UPROAR

Project title: *In silico*-guided design of semisynthetic antifungal derivatives targeting the Unfolded Protein Response (UPR) pathway: Towards an alternative crop protection

Acronym: **UPROAR** (Unfolded Protein RespOnse xAnthone cRop protection)

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Summary:

Endoplasmic reticulum is an important cell compartment for protein synthesis and its quality control. During proteogenesis, various biotic, abiotic, or physiological constraints can result in homeostasis imbalance, leading to an accumulation of (un)(mal)formed proteins. To cope with this imbalance, eukaryotes trigger a physiological adaptive response —so-called UPR (Unfolded Protein Response) pathway— in order to ensure the maintenance of homeostasis and cell survival. In mammals, the response to this stress involves the activation of three main effectors *i. e.* the transmembrane proteins PERK, ATF6 and IRE-1. However, in other organisms, such as fungal phytopathogens, IRE1 represents the only effector of the UPR pathway. Previous works showed that this pathway is involved in virulence by promoting the protection of pathogenic fungi against the toxicity of plant defense metabolites and in particular against phytoalexins.

Towards a planned reduction of the use of agrochemicals in crop protection, the present work will aim to develop new and efficient inhibitors of the fungal phytopathogens UPR pathway. We will favor natural inhibitors to be applied at low doses and acting in synergy with natural plant defense metabolites in order to prevent or reduce the pathogen growth.

These inhibitors will be based, after *in silico* screening, on natural xanthones (dibenzo gamma-pyrone scaffold) and chemical modifications will be *in silico*-guided. Xanthones will be obtained from natural and renewable sources such as mangosteen pericarps [harvested from mangosteen tree fruits, *Garcinia mangostana* (*Clusiaceae)*]. Optimized semisynthetic derivatives will be developed, and their ability to bypass the UPR-related defense mechanism of fungal phytopathogens as well as to restore the effectiveness of the natural defenses of crops will be evaluated.