Novel ¹⁸F-labeled D₄-receptor ligands

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Introduction:

- The dopamine D₄-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.

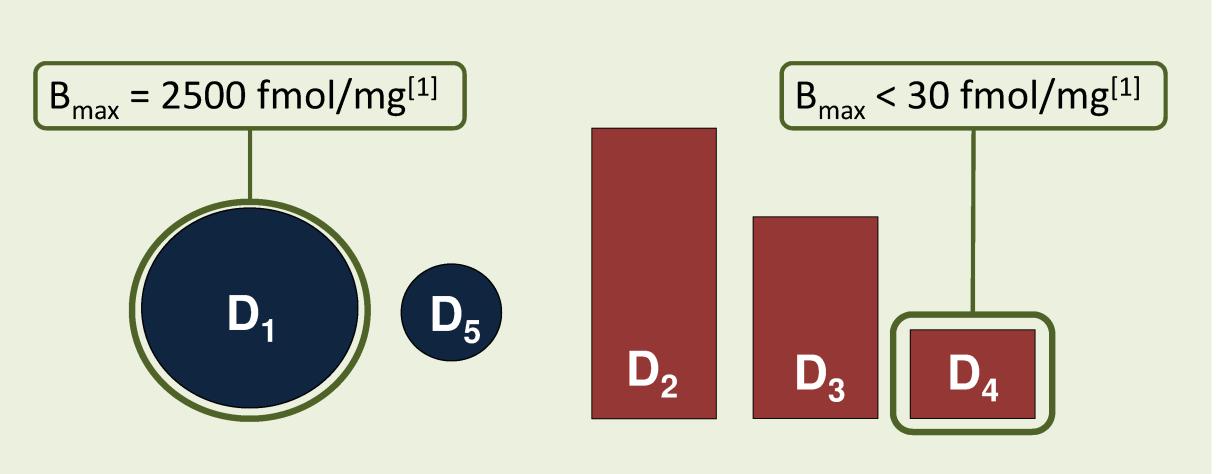
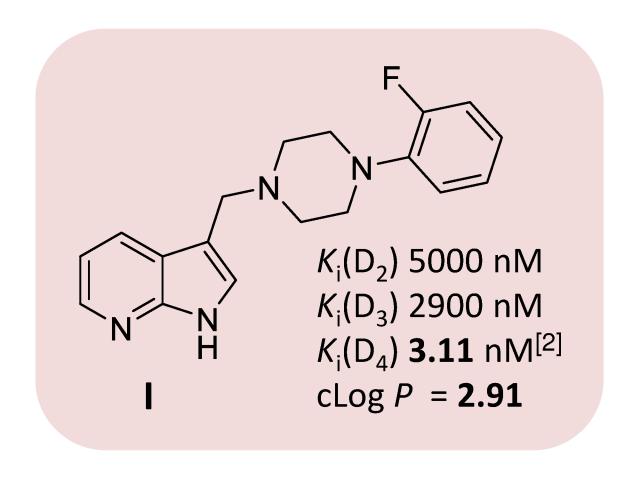


Fig. 1: Schematic illustration of the D_iR's brain concentrations.

Evaluated D₄-specific ligands I & II



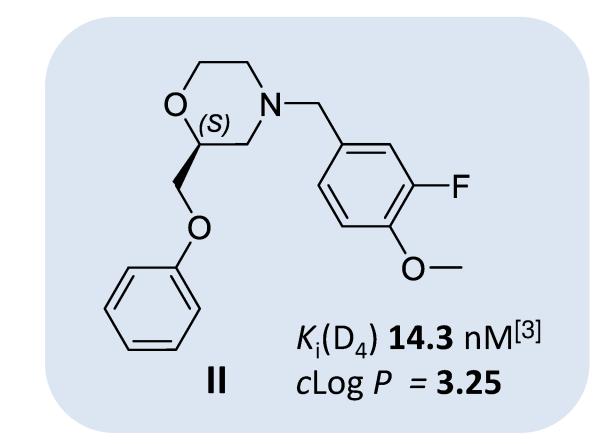


Fig. 2: Receptor ligands I & II selected for radiofluorination and in vitro autoradiographic studies. Log P values calculated using ChemDraw v16.0.0.82.

Radiosynthesis of [18F]I

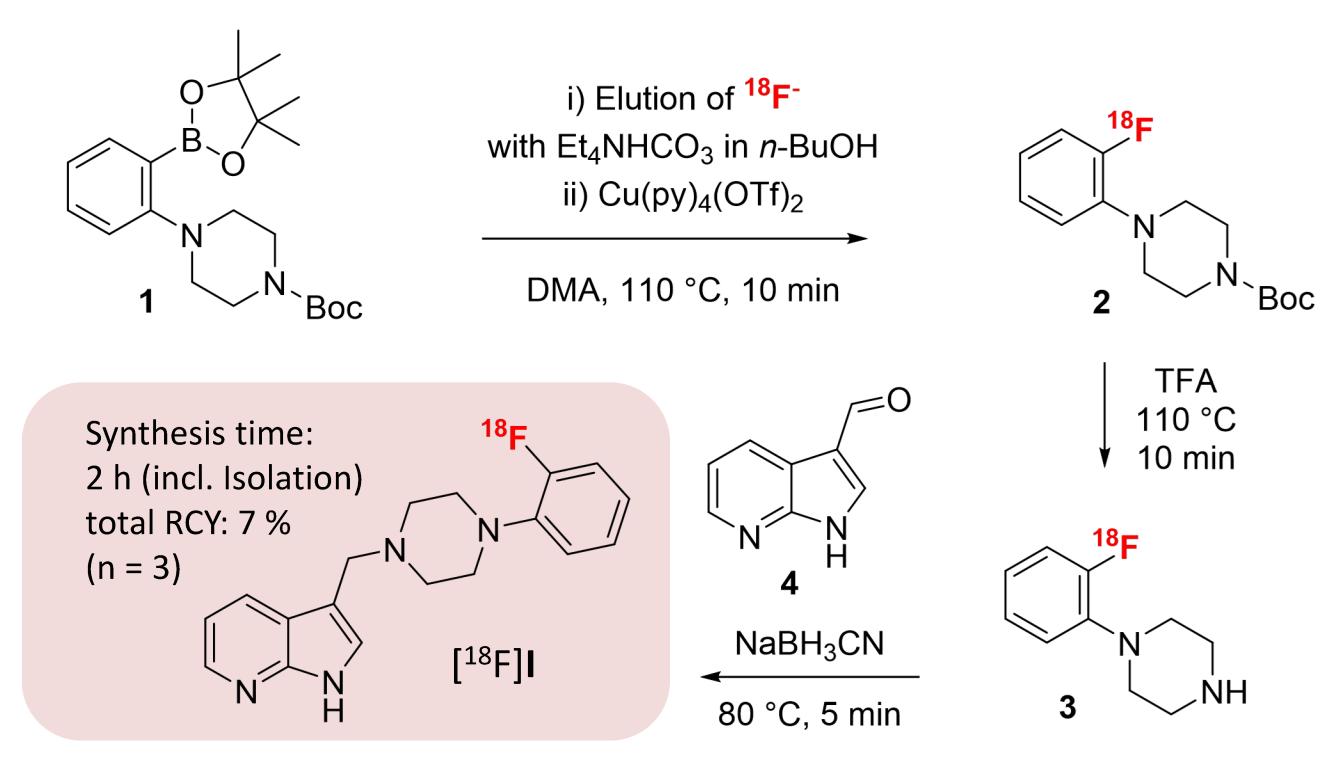


Fig. 3: Three step synthesis of [18F]1.

- Three step synthesis of [¹⁸F]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-[18F]fluorophenylpiperazines.

In vitro autoradiography with [18F]I

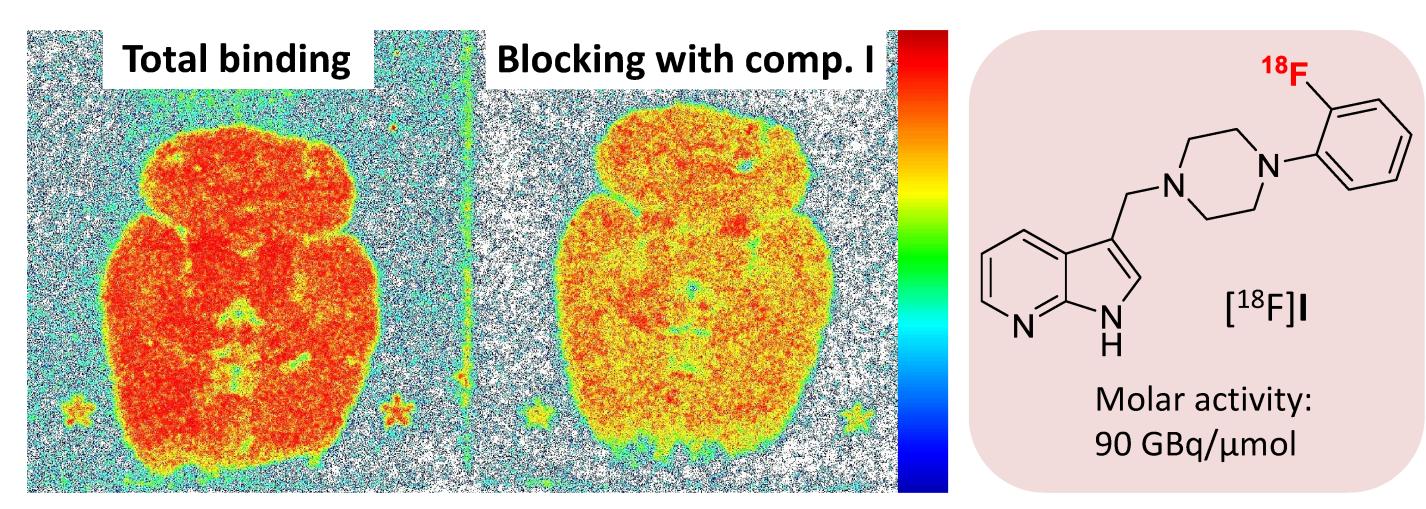


Fig. 4: In vitro autoradiography of $[^{18}F]$ **I** in horizontal rat brain slices (left: total binding profile. Right: blocking with "cold" **I**, displaying non-specific binding).

- 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 [18F]II

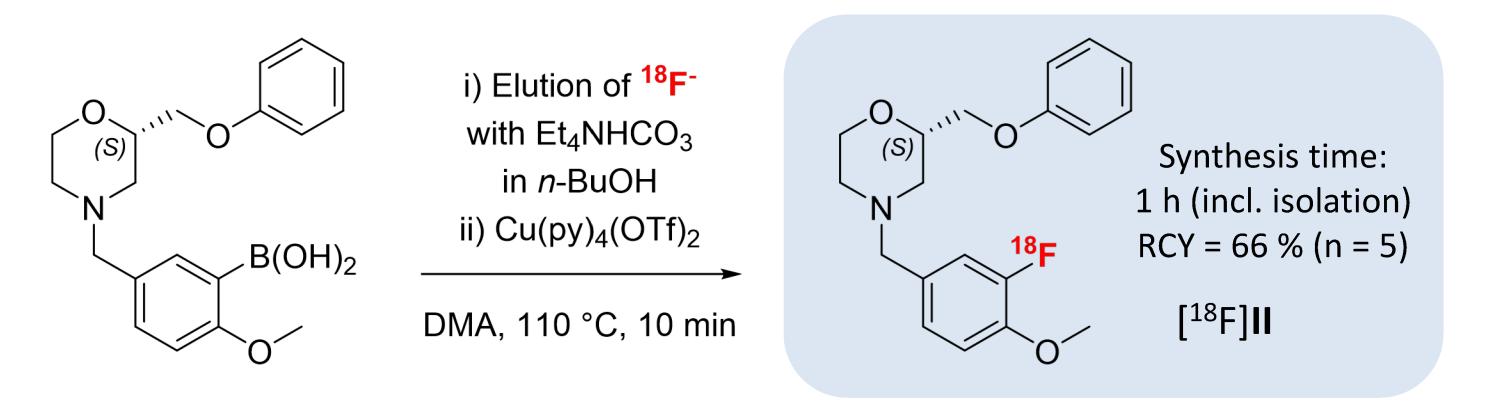


Fig. 5: Synthesis of [18F]II by alcohol enhanced Cu(II)-mediated radiofluorination. [4]

• [18 F]II was obtained by alcohol enhanced Cu^{II}-mediated radiofluorination^[4] in a RCY of 66 ± 5 % (n = 5).

In vitro autoradiography with [18F]II

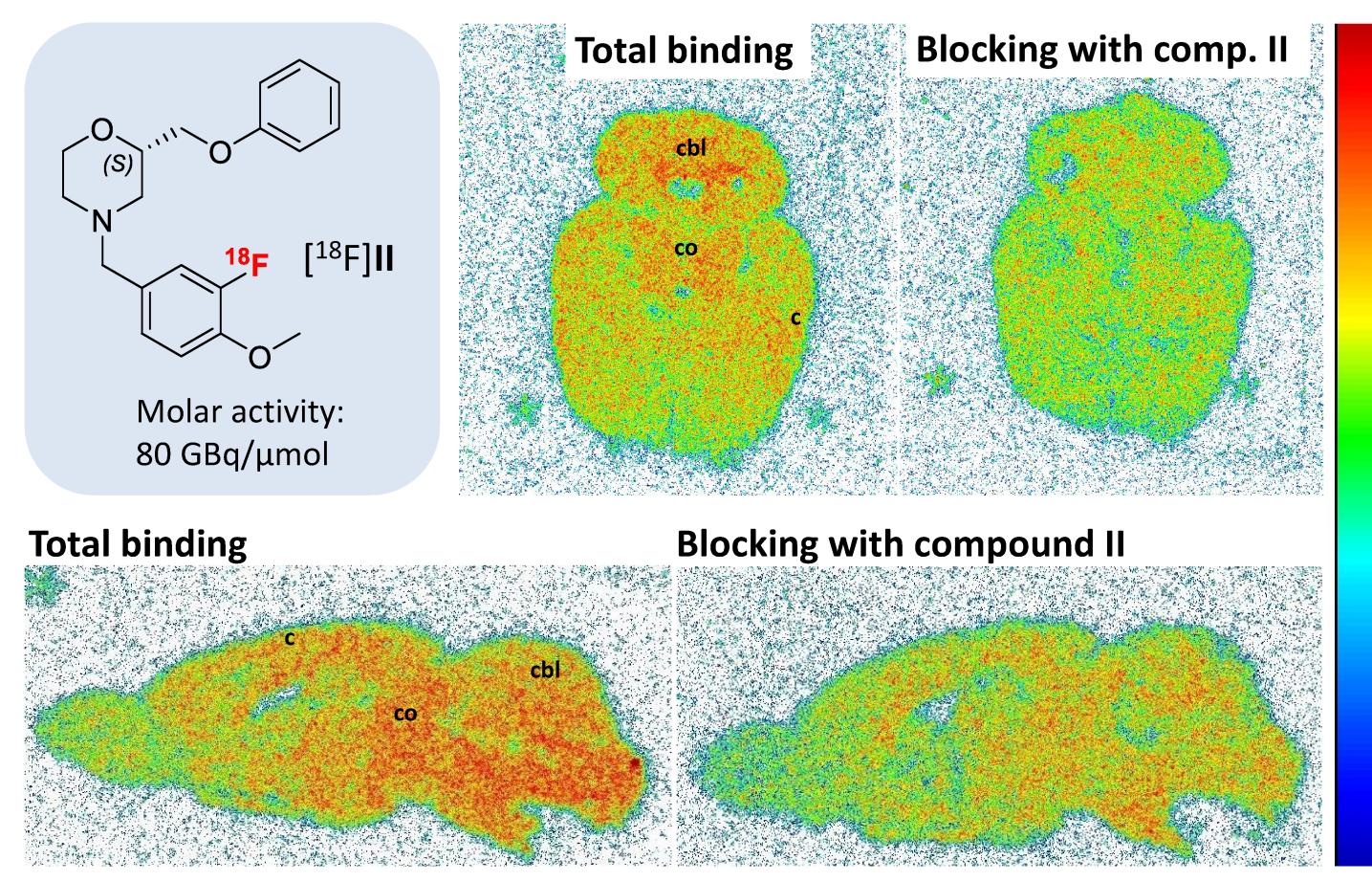


Fig. 6: In vitro autoradiography of $[^{18}F]$ in horizontal and sagittal rat brain slices (left: total binding profile. Right: blocking with "cold" II, displaying non-specific binding; cbl: cerebellum, co: colliculi, c: cortex).

• Uptake of the radiotracer [18F]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-[¹⁸F]fluorophenylpiperazine derivatives was established and successfully applied for the preparation of [¹⁸F]I.
- In vitro autoradiography (n=3) shows high non-specific binding of [18F]I
- [18 F]II was obtained with a RCY of $66\pm5\%$ (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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