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Abstract

Development of Thienopyridines as Potent Antiproliferative Agents [†]

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Abstract: Virtual high throughput screening of a large compound library against the regulatory enzyme phospholipase C (PLC) led to the discovery of the thieno[2,3-*b*]pyridine-2-carboxamides as potential inhibitors. Subsequent biological testing verified the antiproliferative activity of this compound class. Morphology and motility assays, using a number of triple negative breast cancer cell lines, led to the conclusion that PLC is the most probable biomolecular target. Using a combination of computer-aided drug design and synthesis, further analogues have been prepared and tested for their antiproliferative activity, allowing a comprehensive SAR to be developed. Numerous analogues with low nano-molar growth inhibition against various cancers have been prepared. SAR studies suggest that the core structure can be fine-tuned to specific cancers, potentially due to enzyme/isoform specificity. Additionally, mouse xenograft assays showed significant reduction in tumour size after treatment, whilst showing no adverse effects to non-cancerous mice. Here, we report on our recent development of novel thienopyridines and derivatives, expanding the SAR against PLC, and our efforts to prepare potent, soluble, and bioavailable compounds.

Keywords: thienopyridine; antiproliferative; Phospholipase C; SAR study