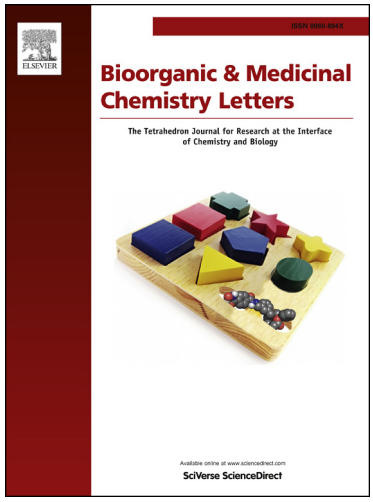

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Synthesis and biological evaluation of picolinamides and thiazole-2-carboxamides as mGluR5 (metabotropic glutamate receptor 5) antagonists

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Abstract: We described here the synthesis and biological evaluation of picolinamides and thiazole-2-carboxamides as potential mGluR5 antagonists. We found that a series of thiazole derivatives **6** showed better inhibitory activity against mGluR5. Compounds **6bc** and **6bj** have been identified as potent antagonists (IC_{50} = 274 and 159 nM) showing excellent in vitro stability profile. Molecular docking study using the crystal structure of mGluR5 revealed that our compounds **6bc** and **6bj** fit the allosteric binding site of mavoglurant well.

Keywords: metabotropic glutamate receptor, antagonist, picolinamides, thiazole-2-carboxamides, molecular docking

Glutamate, the principal excitatory neurotransmitter in the brain, regulates neuronal signal transmission through either inotropic or metabotropic glutamate receptors (iGluRs or mGluRs). The mGluRs belong to class C of the G-protein-coupled receptors (GPCRs), which are categorized into three groups (I, II and III) based on sequence homology, signal transduction mechanism and pharmacology. mGluR5, one of the group I receptors, is expressed postsynaptically and is mainly found in limbic brain areas including forebrain, striatal regions, and amygdala. Interaction of glutamate with mGluR5 results in activation of phospholipase C via G_q protein to release intracellular calcium ions, which leads to a variety of cellular responses.[1]

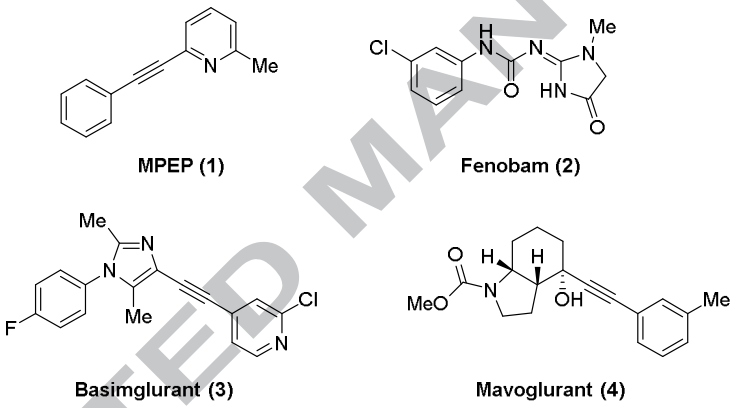


Figure 1. Representative mGluR5 antagonists

Regulation of mGluR5 has therapeutic potential in numerous preclinical models of diseases, including anxiety,[2] gastroesophageal reflux disease (GERD),[3] drug addiction,[4] and neuropathic pain.[5] Furthermore, recent study has demonstrated clinical evidence of the potential utility of mGluR5 antagonists. For example, basimglurant **3**, an mGluR5 negative allosteric modulator developed by Roche, is in phase II clinical trial for the treatment of depression and fragile X syndrome (**Figure 1**).[6] Novartis researchers also developed mavoglurant **4** as a non-competitive mGluR5 inhibitor, which is currently in phase II clinical trial for Levodopa-induced dyskinesia.[7]

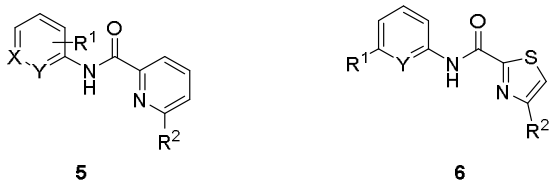


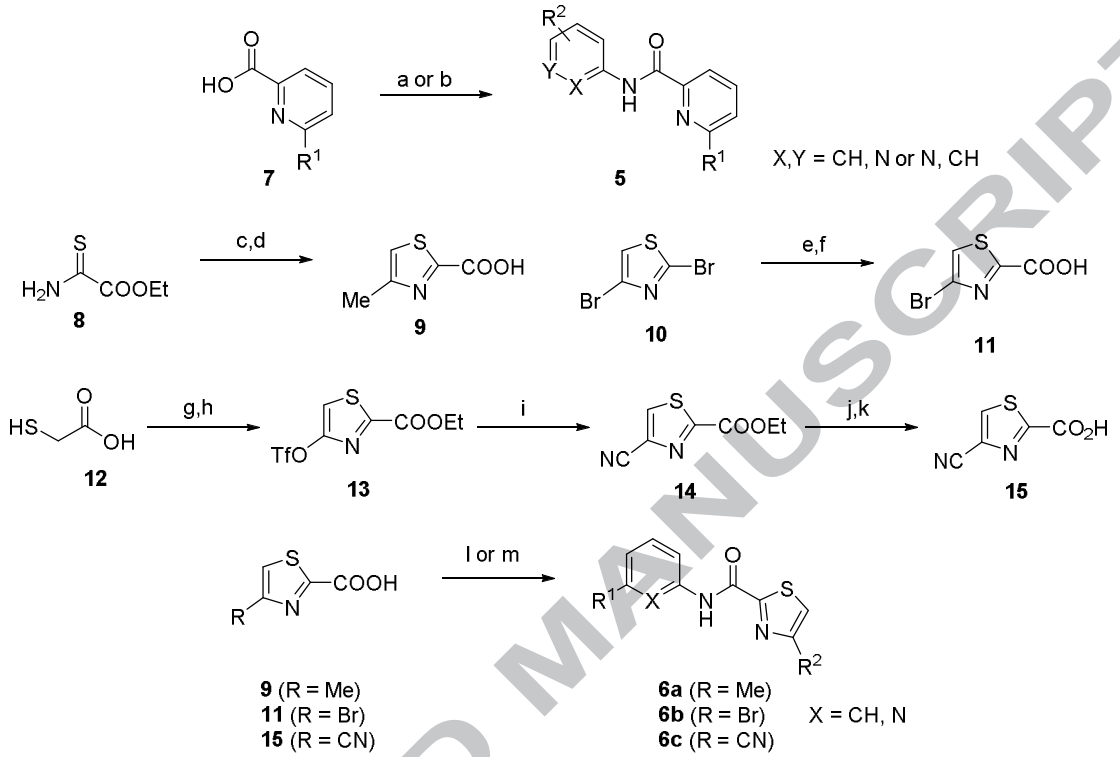
Figure 2. Structures of picolinamides **5** and thiazol-2-carboxamides **6**

Up to date, a number of mGluR5 antagonists containing an alkyne subunit as a key structural motif have been reported and known to show high affinity to mGluR5 receptor.[8] Inspired by their therapeutic potentials, alkynylquinoline analogues have been investigated in our laboratory.[9] In fact, we have discovered 2-(pyridin-2-ylethynyl)quinoline, which has high inhibitory activity against mGluR5 showing excellent stability profile. Furthermore, this compound exhibited favorable in vivo activity in a behavior test of neuropathic pain mouse model. Despite the high potencies of acetylenic analogues, we have attempted to search for new nonalkynyl mGluR5 antagonists because an alkyne moiety is metabolically unstable to cause unfavorable side effects.[10] Recently, several groups reported that a series of arylcarboxamides or arylureas proved to be potent mGluR5 antagonists, which indicated that amide or urea functional group could be appropriate structural motif as a replacement of alkyne linkage.[11] On the basis of the arylamide structure, therefore, we designed a new class of mGluR5 antagonists as shown in Figure 2. Compared to the previously reported compounds, we envisioned that *meta*-substituted pyrdine of **5** or *meta*-substituted thiazole of **6** would occupy the binding pocket of terminal aryl pharmacophore of most mGluR5 antagonists. In addition, incorporation of substituted aromatic ring to the other side of the amide linker would provide molecular diversity in this series of compounds to explore structure-activity relationship (SAR) and stability profile.

Herein we report the synthesis and in vitro evaluation of picolinamides and thiazole-2-carboxamides as potent mGluR5 antagonists including structural insight resulting from

computational docking study of our compounds in the crystal structure of mGluR5.

Scheme 1. Synthesis of picolinamides **5** and thiazole-2-carboxamides **6**.



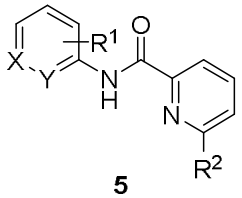
Reagents and conditions: (a) aminopyridines, HBTU, TEA, DMF, rt or 70 °C, 27-94%; (b) aminopyridine, CDI, THF or DMF, rt, 57-68%; (c) chloroacetone, EtOH, reflux, 12 h, 37%; (d) LiOH, H_2O/MeOH/THF(1:1:1), rt, 1 h, 42%; (e) *i*PrMgCl, THF, 0 °C, 15 min, then ethyl cyanoformate, rt, 15 min, 56% (2 steps); (f) LiOH, MeOH, rt, 2 h, 89%; (g) thioglycolic acid, pyridine, 80 °C, 3 h, 24%; (h) Tf_2O, TEA, DCM, rt, 18 h, 49%; (i) $Zn(CN)_2$, $Pd_2(dba)_3$, dppf, DMF, 65 °C, 3 h, 80%; (j) $NaBH_4$, EtOH, 0 °C to rt, 3 h, 87%; (k) PDC, DMF, rt, 5 h, 59%; (l) i) $ClCO_2i$-Bu, NMM, THF, -5 °C, 1 h; ii) anilines or aminopyridines, THF, rt, 18 h, 20-80%; (m) i) oxalyl chloride, DCM, rt; ii) anilines or aminopyridines, DIEA, DCM, rt, overnight, 40-90%.

A series of picolinamide analogues **5** were easily synthesized through an amide coupling reaction using HBTU as a coupling reagent, as described in Scheme 1. In order to synthesize

thiazole-2-carboxamides **6**, thiazole-2-carboxylic acids containing different substituents at the 2-position were required as substrates for amide coupling reactions. First, 4-methyl thiazole-2-carboxylic acid **9** was prepared by condensation of ethyl 2-amino-2-thioxoacetate **8** with chloroacetone followed by hydrolysis. Selective carbonylation of 2,4-dibromothiazole **10** via metal-halogen exchange produced the corresponding thiazole-2-carboxylate, which was also hydrolyzed to afford carboxylic acid **11**. Based on the Negishi type coupling reaction,[12] the synthesis of 4-cyano thiazole derivative **15** was achieved. Thus, thiazoletriflate **13**, derived from condensation of thioglycolic acid **12** with ethyl cyanoformate followed by triflation, was treated with $Zn(CN)_2$ in the presence of palladium catalyst to produce ester **14**, which was converted to desired acid **15** by reduction and oxidation. Finally, a series of thiazole-2-carboxamides **6** were synthesized via either mixed anhydride or acid chloride intermediate.

In vitro antagonistic activities of picolinamides **5** against mGluR5 were evaluated using a fluorescence-based calcium mobilization assay.[13] The results of the in vitro assay of these compounds were shown in Table 1. Although plicolinamides **5** showed relatively low inhibitory activity against mGluR5 at the concentration of 10 μM and 1 μM, we found that the inhibition values of compounds **5a**, **5f**, **5l**, and **5m** were over 50% at 10 μM. Regarding the SAR of aromatic group on the left hand side, it seemed that the 2-pyridyl ring (**5a** and **5b**) was superior to the 3-pyridyl group (**5c**-**5i**). Most importantly, the *meta*-substituted phenyl ring was preferred when R^2 is methyl group (**5l** and **5m**). On the basis of this initial SAR, we decided to use 3-substituted phenyl and 6-substituted-2-pyridyl groups on the left hand side of thiazole derivatives for the next phase of SAR study.

Table 1. In vitro inhibitory activity of picolinamide derivatives **5** against mGluR5



5

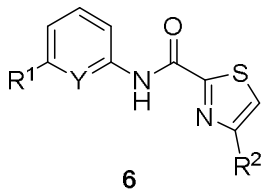
compds	X	Y	R^1	R^2	% Inhibition (mGluR5)[a]	
					10 μM	1 μM
5a	CH	N	H	H	65.46	34.45
5b	CH	N	5-Cl	H	30.68	16.18
5c	N	CH	H	H	30.28	25.62
5d	N	CH	2-Cl, 4-Me	H	17.72	16.06
5e	N	CH	6-MeO	H	25.52	13.99
5f	N	CH	2,5-diCl	H	51.04	13.77
5g	N	CH	2,6-diCl	H	35.40	3.85
5h	N	CH	H	OMe	23.10	22.79
5i	N	CH	H	Cl	33.42	19.11
5j	N	CH	2-Cl, 4-Me	Cl	18.57	15.65
5k	N	CH	6-MeO	Cl	43.38	18.48
5l	CH	CH	3-Cl	Me	52.08	10.51
5m	CH	CH	3-CN	Me	68.07	18.42
5n	CH	CH	3-Cl	F	33.35	13.13
5o	CH	CH	3-CN	F	33.99	3.20

[a] Ca^{2+} flux assay using glutamate as agonist.

Next, thiazole-2-carboxamide derivatives **6** were tested for their inhibitory activity against mGluR5 and the result is summarized in Table 2. At this time, the calcium-based functional assay was performed at the concentration of 1μM because higher selection criteria were necessary due to searching for more potent lead compounds.[14] Among the tested compounds, eight compounds have more than 40% inhibitory activity against mGluR5. When R^2 is methyl group, compounds **6af**, **6ah**, and **6ai** bearing hydrogen, chloro and methyl groups on the pyridine ring showed potent inhibitory activity, comparable to the corresponding picolinamide **5a**. In case of 4-bromothiazole derivatives **6b**, substitution of either pyridyl ring or phenyl ring at the *meta*-position resulted in significant enhancement of potency. In particular, compounds **6bc** and **6bj** exhibited high antagonistic effect against mGluR5 at 1

μM. On the other hand, a set of 4-cyanothiazole derivatives **6c** showed a loss in potency. The overall SAR results indicated that the inhibitory activity of this series is highly sensitive to substitution at the 4-position of thiazole.

Table 2. In vitro inhibitory activity of thiazole-2-carboxamides **6** against mGluR5



6

compds	Y	R^1	R^2	% Inhibition (mGluR5, 1μM)[a]
6aa	CH	F	Me	3.1
6ab	CH	Cl	Me	32.2
6ac	CH	Br	Me	18.0
6ad	CH	Me	Me	11.6
6ae	CH	CN	Me	16.6
6af	N	H	Me	47.1
6ag	N	F	Me	-21.2
6ah	N	Cl	Me	45.0
6ai	N	Me	Me	50.1
6aj	N	CN	Me	-22.6
6ba	CH	F	Br	13.7
6bb	CH	Cl	Br	58.1
6bc	CH	Br	Br	71.1
6bd	CH	Me	Br	40.9
6be	CH	CN	Br	-0.1
6bf	N	H	Br	-20.4
6bg	N	F	Br	27.6
6bh	N	Cl	Br	60.0
6bi	N	Br	Br	19.8
6bj	N	Me	Br	81.0
6bk	N	CN	Br	9.6
6ca	CH	Cl	CN	-7.3
6cb	CH	Br	CN	19.5
6cc	CH	Me	CN	-32.7
6cd	CH	CN	CN	-23.0
6ce	N	F	CN	-0.4
6cf	N	Cl	CN	-9.4
6cg	N	Br	CN	-21.5
6ch	N	Me	CN	24.7
6ci	N	CN	CN	8.3

[a] Ca^{2+} flux assay using glutamate as agonist.

To further investigate pharmacological properties of the most potent compounds **6bc** and **6bj**,

we examined their IC_{50} values, hERG inhibition, microsomal stability, and CYP inhibition. The results are summarized in **Table 3**. IC_{50} values of compounds **6bc** and **6bj** were obtained by measuring inhibition values against mGluR5 at varied concentrations. In the hERG assay, depolarization potential inhibited by our compounds was measured using automated patch clamp device. The microsomal stability was determined by analysis of the remaining amount of compounds incubated in the human liver microsomes. For the CYP assay, the % remaining activity values of five human CYP450 isozymes after treatment with compounds **6bc** and **6cj** were obtained. The data confirmed that compounds **6bc** and **6bj** have excellent inhibitory activity against mGluR5 with IC_{50} values of 274 and 159 nM, which is comparable to that of mavoglurant **4** (IC_{50} = 110 nM in Ca^{2+} assay).[16] With regard to in vitro safety and stability, compound **6bc** had relatively higher % remaining activity of all the tested CYP isozymes compared to compound **6bj**, which suggested that **6bc** has better CYP stability than **6bj**. In addition, both compounds showed low blocking activity of hERG channel at three different concentrations. Compound **6bc** exhibited considerably good microsomal stability, whereas **6bj** was found to be rapidly metabolized in hepatic microsomes.

Table 3. The results of IC_{50} (mGluR5), hERG channel inhibition, microsomal stability, and CYP inhibition

compds	mGluR5 IC_{50} (μM)[a]	hERG % inhibition @ 10/1/0.1 μM[b]	HLM %remaining @ 1μM after 30 min	CYP (% remaining @ 10μM)				
				1A2	2D6	2C9	3A4	2C19
6bc	0.274	39.6/29.3/16.3	37.31	38.3	102.1	99.0	84.9	86.3
6bj	0.159	34.8/19.4/15.0	7.25	11.0	99.2	88.2	87.3	7.4

[a]IC_{50} value (±SD) was obtained from a dose-response curve. [b]Only % inhibition values at 10, 1, and 0.1 μM were provided due to low inhibitory activity.

In order to rationalize the structure-activity relationship of thiazole derivatives, the binding modes of the most potent compounds **6bc** and **6bj** were evaluated using docking simulation with the crystal structure of the mGluR5 receptor recently reported by Heptares

Therapeutics.[17] The energy-minimization of compounds **6bc** and **6bj** in the mGluR5 crystal structure confirmed that these compounds comparatively fit the allosteric binding site of mavoglurant **4**, as shown in Figure 3.[18] The 3-bromophenyl ring of compound **6bc** docks to the hydrophobic pocket formed by the 3-methylphenyl ring of **4** and the amide linker moiety sits well in a narrow channel surrounded by Pro655, Tyr659, Val806, and Ser809. The carbonyl group of **6bc** forms a hydrogen bond with Tyr659, which is likely to compensate for a loss of binding affinity in this region, where the hydrogen bonding between Ser809 and the hydroxyl group of **4** exists. Interestingly, the binding mode of compound **6bj** is opposite to that of compound **6bc**. Thus, the 4-bromothiazole segment of **6bj** sits in a cavity defined by several hydrophobic residues such as Ala813, Ala810, Ile625 and Pro655, which corresponds to the binding site of the 3-bromphenyl moiety of **6bc**. The hydrogen bonding between Tyr659 and the carbonyl oxygen of **6bj** was also observed. In addition, the methylpyridine tail of **6bj** favorably docks to the other side of hydrophobic binding pocket, which is contributed to a slight rotational twist of C-N bond between pyridine and amide for proper positioning.

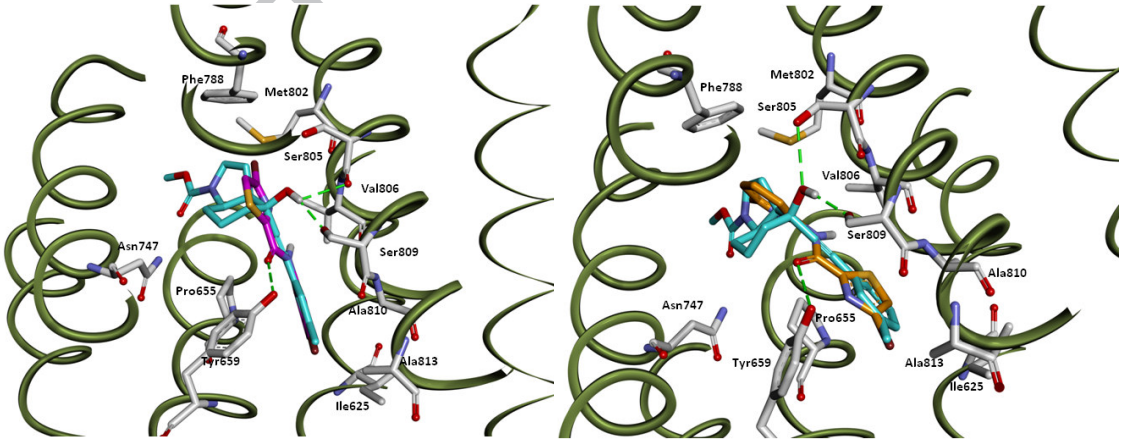


Figure 3. Superimposed binding modes of compounds **6bc** and **6bj** in the allosteric binding site of mavoglurant **4** complexed with mGluR5 (PDB code 4oo9). This docking study was peformed by using CDocker in Discovery Studio 3.1.

In conclusion, we have synthesized pincolinamides **5** and thiazole-2-carboxamides **6** as potential mGluR5 antagonists. The in vitro evaluation of these compounds turned out that a series of thiazole derivatives showed better inhibitory activity against mGluR5. Among them, compounds **6bc** and **6bj** were identified as most potent mGluR5 antagonists with IC_{50} values of 274 and 159 nM. Additionally, the in vitro stability experiments of these compounds proved that these compounds have excellent hERG selectivity and CYP stability, but they should be further improved with regard to microsomal stability. Molecular docking study using the mGluR5 crystal structure elucidates that the binding modes of compounds **6bc** and **6bj** are well correlated with the allosteric binding site of mavoglurant **4** although they are located in the opposite direction. Based on the current study, compound **6bc** and **6bj** will be optimized as potential lead compounds and further applied to preclinical evaluation of mGluR5 associated diseases.

Acknowledgments

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(13) *Experimental procedure for calcium mobilization assay.* Human embryonic kidney cells which stably express mGluR5 were obtained from Yonsei University. Cells were grown in DMEM medium supplemented with 10% (v/v) fetal bovine serum, penicillin (100 U/ml), streptomycin (100 μg/ml), and puromycin (10 μg/mL) at 37 °C in a humid atmosphere of 5 % CO_2 and 95 % air. For calcium assay, cells were harvested and dispensed into 96-well black wall clear bottom plates at a density of 40,000 cells per a well. After 18 hrs of incubation, cells were treated with Calcium-5 assay reagent, which is prepared by manufacture's instruction (Molecular Devices Corporation, California). During fluorescence-based FDSS6000 assay, mGluR5 was activated using a high concentration of L-glutamate (10 μM) in HBSS, and various concentrations of synthesized compounds were treated to cells 75 seconds before mGluR5 activation. All data were collected and analyzed using FDSS6000 and related software (Hamamatsu, Japan).

(14) A second series of compounds **6** were tested in antagonist mode with the GRM5 Calcium Biosensor Assay serviced by DicoveRx Corporation.

(15) For detailed experimental procedures for hERG, microsmal stability, and CYP inhibition assays, see: Kim, Y.; Kim, J.; Kim, S.; Ki, Y.; Seo, S. H.; Tae, J.; Ko, M. K.; Jang, H.-S.; Lim, E. J.; Song, C.; Cho, Y. J.; Koh, H.-Y.; Chong, Y.; Choo, I. H.; Keum, G.; Min, S.-J.; Choo, H. *Eur. J. Med. Chem.* **2014**, *85*, 629-637.

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Graphical Abstract

Synthesis and biological evaluation of picolinamides and thiazole-2-carboxamides as mGluR5 (metabotropic glutamate receptor 5) antagonists

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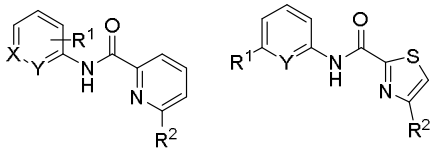

R^1 = H, F, Cl, Br, Me, OMe, CN,
X, Y = CH or N
R^2 = H, OMe, Me, F, Cl, Br, CN