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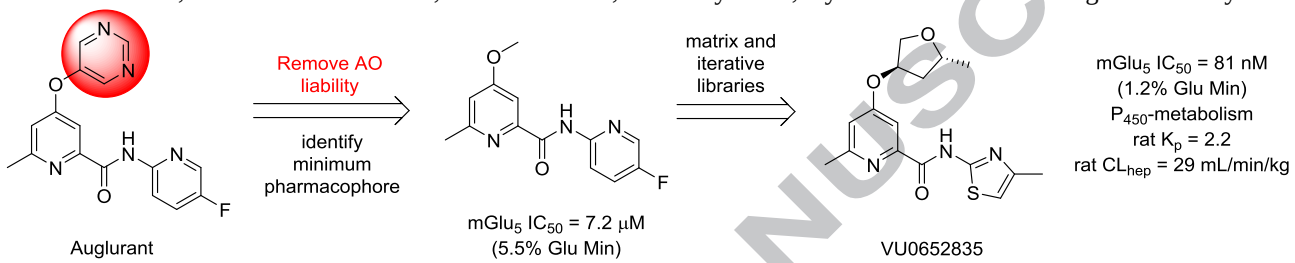

Auglurant

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Discovery of 4-alkoxy-6-methylpicolinamide negative allosteric modulators of metabotropic glutamate receptor subtype 5

Andrew S. Felts,[a,b] Katrina A. Bollinger,[a,b] Christopher J. Brassard,[a,b] Alice L. Rodriguez,[a,b] Ryan D. Morrison,[a,b] J. Scott Daniels,[a,b] Anna L. Blobaum,[a,b] Colleen M. Niswender,[a,b,e] Carrie K. Jones,[a,b,e] P. Jeffrey Conn,[a,b,e] Kyle A. Emmitte,[a,b,c†*] and Craig W. Lindsley [a,b,c,d*]

[a]*Vanderbilt Center for Neuroscience Drug Discovery, Vanderbilt University Medical Center, Nashville, TN 37232, USA*
[b]*Department of Pharmacology, Vanderbilt University School of Medicine, Nashville, TN 37232, USA*
[c]*Department of Chemistry, Vanderbilt University, Nashville, TN 37232, USA*
[d]*Department of Biochemistry, Vanderbilt University, Nashville, TN 37232, USA*
[e]*Vanderbilt Kennedy Center, Vanderbilt University School of Medicine, Nashville, TN 37232, USA*
[†]*Current address: Dept. of Pharmaceutical Sciences, UNT System College of Pharmacy, University of North Texas Health Science Center, 3500 Camp Bowie Blvd., Fort Worth, TX 76107; Tel.; +1 817 735 0241; fax: +1 817 735 2603*

**To whom correspondence should be addressed: kyle.emmitte@unthsc.edu; craig.lindsley@vanderbilt.edu*

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ABSTRACT

This letter describes the further chemical optimization of VU0424238 (auglurant), an $mGlu_5$ NAM clinical candidate that failed in non-human primate (NHP) 28 day toxicology due to accumulation of a species-specific aldehyde oxidase (AO) metabolite of the pyrimidine head group. Here, we excised the pyrimidine moiety, identified the minimum pharmacophore, and then developed a new series of saturated ether head groups that ablated any AO contribution to metabolism. Putative back-up compounds in this novel series provided increased sp^3 character, uniform CYP_{450}-mediated metabolism across species, good functional potency and high CNS penetration. Key to the optimization was a combination of matrix and iterative libraries that allowed rapid surveillance of multiple domains of the allosteric ligand.

Allosteric modulation of metabotropic glutamate receptor subtype 5 ($mGlu_5$) has long been of great therapeutic interest for a number of CNS disorders.[1-3] Negative allosteric modulators (NAMs) of $mGlu_5$ **1-7** (**Figure 1**) are the most advanced,[4-7] providing preclinical and clinical efficacy for Parkinson's disease (PD), levodopa-induced dyskinesia (LID),[8-10] addiction disorder,[11-13] anxiety,[14,15] major depressive disorder (MDD),[16,17] fragile X syndrome (FXS),[18-20] autism spectrum disorder (ASD),[21,22] and obsessive-compulsive disorder (OCD).[23] From the beginning, a pharmacophore based on aryl/heterobiaryl acetylenes emerged (eg., **1** and **2**),[24,25] and subsequent medicinal chemistry optimization efforts retained this key pharmacophore (eg., **4-6**);[26,14,27] however, alkynes (especially those in conjugation to an α-heteroatom) are potentially reactive functional groups.[28] Furthermore, acetylene-based $mGlu_5$ NAMs have been linked to both pre-clinical and clinical hepatotoxicity and glutathione conjugation has been noted.[29,30] AZD9272 (**7**)[31] employed an acetylene biosiostere and was advanced to Phase I clinical studies; however, its development was halted.[32] Not surprisingly,

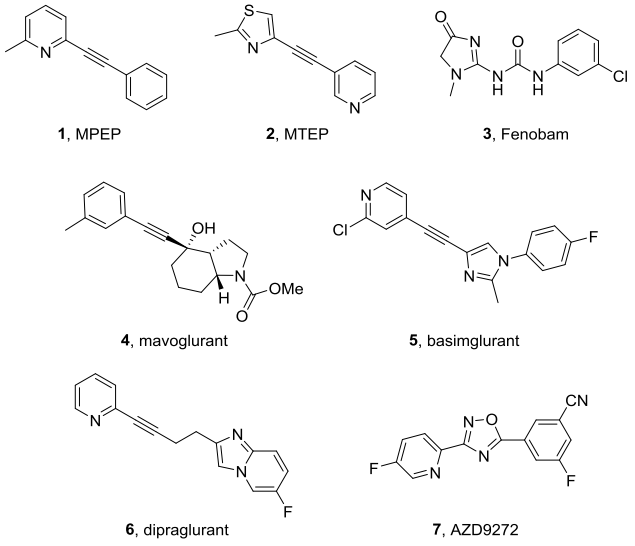


Figure 1. Prototypical $mGlu_5$ NAM chemotypes. NAMs **1-3** were pivotal early tool compounds, and NAMs **4-7** entered human clinical testing.

efforts in the field have largely shifted to the identification of novel, non-acteylene containing $mGlu_5$ NAMs to exploit the broad therapeutic utility while avoiding the pharmacophore-mediated adverse effect liability.[4]

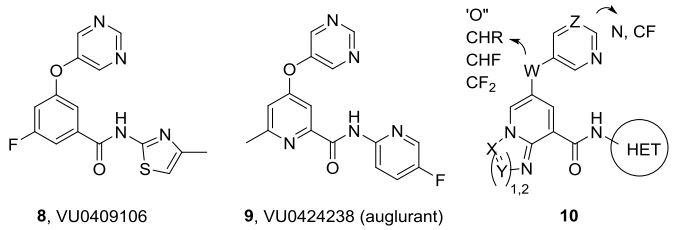


Figure 2. Previously published compounds that emerged from optimization of HTS hits: rodent tool VU0409106 (**8**), clinical candidate VU0424238 (auglurant, **9**), and backup scaffold **10**.

Optimization of hits from a functional HTS campaign led to the discovery of a key *in vivo* tool compound, VU0409106 (**8**),[33] devoid of the undesired acetylene motif (**Figure 2**). Subsequent efforts led to the clinical candidate **9** (auglurant).[34] While rat 28-day toxicology was unremarkable, **9** failed in development due to accumulation (only after day 14) of a non-human primate (NHP) species-specific aldehyde oxidase (AO) metabolite of the pyrimidine head group, resulting in pronounced anemia (non-mechanism-based).[35] Efforts to identify a back-up compound devoid of an AO contribution to metabolism focused on diverse analogs **10**;[36] however, the role of AO could ony be diminished, but not eliminated. Thus, a more significant departure from **9** was required. In this Letter, we describe novel saturated etheral head groups as replacements for the pyrimidine moiety which ablate AO-mediated metabolism and enhance sp^3 character,[37] while mainitaining $mGlu_5$ NAM potency and high CNS penetration (rat K_ps > 1).

In order to avoid AO metabolism, we focused on replacing/eliminating the pyrimdine head group. We elected to truncate multiple regions of **9** (**Figure 3**) in an attempt to identify a minimum $mGlu_5$ NAM pharmacophore within this series. Deletion or modification of the heteroaryl amide, in combinaton with removal of the pyrimidine, led to inactive compounds. Thus, the minimum pharmacophore proved to be a simple methyl ether **11**, with weak $mGlu_5$ NAM activity (IC_{50} = 7.2 μM, 5.5% Glu Min), and an attactive profile (MW =262, clogP = 2.2, CNS MPO[38] = 5.3) as a new lead.

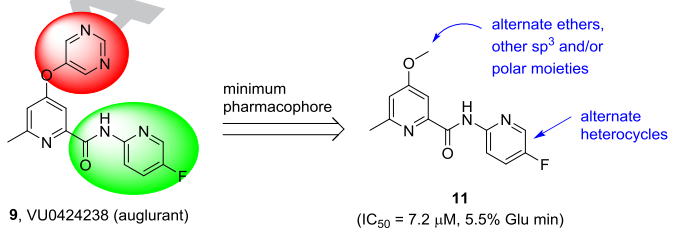
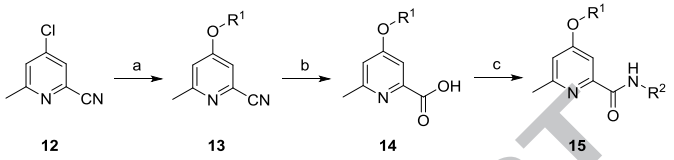


Figure 3. Truncation and evaluation of multiple regions of **9** to identify the minimum pharmacophore led to the discovery that a simple methyl ether **11** retained weak $mGlu_5$ NAM activity, and would serve as a new lead for further exploration.

The synthesis of diverse ether analogs **15** was straightforward and starting materials were readily available from commercial sources (**Scheme 1**). Various S_NAr protocols with 4-chloro-6-methylpicolinonitrile **12** and a diverse array of alcohols delivered ether analogs **13** in yields ranging from 28-95%. Basic hydrolysis of the nitrile to the corresponding

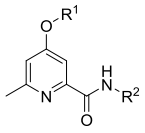
Scheme 1. Synthesis of ether head group analogs **15**.[a]



[a]Reagents and conditions: (a) R^1OH, NaH, DMF, rt, 3 h, 76-95% or R^1OH, K_2CO_3, NMP, mw, 180 °C, 30 min, 28-31%; (b) 2N NaOH, dioxane, 100 °C, 24 h, 64-99%; (c) $POCl_3$, R^2NH_2, pyridine, -15 °C, 1 h, 7-71%.

carboxylic acid proceeded smoothly in 64-99% yield. Finally, conversion to the acid chloride and reaction with *in situ* various heterocyclic amines provided analogs **15**. In order to more accurately capture SAR for this series, we employed a 3x13

Table 1. Structures and activities for $mGlu_5$ NAM analogs **15**.



R^1 \ R^2	A $mGlu_5$ IC_{50} (nM)[a] [% Glu Min]	B $mGlu_5$ IC_{50} (nM)[a] [% Glu Min]	C $mGlu_5$ IC_{50} (nM)[a] [% Glu Min]
a	43 [1.5]	182 [1.6]	58 [1.5]
b	182 [2.1]	3660 [-0.7]	149 [1.5]
c	1420 [2.1]	3350 [10.4]	2100 [1.9]
d	66 [1.3]	228 [1.1]	51 [0.5]
e	23 [1.7]	38 [1.7]	28 [1.3]
f	194 [1.3]	657 [1.0]	107 [1.4]
g	1560 [0.9]	1960 [-0.2]	446 [0.7]
h	224 [0.7]	497 [0.2]	140 [0.9]
i	392 [0.8]	4300 [-3.4]	134 [1.5]
j	646 [0.5]	2480 [-1.1]	399 [1.2]
k	725 [0.8]	2330 [-0.9]	273 [1.5]
l	210 [1.1]	700 [1.0]	200 [1.1]
m	120 [1.1]	694 [0.1]	103 [1.9]

[a] For SAR determination, calcium mobilization human $mGlu_5$ assays were performed n = 1 independent times in triplicate with an EC_{80} fixed

concentration of glutamate. The % Glu min is the measure of efficacy of the NAM to reduce an EC_{80} concentration of glutamate.

matrix library, simultaneously gaining insight and direct comparison of the three preferred amides with a diverse array of ethers (**Table 1**). We were pleased to see that a wide-range of saturated head group replacements for the pyrimidine were tolerated as $mGlu_5$ NAMs. Uniformly, the 3-fluoropicolinamide analogs **15B** were far less potent than the naked picolinamide **15A** and the 4-methylthiazole **15C** derivatives, with one exception, the (*S*)-furanyl head group (**15Ae** IC_{50} = 23 nM, 1.7% Glu Min, **15Be** IC_{50} = 38 nM, 1.7% Glu Min, and **15Ce** IC_{50} = 28 nM, 1.3% Glu Min). Moreover, we observed enantioselective inhibition, as the (*R*)-furnayl congeners (**15Af**, **15Bf**, **15Cf**) were 5-to 20-fold less potent than the (*S*)-comparator. Table 2 highlights select physiochemical and *in vitro* and *in vivo* DMPK properties for select analogs of **15**. While all these analogs displayed improved fraction unbound in rat and human plasma (f_us 0.05 to 0.3) and rat K_ps >1.7 relative to **9**, highly variable predicted hepatic clearance for both human and rat was observed. Within the set of analogs **15**, **15Ce** stood out as worthy of further attention. NAM **15Ce** was a low molecular weight compound

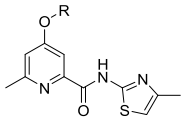
Table 2. *In vitro* and *In vivo* DMPK data for select $mGlu_5$ PAMs **15**.

Property	**15Be**	**15Ce**	**15Bd**	**15Ce**
MW	317	319	303	305
cLogP	1.96	2.13	1.82	1.98
TPSA	72.2	72.2	72.2	72.2
***In vitro* PK parameters**				
Rat CL_{HEP} (mL/min/kg)	50.9	42.3	46.5	43.5
Human CL_{HEP} (mL/min/kg)	6.8	18.7	10.7	16.1
Rat f_u (plasma)	0.26	0.11	0.16	0.11
Human f_u (plasma)	0.07	0.08	0.16	0.14
CYP_{450}				
3A4 2D6	>30 >30	>30 >30	>30 >30	>30 >30
1A2 2C9	>30 >30	0.3 >30	5.8 >30	0.3 >30
Rat *In vivo* (IV, 0.2 mg/kg)				
$t_{1/2}$	46	63	28	ND
CL_p (mL/min/kg)	136	34	179	ND
V_{ss} (L/kg)	5.5	2.7	4.5	ND

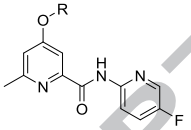
(MW = 319) with an attractive cLogP (2.13), good free fraction (f_u 0.11 and 0.08, for rat and human, respectively), a favorable CYP profile (>30 μM, except 1A2) and an IVIVC in rat (CL_{hep} = 42.3 mL/min/kg and CL_p = 34 mL/min/kg). Moreover, metabolite identification studies in rat, dog and human S9 all showed the same profile, with extensive NADPH-dependent oxidation of the furanyl moiety, indicating no contribution from AO.

Following literature procedures to access functionalized furans and following the route outlined in Scheme 1, we were able to assess analogs **16** and **17** (**Table 3**). Here, diastereoselective inhibition was noted, with the (2*R*, 4*R*)-**16a** being the most potent in this sub-series (IC_{50} = 81 nM, 1.2% Glu Min), yet ~3-fold less potent than **15Ce**, but with excellent CNS penetration (rat K_p of 2.2). Beyond this, **16a** showed good fraction unbound (f_us of 0.1 and 0.05 for rat and human, respectively), and low predicted hepatic clearance in rat (CL_{hep} = 25 mL/min/kg), but high for human (CL_{hep} = 16.4 mL/min/kg), the latter of which precluded further advancement as a back-up candidate (albeit still useful as a rodent tool compound). The 3-fluoropicolinamide analogs **17** were once again uniformly less potent and not progressed further.

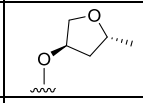
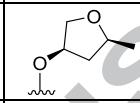
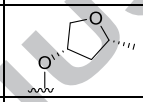
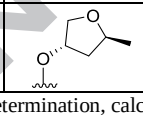
Table 3. Structures and activities for $mGlu_5$ NAM analogs **16** and **17**.



16



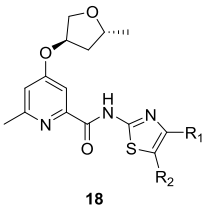
17

Compound	R	$mGlu_5$ IC_{50} (nM)[a]	% Glu Min[a]
16a		81	1.2
17a		175	1.3
16a		684	1.1
17a		4470	1.9
16a		112	2.1
17a		389	1.4
16a		395	1.7
17a		2040	2.6

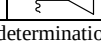
[a] For SAR determination, calcium mobilization human $mGlu_5$ assays were performed n = 1 independent times in triplicate with an EC_{80} fixed concentration of glutamate. The % Glu min is the measure of efficacy of the NAM to reduce an EC_{80} concentration of glutamate

Based on these data, we then elected to hold the **16a** (2*R*,4*R*)-head group constant, and explore other functionalized thiazoles (**Table 4**). Here, all new analogs **18** were less potent than **16a**, and while they displayed low to moderate predicted hepatic clearance in rat (CL_{hep}s < 30 mL/min/kg), they showed high predicted human hepatic clearance (CL_{hep} >17 mL/min/kg). Thus, their progression down the lead optimization flow chart was also terminated.

Table 4. Structures and activities for $mGlu_5$ NAM analogs **18**.



18

Compound	R_1	R_2	$mGlu_5$ IC_{50} (nM)[a]	% Glu Min[a]
16a	CH_3	H	81	1.2
18a	CH_3	F	1290	3.8
18b	CH_2F	H	180	1.1
18c	CHF_2	H	902	1.6
18d	CF_3	H	5200	2.7
18e		H	899	1.3

[a] For SAR determination, calcium mobilization human $mGlu_5$ assays were performed n = 1 independent times in triplicate with an EC_{80} fixed concentration of glutamate. The % Glu min is the measure of efficacy of the NAM to reduce an EC_{80} concentration of glutamate

Before leaving the ether head groups, we wondered if an open chain version of the chiral furans would offer any advantages, as the aliphatic ethers 1**5ABCm** each retained

$mGlu_5$ NAM activity. As shown in Figure 4, analogs **19a-d** were intriguing. NAMs harboring a chiral methyl group in the 1-position were weak and equipotent, while addition of a chiral methyl group at the 2-position of the linker showed enantioselectivity (>5-fold) for the (*R*)-isomer, **19c**. While **19c** displayed a favorable *in vitro* DMPK profile (f_u (r, h) = 0.09, 0.07; human CL_{hep} = 13.4 mL/min/kg and rat CL_{hep} = 45.5 mL/min/kg), the modest functional potency once again precluded advancement.

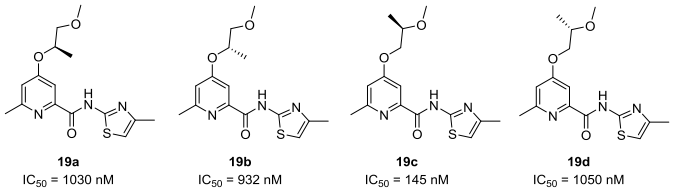


Figure 4. $mGlu_5$ NAMs harboring chiral, aliphatic head groups **19**. Enantioselectivity noted for the 2-(*R*)-Me analog **19c** versus 2-(*S*)-Me analog **19d**. Methyl groups in the 1-position showed no bias.

Lastly, we considered other saturated polar moieties as a replacement for the AO-metabolized pyridine (**Figure 5**), including cyclic thioethers **20**-**21** (and related sulfoxide **22** and sulfone **23**) as well as amides (e.g., **24**) and sulfonamides (e.g., **25**). Within each subseries, SAR proved to be incredibly steep, with any amide or sulfonamide larger than methyl leading to a 50- to 100-fold loss in potency. While thioethers retained good functional $mGlu_5$ NAM potency, they proved metabolically unstable, and therefore were not advanced.

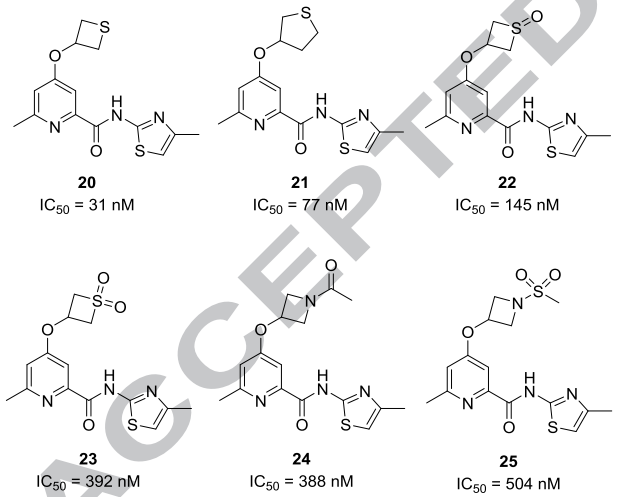


Figure 5. Other saturated, polar head groups explored as a replacement for the heteroaromatic, AO-metabolized pyrimidine.

In summary, attempts to identify a potential $mGlu_5$ NAM back-up candidate to **9** (auglurant) devoid of AO-mediated metabolism were partially successful in the optimization campaign described here. Saturated ether head groups, exemplified by the new rodent tool compound **16a**, afforded potent CNS penetrant ligands with acceptable rat PK, enhanced sp^3 character, and were devoid of an AO-contribution to metabolism. However, all of the novel analogs disclosed herein possessed either a potency or DMPK liability that precluded further advancement and consideration as back-up compounds. By transitioning from exclusively sp^2-based ligands to ones possessing considerable sp^3 character, we were also able to incorporate chiral centers, from which enantioselective inhibition was noted. SAR insights gained and lessons learned from this campaign, including the value of matrix libraries, have since been applied to other $mGlu_5$ NAM scaffolds en route to viable back-up compounds. These efforts will be reported in due course.

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Highlights

- Identification of the minimum pharmacophore of auglurant
- Development of novel saturated ethers that enhanced sp^3 character
- Ether head group ablated undesired aldehyde oxidase (AO) metabolism
- Matrix and iterative libraries were essential in establishing SAR