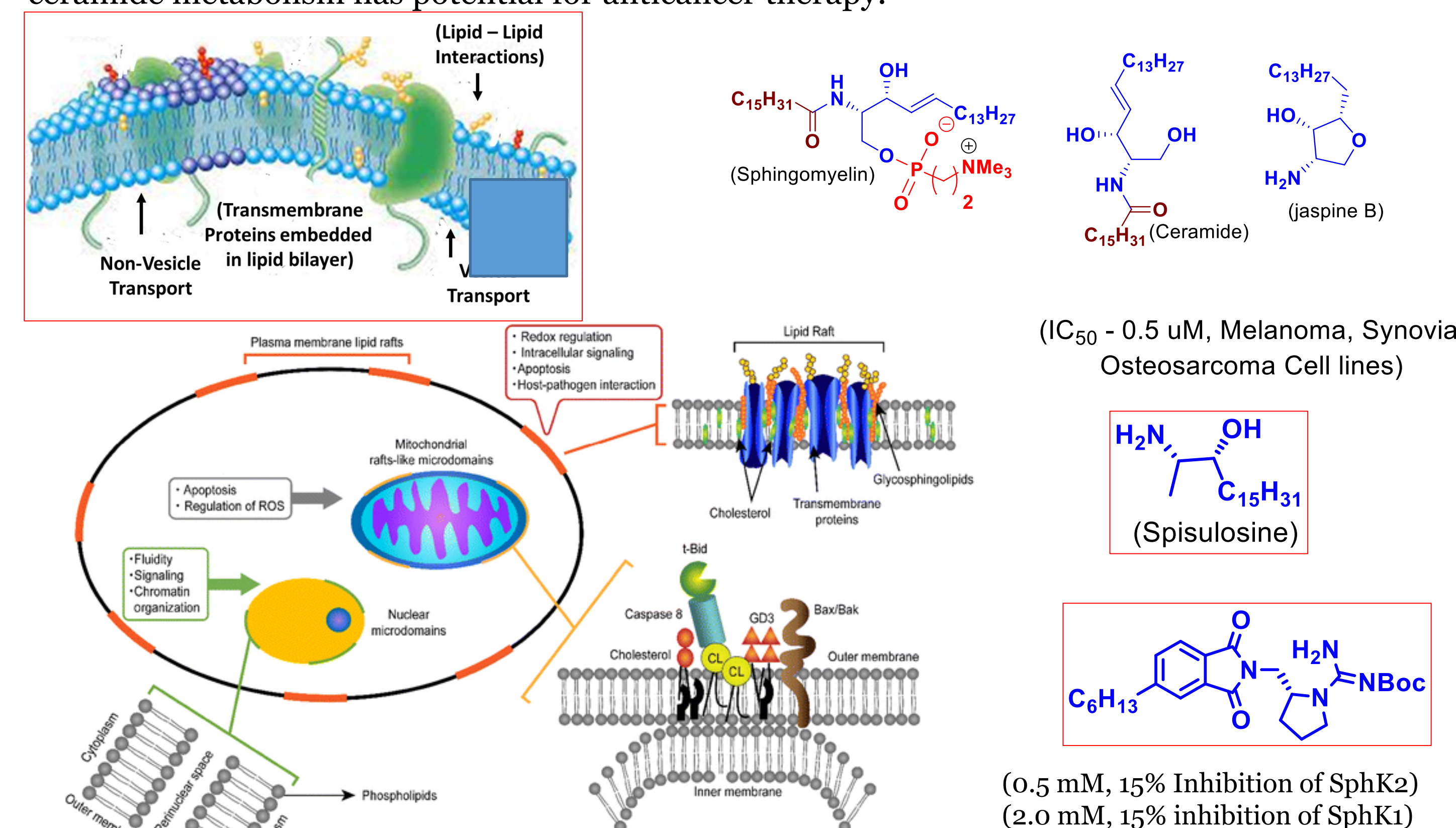


Background

Sphingolipids (SLs) are key modulators of physiological/pathophysiological processes. Sphingoid base constitutes a derivative of 1,2-anti amino alcohol polar head group and lipophilic tail. Sphingolipid constitute the basic building block of a lipid membrane. Interfering with biosynthesis and metabolism of lipid membrane has deleterious effects on the stability, functioning of membrane bound receptors, structural proteins, and enzymes. For example, disruption of mitochondrial membrane potential and cytochrome C release was observed in cancer cells by utilizing anhydrophytosphingosine, jaspine B. Significance of sphingolipids in preventing cancer progression was evidenced by in vitro studies involving increase in cellular ceramide levels. Inhibition of ceramide metabolism and increasing ceramide levels induced apoptosis in cancer cells. Interference with mitochondrial membrane potential targeting ceramide metabolism has potential for anticancer therapy.



Targeting Ceramide Biosynthesis and Metabolism

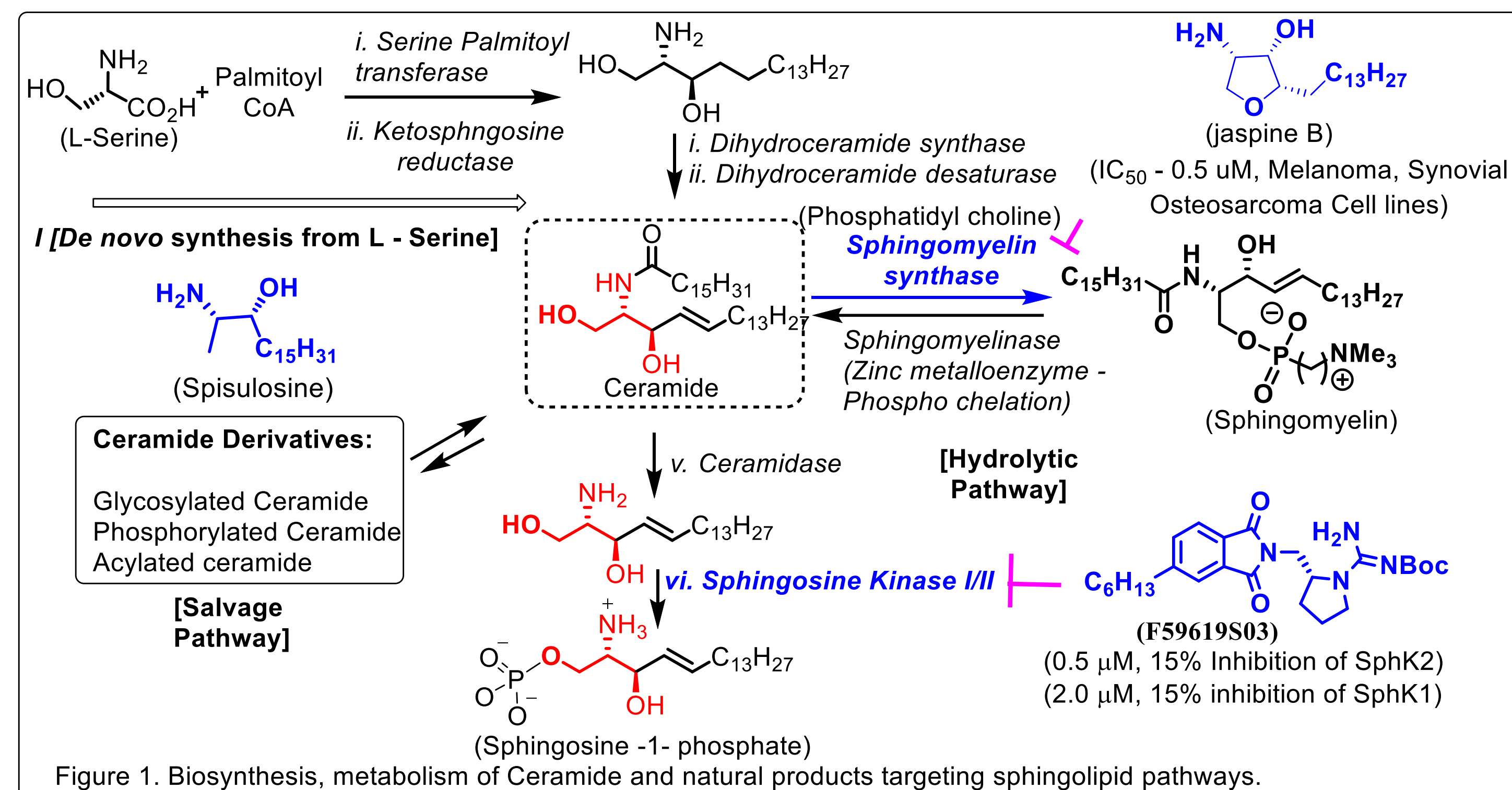
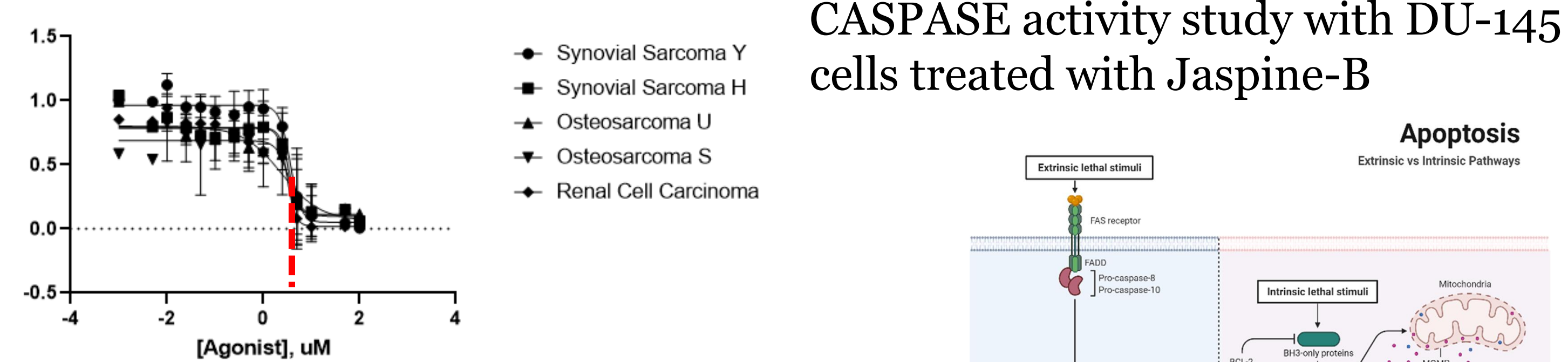
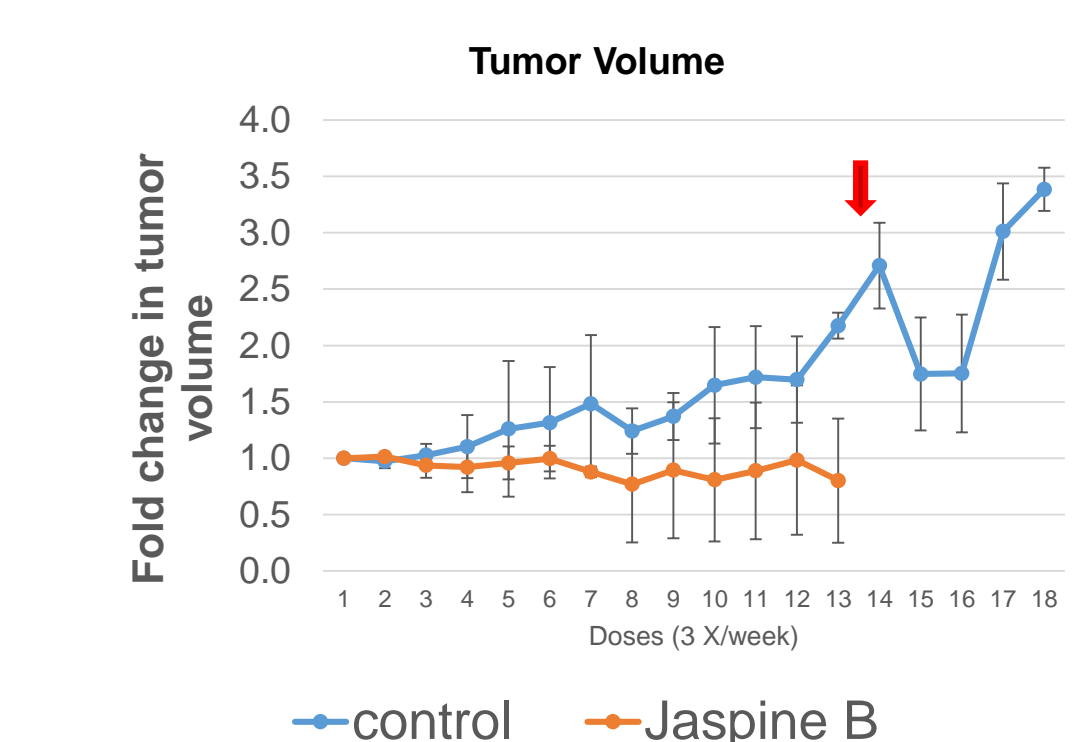


Figure 1. Biosynthesis, metabolism of Ceramide and natural products targeting sphingolipid pathways.

Results : In vitro, In vivo Assays of jaspine

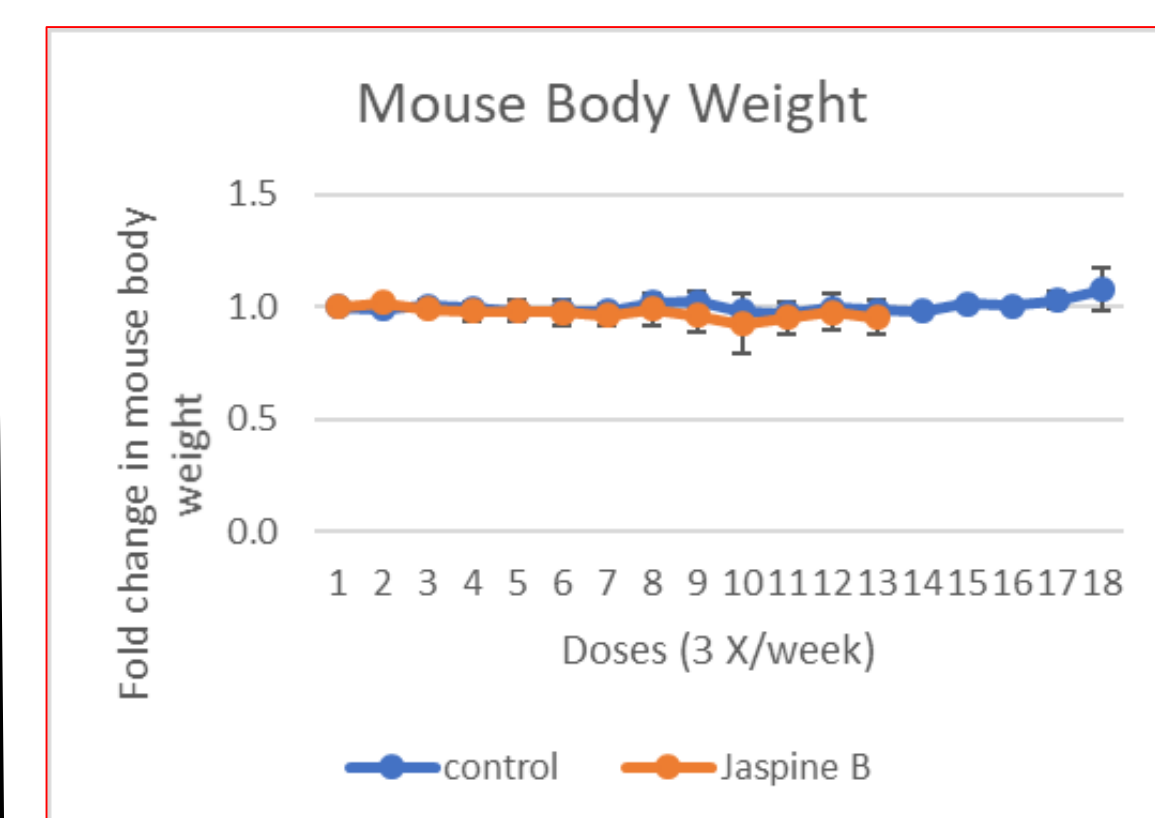


Result 1: Jaspine B exhibited Sub micromolar cytotoxicity.

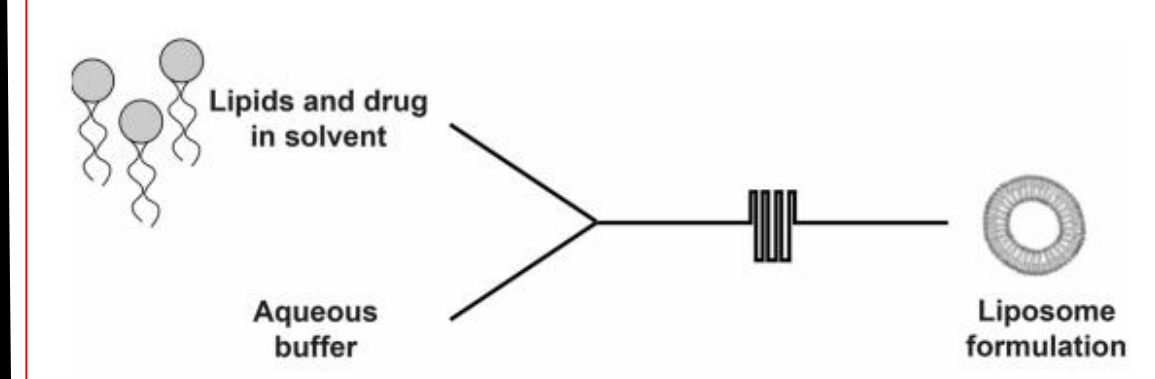


Result 2.

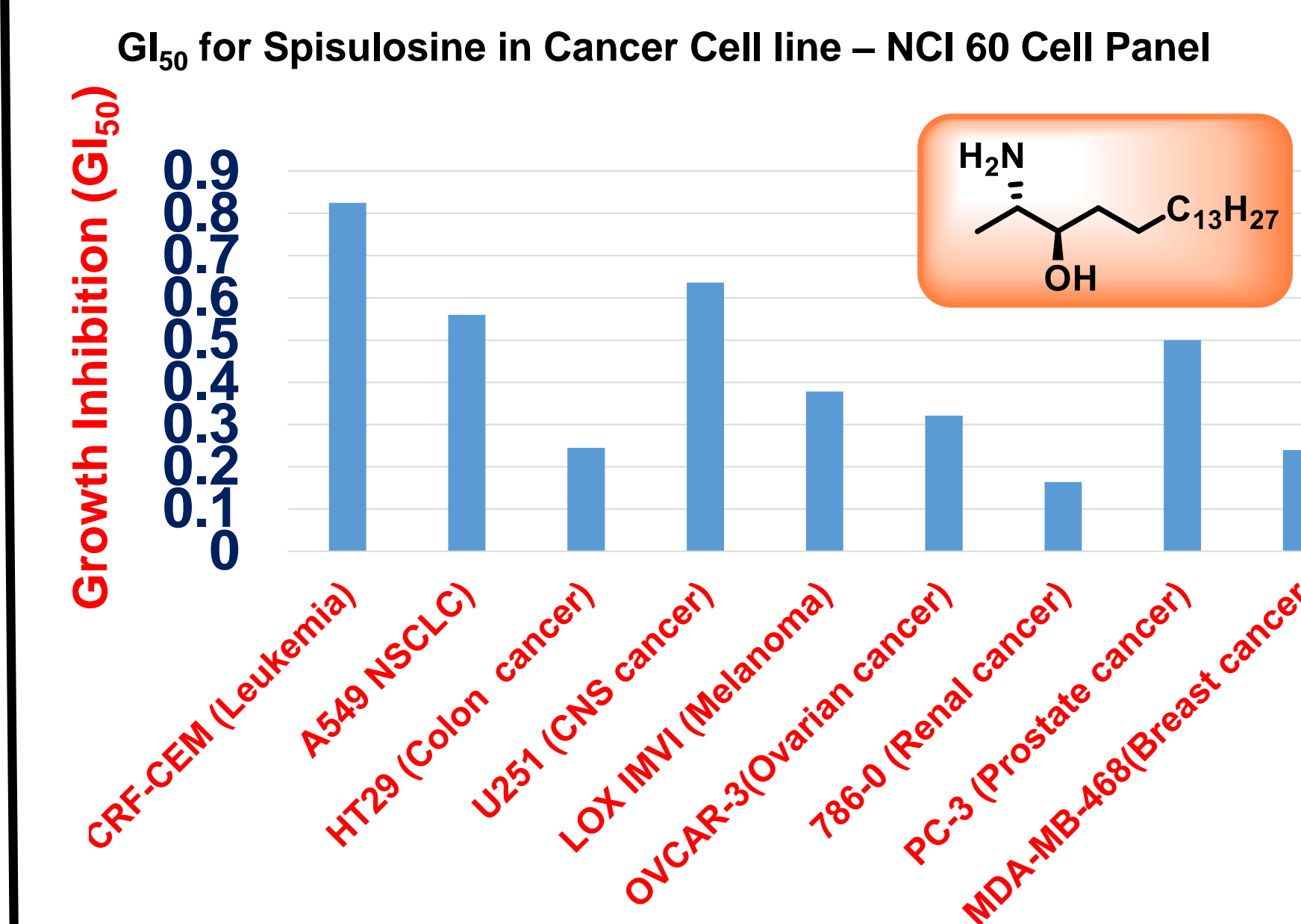
In vivo studies in synovial sarcoma exhibited tumor volume decrease after 12 weeks



Result 4. There is no significant loss in synovial sarcoma mouse body weight during the treatment period.

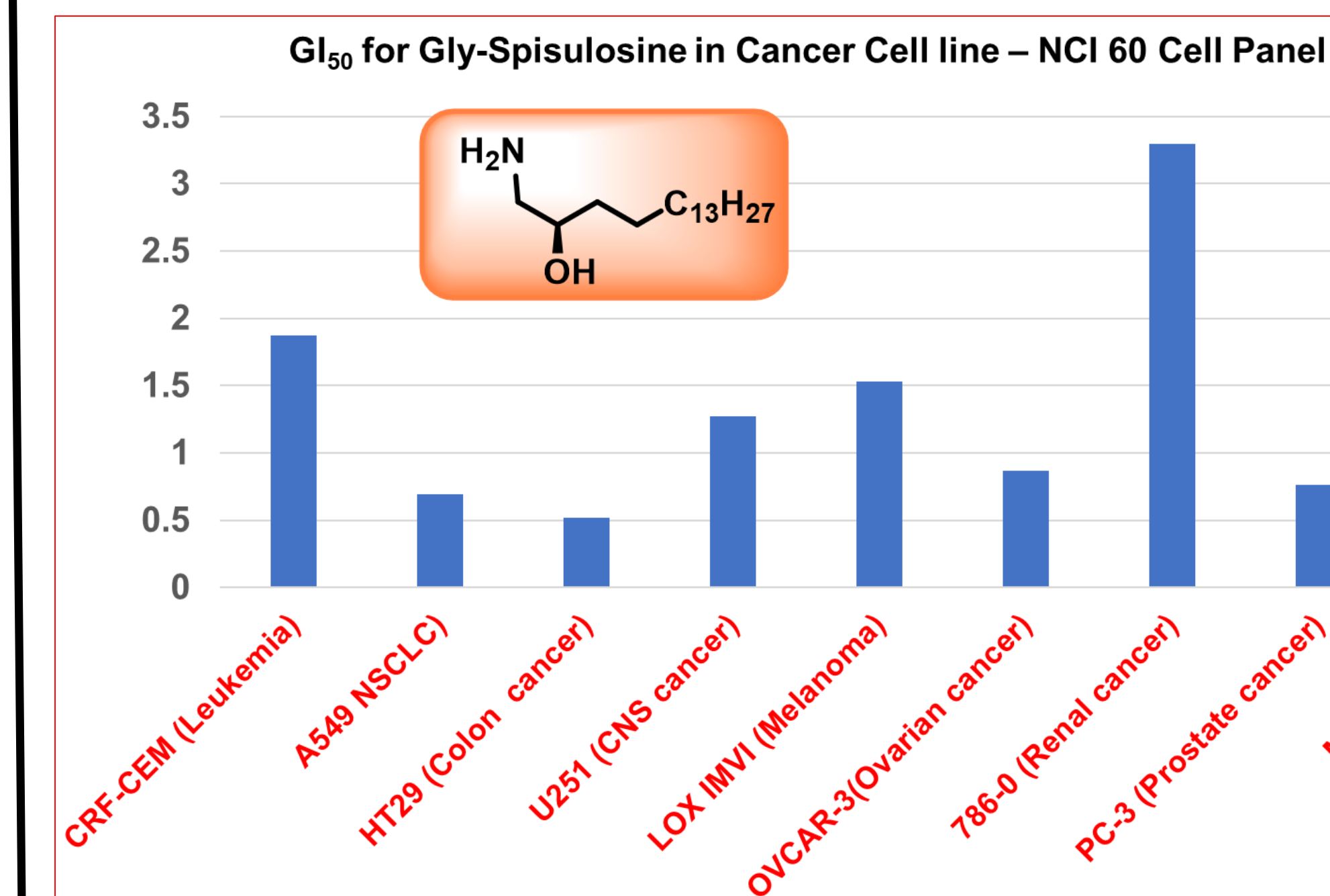


Result 5: a. Control mice synovial sarcoma with swollen joints with tumor microenvironment. b. Anticancer potential of jaspine B treated synovial sarcoma mice. c. Liposomal formulation of jaspine B reduced the tumor size compared with control.



Result 6

- Chiral pool strategy was utilized towards synthesis of Spisulosine and its analogs.
- Cell viability assays using Rhodamine B Assay.
- Spisulosine exhibited anticancer potential in several aggressive cancer cells.
- Potency in triple negative breast cancer, Colon cancer, Renal cancer.



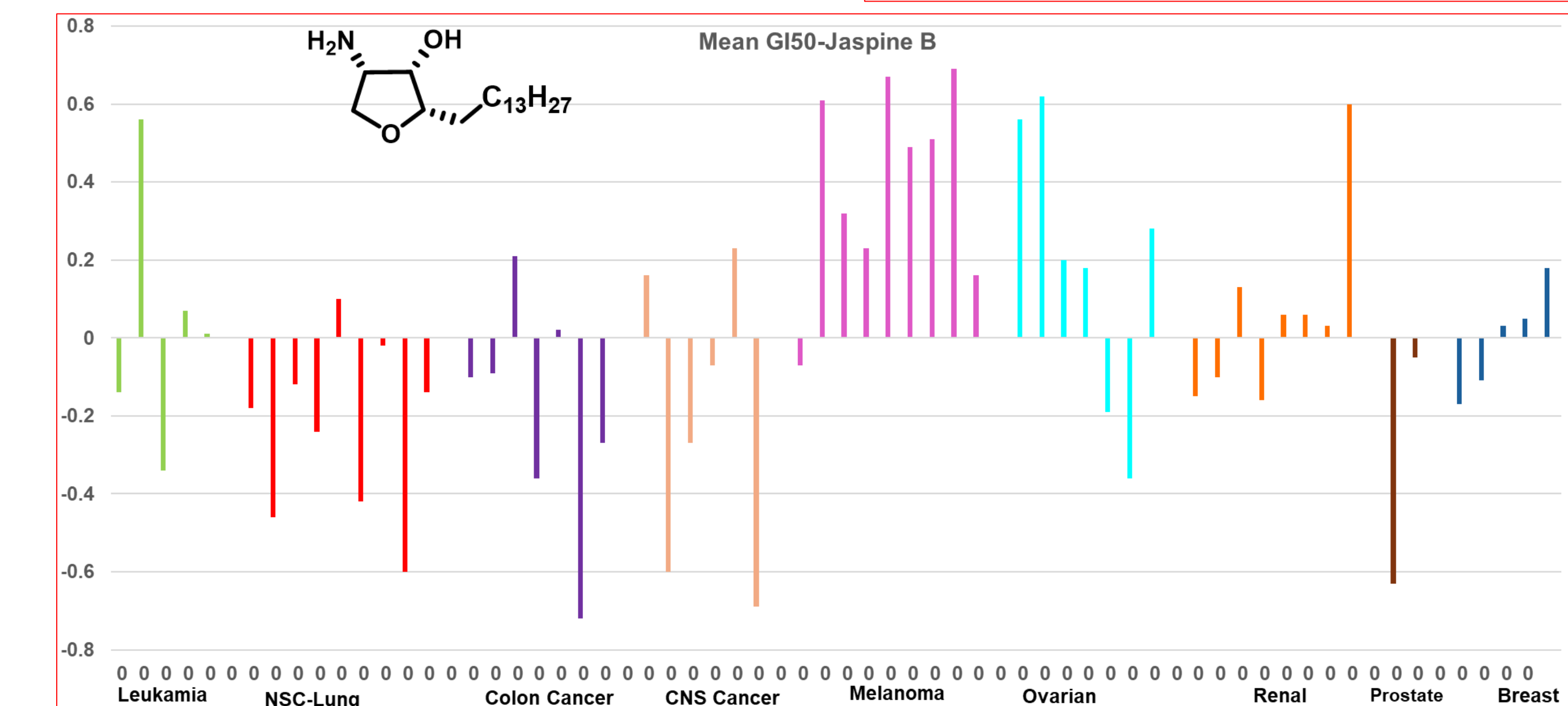
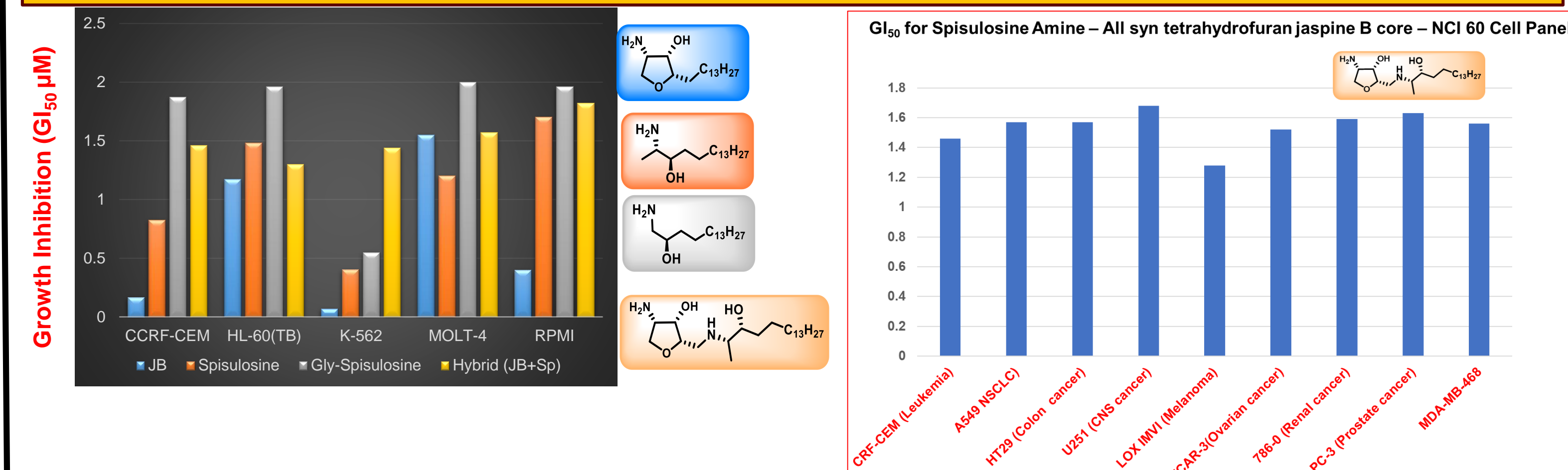
Result 7.

- Chiral pool strategy was utilized towards synthesis of des-methyl Spisulosine.
- Anticancer potential in several cancer cells.

Significance: Roles of Oxysphingolipids Vs. Deoxysphingolipids in membrane function.

Can Deoxysphingolipid probes interfere with Cell membrane, mitochondrial membrane, endosomes?

Aim 2. Spisulosine, jaspine B and their analogs in vitro studies in NCI 60 Panel



Conclusions

- Chiral pool strategy is applied towards stereoselective synthesis of natural products jaspine B, Spisulosine in gram quantities.
- 1,2-anti-amino alcohol system was achieved using chelation-controlled reduction, scalable robust synthetic methodologies.
- Analogs of jaspine B exhibited anticancer properties in vitro and in vivo.
- Apoptosis is induced via mitochondrial membrane depolarization in DU-145 cell line and Synovial sarcoma cell line.
- Novel liposomal formulation of jaspine B was developed using microfluids technology. Efficacy was increased approx. 20%.

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