Approaches towards the Synthesis of Potentially Bioactive Furophenanthraquinones Related to *Salvia* Metabolites and Their Condensed and Doubly Condensed Analogues

1. Introduction:

A brief review on the synthesis of naturally occurring 'S'-shaped and 'U'-shaped furophenanthraquinones

Danshen (also known as Tanshen) is the dried red root of a perennial medicinal Chinese herb that grows on sunny hillsides and stream edges in China, Mongolia, Korea and Japan. Scientific name of the plant is *Salvia miltiorrhiza* Bunge (Family: Labiatae).[1]

***Salvia miltiorrhiza* Bunge**

Salvia glutinosa

Salvia columbariae

Red root of *Salvia miltiorrhiza* Bunge

Powder of Danshen

The dried red root of the plant has high safety profile and the crude powder of it is till date largely used for the treatment of various diseases such as cardiac and vascular disorder, viral hepatitis, , inflammation, cancer, menstrual disorder and miscarriage, hypertension, insomnia, urolithiasis, etc. in many Asian countries with 1000 years of clinical applications.[2-6] Even today, Danshen products are commercially available in herbal shops of China, Japan, the United States and European countries, etc.[7] In fact, the Food and Drug Administration was approved it as the first Chinese herbal medicine, for clinical tests in the United States.[8] In last 9-10 decades,

extensive studies have been made on the chemical composition of Danshen. A large number of hydrophilic and lipophilic components have been isolated from Danshen.[9] The lipophilic components include a number of condensed furophenanthraquinones and their di-, tetra- and hexahydro derivatives (fig. 1).[3,10] Such types of furophenanthraquinones have been isolated not only from Danshen but also from other *Salvia* species such as *Salvia glutinosa* and *Salvia columbariae.* Some tetracyclic furophenanthraquinones, isolated from *Salvia* species, are given below (fig. 1).

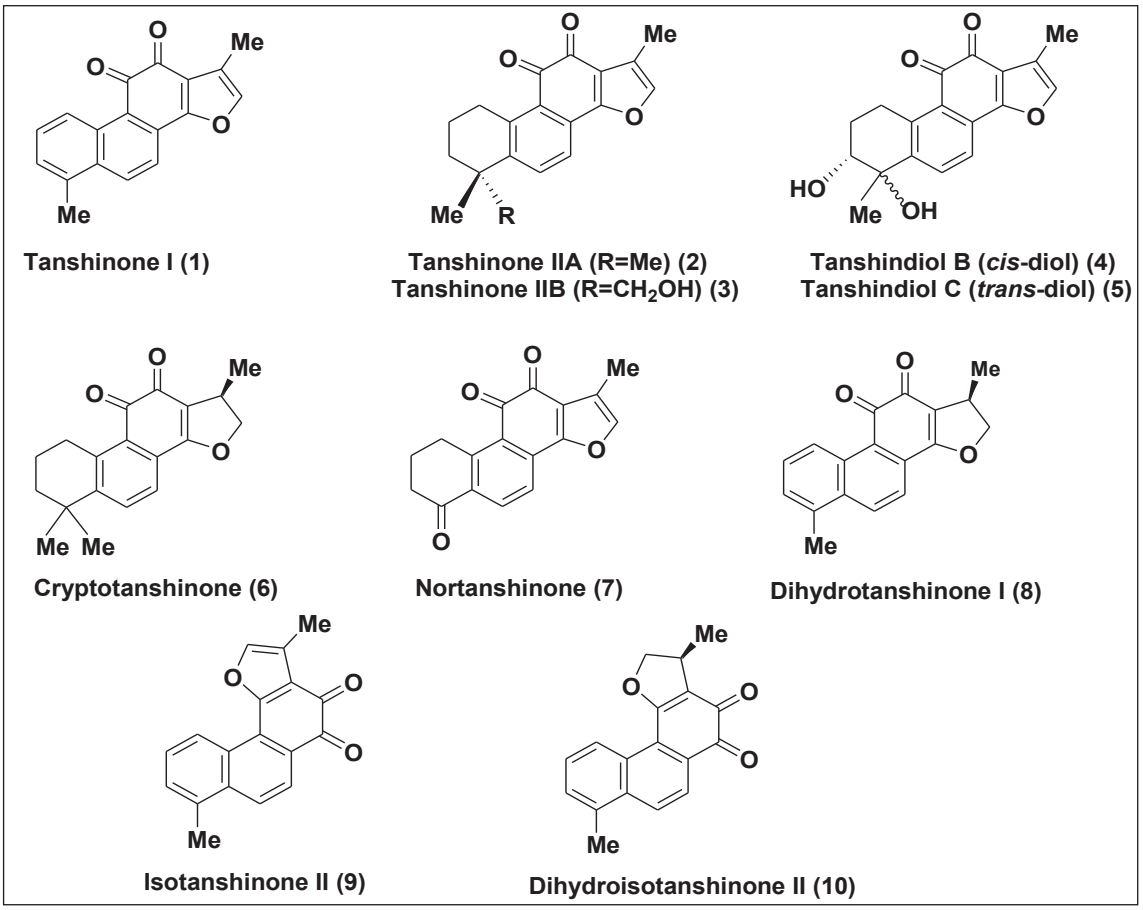


Figure 1: **Some tetracyclic furophenanthraquinone derivatives isolated from *Salvia miltiorrhiza* and *Salvia glutinosa***

Structurally, all the isolated furophenanthraquinones contain a tetracyclic framework either in 'S'-shaped form *i.e.* phenanthro[1,2-*b*]furan-10,11-dione derivatives (or its di-/tetra-/hexahydro derivatives) or in 'U'-shaped form *i.e.* phenanthro[4,3-*b*]furan-4,5-dione derivatives (or its dihydro derivatives) (fig. 2). Both are composed of four rings, including tetrahydronaphthalene

or naphthalene part as rings A and B, an *o*-benzoquinone moiety as ring C and a furan or dihydrofuran moiety as ring D, commonly recognised as furophenanthraquinone.[8] Even the tricyclic furonaphthoquinones,[11] simulating BCD rings of tanshinones, show cancer chemopreventive activity,[12] which indicate that such type of condensed furophenanthraquinones / furonaphthoquinones have general medicinal importance.

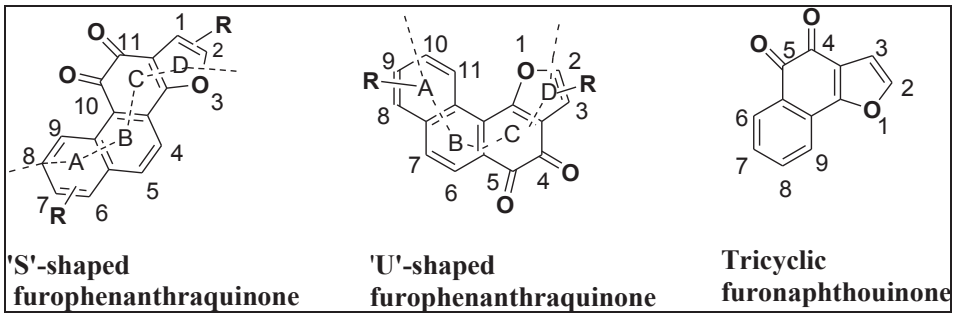


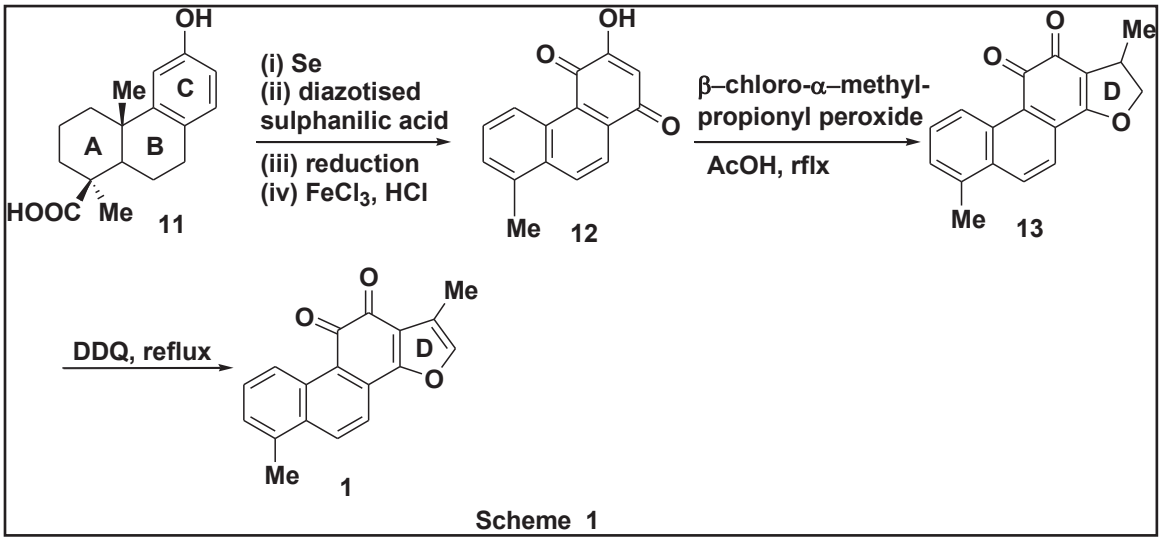
Figure 2: Core nucleus of 'S'- and 'U'-shaped furophenanthraquinones and furonaphthoquinone

People believe that a wide variety of biological activities displayed by Danshen is possibly due to the presence of these tetracyclic furophenanthraquinone derivatives. As a result, keen interests have been focused on these classes of compounds by various groups of scientist, all over the world, since 1934. Though, Nakao and Fukushima isolated three to four tanshinones as orange / red pigment from Danshen as early in 1930-1934,[12-15] but they couldn't predict the structures. The extensive works,[16-21] of Takiura and Wessely *et al.* confirmed the structure of tanshinone I, tanshinone II and cryptotanshinone during 1941-1962. The interest on the synthesis of these classes of compounds initiated from 1968 onwards. A large number of syntheses of phenanthro[1,2-*b*]furan-10,11-dione derivatives ('S'-shaped) came out in last 50 years while the synthesis on the phenanthro[4,3-*b*]furan-4,5-dione ('U'-shaped) derivatives are relatively less available in literature. A possible reason might be that the 'U'-shaped furophenanthraquinone derivatives (*eg*. isotanshinone II and dihydroisotanshinone II) have only been isolated from *S. glutinosa* in last decads.[22]

A large number of syntheses of furophenanthraquinones have appeared in literature in last 4-5 decades. Most of the syntheses deal with the synthesis on phenanthro[1,2-*b*]furan-10,11-dione derivatives ('S'-shaped furophenanthraquinones). The biological activities of such

compounds have been explored enormously in last 50 years. The recent studies show that tanshinone I , tanshinone IIA as well as cryptotanshinone are quite promising as antibacterial, anticancer, antifeedant, antioxidant, antimutagenic, anti-inflammatory and antiatherogenesis agents, These are also very effective in coronary disease, alzheimer's disease and diabetics.[23, 24] Several authors have published reviews about the structures, syntheses and biological activities of diterpenoids from *Salvia* species, considering the recent flurry of reports in this area,.[3,6,8,23- 26] These activities further stimulated the studies on synthesis of such furophenanthraqinones. Herein we depict briefly / schematically some of the important syntheses achieved by earlier workers.

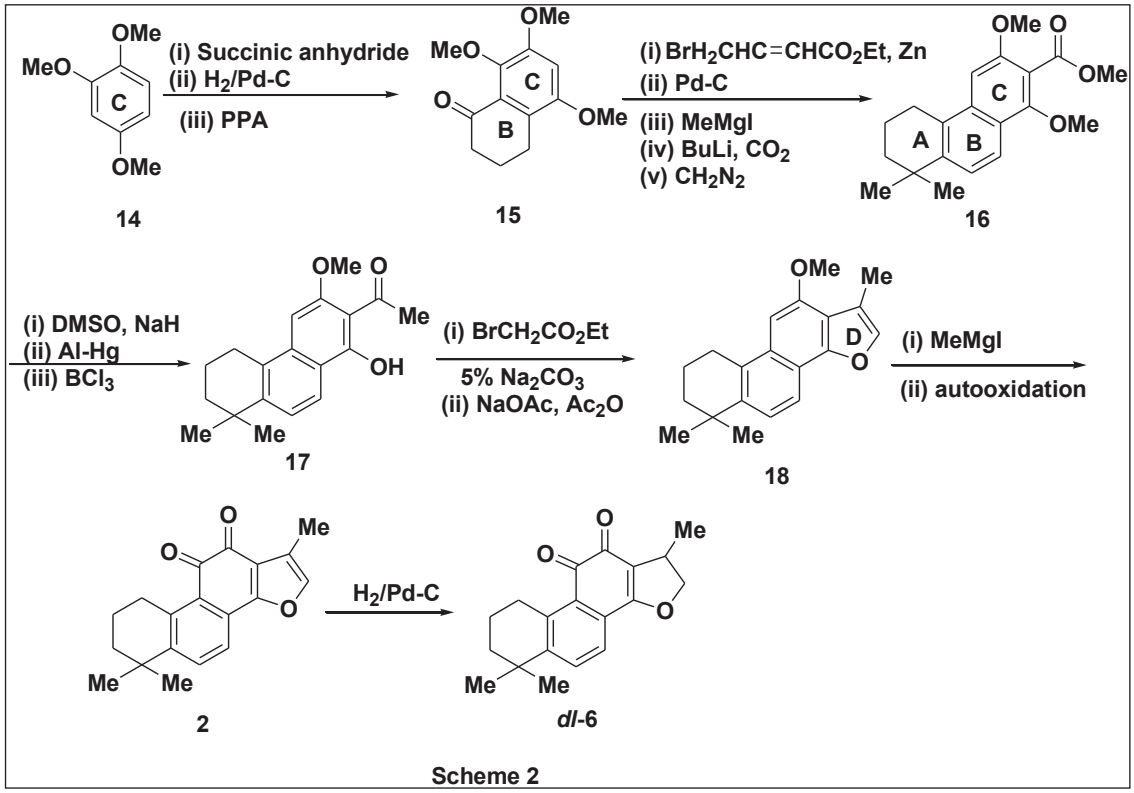
The first synthesis of Tanshinone I was achieved by Ballie and Thomson,[27] in **1968**. It was synthesised from the natural product podocarpic acid (**11**) as ABC ring precursor *via* the quinone intermediates **12** and **13** in six steps (scheme 1).



Scheme 1

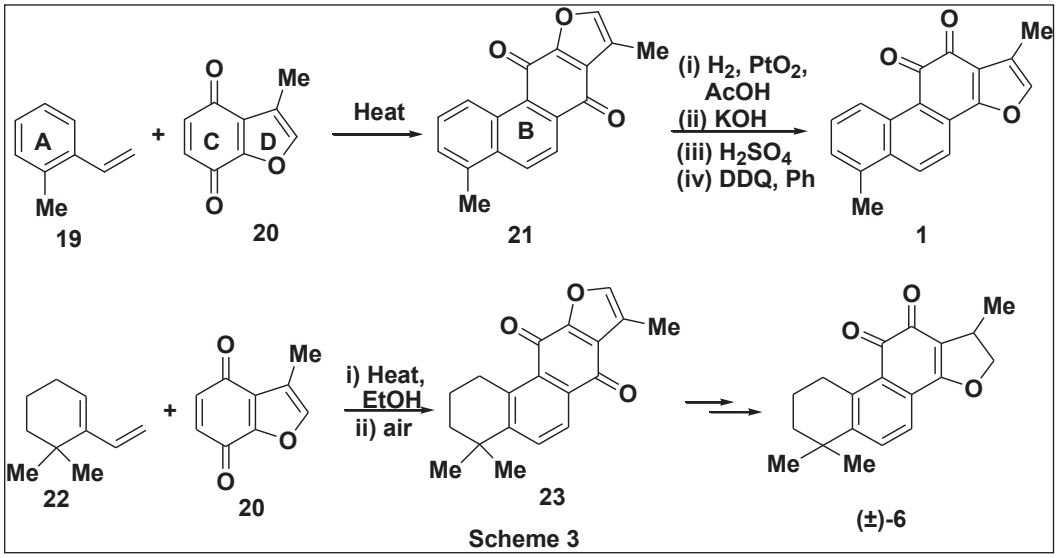
Following almost a similar route, the author also reported in the same paper the synthesis of cryptotanshinone (**6**) and tanshinone IIA (**2**) starting from 7-methoxy-1-tetralone *via* the same quinone intermediate **12.**

In **1971,** Tateishi, Kusumi and Kakisawa,[28, 29] followed a somehow lengthy process (fourteen steps) to achieve the total synthesis of tanshinone IIA (**2**) and (±)-cryptotanshinone (**6**) through a stepwise cyclisation approach from 1,2,4-trimethoxybenzene (**14**) (the C ring precursor of furophenanthraquinones). The authors followed the sequential construction of the B, A and then D ring to complete the total synthesis, as outlined in scheme 2.



Scheme 2

Kakisawa *et al.* from Takyo Kyoku University, Japan and Snyder *et al.* from Boston University, USA adopted a novel strategy for the synthesis of furophenanthraquinones. They both followed a Diels-Alder reaction to construct the B ring starting from A and CD ring precursors.

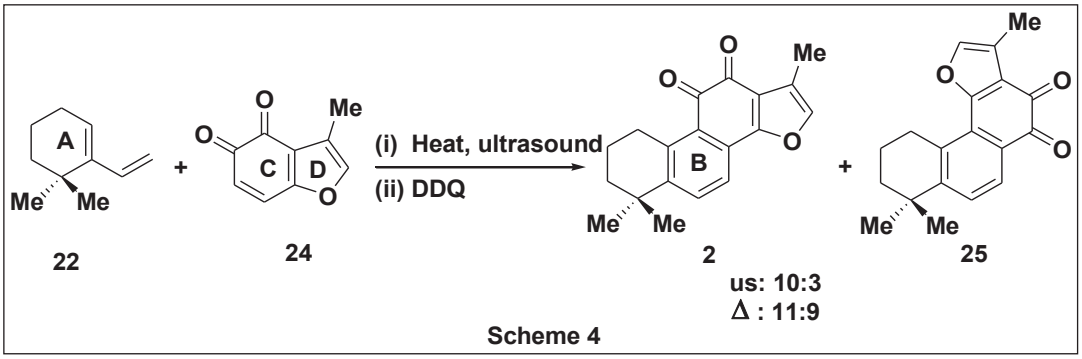


Scheme 3

In **1969,** Inouye and Kakisawa[30] reported the synthesis of tanshinone I (**1**) and cryptotanshinone (**6**), as shown in scheme 3. In this synthesis, 3-methylbenzofuroquinone was used as common

CD ring precursor for both syntheses. When a mixture of *o*-methylstyrene (**19**) (A ring) and 3-methylbenzofuran-4,7-quinone (**20**) (CD ring) was heated, the *p*-furophenanthraquinone derivative **21** was formed. It was converted to tanshinone I (**1**) in 4 % overall yield *via* reduction, hydrolysis, acidification and aromatisation Using the same methodology, tanshinone IIA (**2**) and cryptotanshinone (**6**) were also produced from the diene 6,6-dimethyl-l-vinylcyclohexene (**22**) (scheme 3).

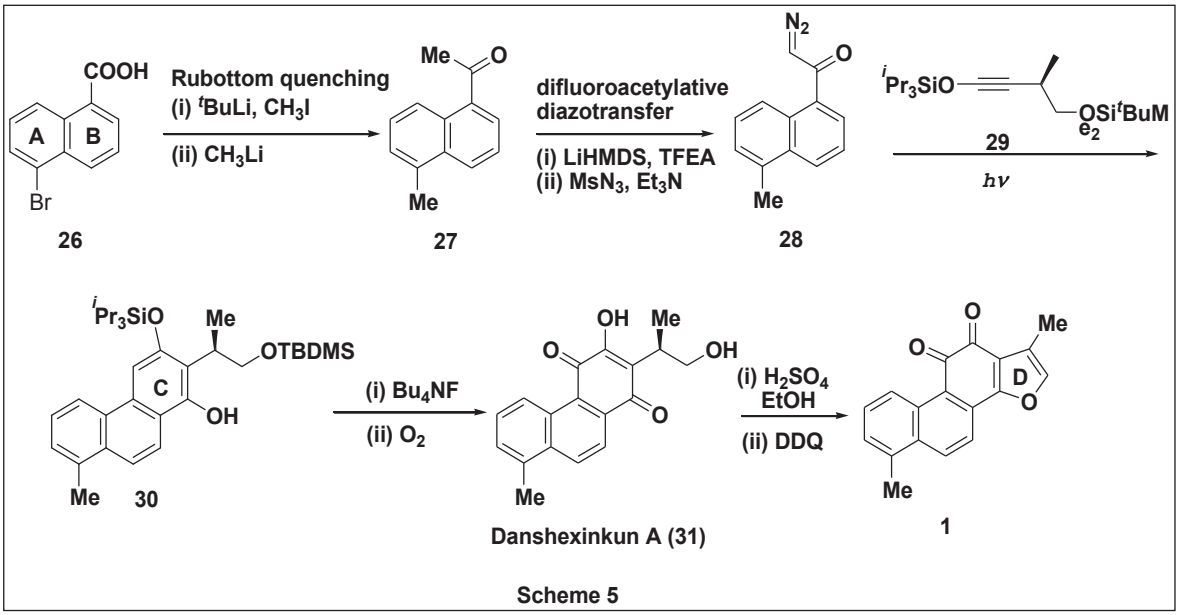
During **1989-90**, Lee and Snyder adopted an ultrasound-promoted Diels-Alder reaction [31, 32] as a key step to generate the B ring of tanshinones. Thus, the reaction of the diene **22** (A ring precursor) and *o*-quinone dienophile **24** (CD ring precursor), followed by aromatisation with DDQ, afforded compound **2** along with a regio-isomer **25** in 10:3 ratio (scheme 4).



Scheme 4

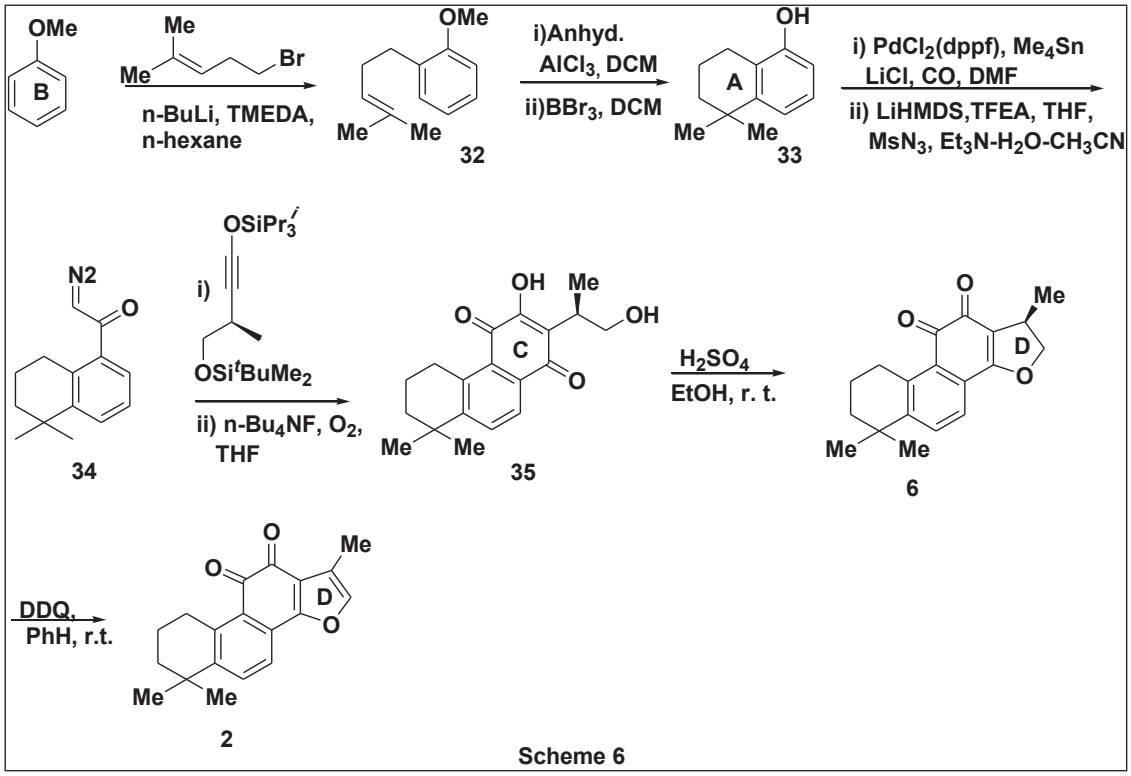
Using a similar strategy, they also synthesised tanshinone IIB, tanshindiol B, nortanshinone, methyl tanshinonate, and methyltanshinquinone, etc.

In **1992**, Danheiser *et al.* developed "second generation" version of aromatic annulation strategy,[33] by which tanshinone I (**1**) has been synthesised starting from 5-bromo-1-naphthoic acid (**26**) (AB ring precursor) which was made to undergo Rubottom quenching, followed by a two-step detrifluoroacetylative diazotransfer method to obtain the diazoketone **28**. The diazoketone on irradiation with the alkyne **29**, compound **30** was obtained which on O-deprotection followed by oxidation afforded danshexinkun A intermediate (**31**) and it was converted to tanshinone I in two steps (scheme 5). The overall yield in this multistep synthesis was 33 %.



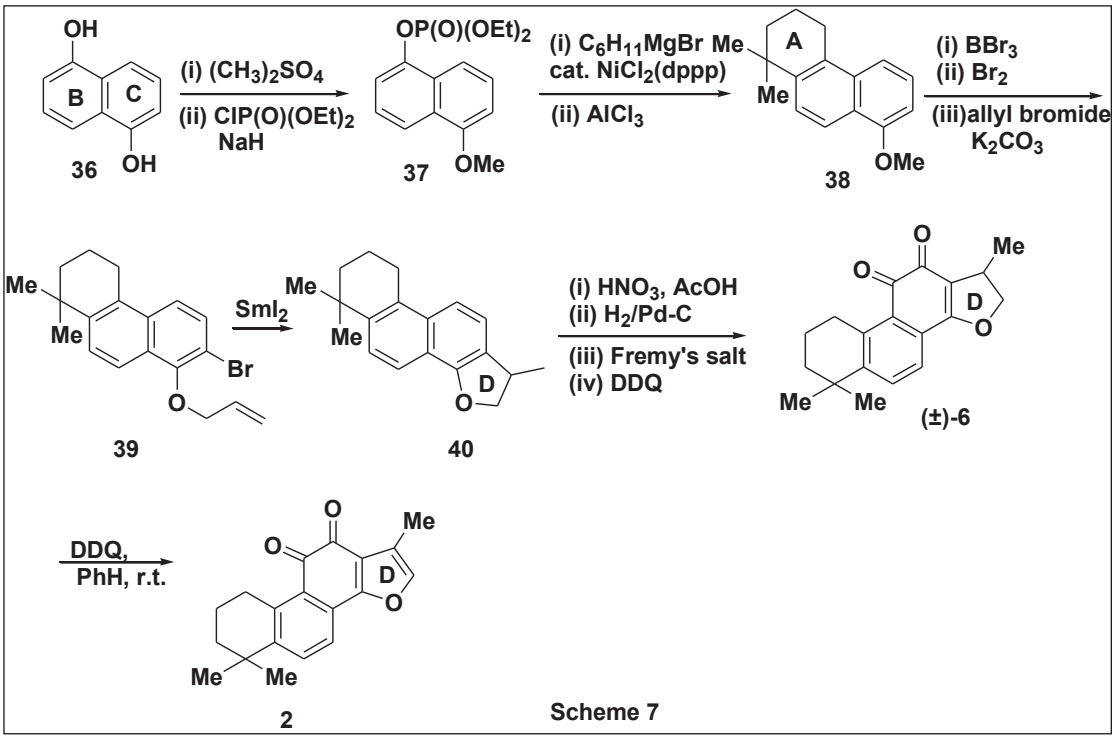
Scheme 5

The author also extended further this methodology to synthesise tanshinone IIA and (-) cryptotanshinone starting from anisole *via* neocryptotanshinone (**35**) (scheme 6).[34]



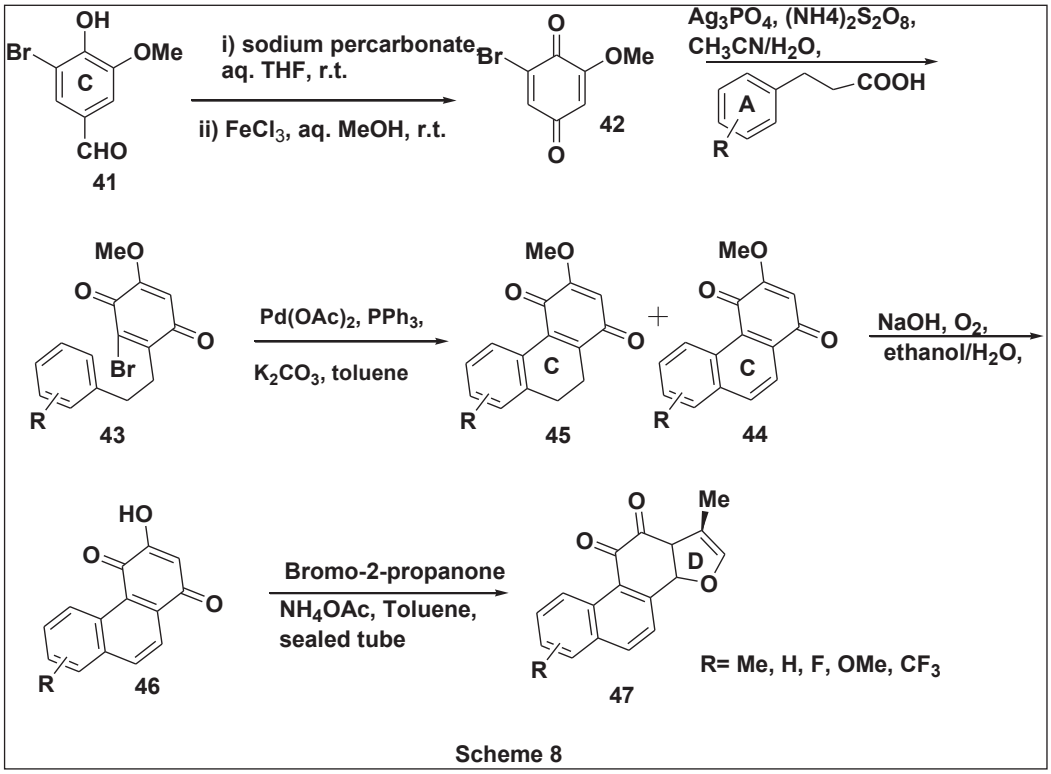
Scheme 6

In **2003**, Jiang *et al.* synthesised (±)-cryptotanshinone (**6**) and tanshinone IIA (**2**) starting from naphthalene-1,5-diol (**36**) (AB ring precursor). They developed SmI_2-promoted radical cyclisation as the key step. 1,5-Naphthalenediol was converted to aryl diethyl phosphate **37** in two steps, and it was subjected to Ni-catalysed cross-coupling with the Grignard reagent, followed by Friedel-Crafts alkylation to afford the tetrahydrophenanthrene **38** which comprises the A, B and C rings. The tetracyclic intermediate **40** was produced by successive O-demethylation, bromination and O-allylation of **38** followed by cyclisation of intermediate **39** with SmI_2. Finally, it was converted into the tanshinone IIA (**6**) *via* successive nitration, reduction to amine, oxidation to *o*-quinone by Fremy's salt and aromatisation (scheme 7).[35] The overall yield of **6** was 7 % in eleven steps.



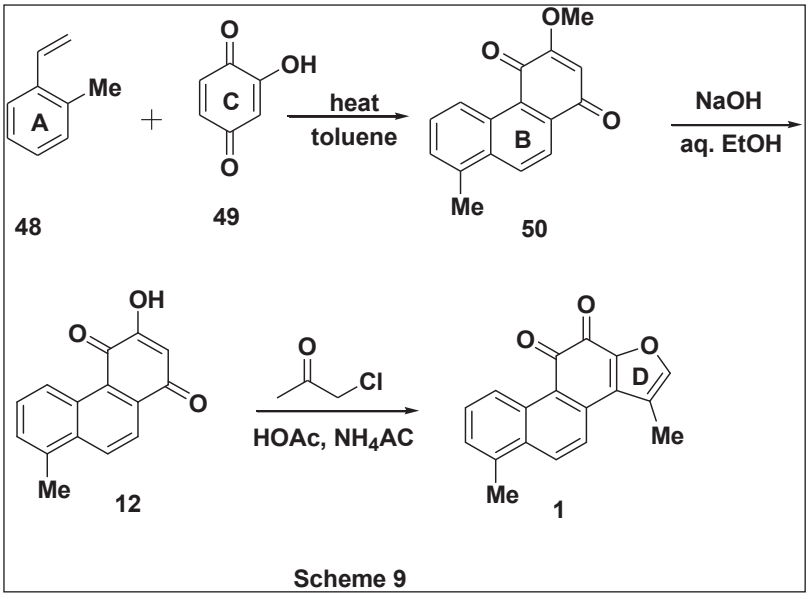
Scheme 7

In **2014**, Jiao *et al.* reported the synthesis of tanshinone I and its analogue following a modified Feist-Benary reaction in the last stage to construct D ring (scheme 8).[36] Jiao's group synthesised tricyclic hydroxyphenanthraquinones, *viz.* 3-hydroxy-8-methylphenanthrene-1,4-diones (**46**) (R = 8-Me) as the key precursor for the total synthesis of tanshinone I (**1**).



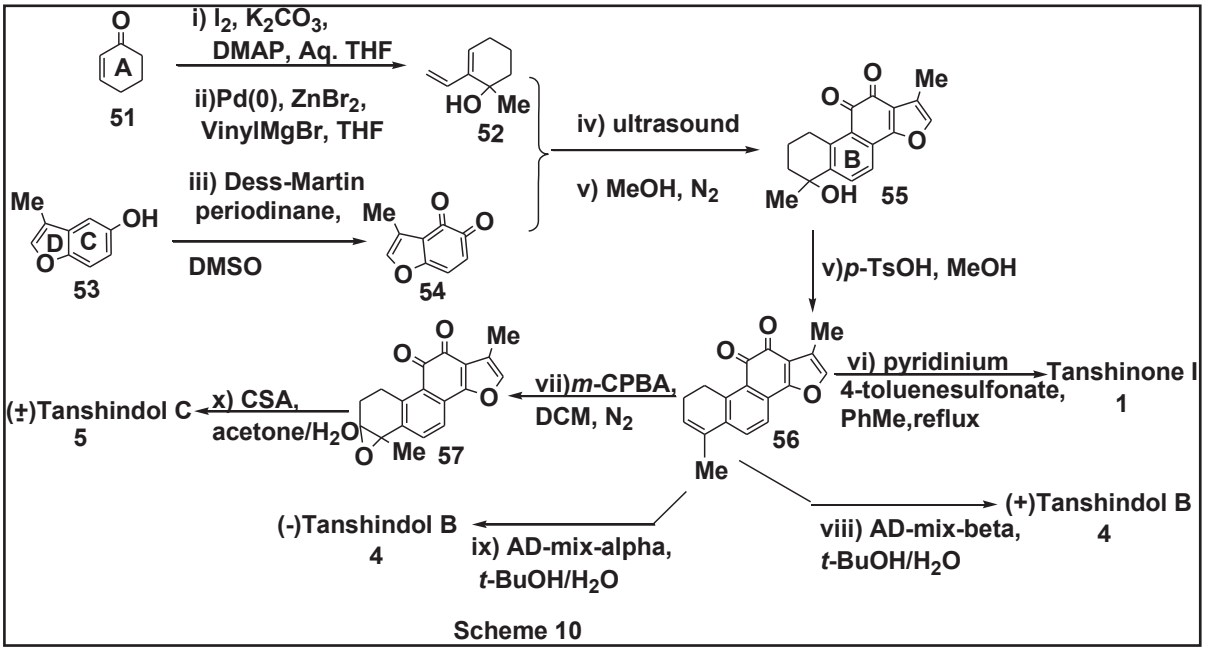
Scheme 8

In **2017,** Wu *et al.* developed an efficient three-step total synthesis,[37] of tanshinone I (**1**) starting from 2-methylstyrene (**48**) and 2-methoxy-1,4-benzoquinone (**49**) *via* uncatalysed Diels−Alder reaction followed by demethylation, to furnish compound **12**. In the final step, the Feist−Benary reaction of compound **12** with chloroacetone in HOAc−NH_4OAc formed the furan moiety to complete the synthesis of tanshinone I (scheme 9)**.**



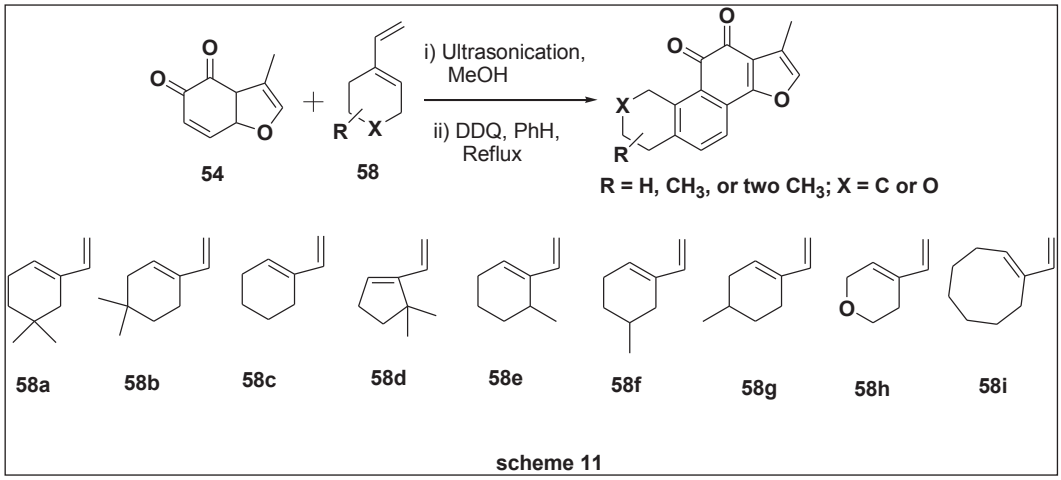
Scheme 9

Very recently, Ding and his co-workers reported the total synthesis of a series of naturally occurring furophenanthraquinone derivatives such as (±)-tanshinol B (**55**) and (±)-tanshindiol C (**5**) (first total synthesis) along with the synthesis of tanshinone I (**1**), (±)-tanshindiol B (**4**)[38] as per scheme 10. They also adopted the Diels-Alder reaction strategy, as reported by Lee and Snyder.[32] The only difference is that the A-ring component (diene) is 1-methyl-2-vinyl-2-cyclohexenol derivative (**52**).

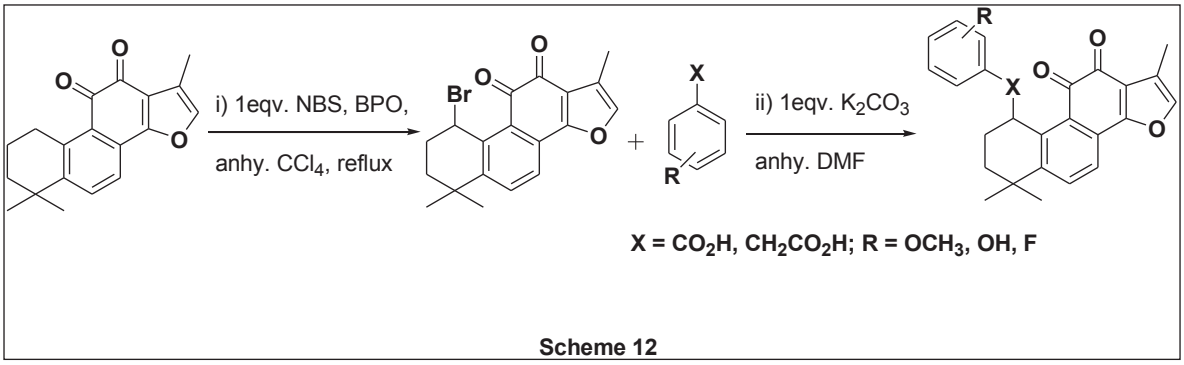


Scheme 10

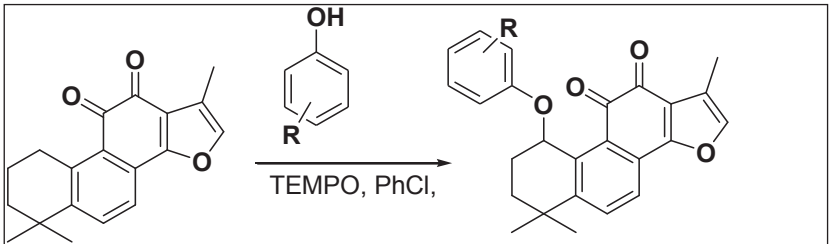
During **2012-2017**, the syntheses of several novel derivatives of the naturally occurring 'S'-shaped furophenanthraquinones has been reported,[39-42] with A-ring modification as per schemes (11-14).



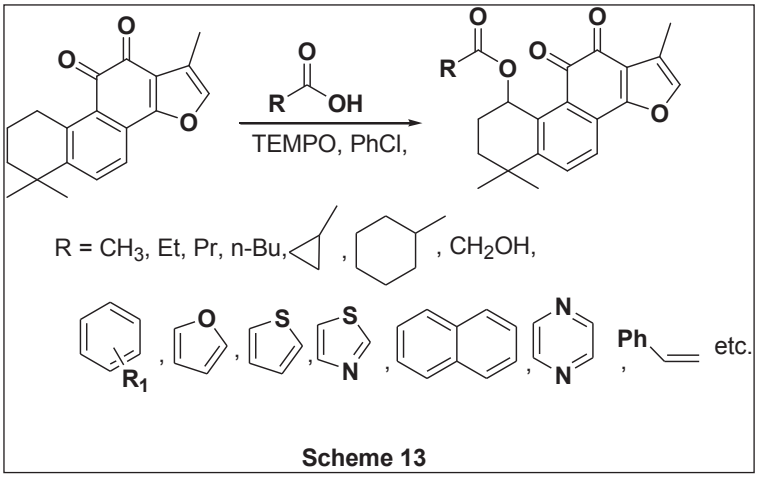
scheme 11



Scheme 12



Scheme 14

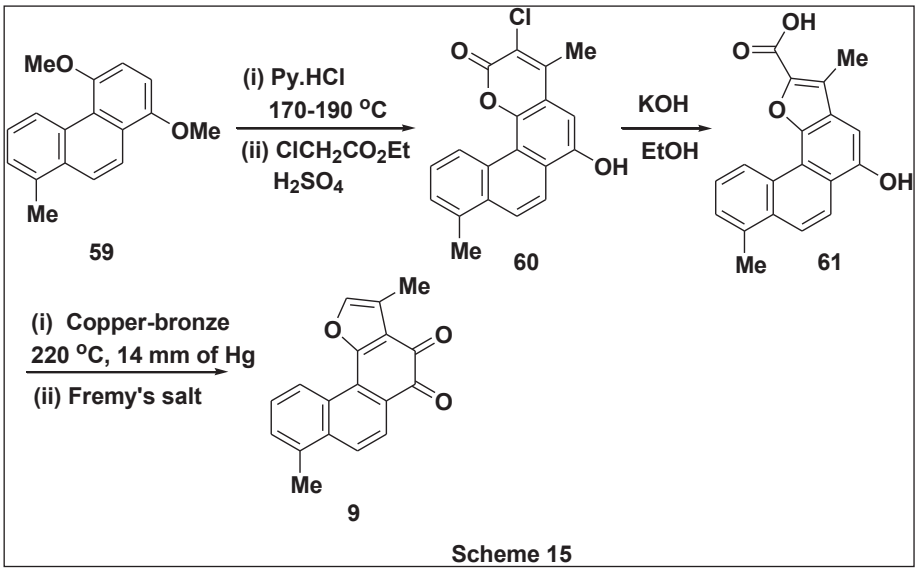


Scheme 13

1.2 Objective of our work:

As these 'S'-shaped furophenanthraquinones have shown significant pharmacological activities including cardioprotection,[43] neuroprotection,[44] antileukaemic,[45] antioxidative and anticancer activities against different type of cancers,[46-52] large number of research groups all around the world have shown interest in the synthesis and biological evaluation of mostly tanshinones and their analogues.[53-56] Thus, such condensed furonaphtho/phenanthraquinones in general are in the focus as an important field of research in recent times too.

Though extensive research work on the synthesis and bioactivity studies on 'S'-shaped furophenanthraquinones have been taken up in the last few decades, studies on the synthesis of the 'U'-shaped furophenanthraquinones are limited so far.[32,33,57] (though an isomeric 'U'-shaped furophenanthraquinone isotanshinone II, has also been isolated from *Salvia glutinosa* [22]). The reason for the limited number of studies is two-fold: i) extremely poor natural abundance of the 'U'-shaped furophenanthraquinone metabolites. To cite an example only1.5 mg of isotanshinone II along with 14 other diterpenoids were isolated from 930 gm of dried root of *Salvia glutinosa*.[22] ii) The second reason is the relatively late isolation of this type of metabolites. The 'U'-shaped furophenanthraquinone isotanshinone II (**9**) and dihydroisotanshinone II (**10**) was isolated as late as in 1999.[22]



Scheme 15

Pertinently, only one total synthesis of isotanshinone II has so far been reported by King and Read[57] in 1961 even before its isolation from *Salvia glutinosa.* The authors adopted the total

synthesis utilising a base-catalysed ring contraction of 3-chloro-2-pyranone moiety in compound **60** which was synthesised from 1,4-dimethoxy-8-methylphenanthrene (**59**) in two steps**.** Decarboxylation of the intermediate **61**, followed by oxidation of the resulting furophenanthrenol, furnished furophenanthraquinone derivative **9** (scheme 15) (later on isolated from *Salvia glutinosa* and named as isotanshinone-II).

During their studies on 'S'-shaped furophenanthraquinones, using Diels-Alder reaction, Snyder and his co-workers reported the synthesis of some non-natural tetracyclic 'U'-shaped furophenanthraquinones.[58] But their bioactivities were not well exposed. Very recently, F.S. Senol *et al.* studied for the first time the bioactivity of isotanshinone II against Alzheimer's disease.[59] Isotanshinone II has been found in vitro to inhibit butylcholineesterase and thus acts as promising nuroprotective agent for treatment of Alzheimer's disease. Hence very little is known so far about such 'U'-shaped furophenanthraquinones.

Inspired by the importance of such furophenanthraquinones, our group has also taken up a project on the synthesis of condensed furophenanthraquinones and their analogues. Literature reports on the synthesis of tanshinones disclosed that the disadvantages of the previous syntheses were lack of easy availability of the starting material, harsh reaction conditions and poor overall yields of the final products. Our objective was to develop a convergent strategy to build the ABCD ring system present in tanshinones using easily available starting materials and simple reactions. Also, most of these syntheses, reported earlier, started with either A, B or C ring precursors and ring D was built up in the last phase of the synthesis. Possibly, the authors thought of unstable nature of the furan ring under acidic conditions.

Our group have developed a method[60-62] for the synthesis of both phenanthro[1,2-*b*]furan-10,11-dione derivatives ('S'-shaped furophenanthraquinones) and phenanthro[4,3-*b*]furan-4,5-dione derivatives ('U'-shaped furophenanthraquinones) simulating ABCD rings of tanshinones and isotanshinones nucleus. The method is based on two important key steps: i) construction of aryl-furyl bond *via* Suzuki reaction and ii) generation of the quinone moiety by oxidation of a furophenanthrenol derivative (fig. 3 and 4). In this strategy, ring C was built up in a later stage starting with AB and D ring precursors.The furan ring was found to survive under reaction conditions employed.

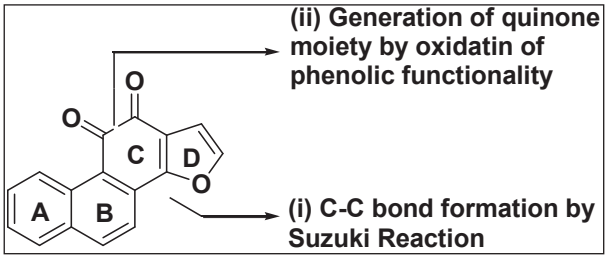


Figure 3: Synthetic strategy for 'S'-shaped furophenanthraquinone nucleus

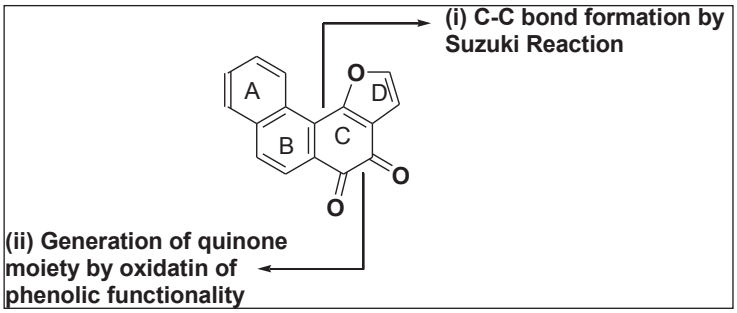
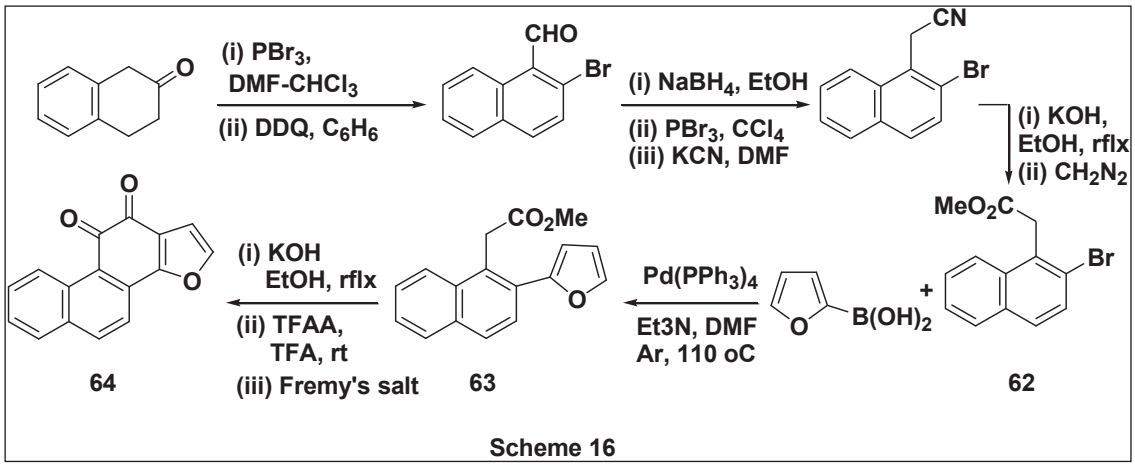


Figure 4: Synthetic strategy for 'U'-shaped furophenanthraquinone nucleus

Kar *et al.* have already reported a new general stepwise route towards the synthesis of phenanthroquinone diterpenoids as nuclear analogues of tanshinon I[60] as per scheme-16.



Methyl 2-(2-bromo-1-naphthyl)acetate (**62**) was prepared in five steps from 2-tetralone *via* 2-bromo-1-naphthaldehyde and 2-bromo-1-cyanomethylnaphthalene. The Suzuki reaction with 2-furanboronic acid and this bromo ester **62** produced **63**. Hydrolysis of the compound **63**, followed by cyclisation and oxidation of furophenanthrenol intermediate by Fremy's salt, furnished phenanthro[1,2-*b*]furan-10,11-dione (**64**) (the core nucleous of tanshinone I) in overall

good yeilds (scheme 16). The synthesis of compound **63** was also achieved *via* an alternative intermediate *i.e.* 2-[2-(2-furyl)naphthalene-1-yl]acetonitrile**.**[60]

Our objective is to synthesise novel U-shaped furophenanthraquinones as well as to modify A ring and D ring in the tetracyclic framework to synthesise more and more novel furophenanthraquinone and their analogues such as thienophenanthraquinones, doubly condensed theinonaphthoquinones following the strategy developed in our laboratory.