Synthesis of mitochondria-targeting ion channel inhibitor in the final round of Synthetic Masterchef of the Faculty of Pharmacy

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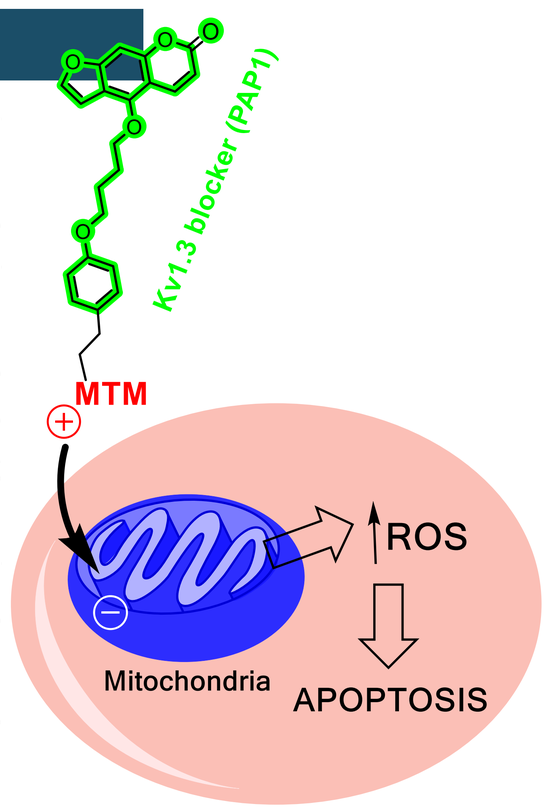
Abstract

Calcium and potassium ion channels have an important role in regulating cell cycle and proliferation. Cancerous cells have a higher expression rate of voltage-gated potassium channels Kv1.3 than the healthy ones. **Kv1.3 channels** are also embedded in the mitochondrial inner membrane and their inhibition causes apoptosis.[1] **PAP1** is a small-molecular selective inhibitor of Kv1.3 channels, which has previously been combined with a **M**itochondria **T**argeting **M**oiety (**MTM**), a triphenylphosphonium cation, to promote selective apoptosis of cancer cells in vivo.[2] The aim of our work within the final round of Synthetic Masterchef was to prepare a conjugate between PAP1 and any non-phosphonium MTM, during a two-week laboratory pressure test. We have improved the literature synthetic procedure towards the alkyl iodide intermediate **4**,[3] and successfully used it for quaternization of a precursor of **F16**, a fluorescent molecule known to accumulate in mitochondria and induce cell apoptosis.[4] The **PAP1–F16 conjugate** thus prepared will be evaluated for its potential in anticancer therapy and fluorescence-based imaging.

MTM in brief

- Mitochondria regulate cellular metabolism and are pivotal drug targets
- Mitochondria have negative membrane potential which is even lower in cancer cells.
- Lipophilic and delocalized cations are accumulated in mitochondria and are referred to as Mitochondria Targeting Moiety (MTM)
- MTM–inhibitor conjugates deliver active agents to mitochondria which is a basis of selectivity.
- Intrinsic toxicity of known MTMs drives the development of new moieties.



About Synthetic Masterchef

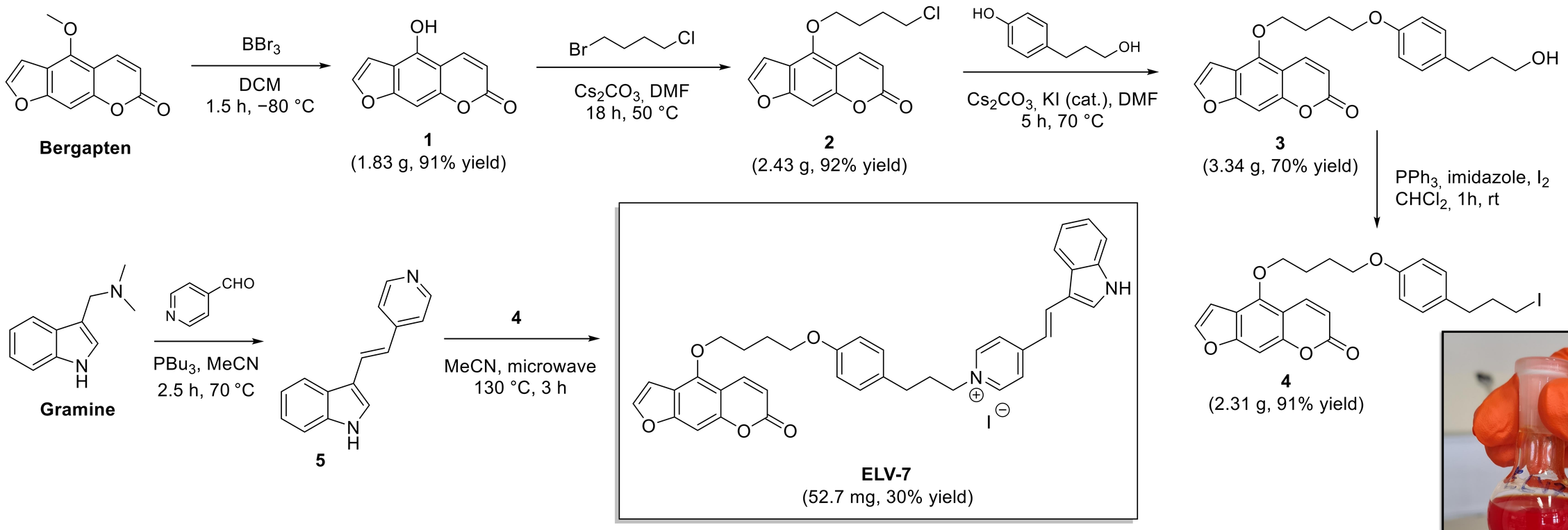
Synthetic Masterchef of the Faculty of pharmacy was a pilot project aimed at implementation of the principles of research-based curriculum. In the first round, the 3rd year MPharm students were given 23 weekly theoretical synthetic challenges prepared by researchers at the Department of Pharmaceutical Chemistry in connection to their current scientific projects. 6 best students were selected for the final round, where they were challenged with a "mystery box molecule". The task was to propose a new PAP1–MTM conjugate and carefully plan the synthetic route. The three pairs then had two weeks to perform the synthesis in the lab, supervised by experienced researchers.

The goals of the project were:

- to establish regular contact of students with current academic research at the Department of Pharmaceutical Chemistry.
- to encourage students to independently research the literature in the field of chemical synthesis.
- to enable networking of the most motivated students with researchers in their working environment
- to identify good candidates for future employment on research projects.

Synthesis

- ✓ **Improvements** from state-of-the-art: ***a)*** In situ catalytic Filkenstein reaction for the synthesis of **3**. ***b)*** One-pot-one-hour Appel-type synthesis of **4**.
- ✓ 53% yield from bergapten to modular PAP1–MTM alkyl iodide precursor **4**.
- ✓ Only one flask dropped into the rotavapor bath.



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