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Complexes of Lapachol and Lawsone with Lanthanides

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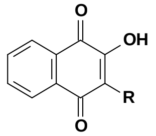
Naturally occurring 2-hydroxy-1,4-naphthoquinones are well known to form readily stable complexes with transition metals. In this short communication we describe for the first time the synthesis and preliminary data about structural characterization of complexes between two naturally widespread 2-hydroxy-1,4-naphthoquinones, namely lapachol (**1**) and lawsone (**2**), with selected lanthanides like lanthanum, gadolinium, and ytterbium. When tested as cytotoxic compounds, such complexes exhibited an activity that was either higher or equal to that of the parent naphthoquinone.

Keywords: Lanthanides, Lapachol, Lawsone, Naphthoquinones.

1,4-Naphthoquinones are a wide group of natural products and are found in several plant families and also in fungi and bacteria. Notable examples include the K vitamins, juglone (isolated from the black walnut, *Juglans nigra* L. [Juglandaceae] and other genera), and plumbagin (obtained from *Plumbago*, *Drosera*, and *Nepenthes* spp. and other genera). Naturally occurring naphthoquinones have been shown to exert promising and interesting pharmacological effects, acting as cytotoxic, anti-bacterial, anti-fungal, anti-viral, anti-protozoal, insecticidal, anti-inflammatory, and anti-pyretic agents [1]. A derivative of lapachol (**1**), patented with the name of Atovaquone®, has been approved for the treatment of pneumonia, toxoplasmosis, and malaria [2]. This compound has been also tested as an anticancer agent by the National Cancer Institute (Bethesda, MD, USA) in the 60-cell-line panel under the NSC-759582 NCI code, but displaying a poor activity compared with lapachol (**1**) with a maximal growth inhibition percentage of 24.6% in UO-31 renal cancer cells at 10 µM.

For what concerns the mechanisms of action of naphthoquinone derivatives responsible for the observed biomolecular effects, it has been seen that such phytochemicals are able to interact with topoisomerases and to generate semiquinone radicals and reactive oxygen species (ROS) in the endocellular environment [3]. Plants containing naphthoquinones are an important part of the ethnomedical traditions of local people in South America and Southeast Asia to cure severe parasitic diseases. In this context, lapachol (**1**) (2-hydroxy-3-isopentenyl-1,4-naphthoquinone) and lawsone (**2**) are two of the most well-known examples of a research topic in natural product chemistry. Their phytochemistry and pharmacognosy have been recently exhaustively reviewed [4-5].

As a continuation of our ongoing studies to define better the pharmacological properties and mechanism of action of selected classes of known and novel natural products [6-8], we wish to report herein the synthesis and preliminary data about the structural characterization of complexes of lapachol (**1**) and lawsone (**2**) with selected rare earth metals belonging to the lanthanide series, namely lanthanum, gadolinium, and ytterbium. To the best of our knowledge, such an investigation is described herein for the first time in the literature. Both lapachol [9-10] and lawsone [11], like several other 2-hydroxynaphthoquinones, are well known to form stable complexes with a wide range of transition metals like zinc, cobalt, manganese, nickel, copper, antimony, tin, bismuth, and many others. Such complexes in some cases have been shown to exert valuable and potent cytotoxic and anti-parasitic activities.



1 R = CH_2-CH-C=$C(CH_3)_2$
2 R = H

The synthesis of the six complexes between lapachol (**1**) and lawsone (**2**) and the three lanthanides mentioned above has been accomplished using a slight modification of already reported experimental protocols used for the synthesis of complexes with transition metals [9,10]. Thus commercially available lanthanide triacetate (0.45 mmol) was dissolved in ethanol (25 mL) and the resulting suspension magnetically stirred at 80°C until complete dissolution. To the obtained solution lapachol (lawsone) (1.5 mmol) was added at the same temperature and a rapid formation of a red orange precipitate was observed. After cooling the reaction medium, the precipitate was filtered under reduced pressure, washed three times with aliquots of EtOH (10 mL each), and finally collected. The desired complexes have been obtained in discrete to good yields, namely 54% for La, 65% for Gd, and 82% for Yb. Preliminary data about the structural characterization of the synthesized lanthanide complexes were obtained by mass spectrometry (MS), IR and UV spectroscopy.

MS, although not satisfactorily resolved, probably due to the isotopic abundance typical of rare earth metals, showed molecular peaks corresponding to the formation of hexadentate complexes with a 3:1 2-hydroxynaphthoquinone / lanthanide ratio. More significant data of the interaction between lapachol (**1**) and lawsone (**2**) and the metal center have been obtained using IR and UV spectroscopy. Using the first technique the shifts of the two carbonyls in positions 1 and 4 of the naphthoquinone core were monitored. For the IR spectra of individual lapachol and lawsone recorded values were 1640 cm^{-1} and 1680 cm^{-1} respectively. Upon addition of the lanthanide these values decreased to 1635 cm^{-1} and 1670 cm^{-1} for La, 1620 cm^{-1} and 1645 cm^{-1} for Gd, and finally

1605 cm^{-1} and 1635 cm^{-1} for Yb. Thus a parallelism between the decrease of the atomic radius in the lanthanide series and the values of IR carbonyl absorptions of the complexes has been observed. This may reflect the more oxophilicity of Yb with respect to "larger" metal centers like La and Gd, and thus a tighter interaction between Yb and naphthoquinone ligands [12]. UV spectra were recorded in EtOH solutions and shifts of absorbance were monitored of the naphthoquinone alone and of each La, Gd, and Yb complex at two different wavelengths, 455 nm and 271 nm. For lawsone and its complexes (at a concentration of 0.01 mg/mL) recorded absorbance values at 455 nm decreased from 0.294 (individual lawsone) to 0.196 (La-complex), 0.113 (Gd-complex), and 0.076 (Yb-complex) and at 271 nm from 1.873 (individual lawsone) to 1.189 (La-complex), 0.531 (Gd-complex), and 0.255 (Yb-complex). Lapachol exhibited the same pattern of recorded absorbance values at both wavelengths. Also in this case a parallelism between the atomic radius of the metal center and the decrease in absorbance have been put in evidence and the same hypothesis as depicted above may be formulated.

The six complexes were also assayed for their cytotoxic properties using a well validated model already reported [6, 7], but not one exhibited a more potent activity with respect to the parent lapachol (**1**) or lawsone (**2**), revealing that their complexation to lanthanides is not determinant for the enhancement of the *in vitro* anticancer effects, as occurs after complexation of either lapachol (**1**) or lawsone (**2**) with transition metals [9].

In conclusion we report herein the first synthesis of naturally occurring 2-hydroxy-1,4-naphthoquinones with rare earth metals. The formation of complexes was accomplished by means of an easy to handle and short procedure. Although they do not exhibit a significative pharmacological effect in terms of growth inhibition against cancer cell lines, data preliminarily collected about their structural characterization are more than encouraging to continue with further experiments (e.g. X-ray crystallography) aimed to get further insights into the structural assignments of the already obtained complexes and to pursue the synthesis of additional complexes between lapachol and lawsone with other lanthanides, as well as the synthesis of further complexes using other naturally occurring naphthoquinones. Such experiments are now on course in our laboratories.

References

[1] Grolig J, Wagner R. (**2005**) Naphthoquinones. In *Ullmann's Encyclopedia of Industrial Chemistry*, Wiley-VCH, Weinheim:10.1002/14356007.a17_067

[2] Eyong KO, Kumarì PS, Kuete V. (**2008**) Semisynthesis and antitumoral activity of 2-acetylfuranonaphthoquinone and other naphthoquinone derivatives from lapachol. *Bioorganic & Medicinal Chemistry Letters*, ***18***, 5387-5390.

[3] da Silva AJ, Buarque CD, Brito FV. (**2002**) Synthesis and preliminary pharmacological evaluation of new (+/-) 1,4-naphthoquinones structurally related to lapachol. *Bioorganic & Medicinal Chemistry Letters, **10***, 2731-2738.

[4] Epifano F, Genovese S, Fiorito S, Mathieu V, Kiss R. (**2014**) Lapachol and its congeners as anticancer agents: a review. *Phytochemistry Reviews*, ***13***, 37-49.

[5] Badoni Semwal R, Semwal DK, Combrinck S, Cartwright-Jones C, Viljoen A. (**2014**) *Lawsonia inermis* L. (henna): ethnobotanical, phytochemical and pharmacological aspects. *Journal of Ethnopharmacology*, ***8***, 80-103.

[6] Bruyere C, Genovese S, Lallemand B, Ionescu-Motatu A, Curini M, Kiss R, Epifano F. (**2011**) Growth inhibitory activities of oxyprenylated and non-prenylated naturally occurring phenylpropanoids in cancer cell lines. *Bioorganic & Medicinal Chemistry Letters*, ***21***, 4173-4178.

[7] Fiorito S, Epifano F, Bruyere C, Mathieu V, Kiss R, Genovese S. (**2014**) Growth inhibitory activity for cancer cell lines of lapachol and its natural and semisynthetic derivatives. *Bioorganic & Medicinal Chemistry Letters*, ***24***, 454-457.

[8] Shimizu M, Kochi T, Shirakami Y, Genovese S, Epifano F, Fiorito S, Mori T, Tanaka T, Moriwaki H. (**2014**) A newly synthesized compound, 4'-geranyloxyferulic acid–*N*(omega)-nitro-L-arginine methyl ester suppresses inflammation associated colorectal carcinogenesis in male mice. *International Journal of Cancer*, ***135***, 774-785.

[9] Kandioller W, Balsano E, Meier SM, Jungwirth U, Göschl S, Roller A, Jakupec MA, Berger W, Keppler BK, Hartinger CG. (**2013**) Organometallic anticancer complexes of lapachol: metal centre-dependent formation of reactive oxygen species and correlation with cytotoxicity. *Chemical Communications*, ***49***, 3348-3350.

[10] Rocha MN, Nogueira PM, Demicheli C, de Oliveira LG, da Silva MM, Frézard F, Melo MN, Soares RP. (**2013**) Cytotoxicity and *in vitro* antileishmanial activity of antimony (V), bismuth (V), and yin (IV) complexes of lapachol. *Bioinorganic Chemistry and Applications*, 2013:961783. doi: 10.1155/2013/961783.

[11] Oramas-Rovo S, Torrejón C, Cuadrado I, Hernández-Molina R, Hortelano S, Estévez-Braun A, de Las Heras B. (**2013**) Synthesis and cytotoxic activity of metallic complexes of lawsone. *Bioorganic & Medicinal Chemistry Letters*, ***22***, 2471-2477.

[12] Pitzer KS. (**1979**) Relativistic effects on chemical properties. *Accounts of Chemical Research*, ***12***, 271-276.