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

Carlos R. Polaquini[1](PG), Guilherme S. Torrezan[1](PG), Gabriela M. Ayusso[1](IC), Laiza A. Almeida[1](IC), Isabel Silva[2](PQ), Fernando R. Pavan[2](PQ), Henrique Ferreira[2](PQ), Luis O. Regasini[1]*(PQ)

***regasini@ibilce.unesp.br**

[1] LQVM – Laboratório de Química Verde e Medicinal, Departamento de Química e Ciências Ambientais, IBILCE - Instituto de Biociências, Letras e Ciências Exatas, Unesp, São José do Rio Preto, SP, Brasil. [2] Departamento de Bioquímica e Microbiologia, Instituto de Biociências, Unesp, Rio Claro, SP, Brasil.

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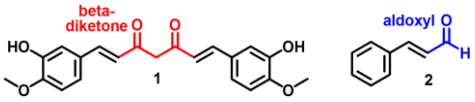
Abstract

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**)

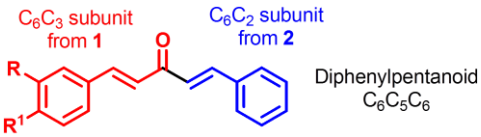


Altogether, we designed and synthesized a series of 30 curcumin-cinnamaldehyde hybrids, as well as evaluated their toxic effect against three human tumorigenic cell lines, A549 (lung), DU145 (prostate), and HepG2 (liver), as well as MRC-5, a non-tumorigenic lung cells. Selectivity index (SI) was calculated from the IC_{50} values of MRC-5 and A549, using formula; $IS=IC_{50}(MRC\text{-}5)/IC_{50}(A549)$. 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. C_6C_3 and C_6C_2 subunits of **1** and **2**, respectively, were fused and lead to diphenylpentanoid hybrid ($C_6C_5C_6$). This skeleton does not exhibit two toxic and reactive subunits, aldoxyl and β-diketone of **1** and **2**, respectively, which have been indicated as responsibles 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, CF_3 and NO_2) and electron-donor groups (CH_3, OH and OCH_3) 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 IC_{50} values bellow to IC_{50} 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. IC_{50} and SI Values of **1**, **2** and their Hybrids

	R	R^1	MRC-5	A549	SI	DU 145	Hep G2
1	-	-	42.0	87.6	0.48	47.0	45.9
2	-	-	117	291	0.40	110	179
114	OH	H	22.9	19.4	1.18	15.4	20.5
115	H	OH	100	161	0.62	108	127
116	OH	OH	13.3	18.6	0.71	17.7	27.7

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**.

Agradecimentos

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