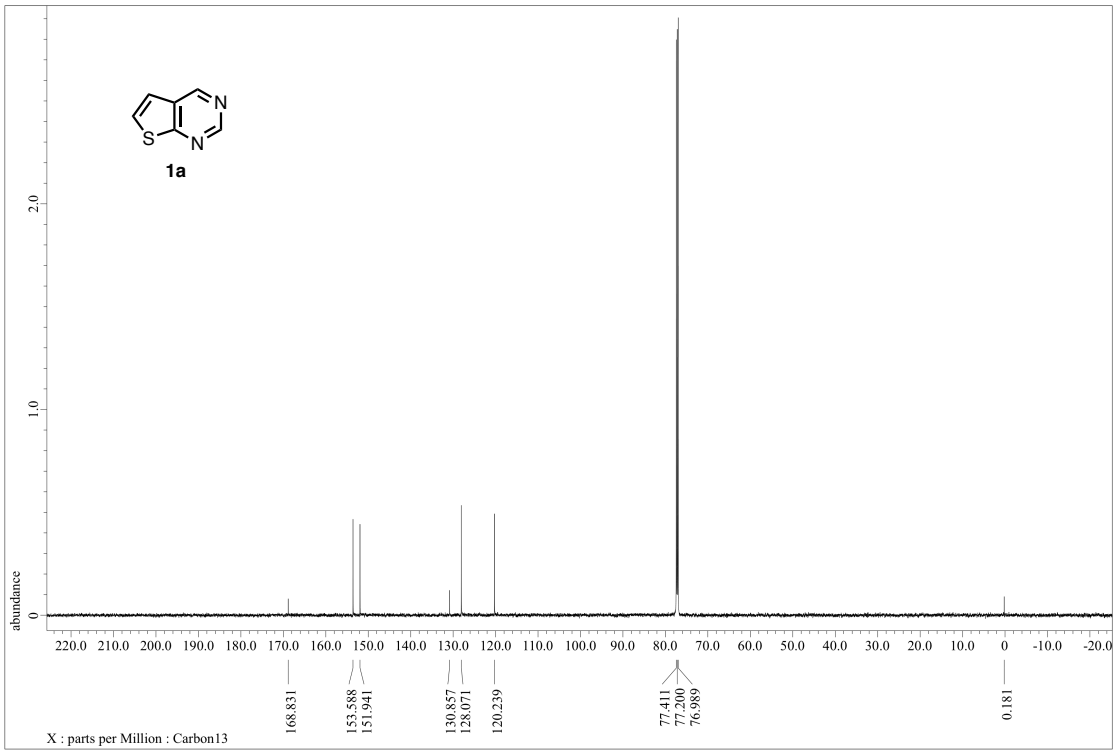

Figure S3. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **1a**.

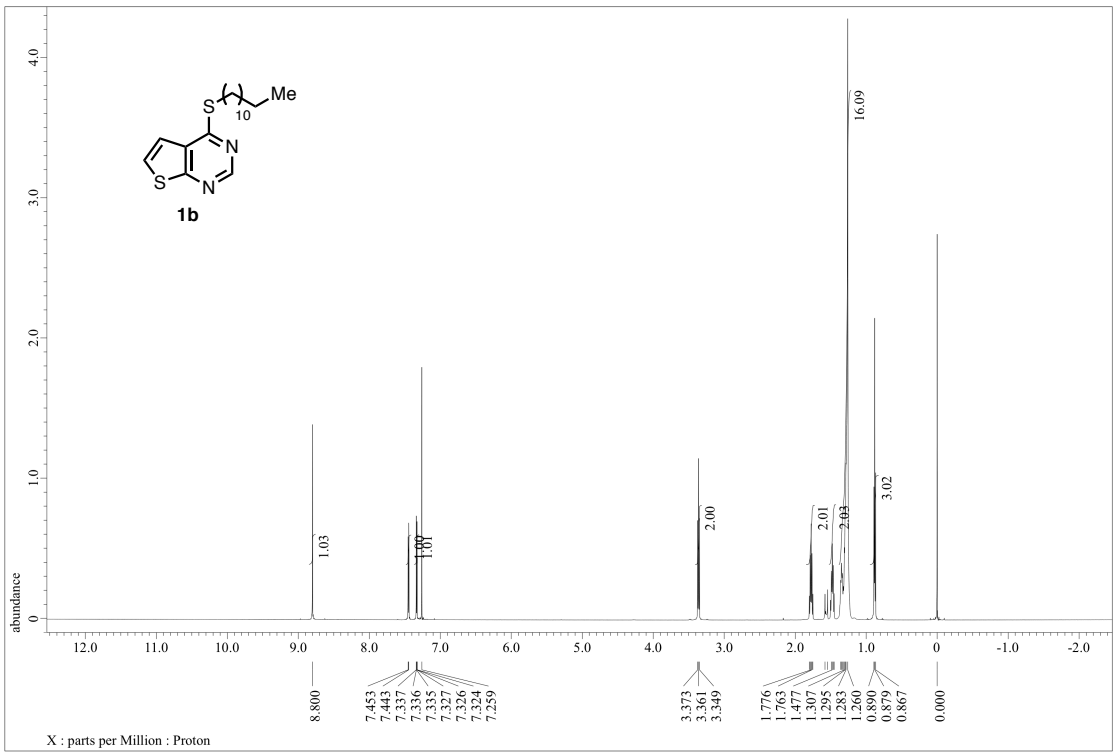

Figure S4. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **1b**.

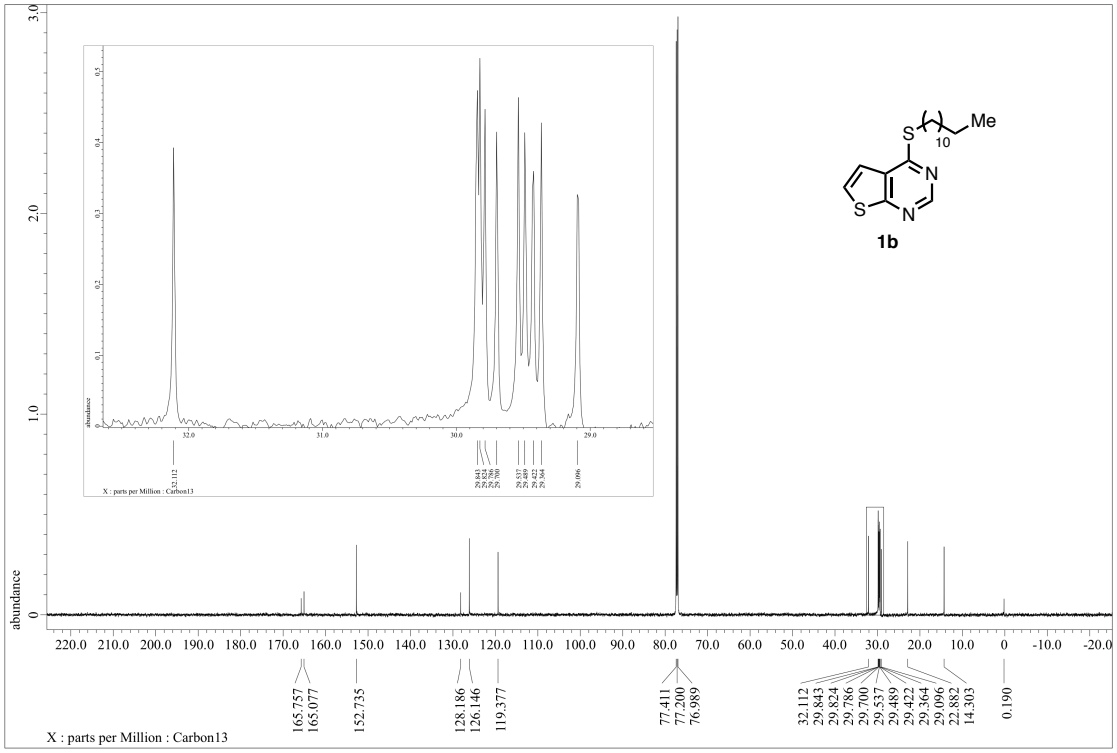

Figure S5. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **1b**.

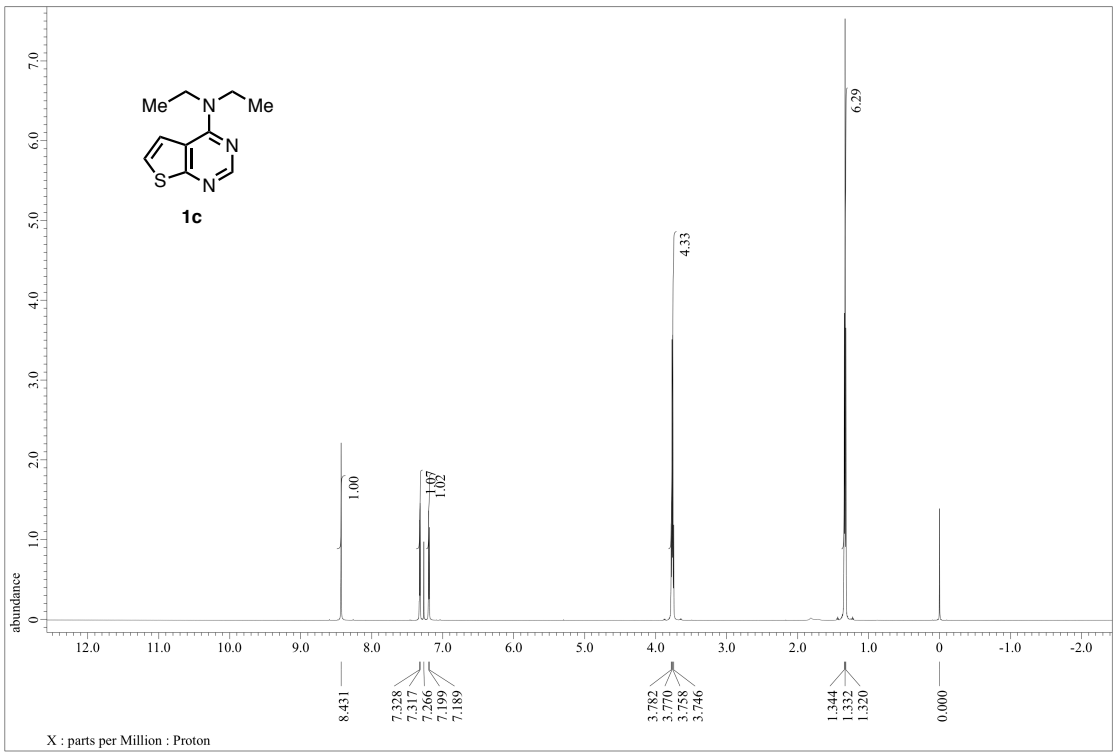

Figure S6. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **1c**.

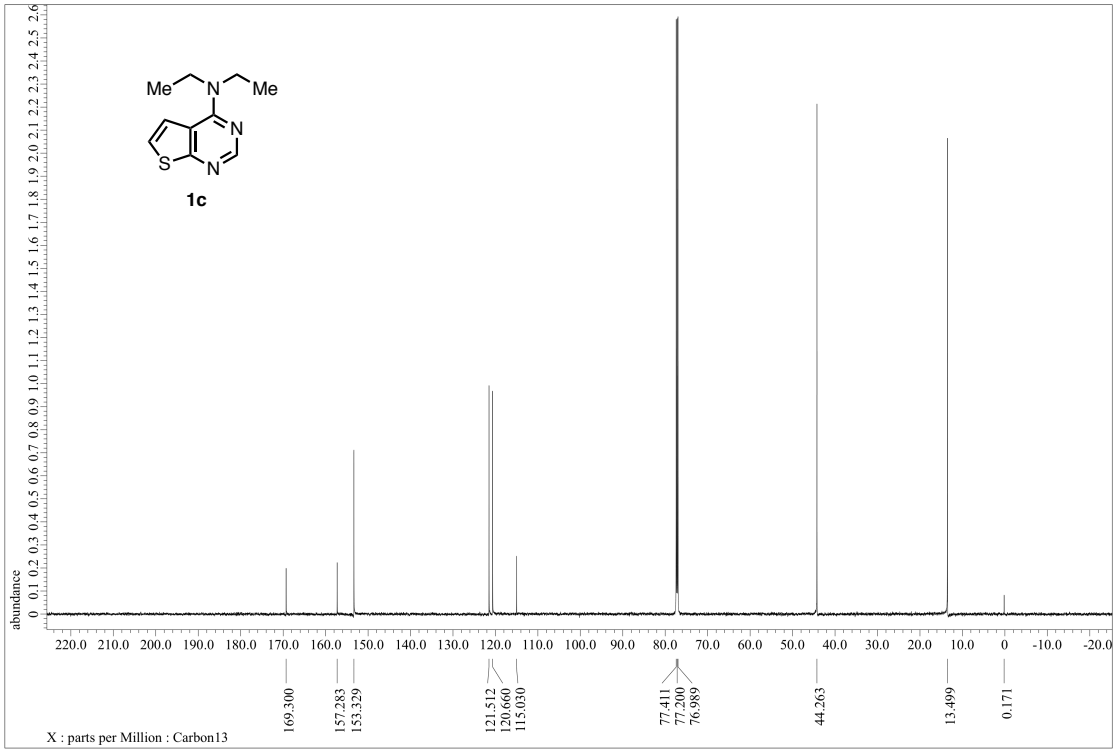

Figure S7. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **1c**.

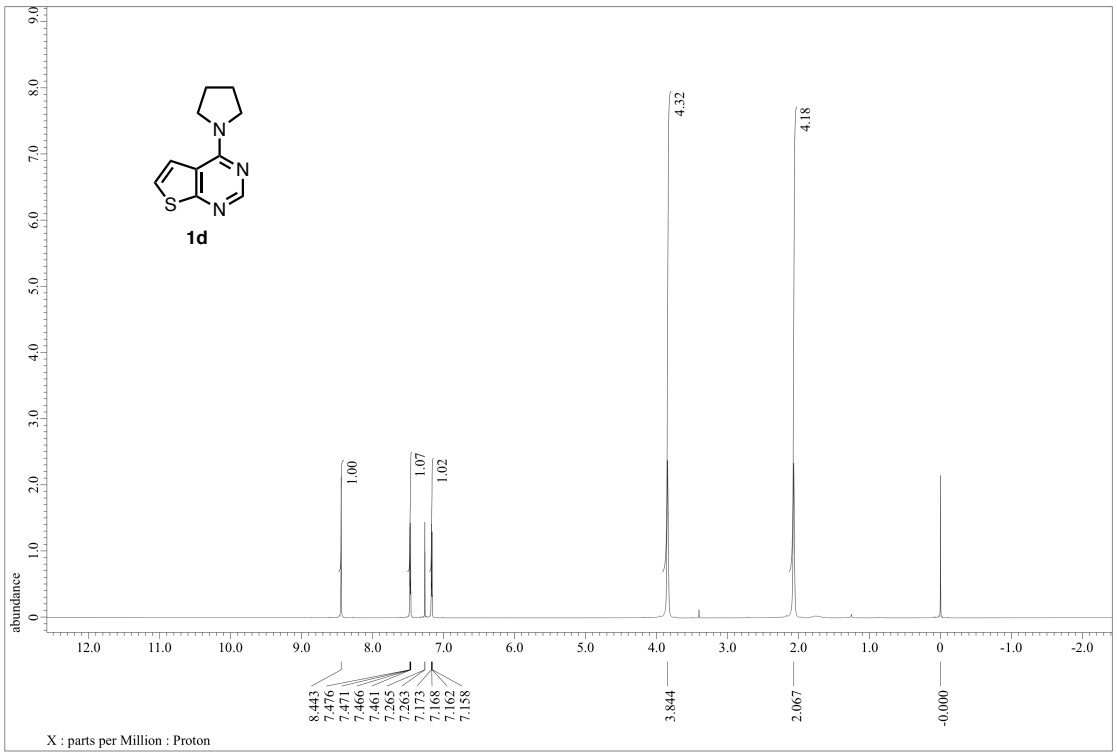

Figure S8. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **1d**.

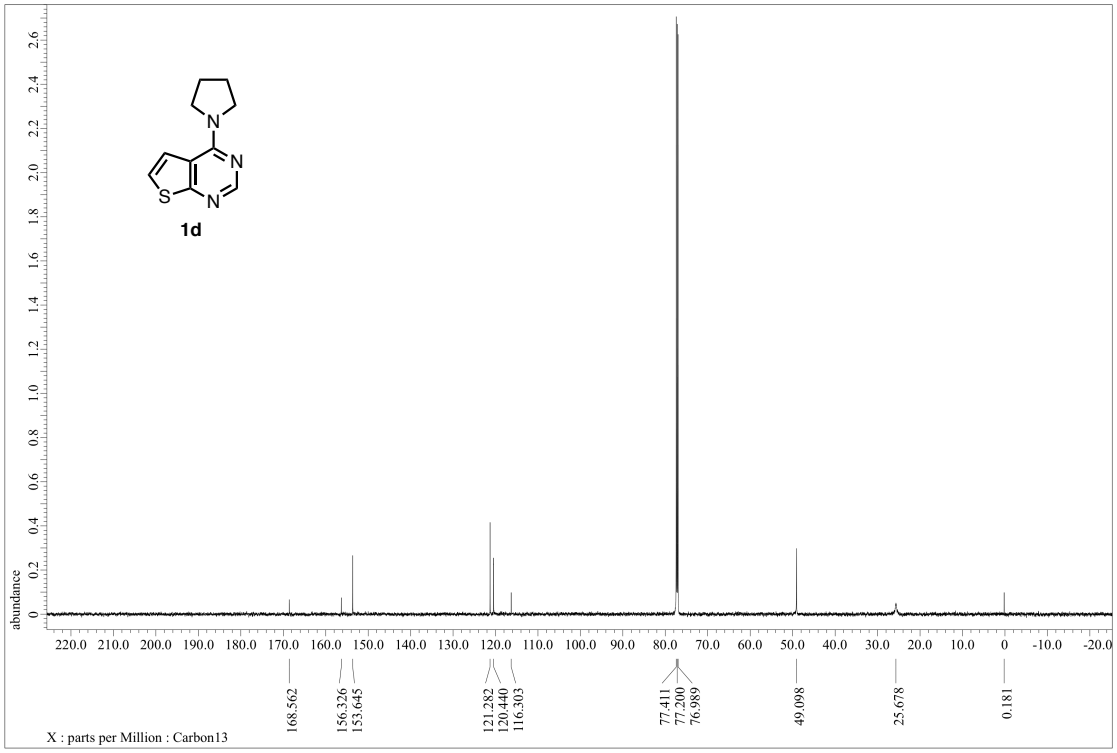

Figure S9. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **1d**.

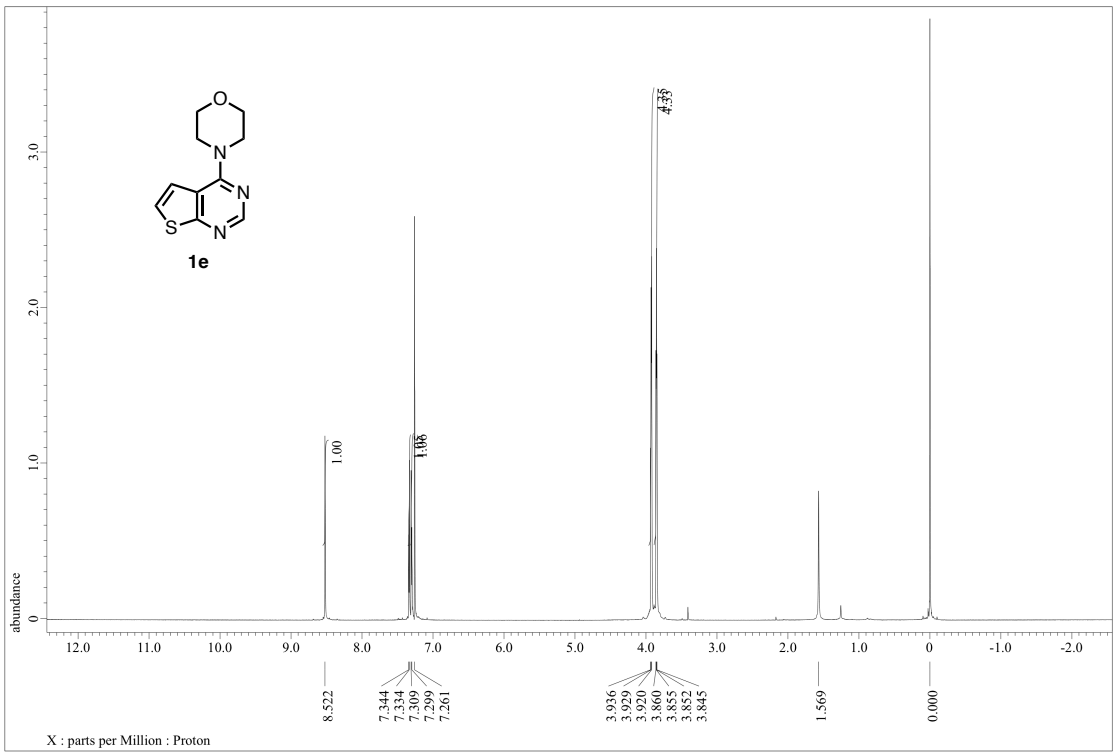

Figure S10. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **1e**.

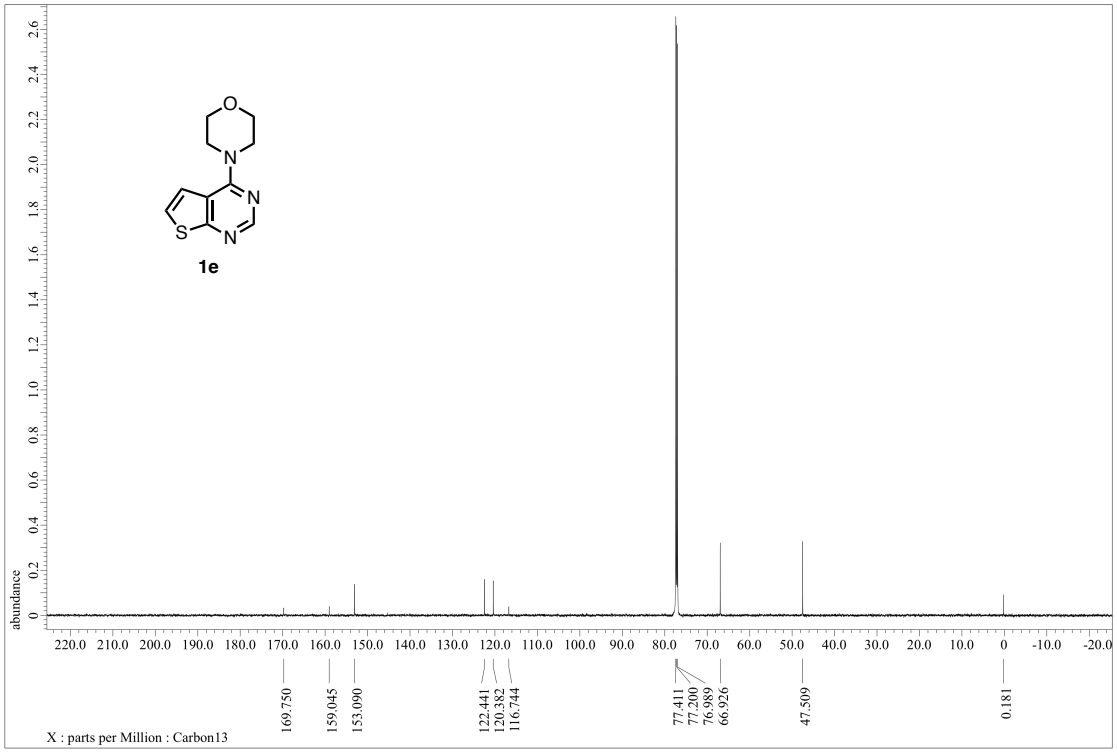

Figure S11. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **1e**.

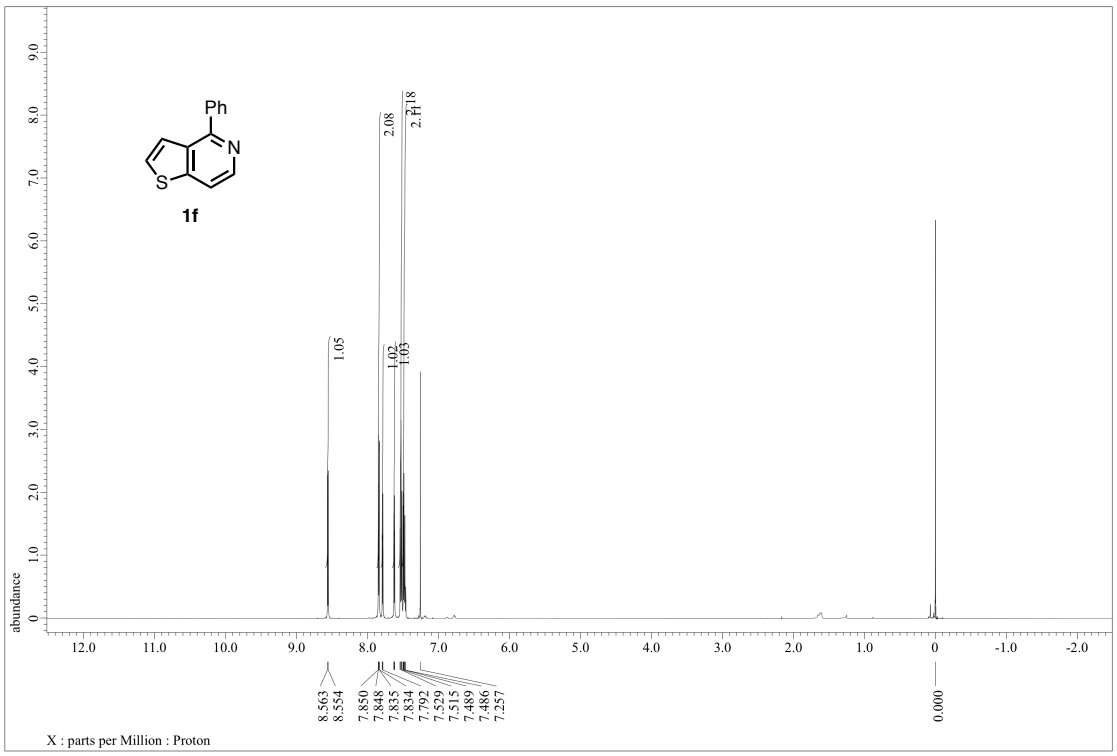

Figure S12. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **1f**.

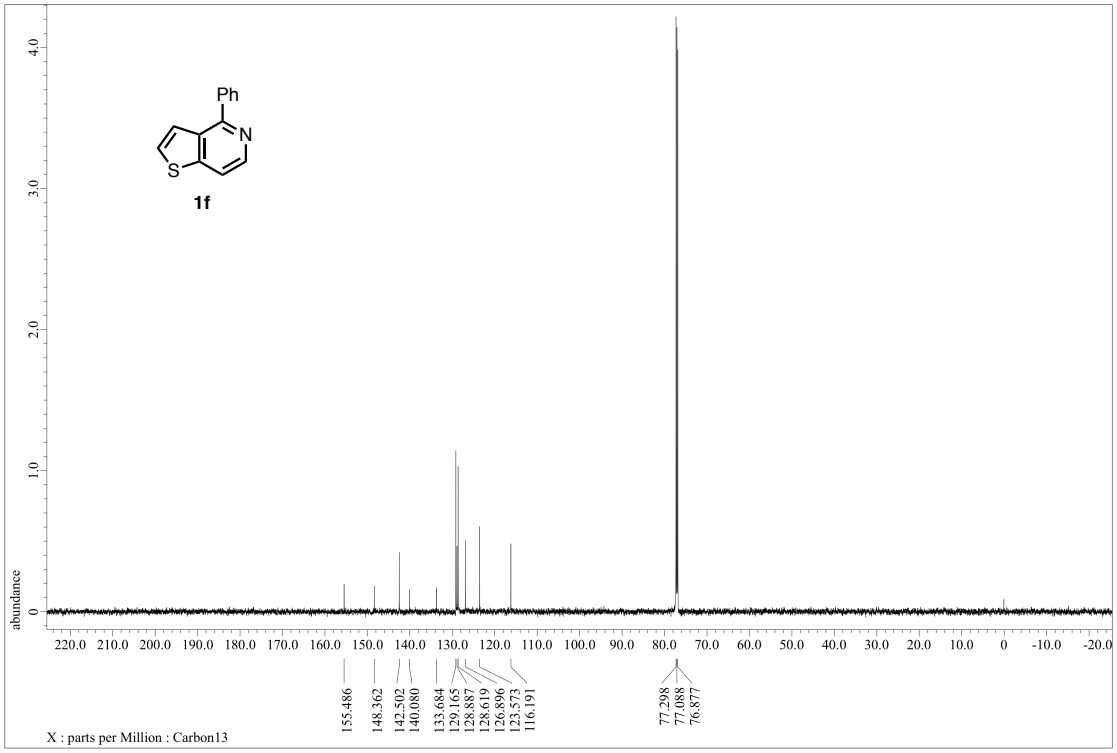

Figure S13. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **1f**.

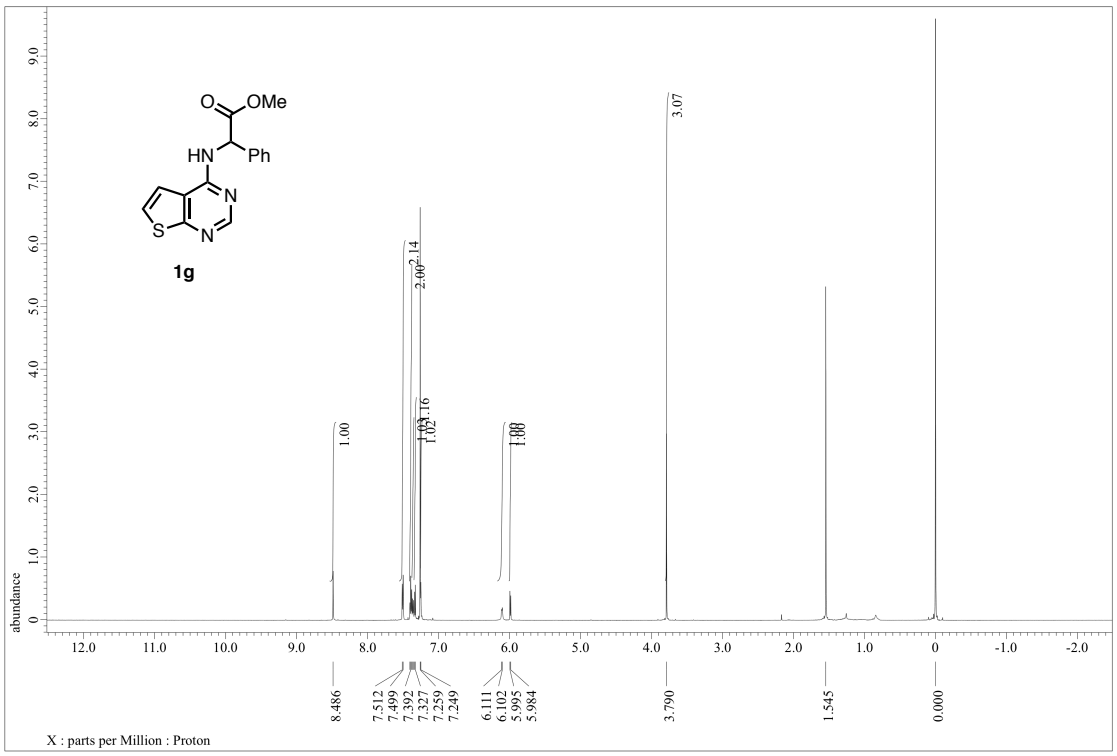

Figure S14. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **1g**.

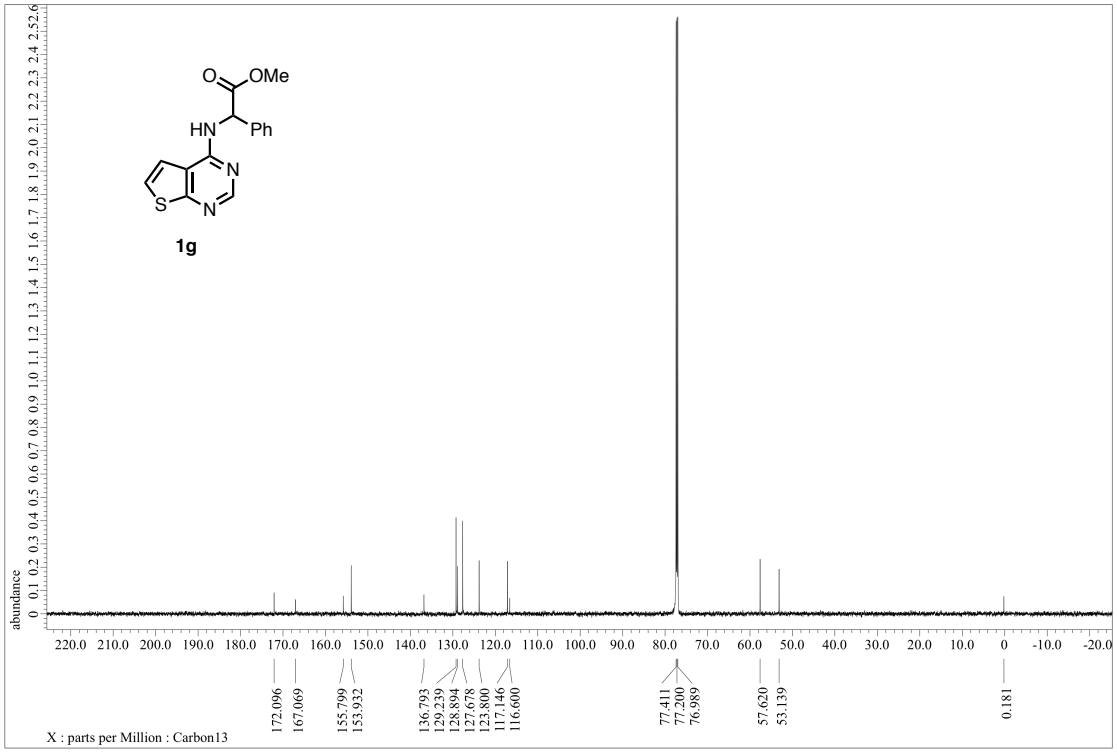

Figure S15. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **1g**.

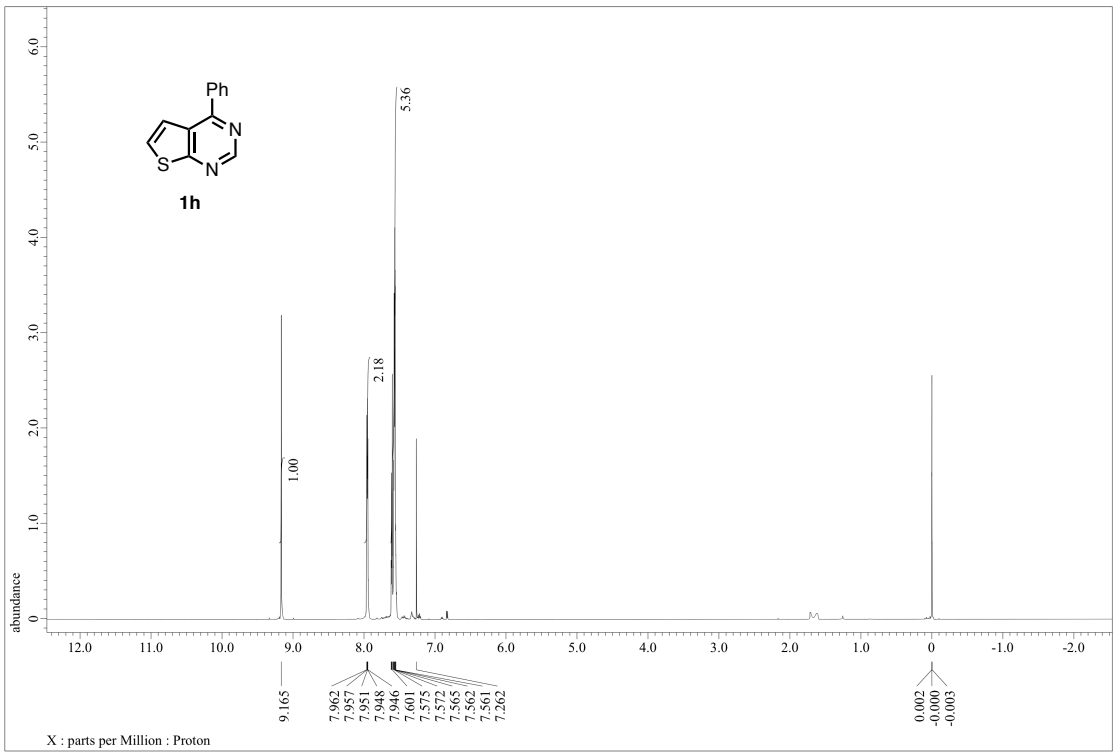

Figure S16. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **1h**.

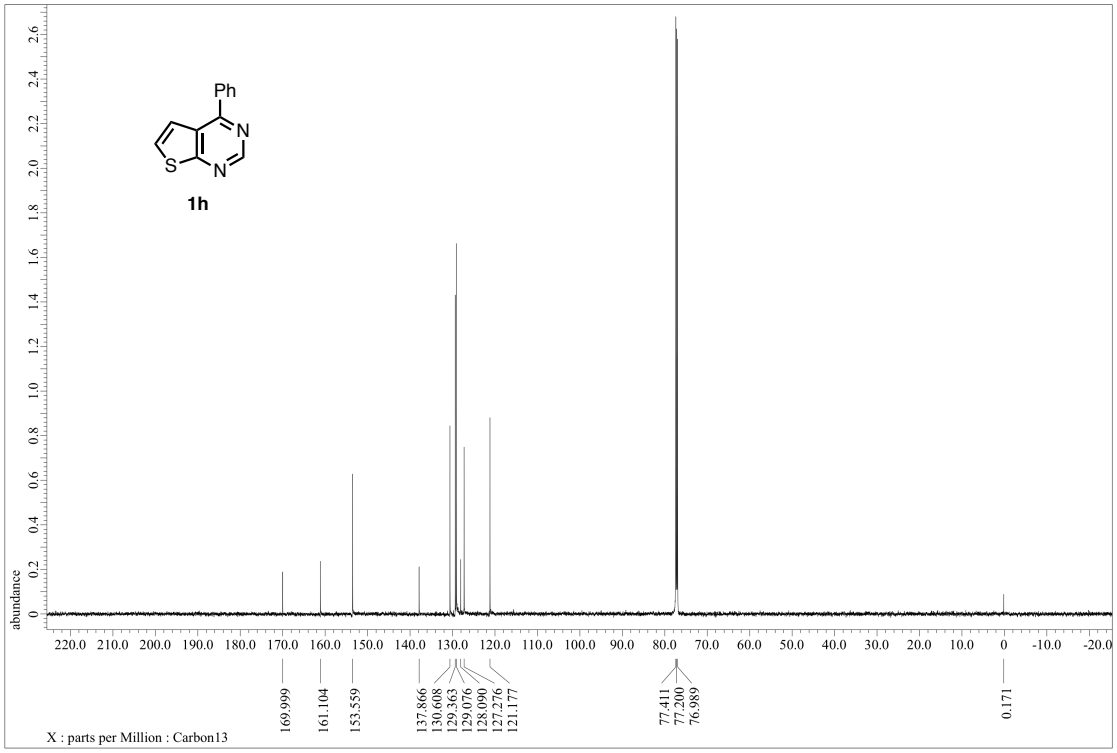

Figure S17. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **1h**.

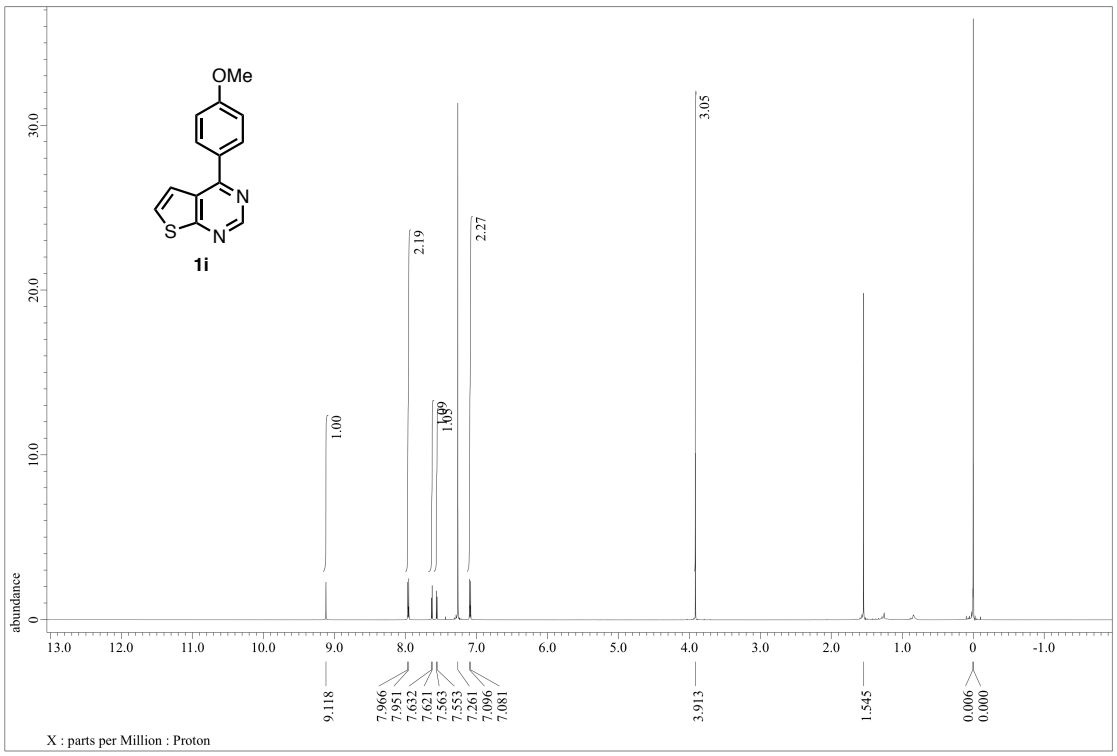

Figure S18. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **1i**.

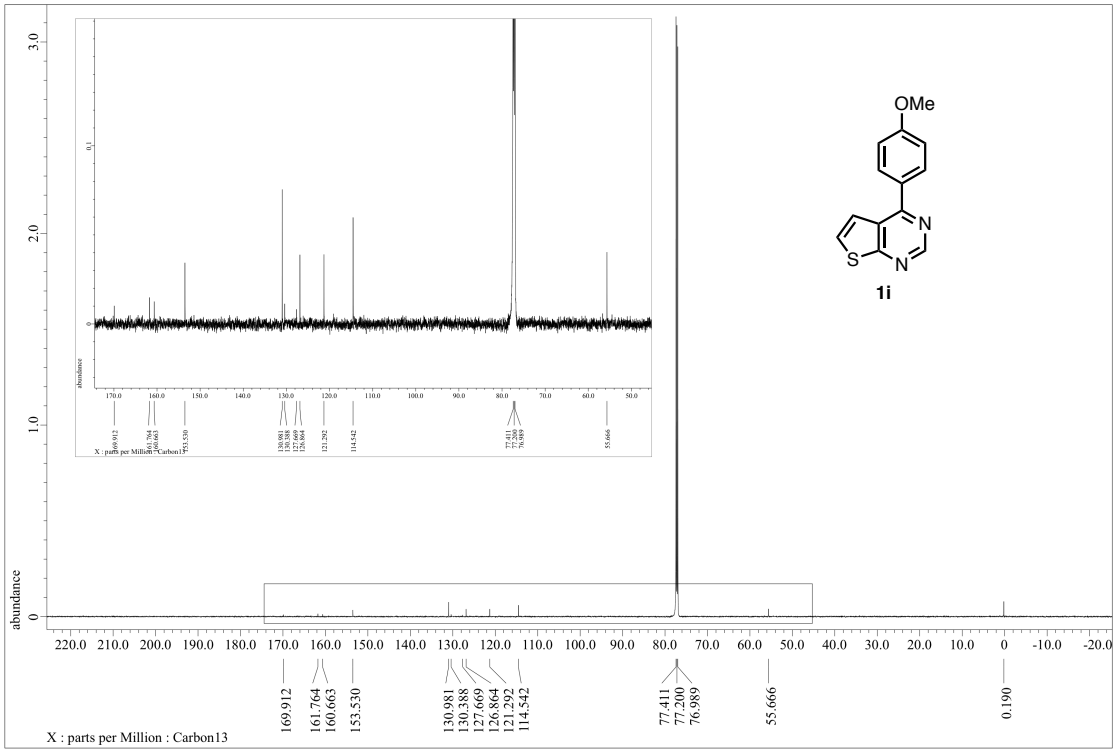

Figure S19. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **1i**.

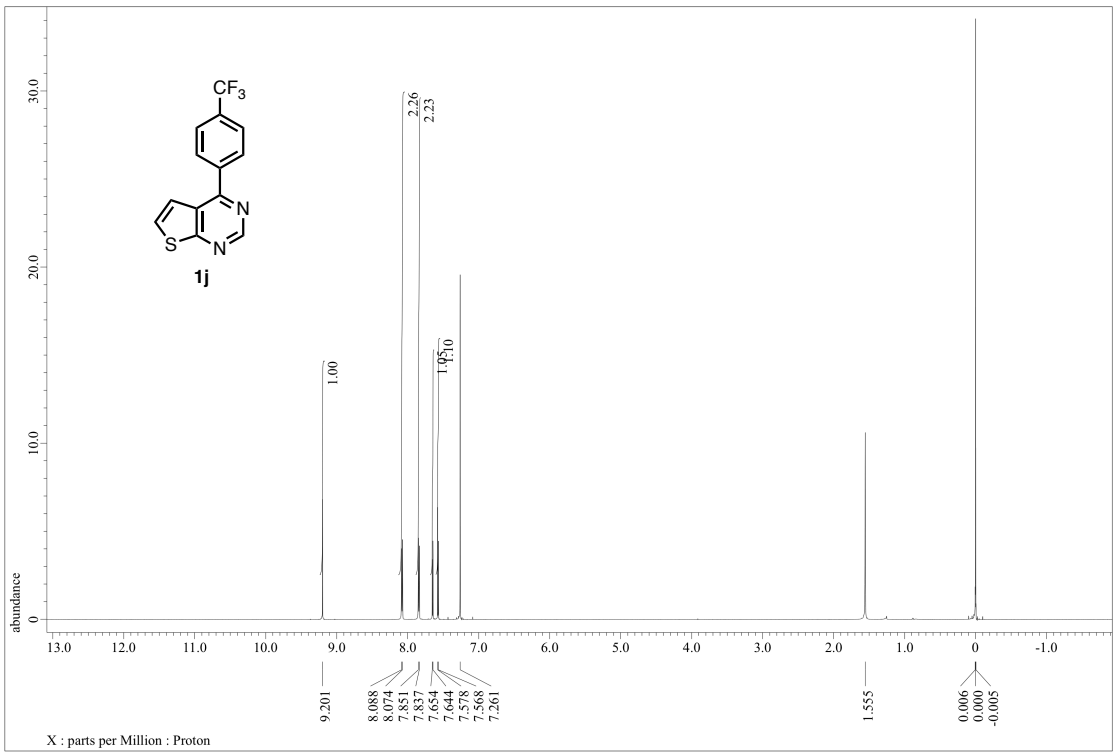

Figure S20. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **1j**.

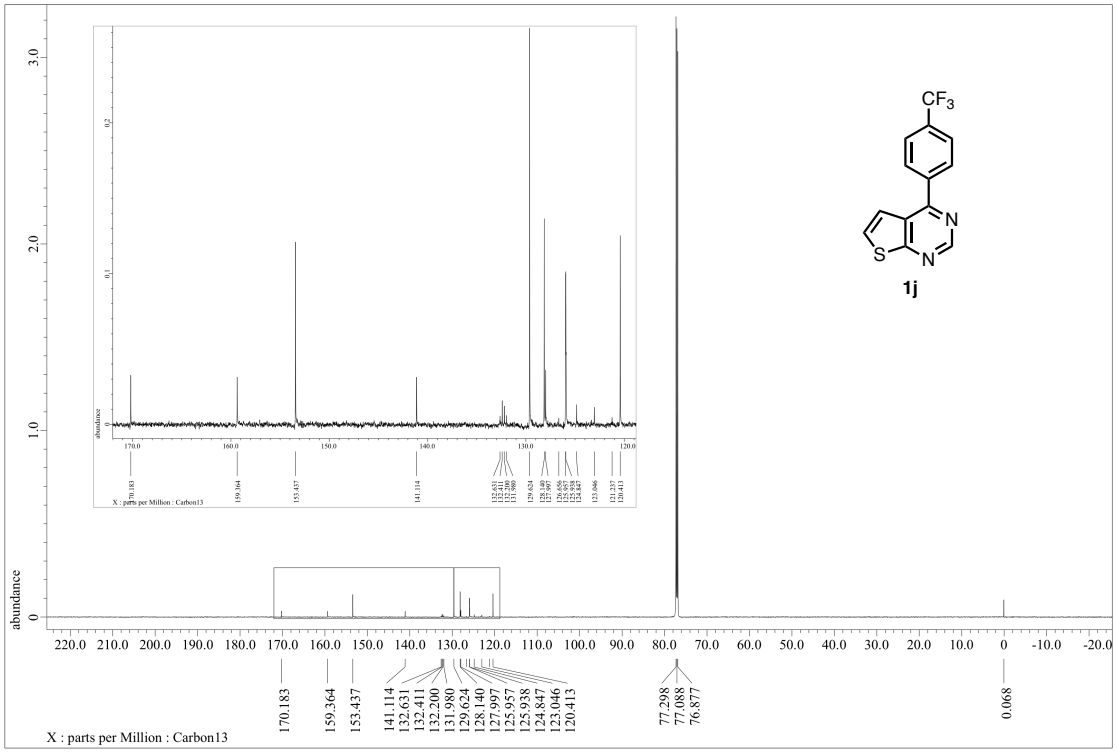

Figure S21. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **1j**.

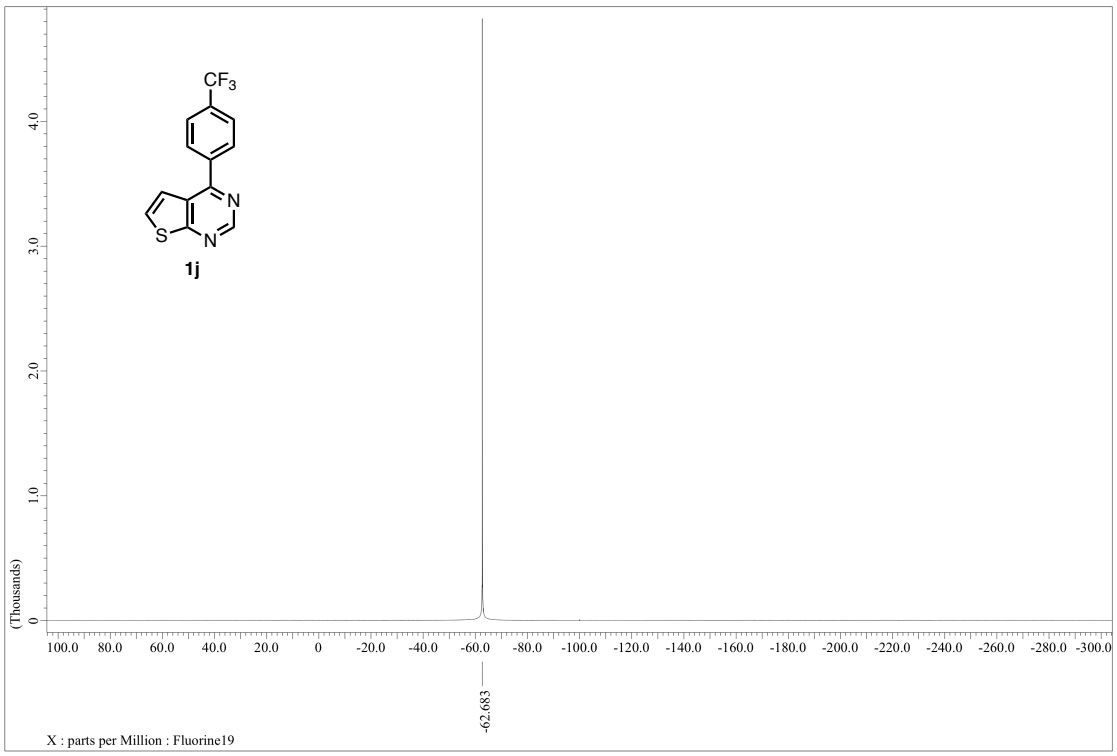

Figure S22. ^{19}F NMR spectrum (470 MHz, $CDCl_3$) of **1j**.

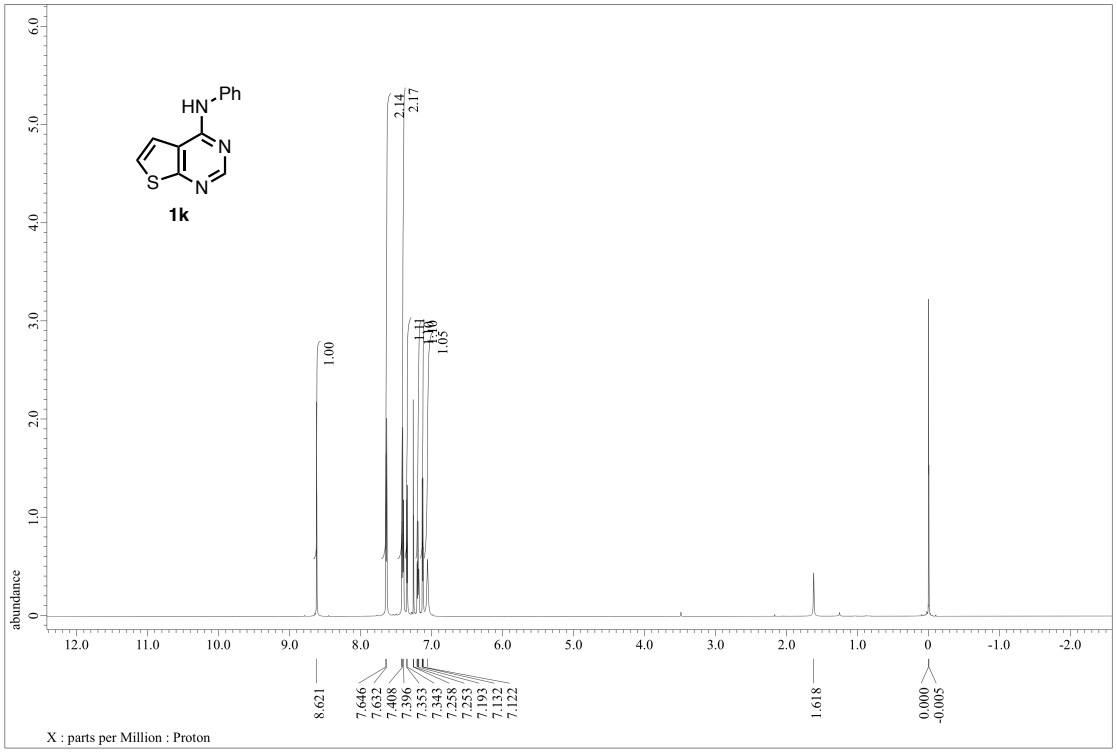

Figure S23. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **1k**.

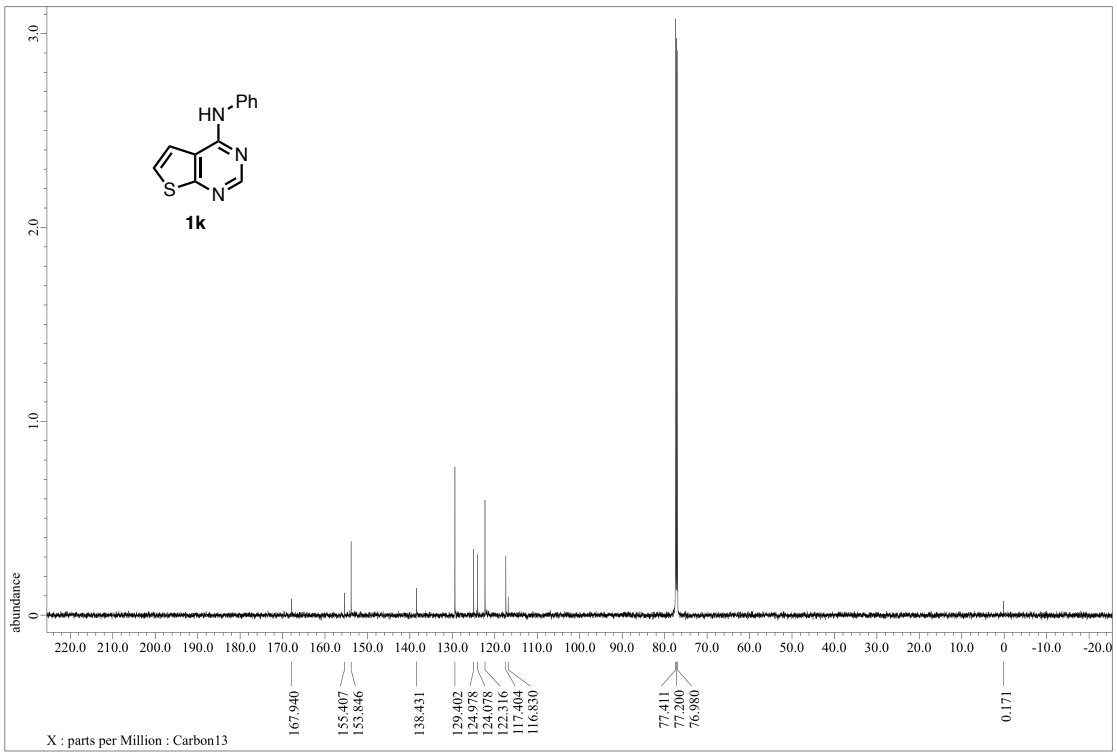

Figure S24. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **1k**.

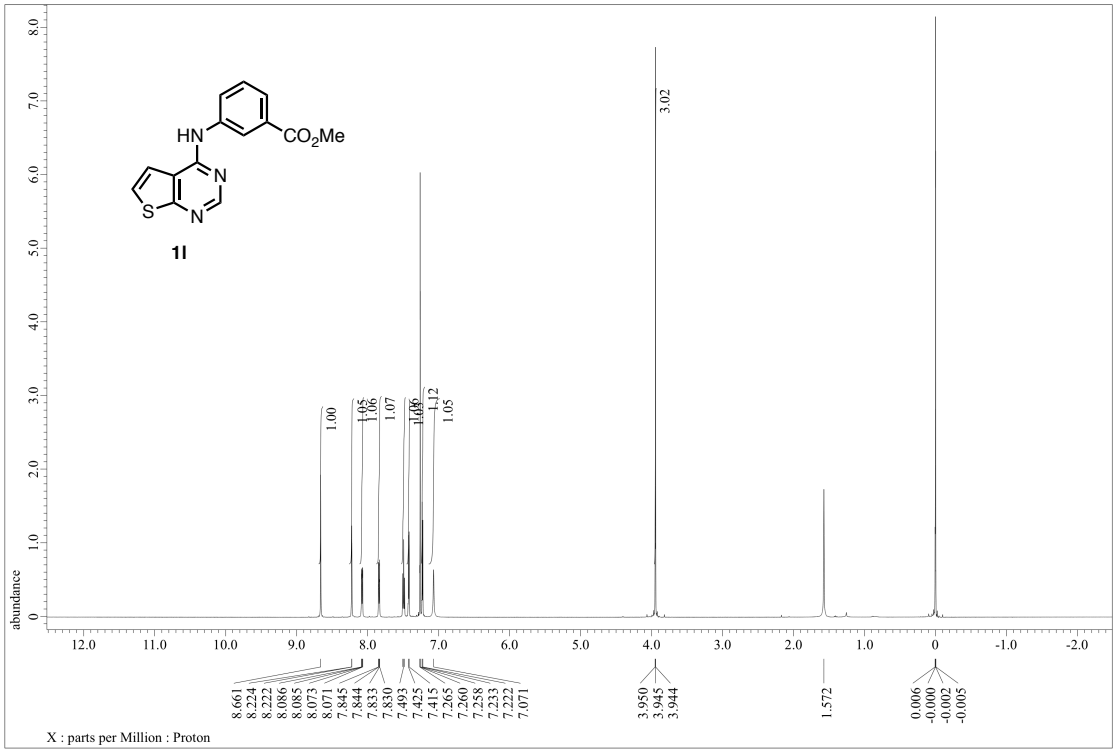

Figure S25. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **1l**.

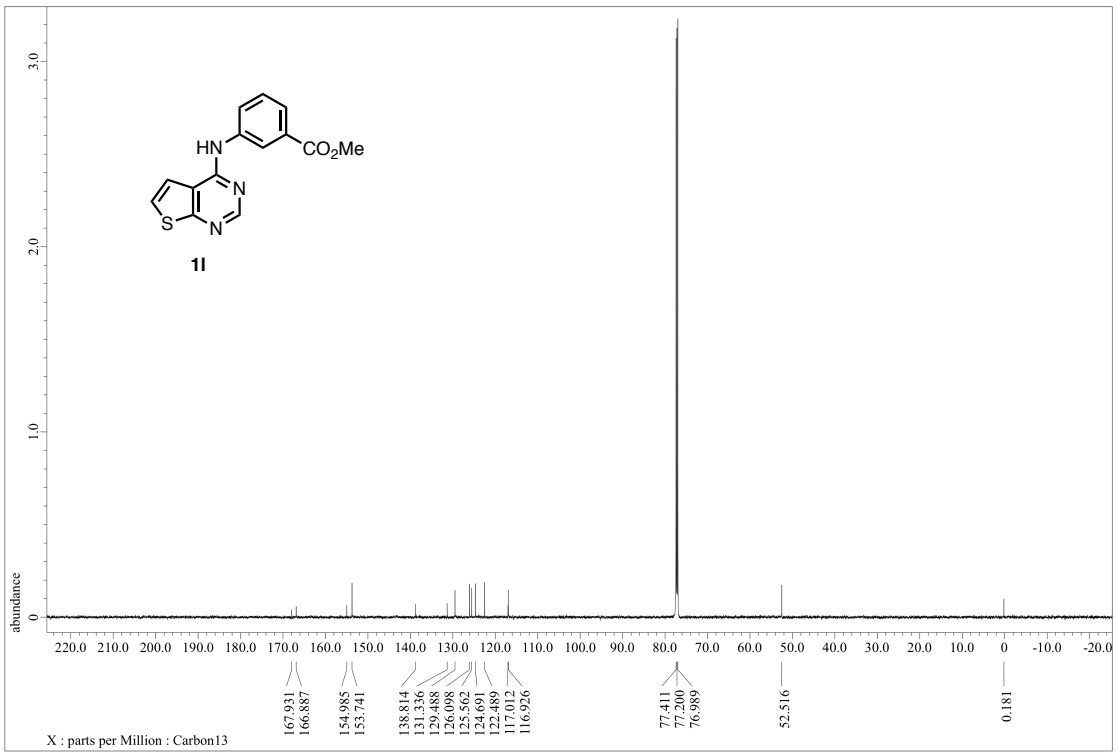

Figure S26. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **1l**.

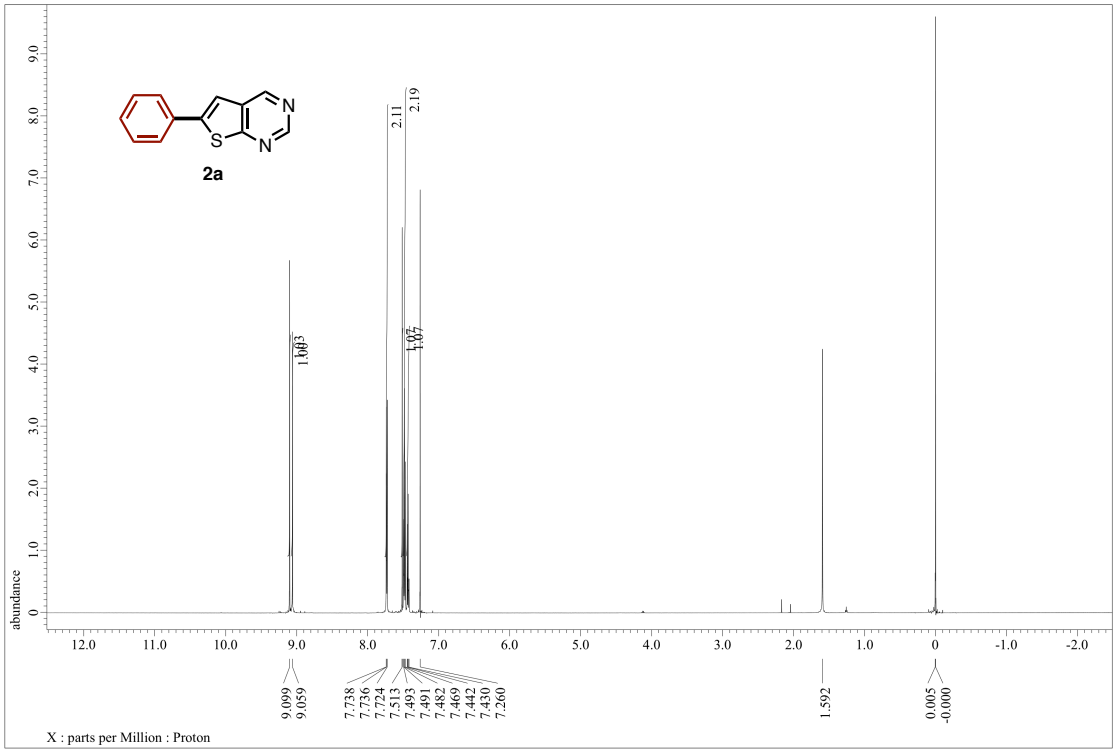

Figure S27. ^{1}H NMR spectrum of **2a**.

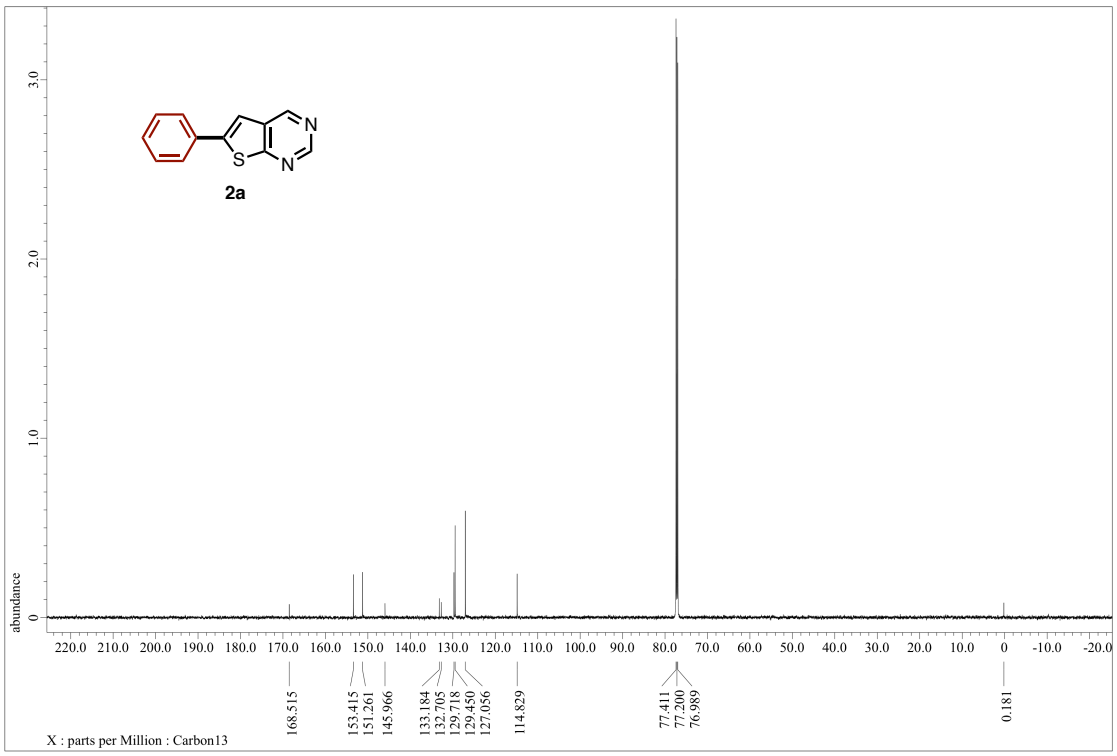

Figure S28. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2a**.

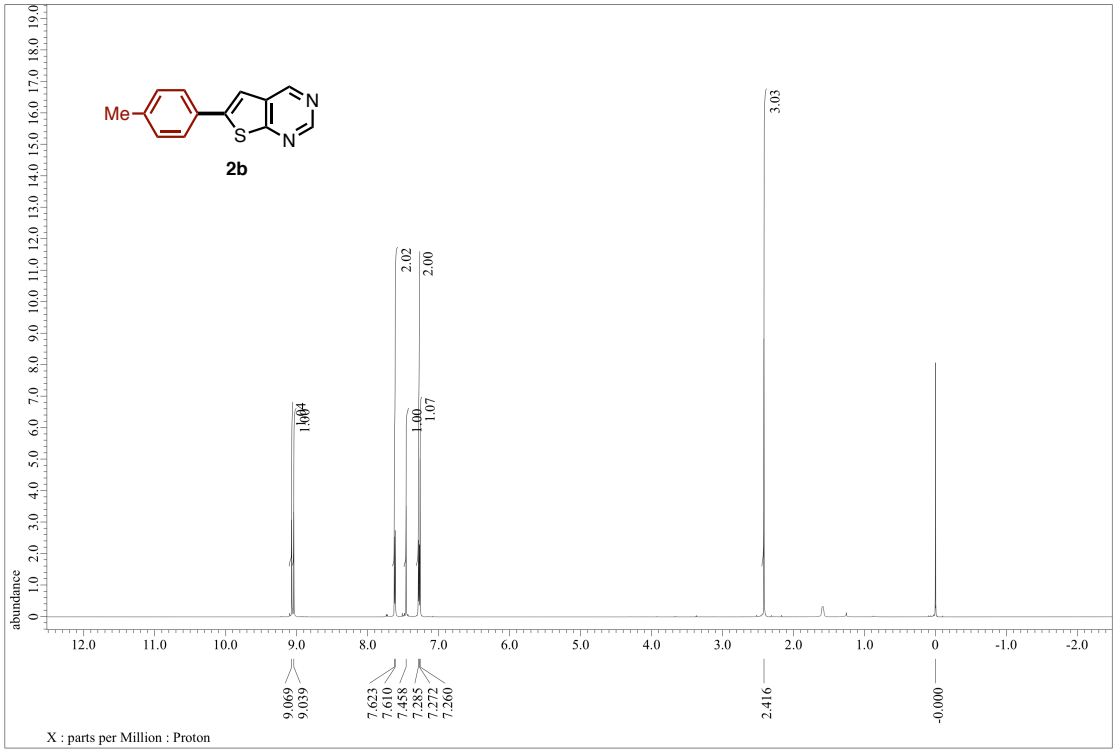

Figure S29. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2b**.

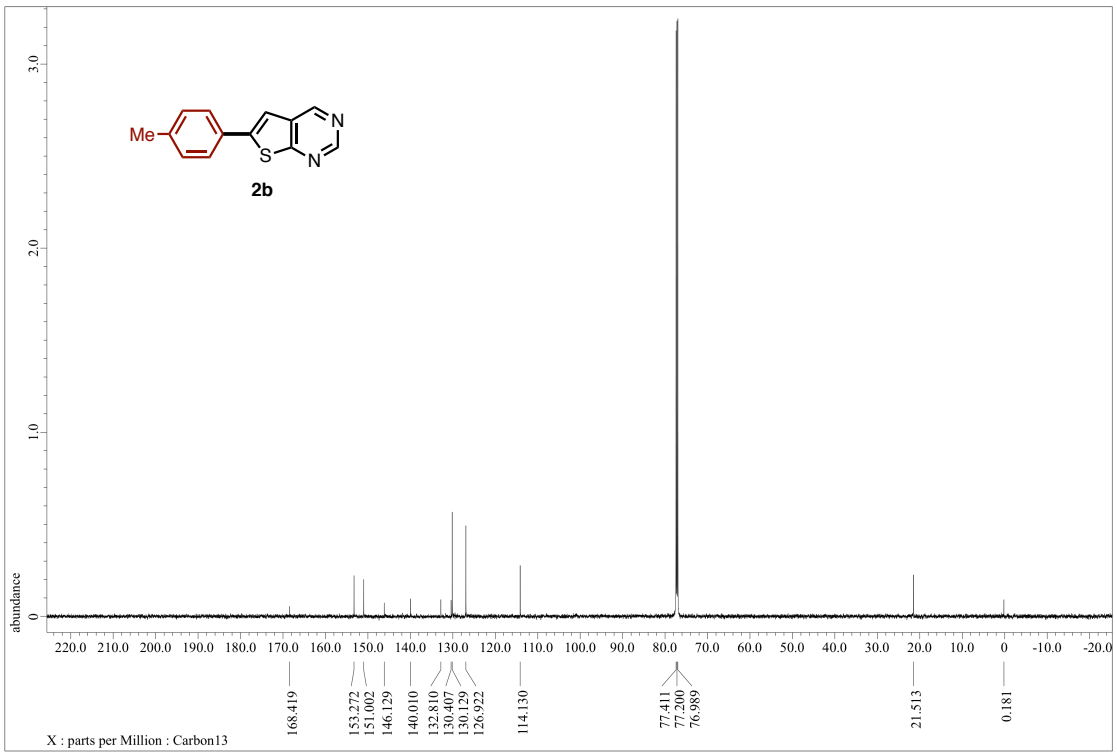

Figure S30. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2b**.

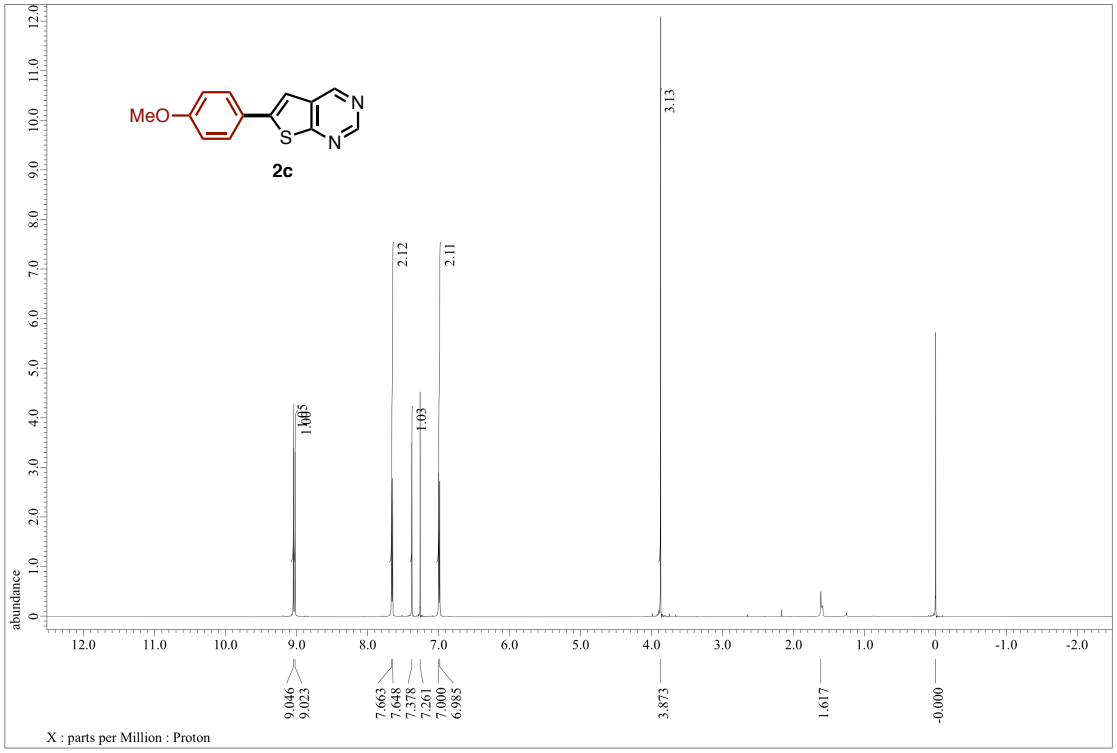

Figure S31. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2c**.

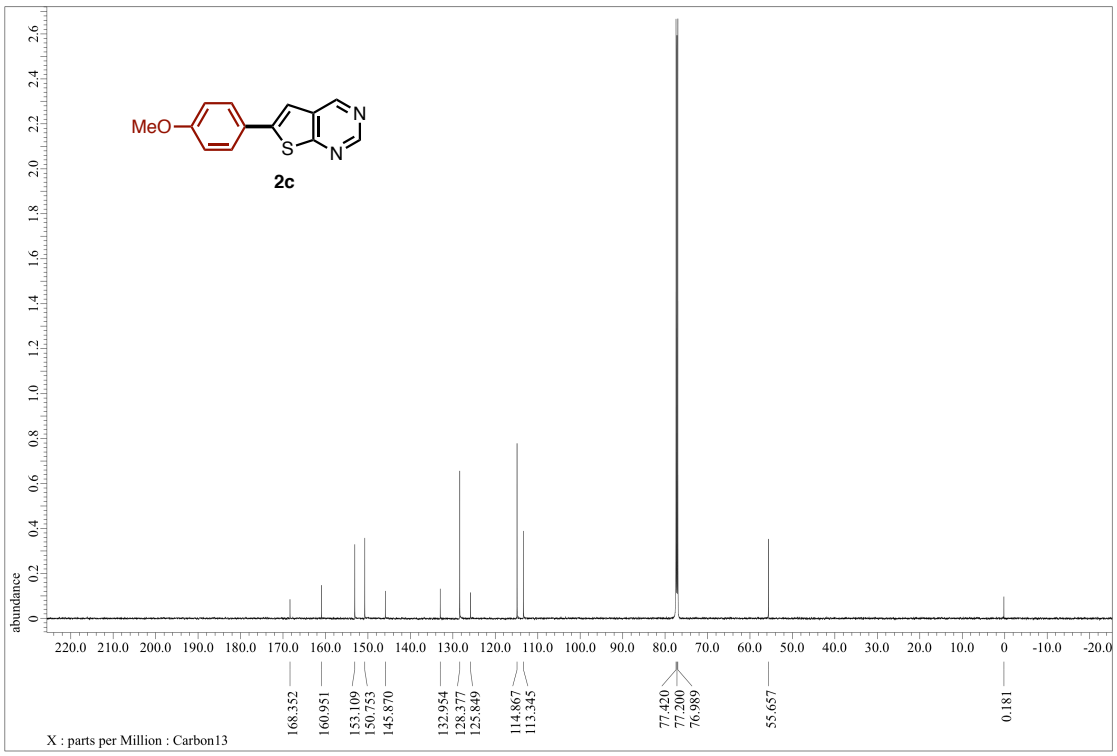

Figure S32. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2c**.

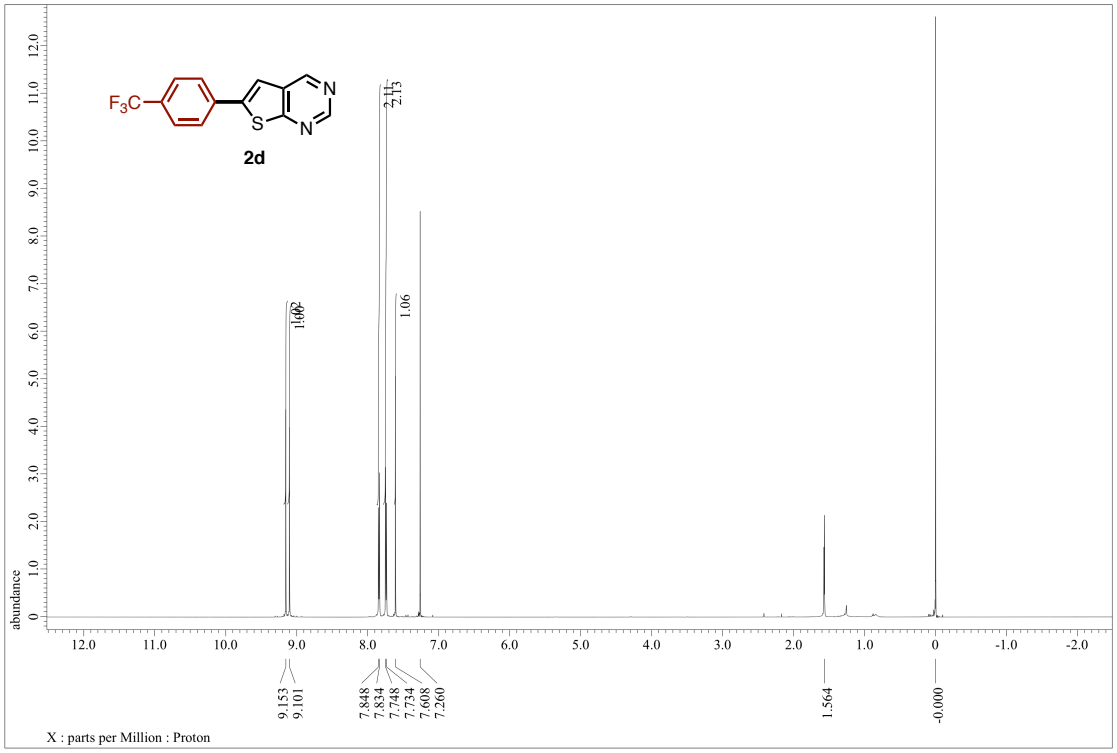

Figure S33. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2d**.

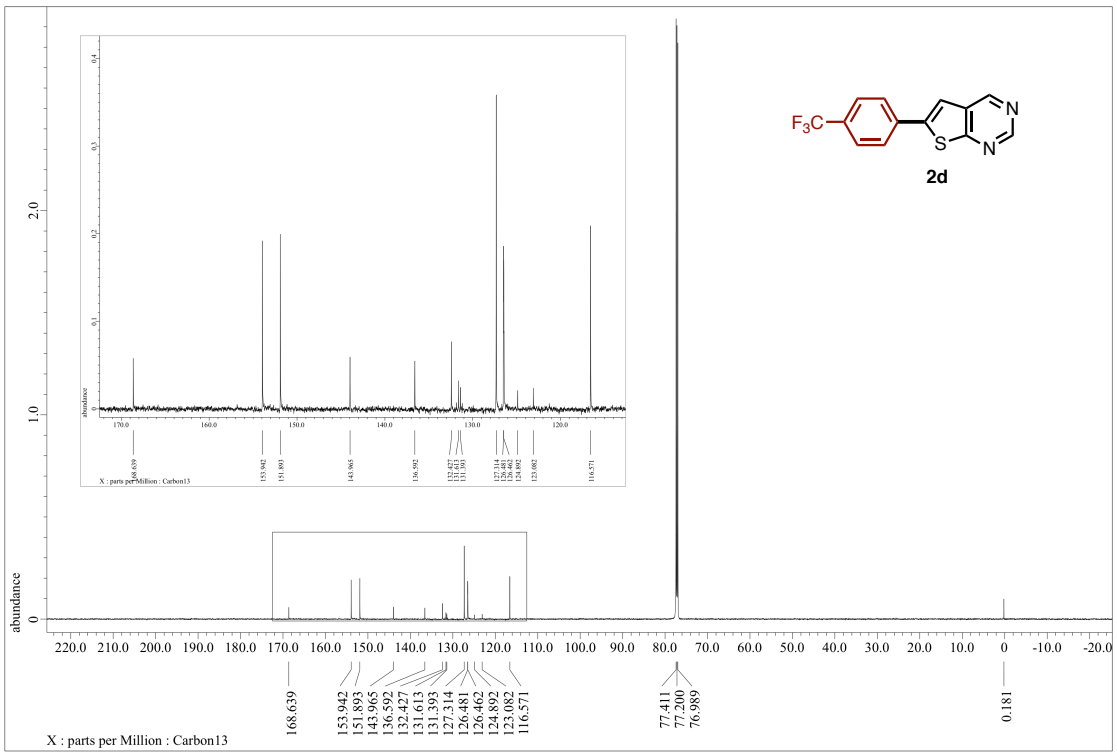

Figure S34. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2d**.

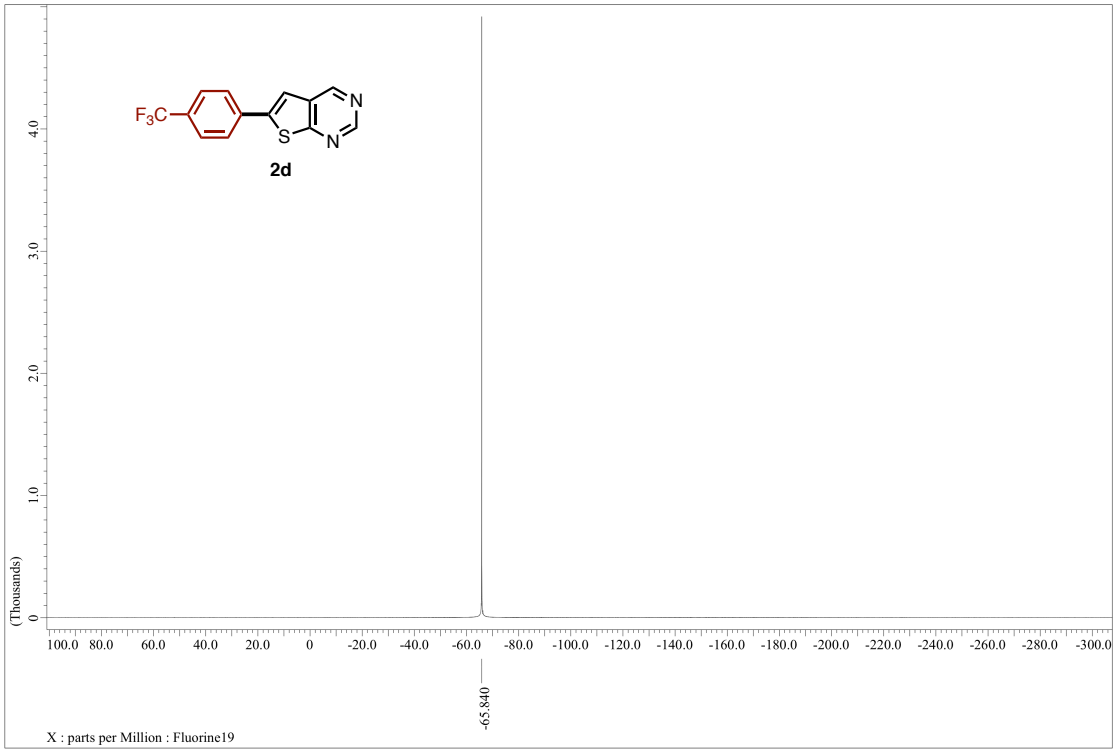

Figure S35. ^{19}F NMR spectrum (470 MHz, $CDCl_3$) of **2d**.

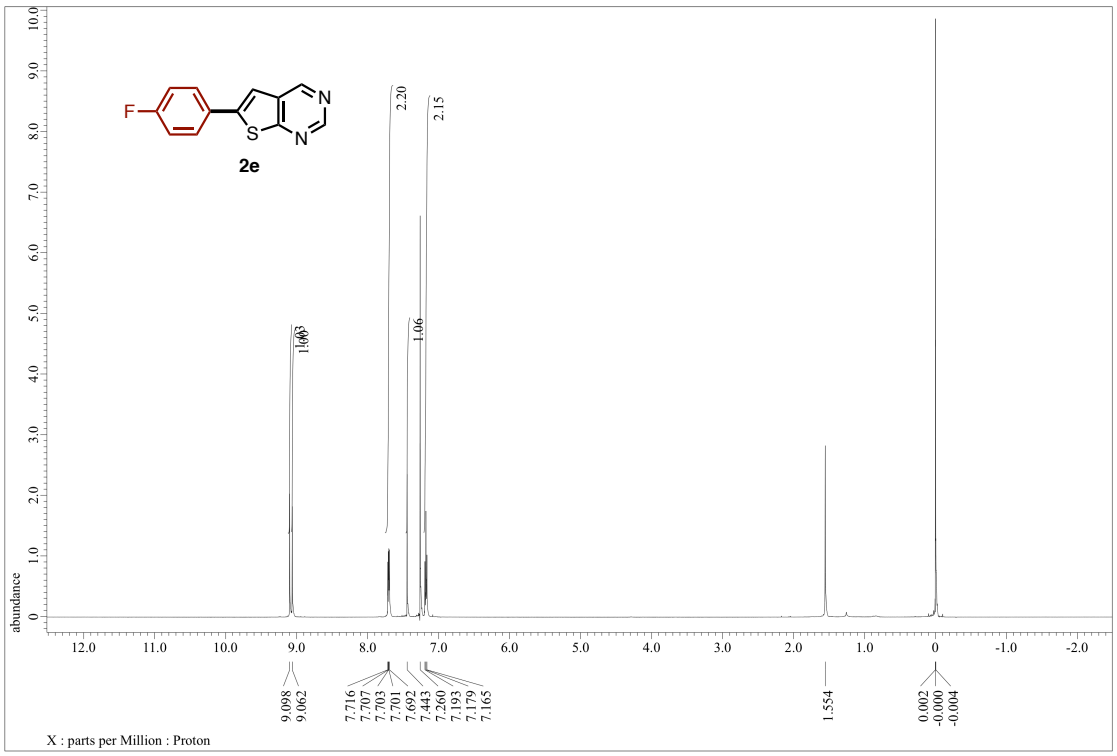

Figure S36. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2e**.

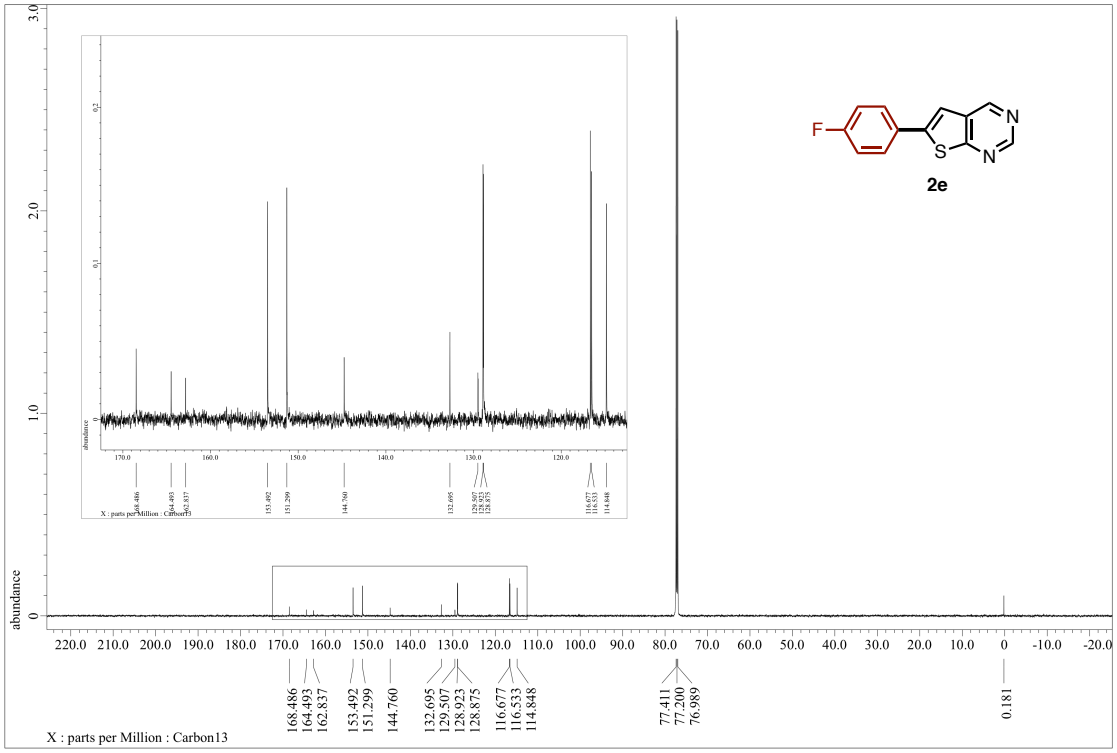

Figure S37. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2e**.

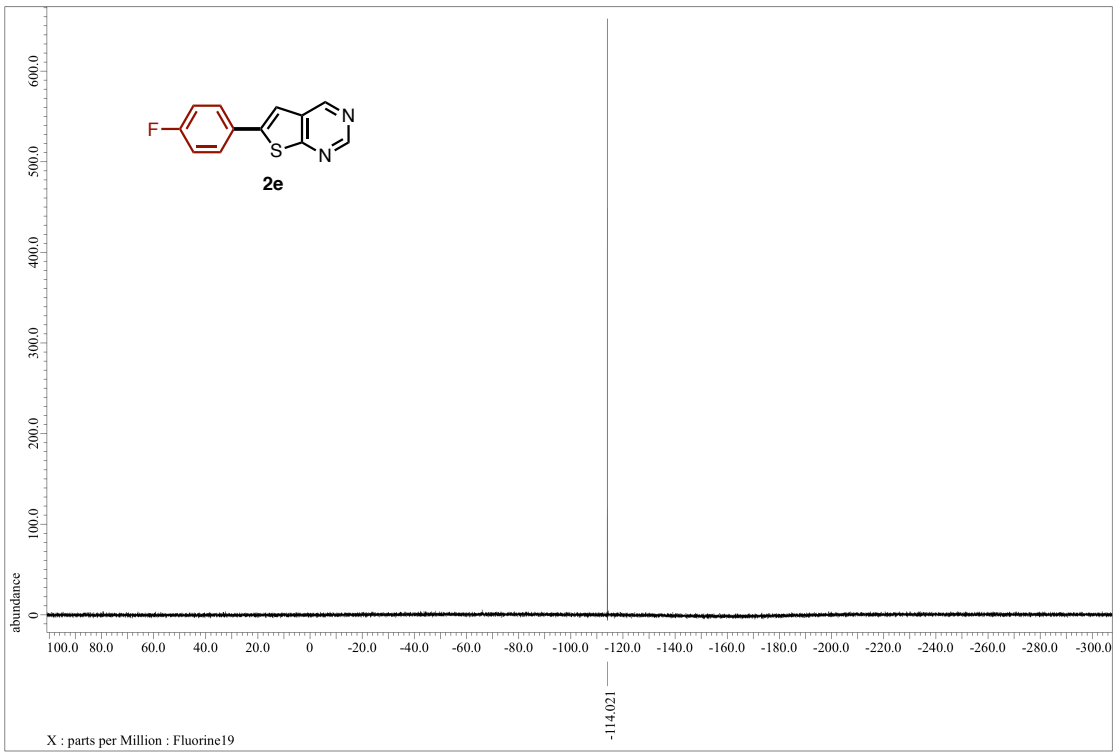

Figure S38. ^{19}F NMR spectrum (470 MHz, $CDCl_3$) of **2e**.

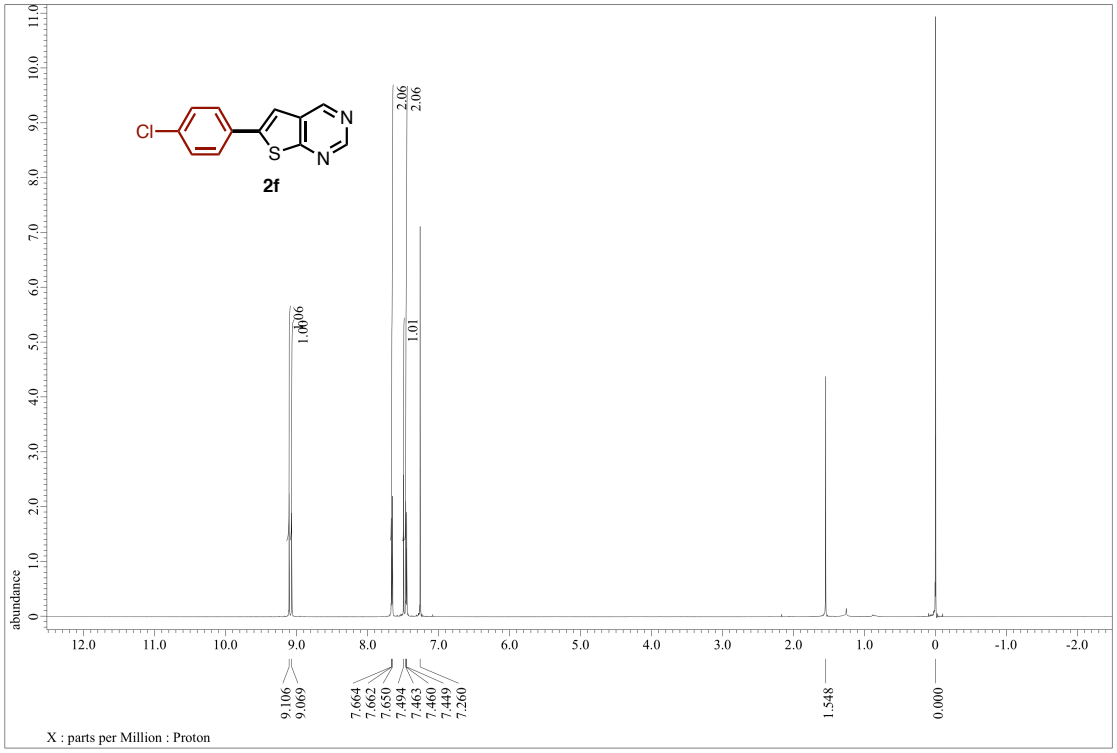

Figure S39. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2f**.

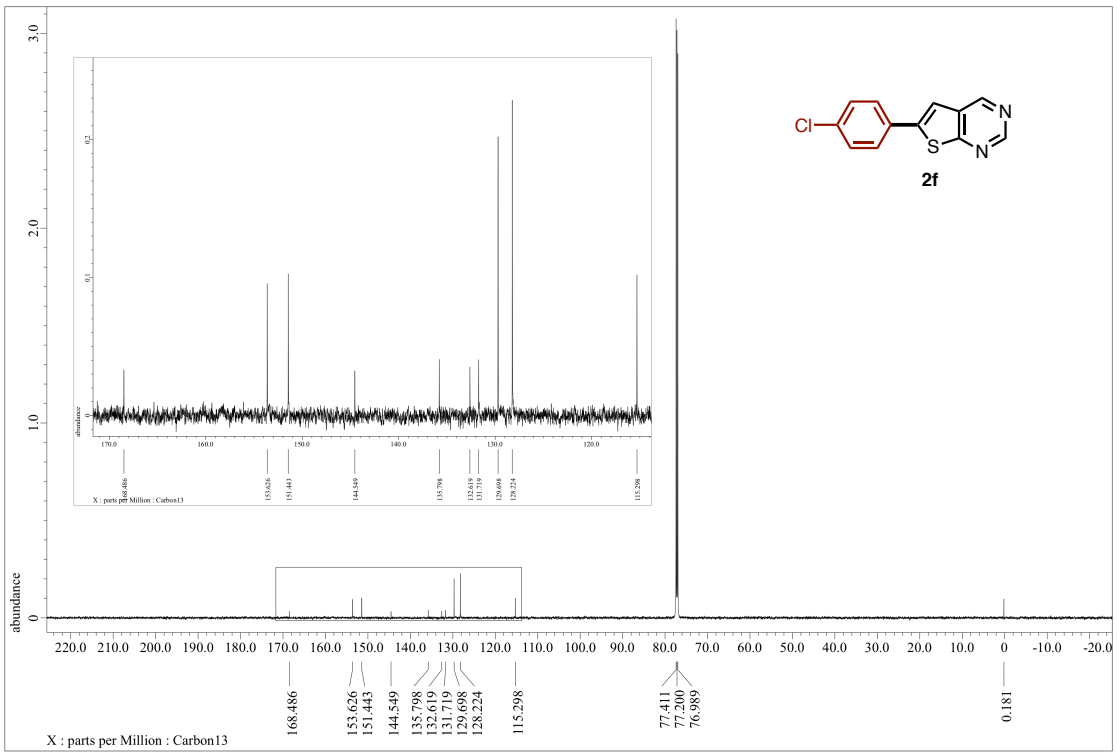

Figure S40. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2f**.

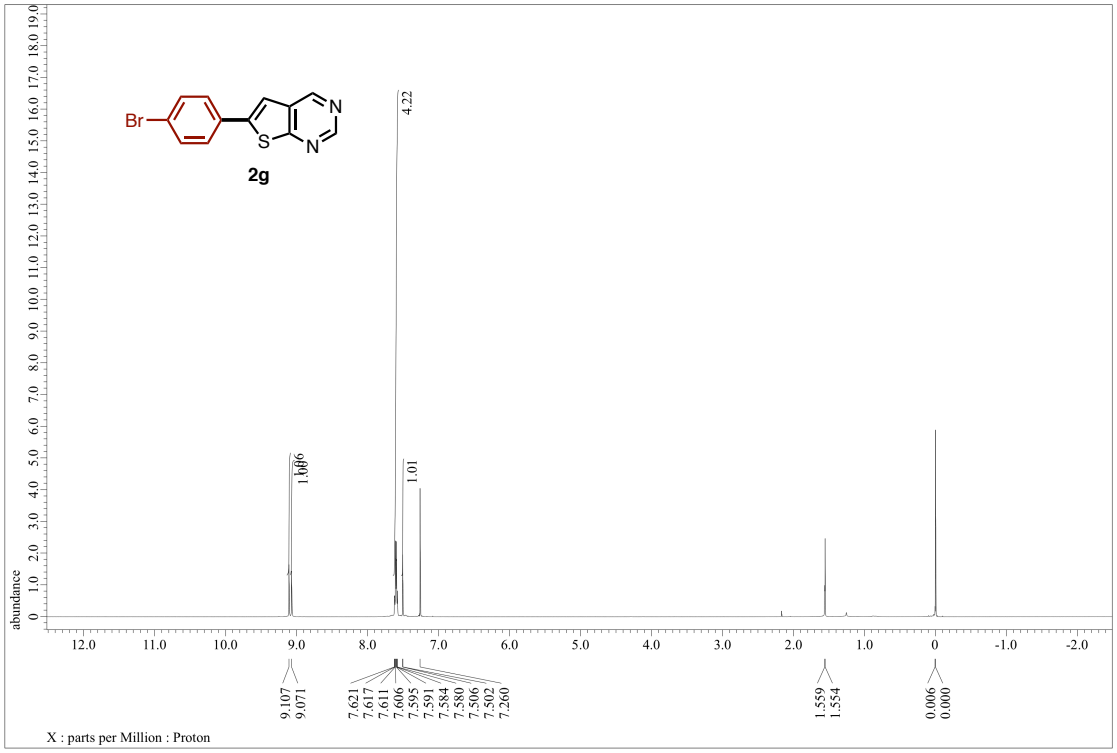

Figure S41. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2g**.

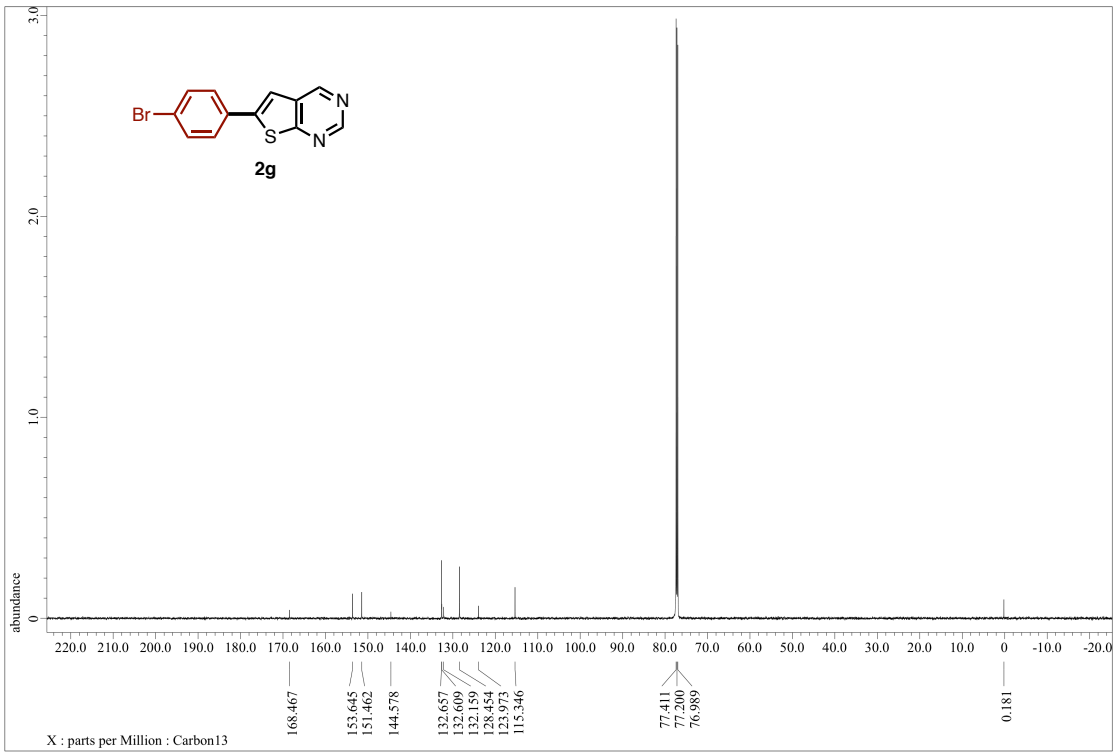

Figure S42. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2g**.

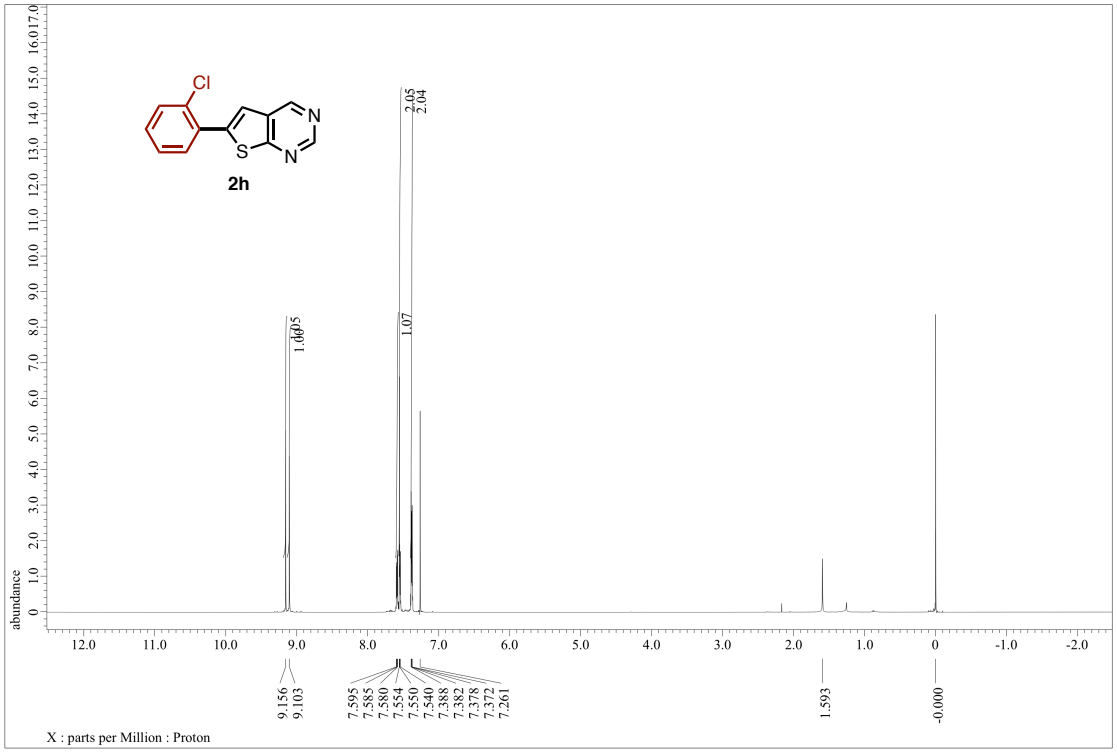

Figure S43. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2h**.

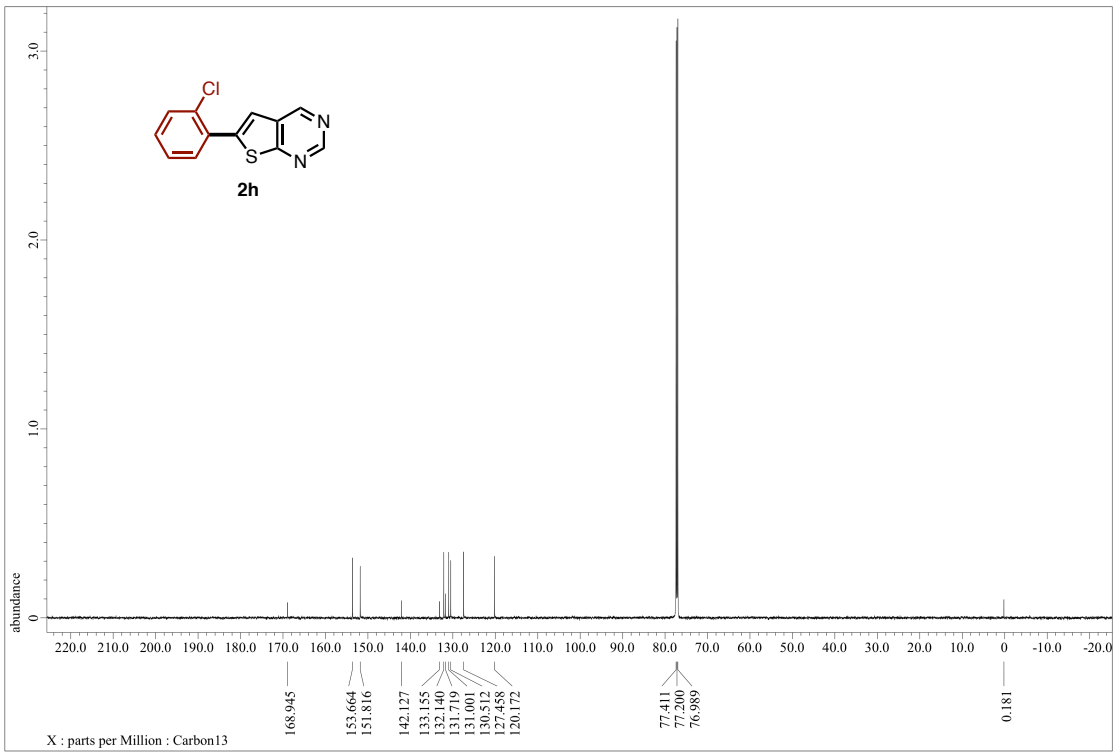

Figure S44. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2h**.

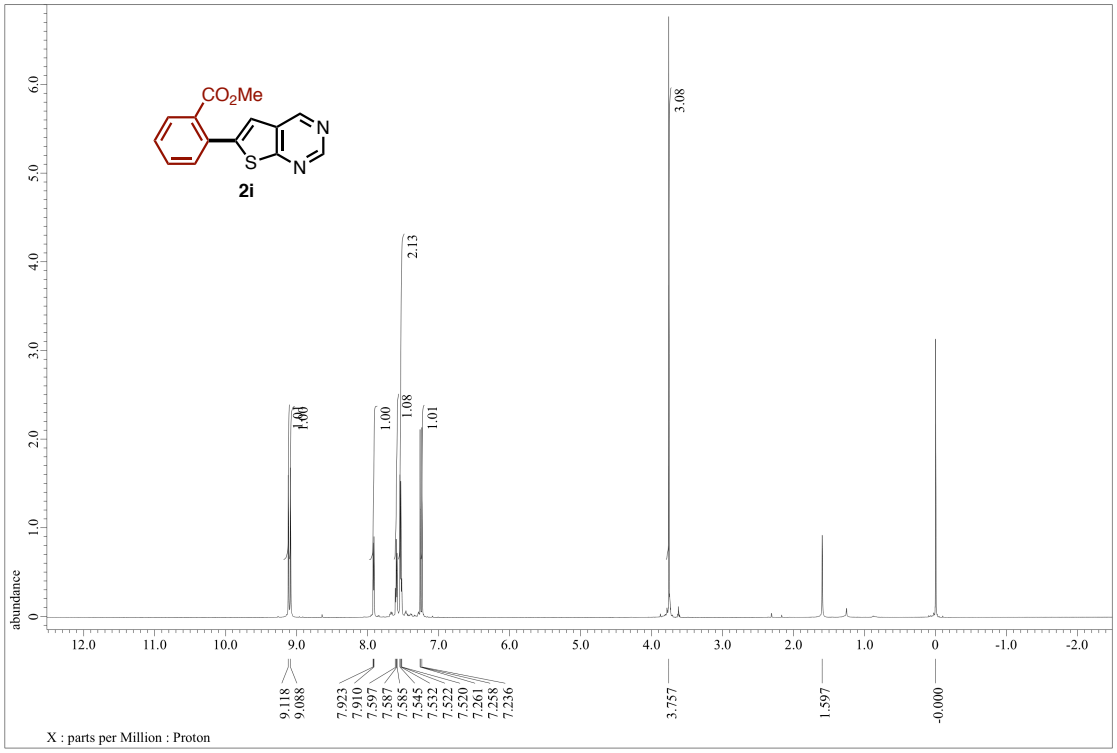

Figure S45. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2i**.

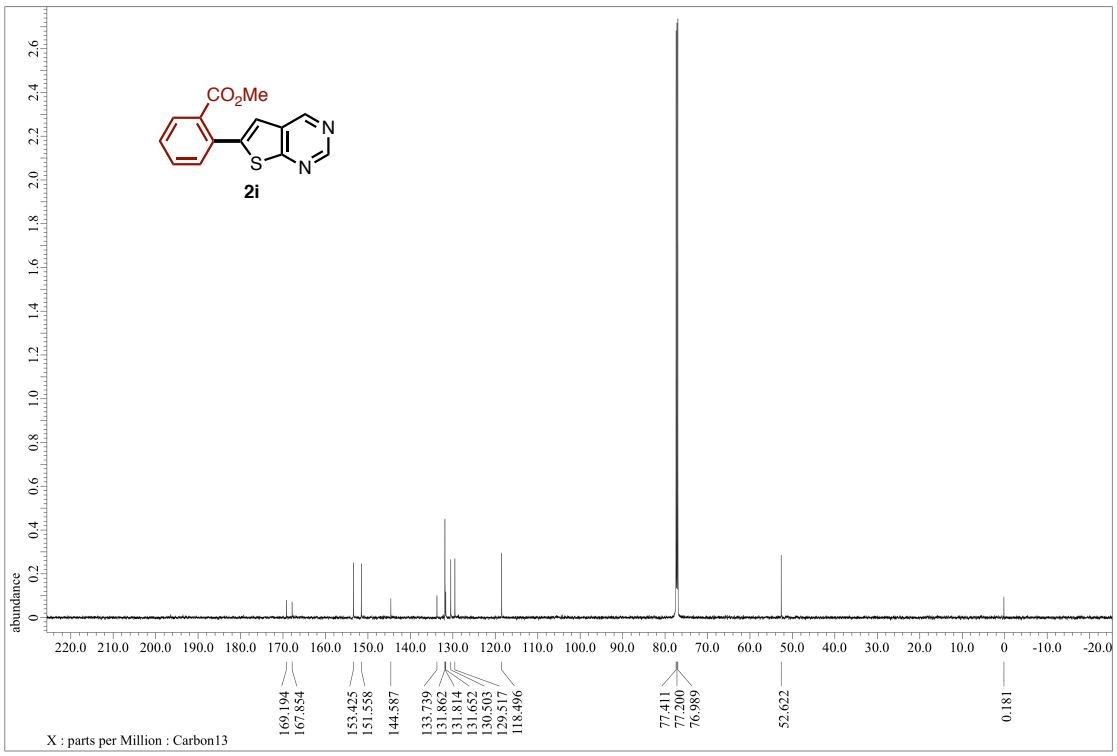

Figure S46. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2i**.

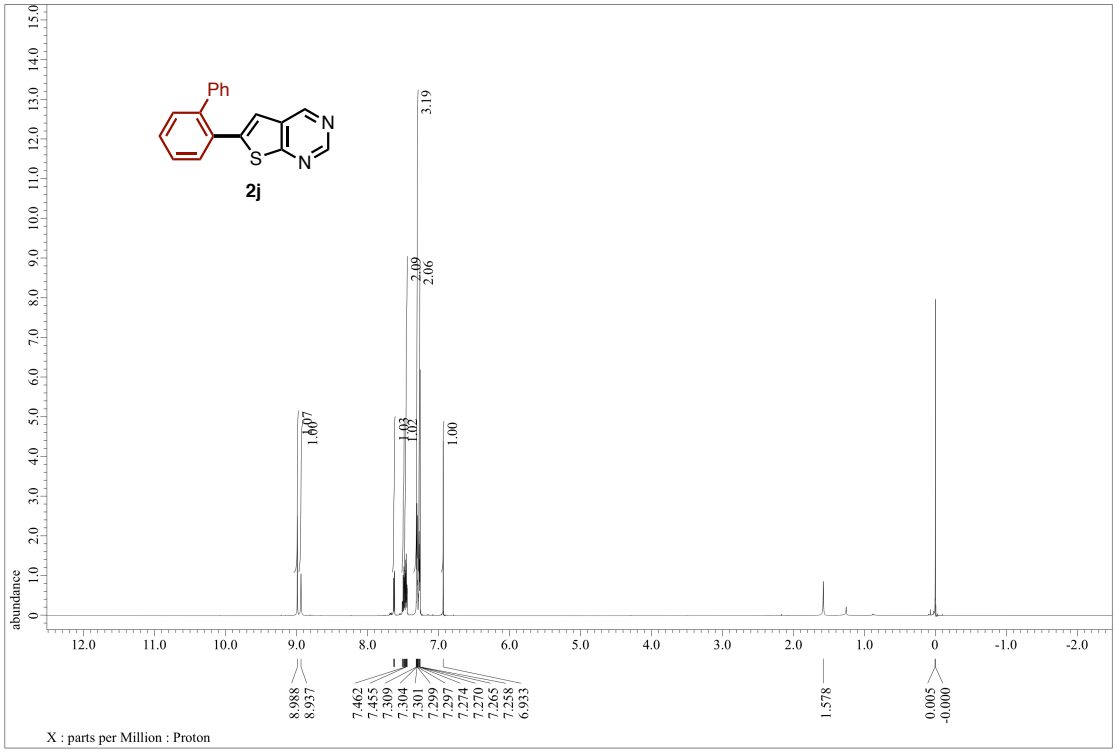

Figure S47. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2j**.

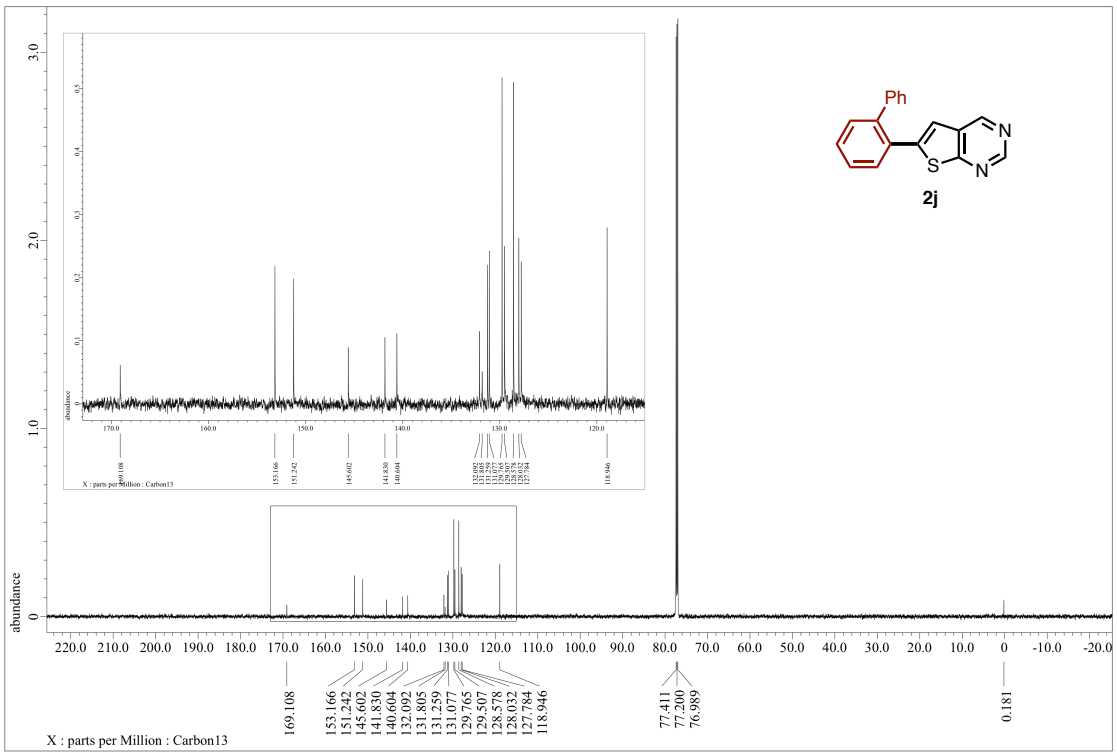

Figure S48. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2j**.

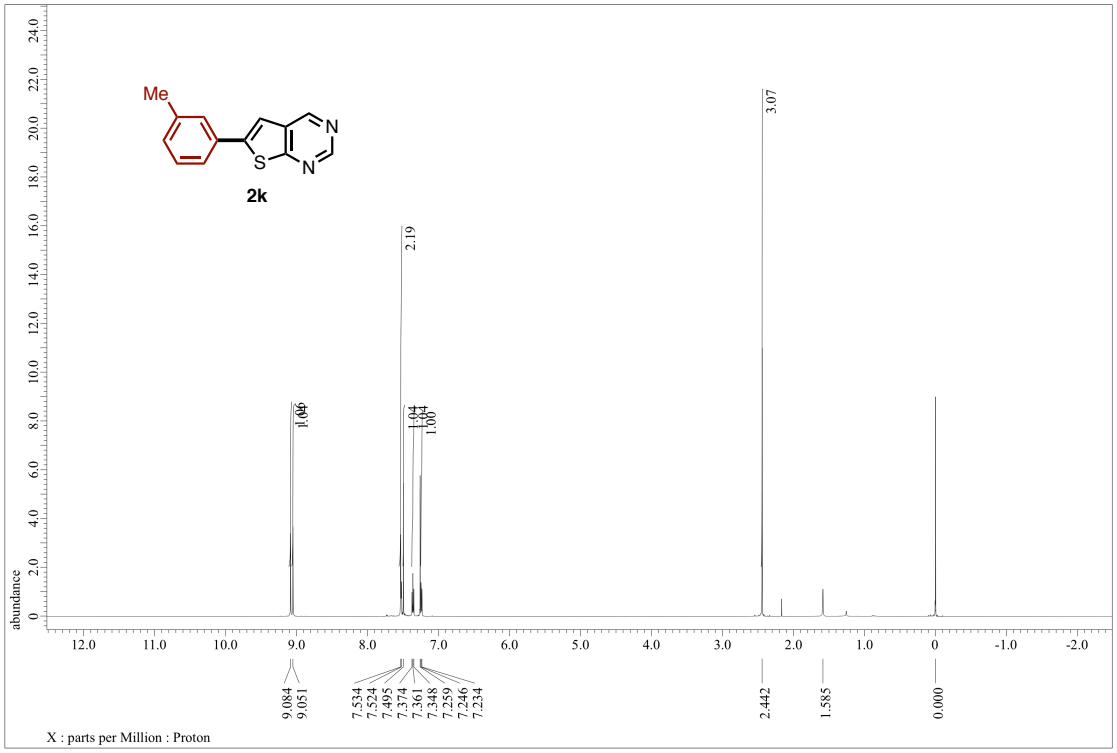

Figure S49. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2k**.

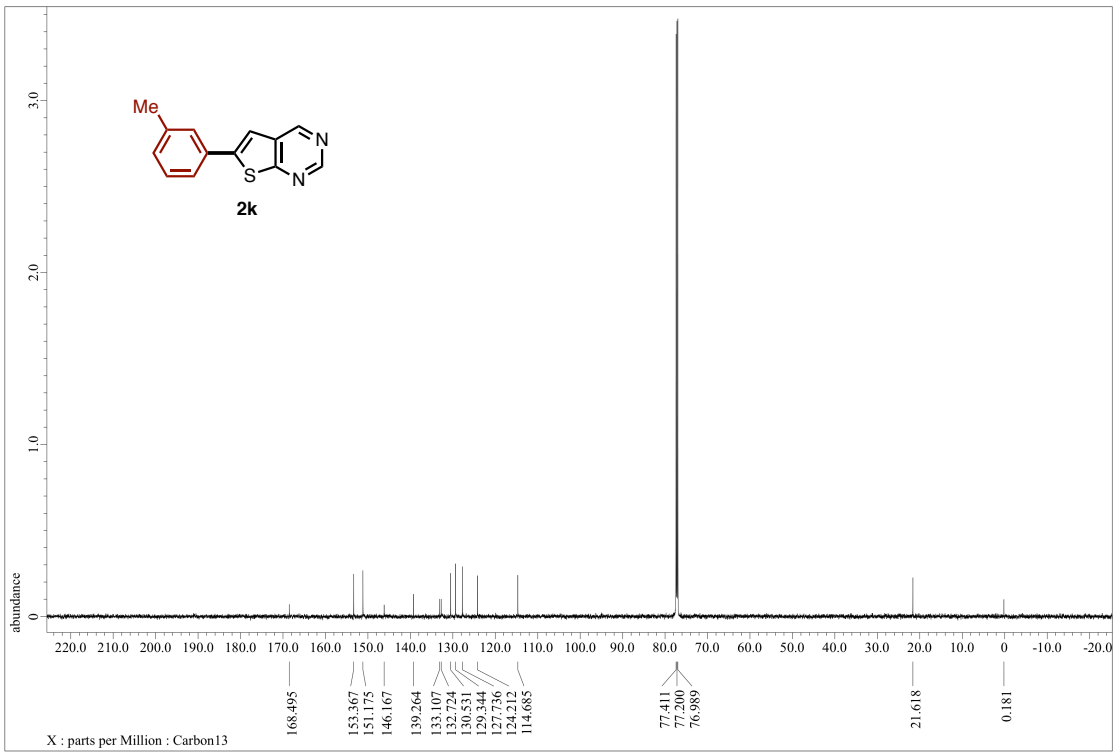

Figure S50. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2k**.

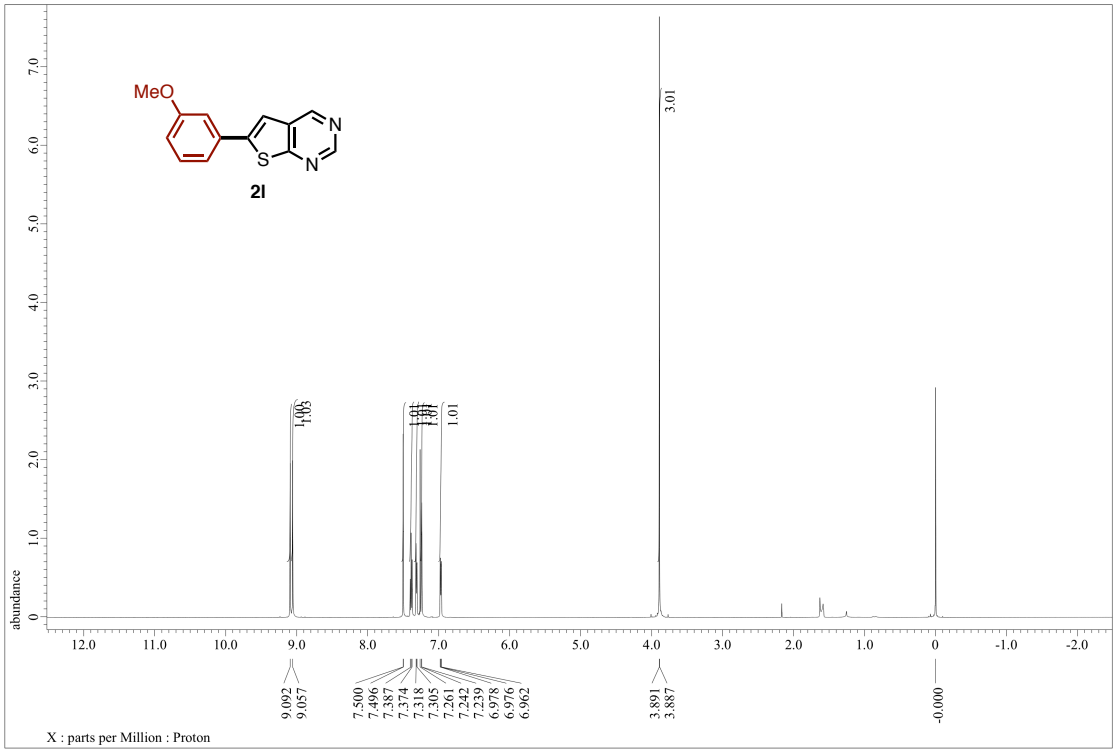

Figure S51. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2l**.

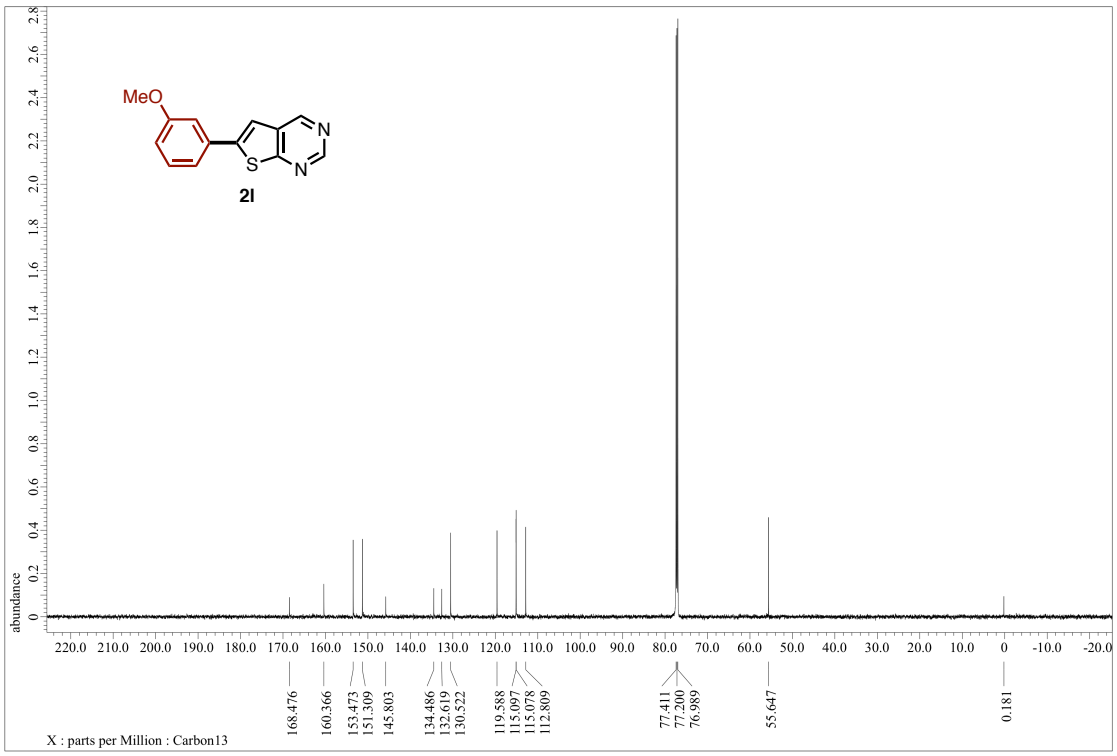

Figure S52. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2l**.

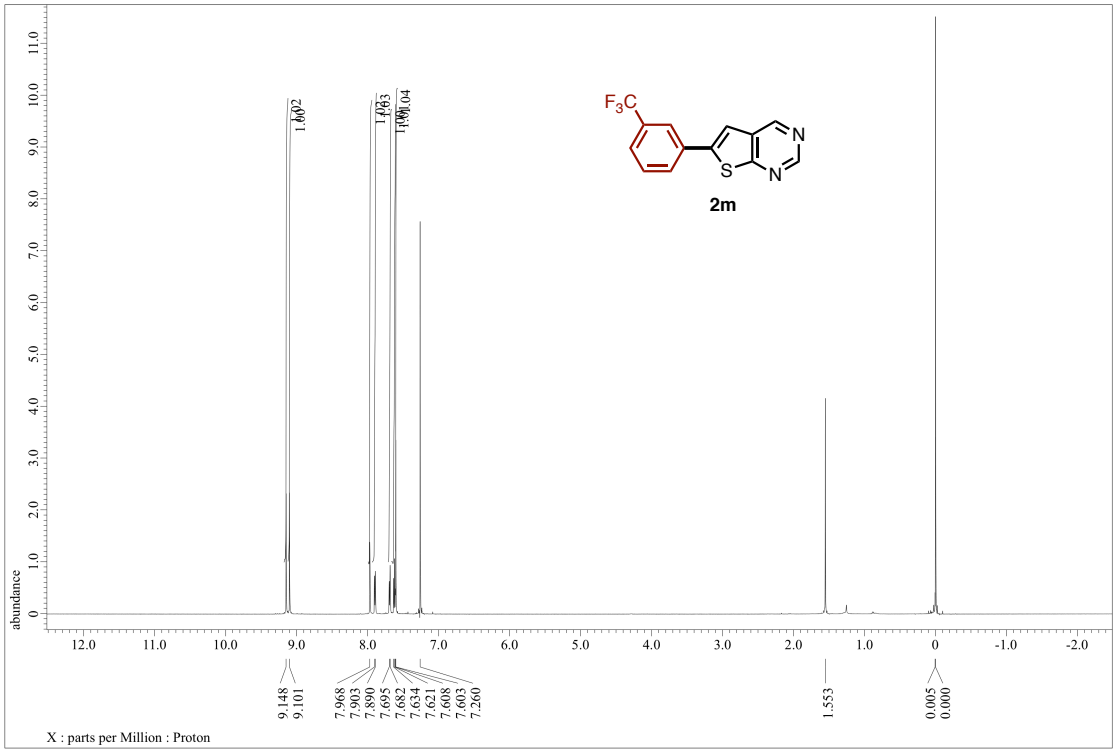

Figure S53. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2m**.

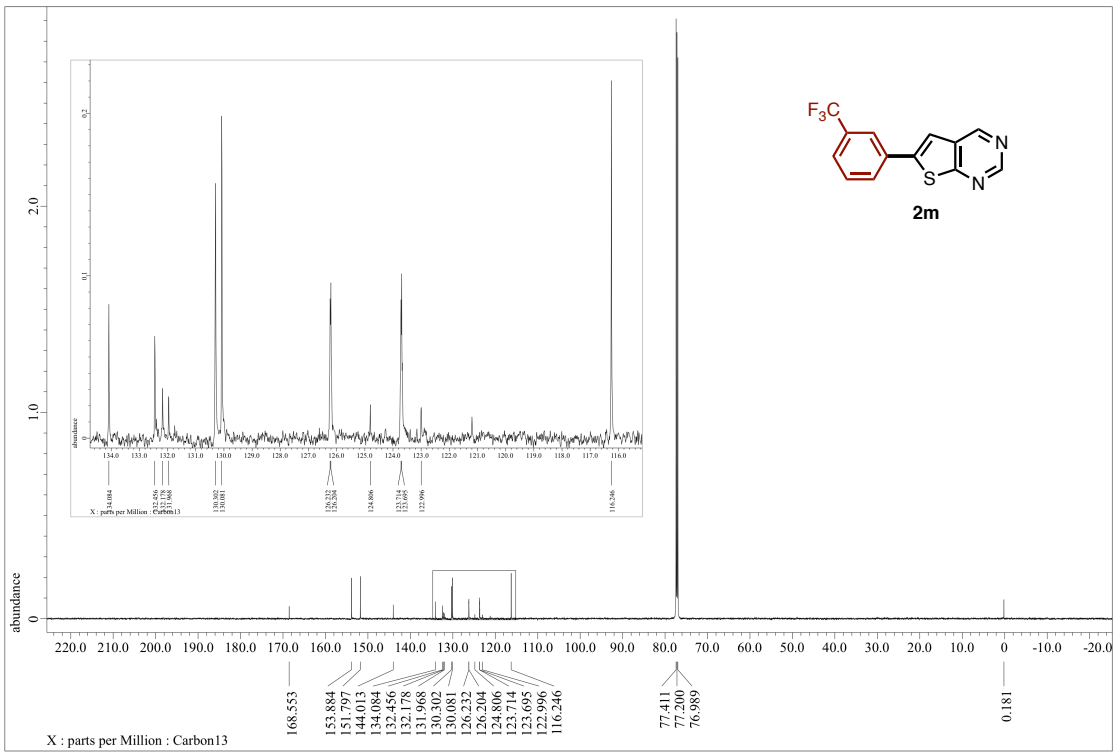

Figure S54. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2m**.

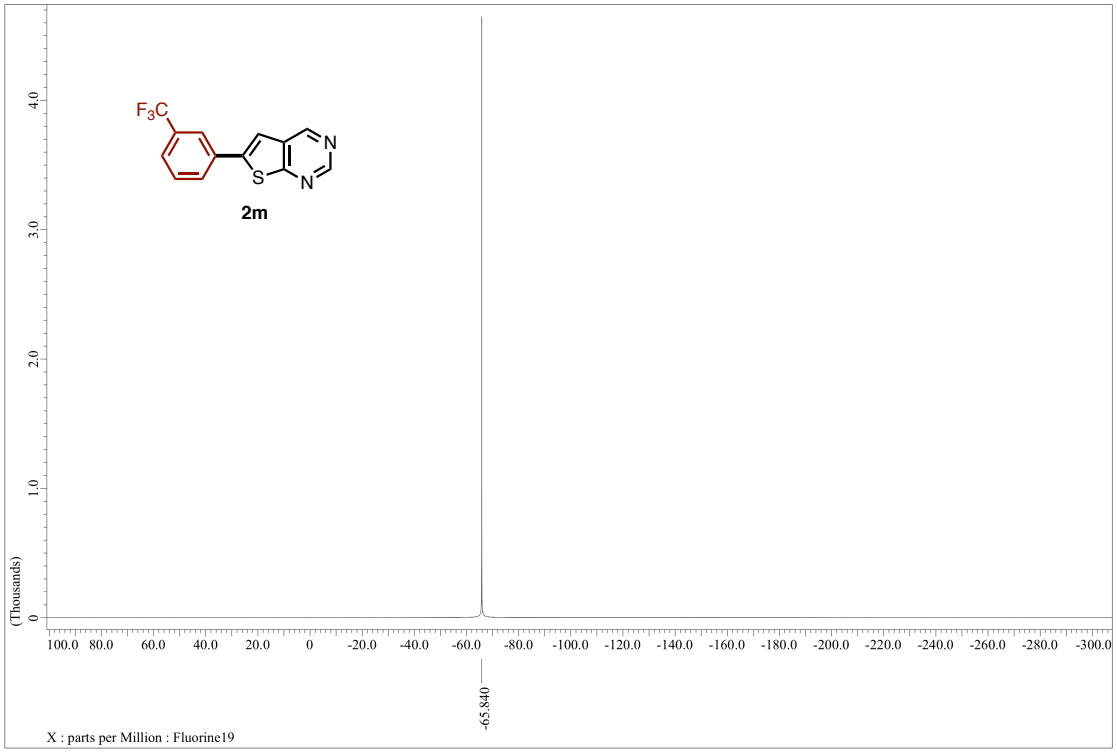

Figure S55. ^{19}F NMR spectrum (470 MHz, $CDCl_3$) of **2m**.

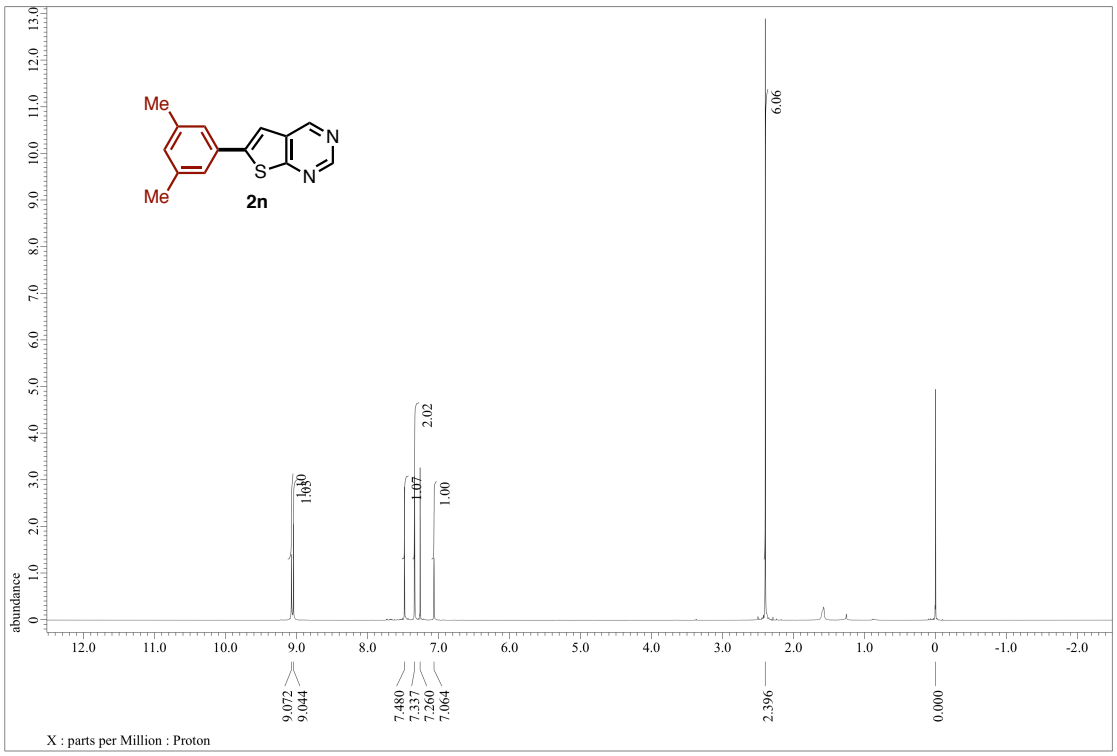

Figure S56. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2n**.

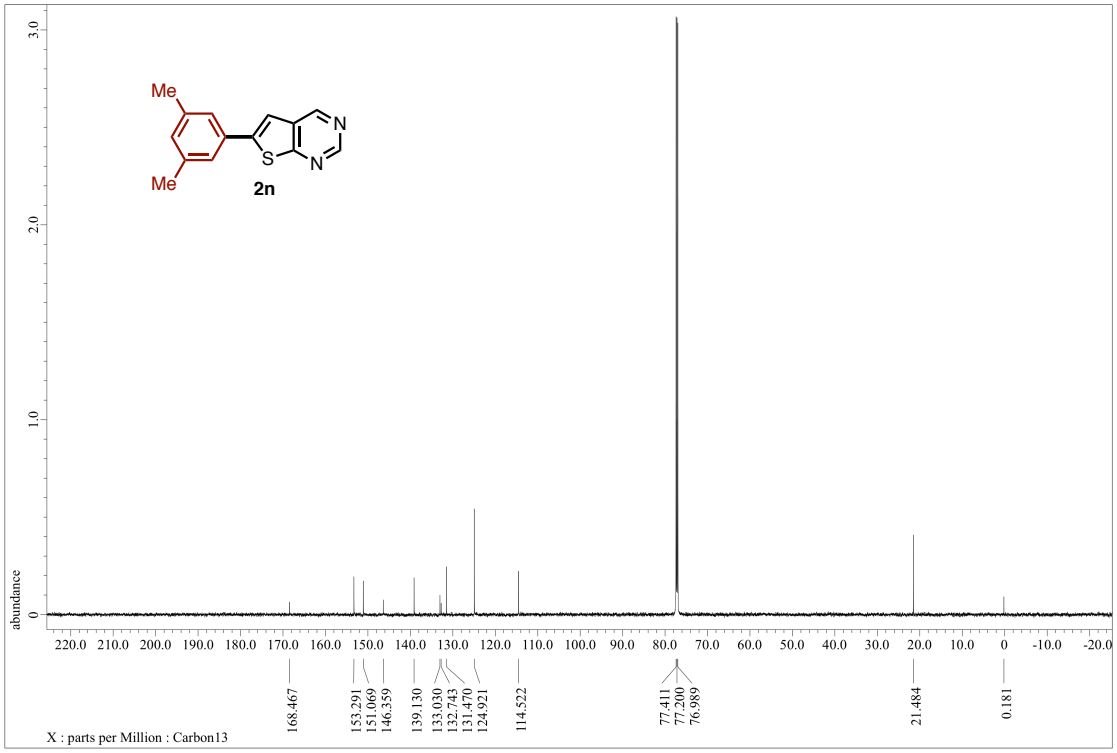

Figure S57. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2n**.

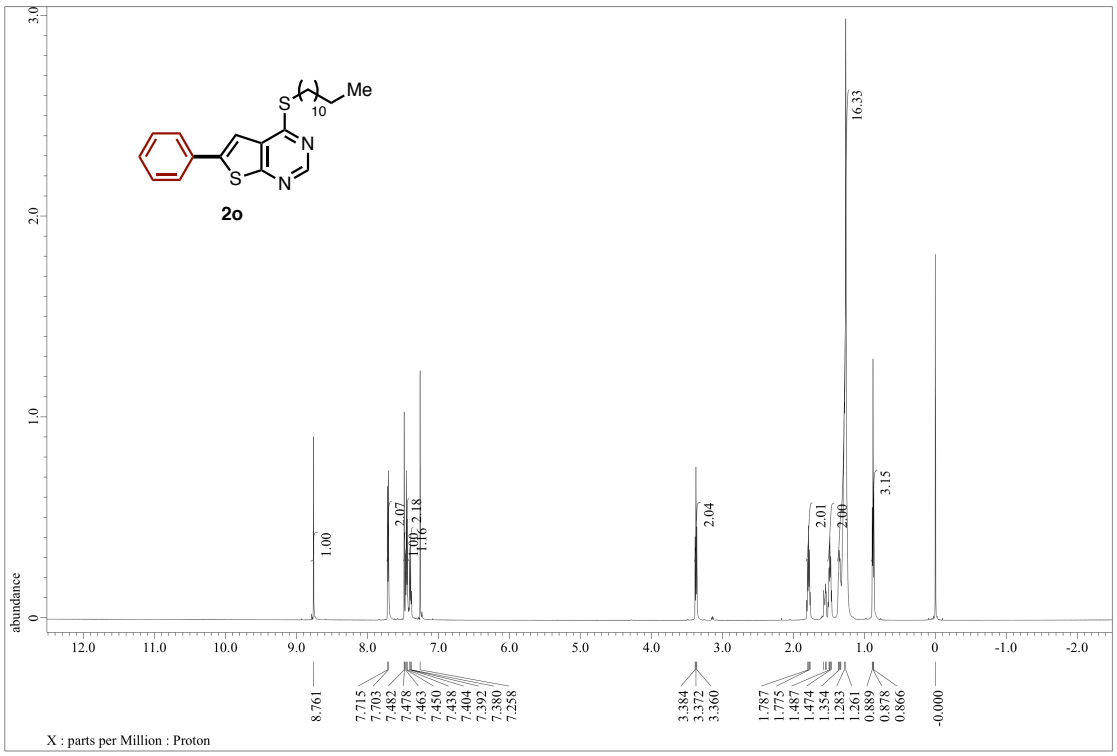

Figure S58. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2o**.

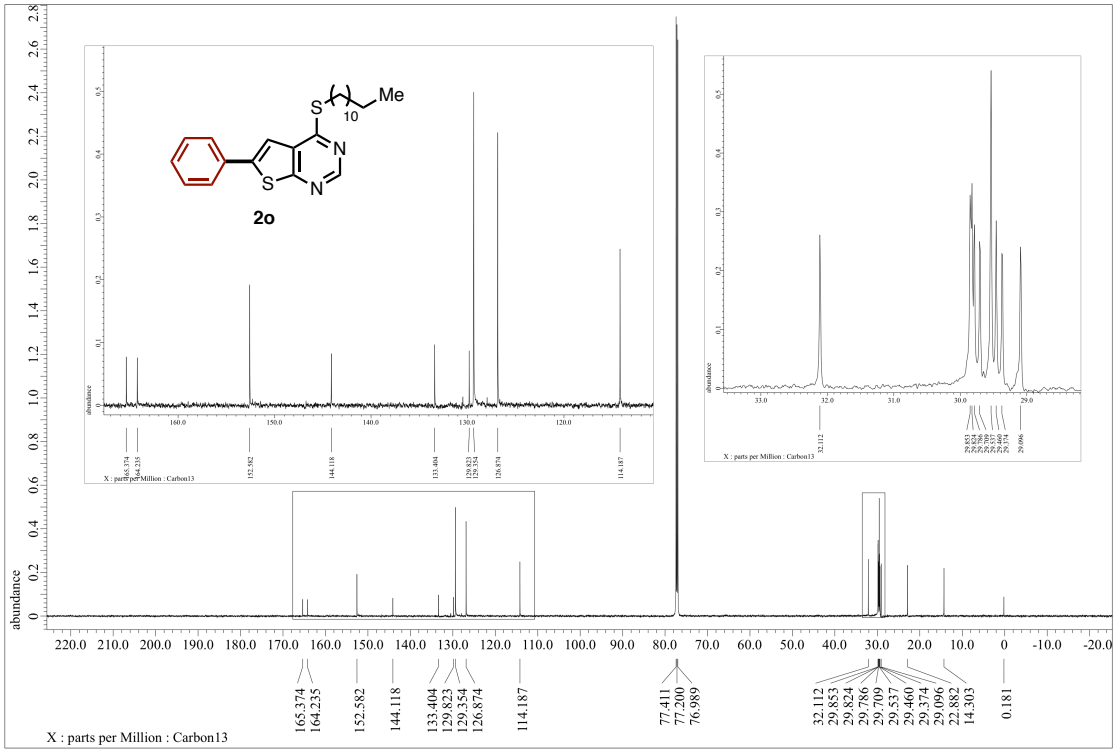

Figure S59. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2o**.

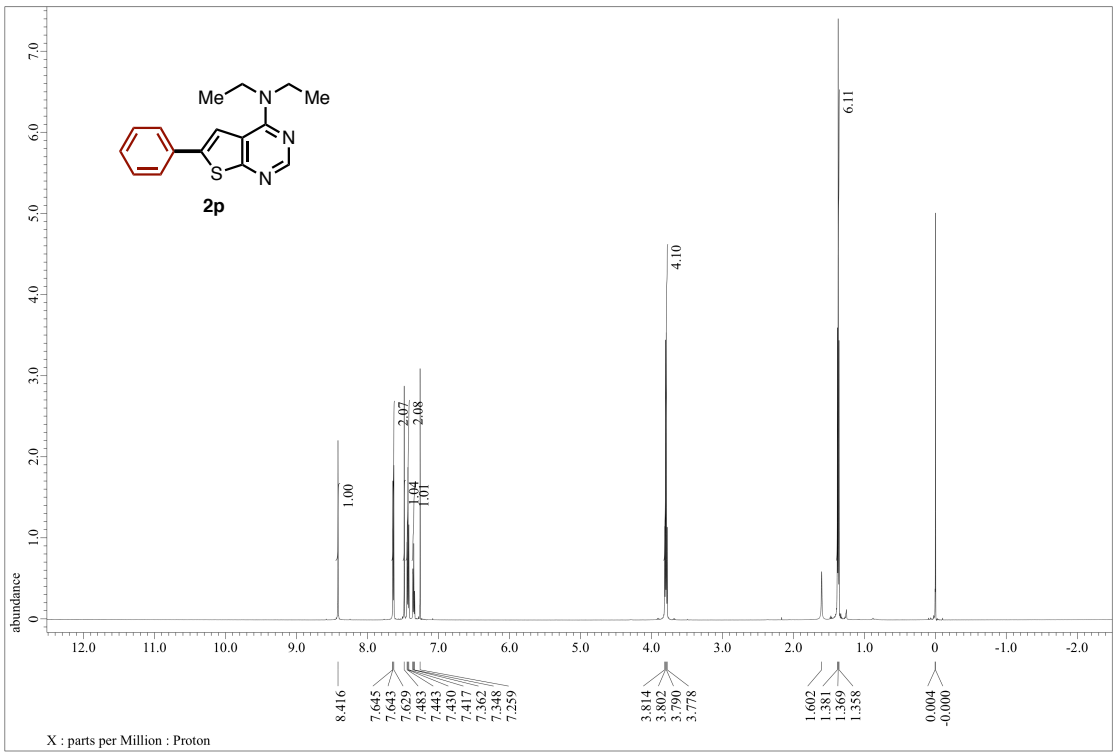

Figure S60. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2p**.

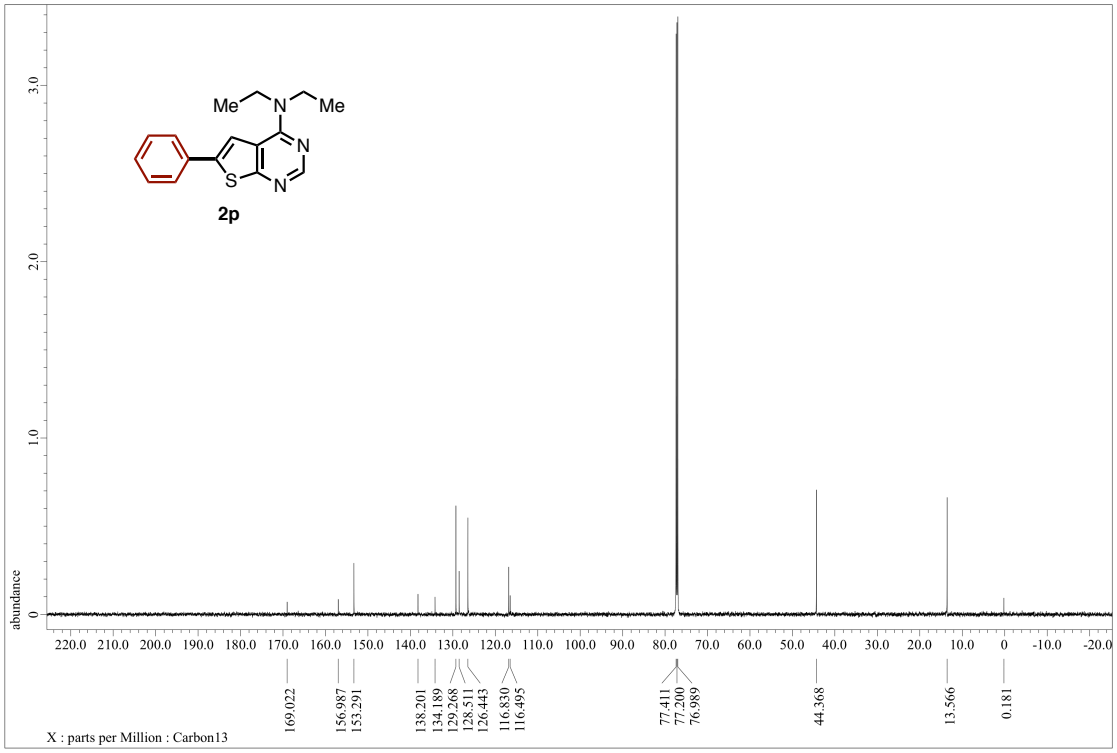

Figure S61. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2p**.

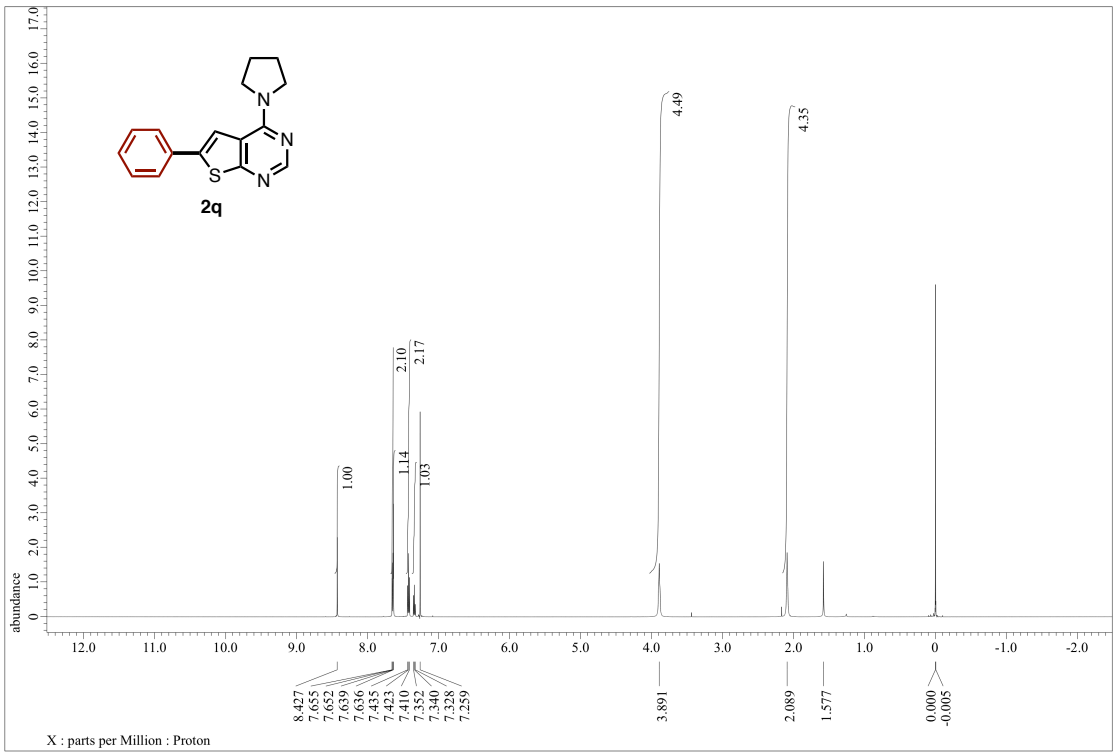

Figure S62. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2q**.

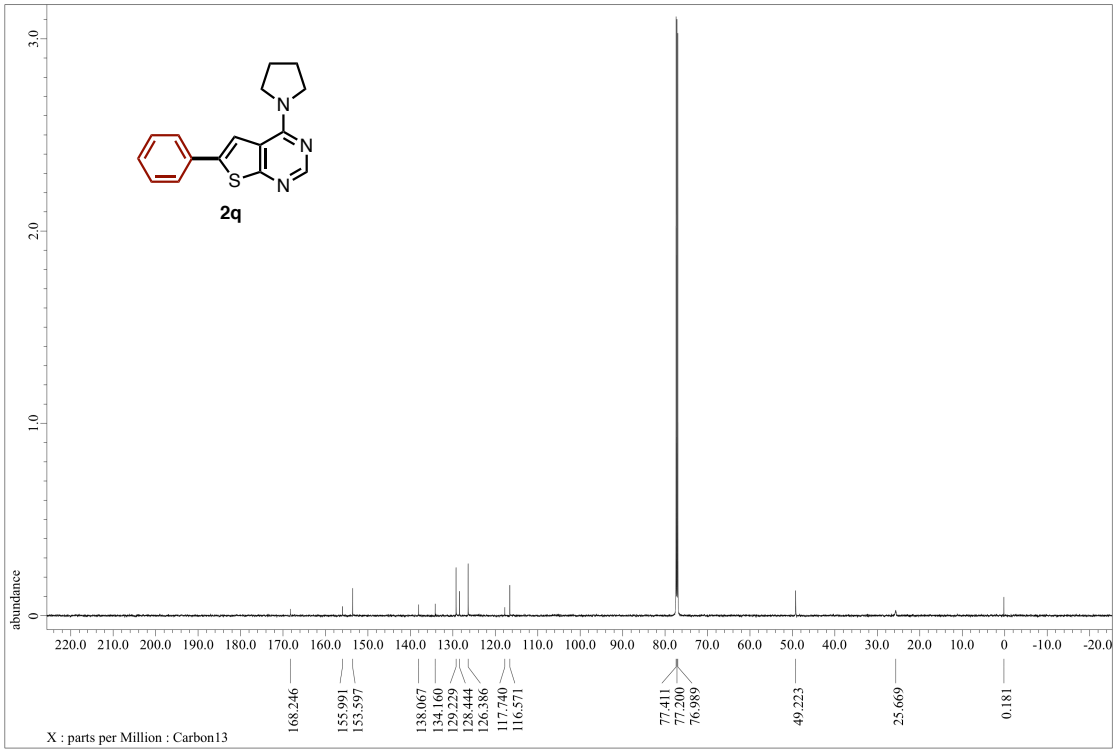

Figure S63. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2q**.

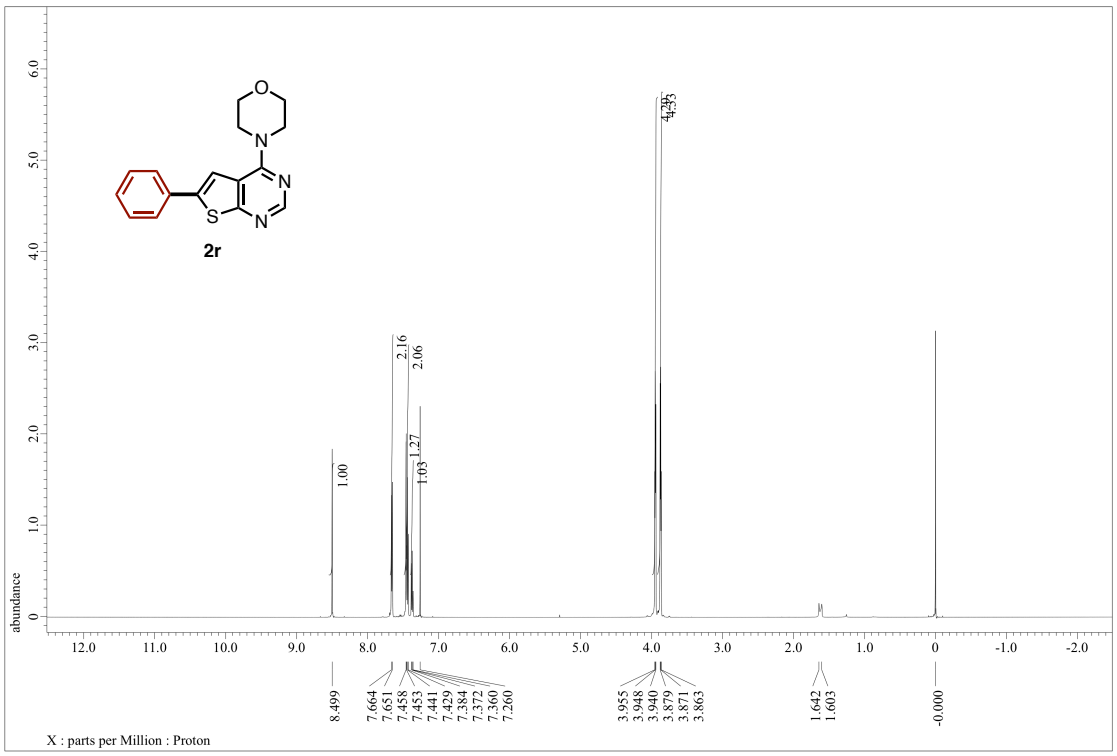

Figure S64. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2r**.

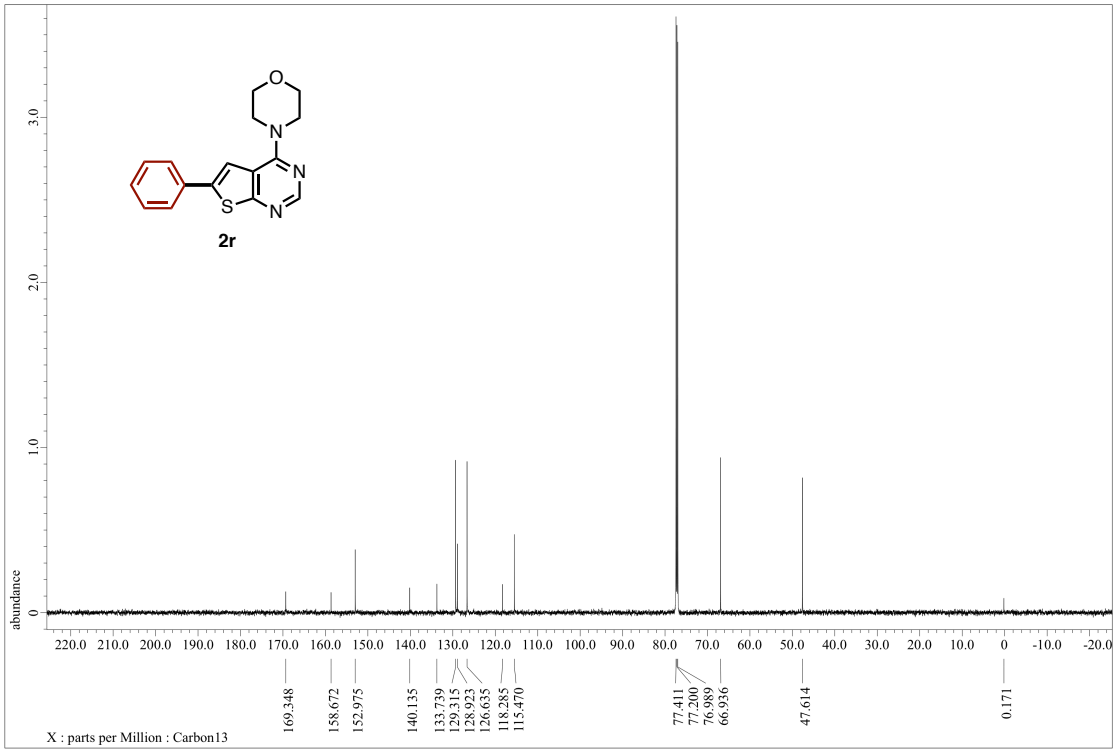

Figure S65. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2r**.

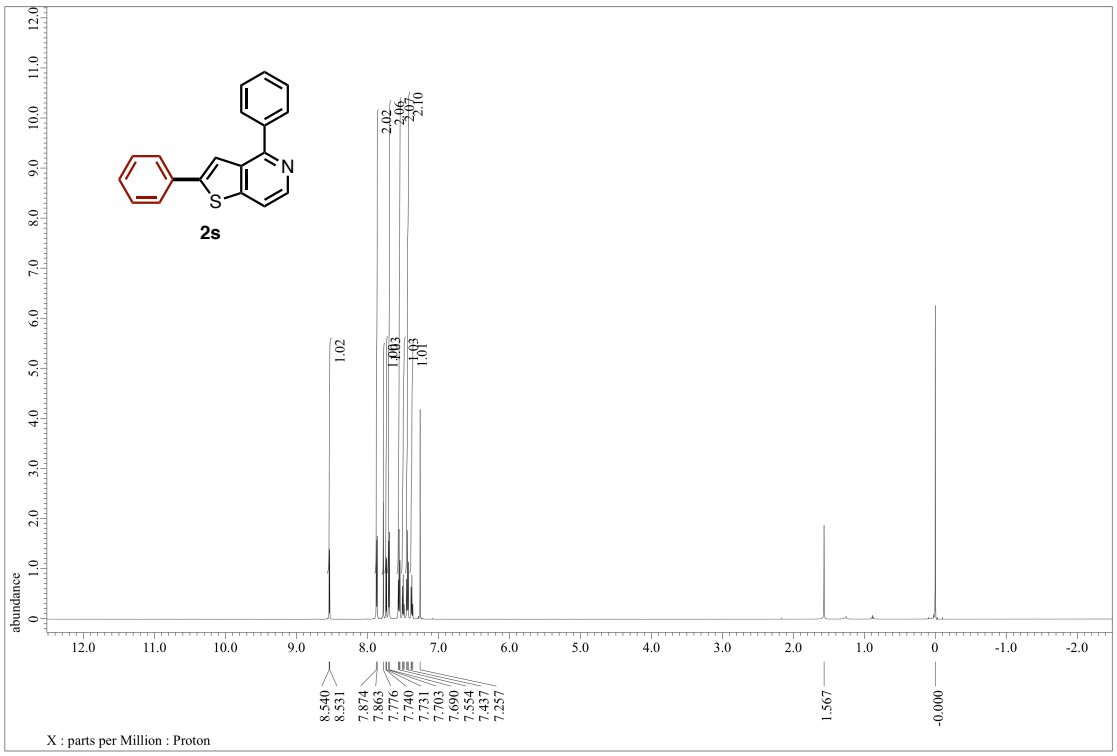

Figure S66. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2s**.

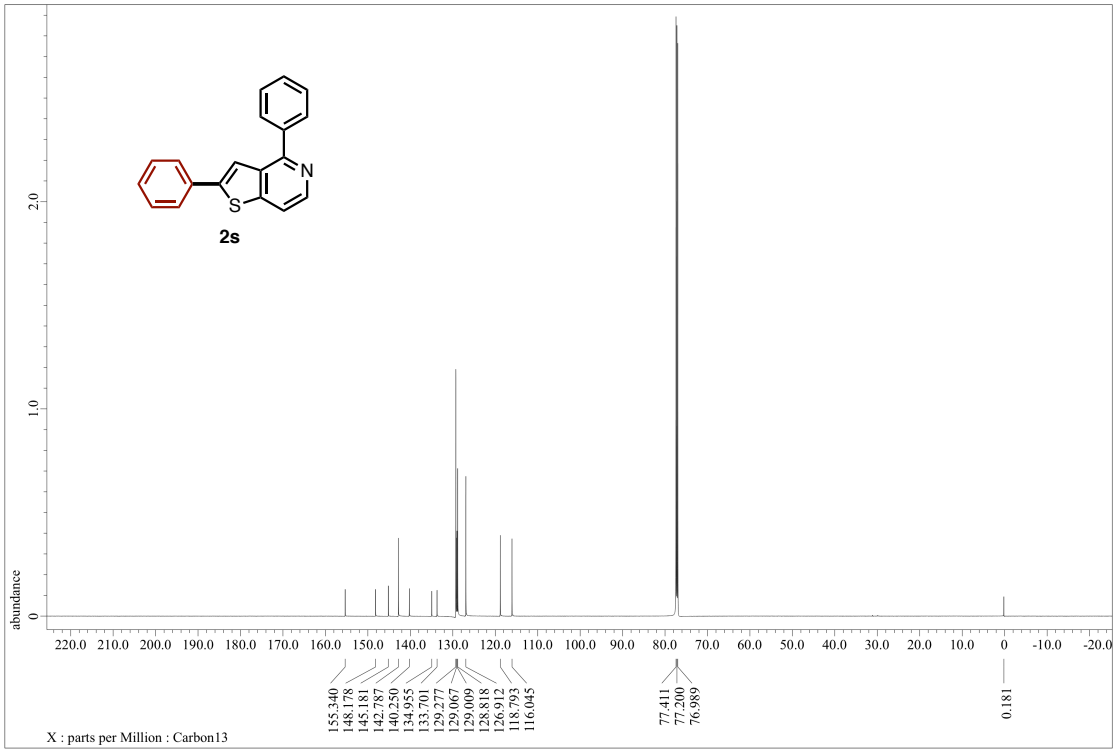

Figure S67. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2s**.

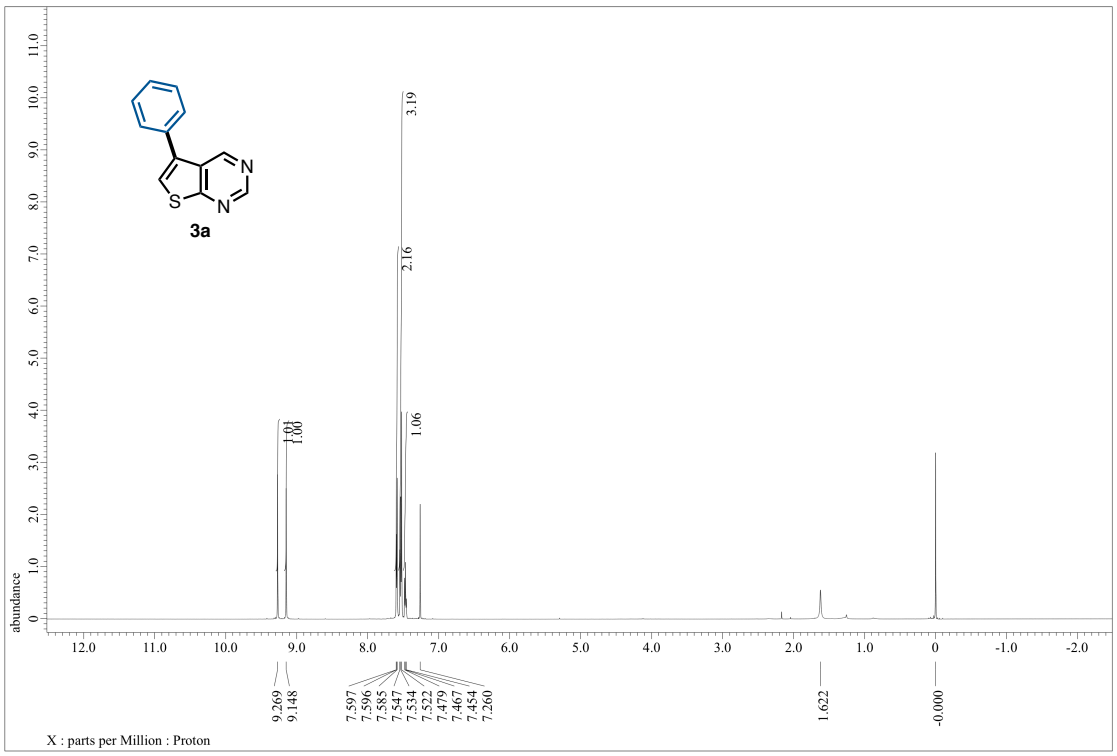

Figure S68. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3a**.

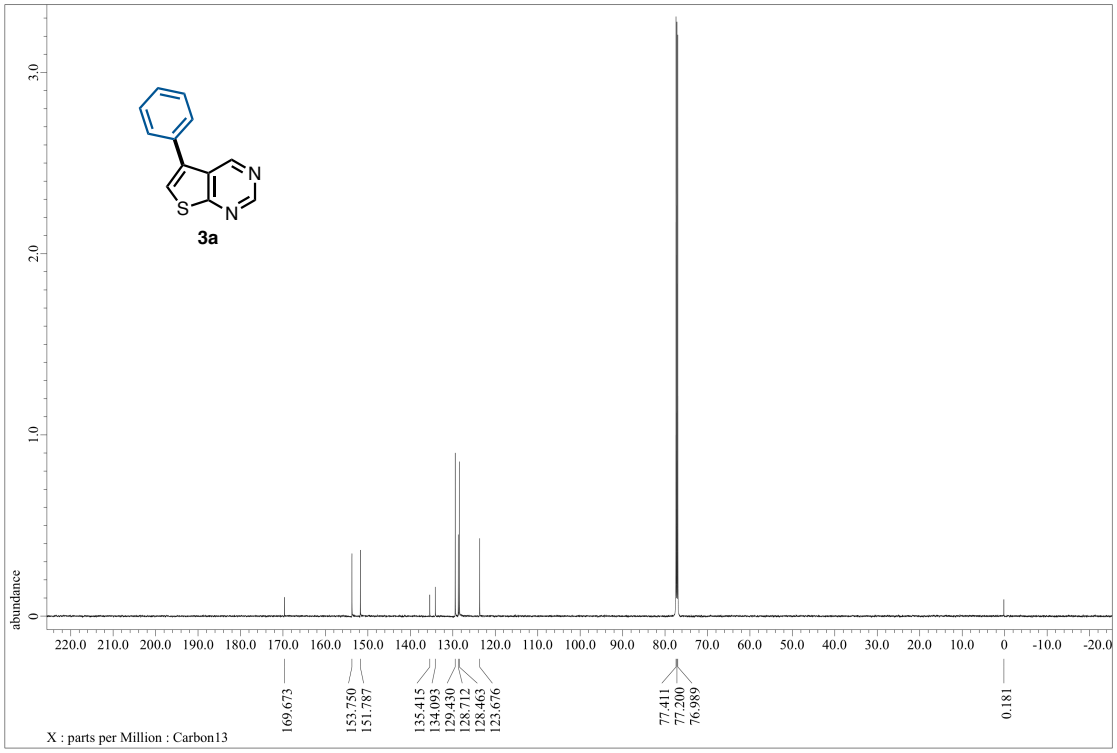

Figure S69. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3a**.

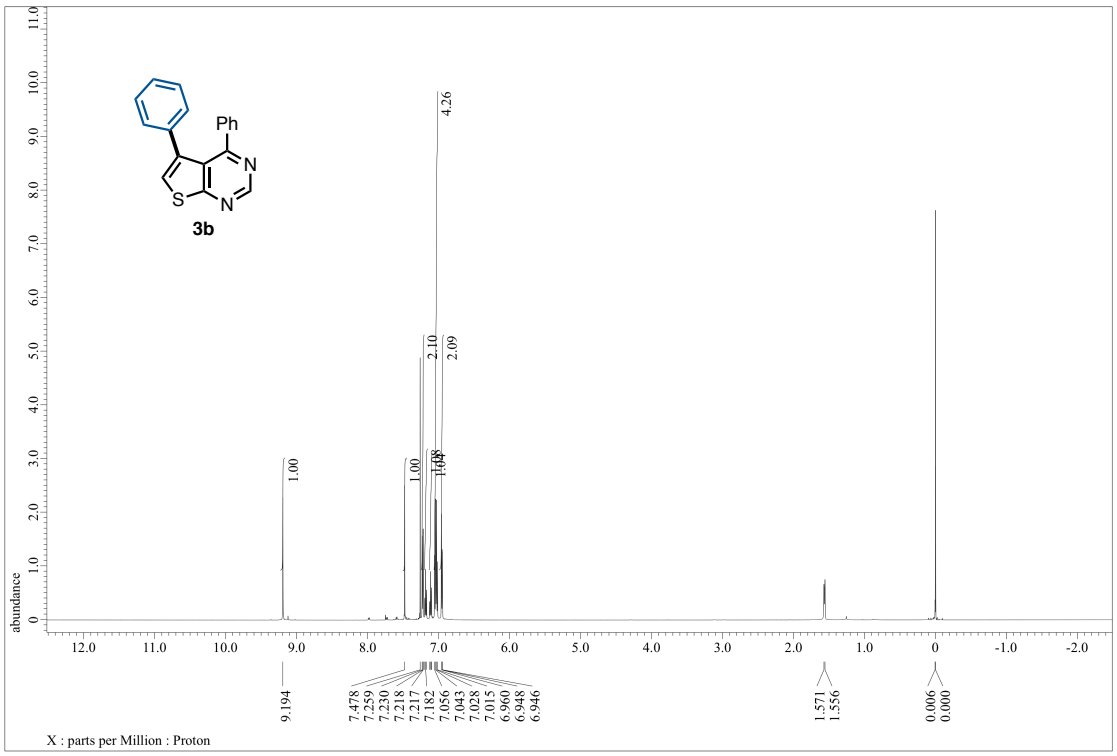

Figure S70. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3b**.

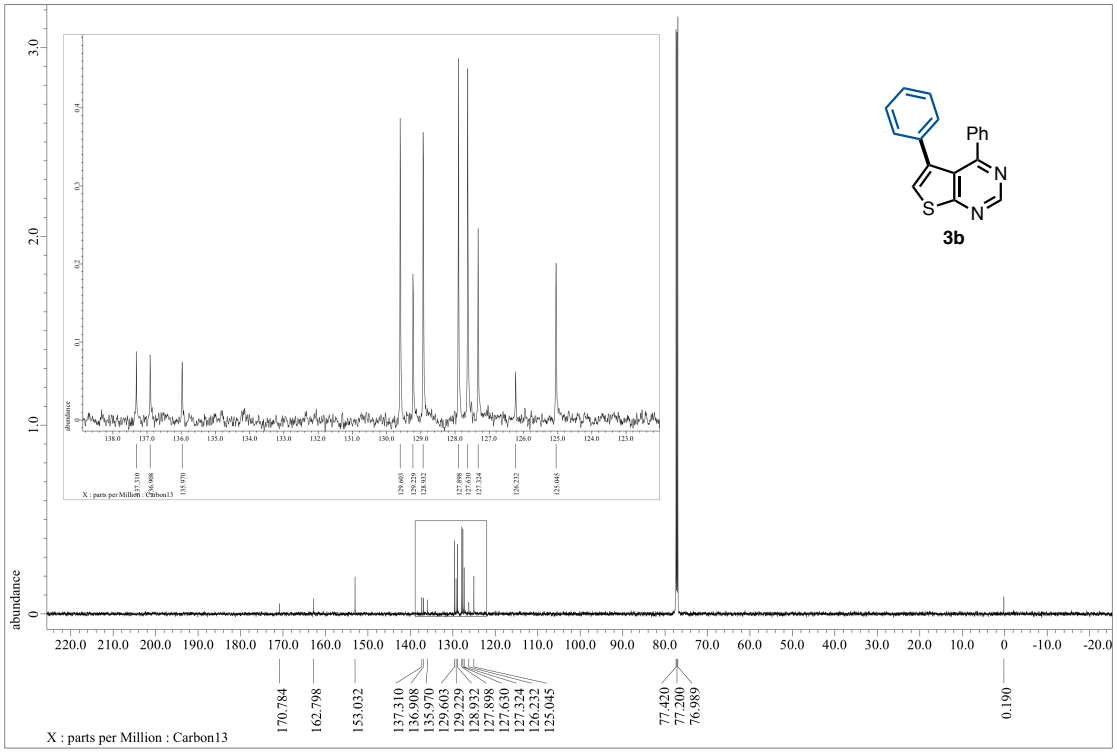

Figure S71. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3b**.

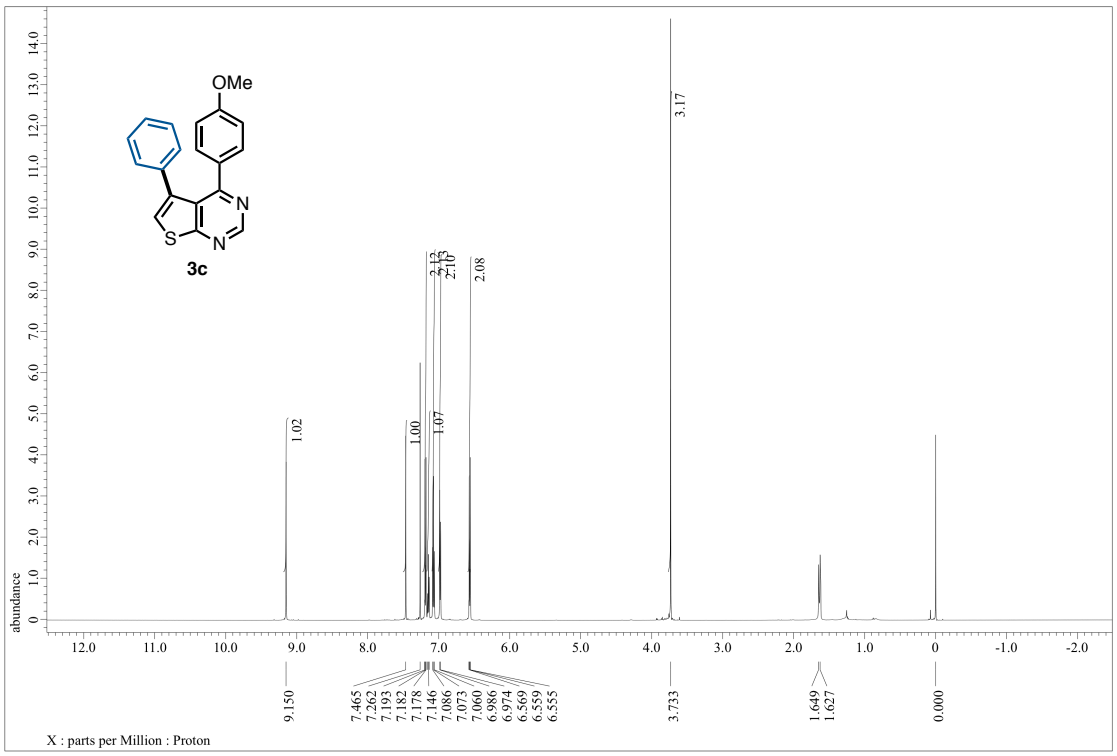

Figure S72. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3c**.

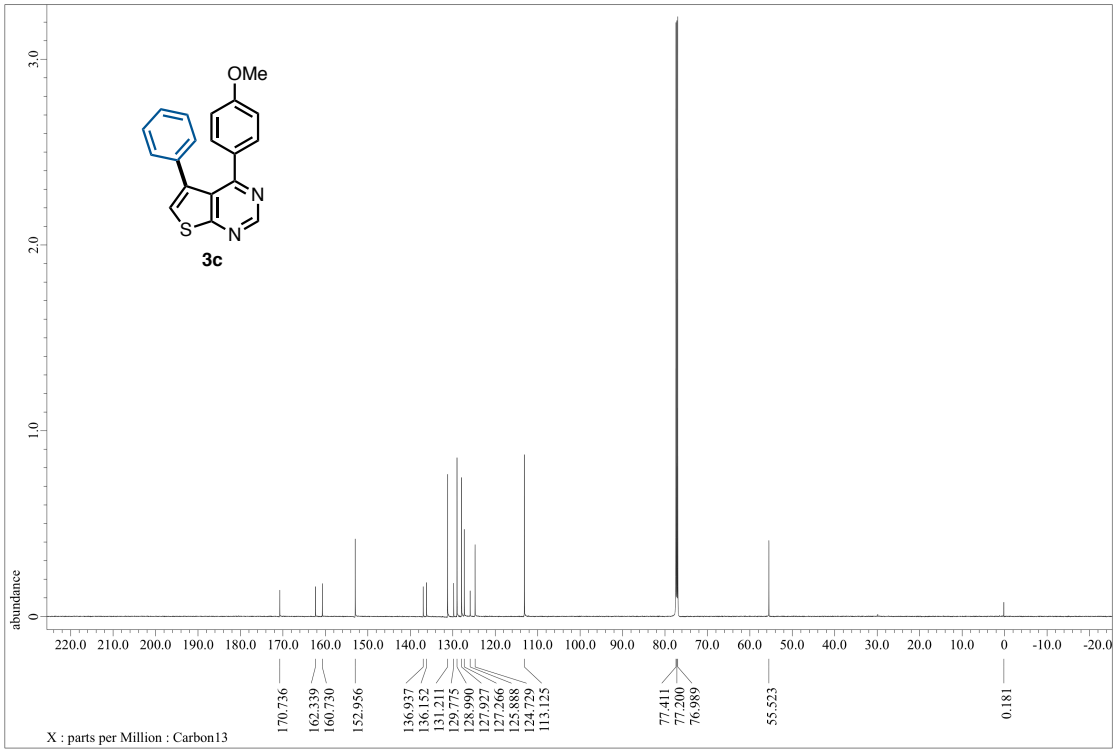

Figure S73. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3c**.

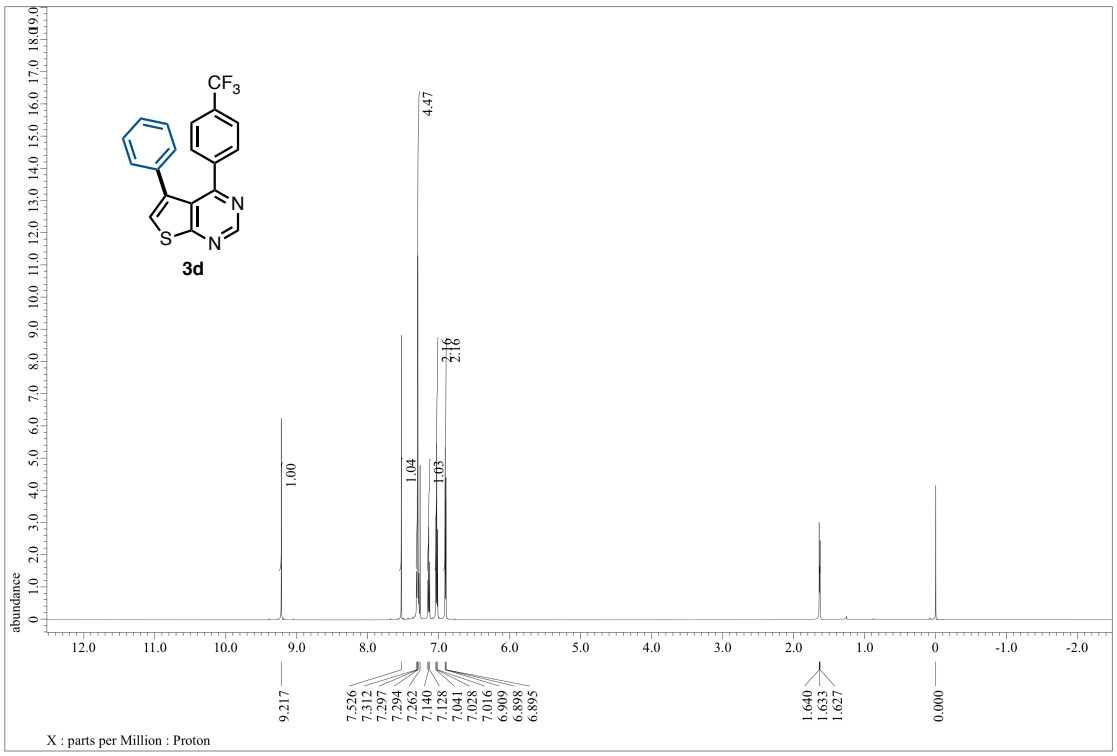

Figure S74. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3d**.

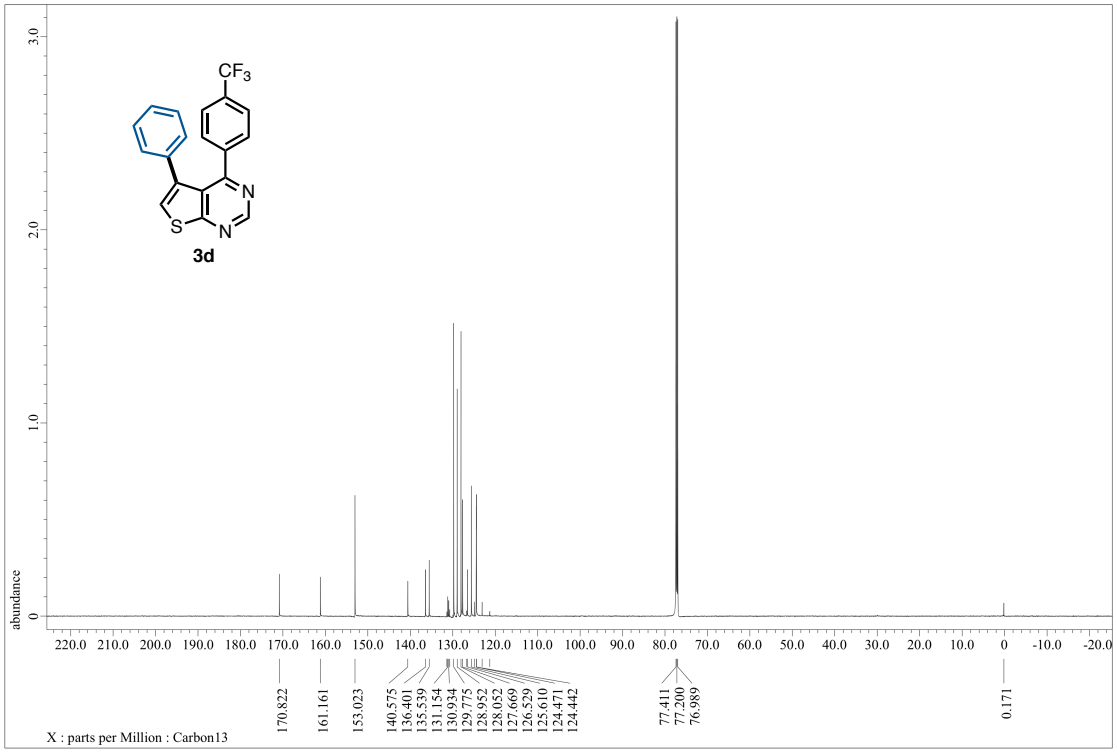

Figure S75. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3d**.

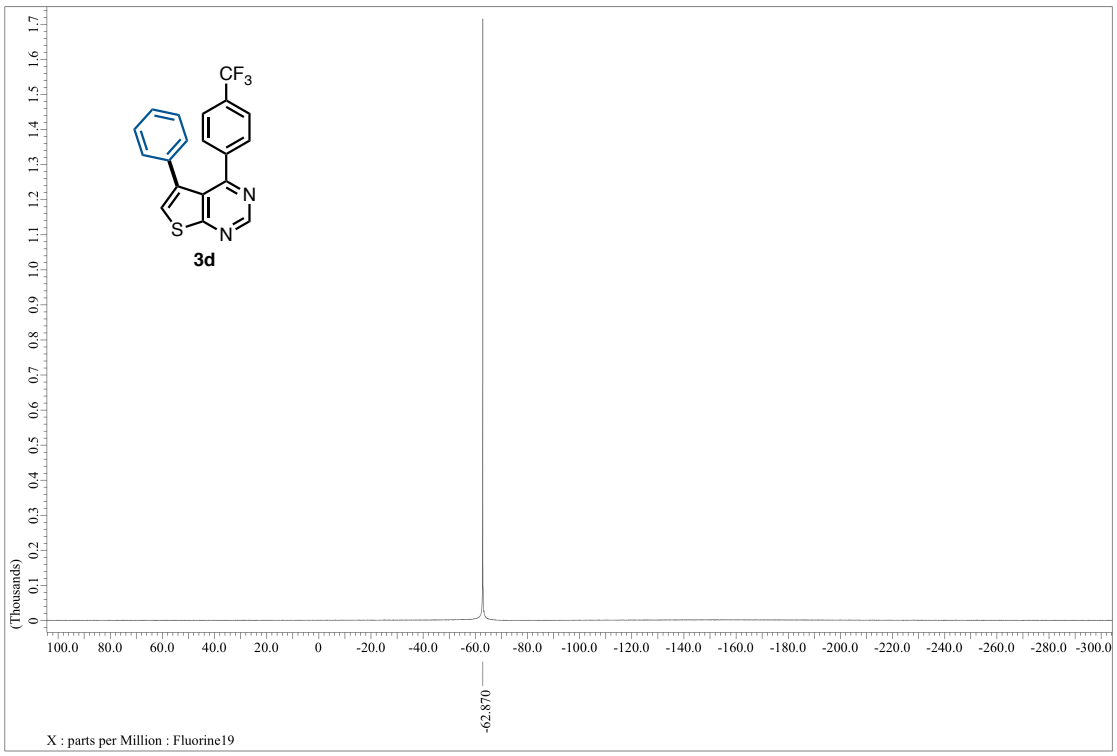

Figure S76. ^{19}F NMR spectrum (470 MHz, $CDCl_3$) of **3d**.

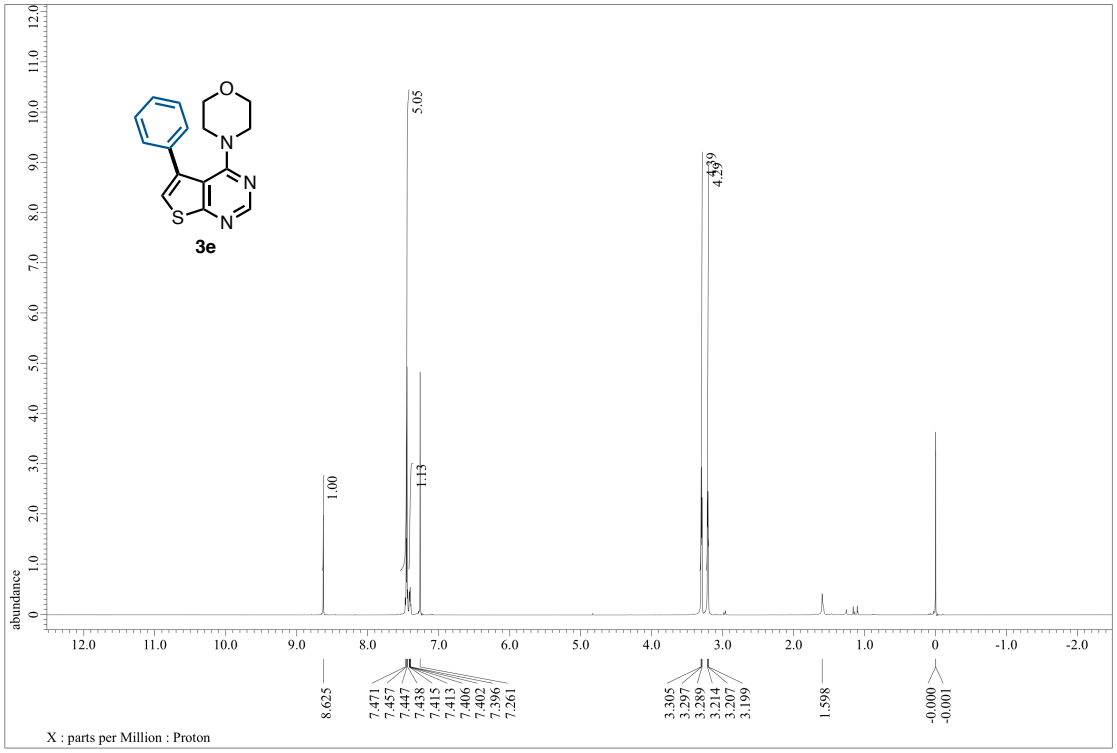

Figure S77. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3e**.

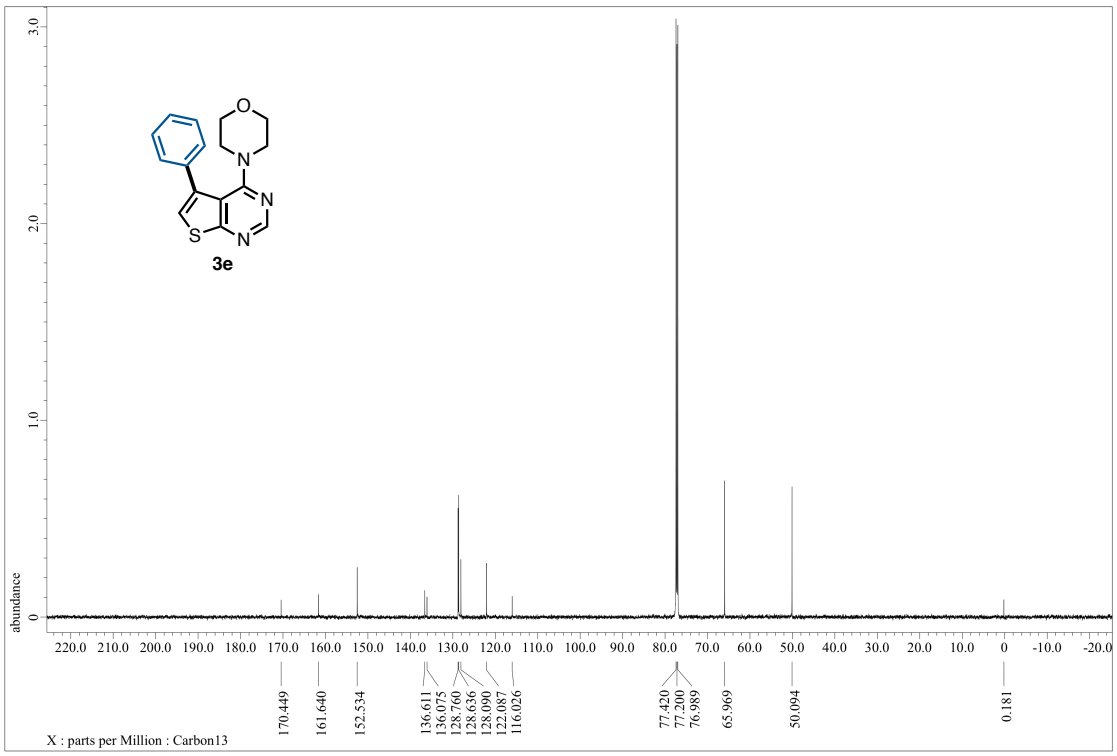

Figure S78. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3e**.

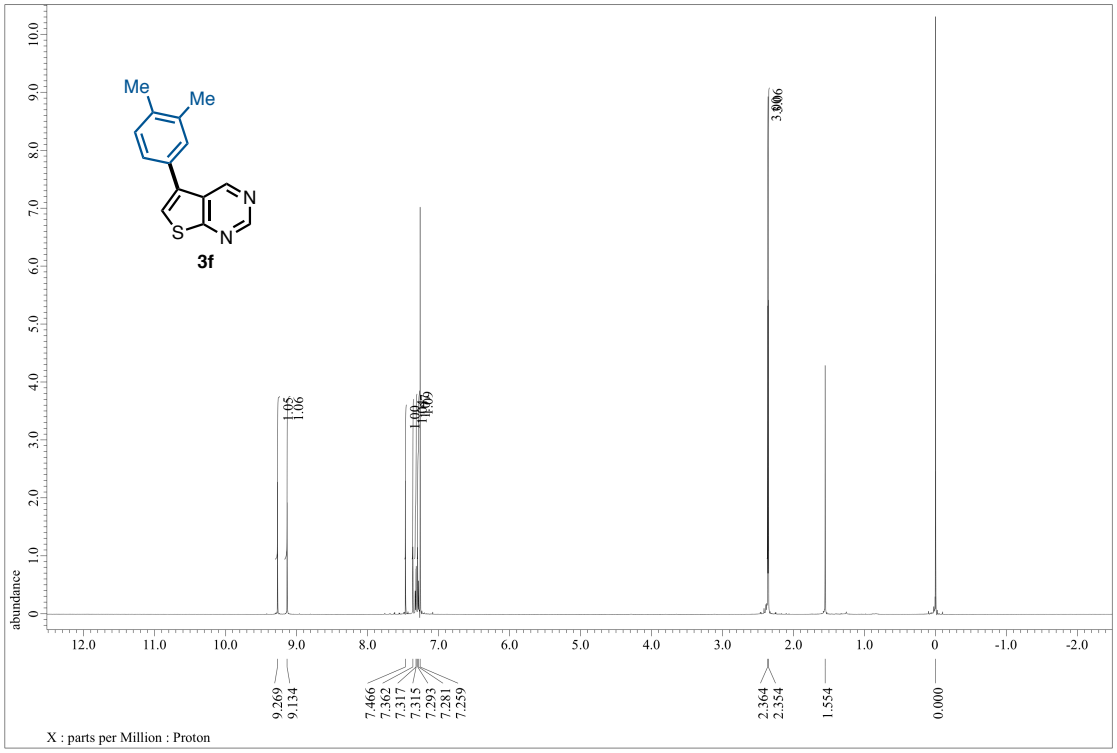

Figure S79. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3f**.

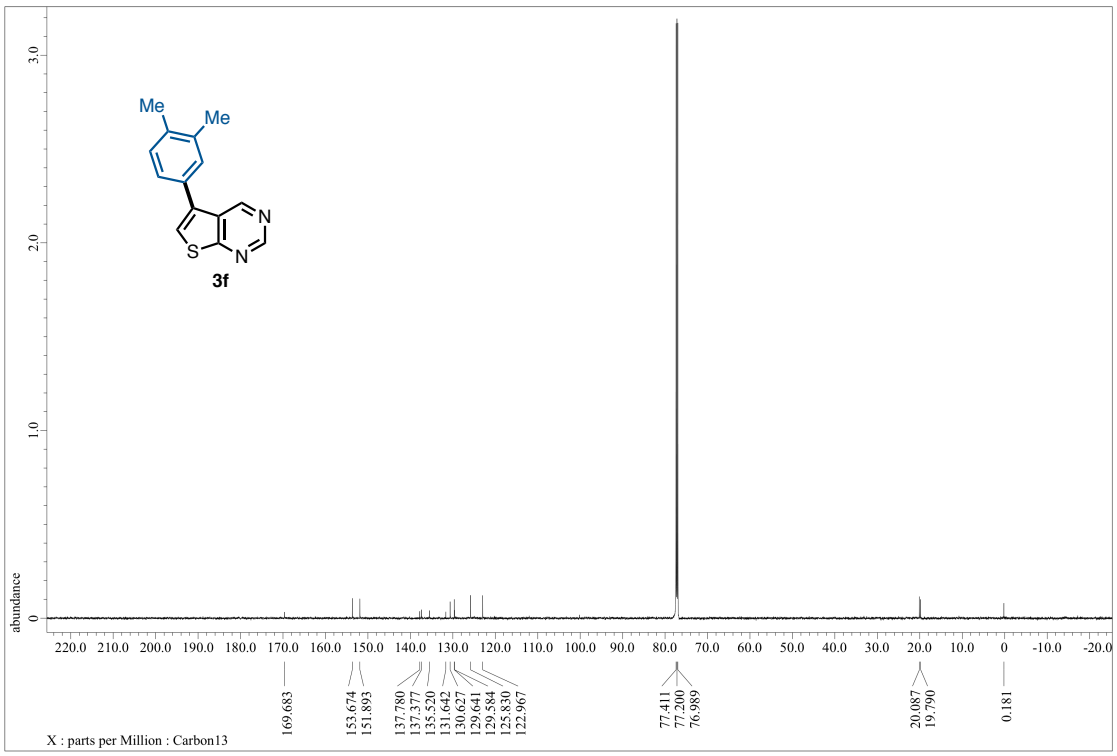

Figure S80. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3f**.

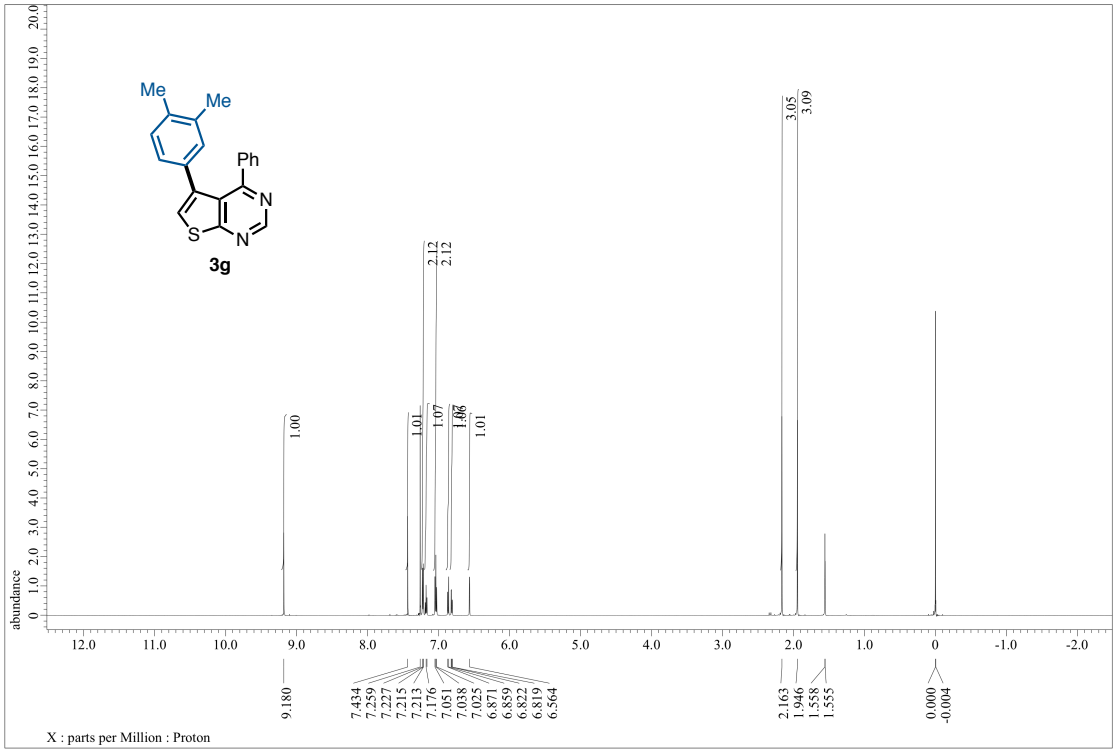

Figure S81. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3g**.

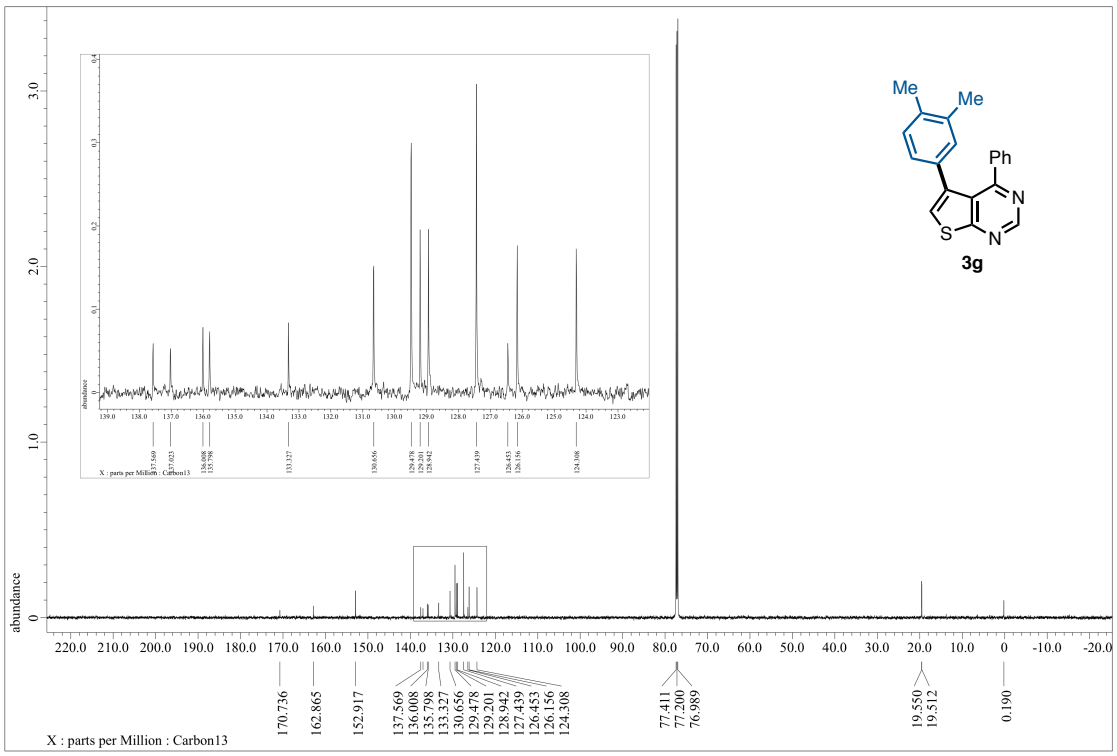

Figure S82. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3g**.

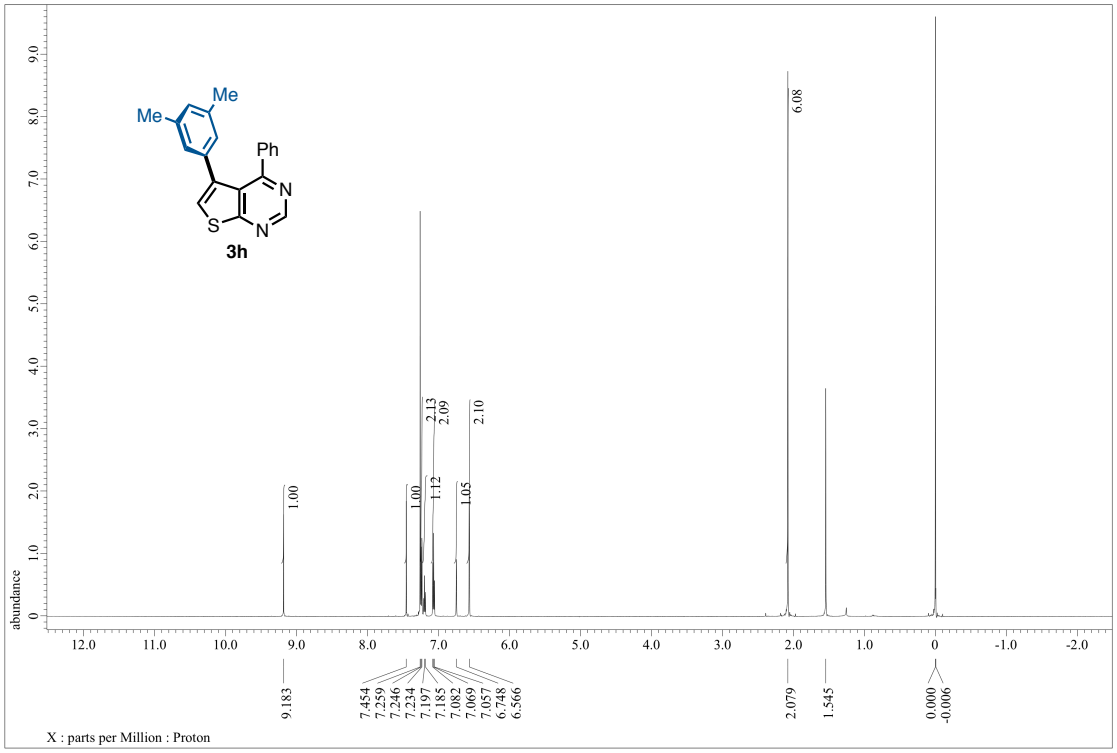

Figure S83. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3h**.

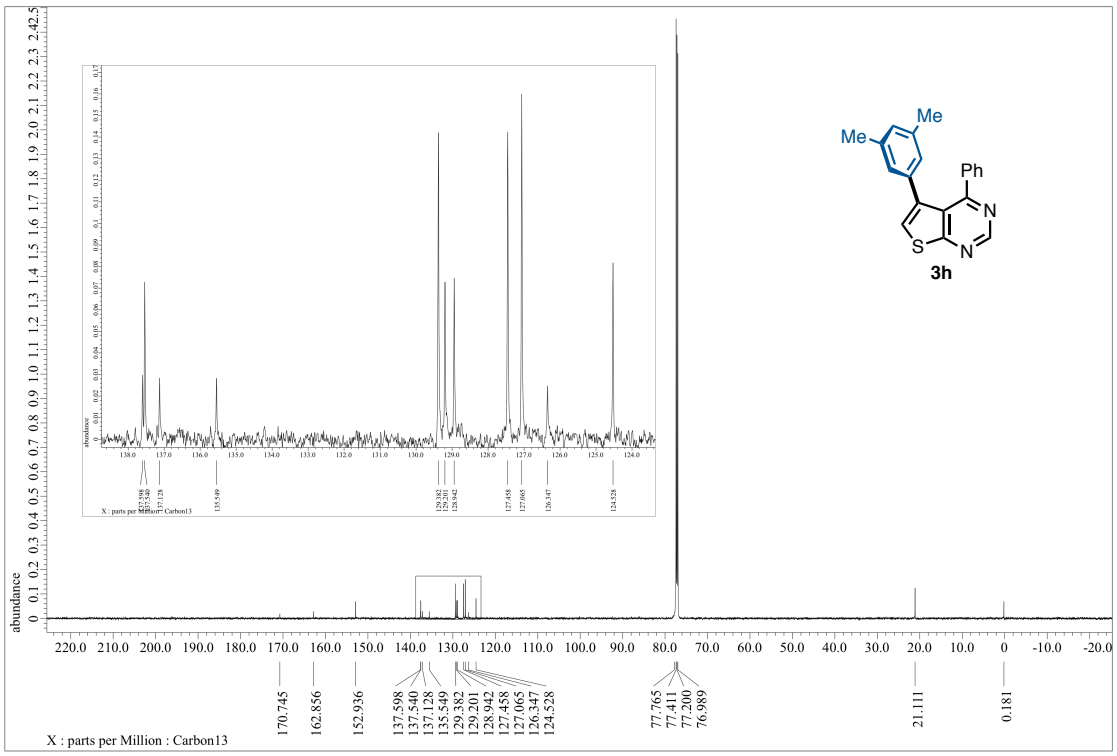

Figure S84. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3h**.

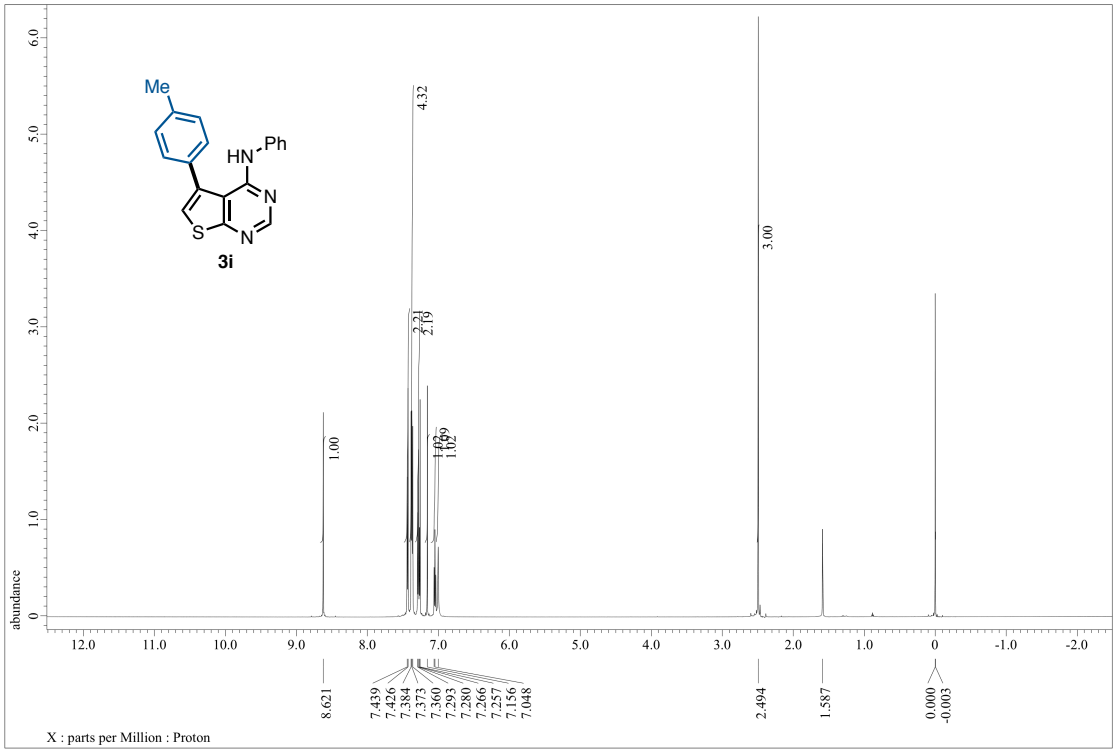

Figure S85. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3i**.

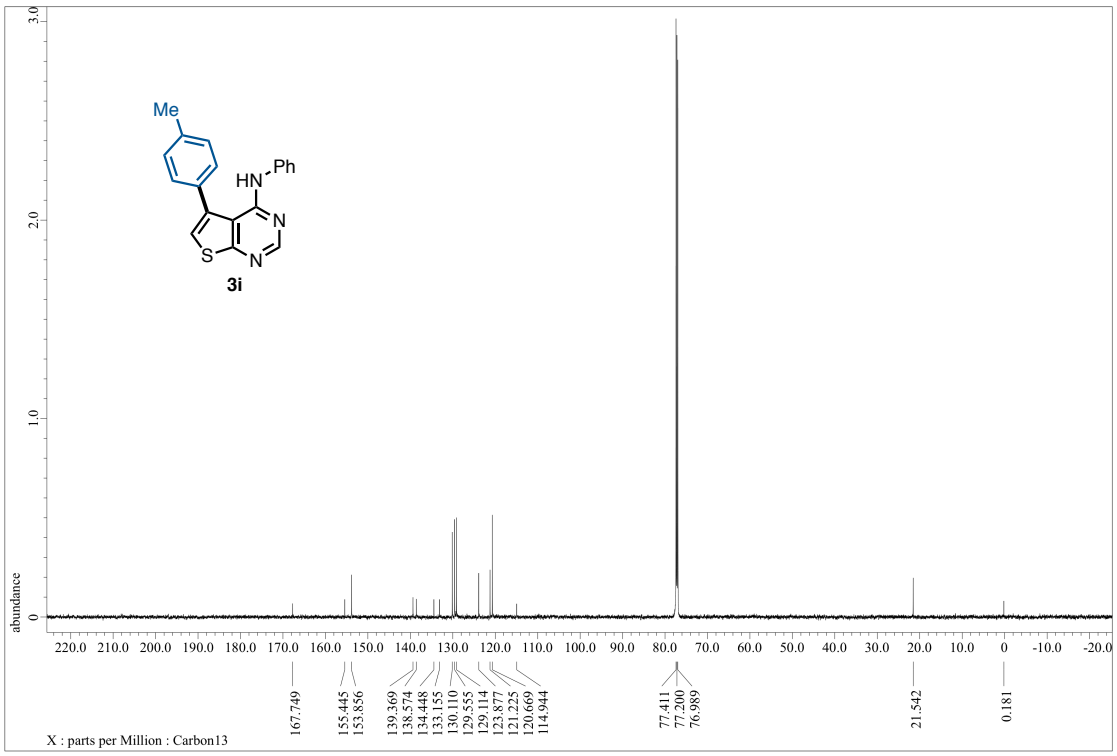

Figure S86. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3i**.

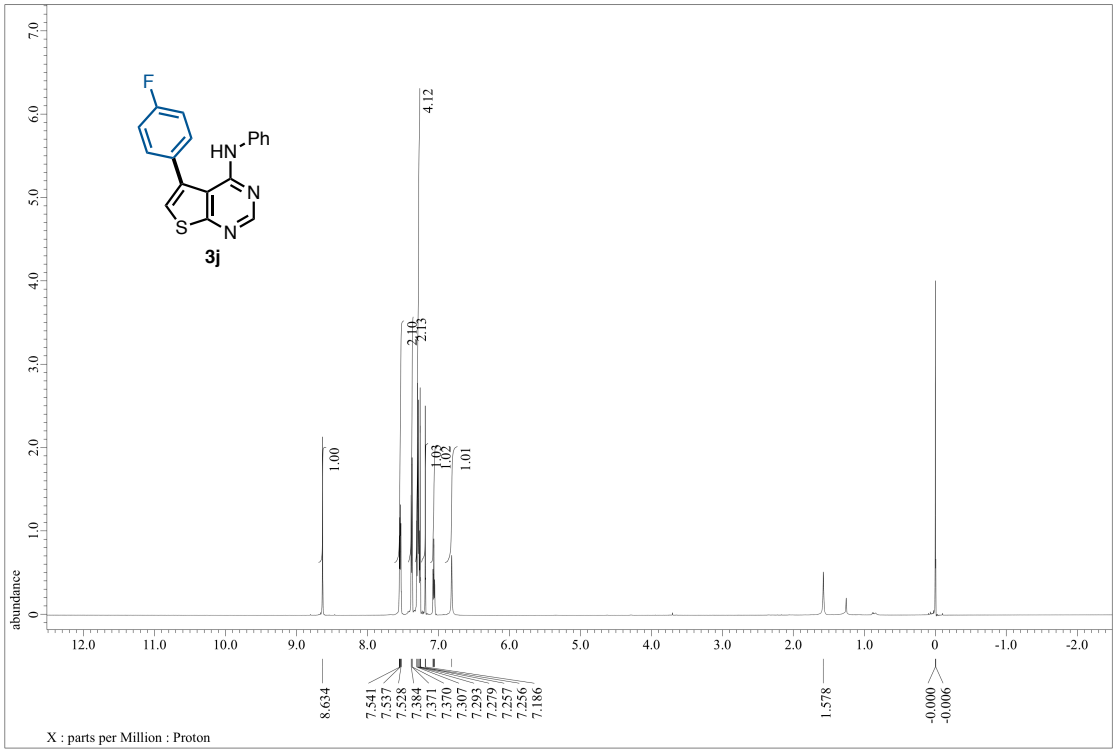

Figure S87. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3j**.

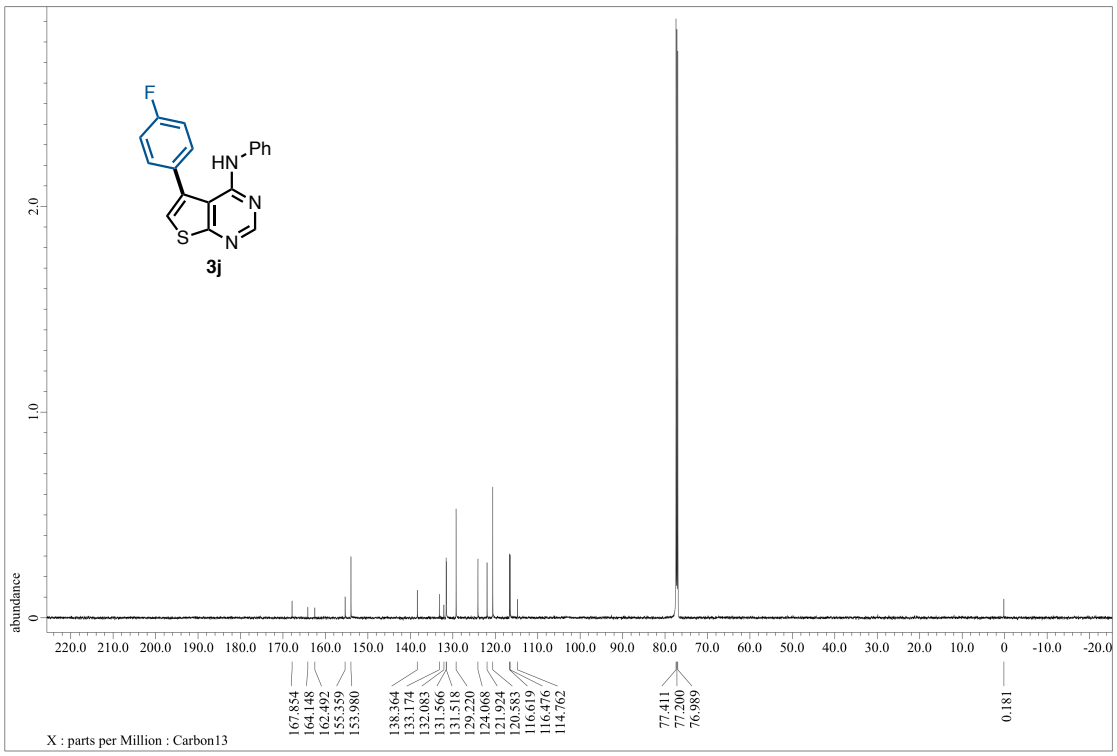

Figure S88. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3j**.

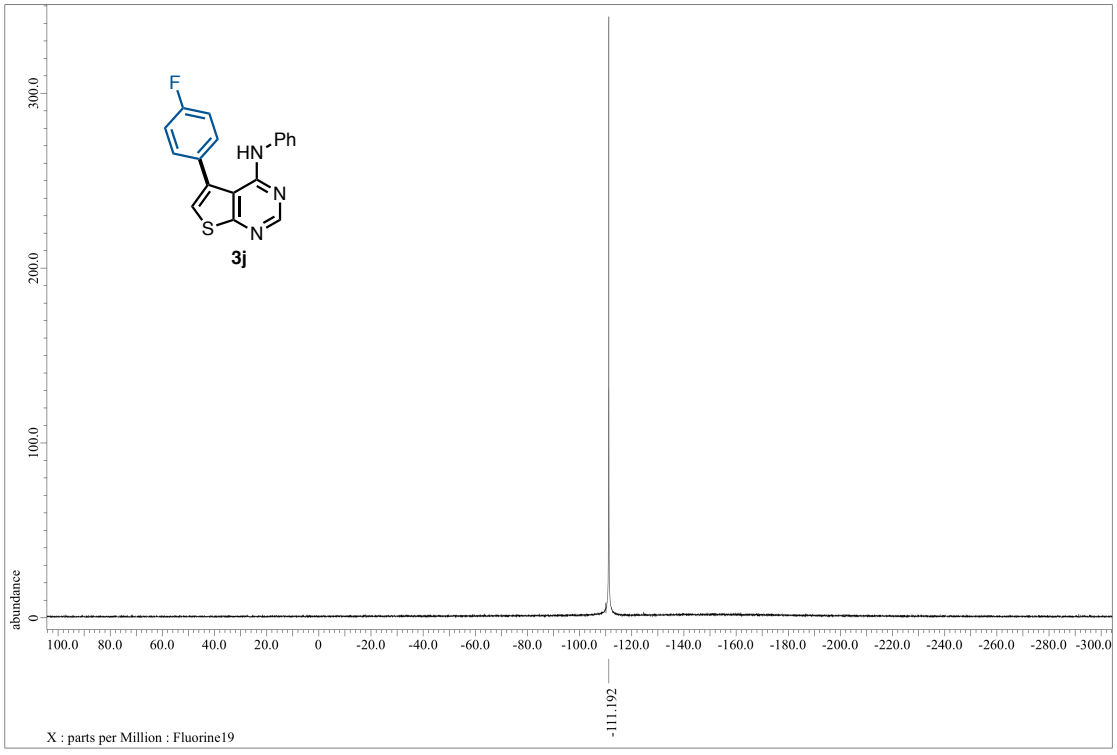

Figure S89. ^{19}F NMR spectrum (470 MHz, $CDCl_3$) of **3j**.

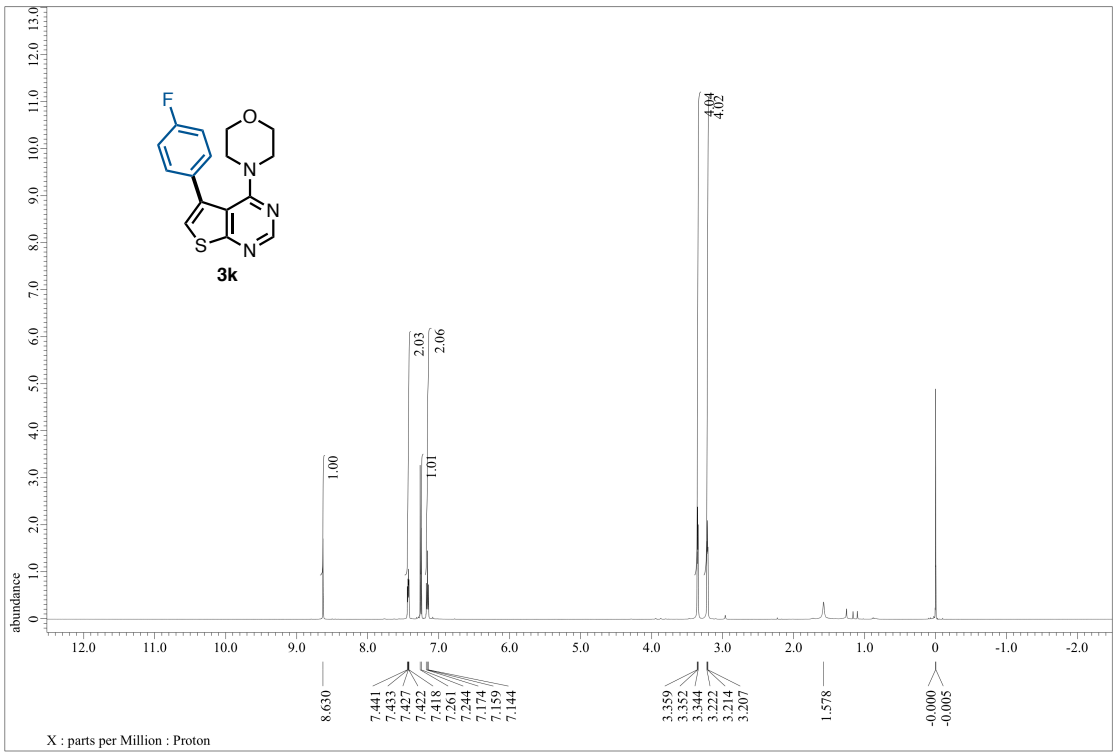

Figure S90. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3k.**

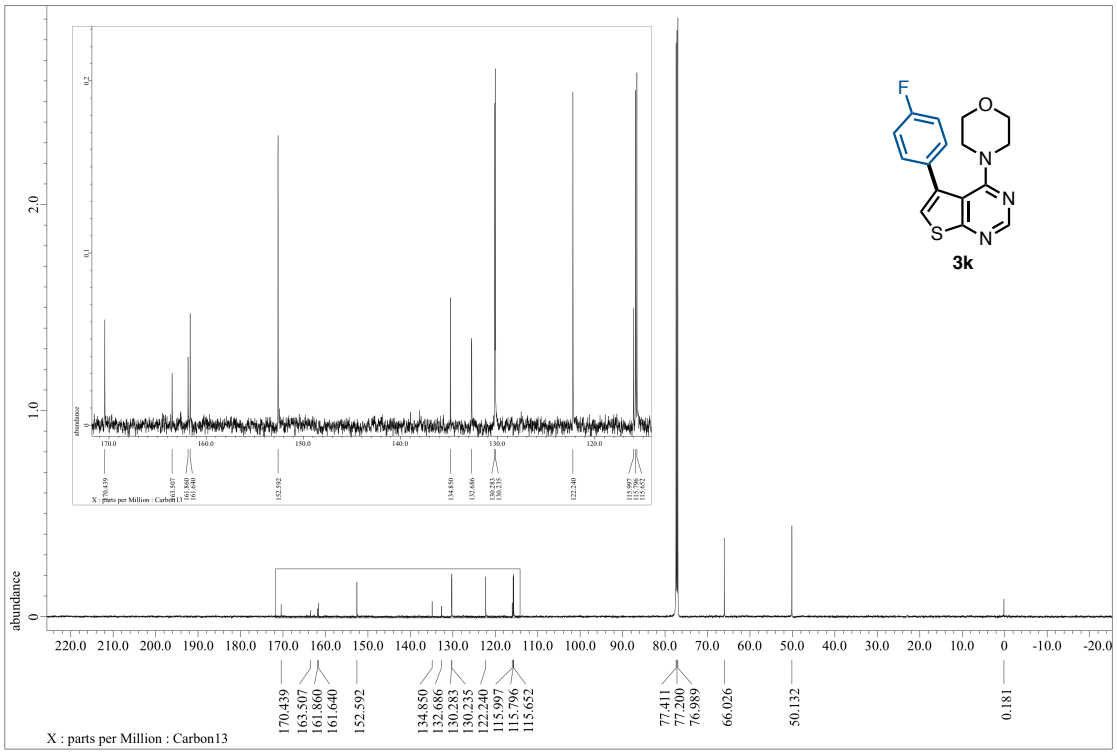

Figure S91. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3k**.

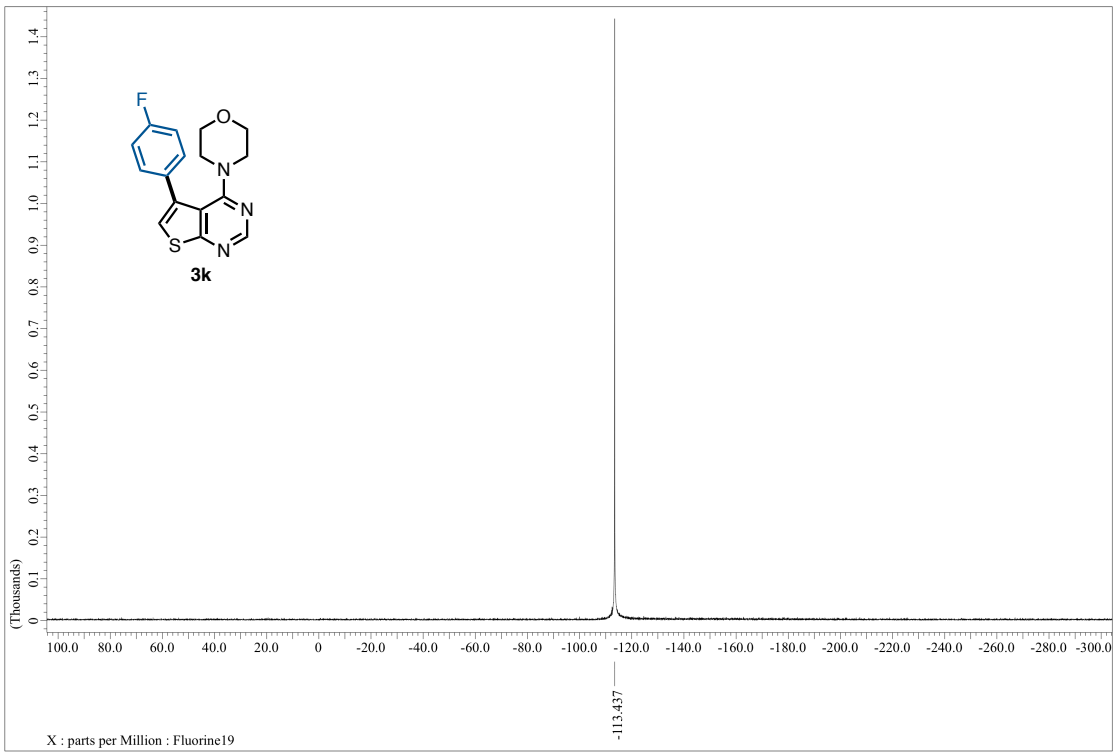

Figure S92. ^{19}F NMR spectrum (470 MHz, $CDCl_3$) of **3k**.

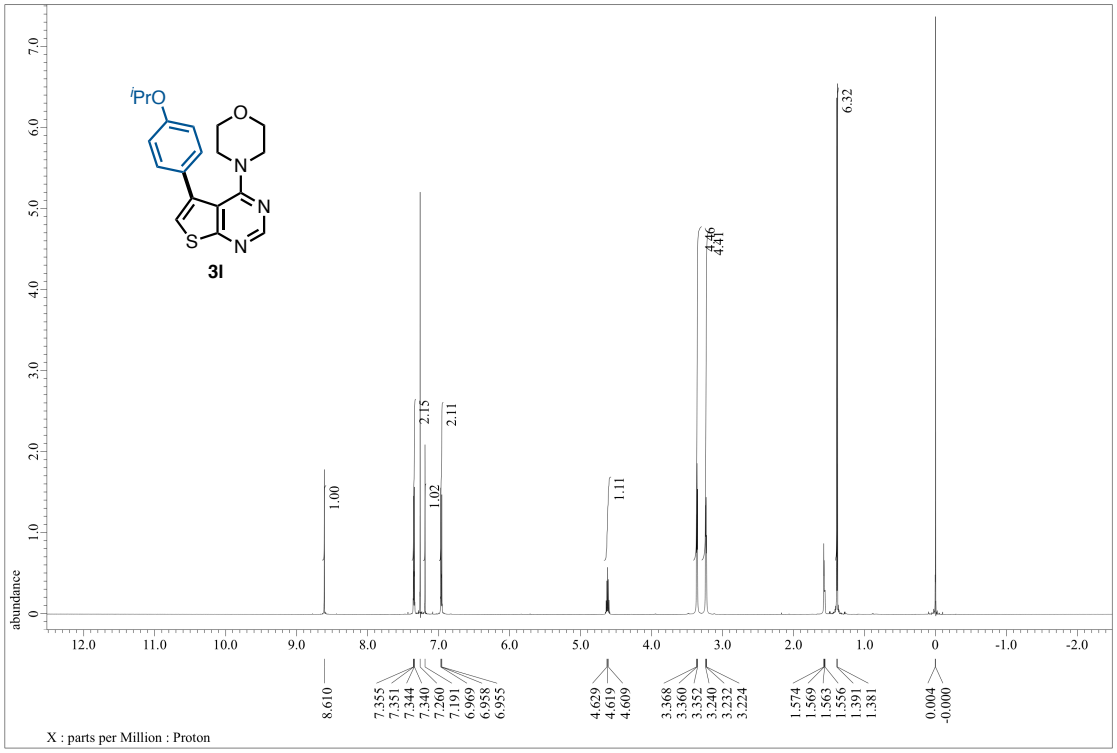

Figure S93. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3l**.

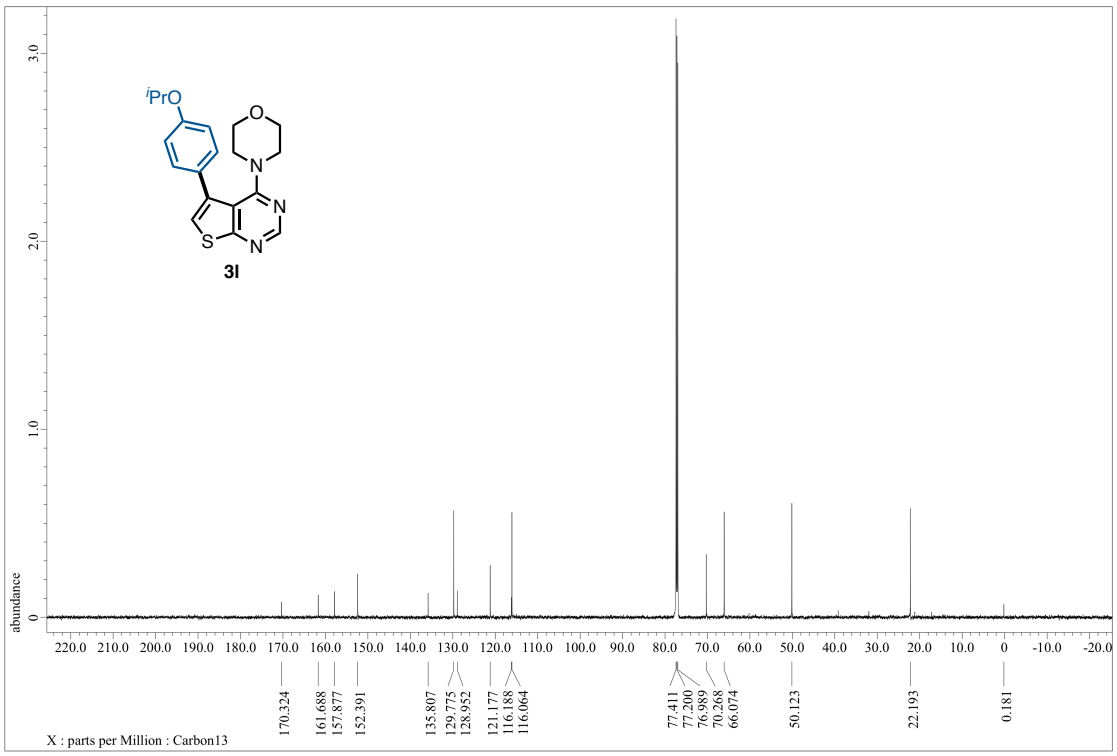

Figure S94. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3l**.

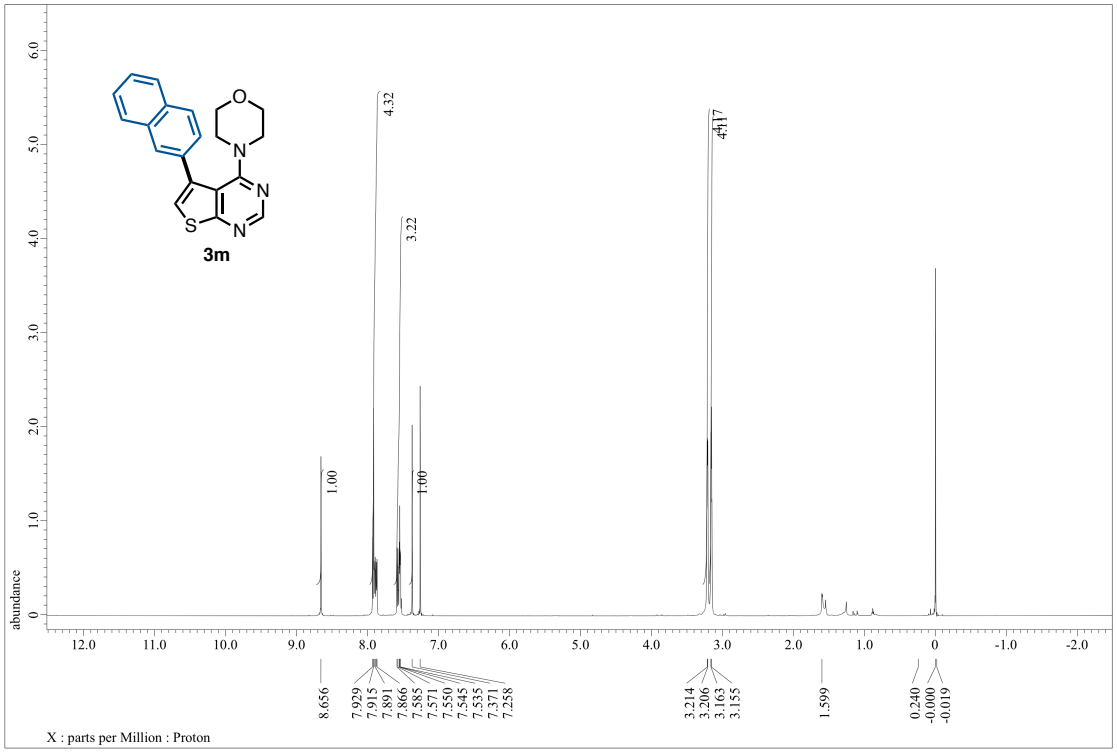

Figure S95. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3m**.

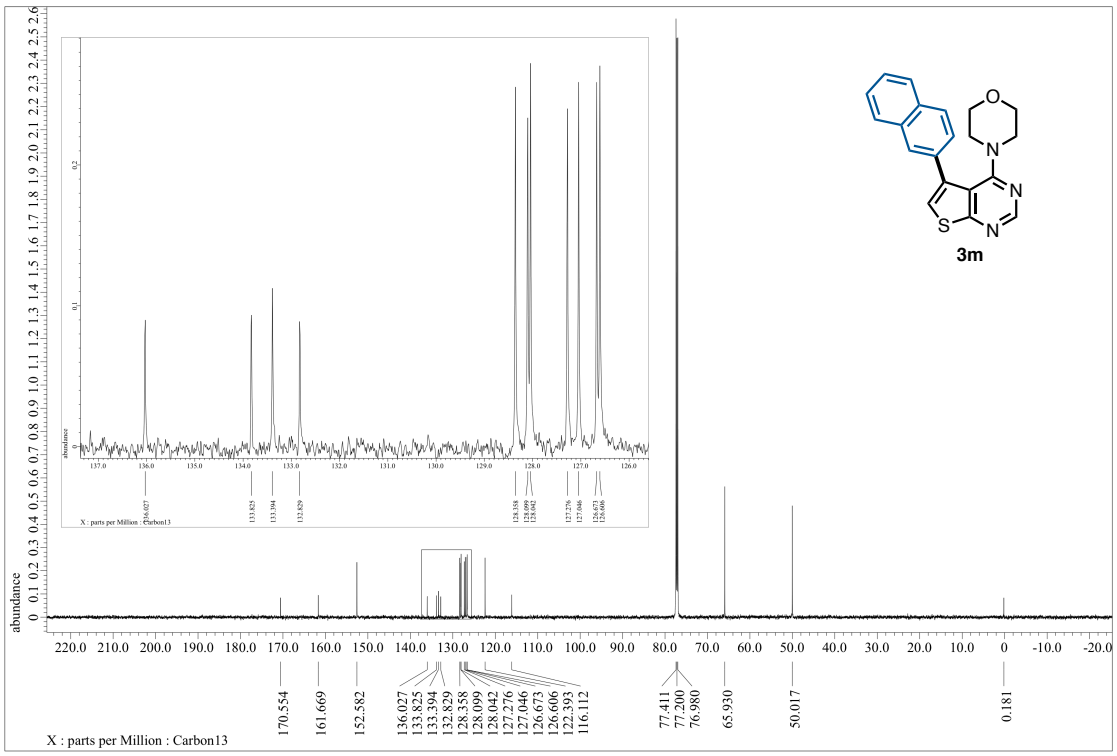

Figure S96. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3m**.

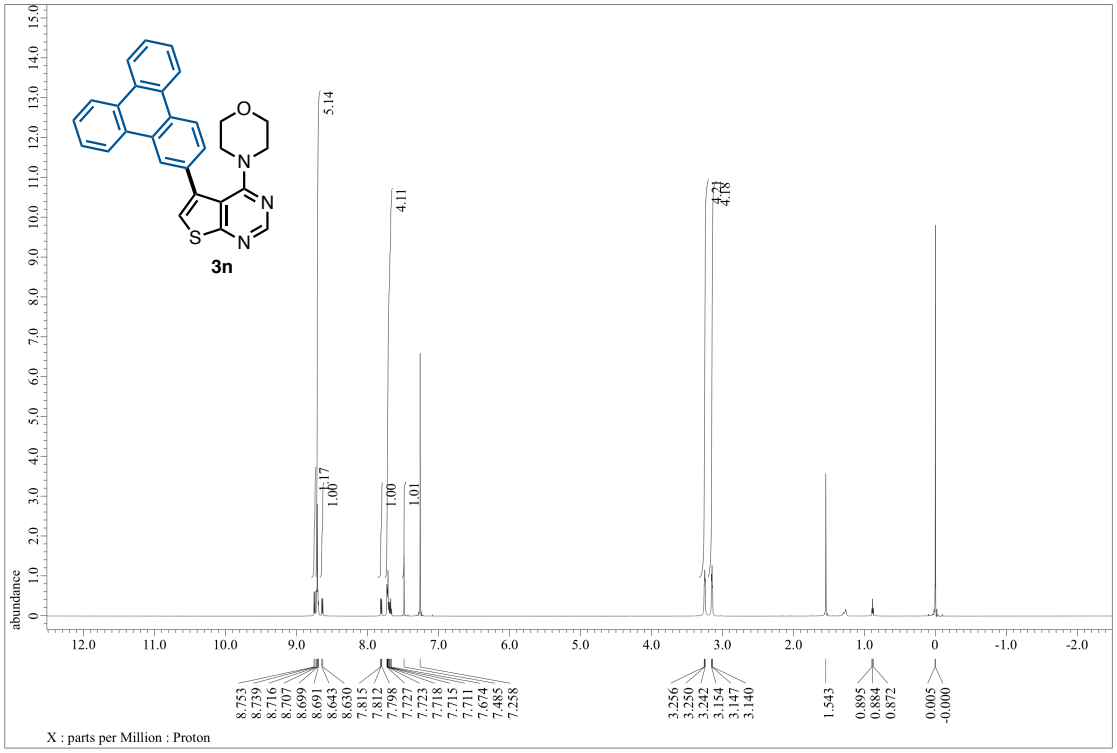

Figure S97. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3n**.

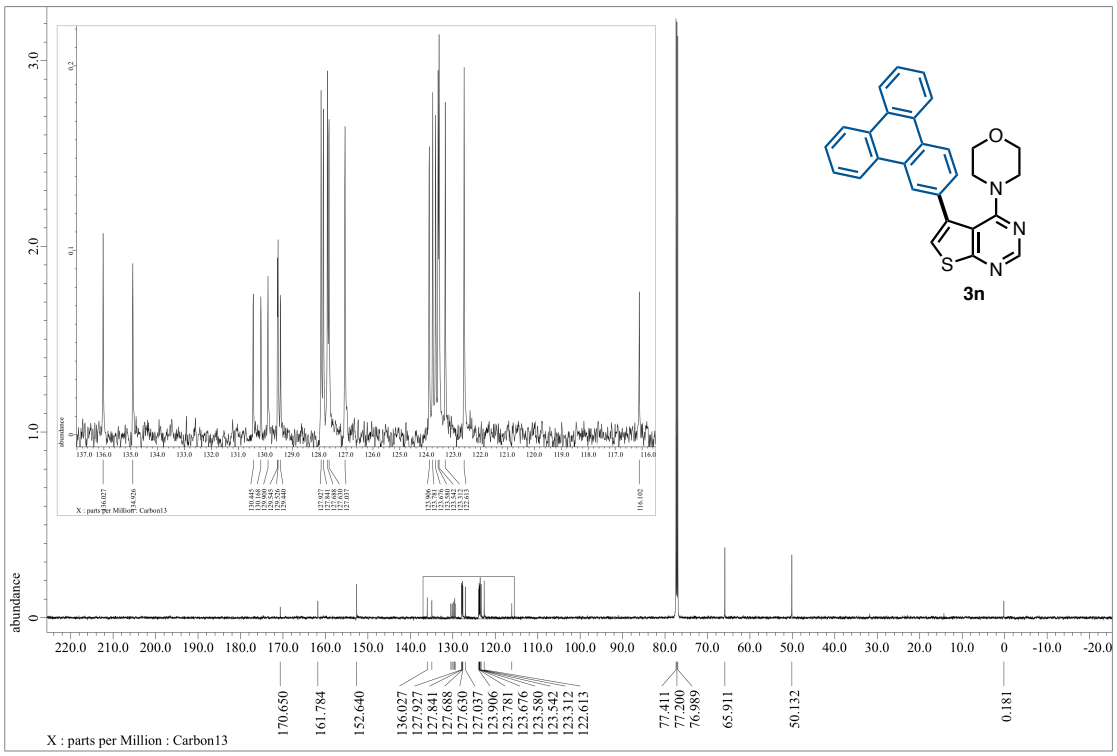

Figure S98. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3n**.

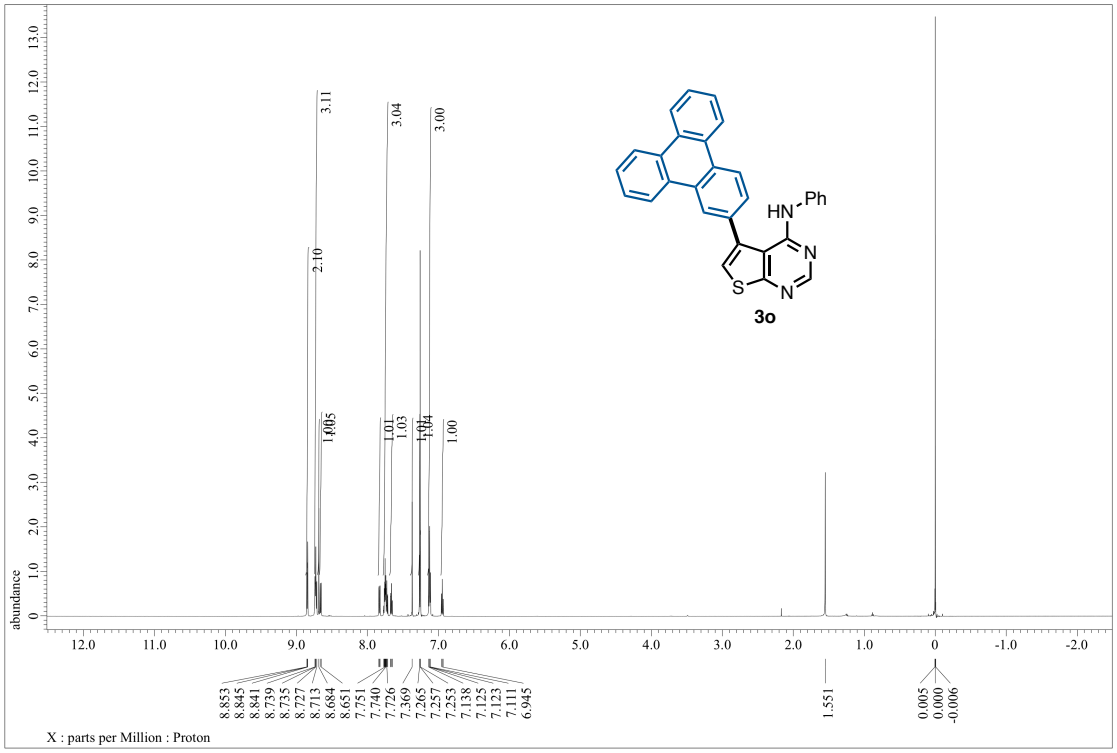

Figure S99. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3o**.

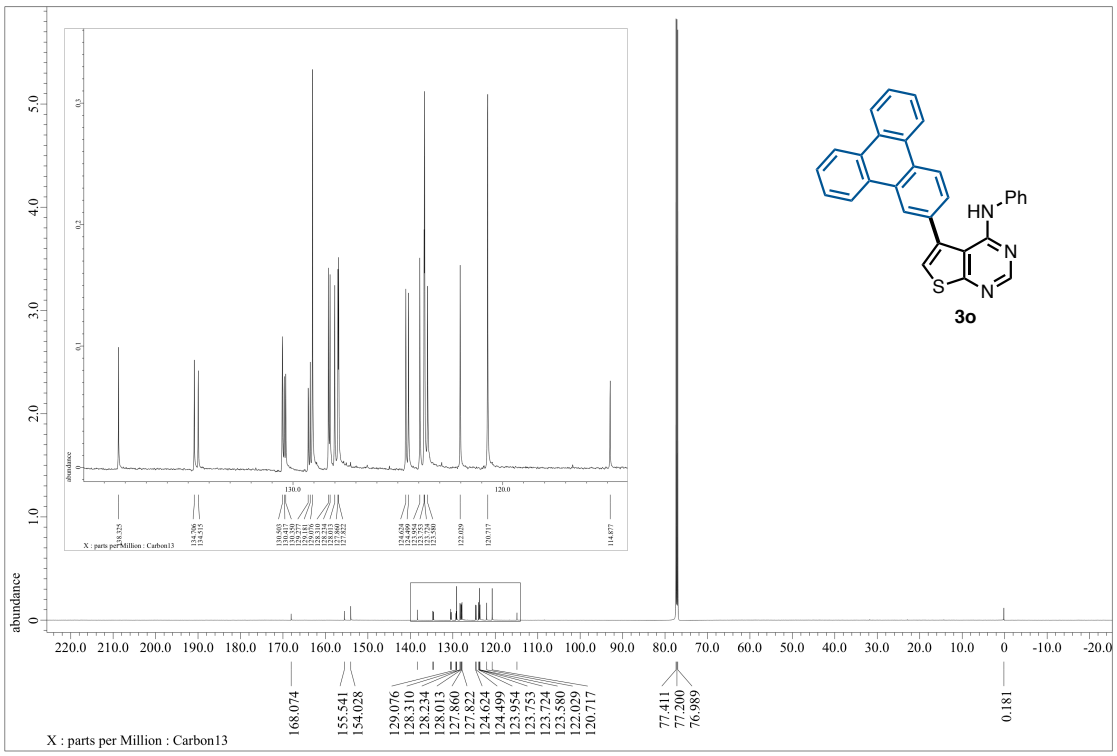

Figure S100. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3o**.

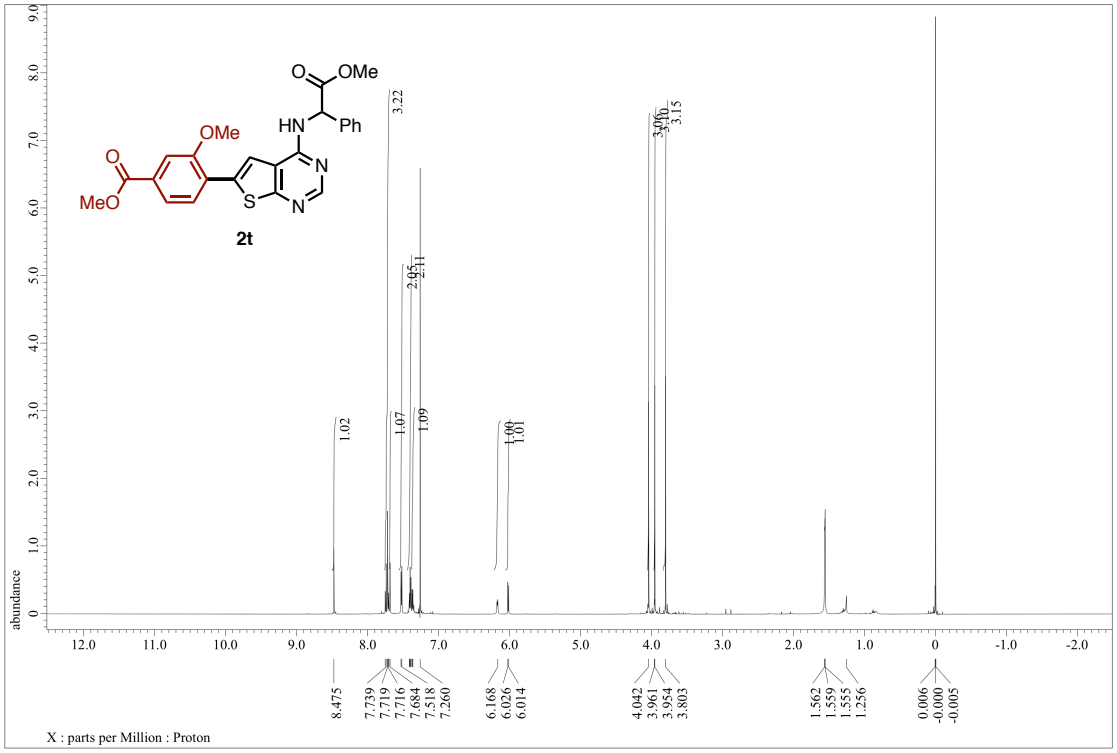

Figure S101. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2t**.

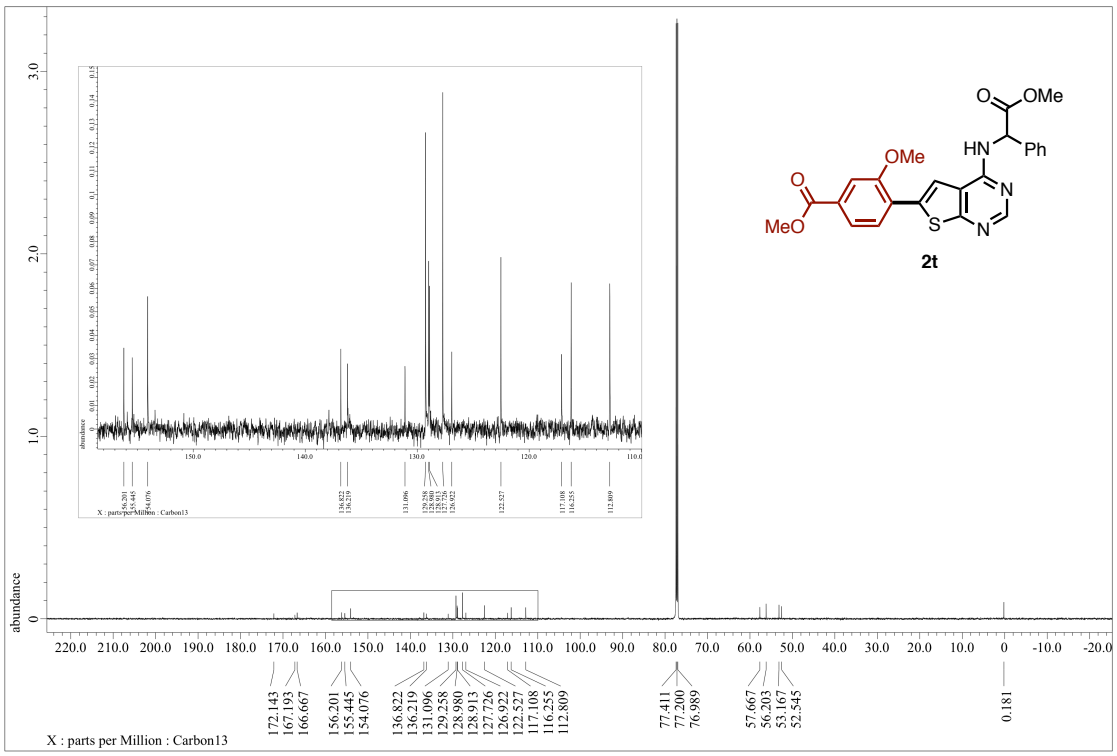

Figure S102. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2t**.

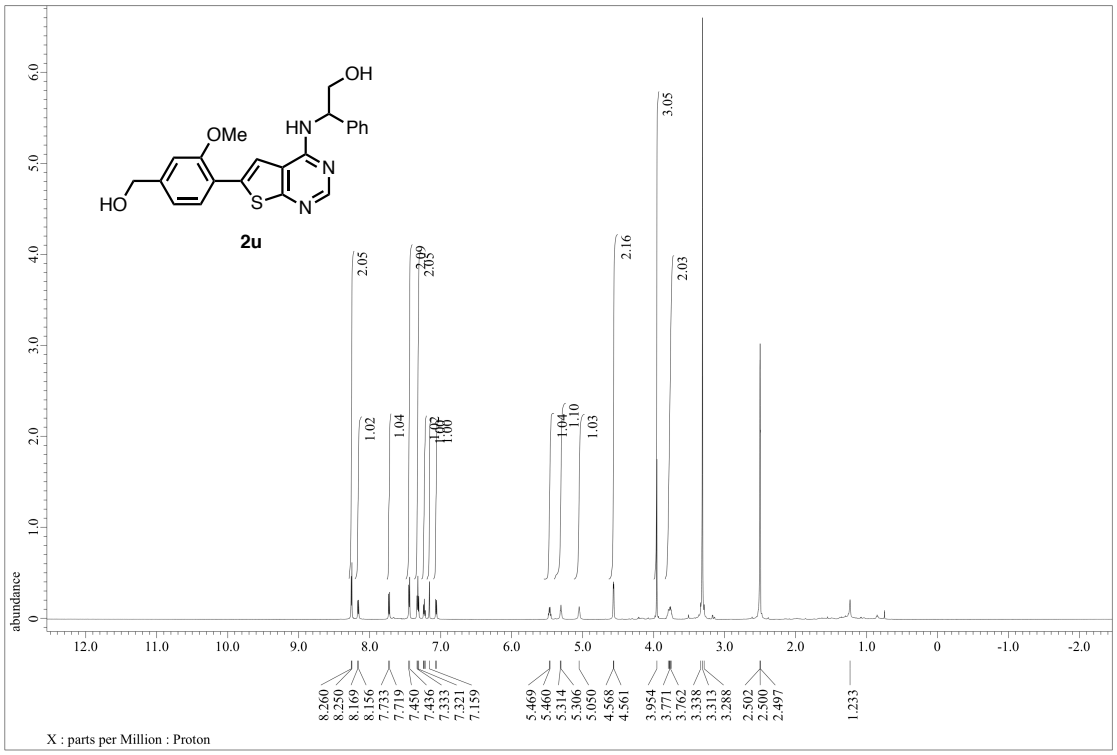

Figure S103. ^{1}H NMR spectrum (600 MHz, $(CD_3)_2SO$) of **2u**.

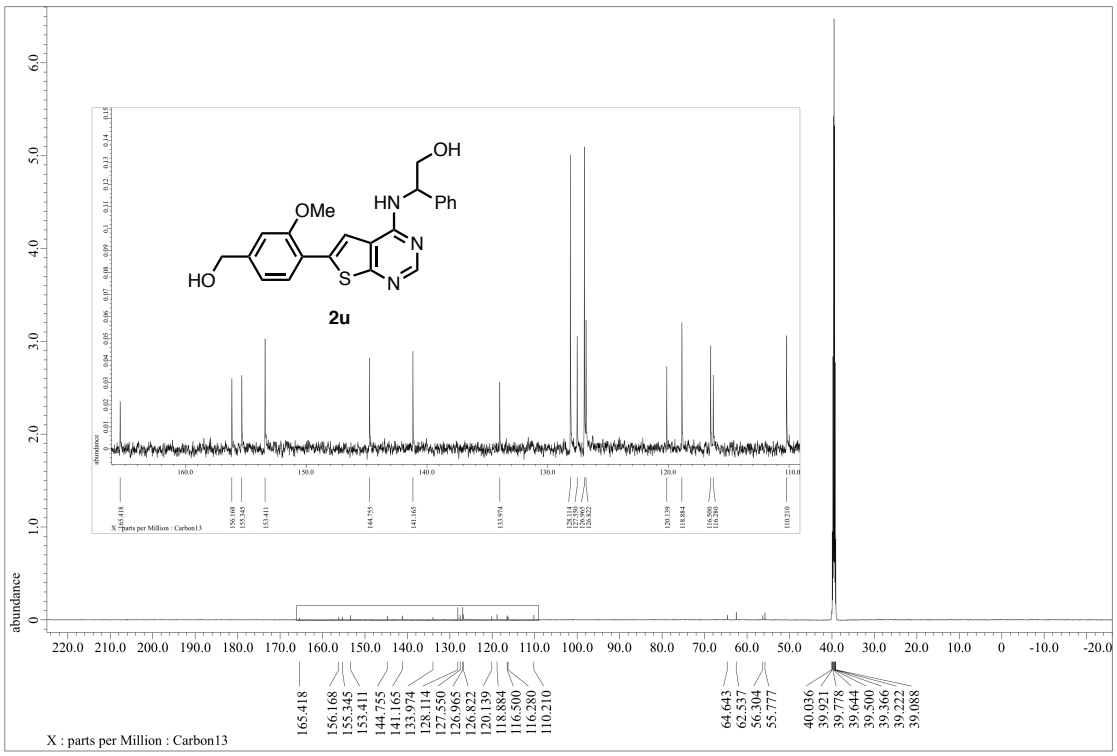

Figure S104. ^{13}C NMR spectrum (150 MHz, $(CD_3)_2SO$) of **2u**.

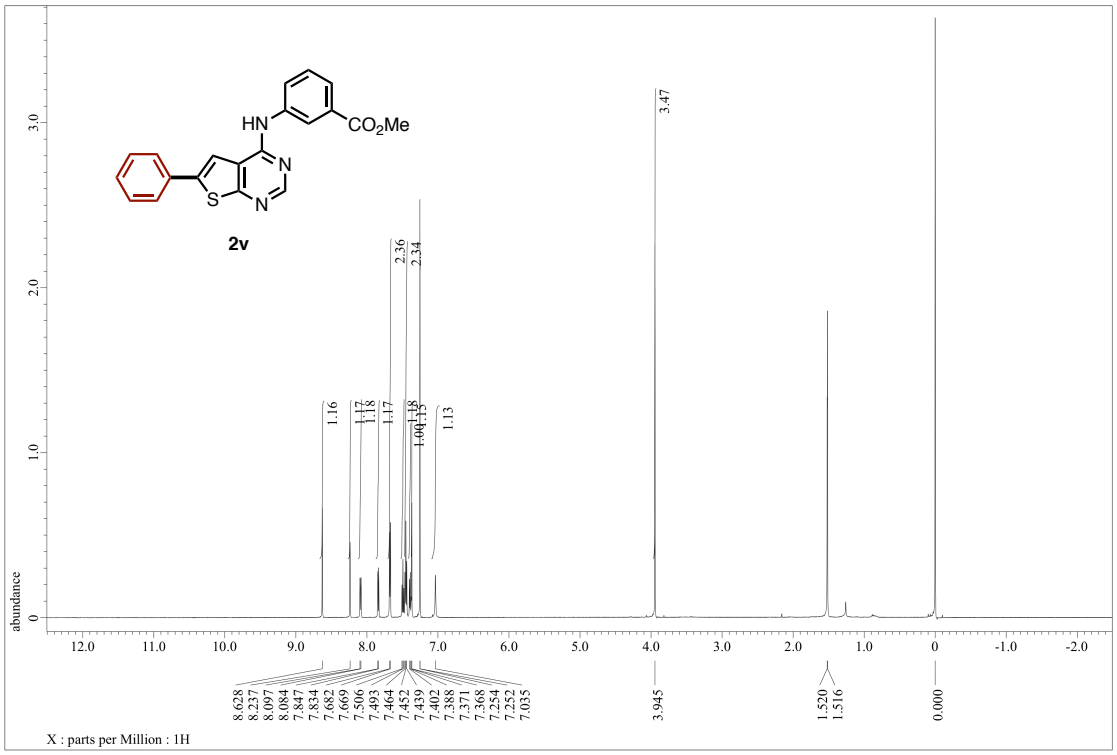

Figure S105. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **2v**.

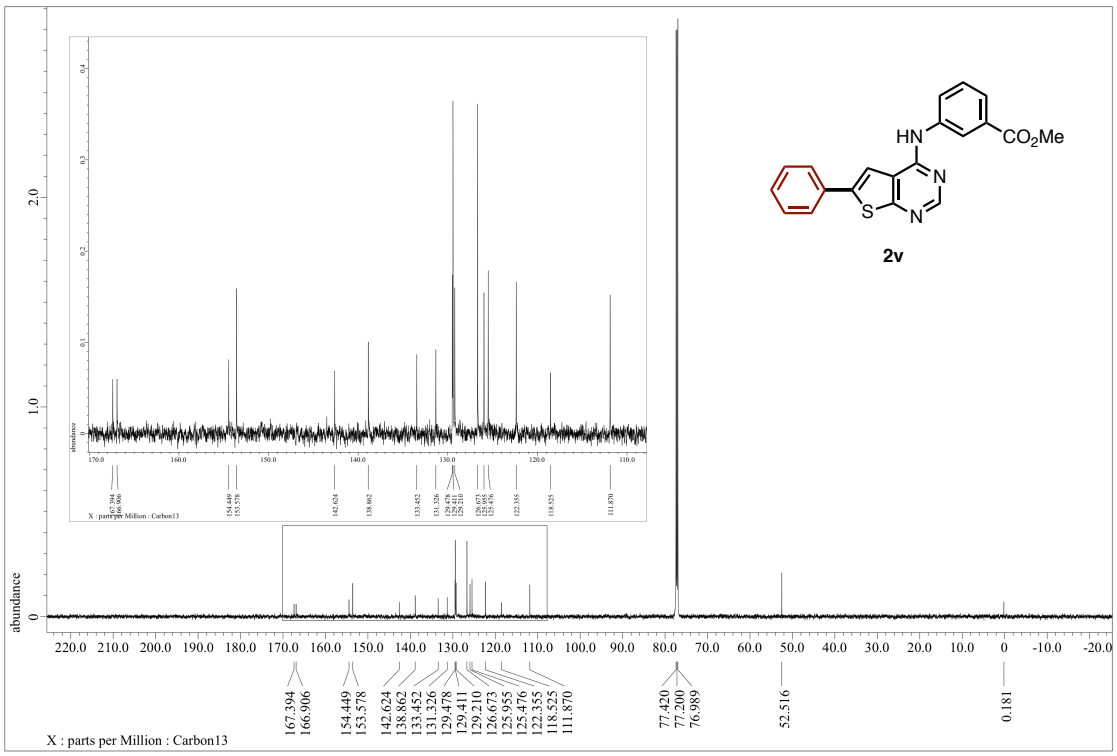

Figure S106. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **2v**.

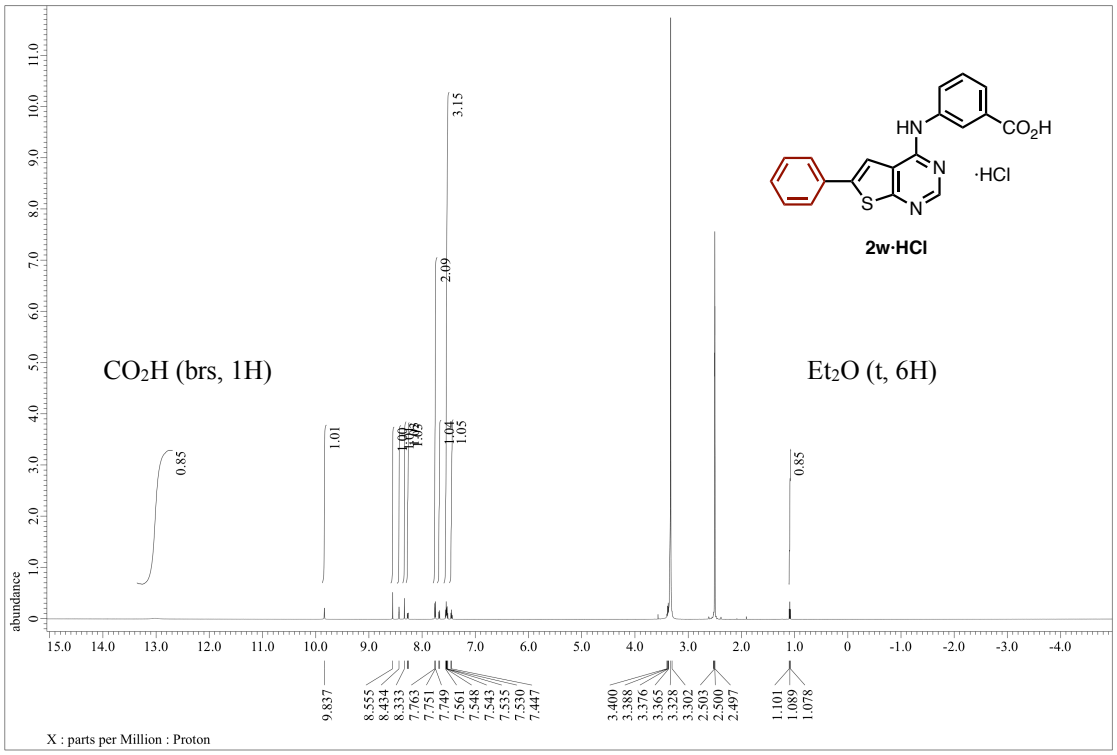

Figure S107. ^{1}H NMR spectrum of (600 MHz, $(CD_3)_2SO$) **2w·HCl**.

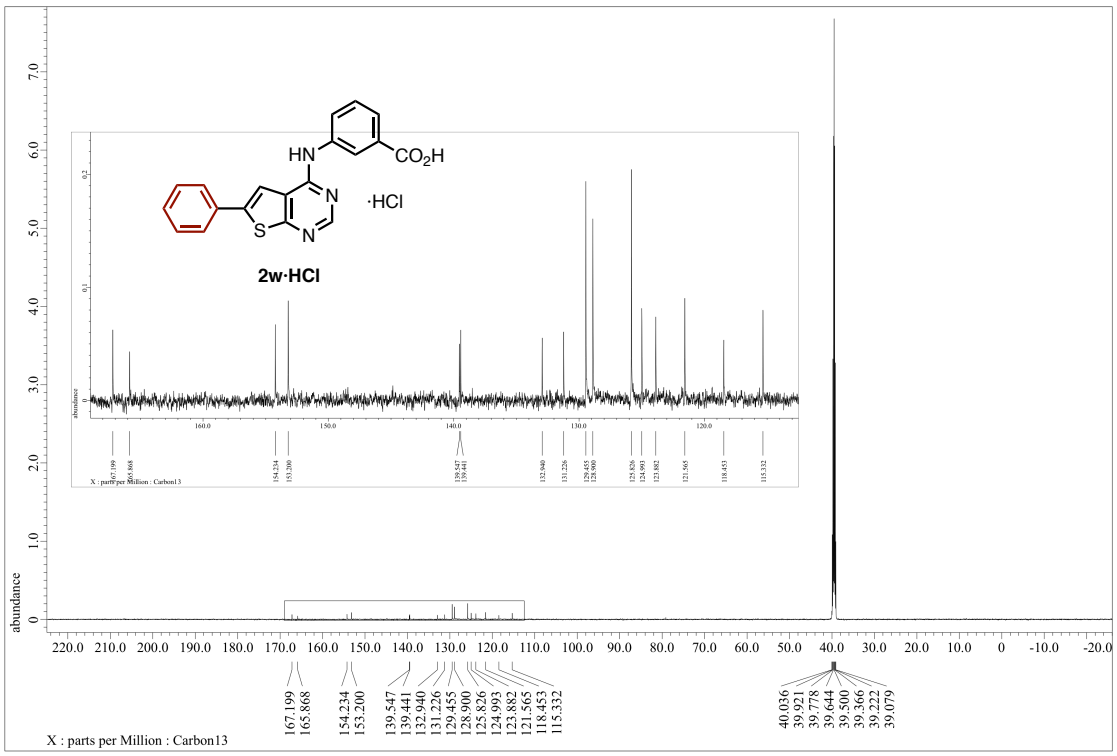

Figure S108. ^{13}C NMR spectrum (150 MHz, $(CD_3)_2SO$) of **2w·HCl**.

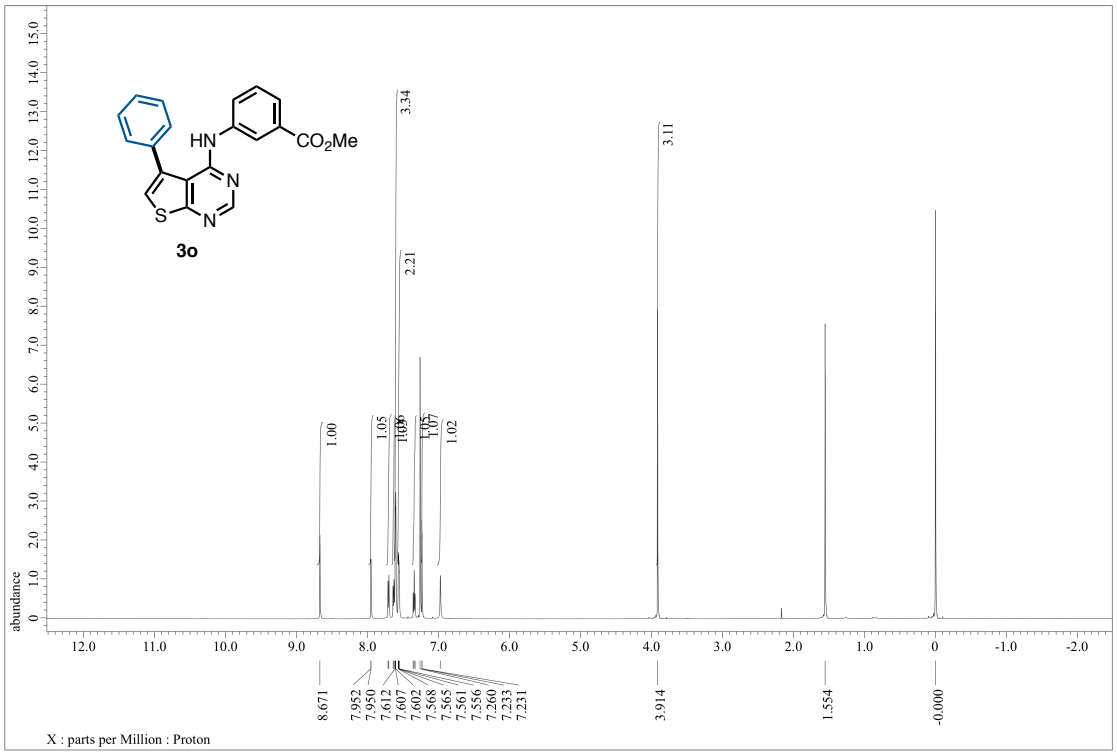

Figure S109. ^{1}H NMR spectrum (600 MHz, $CDCl_3$) of **3o**.

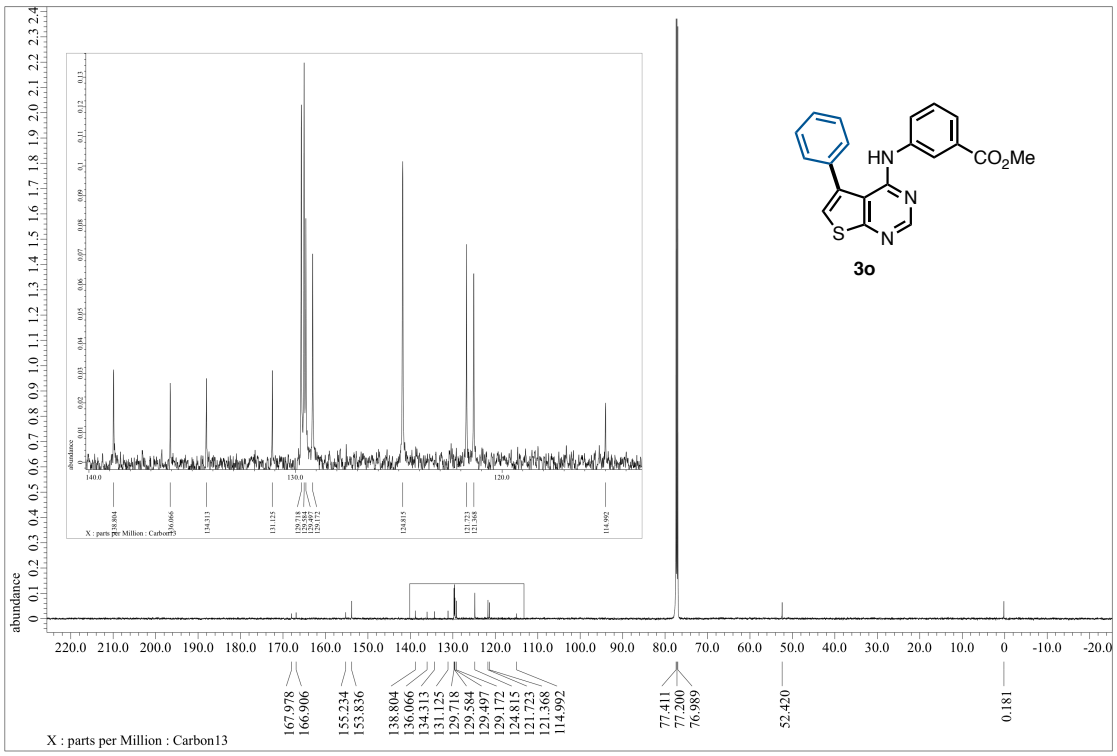

Figure S110. ^{13}C NMR spectrum (150 MHz, $CDCl_3$) of **3o**.

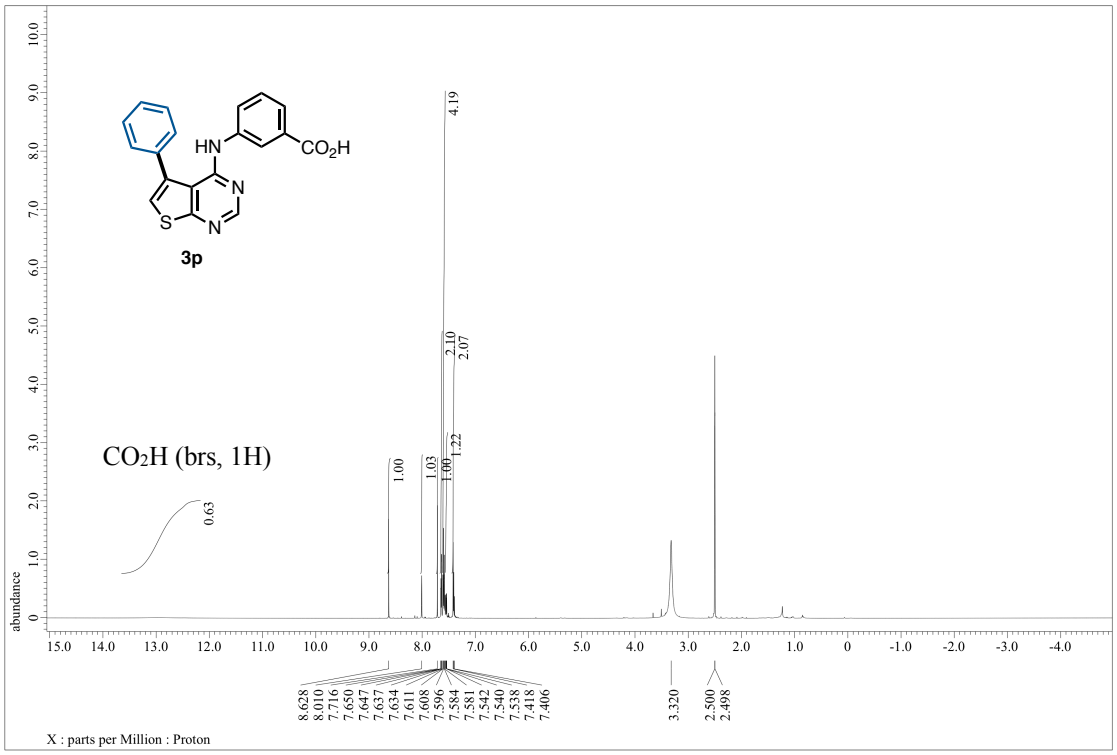

Figure S111. ^{1}H NMR spectrum (600 MHz, $(CD_3)_2SO$) of **3p**.

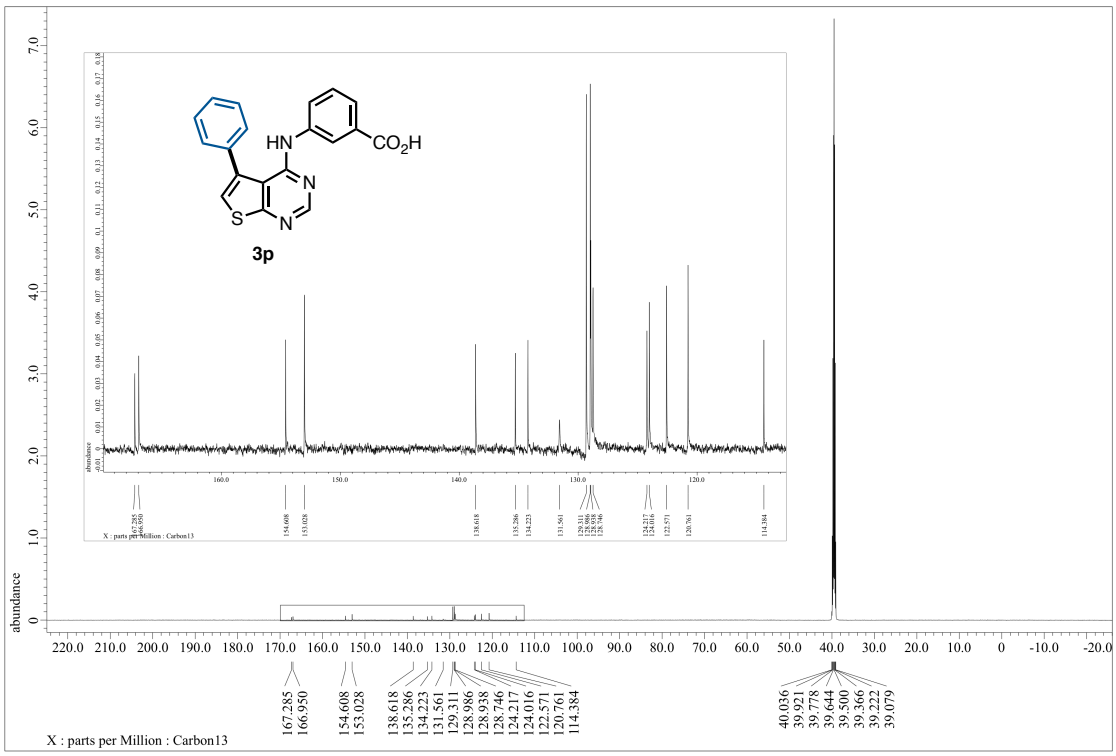

Figure S112. ^{13}C NMR spectrum (600 MHz, $(CD_3)_2SO$) of **3p**.