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374 - 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

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.