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Functionalization at position 3 of the phenyl ring of the potent mGluR5 noncompetitive antagonists MPEP

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Abstract—We described the synthesis and biological evaluation of MPEP analogs functionalized at the position 3 of the phenyl ring. The results point out the limitation in the choice of a functional group at this position; the only substituents leading to retention of activity are NO_2 (IC_{50} = 13 nM) and CN (IC_{50} = 8 nM).

(−)-Cocaine (CAS number [50-36-2]) is a natural alkaloid produced by *Erythroxylum Coca*. Early medicinal application of cocaine was mainly restricted in its use as local anesthetic for minor surgery and was rapidly replaced by simpler, cheaper, more potent synthetic compounds. However, it found new notoriety as being the most widely used psychostimulant drug worldwide. Cocaine abuse continues to be a major public health problem, and despite increased scientific investigation, the basic biological processes underlying this disorder are still not well understood, limiting the availability of pharmacological adjuncts for cocaine treatment. The role for glutamatergic neurotransmission in the behavioral and reinforcing effects of cocaine is becoming increasingly evident,[1,2] especially for the type 5 metabotropic receptor (mGluR5). Chiamulera et al.[3] demonstrated that genetic deletion of mGluR5 in mice resulted in reduction of intravenous cocaine self administration. These investigators also found that cocaine self administration was reduced following treatment with the selective mGluR5 antagonist MPEP (**1**). In our continuing effort to better understand the biological process of cocaine reward and craving, we initiated a program of mGluR5 antagonists discovery and focused our effort on the systematic exploration of SAR around the known prototypical noncompetitive mGluR5 antagonists MPEP, in which the introduction of the methoxy moiety as in M-MPEP (**2**) significantly increased the activity. We report in this paper the synthesis and biological evaluation of MPEP and M-MPEP analogs functionalized at the 3 position of the phenyl ring (Fig. 1). Since previous studies indicated the 3-position to be preferred, we selected a set of functional groups at this position that would encompass a broad range of physicochemical properties in a controlled environment.

The synthesis of intermediate 3-hydroxy-MPEP (**3**) was achieved in two steps from 2-bromo-6-methylpyridine (Scheme 1). The key step of this synthesis was modified Sonogashira cross coupling between the silyl acetylene precursor **4** and 3-iodophenol, which led to the desired compound **3**. In contrast, 3-bromophenol under the same conditions led to degradation of the starting material without formation of **3**.

Esters **5**–**10** were prepared by reaction of **3** with the appropriate acyl chloride in THF using Et_3N as scavenger (Scheme 2). Esters **11** and **12** were obtained in good yield by coupling of **3** with the corresponding carboxylic acid using DCC as activating agent. Sulfonic esters **13**

Keywords: Metabotropic; mGluR5; MPEP; Antagonist.
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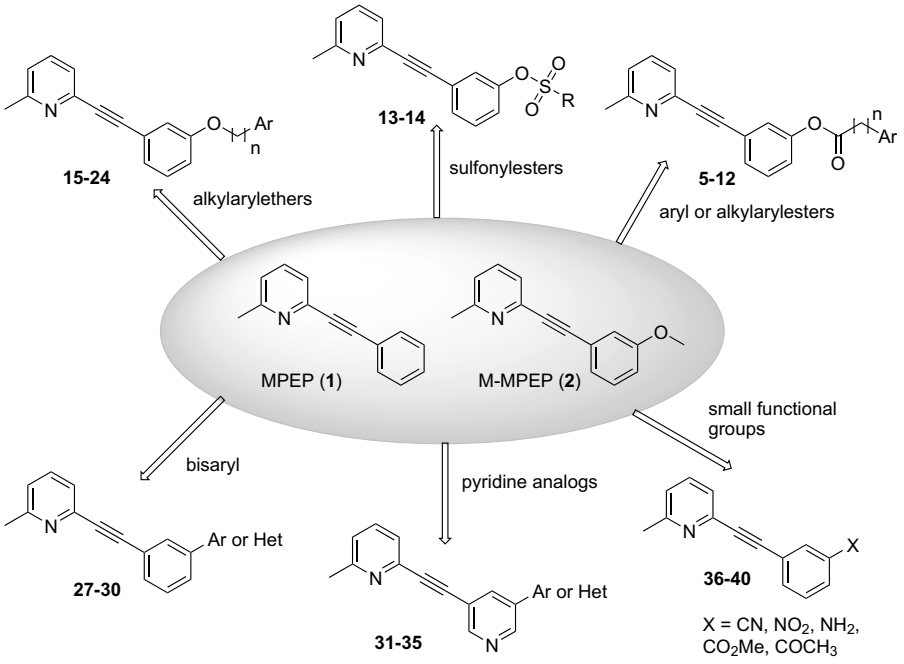
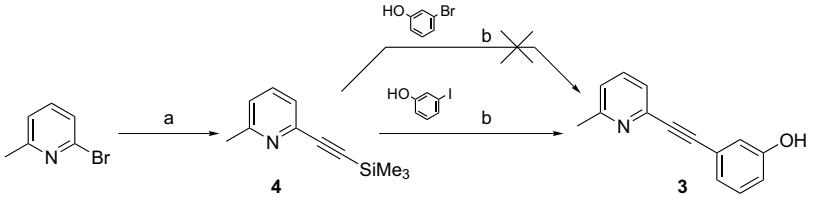
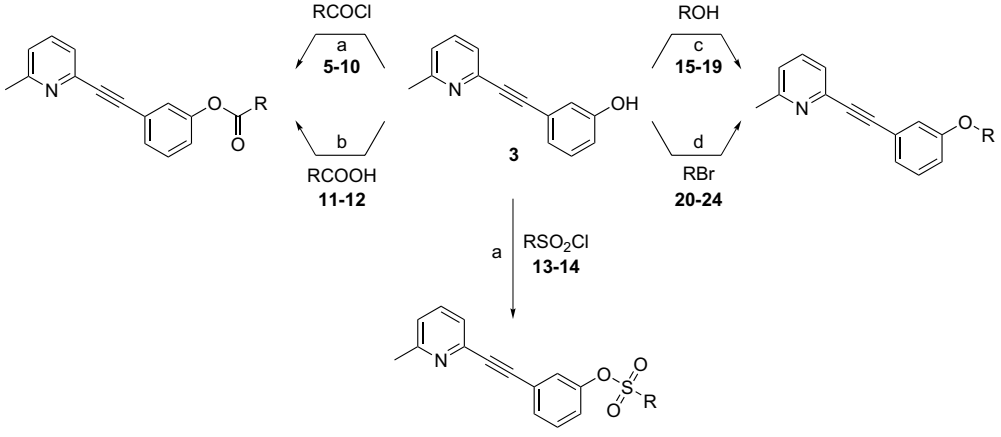


Figure 1.



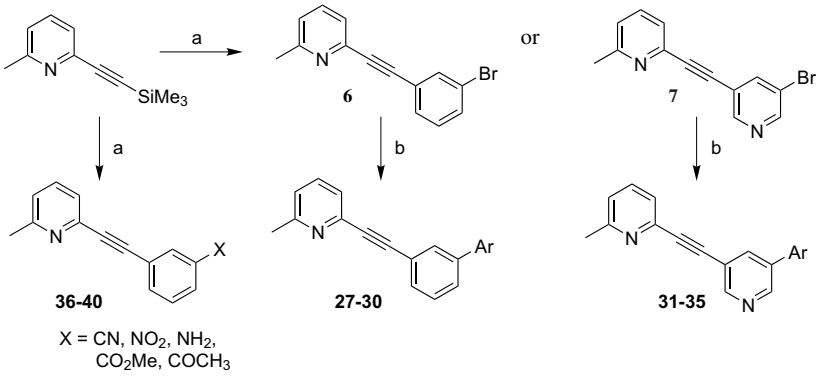
Scheme 1. Reagents and conditions: (a) $Me_3SiC{\equiv}CH$, CuI, $PdCl_2(PPh_3)_2$, Et_3N, rt, 16 h (71%); (b) TBAF, CuI, $PdCl_2(PPh_3)_2$, Et_3N, DMF, 70 °C, 16 h (67%).



Scheme 2. Reagents and conditions: (a) Et_3N, THF, rt, 3–16 h (70–97%); (b) DCC, DMAP, THF, rt, 16 h (89–93%); (c) PPh_3, DEAD, THF, rt, 3 h (73–91%); (d) NaH, THF or DMF, rt, 16 h (65–97%).

and **14** were synthesized by reaction of **3** with mesyl chloride or tosyl chloride in THF in the presence of Et_3N. We used two different routes to the ether derivatives of MPEP. Compounds **15**–**19** were obtained by Mitsunobu reaction between phenol **3** and the desired alcohol in THF. Compounds **20**–**24** were obtained by nucleophilic substitution of the alkyl halide by the anion of **3** generated with NaH (Scheme 2).

The synthesis of compounds **27**–**35** was achieved in satisfactory yield (46–90%) using a simple Stille reaction between the appropriate aryl or heteroaryltrialkyl

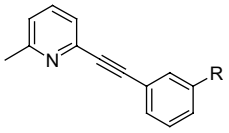


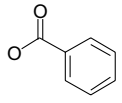
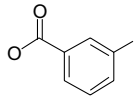
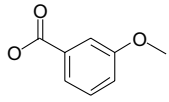
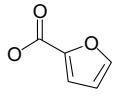
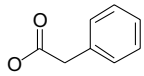
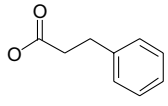
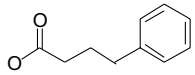
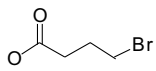
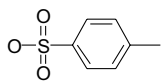
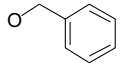
Scheme 3. Reagents and conditions: (a) aryl or heteroaryl bromide, CuI, $PdCl_2$ $(PPh_3)_2$, Et_3N, Bu_4NF, DMF, 70 °C; (b) aryltrialkylstanane, $Pd(PPh_3)_4$, toluene, reflux.

stannane and the bromo intermediate **6** or **7**. Those keys intermediates as well as compounds **36**–**40** were easily obtained (40–69%) using a modified Sonogashira reaction involving the in situ desilylation of 2-methyl-6-trimethylsilylethynylpyridine using tetrabutylammonium fluoride and subsequent palladium cross coupling with the appropriate aryl or heteroaryl bromide as shown in Scheme 3. All compounds were tested for antagonism at mGluR5, a receptors stably expressed in Chinese hamster ovary (CHO) cells.[4] Cultured in 96-well plates, the receptor-expressing cells were incubated with 0.75 μCi myo-[^{3}H]inositol to label the cell membrane phosphoinositides. Incubations with test compounds were carried out for 45 min at 37 °C in Locke's buffer (156 mM NaCl, 5.6 mM KCl, 3.6 mM $NaHCO_3$, 1 mM $MgCl_2$, 1.3 mM $CaCl_2$, 5.6 mM glucose, and 20 mM HEPES, pH 7.4) containing 20 mM LiCl, which blocks the degradation of inositol phosphates (IPs). The reaction was terminated by aspiration and addition of 0.1 M HCl. The extracted IPs were separated by anion exchange chromatography and measured by a liquid scintillation counting (LKB, Uppsala, Sweden) as previously described.[5] Inhibition of the mGluR5 response by the test compounds was evaluated by performing duplicate concentration–response curves using seven concentrations in presence of 10 μM glutamate. Data from 4 to 6 separate experiments were normalized to the percent of maximal glutamate response. IC_{50} values of antagonists were determined by fitting the normalized data to the logistic equation by nonlinear regression using SigmaPlot (SPSS Science, Chicago, IL) and are summarized in Tables 1 and 2. For selected compounds, binding to mGluR5 receptors in vitro was determined by measuring the displacement by test compounds of [^{3}H]M-MPEP from rat whole brain as previously described[6,7] and are summarized in Table 2.

Compounds **5**–**38** proved to be less active than MPEP or M-MPEP. Functionalization of the 3-hydroxy moiety of M-MPEP (carboxylic ester, sulfonic ester, and ether) did not seem to influence the activity. Similarly, the carboxylic compounds **5**, **7**, and **11** showed the same range of activity as the corresponding ester **20**–**22** and the same observation can be made for compounds **10**, **12** versus **17**, **18**. The introduction of an aryl moiety spaced by a linker (**9**, **10**, **12**, **15**–**18**, and **20**–**22**) was envisaged to reach a new

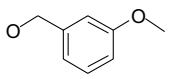
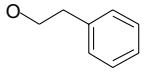
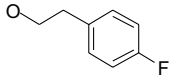
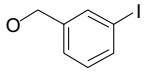
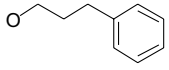
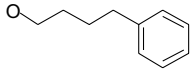
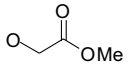
Table 1. mGluR5 IC_{50} values of selected compounds using IP hydrolysis assay (triplicate determinations)[a]



Compound	R	Yield %[b]	IC_{50} ± SEM (μM)
5		96	1.50 ± 0.31
11		93	1.10 ± 0.13
7		97	1.72 ± 0.21
8		87	1.01 ± 0.29
9		38	0.74 ± 0.23
10		53	0.89 ± 0.74
12		89	1.17 ± 0.37
6		95	3.35 ± 0.76
13		66	0.18 ± 0.11
14		84	>10
20		97	1.84 ± 0.33

(*continued on next page*)

Table 1 (*continued*)

Compound	R	Yield % [b]	IC_{50} ± SEM (μM)
22		81	1.30 ± 0.22
15		91	1.59 ± 2.31
16		76	2.05 ± 1.97
21		65	1.98 ± 0.36
17		73	1.19 ± 0.60
18		85	1.16 ± 0.68
23		72	2.40 ± 1.51
24		60	0.29 ± 0.03
19		80	0.42 ± 0.02
36	NH_2	40	0.188 ± 0.01
37	CO_2Me	69	0.208 ± 0.05
38	COMe	58	0.146 ± 0.11
39	NO_2	47	0.013 ± 0.002
40	CN	44	0.005 ± 0.001
MPEP	H	—	0.036[8]
M-MPEP	OMe	—	0.008

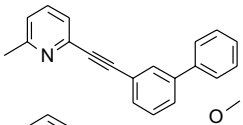
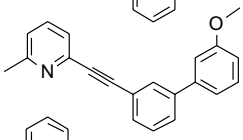
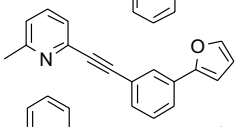
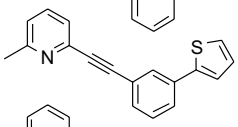
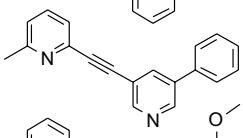
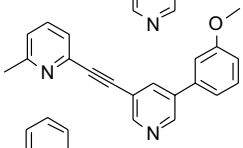
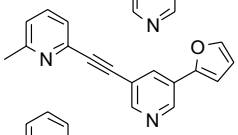
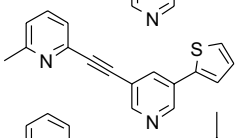
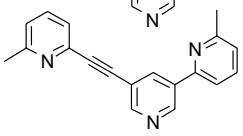
[a] IP hydrolysis assay. All values represent means ± SEM.
[b] Isolated yield.

interaction with the close trans-membrane domain TMI and or TMII[9] of the receptor, but this modification led to inactive compounds. The only functional group leading to activity comparable to the reference compound were the nitro (**39**, IC_{50} = 13 nM) and cyano (**40**, IC_{50} = 8 nM) derivatives. Recently, Roppe et al.[10] reported a series with good to low binding affinity for various 3-aryl substituted of analogs of MTEP. As with the thiazole moiety of MTEP, we found similar results with the pyridine ring of MPEP. Compounds **27**–**30** presented a weak affinity for mGluR5 receptors. In contrast, introduction of a pyridine moiety led to remarkably increased binding, especially for compound **31** (K_i = 1.7 nM), which is 584-fold more active than the carbocyclic parent **27**.

The results in Table 2 also indicate that the rank order of potency (IC_{50}) shown by the particular compounds in the PI hydrolysis assay does not correlate with their binding affinities (K_i). This suggests that while some of the compounds may bind with high affinity to the mGluR5 receptors they may not be able to induce the conformational change necessary to inhibit receptor signal transduction.

In conclusion, we synthesized a large number of new analogs of the potent mGluR5 noncompetitive antagonists

Table 2. mGluR5 IC_{50} values of selected compounds using IP hydrolysis assay (mean of n = 3 determinations) and in vitro binding affinity (n = 2)[a]

Compound	Structure	K_i (nM)	IC_{50} (nM)
27		993	629
28		2360	493
29		36	371
30		147	656
31		1.7	20
32		74	282
33		6.5	205
34		155	271
35		13	257

[a] IP hydrolysis assay and displacement by test compounds of [^{3}H]M-MPEP bound to rat whole brain.[6,7]

MPEP with various functionalities at the 3 position of the phenyl ring. These modification point out the limitation in the choice of a functional group at this position; the only substituents leading to retention of activity are NO_2 (**39**) and CN (**40**). In the bis-aryl series, only the pyridine analogs (**31**–**35**) showed good binding for mGluR5, despite a lack of activity in the functional receptor assay.

Acknowledgments

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