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Dipyridyl amides: potent metabotropic glutamate subtype 5 (mGlu5) receptor antagonists

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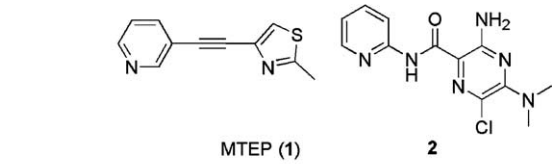
Abstract—The mGlu5 receptor has been implicated in a number of CNS disorders. Herein, we report on the discovery, synthesis, and biological evaluation of dipyridyl amides as small molecules mGluR5 antagonists.

Metabotropic glutamate (mGlu) receptors are a family of G-protein coupled receptors in the mammalian nervous system that are activated by L-glutamate.[1,2] 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 ($[Ca^{2+}]_i$) 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] mental retardation,[13] and obesity.[14] The development of potent and selective mGlu5 receptor antagonists as potential therapeutic agents has therefore been the focus of significant research in these laboratories.

Our previous research efforts for mGlu5 receptor antagonist had been focused on alkyne derivatives such as 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]-pyridine (MTEP, **1**) which proved to be a potent and highly selective mGlu5 receptor antagonist with in vivo activity in animal models of anxiety.[15] In the search for novel structural leads, compound **2** was identified as a modest mGlu5 receptor antagonist in a high throughput screen.[16] In the present communication, a detailed structure–activity relationship (SAR) study of this molecule will be discussed.



Compounds **2–24** (Tables 1 and 2) were readily prepared as outlined in Scheme 1. The appropriate 2-aminopyridines were coupled to pyrazine-2-carboxylic acids,[17] pyridine-2-carboxylic acids, or aryl carboxylic acids using HATU and a base. Compound **25** (Table 1) was obtained by dechlorination of **2** via hydrogenolysis.

Compound **26** (Table 2) was prepared in eight steps from commercially available 6-methylpyridine-2,3-dicarboxylic acid (**27**) as described in Scheme 2. The dicarboxylic acid **27** was dehydrated to give anhydride **28** and was chemoselectively opened with methanol to form ester–acid **29**. The acid was then converted into allyl carbamate **30** via Curtius rearrangement.

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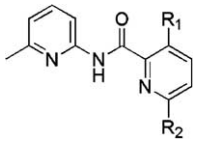
Table 1. In vitro potency data[20] for mGlu5 receptor antagonists **2**–**17**, **and 25**

Entry	R	R_1	R_2	R_3	hmGlu5 Ca^{2+} flux IC_{50} (nM)[a]
2	H	NH_2	Cl	$N(Me)_2$	134
3	H	H	Cl	$N(Me)_2$	158
25	H	NH_2	H	$N(Me)_2$	5084
4	H	NH_2	Cl		103
5	H	NH_2	Cl	NH*i*-Pr	23
6	H	NH_2	Cl	NH_2	3800
7	H	NH_2	Cl	H	11
8	H	H	Cl	H	254
9	H	H	Me	H	165
10	H	NH_2	H	H	3536
11	H	H	H	H	NA[b]
12	H	NH_2	Br	H	12
13	H	NH_2	Me	H	28
14	H	NHMe	Cl	H	145
15	H	$N(Me)_2$	Br	H	NA[b]
16	6-Me	NH_2	Cl	H	5
17	6-Me	NH_2	Me	H	8

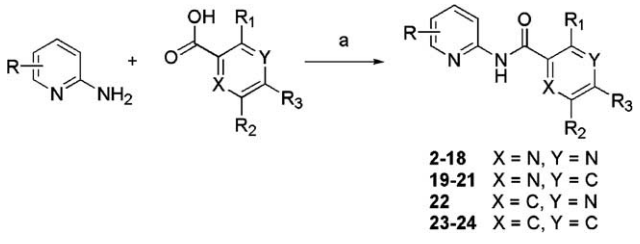
[a] Value are means of two to three experiments.
[b] NA: not active (hmGlu5 Ca^{2+} flux IC_{50} > 10 μM).

Table 2. In vitro potency data[20] for mGlu5 receptor antagonists **19**–**21, 26**, and **31**

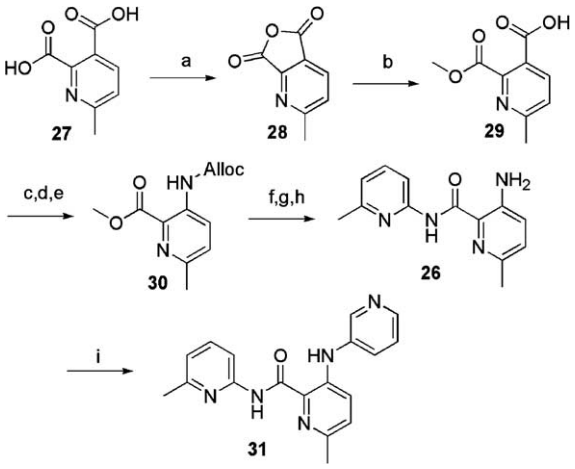


Entry	R_1	R_2	hmGlu5 Ca^{2+} flux IC_{50} (nM)[a]
19	H	Me	32
20	OH	Me	7
21	H	Br	21
26	NH_2	Me	22
31		Me	11

[a] Value are means of two to three experiments.



Scheme 1. Reagents and conditions: (a) HATU, *i*-Pr_2NEt, CH_2Cl_2, rt, 18 h.



Scheme 2. Reagents and conditions: (a) Ac_2O, 100 °C, 4 h; (b) MeOH, 0 °C to rt, 18 h; (c) ethyl chloroformate, Et_3N, THF, 0 °C to rt, 1.5 h; (d) NaN_3, rt, 2 h; (e) allyl alcohol, toluene, 100 °C, 18 h; (f) LiOH, THF, rt, 5 h; (g) 2-amino-6-methylpyridine, *O*-(7-azabenzotriazol-1-yl)-*N*,*N*,*N*′,*N*′-tetramethyluronium hexafluorophosphate (HATU), *i*-Pr_2NEt, CH_2Cl_2, rt, 48 h; (h) $Pd(PPh_3)_4$, $PhSiH_3$, THF, 0 °C; (i) 3-bromopyridine, $Pd_2(dba)_3$, *rac*-2,2′-bis(diphenylphosphino)-1,1′-binaphthyl (binap), sodium *tert*-butoxide, toluene, microwave irradiation,[18] 140 °C, 15 min.

Hydrolysis of the ester, HATU coupling with 2-amino-6-methylpyridine, and alloc deprotection yielded the desired amine **26**. Compound **31** (Scheme 2, Table 2) was obtained via microwave[18] assisted Buchwald amination of 3-bromopyridine with amine **26**.

Initial modifications focusing on the pyrazine ring allowed us to simplify and improve the potency of the lead (**2**) (Table 1). Firstly, it appears that groups capable of internal hydrogen bonding with the amide carbonyl (i.e., **7**, **14** compared to **15**) are optimal at the R_1 position, although substitution is not required to maintain potency (i.e., **3**, **9**). The R_3 position appeared to be the most variable. A wide variety of substituted amines such as $N(Me)_2$ (**3**), NH*i*-Pr (**5**), or N-piperidyl (**4**) were tolerated while a free NH_2 group (**6**) was not. This perhaps suggests that the R_3 substituent may occupy a hydrophobic pocket in the mGlu5 binding site. It is also worth noting that R_3, like R_1, is not required for potency (**7**, **8**, **12**, and **13**). The most important position, however, on the pyrazine ring appears to be R_2. It is amenable to a wide variety of substituents, however, when R_2 = H, all compounds are inactive (**10**, **11**, and **25**). Having identified a potency enhancing substitution pattern on the pyrazine ring (R_1 = NH_2, R_3 = H, and R_2 = Cl (**7**) or R_2 = Me (**13**)), SAR around the pyridine ring was then investigated. Probing all the positions on the pyridine ring revealed that only the 6-position was amenable to substitution (**16** and **17**).[19]

The molecule could be further simplified by removing one of the pyrazine nitrogen atoms, leading to a new dipyridyl-amide series (Table 2). Compound **26** showed similar potency to **17**, its direct analogue in the pyrazine series. Further substitution around the new pyridine ring showed that R_1 could be hydrogen or better yet, a group

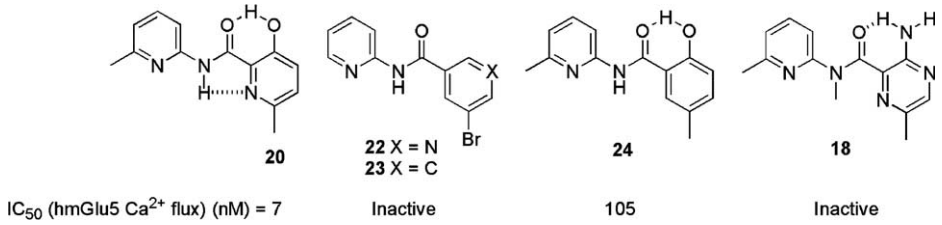


Figure 1. Important hydrogen binding motifs of mGlu5 antagonists.

that could engage in an internal hydrogen bonding interaction with the amide oxygen (**20**, **26**, and **31**). This SAR tracks with the pyrazine series (Table 1). Compound **31** was the second most potent analog synthesized in this series and reveals that there is ample space for substitution at the R_1 position. Also there may be additional opportunities to improve potency by substitution with aromatic groups or with hydrogen bond acceptors. Further SAR revealed that removal of the other pyrazine nitrogen atom (**22**) or both (**23**) led to complete loss of activity (Fig. 1). However, both heteroatoms could be removed without a significant loss of potency, as long as one substituent on the phenyl ring could engage in an internal hydrogen bonding interaction with the amide carbonyl as seen in **24**. Additionally, the N-methyl derivative **18** (Fig. 1) is inactive, indicating that the amide NH bonding interaction may be the more important of the two, however other considerations such as sterics and rotamer population may be overriding factors in this case. Based on the SAR conducted in both the pyrazine and pyridine series, we postulate that these molecules require at least one (**21** and **24**) or even better, two critical internal hydrogen bonding interactions (**20**, **26**, and **31**) to achieve the proper conformation for binding to the mGlu5 receptor (Fig. 1).

The pharmacokinetic properties of several of the most active derivatives were measured in rats (Table 3). As a class, the amides have poor rat PK characterized by high plasma clearance (56–176 mL/min/kg), modest half lives (1.25–4.4 h), and low oral bioavailability (0–20%).[21] Additionally, most compounds had short half lives when incubated with rat and human liver microsomes. Pyrazine **13** shows an improved PK profile compared to pyridines **20** and **31**. The additional aromatic heteroatom may impart improved solubility in **13**, and the lack of the additional aromatic methyl group may reduce metabolism as well. Nonetheless, additional studies will have to be done to make any definitive conclusions.

Table 3. Pharmacokinetic parameters of selected compounds

Compd	13	20	31
Clp (ml/min/kg)[a]	56	>100	176
$t_{1/2}$ (iv, h)[a]	4.4	<LOQ[d]	1.25
%*F* (po)[b]	20	<LOQ[d]	ND[c]

[a] Iv dosing at 2 mg/kg.
[b] Po dosing at 10 mg/kg.
[c] ND: not determined.
[d] LOQ: limit of quantitation.

In summary, high throughput screening identified **2** as a structurally distinct mGlu5 receptor antagonist with modest in vitro potency. Optimization of the lead led to the discovery of new compounds (**16** and **20**) in this class, with potencies comparable to MTEP (**1**). Although initial pharmacokinetic evaluations suggest that these compounds are rapidly cleared from plasma, they may have some use in evaluating the role of mGlu5 in animal models of diseases.

Acknowledgements

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18. Using SmithCreator™ microwave from Personal Chemistry.
19. Substitution and the 3-, 4-, and 5- position led to inactive compounds. 3- and 4-Pyridyl derivatives were also synthesized and were found to be inactive.
20. 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.[22–24]
21. Despite rapid clearance in rats several compounds exhibited good to excellent receptor occupancy (ro). For example, compound **31**: ro = 86% (iv dosing at 10 mg/kg).
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