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Synthesis and SAR of centrally active mGlu₅ 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 mGlu₅ 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 i.p. dosing, a preclinical model that shows similar positive effects with known antipsychotic agents.

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 mGlu₅ continue to offer promise as one such approach.^{3–6} After nearly a decade since the identification of the first mGlu₅ 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 mGlu₅, 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 mGlu₅ PAM to be

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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 bicyclic 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 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 % GluMax) and leftward fold-shifts of a full glutamate concentration-response curve (5.7 - to 11.8x). 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 activity.^{10,11} Compounds **9a**, **9c** and **9f** all displayed significant reversal of amphetamine-induced hyperlocomotion at 30 mg/kg i.p., 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*-CH₃ derivative **9k** ($EC_{50} = 170$ nM, 76% Glu Max). Substituents in the *para*-position, such as *para*-OCH₃ (**9n**) or *para*-Cl (**9r**) resulted in inactive compounds (mGlu₅ $EC_{50} > 10$ μ M) 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 physicochemical 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 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 mGlu₅ PAMs.²² Again PAMs, **10a**, **10c**, **10d** and **10f**, all lost potency and significant efficacy relative to **9a**; however, the *N*-CH₃ (**10b**) and *N*-cyclopropylmethyl

(10e) congeners proved to be partial antagonists with IC_{50} s of 170 nM 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 6-membered lactam ring to the corresponding 5-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 nM to 5.7 μ M. Compound **11a**, wherein both R_1 and R_2 are H, represents the most potent mGlu₅ 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 >1,000-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 mGlu₅ 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 mGlu₅ PAMs in the 50 nM to 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 6-membered lactam series, both the *ortho*- and *para*-fluorophenyl derivative were reasonable mGlu₅ PAMs (EC_{50} s of 200 nM and 350 nM, respectively).

In summary, we introduced three types of cyclic constraints into our acyclic amide scaffolds, VU0092273 and VU0360172, and developed four series, **9-12**, of highly potent and efficacious (EC_{50} s as low as 5.9 nM, >100% Glu Max) mGlu₅ 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.

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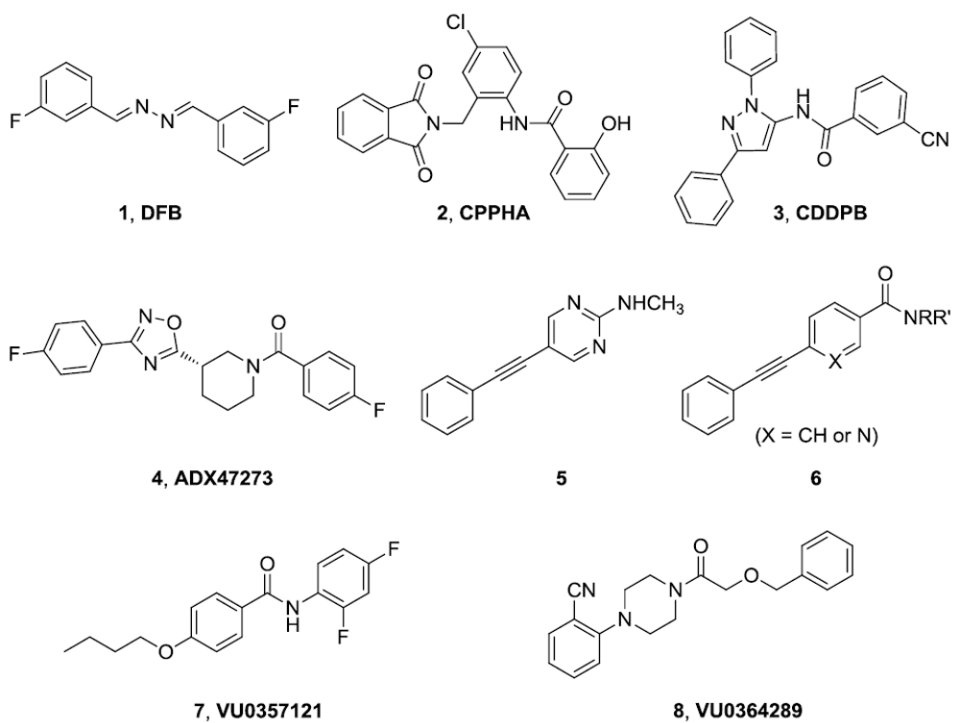


Figure 1.
Prototype and recent mGlu₅ positive allosteric modulators.

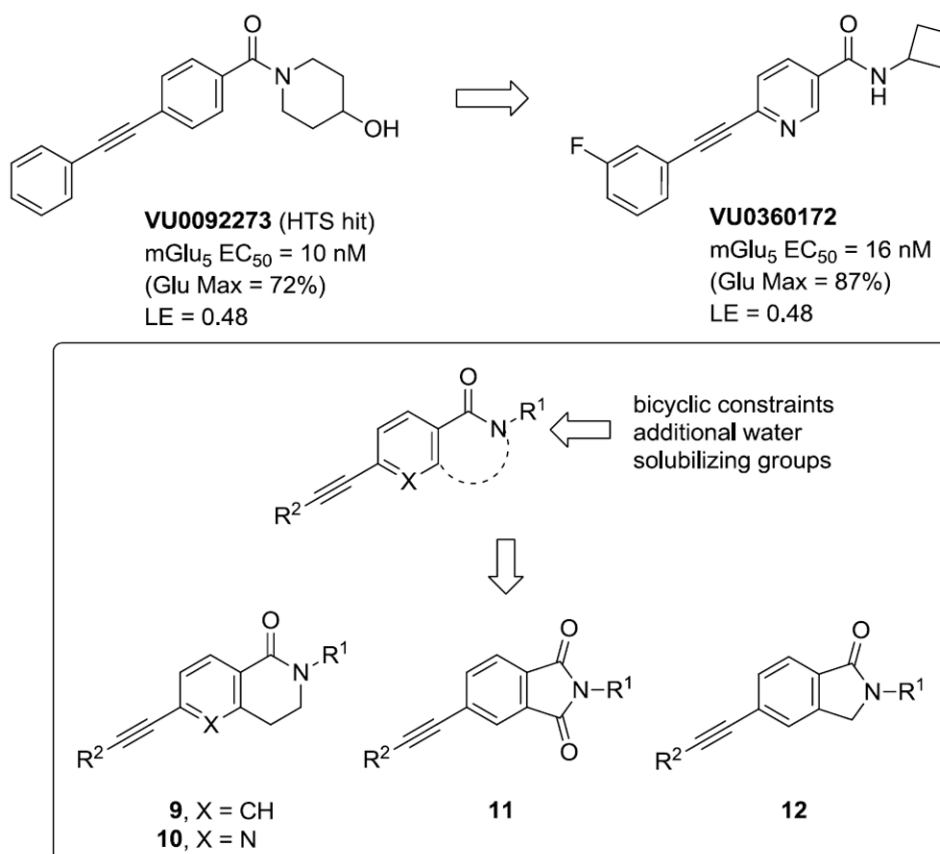


Figure 2.
 Nicotinyl amide and proposed bicyclic constraints **9-12**.

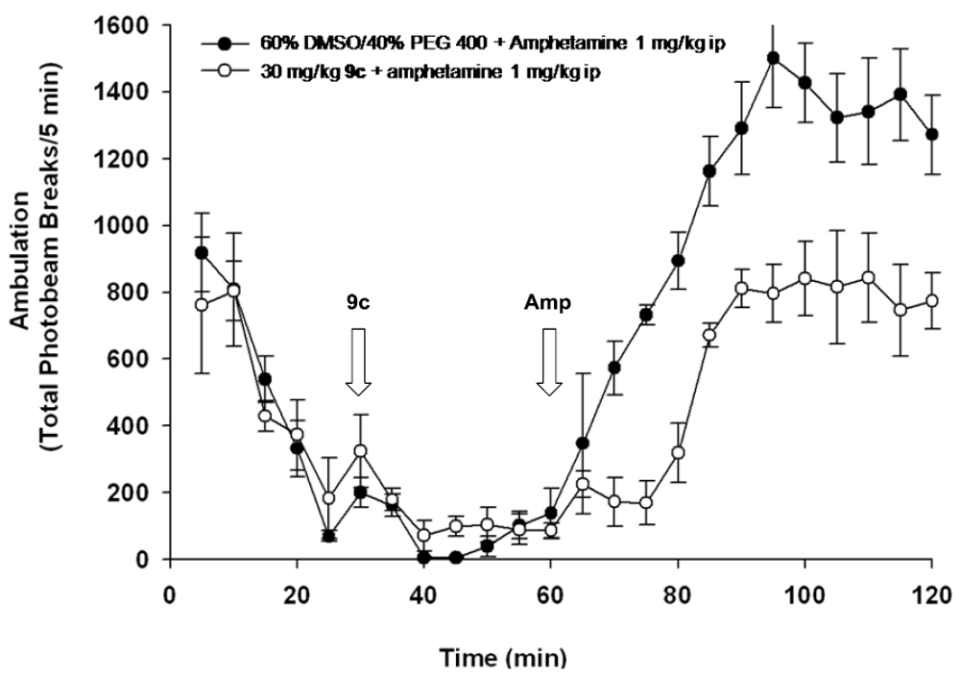
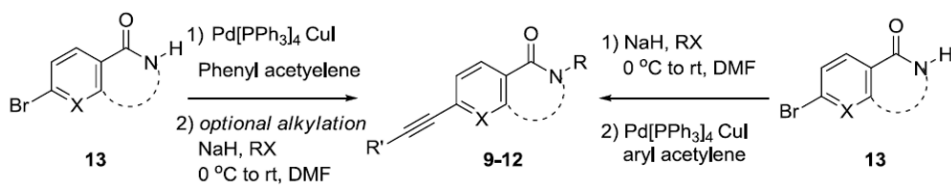
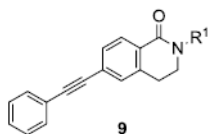


Figure 3. Reversal of amphetamine-induced hyperlocomotion with bicyclic Glu5 PAMs **9c** at a dose of 30 mg/kg ip.



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

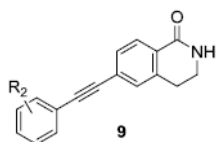
Table 1Structures and activities of bicyclic lactam mGlu₅ PAMs **9a-i**.

Cmpd	R ¹	mGlu ₅ EC ₅₀ (nM) ^a	% Glu Max ^b	Category
9a	H	50	112	Ago-PAM
9b	CH ₃	250	53	PAM
9c	<i>n</i> -Pr	160	97	Ago-PAM
9d	<i>n</i> -Bu	96	97	Ago-PAM
9e	Bn	550	90	Ago-PAM
9f		180	69	Ago-PAM
9g		270	91	Ago-PAM
9h		4,000	77	PAM
9i		3,600	84	PAM

^aEC₅₀s are the average of three determinations and are reproducible with a coefficient of variation of 0.3.

^bDetermined at 30 μM test compound wherein %max vehicle is 10-30%.

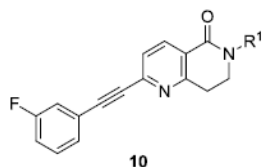
Table 2



Pendant Aryl SAR of Bicyclic PAMs **9i-t**.

Cmpd	R ₂	mGlu ₅ EC ₅₀ (nM) ^a	% Glu Max ^b	Category
9j	<i>o</i> -CH ₃	610	53	PAM
9k	<i>m</i> -CH ₃	170	76	Ago-PA
9l	<i>p</i> -F	260	81	PAM
9m	<i>o</i> -F	150	80	Ago-PA
9n	<i>p</i> -CH ₃ O	>10,000	ND	ND
9o	<i>m</i> -CH ₃ O	3,400	58	PAM
9p	<i>m</i> -CH ₃ , <i>p</i> -F	4,900	53	PAM
9q	<i>o</i> -Cl	3,700	50	PAM
9r	<i>p</i> -Cl	>10,000	ND	ND
9s	<i>m</i> -Cl	470	68	PAM
9t	<i>p</i> -F, <i>o</i> -F	850	59	PAM

^aEC₅₀s are the average of three determinations and are reproducible with a coefficient of variation of 0.3.

^bDetermined at 30 μM test compound wherein %max vehicle is 10-30%.

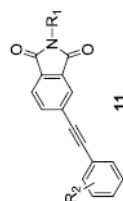
Table 3Structures and activities of dihydronaphthyridinones **10**.

Cmpd	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

^aEC₅₀s and IC₅₀s are the average of three determinations and are reproducible with a coefficient of variation of 0.3.

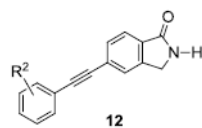
^bGlu Max is relative to vehicle/EC₂₀ (PAM) or vehicle/EC₈₀ glutamate (antagonist) window.

Table 4

Structures and activities of phthalimides **11**.

Cmpd	R ₁	R ₂	mGlu ₅ EC ₅₀ (nM) ^a	% Glu Max ^b	Category
11a	H	H	5.9	104	Ago-PAM
11b		H	870	40	PAM
11c		H	900	76	PAM
11d		H	5,700	44	pAM
11e	H	<i>m</i> -F	35	99	Ago-PAM
11f	H	<i>m</i> -F, <i>p</i> -F	170	84	PAM
11g	H	<i>p</i> -F	160	88	PAM
11h	H	<i>o</i> -F	12	93	Ago-PAM

^aEC₅₀s are the average of three determinations and are reproducible with a coefficient of variation of 0.3.^bDetermined at 30 μM test compound wherein % max vehicle is 10-30%.

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

Cmpd	R ²	mGlu ₅ EC ₅₀ (nM) ^a	% Glu Max ^b	Category
12a	H	51	69	Ago-PAM
12b	<i>o</i> -F	200	67	PAM
12c	<i>m</i> -F	66	71	PAM
12d	<i>p</i> -F	350	60	PAM

^aEC₅₀s are the average of three determinations and are reproducible with a coefficient of variation of 0.3.

^bDetermined at 30 μM test compound wherein %max vehicle is 10-30%.