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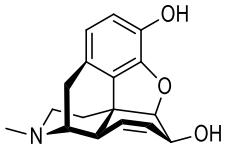

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Novel ^{18}F-labeled D_4-receptor ligands

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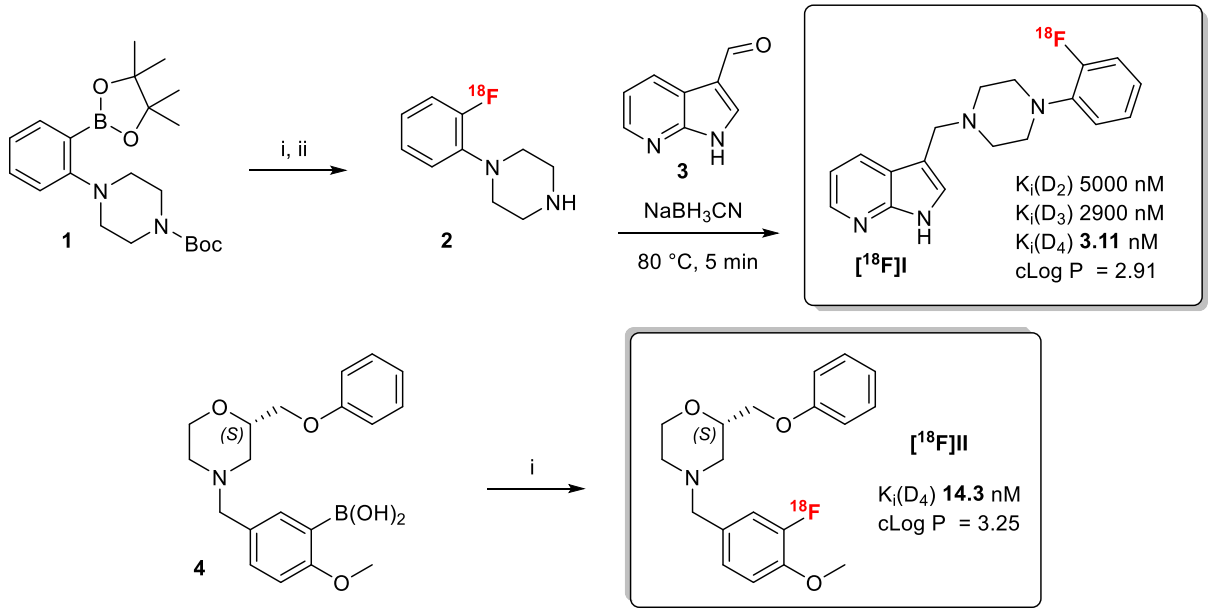
The role of the dopamine D_4-receptor subtype in the development of neurodegenerative diseases such as schizophrenia has been discussed for several decades. Specific radiotracers for more detailed preclinical and clinical investigations are still missing so far. The objective of this study was to develop D_4-selective radioligands for positron emission tomography (PET). The selected lead structures exhibit high D_4R subtype selectivity and a suitable Log*P* values, rendering them attractive for the development of a D_4-selective radioligand for PET-imaging [1]. Two D_4R-ligands, know from literature [2,3], were selected for labeling with fluorine-18 ($t_{1/2}$=108 min), the most ideal positron emitting nuclide.

D_4R-radioligand **[^{18}F]I** was synthesized from 2-[^{18}F]fluorophenylpiperazine **2**, obtained by an alcohol enhanced Cu(II)-mediated radiofluorination [4] of the Boc-protected precursor **1** followed by deprotection of the radiolabeled intermediate with TFA. Subsequently, **[^{18}F]I** was obtained by reductive amination with **3** in a total isolated radiochemical yield of 7 % within 2 h. Three independent auto radiographic studies with molar activities up to 90 GBq/µmol showed high content of non-specific binding that covers any possible specific binding.

The chiral D_4R-radioligand **[^{18}F]II** was also obtained by alcohol enhanced Cu(II)-mediated radiofluorination [4] of the boronic acid precursor **4** in a RCY of 66±5 % within 60 min after isolation by semi-preparative HPLC. Preliminary in vitro autoradiographic study indicates specific binding of [^{18}F]**II** in areas with D_4-expression, consistent with results published earlier [5].



i) Elution of $^{18}F^-$ with Et_4NHCO_3 in *n*-BuOH. $Cu(py)_4(OTf)_2$, DMA, 110 °C, 10 min. ii) TFA, 110 °C, 10 min.
iii) $NaBH_3CN$, 80 °C, 5 min.

References:

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