Synthesis of various benzamide-derivatives as potential targeting-vectors for D_2-Receptor imaging

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Introduction:
Benzamides have been in the focus to target D_2-like receptors in the brain but also as imaging agents for tumors. Today, especially several (*S*)-(pyrolidinyl)methyl-2-methoxy-benzamides such as [^{11}C]raclopride, [^{18}F]fallypride, [^{123}I]IBMZ are used routinely for imaging D_2/D_3-receptor availabilty in the human brain and studing neurological disorders. In addition it was shown that these tracers may also be valuable for imaging tumors, which overexpress D_2-receptors. Concerning ^{11}C- and ^{18}F-labelled derivatives, their routine application is limited due to the short half-life of the radionuclides and the need of a nearby cyclotron for producing the nuclides. Because of this PET nuclides such as ^{68}Ga which can be provided by a radionuclide generator are currently considered in novel tracers and may amend an enhancement in nuclear imaging. Thus, it was our intention to develop a reliable multi-gram synthesis of various *(S)*-N-[(1-allyl-2-pyrolidinyl)methyl]-2,3-dimethoxy-5-propyl-benzamide derivates bearing different functional groups at the 3-position of the propyl-group for allowing a direct and easy coupling with chelators necessary to coordinate radiometals.

Methods:
Because of different requirements for the various chelators it was the aim to consider different functional groups such as -NH_2, -N_3, -Br, -OH, -Tosyl, -COOH at the 3-position of the propyl group. Furthermore, a new synthetical route towards the tosyl derivative, i.e. the ^{18}F-labelling precursor, was developed. Based on the published procedure [1] for the 3-hydroxypropyl derivative, the gently modified synthesis started from 2-hydroxy-3-methoxy benzoic acid to give the cooresponding hydroxy-benzamide. Further reactions resulted in benzamides bearing various functional groups. The carboxy derivative was synthesised in a different and novel 8 step synthesis.

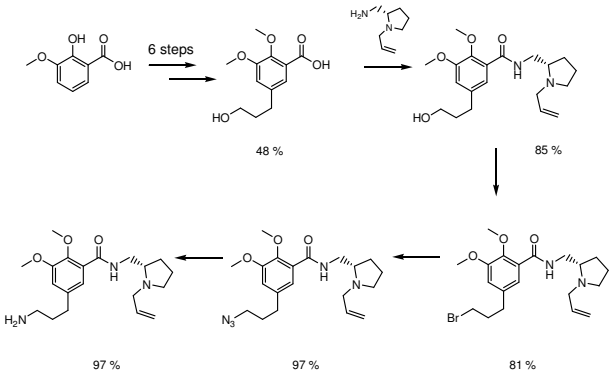

Figure 1. Synthesis of various benzamide derivatives

Results:
The desired hydroxy derivative was synthesised in excellent yields of 40% over 7 steps. Conversion of the hydroxyl group into the various groups was achieved via Appel-reaction, nucleophile substitution and Staudinger reduction. Replacement of pyridine by triethylamine increased the yield of the tosylation to over 85 %. The carboxy derivative was obtained from 3-methoxy-2-hydroxy benzoic acid over 8 steps.

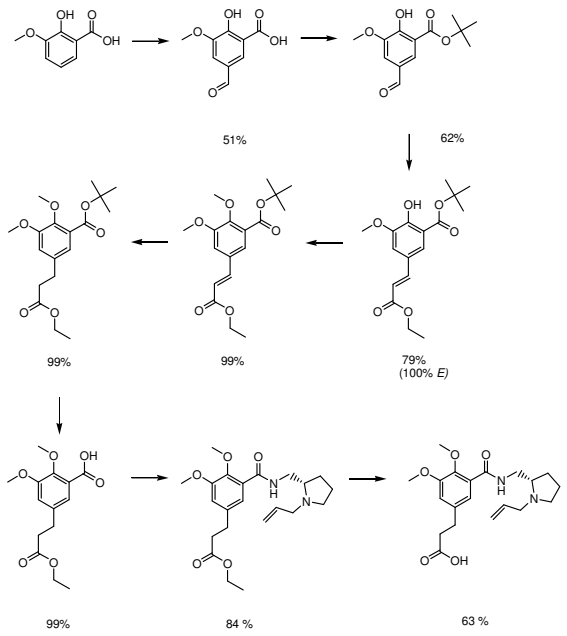

Figure 1. Synthesis of carboxy-fallypride

First reactions using the different derivatives gave N2S2-, and DOT_3A-conjugated benzamides.

Conclusions:
4 novel benzamide derivatives as potential targeting vectors were synthesised and are currently tested for their *in vitro* affinities. First conjugations to different chelators resulted in N2S2-, and DOT3A-benzamides. In additional experiments more conjugates shall be synthesised as well as radiolabelled.
The synthesis of the ^{18}F-labelling precursor of [^{18}F]fallypride was optimized for a multi-scale synthesis.

References
[1] Bishop J. E., Mathis C. A., Gerdes J. M., Whitney J. M., Eaton A. M., Mailman R. B., *J.Med. Chem.,* **34** (5), 1612-1624 (1991)