# Iodine-catalyzed three-component annulation: Access to highly fluorescent trisubstituted thiophenes

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† Electronic Supplementary Information (ESI) available: [details of any supplementary information available should be included here]. See DOI: 10.1039/x0xx00000x

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## 1. General Information

All chemicals were purchased from Sigma-Aldrich, Merck, Finar and Avra Synthesis, Pvt. Ltd. India and used as received. ACME silica gel (100-200 mesh) was used for column chromatography and thin-layer chromatography (TLC) was performed on Merck-precoated silica gel 60-$F_{254}$ plates.The steady-state UV-Vis absorption and fluorescence measurements were performed using JASCO V-730 UV-Visible spectrophotometer and JASCO FP-8350 spectrofluorometer, respectively. The spectroscopic grade solvents used for spectral measurements were purchased from Spectrochem. $^{1}$H NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the $CHCl_3$ peak around 7.26 ppm used as standard respectively). $^{13}$C NMR chemical shifts are expressed in parts per million (δ) downfield from tetramethylsilane (with the central peak of $CHCl_3$ around 77.2 ppm used as standard respectively). All $^{13}$C spectra were measured with complete proton decoupling. NMR coupling constants (*J*) are reported in Hertz (Hz), and splitting patterns are indicated as follows: br, broad; s, singlet; d, doublet; dd, doublet of doublet; ddd, doublet of doublet of doublet; dt, doublet of triplet; t, triplet; q, quartet; m, multiplet.

## 2. Single Crystal X-ray Diffraction

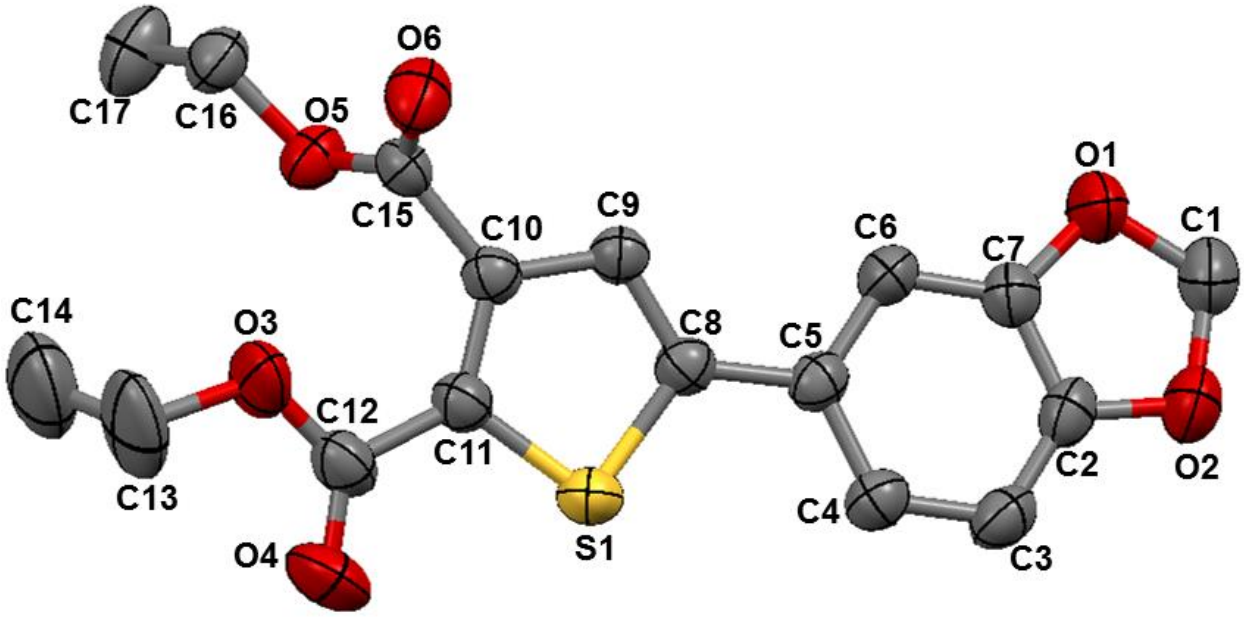



**Fig 1.** The ORTEP (50% probability) diagram of the compound

**X-ray crystal data collection and structure solution:**

The single crystal suitable for the study was chosen by Euromex Holland stereo zoom microscope and mounted at room temperature on diffractometer. X-ray data were collected on a Bruker D8 Quest with MoK $\alpha$ radiation ( $\lambda$ = 0.71073 Å) at 297 K. The empirical absorption correction on the collected reflections were performed using SADABS.[1] The structure was solved directly with SHELXS-97 (Sheldrick, 2008)[2] and refined with SHELXL-2018/3 (Sheldrick, 2018).[3,4] The molecular graphics was generated using Mercury-3.8 for Windows.[5]

Crystal data for compound: $C_{17}H_{16}O_6S$; Fw: 348.36; Crystal system: Monoclinic; Space group: P2(1)/c; a: 7.7764(2) Å; b: 24.8373(6) Å; c: 9.1903(3) Å; $\alpha$ = 90.0; $\beta$ = 113.534(3); $\gamma$ = 90º; V: 1627.41(9) Å3; $D_{calc}$: 1.422 Mg $m^{-3}$; Z: 4; μ (Mo K$\alpha$) ($mm^{-1}$): 0.229; Reflections collected/unique: 19686/9843; Parameters: 219; $R_{int}$: 0.0470; R (observed data): R1 = 0.0470; wR2 = 0.1346; R (all data): R1 = 0.0621; wR2 = 0.1236; Goodness-of-fit on F2: 1.058; $\theta_{min}$ and $\theta_{max}$ (eÅ-3): 2.553 and 26.955.[6]

## 3. General procedure

### 3.1. General procedure for synthesis of 2,3,5- Trisubstituted thiophenes:

To the dry reaction vial, 4-Methoxyanline (1.25 mmol), Activated alkynes (1.5 mmol), Acetophenone (1.0mmol) were added and to this 2.0 equiv. of Sulfur and 10 mol% of iodine were added and the reaction mixture was stirred under 120 ºC in a sealed tube. Progress of the reaction was monitored by commercially available Thin Layer Chromatography (TLC) plate, and after the disappearance of all the starting materials, crude reaction mixture was washed with saturated aqueous Sodiumthiosulphate solution, washed with brine, extracted with Ethyl Acetate and dried with anhydrous $Na_2SO_4$. Remove the solvent under vacuum distillation using Rota-evaporator followed by column chromatography performed with 100-200 mesh silica gel using a solvent mixture of Hexane:Ethyl Acetate in the ratio of 9:1 and the final product was analyzed by $^{1}H$, $^{13}C$-NMR and HRMS.

## 4. Result and Discussion

### 4.1. Biologically Significant thiophene derivatives

Raloxifene **I**, used for breast cancer treatment;[7a] Olanzapine **II**, an anti-psychotic;[7b] PaTrin **III**, a marketed drug employed for inactivating MGMT;[7c] Clopidogrel **IV**, to treat peripheral artery disorders;[7d] Dorzolamide **V**, to treat glaucoma;[7e] and Duloxetine **VI**, an anti-depressant.[7e]

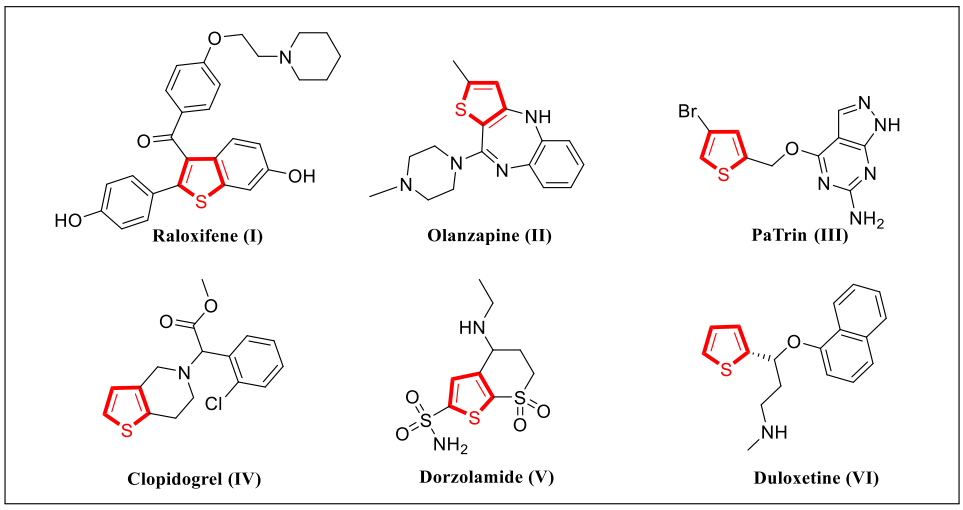
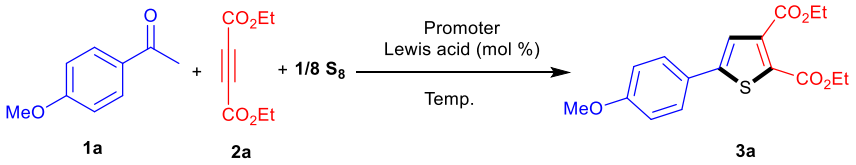



**Fig. 2.** Structure of thiophene containing drugs approved by US-FDA.

## 4.2. Optimization of reaction condition

**Table 1.** Optimization of reaction condition for the synthesis of substituted thiophene[a]




1a 2a 3a

| Entry | 1/8 $S_8$ (equiv.) | Catalyst (equiv.) | Promoter | Time (h) | Yield (%) |
|---|---|---|---|---|---|
| 1 | 1.0 | - | *p*-toluidine | 8.0 | Trace |
| 2 | 1.0 | $SnCl_2$ (0.2) | *p*-toluidine | 5.0 | 34 |
| 3 | 1.0 | $FeCl_3$ (0.2) | *p*-toluidine | 5.0 | 39 |
| 4 | 1.0 | $BF_3{\cdot}OEt_2$ (0.2) | *p*-toluidine | 5.0 | Trace |
| 5 | 1.0 | $I_2$ (0.2) | *p*-toluidine | 2.0 | 48 |
| 6 | 1.0 | $I_2$ (0.1) | *p*-toluidine | 3.0 | 52 |
| 7 | 1.0 | $I_2$ (0.05) | *p*-toluidine | 6.0 | 54 |
| 8 | 1.0 | $I_2$ (0.1) | *p*-anisidine | 3.0 | 65 |
| 9 | 1.0 | $I_2$ (0.1) | *m*-anisidine | 3.0 | 52 |
| 10 | 1.0 | $I_2$ (0.1) | *o*-anisidine | 3.0 | 35 |
| 11 | 1.0 | $I_2$ (0.1) | 2,4-dimethyl aniline | 3.0 | 42 |
| 12 | 1.0 | $I_2$ (0.1) | *n*-butyl amine | 3.0 | 23 |
| 13 | 1.0 | $I_2$ (0.1) | piperidine, morpholine, DIPEA | 3.0 | Trace |
| 14 | 1.0 | $I_2$ (0.1) | $K_2CO_3$/ $Cs_2CO_3$/ *t*-BuOK | 3.0 | N. R |
| 15 | 1.5 | $I_2$ (0.1) | *p*-anisidine | 2.5 | 73 |
| **16** | **2.0** | **$I_2$ (0.1)** | ***p*-anisidine** | **2.0** | **82** |
| 17[b] | 2.0 | $I_2$ (0.1) | *p*-anisidine | 6.0 | 69 |
| 18[c] | 2.0 | $I_2$ (0.1) | *p*-anisidine | 5.0 | 66 |
| 19[d] | 2.0 | $I_2$ (0.1) | *p*-anisidine | 7.0 | 20 |
| 20[e] | 2.0 | $I_2$ (0.1) | *p*-anisidine | 7.5 | 55 |
| 21[f] | 2.0 | $I_2$ (0.1) | *p*-anisidine | 8.0 | N. R |
| 22 | 2.0 | IBX,KI (0.1) | *p*-anisidine | 7.0 | Trace |
| 23 | 2.0 | DIB (0.1) | *p*-anisidine | 8.0 | 26 |
| 24 | 2.0 | TBAI (0.1) | *p*-anisidine | 8.0 | 31 |
| 25 | 2.0 | $NH_4I$ (0.1) | *p*-anisidine | 8.0 | 22 |

[a]Reaction condition: **1a** (1.0 equiv.), **2a** (1.5 equiv.), Sulfur, Promoter (1.25 equiv.), catalyst, solvent at 120 ºC. [b]DCB as solvent. [c]toluene as solvent, [d]Glycerol as solvent, [e]PEG as solvent, [f]$H_2O$ as solvent at 100 °C

### 4.3. Photophysical properties

#### 4.3.1. Absorption and emission Spectra

Absorption and emission spectra of synthesized thiophene derivatives was recorded using acetonitrile as solvent

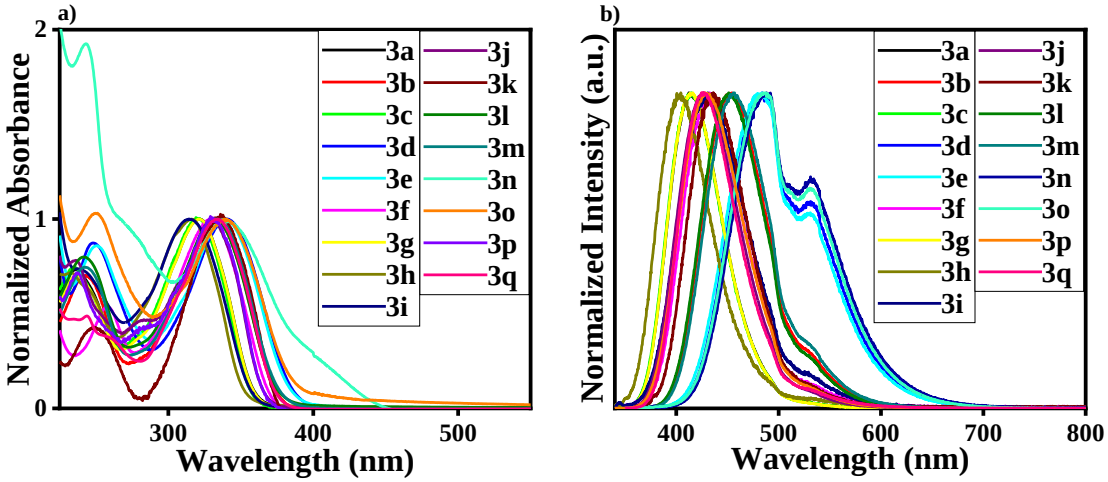



**Fig. 3.** Absorption and Emission Spectra of compound **3a-3q**

### 4.3.2. Quantum yield

The relative quantum yield of the compounds **3a**-**3q** in $CH_3CN$ have been determined using quinine sulphate in 0.5 M $H_2SO_4$ as a reference. Photophysical parameters are tabulated in Table. 2 and from the quantum yield values, it is clear that these derivatives are excellent fluorescent materials with high quantum efficiency (**3b**, **3m**, **3p**, **3q**).

| Compound | Absorption Maxima ($\lambda_{ab}$ [nm]) | Emission maxima ($\lambda_{em}$ [nm]) | $\Phi_f$ |
|---|---|---|---|
| 3a | 321.6, 236.0 | 414.2 | 0.53 |
| **3b** | **338.4, 251.0** | **528.8 (sh), 480.8** | **0.62** |
| 3c | 338.6, 251.0 | 415.6 | 0.36 |
| 3d | 340.4, 248.0, 211.4 | 529.2(sh), 483.4 | 0.36 |
| 3e | 332.0, 241.4 | 532.2(sh), 451.4 | 0.44 |
| 3f | 330.4, 258.0, 202.0 | 430.0 | 0.10 |
| 3g | 321.0, 236.8 | 415.0 | 0.44 |
| 3h | 315.0, 232.4 | 404.8 | 0.11 |
| 3i | 314.6, 240.8, 212.2 | 430.2 | 0.15 |
| 3j | 330, 280 | 426.0 | 0.57 |
| 3k | 336.0, 249.8 | 433.6 | 0.10 |
| 3l | 332.0, 242.2 | 531.0(sh), 451.2 | 0.56 |
| **3m** | **332.8, 242.2** | **454.0** | **0.65** |
| 3n | 339.6, 243.2, 217.2 | 532.6(sh), 488.4 | 0.32 |
| 3o | 338.6, 251.0 | 530.4(sh), 486.2 | 0.36 |
| **3p** | **329, 237.5, 209.0** | **428.5** | **0.62** |
| **3q** | **334.0, 243.8, 260.0** | **426.2** | **0.61** |

**Table.2.** Photophysical parameters of phenyl-thiophene derivatives.

### 4.3.3. +Solvatochromism

Solvatochromic behavior of **3o**, **3b** and **3d** were investigated in different solvents like cyclohexane, toluene, THF, DMSO, $CH_3CN$ (ACN) and MeOH. The absorption maxima of **3b**, **3d and 3o** remained almost constant with increase in solvent polarity, whereas, the emission maxima show significant bathochromic shift with increase in solvent polarity. Due to Intramolecular Charge Transfer (ICT) shoulder peak was found around 530 nm and it was high in polar solvents.

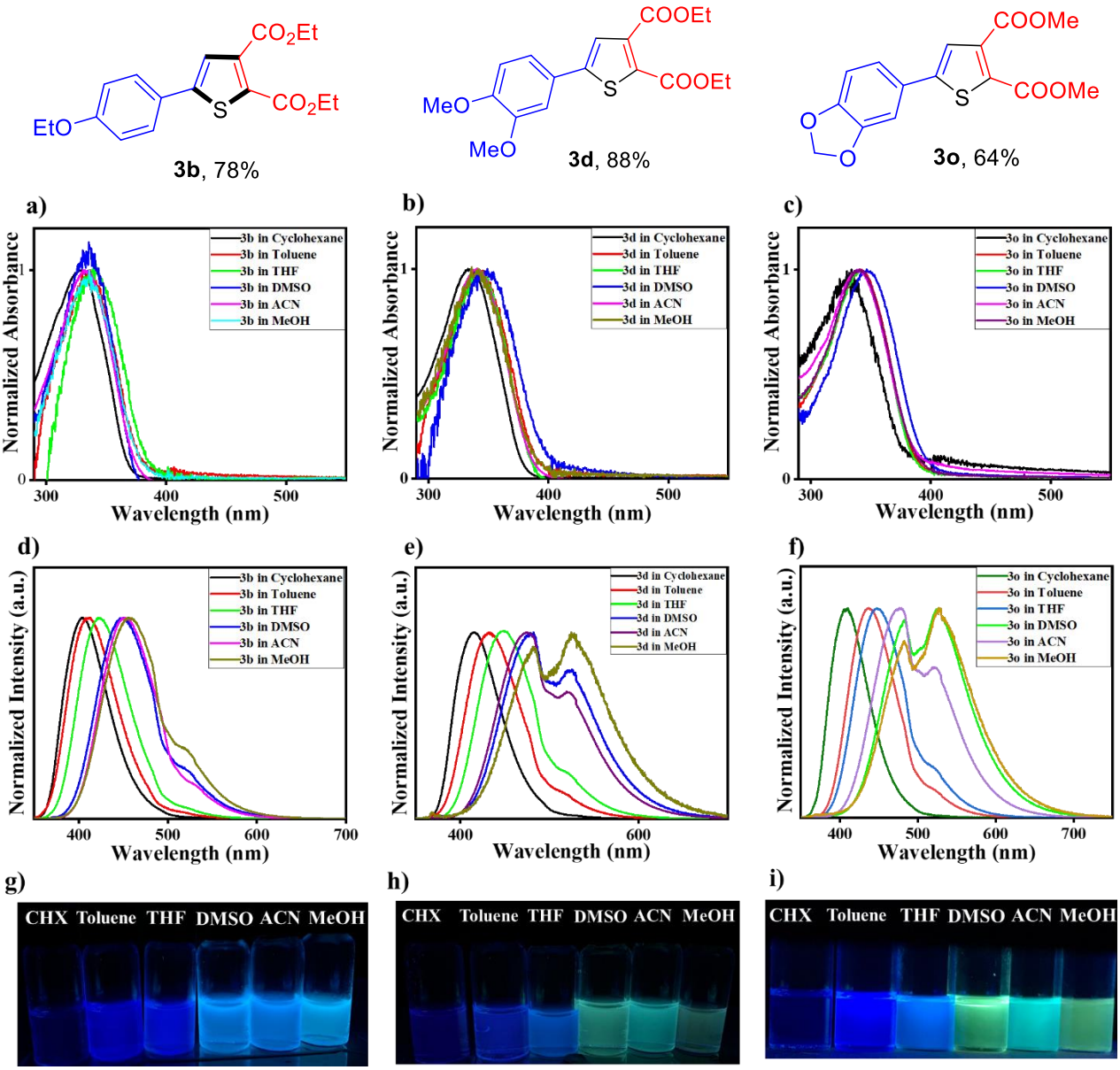



**Fig. 4.** Solvatochromic behavior of **3o**, **3b**, **3d** in various solvents: a) Normalized absorbance of **3b** in different solvents. b) Normalized absorbance of **3d** in different solvents. c) Normalized absorbance of **3o** in different solvents. d) Normalized emission spectra of **3b** in different solvents. e) Normalized emission spectra of **3d** in different solvents. f) Normalized emission spectra of **3o** in different solvents. g) Fluorescence image of **3b** in different solvents. h) Fluorescence image of **3d** in different solvents. i) Fluorescence image of **3o** in different solvents.

### 4.3.4. Solid state excitation and emission spectra

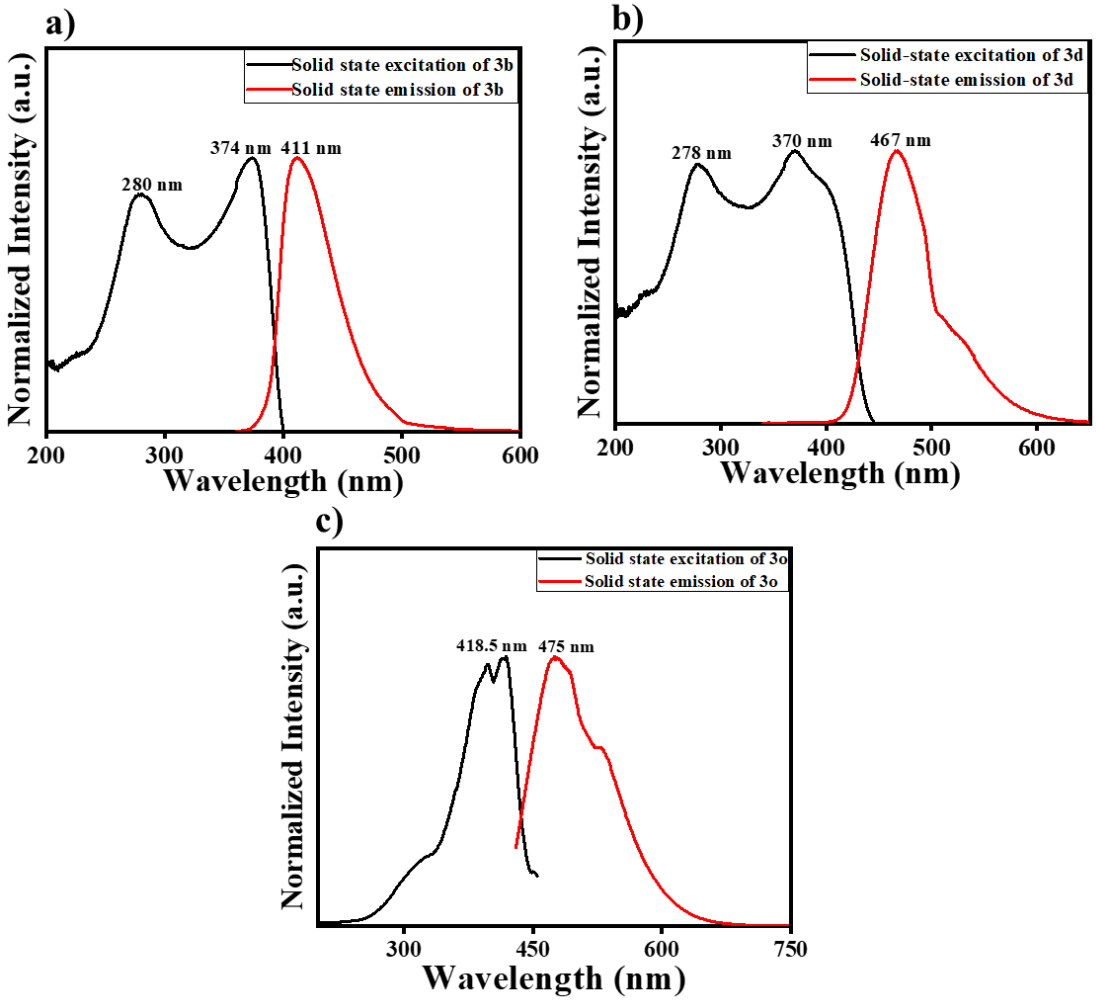



**Fig. 5.** a) Solid state excitation and emission of **3b,** b) Solid state excitation and emission of **3d**, c) Solid state excitation and emission of **3o.**

#### 4.3.5. Solid-state fluorescence

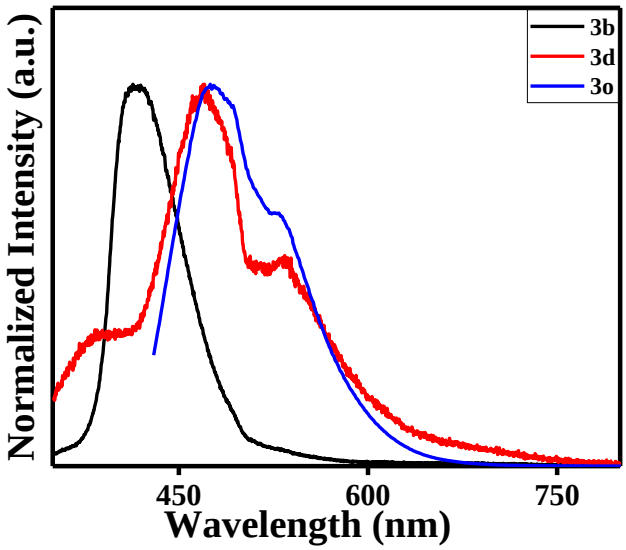
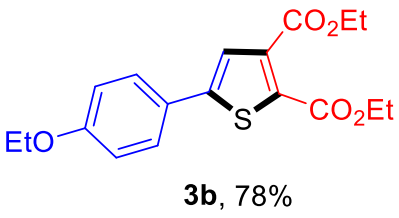
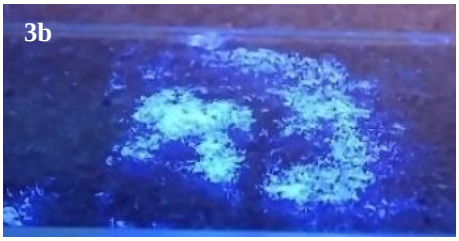
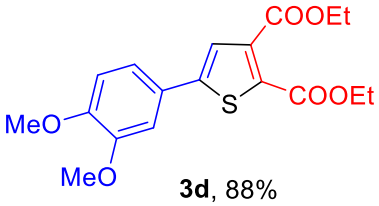



**Fig. 6.** Solid-State fluorescence spectra of compounds **3b, 3d, 3o.**

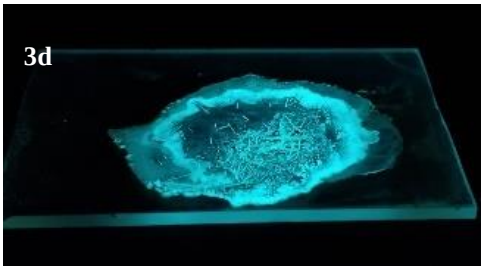


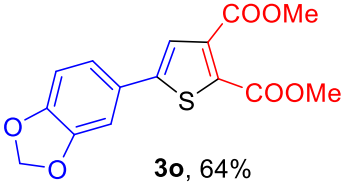

**3b**, 78%




**3d**, 88%




**3o**, 64%

### 4.3.6. Quantum chemical study

Quantum chemical calculation was executed with the B3LYP[8-10] functional in Gaussian software package[11] for the structural optimization of **3e**. The 6-311G(d,p) basis set for H, C, N, O atoms was employed. The HOMO and LUMO diagram were visualized using GaussView 5.0 software.[12] The vibrational frequency calculation for **3e** was performed to confirm the structures located at local minima

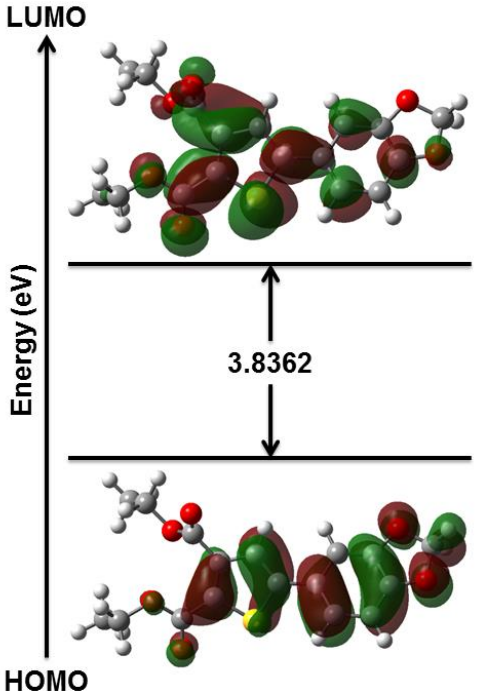



**Fig. 6.** Frontier MO diagram of **3e**.

Table 3. The Cartesian coordinates of **3e** calculated from Gaussian-09 at B3LYP computational level

| Atom | X | Y | Z |
|---|---|---|---|
| S | 3.065 | 14.298 | 5.208 |
| O | 1.547 | 18.184 | 3.211 |
| O | 0.974 | 16.729 | 1.619 |
| O | -1.461 | 10.179 | 7.881 |
| O | -2.677 | 11.822 | 6.81 |
| O | 4.179 | 17.109 | 2.763 |
| O | 5.385 | 15.934 | 4.242 |

| | | | |
|---|---|---|---|
| C | 1.406 | 16.963 | 2.713 |
| C | 0.664 | 13.045 | 5.843 |
| C | 1.775 | 15.902 | 3.692 |
| C | 1.359 | 14.096 | 5.09 |
| C | 0.816 | 15.025 | 4.237 |
| H | -0.091 | 15.069 | 4.037 |
| C | 3.048 | 15.623 | 4.123 |
| C | 1.378 | 12.049 | 6.504 |
| H | 2.307 | 12.063 | 6.466 |
| C | -1.335 | 12.035 | 6.608 |
| C | -0.742 | 13.035 | 5.896 |
| H | -1.246 | 13.684 | 5.461 |
| C | -0.615 | 11.059 | 7.257 |
| C | 1.302 | 19.284 | 2.284 |
| H | 0.441 | 19.173 | 1.851 |
| H | 1.99 | 19.308 | 1.602 |
| C | 0.751 | 11.034 | 7.216 |
| H | 1.238 | 10.369 | 7.646 |
| C | 4.33 | 16.231 | 3.739 |
| C | -2.766 | 10.71 | 7.684 |
| H | -3.345 | 10.033 | 7.301 |
| H | -3.141 | 10.988 | 8.534 |
| C | 1.319 | 20.542 | 3.075 |
| H | 1.158 | 21.289 | 2.493 |
| H | 2.176 | 20.644 | 3.497 |
| H | 0.634 | 20.508 | 3.748 |
| C | 5.344 | 17.868 | 2.326 |
| H | 6.143 | 17.485 | 2.72 |
| H | 5.425 | 17.805 | 1.361 |
| C | 5.243 | 19.209 | 2.695 |
| H | 5.903 | 19.721 | 2.222 |
| H | 5.39 | 19.292 | 3.64 |
| H | 4.367 | 19.536 | 2.477 |
| H | 5.903 | 19.721 | 2.222 |
| H | 5.39 | 19.292 | 3.64 |
| H | 4.367 | 19.536 | 2.477 |

## 5. Reference


1. SADABS, Empirical Absorption Correction Program; University of Goottingen: Germany, **1997**.

2. G. M. Sheldrick, SHELXS-97: Program for Crystal Structure Solution and refinement;University of Gottingen: Gottingen, Germany, **1997**.

3. G. M. Sheldrick, A short history of SHELX. *Acta. Cryst.* A64, **2008**, 112−122.

4. G. M. Sheldrick, Crystal structure refinement with SHELXL, *Acta. Cryst.* C71, **2015,** 3−8.

5. C. F. Macrae, I. J. Bruno, J. A. Chisholm, P. R. Edgington, P. McCabe, E. Pidcock, L. Rodriguez-Monge, R. Taylor, J. van de Streek and P. A. Wood, J. Appl. Cryst., 41, **2008**, 466−470.

6. CCDC 2241454, contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif

7. (a) Kim, D. E.; Kim, Y.; Cho, D. H.; Jeong, S. Y.; Kim, S. B.; Suh, N.; Lee, J. S.; Choi, E. K.; Koh, J. Y.; Hwang, J. J. Raloxifene Induces Autophagy-Dependent Cell Death in Breast Cancer Cells via the Activation of AMP-Activated Protein Kinase. *Mol. Cell.* **2015**, *38*, 138–144. (b) Taylor, D.; Paton, C.; Kapur, S.; **2015**. *The Maudsley Prescribing Guidelines in Psychiatry (12th ed.). London, U K: Wiley-Blackwell.* p. 16. (c) McMurry, T.; Brian, H. MGMT inhibitors—The Trinity College–Paterson Institute experience, a chemist's perception. *DNA Repair*, **2007**, *6*, 1161–1169. (d) Nayak, K. R.; Cavendish, J. J. Risk reduction with clopidogrel in the management of peripheral arterial disease, Vasc. *Health Risk Manag.* **2007**, *3*, 289–297. (e) Grover, S.; Apushkin, M.; Fishman, G. Topical Dorzolamide for the Treatment of Cystoid Macular Edema in Patients with Retinitis Pigmentosa. *Am J Ophthalmol.* **2006,** *5*, 850–858. (f) Carter, N. J.; McCormack, P. L. Duloxetine: a review of its use in the treatment of generalized anxiety disorder. *CNS Drugs*. **2009**, *23*, 523–541.

8. A.D. Becke, Density-Functional Thermochemistry. III. The Role of Exact Exchange, *J. Chem. Phys.* **1993**, 98, 5648–5652.

9. C. Lee, W. Yang, R.G. Parr, Development of the Colle-Salvetti correlation-energy formula into a functional of the electron density, *Phys. Rev B*. **1988**, 37, 785–789.

10. S.H. Vosko, L. Wilk, M. Nusair, Accurate spin-dependent electron liquid correlation energies for local spin density calculations: a critical analysis, *Can. J. Phys.* **1980**, 58, 1200–1211.

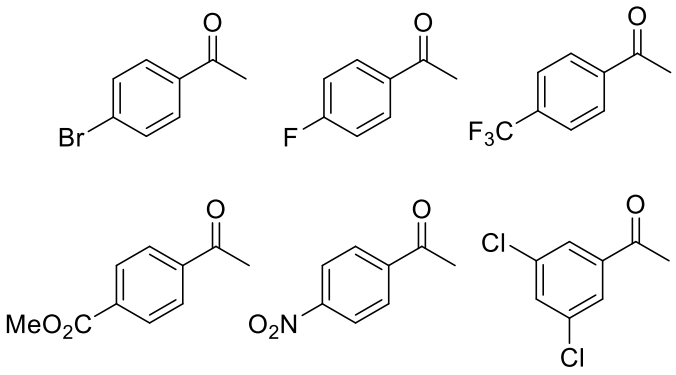
11. M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, G. Scalmani, V. Barone, B. Mennucci, G.A. Petersson, H. Nakatsuji, M. Caricato, X. Li, H.P. Hratchian, A.F. Izmaylov, J. Bloino, G. Zheng, J. L. Sonnenberg, M. Hada, M. Ehara, K. Toyota, R. Fukuda, J. Hasegawa, M. Ishida, T. Nakajima, Y. Honda, O. Kitao, H. Nakai, T. Vreven, J. A. Montgomery, Jr., J. E. Peralta, F. Ogliaro, M. Bearpark, J. J. Heyd, E. Brothers, K. N. Kudin, V. N. Staroverov, R. Kobayashi, J. Normand, K. Raghavachari, A. Rendell, J. C. Burant, S.S. Iyengar, J. Tomasi, M. Cossi, N. Rega, J. M. Millam, M. Klene, J. E. Knox, J. B. Cross, V. Bakken, C. Adamo, J. Jaramillo, R. Gomperts, R. E. Stratmann, O. Yazyev, A. J. Austin, R. Cammi, C. Pomelli, J. W. Ochterski, R. L.

Martin, K. Morokuma, V. G. Zakrzewski, G. A. Voth, P. Salvador, J. J. Dannenberg, S. Dapprich, A. D. Daniels, O. Farkas, J. B. Foresman, J. V. Ortiz, J. Cioslowski, and D. J. Fox, Gaussian 09, Revision A.02, Gaussian, Inc., Wallingford CT, **2009**.

12. V. GaussView, 5, Roy Dennington, Semichem Inc., Shawnee Mission, K S, Todd Keith, John Millam, **2009**.

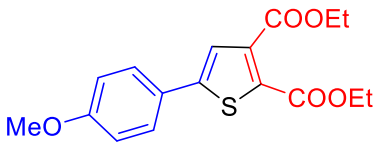
## 6. Unsuccessful Substrates

***Unsuccessfull electron deficient aryl ketons***



## 7. Characterization data of compounds

**Diethyl 5-(4-methoxyphenyl)thiophene-2,3-dicarboxylate (3a):**

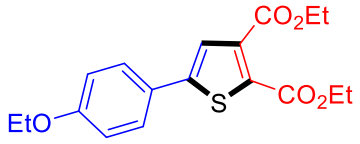



**3a**, 82%

Isolated yield = 82%, yellow solid, mp = 40-42 °C

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, *J* = 8.4 Hz, 2H), 7.32 (s, 1H), 6.93 (d, *J* = 8.4 Hz, 2H), 4.41-4.33 (m, 4H), 3.84 (s, 3H), 1.40-1.36 (m, 6H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 164.26, 161.05, 160.09, 148.74, 138.18, 133.85, 132.00, 130.26, 124.35, 118.73, 114.79, 61.79, 55.40, 14.20, 14.12.. HRMS (ESI): calculated for m/z 334. 0875 ($[M+H]^+$); found. m/z 335.0950.

**diethyl 5-(4-ethoxyphenyl)thiophene-2,3-dicarboxylate (3b):**

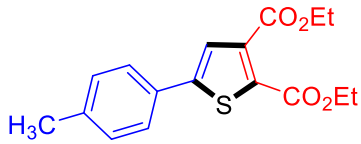



**3b**, 78%

Isolated yield = 78%, White crystalline solid, mp = 117 °C

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.53 (d, *J* = 8.4 Hz, 2H), 7.32 (S, 1H), 6.91 (d, *J* = 8.4 Hz, 2H), 4.37 (m, 4H), 4.06 (q, *J* = 7.2 Hz, 2H), 1.41 (t, *J* = 7.2 Hz, 3H), 1.37 (m, 6H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 164.5, 161.2, 159.9, 149.3, 138.5, 130.7, 127.6, 125.2, 123.1, 115.1, 63.7, 61.8, 61.7, 14.8, 14.3, 14.2. HRMS (ESI): calculated for m/z 348.1031 ($[M+H]^+$); found. m/z 349.1107.

**diethyl 5-(*p*-tolyl)thiophene-2,3-dicarboxylate (3c):**

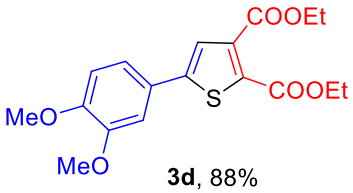



**3c**, 71%

Isolated yield = 71%, White crystalline solid, mp = 60 °C

$^1$H NMR (600 MHz, $CDCl_3$) δ 7.49 (d, *J* = 8.4 Hz, 2H), 7.48 (s, 1H), 7.20 (d, *J* = 7.2 Hz, 2H), 4.36 (m, 4H), 2.36 (s, 3H), 1.37 (m, 6H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 164.5, 161.2, 149.3, 139.4, 138.4, 131.4, 129.9, 126.1, 123.7, 61.8, 61.8, 21.4, 14.3, 14.2. HRMS (ESI): calculated for m/z 318.0926 ($[M+H]^+$); found. m/z 319.1005.

**diethyl 5-(3,4-dimethoxyphenyl)thiophene-2,3-dicarboxylate (3d):**

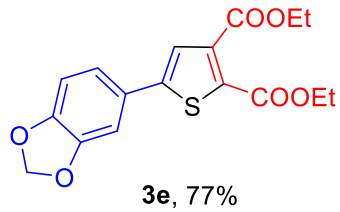



**3d**, 88%

Isolated yield = 88%, White crystalline solid, mp = 71 °C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.34 (s, 1H), 7.10 (m, 1H), 7.0 (d, 1H), 6.9 (d, 1H), 4.4-4.3 (m, 4H), 3.94 (s, 3H), 3.92 (s, 3H), 1.4-1.3 (m, 6H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 164.6, 161.2, 150.2, 149.5, 149.4, 149.3, 148.4, 131.0, 125.7, 123.4, 119.2, 111.6, 109.4, 61.9, 61.8, 56.1, 14.3, 14.2. HRMS (ESI): calculated for m/z 364.0981($[M+H]^+$); found. m/z 365.1061

**diethyl 5-(benzo[d][1,3]dioxol-5-yl)thiophene-2,3-dicarboxylate (3e):**

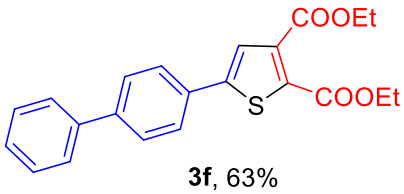



**3e**, 77%

Isolated yield = 77%, Brown crystalline solid, mp = 90 °C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.28 (s, 1H), 7.1 (m, 1H), 7.0 (d,1H), 6.8 (d, 1H), 6.0 (s, 2H), 4.39-4.32 (m, 4H), 1.5-1.34 (m, 6H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 164.4, 161.1, 149.0, 148.7, 148.6, 138.4, 131.0, 126.9, 123.6, 120.6, 109.0, 106.8, 101.7, 61.9, 61.8, 14.3, 14.2. HRMS (ESI): calculated for m/z 348.0668 ($[M+H]^+$); found. m/z 349.0735.

**diethyl 5-([1,1'-biphenyl]-4-yl)thiophene-2,3-dicarboxylate (3f):**

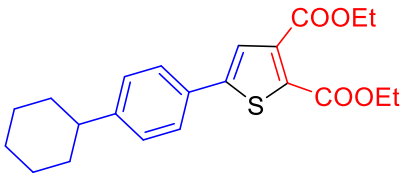



**3f**, 63%

Isolated yield = 63% White amorphous solid, mp = 89-91 °C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.70-7.61 (m, 6H), 7.47-7.45 (m, 3H), 7.39-7.36 (m, 1H), 4.39 (m, 4H), 1.39 (m, 6H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 164.37, 161.126, 148.621, 142.035, 140.109, 138.460, 131.950, 131.578, 129.012, 127.891, 127.067, 126.655, 124.224, 61.893, 61.863, 14.295, 14.219. HRMS (ESI): calculated for m/z 380.1082 ($[M+H]^+$); found. m/z 381.1162.

**diethyl 5-(4-cyclohexylphenyl)thiophene-2,3-dicarboxylate (3g):**

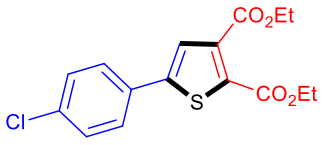



**3g**, 50%

Isolated yield = 50%, amorphous white solid, mp = 50-52 °C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.51 (d, 2H), 7.24 (d, 2H), 4.39-4.32 (m, 4H), 2.53-2.50 (m, 1H), 1.88-1.83 (m, 4H), 1.76-1.73 (m, 1H), 1.39-1.34 (m, 6H), $^{13}$C NMR (150 MHz, $CDCl_3$) δ 164.477, 161.202, 149.569, 149.330, 138.385, 131.394, 130.256, 127.719, 126.263, 123.747, 61.817, 61758, 44.447, 34.345, 26.867, 26.148, 22.770, 14.279, 14.191. HRMS (ESI): calculated for m/z 386.1552 ($[M+H]^+$); found. m/z 387.1621

**diethyl 5-(4-chlorophenyl)thiophene-2,3-dicarboxylate (3h):**

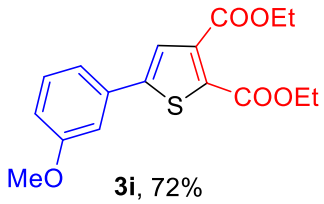



**3h**, 62%

Isolated yield = 62%, amorphous white solid, mp = 79 °C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.54 (d, 2H, *J* = 4.2 Hz), 7.44 – 7.36 (m, 3H), 4.38 (dq, 4H, *J* = 9.2, 3.6 Hz), 1.39 (dt, 6H, *J* = 4.7, 3.6 Hz). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 163.03, 159.88, 146.33, 137.28, 134.12, 131.36, 130.09, 126.37, 123.50, 60.83, 13.12 (d, J = 20.5 Hz). HRMS (ESI): calculated for m/z 338.0380 ($[M+H]^+$); found. m/z 339.0450.

**diethyl 5-(3-methoxyphenyl)thiophene-2,3-dicarboxylate (3i):**

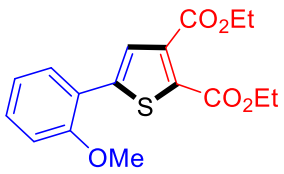



**3i**, 72%

Isolated yield = 72% White amorphous solid, mp = 63-65 °C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.43 (s, 1H), 7.33 (t, 1H), 7.20 (d, 1H), 7.13 (t, 1H), 6.92 (d, 1H), 4.384 (m, 4H), 3.859 (s, 3H), 1.390 (m, 6H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 164.34, 161.12, 160.16, 148.81, 138.25, 133.92, 132.07, 130.33, 124.42, 118.80, 114.86, 111.77, 61.86, 55.47, 14.27, 14.20. HRMS (ESI): calculated for m/z 334.0875 ($[M+H]^+$); found. m/z 335.0955.

**diethyl 5-(2-methoxyphenyl)thiophene-2,3-dicarboxylate (3j):**

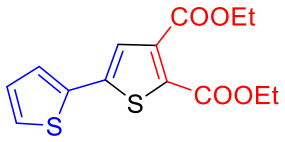



**3j**, 61%

Isolated yield = 61% White amorphous solid, mp = 67-69 °C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.685 (d, 1H), 7.62 (s, 1H), 7.35-7.32 (m, 1H), 7.04-7.00 (m, 2H), 4.38 (m, 4H), 3.97 (s, 3H), 1.385 (m, 6H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 166.53, 160.01, 159.53, 136.79, 132.64, 130.42, 129.28, 127.67, 127.53, 126.04, 124.49, 123.25, 121.85, 113.98, 61.35, 60.79, 55.60, 21.23, 14.17, 14.04. HRMS (ESI): calculated for m/z 334.0875 ($[M+H]^+$); found. m/z 335.094.

**diethyl [2,2'-bithiophene]-4,5-dicarboxylate (3k):**

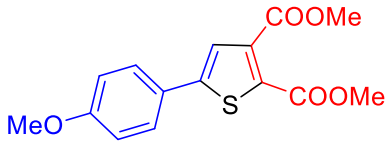



**3k**, 48%

Isolated yield = 48%, White crystalline solid, mp = 47 °C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.2 (d, *J* = 3.6 Hz, 1H), 7.2 (s, 1H), 7.6 (d, *J* = 2.4 Hz, 1H), 7.0 (d, *J* = 3.6 Hz, 1H), 4.3 (m, 4H), 1.3 (m, 6H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 164.1, 160.9, 142.1, 138.4, 135.4, 131.4, 131.1, 128.3, 126.7, 125.8, 124.4, 61.9, 61.9, 14.3, 14.2. HRMS (ESI): calculated for m/z 310.0334 ($[M+H]^+$); found. m/z 311.0412.

**dimethyl 5-(4-methoxyphenyl)thiophene-2,3-dicarboxylate (3l):**

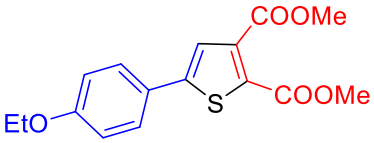



**3l**, 67%

Isolated yield = 67%, White crystalline solid, mp = 75 °C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.5 (d, *J* = 8.5 Hz, 2H),7.3 (s, 1H), 6.9 (d, *J* = 8.4 Hz, 2H), 3.93(s, 3H), 3.89 (s, 3H), 3.8 (s, 3H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 164.8, 161.5, 160.6, 149.4, 138.3, 130.4, 130.4, 127.7, 125.3, 123.3, 114.7, 55.5, 52.8, 52.4. HRMS (ESI): calculated for m/z 306.0562 ($[M+H]^+$); found. m/z 307.0640.

**dimethyl 5-(4-ethoxyphenyl)thiophene-2,3-dicarboxylate (3m):**

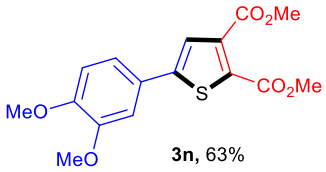



**3m**, 61%

Isolated yield = 61% White amorphous solid, mp = 95-97 °C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.45 (d, 2H), 7.19 (s, 1H), 6.85 (d, 2H), 4.00 (q, 2H), 3.86 (s, 3H), 3.82 (s, 3H), 1.36 (t, 3H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 164.71, 161.45, 159.90, 149.42, 138.19, 130.25, 127.54, 125.01, 123.16, 115.06, 63.65, 52.65, 52.55, 14.73. HRMS (ESI): calculated for m/z 320.0718 ($[M+H]^+$); found. m/z 321.0801.

**dimethyl 5-(3,4-dimethoxyphenyl)thiophene-2,3-dicarboxylate (3n):**

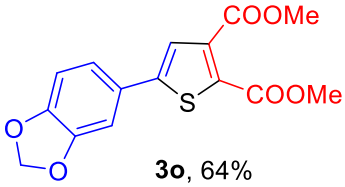



**3n**, 63%

Isolated yield = 63%, White solid, mp = 45-47 °C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.29(s, 1H), 7.12 (dd, 1H, *J* = 4.2, 1.1 Hz), 7.01 (d, 1H, *J* = 1.1 Hz), 6.83 (d, 1H, *J* = 4.2 Hz), 3.97 – 3.71 (m, 12H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 161.84, 159.25, 148.39, 135.99, 135.05, 126.41, 124.45, 122.45, 118.13, 113.40, 110.52, 108.28, 55.02, 52.24, 52.12, 51.59. HRMS (ESI): calculated for m/z 336.0668 ($[M+H]^+$); found. m/z 337.0748.

**dimethyl 5-(benzo[d][1,3]dioxol-5-yl)thiophene-2,3-dicarboxylate (3o):**

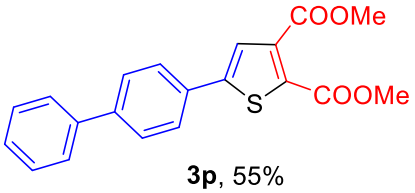



**3o**, 64%

Isolated yield = 64% White amorphous solid,mp= 58-60 °C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.31 (s, 1H), 7.11 (d, 1H), 7.06 (d, 1H), 6.84 (d, 1H), 6.02 (s, 2H), 3.93 (s, 3H), 3.89 (s, 3H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 164.66, 161.46, 149.19, 148.74, 148.53, 138.16, 130.73, 126.73, 126.78, 123.72, 120.55, 108.99, 106.71, 101.69, 52.76, 52.70. HRMS (ESI): calculated for m/z 320.0355 ($[M+H]^+$); found. m/z 321.0433

**dimethyl 5-([1,1'-biphenyl]-4-yl)thiophene-2,3-dicarboxylate (3p):**

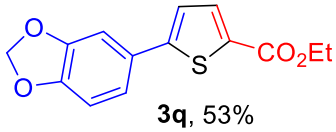



**3p**, 55%

Isolated yield = 55% White Crystalline solid, mp = 105 °C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.69-7.61 (m, 6H), 7.49 (s, 1H), 7.47-7.45 (t, 2H), 7.38 (t, 1H), 3.95 (s, 3H), 3.91 (s, 3H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 163.52, 160.38, 147.73, 141.05, 138.98, 137.11, 130.54, 130.36, 127.91, 126.82, 125.96, 125.56, 123.27, 51.69, 51.66. HRMS (ESI): calculated for m/z 352.0769 ($[M+H]^+$); found. m/z 353.0852.

**ethyl 5-(3,4-dimethoxyphenyl)thiophene-2-carboxylate (3q):**

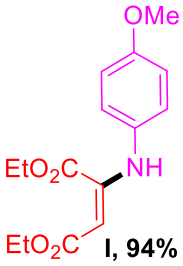



**3q**, 53%

Isolated yield = 53%, white solid, mp = 80-83 ˚C

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 7.72 (d, *J* = 1.9 Hz, 1H), 7.16 – 7.13 (m, 1H), 7.10 (d, *J* = 0.9 Hz, 1H), 6.84 (d, *J* = 4.0 Hz, 1H), 6.01(s, 2H), 4.35 (q, 2H), 1.39 (t, 3H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 161.28, 150.03, 147.31, 133.19, 130.67, 126.77, 121.91, 119.30, 107.80, 105.67, 100.46, 60.12, 13.36. m/z 276.0456 ($[M+H]^+$); found. m/z 277.0534.

**diethyl 2-((4-methoxyphenyl)amino)maleate (Intermediate I):**



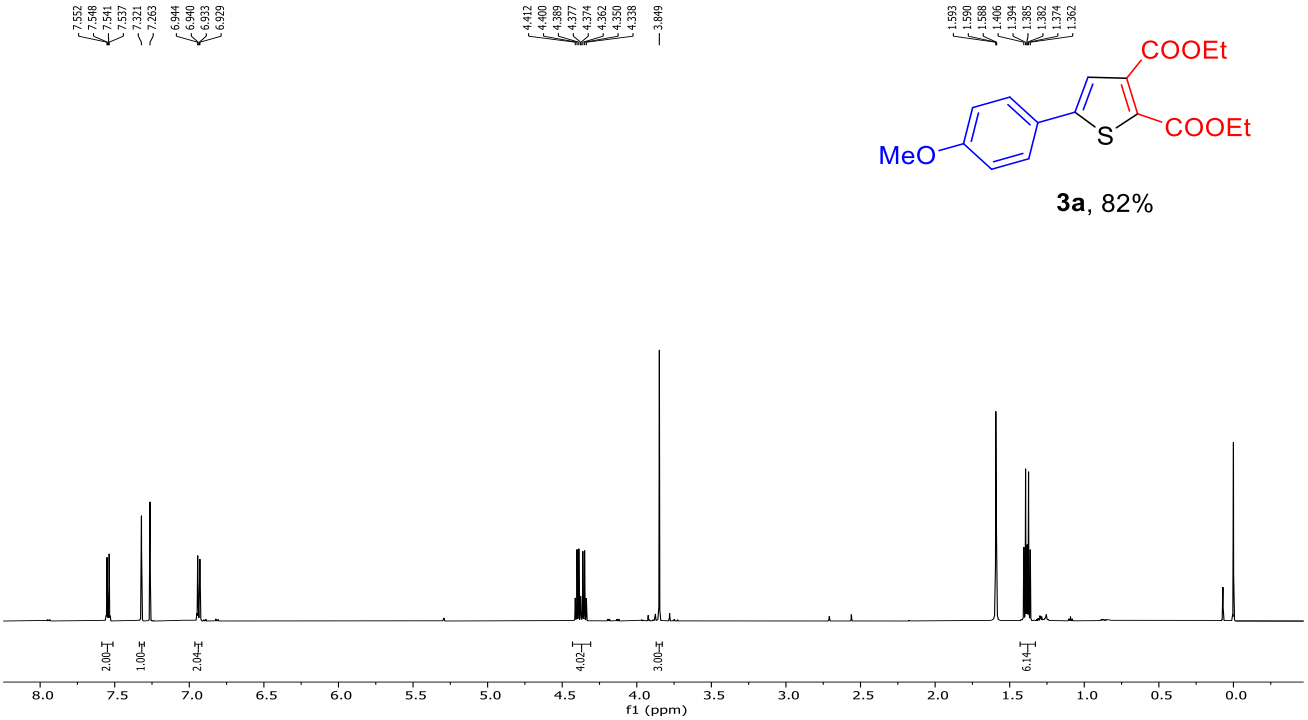

**I, 94%**

Isolated yield = 94%, yellow oil,

$^{1}$H NMR (600 MHz, $CDCl_3$) δ 9.57 (Broad, s, 1H), 6.90 (d, *J* = 4.5 Hz, 2H), 6.81 (d, *J* = 4.4 Hz, 2H), 5.29, 4.19 (q, *J* = 3.6 Hz, 2H), 4.13 (q, *J* = 3.6 Hz, 2H), 3.78, 1.30 (t, *J* = 3.6 Hz, 3H), 1.09 (t, *J* = 3.6 Hz, 3H). $^{13}$C NMR (150 MHz, $CDCl_3$) δ 168.77, 163.35, 155.91, 148.42, 132.54, 122.25, 113.26, 90.88, 60.89, 58.76, 13.35, 12.69.

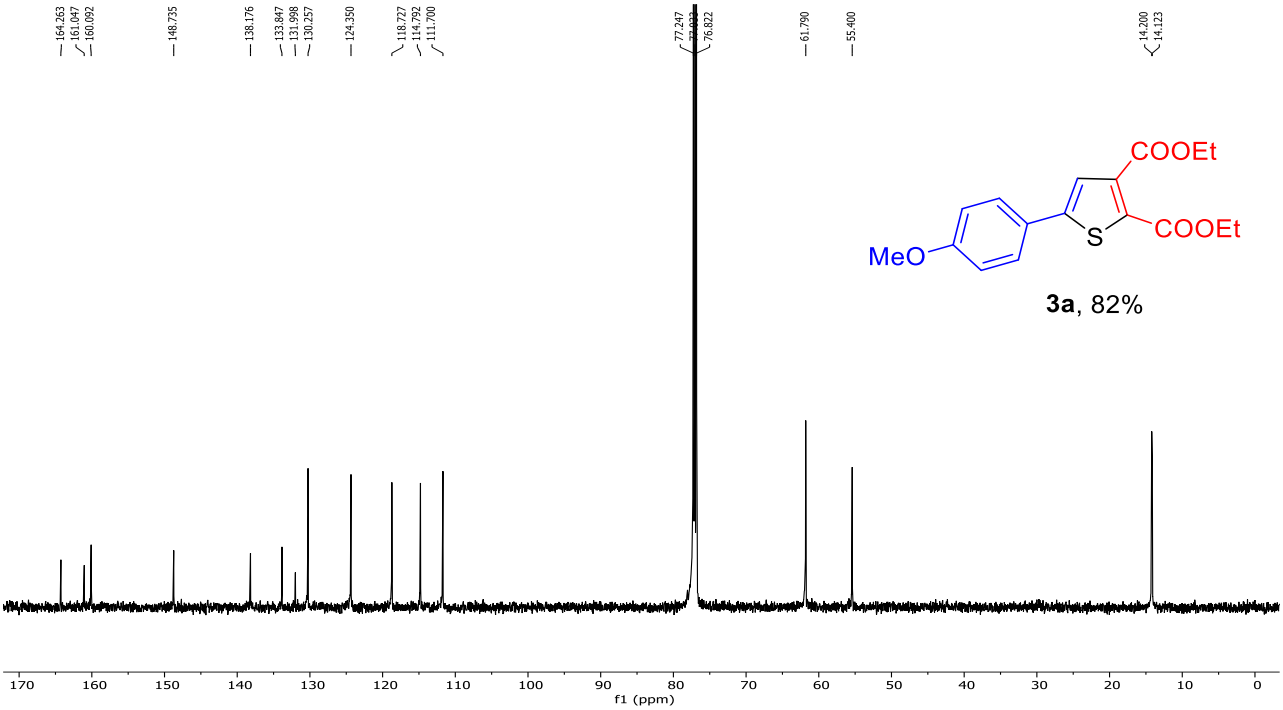
## 8. Copies of NMR Spectra

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



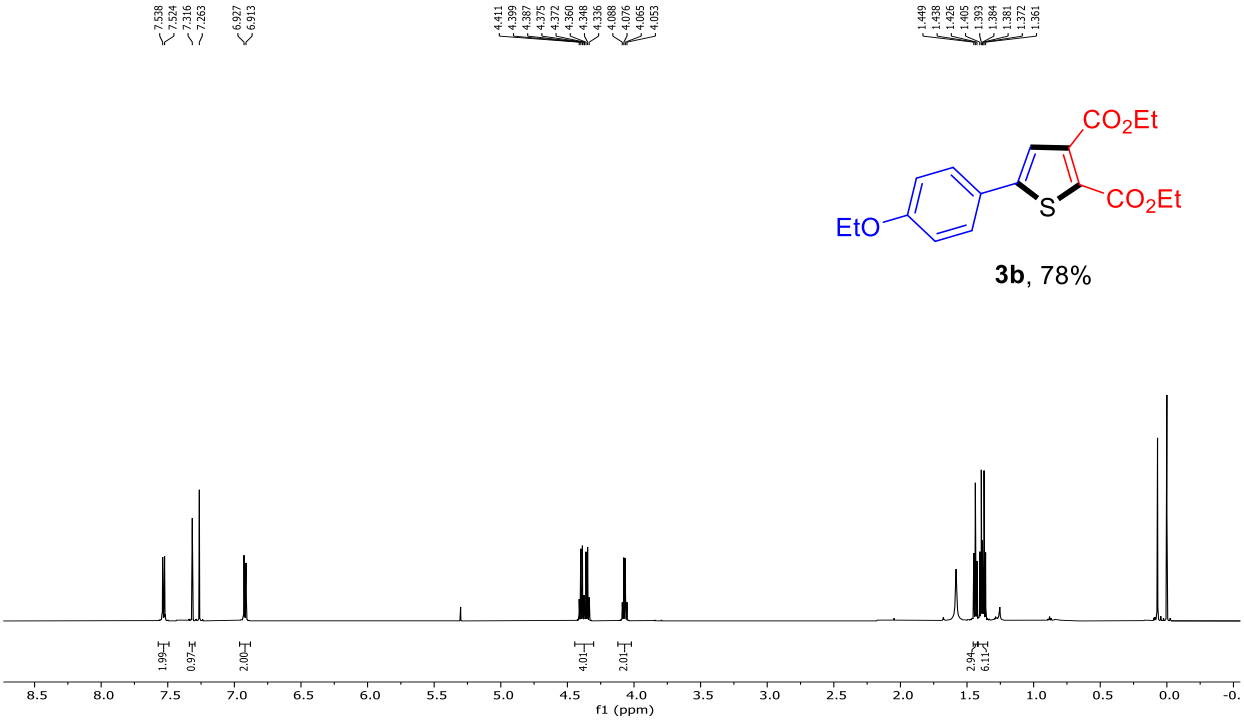

**3a**, 82%

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

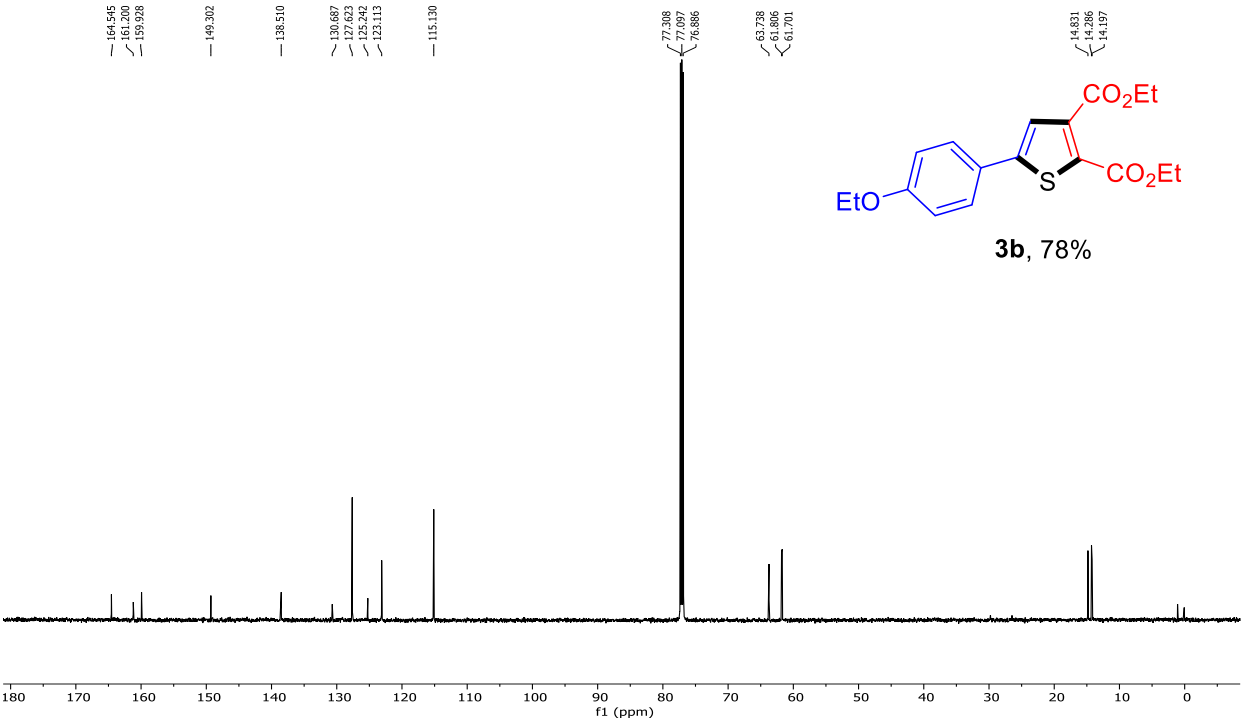



**3a**, 82%

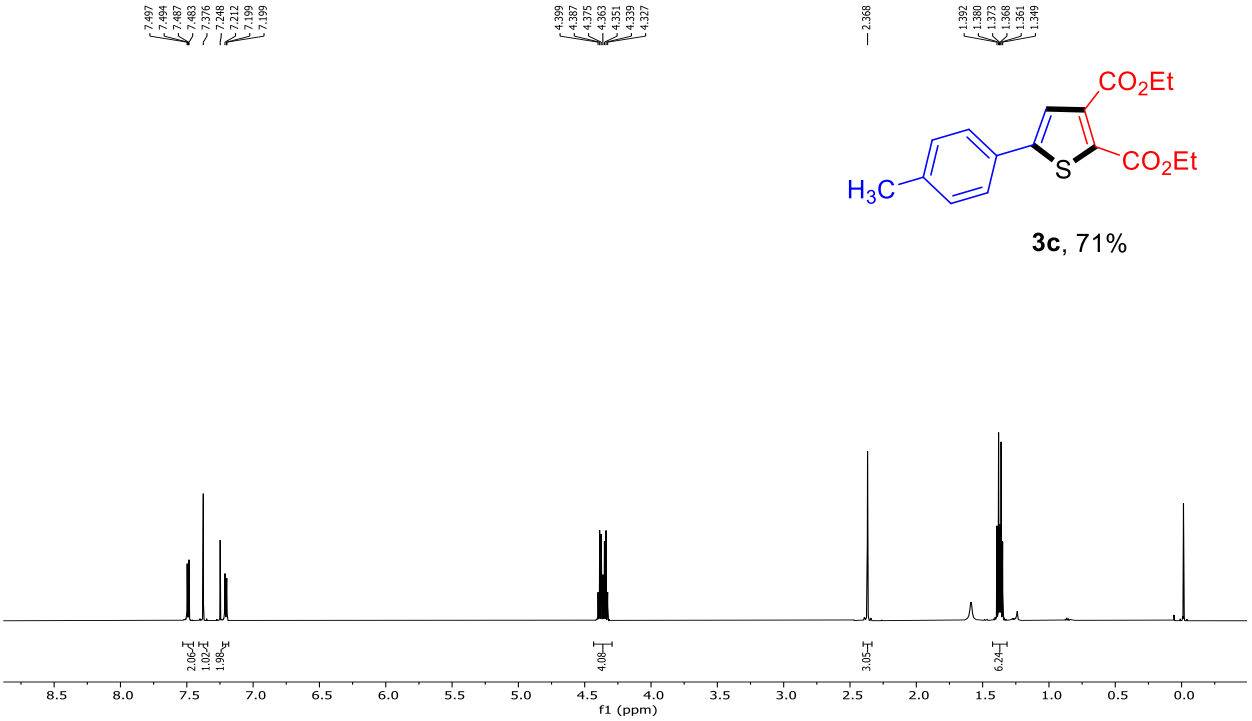
$^{1}$H NMR spectrum of **3b** (600 MHz, $CDCl_3$)



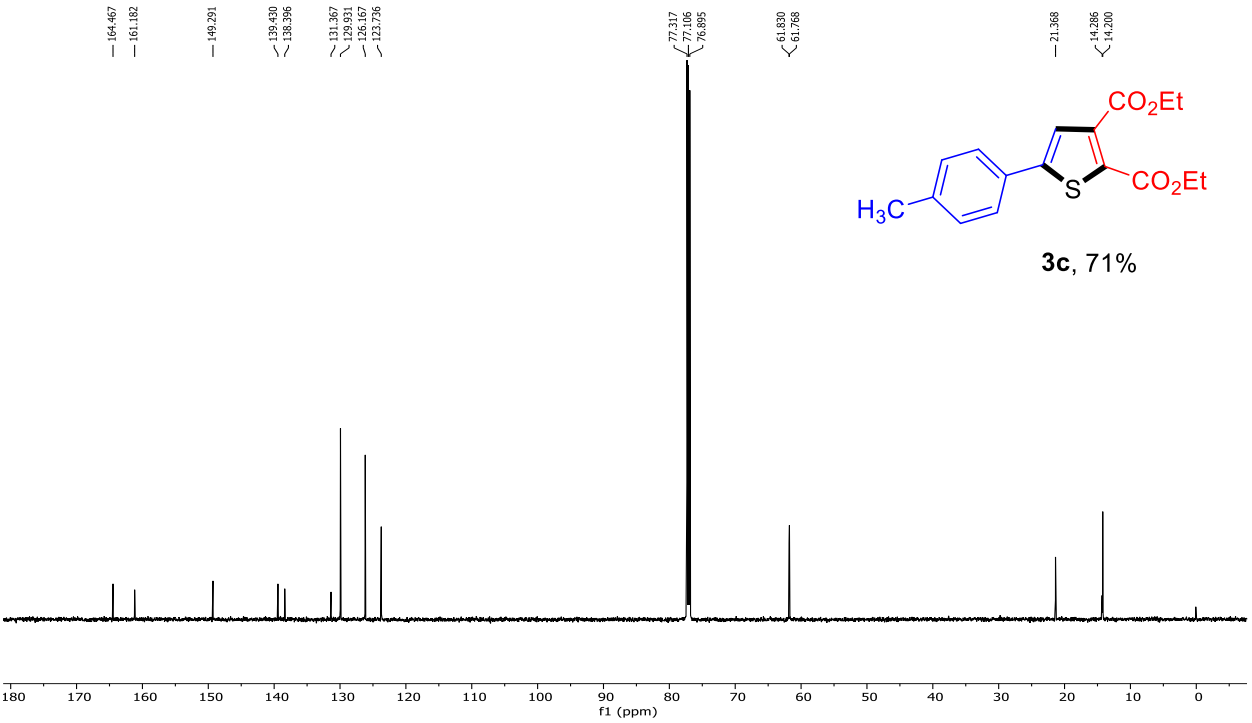

$^{13}$C NMR spectrum of **3b** (150 MHz, $CDCl_3$)



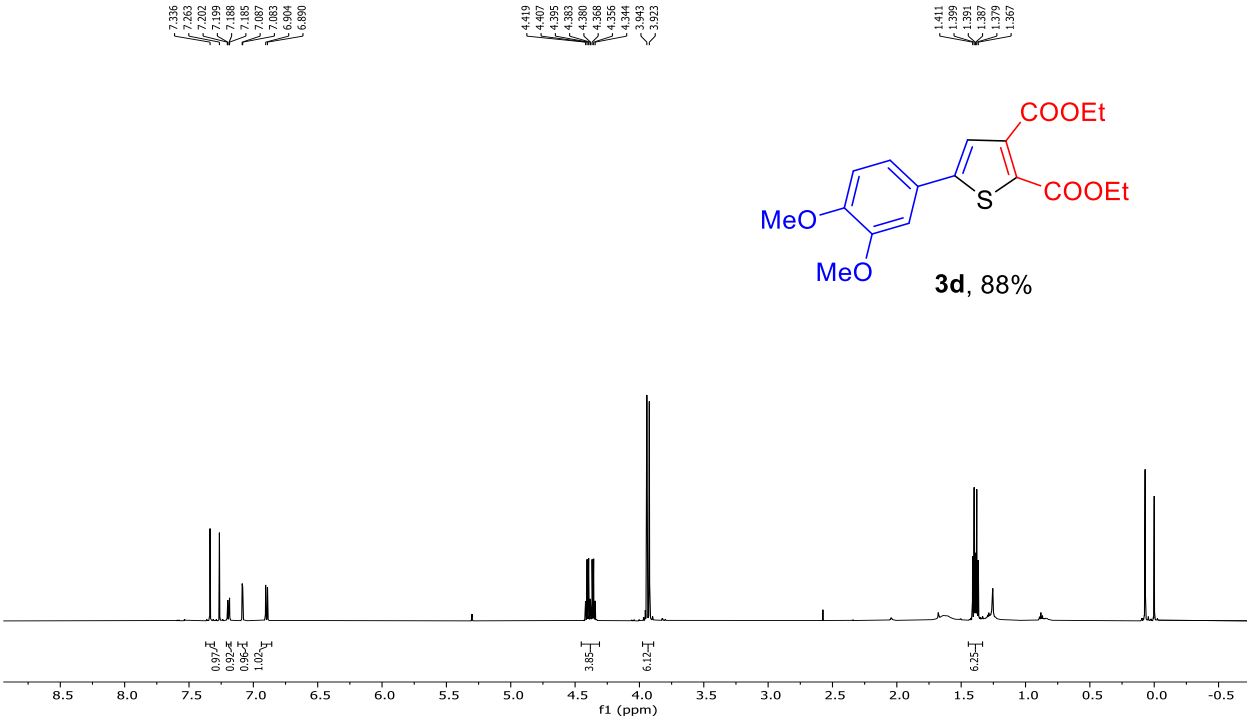
$^{1}$H NMR spectrum of **3c** (600 MHz, $CDCl_3$)



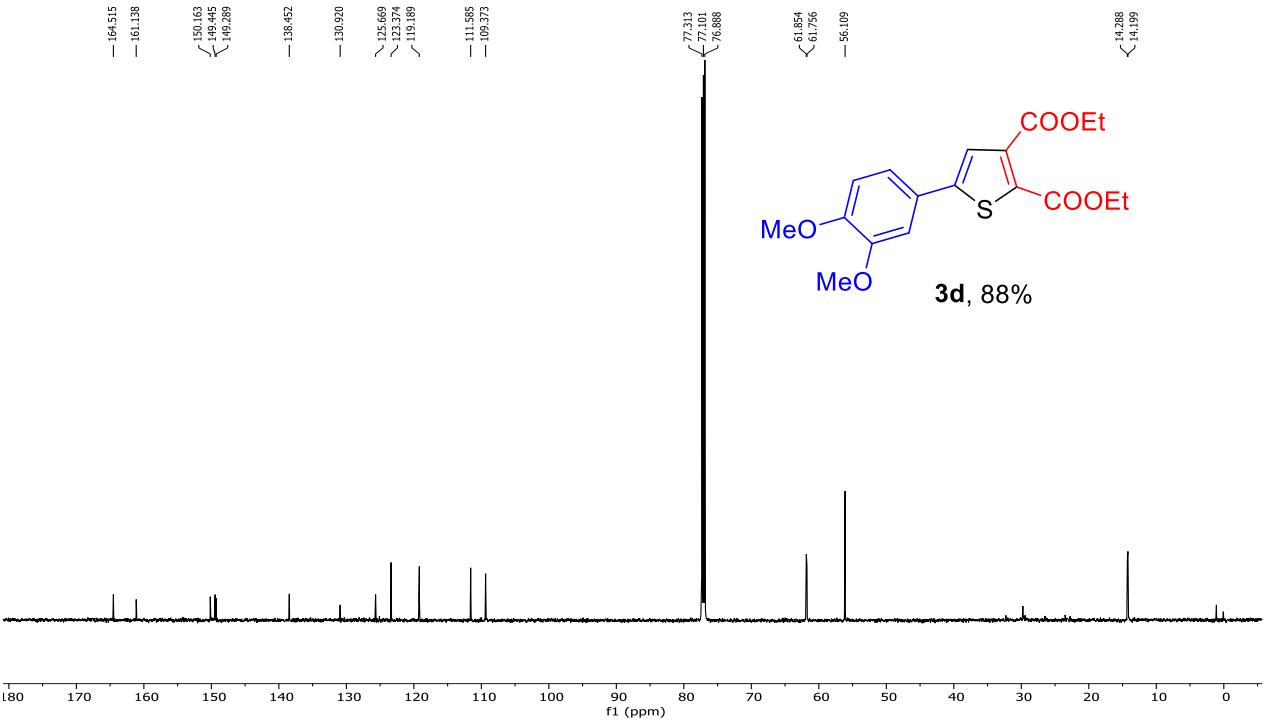

$^{13}$C NMR spectrum of **3c** (150 MHz, $CDCl_3$)



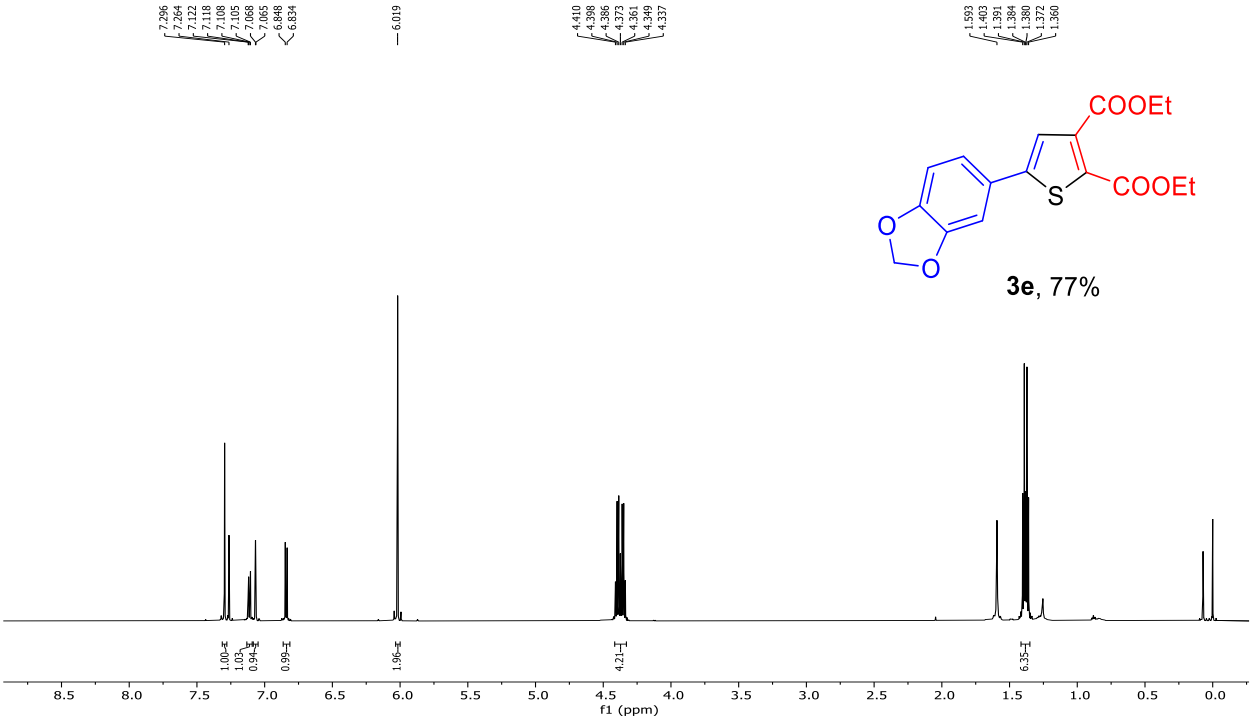
$^{1}$H NMR spectrum of **3d** (600 MHz, $CDCl_3$)



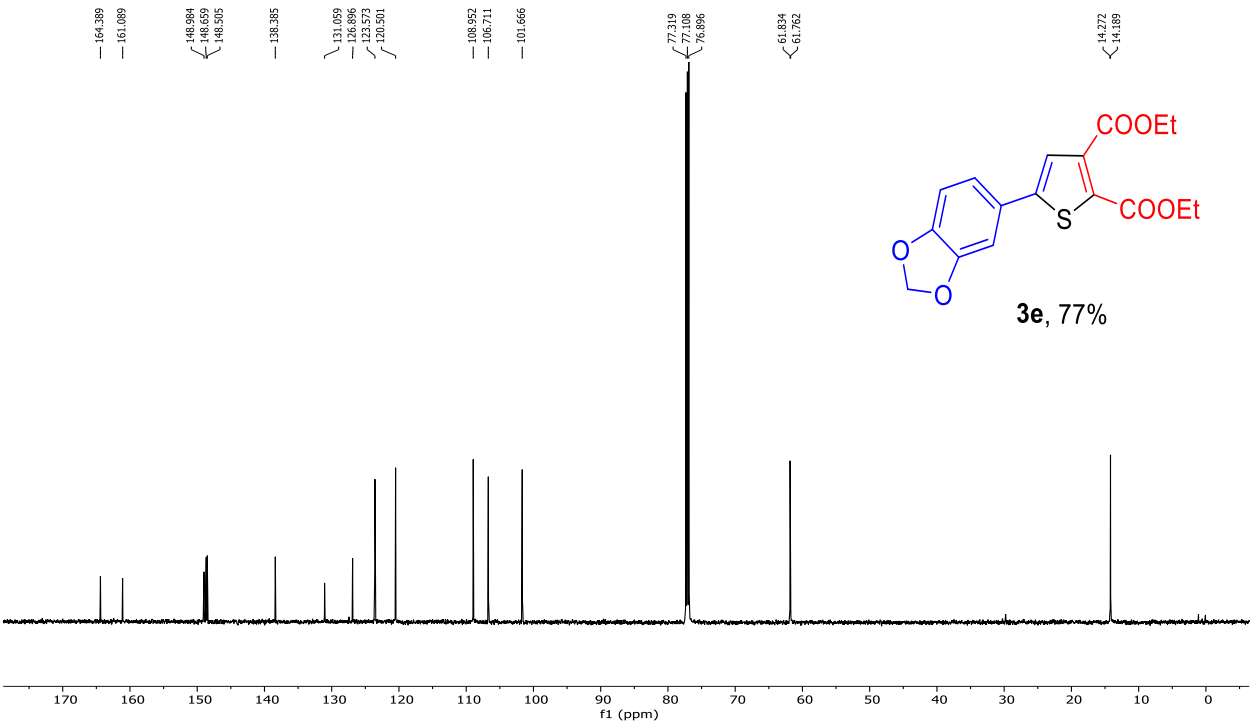

$^{13}$C NMR spectrum of **3d** (150 MHz, $CDCl_3$)



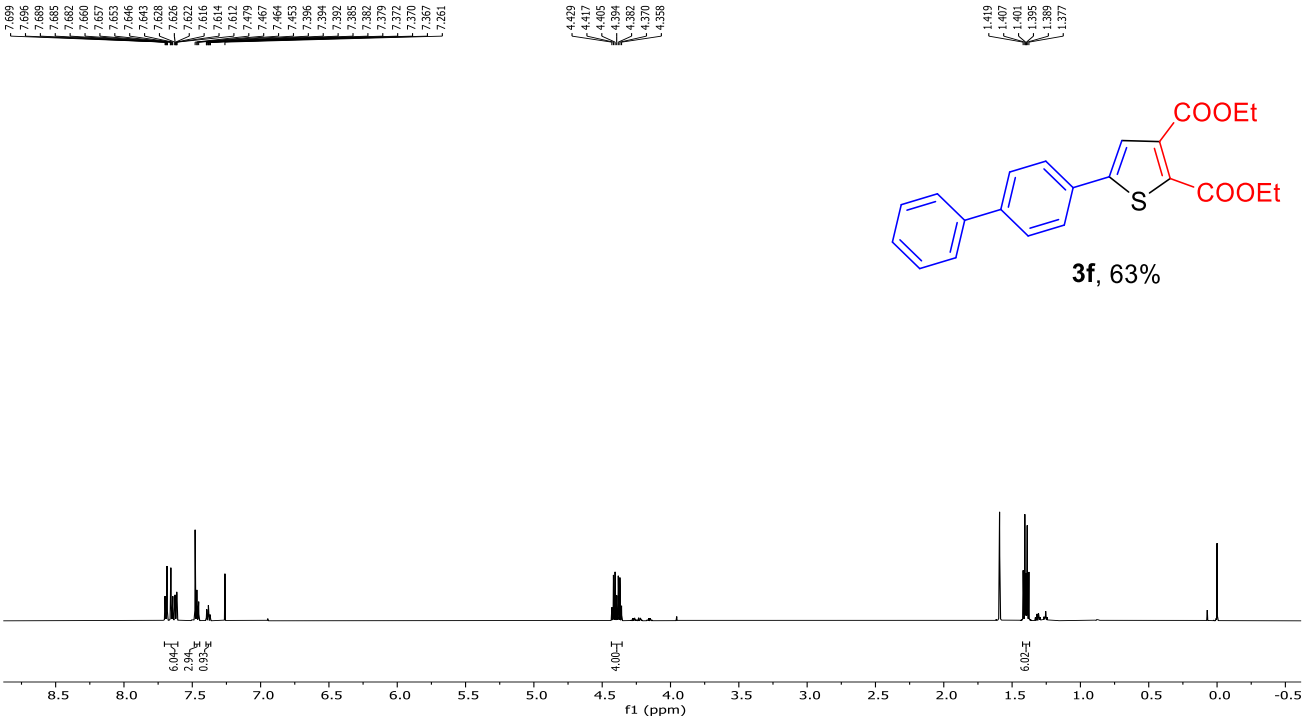
$^{1}$H NMR spectrum of **3e** (600 MHz, $CDCl_3$)



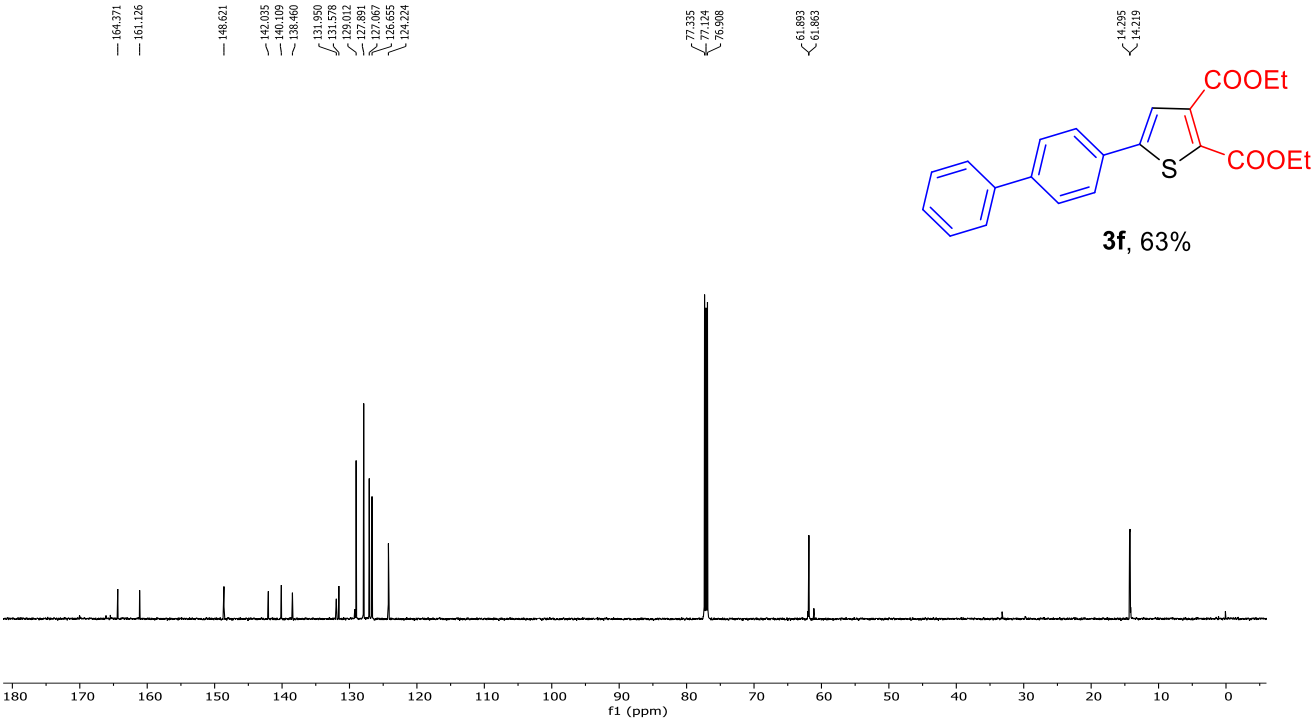

$^{13}$C NMR spectrum of **3e** (150 MHz, $CDCl_3$)



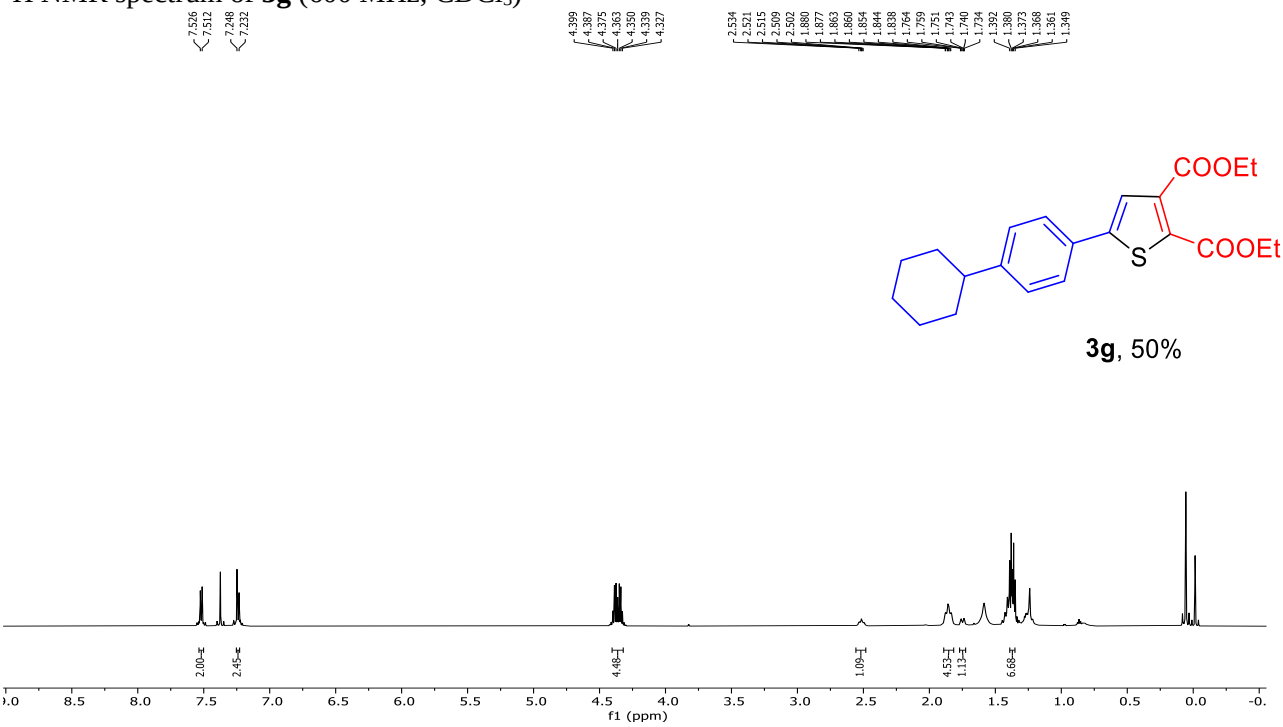
$^{1}$H NMR spectrum of **3f** (600 MHz, $CDCl_3$)




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

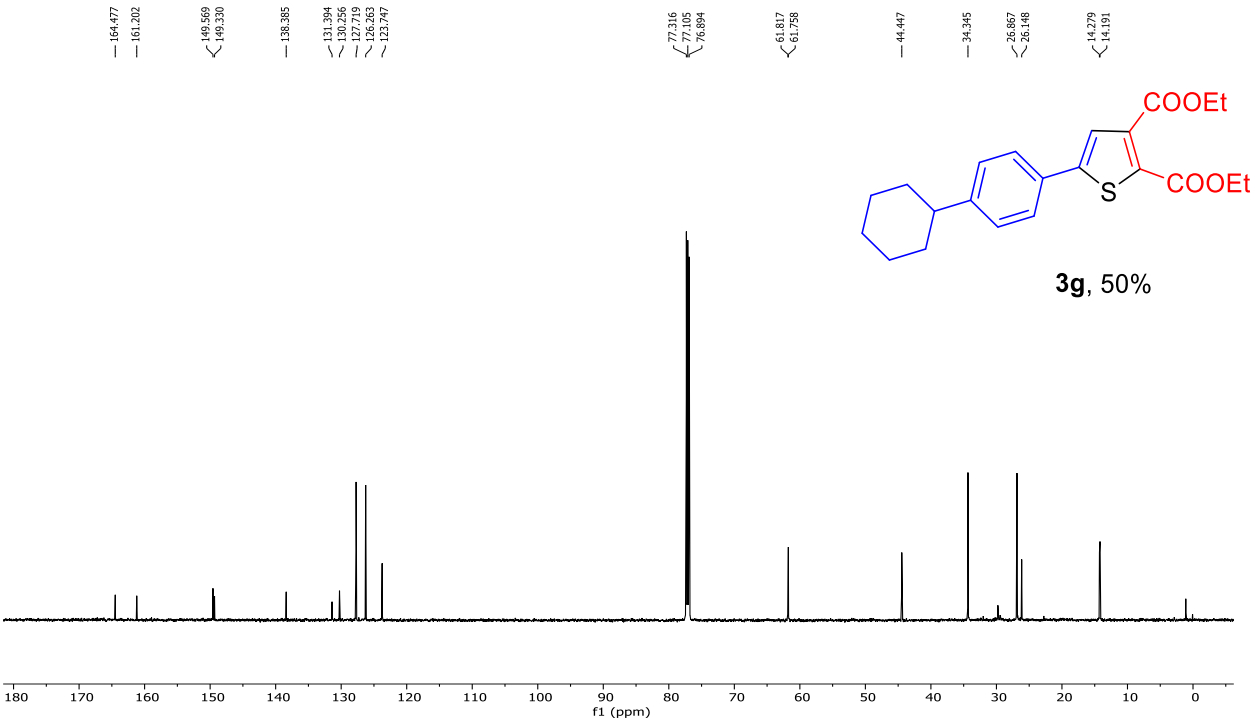


$^{1}$H NMR spectrum of **3g** (600 MHz, $CDCl_3$)



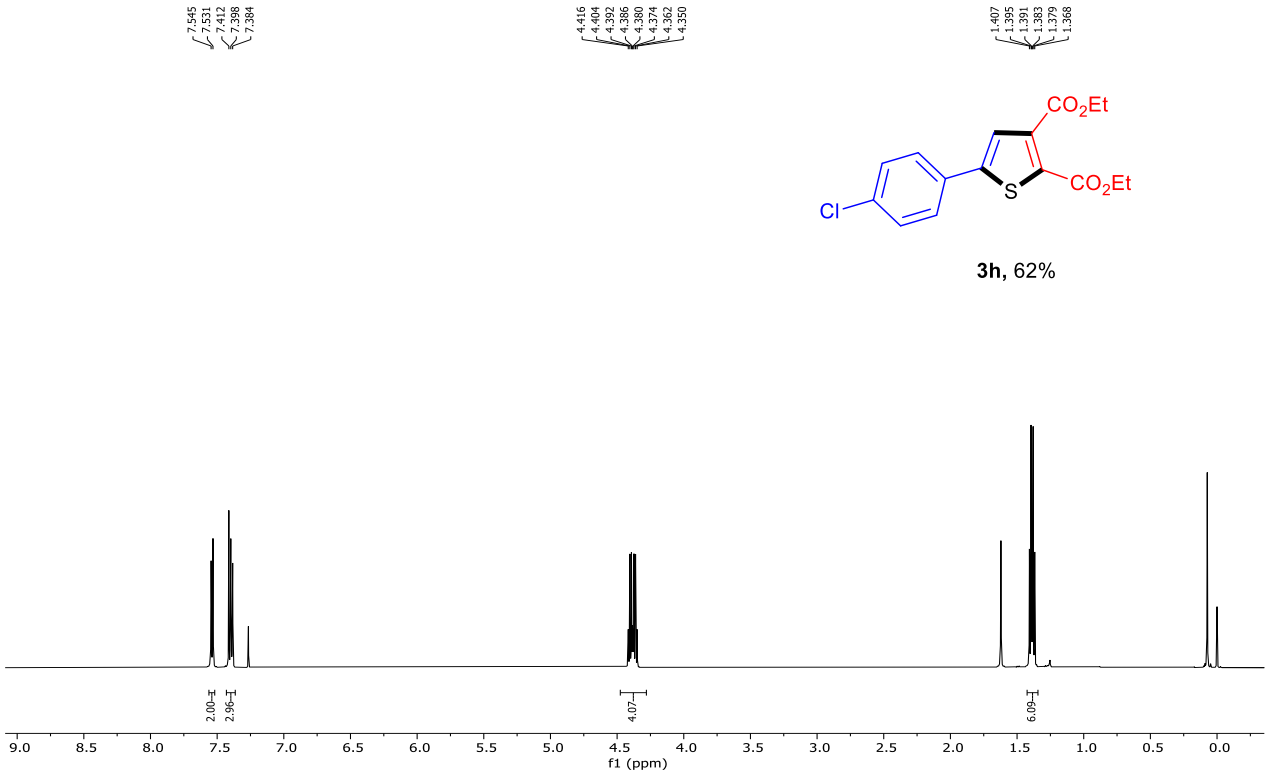

**3g**, 50%

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

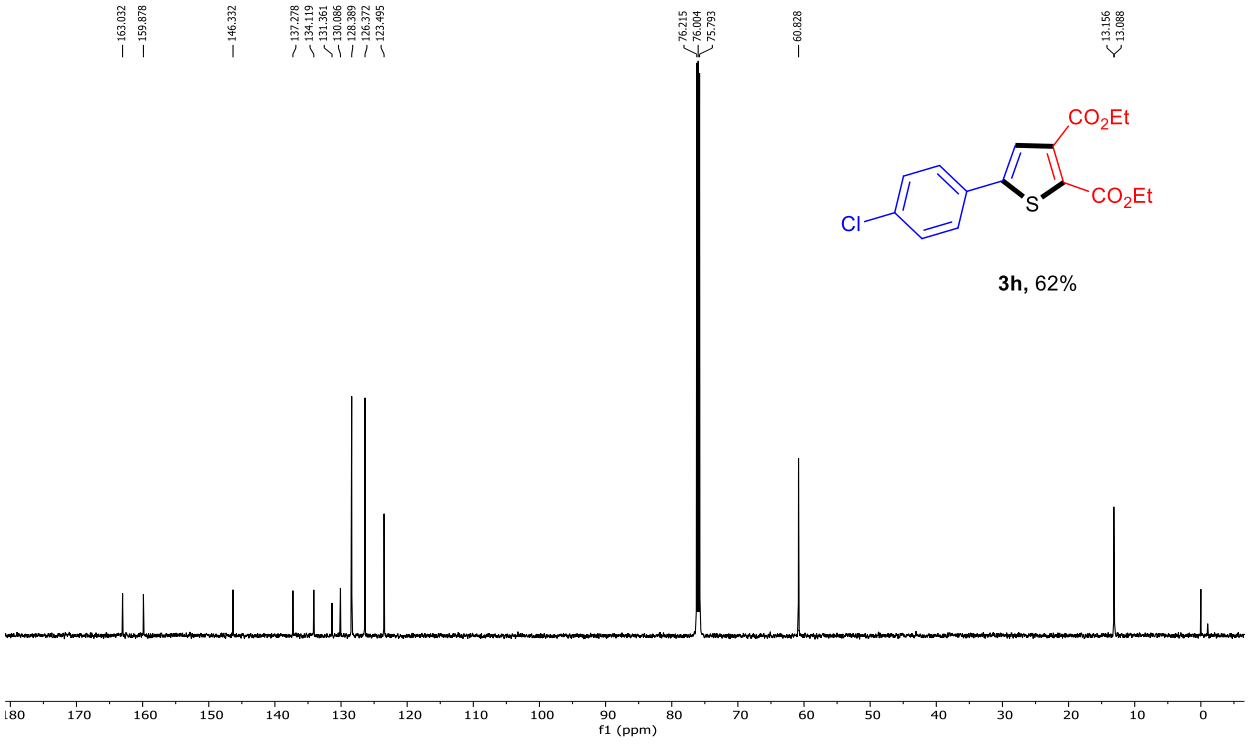



**3g**, 50%

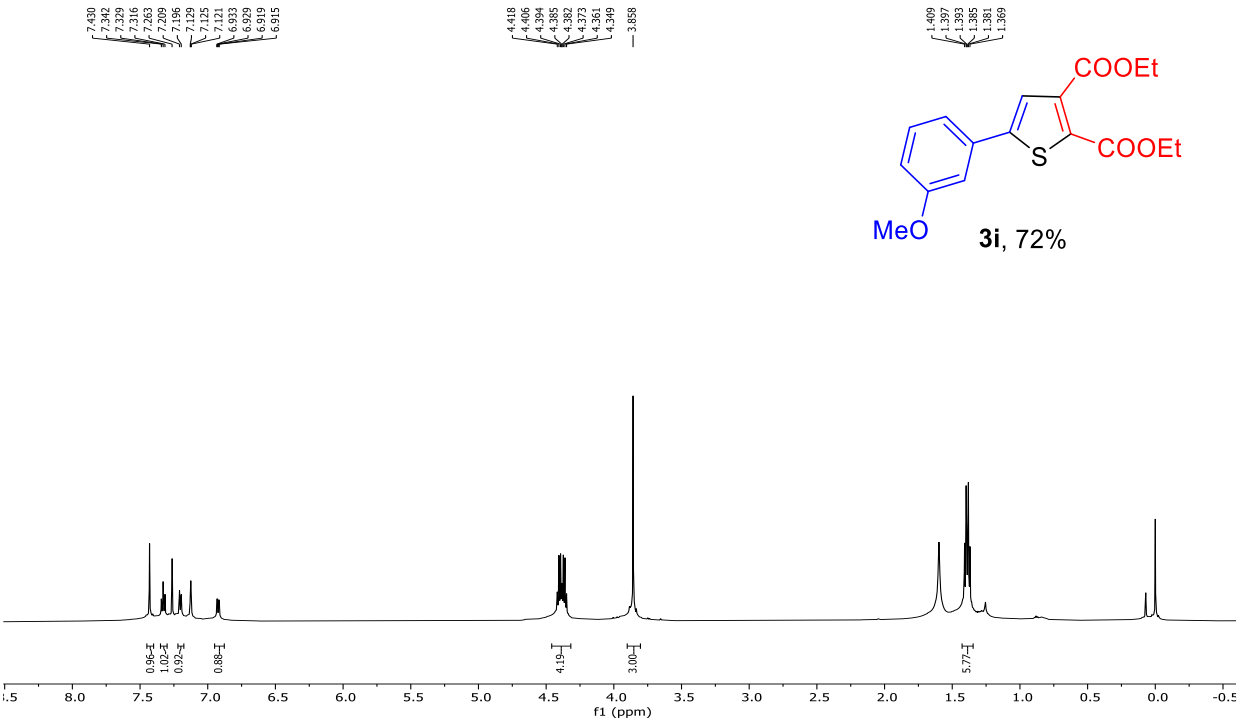
$^{1}$H NMR spectrum of **3h** (600 MHz, $CDCl_3$)



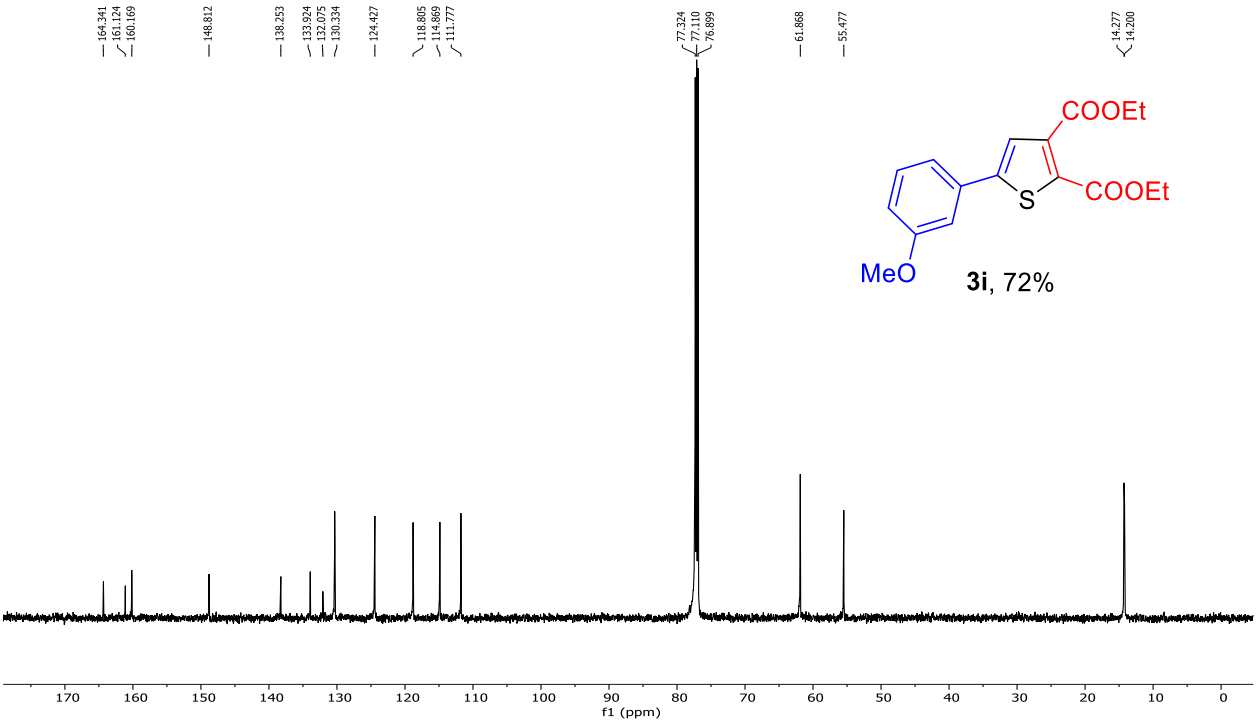

$^{13}$C NMR spectrum of **3h** (150 MHz, $CDCl_3$)



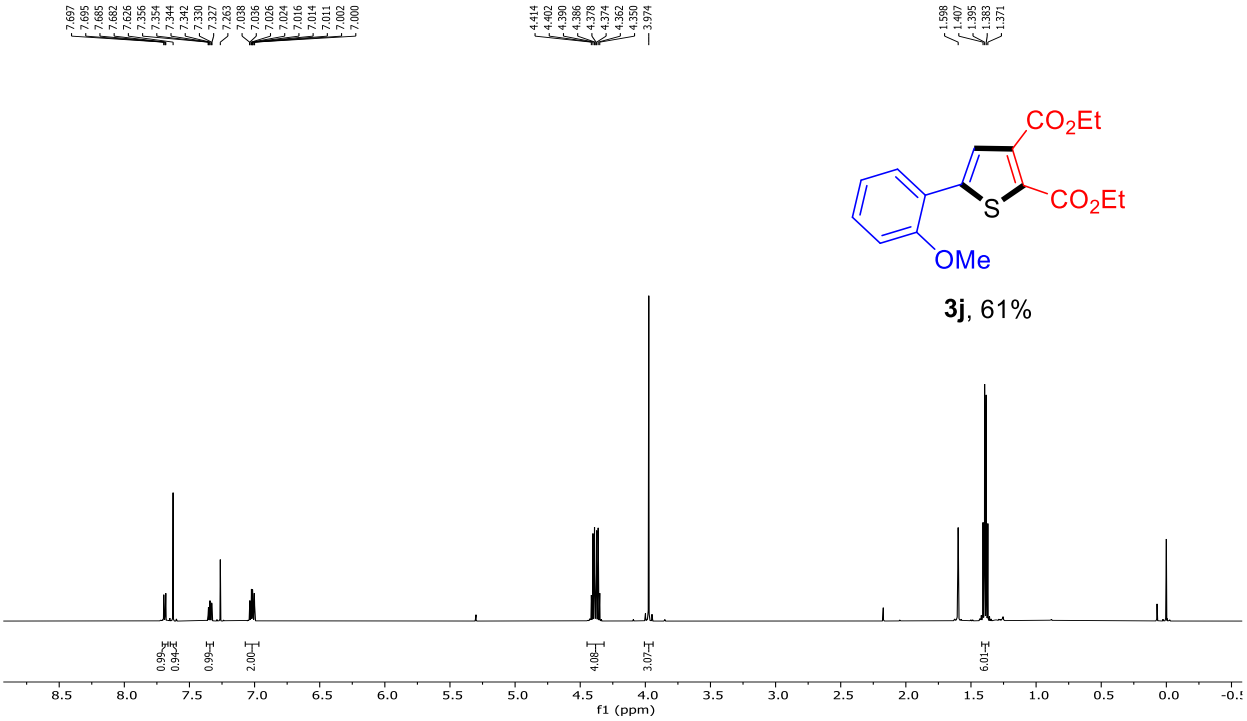
$^{1}$H NMR spectrum of **3i** (600 MHz, $CDCl_3$)




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

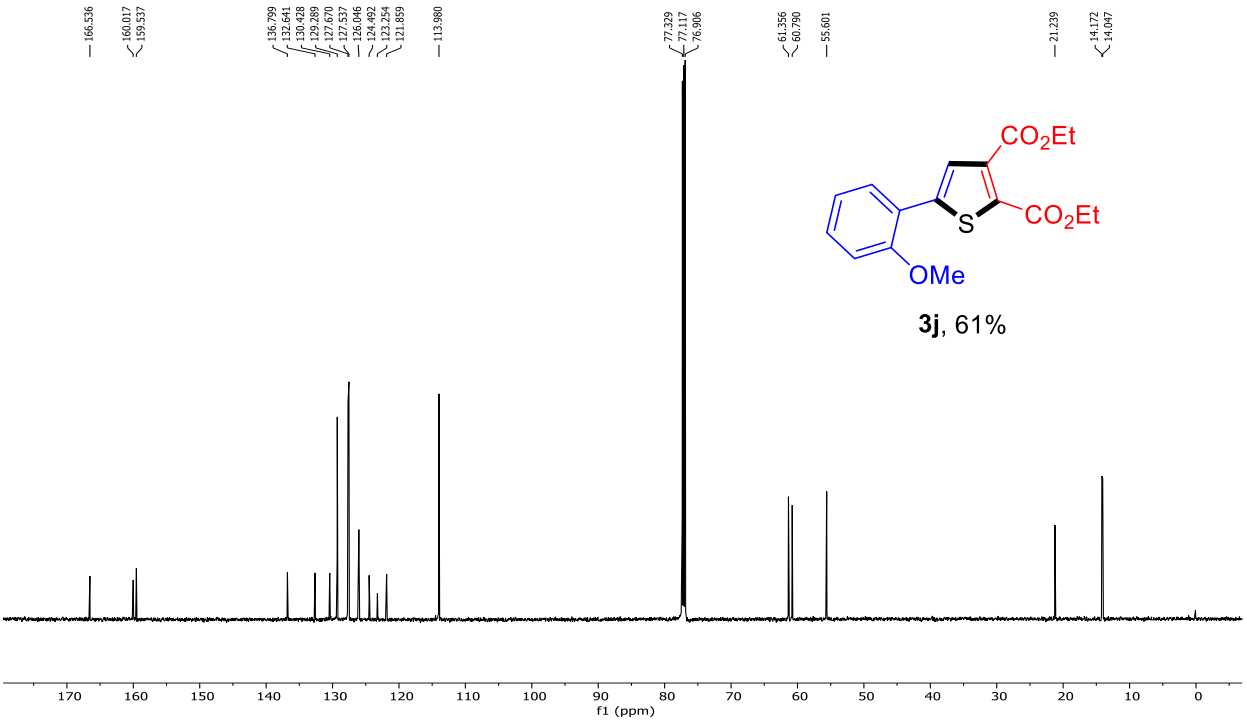


$^{1}$H NMR spectrum of **3j** (600 MHz, $CDCl_3$)



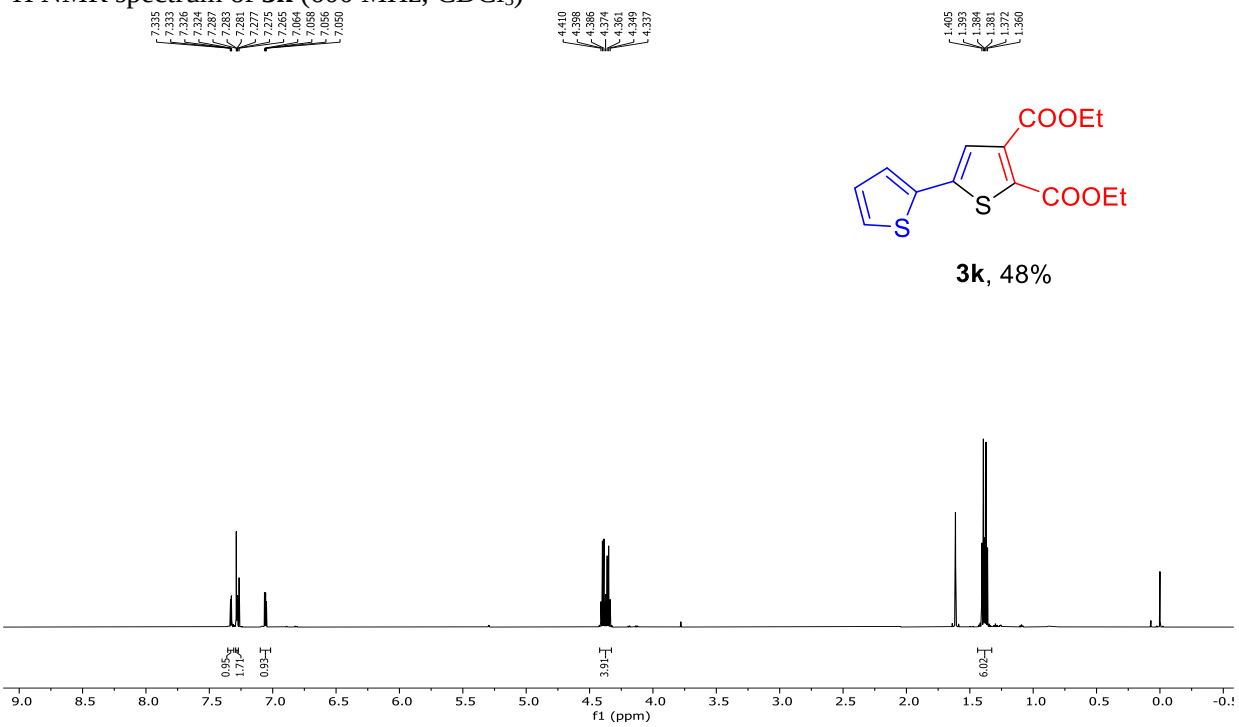

**3j**, 61%

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

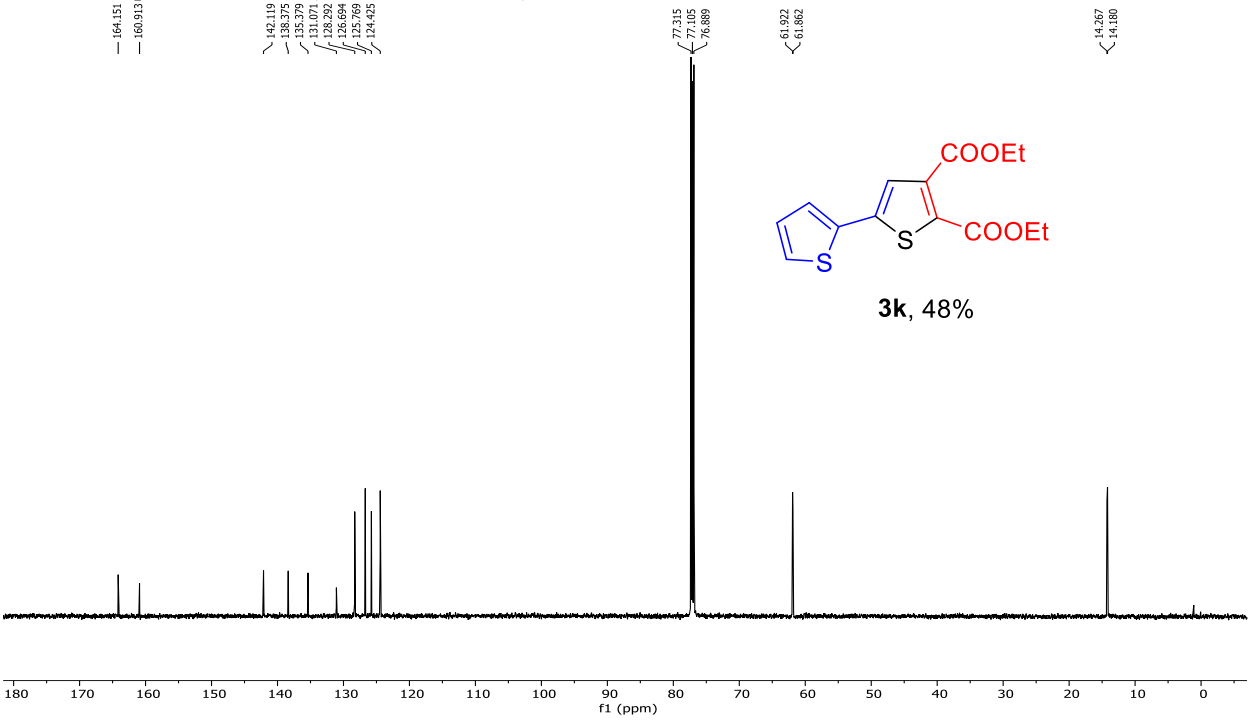



**3j**, 61%

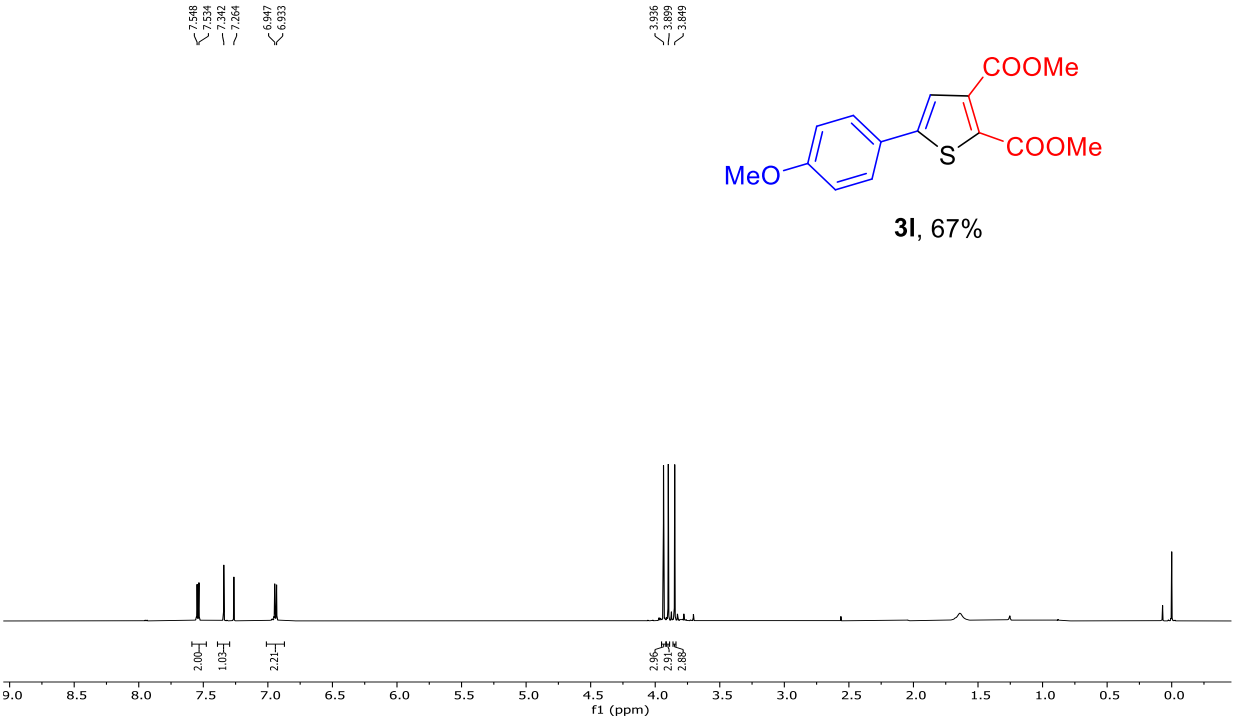
$^{1}$H NMR spectrum of **3k** (600 MHz, $CDCl_3$)




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

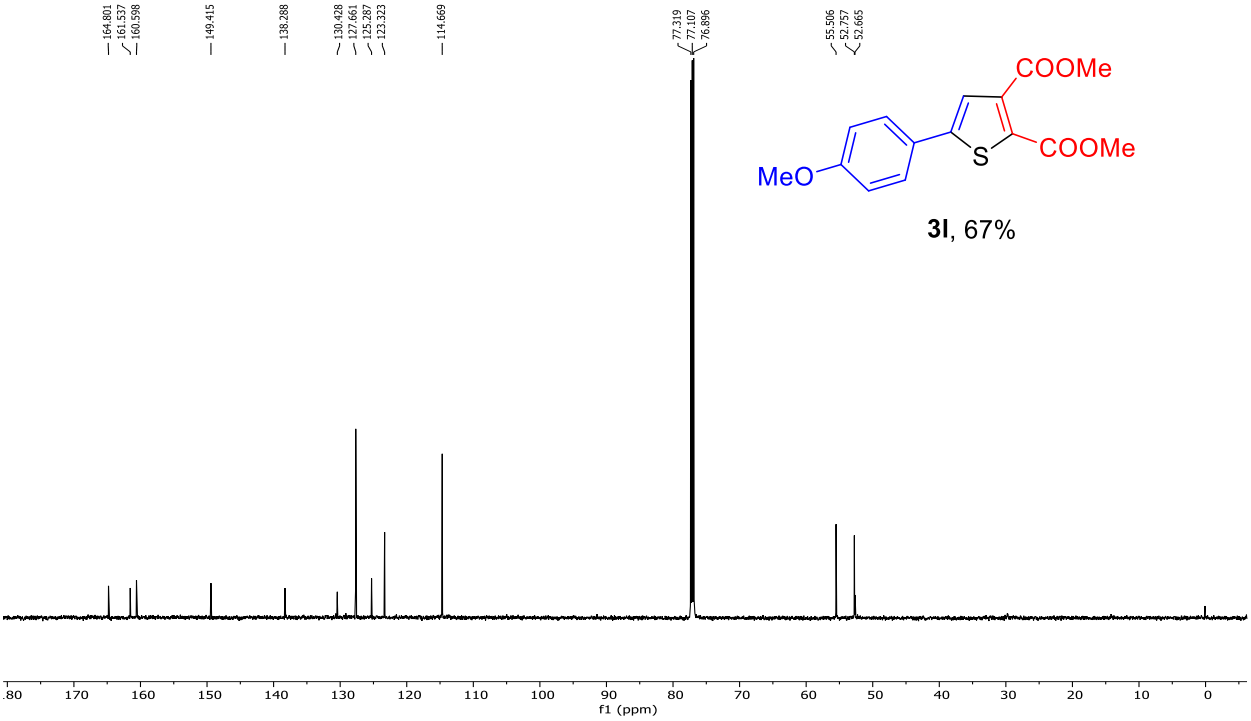


$^{1}$H NMR spectrum of **3l** (600 MHz, $CDCl_3$)



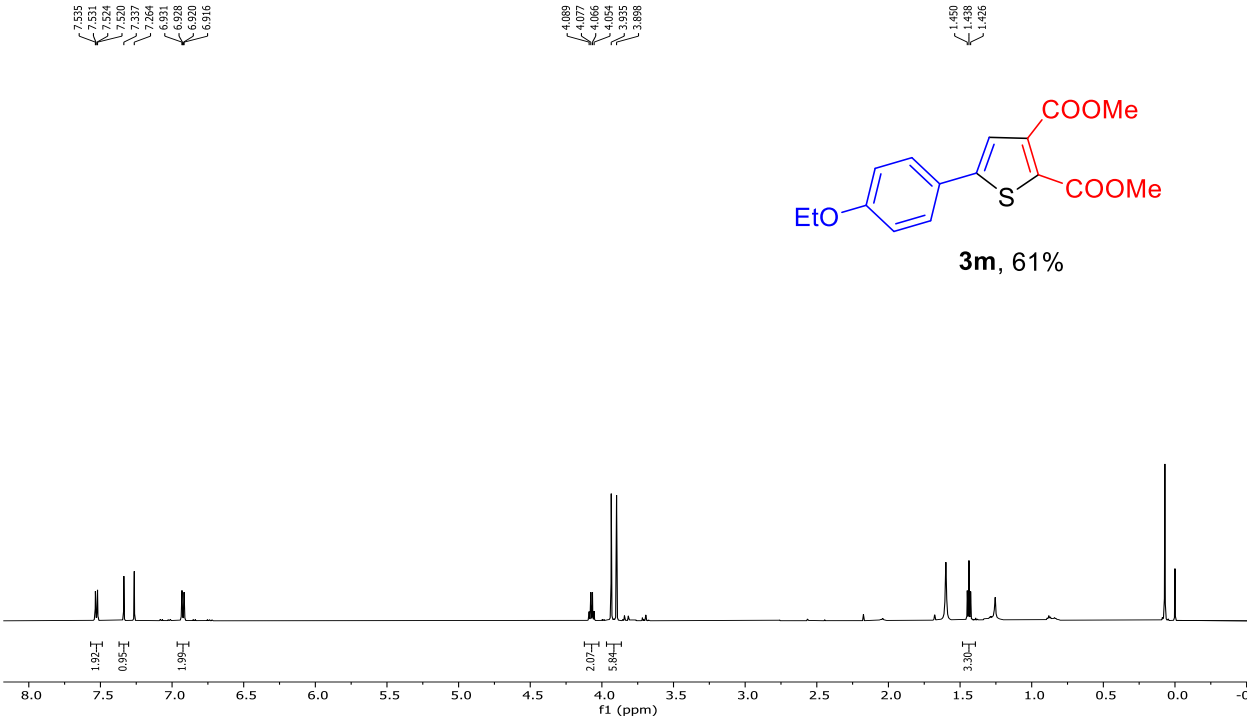

**3l**, 67%

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

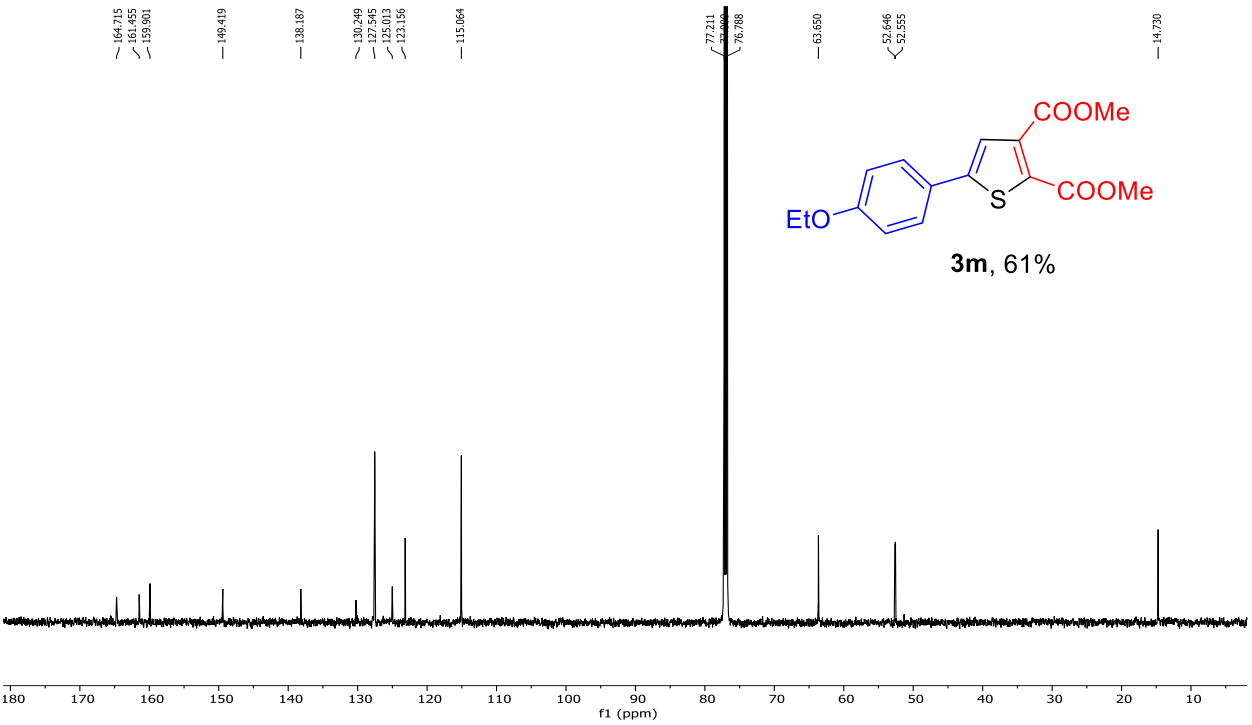



**3l**, 67%

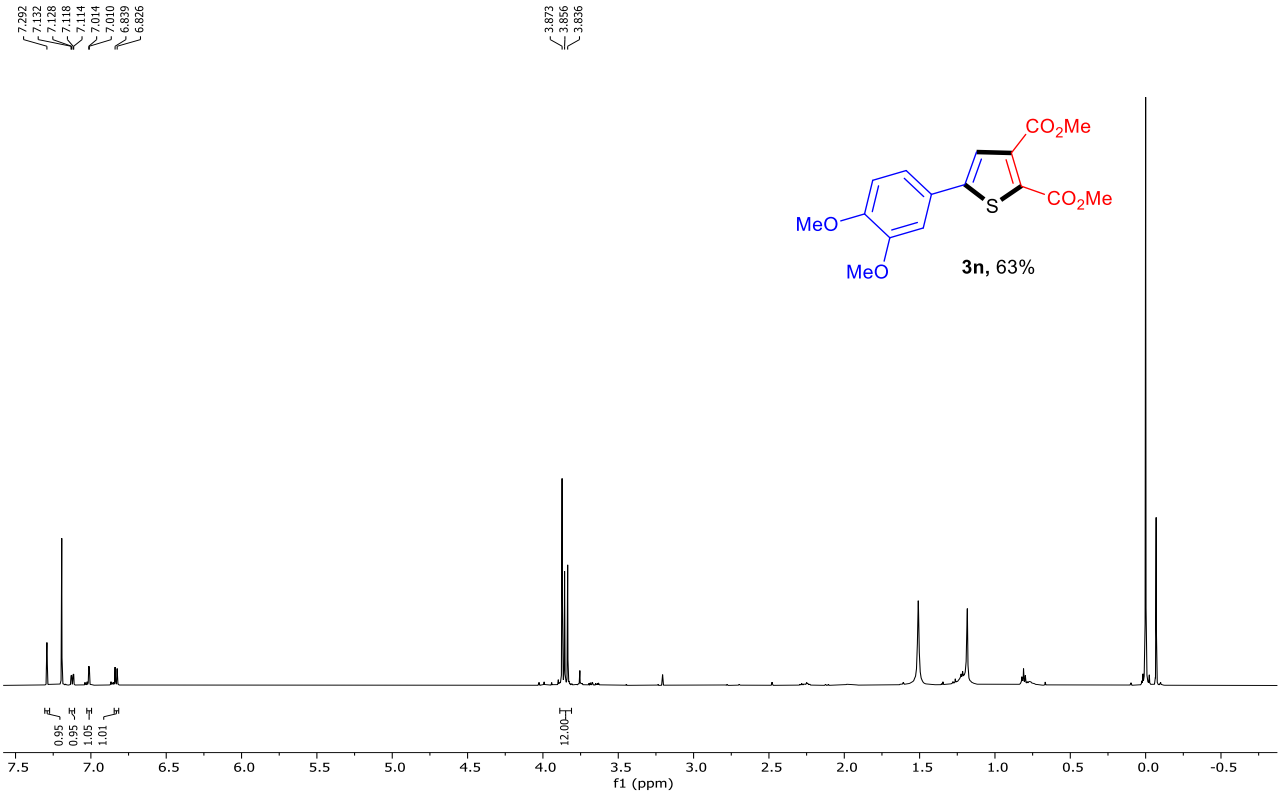
$^{1}$H NMR spectrum of **3m** (600 MHz, $CDCl_3$)



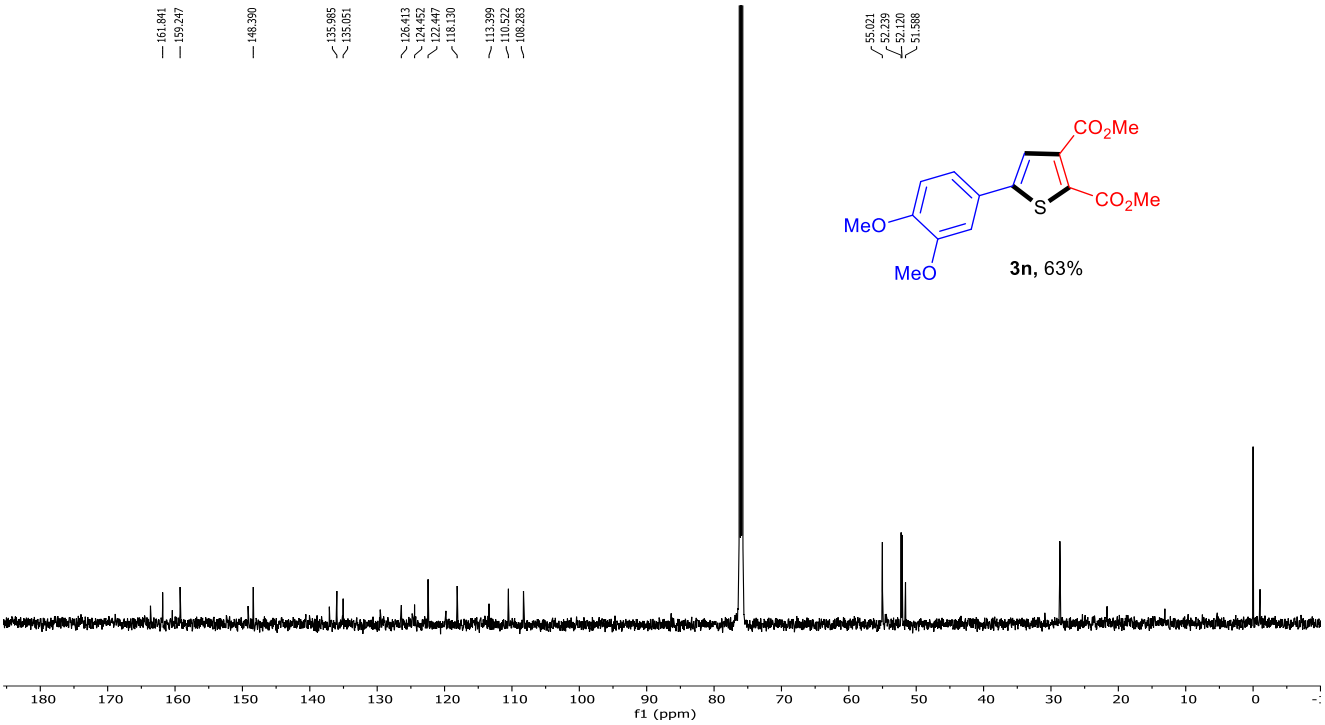

$^{13}$C NMR spectrum of **3m** (150 MHz, $CDCl_3$)



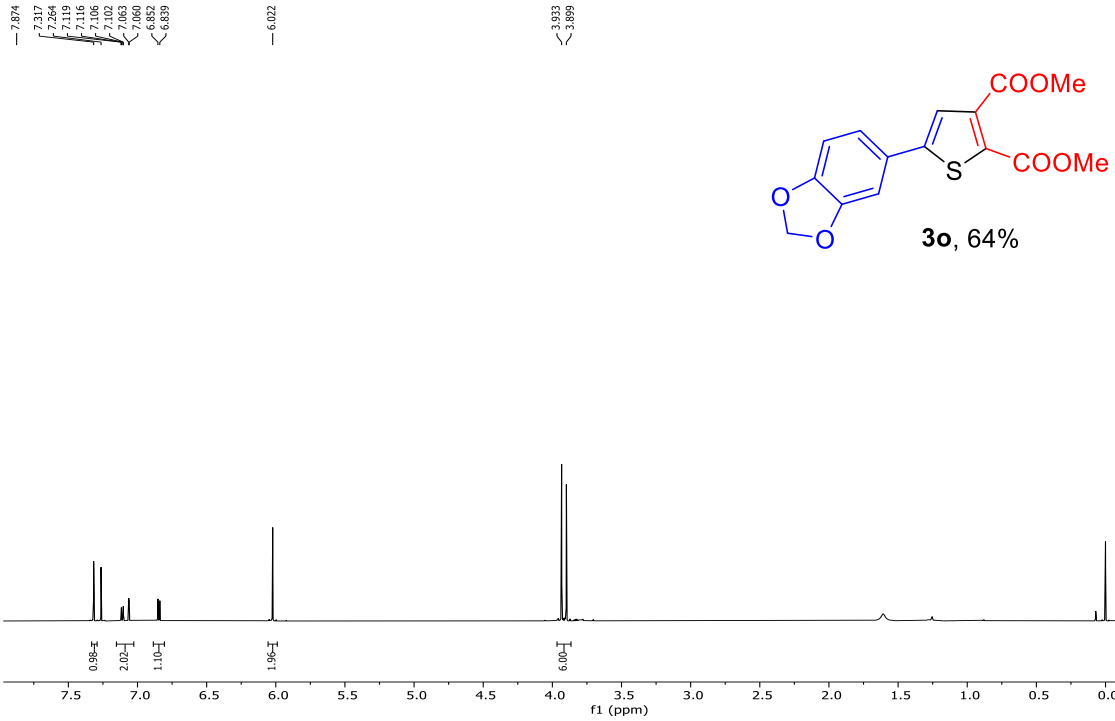
$^{1}$H NMR spectrum of **3n** (600 MHz, $CDCl_3$)



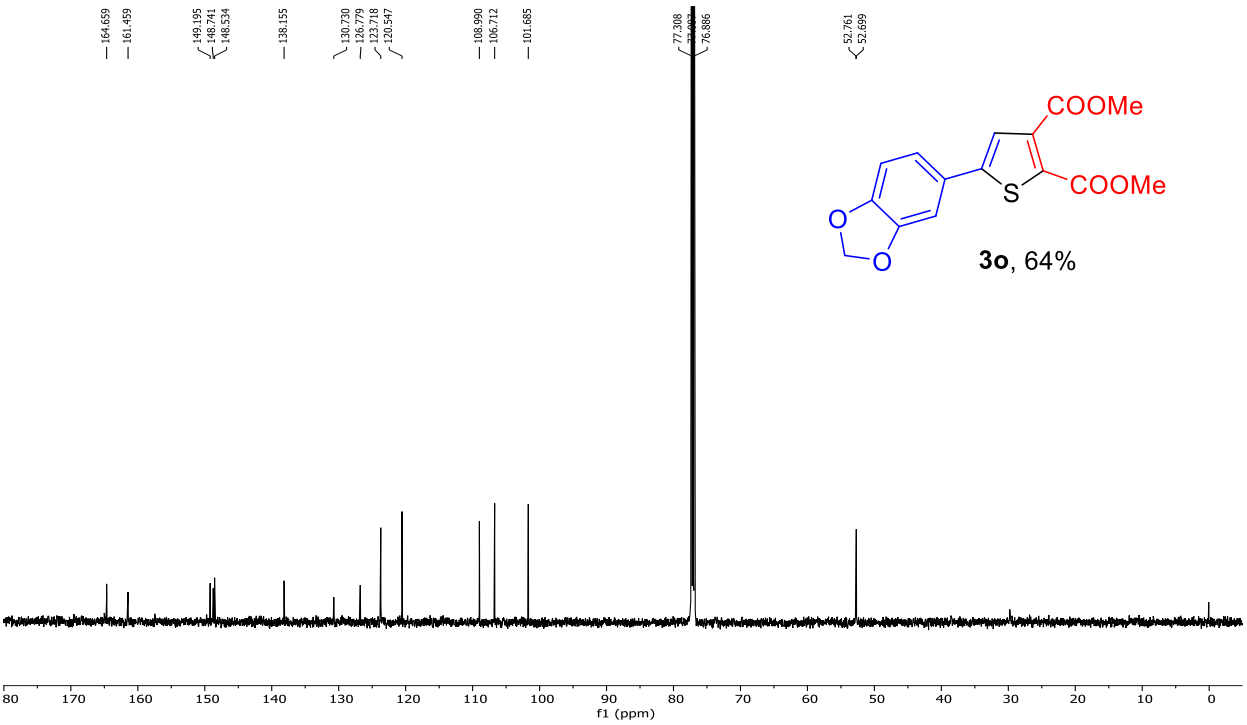

$^{13}$C NMR spectrum of **3n** (150 MHz, $CDCl_3$)



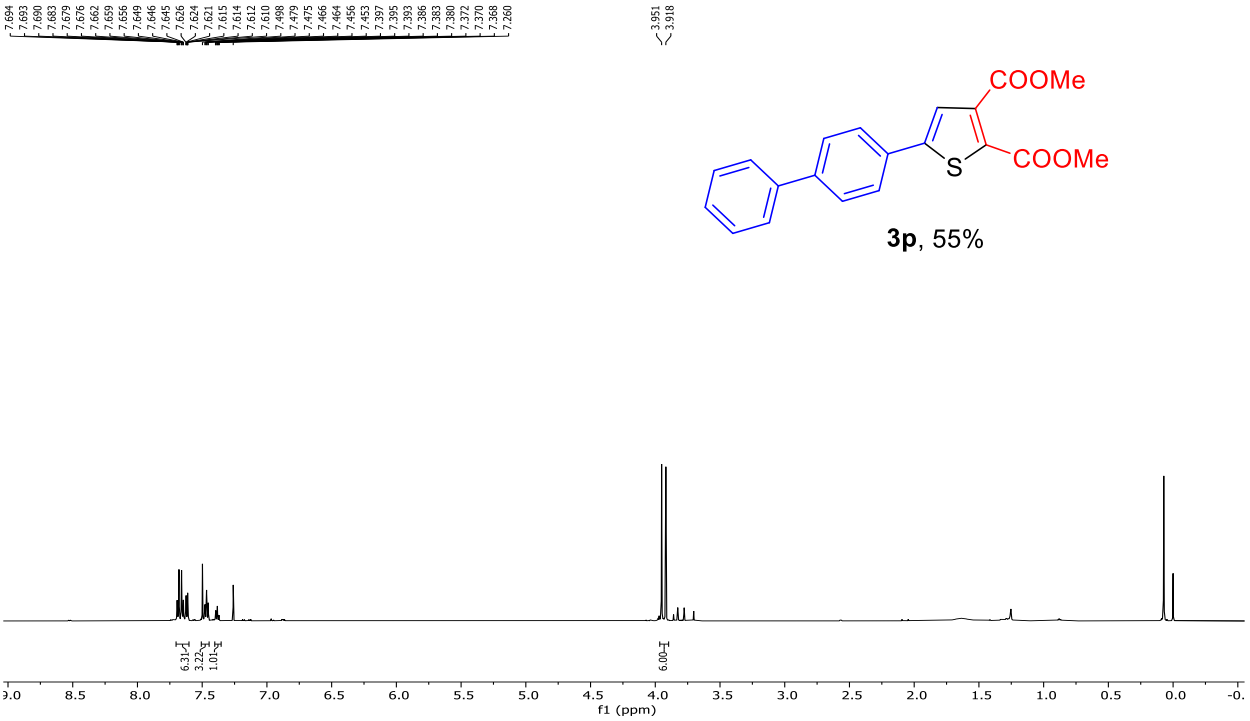
$^{1}$H NMR spectrum of **3o** (600 MHz, $CDCl_3$)




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

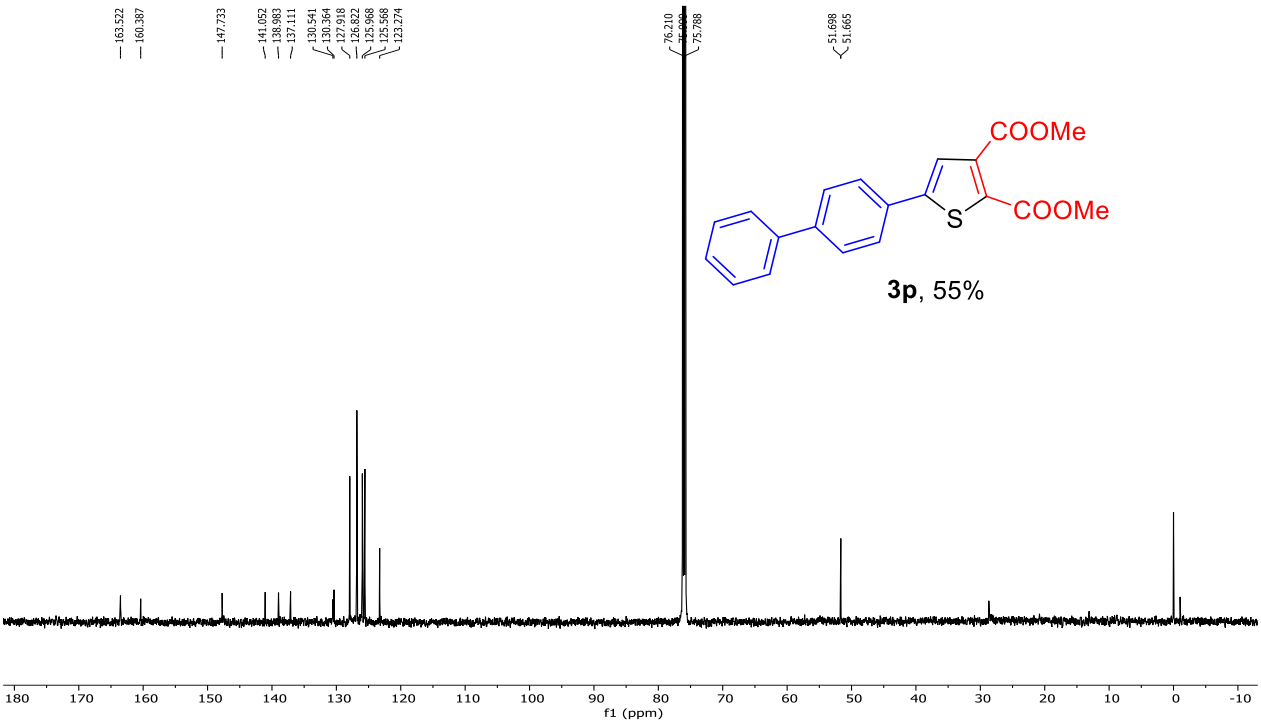


$^{1}$H NMR spectrum of **3p** (600 MHz, $CDCl_3$)

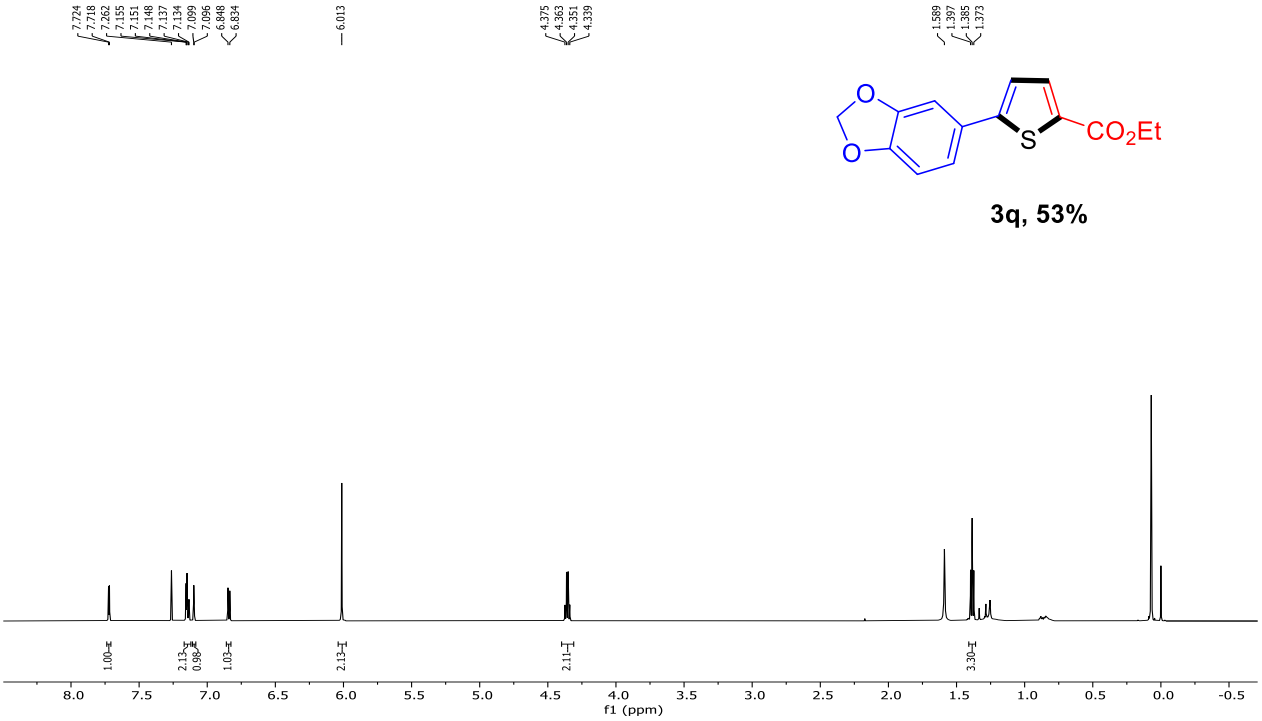



S

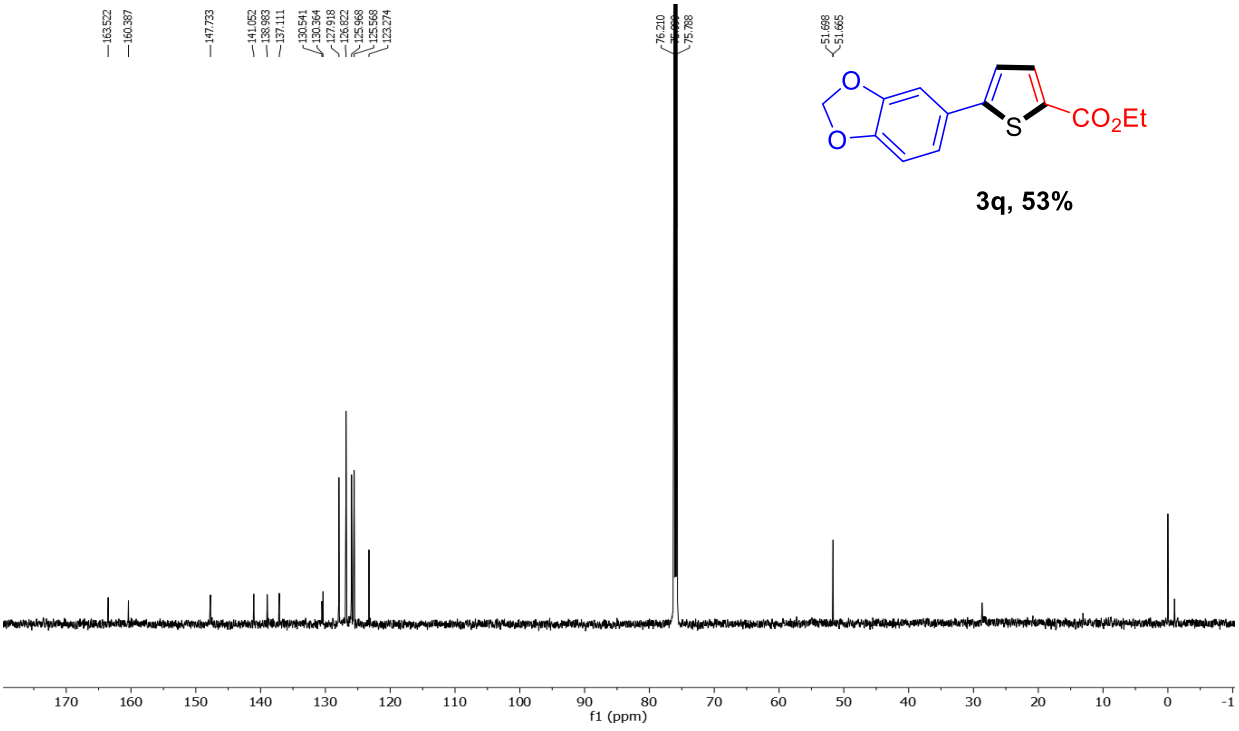
$^{13}$C NMR spectrum of **3p** (150 MHz, $CDCl_3$)



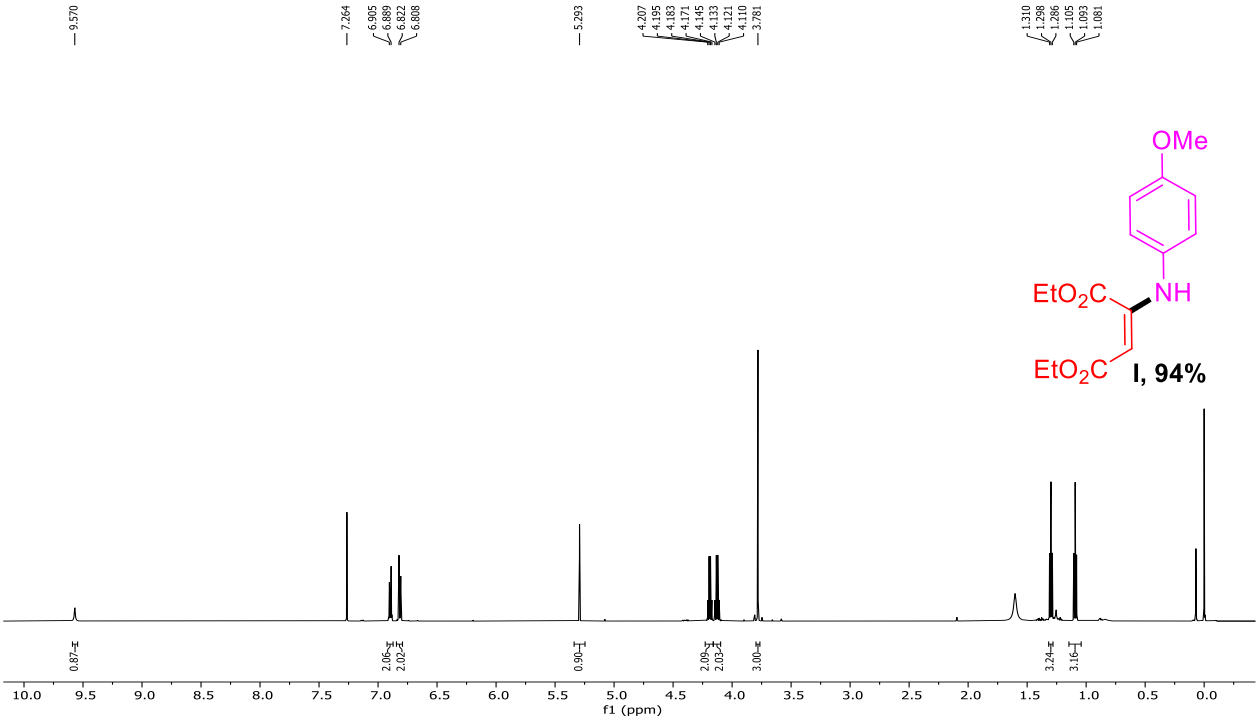
$^{1}$H NMR spectrum of **3q** (600 MHz, $CDCl_3$)




$^{13}$C NMR spectrum of **3q** (150 MHz, $CDCl_3$)



$^{1}$H NMR spectrum of **I** (600 MHz, $CDCl_3$)




$^{13}$C NMR spectrum of **3q** (150 MHz, $CDCl_3$)