

Recent Advances in 1,4-Benzoquinone Chemistry

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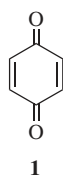
As 1,4-benzoquinonas são encontradas em toda a natureza, podendo ser sintetizadas por diversas estratégias. Esta revisão apresenta os desenvolvimentos recentes das metodologias de síntese, das reações de ciclo adição, da química computacional e dos estudos de pulso radiolítico. Destaca ainda a sua significância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

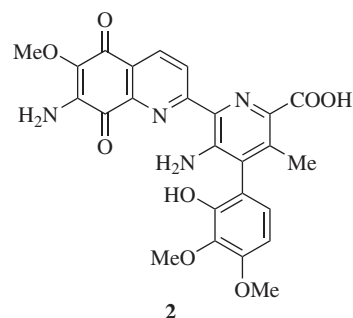


They are widely distributed in the natural world,² being found in bacteria, plants and arthropods and hence quinones are ubiquitous to living systems. Quinones play pivotal role in biological functions including oxidative phosphorylation and electron transfer.³ Their role as electron transfer agents 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 anticoagulant¹² 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 materials²¹ and

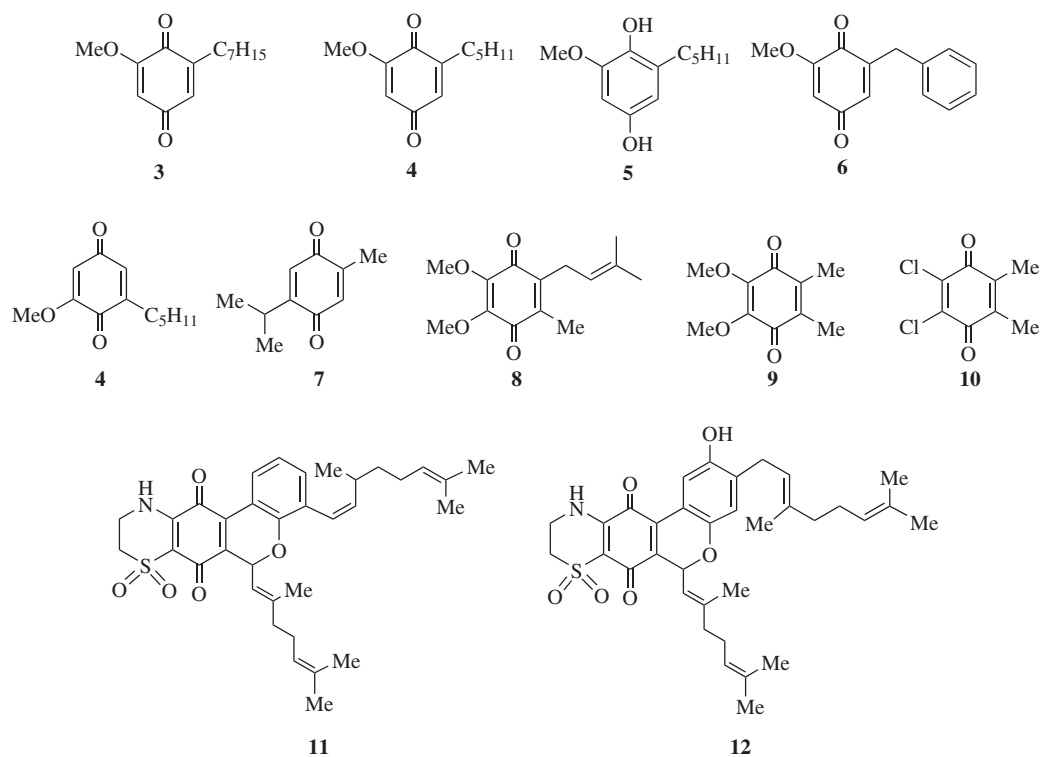
understanding photophysical properties.²² The studies of quinonoid compounds have focused on a broad spectrum of topics *viz* occurrence in nature,² syntheses,²³ cycloaddition reactions,²⁴ photochemistry and pulse radiolysis,^{1,25,26} computational chemistry, etc.²⁷ The copiousness of articles describing 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.

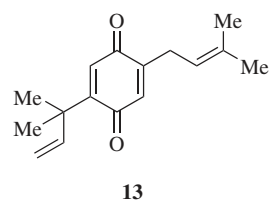
Kingston and co-workers³³ have isolated two new benzoquinones 2-methoxy-6-heptyl-1,4-benzoquinone (**3**) and 2-methoxy-6-pentyl-1,4-benzoquinone (**4**) from the leaves of *Miconia lepidota* present in Surinam forests. Both quinones **3** and **4** exhibited activity towards mutant yeast strains based 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*.

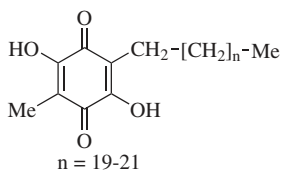
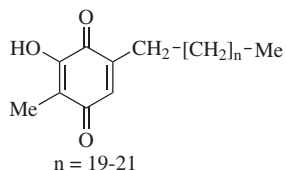
In the chemical investigations on quinones major thrust is being given to the study of their antitumor activity;³⁸ which is directly related to the cytotoxic actions of quinones.³⁹⁻⁴² Vast amount of research has been carried out to establish the antitumor activity of quinones.⁴³⁻⁴⁷ Aiello *et al.*⁴⁸ 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.



Polyhalogenated benzo- and naphthoquinones were found to be potent inhibitors of plant and bacterial ureases. Ashiralieva and Kleiner⁵⁰ 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*.

**14****15**

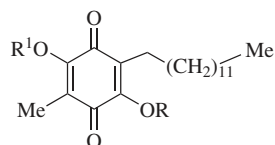
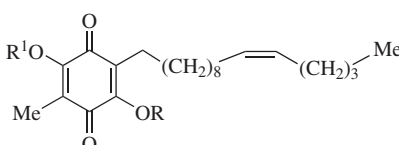
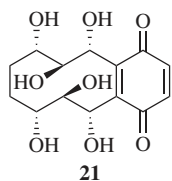
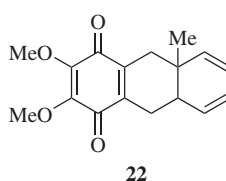
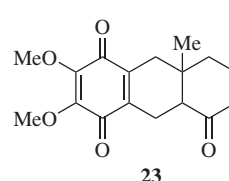
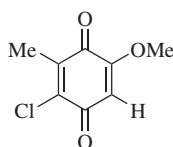
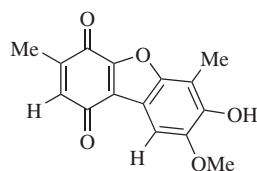
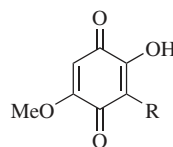
El-Ferly and co-workers⁵² isolated five new alkylated benzoquinones (**16-20**) as methyl ether derivatives from a complex mixture of alkylated hydroxy benzoquinones obtained from the fruits of *Maesa lanceolata*.

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 emollient, analgesic and anti-helminthic.

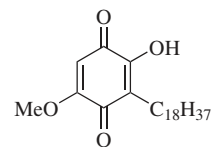
Hosttetman and co-workers⁵⁴ isolated two novel benzoquinones heliotropinones A (**22**) and B (**23**), from the aerial parts of *Heliotropium ovalifolium*. These two quinones demonstrated antifungal activities against *Cladosporium cucumerinum* and *Candida albicans* as well as antibacterial activity against *Bacillus subtilis*. Kaul and co-workers⁵⁵ 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 angustifolia*. 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*.

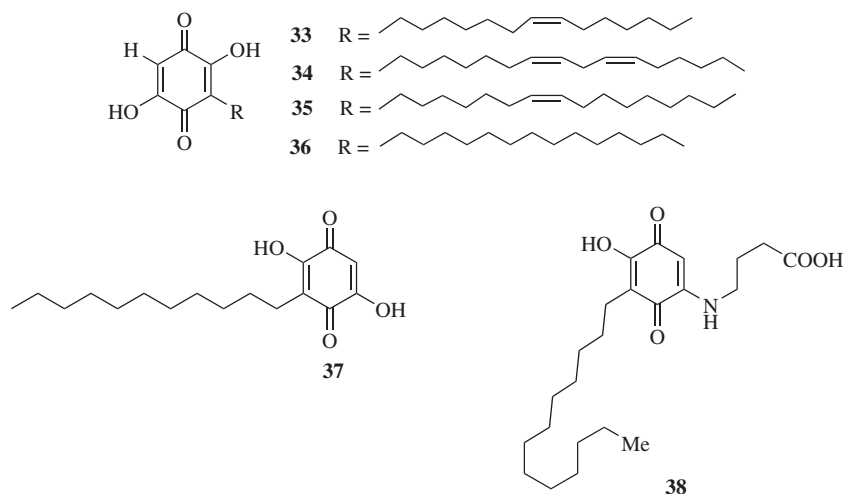
**16** R = Ac; R¹ = Me**17** R = Me; R¹ = Ac**18** R = Me; R¹ = Me**19** R = Ac; R¹ = Me**20** R = Me; R¹ = Ac**21****22****23****31****32**

Irisoquin A-F

24 R = C₁₆H₁₃ **27** R = C₂₀H₄₁**25** R = C₁₇H₃₅ **28** R = C₂₁H₄₃**26** R = C₁₉H₁₉ **29** R = C₂₂H₄₅

Irisoquin

30



Embelin is reported to elicit a wide range of biological effects including anti-helminthic, 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.

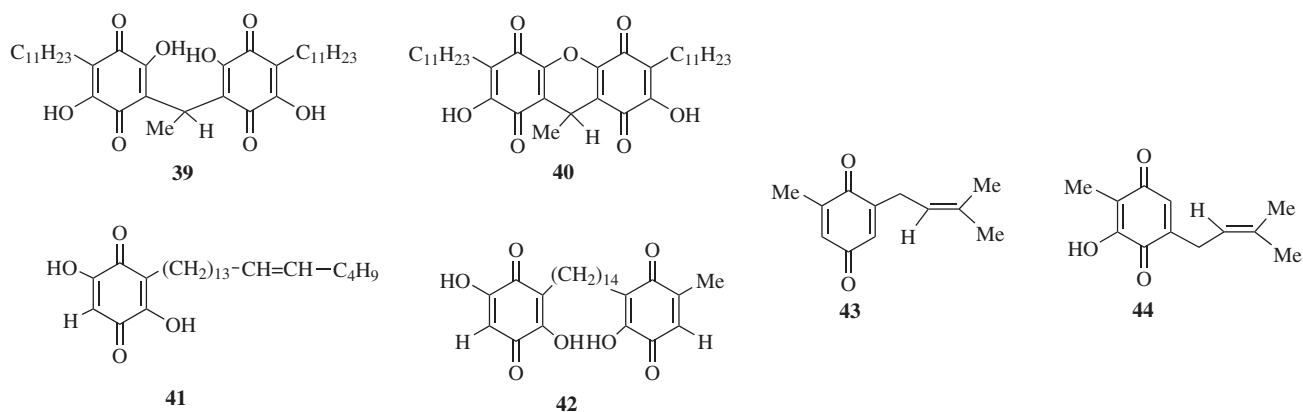
Myrsine, Maesa, Rapanea and Embelia are four genera of trees and shrubs that are widely used in herbal medicine in Kenya. The fruits of *Myrsine africana* afforded two new benzoquinone derivatives,⁶⁰ methylvilangin (**39**) and methylanhydrovilangin (**40**); while the fruits of *Maesa lanceolata* afforded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

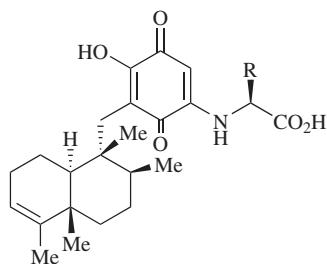
Gunnera perpensa is another plant with high medicinal value.^{61,62} Drewes *et al.*⁶³ isolated olefinic 1,4-benzoquinone

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.

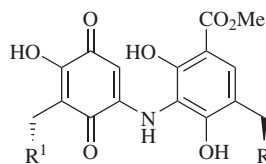
Sesquiterpene quinones are biologically important class of compounds isolated mainly from various species of marine sponges.⁶⁴ They are characterized by pronounced and manifold biological properties.⁶⁵ For instance, Kobayashi and co-workers⁶⁶⁻⁶⁹ have done a pioneering work in isolating a series of nakijiquinones 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

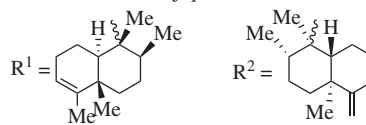




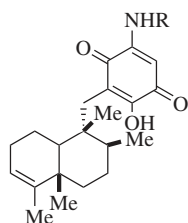
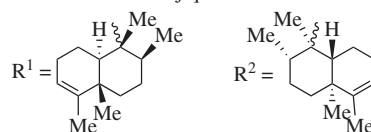
- 45 Nakijiquinone A R = H
 46 Nakijiquinone B R = CHMe₂
 47 Nakijiquinone C R = CH₂OH
 48 Nakijiquinone D R = CH(OH)Me



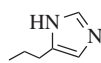
49 Nakijiquinone E



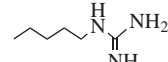
50 Nakijiquinone F



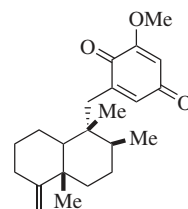
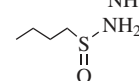
51 Nakijiquinone G R =



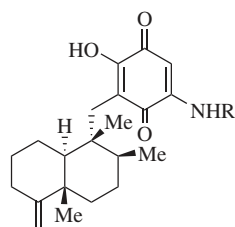
52 Nakijiquinone H R =



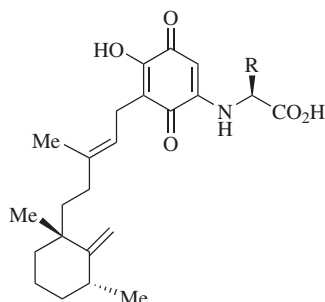
53 Nakijiquinone I R =



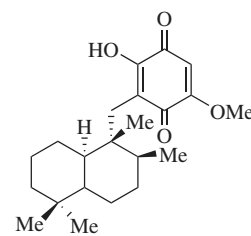
54 Ilimaquinone



- 55 Smenospongine R = H
 56 Smenospongorine R = CH₂CHMe₂
 57 Smenospongidine R = CH₂CH₂Ph



- 58 Metachromin L R = H
 59 Metachromin N R = CH(OH)Me
 60 Metachromin P R = CH₂OH

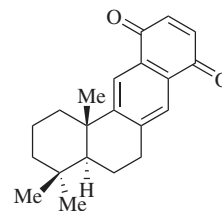


61 Mamanuthaquinone

alga *Dictyopterus undulata*.⁷⁵ **62** showed potent feeding-deterrent activity toward young abalones.

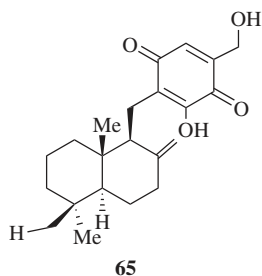
Yamada and co-workers⁷⁶ isolated structurally unique new sesquiterpenoid quinones dactyloquinones A (**63**) and B (**64**) from an Okinawan sponge *Dactylospongia elegans*. Both **63** and **64** possess a dihydropyran moiety.

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

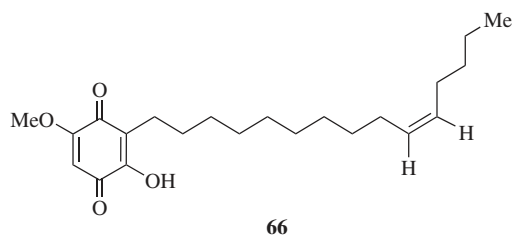


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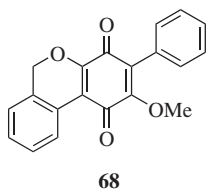
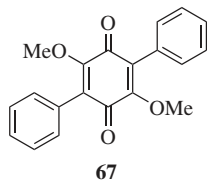
antiproliferative and apoptic activity towards several cancer cell lines.



Maesanin, 2-hydroxy-5-methoxy-3-(10¹-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.

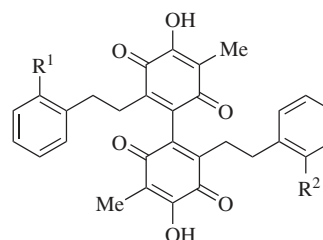
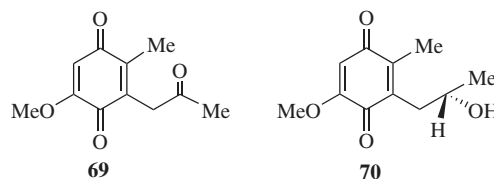


Disintegration of cells and organellar membranes by reactive oxygen species (ROS) has been implicated in various pathological processes and especially involved in the pathogenesis of diseases such as myocardial and cerebral ischemia, atherosclerosis, diabetes, rheumatoid arthritis and cancer-initiation 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*.



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.



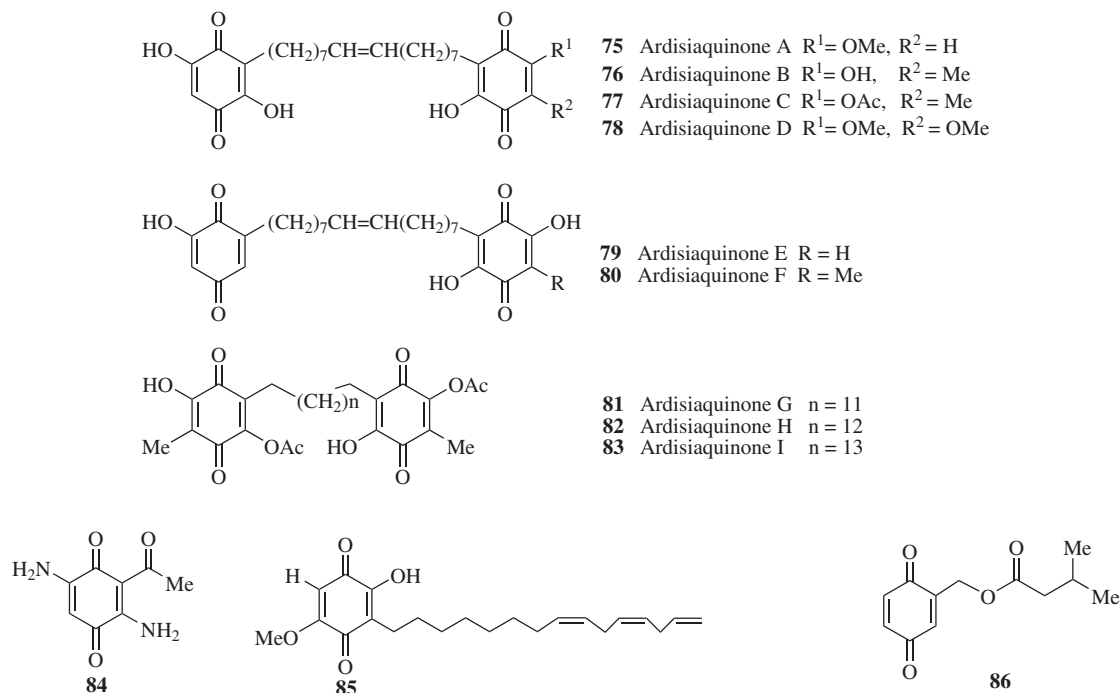
- 71** Parvistemin A R¹ = R² = H
72 Parvistemin B R¹ = R² = OH
73 Parvistemin C R¹ = R² = OMe
74 Parvistemin D R¹ = H; R² = OMe

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 ardisiaquinones A-C (**75-77**) from the root bark of *A. sieboldii*. In 1995, Fukuyama *et al.*⁸⁶ reported the isolation of ardisiaquinone 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-workers⁸⁹ 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

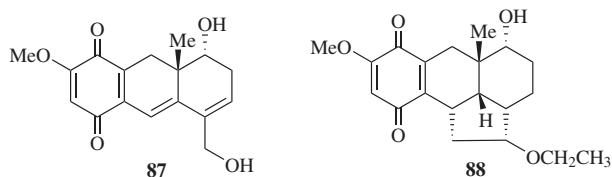
Kanakubo and Isobe⁹² reported the isolation of tetrabromo-1,4-benzoquinone from acorn worm. Structure-activity relationship of chemiluminescence activity of halogenated quinone derivatives reveals that a highly halogen substitution and 1,4-quinone skeleton are important for high chemiluminescence activity. Gentisyl quinone isovalerate, or blatellaquinone (BTQ) (**86**) has been reported⁹³ 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



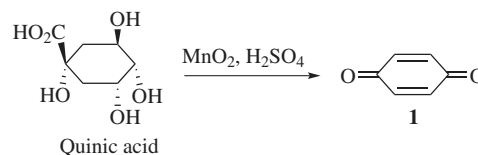
contributing to allergic reactions in cockroach sensitized patients.

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



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.

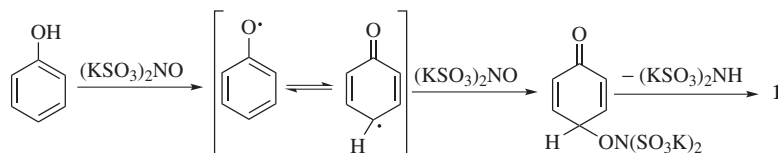


Scheme 1. First synthesis of 1,4-benzoquinone.

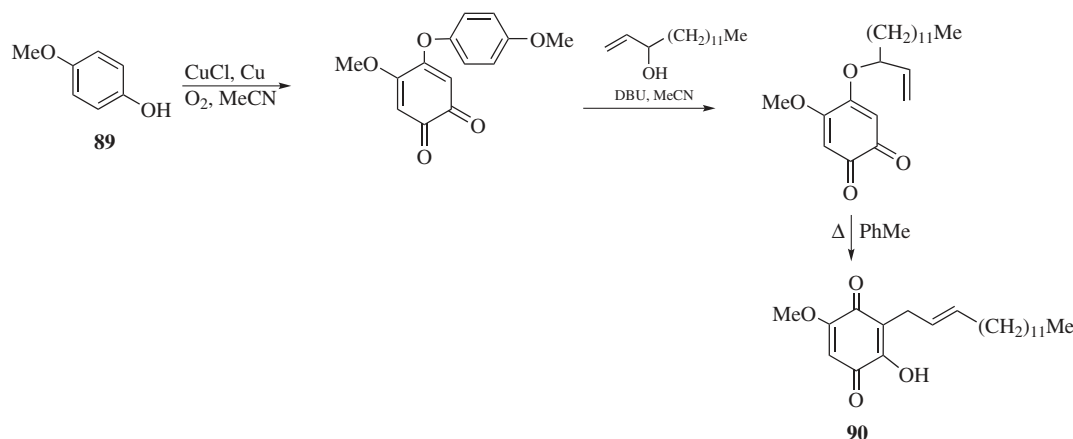
The same reagents can also react with aniline *via* a free radical condensation mechanism to afford benzoquinones. Succeeding these initial preparations of quinones, an array of reactions involving diverse starting compounds and efficient synthetic strategies have been reported in the literature till 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, $(\text{KSO}_3)_2\text{NO}$] 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).



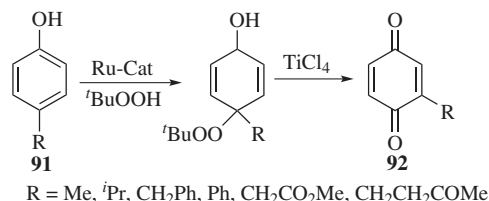
Scheme 2. Mechanism of Teuber reaction.



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

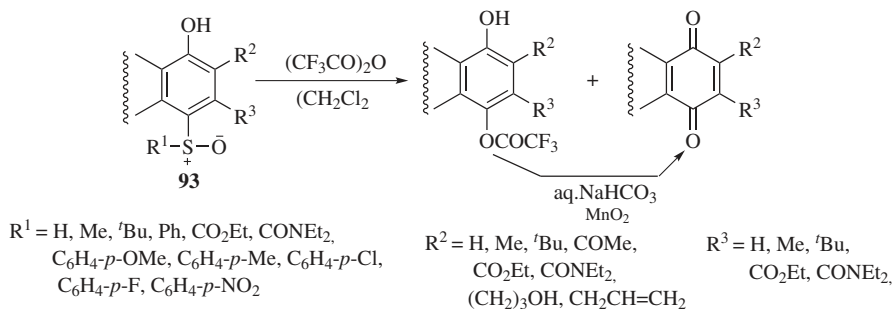
Teuber reaction is especially useful for the synthesis of heterocyclic quinones, where other oxidizing agents fail.¹⁰⁶ Later on, several groups have developed direct and stepwise oxidation of phenols and their derivatives to *p*-quinones. Reinaud *et al.*¹⁰⁷ synthesized biologically active unsymmetrical alkyl-hydroxymethoxyquinone analogs (**90**) from *p*-methoxyphenol (**89**). The alkyl side chain was introduced regioselectively *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-substituent to the 2-position of the benzoquinone (Scheme 4).



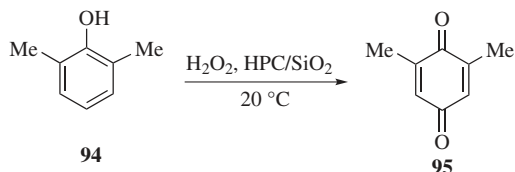
Scheme 4. Ruthenium catalyzed oxidation of phenols to quinones by Murahashi *et al.*¹⁰⁸

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



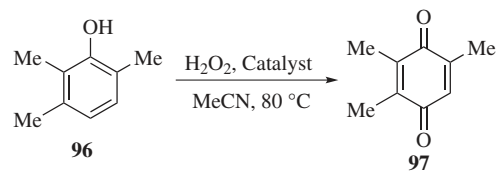
Scheme 5. Conversion of *p*-sulfonylphenols to corresponding quinones by Akai *et al.*¹⁰⁹

Caceras and co-workers¹¹⁰ 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/SiO₂) as catalysts (Scheme 6).



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

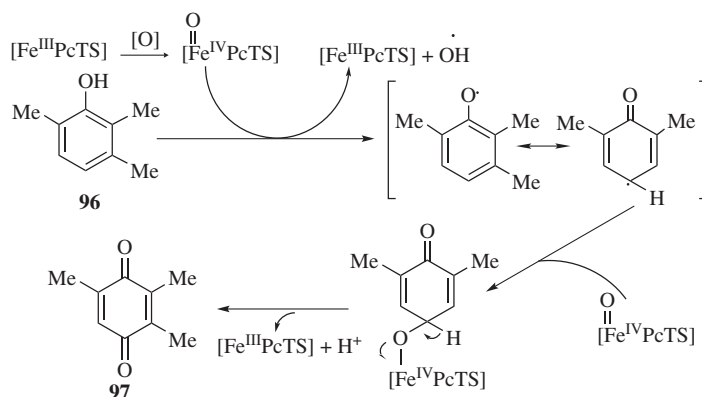
2,3,6-Trimethyl-1,4-benzoquinone, TMQ (**97**) synthesized by the oxidation of 2,3,6-trimethylphenol, TMP (**96**), is used as a precursor in the synthesis of vitamin E.^{111,112} Molecular oxygen, hydrogen peroxide or *t*-butyl hydroperoxide are being used as common oxygen sources and different catalytic systems metallophthalocyanins,^{113,114} heteropolyoxometallates,^{115,116} spinel CuCo₂O₄,¹¹⁷ copper hydroxyl phosphate,¹¹⁸ iron halides,¹¹⁹ copper (II) chloride,^{120,121} metal acetylacetonates¹²² 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 H₂O₂ over titanium (IV) grafted on commercial mesoporous silica catalyst produced TMQ in nearly quantitative yield (Scheme 7).¹²⁶



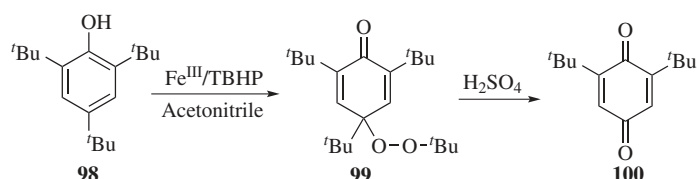
Scheme 7. Oxidation of TMP to TMQ using H₂O₂ and grafted Ti (IV)/SiO₂ catalyst by Kholdeeva *et al.*¹²⁵

Cimen *et al.*¹²⁷ have recently reported TMP to TMQ oxidation with potassium peroxomonosulfate, KHSO₅, 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).

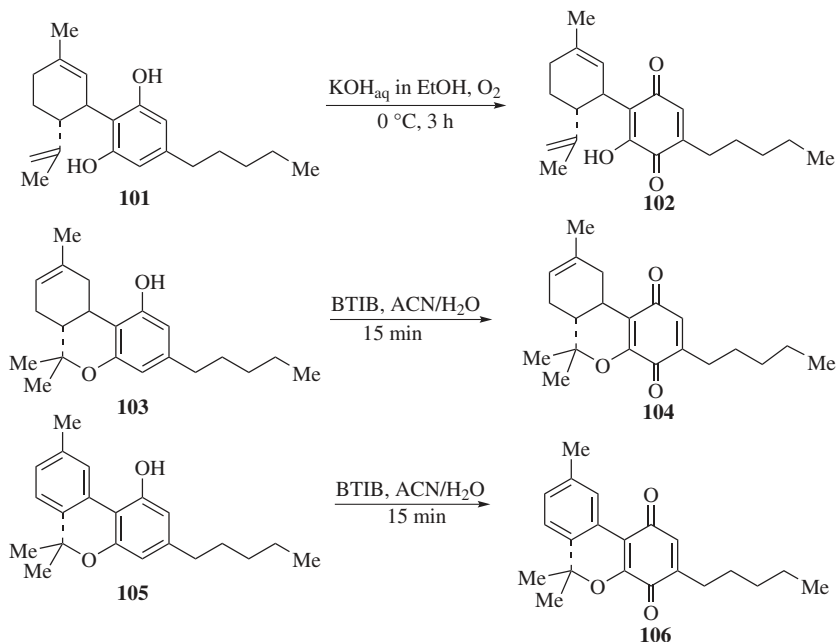
The highlight of the above strategy is that the reaction proceeded with 100% yield when the oxidant:substrate:catalyst molar ratios were 1200:300:1. Phenols with bulky substituents can also be converted to corresponding benzoquinones. Barton and Gloahc¹²⁸ reported a convenient high yield synthesis of 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 Murahashi *et al.*¹⁰⁸ also reported a



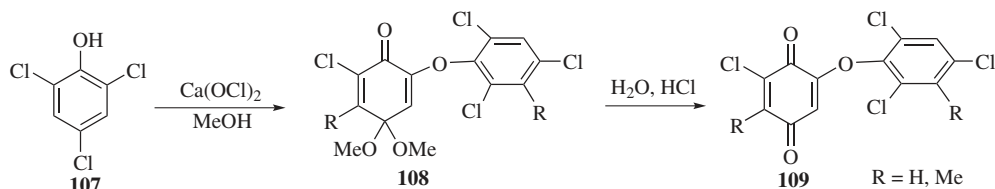
Scheme 8. Mechanism proposed for the oxidation of TMP with KHSO₅ catalysed by [Fe^{III}PcTS].¹²⁷



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



Scheme 10. Oxidation of phenol derivatives in *Cannabis* to quinones.¹²⁹



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**), Δ^8 -tetrahydrocannabinol (**103**) and cannabinol (**105**) have been oxidized to their *p*-quinones **102**, **104** and **106** and respectively (Scheme 10).¹²⁹

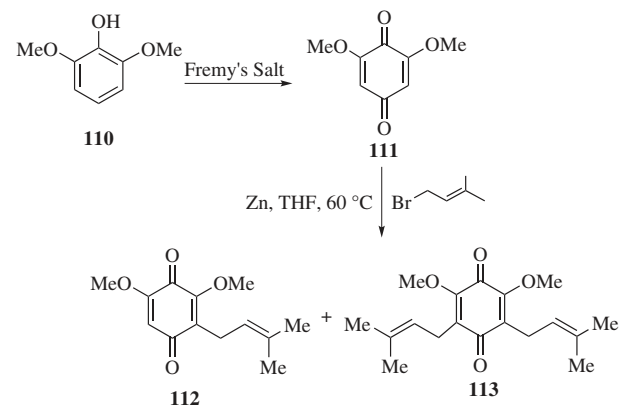
Cannabidiol (**101**) has been oxidized by air in an alcoholic solution in the presence of 5% KOH over 24 h at 0 °C to hydroxyquinone (**102**) at *ca.* 20% yield. Compounds **103** and **105** have been converted to corresponding quinones **104** and **106** by oxidation with bis(trifluoroacetoxy) iodobenzene (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). Heasley and co-workers¹³⁷ 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** (Scheme 12).

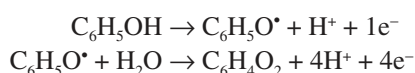
Polymer supported vanadium complexes have been reported as catalysts for the *t*-butyl hydroperoxide oxidation



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

of phenols to 1,4-benzoquinones 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-workers¹⁴² undertook a comparative study on the oxidation of monophenols 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 α -PbO₂ and β -PbO₂ electrodes. Conversion of 61-74% has been achieved by this method. The phenol oxidation mechanism^{144,145} is shown in Scheme 13.



Scheme 13. Electrosynthesis of benzoquinone by oxidation of phenol.

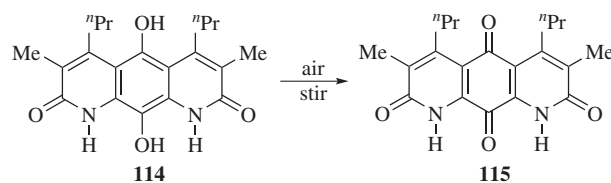
The recent advancement in the synthesis of quinone from phenol is the green chemistry route. Oelgemoller and co-workers¹⁴⁶ described the solar chemical synthesis of quinones by the photo-oxygenation of phenols. The yields were high when the reactions were performed in sunlight rather than artificial 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 Vliet¹⁴⁷ 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.

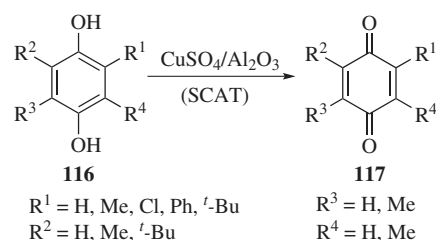
Simple air-oxidation also is a successful method if the hydroquinone is sufficiently activated towards oxidation. An example of this is reported by Kelly *et al.*¹⁵⁸ in a short synthesis of diazaquinomycin A (**115**) from hydroquinone (**114**) (Scheme 14).

Nitric acid-impregnated manganese dioxide¹⁵⁹ in methylene chloride is also used as an oxidant. Tapia and co-workers¹⁶⁰ synthesized nitro-1,4-benzoquinone from nitrohydroquinone applying the above oxidant



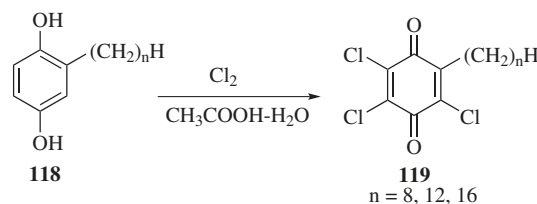
Scheme 14. Synthesis of diazaquinomycin A (**114**) by simple air oxidation by Kelly *et al.*¹⁵⁸

by stirring the solution at 0 °C for 30 min. About three decades back we applied MnO₂ 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



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).



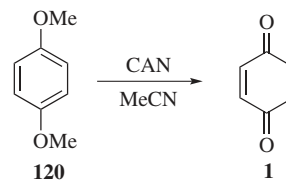
Scheme 16. Synthesis of alkyltrichloro-1,4-benzoquinones (**119**) by Shi *et al.*¹⁶²

Owsik and Kolarez¹⁶³ 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 acid¹⁶⁴ and silver oxide¹⁶⁵ 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-workers¹⁶⁶ introduced a facile and efficient oxidizing agent ceric ammonium nitrate, $[\text{Ce}(\text{NH}_4)_2(\text{NO}_3)_6]$ 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 acetonitrile¹⁶⁷⁻¹⁷¹ then became the most versatile oxidizing agent for the dimethoxybenzene-benzoquinone transformation. For instance, the total syntheses of various



Scheme 17. Synthesis of quinone by oxidative demethylation.¹⁶⁶

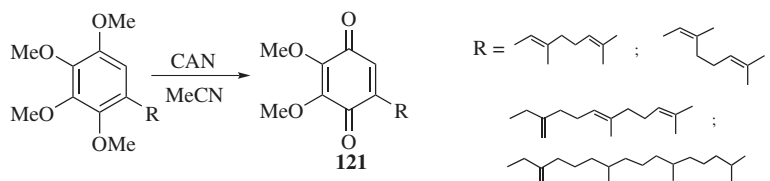
biologically important short-chain ubiquinones (**121**) were accomplished via oxidative demethylation using CAN in good yield by Keinan *et al.*¹⁷² (Scheme 18).

Hart and Huang¹⁷³ employed CAN oxidation in the penultimate step of the synthesis of an antitumor, antibiotic, pleurotin **122** (Scheme 19).

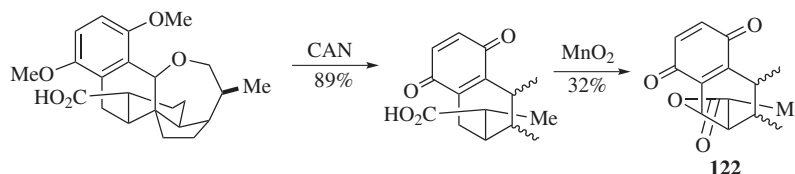
The CAN oxidation lies at the heart of an elegant synthesis of symmetrical 2,5-disubstituted 1,4-benzoquinones (**124**) from 1,4-dimethoxybenzene (**123**) via a palladium catalysed double Negishi coupling (Scheme 20).¹⁷⁴ For R = aryl, the yields of the couplings are good (53-93%) and for R = alkyl,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

2,5-Dibromo-, 2,5-dichloro- and 2,5-diiodobenzoquinones (**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).

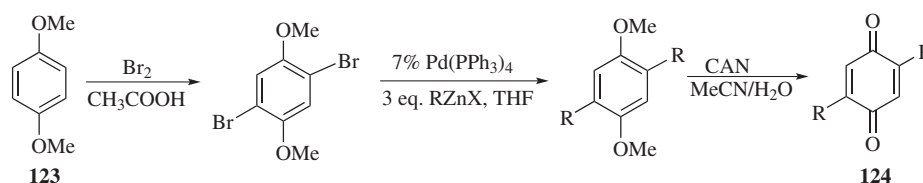
A series of 2-(quinazoline-4-ylamino)-1,4-benzoquinones (**127**) that function as potent covalent-binding, irreversible inhibitors of the kinase domain of vascular endothelial growth factor receptor-2 (VEGFR-2)



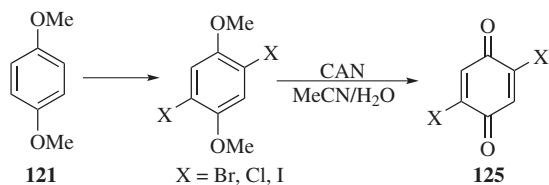
Scheme 18. Synthesis of ubiquinones (**121**) by oxidative demethylation.¹⁷²



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



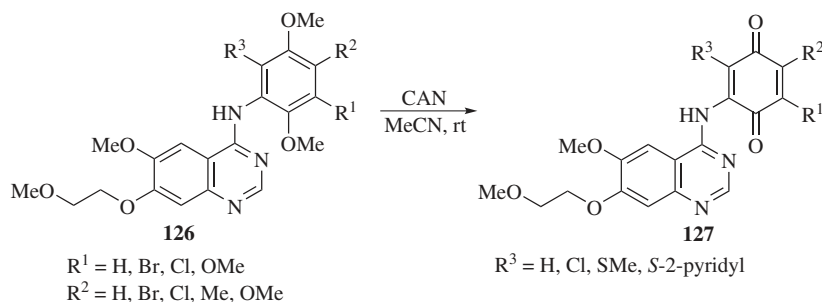
Scheme 20. Synthetic strategy towards 2,5-disubstituted 1,4-benzoquinones by Palmgren *et al.*¹⁷⁴



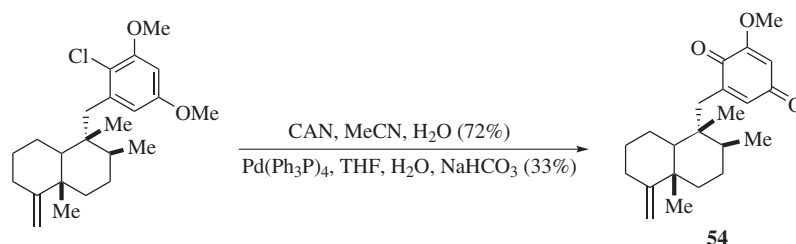
Scheme 21. Synthetic strategy towards 2,5-dihalobenzoquinones by Lopez-Alvarado *et al.*¹⁷⁵

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

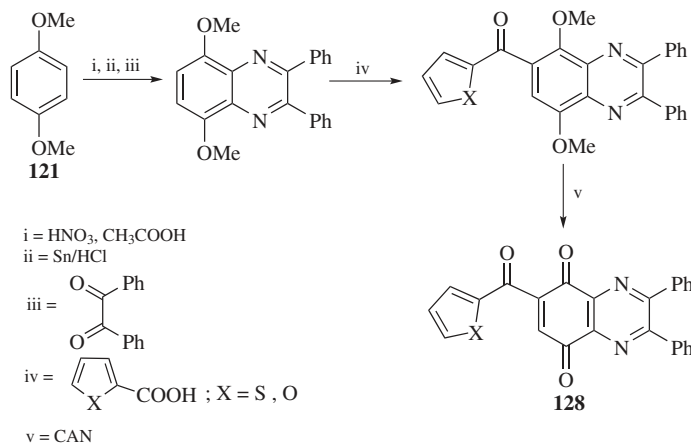
Snapper and co-workers¹⁷⁷ reported the synthesis of structural variants of biologically active marine sponge metabolite, ilimaquinone (**54**) in which CAN oxidative demethylation is a key step (Scheme 23).



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



Scheme 23. Synthesis of ilimaquinone by oxidative demethylation.¹⁷⁷

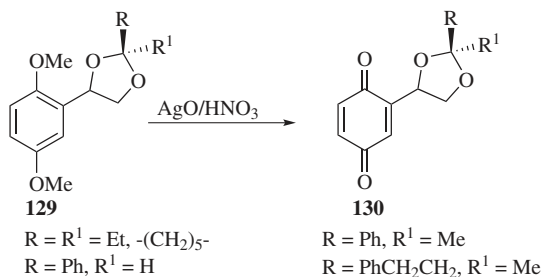


Scheme 24. Multi-step synthesis of quinoxaline quinones (**128**) by Pardasani and co-workers.¹⁷⁸

In our successful attempt to synthesize thienoyl- and furanoyl- substituted quinoxaline quinones¹⁷⁸ (**128**) from 1,4-dimethoxybenzene precursor, we have employed ceric ammonium nitrate (CAN) oxidative demethylation (Scheme 24).

Besides CAN in MeCN-H₂O, THF-water¹⁷⁹ is also used for the oxidative demethylation of 1,4-benzoquinones.

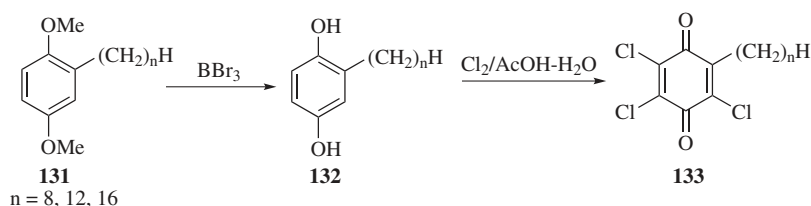
Tomatsu *et al.*¹⁸⁰ synthesized quinones from hydroquinone dimethyl ethers by the oxidative demethylation with Co(III) fluoride in good to excellent yield. Oxidative demethylation was also achieved using silver oxide/nitric acid reagent.¹⁸¹ Recently Popik and co-workers¹⁸² synthesized (1,3-dioxolane-4-yl)-1,4-benzoquinones (**130**) from their dimethoxy precursors (**129**) using silver oxide/nitric acid reagent in good yield (Scheme 25).



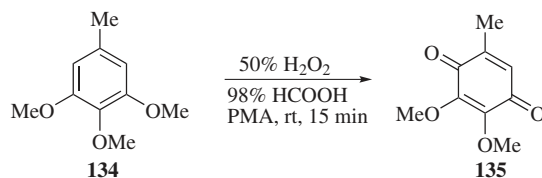
Scheme 25. Oxidative demethylation using silver oxide/nitric acid.¹⁸²

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 $\text{Cl}_2/\text{AcOH}-\text{H}_2\text{O}$ resulting in the formation of chlorinated quinones (**133**) (Scheme 26).

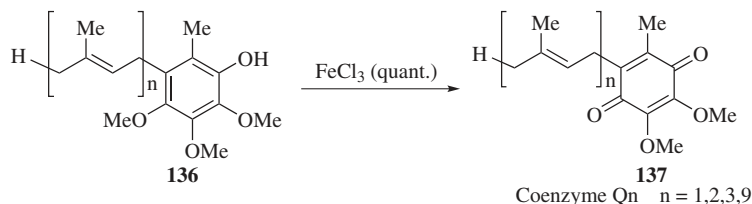
1,4-Benzoquinones have also been prepared from 1,3-dimethoxybenzenes where only one methoxy group converts to the keto group while other methoxy functionality remains intact in the resulting quinone. Singh and co-workers¹⁸³ synthesized 2,3-dimethoxy-5-methyl-1,4-benzoquinone (ubiquinone Q_0) (**135**) by a reaction sequence starting from 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%.



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

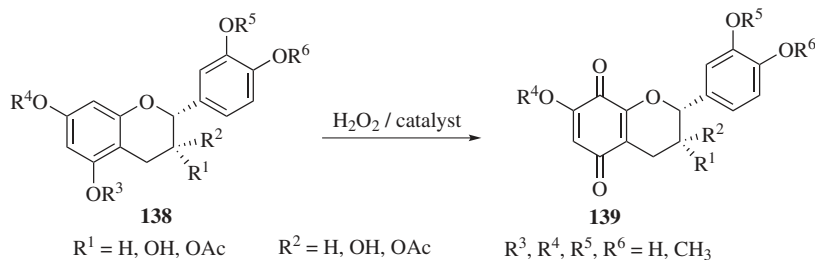


Scheme 28. Syntheses of coenzymes Q_n via FeCl_3 oxidation by Bovicelli *et al.*¹⁸⁵

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 proceeded 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 29. Synthesis of bioactive *p*-benzoquinones by Bernini *et al.*¹⁸⁶

i) oxidation using hydrogen peroxide and in the presence of a Brønsted acid, HNO_3 as a catalyst; *ii*) elimination of excess oxidant using sodium metasilicate 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 Moody¹⁸⁸ synthesized 2-(3'-methylbut-2'-enyl)-5-(2'-methylbut-3'-en-2'-yl)-1,4-benzoquinone (**143**), a novel prenylated quinone derivative

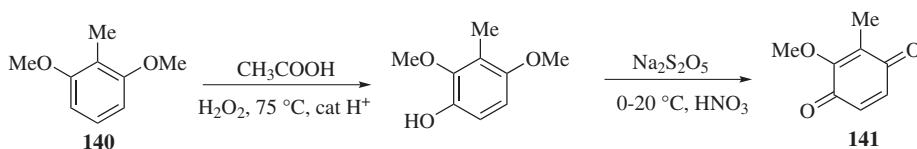
from the New Zealand brown algae *Perithalia capillaries*, by the oxidation of a hydroquinone acetate (**142**) with an excess of lithium aluminum hydride, THF and O_2 (Scheme 31).

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

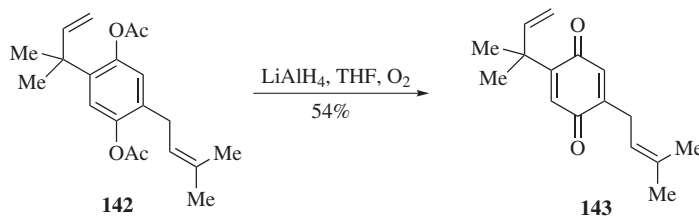
A convergent general synthesis of annelated quinones and highly substituted quinones (**149-151**) from conjugated ketenes (**146-148**) was reported by Moore and co-workers.¹⁹⁰ The reaction proceeds via a thermal rearrangement (Schemes 33-35).

Later Xiong and Moore¹⁹¹ also carried out the ring expansion of 4-alkylcyclobutenones by thermolysis to furnish a variety of *N*-heterocyclic quinones.

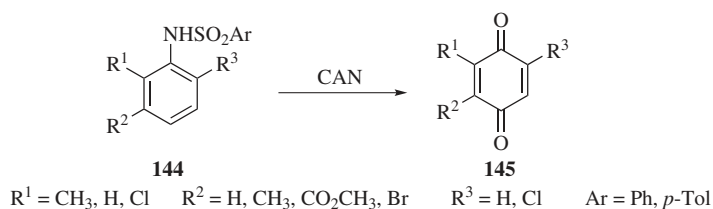
Danheiser *et al.*¹⁹² employed vinylketene/alkyne cycloaddition reaction for quinone synthesis. The sequence of the quinone transformation starts with a photochemical Wolf rearrangement producing a vinylketene (**152**), which undergoes a cycloaddition to the alkyne to give



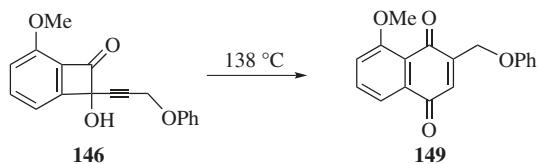
Scheme 30. A green telescoped process for the synthesis of quinones.¹⁸⁷



Scheme 31. Oxidation of hydroquinone acetate to quinone.¹⁸⁸



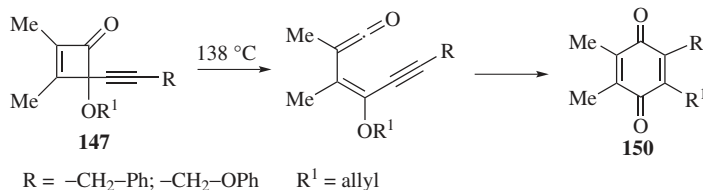
Scheme 32. Conversion of *N*-arylsulphonamides to *p*-benzoquinones.¹⁸⁹



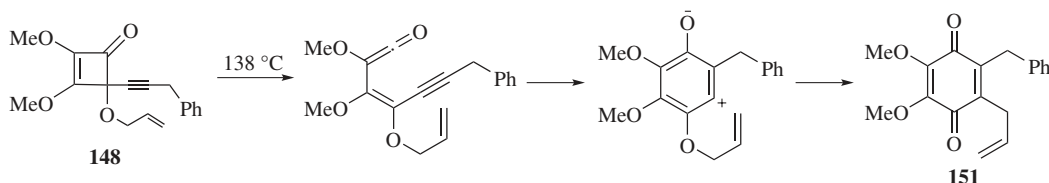
Scheme 33. Synthesis of quinone (**149**) by thermolysis of benzocyclobutenone.¹⁹⁰

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).

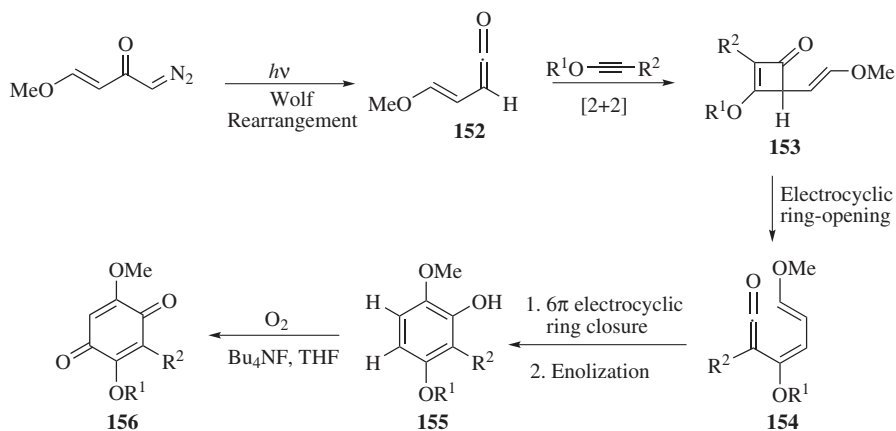
Langer and co-workers¹⁹³ reported the synthesis of functionalized *p*-benzoquinones (**159**) based on [3+3] cyclizations of 1,3-bis-silyl enol ethers (**157**) with 2-acyloxy-3-(silyloxy-2-en-1-ones) (**158**). Deprotection and oxidation of the products afforded the benzoquinones (**159**). This elegant transformation of 2-chloro-1,3-diketone is depicted in Scheme 37.



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



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

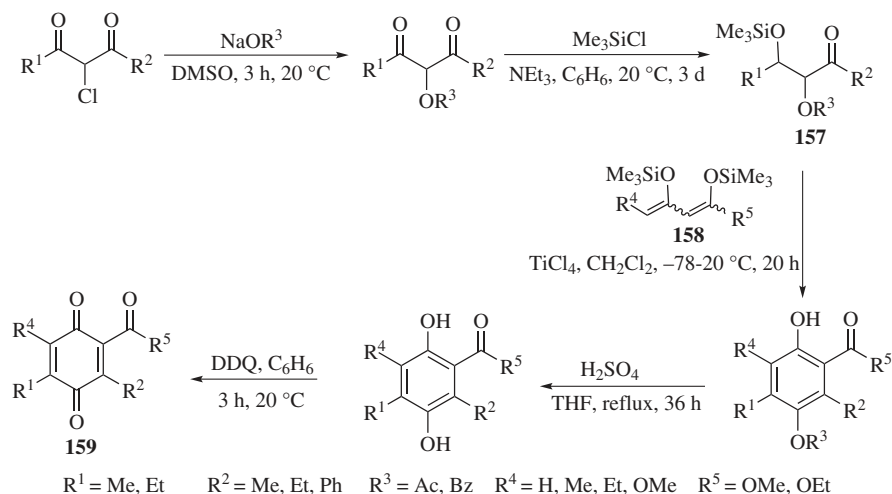


Scheme 36. Mechanism of vinylketene/alkyne cycloaddition reaction for quinone synthesis.¹⁹²

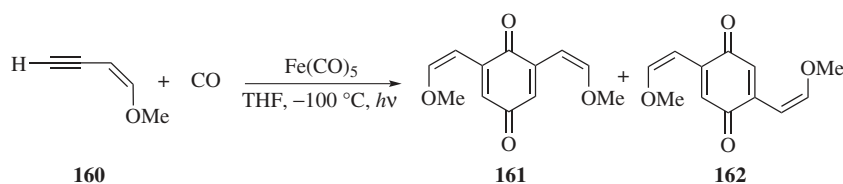
Recently Mathur *et al.*¹⁹⁴ reported a photochemically promoted one-step synthesis of 1,4-benzoquinones, which bear vinyl substituents in 2,5- and 2,6- position. Photochemical reaction between (*Z*)-1-methoxybut-1-ene-3-yne (**160**) with CO in the presence of Fe(CO)₅ yields 2,6-bis{(*Z*)-2-methoxyvinyl}-1,4-benzoquinone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

Moody and co-workers¹⁹⁵ 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).

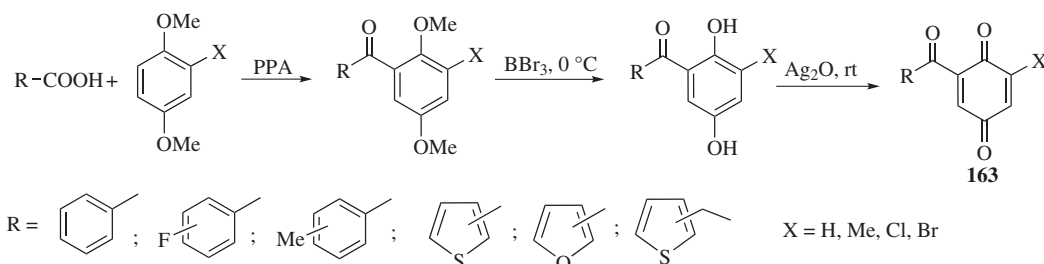
The central theme of our strategy is to attach varieties of substituents into the main skeleton, which would be transformed into a quinone moiety. It is efficiently achieved in the initial Friedel Craft's acylation step. Then successive demethylation and oxidation of hydroquinones yielded



Scheme 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-benzoquinones¹⁹⁹ and thiophenacetyl-1,4-benzoquinones.²⁰⁰

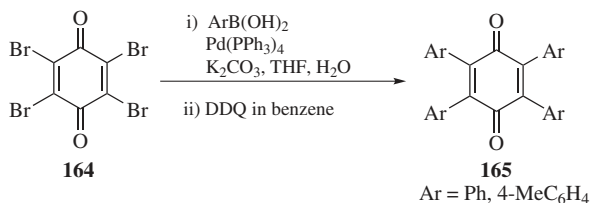
3.5 Synthesis of higher 1,4-benzoquinones derivatives by the reaction of simple 1,4-benzoquinones

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 $\text{Pd}(\text{PPh}_3)_4$ and K_2CO_3 ($\text{THF}/\text{H}_2\text{O}$, 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

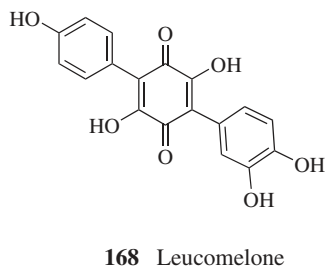
formation of pure **165** in 70% overall yield (Scheme 40). The yield could be further increased by increasing the amount of catalyst.

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.

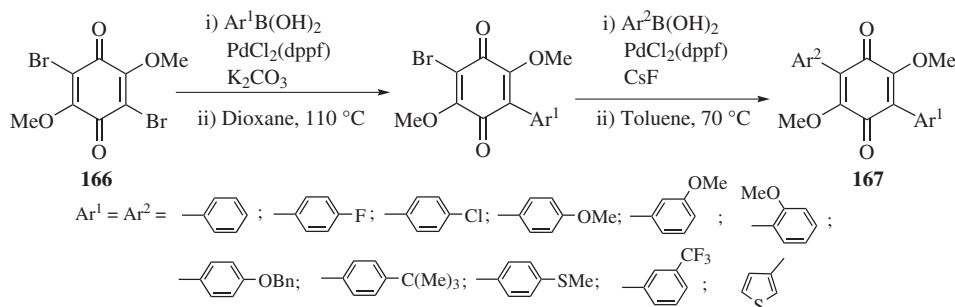
Another method was also reported by Pirrung *et al.*²⁰³ which sequentially adds indole-3-mercurials to dichlorinated quinones using palladium catalysis. These reactions can be used in the modular assembly of bis(indol-3-yl)-benzoquinones, a significant natural product family.



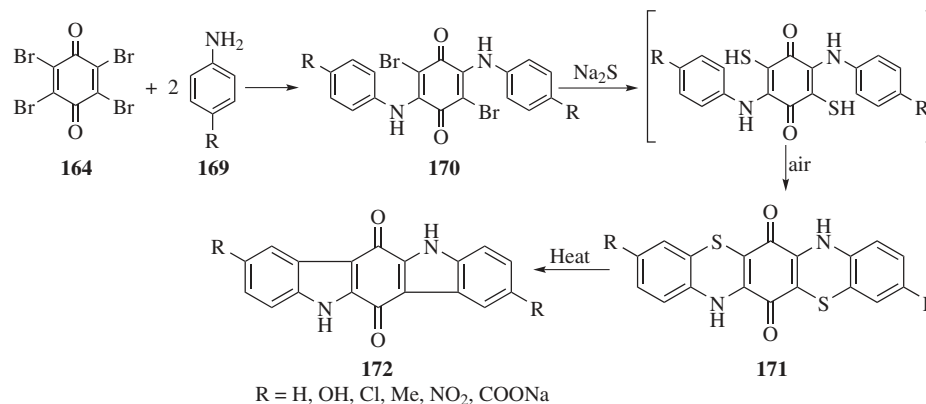
Scheme 40. Synthesis of tetraaryl-1,4-benzoquinones by Ullah *et al.*²⁰¹



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-diaryl-amino-3,6-dibromo-*p*-benzoquinones (**170**). On heating with sodium sulfate in alcohol in the presence of air gave triphenediazones (**171**). Heating with copper powder in nitrobenzene transformed those compounds into the respective indole carbazole diones (**172**) (Scheme 42).



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



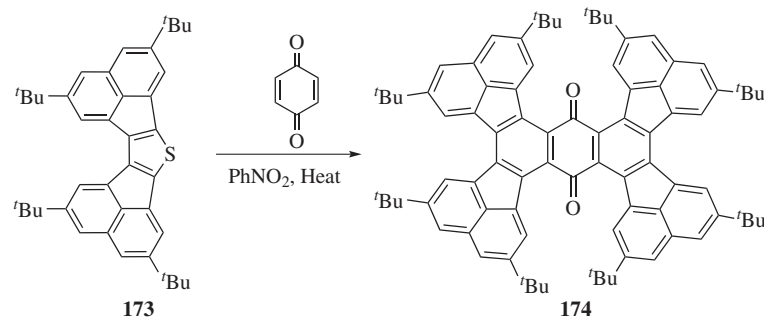
Scheme 42. Synthesis of indole carbazole diones (**172**).²⁰⁴

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 $\text{Pd}(\text{OAc})_2$ /heteropoly acid ($\text{H}_3\text{PMo}_6\text{V}_6\text{O}_{40}$) redox system with dioxygen as the final oxidant.²⁰⁶

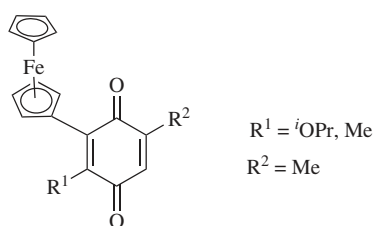
Watson *et al.*²⁰⁷ reported the synthesis of a very large quinone (**174**) by a double Diels-Alder reaction of 2,5,9,12-tetra(*t*-butyl)-diacenaphtho[1,2-*b*:1',2'-*d*] thiophene (**173**) and benzoquinone (**1**) (Scheme 43).

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

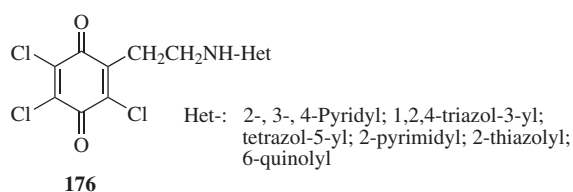


Scheme 43. Synthesis of quinone by double Diels-Alder reaction.²⁰⁷



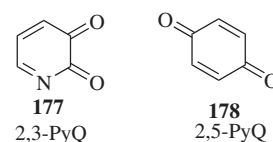
175 Ferrocenyl quinones

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

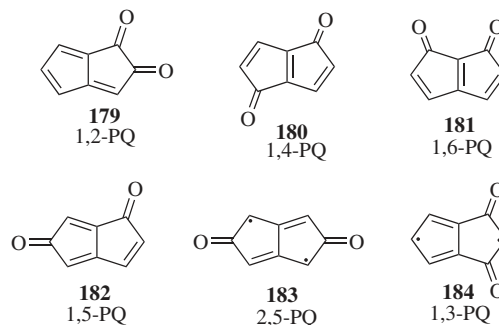


4. Computational Investigations on 1,4-Benzoquinones

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 Kovak²¹⁰ 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).

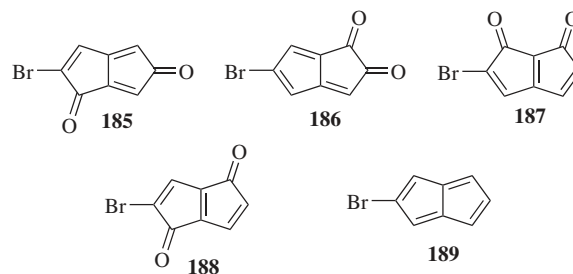


Among the possible isomers of pyridoquinones the 2,5-isomer was calculated to be the most stable. Apart from pyridoquinones, Yavari *et al.*²¹³ also modelled another interesting group of quinones, pentaloquinones (PQ) (**179-184**).



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.

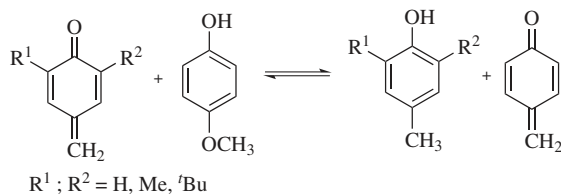
Recently Atalar *et al.*²¹⁴ extended the investigation on pentalenoquinones (PQs) to bromopentalenoquinones (**185-189**) to reveal the stability and aromatic character.



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 equation²¹⁶ (Scheme 44) shown below.

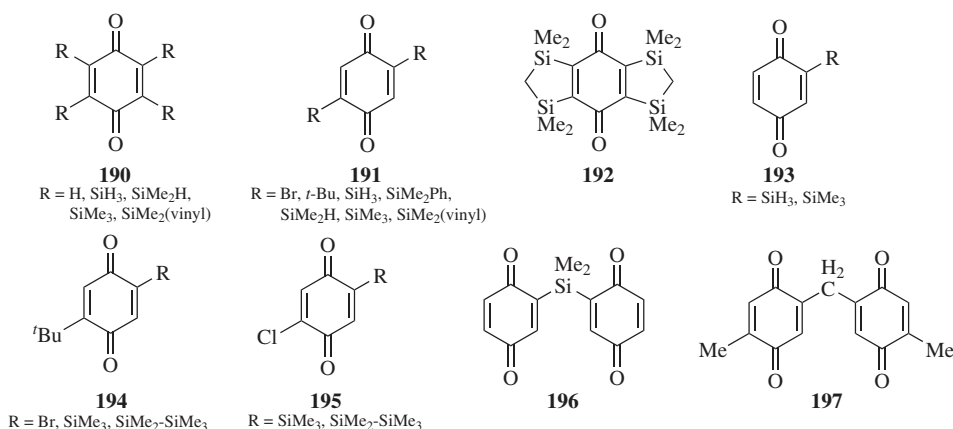


Scheme 44. Isodesmic equation to evaluate the relative stabilities of benzoquinone methides.²¹⁵

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.

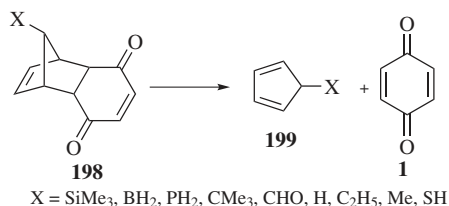
Quantum chemical calculations were also used to explain the tetrahertz time domain spectrum of several compounds satisfactorily.²¹⁹⁻²²² Recently Min *et al.*²²³ applied theoretical calculation to assign individual THz absorption spectra of the *p*-quinones with semiempirical AM1, hartree-fock (HF) and 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.

Bangal²²⁸ 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

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

Patil and Sunoj²³⁰ 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).

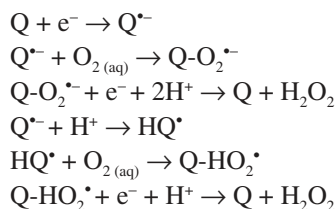


Scheme 45. Retro Diels-Alder reaction studied by Patil and Sunoj.²³⁰

The transition state study on the cycloreversion reaction demonstrated that $-\text{SiMe}_3$ 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.

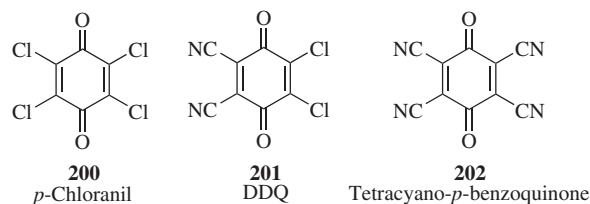


Scheme 46. Quinone mediated reduction of oxygen to peroxide.

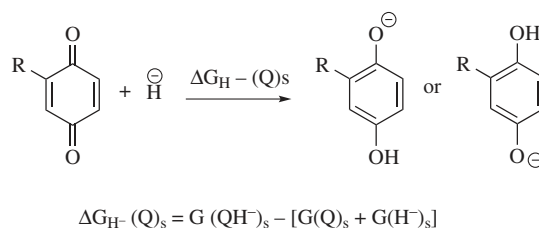
DFT-B3LYP level study was done to map the course of the reaction constituting the above steps.

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).



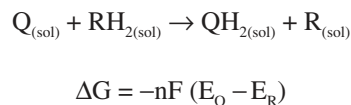
Scheme 47. Reaction of quinone with a free hydride ion and the corresponding free energy change.²³⁵

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).

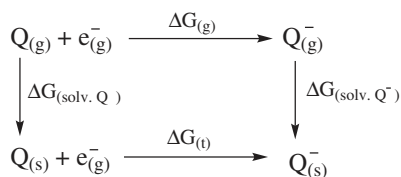


Scheme 48. Reduction of quinone and the corresponding free energy change.

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 Almodarresieh²⁵⁶ 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).

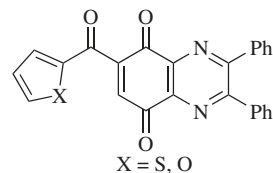


Scheme 49. Thermodynamic cycle designed to calculate $\Delta G^0_{(t)}$ of one-electron reduction.²⁶²

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 synthesis²⁶³⁻²⁶⁵ 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

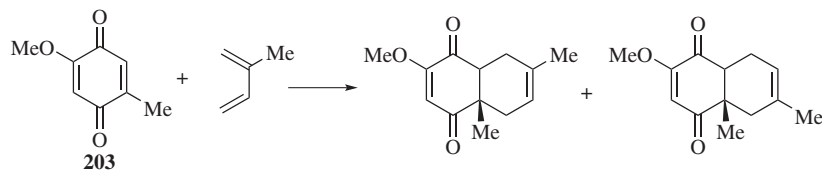
Results of the computational study revealed that by choosing appropriate diene such as electron-withdrawing diene, it is possible to reverse the course of Diels-Alder cycloaddition from quinonoid ring to the heterocyclic moiety.

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

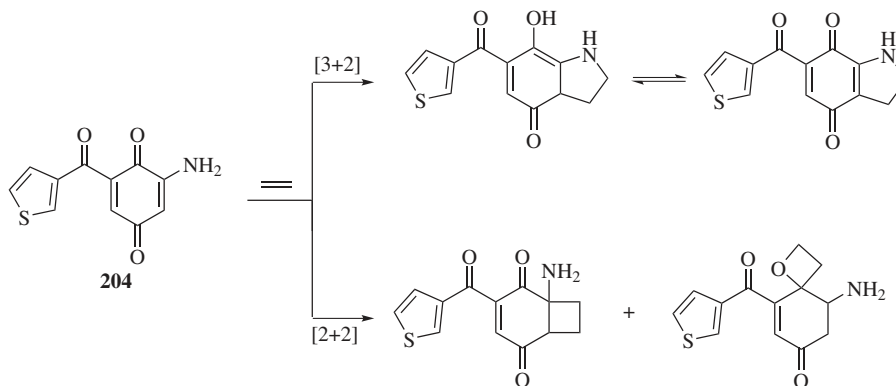
The theoretical results obtained by DFT-B3LYP level calculation provided a useful tool for the interpretation of the reaction mechanisms. Transition state studies showed that there is a larger activation barrier associated with the uncatalyzed processes.

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'-thienyl)-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

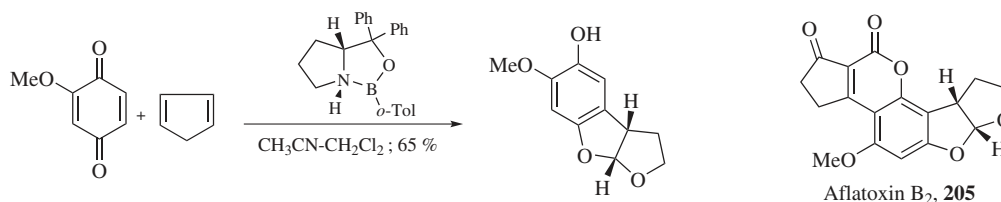
5. Cycloaddition Reactions of 1,4-Benzoquinones

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} (cortisone²⁷⁸ and estrone²⁷⁹), reserpine,^{280,281} yohimbine,²⁸² and terramycin.²⁸³ The [2+2]-cycloadditions involving quinone reactant and

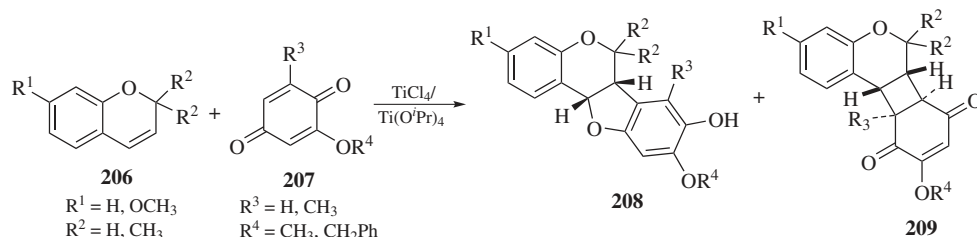
leading to cyclobutane have been reported abundantly in the literature.²⁸⁴ Engler *et al.*^{285,286} have reported Ti(IV) promoted [2+2] cycloaddition between propenyl benzenes and 1,4-benzoquinones. Neville and Murphy²⁸⁷ reported [2+2] cycloaddition of dihydrofuran with 1,4-benzo- and naphthoquinones 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 Corey²⁸⁹ 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 B₂ (**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



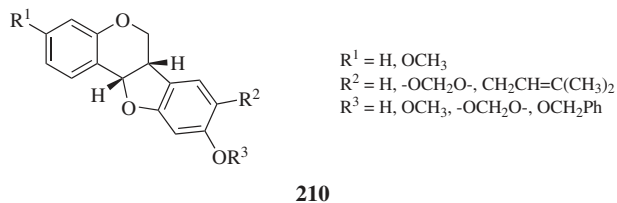
Scheme 52. Novel enantioselective [3+2] addition of 1,4-benzoquinones by Corey *et al.*²⁸⁹



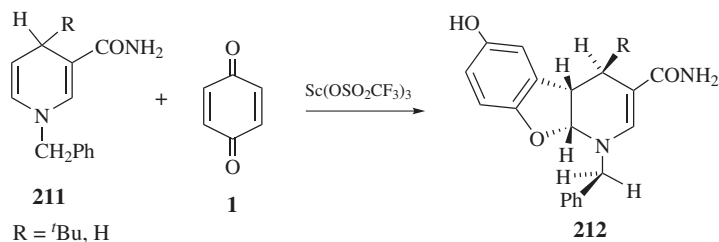
Scheme 53. [2+2] and [3+2] Cycloadditions of **206** and **207** by Engler *et al.*²⁹¹

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 pterocarpan (**208**) were found to be the major product, instead of the [2+2] cycloadducts, cyclobutanes (**209**).

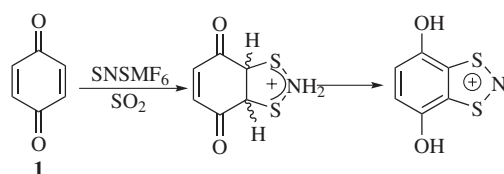
The synthetic utility of these cycloaddition reactions has been demonstrated by the synthesis of different antimicrobial pterocarpan phytoalexins (**210**).



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 $\text{Sc}(\text{OSO}_2\text{CF}_3)_3$ in deaerated acetonitrile



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



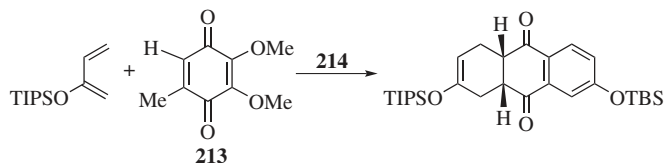
Scheme 55. Pseudo-1,3-dipolar cycloaddition of SNSAsF₆ with 1,4-benzoquinone.²⁹⁴

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

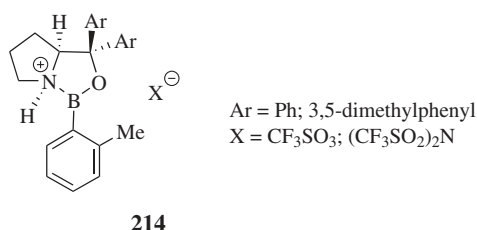
The extreme enthusiasm in the [3+2] cycloaddition reactions led to the emergence of very interesting pseudo-1,3-dipolar cycloaddition chemistry. Passmore and co-workers²⁹⁴ identified this pseudo-1,3-dipolar cycloaddition as a powerful tool for accessing a variety of mono- and bi-functional 6π heterocyclic 1,3-dithiazolium cations. They reported the unprecedented formation of a benzo-fused 1,3,2-dithiazolium $[\text{AsF}_6^-]$ salt by a one step quantitative cycloaddition of SNSAsF₆ 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 works³⁰⁶ have reported an enantioselective and structure-

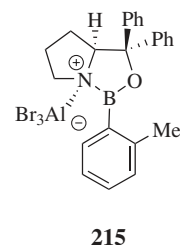


Scheme 56. Diels-Alder reactions of unsymmetrical quinones by Corey *et al.*³⁰⁶

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.



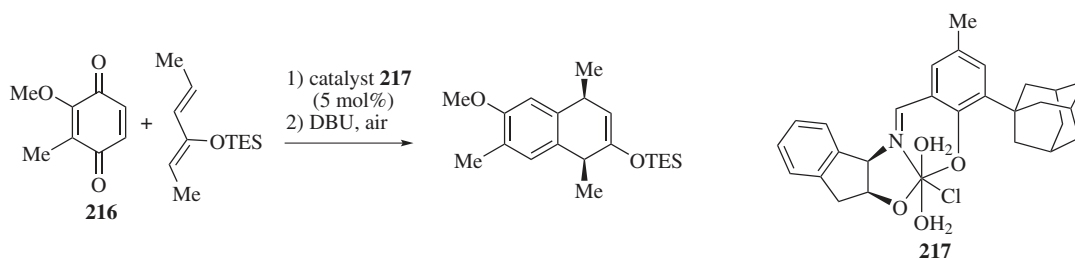
Another glorious achievement of this group using the chiral catalyst (**214**) has been the transformations of some of the classical synthesis of racemic natural products.³⁰⁷ Hence the enantioselective versions of the Sarett's total synthesis of cortisone, Kende's total synthesis of dendrobine, Chu-Moyer/Danishefsky synthesis of (±)-myrocin C and Mehta's synthesis of (±)-triquinanes have been accomplished with excellent yields. Later Corey and co-workers³⁰⁸ 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.



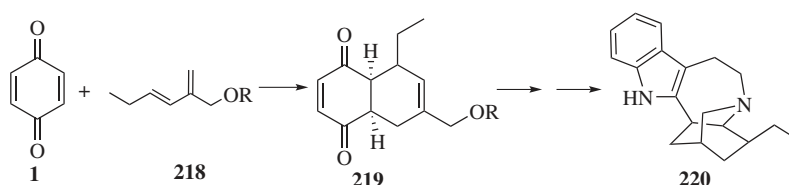
Jarvo *et al.*³⁰⁹ discovered a highly enantio- and regioselective Diels-Alder reaction of quinones (**216**) which is also catalyzed by a new, monomeric tridentate [(Schiff base)Cr^{III}] complex (**217**) (Scheme 57).

White and Choi³¹⁰ 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 (**218**) in the presence of a chiral catalyst, (S)-BINOL-TiCl₂ to give for the adduct (**219**), which on subsequent reactions yielded (**220**) (Scheme 58).

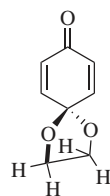
Masked 1,4-benzoquinones (**221**) are quinones in which a carbonyl group is masked by converting into monoketals. The monoketals of *p*-benzoquinones have been used as starting materials for the synthesis of a wide range of bioactive natural products including antitumor



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



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

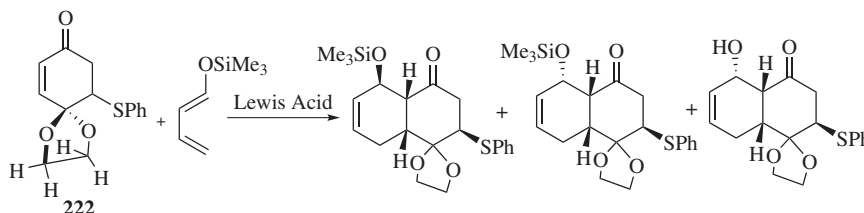


221

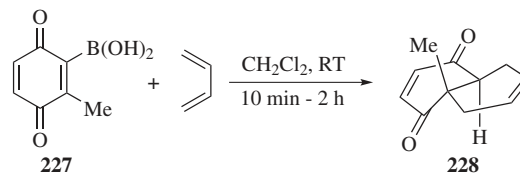
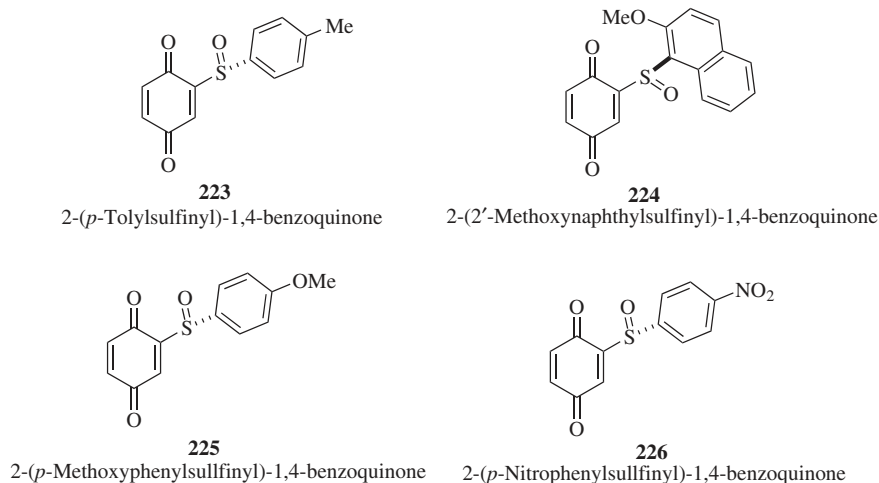
antibiotic LL-C10037a.³¹¹⁻³¹³ March *et al.*³¹⁴ reported that phenylthiomonoketal (**222**) works efficiently as a masked *p*-benzoquinone in Diels-Alder reactions. These cycloadditions may be performed with certain Lewis acid catalyst like ZnBr₂ and give rise exclusively to *endo* adducts with a good 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 colleges³¹⁶ 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).

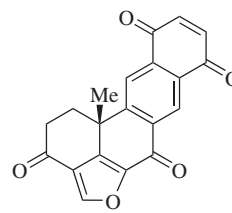


Scheme 59. Diels-Alder reaction of masked benzoquinone **222** reported by March *et al.*³¹⁴



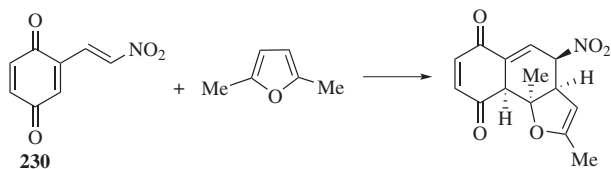
Scheme 60. Diels-Alder reaction of boronic acid substituted quinone reported by Carreno and colleges.³¹⁶

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 colleges³¹⁷ demonstrated the viability of vinyl quinones in Diels-Alder reactions. They utilized this strategy to synthesize medicinally significant (-)-halenaquinone (**229**).



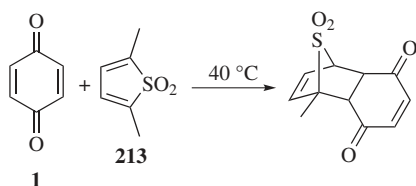
229

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



Scheme 61. Cycloaddition of vinylnitroquinone with furan.^{318,319}

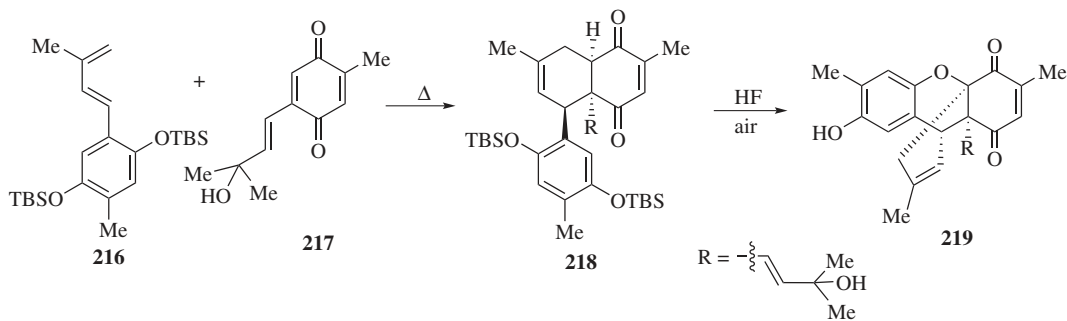
Kang *et al.*³²⁰ studied a specific Diels-Alder reaction of 1,4-benzoquinone (**1**) with a thiophene dioxide derivative (**213**) catalyzed by a self assembled molecular capsule (Scheme 62).



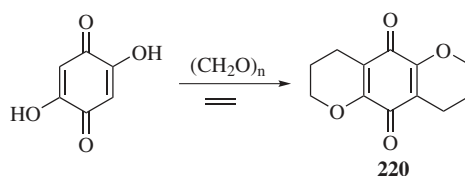
Scheme 62. Diels-Alder reaction of 1,4-benzoquinone with thiophene dioxide by Kang *et al.*³²⁰

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).

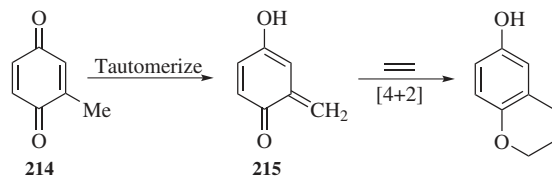
Stratakis and co-workers³²² reported an efficient biomimetic route to acremine G (**219**) featuring a highly regioselective and stereoselective Diels-Alder reaction between a TBS-protected hydroquinone diene (**216**) and a structurally related alkenyl quinone (**217**). The *endo* [4+2] cycloadduct (**218**) slowly transforms to acremine G (**219**)



Scheme 64. Synthesis of acremine 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 63. Intramolecular Diels-Alder cycloaddition of 1,4-benzoquinone by Trauner and co-workers.³²¹

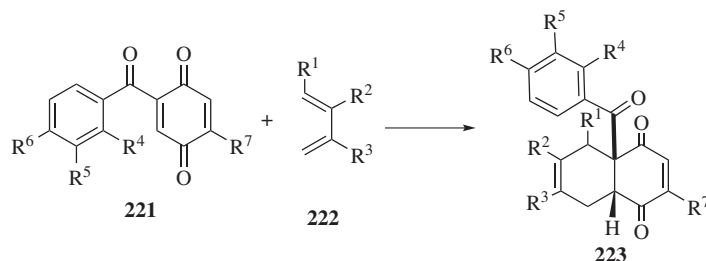
by the atmospheric air under deprotection conditions (Scheme 64).

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.

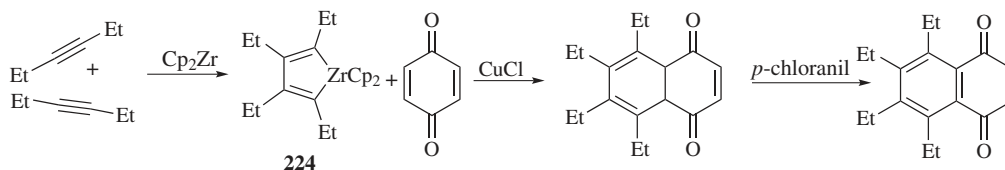
Pardasani *et al.*³²⁴ studied the base-induced benzoyl migrations in Diels-Alder adducts of benzoyl-1,4-benzoquinones. Later, we carried out the Diels-Alder reaction of some fluorinated *p*-benzoquinones (**221**) with substituted dienes (**222**) furnishing the adducts 4a,5,8,8a-tetrahydro-1,4-naphthaquinones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

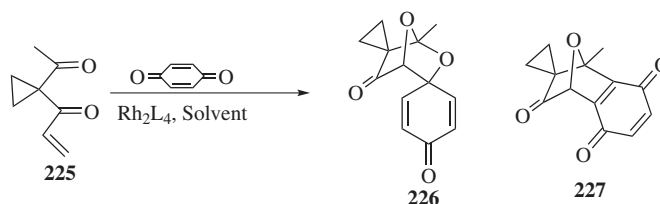
Chen *et al.*³²⁸ achieved a typical cycloaddition reaction of zirconacyclopentadiene (**224**) to various quinones leading to a 6-membered adduct (Scheme 67).



Scheme 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



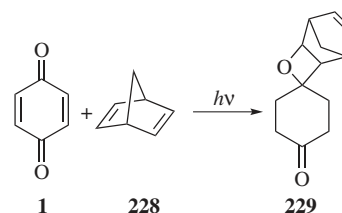
Scheme 68. Dipolar cycloaddition reaction carbonyl ylides with *p*-benzoquinones.³²⁹

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.

Pirring and Kaliappan³²⁹ 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 substances³³⁰⁻³³⁴ 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 derivatives³³⁸⁻³⁴⁰ and Paterno-Buchi adducts³⁴¹⁻³⁴³ respectively, depending on the identities of the quinone as well as the alkenes. We studied³⁴⁴ the photocyclisation of benzoyl-1,4-benzoquinones leading to xanthenes and phenyl gentisate esters while pursuing studies on the synthesis of anthracyclinones and heteroanthracyclinones.

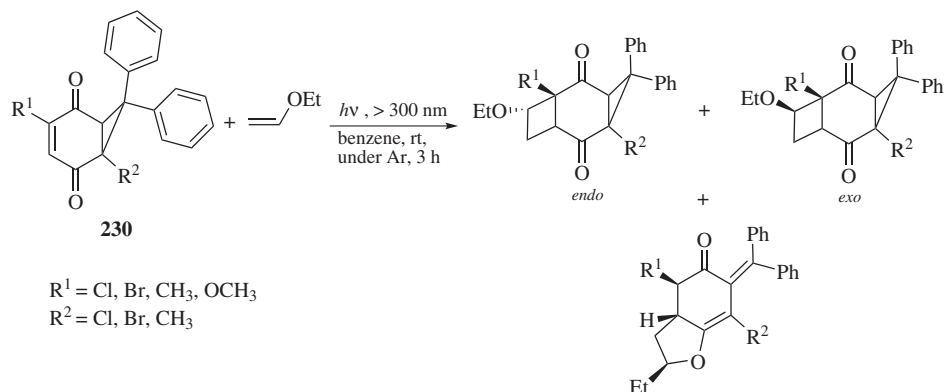
Bryce-Smith *et al.*³⁴⁵ reported the photoaddition of 1,4-benzoquinone (1) to norbornadiene (228) to give the spirooxetane (229) in 22% yield (Scheme 69).



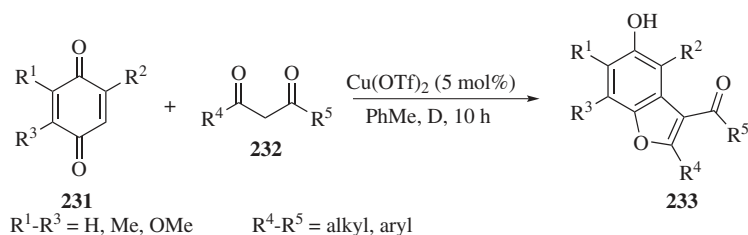
Scheme 69. Photoaddition of 1,4-benzoquinone (1) to norbornadiene.³⁴⁵

Oshima and co-workers³⁴⁶ 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

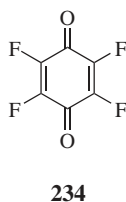


Scheme 71. Cycloadditions 1,4-benzoquinones with 1,3-dicarbonyl compounds by Mothe *et al.*³⁴⁷

6. Pulse Radiolytic Studies on 1,4-Benzoquinones

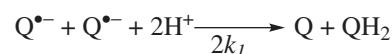
Pulse radiolysis is a method of studying fast chemical reactions in which a sample is subjected to a pulse of ionizing radiation, and the products formed by the resulting reactions are studied stereospecifically.³⁴⁸ Pulse radiolysis technique has been used extensively by several groups to study the electron 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 Hayon³⁵⁸ 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 Mittal³⁵⁹ carried out pulse radiolysis study of one-electron reduction reaction of fluoranil (**234**) in aqueous solution.



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

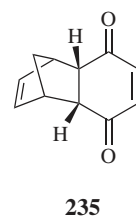
Bors and co-workers³⁶⁰ investigated the disproportionation of semiquinones ($Q^{\bullet-}$) when other reactions are hindered (Scheme 72).



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**).



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.



R. T. Pardasani received his MSc and PhD from the University of Rajasthan. From 1979 he was a post-doctoral fellow at the University of Manchester and earned another PhD degree on synthetic organic chemistry. In 1984 he moved to the University of Wales, Swansea to work under supervision of Professor A. Pelter on Organoboron Chemistry. He joined the Faculty of Rajasthan University in 1986. R. T. Pardasani is the recipient of INSA, New Delhi Visiting Fellowship (1995), G. Srivastava Memorial Award of the Indian Chemical Society (1966), and Royal Society Study Fellowship (1999), SERC Research Officer (Swansea University, UK 2005-2006). His principal research interests are in the area of synthetic organic and photochemistry, heterocyclic and theoretical chemistry.



Pushpa Pardasani received her BSc, MSc and PhD degrees from the University of Rajasthan. From 1980-1981 and later from 1984-1985 she worked as post-doctoral fellow with Professor A. Pelter at the University of Wales Swansea on organoboron compounds. Recently she delivered invited talk at 22nd ICHC (St. John's Canada, August 2009). She joined the Faculty of Rajasthan University in 1985. Her research interests include synthetic, structural, mechanistic organometallic chemistry, heterocyclic chemistry and pulse radiolytic studies. In addition she teaches at University Maharani's College, Jaipur.



Rahul Joshi obtained his BSc degree from St. Stephens College, New Delhi and did his masters from IIT, Kanpur. In 1996, he joined the faculty of Rajasthan University as an Assistant Professor. His area of research includes heterocyclic chemistry, chemical and distance education. He has published 25 research papers in various journals. He is also a former associate editor of the Journal of Indian Chemical Society.



Ignatious Abraham received his BSc and MSc degrees from the Mahatma Gandhi University, Kottayam, Kerala. He is currently working as senior research fellow (CSIR) under the guidance of Dr. R. T. Pardasani at the University of Rajasthan, Jaipur. His area of research includes the synthetic and theoretical studies on the photocycloaddition of 1,4-benzoquinones and the pulse radiolytic investigations of quinones.

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Submitted: March 8, 2010

Published online: January 6, 2011