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Rational design of 7-arylquinolines as non-competitive metabotropic glutamate receptor subtype 5 antagonists

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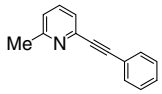
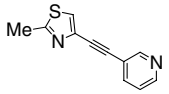
Abstract—Rational replacement of the alkyne linker of mGluR5 antagonist MPEP gave 7-arylquinolines. SAR optimization gave an orally active compound with high affinity for the MPEP binding site.

A recurring structural motif in published reports of mGluR5 non-competitive antagonists[1–6] is the acetylene linker present in the known MPEP (2-methyl-6-(phenylethynyl)-pyridine, **1**)[7] and MTEP (3-[2-(2-methyl-4-thiazolyl)ethynyl]pyridine, **2**).[8] A major concern with acetylenes in potential drugs is the possibility of chemical or metabolic reactivity. Terminal acetylenes are well known to be mechanism-based CYP-inactivators[9,10] and there is an increasing body of information that suggests internal acetylenes can be activated by CYPs[11–13] or even undergo uncatalyzed addition of glutathione.[14,15] Indeed, we found that incubation of MPEP with triply-labeled glutathione[16] gave compounds with molecular weights and fragmentations consistent with both activated and unactivated addition of GSH to the alkyne.[17] These events are potential sources of hepatic or idiosyncratic toxicity.



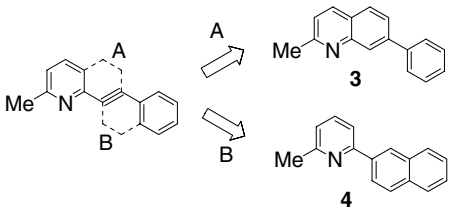
MPEP (**1**)



MTEP (**2**)

In an attempt to remove the acetylene as a potential metabolic liability, we sought to rationally design analogs without it. One approach to this end, that maintains an approximate relative geometry of the two aryl rings present in MPEP and MTEP, was to introduce another ring from either the pyridine or phenyl of MPEP onto the acetylene (Scheme 1).[18]

Both alternatives were systematically investigated. Analog **3**, derived by connecting in mode A, could be accessed by Suzuki coupling of commercially available 7-chloroquinaldine and phenylboronic acid under Büchwald conditions,[19,20] while analog **4**, derived by connecting in mode B, was readily accessible by Suzuki coupling of 2-bromo-6-methylpyridine and naphthalene-2-boronic acid. Conceptual annelation of the alkyne with the phenyl ring produced **4** that was found to be functionally inactive at 10 μM in blocking quisqualate-mediated



Scheme 1. Potential removal of the MPEP acetylene by introduction of a phenyl ring.

Keywords: mGluR5; Antagonist; MPEP.
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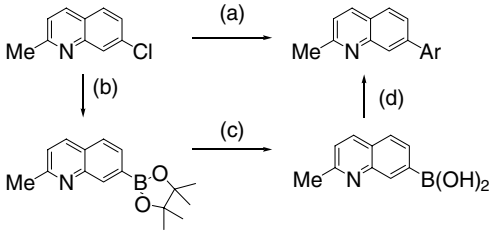
calcium mobilization using FLIPR,[21] whereas annelation of the pyridine onto the alkyne gave **3**, that had an IC_{50} of 9.0 μM.

It is known that the activity of MPEP can be modulated by substitution on the phenyl ring. In particular, some *meta*-substituted aryls have shown improved potency in the MPEP series. For example, a *meta* methoxy group gives M-MPEP,[22] which is 3- to 6-fold more potent than MPEP,[23] and *meta*-cyano substitution gives a 7-fold more potent compound.[5] Since 7-phenylquinoline **3** had an approximately 1000-fold decrease in potency over MPEP, we investigated this type of readily accessible variation by way of substituted phenyl boronic acids.

In the case of 7-aryl quinolines, *meta*-substitution resulted in modulation in potency in the desired direction (Table 1). For example, the compound with a *meta*-methoxy group (**8**) had a 111-fold improvement in potency. Surprisingly, a *meta*-cyano substituent gave greater than 1000-fold improvement to give a 7.7 nM inhibitor (compound **5**). Exploration of substitution at the *ortho*- and *para*-positions showed that the methoxy and cyano groups did not have the same enhancing effects in these positions (compounds **19**–**22**).

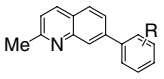
Several other changes gave enhanced activity over the parent phenyl quinoline **3**. For example, 3-aza analog **7** (a potential isostere of cyanophenylquinoline **5**) was 17 times more potent and 3-fluoro analog **9** was 5-fold more potent. One interesting change is introduction of a *meta*-cyanomethyl substituent to give compound **6**, which exhibited a 20-fold improvement in potency (IC_{50} = 430 nM), since this bears a similarity to a previously reported series of 4-(cyanomethyl)phenylbenzoxazoles.[24]



Scheme 2. Reagents and conditions: (a) $ArB(OH)_2$, $Pd(OAc)_2$, *o*-(dicyclohexylphosphino)biphenyl, K_3PO_4, toluene, 100 °C; (b) $Pd(OAc)_2$, KOAc, bis(pinacolato)diboron, bis(diisopropylphenyl)imidazolium chloride, THF, reflux, overnight; (c) THF, $NaIO_4$, aq. HCl; (d) ArX (X = Cl, Br, or OTf), and either $Pd(OAc)_2$, *o*-(dicyclohexylphosphino)biphenyl, K_3PO_4, toluene, 100 °C; or Pd(dppf), aq. K_2CO_3, DME, 60 °C.

Mindful of the significant enhancing effect of a *meta*-cyano and the mild enhancing effects of some other *meta* substitutions, we wondered whether combinations of substituents would lead to additive effects. Although the Suzuki reaction noted earlier provided great flexibly, some of the disubstituted phenylboronic acids required to examine this SAR were not readily available. In these cases, the sense of the Suzuki coupling could be reversed (Scheme 2) by conversion of 7-chloroquinaldine to the 7-boronic acid. This was accomplished by treatment with bis(pinacolato)diboron, palladium acetate and bis(diisopropylphenyl)imidazolium chloride[25] and sub-

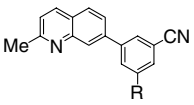
Table 1. FLIPR activity for monosubstituted 7-arylquinolines



Compound	R	FLIPR IC_{50}[a] (nM)	SEM[b]
MPEP	—	0.2	
3	H	9000	1200
5	3-CN	7.7	5.3
6	3-CH_2CN	430	350
7	3-aza	510	400
8	3-OMe	860	110
9	3-F	1800	200
10	3-Me	3400	400
11	3-Ac	4760	700
12	3-CH_2OMe	5800	900
13	3-CH_2OH	8700	2100
14	3-Cl	14000	500
15	3-OH	19000	4000
16	3-OCF_3	IA	—
17	3-CF_3	IA	—
18	3-$CONH_2$	IA	—
19	2-CN	9800	3100
20	2-OMe	4200	1700
21	4-OMe	16000	300
22	4-CN	IA	—

[a] Compounds were measured for potency to inhibit quisqualate stimulated calcium mobilization using FLIPR. The data shown were obtained using CHO cells stably expressing rat mGlu5 receptors. Values are geometric means of two or more experiments (IA, inactive; IC_{50} > 10 μM).
[b] SEM is the standard error of the mean of the measurements.

Table 2. FLIPR activity for 3′-cyano 5′-substituted 7-arylquinolines



Compound	R	FLIPR IC_{50}[a] (nM)	SEM[b]
6	H	7.7	5.3
23	5-F	0.8	0.1
24	5-Cl	1.4	0.5
25	5-Me	1.6	0.4
26	5-CN	2.0	0.3
27	5-CH_2OMe	2.0	0.4
28	5-OMe	2.4	0.6
29	5-Br	13	0.2
30	5-OEt	17	2
31	5-aza	23	6
32	5-SEt	72	22
33	5-OCF_3	75	18
34	5-$O(CH_2)_2OMe$	82	38
35	5-O^{i}Pr	310	70
36	5-OH	360	70
37	5-SO_2Et	1090	100
38	5-O^{i}Bu	12000	6000

[a] Values are geometric means of two or more experiments (IA, inactive; IC_{50} > 10 μM).
[b] SEM is the standard error of the mean of the measurements.

sequent cleavage of the pinacolato boronate with periodate.[26] The 3,5-disubstituted benzonitrile precursors were typically readily available as chlorides, bromides or triflates and could be coupled under Büchwald or conventional Suzuki conditions.

Many of these substitutions gave compounds with enhanced potency over parent compound **5** (Table 2). In general, small lipophilic substituents caused enhancements in potency (e.g., F, Cl, Me, OMe). Larger substituents gave modulated reductions in potency. For example, a bromo substituent gave a 2-fold reduction, whereas the series –OMe, –OEt, –O^{i}Pr, –O^{i}Bu gave stepwise reductions in potency to 12 μM. The small, polar cyano substituent caused an enhancement in potency, but phenol, a hydrogen-bond donor, caused a significant loss.

Given the high functional potency of some of the compounds, we were interested to see if this would translate into in vivo efficacy. We tested the most potent compound (**23**) for anxiolytic activity in the Vogel assay.[27,28] Notably, at a dose of 10 mg/kg (po), compound **23** showed a statistically significant reversal of punished drinking behavior compared to concurrent vehicle treatment (Fig. 1). The magnitude of the response was similar to that of MPEP at the same dose.

One remaining question was whether these 7-aryl quinolines, which we envisaged as arising from an isosteric replacement of a linker in MPEP, were in fact binding to the same site as MPEP itself. A pharmacophoric overlay of 3′-cyano MPEP and 7-(3-cyanophenyl)-2-methylquinoline (**5**) (Fig. 2) strongly suggested they should, since there is a remarkable overlap between the MPEP pyridine and phenyl rings and the corresponding rings of the 7-arylquinoline. The overlay additionally shows that the 7-arylquinoline is able to mimic torsional changes in the acetylene bond of MPEP, and this allows for an almost identical trajectory of the cyano groups.

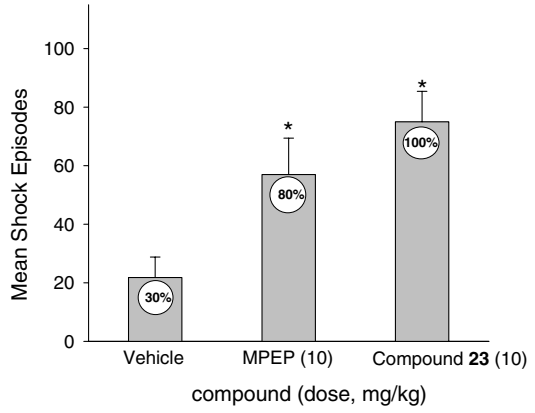


Figure 1. Comparison of MPEP and compound **23** in the Vogel assay. Bars show means ± SEM, $n = 10$ per group, dosing was 1 hour pretreatment (po). $^*p < 0.05$ Mann–Whitney Rank Sum test versus vehicle control. The values on the bars show the percentage of subjects receiving >20 shock episodes. This is an indicator of the reliability of the behavioral response; in general, a robust anxiolytic-like response is represented by 60–100% of the rats responding with greater than 20 shock episodes.

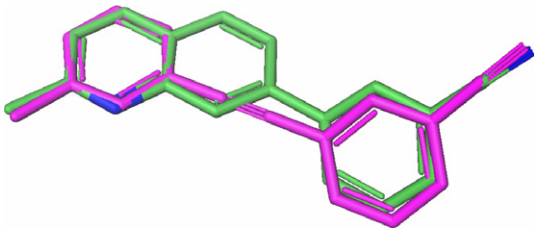
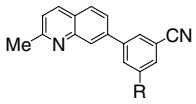


Figure 2. Overlay of 3′-cyano MPEP (magenta) and compound **5** (green).

Table 3. Comparison of functional potency and binding affinity for select compounds



Compound	R	FLIPR IC_{50}[a] (nM)	[^{3}H]MPEP binding K_i (nM)[b]
MPEP		0.2	5.7
23	5-F	0.8	22
5	H	7.7	72

[a] Values from Tables 1 and 2.
[b] Values are means of two or more experiments.

In a binding assay with radiolabeled MPEP[29] compounds **5** and **23** completely inhibited the binding of [^{3}H]MPEP to rat brain membrane preparations (Table 3). This confirms that compounds **5** and **23** do bind to the same site as MPEP.

Overall, we have shown that the potentially toxicophoric acetylene of MPEP can be replaced by ring fusion to give 7-arylquinolines. Additional substitution on the pendant phenyl is required for high potency. Compound **23** is functionally active, potent, has been shown to bind to the same site as MPEP, and is active in an in vivo model of anxiety.

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