New Efficient Route to Dissymetric 2,4-Di(het)aryl-pyrido[3,2-*d*]pyrimidines *via* Regioselective Cross-Coupling Reactions

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SUPPORTING INFORMATION

Instrumentation and Materials. ^{1}H NMR and ^{13}C NMR were recorded on a Bruker Avance DPX250 spectrometer (250.19 MHz ^{1}H, 62.89 MHz ^{13}C) using tetramethylsilane as the internal standard, multiplicities were determined by the DEPT 135 equivalence, chemical shifts were reported in parts par million (ppm, δ units). Coupling constants were reported in units of hertz (Hz) if applicable. Infrared (IR) spectra were obtained on Perkin-Elmer Paragon 1000 PC FT-IR. Infrared spectra recorded using a Ge ATR equipment. Low-resolution mass spectra (MS) were recorded on a Perkin-Elmer SCIEX API 3000 spectrometer. Exact mass were performed in CRMPO, Rennes, France. Melting points were determined in open capillary tubes and are uncorrected. Flash chromatography was performed on silica gel 60 (40-63 mesh). Thin layer chromatography (TLC) was carried out on Merck silica gel 60F254 precoated plates. Visualization was made with ultraviolet light. Reactions requivuiring anhydrous conditions were performed under argon. All solvents were freshly distilled under argon prior to use. Chemicals products were obtained from the following sources: Aldrich and Acros organics. Copper(I) thiophene-2-carboxylate was prepared from procedure described in the literature. [1]

[1] Allred, G. D. ; Liebeskind, L. S. *J. Am. Chem. Soc.* **1996**, *118*, 2748.

General procedure A : synthesis of 2-chloro-4-((het)aryl)pyrido[3,2-*d*]pyrimidine (I) *via* Suzuki cross-coupling reaction : To a Argon degassed solution of 2,4-dichloropyrido[3,2-*d*]pyrimidine **1** (100 mg, 0.5 mmol) in toluene (7mL) were successively added the desired (het)Ar boronic acid (1.05 equiv), potassium carbonate (1.5 equiv) and $Pd(PPh_3)_4$ (29 mg, 0.05 equiv). The reaction was heated at 100°C under vigorous stirring for the desired time. After complete disappearance of **1**, water (10 mL) was added. After extraction with CH_2Cl_2 (3 x 10 mL), the combined organic layers were dried over Mg SO_4 and the solvent were removed under reduced pressure. The crude material was purified by column chromatography to afford compound of type **I**.

General procedure B : synthesis of 2-chloro-4-((het)aryl)pyrido[3,2-*d*]pyrimidine (I) *via* Stille cross-coupling reaction : A solution of 2,4-dichloropyrido[3,2-*d*]pyrimidine **1** (100 mg, 0.5 mmol), the desired $(alk)_3Sn(het)Ar$ (1.05 equiv) and LiCl (2.8 equiv) in toluene (7 mL) was degassed by argon bubbling during 15 min. $Pd(PPh_3)_4$ (29 mg, 0.05 equiv) was added in one portion and the reaction mixture was immerged in a pre-heated oil bath (100°C) for the adapted time. After disappearance of **1**, the reaction mixture was cooled to room temperature and the volatiles were concentrated under reduced pressure. The crude residue was dissolved in CH_2Cl_2 (10 mL) and a saturated solution of KF (20 mL) was added. After filtration and extraction, the aqueous layer was extracted three times with CH_2Cl_2 (10 mL).The combined organic layers were dried over $MgSO_4$, and evaporated under reduced pressure. The crude material was purified by flash chromatography to afford compound compounds of type **I.**

General procedure C : synthesis of 2-(het)aryl-4-(isopropylsulfanyl)pyrido[3,2-*d*] pyrimidine (II) To a solution containing **2** (0.5 mmol) in a mixture of DME and water (10 mL, 3/1) were successively added the desired (het)Ar boronic acid (1.2 equiv), sodium carbonate (2.0 equiv) and $Pd(PPh_3)_4$ (0.05 equiv). The reaction was heated at 75°C under

vigorous stirring for the desired time. After complete disappearance of **2** water (10 mL) and CH_2Cl_2 (10 mL) were added. After extraction with CH_2Cl_2 (3 x 10 mL), the combined organic layers were dried over Mg SO_4 and the solvent were removed under reduced pressure. The crude material was purified by flash chromatography to afford compound of type **I**.

General procedure D : synthesis of compounds type (III) *via* a Suzuki cross-coupling reaction in the presence of CuTc:[2] A solution containing 2-(HetAr)-4-(isopropylsulfanyl)pyrido[3,2-*d*]pyrimidine **II** (0.35 mmol), the (het)aryl boronic acid (2.2 equiv), CuTC (2.2 equiv) and $Pd(PPh_3)_4$ (0.05 equiv) in dry THF (6 mL). was flushed with argon for 15 min. The brown suspension was stirred under argon at 50 °C for 3 h. After complete disappearance of starting material **II**, a saturated aqueous solution of $NaHCO_3$ was added, and the mixture was extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with saturated $NaHCO_3$ (2 x 10 mL). The solvent were evaporated under reduced pressure the residue was next purified by flash chromatography to give the attempted products of type **III**.

General procedure E : synthesis of compounds type (III) *via* a Stille cross-coupling reaction in the presence of CuBr.Me_2S (III):[3] To a solution of 2-(HetAr)-4-(isopropylsulfanyl)pyrido[3,2-*d*]pyrimidine **II** (0.35 mmol) **in** DME (6 mL) were successively added $(Alk)_3Sn(het)Ar$ (2.2 equiv), CuBr.Me_2S (2.2 equiv) and $Pd(PPh_3)_4$ (0.05 equiv). The reaction mixture was stirred under argon at reflux for the desired time. After cooling to room temperature, a 5% aqueous NH_4OH (10 mL) was added and the mixture was stirred for an additional 10 min. The reaction mixture was filtered through a pad of Celite, and the filtrate was extracted with dichloromethane (3 x 15 mL). The combined organic layers were washed with brine (10 mL), dried over $MgSO_4$, and evaporated under reduced pressure. After purification by flash chromatography compounds of **III** were isolated.

[2] Liebeskind, L. S. ; Srogl, J. *Org. Lett*. **2002**, *4*, 979.
[3] Alphonse, F.A.; Susenet, F.; Keromnes, A.; Lebret, B.; Guillaumet, G. *Org. Lett*. **2003**, 5, 803.

General procedure F: Compounds **III** were obtained *via* a Suzuki reaction from **I** (0.5 mmol) by modification of the procedure **A** and also using (het)Ar boronic acid (1.2 equiv), Na_2CO_3 (1.5 equiv), $Pd(PPh_3)_4$ (0.05 equiv) in a mixture of toluene and EtOH (10mL, 3/1) at 100°C.

General procedure G : Compounds **III** were obtained *via* a Stille reaction from **I** (0.5 mmol) by modification of the procedure **B** and also using $(Alk)_3Sn(Het)Ar$ (1.25 equiv), LiCl (2.8 equiv), $Pd(PPh_3)_4$ (0.05 equiv) in DMF (10mL, 3/1) at 90°C.

2-Chloro-4-phenyl-pyrido[3,2-*d*]pyrimidine (3). Compound **3** was obtained with $PhB(OH)_2$ following the Procedure **A** after 2h or following the procedure **B** after 12h and isolated after flash chromatography (PE:EtOAc, 95:5) as a white solid in a 84 or 83% yield respectively. Compound **3** was recristallized from dichloromethane/petroleum ether. Mp 140-141°C ; IR (cm^{-1}) ν 1523, 1465, 1279, 1135, 884, 811, 761, 682 ; ^1H NMR (250 MHz, $CDCl_3$) δ 7.53-7.59 (m, 3H, H_{Ph}), 7.83 (dd, 1H, *J* = 4.0 Hz, *J* = 8.7 Hz, H_7), 8.32 (dd, 1H, *J* = 1.5 Hz, *J* = 8.7 Hz, H_8), 8.38 (m, 2H, H_{Ph}), 9.10 (dd, 1H, *J* = 1.5 Hz, *J* = 4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 128.4 (2xCH), 128.6 (CH), 131.7 (CH), 132.0 (2xCH), 134.8 (Cq), 136.0 (CH), 137.6 (Cq), 149.6 (Cq), 151.9 (Cq), 157.5 (Cq), 169.8 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{13}H_8N_3{}^{35}Cl$: 241.0407, found: 241.0414.

2,4-diphenyl-pyrido[3,2-*d*]pyrimidine (4). Compound **4** was obtained following the procedure **A** with $PhB(OH)_2$ (2.1 equiv) after 1 h changing the catalytic system for $Pd(OAc)_2$ (0.05 equiv)/ PPh_3 (0.1 equiv). A flash chromatography (PE:EtOAc, 98:2) afforded **4** as a white solid. Mp 129-130°C ; IR (cm^{-1}) ν 1545, 1470, 1450, 1371, 1022, 812, 771, 709 ; ^1H NMR (250 MHz, $CDCl_3$) δ 7.52-7.60 (m, 6H, H_{Ph}), 7.74 (dd, 1H, *J* = 4.1 Hz, *J* = 8.6 Hz, H_7), 8.39 (dd, 1H, *J* = 1.5 Hz, *J* = 8.6 Hz, H_8), 8.46-8.50 (m, 2H, H_{Ph}), 8.70-8.74 (m, 2H, H_{Ph}), 9.00 (dd, 1H, *J* = 1.5 Hz, *J* = 4.1 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 127.7 (CH), 128.2 (2xCH), 128.6 (2xCH), 128.9 (2xCH), 130.7 (CH), 130.9 (CH), 131.8 (2xCH), 136.5 (Cq),

137.0 (CH), 137.7 (Cq), 137.9 (Cq), 148.2 (Cq), 150.8 (CH), 160.7 (Cq), 166.5 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{19}H_{13}N_3$: 283.1109, found: 283.1104.

2-Chloro-4-(-2-naphthyl)-pyrido[3,2-*d*]pyrimidine (5). Compound **5** was obtained with 2-naphthylB$(OH)_2$ following the Procedure **A** after 3h and isolated after flash chromatography ((PE:DCM, 6:4) as a yellow solid in a 72% yield. Mp 174-175°C ; IR (cm^{-1}) ν 1554, 1528, 1463, 1286, 1181, 1110, 899, 812, 742, 697 ; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.59-7.70 (m, 2H, H_{arom}), 8.00-8.14 (m, 4H, H_7, H_{arom}), 8.36-8.47 (m, 2H, H_8, H_{arom}), 9.00 (s, 1H, H_{arom}), 9.20 (dd, 1H, *J* = 1.5 Hz, *J* = 4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, DMSO-d_6) δ 126.7 (CH), 127.5 (CH), 127.6 (CH), 127.8 (CH), 128.2 (CH), 129.3 (CH), 129.6 (CH), 132.0 (Cq), 132.1 (Cq), 133.1 (CH), 134.1 (Cq), 135.8 (CH), 137.3 (Cq), 149.4 (Cq), 152.8 (CH), 156.0 (Cq), 168.7 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{17}H_{10}N_3{}^{35}Cl$: 291.0563, found: 291.0556.

2-Chloro-4-(3-methoxyphenyl)-pyrido[3,2-*d*]pyrimidine (6). Compound **6** was obtained with 3-OMePhB$(OH)_2$ following the Procedure **A** after 8h and isolated after flash chromatography (PE:EtOAc, 8:2) as a yellow solid in a 89% yield. Mp 119-120°C ; IR (cm^{-1}) ν 1524, 1468, 1441, 1250, 1029, 865, 779, 699 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 3.92 (s, 3H, OCH_3), 7.15 (dd, 1H, *J* = 1.7 Hz, *J* = 8.0 Hz, H_{arom}), 7.49 (t, 1H, *J* = 8.0 Hz, H_{arom}), 7.83 (dd, 1H, *J* = 4.0 Hz, *J* = 8.5 Hz, H_7), 7.96-8.01 (m, 2H, H_{arom}), 8.32 (dd, 1H, *J* = 1.7 Hz, *J* = 8.5 Hz, H_8), 9.10 (dd, 1H, *J* = 1.7 Hz, J = 4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.6 (CH_3), 117.1 (CH), 117.7 (CH), 124.7 (CH), 128.7 (CH), 129.5 (CH), 136.0 (Cq), 136.1 (CH), 137.8 (Cq), 149.7 (Cq), 152.0 (CH), 157.6 (Cq), 159.5 (Cq), 169.8 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{14}H_{10}N_3O^{35}Cl$: 271.0512, found: 271.0511.

2-chloro-4-(-3,4-methylenedioxyphenyl)-pyrido[3,2-*d*]pyrimidine (7). Compound **7** was obtained with 3,4-(OCH_2O)PhB$(OH)_2$ following the Procedure **A** after 24h and isolated after flash chromatography (DCM:MeOH, 99:1) as a yellow solid in a 75% yield. Mp 228-229°C ; IR (cm^{-1}) ν 1528, 1465, 1448, 1246, 1187, 1048, 860, 815, 698 ; ^{1}H NMR (250 MHz, $CDCl_3$)

δ 6.09 (s, 2H, CH_2), 7.00 (d, 1H, *J* = 8.2 Hz, H_{het}), 7.80 (dd, 1H, *J* = 4.0 Hz, *J* = 8.7 Hz, H_7), 8.09 (d, 1H, *J* = 1.7 Hz, H_{het}), 8.21 (dd, 1H, *J* = 1.7 Hz, *J* = 8.25 Hz, H_{het}), 8.29 (dd, 1H, *J* = 1.7 Hz, *J* = 8.75 Hz, H_8), 9.07 (dd, 1H, *J* = 1.7 Hz, *J* = 4.0 Hz, H_6) ; **^{13}C NMR** (62.5 MHz, $CDCl_3$) δ 101.9 (CH_2), 108.5 (CH), 112.2 (CH), 128.3 (CH), 128.6 (CH), 128.9 (Cq), 136.2 (CH), 137.7 (Cq), 147.9 (Cq), 149.7 (Cq), 151.2 (Cq), 151.5 (CH), 157.5 (Cq), 168.3 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{14}H_8N_3O_2{}^{35}Cl$: 285.0305, found: 285.0301.

2-Chloro-4-(-2-thienyl)-pyrido[3,2-*d*]pyrimidine (8). Compound **8** was obtained with 2-thienyl$SnBu_3$ following the Procedure **B** after 12h and isolated after flash chromatography (PE:EtOAc, 95:5) as a yellow solid in a 72% yield. Mp 150-151°C ; IR (cm^{-1}) ν 1525, 1505, 1469, 1436, 1421, 1284, 1190, 825, 705 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.27-7.29 (m, 1H, H_{het}), 7.78-7.83 (m, 2H, H_7, H_{het}), 8.24 (dd, 1H, *J* = 1.5 Hz, *J* = 8.5 Hz, H_8), 8.9 (d, 1H, *J* = 2.7 Hz, H_{het}), 9.07 (dd, 1H, *J* = 1.5 Hz, *J* = 4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 128.5 (CH), 128.9 (CH), 136.0 (CH), 136.1 (Cq), 136.2 (CH), 136.4 (CH), 137.7 (Cq), 149.2 (Cq), 151.1 (CH), 157.6 (Cq), 162.6 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{11}H_6N_3{}^{35}ClS$: 246.9971, found: 246.9977.

2-Chloro-4-(-2-furyl)-pyrido[3,2-*d*]pyrimidine (9). Compound **9** was obtained with 2-Furyl$SnBu_3$ following the Procedure **B** after 8h and isolated after flash chromatography (PE:EtOAc, 9:1) as a yellow solid in a 71% yield. Mp 195-196°C ; IR (cm^{-1}) ν 1569, 1521, 1465, 1432, 1280, 1158, 1036, 987, 826, 686 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.72 (dd, 1H, *J* = 1.7 Hz, *J* = 3.5 Hz, H_{het}), 7.78-7.83 (m, 2H, H_7, H_{het}), 8.23 (dd, 1H, *J* = 1.5 Hz, *J* = 8.5 Hz, H_8), 8.46 (d, 1H, *J* = 3.5 Hz, H_{het}), 9.04 (dd, 1H, *J* = 1.5 Hz, *J* = 4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 113.7 (CH), 125.0 (CH), 128.8 (CH), 135.7 (Cq), 136.0 (CH), 147.7 (CH), 148.4 (Cq), 148.8 (Cq), 151.6 (CH), 157.5 (Cq), 157.8 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{11}H_6N_3O{}^{35}Cl$: 231.0199, found: 231.0210.

4-(-2-benzenesulfonyl-1H-indolyl)-2-chloro-pyrido[3,2-*d*]pyrimidine (10). Compound **10** was obtained with 2-($SnMe_3$)-*N*-(SO_2Ph)indole following the Procedure **B** after 24h and isolated after flash chromatography (PE:EtOAc, 95:5) as a yellow solid in a 34% yield. Mp 201-202°C ; IR (cm^{-1}) ν 1530, 1438, 1365, 1173, 1100, 830, 749, 727 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.24-7.30 (m, 2H, H_{arom}), 7.37-7.60 (m, 5H, H_{arom}), 7.79-7.88 (m, 3H, H_{arom}), 8.10 (d, 1H, *J* = 8.5 Hz, H_7), 8.33 (dd, 1H, *J* = 1.6 Hz, *J* = 8.5 Hz, H_8), 9.08 (dd, 1H, *J* = 1.6 Hz, *J* = 4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 115.4 (CH), 119.0 (CH), 122.4 (CH), 124.5 (CH), 126.7 (2xCH), 127.2 (2xCH), 129.1 (2xCH), 129.8 (Cq), 133.9 (CH), 134.3 (Cq), 135.7 (CH) 137.8 (Cq), 138.2 (Cq), 138.8 (Cq), 148.7 (Cq), 152.6 (CH), 156.7 (Cq), 164.8 (Cq) ppm. HRMS (EI-MS): m/z calcd for $C_{21}H_{13}N_4O_2{}^{35}ClS$: 420.0447, found: 420.0433.

4-Phenyl-2-(-2-thienyl)-pyrido[3,2-*d*]pyrimidine (11). Compound **11** was obtained from **3** with 2-thienyl$B(OH)_2$ following the Procedure **F** after 4h or following the procedure **G** with 2-thienyl$SnBu_3$ after 3h and isolated after flash chromatography (PE:EtOAc, 98:2) as a yellow solid in a 98 or 87% yield respectively. Alternatively, compound **11** was obtained from **24** following the Procedure **D** with $PhB(OH)_2$ after 3h or following the procedure **E** with$PhSnBu_3$ after 10 min in a 90% or 89 yield respectively. Mp 164-165°C ; IR (cm^{-1}) ν 1541, 1451, 1423, 1371, 1052, 843, 804, 732, 704 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.17 (dd, 1H, *J* = 3.7 Hz, *J* =5.0 Hz, H_{het}), 7.51 (dd, 1H, *J* = 1.2 Hz, *J* = 5.0 Hz, H_{het}), 7.55-7.58 (m, 3H, H_{Ph}), 7.67 (dd, 1H, *J* = 4.0 Hz, *J* = 8.5 Hz, H_7), 8.20 (dd, 1H, *J* = 1.2 Hz, *J* = 3.7 Hz, H_{het}), 8.28 (dd, 1H, *J* = 1.5 Hz, *J* = 8.5 Hz, H_8), 8.43-8.46 (m, 2H, H_{Ph}), 8.92 (dd, 1H, *J* = 1.5 Hz, J = 4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 127.9 (CH), 128.2 (2xCH), 128.5 (CH), 130.0 (CH), 130.6 (CH), 130.9 (CH), 131.8 (2xCH), 136.1 (Cq), 136.5 (CH), 137.7 (Cq), 143.7 (Cq), 148.2 (Cq), 150.4 (CH), 157.8 (Cq), 166.6 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{17}H_{11}N_3S$: 289.0674, found: 289.0684.

2-(3,4-methylenedioxyphenyl)-4-phenyl-pyrido[3,2-*d*]pyrimidine (12). Compound **12** was obtained from **3** with 3,4-(OCH_2O)$PhB(OH)_2$ following the Procedure **F** after 5h and isolated after flash chromatography (PE:EtOAc, 98:2) as a yellow solid in a 98% yield. Mp 162-163°C ; IR (cm^{-1}) ν 1543, 1503, 1452, 1326, 1255, 1028, 822, 803, 740, 689 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.07 (s, 2H, CH_2), 6.97 (d, 1H, *J* = 8.2 Hz, H_{het}), 7.58-7.60 (m, 3H, H_{arom}), 7.75 (dd, 1H, *J* = 4.0 Hz, *J* = 8.5 Hz, H_7), 8.21 (d, 1H, *J* = 1.7 Hz, H_{het}), 8.33-8.38 (m, 2H, H_8, H_{het}), 8.43-8.47 (m, 2H, H_{arom}), 8.99 (dd, 1H, *J* = 1.5 Hz, *J* = 4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 101.6 (CH_2), 108.4 (CH), 109.0 (CH), 124.0 (CH), 127.8 (CH), 128.2 (2xCH), 130.8 (CH), 131.8 (2xCH), 132.2 (Cq), 136.6 (Cq), 136.9 (CH), 137.8 (Cq), 148.2 (Cq), 148.3 (Cq), 150.2 (Cq), 150.5 (CH), 160.2 (Cq), 166.4 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{20}H_{13}N_3O_2$: 327.10078, found: 327.0998.

2-(-2-Naphthyl)-4-phenyl-pyrido[3,2-*d*]pyrimidine (13). Compound **13** was obtained from **3** with 3-naphthyl$B(OH)_2$ following the Procedure **G** after 5h and isolated after flash chromatography (PE:EtOAc, 9:1) as a yellow solid in a 98% yield. Mp 170-171°C ; IR (cm^{-1}) ν 1542, 1463, 1447, 1385, 1326, 916, 824, 772, 694 ; ^{1}H NMR (250 MHz, DMSO-d_6) δ 7.61-7.67 (m, 5H, H_{arom}), 8.01-8.08 (m, 2H, H_{arom}), 8.13 (d, 1H, *J* = 8.5 Hz, H_7), 8.18-8.22 (m, 1H, H_{arom}), 8.47-8.50 (m, 2H, H_{arom}),. 8.58 (d, 1H, *J* = 8.5 Hz, H_8), 8.75 (d, 1H, *J* = 8.7 Hz, H_{arom}), 9.13 (d, 1H, *J* = 2.7 Hz, H_6), 9.24 (m, 1H, H_{arom}) ; ^{13}C NMR (62.5 MHz, DMSO-*d6*) δ 125.0 (CH), 126.5 (CH), 127.4 (CH), 127.5 (CH), 127.9 (2xCH), 128.2 (CH), 128.5 (CH), 128.8 (CH), 129.1 (CH), 130.6 (CH), 131.5 (2xCH), 132.7 (Cq), 134.2 (Cq), 134.4 (Cq), 136.0 (Cq), 136.6 (CH), 137.1 (Cq), 147.6 (Cq), 151.7 (CH), 159.3 (Cq), 165.9 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{23}H_{15}N_3$: 333.1266, found: 333.1254.

2-(-3-methoxyphenyl)-4-phenyl-pyrido[3,2-*d*]pyrimidine (14). Compound **14** was obtained from **3** with 3-OMe$PhB(OH)_2$ following the Procedure **F** after 4h and isolated after flash chromatography (PE:MeOH, 99:1) as a yellow solid in a 89% yield. Alternatively, compound

14 was obtained from **23** following the Procedure **D** with $PhB(OH)_2$ after 1h or following the procedure **E** with $PhSnBu_3$ after 10 min in a 86 and 85 %yield respectively. Compound **14** was recristallized from dichloromethane/petroleum ether. Mp 104-105°C ; IR (cm^{-1}) ν 1600, 1541, 1467, 1447, 1340, 1253, 1038, 831, 737, 694 ; ^1H NMR (250 MHz, $CDCl_3$) δ 3.94 (s, 3H, OCH_3), 7.07 (d, 1H, *J* = 2.8 Hz, H_{arom}), 7.47 (t, 1H, *J* = 8.0 Hz, H_{arom}), 7.57-7.60 (m, 3H, H_{Ph}), 7.74 (dd, 1H, *J* = 4.0 Hz, *J* = 8.7 Hz, H_7), 8.27-8.34 (m, 2H, H_{arom}), 8.39 (dd, 1H, *J* = 1.7 Hz, *J*= 8.7 Hz, H_8), 8.46-8.50 (m, 2H, H_{Ph}), 9.01 (dd, 1H, *J* = 1.7 Hz, 4 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 55.6 (CH_3), 117.1 (CH), 113.7 (CH), 117.2 (CH), 121.6 (CH), 127.8 (CH), 128.3 (2xCH), 129.7 (CH), 130.8 (CH), 131.9 (2xCH), 136.6 (Cq), 137.1 (CH), 138.0 (Cq), 139.2 (Cq), 148.2 (Cq), 150.9 (CH), 160.1 (Cq), 160.6 (Cq), 166.6 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{20}H_{15}N_3O$: 313.1215, found: 313.1219.

4-(3,4-methylenedioxyphenyl)-2-phenyl-pyrido[3,2-*d*]pyrimidine (15). Compound **15** was obtained from **7** with $PhB(OH)_2$ following the Procedure **F** after 5h and isolated after flash chromatography (PE:EtOAc, 99:1) as a yellow solid in a 89% yield. Alternatively, compound **15** was obtained following the Procedure **D** from **22** with 3,4-$(OCH_2O)PhB(OH)_2$ after 30 min in a 99% yield. Mp 141-142°C ; IR (cm^{-1}) ν 1533, 1469, 1442, 1325, 1255, 1037, 930, 816, 710 ; ^1H NMR (250 MHz, $CDCl_3$) δ 6.09 (s, 2H, CH_2), 7.03 (d, 1H, *J* = 8.2 Hz, H_{het}), 7.53-7.58 (m, 3H, H_{arom}), 7.76 (dd, 1H, *J* = 4.0 Hz, *J* = 8.7 Hz, H_7), 8.15 (d, 1H, *J* = 1.7 Hz, H_{het}), 8.26 (dd, 1H, *J* = 1.7 Hz, *J*= 8.2 Hz, H_{het}), 8.39 (dd, 1H, *J* = 1.7 Hz, *J* = 8.7 Hz Hz, H_8), 8.68-8.72 (m, 2H, H_{arom}), 9.01 (dd, 1H, *J* = 1.7 Hz, *J* = 4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 161.6 (CH_2), 108.3 (CH), 112.0 (CH), 127.5 (CH), 127.7 (CH), 128.7 (2xCH), 128.9 (2xCH), 130.6 (Cq), 130.9 (CH), 137.1 (CH), 137.8 (Cq), 137.9 (Cq), 147.7 (Cq), 148.3 (Cq), 150.2 (Cq), 150.6 (CH), 160.6 (Cq), 165.2 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{20}H_{13}N_3O_2$: 327.1007, found: 327.0998.

2-phenyl-4-(-2-thienyl)-pyrido[3,2-*d*]pyrimidine (16). Compound **16** was obtained from **8** with $PhB(OH)_2$ following the Procedure **F** after 4h or following the procedure **G** after 16h and isolated after flash chromatography (PE:EtOAc, 98:2) as a yellow solid in a 94 or 67% yield respectively. Alternatively, compound **16** was obtained following the Procedure **E** from **22** with 2-thienyl$SnBu_3$ after 10 min in a 95% yield. Mp 124-125°C ; IR (cm^{-1}) ν 1622, 1476, 1402, 1343, 1149, 1056, 962, 790, 711 ; ^1H NMR (250 MHz, $CDCl_3$) δ 7.22-7.25 (m, 1H, H_{het}), 7.51-7.56 (m, 3H, H_{Ph}), 7.64-7.69 (m, 2H, H_{het}, H_7), 8.26 (dd, 1H, *J* = 1.75, 8.5 Hz, H_8), 8.64-8.68 (m, 2H, H_{Ph}), 8.92-8.94 (m, 2H, H_{het}, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 127.9 (CH), 128.3 (CH), 128.7 (2xCH), 128.8 (2xCH), 130.9 (CH), 133.6 (CH), 134.9 (CH), 136.7 (Cq), 136.9 (CH), 137.6 (Cq), 140.2 (Cq), 147.9 (Cq), 150.3 (CH), 159.5 (Cq), 160.7 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{17}H_{11}N_3S$: 289.0674, found: 289.0684.

4-(-2-Naphthyl)-2-phenyl-pyrido[3,2-*d*]pyrimidine (17). Compound **17** was obtained from **5** with $PhB(OH)_2$ following the Procedure **F** after 6h and isolated after flash chromatography (PE:EtOAc, 99:1) as a yellow solid in a 96% yield. Alternatively, compound **17** was obtained following the Procedure **D** from **22** with 2-naphthyl$B(OH)_2$ after 1h in a 91% yield. Mp 153-154°C ; IR (cm^{-1}) ν 1540, 1479, 1450, 1329, 1022, 905, 822, 755, 717 ; ^1H NMR (250 MHz, DMSO-*d6*) δ 7.61-7.70 (m, 5H, H_{arom}), 8.03-8.08 (m, 2H, H_{arom}), 8.12-8.18 (m, 2H, H_7, H_{arom}), 8.52-8.57 (m, 2H, H_8, H_{arom}), 8.67-8.71 (m, 2H, H_{arom}), 9.12 (s, 1H, H_{arom}), 9.17 (dd, 1H, *J* = 1.7 Hz, *J* = 4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, DMSO-*d6*) δ 126.5 (CH), 127.3 (CH), 127.5 (CH), 127.7 (CH), 127.9 (CH), 128.3 (CH), 128.8 (2xCH), 128.9 (2xCH), 129.1 (CH), 131.1 (CH), 132.2 (Cq), 132.5 (CH), 133.5 (Cq), 133.8 (Cq), 136.7 (CH), 137.0 (Cq), 137.3 (Cq), 147.7 (Cq), 151.9 (CH), 159.4 (Cq), 165.5 (Cq) ppm. HRMS (EI-MS): m/z calcd for $C_{23}H_{15}N_3$: 333.1266, found: 333.1254.

2-(-2-Furyl)-4-phenyl-pyrido[3,2-*d*]pyrimidine (18). Compound **18** was obtained from **3** with 2-furyl$SnBu_3$ following the Procedure **G** after 1h and isolated after flash chromatography

(PE:EtOAc, 95:5) as a sandy solid in a 88% yield. Mp 146-147°C ; IR (cm^{-1}) ν 1584, 1542, 1487, 1469, 1334, 1010, 813, 762, 692 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.64 (dd, 1H, *J* = 1.5 Hz, J = 3.2 Hz, H_{het}), 7.58-7.60 (m, 4H, H_{Ph}, H_{het}), 7.72 (s, 1H, H_{het}), 7.78 (dd, 1H, *J* = 4.0 Hz, J = 8.7 Hz, H_7), 8.39-8.47 (m, 3H, H_8, H_{Ph}), 9.01 (dd, 1H, *J* = 1.5 Hz, J = 4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 112.5 (CH), 115.2 (CH), 128.1 (CH), 128.2 (2xCH), 130.9 (CH), 131.8 (2xCH), 136.1 (Cq), 136.7 (CH), 137.7 (Cq), 145.8 (CH), 148.0 (Cq), 150.7 (CH), 152.5 (Cq), 154.0 (Cq), 167.3 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{17}H_{11}N_3O$: 273.0902, found: 273.0901.

4-Phenyl-2-(-2-pyridyl)-pyrido[3,2-*d*]pyrimidine (19). Compound **19** was obtained from **3** with 2-$PySnBu_3$ following the Procedure **G** after 14h and isolated after flash chromatography (PE:EtOAc:Et_3N, 5:4:1) as a yellow solid in a 77% yield. Mp 145-146°C ; IR (cm^{-1}) ν 1541, 1472, 1450, 1378, 1336, 811, 771, 746, 697 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.42-7.47 (m, 1H, H_{Pyr}), 7.59-7.61 (m, 3H, H_{Ph}), 7.82 (dd, 1H, *J* = 4.0 Hz, J = 8.5 Hz, H_7), 7.89-7.96 (m, 1H, H_{Pyr}), 8.47-8.51 (m, 2H, H_{Ph}), 8.66 (dd, 1H, *J* = 1.7 Hz, *J* = 8.5 Hz, H_8), 8.84 (d, 1H, *J* = 7.5 Hz, H_{Pyr}), 8.94 (d, 1H, *J* = 3.7 Hz, H_{Pyr}), 9.09 (dd, 1H, *J* = 1.7 Hz, *J* = 4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 124.7 (CH), 125.0 (CH), 128.0 (CH), 128.3 (2xCH), 130.9 (CH), 131.9 (2xCH), 136.2 (Cq), 137.1 (CH), 137.8 (CH), 138.2 (Cq), 148.5 (Cq), 150.4 (CH), 151.8 (Cq), 154.9 (CH), 159.6 (Cq), 167.1 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{18}H_{12}N_4$: 284.1062, found: 284.1069.

4-(-2-Furyl)-2-phenyl-pyrido[3,2-*d*]pyrimidine (20). Compound **20** was obtained from **9** with $PhB(OH)_2$ following the Procedure **G** after 24h and isolated after flash chromatography (PE:EtOAc, 95:5) as a tan solid in a 52% yield. Alternatively, compound **20** was obtained following the Procedure **E** from **22** with 2-furyl$SnBu_3$ after 10 min in a 89% yield. Mp 127-128°C ; IR (cm^{-1}) ν 1572, 1540, 1473, 1454, 1330, 1022, 807, 762, 712 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 6.73 (dd, 1H, *J* = 1.5 Hz, J = 3.2 Hz, H_{het}), 7.54-7.56 (m, 3H, H_{Ph}), 7.78 (dd, 1H, *J* =

4.0 Hz, J = 8.7 Hz, H_7), 7.86 (s, 1H, H_{het}), 8.35 (d, 1H, *J* = 1.5 Hz, H_{het}), 8.35-8.40 (m, 1H, H_8), 8.68-8.71 (m, 2H, H_{Ph}), 9.01 (dd, 1H, *J* = 1.5 Hz, *J* =4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 113.1 (CH), 122.5 (CH), 128.0 (CH), 128.8 (2xCH), 129.0 (2xCH), 131.0 (CH), 136.2 (Cq), 137.1 (CH), 137.8 (Cq), 146.4 (CH), 147.7 (Cq), 150.0 (Cq), 150.7 (CH), 155.5 (Cq), 161.2 (Cq) ; HRMS (EI-MS): m/z calcd for $C_{17}H_{11}N_3O$: 273.0902, found: 273.0901.

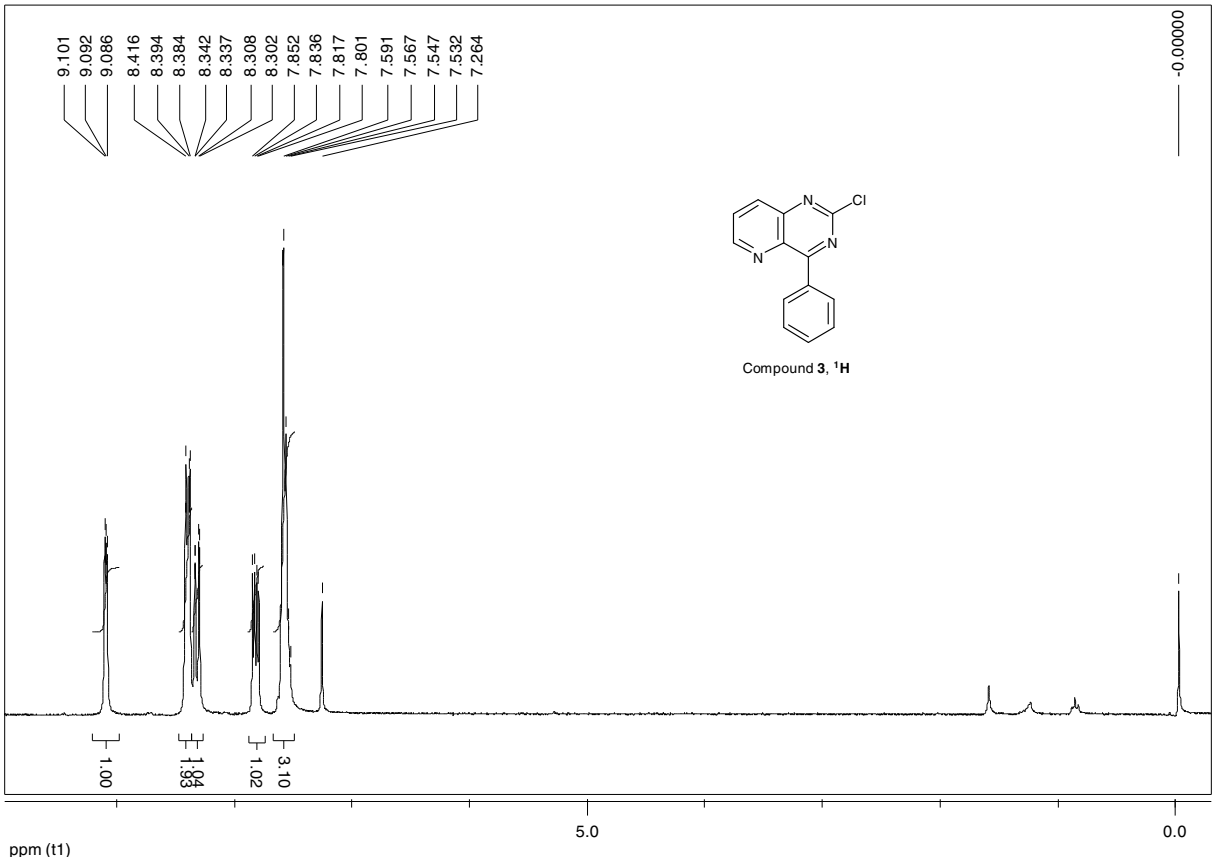
4-(-2-Benzenesulfonyl-1H-indolyl)-2-phenyl-pyrido[3,2-*d*]pyrimidine (21). Compound **21** was obtained from **10** with $PhB(OH)_2$ following the Procedure **G** after 24h and isolated after flash chromatography (PE:EtOAc, 95:5) as a pale brown solid in a 58% yield. Alternatively, compound **21** was obtained following the Procedure **E** from **22** with 2-($SnBu_3$)-*N*-SO_2Ph)indole after 30 min in a 75% yield. Mp 202-203°C ; IR (cm^{-1}) ν 1545, 1444, 1368, 1249, 1178, 1091, 808, 749, 710 ; ^{1}H NMR (250 MHz, $CDCl_3$) δ 7.16 (s, 1H, H_{indol}), 7.29-7.41 (m, 4H, H_{arom}), 7.48-7.61 (m, 5H, H_{Ph}), 7.78 (m, 3H, H_{Ph}), 8.16 (d, 1H, *J* = 8.5 Hz, H_7), 8.46 (dd, 1H, *J* = 1.5 Hz, *J* = 8.5 Hz, H_8), 8.61-8.64 (m, 2H, H_{Ph}), 9.03 (dd, 1H, *J* = 1.5 Hz, *J* = 4.0 Hz, H_6) ; ^{13}C NMR (62.5 MHz, $CDCl_3$) δ 115.5 (CH), 116.7 (CH), 122.1 (CH), 124.3 (CH), 126.0 (CH), 127.2 (2xCH), 128.4 (CH), 128.8 (2xCH), 129.0 (2xCH), 129.1 (2xCH), 130.1 (Cq), 131.2 (CH), 133.7 (CH), 136.0 (Cq), 136.7 (CH), 137.3 (Cq), 137.8 (Cq), 138.0 (Cq), 139.2 (Cq), 147.1 (Cq), 151.7 (CH), 160.5 (Cq), 162.6 (Cq) ppm. HRMS (EI-MS): m/z calcd for $C_{27}H_{18}N_4O_2S$: 462.1150, found: 462.1159.

4-isopropylsulfanyl-2-phenyl-pyrido[3,2-*d*]pyrimidine (22). Compound **22** was obtained with $PhB(OH)_2$ following the Procedure **C** after 1h and isolated after flash chromatography (DCM:Pentane, 6:4) as a beige solid in a 90% yield . Mp 110-110°C ; IR (cm^{-1}) ν 1536, 1466, 1446, 1380, 1326, 1242, 1006, 858, 711 ; **^{1}H RMN** (250 MHZ, $CDCl_3$) δ 1.60 (d, 6H, *J* = 6.9 Hz, C**H**$_3$), 4.33-4.44 (m, 1H, *J* = 6.9 Hz, C**H**), 7.49-7.55 (m, 3H, $\mathbf{H}_{Ph}$), 7.72 (dd, 1H, *J* = 4.1, 8.5 Hz, $\mathbf{H}_7$), 8.26 (dd, 1H, *J* = 1.6, 8.5 Hz, $\mathbf{H}_8$), 8.59-8.63 (m, 2H, $\mathbf{H}_{Ph}$), 8.85 (dd, 1H, *J* = 1.6, 4.1 Hz, $\mathbf{H}_6$) ; **^{13}C RMN** (62.5 MHZ, $CDCl_3$) δ 22.8 (2xCH_3), 34.8 (CH), 128.5 (CH),

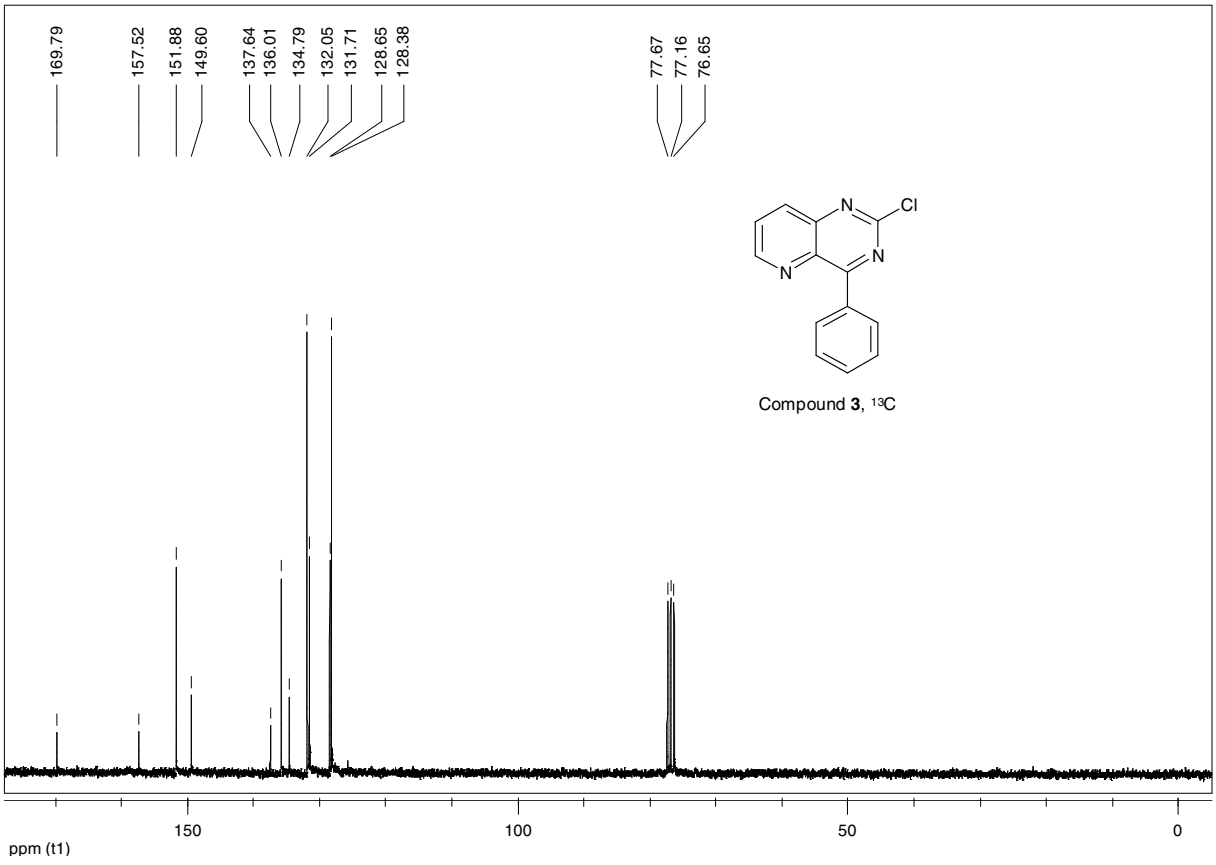
128.7 (2xCH), 128.8 (2xCH), 131.0 (CH), 136.9 (CH), 137.7 (Cq), 138.3 (Cq), 144.4 (Cq), 149.6 (CH), 159.7 (Cq), 174.3 (Cq) ppm. HRMS (EI-MS): m/z calcd for $C_{16}H_{15}N_3S$: 282.1060, found: 282.1060.

4-isopropylsulfanyl-2-(3-methoxyphenyl)-pyrido[3,2-*d*]pyrimidine (23). Compound **23** was obtained with 3-OMePhB$(OH)_2$ following the Procedure **C** after 3h and isolated after flash chromatography (PE:DCM, 2:8) as a yellow solid in a 81% yield . Mp 115-116°C ; IR (cm^{-1}) ν 1596, 1536, 1434, 1318, 1244, 1038, 1006, 820, 732 ; **RMN ^{1}H** (250 MHZ, $CDCl_3$) δ 1.61 (d, 6H, *J* = 6.6 Hz, C**H**$_3$), 3.95 (s, 3H, OC**H**$_3$), 4.33-4.44 (m, 1H, *J* = 6.6 Hz, C**H**), 7.06 (dd, 1H, *J* = 2.5, 8.2 Hz, **H**$_{arom}$), 7.45 (t, 1H, *J* = 8.2 Hz, **H**$_{arom}$), 7.74 (dd, 1H, *J* = 4.1, 8.5 Hz, **H**$_7$), 8.18-8.31 (m, 3H, **H**$_8$, **H**$_{arom}$), 8.86 (dd, 1H, *J* = 1.6, 4.1 Hz, **H**$_6$) ; **RMN ^{13}C** (62.5 MHZ, $CDCl_3$) δ 22.7 (2xCH_3), 34.8 (CH), 55.4 (OCH_3), 113.6 (CH), 117.1 (CH), 121.4 (CH), 128.4 (Cq), 129.6 (CH), 136.9 (CH), 138.3 (Cq), 139.0 (Cq), 144.3 (Cq), 149.6 (CH), 159.3 (Cq), 159.9 (Cq), 174.2 (Cq) ppm. HRMS (EI-MS): m/z calcd for $C_{27}H_{18}N_4O_2S$: 311.1092, found: 311.1087.

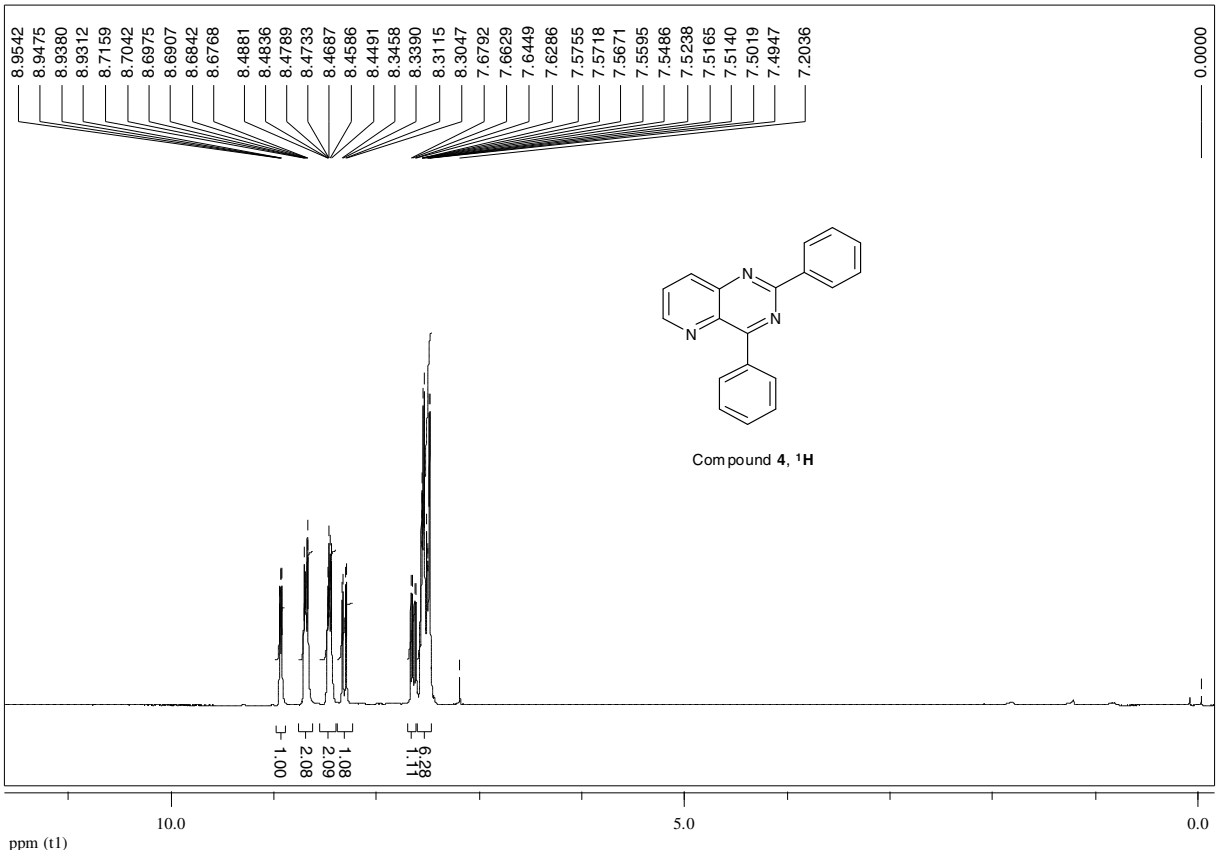
4-isopropylsulfanyl-2-(2-thienyl)-pyrido[3,2-*d*]pyrimidine (24). Compound **24** was obtained with 2-thienylPhB$(OH)_2$ following the Procedure **C** after 3h and isolated after flash chromatography (PE:EtOAc, 95:5) as a beige solid in a 73% yield . Mp 118-119°C ; IR (cm^{-1}) ν 1646, 1534, 1439, 1372, 1322, 1236, 1007, 873, 729 ; **RMN ^{1}H** (250 MHZ, $CDCl_3$) δ 1.58 (d, 6H, *J* = 6.3 Hz, C**H**$_3$), 4.20-4.36 (m, 1H, *J* = 6.3 Hz, C**H**), 7.16 (dd, 1H, *J* = 3.8, 5.0 Hz, **H**$_{het}$), 7.50 (dd, 1H, *J* = 1.3, 5.0 Hz, **H**$_{het}$), 7.67 (dd, 1H, *J* = 4.1, 8.5 Hz, **H**$_7$), 8.08 (dd, 1H, *J* = 1.3, 3.8 Hz, **H**$_{het}$), 8.17 (dd, 1H, *J* = 1.6, 8.5 Hz, **H**$_8$), 8.79 (dd, 1H, *J* = 1.6, 4.1 Hz, **H**$_6$) ; **RMN ^{13}C** (62.5 MHZ, $CDCl_3$) δ: 22.7 (2xCH_3), 35.0 (CH), 128.4 (CH), 128.5 (CH), 129.7 (CH), 130.6 (CH), 136.4 (CH), 138.0 (Cq), 143.6 (Cq), 144.4 (Cq), 149.1 (CH), 156.5 (Cq), 174.3 (Cq) ppm. HRMS (EI-MS): m/z calcd for $C_{14}H_{13}N_3S_2$: 288.0629, found: 288.0633.



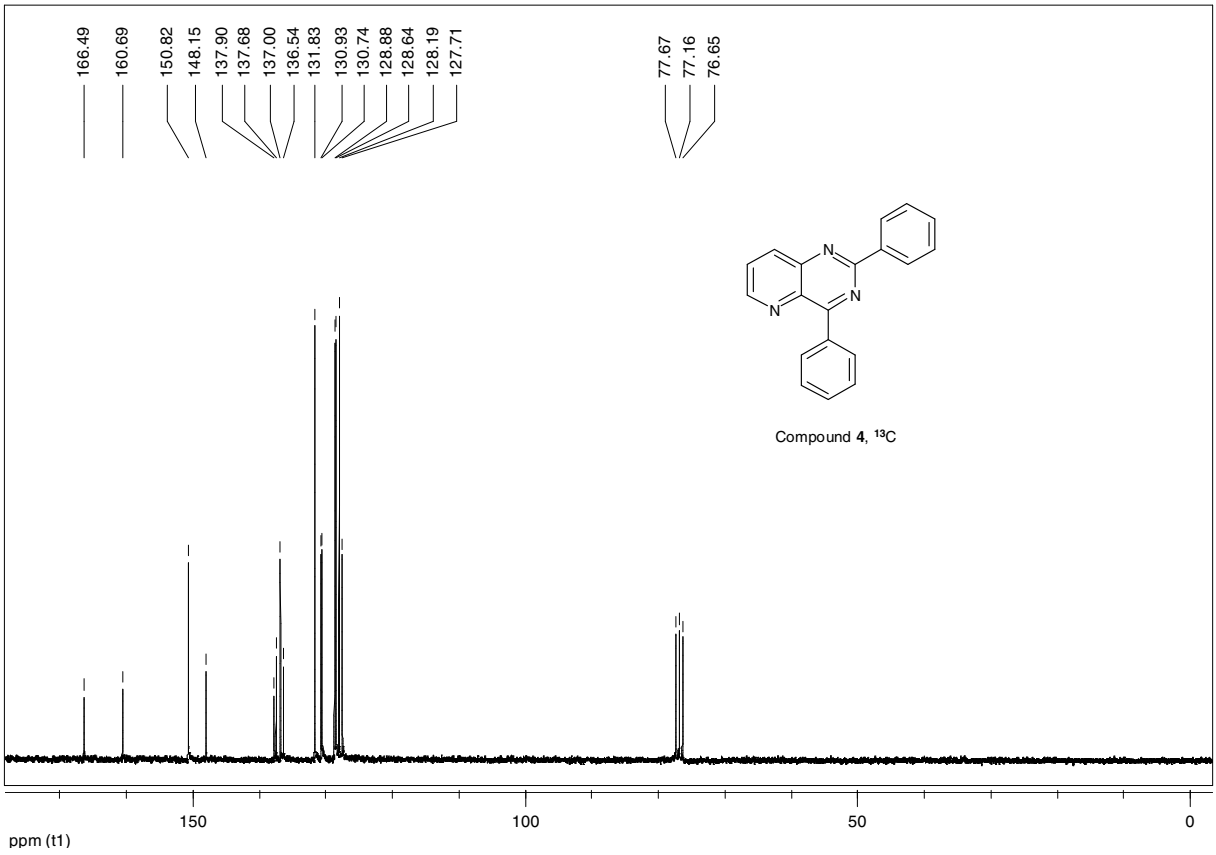
Compound **3**, **^{1}H**



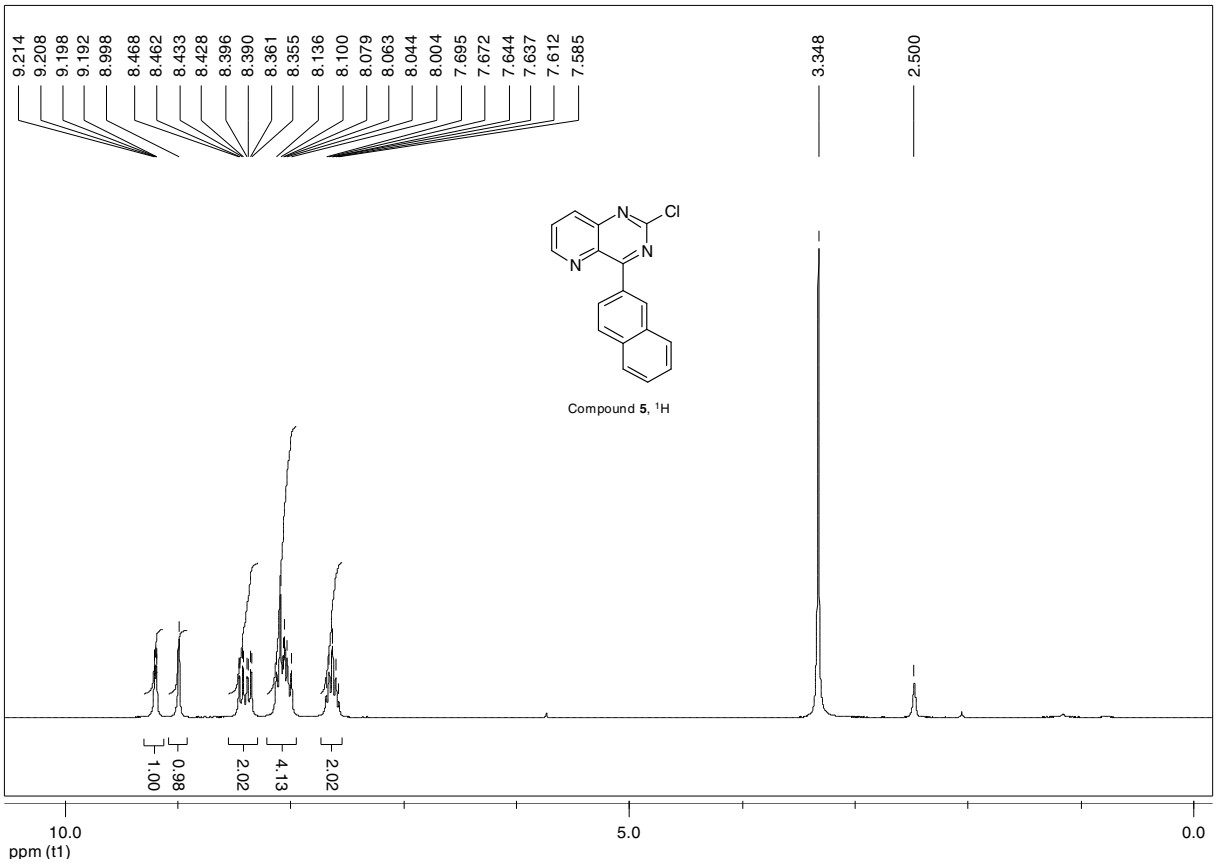
Compound **3**, ^{13}C



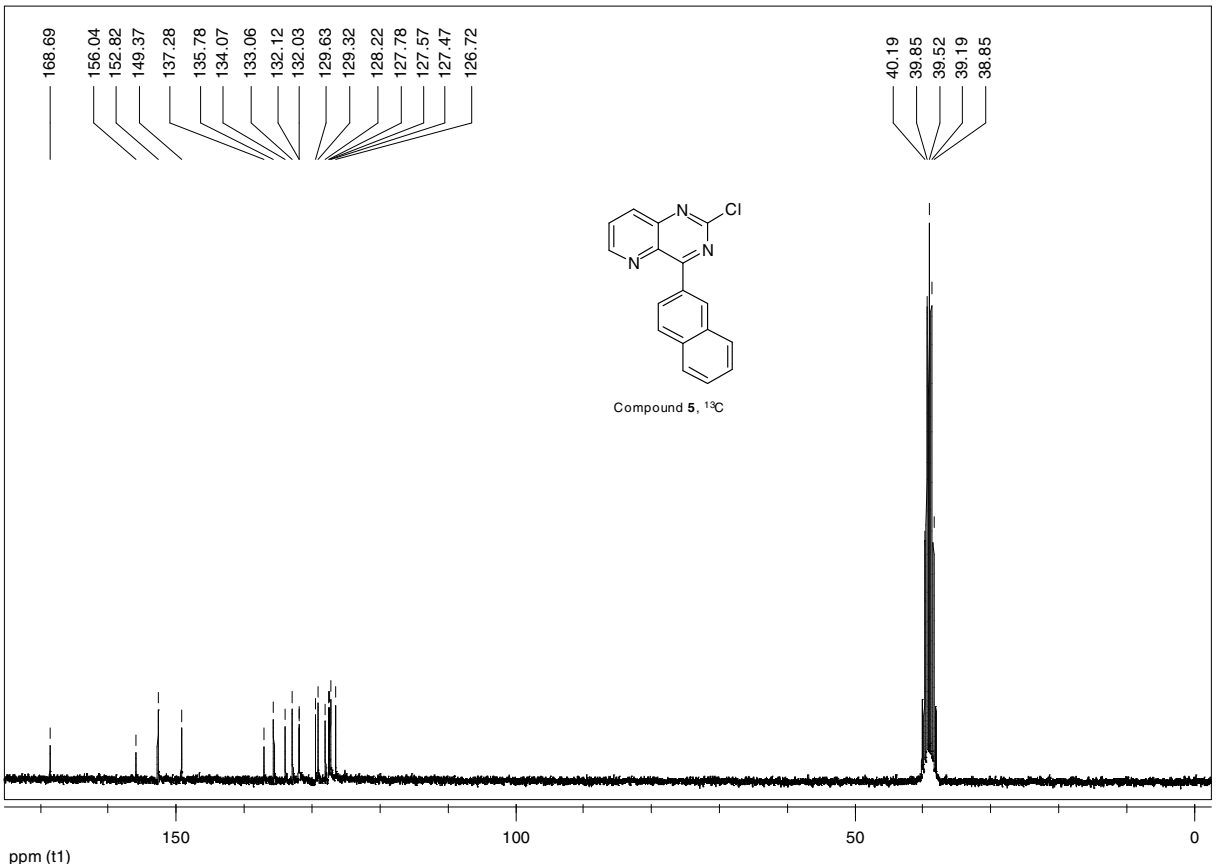
Compound **4**, ^{1}**H**



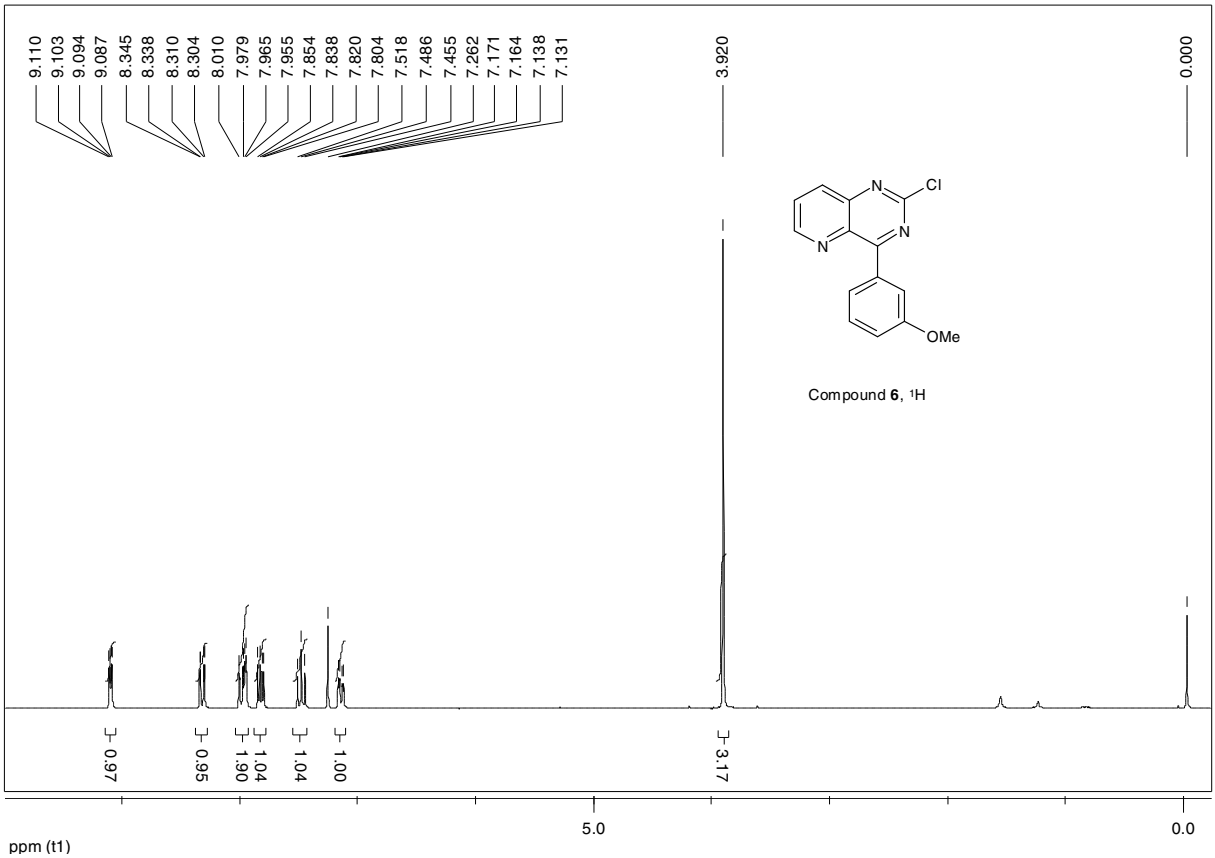
Compound **4**, ^{13}C



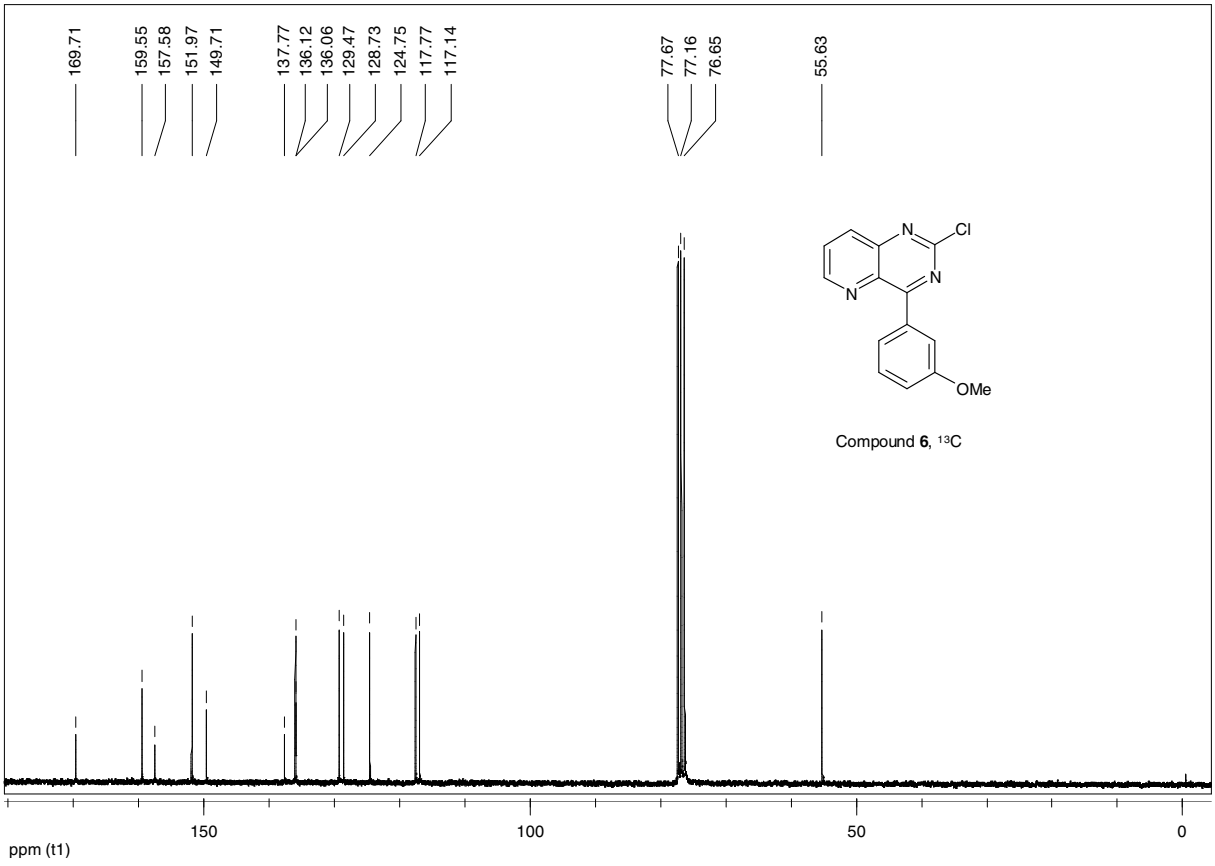
Compound **5**, ^{1}H



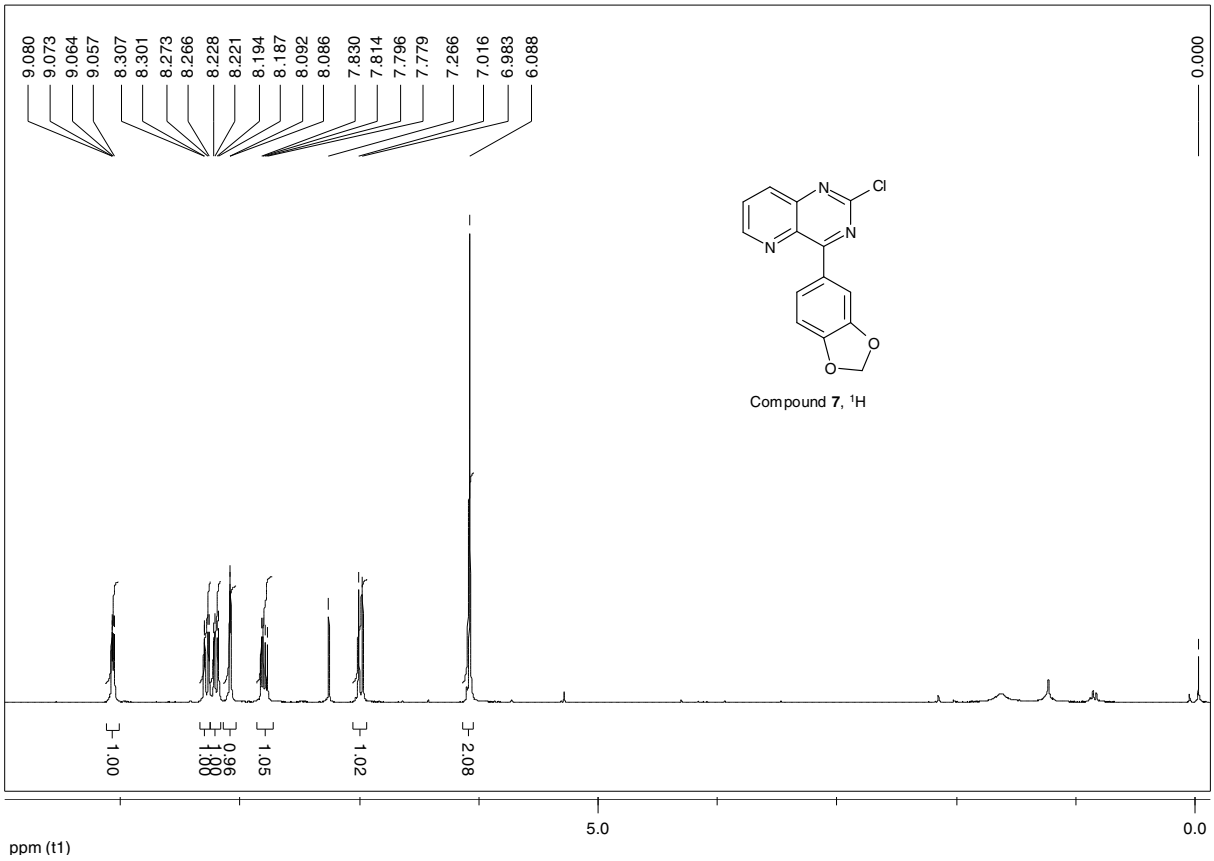
Compound **5**, ^{13}C



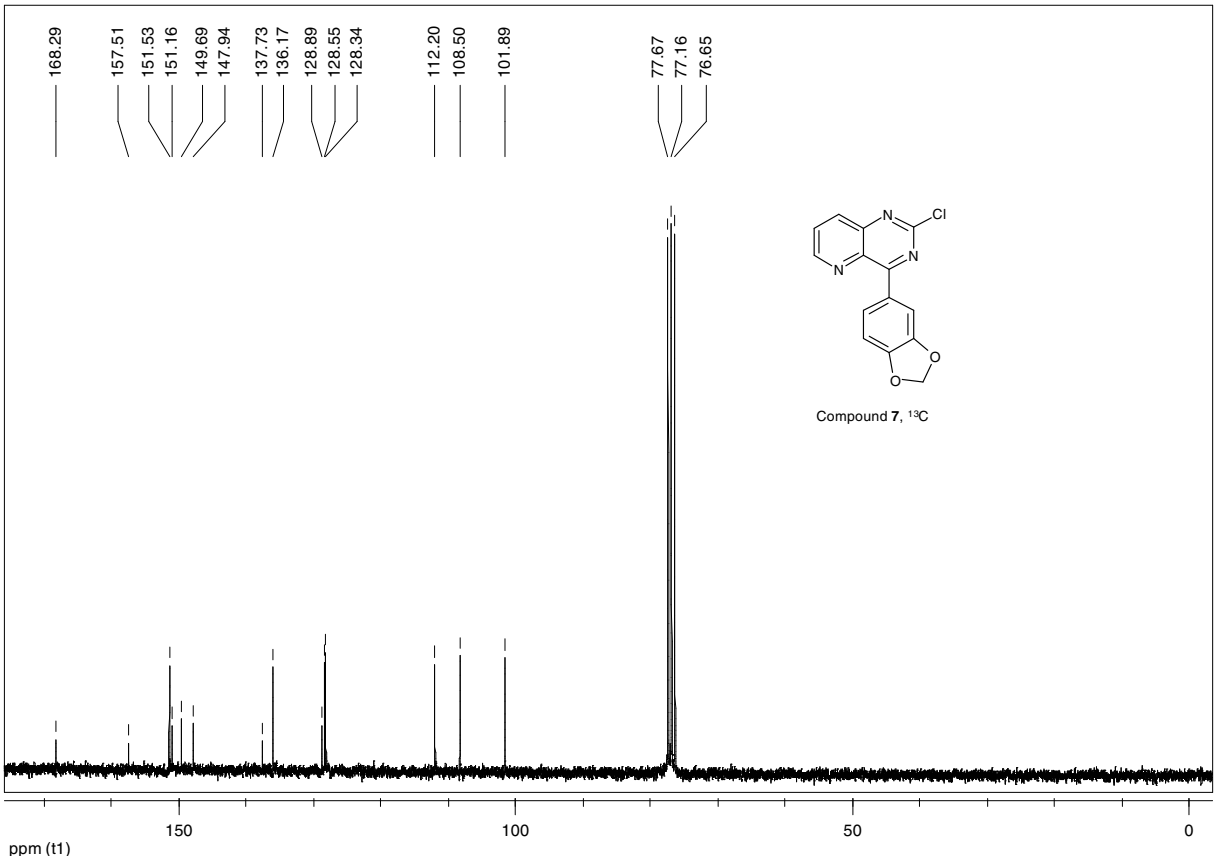
Compound **6**, ^{1}H



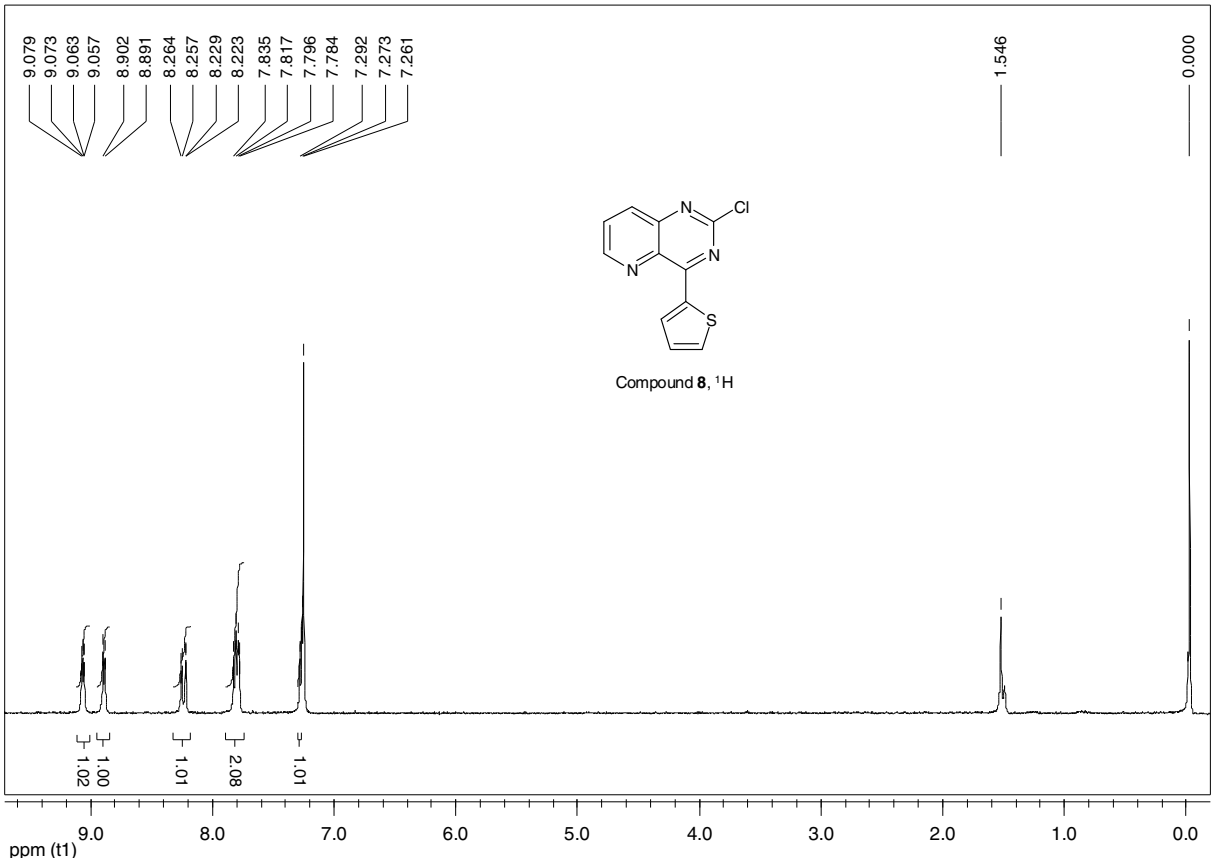
Compound **6**, ^{13}C



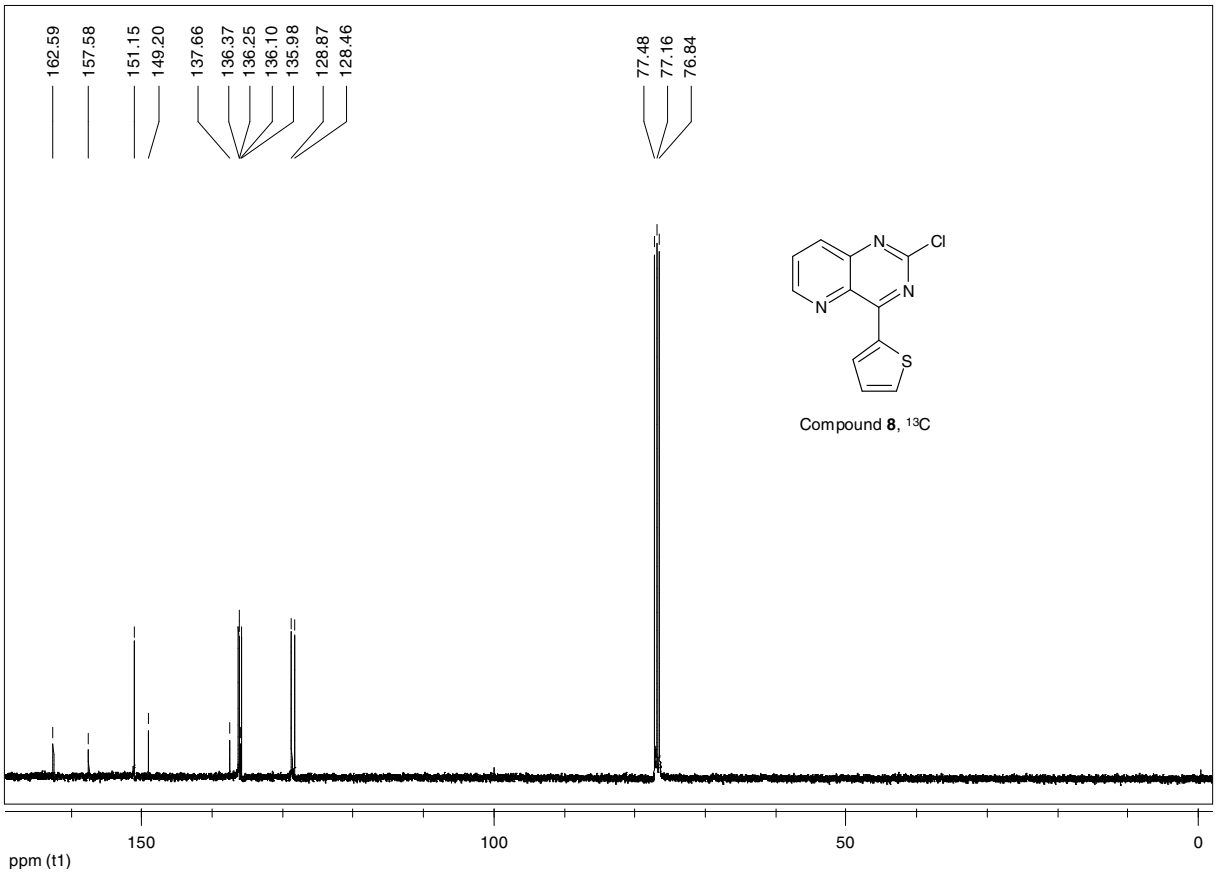
Compound **7**, ^{1}H



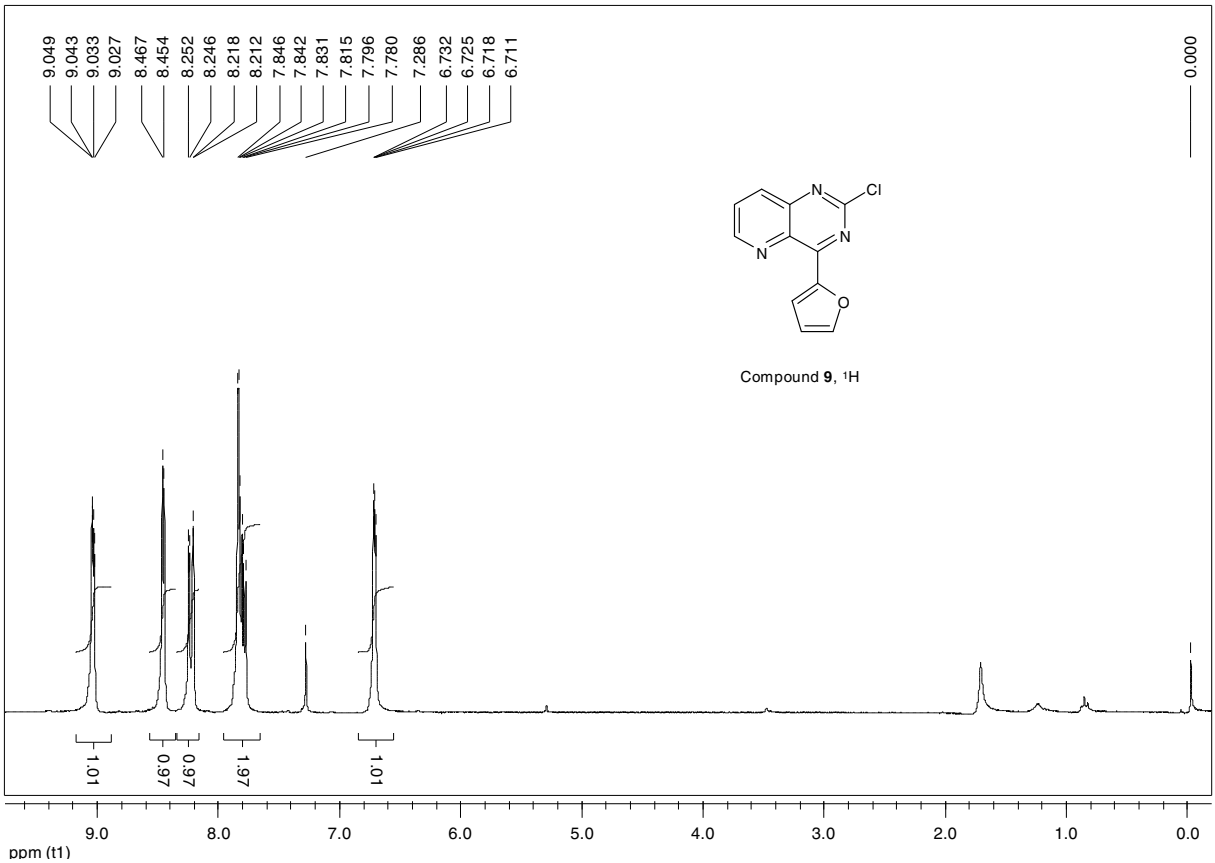
Compound **7**, ^{13}C



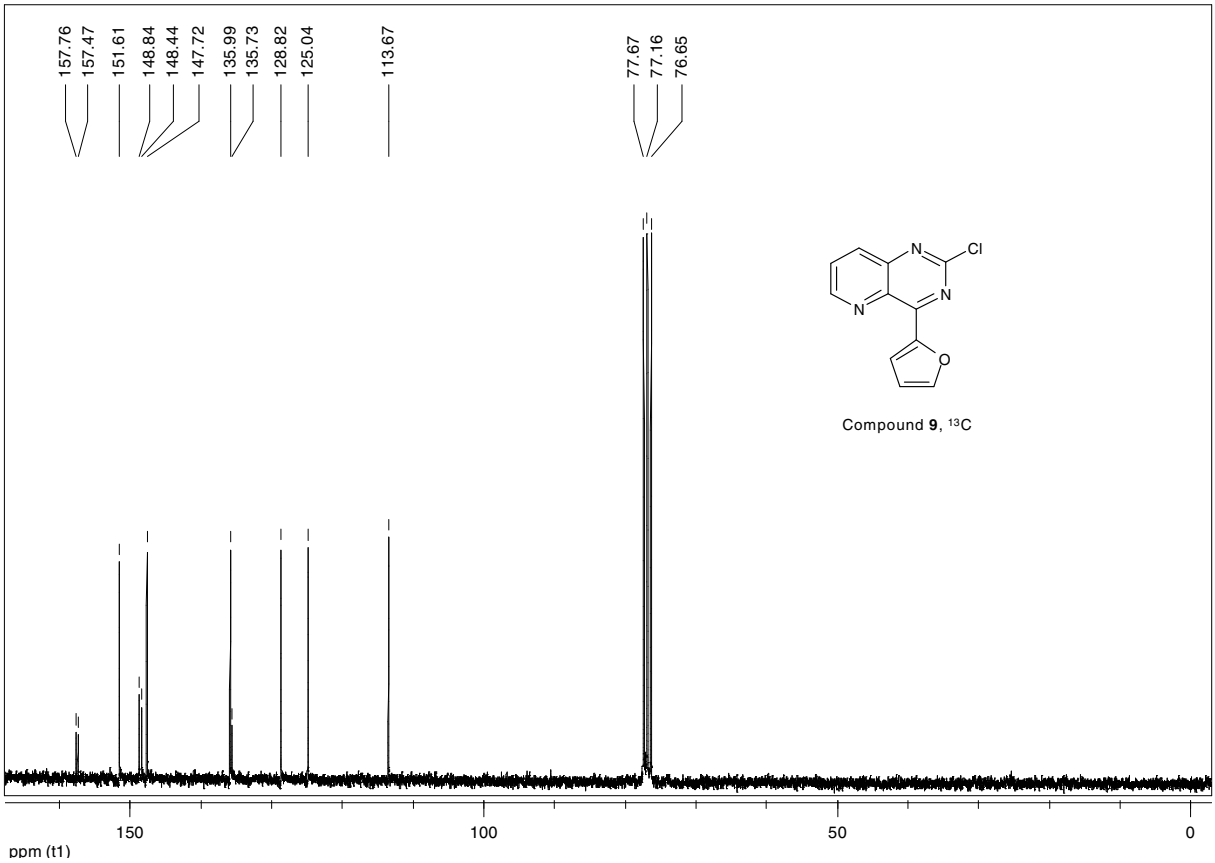
Compound **8**, ^{1}H



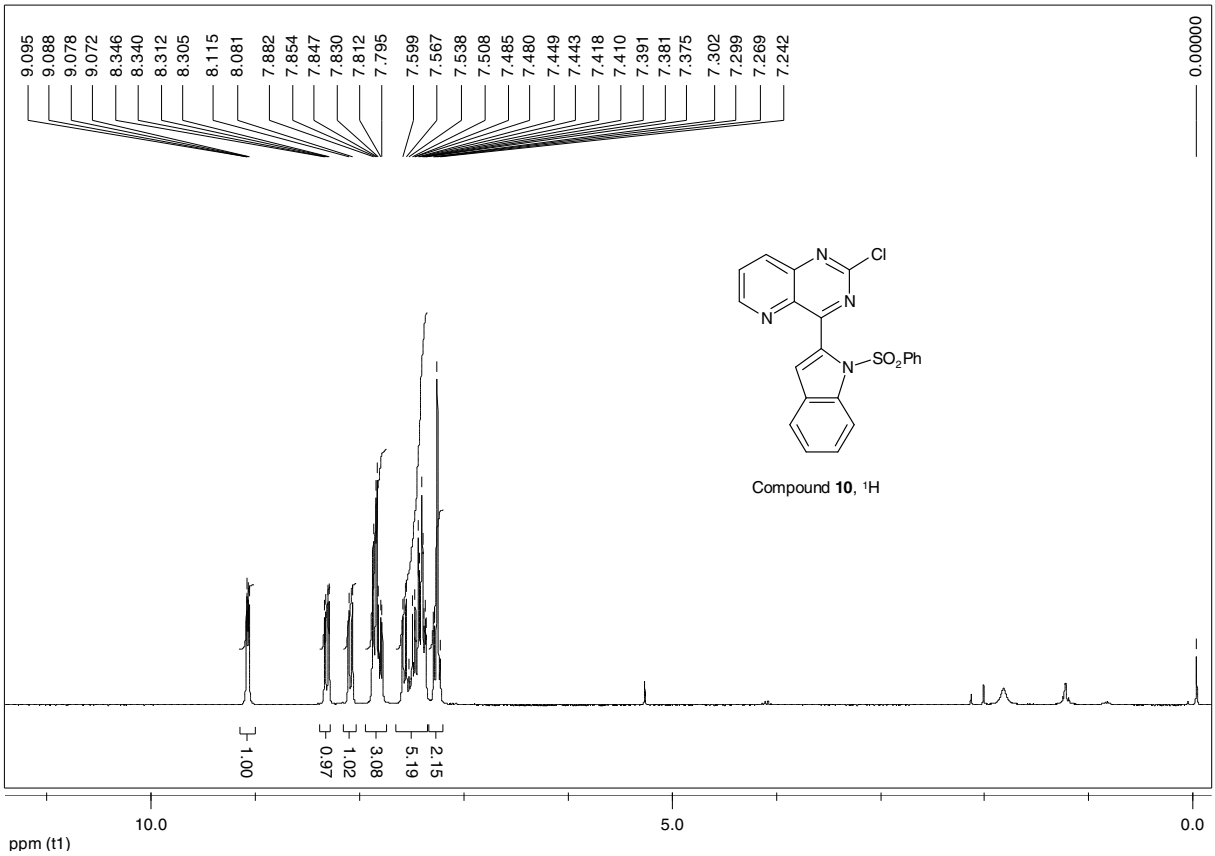
Compound **8**, ^{13}C



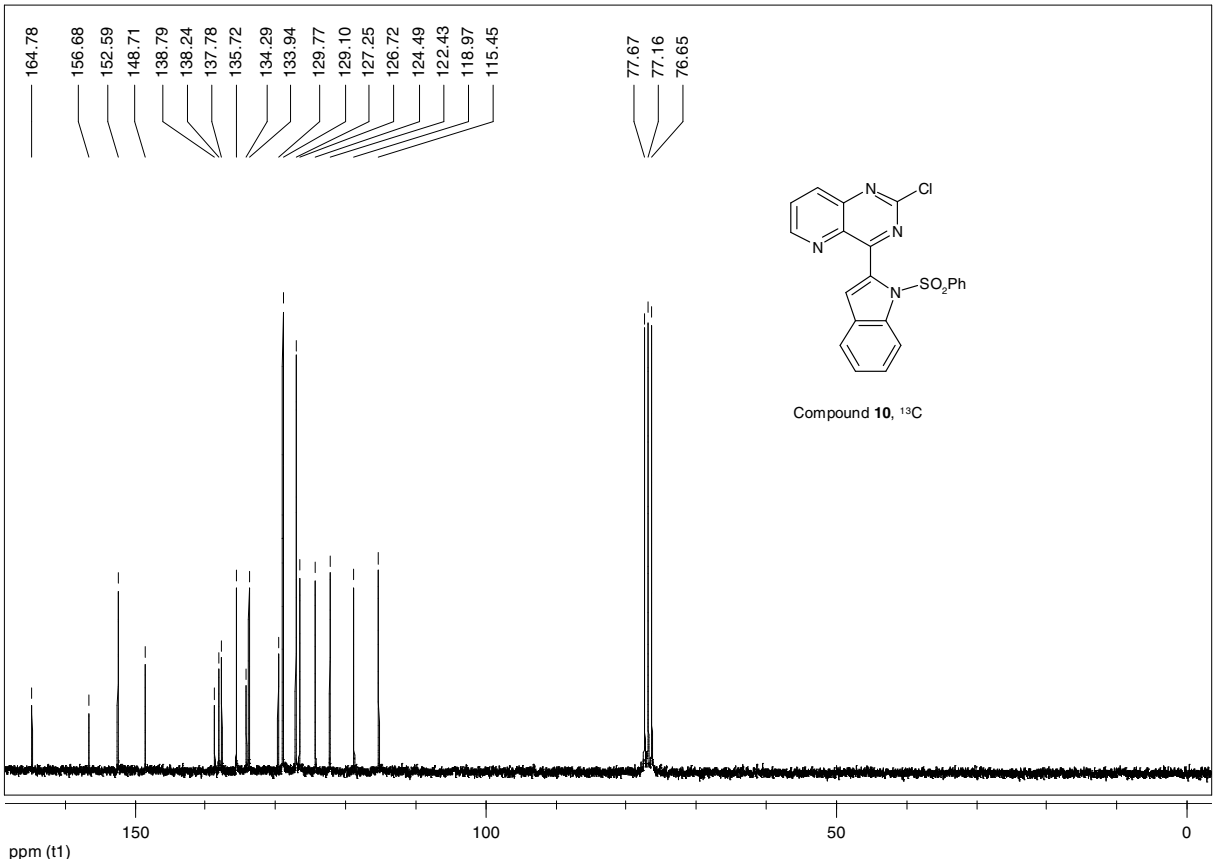
Compound **9**, ^{1}H



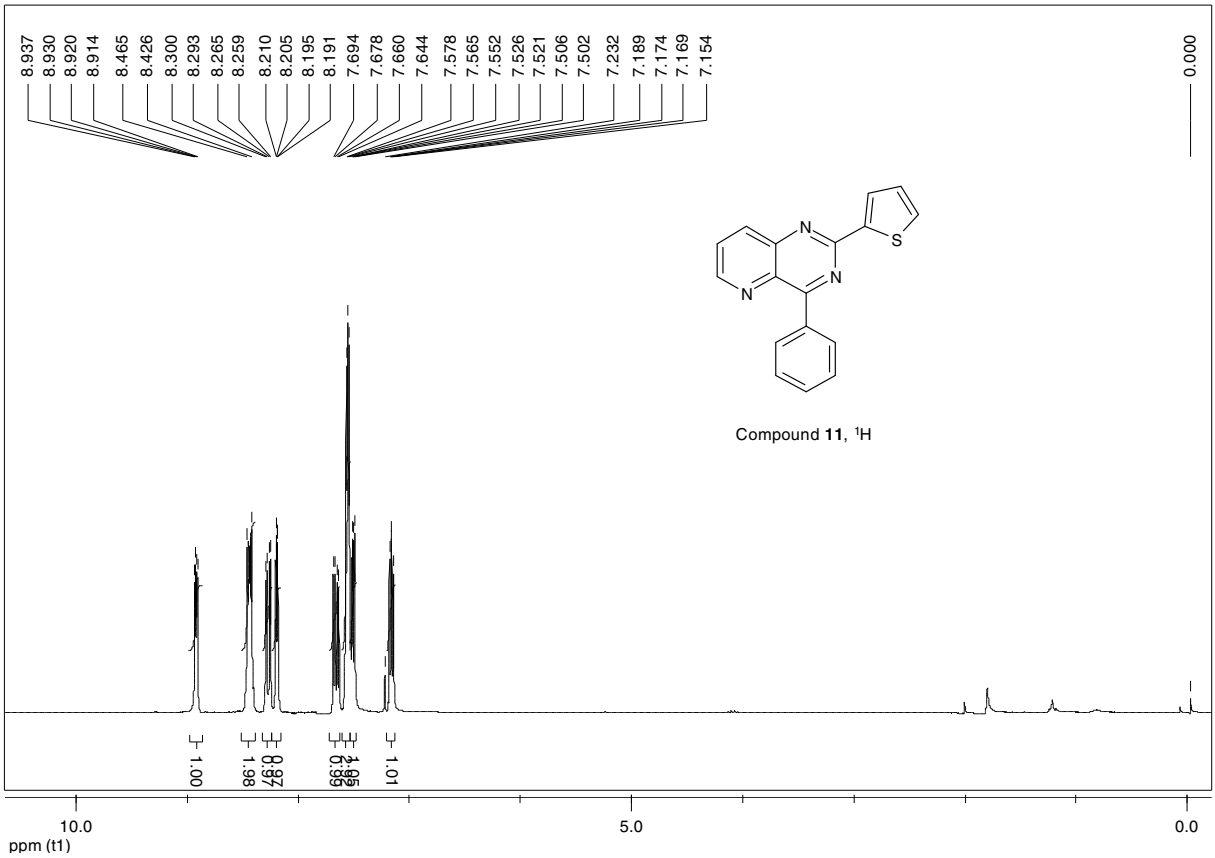
Compound **9**, ^{13}C



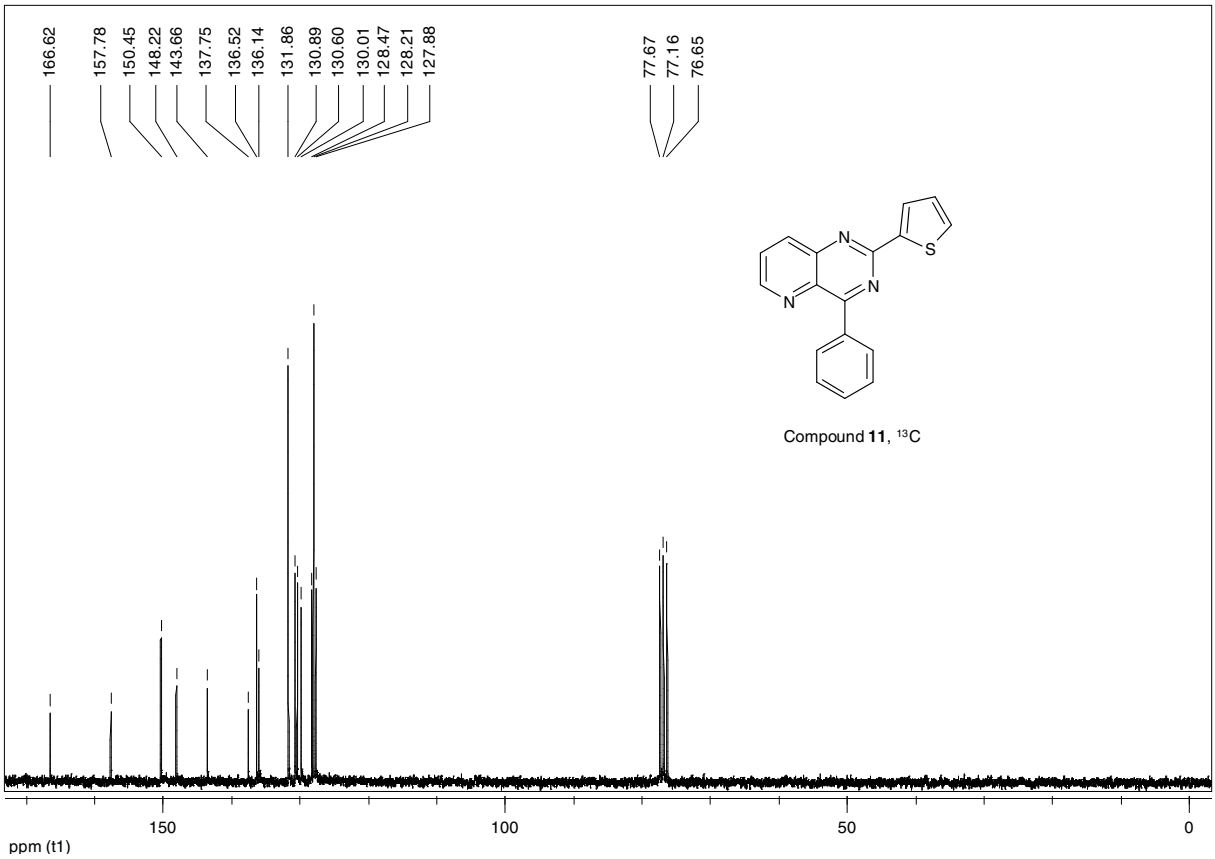
Compound **10**, ^{1}H



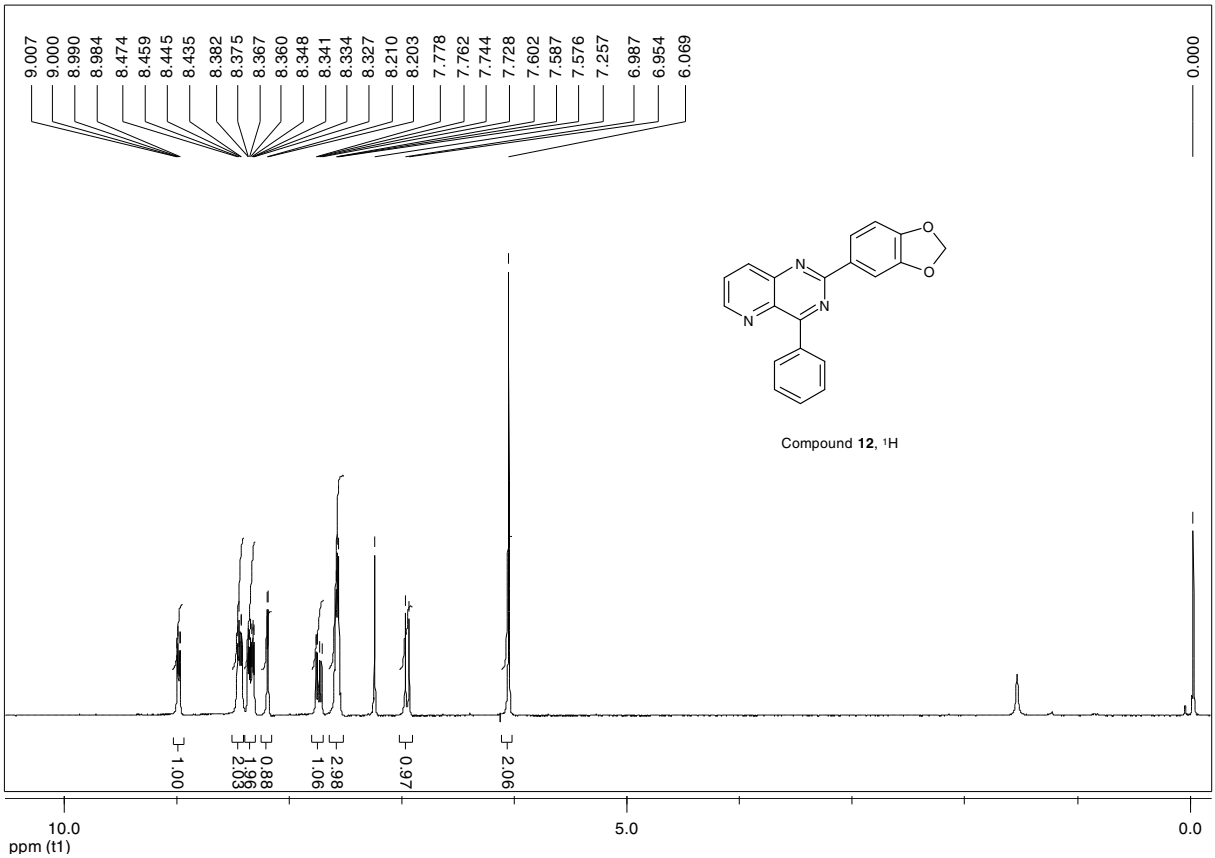
Compound **10**, ^{13}C



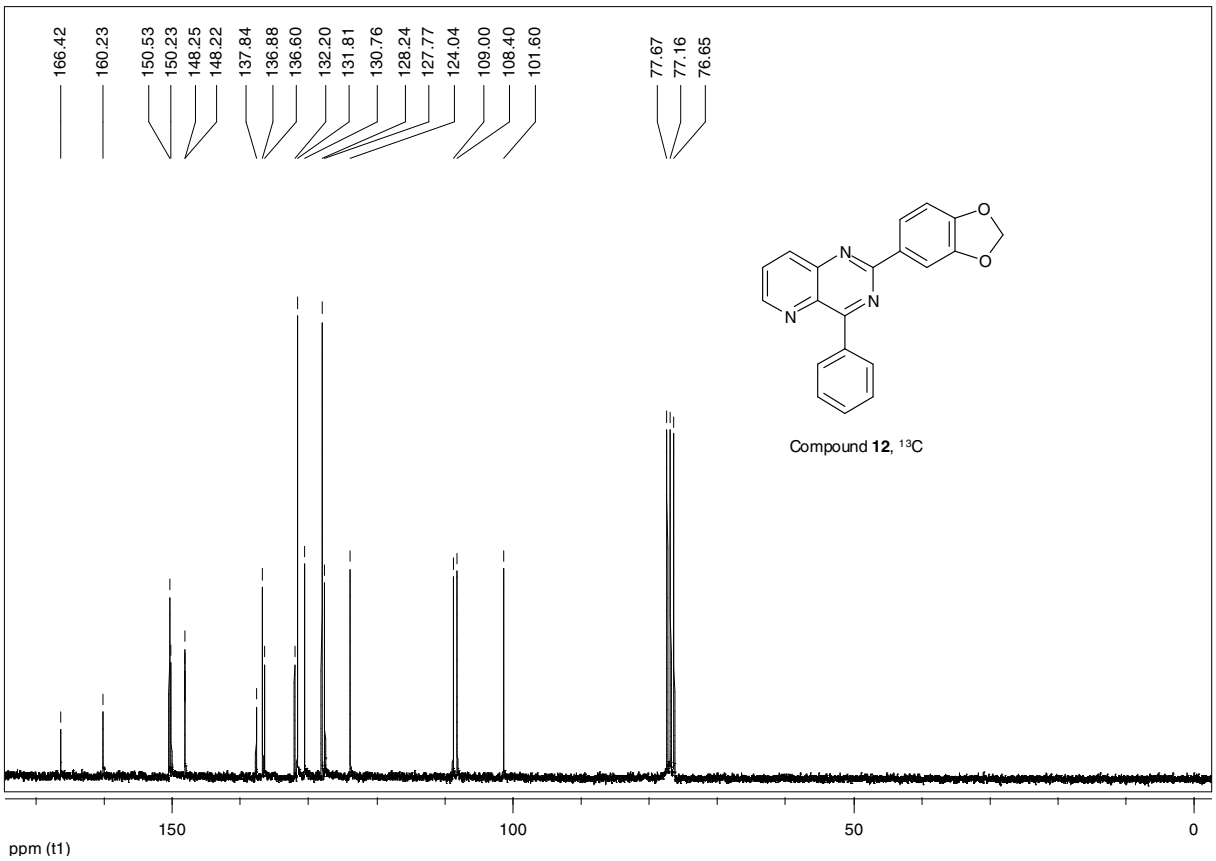
Compound **11**, ^{1}H



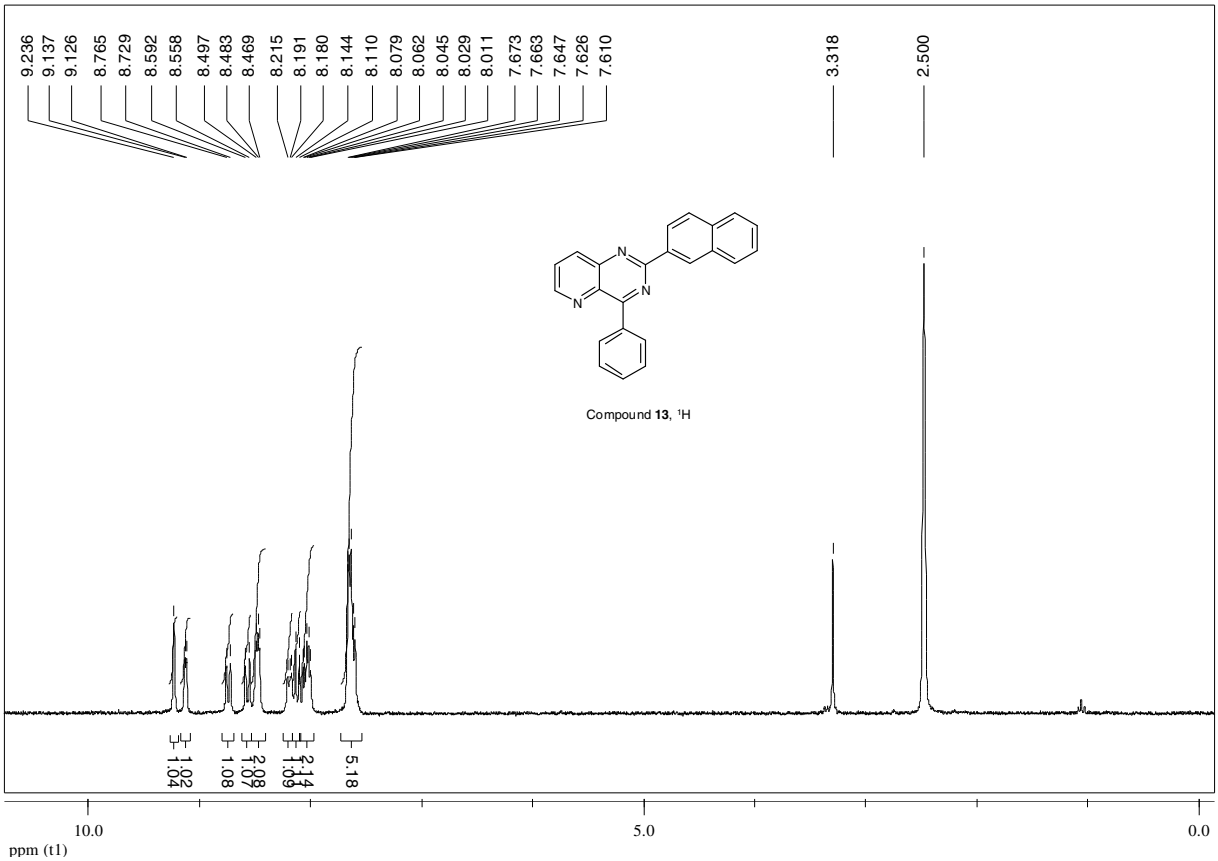
Compound **11**, ^{13}C



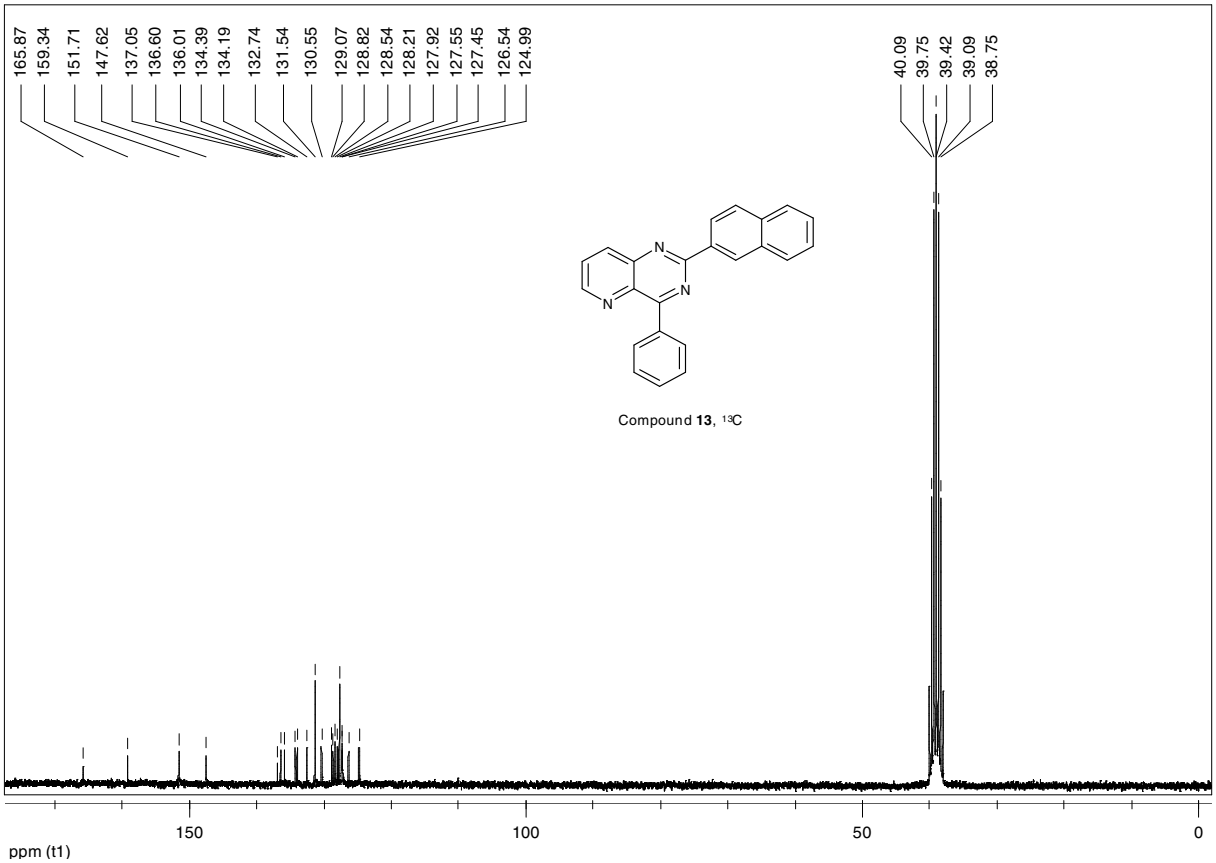
Compound **12**, ^{1}H



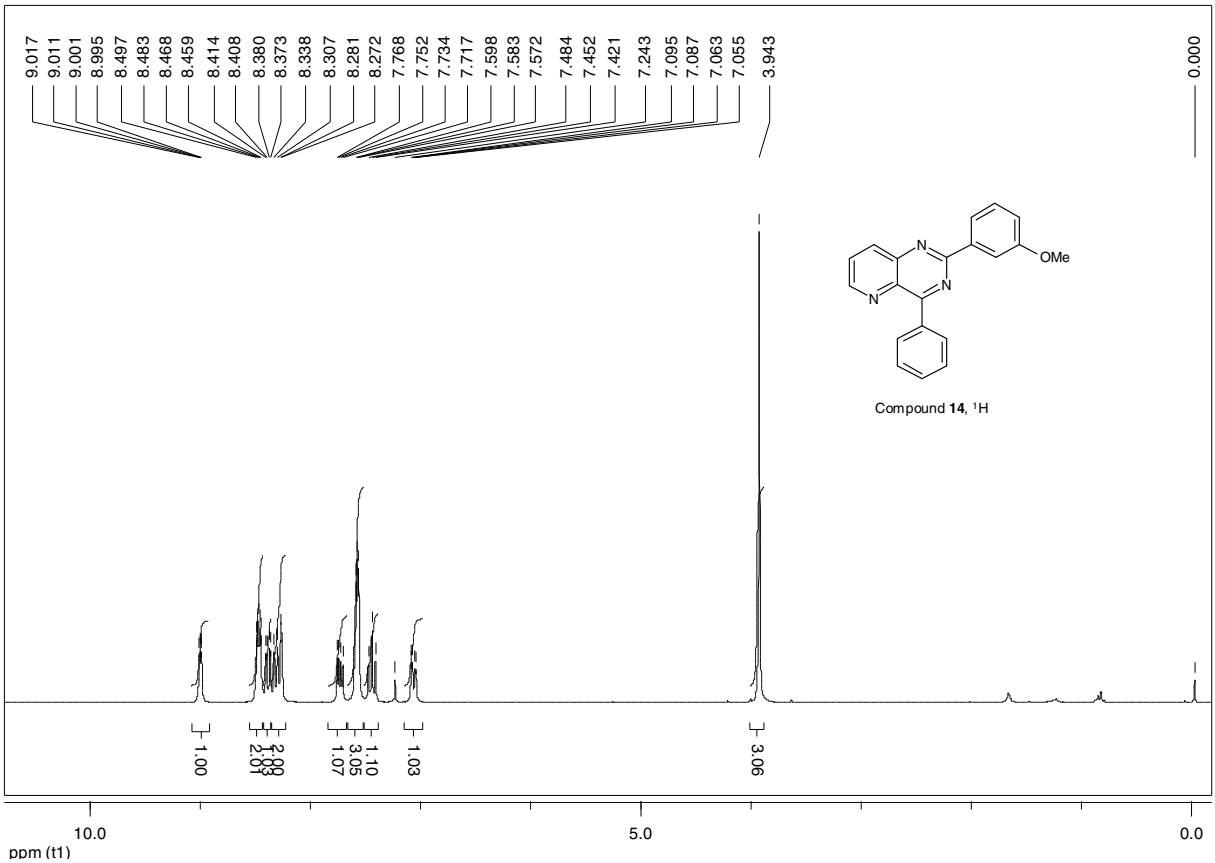
Compound **12**, ^{13}C



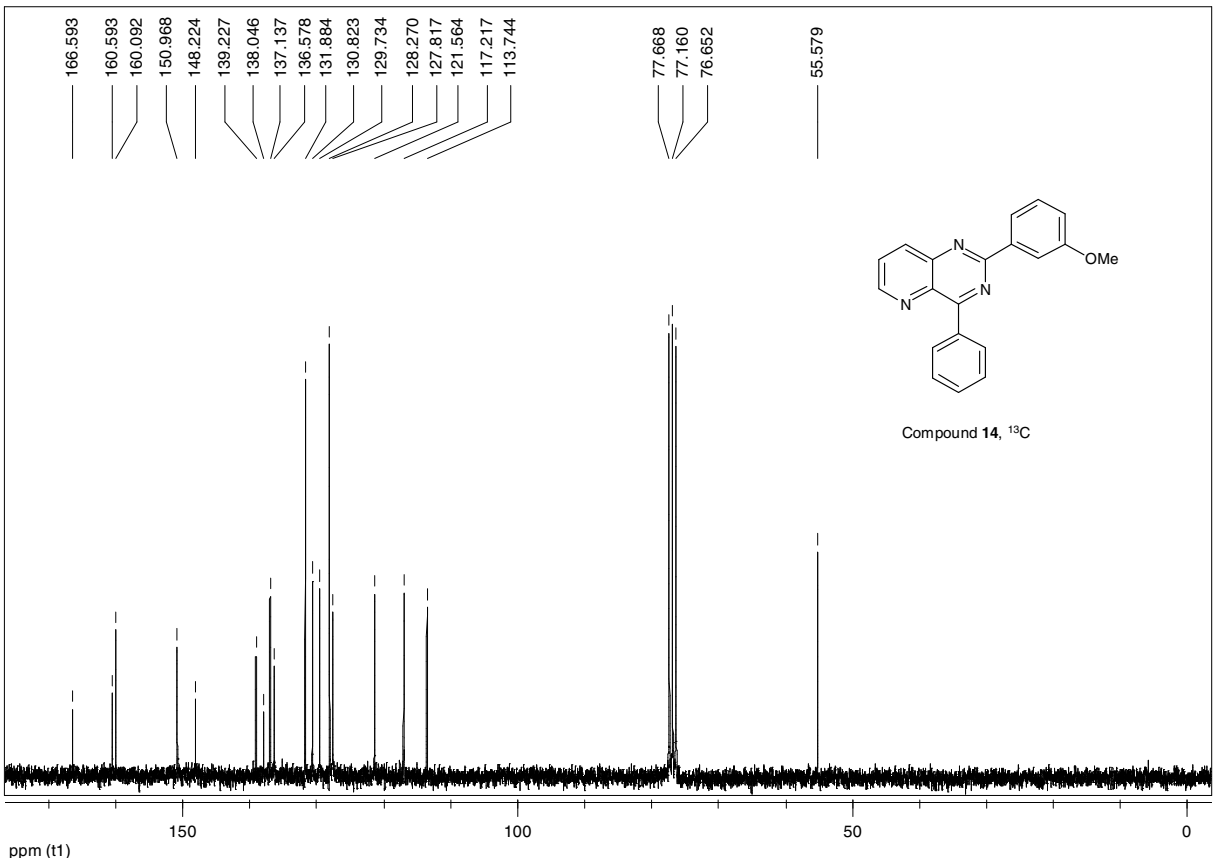
Compound **13**, ^{1}H



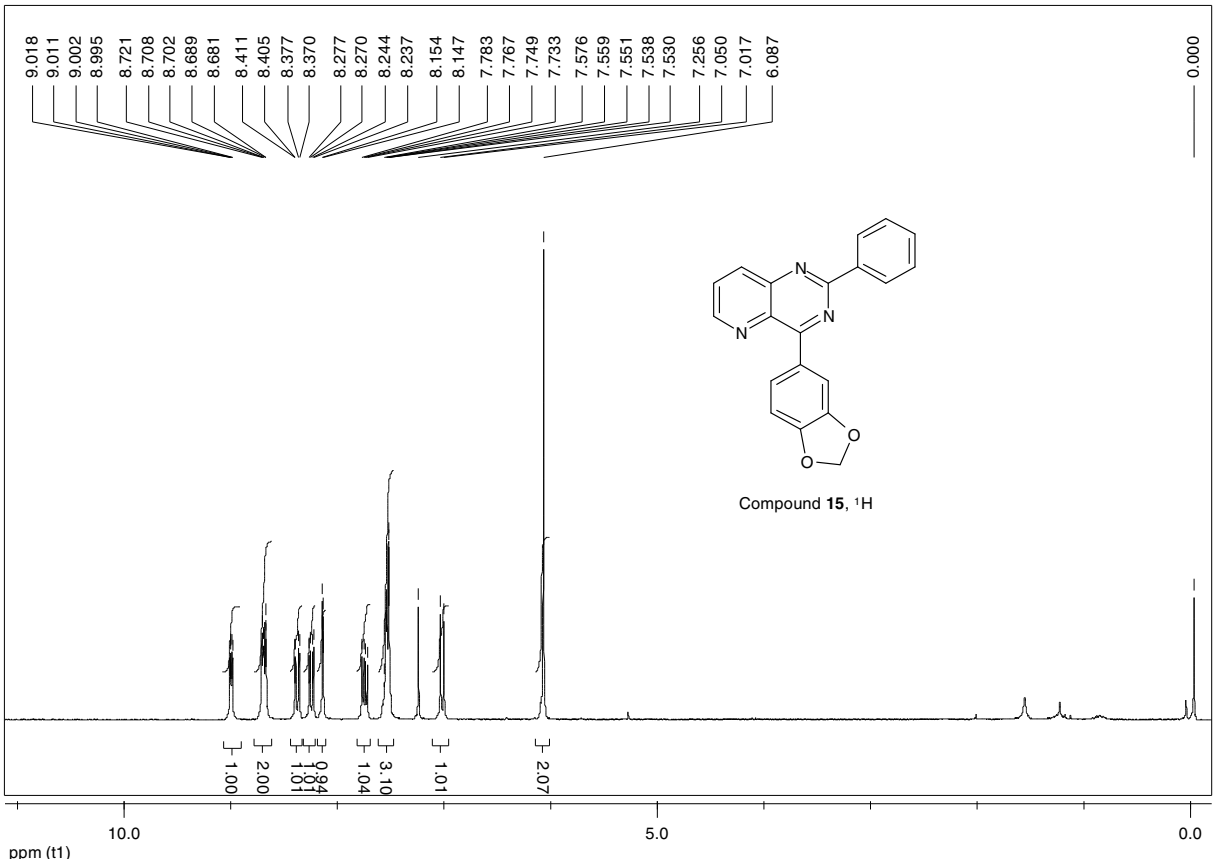
Compound **13**, ^{13}C



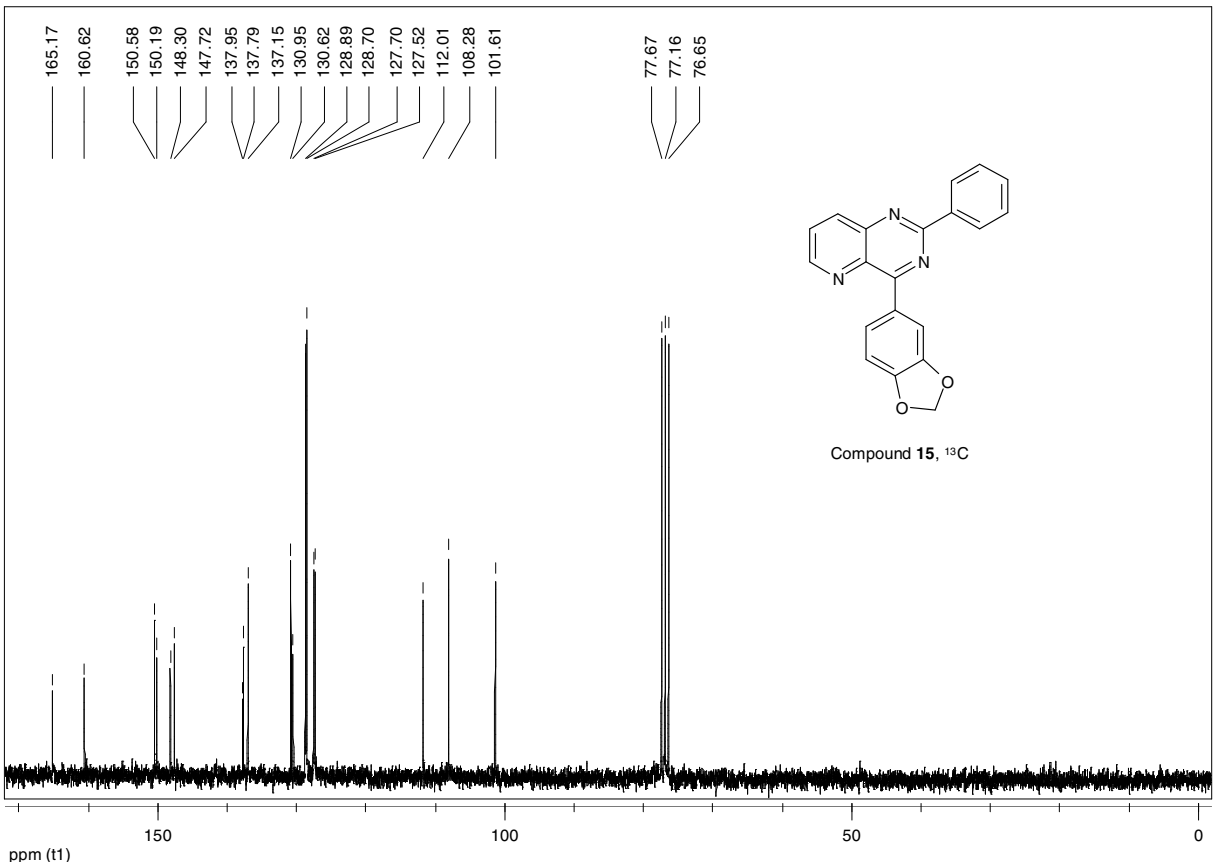
Compound **14**, ^{1}H



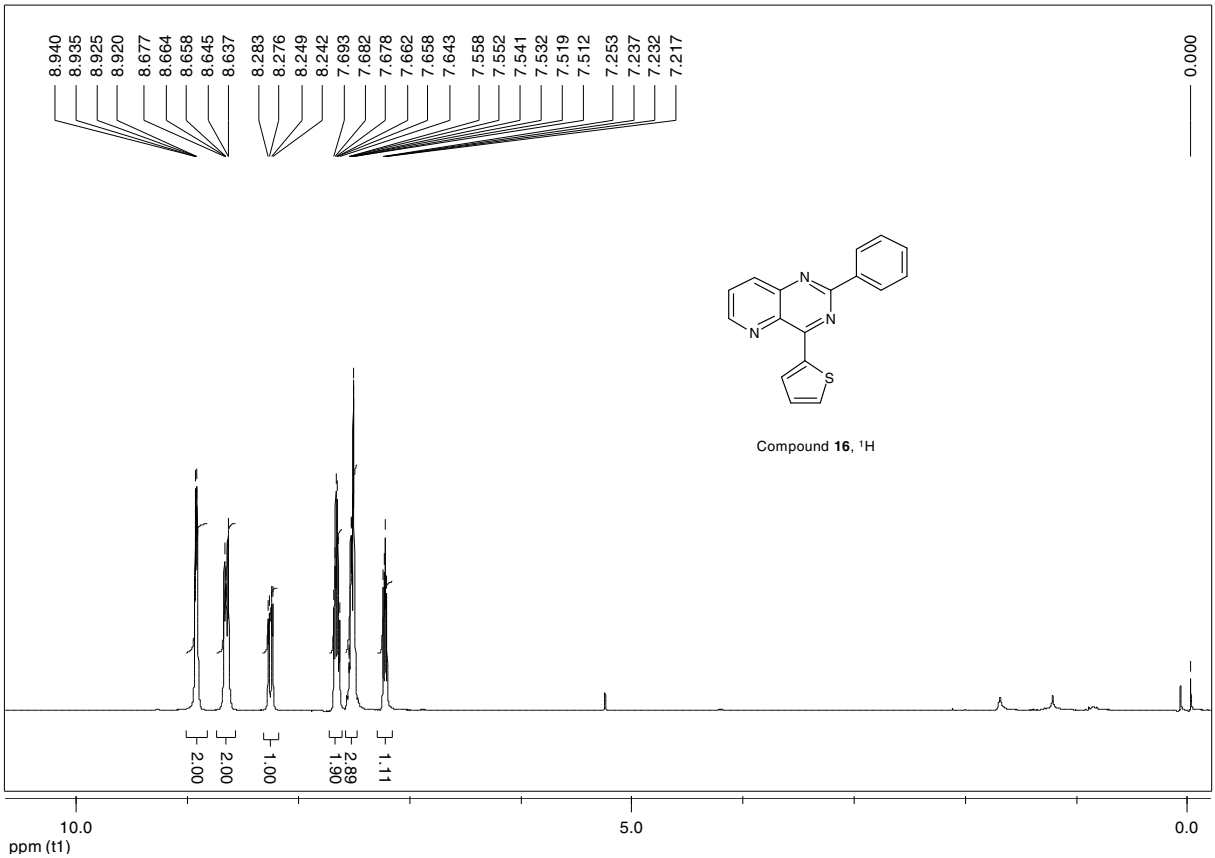
Compound **14**, ^{13}C



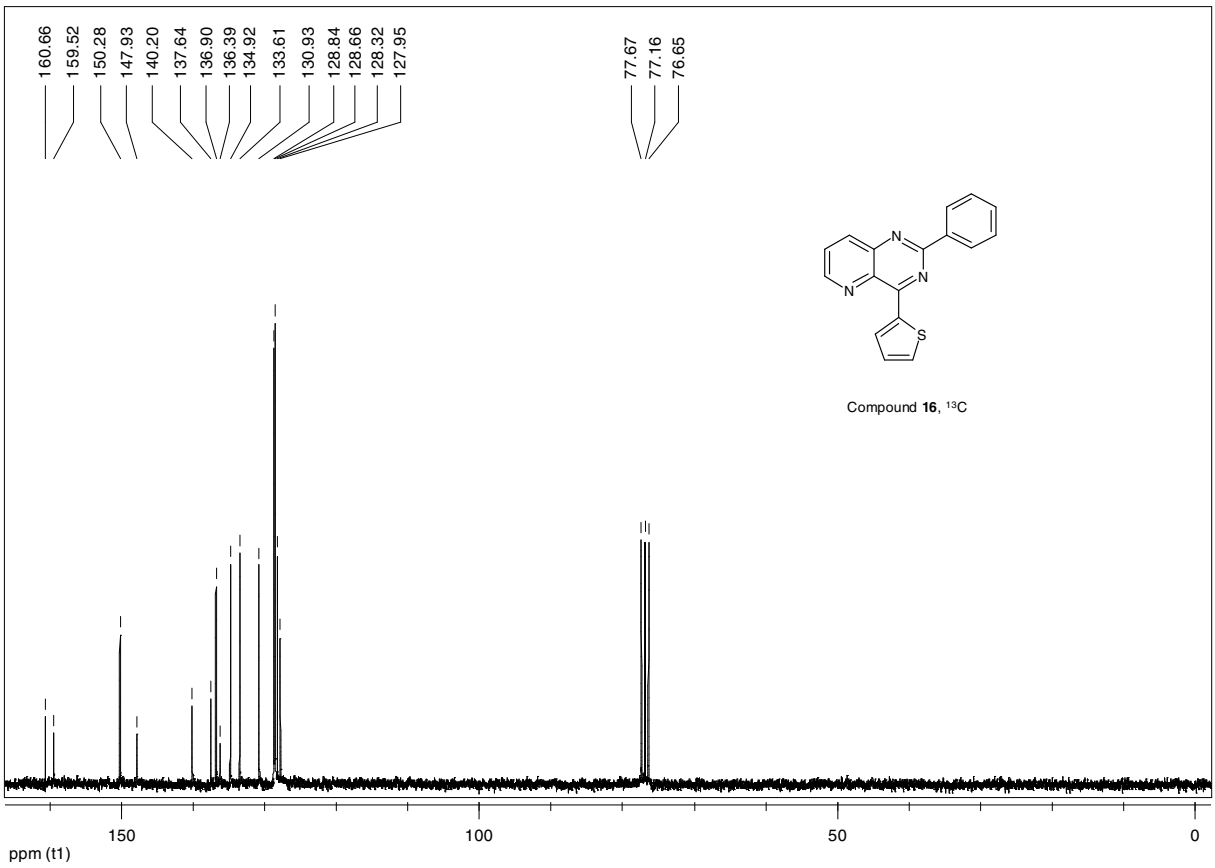
Compound **15**, ^{1}H



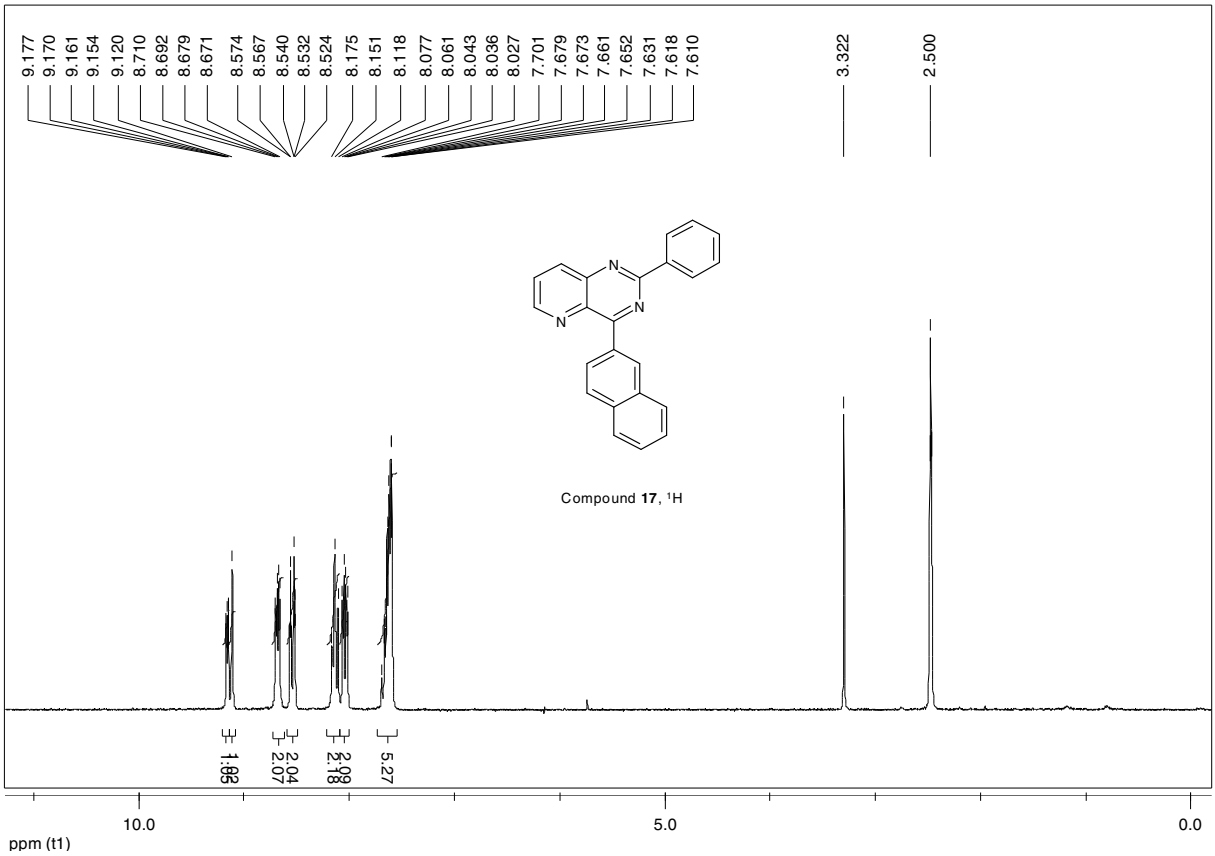
Compound **15**, ^{13}C



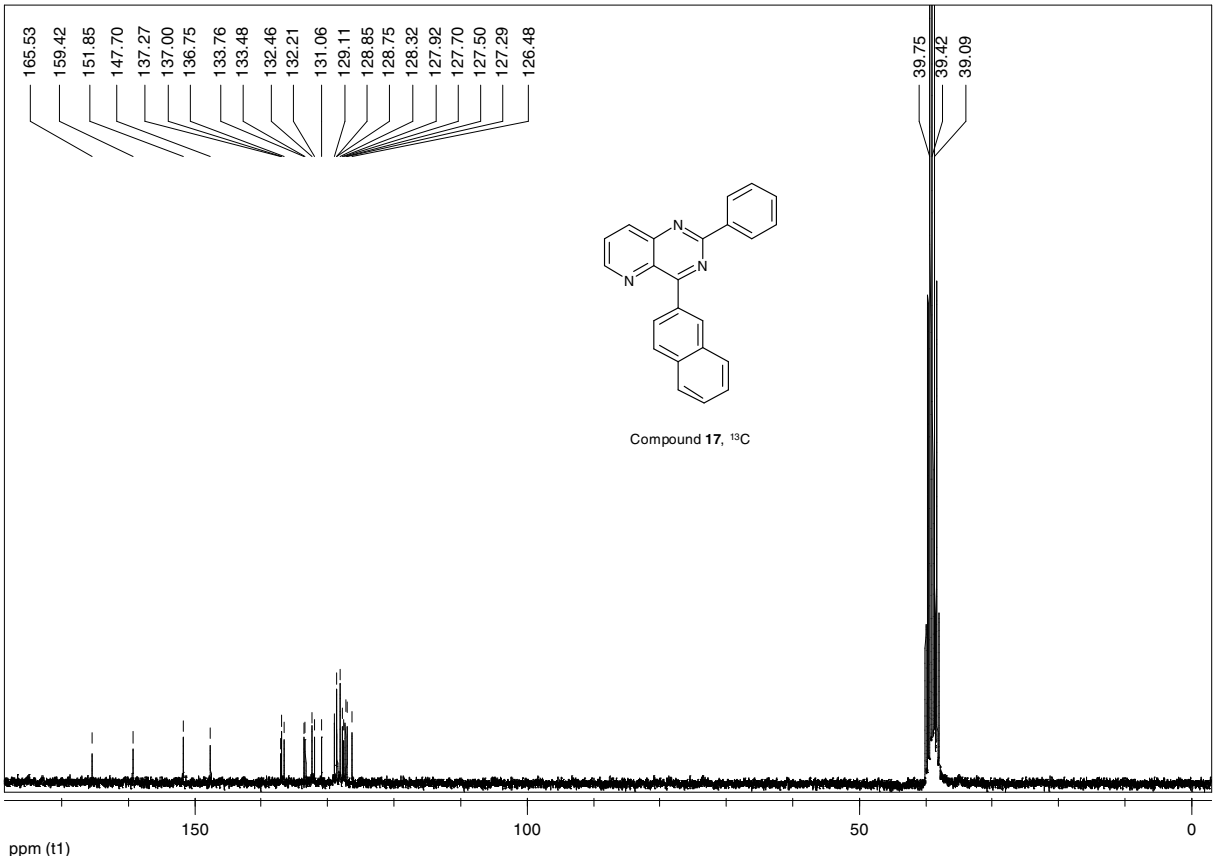
Compound **16**, ^{1}H



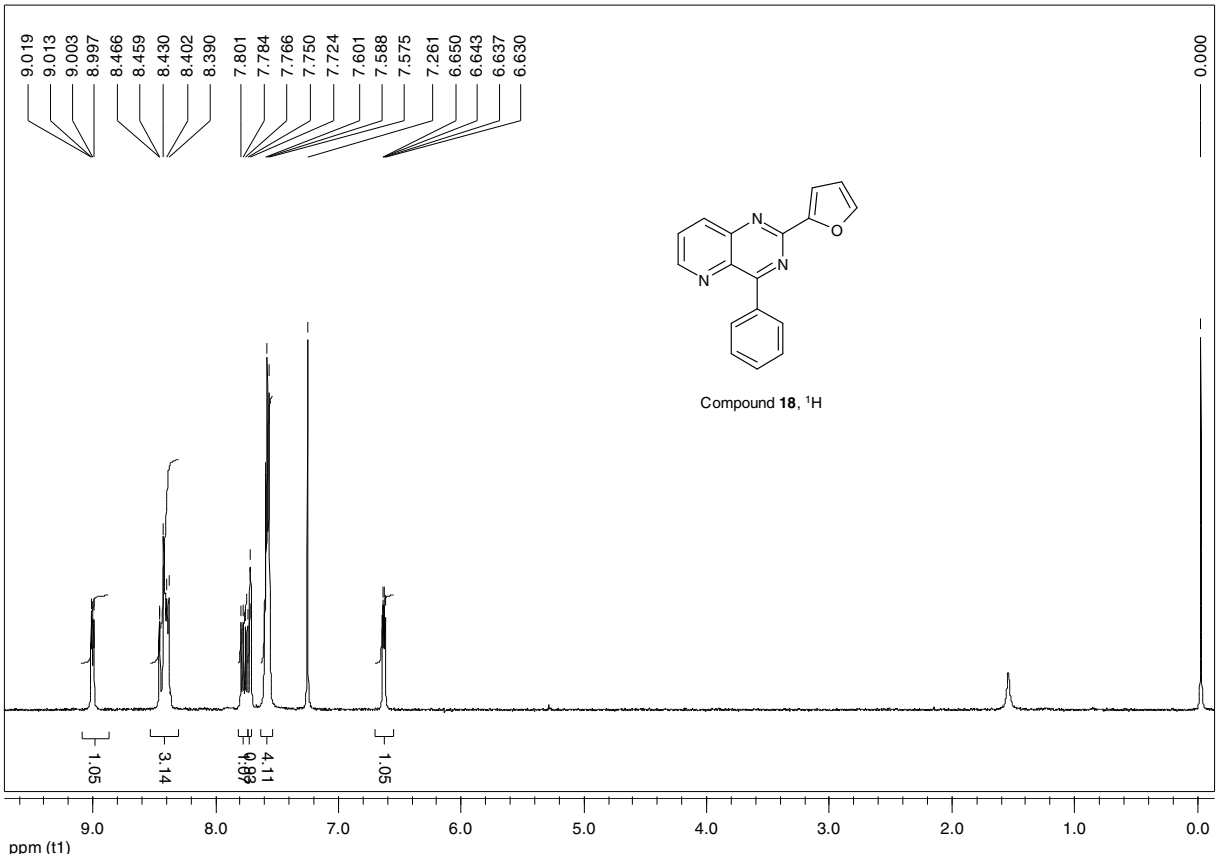
Compound **16**, ^{13}C



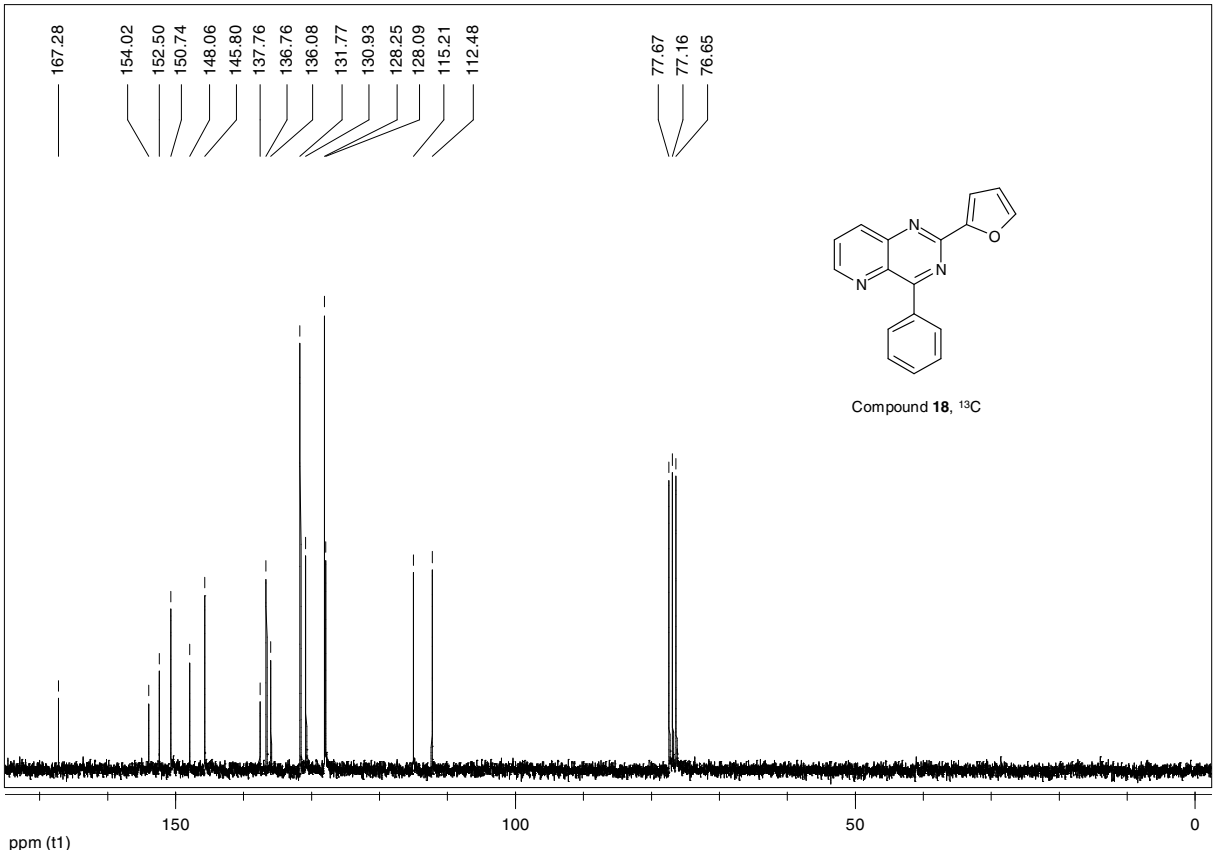
Compound **17**, ^{1}H



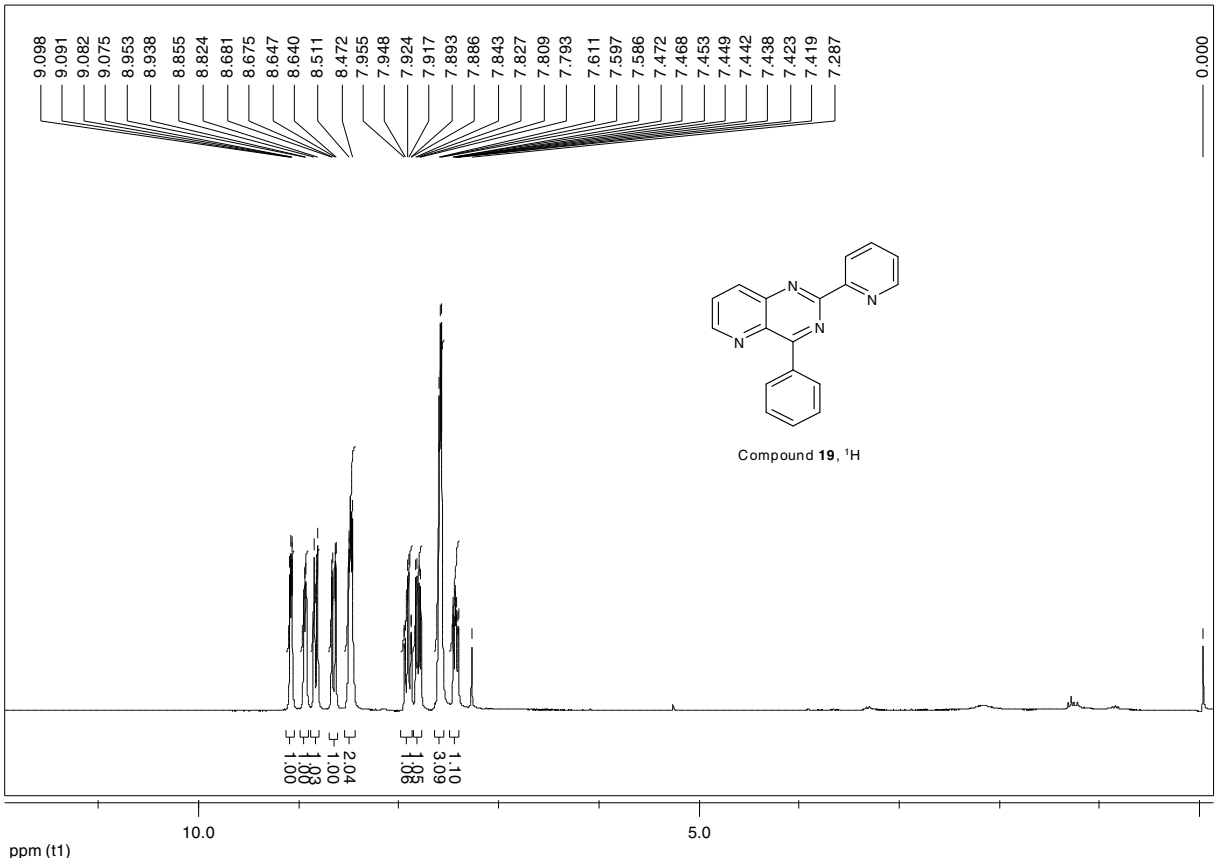
Compound **17**, ^{13}C



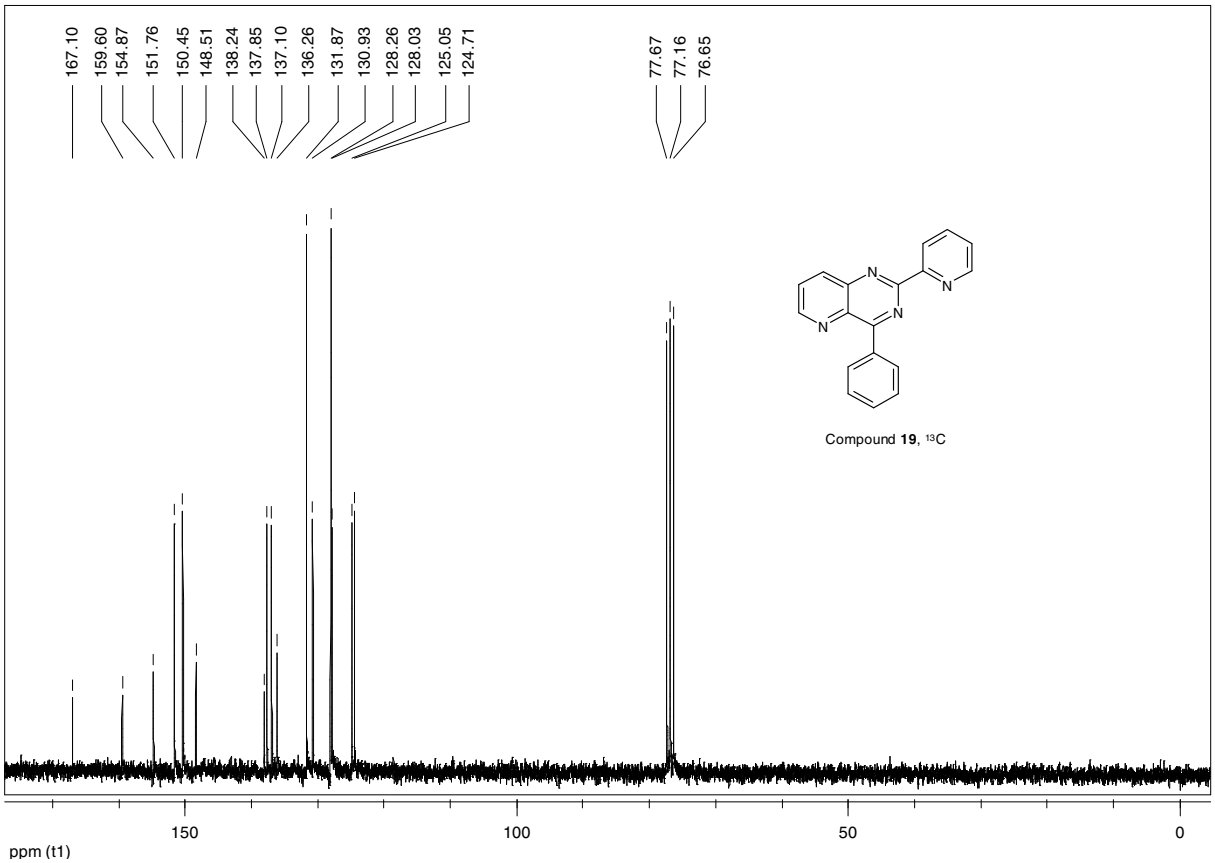
Compound **18**, ^{1}H



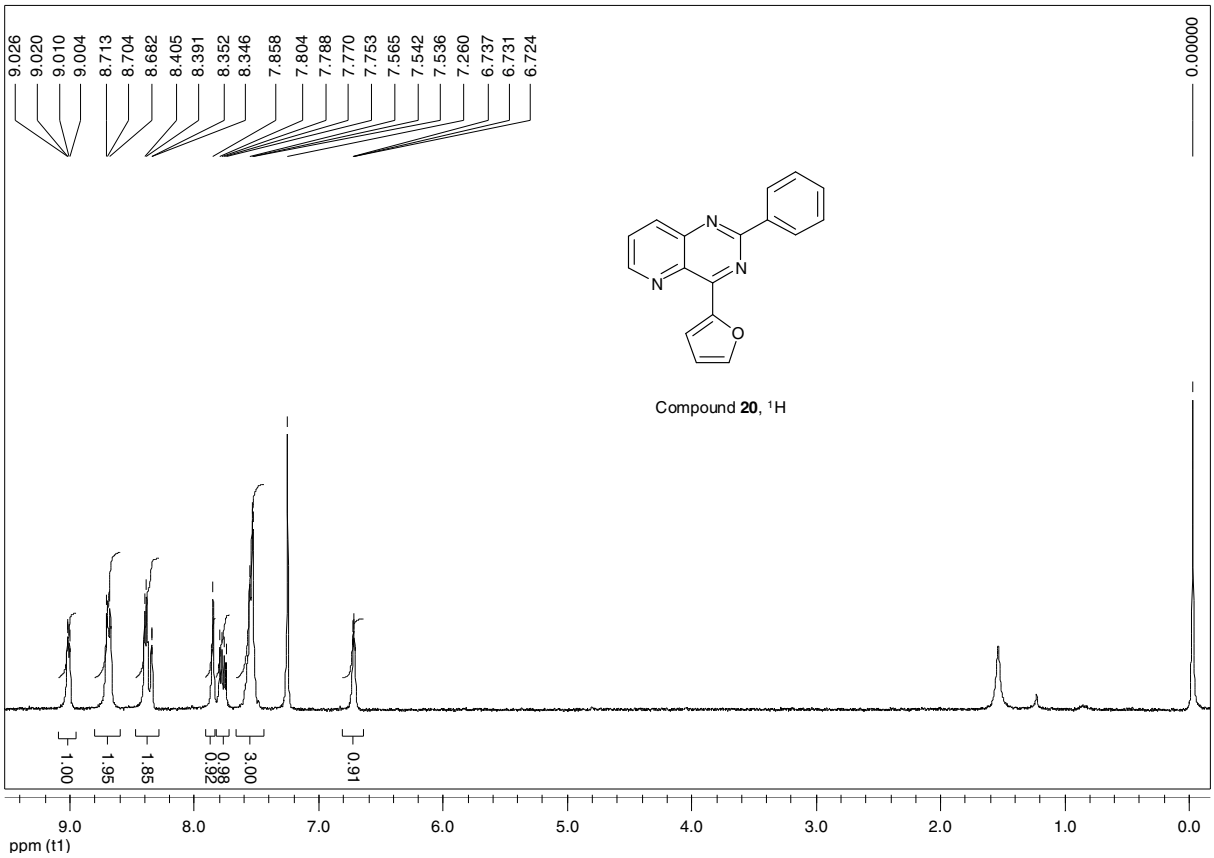
Compound **18**, ^{13}C



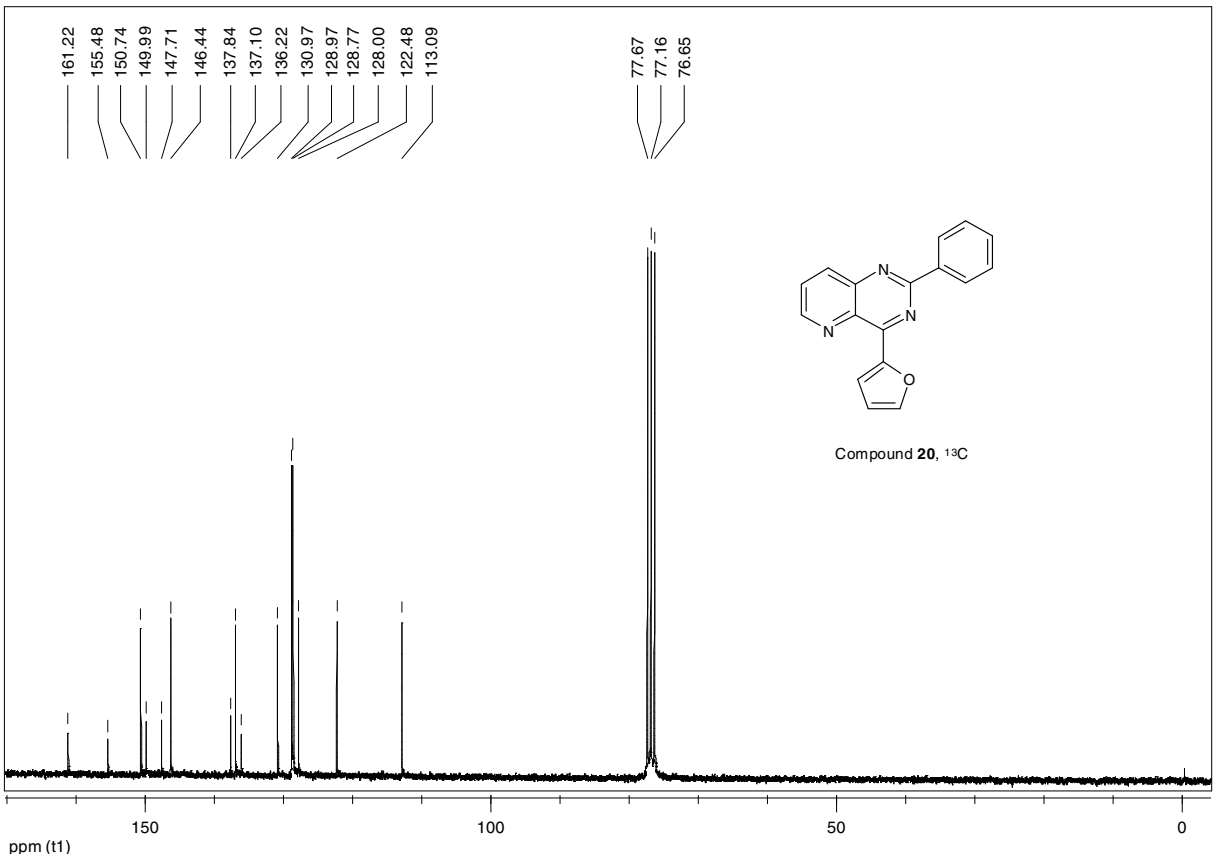
Compound **19**, ^{1}H



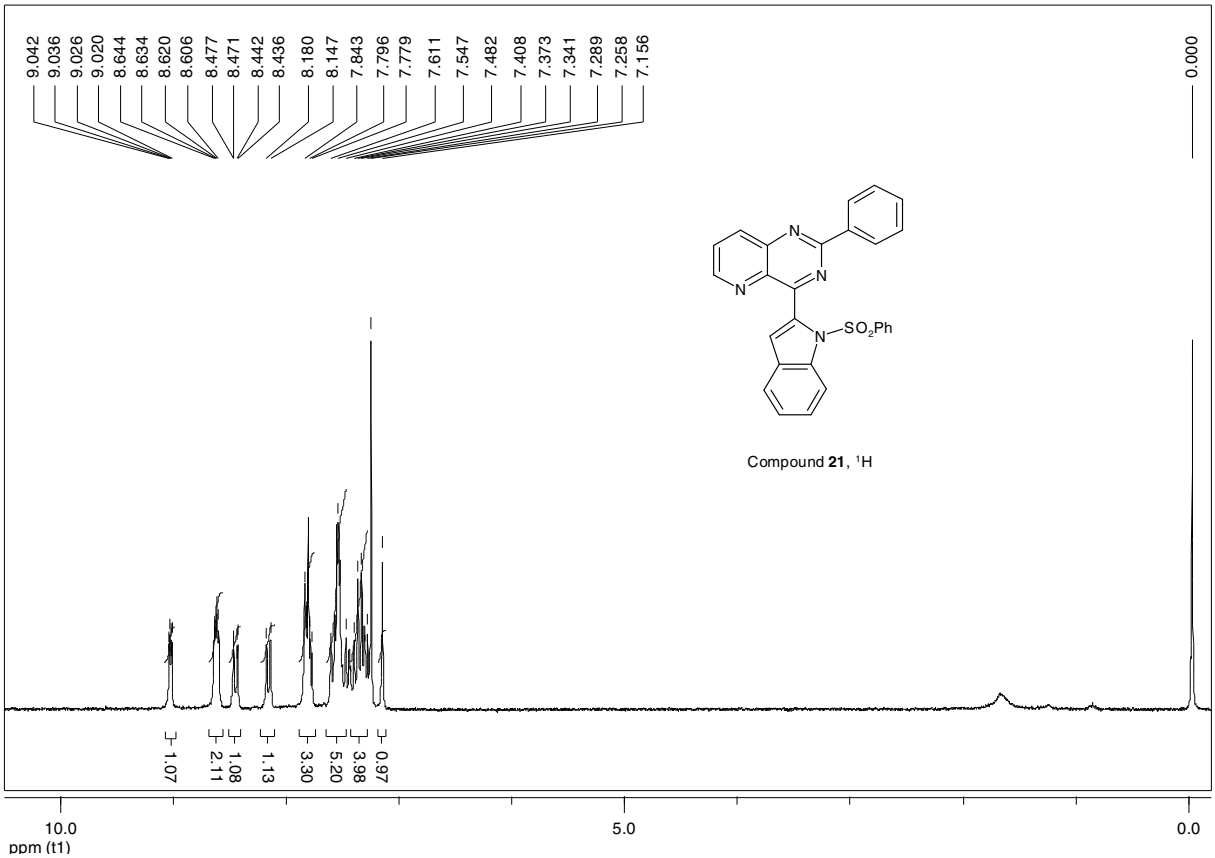
Compound **19**, ^{13}C



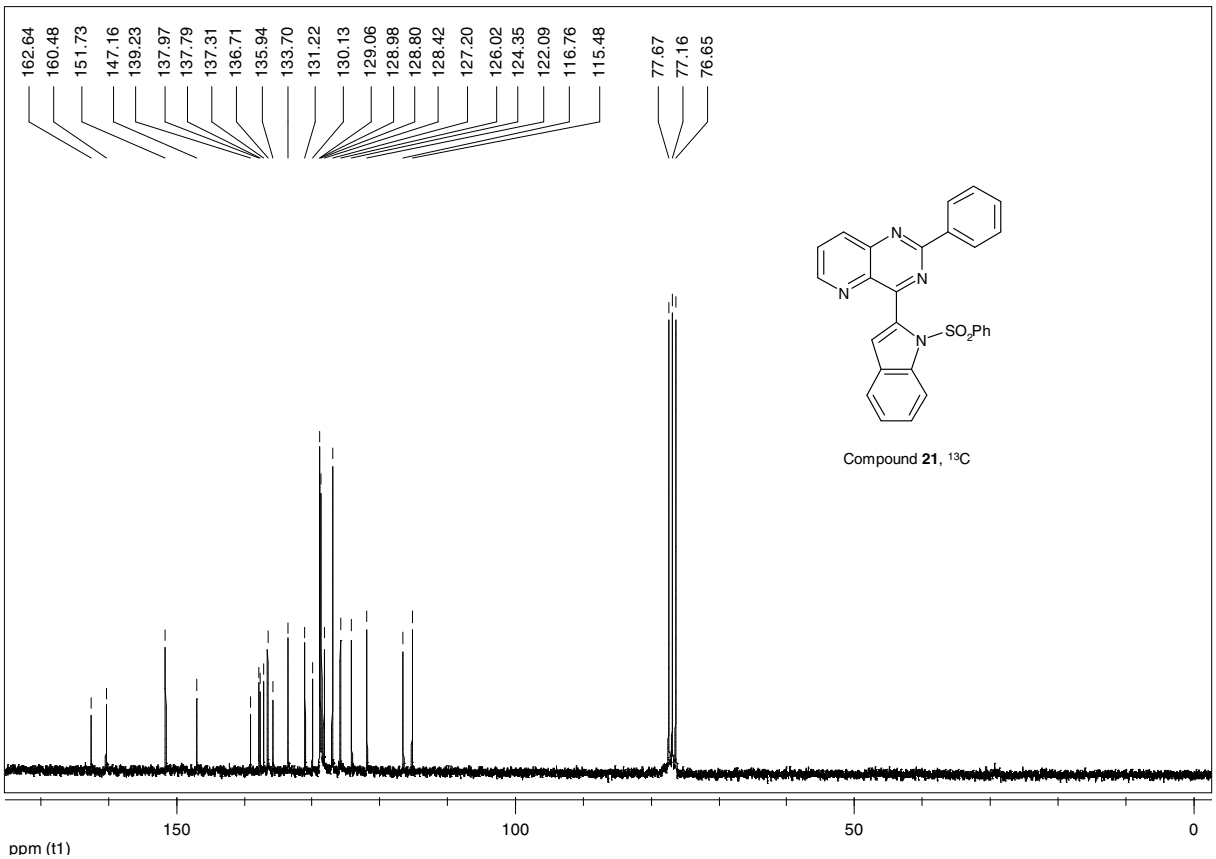
Compound **20**, ^{1}H



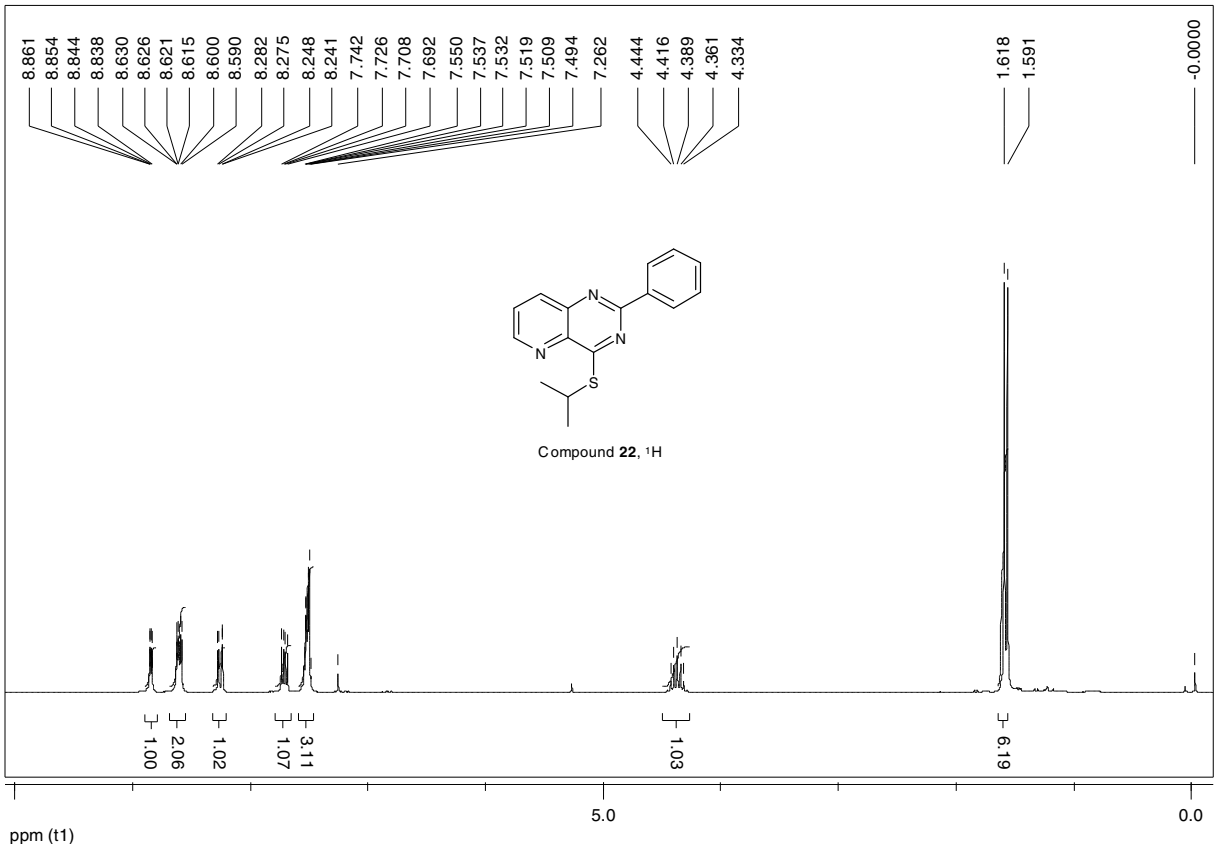
Compound **20**, ^{13}C



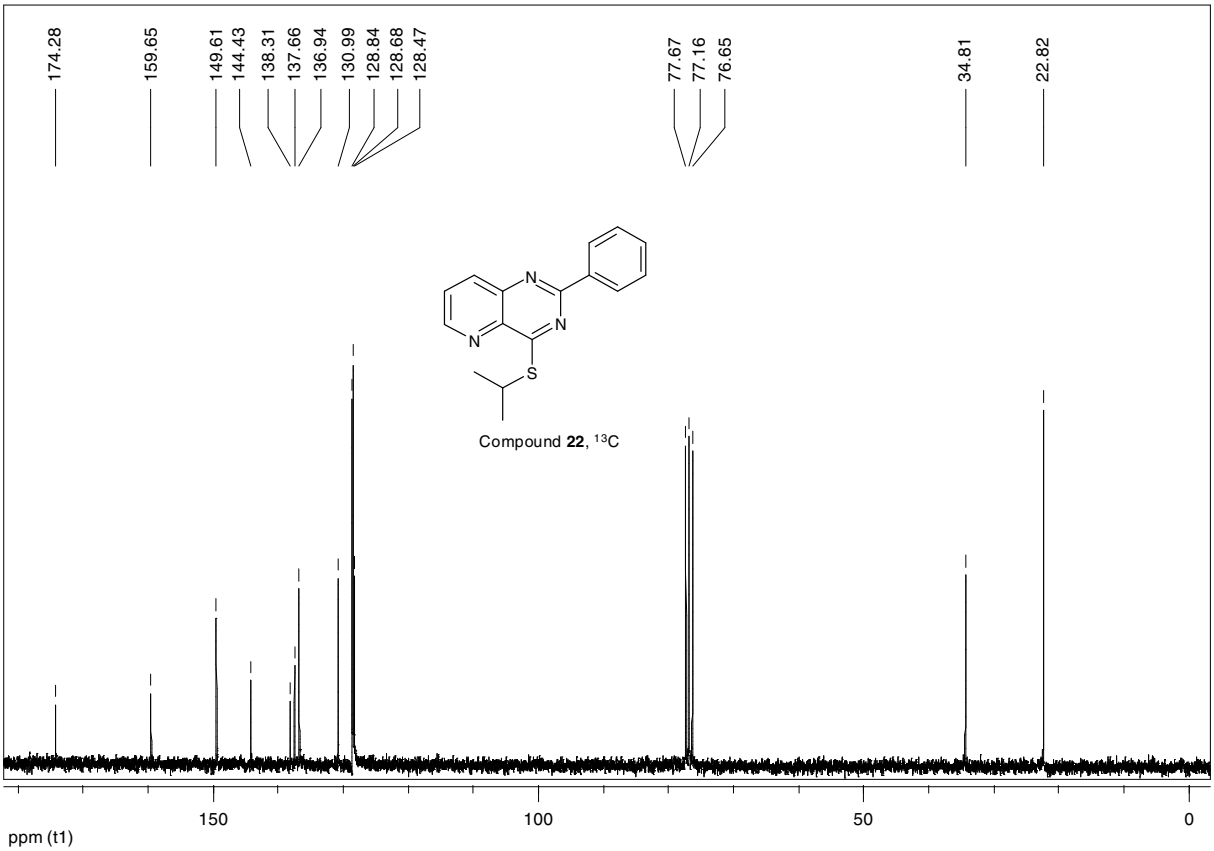
Compound **21**, ^{1}H



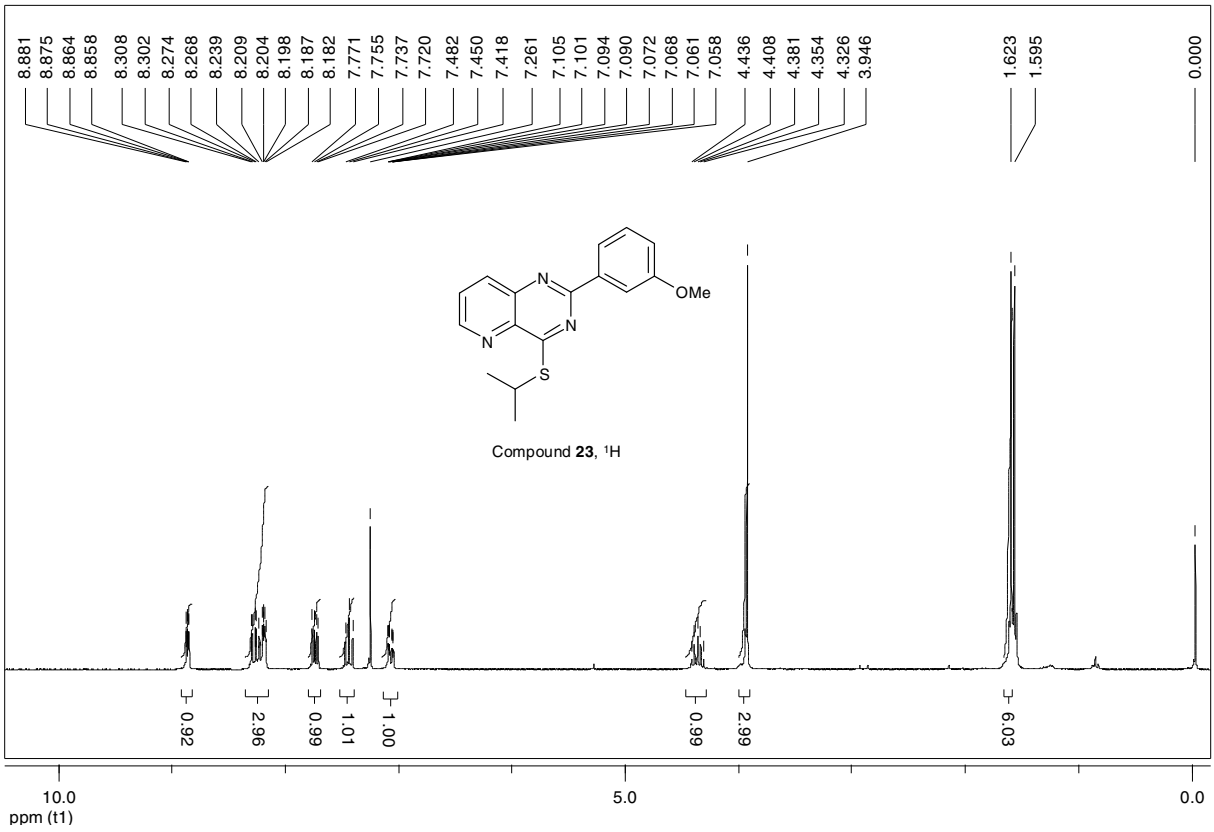
Compound **21**, ^{13}C



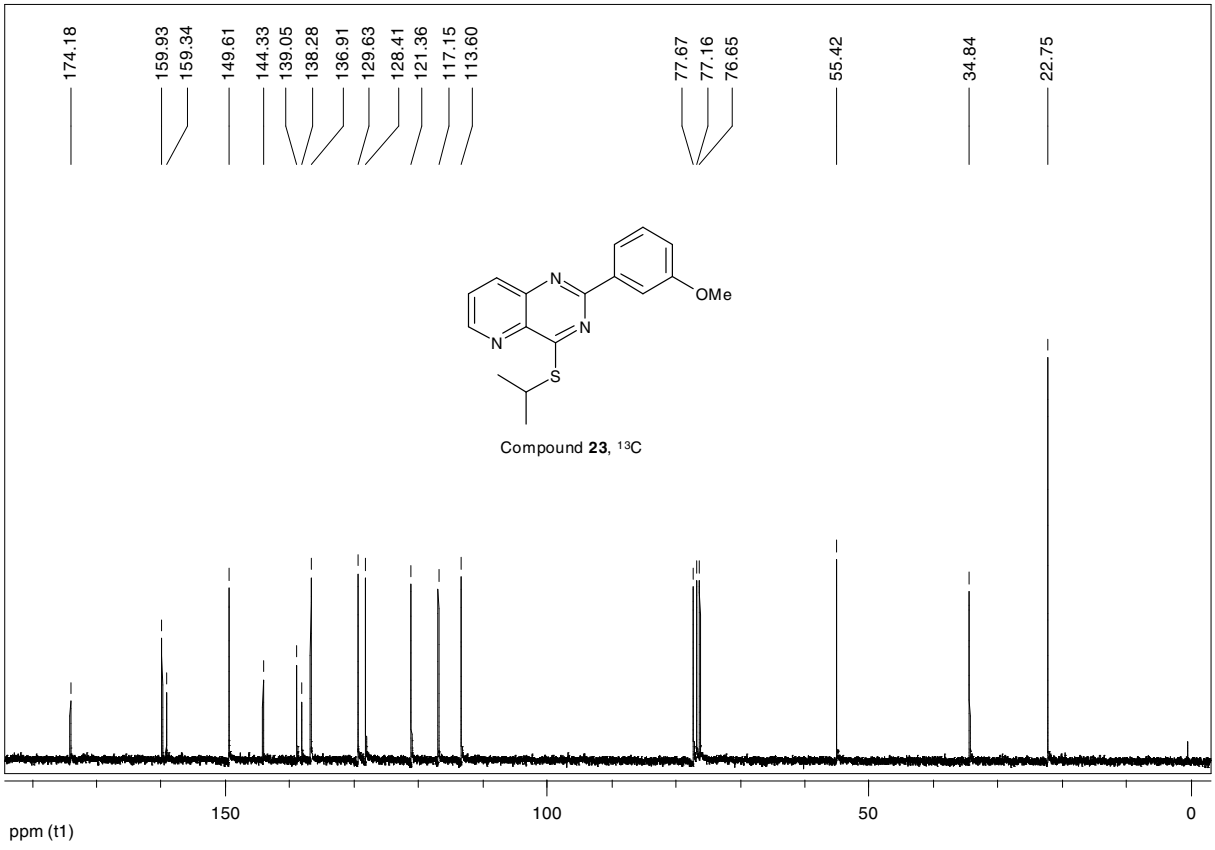
Compound **22**, ^{1}H



Compound **22**, ^{13}C



Compound **23**, ^{1}H



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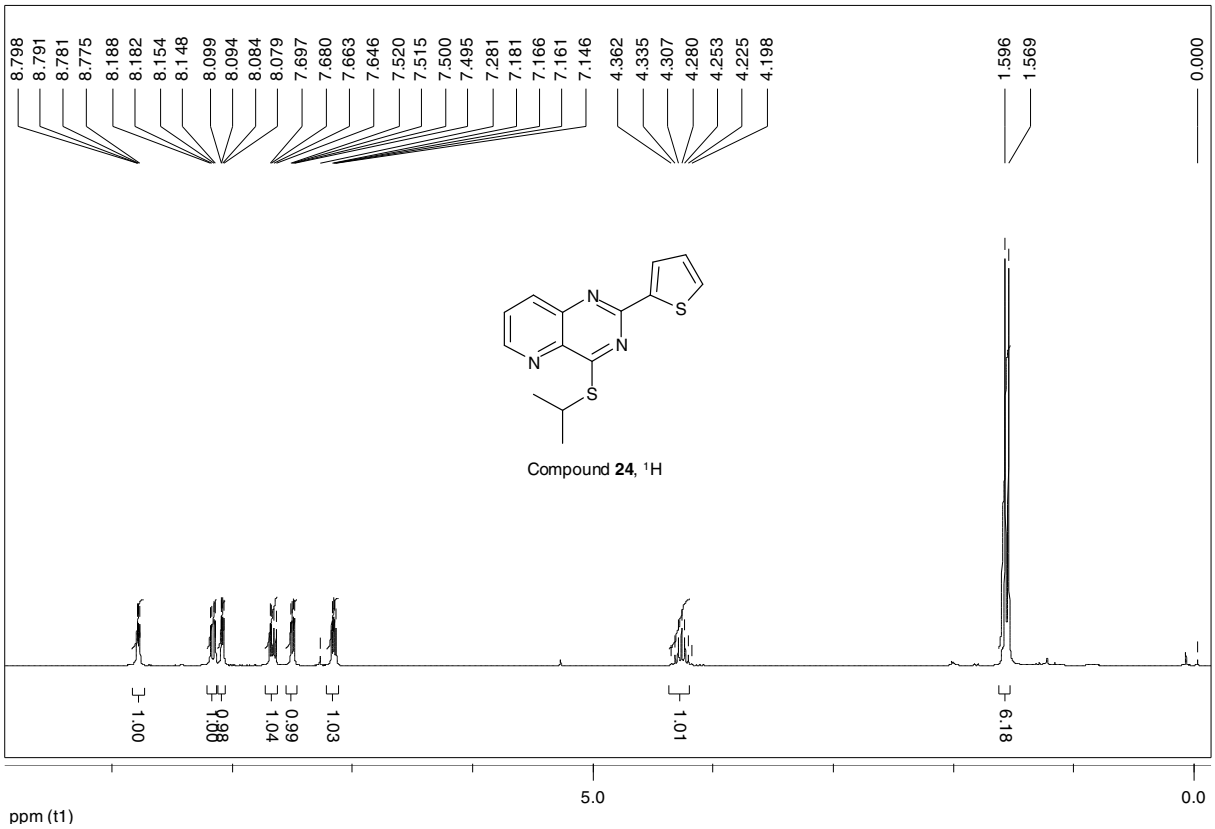
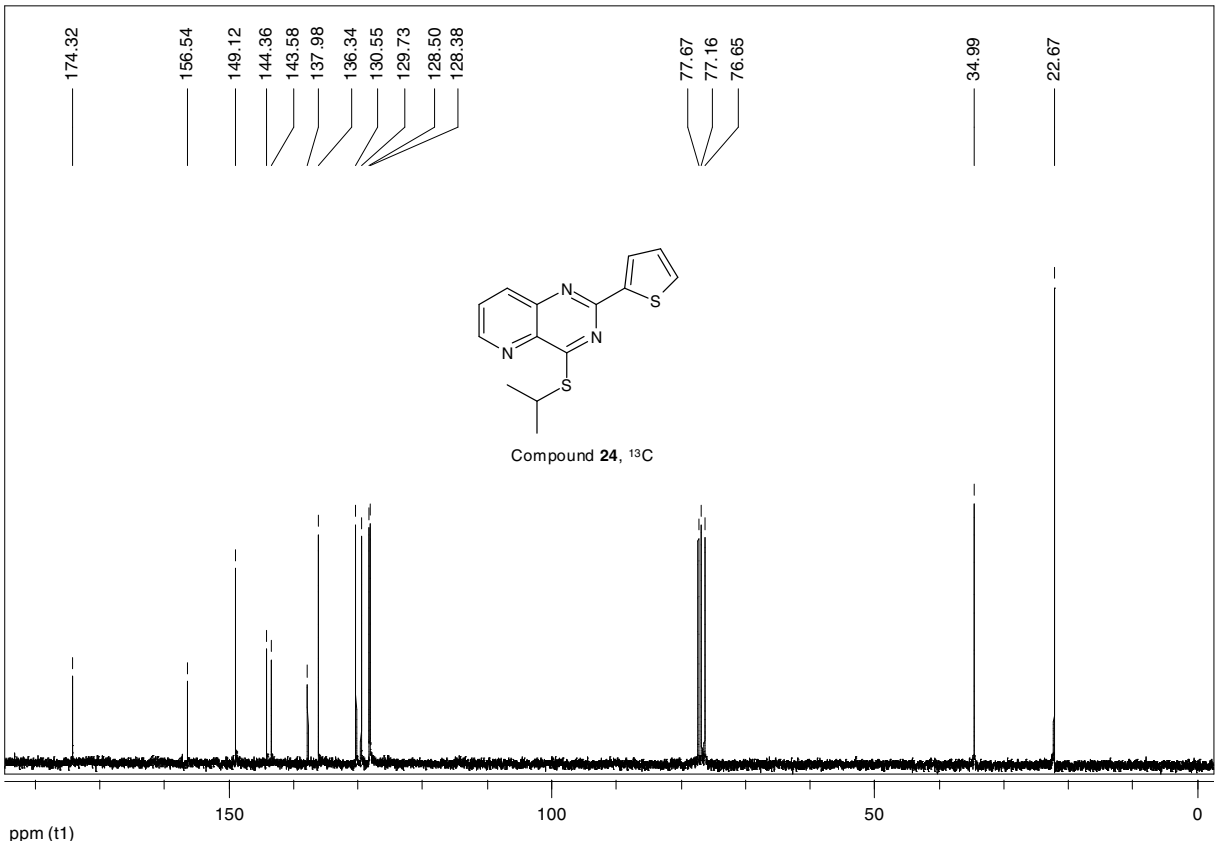


Compound **24**, ^{1}H



Compound **24**, ^{13}C