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Synthesis, SAR and Unanticipated Pharmacological Profiles of Analogues of the mGluR5 Ago-potentiator ADX-47273

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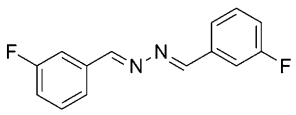
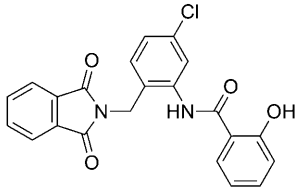
With an onset in late adolescence, schizophrenia, a complex psychiatric disorder characterized by a combination of negative (social withdrawal, blunting of emotional responses, anhedonia) and positive (hallucinations, delusions, paranoia, disorganized behavior) symptoms along with significant cognitive dysfunction is a debilitating disease that requires lifelong, daily maintenance therapy at a cost to society of $65 billion a year.[1] The prevailing dogma by which schizophrenia has been managed for decades states that excessive dopaminergic transmission in the forebrain underlies the disease—the so-called "dopamine hypothesis" or "dopamine hyperfunction hypothesis".[2] The rationale for this hypothesis is based on the fact that all clinically relevant antipsychotic agents, both typical (haloperidol) and atypical (clozapine, olanzapine), possess significant antagonist activity of the dopamine D2 receptor. However, these agents have a slow onset of action and mainly treat the positive symptoms of schizophrenia, with limited or no effect on the negative and cognitive symptoms, thereby leaving a substantial unmet medical need.[3] Moreover, all of these agents bind to a number of neurotransmitter receptors such as dopamine (D1–D4), serotonin (5-HT1A, 1D, 2A, 2C, 6 and 7), adrenergic (α1, α2), histamine (H1) and muscarinic (M1), and therefore, the observed efficacy can more accurately be ascribed to polypharmacology.[4–10]

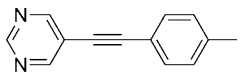
The *N*-methyl-D-aspartate (NMDA) receptor antagonist phencyclidine (PCP) has been shown to induce the positive, negative and cognitive symptoms of schizophrenia in healthy patients and elicit a resurgence of symptoms in stable schizophrenics.[10] In the clinic, the observation that administration of the NMDA receptor co-agonist glycine provides a modest improvement in schizophrenic patients suggests that increasing NMDA receptor activation may provide a therapeutic benefit.[11] These observations led to the NMDA receptor hypofunction hypothesis as an alternative theory for the underlying cause of schizophrenia.[12] According to this hypothesis, any agent that can potentiate NMDA receptor currents, either directly by action on modulatory sites on the NMDA receptor (i.e., the glycine co-agonist binding site) or indirectly by activation of GPCRs known to potentiate NMDA receptor function (i.e., mGluR5), has the potential to improve the symptoms of schizophrenia.[13] Glutamate is the major excitatory transmitter in the central nervous system, exerting its effects through either ionotropic or metabotropic glutamate receptors. The metabotropic glutamate receptors (mGluRs) are members of the GPCR family C, characterized by a large extracellular N-terminal binding domain. To date, eight mGluRs have been cloned, sequenced and assigned to three groups (Group I: mGluR1 and mGluR5; Group II: mGluR2 and mGluR3; Group III: mGluRs 4,6,7,8) based on their structure, coupling to effector mechanisms and pharmacology.[14] Achieving mGluR subtype selectivity has been difficult with orthosteric agonists, which are typically glutamate, quisqualate or phenyl glycine analogues. Recently, our laboratories have reported the discovery of positive allosteric modulators (PAMs) of mGluR5, compounds which alone have no effect on mGluR5 function, but potentiate mGluR5 receptor response in the presence of sub-threshold levels of the native agonist glutamate. We have also identified compounds that display allosteric agonist activity at higher concentrations and are more accurately termed mGluR5 ago-potentiators. By virtue of binding at an allosteric site on the receptor, these ligands afford high mGluR5 sub-type selectivity (>100-fold selectivity vs mGluR1,2,3,4,7,8).[15] We have identified three chemotypes of mGluR5 PAMs, represented by DFB (**1**),[16] CPPHA (**2**),[17] and the MPEP-like compound **3**.[18] In addition, we discovered the ago-potentiator CDPPB (**4**).[19] Interestingly, compounds **1**, **3**, and **4** have been shown to bind at the MPEP binding site, while compound **2** binds at a yet undefined



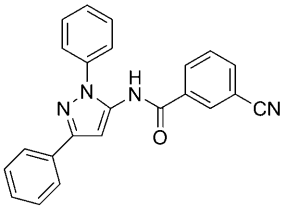
1 DFB



2 CPPHA



3



4 CDPPB

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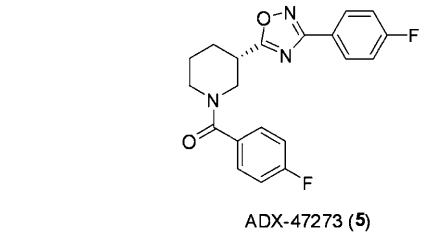
second allosteric site on mGluR5.[16–19] CDPPB (**4**) was the first centrally active mGluR5 PAM/ago-potentiator, which allowed us to validate in vivo our hypothesis that allosteric activation of mGluR5 possessed an antipsychotic profile in rat behavioral models.[19] However, CDPPB (**4**) displayed poor solubility in most vehicles, limiting its utility for further in vivo studies, and a disparity between binding affinity and functional potency. Moreover, due to the intrinsic allosteric agonist activity, though weak, we were unable to validate pure mGluR5 potentiation as the mechanism for the in vivo activity. Lead optimization efforts of the CDPPB (**4**) scaffold were unable to address these issues.[19,20]

In 2005, Addex disclosed the structurally distinct ago-potentiator ADX-47273 (**5**) and subsequently produced patents.[21,22] Researchers at both Addex[21,22] and Wyeth[23] have recently reported on the in vivo efficacy of ADX-47273 (**5**) in a number of preclinical antipsychotic and cognition models, further validating selective mGluR5 activation as a potential new mechanism to address the complex symptom clusters (positive, negative and cognitive symptoms) of schizophrenia. However, ADX-47273 is a more potent ago-potentiator (mGluR5 PAM EC_{50} = 168 nM, 107% Glu Max, ninefold shift at 1 μM; allosteric agonist EC_{50} = 9.5 μM, 65% Glu Max) than CDPPB (**4**), but still suffers from poor physiochemical properties due to a lack of solublizing moieties (Figure 1).[18–22]

In order to further validate potentiation of mGluR5 as a therapeutic approach for the treatment of the positive, negative and cognitive symptom clusters of schizophrenia and advance the science concerning mGluR5, pure mGluR5 PAMs and mGluR5 ago-potentiators with improved pharmacological and physiochemical properties are required. Little has been disclosed concerning the SAR and pharmacological profiles of ADX-47273 and its analogues.[21,22] A campaign was initiated to explore the ADX-47273 scaffold in an effort to improve the physiochemical properties of ADX-47273, determine if a pure PAM could be identified in this series and address three questions: 1) are alternative aryl/heteroaryl rings tolerated at the 3-position of the oxadiazole, 2) are alternative amides tolerated and 3) is the (*S*) stereochemistry required for mGluR5 PAM activity (Figure 2)?



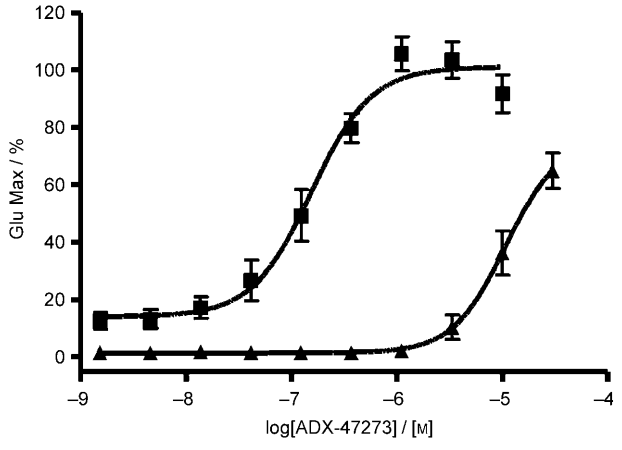


Figure 1. In vitro profile of the mGluR5 ago-potentiator ADX-47273 (**5**), highlighting the intrinsic allosteric agonist activity of compound **5** alone to activate mGluR5 in the absence of an EC_{20} of glutamate (▲). In the presence of an EC_{20} of glutamate, ADX-47273 (**5**) is a potent mGluR5 positive allosteric modulator with an EC_{50} value for potentiation of 168 nM and a ninefold shift of the glutamate response curve at 1 μM (■).

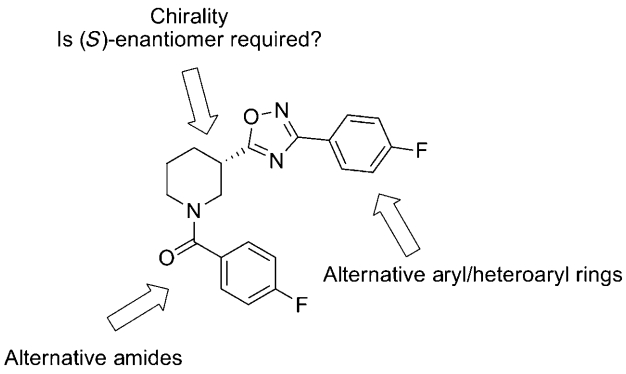


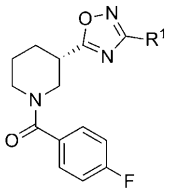
Figure 2. Three key areas to explore in the lead optimization of ADX-47273 (**5**).

We pursued a focused library approach to explore the SAR of ADX-47273. First, we prepared a small library of analogues **6** evaluating known phenyl isosteres to replace the 4-FPh moiety of the 3-position of the oxadiazole within ADX-47273 in an attempt to incorporate solubilizing and/or polar groups while maintaining the 4-FPh amide and the (*S*)-stereochemistry (Table 1). Pyridine isosteres afforded intriguing SAR; analogue **6a**, a pyridyl congener of the 4-FPh moiety of ADX-47273, lost approximately eightfold in potency (EC_{50} = 1460 nM), while the 2-pyridyl analogue **6b** lost only twofold in potency, but maintained efficacy (EC_{50} = 348 nM, 109% Glu Max). The 4-pyridyl isomer **6d** was comparable to compound **6a**, while the 3-pyridyl analogue **6c** lost significant potency (EC_{50} = 5000 nM). The 2-thienyl congener **6e** (EC_{50} = 170 nM) was equipotent to ADX-47273, and the 2-pyrimidinyl analogue **6f** lost all PAM activity.

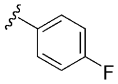
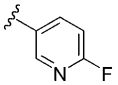
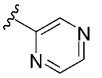
These data then led to the design of a second generation library wherein the optimal 3-position groups with submicromolar EC_{50} values (R^1 = 4-FPh (**5**), 2-pyridyl (**6b**) and 2-thienyl (**6e**), Table 1) and the (*S*)-stereochemistry of the 3-piperidine carboxylic acid were maintained while evaluating a diverse set of twelve *N*-acyl substituents (R^2) to give analogues **10a-l**, **11a-l** and **12a-l** (Figure 3).

Ultimately, we followed two synthetic routes to access ADX-47273 analogues **10**–**12** (Scheme 1).[24] In route 1, three (*Z*)-*N*′-hydroxyimidamides **7** (R = 4-FPh, 2-thienyl, 2-pyridyl) were coupled under standard EDCI/HOBt conditions with (*S*)-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid, followed by re-

Table 1. Structures and activities of ADX-47273 analogues **6**.



6

Compound	R^1	Potentiator EC_{50} (nM)[a]	Glu Max (%)[b]
ADX-47273 (**5**)		168±28	107±5
6a		1460±84	83±28
6b		348±70	109±2
6c		5000±807	82±7
6d		1410±216	93±5
6e		170±28	98±4
6f		>10000	15±5

[a] EC_{50} values are the average of at least three determinations at an EC_{20} concentration of glutamate; [b] Glu Max (%) is the maximum response of compounds relative to the maximal glutamate response; at least three determinations.

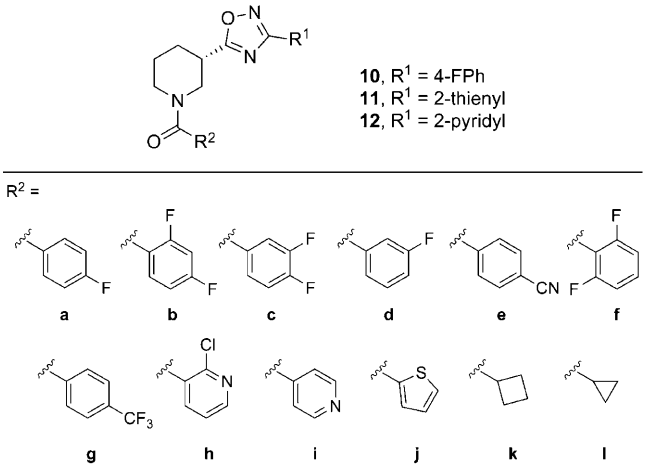
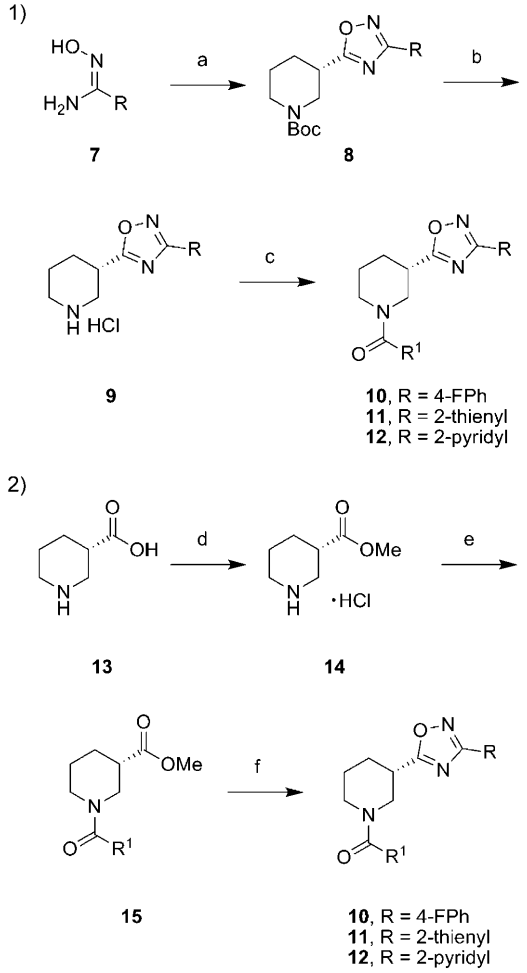


Figure 3. Second generation (3×12) library design for analogues **10**–**12**.

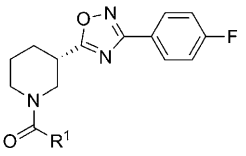
fluxing in 1,4-dioxane to afford oxadiazoles **8**. The Boc group was removed with 4 N HCl/dioxane to provide compounds **9**, followed by typical acylation chemistry with 12 diverse acid chlorides to provide ADX-47273 analogues **10** (R=4-FPh), **11** (R=2-thienyl) and **12** (R=2-pyridyl). Alternatively, analogues **10**–**12** could be accessed according to route 2, wherein the oxadiazole is installed in the final step. In this scenario, (*S*)-piperidine-3-carboxylic acid **13** is converted to the corresponding methyl ester **14**, followed by typical acylation chemistry to deliver analogues **15** in good yields. Saponification with LiOH provides the corresponding acids, which were then converted into the corresponding analogues **10** (R=4-FPh), **11** (R=2-thienyl) and **12** (R=2-pyridyl). We employed route 1 for the initial library generation of 36 ADX-47273 analogues **10**–**12**, and generally relied on route 2 for scale-up of interesting compounds.[24]



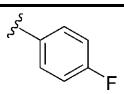
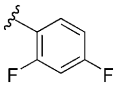
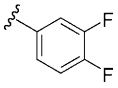
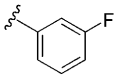
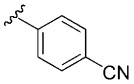
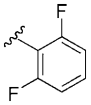
Scheme 1. Synthesis of analogues **10**–**12** of ADX-47273 (**5**). *Reagents and conditions*: Route 1: a) (*S*)-1-(*tert*-butoxycarbonyl)piperidine-3-carboxylic acid, EDCI, HOBt, 1,4-dioxane, reflux (R=4-FPh, 51%; R=2-thienyl, 66%; R=2-pyridyl, 44%); b) 4 N HCl/dioxane, DCM (82–99%); c) R^1COCl, DIEA, DCM (74–95%); Route 2: d) $SOCl_2$, MeOH (99%); e) R^1COCl, DIEA, DCM; f) 1. LiOH, THF/MeOH (88–92%); 2. (*Z*)-*N*′-hydroxyimidamide, EDCI, HOBt, 1,4-dioxane, reflux (R=4-FPh, 56%; R=2-thienyl, 68%; R=2-pyridyl, 57%).

Robust SAR was observed for ADX-47273 analogues **10**–**12**, but the most striking finding was that a subtle change in the nature of the substituent in the 3-position of the oxadiazole afforded either potent mGluR5 ago-potentiators (**10** and **11**) or pure mGluR5 positive allosteric modulators (**12**), with little or no detectable agonist activity. As shown in Table 2, analogues

Table 2. Structures and activities of ADX-47273 analogues **10**.

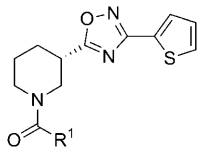


10

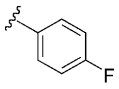
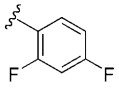
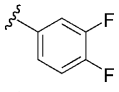
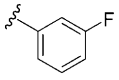
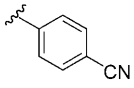
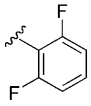
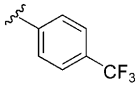
Compound	R^1	Potentiator EC_{50} (nM)[a]	Glu Max (%)[b]
5/10a ADX-47273		168 ± 28	107 ± 5
10b		219 ± 35	101 ± 7
10c		133 ± 11	105 ± 5
10d		164 ± 29	104 ± 6
10e		714 ± 78	92 ± 5
10f		526 ± 32	93 ± 8
10j		439 ± 46	94 ± 10

[a] EC_{50} values are the average of at least three determinations at an EC_{20} concentration of glutamate; [b] Glu Max (%) is the maximum response of compounds relative to the maximal glutamate response; at least three determinations.

Table 3. Structures and activities of ADX-47273 analogues **11**.



11

Compound	R^1	Potentiator EC_{50} (nM)[a]	Glu Max (%)[b]
6e/11a		170 ± 28	98 ± 4
11b		212 ± 24	103 ± 7
11c		144 ± 29	101 ± 5
11d		183 ± 28	109 ± 5
11e		1150 ± 194	90 ± 8
11f		1090 ± 130	93 ± 5
11g		1170 ± 297	91 ± 5

[a] EC_{50} values are the average of at least three determinations at an EC_{20} concentration of glutamate; [b] Glu Max (%) is the maximum response of compounds relative to the maximal glutamate response; at least three determinations.

10a-f and **10j** were potent with submicromolar EC_{50} values (133–714 nM) and efficacious mGluR5 ago-potentiators (92–107% Glu Max) when the amide moiety was a either a fluorinated or cyano-containing benzamide or a 2-thienyl amide. Other amides (heterocyclic, aryl and cycloalkyl) possessed EC_{50} values $>1\,\mu M$, and were therefore not useful as potential in vivo candidates.

A strikingly similar trend of activity was noted with amide analogues in the 2-thienyl series **11** (Table 3). Both potency and efficacy paralleled the 4-FPh series **10** for analogues **11a-g** (EC_{50} values 144–1170 nM) and efficacious (90–109% Glu Max). As previously observed, other amides (heterocyclic, aryl and cycloalkyl) possessed EC_{50} values $>1\,\mu M$, and were therefore not useful as potential in vivo candidates.

All of the analogues **10a-f**, **10j** and **11a-g** possessed significant mGluR5 allosteric agonist activity as well as positive allosteric modulator activity, and are therefore more accurately described as ago-potentiators, like the parent ADX-47273 (**5**/**10a**). With many of these analogues, the agonist activity was so strong that it precluded fold-shift data from being calculated, or forced these experiments to be conducted at very low doses (i.e., fold shifts at 370 nM vs the typical 1–10 μM). Figure 4 highlights a prototypical ago-potentiator from this series. The raw calcium fluorescence trace clearly illustrates the intrinsic mGluR5 agonist activity as well as the potentiation of an EC_{20} concentration of glutamate. Full CRCs confirm an EC_{50} value for potentiation of 133 nM and an agonist EC_{50} value of 5 μM for compound **10c**. Like most of the analogues **10a-f**, **10j** and **11a-g**, the intrinsic agonist activity required that fold shift experiments be conducted at 370 nM; however, four- to fivefold shifts of the glutamate CRC were still observed. Moreover, all of these analogues were selective for mGluR5 (no activity at mGluRs 1, 2, 3, 4, 7 or 8). As with the parent compound, ADX-47273 (**5**), none of these analogues offered an improvement in solubility in pharmaceutically acceptable vehicles (clogPs were >4.5) and overall physiochemical properties were poor. Still, this effort provided potent and efficacious ago-potentiators for further studies.

Analogues **12a-d, 12f and 12g**, which contained a 2-pyridyl moiety in the 3-position of the oxadiazole, afforded an unanticipated pharmacological profile. The potency and efficacy of analogues **12** were comparable to, or slightly less potent (EC_{50} values 244-757 nM) and efficacious (89–109% Glu Max) than compounds **10a-f**, **10j** and **11a-g** (Table 4). In addition to

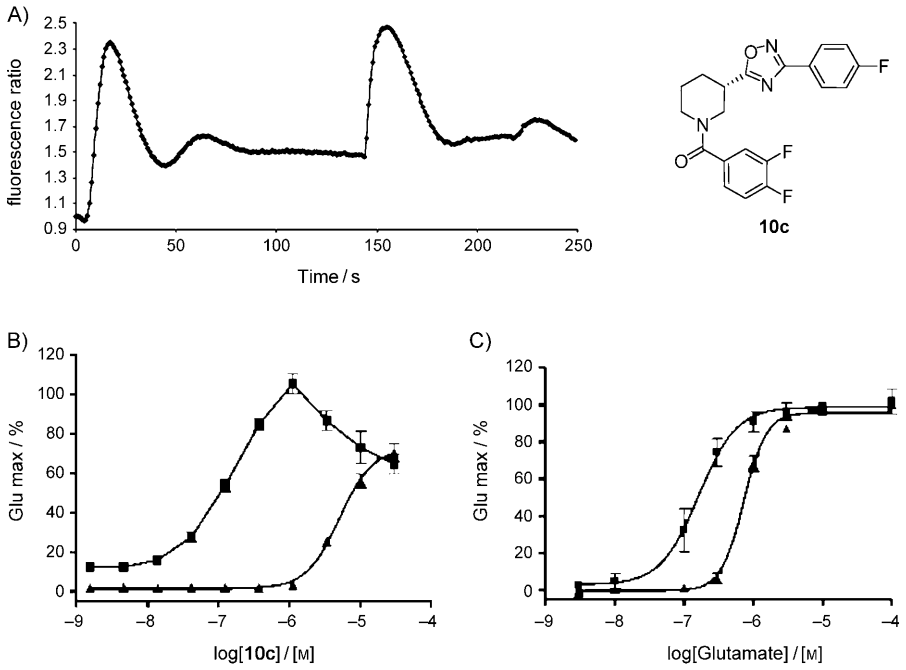
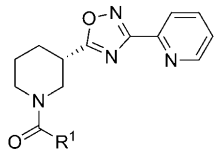
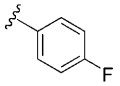
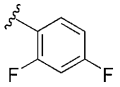
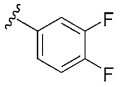
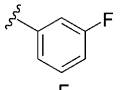
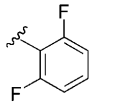
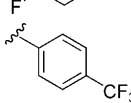


Figure 4. In vitro pharmacological profile of **10c**. a) Raw calcium fluorescence trace showing mGluR5 receptor activation (agonism) in the presence of **10c** alone added at $t = 4$ s, followed by potentiation of an EC_{20} concentration of glutamate added 140 s later, indicating **10c** is also an mGluR5 PAM; b) Concentration-response curves for both potentiation ($EC_{50} = 133$ nM, ■) and agonism ($EC_{50} = 5$ μM, ▲); c) Fold-shift assay with compound **10c** (370 nM, ■) elicits a fivefold leftward shift of the glutamate CRC (▲).

Table 4. Structures and activities of ADX-47273 analogues **12**.



12

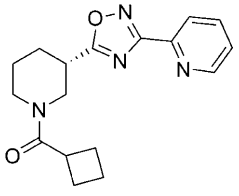
Compound	R^1	Potentiator EC_{50} (nM)[a]	Glu Max (%)[b]
6b/12a		348 ± 70	109 ± 2
12b		244 ± 22	106 ± 1
12c		304 ± 33	110 ± 1
12d		594 ± 86	110 ± 1
12f		566 ± 99	89 ± 1
12g		757 ± 202	100 ± 1

[a] EC_{50} values are the average of at least three determinations an EC_{20} concentration of glutamate; [b] Glu Max (%) is the maximum response of compounds relative to the maximal glutamate response; at least three determinations.

providing a basic nitrogen atom capable of salt formation, analogues **12a-d, 12f and 12g** demonstrated an unexpected profile—pure mGluR5 positive allosteric modulation. Indeed, all of these analogues either displayed no mGluR5 agonism, or only a trace at high compound concentrations (<10% at 30 μM).

Figure 5 highlights a prototypical mGluR5 positive allosteric modulator (compound **12b**) from this series. The raw calcium fluorescence trace clearly illustrates a complete lack of intrinsic mGluR5 agonism but a robust potentiation of an EC_{20} concentration of glutamate. Full CRCs confirm an EC_{50} value for potentiation of 244 nM with no agonism by the compound alone up to 30 μM, a finding in sharp contrast to **10a-f**, **10j** and **11a-g**. As there was no agonist activity, fold-shift experiments could be conducted at standard concentrations, and compound **12b** afforded a strong 14-fold shift of the glutamate CRC at 1 μM. Other analogues in this series provided similar fold shifts, but compound **12c** elicited an unprecedented 27.9-fold shift of the glutamate CRC at 1 μM—the largest fold shift reported to date for an mGluR5 PAM. Moreover, all of these analogues were selective for mGluR5 (no activity at mGluRs 1, 2, 3, 4, 7 or 8). Unlike the parent compound ADX-47273 (**5**) and analogues **10a-f**, **10j** and **11a-g**, the corresponding HCl salts of **12a-d, 12f and 12g** offered an improved solubility in pharmaceutically acceptable vehicles (clogP <3.6—a full log improvement) and overall physiochemical properties were improved, such that homogeneous dosing solutions could be obtained in physiologically inert vehicles (saline, 5–25 mg mL^{-1}; β-cylcodextrin, 10–20 mg mL^{-1}) as opposed to analogue series **10** and **11**, which only afforded homogeneous solutions/microsuspensions in toxic PEG/DMSO vehicles (~5 mg mL^{-1}).

Surprisingly, analogue **12k**, with a cyclobutyl amide, demonstrated a switch in activity compared to the parent compound and was found to be an mGluR5 negative allosteric modulator (NAM). While weak ($IC_{50} = 8.7$ μM, 23% Glu Max), this is the first time we have observed this switch in pharmacological modes in a non-MPEP chemotype.[16,18]



12k

Finally, we wanted to evaluate the stereochemistry at the C3 position of the piperidine-3-carboxylic acid **13**, as ADX-47273

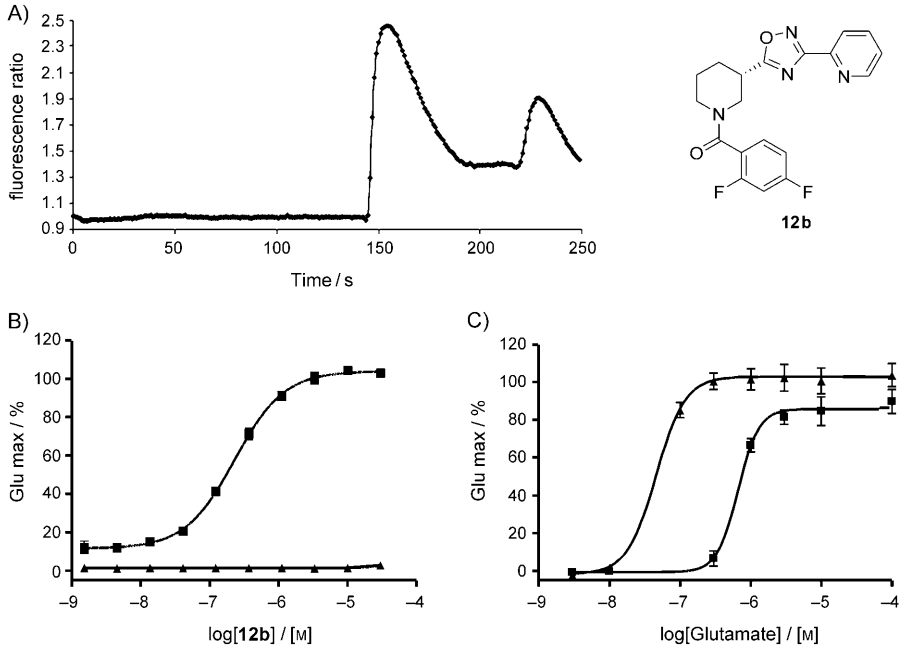


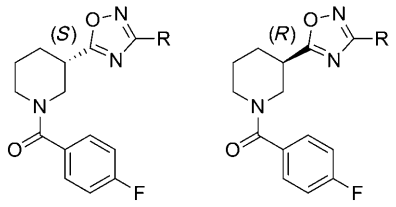
Figure 5. In vitro pharmacological profile of **12b**. a) Raw calcium fluorescence trace showing no mGluR5 receptor activation (agonism) in the presence of **12b** alone added at $t = 4$ s, followed solely by potentiation of an EC_{20} concentration of glutamate added 140 s later, indicating **12b** is an mGluR5 PAM; b) Concentration-response curve for potentiation ($EC_{50} = 244$ nM, ■) and again showing no mGluR5 activation by **12b**/vehicle alone (▲); c) Fold-shift assay with compound **12b** (1 μM, ▲) elicits a 14-fold leftward shift of the glutamate CRC (■).

(**5**) was the first reported mGluR5 PAM possessing a chiral center, and we wanted to determine if there was enantioselective potentiation. Following the synthetic routes in Scheme 1 and substituting (*R*)-piperidine-3-carboxylic acid for the previously employed (*S*)-congener **13**, allowed us to synthesize and evaluate the corresponding (*R*)-enantiomers of representative analogues from the **10**–**12** series. As shown in Table 5, the (*R*)-enantiomers are uniformly nine- to tenfold less potent than the corresponding (*S*)-enantiomers, but equally efficacious. This constitutes the first reported example of enantioselective potentiation of mGluR5, and while Addex has reported the (*S*)-enantiomers, this work quantifies the importance of the (*S*)-stereochemistry for activation of mGluR5.

In summary, we explored the chemical space surrounding the mGluR5 ago-potentiator ADX-47273 (**5**) employing an iterative library design comprised of three small libraries (~60 compounds). This effort identified potent mGluR5 ago-potentiators **10a-f**, **10j** and **11a-g**, which possessed either a 4-FPh or 2-thienyl moiety in the 3-position of the oxadiazole core. Quite unexpectedly, when the 3-position was substituted with a 2-pyridyl moiety **12a-d, 12f and 12g**, a new series of potent mGluR5 PAMs resulted that lacked the intrinsic agonist activity of **10a-f**, **10j** and **11a-g**, and afforded 14-to 27.9-fold shifts—the largest ever observed for mGluR5. Moreover, analogues **12a-d, 12f and 12g** could form HCl salts that displayed improved solubility and physiochemical properties. Additionally, we identified one ADX-47273 analogue **12k** that demonstrated a switch in pharmacology to a negative allosteric modulator—an observation previously reserved to MPEP-like scaffolds. Finally, we discovered that the (*S*)-enantiomer of analogues **10**–**12** is required for mGluR5 activation, and represents the first example of enantioselective potentiation. With these new tools, we are poised to evaluate in vivo the effects of pure mGluR5 potentiation versus ago-potentiation of mGluR5 in preclinical antipsychotic and cognition models. These experiments are in progress and will be reported in due course.

Full experimental details for representative mGluR5 PAMs, general details for analogue synthesis and full experimental details for the in vitro assays are available in the Supporting Information.

Table 5. Comparison of activities of (*R*)- and (*S*)-enantiomeric ADX-47273 analogues.



10–12 **16–18**

Compound	R	Potentiator EC_{50} (nM)[a]	Glu Max (%)[b]
5/**10a** (*S*), ADX-47273	4-FPh	168 ± 28	107 ± 5
16a (*R*)		1680 ± 362	108 ± 6
6e/**11a** (*S*)	2-thienyl	170 ± 28	98 ± 4
17a (*R*)		2170 ± 189	101 ± 5
6b/**12a** (*S*)	2-pyridyl	348 ± 70	109 ± 2
18a (*R*)		2440 ± 487	92 ± 2

[a] EC_{50} values are the average of at least three determinations an EC_{20} concentration of glutamate; [b] Glu Max (%) is the maximum response of compounds relative to the maximal glutamate response; at least three determinations.

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Keywords: glutamate receptors · allosteric modulation · neurological agents · structure–activity relationships

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[24] For full synthetic and pharmacology details, please see the Supporting Information.

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