Perturbing dissimilar biomolecular targets from natural product scaffolds and focused chemical decoration.

Nielsen, John; Tung, Truong Thanh; Tim, Holm Jakobsen; Trong Tuan, Dao; Anja T., Fuglsang; Michael, Givskov; Christensen, Søren Brøgger

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425 - Perturbing dissimilar biomolecular targets from natural product scaffolds and focused chemical decoration

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John Nielsen[1]*, john.nielsen@sund.ku.dk,* ***Truong Thanh Tung***[1]*, truong.tung@sund.ku.dk, Tim Holm Jakobsen*[2]*, Trong Tuan Dao*[1]*, Anja Fuglsang*[3]*, Michael Givskov*[2]*, Søren Christensen*[1]

[1] Department of Drug Design and Pharmacology, University of Copenhagen, Copenhagen, Denmark; [2] Immunology and Microbiology, University of Copenhagen, Copenhagen, Denmark; [3] Plant and Environmental Sciences, University of Copenhagen, Copenhagen, Denmark

Abstract: Fungal plasma membrane H^+-ATPase (Pma1) has recently emerged as a potential target for the discovery of new antifungal agents. This p-type pump plays a pivotal role in many physiological functions and processes inside the cell. Therefore, inhibition of Pma1 could lead to discovery of new antifungal agents. On first attempt, by screening natural product sources we have successfully discovered that curcuminoids as potent inhibitors of p-type ATPases from diverse kingdoms of life including Pma1. On other attempt, the fungal metabolite fusaric acid was reported to reduce stomatal conductance in banana plants infected by *Fursarium spp.* suggesting that the agent might stimulate the H^+-ATPase. The possibilities that fusaric acid could affect the H^+-ATPase inspired us to design and synthesize a focused library of structural analogues. However, a number of bioassays revealed no significant effect on the plasma membrane proton pump. To our delight, we took notice of the structure of fusaric acid being homologous to the gram-negative quorum sensing (QS) signal molecules and to some reported quorum sensing inhibitors (QSI). This encouraged us to test the QS inhibitory activity of the fusaric acid library in three cell-based biological screens. Consequently, we identified several compounds showing good QSI activity and a structure-activity relationship has been established. Herein, we present our story from natural product scaffolds to macromolecular biological target via focused chemical synthesis.