Abstract

Ellipticine and its derivatives are molecules which possess potent anticancer activity. This thesis explores the synthesis of novel ellipticine derivatives, as well as modifications of the template, and evaluates their biological activity as anticancer agents.

The first section of this work, expands on previous work within the group, exploring derivatisation at the 9-position of the ellipticine template. This methodology was then extended to encompass isoellipticine and neoellipticine, two of the isomeric forms of ellipticine. This range of analogues allows for assessment of the role of the pyridine nitrogen for bioactivity and explores the theme of D-ring modification. A panel of novel ellipticinium salts were generated, which encompass a range of substituents at the *N*-2, *N*-6 and *C*-9 position.

To further explore the role of the D-ring, three anhydrides were subjected to the methodology for the synthesis of ellipticine but none of the coupling reactions proved successful. However, by implementing an alternative synthetic route, new maleimide-type D-rings were successfully introduced, maintaining the carbazole core. This work was extended further, examining the use of benzofuran as a starting material, in place of indole, allowing for the generation of new tetracyclic scaffolds and corresponding derivatives. Substitution of 2-position of the D-ring took a fragment based approach, generating a panel of the novel analogues of the tetracyclic dibenzofuran fused imide compounds.

A panel of 27 novel derivatives was prepared encompassing derivatives of ellipticine and its isomers. A further 43 novel benzofuran derivatives and 7 novel maleic anhydride intermediates were generated across 7 different templates. From both families, a total of 66 compounds were sent for biological evaluation, with the primary source of information gathered from the NCI 60-human tumour cell lines screen. This *in vitro* information allowed the identification of new lead compounds, highlighting compounds with nanomolar GI50 values and selectivity for specific cell lines. One isoellipticine analogue displayed a mean growth of −5.64% and on progression to five-dose screening, a mean GI50 of 0.42 μM was obtained with selectivity observed for the renal cell line A498 (GI50 0.02 μM). Novel ellipticinium salts were biologically evaluated by our collaborators in the University of Newcastle, Australia, identifying long chain alkyl ellipticinium salts with very good bioactivity, which is corroborated by findings from the NCI, where a mean GI50 value of 3.09 μM was recorded for one such derivative. In the benzofuran series, preliminary results have shown excellent activity, with diethylamino propyl and diethylamino ethyl substituents generating mean growths as low as 3.77% and have progressed to five-dose screening.