Synthesis of Lapachol Analogues through Suzuki-Miyaura Cross-Coupling. Antitumoral Evaluation.

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INTRODUCTION

Lapachol (Figure 1) is a naphtoquinone extracted from the bark of Pau d`Arco. This compound presents antineoplasic activity that is associated to the DNA repair inhibition and also acts as an oxidation and phosphorylation inhibitor in the mitochondria. It is believed that the presence of the prenyl group is important to the observed activity. Recently, the molluscicidal, antimalarial, antitrypanosomal and antiviral activities of lapachol and analogues have been reported.[1]

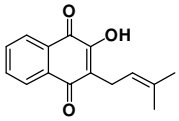
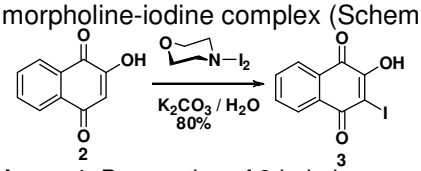


Figure 1. Lapachol

RESULTS AND DISCUSSION

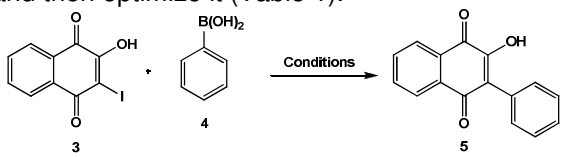
Our purpose in this work is to synthesize new lapachol analogues type (**5**), in which the olefin moiety at the side chain in **1** is replaced for aromatic groups, employing the Suzuki-Miyaura cross-coupling reactions between (**3**) and (4) and analyze their antitumoral profiles.

Lawsone (**2**), used as starting material, was transformed into 3-iodine-lawsone (3) in 80% yield, using the morpholine-iodine complex (Scheme 1).[2]



Scheme 1. Preparation of 3-iodo-lawsone

Then, the cross-coupling reactions were conducted under different reactional conditions[3a,b,c] in order to find the most favorable to our system (Scheme 2), and then optimize it (Table 1).



Conditions: A= $Pd(PPH_3)_4$, Na_2CO_3, DME/EtOH, 85ºC (60%); B= $Pd(PPH_3)_4$, K_3PO_4, DMF, 110ºC (%) not determinated; C= Pd/C, K_2CO_3, Dioxane/H_2O, 95ºC (83%)

Scheme 2. Suzuki-Miyaura reaction between **3** and **4**.

Table 1. Yields for reactions of Scheme 1

Entry	(**3**)	(**4**)	Pd/C	(**5**) Yield%
1	1eq	2eq	10mol%	89%
2	1eq	2eq	5mol%	99%
3	1eq	2eq	1mol%	95%
4	1eq	1.4eq	5mol%	85%

Other aryl-boronic acids were tested under the optimized conditions C, which gave better results providing the expected products in good yields. Afterward, the hydroxyl group of the lapachol analogues was protected in the form of OAc or $OCONEt_2$[4] in order to enhance their lipophilic character, and their antitumoral profiles were also analyzed, rendering promising results.

CONCLUSION

The cross-coupling reaction conducted under conditions C, presented better results and the optimization of the reaction allowed excellent yields of the synthesis of lapachol analogues, using few quantity of the catalyst.

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