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Extended Abstract

Syntheses of Hydrazino-and Azo-Sphingosine Derivatives and Their Evaluation as SphK Inhibitors †

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Bioactive sphingolipids have been recognized to play important roles in both normal and pathological physiology related to the regulations of cell proliferation, differentiation, survival, trafficking, and cell death. Specifically, overproduction of sphingosine-1-phosphate (S1P) has been associated with a variety of cellular effects that, as a whole, can be described as anti-apoptotic and therefore related with cancer progress. In this respect, sphingosine kinase (SphK), which catalyzes the transfer of phosphate from ATP to sphingosine to generate S1P, has arisen as a therapeutical target in oncologic treatments. Many synthetic sphingolipid analogs have been synthesized with this aim. Thus, FTY720 or CS-0777 are employed as inhibitors of sphingosine kinase in cancer therapies [1]. These compounds, which are characterized by the fact that they contain a quaternary center in the α-position of the amino moiety, could be synthesized through an aziridination reaction. Taking into account the synthesis of N-phthalimido alkynylaziridines in the absence of a metal catalyst reported by Liu [2], we built a family of sphingosine analogues. Syntheses of the starting 2-alkyl substituted α,β-unsaturated esters were accomplished from the corresponding alkyne by a formylation reaction followed by a Wadsworth–Emmons olefination of the aldehyde intermediate. The esters were then submitted to metal-free aziridination followed by a nucleophilic ring-opening process. Final deprotection and further protection of hydrazine moiety and subsequent reduction of ester gave access to a library of analogues. The activity of these analogues as SphK1 and SphK2 inhibitors will also be presented.

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