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Title: Synthesis of bioactive molecules for the investigation of ion channels and transporters

The present thesis has three major subjects, the synthesis of (i) piperine analogs and (ii) pyrazoloquinolinones as $GABA_A$ receptor modu-lators, and (iii) the synthesis of methcathinones and related metabolites for the investigation of monoamine transporters (MATs).

(i) γ-Aminobutyric acid type A ($GABA_A$) receptors are the major inhibitory neurotransmitter receptors in the central nervous system. Activation of $GABA_A$ receptors leads to opening of the chloride ion channel and ultimately to hyperpolarization of the neuron. Compounds enhancing the effect of the endogenous ligand GABA, many of which are currently in clinical use, possess sedative, anxiolytic or anticonvulsant effects. The insufficient separation of these properties, and thus the occurrance of severe side effects, is closely associated with a lack of receptor subtype selectivity of currently available drugs. In this context, patients would greatly benefit from the development of novel subtype selective ligands with improved side-effect profiles.

The natural product piperine, the pungent alkaloid of black pepper, was recently identified as $GABA_A$ receptor modulator and TRPV1 agonist. The structure of piperine is comprised of a piperidine amide, a conjugated diene and the benzodioxole moiety. Preliminary work by the group of T. Erker established that both potency and efficacy could be improved by modification of the amide moiety.

Based on a hypothesis generated through analysis of biological data available from synthetic analogs and related natural products, a library of derivatives with rigidified linkers (e.g. replacement of double bonds with aromatic rings) was synthesized. To facilitate the preparation of aryl-modified piperine analogs a novel Heck-coupling protocol of conjugated dienes was developed enabling the synthesis of target compounds in a single reactions step from commercially available starting materials. Eventually, a separation of $GABA_A$ and TRPV1 activity, an improvement of efficacy and the discovery of functionally selective compounds for β2-containing receptors (relevant for non-sedative anxiolysis) has been achieved.

ii) As a second class of $GABA_A$ ligands pyrazoloquinolinones were investigated. After the recent discovery of their binding site at the α+β- interface a focused library of ligands was prepared to elucidate determinants for efficacy and potency. In this work, functionally selective ligands for δ- and α6-containing receptors have been discovered which exert their effect at the α+β- interface. Furthermore, ligands with suppressed affinity to the benzodiazepine binding site were designed and

synthesized. In an effort to extend the scope of α+β- ligands, two novel active scaffolds, imidazoquinolines and an indole-based structure, were discovered.

iii) Methcathinones are widely used recreational drugs. These inhibitors of MATs are typically consumed as racemic mixtures. In this work, enantiomerically pure samples of representative methcathinone derivatives were prepared through asymmetric synthesis and pharamcologically characterized, revealing a significantly higher potency of the (*S*)-methcathinones.

One of the most commonly used methcathinones is mephedrone. Despite its short half-life in blood plasma this compound has a long-lasting effect in humans. A range of potentially bioactive metabolites have previously been identified by mass-spectrometry. In this project, these metabolites were synthesized in their racemic and optically pure forms. An investigation into the pharmacology of these synthetic metabolites revealed that nor-methylmephedrone and 4'-hydroxymephedrone act as potent inhibitors of MATs or even reverse the direction of transport. Thereby they further increase the concentration of monoamine neurotransmitters in the synaptic cleft. Taken together, these results clearly confirmed the existence of psychoactive mephedrone metabolites