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Discovery of molecular switches within the ADX-47273 $mGlu_5$ PAM scaffold that modulate modes of pharmacology to afford potent $mGlu_5$ NAMs, PAMs and partial antagonists

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ABSTRACT

This Letter describes a chemical lead optimization campaign directed at a weak $mGlu_5$ NAM discovered while developing SAR for the $mGlu_5$ PAM, ADX-47273. An iterative parallel synthesis effort discovered multiple, subtle molecular switches that afford potent $mGlu_5$ NAMs, $mGlu_5$ PAMs as well as $mGlu_5$ partial antagonists.

The metabotropic glutamate receptor subtype 5 ($mGlu_5$) has become a prominent molecular target for a number of CNS pathologies.[1,2] mGlu5 negative allosteric modulators (NAMs) are being actively pursued for anxiety, pain, Parkinson's disease, cocaine addiction and Fragile X Syndrome, while $mGlu_5$ positive allosteric modulators (PAMs) are under development for the treatment of schizophrenia.[3–9] The prototypical $mGlu_5$ allosteric ligand is MPEP (**1**),[10] a NAM, and many allosteric ligands, both PAM and NAM, bind at the MPEP-site.[1–10] Recently, we reported on the discovery of molecular switches in a series of MPEP-site phenylethynyl pyrimidines in which incorporation of a single methyl group in either the 3- or 4-position converted an $mGlu_5$ partial antagonist lead **2** (IC_{50} = 486 nM, 71% partial) into either a NAM **3** (IC_{50} = 7.5 nM) or PAM **4** (EC_{50} = 3.3 μM, 4.2-fold shift), respectively (Fig. 1).[11] Further SAR identified additional, subtle molecular switches that afforded centrally penetrant and in vivo active $mGlu_5$ NAMs and PAMs.[12] After these key findings, we began to take note of pharmacology switches, and identified these in multiple $mGlu_5$ allosteric modulator scaffolds.[13,14] Interestingly, our initial SAR work in the $mGlu_5$ PAM ADX-47273 **5** series in 2009 produced potent PAMs, such as **6** (EC_{50} = 240 nM, 14-fold shift), and ago-PAMs such as **7** (EC_{50} = 170 nM, 20-fold shift), but only one weak NAM **8** (IC_{50} = 8.7 μM).[15] This was the first indication that pharmacology switching is possible in the ADX-47273 series by replacing an aryl amide, as in **6**, with a cyclobutyl amide in **8**.[15]

While we were exploring this finding, a manuscript appeared in 2010 describing the identification of racemic $mGlu_5$ NAM **9**, closely related to our NAM **8**, from an HTS screen, and the parallel synthesis of over 1300 analogs.[16] However, within this manuscript, there is little discussion of the impact of stereochemistry and *no* mention of pharmacology switching. Here, we present our SAR study, developed though an iterative parallel synthesis approach, that afforded potent $mGlu_5$ PAMs, NAMs and partial antagonists from subtle modifications to the ADX-47273 scaffold.

Our initial library evaluated two dimensions: stereochemistry at the 3-postion and replacement for the 2-pyridyl moiety while holding the cyclobutyl amide constant. In our earlier work in the ADX-47273 series,[15] the (*S*)-stereochemistry at the 3-position was essential for $mGlu_5$ PAM activity, and it was important to ascertain the stereochemical bias, if any, to produce NAMs. In the event, (*S*)-**10** was converted to the methyl ester **11**, followed by acylation to yield **12**. Saponification provides **13**, which is then

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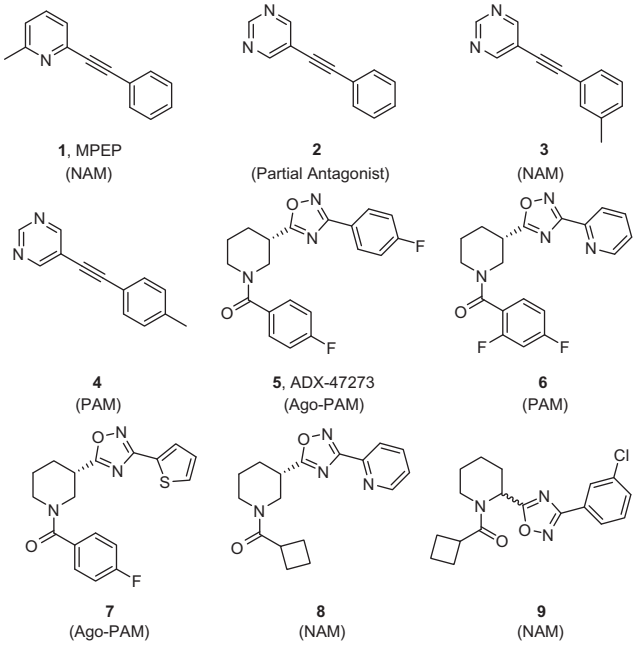
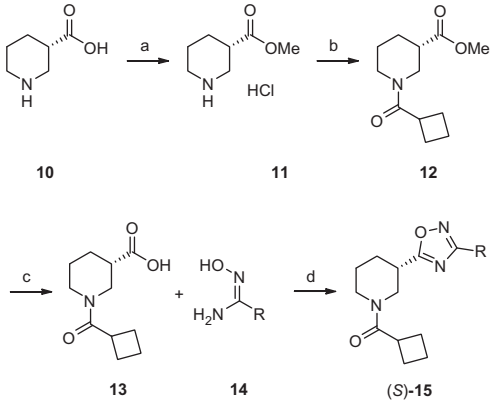


Figure 1. Structures of selected MPEP-site allosteric ligands that display a range of $mGlu_5$ pharmacology with subtle modifications.

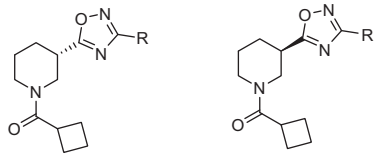
coupled to various (*Z*)-*N*'-hydroxylimidamides **14** and refluxed to deliver analogs (*S*)-**15** (Scheme 1). The analogous (*R*)-**15** congeners were made via the same scheme except (*R*)-**10** was used.

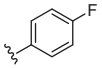
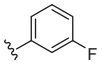
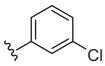
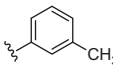
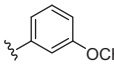
As shown in Table 1, the stereochemical preference we identified in our earlier PAM work in this series carried over into the NAM pharmacology with the (*S*)-enantiomer preferred, that is, (*S*)-**15e** (IC_{50} = 0.2 μM) versus (*R*)-**15e** (IC_{50} = 3.1 μM). Significantly, 3-substituted aryl congeners (*S*)-**15e–f**, proved most enlightening, affording submicromolar $mGlu_5$ NAMs, with in the case of (*S*)-**15e**, an ~41-fold increase in potency over **8**.[15] These data led us to consider if there is stereochemical bias for pharmacological mode of action within the **9** scaffold. Thus we prepared small, enantiopure libraries of analogs (*S*)-**20** and (*R*)-**20**, from either (*S*)-**16** and (*R*)-**16**, respectively, and evaluated them in our $mGlu_5$ assays (Scheme 2). As shown in Table 2, this effort found that both enantiomers afford comparable activity and mode of pharmacology. This library provided an efficacious submicromolar PAM (*S*)-**20c** (EC_{50} = 730 nM, 71% Glu Max) as well as several submicromolar NAMs ((*S*)- and (*R*)-**20e–f**) which also afforded a full blockade of the EC_{80}, and in the case of (*S*)-**20f**, an 77 nM NAM. Based on these data, our next round of library synthesis employed both the **20e** NAM scaffold and the **20c** PAM scaffold, and focused on evaluating other amide moieties beyond the cyclobutyl amide. These analogs **21** and **22** were readily prepared following a variation of Scheme 2.



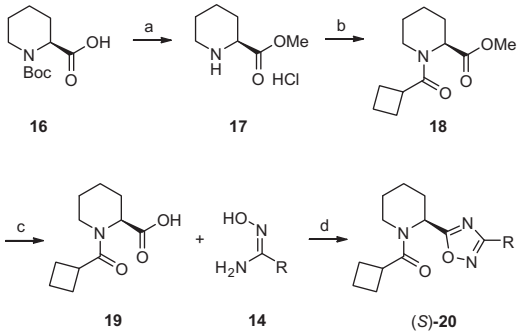
Scheme 1. Reagents and conditions: (a) $SOCl_2$, MeOH (99%), cylcobutane carbonyl chloride, DIEA, DCM (96%); (c) LiOH, THF, H_2O (95%); (d) EDCI, HOBt, DIEA, dioxane, reflux, 24 h (45–59%).

Table 1
Structures and activities of analogs (*S*)-**15** and (*R*)-**15**



Compd	R	Pharmacology	IC_{50}[a] (μM)	EC_{50}[a] (μM)	Glu Max[a] (%)
(*S*)-**15a**		NAM	9.3	NA	67
(*R*)-**15a**		Inactive	—	—	—
(*S*)-**15b**		Inactive	—	—	—
(*R*)-**15b**		Inactive	—	—	—
(*S*)-**15c**		NAM	>10	NA	33
(*R*)-**15c**		NAM	9.9	NA	19
(*S*)-**15d**		NAM	2.4	NA	31
(*R*)-**15d**		NAM	>10	NA	60
(*S*)-**15e**		NAM	0.2	NA	2.4
(*R*)-**15e**		NAM	3.1	NA	18
(*S*)-**15f**		NAM	0.7	NA	2.5
(*R*)-**15f**		NAM	4.7	NA	14
(*S*)-**15g**		NAM	1.8	NA	2.1
(*R*)-**15g**		NAM	>10	NA	54

[a] Average of at least three independent determinations. NA, not applicable.



Scheme 2. Reagents and conditions: (a) $SOCl_2$, MeOH (99%), cylcobutane carbonyl chloride, DIEA, DCM (95%); (c) LiOH, THF, H_2O (95%); (d) EDCI, HOBt, DIEA, dioxane, reflux, 24 h (40–55%).

The library of **20e** analogs, **21a–i**, afforded both NAMs and partial antagonists,[17] with no evidence of PAM activity (Table 3). Interestingly, the three and five-membered saturated ring amides **21a** and **21c**, afforded partial antagonists, while the four and six-membered saturated ring amides **21b** and **21d** afforded full non-competitive antagonists (NAMs). In contrast, the library of **20c** analogs, **22a–i**, afforded predominantly PAMs and ago-PAMs. For example, **22a** proved to be a potent (EC_{50} = 78 nM, 70% Glu Max) $mGlu_5$ PAM, more potent than the previous PAMs **6** and **7** we