

## **Chapter III**

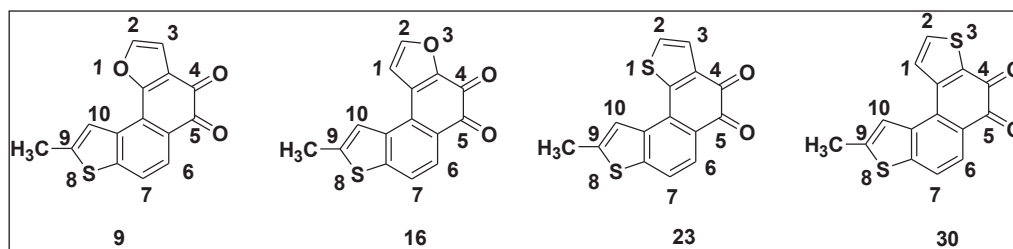
**Nuclear modifications in core nucleus of  
isotanshinone II: Synthesis of hitherto unknown  
bis(heteroannulated)naphthoquinones with  
antibacterial potential**

## Nuclear modifications in core nucleus of isotanshinone II: Synthesis of hitherto unknown bis(heteroannulated)naphthoquinones with antibacterial potential

### 7.1 Introduction

Like furophenanthraquinones, condensed furo/thienonaphthoquinones are also known to act as antitumor and antibacterial agents.<sup>1</sup> Moreover, naphthothiophene derivatives are used in solar cells and subjugated in the preparation of organic nanotubes for its unique semiconducting properties. Thus condensed naphthothiophene/ naphthofurans and their quinone derivatives are subject matter of studies for organic synthesis or materials research.<sup>2-6</sup>

In the earlier chapter (chapter IIB), the synthesis of some phenanthro[4,3-*b*]thiophene-4,5-dione derivatives have been described as thiophene analogues of isotanshinone II core nucleus. In those compounds, ring D of isotanshinone II, has been replaced by a thiophene moiety. It is well known that bioisosteric relationship exists between benzene and thiophene ring where 'CH=CH' is considered as equivalent to 'S'. This chapter of thesis, describes the synthesis of four hitherto unknown doubly condensed naphthoquinones, *viz.* 9-methylnaphtho[1,2-*b*]furan[7,8-*b*]thiophene-4,5-dione (**9**), 9-methylnaphtho[2,1-*b*]furan[7,8-*b*]thiophene-4,5-dione (**16**), 9-methylnaphtho[1,2-*b*:7,8-*b'*]bisthiophene-4,5-dione (**23**) and 9-methylnaphtho[2,1-*b*:7,8-*b'*]bisthiophene-4,5-dione (**30**) in which ring A of phenanthro[4,3-*b*]furan-4,5-dione (the core nucleus of isotanshinone II) has been replaced by a 2-methylthiophene moiety whereas ring D has been modified with either a furan or a thiophene moiety (fig. 1).



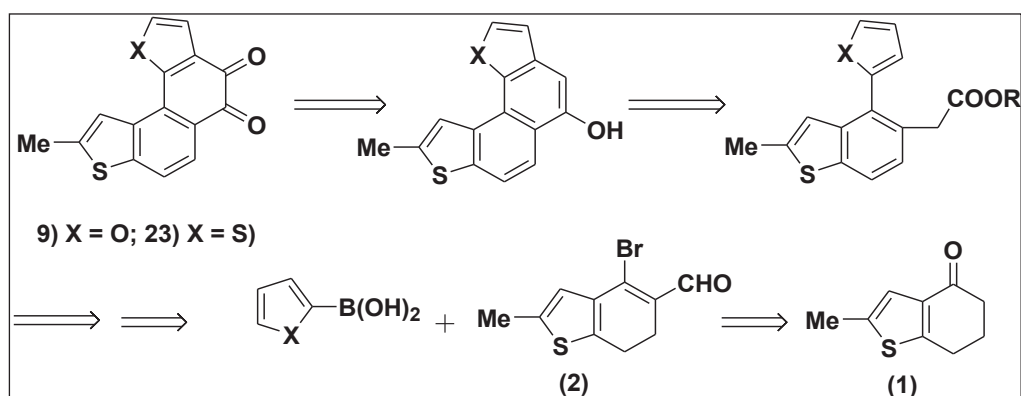
**Figure 1: Bis(heteroannulated)naphthoquinones 9, 16, 23 and 30**

We believe that, the studies on the biophysical and biological properties of such doubly condensed naphthoquinones may contribute significant informations and may also throw some light on structure-activity relationship as well as mutagenic and antibacterial activities. The furan analogue (**9**) may be considered as bioisoster of isotanshinone II nucleus, and the thiophene

analogue (**23**) may be considered as bioisoster of thienophenanthraquinone. The other two compounds (**16** and **30**) are also the nuclear analogues of ‘U’-shaped furophenanthraquinone. These compounds have been synthesised with expectation to show potential antibacterial activity.

## 7.2 Present work:

The retrosynthesis of doubly condensed naphthoquinones (**9** and **23**) has been outlined in scheme 1. The target molecules can be synthesised starting from 4-bromo-6,7-dihydro-2-methylbenzo[b]thiophene-5-carbaldehyde (**2**) (which may be obtained from 6,7-dihydro-2-methylbenzo[b]thiophen-4(5*H*)-one<sup>8</sup> via Vilsmeier-Haack reaction) and 2-furanboronic acid or 2-thiopheneboronic acid .

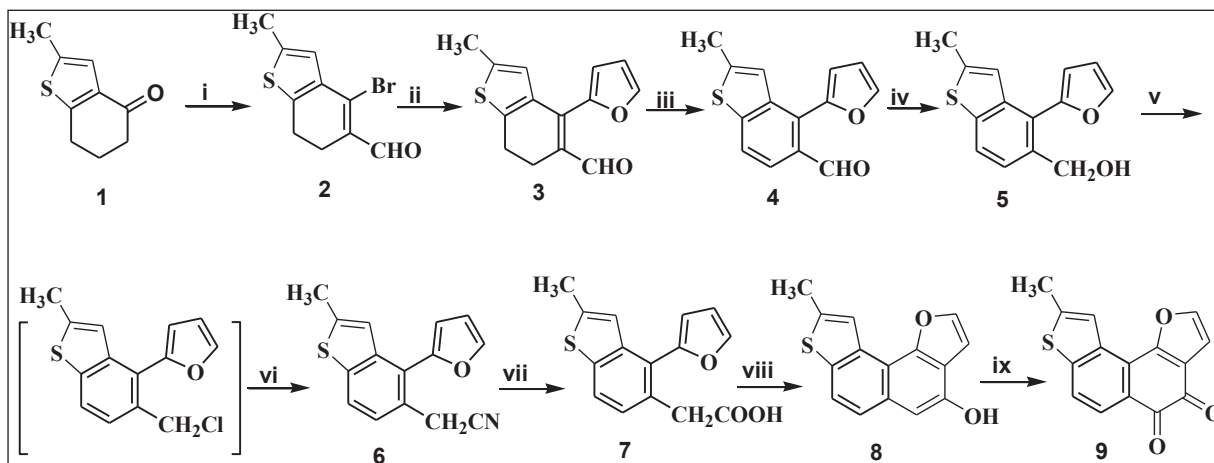


**Scheme 1: Retrosynthesis of doubly condensed naphthoquinone derivatives 9 and 23**

It is also an extension of the method for the synthesis of condensed furophenanthraquinones, as developed by us, which also shows the importance of our method for the synthesis of doubly condensed or doubly heteroannulated naphthoquinones.

## 7.3 Results and discussions

Our first target molecule was 9-methylnaphtho[1,2-*b*]furan[7,8-*b*]thiophene-4,5-dione (**9**), a bioisoster of isotanshinone II nucleus. The synthesis has been achieved from ketone **1** in nine steps (scheme 2).

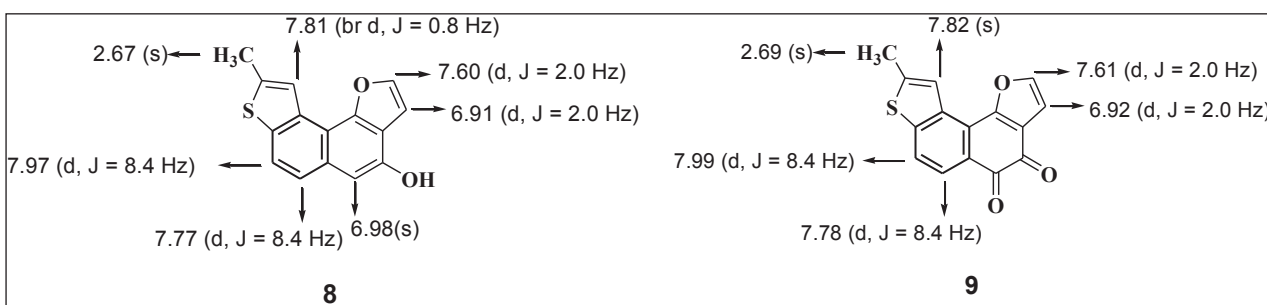


**Reagents and Conditions:** i)  $\text{PBr}_3$ , DMF,  $\text{CHCl}_3$ ,  $0^\circ\text{C}$ -r. t., 16 hrs, 73 %; ii) 2-furanboronic acid,  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Et}_3\text{N}$ , DMF,  $110^\circ\text{C}$ ,  $\text{N}_2$  atm., 15 hrs, 63 %; iii) DDQ, benzene, reflux, 27 hrs, 87 %; iv)  $\text{NaBH}_4$ , EtOH, r.t., 2 hrs, 92 %; v)  $\text{MsCl}$ ,  $\text{LiCl}$ , *s*-collidine, DMF,  $0^\circ\text{C}$ , overnight; vi)  $\text{KCN}$ , DMF, 6 hrs, 68 %; vii)  $\text{KOH}$ , EtOH- $\text{H}_2\text{O}$ , reflux, 21 hrs, 39 %; viii) TFAA-TFA,  $0^\circ\text{C}$ , overnight, 84 %; ix) Fremy's salt, 1/6M  $\text{Na}_2\text{HPO}_4$  buffer solution, MeOH,  $0$ - $5^\circ\text{C}$ , overnight, 79 %.

### Scheme 2: Synthesis of 9-methylnaphtho[1,2-*b*]furan[7,8-*b*]thiophene-4,5-dione (9)

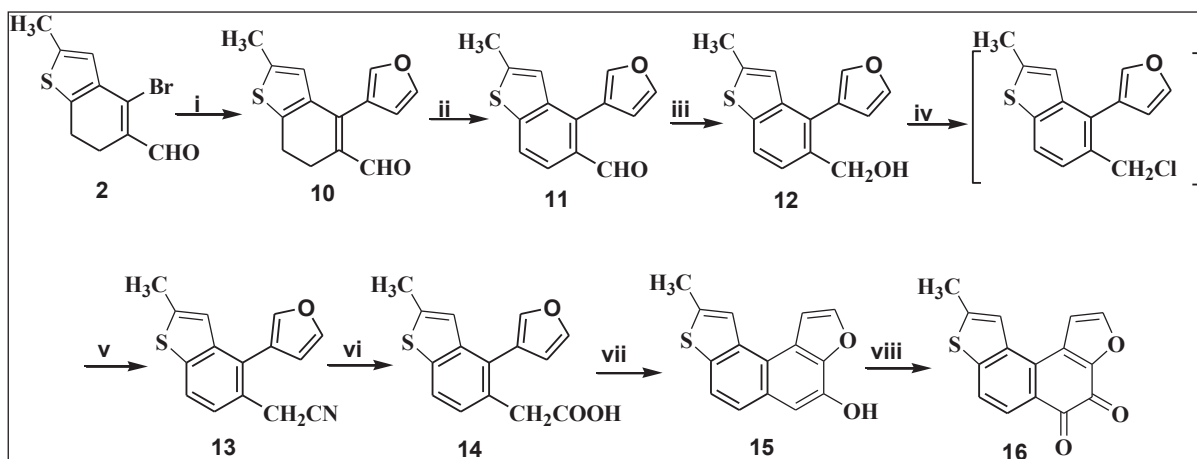
The bromoaldehyde **2** was prepared in very good yield from the ketone **1**,<sup>8</sup> using modified Vilsmeier-Haack reagent ( $\text{PBr}_3$ , DMF in anhydrous  $\text{CHCl}_3$ ). IR spectrum of compound **2** showed strong absorption at  $1634\text{ cm}^{-1}$  for the  $-\text{CHO}$  functionality.  $^1\text{H}$  NMR,  $^{13}\text{C}$  NMR and HRMS analysis justified the structure.  $^1\text{H}$  NMR ( $\text{CDCl}_3$ ) spectra of the compound **2** showed signals at  $\delta = 2.38$  (s, 3H) [characteristics of  $-\text{CH}_3$  group], 2.69-2.64 (m, 2H), 2.79-2.75 (m, 2H), 6.90 (s, 1H), 9.97 (s, 1H) [characteristics of  $-\text{CHO}$  group] ppm, whereas  $^{13}\text{C}$  NMR showed signals at  $\delta = 15.26, 22.57, 23.94, 124.72, 129.18, 135.37, 135.65, 137.12, 142.00, 192.43$  [characteristics of  $-\text{CHO}$  group] ppm. The bromoaldehyde **2** when subjected to Suzuki Reaction with 2-furanboronic acid resulted in the formation of 6,7-dihydro-4-(2-furyl)-2-methylbenzo[*b*]thiophene-5-carbaldehyde (**3**) in 63 % yield. Compound **3** was characterised by usual IR, NMR and HRMS data (*vide* experimental). It was aromatised (DDQ, benzene, reflux) to 4-(2-furyl)-2-methylbenzo[*b*]thiophene-5-carbaldehyde (**4**) in 87 % yield. In IR spectrum, it showed strong absorption at  $1690\text{ cm}^{-1}$  for the  $-\text{CHO}$  functionality. In  $^1\text{H}$  NMR spectrum of this compound **4**, two methyl signals were observed as two sets of signal at  $\delta$  2.600 and 2.603 (both s, total 3H). It

is due to atropisomers of the resulting product. Reduction of the compound **4** with NaBH<sub>4</sub> in ethanol produced the alcohol in excellent yield. The <sup>1</sup>H NMR of the compound **5** was somewhat complicated and shows the following signals (400 MHz, CDCl<sub>3</sub>): δ = 2.57 & 2.59 (both s, total 3H), 4.69 & 4.78 (both s, total 2H), 6.59 (dd, J = 2.0 & 3.2 Hz) and 6.66 (br d, J = 2.8 Hz) (total 1H), 6.96 & 7.11 (both br. s, total 1H), 7.25 & 7.26 (both d, J = 1.6 Hz, total 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 1.2 Hz) and 7.65 (br s) (total 1H), 7.73 & 7.77 (both d, J = 8.4 Hz, total 1H) (OH proton was not observed) ppm. This is due to possible atropisomers. The alcohol **5** was then converted to the nitrile **6** by treatment with MsCl, LiCl, *s*-collidine, 0 °C, followed by reaction of the resulting crude chloride with KCN in DMF. The nitrile derivative has been characterised by usual spectroscopic data (IR, <sup>1</sup>H NMR and HRMS data). Both the compounds **5** and **6** showed some extra signals in <sup>1</sup>H NMR due to atropisomers. The details have been given in experimental section. The nitrite **6** on hydrolysis (KOH, H<sub>2</sub>O-EtOH, reflux), produced carboxylic acid **7** in moderate yield. In IR spectrum, it showed strong absorbance at 1696 cm<sup>-1</sup> for the –CO<sub>2</sub>H functionality. Cyclisation of the acid **7** with trifluoro acetic acid and trifluoro acetic anhydride mixture furnished the phenolic intermediate **8** in excellent yield. The oxidation (with Fremy's salt) of the phenol **8** ultimately resulted in formation of the target compound **9** to complete the synthesis. Both the phenol and the quinone were characterised by usual spectroscopic data. The tentative assignments of <sup>1</sup>H NMR spectral data of the Phenol **8** and the quinone **9** have been depicted in fig. 2.



**Figure 2: Tentative assignments of <sup>1</sup>H NMR spectral data of the Phenol **8** and the quinone **9****

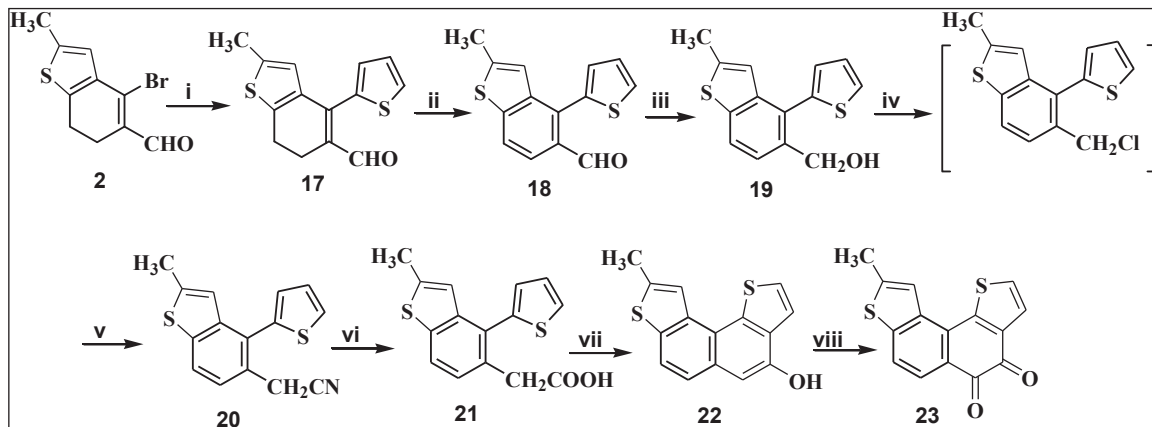
In a similar way, the synthesis of an isomeric quinone **16** was executed starting from the same bromoaldehyde **2** and 3-furanboronic acid (scheme 3).



**Reagents and Conditions:** i) 3-furanboronic acid,  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Et}_3\text{N}$ , DMF,  $110^\circ\text{C}$ ,  $\text{N}_2$  atm., 12 hrs, 67 %; ii) DDQ, benzene, reflux, 24 hrs, 89 %; iii)  $\text{NaBH}_4$ , EtOH, r.t., 2 hrs, 92 %; iv)  $\text{MsCl}$ ,  $\text{LiCl}$ , *s*-collidine, DMF,  $0^\circ\text{C}$ , overnight; v)  $\text{KCN}$ , DMF, 10 hrs, 76 %; vi)  $\text{KOH}$ , EtOH- $\text{H}_2\text{O}$ , reflux, 23 hrs, 43 %; vii) TFAA-TFA,  $0^\circ\text{C}$ , overnight, 85 %; viii) Fremy's salt, 1/6M  $\text{Na}_2\text{HPO}_4$  buffer solution, MeOH,  $0-5^\circ\text{C}$ , overnight, 86 %.

### Scheme 3: Synthesis of 9-methylnaphtho[2,1-*b*]furan[7,8-*b*]thiophene-4,5-dione (16)

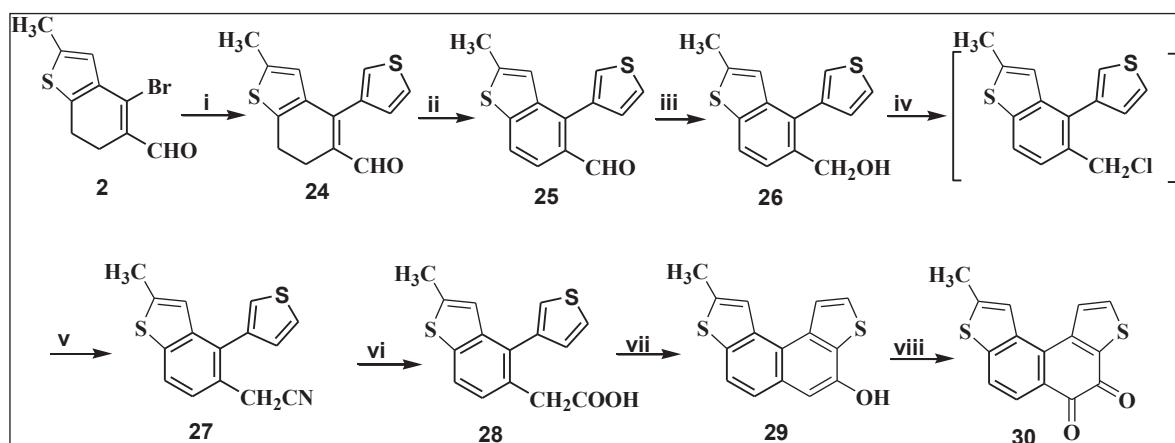
The syntheses of other bis thiophene condensed naphthoquinones (**23** and **30**) were achieved as per scheme 4 and scheme 5 using 2-thiopheneboronic acid and 3-thiopheneboronic acid, respectively instead of 2/3-furanboronic acids.



**Reagents and Conditions:** i) 2-thiopheneboronic acid,  $\text{Pd}(\text{PPh}_3)_4$ ,  $\text{Et}_3\text{N}$ , DMF,  $110^\circ\text{C}$ ,  $\text{N}_2$  atm., 10 hrs, 61 %; ii) DDQ, benzene, reflux, 24 hrs, 86 %; iii)  $\text{NaBH}_4$ , EtOH, r.t., 2 hrs, 91 %; iv)

MsCl, LiCl, *s*-collidine, DMF, 0 °C overnight; v) KCN, DMF, 11 hrs, 84 %; vi) KOH, EtOH-H<sub>2</sub>O reflux, 20 hrs, 50 %; vii) TFAA-TFA, 0 °C overnight, 80 %; viii) Fremy's salt, 1/6M Na<sub>2</sub>HPO<sub>4</sub> buffer solution, MeOH, 0-5 °C, overnight, 77 %.

**Scheme 4: Synthesis of 9-methylnaphtho[1,2-*b*:7,8-*b'*]bisthiophene-4,5-dione**

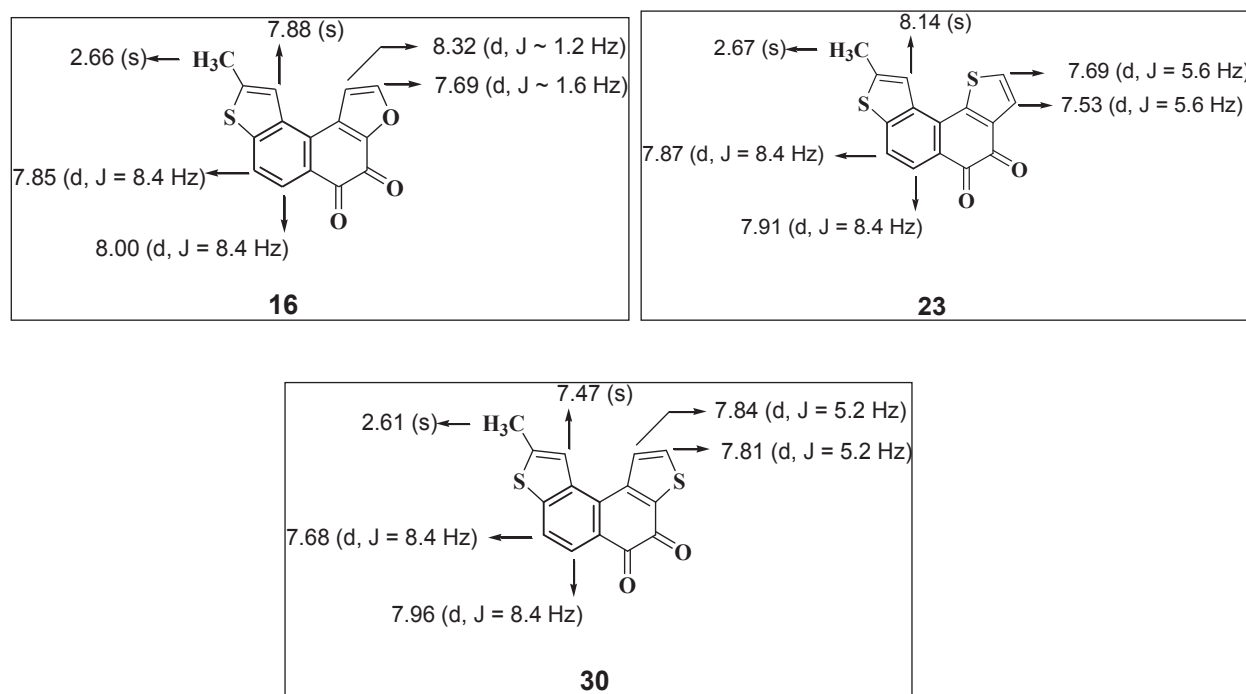


**Reagents and Conditions:** i) 3-thiopheneboronic acid, Pd(PPh<sub>3</sub>)<sub>4</sub>, Et<sub>3</sub>N, DMF, 110 °C, N<sub>2</sub> atm., 10 hrs, 67 %; ii) DDQ, benzene, reflux, 24 hrs, 89 %; iii) NaBH<sub>4</sub>, EtOH, r.t., 2 hrs, 94 %; iv) MsCl, LiCl, *s*-collidine, DMF, 0 °C overnight; v) KCN, DMF, 11 hrs, 89 %; vi) KOH, EtOH-H<sub>2</sub>O reflux, 20 hrs, 58 %; vii) TFAA-TFA, 0 °C overnight, 93 %; viii) Fremy's salt, 1/6M Na<sub>2</sub>HPO<sub>4</sub> buffer solution, MeOH, 0-5 °C, overnight, 83 %.

**Scheme 5: Synthesis of 9-methylnaphtho[2,1-*b*:7,8-*b'*]bisthiophene-4,5-dione**

All other compounds have been characterised by <sup>1</sup>H NMR, <sup>13</sup>C NMR, IR (wherever applicable), HRMS spectral data. Details have been given in experimental section.

Tentative analysis of <sup>1</sup>H NMR spectral data of other three *o*-quinonoes **16**, **23** and **30** has been depicted in fig. 3.



**Figure 3: Tentative assignments of <sup>1</sup>H NMR spectral data of the *o*-quinones 16, 23 and 30**

#### 7.4. Conclusion

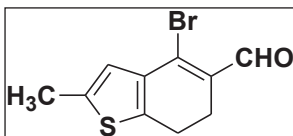
Thus, we have successfully synthesised a total of four novel ‘U’-shaped doubly condensed (with thiophene and furan moieties) naphthoquinone derivatives. Modifications have been made in ring A or in both rings A and D of the core nucleus present in naturally occurring furophenanthraquinone: isotanshinone II. The process involved a diversity-oriented synthesis (DOS). In future, the boronic acid components can be replaced with substituted 2/3-thiopheneboronic acid derivatives as well as substituted 2/3-furanboronic acid derivatives to prepare a compound library of several doubly condensed naphthoquinones. Ring A may also be substituted with other heterocyclic/substituted heterocyclic rings to obtain more and more novel bis-annulated naphthoquinones as an application of this methodology. Biological evaluations of the synthesised compounds are under progress as collaborative work with other research groups and the result will be published in due course.



## 7.5 Experimental Section

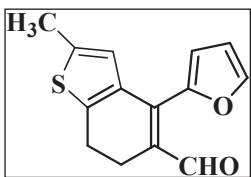
6,7-Dihydro-2-methylbenzo[*b*]thiophene-4(5*H*)-one (**1**) was synthesised following the standard procedure.<sup>8</sup>

### 4-Bromo-6,7-dihydro-2-methylbenzo[*b*]thiophene-5-carbaldehyde (**2**)



2.3 ml PBr<sub>3</sub> (24.4 mmol) was added drop wise to an ice cold mixture of 2.5 ml DMF (27.2 mmol) in 10 ml chloroform at 0-5 °C and the stirring was continued for 30 minutes protecting from moisture. A solution of 2-methyl-6,7-dihydrobenzo[*b*]thiophen-4(5*H*)-one (**1**) (1.28 gm, 7.7 mmol) in 5 ml chloroform was added drop wise to it. The reaction mixture was gradually allowed to attain r.t. and stirring was continued for another 16 hrs when the reaction was found to be completed. It was poured into ice cold saturated sodium acetate solution, stirred well for about 5 minutes and extracted with chloroform (3x20 ml). Combined chloroform layer was washed successively with cold brine solution, NaHCO<sub>3</sub> solution and finally with brine solution and dried (anhyd. Na<sub>2</sub>SO<sub>4</sub>). After removal of the solvent, resulting crude product was purified by column chromatography [silica gel. (100-200 mesh) / pet. ether (60-80 °C)-EtOAc: 1:50] to obtain the title compound as light yellow solid. Yield 1.45 gm (73 %), mp: 70-72 °C; IR (KBr)  $\nu_{\text{max}}$ : 1634 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.38 (s, 3H), 2.69-2.64 (m, 2H), 2.79-2.75 (m, 2H) 6.90 (s, 1H), 9.97 (s, 1H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 15.26, 22.57, 23.94, 124.72, 129.18, 135.37, 135.65, 137.12, 142.00, 192.43 ppm; HRMS (ESI+): *m/z* (M+H<sup>+</sup>) calcd. for C<sub>10</sub>H<sub>10</sub>O<sup>81</sup>Br: 258.9615; found: 258.9158.

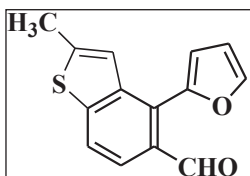
### 6,7-Dihydro-4-(2-furyl)- 2-methylbenzo[*b*]thiophene-5-carbaldehyde (**3**)



A mixture of the bromoaldehyde **2** (1.0 gm, 3.98 mmol), 2-furanboronic acid (535 mg, 4.77 mmol), Et<sub>3</sub>N (3.7 ml) and DMF (5 ml) was degasified with N<sub>2</sub> for 30 minutes. Now the catalyst [Pd(PPh<sub>3</sub>)<sub>4</sub>, 2 mol %] was added quickly to it and degasified for another 10-12 minutes. The mixture was heated with stirring under N<sub>2</sub> atm. at 110 °C for 15 hrs when the reaction was found to be completed. The resulting reaction mixture was then cooled to r.t., poured into ice water and extracted with ether (3x20 ml). Combined organic layer was washed successively with cold saturated NaHCO<sub>3</sub> solution, finally with brine solution and dried over (anhyd. Na<sub>2</sub>SO<sub>4</sub>). Removal

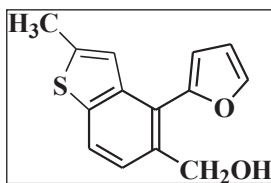
of the solvent, afforded the crude product. It was purified by column chromatography [silica gel. (100-200 mesh) / pet. ether (60- 80 °C) and EtOAc, 15:1) and the title compound was obtained as a pale yellow solid. Yield : 600 mg (2.46 mmol, 63 %); mp: 95-96 °C; IR (KBr)  $\nu_{\text{max}}$ : 1650  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.43 (s, 3H), 2.79 - 2.89 (m, 4H), 6.55 (t,  $J$  = 1.6 Hz, 1H), 6.62 (d,  $J$  = 2.8 Hz, 1H), 6.68 (s, 1H), 7.61 (s, 1H), 9.911 & 9.913 (both s, total 1H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 15.20, 21.91, 22.60, 111.31, 115.16, 124.33, 131.36, 133.73, 136.76, 138.73, 141.91, 144.03, 148.35, 192.24 ppm; HRMS (ESI+):  $m/z$  ( $\text{M}+\text{H}^+$ ) calcd for  $\text{C}_{14}\text{H}_{13}\text{O}_2\text{S}$ : 245.0558; found: 245.0986 &  $m/z$  ( $\text{M}+\text{Na}$ ) calcd for  $\text{C}_{14}\text{H}_{12}\text{O}_2\text{SNa}$ : 267.0456; found: 267.0734.

#### 4-(2-Furyl)-2-methylbenzo[b]thiophene-5-carbaldehyde (4)



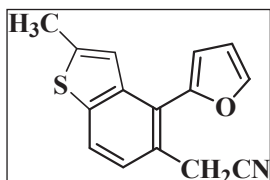
A mixture of 580 mg (2.38 mmol) of compound **3** in 25 ml dry benzene was refluxed with 650 mg (2.87 mmol) of DDQ on a water bath for 27 hrs protecting from moisture. After completion of the reaction, crude reaction mixture was filtered through a short column of 60-120 mesh silica gel and further eluted with benzene. The filtrate was then washed thoroughly with saturated  $\text{Na}_2\text{CO}_3$  solution until the aq. layer become colourless. Finally it was washed with water. The organic layer was collected, dried (anhyd.  $\text{Na}_2\text{SO}_4$ ) and solvent removed. The crude product thus obtained was recrystallised from pet. ether(60- 80 °C) -ethyl acetate mixture to obtain compound **4** as a pale yellow solid. Yield : 500 mg (2.07 mmol, 87 %); mp: 112-113 °C; IR (KBr)  $\nu_{\text{max}}$ : 1690  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.600 & 2.603 (both s, total 3H), 6.63 & 6.65 (both d,  $J$  = 3.6 Hz, total 1H), 7.09 & 7.24 (both br s, total 1H), 7.68 & 8.12 (both d,  $J$  = 0.8 Hz, total 1H), 7.75 & 7.77 (both d,  $J$  = 1.6 Hz, total 1H), 7.82 & 7.85 (both d,  $J$  = 8.4 Hz, total 1H), 7.89 (d,  $J$  = 8.4 Hz, 1H), 10.06 & 10.12 (both s, total 1H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.19, 16.30, 111.50, 113.52, 121.73, 121.83, 122.01, 122.45, 122.53, 122.93, 125.54, 128.88, 130.92, 133.13, 139.26, 140.37, 143.00, 143.06, 143.75, 145.36, 145.80, 148.60, 192.18, 192.27 ppm (excess carbon signals are possibly due to atropisomers); HRMS (ESI+):  $m/z$  [ $\text{M}+\text{H}$ ] $^+$  calcd for  $\text{C}_{14}\text{H}_{11}\text{O}_2\text{S}$ : 243.0402; found: 243.0578 &  $m/z$  [ $\text{M}+\text{Na}$ ] calcd for  $\text{C}_{14}\text{H}_{10}\text{O}_2\text{SNa}$ : 265.0299; found: 265.0304.

#### [4-(2-Furyl)-2-methylbenzo[b]thiophen-5-yl]methanol (**5**)



69 mg (1.98 mmol) of NaBH<sub>4</sub> was added pinch by pinch to an ice cold ethanolic solution of compound **4** (480 mg, 1.98 mmol) and stirring was continued at r.t. for further 2 hrs. Excess ethanol was removed by distillation and the residue was diluted with 2-3 ml ice water containing a drop of dil. HCl. Then the mixture was extracted with DCM, washed thoroughly with cold water and dried (anhyd. Na<sub>2</sub>SO<sub>4</sub>). Removal of the DCM, afforded the crude product which was further purified by column chromatography [silica gel (100-200 mesh) / pet. ether (60-80 °C)-EtOAC, 1:10] to obtain the compound **5** as a off white semi-solid mass; Yield : 450 mg (1.84 mmol, 92 %); <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>): δ = 2.57 & 2.59 (both s, total 3H), 4.69 & 4.78 (both s, total 2H), 6.59 (dd, J = 2.0 & 3.2 Hz) and 6.66 (br d, J = 2.8 Hz) (total 1H), , 6.96 & 7.11 (both br. s, total 1H), 7.25 & 7.26 ( both d, J=1.6 Hz, total 1H), 7.43 (d, J = 8.4 Hz, 1H), 7.60 (d, J = 1.2 Hz) and 7.65 (br s) (total 1H), 7.73 & 7.77 (both d , J = 8.4 Hz, total 1H) (OH proton was not observed) ppm; HRMS (ESI<sup>+</sup>): *m/z* [M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>13</sub>O<sub>2</sub>S: 245.0558; found: 245.1239.

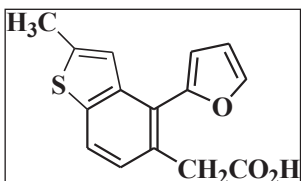
#### 2-[4-(2-Furyl)-2-methylbenzo[b]thiophen-5-yl]acetonitrile (**6**)



A mixture of alcohol **5** (430 mg, 1.76 mmol), *s*-collidine (255 mg, 2.11 mmol), mesyl chloride (306 mg, 2.66 mmol) and lithium chloride (89 mg, 2.23 mmol) in DMF (5 ml) was stirred overnight at 0-5 °C protecting from moisture. After the completion of the reaction, the resulting mixture was then poured into crushed ice and extracted with ether (3x20 ml). The combined organic layer was washed with ice-cold aq. 5 % HCl and finally thoroughly with cold water and dried (anhyd. Na<sub>2</sub>SO<sub>4</sub>). The solvent was then removed to furnish the crude chloride as brown oil. It was immediately used without further purification. The chloride was dissolved in dry DMF (4 ml) and KCN (185 mg, 2.83 mmol) was added to it, stirred at r.t. for 6 hr and then at 50 °C for 1 hr. The reaction mixture was diluted with ice water (10 ml) and extracted with ether (3x15 ml). The organic layer was washed thoroughly with ice-cold brine solution, dried (anhyd. Na<sub>2</sub>SO<sub>4</sub>) and after removal of the solvent, the crude product obtained was purified by column chromatography [silica gel (100-200 mesh) / pet. ether (60-80 °C)-EtOAC, 1:20]. The nitrile derivative **6** was obtained as an off white solid. Yield: 300 mg (1.19 mmol, 68 %); mp: 70-72 °C; IR (KBr) ν<sub>max</sub>:

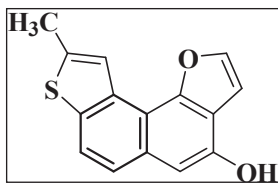
2256  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.57 & 2.59 (both s, total 3H), 3.83 & 3.85 (both s, total 2H), 6.60-6.62 (m, total 1H), 6.96 & 7.04 (both s, total 1H), 7.15 & 7.17 (both d,  $J$  = 1.2, Hz, total 1H), 7.39 (d,  $J$  = 8.0 Hz, 1H), 7.62 (br s, 1H), 7.73 and 7.76 (both d,  $J$  = 8 Hz, total 1H) ppm; HRMS (ESI+):  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{12}\text{NOS}$ : 254.0561; found: 253.8439.

## 2-[4-(2-Furyl)-2-methylbenzo[b]thiophen-5-yl]acetic acid (7)



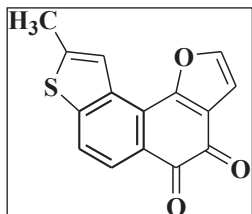
An ethanolic solution of nitrile **6** (260 mg, 0.103 mmol) and 4 ml 30 % KOH aq. solution were refluxed for 21 hrs. Excess EtOH was distilled out; the residual mass was diluted with ice water (5 ml) and extracted with ether (2x15 ml) to remove the neutral part. The aq. part was acidified with 5 % HCl under ice cold condition, and the oil that separated was extracted with EtOAc (3x20 ml). The combined organic layer was washed once with cold water, dried (anhyd.  $\text{Na}_2\text{SO}_4$ ) and the solvent removed. The residue was redissolved in saturated aq.  $\text{NaHCO}_3$ , filtered and the filtrate was acidified with 10 % HCl in ice-cold condition. The separated white solid was filtered and dried. Yield: 110 mg (0.40 mmol, 39 %); mp: 130  $^\circ\text{C}$ ; IR (KBr)  $\nu_{\text{max}}$ : 1696  $\text{cm}^{-1}$ ; HRMS (ESI+):  $m/z$   $[\text{M}+\text{Na}]$  calcd for  $\text{C}_{15}\text{H}_{12}\text{O}_3\text{SNa}$ : 295.0405; found: 295.1358.

## 9-Methylnaphtho[1,2-b]furan[7,8-b]thiophene-4-ol (8)



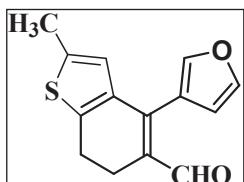
To a stirred solution of acid **7** (100 mg, 0.37 mmol) in 4.0 ml of trifluoroacetic anhydride, 1.5 ml of trifluoroacetic acid was added drop wise at 0-5  $^\circ\text{C}$  and stirring was continue for overnight protecting from moisture. The reaction mixture was poured into ice cold saturated aq.  $\text{NaHCO}_3$  solution and extracted thoroughly with DCM (3x20 ml). The organic layer was washed with saturated aq.  $\text{NaHCO}_3$ , water and dried (anhyd.  $\text{Na}_2\text{SO}_4$ ). After the removal of solvent, the crude product was obtained. It was purified by plate chromatography [silica gel GF 254 / benzene] to furnish light red solid. Yield: 80 mg (0.31 mmol, 84 %); mp: 258-260  $^\circ\text{C}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  +  $\text{DMSO}-d_6$ ):  $\delta$  = 2.67 (s, 3H), 6.91 (d,  $J$  = 2.0 Hz, 1H), 6.98 (s, 1H), 7.60 (d,  $J$  = 2.0 Hz, 1H), 7.77 (d,  $J$  = 8.4 Hz, 1H), 7.81 (br d,  $J$  = 0.8 Hz, 1H), 7.97 (d,  $J$  = 8.4 Hz, 1H) ppm; (due to poor solubility of the sample  $^{13}\text{C}$  NMR could not be recorded); HRMS (ESI+):  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{11}\text{O}_2\text{S}$ : 255.0402; found: 255.0463.

### 9-Methylnaphtho[1,2-*b*]furan[7,8-*b*]thiophene-4,5-dione (**9**)



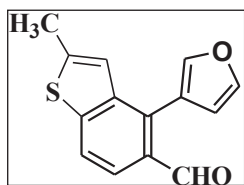
A solution of naphthol derivative **8** (60 mg, 0.24 mmol) in 6 ml methanol was added drop wise to a vigorously stirred solution of Fremy's salt (450 mg., 1.68 mmol) in 20 ml 1/6 (M) aq. Na<sub>2</sub>HPO<sub>4</sub> buffer solution at 0-5 °C. The stirring was continued at 0-5 °C for 3hrs and left in refrigerator for overnight. The resulting reaction mixture was then extracted with DCM (3x20 ml), washed with water and dried (anhyd. Na<sub>2</sub>SO<sub>4</sub>). After removal of the solvent, resulting crude product was purified by plate chromatography [silica gel GF 254 / benzene-methanol, 1:50] followed by recrystallisation from MeOH. The *o*-quinone **9** was obtained as a dark red solid; yield: 50 mg (0.19 mmol, 79 %); mp: 290-292 °C; IR (KBr)  $\nu_{\max}$ : 1694 and 1667 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.69 (s, 3H), 6.92 (d, *J* = 2.0 Hz, 1H), 7.61 (d, *J* = 2.0 Hz, 1H), 7.78 (d, *J* = 8.4 Hz, 1H), 7.82 (br s, 1H), 7.99 (d, *J* = 8.4 Hz, 1H) ppm; (due to poor solubility of the sample <sup>13</sup>C NMR could not be recorded) ; HRMS (ESI<sup>+</sup>): *m/z* [M+H]<sup>+</sup> calcd for C<sub>15</sub>H<sub>9</sub>O<sub>3</sub>S: 269.0194; found: 269.0261 & [M+Na] calcd for C<sub>15</sub>H<sub>8</sub>O<sub>3</sub>SNa: 291.0092; found: 291.0072.

### 6,7-Dihydro 4-(3-Furyl)-2-methylbenzo[*b*]thiophene-5-carbaldehyde (**10**)



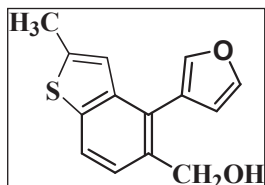
1 gm (3.89 mmol) of the bromoaldehyde **2** was subjected to Suzuki coupling reaction (reaction time 12 hrs) with 3-furanboronic acid (4.78 mmol) under the identical reaction condition, as used for the synthesis of the compound **3**, afforded the compound **10**. After usual work up, crude product was purified by column chromatography [silica gel (100-200 mesh) /pet. ether (60-80 °C) & ethyl acetate mixture, 15:1]. Compound **10** was obtained as yellow solid. Yield : 640 mg (2.62 mmol, 67 %); mp: 85-86 °C; IR (KBr) $\nu_{\max}$ : 1643 cm<sup>-1</sup>; <sup>1</sup>H NMR (400 MHz, CDCl<sub>3</sub>):  $\delta$  = 2.33 (s, 3H), 2.69 - 2.74 (m, 2H), 2.79-2.83 (m, 2H), 6.43 (d, *J*~1 Hz, 1H), 6.46 (s, 1H), 7.46-7.48 (m, 2H), 9.74 (s, 1H) ppm; <sup>13</sup>C NMR (100 MHz, CDCl<sub>3</sub>):  $\delta$  = 15.25, 21.68, 22.76, 112.33, 119.69, 123.96, 131.05, 135.69, 136.96, 141.68, 142.06, 142.90, 143.43, 192.16 ppm; HRMS (ESI<sup>+</sup>): *m/z* [M+H]<sup>+</sup> calcd for C<sub>14</sub>H<sub>13</sub>O<sub>2</sub>S: 245.0558; found: 245.0662.

#### 4-(3-Furyl)-2-methylbenzo[b]thiophene-5-carbaldehyde (**11**)



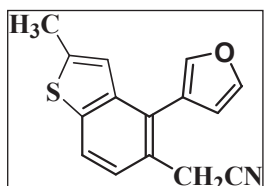
620 mg (2.54 mmol) of Suzuki coupled compound **10** and 690 mg (3.04 mmol) of DDQ in 20 ml dry benzene was refluxed for 24 hrs, under the identical reaction condition, as used for the synthesis of the compound **4**, afforded the compound **11** as pale yellow solid on purification by recrystallisation from pet. ether(60- 80 °C) -ethyl acetate mixture Yield : 550 mg (2.27 mmol, 89 %); mp: 90-92 °C; IR (KBr)  $\nu_{\text{max}}$ : 1677  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.50 (s, 3H), 6.56 (d,  $J$  = 1 Hz, 1H), 6.95 (s, 1H), 7.51 (s, 1H), 7.56 (t,  $J$  = 1.6 Hz, 1H), 7.73 (d,  $J$  = 8.8 Hz, 1H), 7.82 (d,  $J$  = 8.4 Hz, 1H), 10.06 (s, 1H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 15.29, 16.29, 113.15, 119.81, 121.56, 121.58, 1221.78, 130.80, 131.85, 140.51, 142.13, 142.50, 143.43, 145.14, 192.35 ppm (excess carbon signals are possibly due to atropisomers); HRMS (ESI+):  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{11}\text{O}_2\text{S}$ : 243.0402; found: 243.0469.

#### [4-(3-Furyl)-2-methylbenzo[b]thiophen-5-yl]methanol (**12**)



530 mg (2.19 mmol) of the aldehyde **11** on reduction with  $\text{NaBH}_4$  (75-80 mg, 2.19 mmol) reduction under the identical reaction condition, as used for the preparation of the compound **5**, afforded the alcohol **12** as a pale yellowish oil. yield : 490 mg (2 mmol, 92 %);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.45 (s, 3H), 4.54 (s, 2H), 6.27 (d,  $J$  = 8.4 Hz, 1H), 6.48 (br s, 1H), 6.81 (s, 1H), 7.47 (t,  $J$  = 1.4 Hz, 1H), 7.05(br. s, 1H), 7.60(d,  $J$  = 8.4 Hz, 1H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.30, 63.43, 112.59, 121.51, 121.58, 121.92, 124.34, 126.25, 134.75, 139.29, 140.70, 140.98, 141.29, 142.89 ppm; HRMS (ESI+):  $m/z$   $[\text{M}-\text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{11}\text{O}_2\text{S}$ : 243.0480; found: 243.0469.

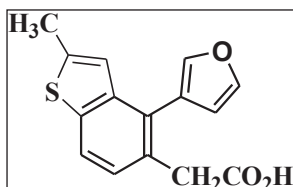
#### 2-[4-(3-Furyl)-2-methylbenzo[b]thiophen-5-yl]acetonitrile (**13**)



The compound **12** (470 mg, 1.92 mmol) was converted to the compound **13** under the identical reaction condition [*i.e.* by treatment with i)  $\text{MsCl}$ ,  $\text{LiCl}$ , *s*-collidine and ii)  $\text{KCN}$ , DMF], as used for the preparation of the compound **6**, as off white semi-solid. Yield: 370 mg (1.46 mmol, 76 %); IR (KBr)  $\nu_{\text{max}}$ : 2249  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.51 (s, 3H), 3.59 (s, 2H), 6.52 (d,

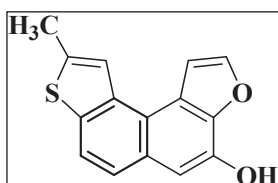
J~1Hz, 1H), 6.83 (br. s, 1H), 7.32 (d, J ~ 8.4 Hz, 1H), 7.51 (t, J = 1.6 Hz, 1H), 7.55 (br s, 1H), 7.65 (d, J ~ 8 Hz, 1H) ppm; HRMS (ESI+):  $m/z$   $[M+H]^+$  calcd for  $C_{15}H_{12}NOS$ : 254.0561; found: 253.8439.

#### 2-[4-(3-Furyl)-2-methylbenzo[b]thiophen-5-yl]acetic acid (**14**)



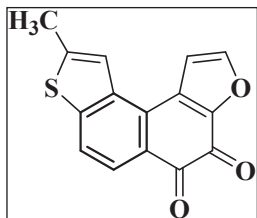
350 mg (1.38 mmol) of compound **13** on hydrolysis (6 ml of 30 % KOH in 5 ml EtOH under reflux for 23 hrs) and usual work up as used for the preparation of the compound **7**, afforded compound **14** as a white solid. Yield: 160 mg (0.59 mmol, 43 %); mp: 133-134 °C; IR (KBr)  $\nu_{\max}$ : 1689  $cm^{-1}$ ; HRMS (ESI+):  $m/z$   $[M+Na]$  calcd for  $C_{15}H_{12}O_3SNa$ : 295.0405; found: 295.2433.

#### 9-Methylnaphtho[2,1-b]furan[7,8-b]thiophene-4-ol (**15**)



Cyclisation of the carboxylic compound **14** (140 mg, 0.51 mmol) with a mixture of 5.0 ml trifluoroacetic anhydride and 1.5 ml trifluoroacetic acid under the identical reaction condition as used for the preparation of the compound **8** afforded the compound **15** as a semisolid mass, after usual work up and purification. Yield: 110 mg (0.43 mmol, 85 %);  $^1H$  NMR (400 MHz,  $CDCl_3$ ):  $\delta$  = 2.74 (s, 3H), 5.30 (s, 1H), 5.64 (br. s, 1H), 7.29 (s, 1H), 7.55 (d, J = 1.6 Hz, 1H), 7.66 (d, J = 8.8 Hz, 1H), 7.78 (d, J = 8.4 Hz, 1H), 7.86 (br d, J = 2.0 Hz, 1H) ppm;  $^{13}C$  NMR (100 MHz,  $CDCl_3$ ):  $\delta$  = 16.53, 108.62, 108.72, 118.63, 119.75, 121.26, 122.99, 124.03, 129.71, 135.12, 136.33, 140.45, 140.76, 143.89, 144.45 ppm; HRMS (ESI+):  $m/z$   $[M+H]^+$  calcd for  $C_{15}H_{11}O_2S$ : 255.0402; found: 255.0566.

#### 9-Methylnaphtho[2,1-b]furan[7,8-b]thiophene-4,5-dione (**16**)

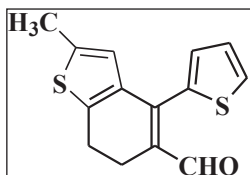


Oxidation of the phenolic compound **15** (90 mg, 0.35 mmol) with fremy's salt (670mg, 1.79 mmol) in 30 ml aq.  $Na_2HPO_4$  solution and 10-12ml MeOH, afforded the compound **16** as a deep violet solid, after usual work up and purification by preparative TLC (silica gel/ benzene-MeOH: 9:1). Yield: 80 mg (0.3 mmol, 86 %); mp: 288-289 °C; IR (KBr)  $\nu_{\max}$ : 1648 and 1690  $cm^{-1}$ ;  $^1H$  NMR (400 MHz,  $DMSO-d_6$ ):  $\delta$  = 2.66 (s, 3H), 7.69 (d, J = 1.6 Hz, 1H), 7.85



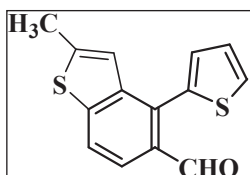
(d,  $J = 8.4$  Hz, 1H), 7.88 (br s, 1H), 8.00 (d,  $J = 8.4$  Hz, 1H), 8.32 (d,  $J = 1.2$  Hz, 1H) ppm; (due to poor solubility of the sample even in DMSO- $d_6$   $^{13}\text{C}$  NMR could not be recorded); HRMS (ESI $^{+}$ ):  $m/z$   $[\text{M}+\text{H}]^{+}$  calcd for  $\text{C}_{15}\text{H}_9\text{O}_3\text{S}$ : 269.0194; found: 269.0269.

#### 6,7-Dihydro-2-methyl-4-(2-thienyl)benzo[b]thiophene-5-carbaldehyde (17)



700 mg (2.69 mmol) the bromoaldehyde **2** was subjected to Suzuki coupling reaction (reaction time 10 hrs) with 2-thiopheneboronic acid (410 mg, 3.2 mmol) under the identical reaction condition, as used for the synthesis of the compound **3**, afforded the compound **17** as orange yellow solid after usual work up and purification. Yield: 430 mg (1.65 mmol, 61 %), mp: 54-56 °C; IR (KBr)  $\nu_{\text{max}}$ : 1645  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz), ( $\text{CDCl}_3$ ):  $\delta$  = 2.37 (s, 3H), 2.78-2.83 (m, 2H), 2.83-2.91 (m, 2H), 6.52 (s, 1H), 7.0 (d,  $J = 3.2$  Hz, 1H), 7.09 (d, ill split,  $J \sim 5$  Hz, 1H), 7.46 (dd,  $J = 4.8$  Hz & 1.6 Hz, 1H), 9.75 (s, 1H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 15.17, 21.82, 22.62, 124.14, 126.94, 127.55, 130.27, 131.85, 135.84, 135.92, 136.78, 141.33, 143.57, 192.22 ppm; HRMS (ESI $^{+}$ ):  $m/z$   $[\text{M}+\text{H}]^{+}$  calcd for  $\text{C}_{14}\text{H}_{13}\text{OS}_2$ : 261.0330; found: 261.1271 &  $[\text{M}+\text{Na}]$  calcd for  $\text{C}_{14}\text{H}_{12}\text{NaOS}_2$ : 283.0227; found: 283.1413.

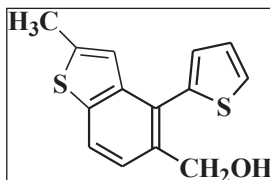
#### 2-Methyl-4-(2-thienyl)benzo[b]thiophene-5-caraldehyde (18)



420 mg (1.61 mmol) of compound **17** and 440 mg (1.94 mmol) of DDQ in 20 ml dry benzene was refluxed (24 hrs) protecting from moisture and after usual work up, as used for the synthesis of the compound **4**, furnished the compound **18** as pale yellow solid. Yield: 360 mg (1.40 mmol, 86 %), mp: 104-106 °C; IR (KBr)  $\nu_{\text{max}}$ : 1676  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.47 & 2.50 (both s, total 3H), 6.95 (br s, 1H), 7.09 and 7.1 (both d, ill split,  $J = 4.8$  Hz, total 1H), 7.13 & 7.14 (both d,  $J = 3.2$  Hz, total 1H), 7.46 & 7.48 (both br s, ill split, total 1H), 7.78 (d,  $J = 8.8$  Hz, 1H), 7.83 (d,  $J = 8.4$  Hz, 1H), 9.97 (s, 1H) ppm;  $^{13}\text{C}$  NMR (75 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.24, 121.40, 121.59, 122.33, 127.20, 127.32, 130.01, 131.43, 133.14, 135.88, 140.98, 142.75, 144.88, 191.97 ppm; HRMS (ESI $^{+}$ ):  $m/z$   $[\text{M}+\text{H}]^{+}$  calcd for  $\text{C}_{14}\text{H}_{11}\text{OS}_2$ : 259.0173; found: 259.0110 &  $[\text{M}+\text{Na}]$  calcd for  $\text{C}_{14}\text{H}_{10}\text{NaOS}_2$ : 281.0071; found: 280.9917.

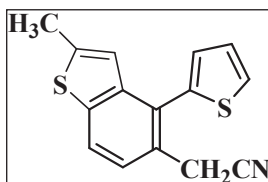


### [2-Methyl-4-(2-thienyl)benzo[b]thiophene-5-yl]methanol (**19**):



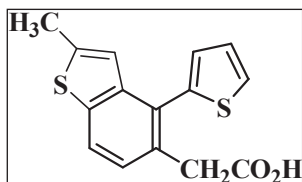
350 mg (1.35 mmol) of the aldehyde **18** on reduction with NaBH<sub>4</sub> (1.35 mmol) in ethanol for 2 hrs at r.t. and after usual work up, afforded the compound **19** as a yellowish oil. Yield: 320 mg (1.23 mmol, 91 %); <sup>1</sup>H NMR (300 MHz, CDCl<sub>3</sub>): δ = 2.13 (br s, 1H), 2.49 & 2.54 ( both s, total 3H), 4.59 & 4.68 (both s, total 2H), & 6.78 & 6.88 ( both s, total 1H), 7.03 (d, J = 2.4 Hz, 1H), 7.11 & 7.12 ( both d, J = 3.6 Hz, total 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.39 -7.41 (m, 1H), 7.71 (d, J = 8.1 Hz, 1H) ppm; NMR (400 MHz, CDCl<sub>3</sub>): δ = 16.23, 63.09, 121.51, 122.28, 123.82, 126.01, 127.10, 127.26, 127.84, 135.93, 138.78, 138.89, 141.36, 141.53 ppm; HRMS (ESI<sup>+</sup>): *m/z* [M]<sup>+</sup> calcd for C<sub>14</sub>H<sub>12</sub>OS<sub>2</sub>: 260.0330; found: 260.1869.

### 2-[2-Methyl-4-(2-thienyl)benzo[b]thiophene-5-yl]acetonitrile (**20**)



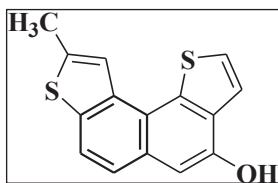
The compound **19** (310 mg, 1.19 mmol) was converted to the nitrile derivative **20** under the identical reaction condition, as used for the preparation of the compound **6**, as off white solid; Yield: 270 mg (1 mmol, 84 %); mp: 106-108 °C; IR(KBr) *v*<sub>max</sub>: 2358 cm<sup>-1</sup>; <sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ = 2.53 (s, 3H), 3.72 (s, 2H), 6.76 (s, 1H), 7.07 (d, J = 3.0 Hz, 1H), 7.19 (t, J = 4.5 Hz, 1H), 7.41 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 5.0 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H) ppm; <sup>13</sup>C NMR (125 MHz, CDCl<sub>3</sub>): δ = 16.39, 22.17, 118.47, 121.58, 122.99, 123.86, 125.85, 126.87, 127.66, 128.23, 128.33, 138.22, 139.57, 142.06, 142.80 ppm; HRMS (ESI<sup>+</sup>): *m/z* [M+Na] calcd for C<sub>15</sub>H<sub>11</sub>NaNS<sub>2</sub>: 292.0231; found: 292.0236.

### 2-[2-Methyl-4-(2-thienyl)benzo[b]thiophen-5-yl]acetic acid (**21**)



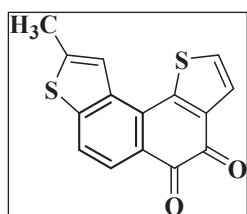
260 mg (0.97 mmol) of the nitrile derivative **20** on hydrolysis with 4 ml 30 % KOH in EtOH (reflux for 20 hrs) afforded the compound **21** as a white solid after usual work up and purification. Yield: 140 mg (0.49 mmol, 50 %); mp: 170-172 °C; IR (KBr) *v*<sub>max</sub>: 1699 cm<sup>-1</sup>; HRMS (ESI<sup>+</sup>): *m/z* [M+Na] calcd for C<sub>15</sub>H<sub>12</sub>O<sub>2</sub>NaS<sub>2</sub>: 311.0176; found: 311.1094.

### 9-Methylnaphtho[1,2-*b*:7,8-*b'*]bisthiophen-4-ol (**22**)



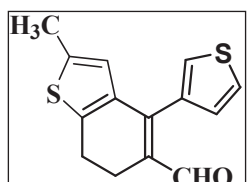
Cyclisation of the carboxylic acid **21** (120 mg, 0.42 mmol) with a mixture of 4.2 ml trifluoroacetic anhydride and 1.5 ml trifluoroacetic acid under the identical reaction condition, as used for the preparation of the compound **8**, afforded the compound **22** as a dark coloured semi solid mass, after usual work up and purification. Yield: 90 mg (0.33 mmol, 80 %);  $^1\text{H}$ NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.78 (s, 3H), 5.47 (br s, 1H), 7.15 (s, 1H), 7.62 (d,  $J$  = 5.0 Hz, 1H), 7.65 (d,  $J$  = 8.5 Hz, 1H), 7.73 (d,  $J$  = 5.5 Hz, 1H), 7.82 (d,  $J$  = 8.5 Hz, 1H) 8.03 (s, 1H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.65, 107.07, 120.38, 120.54, 120.86, 122.21, 123.06, 125.24, 130.39, 130.79, 136.31, 137.07, 141.24, 148.54, 211.40 ppm; HRMS (ESI $^{+}$ ):  $m/z$   $[\text{M}+\text{H}]^{+}$  calcd for  $\text{C}_{15}\text{H}_{11}\text{OS}_2$ : 271.0173; found: 271.3785.

### 9-Methylnaphtho[1,2-*b*:7,8-*b'*]bisthiophen-4,5-dione (**23**)



The phenolic compound **22** (80 mg, 0.3 mmol) on oxidation with 450 mg of Fremy's salt in 1/6 (M)  $\text{Na}_2\text{HPO}_4$  solution (30 ml) and MeOH (12 ml) for overnight at 0-4  $^{\circ}\text{C}$ , afforded the o-quinone derivatives **23** as a deep violet solid, after usual work up and purification. Yield: 65 mg (0.23 mmol, 77 %); mp: 227-228  $^{\circ}\text{C}$ ; IR (KBr)  $\nu_{\text{max}}$ : 1686 & 1657  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$  +  $\text{DMSO}-d_6$ ):  $\delta$  = 2.67 (s, 3H), 7.53 (d,  $J$  = 5.6 Hz, 1H), 7.69 (d,  $J$  = 5.6 Hz, 1H), 7.87 (d,  $J$  = 8.4 Hz, 1H), 7.91 (d,  $J$  = 8.4 Hz, 1H), 8.14 (s, 1H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 21.65, 125.89, 128.21, 129.19, 131.28, 131.98, 133.09, 139.78, 142.14, 151.17, 152.61, 178.93, 185.07 (2C short, sample was poorly soluble even in  $\text{DMSO}-d_6$ ; possibly 2 quaternary carbons didn't appeared with this number of scanning) HRMS (ESI $^{+}$ ):  $m/z$   $[\text{M}+\text{H}]^{+}$  calcd for  $\text{C}_{15}\text{H}_9\text{O}_2\text{S}_2$ : 284.9966; found: 284.8027 &  $[\text{M}+\text{Na}]$  calcd for  $\text{C}_{15}\text{H}_8\text{O}_2\text{NaS}_2$ : 306.9863; found: 306.7510.

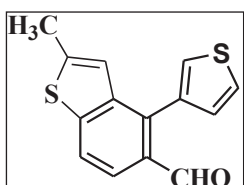
### 6,7-Dihydro-2-Methyl-4-(3-thienyl)-benzo[*b*]thiophene-5-carbaldehyde (**24**)



705 mg (2.71 mmol) the bromoaldehyde **2** was subjected to Suzuki coupling reaction with 3-thiopheneboronic acid (410 mg, 3.2 mmol) under the identical reaction condition, as used for the synthesis of the compound

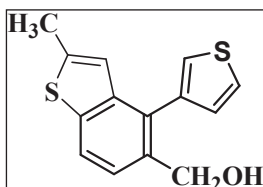
**3**, afforded the compound **24** after usual work up and purification as pale yellow solid; yield: 475 mg (1.82 mmol, 67 %); mp: 55-56 °C; IR (KBr) $\nu_{\text{max}}$ : 1649  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.31 (s, 3H), 2.71-2.75 (m, 2H), 2.81-2.85 (m, 2H), 6.31 (s, 1H), 7.02 (dd,  $J$  = 1.2 & 4.8 Hz, 1H), 7.24 (dd, ill split,  $J$  = 1.2 & 2.8 Hz, 1H), 7.35 (dd,  $J$  = 3.2 & 4.8 Hz, 1H), 9.59 (s, 1H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 15.24, 21.56, 22.82, 124.09, 125.93, 126.47, 129.20, 130.69, 135.70, 136.02, 136.91, 141.52, 146.19, 192.66 ppm; HRMS (ESI+):  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{13}\text{OS}_2$ : 261.0330; found: 261.0750 &  $[\text{M}+\text{Na}]$  calcd for  $\text{C}_{14}\text{H}_{12}\text{OS}_2\text{Na}$ : 283.0227; found: 283.689.

### 2-Methyl-4-(3-thienyl)benzo[b]thiophene-5-carbaldehyde (**25**)



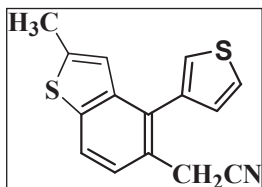
420 mg (1.61 mmol) of compound **24** and 440 mg (1.94 mmol) of DDQ in 20 ml dry benzene was refluxed for 24 hrs protecting from moisture. After usual work up, the compound **25** was obtained as pale yellow solid. yield: 370 mg (1.43 mmol, 89 %); mp: 102-103 °C; IR (KBr)  $\nu_{\text{max}}$ : 1673  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.56 (s, 3H), 6.91 (s, 1H), 7.23 (dd,  $J$  = 0.8 & 4.8 Hz, 1H), 7.36 (dd,  $J$  = 2.8 & 4.8 Hz, 1H), 7.51 (dd,  $J$  = 2.8 & 4.8 Hz, 1H), 7.81 (d,  $J$  = 8.4 Hz, 1H), 7.90 (d,  $J$  = 8.4 Hz, 1H), 9.99 (s, 1H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.35, 121.66, 121.76, 121.86, 125.97, 126.13, 130.05, 130.92, 136.13, 136.22, 140.54, 142.51, 145.23, 192.48 ppm; HRMS (ESI+):  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{14}\text{H}_{11}\text{OS}_2$ : 259.0173; found: 259.0254.

### [2-Methyl-4-(3-thienyl)benzo[b]thiophen-5-yl]methanol (**26**)



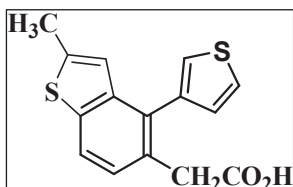
360 mg (1.39 mmol) of the aldehyde **25** on  $\text{NaBH}_4$  (1.39 mmol) reduction in EtOH (2 hrs), under the identical reaction condition, as used for the preparation of the compound **5**, afforded the compound **26** as colourless viscous liquid; yield: 340 mg (1.31 mmol, 94 %);  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.34 (s, 3H), 2.58 (br s, 1H), 4.33 (s, 2H), 6.59 (br s, 1H), 6.93 (dd,  $J$  = 1.2 & 4.8 Hz, 1H), 7.07 (dd,  $J$  = 1.2 & 3.2 Hz, 1H), 7.16 (d,  $J$  = 8.0 Hz, 1H), 7.21 (dd,  $J$  = 2.8 & 4.8 Hz, 1H), 7.48 (d,  $J$  = 8.0 Hz, 1H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.34, 63.02, 121.53, 121.70, 123.98, 124.20, 125.41, 129.53, 130.27, 134.65, 138.62, 139.07, 140.55, 141.13 ppm; HRMS (ESI+):  $m/z$   $[\text{M}+\text{Na}]$  calcd for  $\text{C}_{14}\text{H}_{12}\text{OS}_2\text{Na}$ : 283.0227; found: 283.2804.

## 2-[2-Methyl-4-(3-thienyl)benzo[b]thiophen-5-yl]acetonitrile (27)



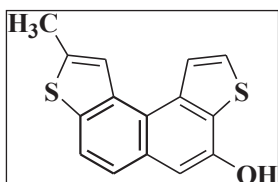
The alcohol **26** (310 mg, 1.19 mmol) was converted to the cyanide **27** (under the identical reaction condition, as used for the preparation of the compound **6**, and the cyanide was obtained as a pale yellow low melting solid; yield: 285 mg (1.06 mmol, 89 %); IR (KBr)  $\nu_{\max}$ : 2242  $\text{cm}^{-1}$ ;  $^1\text{H}$  NMR (400 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.45 (s, 3H), 4.54 (s, 2H), 6.67 (s, 1H), 7.10 (dd,  $J$  = 1.4 & 5.2 Hz, 1H), 7.27 (dd,  $J$  = 1.4 & 2.4 Hz, 1H), 7.34 (d,  $J$  = 8.4 Hz, 1H), 7.38 (dd,  $J$  = 2.4 & 5.2 Hz, 1H), 7.67 (d,  $J$  = 8.0 Hz, 1H) ppm;  $^{13}\text{C}$  NMR (100 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 16.27, 121.56, 123.91, 124.19, 125.48, 129.42, 130.40, 134.62, 138.58, 139.19, 140.62, 141.24 (3C Short, possibly three quaternary carbons didn't appeared with this number of scanning) ppm; HRMS (ESI+):  $m/z$   $[\text{M}+\text{Na}]$  calcd for  $\text{C}_{15}\text{H}_{11}\text{NS}_2\text{Na}$ : 292.0231; found: 292.0465.

## 2-[2-Methyl-4-(3-thienyl)benzo[b]thiophen-5-yl]acetic acid (28)



260 mg (0.97 mmol) of the nitrile derivative **27** on hydrolysis with 4 ml 30 % KOH in EtOH under reflux for 20 hrs, afforded the compound **28** as a white solid after usual work up and purification. Yield: 160 mg (0.56 mmol, 58 %); IR (KBr)  $\nu_{\max}$ : 1697  $\text{cm}^{-1}$ ; HRMS (ESI+):  $m/z$   $[\text{M}+\text{H}]^+$  calcd for  $\text{C}_{15}\text{H}_{13}\text{O}_2\text{S}_2$ : 289.0357; found: 289.0103 &  $m/z$   $[\text{M}+\text{Na}]$  calcd for  $\text{C}_{15}\text{H}_{12}\text{O}_2\text{S}_2\text{Na}$ : 311.0176; found: 310.9653.

## 9-Methylnaphtho[2,1-b:7,8-b']bisthiophen-4-ol (29)

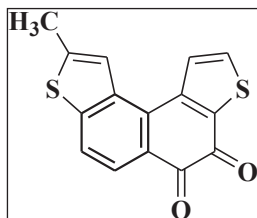


Cyclisation of the carboxylic acid **28** (120 mg, 0.42 mmol) with a mixture of 4 ml trifluoroacetic anhydride and 1.5 ml trifluoroacetic acid under the identical reaction condition, as used for the preparation of the compound **8**, afforded the compound **29** as a reddish semi solid mass, after usual work up and purification. yield: 105 mg (0.39 mmol, 93 %);  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.76 (s, 3H), 5.66 (br s, 1H), 7.18 (s, 1H), 7.65 (d,  $J$  = 8.5 Hz, 1H), 7.72 (d,  $J$  = 5.5 Hz, 1H), 7.82 (d,  $J$  = 8.5 Hz, 1H), 8.00 (s, 1H), 8.4 (d,  $J$  = 5.0 Hz, 1H) ppm;  $^{13}\text{C}$  NMR (125 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 29.85, 95.91, 105.53, 107.04, 108.35, 120.63, 122.42, 125.38, 126.31, 129.42, 131.58, 193.91 (three Carbon short, possibly three quaternary carbons didn't appeared with this

number of scanning) ppm; HRMS (ESI+):  $m/z$   $[M+H]^+$  calcd for  $C_{15}H_{11}OS_2$ : 271.0173; found: 270.9474.

### 9-Methylnaphtho[2,1-*b*:7,8-*b'*]bisthiophene-4,5-dione (**30**)

Oxidation of the phenolic compound **29** (80 mg, 0.3 mmol) with 450 mg (1.68 mmol) of Fremy's salt, under the identical reaction condition as used for the preparation of the compound **9**



afforded the compound **30** as a deep red solid, after usual work up and purification. yield: 70 mg (0.25 mmol, 83 %); mp: 230-232 °C ; IR (KBr)

$\nu_{\max}$ : broad strong peak at  $1652\text{ cm}^{-1}$ ;  $^1\text{H}$  NMR (500 MHz,  $\text{CDCl}_3$ ):  $\delta$  = 2.61 (s, 3H), 7.47 (s, 1H), 7.68 (d,  $J$  = 8.4 Hz, 1H), 7.81 (d,  $J$  = 5.2 Hz, 1H), 7.84 (d,  $J$  = 5.2 Hz, 1H), 7.96 (d,  $J$  = 8.4 Hz, 1H) ppm; HRMS

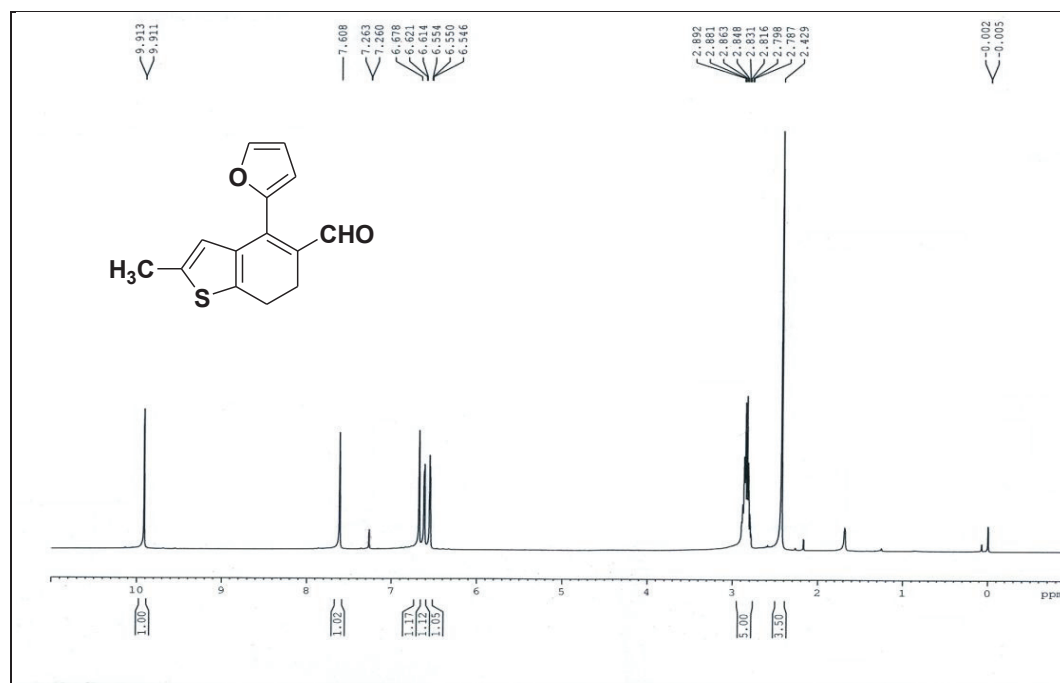
(ESI+):  $m/z$   $[M+H]^+$  calcd for  $C_{15}H_9O_2S_2$ : 284.9966; found: 285.1825 &  $[M+Na]$  calcd for  $C_{15}H_8O_2S_2Na$ : 306.9863; found: 307.1755.

## 7.6 References:

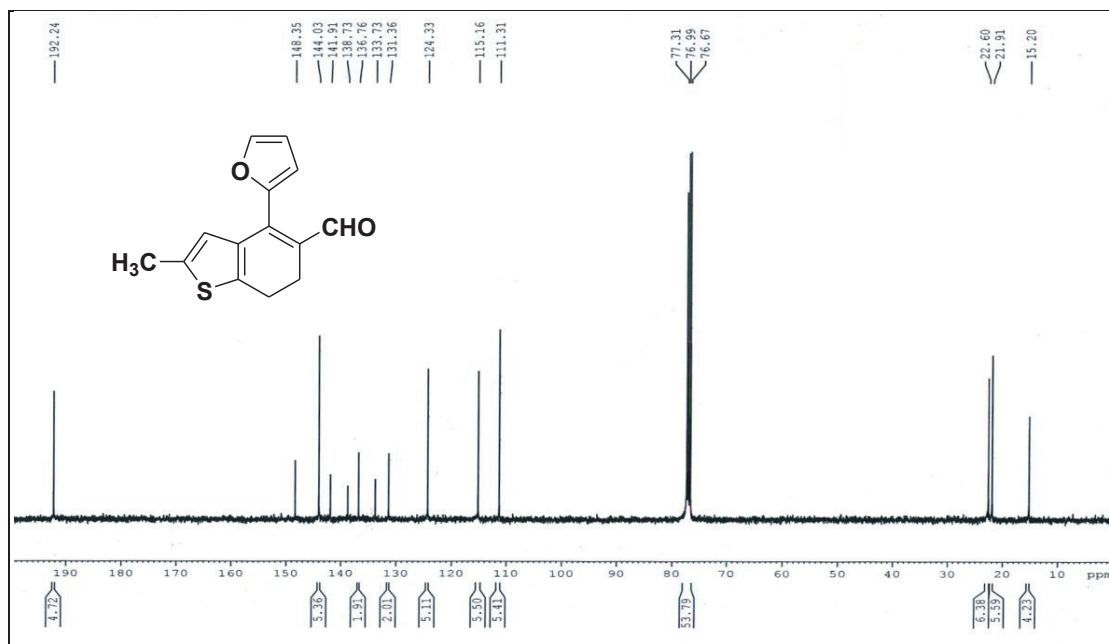
1. J. Acuna, J. Piermattey, D. Caro, S. Bannwitz, L. Barrios, J. Lopez, Y. Ocampo, R. V. Reyes, F. Aristizabal, R. Gaitan, K. Muller, L. Franco, *Molecules* **2018**, *23*, 186 (1-21).
2. J. H. Gao, R. J. Li, L. Q. Li, Q. Ming, H. Jiang, H. X. Li, W. P. Hu, *Adv. Mater.* **2007**, *19*, 3008.
3. V. A. Bren, A. D. Dubonosov, V. I. Minkin, A. V. Tsukanov, T. N. Griбанова, E. N. Shepelenko, Y. V. Revinsky, V. P. Rybalkin, *J. Phys. Org. Chem.* **2001**, *20*, 917.
4. G. Ferrara, T. Jin, M. Akhtaruzzaman, A. Islam, L. Han, H. Jiang, Y. Yamamoto, *Tetrahedron Lett.* **2012**, *53*, 1946.
5. N. Yanai, T. Mori, S. Shinamura, I. Osaka, K. Takimiya, *Org. Lett.* **2014**, *16*, 240.
6. G. Shukla, A. Srivastava, D. Yadav, M. S. Singh, *J. Org. Chem.* **2018**, *83*, 2173.
7. M. R. Kilbourn, *Int. J. Rad. Appl Instrum. B.* **1989**, *16*(7), 681.
8. N. P. Buu-Hoi, N. Hoan, N. H. Khoi, *Recl. Trav. Chim. Pays-Bas* **1950**, *69*, 1053.

## 7.7 Some of selected spectra:

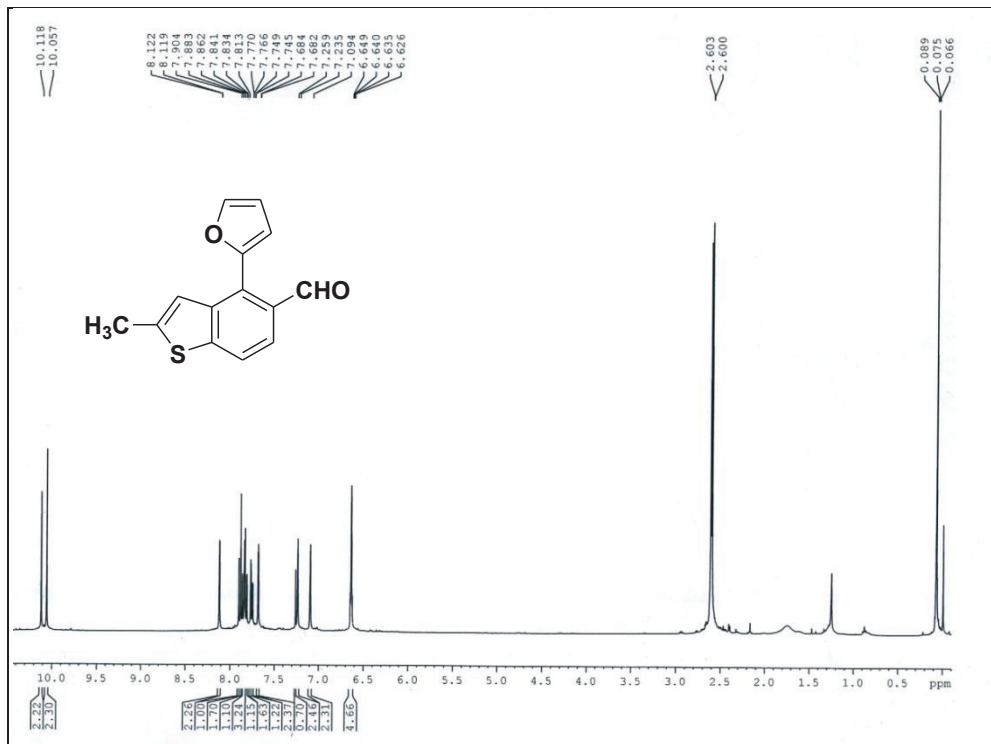
### $^1\text{H}$ NMR spectra of compound 3



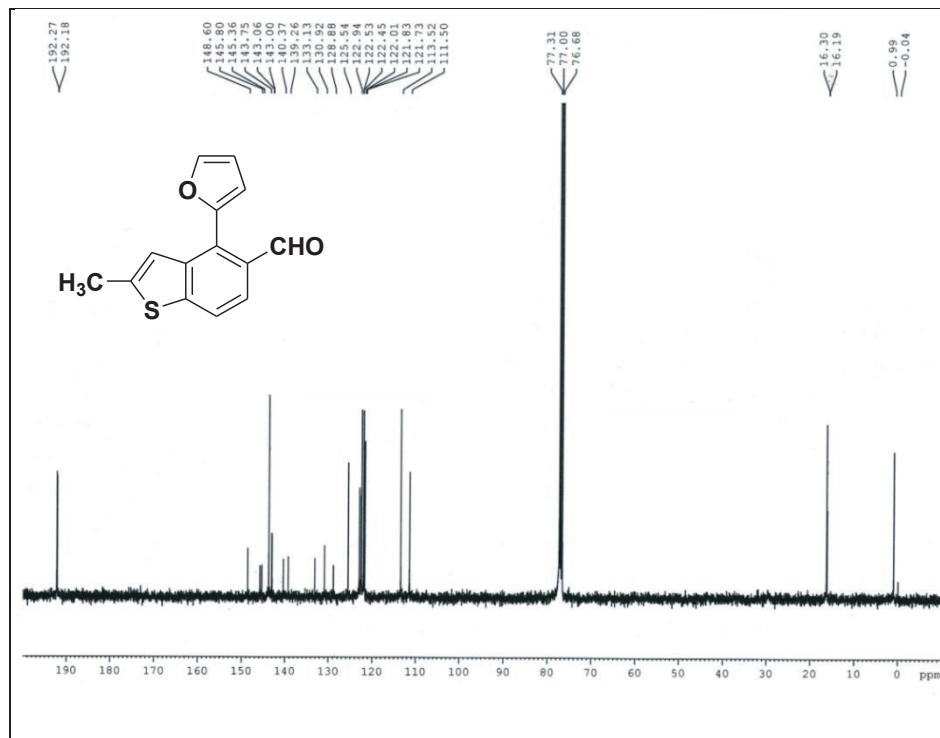
### $^{13}\text{C}$ NMR spectra of compound 3



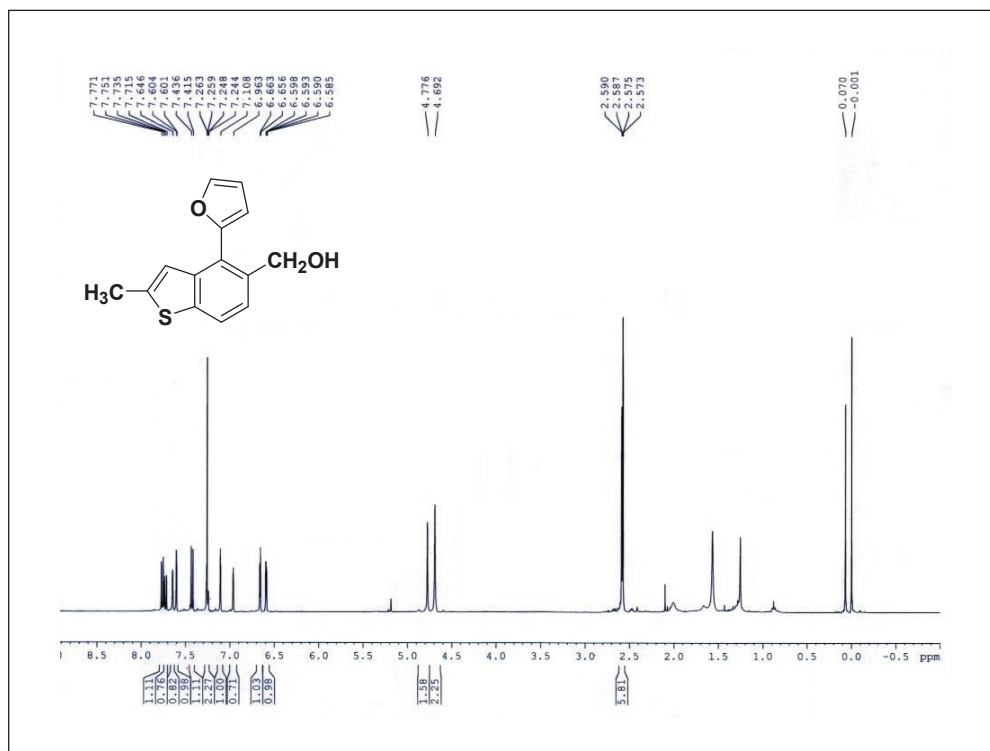
### <sup>1</sup>H NMR spectra of compound 4



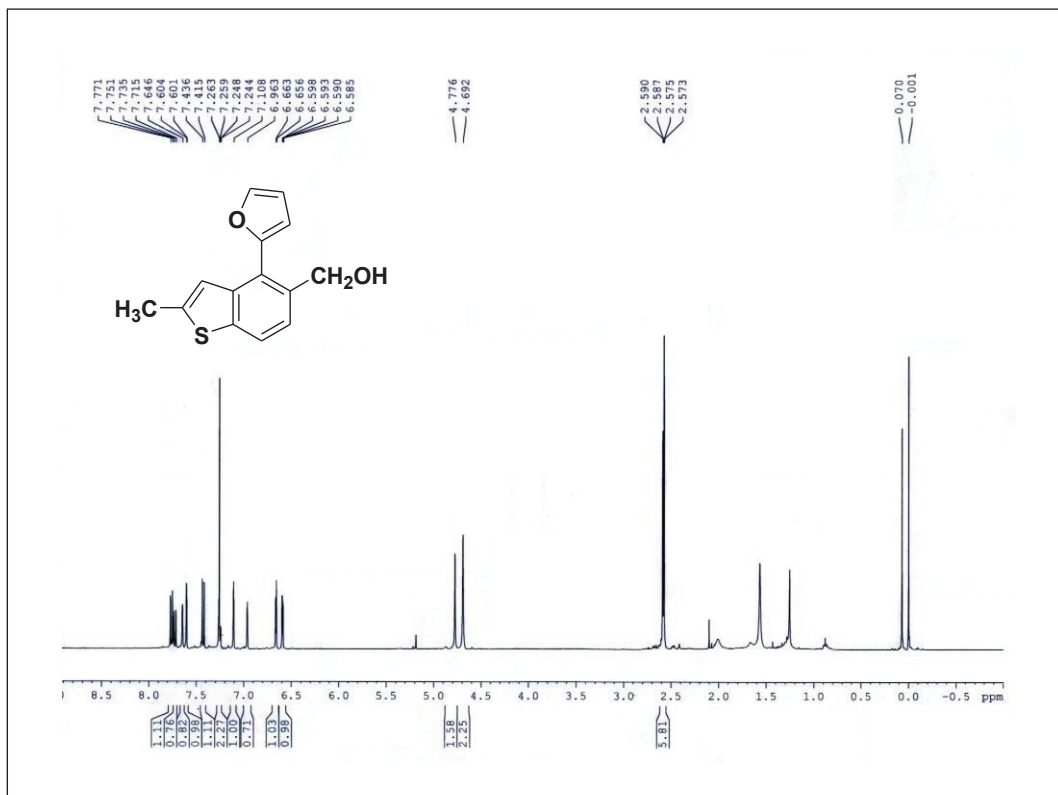
### <sup>13</sup>C NMR spectra of compound 4



<sup>1</sup>H NMR spectra of compound 5

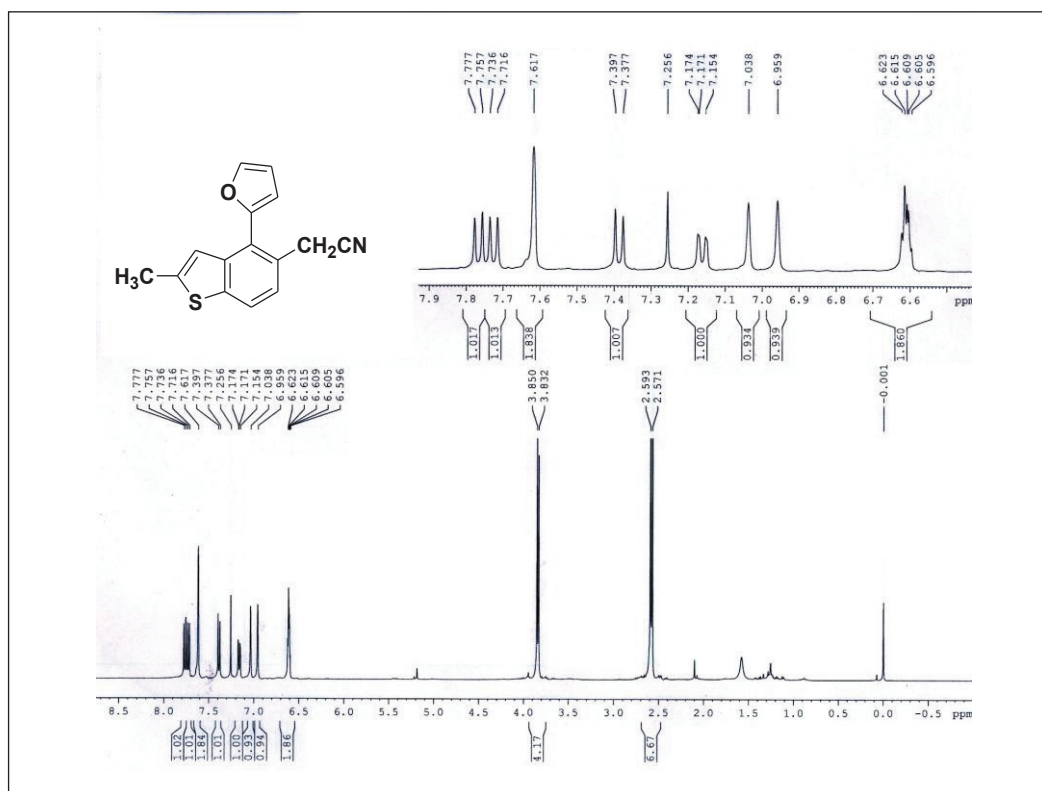


<sup>1</sup>H NMR spectra of compound 5

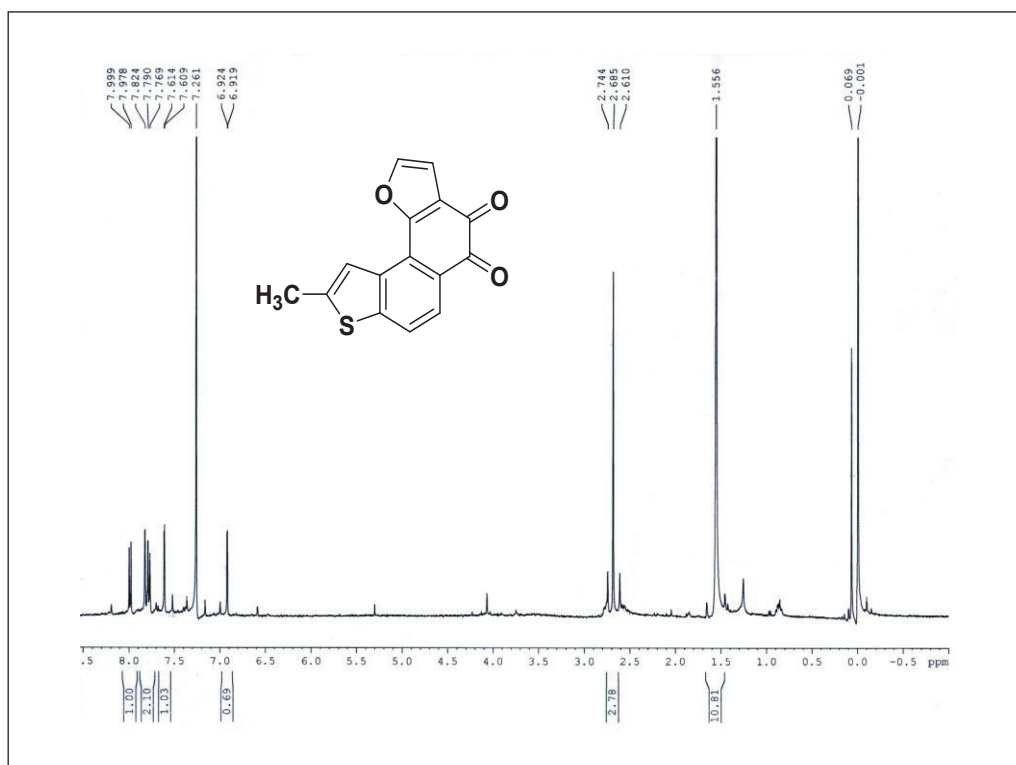




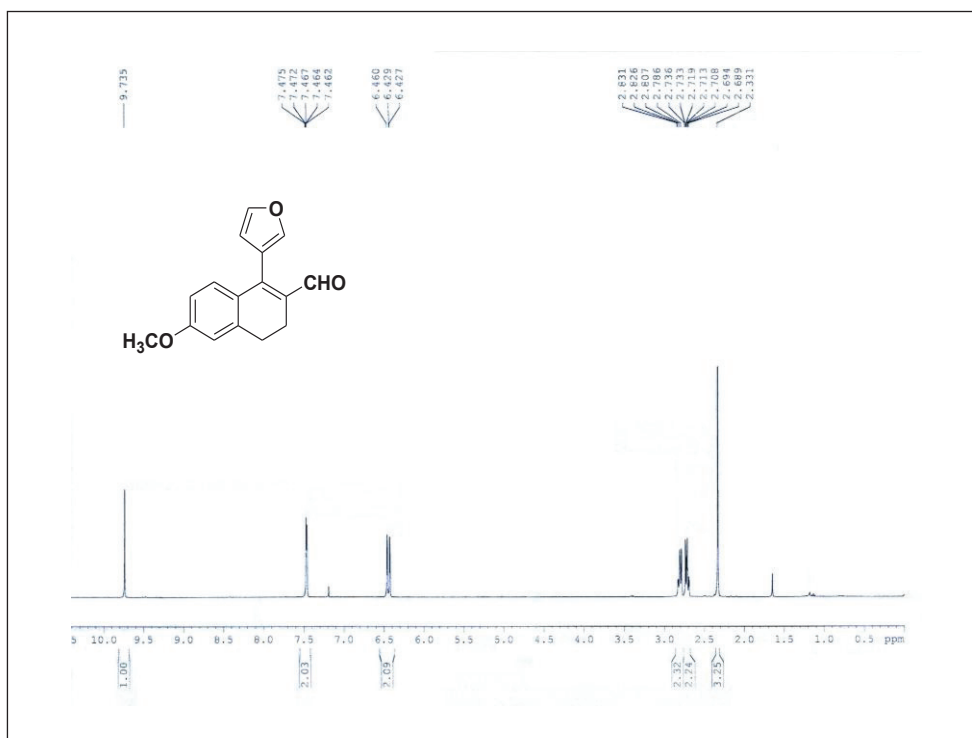
### <sup>1</sup>H NMR spectra of compound 6



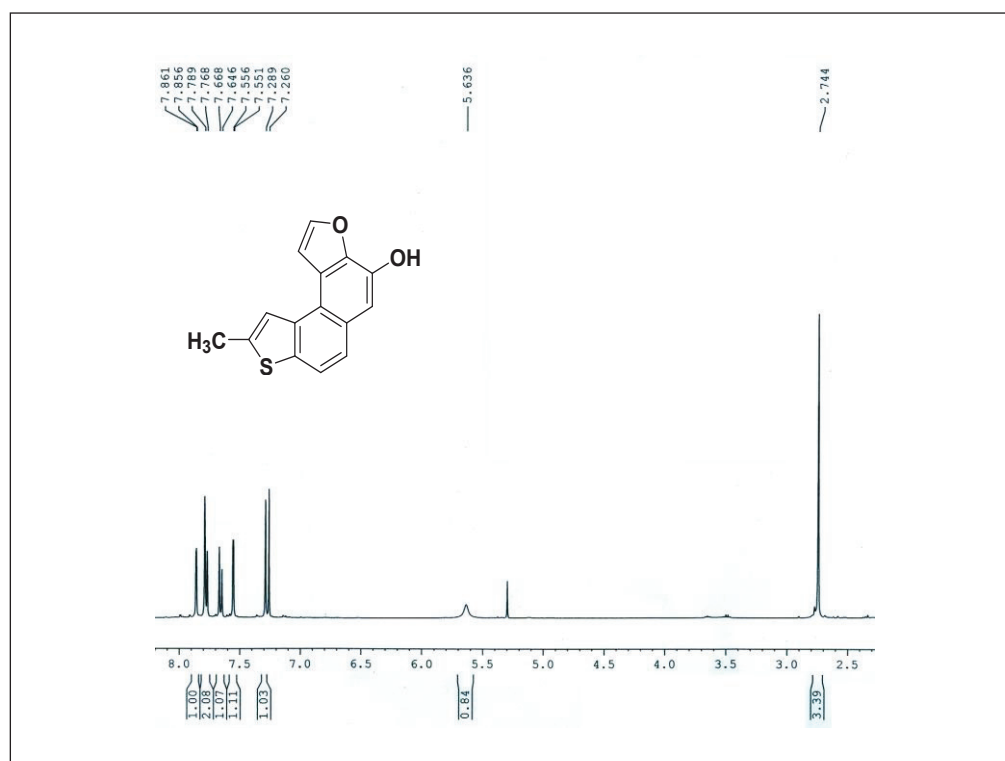
### <sup>1</sup>H NMR spectra of compound 9



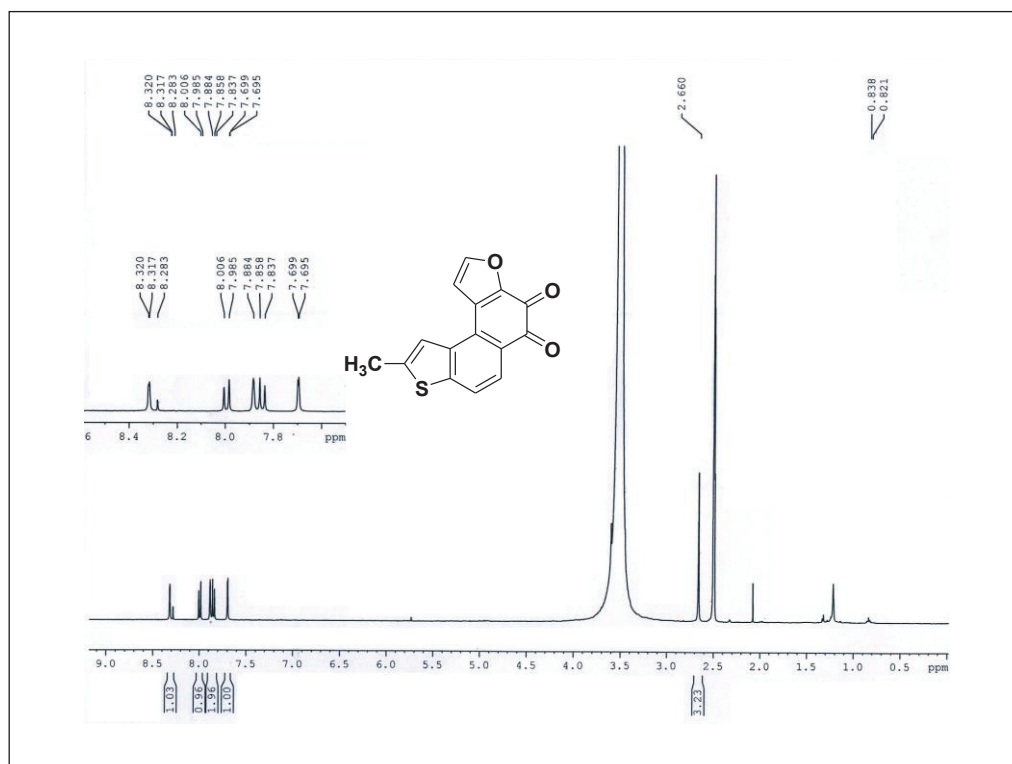
### <sup>1</sup>H NMR spectra of compound 10



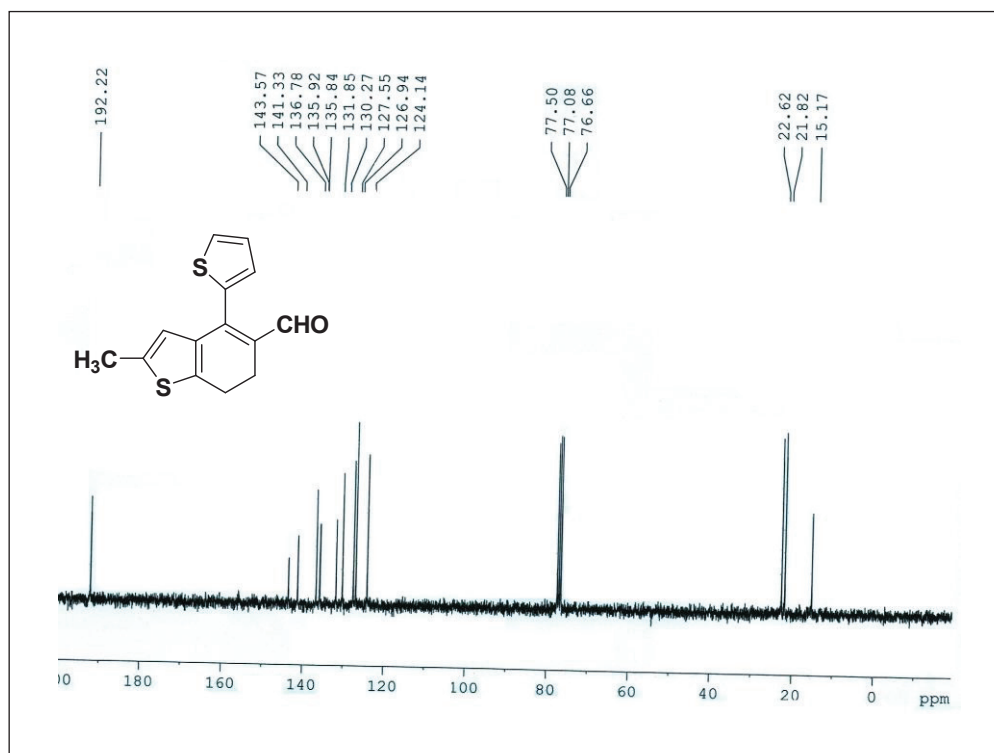
### <sup>1</sup>H NMR spectra of compound 15



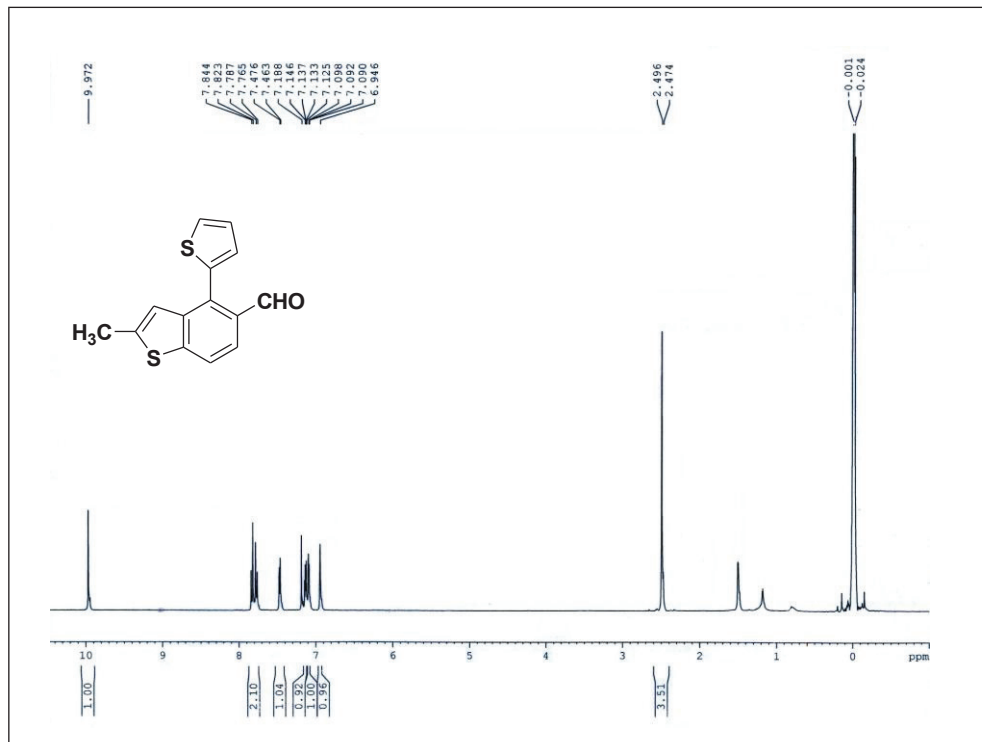
### <sup>1</sup>H NMR spectra of compound 16



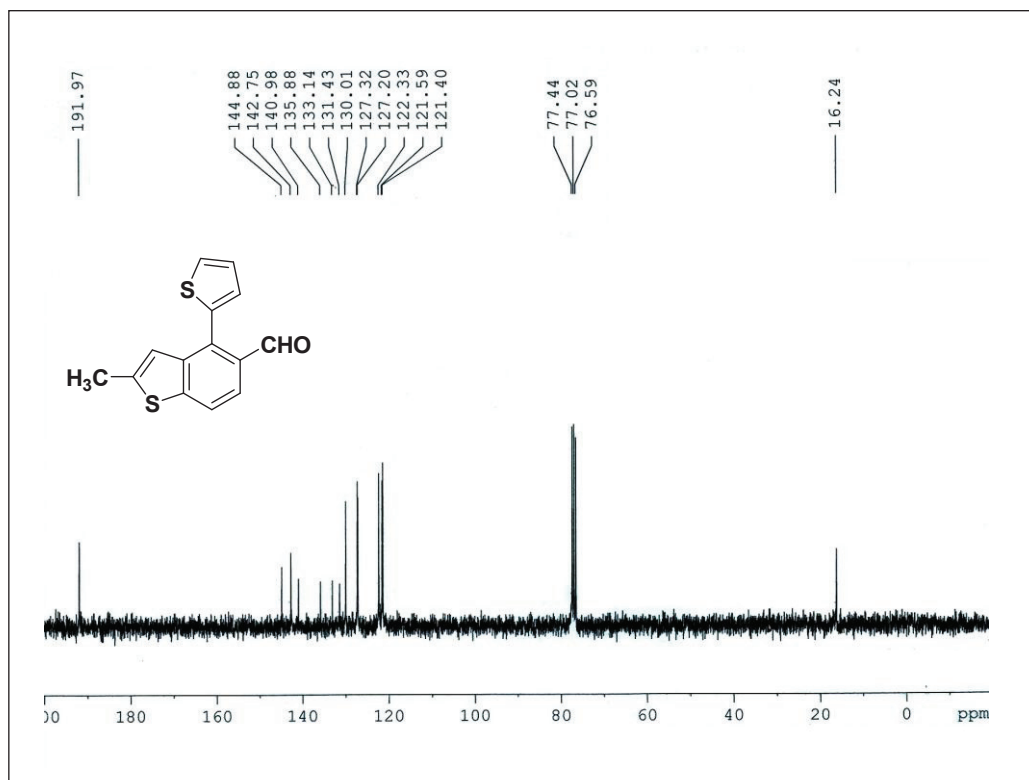
### <sup>13</sup>C NMR spectra of compound 17



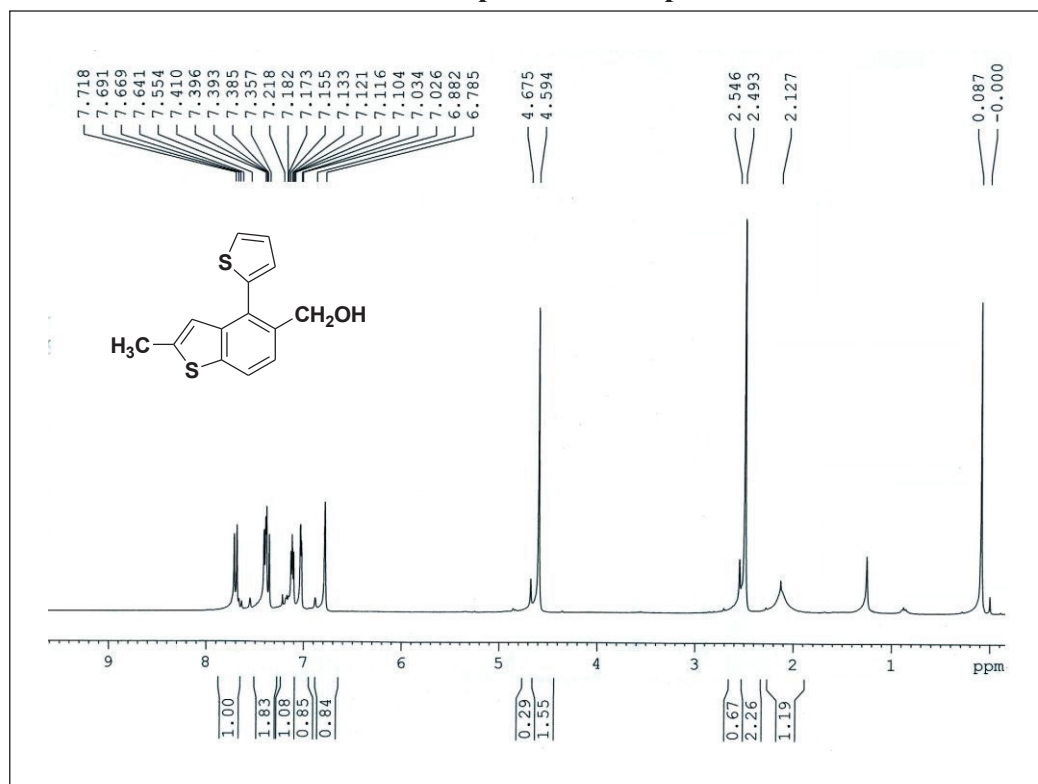
# <sup>1</sup>H NMR spectra of compound 18



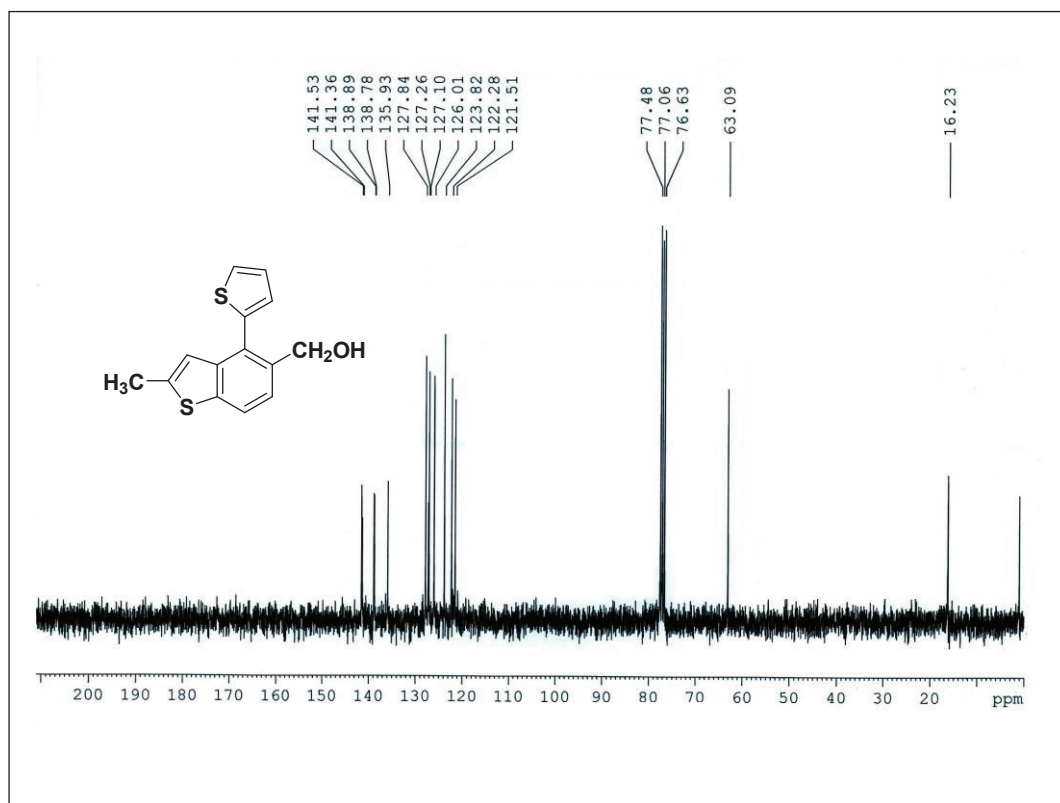
# <sup>13</sup>C NMR spectra of compound 18



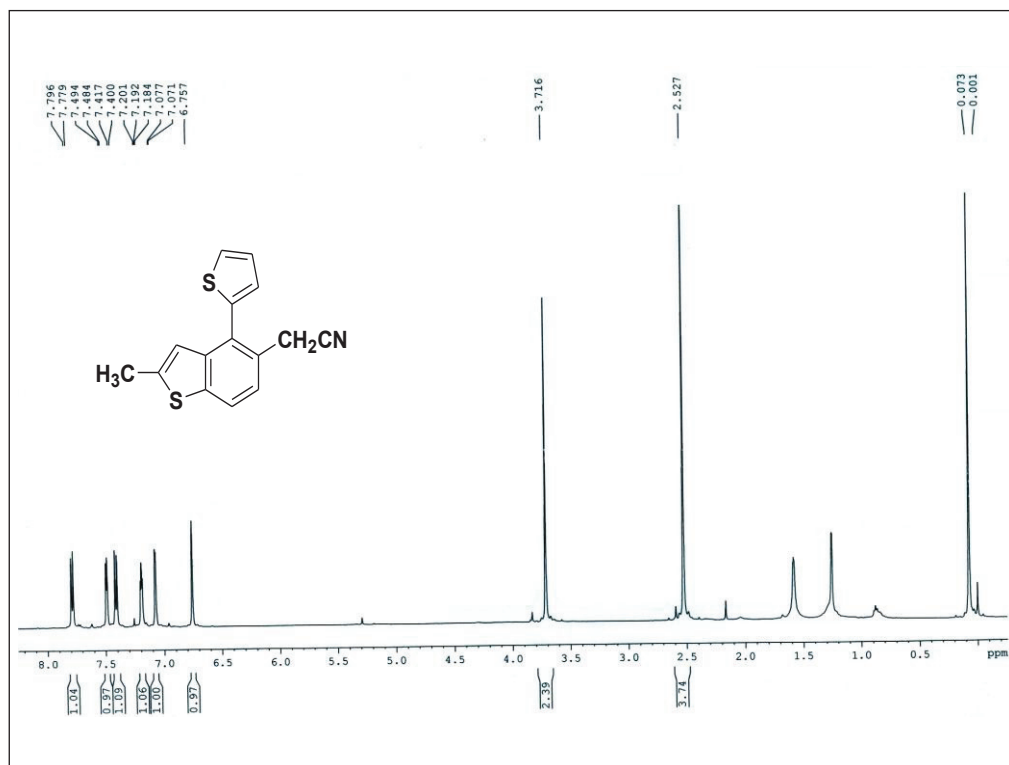
# <sup>1</sup>H NMR spectra of compound 19



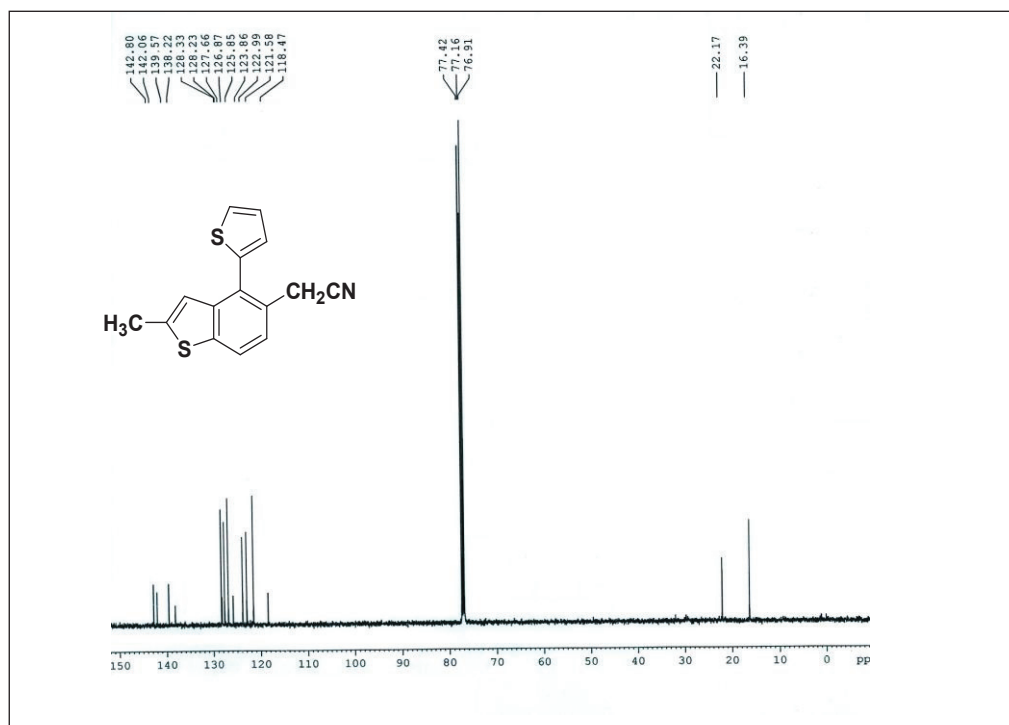
# <sup>13</sup>C NMR spectra of compound 19



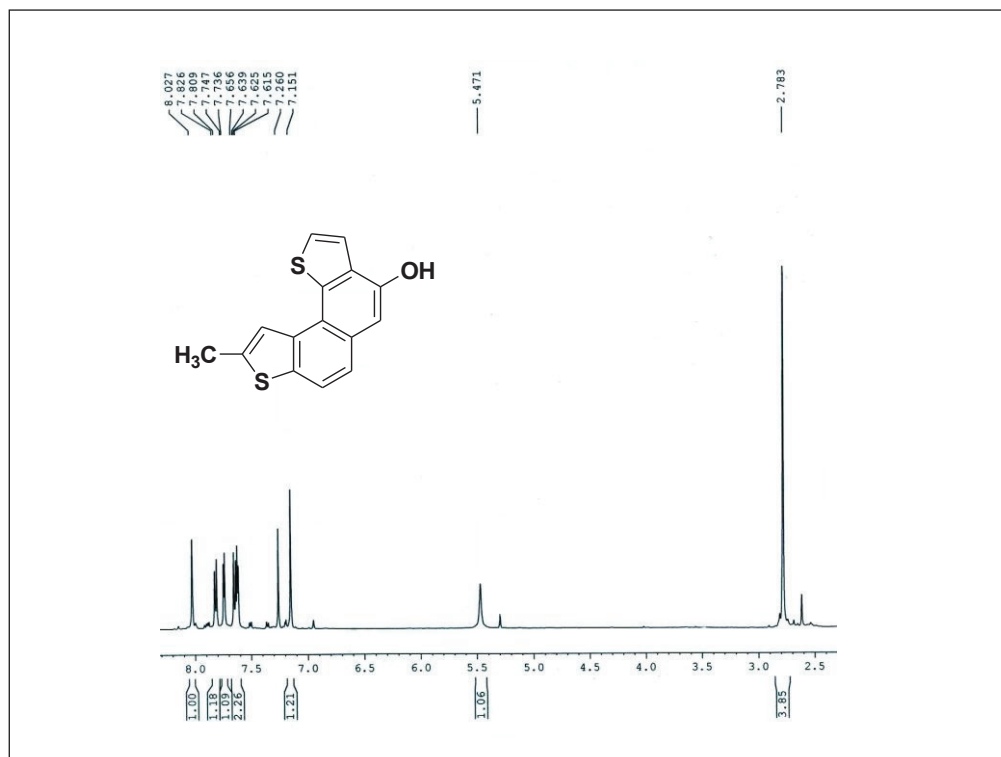
# <sup>1</sup>H NMR spectra of compound 20



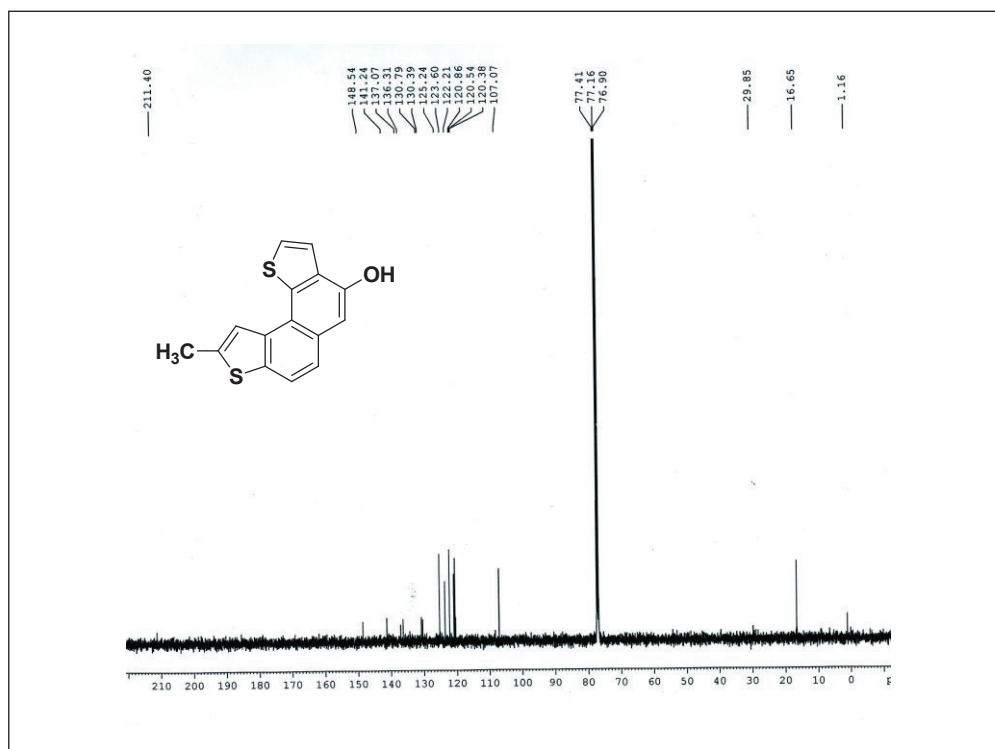
# <sup>13</sup>C NMR spectra of compound 20



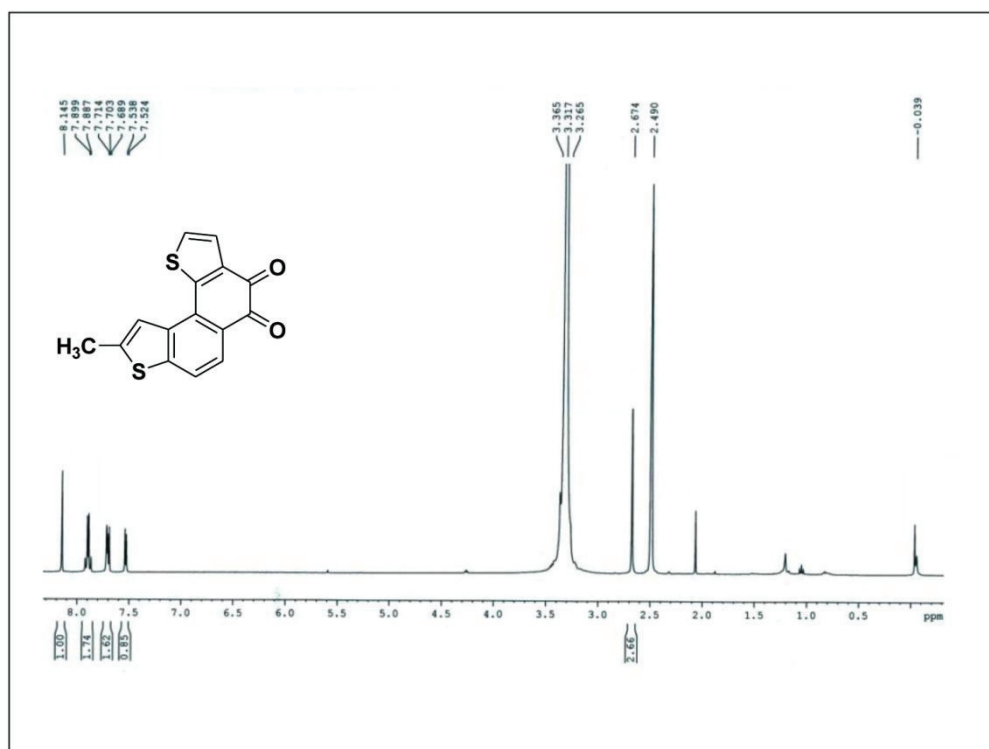
**<sup>1</sup>H NMR spectra of compound 22**



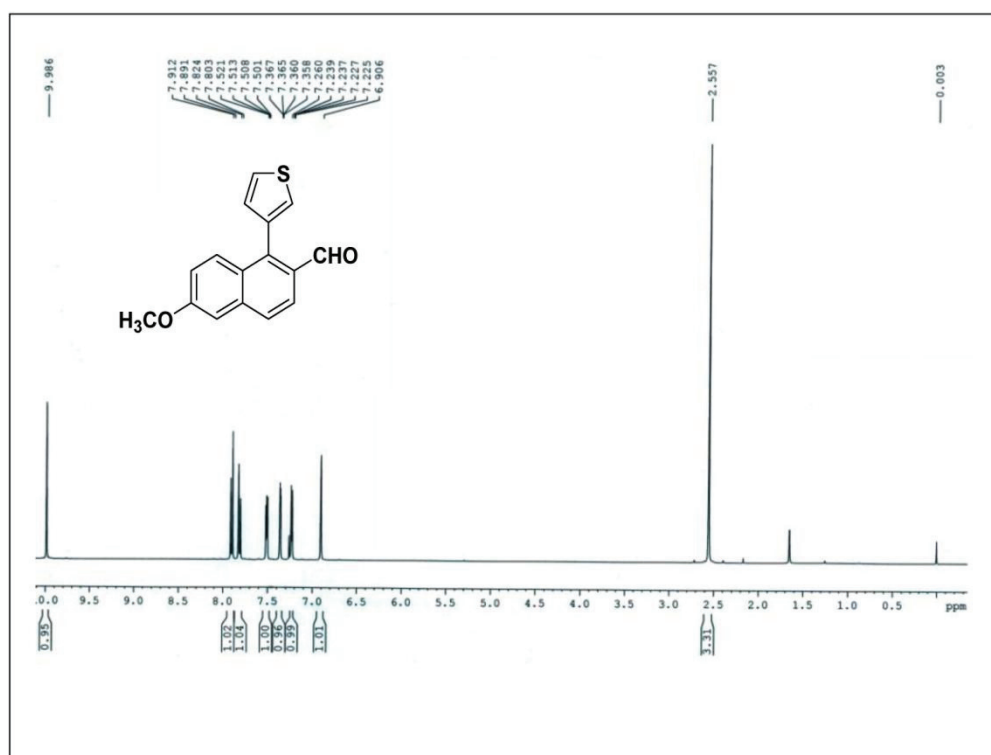
**<sup>13</sup>C NMR spectra of compound 22**



<sup>1</sup>H NMR spectra of compound 23

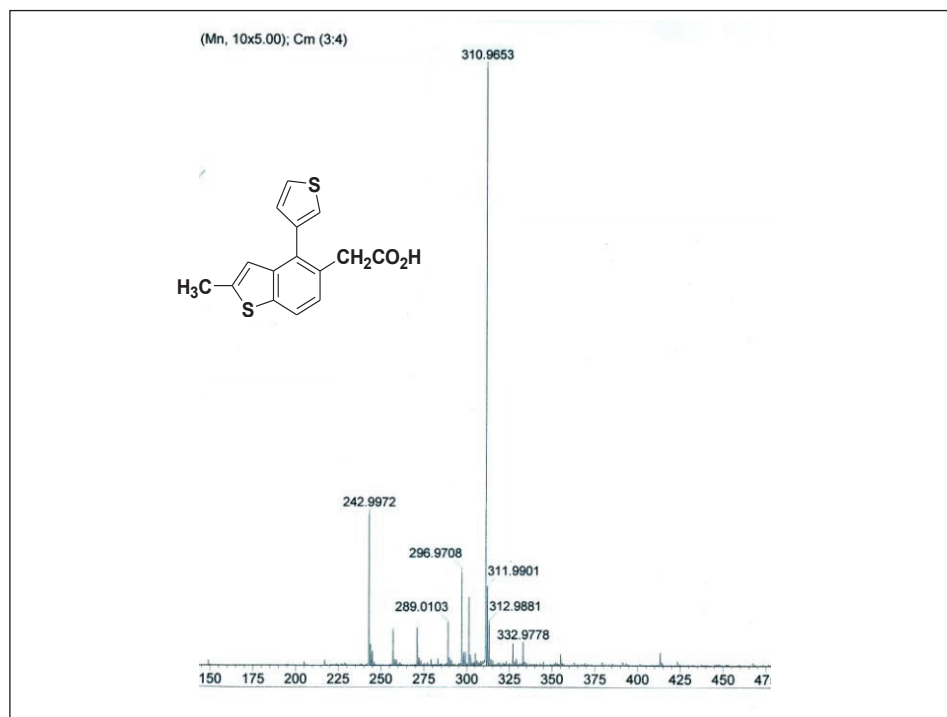


<sup>1</sup>H NMR spectra of compound 26

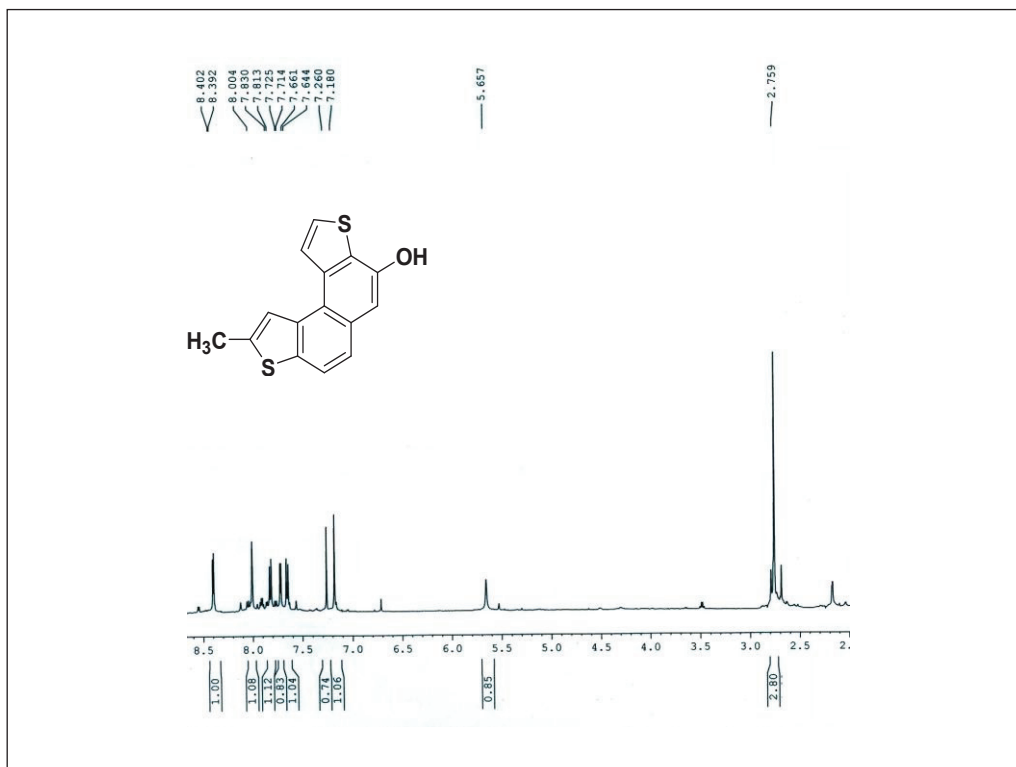




### HRMS data of Compound 28



### <sup>1</sup>H NMR spectra of compound 29



### <sup>1</sup>H NMR spectra of compound 30

