Review

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# Recent Advances in 1,4-Benzoquinone Chemistry

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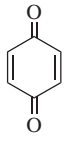
As 1,4-benzoquinonas são encontradas em toda a natureza, podendo ser sintetizadas por diversas estratégias. Esta revisão apresenta os desenvolvimentos recentes das metodologias de síntese, das reações de ciclo adição, da química computacional e dos estudos de pulso radiolítico. Destaca ainda a sua significância química e biológica e de seus compostos derivados.

1,4-Benzoquinones are ubiquitous in nature and can be synthesized by diverse strategies. Recent developments on their synthetic methodologies, cycloaddition reactions, computational chemistry and pulse radiolytic studies are reported in this review. Their chemical and biological significance as well as their derivates' are also covered.

**Keywords:** 1,4-benzoquinone, synthesis, cycloadditions, computational chemistry, pulse radiolysis

## 1. Introduction

Quinones are a large class of compounds endowed with rich and fascinating chemistry.[1] 1,4-Benzoquinone or *p*-benzoquinone (**1**) is the basic structure of quinonoid compounds.

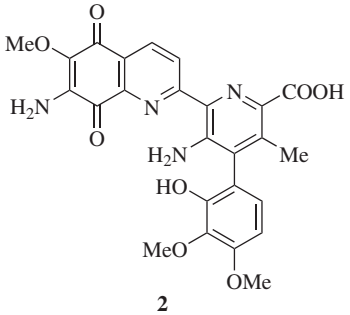


**1**

They are widely distributed in the natural world,[2] being found in bacteria, plants and arthropods and hence quinones are ubiquitous to living systems. Quinones play pivotal role in biological functions including oxidative phosphorylation and electron transfer.[3] Their role as electron transfer agents in primary metabolic processes like photosynthesis and respiration is vital to human life. A large number of chemical derivatives with 1,4-benzoquinone as the basic subunit exhibit prominent pharmacological applications such as antibiotic,[4,5] antitumor,[6-9] antimalarial,[7,10] antineoplastic,[11] anticoagulant[12] and herbicidal activity.[13] Wide applications of quinones can also be found in the field of synthetic organic chemistry.[14-20] Coordination chemistry of quinones is also quite rich from the perspective of designing magnetic materials[21] and understanding photophysical properties.[22] The studies of quinonoid compounds have focused on a broad spectrum of topics *viz* occurrence in nature,[2] syntheses,[23] cycloaddition reactions,[24] photochemistry and pulse radiolysis,[1,25,26] computational chemistry, etc.[27] The copiousness of articles describing the aforementioned multi-functional aspects serves as a grand testimonial to the contemporary interest in quinone chemistry. Hence a comprehensive review has been carried out to explore various scientific reports on 1,4-benzoquinones covering their chemical and biological significance.

## 2. 1,4-Benzoquinones from Nature

Quinones are ubiquitous in nature which occur predominantly in flowering plants, fungi including lichens and in small numbers they are widely scattered in most forms of life.[28] Naturally occurring quinones have captured human attention for thousands of years, initially by reason of their bright colors with possible uses as dyes and drugs.[1,20]



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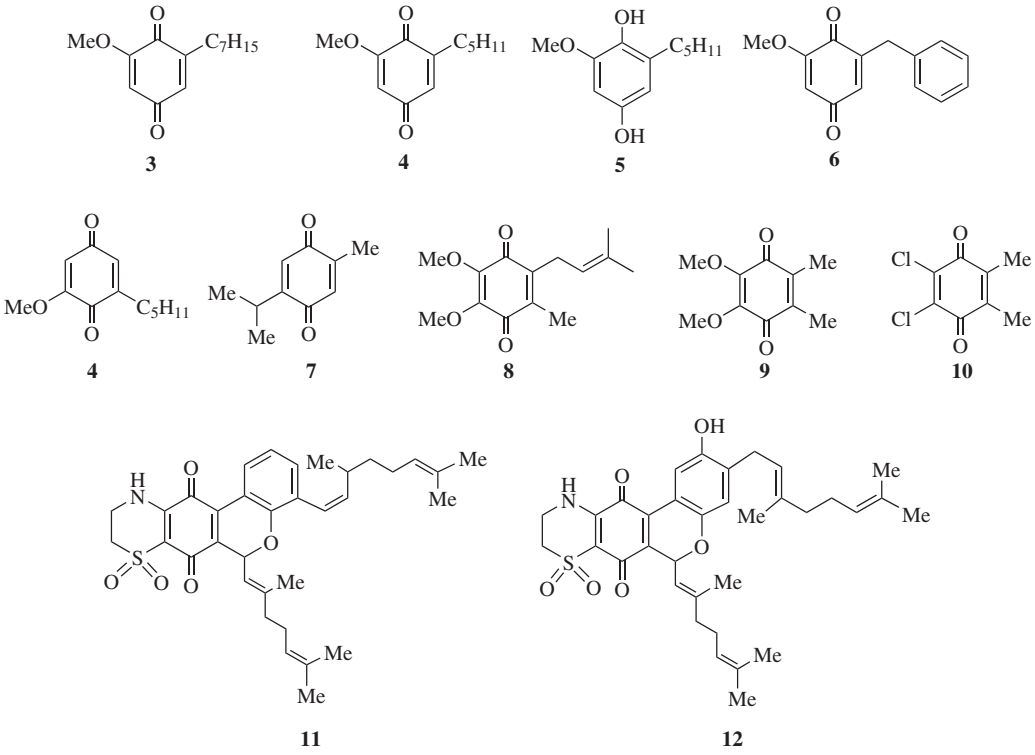


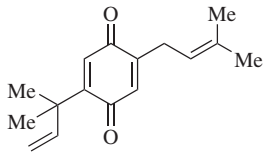
Pigments of various colors isolated from different sources have been identified as quinonoid compounds. Crude preparations of plants presently known to contain quinones as active ingredients were prescribed for more than 4000 years as purgatives or drugs.[29] Throughout history several other medicinal benefits have been added to the list every year. The discoveries of antibiotic and antitumor properties of several naturally occurring quinones have raised interest among scientists to explore their use as pharmaceuticals.[30,31] For instance, streptonigrin (STN)[32] (**2**) is a natural quinone with antitumor and antibiotic activity.

Kingston and co-workers[33] have isolated two new benzoquinones 2-methoxy-6-heptyl-1,4-benzoquinone (**3**) and 2-methoxy-6-pentyl-1,4-benzoquinone (**4**) from the leaves of *Miconia lepidota* present in Surinam forests. Both quinones **3** and **4** exhibited activity towards mutant yeast strains based on *Saccharomyces cerevisiae*, indicative of their cytotoxicity and potential antitumor activity. The compound **4** is an important quinone called primin.[34] It is noteworthy to mention the insect antifeedent,[34] antimicrobial and antineoplastic activities[35,36] of primin and its quinol analogue miconidin (**5**). Another important quinone, 2-methoxy-6-benzyl-1,4-benzoquinone (**6**) was also synthesized and tested in the same strain.

The antitermite activity of selected naturally occurring and synthetic 1,4-benzoquinones have been reported by Mozaina *et al.*[37] They evaluated a set of chosen benzoquinones for activity against the Formosan subterranean termite, *Coptotermes formosanus* and showed that five bioactive naturally occurring 1,4-benzoquinones (**4, 7**-**10**) demonstrated 100% mortality against *C. formosanus*.

In the chemical investigations on quinones major thrust is being given to the study of their antitumor activity;[38] which is directly related to the cytotoxic actions of quinones.[39-42] Vast amount of research has been carried out to establish the antitumor activity of quinones.[43-47] Aiello *et al.*[48] isolated two novel prenylated benzoquinones thiaplidiaquinone A (**11**) and thiaplidiaquinone B (**12**) from the Mediterranean ascidian *Aplidium conicum*. Both thiaplidiaquinones can enter into the cell and induce cell death by apoptosis.

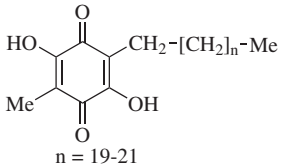
Recently, an antiproliferative bis-prenylated quinone, 5-(1,1-dimethylprop-2-enyl-2-(3-methylbut-2-enyl) cyclohexa-2,5-diene-1,4-dione (**13**) has been isolated from the New Zealand brown alga *Perithalia capillaries*.[49] This compound inhibited superoxide production by human neutrophils *in vitro* and was also reported to inhibit proliferation of HL60 cells.



**13**

Polyhalogenated benzo- and naphthoquinones were found to be potent inhibitors of plant and bacterial ureases. Ashiralieva and Kleiner[50] showed that the inhibitory power

decreased considerably when halogens were replaced by –OH, –CN, alkoxy or alkyl groups. The polyhalogenated quinones can be used for treatment of infections caused by urease producing bacteria. *Polygonatum alte-lobatum* Hayata is a Formosan endemic plant. The rhizome of this plant has been used as a tonic drug in Taiwan. Huang *et al.*[51] isolated two new series of quinones named polyanoquinones A (**14**) and B (**15**) from the rhizomes of *Polygonatum alte-lobatum*.

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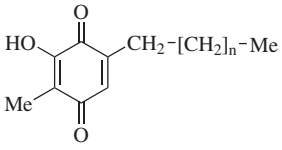



**15**

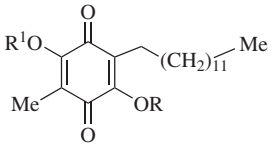
El-Feraly and co-workers[52] isolated five new alkylated benzoquinones (**16**-**20**) as methyl ether derivatives from a complex mixture of alkylated hydroxy benzoquinones obtained from the fruits of *Maesa lanceolata*.

A new benzoquinone named alopecuquinone (**21**) was isolated from the ethanol extract of the inflorescences of *Cyperus alopecuroids* by Nasser *et al.*[53] The ethanol extract of the plant material showed moderate estrogenic activity using a strain of *Saccharomyces cerevisiae*. It has also been reported that *Cyperus* species have medicinal effects such as pectoral emmolient, analgesic and anti-helmintic.

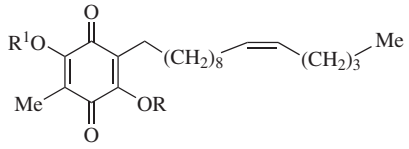
Hosttetman and co-workers[54] isolated two novel benzoquinones heliotropinones A (**22**) and B (**23**), from the aerial parts of *Heliotropium ovalifolium*. These two quinones demonstrated antifungal activities against *Cladosporium cucumerinum* and *Candida albicans* as well as antibacterial activity against *Bacillus subtilis*. Kaul and co-workers[55] isolated six novel alkylated benzoquinone irisoquins A-F (**24**-**29**) and a known cytotoxic quinone, irisoquin (**30**) from the rhizomes of *Iris kumaonensis*. These classes of compounds have attracted considerable attention because of their antioxidant and cytotoxic properties.

Two antimalarial benzoquinones 2-chloro-5-methoxy-3-methyl-cyclohexa-2,5-diene-1,4-dione (**31**) and xylariaquinone A (**32**) were isolated from an endophytic fungus, *Xylaria sp.* Compounds **31** and **32** showed *in vitro* antimalarial activity against *Plasmodium falciparum* (K1 strain).[56] *Embelia ribes* is one of several *Embelia* sp. used in traditional Chinese medicine to treat a range of ailments. Among the diverse array of chemotypes present in the extract, 1,4-benzoquinones are significant. Lund *et al.*[57] isolated a unique series of alkylated dihydroxybenzoquinones from *Embelia angustfolia*. The four 2,5-dihydroxy-3-alkyl-1,4-benzoquinones (**33-36**) demonstrated angiotensin converting enzyme (ACE) inhibition which is related to the diuretic effect.

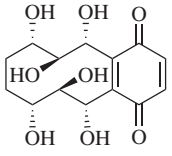
Another important 2,5-dihydroxy-3-alkyl-1,4-benzoquinone is embelin (2,5-dihydroxy-3-undecyl-1,4-benzoquinone) (**37**) which is a major constituent in the extracts of various parts of the shrub *Embelia ribes*.




**16** R = Ac; $R^1$ = Me
**17** R = Me; $R^1$ = Ac
**18** R = Me; $R^1$ = Me




**19** R = Ac; $R^1$ = Me
**20** R = Me; $R^1$ = Ac

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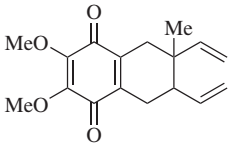


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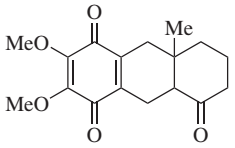


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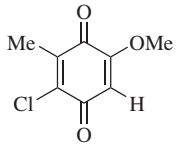


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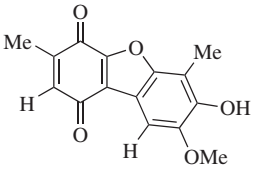


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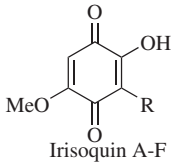
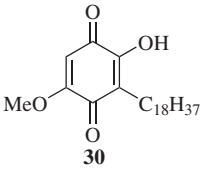
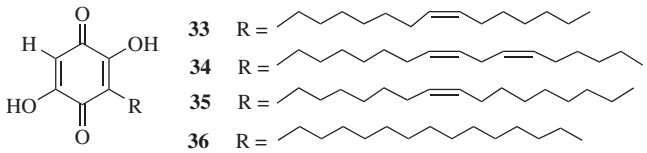


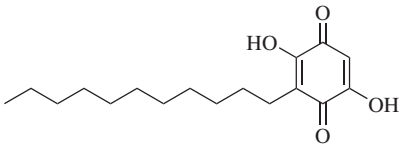

Irisoquin A-F

**24** R = $C_{16}H_{13}$ **27** R = $C_{20}H_{41}$
**25** R = $C_{17}H_{35}$ **28** R = $C_{21}H_{43}$
**26** R = $C_{19}H_{19}$ **29** R = $C_{22}H_{45}$

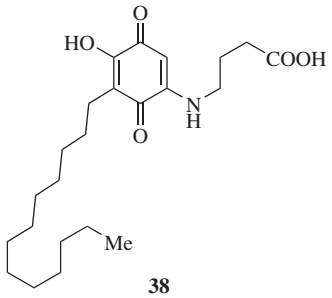



**30**
Irisoquin



**37**



**38**

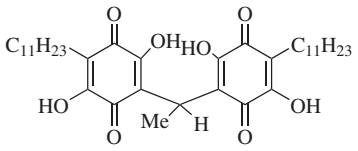
Embelin is reported to elicit a wide range of biological effects including anti-helmintic, analgesic, antifertility, antitumor and antioxidant properties.[58] Recently an unusual *N*-containing benzoquinone derivative was isolated from the roots of *Embelia ribes* by Lin *et al*.[59] and assigned the structure *N*-(3-carboxypropyl)-5-amino-2-hydroxy-3-tridecyl-1,4-benzoquinone, **38**. It shares the long unbranched 3-alkyl side chain of embelin (**37**) although it has two extra carbons and has the unusual incorporation of γ-aminobutyric acid linked to the quinone through the nitrogen. Compound **38** has the distinction of first naturally occurring nitrogen containing 2,5-dihydroxy-3-alkyl-1,4-benzoquinone derivative.

Myrsine, Maesa, Rapanea and Embelia are four genera of trees and shrubs that are widely used in herbal medicine in Kenya. The fruits of *Myrsine africana* afforded two new benzoquinone derivatives,[60] methylvilangin (**39**) and methylanhydrovilangin (**40**); while the fruits of *Maesa lanceolata* afforded two more novel quinones,[60] 2,5-dihydroxy-3-(nonadec-14-enyl)-benzoquinone (**41**) and lanciaquinone (**42**).

*Gunnera perpensa* is another plant with high medicinal value.[61,62] Drewes *et al.*[63] isolated olefinic 1,4-benzoquinone *viz* 2-methyl-6-(3-methyl-2-butenyl)-benzo-1,4-quinone (**43**) and 3-hydroxy-2-methyl-5-(3-methyl-2-butenyl)-1,4-benzoquinone (**44**) from the $CH_2Cl_2$ extract of the stems and leaves of *Gunnera perpensa*. **43** Showed significant antimicrobial activity with the most sensitive organism being *Staphylococcus epidermidis* whereas **44** showed no activity.

Sesquiterpene quinones are biologically important class of compounds isolated mainly from various species of marine sponges.[64] They are characterized by pronounced and manifold biological properties.[65] For instance, Kobayashi and co-workers[66-69] have done a pioneering work in isolating a series of nakijiquinones A-I which are of particular relevance among sesquiterpenoid quinones (**45**-**53**). Stahl *et al.*[70] described the first enantioselective total synthesis of the nakijiquinones and their biological evaluation. Besides ilimaquinone (**54**),[71] smnenospongines (**55**-**57**),[72] metachromins L, N, P (**58**-**60**)[73] and mamanuthaquinone (**61**)[74] display antimicrobial, antiviral and cytotoxic activities.

The wide spectra of biological properties of sesquiterpenoid quinones stimulated several groups to isolate different structures from natural sources. A new sesquiterpene substituted benzoquinone derivative, cyclozonarone (**62**) has been isolated from the brown



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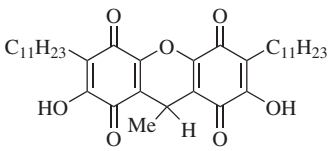

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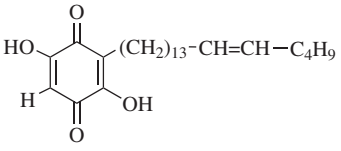

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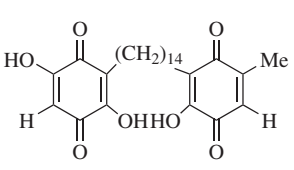

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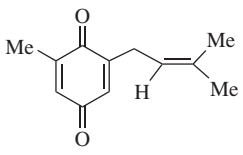

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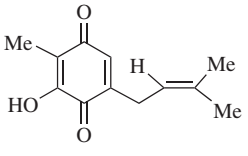

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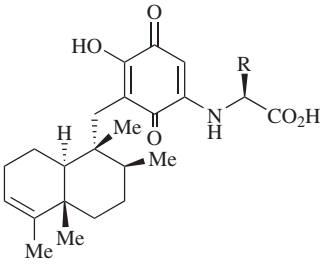
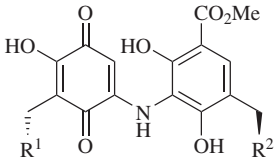
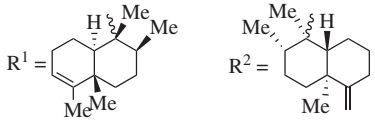


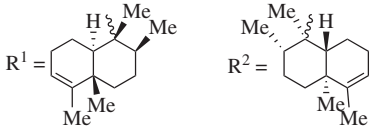
**45** Nakijiquinone A R = H
**46** Nakijiquinone B R = $CHMe_2$
**47** Nakijiquinone C R = $CH_2OH$
**48** Nakijiquinone D R = CH(OH)Me

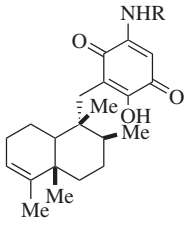


**49** Nakijiquinone E

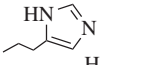


**50** Nakijiquinone F

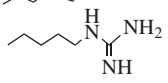




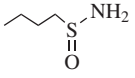
**51** Nakijiquinone G R =

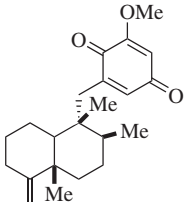


**52** Nakijiquinone H R =

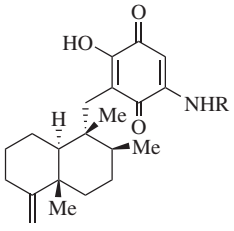


**53** Nakijiquinone I R =

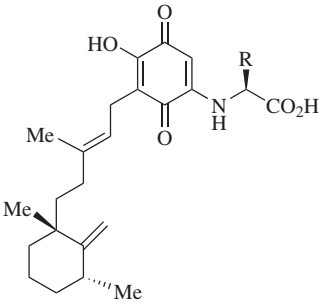




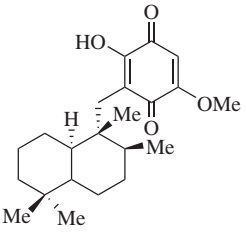
**54** Ilimaquinone



**55** Smenopongine R = H
**56** Smenospongorine R = $CH_2CHMe_2$
**57** Smenospongidine R = $CH_2CH_2Ph$



**58** Metachromin L R = H
**59** Metachromin N R = CH(OH)Me
**60** Metachromin P R = $CH_2OH$

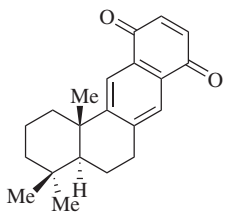


**61** Mamanuthaquinone

alga *Dictyopteris undulata*.[75] **62** showed potent feeding-deterrent activity toward young abalones.

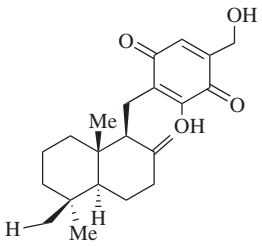
Yamada and co-workers[76] isolated structurally unique new sesquiterpenoid quinones dactyloquinones A (**63**) and B (**64**) from an Okinawan sponge *Dactylospongia elegans*. Both **63** and **64** possess a dihydropyran moiety.

Very recently Wijeratne *et al.*[77] isolated many sesquiterpene quinones including tauranin (**65**) from *Phyllosticta spinarum*, a fungal strain endophytic in *Platycladus orientalis*. Tauranin (**65**) is reported to have



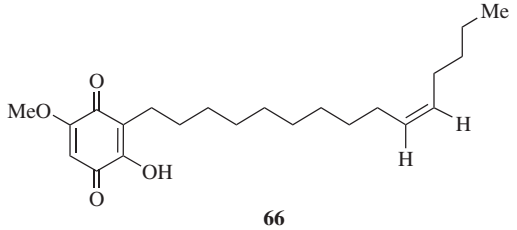
**62**

antiproliferative and apoptic activity towards several cancer cell lines.



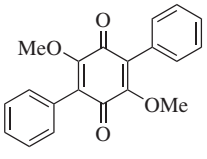
**65**

Maesanin, 2-hydroxy-5-methoxy-3-(10'-pentadecenyl)-1,4-benzoquinone (**66**) is a natural *p*-benzoquinone isolated from the fruits of *Maesa lanceolata* and *Ardisia japonica*.[78] Maesanin possess pronounced biological activities including non-specific immunostimulation, 5-lipoxygenase inhibition, aldose reductase inhibition in addition to potentiation of the anticandidal effect of the sesquiterpene dialdehyde, polygodial.

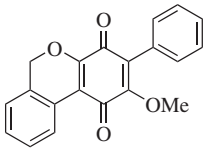


**66**

Disintegration of cells and organellar membranes by reactive oxygen species (ROS) has been implicated in various pathological processes and especially involved in the pathogenesis of diseases such as myocardial and cerebral ischemia, atherosclerosis, diabetis, rheumatoid arthiritis and cancer-initiation and aging processes.[79-81] Thus, free radical scavengers have the potential as protective agents against various diseases. Lee *et al.*[82] isolated two such free radical scavenging quinones, betulinan A (**67**) and B (**68**) from the methanolic extract of *Lenzites betulina*.



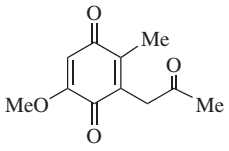
**67**



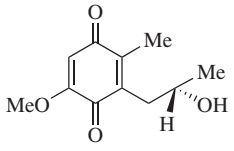
**68**

Wang *et al.*[83] isolated two new benzoquinones, anserinone A (**69**), and B (**70**) with antifungal, antibacterial and cytotoxic activities from the liquid cultures of the coprophilous fungus *Podospora anserina*.

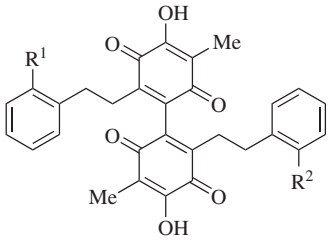
Yang *et al.*[84] isolated four new type of dimeric phenylethyl benzoquinones parvistemins A-D (**71**-**74**) from *Stemona parviflora* Wright.



**69**



**70**



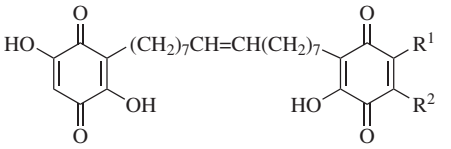
**71** Parvistemin A $R^1 = R^2 = H$
**72** Parvistemin B $R^1 = R^2 = OH$
**73** Parvistemin C $R^1 = R^2 = OMe$
**74** Parvistemin D $R^1 = H$; $R^2 = OMe$

Ardisiaquinones are another interesting class of quinones derived from natural sources which are characterized by long carbon chains connecting two benzoquinone moieties. Ogawa *et al.*[85] first isolated ardisiquinones A-C (**75**-**77**) from the root bark of *A. sieboldii*. In 1995, Fukuyama *et al.*[86] reported the isolation of ardisiquinone D-F (**78**-**80**) from the same species and later published their total synthesis.[87] In 2001, Yang *et al.*[88] extended the series to isolate ardisiaquinones G-I (**81**-**83**) from the leaves of *Ardisia teysmanniana*. All these quinones showed antimicrobial activity.

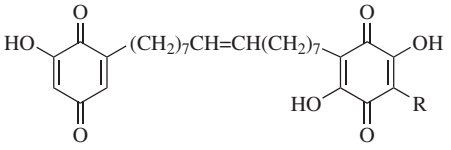
Carazza and co-workers[89] investigated the antibacterial activity of some new benzoquinones derivatives. The study points to the antibacterial activity of 2-aryl-3,5-dimethoxy-1,4-benzoquinone derivatives. *Cynanchum wilfordii* Hemsley has been used as a tonic in Korea. A novel amino-substituted *p*-benzoquinone (**84**) has been isolated from this medicinally important plant by Yeo and Kim.[90] Another potent antifungal benzoquinone (**85**) has been isolated from etiolated sorghum seedlings.[91]

Kanakubo and Isobe[92] reported the isolation of tetrabromo-1,4-benzoquinone from acorn worm. Structure-activity relationship of chemiluminescence activity of halogenated quinone derivatives reveals that a highly halogen substitution and 1,4-quinone skeleton are important for high chemiluminescence activity. Gentisyl quinone isovalerate, or blatellaquinone (BTQ) (**86**) has been reported[93] as a female sex pheromone produced by the German Cockroach, *Blatella germanica*. Bennet *et al.*[94] recently investigated the cytotoxic effects of BTQ in human lung adenocarcinoma cells.

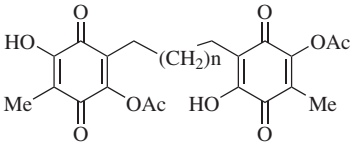
Given its effectiveness to conjugate GSH, and possibly proteins, BTQ may be a potential chemical allergen



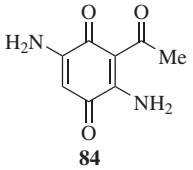
**75** Ardisiaquinone A $R^1$= OMe, $R^2$ = H
**76** Ardisiaquinone B $R^1$= OH, $R^2$ = Me
**77** Ardisiaquinone C $R^1$= OAc, $R^2$ = Me
**78** Ardisiaquinone D $R^1$= OMe, $R^2$ = OMe



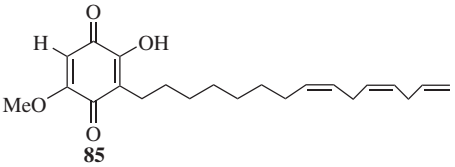
**79** Ardisiaquinone E R = H
**80** Ardisiaquinone F R = Me



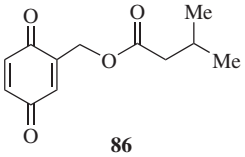
**81** Ardisiaquinone G n = 11
**82** Ardisiaquinone H n = 12
**83** Ardisiaquinone I n = 13



**84**



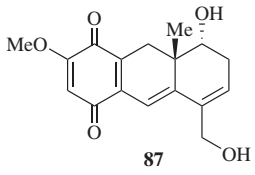
**85**



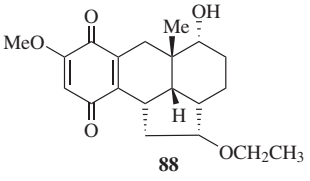
**86**

contributing to allergic reactions in cockroach sensitized patients.

Pessoa *et al.*[95] isolated and characterized two significant quinones oncocalyxone A (**87**) and oncocalyxone C (**88**) from the ethanolic extract of heartwood of *Auxemma oncocalyx*. Later both oncocalyxones have been reported to exhibit antitumor activity.[96]



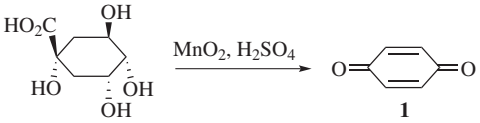
**87**



**88**

## 3. Synthesis of 1,4-Benzoquinones

1,4-Benzoquinones are an important class of compounds, which serve as valuable building blocks in synthesis and are key moieties in the synthesis of biologically active compounds. A comprehensive report on various methodologies developed for the construction of benzoquinones and their derivatives is presented in this section. The immense interest on quinone chemistry has been observed from the middle of 19th century. The most common quinone, benzoquinone (**1**) was the first synthesized quinone in the late 1830's in Liebig's laboratory as a result of the oxidation of quinic acid with manganese dioxide and sulfuric acid (Scheme 1).[29] This reaction involves dehydration, decarboxylation and oxidation.



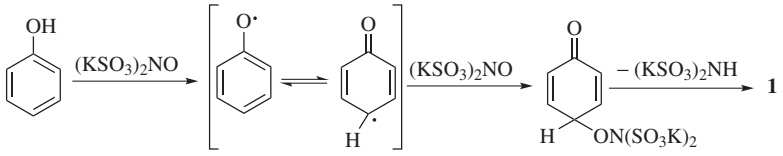
Quinic acid

**Scheme 1.** First synthesis of 1,4-benzoquinone.

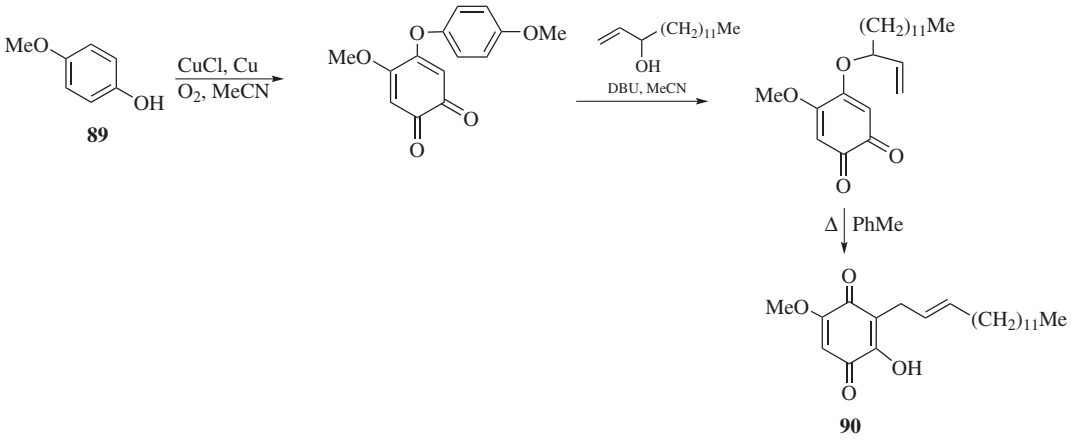
The same reagents can also react with aniline *via* a free radical condensation mechanism to afford benzoquinones. Succeeding these initial preparations of quinones, an array of reactions involving diverses starting compounds and efficient synthetic strategies have been reported in the literature till date for the synthesis of simple to highly complex benzoquinones. In general, quinones are being synthesized from phenols, 1,4-dihydroxybenzenes or hydroquinones and dimethoxybenzenes. Besides these traditional precursors some miscellaneous compounds also lead to benzoquinones. The commonly used oxidizing agents employed for quinone synthesis are silver oxide,[97] manganese oxide,[98] nitric acid,[99] salcomine/$O_2$,[100] chromium oxidants,[101] benzene selenic anhydride,[102] ceric ammonium nitrate (CAN)[103] and DDQ.[104]

### *3.1. Synthesis of 1,4-benzoquinones from phenols*

Several techniques have been reported for the oxidation of phenols to benzoquinones. The Teuber reaction,[105] which uses Fremy's salt [potassium nitrodisulfonate, $(KSO_3)_2NO$] as oxidizing agent has been the earliest reported and widely used method. It gives good to excellent yields and proceeds under mild conditions (Scheme 2).



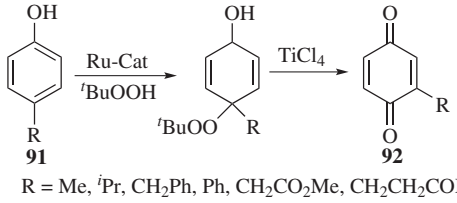
**Scheme 2.** Mechanism of Teuber reaction.



**Scheme 3.** Synthesis of biologically active quinone *via* Claisen rearrangement.[107]

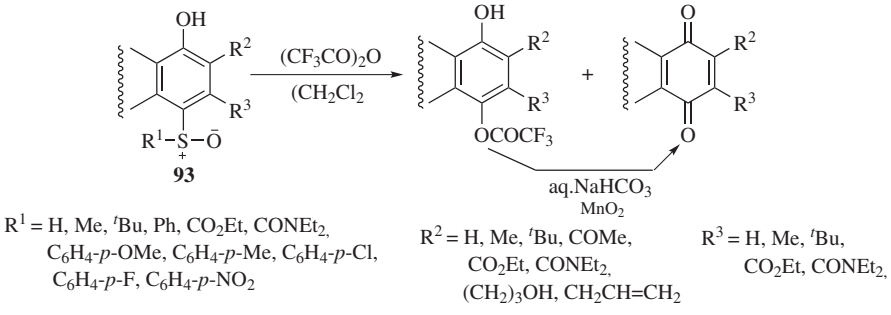
Teuber reaction is especially useful for the synthesis of heterocyclic quinones, where other oxidizing agents fail.[106] Later on, several groups have developed direct and stepwise oxidation of phenols and their derivatives to *p*-quinones. Reinaud *et al.*[107] synthesized biologically active unsymmetrical alkyl-hydroxymethoxyquinone analogs (**90**) from *p*-methoxyphenol (**89**). The alkyl side chain was introduced regiospecifically *ortho* to the hydroxyl group *via* a Claisen rearrangement (Scheme 3).

4-Substituted phenols can be converted into 2-substituted benzoquinones. Murahashi *et al.*[108] demonstrated a ruthenium catalyzed oxidation of 4-substituted phenols (**91**) with *t*-butyl hydroperoxide in ethyl acetate or benzene followed by treatment with titanium tetrachloride to obtain high yields (70-80%) of 2-substituted benzoquinones (**92**) with the migration of 4-substitutent to the 2-position of the benzoquinone (Scheme 4).



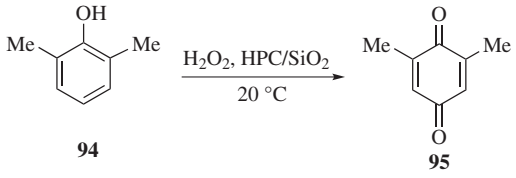
**Scheme 4.** Ruthenium catalysed oxidation of phenols to quinones by Murahashi *et al.*[108]

Phenols have been oxidized to 1,4-benzoquinones in a two step procedure *via para*-sulfinylation followed by a Pummerer rearrangement induced by trifluoroacetic anhydride on the resulting *p*-sulfinylphenols (Scheme 5).[109] The *p*-sulfinylphenols (**93**) were prepared by successive thiocyanation reaction with Grignard reagent and oxidation of phenols. Overall yields for this process are moderate.



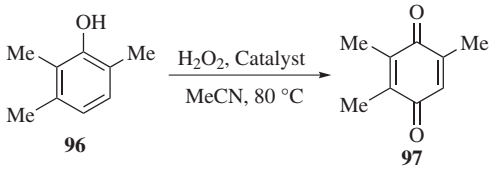
**Scheme 5.** Conversion of *p*-sulfinylphenols to corresponding quinones by Akai *et al.*[109]

Caceras and co-workers[110] undertook a clean liquid phase oxidation of 2,6-dimethylphenol (**94**) to 2,6-dimethyl-1,4-benzoquinone (**95**) using aqueous hydrogen peroxide as oxidant and Keggin type heteropoly compounds of vanadium and molybdenum supported on silica (HPC/$SiO_2$) as catalysts (Scheme 6).




**Scheme 6.** Clean liquid phase oxidation of 2,6-dimethylphenol to 2,6-dimethylbenzoquinone.[110]

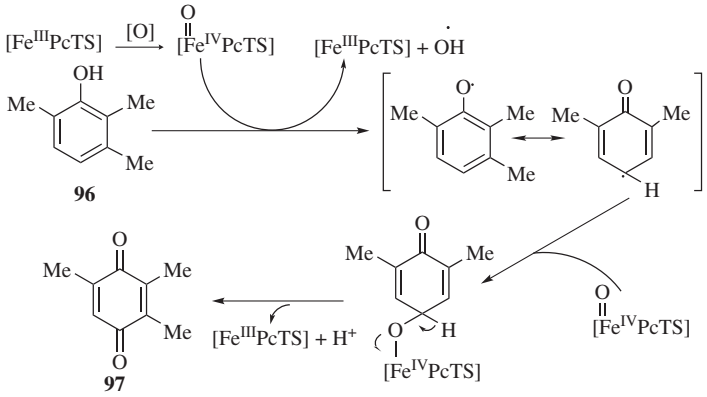
2,3,6-Trimethyl-1,4-benzoquinone, TMQ (**97**) synthesized by the oxidation of 2,3,6-trimethylphenol, TMP (**96**), is used as a precursor in the synthesis of vitamin E.[111,112] Molecular oxygen, hydrogen peroxide or *t*-butyl hydroperoxide are being used as common oxygen sources and different catalytic systems metallophthalocyanins,[113,114] heteropolyoxometallates,[115,116] spinel $CuCo_2O_4$,[117] copper hydroxyl phosphate,[118] iron halides,[119] copper (II) chloride,[120,121] metal acetylacetonates[122] and titanium silicates.[123,124] Kholdeeva *et al.*[125] reported the TMP oxidation to TMQ with aqueous hydrogen peroxide. Later they modified the oxidation process using aqueous $H_2O_2$ over titanium (IV) grafted on commercial mesoporous silica catalyst produced TMQ in nearly quantitative yield (Scheme 7).[126]



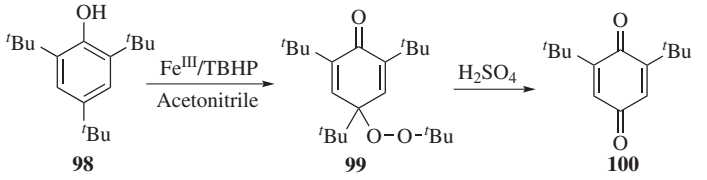

**Scheme 7.** Oxidation of TMP to TMQ using $H_2O_2$ and grafted Ti (IV)/$SiO_2$ catalyst by Kholdeeva *et al.*[125]

Cimen *et al.*[127] have recently reported TMP to TMQ oxidation with potassium peroxomonosulfate, $KHSO_5$, present in oxone catalysed by either iron phthalocyanin tetrasulfonate, [FePcTS] or cobalt phthalocyanin tetrasulfonate, [CoPcTS] in methanol-water mixture. The proposed mechanism for this oxidation involves, first the hydrogen abstraction from TMP by [$Fe^{IV}$(O)PcTS] generating the 2,3,6-trimethylphenoxy radical. This radical is attacked by [$Fe^{IV}$(O)PcTS] at the carbon *para* to the phenoxide oxygen resulting in the formation of an intermediate. Then proton mediated elimination produces catalyst and TMQ (Scheme 8).

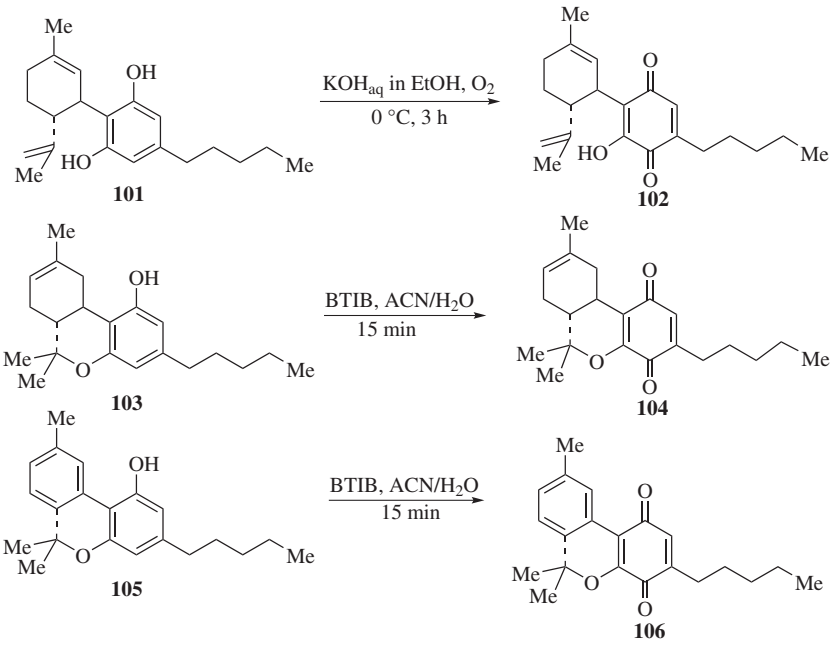
The highlight of the above strategy is that the reaction proceeded with 100% yield when the oxidant:substrate:catalyst molar ratios were 1200:300:1. Phenols with bulky substituents can also be converted to corresponding benzoquinones. Barton and Gloahec[128] reported a convenient high yield synthesis of 2,6-di-*t*-butyl-1,4-benzoquinone (**100**) from the iron catalysed oxidation of 2,4,6-tri-*t*-butyl phenol (**98**) with *t*-butylhydroperoxide (TBHP) (Scheme 9). Compound **99** is a useful synthetic intermediate. Earlier Muruhashi *et al.*[108] also reported a




**Scheme 8.** Mechanism proposed for the oxidation of TMP with $KHSO_5$ catalysed by [$Fe^{III}$PcTS].[127]

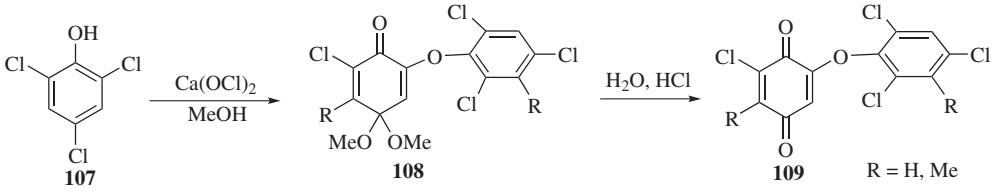



**Scheme 9.** Synthesis of 2,6-di-*t*-butyl-1,4-benzoquinone (**100**).




**101** **102** **103** **104** **105** **106**

**Scheme 10.** Oxidation of phenol derivatives in *Cannabis* to quinines.[129]




**107** **108** **109**

**Scheme 11**. Synthesis of quinones (**109**) through a dimer type ketal (**108**) intermediate.[137]

similar intermediate (Scheme 4) where the action of a Lewis acid, $TiCl_4$, leads to the formation of a substituted quinone, **92** by a rearrangement involving 1,2-migration. In this case (Scheme 9) the loss of bulky *t*-butyl group takes place.

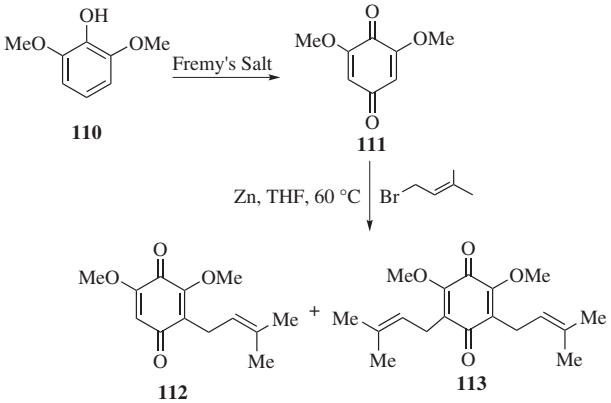
Three different phenol derivatives in *Cannabis*, cannabidiol (**101**), $\Delta^8$-tetrahydrocannabinol (**103**) and cannabinol (**105**) have been oxidized to their *p*-quinones **102**, **104** and **106** and respectively (Scheme 10).[129]

Cannabidiol (**101**) has been oxidized by air in an alcoholic solution in the presence of 5% KOH over 24 h at 0 °C to hydroxyquinone (**102**) at *ca.* 20% yield. Compounds **103** and **105** have been converted to corresponding quinones **104** and **106** by oxidation with bis(trifluoroacetoxy) iodobenzene (BTIB).[130-134]

The nitric acid oxidation of phenols into the corresponding quinones has been known for a century. Nakao *et al.*[135] used such a protocol in the synthesis of antileukemic agents. Such a protocol has also been used by Cohen *et al.*[136] in the total synthesis of vitamin E (tocopherol). Heasely and co-workers[137] designed a two-step synthetic strategy for substituted quinones (**109**) from 2,4,6-trichlorophenol (**107**) (Scheme 11). A dimer type ketal (**108**) is formed in the first step which was easily hydrolyzed to respective quinones.

Oliviera *et al.*[138] used Fremy's salt[105,139] to oxidize 2,6-dimethoxyphenol (**110**) to 2,6-dimethoxy-1,4-benzoquinone (**111**) in an attempt to prepare prenylated quinones **112** and **113** (Scheme12).

Polymer supported vanadium complexes have been reported as catalysts for the *t*-butyl hydroperoxide oxidation




**110** **111** **112** **113**

**Scheme 12.** Synthesis of prenylated quinones **112** and **113**.

of phenols to 1,4-benzoquinoes in 69-95% yield.[140] Yet in another method a mixture of cobalt and manganese salts of *p*-aminobenzoic acid supported on silica gel catalyses the oxidation.[141] Recently, Brocksom and co-workers[142] undertook a comparative study on the oxidation of mono-phenols to *p*-benzoquinones. They used a range of oxidants such as cobalt, nickel, copper and vanadyl with different salen type ligands. Besides, the study also reported the use of hydrogen peroxide, oxone, dimethyl oxirane and iodoxybenzoic acid.

The electrosynthesis of benzoquinone is also reported.[143] It is done by the anodic oxidation of phenol in acetonitrile-water mixtures on $\alpha$-$PbO_2$ and $\beta$-$PbO_2$ electrodes. Conversion of 61-74% has been achieved by this method. The phenol oxidation mechanism[144,145] is shown in Scheme 13.

$$C_6H_5OH \rightarrow C_6H_5O^{\bullet} + H^+ + 1e^-$$
$$C_6H_5O^{\bullet} + H_2O \rightarrow C_6H_4O_2 + 4H^+ + 4e^-$$

**Scheme 13.** Electrosynthesis of benzoquinone by oxidation of phenol.

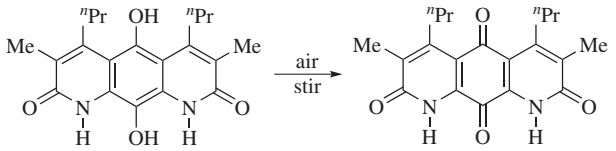
The recent advancement in the synthesis of quinone from phenol is the green chemistry route. Oelgemoller and co-workers[146] described the solar chemical synthesis of quinones by the photo-oxygenation of phenols. The yields were high when the reactions were performed in sunlight rather than artificial light.

### *3.2. Oxidation of hydroquinones to 1,4-benzoquinones*

One of the earliest synthetic protocol of 1,4-benzoquinones from hydroquinone was disclosed by Vliet[147] more than 70 years ago. He used a Cr(VI) salt for the oxidation resulting in the high selectivity and yield (86-92%). An array of oxidizing agents such as Cu(II) sulfate on alumina (92-88% yield),[148] ferric chloride in DMF (9-36% yield),[149] ceric ammonium nitrate (CAN) in acetonitrile-water (70-95% yield),[150-152] silver oxide in benzene (50-95% yield)[153-156] and sodium hypochlorite (95% yield)[157] have been utilized for the oxidation of hydroquinones to 1,4-benzoquinones.

Simple air-oxidation also is a successful method if the hydroquinone is sufficiently activated towards oxidation. An example of this is reported by Kelly *et al.*[158] in a short synthesis of diazaquinomycin A (**115**) from hydroquinone (**114**) (Scheme 14).

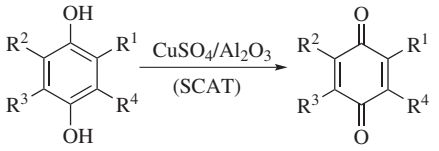
Nitric acid-impregnated manganese dioxide[159] in methylene chloride is also used as an oxidant. Tapia and co-workers[160] synthesized nitro-1,4-benzoquinone from nitrohydroquinone applying the above oxidant




**114** **115**

**Scheme 14.** Synthesis of diazaquinomycin A (**114**) by simple air oxidation by Kelly *et al.*[158]

by stirring the solution at 0 °C for 30 min. About three decades back we applied $MnO_2$ as an effective oxidizing agent for the preparation of 1,4-benzoquinones from their hydroquinones.[161] The oxidation reactions of hydroquinones (**116**) occur efficiently by catalysis with alumina-supported copper (II) sulfate, the supported catalyst (SCAT), to give benzoquinones (**117**) in good yield (Scheme 15).[148]

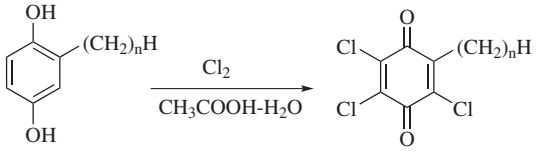



**116** **117**

$R^1$ = H, Me, Cl, Ph, $^t$-Bu $R^3$ = H, Me
$R^2$ = H, Me, $^t$-Bu $R^4$ = H, Me

**Scheme 15.** Oxidation of hydroquinones (**116**) with alumina-supported copper (II) sulfate catalysts.[148]

The synthetic potentiality of the above kind of catalytic reactions has been amply demonstrated by easy isolation of the final products using only filtration and solvent evaporation as well as by application to large scale syntheses. Other interesting oxidation of hydroquinones to benzoquinones has been reported by Shi *et al.*[162] in which 2-alkylhydroquinones (**118**) were converted to 2-alkyl-3,5,6-trichloro-1,4-benzoquinones (**119**) in low yield by reaction with chlorine gas in refluxing acetic acid (Scheme 16).




**118** **119**
n = 8, 12, 16

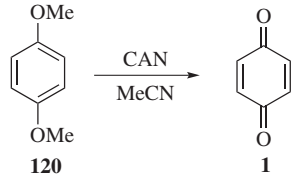
**Scheme 16.** Synthesis of alkyltrichloro-1,4-benzoquinones (**119**) by Shi *et al.*[162]

Owsik and Kolarez[163] carried out the catalytic oxidation of hydroquinone and studied the influence of surface properties of polymeric catalysts with aminoguanidyl ligand. They reported that under optimal conditions only

the main product, *i.e.*, *p*-benzoquinone was obtained after 60 min.

### *3.3. Synthesis of benzoquinones from dimethoxybenzenes*

The synthesis of 1,4-benzoquinones by the oxidative demethylation of dimethoxybenzenes or hydroquinone-dimethyl ethers had been reported in the literature about five decades back. Nitric acid[164] and silver oxide[165] were used as oxidants for the synthesis of benzoquinones. Although nitric acid worked well for highly substituted 1,4-dimethoxybenzene derivatives, in some instances nitration of the aromatic ring occurs in addition to demethylation. Also both nitric acid and silver oxide required strong acidic media which the acid labile functional group could not tolerate. Subsequently Castagnoli and co-workers[166] introduced a facile and efficient oxidizing agent ceric ammonium nitrate, $[Ce(NH_4)_2(NO_3)_6]$ or CAN in acetonitrile for the oxidative demethylation of a variety of hydroquinone dimethyl ether (**120**) to corresponding quinone (**1**) in high yield (Scheme 17). The reaction can be carried out in the absence of a strong acid and is generally quite fast requiring only a few minutes of reaction time at room temperature. The selectivity and mildness of the reaction is illustrated by the fact that a variety of functional groups are tolerated. CAN in acetonitrile[167-171] then became the most versatile oxidizing agent for the dimethoxybenzene-benzoquinone transformation. For instance, the total syntheses of various




**120** **1**

**Scheme 17.** Synthesis of quinone by oxidative demethylation.[166]

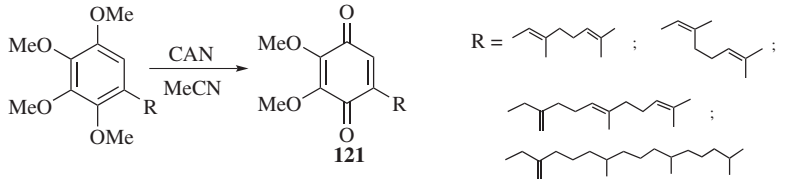
biologically important short-chain ubiquinones (**121**) were accomplished via oxidative demethylation using CAN in good yield by Keinan *et al*.[172] (Scheme 18).

Hart and Huang[173] employed CAN oxidation in the penultimate step of the synthesis of an antitumor, antibiotic, pleurotin **122** (Scheme 19).

The CAN oxidation lies at the heart of an elegant synthesis of symmetrical 2,5-disubstituted 1,4-benzoquinones (**124**) from 1,4-dimethoxybenzene (**123**) *via* a palladium catalysed double Negishi coupling (Scheme 20).[174] For R = aryl, the yields of the couplings are good (53-93%) and for R = alkyl, yields are moderate (30-42%).

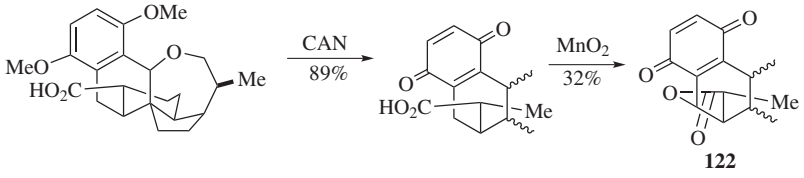
2,5-Dibromo-, 2.5-dichloro- and 2,5-diiodobenzo-quinones (**125**) were prepared from 1,4-dimethoxybenzene (**121**) by a two step synthetic strategy in 87, 97 and 87% overall yields respectively.[175] Neither of the two steps of the synthesis required purification (Scheme 21).

A series of 2-(quinazoline-4-ylamino)-1,4-benzoquinones (**127**) that function as potent covalent-binding, irreversible inhibitors of the kinase domain of vascular endothelial growth factor receptor-2 (VEGFR-2)



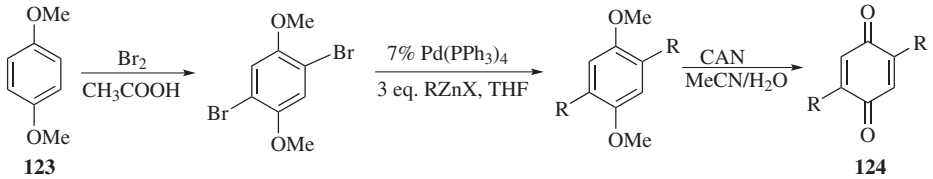

**121**

**Scheme 18**. Synthesis of ubiquinones (**121**) by oxidative demethylation.[172]



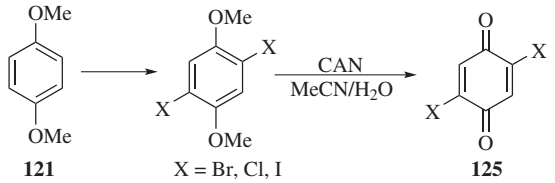

**122**

**Scheme 19**. Synthesis of pleurotin (**122**).[173]




**123** **124**

**Scheme 20.** Synthetic strategy towards 2,5-disubstituted 1,4-benzoquinones by Palmgren *et al.*[174]




**Scheme 21.** Synthetic strategy towards 2,5-dihalobenzoquinones by Lopez-Alvarado *et al.*[175]

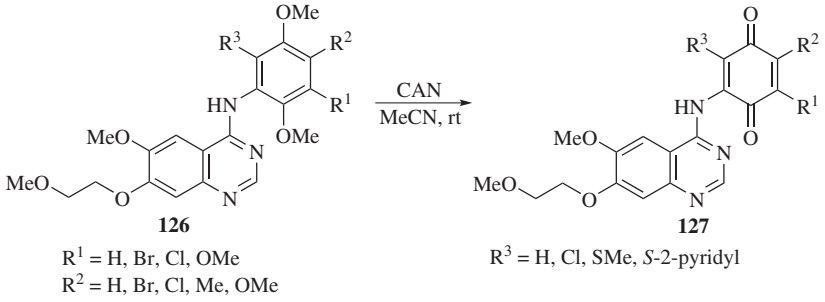
has been prepared by CAN oxidation of substituted (2,5-dimethoxyphenyl)(6,7-disubstituted-quinazolin-4-yl) amines (**126**) (Scheme 22).[176]

Snapper and co-workers[177] reported the synthesis of structural variants of biologically active marine sponge metabolite, ilimaquinone (**54**) in which CAN oxidative demethylation is a key step (Scheme 23).

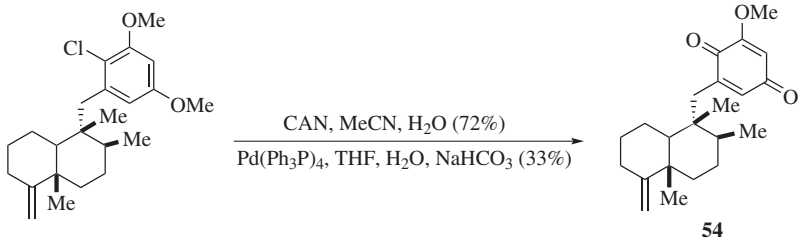
In our successful attempt to synthesize thienoyl- and furanoyl- substituted quinoxaline quinones[178] (**128**) from 1,4-dimethoxybenzene precursor, we have employed ceric ammonium nitrate (CAN) oxidative demethylation (Scheme 24).

Besides CAN in MeCN-$H_2O$, THF-water[179] is also used for the oxidative demethylation of 1,4-benzoquinones.

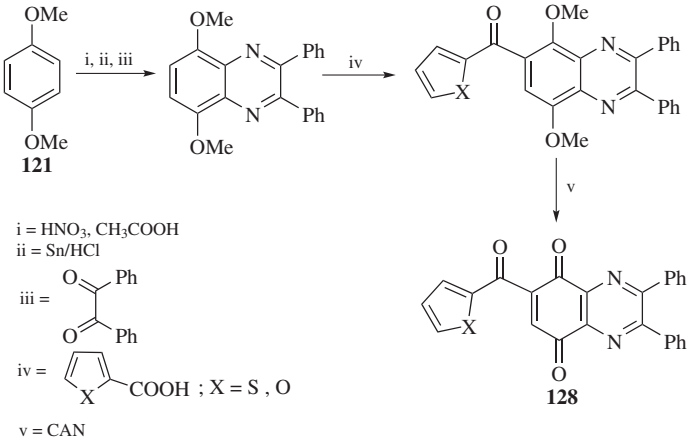
Tomatsu *et al.*[180] synthesized quinones from hydroquinone dimethyl ethers by the oxidative demethylation with Co(III) fluoride in good to excellent yield. Oxidative demethylation was also achieved using silver oxide/ nitric acid reagent.[181] Recently Popik and co-workers[182] synthesized (1,3-dioxolane-4-yl)-1,4-benzoquinones (**130**) from their dimethoxy precursors (**129**) using silver oxide/ nitric acid reagent in good yield (Scheme 25).



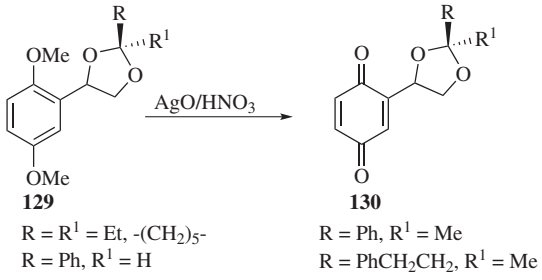

**Scheme 22.** Synthesis of 2-(quinazoline-4-ylamino)-1,4-benzoquinones (**127**).[176]




**Scheme 23.** Synthesis of ilimaquinone by oxidative demethylation.[177]




**Scheme 24.** Multi-step synthesis of quinoxaline quinones (**128**) by Pardasani and co-workers.[178]




**Scheme 25.** Oxidative demethylation using silver oxide/nitric acid.[182]

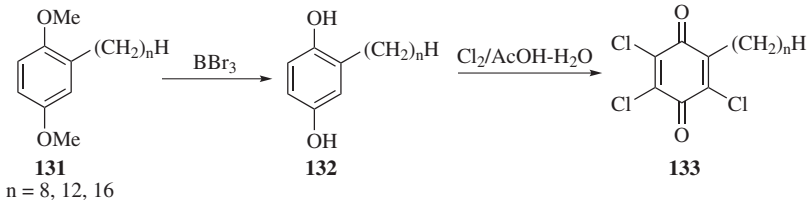
Multistep synthesis of quinones from dimethoxybenzene has also been reported. In a two step procedure, Shi *et al.*[162] first demethylated dimethoxy compounds (**131**) using $BBr_3$ to yield hydroquinones (**132**) and then carried out oxidation with $Cl_2$/AcOH-$H_2O$ resulting in the formation of chlorinated quinones (**133**) (Scheme 26).

1,4-Benzoquinones have also been prepared from 1,3-dimethoxybenzenes where only one methoxy group converts to the keto group while other methoxy functionality remains intact in the resulting quinone. Singh and co-workers[183] synthesized 2,3-dimethoxy-5-methyl-1,4-benzoquinone (ubiquinone $Q_0$) (**135**) by a reaction sequence starting form gallic acid present in mango kernel. In the final step of this synthetic sequence 3,4,5-trimethoxytoluene (**134**) is oxidized to ubiquinone $Q_0$ by 30% $H_2O_2$, HCOOH and phosphomolybdic acid in 57% yield (Scheme 27).[184] When 50% $H_2O_2$ is used in this conversion the yield of product is improved to 80%.

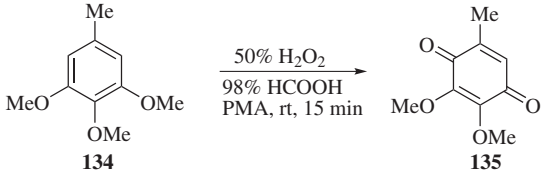
Recently a strategy for the eco-friendly and high yielding syntheses of ubiquinones starting from simple precursors and mild conditions was reported.[185] 3,4,5-Trimethoxytoluene (**134**) is treated with various reagents sequentially to obtain the final product, ubiquinones (**137**). The final oxidation of the 1,3-dimethoxybenzene (**136**) is carried out using ferric chloride, $FeCl_3$ (Scheme 28).

Oxidation of catechin (flavan-3-ols) is an important route to new potential bioactive *p*-benzoquinones. Bernini *et al.*[186] described the first catalytic benign methodology to obtain a new series of *p*-benzoquinones (**139**) by oxidation of catechin (**138**) and epicatechin derivatives with the hydrogen peroxide/methyltrioxo rhenium catalytic system (Scheme 29). Reactions were carried out both in homogenous and heterogeneous conditions and proceded with high conversion and moderate yields. Polymer supported methyltrioxorhenium systems were used as heterogeneous catalysts. After the first oxidation, the catalytic systems can be removed and reused for five consecutive times without loss of stability and efficiency.

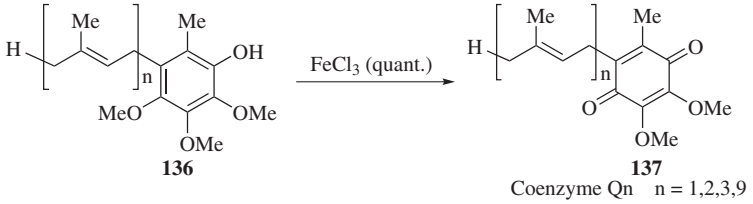
Imparting new dimension to the synthesis of 1,4-benzoquinones a "telescoped process" for the preparation of 2-methoxy-3-methyl-1,4-benzoquinone (**141**) from 1,3-dimethoxytoluene (**140**) was disclosed by Bjorsvik and colleges.[187] The compound **141** is produced selectively in high yield (95%) by a single pot telescoped oxidation process composed of three partial steps:



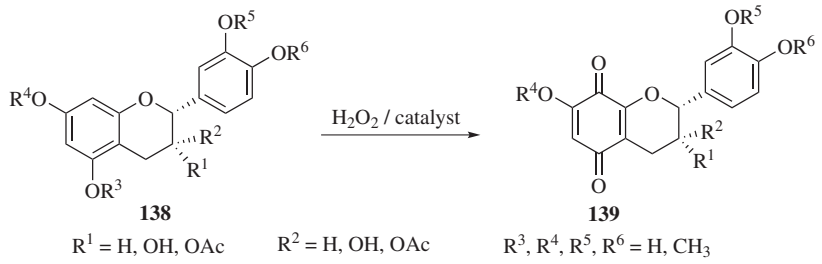

**Scheme 26.** Multistep synthesis of chlorinated quinones by Shi *et al.*[162]




**Scheme 27.** Conversion of 3,4,5-trimethoxytoluene to ubiquinone $Q_0$ by Singh and co-workers.[183]




**Scheme 28.** Syntheses of coenzymes Qn via $FeCl_3$ oxidation by Bovicelli *et al.*[185]




**Scheme 29.** Synthesis of bioactive *p*-benzoquinones by Bernini *et al.*[186]

*i*) oxidation using hydrogen peroxide and in the presence of a Brönsted acid, $HNO_3$ as a catalyst; *ii*) elimination of excess oxidant using sodium metasulfite and then *iii*) oxidation using concentrated nitric acid (Scheme 30). A telescoped process implies that two or more steps are conducted without isolation or workup of the intermediate synthesized compounds. This telescoped process constitutes a green and environmentally benign alternative suitable for large scale use.

### *3.4 Miscellaneous synthesis of 1,4-benzoquinones from unique precursors*

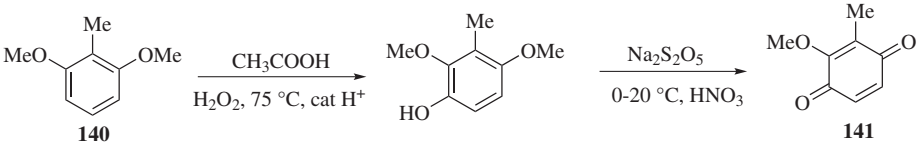
Significant number of reports is available in the literature about the synthesis of quinones from precursors other than commonly applied phenols, hydroquinones and dimethoxybenzenes. Coombes and Moody[188] synthesized 2-(3'-methylbut-2'-enyl)-5-(2'-methylbut-3'-en-2'-yl)-1,4-benzoquinone (**143**), a novel prenylated quinone derivative from the New Zealand brown algae *Perithalia capillaries*, by the oxidation of a hydroquinone acetate (**142**) with an excess of lithium aluminum hydride, THF and $O_2$ (Scheme 31).

*N*-Arylsulphonamides (**144**) also gave *p*-benzoquinones (**145**) on oxidation with ceric ammonium nitrate (Scheme 32).[189]

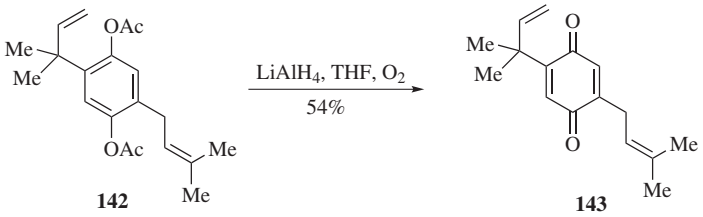
A convergent general synthesis of annelated quinones and highly substituted quinones (**149-151**) from conjugated ketenes (**146-148**) was reported by Moore and co-workers.[190] The reaction proceeds via a thermal rearrangement (Schemes 33-35).

Later Xiong and Moore[191] also carried out the ring expansion of 4-alkylcyclobutenones by thermolysis to furnish a variety of *N*-heterocyclic quinones.

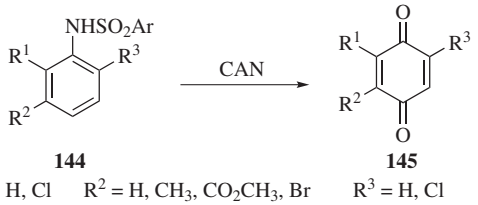
Danheiser *et al.*[192] employed vinylketene/alkyne cycloaddition reaction for quinone synthesis. The sequence of the quinone transformation starts with a photochemical Wolf rearrangement producing a vinylketene (**152**), which undergoes a cycloaddition to the alkyne to give



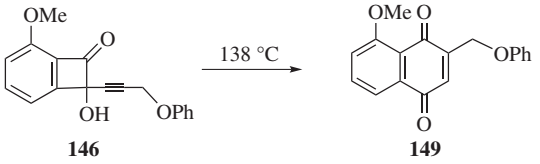

**Scheme 30**. A green telescoped process for the synthesis of quinones.[187]




**Scheme 31.** Oxidation of hydroquinone acetate to quinone.[188]




**Scheme 32.** Conversion of *N*-arylsulphonamides to *p*-benzoquinones.[189]




**Scheme 33.** Synthesis of quinone (**149**) by thermolysis of benzocyclobutenone.[190]

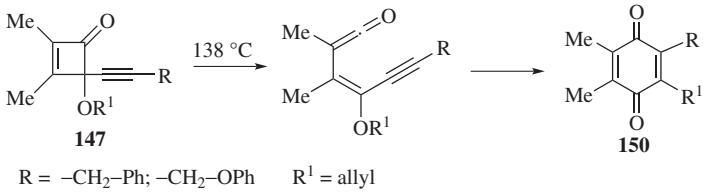
cyclobutenone (**153**). Electrocyclic ring opening of **153** gives the dienyl ketene (**154**) which then undergoes six-electron electrocyclization followed by enolization to yield a phenol (**155**). Subsequent oxidation furnishes the quinone (**156**) (Scheme 36).

Langer and co-workers[193] reported the synthesis of functionalized *p*-benzoquinones (**159**) based on [3+3] cyclizations of 1,3-bis-silyl enol ethers (**157**) with 2-acyloxy-3-(silyloxy-2-en-1-ones) (**158**). Deprotection and oxidation of the products afforded the benzoquinones (**159**). This elegant transformation of 2-chloro-1,3-diketone is depicted in Scheme 37.

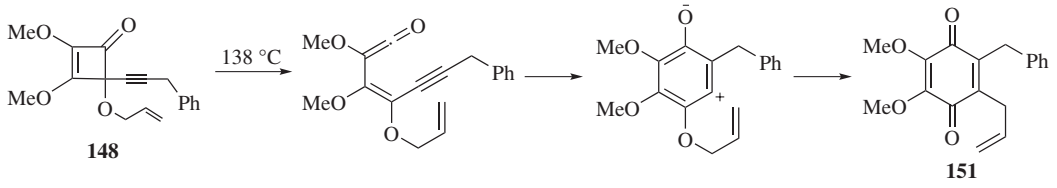
Recently Mathur *et al.*[194] reported a photochemically promoted one-step synthesis of 1,4-benzoquinones, which bear vinyl substituents in 2,5- and 2,6- position. Photochemical reaction between (*Z*)-1-methoxybut-1-ene-3-yne (**160**) with CO in the presence of $Fe(CO)_5$ yields 2,6-bis{(*Z*)-2-methoxyvinyl}-1,4-benzoquinone (**161**) and 2,5-bis{(*Z*)-2-methoxyvinyl}-1,4-benzoquinone (**162**) (Scheme 38).

Moody and co-workers[195] reported a microwave-mediated Claisen rearrangement followed by phenol oxidation to yield many naturally occurring 1,4-benzoquinones from readily available precursors. Our group has been involved in the synthesis of a wide range of 1,4-benzoquinones (**163**) applying a three step synthetic strategy from readily available precursors (Scheme 39).

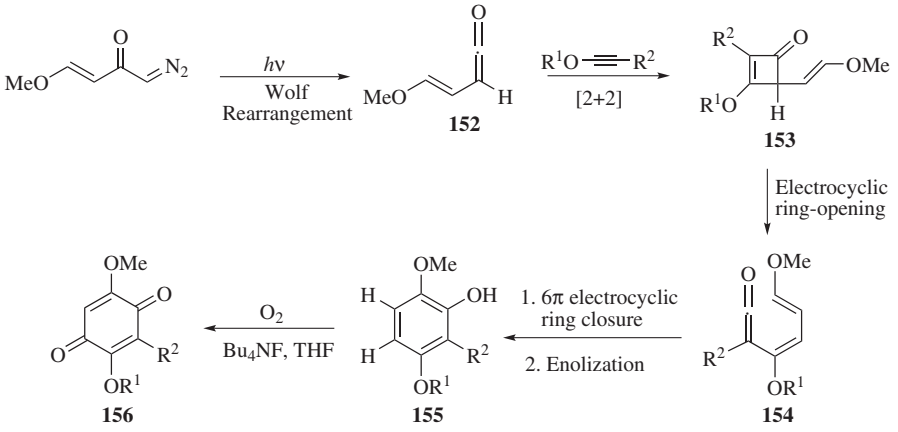
The central theme of our strategy is to attach varieties of substituents into the main skeleton, which would be transformed into a quinone moiety. It is efficiently achieved in the initial Friedel Craft's acylation step. Then successive demethylation and oxidation of hydroquinones yielded



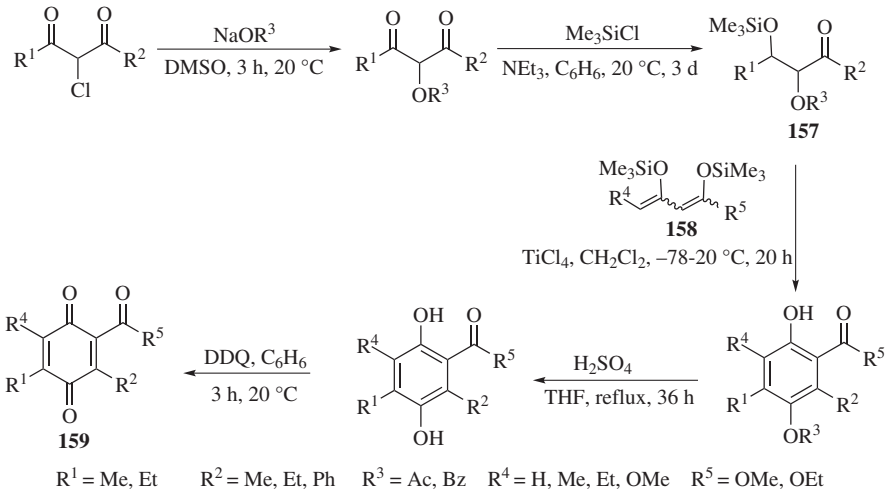

**Scheme 34.** Synthesis of quinone (**150**) by thermolysis of cyclobutenone.[190]



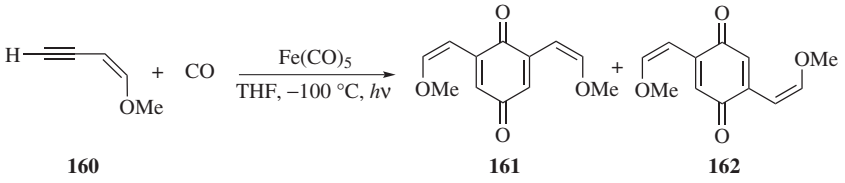

**Scheme 35.** Synthesis of quinone (**151**) by thermolysis showing allyl migration.[190]



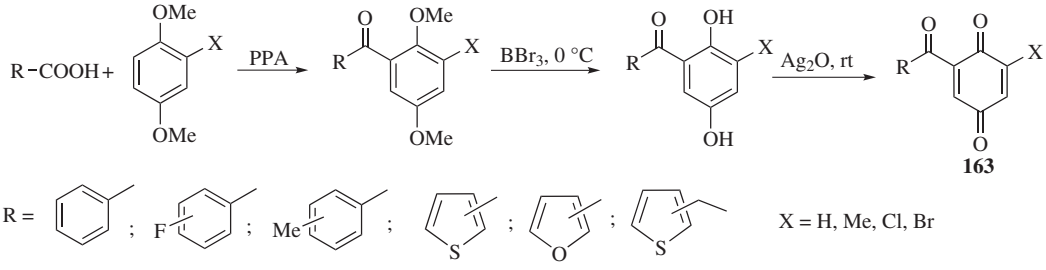

**Scheme 36.** Mechanism of vinylketene/alkyne cycloaddition reaction for quinone synthesis.[192]




**Scheme 37.** Synthesis of benzoquinones *via* a [3+3] cyclization of **151** and **152.**[193]




**Scheme 38.** Single-step photochemical route to vinylbenzoquinones by Mathur *et al.*[194]




**Scheme 39.** Multi-step synthesis of heteroacyl- and aroyl-1,4-benzoquinones by Pardasani and co-workers.[197-200]

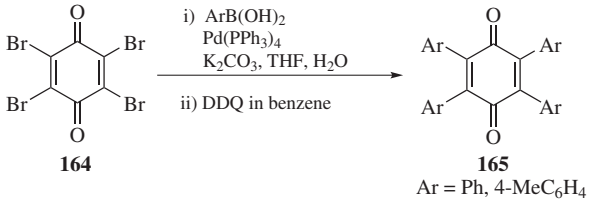
varieties of substituted quinones. Applying this multi-step strategy, we could successfully synthesize differently substituted benzoyl-1,4-benzo-quinones,[196-198] furanoyl/thienoyl-1,4-benzoquinones[199] and thiophenacetoyl-1,4-benzoquinones.[200]

### *3.5 Synthesis of higher 1,4-benzoquinones derivatives by the reaction of simple 1,4-benzoquinones*

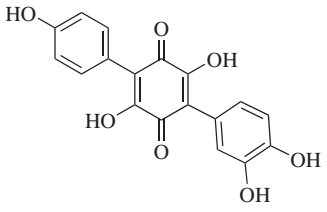
Suzuki-Miyura cross coupling reactions of tetrabromo-1,4-benzoquinone (**164**) provide a convenient approach to tetraaryl-1,4-benzoquinones (**165**).[201] The Suzuki-Miyura reaction of **164** with phenyl boronic acid in the presence of $Pd(PPh_3)_4$ and $K_2CO_3$ (THF/$H_2O$, 90 °C, 8-12 h) resulted in the formation of an inseparable 1:1 mixture of **165** and 2,3,5,6-tetraphenyldihydrobenzoquinone in high yield. Treatment of this mixture with DDQ resulted in the formation of pure **165** in 70% overall yield (Scheme 40). The yield could be further increased by increasing the amount of catalyst.

Gan *et al.*[202] developed a new, convergent and versatile synthetic strategy for efficient synthesis of 2,5-disubstituted-3,6-dimethoxy-1,4-benzoquinones (**167**) from readily available molecules (Scheme 41). By two sequential Suzuki couplings, aromatic components can be selectively introduced into the dihalogenated benzoquinone scaffolds (**166**). This method serves as a key step in the total synthesis of leucomelone (**168**) in three steps and in 61% overall yield.

Another method was also reported by Pirrung *et al.*[203] which sequentially adds indole-3-mercurials to dichlorinated quinones using palladium catalysis. These reactions can be used in the modular assembly of bis(indol-3-yl)-benzoquinones, a significant natural product family.




**Scheme 40.** Synthesis of tetraaryl-1,4-benzoquinones by Ullah *et al.*[201]



**168** Leucomelone

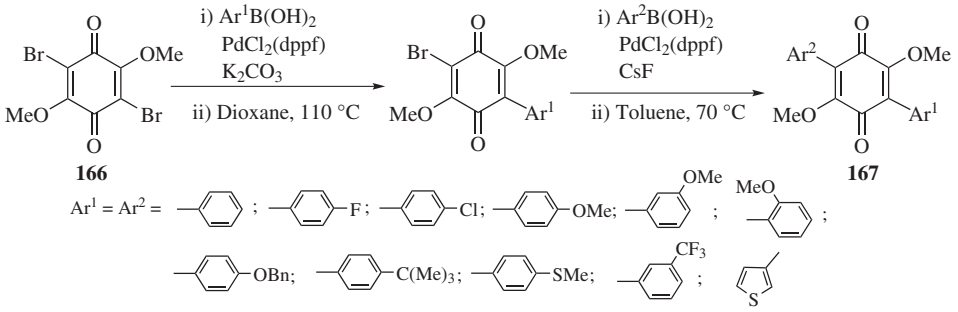
Characteristic quinones containing both quinone and heterocyclic moieties have been synthesized by Youseff and co-workers.[204] Tetrabromo-1,4-benzoquinone (**164**) reacted with excess aromatic amines (**169**) to give 2,5-diarylamino-3,6-dibromo-*p*-benzoquinones (**170**). On heating with sodium sulfate in alcohol in the presence of air gave triphendiazones (**171**). Heating with copper powder in nitrobenzene transformed those compounds into the respective indole carbazole diones (**172**) (Scheme 42).

A series of novel methoxyaryl-substituted 1,4-benzoquinones as well as four structural isomers were synthesized by the reaction of 2-methoxy-1,4-benzoquinone with methoxy phenolic derivative compounds obtained from wood-tar constituents assisted by palladium (II) acetate in acetic acid.[205] Later they developed a catalytic method for the synthesis of methoxyaryl-substituted 1,4-benzoquinones *via* oxidative coupling of 2-methoxy-1,4-benzoquinone and methoxyarenes. The reaction is effectively catalysed by a $Pd(OAc)_2$/heteropoly acid ($H_9PMo_6V_6O_{40}$) redox system with dioxygen as the final oxidant.[206]

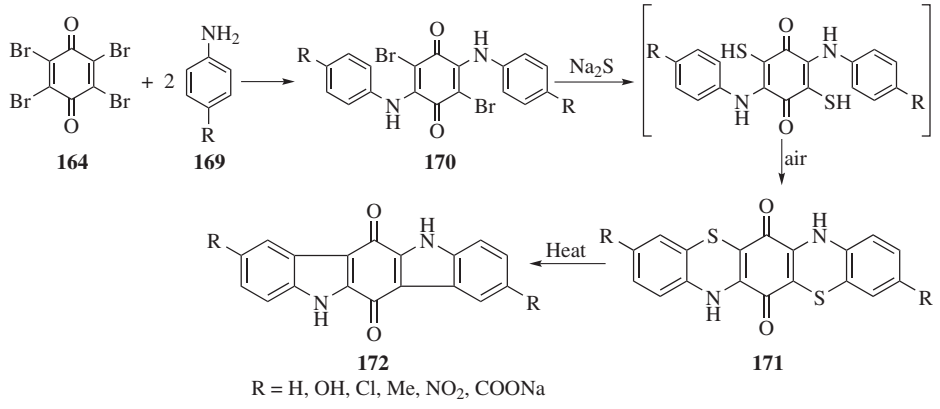
Watson *et al.*[207] reported the synthesis of a very large quinone (**174**) by a double Diels-Alder reaction of 2,5,9,12-tetra(*t*-butyl)-diacenaphtho[1,2-b:1',2'-d] thiophene (**173**) and benzoquinone (**1**) (Scheme 43).

Zora *et al.*[208] demonstrated a concise and synthetically flexible cyclobutenedione based approach to highly substituted ferrocenyl quinones (**175**) which relies on the versatility of cyclobutene diones as scaffolds for the construction of a diverse range of molecular structures.

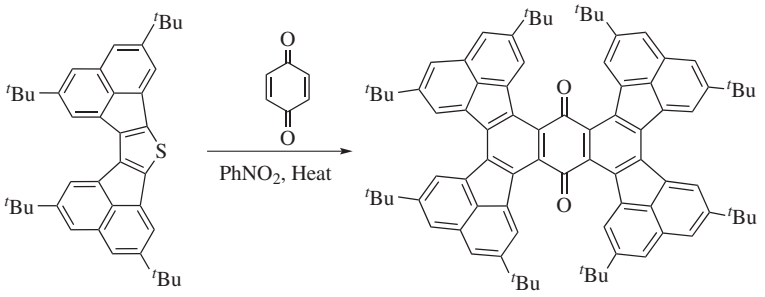
Recently some non-traditional approaches to the synthesis of biologically active substituted 1,4-benzoquinones were reported by Batra *et al.*[209] The synthesis has been accomplished using anhydrous $K_2CO_3$ both as catalyst and solid support under thermal heating, solvent free grinding and solid-phase microwave irradiation




**Scheme 41.** Synthesis of 3,6-disubstituted benzoquinones *via* two sequential Suzuki couplings by Gan *et al.*[202]

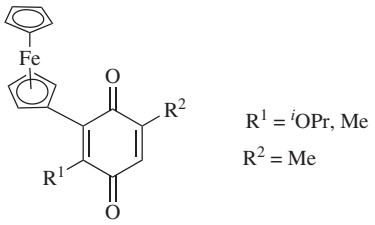



**Scheme 42.** Synthesis of indole carbazole diones (**172**).[204]



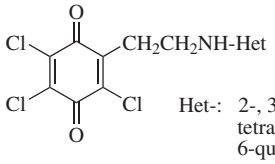

**173** **174**

**Scheme 43.** Synthesis of quinone by double Diels-Alder reaction.[207]




**175** Ferrocenyl quinones

conditions. Synthesis of various hetarylaminoethyl substituted 1,4-benzoquinones (**176**) are also reported.

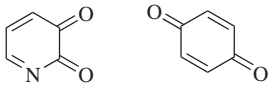



Het-: 2-, 3-, 4-Pyridyl; 1,2,4-triazol-3-yl; tetrazol-5-yl; 2-pyrimidyl; 2-thiazolyl; 6-quinolyl

**176**

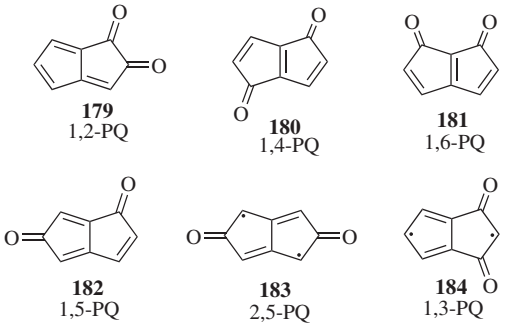
## 4. Computational Investigations on 1,4-Benzoquinones

One of the main areas where computational techniques are often applied is the characterization of the geometry of molecules. This can be achieved by the optimization of energy and geometry of molecules at various levels of theory. Novak and Kovak[210] studied the electronic structure of substituted benzoquinones and quinonechlorimides using the DFT method at the B3LYP/6-31G* level. A single point Green's functions (GF)[211] type calculation was performed in order to obtain vertical ionization energies. The computational results validated the theoretically predicted geometries with measured ones obtained by X-ray or electron diffraction. An *ab initio* molecular orbital study of different pyridoquinones (**177** and **178**) was reported by Yavari and Zabrijad-Shiraz.[212] The structures of both classical and non-classical benzoquinones and pyridoquinones were optimized at HF/6-31G* and B3LYP/6-31G** levels. MP2 level calculations have been performed to calculate the single point energy (SPE).




**177** 2,3-PyQ **178** 2,5-PyQ

Among the possible isomers of pyridoquinones the 2,5-isomer was calculated to be the most stable. Apart from pyridoquinones, Yavari *et al.*[213] also modelled another interesting group of quinones, pentaloquinones (PQ) (**179**-**184**).

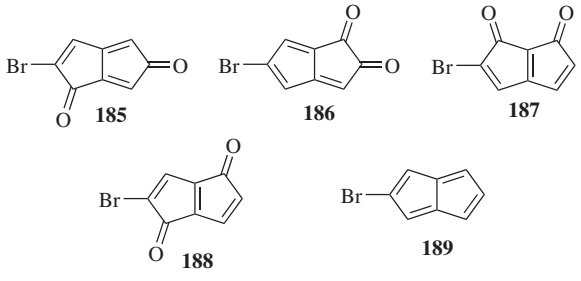



**179** 1,2-PQ **180** 1,4-PQ **181** 1,6-PQ

**182** 1,5-PQ **183** 2,5-PQ **184** 1,3-PQ

The geometry of the PQs were optimized at HF and B3LYP levels and single point energies calculated at QCISD level. 1,5-Pentalenequinone was reported to be the most stable isomer.

Recently Atalar *et al.*[214] extended the investigation on pentalenoquinones (PQs) to bromopentalenoquinones (**185**-**189**) to reveal the stability and aromatic character.

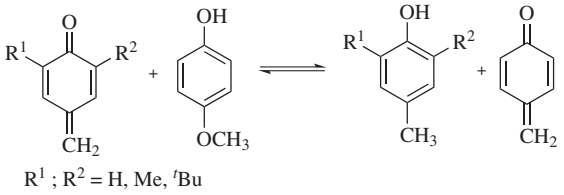



**185** **186** **187** **188** **189**

The stability was determined by comparing the relative energy and the HOMO-LUMO energy gap, while the

aromatic character was established based on the nucleus independent chemical shift (NICS) values. The calculations demonstrated that the insertion of Br atom decreased the HOMO-LUMO energy gap and NICS values.

Baik *et al.*[215] accomplished the reactivity and stability studies of benzoquinones methides by *ab initio* calculations. The relative stabilization energies of differently substituted benzoquinone methides were calculated at the B3LYP/6-31G//B3LYP/6-31G* level by means of isodesmic equation[216] (Scheme 44) shown below.




**Scheme 44.** Isodesmic equation to evaluate the relative stabilities of benzoquinone methides.[215]

The outcome of the theoretical analysis revealed that the symmetrically hindered benzoquinones methides are found to be more stable owing to the effective hyperconjugation of the dialkyl groups with the ring.

Hartree-fock and density functional studies on the structure and vibrational frequencies of quinone derived Schiff's base ligand, 1-imino-(ethyl-2'-pyridine)-2-hydroxynaphthoquinone, have also been reported.[217] The *syn* and *anti* conformers of the aforesaid ligand have been obtained as the local minima on the potential energy surface with the *syn* conformer as more stable than the *anti* conformer due to intramolecular hydrogen bonding.

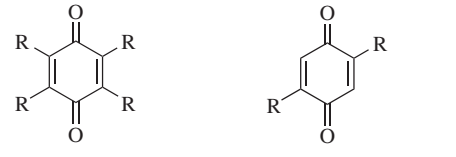
Tsutui *et al.*[218] performed theoretical calculations on silyl-substituted 1,4-benzoquinones (**190**-**197**), to investigate the structure and properties. Geometry optimizations and vibrational frequency calculations were performed at B3LYP/6-31G* level while the SPE calculation is carried out at MP2/6-311+G(2d,p) level.

The HOMOs and the LUMOs shifted to higher energies as the number of silyl groups increased whereas the calculated vibrational frequencies shifted to lower frequencies. The LUMO energy levels of the silyl-1,4-benzoquinones were quantitatively proportional to the first half-wave reduction potentials.

Quantum chemical calculations were also used to explain the tetrahertz time domain spectrum of several compounds satisfactorily.[219-222] Recently Min *et al.*[223] applied theoretical calculation to assign individual THz absorption spectra of the *p*-quinones with semiempirical AM1, hartree-fock (HF) and density functional theory (DFT) method. The results with DFT method at B3LYP/6-311G produced better simulation with the experimental data. The molecular property of a compound is controlled by its molecular geometry. Several studies showed that density functional theory is a powerful method for predicting the geometry and other features related to the structure.[224-226] Song *et al.*[227] carried out an exhaustive DFT and *ab initio* hartree-fock studies on the structural parameters and chemical reactivity of all the free radicals generated by benzoquinones and hydroquinone. The highlight of this study is that the free radicals can be easily generated in aqueous solution and are more reactive.

Bangal[228] studied the proton coupled charge transfer in the formation of charge transfer complexes between 1,4-benzoquinone and 2,6-dimethoxyphenol by DFT-B3LYP/6-311G(d,p) level. The strength of the charge transfer complex formation ability depended on the HOMO-LUMO energy gap which in turn was influenced by the H-bond formation.

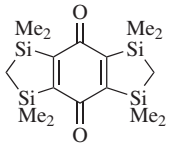
Tormena *et al.*[229] carried out a detailed theoretical analysis of the relative stability of *endo/exo* Diels-Alder adducts formed by the reaction between cyclopentadiene and 1,4-benzoquinone. The energies of both *endo* and *exo* adducts were obtained at CBS-Q level of theory, which showed that *endo* adduct is more stable than *exo*. An NBO electronic structure analysis indicated that the attractive



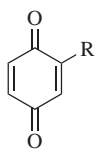
**190**
R = H, $SiH_3$, $SiMe_2H$, $SiMe_3$, $SiMe_2$(vinyl)



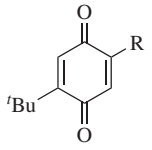
**191**
R = Br, *t*-Bu, $SiH_3$, $SiMe_2Ph$, $SiMe_2H$, $SiMe_3$, $SiMe_2$(vinyl)



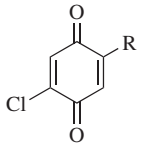
**192**



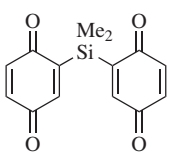
**193**
R = $SiH_3$, $SiMe_3$



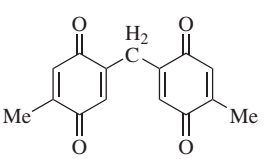
**194**
R = Br, $SiMe_3$, $SiMe_2$-$SiMe_3$



**195**
R = $SiMe_3$, $SiMe_2$-$SiMe_3$



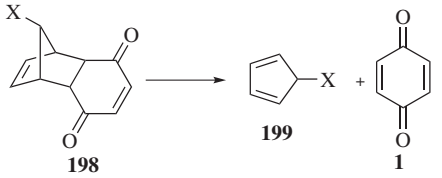
**196**



**197**

delocalization interaction predominates over the steric repulsive interaction in the *endo* adducts.

Patil and Sunoj[230] reported the substituent effects of retro Diels-Alder reaction in benzoquinones. A systematic study has been carried out on the retro Diels-Alder reaction of cycloadducts (**198**) formed between substituted cyclopentadiene (**199**) and *p*-benzoquinone (**1**) based on the hybrid HF-DFT method (Scheme 45).




**Scheme 45.** Retro Diels-Alder reaction studied by Patil and Sunoj.[230]

The transition state study on the cycloreversion reaction demonstrated that $-SiMe_3$ substituents are most effective in lowering the activation barrier.

The influence of hydrogen bonds to nearby molecules direct the quinones to perform a desired function.[231] This principal is verified by the *ab initio* studies of neutral and anionic 1,4-benzoquinone-water clusters by Manojkumar *et al.*[232] They observed that when two water molecules are complexing with 1,4-benzoquinone, a conformer exhibiting a H-bond between two water molecules ($W_2Q$) is energetically more favoured than the conformer WQW in which there is no direct interaction between the water molecules. The geometry of the structures were optimized at MP2 and B3LYP level using the 6-311++G** basis set.

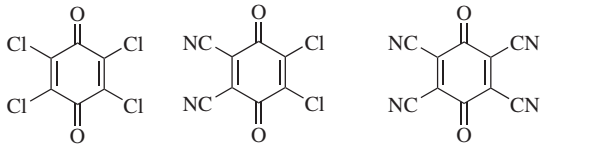
The reaction of quinone mediated reduction of oxygen to peroxide (Scheme 46) has been investigated in detail by Wass *et al.*[233] through quantum chemical modeling.

$$Q + e^- \rightarrow Q^{\bullet -}$$
$$Q^{\bullet -} + O_{2\,(aq)} \rightarrow Q\text{-}O_2^{\bullet -}$$
$$Q\text{-}O_2^{\bullet -} + e^- + 2H^+ \rightarrow Q + H_2O_2$$
$$Q^{\bullet -} + H^+ \rightarrow HQ^{\bullet}$$
$$HQ^{\bullet} + O_{2\,(aq)} \rightarrow Q\text{-}HO_2^{\bullet}$$
$$Q\text{-}HO_2^{\bullet} + e^- + H^+ \rightarrow Q + H_2O_2$$

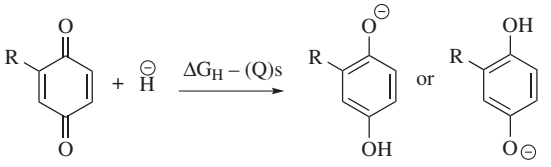
**Scheme 46.** Quinone mediated reduction of oxygen to peroxide.

DFT-B3LYP level study was done to map the course of the reaction constituting the above steps.

Many well known quinones such as *p*-chloranil (**200**), 2,3-dichloro-5,6-dicyano-*p*-benzoquinone (DDQ) (**201**) and tetracyano-*p*-benzoquinone (**202**) have strong power of oxidation and have been extensively used as oxidants in organic synthesis.[234] The hydride affinity of quinones is a measure of their oxidizing power.




Based on this principle, Zhu *et al.*[235] predicted the hydride affinities of a variety of eighty quinones in DMSO solution so as to prepare large and useful library of organic oxidants. They defined hydride affinity of quinone in solution as the free energy change in the reaction of quinone with free hydride ion to form the corresponding hydroquinone anion at 25 °C in solution (Scheme 47).




$$\Delta G_{H^-}(Q)_s = G(QH^-)_s - [G(Q)_s + G(H^-)_s]$$

**Scheme 47.** Reaction of quinone with a free hydride ion and the corresponding free energy change.[235]

A similar study to predict the electron affinities of various methylated and halogenated derivatives of *p*-benzoquinones has been undertaken by Wheeler and co-workers.[236] Among various methods used the B3LYP/6-311G(3d,p) method yielding electron affinities within experimental error and within an average absolute magnitude of 0.05 eV of experimentally measured electron affinities.[237-240]

Very recently the characterization of semiquinones and quinones formed as intermediates in the oxidation of flavonoid epicatechin has been studied by means of computational chemistry.[241] The antifungal and antioxidant activities of flavonoids depend on the stability of these semiquinones and quinones.[242] The antioxidant activity is directly related to the ease of deprotonation of its OH groups. Consequently the structural properties, the bond dissociation energy and total energy of these compounds from epicatechin was determined using B3LYP/6-31G** level of calculation. The results showed that the 4'-OH of the catechol group represents the primary site of deprotonation (the most oxidizable), which gives both the most stable and the easiest formed semiquinones.

The biological actions of quinones are linked to their electron transfer rates and redox potentials.[243-246] Several

studies applying quantum chemical methods to calculate the electrode potentials of benzoquinones have appeared in the literature.[247-254] Namazian *et al.*[255] computed the electrode potentials at DFT-B3LYP level with the inclusion of entropic and thermochemical corrections; by the estimation of Gibb's free energy of the following reaction (Scheme 48).

$$Q_{(sol)} + RH_{2(sol)} \rightarrow QH_{2(sol)} + R_{(sol)}$$

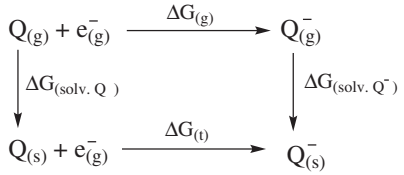
$$\Delta G = -nF\,(E_Q - E_R)$$

**Scheme 48.** Reduction of quinone and the corresponding free energy change.

By this model, the computed electrode potentials are within at most ± 0.087 V and an average error of 0.043 V with experimental values. Namazian and Almodarresieh[256] extended their study to improve the reduction potential values by including the frequency calculations and relaxation of salvation energy.

Recently Pakiari *et al.*[257] further modified the computational techniques and carried out the evaluation of standard two-electron reduction potentials of some quinones at B1B95 level of density functional theory methods. Polarized continuum models, CPCM and DPCM are employed for considering the solvent contribution. In comparison with other methods DFT-B1B95 is a reliable level of theory and less computer time demanding, which gives moderate accuracy even when ordinary sized basis sets are used.

Quinones lead to the generation of reactive oxygen species, through redox cycling in the presence of oxygen. This property can be related to their biological activity.[258-260] The potential of quinone compounds to participate in redox cycling is mainly dependent on the stability of the semiquinone radical relative to the quinone and the quinol forms. A simple and practical method for calculating thermodynamic parameters necessary to estimate semiquinone stability constants and redox potentials for quinone natural products has been reported by Cape *et al.*[261] utilizing DFT-B3LYP method. Accurate calculation of absolute one-electron redox potentials of some *p*-quinone derivatives in acetonitrile was done by Namazian and Coote.[262] A thermodynamic cycle is designed to calculate $\Delta G^0_{(t)}$ of reaction from its components (Scheme 49).

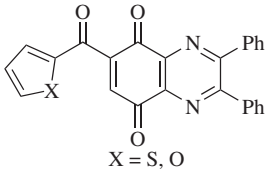



**Scheme 49.** Thermodynamic cycle designed to calculate $\Delta G^0_{(t)}$ of one-electron reduction.[262]

An ONIOM method in which the core is studied at G3(MP2)-RAD is used for calculating the thermodynamic properties.

Tetrafluoro-*p*-benzoquinone (TFBQ) has many applications in chemical synthesis[263-265] owing to the presence of four highly electronegative F atoms. The electron affinity and redox potential of TFBQ has recently been computed by Namazian *et al.*[266] via standard *ab initio* molecular orbital theory at the G3(MP2)-RAD level of theory. Natural bond orbital (NBO) method is used to predict the charge distribution at TFBQ and BQ anions. They correlated the charge distribution with the electron affinity.

Our group carried out a semiempirical (AM1) computational study on the modeling of Diels-Alder cycloadditions at the beginning of this decade.[267] A number of model quinones with both electron donor and acceptor substituents have been studied and the energy gaps to both electron-rich and electron-deficient dienes have been calculated. Then we extended the study to quinoxalin quinones (**128**).[268]




**128**

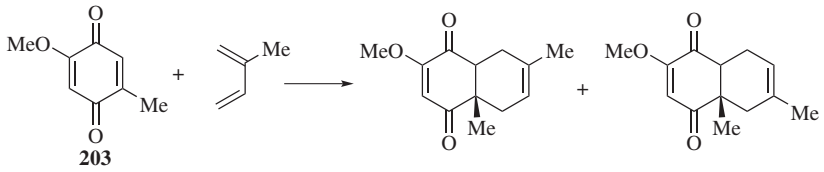
Results of the computational study revealed that by choosing appropriate diene such as electron-withdrawing diene, it is possible to reverse the course of Diels-Alder cycloaddition from quinonoid ring to the heterocyclic moiety.

Very recently an interesting DFT study in understanding the influence of Lewis acid in the regioselectivity of the Diels-Alder reactions of 2-methoxy-5-methyl-1,4-benzoquinone (**203**) (Scheme 50) has been reported by Soto Delgado and co-workers.[269]

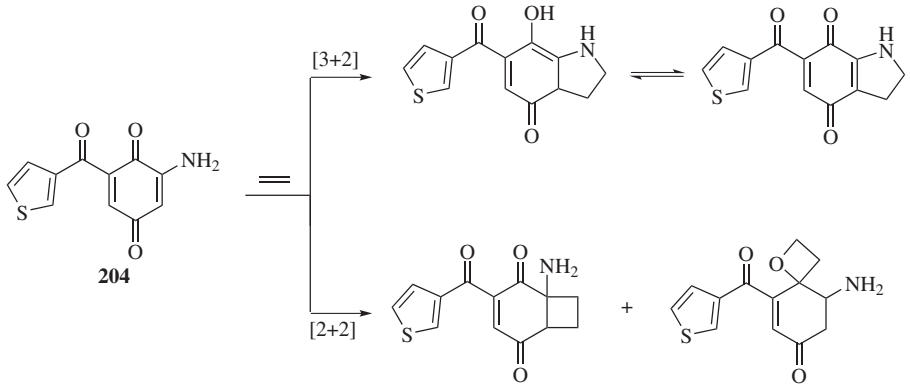
The theoretical results obtained by DFT-B3LYP level calculation provided a useful tool for the interpretation of the reaction mechanisms. Transition state studies showed that there is a larger activation barrier associated with the uncatalyzed processes.

Our noteworthy contribution in the theoretical studies on 1,4-benzoquinones is a comprehensive study on the [3+2]/[2+2] photocycloadditions of a model quinone 6-amino-2-(3'-thienoyl)-1,4-benzoquinone (**204**) with ethene (Scheme 51).[270]

A detailed DFT/B3LYP and CASSCF studies using 6-31G* basis set revealed the preference of



**Scheme 50.** Regiochemistry of Diels-Alder reactions of 2-methoxy-5-methyl-1,4-benzoquinone.[269]



**Scheme 51.** [3+2]/[2+2] Photocycloadditions of 6-amino-2-(3'-thienoyl)-1,4-benzoquinone.[270]

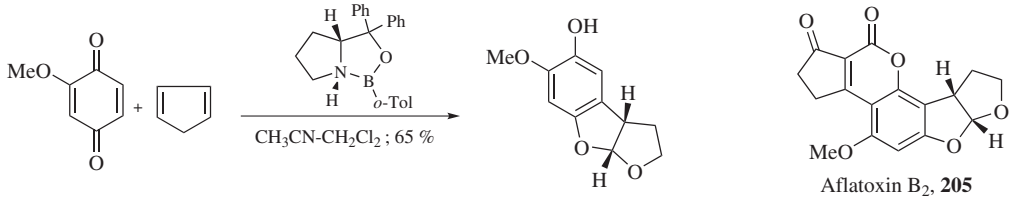
a [3+2] photocycloaddition reaction over the [2+2] photocycloaddition. A biradical mechanism is proposed and described in detail by computational studies. The significant finding of the study is an intramolecular hydrogen shift in the triplet excited state which leads to stable biradical. The predominant [3+2] photocycloaddition takes place from this radical. A DFT study on the regioselectivity of various possible [2+2] photocycloadducts was also carried out.[271]

## 5. Cycloaddition Reactions of 1,4-Benzoquinones

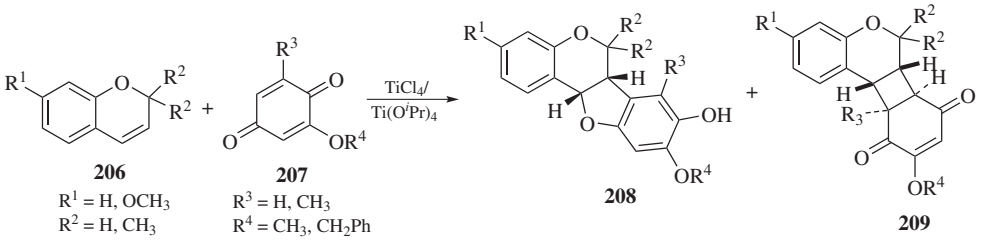
Various cycloaddition reactions of 1,4-benzoquinones are known, e.g., [2+2]-, [3+2]- and [4+2]- cycloadditions yielding unique 4, 5 and 6 membered polycyclic scaffolds. Owing to this synthetic advantage, cycloaddition reactions have been used as the backbone of many artful synthesis of natural products consisting complex structural frameworks.[272-275] In particular cycloaddition reactions of 1,4-benzoquinones comprise the heart of elegant synthesis of steroids[276,277] (cortisone[278] and estrone[279]), reserpine,[280,281] yohimbine,[282] and terramycin.[283] The [2+2]-cycloadditions involving quinone reactant and leading to cyclobutane have been reported abundantly in the literature.[284] Engler *et al.*[285,286] have reported Ti(IV) promoted [2+2] cycloaddition between propenyl benzenes and 1,4-benzoquinones. Neville and Murphy[287] reported [2+2] cycloaddition of dihydrofuran with 1,4-benzo- and naphthoquinones promoted by diethylaluminium chloride. Another noteworthy study of the same group unveiled a novel alkyl-aluminium chloride promoted [2+2] cycloaddition reactions of styrenes with 1,4-naphthoquinones and bromoquinones.[288] The mechanism involves an initial Lewis acid co-ordination to the quinone subsequent Michael addition to styrene, followed by rapid ring closure of the intermediate dipolar ion affording stereospecifically the cyclobutane with *exo* stereochemistry.

Zhou and Corey[289] reported a novel enantioselective [3+2] addition of 1,4-benzoquinones with vinyl ethers catalyzed by the chiral oxazaborolidinium ion (Scheme 52). This methodology has been applied to a short enantioselective synthesis of the potent naturally occurring mutagen aflatoxin $B_2$ (**205**).

Stereoselective [3+2] and stereospecific [2+2] cycloaddition reactions of unactivated alkenes to quinones have been reported by Engler *et al.*[290] The nature of the



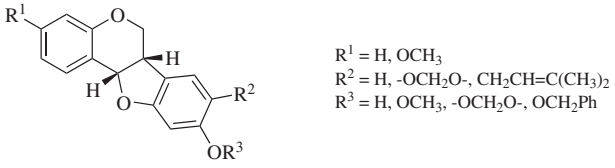
**Scheme 52.** Novel enantioselective [3+2] addition of 1,4-benzoquinones by Corey *et al.*[289]




**Scheme 53**. [2+2] and [3+2] Cycloadditions of **206** and **207** by Engler *et al.*[291]

cycloadduct formed depended on the substituents present on the alkene, the quinone and the catalyst. Later Engler *et al.*[291] extended their study to carry out [2+2] and [3+2] cycloadditions of 2H-chromenes (**206**) and 2-alkoxy-1,4-benzoquinones (**207**) (Scheme 53). The [3+2] cycloadducts, oxygenated pterocarpans (**208**) were found to be the major product, instead of the [2+2] cycloadducts, cyclobutanes (**209**).

The synthetic utility of these cycloaddition reactions has been demonstrated by the synthesis of different antimicrobial pterocarpan phytoxalexins (**210**).



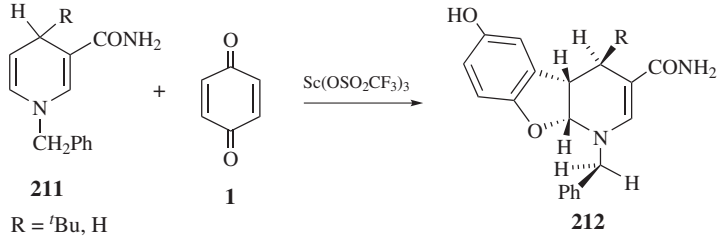

**210**

The mechanistic and kinetic aspects of competing metal-ion catalyzed cycloaddition and hydride transfer reactions of NADH analogues with 1,4-benzoquinones have been studied by Fukuzumi *et al.*[292] 1-Benzyl-4-*t*-butyl-dihydronicotinamide (**211**) reacts efficiently with 1,4-benzoquinone (**1**) to yield a [2+3] cycloadduct (**212**) in the presence of $Sc(OSO_2CF_3)_3$ in deaerated acetonitrile at room temperature (Scheme 54), while no reactions occur in the absence of $Sc^{3+}$.

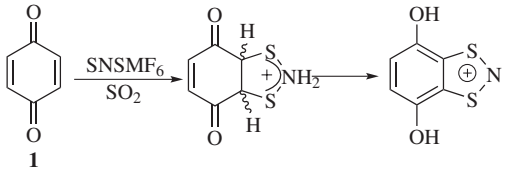
The hydride transfer reaction from **211** to **1** also occurs besides the cycloaddition when the Lewis acidity of metal ion decreases. A change in the type of reaction from a cycloaddition to a hydride transfer depends on the Lewis acidity of metal ions. Another noteworthy [3+2] cycloaddition involves reaction of naphthoquinones with nitrile oxides to generate regiodefined type II polyketide building blocks.[293]

The extreme enthusiasm in the [3+2] cycloaddition reactions led to the emergence of very interesting pseudo-1,3-dipolar cycloaddition chemistry. Passmore and co-workers[294] identified this pseudo-1,3-dipolar cycloaddition as a powerful tool for accessing a variety of mono- and bi-functional 6π heterocyclic 1,3-dithiazolium cations. They reported the unprecedented formation of a benzo-fused 1,3,2-dithiazolium [$AsF_6^-$] salt by a one step quantitative cycloaddition of $SNSAsF_6$ with 1,4-benzoquinone (**1**) (Scheme 55).

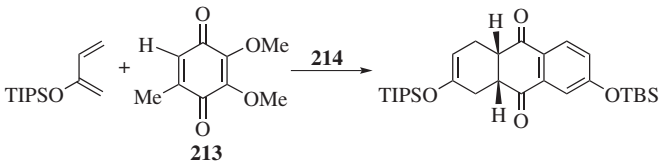
1,4-Benzoquinone and its derivatives are extensively used in Diels-Alder reactions.[295-300] Corey *et al.*[301-305] have carried out pioneering work on the enantioselective Diels-Alder cycloaddition reactions using versatile chiral catalysts oxazaborolidinium salts (**214**). For instance, recent works[306] have reported an enantioselective and structure-




**Scheme 54.** Metal ion catalysed [2+3] cycloaddition of **211** and *p*-benzoquinone by Fukuzumi *et al.*[292]



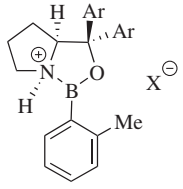

**Scheme 55.** Pseudo-1,3-dipolar cycloaddition of $SNSAsF_6$ with 1,4-benzoquinone.[294]




**213**

**Scheme 56.** Diels-Alder reactions of unsymmetrical quinones by Corey *et al.*[306]

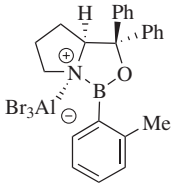
selective Diels-Alder reactions of unsymmetrical quinones (**213**) (Scheme 56). A set of rules has been framed to predict the structure and absolute configuration of the predominant product.




Ar = Ph; 3,5-dimethylphenyl
X = $CF_3SO_3$; $(CF_3SO_2)_2N$

**214**

Another glorious achievement of this group using the chiral catalyst (**214**) has been the transformations of some of the classical synthesis of racemic natural products.[307] Hence the enantioselective versions of the Sarett's total synthesis of cortisone, Kende's total synthesis of dendrobine, Chu-Moyer/Danishefsky synthesis of (±)-myrocin C and Mehta's synthesis of (±)-triquinanes have been accomplished with excellent yields. Later Corey and co-workers[308] have improved the catalyst **214** by synthesizing chiral oxazaborolidine-aluminium bromide complexes (**215**) and reported the enantioselective Diels-Alder cycloadditions of cyclopentadiene with various quinones.

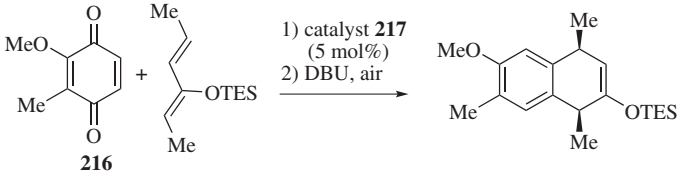



**215**

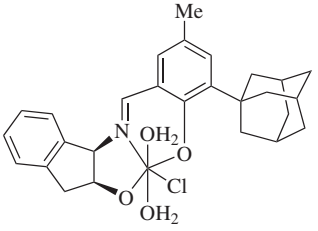
Jarvo *et al.*[309] discovered a highly enantio- and regioselective Diels-Alder reaction of quinones (**216**) which is also catalyzed by a new, monomeric tridentate [(Schiff base)$Cr^{III}$] complex (**217**) (Scheme 57).

White and Choi[310] demonstrated the synthetic utility of Diels-Alder reaction of benzoquinone (**1**) through the asymmetric synthesis of the indole alkaloid (−)-ibogamine (**220**). The key step in this synthesis is the Diels-Alder addition of (**1**) to an achiral diene (2**18**) in the presence of a chiral catalyst, (S)-BINOL-$TiCl_2$ to give for the adduct (**219**), which on subsequent reactions yielded (**220**) (Scheme 58).

Masked 1,4-benzoquinones (**221**) are quinones in which a carbonyl group is masked by converting into monoketals. The monoketals of *p*-benzoquinones have been used as starting materials for the synthesis of a wide range of bioactive natural products including antitumor

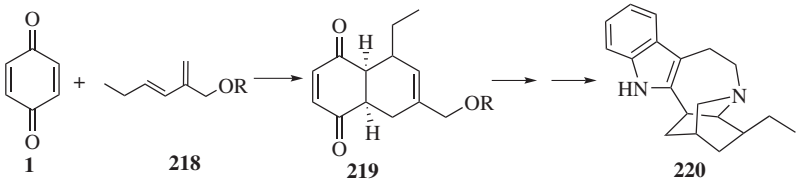



**216**



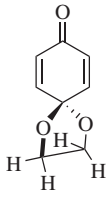

**217**

**Scheme 57.** Enantio- and regioselective Diels-Alder reactions of quinones by Jarvo *et al.*[309]

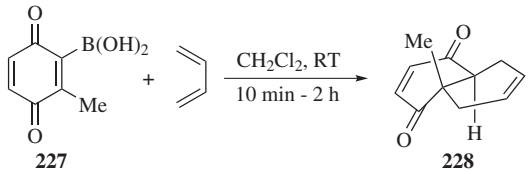



**1** **218** **219** **220**

**Scheme 58.** Asymmetric Diels-Alder reaction White and Choi.[310]



**221**



**227** **228**

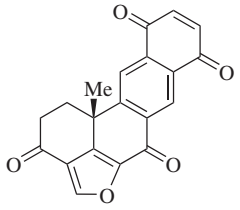
**Scheme 60.** Diels-Alder reaction of boronic acid substituted quinone reported by Carreno and colleges.[316]

antibiotic LL-C10037a.[311-313] March *et al.*[314] reported that phenylthiomonoketal (**222**) works efficiently as a masked *p*-benzoquinone in Diels-Alder reactions. These cycloadditions may be performed with certain Lewis acid catalyst like $ZnBr_2$ and give rise exclusively to *endo* adducts with a good to excellent anti-facial selectivity (Scheme 59).

Carreno *et al.*[315] studied the effect of aryl substitution on reactivity, chemoselectivity and π-facial diastereoselectivity of Diels-Alder reactions of various 2-(arylsulfinyl)-1,4-benzoquinones (**223**-**226**) with cyclopentadienes. The reactivity and selectivity of the process proved to be dependent on the electron density of the arylsulfinyl group.

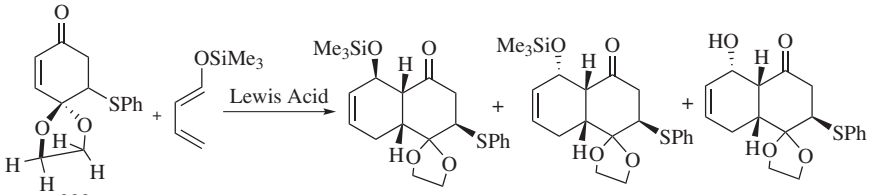
Later Carreno and colleges[316] observed that the dienophilic reactivity of the 2-methyl substituted quinones have been increased upon boronic acid substitution. The Diels-Alder reaction of this substrate (**227**) followed by a spontaneous and stereoselective protodeboronation to give the *trans*-fused cycloadduct, **228** (Scheme 60).

The role of boron group in this typical cycloaddition is to act as a temporal regiocontroller and leads to the uncommon *meta*- regioisomer of the cycloadduct. Trauner and colleges[317] demonstrated the viability of vinyl quinones in Diels-Alder reactions. They utilized this strategy to synthesize medicinally significant (–)-halenaquinone (**229**).



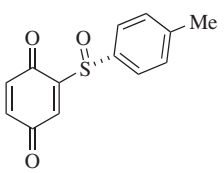
**229**

Nolan and Kedrowski[318,319] have shown that extremely electron deficient vinylnitroquinone (**230**) undergoes facile cycloaddition to electron rich furan and indole (Scheme 61).

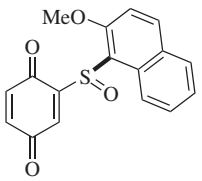


**222**

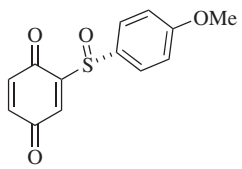
**Scheme 59.** Diels-Alder reaction of masked benzoquinone **222** reported by March *et al.*[314]



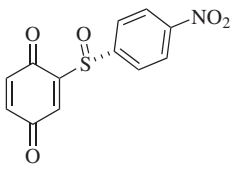
**223**
2-(*p*-Tolylsulfinyl)-1,4-benzoquinone



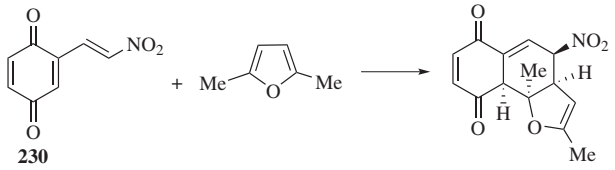
**224**
2-(2′-Methoxynaphthylsulfinyl)-1,4-benzoquinone



**225**
2-(*p*-Methoxyphenylsullfinyl)-1,4-benzoquinone

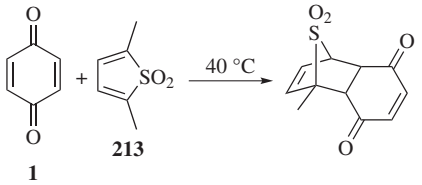


**226**
2-(*p*-Nitrophenylsullfinyl)-1,4-benzoquinone



**Scheme 61.** Cycloaddition of vinylnitroquinone with furan.[318,319]

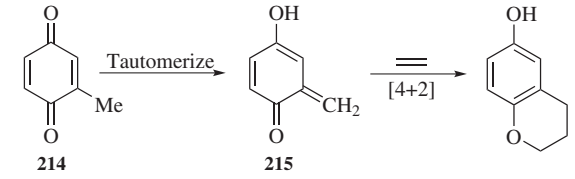
Kang *et al.*[320] studied a specific Diels-Alder reaction of 1,4-benzoquinone (**1**) with a thiophene dioxide derivative (**213**) catalyzed by a self assembled molecular capsule (Scheme 62).



**Scheme 62.** Diels-Alder reaction of 1,4-benzoquinone with thiophene dioxide by Kang *et al.*[320]

A typical intramolecular Diels-Alder [IMDA] cycloaddition of 1,4-benzoquinone was recently reported by Trauner and co-workers.[321] A facile tautomerization of alkyl substituted 1,4-benzoquinone (**214**) to *o*-quinone (**215**) methide is the highlight of this cycloaddition (Scheme 63).

Stratakis and co-workers[322] reported an efficient biomimetic route to acremin G (**219**) featuring a highly regioselective and stereoselective Diels-Alder reaction between a TBS-protected hydroquinone diene (**216**) and a structurally related alkenyl quinone (**217**). The *endo* [4+2] cycloadduct (**218**) slowly transforms to acremin G (**219**)



**Scheme 63.** Intramolecular Diels-Alder cycloaddition of 1,4-benzoquinone by Trauner and co-workers.[321]

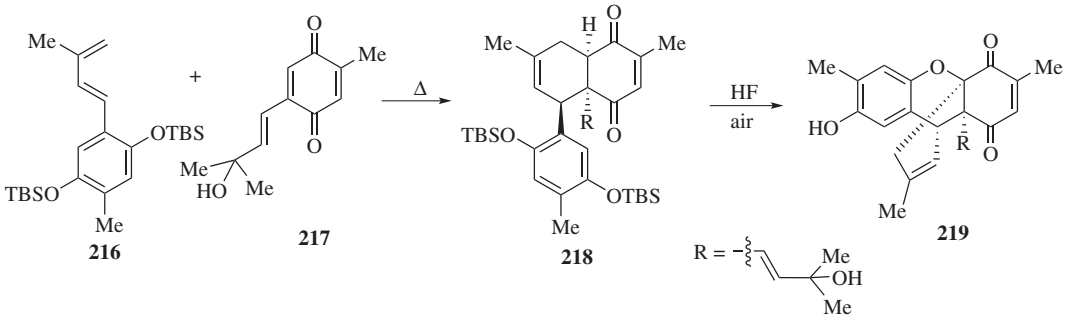
by the atmospheric air under deprotection conditions (Scheme 64).

The construction of complex polycyclic frameworks has also been reported by a double domino Knoevenagel hetero Diels-Alder synthetic strategy. Jimenez-Alonso *et al.*[323] synthesized several bis-pyrano-1,4-benzoquinones (**220**) using this strategy for the first time (Scheme 65). Using microwave radiations these reactions proceeded more efficiently and rapidly.

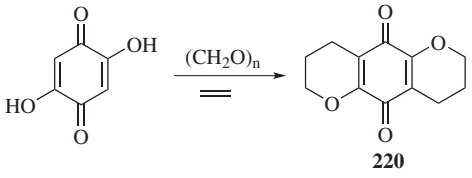
Pardasani *et al.*[324] studied the base-induced benzoyl migrations in Diels-Alder adducts of benzoyl-1,4-benzoquinones. Later, we carried out the Diels-Alder reaction of some fluorinated *p*-benzoquinones (**221**) with substituted dienes (**222**) furnishing the adducts 4a,5,8,8a-tetrahydro-1,4-naphthaquinones (**223**) in good yield (Scheme 66).[325]

The potential utility of such a cycloaddition reaction lies in the synthesis of a number of anthracyclinone analogues. Similar Diels-Alder reactions of numerous 1,4-benzoquinones have been subsequently reported by our group.[198, 326,327]

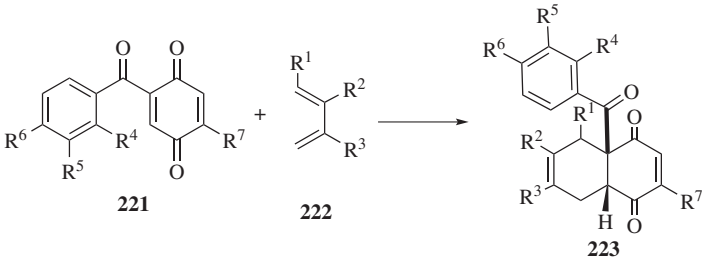
Chen *et al.*[328] achieved a typical cycloaddition reaction of zirconacyclopentadiene (**224**) to various quinones leading to a 6-membered adduct (Scheme 67).



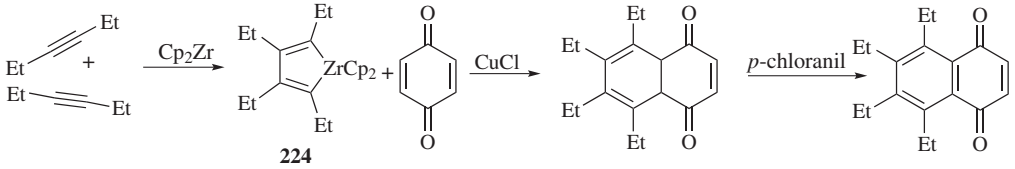
**Scheme 64.** Synthesis of acremin G *via* Diels-Alder cycloaddition by Stratakis and co-workers.[322]



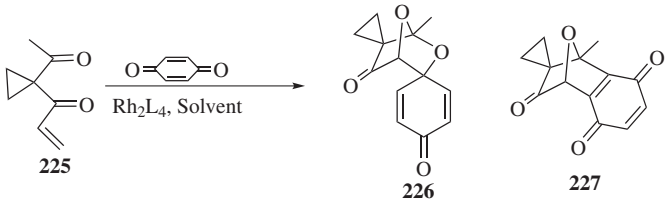
**Scheme 65.** Synthesis of bis-pyrano-1,4-benzoquinone *via* double domino Knoevenagel hetero Diels-Alder reaction by Jimenez-Alonso *et al.*[323]



**Scheme 66.** Diels-Alder reactions of benzoyl-1,4-benzoquinones by Pardasani *et al.*[324]



**Scheme 67.** Cycloaddition of zirconacyclopentadiene (**224**) to quinone by Chen *et al.*[328]



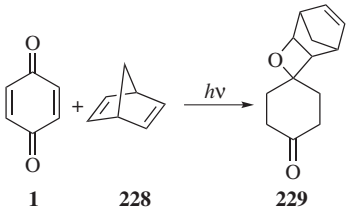
**Scheme 68.** Dipolar cycloaddition reaction carbonyl ylides with *p*-benzoquinones.[329]

This is an efficient method for higher quinones by a zirconium/CuCl mediated cycloaddition reactions of two alkynes and quinone in a one-pot procedure.

Pirrung and Kaliappan[329] developed a cycloaddition strategy based on the dipolar cycloaddition reactions of rhodium-generated carbonyl ylides (**225**) with *p*-benzoquinones to synthesize biologically important compounds containing spirocyclopropyl group. This cycloaddition generated both the C=O (**226**) and C=C (**227**) addition products (Scheme 68).

Photocycloaddition of cyclic conjugated enones with alkenes is a convenient method to construct a cyclobutane containing polycyclic system. This reaction has also been applied to the synthesis of a number of naturally occurring substances[330-334] and has attracted much attention from the mechanistic viewpoint.[335-337] Quinones occupy a very important position in the photoreactions with alkenes in which the conjugated C=C and C=O double bonds competitively take part in the [2+2] photocycloaddition to provide cyclobutane derivatives[338-340] and Paterno-Buchi adducts[341-343] respectively, depending on the identities of the quinone as well as the alkenes. We studied[344] the photocyclisation of benzoyl-1,4-benzoquinones leading to xanthones and phenyl gentisate esters while pursuing studies on the synthesis of anthracyclinones and heteroanthracyclinones.

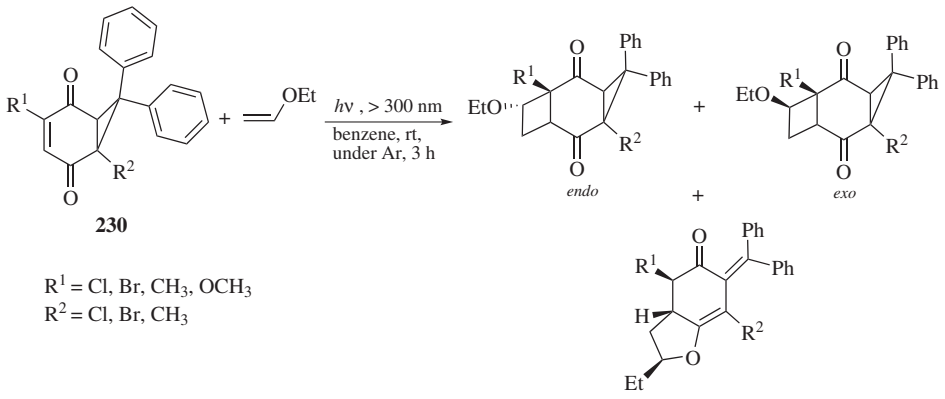
Bryce-Smith *et al.*[345] reported the photoaddition of 1,4-benzoquinone (**1**) to norbornadiene (**228**) to give the spirooxetane (**229**) in 22% yield (Scheme 69).



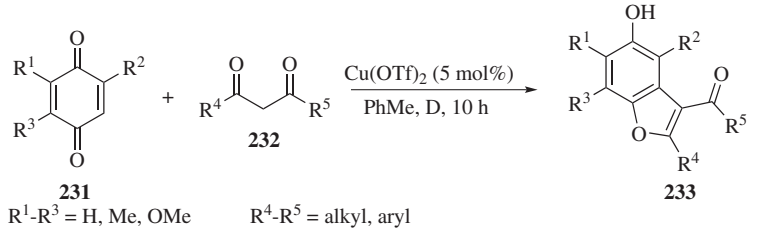
**Scheme 69.** Photoaddition of 1,4-benzoquinone (**1**) to norbornadiene.[345]

Oshimaand co-workers[346] studied the regio- and endo-selective [2+2] photocycloadditions of homobenzoquinone (**230**) with ethyl vinyl ether (Scheme 70).

Very recently, Mothe *et al.*[347] reported an efficient synthesis of a variety of 3-acyl-5-hydroxybenzofurans (**233**) from the cycloaddition reactions of unactivated 1,4-benzoquinones (**231**) with 1,3-dicarbonyl compounds (**232**) (Scheme 71). The highlight of the method is the use of a copper (II) triflate catalyst. The cycloaddition proceeded with excellent yields (40-95%) and complete regioselectivity.




**Scheme 70.** [2+2] Photocycloadditions of homobenzoquinone (**230**) with ethyl vinyl ether.[346]

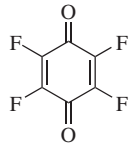



**Scheme 71.** Cycloadditions 1,4-benzoquinones with 1,3-dicarbonyl compounds by Mothe *et al.*[347]

## 6. Pulse Radiolytic Studies on 1,4-Benzoquinones

Pulse radiolysis is a method of studying fast chemical reactions in which a sample is subjected to a pulse of ionizing radiation, and the products formed by the resulting reactions are studied stereospecifically.[348] Pulse radiolysis technique has been used extensively by several groups to study the electron transfer processes involving quinones.[349-354] Quinones participate in a range of biological redox processes owing to their efficiency in undergoing reduction. Predominantly, pulse radiolysis is an established methodology for studying one-electron transfer processes in liquid media.[355-357]

Rao and Hayon[358] studied in detail the ionization constants, absorption spectra and extinction coefficients of numerous semiquinone radicals in aqueous solution and correlated their increased reduction potential with increased acidity. Shoute and Mittal[359] carried out pulse radiolysis study of one-electron reduction reaction of fluoranil (**234**) in aqueous solution.




**234**

They found that in acidic environment fluoranil can be a better electron acceptor than 1,4-benzoquinones.

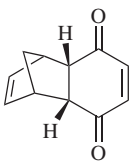
Bors and co-workers[360] investigated the disproportionation of semiquinones ($Q^{\bullet-}$) when other reactions are hindered (Scheme 72).

$$Q^{\bullet-} + Q^{\bullet-} + 2H^{+} \xrightarrow[2k_1]{} Q + QH_2$$

**Scheme 72.** Disproportionation of semiquinones.

They studied the kinetics of semiquinone disproportionation by pulse radiolysis and attributed lower rate of disproportionation of $Q^{\bullet-}$ to outstanding antitumor activity of the corresponding quinone (Q).

Rath *et al.*[361] carried out the pulse radiolytic reduction studies of a substituted 5,8-naphthadione: 1,4,4a,8a-tetrahydro-endo-1,4-methano-naphtha-5,8-dione (THMND) (**235**).

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A series of newly synthesized nine aroyl/heteroacyl-1,4-benzoquinones (RCO-BQ) undergoes one-electron

reduction in pulse radiolytic reducing conditions in an aqueous 2-propanol/acetone mixed solvent (MS).[362] The radical centre is mainly located in the quinone ring, though a small probability exists for reduction at the carbonyl (CO) group. The intramolecular hydrogen bonding between the OH group of the semiquinone ring and the adjacent CO group makes the radical more stable as compared to the simple benzosemiquinone radical. A red-shifted absorption band arises mainly due to large conjugation in the semiquinone. The substitutions (R), thiophenyl, phenyl and furanyl groups at the keto position reduce their one electron reduction potential (E1) values from −30 mV for BQ to < −300 mV in some of these quinones.

## 7. Conclusion

The comprehensive literature survey pertaining to multiple aspects of quinone chemistry unveiled the sustaining importance of quinonoid compounds in many fields of science. The isolation of different quinones from plants and micro-organisms are still being carried out ambitiously. Synthetic organic chemists encouraged by the potential applications of quinones have devised a plethora of synthetic strategies which led to the explosion of articles reporting newer and interesting benzoquinone derivatives. With the advancement of computational methods in solving chemical problems, theoretical studies in various properties of quinones had also been started to report abundantly in the last decade. All these and other significant developments in the cycloaddition and pulse radiolysis of quinones are presented in this review.

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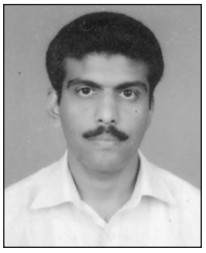

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