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

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INTRODUCTION

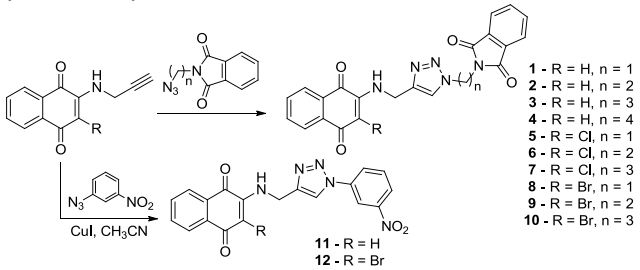
Chagas disease (CD), caused by the protozoan *Trypanosoma cruzi*, affects approximately eight million individuals in Latin America.[1]

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.

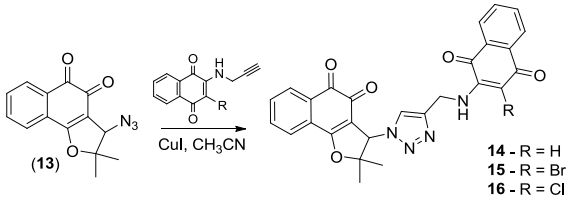
RESULTS AND DISCUSSION

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.[3] 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 IC_{50}/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 IC_{50}/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.

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