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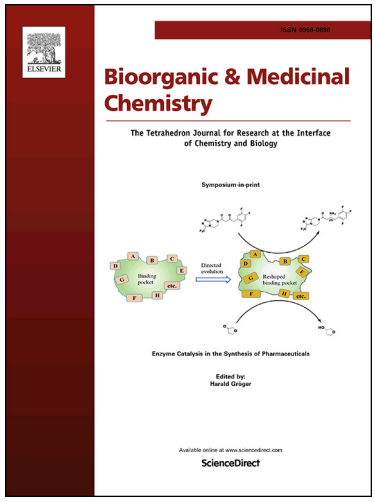

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Discovery of novel serine palmitoyltransferase inhibitors as cancer therapeutic agents

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Abstract

We pursued serine palmitoyltransferase (SPT) inhibitors as novel cancer therapeutic agents based on a correlation between SPT inhibition and growth suppression of cancer cells. High-throughput screening and medicinal chemistry efforts led to the identification of structurally diverse SPT inhibitors **4** and **5**. Both compounds potently inhibited SPT enzyme and decreased intracellular ceramide content. In addition, they suppressed cell growth of human lung adenocarcinoma HCC4006 and acute promyelocytic leukemia PL-21, and displayed good pharmacokinetic profiles. Reduction of 3-ketodihydrosphingosine, the direct downstream product of SPT, was confirmed under in vivo settings after oral administration of compounds **4** and **5**. Their anti-tumor efficacy was observed in a PL-21 xenograft mouse model. These results suggested that SPT inhibitors might have potential to be effective cancer therapeutics.

Keywords: SPT; 3-KDS; antitumor efficacy