

DISCOVERY OF GS27, A NOVEL, OLEOCANTHAL BASED COMPOUND, AS NOVEL INHIBITOR OF ATP CITRATE LYASE

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Oleocanthal, a key ingredient of EVOO, has attracted considerable scientific attention in recent years because of its biological activities and contribution to many aspects of human health. Prompted by the outstanding interest of this high-value natural compound, herein we describe the development of a concise and scalable procedure for the synthesis of various Oleocanthal analogues. The synthesis is performed by a convenient biomimetic and stereo-controlled approach, starting from oleuropein, an abundant raw material in olive leaves [1].

All synthesized compounds were evaluated for their anticancer activity against nine cancer cell lines with interesting activities. One of them, namely GS27, displayed significant activity against all cancer cell lines, bearing appropriate ADME properties. GS27 altered the phosphorylation profile of ACLY, AMPK, and p70S6 in different cell types. ACLY is the “gate”-keeping enzyme that controls the *de novo* liposynthesis in cells, thus, targeting ACLY activity is a promising strategy to tackle the needful glucose dependent lipid synthesis for the propagating cancer cells. Furthermore, since GS27 decreases the phosphorylation of both ACLY and p70S6, is able to inhibit two major metabolic pathways like *de novo* liposynthesis and protein synthesis.

[1] Sarikaki G., Christoforidou N., Gaboriaud-Kolar N., Smith A. B. III, Kostakis I.K., Skaltsounis A. L. Biomimetic Synthesis of Oleocanthal, Oleacein, and Their Analogues Starting from Oleuropein, A Major Compound of Olive Leaves. *J. Nat. Prod.* 2020, 83, 6, 1735–1739