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 furophenantheraquinones

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

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.\textsuperscript{9} The lipophilic components include a number of condensed furophenanthraquinones and their di-, tetra- and hexahydro derivatives (fig. 1).\textsuperscript{3,10} Such types of furophenanthraquinones have been isolated not only from Danshen but also from other \textit{Salvia} species such as \textit{Salvia glutinosa} and \textit{Salvia columbariae}. Some tetracyclic furophenanthraquinones, isolated from \textit{Salvia} species, are given below (fig. 1).

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\textbf{Figure 1: Some tetracyclic furophenanthraquinone derivatives isolated from} \textit{Salvia miltiorrhiza} and \textit{Salvia glutinosa}

Structurally, all the isolated furophenanthraquinones contain a tetracyclic framework either in ‘S’-shaped form \textit{i.e.} phenanthro[1,2-\textit{b}]furan-10,11-dione derivatives (or its di-/tetra-/hexahydro derivatives) or in ‘U’-shaped form \textit{i.e.} phenanthro[4,3-\textit{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.\textsuperscript{8} Even the tricyclic furonaphthoquinones,\textsuperscript{11} simulating BCD rings of tanshinones, show cancer chemopreventive activity,\textsuperscript{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,\textsuperscript{12-15} but they couldn't predict the structures. The extensive works,\textsuperscript{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 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) 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 \textit{S. glutinosa} in last decades.\textsuperscript{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.\textsuperscript{23, 24} Several authors have published reviews about the structures, syntheses and biological activities of diterpenoids from \textit{Salvia} species, considering the recent flurry of reports in this area.\textsuperscript{3,6,8,23-26} These activities further stimulated the studies on synthesis of such furophenanthraquinones. 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,\textsuperscript{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).

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,\textsuperscript{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.
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.

In 1969, Inouye and Kakisawa\textsuperscript{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-1-vinylicyclohexene (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](image)

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

In 1992, Danheiser \textit{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 detrifluoroacetylatative 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%.
The author also extended further this methodology to synthesise tanshinone IIA and (-) cryptotanshinone starting from anisole via neocryptotanshinone (35) (scheme 6).³⁴
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). The overall yield of 6 was 7% in eleven steps.

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). 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).
In 2017, Wu et al. developed an efficient three-step total synthesis,\textsuperscript{37} of tanshinone I (1) starting from 2-methylstyrene (48) and 2-methoxy-1,4-benzoquinone (49) via uncatenised 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–NH₄OAc formed the furan moiety to complete the synthesis of tanshinone I (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)\textsuperscript{38} as per scheme 10. They also adopted the Diels-Alder reaction strategy, as reported by Lee and Snyder.\textsuperscript{32} The only difference is that the A-ring component (diene) is 1-methyl-2-vinyl-2-cyclohexenol derivative (52).

During 2012-2017, the syntheses of several novel derivatives of the naturally occurring “S”-shaped furophenanthraquinones has been reported,\textsuperscript{39-42} with A-ring modification as per schemes (11-14).
i) 1eqv. NBS, BPO, anhy. CCl$_4$, reflux

$\text{R} = \text{H, OBn, CH$_2$OH, Br, Cl, CH$_3$CH$_2$CO, NO$_2$, CH$_3$, CF$_3$, OCH$_3$ etc.}$

$X = \text{CO$_2$H, CH$_2$CO$_2$H; R = OCH$_3$, OH, F}$

Scheme 12

ii) 1eqv. K$_2$CO$_3$ anhy. DMF

$\text{R} = \text{H, OBn, CH$_2$OH, Br, Cl, CH$_3$CH$_2$CO, NO$_2$, CH$_3$, CF$_3$, OCH$_3$ etc.}$

Scheme 14

$\text{R = CH$_3$, Et, Pr, n-Bu, , , CH$_2$OH,}$

$\text{R$_1$, , , , , etc.}$

Scheme 13
1.2 Objective of our work:

As these ‘S’-shaped furophenanthraquinones have shown significant pharmacological activities including cardioprotection, neuroprotection, antileukaemic, antioxidative and anticancer activities against different type of cancers, large number of research groups all around the world have shown interest in the synthesis and biological evaluation of mostly tanshinones and their analogues. 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. (though an isomeric ‘U’-shaped furophenanthraquinone isotanshinone II, has also been isolated from *Salvia glutinosa*). 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 only 1.5 mg of isotanshinone II along with 14 other diterpenoids were isolated from 930 gm of dried root of *Salvia glutinosa*. 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.

Pertinently, only one total synthesis of isotanshinone II has so far been reported by King and Read 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 butyrylcholineesterase 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 method60-62 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.
Kar et al. have already reported a new general stepwise route towards the synthesis of phenanthroquinone diterpenoids as nuclear analogues of tanshinone I 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 yields (scheme 16). The synthesis of compound 63 was also achieved via an alternative intermediate \textit{i.e.} 2-[2-(2-furyl)naphthalene-1-yl]acetonitrile.\textsuperscript{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.