Quinonoid and phenazine compounds: synthesis of new antimycobacterial prototypes

Paula F. Carneiro,[a] Maria do Carmo F.R. Pinto,[a] Tatiane S. Coelho,[b] Antonio V. Pinto,[a†] Kelly C.G. Moura,[a] Pedro A. da Silva[b] and Eufrânio N. da Silva Júnior[c*]

[a]Núcleo de Pesquisas em Produtos Naturais, UFRJ, RJ, Brazil; [b]Laboratório de Micobacterias, Departamento de Patologia, FURG, RS, Brazil; [c]Laboratório de Química Sintética e Heterocíclica, Instituto de Ciências Exatas, Departamento de Química, UFMG, MG, Brazil.

**eufranio@ufmg.br*

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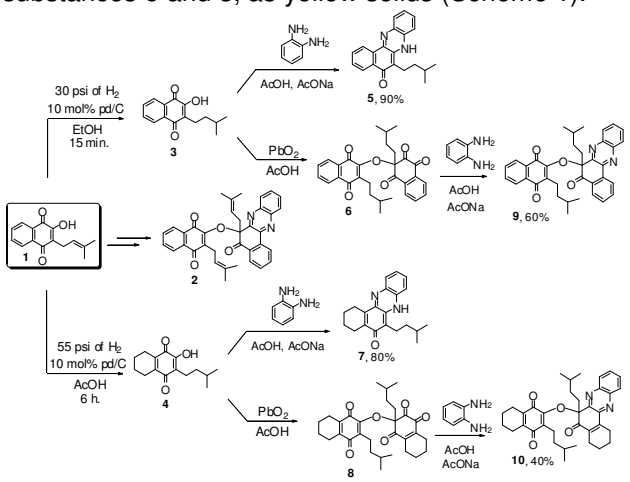
INTRODUCTION

Tuberculosis (TB) is a very aggressive disease caused by *Mycobacterium tuberculosis* (MT) and still represents nowadays a cause of globally death.[1]

Recently, our research group has investigated the antitumor,[2] trypanocidal[3] and antimycobacterial[4] activity of a large number of compounds obtained from lapachol (**1**). In this context, we present the synthesis and evaluation of phenazine compounds obtained from diverse quinones against MT pan-susceptible and resistant strains.

RESULTS AND DISCUSSION

Initially, from lapachol (**1**) the phenazine **2** was prepared. Lapachol (**1**) was reduced by catalytic reduction and the substances **3** and **4** were prepared and used to synthesize the phenazines **5** and **7** in good yields and the ether derivatives **6** and **8**, respectively. Finally, the ether phenazine derivatives **9** and **10** were obtained from the substances **6** and **8**, as yellow solids (Scheme 1).



Scheme 1. Obtention of phenazine compounds.

The minimum inhibitory concentrations (MICs) for the compounds were evaluated against MT $H_{37}Rv$, MT rifampicin resistance (ATCC 35338) and MT isoniazid resistance (ATCC 35822). The toxicity of compounds toward a normal proliferating cell was investigated using the Alamar Blue assay. The compounds were classified by us according to their activity against MT as highly active (MIC ≤ 3 µg/mL), lowly active (3 µg/mL < MIC < 100 µg/mL and), or inactive (MIC > 100 µg/mL).

Lapachol (**1**) and the compounds **2**, **9** and **10**, were considered inactive when MIC >100 µg/mL for $H_{37}Rv$, ATCC 35338 and ATCC 35822 strains and the substances **3** and **4** were lowly active.

With MIC value of 25, 12.5 and 25 µg/mL for MT $H_{37}Rv$, MT rifampicin resistance and MT isoniazid resistance the reduced quinone **4** can be considered as an important prototype.

The substance **7** was highly active [MIC ≤ 3 µg/mL (9.75 µM)] against MT $H_{37}Rv$. For ATCC 35822 strains the compound was less active with MIC value of 12.5 µg/mL and for ATCC 35822 strain was inactive. The substance **7** was not cytotoxic against normal cells (IC_{50} > 25 µg/mL).

CONCLUSION

All the new compounds were synthesized in good yields, by the proposed methodology. The substance **7** was highly active [MIC ≤ 3 µg/mL (9.75 µM)] against MT $H_{37}Rv$ and emerge as interesting new lead compound in drug development for the treatment of TB.

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