Synthesis and ^{99m}Tc-labelling of benzamide-derivatives for visualisation of D_2/D_3-receptors

T. Heß[1], H. Hübner[2], R. Alberto[3], P. Gmeiner[2], F. Roesch[1]
[1]Institute of Nuclear Chemistry, Johannes-Gutenberg-University Mainz, Germany; [2]Institute of Medicinal Chemistry, Friedrich-Alexander-University Erlangen, Germany; [3]Institute of Inorganic Chemistry, University of Zürich, Switzerland

Introduction:
Dopamine is the predominant catecholamine-neurotransmitter in the human brain, where it controls a variety of physiologic functions. Changes in the dopaminergic neurotransmission are linked to different neurological and psychic diseases, such as e.g. Parkinson's disease. Several tracers as [^{18}F]fallypride or [^{11}C]raclopride are used to image the D_2/D_3-receptors *in vivo* by means of PET. Up to now, ^{99m}Tc-SPECT analogs that are highly selective for dopaminergic neurotransmitter receptor sites are uncommon. A ^{99m}Tc-labelled, at least medium-affine D_2-postsynaptic receptor ligand would allow a cost-effective technique for the diagnosis of Parkinson disease.
It was our intention to synthesise ^{99m}Tc-containing fallypride derivatives introducing different chelators at the 5 position of the benzamide. Starting from fallypride as lead structure a number of derivatives were synthesised, which contained a chelator that is suitable for the labelling with ^{99m}Tc.

Methods:
Due to lacking information of structure activity relationships concerning modifications in position 5 of the benzamide, we first synthesised model compounds containing a phenyl ring connected to the 5 position of the Benzamide via an aliphatic chain. The phenyl ring can be considered as a comparable structure to the desired ^{99m}Tc-cp-$(CO)_3$ core. Variation of the alkyl chain length between the pharmacophore benzamide structure and the phenyl ring gave 12 compounds which were analysed towards their *in vitro* affinities. The in vitro affinities were determined for the following receptors D_1, D_{2s}, D_{2l}, D_3, D_4, $5HT_{1A}$, $5HT_{2A}$ and $\alpha 1$ using striatale porkin membranes and cloned chinese hamster ovar cells. After choosing the right chain length, 4 different chelators such as cyclopentadienyl, 2-pyridine-imine, amido-cyclopentadienyl and MAMA (N_2S_2) were linked to the benzamide structure. The corresponding rhenium complexes were synthesised, purified and determined towards their *in vitro* affinities. Finally, two compounds were labelled with ^{99m}Tc.

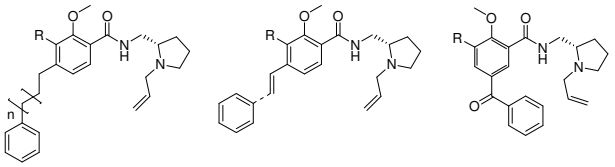

Figure 2. Structures of model benzamides – derivatives

Results:
The obtained phenyl-derivatives showed excellent affinities and selectivities towards the D_2/D_3-receptors. The chain length of n=3 showed best values and was chosen for all further compounds. For the synthesis of the labelling precursors various novel benzamide-derivatives were synthesised. The introduction of the different chelators resulted in 4 labelling precursors and 3 rhenium-analogues.

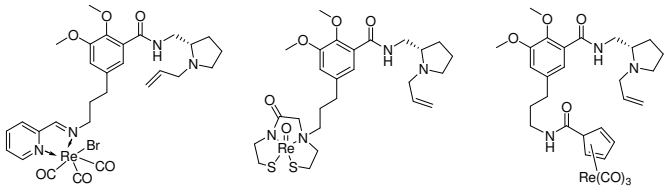

Figure 2. Structures of synthesised rhenium-analogues

Two rhenium-analogues showed good values for the D_2/D_3-receptors of up to 70 nM and were labelled with ^{99m}Tc. Labelling with ^{99m}Tc was achieved using $[^{99m}Tc(CO)_3(H_2O)]^+$ with labelling yields of up to 95%.

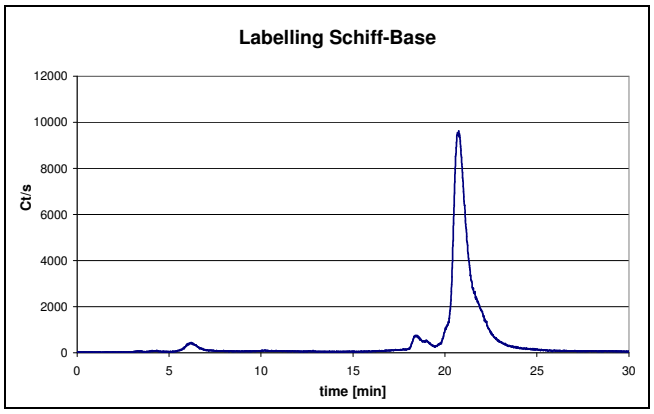

Figure 3 Labelling of the 2-pyridine-imine-derivative (HPLC profile)

Conclusions:
12 novel phenyl-benzamide model derivatives were synthesised retaining excellent affinities to D_2/D_3-receptors. Four novel labelling precursors and 3 rhenium-analogues were prepared. Two of the rhenium-analogues showed good affinities and may have potential as ligands for the visualisation of the D_2/D_3-receptors. In further experiments, their *in vitro* and *in vivo* behaviour shall be investigated.