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Organic Chem Curr Res 2018, Volume:7
DOI: 10.4172/2161-0401-C1-023

Synthesis of complex natural products analogues overcoming cancer resistance

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Flavaglines constitute a family of anticancer natural products that relieve the resistance to cancer chemotherapies and display a strong cytotoxicity that is specific to cancer cells. These natural cyclopenta[b]benzofurans are characterized by a densely functionalized tricyclic framework, as exemplified by the structures of rocaglamide. In this presentation, we will describe our own recent endeavor toward the synthesis of new flavagline derivative that display enhanced *in vivo* anticancer activities, due to their actions on scaffold proteins, prohibitins, and the translation initiation factor eIF4a. Our *in vivo* studies indicate that flavaglines could greatly improve the treatment of chemoresistant metastatic melanoma. These compounds are also able to inhibit KRAS, a considered undruggable oncogene. Considering that clinically effective KRAS inhibitors have remained elusive for more than three decades of intensive research, flavaglines thus appear to hold great promise for the treatment of chemoresistant cancers.

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