Abstract

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Title: Synthesis of natural product analogues as potential antitumour agents
Keywords: combretastatin, combretafuranone, purpurealidin, cytotoxic, $K_V10.1$ inhibitors, analogue synthesis

Despite numerous efforts and advances in prevention, diagnostics and treatment of human malignancies, cancer is still one of the leading causes of mortality worldwide. In the search for novel drug candidates, the rich biodiversity in the nature remains a valuable source of lead structures. Combretastatin A-4 (CA4) isolated from *Combretum caffrum* tree and purpurealidin I isolated from marine sponge *Pseudoceratina purpurea* are examples of such structures that served as an inspiration in the synthesis of potential anti-cancer agents within my thesis work.

Combretastatin A-4 is a well-known suppressor of tubulin polymerization via interaction with the colchicine binding site. It causes inhibition of cell growth and concurrently acts as a vascular disrupting agent and angiogenesis inhibitor. Being a *cis* stilbene derivative, it can readily isomerize into a thermodynamically more stable, but less active *trans* form. Furthermore, its low aqueous solubility is an issue. The first aim of this project was therefore to synthesize analogues that would overcome the above disadvantages, and to subject them to biological activity testing.

Following the group's previous work on antifungal lactones, the olefinic linker in CA4 was replaced with a furanone moiety and the effects of both oxygenated and halogen-bearing analogues on the biological activity were evaluated. 13 variously functionalized furanones were successfully synthesized in three to five steps starting from commercially available acetophenones or phenacylbromides.

Cytotoxic effects on a panel of cancer and normal cell lines as well as anti-infective activity were evaluated in due course for 12 compounds. Seven derivatives showed cytotoxicity against cancerous cells (the lowest IC_{50} = 0.12 μM) but they retained relatively high toxicity against non-malignant control cell lines. One hydroxymethylated derivative showed activity towards *Staphylococcus aureus* (MIC_{95} = 7.81–15.62 μM) without being cytotoxic up to 40 μM. All tested compounds were antifungally inactive.

The second natural product that inspired the syntheses of potential drug leads was the recently identified purpurealidin I that belongs to the class of marine bromotyrosine alkaloids. Many marine compounds possess a broad spectrum of biological activities, including cytotoxic activity or ion channel inhibition activity. The second aim of this thesis was the synthesis of simplified analogues of purpurealidin I via purpurealidin E to be tested for their cytotoxicity and activity towards the voltage-gated potassium channel K_V10.1. K_V10.1 represents an attractive cancer target since it is expressed ectopically in over 70% of human cancers. Such specificity in treatment could potentially decrease negative side effects connected to cancer treatments and K_V10.1 inhibitors are thus considered to be interesting lead compounds in the development of novel anticancer drugs.

Within the project, purpurealidin E was successfully synthesized in four steps from tyramine in an overall yield of 80%, improving the literature yields. A well-established synthetic route allowed for the synthesis of two novel analogues and the intermediates were coupled with miscellaneous aromatic carboxylic acids to yield the final amides. 12 compounds were then studied for their activity towards the K_V10.1 channel. Apparent inhibition was observed in some derivatives in the micromolar range. Two compounds showed activity against malignant melanoma cell line (IC_{50} < 15.00 μM) but they were comparably toxic to non-malignant cell control.

In conclusion, 27 novel natural product analogues were prepared within this thesis, some of which possessed interesting biological activities. Both projects provided valuable structure-activity data that served as a basis for further research and discovery of more selective analogues.