Synthesis of new naphthotriazoles derived from juglone as anticancer agents

Wanderson A. da Silva[a], Vinicius N. Moreira [a], Vinícius R. Campos[a], Vitor F. Ferreira[a], David R. da Rocha[a], Jackson A. L. C. Resende[b], Raquel C. Montenegro[c], Maria Cecília B. V. de Souza[a], and Anna C. Cunha[a*]

[a]Universidade Federal Fluminense, Departamento de Química Orgânica, Programa de Pós-Graduação em Química, Outeiro de São João Batista, 24020-141 Niterói, RJ, Brasil

[b]Universidade Federal Fluminense, Departamento de Química Inorgânica, Programa de Pós-Graduação em Química, Outeiro de São João Batista, 24020-141 Niterói, RJ, Brasil

[c]Universidade Federal do Pará, Instituto de Ciências Biológicas, Belém, PA, Brasil.

**corresponding author. Tel.: +55 21 26292364; Fax: +55 21 26292135; e-mail: annac@vm.uff.br*

Keywords: triazole, anticancer activity and juglone

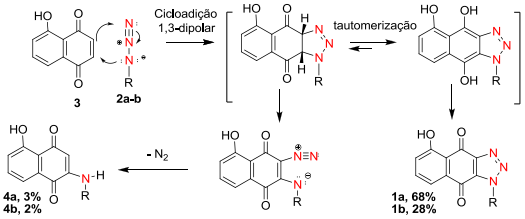
INTRODUCTION

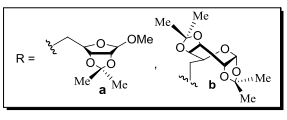
Juglone (**3**) is a natural compound isolated from nogueira plants (Juglans nigra) which has shown important cytotoxic activity[1].Quinones fused to *N*-heterocyclic aromatic rings have been reported in the literature[2] as potential anticancer agents.

On the basis of our experience in the field of the synthesis and biological evaluation of new quinone-carbohydrate conjugates[3] and 1,2,3-triazole derivatives, we described the synthesis and *in vitro* anticancer activity studies of new compounds type **1** in which Juglone and 1,2,3-triazole frameworks are directly attached (Scheme).

RESULTS AND DISCUSSION

The thermal 1,3-dipolar cycloaddition reaction between glycosyl azides **2a-b** and juglone (**3**) afforded corresponding 5-hydroxy-1-substituted-1*H*-naphtho[2,3-d][1,2,3-]triazole-4,9-diones **1a-b**, in moderated yields, and unexpected naphthoquinone derivatives **4a-b**, which possess an aminocarbohydrate chain at the C-2 position of the quinone ring.





Scheme1: Synthesis of naphthoquinone glycoconjugates 1a-b e 4a-b.

The regiochemistry of the reactions was determinated on the basis of X-ray crystallographic data of the molecular structures of compounds **1a** and **4a**.

The *in vitro* anticancer activity of the new Juglone derivatives **1a-b** and **4a-b** were assessed against HL-60, MDA-MB 435, HCT-116, SF-295, A-549 and OVCAR-8 human cancer cell lines.

Among the **1a-b** and **4a-b**, only the naphthotriazole compounds **1a and 1b** showed potential activity (IC_{50} below 1.0 μg/mL^{-1}) against five cell lines.

CONCLUSION

The cycloaddition reaction of the glycosyl azides **2a-b** with Juglone (**3**) furnished the corresponding naphthotriazole derivatives **1a-b** in moderated yields, together with unexpected aminonaphthoquinones **4a-b**.

The compounds **1a** and **1b** were screened for their anticancer activity and exhibited an expressive cytotoxic effect against five cancer cell lines.

To analyze the eventual effect of the pharmacophoric 1,2,3-triazole moiety fused to homoaromatic ring, we also evaluated the biological activity of the aminonaphthoquinones **4a** and **4b**. They weren´t citotoxic against all tested cancer cell lines. This result shows that the aza-heterocyclic moiety conjugated with naphthoquinone ring is a considerably important factor that confers anticancer activity of new quinone derivatives **1a** and **1b**.

ACKNOWLEDGEMENTS

This work was supported by the Brazilian agency FAPERJ-Pronex. Fellowship granted to UFF, by FAPERJ, Capes, CNPq-PIBIC is gratefully acknowledged.

REFERENCES

[1]Silva, M. N.; Ferreira, V. F.; Souza, M. C. B. V., *Quím. Nova* 2003, 26, 407.

[2]Oliveira,R.B.A., José, R., *Quím. Nova* 2002, 25, 976.

[3] Ferreira, V. F.; Jorqueira, A.; Souza, A. M. T; Silva, M. N.; Souza, M. C. B. V.; Gouve, R. M.; Rodrigues, C. R.; Pinto, A. V.; Castro, H. C.; Santos, D. O.; Araújo, H. P.; Bourguignon, S. C., *Bioorg. Med. Chem.* 2006, 14, 5459.