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SAR study of a subtype selective allosteric potentiator of metabotropic glutamate 2 receptor, *N*-(4-phenoxyphenyl)-*N*-(3-pyridinylmethyl)ethanesulfonamide

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Abstract—The major excitatory neurotransmitter in the Central Nervous System is L-glutamic acid. As a result much attention has been given to the discovery of selective modulators of both the ionotropic glutamate receptors (iGluRs) and the metabotropic glutamate receptors (mGluRs). In this study we describe a novel class of subtype selective allosteric potentiators of the mGlu2 receptor. An active compound *N*-(4-phenoxyphenyl)-*N*-(3-pyridinylmethyl)ethanesulfonamide, LY181837, was identified in the course of compound screening. The synthesis of two series of analogs examined the structural requirements of the diaryl region of this compound. This SAR study also resulted in compounds with an increase in potency of over 100-fold where the most potent compound reported has $EC_{50} = 14$ nM.

L-Glutamic acid is the primary excitatory neurotransmitter in the brain. Glutamate acts via two main classes of receptors known as ionotropic, a series of ligand gated ion channels (iGluRs), and metabotropic (mGluRs).[1] The eight known subtypes of mGluRs belong to the type III superfamily of G-protein coupled receptors by virtue of their structural homology to other members of this class including the calcium sensing receptors, $GABA_B$ receptors, and phermone receptors. The subtypes can be further classified into three groups as a result of their sequence homology and function. The group II mGluRs, which consist of the mGlu2 and mGlu3 subtypes, have been shown to be negatively coupled to adenylate cyclase via activation of Gαi-protein.

Efforts from these laboratories and others toward effecting the direct modulation of group II metabotropic glutamate receptors has resulted in a number of group II selective agonists.[1,2] These direct acting agonists (e.g. LY354740, **1** and LY379268, **2**)[2] bind to the extracellular glutamate binding domain and displace other glutamate-site ligands, which include the group II-selective antagonist LY341495 (**3**) (Fig. 1).[3] These compounds have shown efficacy in a number of behavioral models, for example behavioral models of anxiety.[2] While these compounds are selective for group II mGluRs, agonists selective for mGlu2 have not been identified. As a result, the physiological role and therapeutic potential of selective modulation of individual

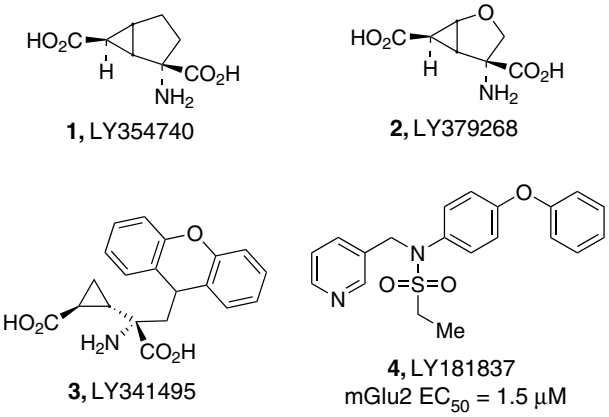

Figure 1. Metabotropic glutamate receptor compounds.

Keywords: Glutamate; Allosteric potentiators; mGlu2 Receptor.
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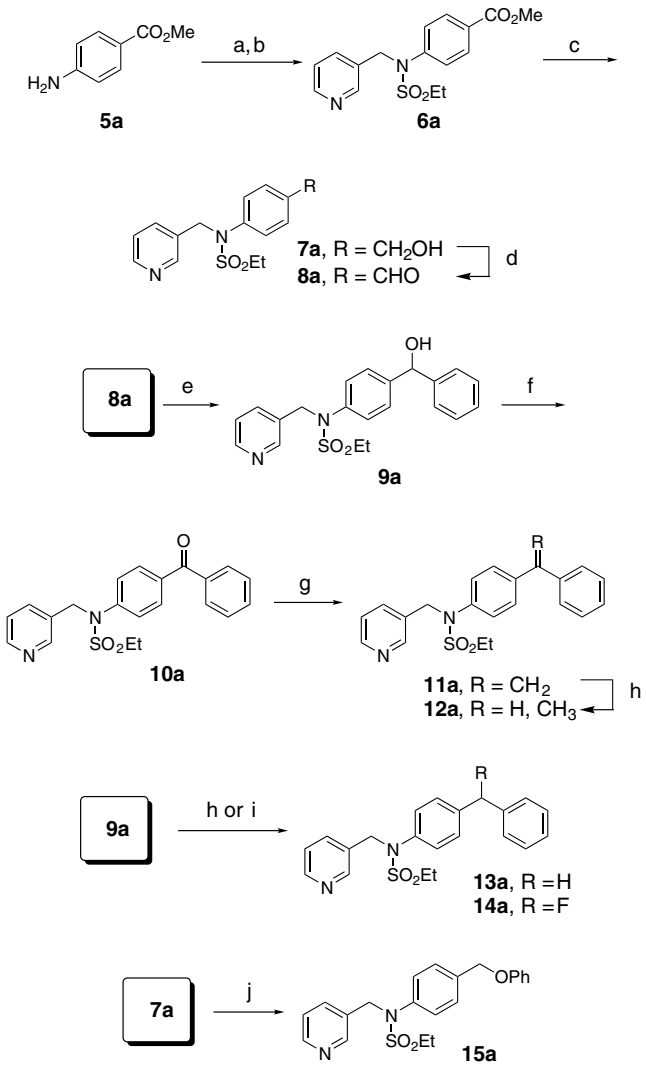
receptor subtypes in this class is essentially unknown. Binding allosteric to the glutamate binding site allows for the possibility of more differentiated binding sites for the different subtypes and as a result, the potential for subtype selectivity. Positive allosteric modulators or potentiators of related receptor systems have been recently described.[4] Previous communications describe the discovery of a series of mGlu2 selective potentiators[5] and aspects of their in vitro and in vivo activities.[5,6]

A functional assay was designed to identify subtype selective modulators of mGluRs. The assay which links receptor activation to a fluorescent response via a G-protein mediated intracellular calcium release, has been previously described in detail.[5] Lilly compound files were screened against this assay in a high-throughput format. This effort led to the identification of LY181837, **4**, a selective potentiator at mGlu2 having an EC_{50} of 1.5 μM.[5,7] The EC_{50} in this case, and as it is used to characterize and compare the allosteric potentiators presented herein, is the concentration of the potentiator required to achieve 50% of the maximal glutamate response in the functional assay in the presence of a submaximal glutamate concentration of 1 μM.

In this report we describe studies to develop the structure–activity relationship surrounding **4** and its activity at mGlu2. These results provide an understanding of the structural requirements surrounding the diaryl ether region of **4**. One question we set out to answer was whether we could replace the diaryl ether linkage with other groups. We prepared both the *meta* and *para* isomers to determine, which regioisomeric substitution pattern was preferred on the central aniline. In a second series we also examined the possibility of aryl alkyl ethers in that region.

A series of 4-substituted anilines was prepared as shown in Scheme 1.[8] Methyl 4-aminobenzoate underwent reductive amination with 3-pyridine carboxaldehyde. The product of this reaction was subjected to ethanesulfonyl chloride and pyridine to give **6a**. DIBAL reduction of **6a** to the alcohol followed by Swern oxidation resulted in aldehyde **8a**. This intermediate was treated with PhMgCl in THF to give **9a**. The benzylic alcohol **9a** gave rise to **10a**, **11a**, and **12a** through a sequence of oxidation (MnO_2), olefination ($CH_2{=}PPh_3$), and reduction (TFA/triethylsilane). As a route to two other derivatives, **9a** could be converted to **13a** or **14a** by treatment with TFA/triethysilane or DAST, respectively. Starting from intermediate **7a**, we were also able to obtain the benzyl, phenyl ether, **15a** using Mitsunobu conditions.

EC_{50} determinations on these compounds indicated that the ether linkage could be replaced in some cases with a carbon or with a substituted carbon without a significant loss in activity (**10a**–**13a**) (Table 1). In a couple of cases substitution on the benzylic position was not well tolerated (**9a** and **14a**). In the case of **15a**, lengthening the linker by the insertion of a methylene into the chain was also tolerated.

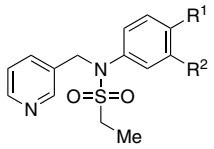


Scheme 1. Reagents and conditions: (a) 3-pyridine carboxaldehyde, MeOH, $NaBH_4$, (b) $EtSO_2Cl$, pyridine, (c) DIBAL, THF, (d) DMSO, $Cl_2(CO)_2$, NEt_3, (e) PhMgCl, THF, (f) MnO_2, CH_2Cl_2, (g) $CH_2{=}PPh_3$, (h) TFA, Et_3SiH, (i) DAST, CH_2Cl_2, (j) DEAD, Ph_3P, PhOH, THF.

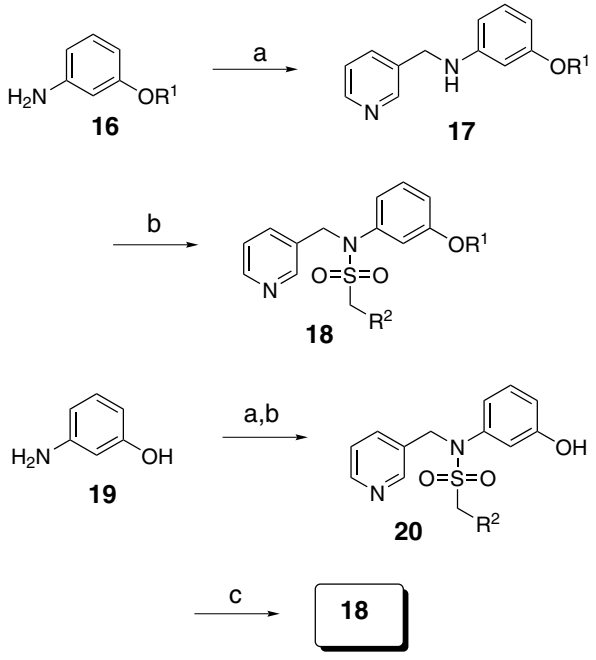
A complementary set of compounds was prepared starting from methyl 3-aminobenzoate.[8] Similar chemistry as shown in Scheme 1 was used to prepare **9b**–**15b**. The 3-substituted aniline series was more potent in every case. Analogs **10b**, **11b**, and **13b** were several times more potent than **10a**, **11a**, and **13a**. Examples **9b**, **12b**, and **15b** were 10–20 times more active than their counterparts, **9a**, **12a**, and **15a**. And in the most dramatic case, **14b** was more than 150 times more potent than **14a**. The most potent compound in this series **12b** with and EC_{50} value of 72 nM was about 20 times more potent that **4** itself. The general trend was that substitution 1,3 to the aniline nitrogen on the central ring gave more potent potentiation of mGlu2 than the corresponding 1,4 regioisomers.

Another series of active compounds was identified by modifying the diaryl ether in **4** to give aryl alkyl ethers.[8] These studies focused on the 3-substituted aniline iso-

Table 1. EC_{50} values for $mGluR_2$ potentiation of selected compounds



Compound	R^1	R^2	$mGluR_2$ Potentiator EC_{50} (nM)
4	OPh	H	1500
9a	CH(OH)Ph	H	>30,000
10a	C(O)Ph	H	4200
11a	$C(=CH_2)Ph$	H	780
12a	$CH(CH_3)Ph$	H	1400
13a	CH_2Ph	H	1600
14a	CH(F)Ph	H	>30,000
15a	CH_2OPh	H	2100
9b	H	CH(OH)Ph	2500
10b	H	C(O)Ph	1100
11b	H	$C(=CH_2)Ph$	200
12b	H	$CH(CH_3)Ph$	72
13b	H	CH_2Ph	310
14b	H	CH(F)Ph	180
15b	H	CH_2OPh	160



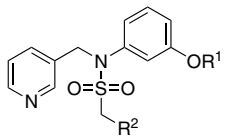
Scheme 2. Reagents and conditions: (a) 3-pyridine carboxaldehyde, $NaBH_4$, (b) $R^2CH_2SO_2Cl$ pyridine, (c) NaH, R^1Br.

mers since they were found to be more potent in the previously described carbon-linker series. The chemistry of this series (Scheme 2) consisted of two short routes. First, reductive amination of commercially available ether anilines **16** with pyridine 3-carboxaldehyde followed by sulfonylation with either ethanesulfonyl chloride or 2,2,2-trifluoroethanesulfonyl chloride provided access to compounds **18a**, and **18d–h**. A second route involved reductive amination of 3-aminophenol with 3-pyridine carboxaldehyde followed again by sulfonylation to give phenol **20**. This intermediate was alkylated with alkyl bromides to give the corresponding ethers **18b**, **c**, and **18i–t**.

As would have been expected from our results in the carbon-linker series, the 1,3 phenyl ether, **18a**, was about 4-fold more potent than the 1,4 regioisomer, **4** (Table 2). In two cases both the ethane-sulfonamide and the 2,2,2-trifluoroethanesulfonamide were prepared. The differences in activity between the two different sulfonamides ranged from little difference in the case of the benzyl ether (compare **18b** with **18c**) to a 11-fold difference favoring the 2,2,2-trifluoroethyl sulfonamide in the case of the trifluoromethoxy ethers (compare **18d** with **18e**). Due to the tendency for the trifluoroethyl sulfonamides to be more potent, we prepared those sulfonamides throughout the remainder of this series. The ethers prepared showed a few key trends. Small alkyl groups like Me resulted in a significant loss in activity (**18f**). Fluorinated alkyl ethers trifluoromethyl and 2,2,2-trifluoroethyl showed good potency (**18d** and **18g**). Interestingly, α- and β-branched alkyl ethers such as isopropyl, isobutyl, 2-butyl, 2-pentyl, 3-pentyl, and 2-methyl pentyl were found to be especially potent potentiators (**18g–m**). The cyclic alkyl ethers **18n–p** also showed a similarly high level of activity. The glycolate ester ethers **18q–s** provided another illustration of the correlation between more branching and greater potency. Synthesis of the alkyl aryl ethers resulted in the branched alkyl ethers, e.g. **18l** (EC_{50} = 16 nM), the most potent mGlu2 potentiators reported to date.

These compounds were also tested for their ability to act as agonists in the absence of glutamate. In most cases, including the most potent potentiators described, e.g. **18k** or **18l**, the compounds showed less than 5% of the maximal glutamate response at 50 μM concentrations of compound. In select cases (**12b**, **14b**, and **15b**) we observed partial agonist-like behavior but only at much higher concentrations than what was required for potentiator activity. In the most potent case, **14b** generated 50% of the maximal glutamate response at 2.5 μM but gave only a 73% maximal response at 50 μM.

Table 2. EC_{50} values for $mGluR_2$ potentiation of compounds **18a–t**



Compound	R^1	R^2	$mGluR_2$ Potentiator EC_{50} (nM)
18a	Ph	CH_3	360
18b	Bn	CF_3	620
18c	Bn	CH_3	440
18d	CF_3	CF_3	140
18e	CF_3	CH_3	1600
18f	CH_3	CF_3	2100
18g	CH_2CF_3	CF_3	100
18h	$CH(CH_3)_2$	CF_3	32
18i	$CH_2CH(CH_3)_2$	CF_3	27
18j	$CH(CH_3)CH_2CH_3$	CF_3	18
18k	$CH(CH_3)CH_2CH_2CH_3$	CF_3	14
18l	$CH(CH_2CH_3)_2$	CF_3	16
18m	$CH_2CH(CH_3)CH_2CH_3$	CF_3	17
18n	$CH(CH_2)_3$	CF_3	36
18o	$CH(CH_2)_4$	CF_3	24
18p	$CH(CH_2)_5$	CF_3	29
18q	$CH_2CO_2CH_2CH_3$	CF_3	640
18r	$CH(CH_3)CO_2CH_2CH_3$	CF_3	230
18s	$C(CH_3)_2CO_2CH_2CH_3$	CF_3	88

Limited pharmacokinetic data is available on the compounds in these series, although they tended to show relatively low plasma exposure, after oral dosing. For example after **14b** and **18d** were administered at 20 mg/kg p.o. in rats, only low concentrations of compound were detected in plasma ($C_{max} = 61$ and 100 ng/mL, respectively).

These studies provided us with an understanding of the structural requirements for mGlu2 activity in this series and ultimately with highly potent selective mGlu2 potentiators for further in vitro and in vivo studies.

Acknowledgements

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References and notes

1. For recent reviews on the pharmacology of Metabotropic Glutamate Receptors see: (a) Monn, J. A.; Schoepp, D. D. *Annu. Rep. Med. Chem.* **1997**, *32*, 1; (b) Schoepp, D. D.; Jane, D. E.; Monn, J. A. *Neuropharmacology* **1999**, *38*, 1431.
2. (a) Monn, J. A.; Valli, M. J.; Massey, S. M.; Wright, R. A.; Salhoff, C. R.; Johnson, B. G.; Howe, T.; Alt, C. A.; Rhodes, G. A.; Robey, R. L.; Griffey, K. R.; Tizzano, J. P.; Kallman, M. J.; Helton, D. R.; Schoepp, D. D. *J. Med. Chem.* **1997**, *40*, 528; (b) Monn, J. A.; Valli, M. J.; Massey, S. M.; Hansen, M. M.; Kress, T. K.; Wepsiec, J. P.; Harkness, A. R.; Grutsch, J. L.; Wright, R. A.; Johnson, B. G.; Andis, S. L.; Kingston, A. E.; Tomlinson, R.; Lewis, R.; Griffey, K. R.; Tizzano, J. P.; Schoepp, D. D. *J. Med. Chem.* **1999**, *42*, 1027; (c) Schoepp, D. D.; Wright, R. A.; Levine, L. R.; Gaydos, B.; Potter, W. Z. *Stress* **2003**, *6*, 189.
3. Kingston, A. E.; Ornstein, P. L.; Wright, R. A.; Johnson, B. G.; Mayne, N. G.; Burnett, J. P.; Belagaje, R.; Wu, S.; Schoepp, D. D. *Neuropharmacology* **1998**, *37*, 1.
4. (a) Knoflach, F.; Mutel, V.; Jolidon, S.; Kew, J. N. C.; Malherbe, P.; Vieira, E.; Wichmann, J.; Kemp, J. A. *Proc. Natl. Acad. Sci. U.S.A.* **2001**, *98*, 13402; (b) Urwyler, S.; Mosbacher, M.; Lingenhoel, K.; Heid, J.; Froestl, W.; Bettler, B.; Kaupmann, K. *Mol. Pharm.* **2001**, *60*, 963; (c) Gasparini, F.; Kuhn, R.; Pin, J.-P. *Curr. Opin. Pharmacol.* **2002**, *2*, 43.
5. (a) Johnson, M. P.; Baez, M.; Jagdmann, G. E., Jr.; Britton, T. C.; Large, T. H.; Callagaro, D. O.; Tizzano, J. P.; Monn, J. A.; Schoepp, D. D. *J. Med. Chem.* **2003**, *46*, 3189; (b) Britton, T.; Barda, D.; Hornback, W.; Jagdmann, G. E.; Henry, S.; Fichtner, M.; Wang, Z.-Q.; Coleman, D.; Chenoweth, D.; Vaught, G.; Fivush, A.; Dressman, B.; White, R.; Milot, G.; Herr, R. J.; Burry, L.; Johnson, M. P.; Large, T.; Monn, J.; Schoepp, D. *Neuropharmacology* **2002**, *43*, 279.
6. (a) Johnson, K.; Dieckman, D.; Britton, T.; Johnson, M.; Jagdmann, E.; Monn, J.; Barda, D.; Henry, S.; Chenoweth, D.; Coleman, D.; Schoepp, D. *Neuropharmacology* **2002**, *43*, 291; (b) Johnson, M.; Baez, M.; Britton, T.; Jagdmann, G. E., Jr.; Johnson, K.; Johnson, B.; Hornback, W.; Large, T.; Nisenbaum, E.; Tizzano, J.; Monn, J.; Schoepp, D. *Neuropharmacology* **2002**, *43*, 291; (c) Schaffhauser, H.; Rowe, B. A.; Morales, S.; Chavez-Noriega, L. E.; Yin, R.; Jachec, C.; Rao, S. P.; Bain, G.; Pinkerton, A. B.; Vernier, J.-M.; Bristow, L. J.; Varney, M. A.; Daggett, L. P. *Mol. Pharmacol.* **2003**, *64*, 798; (d) Lorrain, D. S.; Schaffhauser, H.; Campbell, U. C.; Baccei, C. S.; Correa, L. D.; Rowe, B.; Rodriguez, D. E.; Anderson, J. J.; Varney, M. A.; Pinkerton, A. B.; Vernier, J.-M.; Bristow, L. J. *Neuropsychopharmacology* **2003**, *28*, 1622.
7. As an example of the subtype selectivity of these compounds, LY181837 showed no potentiation at the mGlu subtypes tested: 1, 3, 4, 5, and 8, up to 12.5 μM. mGluR subtype selectivity was also monitored for representative compounds from this series. In none of these cases did we find activity at any of the other mGlu receptor subtypes at concentrations up to 12.5 μM.
8. Each final product and synthetic intermediate described was fully characterized. All spectral data were consistent with the assigned structures.