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Generation and Capture of Naphthoquinonynes: A New Frontier in the Development of Trypanocidal Quinones via Aryne Chemistry

Laura P. R. Figueroa,[1,2] Renato L. de Carvalho,[1] Luana A. Machado,[1] Renata G. Almeida,[1] Esther R. S. Paz,[1] Emilay B. T. Diogo,[1] Maria H. Araujo,[1] Warley S. Borges,[2] Victor F. S. Ramos,[3] Rubem F. S. Menna-Barreto,[3] James M. Wood,[4] John F. Bower*[5] and Eufrânio N. da Silva Júnior*[1]

1) Department of Chemistry, Universidade Federal de Minas Gerais, UFMG, 31270-901, Brazil
2) Department of Chemistry, Universidade Federal do Espírito Santo, CEP 29075-910, Vitória, ES, Brazil.
3) Laboratory of Cellular Biology, IOC, FIOCRUZ, 21045-900, Brazil
4) The Ferrier Research Institute, Victoria University of Wellington, Wellington, 6012, New Zealand.
5) University of Liverpool, Crown Street, Liverpool, L69 7ZD, United Kingdom.

e-mail: john.bower@liverpool.ac.uk; eufranio@ufmg.br

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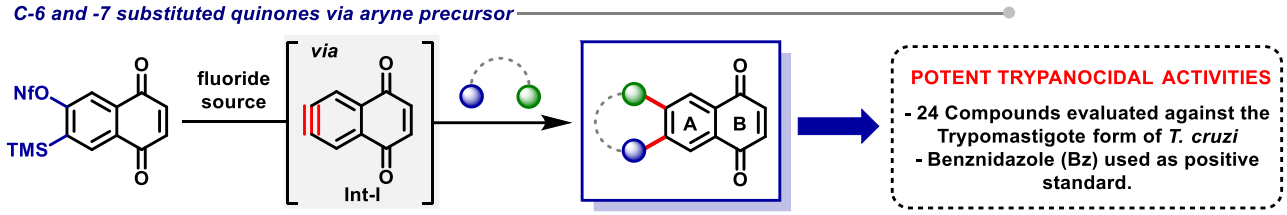
ABSTRACT

Chagas disease, caused by the parasite *Trypanosoma cruzi*, presents significant challenges in treatment, particularly due to the limitations of the currently available drugs, benznidazole (BZ) and nifurtimox (NFX).[1] Quinones are involved in key biochemical processes and have numerous pharmacological applications, including remarkable trypanocidal activity.[2-7]Studies made by our research group have demonstrated that A-ring functionalization of naphthoquinones can (i) improve trypanocidal activity and (ii) provide compounds with lower cytotoxicity.[2-7] Recently, we have described methods for the generation and *in situ* capture of naphthoquinonynes, and this enables polyfunctionalizations at the C-5, -6 and -7 positions.[8] The current study investigated the use of amines and pyridine-*N*-oxides as reaction partners to achieve regioselective functionalization of A-ring naphthoquinones. This approach led to the discovery of 14 new compounds that demonstrated higher activity compared to benznidazole, in which two of these newly identified compounds exhibited approximately 10-fold greater activity than BZ.



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