# Discovery of Positive Allosteric Modulators for the Metabotropic Glutamate Receptor Subtype 5 from a Series of *N*-(1,3-Diphenyl-1*H*-pyrazol-5-yl)benzamides That Potentiate Receptor Function in Vivo

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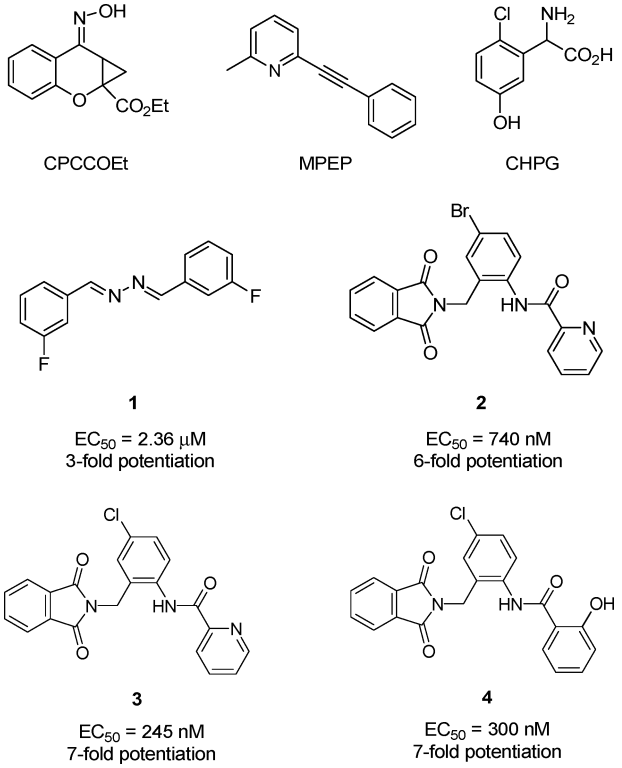
**Abstract:** This report describes the discovery of the first centrally active allosteric modulators of the metabotropic glutamate receptor subtype 5 (mGluR5). Appropriately substituted *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamides (e.g., **8**) have been identified as a novel class of potent positive allosteric modulators of mGluR5 that potentiate the response to glutamate. An iterative analogue library synthesis approach provided potentiators with excellent potency and selectivity for mGluR5 (vs mGluRs 1−4, 7, 8). Compound **8q** demonstrated in vivo proof of concept in an animal behavior model where known antipsychotics are active, supporting the development of new antipsychotics based on the NMDA hypofunction model for schizophrenia.

Glutamate is the major excitatory transmitter in the mammalian 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 amino-terminal agonist binding site. To date, eight mGluRs have been cloned and sequenced and have been assigned to three groups based on their structure, coupling to effector mechanisms and pharmacology.[1] Group I receptors (mGluR1 and mGluR5) are coupled to Gαq and its associated effector mechanisms, resulting in increases in intracellular calcium. Group I mGluRs are predominantly located postsynaptically and have a modulatory effect on postsynaptic signaling. Group II (mGluR2 and mGluR3) and Group III (mGluR4, mGluR6, mGluR7, and mGluR8) receptors are coupled through Gαi to decrease cAMP synthesis and are located presynaptically.[1,2,3]

Dysfunction in glutaminergic systems has been implicated in a number of CNS pathologies including pain, anxiety, addiction, and schizophrenia.[4] Recently, hypofunction of the NMDA receptor has been suggested as playing a major role in the positive, negative, and cognitive symptoms of schizophrenia as an alternative to the prevailing "Dopamine Hypothesis".[5] Unfortunately, direct agonists of the NMDA receptor tend to be neurotoxic; therefore, alternative strategies to increase NMDA receptor function are needed. Mannaioni et al. recently reported that activation of mGluR5 results in an increase in NMDA function in rat brain slices, indicating a functional interaction between mGluR5 and the NMDA receptor, suggesting that activation of mGluR5 may ammeliorate the symptoms of schizophrenia.[6]

**Chart 1.** Group I mGlu Receptor Ligands




A number of agonists and antagonists of the mGluRs, typically analogues of glutamate, quisqualate, or phenyl glycine, have been identified that interact with the agonist (orthosteric) binding site.[1,7] With this traditional approach, Group selective agonists and antagonists have been identified, but it has been historically difficult to identify compounds selective for a single mGluR subtype. Only with the advent of high throughput functional assays has it become possible to systematically screen for compounds that affect the activity of a receptor through novel, allosteric mechanisms.[8] The first small molecules that clearly interacted allosterically with the mGluRs were CPCCOEt (mGluR1 selective) and MPEP (mGluR5 selective), both negative allosteric modulators.[9] More recently, positive allosteric modulators, compounds that increase the sensitivity of the receptor to the native agonist, have been reported for mGluR1 and mGluR2.[10]

Our laboratory initiated an effort to identify potent and selective positive allosteric modulators for mGluR5 that potentiate NMDA receptor function. Our screening

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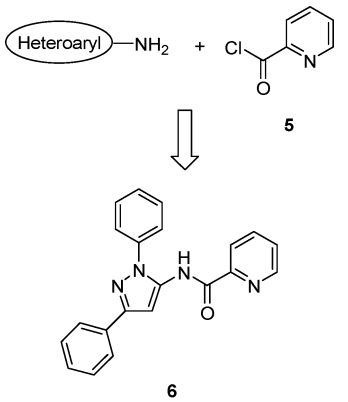
**Scheme 1**




$EC_{50}$ = 290 nM
2.8 to 3.6-fold potentiation

paradigm centered on investigating compounds that displayed negative inhibition in an ongoing mGluR5 antagonist high-throughput screen as well as evaluation of compounds from our sample collection. These compounds were analyzed in a FLIPR assay measuring their ability to increase the response of CHO cells transfected with human mGluR5 to a low concentration of glutamate (300 nM) without eliciting a response in the absence of the native agonist. This screening paradigm identified positive allosteric modulators for mGluR5 from two different structural series, exemplified by **1** and **2**, that potentiated receptor function (shifted the agonist concentration curve to the left) 3- to 6-fold.[11] Surprisingly, analogues of **1**, with only slight structural changes, exerted a spectrum of effects, ranging from positive to negative allosteric modulation as well as neutral cooperativity.[11a] Similarly, little tractable SAR resulted from an iterative analogue library synthesis effort aimed at improving the potency and physical properties of **2**. Out of 1000 analogues prepared, only **3** and **4** displayed improved potency and comparable potentiation to **2**.[11b]

Although **1**−**4** were specific for mGluR5 (selective vs mGluRs 1−4, 7, 8), poor physical properties and modest potencies of these analogues for rat mGluR5 ($EC_{50}$>1 $\mu$M), prevented their evaluation in vivo, including in animal behavioral models.[11,12]

With no other lead structures from the screening effort and a lack of tractable SAR in our existing series, we employed a fragment library approach in an effort to discover a new lead structure. Because of potential metabolic liabilities of the salicylic amide moiety in **4**, fragment libraries were designed wherein the picolinoyl amide moiety, present in both **2** and **3**, was conserved in order to survey diverse aryl and heteroaryl templates as potential lead structures. As shown in Scheme 1, several libraries, employing aryl and heteroarylamines from both commercial and proprietary sources were acylated with picolinoyl chloride, **5**. From this effort, a new lead structure, an *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)picolinoyl amide **6** was discovered that was equipotent to the optimized leads in earlier series against human mGluR5 ($EC_{50}$ = 290 nM, 2.8 to 3.6-fold potentiation) and more potent against rat mGluR5 ($EC_{50}$ = 585 nM, 8-fold potentiation).

Specifically, **6** caused a concentration-dependent potentiation of the response of CHO cells overexpressing

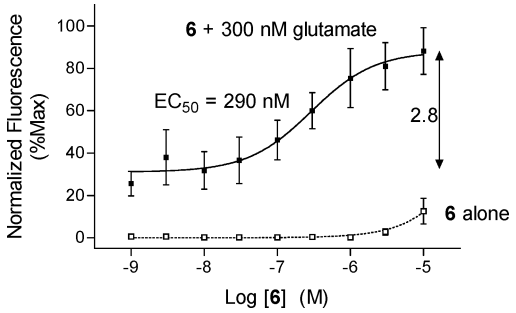



**Figure 1.** **6** potentiates mGluR5 activation by glutamate.

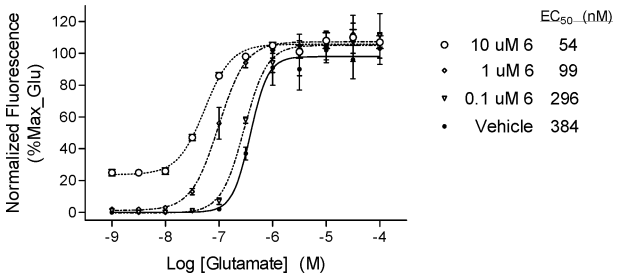
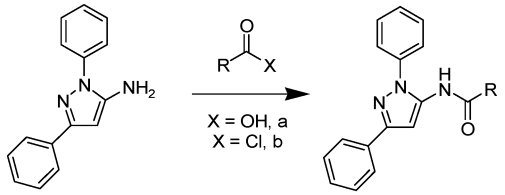



**Figure 2.** **6** potentitaion of response to glutamate is manifested as increased mGluR5 sensitivity. The glutamate $EC_{50}$ value is shifted from 384 nM to 54 nM with the addition of **6**.

**Scheme 2**[a]



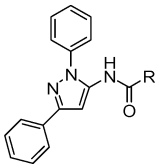

7 8

[a] Reagents: (a) PS-DCC, HOBt, DCM; MP-carbonate; (b) PS-DIEA, DCM; PS-Trisamine.

human mGluR5 to 300 nM glutamate (Figure 1). The maximal potentiation at this concentration of glutamate ranged from 2.8 to 3.6-fold, with an $EC_{50}$ for potentiation of 290 nM. Importantly, **6** alone (up to 100 $\mu$M) caused no response by either human or rat mGluR5 in this assay. In addition, when mGluR5 CHO cells were exposed to **6** (0.1 to 10 $\mu$M), the glutamate dose−response curve experienced a parallel leftward shift, providing a 7.1-fold decreased $EC_{50}$ value (54 nM vs 384 nM, Figure 2) with no increase in maximal response. Similar results were obtained with the other mGluR5 agonists quisqualate and 3,5-dihydroxyphenylglycine (3,5-DHPG). As in the earlier series, **6** was specific for mGluR5, failing to exhibit any positive modulatory activity at any of the other six mGluRs examined.[12] These data suggest that these modulators/potentiators act at an allosteric site to increase the sensitivity of the receptor to the orthosteric agonists. Only at concentrations of above 10 $\mu$M was a slight agonist-like effect observed.

Analogues of pyrazole amide **6** were synthesized in a library format utilizing Bohdan Mini-Blocks, as shown in Scheme 2. Commercially available 5-amino-1,3-diphenylpyrazole **7** was coupled to a range of carboxylic acids or acylated with acid chlorides, under standard conditions employing polymer- supported reagents and scavengers, to provide analogues **8**. All analogues were purified by mass-guided HPLC to analytical purity.[13]

**Table 1.** Functional Activity and Potentiation of Pyrazole Amides



| | R | human $EC_{50}$ (nM)[a] | human potentiation | rat $EC_{50}$ (nM)[a] | rat potentiation |
|---|---|---|---|---|---|
| **6** | 2-pyridyl | 290 | 3.6 | 585 | 8.0 |
| **8a** | Ph | 40 | 5.0 | 300 | 5.0 |
| **8b** | 2-OHPh | >10000 | 0.9 | >10000 | 0.9 |
| **8c** | 2-ClPh | 2500 | 3.7 | ND | ND |
| **8d** | 3-ClPh | 40 | 5.4 | 200 | 3.3 |
| **8e** | 4-ClPh | 20 | 5.0 | 100 | 4.9 |
| **8f** | 2-Tolyl | >10000 | 0.9 | ND | ND |
| **8g** | 3-Tolyl | 90 | 9.0 | 100 | 9.4 |
| **8h** | 4-Tolyl | 30 | 9.0 | 40 | 10.9 |
| **8i** | 2-FPh | 75 | 6.4 | 100 | 6.3 |
| **8j** | 3-FPh | 20 | 2.6 | 65 | 7.7 |
| **8k** | 4-FPh | 30 | 2.9 | 50 | 8.0 |
| **8l** | 2-thienyl | 200 | 2.9 | 400 | 5.3 |
| **8m** | 3-thienyl | 1800 | 2.5 | 2900 | 3.7 |
| **8n** | 2-pyrazinyl | 200 | 4.3 | 400 | 4.8 |
| **8o** | 3,4-diFPh | 10 | 2.6 | 20 | 6.4 |
| **8p** | 4-CF3Ph | 19 | 5.2 | 20 | 6.8 |
| **8q** | 3-CNPh | 10 | 4.0 | 20 | 4.3 |

[a] EC50s and fold potentiation are the mean of three values. Note: potencies and efficacies of allosteric modulators determined at a fixed concentration of agonist depend on the response of the cells to the agonist, which varies slightly from day to day. The agonist curves in the mGluR5 FLIPR assay are steep (nH ~ 2) and the $EC_{50}$s determined at a fix concentration may therefore vary by a factor of 5. For **8o**, **8p**, and **8q**, ±SEM is ±7 nM.

The initial exploration of the pyrazole amides was provided by three 48-membered libraries focused on providing diversity at the amide moiety of the lead **6**, as shown in Table 1. Surprisingly, when **7** was coupled with salicylic acid, the resulting compound **8b**, the pyrazole analogue of **4**, was inactive, suggesting this series may have a different mode of allosteric binding. A key discovery was the finding that a simple phenyl amide congener, **8a**, was significantly more potent than **6** on both human mGluR5 ($EC_{50}$ = 40 nM, 5.0-fold potentiation) and rat mGluR5 ($EC_{50}$ = 300 nM, 5.0-fold potentiation). The positioning of substituents on the phenyl ring of the amide was found to be a highly sensitive determinant of potency. For active congeners with a single substituent on the aromatic ring, the potency increased in the order 2 ≪ 3 < 4. For example, the 2-tolyl analogue **8f** was inactive whereas the 3-tolyl **8g** and 4-tolyl **8h** congeners displayed potencies at human mGluR5 of 90 nM and 30 nM, respectively. Fluorine substitution proved to be an exception to this trend, where **8i**−**k** displayed roughly comparable potencies. However, when two fluorine atoms were incorporated at the 3- and 4-positions of the phenyl ring to provide **8o**, the potency at both human and rat mGluR5 ($EC_{50}$ = 10 nM, 2.6-fold potentiation and $EC_{50}$ = 20 nM and 6.4-fold potentiation, respectively) increased dramatically. Similarly, **8p**, possessing a 4-$CF_3$ moiety demonstrated equivalent potency on human and rat mGluR5 ($EC_{50}$ = 19 nM, 5.2-fold potentiation and $EC_{50}$ = 20 nM, 6.8-fold potentiation, respectively) as did the 3-cyano analogue **8q**, with potencies on human and rat mGluR5 ($EC_{50}$ = 9 nM, 4.0-fold potentiation and $EC_{50}$ = 20 nM, 4.3-fold potentiation, respectively).

Of these potent analogues, **8q** was selected for further evaluation. Similar to **6**, increasing concentrations of **8q** caused a parallel, leftward shift of mGluR5 CHO cell glutamate response curves with no increase in maximal reponse. As with **6**, addition of 0.1 to 10 $\mu$M **8q** shifted glutamate $EC_{50}$ values from 413 nM to 49 nM (8.4-fold shift), and similar shifts in agonist concentration−response curves were observed for quisqualate and 3,5-DHPG in both human and rat mGluR5 cells with no increase in maximal response.[14]

Prior to conducting in vivo experiments, the selectivity of **8q** was evaluated. All of the analogues in this series bear a striking resemblance to known kinase inhibitors, especially reported p38 kinase inhibitors.[15] Importantly, **8q** displayed no off-target activities against an in-house kinase panel and a more thorough, broad spectrum panel of receptors. In other functional assays, **8q** was also found to be specific for mGluR5 and did not potentiate the activity of the other mGluRs (mGluRs 1−4, 7,8).[12,16]

Both in vitro and in vivo brain penetration experiments were conducted to evaluate the viability of **8q** as a potential CNS agent for proof of concept.[17] Clearly, **8q** was not subject to P-gp efflux in vitro in either human or mouse P-gp assays (B−A/A−B ratios of 0.6 and 0.8, respectively) and **8q** exhibited excellent passive permeability ($24.7 \times 10^{-6}$ cm/s). Additional in vivo experiments in mdr1a mice demonstrated that **8q** was not subject to P-gp efflux in vivo (mdr1a brain/plasma ratios (−/−)/(+/+) = 1.69), supporting its use in the animal behavioral models.

While a body of in vitro evidence indicates that activation of mGluR5 causes activity-dependent increases in NMDA receptor function, in vivo evidence has only recently begun to accrue. In 2003, Kinney demonstrated that intracerebroventrical administration of the mGluR5 selective partial agonist, CHPG, enhances prepulse inhibition (PPI) of the rodent acoustic startle response following amphetamine administration.[18] PPI is a measure of sensorimotor gating known to be deficient in schizophrenic patients and in laboratory animals following administration of dopamine agonists such as amphetamine. Thus, a reversal of amphetamine-induced disruption of PPI is consistent with an antipsychotic pharmacological profile in this preclinical model.[19] Now, with **8q** in hand, our laboratory was poised to evaluate the effect of positive allosteric modulators of mGluR5 in the PPI model in an effort to validate the NMDA hypofunction theory for schizophrenia in vivo.[8−20] Amphetamine was dosed at 2 mg/kg in saline 30 min pretest, followed by **8q** 10 min pretest at doses of 3, 10, and 30 mg/kg sc.. At all three doses and at different prepulse intensities (5, 10, 15, and 20 dB above background), **8q** clearly reversed amphetamine-induced disruption of PPI in a dose-dependent manner, as shown in Figure 3. Moreover, **8q** had no effect on basal activity (no stimulus condition) or startle amplitude (pulse alone condition) at all three doses of **8q** relative to amphetamine/vehicle. Thus, selective potentiation of mGluR5 has a significant, positive effect in a

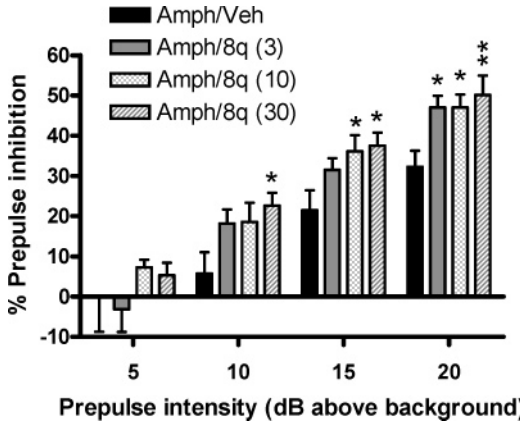



**Figure 3.** **8q** reverses amphetamine-induced disruption of PPI.

behavioral model of sensorimotor gating in which well-characterized antipsychotic drugs show similar positive effects.

Screening efforts identified **1** and **2** as positive allosteric modulators of mGluR5. An iterative analogue library synthesis approach for the optimization of **2** resulted in little tractable SAR, only slight increases in potency and no improvement in physical properties. Fragment libraries based on **2** generated a novel lead structure **6** that was further optimized through library synthesis to provide a series of potent and selective mGluR5 positive allosteric modulators based on an *N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide scaffold. These analogues represent the first pharmacological tools to investigate the role of mGluR5 potentiation in NMDA receptor function in vivo. Of these analogues, 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide **8q**, by selective potentiation of mGluR5, displayed a significant, positive effect in the amphetamine-induced disruption of PPI model, a behavioral model of sensorimotor gating, in which well-characterized antipsychotic drugs show similar positive effects, providing support for the NMDA hypofunction model for schizophrenia.

**Supporting Information Available:** Experimental procedures and analytical data for compounds **6**, **8o**, **8p**, and **8q** are provided, as well as details of the prepusle inhibition (PPI) behavioral model. This material is available free of charge via the Internet at http://pubs.acs.org.

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