

Novel ^{18}F -labeled D_4 -receptor ligands

Michael Willmann, Johannes Ermert and Bernd Neumaier



Forschungszentrum Jülich GmbH, Institute of Neuroscience and Medicine, INM-5, Nuclear Chemistry, Germany

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 D₄-radioligand with high D₄R subtype selectivity and suitable Log *P* values for *in vitro*/*vivo* PET-studies.
- Due to the low concentration of the D₄R in the brain compared to the other D₁R subtypes (Fig.1), requirements for receptor subtype-selectivity are high.

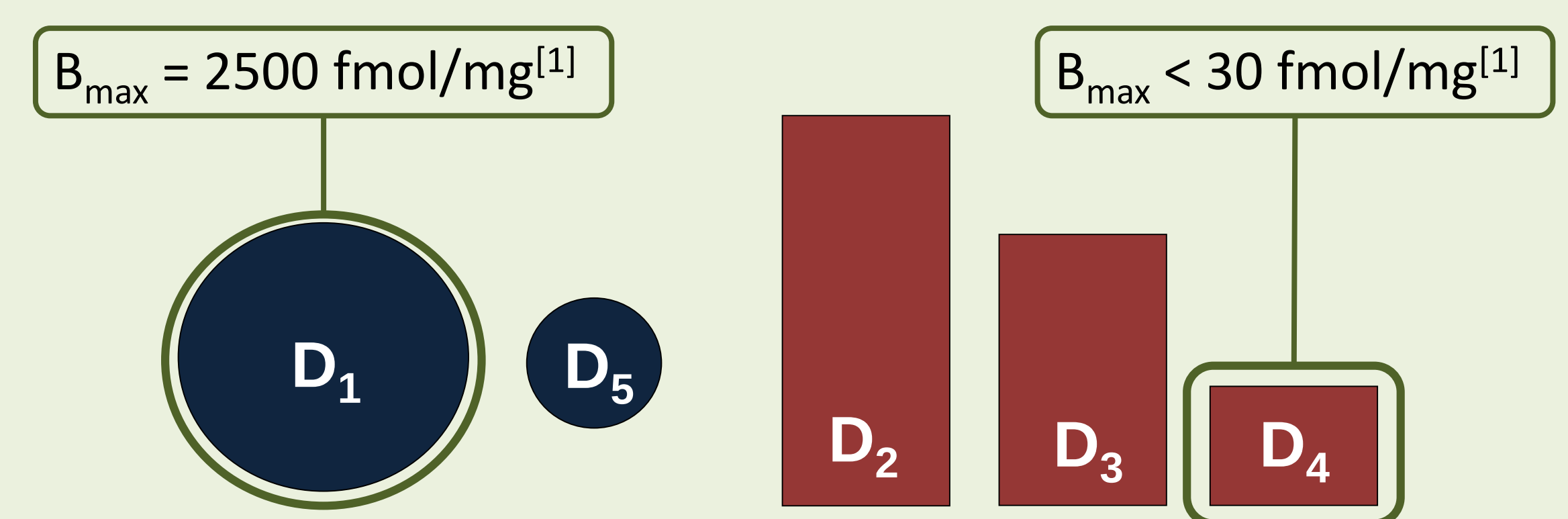


Fig. 1: Schematic illustration of the D_iR 's brain concentrations.

Evaluated D₄-specific ligands I & II

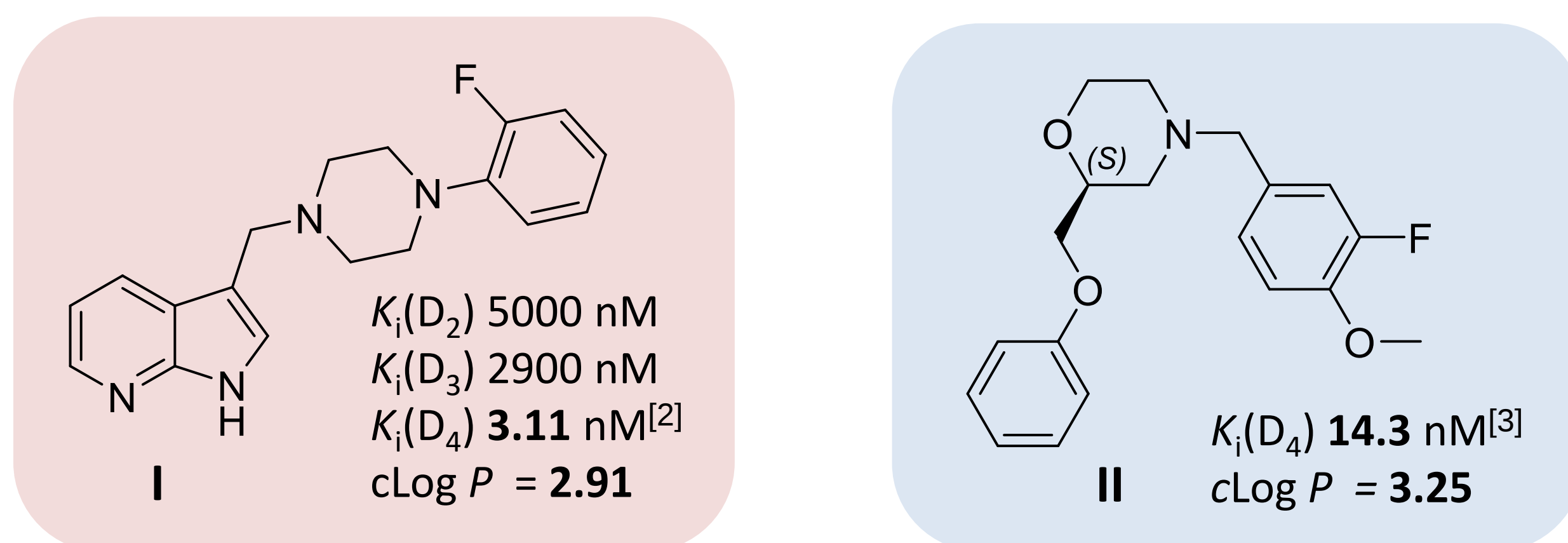


Fig. 2: Receptor ligands I & II selected for radiofluorination and *in vitro* autoradiographic studies. Log *P* values calculated using ChemDraw v16.0.0.82.

Radiosynthesis of [^{18}F]II

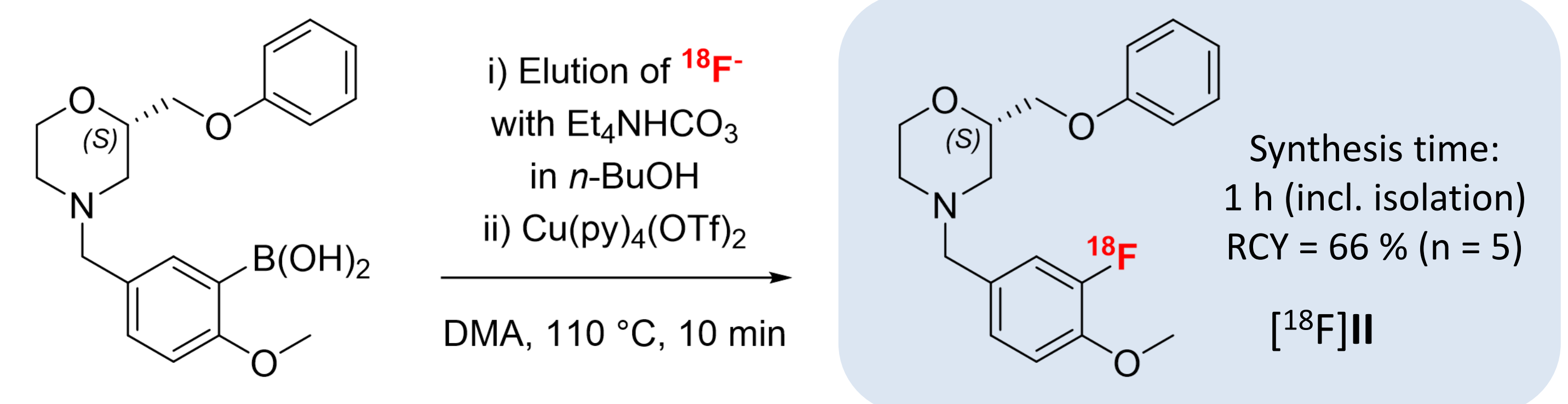


Fig. 5: Synthesis of $[^{18}\text{F}]\text{II}$ by alcohol enhanced $\text{Cu}(\text{II})$ -mediated radiofluorination. ^[4]

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

Radiosynthesis of [¹⁸F]I

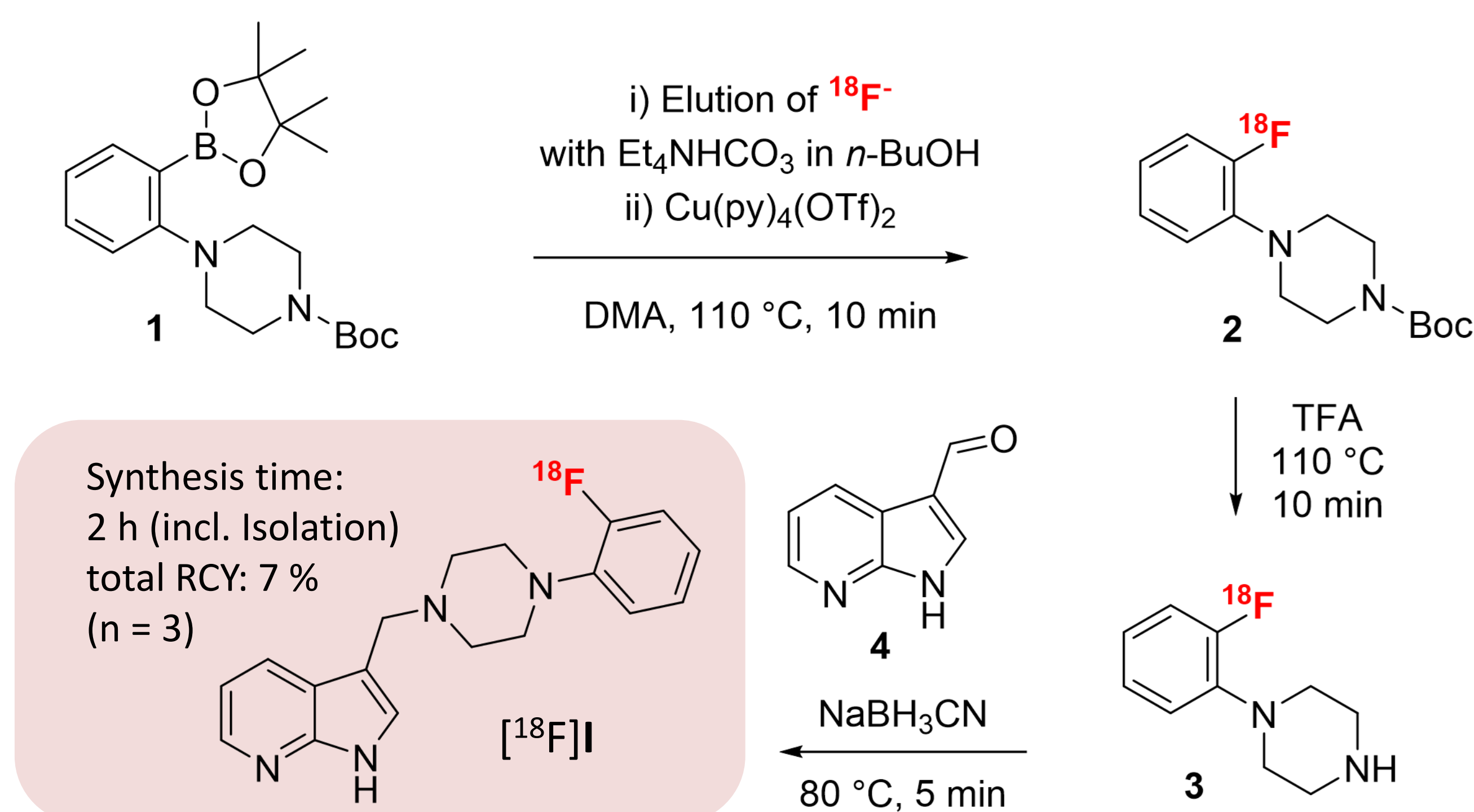


Fig. 3: Three step synthesis of [^{18}F]I.

- Three step synthesis of [**¹⁸F**] 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**

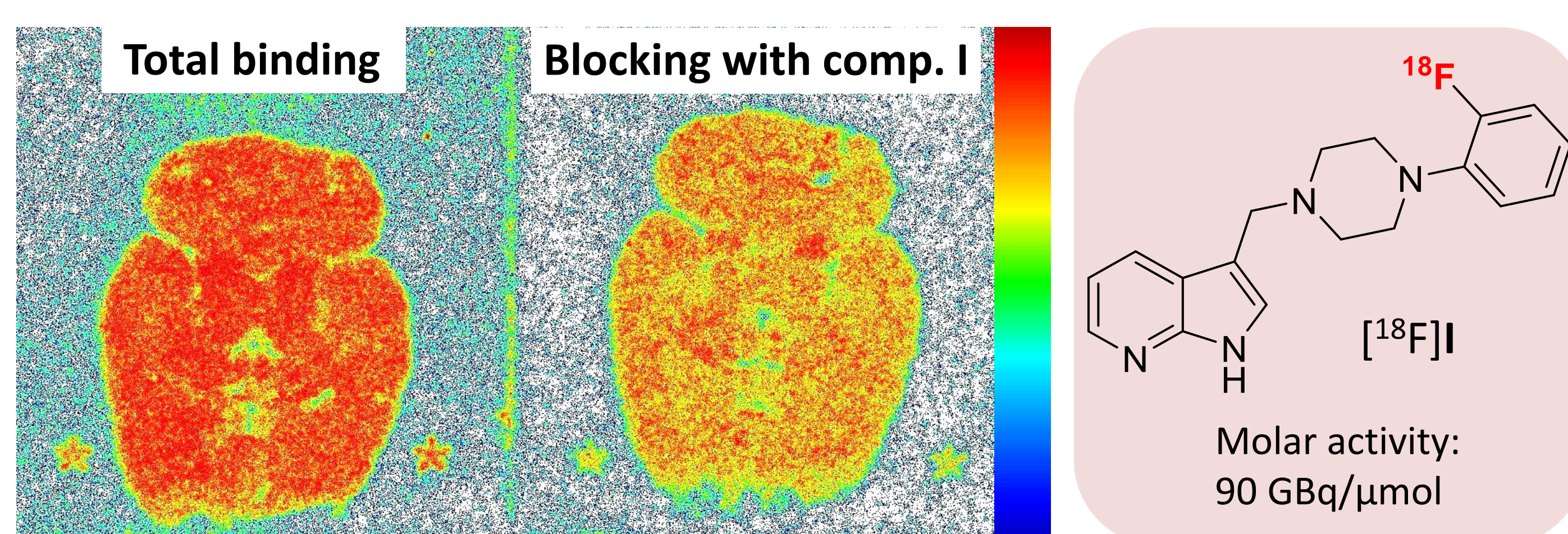


Fig. 4: In vitro autoradiography of [^{18}F]I in horizontal rat brain slices (left: total binding profile. Right: blocking with "cold" I, displaying non-specific binding).

- 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.

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

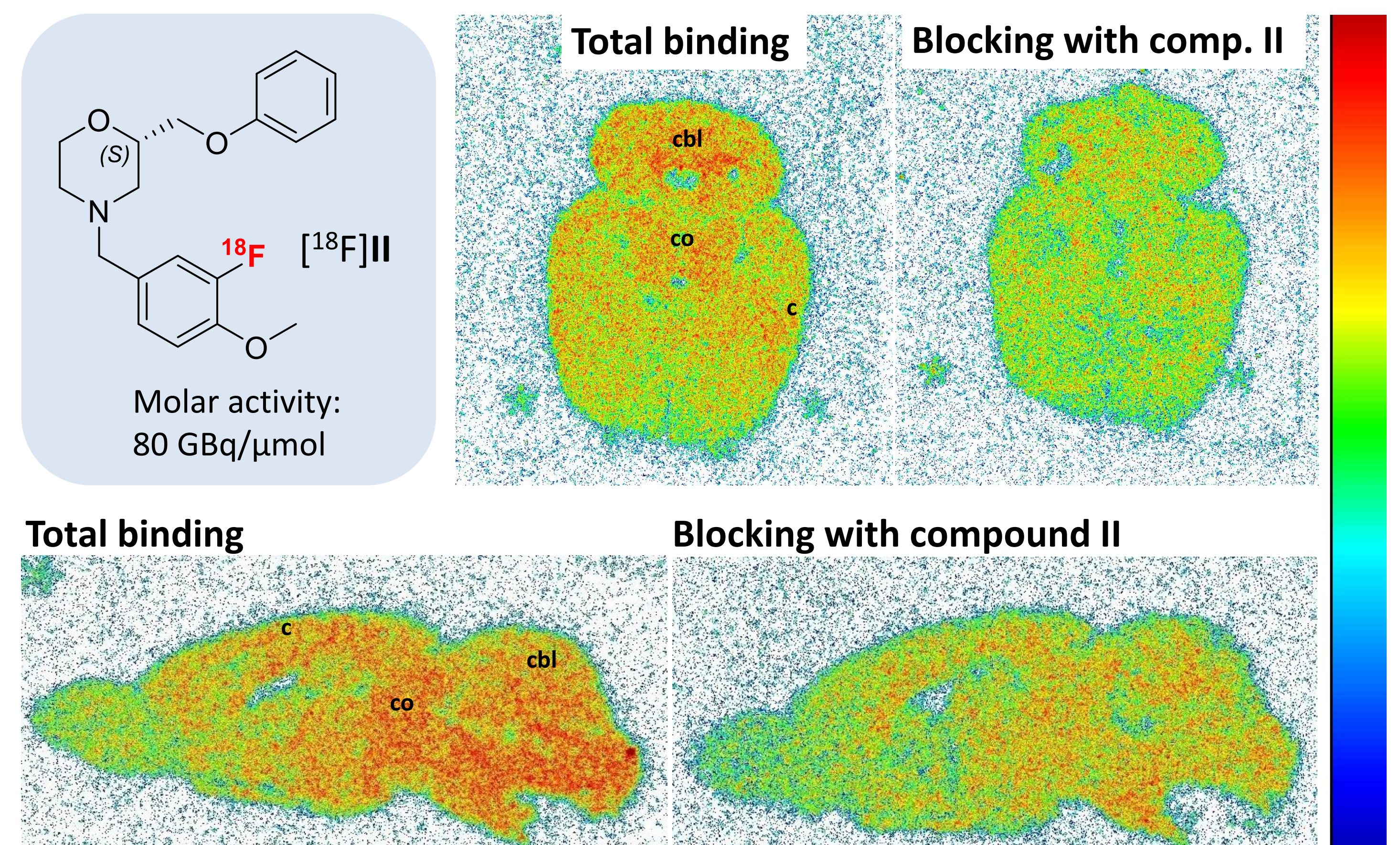


Fig. 6: In vitro autoradiography of [^{18}F]II in horizontal and sagittal rat brain slices (left: total binding profile. Right: blocking with “cold” II, displaying non-specific binding; cbl: cerebellum, co: colliculi, c: cortex).

- Uptake of the radiotracer [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- ^{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.

[4] J. Zischler *et al.* (2017) *Chem. Eur. J.* **23**: 3251-3256.

[5] F. Kügler *et al.* (2011) *J. Med. Chem.* **54**: 8343-8352.