LEGO-inspired drug design: Discovery of novel fungal Plasma membrane H+-ATPase (Pma1) inhibitors from small molecule libraries: An introduction of HFSA-SBS_DOS-RD strategy in drug discovery.

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View Session Detail

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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 which localized on the surface of fungal cells plays a crucial role in many physiological functions and processes inside the cell. Especially, by pumping proton to extracellular, this enzyme generates a transmembrane electrochemical gradient, as a consequence, fungi can uptake nutrients by secondary transport systems. Until now, only low resolution of protein structure has been reported, and notably there a no report of co-crystal structure of Pma1 with inhibitors. Therefore, we have identified the need for small molecule library of high quality for targeting Pma1. The ***LEGO***®-inspired hypothesis encouraged us to first develop new strategy from the combination of hypothesis-based fragment selection and assembly (**HFSA**), specific biological relevance scaffold based diversity-oriented synthesis (**SBS_DOS**) and rational design (**RD**), so called ***HFSA-SBS_DOS-RD*** strategy in drug discovery and development process. Using ***HFSA-SBS_DOS-RD***, our group successfully designed, synthesized, and performed SAR studies of novel compounds potent Pma1 inhibitors. An expeditious, high yield and scalable microwave-assisted synthesis was developed and applied for synthesis of library compounds. To our delight, ours compound libraries were able to inhibit Pma1 activity and growth inhibitory activity of *C. albican* and *S. cerevisiae* revealed the most promising example for future development of antifungal drugs on this target.