Abstract

G proteins are key mediators of G protein-coupled receptor signalling, which facilitate a plethora of important physiological processes, such as the regulation of immune system and the modulation of homeostasis. The natural cyclic depsipeptide YM-254890 and the structurally similar natural product FR900359 are the only known inhibitors of the Gq subfamily. Despite the great interest of YM-254890 and FR900359 in the study of Gq-mediated signalling, none of them was generally available.

Previous limited supply of YM-254890 and FR900359 depends on the isolation from bacteria and natural plants, respectively and the chemical synthesis of YM-254890 and FR900359 has never been successful. Thus, the generation of YM-254890 and FR900359 is in urgent need to study the Gq-mediated signalling as tool compounds.

In this study, by using a combination of solid and solution phase synthesis, we achieved the first total synthesis of YM-254890 and FR900359, as well as did the first head-to-head pharmacological comparison of these two compounds on Gs-, Gi- and Gq-mediated signalings, which revealed that FR900359 is 3-fold more potent than YM-254890. In addition, the pharmacological comparison of the synthetic FR900359 with the natural FR900359 confirmed that the synthetic FR900359 and natural product are pharmacologically equivalent.

Next, the versatile synthetic route was used to generate a series of analogues of YM-254890, which provided the first systematic SAR study of this kind of compounds, nearly targeting every amino acid in YM-254890. The pharmacological characterization of these YM-254890 analogues led to the discovery of several equivalently potent and selective Gq inhibitors (YM-10, YM-13, YM-14, YM-18, YM-27) and demonstrated that the structural integrity of YM-254890 is very important to the maintain of potency as very small changes could dramatically change the potency.

Finally, the fluorescent Gq inhibitors were designed to visualize the GPCR signalling. Successful synthesis of the selected fluorescent Gq inhibitors gave the possibility of GPCR signalling visualization.