Chapter – 1

Introduction

1 Introduction

1.1 Chemistry

The study of matter's composition, structure, and properties that can be most effectively explained and characterized in terms of these fundamental components of the matter is the subject matter of chemistry, which is also known as the science of atoms and molecules. Chemistry is the branch of science that has uncovered information on the structure of objects as well as their characteristics and reactivity. All facets of our daily lives are affected by chemistry. Chemistry has made a significant contribution to the advancement of medical, agricultural, industrial, and other technology. Particularly, researchers from all over the world have developed a keen interest in the chemistry subfield known as organic chemistry.

The study of carbon-containing compounds, including their characteristics, syntheses, and reactions, is known as organic chemistry. In addition to hydrocarbons, organic molecules can also contain nitrogen, oxygen, halogens, sulphur, phosphorus, and other elements in addition to carbon and hydrogen atoms. Because of this, organic chemistry includes both naturally occurring and artificially created molecules. Thus, organic chemistry demonstrates its uses in the petrochemical, food, paint, and other chemical-based sectors. Organic chemists frequently try to make new molecules and investigate more effective techniques to make already well-known substances.

1.2 What is Quinone?

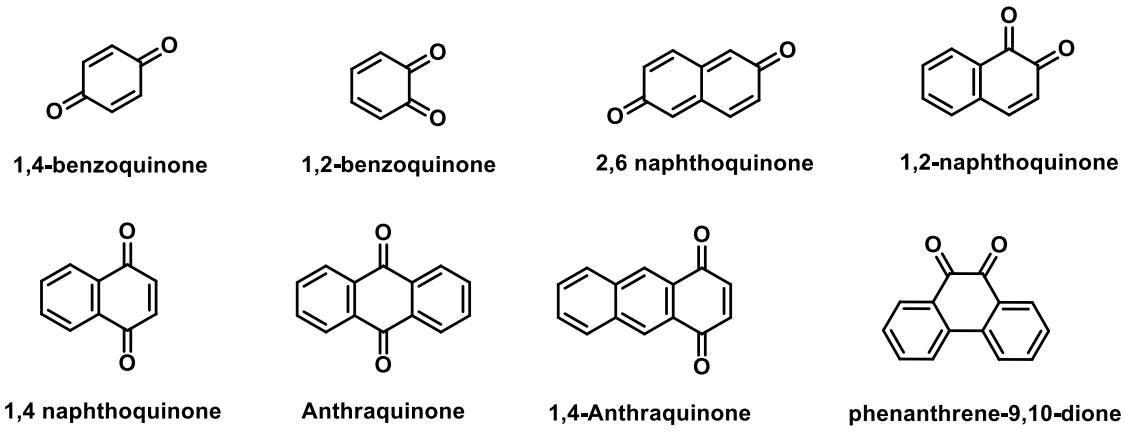
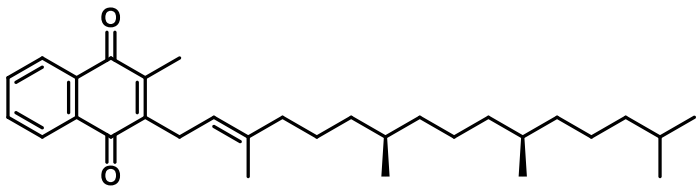


Figure 1.1 Chemical structure of quinones

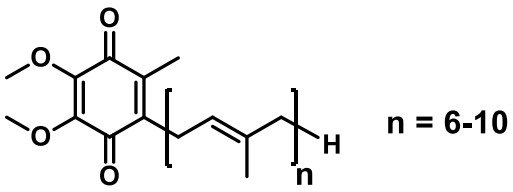
Quinone represents a class of quinoid organic compounds bearing two carbonyl oxygen atom and is widely distributed in nature. Over 1,200 quinones have been reported so far. Quinones are categorized by their common structural pattern that is shared by all of them, such as para or ortho-substituted dione attached to either an aromatic nucleus (benzoquinones) or a condensed polycyclic aromatic system like naphthalene, phenanthrene, or anthracene. In nature, 1,4 or para-substituted quinones have more abundance than 1,2 or ortho quinones [1–4] **(figure 1.1)**

1.3 Occurrence and medicinal applications of quinones

Quinones are widely abundant in nature and can be found in plants, animals, and microbes. Quinones frequently serve as crucial linkages in the biochemistry of energy production in living cells. Coenzyme Q serves as an electron transporter in the respiratory chain, while vitamin K_1 is necessary for blood coagulation [5,6] **(figure 1.2)**



Vitamin K_1



Coenzyme Q or Ubiquinones

Figure 1.2 Natural quinones involved in the biochemical process

Nearly four decades ago, the National Cancer Institute (NCI-USA) conducted important investigations on several synthetic and natural quinones that demonstrated anticancer potential. Important sources of anticancer drugs include both naturally occurring quinones and their analogs.

Numerous synthetic and natural product based drugs used in clinical trials for various diseases include daunorubicin, doxorubicin, epirubicin, idarubicin, streptonigrin, valrubicin, mitoxantrone, amentantrone, pirarubicin, bleomycin, dactinomycin, and mitomycin [7–11] **(figure 1.3).**

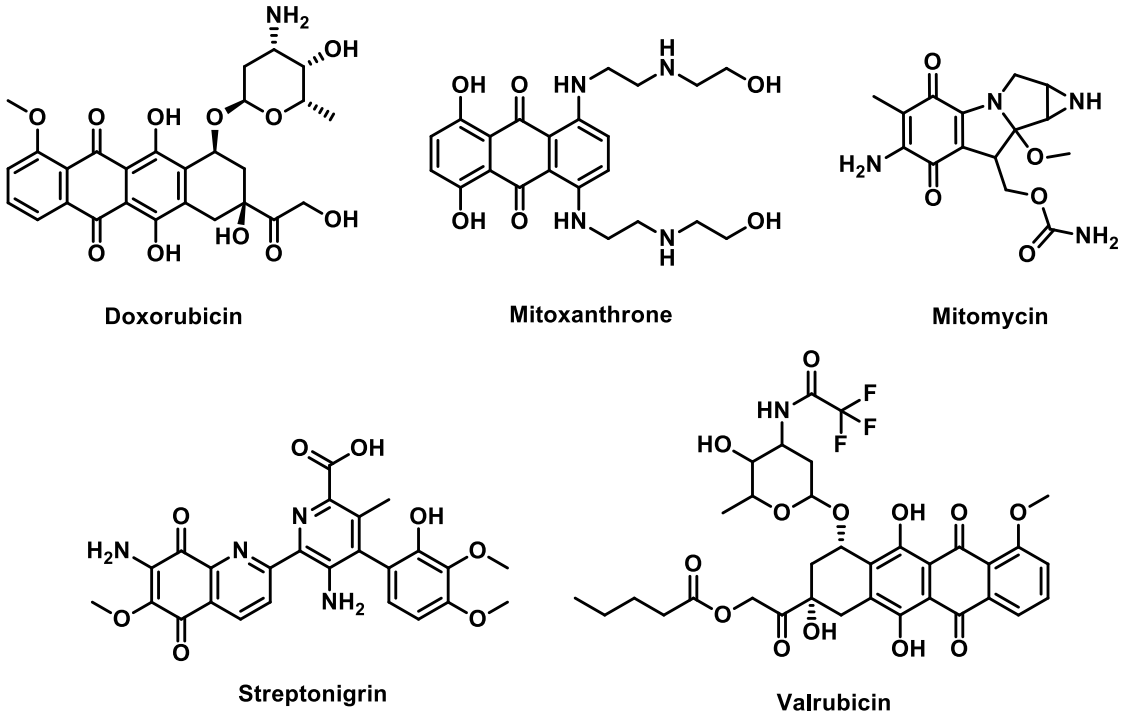


Figure 1.3 Examples of natural and synthetic quinone based drugs

The 1,4-naphthoquinones are the most stable and significantly used in the quinone family for various biological activities [12]. Their derivatives have demonstrated a wide range of biological properties including anti-inflammatory, anti-bacterial, anti-fungal, anti-allergic, antithrombotic, lipoxygenase, antiplatelet, antiviral, radical scavenging, and anti-ringworm properties. The 1, 4-naphthoquinones have also been found to have anticancer activity [13–22] **(figure 1.4).**

These compounds are regarded as favored structures in medicinal chemistry due to their biological activity and structural characteristics. The clinical significance of quinones and naphthoquinones has sparked intense interest among researchers due to their involvement in numerous physiological and toxicological processes.

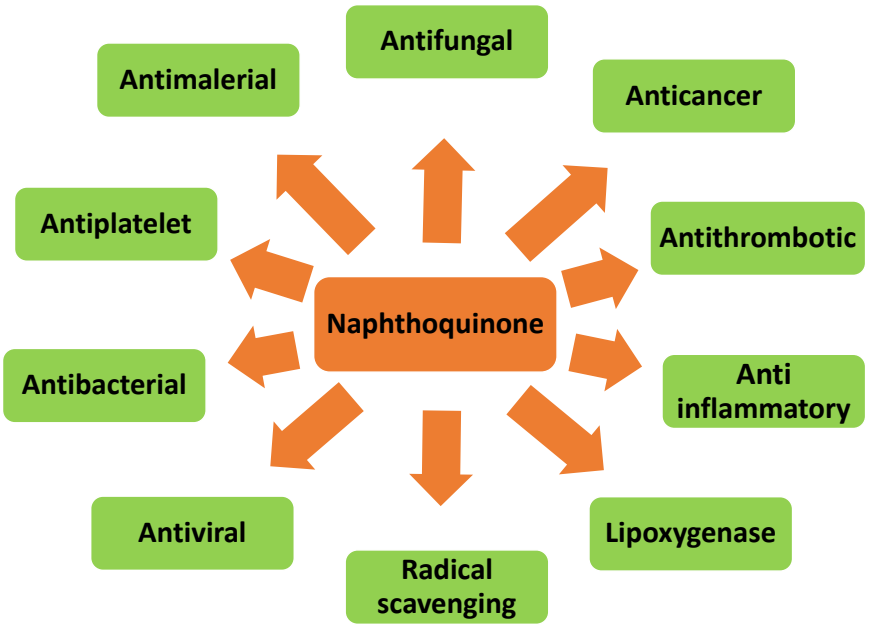
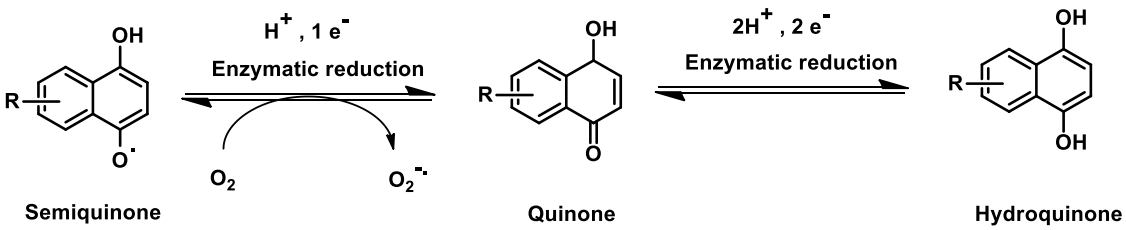


Figure 1.4 Various biological activities exhibited by naphthoquinones

Understanding quinone's intrinsic chemical reactivity is important for comprehending both their physiological and toxicological characteristics. The p-quinone moiety in these compounds functions as a precursor for the formation of Reactive Oxygen Species (ROS). Quinones' ease of reduction and consequent capacity to function as oxidising or dehydrating agents are primarily blamed for the mechanism behind their cytotoxicity. Quinones can undergo one or two electron reductions in biological systems via cellular reductases, resulting in the corresponding semiquinones or hydroquinones, respectively [23,24].



Scheme 1.1 Schematic for the transformation of quinone to semiquinone and hydroquinone

One or two electron reductions start the redox cycling of naphthoquinones. Semiquinone is produced by a one electron reduction, while the comparable hydroquinone is produced by a two electron reduction. Equilibrium exists between quinone and hydroquinone. Under aerobic conditions, the semiquinone can be oxidised by molecular oxygen to the original quinone. Quinone redox cycling is the name given to this reduction by reductase and auto oxidation mechanism [25–27] **(scheme 1).**

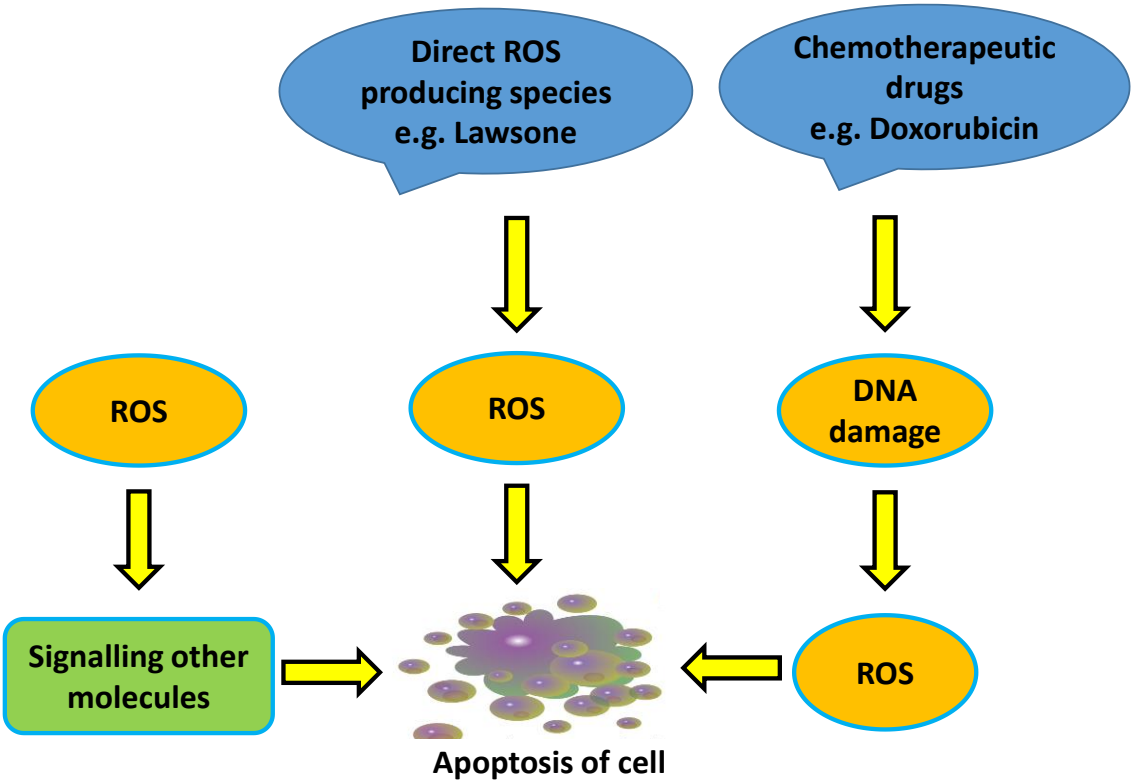


Figure 1.5 Mechanism of death induced by cell ROS

Flavoenzymes like cytochrome P 450 reductase or cytochrome b_5 reductase use NADPH as an electron source to catalyse the one electron reduction, which produces unstable semiquinone radicals. While The enzyme NAD(P)H: quinone oxidoreductase (NQO1, DT-diaphoresis) catalyses the two electron reduction, which results in hydroquinones. These hydroquinones can be excreted and have a low propensity to transmit electrons and detoxification generally results from two electron reduction. However, in rare instances, quinone undergoes a two-electron reduction to yield a reactive hydroquinone form that has stronger pharmacological activity than the parent quinone, such as mitomycin C [28].

The electron-donating and electron-withdrawing substituents linked to the naphthoquinone ring can change the ability to receive one or two electrons to generate the corresponding semiquinone and hydroquinone. ROS-induced cell death is a direct technique that is being used. Most significantly, naphthoquinones are preferred structures in medicinal chemistry due to their biological activity and structural characteristics [29–32] **(figure 1.5)**

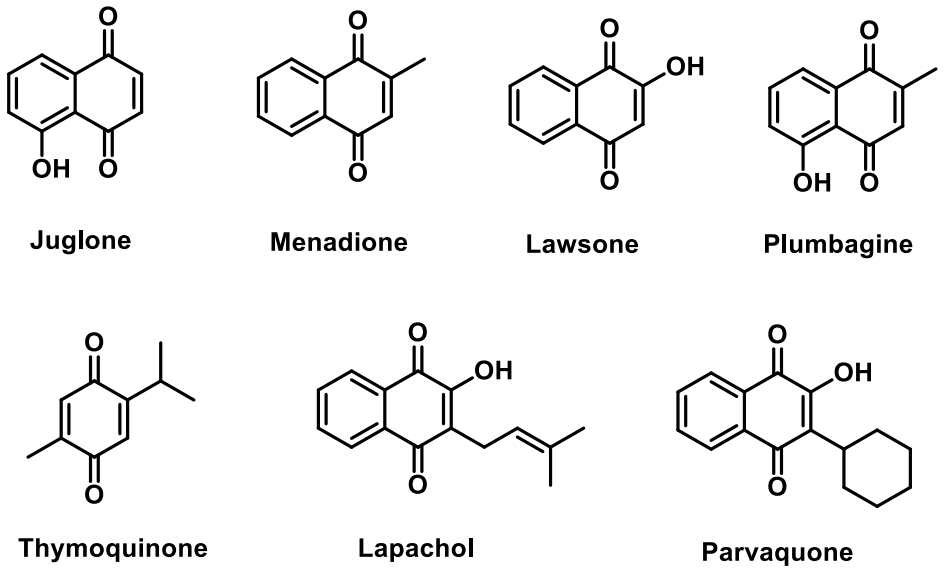


Figure 1.6 Important derivatives of naturally occurring 1, 4-napththoquinone

Recently, important derivatives of naturally occurring 1,4-naphthoquinones such as Lawsone, Plumbagin, Juglone, Menadione, Thymoquinone, Lapachol, and Parvaquone have gained considerable attention due to their interesting biological activities including anticancer activity [33–41] **(figure 1.6)**

1.4 Lawsone (2-hydroxy-1,4-naphthoquinone)

The position of the hydroxy group in naphthoquinone compounds is crucial to their biological activity as it affects redox potential [42,43]. 2-hydroxy-1,4-naphthoquinone or Lawsone or hannotanic acid is one of the simplest naturally occurring naphthoquinone. The extract of dried, powdered leaves of henna (*Lawsonia* spp., family Lythraceae), a branching shrub or small tree with grayish-brown bark, can be used to create this reddish-orange pigment known as Natural Orange 6 (C.I.75480) [44]**(figure 1.7)**

It has historically been used to dye wool, cotton, and nails, as well as to colour hair. In addition, it has numerous other applications, such as oxidising chlorinated compounds,

protecting skin from UV radiation, inhibiting corrosion in steel, and acting as a sensitive colorimetric and electrochemical anions sensor [45–49]. Additionally, it interacts with the latent amino acids that are deposited with fingerprints on paper surfaces. It results in a sharp, detailed, photoluminescent purple brown impression [50].

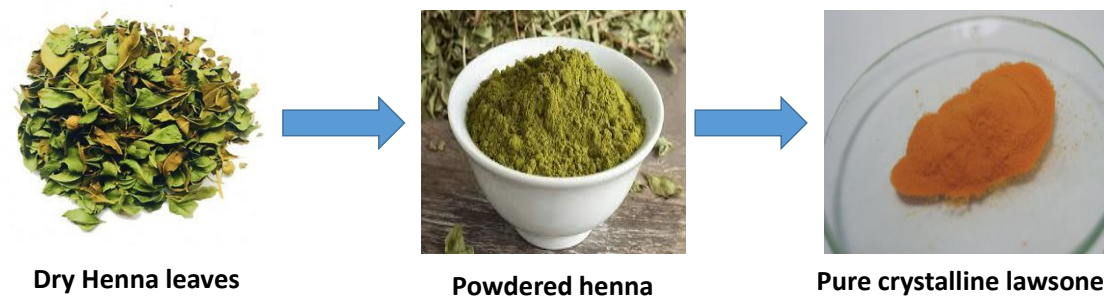
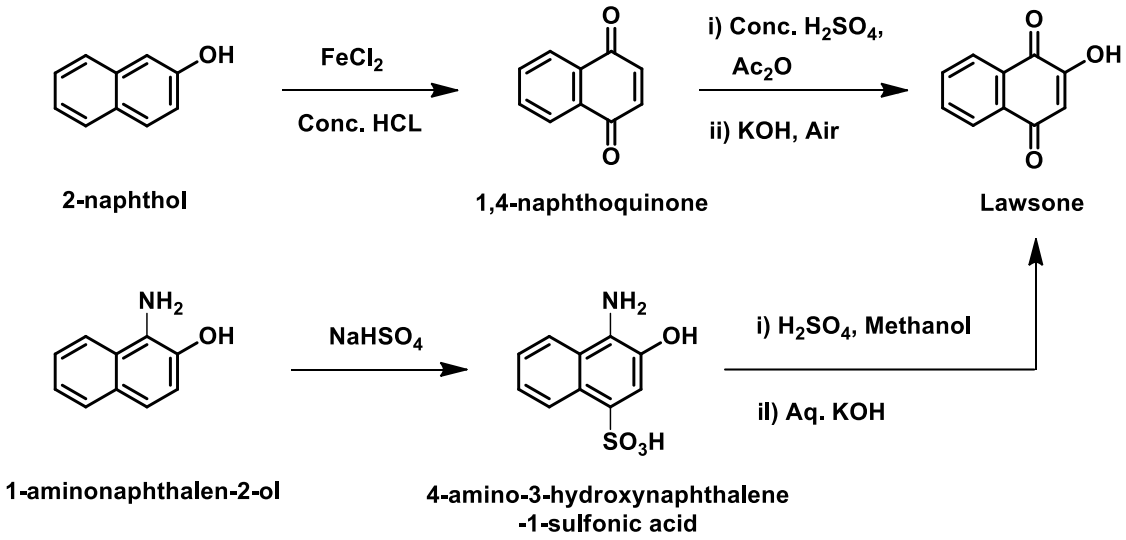


Figure 1.7 Graphical representation for extraction of lawsone from henna leaves

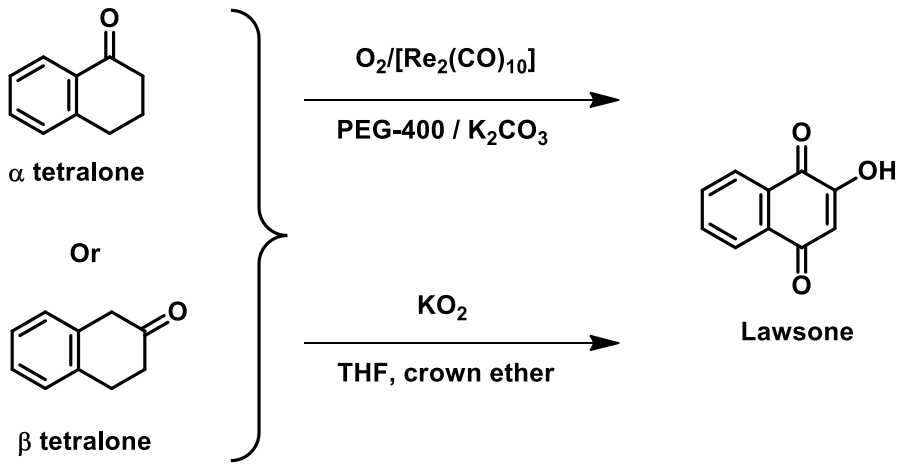
As demonstrated in **figure 1.7**, lawsone can be easily extracted from dried henna leaf powder and is also simple to manufacture. For the synthesis of lawsone, many techniques have been published in the literature. These techniques either rely on the de novo synthesis of the naphthoquinone system or the utilization of naphthalene derivatives as starting materials. The two approaches are sometimes complementary.

Naphthalene yields several naphthol derivatives that are simple to produce, making them the most practical starting materials for the production of lawsone. Five decades ago Louis F. Fieser and co-workers have developed methods to synthesize lawsone using naphthols and amino naphthols **(scheme 1.2)**. It involves the reaction of 2-naphthol with a solution of ferric chloride hexahydrate in strong hydrochloric acid, to give 1,4-naphthoquinone. Which was transformed to 1,2,4-trihydroxynaphthalene triacetate by reaction with acetic anhydride-sulfuric acid followed by hydrolysis gives Lawsone. Similarly, a different starting material 1-amino-2-naphthol has been used to create 1-amino-2-naphthol-4-sulfonic acid. Which on treatment with concentrated sulphuric acid followed by hydrolysis in aqueous sodium hydroxide solution gives Lawsone. Lawsone can be produced utilising this sequence beginning with 2-naphthol [51,52].



Scheme 1.2 Synthesis of Lawsone from naphthols

In recent times, numerous new, more advantageous, and sustainable techniques have been created as a result of the development of "green chemistry," which was created in response to the requirement to reduce the environmental impact of the traditional chemical processes. Scientists have developed different catalysts that selectively converts 2-naphthols to lawsone with good yield [53,54]. These methods are environmentally benign and relatively cheap.



Scheme 1.3 Synthesis of Lawsone from tetralone

Lawsone can also be synthesized by oxidizing tetralones by using Thomson's autoxidation process, which involves the use of catalytic quantities of rhenium carbonyl, polyethylene glycol (PEG400), potassium carbonate, and potassium superoxide in THF with crown ether [55] **(scheme 1.3).** Recently, in the entire synthesis of β-lapachones

modified on the aromatic ring, Ashwell et al. converted substituted tatetralones into hydroxy-naphthoquinones using Thomson's oxidation technique[56].

1.5 Lawsone derivatives and metal complexes

Lawsone is a unique naphthoquinone that has several uses in numerous branches of science and technology. It has been utilized as a starting point for the synthesis of numerous biologically active chemicals and materials with intriguing features for more than 100 years. It has been employed in numerous processes in organic synthesis. A few selected compounds with various biological activities such as anticancer, antifungal, antibacterial, parasitic, antiplatelet, and antioxidant derived from Lawsone in recent years are shown in **figure 1.8** [16,21,29,57,58].

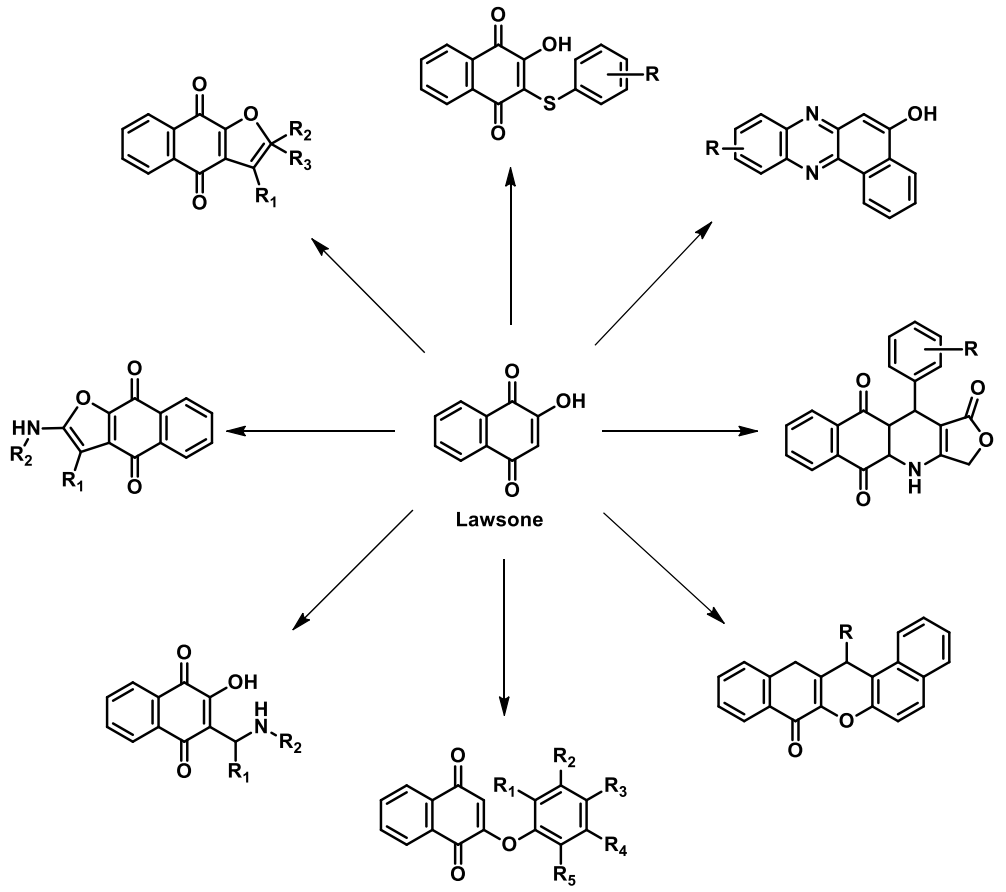
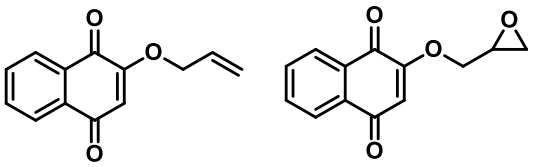
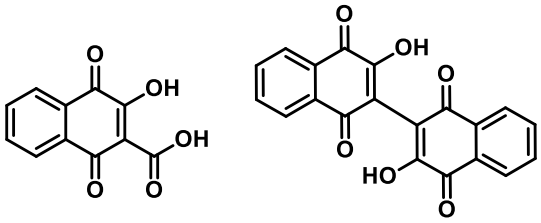


Figure 1.8 Lawsone derivatives with biological activities

As described earlier, apart from biological activities, lawsone and its derivatives also have applications in material science. Recently, Christine E. and co-workers have synthesized lawsone derivatives as efficient photopolymerizable initiators for free radical, cationic photopolymerization, and thiol ene reaction [59] **(figure 1.9 a)**.



(a) Lawsone derivative as photopolymeriztion initiators



(b) Lawsone derivative as organic electrolyte for aqueous organic flow batteries

Figure 1.9 Applications of lawsone derivatives in material science

A fast-charging, high-capacity, recyclable tetrakis lawsone cathode material for lithium-ion batteries made from naturally occurring henna (i.e lawsone) was created by Mikhail Miroshnikov and colleagues. Tetramers made from lawsone offer a promising cathode material for environmentally friendly and recyclable lithium-ion batteries[60] **(figure 1.10).**

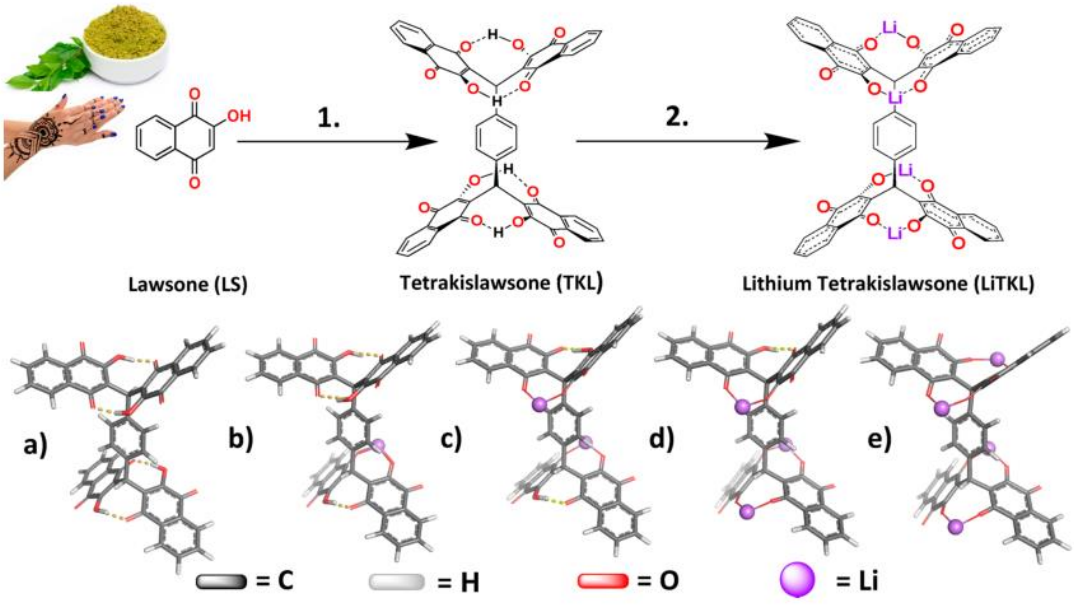
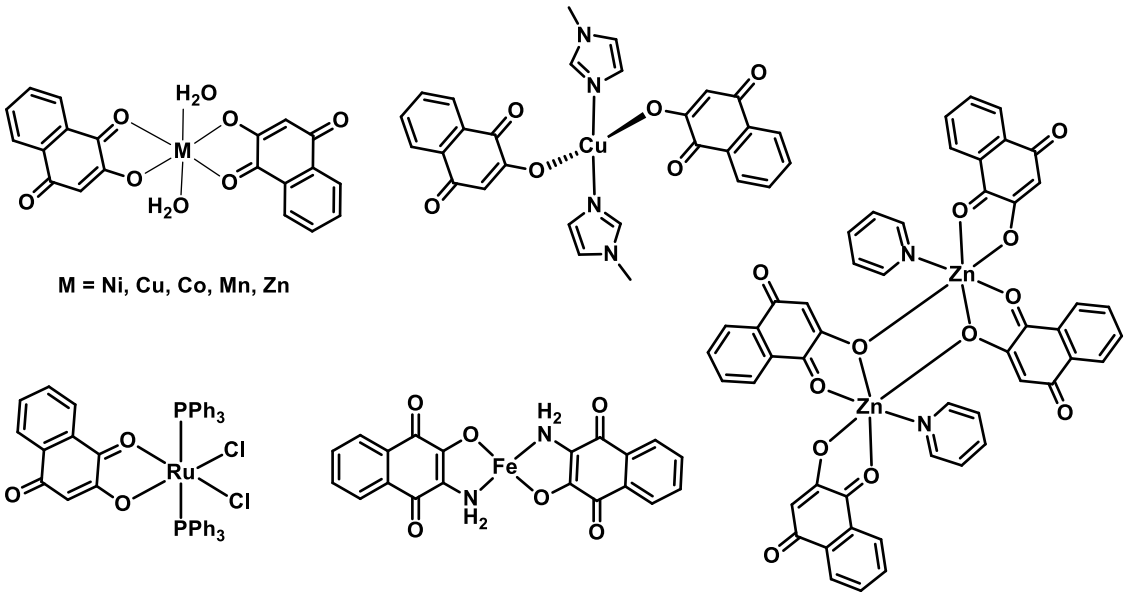


Figure 1.10 Tetramerization of lawsone and Li binding geometries of tetrakislawsone

Metals can significantly alter the pharmacological characteristics of well-known medicines. As described earlier analogs of quinone or naphthoquinones have potential to bind the metal ions in three different oxidation states. As a result, research on the

complexation reactions of lawsone for a number of metal ions with various structural traits has been published in the literature [34,61–65]**(figure 1.11).**



To mimic the iron quinone couple found in bacteria, complexes of lawsone have been studied. Whereas, copper complexes of lawsone were studied to emulate the structural and functional models of copper-containing enzymes. The copper (II) complex was discovered to induce apoptosis in HepG2 human cancer cells through protein modulation involved in apoptosis. In this way, metal complexes of lawsone with Zinc, Manganese, Cobalt, and Nickel along with Copper were examined for their potential cytotoxicity against cancer cells [65,66]. At last, the ruthenium (III) lawsonate complex can stabilize the coordinated semiquinone form of the naphthoquinone, which activates the catalytic cycle of oxidation **(figure 1.11)**. Thus ruthenium complex oxidizes primary and secondary alcohols to aldehydes and ketones, respectively [64].

1.6 Aim and objectives of the thesis

Apart from the typical use of lawsone as hair and skin dye, reactions of lawsone, which have been extensively documented in hundreds of articles, have made it possible to create a wide range of physiologically active compounds that may be used to treat several ailments. Therefore, the chemistry of this molecule is sufficient to warrant investigation.

The goal of the research that went into this thesis was to create novel derivatives of the naturally occurring chemical 2-hydroxy-1,4-naphthoquinone (Lawsone) and their metal

complexes to learn more about their biological characteristics and possible uses in catalysis.

The thesis is primarily divided into five segments. **Chapter 2** describes the synthesis and Structure Activity Relationship (SAR) of novel Mannich bases. **Chapters 3** and **4** discusses the chemistry of complexes derived from Mannich bases of lawsone and their application in anticancer and antimicrobial activity along with interaction with biomolecules like DNA and BSA. The creation and use of lawsone vanadium complex for catalytic oxidation are covered in **Chapter 5**. **Chapter 6** concludes with a study of new isoindolinones' synthesis, anticancer efficacy, and molecular docking.

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