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Auronas based on dihydroeugenol: attempts to synthesize new potentially antifungal compounds

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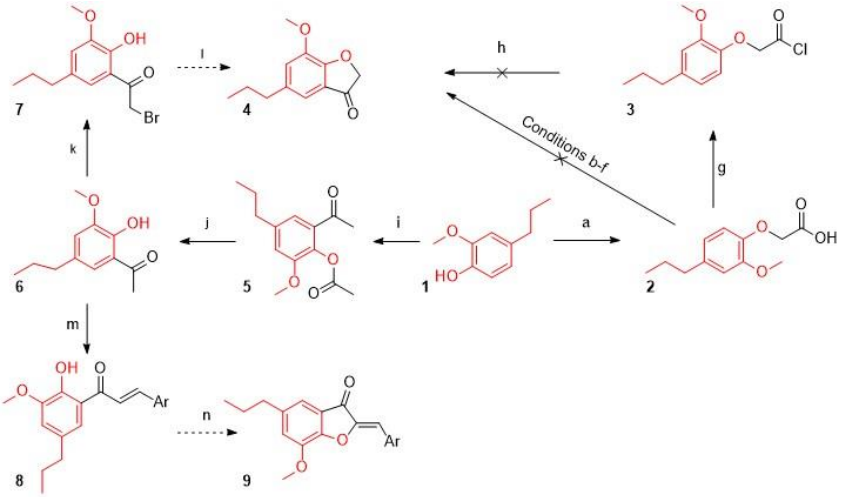
ABSTRACT

Aurones are heterocyclic compounds related to flavonoids that are found in nature or are obtained by synthesis. They present a myriad of biological activities (*e.g.*, antimicrobial, antiparasitic, antineoplastic, anti-inflammatory etc.), so several works report the creation of aurones with the most diverse structural patterns aiming at optimized properties[1]. Starting from findings not yet published concerning to antifungal activity, our working group has dedicated itself to the synthesis of new aurones with the general structure shown as **9** in the Scheme 1. Thus, it seemed feasible to use dihydroeugenol (**1**) as a starting compound, which could, by different routes, lead to the key intermediate benzofuranone (**4**) or to the aurones themselves (**9**). Based on a traditional methodology[2], **1** was converted to the acetic intermediate (**2**) which, as such or via its corresponding acid chloride, was tentatively subjected to intramolecular aromatic acylation conditions based on the available reagents at that time (steps **b**-**h**), but none of them led to the desirable product or even to a mixture of products accessible to separation. On the other hand, **1** could be led to the acetophenone **6** in two steps by aromatic acetylation reaction with acetic anhydride and zinc chloride followed by methanolysis of the ester. This ketone intermediate (**6**) followed two paths, one that led to the α-bromo ketone intermediate (**7**) by reaction with $CuBr_2$ and the other, through condensation with the respective aldehydes, to the corresponding chalcones (**8**)[3,4]. The next steps will be the formation of the benzofuranone intermediate (**4**) by cyclization of **7** in a basic medium or the final aurones (**9**) by oxidative cyclization of **8**.



a: NaH, Chloroacetic acid, DMF, 25 °C; b: Amberlite IR 120, $CaCl_2$, $CHCl_3$, 25 °C; c: H_2SO_4, 25 °C; d: PPA, 80 °C; e: MSA, 25 °C; f: PTSA, Graphite, 100 °C; g: $SOCl_2$ 70 °C; h: $AlCl_3$, $CHCl_3$, 0 °C or 150 °C; i: Ac_2O, $ZnCl_2$, 25 °C; j: $NaHCO_3$, MeOH, 25 °C; k: $CuBr_2$, EtOAc/CH_2Cl_2, 80 °C; l: TEA, ACN, 70 °C; m: NaOH, EtOH, Ar-CHO, 25 °C; n: $Hg(AcO)_2$, Pyridine, 25 °C.

Scheme 1: Synthesis route to new potentially bioactive aurones (Ar is an aromatic unit not yet to be disclosed).

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