Abstract

The enzyme sphingosine kinase is responsible for conversion of sphingosine to its phosphorylated form. The phosphorylated form of sphingosine is known to participate in cell proliferation, migration, anti-apoptosis and angiogenesis. Two isoforms of the enzyme are known, SphK1 and SphK2. The three-dimensional structure of SphK1 is better understood and has served as a target for inhibition by small molecules. In contrast, the structure of SphK2 is yet to be experimentally elucidated. Small molecule inhibitors of SphK1 are purported as therapeutic agents for various cancers and inflammatory disease. Nevertheless, isoform selectivity of such small molecules remains to be addressed. In the first part of this work, we have completed synthesis and characterization of triarylbenzenesulfonamide-containing small molecules for study as SphK1 inhibitors. Lead molecules based on the triarylbenzenesulfonamide scaffold have been previously reported from our research group and indicated attractive scope of refinement based on substitution patterns. We have synthesized an additional derivative bearing the triarylbenzenesulfonamide scaffold for examination of antibacterial properties. In the second part of this work, we have developed molecular models of the SphK2 isoform to facilitate *in silico* screening of small molecule inhibitors. Homology models of the SphK2 have been exposed to known small molecule binders that prefer SphK2 versus SphK1, and vice versa. Our model is able to distinguish between such small molecule ligands, that are known to exert different affinities towards the two isoforms. The work in this thesis is likely to enable identification of new molecules that exhibit isoform selective inhibition of enzyme sphingosine kinase.