FACULTY OF BIOSCIENCE ENGINEERING

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SYNTHESIS OF NITROGEN-CONTAINING CURCUMIN ANALOGUES IN THE PURSUIT OF NEW ANTICANCER CANDIDATES

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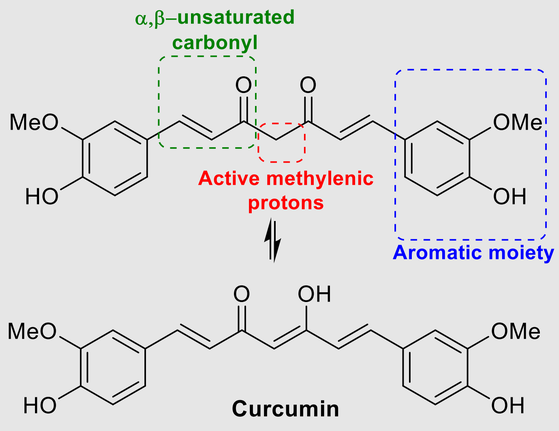
Introduction

Isolation of curcumin from the rhizomes of *Curcuma longa*
Broad spectrum of biological activities
Main concerns: low bioavailability, fast metabolism and aspecific activity
Objective: the design of new nitrogen analogues with improved bioavailability and stability without compromising their bioactivity

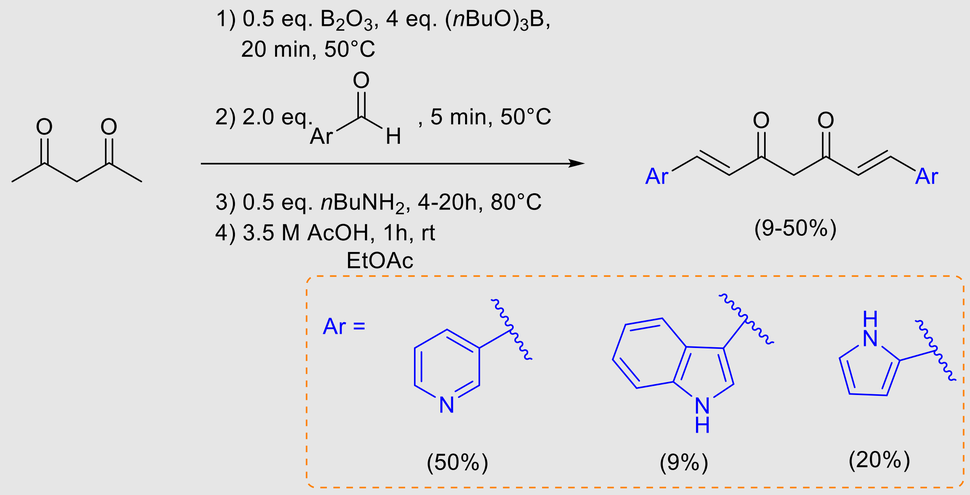
Structural features of curcumin

Key parts of the curcumin scaffold



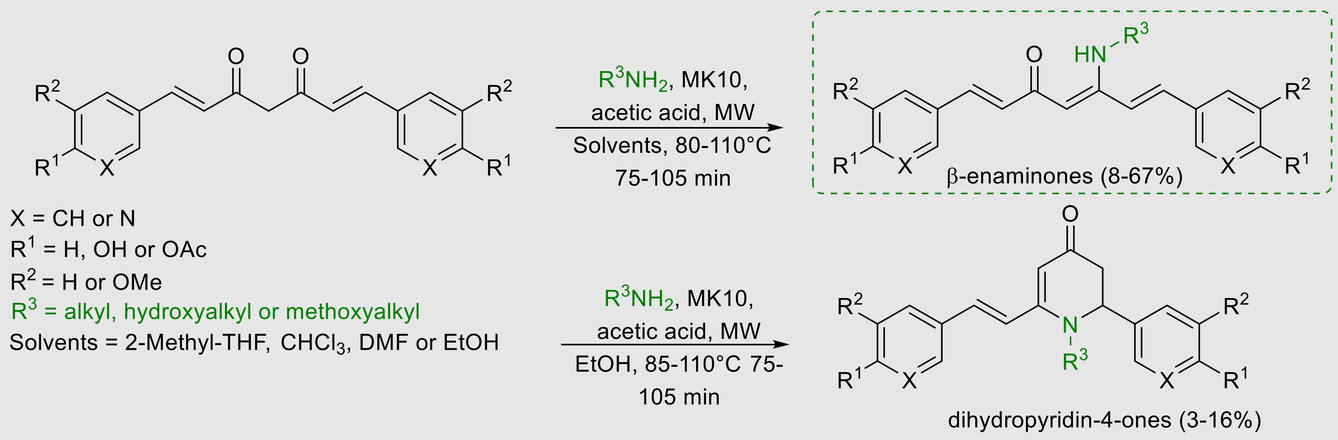
- Keto-enol tautomerism
- Three important parts: α,β-unsaturated carbonyl, active methylenic protons and aromatic moiety
- Interesting anchor points for structural modification

Chemical synthesis of symmetrical azaheteroaromatic derivatives[1c]

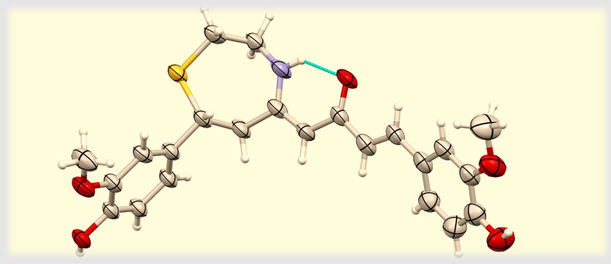


Chemical synthesis of β-enaminone-, thiazepane-based and non-symmetrical azaheteroaromatic curcuminoids[1, 2]

- **Class I**: Imination of the labile β-diketone moiety using microwave irradiation [1a-c]

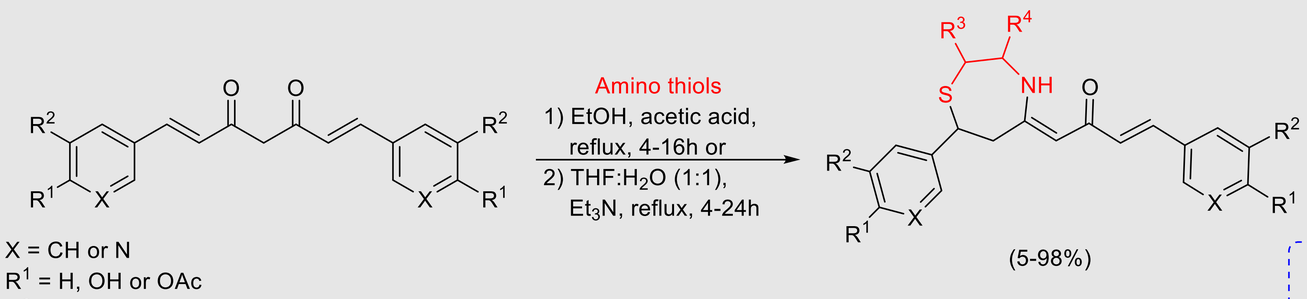


- Facile procedure to deliver β-enaminones and dihydropyridin-4-ones (ratio 60-70/40-30, 32 derivatives)
- Moderate to good yields
- Further extension of compound library and bioactivity evaluation



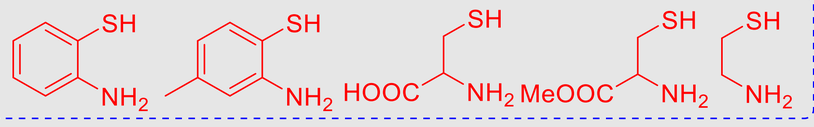
X-ray crystallography of a 1,4-thiazepane analogue[2]

- **Class II**: 1,4-thiazepane-based curcumin systems [2]

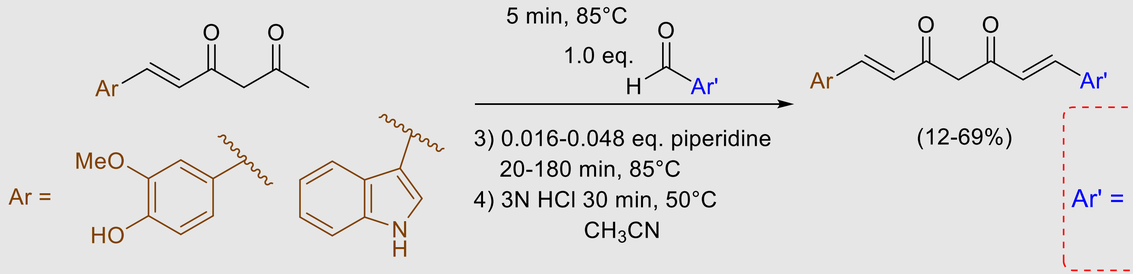


- Convenient procedure to afford novel thiazepane-based curcuminoids
- Tandem imination/conjugate addition

Amino thiols =

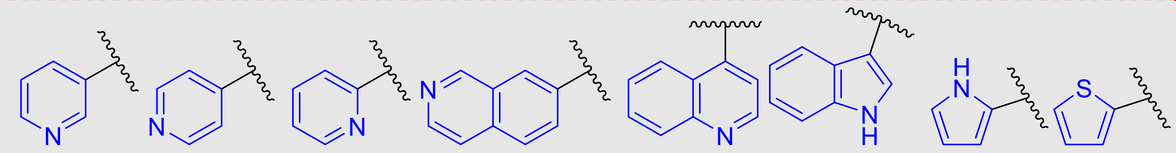


- **Class III**: Non-symmetrical azaheteroaromatic curcumin systems [2]

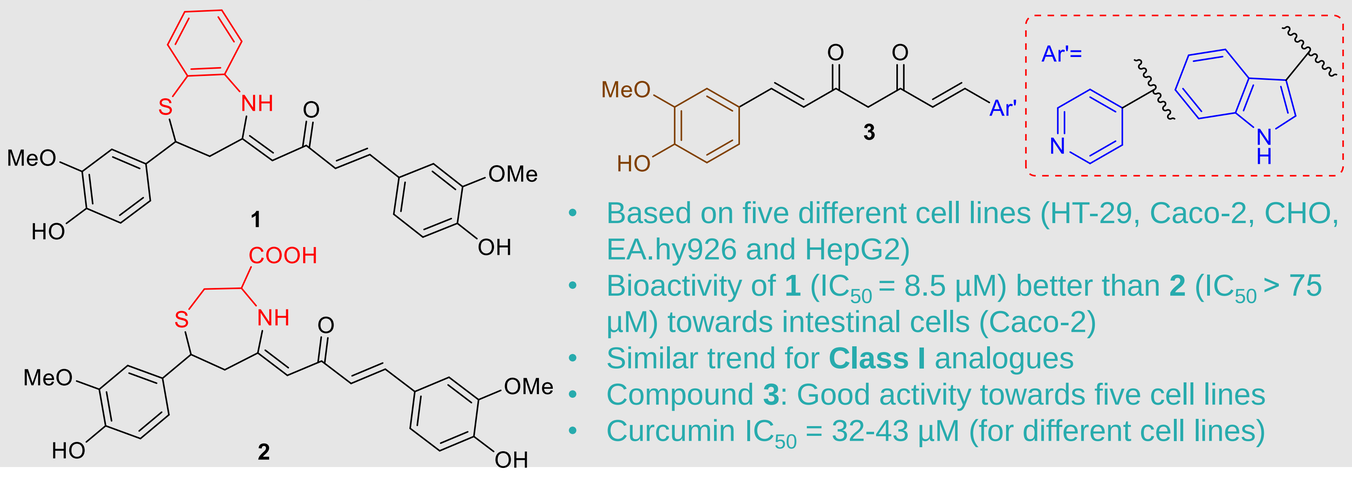


- Similar procedure as symmetrical azaheteroaromatic curcuminoids
- Optimized conditions to obtain higher yields using the combination of acetonitrile and piperidine

Ar' =



Preliminary Bioactivity of Class I-III derivatives



- Based on five different cell lines (HT-29, Caco-2, CHO, EA.hy926 and HepG2)
- Bioactivity of **1** (IC_{50} = 8.5 µM) better than **2** (IC_{50} > 75 µM) towards intestinal cells (Caco-2)
- Similar trend for **Class I** analogues
- Compound **3**: Good activity towards five cell lines
- Curcumin IC_{50} = 32-43 µM (for different cell lines)

Conclusions

- Design of a broad compound library with 69 new potential anticancer candidates (β-enaminone derivatives, 1,4-thiazepane analogues and (non)symmetrical azaheteroaromatic)
- Hydroxy/methoxyalkyl-β-enaminone derivatives showed significantly improved water solubility with compromised bioactivity, whereas alkyl-β-enaminones showed slightly improved water solubility with good activity
- Novel curcuminoid scaffolds for advanced anticancer studies

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[1] (a) R. De Vreese, C. Grootaert, S. D'hoore, A. Theppawong, S. Van Damme, M. Van Bogaert, J. Van Camp, M. D'hooghe. *Eur. J. Med. Chem.* **2016**, *123*, 727. (b) A. Theppawong, R. De Vreese, L. Vannecke, C. Grootaert, J. Van Camp, M. D'hooghe. *Bioorg. Med. Chem. Lett.* **2016**, *26*, 5650. (c) A.Theppawong, T. Van de Walle, C. Grootaert, M. Bultinck, T. Desmet, J. Van Camp, M. D'hooghe. *ChemistryOpen* **2018**, 7, 392.

[2] Unpublished results