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Water Based Surfactant-Assisted Synthesis of Thienylpyridines and Thienylbipyridine Intermediates

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Abstract

The connection between heterocyclic systems by forming new C-C bond is a relevant topic for the easy preparation of intermediates and functional dyes for technological applications. Several methods were developed in the last decades and the urge for sustainable synthetic chemical methods pushed us to prepare thienylpyridines and two thienylbipyridine ligands by the Suzuki reaction in aqueous CTAB micellar medium and in presence of a Pd catalyst.

These intermediates can be found as component of dyes and functional thiophene monomers. Reaction conditions were optimized under both thermal and microwave (MW) activation obtaining good yields (70-93%) using Pd(PPh$_3$)$_4$ as catalyst. Two thienylbipyridine ligands were prepared and the transformation of one of them into a terthiophene-based bipyridine ligand was easily obtained by almost green methods and with very good yield. This clean and sustainable method can be proposed as a green step to obtain intermediates and final dyes for technological applications, such as CO_2 reduction, in gram-multigram scale.

1. Introduction

The synthesis of functional dyes for high-tech applications such as organic electronics[1, 2], organometallic dyes[3-6], sensors[7], OLEDs[8, 9], fully organic dyes[10] for solar energy harvesting in Dye-sensitized Solar Cells (DSC), nanomedicine[11, 12] and surfactants[13-16] among others, deeply relies on simple, easy, low cost and reproducible preparation of heterocycle intermediates.

Pyridines and oligopyridines were efficiently exploited in the last decades as ligands for organometallic dyes or in fully organic dyes[17], OLEDs [8, 18] as photoswitchable dyes,[19] as inhibitors of enzymes such as 5-lipoxygenase[20] and as ligands in CO_2 photoreduction systems.[21]

Thiophene is interesting to prepare heteroleptic dyes for DSC[22] and conducting polymers.[23-26] Since in the past we prepared several ligands based on bi-, ter- and quaterpyridines[27] we tried to find a way to assemble pyridines and bipyridines with thiophene using water as a solvent.

While thienylpyridines can be assembled by the closure of heterocyclic rings [28, 29] [30] the direct C-C bond formation between the two heterocycles is a straightforward way to

connect them, by using Stille[31] [32]or Suzuki-Miyaura couplings.[33, 34] In most relevant

papers dealing with Suzuki coupling, [32, 34-38] only a few isomers of thienylpyridines were

prepared, especially those with 3-bromopyridine, while the most interesting ones, from a

material point of view, are based on the 2- or 4-pyridines since the properties of related dyes

or ligands are driven by the highest conjugation of the heterocyclic system. Most protocols

show problems that hamper a large scale application, such as the use of toxic organic

solvents (DME, THF, toluene, benzene). In the recent years, the Suzuki reaction was

performed by using water/ethanol and water/n-butanol as green solvents. [32, 34-38] While

those solvents are more benign, water alone can be used in presence of surfactants. After

fundamental kinetic studies on the micellar catalysis,[39] micellar systems were employed for

preparative synthesis only in the last two decades, also giving access to Pd catalyzed

reactions. [40-45] In particular, Cerichelli, et al. studied the Suzuki reaction to assemble

benzene-based intermediates in hexadecyltrimethylammonium bromide (CTAB)

micelles,[42] working at rt or slightly higher temperature (40°C), demonstrating the broad

applicability of those systems. More recently, Lipshutz [40, 44] prepared novel surfactants,

performing several reactions, in particular, the Pd catalyzed ones (Suzuki, Stille, Heck,

Sonogashira) and, not less important, the Miyaura borylations to obtain the boronic acid used

in Suzuki reactions.

   In this paper we report the green chemistry approach to the surfactant-assisted synthesis in

water of a series of thienylpyridines and of two thienylbipyridines, having practical interest

in CO_2 reduction and Dye–sensitized Solar Cells, using the Suzuki-Miyaura reaction .

2. Experimental Section

2.1 Materials and Methods

All chemicals were purchased from Aldrich or Fluka and were used without further purification except for 4-bromopyridine whose hydrochloride salt is commercially available. The free 4-bromopyridine was obtained adding solid powdered NaOH as detailed in the general procedures. All reactions were performed in micellar medium, under Argon atmosphere, using deionized water as solvent carefully degassed by freeze-thaw-pump method (3 times, 20' each), and working at 60-150 °C under both thermal or MW conditions. The reactions were monitored by thin layer chromatography (TLC) using silica gel as stationary phase on plastic sheets and eluents as reported for the purification in every procedure. The products were purified using a Biotage Isolera automated medium pressure purification system, equipped with UV detector (using variable / fixed wavelength and a Diode array, from 200 to 400 nm), working with silica stationary phase. The eluents used are indicated, for every product, in the proper synthetic procedure.

MW reactions were performed with an Initiator Exp 2.5 Biotage microwave synthesizer (power range 0-400 W at 2.45 GHz). The MW vials of 5 ml were used for routine experiments while 20 ml vials were used for scale-up batches. Vials were crimped and sealed with PTFE septa caps.

NMR spectra were recorded with an Bruker Avance 200, working at 200 MHz for ^{1}H and 50 MHz for ^{13}C. The deuterated solvent were CDCl3 and DMSO-d6 and chemical shifts were reported in parts per million (δ) using TMS and residual solvent peaks as a reference. Multiplicity is reported as usual: s: singlet; d: doublet; dd: doublet of doublet; ddd: double doublet of doublets; t: triplet; m: multiplet.

ESI-MS experiments were performed with a Thermo Fisher Scientific LCQ Advantage Max ion-trap mass spectrometrer, equipped with a ESI source.

Qualitative mass spectra were perfomed using a Thermo Finningan Trace GC GC-MS instrument equipped with a Zebron-5MS fused silica column of Phenomenex (30 x 0.25 mm

i.d., 0.25 μm film tickness), injector temperature of 250 °C, split flow of 10 mL/min, carrier gas Helium at costanf flow of 1.2 mL/min. The GC-MS was used to monitor the reaction outcome.

TEM images were obtained on a *Jeol 3010 TEM*, operated at 300 kV, equipped with an Oxford Inca Energy TEM 200 EDS X-rays analyzer. A 10 μl drop of the proper solution was deposited on the grid and was immediately blotted with filter paper. The solvent was evaporated and the grid was used for the analysis. EDS analysis confirmed that Pd nanoparticles were observed.

ICP-MS measurements were performed with a Perkin Elmer, model ICP-OES Optima 7000DW, on 1 ml of starting solution preliminary diluted to 25 ml.

2.2 Synthesis

2.2.1 General procedure for the synthesis of thienylpyridines isomers (2-7) starting from thiophenes 1a-1b in micellar medium.

In a 5 mL MW vial, purged with Argon for 15 min, CTAB (219 mg, 0.6 mmol), K_2CO_3 (278 mg, 2 mmol), 2- or 3–thiopheneboronic acid (256 mg, 2 mmol) and Pd catalyst (0.025 mmol) were introduced. The vial was purged for further 5 min and 4 mL of degassed water was added. The proper bromopyridine isomer (158 mg, 1 mmol) was added, and in the case of a 4-bromopyridine hydrocloride, NaOH (powder, 44 mg, 1.1 mmol) was added to release the pyridine in solution as a free base. The use of only one more additional equivalent of K_2CO_3 was not enough to make the 4-bromopyridine hydrocloride able to react considerably. The mixture was stirred and sonicated to obtain a homogeneous solution that was introduced into a pre-heated oil bath for 24 h or reacted in a MW reactor for 30 minutes at the proper temperature. When the starting material was consumed, the reaction was diluted with further 5 mL of water and extracted with ethyl acetate (3x5ml). For comparison a few solvents were

used: CH_2Cl_2 (5x5mL) or Et_2O (2-3x5ml) and EtOAc (2-3x5ml), with comparable efficiencies. The organic layers were then collected, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography of the crude residue afforded the desired products **2-7**. Yields of isolated products are based on the starting pyridine.

2.2.2 General procedure for the synthesis of the thienylpyridine 5 in micellar medium using PdCl$_2$ as catalyst.

In a 10 mL MW vial, purged with Argon for 15 min, 3–thiopheneboronic acid (256 mg, 2 mmol), CTAB (219 mg, 0.6 mmol) and K_2CO_3 (278 mg, 2 mmol) were introduced and the vial was purged with argon for 10 minutes. Degassed water (4 mL) was added and the mixture was stirred and sonicated to obtain an homogeneous solution. The 2-bromopyridine (158 mg, 1 mmol) and $PdCl_2$ catalyst (1.8 mg, 0.010 mmol, or 4.4 mg, 0.025 mmol, depending on the trial) were introduced in this order. The vial was purged for further 10 min. The solution was introduced into a pre-heated oil bath for 24 h or reacted in a MW reactor for 30 minutes at the proper temperature. When the starting material was consumed, the reaction was diluted with further 5 mL of water and extracted with ethyl acetate (3x5ml). The organic layers were then collected, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography of the crude residue with Biotage using 25g packed column, and an isocratic method (Petroleum ether/EtOAc 8:2 + 0.5% CH_3COOH), afforded the product **5**. Yields of isolated product are based on the starting pyridine.

2.2.3 General Procedure for the synthesis of the thienylpyridine 5 in micellar medium using Pd/C as Catalyst.

In a 5 mL MW vial, purged with Argon for 15 min, 3–thiopheneboronic acid (256 mg, 2 mmol), CTAB (219 mg, 0.6 mmol) and K_2CO_3 (278 mg, 2 mmol) were introduced. The vial was purged for further 10 min and 4 mL of degassed water were added. The mixture was stirred and sonicated to obtain a homogeneous solution. The 2-bromopyridine (158 mg, 1 mmol) and 10% Pd/C catalyst (27 mg, 0.025 mmol) were introduced in this sequence. The mixture was stirred for 10 min under Argon flux and the suspension was introduced into a pre-heated oil bath for 24 h or reacted in a MW reactor for 30 minutes at the proper temperature. When the starting material was consumed, the reaction was diluted with further 5 mL of water and extracted with ethyl acetate. The organic layers were then collected, dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. Purification by flash chromatography of the crude residue afforded the desired product **5**. Yields of isolated product are based on the starting pyridine.

2.2.4 Notes on the choice of the solvent for solvent extraction of the reaction mixture:
Three organic solvents, dichloromethane, diethyl ether and ethyl acetate were compared to find the best solvent to be used for extraction of the reaction mixture. Dichloromethane required a higher number of extraction (in general at least five) to remove the product, while also removing catalyst, more byproducts (when present) and a quantity of the surfactant from water. Ethyl acetate and diethyl ether were found to be similar in their extracting behavior. They did not extract the surfactant from water and required from two to three extraction to extract all the product, showing low tendence to form emulsions. Due to its better classification as green solvent,[46] ethyl acetate was used as the solvent of choice.

2.2.5 Isolation and characterization of the products.

All the reaction products **2-12** were isolated by flash chromatography and fully characterizated by MS, ^{1}H and ^{13}C NMR (see SI for compound spectra). Products **2-7** are all well known and were identified by comparison of physical and spectroscopic data with those given in the cited reference: **2**, [47] **3**, [47] **4**,[48] **5**, [47] **6**,[47] **7**.[49] Spectroscopic traces for every product are reported in the Supporting Information.

2.2.5.1 *2-(thiophen-2-yl)pyridine.(2)* The crude product was purified by flash chromatography with Biotage using 25g packed column, with an isocratic method (Petroleum ether/EtOAc 9:1 + 0.2% CH_3COOH, R_f=0.32) affording an orange oil. ^{1}H NMR (200 MHz, $CDCl_3$) = δ 8.56 (d, J= 4.8 Hz, 1H), 7.70-7.60 (m, 2H), 7.57 (dd, J = 3.7, 1.0 Hz, 1H), 7.38 (dd, J = 5.0, 1.0 Hz, 1H), 7.17 – 7.03 (m, 2H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 152.42, 149.37, 144.73, 136.52, 127.95, 127.45, 124.47, 121.77, 118.65. Elemental analysis, found: C, 67.10; H, 4.41; N, 8.62, molecular formula for C_9H_7NS requires: C, 67.05; H, 4.38; N, 8.69;. MS (ESI) calcd. for C_9H_7NS [M+H]$^+$ *m/z:*162.03 found 162.19.

2.2.5.2 *3-(thiophen-2-yl)pyridine.(3)* The crude product was purified by flash chromatography with Biotage using 25g packed column with an isocratic method (Petroleum ether/EtOAc 9:1 + 0.5% CH_3COOH, R_f=0.33) affording a yellow oil. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.87 (d, J = 2.1 Hz, 1H), 8.56 – 8.44 (m, 1H), 7.86 (ddd, J = 8.0, 2.3, 1.6 Hz, 1H), 7.44 – 7.23 (m, 3H), 7.10 (dd, J = 4.8, 3.9 Hz, 1H). ^{13}C NMR (50 MHz, $CDCl_3$) δ 148.08, 146.65, 140.20, 133.15, 130.50, 128.28, 126.10, 124.29, 123.71. Elemental analysis, found: C, 67.08; H, 4.36; N, 8.66, molecular formula for C_9H_7NS requires: C, 67.05; H, 4.38; N, 8.69; . MS (ESI) calcd. for C_9H_7NS [M+H]$^+$ *m/z:*162.03 found 162.21.

2.2.5.3 *4-(thiophen-2-yl)pyridine.(4)* The crude product was purified by flash chromatography with Biotage using 25g packed column, with an isocratic method (Petroleum ether/EtOAc 9:1 + 0.2-0.5% CH_3COOH, R_f = 0.33) affording a white powder. ^{1}H NMR (200 MHz, $CDCl_3$) δ 8.59 (d, J = 6.1 Hz, 1H), 7.58 – 7.45 (m, 2H), 7.42 (dd, J = 5.1, 0.6 Hz, 1H),

7.14 (dd, J = 5.1, 3.7 Hz, 1H). ^{13}C NMR (50 MHz, Acetone) δ 151.36, 141.90, 129.52, 128.38, 126.71, 125.42, 120.42. Elemental analysis, found: C, 67.02; H, 4.45; N, 8.65, molecular formula for C_9H_7NS requires: C, 67.05; H, 4.38; N, 8.69. MS (ESI) calcd. for C_9H_7NS [M+H]$^+$ *m/z:*162.03 found 162.22.

2.2.5.4 *2-(thiophen-3-yl)pyridine.(5)* The crude product was purified by flash chromatography with Biotage using 25g packed column, with an isocratic method (Petroleum ether/EtOAc 8:2 + 0.5% CH_3COOH, R_f=0.32) affording a pale yellow oil. ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.62 (d, J = 4.8 Hz, 1H), 7.91 (dd, J = 3.0, 1.3 Hz, 1H), 7.81 – 7.56 (m, 3H), 7.40 (dd, J = 5.1, 3.0 Hz, 1H), 7.17 (ddd, J = 7.1, 4.9, 1.4 Hz, 1H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 153.52, 149.64, 142.20, 136.75, 126.36, 126.21, 123.53, 121.85, 120.32. Elemental analysis,found: C, 67.12; H, 4.36; N, 8.68, molecular formula for C_9H_7NS requires: C, 67.05; H, 4.38; N, 8.69. MS (ESI) calcd. for C_9H_7NS [M+H]$^+$ 162.03 found 162.15.

2.2.5.5 *3-(thiophen-3-yl)pyridine. (6)* The crude product was purified by flash chromatography with Biotage using 25g packed column, with an isocratic method (Petroleum ether/EtOAc 8:2 + 0.5 % CH3COOH, R_f=0.33) affording a yellow oil. ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.87 (s, 1H), 8.52 (d, J = 4.8 Hz, 1H), 7.85 (dd, J = 7.9, 1.6 Hz, 1H), 7.51 (d, J = 1.4 Hz, 1H), 7.49 – 7.20 (m, 3H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 147.90, 147.34, 138.39, 133.09, 131.10, 126.69, 125.54, 123.30, 121.14. Elemental analysis, found: C, 67.08; H, 4.40; N, 8.63, molecular formula for C_9H_7NS requires: C, 67.05; H, 4.38; N, 8.69. MS (ESI) calcd. for C_9H_7NS [M+H]$^+$ *m/z:* 162.03 found 162.14.

2.2.5.6 *4-(thiophen-3-yl)pyridine. (7)* The crude product was purified by flash chromatography with Biotage using 25g packed column with an isocratic method (Petroleum Ether/EtOAc 8:2 + 0.2% CH_3COOH, R_f=0.32) affording a white solid (93 % isolated yield) ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.35 (d, J=5.84 Hz, 2H), 7.58 (s, 1H), 7.41-7.35 (m, 4H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 150.16, 142.37, 139.22, 126.91, 125.48, 122.92, 120.57. Elemental

analysis, found: C, 67.08; H, 4.40; N, 8.63 molecular formula for C_9H_7NS requires: C, 67.05; H, 4.38; N, 8.69. MS (ESI) calcd. for C_9H_7NS [M+H]$^+$ *m/z:*162.03 found 162.19.

2.2.5.7 *4-(thiophen-3-yl)-2,2'-bipyridine. (8)* In a 5 mL MW vial, purged with Argon for 15 min, 3–thiopheneboronic acid (256 mg, 2 mmol), CTAB (219 mg, 0.6 mmol), K_2CO_3 (278 mg, 2 mmol), and 4-bromobipyridine (235 mg, 1 mmol) were introduced. The vial was purged for further 10 min and 4 mL of degassed water were added. The mixture was stirred and sonicated to obtain an homogeneous solution. The Pd catalyst (0.025 mmol) was introduced, the vial was crimped and purged with argon for 10 min. The vial was introduced into a pre-heated oil bath, at 80 °C for 24 h or reacted in a MW reactor for 2h at 150 °C. When the starting material was consumed, the reaction was diluted with further 5 mL of water and extracted with ethyl acetate (3x5ml). The organic layers were then collected, dried over anhydrous Na_2SO_4 and concentrated *in vacuo.*The crude product was purified by flash chromatography with *Biotage* using 25g packed column with an isocratic method (Petroleum Ether/EtOAc 9:1 to 8:2 + 0.5% TEA, R_f=0.37) affording a white solid product. Yield: 198 mg. 83% for classical heating, and 219 mg, 92% for the MW reaction. Yields of isolated products are based on the starting 4-bromobipyridine. ^{1}H NMR (200 MHz, CDCl$_3$) *δ* 8.69 (m, 3H), 8.44 (dt, *J*=8.0, 0.9 Hz, 1H), 7.83 (m, 2H) 7.57 (dd, *J*=5.1, 1.4 Hz, 1H), 7.51 (dd, *J*=5.1, 1.8 Hz, 1H), 7.45 (dd, *J*=5.1, 2.9 Hz, 1H), 7.33 (dd, *J*=7.5, 4.8, 1.2 Hz, 1H). ^{13}C NMR (50 MHz, CDCl$_3$) *δ* 156.76, 156.11, 149.79, 149.19, 143.73, 139.73, 137.03, 126.97, 126.03, 123.90, 123.48, 121.33, 120.87, 118.27. Elemental analysis, found: C, 70.52; H, 4.27; N, 11.71, molecular formula for $C_{14}H_{10}N_2S$ requires: C, 70.56; H, 4.23; N, 11.76; S, 13.46. MS (ESI) calcd. for $C_{14}H_{10}N_2S$ [M+H]$^+$ *m/z:* 239.06, found 239.25.

2.2.5.8 *4-(2-bromothiophen-3-yl)-2,2'-bipyridine. (9)* In a 10 ml vial compound **8** (480 mg, 2 mmol) and NBS (350.03 mg, 3 mmol) were introduced. EtAc was added and the vial was closed with a rubber stopper. The reaction was left to react under stirring overnight, when the

starting material disappeared. The solvent was removed under vacuum, leaving about 940 mg of crude. After chromatography with Biotage (silica, petroleum ether : ethyl acetate 8:2 + 0.5% triethylamine) and solvent evaporation, a white powder was obtained, 870 mg (91%). ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.72 (dd, J = 5.1, 0.7 Hz, 1H), 8.68 (ddd, J = 4.8, 1.7, 0.9 Hz, 1H), 8.58 (dd, J = 1.7, 0.8 Hz, 1H), 8.42 (dt, J = 8.0, 1.0 Hz, 1H), 7.82 (td, J = 7.8, 1.8 Hz, 1H), 7.55 (dd, J = 5.1, 1.8 Hz, 1H), 7.35 (t, J = 3.3 Hz, 1H), 7.30 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 7.17 (d, J = 5.7 Hz, 1H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 155.69, 155.08, 149.10, 148.95, 144.50, 138.44, 137.69, 128.84, 126.98, 124.34, 123.46, 121.87, 121.21, 111.23. Elemental analysis, found: C, 52.98; H, 2.83; N, 8.88; S, 10.06, molecular formula for C$_{14}$H$_9$BrN$_2$S requires: C, 53.01; H, 2.86; N, 8.83; S, 10.11. MS (ESI) calcd. for C$_{14}$H$_9$BrN$_2$S [M+H]$^+$ m/z: 315.97, 315.99.

2.2.5.9 *4-(2,5-dibromothiophen-3-yl)-2,2'-bipyridine. (10)* In a 20 ml MW vial, previously degassed with Argon, compound **8** (422 mg, 1.77 mmol) and EtAc (20 ml) were added with a stir bar. The solution was stirred and degassed with argon for 10 min. NBS was added (1.576 g., 8.85 mmol,). The reaction was run at RT for 5 days. When the reaction was stopped, the suspension was filtered to remove NBS and the solvent was evaporated. The solid was dissolved with dichloromethane and extracted 3 times with water to eliminate NHS. The organic phase was dried with Na$_2$SO$_4$ and the solvent was evaporated under vacuum. The product was obtained as white solid: 701 mg (100%). ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.74 (dd, J = 5.1, 0.7 Hz, 1H), 8.70 (d, J = 3.9 Hz, 1H), 8.59 – 8.52 (m, 1H), 8.44 (d, J = 7.9 Hz, 1H), 7.84 (td, J = 7.8, 1.8 Hz, 1H), 7.51 (dd, J = 5.1, 1.8 Hz, 1H), 7.33 (ddd, J = 7.5, 4.8, 1.2 Hz, 1H), 7.18 (s, 1H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 156.68, 155.73, 149.53, 149.36, 142.76, 139.58, 137.23, 131.36, 131.33, 124.16, 122.98, 121.45, 120.61, 112.31, 109.99. Elemental analysis, found: C, 42.50; H, 2.02; N, 7.11; S, 8.07, molecular formula for C$_{14}$H$_8$Br$_2$N$_2$S

requires: C, 42.45; H, 2.04; N, 7.07; S, 8.10, 11.36. MS (ESI) calcd. for $C_{14}H_8Br_2N_2S$ [M+H]$^+$ m/z: 393.88, found 393.92.

2.2.5.10 *4-([2,2':5',2''-terthiophen]-3'-yl)-2,2'-bipyridine. (11)* In a 20 MW vial , compound **10** (200 mg, 0.51 mmol), 2-thiopheneboronic acid (0.213 g, 1.66 mmol), CTAB (0.219 g, 0.6 mmol) and Pd(PPh$_3$)$_4$ (14.6 mg, 0.013 mmol, 2.5%) catalyst were introduced after degassing. Water (4 ml) was added and the mixture was stirred and flushed with argon. A 2M Na$_2$CO$_3$ solution (1.19 ml, 2.37 mmol, 0.251 g of Na$_2$CO$_3$) was added and the suspension was stirred and sonicated to solubilize the reagents. The reaction was run under MW for 30 min at 120°C. The final suspension was filtered and the solid was washed with EtAc. The aqueous phase was extracted with EtAc (3 x 10 ml). The collected organic phases were dried with Na$_2$SO$_4$, filtered and evaporated, thus giving 0.155 g of orange/brown viscous oil. After chromatography with Biotage (silica, petroleum ether : ethyl acetate 8:2), the product was collected and the solvent was removed, giving a yellow oil, 0.122 g (60%). ^{1}H NMR (200 MHz, CDCl$_3$) δ 8.69 – 8.62 (m, 1H), 8.58 (dd, J = 5.1, 0.8 Hz, 1H), 8.50 – 8.44 (m, 1H), 8.42 – 8.33 (m, 1H), 7.80 (td, J = 7.7, 1.8 Hz, 1H), 7.36 – 7.13 (m, 7H), 7.06 – 6.97 (m, 2H), 6.93 (dd, J = 5.0, 3.6 Hz, 1H). ^{13}C NMR (50 MHz, CDCl$_3$) δ 149.34, 148.78, 145.62, 137.35, 136.92, 136.75, 136.44, 134.57, 132.36, 128.15, 127.76, 127.59, 126.88, 126.12, 126.09, 125.28, 124.47, 124.23, 121.64. LC-MS (ESI+) calcd. for C_9H_7NS [M+H$^+$] 403.04, found 403.27. Elemental analysis, found: C, 65.69; H, 3.58; N, 6.88; S 23.86, molecular formula for $C_{22}H_{14}N_2S_3$ requires: C, 65.64; H, 3.51; N, 6.96; S, 23.90. MS (ESI) calcd. for $C_{22}H_{14}N_2S_3$ [M+H]$^+$ m/z: 403.03, found 403.27.

2.2.5.11 *5-([2,2'-bipyridin]-4-yl)thiophene-2-carboxylic acid. (12)* In a 5 mL MW vial, purged with Argon for 15 min, 5-carboxy-2–thiopheneboronic acid **1c** (732 mg, 2 mmol, 2eq.), CTAB (465 mg, 1.276 mmol, 0.6 eq.), K$_2$CO$_3$ (1.764 g, 12.76 mmol, 6 eq.), and 4-

bromobipyridine (500 mg, 1.276 mmol, 1 eq.) were introduced. The vial was purged for further 15 min and 4 mL of degassed water were added. The mixture was stirred and sonicated to obtain an homogeneous solution. The Pd catalyst, $Pd(PPh_3)_4$ (0.025 mmol) was introduced, the vial was crimped and purged with argon for 10 min. The vial was introduced into a pre-heated oil bath, at 80 °C for 24 h or in a MW reactor for 1h at 120 °C. When the starting material was consumed, the reaction mixture was filtered in a Hirsch funnel under vacuum. Care should be taken since the formation of foams into the receiving flask. The crude product (0.61 g) was suspended in the minimal water (about 10 ml) and 6M HCl was added under stirring until pH = 3 was obtained. After 10 minutes of further stirring, the supsension was filtered under vacuum on a Hirsch funnel and the product was recovered. Futrher acidification of the mother liquor gave after filtration another crop of pure material. The product was obtained as a faint yellow powder: 0.3823 g. (63.7%). ^{1}H NMR (200 MHz, DMSO) ^{1}H NMR (200 MHz, DMSO) δ 8.78 (m, J = 5.0 Hz, 2H), 8.70 (s, 1H), 8.54 (d, J = 8.1 Hz, 1H), 8.12 (td, J = 7.8, 1.7 Hz, 1H), 8.00 (d, J = 4.0 Hz, 1H), 7.91 (dd, J = 5.3, 1.9 Hz, 1H), 7.82 (d, J = 4.0 Hz, 1H), 7.68 – 7.54 (m, 1H).. ^{13}C NMR (50 MHz, DMSO-d6) δ 156.76, 156.11, 149.79, 149.19, 143.73, 139.73, 137.03, 126.97, 126.03, 123.90, 123.48, 121.33, 120.87, 118.27. Elemental analysis, found: C, 63.77; H, 3.62; N, 9.85; S 11.40, molecular formula for $C_{15}H_{10}N_2O_2S$ requires: C, 63.81; H, 3.57; N, 9.92; S, 11.36. MS (ESI) calcd. for $C_{15}H_{10}N_2O_2S$ $[M+H]^+$ *m/z:* 282.05, found 281.09.

3. Results and discussion

Following our engagement in the synthesis of heterocycles for dyes and ligands, in the present paper we tried to assemble heterocycles, e.g. thienylpyridines (**2-7**) and thienylbipyridines (**8-12**) (Figure 1) by applying Green Chemistry compliant procedures,[50]

to prepare ligands for several applications, like CO_2 reduction[51] to produce fuels or other chemicals for industry.[21, 52, 53]
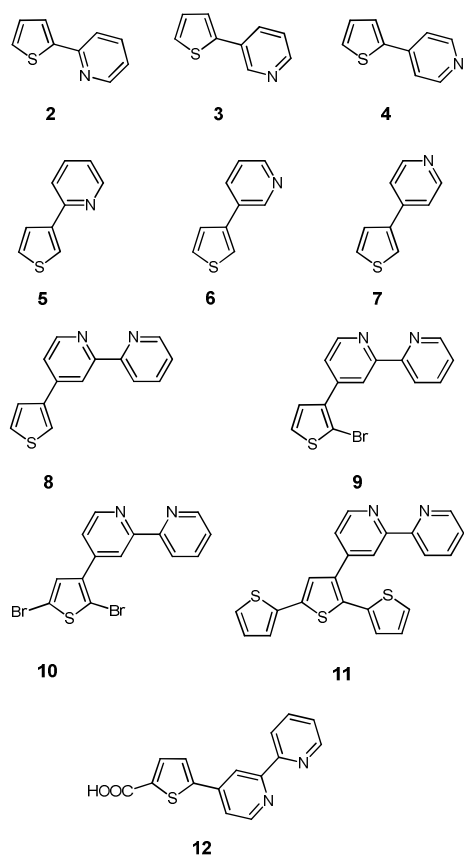

Figure 1. Structures of the products obtained in this work.

Since our activity was dealing with preparation of ligands, it was interesting to explore the coupling of thiopheneboronic acids and bromopyridines by the Suzuki reaction (Scheme 1) trying to satisfy some of the principles of Green Chemistry and limiting the scope to the simple unsubstituted bromopyridines and to the 4-bromobipyridine.

We applied the protocol developed by Cerichelli et al.[42] to our system and tried to find ways for optimization. Typically, Suzuki coupling protocols for thiophene and pyridines use temperatures ranging from 80 up to 130°C.[54] Since saving energy is one of the important issues to be addressed for Green Chemistry, in order to limit the energy consumption we studied the effect of temperature on those reactions and also the effect of microwaves (MW)

to shorten considerably the reaction time. The protocol was adapted and successfully used for the preparation of thienylbypiridine ligands, since two of them gave rhenium complexes that after electropolymerization (in particular, ligand **8**) proved to be efficient in catalytic CO_2 reduction.[51]

1a: X= H, Y = B(OH)$_2$, R = H
1b: X= B(OH)$_2$, Y = H, R = H
1c: X= H, Y = B(OH)$_2$, R = COOH
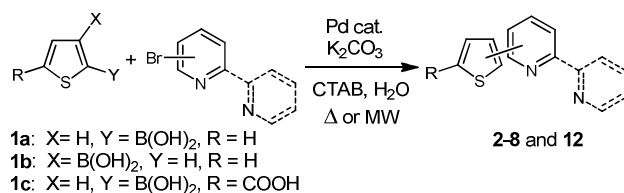
2-8 and **12**

Scheme 1. General reaction for the synthesis of thienylpyridines (**2-7**) and thienylbipyridines (**8** and **12**) in surfactant solution.

In a preliminary set of experiments, 2- and 3-thiopheneboronic acids **1a** and **1b** reacted with 2-, 3- and 4-bromopyridines (Scheme 1) following a standard Suzuki protocol,[33] working in the presence of 2.5% Pd(PPh$_3$)$_4$ and Na$_2$CO$_3$ in DME at 80 °C overnight, for a comparison with the literature. The same yields were obtained. Then, we checked the possibility of substituting the organic solvent DME with water in agreement with Cerichelli et al. approach.[42]

In Table 1 the yields for the reaction of 2-thiopheneboronic acid **1a** with bromopyridines in thermal conditions are reported working for 24h, typical reaction time of Suzuki protocols. This set of reactions was performed at 25 °C and 80 °C and 1 mmol scale, using Pd(PPh$_3$)$_4$ as catalyst and K$_2$CO$_3$ as base, CTAB at 0.60 mmol, and water as a solvent. No differences in yields were observed by keeping in excess (2 mmol) the boronic acid or the bromopyridine. The 2-thiopheneboronic acid reacted with bromopyridines giving good yields (74-93%) at 80 °C while the reaction at rt appeared more selective giving, after 24h, compound **2** in isolated yield of 73% and compounds **4** and **3** in isolated yield of 5% and in small quantity detected only by GC-MS (product not isolated) respectively.
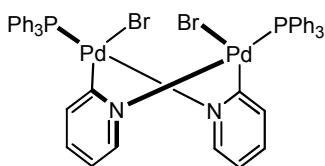
Figure 2. Dinuclear Pd complex formed by reaction of Pd(PPh$_3$)$_4$ and 2-bromopyridine.

The higher reactivity shown by the 2-bromopyridine was peculiar. In the literature it was reported that the reaction of 2-bromopyridine with Pd(PPh$_3$)$_4$, by oxidative addition, gave a dinuclear complex in which the two pyridine nitrogens coordinate two Pd atoms, as reported in Figure 2; while 3- and 4-bromopyridines formed only mononuclear complexes.[55]

Table 1. Results for the reaction of 2-thiopheneboronic acid **1a** with bromopyridines[a]

Pyridine	Thermal	MW	Yield
	°C	°C	(%)
	(24h)	(0.5h)	(product)[b]
2-Br	25	-	73 (**2**)
2-Br	80	-	74 (**2**)
2-Br	-	80	77 (**2**)
3-Br	25	-	0 (**3**)
3-Br	80	-	79 (**3**)
3-Br	-	80	63 (**3**)
4-Br	25	-	5 (**4**)
4-Br	80	-	93 (**4**)
4-Br	-	80	82 (**4**)

[a] Reaction conditions: CTAB (0.60 mmol), 4 ml of degassed water, boronic acid (2 mmol), bromopyridine (1 mmol), K$_2$CO$_3$ (2 mmol), were mixed into a MW vial, stopped with rubber septum and stirred until clear solution was obtained. Palladium catalyst, Pd(PPh$_3$)$_4$, (0.025 mmol) was then added and the reaction was run with proper condition as reported in the table. [b] isolated yield.

The dinuclear complex was tested in literature as a precatalyst in Suzuki couplings and showed high activity,[56] supposed to be related to the lability of the Pd-N bond, prone to

break easily, giving a very rapid transmetallation. In the case of mononuclear complexes formed by the 3- and 4-bromopyridines, a phosphine ligand has to be removed before the transmetallation with the boronic acid takes place. Probably, the stronger bond of Pd with phosphine requires more energy to break and this could be the reason of the lower reactivity in the case of 3- and 4-bromopyridines. In the case of the less reactive 3-thiopheneboronic acid **1b**, no reaction was observed at room temperature for 2-bromopyridine (vide infra).

MW was tested as alternative heating system to activate the reaction at 80 °C choosing to check the reaction already after 30 min because the extraordinary increment of MW on reaction kinetics, is well established. Comparable yields (Table 1) with traditional heating already after 30 min have been obtained: 77% for compound **2**, 63% for compound **3** and 82% for compound **4**. MW are confirmed as efficient heating system able to reduce reaction time and, as consequence, to save energy. Working at the same temperature (80 °C), the expected increase of reactivity by using MW is only due to the better warming effect. The temperature is rapidly attained and constantly maintained in the vessel, while the heat distribution in the case of thermally activated reactions is more difficult to be controlled.[57] The dependence of yields from temperature was studied in more detail with 3-thiopheneboronic acid **1b** to obtain compound **5**, as a model reaction for the preparation of 4-(thiophen-3-yl)-2,2'-bipyridines, e.g. compound **8** and **11**, precursors for the synthesis of conductive side-chain functionalised polythiophenes, of interest for the photo- and electrochemical CO_2 reduction. Meaningful yields were observed only in the temperature range of 45-100 °C. In Figure 3 the comparison of yields obtained in thermal and under MW activation for the reaction of **1b** with 2-bromopyridine is reported.

At 45 °C the yield obtained under MW irradiation for 30 min is negligible while in thermal condition a yield of about 30% was observed suggesting that the Suzuki reaction is too slow

at 45 °C and needs time to give significant quantity of compound **5**. Higher temperatures

accelerated the reaction with a clear increasing of yields.
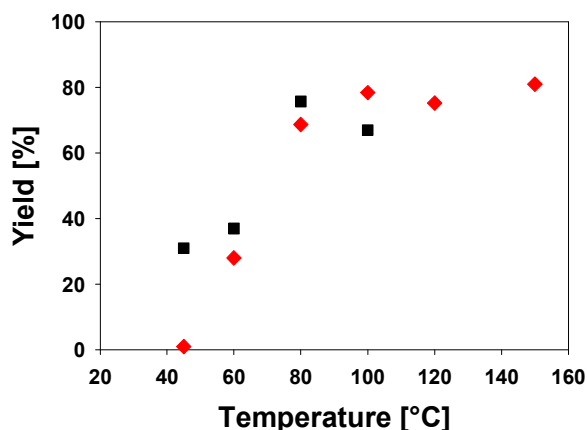
Figure 3. Yield dependence on temperature, for both thermal (24h) (■) and microwave (30')

(◆) activated reactions of 3-thiopheneboronic acid **1b** reaction with 2-bromopyridine,

obtaining product **5**.

Table 2. Results for the reaction of 3-thiopheneboronic acid **1b** with bromopyridines[a]

Pyridine	Thermal	MW	Yield[b]
	°C	°C	(%)
	(24h)	(30min)	(product)
2-Br	80	-	76 (**5**)
2-Br	-	80	70 (**5**)
3-Br	80	-	86 (**6**)
3-Br	-	80	78 (**6**)
4-Br	80	-	70 (**7**)
4-Br	-	80	73 (**7**)

[a] Reaction conditions: CTAB (0.60 mmol), 4 ml of degassed water, boronic acid (2 mmol), bromopyridine (1 mmol), K_2CO_3 (2 mmol), were mixed into a MW vial, closed with rubber septum and stirred until clear solution was obtained. Palladium catalyst, $Pd(PPh_3)_4$, (0.025 mmol) was then added and the reaction was run under proper conditions, as reported in the table. [b] isolated yield.

Noteworthy is the comparison of data at 100 °C where MW gave better yields confirming

that the positive activation of MW allows to reduce the reaction time and the thermal

degradations that typically occur in prolonged heating steps. Working with closed vessel, MW irradiation allowed to explore temperatures also over 100 °C. Isolated yields of 75% and 81% were obtained at 120 °C and 150 °C respectively. Data reported in Figure 3 suggested that a further increase in temperature can result to be beneficial under MW. The short reaction time (30 min) allows this approach interesting also from the energy saving point of view.

The yields obtained for the reaction of 3-thiopheneboronic acid with 3- and 4-bromopyridines at 80 °C are reported in Table 2. As in the case of 2- isomer, the 3-bromopyridine showed a slightly lower yield when performed with MW activation instead of thermal conditions while the yield observed with 4-bromopyridine appeared comparable.

In order to complete the study with MW for the reaction of 3-thiopheneboronic acid **1b** with 2-bromopyridine at 80°C, we tried to explore the effect of the reaction time by GC-MS, since the short time of 30 min seemed to be enough to obtain a yield similar to that of the thermal reaction. The extension of time until 1h indicated an increase of the yield. However, after 2 h the quantity of byproducts increased considerably and it was estimated that a reaction time of 30 min-1h was the best choice. Isolated yield of 73% for compound **5** obtained after 1 h of reaction, slightly better than the reaction performed over 30 min, confirmed the GC-MS study.

3.1 Effect of the Pd Catalyst.

All the previous reactions were performed in homogeneous conditions with the Pd(PPh$_3$)$_4$ catalyst. In order to search for phosphine-free and cheaper catalysts, to fulfill both sustainability requirements for Green Chemistry and economical aspects, we explored PdCl$_2$

and Pd/C as possible catalysts for the reaction of 3-thiopheneboronic acid **1b** with 2-bromopyridine, for the synthesis of compound **5**.

3.1.1 Use of PdCl$_2$.

Usually reactions dealing with PdCl$_2$ are not performed in water, but at least in organic solvent/water mixtures. We tried to use PdCl$_2$ (at 2.5% loading) in micellar media.

In Figure 4 the observed isolated yields in compound **5** vs temperature are reported working in thermal conditions for 24 h and under MW activation for 30 min. Lower yields (ranged in between 52-60% as a maximum) were obtained for both heating systems than in presence of Pd(PPh$_3$)$_4$ as catalyst. Extending the reaction time to 2 hours under MW, the isolated yield for compound **5** increased to 74% and 75% with catalyst loading of 2.5% or 1% respectively. The yields are comparable to those obtained in presence of Pd(PPh$_3$)$_4$ but with about half of time. This result can make us to propose this phosphine-free catalyst at lower loading as a valid substitute for the Pd(PPh$_3$)$_4$, just accepting a longer reaction time.

The almost immediate formation of a brown color on the addition of the 3-thiopheneboronic acid in the classical reaction conditions (see Figure 5a) suggested the Pd(0) nanoparticles formation, as some papers described.[43, 58-63] UV-visible spectroscopic study was performed in order to confirm the hypothesis that the observed catalytic activity could be related to Pd(0) nanoparticles generated from PdCl$_2$, stabilized from CTAB, that avoids particle aggregation and the growth of larger nanoparticles. Figure 5 shows the color changes following the addition of different components. UV-visible spectra of transparent solutions are reported in Figure 6a.
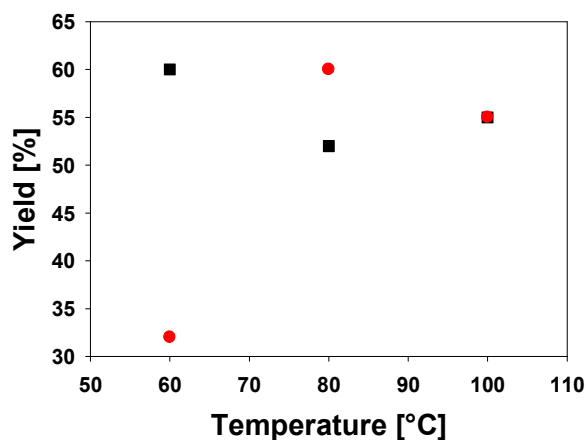
Figure 4. Reaction yield for 3-thiopheneboronic acid with 2-bromopyridine obtained with PdCl$_2$ (obtaining **5**): (■) Thermal reaction, 24h, (●) Microwave activation, 30 min.
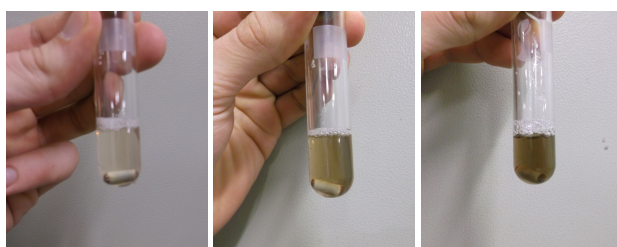
Figure 5. Photos of reaction mixtures: a) reaction mixture of **1b** just added to a solution of CTAB and PdCl$_2$ (typical reaction conditions), b) solution of CTAB and PdCl$_2$; c) **1b** (about 5 mg) added to the solution of CTAB and PdCl$_2$; d) **1b** (about further 5 mg) added to the solution of CTAB and PdCl$_2$, already shown in image c.

PdCl$_2$ dissolves sparingly in water but readily in water in presence of CTAB (Figure 5b) showing a main peak around 340 nm (Figure 6a), ascribed to a strong PdCl$_2$-CTAB

interaction.[47] After the addition of the 3-thiopheneboronic acid **1b**, the UV-visible

spectrum shows the disappearance of the peak at 340 nm and the appearance of a large

absorption in the visible region, in agreement with the observed color change (Figure 5c); the

absorption increases with a successive addition of reagent **1b** (Figure 5d and UV-visible

spectrum reported in Figure 6a).

Similar absorption is reported by true Pd(0) nanoparticles preparation[60-62] and in a

CTAB assisted Heck reaction where Bhattacharya et al. hypothesized the catalytic activity of

colloidal dispersion of Pd(0), formed from $PdCl_2$ in water in presence of cationic surfactant at

80-130 °C.[43] Yang et al. demonstrated that $Pd(OAc)_2$ in presence of a phosphine ligand

was rapidly reduced to Pd(0) by the use of the phenylboronic acid, producing the

homocoupling product, biphenyl.[49] Also Jutand[64] and Hartwig,[65] in an independent

way, collected kinetic evidence of the reducing role of the boronic acid towards Pd(II).

No brown coloration appeared in absence of 3-thiopheneboronic acid **1b** so its presence is

essential for the reduction of the Pd(II), giving the 3,3'-bisthiophene as the only

homocoupling product,[34, 49, 66] identified by GC-MS. The role of the base appeared

important too. When the experiment was conducted in presence of K_2CO_3 the reaction was

qualitatively much faster, following the coloration change by the naked eye to occur in about

a minute. Similar UV-visible spectra were obtained in presence of base. This agrees with the

observations of Jutand[64] and Hartwig,[65] who recorded a kinetic increment of Pd(II)

reduction if a high $[OH^-]/[ArB(OH)_2]$ ratio was used. They suggested that the base promotes

the transmetallation of an arylboronic acid to give the ArLPd-(OH) (L is a phosphine ligand),

helping the formation of pentacoordinate Pd complex which was imagined to be the species

activating the reductive elimination process. Noteworthy is the fact that Jutand[64] and

Hartwig,[65] reported about a homogeneous catalytic system; while we are showing that Pd

nanoparticles are formed.
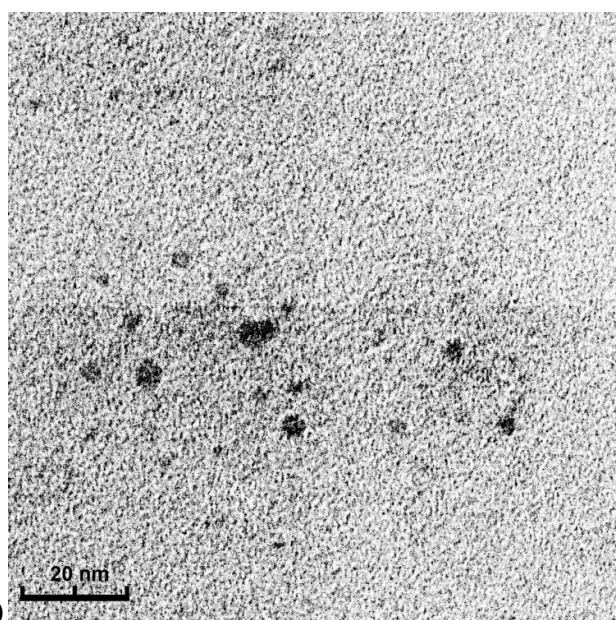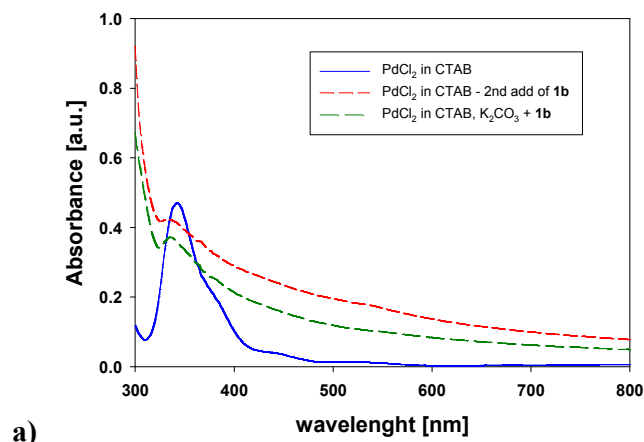
Figure 6. Panel a: UV spectra for $PdCl_2$ in CTAB (blue, solid line); in CTAB after the second addition of **1b** (red, short dash line); in CTAB and K_2CO_3 after a first addition of **1b** (green, medium dash line). Panel b: TEM image of the Pd nanoparticles formed by Pd reduction in the solution showing UV spectrum marked in red in Panel a.

At last, we recorded TEM images (Figure 6b) depositing a drop of the solution, prepared as in Figure 5d, on a grid. After evaporation, the grid was used for the analysis. Nanoparticles of Pd, confirmed by EDS analysis, having diameter of 2-5 nm were detected. All considering, it is reasonable to assume that when the 3-thiopheneboronic acid **1b** is added to the $CTAB/PdCl_2$ solution it gives a rapid transmetallation to Pd(II) followed by the

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transmetallation of a second boronic acid molecule to the same Pd ion after which the reductive elimination occurs giving Pd(0), that becomes available to start the Suzuki reaction catalytic cycle.

This process in considerably accelerated by the presence of a base but it occurs even in absence of the base. Pd(0) atoms are grouping into nanoparticles, the real source of the catalytic effect. The nanoparticles are highly stable towards further aggregation thanks to the interaction with the cationic surfactant CTAB, which acts as a stabilizer towards the Pd nanoparticles, and as solubilizer for the reactants.[42, 67-70]

3.1.2 Use of Pd/C.

Pd/C was used in several Pd catalyzed reactions.[42, 71-74] It does not contain toxic phosphines, it is cheap and can be separated easily by filtration and recycled. Its application to Suzuki coupling was explored in recent years showing good results and the ability to activate, sometimes, also aryl chlorides.[42, 47, 71-73, 75]

We tested 5% and 10% Pd/C from Aldrich and 10% Pd/C from Degussa always for the reaction of 3-thiopheneboronic acid **1b** with 2-bromopyridine to obtain compound **5** working in thermal conditions or under MW activation. The preparation method of this catalyst can heavily influence the defectivity of the Pd particle, the particle size, Pd distribution on the active carbon support, and thus its catalytic activity.[73] The 5% Pd/C from Aldrich was substantially unreactive while the 10% Pd/C from Aldrich (used at 2% loading in the reactions) appeared more active in particular at high temperature with about 40% of yield after 30 min under MW (see Figure 7). In thermal conditions after 24 h only 20% of yield was observed confirming that prolonged heating does not work well also in this case.

In order to compare the performance of 10% Pd/C from Degussa at the same catalyst loading and in thermal conditions and under MW activation some experiments were performed at 80°C. Isolated yield for compound **5** of about 60% was observed in thermal activation (24h, 80 °C) and 51% under MW irradiation (90 minutes, 80 °C). This catalyst is clearly less active than Pd(PPh$_3$)$_4$ so reaction time of 90 min is insufficient. Better isolated yields of 72% and 82% were observed at 120 °C and 150 °C (30 min) respectively. They are comparable with the yields obtained working with Pd(PPh$_3$)$_4$ as catalyst. When the reaction of 3-thiopheneboronic acid **1b** with 2-bromopyridine was performed under MW at 80°C for 2h with lower catalyst loading (1.25% mol) final isolated yield of 62% was obtained for compound **5**.

Also in this case the MW activation appeared fruitful allowing to work for a short time, at higher temperature than classical thermal conditions. An important aspect of the reactivity of Pd/C was taken into account in a paper of Kohler et al.[76] on the use of Pd(0) nanoparticles as catalyst for Heck reaction. They studied the nature of the species that promote catalysis in a heterogeneous system. They noted that the reaction is not heterogeneous but at least "quasi-homogeneous", since Pd leaching was found to account for the presence of nanoparticles and / or single atoms in solution, responsible for catalysis. Their presence reached the maximum concentration when the conversion rate was fast and the nanoparticles concentration decreased suddenly when the reaction was finished, by redepositiom on the active carbon substrate.
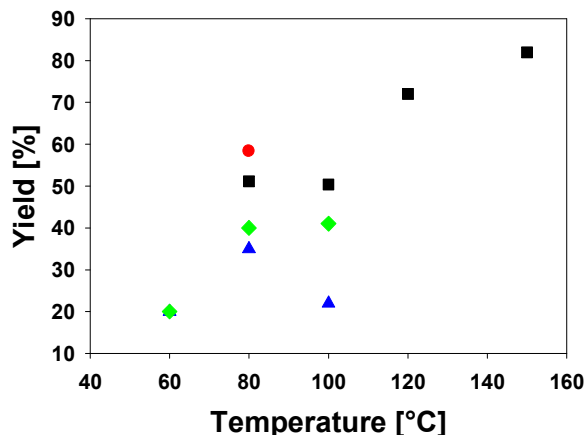
Figure 7. Effect of temperature for the model reaction of 3-thiopheneboronic acid **1b** with 2-bromopyridine to obtain compound **5**, performed with 10% Pd/C catalyst. (▲): Pd/C Aldrich, thermal reaction; (◆): Pd/C Aldrich, MW; (●): Pd/C Degussa, thermal reaction; (■):Pd/C Degussa, MW.

Taking this into account and the fact that tetrabutylammonium bromide accelerated the reaction,[70] we can suppose that the leaching of Pd atoms and, possibly, nanoparticles can occur also in our micellar system and that the presence of cationic surfactants can stabilize the Pd in solution. We performed a few experiments, to search for Pd leaching from the Pd/C determining it by ICP-MS technique. We prepared a solution of CTAB in water at the same concentration used for the reactions. Pd/C (33.75 mg) was suspended into 5ml of this solution at rt for 1 h and the Pd/C was then separated by centrifugation. We found a concentration of Pd in the liquid phase of 0.9748 mg/L. When the experiment was performed also in presence of 1 mmol of 2-bromopyridine, the leaching was about twice, 2.133 mg/L. When speaking of absolute quantities, only 0.14% and 0.32% of Pd were removed by CTAB from Pd/C. When the same experiments were performed at 150 °C under MW irradiation, we obtained a concentration of Pd in the liquid phase of 2.775 mg/L and 14.700 mg/L, respectively, and the leaching from Pd/C was 0.41% and 2.17% of the total Pd. The leaching phenomenon was very limited at rt and higher at 150°C but however we can say that most of the Pd is still

firmly kept onto Pd/C. This agrees with our TEM results that, differently from the PdCl$_2$ case, did not show any detectable nanoparticles in those solutions. The leaching of Pd from Pd/C can be ascribed to a partial dissolution of atomic species due to the oxidative addition of the aryl halide that takes the Pd atoms from the surface and bring them into the solution. The removal of the small Pd nanoparticles from the carbon surface is still not demonstrated.[76]

3.3 Effect of different surfactants.

Among the cationic surfactants, only CTAB was used in the literature.[42, 43] Surfactants structurally related to CTAB could be in principle interesting to be used for modifying reaction conditions in place of CTAB. In particular, gemini surfactants could be of interest since those amphiphiles demonstrated a lot of interesting properties in the colloidal domain. Gemini surfactants are made of two normal surfactants, having one hydrophilic headgroup and one hydrophobic tail, connected by a spacer. For the catalysis of organic reactions it is worth to be mentioned that a gemini surfactant normally shows a cmc that is at least 10 times lower than that of its monomeric counterpart.[77, 78] This should reflect positively, in principle, on the quantity of surfactant that is needed to have a micellar environment in solution. Due to this, a very small quantity of gemini surfactant, about 5 times lower, can be used. The gemini cationic surfactants were found able to catalyse the hydrolysis of both carboxylic and phosphoric esters, demonstrating that their micelles can collect organic molecules from the solution and help them to react.[79-85] Surprisingly, no results, nor trials with negative results were reported in the literature on the use of gemini surfactants to perform Suzuki reactions or other Pd-catalyzed reactions. We tried to apply them to our protocol in order to see if any beneficial outcome could be found.

We performed a few trials with two gemini surfactants, in order to ascertain for the possibility to use lower quantity of organic materials to assist the reaction. Two gemini surfactants were used, 16-3-16 2Br and 16-12-16 2Br, having largely different spacers, namely three and twelve methylenes long (Figure 8). The reaction of 2-bromopyridine and 2-thiopheneboronic acid **1a** to obtain compound **2** was used to test this hypothesis. Unfortunately, by working in the same conditions at 80 °C under MW irradiation (30 min), the product was obtained only in very small quantities, ranging between 5-15% (15% for 16-3-16 2Br and 5% for 16-12-16 2Br).
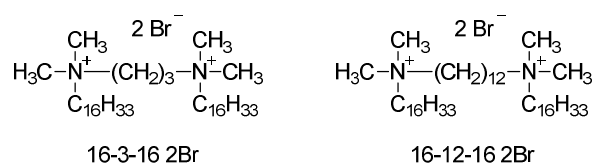
Figure 8. Structures of gemini surfactants 16-3-16 2Br and 16-12-16 2Br used as an alternative to CTAB.

This evidence shows that the micellar system produced by geminis is quite different and seems not to be able to perform in the same way as CTAB. We showed previously that the micellar surface compactness is important to detect the conditions in which a host molecule can be entrapped in the micelle.[77, 78] Pyrene fluorescence showed that its accommodation site in the micelle is deeper or, however, most dehydrated in the case of CTAB that in the case of 16-3-16 2Br and similar to the 16-12-16 2Br. The micellar surface compactness of gemini cationic surfactants, as determined by fluorescence anisotropy, was depending on the spacer length. following the order 16-3-16 > 16-12-16. By considering also the CTAB, the order is 16-3-16 > CTAB > 16-12-16. Those data are showing that for more polar organic solutes, the preferred solubilization site is near the cationic headgroups and, since the presence of aromatic groups, our reagents are highly probable to locate in this place in the

micelle. Owing to their relative polar nature, our reactants are solubilized among the headgroups in the outer palisade of the micelle. Depending on the compactness of the micellar surface and on the dehydration conditions for organic molecules, available for different micelles, it results that the CTAB plays an advantageous role with respect to the two tested gemini surfactants. In order to better explain the performance of those different micellar systems in the Suzuki reaction catalysis, a careful characterization of the system is under study.

3.4. Synthesis of thienylbipyridine ligands

In order to check the potential of our synthetic approach, we tried a preliminary gram scale-up of the compound **7** synthesis by reaction of 3-thiopheneboronic acid with 4-bromopyridine under MW irradiation at 80 °C. We worked with 1 gram of limiting reagent obtaining the desired product with nearly unchanged yield (82%).

At last, we checked this synthetic approach with a more complex structure just to evaluate its general applicability (see Scheme 2). We prepared the ligand **8** where a 2,2'-bypyridine is linked to thiophene, useful as precursor of a conductive polythiophene, side-chain functionalized with a transition metal complex.[51] We performed a trial reaction in the best thermal conditions previously identified studying the reaction of 3-thiopheneboronic acid **1b** with 4-bromopyridine: with $Pd(PPh_3)_4$ as catalyst and K_2CO_3 as base at 80 °C for 24h. A remarkably high yield of 83% was obtained. A trial under MW activation was also performed at 150 °C. The monitoring of reaction by GC-MS analysis suggested to extend the reaction time at 2h instead of 30 min. Compound **8** was obtained in isolated yield of 92%. However, the quantity of impurities in the reaction was increasing and we searched for the optimization of the temperature by reducing it to 120°C. The reaction was cleaner and the product **8** was

obtained in quantitative yield. This reaction was tried several times and showed to be reproducible, also when we raised the loading of 4-bromo-2,2'-bipyridine to 1g using the same solvent volume.

Starting from the ligand **8**, we prepared the ligand **11**, by brominating the thiophene ring and subsequent Suzuki reaction with the 2-thiopheneboronic acid. Among the different literature protocols, at first we used NBS and acetic acid as solvent at rt for 1 day. When the reaction was performed with 2 equivalents of NBS, **8** was brominated with some difficulty we isolated mostly the monobrominated compound **9**. We had to increase NBS to 5 equivalents, i.e. 2.5 equivalents per C-H bond to be brominated, thus obtaining compound **10** in 60% yield. We also found useful to explore different solvents to perform this bromination reaction, according to a recent paper.[86] While acetic acid can be produced by green means and is considered a green solvent, also ethyl acetate was considered a mild solvent.[87] By using ethyl acetate at 25°C with an excess of NBS (5 eq.), we obtained **10** in 65 % yield after 2 days of reaction, while after 5 days, the reaction gave **10** in quantitative yield (100%). Finally the Suzuki coupling of **10** with 2-thiopheneboronic acid **1a**, in the conditions already established for 4-bromopyridine, gave the ligand **11** in 60% yield. It is remarkable that using always green conditions the ligand **11** could be prepared in three steps in 60% total yield. In a previous paper,[51] the synthetic pathway started by coupling the 2,3,5-tribromothiophene with 2-thiopheneboronic acid to obtain 3'-bromo-2:5'-2':5"-terthiophene. This compound was transformed into the correspondent boronic acid that was not isolated and directly used to couple with 4-bromo-2,2'-bipyridine to obtain **11**. The synthesis was thus performed in three steps in a total yield of about 17%. The protocol established in this paper is a relevant improvement from the synthetic point of view, for a product that showed great practical importance for an environmental and energy-based application. In fact, we used recently ligands **8** and **11** to prepare Re(I) complexes and to electropolymerize them on glassy carbon

electrodes to reduce CO_2, by electrochemistry.[51] Only ligand **11** could be electropolymerized, since theoretical calculations demonstrated that compound **8** had low electron density on the positions 2- and 5- of thiophene and, due to this, its reactivity was very low. Remarkably, while the rhenium complex obtained from **8** and **11** were not particularly active in solution in reducing CO_2, the polymer derived from the rhenium complex obtained from **11** was very active, attaining a faradaic activity of nearly 85% for CO production, and one of the higher turnover numbers found in the literature (TON_{CO} = 489) for this kind of supported polymers.[88]

Finally, in order to demonstrate the broad applicability of the synthetic method to obtain products having practical interest, compound **12** was also prepared as a ligand for ruthenium to be used for Dye-sensitized Solar Cells (DSC) application. The reaction was tried first in thermal conditions at 80°C for 24h, by using 5-carboxy-2-thiopheneboronic acid **1c** and 4-bromo-2,2'-bipyridine and K_2CO_3. The mixture became highly viscous just after the addition of the boronic acid and the temperature of 80°C was not enough to make the solution fluid. The yield was quite modest, around 45-50%. When the same reaction was performed at 120°C for 1 h, using MW, the product could be obtained in 64% yield. It is noteworthy that the product separated from the solution as a solid by precipitating as complex 1:1 with the organic surfactant ammonium ion. The product was isolated by dissolving in the minimum water and by adding 6M HCl until pH 3, which helped the target compound to separate as a solid. This evidence suggested to add more surfactant in the reaction, to reduce the viscosity, since this should be related to the interaction of the dianion of 5-carboxy-2-thiopheneboronic acid with the micellized surfactant. By using an equimolar ratio of surfactant vs reagents (normally this was 0.6 : 1), the reaction was performed again with MW at 120°C for 30'-1h, giving a yield of 86% of compound **12**. This product is currently under study to complex ruthenium for DSC applications.
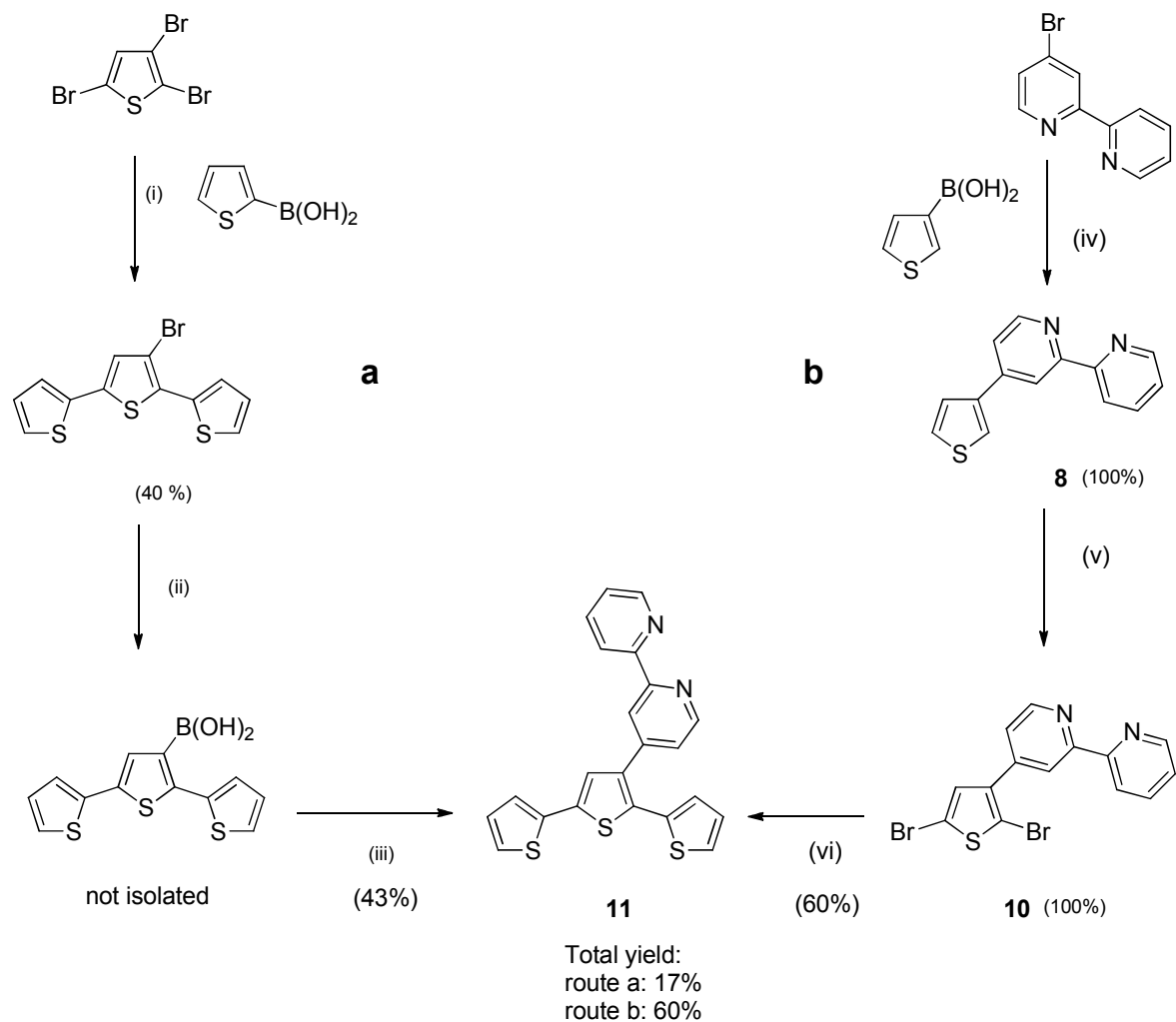
Scheme 2. Synthesis of the proposed ligands. Reactions conditions: (i) Pd(PPh$_3$)$_4$, DME, Na$_2$CO$_3$ 1.5 M, 80°C, 24h.; (ii) THF, B(OCH$_3$)$_3$, BuLi, -78°C -> -20°C, 2h; (iii) 4-bromo-2,2'-bispyridine, Pd(PPh$_3$)$_4$, DME, NaHCO$_3$, MW 130°C, 30 min; (iv) 4-bromo-2,2'-bispyridine, Pd(PPh$_3$)$_4$, CTAB, K$_2$CO$_3$, Argon, 120°C, 30 min; (v) NBS, ethyl acetate, 25°C, 5 d; (vi) Pd(PPh$_3$)$_4$, CTAB, Na$_2$CO$_3$ 1.5 M, MW, 120°C, 30 min.

4. Conclusions

With the aim of obtaining reliable protocols to link pyridine and bispyridine ligands to a thiophene, we tested Suzuki reaction between bromopyridines and thiopheneboronic acids in

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water using CTAB surfactant to disperse the reactants. The reaction conditions were optimized by tuning reaction time, temperature and using both classical thermal conditions and microwaves. Very good to excellent yields were obtained with $Pd(PPh_3)_4$ as the catalyst. The activity of other Pd catalysts was studied, namely $PdCl_2$ and Pd/C. $PdCl_2$ showed to be reasonably active at 80 °C for 30 min and performed even better when the reaction time was extended to 2h, giving a 74% yield. This made us able to propose this system as an alternative to the $Pd(PPh_3)_4$ catalyst, avoiding the use of toxic phosphines. Besides, it was shown that $PdCl_2$ forms small nanoparticles in solution due to the reducing action of the thiopheneboronic acids and that the nanoparticles are highly stabilized by the CTAB surfactant, whose role is thus extended. TEM analysis confirmed the formation of 2-5 nm nanoparticles of Pd(0). The quantity of $PdCl_2$ was reduced from 2.5% to 1% without any appreciable reduction of yield. The study on cheap, phosphine-free, and easily separable and recyclable Pd/C showed that the source and preparation of the catalysts is crucial for the reaction outcome. Only 10% Pd/C showed to be active and the best performing catalyst was shown to perform better at very high temperatures such as 150 °C, giving a 82% yield under MW activation.

The method was successfully applied for the synthesis of thienylbipyridines, useful for practical applications (CO_2 reduction, DSC). The further elaboration of one of these thienylbipyridines, to obtain a terthiophene-based bipyridine ligand, demonstrated how the method can be exploited as a green step for the preparation of more complex molecules. By all these results we can propose that Suzuki reaction can be performed in water by using surfactants not only to perform speculative experiments but also to obtain intermediates and final products for practical applications. This can be done avoiding the use of toxic organic solvents, by using catalytic quantities of palladium and there are evidences that in some cases

the Pd content can be further reduced. This makes this approach highly interesting in view of more sustainable synthetic procedures from both industrial and environmental points of view.

Acknowledgements

Supplementary data.

Figures of ^{1}H-NMR, and ^{13}C-NMR spectra are available.

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Supplementary Information for:

Water Based Surfactant-Assisted Synthesis of Thienylpyridines and Thienylbipyridine Intermediates

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Contents:

characterization data (^{1}H-NMR, ^{13}C-NMR) for compounds **2-12**: Fig. SI-1 – Fig. SI-22.

2-(thiophen-2yl)pyridine.(2)
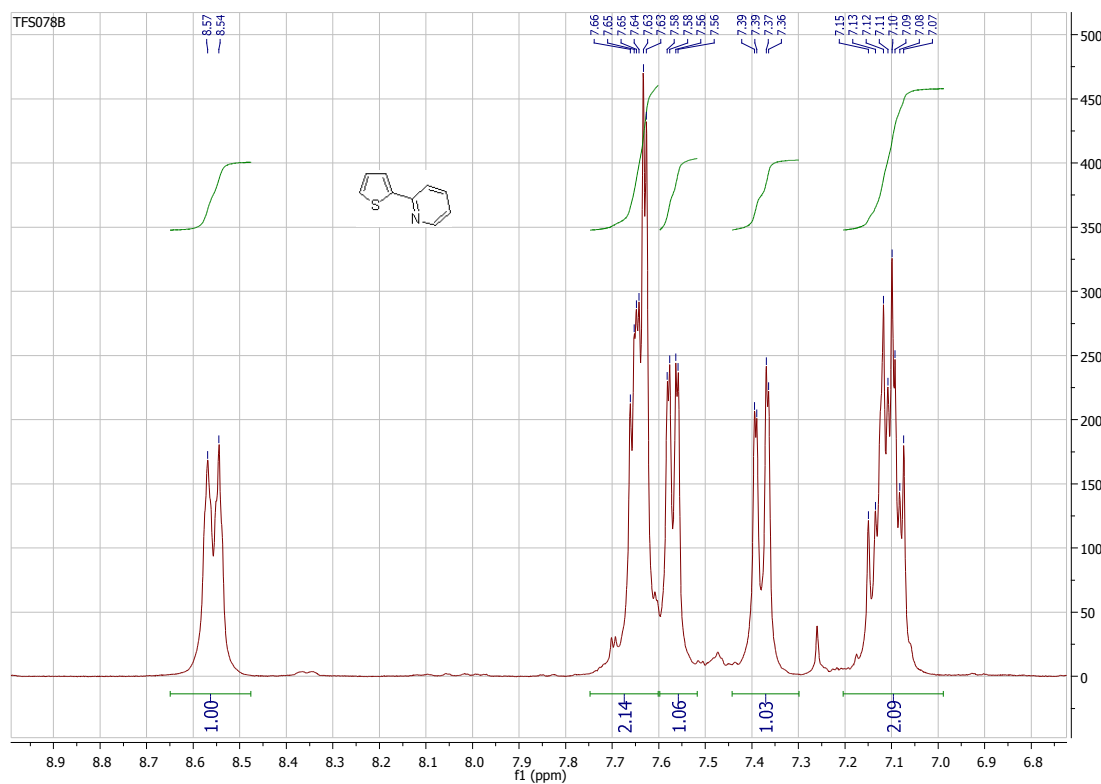
Fig-SI-1. ^{1}H-NMR for Compound **2**.
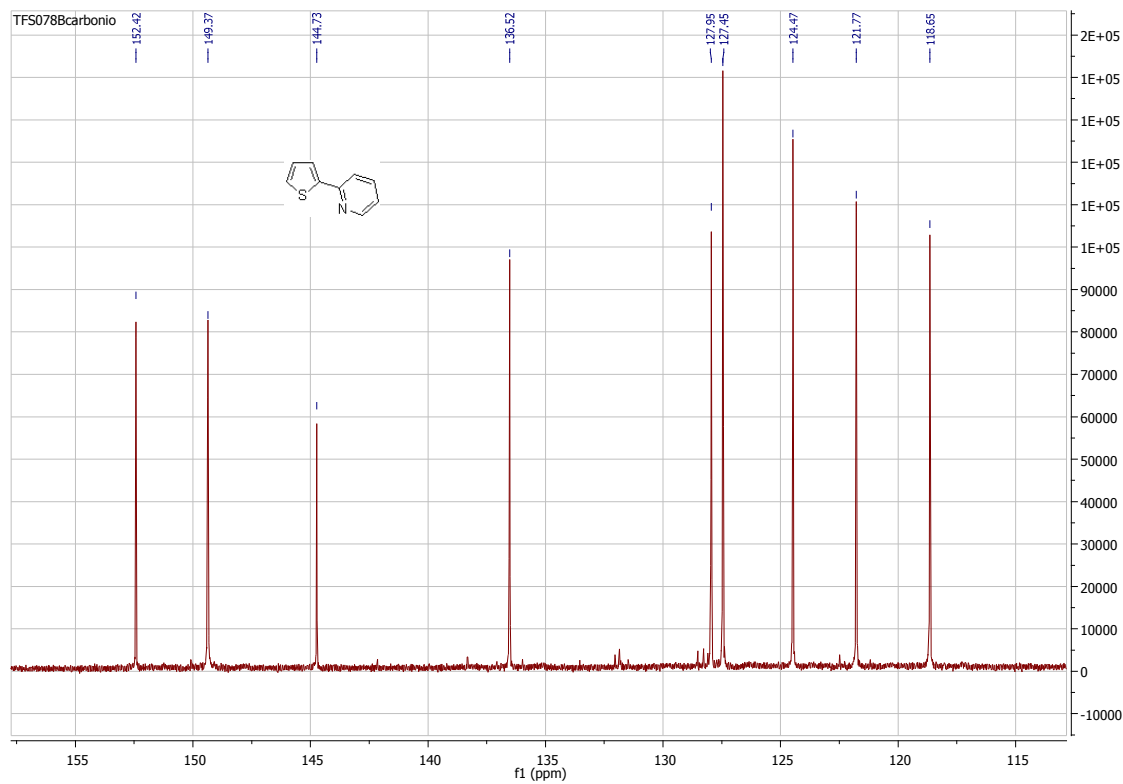
Fig-SI-2. ^{13}C-NMR for Compound **2**.

3-(thiophen-2-yl)pyridine.(3)
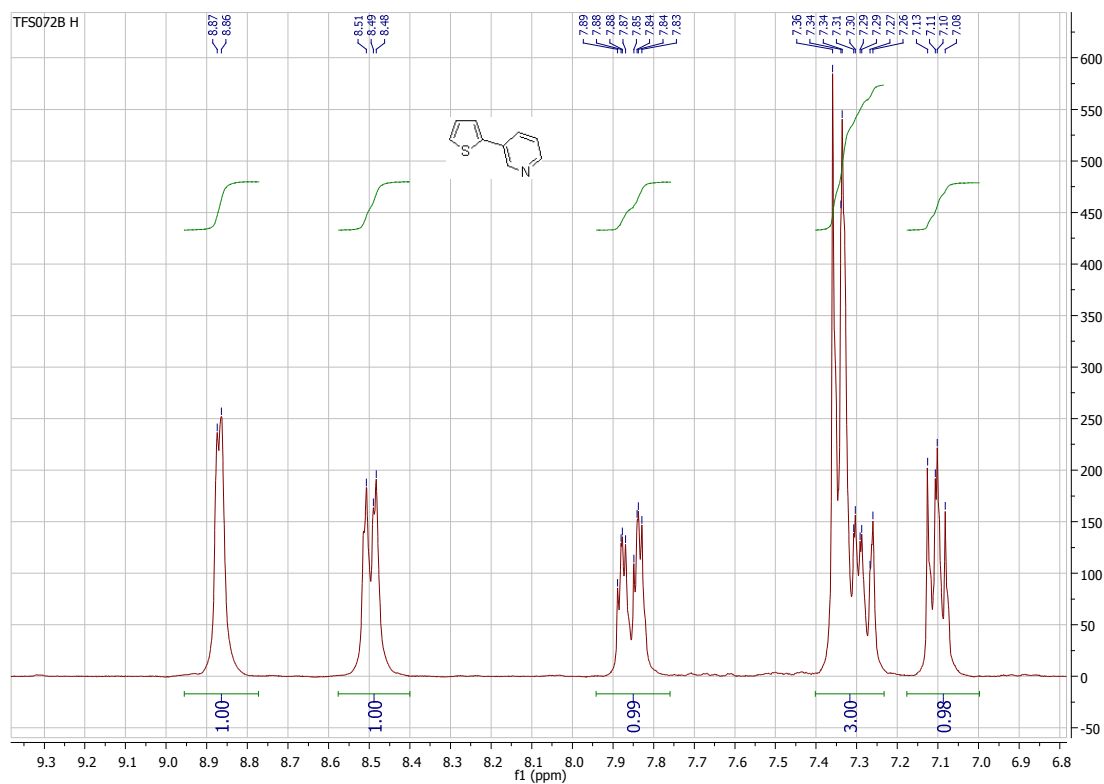
Fig-SI-3. ^{1}H-NMR for Compound **3**.
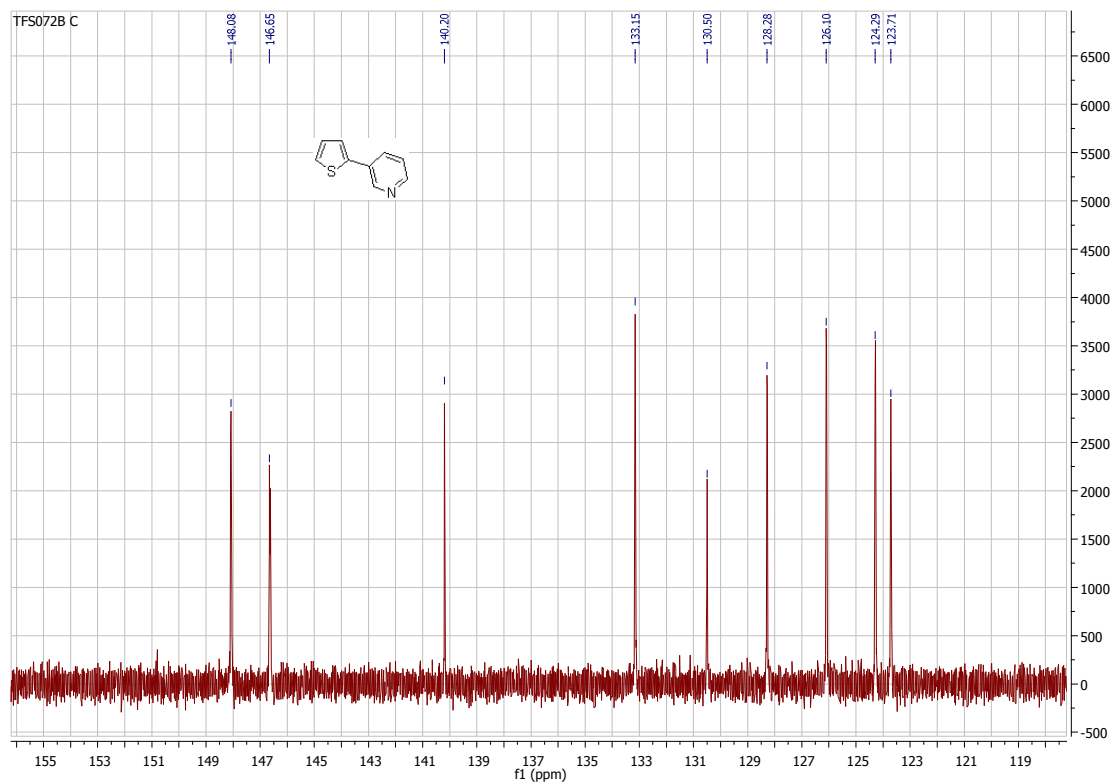
Fig-SI-4. ^{13}C-NMR for Compound **3**.

4-(thiophen-2-yl)pyridine.(4)
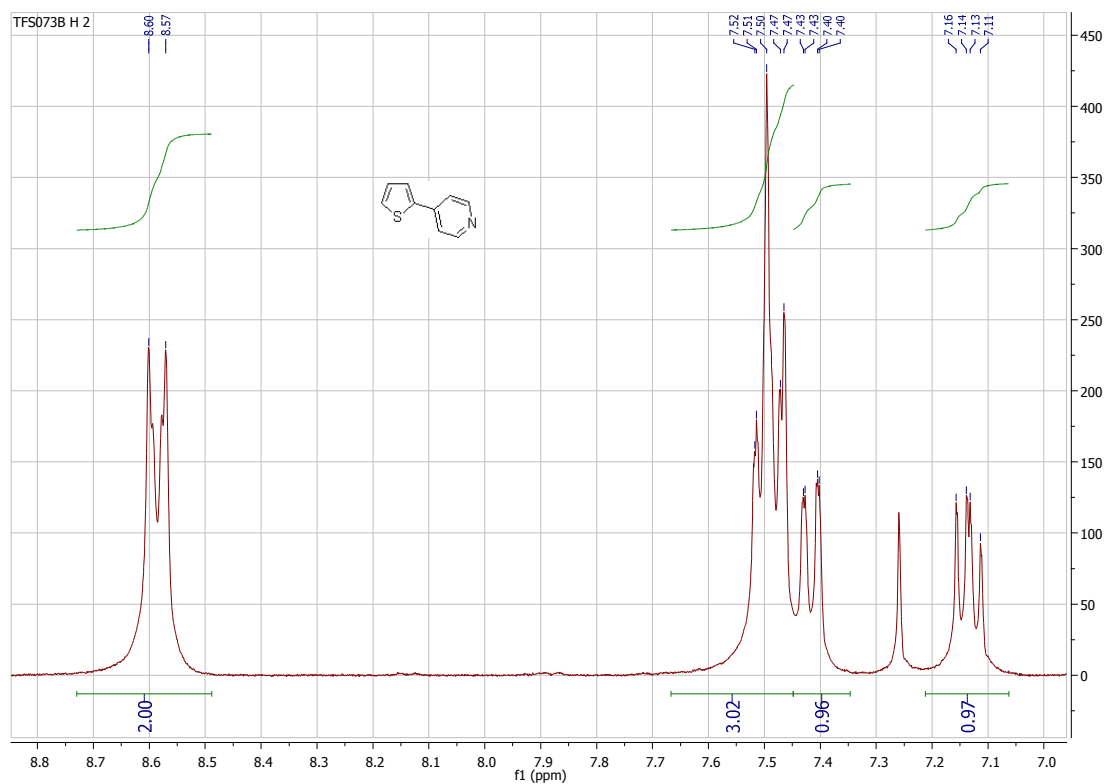
Fig-SI-5. ^{1}H-NMR for Compound **4**.
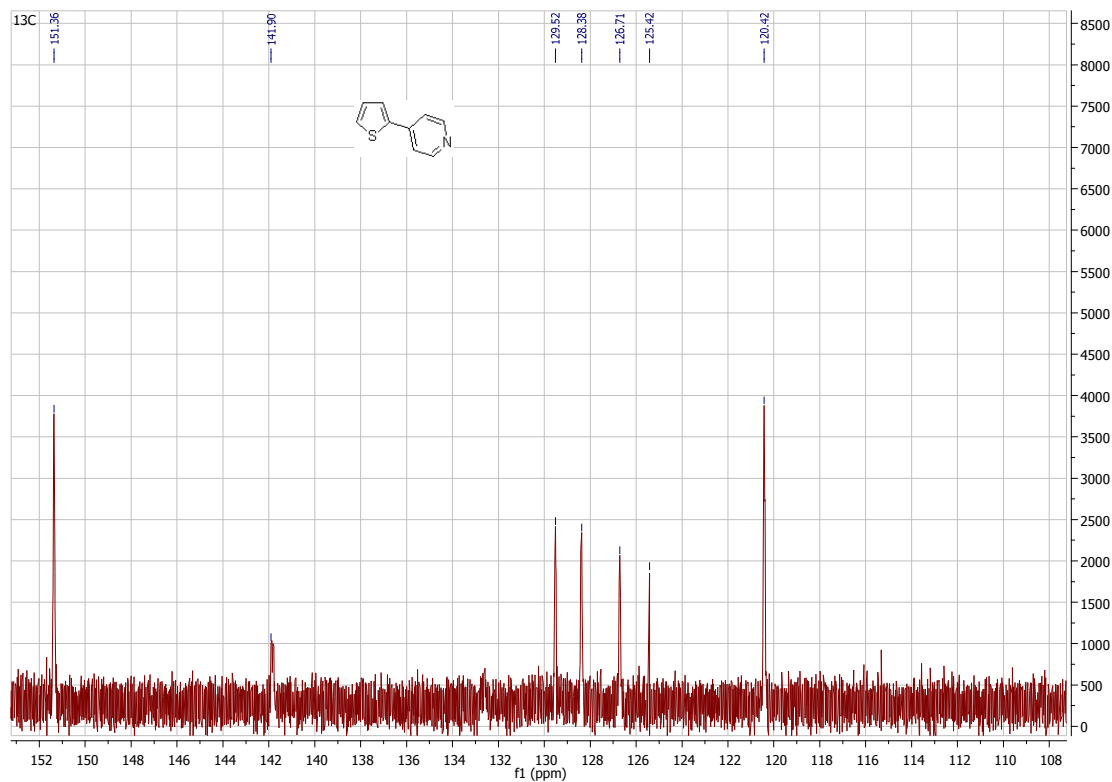
Fig-SI-6. ^{13}C-NMR for Compound **4**.

2-(thiophen-3-yl)pyridine.(5)
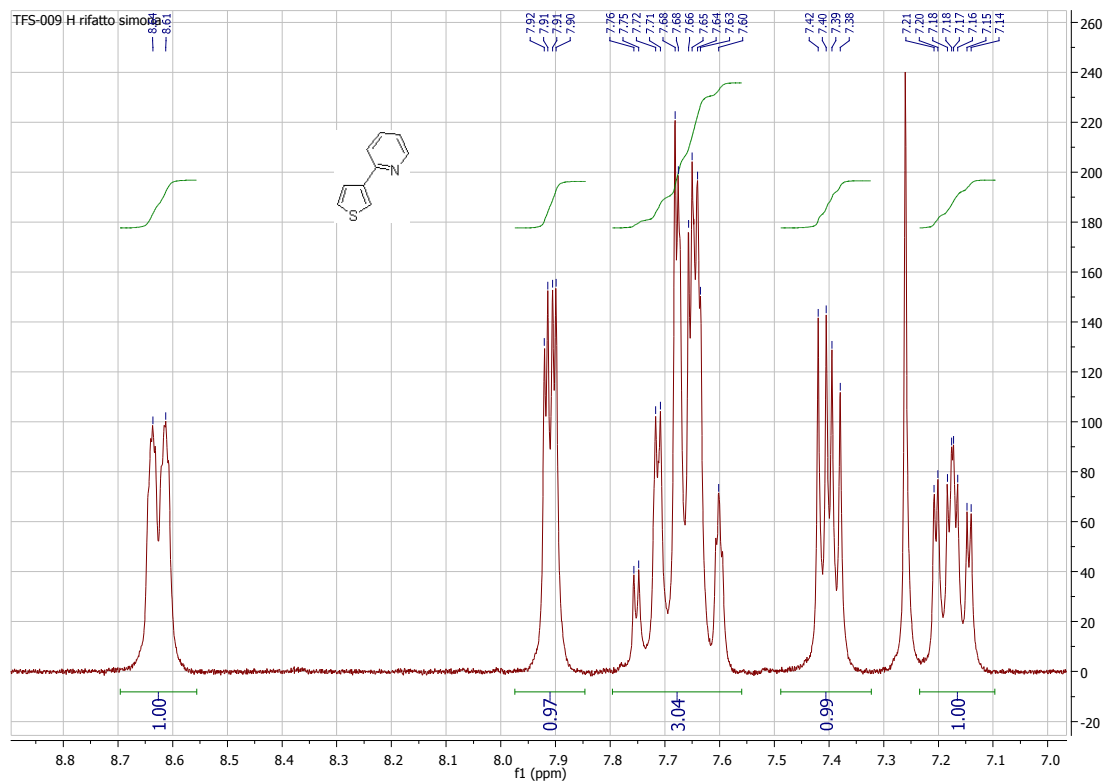
Fig-SI-7. ^{1}H-NMR for Compound **5**.
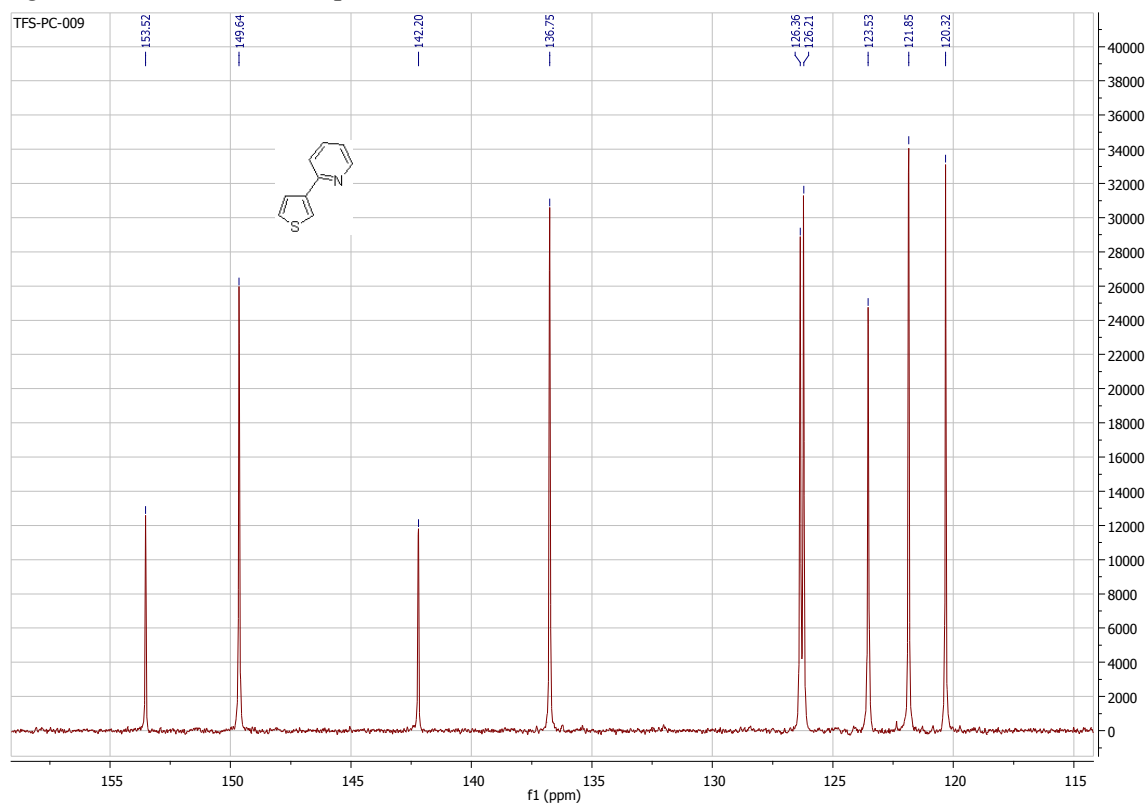
Fig-SI-8. ^{13}C-NMR for Compound **5**.

3-(thiophen-3-yl)pyridine. (6)
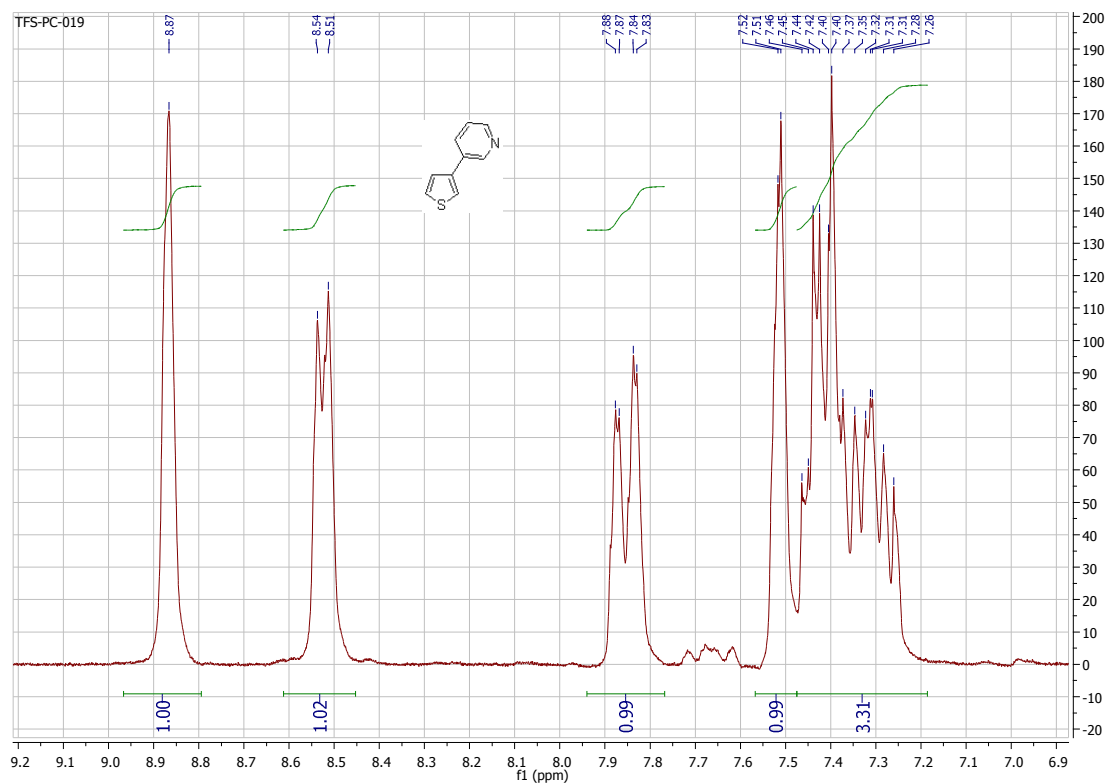
Fig-SI-9. ^{1}H-NMR for Compound **6**.
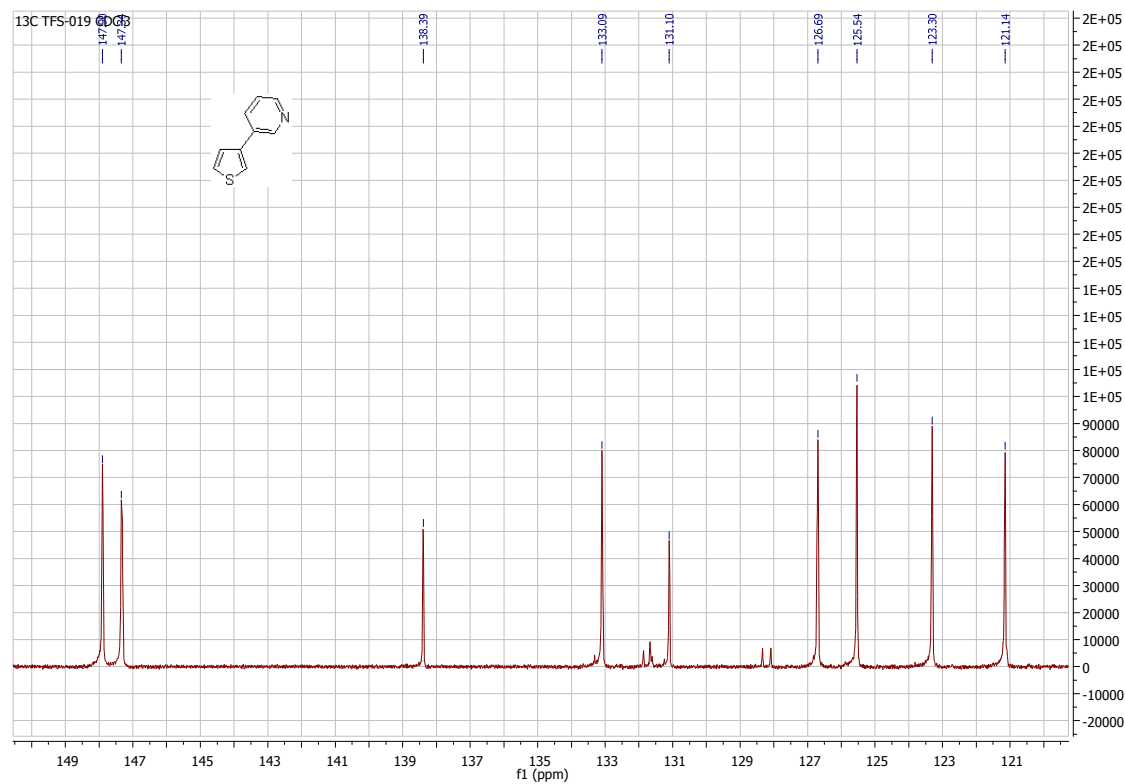
Fig-SI-10. ^{13}C-NMR for Compound **6**.

4-(thiophen-3-yl)pyridine. (7)
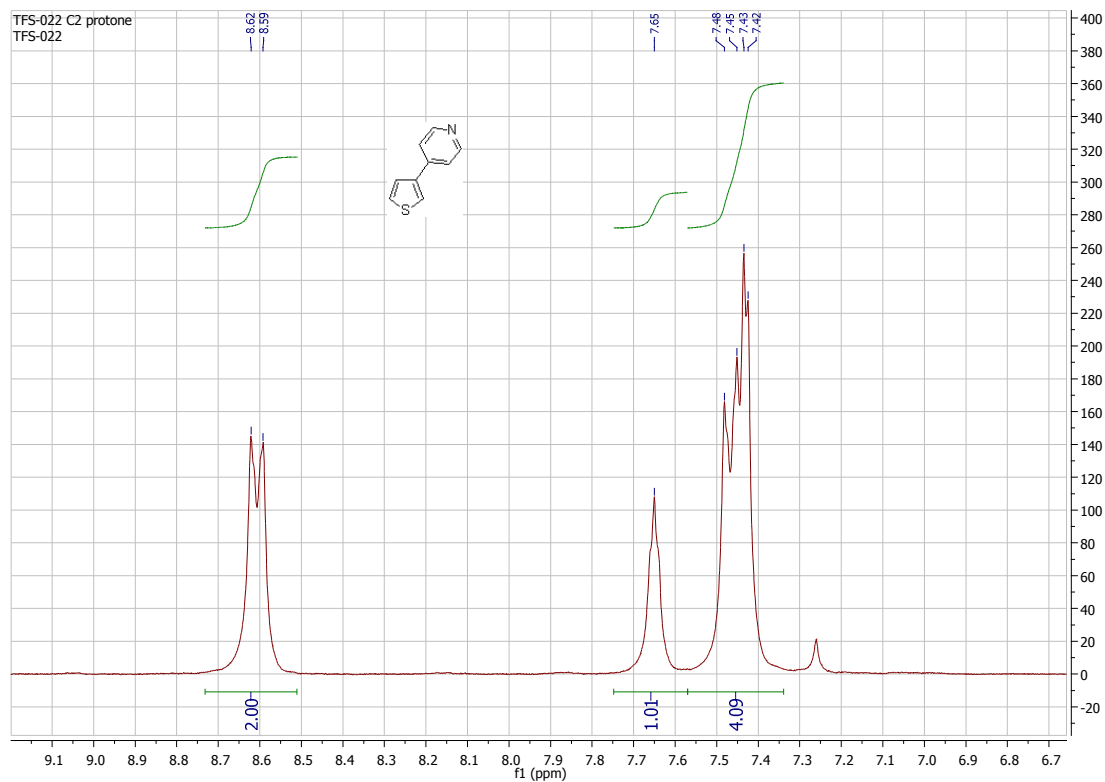
Fig-SI-11. ^{1}H-NMR for Compound **7**.
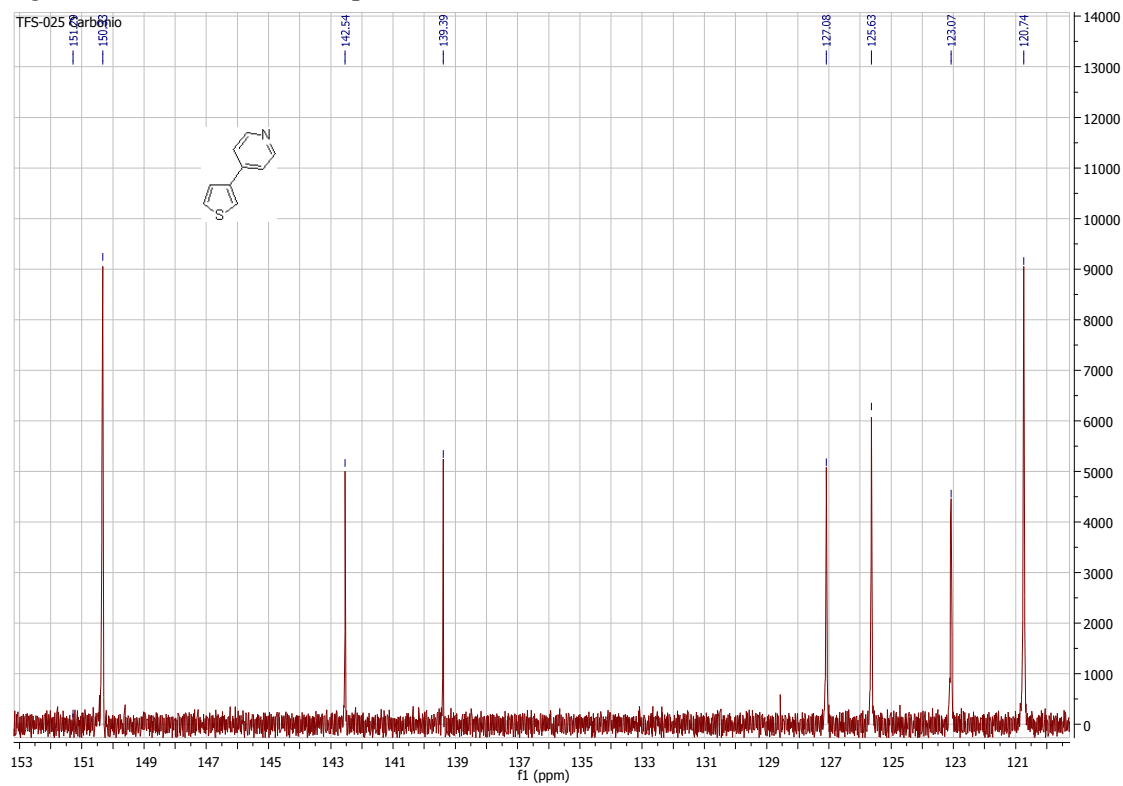
Fig-SI-12. ^{13}C-NMR for Compound **7**.

4-(thiophen-3-yl)-2,2'-bipyridine. (8)
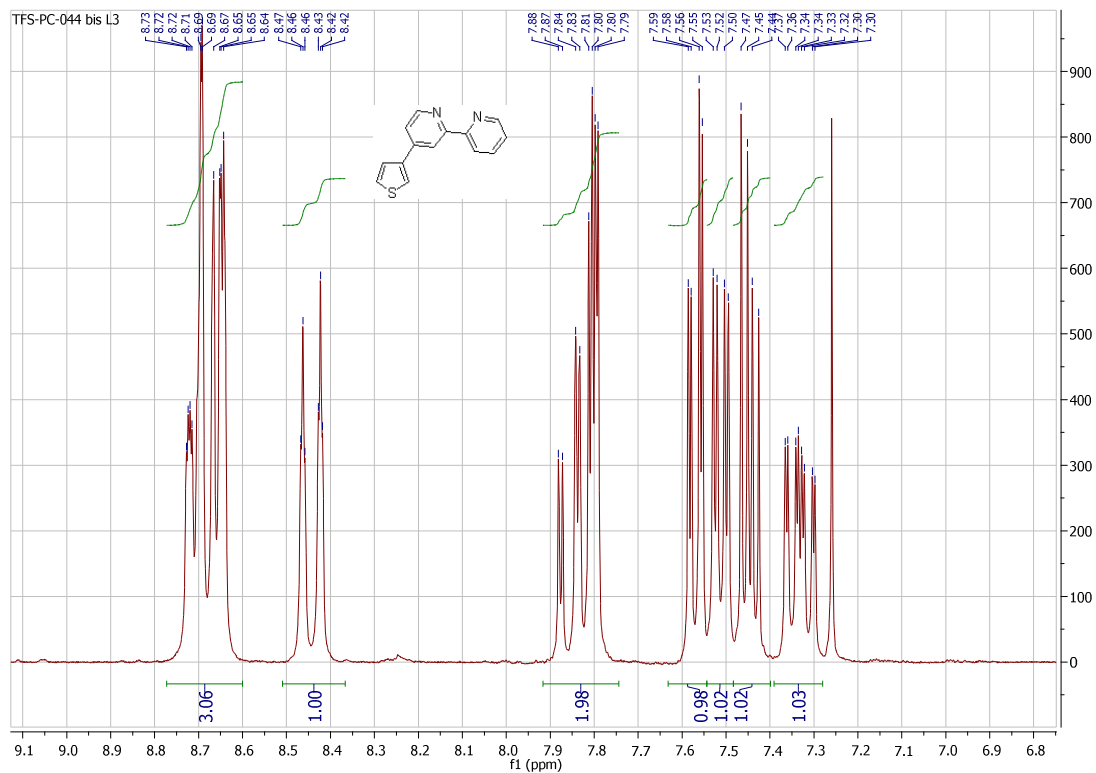
Fig-SI-13. ^{1}H-NMR for Compound **8**.
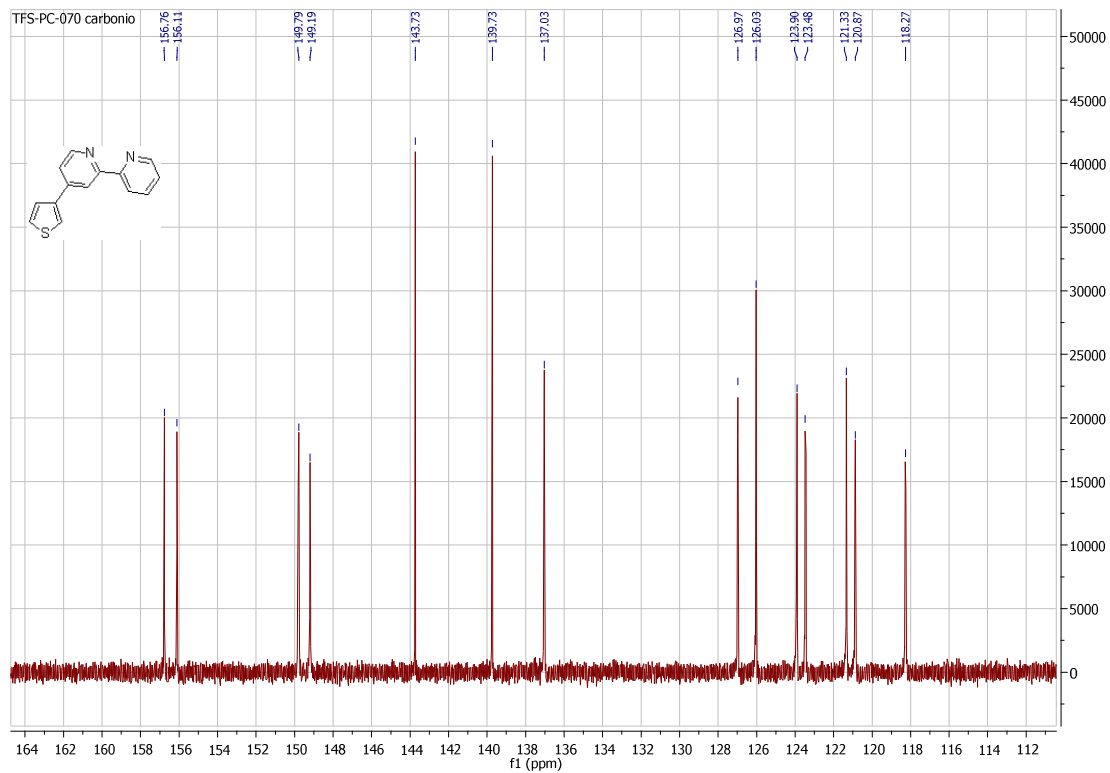
Fig-SI-14. ^{13}C-NMR for Compound **8**.

4-(2-bromothiophen-3-yl)-2,2'-bipyridine. (9)
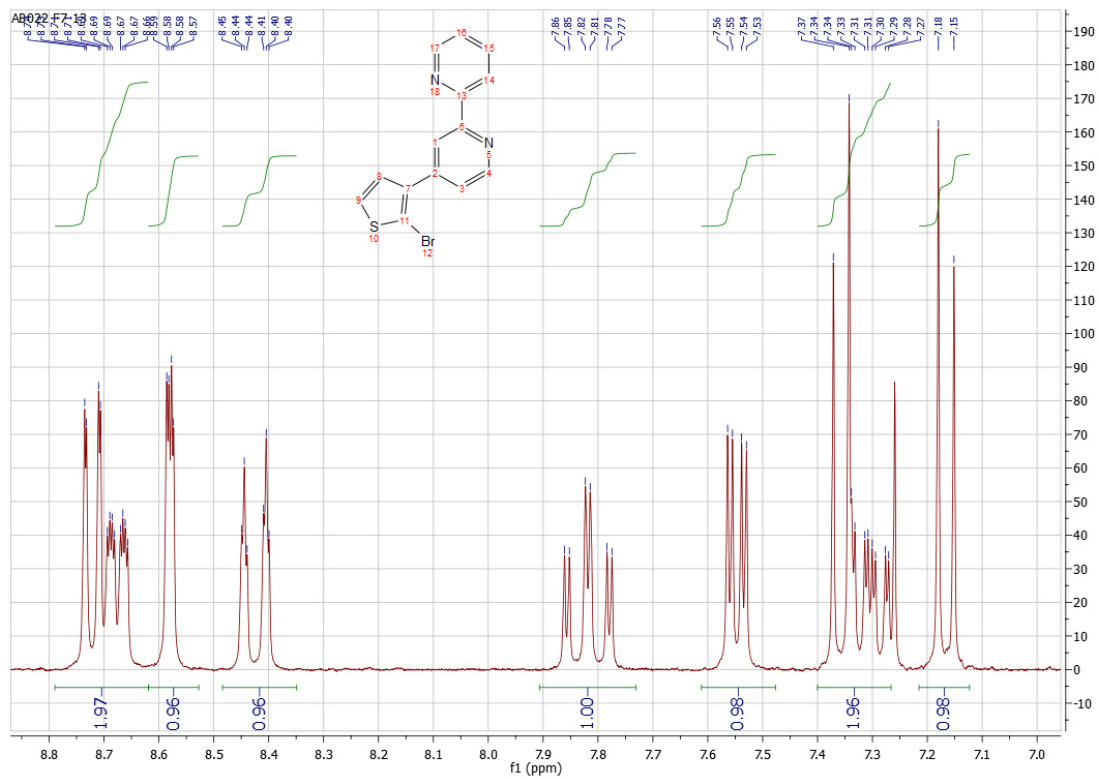
Fig-SI-15. ^{1}H-NMR for Compound **9**.
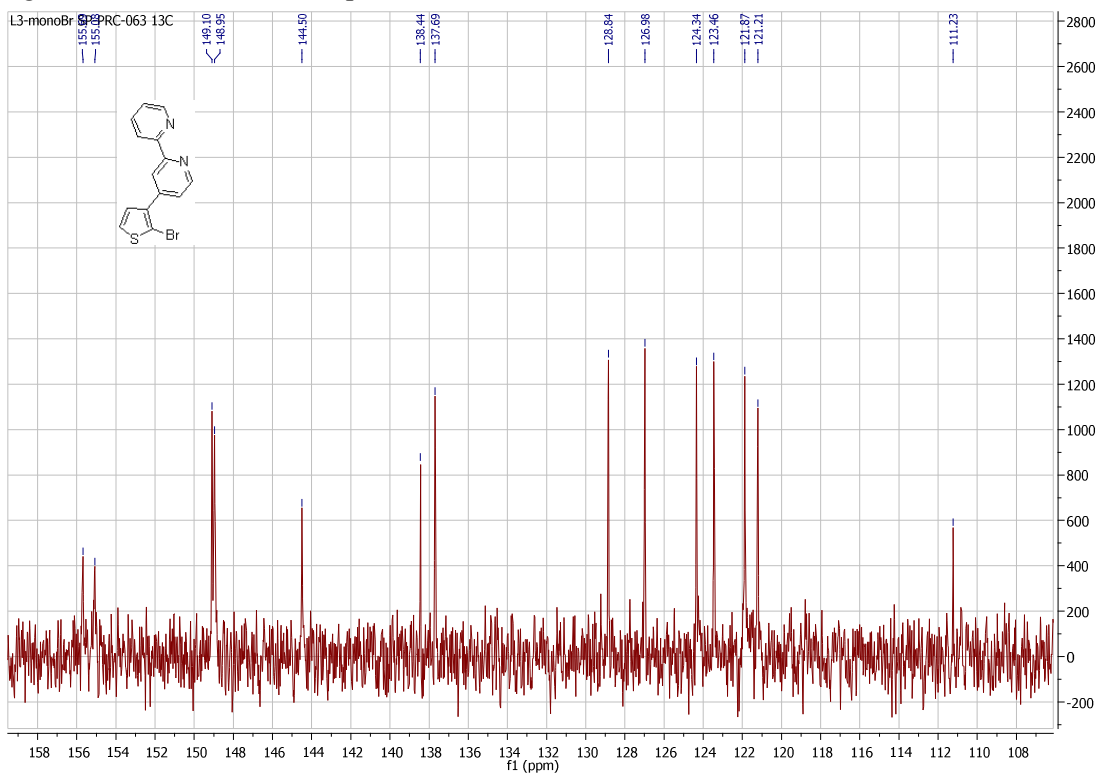
Fig-SI-16. ^{13}C-NMR for Compound **9**.

4-(2,5-dibromothiophen-3-yl)-2,2'-bipyridine (10)
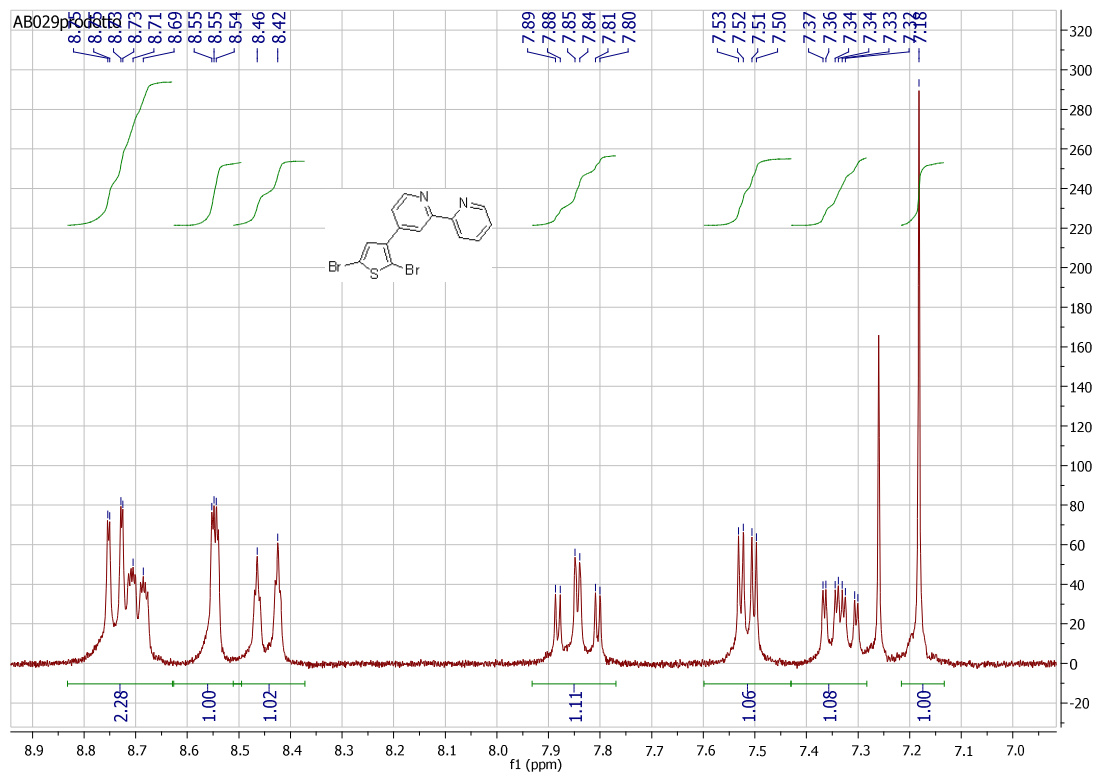
Fig-SI-17. ^{1}H-NMR for Compound **10**.
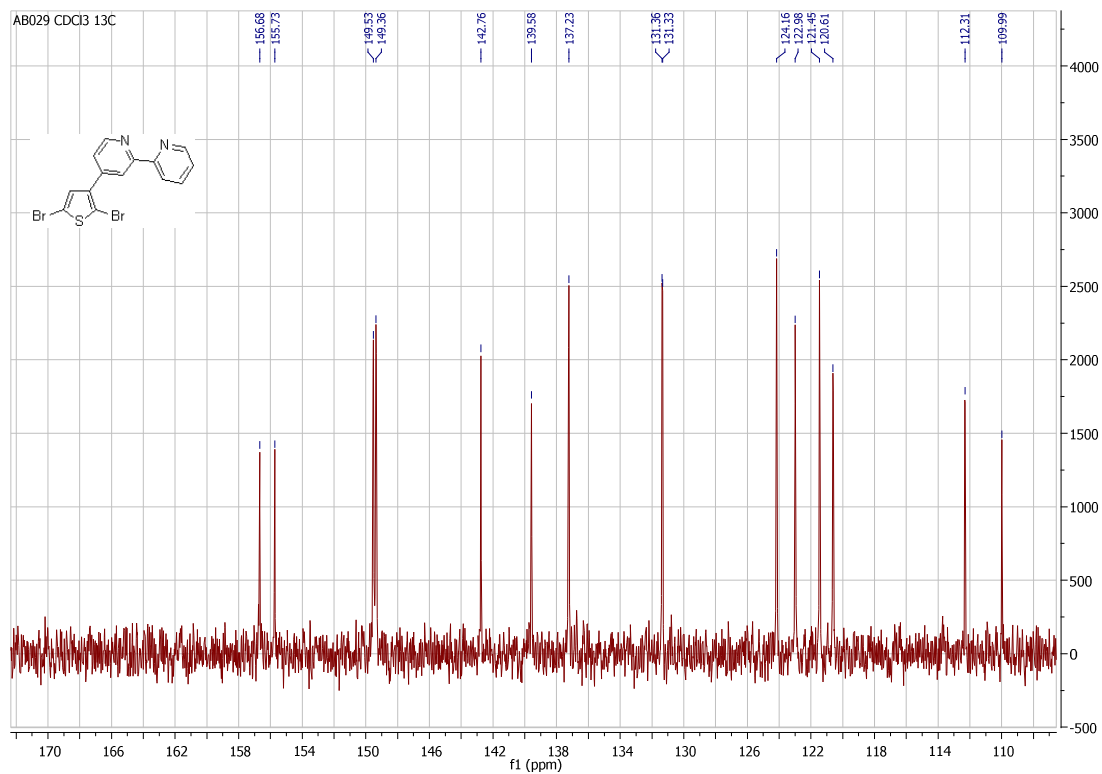
Fig-SI-18. ^{13}C-NMR for Compound **10**.

4-([2,2':5',2''-terthiophen]-3'-yl)-2,2'-bipyridine (11)
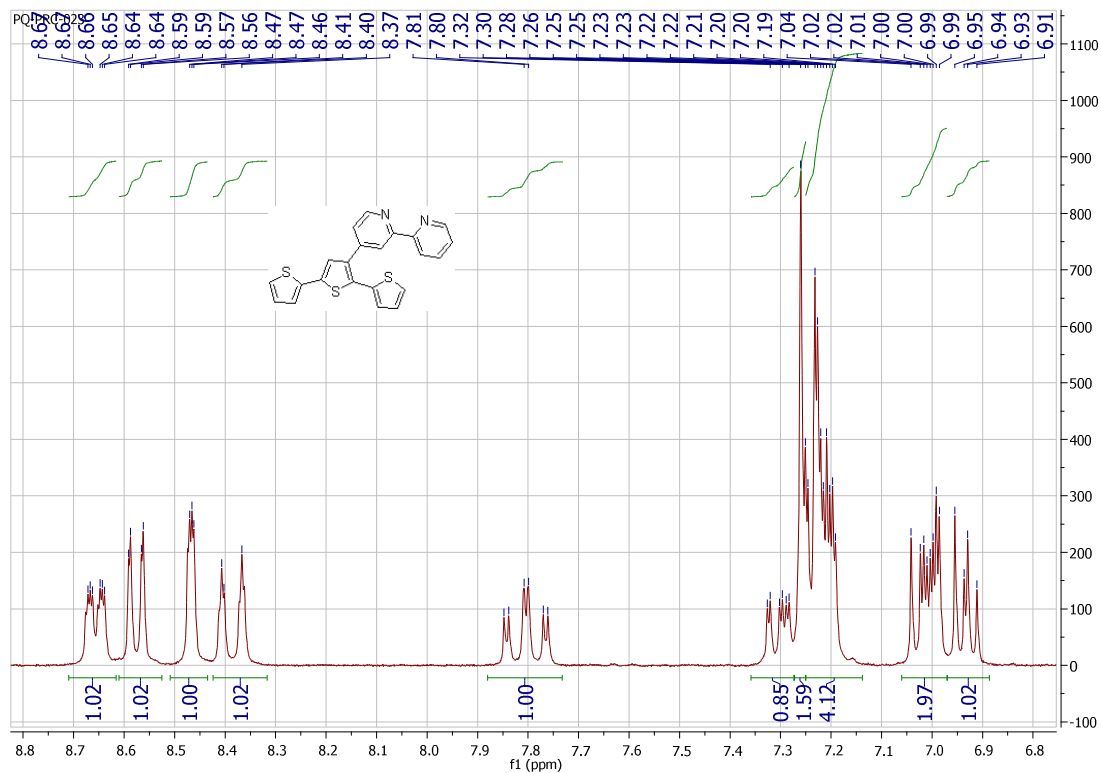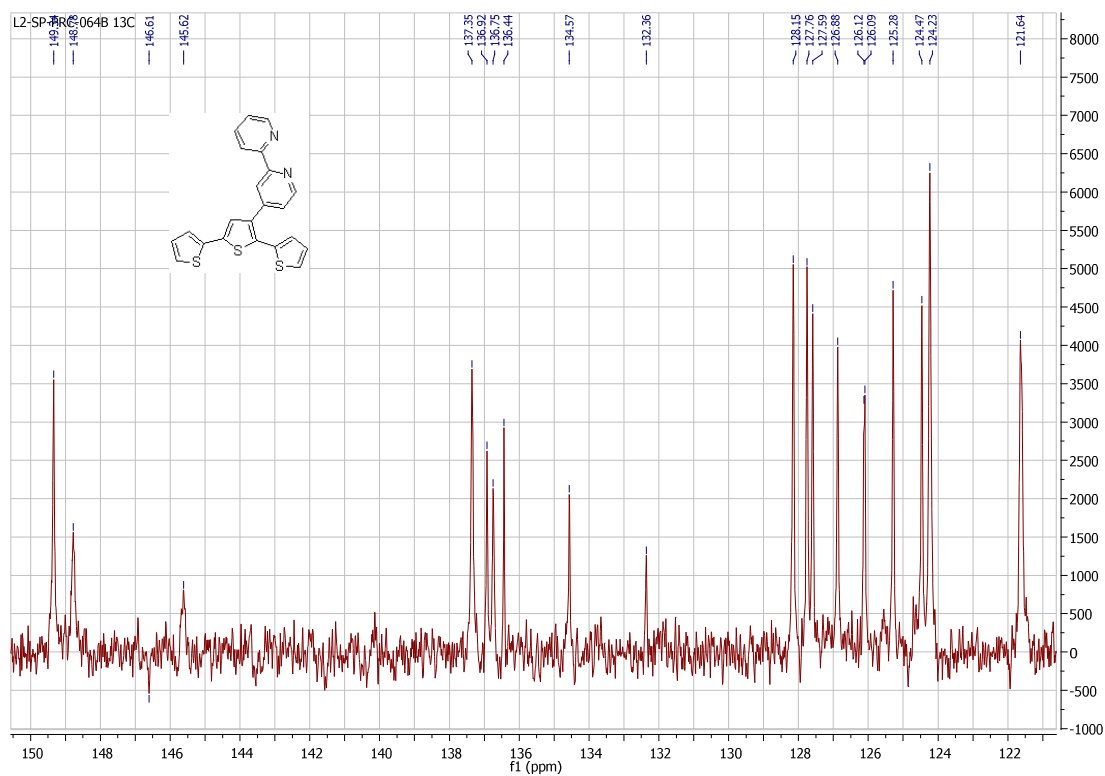

Fig-SI-19. ^{1}H-NMR for Compound **11**.

Fig-SI-20. ^{13}C-NMR for Compound **11**.

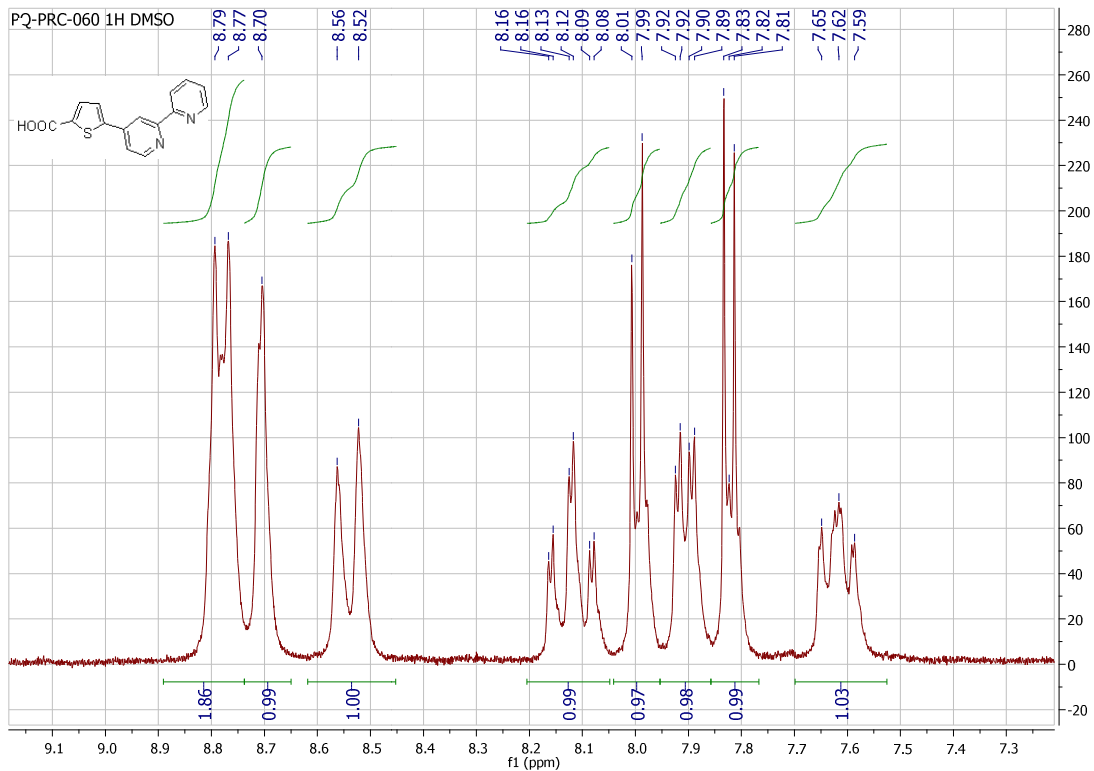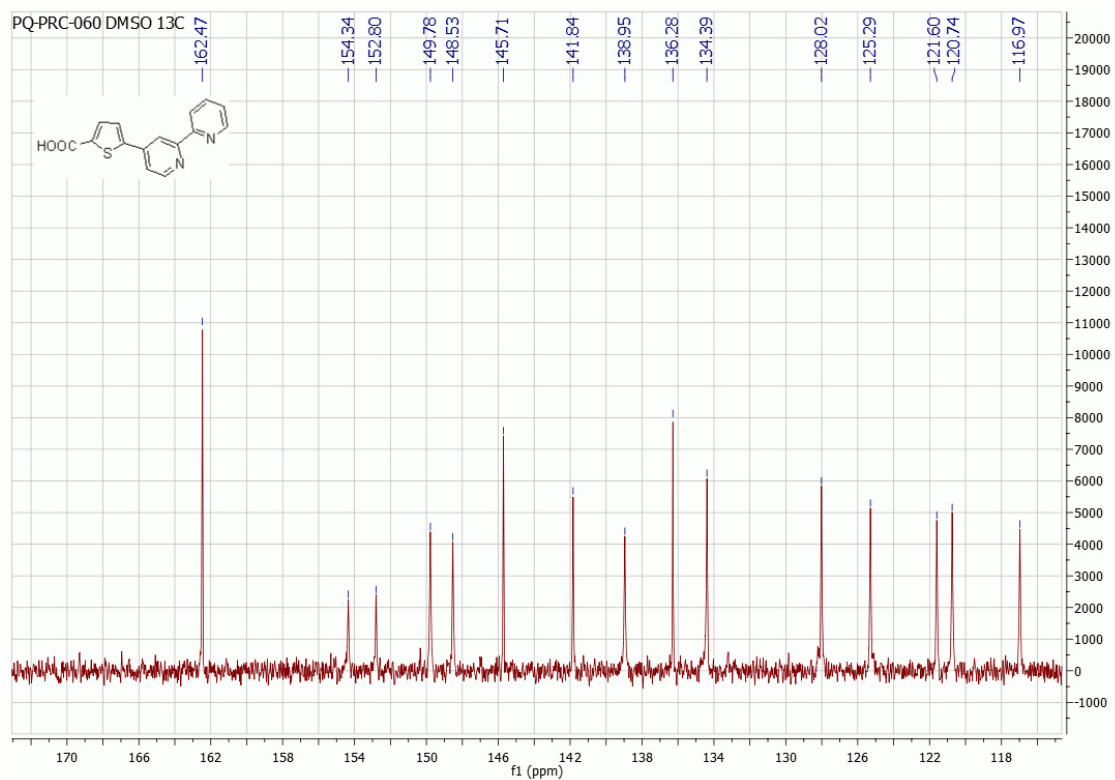# 5-([2,2'-bipyridin]-4-yl)thiophene-2-carboxylic acid. (12)

Fig-SI-21. ^{1}H-NMR for Compound **12**.

Fig-SI-22. ^{13}C-NMR for Compound **12**.