

PP17.1. THE DESIGN, SYNTHESIS AND ANTITUMOUR EVALUATION OF BCL3 INHIBITORS TARGETING ADVANCED COLORECTAL AND BREAST CANCERS

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The B-cell lymphoma 3 protein (BCL3) is a transcriptional facilitator protein and anti-cancer drug target driving intracellular cancer signalling pathways including NF- κ B (advanced breast) and Wnt- β -catenin (colorectal). BCL3 governs pro-oncogenic processes such as tumour initiation, metastasis, and therapy resistance.

The purpose of this study was twofold:

- to extend our previously published work on a BCL3-p50 interface protein-protein inhibitor (JS6) and a structurally related orally bioavailable preclinical candidate, to synthesise new JS6 chemical analogues for structure-activity relationship (SAR)-based optimisation, alongside novel conformationally restricted analogues.
- to design and synthesise the first BCL3 PROTACs (PROteolysis TArgeted Chimeras), to compare and contrast therapeutic activity between BCL3 inhibitors and PROTAC-based targeted degraders.

Our previously published computational model of the BCL3/p50 interface was updated for the new inhibitor target molecules, through the use of AlphaFold, Schrödinger's Maestro and Molecular Operating Environment (MOE). New JS6 analogues and pomalidomide-based PROTACs were synthesised using established chemical synthetic methods. New compounds were purified and characterised using NMR spectroscopy and mass spectrometry, and initially tested for efficacy and cytotoxicity within established cellular models of advanced breast and colorectal cancer.

The design and synthesis of a series of new BCL3 inhibitors and BCL3 PROTAC degraders has been successfully accomplished. *In vitro* evaluation indicates that the new compounds are devoid of general cytotoxicity in normal and triple-negative breast cancer cell models, and induce BCL3 degradation (PROTACs).

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