Thesis at a glance

Studies towards the synthesis of various condensed ‘U’-shaped furophenanthraquinones and their thiophene analogues as well as bis(heteroannulated)naphthoquinones have been described in the thesis entitled “Approaches towards the Synthesis of Potentially Bioactive Furophenanthraquinones Related to Salvia Metabolites and Their Condensed and Doubly Condensed Analogues”. The thesis comprises three chapters (chapter I, chapter II and chapter III), in which chapter II has further been divided into three subsections IIA, IIB and IIC. A chapterwise brief description of the actual work is presented below.

Chapter I

Studies on the synthesis of some angularly fused novel ‘U’-shaped tetracyclic furophenanthraquinones simulating ABCD rings of isotanshinone II

In this chapter, the synthesis of two novel ‘U’-shaped furophenanthraquinone derivatives (9-methoxyphenanthro[4,3-b]furan-4,5-dione and phenanthro[4,3-b]furan-4,5-dione) have been described. 1-(2-furyl)-2-naphthaldehyde derivatives (R = OMe or H) was successively converted into the corresponding furophenanthrenols in five steps following the protocol of functional group transformations CHO → CH₂OH → CH₂CN → CH₂COOH → furophenanthrenol. Finally, oxidation of the furophenanthrenols using Fremy’s salt furnished the desired furophenanthraquinones (scheme A).

Reagents and conditions: i) DDQ, benzene, reflux, 23 hrs, 95-97 %; ii) NaBH₄, EtOH, r.t., 2 hrs, 93-95 %; iii) MsCl, s-collidine, LiCl, DMF, 0 °C-r.t., overnight; iv) KCN, DMF, 12 hrs, 74-
78 %; v) Aq. KOH, EtOH, reflux, 27-32 hrs, 49-53 %; vi) (CF₃CO)₂O, CF₃CO₂H, 0 °C-r.t., overnight, 73-80 %; vii) Fremy's salt, Na₂HPO₄-H₂O, MeOH, overnight, 83-91 %.

Scheme A: Synthesis of phenanthro[4,3-b]furan-4,5-dione derivatives

Publication:

‘Synthesis and characterization of a novel furophenanthraquinone, 9-methoxyphenanthro[4,3-b]-furan-4,5-dione : Exploration of specific solvent interaction by photoluminescence study.’ Aparna Sarkar, Dinesh K. Pyne, Tuyan Biswas, Rumpa Das, Gandhi K. Kar, Arnab Halder (Manuscript under communication)

Oral presentation:

‘Model studies towards the synthesis of Isotanshinone-II: General method for synthesis of some angularly fused novel “U” Shaped furoquinones simulating ABCD rings of Isotanshinone-II.’ Aparna Sarkar, Rumpa Das, Khokan Samanta, Gandhi K. Kar; Proceedings of the National Symposium on Recent Advances in Chemistry and Industry 2015, Indian Chemical Society, Calcutta University, Kolkata.

Chapter-IIA

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

A number of 2-(2/3-thienyl)cycloalk-1-ene-1-carbaldehydes were synthesised efficiently by the Pd(0) catalysed Suzuki coupling reaction of 2-bromocycloalk-1-ene carbaldehyde derivatives and 2- thiopheneboronic acid or optionally substituted 3-thiopheneboronic acids (scheme B).

Reagents and conditions: i) 2-thiopheneboronic acid, Pd(PPh₃)₄ (1 mol %), Et₃N, DMF, 110-
120 °C, 6.5-7 hrs under N\textsubscript{2} atm., 70-80 %; ii) Optionally substituted 3-thiopheneboronic acid, Pd(PPh\textsubscript{3})\textsubscript{4} (1 mol%), Et\textsubscript{3}N, DMF, 110-120 °C, 4-12 hrs under N\textsubscript{2} atm., 55-90 %.

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

As many as seventeen 2-(2/3-thienyl)cycloalk-1-ene-1-carbaldehyde derivatives have been synthesised.

**Publication:**


**Chapter-IIB**

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

In chapter IIB of the thesis, the synthesis of three novel phenanthro[4,3-\textit{b}]thiophene-4,5-dione derivatives and one phenanthro[3,4-\textit{b}]thiophene-4,5-dione derivative have been described (scheme C).

**Reagents and conditions:** i) DDQ, benzene, reflux, 20-24 hrs, 87-97 %; ii) NaBH\textsubscript{4}, EtOH, r.t.,
2 hrs, 94-97 %; iii) MsCl, 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$_2$HPO$_4$ buffer, MeOH, 0-5 °C, overnight, 77-97 %.

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

Phenanthro[4,3-b]thiophene-4,5-dione derivatives were synthesised starting from 1-(2-thienyl)-3,4-dihyronaphthalene-2-carbaldehyde derivatives and these compound are the thiophene analogues of the ABCD ring nucleus present in isotanshinone II.

![Chemical Structures](image)

**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$_2$HPO$_4$-H$_2$O, MeOH, 0-5 °C, overnight, 87 %.

**Scheme D: Synthesis of 10-methoxyphenanthro[3,4-b]thiophene-4,5-dione**

The synthesis of another novel thienophenanthraquinone: 10-methoxyphenanthro[3,4-b]-thiophene-4,5-dione, was executed starting from 3,4-dihydro-1(3-thieryl)-7-methoxy-naphthalene-2-carbaldehyde, following a similar pathway (scheme D).

**Publication**:

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

Chapter-IIC

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

The synthesis of two thienonaphthoquinones, viz. naphtho[1,2-b]thiophene-4,5-dione and naphtho[2,1-b]thiophene-4,5-dione have been described staring from commercially available methyl 2-(2-bromophenyl)acetate and 2/3-thiopheneboronic acids. The results have been included in chapter IIC (schemes E and F).

![Diagram of synthesis of naphtho[1,2-b]thiophene-4,5-dione](image)

**Reagents and conditions:** (i) 2-thiopheneboronic acid, Et3N, DMF, Pd(PPh₃)₄, 110 °C, nitrogen atm, 6 hrs, 65 %; (ii) KOH, EtOH, H₂O, reflux, 12 hrs, 78 %; (iii) TFAA, TFA, 0 °C, overnight, 80 %; (iv) Fremy’s salt, 1/6 M aq. Na₂HPO₄, MeOH, r.t., overnight, 72 %.

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

![Diagram of synthesis of naphtho[2,1-b]thiophene-4,5-dione](image)

**Reagents and conditions:** (i) 3-thiopheneboronic acid, Et₃N, DMF, Pd(PPh₃)₄, 110 °C, nitrogen, 5 hrs, 72 %; (ii) KOH, EtOH, H₂O, reflux, 10 hrs, 83 %; (iii) TFAA, TFA, 0 °C, overnight, 75 %; (iv) Fremy’s salt, MeOH, 1/6 M aq. Na₂HPO₄, r.t., overnight, 86 %.

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

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

In this last chapter of the thesis, the synthesis of four hitherto unknown doubly condensed naphthoquinones i.e. 9-methylnaphtho[1,2-\textit{b}]furan[7,8-\textit{b}]thiophene-4,5-dione, 9-methylnaphtho[2,1-\textit{b}]furan[7,8-\textit{b}]thiophene-4,5-dione, 9-methylnaphtho[1,2-\textit{b}:7,8-\textit{b}']bisthiophene-4,5-dione and 9-methylnaphtho[2,1-\textit{b}:7,8-\textit{b}']bisthiophene-4,5-dione (fig. 1) has been described. In these molecules, ring A of phenanthro[4,3-\textit{b}]furan-4,5-dione (the core nucleus of isotanshinone II) has been replaced by a 2-methylthiophene moiety whereas ring D has been modified with either a furan or a thiophene moiety.

![Figure 1: Bis(heteroannulated)naphthoquinones](image)

All the target molecules (fig. 1) were synthesised starting from 4-bromo-6,7-dihydro-2-methylbenzo[b]-thiophene-5-carbaldehyde (the CD ring precursor). Suzuki coupling of the CD ring precursor with 2-furanboronic acid produced 6,7-dihydro-4-(2-furyl)-2-methylbenzo[b]thiophene-5-carbaldehyde which was converted to 9-methylnaphtho[1,2-\textit{b}]furan[7,8-\textit{b}]thiophene-4,5-dione as per scheme G.

![Scheme G](image)

**Reagents and Conditions:** i) PBr$_3$, DMF, CHCl$_3$, 0 °C-r.t., 16 hrs, 73 %; ii) 2-furan/thiophene
boronic acid, Pd(PPh₃)₄, Et₃N, DMF, 110 °C, N₂ atm., 15 hrs, 61-63 %; iii) DDQ, benzene, reflux, 27 hrs, 86-87 %; iv) NaBH₄, EtOH, r.t., 2 hrs, 91-92 %; v) MsCl, LiCl, s-collidine, DMF, 0 °C, overnight; vi) KCN, DMF, 7 hrs, 68-84 %; vii) KOH, EtOH-H₂O, reflux, 21 hrs, 39-50 %; viii) TFAA-TFA, 0°C, overnight, 80-84 %; ix) Fremy's salt, 1/6M Na₂HPO₄ buffer solution, MeOH, 0-5 °C, overnight, 77-79 %.

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

In a similar way, the syntheses of three other novel condensed naphthoquinones were achieved starting from the same bromoaldehyde and using 2-thiopheneboronic acid (scheme G), 3-furanboronic acid, and 3-thiopheneboronic acid, respectively instead of 2-furanboronic acid (scheme H).

![Diagram of Scheme G](image)

**Reagents and Conditions:** i) 3-furan / thiopheneboronic acid, Pd(PPh₃)₄, Et₃N, DMF, 110 °C, N₂ atm., 12 hrs, 67 %; ii) DDQ, benzene, reflux, 24 hrs, 89 %; iii) NaBH₄, EtOH, r.t., 2 hrs, 94-92 %; iv) MsCl, LiCl, s-collidine, DMF, 0 °C, overnight; v) KCN, DMF, 10 hrs, 76-89 %; vi) KOH, EtOH-H₂O, reflux, 23 hrs, 43-58 %; vii) TFAA-TFA, 0 °C, overnight, 85-93 %; viii) Fremy's salt, 1/6M Na₂HPO₄ buffer solution, MeOH, 0-5 °C, overnight, 83-86 %.

Poster Presentation:

1. ‘Search for novel antibacterial: Synthesis of doubly condensed naphthoquinone derivatives as “AD”-ring modified Isotanshinone-II analogue’ Aparna Sarkar, Ankita Dey, Gandhi K. Kar. poster presentation in International Conference on Advancement in Science and Technology (ICAST-2018), 3-4th September, 2018 at Visva-Bharati University, Santiniketan, West Bengal, India organized by the Indian JSPS Alumni Association in association with the Department of Physics, Visva-Bharati.

General Experimental Conditions:

Chemicals and solvents

All reactions were carried out using oven-dried or flame dried clean glass wares. Commercial grade reagents were used without further purification. The solvents, chloroform (CHCl₃), dichloromethane (DCM), diethyl ether (Et₂O), ethanol (EtOH), DMF, Benzene, ethanol (EtOH), methanol (MeOH), Petroleum ether (P.E) and ethyl acetate (EtOAc) were purchased from E. Merck (India) Ltd. or SRL (India) Ltd. and distilled prior to use. Petroleum ether (P.E) refers to the fraction boiling in the range 60 - 80 ºC. All common solvents (CHCl₃, DMF, Et₃N, benzene, s-collidine, etc.) were dried as per literature procedure. Furanboronic acids, thiophene boronic acids, 1-tetralone, 4-methyl-1-tetralone, 6-methoxy-1-tetralone, cyclohexanone, cyclopentanone, cyclooctanone, 4-tert-butylcyclohexanone, tetrakis(triphenylphosphine)palladium(0), 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ), CDCl₃ and DMSO-d⁶ were purchased from Sigma-Aldrich (USA) or E. Merck (Germany). Trifluoroacetic anhydride (TFAA), trifluoroacetic acid (TFA), phosphorous tribromide, Pd/C, sodium borohydride (NaBH₄), Mesyl chloride and s-collidine were purchased from Spectrochem, India. Fremy’s salt (potassium nitrosodisulfonate) was prepared in the laboratory as per literature procedure. Anhydrous sodium sulfate (Na₂SO₄) was used for drying solutions.

Chromatography and melting points

Purification by column chromatography was done using 100-200 mesh, 230-400 mesh and GF₂₅₄ silicagel (E. Merck, India or SRL) using petroleum ether (P.E) (60º-80 ºC) and ethyl acetate (EtOAc) as eluents, unless otherwise mentioned. Precoated silica gel 60 GF₂₅₄ TLC sheets on alumina plate (E. Merck, Germany) were used for thinlayer chromatography (TLC). Melting points were recorded in open capillaries using conc. H₂SO₄ bath or electrical melting apparatus and are uncorrected.

Spectroscopic and analytical instruments

Infrared spectra were recorded on KBr pellets using a Shimadzu Fourier Transform (FT-IR) 8300 spectrophotometer, unless otherwise mentioned.
Unless otherwise mentioned, \( ^1\text{H} \) NMR (500 MHz or 400 MHz or 300 MHz) and \( ^{13}\text{C} \) NMR (125 MHz or 100 MHz or 75 MHz) spectra were recorded on a Bruker AVANCE III 500 MHz or 400 MHz or 300 MHz NMR spectrometer using tetramethylsilane as the internal standard. The ESI-MS was recorded on a JEOL JMSAX505HA and HRMS spectra on either a TRACE GC ULTRA POLARIS Q or a Waters Qtof Micro YA263 mass spectrometer.

Since a large number of spectra are there, only of some relevant and selected spectra (\( ^1\text{H} \) and \( ^{13}\text{C} \) NMR) of the synthesised compounds have been appended at the end of the respective chapters.