Radiosynthesis and preliminary evaluation of novel ^{18}F-labeled dopamine D_4-receptor ligands

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Introduction:

- The dopamine D_4-receptor subtype plays an essential role in the development of neurodegenerative diseases, but specific PET-tracers for further examinations are still missing.
- The objective of this work was the design of a D_4-radioligand with high D_4R subtype selectivity and suitable Log *P* values for *in vitro/vivo* PET-studies.
- Due to the low concentration of the D_4R in the brain compared to the other D_iR subtypes (Fig.1), requirements for receptor subtype-selectivity are high.

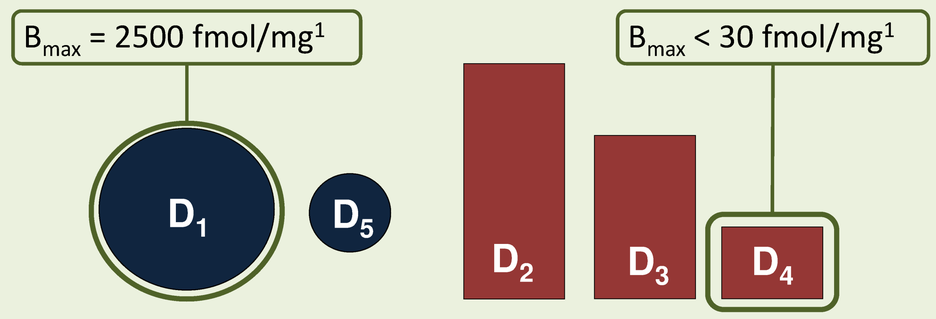

Fig. 1: Schematic illustration of the D_iR's brain concentrations.

Evaluated D_4-specific ligands I & II

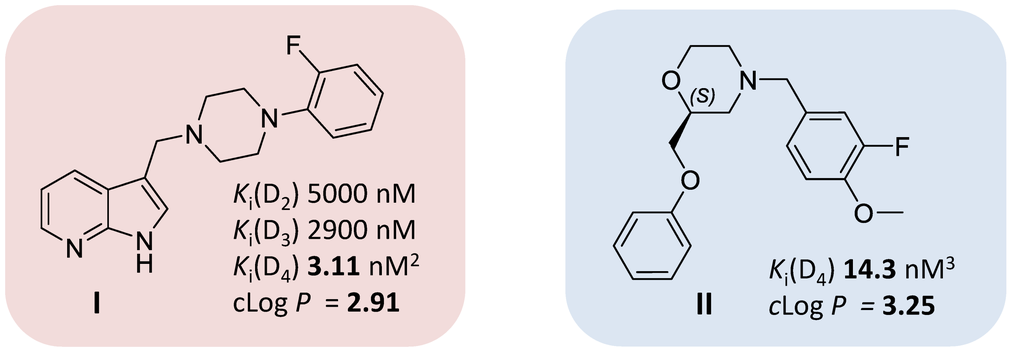

Fig. 2: Receptor ligands **I** & **II** selected for radiofluorination and *in vitro* autoradiographic studies. Log *P* values calculated using ChemDraw v16.0.0.82.

Radiosynthesis of [^{18}F]I

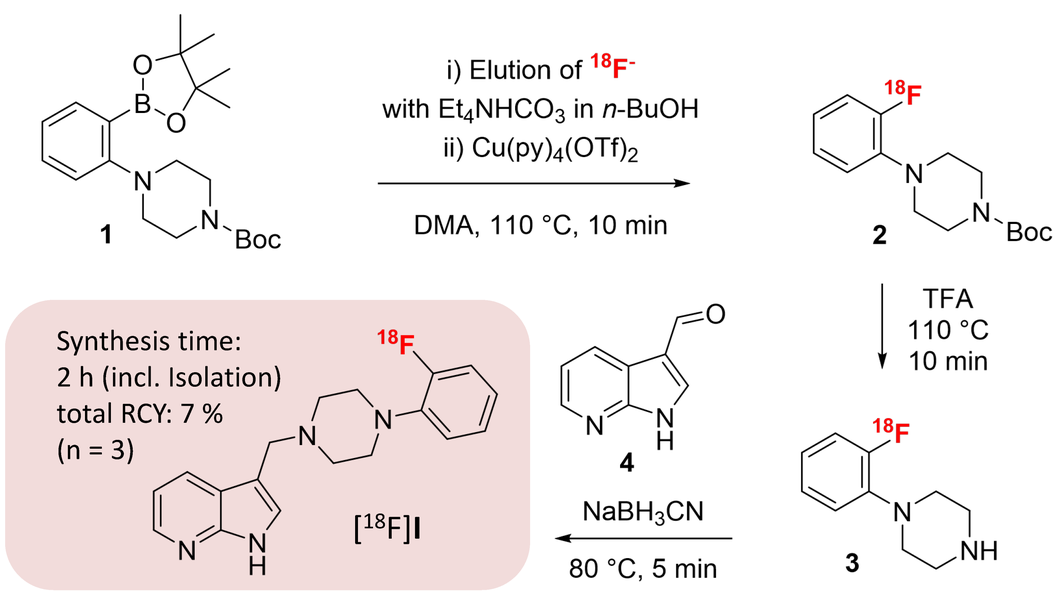

*Fig. 3: Three step synthesis of [^{18}F]**I**.*

- Three step synthesis of **[^{18}F]I** by alcohol enhanced Cu(II)-mediated radiofluorination,[4] followed by subsequent deprotection and reductive amination in a one-pot synthesis.
- The lability of *ortho*-boronic acid(ester) phenylpiperazine derivatives complicates copper-mediated late-stage radiofluorination.
- This procedure enables reliable access to 2-[^{18}F]fluorophenylpiperazines.

In vitro autoradiography with [^{18}F]I

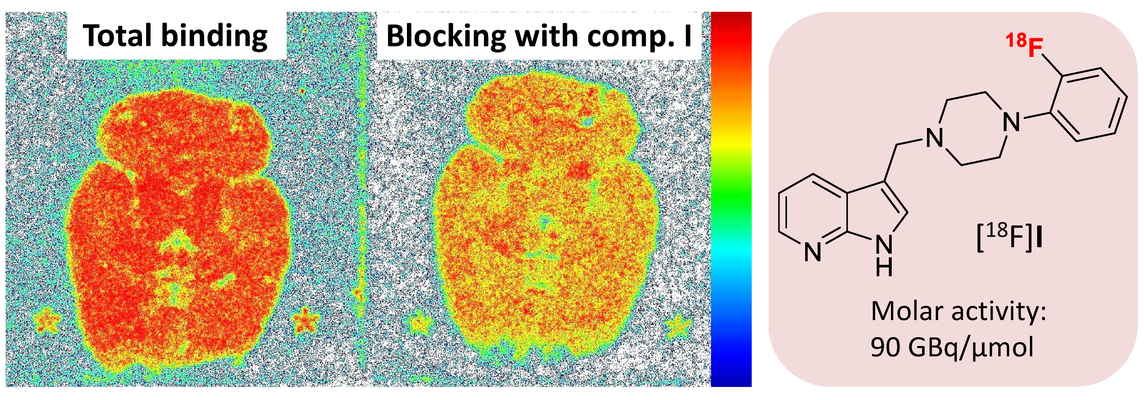

*Fig. 4: In vitro autoradiography of [^{18}F]**I** in horizontal rat brain slices (left: total binding profile. Right: blocking with "cold" **I**, displaying non-specific binding).*

- Three independent autoradiographic studies with molar activities up to 90 GBq/µmol showed high content of non-specific binding.
- The high content of non-specific binding covers any possible specific binding.

Radiosynthesis of [^{18}F]II

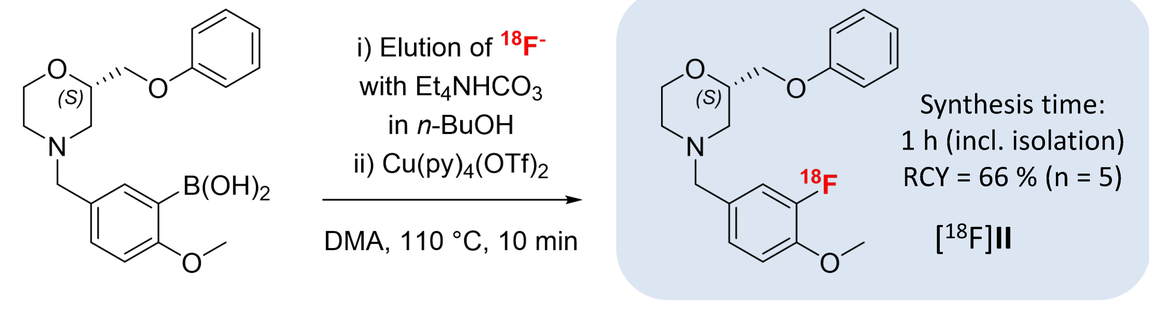

*Fig. 5: Synthesis of [^{18}F]**II** by alcohol enhanced Cu(II)-mediated radiofluorination.*[4]

- The 3-step radiosynthesis could be done *one-pot*, without isolation of intermediates.

In vitro autoradiography with [^{18}F]II

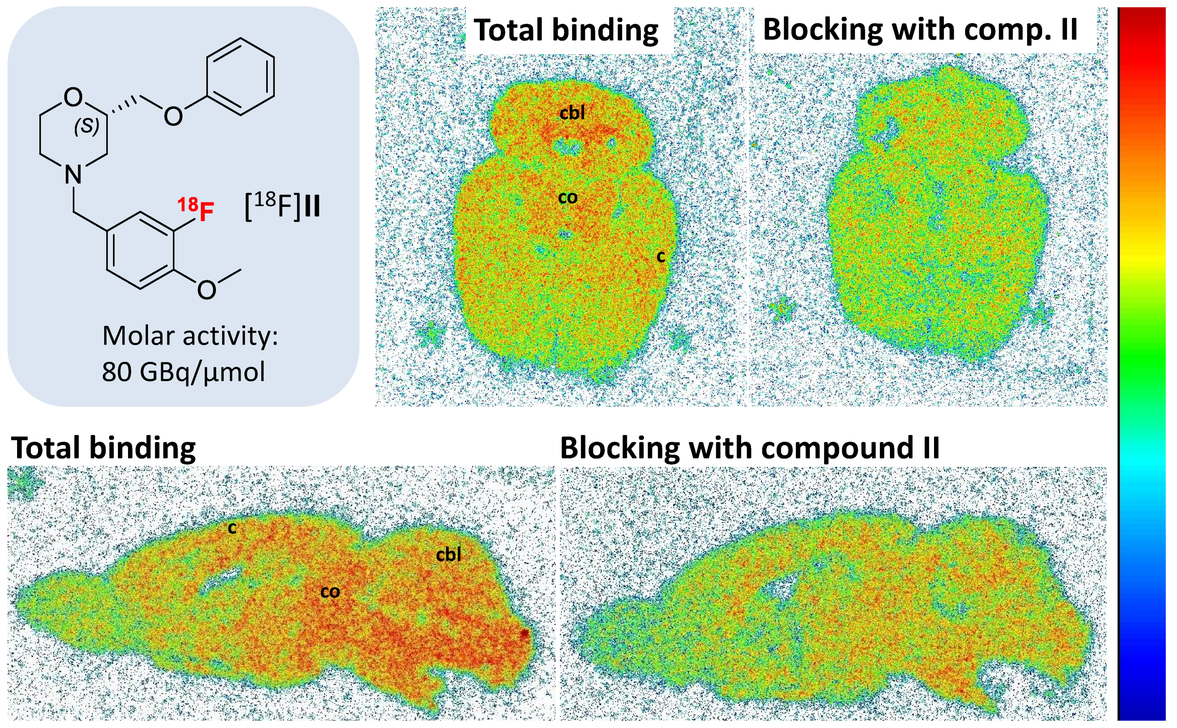

*Fig. 6: In vitro autoradiography of [^{18}F]**II** in horizontal and sagittal rat brain slices (left: total binding profile. Right: blocking with "cold" **II**, displaying non-specific binding; cbl: cerebellum, co:* colliculi, *c: cortex).*

- Uptake of the radiotracer **[^{18}F]II** in cerebellum, colliculi, and cortex of rat brain.

Conclusion:

- Two novel ^{18}F-labeled radiotracers for the D_4-receptor were synthesized and evaluated by *in vitro* autoradiography.
- An efficient radiosynthesis for 2-[^{18}F]fluorophenylpiperazine derivatives was established and successfully applied for the preparation of [^{18}F]**I**.
- *In vitro* autoradiography (n=3) shows high non-specific binding of [^{18}F]**I**
- [^{18}F]**II** was obtained with a RCY of 66±5 % (n = 5) within 60 min.
- Preliminary *in vitro* autoradiographic study indicates specific binding of [^{18}F]**II** in areas with D_4-expression, consistent with results published earlier.[5]

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[3] S. J. Oh *et al.* (2004) *Bioorg. Med. Chem.* **12**: 5505-5513.
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