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Molecular structures and biological activities of (N)-*n*-alkylammonium 2-chloro-3-oxido-1,4-naphthoquinone salts

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ABSTRACT

Single crystal X-ray structures and vibrational spectra of (N)-*n*-alkylammonium 2-chloro-3-oxido-1,4-naphthoquinone salts (alkyl = methyl to octyl, CS-1 to CS-8) possessing X-H···Y (X = N, C and Y=O, Cl) hydrogen bonding and diverse noncovalent interactions have been characterized. Except for the CS-2 and CS-7 rest of the compounds facilitate π···π and Cl···π interactions. The compound CS-3 showed the presence of Cl···O interactions. Electronic structure and spectral characteristics of obtained are in consonance with the density functional theory. These complexes showed remarkable antiproliferative and antifungal activities.

1. Introduction

Biologically active quinones representing naturally occurring secondary metabolites and are found in a variety of plants, fungi, bacterial and insect families attracted significant attention in the literature. Amongst these hydroxynaphthoquinones find applications in medicines, pigmentations, cosmetics, agrochemicals and other functional chemicals for quite some time [1]. Naphthoquinones exhibit wide range biological activities viz., antibacterial, fungicidal, antiinflammatory, antiviral, antiparasitic, antitrypanosome, antiplasmodial agent, antiproliferative, anticancer and antimalarial [2–7]. The toxicological and pharmacological effects of hydroxy naphthoquinone displaying strong dependence on the chemical structure in particular, the number and positions of hydroxy groups, significantly influence the chemical, physical, redox or biological properties. Hydroxynaphthoquinones for example, lawsone, phthiocol, plumbagin, laphachol, juglone are naturally occurring and possess wide range of pharmacological applications (Fig. 1). Lawsone (2-hydroxy-1,4-naphthoquinone) is a natural colorant obtained from heena leaves and widely used in cosmetic industry and explored in pharmacological applications [8]. Phthiocol (2-hydroxy-3-methyl-1,4-naphthoquinone) is synthesized by tubercular bacteria in human intestine [9]. Lapachol (2-hydroxy-3-(2-methyl-1-propenyl)-1,4-naphthoquinone) extracted from lapacho tree and shows cytotoxic activity against several human cancers, among other biological properties [10]. Plumbagin (5-hydroxy-2-methyl-1,4-naphthoquinone) is also known as Chinese medicine and it is isolated from plants of the plumbago family, that shows a wide range of pharmacological activities, including anticancer, antimicrobial, etc [11]. Juglone (5-hydroxy-1,4-naphthoquinone) is a dye commonly used in food and cosmetic industry, with herbicidal properties [12]. 2-chloro-3-hydroxy-1,4-naphthoquinone is a synthetic derivative of lawsone, its successful synthesis [13] dates back to 1924. Hydroxynaphthoquinones are sparingly soluble in water; their solubility can be increased by salt formation. Deprotonation of hydroxyl group occurs in basic medium and the anionic forms generated trigger keto-enol tautomerism in solutions which renders biological activity [14,15] to these systems. In the present endeavor X-ray single crystal structures of (N)-*n*-alkylammonium 2-chloro-3-oxido-1,4-naphthoquinone salts were elucidated following their successful syntheses by *n*-alkyl amines (CS-1 to CS-8 displayed in Fig. 2). The structures were further derived using the density functional theoretic calculations. The earlier investigations

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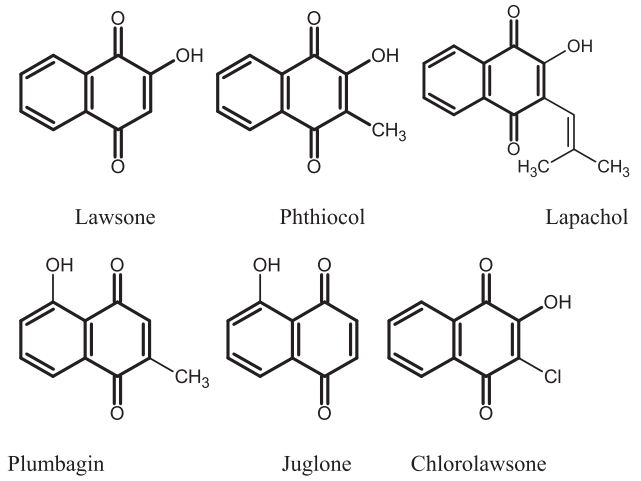

Fig. 1. Naturally occurring hydroxynaphthoquinones.

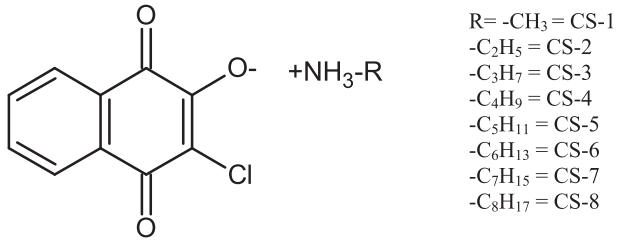

Fig. 2. Molecular structures of CS-1 to CS-8.

on *n*-alkylamino derivatives of 1,4-naphthoquinones have demonstrated that these derivatives possess distinct molecular interactions and biological properties [16–19]. The present investigations focus on how varying alkyl chain of (N)-*n*-alkylammonium cations in chlorolawsonote anion brings forth the distinct molecular interactions which influence their antifungal and anticancer activities. Antifungal activity of CS-1 to CS-6 was evaluated against *Saccharomyces cerevisiae* and *Candida albicans*. Antiproliferative activity was evaluated against breast cancer cell line (MDA-MB-231) and lung cancer cell line (L-132, HeLa derivative).

2. Experimental section

2.1. Materials and methods

2,3-dichloro-1,4-naphthoquinone, ethyl amine solution (70%), propylamine (99%), butylamine (99%), pentylamine (99%), hexylamine (99%), heptylamine (99%) and octylamine (99%) were purchased from Sigma-Aldrich, Methyl amine solution (40%) from Loba chemicals, KOH pellets obtained from Merck Chemicals. Analytical grade dichloromethane, methanol, pet ether, ethyl acetate solvents were purchased from Merck Chemicals. The solvents were distilled by standard methods [20] and dried wherever necessary. FT-IR spectra were recorded between 4000 and 400 cm^{-1} as KBr pellets on the Shimadzu FT 8400 Spectrophotometer. Melting points of compounds were determined using (Make- METLER). ^{1}H (400 MHz) and ^{13}C (100 MHz) NMR of compounds are recorded in DMSO-d_6, on Varian 400 MHz NMR instrument using the TMS (tetramethylsilane) as the reference. UV–Visible spectra of all compounds in methanol were recorded from 200 nm to 800 nm on Shimadzu UV 1800 Spectrophotometer. Elemental analysis was carried out with the Thermo Finnigan EA 1112 Flash series. Elemental Analyzer and on Elementar Vario EL III. The HR-MS spectra were recorded on Bruker impact HD with the ESI source. Gas chromatograph mass spectrums (GC-MS) were recorded on Shimadzu, GC-MS-QP5050.

2.2. Synthesis of 2-chloro-3-hydroxy-1,4-naphthoquinone:chlorolawsone

Modified procedure [21] has been used for synthesis of chlorolawsone. Recrystallized 2,3-dichloro-1,4-naphthoquinone (0.5 g, 2.2 mmol) have been added in 10 ml of water. To this suspension, 10 ml aqueous solution of KOH (0.247 g, 4.4 mmol) was added with constant magnetic stirring. This reaction mixture was heated for 3 hrs at 70 °C. Red color solution was obtained. Unreacted dichlone was extracted with dichloromethane from aqueous reaction mixture and was acidified by adding a few drops of concentrated hydrochloric acid till pH of the reaction mixture becomes pH = 2. Yellow color residue obtained was filtered and washed with diethyl ether and dried over vacuum and subsequently purified by column chromatography and eluted with the ethyl acetate/pet-ether (1:9).

2.3. Synthesis of salts of 2-chloro-3-oxido-1,4-naphthoquninone (N)-n-alkylammonium salts: CS-1 to CS-8

Recrystallization of 2-chloro-3-hydroxy-1,4-naphthoquinone (0.5 g, 2.2 mmol) was carried out by dissolving with 15 ml of dichloromethane (Scheme 1). The mixture was stirred for about 15 min. To this solution, corresponding amines (0.1 ml methyl (CS-1)), (0.29 ml ethyl (CS-2)), (0.485 ml propyl (CS-3)), (0.475 butyl (CS-4)), (0.40 ml pentyl (CS-5)), (0.412 hexyl (CS-6)), (0.428 heptyl (CS-7)), (0.476 octyl amine (CS-8)) solutions were added by drop wise. The reaction mixture was stirred for 24 h at the room temperature (26 °C) with constant magnetic stirring till completion of the reaction that is monitored on TLC. Red colored precipitate thus obtained was filtered and washed with dichloromethane followed by diethyl ether and the residue was dried in vacuum. Subsequently X-ray quality crystals for all these compounds were obtained after recrystallization of solid products in the methanol.

2.3.1. Analytical data of 2-chloro-3-hydroxy-1,4-naphthoquinone: cholorolawsone

Yellow solid, Yield: 0.4 g (87.14%). FT-IR (KBr, cm^{-1}): 3269, 1668, 1639, 1585, 1454, 1363, 1330, 1298, 1273, 1219, 1128, 1008, 856, 727, 682, 599, 538. ^{1}H NMR (400 MHz, DMSO-d_6, δ(ppm)): 8.04 (d, J = 7.5 Hz, 1H), 8.02 (d, J = 7.84 Hz, 1H), 7.86 (td, J = 7.3, 1.3 Hz, 1H), 7.8 (m, 1H).^{13}C NMR (100 MHz DMSO-d_6 (ppm)): 180, 178, 158, 135, 133, 132, 130, 126, 126, 126. UV–Vis: (methanol, λ_{max}, nm): 287, 321, 473. GC-MS (m/z): calcd. for $C_{11}H_{10}ClNO_3$: 208.60; Found: 208.

2.3.2. Analytical data of methyl ammonium-3-chlorolawsonate: CS-1

Red solid, Yield: 0.55 g. (79.82%). Anal. data calcd. for $C_{11}H_{10}ClNO_3$: C, 55.13; H, 4.21; N, 5.84. Found: C, 55.39; H, 4.57; N, 5.90. FT-IR (KBr, cm^{-1}): 3022, 2991, 2980, 1676, 1621, 1516, 1377, 1269, 1155, 1001, 837, 736, 555. ^{1}H NMR (400 MHz, DMSO-d_6, δ (ppm)): 7.91 (d, J = 7.6 Hz, 1H), 7.80 (d, J = 7.5 Hz, 1H), 7.73 (s, 3H), 7.69 (m, 1H), 7.56 (t, J = 7.5 Hz, 1H), 2.42 (s, 3H).^{13}C NMR (100 MHz, DMSO-d_6, δ (ppm)): 25, 113, 125, 125, 130, 131, 134, 135, 167, 174, 184. UV–Vis: (methanol, λ_{max}, nm): 468.

2.3.3. Analytical data of ethyl ammonium-3-chlorolawsonate: CS-2

Red solid, Yield: 0.51 g (83.46). Anal. data calcd. for $C_{12}H_{12}ClNO_3$: C, 56.81; H, 4.77; N, 5.52 Found: C, 56.63; H, 4.52; N, 5.52. FT-IR (KBr, cm^{-1}): 3045, 3010, 2982, 1681, 1579, 1527, 1500,