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Bioorganic & Medicinal Chemistry Letters
Bioorganic & Medicinal Chemistry Letters 15 (2005) 4350–4353

# Dipyridyl amines: Potent metabotropic glutamate subtype 5 receptor antagonists

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Received 28 April 2005; revised 9 June 2005; accepted 13 June 2005
Available online 21 July 2005

**Abstract**—Modulation of the metabotropic glutamate subtype 5 (mGlu5) receptor may be useful in the treatment of a variety of central nervous system disorders. Herein, we report on the discovery, synthesis, and biological evaluation of dipyridyl amines as small molecule mGlu5 antagonists.


Glutamate is the primary excitatory neurotransmitter in the central nervous system (CNS).[1,2] As such, it performs a critical role in activating modulatory pathways through G protein-coupled metabotropic glutamate (mGlu) receptors. Group I mGlu receptors (mGlu1 and mGlu5) are primarily localized postsynaptically and are widely distributed in many brain regions, including the hippocampus, thalamic nuclei, and spinal cord. Stimulation of mGlu1 and mGlu5 leads to phosphoinositide (PI) hydrolysis and elevation of intracellular $Ca^{2+}$ levels via G-protein coupling to phospholipase C.[3,4] Excessive activation of mGlu5 receptors has been implicated in a number of CNS disorders including pain,[5] anxiety and depression,[6–11] and other neurological impairments such as drug addiction,[12] and Parkinson's disease.[13] As such, development of a potent and selective mGlu5 receptor antagonist as a potential therapeutic agent has been a major impetus for our labs.

Our previous research efforts on mGlu5 had been focused on alkyne derivatives such as 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP) which proved to be a potent and highly selective mGlu5 receptor antagonist with in vivo activity in animal models of anxiety.[14]

We recently disclosed the discovery of a new class of compounds (amides) demonstrating potency and selectivity toward the mGlu5 receptor.[15] With an $IC_{50}$ of 7 nM (hmGlu5 $Ca^{2+}$ flux), 3-hydroxy-6-methyl-*N*-(6-methylpyridin-2-yl)pyridine-2-carboxamide (**1**) was identified as a potent antagonist.[16] Key to this series potency was the conformational lock provided by one or two intramolecular hydrogen bonds (Fig. 1). Unfortunately, **1** and compounds of this type suffered from poor rat pharmacokinetics. In an effort to improve the overall physical and pharmacokinetic properties, compounds such as **2** were envisioned wherein the amide bond is replaced with a heteroaromatic ring and the ether maintains the same hydrogen bonding interaction with the amine NH. Quite surprisingly, this new compound retained activity in vitro, and represented a new and novel lead class of mGlu5 receptor antagonists. In the present communication, a detailed structure–activity relationship (SAR) of this series will be discussed.

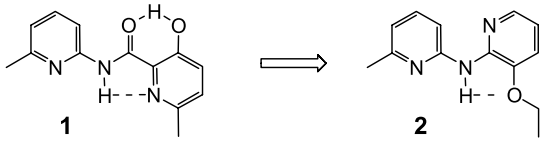


**Figure 1.** Transition from the dipyridyl-amide to the dipyridyl amine series.

*Keywords*: mGlu5; Metabotropic.
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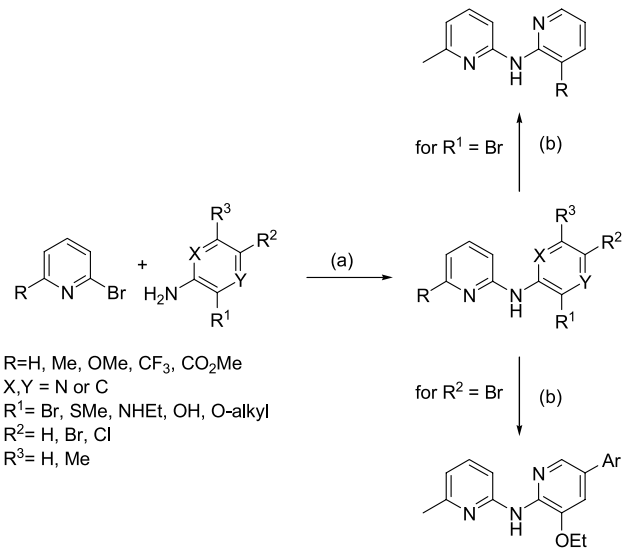
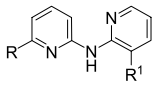
doi:10.1016/j.bmcl.2005.06.059




**Scheme 1.** Reagents and conditions: (a) $Pd_2dba_3$, BINAP, KO$^t$Bu, toluene, 110 °C; (b) $Pd(Ph_3P)_4$, $K_2CO_3$, toluene, MeOH, 90 °C.

**Table 1.** In vitro potency for mGlu5 receptor antagonists[22]



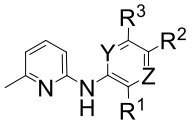
| Compound | R | $R^1$ | $Ca^{2+}$ flux[a] |
|---|---|---|---|
| **2** | Me | OEt | 40 |
| **3** | H | OEt | 138 |
| **4** | OMe | OEt | 556 |
| **5** | $CF_3$ | OEt | 1900 |
| **6** | $CO_2Me$ | OEt | 6200 |
| **7** | Me | OH | NA |
| **8** | Me | OMe | 458 |
| **9** | Me | *n*-OPr | 1600 |
| **10** | Me | *i*-OPr | 1000 |
| **11** | Me | OBn | 870 |
| **12** | Me | SMe | 790 |
| **13** | Me | NHEt | 3000 |
| **14** | Me | Me | NA |
| **15** | Me | *n*-Pr | 394 |
| **16** | Me | CN | NA |
| **17** | Me | $CO_2Me$ | NA |
| **18** | Me | Ph | NA |
| **19** | Me | 3-Pyr | NA |

NA—not active at 10 μM.
[a] hmGlu5 $Ca^{2+}IC_{50}$ nM.

Compounds **2**–**40** (Tables 1–3) were readily prepared as outlined in Scheme 1. The same general protocol was followed to synthesize most compounds. Typically, the appropriately substituted 2-aminopyridine or aniline was coupled with a 6-substituted 2-bromopyridine under palladium catalysis.[18] The aminopyridines or anilines could be fully assembled prior to coupling so that the end result of the palladium reaction was the final target compound, or in some cases (where $R^1$ or $R^2$ = Br), further palladium-mediated or $S_NAr$ reactions were carried out post coupling.[19,20]

With **2** as the lead, SAR of the first pyridine ring was conducted (Table 1).[21] Similar to the previous amide series,[15] substitution at C-3 or C-4 led to inactive compounds, while substitution at C-5 resulted in a loss in potency (not shown). However, C-6 was amenable to

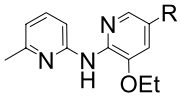
**Table 2.** In vitro potency for mGlu5 receptor antagonists **2**, **20**–**29**

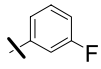
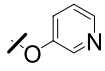


| Compound | Y | Z | $R^1$ | $R^2$ | $R^3$ | $Ca^{2+}$flux[a] |
|---|---|---|---|---|---|---|
| **2** | N | CH | OEt | H | H | 40 |
| **20** | N | N | OEt | H | H | 497 |
| **21** | CH | N | OEt | H | H | NA |
| **22** | CH | CH | OEt | H | H | NA |
| **23** | CF | CH | OMe | H | H | NA |
| **24** | N | CMe | OEt | H | H | 2700 |
| **25** | N | CH | OEt | H | Me | NA |
| **26** | N | CH | OEt | Br | H | 47 |
| **27** | N | CH | OEt | Cl | H | 17 |
| **28** | N | CH | OEt | CN | H | 46 |
| **29** | N | CH | OEt | Me | H | 119 |

NA—not active at 10 μM.
[a] hmGlu5 $Ca^{2+}$ $IC_{50}$ (nM).

**Table 3.** In vitro potency for mGlu5 receptor antagonists **31**–**40**



| Compound | $R^3$ | $Ca^{2+}$flux[a] |
|---|---|---|
| **30** |  | 267 |
| **31** |  | 37 |
| **32** |  | 126 |
| **33** |  | 513 |
| **34** |  | 243 |
| **35** |  | 193 |
| **36** |  | 12 |
| **37** |  | 36 |
| **38** |  | 18 |
| **39** |  | 45 |
| **40** |  | 80 |

[a] hmGlu5 $Ca^{2+}$ flux $IC_{50}$ (nM).

some modifications. The unsubstituted analog **3** was 3-fold less potent, whereas larger groups (**4**–**6**) led to greater losses in potency. With a C-6 methyl group as optimal, the $R_1$ groups were varied. Once again, the initial choice of –OEt proved optimal as the free phenol (**7**) and different alkoxy substitutions (**8**–**11**) only led to loss in potency. Larger groups were also detrimental as –SMe was worse than –OMe, whereas –NHEt was completely inactive. Substitution of the oxygen atom with carbon as in **15** results in a 10-fold drop in potency, reinforcing the importance of the intramolecular hydrogen bond. All other carbon-based substitutions were inactive (**14**, **16**–**19**). Oddly, ester **17** can participate in an intramolecular hydrogen bonding interaction with the aminopyridine NH and is of the same tether length as –OEt, yet is not active. Lastly, substitution on the nitrogen atom linking the two aromatic residues (i.e., NMe) leads to complete loss of activity (not shown).

Further SAR of the second pyridine ring is outlined in Table 2. Although installation of a second nitrogen atom in the ring as in pyrazine **20** leads to a 10-fold drop in potency, removing the initial nitrogen atom (**21**), or both heteroatoms (**22**) completely abolishes activity. Attempts to replace this pyridine ring heteroatom with a bioisosteric C–F bond (**23**) also results in complete loss of activity. Substitution at C-4 (**24**) or C-6 (**25**) with a methyl group was not tolerated resulting in either a large or complete loss in activity. Fortunately, the last remaining position on the ring ($R_2$) was amenable to substitution (**26**–**29**) and further SAR was evaluated at this position.

With the dipyridylamine substitution optimized with the exception of the $R_2$-group, rapid analog synthesis was carried out to optimize this position. Small groups such as halogen (**26**, **27**) or CN (**28**) maintain or slightly improve potency, whereas a large phenyl group (**30**) results in a 6-fold loss (Tables 2 and 3). Potency can be recovered by substitution on the aromatic ring especially at the *ortho*- and *meta*-positions (**31**, **32**). Additionally, heteroaromatic rings such as 3-pyridyl (**36**), 3,5-pyrimidyl (**37**), and an O-linked 3-pyridyl (**38**) provide a large boost in potency relative to phenyl. Unfortunately, these effects are not additive as **40** was less potent than the two independent modifications (**31** and **36**).[26]

**Table 4.** Rat pharmacokinetics of selected mGlu5 receptor antagonists

| Compound | $Cl_p$ (mL/min/kg) | $T_{1/2}$ (h) | $F^{a,b}$ (%) | $V_d$ (L/Kg) |
|---|---|---|---|---|
| **2** | 16 | 2.1 | 11 | 1.2 |
| **3** | 78 | 0.8 | 16 | 2.9 |
| **15** | 320 | 1 | ND | ND |
| **20** | 102 | 1 | ND | ND |
| **28** | 90 | 1.6 | 13 | 7 |
| **32** | 93 | 0.5 | 19 | 3 |
| **35** | 124 | 1 | 0 | 6.1 |
| **36** | 50 | 1 | 38 | ND |
| **37** | 79 | 0.6 | 67 | 2.3 |
| **38** | 52 | 1.2 | ND | 3.7 |
| **39** | 105 | 0.7 | 8 | 4.7 |

ND—not determined.
[a] Sprague–Dawley rats.
[b] Dose: 2 mg/kg iv; 10 mg/kg po.

The pharmacokinetic parameters of representative examples were measured in rats (Table 4). Generally, most of the compounds had low to moderate oral bioavailability and moderate to fast plasma clearances.[27] Several analogs were profiled in rat and human liver microsomes to investigate in vitro metabolism. Most compounds were relatively stable with the major metabolites arising from hydroxylation of the pyridine rings.[28] Little O-dealkylation was observed. These compounds are also fairly hydrophobic given their higher log *D*s (3–5). That fact along with their higher volumes of distribution may help to explain the apparent higher plasma clearance rates.[29]

In summary, we have successfully identified a potent and novel class of mGlu5 receptor antagonists. Compounds such as **2** and **36** are two such examples that have slightly better pharmacokinetic profiles than their amide counterparts. Additionally, these dipyridyl amines may prove to be viable tools for studying the effects of mGlu5 antagonists in in vivo models of disease states such as anxiety, pain, and drug addiction.

## Acknowledgments

The authors thank Merryl Cramer and Christopher King for expert technical assistance.

## References and notes

1. Ozawa, S.; Kamiya, H.; Tsuzuki, K. *Prog. Neurobiol. (Oxford)* **1998**, *54*, 581.
2. Brauener-Osborne, H.; Egebjerg, J.; Nielsen, E. O.; Madsen, U.; Krogsgaard-Larsen, P. *J. Med. Chem.* **2000**, *43*, 2609.
3. Pin, J.-P.; Acher, F. *Curr. Drug Targets: CNS Neurol. Disord.* **2002**, *1*, 297.
4. Conn, P. J.; Pin, J.-P. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 205.
5. Varney, M. A.; Gereau, R. W. I. *Curr. Drug Targets: CNS Neurol. Disord.* **2002**, *1*, 283.
6. Brodkin, J.; Busse, C.; Sukoff, S. J.; Varney, M. A. *Pharmacol., Biochem. Behav.* **2002**, *73*, 359.
7. Spooren, W. P. J. M.; Vassout, A.; Neijt, H. C.; Kuhn, R.; Gasparini, F., et al. *J. Pharmacol. Exp. Ther.* **2000**, *295*, 1267.
8. Spooren, W. P. J. M.; Schoeffter, P.; Gasparini, F.; Kuhn, R.; Gentsch, C. *Eur. J. Pharmacol* **2002**, *435*, 161.
9. Tatarczynska, E.; Klodzinska, A.; Chojnacka-Wojcik, E.; Palucha, A.; Gasparini, F., et al. *Br. J. Pharmacol.* **2001**, *132*, 1423.
10. Klodzinska, A.; Tatarczynska, E.; Chojnacka-Wojcik, E.; Pilc, A. *Pol. J. Pharmacol.* **2000**, *52*, 463.
11. Schulz, B.; Fendt, M.; Gasparini, F.; Lingenhohl, K.; Kuhn, R., et al. *Neuropharmacology* **2001**, *41*, 1.
12. Chiamulera, C.; Epping-Jordan, M. P.; Zocchi, A.; Marcon, C.; Cottiny, C., et al. *Nat. Neurosci.* **2001**, *4*, 873.
13. (a) Spooren, W. P. J. M.; Gasparini, F.; Bergmann, R.; Kuhn, R. *Eur. J. Pharmacol.* **2000**, *406*, 403; (b) Awad, H.; Hubert, G. W.; Smith, Y.; Levey, A. I.; Conn, P. I. *J. Neurosci.* **2000**, *20*, 7871.
14. (a) Cosford, N. D. P.; Tehrani, L.; Roppe, J.; Schweiger, E.; Smith, N. D., et al. *J. Med. Chem.* **2003**, *46*, 204; (b)

Gasparini, F.; Kuhn, R.; Stoehr, N.; Flor, P. J.; Heinrich, M., et al. *Neuropharmacology* **1999**, *38*, 1493.
15. Bonnefous, C.; Vernier, J.-M.; Hutchinson, J. H.; Chung, J.; Reyes-Manalo, G.; Kamenecka, T. M. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1197.
16. MTEP (see Ref. 14), **1** and **2** all bind at the same binding site of the mGlu5 receptor: $K_i$ (mGlu5) = 16, 295, and 101 nM, respectively. Binding to native mGlu5 receptors was determined by measuring the displacement by test compounds of [$^3$H]-3-methoxy-5-(pyridin-2-ylethynyl)pyridine from rat cortical membranes.[17]
17. Cosford, N. D. P.; Roppe, J.; Tehrani, L.; Seiders, T. J.; Schweiger, E. J., et al. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 351.
18. (18) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240; (b) Bolm, C.; Frison, J-C.; Le Paih, J.; Moessner, C. *Tetrahedron Lett.* **2004**, *45*, 5019.
19. (a) Bellina, F.; Carpita, A.; Rossi, R. *Synthesis* **2004**, *15*, 2419; (b) Kotha, S.; Lahiri, K.; Kashinath, D. *Tetrahedron* **2002**, *58*, 9633.
20. (a) Xu, L-W.; Xia, C-G.; Li, J-W.; Hu, X-X. *Synlett* **2003**, 2071; (b) Oi, R.; Shimakawa, C.; Takenaka, S. *Chem. Lett.* **1988**, *5*, 899.
21. The 3- and 4-pyridyl linked aminopyridines were also investigated as was phenyl, but all were inactive. Only the 2-substituted pyridines were active.
22. Functional potencies assessed using an automated assay employing Ltk cells that stably express human recombinant mGlu5 receptors. 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.[23–25]
23. Varney, M. A.; Cosford, N. D. P.; Jachec, C.; Rao, S. P.; Sacaan, A., et al. *J. Pharmacol. Exp. Ther.* **1999**, *290*, 170.
24. Varney, M. A.; Suto, C. M. *Drug Discovery Today: HTS Suppl.* **2000**, *1*, 20.
25. Daggett, L. P.; Sacaan, A. I.; Akong, M.; Rao, S. P.; Hess, S. D., et al. *Neuropharmacology* **1995**, *34*, 871.
26. The other cyanopyridine isomer was also made and was also less potent.
27. Despite rapid plasma clearance in rats several compounds exhibited good to excellent in vivo receptor occupancy (ro). For example compounds **37** and **38** had ro's = 79% and 82%, respectively (iv dosing at 10 mg/kg).
28. Generally, 60–97% of the parent compound remained after incubating with rat and human liver microsomes for 1 h.
29. Additional clearance mechanisms such as Phase II metabolism or transporters cannot be ruled out.