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# Synthesis and SAR of substituted pyrazolo[1,5-*a*]quinazolines as dual mGlu<sub>2</sub>/mGlu<sub>3</sub> NAMs



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# ABSTRACT

Herein we report the design and synthesis of a series of substituted pyrazolo[1,5-*a*]quinazolin-5(4*H*)ones as negative allosteric modulators of metabotropic glutamate receptors 2 and 3 (mGlu<sub>2</sub> and mGlu<sub>3</sub>, respectively). Development of this series was initiated by reports that pyrazolo[1,5-*a*]quinazolinederived scaffolds can yield compounds with activity at group II mGlu receptors which are prone to molecular switching following small structural changes. Several potent analogues, including 4-methyl-2-phenyl-8-(pyrimidin-5-yl)pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (**10b**), were discovered with potent in vitro activity as dual mGlu<sub>2</sub>/mGlu<sub>3</sub> NAMs, with excellent selectivity versus the other mGluRs. © 2014 Elsevier Ltd. All rights reserved.

Since their discovery, the metabotropic glutamate receptors (mGlus) have elicited a great deal of interest from the neuropharmacology community, both in academia and in the pharmaceutical industry. As a group, this family of GPCRs has been suggested to represent a host of novel targets for the treatment of many of the most prevalent psychiatric and neurodegenerative diseases.<sup>1–3</sup> Within the mGlu family, the group II receptors, metabotropic glutamate receptor 3 (mGlu<sub>2</sub>) and metabotropic glutamate receptor 3 (mGlu<sub>3</sub>) have received significant attention for their roles in the treatment of schizophrenia, depression, anxiety disorders, and substance abuse.<sup>4–9</sup>

Early medicinal chemistry efforts, pioneered by Eli Lilly and Co., focused on the development of constrained-glutamate analogues that could preferentially activate or inactivate the group II receptors in comparison to the group I and group III mGlus.<sup>10,11</sup> While these compounds are among the most frequently used and widely available tools to study group II mGlu function, independent lines of anatomical, pharmacological, and electrophysiological evidence suggest that mGlu<sub>2</sub> and mGlu<sub>3</sub> have separate, and in some cases, competing functions.<sup>12–17</sup> In order to more effectively elucidate the individual functions of mGlu<sub>2</sub> and mGlu<sub>3</sub>, there have been several campaigns to develop compounds capable of discriminating between these two receptors.

Many of the most successful efforts to develop such subtypeselective ligands have targeted allosteric sites on mGlu<sub>2</sub> or mGlu<sub>3</sub>.<sup>18</sup> These ligands bind at a distinct site from the orthosteric pocket, and act to either potentiate signaling by the endogenous ligand, in the case of positive allosteric modulators (PAMs) or to diminish signaling by the endogenous ligand, in the case of negative allosteric modulators (NAMs).<sup>3,19</sup> This strategy has led to the development of several selective mGlu<sub>2</sub> PAMs, and more recently, selective mGlu<sub>3</sub> NAMs.<sup>18,20,21</sup> However, aside from claims in the patent literature with minimal selectivity data, there have been no formal reports of functionally-selective mGlu<sub>2</sub> NAMs or mGlu<sub>3</sub> PAMs.<sup>22</sup> This lack of tool compounds represents a significant barrier to progress in understanding the biological roles and therapeutic relevance of these two receptors.

Recent disclosures have provided some evidence that pyrazolo[1,5-*a*]quinazolines can act as dual inhibitors of mGlu<sub>2</sub> and mGlu<sub>3</sub> in a DtectAll<sup>™</sup> FRET-based binding assay system.<sup>23</sup> Also, it has been reported that mGlu<sub>2</sub> NAMs, mGlu<sub>3</sub> NAMs, and mGlu<sub>3</sub> PAMs have been developed via directed alterations to this chemotype (Fig. 1A).<sup>24</sup> Such molecular switching has been previously reported for compounds targeting mGlu<sub>5</sub>, a group I mGlu, and compounds targeting mGlu<sub>4</sub>, a group III mGlu, but there has been limited information regarding the phenomenon amongst compounds targeting group II mGlus.<sup>25-28</sup>

In order to improve understanding of the structure-activity relationship (SAR) underlying molecular switching amongst group II mGlus, several chemical libraries were developed around a

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**Figure 1.** (A) Structural alterations to a pyrazolo[1,5-*a*]quinazoline core have been reported to result in mode switching. (B) Structural features selected for alteration in library design to explore group II SAR.

pyrazolo[1,5-*a*]quinazoline-5(4*H*)-one core. These libraries focused on alterations to three distinct areas of the molecule: aryl-substitutions on the pyrazole ring, aryl-additions to the quinazoline, and *N*-alkyl-substitutions on the quinazoline (Fig. 1B).

The initial compounds were synthesized using a matrix-library strategy, where alterations at  $R^1$  and  $R^2$  were combined in order to rapidly generate a large amount of structural diversity (Scheme 1). Briefly, 2-amino-4-bromo-benzoic acid **3** is converted to the hydrazine **4**, which is condensed with an array of substituted benzoyl-acetonitriles under microwave conditions in order to form a series of 8-bromo-pyrazolo[1,5-*a*]quinazolin-5(4*H*)-ones that are differentially substituted at the 2-position **5**. These products are subjected to Suzuki coupling conditions with a diverse group of aryl and heteroaryl boronic acids to afford analogs **6**, and then N-alkylated in order to generate the desired analogues **7**. All final products were purified using reverse-phase HPLC to >98% purity, as determined by analytical LC/MS (215, 254 and ELSD). Overall yields (5–57%) were good for the four step sequence.

The compounds generated were initially screened at a single concentration of 3 µM for their ability to alter glutamate-dependent signaling, against cell lines stably expressing either rat mGlu<sub>2</sub> or rat mGlu<sub>3</sub> and mouse  $G_{\alpha 15}$  (Fig. 2). All assays were carried out using a kinetic, plate-based, calcium-induced fluorescence reader, using previously reported methods.<sup>21</sup> From the initial group of compounds, none appeared to potentiate glutamate-dependent calcium signaling (EC<sub>20</sub> of Glu) at either mGlu<sub>2</sub> or mGlu<sub>3</sub> when applied at 3 µM. Conversely, 6 of the 53 analogs 7 screened showed robust inhibition of mGlu<sub>2</sub>, and 18 of the analogs **7** showed robust inhibition of mGlu<sub>3</sub>, meaning they inhibited an ~EC<sub>80</sub> glutamate response by  $\geq$  50%. Thus, the initial library generated analogs biased towards inhibition of mGlu<sub>3</sub>, based on the single point screen. The most active compounds from this initial screen were selected, and a concentration-response curve (CRC) was generated for each one. These curves were generated using the cell lines and



**Figure 2.** Inhibition of  $mGlu_2$  response to an  $EC_{76}$  of glutamate and inhibition of  $mGlu_3$  response to an  $EC_{87}$  of glutamate. Results are representative of three independent experiments.

agonist concentrations as in the single point assay, while using a broad range of test-compound concentrations (30  $\mu$ M-1 nM).

As has been previously reported with allosteric modulators for mGlus, the SAR profile of these compounds was fairly steep, with small structural changes leading to significant losses in efficacy.<sup>21,25</sup> When the R<sup>1</sup> position was held constant as a phenyl ring,



Scheme 1. Reagents and conditions: (a) NaNO<sub>2</sub>, HCl, SnCl<sub>2</sub>, -5 °C to rt, 2 h, 90%; (b) AcOH, NCCH<sub>2</sub>COR<sup>1</sup> 150 °C, μW, 5 min, 27–88%; (c) 10 mol % Pd(dppf)<sub>2</sub>Cl<sub>2</sub>, K<sub>3</sub>PO<sub>4</sub>, B(OH)<sub>2</sub>R<sup>2</sup>, dioxane/H<sub>2</sub>O,130 °C, μW, 40 min, 34–95%; (d) LIHMDS, ICH<sub>3</sub>, THF, 50 °C, 2 h, 52–76%.

and R<sup>3</sup> was held as a methyl, installation of a 3-sulfonylphenyl or 3-pyridyl group at R<sup>2</sup> yielded inhibitors with low-micromolar to high nanomolar IC<sub>50</sub>s at both mGlu<sub>2</sub> and mGlu<sub>3</sub>. In contrast, installation of a phenyl or 4-methoxyphenyl at this position yielded compounds with very little effect. Truncation of this position to a methyl group also resulted in much attenuated activity at both receptors. Results from installation of 3-subsituted phenyl groups at R<sup>1</sup> are summarized in Table 1. In general, the presence of a 3-sulfonamidephenyl or 3-pyridyl at R<sup>2</sup> again induces more robust inhibition than their phenyl, 4-methoxyphenyl, or methyl comparators. Some additional interesting trends can be seen by comparing similar compounds across alterations at R<sup>1</sup> exclusively. When replacing the phenyl at  $R^1$  (as in **7a–7e**) with a 3-fluoro phenyl (as in **7f-7j**), the analogous compounds generally exhibit a reduction in potency at mGlu<sub>2</sub> and mGlu<sub>3</sub>. In the case where a 3pyridyl is present at  $R^2$ , this reduction is approximately 2-fold. However, in the case where a 3-sulforvl phenvl is at  $R^2$ , the potency reduction is even more pronounced: greater than 5-fold at mGlu<sub>2</sub>, and greater than 10-fold at mGlu<sub>3</sub>. When a 3-methoxyphenyl is installed at  $R^1$  (**7k**-**7o**), the potencies of the resulting compounds are similar to their phenyl analogues. An exception to this trend is when a 3-pyridyl group is present at R<sup>2</sup>, as this compound has notably diminished potency at the group II mGlu receptors in relation to its phenyl comparator. For the analogues screened here, having a 3-methylphenyl at  $R^1$  (**7p**-**7r**) results in an overall decrease in potency. This decrease has a similar magnitude as was observed with 3-fluorophenyl at this position.

Several 3-chlorophenyl (7s-7u) and 3-bromophenyl (7v-7x) analogues were screened at R<sup>1</sup> as well, allowing for analysis of increasing size of halogens at this position. The general trend seen is that potency decreases as halogen size increases, with **7u** providing one notable exception. This compound has an increased potency over its 3-fluoromethyl and phenyl comparators at mGlu<sub>2</sub>, while its potency at mGlu<sub>3</sub> is retained. The SAR data for 4-substituted phenyl groups at R<sup>1</sup> is also summarized in Table 1. Those compounds with phenyl, 4-methoxyphenyl, and methyl substitutions at R<sup>2</sup> are once again less active than their 3-sulfonamidephenvl and 3-pyridyl analogues. The presence of a 4-fluorophenyl group at R<sup>1</sup> (**7y-7ac**) yielded compounds with retained or modestly increased potencies at mGlu<sub>2</sub> and mGlu<sub>3</sub>, as compared to 7a-7e. The exception to this is 7y, which has an approximately 2-fold decrease in potency. Notably, the presence of a 3-pyridyl group at R<sup>2</sup> resulted in the most potent compound generated from this initial screen, **7ab**, with an IC<sub>50</sub> of 427 nM at mGlu<sub>2</sub> and 67 nM at mGlu<sub>3</sub>. Placing a 4-chlorophenyl group at  $R^1$  (**7ad**-**7ah**) decreased the maximal inhibition achieved, as compared to 7a-7e. These compounds appear to be partial antagonists with relatively high affinity for the group II mGlus; their CRC's reach a maximum of around 60% inhibition at  $1 \mu$ M, and do not cause any further decrease in signal when applied at higher concentrations. Finally, analogs 7 that contained a 4-methoxyphenyl, a 4-trifluoromethoxyphenyl, or a 4-ethylphenyl group at R<sup>1</sup> resulted in compounds with severely attenuated potency. Likewise, the presence of multiply substituted phenyl rings at R<sup>1</sup>, specifically 3,4-difluorophenyl and 3,5-dimethoxyphenyl groups, resulted in compounds with little inhibitory activity at mGlu<sub>2</sub> or mGlu<sub>3</sub> (data not shown in Table 1).

In a further attempt to expand the search for the molecular basis of mode switching that had been reported with this series, several analogues were made which examined alternative *N*-alkyl groups (Table 2), following the synthetic scheme depicted in Scheme 2. Starting from **8**, an analog of **6**, deprotonation with LiHMDS and trapping with either 2-iodoethanol or acetyl chloride afforded analogs **9**. These compounds retained a phenyl group at  $R^1$ , and either a 3-pyridinyl or phenyl group at  $R^2$ . The presence of a hydrogen (**8a**, **8b**) or acetyl group (**9a**, **9c**) at  $R^3$  did not appear

#### Table 1

Structure and activities of analogs 7



			7	
Entry	R <sup>1</sup>	R <sup>2</sup>	$IC_{50} \text{ mGlu}_2{}^{a} \left( \mu M \right)$	$IC_{50} \text{ mGlu}_3{}^a \left( \mu M \right)$
7a	×	SO 2NH2	1.93	0.884
7b	×́	$\bigcirc$	>10	>10
7c	× D	MeO	(-4)	(0)
7d	× D	<b>N</b>	0.852	0.165
7e	× D	H <sub>3</sub> C	(17)	(59)
7f	F	SO2NH2	>10	>10
7g	F	$\mathbb{O}^{+}$	(2)	(39)
7h	F	MeO	(6)	(2)
<b>7</b> i	F	() N	1.56	0.247
7j	× F	H₃C <sup>∽</sup> ́	(16)	(38)
7k	OMe	SO2NH2	1.39	0.696
71	OMe	$\mathbb{O}^{+}$	>10	>10
7m	) OMe	MeO	(6)	(48)
7n	OMe	N	3.12	1.18
70	OMe	H₃C <sup>大</sup>	>10	>10
7p	×		(7)	(49)
7q	Ŷ	MeO	(0)	(34)
7r	×	N	1.79	0.53
7s	× CI		(7)	(19)
7t	× CI	MeO	(9)	(31)
7u	× G	N N	0.564	0.293

(continued on next page)

Table 1 (continued)

Entry	R <sup>1</sup>	R <sup>2</sup>	$IC_{50} mGlu_2^a (\mu M)$	IC <sub>50</sub> mGlu <sub>3</sub> <sup>a</sup> (µM
7v	) Br		(8)	(28)
7w	Br	MeO	(4)	(23)
7x	Br	N K	>10	>10
7y	× F	SO2NH2	3.95	1.99
7z	× C	$\bigcirc$	(12)	(64)
7aa	, C	MeO	>10	>10
7ab	× C		0.427	0.067
7ac	× C	H₃C <sup>∕</sup> ∖́	>10	>10
7ad	×C ci	SO <sub>2</sub> NH <sub>2</sub>	0.847	1.25
7ae	) Cl ci	$\bigcirc$	(4)	(31)
7af	Ϋ́C <sub>CI</sub>	MeO	(6)	(21)
7ag	×́С,	() N	1.11	0.645
7ah	) Cl	H₃C <sup>∕</sup> ́	(11)	(33)

 $^a$  Where IC<sub>50</sub>s were not determined, percent inhibition of EC<sub>76</sub> (mGlu<sub>2</sub>) or EC<sub>87</sub> (mGlu<sub>3</sub>) at 3  $\mu M$  is reported in parentheses. Results are representative of three independent experiments.

#### Table 2

Structure and activities of analogs 8 and 9

$ \begin{array}{cccccccccccccccccccccccccccccccccccc$				
Entry	R <sup>2</sup>	R <sup>3</sup>	$IC_{50} mGlu_2 (\mu M)^a$	$IC_{50}\ mGlu_{3}\ (\mu M)^{a}$
8a	$\bigcirc $	ХH	(2)	(6)
9a	$\bigcirc$	, L	(3)	(8)
9b	$\bigcirc$	, OH	(0)	(3)
8b		×H	(4)	(8)
9c	<b>N</b>	, C	>10	>10
9d	<b>N</b>	X∕∕∕OH	4.65	3.15

 $^a$  Where IC<sub>50</sub>s were not determined, percent inhibition of EC<sub>76</sub> (mGlu<sub>2</sub>) or EC<sub>87</sub> (mGlu<sub>3</sub>) at 3  $\mu M$  is reported in parentheses. Results are representative of three independent experiments.

to be tolerated for these compounds, and installation of an ethanol group resulted in a significant decrease in potency at  $mGlu_2$  and  $mGlu_3$  (**9b**, **9d**).

Given the trend seen with **7a–7ah**, wherein the presence of a 3pyridyl group at R<sup>2</sup> resulted in compounds with elevated potency at mGlu<sub>2</sub> and mGlu<sub>3</sub>, it was decided to explore the effects of additional heterocyclic replacements at R<sup>2</sup> while retaining R<sup>1</sup> as a phenyl group (Table 3). As compared to **7d**, the analogues with benzofused heterocycles at R<sup>2</sup> (**10c–10g**) all had significantly diminished potency at mGlu<sub>2</sub> and mGlu<sub>3</sub>. Installation of a 4-pyridyl group also caused a relative decrease in potency. In contrast, when a 3,5pyrimidyl group is present at the R<sup>2</sup> position, it increased potency by nearly 3.5-fold at mGlu<sub>2</sub> and by over 2-fold at mGlu<sub>3</sub>. The resulting compound, 4-methyl-2-phenyl-8-(pyrimidin-5-yl)pyrazolo[1,5-*a*]quinazolin-5(4*H*)-one (**10b**), was the most potent inhibitor of group II mGlus discovered from this scaffold, with an IC<sub>50</sub> of 245 nM (pIC<sub>50</sub> = 6.611 ± 0.055) at mGlu<sub>2</sub>, and 78 nM (pIC<sub>50</sub> = 7.108 ± 0.073) at mGlu<sub>3</sub>.

Due to its potency, **10b** was selected as an exemplar compound from this series for further pharmacological characterization. In order to determine its mechanism of action (competitive orthosteric antagonism or negative allosteric modulation), **10b** was screened at several fixed concentrations against mGlu<sub>2</sub> and mGlu<sub>3</sub> against an increasing concentration of glutamate (1 nM– $30 \mu$ M). It diminished the response to glutamate in a dose-dependent manner at both mGlu<sub>2</sub> and mGlu<sub>3</sub>, indicating that it is acting as a NAM, rather than a competitive antagonist (Fig. 3).

Additionally, to measure the broader selectivity profile of this compound, it was screened against the entire family of mGlu



Scheme 2. Reagents and conditions: (a) LiHMDS, electrophile, THF, 50 °C, 2–8 h, 30-54%.

#### Table 3

Structure and activities of analogs **10** 

R <sup>2</sup>	
10	$\sim$

Entry	R <sup>2</sup>	$IC_{50} mGlu_2{}^a (\mu M)$	$IC_{50} mGlu_3^a (\mu M)$
10a	N	1.77	0.509
10b	N	0.245	0.078
10c	H.	(9)	(34)
10d	N N	>10	>10
10e	C C C C C C C C C C C C C C C C C C C	(4)	(33)
10f	N	>10	4.51
10g		(0)	(16)

 $^a$  Where IC\_{50}s were not determined, percent inhibition of EC\_{76} (mGlu\_2) or EC\_{87} (mGlu\_3) at 3  $\mu M$  is reported in parentheses. Results are representative of three independent experiments.

receptors at a fixed concentration of 10  $\mu$ M. At this concentration **10b** showed a 3-fold shift of mGlu<sub>1</sub> and had completely blocked the glutamate response at mGlu<sub>2</sub> and mGlu<sub>3</sub>, but it did not alter the responses of the other mGlus to glutamate (Fig. 4). These data indicate that this scaffold can deliver compounds with highly preferential activity at group II mGlus, in comparison to the group I and group III receptors. Overall, these results indicate that potent dual inhibitors of mGlu<sub>2</sub> and mGlu<sub>3</sub>, such as **10b**, are rapidly accessible via alterations to a pyrazolo[1,5-*a*]quinazoline-5(4*H*)-one scaffold.

Based on the attractive mGlu selectivity profile and favorable calculated properties (MW = 353,  $c\log P = 2.72$ , tPSA = 60), we evaluated **10b** in a tier 1 DMPK panel to assess its disposition profile. Unfortunately, **10b** was very highly bound to protein in both rat ( $f_u$  0.003) and human ( $f_u$  0.008) plasma, and had a predicted clearance near hepatic blood flow in rat and human (CL<sub>hep</sub> of 54.7 mL/min/kg and 18.7 mL/min/kg, respectively). Compound **7ab** exhibited similarly poor DMPK properties. Due to the flat, aromatic character of **10b** and **7ab**, these results are understandable. Future efforts in this series will employ metabolite identification studies to identify soft spots, as well as increasing sp<sup>3</sup> character in an attempt to improve free fraction and lower clearance.

Notably, all of the compounds derived from this scaffold thus far have been either equipotent at mGlu<sub>2</sub> and mGlu<sub>3</sub>, or mGlu<sub>3</sub>-preferring. Indeed, of the compounds in this series that had  $\ge 90\%$  inhibition at mGlu<sub>2</sub> and mGlu<sub>3</sub>, all of them were more potent at mGlu<sub>3</sub>. It remains to be seen whether further exploration



**Figure 3.** Progressive fold-shift experiments with **10b**. (A) Progressive fold-shift of glutamate response by **10b** at mGlu<sub>2</sub>. (B) Progressive fold-shift of glutamate response by **10b** at mGlu<sub>3</sub>. Results are representative of three independent experiments. The decrease in Glu max indicates non-competitive antagonism, and hence a dual mGlu<sub>2</sub>/mGlu<sub>3</sub> NAM.



**Figure 4.** Fold-shifts of mGlu signaling across the group I and group III receptors. Group I signaling measured using calcium response, group III measured using GIRK response. All responses measured at rat receptors, aside from mGlu<sub>1</sub> and mGlu<sub>6</sub>, which used human receptors.

of substitutions off of the quinazoline or pyrazole rings will yield compounds with an increased preference for inhibition of mGlu<sub>3</sub>, and whether the generation of selective mGlu<sub>2</sub> NAMs or mGlu<sub>3</sub> PAMs from this series requires more extensive alterations. Continued efforts to develop subtype selective tool compounds are underway and will be reported in due course.

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