SYNTHESIS, ^{18}F-LABELING AND EVALUATION OF α_5-SUBTYPE-SELECTIVE GABA$_A$-RECEPTOR-LIGANDS

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Introduction: The visualization and quantification of the α_5-subunit of the GABA$_A$-receptor by PET may allow a better diagnosis and therapy control of miscellaneous neurological disorders, e.g. Alzheimer's disease (AD) and posttraumatic stress disorder (PTSD). α_5-Subtype-selective GABA$_A$-receptor ligands also provide an opportunity to give a deeper understanding of the important processes of learning and memory. 7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine[1] seems to be a promising lead structure for those new ligands, especially for PET tracers, which allow non-invasive measurement of ligand biodistribution and accumulation kinetics related to GABA$_A$-receptor studies in the living brain.

Experimental: A novel series of 6-(6-fluoro-pyridine-2-yl)methyloxy-7,8,9,10-tetrahydro-(7,10-ethano)-1,2,4-triazolo[3,4-a]phthalazine derivatives TC 07-TC12 were synthesized in a multi-step organic synthesis [Fig.1].

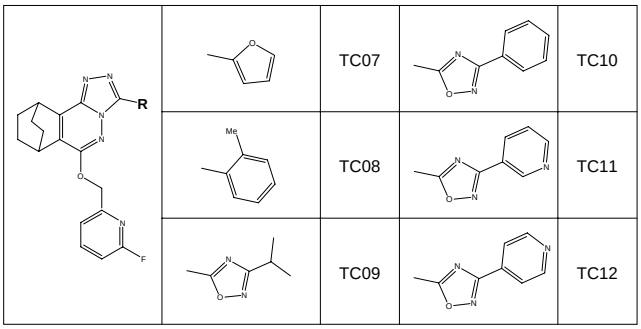

Fig.1: Synthesized derivatives TC07-TC12

The reference substances were evaluated in receptor binding assays and by autoradiography of [^{3}H]Ro15-4513 binding against increasing concentrations of the synthesized derivatives.
The corresponding precursors for ^{18}F-syntheses were built in a multi-step-synthesis. The subsequent ^{18}F-labeling was achieved by direct ^{18}F-fluorination via nucleophilic substitution using [^{18}F]fluoride.

Results and Discussion: For the fluoro-reference compounds, both binding assays and autoradiographic data showed nanomolar affinities (K_i) and a very high selectivity for the α_5-subunit of the GABA$_A$-receptor. Autoradiographic data indicate a dose dependent selective displacement of the radioligand from α_5-subunit containing GABA$_A$-Receptors. Figure 2 shows the displacement of [^{3}H]Ro15-4513 with increasing concentrations of compound TC12. For the most relevant compounds, the ^{18}F-labeling reactions were optimized in terms of temperature, time of reaction and precursor concentration.

Conclusion: The experiments identified the synthesized substances to be potent substrates concerning the α_5-subtype of the GABA$_A$-receptor. Based on the obtained results so far, *ex vivo* and *in vivo* small-animal-studies using PET will be carried out next. Thus, new and highly selective PET-ligands for imaging the α_5-subunit in cell studies and in *ex vivo* and *in vivo* small-animal-studies using PET might soon be available.

References:
[1] L.J. Street et al., J Med Chem 47 (2004), 3642-57

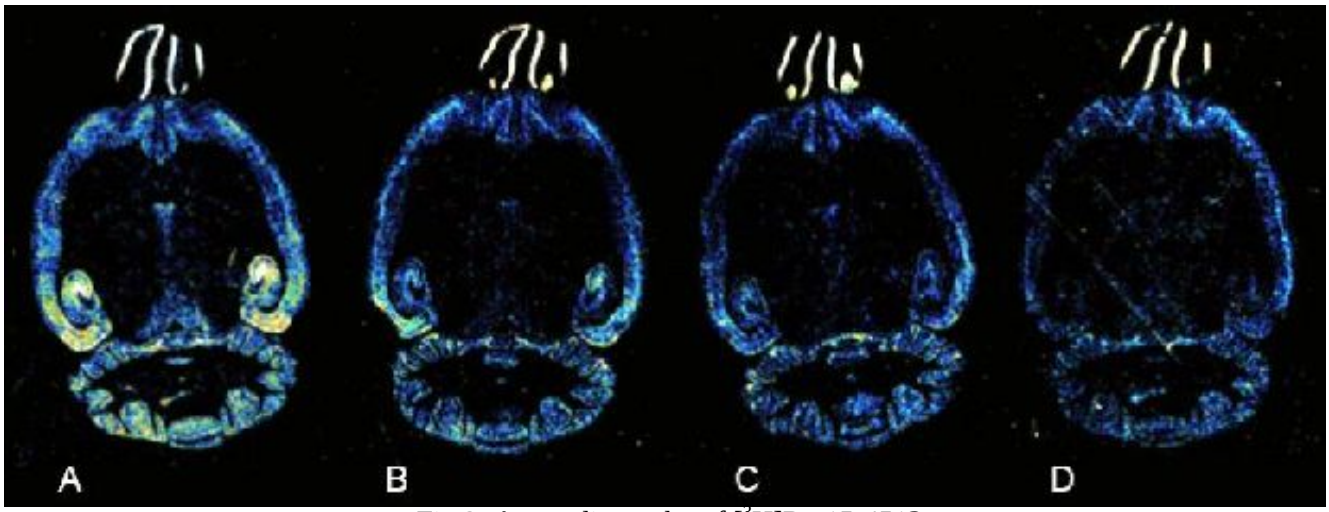

Fig.2: Autoradiography of [^{3}H]Ro 15-4513
A: total binding of radioligand, B: 20 nM TC12, C: 200 nM TC12, D: 2000 nM TC12