Published in final edited form as:

Bioorg Med Chem Lett. 2014 June 15; 24(12): 2693–2698. doi:10.1016/j.bmcl.2014.04.051.

Synthesis and SAR of substituted pyrazolo[1,5-*a*]quinazolines as dual mGlu₂/mGlu₃ NAMs

Cody J. Wenthur^{a,b}, Ryan D. Morrison^{a,b}, J. Scott Daniels^{a,b}, P. Jeffrey Conn^{a,b}, and Craig W. Lindsley^{a,b,c,*}

^aDepartment of Pharmacology, Vanderbilt University Medical Center, Nashville, TN 37232, USA

^bVanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center, Nashville, TN 37232, USA

^cDepartment of Chemistry, Vanderbilt University, Nashville, TN 37232, USA

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 (mGlu₂ and mGlu₃, respectively). Development of this series was initiated by reports that pyrazolo[1,5-*a*]quinazoline-derived 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 mGlu₂/mGlu₃ NAMs, with excellent selectivity versus the other mGluRs.

Keywords

Metabotropic glutamate receptor 2; Metabotropic glutamate receptor 3; mGlu₂ receptor; mGlu₃ receptor; negative allosteric modulator (NAM)

Since their discovery, the metabotropic glutamate receptors (mGlu_s) 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.¹⁻³ Within the mGlu family, the group II receptors, metabotropic glutamate receptor 2 (mGlu₂) and metabotropic glutamate receptor 3 (mGlu₃) have received significant attention for their roles in the treatment of schizophrenia, depression, anxiety disorders, and substance abuse.⁴⁻⁹

© 2014 Elsevier Ltd. All rights reserved.

*To whom correspondence should be addressed: craig.lindsley@vanderbilt.edu.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

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 mGlu_s.^{10,11} 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 mGlu₂ and mGlu₃ have separate, and in some cases, competing functions.¹²⁻¹⁷ In order to more effectively elucidate the individual functions of mGlu₂ and mGlu₃, there have been several campaigns to develop compounds capable of discriminating between these two receptors.

Many of the most successful efforts to develop such subtype-selective ligands have targeted allosteric sites on mGlu₂ or mGlu₃.¹⁸ 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).^{3,19} This strategy has led to the development of several selective mGlu₂ PAMs, and more recently, selective mGlu₃ NAMs.^{18,20,21} However, aside from claims in the patent literature with minimal selectivity data, there have been no formal reports of functionally-selective mGlu₂ NAMs or mGlu₃ PAMs.²² 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 mGlu₂ and mGlu₃ in a DtectAll™ FRET-based binding assay system.²³ Also, it has been reported that mGlu₂ NAMs, mGlu₃ NAMs, and mGlu₃ PAMs have been developed via directed alterations to this chemotype (Figure 1A).²⁴ Such molecular switching has been previously reported for compounds targeting mGlu₅, a group I mGlu, and compounds targeting mGlu₄, a group III mGlu, but there has been limited information regarding the phenomenon amongst compounds targeting group II mGlu_s.²⁵⁻²⁸

In order to improve understanding of the structure-activity relationship (SAR) underlying molecular switching amongst group II mGlu_s, several chemical libraries were developed around a 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 (Figure 1B).

The initial compounds were synthesized using a matrix-library strategy, where alterations at R¹ and R² 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 benzoylacetonitriles 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 μ M for their ability to alter glutamate-dependent signaling, against cell lines stably expressing either rat mGlu₂ or rat mGlu₃ and mouse G_{α15} (Figure 2). All assays were carried out using a kinetic, plate-based, calcium-induced fluorescence reader, using previously reported methods.²¹ From the initial group of compounds, none appeared to potentiate glutamate-dependent calcium signaling (EC₂₀ of Glu) at either mGlu₂ or mGlu₃ when applied at 3 μ M. Conversely, 6 of the 53 analogs **7** screened showed robust inhibition of mGlu₂, and 18 of the analogs **7** showed robust inhibition of mGlu₃, meaning they inhibited an ~EC₈₀ glutamate response by 50%. Thus, the initial library generated analogs biased towards inhibition of mGlu₃, 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 agonist concentrations as in the single point assay, while using a broad range of test-compound concentrations (30 μ M – 1 nM).

As has been previously reported with allosteric modulators for mGlu, the SAR profile of these compounds was fairly steep, with small structural changes leading to significant losses in efficacy.^{21, 25} When the R¹ position was held constant as a phenyl ring, and R³ was held as a methyl, installation of a 3-sulfonylphenyl or 3-pyridyl group at R² yielded inhibitors with low-micromolar to high nanomolar IC₅₀s at both mGlu₂ and mGlu₃. 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-substituted phenyl groups at R¹ are summarized in **Table 1**. In general, the presence of a 3-sulfonamidephenyl or 3-pyridyl at R² 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 R¹ exclusively. When replacing the phenyl at R¹ (as in **7a-7e**) with a 3-fluoro phenyl (as in **7f-7j**), the analogous compounds generally exhibit a reduction in potency at mGlu₂ and mGlu₃. In the case where a 3-pyridyl is present at R², this reduction is approximately 2-fold. However, in the case where a 3-sulfonyl phenyl is at R², the potency reduction is even more pronounced: greater than 5-fold at mGlu₂, and greater than 10-fold at mGlu₃. When a 3-methoxyphenyl is installed at R¹ (**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 R², 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 R¹ (**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 R¹ 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 mGlu₂, while its potency at mGlu₃ is retained. The SAR data for 4-substituted phenyl groups at R¹ is also summarized in Table 1. Those compounds with phenyl, 4-methoxyphenyl, and methyl substitutions at R² are once again less active than their 3-sulfonamidephenyl and 3-pyridyl analogues. The presence of a 4-fluorophenyl group

at R¹ (**7y-7ac**) yielded compounds with retained or modestly increased potencies at mGlu₂ and mGlu₃, 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 R² resulted in the most potent compound generated from this initial screen, **7ab**, with an IC₅₀ of 427 nM at mGlu₂ and 67 nM at mGlu₃. Placing a 4-chlorophenyl group at R¹ (**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 mGlu; their CRC's reach a maximum of around 60% inhibition at 1 μM, 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 R¹ resulted in compounds with severely attenuated potency. Likewise, the presence of multiply substituted phenyl rings at R¹, specifically 3,4-difluorophenyl and 3,5-dimethoxyphenyl groups, resulted in compounds with little inhibitory activity at mGlu₂ or mGlu₃ (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), follow 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 R¹, and either a 3-pyridinyl or phenyl group at R². The presence of a hydrogen (**8a, 8b**) or acetyl group (**9a, 9c**) at R³ did not appear to be tolerated for these compounds, and installation of an ethanol group resulted in a significant decrease in potency at mGlu₂ and mGlu₃ (**9b, 9d**).

Given the trend seen with **7a-7ah**, wherein the presence of a 3-pyridyl group at R² resulted in compounds with elevated potency at mGlu₂ and mGlu₃, it was decided to explore the effects of additional heterocyclic replacements at R² while retaining R¹ as a phenyl group (Table 3). As compared to **7d**, the analogues with benzo-fused heterocycles at R² (**10c-10g**) all had significantly diminished potency at mGlu₂ and mGlu₃. Installation of a 4-pyridyl group also caused a relative decrease in potency. In contrast, when a 3,5-pyrimidyl group is present at the R² position, it increased potency by nearly 3.5-fold at mGlu₂ and by over 2-fold at mGlu₃. 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 mGlu discovered from this scaffold, with an IC₅₀ of 245 nM (pIC₅₀ = 6.611±0.055) at mGlu₂, and 78 nM (pIC₅₀ = 7.108±0.073) at mGlu₃.

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 mGlu₂ and mGlu₃ against an increasing concentration of glutamate (1 nM – 30 μM). It diminished the response to glutamate in a dose-dependent manner at both mGlu₂ and mGlu₃, indicating that it is acting as a NAM, rather than a competitive antagonist (Figure 3).

Additionally, to measure the broader selectivity profile of this compound, it was screened against the entire family of mGlu receptors at a fixed concentration of 10 μM. At this concentration **10b** showed a 3-fold shift of mGlu₁, and had completely blocked the

glutamate response at mGlu₂ and mGlu₃, but it did not alter the responses of the other mGlu_s to glutamate (Figure 4). These data indicate that this scaffold can deliver compounds with highly preferential activity at group II mGlu_s, in comparison to the group I and group III receptors. Overall, these results indicate that potent dual inhibitors of mGlu₂ and mGlu₃, 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, clogP = 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_{hep} 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 sp³ 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 mGlu₂ and mGlu₃, or mGlu₃-preferring. Indeed, of the compounds in this series that had 90% inhibition at mGlu₂ and mGlu₃, all of them were more potent at mGlu₃. It remains to be seen whether further exploration of substitutions off of the quinazoline or pyrazole rings will yield compounds with an increased preference for inhibition of mGlu₃, and whether the generation of selective mGlu₂ NAMs or mGlu₃ 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.

Acknowledgments

Thanks to Darren Engers and Corey Hopkins for their several helpful discussions regarding analogue selection, to Meredith Noetzel and Atin Lamsal for their assistance with the mGlu selectivity panel, and to Caitlin Li for her synthetic support. This work was supported by the NIH/MLPCN and houses the Vanderbilt Specialized Chemistry Center for Accelerated Probe Development supported by U54 MH084659. The support of William K. Warren, Jr. who funded the William K. Warren, Jr. Chair in Medicine (to C.W.L.) is gratefully acknowledged.

References

1. Conn PJ, Pin J-P. Annu. Rev. Pharmacol. Toxicol. 1997; 37:205. [PubMed: 9131252]
2. Melancon BJ, Hopkins CR, Wood MR, Emmitte KA, Niswender CM, Christopolous A, Conn PJ, Lindsley CW. J. Med. Chem. 2012; 55:1445. [PubMed: 22148748]
3. Conn PJ, Christopolous A, Lindsley CW. Nat. Rev Drug Disc. 2009; 8:41.
4. Conn PJ, Lindsley CW, Jones C. Trends Pharmacol Sci. 2009; 30:25. [PubMed: 19058862]
5. Harrison PJ, Lyon L, Sartorius LJ, Burnet PWJ, Lane TA. J. Psychopharmacol. 2008; 22:308. [PubMed: 18541626]
6. Palucha A, Pilc A. Drug News Perspect. 2005; 4:262. [PubMed: 16034483]
7. Matrisciano F, Panaccione I, Zusso M, Giusti P, Tatarelli R, Iacovelli L, Mathé AA, Gruber SHM, Nicoletti F, Giardi P. Mol. Psychiatry. 2007; 12:704. [PubMed: 17653204]
8. Pistakas N. Eur. J. Pharmacol. 2014; 723:181. [PubMed: 24361306]
9. Olive MF. Curr Drug Abuse Rev. 2009; 2:83. [PubMed: 19630739]

10. Monn JA, Valli MJ, Massey SM, Hansen MM, Kress TJ, Wepsiec JP, Harkness AR, Grutch JL Jr, Wright RA, Johnson BG, Andis SL, Kingston AE, Rosemarie T, Lewis R, Griffey KR, Tizzano JP, Schoepp DD. *J Med. Chem.* 1999; 42:1027. [PubMed: 10090786]
11. Kingston AE, Ornstein PL, Wright RA, Johnson BG, Mayne NG, Burnett JP, Belagaje R, Wu S, Schoepp DD. *Neuropharmacology.* 1998; 37:1. [PubMed: 9680254]
12. Wright RA, Johnson BG, Zhang C, Salhoff C, Kingston AE, Calligaro DO, Monn JA, Schoepp DD, Marek GJ. *Neuropharmacology.* 2013; 66:89. [PubMed: 22313530]
13. Battaglia G, Molinaro G, Riozzi B, Storto M, Busceti CL, Spinsanti P, Bucci D, Di Liberto V, Mudó G, Corti C, Corsi M, Nicoletti F, Belluardo N, Bruno V. *PLoS One.* 2009; 8:e6591. [PubMed: 19672295]
14. Hanna L, Ceolin L, Lucas S, Monn JA, Johnson BG, Collingridge G, Zuner B, Lodge D. *Neuropharmacology.* 2013; 66:114. [PubMed: 22445601]
15. Linden A-M, Baez M, Bergeron M, Shoep DD. *Neuropharmacology.* 2006; 51:213. [PubMed: 16733060]
16. Corti C, Battaglia G, Molinaro G, Riozzi B, Pittaluga A, Corsi M, Mugnaini M, Nicoletti F, Bruno V. *Neuroscience.* 2007; 27:8297. [PubMed: 17670976]
17. Caraci F, Molinaro G, Battaglia G, Giuffrida ML, Riozzi B, Trafficante A, Bruno V, Cannella M, Merlo S, Wang X, Heinz BA, Nisenbaum ES, Britton TC, Drago F, Sortino MA, Copani A, Nicoletti F. *Mol. Pharmacol.* 2011; 79:618. [PubMed: 21159998]
18. Sheffler DJ, Pinkerton AB, Dahl R, Markou A, Cosford NDP. *ACS Chem. Neurosci.* 2011; 2:382. [PubMed: 22860167]
19. Keov P, Sexton P, Christopoulos A. *Neuropharmacology.* 2011; 60:24. [PubMed: 20637785]
20. Andres J-I, Alcàzar J, Cid JM, De Angelis M, Iturrino L, Langlois X, Lavreysen H, Trabanco AA, Celen S, Bormans GM. *J Med. Chem.* 2012; 55:8685. [PubMed: 22992024]
21. Wenthur CJ, Morrison R, Felts AS, Smith KA, Engers JL, Byers FW, Daniels J,S, Emmitte KA, Conn PJ, Lindsley CW. *J Med. Chem.* 2013; 56:5208. [PubMed: 23718281]
22. Merck Sharp & Dohme Corp.. International Patent Application PCT/US2012/062027. 2012.
23. Schann, S. GPCR/Membrane Protein Targets Brochure; 11th Annual Discovery on Target Meeting; Boston, MA. 2013; Sep 24-26.
24. Schann, S.; Manteau, B.; Franchet, C.; Frauli, M.; Mayer, S. General Poster Session – EVE Session; 246th ACS National Meeting and Exposition; Indianapolis, IN. 2013; Sep 8-12.
25. Sharma S, Rodriguez A, Conn PJ, Lindsley CW. *Bioorg. Med. Chem. Lett.* 2008; 18:4098. [PubMed: 18550372]
26. Sharma S, Kedrowski J, Rook JM, Smith RL, Jones CK, Rodriguez AL, Conn PJ, Lindsley CW. *J. Med. Chem.* 2010; 52:4103. [PubMed: 19537763]
27. Utley T, Haddenham D, Salovich JM, Zamorano R, Vinson PN, Lindsley CW, Hopkins CR, Niswender CM. *Bioorg. Med. Chem. Lett.* 2011; 21:6955. [PubMed: 22030026]
28. Schann S, Mayer S, Franchet C, Frauli M, Steinberg E, Thomas M, Baron L, Neuville P. *J Med. Chem.* 2010; 53:8775. [PubMed: 21105727]

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.

Figure 2.

Inhibition of mGlu₂ response to an EC₇₆ of glutamate and inhibition of mGlu₃ response to an EC₈₇ of glutamate. Results are representative of three independent experiments.

Figure 3.

Progressive fold-shift experiments with **10b**. A) Progressive fold-shift of glutamate response by **10b** at mGlu₂. B) Progressive fold-shift of glutamate response by **10b** at mGlu₃. Results are representative of three independent experiments. The decrease in Glu max indicates non-competitive antagonism, and hence a dual mGlu₂/mGlu₃ NAM.

Figure 4.

Fold-shifts of mGlu signaling across the group I and group III measured using GIRK response. All responses measured at rat receptors, aside from mGlu1 and mGlu6, which used human receptors.

Scheme 1.

Reagents and conditions: (a) NaNO_2 , HCl , SnCl_2 , -5°C to RT , 2h, 90%; (b) AcOH , $\text{NCCH}_2\text{COR}^1$ 150°C , μW , 5 min, 27-88%; (c) 10 mol% $\text{Pd(dppf)}_2\text{Cl}_2$, K_3PO_4 , $\text{B(OH)}_2\text{R}_2$, Dioxane/ H_2O , 130°C , μW , 40 min, 34-95%; (d) LiHMDS , ICH_3 , THF , 50°C , 2 h, 52-76%.

Scheme 2.

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

Table 1

Structure and activities of analogs 7.

Entry	R ¹	R ²	IC ₅₀ mGlu ₂ [μM] ^a	IC ₅₀ mGlu ₃ [μM] ^a
7a			1.93	0.884
7b	"		> 10	> 10
7c	"		(-4)	(0)
7d	"		0.852	0.165
7e	"	H ₃ C ⁻	(17)	(59)
7f			> 10	> 10
7g	"		(2)	(39)
7h	"		(6)	(2)
7i	"		1.56	0.247
7j	"	H ₃ C ⁻	(16)	(38)
7k			1.39	0.696
7l	"		> 10	> 10
7m	"		(6)	(48)
7n	"		3.12	1.18
7o	"	H ₃ C ⁻	> 10	> 10
7p			(7)	(49)
7q	"		(0)	(34)
7r	"		1.79	0.53

7s			(7)	(19)
7t	"		(9)	(31)
7u	"		0.564	0.293
7v			(8)	(28)
7w	"		(4)	(23)
7x	"		> 10	> 10
7y			3.95	1.99
7z	"		(12)	(64)
7aa	"		> 10	> 10
7ab	"		0.427	0.067
7ac	"		> 10	> 10
7ad			0.847	1.25
7ae	"		(4)	(31)
7af	"		(6)	(21)
7ag	"		1.11	0.645
7ah	"		(11)	(33)

^aWhere IC₅₀s were not determined, percent inhibition of EC₅₀ (mChl₂) or EC₅₀ (mChl₃) at 3 μM is reported in parentheses. Results are representative of three independent experiments.

Table 2Structure and activities of analogs **8** and **9**.

Entry	R ² ^a	R ³ ^a	IC ₅₀ mGlu ₂ [μM] ^b	IC ₅₀ mGlu ₃ [μM] ^b
8a			(2)	(6)
9a	"		(3)	(8)
9b	"		(0)	(3)
8b			(4)	(8)
9c	"		> 10	> 10
9d	"		4.65	3.15

^aWhere IC₅₀S were not determined, percent inhibition of EC76 (mGlu₂) or EC87 (mGlu₃) at 3 μM is reported in parentheses. Results are representative of three independent experiments.

Table 3Structure and activities of analogs **10**.

Entry	R ²	IC ₅₀ mGlu ₂ [μM] ^a	IC ₅₀ mGlu ₃ [μM] ^a
10a		1.77	0.509
10b		0.245	0.078
10c		(9)	(34)
10d		> 10	> 10
10e		(4)	(33)
10f		> 10	4.51
10g		(0)	(16)

^aWhere IC₅₀s were not determined, percent inhibition of EC76 (mGlu₂) or EC87 (mGlu₃) at 3 μM is reported in parentheses. Results are representative of three independent experiments.