Synthesis of 3-triazole-*nor*-β-lapachones with potential trypanocidal activity

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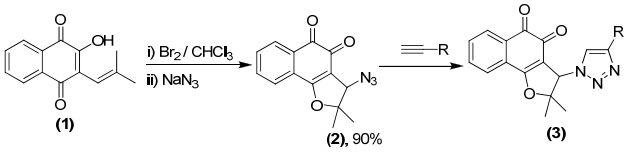
INTRODUCTION

Quinones are a class of natural and synthetic substances which have a wide variety of beneficial effects. They characterize a class of molecules for prevention and treatment against several diseases, such as osteoporosis and cardiovascular disease.

The quinone compounds have been described as important structures present in substances possessing diverse pharmacological activity as demonstrated antitumoral[1] and trypanocidal[2]. The objective of this work consisted in the development of new synthetic substances derived from *nor*-β-lapachone containing triazole cores, aimed at expanding the trypanocidal activity of *nor*-β-lapachone.

RESULTS AND DISCUSSION

The general protocol for the synthesis of the [1,2,3]-triazole-1,2-furanonaphthquinones used in this study is reported below. Briefly, the compounds *nor*-β-lapachone were reacted with excess of bromine then sodium azide to yield compound **2**, which them through Huisgen[3] 1,3-dipolar cyclyzation with an appropriate terminal alkyne catalyzed by copper (I) ion, also known as click reaction[i], led to the [1,2,3]-triazole-1,2-furanonaphthquinones (**3a-n**) (Scheme 01)[4].



3a, R = Bu, 90%
3b, R = Pr, 80%
3c, R = Pent, 70%
3d, R = Hex, 88%
3e, R = CH_2OH, 88%
3f, R = CH_2OAc, 75%
3g, R = CH_2OTHP, 98%
3h, R = $C(OH)Me_2$, 83%
3i, R = C(OH)MeEt, 90%
3j, R = C_6H_5, 92%
3k, R = p-$OMeC_6H_5$, 56%
3l, R = C_6H_{10}, 52%
3m, R = C_6H_9, 48%
3n, R = p-C_6H_4-nPent, 65%

Scheme 01: Triazoles synthesized

All compounds obtained so far have been sent to pharmacological tests against trypomastigotes forms of *T. cruzi*, the causative agent of Chagas disease.

Table 01: Trypanocidal activity of thiol derivatives

Compounds	IC_{50}/24h (μM) 4°C 5% blood	Compounds	IC_{50}/24h (μM) 4°C 5% blood
3a	**50,0 ± 7,4**	**3h**	**126,9 ± 12,2**
3b	**150,93 ± 45,44**	**3i**	**94,4 ± 7,7**
3c	**47,2 ± 7,4**	**3j**	**22,6 ± 3,2**
3d	**23,2 ± 3,2**	**3k**	**357,4 ± 21,6**
3e	**155,9 ± 15,2**	**3l**	**60,1 ± 9,3**
3f	**102,04 ± 13,70**	**3m**	**51,4 ± 2,0**
3g	**51,4 ± 2,0**	**3n**	**127,8 ± 15,7**
Nor-lapachol	**1281,0 ± 167,0**	**Crystal Violet**	**536,0 ± 3,0**
Benznidazole	**103,6 ± 0,6**		

All compounds were more active than the *nor*-lapachol and crystal violet. Among all evaluated the two most active were the **3d** (R = hexyl) and **3j** (R = C_6H_5), which demonstrated better trypanocidal profile than benznidazole.

CONCLUSION

The results of that work are satisfactory, being within our planning, which makes us optimistic about obtaining the other desired substances, which will be submitted to biological tests trypanocidal and other. The implemented methodology was effective to obtain the triazole-*nor*-β-lapachone derivatives with excellent yields.

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CAPES CNPq FAPERJ PRONEX FAPERJ

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