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2-{2-[3-(Pyridin-3-yloxy)phenyl]-2*H*-tetrazol-5-yl}pyridine: a highly potent, orally active, metabotropic glutamate subtype 5 (mGlu5) receptor antagonist

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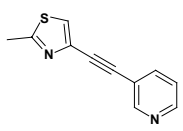
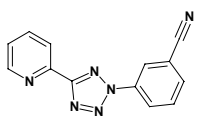
Abstract—Structure–activity relationship studies on 3-(5-pyridin-2-yl-2*H*-tetrazol-2-yl)benzonitrile **2** led to the discovery of 2-{2-[3-(pyridin-3-yloxy)phenyl]-2*H*-tetrazol-5-yl}pyridine (**10**)—a highly potent and selective mGlu5 receptor antagonist with good brain penetration and in vivo receptor occupancy in rat and cross-species oral bioavailability.

The major excitory neurotransmitter in the central nervous system, glutamate, activates both ionotropic and metabotropic glutamate (mGlu) receptors.[1] The G protein-coupled mGlu receptor subtype 5 (mGlu5), which is predominantly localized post-synaptically couples via phospolipase C leading to an increase in intracellular Ca^{2+} levels.[2] A number of reports have indicated that selective antagonism of mGlu5 receptors may improve disease states such as anxiety and depression,[3–8] pain,[9] drug dependence[10] and mental retardation.[11]



1: MTEP



2

Recent publications from this laboratory have described the discovery of MTEP (**1**), a potent and selective mGlu5 receptor antagonist.[12] In our search for further structural classes, we examined the replacement of the alkyne linker in **1** with a series of heteroaromatic azoles.[13] Of the 16 N-linked azoles examined, tetrazole **2** was found to be the most promising in terms of potency, selectivity,[14] brain penetration, and rat pharmacokinetics. However, tetrazole **2** showed only moderate in vitro potency and binding affinity and suffered from relatively poor aqueous solubility.[15] Due to these short comings we sought to replace the nitrile moiety of **2** with groups that would confer improved potency and physicochemical properties. Herein we describe our efforts towards these goals.

The tetrazole derivatives described herein were synthesized as outlined in Schemes 1–3. A 1,3-dipolar cycloaddition was employed between a diazonium salt and a tosyl hydrazone (derived from condensation of 2-pyridylaldehyde with tosyl hydrazide, Scheme 1).[16]

In the case of oxygen and sulfur linked biaryls **3**–**8**, **10**, and **11**, the required aniline derivative was prepared

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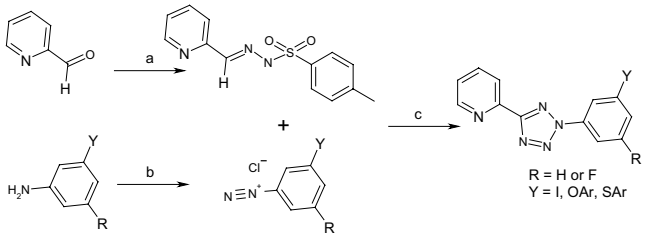
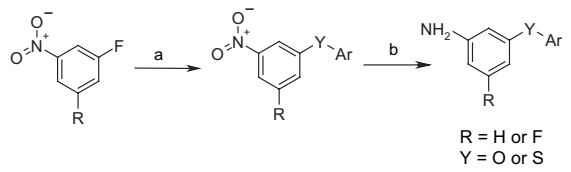
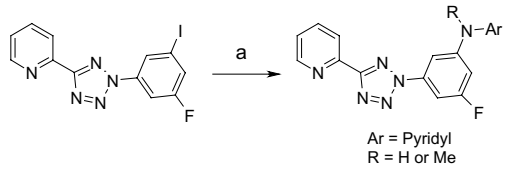


Scheme 1. Reagents and conditions: (a) tosyl hydrazide, EtOH, rt; (b) $NaNO_2$, HCl, H_2O, EtOH, 0 °C; (c) NaOH, 0 °C.



Scheme 2. Reagents and conditions: (a) K_2CO_3, Ar–OH or ArSNa; DMF, 80–150 °C; (b) H_2, Pd/C.



Scheme 3. Reagents and conditions: (a) NaO^{t}Bu, biphenyl-2-yl(dicyclohexyl)phosphine, $Pd_2(dba)_3$, Ar–NH_2, dioxane, 110 °C.

via an SN_{Ar} reaction of a phenol or thiophenol with an appropriately substituted nitroarene (Scheme 2).

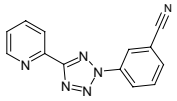
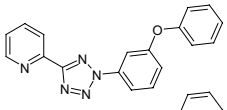
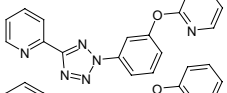
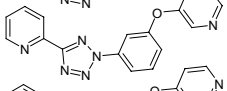
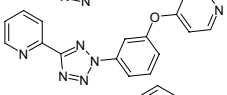
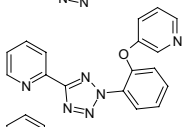
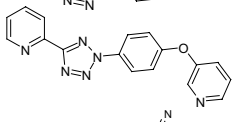
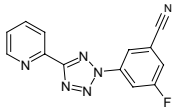
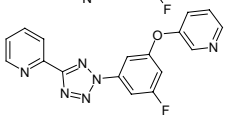
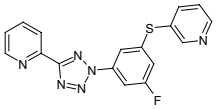
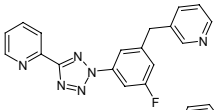
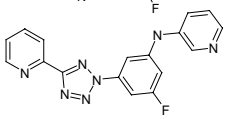
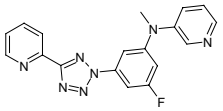
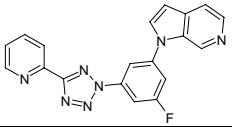
As shown in Scheme 3, for the N-linked biaryls **13** and **15**, the fourth ring was appended using palladium-catalyzed heteroatom cross-coupling chemistry between an aryl iodide and an appropriately substituted aniline (or for compound **15**, 7-azaindole).[17,18]

The data in Table 1 illustrate the effect of replacing the nitrile moiety in **2** with oxygen-linked aryl groups. Thus O-phenyl derivative **3** and O-2-pyridyl derivative **4** both showed a significant loss in potency compared to **2**. However, moving the pyridyl nitrogen to the 3-position as in **5** gave an increase in the functional Ca^{2+} flux (IC_{50} = 30 nM) and binding (K_i = 59 nM) assays. Moving the pyridyl nitrogen to the 4-position as in **6** led to a loss of potency.[19] Finally, if the O-3-pyridyl group of **5** is placed at the 2- or 4-positions of the phenyl ring as in **7** and **8**, again potency was lost relative to **2** (Table 1).

Previous research from this laboratory demonstrated the dramatic increase in potency obtained when benzonitrile **2** is substituted at the 5-position with fluorine to give **9** (Ca^{2+} flux IC_{50} = 3.8 nM compared to 73 nM for **2**; Table 1).[13]

A key question was whether application of this SAR to 3-pyridyl derivative **5** would lead to a similar increase in potency. Gratifyingly compound **10,** containing a 5-fluorine substituent, demonstrated an increase in mGlu5

Table 1. In vitro potencies of tetrazole mGlu5 receptor antagonists

Compd	Structure	hmGlu5 Ca^{2+} flux IC_{50} (nM)[a]	mGlu5 K_i (nM)[b]
2		73	186
3		1458	617
4		2859	633
5		30	59
6		NA[c]	NA[c]
7		1577	NT[d]
8		737	633
9		3.9	14
10		6.7	12
11		13	16
12		17	38
13		124	29
14		22	30
15		16	25

[a] Ca^{2+} flux assay using glutamate (10 μM) as agonist (n = 2–4, SD < +/−25%).[20]

[b] Displacement by test compounds of [^{3}H]-3-methoxy-5-(pyridin-2-ylethynyl)pyridine from rat cortical membranes (n = 2–4, SD < +/−25%).[21]

[c] Not active at 2 μM.

[d] Not tested.

receptor functional (IC_{50} = 6.7 nM) and binding (K_i = 12 nM) potency compared to **5** (IC_{50} = 30 nM and K_i = 59 nM).

Encouraged by this result, we decided to also investigate the effect of the atom linker between the phenyl and 3-pyridyl rings. As seen from the data in Table 1, sulfur linked derivative **11** and carbon linked derivative **12** both maintain good potency in the Ca^{2+} flux assay at IC_{50} = 13 and 17 nM, respectively, while nitrogen linked derivative **13** lost functional potency (IC_{50} = 124 nM). Interestingly, functional potency can be regained with a nitrogen linkage by methylation of the secondary aniline as in **14** (IC_{50} = 22 nM) or by using the conformationally restricted 7-azaindole derivative **15** (IC_{50} = 16 nM).

Having identified compounds with good potency at the mGlu5 receptor, brain penetration and receptor occupancy was evaluated using receptor occupancy assay in rats (Table 2).[22] As represented by **10**, **11**, **12**, and **14**, this class of compounds has good rat brain penetration with levels of 1.5–9.7 μM at 1 h following a dose 10 mg/kg ip. In particular, compound **10** showed brain levels of 6.7 μM, which translated into excellent rat receptor occupancy of 90%.

Since derivative **10** exhibited excellent mGlu5 receptor potency and in vivo receptor occupancy and the corresponding hydrochloride salt showed improved water solubility[15] (compared to hydrochloride salts of **2** and **9**). It was selected for further in vivo profiling.

The pharmacokinetic data for **10** in rat, dog and monkey are summarized in Table 3. In all three species good to excellent bioavailability was observed (27–100%), with a similar half-life across species ($t_{1/2}$ = 2.3–2.7 h). A rat receptor occupancy–dose titration for **10** was also carried out with the occupancy ED_{50} determined to be 10.7 mg/kg, p.o.

In conclusion, we have demonstrated that the 3-nitrile moiety of **2** and **9** may be replaced with an oxygen linked 3-pyridyl group leading to compounds **5** and **10**, respectively. Tetrazole **10** has excellent potency and selectivity against the mGlu5 receptor, has good rat brain penetration and cross-species pharmacokinetics and demonstrates good rat receptor occupancy when dosed orally.

Table 2. Rat receptor occupancy, brain levels and plasma for selected compounds[a,b]

Compd	Recep. occ (%)	Hippocampus levels (μM)	Plasma levels (μM)
2	96	12	13
5	60	ND[c]	ND[c]
9	97	9.7	8.7
10	90	6.7	7.4
11	83	1.5	3.4
12	43	2.7	0.9
14	58	4.9	3.5

[a] Measured at 1 h following 10 mg/kg dose ip.[19]
[b] All compounds were administered in solution, except **2**, **9** in the form of suspension, of PEG 400/water (V:V = 1:1).
[c] Not determined.

Table 3. Pharmacokinetic data for compound **10**

	Rat[a]	Dog[b]	Monkey[b]
Cl_p (mL/min/kg)	21	14	7.7
Vd (L/kg)	22	1.5	0.7
$t_{1/2}$ (h)	2.7	2.3	2.5
%F	100	54	27
Cmax (μM)	11	1.4	0.3

[a] Iv dosing at 2 mg/kg, p.o. dosing at 10 mg/kg. In solution of PEG 400/water (V:V = 1:1).
[b] Iv dosing at 1 mg/kg, p.o. dosing at 1 mg/kg. In solution of PEG 400/water (V:V = 1:1).

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14. The selectivity of the prototypical tetrazole **2** was determined by extensive profiling against a battery of in vitro assays (MDS Pharma Services screen). In addition, **2** is highly selective for mGlu5 over mGlu1 (mGlu1 Ca^{2+} flux IC_{50} > 10 μM).

15. Solubility of HCl salt of **2** is 1.6 mg/mL in PEG 400/water (V/V = 1:1). While the HCl salt of **9** is 36 mg/mL in PEG/400 water (V/V = 1:1).
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