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Design and synthesis of novel heterobiaryl amides as metabotropic glutamate receptor subtype 5 antagonists

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Abstract—A series of heterobiaryl amides was designed and synthesized as novel mGluR5 antagonists. The synthesis using palladium catalyzed Suzuki–Miyaura cross-coupling reactions provided an array of compounds with a range of in vitro activities. In particular, compound **9e**, 4(3,5-difluorophenyl)-*N*-(6-methylpyridin-1-yl)picolinamide, exhibited nanomolar affinity at the mGluR5 and will serve as a template for future drug design.

Glutamate is a major excitatory neurotransmitter in the central nervous system (CNS) that acts through ligand-gated ionotropic glutamate receptors or through the G-protein coupled (GPCR) metabotropic glutamate receptors (mGluR).[1] The mGluRs belong to group C GPCRs, which contain a large N-terminal domain for substrate binding, followed by seven transmembrane domains. There are eight different subtypes of mGluRs; mGluR5 belongs to the Group I subclass and is coupled to the phosphoinositide/Ca^{2+} pathway.[1–3] Overstimulation of mGluR5s has been implicated in anxiety, depression, pain, mental retardation and drug dependence.[4] MGluR5 has been shown to be involved in the rewarding effects of morphine, nicotine and ethanol.[5] Further, studies using either an mGluR5 antagonist or mGluR5 knockout mice showed reduced locomotor stimulant effects induced by cocaine.[6] Thus development of selective mGluR5 antagonists may provide a novel non-dopaminergic strategy toward the discovery of drug abuse medications and other neuropsychiatric disorders.

The non-competitive mGluR5 antagonists **1** and **2** (Fig. 1) have served as important tools to investigate the role of mGluR5 in CNS pathophysiology and drug abuse.[7] We have recently reported a series of diaryl amides, wherein **3** and **4** showed promising in vitro binding and functional activity at mGluR5.[8] Herein we describe further structure–activity relationship (SAR) studies to improve the in vitro binding and functional activity of these compounds at the mGluR5.

Based on site directed mutagenesis data and homology modeling with the bovine rhodopsin crystal structure as a template, the MPEP type ligands are predicted to bind at the transmembrane domain.[9] The binding site consists of two hydrophobic regions with a limited tolerance for structural variation, which is further substantiated with the SAR in the alkynes and amide based compounds, as well as compounds from other structural classes.[10] Furthermore hydrophobic interactions seem to be important, as the allosteric ligand binding site of mGluR5 is lined with aromatic amino acid residues.[9] A comparison of the molecular models of MPEP **1** and MTEP **2** with compounds **3** and **4** showed that

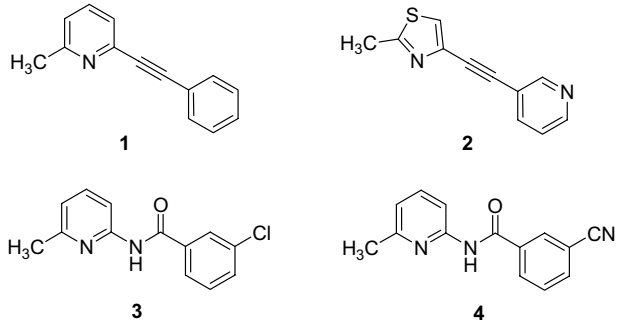

Figure 1. Non-competitive antagonists of mGluR5: MPEP **1**, MTEP **2**, compounds **3** and **4**.

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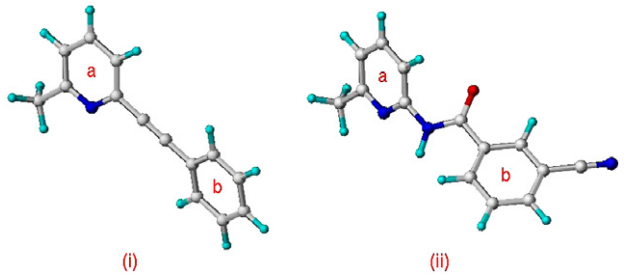


Figure 2. Comparison of MPEP **1** (i) and compound **4** (ii) in low energy conformations.

for the diarylamides, the aryl ring '**b**' is out of plane (~65°) from the aryl ring '**a**' (Fig. 2).

Thus it was hypothesized that perhaps a restricted binding site in the mGluR5 hinders optimal interactions of compounds **3** and **4** and if the aryl ring '**b**' is made coplanar with the aryl ring '**a**' the activity of compounds might be improved. Hence, we introduced a hydrogen bond acceptor atom at the 5′ position of the aryl ring '**b**' which would force this ring to be coplanar with the aryl ring '**a**' due to an intramolecular hydrogen bond with the amide N–H (Fig. 3). The importance of an intramolecular hydrogen bond to attain higher binding affinity at mGluR5 has been reported recently.[11] Herein, we report the synthesis and pharmacological evaluation of a series of heterobiaryl amides that used this strategy.

The series of compounds was synthesized as shown in Schemes 1–3, wherein 2-amino 6-methyl pyridine **5** was reacted with a set of acid chlorides containing a hydrogen bond acceptor atom at the 5′ position (Scheme 1) to provide compounds of type **6**.

Compounds **9a–h** and **12** were synthesized as shown in Scheme 2. The chloro (**6h**) and bromo (**8**) substituted picolinamides were obtained as shown in Schemes 1 and 2. These compounds were then further elaborated into compounds **9a–h** by either Suzuki coupling reactions on compound **8** or by cross-coupling reactions using the biphenyl phosphine ligand, 2-dicyclohexylphosphino-2′,6′-dimethoxybiphenyl **10**, on the chloro picolinamide (**6h**). Significantly lower yields of compound **8** led to the employment of the much more economical chloro picolinamide (**6h**) for the synthesis of a set of related compounds. The reaction using the biphenyl ligand **10**, proved to be more efficient and yielded compounds **9b–h** in good yields (~70%). To substitute with heteroaryl rings, compound **6h** was reacted with bis(pinacolato)diboron, $Pd(OAc)_2$ and the biphenyl ligand **10** to obtain compound **11** in ~90% yield, which was treated with 2-bromo pyrimidine to obtain compound **12**. The synthesis of boronic ester **11** from the chloroarene (**6h**) provides another example of the versatility of the biphenyl ligand **10** in the palladium catalyzed cross-coupling reactions.[12]

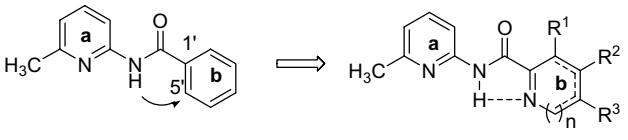
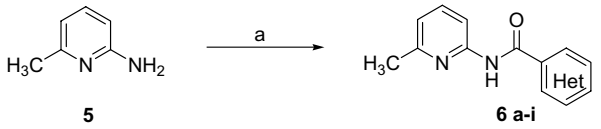


Figure 3. Design of heterobiaryl amides.



Scheme 1. Reagents and conditions: (a) acid chlorides, pyridine/TEA, $CHCl_3$, rt, 1–2 h, 30–70%.

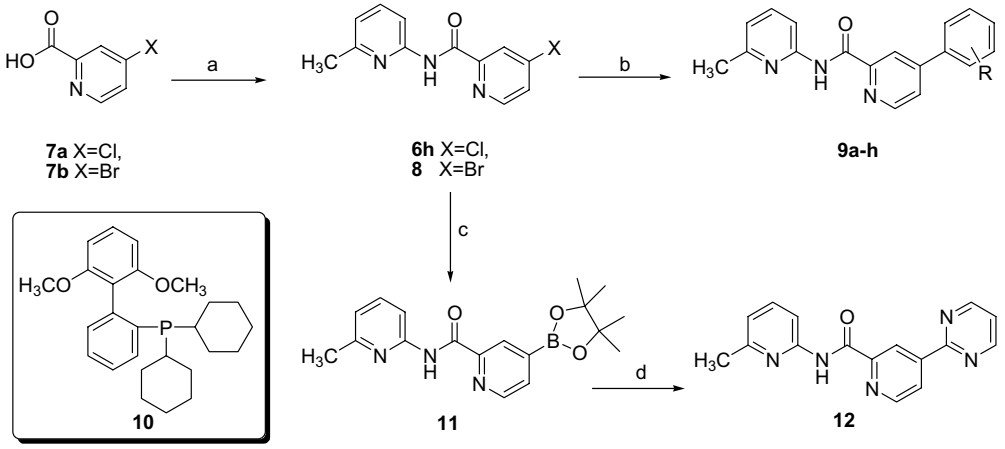
Using an analogous approach, compounds with substitution at the 4′ position of the aryl ring '**b**' were synthesized as shown in Scheme 3. The 5-bromo picolinic acid **14**, was obtained from compound **13** after refluxing with 10 N HCl. The standard amide synthesis yielded compound **15**, which was used for Suzuki coupling reactions to give compounds **16a–d**. Additionally, bipyridyl amide **18** was synthesized from the boronic ester **17** using the standard Miyuara borylation conditions followed by the Suzuki coupling reaction.[13,14]

All novel compounds were evaluated for binding at mGluR5 in a rat brain membrane preparation using [^{3}H]MPEP as the radioligand.[8,10b] Representative compounds and binding data are shown in Table 1 and are compared to previously, reported diarylamides in which substitution with Cl (**3**) and CN (**4**) at the 3′ position of the aryl ring '**b**' provided the most active compounds in that series.[8]

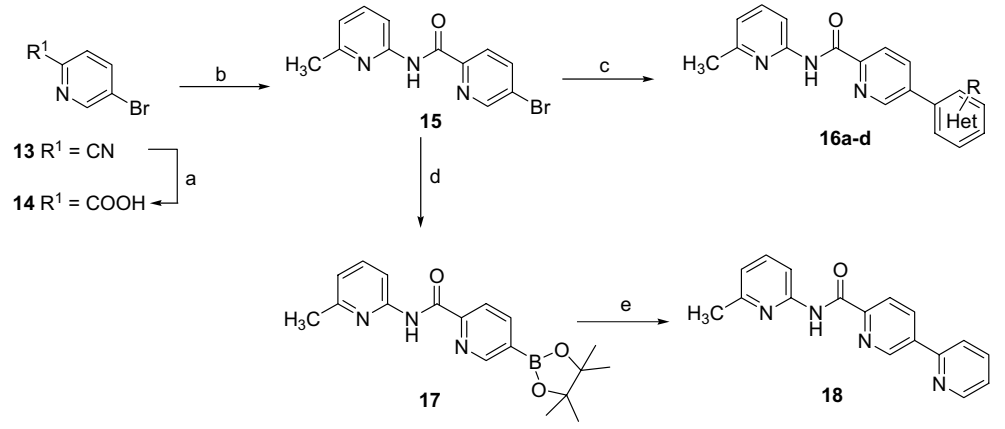
Incorporating a H-bond acceptor atom in the aryl ring '**b**' in **6b** as compared to **6a** suggested that intramolecular H-bonding improved mGluR5 binding affinity by >3-fold. The imidazole 'N' in compound **6b** could form a H-bond with the amide N–H whereas such a H-bond is not possible for compound **6a**. The formation of an intermolecular H-bond was confirmed by a downfield shift in the chemical shift of amide N–H proton to δ 9.74 ppm in compound **6b** from δ 8.22 ppm for compound **6a**. However substitution with additional aromatic rings on the aryl ring '**b**' (**6c–g**) substantially reduced binding affinity at mGluR5. The loss in activity of compound **6h** was surprising considering the activity of compound **3** as both have a chloro substitution at the 3′ position of the aryl ring '**b**'. However there was substantial improvement in activity for compound **6i** as compared to **6j**. Based on this SAR, it may be possible to improve the activity by substitution with a H-bond acceptor at the 5′ position and additional hydrophobic interactions by aromatic substitution at the 3′ and 4′ positions of the aryl ring '**b**'.

Thus a second series of compounds was designed to further explore SAR using this hypothesis and retaining the dipyridyl amide template (Tables 2 and 3).

The compounds **9a** and **9b** showed comparable affinities to compound **6i**. Substitution with a group at the 3″ position of the appended phenyl ring (**9c**) reduced



Scheme 2. Synthesis of compounds **9**–**12**. Reagents and conditions: (a) i—$SOCl_2$, DCM, cat. DMF, reflux, 2 h; ii—2-amino-6-methyl pyridine **5**, pyridine, DCM, rt, 2 h, 71% (**6h**), 20% (**8**); (b) $ArB(OH)_2$, $Pd(OAc)_2$, **10**, K_3PO_4, toluene, EtOH, 120 °C, overnight, 55–88%; (c) **6h**, bis(pinacolato)diboron, KOAc, $Pd(OAc)_2$, **10**, dioxane, 100 °C, 60 h, ~90%; (d) 2-bromopyrimidine, $PdCl_2$(dppf), 2 M aq Na_2CO_3, dioxane, 100 °C, 6 h, 55%.



Scheme 3. Synthesis of compound **16**–**18**. Reagents and conditions: (a) 10 N HCl, reflux, 24 h, 85%; (b) i—$SOCl_2$, DCM, cat. DMF, reflux, 3 h; ii—2-amino-6-methyl pyridine **5**, pyridine, rt, 2 h, 20%; (c) **16a**, **b**, **d**: $ArB(OH)_2$, $Pd(PPh_3)_4$, 2 M aq Na_2CO_3, toluene/DME, EtOH, reflux, overnight, 80%, **16c** 2-OCH_3–Ph–$B(OH)_2$, $Pd(OAc)_2$, **10**, K_3PO_4, toluene, EtOH, reflux, 1 h, 90%; (d) bis(pinacolato)diboron, KOAc, $PdCl_2$(dppf), DMF, 105 °C, 3 h, 65%; (e) 2-bromo pyridine, $PdCl_2$(dppf), 2 M aq Na_2CO_3, IPA, DMF, 105 °C, 3 h, 45%.

mGluR5 affinity, however, substitution at the 2″ position provided compound, **9d** with favorable activity. Substitution with the 3″, 5″-difluoro phenyl group provided the most potent compound, **9e**, in this series with an affinity of 43 nM. Substitution with a bulky 1-naphthyl group (**9f**) maintained moderate affinity, whereas a close homologue, the 2-naphthyl compound **9g**, was inactive, suggesting a restricted binding site in this region of the receptor. Substitution with heteroaryl rings (**9h** and **12**) reduced binding affinity suggesting perhaps hydrophobic interactions are more important in this region of the receptor.

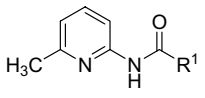
In order to visualize the tolerated and restricted substitutions on the aryl ring '**b**' in the present series of compounds, a comparison of the van der waals volume (vdw) of active and inactive compounds was carried out (Fig. 4). Inactive compounds **9c** and **9g** have bulky substituents that perhaps overlap in the non-tolerated space (depicted as blue contour), thus reducing their potency.

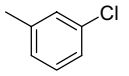
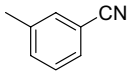
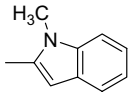
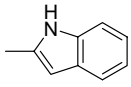
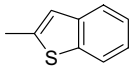
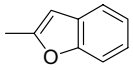
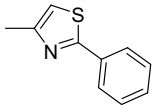
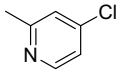
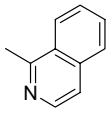
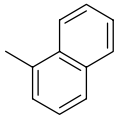
Substitution at the 4′ position (Table 3) provided compounds with mixed results as compounds **16a** and **16b** were substantially less active. However substitution with a methoxy group at the 2″ position provided compound **16c** with moderate affinity. Substitution with the 2-pyridyl group **18** improved the affinity, however substitution with another heteroaromatic ring, thiophene (**16d**) reduced mGluR5 binding affinity. These data further emphasize the sensitivity of the mGluR5 binding site to substitutions on the dipyridyl amide template.

Several of the active compounds were evaluated in a functional assay measuring phosphoinositide hydrolysis at mGluR5 in CHO cells (Table 4).[15] All compounds showed an antagonist profile like the alkyne based compounds **1** and **2** with favorable lipophilic character for CNS penetration and activity, as calculated by Clog *P*.

As observed previously, the diaryl amides showed loss in potency in the functional assay as compared to their binding affinities at mGluR5.[8] In the present series of

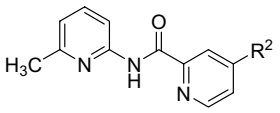
Table 1. Representative structures and in vitro activities of compounds **6**

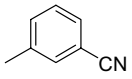
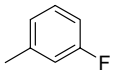
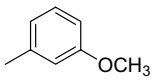
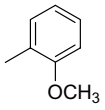
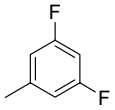
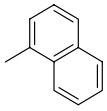
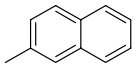


Compound	R^1	mGluR5 binding affinity $K_i \pm$ SEM (μM)
3		1.73 ± 0.10[a]
4		0.33 ± 0.02[a]
6a		>10
6b		3.07 ± 0.96
6c		8%[b]
6d		<1%[b]
6e		11%[b]
6f		40%[b]
6g		<1%[b]
6h		28%[b]
6i		0.44 ± 0.13
6j		62.76 ± 1.74[a]

[a] IC_{50} (μM) from Ref. 8.
[b] Percent inhibition at 10 μM.

Table 2. Representative structures and in vitro activities of compounds with substitution at the 3′ position of the aryl ring '**b**'



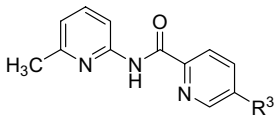
Compound	R^2	mGluR5 binding affinity $K_i \pm$ SEM (μM)
9a		0.32 ± 0.09
9b		0.50 ± 0.10
9c		13%[a]
9d		91%[a]
9e		0.043 ± 0.01
9f		0.25 ± 0.05
9g		32%[a]
9h		<1%[a]
12		2.48 ± 1.15
MPEP, 1	—	0.021 ± 0.001

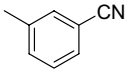
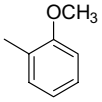
[a] Percent inhibition at 10 μM.

heterobiaryl amides, there was a similar loss in functional potency. This could be due to differences in the assay conditions. Also such differences in the activity have been observed in various other chemical classes of mGluR5 allosteric modulators.[16,17] Conversely, such differences could also suggest different interactions at the protein level and these binding differences will be further explored with future SAR studies.

In summary, a series of heterobiaryl amides were synthesized using palladium catalyzed cross-coupling reactions. Novel mGluR5 antagonists with comparable or improved binding affinities over previously described **3** and **4** were discovered. Further SAR for the mGluR5 were deduced based on these and previously reported ligands. In addition, during the course of this work

Table 3. Representative structures and in vitro activities of compounds with 4′ substitution in the aryl ring '**b**'



Compound	R^3	mGluR5 binding affinity $K_i \pm$ SEM (μM)
16a		2.80 ± 0.90
16b		7.4%[a]
16c		0.56 ± 0.08
16d		40%
18		0.10 ± 0.03

[a] Percent inhibition at 10 μM.

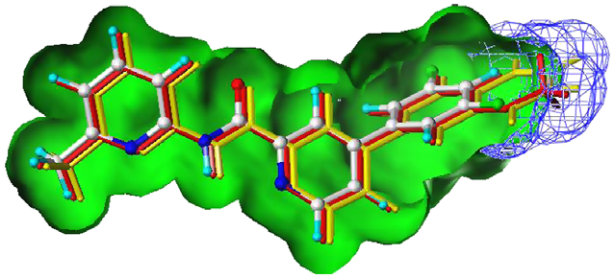


Figure 4. Comparison of vdw volumes for 3′ substituted compounds (Sybyl 7.2.3, Tripos Inc.).

Table 4. Functional activity at mGluR5

Compound	Functional activity $IC_{50} \pm$ SEM (μM)	Clog P[a]
3	66% at 10 μM	3.26
4	5.33 ± 1.20	2.08
9a	7.30 ± 0.74	2.99
9e	0.16 ± 0.03	3.84
18	12.40 ± 1.01	2.35
MPEP, **1**	0.04 ± 0.01[b]	3.78
MTEP, **2**	0.46 ± 0.11[b]	2.13

[a] Calculated by Sybyl 7.2.3 from Tripos Inc.
[b] From Ref. 10b.

Bonnefous et al. reported the identification of a series of pyridyl amides and described similar SAR wherein the importance of intramolecular hydrogen bonding between two aromatic rings to improve the binding affinity at mGluR5 was described.[11] The SAR of these compounds will be utilized for the future design of potent and selective mGluR5 antagonists.

Acknowledgments

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.bmcl.2006.12.083.

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14. All compounds were purified by flash chromatography and characterized by spectroscopic and microanalytical techniques. The final products were crystallized as the HBr salts for biological evaluation. The spectral data supported the assigned structures, for example, 4-(3,5-difluorophenyl)-*N*-(6-methylpyridin-2-yl)picolinamide hydrobromide, **9e** yield 0.11 g, 55%, mp 260–264 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ .53 (s, 3H), 6.91–6.96 (m, 1H), 6.95–6.97 (d, J = 7.6 Hz, 1H), 7.22–7.28 (m, 2H), 7.64–7.66 (dd, J = 2.0, 3.2 Hz, 1H), 7.66–7.69 (t, J = 7.2 Hz, 1H), 8.23–8.25 (d, J = 8.4 Hz, 1H), 8.47–8.48 (dd, J = 0.8, 1.2 Hz, 1H), 8.70–8.72 (d, J = 5.2 Hz, 1H), 10.49 (br s, 1H); ^{13}C NMR (101 MHz, $CDCl_3$) δ 24.19, 104.62, 104.87, 105.13, 110.13, 110.19, 110.31, 110.38, 110.82, 119.53, 120.14, 124.14, 138.62, 140.66, 147.77, 149.01, 150.35, 150.42, 157.28, 162.17, 162.25, 162.38, 164.73, 164.86; IR (Neat, cm^{-1}) 3435.7, 1694.7, 1598.4, 1532.9, 1457.2; GC-MS (EI) *m/z* 325 (M^+); Anal. ($C_{18}H_{13}F_2N_3O\cdot HBr\cdot 1.5H_2O$) C, H, N. The experimental and spectral data for all other compounds are reported in the Supplementary information.
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