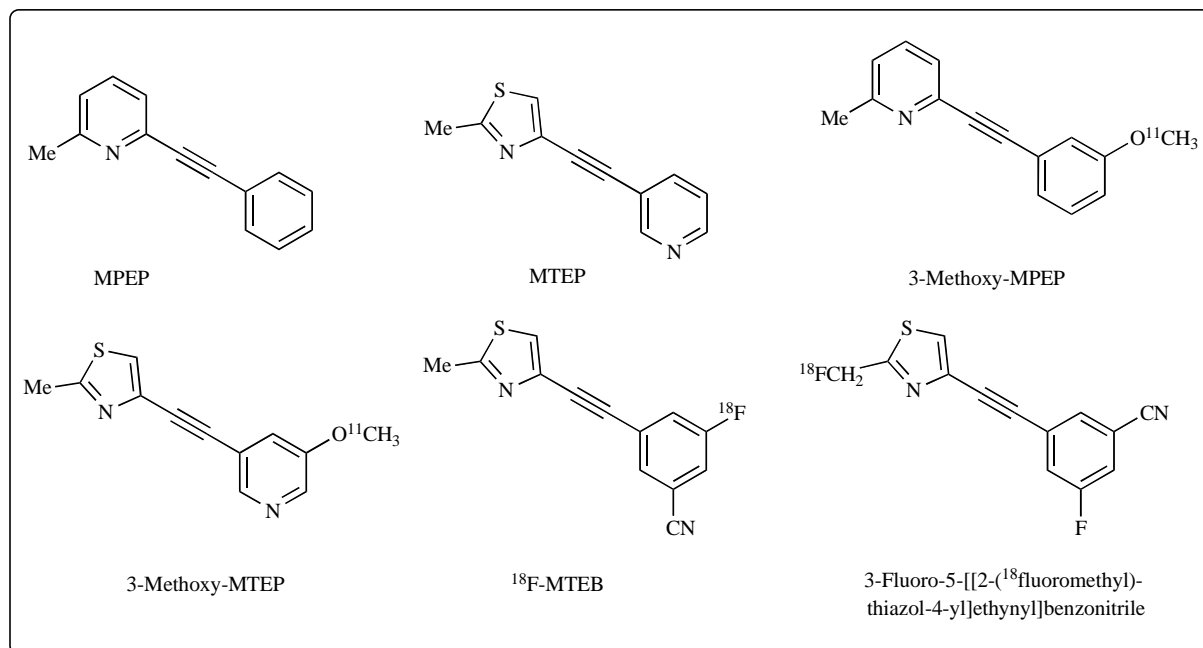


## Molecule of the Month

**A new high affinity PET tracer for the metabotropic glutamate receptor subtype 5 (mGluR5).** Positron emission tomography (PET) plays a critical role in the development of potential therapeutics for CNS disorders by measuring receptor occupancy of potential drug candidates in the brain [1]. *In vivo* receptor occupancy can help answer many questions in the drug discovery process such as elucidating whether potential drugs reach their molecular targets, establishing the relationship between therapeutic dose and receptor occupancy, finding the correlation between receptor occupancy and plasma drug levels, and measuring the duration of time a drug remains at its target [1]. Moreover, PET tracers serve as invaluable biomarkers during the clinical development of novel CNS agents [1]. A PET scan utilizes a tracer injected into living subjects and contains a short-lived radioisotope, which emits a positron as it decays. The positrons collide with electrons resulting in

colleagues at the Molecular Imaging Branch of the NIH recently reported a new high affinity radioligand for mGluR5 [3].

Initial PET tracers for mGluR5 were derivatives of the antagonists MPEP and MTEP but were not effective. Adding a radiolabel to these compounds while maintaining high affinity and selectivity was difficult because of their small size and the presence of few functional groups. 3-Methoxy-MPEP [17,18] and 3-methoxy-MTEP [19,20] were more attractive tracers because they demonstrated rapid uptake into the brain, but these compounds showed little retention by the receptor and employed short-lived  $^{11}\text{C}$ . The compound  $^{18}\text{F}$ -MTEB described by Hamill and colleagues from Merck produced the first successful PET imaging of mGluR5 in rhesus monkeys [21]. This compound was highly selective and bound with high affinity ( $\text{IC}_{50} = 80 \text{ pM}$ ) to the receptor [21]. However, the synthesis of this tracer in the cyclotron



high-energy radiation that escapes the body of the subject and is measured by detectors in the PET scanner [2]. The imaging radionuclides commonly employed include  $^{11}\text{C}$  (carbon-11,  $t_{1/2} = 20.4 \text{ min.}$ ),  $^{18}\text{F}$  (fluorine-18,  $t_{1/2} = 109.7 \text{ min.}$ ) and  $^{123}\text{I}$  (iodine-123,  $t_{1/2} = 13.13 \text{ h}$ ) [3].

Metabotropic glutamate receptors (mGluRs) are class C GPCRs that regulate synaptic transmission and neuron excitability [4,5]. The mGluR5 subtype is coupled to phosphoinositide hydrolysis and causes an increase in intracellular  $\text{Ca}^{2+}$  [4,5]. This receptor is distributed throughout the brain [6] and its regulation, through either agonism, positive allosteric modulation or antagonism, has been demonstrated to offer a therapeutic benefit for a number of disorders of the central nervous system (CNS) including Parkinson's disease, pain, anxiety, depression, addiction, schizophrenia and fragile X syndrome [7-16]. In order to advance mGluR5-derived therapeutics into clinical development, a PET tracer suitable for clinical use in humans is needed. Siméon and

colleagues at the Molecular Imaging Branch of the NIH recently reported a new high affinity radioligand for mGluR5 [3]. Initial PET tracers for mGluR5 were derivatives of the antagonists MPEP and MTEP but were not effective. Adding a radiolabel to these compounds while maintaining high affinity and selectivity was difficult because of their small size and the presence of few functional groups. 3-Methoxy-MPEP [17,18] and 3-methoxy-MTEP [19,20] were more attractive tracers because they demonstrated rapid uptake into the brain, but these compounds showed little retention by the receptor and employed short-lived  $^{11}\text{C}$ . The compound  $^{18}\text{F}$ -MTEB described by Hamill and colleagues from Merck produced the first successful PET imaging of mGluR5 in rhesus monkeys [21]. This compound was highly selective and bound with high affinity ( $\text{IC}_{50} = 80 \text{ pM}$ ) to the receptor [21]. However, the synthesis of this tracer in the cyclotron

gave low yields (2-5%), which limited its potential utility as a ligand for clinical trials in humans [21]. Recently 3-fluoro-5-[[2-( $^{18}\text{F}$ -fluoromethyl)thiazol-4-yl]ethynyl]benzonitrile was developed by Siméon and colleagues. This compound shows high affinity ( $\text{IC}_{50} = 36 \text{ pM}$ ) and potency in a PI hydrolysis assay ( $\text{IC}_{50} = 0.71 \text{ pM}$ ) for mGluR5 [3]. It is also metabolically stable and demonstrates a high uptake in mGluR receptor rich regions of the rat and rhesus brain [3]. The major advantage of the Siméon tracer over F-MTEB is its high radiochemical yield (87%) [3]. Also, the location of  $^{18}\text{F}$  on the methyl group at the 2-position of the thiazole ring allows for ease of radiosynthesis and the preparation of analogs [3]. In summary, 3-fluoro-5-[[2-( $^{18}\text{F}$ -fluoromethyl)thiazol-4-yl]ethynyl]benzonitrile is a PET tracer that may be suitable for use in humans and could play a pivotal role in the discovery and clinical evaluation of drugs that modulate mGluR5.

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