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Abstract

This thesis outlines the design and application of new routes towards a range of novel bisindolylmaleimide and indolo[2,3-*a*]carbazole derivatives, and evaluation of their biological effects and their chemotherapeutic potential.

A key part of this work focussed on utilising a hydroxymaleimide as a replacement for the prevalent lactam/maleimide functionality and forming a series of novel derivatives through substitution on the indole nitrogens. To achieve this, a robust synthetic strategy was developed which allowed access to key maleic anhydride intermediates using Perkin-type methodology. These hydroxymaleimides were further modified *via* a Lossen rearrangement to furnish a series of analogues containing a 6-membered F-ring.

The theme of F-ring modulation was further expanded through the utilisation of a second route involving the design and synthesis of β-keto ester intermediates, which afforded novel derivatives containing pyrazolone and isocytosine headgroups, and various *N*-substituents. Work on a further route involving a dione intermediate resulted in the isolation of a bisindolyl derivative with a novel imidazole F-ring.

Following the synthesis of 42 novel compounds, extensive screening was undertaken using the NCI-60 cell line screen, with twelve candidates progressing to evaluation *via* the five dose assay. This led to the identification of several lead compounds with high cytotoxicity and excellent selectivity profiles, which included derivatives with low nanomolar GI_{50} values against specific cancer cell lines, and also derivatives with selective cytotoxicity. Preliminary results from a kinase screen indicated noteworthy selectivity towards GSK3α/β and PIM1 kinases, with low micromolar IC_{50} values being observed for these enzymes.