Synthesis of a goniothalamin triazolic analogue.

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Abstract
Goniothalamin 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: Goniothalamin, Triazole, Click Chemistry.

Introduction
Goniothalamin (1) is a styryl α,β-unsaturated lactone isolated from plants of genera Goniothalamus and it has been also isolated from native species Cryptocarya moschata. Goniothalamin shows antimicrobial, antifungal, trypanocidal and citotoxic biological activity.

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

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 goniothalamin it would be possible to access information about goniothalamin mode of action and click chemistry was envisaged to promote the coupling of goniothalamin to fluorescent probes through a copper (I) catalysed alkyne-azole coupling (CuAAC).

Results and Discussion
To merge BDT probes with goniothalamin would be necessary to synthesize an azido goniothalamin so it could be coupled to the acetylenic moiety from the probe. As a proof of concept, phenylacetylene was coupled to goniothalamin resulting in 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 Sn2 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. CuACC 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 10 converted 9 to the goniothalamin 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).

Scheme 1. Synthetic route towards triazolic goniothalamin analogue

Chart 1. Gl50 values, in μM, for compounds 1 and 12.

<table>
<thead>
<tr>
<th>Compound</th>
<th>HCT 116</th>
<th>MCF-7</th>
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<tbody>
<tr>
<td>1</td>
<td>5.2 ± 0.9</td>
<td>6.0 ± 1.0</td>
</tr>
<tr>
<td>10</td>
<td>1.8 ± 0.1</td>
<td>22.5 ± 24.8</td>
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Compound 10 showed good cytotoxic activity in HCT 116 cells and moderate in MCF-7 tumor cell line when compared to goniothalamin (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
Goniothalamin triazolic analogue 10 was synthesized successfully and showed good results in MTT assays against HCT 116 tumor cell line.

Acknowledgement