Synthesis, Biological Evaluation and 2D-QSAR analysis of Chalcones as Anti-Invasive Cancer Agents

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Because invasion is, either directly or via metastasis formation, the main cause of death in cancer patients, the development of efficient anti-invasive agents forms an important research challenge in medicinal chemistry. In the quest for potent lead compounds, a large group of plant polyphenolics and alkaloids were screened *in vitro* for their anti-invasive activity.[1,2]

The assay was based on organotypic confronting cultures between human MCF-7/6 invasive mammary cancer cells and a fragment of precultured normal heart tissue (PHF) from 9-days old chick embryos. Anti-invasive activity was observed at concentrations as low as 1μmol/l for several flavonoids, 5 of which contained the 1,3-diphenylpropenone (chalcone) skeleton. Furthermore, a large number of chalcones possessed good activity at higher concentrations.[3]

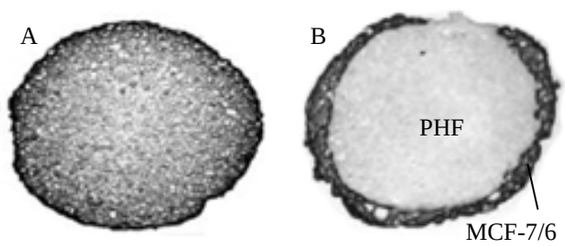
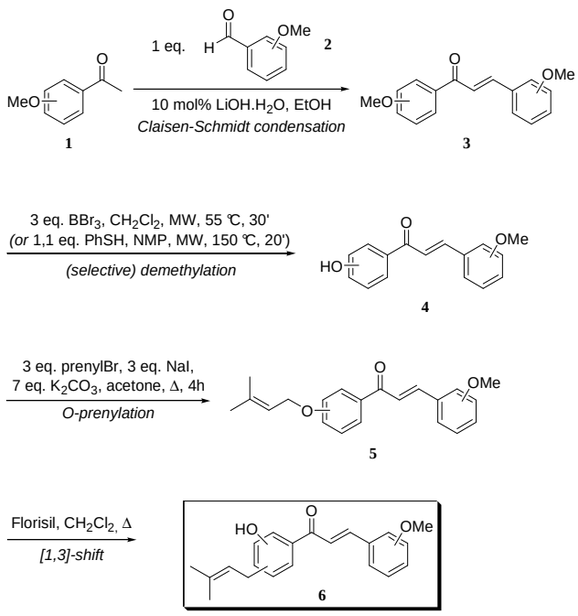


Figure 1: Illustration of the chick heart invasion assay. Panel A shows the invasion of untreated cultures by the carcinoma cells after 8 days of incubation, while in panel B invasion was inhibited by addition of an anti-invasive agent to the culture medium.

As such, a dataset of 68 differentially functionalized chalcones with various activity levels was obtained, and used to establish two-dimensional quantitative structure-activity relationships (2D-QSAR). Using the best multilinear regression method of CODESSA Pro, a statistically satisfactory correlation between the lowest active concentration and 6 molecular descriptors was obtained.

The model is now used to predict the anti-invasive activity of hypothetical compounds *in silico*, thus solely based on their molecular structure. This way, synthetic efforts can be focussed on promising targets. Meanwhile, preparation and derivatisation protocols for chalcones and related polyphenolics will be optimized, enabling the synthesis of compounds with a high potential activity.

In this context, a mild, high yielding preparation of chalcones *via* a LiOH catalyzed Claisen-Schmidt condensation was developed, and substituent and reaction temperature effects were studied (Scheme 1). Several demethylation techniques were evaluated on the thus prepared methoxychalcones. Selective demethylation on the A-ring of methoxychalcones can be achieved by treatment with thiophenolate and is explained by comparison of the Hammett constants of the methoxy groups on the two rings. Still, C-prenylated chalcones were prepared *via* a Florisil catalyzed *[1,3]*-shift of their intermediately generated O-prenylated analogues.



Scheme 1: Synthesis of functionalized chalcones.

References

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