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Pyrimidine methyl anilines: selective potentiators for the metabotropic glutamate 2 receptor

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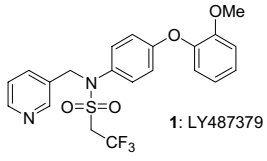
Abstract—Pyrimidine methyl anilines as potent and selective mGlu2 potentiators are described. Findings from the structure–activity-relationship investigations are discussed.

1. Introduction

Abnormally high levels of glutamate, a major excitatory neurotransmitter in the central nervous system, have been linked to several neurological diseases, such as Parkinson's disease, schizophrenia, Huntington's chorea, and Alzheimer's disease.[1,2] There are two types of glutamate receptors in the CNS: the ionotropic glutamate (iGlu) receptors and the metabotropic glutamate (mGlu) receptors. The iGlu receptors are glutamate-gated ion channels, which mediate fast synaptic transmission. The mGlu receptors modulate glutamate transmission by second messenger activation. Excessive accumulation of glutamate in the perisynaptic extracellular region triggers both group II (mGlu2 and 3) and group III (mGlu4, 6, 7, and 8) receptors to inhibit further release of glutamate.[2,3] Thus, stimulation of these presynaptic receptors could be a therapeutic means to reduce excess glutamate in the CNS.

Several small molecule agonists that simultaneously activate both mGlu2 and mGlu3 receptors have been reported.[4] A selective mGlu2 receptor agonist, however, has not yet been identified, presumably due to significant homology between the two receptor binding sites. Recently, selective activation of mGlu2 was reported using pyridine sulfonamide derivatives (such as compound **1**: LY487379) as potentiators (or positive allosteric modulators), which bind to the transmembrane region instead of the agonist binding pocket in the extracellular domain.[5,6] Comparative pharmacological analyses further revealed that selectivity was attributed to distinct differences in the amino acid sequences of the mGlu2 and mGlu3 transmembrane regions.[7] These reports prompted the current disclosure of the discovery of novel pyrimidine methyl anilines as selective positive modulators of mGlu2 receptor.



1: LY487379

2. Structure–activity relationships

In order to gain insight into the binding region of mGlu2 receptor potentiators, our investigation began with structure–activity-relationship (SAR) studies of the pyridyl region of the pyridine sulfonamides, which was not presented in detail in the recent reports.[5] Replacement of the 3-pyridyl moiety on compound **1** with other aromatic rings such as 3-fluorobenzene, 3-thiophene, 3-furan, 2-benzimidazole, 3-nitrobenzene, 3-aminobenze, or 4-imidazole all resulted in complete loss of potency. Nevertheless, quinoline and pyrimidine

Keywords: Metabotropic glutamate receptor; mGlu2; Potentiator.
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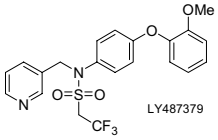
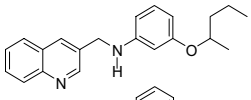
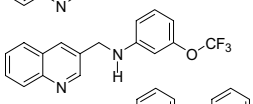
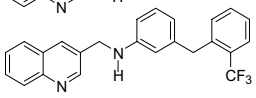
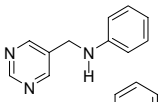
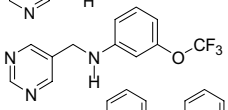
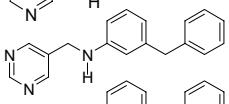
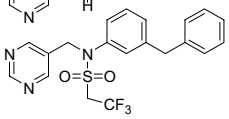
Table 1. Quinoline and pyrimidine anilines

Compd	Structure	mGlu2 EC_{50} μM[a] [% potentiation][b]
1	 LY487379	1.70 [52%]
2		4.30 [41%]
3		5.20 [40%]
4		1.00 [18%]
5		9.60 [68%]
6		0.19 [26%]
7		0.71 [31%]
8		0.54 [43%]

[a] Concentration of compound required to activate 50% of [^{35}S]GTPγS in the presence of 10 μM glutamate as agonist.

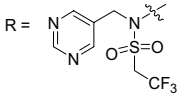
[b] 100% potentiation is defined as [^{35}S]GTPγS activation with 1 mM glutamate alone.

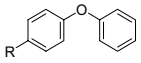
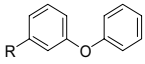
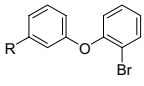
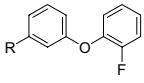
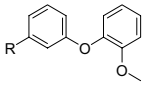
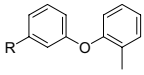
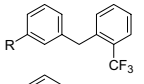
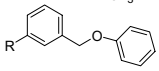
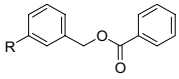
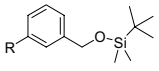
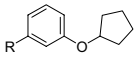
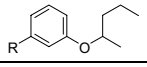
substitutions retained some activity (Table 1). Assessment of the efficacy of these compounds was based on two criteria: the potency (EC_{50}) and the level of potentiation (%) in the GTPγS binding assay (see footnotes of Table 1). As a point of reference, compound **1** (LY4873739) in our assay gave an EC_{50} value of 1700 nM with 52% potentiation,[7a] compared with a reported EC_{50} of 270 nM.[5b]

Using select right hand pieces described by Barda and co-workers,[5a,c] the quinoline and pyrimidine analogs exhibited some surprising structure–activity trends (Table 1). Unlike the pyridine sulfonamide series where the sulfonamide functionality was essential for potency,[5c] both quinoline and pyrimidine derivatives in Table 1 were active as secondary amines. Quinolines **2** and **3** were weakly potent; however, quinoline **4** had a modest potency of 1.0 μM but a low level of potentiation. Pyrimidine methyl aniline **5** had a good level of potentiation despite its low potency. Both pyrimidines **6** and **7** had submicromolar activity, with compound **6** showing an impressive EC_{50} of 0.19 μM. Interestingly, *the sulfonamide analogs* (*structures not shown*) *of active secondary amines* **2**–**6** *were inactive up to 10 μM*. The exception was sulfonamide **8**, which retained the activity and level of potentiation of its amine precursor (**7**). It should also be noted that the trifluoromethoxy moiety appeared to be critical for the activity of pyrimidine (**6**). Other alkoxy phenyl amine analogs of pyrimidine **6** were inactive.

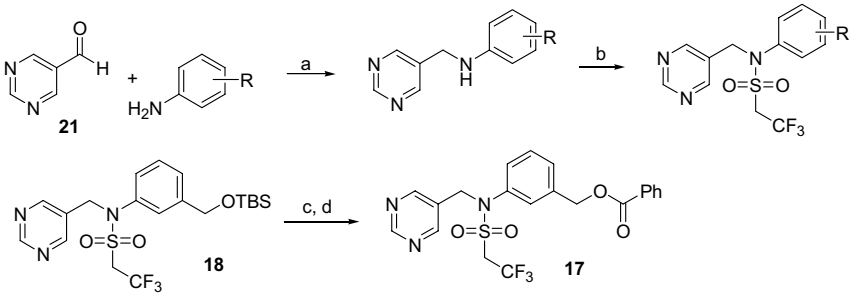
These observations prompted a systematic investigation of the more potent pyrimidine methyl aniline series, beginning with the phenyl aryl ether right hand piece on compound **1** (LY4873739). Gratifyingly, pyrimidine phenyl ether **9** exhibited better potency than the pyridyl analog (**1**) (Table 2). Moving the phenyloxy substituent to the 3 position (**10**) enhanced the level of potentiation with only slight loss of potency. This was in contrast to the pyridine sulfonamide series, which was reported be three- to fourfold more potent with the 3-phenyloxy group than the 4-phenyloxy group.[5c] Furthermore, while additional substituents *ortho* to the phenoxy ring increased the activity of the pyridine sulfonamides,[5c] similar substitutions on the pyrimidine sulfonamide with bromine (**11**) or fluorine (**12**), or methoxy (**13**) groups slightly reduced the potency in this series instead. Only the methyl analog **14** retained the potency and level of potentiation of **10**. Thus, the SAR of the pyrimidine

Table 2. Aryloxy substituents and linker modifications

R = 

Compd	Structure	mGlu2 EC_{50} μM [% potentiation][a]
9		0.56 [37%]
10		0.66 [52%]
11		1.10 [40%]
12		0.86 [46%]
13		0.76 [62%]
14		0.63 [53%]
15		0.97 [73%]
16		1.20 [51%]
17		0.81 [39%]
18		0.66 [48%]
19		0.84 [60%]
20		0.35 [31%]

[a] See footnotes a and b in Table 1.



Scheme 1. Reagents and conditions: (a) MeOH, reflux; $NaBH_4$; or $NaBH(OAc)_3$, AcOH, dichloroethane; (b) 2,2,2-trifluoroethanesulfonyl chloride, pyridine, dichloroethane; (c) TBAF, AcOH; (d) benzoyl chloride.

series exhibited distinct differences from the SAR of the pyridine series.

The divergence of SAR between the two series was also observed with benzyl pyrimidines. *ortho* Trifluoromethylbenzyl and phenyloxymethyl were two right hand pieces reported to be more potent in the pyridine series than the phenyl ether right hand piece on compound **9**.[5c] However, when applied to the pyrimidine methyl aniline series, these moieties reduced the potency of their pyrimidine sulfonamide analogs (**15**, **16**) even though their levels of potentiation improved. Interestingly, the activity was restored by replacing the phenyloxy substituent with a benzoyl group (**17**) or bulky trialkysilyl group (**18**), suggesting the presence of a lipophilic pocket. Indeed, bulky substituents such as cyclopentyloxy (**19**) and 2-pentyloxy (**20**) groups produced potent compounds while their methoxy, and ethoxy analogs (structures not shown) were inactive. In fact, pyrimidine **20** was the most potent compound (0.35 μM) in the pyrimidine sulfonamide series in this investigation, even though its level of potentiation was moderate (sulfonamide **15** had the highest level of potentiation with 73%).

The nature of the right binding region was further elucidated by changing the position of the 2-pentyloxy group *meta* to the aniline ring on compound **20**. Both *para* and *ortho* substituted 2-pentyloxy pyrimidine sulfonamides (structures not shown) were inactive. In contrast, *para* phenyloxy sulfonamides (**9**) exhibited potency comparable to its *meta* phenyloxy analog (**10**). Therefore, the binding region *para* to the aniline phenyl group appeared to be less tolerant of bulky groups than the binding region *meta* to the phenyl group.

3. Chemistry

The synthesis of these compounds was relatively facile. In most cases, the fully elaborated aniline was alkylated by reductive amination with pyrimidine-5-carboxaldehyde (**21**) using either sodium borohydride or sodium triacetoxyborohydride.[8] The sulfonamides were prepared by addition of 2,2,2-trifluoroethanesulfonyl chloride and an amine base.[5] Compound **17** was prepared by TBAF deprotection of sulfonamide **18** followed by acylation with benzoyl chloride (Scheme 1).

4. Conclusion

In conclusion, we have identified pyrimidine methyl anilines as novel mGlu2 potentiators. The most potent compound in this study (**20**) was also determined to be inactive against the mGlu3 receptor up to 10 μM (mGlu3 receptor binding potency and level of potentiation were determined using the same protocol as the mGlu2 receptor binding assay described in the footnotes of Table 1). Comparative analyses of the analogs have revealed these pyrimidines as a distinct series with structure–activity relationships unlike those previously reported for the pyridine sulfonamides. In addition, quinolines (**2**, **3**, **4**) and pyrimidines (**5**, **6**, **7**) were found to be active as just secondary amines. The pyrimidine methyl anilines are useful probes to elucidate the nature of the mGlu2 transmembrane binding site.

Acknowledgements

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