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Cyclohexenyl- and dehydropiperidinyl-alkynyl pyridines as potent metabotropic glutamate subtype 5 (mGlu5) receptor antagonists

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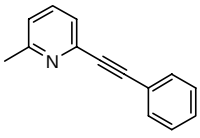
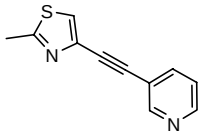
Abstract—Structure–activity relationship studies leading to the discovery of novel mGlu5 receptor antagonists are described. These compounds show high in vitro potency, have good in vivo receptor occupancy, and a reasonable intravenous pharmacokinetic profile.

Metabotropic glutamate (mGlu) receptors are a family of G-protein coupled receptors in the mammalian nervous system that are activated by L-glutamate.[1,2] Eight mGlu receptor subtypes have been identified to date and these are organized into 3 groups (Groups I, II, and III) based on sequence homology. Group I mGlu receptors (mGlu1 and mGlu5) are localized primarily in the postsynaptic region, but are also widely distributed in the hippocampus, thalamic nuclei, and spinal cord. Stimulation of mGlu1 and mGlu5 receptors leads to phosphoinositide (PI) hydrolysis and elevation of intracellular Ca^{2+} levels ($[Ca^{2+}]_i$) via G-protein coupling to phospholipase C.[3,4] Excessive activation of mGlu5 receptors has been implicated in a number of CNS disorders including pain,[5] anxiety and depression,[6–12] drug dependence[13], and mental retardation.[14] It is for these reasons that efforts have been directed toward the development of potent and selective mGlu5 receptor antagonists.



1 MPEP



2 MTEP

The discovery of a number of potent and highly selective ligands for the mGlu5 receptor, such as 2-methyl-6-(phenylethynyl)-pyridine (MPEP, **1**)[15] and 3-[(2-methyl-1,3-thiazol-4-yl)-ethynyl] pyridine (MTEP, **2**)[16,17], has been recently reported. Our colleagues have previously reported SAR studies on the pyridyl ring of MPEP,[18] on replacing the alkyne moiety with various heterocycles,[19] and on the pyridyl ring of MTEP.[20] In this communication, SAR studies focused on replacing the aryl group appended to the pyridine–alkyne motif are described. The direction was to explore novel saturated moieties, which were not previously investigated. These efforts led to the discovery of new derivatives of **1** that display good in vitro potency, receptor occupancy, and pharmacokinetics in rat. The functional

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potencies of these compounds in vitro were assessed using an automated assay employing Ltk cells that stably express human recombinant mGlu5 receptors (Table 1). This cell-based assay measures changes in cytosolic Ca^{2+} concentrations ($[Ca^{2+}]_i$) by fluorescence detection using the Ca^{2+}-sensitive dye fura-2.[21–23] Binding to native mGlu5 receptors in vitro was determined by measuring the displacement by test compounds of [3H]-3-methoxy-5-(pyridin-2-ylethynyl)pyridine from rat cortical membranes.[17] Research from this laboratory has demonstrated that most alkyne derivatives, such as **1** and **2**, are inhibitors of CYP1A2;[24] therefore, all compounds were assayed for potency as CYP1A2 inhibitors using recombinant CYP450 under Gentest-based protocols.[25] Furthermore, the hydrophobic nature of many of these compounds could limit their solubility in CSF and very likely reduce in vivo efficacy, so the log *D* was measured to assist in developing a compound with better physical properties.[26]

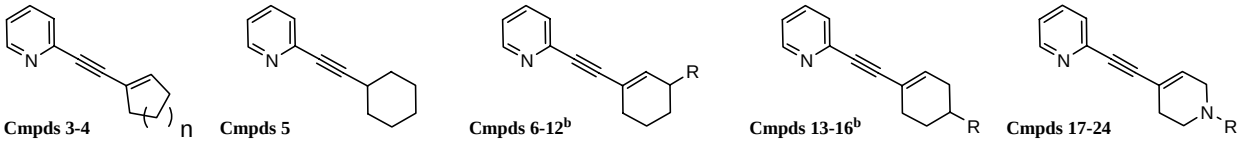
The general scheme for the synthesis of alkyne derivatives **3** and **4** involved the formation of lithium 2-pyridylacetylide and subsequent trapping of this anion with a carbonyl compound. The corresponding tertiary alcohol was then dehydrated with phosphorus oxychloride. Compound **5** was readily prepared using a Sonogashira reaction between 2-bromopyridine and ethynylcyclohexane to furnish the product directly (Scheme 1).

Compounds **6–12** were synthesized by the addition of lithium 2-pyridylacetylide to 3-ethoxy cyclohexenone, which gave the corresponding α,β-unsaturated ketone after work-up. Reduction with sodium borohydride in methanol gave the corresponding allylic alcohol, which could be derivatized using Mitsunobu conditions (Scheme 2).

The synthesis of compounds **13–16** also utilized lithium 2-pyridylacetylide which was added to 1,4-cyclohexanedione monoethylene ketal to afford the corresponding tertiary alcohol. The ketal was then removed and the ketone was subjected to reductive amination conditions using sodium triacetoxyborohydride. Subsequent treatment with phosphorus oxychloride furnished the desired compounds (Scheme 3).

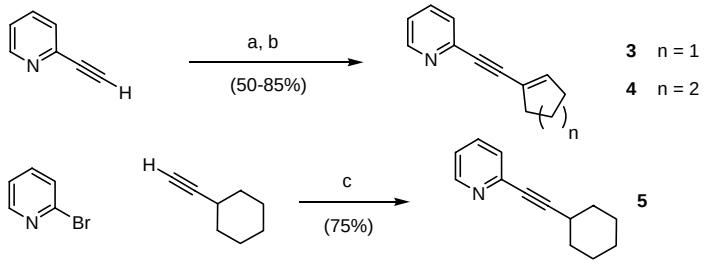
For compounds **17–24**, lithium 2-pyridylacetylide was added to *N*-(*t*-butoxycarbonyl)-4-piperidone and then dehydrated with phosphorus oxychloride. Deprotection with TFA gave the free amine, which was derivatized with the corresponding carbonyl or sulfonyl chloride (Scheme 4).

Table 1. In vitro potency data for mGlu5 receptor antagonists[a]

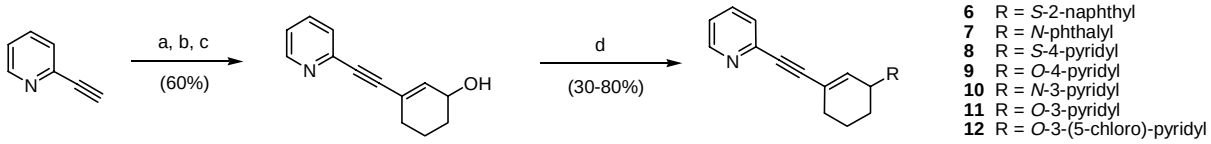


Compound	R	hmGlu5 Ca^{2+} Flux IC_{50} (nM)[c]	mGlu5 Ki (nM)[d]	CYP1A2 IC_{50} (nM)	log *D*[e]
3	*n* = 1	3.1 (1.0, 4)	10	2184	3.5
4	*n* = 2	2.4 (0.7, 2)	0.65	676	3.8
5	—	106 (33, 3)	163	2779	3.9
6	*S*-2-naphthyl	213 (160, 5)	75	5308	Fluorescent
7	*N*-phthalyl	27 (4.0, 2)	5.8	5249	3.9
8	*S*-4-pyridyl	22 (1.0, 4)	43	505	4.0
9	*O*-4-pyridyl	16 (14, 5)	21	1021	3.5
10	*N*-3-pyridyl	8.6 (0.4, 3)	7.3	3418	3.3
11	*O*-3-pyridyl	2.2 (1.0, 2)	1.8	1038	3.4
12	*O*-3-(5-chloro)-pyridyl	0.90 (0.3, 4)	1.1	608	3.9
13	*N*-2-naphthyl	306 (68, 2)	304	>20000	5.1
14	*N*-c-pentyl	987 (193, 2)	7200	>20000	2.1
15	*N*-morpholino	164 (37, 5)	683	>20000	2.8
16	*N*-3-pyridyl	12.6 (3.0, 6)	35	>20000	3.2
17	*t*-Boc	2.6 (0.9, 4)	20	>20000	—
18	H	580 (221; 3)	3400	>20000	1.6
19	Phenoxy carbonyl	35 (13, 2)	171	>20000	3.7
20	cBz	12 (12, 3)	0.83	>20000	—
21	Benzylsulfonyl	58 (12, 2)	389	>20000	3.4
22	*m*-tosyl	8.2 (2, 2)	13	>20000	4.6
23	*p*-tosyl	7.9 (10; 4)	12	>20000	3.3
24	*p*-brosyl	2.2 (0.4, 3)	3.1	>20000	3.7

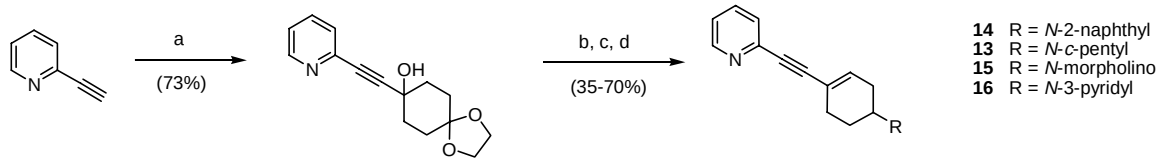
[a] Data are presented as the geometric mean followed in parentheses by the standard deviation and the number of replicates.
[b] Compounds were tested as racemates.
[c] Ca^{2+} flux assay using glutamate (10 μM) as agonist.[18–20]
[d] Displacement by test compounds of [3H]-3-methoxy-5-(pyridin-2-ylethynyl)pyridine from rat cortical membranes.[16]
[e] See Ref. 16.



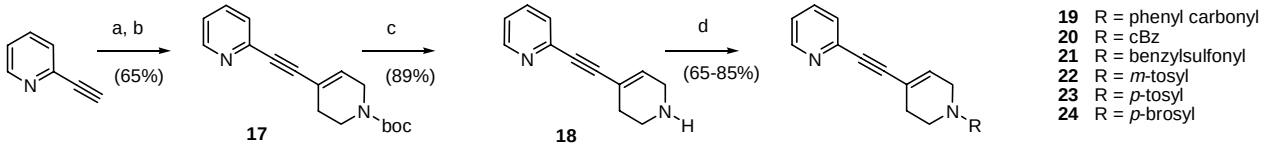
Scheme 1. Reagents and conditions: (a) *n*-BuLi/THF, −78 °C, then cycloalkanone. (b) $POCl_3$, pyridine, 70 °C. (c) $Pd(PPh_3)_4$, CuI, pyrrolidine, 80 °C.



Scheme 2. Reagents and conditions: (a) *n*-BuLi/THF, −78 °C, then cycloalkanone. (b) Pyridine, $POCl_3$, 70 °C. (c) $NaBH_4$, MeOH, rt. (d) Diethylazidodicarboxylate, PPh_3, THF, phenol, thiol, or phthalimide.



Scheme 3. Reagents and conditions: (a) *n*-BuLi/THF, −78 °C, then cycloalkanone. (b) THF, 10% H_2SO_4 (aq), 70 °C. (c) $NaBH_3CN$, CH_2Cl_2, AcOH. (d) $POCl_3$, pyridine, 70 °C.



Scheme 4. Reagents and conditions: (a) *n*-BuLi/THF, −78 °C, then cycloalkanone. (b) $POCl_3$, pyridine, 70 °C. (c) TFA, CH_2Cl_2. (d) Triethylamine, CH_2Cl_2, acid chloride.

In replacing the phenyl ring of MPEP, these efforts initially gave rise to compounds **3** and **4** that contained cycloalkenes. Interestingly, the fully saturated cyclohexane **5** resulted in a 50-fold loss in potency, suggesting the importance of the double bond for potency. Incorporating a large non-polar group, such as the sulfur-linked 2-naphthyl group in compound **6**, resulted in a 100-fold loss in potency. The direction turned towards smaller and more polar groups to improve the log *D* and potency of these compounds. By directly linking a phthalyl group, compound **7** was found to be 10-fold less potent. Further reduction in size, but maintaining the presence of basic moieties to decrease the log *D* gave rise to **8** and **9** which were slightly more potent. Changing the 4-pyridyl to a 3-pyridyl gave rise to **10** and **11**, which were equipotent with the original hits. The 5-chloro-3-pyridyl analog (**12**) was found to be 2-fold more potent in both the functional assay, as well as the binding assay. Unfortunately, with increasing potency as mGlu5 inhibitors, these compounds were also found to be increasingly potent as inhibitors of cytochrome P450 1A2 (CYP1A2).

Concurrently, substitution at the homo-allylic position was investigated (compounds **13-16**). Similar to substitution at the allylic position (compounds **6-12**), a large naphthyl group (**13**) was found to be detrimental to potency. Smaller substituents in **14** and **15** had improved potency and even the *N*-3-pyridyl **16** was found to be 5-fold less potent. Although these compounds were not quite as potent as their allylic counterparts, they were found to be completely non-inhibitory toward CYP1A2, which led to further investigation at this position.

For additional studies at the homo-allylic position, we chose to replace the carbon with a more polar atom, such as nitrogen. Compound **17** was surprisingly equipotent with our original hit and not inhibitory toward CYP1A2. Removal of the Boc-group gave secondary amine (**18**), which had a much lower log *D*.

Table 2. Selected rat pharmacokinetic data[a]

Compound	R	$T_{1/2}$ (h)	Cl (mL/min/kg)	V_d (L/kg)
4	*n* = 2	3.9	45	9.1
9	*O*-4-pyridyl	0.8	41	1.2
11	*O*-3-pyridyl	0.3	94	2.2
12	*O*-(5-chloro)-3-pyridyl	4.8	32	7.2
16	*N*-3-pyridyl	0.5	34	1.4
23	*N*-*p*-tosyl	1.5	29	14.7
24	*N*-*p*-brosyl	1.1	64	3.98

[a] i.v. dosing at 2 mg/kg.

Table 3. Selected rat receptor occupancy data

Compound	R	Occupancy (%)
4	*n* = 2	94
12	*O*-(5-chloro)-3-pyridyl	97
23	*N*-*p*-tosyl	25
24	*N*-*p*-brosyl	57

Unfortunately, compound **18** lost a significant amount of potency, suggesting that positively charged atoms are not well-tolerated in this SAR. In an effort to make this nitrogen less basic, derivatization as a phenoxycarbamate (**19**) and the benzyloxycarbamate (**20**) was found to be less potent than the *t*-butoxycarbamate (**17**). Derivatization as sulfonamides proved to be more fruitful. The corresponding benzylsulfonamide **21** was almost equipotent with carbamate **17**. More rigid sulfonamides, such as **22**, **23**, and **24**, had increased potency, with **24** being equipotent with the orginal hit **4**. It was gratifying to find that these sulfonamides were not inhibitors of CYP1A2.

Ongoing pharmacokinetic evaluation revealed that some compounds had reasonable profiles (Table 2). Compounds **9**, **11** and **16** were abandoned due to poor half-lives, as well as CYP1A2 issues. Compounds **4** and **12** had better half-lives, but were not pursued further due to CYP1A2 concerns. Compounds **23** and **24** had somewhat shorter half-lives, but warranted further investigation. Compound **24** was dosed orally at 10 mg/kg to reveal a bioavailability of 10% and C_{max} of 0.02 μM (which is 10-fold the IC_{50}).

Concurrently with intravenous pharmacokinetic analysis, compounds were also evaluated for in vivo receptor occupancy (Table 3). The test compound was administered intraperitoneally at 10 mg/kg and at 59 min, while [3H]-3-methoxy-5-(pyridin-2-ylethynyl)pyridine was injected via the tail vein. One minute later, the rats were euthanized and binding was measured from the brain homogenate.[27] Compounds **4** and **12** were found to be highly occupant at 10 mg/kg (IP dosing). Unfortunately, compounds **23** and **24**, which were not CYP1A2 inhibitory, were less potent in the occupancy assay.

Replacing the aromatic or hetero-aromatic moieties of MPEP (**1**) or MTEP (**2**) with semi-saturated rings allowed us to identify several novel compounds that are highly potent antagonists of mGlu5 receptors. These compounds tend to have moderate log *D*. Furthermore, substitution at the homo-allylic position allowed us to generate potent compounds, such as **23** and **24**, which were non-inhibitory toward CYP1A2. In vivo experiments revealed that these compounds have moderate half-lives and moreover, a lower receptor occupancy in the rat brain model than their CYP-inhibiting counterparts. It is for this reason that this series of compounds was excluded from further development.

Acknowledgments

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