Tyrosol and hydroxytyrosol carbonates and carbamates as novel antiradical and antimicrobial agents: a chemo-enzymatic flow synthesis

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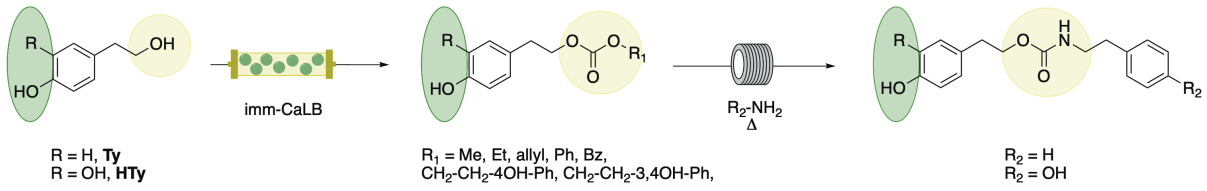
Most chemical and pharmaceutical industries aim at developing new synthetic strategies towards the concepts of eco-sustainability described by the twelve principles of green chemistry, reducing pollution, waste and hazardous effects on workers' health. Food-derived phenolic compounds have recently been described as object of interest by nutraceutical, cosmetic and phamaceutical companies for their antioxidant, metal chelator, free radical scavenger, antimicrobial and antiinflammatory properties.[1,2] However, their relevance as active ingredients is still limited due to metabolic/chemical instability, solubility and bioavailability issues.

Carbonate and carbamate chemical moieties play an important role in modern drug discovery and medicinal chemistry; thus, the development of environmentally friendly processes, exploiting no-toxic and biodegradable chemicals, is necessary. In this context, we developed a chemo-enzymatic continuous flow synthesis of tyrosol (Ty) and hydroxytyrosol (HTy) carbonates and carbamates. Starting from these natural molecules, a series of lipophilic derivatives were synthetized, increasing or leaving unaltered the antiradical and antimicrobial properties of the parent compounds. *Candida antarctica* lipase B (CaLB) was adopted as commercially available immobilized biocatalyst, suitably packed in a glass column reactor, and used in an unconventional organic medium as *tert*-amyl alcohol. A reproducible, efficient, safe, phosgene-free procedure to obtain carbonates has been set-up, followed by the nucleophilic attack using appropriate amines to obtain the desired carbamates (**Scheme 1**).[3,4] Moreover, a telescoped two-step process was developed to reduce manual handling, time and costs.



Scheme 1: Schematic representation of the chemo-enzymatic continuous synthesis of Ty and HTy derivatives.

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