Discovery of Novel Heteroarylazoles That Are Metabotropic Glutamate Subtype 5 Receptor Antagonists with Anxiolytic Activity

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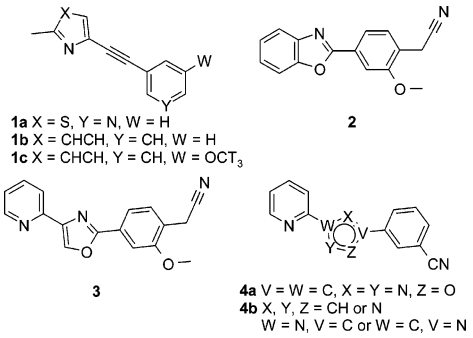
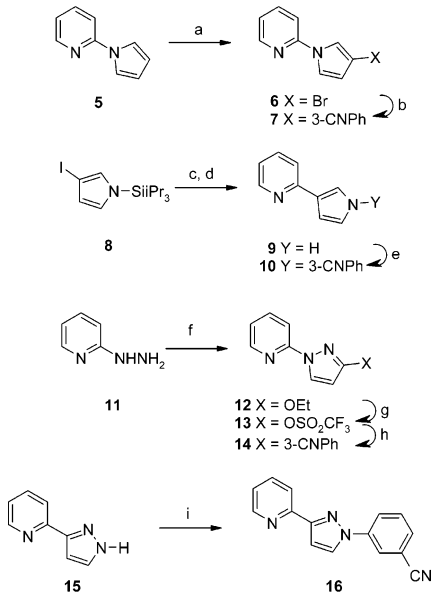
Abstract: The highly potent, selective, and brain-penetrant metabotropic glutamate subtype 5 (mGlu5) receptor antagonists 3-(5-pyridin-2-yl-2*H*-tetrazol-2-yl)benzonitrile (**47**) and 3-fluoro-5-(5-pyridin-2-yl-2*H*-tetrazol-2-yl)benzonitrile (**48**) are reported. Compound **47** is active in the rat fear-potentiated startle (FPS) model of anxiety with $ED_{50} = 5.4$ mg/kg (po) when dosed acutely. In this model the anxiolytic effects of **47** rapidly tolerate on repeated dosing.

Excessive activation of G-protein-coupled metabotropic glutamate subtype-5 (mGlu5) receptors in the central nervous system, leading to aberrant glutamatergic neurotransmission, has been implicated in a number of disease states.[1,2] Selective mGlu5 receptor antagonists, therefore, may be of therapeutic benefit in the treatment of pain,[3] anxiety and depression,[4−6] drug dependence,[7] or mental retardation.[8] We have recently reported the design and synthesis of the potent and selective noncompetitive mGlu5 receptor antagonists 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (**1a**),[9] an analogue of the prototypical mGlu5 receptor antagonist 2-methyl-6-(phenylethynyl)pyridine (**1b**) with anxiolytic activity, and 2-[4-(1,3-benzoxazol-2-yl)-2-methoxyphenyl]acetonitrile (**2**)[10] from a different structural series.



During structure−activity relationship (SAR) studies focused on defining the common structural features of **1a**, **1b**, and **2**, the benzoxazole unit in **2** was replaced with a 2-(1,3-oxazol-4-yl)pyridine moiety to give [2-methoxy-4-(4-pyridin-2-yl-1,3-oxazol-2-yl)phenyl]acetonitrile **3**. Compound **3** inhibited mGlu5 receptors in vitro (vide infra) in a functional assay (Ca^{2+} flux $IC_{50} = 0.05$ μM) and a binding assay ($K_i = 0.21$ μM), and these results led us to speculate that the oxazole in **3** might be a surrogate for the ethyne moiety in **1a** and **1b**. During these investigations, a series of heteroarylpyridine mGlu5 receptor antagonists, including the oxadiazole derivative **4a**, with a clear structural resemblance to **3** were disclosed in a patent application.[11] The compounds described in this patent application contained five-membered heteroaryl moieties linking pyridine and phenyl via ring carbon atoms of the heteroaryl linker. It was apparent, however, that an almost identical pharmacophore would result from structures in which one of the carbon attachment atoms was replaced with a nitrogen atom. For analogues containing one phenyl and one 2-pyridyl unit there are 16 possible five-membered ring derivatives containing isomers of pyrrole, pyrazole, imidazole, triazole, or tetrazole, as in structure **4b**. The synthesis of each of the 16 "N-linked" analogues of **4a** (i.e., 2-pyridyl/linker/3-cyanophenyl) was therefore undertaken in order to assess the relative in vitro potency of each compound compared with **4a**.

Scheme 1[a]



[a] Reagents and conditions: (a) TMSBr, DMSO, MeCN, 0−25 °C, 3 h; (b) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DME, H_2O, 84 °C, 18 h, two steps 14%; (c) 2-bromo(pyridin-2-yl)zinc, $Pd(PPh_3)_4$, PPh_3, THF, 70 °C, 5 h, 9%; (d) TBAF, THF, 10 min, 80%; (e) 3-fluorobenzonitrile, K_2CO_3, DMF, 145 °C, 14 h, 37%; (f) (i) ethylvinyl ether, $(COCl)_2$, 0 °C, 12 h; (ii) NEt_3, THF, 5 h, Δ; (g) (i) concentrated HCl, 25 °C, 3 h, 45%; (ii) $(CF_3SO_2)O$, THF, −78 to 25 °C, 4 h, 80%; (h) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DME, H_2O, 65 °C, 12 h, 39%; (i) 3-fluorobenzonitrile, K_2CO_3, DMF, 145 °C, 18 h, 38%.

The chemical synthesis of the N-linked azole analogues is summarized in Schemes 1−3 (detailed procedures may be found in the Supporting Information). Yields reported are unoptimized. The nature of the structures required that a different preparative sequence had to be developed for each unique heterocyclic scaffold to provide the desired target compounds.

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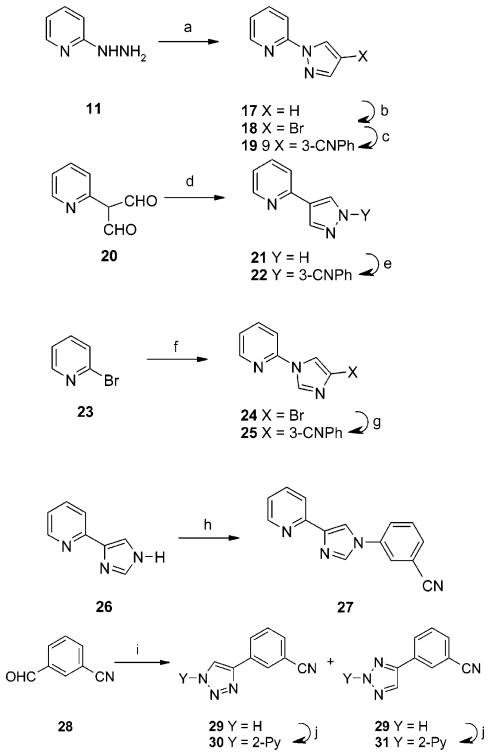
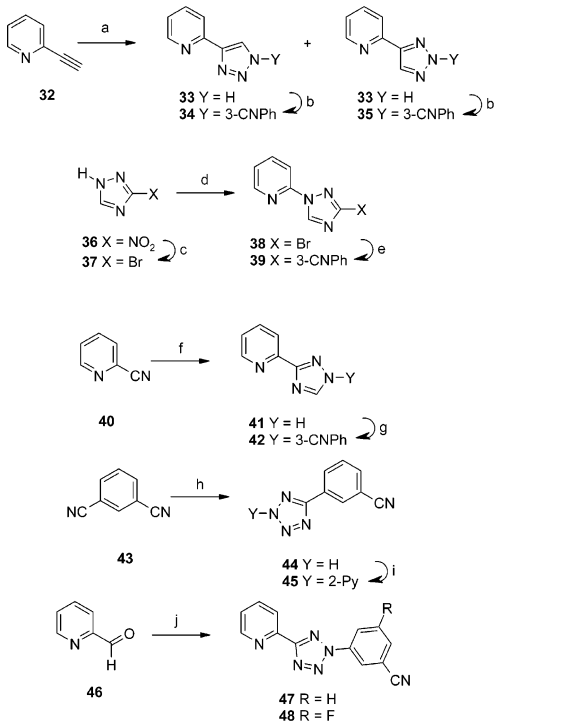
Scheme 2[a]



[a] Reagents and conditions: (a) $(MeO)_2CHCH_2CH(OMe)_2$, HCl, EtOH, 75 °C, 2 h; (b) Br_2, AcOH, 25 °C, 3 h, two steps 82%; (c) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DME, H_2O, 70 °C, 14 h, 12%; (d) NH_2NH_2, EtOH, 75 °C, 18 h, 86%; (e) 3-cyanophenylboronic acid, $Cu(OAc)_2$, pyridine, CH_2Cl_2, 25 °C, 48 h, 8%; (f) 4-bromo-1*H*-imidazole, NMP, 165 °C, 18 h, 44%; (g) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, DME, H_2O, 80 °C, 18 h, 4%; (h) 3-fluorobenzonitrile, K_2CO_3, DMF, 145 °C, 18 h, 38%; (i) (i) $MeNO_2$, $HNEt_2$, THF, 55 °C, 48 h, 77%; (ii) $MeSO_2Cl$, NEt_3, CH_2Cl_2, 0−25 °C, 93%; (iii) $TMSN_3$, TBAF, DMF, 50 °C, 20 min, 81%; (j) *N*-fluoropyridinium triflate, NaOMe, MeOH, −78 to 25 °C, 18 h, 20% (**30**) and 17% (**31**).

Scheme 3[a]



[a] Reagents and conditions: (a) $TMSN_3$, 95 °C, 18 h, 25%; (b) 3-fluorobenzonitrile, K_2CO_3, DMF, 140 °C, 18 h, 13% (**34**) and 29% (**35**); (c) concentrated HBr, 8 h, Δ, 80%; (d) *N*-fluoropyridinium triflate, NaOMe, MeOH, −78 to 25 °C, 16 h, 20%; (e) 3-cyanophenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3, PhMe, MeOH, 90 °C, 16 h, 54%; (f) (i) NH_2NH_2, EtOH, 25 °C, 18 h, 57%; (ii) HCO_2H, 0−25 °C, then Δ, 4 h, 38%; (g) 3-fluorobenzonitrile, K_2CO_3, DMF, 145 °C, 16 h, 60%; (h) $TMSN_3$, Bu_2SnO, PhMe, 110 °C, 1 h, 34%; (i) *N*-fluoropyridinium triflate, NaOMe, MeOH, −78 to 25 °C, 3 h, 31%; (j) (i) $CH_3C_6H_4SO_2NHNH_2$, EtOH, 25 °C, 0.5 h; (ii) NaOH, 25 to −5 °C; (iii) HCl (6 M), $NaNO_2$, H_2O, 3-aminobenzonitrile (R = H) or 3-amino-5-fluorobenzonitrile (R = F), −5 °C, 55% (**47**), 80% (**48**).

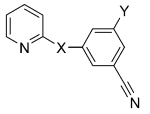
Worthy of note is the SN_{Ar} substitution protocols employed to synthesize pyrrole **10**, pyrazole **16**, imidazole **27**, and triazoles **34**, **35**, and **42**; a C−N cross-coupling procedure to prepare pyrazole **22**;[12] and the use of *N*-fluoropyridinium triflate to construct triazoles **30** and **31** and tetrazole **45**.[13] We have recently described an alternative procedure for the synthesis of pyrrole derivatives such as **6**.[14]

Each of the N-linked azole analogues, synthesized as described in Schemes 1−3, was initially profiled in two in vitro assays. Functional potency was assessed using an automated assay employing Ltk cells stably expressing human recombinant mGlu5 receptors.[15] 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. Binding to native mGlu5 receptors in vitro was determined by measuring the displacement by test compounds of [^{3}H]-3-methoxy-5-(pyridin-2-ylethynyl)pyridine (**1c**) from rat cortical membranes.[16] The results of the in vitro profiling of the new compounds are presented in Table 1.

Oxadiazole **4a**, which was evaluated for comparison, exhibited good potency in the Ca^{2+} flux assay (IC_{50} = 0.10 μM) and modest binding potency (K_i = 0.49 μM). Considering the relatively minor structural differences between the 16 N-linked azole analogues, there is wide variation in potency in vitro. For example, the pyrrole N-linked to pyridyl **7** was a very weak antagonist in both assays while its isomer **10** is relatively potent in the Ca^{2+} flux assay. Of the four pyrazole isomers, only **16** (Ca^{2+} flux IC_{50} = 0.44 μM; K_i = 0.53 μM) and **22** (Ca^{2+} flux IC_{50} = 0.14 μM; K_i = 0.25 μM), which are both N-linked to phenyl, showed comparable potency with **4a**. Interestingly, both of the imidazole isomers[11] (**25** and **27**) are very weak antagonists. In the 1,2,3-triazole series the isomers linked at 1-N (**30** and **34**) and the 1,2,4-triazole isomers (**39** and **42**) show very weak activity.

By comparison, the 1,2,3-triazole isomers linked at 2-N, i.e., **31** (Ca^{2+} flux IC_{50} = 0.21 μM; K_i = 0.20 μM) and **35** (Ca^{2+} flux IC_{50} = 0.08 μM; K_i = 0.30 μM) both show reasonable potency. Finally, the tetrazole N-linked to pyridyl (**45**) shows moderate potency (Ca^{2+} flux IC_{50} = 0.27 μM; K_i = 0.45 μM) while the isomer that is N-linked to phenyl (**47**) proved to be more potent in vitro than **4a** (Ca^{2+} flux IC_{50} = 0.07 μM; K_i = 0.19 μM). On the basis of the in vitro data, **10**, **22**, **31**, **35**, and **47** were selected for further evaluation. The pharmacokinetic properties of each compound were measured in rats, and the data are displayed in Table 2. While pyrazole **22** exhibited a promising half-life in rats ($t_{1/2}$ = 5.5 h), neither **10**, **22**, nor **35** showed any appreciable oral bioavailability. Compound **31** exhibited an oral bioavailability in rats of 13% although the half-life was rela-

Table 1. In Vitro Potency Data for mGlu5 Receptor Antagonists[a]



	X	Y	hmGlu5 Ca^{2+} Flux IC_{50} (μM)[b]	mGlu5 K_i (μM)[c]
4a		H	0.10 (0.07, 0.17, 3)	0.49 (0.17, 1.47, 5)
7		H	4.62 (2.58, 8.28, 5)	> 0.60 (n/a, 6)
10		H	0.19 (0.16, 2.31, 3)	> 0.60 (n/a, 3)
14		H	3.60 (1.72, 7.51, 6)	> 0.60 (n/a, 3)
16		H	0.44 (0.27, 0.71, 6)	0.53 (0.43, 0.66, 6)
19		H	0.89 (0.28, 0.28, 6)	> 0.63 (n/a, 3)
22		H	0.14 (0.09, 0.22, 10)	0.25 (0.19, 0.32, 5)
25		H	> 10.0 (n/a, 6)	> 0.60 (n/a, 6)
27		H	1.15 (0.43, 0.31, 6)	> 0.60 (n/a, 4)
30		H	> 10.0 (n/a, 7)	> 0.63 (n/a, 2)
34		H	0.98 (0.51, 1.86, 7)	> 0.60 (n/a, 7)
31		H	0.21 (0.19, 0.23, 6)	0.20 (0.14, 0.28, 6)
35		H	0.08 (0.03, 0.18, 9)	0.30 (0.26, 0.34, 7)
39		H	6.15 (2.58, 14.6, 6)	> 0.60 (n/a, 3)
42		H	0.69 (0.51, 0.92, 7)	> 0.60 (n/a, 5)
45		H	0.27 (0.14, 0.51, 9)	0.45 (0.30, 0.67, 5)
47		H	0.07 (0.05, 0.12, 6)	0.19 (0.18, 0.19, 2)
48		F	0.004 (0.003, 0.005, 5)	0.012 (0.007, 0.023, 4)

[a] Data are presented as the geometric mean followed in parentheses by the lower and upper limits of the mean and the number of replicates. [b] Ca^{2+} flux assay using glutamate as agonist.[15] [c] Displacement by test compounds of [^{3}H]-3-methoxy-5-(pyridin-2-ylethynyl)pyridine (**1c**) bound to rat cortical membranes.[16]

Table 2. Rat Pharmacokinetic Data for mGlu5 Receptor Antagonists[a]

	Cl_p (mL min^{-1} kg^{-1})[b]	V_d (L/kg)[b]	$t_{1/2}$ (h)[b]	F (%)[c]	C_{max} (μM)[c]
10	32.5 ± 2.0	3.6 ± 0.7	1.7 ± 0.8	4	0.9 ± 0.2
22	9.7 ± 1.1	3.7 ± 0.3	5.5 ± 0.3	3	1.2 ± 0.1
31	15.1 ± 1.6	1.0 ± 0.5	1.7 ± 0.6	13	2.7 ± 0.8
35	15.7 ± 5.6	1.1 ± 0.5	2.5 ± 0.8	3	0.6 ± 0.3
47	32.9 ± 2.8	5.0 ± 1.1	6.9 ± 1.0	100	5.8 ± 0.5
48	16.9 ± 2.5	1.1 ± 0.1	2.9 ± 2.6	26	2.5 ± 1.6

[a] Cl_p = clearance; V_d = volume of distribution; $t_{1/2}$ = half-life; F = biovailability; C_{max} = maximum concentration. [b] 2 mg/kg dosed iv (n = 2 Sprague-Dawley rats/group). [c] 10 mg/kg dosed po (n = 3 Sprague-Dawley rats/group).

tively short ($t_{1/2}$ = 1.7 h). This is in marked comparison with the tetrazole (**47**), which is both bioavailable (F = 100%) and has a long half-life in rats ($t_{1/2}$ = 6.9 h). Continued structure−activity optimization studies around tetrazole **47** led to the observation that fluoro substitution at the 3-position of the benzonitrile moiety in **47** resulted in a significant enhancement in potency at mGlu5 receptors. Thus, tetrazole **48**, with Ca^{2+} flux IC_{50} = 0.004 μM and K_i = 0.012 μM, is equipotent with **1a** with respect to both functional (Ca^{2+} flux IC_{50} = 0.005 μM) and binding potency (K_i = 0.016 μM) in vitro. Furthermore, **48** exhibits promising pharmacokinetics in rats ($t_{1/2}$ = 2.9 h, F = 26%; Table 2). The impressive in vitro potency and pharmacokinetic profiles of **47** and **48** led to selection of these compounds for further in vitro and in vivo evaluation.

Table 3. In Vivo Data for mGlu5 Receptor Antagonists **47** and **48**[a]

	Occ ED_{50} (mg/kg ip)	Occ ED_{50} (mg/kg po)	plasma levels (μM)	brain levels (μM)	FPS ED_{50} (mg/kg po)
47	3.0[b]	3.0[c]	10.5 ± 4.5[e]	15.3 ± 6.0[e]	5.4[g]
48	1.3[b]	3.6[d]	2.7 ± 0.9[f]	2.4 ± 0.1[f]	NT

[a] Occ = in vivo receptor occupancy; FPS = fear-potentiated startle. [b] Measured 1 h postadministration (n = 5−6 Sprague-Dawley rats/group). [c] Measured 30 min postadministration (n = 6−7 Sprague−Dawley rats/group). [d] Measured 2 h postadministration (n = 5−7 Sprague-Dawley rats/group). [e] Measured at 1 h following 10 mg/kg dose ip. [f] Measured at 1 h following 3 mg/kg dose ip. [g] Measured 1 h postadministration (n = 8 Wistar rats/group).

To identify any off-target activities, tetrazole **47** was profiled extensively against a battery of in vitro assays (MDS Pharma Services screen). Experiments were performed at a drug concentration of 10 μM; under this paradigm no significant off-target effects were observed. As with the alkyne derivative **1a**, **47** is highly selective for the mGlu5 receptor over the mGlu1 receptor (mGlu1 Ca^{2+} flux IC_{50} > 10 μM) although the effect of **47** as a positive or negative modulator of other mGlu receptor subtypes is yet to be determined. Evaluation of the brain penetration of **47** and **48** was undertaken using an in vivo receptor occupancy assay, which has been described previously, and this allowed correlation of affinity at mGlu5 receptors with in vivo efficacy.[17,18] Briefly, at time zero rats were dosed with the test compound and **1c**[16] was administered via tail vein injection at the time of maximum drug concentration (T_{max}). One minute later the animals were sacrificed and binding of the drug to brain tissue was measured. By use of this procedure, dose−response relationships were generated for the binding of **47** and **48** to mGlu5 receptors in vivo. In addition, plasma and brain levels for **47** and **48** were measured (Table 3). Thus, **47** exhibits an occupancy ED_{50} of 3 mg/kg when administered either intraperitoneally or perorally. Compound **48**, with an oral bioavailability of 26%, exhibits occupancy ED_{50} values of 1.3 mg/kg (ip) and 3.6 mg/kg (po). Both tetrazole derivatives show good brain penetration and similar brain/plasma ratios (Table 3).

Several recent studies suggest a role for mGlu5 receptors in the modulation of mood disorders such as anxiety.[4−6] Experiments in this laboratory have demonstrated that **1a** blocks fear-conditioning in rats as determined in the fear-potentiated startle (FPS) model of anxiety.[9] Thus, in the FPS model it was found that acute administration of **47** perorally in rats blocked the expression of fear with an ED_{50} of 5.4 mg/kg. This finding with **47**, a compound derived from a new structural class, is fully consistent with results in the FPS model observed with alkyne derivative mGlu5 receptor antagonists such as **1a**. To assess the anxiolytic profile on chronic dosing, rats were tested using the FPS protocol each day for 5 consecutive days immediately

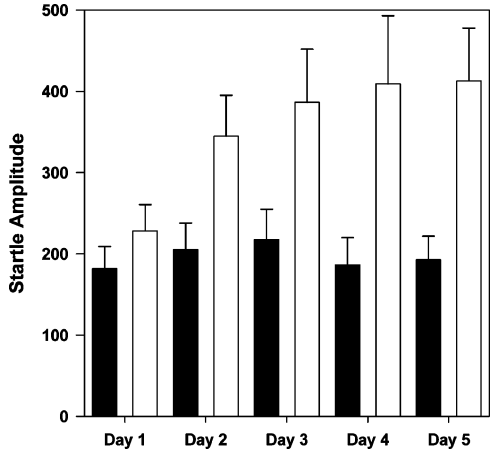


Figure 1. Chronic dosing of mGlu5 receptor antagonist **47** in the rat FPS model. Closed bars represent the mean startle amplitude in the dark, and open bars represent the mean startle amplitude in the light. Measurements were at 1 h postadministration following 10 mg/kg dose ip (±SEM; $n = 8$ Wistar rats per bar set).

following administration of **47** (Figure 1). Under this regimen the anxiolytic effects of **47** observed following acute dosing were rapidly tolerated such that by day 5 no significant anxiolysis was observed (light bars; see Figure 1 caption). This is in marked contrast with the conservation of efficacy observed for **1b** on chronic dosing in the Vogel conflict drinking test[6] but agrees with recent observations from this laboratory showing that the anxiolytic effects of **1a** were tolerated in the rat Geller−Seifter conflict model.[19] Pharmacokinetic studies suggest that the reduced efficacy on chronic dosing is not a result of **47** inducing its own metabolism. Thus, **47** (10 mg/kg ip) was dosed in rats for 4 consecutive days. On the fifth day, the pharmacokinetic profile of **47** (10 mg/kg, ip) was determined and found to be similar to that of vehicle-treated rats. Furthermore, there was no difference in cytochrome P450 metabolism of phenacetin in microsomes prepared from the liver tissue of rats chronically dosed with **47** compared with microsomes derived from untreated rats.[20]

In conclusion, a series of novel non-alkyne mGlu5 receptor antagonists have been discovered. Tetrazole derivatives **47** and **48** have a profile comparable with that of alkyne derivative **1a**. These compounds are potent and selective in vitro and show good brain penetration and in vivo receptor occupancy in rats, and **47** is orally active in a rat conditioned model of anxiety. The rapid tolerance to the anxiolysis observed with tetrazole **47** in the rat FPS model is consistent with our data for alkyne **1a** in the rat Geller−Seifter model[19] and warrants further investigation. These compounds should be useful tools to further elucidate the therapeutic potential of mGlu5 receptor antagonists.

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Supporting Information Available: Experimental details for the synthesis of **7**−**48**. This material is available free of charge via the Internet at http://pubs.acs.org.

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