# Positive Allosteric Modulators as PET Imaging Ligans for mGluR4

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5

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Parkinson's disease & PD-related disorders

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metabotropic glutamate receptor 4, positive allosteric modulator, Positron-Emission Tomography, Fluorine, GRM5 gene

**Research Abstract**
ABSTRACT: Half a million Americans suffer from Parkinson's disease (PD) and the incurring health cost is $6 billion in a year. There are several other neurological disorders with extremely

high cost for treatment, but in this context the focus is on the disorders, which have strong connection to glutamate neurotransmission. Presynaptic location of mGlu4 makes them important contributors for glutamate neurotransmission since glutamate as well as dopamine is released from the presynaptic site of the neuron and activation of mGlu4 can inhibit the release of neurotransmitters such as glutamate and GABA and thus balance neurotransmission through direct and indirect pathways in PD. Several recent publications propose especially mGlu4 as therapeutic target for different neurological diseases including PD. We have extensively investigated positive allosteric modulators (PAMs) as PET imaging ligands for mGlu4. We investigated also biological activity of the developed compounds using pharmacological MRI approaches. These studies opened a new way to characterize compounds and explore their usability for therapeutic purposes. We have synthetized 32 different compounds based on two different chemo-types of the mGlu4 PAMs. Six of these compounds have been characterized with in vivo studies as PET imaging ligands for mGlu4. The main limitation in our developed ligands has been fast washout and metabolism, even though binding affinities have been decent. We also developed specific cell lines to express mGlu4 and the cell studies have been fundamental in ligand characterization to determine the structure-affinity relationship (SAR) of our experimental PAMs and determine co-operative relationship between endogenous glutamate binding to orthosteric binding sites and affinity of allosteric modulators. These approaches are radically different from classical approach in which orthosteric ligands compete with endogenous ligands at the same binding site. Based on the pioneering work and worldwide interest we are looking for to develop especially fluorine-18 labeled positive allosteric imaging ligands for mGlu4 allowing medical applications and distribution of the ligands. Precisely, in Aim 1 we are proposing to synthesize two F-18 labeled lead compounds from the N-phenylpicolinamide- and thiazolopyrazole-based mGlu4 PAMs to study their imaging efficacy, Bmax, selectivity, brain penetration, pharmacokinetics, metabolic stability and other properties. In Aim 2 we will synthesize new series of eight fluorine-containing N-phenylpicolinamide derivatives and twelve fluorine- containing thiazolopyrazole derivatives for SAR analyses. This effort will be supported by computational chemistry. Two best compounds will be selected for the development as PET imaging ligands for mGlu4. In Aim 3 we will conduct in vivo characterization of these ligands using mGlu4 knockout mice, rat and primate models with an ultimate goal to validate the best compound for human studies and obtain IND approval.

**Lay Summary**
Narrative Parkinson's disease is a devastating neurodegenerative disorder and there is not yet cure for it although there are several theories of its pathology including modulation of dopamine and glutamate neurotransmission. In preclinical investigation mGlu4 positive allosteric modulators (PAMs) have demonstrated anti-parkinsonian effects making them a new therapeutic approach for PD and the first clinical trial of using mGlu4 PAM based drug is in process. In this application we propose to develop mGlu4 PET imaging ligand for diagnostic purposes to support drug development and medical applications.

**Further information available at:**

**Types:**
Investments > €500k

**Member States:**
United States of America

**Diseases:**

Parkinson's disease & PD-related disorders

**Years:**
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