SYNTHESIS AND BIOLOGICAL EVALUATION OF CURCUMINE ANALOGUES AS APOPTOSIS-INDUCING AGENTS

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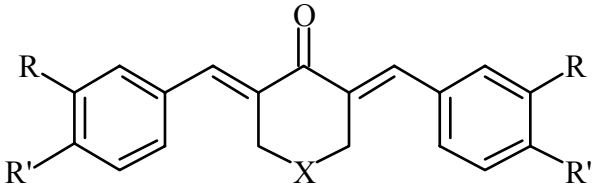
Apoptosis, also known as programmed cell death, is a physiological cell suicide mechanism, whose morphological appearance relies on the activation of caspase-family cisteine proteases and on the alterations in mitochondrial membrane structure. Recent studies focused the attention on the potential anticancer properties of hydroxylated compounds such as curcumin **1** and resveratrol [1,2].
In particular curcumin (**1**), a natural product endowed with a wide range of pharmacological properties, displayed good antiproliferative activity due to its ability to induce apoptosis in tumor cells. On the bases of these premises, we designed various derivatives in order to explore new areas of structural alteration of curcumin. In particular, we replaced the α,γ-diketo moiety of **1,** with a cyclohexanone, *N*-methylpiperidone, *N*-ethylpiperidone, and *N*-benzylpiperidone rings, obtaining derivatives **2** as conformationally restrained analogues of curcumin.



2

X= NCH_2CH_3, NCH_3 , NBz, CH_2
R = OH, OCH_3, NO_2 , Cl

The antiproliferative (IC_{50}, inhibition concentration 50%) and apoptotic (AC_{50}, concentration able to induce apoptosis in 50% of cells) activities of these compounds were evaluated *in vitro* on a myeloblastic leukemia cell line (HL60).
Interestingly, a number of derivatives **2** were endowed with antiproliferatie and apoptotic activities at concentrations ranging from 0.5 to 3 μM.

[1] H. Ligeret, S. Bathelemy, R. Zini, JP. Tillement, S. Labidalle, D Morin, et al. *Free Radical Biology and Medicine*, *Vol 36*, No. 7, pp 919-929, **2004** .
[2] M. Roberti, D. Pizzani, D. Simoni, R. Rondanin, R. Baruchello, C. Bonora, F. Buscemi, S. Grimaudo, M. Tolomeo, et al. *J. Med. Chem*. **2003**, *46*, 3546.