Syntheses and biological evaluation of new compounds as potential imaging agents for the NMDA-receptor

T. Betzel[1], C. Edinger[2], G. Dannhardt[2], F. Rösch[1]
[1]Institute of Nuclear Chemistry, Johannes Gutenberg-University, 55128 Mainz, Germany;
[2]Institute of Pharmacy, Johannes Gutenberg–University, 55128 Mainz, Germany

Introduction: The NMDA receptor plays a central role in several disorders in the CNS. To provide effective ligands for the glycine binding site for PET imaging, a new series of indole-2-carboxylate derivatives have been synthesized.

Experimental: Based on the indole-2-carboxylate GV150526 (1), a series of ethyl esters and free acids were synthesized, which are conjugated with a fluoroethoxy group in the terminal phenyl ring in ortho, meta and para position. These new compounds, namely ethyl-3-((E)-2-((2/3/4-fluoroethoxy)-phenylcarbamoyl)-vinyl)-4,6-dichloro-1H-indole-2-carboxylate (**1**, **3**, **5**) and the corresponding carboxylic acids (**2**, **4**, **6**) were synthesized, cf. Figure 1.

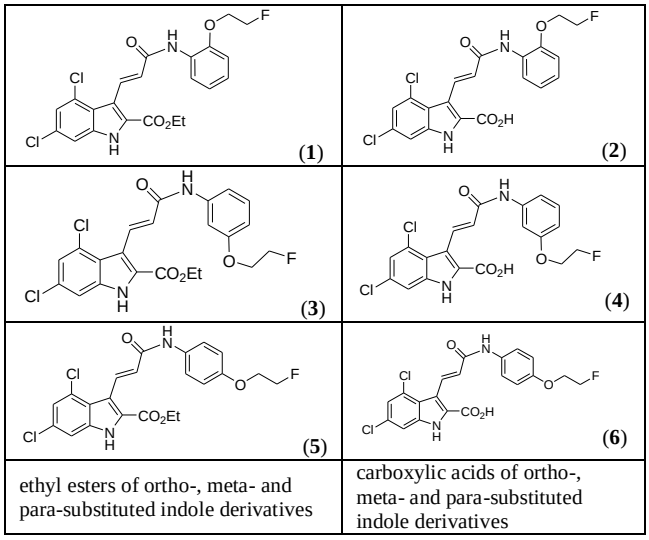

Figure 1. Structures of synthesized NMDA-ligands

Each target compounds can be synthesized in a 8 step reaction. The reaction scheme is shown in Figure 2. The IC_{50} values of the ^{19}F-inactive compounds were determined using a [^{3}H]MDL-105,519 receptor binding assay [2].
The fluorine-18 labelled analogue of the most promising compound could be used for imaging the NMDA receptor by PET.

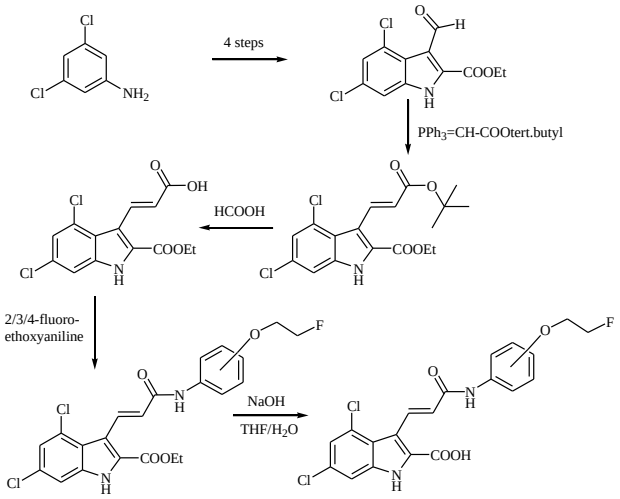

Figure 2. Reaction scheme for the inactive reference compounds

Results: The affinity data of the ethyl esters show affinities about 300 µM, c.f. Table 1. But the affinities improve dramatically for the free acids in the order ortho (1438 nM) > meta (595 nM) > para (0.23 nM) for the substitution of the terminal phenyl ring. The data demonstrate that affinity depends on the variation of the fluoroethoxy group. Especially the para substituted compound shows affinity in the low nanomolare range. The radiolabelled analogue could be used as imaging agent. Therefore the design of the precursor has to carry the phenolic hydroxyl group in para postion. Hence the precursor could be labelled with [^{18}F]fluoroethyltosylate. The synthesis of the precursor molecule for this promising compound is in process.

compound	substitution	IC_{50} / µmol
1	ortho-fluoroethoxy substituted ester	258,45
3	meta-fluoroethoxy substituted ester	276,54
5	para-fluoroethoxy substituted ester	401
2	ortho-fluoroethoxy substituted acid	1,438
4	meta-fluoroethoxy substituted acid	0,595
6	para-fluoroethoxy substituted acid	0,00023

Table 1. Affinity of the synthesized compounds

References

[1] Di Fabio, R. et al.; J. Med. Chem. 1997, 40, 841-850
[2] Jansen, M.; Potschka, H.; Brandt, C.; Löscher, W.; Dannhardt G.; J. Med. Chem. 2003, 46, 64-73

Acknowledgement

This work was financially supported by DFG grant RO 985/20-1.