



Synthesis of naphthoxazole derivatives from lapachol and their isolation by countercurrent chromatography

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INTRODUCTION

In recent years, a number of studies showed that the heterofunctionalization of the quinone structure of β -lapachone in the preparation of bioactive imidazoles and oxazoles were of great value in the treatment of Chagas's disease.^{1,2}

The use of other natural quinones, such as lapachol (**1**), in the synthesis of new heterocycles becomes important in the development of new bioactive substances, either in the combat of Chagas's disease or in the treatment of other diseases.

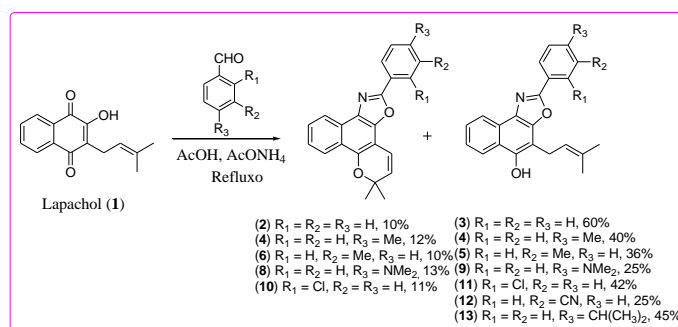
Silica gel column chromatography is the chromatographic method conventionally used for the purification of these derivatives, however it consumes much time and large amounts of solvent. In order to improve the isolation procedure, high speed countercurrent chromatography was used instead.³

RESULTS AND DISCUSSION

Lapachol (**1**) was obtained by extraction of milled wood of *Tabebuia* sp. The heterocycles were synthesized by nucleophilic condensation of lapachol (**1**) with aldehydes which generated the most active imidazoles in previous studies with β -lapachone in the presence of ammonium acetate and acetic acid as solvent under reflux (Scheme 1).

The formation of products, as well as the end of the reactions were monitored by thin layer chromatography (TLC) using silica gel chromatographic plates where the main products were oxazole derivatives together with byproducts of different polarities.

Each reaction lead to the formation of two products with very close polarities, which were purified by countercurrent chromatography (PC Inc.), using hexane:acetonitrile:methanol (2:2:1) as solvent system, upper phase as mobile phase (normal phase) at a flow rate of 2 mL/min. The sample reaction (100 mg) was dissolved in 5 mL of the solvent system (2,5 mL of each phase) and injected on a 80 mL column. 60 fractions of 4 mL were collected, and the substances retained on the column were recovered in the elution-extrusion mode (over 20 fractions) using the stationary phase as mobile phase.



Scheme 1: Obtention of naphthoxales derivatives.

Spectroscopic data analyses showed that one of the products was the naphthoxazole of β -xiloidone, and the other, the naphthoxazole with the isoprenyl side chain derived from lapachol (**1**).

CONCLUSION

The condensation reactions with lapachol (**1**) led to the formation of naphthoxazoles as major reaction products. High speed countercurrent chromatography proved to be an efficient technique for the separation and purification of these derivatives. using the same solvent system, economy of time and solvent when compared to conventional liquid chromatography technique (with solid support).

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