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Discovery and characterization of a novel series of *N*-phenylsulfonyl-1*H*-pyrrole picolinamides as positive allosteric modulators of the metabotropic glutamate receptor 4 ($mGlu_4$)

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ABSTRACT

Herein we report the synthesis and characterization of a novel series of *N*-phenylsulfonyl-1*H*-pyrrole picolinamides as novel positive allosteric modulators of $mGlu_4$. We detail our work towards finding phenyl replacements for the core scaffold of previously reported phenyl sulfonamides and phenyl sulfone compounds. Our efforts culminated in the identification of *N*-(1-((3,4-dimethylphenyl)sulfonyl)-1*H*-pyrrol-3-yl)picolinamide as a potent PAM of $mGlu_4$.

The metabotropic glutamate receptors are Class C G-protein coupled receptors (GPCRs) and are further separated into three family classes based on their receptor structure, G-protein coupling and ligand selectivity (Group I: $mGlu_1$ and $mGlu_5$; Group II: $mGlu_2$ and $mGlu_3$; Group III: $mGlu_4$, $mGlu_6$, $mGlu_7$ and $mGlu_8$).[1] This family of GPCRs has received significant attention over the past 10 years as potential therapeutic targets for a number of CNS disorders, such as schizophrenia,[2–4] Fragile X,[5,6] generalized anxiety disorder[7,8] and Parkinson's disease.[9–14] Until recently, the Group III family had received less attention than the Group I and Group II family receptors; however, many tool compounds for the $mGlu_4$ subtype have been disclosed recently from our laboratories,[15–17] and others.[18–20] A common motif in many of the disclosed compounds is the presence of an *N*-phenyl picolinamide core scaffold.[15,16,21,22] There have been reports of efforts aimed at discovering amide replacements[23]; however, there have not been disclosures around replacement of the central phenyl ring system. Herein, we report our efforts towards phenyl ring replacements culminating in the discovery of a unique series of *N*-pyrrolesulfonamides as novel PAMs of $mGlu_4$.

The starting point for our exploration centered around a series of phenylsulfonamides and phenylsulfones that were previously disclosed (Fig. 1).[24,25] Our first attempts at replacing the phenyl group centered on a thiazole ring and utilized the sulfone moiety as in **2** in order to limit the number of H-bond donors in the molecule.[26] The synthesis started with the commercially available 5-bromo-thiazol-2-amine (4-Me, Et, or H) which was acylated to yield the picolinamide **5** (picolinyl chloride, DiPEA, CH_2Cl_2) (Scheme 1). Next, palladium catalyzed cross-coupling of the bromothiazole, **5**, with an appropriately substituted benzylthiol ($Pd_2(dba)_3$, XantPhos, DIEA, 1,4-dioxane, 100 °C) yielded the *N*-(5-(benzylthio)-thiazol-2-yl)picolinamide, **6**.[27] Lastly, oxidation of the sulfide to the sulfone (*m*-CPBA, CH_2Cl_2) yielded the desired compounds, **7a**–**h**.

The SAR analysis of the thiazole sulfone analogs is summarized in Table 1. Gratifyingly, the thiazole is a tolerated replacement for the internal phenyl ring as the thiazole derivative, **7a**, is equipotent with the phenyl derivative, **2** (**7a**, EC_{50} = 189 nM vs **2**, EC_{50} = 237 nM). In addition to R^1 = H, the methyl and ethyl substituents are also tolerated in the 4-position (**7b**, EC_{50} = 448 nM; **7e**,

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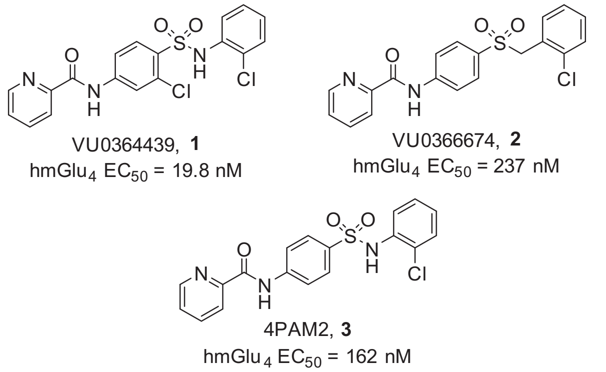


Figure 1. Previously disclosed phenylsulfonamide and phenylsulfone $mGlu_4$ PAMs.

EC_{50} = 217 nM). Overall, the replacement of the phenyl group with a thiazole was a productive change in terms of potency with **7c** being one of the most potent compounds discovered to date (EC_{50} = 83 nM). The sulfide intermediates, **6**, were tested and were significantly less potent (EC_{50}'s = 5000–8000 nM); the sulfoxides were not tested as the oxidation procedure led directly to the sulfones. Unfortunately, these compounds suffered from significant pharmacokinetic liabilities (poor brain penetration, metabolic instability) limiting the utility of these compounds to in vitro tool compounds.

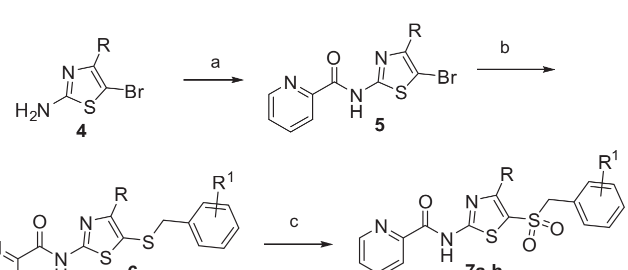
Next, we turned our attention to other replacement groups, namely, pyrrole and pyrazole.[28,29] The synthesis of these groups is detailed in Scheme 2. The nitro pyrrole (or pyrazole) was converted to the sulfonamide (DBU, RSO_2Cl) and then the nitro was reduced to the amino compound using Raney Nickel, **10** (EtOH, Ra–Ni, 40 psi H_2). The final compounds were completed via acylation of the amino group with the acid chloride (picolinyl chloride, DIEA) yielding the desired compounds, **11a**–**w**.[30,31]

The initial set of compounds evaluated were the benzyl sulfonamides, comparators to the thiazole benzylsulfones. Similar to the thiazole core compounds, the pyrrole compounds were well tolerated, with the 2-chlorobenzyl sulfonamide being equipotent to the thiazole (**7a**) and phenyl (**2**) derivatives (**11g**, EC_{50} = 174 nM). As seen previously, most of the benzyl compounds that we evaluated were active as $mGlu_4$ PAMs with most EC_{50}'s < 500 nM. Although these compounds were active as PAMs, they suffered from the same PK liabilities as the thiazole compounds, namely, metabolic stability issues. It was determined that oxidation of the benzylic CH_2 group was the major metabolic liability and efforts were undertaken to block this site. Thus, compounds **11i**–**k** were synthesized. Unfortunately, these compounds were significantly less potent as $mGlu_4$ PAMs, with the mono-fluoro compound being the most active (**11j**, EC_{50} = 1024 nM). In addition, blocking the presumed site of metabolism did not inherently improve the metabolic stability of these compounds, presumably due to a shift of the site of instability to other areas of the molecule (Table 2).

Next, we turned our efforts to eliminating the benzylic site altogether by evaluating a series of phenyl sulfonamides. Much like the benzyl derivatives, the phenylsulfonamides were well tolerated as a substituent. Alkyl substituted pyrrole sulfonamides were the most potent of the series (**11l**, EC_{50} = 122 nM; **11m**, EC_{50} = 104 nM; **11r**, EC_{50} = 62 nM), with the halogen substituted analogs being less potent (e.g., **11n**, EC_{50} = 740 nM; **11o**, EC_{50} = 1238 nM). Some potency could be recaptured by the addition of an alkyl group as in **11t** (EC_{50} = 163 nM) and **11u** (EC_{50} = 268 nM). The pyrazole moiety was also tolerated as a phenyl replacement (Table 3).

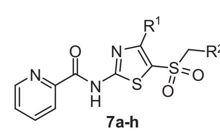
Having established the pyrrole scaffold as a novel phenyl replacement as $mGlu_4$ PAMs, we next evaluated the compounds in our battery of Tier 1 in vitro PK assays (Table 4). The intrinsic clearance (CL_{INT}) was assessed in rat hepatic microsomes and the subsequent predicted hepatic clearance (CL_{HEP}) was calculated.[23,32] Many of the compounds displayed high intrinsic and predicted hepatic clearance, except for the 3,4-dimethylphenyl analog, **11r**, which had moderate predicted hepatic clearance (CL_{HEP} = 38.3 mL/min/kg). Utilizing an equilibrium dialysis approach, the protein binding of the compounds was evaluated in rat plasma. The fraction unbound (F_u) of the analogs tested was very low, except, again, in the case of **11r** which showed slightly better unbound fraction (F_u = 0.012).

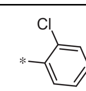
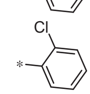
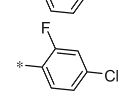
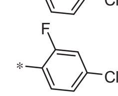
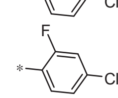
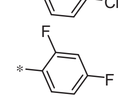
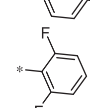
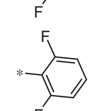
Lastly, we evaluated two analogs in an in vivo IV clearance experiment in order to assess whether the in vitro data would be



Scheme 1. Reagents and conditions. (a) Picolinyl chloride·HCl, diisopropylethylamine, CH_2Cl_2, 24–39%; (b) $Pd_2(dba)_3$, XantPhos, $HSCH_2Ar$, diisopropylethylamine, 1,4-dioxane, 100 °C, 51–87%; (c) *m*-CPBA, CH_2Cl_2, 38–87%.

Table 1
SAR of the sulfonylthiazoles, **7a**–**h**



Compd	R^1	R^2	$mGlu_4$ EC_{50}[a] (nM)	pEC_{50} ± SEM[a]	%GluMax[b]
7a	H		189	6.72 ± 0.13	30.6 ± 0.5
7b	Me		448	6.35 ± 0.06	94.8 ± 3.6
7c	H		83	7.08 ± 0.14	35.1 ± 1.2
7d	Me		4137	5.38 ± 0.06	112.5 ± 1.6
7e	Et		217	6.66 ± 0.09	119.9 ± 1.3
7f	Me		547	6.26 ± 0.05	93.5 ± 1.8
7g	Me		295	6.53 ± 0.09	99.3 ± 1.7
7h	Et		150	6.82 ± 0.12	109.0 ± 1.4

[a] Calcium mobilization human $mGlu_4$ assay; values are the average of n = 3.
[b] Amplitude of response in the presence of 30 μM test compound, normalized to a standard compound, PHCCC, and represented as %GluMax.