Chapter II

Suzuki reaction-based generalised studies towards the synthesis of 2-(2/3-thineyl)cycloalk-1-ene-1-carbaldehyde derivatives and its implication towards the synthesis of condensed thienophenanthraquinones and thienonaphthoquinones

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3.1 Introduction

Second chapter of the thesis describes the synthesis of thiophene analogues [phenanthro[4,3-*b*]thiophene-4,5-dione derivatives (**25d-f**) and 10-methoxyphenanthro[3,4-*b*]thiophene-4,5-dione (**31**)] (fig. 1) of 'U'-shaped furophenanthraquinones simulating ABCD rings of isotanshinone II, following the methodology as used in previous chapter. In this work, the D ring of the isotanshinone II core nucleus has been modified by replacing the furan ring with thiophene ring.

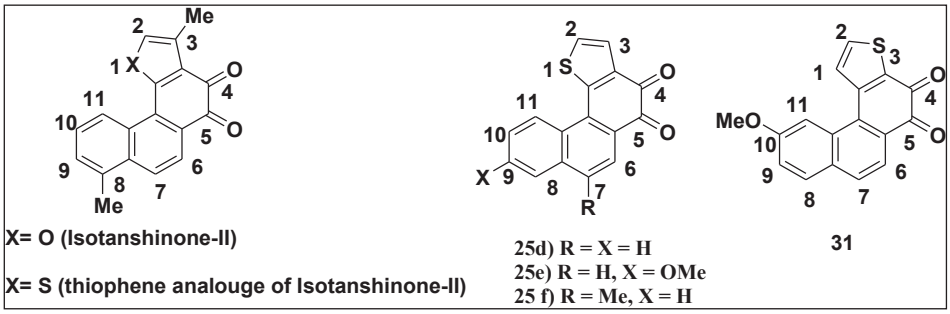
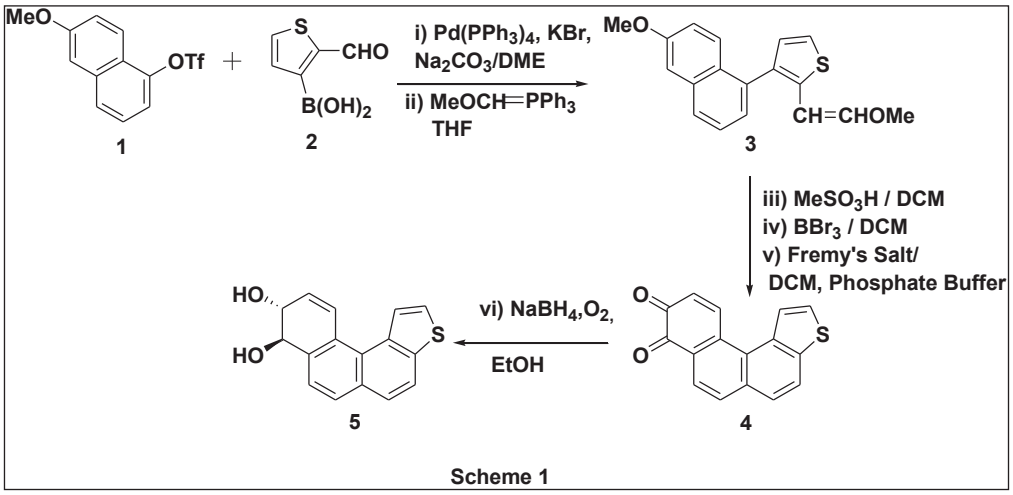
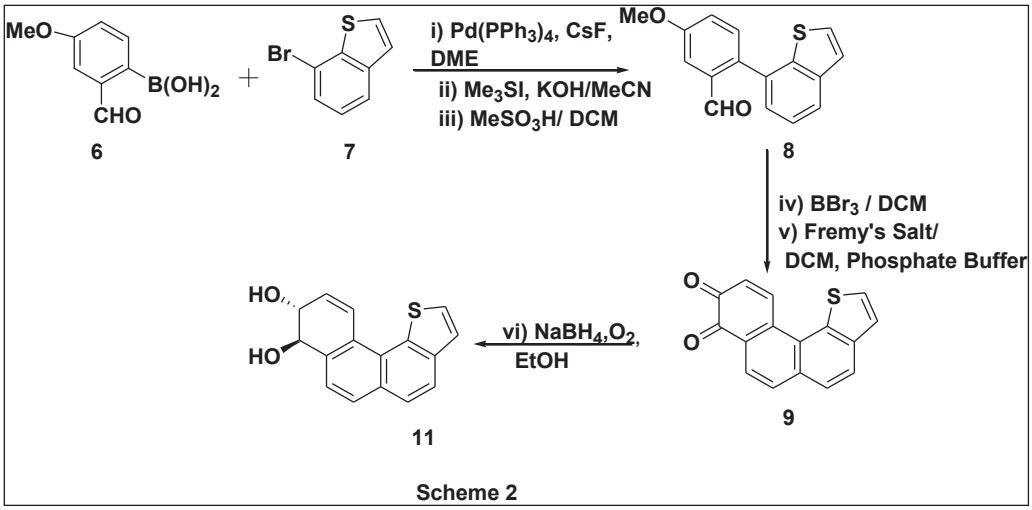


Figure 1: Isotanshinone II and its thiophene analogues

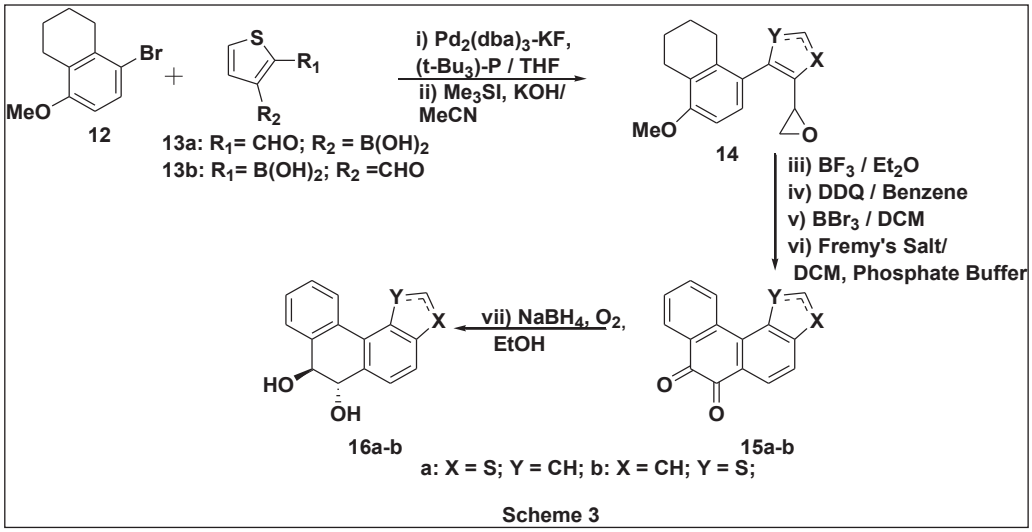
To our surprise, the synthesis of phenanthro[4,3-*b*]thiophene-4,5-dione derivatives are not available in the literature, although in connection with the study of the mutagenic activities of *trans*-dihydrodiol derivatives of phenanthro[3,4-*b*]thiophene and phenanthro[4,3-*b*]thiophene, synthesis of phenanthro[3,4-*b*]thiophene-8,9-dione (**4**), phenanthro[4,3-*b*]thiophen-8,9-dione (**9**), phenanthro[3,4-*b*]thiophen-6,7-dione (**15a**) and phenanthro[4,3-*b*]thiophen-6,7-dione(**15b**) intermediates have been reported.[1-3] S. Kumar and his co-workers achieved the synthesis of these intermediate quinones following the schemes 1-3, respectively.



Scheme 1



Scheme 2



Scheme 3

For the synthesis of hitherto unknown phenanthro[4,3-*b*]thiophene-4,5-dione derivatives **25** and 10-methoxyphenanthro[4,3-*b*]thiophene-4,5-dione (**31**), the methodology, as used in previous chapter, may be a proper pathway and we have explored it. Suzuki reaction[4] with commercially available 2/3-thiopheneboronic acid to form the aryl-thieny bond is one of the key step towards the synthesis of target molecules (fig. 2).

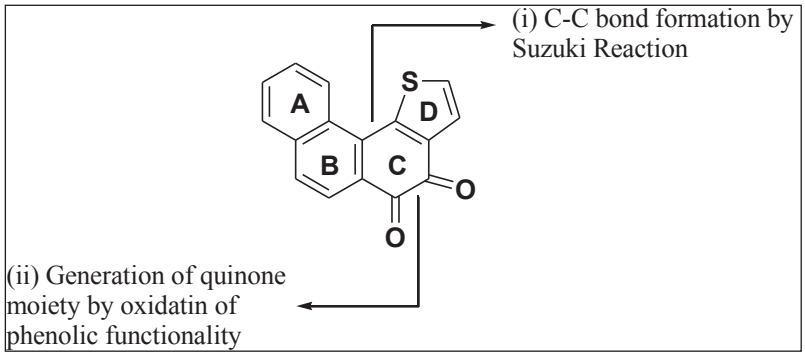
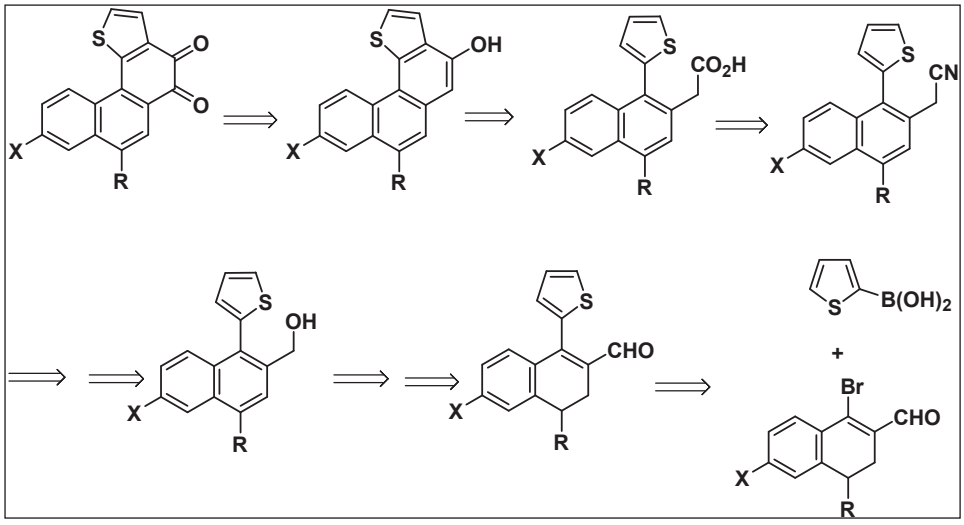


Figure 2: Synthetic strategy for 'U'-shaped thienophenanthraquinones

As usual, the retrosynthesis of the phenanthro[4,3-*b*]thiophene-4,5-dione derivatives (thienophenanthraquinones) reveals that the synthesis may be achieved from 1-bromo-3,4-dihydronaphthalene-2-carbaldehydes and 2-thiopheneboronic acid (scheme 4).



Scheme 4: Retrosynthesis of phenanthro[4,3-*b*]thiophene-4,5-dione derivatives

In this connection, first of all, detailed studies of Suzuki reaction between β-bromo-α,β-unsaturated carbaldehydes and thiopheneboronic acids were necessary. Thus, the chapter II was divided in three subsections IIA, IIB and IIC, in which chapter IIA described a generalised study on Suzuki reaction of various β-bromo-α,β-unsaturated carbaldehydes with 2/3-thiopheneboronic acids.

Chapter IIA

Suzuki reaction-based generalised studies towards the synthesis of 2-(2/3-thineyl)cycloalk-1-ene-1-carbaldehyde derivatives

Suzuki reaction-based generalised studies towards the synthesis of 2-(2/3-thineyl)cycloalk-1-ene-1-carbaldehyde derivatives

4.1 Introduction

For the synthesis of various thienophenanthraquinones like phenanthro[4,3-*b*]thiophene-4,5-dione or phenanthro[3,4-*b*]thiophene-4,5-dione derivatives, various 2-(2/3-thienyl)cycloalk-1-ene-1-carbaldehyde derivatives might be the possible building blocks.

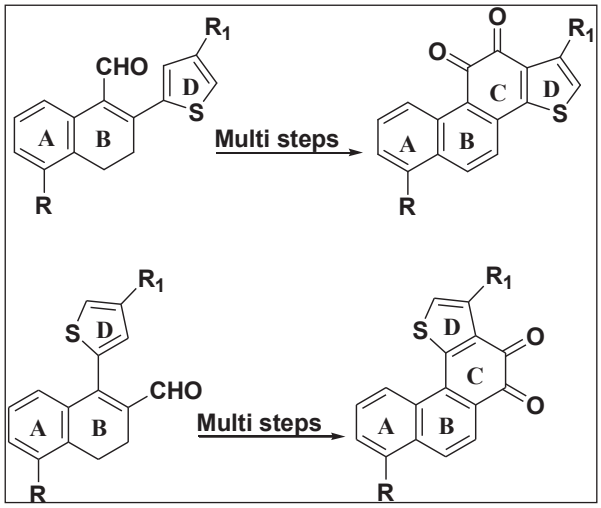
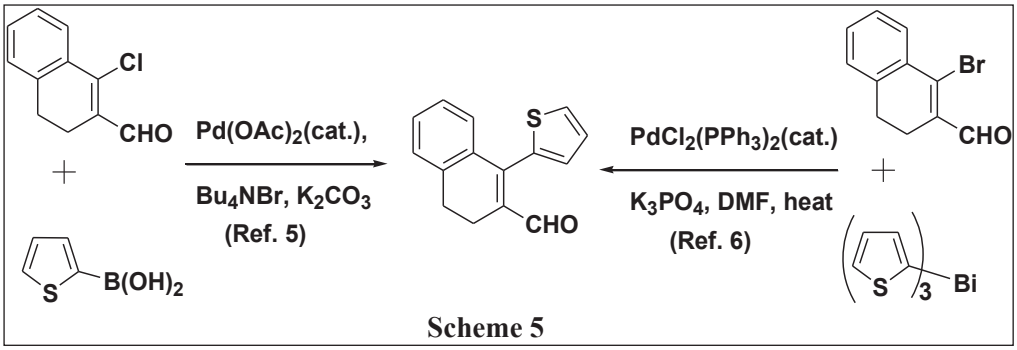


Figure 3: Possible building blocks for the synthesis of thienophenanthraquinones

So far, only two isolated examples of the synthesis of 3,4-dihydro-1-(2-thienyl)naphthalene-2-carbaldehyde have been reported in the literature.[5,6] Hesse and Kirsch[5] reported the synthesis of 3,4-dihydro-1-(2-thienyl)naphthalene-2-carbaldehyde using Suzuki coupling of 3,4-dihydro-1-chloronaphthalene-2-carbaldehyde and 2-thiopheneboronic acid, while the same thienylated naphthaldehyde has also been synthesised by M. N. L. Rao *et al.* by coupling of 1-bromo-3,4-dihydronaphthalene-2-carbaldehyde and organobismuth reagent, trithienylbismuth[6] (scheme 5).



Scheme 5

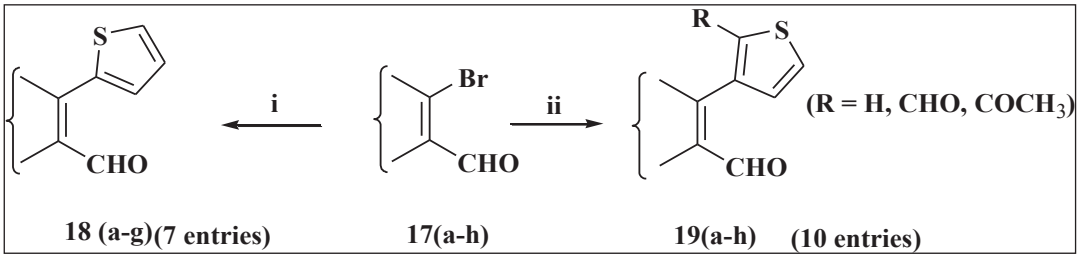
Thus, no generalised studies on such thienylation using Suzuki Reaction have yet been taken up by any group prior to our work. Also the report of Rao *et al.*[6] used toxic organobismuth compounds in their synthesis.[7]

4.2 Present Work

From our laboratory, G. K. Kar and his group have already reported a generalised route for the synthesis of β-(2-furyl)-α,β-unsaturated aldehydes[8] using Suzuki coupling of 2-bromocycloalk-1-ene-1-carbaldehydes and 2-furanboronic acid. As an extension of the methodology, in this chapter, comprehensive studies on the synthesis of 2-(2/3-thienyl)cycloalk-1-ene-1-carbaldehydes have been taken up *via* Pd(0)-catalysed Suzuki reaction of various 2-bromocycloalk-1-ene-1-carbaldehydes (which were prepared following standard protocol[8,9,10]) and 2/3-thiopheneboronic acids. The method is relatively simple, short and high yielding and the products have great potential as building blocks in synthetic organic chemistry.

4.3 Result and discussion

Thus the bromoaldehydes **17a-h** were subjected to Suzuki coupling with 2-thiopheneboronic acid or 3-thiopheneboronic acid derivatives in presence of $Pd(PPh_3)_4$ catalyst, Et_3N in DMF at 110-120 °C under N_2 atmosphere, and the respective thienylated aldehydes were obtained in good to excellent yields (table 1). As many as seventeen 2-(2/3-thienyl)cycloalk-1-ene-1-carbaldehyde derivatives 1**8a-g** and **19a-h** were synthesised from eight β-bromo-α,β-unsaturated aldehyde derivatives **17a-h** and four thiopheneboronic acids [2-thiophenelboronic acid (**A**), 3-thiopheneboronic acid (**B**), 2-formyl-3-thiopheneboronic acid (**C**) and 2-acetyl-3-thiopheneboronic acid (**D**)] to study the Suzuki reactions (scheme 6).



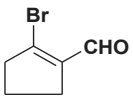
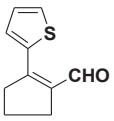
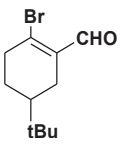
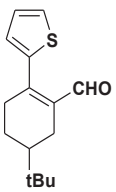
Reagents and conditions: i) 2-thiopheneboronic acid, $Pd(PPh_3)_4$ (1 mol %), Et_3N, DMF, 110-120 ^oC, 6.5-7 hrs under N_2 atm., 70-82 %; ii) optionally substituted 3-thiopheneboronic acid,

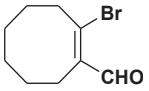
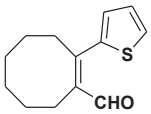
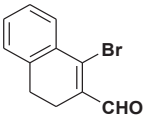
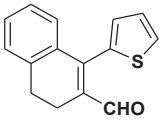
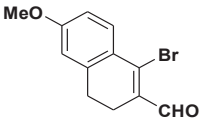
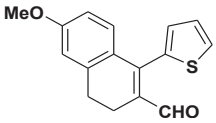
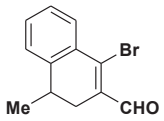
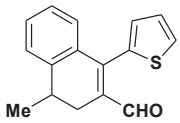
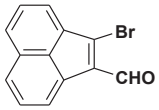
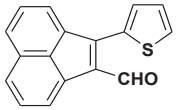
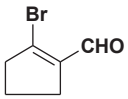
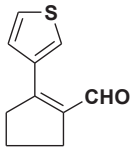
$Pd(PPh_3)_4$ (1 mol%), Et_3N, DMF, 110-120 ^oC, 4-12 hrs under N_2 atm., 55-90 %.

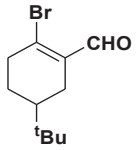
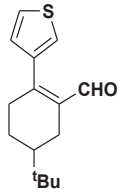
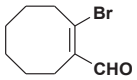
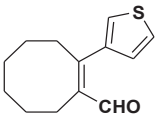
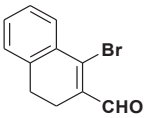
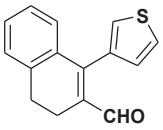
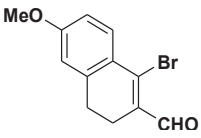
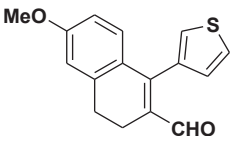
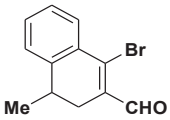
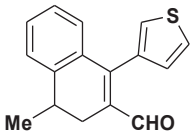
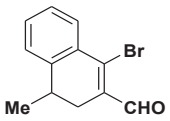
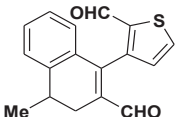
Scheme 6: Suzuki reactions of β-bromo-α,β-unsaturated aldehydes with 2/3-thiopheneboronic acid

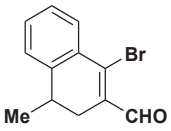
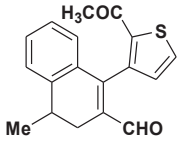
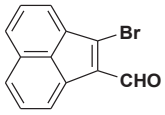
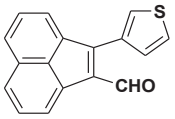
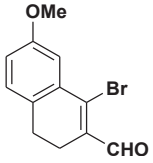
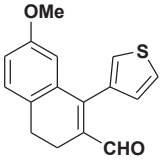
Thus when the bromoaldehyde **17f** was subjected to Suzuki reaction with 2-thiopheneboronic acid in anhydrous DMF in presence of Et_3N and $Pd(PPh_3)_4$ (1 mol %) as a catalyst under nitrogen atmosphere, 3,4-dihdro-4-methyl-1-(2-thienyl)naphthalene-2-carbaldehyde (**18f**) was obtained in 82 % yield (table 1, entry 6). The ^1H NMR ($CDCl_3$) spectra of **18f** showed signals at δ 1.20 (d, J = 7.2 Hz, 3H), 2.49 (dd, J = 7.6 Hz & 16.4 Hz, 1H), 2.65 (dd, J = 6.0 Hz & 16.4 Hz, 1H), 2.93-2.98 (m, 1H), 7.03-7.06 (m, 3H), 7.09 (ddd, J = 1.6 Hz, 7.2 Hz & 7.4 Hz, 1H), 7.20 (br d, J = 7.2 Hz, 1H), 7.25 (ddd, J = 1.6 Hz, 7.2 Hz & 7.4 Hz, 1H), 7.42 (dd, J = 1.2 & 5.2 Hz, 1H), 9.71 (s, 1H) ppm whereas ^{13}C NMR showed signals at δ 19.71, 28.21, 31.48, 126.30, 126.63, 127.08, 127.77, 128.41, 130.76, 130.84, 134.16, 135.35, 135.51, , 143.35, 146.29, 193.20 ppm for the 16 carbon atoms; these spectral data are in agreement with the assigned structure. In IR spectrum, a strong absorptions at 1655 cm^{-1} (characteristics of -CHO group) and HRMS data [*m/z* = 255.0835 $[M+H]^+$ (calcd. for $C_{16}H_{15}SO$: 255.0765) also supported the structure and confirmed the purity of compound **18f**.

Table-1

Entry No.	β-Bromo-α,β-unsaturated aldehyde	Boronic acid	Product	Time (hrs)	% yield
1	 **17a**	A	 **18a**	6	72
2	 **17b**	A	 **18b**	7	73

3	 **17c**	A	 **18c**	6	80
4	 **17d**	A	 **18d**	7	72
5	 **17e**	A	 **18e**	6.5	70
6	 **17f**	A	 **18f**	7	82
7	 **17g**	A	 **18g**	7	78
8	 **17a**	B	 **19a**	4	78

9	 **17b**	B	 **19b**		5.5	80
10	 **17c**	B	 **19c**		5	86
11	 **17d**	B	 **19d**		6.7	80
12	 **17e**	B	 **19e**		6	77
13	 **17f**	B	 **19f$_1$**		5	90
14	 **17f**	C	 **19f$_2$**		12	55

15	 **17f**	D	 **$19f_3$**	10	59
16	 **17g**	B	 **19g**	7	82
17	 **17h**	B	 **19h**	7	88

[*A = 2-thiopheneboronic acid; B = 3-thiopheneboronic acid; C = 2-formyl-3-thiopheneboronic acid; D = 2-acetyl-3-thiopheneboronic acid]

Other bromoaldehydes **17a-e** and **17g** on reactions with 2-thiopheneboronic acid, gave the corresponding thienylated compounds **18a-e** (entries 1-5) and **18g** (entry 7) in 70-80 % yield.

Similarly, bromoaldehydes **17a-h** on Suzuki coupling with 3-thiopheneboronic acid afforded compounds **19a-e, $19f_1$, 19g** and **19h** in 77-90 % yield under identical reaction conditions (entries 8-13, 16 and 17). Thus, 1-bromo-3,4-dihydro-7-methoxy-2-naphthalene-2-carbaldehyde (**17h**),[9,10] on Pd(0)-catalysed Suzuki coupling reaction with 3-thiopheneboronic acid in DMF at 100-110 °C produced 3,4-dihydro-7-methoxy-1-(3-thienyl)naphthalene-2-carbaldehyde (**19h**) in 88 % yield (entry no 17). IR spectra of compound **19h** showed an intense absorption at 1689 cm^{-1} (characteristics of α,β unsaturated CHO group). ^1H NMR (400 MHz, $CDCl_3$) of **19h** indicated the existence of atropisomers and the observed chemical shifts and splitting pattern for the protons are as follows: δ = 2.65 (t, J = 8.4 Hz, 2H), 2.81 (t, J = 8.4 Hz, 2H), 3.68 & 3.68 (both s, total 3H), 6.54 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 2.4 & 8.4 Hz, 1H), 7.05 (dd, J = 1.2 & 5.2 Hz, 1H), 7.16 (br d, J = 8.0 Hz, 1H), 7.30 (dd, J = 1.2 & 2.8 Hz, 1H), 7.44 (dd, J = 2.8 & 4.8 Hz, 1H),

9.69 & 9.68 (both s, total 1H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.94, 26.63, 55.32, 114.34, 114.98, 126.16, 126.91, 128.56, 129.63, 130.71, 135.06, 135.78, 135.92, 149.34, 158.29, 193.33 ppm and HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{16}H_{15}OS$: 271.0774; found: 271.0804 also are in conformity with the assigned structure. Tentative assignment of ^{1}H NMR chemical shift (δ, ppm) and splitting pattern of some of the representative thienylated products **18e**, **18f** and **19h** are depicted in fig. 4.

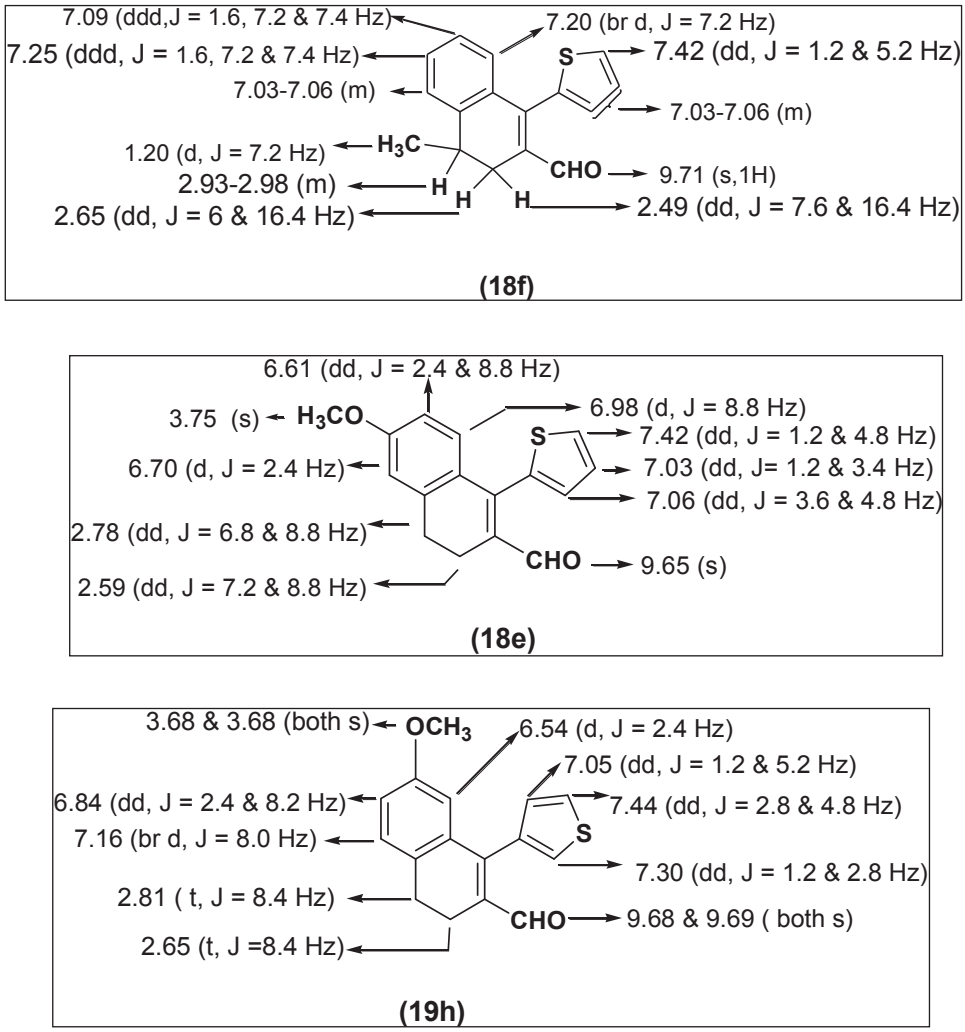


Figure 4: **Tentative assignment of ^{1}H NMR chemical shifts of compounds 18e, 18f and 19h**

In a similar way, thienylation of **17f** with substituted 3-thiopheneboronic acid derivatives such as 2-formyl-3-thiopheneboronic acid (**C**) or 2-acetyl-3-thiopheneboronic acid (**D**) also successfully furnished 3-(2-formyl-4-methyl-3,4-dihydronaphthalen-1-yl)thiophene-2-carbaldehyde (**19f$_2$**)

and 1-(2-acetyl-3-thienyl)-4-methyl-3,4-dihydronaphthalene-2-carbaldehyde (**19f$_3$**) respectively in moderate to good yields. However, the reactions required longer time (10-12 hrs) to reach completion (table 1, entries 14 and 15). In ^{1}H-NMR spectrum of **19f$_2$**, the aryl aldehyde proton showed two singlets at δ = 9.638 and 9.64 ppm (total 1H) and the heteroaryl aldehyde gave signals at δ = 9.585 and 9.596 ppm (total 1H), respectively. The methyl protons also appeared as a pair of doublets (J = 6.4 Hz) at δ = 1.299 and 1.315, respectively. The C_3 methylene proton and C_4 methyne proton compose a ABX spin systems and appeared (with complex splitting) at 2.618 (dd, J ~7.6 & 16.8 Hz), 2.73 (dd, J ~6.4 & 14.8 Hz) and 2.818 (dd, J ~ 6.4 & 16.8 Hz) (total 2H). For compound **19f$_3$**, the signals for the –CHO protons appeared at δ = 9.545 and 9.561 ppm (both singlet; total 1H), and those for the –$COCH_3$ protons appeared as two signals at δ = 2.282 and 2.350 ppm (both singlets; total 3H). In this case, two signals were also observed at δ = 1.337 and 1.366 ppm (both doublets, total 3H, J = 7.2 Hz), corresponding to the C_4-CH_3 protons. The methylene protons, as usual, like those of compound **19f$_2$,** appeared (with complex splitting) at 2.465 (dd, J ~ 9 & 16.8 Hz), 2.688 (dd, J ~ 6.6 & 14 Hz) and 2.805 (dd, J ~ 6.2 & 16.8 Hz) (total 2H). This might be due to the presence of atropisomers / rotamers in compounds **19f$_2$** and **19f$_3$**. In general, the yields of the Suzuki reactions, with 3-thiopheneboronic acid were higher than those with 2-thiopheneboronic acids. The compounds have been characterised by usual spectroscopic methods (vide experimental).

4.4 Conclusion

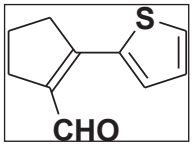
Thus, we have developed a general method for the synthesis of a large number of 2-(2-thienyl)-cycloalk-1-ene-1-cabalaldehydes as well as 2-(3-thienyl)-cycloalk-1-ene-1-cabalaldehyde derivatives. In total synthesis of seventeen 2-(2/3-thienyl)cycloalk-1-ene-1-carbaldehyde derivatives **18a-g** and **19a-h** have been achieved (table 1). This short, high yielding diversity-oriented method is relatively simple and has pronounced prospective for the synthesis of small molecules such as condensed tetracyclic thienophenanthraquinones, tricyclic thienonaphthraquinones and might also be useful for the synthesis of condensed thienophenanthrenol intermediates as bioisosters of the corresponding mutagenic polynuclear hydrocarbons. In compounds such as **19f$_2$** and **19f$_3$**, the two carbonyl functionalities can further be coupled (McMurry coupling) and thus can be good precursors for synthesis of polycyclic thiaarene derivatives too.

4.5 Experimental:

General procedure for the thienylation; preparation of 2-(2/3-thienyl)cycloalk-1-ene aldehyde (18 & 19)

A stirred mixture of 2-bromocycloalk-1-ene aldehyde (**17**) (1.0 mmol), thiopheneboronic acid (**A** or **B** or **C** or **D**) (1.2 mmol), triethylamine (2.5 mmol) in 2 ml of DMF was degasified for 25 minutes by bubbling N_2 through it. Now to it 1.0 mol % of $Pd(PPh_3)_4$ catalyst was added quickly and degasified for another 10-12 minutes. The mixture was then heated at 110-120 ^oC for 4 to 12 hours under N_2 atmosphere. When the reaction was completed (checked by TLC), the mixture was poured into ice water (15-20 ml) and extracted thoroughly with ether (3x20 ml). Organic layer was washed with ice water, 5 % aq. $NaHCO_3$ solution and finally with ice water. Removal of solvent under reduced pressure afforded the crude product which on purification by column chromatography (silica gel 100-200 mesh / pet ether (60-80 °C)-EtOAc, 15:1) and or by recrystallisation from suitable solvents furnished the compound **18** or **19** in 55-90 % yields. Yields and melting points of the products have been listed in the table-1. All the compounds were characterized by usual spectroscopic analysis (IR/NMR/HRMS/LCMS).

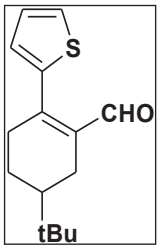
2-(2-Thienyl)cyclopent-1-ene-1-carbaldehyde (18a)



Light yellow viscous oil, yield 72 % [128 mg (0.72 mmol) of **18a** was obtained from 175 mg (1 mmol) of **17a**]. IR (KBr) ν_{max}: 1653 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.0 (quintet, J = 7.6 Hz, 2H), 2.78 (t, J = 7.6 Hz, 2H), 3.04 (t, J = 7.6 Hz, 2H), 7.11 (dd, J = 4.0 Hz & 5.0 Hz,1H), 7.27 (br d, J ~ 4.5 Hz, 1H), 7.46 (d, J = 5.0 Hz, 1H), 10.32 (s, 1H) ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{10}H_{11}SO$: 179.0531; found: 179.0619.

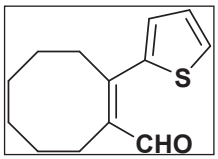
5-(*Tert*-butyl)-2-(2-thienyl)cyclohex-1-ene-1-carbaldehyde (18b)

Colourless solid, yield 73 % [181 mg (0.73 mmol) of **18b** was obtained from 245 mg (1 mmol) of **17b**], mp: 68-70 °C; IR (KBr) ν_{max}: 1667 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 0.93 (s, 9H), 1.26-1.33 (m, 2H), 1.94-1.97 (m, 2H), 2.61-2.72 (m, 3H), 6.99-7.05 (m, 2H), 7.41 (dd, J = 0.9 Hz & 4.5 Hz, 1H), 9.78 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.94, 24.83, 27.22, 32.31,



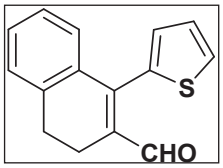
36.03, 43.25, 127.12, 127.49, 129.55, 137.44, 140.62, 150.19, 193.08 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{15}H_{21}SO$: 249.1313; found: 249.1705.

2-(2-Thienyl)cyclooct-1-ene-1-carbalaldehyde (18c)



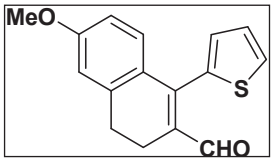
Faint yellow viscous oil; yield: 176 mg (80 %, 0.8 mmol). IR (KBr) ν_{max}: 1660 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.40-1.41 (m, 4H), 1.53 (m, ill split, 2H), 1.63 (m, ill split, 2H), 2.48 (t, J = 6.0 Hz, 2H), 2.68 (t, J = 6.3 Hz, 2H), 6.88-6.95 (m, 2H), 7.33 (dd, J = 1.2 Hz & 5.1 Hz, 1H), 9.58 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 24.94, 26.09, 26.69, 29.13, 30.02, 36.21, 126.98, 127.81, 130.47, 140.67, 140.76, 153.68, 192.65 ppm; HRMS (ESI+): *m/z* $[M+H]^+$calcd. for $C_{13}H_{17}SO$: 221.0922; found: 221.0997.

3,4-Dihydro 1-(2-thienyl)naphthalene-2-carbaldehyde (18d)



Colourless solid; yield: 173 mg (72 %, 0.72 mmol), mp. : 84-86 °C. IR (KBr) ν_{max}: 1655cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.60 (dd, J = 7.2 Hz & 9.2 Hz, 2H), 2.79 (dd, J = 7.2 Hz & 14.4 Hz, 2H), 7.01-7.04 (m, 2H), 7.06 (dd, J = 3.6 Hz & 5.2 Hz, 1H), 7.10 (br d, J = 8 Hz, 1H), 7.16 (br. d, J = 1.2 Hz, 1H), 7.20-7.24 (m, 1H), 7.42 (dd, J = 1.2 Hz & 5.2 Hz, 1H), 9.70 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.78, 27.41, 126.79, 127.07, 127.79, 128.18, 130.47, 130.66, 135.00, 135.37, 136.90, 138.38, 146.78, 192.94 ppm (one carbon signal not observed probably due to insufficient number of scanning); HRMS (ESI+): *m/z* $[M+H]^+$calcd. for $C_{15}H_{13}SO$: 241.0690: found: 241.0682 & [M+Na] calcd. for $C_{15}H_{12}SONa$: 263.0507: found: 263.0498

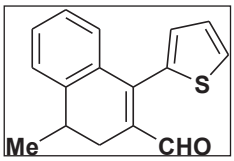
3,4-Dihydro-6-methoxy-1-(2-thienyl)naphthalene-2-carbaldehyde (18e)



Light orange solid; yield: 189 mg (70 %, 0.7 mmol); mp.: 80-82 °C. IR (KBr) ν_{max}: 1656 cm^{-1}; H NMR (400 MHz, $CDCl_3$): δ = 2.59 (dd, J = 7.2 Hz & 8.8 Hz, 2H), 2.78 (dd, J = 6.8 Hz & 8.8 Hz, 2H), 3.75 (s, 3H), 6.61 (dd, J = 2.4 Hz & 8.8 Hz, 1H), 6.70 (d, J = 2.4 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 7.03 (dd , J= 1.2 Hz & 3.4 Hz, 1H), 7.06 (dd, J = 3.6 Hz & 4.8 Hz, 1H), 7.42 (dd, J = 1.2 Hz & 4.8 Hz, 1H), 9.65 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.69, 27.96, 55.39,

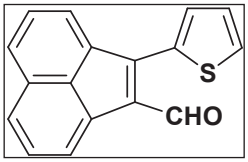
111.73, 113.64, 126.98, 127.62, 128.00, 130.07, 130.61, 134.71, 135.71, 140.72, 146.93, 161.38, 192.69 ppm; HRMS (ESI+): *m/z* $[M+H]^+$calcd. for $C_{16}H_{15}SO_2$: 271.0715: found: 271.0786.

3,4-Dihydro-4-methyl-1-(2-thienyl)naphthalene-2-carbaldehyde (18f)



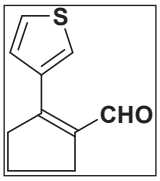
Pale yellow solid; yield: 208 mg (82 %, 0.82 mmol); m.p. 90-92 °C. IR (KBr) ν_{max}: 1655 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.20 (d, J = 7.2 Hz, 3H), 2.49 (dd, J = 7.6 Hz & 16.4 Hz, 1H), 2.65 (dd, J = 6.0 Hz & 16.4 Hz, 1H), 2.93- 2.98 (m,1H), 7.03-7.06 (m, 3H), 7.09 (ddd, J = 1.6 Hz, 7.2 Hz & 7.4 Hz, 1H), 7.20 (br. d, J = 7.2 Hz, 1H), 7.25 (ddd, J = 1.6 Hz, 7.2 Hz & 7.4 Hz, 1H), 7.42 (dd, J = 1.2 Hz & 5.2 Hz, 1H), 9.71 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.71, 28.21, 31.48, 126.30, 126.63, 127.08, 127.77, 128.41, 130.76, 130.84, 134.16, 135.35, 135.51, 143.35, 146.29, 193.20 ppm; HRMS (ESI+): *m/z* $[M+H]^+$calcd. for $C_{16}H_{15}SO$: 255.0765: found: 255.0835.

2-(2-Thienyl)acenaphthylene-1-carbaldehyde (18g)



Orange solid; yield: 204 mg (78 %, 0.78 mmol); mp.: 100-102 °C. IR (KBr) ν_{max}: 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.15 (dd, J = 5.2 Hz & 3.6 Hz, 1H), 7.38 (dd, J = 3.6 Hz & 0.8 Hz, 1H), 7.48-7.52 (m, 2H), 7.54 (d, J = 6.8 Hz, 1H), 7.73 (d, J = 8.4 Hz, 1H), 7.88 (d, J = 8.0 Hz, 1H), 7.98 (d, J = 6.8 Hz, 1H), 8.31 (d, J = 6.8 Hz, 1H), 10.34 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 127.55, 127.87, 127.96, 128.12, 128.23, 128.47, 128.78, 128.80, 129.63, 130.57, 131.52, 132.95, 134.02, 135.58, 137.32, 146.61, 189.41 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{17}H_{11}SO$: 263.0452; found: 263.0250.

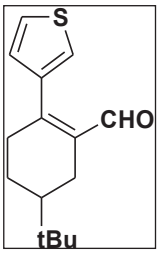
2-(3-Thienyl)cyclopent-1-ene-1-carbaldehyde (19a)



Pale yellow oil, yield 78 % [139 mg (0.78 mmol) of **19a** was obtained from 175 mg (1 mmol) of **17a**]. IR (KBr) ν_{max}: 1650 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 1.86 (quin, J = 7.8 Hz, 2H), 2.59-2.65 (m, 2H), 2.82-2.81 (m, 2H), 7.08 (dd, J =

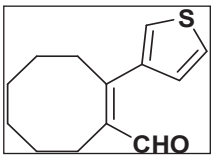
1.2 Hz & 4.8 Hz, 1H), 7.24-7.30 (m, 2H), 9.93 (s, 1H,) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.30, 30.90, 39.25, 125.8, 126.21, 127.57, 135.62, 138.69, 155.45, 189.45 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{10}H_{11}SO$: 179.0452: found: 179.0523.

5-*Tert*-butyl-2-(3-thienyl)cyclohex-1-ene-1-carbaldehyde (19b)



Colourless solid; yield: 198 mg (80 %, 0.8 mmol); mp.: 70-72 °C. IR (KBr) ν_{max}: 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.84 (s, 9H), 1.15-1.22 (m, 2H), 1.80-1.89 (m, 2H), 2.44-2.62 (m, 3H), 6.95 (dd, J = 1.6 Hz & 6.4 Hz, 1H), 7.08 (dd, J = 1.6 Hz & 4.0 Hz, 1H), 7.34 (dd, J = 4.0 Hz & 6.8 Hz, 1H), 9.58 (s, 1 H) ppm; ^{13}C NMR (400 MHz, $CDCl_3$): δ = 23.67, 24.25, 27.13, 32.28, 34.74, 43.24, 125.01, 125.85, 127.95, 136.65, 139.27, 153.16, 193.39 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{15}H_{21}SO$: 249.1235: found: 249.1952.

2-(3-Thienyl)cyclooct-1-ene-1-carbaldehyde (19c)



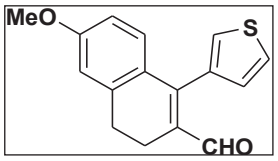
Pale yellow oil, yield 86 % [189 mg (0.86 mmol) of **19c** was obtained from 217 mg (1 mmol) of **17c**]; IR (KBr) ν_{max}: 1668 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.39 (br s, ill split, 4H), 1.52 (br s, ill split, 4H), 2.43 (t, J ~ 6.0 Hz, 2H), 2.58 (t, J~ 6.0 Hz, 2H), 6.93 (dd, J~ 1.2 Hz & 5.0 Hz, 1H), 7.04 (dd, J = 1.6 Hz & 3.0 Hz, ill split, 1H), 7.23 (dd, J ~3.0 Hz & 5.0 Hz, 1H), 9.45 (s, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 23.93, 26.00, 26.39, 28.75, 29.59, 34.65, 125.29, 125.81, 127.65, 139.18, 139.67, 156.25, 192.53 ppm. HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{13}H_{17}SO$: 221.0922; found: 221.0478.

3,4-Dihydro-1-(3-thienyl)naphthalene-2-carbaldehyde (19d)

Faint yellow solid; yield: 192mg (80 %, 0.8mmol); mp.: 80-82 °C. IR (KBr) ν_{max}: 1655 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.60 (dd, J = 7.6 Hz & 8.6 Hz, 2H), 2.82 (t, J ~ 7.5 Hz, 2H), 6.89 (d, J = 7.6 Hz, 1H), 6.98 (dd, J = 0.8 Hz and 4.0 Hz, 1H), 7.08 (t, J = 7.6 Hz, 1H), 7.18 (t, J = 7.6 Hz,1H), 7.23 (dd, J = 1.2 Hz & 2.4 Hz, 1H), 7.24 (d, J = 1.2 Hz, 1H), 7.38 (dd, J = 2.8 Hz & 4.8 Hz, 1H), 9.62 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.54, 27.54, 126.08, 126.72, 126.82, 127.87, 128.16,

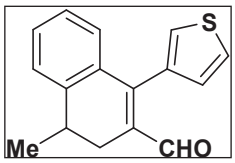
128.60, 129.68, 130.35, 132.33, 135.19, 135.50, 138.62, 193.31 ppm; HRMS (ESI+): *m/z* $[M+H]^+$calcd. for $C_{15}H_{13}SO$: 241.0690; found: 241.0684.

3,4-Dihydro-6-methoxy-1-(3-thienyl)naphthalen-2-carbaldehyde (19e)



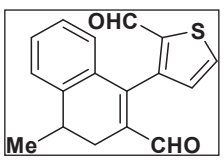
Light orange solid; yield: 208 mg (77 %, 0.77 mmol); mp. : 74-76 °C. IR (KBr) ν_{max}: 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.58 (t, J ~ 8.0 Hz, 2H), 2.78 (t, J ~ 8.0 Hz, 2H), 3.75 (s, 3H), 6.59 (dd, J = 2.4 Hz & 8.6 Hz, 1H), 6.71 (d, J = 2 Hz, 1H), 6.83 (d, J = 8.8 Hz, 1H), 6.97 (br. d, J = 4.8 Hz, ill split, 1H), 7.22 (dd,J = 1.2 Hz & 2.4 Hz, 1H), 7.36 (dd, J = 3.2 Hz & 4.4 Hz, 1H), 9.56 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.46, 28.10, 55.39, 111.70, 113.68, 125.92, 126.65, 127.74, 129.72, 130.00, 133.42, 135.48, 140.92, 149.64, 161.29, 193.00 ppm; HRMS (ESI+): *m/z* $[M+H]^+$calcd. for $C_{16}H_{15}SO_2$: 271.0715; found: 271.2341.

3,4-Dihydro-4-methyl-1-(3-thienyl)naphthalen-2-aldehyde ($19f_1$)



Pale yellow solid, yield 90 % [228 mg (0.9 mmol) of **$3f_1$** was obtained from 251 mg (1 mmol) of **1f**]; mp.: 88-90 °C; IR (KBr) ν_{max}: 1650 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.12 (d, J = 7.2 Hz, 3H), 2.41 (dd, J = 7.2 Hz& 16.4 Hz, 1H), 2.58 (dd, J = 6.4 Hz & 16.4 Hz, 1H), 2.88 (sextet, J = 7.2 Hz, 1H), 6.85 (br d, J = 7.6 Hz, 1H), 6.89 (dd, J = 1.2 Hz & 5.0 Hz, 1H), 6.98 (ddd, J = 1.6 Hz, 7.2 Hz & 7.8 Hz, 1H), 7.12 -7.15 (m, 2H), 7.17 (ddd, J = 0.8 Hz, 7.2 Hz & 7.8 Hz, 1H), 7.27 (dd, J ~ 3.0 Hz & 4.8 Hz, 1H), 9.57 (s, 1H) ppm; ^{13}C NMR (100MHz, $CDCl_3$): δ = 19.87, 28.08, 31.61, 126.15, 126.44, 126.64, 126.88, 128.41, 129.73, 130.76, 133.94, 134.06, 135.19, 143.57, 148.81, 193.30 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{16}H_{15}SO$: 255.0765; found: 254.8301 & [M+Na] calcd. for $C_{16}H_{14}SONa$: 277.0763; found: 276.7933.

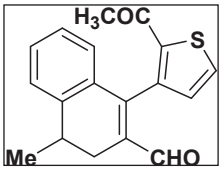
3-(2-Formyl-4-methyl-3,4-dihydronaphthalen-1-yl)thiophene-2-carbaldehyde ($19f_2$)



Yellow viscous oil; yield: 155 mg (55 % , 0.55 mmol); IR (KBr) ν_{max}: 1654 cm^{-1} (broad and strong); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.299 and 1.315 (d, J = 6.4 Hz, total 3H), 2.618 (dd, J ~7.6 & 16.8 Hz), 2.73 (dd, J ~ 6.4 & 14.8 Hz) and 2.818 (dd, J ~ 6.4 & 16.8 Hz) (total 2H), 3.09-3.16 (m, 1H),

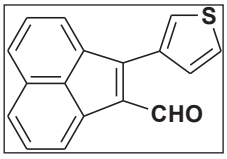
6.81 (d, J = 7.6 Hz, 1H), 7.14-7.18 (m, 2H), 7.33-7.38 (m, 2H), 7.88 (dd, J = 1.2 & 4.4 Hz, ill split, 1H), 9.585 & 9.596 (both s, total 1H), 9.638 and 9.64 (both s, total 1H) ppm; MS (ES+): *m/z* 283.0 $[M+H]^+$, 255.0, 237.0, 212.9 (purity of the sample as per LCMS was found to be 97.73%).

4-Methyl-1-(2-acetyl-3-thienyl)-3,4-dihydronaphthalen-2-aldehyde (19f$_3$)



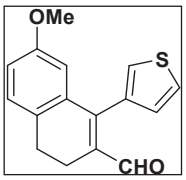
Pale yellow oil, yield 59 % [175 mg (0.59 mmol) of **19f$_3$** was obtained from 250 mg (~1 mmol) of **1f**]; IR (KBr) ν_{max}: 1653 cm^{-1}(broad and strong); ^1H NMR (400 MHz, $CDCl_3$): δ = 1.337 & 1.366 (total 3H, both as d, J = 7.2 Hz), 2.282 & 2.350 (total 3H, both as s), 2.465 (dd, J ~9 & 16.8 Hz), 2.688 (dd, J ~ 6.6 & 14 Hz) and 2.805 (dd, J ~ 6.2 & 16.8 Hz) (total 2H), 3.09-3.14 (m, 1H), 6.90 & 6.74 (total 1H, both as d, J = 7.6 Hz), 7.04 (d, J = 4.8 Hz, 1H), 7.08-7.15 (m, 1H), 7.29-7.37 (m, 2H), 7.71 & 7.94 (total 1H, both d, J = 5.2 Hz), 9.545 and 9.561 (both singlet, total 1H); MS (ES+): *m/z* 297.0 $[M^+$+H], 269.0, 237.0 (purity of the sample as judged by LCMS: 97.88%).

2-(3-Thienyl)acenaphthylene-1-carbaldehyde (19g)



Orange solid; yield: 215 mg (82 %, 0.82 mmol); mp.: 104-106 °C. IR (KBr) ν_{max}: 1644 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 7.49 (d, J = 4.5 Hz, 1H), 7.58 (dd, J = 3.0 Hz & 5.7 Hz, 1H), 7.65-7.70 (m, 3H), 7.90 (d, J = 8.5 Hz, 1H), 8.0 (d, J = 7.0 Hz, 1H), 8.05 (d, J = 8.5 Hz, 1H), 8.44 (d, J = 6.5 Hz, 1H), 10.36 (s, 1H) ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{17}H_{11}SO$: 263.0452; found: 263.0354.

3,4-Dihydro-7-methoxy-1-(3-thienyl)naphthalen-2-carbaldehyde (19h)



Yellow solid; yield: 88 % (620 mg / 2.3 mmol of **17h** produced 550 mg / 2.04 mmol of **19h**); mp.: 110-112 °C; IR (KBr) ν_{max}: 1689 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.65 (t, J = 8.4 Hz, 2H), 2.81 (t, J = 8.4 Hz, 2H), 3.68 & 3.68 (both s, total 3H), 6.54 (d, J = 2.4 Hz, 1H), 6.84 (dd, J = 2.4 & 8.2 Hz, 1H), 7.05 (dd, J = 1.2 & 5.2 Hz, 1H), 7.16 (br d, J = 8.0 Hz, 1H), 7.30 (dd, J = 1.2 & 2.8 Hz, 1H), 7.44 (dd, J = 2.8 & 4.8 Hz, 1H), 9.69 & 9.68 (both s, total 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ =

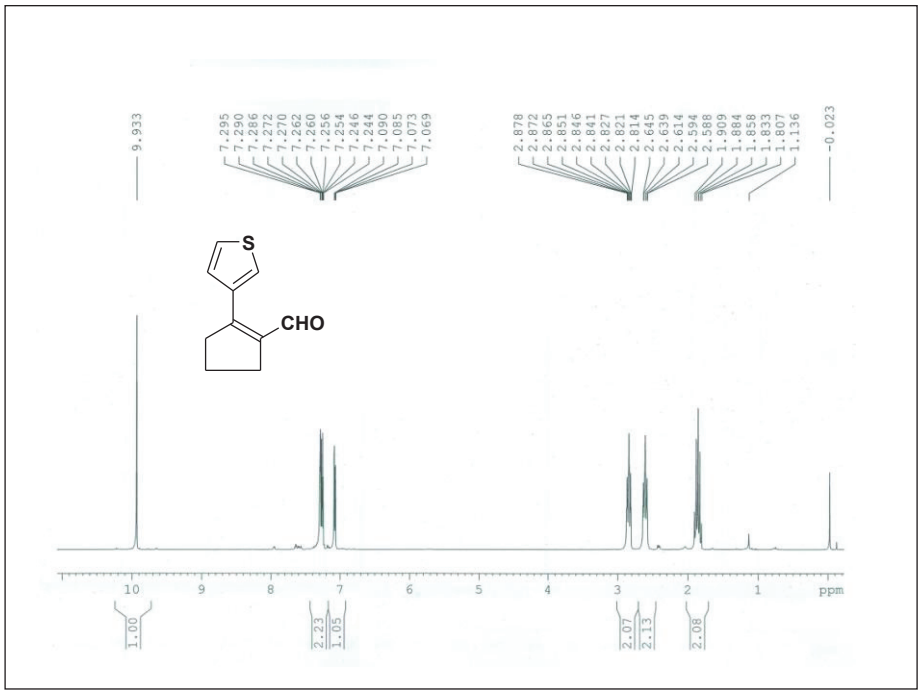
20.94, 26.63, 55.32, 114.34, 114.98, 126.16, 126.91, 128.56, 129.63, 130.71, 135.06, 135.78, 135.92, 149.34, 158.29, 193.33 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd. for $C_{16}H_{15}OS$: 271.0774; found: 271.0804.

4.6 Publication:

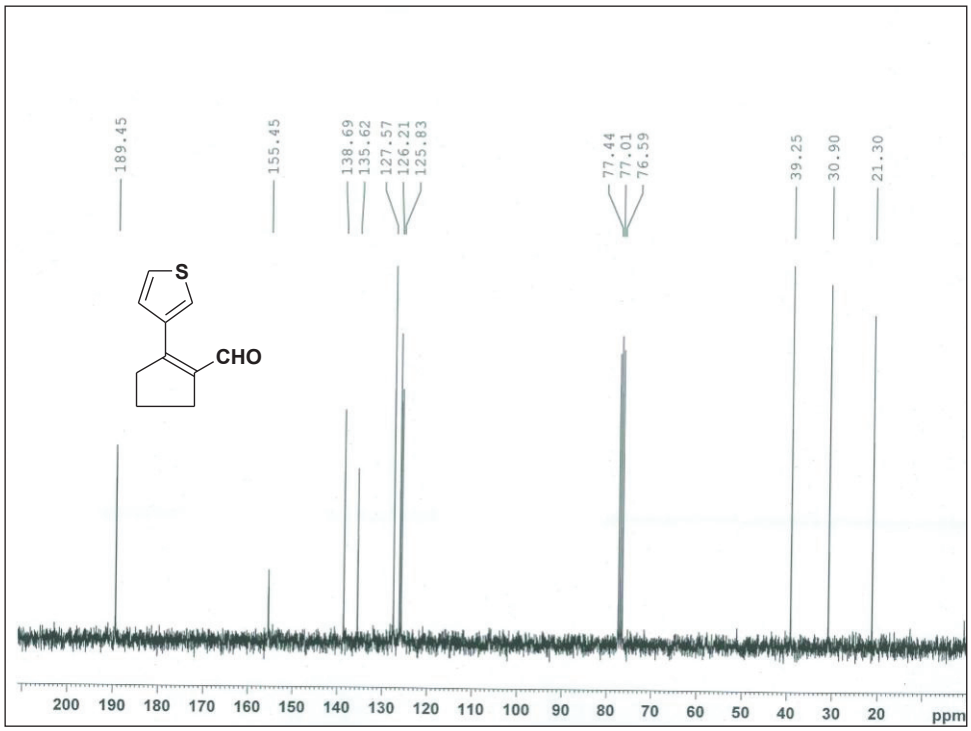
'*A Suzuki-Coupling-Based Generalized Route for the Synthesis of 2-(2/3-thienyl)-cycloalk-1-ene-1-carbaldehydes as Precursors for Condensed Thienophenanthraquinones*' Aparna Sarkar, Rumpa Das, Gandhi K. Kar; ***Synlett* 2018**, *29*, 344-348.

4.7 Selected Spectra

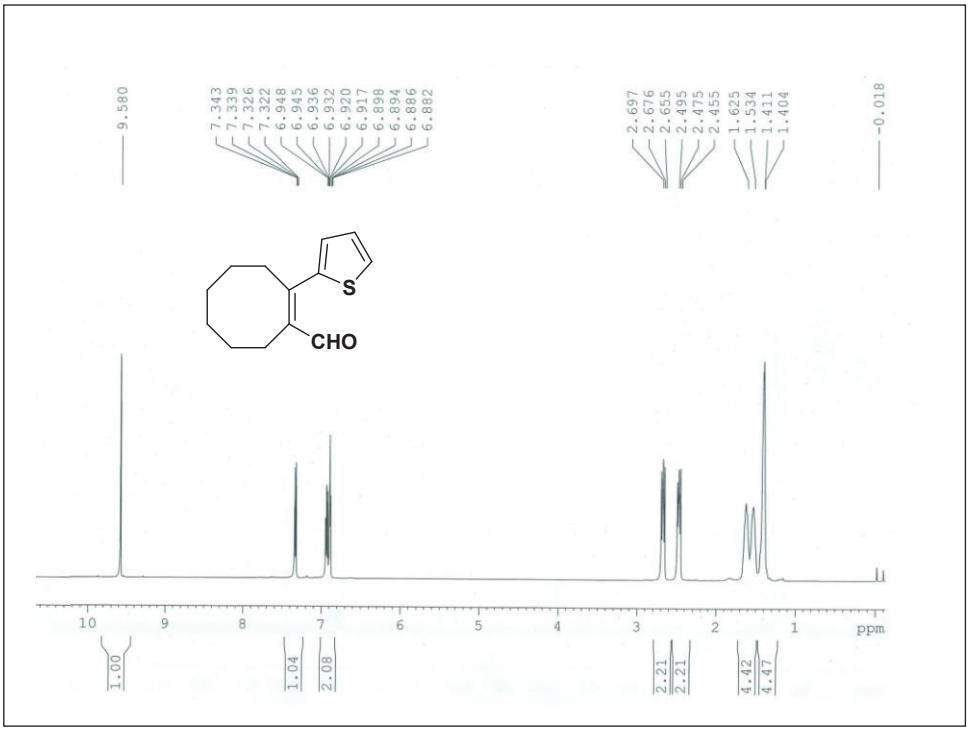
^{1}H NMR spectra of 19a:



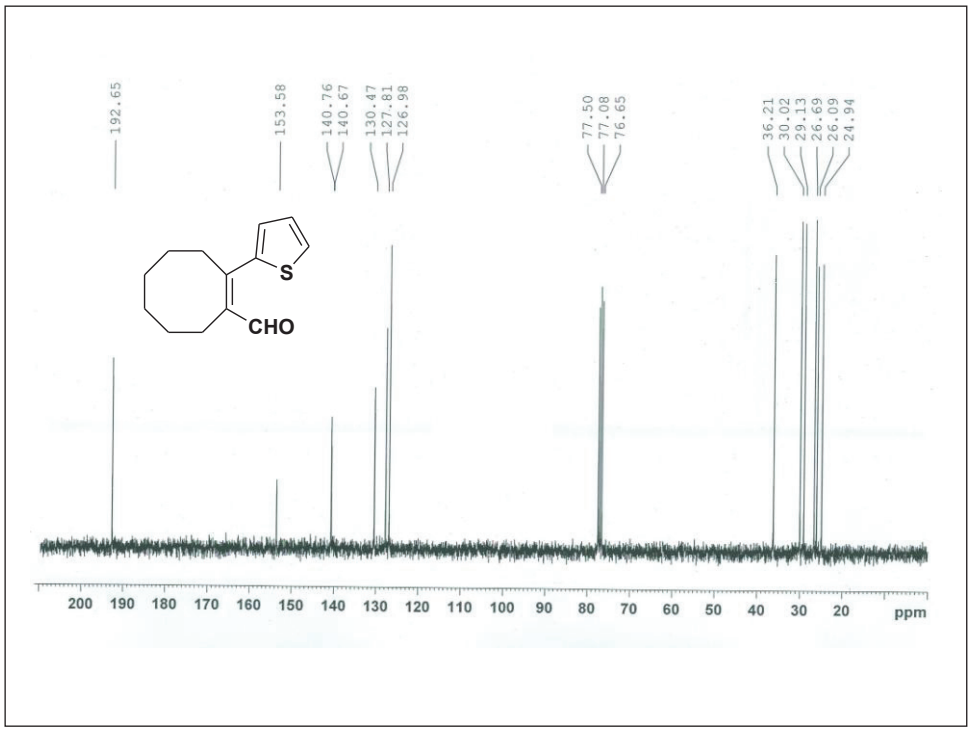
^{13}C NMR Spectra of 19a:



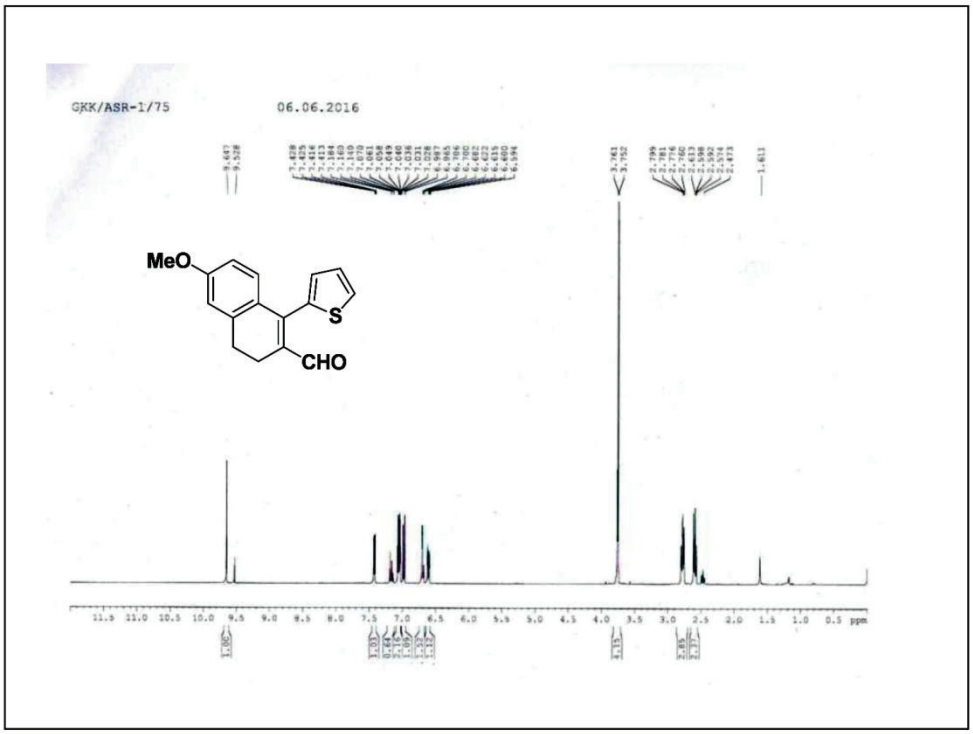
^{1}H NMR spectra of 18c:



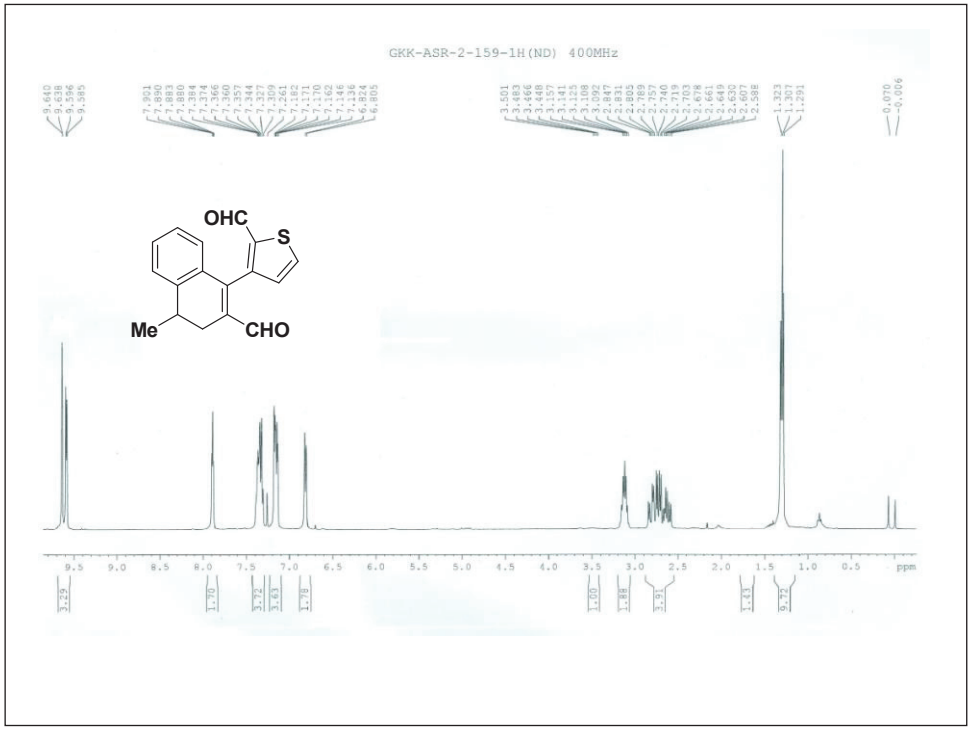
^{13}C NMR Spectra of 18c:



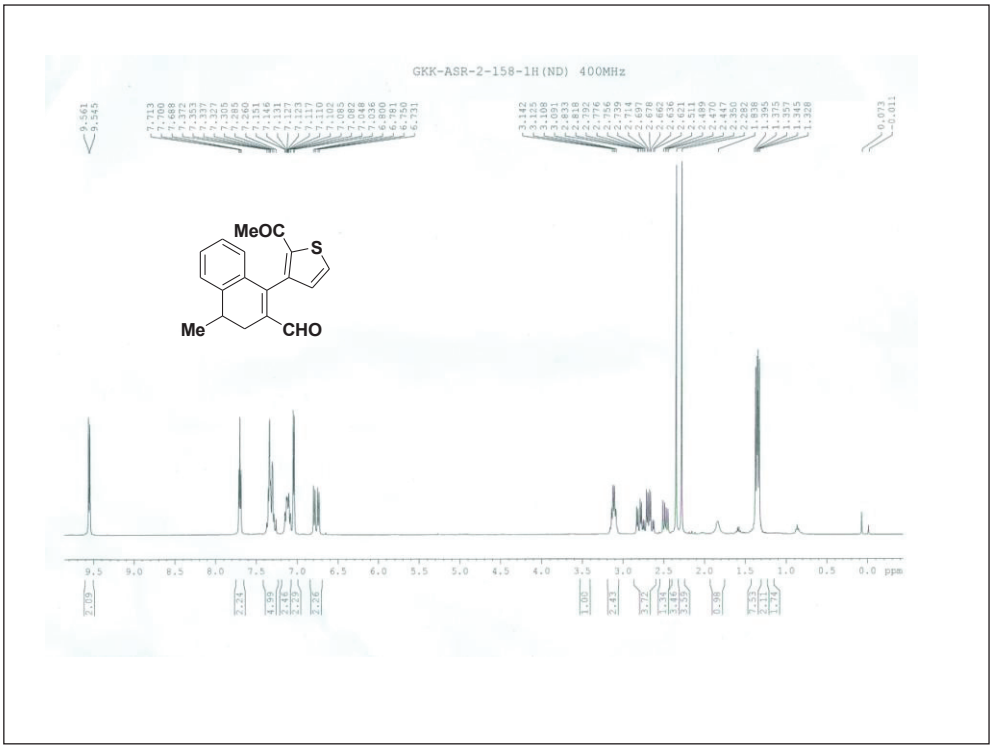
^{1}H NMR spectra of 18e



^{1}H NMR spectra of 19f$_2$



^{1}H NMR spectra of 19f$_3$



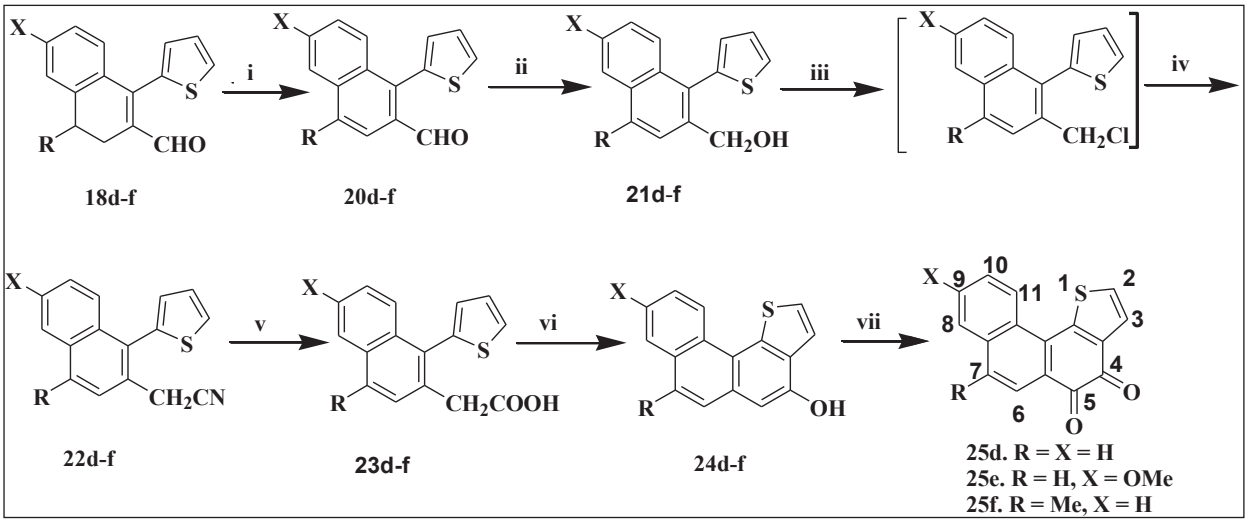
Chapter IIB

Thiophene analogues of isotanshinone II nucleus: A novel approach towards the synthesis of phenanthro[4,3-*b*]thiophene-4,5-dione and phenanthro[3,4-*b*]thiophene-4,5-dione derivatives

Thiophene analogues of isotanshinone II nucleus: A novel approach towards the synthesis of phenanthro[4,3-*b*]thiophene-4,5-dione and phenanthro[3,4-*b*]thiophene-4,5-dione derivatives

5.1 Present work: result and discurssion

Our ultimate intension is to synthesise thiophene analogue of 'U'-shaped furophenanthraquinone derivatives, and with this aim, an extensive studies on the synthesis of 2-(2/3-thienyl)cycloalk-1-ene-1-carbaldehyde derivatives, have been described in previous chapter-IIA of the thesis. In this part of the thesis, we have explored some of the thienylated compounds **18d-f** and **19h** (synthesised in chapter IIA) for the synthesis of hitherto unknown phenanthro[4,3-*b*]thiophene-4,5-dione derivatives **25d-f** as well as 10-methoxyphenanthro[3,4-*b*]thiophene-4,5-dione (**15**) following the scheme 7 and scheme 8, respectively. The compounds **25d-f** represent thiophene analogues of the ABCD ring system of isotanshinone II.



Reagents and conditions : i) DDQ, benzene, reflux, 20-24 hrs, 87-97 %; ii) $NaBH_4$, EtOH, r.t., 2 hrs, 94-97 %; iii) Mesyl chloride, *s*-collidine, LiCl, DMF, 0-5 °C, overnight; iv) KCN, DMF, overnight, 63-82 %; v) Aq KOH, EtOH, reflux, 20-30 hrs, 44-52 %; vi) TFAA, TFA, 0-5 °C, overnight, 64-87 %; vii) Fremy's salt, aq. Na_2HPO_4 buffer, MeOH, 0-5 °C, overnight, 77-97 %.

Scheme 7: Synthesis of phenanthro[4,3-*b*]thiophene-4,5-dione derivatives 25d-f

1-(2-Thienyl)-3,4-dihydronaphthalene-2-carbaldehyde (**18d**) was aromatised to 1-(2-thienyl)naphthalene-2-carbaldehyde (**20d**) in 97 % yield on refluxing with DDQ in dry benzene. The aldehyde **20d** was then reduced with $NaBH_4$ in EtOH to the alcohol **21d** in 97 % yield. Interestingly, in ^{1}H NMR spectra of **21d**, the hydroxymethyl protons appeared as two singlets at respectively δ 4.65 and 4.83 ppm (total 2H) due to possible atropisomerism in the 2-thienyl-1-naphthyl system. Side chain homologation of -CH_2OH to -CH_2CO_2H was achieved in four steps to obtain the carboxylic acid **23d** in overall good yields. Thus compound **21d** on reaction with MsCl, LiCl, *s*-collidine at 0-5 ^oC afforded the crude chloride intermediate which on reaction with KCN in DMF furnished the nitrile derivative **22d** in 82 % yield. Spectral data supported the assigned structure compound **22d**: IR (KBr) ν_{max} = 2246 cm^{-1} (characteristics of the nitrile group); ^{1}H NMR (400 MHz, $CDCl_3$) : δ = 3.65 (s, 2H), 6.99 (d, J = 3.2 Hz, 1H), 7.16 (dd, J = 3.2 Hz & 5.2 Hz , 1H), 7.37 (br t, ill split J ~7.0 Hz, 1H), 7.43 (br t, ill split, J ~7.0 Hz, 1H), 7.47 (br d, J = 5.2 Hz, 1H), 7.53 (d, J = 8.8 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.8 (d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.65, 118.13, 125.58, 126.35, 126.51, 127.10, 127.17, 127.67, 127.91, 128.03, 128.92, 129.84, 131.41, 132.83, 134.02, 137.35 ppm; HRMS (ESI, 70 ev): *m/z* $[M+H]^+$ calcd. for $C_{16}H_{12}NS$: 250.0612; found: 250.0201 and [M + Na] calcd. for $C_{16}H_{11}NSNa$: 272.0510; found: 272.0052. The nitrile **22d** was then hydrolysed (KOH, EtOH-water, reflux) to the acid **23d** in moderate yield. Compound **23d** showed strong absorption at ~1694 cm^{-1} in IR spectra as charcteristics of –COOH group. The acid **23d** on cyclisation with TFAA-TFA mixture furnished the phenanthro[4,3-b]thiophen-4-ol (**24d**) in excellent yield. Tentative assignment of ^{1}H NMR signals and splitting pattern of **24d** was shown in fig. 5.

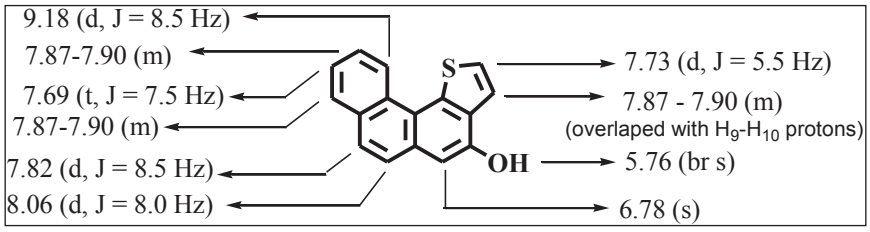
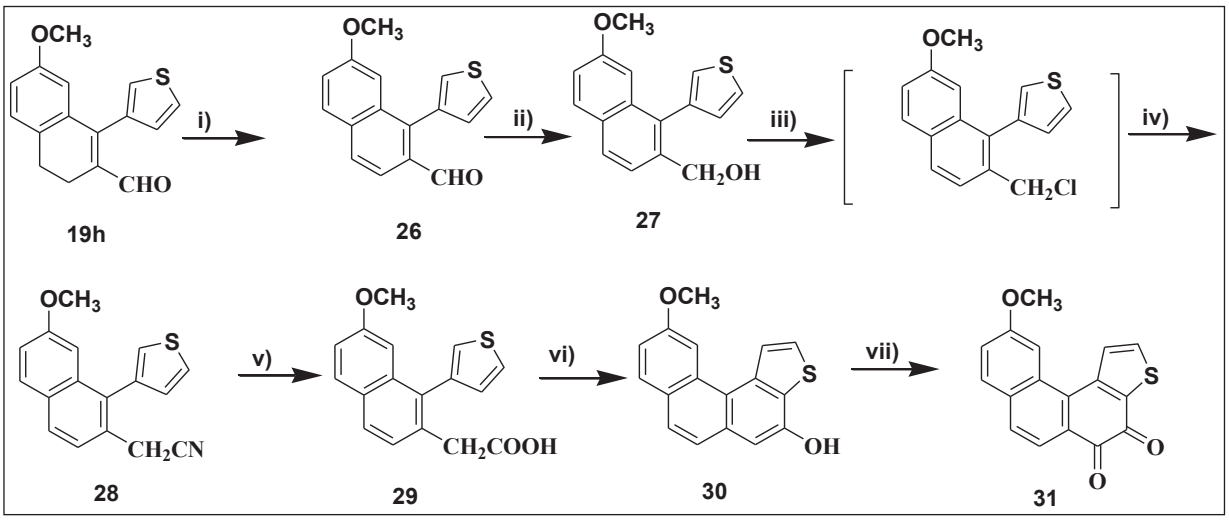


Figure 5: ^{1}H NMR (500 MHz, $CDCl_3$) chemical shifts and splitting of 24d

Oxidation of **24d** with Fremy's salt[11] in MeOH, aq. Na_2HPO_4 buffer at 0-5 °C afforded phenanthro[4,3-*b*]thiophene-4,5-dione (**25d**) as dark violet solid in 77 % yield. IR (KBr) ν_{max}: 1661 and 1686 cm^{-1} (characteristics of *o*-quinone group) and ^1H NMR (400 MHz, $CDCl_3$) spectral data (fig. 6) of the compounds **25d** are in conformity with the assigned structure. ^{13}C NMR data [(100 MHz, $CDCl_3$): δ = 124.81, 125.97, 127.01, 127.46, 128.05, 128.54, 128.79, 129.29, 129.90, 130.14, 131.15, 137.48, 137.73, 148.10, 174.26, 181.26 ppm] as well as HRMS [(ESI, 70 ev): *m/z* $[M+H]^+$calcd. for $C_{16}H_9O_2S$: 265.0245; found: 265.0413] also supported the structure.

Following a similar sequence of reactions, two more phenanthro[4,3-*b*]thiophene-4,5-dione derivatives **25e-f** have been synthesised starting from 3,4-dihydro-6-methoxy-1-(2-thienyl)naphthalene-2-carbaldehyde (**18e**) and 3,4-dihydro-4-methyl-1-(2-thienyl)naphthalene-2-carbaldehyde (**18f**), respectively (scheme 8). All the compounds have been characterised by usual spectroscopic methods IR, ^1H NMR (fig. 6), ^{13}C NMR, HRMS. Details have been given in the experimental section.



Reagents and conditions : i) DDQ, Benzene, reflux, 20 hrs, 97 %; ii) $NaBH_4$, EtOH, r.t, 2 hrs, 94 %; iii) Mesyl chloride, *s*-collidine, LiCl, DMF, 0-5 °C, overnight; iv) KCN, DMF, overnight, 80 %; v) Aq. KOH, EtOH, reflux, 22 hrs, 44 %; vi) TFAA, TFA, 0-5 °C, overnight, 92 %; vii) Fremy's salt, Na_2HPO_4-H_2O, MeOH, 0-5 °C, overnight, 87 %.

Scheme 8: Synthesis of 10-methoxyphenanthro[3,4-*b*]thiophene-4,5-dione (31)

We then focussed our attention for the synthesis of a regioisomeric 'U'-shaped novel thienophenanthraquinone, 10-methoxyphenanthro[3,4-*b*]thiophene-4,5-dione (**31**) starting from a 3,4-dihydro-1(3-thienyl)-7-methoxynaphthalene-2-carbaldehyde (**19h**)[9,10] following a similar pathway (scheme 8) with good to very good yeilds.

All the compounds have been characterised by usual spectroscopic data (vide experimental). Tentative assignment of ^{1}H NMR spectral data of the representative thienophenanthraquinones **25e-f** and **31** are depicted in fig. 6.

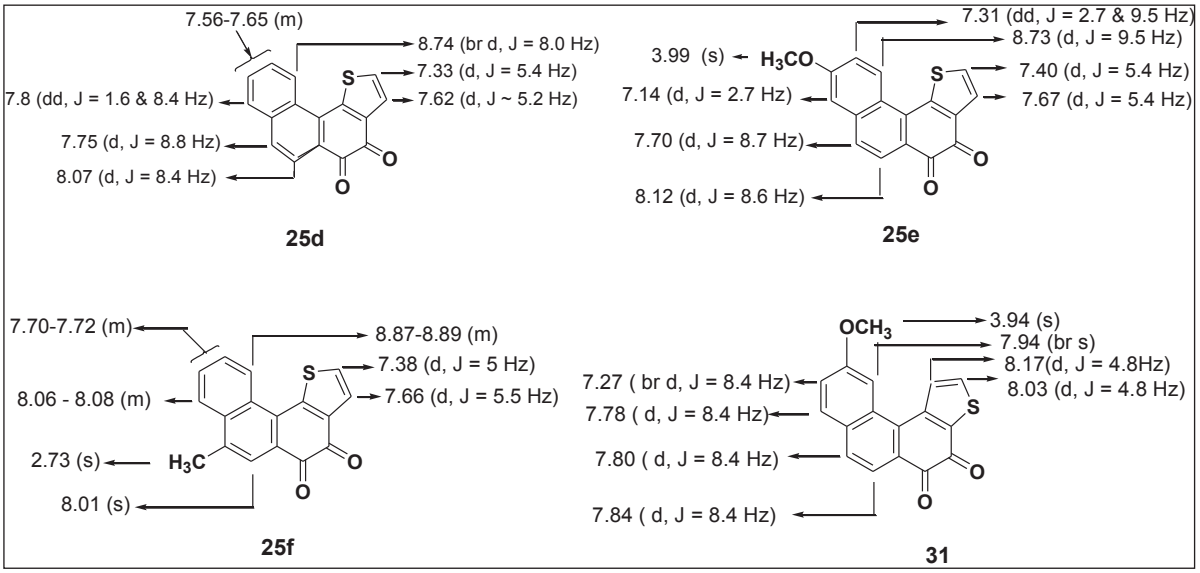


Figure 6: Tentative assignment of ^{1}H NMR spectral data of 25d-f and 31

5.2 Conclusion

In conclusion, four novel phenanthro[4,3-*b*]thiophene-4,5-dione derivatives **25d-f** and 10-methoxyphenanthro[3,4-*b*]thiophene-4,5-dione (**31**) have been synthesised as an extension of the work described in chapter I. The yields in most of the steps are very good to excellent. To our belief, the process is much easier and not too lengthy. The method is a general one and each of the 1-(2/3-thienyl)-3,4-dihydronaphthalene-2-carbaldehyde derivatives as reported in this chapter IIA, may lead to some novel condensed thienophenanthraquinone derivatives. The compounds may be unique for study of the biological as well as biophysical activities. However, due to lack of infrastructural facility and our limitations, we are unable to take up biological or biophysical studies at this moment. The biological evaluations will be taken up at a latter stage if suitable collaborators are available. In the dicarbonyl compounds such as **19f$_2$** and **19f$_3$**, the two carbonyl

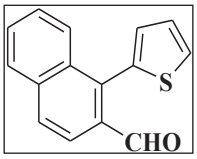
functionalities can be further utilised *via* Benzoin condensation, and the resulting theenophenanthrenediol intermediate on oxidation may lead to condensed thienophenanthraquinone derivatives. In addition these substrates can be good precursors for synthesis of polycyclic thiaarenes (as mentioned in earlier chapter) as bioisosters of respective polycyclic aromatic hydrocarbons (PAHs). Further detailed studies of Suzuki reactions of various bromoaldehydes with formyl/acyl substituted thiopheneboronic acids are necessary for synthesising more number of dicarbonyl derivatives as precursors for novel polycyclic thiaarenes.

5.3 Experimental:

Preparation of 1-(2-thienyl)naphthalene-2-cabaldehyde derivatives 20d-f and 7-methoxy-1-(3-thienyl)naphthalene-2-cabaldehyde (26): General method

To a solution of compound **18** or **19h** (2.04-3.15 mmol scale) in 15 - 20 ml dry benzene, DDQ (1.2 to 1.3 equivalent) was added. The mixture was refluxed for 20 to 24 hrs protecting from moisture. When the reaction was found to be completed (as checked by TLC), the reaction mixture was filtered. The benzene layer was washed with 5 % aq. $NaCO_3$ solution till the aqueous washings are almost colourless. Finally it was washed with water, the organic layer was collected and dried (anhyd. $Na_2SO_{4)}$. Removal of benzene afforded the 1-(2-thienyl)naphthalene-2-carbaldehyde derivative **20** or 7-methoxy-1-(3-thienyl)naphthalene-2-carbaldehyde (**26**) (as the case may be) as yellow solid. It was further purified by recrystallisation from Pet. ether-EtOAC mixture. Yields: 87-97 %.

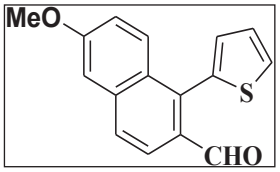
1-(2-Thienyl)naphthalene-2-carbaldehyde (20d)



Yellow solid; yield: 97 % (520 mg / 2.18 mmol of product obtained from 540 mg / 2.25 mmol of **18d**); mp: 120-122 °C; IR (KBr) ν_{max}: 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.11 (dd, J ~1 Hz & 3.2 Hz, 1H), 7.15 (dd, J = 3.6 Hz & 5.2 Hz, 1H), 7.42 (ddd, J = 1.2, 7.2 & 7.6 Hz, 1H), 7.50 (dd, J = 1.2 & 5.2 Hz, 1H), 7.54 (ddd, J = 0.8, 6.8 & 8.0 Hz, 1H), 7.79 (br d, J = 8.8 Hz, 1H), 7.82 (br d, J = 8.4 Hz, 1H), 7.87 (br d, J = 8.8 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 9.96 (s, 1H) ppm; ^{13}C NMR (100

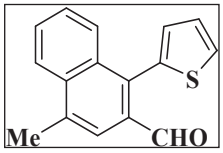
MHz, $CDCl_3$): δ = 122.11, 127.23, 127.27, 127.33, 127.69, 128.20, 128.94, 129.39, 130.76, 132.98, 133.46, 134.97, 135.92, 138.50, 192.29 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{15}H_{11}OS$: 239.0452; found: 239.0796 and [M+Na] calcd for $C_{15}H_{10}O_2SNa$: 261.0456; found: 261.0663.

6-Methoxy-1-(2-thienyl)naphthalene-2-carbaldehyde (20e)



Yellow solid; yield: 87 % (605 mg / 2.26 mmol of **20e** obtained from 700 mg / 2.59 mmol of **18e**); mp 92-94 °C; IR (KBr) ν_{max}: 1644 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.95 (s, 3H), 7.14 (dd, J = 2.8 & 9.2 Hz, 1H), 7.17-7.19 (m, 2H), 7.22 (dd, J = 3.6 & 5.2 Hz, 1H), 7.56 (dd, J ~1.0 & 5.2 Hz, 1H), 7.77 (d, J = 9.2 Hz, 1H), 7.82 (d, J = 8.8 Hz, 1H), 8.0 (d, J = 8.4 Hz, 1H), 9.98 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.52, 106.26, 119.84, 122.90, 127.16, 127.53, 128.06, 128.57, 129.04, 130.57, 131.28, 135.17, 137.83, 138.52, 160.04, 192.05 ppm; HRMS(ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}O_2S$: 269.0558; found: 269.0774 and [M+Na] calcd for $C_{16}H_{12}O_2SNa$: 291.0456; found: 291.0686.

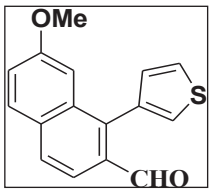
4-Methyl-1-(2-thienyl)naphthalene-2-carbaldehyde (20f)



Yellow solid; Yield: 91 %; (720 mg / 2.86 mmol of **20f** obtained from 800 mg / 3.15 mmol of **18f**); mp 100-102 °C; IR (KBr) ν_{max}: 1679 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ = 2.76 (s, 3H), 7.18 (dd, J = 1.2 & 3.4 Hz, 1H), 7.23 (dd, J = 2.8 & 5.2 Hz 1H), 7.52 (br t, J ~7.0 Hz, 1H), 7.57 (dd ill split, J = 1.2& 5.2 Hz, 1H), 7.66 (br t, J = 7.6 Hz, 1H), 7.88 (s, 1H), 7.89 (br d, J = 8.9 Hz, 1H), 8.06 (br d, J = 8.3 Hz, 1H), 10.03 (1H, s) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.58, 122.32, 124.33, 126.80, 127.10, 127.52, 127.92, 128.78, 130.71, 132.45, 133.51, 135.18, 135.24, 136.02, 136.82, 192.48 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}OS$: 253.0609; found: 253.1763 and [M+Na] calcd for $C_{16}H_{12}OSNa$: 275.0507; found: 275.1985.

7-Methoxy-1-(3-thienyl)naphthalene-2-carbaldehyde (26)

Yellow crystal; Yeild: 97 % (530 mg / 1.98 mmol of **26** obtained from 550 mg / 2.04 mmol of **19h**); mp: 94-96 °C; IR (KBr) ν_{max}: 1683 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.68 (s, 3H), 6.97 (d, J = 2.4 Hz, 1H), 7.16 (dd, J ~1.0 & 4.8 Hz, 1H), 7.20 (dd, J = 2.4 & 8.8 Hz, 1H), 7.30

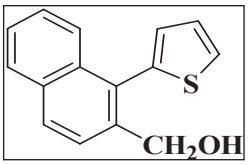


(dd, J ~1.0 & 3.2 Hz, 1H), 7.49 (dd, J = 3.2 & 4.8 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H),7.83 (d, J = 8.8 Hz, 1H), 9.87 (s, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.23, 105.85, 120.07, 121.11, 126.21, 126.29, 128.21, 129.71, 130.23, 131.54, 132.48, 134.13, 135.36, 140.12, 158.41, 192.95 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{13}O_2S$: 269.0558; found: 269.1126 and [M+Na] calcd for $C_{16}H_{12}O_2SNa$: 291.0456; found: 291.1053.

Preparation of [1-(2-thienyl)naphthalen-2-yl]methanol derivatives 21d-f and [7-methoxy-1-(3-thienyl)naphthalen-2-yl]methanol (27): General method

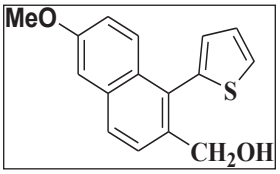
To a stirred suspension of the 1-(2/3-thienyl)-2-naphthaldehyde derivative **20 or 26** (1.9-2.78 mmol scale) in 10-15 ml EtOH, $NaBH_4$ (1.5-2.19 mmol scale) was added in portions. The mixture was further stirred at r.t. till the reaction was completed (2 hrs). Excess EtOH was removed by distillation and the residue thus obtained was decomposed with cold water containing 2-3 drops of dil HCl. The reaction mixture was extracted with DCM thoroughly. The organic layer was washed with cold water, dried (anhyd. Na_2SO_4). Removal of solvent furnished the crude alcohol which was purified by column chromatography (silica gel 100-200 mesh; pet. ether 60-80 °C and EtOAc, 10:1) to obtain the title compound **21d-f** or **27** as pale yellow liquid. Yield 94-97 %.

[1-(2-Thienyl)naphthalen-2-yl]methanol (21d)



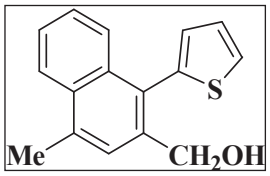
Viscous pale yellow liquid; yield : 97 % (490 mg / 2.0 mmol of **21d** obtained from 500 mg/ 2.10 mmol of **20d**); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.85 (br s, 1H), 4.65 & 4.83 (both s, total 2H), 7.03 (dd, J = 1.2 & 3.2 Hz, 1H), 7.19 (dd, J = 3.2 & 4.8 Hz, 1H), 7.39-7.50 (m, 3H), 7.63 (br d, J = 8.8 Hz, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.85 (d, J = 7.6 Hz, 1H), 7.91 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 63.50, 125.19, 125.45, 125.69, 125.95, 126.31, 126.47, 127.27, 127.84, 128.58, 129.20, 129.94, 132.81, 133.88, 138.28 ppm; HRMS (ESI+): *m/z* [M+Na] calcd for $C_{15}H_{12}NaOS$: 263.0507; found: 263.2552.

[6-Methoxy-1-(2-thienyl)naphthalen-2-yl]methanol (21e)



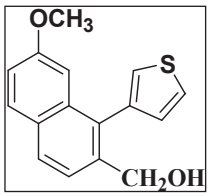
Viscous pale yellow liquid; yield: 94 % (550 mg / 2.04 mmol of the product obtained from 580 mg / 2.16 mmol of **20e**); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.89 (br s, 1H), 3.79 (s, 3H), 4.49 (s, 2H), 6.89 (dd, ill split, J = 1.2 & 3.2 Hz, 1H), 6.96 (dd, J = 2.8 & 9.6 Hz, 1H), 7.01 (d, J = 2.4 Hz, 1H), 7.05 (dd, J = 3.2 & 5.2 Hz, 1H), 7.35 (dd, ill split, J ~0.8 & 5.0 Hz, 1H), 7.42 (d, J = 9.2 Hz, 1H), 7.49 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.37, 63.36, 105.78, 119.09, 126.37, 126.43, 127.21, 127.96, 128.51, 129.28, 130.01, 134.11, 136.04, 138.27, 157.62 (one C was not observed possibly more scan necessary) ppm; HRMS(ESI+): *m/z* [M+Na] calcd for $C_{16}H_{14}O_2SNa$: 293.0612; found: 292.9616.

[4-Methyl-1-(2-thienyl)naphthalen-2-yl)]methanol (21f)



Viscous pale yellow liquid; yield: 96 % (680 mg / 2.68 mmol of **20f** obtained from 700 mg / 2.78 mmol of **21f**); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.77 (br s, 1H), 2.68 (s, 3H), 4.56 & 4.73 (both s, total 2H), 6.96 (dd, J = 0.8 & 3.6 Hz, 1H), 7.12 (dd, J = 3.6 & 5.2 Hz, 1H), 7.36 (ddd, ill split, J = 1.2, 8.0 & ~7.2 Hz, 1H), 7.41-7.46 (m, 2H), 7.47 (s, 1H), 7.59 (br d, J = 8.4 Hz, 1H), 7.95 (br d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.61, 63.51, 124.00, 125.81, 126.15, 126.40, 126.54, 126.95, 127.21, 128.13, 128.66, 132.01, 133.99, 135.74, 137.85, 138.43 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}OS$: 255.0765; found: 255.0835 and [M+Na] calcd for $C_{16}H_{14}OSNa$: 277.0668; found: 277.0683.

[7-Methoxy-1-(3-thienyl)naphthalen-2-yl)]methanol (27)



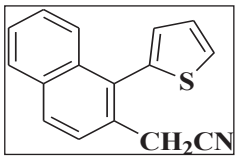
Viscous pale yellow liquid; yield 94 % (480 mg / 1.78 mmol of **27** obtained from 520 mg/ 1.94 mmol of **26**); ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.95 (br s, 1H), 3.69 & 3.87 (both s, total 3H), 4.54 & 4.75 (both s, total 2H), 6.82 (d, J = 2.4 Hz, 1H), 7.06 (dd, J = 1.2 & 4.8 Hz, 1H), 7.12 (dd, J = 2.8 & 8.8 Hz, 1H), 7.22 (dd, J = 1.2 & 2.8 Hz, 1H), 7.46 (dd, J = 2.8 & 4.8 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.73 (d, J = 8.8 Hz, 1H), 7.76 (dd, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.12, 63.65, 105.03, 118.21, 123.64, 124.11, 125.84, 127.93, 128.47, 129.45, 129.68, 131.85, 134.37,

137.14, 138.12, 157.88 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{15}O_2S$: 271.0715; found: 271.2811 & (M+Na) calcd for $C_{16}H_{14}O_2SNa$: 293.0612; found: 293.2294.

Preparation of 2-[1-(2-thienyl)naphthalen-2-yl]acetonitrile derivatives 22d-f and 2-[7-methoxy-1-(3-thienyl)naphthalen-2-yl]acetonitrile (28): General method

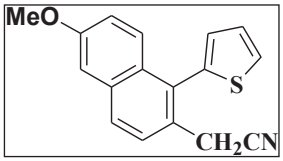
To an ice cold solution mixture of the alcohol **21** or **27** (1.70 -2.60 mmol scale), LiCl (2.22-3.40 mmol scale) in s-collidine (2.10-3.2 mmol scale) taken in a 25ml two necked flask, MsCl (2.32-3.56 mmol scale) was injected slowly protecting from moisture . The mixture was stirred at 0-4 °C for overnight. Now crushed ice was added to the reaction mixture and extracted thoroughly with diethyl ether. The organic part was washed successively with ice cold dil. HCl, cold brine solution, 5 % aqueous $NaHCO_3$ solution and finally with cold brine solution. The ether solution was dried (anhyd. Na_2SO_4) and removal of solvent furnished the crude halide. Without further purification, the crude alkyl chloride was immediately dissolved in 6-8 ml dry DMF taken in a 50 ml r.b flask. Now to it KCN (2.69-4.10 mmol scale) was added and stirred protecting from moisture for overnight. The mixture was then diluted with ice water and extracted with Et_2O. Organic layer was washed with cold brine solution thoroughly, dried (anhyd. Na_2SO_4) and solvent removed. The acetonitrile derivative **22** or **28** obtained as off white to pale yellow solid was further purified by column chromatography (silica gel 100-200 mesh; pet. ether 60-80 °C and EtOAc, 20:1). Yield 63-82 %.

2-[1-(2-Thienyl)naphthalen-2-yl]acetonitrile (22d)



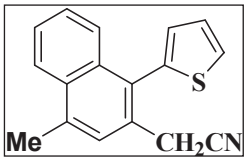
Off white solid; yield 82 % (400 mg / 1.61 mmol of **22d** from 470 mg / 1.96 mmol of **21d**); mp 104-106 °C; IR (KBr) ν_{max}: 2246 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ= 3.65 (s, 2H), 6.99 (d, J = 3.2 Hz, 1H), 7.16 (dd, J = 3.2 Hz & 5.2 Hz , 1H), 7.37 (br t, ill split, J ~7.0 Hz, 1H), 7.43 (br t, ill split, J ~7.0 Hz, 1H), 7.47 (br d, J = 5.2 Hz, 1H), 7.53 (d, J = 8.0 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1H), 7.8 (br d, J = 8.0 Hz, 1H), 7.87 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.65, 118.13, 125.58, 126.35, 126.51, 127.10, 127.17, 127.67, 127.91, 128.03, 128.92, 129.84, 131.41, 132.83, 134.02, 137.35 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{12}NS$: 250.0612; found: 250.0201 & [M+Na] calcd for $C_{16}H_{11}NSNa$: 272.0510; found: 272.0052.

2-[6-Methoxy-1-(2-thienyl)naphthalen-2-yl]acetonitrile (22e)



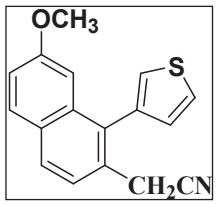
White solid; yield: 66 % (380 mg / 1.36 mmol of **22e** obtained from 560 mg / 2.07 mmol of **21e**); mp: 122-124 °C; IR (KBr) ν_{max}: 2247 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 3.61 (s, 2H), 3.84 (s, 3H), 6.97 (d, J = 3.4 Hz, 1H), 7.05 (dd, J = 3.5 & 8.7 Hz, 1H), 7.08 (d, J ~ 2.5 Hz, 1H), 7.14 (t, J = 3.5 Hz, 1H), 7.42 (d, J = 8.6 Hz, 1H), 7.45 (d, J = 4.1 Hz, 1H), 7.50 (d, J = 8.6 Hz, 1H), 7.75 (d, J = 8.6 Hz, 1H) ppm; ^{13}C NMR (75 MHz, $CDCl_3$): δ = 22.38, 55.37, 105.70, 118.28, 119.72, 125.55, 126.15, 127.03, 127.57, 127.92, 128.51, 128.79, 129.41, 131.29, 134.17, 137.48, 158.00 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{14}NOS$: 280.0718; found: 280.2640.

2-[4-Methyl-1-(2-thienyl)naphthalen-2-yl]acetonitrile (22f)



Off white solid; yield 63 % (430 mg / 1.63 mmol of **22f** obtained from 660 mg / 2.60 mmol of **21f**); mp 130-131 °C; IR (KBr) ν_{max}: 2247 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.77 (s, 3H), 3.70 (s, 2H), 7.04 (dd, J = 1.0 Hz & 3.5 Hz, 1H), 7.2 (dd, J = 3.5 Hz & 5.1 Hz, 1H) 7.45-7.59 (m, 3H), 7.49 (s, 1H), 7.81 (dd, J =1.0 & 5.5 Hz, 1H), 8.04 (dd, J = 3.0 & 8.4 Hz, 1H); HRMS (ESI+): *m/z* $[M+Na]^+$ calcd for $C_{17}H_{13}NSNa$: 286.0666; found: 286.0171.

2-[7-Methoxy-1-(3-thienyl)naphthalen-2-yl]acetonitrile (28)

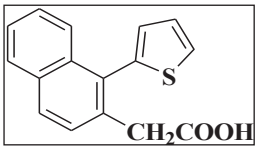


Yellow solid; yield 80 % (380 mg / 1.36 mmol of **28** obtained from 460 mg / 1.70 mmol of **27**); mp 104-106 °C; IR (KBr) ν_{max}: 2241 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.62 (s, 2H), 3.71 (s, 3H), 6.78 (d, J = 2.0 Hz, 1H), 7.08 (dd, ill split, J = 1.6 & 5.2 Hz, 1H), 7.16 (dd, J = 2.4 & 8.8 Hz, 1H), 7.29 (dd, J = 1.2 & 2.4 Hz, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.55 (dd, J = 3.2 & 4.8 Hz, 1H), 7.77 (d, J = 8.8 Hz, 1H), 7.82 (d, J = 8.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 22.67, 55.14, 105.01, 118.77, 123.60, 124.53, 126.80, 126.91, 128.45, 128.57, 129.13, 129.43, 129.53, 133.02, 134.59, 137.62, 158.30 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{14}NOS$: 280.0718; found: 279.1039 and [M+Na] calcd for $C_{17}H_{13}NOSNa$: 302.0616; Found: 302.0607.

Preparation of 2-[1-(2-thienyl)naphthalen-2-yl]acetic acid derivatives 23d-f and 2-[7-methoxy-1-(3-thienyl)naphthalen-2-yl)]acetic acid (29): General method

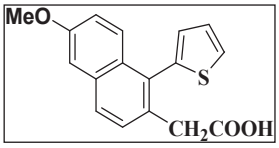
The aqueous alcoholic solution of the nitrile derivative **22** or **28** (1.29-1.53 mmol scale) was refluxed with 4-5 ml 30 % KOH solution for 20 to 30 hours when the evolution of ammonia was ceased indicated the completion of the hydrolysis. Excess of alcohol was removed by distillation and the residue was diluted with ice water. On acidification of this aqueous part with 1:1 HCl, the acid was precipitated. It was filtered and washed thoroughly and dried. The crude carboxylic acid thus obtained was redissolved in saturated aq. $NaHCO_3$ solution, filtered to remove any suspended impurities. The filtrate was cooled in ice bath was acidified 1:2 aq. HCl. The carboxylic acid precipitated as white solid was filtered and dried to furnish the title compounds **23** or **29**. Yield 44-52 %.

2-[1-(2-Thienyl)naphthalen-2-yl]acetic acid (23d)



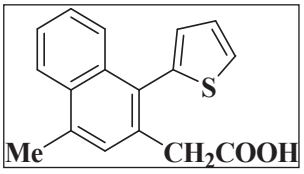
White solid; yield: 44 % (180 mg / 0.67 mmol of **23d** obtained from 380 mg / 1.53 mmol of **22d**); mp: 120-122 °C; IR (KBr) ν_{max}: 1694 cm^{-1}, HRMS (ESI+): *m/z* [M+Na] calcd for $C_{16}H_{12}O_2SNa$: 291.0456; found: 290.9686.

2-[6-Methoxy-1-(2-thienyl)naphthalen-2-yl]acetic acid (23e)



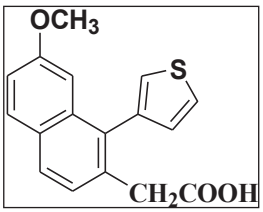
White solid; yield: 52 % (200 mg / 0.67 mmol of **23e** obtained from 360 mg / 1.29 mmol of **22e**); mp: 166-168 °C; IR (KBr) ν_{max}: 1697 cm^{-1}; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{15}O_3S$: 299.0664; found: 299.0732 and [M+Na] calcd for $C_{17}H_{14}O_3SNa$: 321.0561; found: 321.0561.

2-[4-Methyl-1-(2-thienyl)naphthalen-2-yl]acetic acid (23f)



White solid; yield: 49 % (220 mg / 0.78 mmol of **23f** obtained from 420 mg / 1.60 mmol of **22f**); mp: 170-172 °C ; IR (KBr) ν_{max}: 1706 cm^{-1}; HRMS (ESI+): *m/z* [M+Na] calcd for $C_{17}H_{14}O_2SNa$: 305.0612; found: 305.2187.

2-[7-Methoxy-1-(3-thienyl)naphthalen-2-yl)]acetic acid (29)

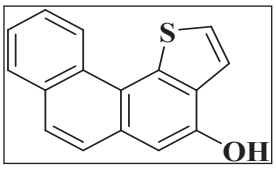


Off white solid; yield: 44 % (170 mg / 0.57 mmol of **29** obtained from 360 mg / 1.29 mmol of **28**); mp: 112-114 °C; IR (KBr) ν_{max}: 1710 cm^{-1}; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{15}O_3S$: 299.0664; found: 299.0592 and [M+Na] calcd for $C_{17}H_{14}O_3SNa$: 321.0561; found: 321.0389.

Preparation of Phenanthro[4,3-*b*]thiophen-4-ol derivatives 24d-f and 10-methoxy-phenanthro[3,4-*b*]thiophen-4-ol (30): General method

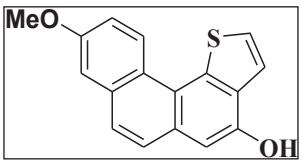
To an magnetically ice cold stirred mixture of the carboxylic acid (0.50-0.71 mmol scale) in trifluoroacetic anhydride (4.7-6.6 ml) taken in a 25 ml two necked r.b flask fitted with anhydrous $CaCl_2$ guard tube, trifluoroacetic acid (1.2-1.7 ml) was injected slowly at 0-4 °C and stirred further for 1 hr, then left in the refrigerator for overnight. Then the reaction mixture was decomposed with crushed ice and extracted with dichloromethane thoroughly. The organic layer was washed with cold aq. $NaHCO_3$ solution, cold brine solution and dried (anhyd. Na_2SO_4). Removal of dichloromethane produced the phenolic compounds which on purification by plate chromatography (Silica gel GF254; benzene) furnished the thienophenanthrenol derivative **24** or **30** as off white to light reddish brown solid. Yield: 64-92 %.

Phenanthro[4,3-b]thiophen-4-ol (24d)



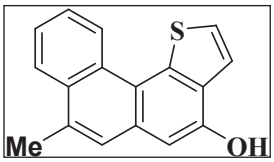
Light reddish brown solid; yield: 87 % (130 mg / 0.52 mmol of **24d** obtained from 160 mg / 0.60 mmol of **23d**); mp: 140-142 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 5.76 (br s, 1H), 6.78 (s, 1H), 7.69 (t, J = 7.5 Hz, 1H), 7.73 (d, J = 5.5 Hz, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.87-7.90 (m, 3H), 8.06 (d, J = 8.0 Hz, 1H), 9.18 (d, J = 8.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 108.12, 116.35, 120.50, 121.46, 125.23, 125.37, 125.62, 127.00, 127.12, 127.34, 129.19, 130.99, 131.96, 132.49, 137.35, 149.76 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_{11}OS$: 251.0452; found: 251.0197

9-Methoxyphenanthro[4,3-*b*]thiophen-4-ol (24e)



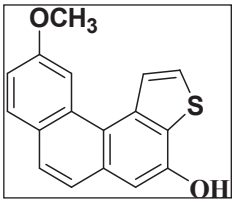
Off white solid; yield: 71 % (120 mg / 0.43 mmol of **24e** obtained from 180 mg / 0.60 mmol of **23e**); mp: 181-182 °C; ^{1}H NMR (300 MHz, $CDCl_3$+DMSO-d_6): δ = 3.71 (s, 1H), 3.96 (s, 3H), 7.08 (dd, J = 2.5 & 9.2 Hz, 1H), 7.16-7.20 (m, 2H), 7.40 (d, J = 3.6 Hz, 1H,) 7.44 (d, J = 8.5 Hz, 1H), 7.49 (d, J = 5.2 Hz, 1H), 7.52 (d, J = 9.3 Hz, 1H), 7.79 (d, J = 8.5 Hz, 1H) ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}O_2S$: 281.0558; found : 281.0630.

7-Methylphenanthro[4,3-*b*]thiophen-4-ol *(*24f)



Light brown solid; yield: 64 % (120 mg / 0.45 mmol of **24f** obtained from 200 mg / 0.71 mmol of **23f**); mp: 190-192 °C; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.78 (s, 3H), 5.50 (br. s, 1H), 7.12 (s, 1H), 7.61 (s,1H), 7.62 (d, J = 7.5 Hz, 1H), 7.68 (d, J = 7.5 Hz, 1H), 7.76-7.84 (m, 2H), 8.16 (d, J = 7.9 Hz, 1H), 9.13 (d, J = 8.2 Hz, 1H) ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}OS$: 265.0609; found: 265.1509.

10-Methoxyphenanthro[3,4-*b*]thiophen-4-ol (30)



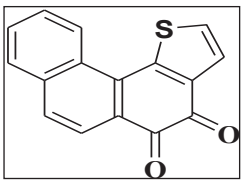
Light brown solid, yield: 92 % (130 mg / 0.46 mmol of 3**0** obtained from 150 mg / 0.50 mmol of **29**); mp: 164-166 °C; ^{1}H NMR (500 MHz, $CDCl_3$): δ = 4.17 (s, 3H), 5.94 (br s, 1H), 7.26 (s, 1H), 7.36 (dd, ill split, J = 2.0 & 9.5 Hz, 1H), 7.71 (d, J = 8.5 Hz, 1H), 7.83 (d, J = 9.0 Hz, 1H), 7.88 (d, J = 5.0 Hz, 1H), 7.98 (d, J = 9.0 Hz, 1H), 8.57 (br s, 1H), 8.72 (d, J = 5.5 Hz, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 55.76, 107.50, 107.62, 115.41, 121.43, 124.53, 125.80, 126.68, 127.02, 127.09, 130.25, 130.33, 131.94, 133.17, 137.71, 149.16, 158.62 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{13}O_2S$: 281.0558; found: 281.1829.

Preparation of phenanthro[4,3-*b*]thiophene-4,5-dione derivatives 25d-f and 10-methoxyphenanthro[3,4-*b*]thiophene-4,5-dione (31): General method

To a vigorously stirred solution of Fremy's salt (0.72-0.88 mmol scale) in 1/6M disodium hydrogen phosphate (10-12 ml) at 0-5 °C, the solution of the phenol (0.36-0.44 mmol scale)

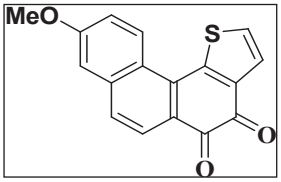
dissolved in minimum volume of MeOH (3-4 ml) was added drop wise. The colour of the solution quickly changes from violet to reddish brown with formation of dark red to deep violet solid. Stirring was continued at 0-5 °C for an additional hour and the mixture was left in the refrigerator for overnight. Next day it was extracted with methylene chloride, washed with cold water, dried (anhyd. Na_2SO_4) and solvent removed. Crude quinone derivative thus obtained was further purified either by column chromatography (silica gel, 100-200 mesh; benzene-methanol, 5:1) or by preparative TLC (Silica gel GF254 mesh; benzene-methanol, 5:1) and recrystallisation from suitable solvents like MeOH, EtOH to furnish the title compound as dark red solid. Yields: 77-97 %.

Phenanthro[4,3-*b*]thiophene-4,5-dione (25d)



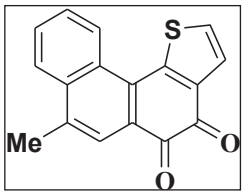
Deep violet solid; yield: 77 % (90 mg / 0.34 mmol of **25d** obtained from 110 mg / 0.44 mmol of **24d**); mp: 208-210 °C; IR (KBr) ν_{max}: 1661 cm^{-1} and 1686 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.33 (d, J = 5.4 Hz, 1H), 7.56-7.65 (m, 2H), 7.62 (d, J ~ 5.2 Hz, 1H), 7.75 (d, J = 8.8 Hz, 1H), 7.8 (dd, J = 1.6 & 8.4 Hz, 1H), 8.07 (d, J = 8.4 Hz, 1H), 8.74 (d, J = 8.0 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.81, 125.97, 127.01, 127.46, 128.05, 128.54, 128.79, 129.29, 129.90, 130.14, 131.15, 137.48, 137.73, 148.10, 174.26, 181.26 ppm ; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{16}H_9O_2S$: 265.0245; found: 265.0413.

9-Methoxyphenanthro[4,3-*b*]thiophene-4,5-dione (25e)



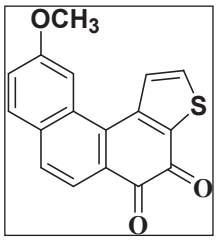
Dark red solid;yield: 94 % (100 mg / 0.34 mmol of **25e** obtained from 100 mg / 0.36 mmol of **24e**); mp: 206-208 °C; IR (KBr) ν_{max}: 1661 cm^{-1} and 1687 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6): δ = 3.99 (s, 3 H), 7.14 (d, J = 2.7 Hz, 1H), 7.32 (dd, J = 2.7 & 9.5 Hz, 1H), 7.40 (d, J = 5.4 Hz, 1H), 7.67 (d, J = 5.4 Hz, 1H), 7.70 (d, J = 8.7 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 8.75 (d, J = 9.5 Hz, 1H) ppm; ^{13}C NMR (75 MHz, DMSO-d_6): δ = 56.21, 108.84, 121.92, 123.40, 125.45, 127.11, 127.27, 127.80, 128.98, 129.00, 130.84, 138.47, 139.81, 146.82, 159.93, 174.36, 180.26 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{11}O_3S$: 295.0351; found: 295.0391 and [M+Na] calcd for $C_{17}H_{10}O_3S$: 317.0248; found : 317.0168.

7-Methylphenanthro[4,3-*b*]thiophene-4,5-dione (25f)



Dark red solid; yield: 97 % (102 mg / 0.37 mmol of **25f** obtained from 100 mg / 0.38 mmol of **24f**); mp: 220-221 °C; IR (KBr) ν_{max}: 1687 cm^{-1} and 1749 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): δ = 2.73 (s, 3H), 7.38 (d, J = 5.0 Hz, 1H), 7.66 (d, J = 5.5 Hz, 1H), 7.70-7.72 (m, 2H), 8.01 (s, 1H), 8.06-8.08 (m, 1H), 8.87-8.89 (m, 1H) ppm; ^{13}C NMR (125 MHz, $CDCl_3$): δ = 19.77, 91.08, 125.55, 125.82, 126.53, 126.60, 127.51, 127.61, 128.34, 128.93, 129.25, 129.87, 137.02, 148.52, 174.46, 181.56 ppm (one carbon was not observed, may be a quaternary carbon has not appeared with this number of scanning); HRMS (ESI+): *m/z* [M+Na] calcd for $C_{17}H_{10}O_2SNa$: 301.0299; found: 301.0327.

10-Methoxyphenanthro[3,4-*b*]thiophene-4,5-dione (31)



Dark red crystal, yield: 87 % (100 mg / 0.34 mmol of **31** obtained from 110 mg / 0.39 mmol of **30**); mp: 218-220 °C; IR (KBr) ν_{max}: 1621 cm^{-1} and 1647 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$ + DMSO d_6) : δ = 3.94 (s, 3H), 7.27 (br d, ill split, J = 8.4 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H), 7.80 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.94 (br s, 1H), 8.03 (d, J = 4.8 Hz, 1H), 8.17 (d, J = 4.8 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$ + DMSO d_6): δ = 56.03, 105.45, 122.27, 122.79, 129.55, 129.96, 130.18, 131.04, 131.32, 131.47, 133.64, 136.83, 139.97, 146.01, 159.74, 173.15, 181.74 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{17}H_{11}O_3S$: 295.0351; found: 294.8620 and [M+Na] calcd for $C_{17}H_{10}O_3SNa$: 317.0248; found: 316.8141.

5.4 Publication:

'*Thiophene Analogue of Isotanshinone-II Nucleus: A Novel Approach towards the Synthesis of Phenanthro[4,3-b]thiophene-4,5-dione and Phenanthro[3,4-b]thiophene-4,5-dione Derivatives'* Aparna Sarkar, Rumpa Das, and Gandhi K. Kar; **ChemistrySelect 2018**, 3, 11422-11426**.**

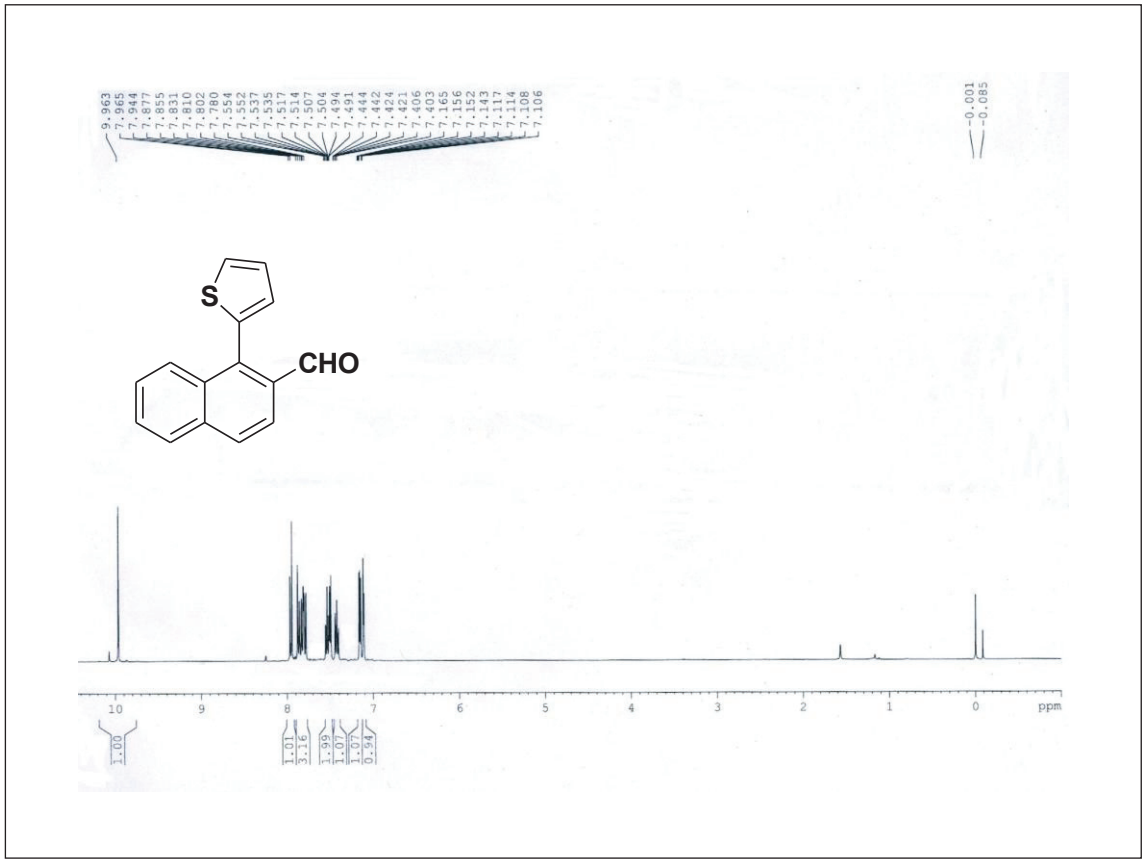
5.4 Oral presentation:

'*An approach towards the synthesis of phenanthro[4,3-b]thiophen-4,5-dione derivatives as thiophen analogue of core nucleus of Isotanshinone-II isolated from Salvia species*' Aparna

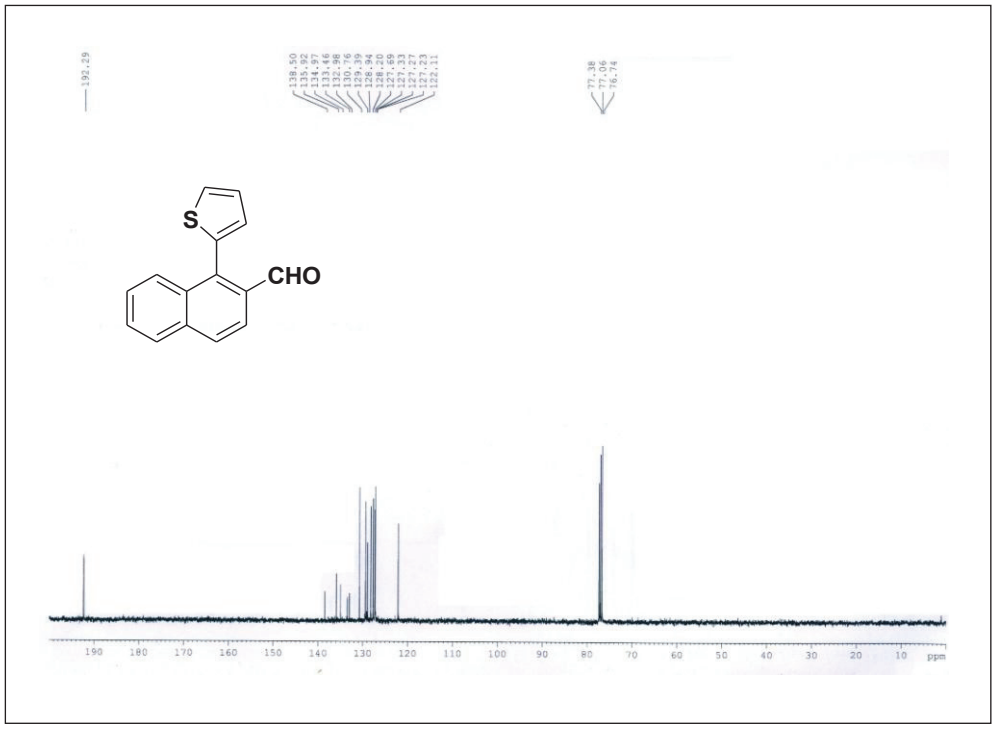
Sarkar, Gandhi K. Kar; oral presentation in *"National Symposium on contribution of Women in Science in India (NSCWSI 2018)"*, organized by Indian Science News Association (ISNA) at Calcutta University, Feb. 15-16, **2018**

5.5 Selected NMR spectra:

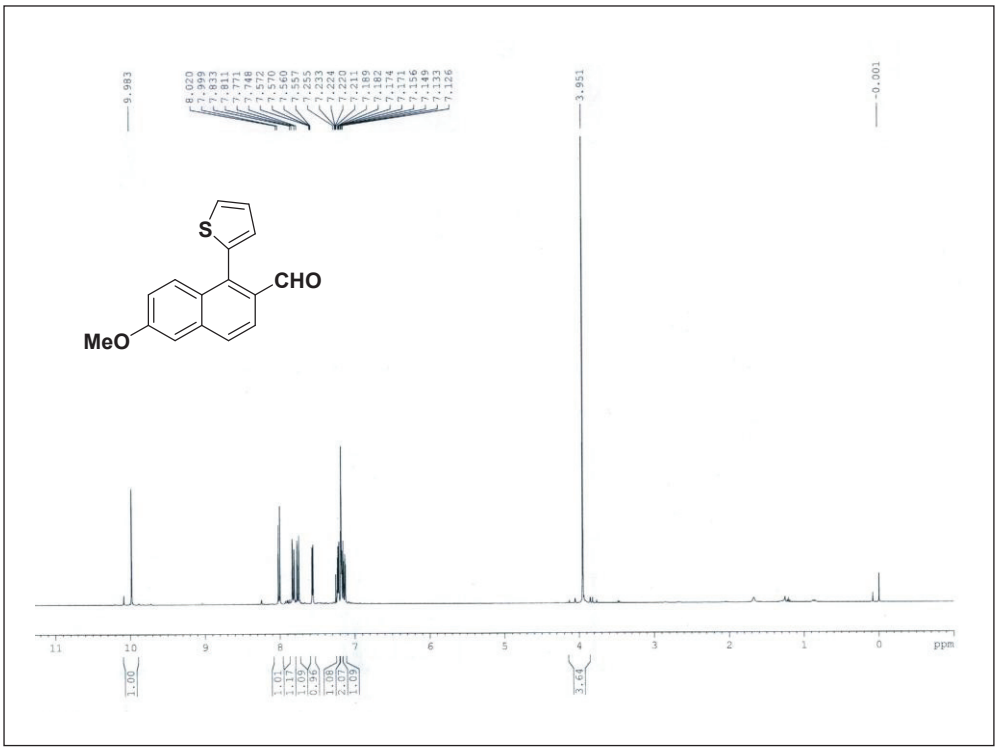
^{1}H NMR spectra for compound 20d:



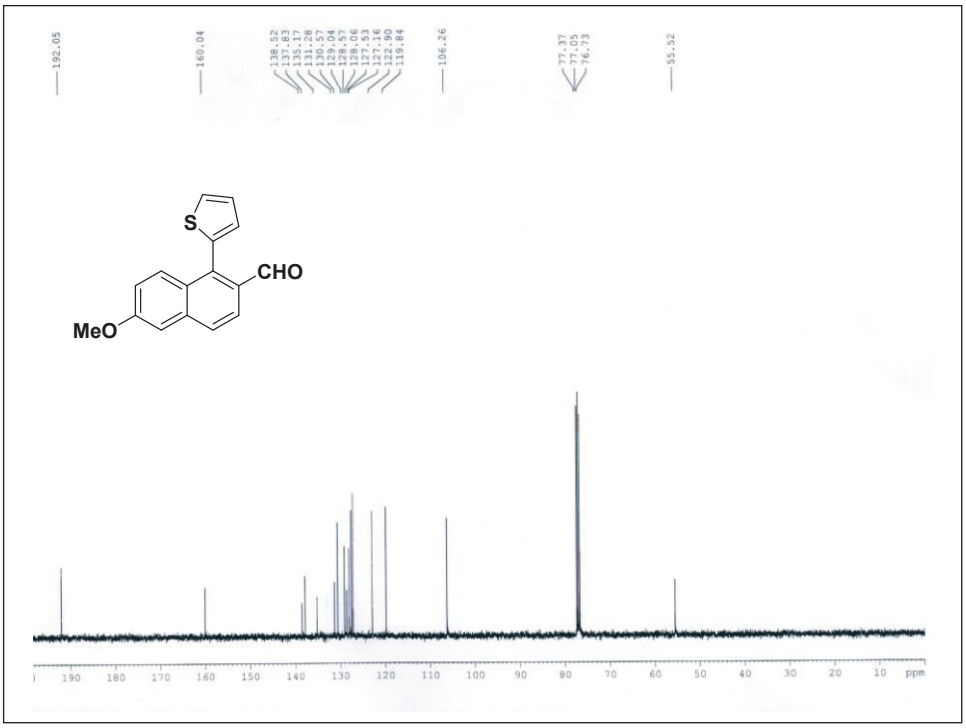
^{13}C NMR spectra for compound 20d:



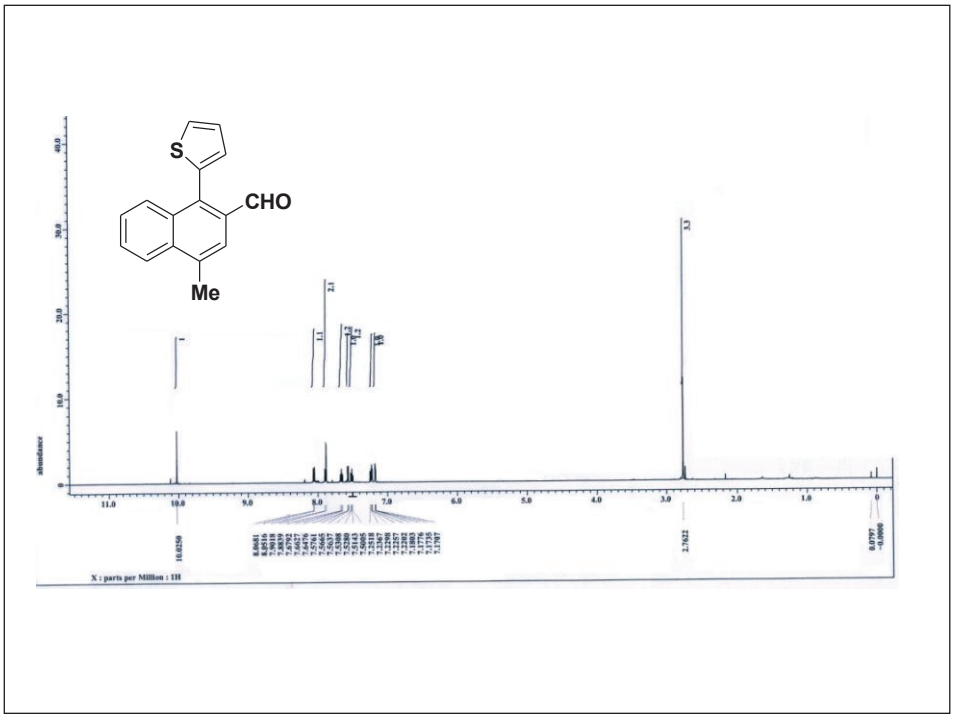
^{1}H NMR spectra for compound 20e:



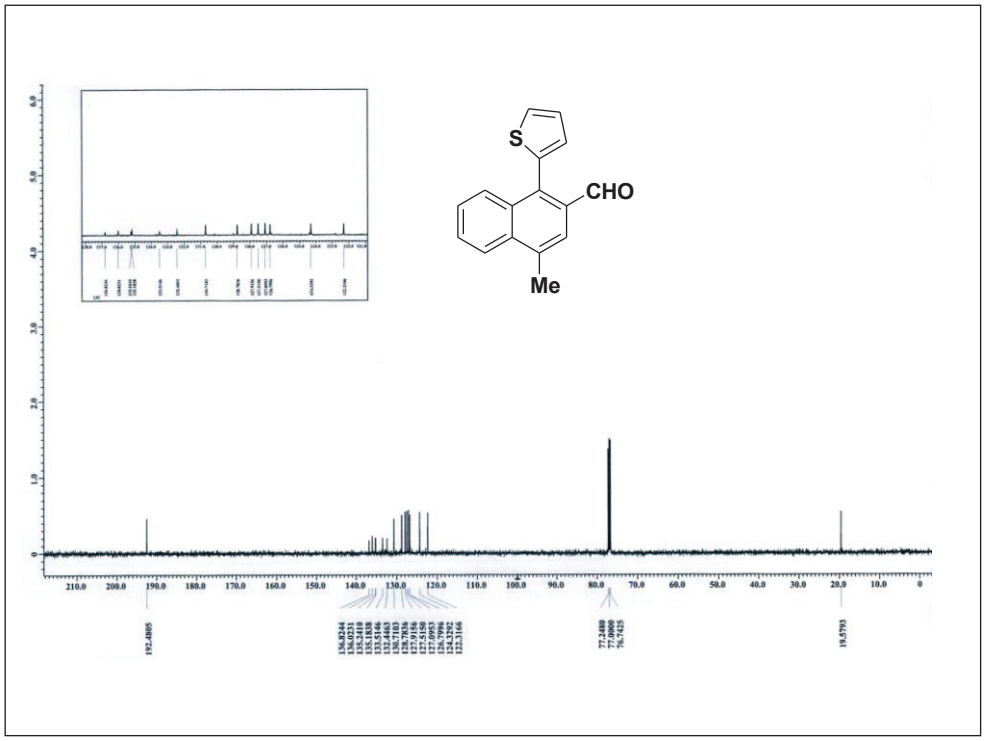
^{13}C NMR spectra for compound 20e:



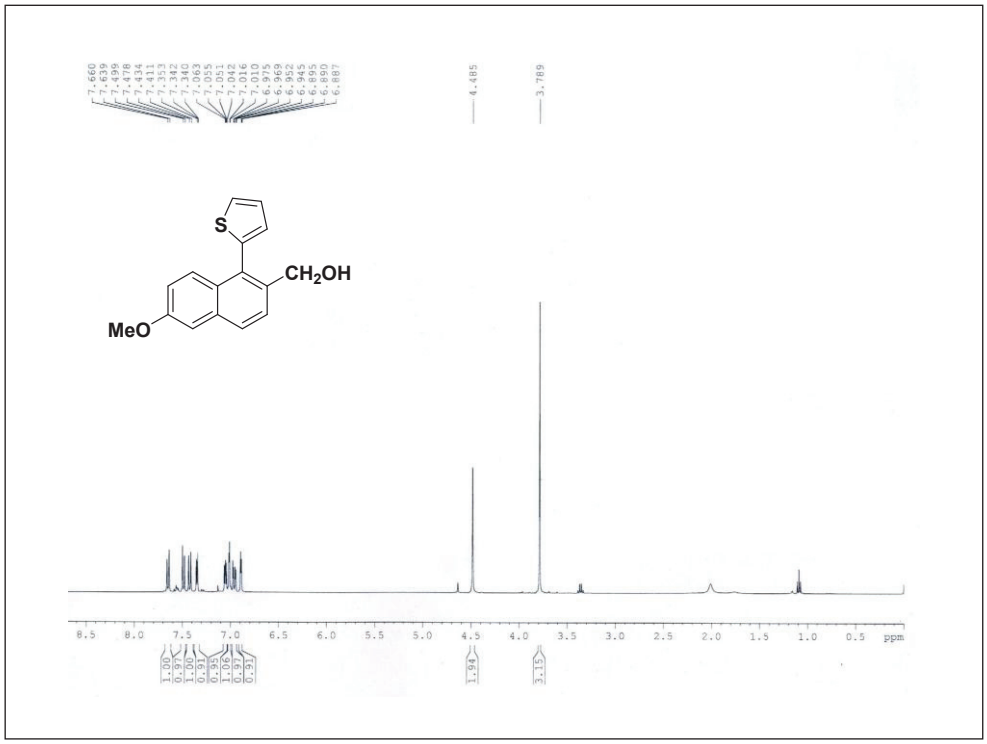
^{1}H NMR spectra for compound 20f:



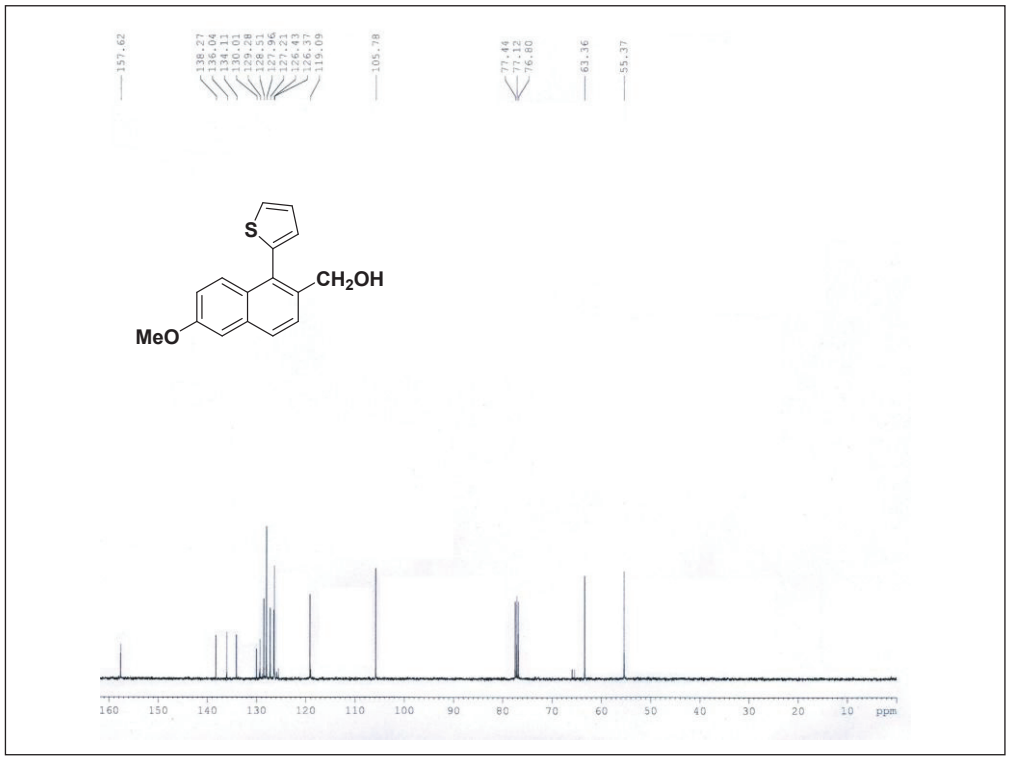
^{13}C NMR spectra for compound 20f:



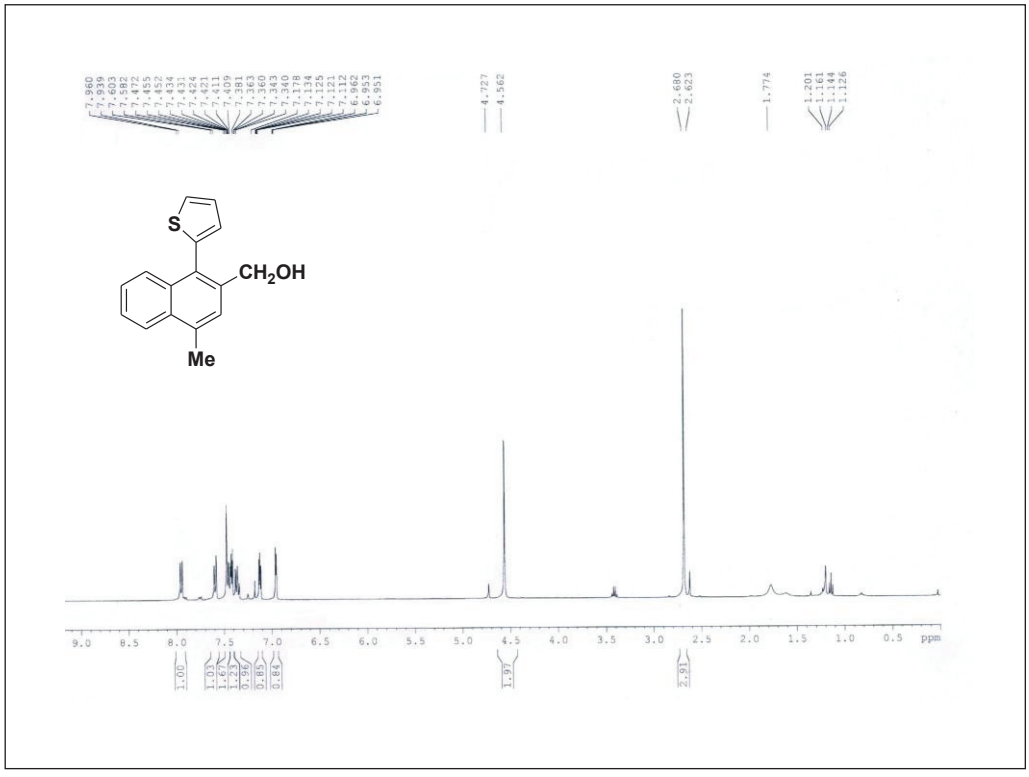
^{1}H NMR spectra for compound 21e:



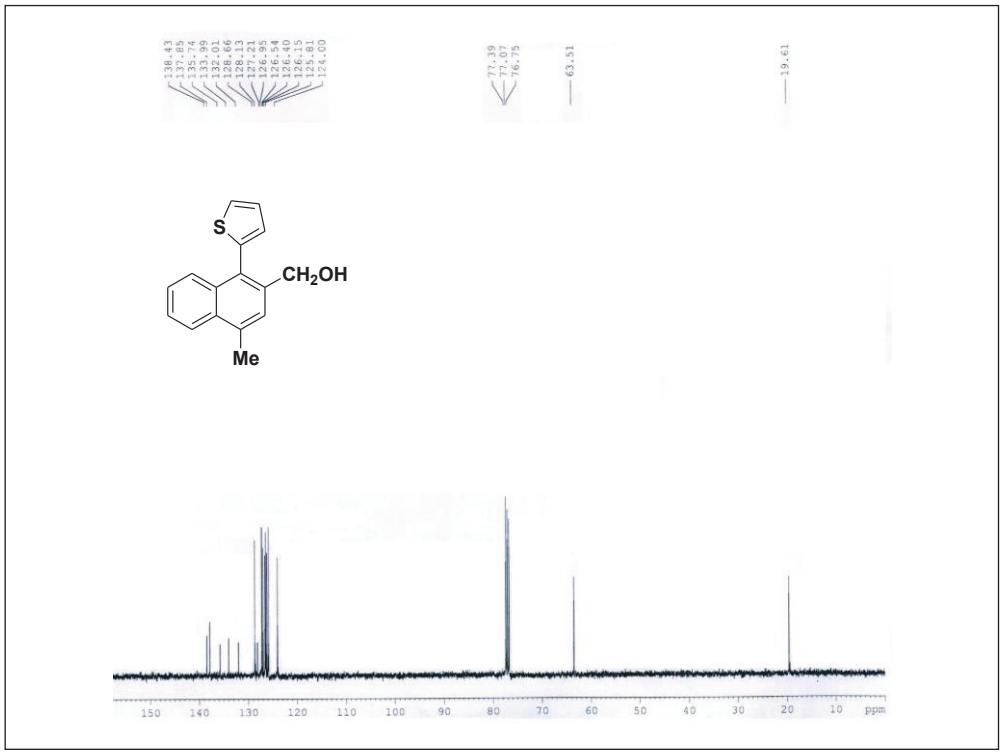
^{13}C NMR spectra for compound 21e:



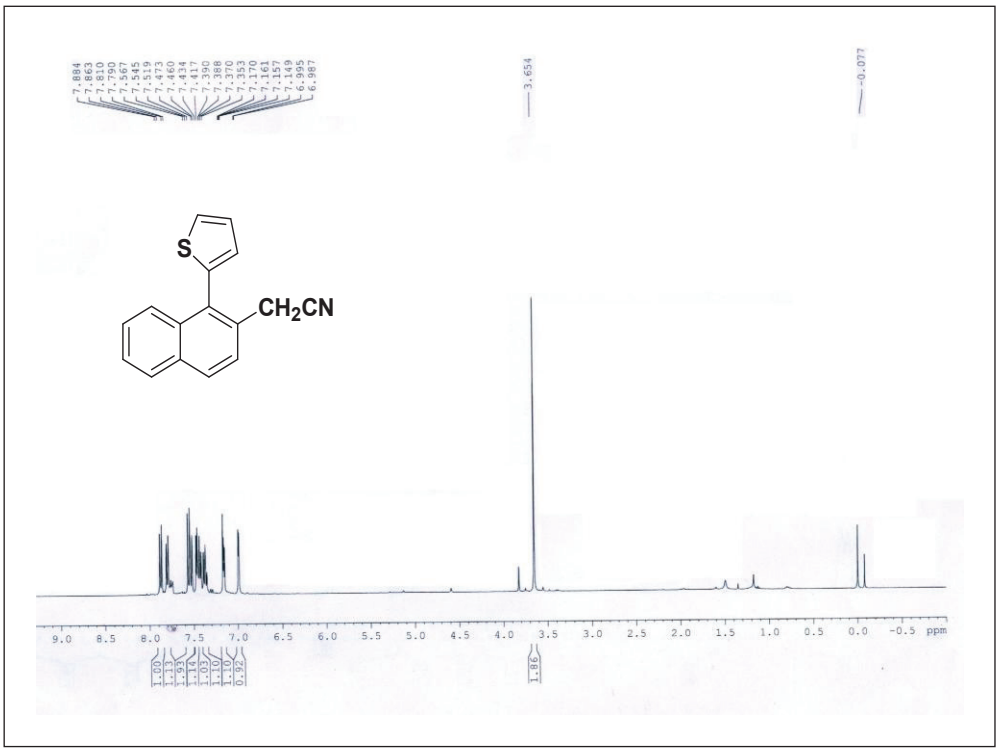
^{1}H NMR spectra for compound 21f:



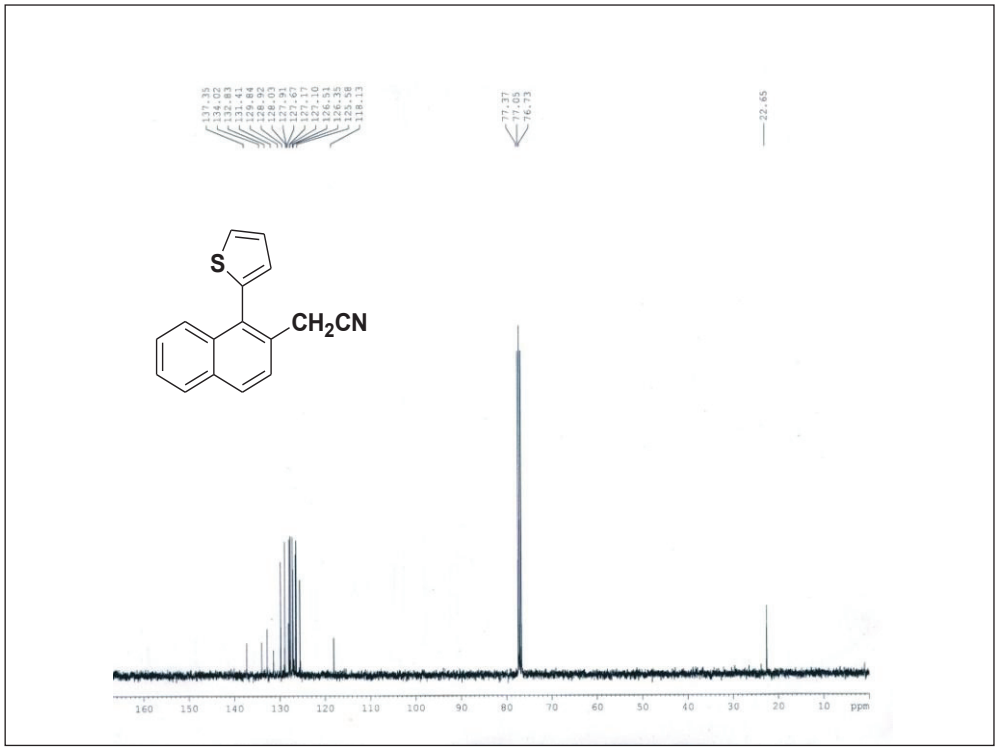
^{13}C NMR spectra for compound 21f:



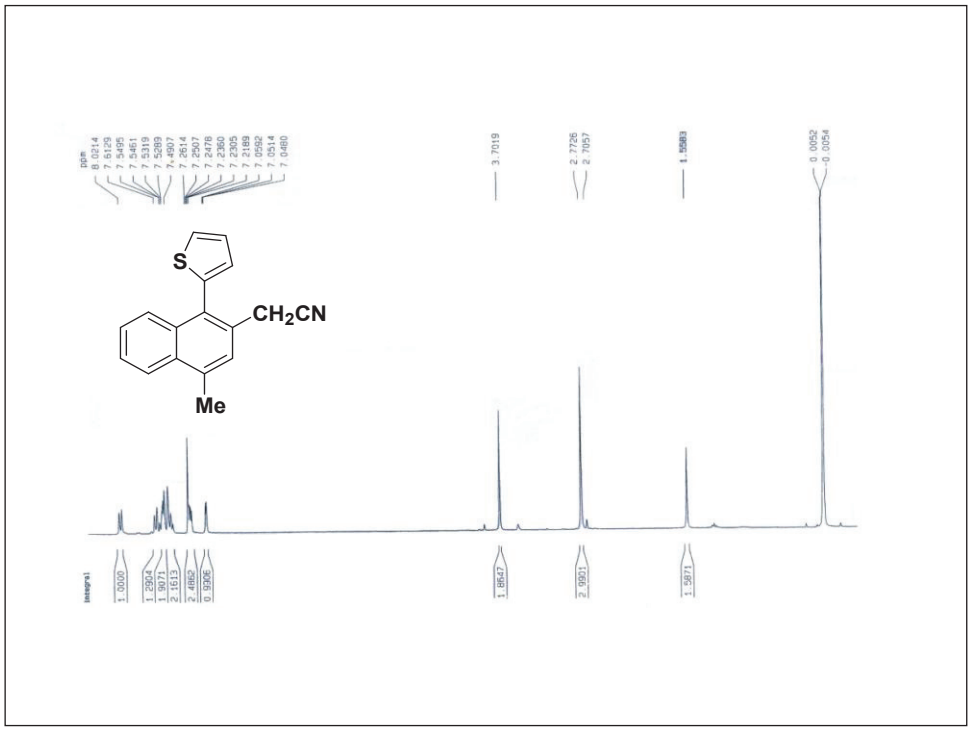
^{1}H NMR spectra for compound 22d:



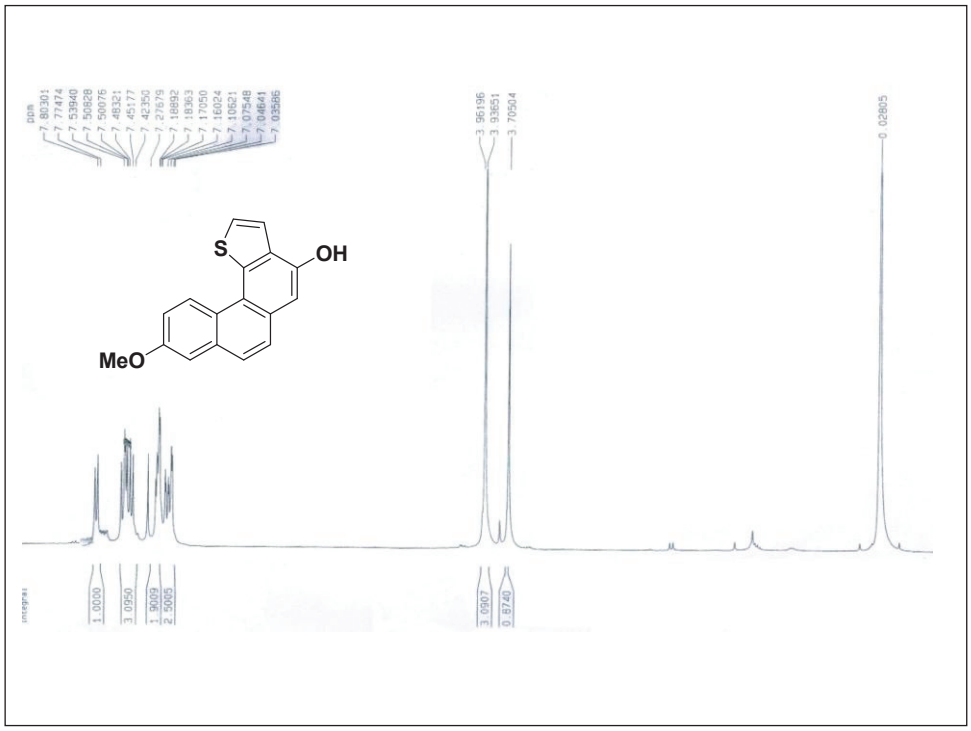
^{13}C NMR spectra for compound 22d:



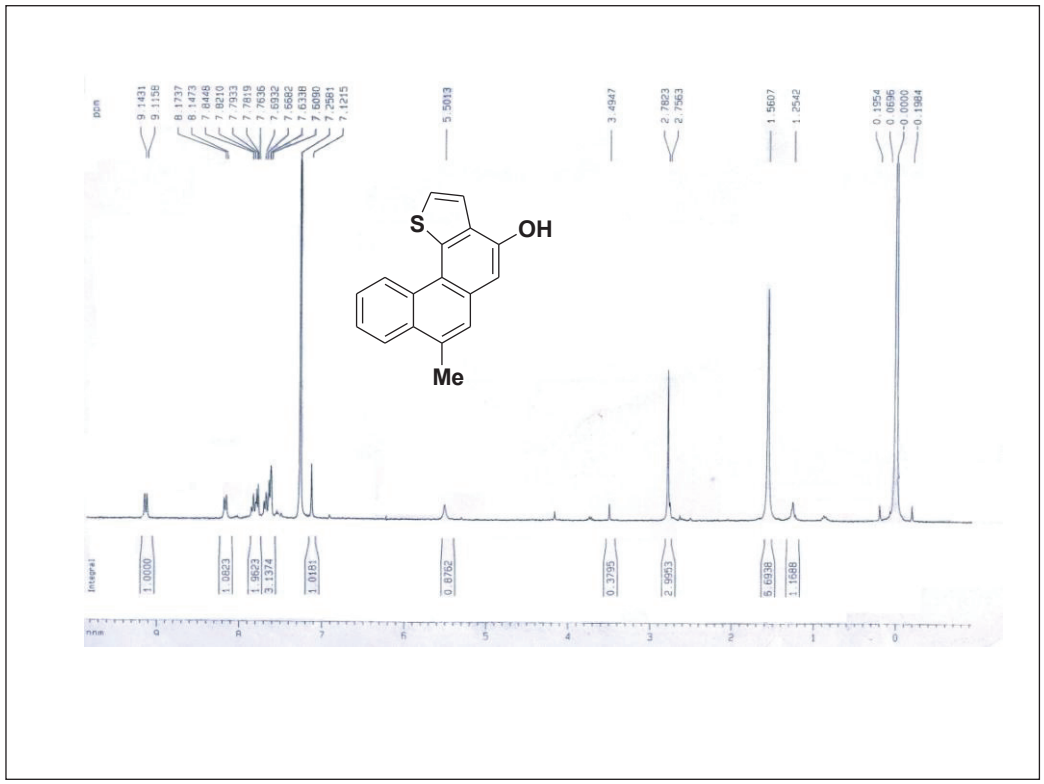
^{1}H NMR spectra for compound 22f:



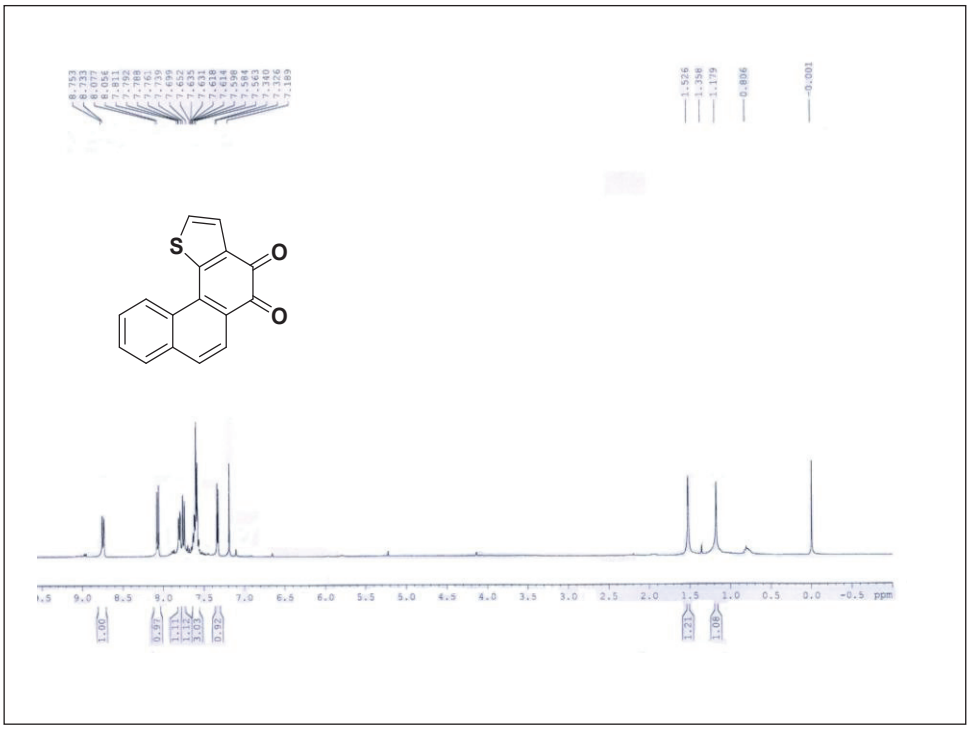
^{1}H NMR spectra for compound 24e:



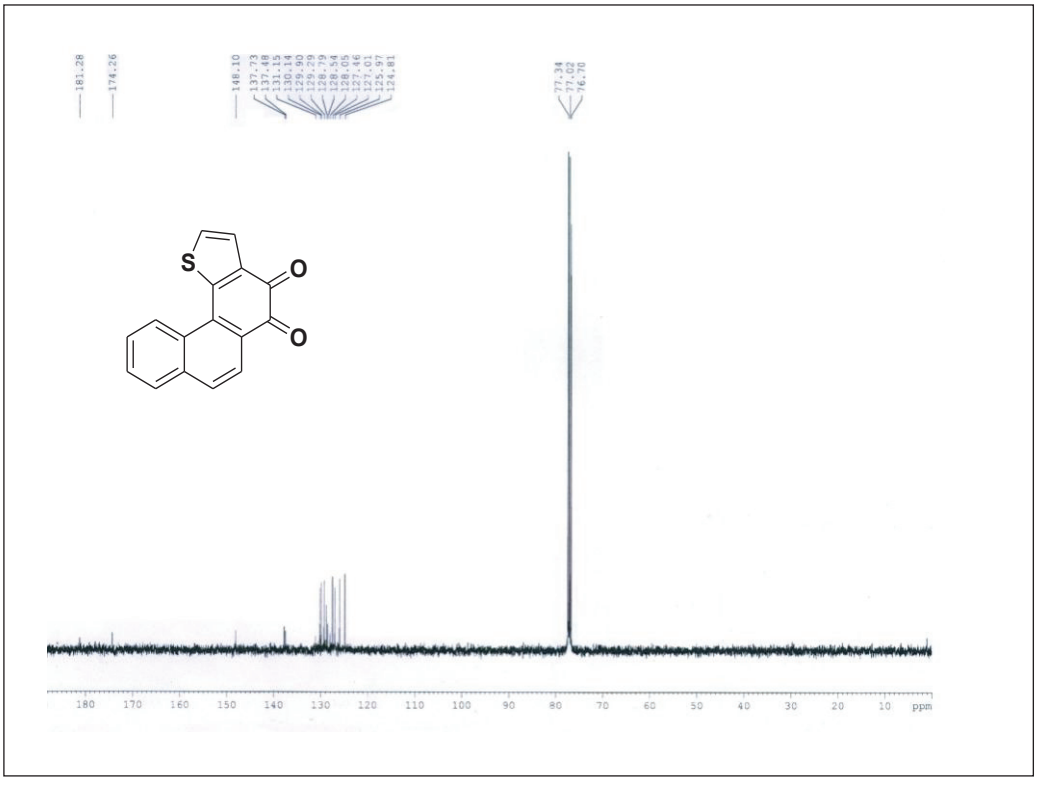
^{1}H NMR spectra for compound 24f:



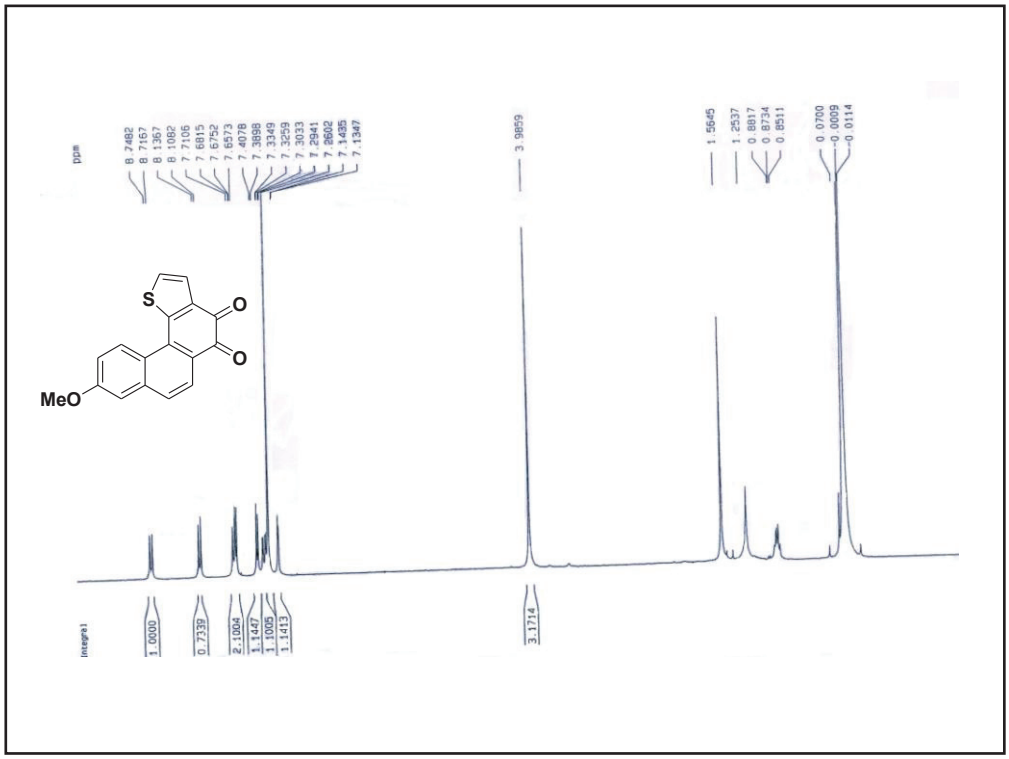
^{1}H NMR spectra for compound 25d:



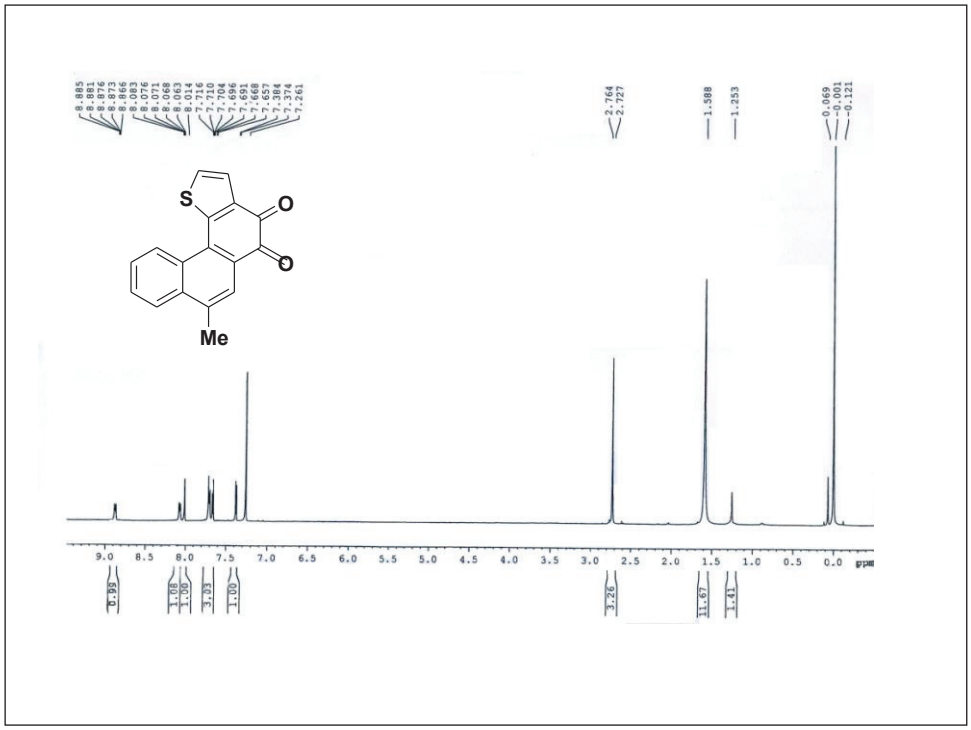
^{13}C NMR spectra for compound 25d:



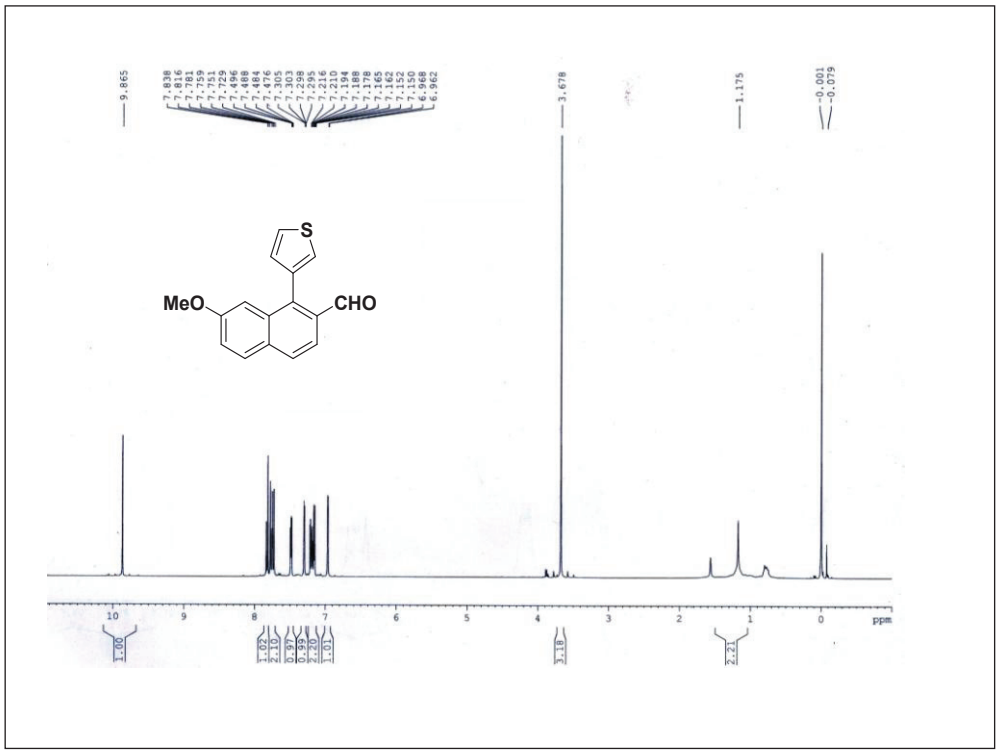
^{1}H NMR spectra for compound 25e:



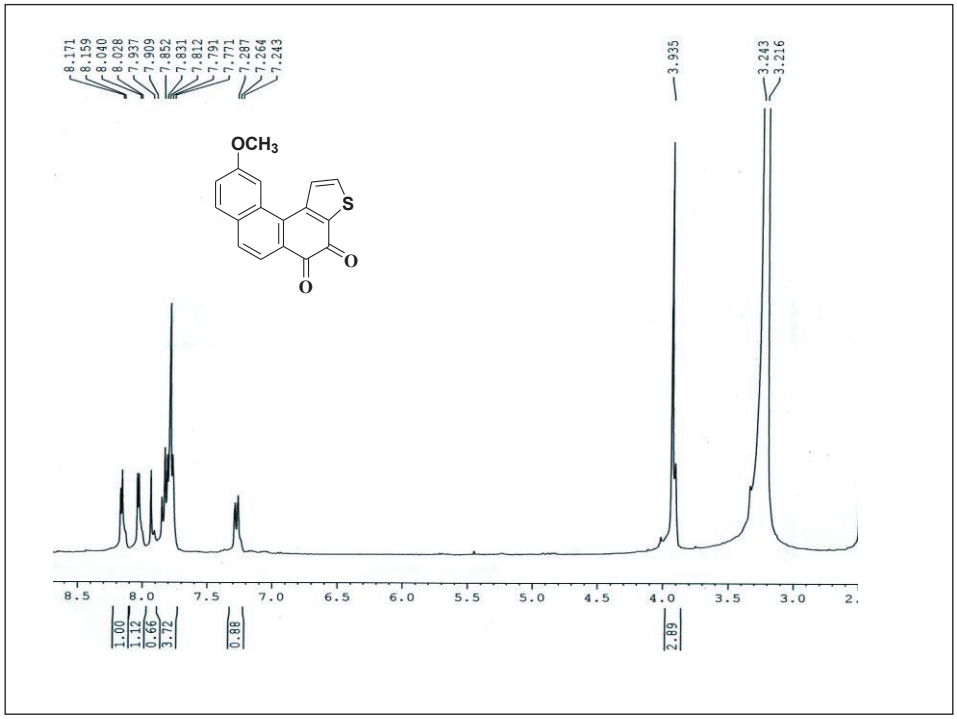
^{1}H NMR spectra for compound 25f:



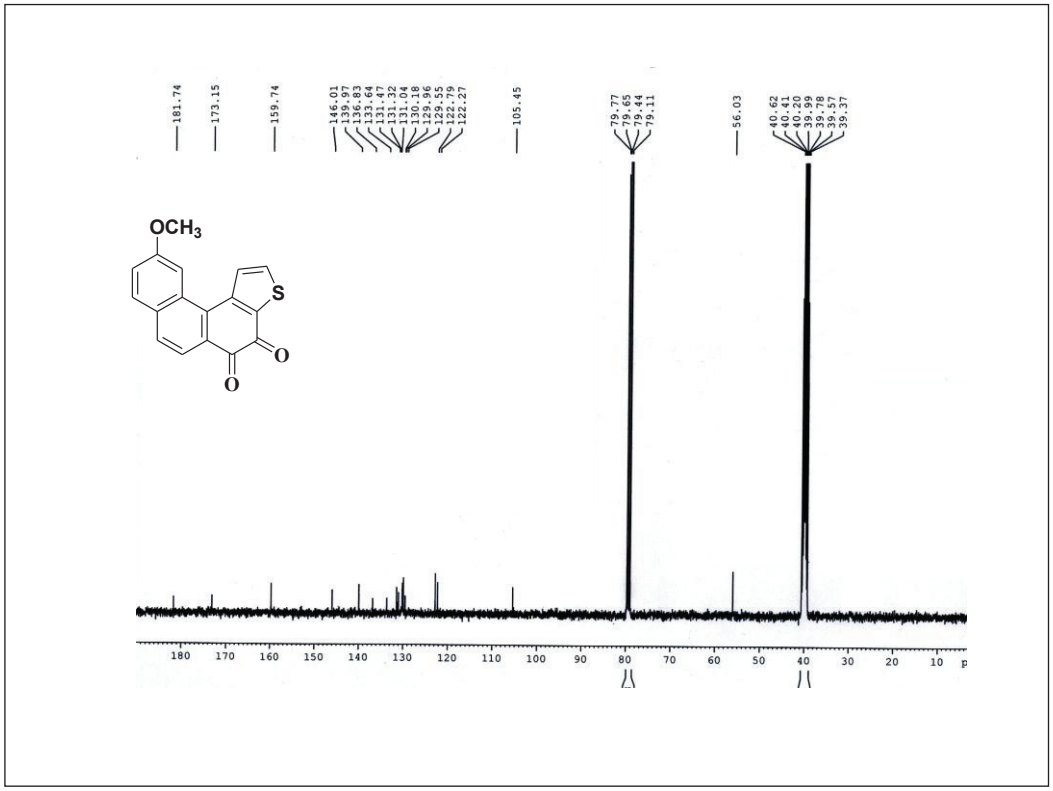
^{1}H NMR spectra for compound 26:



^{1}H NMR spectra for compound 31:



^{13}C NMR spectra for compound 31:



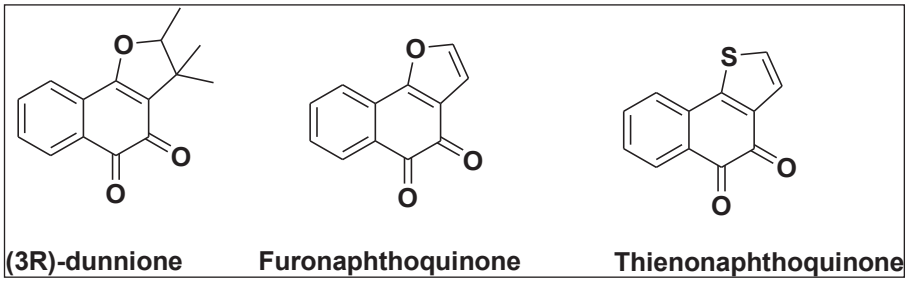
Chapter IIC

Studies towards the synthesis of thienonaphthoquinone derivatives simulating BCD rings of isotanshinone II core nucleus

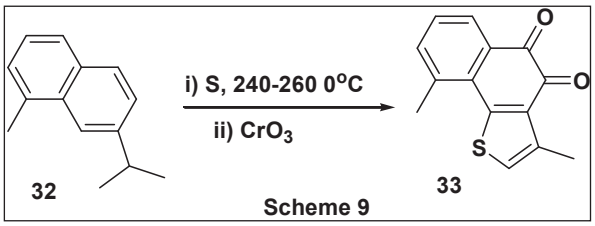
Studies towards the synthesis of thienonaphthoquinone derivatives simulating BCD rings of isotanshinone II core nucleus

6.1 Introduction

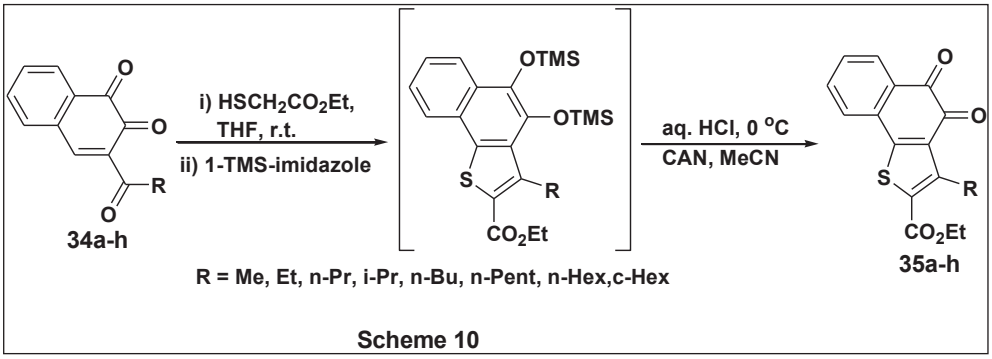
Various naphthoquinones condensed with heterocyclic moieties like furan, dihydrofuran, thiophene, pyran, etc. are well known for their antitumour activities.[12] Furonaphthoquinone derivatives are also known as natural products and posseses cancer chemopreventive activity.[13] More than 140 studies with cultures of *S. dunnii* (Lamiales) have demonstrated that natural occurring furonaphthoquinone derivatives are cytotoxic against a range of breast cancer and a pancreatic tumour. (3R)-Dunnione (1)[14] inhibited T-cell motility in the human Jurkat T-cell line. Thienonaphthoquinones, however, are not available from natural sources though many of condensed thienonaphthoquinone derivatives are well known for their bioactivity.



Notably, studies on the biological activities of naphtho[2,1-*b*]thiophene-4,5-diones, naphtho[1,2-*b*]thiophene-4,5-diones and naphtho[2,3-*b*]thiophene-4,9-diones are of special importance as some of such derivatives also show antitumor, antibacterial or antimicrobial activities and are highly active even towards the doxorubicin-resistant cell lines like MDA-MB435 (melanoma), SF-295 (glioblastoma), IGROV (ovarian) and human cell lines.[15-18] Though not too many but some reports on the synthesis of thienonaphthoqunone derivatives available in literature. In **1970**, Karokawa reported the synthesis of 3,9-dimethylnaphtho[1,2-*b*]thiophene-4,5-dione (**33**) starting from 7-isopropyl-1-methylnaphthalene (**32**), as outlined in scheme 9.[19]

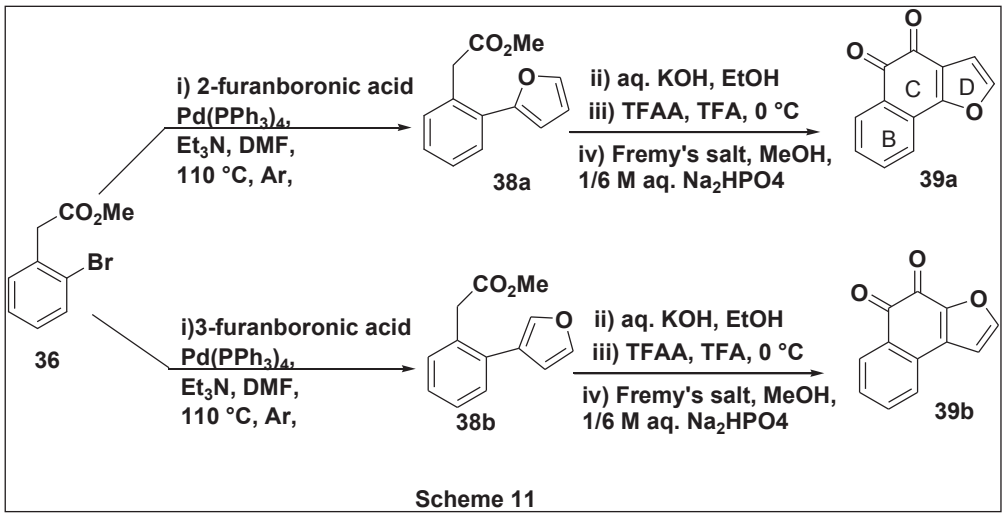


In **2005**, Kobayashi *et al.* reported the synthesis of ethyl 4,5-dioxo-4,5dihydronaphtho[1,2-*b*]thiophene-2-carboxylate derivatives **35a-h** starting from 3-acyl-1,2-naphthoquinones **34a-h** (scheme 10).[20]



6.2 Present Work:

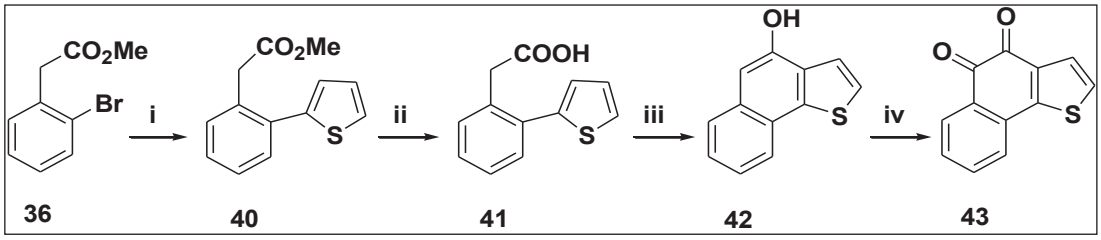
Recently, a synthetic route for the furonaphthoquinones simulating BCD rings of tanshinones and isotanshinone II have been developed by Kar's group[21,22] starting from methyl 2-(2-bromophenyl)acetate (**36**) and furanboronic acid (scheme 11).



Following the same protocol, synthesis of two thienonaphthoquinones, naphtho[1,2-*b*]thiophene-4,5-dione and naphtho[2,1-*b*]thiophene-4,5-dione have been described in this chapter IIC. Commercially available methyl 2-(2-bromophenyl)acetate (**36**) and 2/3-thiopheneboronic acids have been used as staring materials to execute the desired synthesis (scheme 12 and 13).

6.3 Result and discussion

The Pd(0)-catalysed Suzuki coupling of the ester 3**6** with 2-thiopheneboronic acid produced methyl 2-[2-(2-thienyl)phenyl]acetate (**40**) as a pale yellow oil in good yield. In IR spectrum, it showed strong absorbtion at 1738 cm^{-1} for the $–CO_2CH_3$ functionality. ^1H NMR, ^{13}C NMR and HRMS data also justified the assigned structure (vide experimental). Subsequent hydrolysis of **40** to the carboxylic acid **41**, followed by cyclisation to the naphtho[1,2-*b*]thiophen-4-ol (**42**) was achieved in excellent yield. The carboxylic acid **40** exhibited a strong absorption band around 1693 cm^{-1} for the presence of $–CO_2H$ group. ^1H NMR (signals and splitting pattern shown in fig. 4), ^{13}C NMR and HRMS analysis also justified the assigned structure of the compound **42** (*vide* experimental).



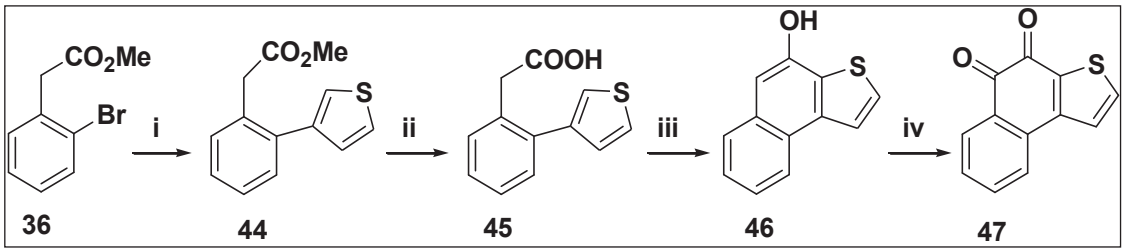
Reagents and conditions: (i) 2-thiopheneboronic acid, Et_3N, DMF, $Pd(PPh_3)_4$, 110 °C, nitrogen atm, 6 hrs, 65 %; (ii) KOH, EtOH, H_2O, reflux, 12 hrs, 78 %; (iii) TFAA, TFA, 0 °C, overnight, 80 %; (iv) Fremy's salt, 1/6 M aq. Na_2HPO_4, MeOH, r.t., overnight, 72 %.

Scheme 12: Synthesis of naphtho[1,2-*b*]thiophene-4,5-dione

Oxidation of the intermediate phenol **42** with Fremy's salt furnished the target molecule **43** in very good yield (scheme 12). In IR spectrum, the compound **43** exhibited a broad absorption band around 1659 cm^{-1} for the presence of carbonyl groups. ^1H NMR (400 MHz, $CDCl_3$)

spectral data (fig. 7) of the compounds **43** is in conformity with the assigned structure. ^{13}C NMR [(100 MHz, $CDCl_3$): δ = 124.72, 126.08, 127.80, 129.10, 129.73, 130.28, 132.41, 135.85, 136.55, 151.27, 173.86, 180.47 ppm] as well as HRMS data [(ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_7O_2S$: 215.0089; found: 214.9340 and [M+Na] calcd for $C_{12}H_6O_2SNa$: 236.9986; found: 236.9225] also supported the structure.

Following a similar reaction sequence starting from same ester **36** and 3-thiopheneboronic acid, the synthesis of naphtho[2,1-*b*]thiophene-4,5-dione (**47**) was accomplished successfully (scheme 13).



Reagents and conditions: (i) 3-thiopheneboronic acid, Et_3N, DMF, $Pd(PPh_3)_4$, 110 °C, nitrogen, 5 hrs, 72 %; (ii) KOH, EtOH, H_2O, reflux, 10 hrs, 83 %; (iii) TFAA, TFA, 0 °C, overnight, 75 %; (iv) Fremy's salt, MeOH, 1/6 M aq. Na_2HPO_4, r. t., overnight, 86 %.

Scheme 13: Synthesis of naphtho[2,1-*b*]thiophene-4,5-dione

All the compounds were characterised by usual spectroscopic analysis (IR, ^1H NMR, ^{13}C NMR, HRMS). Details have been given in experimental section. Tentative interpretations of ^1H NMR spectral data of the thienonaphthoquinones (**43** and **47)** are presented in fig. 7.

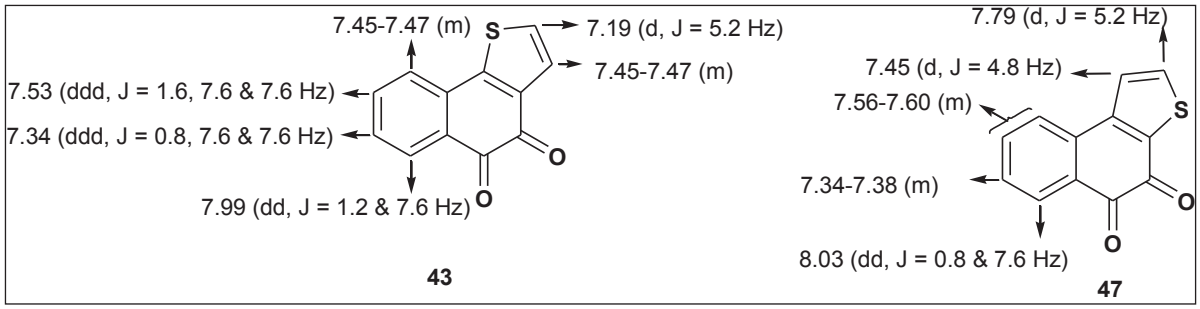


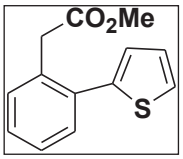
Figure 7: Tentative assignments of ^1H NMR chemical shift of the *o*-quinones 43 and 47

6.4 Conclusion

In conclusion, we have achieved the synthesis of two thienonaphthoquinone derivatives **43** and **47** *via* a novel and very short synthetic route. The naphthoquinone **43**, as a thiophene analogue, simulates BCD rings of isotanshinone II core nucleus. The method has great potential for the synthesis of many other substituted thenonaphthoquinones using substituted 2-phenylacetic ester derivatives and substituted thiopheneboronic acids. Biophysical and biological studies of the synthesised compounds are under progress as collaborative work, and results will be published in due time.

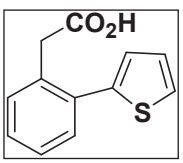
6.5 Experimental:

Methyl 2-[2-(2-thienyl)phenyl]acetate (40)



A stirred mixture of 500 mg (2.18 mmol) of bromo ester (**36**), 2-thiopheneboronic acid (2.62 mmol), triethylamine (5.45 mmol) in 4 ml of DMF was degasified for 25 minutes by bubbling N_2 through it. Now to it, $Pd(PPh_3)_4$ catalyst (2 mol %) was added quickly and degasified for another 15 minutes. The mixture was then heated at about 110 ^oC for 6 hrs under N_2 atmosphere. When the reaction was completed (checked by TLC), the mixture was poured into ice water (15-20 ml) and extracted thoroughly with ether (3x20 ml). Organic layer was washed with ice water, 5 % aq. $NaHCO_3$ solution and finally with ice water. Removal of solvent afforded the crude product which on purification by column chromatography [silica gel 100-200 mesh / pet ether (60-80 °C)-EtOAc, 15:1] furnished the compound **40** as a yellow oil. Yield: 330 mg, 65 %. IR (KBr) ν_{max}: 1738 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ 3.57 (s, 3H), 3.67 (s, 2H), 6.96- 7.01(m, 2H), 7.21-7.26 (m, 4H), 7.34 (dd, J = 2 Hz and 8.0 Hz, 1H) ppm;^{13}C NMR (100 MHz, $CDCl_3$): δ = 39.14, 52.08, 125.79, 127.01, 127.26, 127.29, 128.25, 130.76, 131.27, 132.74, 134.77, 141.94, 172.20 ppm; HRMS (ESI+): *m/z* [M+Na] calcd for $C_{13}H_{12}O_2SNa$: 255.0456; found: 254.8899.

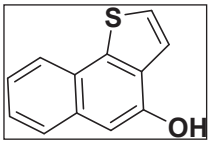
2-[2-(2-Thienyl)phenyl]acetic acid (41)



To a solution of the compound **40** (310 mg, 1.34 mmol) in ethanol (3 ml), 4 ml 30 % aq. KOH solution was added. It was refluxed for 12 hrs. Excess ethanol

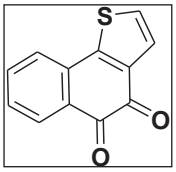
was removed by distillation and the residue was diluted with ice-water (5 ml). It was extracted with ether (2x15 ml).The aqueous part was acidified with 1:1 HCl under ice-cold condition. The precipitated acid was filtered and washed thoroughly with cold water and dried. The crude acid **41** thus obtained was redissolved in saturated aq. $NaHCO_3$ solution, filtered to remove any suspended impurities. The filtrate was cooled in ice bath was acidified 1:1 aq. HCl. The acid **41** precipitated as white solid was filtered and dried to furnish the title compound **41** as off white solid. Yield: 240 mg, 78 %. Mp: 185-186 ^oC. IR (KBr) ν_{max}: 1693 cm^{-1}; HRMS (ESI+): *m/z* [M+Na] calcd for $C_{12}H_{10}O_2SNa$: 241.0299; found: 241.1128.

Naphtho[1,2-*b*]thiophene-4-ol (42)



To an ice cold magnetically stirred mixture of 230 mg (1 mmol) of the acid **41** and 9 ml of trifluoroacetic anhydride, 2.5 ml trifluoroacetic acid was injected slowly at 0-4 °C and stirred further for 1 hr protecting from moisture and then left in the refrigerator for overnight. The reaction mixture was decomposed with crushed ice and extracted with dichloromethane thoroughly. The organic layer was washed with cold aq. $NaHCO_3$ solution, cold brine solution and dried (anhyd. Na_2SO_4). Removal of the solvent and purification of the crude product by plate chromatography (Silica gel GF254; benzene), the phenol **42** was obtained as semi solid mass. Yield: 160 mg (0.8 mmol, 80 %); ^1H NMR (400 MHz, $CDCl_3$): δ = 5.48 (br s, 1H), 7.01 (s, 1H), 7.43-7.46 (m, 2H), 7.51 (d, J = 5.4 Hz, 1H), 7.63 (d, J = 5.4 Hz, 1H), 7.76 (d, J = 7.4 Hz, 1H), 8.06 (d, J = 7.4 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 105.46, 122.63, 123.23, 123.79, 124.24, 124.53, 125.94, 126.57, 127.04, 127.45, 134.44, 148.75 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_9OS$: 201.0296; found: 201.0602

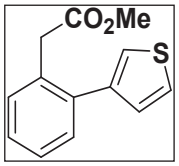
Naphtho[1,2-*b*]thiophene-4,5-dione (43)



To a vigorously stirred solution of 900 mg Fremy's salt in 20 ml aq. 1/6M disodium hydrogen phosphate at 0-5 °C, a solution of the phenol **42** (130 mg, 0.65 mmol) in MeOH (8 ml) was added drop wise. The colour of the solution quickly changes from violet to reddish brown with formation of dark red to deep red ppt. Stirring was continued at 0-5 °C for an additional hour and the mixture was left in the refrigerator for overnight. The reaction mixture was then extracted with dichloromethane, washed with cold

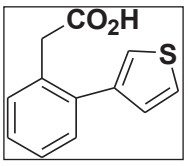
water, dried (anhyd. Na_2SO_4) and solvent removed. Crude *o*-quinone derivative thus obtained on further purification by preparative TLC (Silica gel GF254 mesh; benzene-methanol, 5:1) followed by recrystallisation from MeOH afforded the title compound **43** as deep orange solid. Yields: 100 mg (0.47 mmol), 72 %; mp: 207-208 ^oC. IR (KBr) ν_{max}: br peak 1659 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, J = 5.2 Hz, 1H), 7.34 (ddd, J = 0.8, 7.6 & 7.6 Hz, 1H), 7.45 (d, J = 7.6 Hz, 1H), 7.46 (d, J = 5.2 Hz, 1H), 7.53 (ddd, J = 1.6, 7.6 & 7.6 Hz, 1H), 8.00 (d, J = 0.8 and 7.2 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.72, 126.08, 127.80, 129.10, 129.73, 130.28, 132.41, 135.85, 136.55, 151.27, 173.86, 180.47 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_7O_2S$: 215.0089; found: 214.9340 and [M+Na] calcd for $C_{12}H_6O_2SNa$: 236.9986; found: 236.9225.

Methyl 2-[2-(3-thienyl)phenyl]acetate (44):



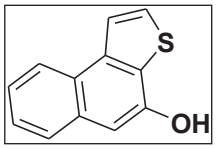
500 mg (2.18 mmol) of the bromoester **36** was subjected to Suzuki coupling reaction with 3-thiopheneboronic acid (2.62 mmol) under the identical reaction condition, as used for the preparation of the compound **40,** and 365 mg (1.57 mmol, 72 %) of the compound **44** (yellowish oil) was obtained after usual work up and purification . IR (KBr) ν_{max}: 1727 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 3.55 (s, 3H), 3.57 (s, 2H), 7.03 (dd, J =1.6 and 4.8 Hz, 1H), 7.17 (dd, J =1.6 and 3.2 Hz, 1H), 7.21-7.27 (m, 5H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 38.95, 52.07, 123.20, 125.45, 127.29, 127.69, 129.04, 130.30, 130.51, 132.16, 137.24, 141.27, 172.42 ppm. HRMS (ESI+): *m/z* [M+Na] calcd for $C_{13}H_{12}O_2SNa$: 255.0456; found: 254.8899.

2-[2-(3-Thienyl)phenyl]acetic acid (45)



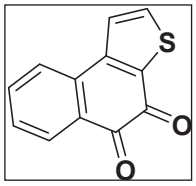
340 mg (1.47 mmol) of the ester **44** on hydrolysis with 4 ml ethanolic 30 % KOH, under the identical reaction condition, as used for the preparation of the compound **41** afforded the compound **45** as a white solid, after usual work up and purification. Light brown solid. Yield: 280 mg (1.22 mmol, 83 %); mp: 188-190 ^oC. IR (KBr) ν_{max}: 1699 cm^{-1}; HRMS (ESI+): *m/z* [M+Na] calcd for $C_{12}H_{10}O_2SNa$: 241.0299; found: 241.1128.

Naphtho[2,1-*b*]thiophene-4-ol (46)



Cyclisation of the carboxylic acid **45** (260 mg, 1.13 mmol) with the mixture of 7 ml trifluoroacetic anhydride and 3 ml trifluoroacetic acid, under the identical reaction condition, as used for the preparation of the compound **42** afforded after usual work up the compound **46** and purification of it the phenol **46** was obtained as a brown low melting solid. Yield: 170 mg (0.85 mmol, 52 %). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 6.89 (br s, 1H), 7.17 (s, 1H), 7.41(d, J = 5.2 Hz,1H), 7.43- 7.48 (m, 2H), 7.64 (d, J = 5.2 Hz, 1H), 7.91 (d, J = 7.6 Hz, 1H), 7.95 (d, J = 7.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 105.41, 108.45, 121.23, 123.48, 124.20, 124.36, 125.86, 125.92, 127.58, 129.40, 148.65, 162.61 ppm; HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_9OS$: 201.0296; found: 201.0256.

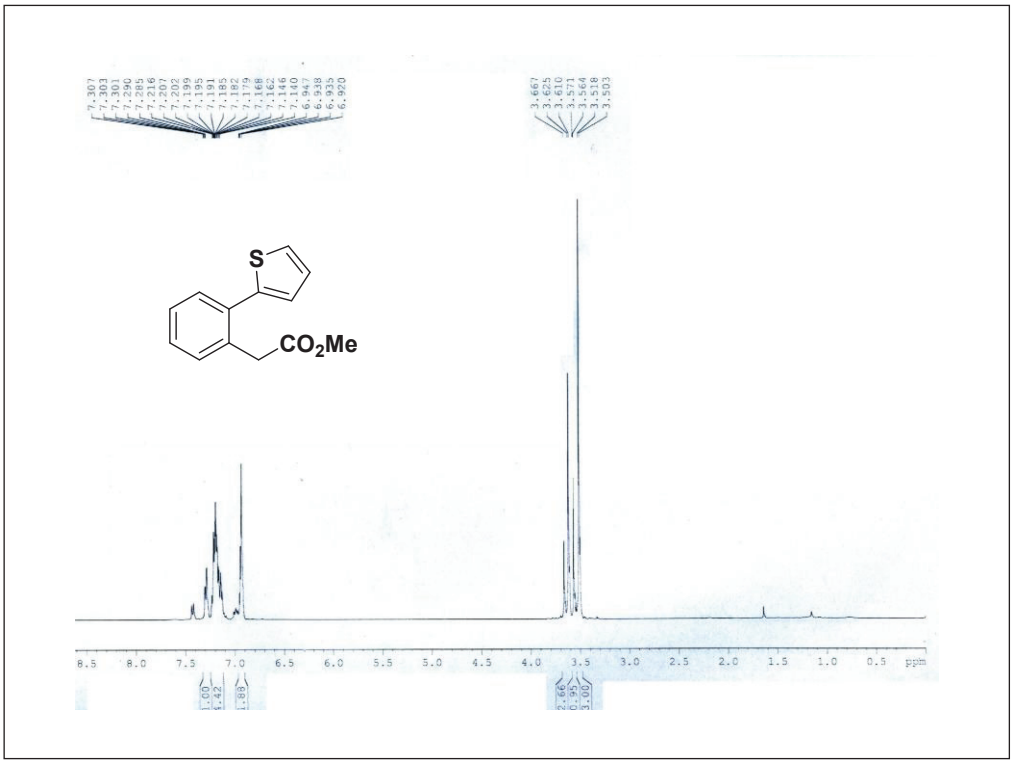
Naphtho[2,1-*b*]thiophene-4,5-dione (47)



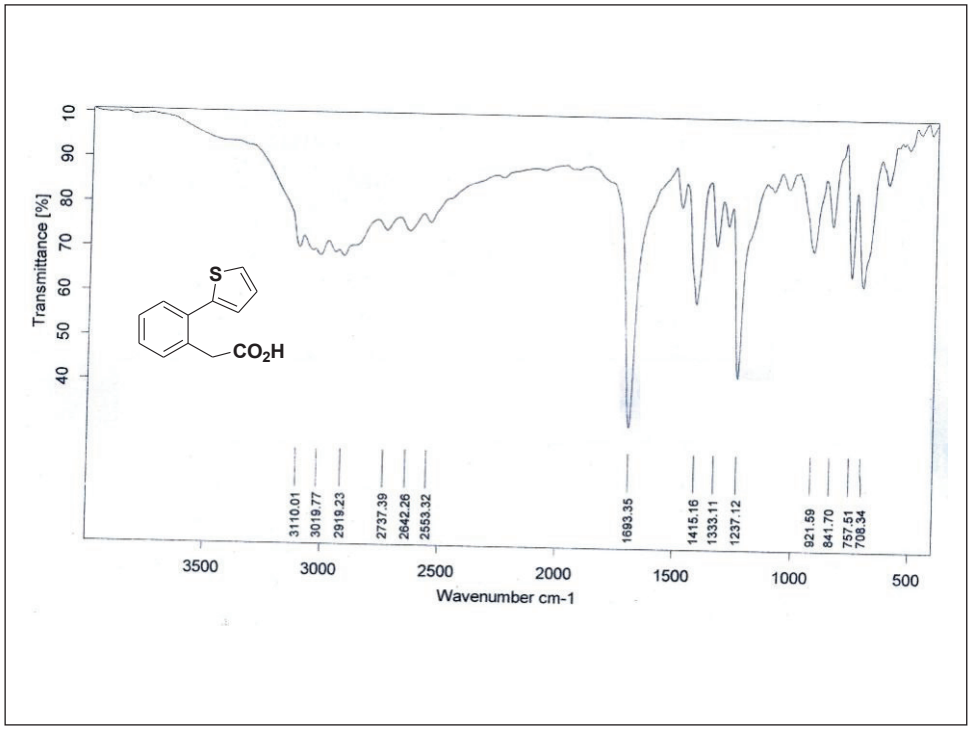
The phenolic compound **46** (130 mg, 0.65 mmol) on oxidation with 900 mg of Fremy's salt under the identical reaction condition, as used for the preparation of the compound **43,** afforded the *o*-quinone **47** as a deep yellow solid, after usual work up and purification. Yield: 120 mg (0.56 mmol, 86 %). Mp: 210-212 ^{o}C. IR (KBr) ν_{max}: 1634 and 1651 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.34-7.38 (m,1H), 7.45 (d, J= 4.8 Hz 1H), 7.56-7.60 (m, 2H), 7.79 (d, J = 5.2 Hz, 1H), 8.03 (dd, J = 0.8 and 7.6 Hz, 1H) ppm; ^{13}C NMR (100 MHz, $CDCl_3$): δ = 124.58, 125.16, 129.70, 130.09, 130.80, 133.00, 135.86, 138.74, 146.70, 172.57, 180.94 ppm (one quarternary carbon was not observed possibly due to insufficient number of scanning); HRMS (ESI+): *m/z* $[M+H]^+$ calcd for $C_{12}H_7O_2S$: 215.0089; found: 215.1627 and [M+Na] calcd for $C_{12}H_6O_2SNa$: 236.9986; found: 237.1626.

6.6 Selected Spectra

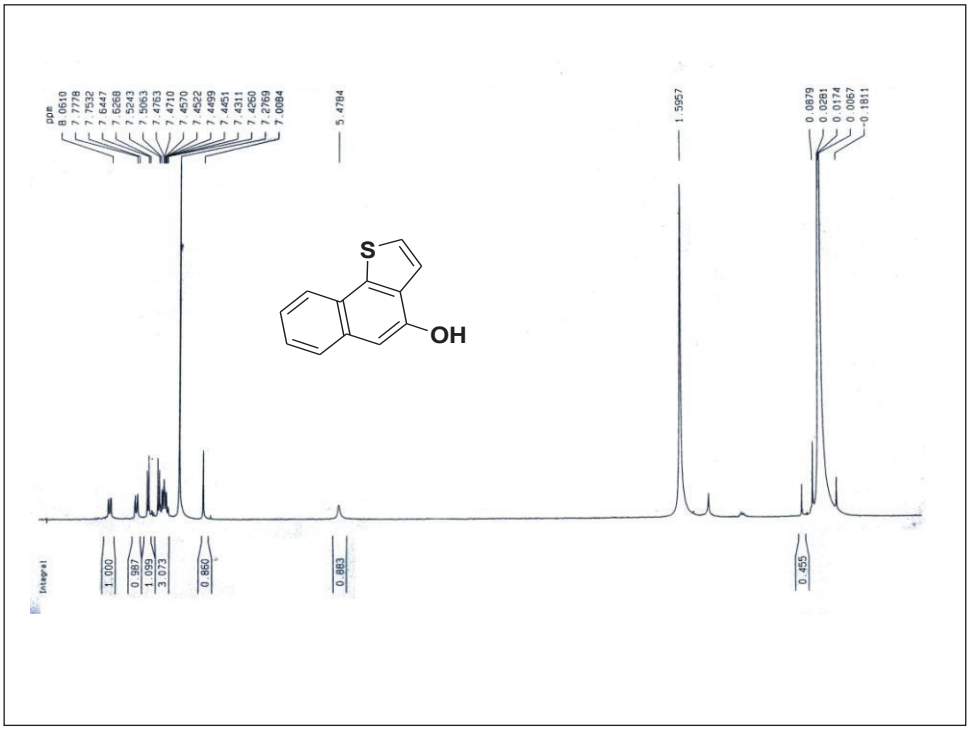
^{1}H NMR spectra of compound 40



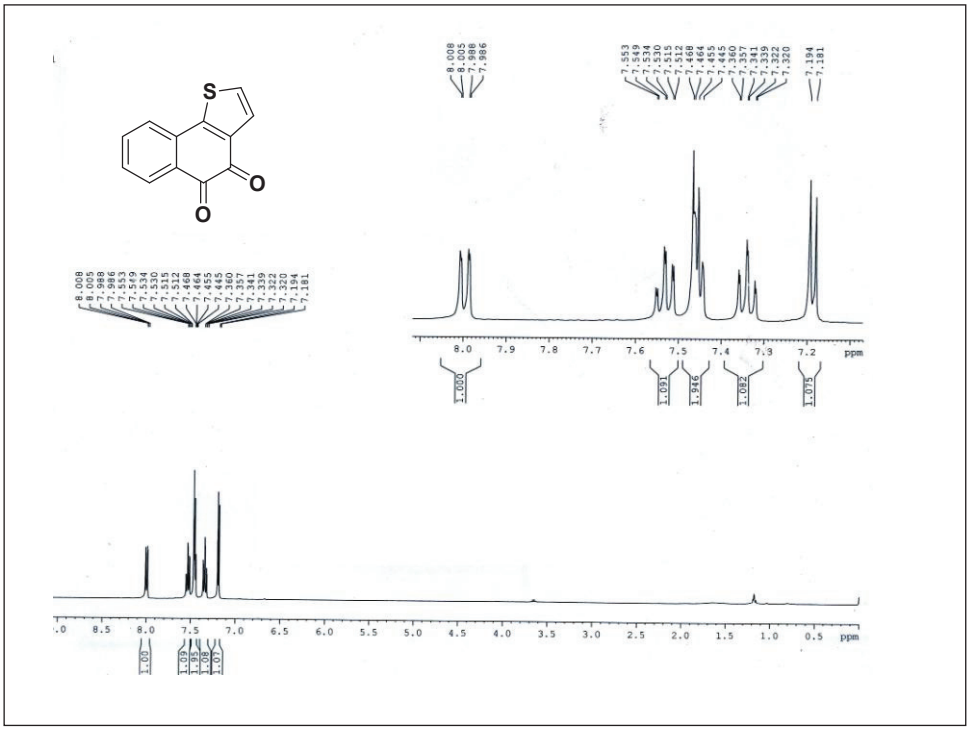
Ir spectra of Compound 41



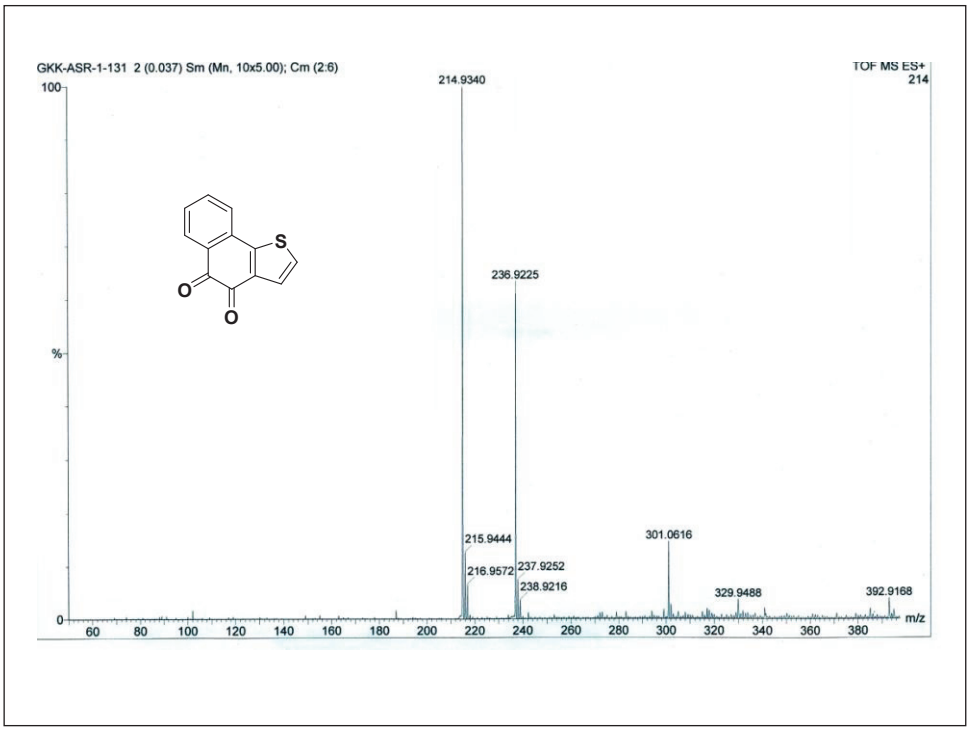
^{1}H NMR spectra of compound 40



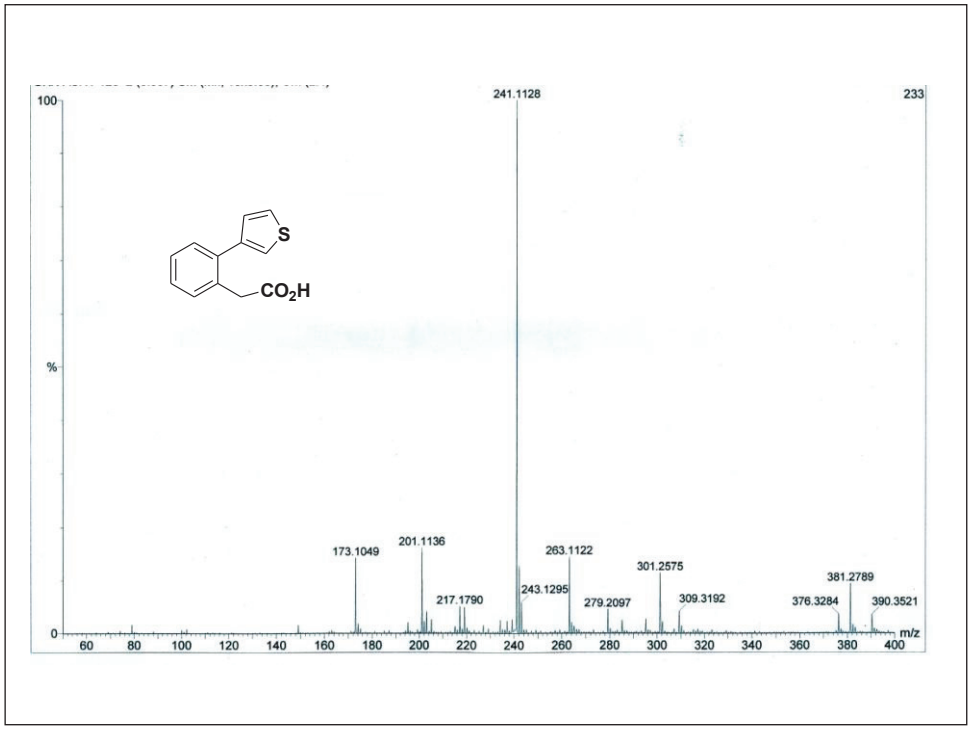
^{1}H NMR spectra of compound 43



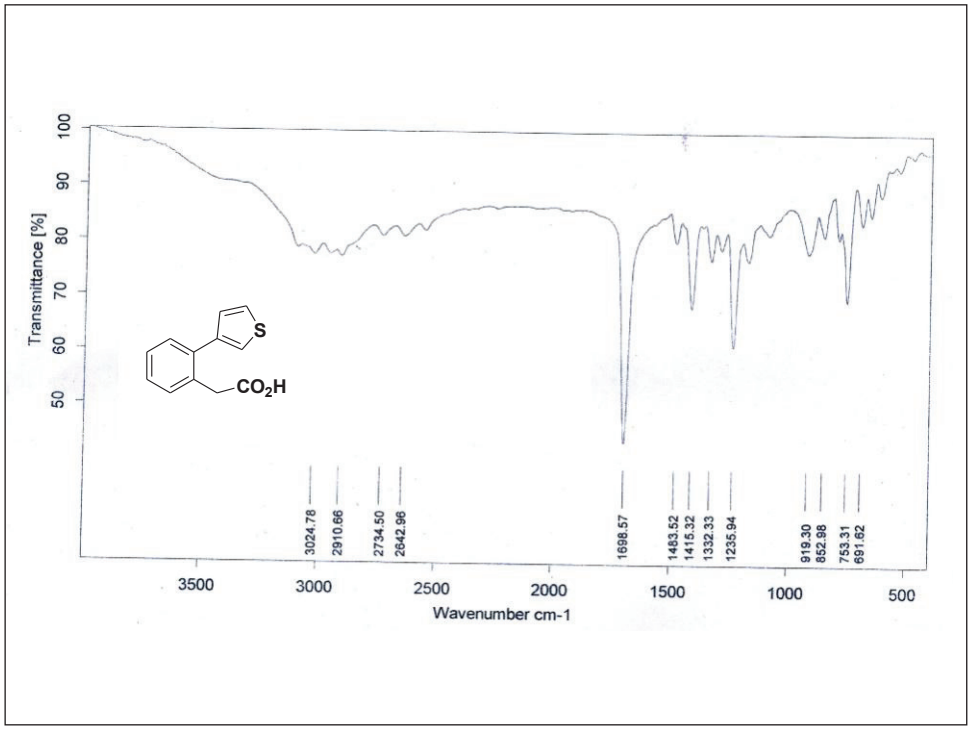
HRMS spectra of Compound 43



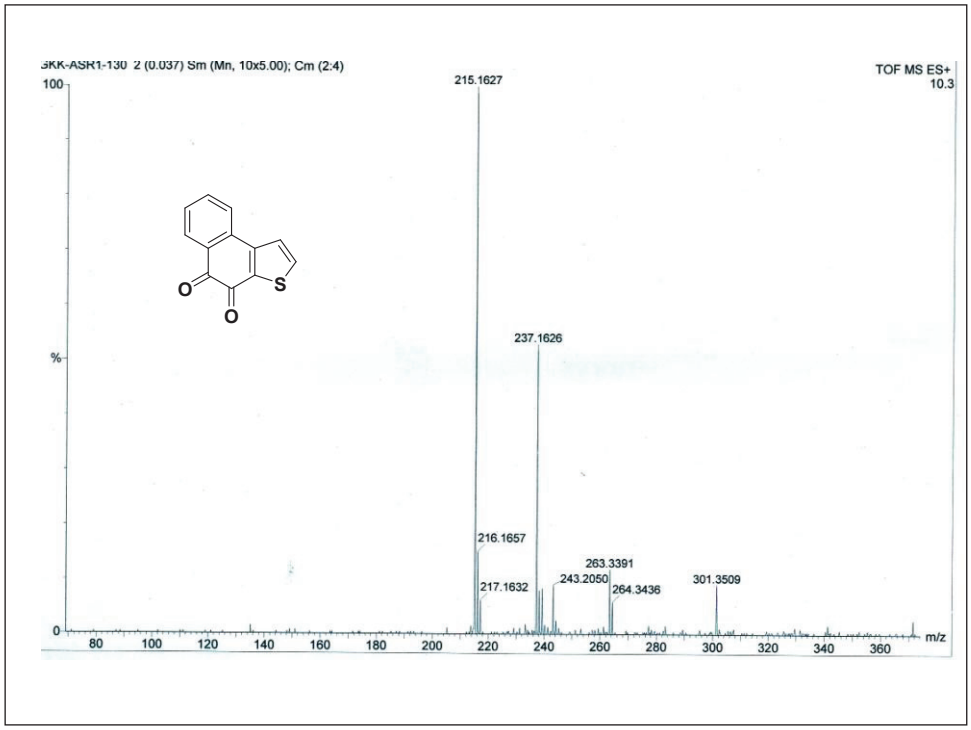
HRMS spectra of Compound 45



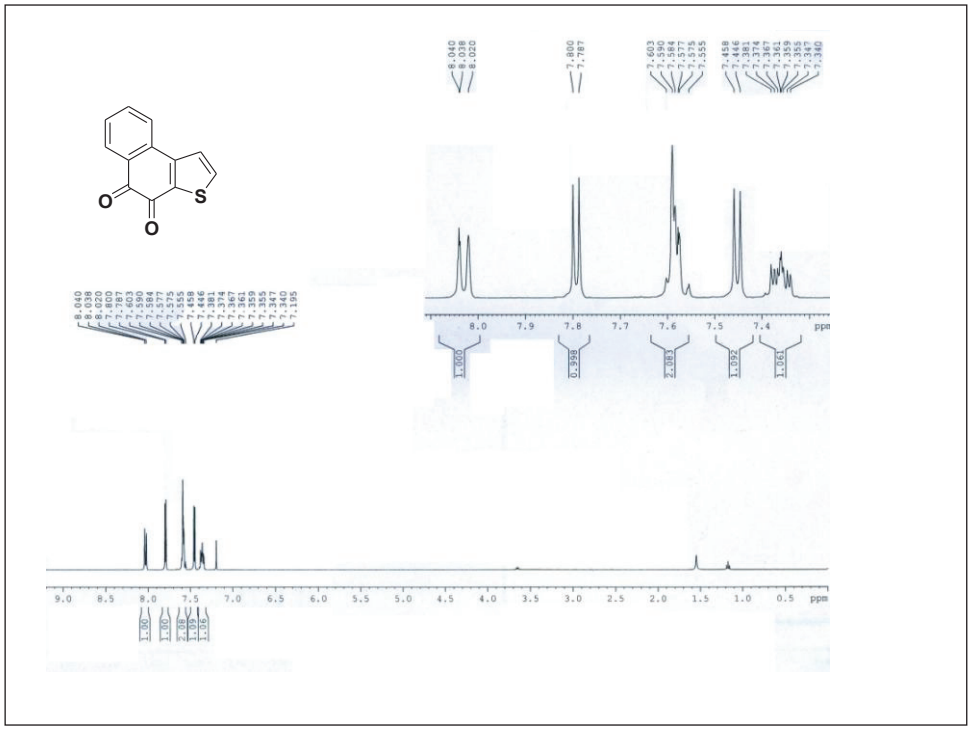
Ir spectra of Compound 45



HRMS spectra of Compound 47



^{1}H NMR spectra of compound 47



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