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Discovery and SAR of 6-substituted-4-anilinoquinazolines as non-competitive antagonists of $mGlu_5$

Andrew S. Felts [a,c], Sam A. Saleh [a,c], Uyen Le [a,c], Alice L. Rodriguez [a,c], C. David Weaver [a,c], P. Jeffrey Conn [a,c], Craig W. Lindsley [a,b,c], Kyle A. Emmitte [a,c,*]

[a] Department of Pharmacology, Vanderbilt University Medical Center, Nashville, TN 37232, USA
[b] Department of Chemistry, Vanderbilt University, Nashville, TN 37232, USA
[c] Vanderbilt Program in Drug Discovery, Vanderbilt Institute of Chemical Biology, Nashville, TN 37232, USA

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ABSTRACT

A high-throughput cell-based screen identified a series of 6-substituted-4-anilinoquinazolines as non-competitive antagonists of metabotropic glutamate receptor 5 ($mGlu_5$). This Letter describes the SAR of this series and the profile of selected compounds in selectivity and radioligand binding assays.

Glutamate is the major excitatory transmitter in the mammalian CNS, exerting its effects through both ionotropic and metabotropic glutamate receptors. The metabotropic glutamate receptors (mGlus) belong to family C of the G-protein-coupled receptors (GPCRs). These receptors are characterized by a seven transmembrane (7TM) α-helical domain that is connected via a cysteine-rich region to a large bi-lobed extracellular amino-terminal domain. The eight mGlus discovered to date have been further divided according to their structure, preferred signal transduction mechanisms, and pharmacology (Group I: $mGlu_1$ and $mGlu_5$; Group II: $mGlu_2$ and $mGlu_3$; Group III: $mGlu_4$, $mGlu_6$, $mGlu_7$, and $mGlu_8$).[1]

Whereas orthosteric ligands of mGlus bind in the amino-terminal domain of the receptor, known allosteric binding sites are located in the 7TM domain. Orthosteric ligands often suffer from poor selectivity among the mGlus due to a highly conserved binding site. The discovery of non-competitive antagonists, also known as negative allosteric modulators (NAMs), has offered a potential solution to such selectivity issues.[2] The $mGlu_5$ NAMs 2-methyl-6-(phenylethynyl)pyridine (MPEP)[3] and 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine (MTEP)[4] (Fig. 1) have demonstrated efficacy in numerous preclinical models of disease, including pain,[5] anxiety,[6] gastroesophageal reflux disease (GERD),[7] and fragile X syndrome.[8] In addition, there have been recent positive disclosures from phase II clinical studies with two small molecule $mGlu_5$ NAMs, ADX10059 in GERD[9] and acute migraine[10] and fenobam (Fig. 1) in fragile X syndrome.[11] With such a large body of compelling evidence, the search for new and improved $mGlu_5$ NAMs remains an attractive and active area for drug discovery research.[12]

We have recently reported our initial results from an effort to identify $mGlu_5$ antagonists from multiple diverse chemotypes.[13] A functional cell-based high-throughput screen of a collection of 160,000 compounds identified 624 $mGlu_5$ antagonists. The confirmation of hits using full concentration response curves left 345 verified non-competitive antagonists of the target. Among that set of confirmed hits were a few 6-bromo-4-anilinoquinazolines. 3-Chloroaniline analog **1** (Fig. 2) represented the most potent compound in our functional assay, which measures the ability of the compound to block the mobilization of calcium by an EC_{80} concentration of glutamate in HEK293A cells expressing rat $mGlu_5$.[14] A binding affinity determination measuring the ability of the com-

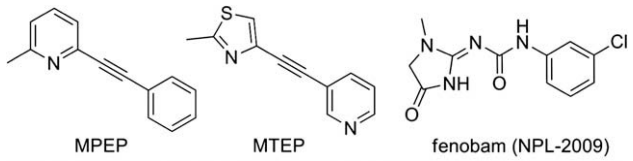

Figure 1. $mGlu_5$ NAMs MPEP, MTEP, and fenobam.

* Corresponding author.
E-mail address: kyle.a.emmitte@Vanderbilt.edu (K.A. Emmitte).

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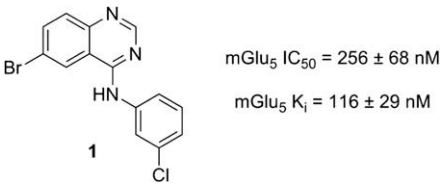
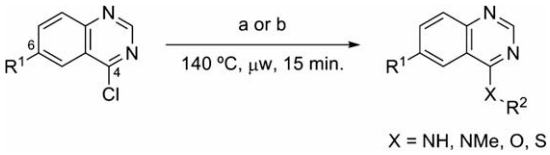


Figure 2. $mGlu_5$ NAM quinazoline screening hit.

pound to compete with the equilibrium of [^{3}H]3-methoxy-5-(pyridin-2-ylethynyl)pyridine,[15] a close structural analog of MPEP, confirmed the interaction of **1** with the known allosteric binding site.[16]

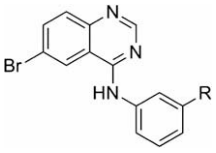
The quinazoline scaffold as a chemotype for $mGlu_5$ antagonists has been disclosed by Grüenenthal GmbH in the patent literature in the form of 6-aryl-4-aminoquinazolines.[17] Quinazolines were also used by Yamanouchi Pharmaceutical Company,[18] Eli Lilly,[19] and Pfizer[20] to design $mGlu_1$ antagonists. Nonetheless, an investigation of the SAR of 6-substituted-4-anilinoquinazolines as non-competitive antagonists of $mGlu_5$ has yet to be disclosed. The development of such SAR is the subject of this Letter.

Quinazoline derivatives of interest were readily accessible through S_NAr reaction of the appropriate nucleophiles with commercially available 6-substituted-4-chloroquinazolines using microwave-assisted organic synthesis (MAOS)[22] (Scheme 1). Such chemistry was amenable to our preferred iterative library synthesis approach, which in combination with our custom mass-directed HPLC purification system allows for rapid evaluation of new screening hits.[23] Prior to biological testing, all compounds were analyzed by LC–MS and determined to be ⩾95% pure, and selected compounds were further characterized by proton NMR.[24] Initially, we decided to conduct a small scan with commercially available 3-substituted anilines while maintaining the 6-bromoquinazoline functionality (Table 1). Substitution at the 3-position of the aniline



Scheme 1. Reagents and conditions: (a) 3.0 equiv of Et_3N, 1.0 equiv of R^2-NH_2 or R^2-NHMe, EtOH; (b) 1.2 equiv of K_2CO_3, 1.0 equiv of R^2-SH or R^2-OH, acetone.

Table 1
SAR of 3-substituted anilines



Compound	R	$mGlu_5$ IC_{50}[a] (nM)	% Glu max[b]
1	Cl	256 ± 68	1.5 ± 0.3
2	H	>10,000[c]	42 ± 13
3	F	1970 ± 235	8.8 ± 3.0
4	Br	174 ± 26	2.5 ± 0.7
5	Me	246 ± 48	1.2 ± 0.3
6	CF_3	1720 ± 127	3.2 ± 0.6
7	OMe	>10,000[c]	34 ± 14

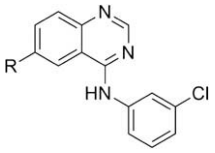
[a] Calcium mobilization $mGlu_5$ assay; values are average of $n \geqslant 3$.
[b] Amplitude of response in the presence of 30 μM test compound as a percentage of maximal response (100 μM glutamate); average of $n \geqslant 3$.
[c] CRC does not plateau.

ring appeared to improve potency as unsubstituted aniline **2** was only weakly active. 3-Fluoroaniline **3** exhibited improved potency relative to **2**, while 3-bromoaniline **4** and 3-methylaniline **5** were comparable in activity to the hit compound **1**. The sensitivity of this position to subtle modifications was evident as 3-trifluoromethylaniline **6** was sevenfold less potent than **5**. 3-Methoxyaniline **7** was only weakly active, similar to **2**.

We also decided to examine various substituents at the 6-position of the quinazoline ring while maintaining the 3-chloroaniline substituent (Table 2). Other halogens at this position (**8** and **9**) were similar in potency to the hit compound (**1**). 6-Nitroquinazoline **10** had comparable activity to the 6-halogen compounds. 6-Methoxy (**11**) and 6-cyano (**12**) quinazolines were less potent. Other substituents, including larger aryl and heteroaryl groups (data not shown) were not tolerated and resulted in a complete loss of activity.

Another area of interest was the quinazoline core of the template. As such, we prepared a few modified cores (Table 3). 6-Chloroquinoline analog **14** was essentially inactive in our assay, which was a dramatic change from the potent antagonist activity observed with comparator 6-chloroquinazoline **13**. Modification of the template to afford 7-bromoisoquinoline **15** reduced the activity by approximately 25-fold relative to 6-bromoquinazoline comparator **4**. Such results further illustrate how small structural modifications within this chemotype can profoundly impact the observed $mGlu_5$ activity.

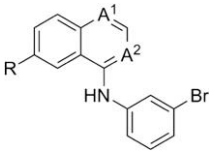
Table 2
SAR of 6-substituted quinazolines



Compound	R	$mGlu_5$ IC_{50}[a] (nM)	% Glu max[b]
1	Br	256 ± 68	1.5 ± 0.3
8	F	311 ± 74	0.9 ± 0.2
9	Cl	130 ± 28	2.8 ± 0.4
10	NO_2	274 ± 70	2.4 ± 0.6
11	OMe	1510 ± 365	13 ± 7
12	CN	>10,000[c]	35 ± 11

[a] Calcium mobilization $mGlu_5$ assay; values are average of $n \geqslant 3$.
[b] Amplitude of response in the presence of 30 μM test compound as a percentage of maximal response (100 μM glutamate); average of $n \geqslant 3$.
[c] CRC does not plateau.

Table 3
Core modifications



Compound	R	A^1	A^2	$mGlu_5$ IC_{50}[a] (nM)	% Glu max[b]
13	Cl	N	N	124 ± 29	1.2 ± 0.1
14	Cl	N	CH	>30,000	—
4	Br	N	N	174 ± 26	2.5 ± 0.7
15	Br	CH	N	4330 ± 1200	5.4 ± 1.7

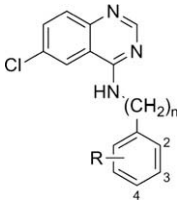
[a] Calcium mobilization $mGlu_5$ assay; values are average of $n \geqslant 3$.
[b] Amplitude of response in the presence of 30 μM test compound as a percentage of maximal response (100 μM glutamate); average of $n \geqslant 3$.

We also explored the concept of extending the linker between the 4-amine substituent and the aryl ring (Table 4). Both benzyl amines (**17–20**) and phenethylamines (**21**–**24**) were investigated. Only unsubstituted phenethylamine analog **21** exhibited any antagonist activity, albeit weak. Chloro-substituted analogs failed to demonstrate any improved activity, which was a significant contrast to the enhanced potency of 3-chloroaniline analog **9** relative to unsubstituted analog **16**.

An additional area of interest was a survey of potential alternatives to the secondary amine linker. Such work was accomplished in the context of the 6-chloro and 6-bromoquinazolines (Table 5). The *N*-methyl (**25** and **28**) and thiol (**27** and **30**) analogs proved inactive in our assay. Only the ether analogs (**26** and **29**) demonstrated weak antagonist activity. The consequences of the secondary amine (**13** and **4**) to ether (**26** and **29**) modifications were severe, reducing potency by more than 50-fold in each case.

Once we concluded that secondary anilines were likely optimal in this series, we sought to further evaluate the SAR around that portion of the scaffold. One of the potential issues with this series was the relatively high lipophilicity of the initial screening hit **1** (*c*Log *P* = 5.49).[25] Having achieved a potent hit with 6-fluoroquinazoline **8** (*c*Log *P* = 4.77), we decided to examine additional substituted anilines in the context of this core (Table 6). As was the case with the 6-bromoquinazolines, unsubstituted aniline **31** and 3-trifluoromethylaniline **34** were weak antagonists. 3-Bromo aniline **32** was a potent antagonist, while 3-methyl aniline **33** was only moderately potent. The moderate potency of **33** represented a departure from the SAR observed with the 6-bromoquinazolines, where 3-methylaniline **5**, 3-chloroaniline **1**, and 3-bromoaniline **4** were essentially equipotent. The 3-cyanoaniline **35** was moderately potent, similar to **33**. Interestingly, 3-ethylaniline **36** was a weak potentiator, or positive allosteric modulator (EC_{50} >10 μM; % Glu max = 52 ± 5 in the presence of an EC_{20} concentration of glutamate). Such a switch in $mGlu_5$ pharmacology has been noted and reported before in our laboratory in the context of other chemotypes.[13,14] 3-Methoxyaniline **37** was a weak antagonist. We also prepared a few analogs (**38**–**41**) in order to evaluate the effect of fluoro substitution in the context of the 3-chloroaniline. In every case, fluoro substitution proved detrimental to potency. 2-Fluoro-3-chloroaniline **39** demonstrated moderate potency, while other analogs were only weak antagonists.

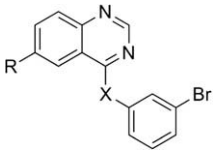
Table 4
SAR of extended linkers



Compound	R	*n*	$mGlu_5$ IC_{50}[a] (nM)	% Glu max[b]
16	H	0	>10,000[c]	31 ± 12
9	3-Cl	0	130 ± 28	2.8 ± 0.4
17	H	1	>30,000	—
18	4-Cl	1	>30,000	—
19	3-Cl	1	>30,000	—
20	2-Cl	1	>30,000	—
21	H	2	>10,000[c]	59 ± 3
22	4-Cl	2	>30,000	—
23	3-Cl	2	>30,000	—
24	2-Cl	2	>30,000	—

[a] Calcium mobilization $mGlu_5$ assay; values are average of $n \geqslant 3$.
[b] Amplitude of response in the presence of 30 μM test compound as a percentage of maximal response (100 μM glutamate); average of $n \geqslant 3$.
[c] CRC does not plateau.

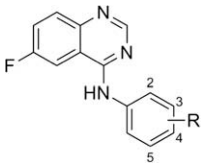
Table 5
Linker modification SAR



Compound	R	X	$mGlu_5$ IC_{50}[a] (nM)	% Glu max[b]
13	Cl	NH	124 ± 29	1.2 ± 0.1
25	Cl	NMe	>30,000	—
26	Cl	O	6570 ± 1010	14 ± 8
27	Cl	S	>30,000	—
4	Br	NH	174 ± 26	2.5 ± 0.7
28	Br	NMe	>30,000	—
29	Br	O	>10,000[c]	49 ± 14
30	Br	S	>30,000	—

[a] Calcium mobilization $mGlu_5$ assay; values are average of $n \geqslant 3$.
[b] Amplitude of response in the presence of 30 μM test compound as a percentage of maximal response (100 μM glutamate); average of $n \geqslant 3$.
[c] CRC does not plateau.

Table 6
Aniline SAR of 6-fluoroquinazolines



Compound	R	$mGlu_5$ IC_{50}[a] (nM)	% Glu max[b]
8	3-Cl	311 ± 74	0.9 ± 0.2
31	H	>10,000[c]	58 ± 8
32	3-Br	96 ± 12	0.6 ± 0.2
33	3-Me	1350 ± 201	3.5 ± 0.8
34	3-CF_3	>10,000[c]	32 ± 16
35	3-CN	1370 ± 198	3.5 ± 0.6
36	3-Et	Weak potentiator	
37	3-OMe	>10,000[c]	50 ± 6
38	3-Cl, 4-F	>10,000[c]	34 ± 17
39	2-F, 3-Cl	3720 ± 573	5.2 ± 1.4
40	3-Cl, 5-F	>10,000[c]	56 ± 8
41	2-F, 5-Cl	>10,000[c]	58 ± 8

[a] Calcium mobilization $mGlu_5$ assay; values are average of $n \geqslant 3$.
[b] Amplitude of response in the presence of 30 μM test compound as a percentage of maximal response (100 μM glutamate); average of $n \geqslant 3$.
[c] CRC does not plateau.

Having identified some molecules with good potency in our cell-based functional assay, we decided to further profile these analogs with regard to binding affinity and selectivity (Table 7). Data for MPEP is shown as a comparator. Binding affinity determinations with [^{3}H]3-methoxy-5-(pyridin-2-ylethynyl)pyridine confirmed the interaction of **13** and **32** with the known MPEP allosteric binding site, as was the case with hit compound **1**. The same three compounds were also examined for their selectivity versus additional mGlus and were determined to be inactive against $mGlu_{2-4}$ and $mGlu_{7-8}$. On the other hand, each compound demonstrated moderate antagonist activity of $mGlu_1$ in a calcium mobilization assay.[26] Recent publications indicate possible links between $mGlu_1$ and anxiety[6a,27] as well as pain[28] and fragile X.[29] Such an overlap with regard to therapeutic applications makes the concept of dual antagonism of $mGlu_1$ and $mGlu_5$ potentially interesting.

It is worth commenting on the fact that 4-anilinoquinazolines are well established as an effective template for the design of

Table 7
Binding affinity and selectivity of selected compounds

Compound	$mGlu_5$ IC_{50}[a] (nM)	$mGlu_5$ K_i[b] (nM)	$mGlu_1$ IC_{50}[a] (nM)
MPEP	3.5 ± 1.4	4.7 ± 1.5	—
1	256 ± 68	116	398 ± 33
13	124 ± 29	249	955 ± 115
32	96 ± 12	736	713 ± 102

[a] Calcium mobilization assays; values are average of $n \geqslant 3$.
[b] K_i values are average of $n = 2$.

inhibitors of epidermal growth factor receptor (EGFR) and other members of the ErbB kinase family.[30] In fact, dichloro analog **9** has been reported to moderately inhibit EGFR autophosphorylation (IC_{50} = 2.7 μM) in A431 cells.[31] While this level of potency is markedly less than that observed toward $mGlu_5$ in our functional cell-based assay, monitoring potential off-target activity against such kinases will be necessary in the further development of this series as $mGlu_5$ non-competitive antagonists.

In summary, we have identified a series of non-competitive antagonists of $mGlu_5$ within the 6-substituted-4-anilinoquinazoline chemotype. Although the series was chemically unrelated to MPEP, selected potent compounds were confirmed to inhibit binding of a radioligand at the MPEP allosteric binding site. While the SAR in this series was somewhat shallow, several compounds demonstrated moderate to good potency. Of further interest was the dual activity of this series with respect to $mGlu_1$.

Acknowledgments

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24. For a large scale synthesis, compounds can also be purified via flash chromatography on silica gel. For example, synthesis and characterization of **1** was conducted as follows: 6-bromo-4-chloroquinazoline (1.0 g, 4.1 mmol), 3-chloroaniline (0.524 g, 4.1 mmol), triethylamine (1.25 g, 12.4 mmol) and ethanol (10 mL) were added to a microwave vial and heated at 140 °C for 15 min. The ethanol was removed under reduced pressure and the crude residue was dissolved in EtOAc and washed with aq NH_4Cl (1×), H_2O (1×), brine (1×). The organic layer was dried ($MgSO_4$), filtered, and concentrated in vacuo. Purification by flash chromatography on silica gel afforded 1.15 g (84%) of the title compound as an off-white solid. ^1H NMR (400 MHz, DMSO-d_6) δ 9.93 (s, 1H), 8.86 (d, J = 1.9 Hz, 1H), 8.68 (s, 1H), 8.11 (t, J = 1.8 Hz, 1H), 8.00 (dd, J = 8.9, 2.0 Hz, 1H), 7.84 (dd, J = 8.2, 1.1 Hz, 1H), 7.74 (d, J = 8.8 Hz, 1H), 7.42 (t, J = 8.1 Hz, 1H), 7.18 (dd, J = 7.9, 1.2 Hz, 1H); ES-MS $[M+1]^+$: 334.0.
25. *c*Log *P* values were calculated using ChemBioDraw Ultra, version 11.0.1 available from CambridgeSoft.
26. For a description of the $mGlu_1$ calcium mobilization assay see Ref. 14. For additional details see: Niswender, C. M.; Johnson, K. A.; Weaver, C. D.; Jones, C. K.; Xiang, Z.; Luo, Q.; Rodriguez, A. L.; Marlo, J. E.; de Paulis, T.; Thompson, A. D.; Days, E. L.; Nalywajko, T.; Austin, C. A.; Williams, M. B.; Ayala, J. E.; Williams, R.; Lindsley, C. W.; Conn, P. J. *Mol. Pharmacol.* **2008**, *74*, 1345.
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