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Re-exploring the *N*-phenylpicolinamide derivatives to develop mGlu₄ ligands with improved affinity and in vitro microsomal stability



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ABSTRACT

In recent years, mGlu₄ has received great attention and research effort because of the potential benefits of mGlu₄ activation in treating numerous brain disorders, such as Parkinson's disease (PD). Many positive allosteric modulators of mGlu₄ have been developed. To better understand the role of mGlu₄ in healthy and disease conditions, we are interested in developing an mGlu₄ selective radioligand for in vivo studies. Thus, we had synthesized and studied [¹¹C]**2** as a PET tracer for mGlu₄, which demonstrated some promising features as a PET radioligand as well as the limitation need to be improved. In order to develop an mGlu₄ ligand with enhanced affinity and improved metabolic stability, we have modified, synthesized and evaluated a series of new *N*-phenylpicolinamide derivatives. The SAR study has discovered a number of compounds with low nM affinity to mGlu₄. The dideuteriumfluoromethoxy modified compound **24** is identified as a very promising mGlu₄ ligand, which has demonstrated enhanced affinity, improved in vitro microsomal stability, good selectivity and good permeability.

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L-Glutamate is the most abundant excitatory neurotransmitter in the CNS (central nerve system) of vertebrates and probably mediates more than 50% of all synapses.^{1,2} Two major classes of receptors, mGlu and iGlu, are involved in glutamate signal transfer. The mGlu belong to Class C of the GPCR (G protein-coupled receptor) super family, which are thought to exist as dimers and have a distinct large extracellular N-terminus. This extracellular N-terminal domain contains two hinged globular domains referred as the venus flytrap domain (VFD), which is the orthosteric binding site for the endogenous ligand, L-glutamate.³ The mGlu can be further divided into three subgroups including eight known receptor subtypes (group I: mGlu₁ and mGlu₅, group II: mGlu₂ and mGlu₃, and group III: mGlu₄, mGlu₆, mGlu₇ and mGlu₈) based on their structural similarity, ligand specificity, and preferred coupling mechanisms.⁴ The mGlu are involved in glutamate signaling in almost every excitatory synapse in CNS, and they have distinctive biodistribution in CNS depending on subtypes and subgroups.⁵ In recent years, mGlu₄ has received great attention and research effort because of the potential benefits of mGlu₄ activation in treating numerous brain disorders, such as Parkinson's disease (PD).^{6,7} As a group III mGlu, mGlu₄ interacts with the $G_{\alpha i/o}$ subunit of

G-protein which negatively couples with adenylate cyclase to inhibit cAMP dependent signal pathways.^{8,9} The mGlu₄ is expressed at multiple synapses throughout the basal ganglia, mainly localized presynaptically and expressed in the striatum, hippocampus, thalamus, and cerebellum.^{4,10,11} Its activation reduces neurotransmitter release, a mechanism implicated in the pathophysiology of PD. The activation of the mGlu₄ receptor can be accomplished by two different mechanisms: orthosteric agonists (competing with L-glutamate) or noncompetitive positive allosteric modulators (PAMs). Most orthosteric ligands of mGlu₄ made in the past lack clear subtype selectivity and BBB (blood-brain barrier) penetration, but notable examples exist of selective and brain penetrant orthosteric agonists, such as LSP4-2022.^{12,13} Much recent effort has been focused on the development of allosteric modulators, which target the seven-transmembrane spanning domain. In particular, the allosteric modulation of mGlu₄ has spurred intense interest after (-)-PHCCC (1, N-phenyl-7-(hydroxyimino)-cyclopropa[b] chromen-1*a*-carboxamide), a partially selective mGlu₄ PAM, was discovered and demonstrated activity in models of neuroprotection and PD. Since then there has been substantial progress in identifying PAMs for mGlu₄.^{6,14,15} Figure 1 shows some representative mGlu₄ PAMs.^{6,14,16–20} Subsequent results with PAMs of mGlu₄ have further validated the antiparkinsonian activity in animal models of PD.^{11,17,21–24} in which this approach has opened a new avenue for

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Figure 1. Some representative mGlu₄ PAMs.

developing nondopaminergic treatments for PD and for identifying a novel disease modifying therapeutics.

To better understand the role of $mGlu_4$ in healthy and disease conditions, we are interested in developing an $mGlu_4$ selective radioligand for in vivo study. As a noninvasive medical imaging technique and a powerful tool in neurological research, positron emission tomography (PET) offers a possibility to visualize and analyze the target receptor expression under physiological and pathophysiological conditions. PET is being applied more often to detect disease-related biochemical changes before the disease-associated anatomical changes could be found by standard medical imaging modalities. Moreover, PET tracers serve as invaluable biomarkers during the development of potential therapeutic drugs. Thus, extensive research efforts have been directed toward the development of PET radioligands suitable for probing mGlu such as mGlu₁ and mGlu₅.¹⁵

Recently, we have reported a carbon-11 labeled PET ligand $[^{11}C]2$ (*N*-(4-chloro-3- $[^{11}C]$ methoxyphenyl)picolinamide),²⁵ which was based on a reported mGlu₄ PAM **2**.¹⁶ In 2009, two research groups at Addex Pharma²⁶ and Vanderbilt University¹⁶ have independently disclosed a series of small arylamide compounds as a new class of mGlu₄ PAMs. Engers et al. found from a high-throughput screening there were a number of small arylamide compounds having mGlu₄ PAM activity. They reported the SAR study, in vitro pharmacokinetic (PK) parameters and in vivo rat PK, which included the SAR results for sixteen N-phenylpicolinamide derivatives.¹⁶ Compounds **2** and **3** were the most potent mGlu₄ PAMs in this series and showed some potentially suitable properties for PET tracer development, which include: (1) rapid penetration into rat brain following intraperitoneal injection (T_{max} for brain: 0.5 h); (2) high brain/plasma (B/P) partition coefficients for both compounds (B/P = 4.1 for 2 and 9.9 for 3), in which B/P was determined by AUC_{0-8h,Brain}/AUC_{0-8h,Plasma}; (3) good in vitro potency and efficacy for both human and rat mGlu₄ compared to previous reported mGlu₄ PAM; (4) good selectivity over other mGlu subtypes; (5) compound 2 was the first mGlu₄ PAM to demonstrate efficacy in a preclinical rodent model of motor impairments associated with PD.⁶ Thus, we had synthesized and studied [¹¹C]**2** as a PET tracers for mGlu₄. This compound demonstrated some promising features as a PET radioligand such as the fast uptake into brain and the specific accumulation in mGlu₄-rich regions of the brain. However, in comparison to one of the best mGlu₅ PET tracer [¹⁸F]FPEB (3-[¹⁸F]fluoro-5-(2-pyridinylethynyl)benzonitrile),^{27,28} [¹¹C]**2** showed the decreased retention time in the brain, which may affect the quality of the imaging. The results indicate that the affinity and metabolic stability of this class of tracers need further optimization. We report here the synthesis and structure–affinity relationship study of new *N*-phenylpicolinamide derivatives to develop mGlu₄ ligands with improved affinity and metabolic stability.

We have modified and synthesized a series of new *N*-phenylpicolinamide derivatives for SAR study, in which the syntheses are shown in Schemes 1–3 (see Supplementary data). Three most active known compounds in this series (**2**, **3**, and **10**) were also synthesized and evaluated as the reference compounds for optimization. On the basis of previous SAR results,¹⁶ we modified compound **2** at three positions (3- or 4-phenyl, 6-pyrindyl) as illustrated in Figure 2. It is known that the SAR of this series was tight,^{6,16} so we started with minor modifications based on the reported data. As shown in Table 1, the modifications include the isosteric replacement of hydrogen by fluorine or deuterium, oxygen by sulfur, methoxy by cyano group and change for different halogen atoms. The radiolabeling strategy was also considered in lead optimization design to generate the facile labeling positions for either C-11 or F-18 tracer.

Since poor BBB permeability and high nonspecific binding (NSB) are among the most frequent causes for failure in CNS PET ligand development, it is necessary to consider some important physicochemical parameter such as MW, ClogP and tPSA at the design stage. It has been recently proposed that more desirable ranges for CNS drugs are ClogP < 3, MW <360 and 40 < tPSA < 90.²⁹ As shown in Table 1, all compounds except **12** and **22** possess the favorable physicochemical parameters, making them ideal candidates for CNS ligand development.



Scheme 1. Synthesis of the *N*-phenylpicolinamide derivatives. Reagents and conditions: (a) for carboxylic acids, EDC-HCl, HOBt-H₂O, DIPEA, dioxane; (b) for carboxylic acids, (1) thionyl chloride, benzene, reflux for 2 h; (2) TEA, THF, 40 °C, 1 h; (c) for acid chloride, DIPEA, CH₂Cl₂, 4 h.



Scheme 2. Synthesis of the *N*-phenylpicolinamides **12** and **22**. Reagents and conditions: (a) (SnMe₃)₂, Pd(PPh₃)₄, Toluene, reflux, 8.5 h; (b) l₂, CH₂Cl₂, 2 h.



Scheme 3. Synthesis of the *N*-(3-fluoromethoxyphenyl)picolinamides **23–25**. Reagents and conditions: (a) Ag(OTs), MeCN, reflux, overnight; (b) CsF, HO(CH₂O)₆H, reflux, 3.5 h; (c) *N*-(4-*R*-3-hydroxyphenyl)picolinamide, K₂CO₃, 40–50 °C, 3 days.



Figure 2. Modificatons on compound 2.

The lead compounds **2** and **3** were identified as mGlu₄ PAMs by using functional assays (calcium mobilization assays for human mGlu₄ and thallium flux assays for rat mGlu₄) and characterized with EC₅₀, the maximum response and the fold shift values.¹⁶ It is known that the EC₅₀ value may not always correlated closely to the affinity value for PAM.³⁰ It is very important to study the binding affinity for developing PET ligands. Thus, we prepared the tritium-labeled compound **2** ([³H]**2**, *N*-(4-chloro-3-(methoxy*t*₃)phenyl)picolinamide) for competitive binding assay.³¹ The synthesized compounds were characterized with competitive binding studies using mGlu₄ transfected CHO cells by increasing the concentration of test materials from 0.01 nM to 10 µM in presence of 2 nM of [³H]**2**, in which the binding affinities to mGlu₄ were described as IC₅₀ values (Table 1).³²

In structure–affinity study, we first evaluated the substitutions at the 4-phenyl position by keeping the 3-methoxy group constant. The 4-phenyl position of *N*-phenylpicolinamide was tolerated with some substitutions as demonstrated in known compounds **6–8**, in which compounds **6** and **7** were reported very potent but poor brain penetration.²⁰ Thus we limited the 4-phenyl substitutions for different halogens. The results show that the 4-chloro substitution give the best affinity, in which the affinity values of **2** and **10–13** are in the following order: Cl < H < F < I < Br. Larger halogen substitutions such as iodine and bromine led to substantial loss in affinity. It was then found that the 3-methylthio group was superior to the 3-methoxy group by comparing compounds **13** and **14**, showing a 2.8 fold enhancement in affinity.

On the other hand, compounds **15–17** had been incorporated a fluorine atom at 6-pyrindyl position of *N*-phenylpicolinamide, which can have a relatively facile fluorine-18 labeling. Compared to **2** and **3**, the affinity of **15** and **16** was not significantly reduced.

Next we turned our attention to the 3-phenyl position. It is considered that the metabolic stability was one of major issues for ML-128 (**2**), in which the 3-methoxy group was identified as the soft group. The 3-phenyl position was also very sensitive with substitutions. It was reported a simple change of 3-difluoromethoxy in compound **3** to 3-trifluoromethoxy group imparted a more than 10 fold loss of activity.¹⁶ Our initial effort was directed at 3-cyano substitution, in which ¹¹C-cyanation may be carried out through a palladium-mediated cyanation or the Rousenmund-von Braun reaction.³³ Five 3-cyanophenyl compounds (**18–22**) with different 4-phenyl substitutions were evaluated. The results show that the 3-cyano-4-chloro-analog 20 give a similar affinity compared to the 3-methoxy-4-chloro-analog 2. The affinity values of 18-22 are depending on 4-phenyl substitution and in the following order: Cl < F < H < Br < I, which shows different substitution effect compared to 3-methoxy analogs 2 and 10-13. We then replaced 3methoxy with 3-fluoromethoxy for two reasons: first, since both 3-methoxy- and 3-difluoromethoxy-analogs exhibited the activity, fluoromethoxy should be also active; second, it generates a position for fluorine-18 labeling. Fluorine-18 is often the radionuclide of choice for both its physical and nuclear characteristics. Its half-life is long enough to carry out relatively extended imaging protocols when compared to what is possible with carbon-11. This facilitates kinetic studies and high-quality metabolic and plasma analysis. However, fluorine-18 labeling is normally limited to chemical structures already containing a fluorine atom and the possible labeling strategies are limited for the preparation of radiotracers of high specific radioactivity. The result shows that 3-fluoromethoxy compound 23 has an improved affinity (3.2 nM) compared to that (5.1 nM) of 2, which improves 1.6 fold. However, 3-fluoromethoxy group may not be metabolically stable, since the 3-methoxy and 3-difluoromethoxy groups were metabolically unstable in compounds 2 and 3. On the other hand, 3-trifluoromethoxy analog of 3 was significantly more stable but lack activity.¹⁶ Hence, we had applied a 3-dideuteriumfluoromethoxy group to replace 3-fluoromethoxy group as shown in compounds 24 and 25. Deuterium isotope effects have been used to reduce in vivo metabolic rates. For example, Zhang et al. reported that a deuterium-substituted analog (with ¹⁸FD₂CO) as a radioligand for peripheral benzodiazepine receptor (PBR) had remarkably prolonged the half-life $(T_{1/2})$ in mice brain.³⁴ The deuterium substitution may reduce the rate of defluorination initiated by cleavage of the C–H bond without altering the binding affinity to mGlu₄. The result shows that the 3-dideuteriumfluoromethoxy modified compounds 24 and 25 have excellent affinity.

On the basis of the affinity of these picolinamide derivatives, we subsequently determined the in vitro microsomal stability of the selected compounds that include 2-4 and 23-24 (Table 2). Compound 4 (ADX88178) is one of a most potent mGlu₄ PAM to date and was shown to be orally active in a number of preclinical in vivo PD models.^{14,22} As Table 2 shows, the dideuteriumfluoromethoxy-compound **24** ($T_{1/2}$ = 7.4 min) is more stable than the corresponding fluoromethoxy-analog **23** ($T_{1/2}$ = 5.8 min) and the methoxy-analog **2** ($T_{1/2}$ = 4.9 min). It was reported that the cleaving rate of the C-H bond was about 6.7 times faster than that of C-D bond at 25 °C.³⁴ On the other hand, the half time and the difference of the metabolic rates of the dideuteriumfluoromethoxy analog and the fluoromethoxy analog depended on the level of the enzyme. In developing the PET ligand for PBR, Zhang et al. found that the half time $(T_{1/2})$ in the plasma was 2.575 min for the deuterium-substituted analog (with ¹⁸FD₂CO) and 2.367 min for the non-deuterated analog. However, the half time $(T_{1/2})$ of the deuterium-substituted analog in the brain was >60 min, whereas that of for the non-deuterated analog was only 2.227 min.³⁴ We anticipate that the difference of the half times in the brain between compounds 24 and 23 as well as 2 could be more significant. Compared to 4, compound 24 has the same affinity and a similar in vitro microsomal stability. It is clear that compound 24 has both enhanced affinity and improved in vitro microsomal stability compared to 2.

The selectivity of compound **24** was also determined among the various mGlu subtypes, in which the functional assays were carried

Table 1 SAR of N-phenylpicolinamide d

SAR of *N*-phenylpicolinamide derivatives

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Compd	R ₁	R ₂	MW	ClogP	tPSA	Affinity IC ₅₀ (nM)	$Log(IC_{50} \pm SE)$		
2	Н	CI CI	262.69	2.80	50.69	5.1	-8.29 ± 0.09		
3	Н	, F O F	264.23	2.67	50.69	4.6	-8.34 ± 0.08		
10	Н	, F	246.24	2.26	50.69	31.6	-7.50 ± 0.09		
11	Н	Br	307.15	2.95	50.69	322	-6.49 ± 0.08		
12	Н		354.15	3.16	50.69	146	-6.84 ± 0.10		
13	Н	× 0-	228.25	2.22	50.69	13.7	-7.86 ± 0.10		
14	Н	s.	244.31	2.81	41.46	4.9	-8.31 ± 0.07		
15	F		280.68	2.96	50.69	7.3	-8.13 ± 0.11		
16	F	, F F	282.22	2.85	50.69	6.7	-8.18 ± 0.10		
17	F	V C	264.23	2.42	50.69	89.2	-7.05 ± 0.10		
18	Н	, CN	223.23	1.89	65.25	10.4	-7.98 ± 0.05		
19	Н	, CN	241.23	2.06	65.25	7.4	-8.13 ± 0.04		
20	Н	CI	257.68	2.50	65.25	5.3	-8.28 ± 0.04		
21	Н	Br	302.13	2.78	65.25	47	-7.33 ± 0.08		
22	Н		349.13	3.04	65.25	172	-6.77 ± 0.08		
23	Н		280.68	2.97	50.69	3.2	-8.49 ± 0.07		
24	Н		282.70	2.97	50.69	3.2	-8.49 ± 0.11		
25	Н	D D D O F	248.25	2.39	50.69	3.7	-8.43 ± 0.03		

Table 2

In vitro properties of the selected compounds

Compd	Affinity IC_{50} (nM) (n = 3)	κ ^a	SEM(κ) (<i>n</i> = 2)	$T_{1/2}$ (min)	Avg. P_e (10 ⁻⁶ cm/s)
2	5.1	0.141	0.010	4.9	256
3 4	4.6 3.2	0.132	0.008	5.2 7.0	214 257
23	3.2	0.120	0.010	5.8	272
24	3.2	0.093	0.005	7.4	

^a The decay constant that is slope of logconcentration versus time profile $(T_{1/2} = \text{Ln } 2/\kappa)$.

out on mGlu₁, mGlu₂, mGlu₅, mGlu₆ and mGlu₈. Compound **24** showed little activity against these mGlu (Supporting information).

In addition, the permeability values of **2–4** and **23** were measured using BBB PAMPA model at pH 7.4, which characterized the rate across the BBB due to passive diffusion. The determined effective permeability (P_e) values are summarized in Table 2, in which the P_e results for internal highly and low permeable standards are 160 for propranolol and <2.8 for atenolol, respectively. This result indicates that compounds **23** and **24** have good BBB permeability. Although high BBB passive permeability does not

necessary translate to sufficient unbound drug concentration in the brain because of potential intrinsic clearance and efflux transport, it is beneficial for CNS drug candidates.

In summary, we have modified, synthesized and evaluated a series of new *N*-phenylpicolinamide derivatives. Our research further demonstrated that *N*-phenylpicolinamide is a good template to develop mGlu₄ ligands, which has offered extensive SAR results by us and other labs.^{16,26} The SAR study has discovered a number of compounds with good affinities (<10 nM) to mGlu₄. The dideuteriumfluoromethoxy modified compound **24** is identified as a very promising mGlu₄ ligand, which has demonstrated enhanced affinity, improved in vitro microsomal stability, good selectivity and good permeability. Compound **24** is considered as an attractive candidate for future labeling with fluorine-18 as an mGlu₄ PET tracer. Since a number of compounds have good affinity we are study-ing their PAM activity to mGlu₄ and potential therapeutic applications.

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Supplementary data

Supplementary data (experimental procedures and spectroscopic characterization of all new compounds) associated with this article can be found, in the online version, at http://dx.doi.org/10. 1016/j.bmcl.2015.07.031.

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