Synthesis and Cytotoxic Activity of Aromatic Guanylhydrazones

Paulo H. B. França¹ (PG)*, Jamyly N. S. Ferro² (PG), Emiliano O. Barreto² (PQ), Cláudia do Ó Pessoa³ (PQ), Antônio E. G. Santana¹ (PQ), João X. de Araújo-Júnior¹ (PQ)

¹Laboratório de Pesquisa em Recursos Naturais, Universidade Federal de Alagoas
²Laboratório de Biologia Celular, Universidade Federal de Alagoas
³Laboratório de Oncologia Experimental, Universidade Federal do Ceará
*
pauloh.barcellos@gmail.com

Table 1. IC₅₀ values for growth inhibition activity of guanylhydrazones on human tumor cell lines

<table>
<thead>
<tr>
<th>Cell Line</th>
<th>10</th>
<th>14</th>
<th>17</th>
<th>19</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDAMB 435</td>
<td>1.13</td>
<td>0.13</td>
<td>1.14</td>
<td>2.70</td>
</tr>
<tr>
<td>HL-60</td>
<td>2.20</td>
<td>0.35</td>
<td>1.08</td>
<td>2.20</td>
</tr>
<tr>
<td>HCT8</td>
<td>1.28</td>
<td>0.20</td>
<td>0.49</td>
<td>1.00</td>
</tr>
<tr>
<td>SF295</td>
<td>1.28</td>
<td>0.19</td>
<td>0.56</td>
<td>1.65</td>
</tr>
</tbody>
</table>

Introduction

Guanylhydrazones comprise a class of substances showing several pharmacological activities including antineoplastic¹. Furthermore, it is widely known that these compounds act as competitive inhibitors of S-adenosyl-L-methionine descarboxylase, which is involved in biosynthesis of the biogenic polyamines spermidine and spermine².

Our aim is to report the cytotoxic activity of a series of aromatic guanylhydrazones in human tumor cell lines.

Results and Discussion

Twenty compounds were synthesized using a convergent methodology with microwave irradiation. The cytotoxic effects of the 20 compounds were evaluated in vitro on three tumor cell lines, including colon cancer (HCT-8), melanoma (MDA-MB435) and glioblastome (SF-295) via MTT assay at the concentration of 5 μg/mL and compared with the control compound doxorubicin.

Compounds 10, 14, 17 and 19 showed average percentage of cell growth inhibition greater than 90% and this was comparable to those of doxorubicin against tumor cell lines at the concentration of 5 μg/mL.

Compounds with the highest growth inhibitory activity were further monitored by surveying the IC₅₀ values against all three previous tumor cell lines and the promyelocytic leukemia cell line (HL-60). The data obtained is presented in Table 1. IC₅₀ values reported in literature for doxorubicin vary in the range of 0.01 and 0.96 μg/mL for tumor cell lines herein described³⁴.

Synthesized guanylhydrazones were also evaluated towards peritoneal macrophages. Results showed that compounds 4, 8, 12, 14, 16 and 17 reduced the cell viability percentage at all tested concentrations including 10, 100 and 1000 μM.

In order to investigate the possible involvement of reactive oxygen species (ROS) generation in the toxicity process, the nitroblue tetrazolium reduction assay was carried out with compounds 10 and 19, which strongly inhibited tumor cell lines rather than peritoneal macrophages at the lowest concentration tested (10 μM). We observed that at this concentration, compounds 10 and 19 led to increased ROS generation when cells were incubated either with vehicle or with lipopolysaccharide.

Conclusions

In connection with the aforementioned results, we conclude that compounds 10 and 19 exhibited the most promising profiles as cytotoxic agents.

Acknowledgements

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