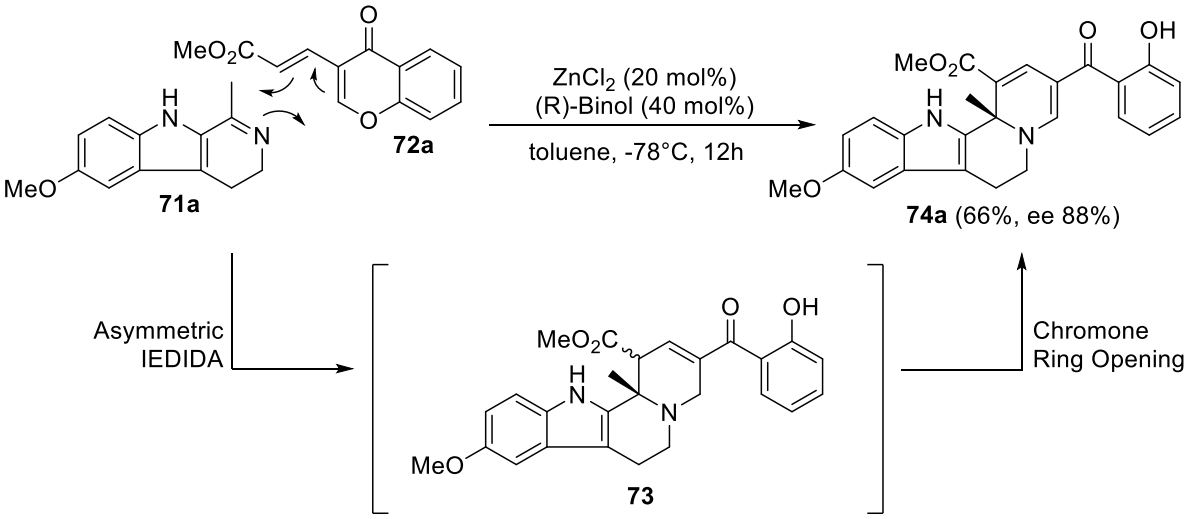
Summary

Natural product- inspired compound libraries are efficient tools for the discovery of compounds with interesting biological activities and may provide inspiration for medicinal chemistry research. The goal is the assembly in the most efficient and concise way of substances with a structural ressemblance to known natural products. The design of these analogues can also rely on the interaction of the substances with the corresponding biological target.

In the syntheses of ring-fused quinolizines described in this work, the inspiration for the construction of the compound collection came from an interesting class of indole alkaloids displaying cytotoxic or anti-cancer activities, and particularly from the centrocountins, mitotic modulators that target centrosomal proteins. A unique 12-step organocatalysed cascade sequence yielded a small collection of centrocountins in a straightforward one-pot procedure from commercially available starting materials: 3-formylchromones, DMAD and tryptamines. Mechanistic investigations of the 12-step cascade reaction were carried out by trapping and characterizing intermediates as well as control experiments. These informations yielded in the development of new alternative cascade synthesis routes to indoloquinolizines and analogues, and overcame the limitations of the long cascade syntehsis established before.



Scheme 33: Synthesis of indoloquinolizine **74a** by asymmetric IEDIDA reaction of cyclic imine **71a** with chromone diene **72a**.

Inspired from the last part of the cascade synthesis of the centrocountins, an inverse electron demand imino-Diels-Alder between cyclic imines and chromone dienes was developed to access new centrocountin analogues (Scheme 33). An enantioselective version of this reaction using a zinc-Binol complex in toluene at low temperature provided access to the indoloquinolizines **74** with enantiomeric excess of up to 94%.

These very encouraging results led to further expansion of the scope of the reaction and further construction of the centrocountin-based compound collection. New subclasses of compounds were synthesized by means of the IEDIDA reaction: various ring-fused quinolizines including benzoquinolizines **96**, dihydropyridoisoindole **111**, ring-closed quinolizines **114** and **117**, as well as internal indolopyridinium **87** and benzopyridinium **97** salts obtained by oxidation (Figure 20).

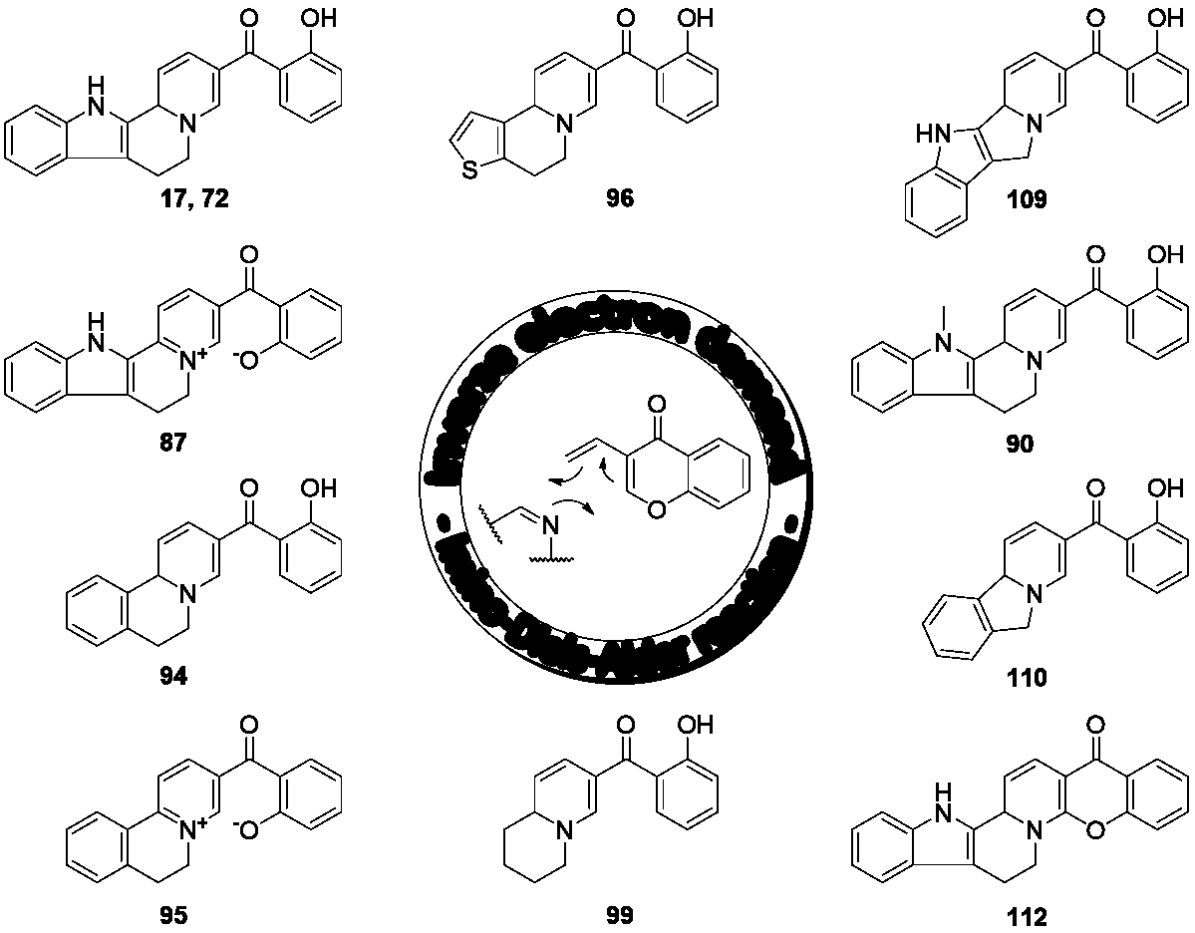


Figure 20: Representation of the diverse quinolizine subclasses synthesized by the inverse electron demand imino-Diels-Alder reaction.

Compound **96a** was identified as a potent mitotic modulator displaying the same phenotype (Figure 21) when exposed to HeLa cells as was observed for centrocountin-1 **17a**, but at lower concentrations. Treatment of cells with (S)-**96a** led to a higher count of mitotic cells at equivalent concentrations (mitotic ratio at 10 µM: 25% instead of 12%), and an effect on the cells was observable at lower concentration than for centrocountin-1 **17a** (IC_{50} : 4.7 ± 0.5 µM instead of 17.2 ± 2.4 µM). Furthermore, it was observed that only the (S)-**96a** enantiomer was active on HeLa cells, experiments carried out with (R)-**96a** rendered no activity at all.

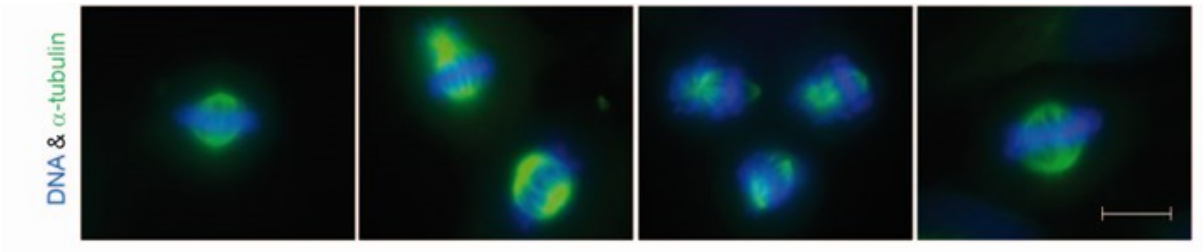


Figure 21: Images of mitotic HeLa cells under the influence of hit compound **96a**.

Further application of the inverse electron demand imino-Diels-Alder reaction can be easily imagined, for instance, using new cyclic dienes to replace the chromones, in order to find new compound classes which may be very different to centrocountins but still provide interesting molecules for chemical biology research.