



Synthesis of a goniotalamin triazolic analogue.

Ian de Toledo*, Ismael Raitz, Ronaldo A. Pilli.

Abstract

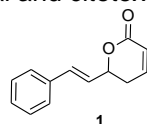
Goniotalamin triazolic analogue **10** was prepared through CuAAC click chemistry and showed good to moderate results in MTT assay against tumor cell lines (HCT 116 and MCF-7).

Key words:

Goniotalamin, Triazole, Click Chemistry.

Introduction

Goniotalamin (**1**) is a styryl α,β -unsaturated lactone isolated from plants of genera *Goniotalamus*^{1a} and it has been also isolated from native species *Cryptocarya moschata*.^{1b} Goniotalamin shows antimicrobial, antifungal, trypanocidal and citotoxic biological activity.²



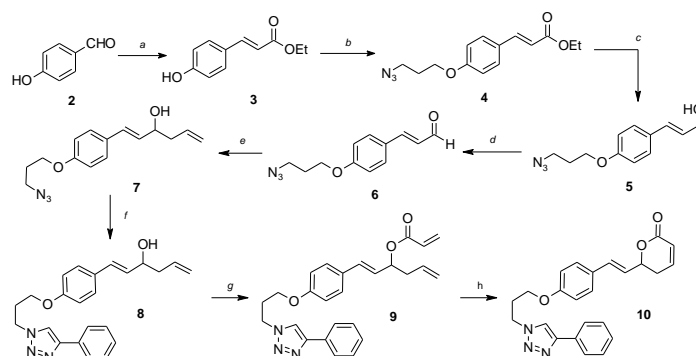
Previous studies from our group showed that goniotalamin is associated with oxidative stress and apoptosis; evidence for mitochondrial impairment has been also reported.³

An approach for elucidation of its mode of action in organelles and exogenous substances is the use of fluorescent probes for cellular imaging and the benzothiadiazole (BTD) system stands out due to reduced size and selectivity for mitochondria, an organelle closely involved with apoptosis. By coupling fluorescent probes to goniotalamin it would be possible to access information about goniotalamin mode of action and click chemistry was envisaged to promote the coupling of goniotalamin to fluorescent probes through a copper (I) catalysed alkyne-azide coupling (CuAAC).

Results and Discussion

To merge BDT probes with goniotalamin would be necessary to synthesize an azido goniotalamin analogue so it could be coupled to the acetylenic moiety from the probe. As a proof of concept, phenylacetylene was coupled to goniotalamin resulting in the triazolic analogue **10**. The synthetic route (**Scheme 1**) starts with a Horner-Wadsworth-Emmons olefination of aldehyde **2** resulting in the ester **3** which is subjected to S_N2 reaction with 3-azido-1-bromopropane yielding azido ester **4**. Reduction followed by oxidation of **4** yields aldehyde **6** which is subjected to Grignard addition with allylmagnesium bromide to yield the homoallylic alcohol **7**. CuAAC reaction with azide moiety of **7** and phenylacetylene results in triazole **8** which is subject to esterification with acryloyl chloride yielding the ester **9**. Ring closing metathesis (RCM) with Grubbs 2nd generation (Grubbs II) catalyst of **9** converted **9** to the goniotalamin triazolic analogue **10**.

MTT assays with **1** and **10** were conducted to evaluate cytotoxicity and cell proliferation against tumor cell lines MCF-7 (breast) and HCT 116 (colon) (**Chart 1**)



a) triethyl phosphonoacetate (2.5 eq.), NaH (3 eq.), THF/DMF, 0 °C to 85 °C, 2h, 79%; b) 3-azido-1-bromopropane (1.1 eq.), K₂CO₃ (5 eq.), KI (1.5 eq.), acetone, 60 °C, 18h 75-80%; c) DIBAL-H (2.5 eq.), DCM, -78 °C, 30 min, 90%; d) MnO₂ (17.8 eq.), DCM, rt, 86%; e) allylmagnesium bromide (1.5 eq.), THF, -78 °C, 1h, 62%; f) phenylacetylene (1.2 eq.), CuI (1 eq.), MeCN, rt, 2h, 54%; g) acryloyl chloride (1.5 eq.), triethylamine (2 eq.), DCM, rt, 1h, 76%; h) Grubbs II (10 mol%), DCM, reflux, 2h, 38%.

Scheme 1. Synthetic route towards triazolic goniotalamin analogue

Chart 1. GI₅₀ values, in μ M, for compounds **1** and **12**.

Compound	HCT 116	MCF-7
1	5.2 \pm 0.9	6.0 \pm 1.0
10	1.8 \pm 0.1	22.5 \pm 24.8

Compound **10** showed good cytotoxic activity in HCT 116 cells and moderate in MCF-7 tumor cell line when compared to goniotalamin (**1**). These results suggest that new molecules can be coupled to **1** through CuAAC since there is no significant decrease in active due to the introduction of alkyl and triazole moieties.

Conclusions

Goniotalamin triazolic analogue **10** was synthesized successfully and showed good results in MTT assays against HCT 116 tumor cell line.

Acknowledgement



¹ (a) Senthil-Nathan, S.; Choi, M. Y.; Paik, C., H. e Kalaivani, K. *Chemosphere*, **2008**, 72, 1393. (b) Cavalheiro, A. J. e Yoshida, M. *Phytochemistry*, **2000**, 53, 811.

² (a) Martins, C. V. B.; et al. *J. Appl. Microbiol.*, **2009**, 107, 1279. (b) de Fátima, A.; et al. *Eur. J. Med. Chem.* **2006**, 41, 1210 (c) Martins, C. V. B et al. *Lett. Drug Design Disc.* **2008**, 5, 74 (d) Fátima, A. de et al. *Bioorg. Med. Chem.* **2006**, 14, 622

³ (a) de Fátima, A. et al. *Chem. Biol. Interact.* **2008**, 176, 143 (b) de Fatima, A et al *J. Curr. Med. Chem.* **2006**, 13, 3371