Bioorganic & Medicinal Chemistry Letters 26 (2016) 2984–2987

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry Letters

journal homepage: www.elsevier.com/locate/bmcl

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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ARTICLE INFO

Article history:
Received 22 April 2016
Revised 9 May 2016
Accepted 10 May 2016
Available online 11 May 2016

Keywords:
Metabotropic glutamate receptor 4
Positive allosteric modulator (PAM)
Pyrrole sulfonamide
Phenyl replacement
PK

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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http://dx.doi.org/10.1016/j.bmcl.2016.05.029
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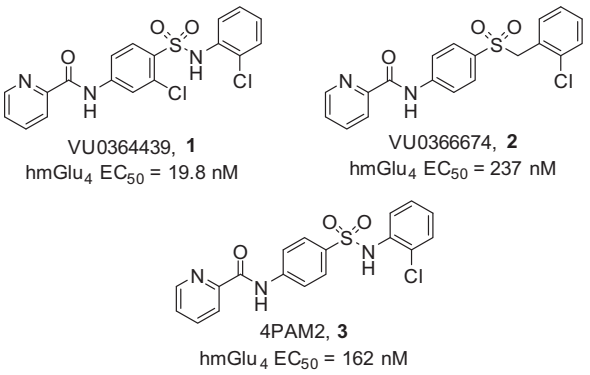


Figure 1. Previously disclosed phenylsulfonamide and phenylsulfone $mGlu_4$ PAMs.

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.

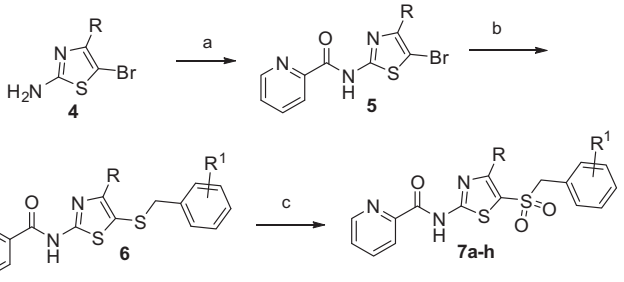
Next, we turned our attention to other replacement groups, namely, pyrrole and pyrazole.[28,29] The synthesis of these groups is detailed in Scheme 2. The nitro pyrrole (or pyrazole) was converted to the sulfonamide (DBU, RSO_2Cl) and then the nitro was reduced to the amino compound using Raney Nickel, **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).

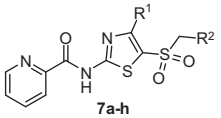
Having established the pyrrole scaffold as a novel phenyl replacement as $mGlu_4$ PAMs, we next evaluated the compounds in our battery of Tier 1 in vitro PK assays (Table 4). The intrinsic clearance (CL_{INT}) was assessed in rat hepatic microsomes and the subsequent predicted hepatic clearance (CL_{HEP}) 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).

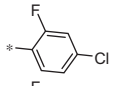
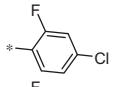
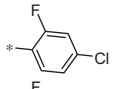
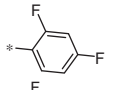
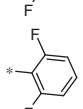
Lastly, we evaluated two analogs in an in vivo IV clearance experiment in order to assess whether the in vitro data would be



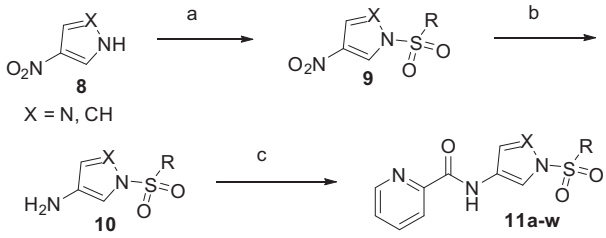
Scheme 1. Reagents and conditions. (a) Picolinyl chloride·HCl, diisopropylethylamine, CH_2Cl_2, 24–39%; (b) $Pd_2(dba)_3$, XantPhos, $HSCH_2Ar$, diisopropylethylamine, 1,4-dioxane, 100 °C, 51–87%; (c) *m*-CPBA, CH_2Cl_2, 38–87%.

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.

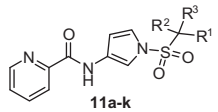


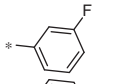
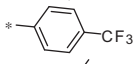
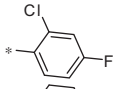
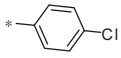
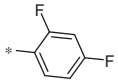
Scheme 2. Reagents and conditions. (a) DBU, $ArSO_2Cl$ or $BnSO_2Cl$, CH_2Cl_2, 50–96%; (b) EtOH, Ra–Ni, 40 psi H_2, 2 h; 93–97%; (c) diisopropylethylamine, picolinyl chloride, CH_2Cl_2, 39–43%.

predictive of in vivo PK (in vitro:in vivo correlation, IV/IVC). The two compounds chosen were **11r** and **11t**, one predicted to be moderately cleared and the other highly cleared. Both compounds were dosed IV (1 mg/kg) and the in vivo plasma clearance closely resembles the in vitro predicted hepatic clearance suggesting the major route of clearance to be hepatic oxidative metabolism. In order to more fully establish this route of metabolism, we co-dosed **11t** with 1-aminobenzotriazole (ABT), a pan-irreversible inhibitor of the cytochrome P450s. After PO dosing, a significant amount of **11t** was detected in the HPV (hepatic portal vein); however, only ~1% of that amount was detected in the plasma, indicating a significant amount of oxidative metabolism. The brain:plasma ratio was ~1:1, although the total amount in the brain was very low, which is in contrast to the phenylsulfones which displayed low brain:-plasma ratios. When co-dosed with ABT, the concentrations of **11t** in the HPV were nearly identical with the non-ABT dosed animals; however, the concentrations detected in the plasma were significantly higher (198.5 ng/mL vs 7.4 ng/mL). Again, while the brain:plasma ratio was ~1:1; as with the total plasma concentrations, the total amount in the brain was higher when co-dosed with ABT (Table 5).

In conclusion, we report the discovery and characterization of unique thiazolesulfone and pyrrolesulfonamide core scaffolds as $mGlu_4$ PAMs. These series were synthesized as a replacement for the previously disclosed phenylsulfonamide/phenylsulfone compounds. The thiazolesulfone analogs were potent $mGlu_4$ PAMs (EC_{50}'s < 500 nM), but suffered from metabolic instability. The pyrrolesulfonamide scaffold also was a well-tolerated change with many compounds exhibiting EC_{50}'s < 500 nM. Compounds from this scaffold displayed an IV/IVC with regards to clearance (CLp) following IV adminstration; however, the compounds were not orally bioavailable and displayed poor exposure following PO dosing (systemic:HPV ratio <0.01). Co-dosing in vivo with the pan-irreversible P450 inhibitor, ABT, blocked extensive P450-mediated

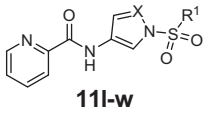
Table 2
SAR of the pyrrole benzylsulfonamides, **11a–k**

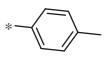
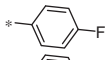
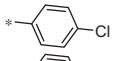
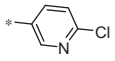
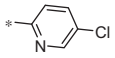
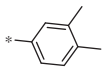
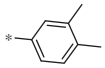
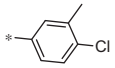
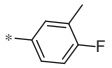
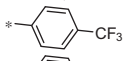
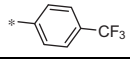


Compd	R^1	R^2	R^3	$mGlu_4$ EC_{50}[a] (nM)	pEC_{50} ± SEM[a]	%GluMax[b]
11a		H	H	572	6.24 ± 0.04	98.6 ± 2.6
11b				188	6.72 ± 0.04	88.7 ± 4.4
11c				4179	5.38 ± 0.16	112.3 ± 5.3
11d				84	7.07 ± 0.04	122.4 ± 3.7
11e				398	6.40 ± 0.06	140.3 ± 1.7
11f				251	6.60 ± 0.07	117.2 ± 7.1
11g				174	6.76 ± 0.02	119.0 ± 3.5
11h				190	6.72 ± 0.04	108.9 ± 5.2
11i		Me	H	2970	5.53 ± 0.26	59.6 ± 12.7
11j		F	H	1021	5.99 ± 0.02	71.0 ± 2.6
11k		F	F	>30,000	<4.5	33.5 ± 4.9

[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.

Table 3
SAR of the pyrrole phenylsulfonamides, **11l–w**



Compd	X	R^1	$mGlu_4$ EC_{50}[a] (nM)	pEC_{50} ± SEM[a]	%GluMax[b]
11l	CH		122	6.91 ± 0.03	88.8 ± 3.4
11m	CH		104	6.98 ± 0.04	84.8 ± 5.3
11n	CH		740	6.13 ± 0.03	78.8 ± 3.5
11o	CH		1238	5.91 ± 0.18	102.8 ± 6.2
11p	CH		440	6.36 ± 0.10	72.9 ± 2.5
11q	CH		344	6.46 ± 0.10	83.0 ± 0.3
11r	CH		62	7.21 ± 0.01	80.3 ± 4.3
11s	N		148	6.83 ± 0.04	92.9 ± 1.9
11t	CH		163	6.79 ± 0.05	72.2 ± 1.7
11u	CH		268	6.57 ± 0.06	98.9 ± 2.3
11v	N		242	6.62 ± 0.06	35.3 ± 3.0
11w	CH		739	6.13 ± 0.07	35.6 ± 3.7

[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.

Table 4
In vitro pharmacokinetic data for selected *N*-phenylsulfonamide pyrroles

Compd	CL (mL/min/kg)		PPB (F_u)
	Rat CL_{INT}	Rat CL_{HEP}	Rat
11l	2704	68.2	0.009
11m	4035.1	68.8	0.001
11o	1126.4	65.9	0.004
11r	293	38.3	0.012
11s	3804	68.7	0.005
11t	3445	68.6	0.004

Table 5
In vivo Rat PK IV clearance (1 mg/kg)

	11r	**11t**
CL (mL/min/kg)	37.2	86.8
$T_{1/2}$ (min)	252	167
MRT (min)	149	84.7
V_{ss} (L/kg)	5.5	7.4
AUC (h ng/mL)	447.5	191.7

po dosing of ***11t*** *with and without ABT, 1 h*

Dose (mg/kg)	Concentration (ng/mg or g)		
	Plasma systemic	Plasma HPV	Brain
10/Veh	7.4	731	8.1
10/ABT	198.5	764.5	175.5

metabolism and significantly improved the systemic plasma and brain concentrations (plasma systemic:HPV ratio 0.26).

Acknowledgment

The authors would like to thank the Michael J. Fox Foundation for Parkinson's Research for their support.

References and notes

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30. All final compounds were purified by high-throughput HPLC and characterized by LCMS and/or ^{1}H NMR and found to be in agreement with their structures (>95% purity).
31. *1-((3,4-Dimethylphenyl)sulfonyl)-3-nitro-1H-pyrrole* (**9**): To a stirred solution of 3-nitro-1*H*-pyrrole (200 mg; 1.78 mmol) in CH_2Cl_2 (8 mL) was added 1,8-diazabicycloundec-7-ene, DBU, (347 μL; 2.32 mmol) followed by 3,4-dimethylbenzenesulfonyl chloride (438 mg; 2.14 mmol). The reaction was stirred at rt overnight and then was diluted with CH_2Cl_2 and washed with 2 N HCl, satd $NaHCO_3$, dried ($MgSO_4$), filtered and concentrated under vacuum. Material was purified by CombiFlash (Isco—40 g column) eluting with 0–30% EtOAc/hexanes to give the final product (329 mg; 85%). LCMS: R_T = 2.41 min, >98% at 215 nm, m/z = 219.1 $[M+H]^+$.
N-(1-((3,4-Dimethylphenyl)sulfonyl)-1H-pyrrol-3-yl)picolinamide (**11r**): To reaction vessel was charged the **9** (180 mg; 0.826 mmol), EtOH (10 mL) and Raney Nickel (cat.) and the mixture was subjected to 40 psi H_2 in a Parr shaker for 2 h. The reaction was worked up by adding a magnetic stir bar to bind the Ra–Ni and the solution was transferred by pipette and filtered through a Whatman filter disc. The filtrate was concentrated to give the crude amine which was taken through without further purification. To the crude amine was added CH_2Cl_2 (10 mL), diisopropylethylamine (374 μL; 2.15 mmol) and picolinyl chloride·HCl (152 mg; 0.860 mmol) and the mixture was stirred at rt overnight. The reaction mixture was diluted with CH_2Cl_2, washed with H_2O, dried ($MgSO_4$) filtered and concentrated. The material was purified by CombiFlash (Isco, 12 g) eluting with 0–40% EtOAc/hexanes to give the final product as a yellow solid (136 mg; 54%). LCMS: R_T = 1.078 min, >98% at 215 and 254 nm, m/z = 356 $[M+H]^+$. ^{1}H NMR (DMSO-d_6) 400 MHz δ 10.9 (s, 1H), 8.70 (d, 1H, J = 4.6 Hz), 8.11–8.03 (m, 2H), 7.74 (d, 2H, J = 7.5 Hz), 7.66 (d, 2H, J = 8.0 Hz), 7.40 (d, 1H, J = 8.0 Hz), 7.29 (s, 1H), 6.71 (d, 1H, J = 2.3 Hz), 2.29, 2.27 (2 s, 6H).
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