Synthesis of new naphthotriazoles derived from juglone as anticancer agents

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INTRODUCTION

Juglone (3) is a natural compound isolated from noqueira plants (Juglans nigra) which has shown important cytotoxic activity¹. Quinones fused to N-heterocyclic aromatic rings have been reported in the literature² as potential anticancer agents. On the basis of our experience in the field of the synthesis and biological evaluation of new quinone-carbohydrate conjugates³ 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-1H-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.

![Scheme 1: Synthesis of naphthoquinone glycoconjugates 1a-b and 4a-b.](Image)

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 (IC₅₀ 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.

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