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Synthesis and SAR of centrally active $mGlu_5$ positive allosteric modulators based on an aryl acetylenic bicyclic lactam scaffold

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ABSTRACT

This Letter describes the hit-to-lead progression and SAR of a series of biphenyl acetylene compounds derived from an HTS screening campaign targeting the $mGlu_5$ receptor. 'Molecular switches' were identified that modulated modes of pharmacology, and several compounds within this series were shown to be efficacious in reversal of amphetamine induced hyperlocomotion in rats after ip dosing, a preclinical model that shows similar positive effects with known antipsychotic agents.

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The NMDA receptor hypofunction hypothesis is generally the favored pathophysiological model for the disease mechanism for schizophrenia.[1,2] As a result, multiple approaches to enhance the glutamate/NMDA system continue to be pursued as a means to ameliorate the major symptom dimensions of the disease.[1,2] Development of positive allosteric modulators (PAMs) of the group I metabotropic glutamate receptor $mGlu_5$ continue to offer promise as one such approach.[3–6] After nearly a decade since the identification of the first $mGlu_5$ PAMs DFB (**1**),[7] CPPHA (**2**),[8,9] and CDPPB (**3**),[10,11] several chemically distinct series have recently emerged including ADX47273 (**4**),[12–14] a series of MPEP-based pyrimidines (**5**)[15,16] and nicotinamide (**6**),[17,18] alkoxy biphenyl amides (**7**)[19] and a chemically distinct series of piperazines (**8**).[20,21] These second generation PAMs offer several physiochemical advantages (e.g., solubility, unbound free fraction in biological relevant matrices) over the first generation PAMs (Fig. 1).

Utilizing an in-house developed triple-add functional calcium mobilization assay, we identified multiple modulators of $mGlu_5$, including—agonists, antagonists, and potentiators.[17] This effort resulted in 1400 confirmed PAMs, including 63 with potency below 500 nM.[17] Amongst these potent lead structures several, including VU0092273, were found to contain a biphenyl acetylene moiety with exceptional ligand efficiency (LE) approaching 0.5 (Fig. 2).[17]

An optimization campaign around VU0092273 followed, focusing on incorporation of water solubilizing groups, leading to VU0360172, the first *orally* active $mGlu_5$ PAM to be efficacious in an in vivo preclinical antipsychotic model.[17] In parallel to these studies, we investigated structurally constrained analogs of these phenyl and nicotinyl amides in order to understand their general activity as PAMs and also as a strategy to mitigate potential amidase activity that might metabolize amides similar to VU0092273 and VU0360172.[17] In this Letter we describe the synthesis, SAR, and in vivo behavioral profile for three chemically distinct bicyclic scaffolds.[22]

We envisioned initially exploring cyclic constraints of the linear amide scaffolds, VU0092273 and VU0360172, including dihydroisoquinolinones (**9**), dihydronaphthyridinones (**10**), phthalimides (**11**), and isoindolinones (**12**) (Fig. 2) in conjunction with evaluating alternate caps (R_1) of the lactam NH and aryl moieties (R_2). Synthetically all analogs were prepared from the parent bicylic scaffolds via a Sonagashira coupling reaction using the appropriate halogen precursors **13** and functionalized phenyl acetylene monomers (Scheme 1). *N*-Alkyl congeners were subsequently prepared using standard alkylation conditions as shown.

Initially, we prepared a library of dihydroisoquinolinones (**9**), wherein an unsubstituted phenyl moiety was held constant for R_2, and the lactam NH was substituted with various R_1 moieties. This bicyclic constraint proved to be highly beneficial, affording potent and efficacious PAMs and ago-PAMs, defined as PAMs with

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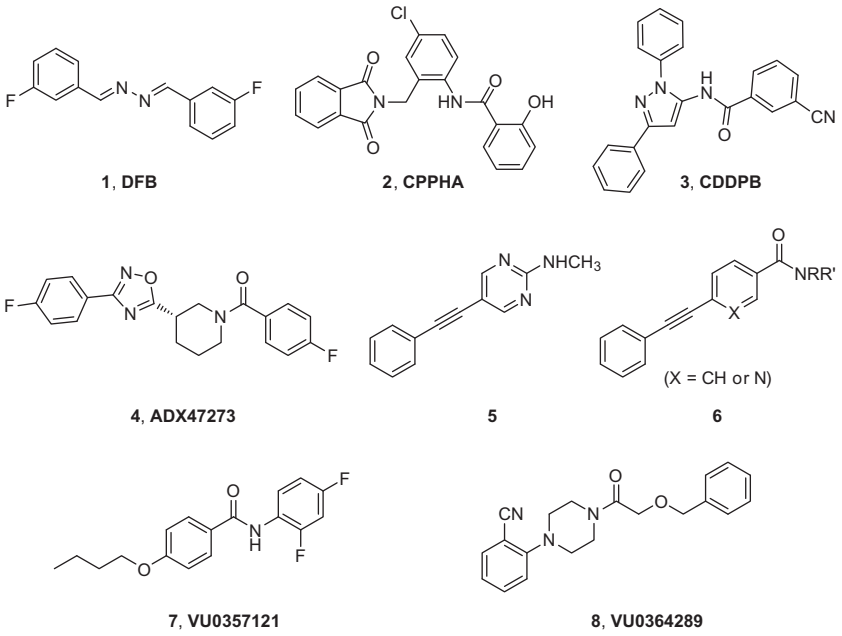


Figure 1. Prototype and recent $mGlu_5$ positive allosteric modulators.

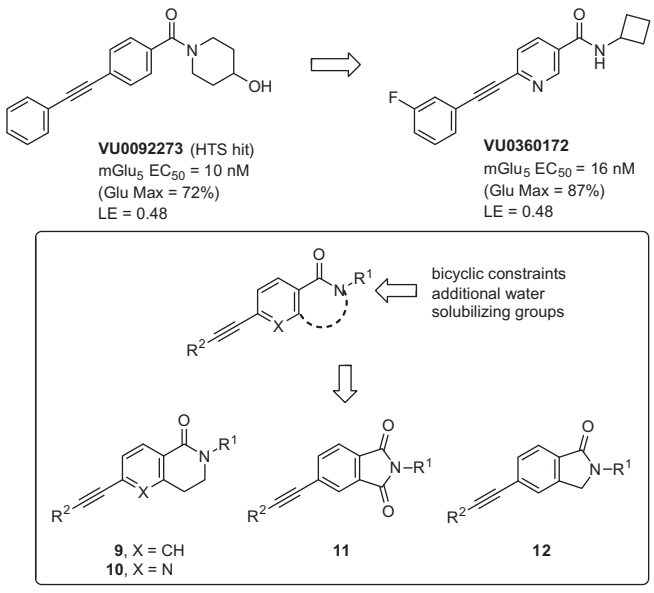


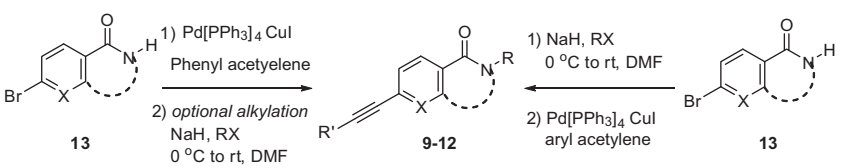
Figure 2. Nicotinyl amide and proposed bicyclic constraints **9**–**12**.

varying degrees of apparent agonist activity (Table 1). The NH congener **9a** proved to be the most potent and efficacious (EC_{50} = 50 nM, 112% Glu Max, 10.8-fold shift) ago-PAM in this small library.

Functionalization of the lactam NH afforded a number of potent PAMs and ago-PAMs with EC_{50}s in the 96–600 nM range with good maximal responses (53–97% of the response elicited by a maximal concentration of glutamate, herein described as % Glu Max) and leftward fold-shifts of a full glutamate concentration–response curve (5.7–11.8×). Encouraged by the in vitro profile, several dihydroisoquinolinones (**9**) were scaled-up and evaluated in our tier one, single-point pharmacodynamic assay, amphetamine-induced hyperlocomotion (AHL), a standard preclinical assay predictive of antipsychotic acitivity.[10,11] Compounds **9a**, **9c**, and **9f** all displayed significant reversal of amphetamine-induced hyperlocomotion at 30 mg/kg ip, and Figure 3 shows representative data obtained with **9c**, the *N*-propyl derivative.

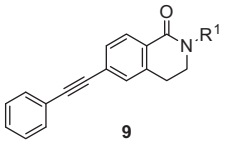
Based on these promising data, we then evaluated a library of analogs wherein we held the NH constant on the lactam, as in **9a**, and surveyed a diverse group of functionalized aryl moieties in the R_2 position (Table 2). Here, all analogs lose potency relative to **9a**, but still afford potent PAMs and ago-PAMs such as the *ortho*-F congener **9m** (EC_{50} = 150 nM, 80% Glu Max) and the *meta*-CH_3 derivative **9k** (EC_{50} = 170 nM, 76% Glu Max). Substituents in the *para*-position, such as *para*-OCH_3 (**9n**) or *para*-Cl (**9r**) resulted in inactive compounds ($mGlu_5$ EC_{50} >10 μM) whereas the smaller fluorine congener **9l** afforded a 260 nM PAM. In our acyclic series, represented by VU0092273 and VU0360172,[17] the *meta*-F derivative proved optimal, and thus far, the *meta*-position appeared the most amenable to substitution and afforded favorable DMPK disposition.[17]

While many of these novel PAMs were active in AHL, they required a DMSO-containing vehicle. Thus, future analogs were designed to incorporate a basic amine to improve physiochemical properties and enable salt formation to enable non-toxic vehicle formulations. Therefore, we elected to prepare a small library of dihydronaphthyridinones (**10**) wherein R_2 was *meta*-F phenyl and

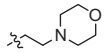


Scheme 1. General routes utilized to prepare **9**–**12**.

Table 1
Structures and activities of bicyclic lactam $mGlu_5$ PAMs **9a–i**

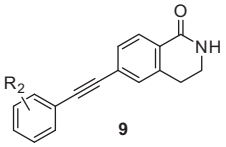


9

Compd	R^1	$mGlu_5$ EC_{50}[a] (nM)	% Glu Max[b]	Category
9a	H	50	112	Ago-PAM
9b	CH_3	250	53	PAM
9c	*n*-Pr	160	97	Ago-PAM
9d	*n*-Bu	96	97	Ago-PAM
9e	Bn	550	90	Ago-PAM
9f		180	69	Ago-PAM
9g		270	91	Ago-PAM
9h		4000	77	PAM
9i		3600	84	PAM

[a] EC_{50}s are the average of three determinations and are reproducible with a coefficient of variation of 0.3.
[b] Determined at 30 μM test compound wherein %max vehicle is 10–30%.

Table 2
Pendant aryl SAR of bicyclic PAMs **9i–t**



9

Compd	R_2	$mGlu_5$ EC_{50}[a] (nM)	% Glu Max[b]	Category
9j	*o*-CH_3	610	53	PAM
9k	*m*-CH_3	170	76	Ago-PAM
91	*p*-F	260	81	PAM
9m	*o*-F	150	80	Ago-PAM
9n	*P*-CH_3O	>10,000	ND	ND
9o	*m*-CH_3O	3400	58	PAM
9p	*m*-CH_3, *p*-F	4900	53	PAM
9q	*o*-Cl	3700	50	PAM
9r	*p*-Cl	>10,000	ND	ND
9s	*m*-Cl	470	68	PAM
9t	*p*-F, *o*-F	850	59	PAM

[a] EC_{50}s are the average of three determinations and are reproducible with a coefficient of variation of 0.3.
[b] Determined at 30 μM test compound wherein %max vehicle is 10–30%.

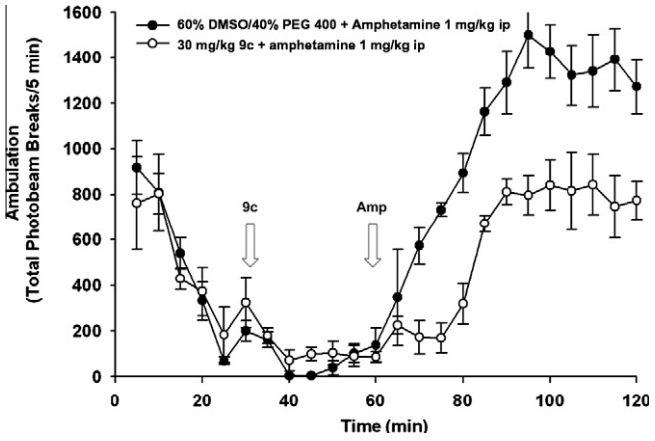
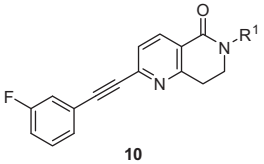


Figure 3. Reversal of amphetamine-induced hyperlocomotion with bicyclic Glu_5 PAMs **9c** at a dose of 30 mg/kg ip.

Table 3
Structures and activities of dihydronaphthyridinones **10**



10

Compd	R^1	$mGlu_5$ EC_{50} (nM)/IC_{50}[a]	% Glu Max[b]	Category
10a	H	290	72	PAM
10b	CH_3	170	34	Partial antag
10c	*i*-Bu	54	40	Weak PAM
10d	*n*-Bu	56	46	Weak PAM
10e		660	34	Partial antag
10f		130	53	PAM

[a] EC_{50}s and IC_{50}s are the average of three determinations and are reproducible with a coefficient of variation of 0.3.
[b] Glu Max is relative to vehicle/EC_{20} (PAM) or vehicle/EC_{80} glutamate (antagonist) window.

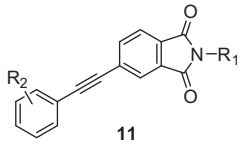
R_1 was varied (Table 3). Surprisingly, this effort uncovered an apparent 'molecular switch.[14–16] that modulated the mode of pharmacology—a first in this class of $mGlu_5$ PAMs.[22] Again PAMs, **10a**, **10c**, **10d**, and **10f**, all lost potency and significant efficacy relative to **9a**; however, the *N*-CH_3 (**10b**) and *N*-cyclopropylmethyl (**10e**) congeners proved to be partial antagonists with IC_{50}s of 170 and 660 nM, respectively. Thus, with slight structural changes, a reasonably potent PAM **10a**, with a free NH, can be converted into a partial antagonist (**10b**) of comparable potency via N-methylation. These data once again highlight the challenges in developing SAR for MPEP-site allosteric ligands.

In parallel, we were exploring the impact of constriction of the six-membered lactam ring to the corresponding five-membered homologs generating two-dimensional libraries of phthalimides (**11**) and isoindolinones (**12**). The chemistry to access these analogs was the same as that shown in Scheme 1, and allowed for diversity at both R_1 and R_2. As shown in Table 4, the library of phthalimides **11** was highly productive, affording PAMs with EC_{50}s ranging from 5.9 to 5.7 μM. Compound **11a**, wherein both R_1 and R_2 are H, represents the most potent $mGlu_5$ PAM reported to date (EC_{50} = 5.9 nM, 104% Glu Max), and **11h**, the *ortho*-fluorophenyl congener is comparable in potency (EC_{50} = 12 nM, 93% Glu Max). The introduction of a basic amine, as in **11b–11d**, was unproductive, leading to 170- to >1000-fold loss in potency relative to **11a**. In addition, the *meta*-fluorophenyl derivative **11e** was again potent (EC_{50} = 35 nM, 99% Glu Max), but in this series, **11f** and **11g** were also reasonable $mGlu_5$ PAMs.

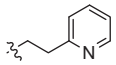
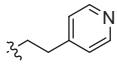
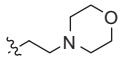
Finally, we deleted one carbonyl of the phthalimide **11** to generate a small set of isoindolinone analogs **12**. This modification also proved productive, affording $mGlu_5$ PAMs in the 50–350 nM range (Table 5), but with diminished efficacy relative to phthalimide analogs **11**. As anticipated, the unfunctionalized congener **12a** (EC_{50} = 51 nM, 69% Glu Max) and the *meta*-fluorophenyl analog **12c** (EC_{50} = 66 nM, 71% Glu Max) proved to be the best in this series. However, unlike the six-membered lactam series, both the *ortho*- and *para*-fluorophenyl derivative were reasonable $mGlu_5$ PAMs (EC_{50}s of 200 and 350 nM, respectively).

In summary, we introduced three types of cyclic constraints into our acyclic amide scaffolds, VU0092273 and VU0360172,

Table 4
Structures and activities of phthalimides **11**

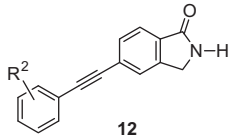


11

Compd	R_1	R_2	$mGluR_5$ EC_{50}[a] (nM)	% Glu Max[b]	Category
11a	H	H	5.9	104	Ago-PAM
11b		H	870	40	PAM
11c		H	900	76	PAM
11d		H	5700	44	PAM
11e	H	*m*-F	35	99	Ago-PAM
11f	H	*m*-F, *p*-F	170	84	PAM
11g	H	*p*-F	160	88	PAM
11h	H	*o*-F	12	93	Ago-PAM

[a] EC_{50}s are the average of three determinations and are reproducible with a coefficient of variation of 0.3.
[b] Determined at 30 μM test compound wherein %max vehicle is 10–30%.

Table 5
Structures and activities of isoindolinones **12**



12

Compd	R^2	$mGluR_5$ EC_{50}[a] (nM)	% Glu Max[b]	Category
12a	H	51	69	Ago-PAM
12b	*o*-F	200	67	PAM
12c	*m*-F	66	71	PAM
12d	*p*-F	350	60	PAM

[a] EC_{50}s are the average of three determinations and are reproducible with a coefficient of variation of 0.3.
[b] Determined at 30 μM test compound wherein %max vehicle is 10–30%.

and developed four series, **9**–**12**, of highly potent and efficacious (EC_{50}s as low as 5.9 nM, >100% Glu Max) $mGlu_5$ PAMs and ago-PAMs. Importantly, several novel compounds were centrally active and displayed significant reversal in an amphetamine-induced hyperlocomotion assay, a preclinical assay predictive of antipsychotic efficacy. In addition, we identified a subtle 'molecular switch' within scaffold **10** that engendered both PAM and partial antagonist activities. Key compounds with the **9**–**12** series are the subject of a comprehensive in vitro molecular pharmacology, electrophysiology, occupancy, and in vivo pharmacology study that will be published shortly.

References and notes

1. Lindsley, C. W.; Shipe, W. D.; Wolkenberg, S. E.; Theberge, C. R.; Williams, D. L., Jr.; Sur, C.; Kinney, G. G. *Curr. Top. Med. Chem.* **2006**, *8*, 771.
2. Meltzer, H. Y. *Biol. Psychiatry* **1999**, *46*, 1321.
3. Conn, J. P.; Lindsley, C. W.; Jones, C. K. *Trends Pharmacol. Sci.* **2009**, *30*, 25.
4. Williams, D. L., Jr.; Lindsley, C. W. *Curr. Top. Med. Chem.* **2005**, *5*, 825.
5. Conn, P. J.; Christopolous, A.; Lindsley, C. W. *Nat. Rev. Durg Disc.* **2009**, *8*, 41.
6. Ayala, J. E.; Chen, Y.; Banko, J. L.; Sheffler, D. J.; Williams, R.; Telk, A. N.; Watson, N. L.; Xiang, Z.; Zhang, Y.; Jones, P. J.; Lindsley, C. W.; Olive, M. F.; Conn, P. *J. Neuropsychopharmacol.* **2009**, *34*, 2057.
7. O'Brien, J. A.; Lemaire, W.; Wittmann, M.; Jacobson, M. A.; Ha, S. N.; Lindsley, C. W.; Sur, C.; Pettibone, D. J.; Conn, J.; Williams, D. L. *Mol. Pharmacol.* **2003**, *64*, 731.
8. O'Brien, J. A.; Lemaire, W.; Wittmann, M.; Jacobson, M. A.; Ha, S. N.; Wisnoski, D. D.; Lindsley, C. W.; Schaffhauser, H. J.; Rowe, B.; Sur, C.; Duggan, M. E.; Pettibone, D. J.; Conn, P. J.; Williams, D. L. *J. Pharmacol. Exp. Ther.* **2004**, *309*, 568.
9. Zhao, Z.; Wisnoski, D. D.; O'Brien, J. A.; Lemaire, W.; Williams, D. L.; Jacobson, M. A.; Wittman, M.; Ha, S. N.; Schaffhauser, H.; Sur, C.; Pettibone, D. J.; Duggan, M. E.; Conn, P. J.; Hartman, G. D.; Lindsley, C. W. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1386.
10. Lindsley, C. W.; Wisnoski, D. D.; Leister, W. H.; O'Brien, J. A.; Lemaire, W.; Williams, D. L.; Burno, M.; Sur, C.; Kinney, G. G.; Pettibone, D. J.; Tiller, P. R.; Smith, S.; Duggan, M. E.; Hartman, G. D.; Conn, P. J.; Huff, J. R. *J. Med. Chem.* **2004**, *47*, 5825.
11. Kinney, G. G.; O'Brien, J. A.; Lemaire, W.; Burno, M.; Bickel, D. J.; Clements, M. K.; Chen, T. B.; Wisnoski, D. D.; Lindsley, C. W.; Tiller, P. R.; Smith, S.; Jacobson, M. A.; Sur, C.; Duggan, M. E.; Pettibone, D. J.; Conn, P. J.; Williams, D. L. *J. Pharmacol. Exp. Ther.* **2005**, *313*, 199.
12. Le Poul, E.; Bessis, A. S.; Lutgens, R.; Bonnet, B.; Rocher, J. P.; Epping-Jordan, M.; Mutel, V. 5th International Metabotropic Glutamate Receptors Meeting, 2005; Taormina, Italy.
13. Engers, D. W.; Rodriguez, A. L.; Williams, R.; Hammond, A. S.; Venable, D.; Oluwatola, O.; Sulikowski, G. A.; Conn, P. J.; Lindsley, C. W. *Chem. Med. Chem.* **2009**, *4*, 505.
14. Lamb, J. P.; Engers, D. W.; Niswender, C. M.; Rodrigeuz, A. L.; Venable, D. F.; Conn, P. J.; Lindsley, C. W. *Bioorg. Med. Chem. Lett.*, available online: doi:10.1016/j.bmcl.2010.11.119.
15. Sharma, S.; Rodriguez, A.; Conn, P. J.; Lindsley, C. W. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 4098.
16. Sharma, S.; Kedrowski, J.; Rood, J. M.; Smith, R. L.; Jones, C. K.; Rodriguez, A. L.; Conn, P. J.; Lindsley, C. W. *J. Med. Chem.* **2009**, *52*, 4103.
17. Rodriguez, A. L.; Grier, M. D.; Jones, C. K.; Herman, E. J.; Kane, A. S.; Smith, R. L.; Williams, R.; Zhou, Y.; Marlo, J. E.; Days, E. L.; Blatt, T. N.; Jadhav, S.; Menon, U.; Vinson, P. N.; Rook, J. M.; Stauffer, S. R.; Niswender, C. M.; Lindsley, C. W.; Weaver, C. D.; Conn, P. *J. Mol. Pharm.* **2010**, *78*, 1105.
18. Conn, P. J.; Lindsley, C. W.; Weaver, C. W.; Rodriguez, A. L.; Niswender, C. M.; Jones, C. K.; Williams, R. Benzamide derivatives as $mGluR_5$ positive allosteric modulators and their preparation, pharmaceutical compositions and use in the treatment of diseases. WO 151184, 2008.
19. Hammond, A. S.; Rodriguez, A. L.; Townsend, S. D.; Niswender, C. M.; Gregory, K. J.; Lindsley, C. W.; Conn, P. J. *ACS Chem. Neurosci.* **2010**, *1*, 702.
20. Zhou, Y.; Manka, J.; Rodriguez, A. L.; Weaver, C. D.; Jones, C. K.; Conn, P. J.; Lindsley, C. W.; Stauffer, S. R. *ACS Med. Chem. Lett.* **2010**, *1*, 433.
21. Xiong, H.; Brugel, T. A.; Balestra, M.; Brown, D. G.; Brush, K. A.; Hightower, C.; Hinkley, L.; Hoesch, V.; Kang, J.; Koether, G. M.; McCauley, J. P., Jr.; McLaren, F. M.; Panko, L. M.; Simpson, T. R.; Smith, R. W.; Woods, J. M.; Brockel, B.; Chhajlani, V.; Gadient, R. A.; Spear, N.; Sygowski, L. A.; Zhang, M.; Arora, J.; Breysse, N.; Wilson, J. M.; Isaac, M.; Slassi, A.; King, M. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7381.
22. For studies on a closely related bicyclic ketone series of 7,8-dihydroquinolin-5(6*H*)-one $mGlu_5$ modulators see: Vandejevs, M.; Jatzke, C.; Renner, S.; Müller, S.; Hechenberger, M.; Bauer, T.; Klochkova, A.; Pyatkin, I.; Kazyulkin, D.; Aksenova, E.; Shulepin, S.; Timonina, O.; Haasis, A.; Gutcaits, A.; Parsons, C. G.; Kauss, V.; Weil, T. *J. Med. Chem.* **2008**, *51*, 634.