“Synthesis and Structure-Activity Relationship Studies of Schwarzinicine Alkaloids as Vasorelaxant Agents”

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Our group has recently isolated from a previously uninvestigated *Ficus* species (*F. schwarzii*) a series of seven new phenethylamine alkaloids, namely, schwarzinicines A–G. Schwarzinicine A, being the most abundant alkaloid of this series, was found to exhibit pronounced vasorelaxant effects in rat isolated aorta. In this study, we have successfully developed the total synthesis of schwarzinicines A and B. In order to explore the structure-activity relationship (SAR) around the structure of schwarzinicine A for vasorelaxant effects, several series of analogues were designed, synthesized and evaluated for their vasorelaxant activity. In addition to the discovery of 13 synthetic analogues that showed superior potency compared to schwarzinicine A, the SAR analysis revealed a few structural features that are associated with enhancement of vasorelaxant effects. Among them, we have demonstrated that the minimum structural requirement for the vasorelaxant activity, with reference to the schwarzinicine A structure, is the presence of two rings with one being an aromatic ring. Potency enhancement effects were observed when one of the phenyl rings was replaced with: a non-aromatic ring incorporating a basic nitrogen atom; a bicyclic heteroaromatic group; a monocyclic heteroaromatic group; a non-aromatic heterocyclic group; and a *p*-hydroxyphenyl group. A certain degree of conformational restriction to one of the phenyl-bearing side arms also appeared to improve the potency. The central nitrogen atom was essential for activity and must be in the ionized form when binding to the biological target. These structural features could be useful to design better vasorelaxant agents in the future.

The above final report has not been presented at the annual “MTSF Grant Research Symposiums” as the scheduled Years 2020 & 2021 Grant Research Symposiums were cancelled due to the Covid-19 pandemic.