Synthesis and evaluation against *Trypanosoma cruzi* of naphthoquinone-containing triazoles

Emilay B. T. Diogo,¹ Gleiston G. Dias,¹ Wagner O. Valença,¹ Celso A. Camara,¹ Mauro G. da Silva,¹ Ronaldo N. de Oliveira,¹ Rubem F. S. Menna-Barreto,² Solange L. de Castro³ and Eufrânio N. da Silva Júnior*a

¹Instituto de Ciências Exatas, Departamento de Química, UFMG, MG, Brazil; ²Departamento de Ciências Moleculares, UFRPE, PE, Brazil; ³Laboratório de Biologia Celular, IOC, FIOCRUZ, RJ, Brazil.

Keywords: Lapachol, β-Lapachone, Quinone, Chagas disease, Click chemistry.

**INTRODUCTION**

Chagas disease (CD), caused by the protozoan *Trypanosoma cruzi*, affects approximately eight million individuals in Latin America.¹

CD is characterized by a short acute phase defined by patent parasitemia and a long and progressive chronic phase. Up to 40%-50% of chronically infected patients develop progressive cardiomyopathy and/or motility disturbances of the esophagus and colon. The available chemotherapy for CD is not satisfactory depending on two heterocyclic agents, nifurtimox and benznidazole.²

Naphthoquinones are considered privileged structures in medicinal chemistry due to their structural properties and biological activities. Recently, we have described the synthesis, trypanocidal and leishmanicidal activity of lapachone-based 1,2,3-triazoles.³ In this context, herein we describe the synthesis and evaluation against *T. cruzi* of 1,2,3-triazole substituted para and ortho-naphthoquinones.

**RESULTS AND DISCUSSION**

Compounds 1-10, N-phthalimidoalkyl-azides, and 11-12 were initially synthesized and used in a click chemistry reaction with substituted 2-(prop-2-yn-1-ylamine)-naphthoquinone to obtain the respective triazole compounds in high yields (Scheme 1).

**Scheme 1.** Obtention of para-quinones 1-12.

Ortho-quinones were synthesized from the intermediate azide 13 previously described.⁴ To prepare the novel derivatives 14-16, naphthoquinones substituted by a terminal alkyne were obtained and used in the click chemistry reaction (Scheme 2). Nor-β-lapachone derivatives 14-16 were isolated in moderate yields.

**Scheme 2.** Obtention of ortho-quinones 14-15.

The substances 1-12 were not active against *T. cruzi* with IC₅₀/24h > 4000 µM. Compounds 14-15 was planned in order to obtain ortho-quinone-coupled to para-quinoidal structure (Scheme 2). Our strategy was effective and the substances 14-16 presented IC₅₀/24 h values = 80.8, 6.8 and 8.2 µM, respectively. When compared with benznidazole, the standard drug used against *T. cruzi*, compounds 15 and 16 were fifteen and twelve times more active than anti-*T. cruzi* drug benznidazole.

**CONCLUSION**

We synthesized and evaluated fifteen substances and three potent trypanocidal compounds were identified, more active than the anti-*T. cruzi* drug benznidazole, the standard anti-*T. cruzi* drug. Compound 15 was fifteen times more active than benznidazole and this substance is a promising candidate for further investigations.

**ACKNOWLEDGEMENTS**

This research was supported by grants from the CNPq, CAPES, FAPEMIG, FAPEAL, FACEPE-PROMEN, Fiocruz and UFMG.

**REFERENCES**