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Synthesis and antiproliferative activity of 2-chlorophenyl carboxamide thienopyridines

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Abstract

3-Amino-2-arylcarboxamide-thieno[2,3-*b*]pyridines are a known class of antiproliferative compounds with activity against the phospholipase C enzyme. To further investigate the structure activity relationships of these derivatives a series of analogues were prepared modifying key functional groups. It was determined that modification of the 3-amino and 2-aryl carboxamide functionalities resulted in complete elimination of activity, whilst modification at C-5 allowed compounds of greater activity to be prepared.

The potent antiproliferative activity of thieno[2,3-*b*]pyridines has driven substantial synthetic interest in this area.[1–7] Activity of these compounds has been reported to be due to their ability to inhibit phospholipase C (PLC), an enzyme that plays a key role in cell signalling pathways involved in cell proliferation and motility.[8,9] More recently, reported interactions with tyrosyl-DNA phosphodiesterase I (TDP1) may also account for the antiproliferative activity exhibited by this class of compounds.[10] Previously, a range of thieno[2,3-*b*]pyridine analogues were prepared and tested for their antiproliferative activity against the National Cancer Institute's human tumour cell lines (NCI-60).[3] These analogues consisted of two main types, those containing a fused cyclohexyl ring adjacent to the pyridine ring (derivative **1**) and those lacking this moiety (derivatives **2** and **3**, **Figure 1**). These two groups contained further variations, with the former group differing by the incorporation of a ketone or alcohol functionality at C-5, whilst the latter group included modifications to the 3-amino group.