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NAPHTHOQUINONES: BIOLOGICAL PROPERTIES AND SYNTHESIS OF LAWSONE AND DERIVATIVES — A STRUCTURED REVIEW

NAFTOQUINONAS: PROPIEDADES BIOLÓGICAS Y SÍNTESIS DE LAWSONA Y DERIVADOS – UNA REVISIÓN ESTRUCTURADA

Lluvia Itzel LÓPEZ LÓPEZ Ph.D.*, Sendar Daniel NERY FLORES Q.F.B., Sonia Yesenia SILVA BELMARES Ph.D., Aidé SÁENZ GALINDO Ph.D.

ABSTRACT

Background: Naphthoquinones are natural pigments that are widely distributed in nature and have important biological activities. Lawsone (2-hydroxy-1,4-naphthoquinone) and its synthetic derivatives, and especially those containing nitrogen, have promising potential for the treatment of different diseases due to their antibacterial, antifungal, antiviral, antitumor and antiparasitic effects, and for pest control via their molluscicidal and insecticidal activities. Their pharmacological activities and mechanisms of action are related to their oxide/reduction and acid/base properties, and can be modulated by directly adding a substituted to the 1,4-naphthoquinone ring. Due to this, naphthoquinones and their derivatives are at the center of multiple areas of research. In this manuscript, we present a structured review of lawsone, a hydroxyl derivative of naphthoquinone, and discuss relevant reports about the chemistry and synthesis of derivatives. Finally, we present the pharmacological activities and mechanism of action reported. **Objective:** The purpose of this review is to present recent reports from the literature about the chemistry, synthesis and pharmacological properties of lawsone and its amine derivatives. **Methods**: This structured review presents a discussion about lawsone literature over the last ten years. The most representative studies including those about the chemistry of lawsone, the synthesis of its derivatives, and pharmacological properties were identified and selected. The information has been compiled, organized and presented into logical topics in order to provide a current review for the field of lawsone chemistry. **Results**: A general overview of the principal aspects of lawsone chemistry, the synthesis of its derivatives and their pharmacological activities and mechanism of action has been obtained. This provides researchers in the area with a framework from which to investigate further. **Conclusions:** Lawsone and its derivatives have promising potential for treating several diseases due to their antibacterial, antifungal, antiviral, antitumor and antiparasitic effects and have the potential to control pests via their molluscicidal and insecticidal properties. For this reason, it would be of interest to evaluate the synthetic derivatives of this compound for their pharmacologic actions; in the future, synthetic derivatives of lawsone could potentially be used to treat disease and be used as pesticides.

Keywords: Naphthoquinone, lawsone, chemical synthesis, pharmacological actions

[1] Departamentos de Química orgánica y Productos naturales. Facultad de Ciencias Químicas, Universidad Autónoma de Coahuila, Blvd. V. Carranza e Ing. José Cárdenas Valdés. C.P. 25280. Saltillo, Coahuila, México.

* Autor a quien se debe dirigir la correspondencia: E-mail: lluvialopez@uadec.edu.mx

RESUMEN

Antecedentes: Las naftoquinonas son pigmentos naturales altamente distribuidos en la naturaleza con importantes actividades biológicas. La lawsona (2-hydroxi-1,4-naftoquinona) y sus derivados sintéticos, en especial aquellos con nitrógeno, tienen potencial para el tratamiento de diversas enfermedades debido a sus efectos antibacterianos, antifúngicos, antivirales, antitumorales, antiparasitarios, y en el control de plagas por sus actividades molusquicida e insecticida. Sus actividades farmacológicas y mecanismos de acción están relacionados con sus propiedades de óxido/reducción y ácido/base, y pueden ser moduladas añadiendo sustituyentes al anillo de la 1,4-naftoquinnona. Debido a esto, las naftoquinonas y sus derivados son el centro de atención de múltiples áreas de investigación. En este manuscrito, presentamos una revisión estructurada de la lawsona y reportes relevantes acerca de la química y síntesis de derivados. Además, presentamos las actividades farmacológicas y el mecanismo de acción reportados. **Objetivos**: El propósito de esta revisión es presentar los reportes recientes de la literatura acerca de la química, síntesis de derivados aminados y propiedades farmacológicas de la lawsona. **M**étodos: Esta revisión estructurada presenta una discusión acerca de la literatura de la lawsona de los últimos diez años. Se identificaron los estudios más representativos incluyendo aquellos de la química de lawsona, la síntesis de derivados y propiedades farmacológicas. La información se compiló, organizó y presentó en tópicos proporcionando una revisión actual en el campo de la química de la lawsona. **Resultados:** Se obtuvo una visión general de los aspectos de la química de la lawsona, la síntesis de derivados y sus actividades farmacológicas y mecanismo de acción. Esto proporciona a los investigadores en el área un marco desde el cual investigar más a fondo. **Conclusiones:** Lawsona y sus derivados poseen potencial para el tratamiento de diversas enfermedades debido a sus efectos antibacterianos, antifúngicos, antivirales, antitumorales y antiparasitarios y tiene potencial para el control de plagas por sus propiedades molusquicida e insecticida. Por esta razón, ha sido de interés evaluar la síntesis de derivados aminados y actividades farmacológicas; en un futuro los derivados de la lawsona podrían potencialmente ser usados para el tratamiento de enfermedades y usados como pesticidas.

Palabras clave: Naftoquinonas, lawsona, síntesis química, acciones farmacológicas

INTRODUCTION

The emergence of bacterial strains with increasing resistance to drugs has led to much research by academic laboratories, the pharmaceutical industry, and government institutions into generating new antimicrobials (1-4). Natural compounds and their derivatives are alternatives to many drugs; they have been shown to have minor secondary effects to comparative synthetic products (5). Among the natural chemicals and their synthetic derivatives are naphthoquinones, a promising group of compounds already shown to have antibacterial (6, 7), antifungal (8-10), antiviral (11, 12), antitumor (13-18) and antimalarial (19-21) activities, among others. We present a structured review on the chemistry of naphthoquinones, focusing on 2-hydroxy-1,4-naphthoquinone (lawsone) and the synthesis of its amine derivatives, as well as its most important pharmacological actions.

METHODS

A structured review of the biological properties and synthesis of naphthoquinones, focusing on the structure of 2-hydroxy-1,4-naphthoquinone (lawsone) and its derivatives has been presented. Initially, we used the ISI Web of Knowledge database to search the literature, which is available from the Digital Library of Universidad Autónoma de Coahuila, México. Search terms included "naphthoquinone", "biological properties", "lawsone" and "synthesis" from January 2004 to July 2014. Only papers where search terms were present in the paper's title were included, and then only where the full text was available. Additional databases available that we used for literature searches included Wiley Online Library, Springer Link, Royal Society of Chemistry, Elsevier-Science direct, Annual Reviews and Redalyc. Then, articles that contained information regarding the synthesis of

lawsone derivatives and the biological activities of naphthoquinones in humans were selected. We excluded the articles whose information was out to the scope of our aims. For example, computational calculations, spectroscopic characterization, dyes, and other topics. Additionally, citation lists from identified articles were subsequently reviewed to identify further relevant articles. The information was compiled and presented in the text in the following manner: Generalities of naphthoquinones; Lawsone: 2-hydroxy-1,4-naphthoquinone; Synthetic derivatives of lawsone; and Pharmacological activities and mechanism of action.

RESULTS

More than 998 articles were identified using the search criteria of "naphthoquinone". However, we selected only 74 articles, including terms such as "lawsone", "synthesis" and "biological properties", and excluding terms such as dyes, computational chemistry, catalysis and spectroscopic characterization. Thus, 74 articles with information relating to the research objective were reviewed. Figure 1 shows the search process.

Generalities of naphthoquinones

Quinones are widely-distributed aromatic compounds present throughout nature, and can be found in several families of plants, as well as isolated of fungi, algae and bacteria. Quinones are classified into benzoquinones, anthraquinones and naphthoquinones according to their chemical structures (22).

Naphthoquinones are structurally related to naphthalene ***(1)*** and are characterized by their two carbonyl groups in the 1,4 position, and as such, are named 1,4-naphthoquinones ***(2)*** (Figure 2). Carbonyl groups may also be present at the 1,2 position, with minor incidence (22). Naphthoquinones are highly reactive organic compounds, used as natural or synthetic dyes whose colors range from yellow to red. These compounds and their derivatives are α,β-unsaturated carbonyl compounds. The conjugation between carbonyl and double bonds give rise to 1,4-naphthoquinone, which has an intense coloration (23).

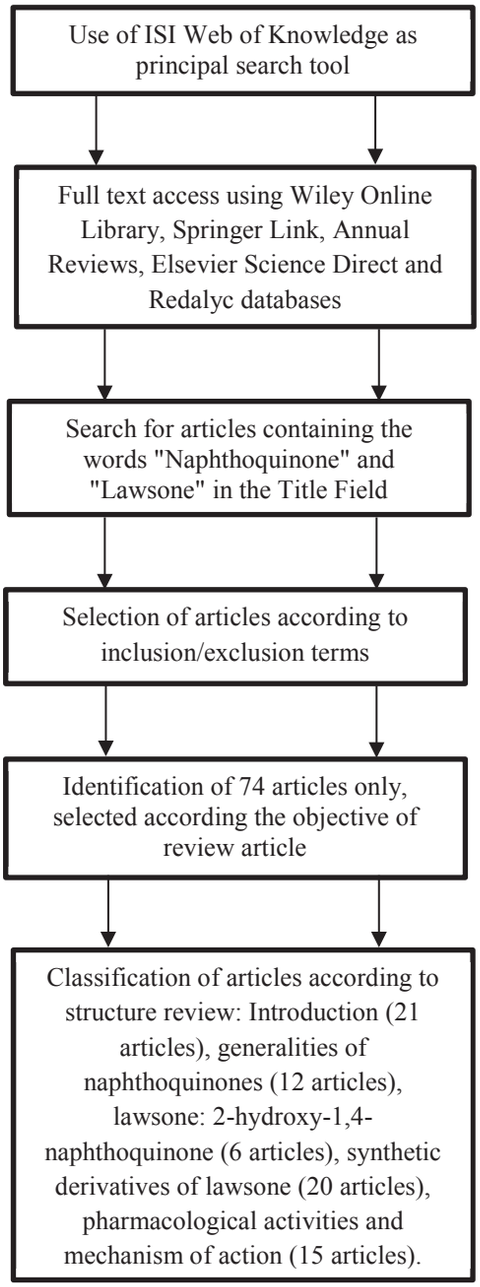

Figure 1. Flowchart of literature search.

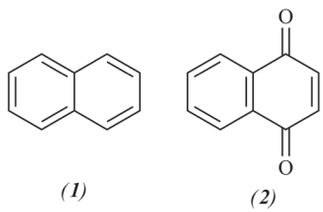

Figure 2. Chemical structure of naphthalene ***(1)*** and 1,4-naphthoquinone ***(2)***.

Naturally occurring 1,4-naphthoquinones are widely distributed in nature, especially in several families of higher plants (*Plumbaginaceae, Juglandaceae, Ebenaceae, Boraginaceae, Dioncophyllaceae, Ancistrocladaceae, Iridaceae, Verbenaceae, Scrophulariaceae, Avicenniaceae, Balsaminceae, Bignoniaceae, Gentianaceae, Droseraceae, Nepenthaceae, Lythraceae* and *Euphorbiaceae)* besides also being present in algae, fungi, some animals and as products of metabolism in some bacteria (22, 23).

Naphthoquinones are compounds present as secondary metabolites of plants and microorganisms; they confer activity in various biological oxidative processes and represent a chemical defense used by many plants. Lapachol, lawsone, juglone and plumbagin are examples of natural naphthoquinones isolated from plants, and can be distinguished by their use in traditional Indian medicine (24-29).

As well as their dye properties, hydroxy-1,4-naphthoquinones and their derivatives have been shown to have important biological activities, such as antimalarial, antibacterial, antifungal and anticancer properties. Among the natural hydroxynaphthoquinones are: lawsone ***(3)***, which can be obtained from the leaves and stems from henna (*Lawsonia inermis L.*) (24, 25); plumbagin ***(4)***, which is mainly extracted from the roots of *Plumbago scandens* L. and is used for the treatment of leprosy and tuberculosis (26, 27); lapachole ***(5)***, which can be isolated from the heartwood of plants of the genus *Tabebuia spp., Tecoma spp.* and *Tecomella undulata* (28); juglone ***(7)***, obtained from the roots, leaves, nuts, bark and wood of black walnut (*Juglans nigra*), European walnut (*Juglans regia*) and American white walnut (*Juglans cinerea)* (29); naphthazarin ***(8)***, which is naturally produced in the wood bark tree *Lomatia obliqua* and Alkana species (30, 31); mompain ***(9)***, isolated from the fungi *Helicobasidium mompa* (20); shikone ***(6)***, which is the mayor constituent of red extracts from the roots of the plant *Lithospermum erythrorhizon*; and the alkaline enantiomer ***(10)*** is found in the roots of *Alkanna tinctoria* (32, 33) (Figure 3).

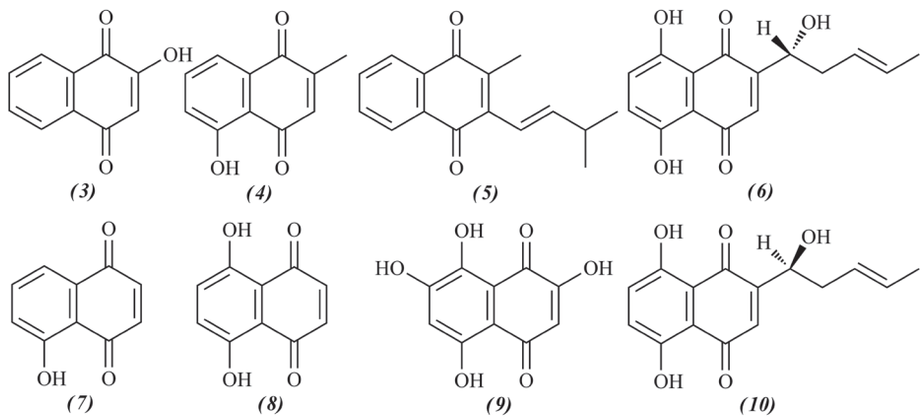

Figure 3. Naturally occurring hydroxy-1,4-naphthoquinones.

Lawsone: 2-hydroxy-1,4-naphthoquinone

Hydroxynaphthoquinones have proved effective due to their chemical and pharmacological properties. An important derivative is 2-hydroxy-1,4-naphthoquinone, also known as lawsone (34).

Lawsone ***(3)*** is the principal active ingredient of the henna plant (24, 35). Henna is a fine powder of a brown-green color. Henna plants are tall flowering shrubs or trees that are about 2–5 m in height, and are native to tropical and subtropical regions of Africa, India, Sri Lanka and the Middle East (36). Lawsone was first isolated from the leaves of *Lawsonia inermis* in 1959. Young henna plants do not have spines, and the amount of lawsone obtained from these plants is poor in comparison to mature plants that have spines (37).

2-Hydroxy-1,4-naphthoquinone is the main natural dye (red-orange) in the leaves of henna plants, present at a concentration of 1.0–1.4% w/w. Humans have used extracts containing lawsone henna as a cosmetic dye for both skin and hair for over 5000 years (26). Thus, lawsone has been re-

ported since around 1890 and it has been extensively distributed in Europe; today is widely available in markets around the world in the form of dyes or hair care products. In several parts of the world it is traditionally used in various festivals and celebrations and is frequently applied to newborn infants for ceremonial purposes (36-39).

Lawsone reacts chemically with the keratin of the hair and skin via a Michael addition, resulting in a permanent coloration that lasts until the skin comes off or hair falls out. Moreover, lawsone also strongly absorbs UV light, so its aqueous extracts can be used as effective sunscreens (39).

The molecular formula of lawsone is $C_{10}H_6O_3$ and its melting point is 190 °C. It is present in three tautomeric forms (Figure 4); the 1,4-naphthoquinone structure ***(11)*** is the most stable form followed by 1,2-naphthoquinone ***(12)*** and 1,2,4-naphthotrione ***(13)***; the trione system is the least stable but is probably in equilibrium in solution with the other two tautomeric forms. This stability is due to cancelation of dipolar moments of carbonyl groups, in combination with intramolecular hydrogen bonds in the 1,4 isomer (34).

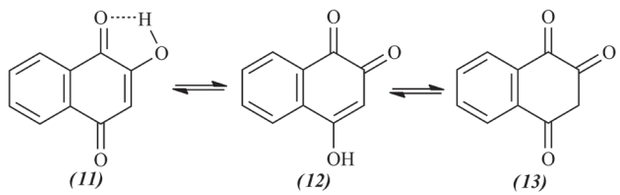

Figure 4. Tautomeric forms of lawsone (34).

Synthetic derivatives of lawsone

Alkyl derivatives of lawsone are interesting organic molecules which as well as having a pigment, also exhibit broad biological activities; in particular, 3-alkyl-2-hydroxy-1,4-naphthoquinone derivatives show activity against several organisms including bacteria, fungi, parasites, protozoa, mites and insects, as well as tumor cells (40, 41). In 2012, da Silva *et al.* showed that 2-hydroxy-3-methylamino and 1,2,3-triazolic napthoquinoidal derivatives inhibit the growth of *Trypanosoma cruzi* due to the influence on parasite respiratory and carbohydrate cycles (40). Furthermore, studies demonstrated that the 2-hydroxy-3-phenylsulfanylmethyl[1,4] naphthoquinones toxicity against *Plasmodium falciparum* is by interaction with respiratory chain in mitochondria of parasite (19).

Several studies have shown that atovaquone ***(14)***, a synthetic 2-hydroxy-1,4-naphthoquinone, and an analogue of ubiquinone, acts as coenzyme Q and selectively inhibits *P. falciparum* by affecting the mitochondrial electron transport in the parasite. Atovaquone-proguanil (Malarone) are used for prophylaxis and therapy of uncomplicated tropical malaria (42-44). Parvaquone ***(15)*** and buparvaquone ***(16)*** are 2-hydroxy-1,4-naphthoquinones substituted at position 3 and are used as drugs for the treatment of pneumonia caused by *Pneumocystis pneumonia*, toxoplasmosis, malaria and leishmaniasis which highlights the importance of this class of compounds (Figure 5) (45).

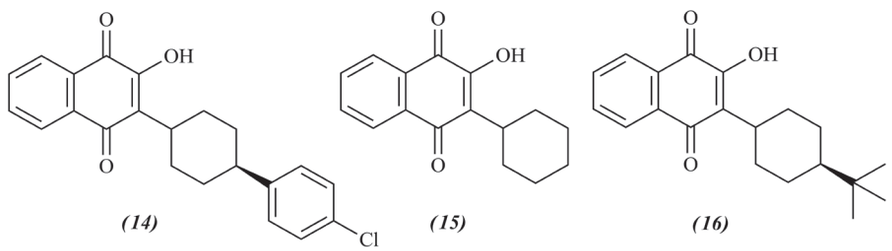

Figure 5. Chemical structure of atovaquone ***(14)***, parvaquone ***(15)*** and buparvaquone ***(16)***.

Besides the alkyl derivatives, another group of interest are the aminonaphthoquinone derivatives. Aminonaphthoquinones are considered potential antifungal agents and are produced by various plants belonging to the *Caryophyllales* family, including *Nepenthaceae*, *Droseraceae*, *Plumbaginaceae*, *Drosophyllaceae* and *Ebenaceae* (23). Andrade *et al.* reported the synthesis and antibacterial activity of 2-amino-1,4-naphthoquinone derivatives (46). Other interesting synthetic naphthoquinone, reported by Baramee *et al.* (2006), are ferrocenyl aminohydroxynaphthoquinones; these compounds were shown to be active against *Toxoplasma gondii* (47) (Figure 6).

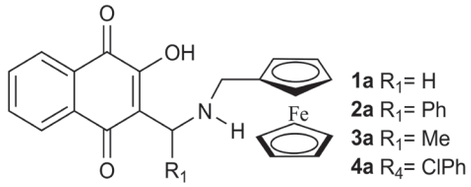

Figure 6. Ferrocenyl aminohydroxynaphthoquinone derivatives (47).

It has been shown that the incorporation of amino groups into 1,4-naphthoquinone structures often results in an increase in their anticancer, antibacterial, antiparasitic and molluscicidal activity (6, 10, 40, 41, 46, 47, 50, 55, 59).

The literature described two main ways to prepare the aminonaphthoquinone derivatives. The first involves a Michael 1,4-addition type reaction between the 1,4-naphthoquinone ring ***(2)*** and the amino compound to generate 2-amino-1,4-naphthoquinone ***(17)***. The second involves a nucleophilic substitution by a mono- or di-halogenated derivative of 1,4-naphthoquinone ***(18)*** by the nucleophilic attack of the amine compound to produce the corresponding amino derivative ***(19)*** (48-50) (Figure 7).

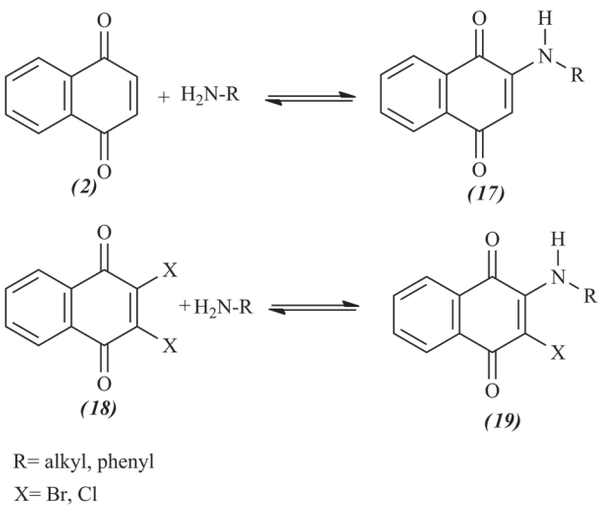

Figure 7. Synthesis of aminonaphthoquinone derivatives, compound (*2*) gave (*17*) after 1,4-addition and oxidation; (19) is formed by nucleophilic displaced of halogen of (*18*).

β-amino carbonyl lawsone derivatives were synthesized for the first time in 1948 by Leffler *et al.*, who further demonstrated that certain compounds of the 3-alkyl-2-hydroxy-1,4-naphthoquinone possess antimalarial activity (19). The Mannich reaction is one of the most important for the formation of carbon-carbon bonds in organic synthesis, besides being a reaction with high atom economy. This reaction produces β-amino carbonyl compounds from three components: an amine, an aldehyde, and an enolizable ketone. β-amino carbonyl compounds, also known as a Mannich bases, are important intermediates for the synthesis of many pharmaceutical and natural products containing nitrogen in their structures (51-54).

In 2009, Neves *et al*. reported the synthesis of 13 novel Mannich bases ***(22)*** using mechanic stirring at room temperature, with a 12 hour reaction time. The compounds were produced via a reaction between lawsone, primary amines ***(21)*** and benzaldehyde substitutes ***(20)***, and yields obtained were in the range of 53% to 93% (Figure 8). The synthesis of these compounds is relatively easy and environmentally clean. Moreover, the HL11 and HL13 compounds that were synthesized inhibited the growth of *E. coli* and *S. aureus* (55) (Table 1). In 2011, Dabiri *et al*. (56) reported the synthesis of lawsone Mannich bases (HL14-33) via reflux heating over 5–7 hours, using water-like solvent and a $InCl_3$ (indium trichloride) -like catalyst; the results showed yields of 78% to 90%, thus, an easy, efficient and clean method for their production was defined (Table 1).

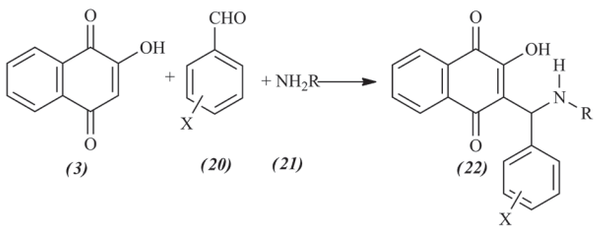

Figure 8. Synthesis of aminonaphthoquinone derivatives using Mannich reaction.

Table 1. Mannich bases of lawsone.

Compound HL	X	R	Yield (%)
1	H	Butyl	74
2	4-NO_2	Butyl	60
3	4-NO_2	Benzyl	73
4	2,4-Cl	Butyl	53
5	2,4-Cl	Benzyl	79
6	2-OH	Allyl	88
7	2-OH	Butyl	80
8	2-OH	Benzyl	93
9	2-OH	$CH_2C_4H_3O$	88
10	2-OH, 5-Me	Butyl	70
11	2-OH, 5-Me	Benzyl	67
12	2-OH, 5-Br	Butyl	61
13	2-OH, 5-Br	Benzyl	75
14	H	H	90
15	4-Me	H	80
16	4-OH	H	86
17	4-NO_2	H	82
18	H	4-MePh	86
19	4-OMe	4-MePh	85
20	4-Me	4-MePh	91
21	4-OH	4-MePh	85
22	4-NO_2	4-MePh	78
23	4-F	4-MePh	80
24	4-Br	4-MePh	79
25	2,4-diCl	4-MePh	89
26	2-Cl	4-MePh	89
27	3-NO_2	4-MePh	90
28	H	4-FPh	85
29	4-Me	4-FPh	78
30	4-NO_2	4-FPh	81
31	H	2-Cl, 4-NO_2Ph	80
32	Me	2-Cl, 4-NO_2Ph	79
33	4-NO_2	2-Cl, 4-NO_2Ph	78

Using the Mannich reaction with lawsone, various amines and substituted benzaldehydes is a good alternative to synthesizing amino derivatives of 2-hydroxy-1,4-naphthoquinone, since these methods have proved to be efficient, environmentally clean and simple, with high atomic economy (51-58). Furthermore, the synthesized compounds have demonstrated antibacterial (55), antiparasitic (47) and molluscicidal activity (59).

Pharmacological activities and mechanism of action

Several natural and synthetic naphthoquinone analogues are important precursors in the synthesis of many natural products and pharmaceuticals, which exhibit antibacterial (6, 7), antifungal (8-10), antiviral (11, 12), antitumor (13-18), trypanocidal (61-63), antimalarial (19-21), antileismanicidal (64, 65), molluscicidal (59) and insecticidal (66, 67) activity. This is the reason why this type of natural organic compounds attractive in different areas of research.

Henna leaves have a bitter flavor and have been used in traditional medicine as an astringent, antiseptic and antipyretic (68). Henna has been used for years by Islamic doctors in the treatment of various diseases such as leprosy, smallpox, chickenpox and tumors (12, 69). Lawsone isolated from lawsone leaves showed significant antifungal activity against *Candida albicans* (8, 9, 60).

2-Hydroxy-1,4-naphthoquinone and its derivatives have been reported to possess important activities. Rahmoun *et al.* reported the antibacterial activity by the disk diffusion method of 2-hydroxy-1,4-naphthoquinone derivatives. Two compounds with chloride and nitro substituents were active against *S. aureus* ATCC 25923 with MIC values of 16–32 μg/mL and 32–64 μg/mL, respectively (60).

Camara *et al.* (2008) reported the synthesis of 2-hydroxy-1,4-naphthoquinone derivatives and evaluated their effectiveness against the brine shrimp *Artemia salina* and against the mollusk *Biomphalaria glabrata*, which is the main transmitting vector of schistosomiasis in Brazil. Of the seventeen compounds tested, nine fell below the threshold of 100 μg/mL set by the World Health Organization for potential molluscicidal activity (59). Other interesting synthetic naphthoquinones reported by Baramee *et al.* (2006) are ferrocenyl aminohydroxynaphthoquinones, which showed antiparasitic activity against *Toxoplasma gondii* (47). In 2010, Vinothkumar *et al.* reported the *in vitro* antioxidant activities of hydroxyl-1,4-naphthoquinone; these compounds were tested and evaluated by the amount of scavenged radical method. The entire synthesized compound exhibited a moderate antioxidant activity particularly for the DPPH radical parameter, and the researcher also showed that the compound had appreciable lipid peroxidation activity (69).

For these reasons, natural naphthoquinones and their synthetic derivatives are interesting compounds of study in diverse areas such as in organic synthesis, and for natural products, pharmacology, toxicology and pharmaceuticals.

Naphthoquinones interact with biological targets by forming covalent bonds or via their ability to undergo reversible oxidation-reduction reactions (48). The mechanism of action usually involves the generation of reactive oxygen species (ROS) by the redox cycle under aerobic conditions, by the inhibition of electron transport, by DNA intercalating and/or alkylating agents of biomolecules, and/or as topoisomerase inhibitors (15, 24, 48, 70). In all of the mechanisms of action *in vivo*, bio reduction is required as a first step in quinone formation.

In general, the biological activity of the naphthoquinone involves the ability to accept one or two electrons to form anion radicals (semiquinone) and dianion (hydroquinone) respectively. These anions are highly reactive.

As seen in Figure 9, the quinone function of 2-hydroxy-1,4-naphthoquinone ***(23)*** can be reduced to the semiquinone ***(24)*** and consequently to the hydroquinone ***(25)*** by a sequence of two one-electron reductions. These species are re-oxidized by molecular oxygen (O_2) and generate ROS such as superoxide, hydroxyl radical and hydrogen peroxide (22, 24). The superoxide radical is a highly reactive species and is unstable, which leads to the formation of hydrogen peroxide, which, although not a free radical, is toxic to cells because it can diffuse through membranes. ROS are powerful oxidizing agents and are probably responsible for damage to macromolecules such as ADN, proteins and lipids, leading to oxidative stress and apoptosis in the cells (22, 24, 70, 71).

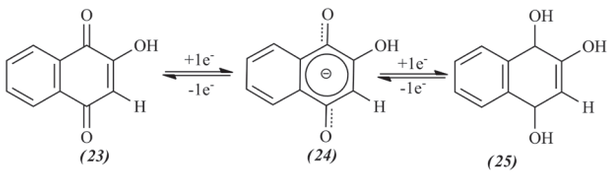

Figure 9. Redox properties of quinone ***(23)***, forming the semiquinone ***(24)*** and hydroquinone ***(25)***.

Thus, as the bio reduction of naphthoquinones is influenced by their redox properties, the ability and capability of these compounds to accept electrons can be modified by adding substituents, which act as acceptors or electron donors, to the 1,4-naphthoquinone ring (39). In addition, the modulation of naphthoquinone reactivity can be changed by modifying the chemical environment, which can improve its pharmacological activity and lower side effects (72).

In biochemical reactions, the quinone ***(2)*** may be reduced to semiquinone ***(26)***, a free radical, and then to hydroquinone ***(27)*** by the enzyme cytochrome P450 reductase and other flavoprotein enzymes. The semiquinone intermediary can be dissociated from flavoprotein and thus be made available for other reactions in the cell. Also, DT-diaphorase (NADPH quinone reductase) directly reduces quinone to hydroquinone (Figure 10) (22).

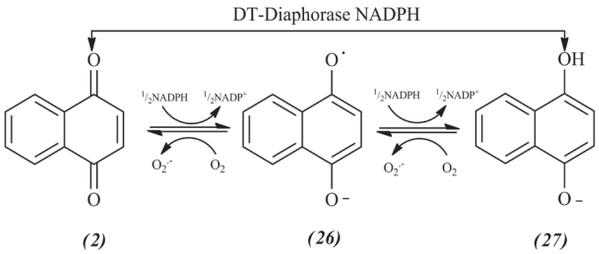

Figure 10. Enzymatic reduction of 1,4-naphthoquinone (22).

Naphthoquinones may also act as electrophiles, by interacting with nucleophilic functions in biological molecules in an arylation reaction. When the nucleophile is a thiol group, the reaction generates a thioether ***(28)***, which is generally stable. The naphthoquinones are considered Michael acceptors because they possess the electrophilic α,β-unsaturated carbonyl system and also due to their ability to form covalent bonds with nucleophilic groups in biological molecules (22) (Figure 11).

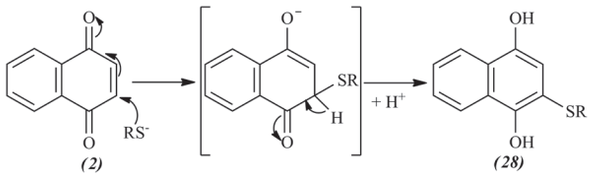

Figure 11. Thioether formation ***(28)*** by 1,4-naphthoquinone ***(2)*** and thiol group reaction.

Another potential mechanism is the inhibition of ADN topoisomerase; this type of mechanism may be involved in the cytotoxic activity of naphthoquinone (73). ADN topoisomerase is an enzyme that regulates the overwinding or underwinding of DNA during DNA replication, which is the re-

ason behind studying it for its potential to inhibit topoisomerase, for novel cancer treatments. In the literature, it has been reported that naphthoquinone derivatives can act as inhibitors of human topoisomerase I; however, the exact mechanism of action is not clear (73, 74).

Finally, it is important to mention that this work presents a structured review about the chemistry and synthetic derivatives of lawsone that have important pharmacological activities. Thus, the inclusion terms for literature searches were as follows: naphthoquinone, lawsone, synthesis of amine derivatives and pharmacological activities. The exclusion terms were: spectroscopic studies, computational chemistry, and other applications as dyes and pigments. The databases used were Web of Science, Wiley, Springer, Annual Review and Redalyc, and the date range consulted was January 2004 to July 2014. The main aim of this review was to present broad information about lawsone, a relevant naphthoquinone, to contribute to study of this bioactive compound and its derivatives.

CONCLUSIONS

We can conclude that naphthoquinones are a promising group of compounds, as shown by the wide variety of biological activities described in the above literature review. 1,4- naphthoquinone and its derivatives are widely distributed in nature and have been used since ancient times in traditional medicine. Lawsone, one of the hydroxy derivatives of 1,4-naphthoquinone, has been used as a dye, and both its natural form and synthetic derivatives exhibit antibacterial, antifungal, antimalarial, antitumor, molluscicidal and antioxidant activity, among others. One way to synthesize amino derivatives such as lawsone, is through the Mannich reaction, as being simple, environmentally benign, economical, fast and efficient. Hydroxynaphthoquinone derivatives are promising compounds for treating disease and/or for pest control.

Conflict of interest

The authors confirm that there is no conflict of interest.

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