Design, Green Synthesis and Cytotoxicity of 30 Curcumin-Cinnamaldehyde Hybrids

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Palavras Chave: curcumin, cinnamaldehyde, molecular hybridization, cytotoxicity, apoptosis

Abstract

Two curcumin-cinnamaldehyde hybrids presented cytotoxicity on cancer cells, which promoted cell death by necrosis.

Introdução

Curcumin (1) and cinnamaldehyde (2) are natural products, which demonstrated potent cytotoxic and antineoplastic activities. These compounds are able to induce death cell by apoptosis pathway.¹,²

Fig 1. Curcumin (1) and Cinnamaldehyde (2)

Altogether, we designed and synthesized a series of 30 curcumin-cinnamaldehyde hybrids, as well as evaluated their toxic effect against three human tumorigenic cell lines, A549 (lung), DU145 (prostate), and HepG2 (liver), as well as MRC-5, a non-tumorigenic lung cells. Selectivity index (SI) was calculated from the IC₅₀ values of MRC-5 and A549, using formula: $IS = IC_{50}(MRC-5)/IC_{50}(A549)$. Additionally, potent cytotoxic compounds were submitted to pro-apoptotic activity assays, using nuclear morphology analysis.

Resultados e Discussão

Compounds were designed by using of molecular hybridization tool. C₆C₆ and C₅C₅ subunits of 1 and 2, respectively, were fused and lead to diphenylpentanoid hybrid (C₆C₆C₅C₅). This skeleton does not exhibit two toxic and reactive subunits, aldoxyl and β-diketone of 1 and 2, respectively, which have been indicated as responsibilities by classification of 1 and 2 as Pan-Assay Interference Substances (PAINS).³

Fig 2. Curcumin-Cinnamaldehyde Hybridization

Aromatic rings of diphenylpentanoids displayed electron-withdrawing groups (F, Cl, Br, CF₃ and NO₂) and electron-donor groups (CH₃, OH and OCH₃) for preliminary SAR analyses. Compounds were synthesized using aldol condensation reactions between aldehydes and ketones, under basic or acidic catalysis. Ethanol, glycerol or PEG400 were used as green solvents. Reaction yields ranging from 12 to 87 %. In general, compounds substituted by hydroxyl groups demonstrated high cytotoxicity, displaying IC₅₀ values bellow to IC₅₀ values of 1 and 2. Among tested compounds, LQVM114 and LQVM116 were more potent and selective than 1 and 2. Preliminary SAR analyses indicated number and position of hydroxyl groups were crucial to antiproliferative effect. Regioisomer LQVM 115 was quite less active than LQVM114.

Tab 1. IC₅₀ and SI Values of 1, 2 and their Hybrids

<table>
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<tr>
<th>R</th>
<th>R¹</th>
<th>MRC 5</th>
<th>A549</th>
<th>SI</th>
<th>DU 145</th>
<th>Hep G2</th>
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<tr>
<td>1</td>
<td>-</td>
<td>-</td>
<td>42.0</td>
<td>87.6</td>
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<tr>
<td>2</td>
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<td>-</td>
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<tr>
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<td>OH</td>
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<td>161</td>
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<tr>
<td>116</td>
<td>OH</td>
<td>OH</td>
<td>13.3</td>
<td>18.6</td>
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</table>

Pro-apoptotic activity evaluation of LQVM114 and LQVM116 on A549 cells, indicating, predominantly necrosis effect. Also, early and late apoptosis were observed to reduced number of cells.

Conclusões

Curcumin-cinnamaldehyde hybrids were more potent and selective than their PAIN prototypes, indicating their specific drug-like interactions with receptors. In contrast, they were not able to induce apoptosis, when compared to 1 and 2.

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