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MDPI

Extended Abstract

Development of Novel, Potent Phosphatidyl–Choline-Specific Phospholipase C Inhibitors †

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† Presented at the 2nd Molecules Medicinal Chemistry Symposium (MMCS): Facing Novel Challenges in Drug Discovery, Barcelona, Spain, 15–17 May 2019.

Published: 12 August 2019

Abstract: The phosphatidyl–choline-specific phospholipase C (PC-PLC) enzyme has been shown to be an important enzyme involved in various cell-signaling processes. Furthermore, PC-PLC has been shown to be upregulated in various cancer cell lines, thereby presenting itself as a potential anti-cancer therapeutic target. Current PC-PLC inhibitors, including the literature standard inhibitor D609 possess characteristics making them unsuitable for clinical use. We have discovered a new class of potent PC-PLC inhibitors with much improved activity and drug-like properties than D609. The synthesis and SAR study of this class of active compounds is presented.

Keywords: PC-PLC; SAR study; enzyme inhibition; phospholipase C

The association of the abnormal metabolism of choline-containing phospholipids with various cancers has resulted in the identification of enzymes involved in the phosphocholine cycle as potential therapeutic targets. Phosphatidyl–choline-specific phospholipase C (PC-PLC) plays a pivotal role in this cycle and has been implicated in many signalling processes, demonstrating overexpression in various cancerous tumors, thus providing a viable target for inhibition of cancer cell growth. It has been reported that PC-PLC activation accounts for 20–50% of the intracellular phosphocholine production in ovarian and breast cancer cells of different subtypes.

By virtue of virtual high throughput screening, a number of lead compounds were identified as inhibitors of the PC-PLC enzyme, all of which were identified to bind to key zinc atoms at the active site. To study the PC-PLC inhibitory activity of these compounds and to verify their SAR, an extensive range of novel analogues have been synthesized, varying a number of different structural features.

Analysis of the biological activity of the synthesized analogues showed significantly improved inhibitory activity over the only well-documented PC-PLC inhibitor, D609. These results, as well as the antiproliferative activities of the synthesised compounds, will be reported, providing a comprehensive SAR of these potent compounds and their potential therapeutic applications.