Brief Articles

Synthesis and Pharmacological Evaluation of Phenylethynyl[1,2,4]methyltriazines as Analogues of 3-Methyl-6-(phenylethynyl)pyridine

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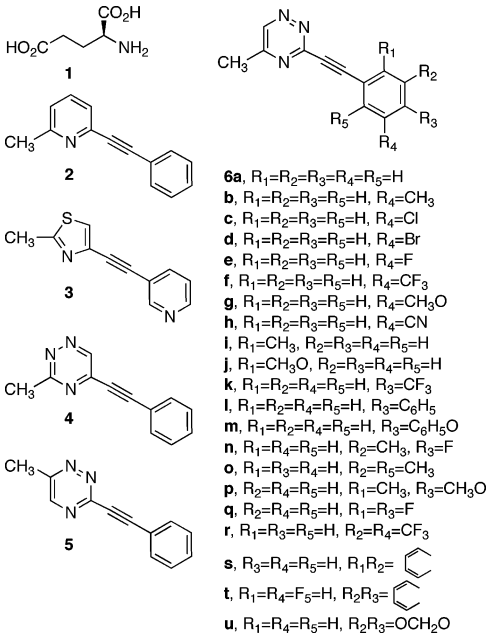
Procedures were developed for the synthesis of 3-methyl-5-phenylethynyl[1,2,4]triazine (**4**), 6-methyl-3-phenylethynyl[1,2,4]triazine (**5**), and 5-methyl-3-phenylethynyl[1,2,4]triazine (**6a**) as analogues of 2-methyl-6-(phenylethynyl)pyridine (**2**). The compounds were evaluated for antagonism of glutamate-mediated mobilization of internal calcium in an mGluR5 in vitro efficacy assay. The most potent of the three analogues was **6a**. Twenty additional analogues of **6a** were synthesized and evaluated for mGluR5 antagonist efficacy. The most potent compounds were 3-(3-methylphenylethynyl)-5-methyl[1,2,4]triazine (**6b**), 5-(3-chlorophenylethynyl)-5-methyl[1,2,4]triazine (**6c**), and 3-(3-bromophenylethynyl)-5-methyl[1,2,4]triazine (**6d**).

Glutamate (**1**), the major excitatory transmitter in the central nervous system, acts on ionotropic and metabotropic glutamate receptors. Several studies have been reported that suggest that metabotropic glutamate 5 receptors (mGluR5)[a] play an important role in regulating the reinforcing actions of drugs of abuse. The selective noncompetitive mGluR5 antagonist MPEP (**2**) was reported to decrease cocaine self-administration in wild-type mice,[1] decrease cocaine self-administration in rats,[2] decrease nicotine self-administration in rats and mice,[3] attenuate cocaine- and morphine-induced condition place preference in mice,[4,5] and decrease ethanol drinking and ethanol-seeking (a relapse model) in rats.[6] Iso et al.[7] showed that the more potent mGluR5 antagonist MTEP (**3**) prevented reinstatement of cocaine self-administration induced by environmental cues associated with cocaine availability.

In this paper we present the synthesis and evaluation of the 3-methyl-5-phenylethynyl[1,2,4]triazine (**4**), 6-methyl-3-phenylethynyl[1,2,4]triazine (**5**), and 5-methyl-3-(substituted phenylethynyl)[1,2,4]triazine (**6a**−**u**) for antagonism of glutamate-mediated mobilization of internal calcium in an mGluR5 in vitro efficacy assay.



Chemistry

The addition of lithium phenylacetylide to **7**[8,9] followed by oxidation with alkaline potassium ferricyanide[10] yielded the desired **4** and *trans*-3-methyl-5-styryl[1,2,4]triazine (**8**), which were separated by chromatography (Scheme 1).

Diazotization of **9**[11] using isoamyl nitrite in diiodomethane afforded 3-iodo-6-methyl[1,2,4]triazine (**10**).[12] Coupling of **10** with phenylacetylene using bis(triphenylphosphine)palladium-(II) chloride and triethylamine in refluxing tetrahydrofuran yielded **5** (Scheme 2).[13,14]

Compounds **6a**−**u** were synthesized as shown in Scheme 3. Condensation of **11**[15] with pyruvic aldehyde gave a mixture of the desired 5-methyl-3-methylthio[1,2,4]triazine (**12**) and 6-methyl-3-methylthio[1,2,4]triazine (**13**), which were separated by fractional recrystallization from a 2-propanol and heptane mixture (9:1). Oxidation of **12** with *m*-chloroperoxybenzoic acid provided the sulfone **14**.[15] Displacement of the methylsulfonyl group with the appropriate lithium substituted phenylacetylide generated from butyllithium in tetrahydrofuran at −78 °C

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[a] Abbreviations: CHO-K1, Chinese hamster ovary; mGluR1, metabotropic glutamate 1 receptor; mGluR5, metabotropic glutamate 5 receptor; MPEP, 3-methyl-6-(phenylethynyl)pyridine; MTEP, (2-methyl-1,3-thiazol-4-yl)ethynlpyrridine.

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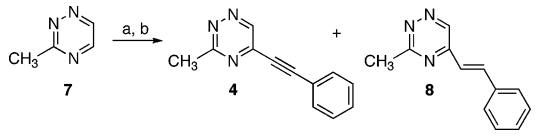
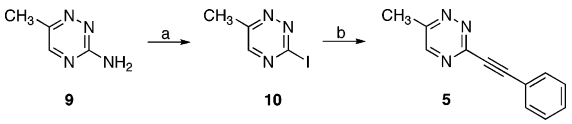
Scheme 1[a]



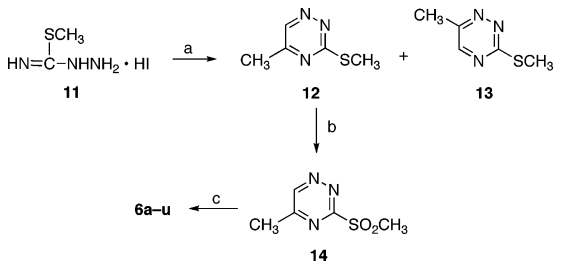
[a] Reagents: (a) *n*-C_4H_9Li, $C_6H_5C{\equiv}CH$, −78 to 0 °C (30 min); (b) K_3FeCN_6, NaOH, H_2O, 24 h.

Scheme 2[a]



[a] Reagents: (a) CH_2I_2, isoamyl nitrite, reflux, 2 h; (b) $C_6H_5C{\equiv}CH$, $Pd[P(C_6H_5)_3]_4$, CuI, Et_3N, THF, reflux 3−4 h.

Scheme 3[a]



[a] Reagents: (a) CH_3COCOH, $NaHCO_3$, 0−25 °C (4 h); (b) *m*-Cl-$C_6H_4CO_3H$, CH_2Cl_2, 0−25 °C (1−2 h); (c) *n*-C_4H_9Li, $C_6H_5C{\equiv}CH$, −78 °C, THF.

Table 1. Inhibition of Human mGluR5-Mediated Intracellular Calcium Mobilization for Phenylethylnyl[1,2,4]methyltriazines[a]

compd	IC_{50} (nM)	$LogD_{(7.4)}$ [b]	compd	IC_{50} (nM)	$LogD_{(7.4)}$ [b]
2	1.5 ± 0.4	3.75	**6j**	IA	2.60
4	IA	2.01	**6k**	IA	3.26
5	IA	2.69	**6l**	510 ± 40	4.45
6a	140 ± 20	2.69	**6m**	80 ± 20	4.68
6b	2.3 ± 0.1	3.15	**6n**	132 ± 20	3.20
6c	4.2 ± 1.0	2.42	**6o**	1890 ± 530	3.61
6d	6.0 ± 1.0	3.46	**6p**	IA	3.06
6e	96 ± 20	2.74	**6q**	IA	2.83
6f	85 ± 20	3.26	**6r**	IA	4.11
6g	312 ± 120	2.60	**6s**	8900 ± 3700	3.92
6h	52 ± 20	2.13	**6t**	IA	3.92
6i	IA	3.15	**6u**	IA	2.55

[a] IA, inactive. [b] Calculated at pH 7.4 with ACD/LogD.

yielded the desired 5-methyl-3-(substituted phenylethynyl)[1,2,4]-triazines (**6a**−**u**).

The LogD for **4**, **5**, and **6a**−**u** along with the standard compound **2** were calculated using ACD/LogD (ACD/Labs, Toronto, Canada), and the results are listed in Table 1. With the exception of compounds **6l**, **6m**, and **6r**−**t**, all compounds possessed lower calculated $LogD_{(7.4)}$ compared with MPEP.

In Vitro Pharmacology

CHO-K1 cells were stably transfected with the human mGluR5, and these cells were used to determine the effects of MPEP and test compounds on glutamate-stimulated mobilization of internal calcium (Table 1). Changes in internal calcium levels were measured using the Calcium 3 dye kit (Molecular Devices Corporation, Sunnyvale, CA) at one-half the recommended dye concentration. The IC_{50} values were determined by measuring the effect of 10 different concentrations of test compound on internal calcium flux caused by 3 μM glutamate (∼EC_{80}). The nature of the inhibition caused by active test compounds was determined by running glutamate concentration response curves in the presence and absence of a single concentration of test compound. Insurmountable antagonism of the effect of glutamate indicated a noncompetitive mode of inhibition. The IC_{50} values were calculated using Prism (GraphPad Software, San Diego, CA). Compounds active at the mGluR5 were screened at the human mGluR1 to determine selectivity. The specifics of how the cell lines expressing the human mGluR5 and mGluR1 were created and our calcium dye assay procedures are detailed in the Supporting Information.

Results and Discussion

The compounds were evaluated for antagonism of glutamate-mediated mobilization of internal calcium in an mGluR5 in vitro efficacy assay (Table 1). The 3-methyl-5-phenylethynyl-, 6-methyl-3-phenylethynyl-, and 5-methyl-3-phenylethynyl[1,2,4]triazine (**4**, **5**, and **6a**, respectively) were first synthesized and evaluated to determine the effect of placing the methyl and phenylethynyl groups at different positions on the [1,2,4]triazine ring. Compound **6a** had an IC_{50} of 140 nM. The other two compounds, **4** and **5**, were totally inactive. On the basis of the assumption that the addition of substituent to **6a** might lead to compounds with improved efficacy in their ability to antagonize the mGluR5, the 5-methyl-3-(substituted phenylethynyl)[1,2,4]-triazines (**6b**−**u**) were synthesized and evaluated. The most interesting compounds were 3-methyl, 3-chloro, and 3-bromophenylethynyl analogues **6b**−**d** with IC_{50} values of 2.3, 4.2, and 6 nM, respectively. The 3-methylphenylethynyl analogue **6b** was almost as potent as MPEP, which had an IC_{50} of 1.5 nM. The smaller, stronger electron-withdrawing 3-fluorophenylethynyl analogue **6e** was 22 times less potent than the 3-chlorophenylethynyl analogue **6c**. Similarly, the 3-trifluoromethylmethyl- and 3-cyanophenylethynyl analogues **6f** and **6h** were 24 and 20 times less potent than the 3-methylphenylethynyl analogue **6b**. The least favored of the 3-substituted analogues was the electron-releasing 3-methoxyphenylethynylphenyl analogue **6g**, which was almost 200 times less potent than the 3-methylphenylethynyl analogue **6b**. Surprisingly, the 4-phenoxyphenylethynyl analogue **6m** with an IC_{50} of 80 nM was the most potent of the 4-substituted analogues studied. The only disubstituted phenylethynyl analogue to show any efficacy was the 4-fluoro-3-methylphenylethynyl analogue **6n**, which had an IC_{50} of 132 nM. Compound **6n** results from the addition of a 4-fluoro substituent to the 3-methylphenylethynyl analogue (**6b**). When viewed from this prospective, the addition of the 4-fluoro substituent to **6b** reduces its efficacy 60-fold.

Compounds **6a**−**h**,**l**−**o**,**s** were also evaluated for antagonism of glutamate-mediated mobilization of internal calcium in an mGluR1 in vitro efficacy assay. None of the compounds tested possessed any efficacy at mGluR1.

MTEP showed a LogD of 2.1 and was more potent than MPEP (LogD = 3.75) in an in vivo binding assay and in the fear-potentiated startle model of anxiety.[13] It is interesting to note that the 3-methyl-, 3-chloro-, and 3-bromophenyl compounds **6b**−**d**, which have IC_{50} values of less than 6 nM in the mGluR5 assay, have LogD values of 3.15, 2.42, and 3.46, respectively.

In summary, synthetic procedures were developed for preparation of 3-methyl-5-phenylethynyl[1,2,4]triazine (**4**), 6-methyl-3-phenylethynyl[1,2,4]triazine (**5**), and 5-methyl-3-(substituted phenylethynyl)[1,2,4]triazines (**6a**−**u**). The meta-substituted 3-methyl-, 3-chloro-, and 3-bromophenyl analogues **6b**−**d**, all possessed low nanomolar IC_{50} values in an mGluR5 efficacy

Table 2. 5-Methyl-3-(substituted phenylethynyl)[1,2,4]triazine Analogues, Yields, and Analytical Data[a]

compd	yield (%)	mp (°C)	recrystallization solvent	molecular formula	analysis
6a	45	154−156	$(CH_3)_2CHOH$	$C_{12}H_9N_3$	C, H, N
6b	31	115−116	EtOAc	$C_{13}H_{11}N_3$	C, H, N
6c	15	119−120	$(CH_3)_2CHOH$	$C_{12}H_8ClN_3$	C, H, N
6d	14	124−126	$(CH_3)_2CHOH-C_7H_{16}$	$C_{12}H_8BrN_3 \cdot 0.5H_2O$	C, H, N
6e	23	141−143	EtOAc	$C_{13}H_8F_3N$	C, H, N
6f	3	73−74	$EtOAc-C_7H_{16}$	$C_{13}H_8F_3N_3$	C, H, N
6g	20	133−135	EtOAc	$C_{13}H_{11}N_3O$	C, H, N
6h	16	142−144	$(CH_3)_2CHOH-C_7H_{16}$	$C_{13}H_8N_4 \cdot 0.5H_2O$	C, H, N
6i	16	99−100	$(CH_3)_2CHOH$	$C_{13}H_{11}N_3$	C, H, N
6j	35	112−113	$(CH_3)_2CHOH$	$C_{13}H_{11}N_3O$	C, H, N
6k	9	115−116	EtOAc	$C_{13}H_8F_3N_3$	C, H, N
6l	8	170−172	EtOAc	$C_{18}H_{13}N_3$	C, H, N
6m	30	167−169	EtOAc	$C_{18}H_{13}N_3O$	C, H, N
6n	20	123−124	EtOAc	$C_{13}H_{10}FN_3$	C, H, N
6o	30	105−106	EtOAc	$C_{14}H_{13}N_3$	C, H, N
6p	40	123−124	EtOAc	$C_{14}H_{13}N_3O$	C, H, N
6q	8	170−172	EtOAc	$C_{12}H_7F_2N_3$	C, H, N
6r	1	108−110	$(CH_3)_2CHOH$	$C_{14}H_7F_6N_3$	C, H, N
6s	23	141−143	EtOAc	$C_{16}H_{11}N_3$	C, H, N
6t	15	138−139	$(CH_3)_2CHOH$	$C_{16}H_{11}N_3$	C, H, N
6u	14	163−164	$(CH_3)_2CHOH$	$C_{13}H_9N_3O_2$	C, H, N

assay. The compounds were selective for the mGluR5 relative to the mGluR1 and possessed LogD values less than that of MPEP.

Experimental Section

Commercial reagents and solvents were used as received. All reactions were run under dry N_2 in oven-dried glassware. The $NaHCO_3$ (saturated), NaCl (saturated), and NH_4Cl (saturated) used in various procedures refer to saturated aqueous solutions. Unless otherwise specified, all organic solvents were anhydrous and used as received. Reactions were monitored by TLC on silica gel GF plates. Preparative separations were performed using flash column chromatography on silica gel (grade 62, 60−200 mesh) or preperative thin layer chromatography (PTLC) on 20 cm × 20 cm silica gel GF plates. Fraction elution was monitored using a hand-held UV lamp. Melting points were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured using a Bruker Advance DPX-300 MHz spectrometer in $CDCl_3$ or DMSO-d_6 at 300 and 75 MHz, respectively, and were referenced to internal $(CH_3)_4Si$. Elemental analysis was conducted by Atlantic Microlab, Norcross, GA. Results were within ±0.4% of calculated values.

3-Methyl-5-phenylethynyl[1,2,4]triazine (4) and *trans*-3-Methyl-5-styryl[1,2,4]triazine (8). To a well-stirred and cooled solution of 5.00 g (0.05 mol) of phenylacetylene in anhydrous THF at −78 °C was added 30.60 mL of 1.6 M solution of BuLi in hexanes, and the mixture was stirred for 30 min. The mixture was transferred by cannulation under N_2 to a well-stirred and cooled solution of 4.60 g (0.05 mol) of **7** in 50 mL of anhydrous THF maintained at −78 °C. After the addition was complete, the mixture was stirred at −78 °C for 30 min, allowed to warm to 0 °C in an ice bath, and stirred for another 30 min. Addition of 0.7 mL of H_2O was followed by 0.3 mL of NH_4Cl solution, and the layers were separated while still cold. The cold organic layer was dried over anhydrous Na_2SO_4, filtered over Celite, and used directly for the next step. The organic layer was stirred with 4.55 g of $K_3Fe(CN)_6$, 65 mL of 3 N NaOH, and 100 mL of water for 24 h according to the procedure of Konno and co-workers.[10] The organic layer was separated, and the aqueous layer was extracted with Et_2O (2 × 100 mL). The organic layers were collected, washed with NaCl solution, dried over anhydrous Na_2SO_4, filtered over Celite, and concentrated to yield a thick brown oil. Chromatographic separation of this oil on silica gel, eluting with hexanes and increasing concentrations of EtOAc, resulted in three fractions. The first fraction on concentration yielded a yellow solid, which was recrystallized from $(CH_3)_2CHOH$ and heptane to give 1.6 g (17%) of 3-methyl-5-phenylethynyl[1,2,4]triazine **(4)**: mp 88−90 °C; ^{1}H NMR ($CDCl_3$) δ 9.15 (s, 1 H), 7.67 (d, 2 H, J = 1.2 Hz), 7.64 (d, 2 H, J = 1.4 Hz), 7.46−7.42 (m, 3 H), 2.91 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.0, 148.3, 144.2, 132.7, 130.8, 129.1, 128.7, 128.0, 120.3, 98.9, 84.6, 23.9. Anal. ($C_{12}H_9N_3$) C, H, N.

The second fraction was obtained as an oil and had a complex spectra. The third fraction on concentration yielded a golden-yellow solid, which was recrystallized from $(CH_3)_2CHOH$ to give 3.20 g (33%) of *trans*-3-methyl-5-styryl[1,2,4]triazine (**8**): mp 98−99 °C; ^{1}H NMR ($CDCl_3$) δ 9.12 (s, 1 H), 8.03 (d, 1 H, J = 16.1 Hz), 7.64−7.61 (m, 2 H), 7.43−7.41 (m, 3 H), 7.03 (d, 1 H, J = 16.1 Hz), 2.87 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 167.3, 154.4, 145.7, 141.3, 135.4, 130.7, 129.4, 128.4, 122.9, 24.3. Anal. ($C_{12}H_{11}N_3$) C, H, N.

3-Iodo-6-methyl[1,2,4]triazine (10). The general procedure of Nair and Richardson[12] was followed. To a well-stirred mixture of 0.50 g (0.005 mol) of **9** in 25 mL of CH_2I_2 was added 8.13 g (0.07 mol, 9.3 mL) of isoamyl nitrite. The mixture was refluxed for 2 h when TLC indicated absence of starting material. Column chromatography eluting with hexanes enabled the recovery of CH_2I_2. This was followed by elution with increasing concentrations of EtOAc in hexanes to give 0.20 g (20%) of **10**: mp 59−60 °C; ^{1}H NMR (DMSO-d_6) δ 8.55 (s, 1 H), 2.56 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 158.0, 151.9, 133.4, 18.6.

6-Methyl-3-phenylethynyl[1,2,4]triazine (5). The general procedure of Cosford[13] and Lautens[14] was followed. To a stirred solution of 280 mg (1.27 mmol) of **10** in 10 mL of dry anhydrous THF under a steady stream of dry N_2 was added 18 mg (0.016 mmol) of $Pd(PPh_3)_4$. After a few minutes, 1 mL of TEA and 10 mg (0.05 mmol) of CuI were added, and the mixture was stirred for 5 min. This was followed by a dropwise addition of phenylacetylene (0.14 mL, 1.27 mmol) over 5 min, and the mixture was gently refluxed for 4 h. TLC using 75:25 hexanes/EtOAc as eluent indicated the absence of **10**. Concentration of the mixture under reduced pressure was followed by column chromatography. Elution with hexanes and increasing concentrations of EtOAc resulted in **5** being eluted as the third fraction, which was recrystallized from EtOAc and heptane to give 200 mg (80%) of **5**: mp 144−146 °C; ^{1}H NMR (DMSO-d_6) δ 8.50 (s, 1 H), 7.70 (d, 1 H, J = 1.5 Hz), 7.68 (d, 1 H, J = 1.8 Hz), 7.45−7.37 (m, 3 H), 2.77 (s, 3 H); ^{13}C NMR (DMSO-d_6) δ 156.5, 153.2, 149.2, 133.0, 130.5, 128.9, 121.3, 92.2, 86.0, 20.0. Anal. ($C_{12}H_9N_3$) C, H, N.

5-Methyl-3-methylthio[1,2,4]triazine (13) and 6-Methyl-3-methylthio[1,2,4]triazine (12). To a well-stirred, ice-cold suspension of 10.8 g (0.06 mol) of 40% solution of commercially available pyruvic aldehyde and 5.00 g (0.06 mol) of solid $NaHCO_3$ in 60 mL of anhydrous EtOH was added dropwise a solution of 14.0 g (0.06 mol) **11**[15] in 60 mL of H_2O over a period of 45 min. After completion of addition, the ice bath was removed, and the

mixture was allowed to warm to room temperature and stirred for 4 h. Removal of EtOH under reduced pressure was followed by extraction of the aqueous residue with CH_2Cl_2 (3 × 100 mL). The organic layers were separated, dried over anhydrous Na_2SO_4, and concentrated to give a 70:30 mixture of 5-methyl and 6-methyl isomers **13** and **12**, respectively, as indicated by ^{1}H NMR analysis. Recrystallization from $(CH_3)_2CHOH$/heptane (9:1) resulted in 5-methyl-3-methylthio[1,2,4]triazine (**12**) containing 3% of **13**: ^{1}H NMR ($CDCl_3$) δ 8.81 (s, 1 H), 2.67 (s, 3 H), 2.50 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.2, 146.2, 22.0, 14.2.

5-Methyl-3-methylsulfonyl[1,2,4]triazine (14).[15] To a well-stirred, ice-cold solution of 7.40 g (0.052 mol) of **13** in 250 mL of anhydrous CH_2Cl_2 was added 25.5 g (0.11 mol) of *m*-chloroperoxybenzoic acid in small portions over 15 min. Once the addition was complete, the mixture was stirred at 0 °C for 30 min and then at room temperature for 2 h (until TLC confirmed absence of starting material). The light-yellow mixture was filtered, and the filtrate was concentrated to yield a dark-yellow solid, which was purified by column chromatography. Elution with 1:1 hexanes/Et_2O followed by EtOAc afforded 7.25 g (80%) of **14** as a pale-yellow, thick oil, which solidified on standing: ^{1}H NMR ($CDCl_3$) δ 9.34 (s, 1 H), 3.49 (s, 3 H), 2.77 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 166.7, 163.3, 152.5, 40.0, 22.5.

General Procedures for the Synthesis of 5-Methyl(substituted phenylethynyl)[1,2,4]triazines (6a−u). A detailed procedure for the synthesis of **6a** is given below. Compounds **6b−u** were prepared by a similar procedure. The percent yields, recrystallization solvents, and analytical data for each compound are given in Table 2.

5-Methyl-3-phenylethynyl[1,2,4]triazine (6a). To a well-stirred and cooled solution of 1.30 g (0.013 mol) of phenylacetylene in anhydrous THF at −78 °C was added 8.73 mL of 1.6 M solution of BuLi in hexanes, and the mixture was stirred for 30 min. A white suspension formed after 25 min of stirring. This mixture was transferred by cannulation under N_2 pressure to a well-stirred and cooled solution of 2.00 g (0.012 mol) of **14** in 50 mL of anhydrous THF at −78 °C. The mixture was stirred at −78 °C and was slowly allowed to warm to room temperature. After the mixture was stirred for 6 h at room temperature, 25 mL of $NaHCO_3$ solution was added, and the organic layers were separated, collected, dried over anhydrous Na_2SO_4, and concentrated to obtain a reddish-yellow solid. Column chromatography on silica gel, eluting with hexanes and increasing concentrations of EtOAc, afforded 1.00 g (45%) of **6a** as a yellow solid, which was recrystallized from $(CH_3)_2CHOH$ and heptane: mp 154−156 °C; ^{1}H NMR ($CDCl_3$) δ 9.05 (s, 1 H), 7.71 (d, 1 H, J = 1.44 Hz), 7.69 (d, 1 H, J = 1.81 Hz), 7.43−7.40 (m, 3 H), 2.61 (s, 3 H); ^{13}C NMR ($CDCl_3$) δ 159.2, 154.2, 147.6, 132.7, 130.2, 129.9, 128.8, 128.5, 120.8, 92.1, 85.7, 21.8. Anal. ($C_{12}H_9N_3$) C, H, N.

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Supporting Information Available: Experimental details for development of cells expressing human mGluR5 and mGluR1; elemental analysis data for **4**, **5**, **6a−u**, and **9**. This material is available free of charge via the Internet at http://pubs.acs.org.

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