

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 $\text{Log } P$ 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.

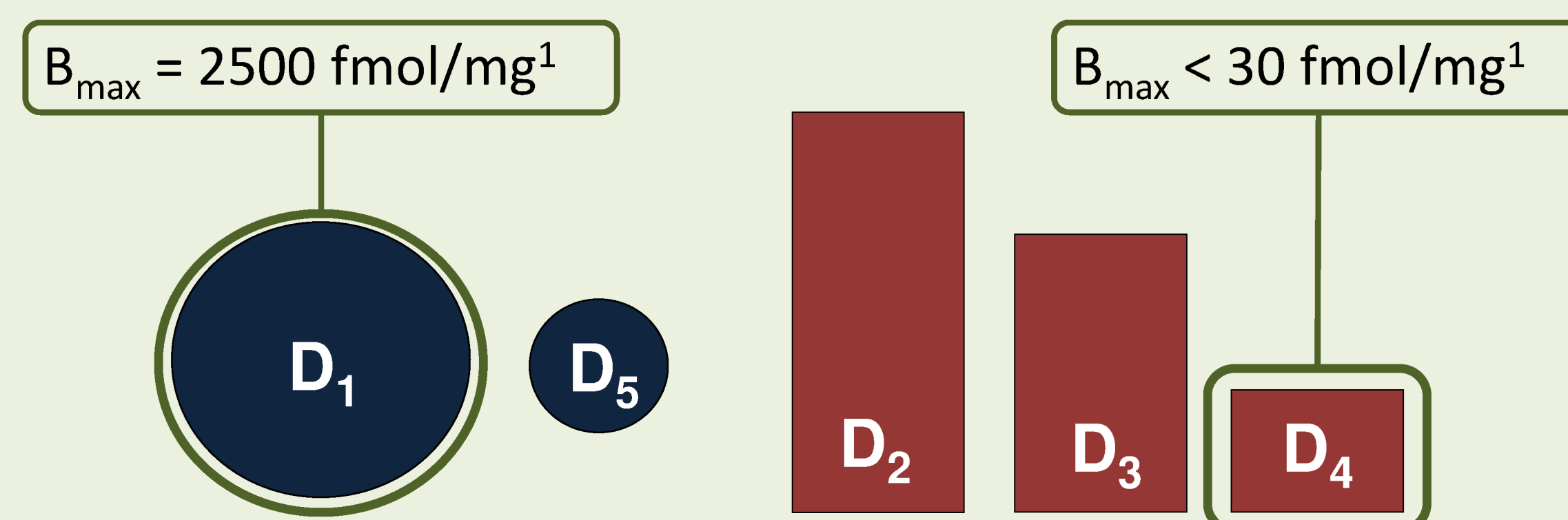


Fig. 1: Schematic illustration of the D_iR 's brain concentrations.

Evaluated D_4 -specific ligands I & II

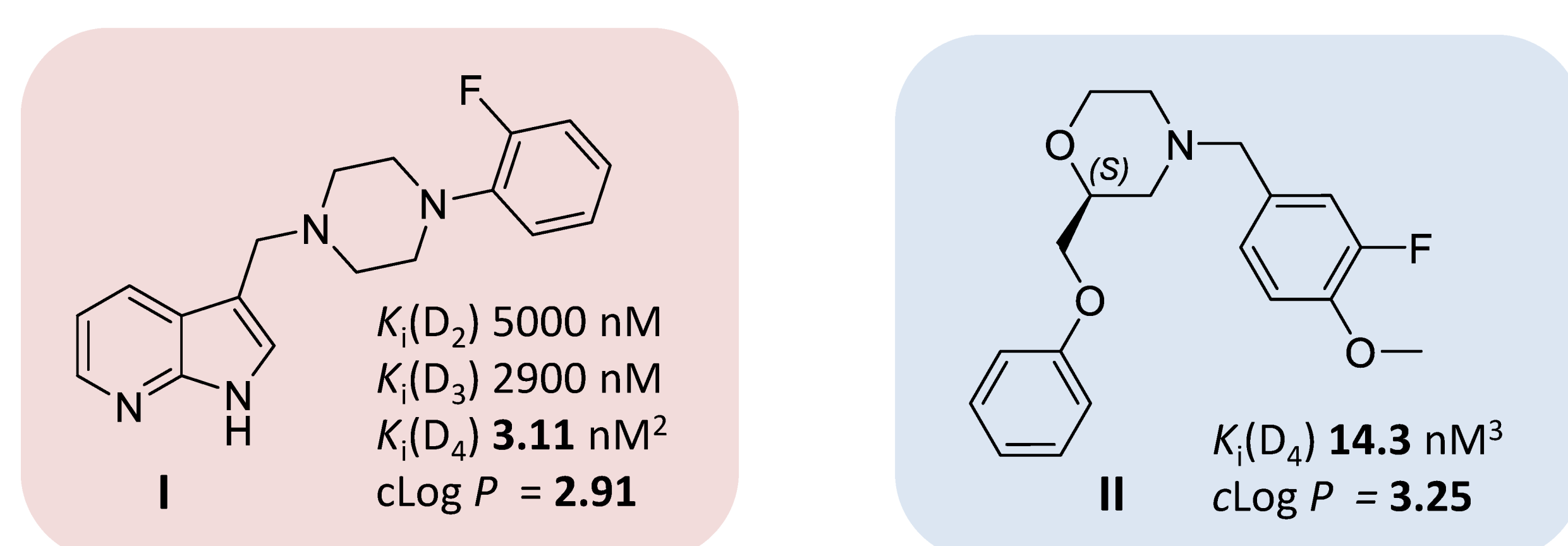


Fig. 2: Receptor ligands I & II selected for radiofluorination and *in vitro* autoradiographic studies. $\text{Log } P$ values calculated using ChemDraw v16.0.0.82.

Radiosynthesis of ^{18}F II

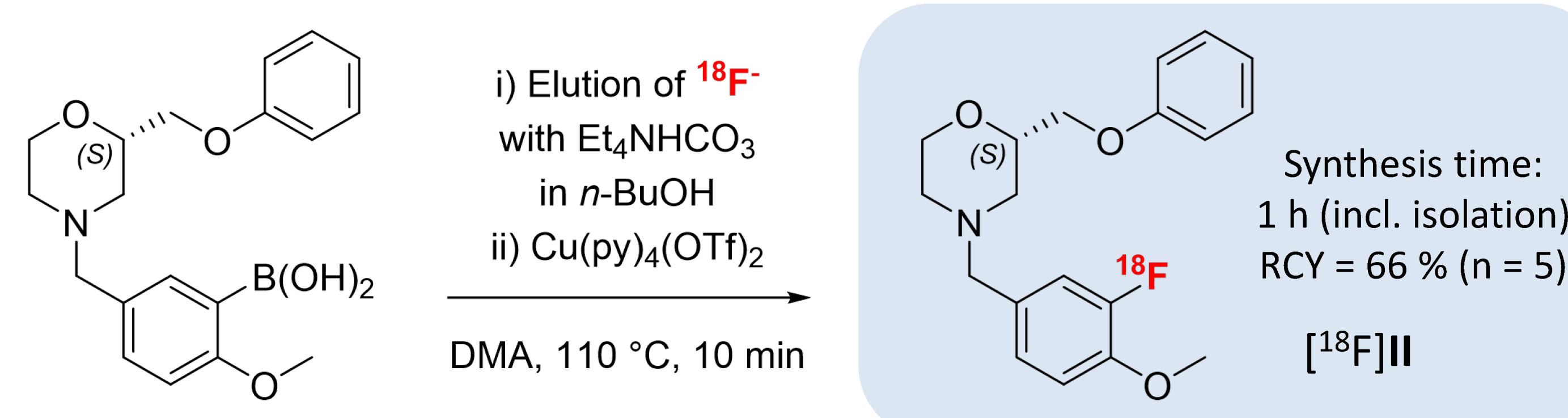


Fig. 5: Synthesis of ^{18}F II by alcohol enhanced $\text{Cu}(\text{II})$ -mediated radiofluorination.⁴

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

Radiosynthesis of ^{18}F I

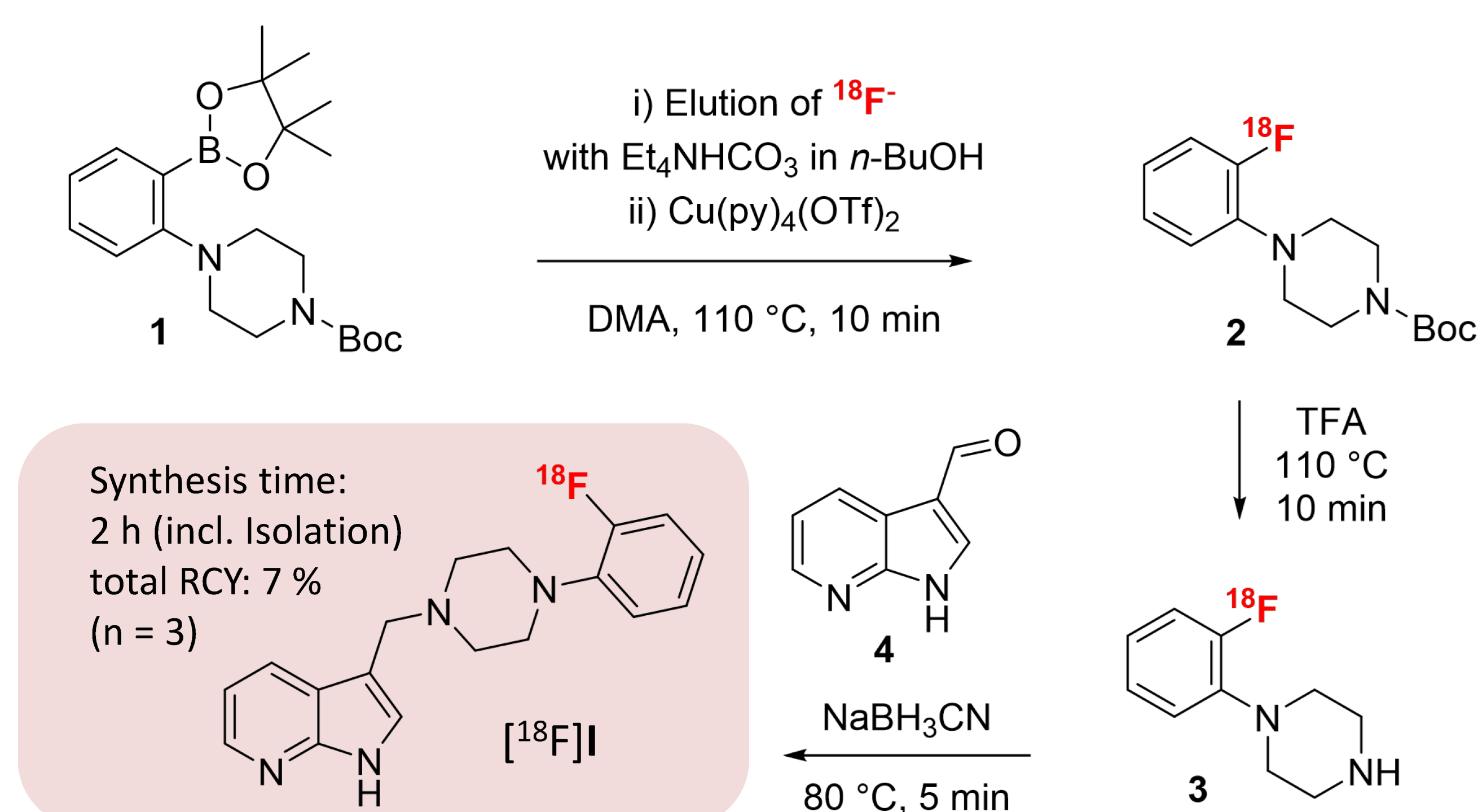


Fig. 3: Three step synthesis of ^{18}F I.

- Three step synthesis of ^{18}F I by alcohol enhanced $\text{Cu}(\text{II})$ -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

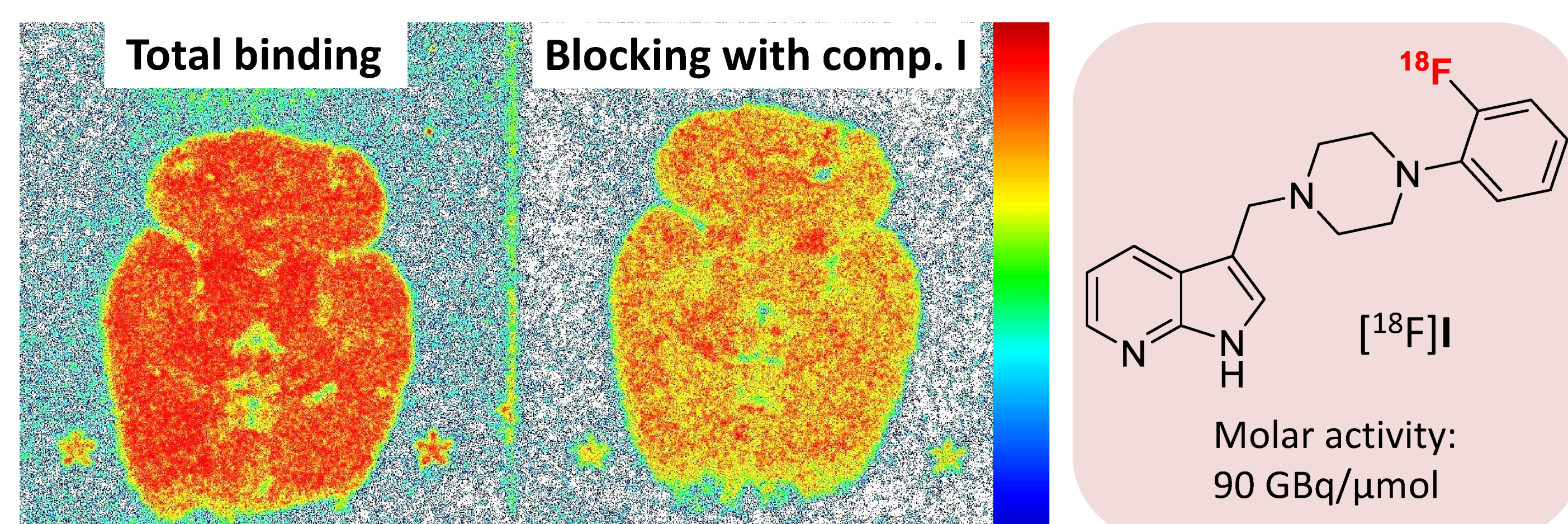


Fig. 4: *In vitro* autoradiography of ^{18}F I in horizontal rat brain slices (left: total binding profile. Right: blocking with "cold" I, displaying non-specific binding).

- 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.

In vitro autoradiography with ^{18}F II

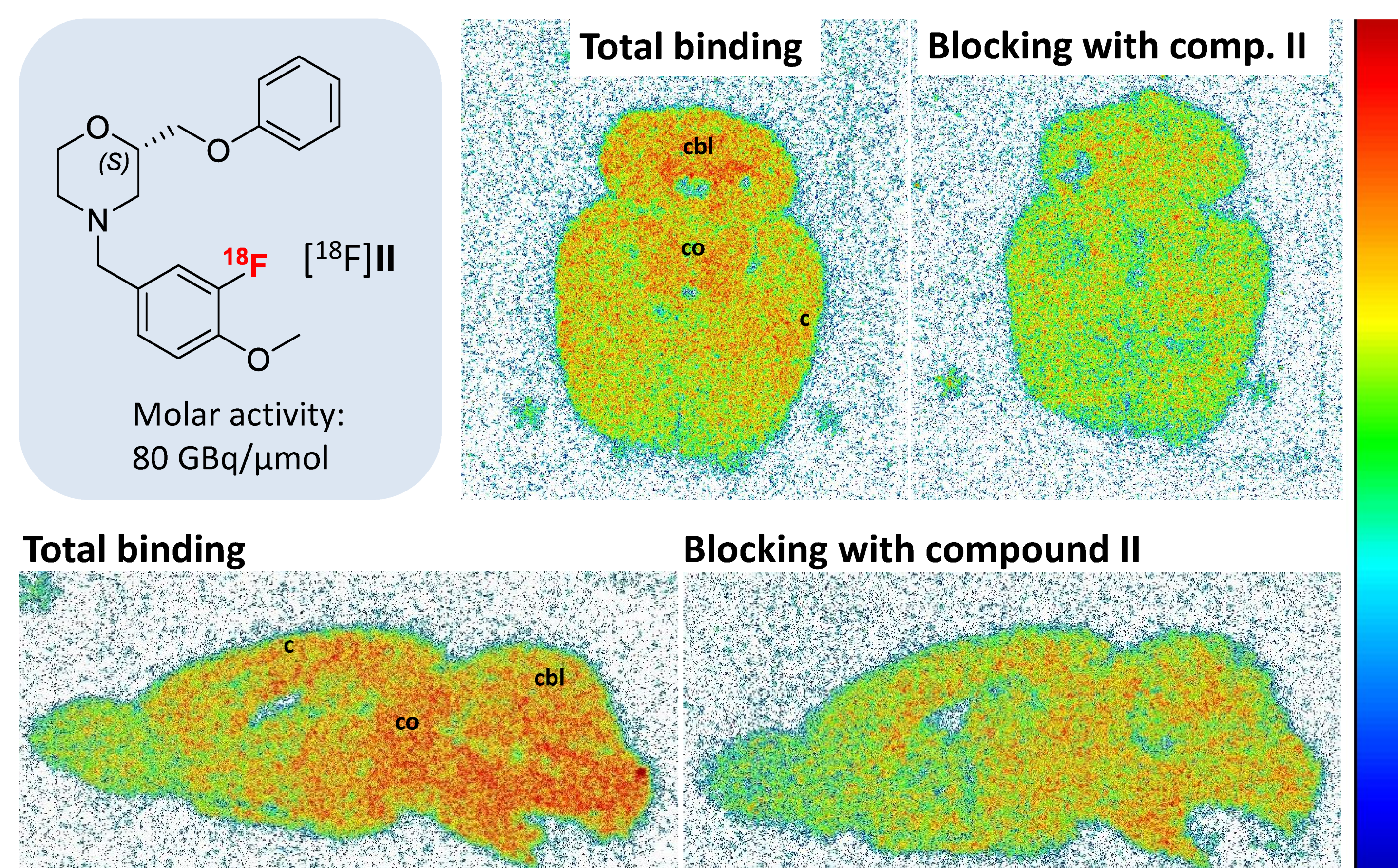


Fig. 6: *In vitro* autoradiography of ^{18}F II in horizontal and sagittal rat brain slices (left: total binding profile. Right: blocking with "cold" II, displaying non-specific binding; cbl: cerebellum, co: colliculi, c: cortex).

- 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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