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Imaging of Metabotropic Glutamate Receptors (mGluRs)

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1. Introduction

The ubiquitous amino acid L-glutamate is thought to act as a neurotransmitter at the majority of synapses in the brain. It mediates the major excitatory pathways in the brain, and is referred to as an excitatory amino acid (EAA). The EAA plays a role in a variety of physiological processes, such as long-term potentiation (learning and memory), the development of synaptic plasticity, motor control, respiration, cardiovascular regulation, emotional states and sensory perception (Bliss & Collingridge, 1993).

The excessive or inappropriate stimulation of EAA receptors leads to neural cell damage or loss by a mechanism known as excitotoxicity (Lucas & Newhouse, 1957; Oney, 1978). EAA receptors are classified in two general types (Kornhuber & Weller, 1997). Receptors that are directly coupled to the opening of cation channels in the cell membranes of the neuron are termed 'ionotropic', which include NMDA, AMPA, and kainate receptors. The second type of receptors are the G-protein or second messenger-linked 'metabotropic' EAA receptors. This second type is coupled to multiple second messenger systems that lead to enhanced phosphoinositide hydrolysis, activation of phospholipase D, increase or decrease in cAMP formation, and changes in ion channel function (Kozikowski et al., 1998).

Metabotropic glutamate receptors belong to Class C of a superfamily of G-protein coupled receptors (GPCRs). Class C GPCRs possess a large extracellular domain that is responsible for endogenous ligand recognition (Pin et al., 2003), in addition to the seven strand transmembrane domain, which is characteristic of all GPCRs. The mGluRs possess a large bi-lobed extracellular N-terminus of ~560 amino acids which has been shown by mutagenesis studies to confer glutamate binding, agonist activation of the receptor, and subtype specificity for group selective agonists (Schoepp et al., 1999).

Since mGluRs have neuromodulatory role in the control of both glutamatergic and GABAergic neurotransmission, there has been much interest to develop novel mGluR ligands for therapeutic purposes of a variety of neurological and psychiatric conditions. The mGluRs have been proposed to be involved in physiological and pathophysiological processes of a number of CNS disorders, including anxiety, pain, depression, neurodegenerative disorders, schizophrenia, epilepsy, and drug abuse. In order to

characterize the role of mGluRs in different physiological processes there is a need to identify novel compounds, which are highly potent and specific for an mGluR group or a subtype. Such compounds are needed to further investigate mGluR function, and as potential therapeutic agents for a variety of neurological diseases, which are associated with the abnormal activation of mGluRs. A large amount of pharmacological agents acting at metabotropic glutamate receptors have been described in the literature (Guitart & Khurdayan, 2005; Kew, 2004; Layton, 2005; Marino et al., 2005; Rudd & McCauley, 2005; Schoepp et al., 1999; Slassi et al., 2005; Williams & Lindsley, 2005; Yang, 2005). According to the mode of binding, these mGluR pharmacological agents can be classified into competitive and non-competitive agents. Based on the mode of action, they can be classified into agonists, antagonists, and positive/negative/neutral modulators (Layton, 2005). Competitive agonists and antagonists bind to the same orthosteric binding site as endogenous glutamate (Niswender et al., 2005; Ritzen et al., 2005; Rudd & McCauley, 2005), which is a cleft between the two lobes in the extracellular N-terminus. Their binding ability depends on how much they can stabilize the closed conformation (Kew, 2004). These ligands received earliest research interest and have been well developed (Schoepp et al., 1999). They are all glutamate analogs or substituted glycines, which imply that they have poor selectivity within their group. In addition, competitive agonists and antagonists have structural carboxyl and amino groups, which make them too polar to penetrate the blood brain barrier (BBB) (Kew, 2004).

Starting from 1996 (Annoura et al., 1996), a number of different types of non-competitive negative, positive and neutral allosteric modulators have been developed as mGluR ligands (Niswender et al., 2005; Ritzen et al., 2005). These ligands modulate mGlu receptor activity by binding to allosteric binding sites that are located in the seven strand transmembrane domain. The allosteric binding sites are structurally distinct from the classical agonist orthosteric binding site (Williams & Lindsley, 2005). Positive and negative modulators thus offer a potential for improved selectivity for individual mGluR family members compared to competitive agonists and antagonists at the glutamate site (Kew, 2004). Positive allosteric modulators (PAM)s have little or no effect on the receptor but can significantly enhance the effect of endogenous ligand. Correspondingly negative allosteric modulators inhibit the activity of orthosteric agonists in a noncompetitive manner. These ligands are structurally diverse and not amino acid derivatives. They are lipophilic and have much better CNS penetrating ability. Thus, positive and negative modulators with high subtype selectivity, and appropriate lipophilicity are good candidates for mGluR radiotracer development. There will be no competitive binding of this kind of tracers with endogenous glutamate, which might otherwise decrease the availability *in vivo*, and thus decrease the sensitivity of potential ligands.

During the last fifteen years the subtype selective modulators have been identified for mGluR1, mGluR2, mGluR3, mGluR4, mGluR5, mGluR7 and mGluR8. Based on these modulators, several positron emission tomography radiotracers have been developed for *in vivo* imaging of specific mGluRs. Presently, three mGluR ligands have been used for human studies. They have been developed as negative allosteric modulators for mGluR5. In this review we intend to summarize the radiotracers which have characteristics to be developed as tracers for *in vivo* PET imaging to investigate modulation of mGluRs in normal and pathological conditions. Emphasis will also be given to the highly potent and subtype selective allosteric modulators which are candidates for radiolabeling with ^{18}F or ^{11}C.

2. Metabotropic glutamate receptors and their physiological function

Recent molecular cloning studies have revealed the existence of eight different subtypes of mGluRs. The mGluR subtypes can be divided into three different groups according to their sequence similarities, signal transduction mechanism, and pharmacological profiles to agonists (Pin & Duvoisin, 1995). The first group comprising mGluR1 and mGluR5 is coupled to stimulating of phosphoinositide hydrolysis/Ca2+ signal transduction (Schoepp et al., 1994). The second group, consisting of mGluR2 and mGluR3, is negatively coupled through adenylate cyclase to cAMP formation (Tanabe et al., 1997). The third group, containing mGluR4, mGluR6, mGluR7 and mGluR8, is also negatively linked to adenylate cyclase activity but shows a different agonist preference (Conn & Pin, 1997; Tanabe et al., 1997).

The neuroanatomical localization of Group I and Group II mGluRs in the rodent brain, as assessed by immunohistochemical or *in situ* hybridization techniques, has revealed overlapping, yet distinct patterns of expression of these receptors. In order to better characterize the roles of mGluRs in physiological processes, there is a need to identify novel compounds that are highly potent and specific for an mGluR group or a subtype. Such compounds are needed as pharmacological tools for further investigation of mGluR function, and as potential therapeutic agents for the treatment of diseases or conditions including epilepsy, cerebral ischemia, pain, spinal cord injury, 'neurotoxicity' and chronic neurodegenerative diseases (e.g. Parkinson's and Huntington's disease), which are associated with abnormal activation of mGluRs (Aguirre et al., 2001; Blakely, 2001; Calabresi et al., 1999; Keyvani et al., 2001; Marino et al., 2001; O'Neill, 2001; Popoli et al., 2001; Rao et al., 2000; Rouse et al., 2000).

It is known that glutamate can act as a neurotoxin when energy supplies are compromised. This has stimulated a hypothesis that injury to neurons in some neurological conditions may be caused, partly, by over stimulation of glutamate receptors and/or glutamate transporters. These neurological conditions may be acute insult like stroke or chronic neurodegenerative states like Parkinson's or Huntington's disease or dementia. To better explore the roles of mGluRs in physiological and pathological processes, there is a need to learn more about functional behavior of these receptors *in vivo*.

3. PET radiotracer development

Positron emission tomography (PET) has become an important clinical diagnostic and research modality, and also a valuable technology in drug discovery and development (Cai et al., 2008). PET tracers have been used for the imaging and quantification of biochemical processes. PET tracers play a critical role for assessing *in vivo* distribution of specific receptors in normal and disease conditions to understand underlying mechanisms of physiology and pathology. Moreover, PET tracers serve as invaluable biomarkers during the clinical development of potential therapeutic mGluR modulators, in which the receptor occupancy of potential drug candidates in the brain is measured (Passchier et al., 2002; Sharma & Lindsley, 2007). *In vivo* receptor occupancy can help to answer many vital questions in the drug discovery and development process such as whether potential drugs reach their molecular targets, the relationship between therapeutic dose and receptor occupancy, the correlation between receptor occupancy and plasma drug levels, and the duration of time a drug remains at its target (Passchier et al., 2002). In PET imaging a small amount of tracer is injected into a living object. The tracer is labeled with a short-lived

radioisotope, which emits positrons as it decays. The positrons collide with electrons resulting in high-energy photons that escape from the object and are detected by the PET scanner. Carbon-11 ($t_{1/2}$ = 20.4 min) and fluorine-18 ($t_{1/2}$ = 109.7 min) are the most commonly used radionuclides in PET imaging (Miller et al., 2008). The characteristics of successful PET tracers include high affinity, high selectivity over other mGluR subtypes as well as other receptors, suitable pharmacological properties including lipophilicity, metabolic stability, no radiolabeled metabolites that can penetrate into the brain, and the chemical structure of the precursor to allow fast labeling.

3.1 Allosteric modulators and radiotracers for Group I mGluRs

The group I receptors mGluR1 and mGluR5 exhibit different patterns of expression in the CNS. The distribution of mGluR1 is found throughout the human brain with high levels in the olfactory bulb, thalamus, hippocampus, lateral septum, superior colliculus and cerebellum (Olive, 2009). Inhibition of mGluR1 has been suggested as potential treatment for various psychiatric disorders including schizophrenia, anxiety, and neuropathic pain.

The mGluR5 is usually found in postsynaptic neurons with moderate to high density in the frontal cortex, caudate, putamen, nucleus accumbens, olfactory tubercle, and hippocampus, whereas in contrast to expression patterns of mGluR1, the density in the cerebellum is low (Olive, 2009). Dysfunction of mGluR5 is implicated in a variety of diseases in the CNS, including anxiety, depression, schizophrenia, Parkinson's disease, and drug addiction or withdrawal.

3.1.1 Allosteric modulators and radiotracers for mGluR1

A variety of mGluR1 modulators have been reported in the literature. Competitive mGluR1 agonists and antagonists historically have been amino acid derivatives, which display poor potency, lack of selectivity and unsatisfactory BBB penetration (Layton, 2005). Although a number of selective competitive mGluR1 ligands appear in literature, they are not good candidates for potential PET tracers. None of the existing orthosteric ligands has a binding affinity (or potency) of $IC_{50}/K_i/K_d$ less than 20 nM with an acceptable selectivity over other members in the same group. There is a consensus that identification of highly potent and subtype selective competitive mGluR ligands has been difficult due to a high degree of sequence similarity at the orthosteric binding site to which the endogenous agonist binds (Layton, 2005; Williams & Lindsley, 2005). Alternatively, several structural types of mGluR1 allosteric modulators have been reported in literature, including negative and positive allosteric modulators which show high binding affinity, high selectivity and good lipophilicity (Layton, 2005).

CPCCOEt (**1**) was the first reported mGluR1 negative allosteric modulator (Fig.1). Before 2008, only compound **4** (3,5-dimethyl PPP) (Micheli et al., 2003b) and a quinoline derivative **5** (JNJ16259685) (Lavreysen et al., 2004b; Mabire et al., 2005) had reported binding affinity (or potency) less than 20 nM (Table 1). 2,4-Dicarboxy-pyrrole ester **4** (3,5-dimethyl PPP), as a racemic mixture, is a highly potent and subtype-selective noncompetitive antagonist of mGluR1, having IC_{50} of 16 nM at rat mGluR1 and > 1000-fold selectivity over mGluR 2, 4, and 5 (Micheli et al., 2003b). Pharmacological studies of its two enantiomers showed that the S-enantiomer had the same activity as the racemic mixture, while the R-enantiomer was less potent (40 nM). Although compound **4** had a poor stability to rat plasma esterase ($t_{1/2}$=12 min versus 2.8 h in mice), a good CNS accumulation was observed 5 min after intravenous administration with a brain/plasma ratio of 20 (Micheli et al., 2003b). Compound **5** (JNJ-

16259685) demonstrated high specificity over other mGlu receptor subtypes and a fast brain penetration with high receptor occupancy after subcutaneous administration (Lavreysen et al., 2004b). In addition to **5**, a series of quinoline derivatives have been synthesized. The *in vitro* pharmacological data showed that they are highly potent noncompetitive mGluR1 antagonists (Mabire et al., 2005) with high binding affinity. However, the quinoline derivatives have issues of poor aqueous solubility and poor stability to human liver microsomes (Layton, 2005; Mabire et al., 2005).

Since 2008, many new compounds (Fig. 1 and Table 1) have been reported having binding affinity (or potency) less than 20 nM and high selectivity over other mGluRs. These compounds are diverse heterocyclic compounds including mono-, di- and tri-cyclic structures. Some of these compounds or their derivatives are amenable to radiolabeling with fluorine-18 or carbon-11. For example, a series of potent 2-fluoro-3-pyridyl-triazol derivatives such as FTIDC (**10**) and FPTQ (**11**) have been developed.. These derivatives are relatively easy to label with fluorine-18 at 2-pyridine position. Other compounds such as **12** are amenable to radiolabeling with carbon-11.

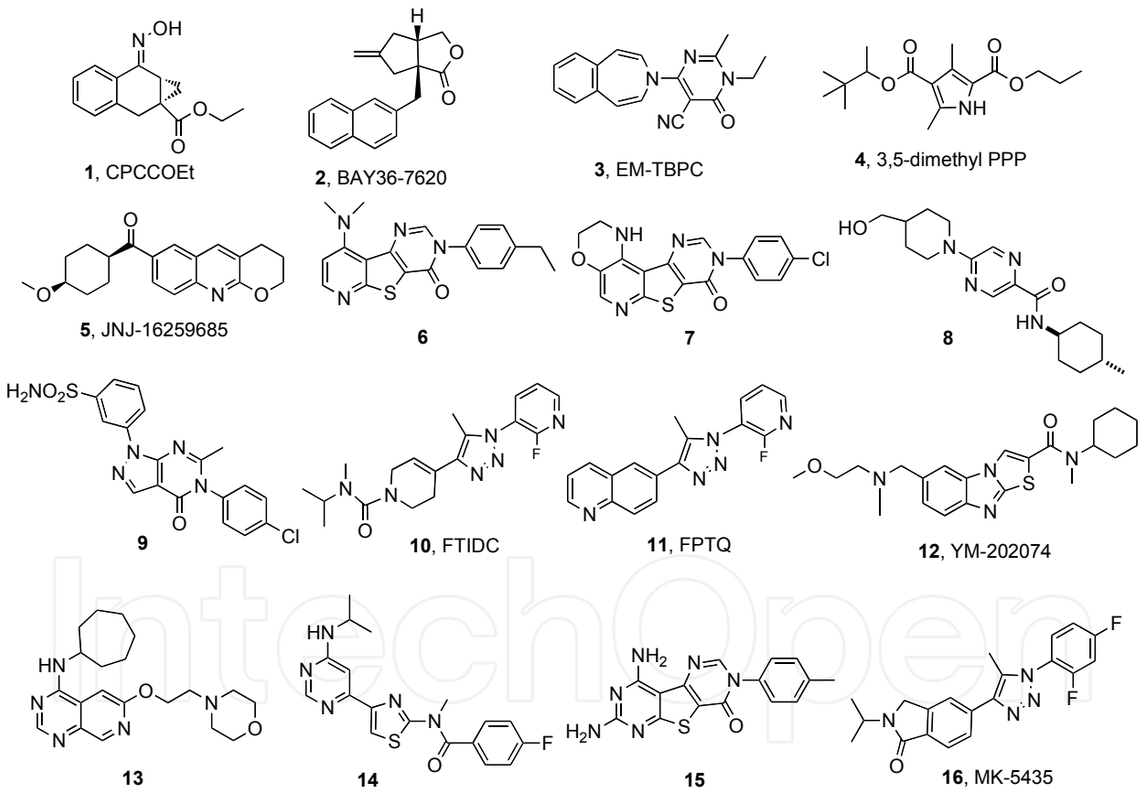

Fig. 1. Chemical structures of mGluR1 negative modulators.

MGluR1 expression is localized throughout the nervous system (Layton, 2005; Spooren et al., 2003). The distribution of mGluR1 in the peripheral nervous system (Bhave et al., 2001; Lesage, 2004; Skerry & Genever, 2001) and in the CNS has been studied using various methods including radioligand autoradiography and immunohistochemical techniques (Lavreysen et al., 2003; Lavreysen et al., 2004a; Shigemoto & Mizuno., 2000; Simonyi et al., 2005). MGlu1 receptors have been observed in the cerebellum, thalamus, hippocampus and

Compound	Rat mGluR1 IC_{50} (nM)	Human mGluR1 IC_{50} (nM)	Selectivity	*In vivo* properties	References
1 (CPCCOEt)		1500-6500	>15 over mGluR2, 4, 5, 7, 8		(Litschig et al., 1999; Ott et al., 2000)
2 (Bay36-7620)	160		>100 over mGluR 2, 3, 4, 5, 7, 8	30% receptor occupancy in cerebellum and thalamus (s.i.)	(Carroll et al., 2001)
3 (EM-TBPC)	130		No binding for rat mGluR5		(Malherbe et al., 2003)
4 (3,5-dimethyl PPP)	16		>1000 over mGluR2, 4, 5	Good CNS exposure with brain/plasma ratio of 20	(Micheli et al., 2003a; Micheli et al., 2003b)
5 (JNJ-16259685)	3	0.55	>400 over rat mGluR5; >20,000 over human mGluR5	Fast brain penetration and high receptor occupancy (s.i.)	(Lavreysen et al., 2004b; Mabire et al., 2005)
6	K_i=5	3	IC_{50}=442 nM for human mGluR5; K_i=194 nM for rat mGluR5	Demonstrated efficacy in various *in vivo* animal models	(Zheng et al., 2005)
7	K_i=0.4	2.9	>1,000 nM for human mGluR5	Demonstrated activity in the rat spinal nerve ligation neuropathic pain model (SNL model) with ED_{50} of 5.1 mg/kg.	(Wu et al., 2007)
8	K_i=9			LogD=3.3; human liver microsomal metabolic stability: Cl_{int}<7 µl/min/mg	(Owen et al., 2007)
9		127	>100,000 nM for human mGluR5	Solubility: 42 µM; microsomal clearance: <2.5 L/h/kg; quantitative bioavailability	(Wang et al., 2007b)

Compound	Rat mGluR1 IC_{50} (nM)	Human mGluR1 IC_{50} (nM)	Selectivity	*In vivo* properties	References
10 (FTIDC)	5.8	5.8	6200 nM for human mGluR5; >1720 over mGluR2, 4, 6, 7, 8	LogD=2.1; demonstrated efficacy in (S)-3,5-DHPG-induced face-washing behavior in mice	(Suzuki et al., 2009; Suzuki et al., 2007a)
11 (FPTQ)	14	3.6			(Suzuki et al., 2009)
12 (YM-202074)	8.6 K_i=4.8		>1000 for rat mGluR2, 3, 4, 6, 7; >100 for rat mGluR5;	Showed efficacy for neuroprotection in rats suffering from transient focal cerebral ischemia;	(Kohara et al., 2008)
13	K_i=6			CSF:C_u=0.5; HLM: Cl_{int}=24 µl/min/mg	(Mantell et al., 2009)
14		5.1	7000 nM for human mGluR5; >10,000 nM for human mGluR2, 8	Mouse brain/plasma concn 0.17 nmol/g/0.19 µM; Rat F: 53%, $T_{1/2}$: 2.3 h, CLp: 28 mL/min/kg; Rat PPI disruption model MED 1.0 mg/kg, PO; Mouse hyperlocomotion model MED 0.3 mg/kg, PO	(Satoh et al., 2009)
15	K_i=9.3	2.1	>3000 nM for human mGluR5	Rat PK, (10 mg/kg), AUC (ng h/mL): 965; Brain concn @ 6 h (ng/g): 100; Brain/plasma: 0.9	(Sasikumar et al., 2010)
16 (MK-5435)		4.3	1500 nM for human mGluR5		(Hostetler et al., 2011)

Table 1. *In vitro* and *in vivo* pharmacological profiles for mGluR1 negative allosteric modulators.

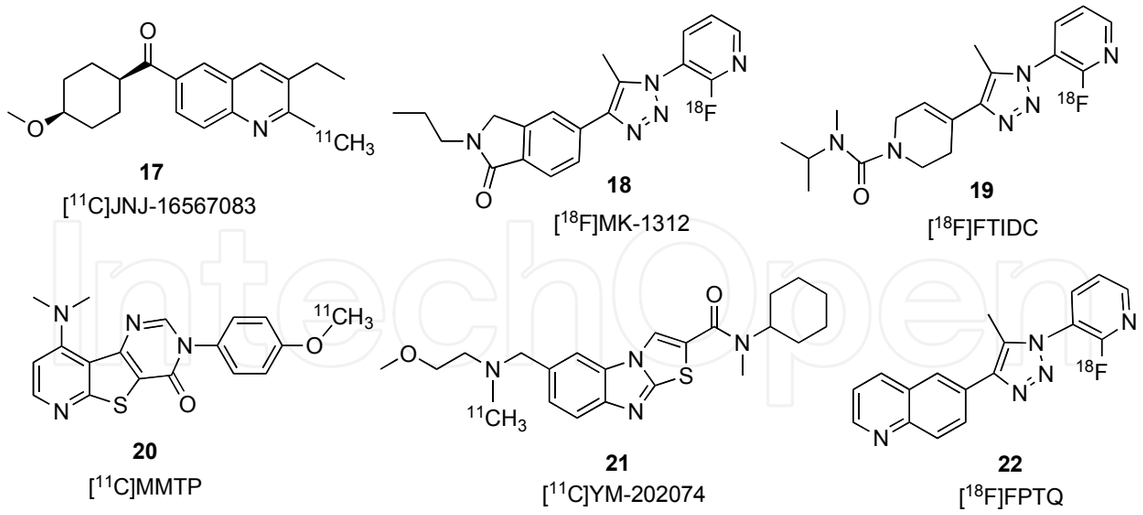

Fig. 2. PET ligands for mGluR1

spinal cord (Karakossian & Otis, 2004; Lavreysen et al., 2003; Shigemoto & Mizuno, 2000; Spooren et al., 2003). Tritium-labeled highly potent and subtype-selective radioligands were used earlier in mapping mGluR1 *ex vivo* (Yang, 2005). Presently, demands on PET radioligands are increasing due to the advantage of *in vivo* noninvasive imaging techniques to investigate pathophysiological processes.

In 2002, a carbon-11 labeled CPCCO-Me analog was described in the literature (Yu & Brownell, 2002), but no animal studies were conducted. In the series of quinoline derivatives (represented by **5**), several compounds are amenable to radiolabeling with either fluorine-18 or carbon-11. Carbon-11 labeling would not be preferred in the methyl ether positions, in spite of methyl ether position is very popular in ^{11}C-methylation, since O-demethylation of the methoxy groups on the quinoline moiety and the cyclohexyl ring are the major metabolic pathways (Mabire et al., 2005). Therefore, practical methods must be developed to label the methyl groups elsewhere in the molecule. Accordingly, Huang et al. successfully labeled a quinoline derivative, providing the first PET tracer, [^{11}C]JNJ-16567083, suitable for *in vivo* imaging of mGluR1 (Huang et al., 2005). [^{11}C]JNJ-16567083 (**17**) is an analog of JNJ-16567083 (**5**). *In vitro* binding experiments showed that JNJ16567083 (cold compound) possesses high affinity for rat mGluR1 (K_i = 0.87 nM) and low affinity for mGluR5 (K_i = 2366 nM). *Ex vivo* biodistribution studies in rats showed that [^{11}C]JNJ-16567083 has high brain uptake and its binding in brain is specific to mGluR1. MicroPET imaging experiments in rats indicated that radioactivity entered the brain rapidly and was localized over time in brain regions with high densities of mGluR1, such as the cerebellum and striatum. Activity in cerebellum peaked at ~10 min after intravenous injection. Radioactivity uptake was highest in the cerebellum, followed by striatum and hippocampus. However, evaluation of this PET tracer in higher species has not been reported.

Yanamoto et al. have labeled an mGluR1 antagonist YM-202074 (**12**, K_i = 4.8 nM) with ^{11}C and evaluated its potential as a PET ligand for mGluR1 (Yanamoto et al., 2010). *In vitro* autoradiographic study demonstrated that [^{11}C]YM-202074 (**21**, Fig.2) had high specific binding with mGluR1 in the rat cerebellum and its regional distribution was consistent with the distribution pattern of mGluR1 in the brain. However, the total accumulation of

[^{11}C]YM-202074 in the brain was very low including lipophilic radiometabolites hampering its usefulness for *in vivo* imaging.

Prahakaran et al. have reported the synthesis for *in vitro* and *in vivo* evaluation of [^{11}C]MMTP (**20**) as a potential PET ligand for mGluR1 (Prabhakaran et al., 2010). Synthesis of the corresponding desmethyl precursor was achieved by demethylation of the methoxyphenyl compound MMTP in 90% yield. Methylation using [^{11}C]MeOTf in presence of NaOH afforded [^{11}C]MMTP in 30% yield (EOS) with >99% chemical and radiochemical purities and with a specific activity of 3–5 Ci/μmol (n = 6). The total synthesis time was 30 min from EOB. *In vitro* autoradiography using phosphor imaging demonstrated that the radiotracer bound selectively mGlu1 receptors in slide-mounted sections of postmortem human brain containing cerebellum, hippocampus, prefrontal cortex and striatum. PET studies in anesthetized baboon showed that [^{11}C]MMTP penetrates the BBB and accumulates in cerebellum, a region of high expression of mGluR1.

Recently, a ^{18}F-labeled triazole analog [^{18}F]FTIDC (**19**, Ki = 3.9 nM) (Ohgami et al., 2009) was presented for imaging of mGluR1 showing high uptake in the rat brain. In addition, Fujinaga et al. have labeled a triazole analog, FPTQ (**11**, IC_{50} = 3.6 nM and 1.4 nM for human and mouse mGluR1, respectively) (Fujinaga et al., 2011). [^{18}F]FPTQ (**22**) was synthesized by [^{18}F]fluorination of the corresponding 2-bromo-3-pyridyl precursor with potassium [^{18}F]fluoride. At the end of synthesis, 35-50 mCi (n = 8) of [^{18}F]FPTQ was obtained with >98% radiochemical purity and 3.2-6.4 Ci/μmol specific activity using 89-108 mCi of [^{18}F]fluoride. *In vitro* autoradiography showed that [^{18}F]FPTQ had high specific binding with mGluR1 in the rat brain. Biodistribution study using a dissection method and small-animal PET showed that [^{18}F]FPTQ had high uptake in the rat brain. The uptake of radioactivity in the cerebellum was reduced by unlabeled FPTQ and mGluR1-selective ligand JNJ-16259685 (Fujinaga et al., 2011), indicating that [^{18}F]FPTQ had *in vivo* specific binding to mGluR1. However, because of a low amount of radiolabeled metabolite present in the brain, this compound may have limiting use for *in vivo* imaging of mGluR1 by PET.

Hostetler et al. have reported a PET radioligand, [^{18}F]MK-1312 (**18**), which was radiolabeled with fluorine-18 via nucleophilic displacement of the corresponding 2-chloropyridine precursor with [^{18}F]potassium fluoride (Hostetler et al., 2011). [^{18}F]MK-1312 was synthesized (n = 25) in good yield (46 ± 15%) with >98% radiochemical purity and high specific activity (2.5 ± 1.4 Ci/μmol). *In vitro* autoradiographic studies with [^{18}F]MK-1312 in rhesus monkey and human brain tissue slices revealed an uptake distribution consistent with the known distribution of mGluR1, with the highest uptake in the cerebellum, moderate uptake in the hippocampus, thalamus, and cortical regions, and the lowest uptake in the caudate and putamen. *In vitro* saturation binding studies in rhesus monkey and human cerebellum homogenates confirmed that [^{18}F]MK-1312 binds to a single binding site with a Bmax/Kd ratio of 132 and 98, respectively. PET studies in rhesus monkey with [^{18}F]MK-1312 showed high brain uptake and a regional distribution consistent with *in vitro* autoradiography results. Blockade of [^{18}F]MK-1312 uptake with mGluR1 allosteric antagonist MK-5435 dose-dependently reduced tracer uptake in all regions of gray matter. These results show that [^{18}F]MK-1312 is a promising PET tracer for clinical studies to determine mGluR1 occupancy of MK-5435.

In summary, several PET radioligands have been developed using highly potent and subtype-selective mGluR1 negative allosteric modulators. Although they showed efficacy in studying the distribution of mGluR1, some compounds may have limited applications

because of low brain uptake and/or brain penetrating radiometabolites. [^{18}F]MK-1312 is the most advanced mGluR1 PET tracer, which has demonstrated efficacy in rhesus monkey.
Although all the published mGluR1 PET tracers are radiolabeled mGluR1 negative allosteric modulators, mGluR1 positive allosteric modulators can also be used for developing mGluR1 PET tracers. Several papers have been published about the functional differences between antagonist and agonist tracers in imaging G-protein coupled receptors, including dopamines D2 receptor (Hwang et al., 2004; Wilson et al., 2005), serotonin receptors (Kumar et al., 2006; Prabhakaran et al., 2006) and mGlu receptors. GPCRs have been postulated to exist in interconvertible high-affinity and low-affinity states. The high-affinity sites are G-protein coupled, whereas the low-affinity sites are those uncoupled with G-protein. Antagonist radiotracers bind with equal affinity to both the high- and low-affinity forms of the receptor, and they do not provide information about *in vivo* affinity of the receptor for antagonist. On the contrary, agonist radioligands bind only to high-affinity form of the receptor, thus giving valuable information about *in vivo* affinity of the receptor for agonists in normal and abnormal states. Concerning the binding sites of allosteric modulators in the seven strand transmembrane domain, there is no evidence for difference between negative and positive modulators in terms of their binding to high-affinity or low-affinity states of mGlu receptors (Kew & Kemp, 2005). Fig. 3 illustrates structures of some representative positive allosteric mGluR1 modulators reported (Knoflach et al., 2001; Layton, 2005; Wichmann et al., 2002).

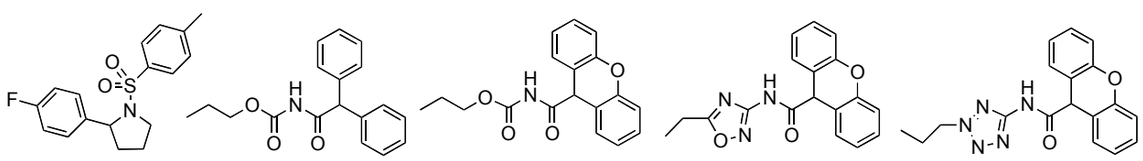

Fig. 3. Chemical structures of mGluR1 positive allosteric modulators.

3.1.2 Allosteric modulators and radiotracers for mGluR5

Since the first selective mGluR5 antagonist was identified in 1999 (Varney et al., 1999), a large number of potent, subtype selective and structurally diverse allosteric modulators have been described. SIB1757 (**28**) and SB1893 (**29**) were discovered through random screening. Subsequent optimization by replacement of the trans-olefinic tether in SIB1893 (**29**) with a C≡C triple bond led to MPEP (**30**), which demonstrated a dramatically improved mGluR5 antagonist activity (Gasparini et al., 1999). Various structure-activity relationship (SAR) studies have been done on MPEP, in which chemical modifications were done to each of the three regions of the lead molecule, identifying a series of highly potent and selective diaryl (heteroaryl) acetylenes as mGluR5 noncompetitive antagonists. By assumption that the (2-methyl-1,3-thiazo-4-yl)ethynyl group is one of the best structural parts to achieve mGluR5 antagonist activity further SAR studies on MTEP (**31**) identified more high-profile ligands containing thiazole moiety as mGluR5 noncompetitive antagonists such as (**33**) (Iso et al., 2006). Many PET tracers have been synthesized by radiolabeling on the derivatives of MPEP and MTEP.
A major concern with acetylenes in potential drugs is the possibility of chemical or metabolic reactivity (Milbank et al., 2007). Terminal acetylenes are well known to be

mechanism-based CYP-inactivators (Testa & Jenner, 1981) and there is an increasing body of information suggesting that internal acetylenes can be activated by CYPs (Fontana et al., 2005; Foroozesh et al., 1997; Shimada et al., 2007) or even undergo uncatalyzed addition of glutathione (Chen et al., 2002; Mutlib et al., 1999). Mutlib et al. reported that incubation of MPEP with triple-labeled glutathione gave compounds with molecular weights and fragmentations consistent with both activated and unactivated addition of GSH to the alkyne (Mutlib et al., 2005). These events are potential sources for hepatic or idiosyncratic toxicity. To avoid a potential metabolic liability, many research groups have designed and synthesized mGluR5 negative allosteric modulators without the acetylene structure. Some structures such as **37** to **48** are given in Fig. 4, which may be useful for development of a new PET tracer.

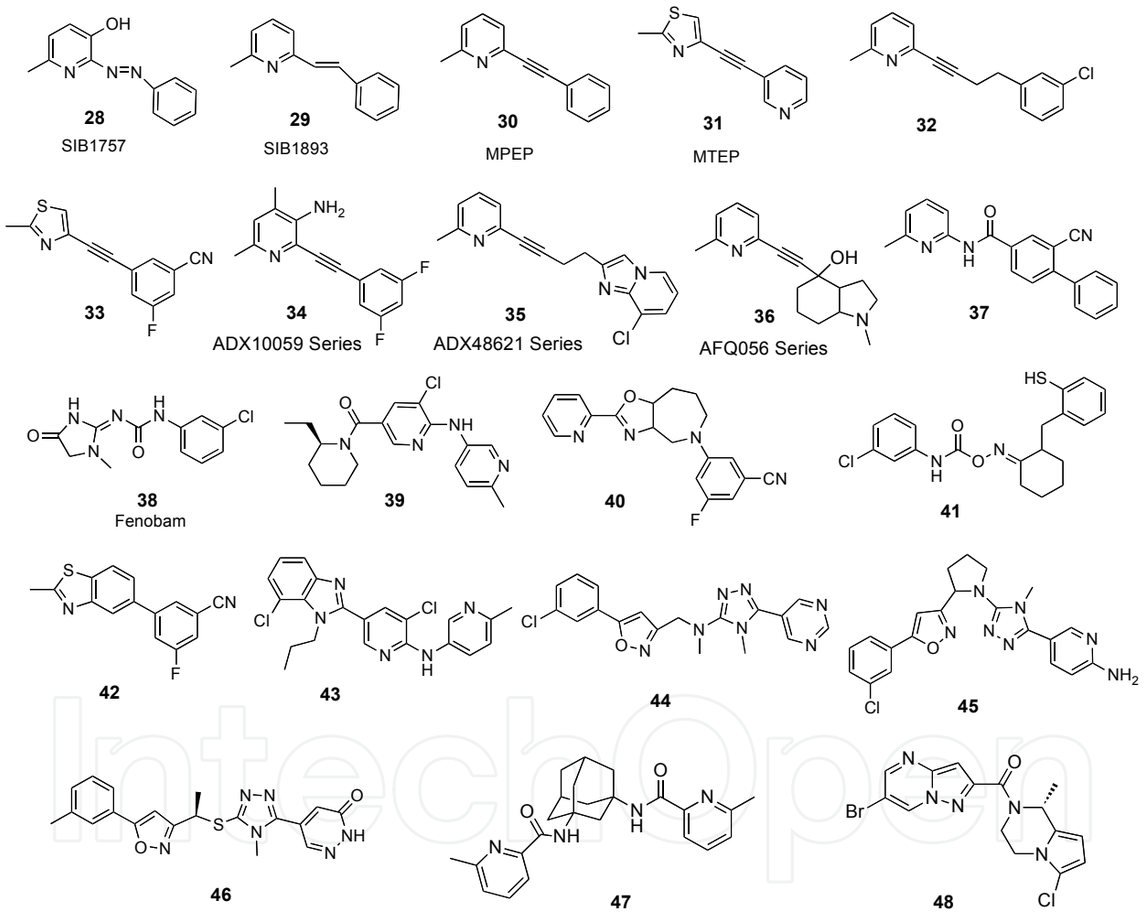

Fig. 4. Chemical structures of mGluR5 negative allosteric modulators

Since the discovery of the first mGluR5 positive modulator, DFB (**49**, Fig. 5) (O'Brien et al., 2003), Merck has reported three series of positive allosteric modulators for mGluR5, which are benzaldazine, benzamide and pyrazole series, exemplified by DFB, CPPHA (**50**) (O'Brien et al., 2004) and CDPPB (**51**) (Kinney et al., 2005; Lindsley et al., 2004), respectively. Subsequent structure-activity relationship study on CDPPB identified several nanomolar potent pyrazole ligands (De Paulis et al., 2006). Although these compounds are potent with an EC_{50} value of less than 20 nM, their poor binding affinity (K_i) and high lipophilicity

Compound	Rat mGluR5 IC_{50} (nM)	Human mGluR5 IC_{50} (nM)	*In vivo* properties	References
28 (SIB1757)				(Varney et al., 1999)
29 (SIB1893)				(Varney et al., 1999)
30 (MPEP)	K_i = 12	2		(Cosford et al., 2003)
31 (MTEP)	K_i = 16	5	MTEP is more potent than MPEP *in vivo* (rats) in both a receptor occupancy assay and in the fear-potentiated startle model of anxiety.	(Cosford et al., 2003)
32	5			(Bach et al., 2006)
33	0.8 K_i = 0.9			(Kulkarni et al., 2009)
34 ADX10059 Series			Positive data from phase II clinical studies in both GERD and acute migraine.	(Keywood et al., 2009; Marin & Goadsby, 2010)
35 ADX48621 Series			Showed efficacy in nonhuman primate model of PD-LID.	(Emmitte, 2011)
36 AFQ056 Series			Reported improvements in certain aberrant behaviors in clinical trial for treating FXS.	(Emmitte, 2011)
37	0.8 K_i = 22		Showed efficacy for anxiolytic activity in the Vogel assay.	(Milbank et al., 2007)
38 (Fenobam)			Using prepulse inhibition as an outcome measure for treating FXS, 50% of patients responded according to the predefined criteria of efficacy.	(Berry-Kravis et al., 2009; Porter et al., 2005)
39	32			(Spanka et al., 2010)
40		16	Showed good brain penetration, robust receptor occupancy and short half-life in rodent.	(Burdi et al., 2010)
41	109 K_i = 9.1			(Galambos et al., 2010)
42	61		Showed efficacy in the OSS model.	(Lindsley et al., 2011)
43	24		Showed a robust anxiolytic-like effect.	(Carcache et al., 2011)

Compound	Rat mGluR5 IC_{50} (nM)	Human mGluR5 IC_{50} (nM)	*In vivo* properties	References
44	20		Rat B/P ratio=0.16.	(Isaac & Waallberg, 2009)
45	<3		Rat B/P ratio=0.085.	(Granberg & Holm, 2009)
46	19		Rat B/P ratio=0.26.	(Granberg & Holm, 2010)
47	K_i=6.7			(Jimenez et al., 2010)
48	7.8	25		(Henrich et al., 2009)

Table 2. *In vitro* and *in vivo* pharmacological profiles for mGluR5 negative allosteric modulators.

(logP) prevent them from being good candidates for radiotracer because high lipophilicity decreases brain penetration. Bessis et al. reported a fourth structural series represented by ADX47273 (**52**) (Bessis et al., 2005). Recently, many mGluR5 positive allosteric modulators**, 53–60**, have been reported to have an EC_{50} value below 20 nM (Fig. 5) (Varnes et al., 2011; Williams et al., 2011). However, no PET tracers have been developed from this class of compounds.

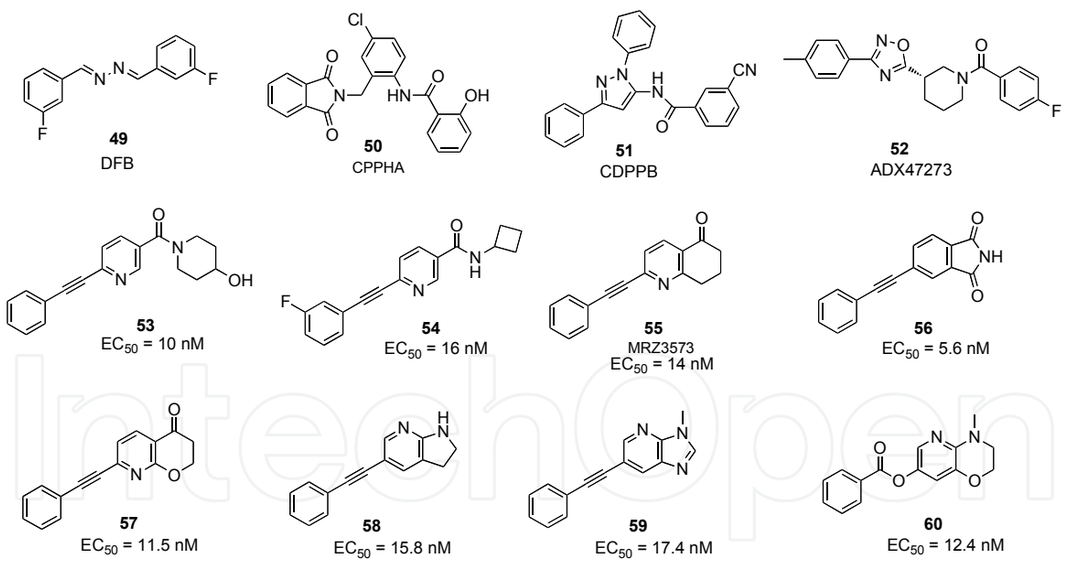

Fig. 5. Chemical structures of mGluR5 positive allosteric modulators

The discoveries of noncompetitive allosteric modulators with high binding affinity and subtype-selectivity entitle the exploration of the physiological functions of mGluR5 in normal and pathological states. Although *in vitro* and *ex vivo* studies using selective mGluR5 allosteric antagonists labeled with tritium (Cosford, 2003; Gasparini et al., 2002) have played important roles in elucidating the distribution and functions of mGluR5, PET tracers are needed for the *in vivo* quantitative visualization of mGluR5 in a living body and to conduct longitudinal studies of modulation of mGluR5 expression.

3.1.3 PET imaging studies of mGluR5 function

MPEP and MTEP have provided leads to some radioligand candidates for imaging human mGlu5 receptors with PET *in vivo*. Great effort was done to identify suitable positron-emitting radiotracers for noninvasive imaging of mGluRs. To date, more than 15 mGluR5-selective PET ligands labeled with ^{18}F or ^{11}C have been reported (Fig. 6) (Ametamey et al., 2006; De Paulis et al., 2006; Hamill et al., 2005; Honer et al., 2007; Krause et al., 2003; Musachio et al., 2003; Patel et al., 2005; Sanchez-Pernaute et al., 2008; Sime´on et al., 2007; Wang et al., 2007a; Yu, 2005; Zhu et al., 2007).

In 2005, Hamill and colleagues from Merck demonstrated the first successful PET imaging of mGluR5 in rhesus monkeys using [^{18}F]F-MTEB (**61**) (Hamill et al., 2005; Patel et al., 2005). This compound was highly selective and bound with high affinity (IC_{50} = 80 pM) to the receptor. 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.

Brownell et al. have synthesized and radiolabeled five noncompetitive antagonists for mGluR5: [^{11}C]M-MPEP (**62**) (Yu et al., 2005), [^{11}C]M-PEPy (**63**) (Sanchez-Pernaute et al., 2008), [^{11}C]MPEP (**64**) (Yu et al., 2005), [^{18}F]FMTEP (**65**) (Zhu et al., 2007) and ^{18}F]FPEB (**66**) (Wang et al., 2007a) and conducted *in vivo* PET imaging studies in different disease models to investigate modulation of mGluR5 function. It was found in these studies that accumulation of pyridine derivatives [^{11}C]M-MPEP (**62**), [^{11}C]M-PEPy (**63**), [^{11}C]MPEP (**64**) and [^{18}F]FMTEP (**65**) into the brain was fast and the highest accumulation was reached in 1-5 min followed by fast washout, suggesting little retention by high affinity receptor binding. This creates limitation to obtain statistically meaningful imaging data without overdosing the object with radiation or saturating the receptor binding sites with accompanying cold compound. These ligands have limitation, due to high lipophilicity, unfavorable brain uptake kinetics, or a high rate of metabolism, though they possess favorable *in vitro* pharmacological profiles. For PET ligands to be used in the central nervous system, a postulated lipophilicity coefficient (logD or logP) value should be between 2 and 3 for good brain accumulation. The compounds [^{11}C]ABP688 (**67**) (Ametamey et al., 2006) and [^{18}F]FPEB (**66**) (Patel et al., 2007; Wang et al., 2007a) have better binding profile for imaging studies of mGluR5. The logD value of 2.3 for [^{11}C]ABP688 and the logP value of 2.8 for [^{18}F]FPEB suggest that the two compounds are sufficiently lipophilic for the BBB penetrating. Both compounds have good binding properties with a K_i Value of 0.2 nM for [^{18}F]FPEB and a K_d value of 1.7 nM for [^{11}C]ABP688. The brain uptake of both compounds is highly selective, with high accumulation in mGluR5-rich brain regions such as the hippocampus, striatum and cortex. Blocking studies by coinjection of [^{11}C]ABP688 and corresponding unlabeled compound revealed up to 80% specific binding in these regions, whereas in cerebellum, a region with negligible mGluR5 density, no significant changes in radioactivity uptake were observed (Ametamey et al., 2006). Specific binding of compounds [^{11}C]ABP688 and [^{18}F]FPEB were also demonstrated with mGluR5-knockout mice which exhibited a homogeneous background level accumulation throughout the brain (Black et al., 2010). The metabolism studies of [^{11}C]ABP688 and [^{18}F]FPEB indicated that more than 95% of the radioactivity found in the brain was parent compound 30 min after injection for [^{11}C]ABP688 and 78% for [^{18}F]FPEB. Both compounds have been translated to human studies to investigate mGluR5 function.

Siméon and colleagues of the NIH reported a new high affinity radioligand, [^{18}F]-SP203 (**68**), for mGluR5 (Sime´on et al., 2007). [^{18}F]-SP203 has high affinity (IC_{50} = 36 pM) and potency in a phosphoinositol hydrolysis assay (IC_{50} = 0.71 pM) for mGluR5. It demonstrates a high

uptake in mGlu5 receptor rich regions of the rat and rhesus brain. The major advantage of this tracer over [^{18}F]F-MTEB is its high radiochemical yield (87%) and easy radiosynthesis. This ligand is presently in NIH administrated clinical trial.

[^{11}C]M-FPEP (**69**, K_D 1.2 nM and B_{max} 84.5 f_{mol}/mg) has an even biodistribution in all brain regions demonstrating that this tracer lacks specific binding (Ametamey et al., 2003). Compound **70** showed little retention by the receptor (Krause et al., 2003). Compound **71** (rat K_i 0.23 nM) had a good brain uptake and slow washout, with high concentration in striatum, frontal cortex and cerebellum of monkey (Hamill et al., 2005). However, the

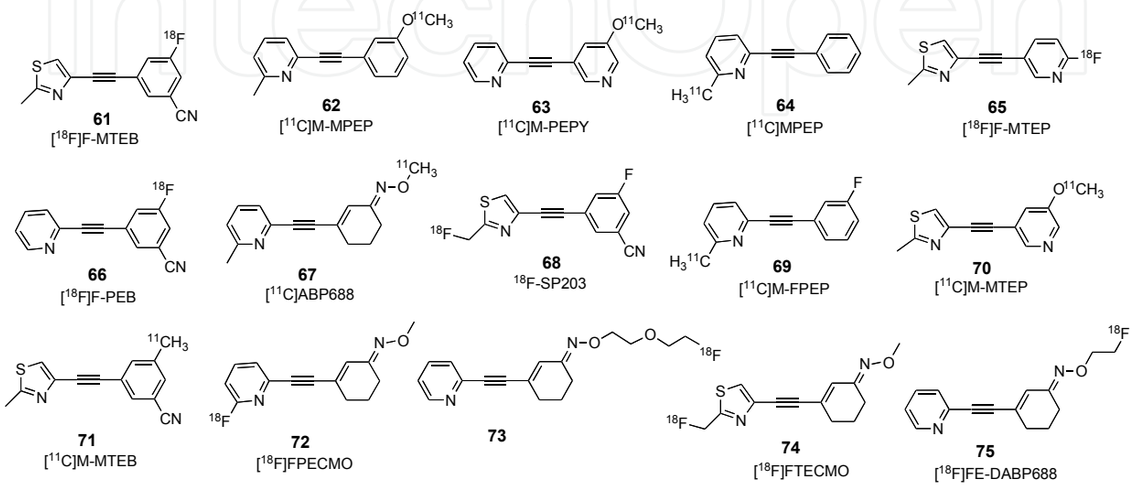

Fig. 6. Chemical structures of mGluR5 PET tracers.

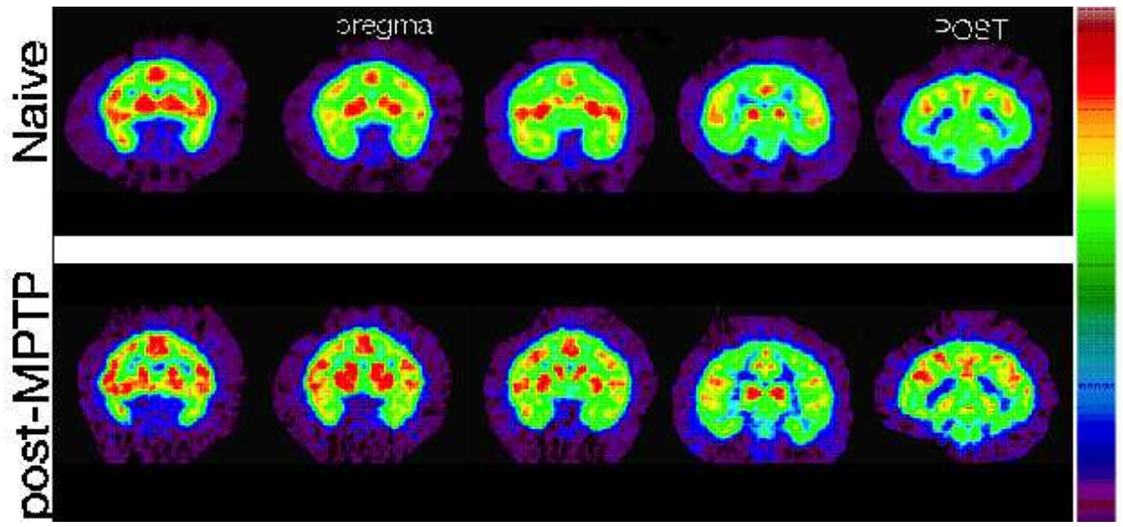

Fig. 7. Expression of mGluR5 in the brain of a naïve (top) and a symptomatic parkinsonian primate, using the highly selective tracer [^{18}F]FPEB (3-[^{18}F]fluoro-5-(2-pyridinylethynyl)benzonitrile). Primate Parkinson's disease (PD) was introduced by low dose long-term systemic administration of MPTP. In PD monkey accumulation of [^{18}F]FPEB was enhanced compared to naïve monkey in several brain areas including caudate, putamen, accumbens and SN/VTA. Distribution of [^{18}F]FPEB accumulation is illustrated at 60-70 min after administration of radioligand (1.2-1.5 mCi iv., specific activity 1.9 Ci/μmol).

cerebellum is an area with fairly low mGluR5 expression indicating that **71** may have non-specific binding.

Four derivatives, **72-75**, were developed of ABP688. PET imaging with **72** (Lucatelli et al., 2009) did not allow visualization of mGluR5-rich brain regions in the rat brain due to fast washout and rapid defluorination. Compound **73** (Baumann et al., 2010a) was reported to have the high binding affinity to mGluR5. Further *in vitro* evaluation and *in vivo* imaging are needed for characterization of this ligand. Baumann et al. (Baumann et al., 2010b) reported that although [^{18}F]-FTECMO (**74**) displayed optimal lipophilicity (log $D_{pH7.4}$ = 1.6 ± 0.2) and high stability in rat and human plasma as well as sufficient stability in rat liver microsomes, PET imaging with [^{18}F]-FTECMO in Wistar rats showed low brain uptake. Uptake of radioactivity into the skull was observed suggesting *in vivo* defluorination. Honer et al. reported that [^{18}F]-FE-DABP688 (**75**) have optimal lipophilicity (logD 2.1±0.1) and high plasma stability (Honer et al., 2007). Saturation assays of [^{18}F]-FE-DABP688 revealed a single high affinity binding site with a dissociation constant (K_d) of 1.6±0.4 nM and a B_{max} value of 119±24 fmol/mg protein. PET scanning indicated radioactivity uptake in mGluR5-rich regions such as the hippocampus, striatum and cortex, and radioactivity accumulation in the cerebellum, a region with negligible mGluR5 density, was significantly lower. Biodistribution studies showed a similar distribution pattern of [^{18}F]-FE-DABP688 binding in the brain. The hippocampus-to-cerebellum and striatum-to-cerebellum ratios were 1.81±0.16 and 1.93±0.36, respectively. Blocking studies using coinjection of [^{18}F]-FE-.

DABP688 and unlabeled M-MPEP (1 mg/kg) revealed more than 45% replacement in the hippocampus and striatum, thus demonstrating the *in vivo* specificity of tracer binding. This result shows that [^{18}F]-FE-DABP688 may be a useful PET tracer for imaging mGluR5

3.2 Allosteric modulators and radiotracers for group II mGluRs

Group II mGluRs have been shown to be expressed in several brain areas. The expression patterns of Group II receptors in the rodent brain parallel those of mGluR5, although the overall abundance of mGluR2/3 receptors appears slightly reduced as compared with that of mGluR5 (Olive, 2009). Expression levels of mGluR2/3 receptors are high in the olfactory bulb and hippocampus, and moderate in the dorsal striatum, nucleus accumbens, amygdala, anterior thalamic nuclei, cerebral cortex and cerebellum. Low levels of mGluR2/3 are found in the pallidum, colliculi, ventral midbrain and hypothalamus.

Group II mGluRs act in the hippocampus to decrease synaptic transmission and glutamate release when activated. These receptors have been targeted extensively by potential neuroprotective agents to develop treatments for anxiety, schizophrenia, Alzheimer's disease, Parkinson's disease, pain, drug withdrawal, and epilepsy (Rudd & McCauley, 2005).

3.2.1 Allosteric modulators for mGluR2

Over the past decade, a number of highly potent (EC_{50} in subnanomolar) mGluR2 agonists and antagonists with high binding affinity (K_i < 2 nM) have been identified (Rudd & McCauley, 2005; Yasuhara et al., 2006). However, their mGluR2-selectivity over mGluR3 in the same group is fairly low with the highest potency ratio being 6.5 (Dominguez et al., 2005). A high potency ratio does not necessarily imply a high binding affinity ratio, whereas the specific binding of a radiotracer depends much on the binding affinity ratio. Considering a low subtype-selectivity and unfavorable brain penetration of classical mGluR2 agonists and antagonists, the focus has presently been to develop noncompetitive allosteric modulators. When the allosteric binding sites on glutamate receptors within a group are sufficiently different it is possible to develop subtype selectivity modulators.

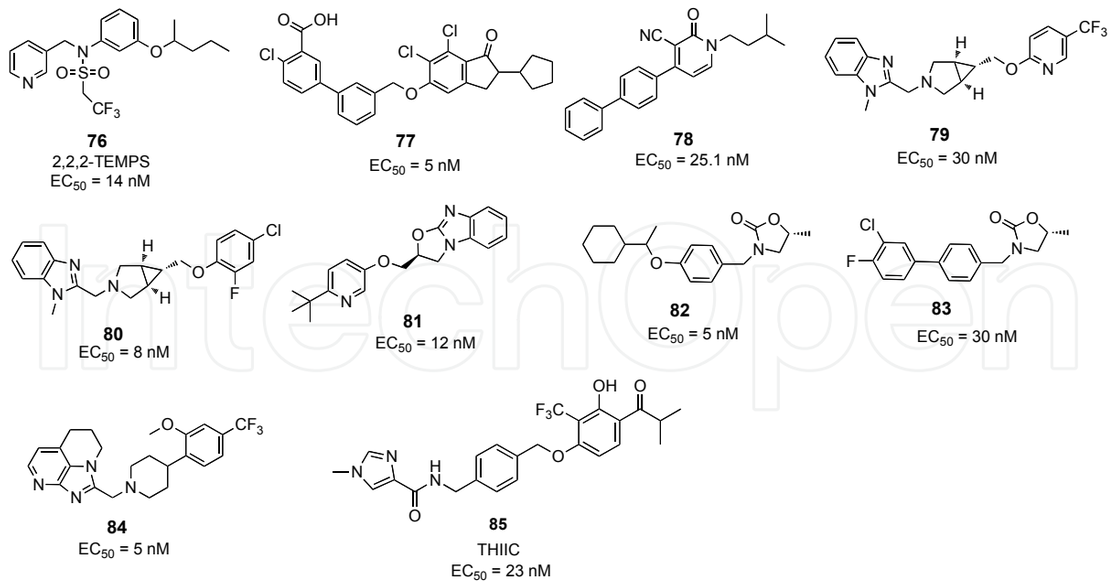

Fig. 8. Chemical structures of mGluR2 positive allosteric modulators

Many series of selective mGluR2 positive allosteric modulators have been reported to date. Figure 8 shows the compounds that were reported to have an EC_{50} value of less than 30 nM. They are N-aryl-N-(pyridylmethyl)ethanesulfonamides (**76**) (Barda et al., 2004; Johnson et al., 2003), biphenyl-indanones (**77**) (Bonnefous et al., 2005), 1,4-disubstituted 3-cyano-pyridone derivatives (**78**) (Imogai et al., 2007), 3-(Imidazolyl methyl)-3-aza-bicyclo[3.1.0]hexan-6-yl)methyl ethers (**79** and **80**) (Zhang et al., 2008), oxazolobenzimidazoles (**81**) (Garbaccio et al., 2010), 3-Benzyl-1,3-oxazolidin-2-ones (8**2** and **83**) (Duplantier et al., 2009), 2-((4-(2-methoxy-4-(trifluoromethyl)phenyl)piperidin-1-yl)methyl)-5,6-dihydro-4*H*-imidazo[4,5,1-*ij*][1,7]naphthyridine (**84**) (Efremov et al., 2008) and THIIC (**85**) (Fell et al., 2011).

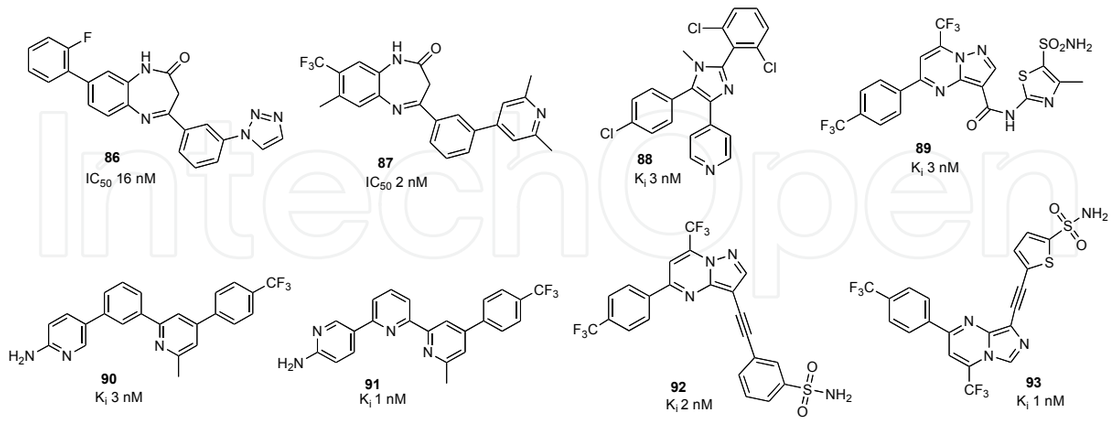

Fig. 9. Chemical structures of mGluR2/3 positive allosteric modulators

Several series of compounds have been developed as mGluR2 or mGluR2/3 allosteric antagonists, which include 8-ethynyl-1,3-dihydrobenzo[b][1,4]diazepin-2-one derivatives (**86** and **87**) (Woltering et al., 2007; Woltering et al., 2008a; Woltering et al., 2008b; Woltering et al., 2010), imidazole derivatives (**88**) (Gatti McArthur et al., 2006b), pyrazolopyrimidines

(**89**) (Gatti McArthur et al., 2006c), Pyridine and pyrimidine derivatives (**90** and **91**) (Gatti Mcarthur et al., 2007), acetylenyl-pyrazolo-pyrimidine derivatives (**92** and **93**) (Gatti McArthur et al., 2006a). Representative compounds listed in Fig. 9 exhibit high binding affinity towards mGluR2, however, their binding selectivity over mGluR3 is either very low or is not disclosed.

Currently, no positron emitting radioligand has been developed for imaging mGluR2.

3.2.2 PET imaging studies of mGluR2/3 expression

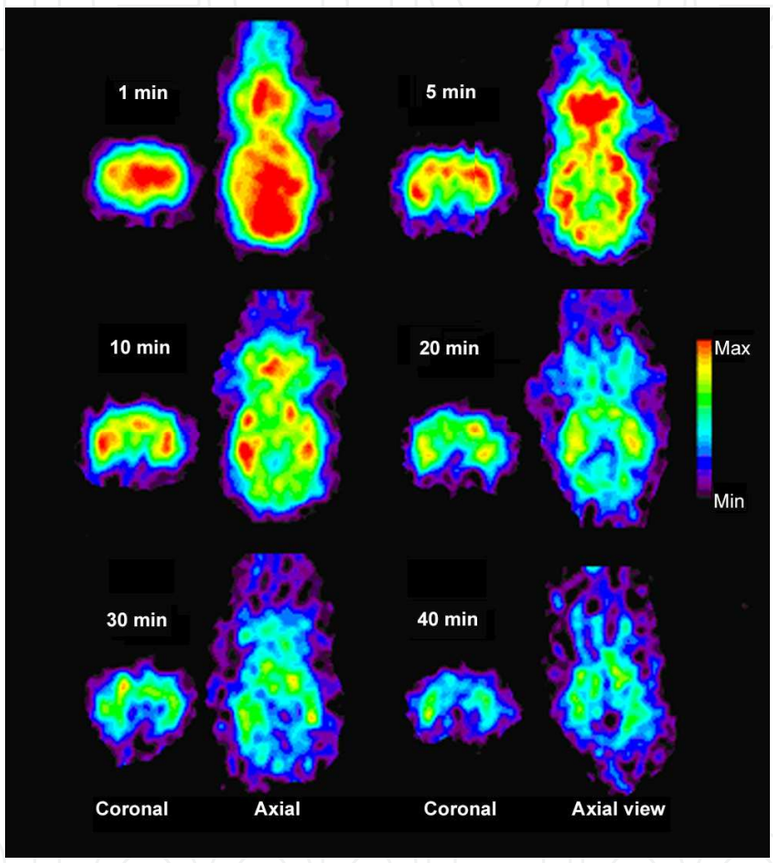

Fig. 10. To investigate preliminary imaging characteristics of (S,S,S)-2-(2-carboxycyclopropyl)-2-(3-[^{11}C]methoxyphenethyl) glycine dimethyl ester ([^{11}C]CMG) 0.4-0.5 mCi of [^{11}C]CMG was administered iv. into the anesthetized (isoflurane 1.5% with O2 flow of 1L/min) rats (male Spraque Dawley) in a microPET scanner (P4, Concord Microsystems). Dynamic volumetric data were acquired in 6 rats for 60 min. Fast reversible binding was observed in several cortical areas, hippocampus, striatum and olfactory bulb, the sites which are known to express group II mGluRs. The maximum binding (1.1-1.6% of the injected dose per cm3) was observed 2 min after administration. These data provide a foundation for future development of specific PET imaging ligands for group II mGluRs. Coronal and axial slices of [^{11}C]CMG distribution in the rat brain from 1 min till 40 min after administration of the radioligand are illustrated. Color coded images are normalized to each other and correspond the acquisition time of 1 min at the same midbrain level (coronal slice at bregma -1.6 mm; axial slice at bregma -5.4 mm).

3.2.3 Allosteric modulators for mGluR3

Eli Lilly and Company reported the first series of compounds, 1-(heteroaryl)-3-(2,4-dichlorobenzyl)amino-pyrolidine, acting as mGluR3 negative allosteric modulators (Britton et al., 2006). Figure 11 shows the chemical structures of two most potent ligands reported in the patent. Compounds, **94** and **95**, have an IC_{50} value of 77 nM, which is insufficient for *in vivo* detection of the receptors. Further SAR studies are needed to find more potent ligands. No PET radioligands have been identified for mGluR3 so far.

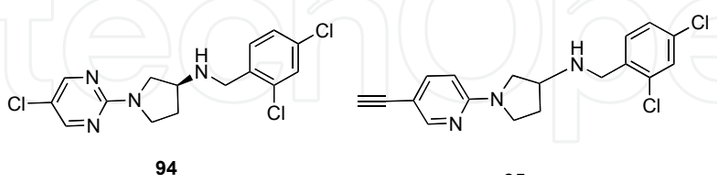

Fig. 11. Chemical structures of mGluR3 negative allosteric modulators

3.3 Allosteric modulators and radiotracers for Group III mGluRs

Group III metabotropic glutamate receptors are mGluR4, mGluR6, mGluR7 and mGluR8. There is no publication reporting mGluR6 allosteric ligands.

3.3.1 Allosteric modulators for mGluR4

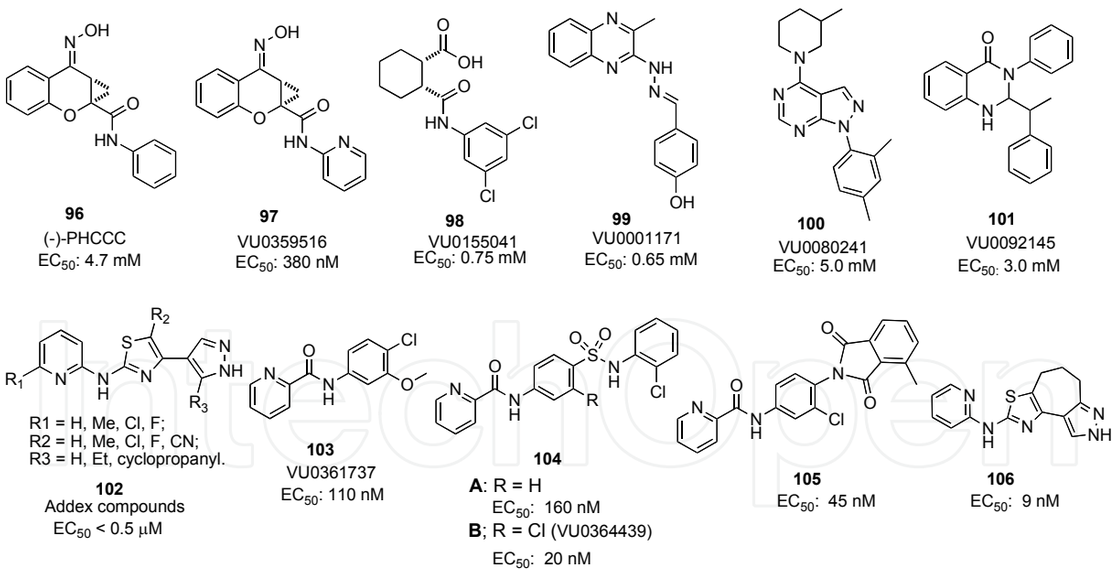

Fig. 12. Chemical structures of mGluR4 positive allosteric modulators

MGluR4 has received much attention lately due to its implication in several diseases, such as PD, epilepsy, and anxiety. There has been substantial progress in identifying positive allosteric modulators for mGluR4. The compound PHCCC (**96**, Fig. 12), a partial selective mGluR4 potentiator, has been studied for many years. Unfortunately PHCCC and other early disclosed mGluR4 PAMs such as **98–101** (Fig.12) are deficient in their BBB penetration (Engers et al., 2009). The potencies of these compounds are also relatively low (EC_{50}: 0.65 –

5.0 μM) and SAR studies around these structures have given 'flat' results. Addex Pharma disclosed a series of heteroaromatic compounds (**102** in Fig. 12) as positive allosteric modulators for mGluR4, with many compounds having EC_{50} < 0.5 μM (Bolea & Celanire, 2009). However, no other information was reported about these compounds.
Two research groups; Addex Pharma (Bolea, 2009) and Vanderbilt University (Engers et al., 2009), have independently disclosed a series of small arylamide compounds as a new class of mGluR4 PAMs. Engers et al (Vanderbilt University) found from a high-throughput screening that there were a number of small arylamide compounds having mGluR4 PAM activity (Engers et al., 2009). They reported studies on SAR and *in vitro* and *in vivo* pharmacokinetic parameters in rat. The most potent compound in this series was **103** shown in Fig. 12. Researchers at Merck presented two new compounds, **104A** and **105**, with improved activity (Reynolds, 2008). Engers et al. further studied SAR of 4-(phenylsulfamoyl)phenylacetamide derivatives and found that **104B** was the most potent (19.8 nM) mGluR4 positive allosteric modulator reported to date (Engers et al., 2010). Doller and co-workers (Lundbeck Research USA) have recently reported on a series of tricyclic thiazolopyrazole derivatives including compound **106**, which was identified as a very potent and orally available compound with excellent brain penetration and good physicochemical properties (Hong et al., 2011).

3.3.2 PET imaging studies of mGluR4 expression

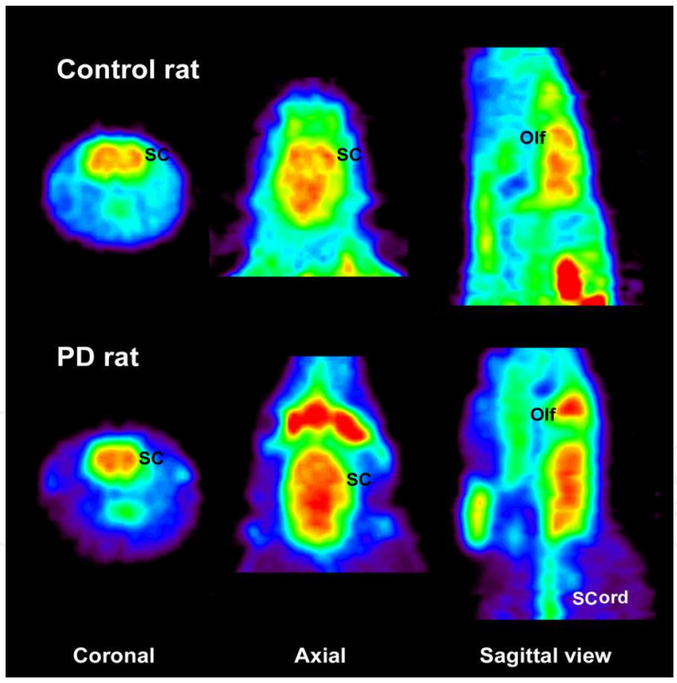

Fig. 13. Distribution of [^{11}C]methyl-PHCCC between 10-20 min after administration of radioligand in a control (1.2 mCi iv.) and PD (1.1 mCi iv.) rat brain. Coronal and axial views localize cortex at the level of S1 and S2 areas. It is noticeable that the accumulation of [^{11}C]methyl-PHCCC is enhanced in PD rat in the areas of subthalamic nucleus and spinal cord. The motor neurons in the ventral horn in the spinal cord express mGluR4 and the observed enhanced accumulation of mGluR4 ligand, [^{11}C]methyl-PHCCC is an indication of excess glutamate. This is the first time, when this aspect has been demonstrated *in vivo* in a PD model.

3.3.3 Allosteric modulators for mGluR7

It is reported that mGluR7 is widely expressed in the central nervous system and is primarily located on presynaptic terminals in brain regions such as the hippocampus, amygdala, and locus coeruleus. Mitsukawa et al. developed the first selective allosteric agonist of mGluR7, AMN082 (**107**), which has an EC_{50} value of 64-290 nM and it is brain penetrating (Mitsukawa, 2005). However, converting it to a PET tracer is not straightforward. Researchers of Banyu Pharmaceutical Co reported a series of isoxazolopyridone derivatives as allosteric mGluR7 antagonists (Suzuki et al., 2007b). Compound MDIP (**108**) that was identified by random screening displayed mGluR7 antagonistic activity (IC_{50} = 20 nM) and had no detectable activity on other mGluRs at 1000 nM. However, MDIP showed poor metabolic stability (predicted F_H: 34%) on rat hepatocyte assay and low aqueous solubility (0.17 μg/mL, pH 7.4). It is assumed that poor metabolic stability and low aqueous solubility may be due to its high lipophilicity ($clogD_{7.4}$: 3.5). Recently, Nakamura et al. have identified some isoxazolopyridone derivatives with potent mGluR7 antagonistic activity and metabolic stability, in which MMPIP (**109**) with improved physicochemical properties and metabolic stability showed good oral bioavailability and brain penetrability in rats (Nakamura et al., 2010).

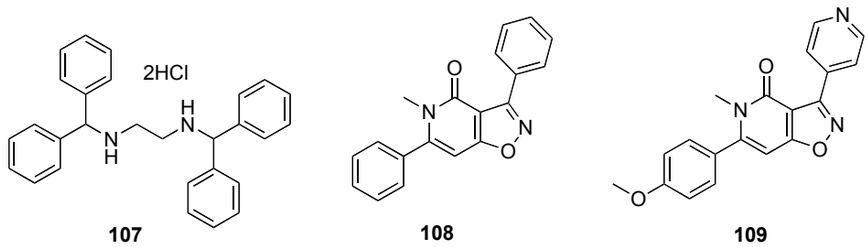

Fig. 14. Chemical structures of mGluR7 modulators

3.3.4 Allosteric modulators for mGluR8

Recently, AstraZeneca developed a positive allosteric modulator for mGluR8 (Duvoisin et al., 2010; Duvoisin et al., 2011). The compound AZ12216052 as injected into the amygdale, reduced measures of anxiety. There is no PET ligand available and AZ12216052 does not cross blood brain barrier.

4. Conclusion

Glutamate is an interesting transmitter since it can participate also on glutamate metabolism to be converted to glutamine and its function as a neurotransmitter can be investigated based on its receptor functions. To understand the diverse physiological effects of glutamate it is important to know molecular identity of mGluRs expressed in distinct subpopulations of neurons. For instance, group I mGluRs are coupled to phospholipase C and subsequent production of inositol triphosphates and induces intracellular calcium release in Purkinje cells and hippocampal CA1 neurons, but the same receptor types are also coupled to inhibition of voltage-dependent calcium channel in hippocampal neurons without intracellular diffusible messengers (Choi & Lovinger, 1996). Group II mGluRs can be coupled to inhibition of cyclic AMP cascade in neural and glial cells while they are also linked to rapid-onset regulation of various channels including calcium channels and G-

protein. The group III mGluRs-mediated effect is inhibition of neurotransmission through suppression of presynaptic voltage-dependent calcium channels (Pekhletski et al., 1996). This basic functional information of mGluRs has been obtained with *in situ* hybridization, immunohistochemistry and *ex vivo* studies with tritium labeled antibodies. While *ex vivo* studies can provide accurate endpoint information in steady state, they cannot provide information of the active inhibitory or stimulating effects in the system or interplay with other systems. To obtain functional information in real time, the investigation has to be done by using *in vivo* imaging methods. However, a lack of specific agonists and antagonists has limited the precise characterization of the role of individual metabotropic glutamate receptors in glutamatergic neurotransmission and hampered progress in identifying the physiological and pathological roles of mGluRs *in vivo*.

Recently, the modern computational chemistry has opened a wide range of technical approaches to design and construct molecules for imaging and to simulate their molecular targets. This technology has been used to design molecules for tracking different mGluRs. Especially, approach of allosteric compounds relies on sophisticated design of three-dimensional arrangement of the tracer molecules responsible for the biological activity. Pharmacophore models can be constructed based on known biological activity. Design of novel allosteric modulators is an iterative process where structure-activity relationship information generated in the biological assays guides how to make structural alternations towards the optimal compound. Recently several non-competitive structurally diverse mGluR ligands have been published. These ligands, positive, negative and neutral modulators, bind to the allosteric binding sites located in the seven strand transmembrane domain. Based on these modulators, a number of radiotracers useful for imaging specific metabotropic glutamate receptors have been developed and their *in vivo* biological properties have been characterized.

Development of metabotropic glutamate receptor ligands will open a new perspective for molecular imaging. Modulation of receptor functions might be used as diagnostic tools as well as to follow progression/regression of neural diseases. Presently, three mGluR ligands have been used in human studies. They are developed as negative allosteric modulators for mGluR5. For example, concerning PD, the death of dopamine neurons in the substantia nigra pars compacta causes a loss of dopamine in the basal ganglia. Dopamine modulation of neurotransmission in the striatum and other basal ganglia structures is crucial to gate cortical and thalamic excitatory input through the direct and indirect pathways. By using *in vivo* PET imaging studies and [^{18}F]FPEB we have found an upregulation of mGluR5 expression following dopamine denervation in animal models of PD (Figures 7 & 13), which probably represents a local compensatory mechanism, directed to dampen an excessive excitability of striatopallidal neurons. Drugs targeting the mGluR5 might provide new approaches by selectively reducing glutamate transmission in the areas where it is abnormally enhanced. In addition, we and others have found enhanced mGluR5 expression in several brain areas related to the indirect pathway in models of L-DOPA induced dyskinesias and some studies have shown promising therapeutic results after using mGluR5 antagonists. In gut glutamate is the main energy source and its neurotransmission is conducted by vagal afferents. The gut expresses also mGlu5 receptors and we have localized them with [^{18}F]FPEB. This phenomenon has raised a hypothesis that gut-brain axis as well as interplay with dopamine transmission might contribute to obesity.

Even mGlu2 receptors had the earliest interest as targets for drug development and Eli Lilly developed several potent ligands targeted to mGluR2 there is not yet any specific allosteric

modulators available for imaging purposes of mGluR2 function. The earlier compounds were missing receptor selectivity and sensitivity for imaging purposes since sequence similarity at the orthosteric binding site to which endogenous agonists bind.
Present application of glutamate transmission has evoked an active drug development especially to develop allosteric modulators for neurodegenerative disorders, pain and schizophrenia. It should be noted that these disorders are affected also by modulation of dopaminergic system supporting hypothesis of interplay of these powerful transmitter systems. Future pharmacological and imaging studies will show which specific ligands acting at individual receptor subtypes could be used as sensitive indicators for diagnostic imaging. Therefore, there is an urgent need for development of allosteric modulators as imaging ligands for different of mGluRs for human use.

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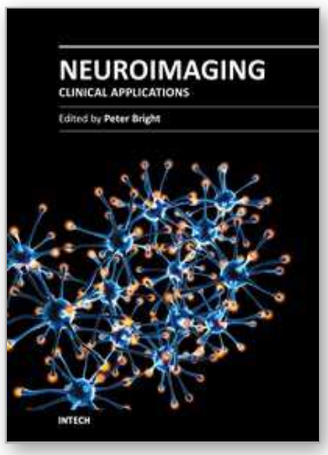

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Modern neuroimaging tools allow unprecedented opportunities for understanding brain neuroanatomy and function in health and disease. Each available technique carries with it a particular balance of strengths and limitations, such that converging evidence based on multiple methods provides the most powerful approach for advancing our knowledge in the fields of clinical and cognitive neuroscience. The scope of this book is not to provide a comprehensive overview of methods and their clinical applications but to provide a "snapshot" of current approaches using well established and newly emerging techniques.

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