Bioorganic & Medicinal Chemistry Letters 22 (2012) 6469–6474

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Azetidinyl oxadiazoles as potent mGluR5 positive allosteric modulators

Mathivanan Packiarajan [a,*], Christine G. Mazza Ferreira [a], Sang-Phyo Hong [a], Andrew D. White [a], Gamini Chandrasena [a], Xiaosui Pu [b], Robbin M. Brodbeck [b], Albert J. Robichaud [a]

[a] Chemical & Pharmacokinetic Sciences, Lundbeck Research USA, 215 College Road, Paramus, NJ 07652, USA
[b] Synaptic Transmission, Disease Biological Unit, Lundbeck Research USA, 215 College Road, Paramus, NJ 07652, USA

ARTICLE INFO

Article history:
Received 29 June 2012
Revised 2 August 2012
Accepted 13 August 2012
Available online 25 August 2012

Keywords:
mGluR5 positive allosteric modulators
Azetidinyl oxadiazoles
Azetidinyl *N*-cyclohexyl carboxamides and carbamates
Azetidinyl *N*-sulfonamides
PAM to *NAM* switching

ABSTRACT

A novel series of aryl azetidinyl oxadiazoles are identified as mGluR5 positive allosteric modulators (*PAMs*) with improved physico-chemical properties. N-substituted cyclohexyl and *exo*-norbornyl carboxamides, and carbamate analogs of azetidines are moderate to potent mGluR5 *PAMs*. The aryl, lower alkyl carboxamides analogs and sulfonamide analogs of azetidines are moderate mGluR5 negative allosteric modulators (*NAMs*). In the aryl oxadiazole moiety, substituents such as fluoro, chloro and methyl are well tolerated at the *meta* position while para substituents led to either inactive compounds or *NAMs*. A tight pharmacophore and subtle '*PAM* to *NAM* switching' with close analogs makes the optimization of the series extremely challenging.

Glutamate is the major excitatory neurotransmitter in the mammalian central nervous system, where it mediates its effects through three ionotropic (AMPA, kainate and NMDA) and eight metabotropic receptors (mGluR1-8).[1] The metabotropic glutamate receptors (mGluRs) are class C GPCRs and contain two distinct domains. A large extracellular domain binds glutamate while the heptahelical transmembrane (7TM) domain binds a variety of ligands at one or more allosteric binding sites.[2] The mGluRs structurally and pharmacologically associate with the NMDA receptor to modulate roles in synaptic plasticity, cognition, and learning and the memory process.[3] The mGluR5 receptors are primarily located post synaptically and are highly expressed in the limbic brain regions.[4] Activation of the mGluR5 receptor potentiates NMDA receptor function and thus positive allosteric activation of mGluR5 could indirectly correct NMDA hypo-function. It has been postulated that positive modulation of mGlu5 receptor could treat the positive symptoms and cognitive deficits in schizophrenia,[5–9] and also improve spatial learning[10,11] and cognition.[12]

There has been considerable interest recently in identification of positive allosteric modulators (*PAMs*) of the mGlu5 receptor.[13] Over the last few years, structurally distinct chemotypes of mGluR5 *PAMs* have been reported from various groups.[14–19] Compounds such as 3-cyano-*N*-(1,3-diphenyl-1*H*-pyrazol-5-yl)benzamide (**1**, CDPPB)[15a,b] and ADX47273 (**2**)[16a–c] have been used extensively as mGluR5 *PAM* tools. Compounds **3**[17f] and **4**[18c] have been shown to reverse amphetamine induced hyperlocomotion and conditioned avoidance responding (Fig. 1). We recently reported the discovery of several novel classes of mGluR5 PAMs including nicotinamides **5a**,[19b] lactams **5b**[19c] and *N*-aryl pyrrolidinonyl oxadiazoles **6**.[19d]

The compound **6** exhibits high potency at mGluR5 (EC_{50} = 10.7 nM) but poor solubility is an issue for this class of compounds. In continuing our efforts to identify novel compounds with improved physio-chemical properties, we initiated the optimization of the pyrrolidinonyl oxadiazole analog **6**. We postulated that the core pyrrolidinone ring could be replaced with a smaller azetidine ring, coupled with exocyclic transposition of the carbonyl group. The resulting 4-fluorobenzamide analog **7a** is devoid of mGluR5 *PAM* potency and exhibits weak *NAM* potency (IC_{50} = 4000 nM) with improved solubility (47 μM). However, replacement of the chlorine atom with a methyl group on the aryl moiety in compound **7d** results in a moderately active *PAM* (Fig. 2). A benzamide was found not to be crucial for *PAM* activity as the cyclohexyl amide **13a** has similar activity to the benzamide **7d**. In this Letter, we report our efforts towards the optimization of azetidinyl oxadiazoles as novel mGluR5 positive allosteric modulators.

Azetidinyl oxadiazole analogs (**7**, **12–14**, **16** and **17**) were synthesized as outlined in Scheme 1. Coupling of *N*-Boc protected azetidine carboxylic acid **9a–b** with aryl-*N*-imidoximes **8a–c** using HBTU in the presence of Et_3N followed by heating under microwave irradiation or refluxing condition affords the aryl oxadiazoles **10a–c** in moderate yield (40–60%).[20a] Alternatively, the oxadiazoles can be

* Corresponding author. Tel.: +1 201 820 1971; fax: +1 201 261 0623.
E-mail address: packiara@yahoo.com (M. Packiarajan).

0960-894X/$ - see front matter © 2012 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2012.08.044

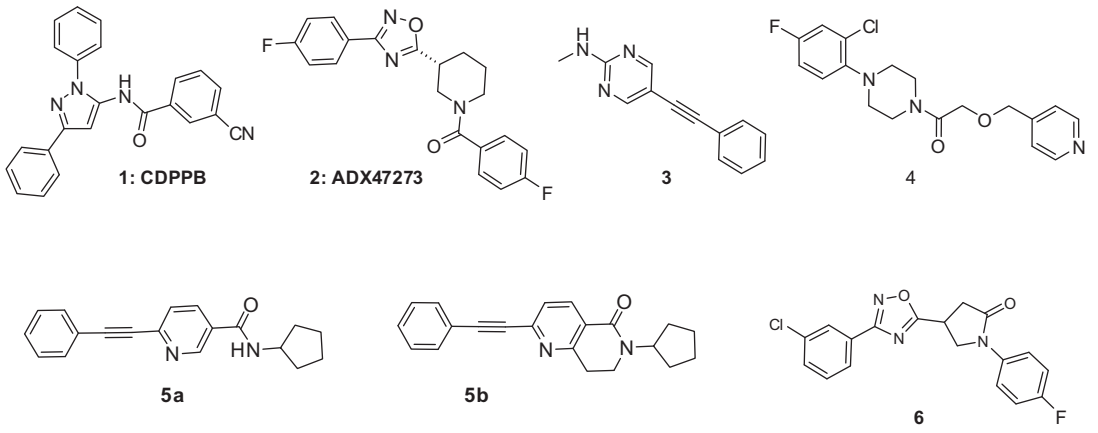


Figure 1. mGluR5 positive allosteric modulators.

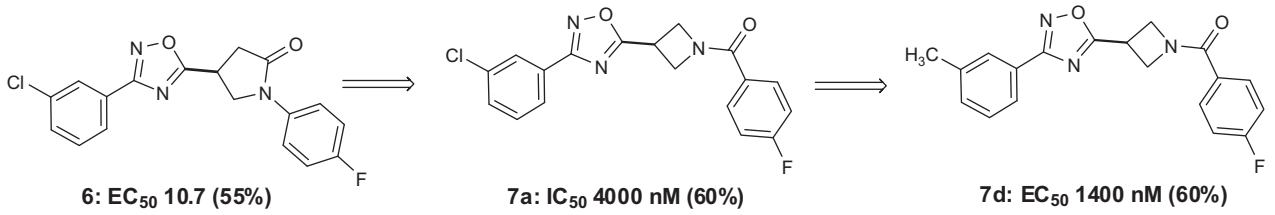
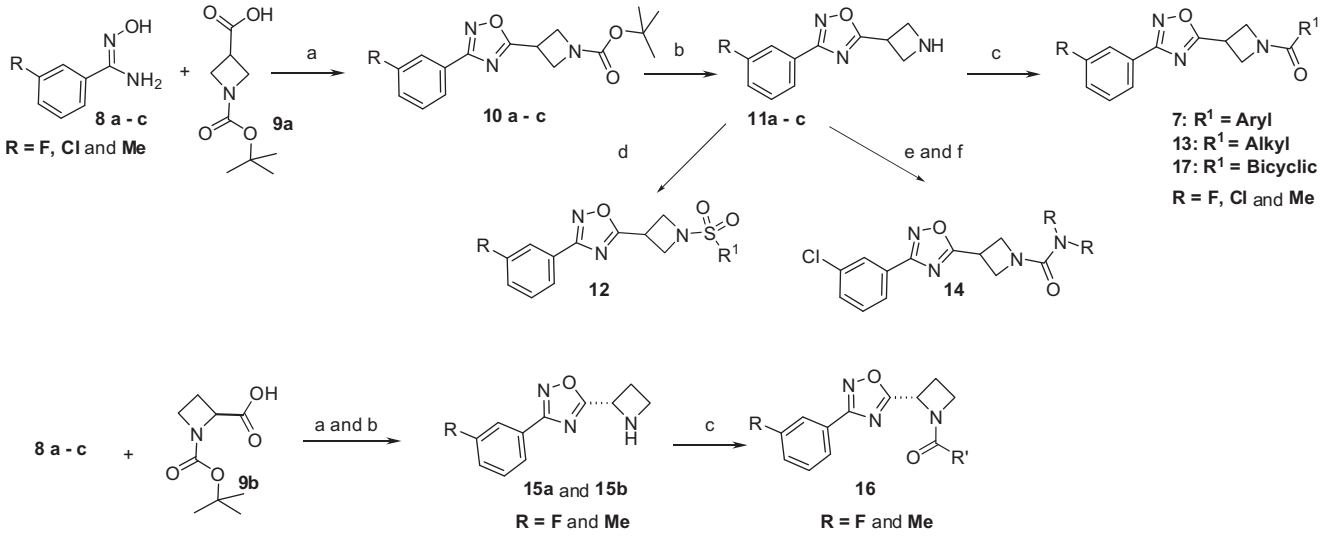


Figure 2. Azetidinyl oxadiazoles as mGluR5 positive allosteric modulators.



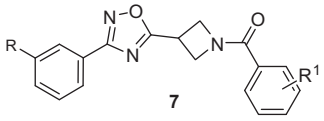
Scheme 1. Reagents and conditions: (a) HBTU, Et_3N, DMF, 5 min, rt, then add **9a** or **9b**, microwave, 190 °C, 15 min, 40–60%; (b) 4 M HCl in dioxan, rt, >99%; (c) RCOOH, HBTU, DIEA, DMF, rt or RCOCl, Et_3N, CH_2Cl_2, rt, 20–70%; (d) Et_3N, CH_2Cl_2, R^1SO_2Cl, rt, 50–75%; (e) trisphosgene, CH_2Cl_2, 0 °C to rt or 4-nitrochloroformate, CH_2Cl_2, Et_3N, 0 °C and (f) R′R′NH, CH_2Cl_2, rt, 30–55%.

synthesized via activation of the acid **9a** with CDI at room temperature followed by treatment with amidoximes **8** under refluxing conditions.[20b] The *N*-Boc group was removed by treatment with 10% TFA in DCM or 4 M HCl in methanol in quantitative yield. In an analogous manner, the 2S-(−) enantiomer of the azetidinyl-2-carboxylic acid **9b** was converted into the corresponding azetidinyl oxadiazoles (**15**) in two steps.

The azetidine salts (**11a**–**11c** and **15**) were treated with suitable aryl or alkyl carboxylic acid chlorides in the presence of Et_3N to afford the amide analogs (**7**, **13** and **16**). Alternatively, treatment of alkyl carboxylic acid with HBTU in the presence of DIEA affords the azetidine carboxamides analogs (**13** and **17**). In analogous manner, the azetidines HCl (**11**) were treated with aryl sulfonyl chlorides at room temperature affording azetidinyl sulfonamides (**12a–12h**) in good yield. The carbamate analogs were synthesized in a two-step process by reaction of azetidines **11a** with triphosgene or 4-nitrophenyl chloroformate followed by treatment with cyclic amines in the presence of base to afford azetidinyl carbamate analogs (**14a**–**14j**).

The SAR of the peripheral aryl rings is shown in Table 1. Replacement of the chloro substituent of compound **7a** with a methyl group resulted in compound **7d** having moderate *PAM*

Table 1
The in vitro mGluR5 functional affinities of aryl carboxamide analogs **7**

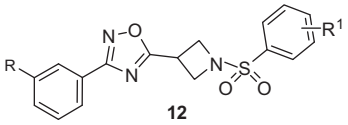


7

Compound	R	R^1	EC_{50}[a] (nM)	E_{max} (%)	IC_{50}[a] (nM)	Inh.[b] (%)
7a	Cl	4-F	>10000	−12	4000	60
7b	Cl	3-F	>10000	−12	780	87
7c	Cl	2-F	>10000	−12	670	86
7d	CH_3	4-F	1400	32	>10000	50
7e	CH_3	3-F	>10000	15	2100	62
7f	CH_3	2-F	>10000	5	1400	64
7g	CH_3	4-Cl	7100	33	>10000	−6.3
7h	F	4-F	2400	40	>10000	−6
7i	F	4-Cl	2500	62	>10000	−82
7j	F	4-CH_3	6800	27	>10000	−30
7k	F	3,4-Di F	3200	35	>10000	−50

[a] The mGluR5 EC_{50} and IC_{50} functional FLIPR data were generated using a human mGluR5 cell line.[21]
[b] A negative % inhibition value represents positive allosteric modulation.

Table 2
SAR of azetidinyl sulfonamide analogs **12**



12

Compound	R	R^1	EC_{50}[a] (nM)	E_{max} (%)	IC_{50}[a] (nM)	Inh. (%)
12a	Cl	4-CH_3	>10000	2	920	75
12b	Cl	4-Cl	>10000	7	170	79
12c	Cl	4-F	>10000	−7	130	85
12d	Cl	3-CH_3	>10000	−2	390	82
12e	CH_3	4-CH_3	>10000	1	670	80
12f	CH_3	4-Cl	>10000	3	1100	75
12g	CH_3	4-F	>10000	6	950	74
12h	CH_3	3-CH_3	>10000	−4	650	76

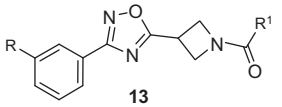
[a] The mGluR5 EC_{50} and IC_{50} functional FLIPR data, see footnote in Table 1.[21]

potency at the mGlu5 receptor. However, moving the fluoro group of the benzamide from the *para* to the *meta* or *ortho* positions caused loss of *PAM* activity and the analogs (**7b**, **7c**, **7e** and **7f**) became weak *NAMs*. The fluoro substituted aryl oxadiazole analogs (**7h–7k**) retain moderate *PAM* potency. To our disappointment, azetidinyl sulfonamide analogs (**12a–12h**) exhibit *NAM* activity at the mGluR5 receptor (Table 2).

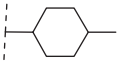
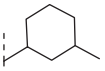
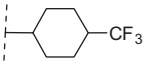
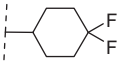
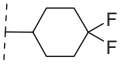
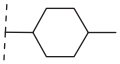
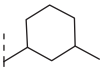
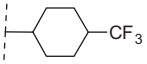
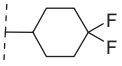
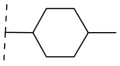
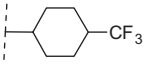
Since the amide analog **7d** was promising, we decided to investigate further with non-aromatic carboxamides. Interestingly, introduction of a cyclohexyl group (**13a**) resulted in an improvement of *PAM* potency. This result led us to further investigate cycloalkyl rings (**13a–13x**) and the results are summarized in Table 3.

Groups such as cyclobutyl, cyclopentyl, tetrahydrofuranyl and tetrahydropyranyl results in compounds with varying degrees of *NAM* potency at mGlu5 receptor. On the other hand, substituted cyclohexyl carboxamide analogs are mGluR5 *PAMs* with moderate potency. The 4,4-difluoro cyclohexyl carboxamide analogs are potent mGluR5 *PAMs* (**13j**, **13n** and **13u** Table 3). In the cyclohexyl moiety, substituents such as methyl, trifluoromethyl and a spirocycle are tolerated, but groups such as methoxy or hydroxyl groups cause complete loss of *PAM* or *NAM* potency (data not shown). In addition, introduction of the smaller acyclic carboxamides such as cyclopropyl, difluorocyclopropyl, fluorocyclopropyl, methyl

Table 3
SAR of azetidinyl amide analogs **13**

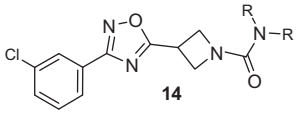


13

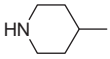
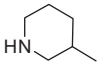
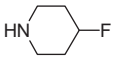
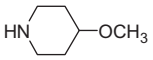
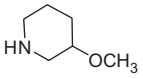
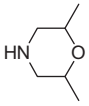
Compound	R	R^1	EC_{50}[a] (nM)	E_{max} (%)	IC_{50}[a] (nM)	Inh.[a] (%)
13a	CH_3		950	45	>10000	−20
13b	CH_3		970	68	>10000	−49
13c	CH_3		500	46	>10000	−19
13d	CH_3		1000	36	>10000	3
13e	CH_3		>10000	−7	2500	70
13f	CH_3		>10000	3	1000	77
13g	CH_3		>10000	−7	1300	80
13h	CH_3		>10000	3	1900	79
13i	CH_3		>10000	−2	1800	74
13j	CH_3		590	36	>10000	−3
13k	Cl		520	43	>10000	−35
13l	Cl		>10000	−7	1500	75
13m	Cl		>10000	−3	890	79
13n	Cl		180	75	>10000	−3
13o	Cl		1500	75	>10000	−120
13p	Cl		410	53	>10000	−34
13q	Cl					
13r	Cl		1000	40	>10000	−5
13s	Cl		1100	40	>10000	−24
13t	F		1000	46	>10000	−19
13u	F		540	87	>10000	−48
13v	F		520	53	>10000	11
13w	F		2200	47	>10000	−11
13x	F		680	56	>10000	−37

[a] The mGluR5 EC_{50} and IC_{50} functional FLIPR data, see footnote in Table 1.[21]

Table 4
SAR of azetidinyl carbamate analogs **14**



14

Compound	HNRR	EC_{50}[a] (nM)	E_{max} (%)	IC_{50}[a] (nM)	Inh.[a] (%)
14a		370	44	>10000	−87
14b		865	66	>10000	n/a
14c		>10000	6	3400	69
14d		990	41	>10000	−61
14e		200	51	>10000	−81
14f		>10000	11	>10000	n/a
14g		>10000	−14	1830	80
14h		>10000	n/a	990	51
14i		47	44	>10000	−41
14j		>10000	88	>10000	80

n/a = not available
[a] The mGluR5 EC_{50} and IC_{50} functional FLIPR data, see footnote in Table 1.[21]

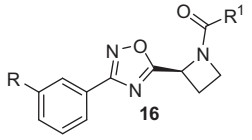
substituted cyclopropyl or linear alkyl groups with or without trifluoromethyl group causes loss of mGluR5 activity (data not shown). In the aryl oxadiazole moiety, the substituents chloro, fluoro and methyl at the *meta* position result in *PAMs* while these groups at the *para* position result in analogs with *NAM* potency (data not shown).

Next we examined carbamate analogs of the azetidinyl oxadiazoles (Table 4). Piperidinyl carbamate analogs (**14a**, **14b**, **14d** and **14e**) retain mGlu5 *PAM* potency similar to carboxamide analogs. Methoxy substituted piperidinyl carbamates (**14f** and **14g**) or a morpholinyl analog **14h** cause complete loss of *PAM* or *NAM* potency similar to the corresponding carboxamide analogs. Replacement of the piperidine with an azepine (**14i**) results in a potent *PAM*. On the other hand, incorporation of a substituted pyrrolidine analog (**14j**) caused loss of *PAM* and *NAM* potency.

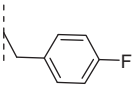
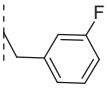
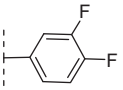
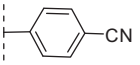
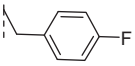
We investigated the regio isomeric 2-azetidinyl oxadiazole analogs (Table 5) with aryl, alkyl and cycloalkyl carboxamides. We noticed that both aryl and cycloalkyl carboxamide analogs exhibit moderate *NAM* activity with the exception of the 3,4-difluoro benzamide analog (**16e**) which shows *PAM* activity. However, elongation of the benzamides to arylacetamides results analogs **16a**, **16b** and **16g** with intermediate PAM potency.

Interestingly, by increasing the lipophilicity of the amide moiety in 3-azetidinyl oxadiazole series, via incorporation of an *exo*-norbornyl carboxamide results in compounds (**17a–f**) having more consistent *PAM* activity (Table 6). For example, the '2S' enantiomers (**17a**, **17c** and **17e**) exhibit higher PAM potency and efficacy than the corresponding '2R' enantiomers (**17b**, **17d** and **17f**).

Table 5
The in vitro mGluR5 functional affinities of amide analogs **16**

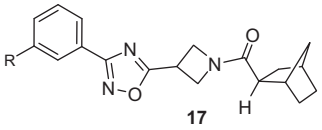


16

Compound	R	R^1	EC_{50}[a] (nM)	E_{max} (%)	IC_{50}[a] (nM)	Inh.[a] (%)
16a	F		1200	29	>10000	−12
16b	F		2400	52	>10000	−75
16c	F		>10000	57	920	68
16d	CH_3		>10000	6.2	1800	58
16e	CH_3		1500	51	>10000	−92
16f	CH_3		>10000	88	1400	72
16g	CH_3		1900	24	>10000	−30

[a] The mGluR5 EC_{50} and IC_{50} functional FLIPR data, see footnote in Table 1.[21]

Table 6
The in vitro mGluR5 functional affinities of bicyclic amide analogs **17**



17

Compound	R	Conf.	EC_{50}[a] (nM)	E_{max} (%)	c Log P[b]
17a	H	2S	120	160	2
17b	H	2R	400	88	2
17c	F	2S	72	140	2.1
17d	F	2R	100	110	2.1
17e	Cl	2S	74	120	2.7
17f	Cl	2R	98	66	2.7

[a] The mGluR5 EC_{50} functional FLIPR data, see Table 1.[21]
[b] *c*Log*P* was calculated using ChemBioDraw Ultra version 12.0.

Compounds **13n**, **13u** and **17c** (Fig. 3) were profiled further and the data is sown in Table 7. The selected compounds have reasonable *c*Log*P*s, lipophilic efficiencies (*LLE*) and solubility. Compound **13n** exhibits moderate *PAM* potency at mGlu5 receptor (EC_{50} = 180 nM) with a weak binding affinity of 3800 nM in the radiolabelled binding assay and has moderate solubility (130 μM). Compound **13n** is highly selective among the other mGluR subtypes tested (mGluR1, mGluR2, mGluR4 and mGluR7) in agonist, *PAM* and *NAM* mode. It does not show significant inhibition of the 2D6 and 3A4 cytochrome P450 (CYP) isoforms (IC_{50} >25 μM). Compound **13n** has moderately high rat (96.9%)

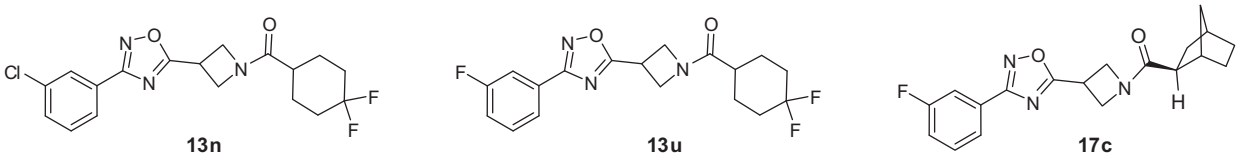


Figure 3. Key compounds.

Table 7
Profiling data of selected key compounds (in vitro metabolic clearance, CYP inhibition and rat in vivo pharmacokinetic data)

Compound	mGluR5 EC_{50}[a] (nM)	Sol[b] (mM)	c Log *P*[c]	*LLE*[d]	hCl_{int}[e] (L/min)	rCl_{int}[e] (mL/min)	hPPB (%)	rPPB (%)	$CYP3A_4$ (IC_{50}, mM)	$CYP2D_6$ ($IC_{50,}$ mM)	Brain[f] (ng/g)	Plasma[f] (ng/mL)	Brain to plasma ratio[f] (B/P)
13n	180	130	1.8	5.1	0.9	24	98.7	96.9	25	33	280	160	1.75
13u	520	180	1.2	5.1	1.6	13	96.6	94.5	25	40	n/a	n/a	n/a
17c	72	54	2.1	5.1	59	16	99.3	99.2	n/a	n/a	84	36	2.33

[a] For the mGluR5 EC_{50} functional FLIPR data see Table 1.[21]
[b] The solubility (μg/mL) was measured using DMSO stock solution[22]
[c] *c*Log*P* was calculated using ChemBioDraw Ultra version 12.0
[d] Lipophilic ligand efficiency (LLE).[24] = pEC_{50}–*c*Log*P*
[e] The hCl_{int} and rCl_{int} are human (L/min) and rat (mL/min) intrinsic clearances, respectively, and were determined according to Obach et al.,[23] rat and human liver blood flow corresponds to 20 mL/min and 1.5 L/min, respectively.
[f] Exposure was determined in brain and plasma after a single oral dose (10 mg/kg po, $n = 2$).[25]

and human (98.7%) plasma protein binding. In rat PK studies, the compound **13n** exhibits a moderate exposure in brain 1 h, following a 10 mg/kg oral (po) dose (brain = 280 ng/g; plasma = 160 ng/mL) with a brain to plasma (B/P) ratio of 1.75. Compound **13u** exhibits moderate *PAM* potency but with improved properties. On the other hand, compound **17c** is highly protein bound (rPB and hPB are 99.2% and 99.3%, respectively) with lower brain exposure at 1 h, following a 10 mg/kg oral (po) dose (brain = 84 ng/g; plasma = 36 ng/mL) with a brain to plasma (B/P) ratio of 2.33.

In summary, we have described a new series of azetidinyl oxadiazoles (**13** and **17**) which are mGluR5 positive allosteric modulators (*PAMs*). The azetidine carboxamides are low molecular weight (<350) optimal *c*Log*P* (<3) compounds with improved physicochemical and PK properties versus the *N*-aryl pyrrolidinonyl oxadiazole lead **6**. Substituted cyclohexyl and *exo*-norbornyl carboxamides, and carbamate analogs are mGluR5 *PAMs* whereas the aryl, lower alkyl carboxamide and sulfonamide analogs are moderate mGluR5 negative allosteric modulators (*NAMs*). The optimization of initial lead **6** led to the identification of the potent compounds **13n** and **17c** with improvements in the solubility, *c*Log*P*, *LLE* and acceptable PK properties. However, the moderate potency remains an issue for this series of compounds. Also, simple structural modifications lead to *PAM*/*NAM* switching, thus making optimization a challenge.

Acknowledgments

We thank our colleagues Manual Cajina, Megan E. Nattini and Kimloan Nguyen (Bioanalysis, pharmacokinetics metabolic stability and CYP inhibition); Xu Zhang, Qing-Ping Han and Chi Zhang (chiral separation and physico-chemical property determination); Michelle B. Uberti and Christina L. Bonvicino (functional data) for providing experimental data to support this work. We thank Diptendu Goswami (Chembiotek, India) for synthetic support for this work.

References and notes

1. Schoepp, D. D.; Jane, D. E.; Monn, J. A. *Neuropharmacology* **1999**, *38*, 1431.
2. Pin, J. P.; Galvez, T.; Prezeau, L. *Pharmacol. Ther.* **2003**, *98*, 325.
3. (a) Anwyl, R. *Neuropharmacology* **2009**, *56*, 735; (b) Neisewander, J. L.; Baker, D. A.; Fuchs, R. A.; Tran-Nguyen, L. T.; Palmer, A.; Marshall, J. F. *J. Neurosci.* **2000**, *20*, 798; (c) Conn, P. J.; Lindsley, C. W.; Jones, C. K. *Trends Pharmacol. Sci.* **2009**, *30*, 25; (d) Rosenbrock, H.; Kramer, G.; Hobson, S.; Koros, E.; Grundl, M.; Grauert, M., et al *Eur. J. Pharmacol.* **2010**, *639*, 40.
4. (a) Abe, T.; Sugihara, H.; Nawa, H.; Shigemoto, R.; Mizuno, N.; Nakanishi, S. *J. Biol. Chem.* **1992**, *267*, 13361; (b) Bell, M. I.; Richardson, P. J.; Lee, K. *J. Neurochem.* **2002**, *81*, 142.
5. (a) Kinney, G. G.; Burno, M.; Campbell, U. C.; Hernandez, L. M.; Rodriguez, D.; Bristow, L. J.; Conn/, P. J. *J. Pharmacol. Exp. Ther.* **2003**, *306*, 116; (b) Homayoun, H.; Stefani, M. R.; Adams, B. W.; Tamagan, G. D.; Moghaddam, B. *Neuropsychopharmacology* **2004**, *29*, 1259; (c) Lecourtier, L.; Homayoun, H.; Tamagnan, G.; Moghaddam, B. *Biol. Psychiatry* **2007**, *62*, 739; (d) Darrah, J. M.; Stefani, M. R.; Moghaddam, B. *Behav. Pharmacol.* **2008**, *19*, 225.
6. (a) Chavez-Noriega, L. E.; Marino, M. J.; Schaffhauser, H.; Campbell, U. C.; Conn, P. J. *Curr. Neuropharmacol.* **2005**, *3*, 9; (b) Kinney, G. G.; O'Brien, J. A.; Lemaire, W.; Burno, M.; Bickel, D. J.; Clements, M. K.; Chen, T. B.; Wisnoski, D. D.; Lindsley, C. W.; Tiller, P. R.; Smith, S.; Jacobson, M. A.; Sur, C.; Duggan, M. E.; Pettibone, D. J.; Conn, P. J.; Williams, D. L., Jr. *J. Pharmacol. Exp. Ther.* **2005**, *313*, 199.
7. Liu, F.; Grauer, S.; Kelley, C.; Navarra, R.; Graf, R.; Zhang, G.; Atkinson, P. J.; Popiolek, M.; Wantuch, C.; Khawaja, X.; Smith, D.; Olsen, M.; Kouranova, E.; Lai, M.; Pruthi, F.; Pulicicchio, C.; Day, M.; Gilbert, A.; Pausch, M. H.; Brandon, N. J.; Beyer, C. E.; Comery, T. A.; Logue, S.; Rosenzweig-Lipson, S.; Marquis, K. L. *J. Pharmacol. Exp. Ther.* **2008**, *327*, 827.
8. Chan, M. H.; Chiu, P. H.; Sou, J. H.; Chen, H. H. *Psychopharmacology (Berl)* **2008**, *198*, 141.
9. (a) Kinney, G. G.; O'Brien, J. A.; Lemaire, W.; Burno, M.; Bickel, D. J.; Clements, M. K.; Chen, T. B.; Wisnoski, D. D.; Lindsley, C. W.; Tiller, P. R.; Smith, S.; Jacobson, M. A.; Sur, C.; Duggan, M. E.; Pettibone, D. J.; Conn, P. J.; Williams, D. L., Jr. *J. Pharmacol. Exp. Ther.* **2005**, *313*, 199; (b) Schlumberger, C.; Pietraszek, M.; Gravius, A.; Danysz, W. *Pharmacol. Biochem. Behav.* **2010**, *95*, 23.
10. (a) Gass, J. T.; Olive, M. F. *Biol. Psychiatry* **2009**, *65*, 717; (b) Olive, M. F. *Eur. J. Pharmacol.* **2010**, *639*, 47.
11. (a) Darrah, J. M.; Stefani, M. R.; Moghaddam, B. *Behav. Pharmacol.* **2008**, *19*, 225; (b) Uslaner, J. M.; Parmentier-Batteur, S.; Flick, R. B.; Surles, N. O.; Lam, J. S.; McNaughton, C. H.; Jacobson, M. A.; Hutson, P. H. *Neuropharmacology* **2009**, *57*, 531.
12. Ayala, J. E.; Chen, Y.; Banko, J. L.; Sheffler, D. J.; Williams, R.; Telk, A. N.; Noreen L Watson, N. L.; Xiang, Z.; Zhang, Y.; Jones, P. J.; Lindsley, C. W.; Olive, M. F.; Conn, P. J. *Neuropsychopharmacology* **2009**, *34*, 2057.
13. (a) Stauffer, R. S. *ACS Chem. Neurosci.* **2011**, *2*, 450; (b) Cleva, R. M.; Olive, F. M. *Molecules* **2011**, *16*, 2097.
14. O'Brien, J. A.; Lemaire, W.; Chen, T. B.; Chang, R. S.; Jacobson, M. A.; Ha, S. N.; Lindsley, C. W.; Schaffhauser, H. J.; Sur, C.; Pettibone, D. J.; Conn, P. J.; Wiliams, D. L. *Mol. Pharmacol.* **2003**, *64*, 731.
15. (a) Lindsley, C. W.; Wisnoski, D. D.; Leister, W. H.; O'Brien, J. A.; Lemiare, W.; Williams, D. L. J.; Burno, M.; Sur, C.; Kinney, G. G.; Pettibone, D. J.; Tiller, P. R.; Smith, S.; Duggan, M. E.; Hartman, G. D.; Conn, P. J.; Huff, J. R. *J. Med. Chem.* **2004**, *47*, 5825; (b) Kinney, G. G.; O'Brien, J. A.; Lemaire, W.; Burno, M.; Bickel, D. J.; Clements, M. K.; Chen, T.-B.; Wisnoski, D. D.; Lindsley, C. W.; Tiller, P. R.; Smith, S.; Jacobson, M. A.; Sur, C.; Duggan, M. E.; Pettibone, D. J.; Conn, P. J.; Williams, D. L. *J. Pharmacol. Exp. Ther.* **2005**, *313*, 199; (c) Chen, Y.; Nong, Y.;

Goudet, C.; Hemstapat, K.; de Paulis, T.; Pin, J. P.; Conn, P. J. *Mol. Pharmacol.* **2007**, *71*, 1389.
16. (a) Bessis, A.-S.; Bonnet, B.; Le Poul, E.; Rocher, J.-P.; Epping-Jordan, M. P. PCT Pat. Appl. WO 2005/044797, 2005.; (b) Epping-Jordan, M. P.; Nayak, S.; Derouet, F.; Dominguez, H.; Bessis, A. S.; Le Poul, E.; Ludwig, B. L.; Mutel, V.; Poli, S. M.; Rocher, J. P. *Neuropharmacology* **2005**, *49*, 231; (c) Engers, D. W.; Rodriguez, A. L.; Williams, R.; Hammond, A. S.; Venable, D.; Oluwatola, O.; Sulikowski, G. A.; Conn, P. J.; Lindsley, C. W. *Chem. Med. Chem.* **2009**, *4*, 505.
17. (a) Lamb, J. P.; Engers, D. W.; Niswender, C. M.; Rodriguez, A. L.; Venable, D. F.; Conn, P. J.; Lindsley, C. W. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2711; Zou, M.-F.; Cao, J.; Rodriguez, A. L.; Conn, P. J.; Newman, A. H. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2650; (c) Williams, R.; Manka, J. T.; Rodriguez, A. L.; Vinson, P. N.; Niswender, C. M.; Weaver, C. D.; Jones, C. D.; Conn, P. J.; Lindsley, C. W.; Stauffer, S. R. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1350; (d) Zhou, Y.; Manka, J. T.; Rodriguez, A. L.; Weaver, C. D.; Days, E. L.; Vinson, P. N.; Jadhav, S.; Hermann, E. J.; Jones, C. K.; Conn, P. J.; Lindsley, C. W.; Stauffer, S. R. *ACS Med. Chem. Lett.* **2010**, *1*, 433; (e) Engers, D. W.; Rodriguez, A. L.; Williams, R.; Hammond, A. S.; Venable, D.; Oluwatola, O.; Sulikowski, G. A.; Conn, P. J.; Lindsley, C. W. *ChemMedChem* **2009**, *4*, 505; (f) Sharma, S.; Kedrowski, J.; Rook, J. M.; Smith, R. L.; Jones, C. K.; Rodriguez, A. L.; Conn, P. J.; Lindsley, C. W. *J. Med. Chem.* **2009**, *52*, 4103.
18. (a) Xiong, H.; Brugel, T. A.; Balestra, M.; Brown, D. G.; Brush, K. A.; Hightower, C.; Hinkley, L.; Hoesch, V.; Kang, J.; Koether, G. M.; McCauley, J. P., Jr.; McLaren, F. M.; Panko, L. M.; Simpson, T. R.; Smith, R. W.; Woods, J. M.; Brockel, B.; Chhajlani, V.; Gadient, R. A.; Spear, N.; Sygowski, L. A.; Zhang, M.; Arora, J.; Breysse, N.; Wilson, J. M.; Isaac, M.; Slassi, A.; King, M. M. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 7381; (b) Varnes, J. G.; Marcus, A. P.; Mauger, R. C.; Throner, S. C.; Hoesch, V.; King, M. M.; Wang, X.; Sygowski, L. A.; Spear, N.; Gadient, R.; Brown, D. G.; Campbell, J. B. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 1402; (c) Spear, N.; Gadient, R. A.; Wilkins, D. E.; Do, M.; Smith, J. S.; Zeller, K. L.; Schroeder, P.; Zhang, M.; Arora, J.; Chhajlani, V. *Eur. J. Pharm.* **2011**, *659*, 146.
19. (a) Ritzen, A.; Mathiesen, J. M.; Thomsen, C. *Basic Clin. Pharmacol. Toxicol.* **2005**, *97*, 202; (b) Ritzén, A.; Sindet, R.; Hentzer, M.; Svendsen, N.; Brodbeck, R. M.; Bundgaard, C. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3275; (c) Sams, A. G.; Mikkelsen, G. K.; Brodbeck, R. M.; Pu, X.; Ritzén, A. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 3407; (d) Packiarajan, M.; Ferreira, C. G.-M.; Hong, S-P.; White, A. D.; Chandrasena, G.; Pu, X.; Brodbeck, R. M.; Robichaud, A. J. *Bioorg. Med. Chem. Lett.* **2012**, *22*, 5658.
20. (a) Brenda Pipik, B.; Ho, G.-J.; Williams, M.; Conlon, D. A. *Synth. Commun.* **2004**, *34*, 186; (b) Ester Muraglia, E.; Altamura, S.; Branca, D.; Cecchetti, O.; Ferrigno, F.; Orsale, M. V.; Palumbi, M. C.; Rowley, M.; Scarpelli, R.; Steinkühler, C.; Jones, P. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6083.
21. Recombinant HEK293 cell lines co-expressing human mGluR5 were plated at a seeding density of 2×10^4 cells/well in clear bottomed, poly D-lysine coated 384 well plates (Greiner). After overnight incubation in glutamate/glutamine-free medium at 37 °C in an atmosphere of 95% O_2/5% CO_2, cells were loaded with calcium dye (calcium 5 assay kit, molecular devices) containing 3 U/ml of glutamic pyruvic transaminase and 3 mM sodium pyruvate, at 37 °C for 1 h. Positive allosteric modulator (*PAM*) activity was assessed by measuring potentiation of the EC_{20} response to L-glutamate in the presence of test compound. Positive modulator activity was calculated from the fluorescence max to min data normalized to yield responses for no modulation (EC_{20} response) and full stimulation (1 mM L-glutamate) as 0% and 100% modulation, respectively. Concentration–response data were fitted to the four parameter logistic equation to estimate compound potency (EC_{50}) and efficacy (E_{max}). *NAM* activity was assessed by measuring a concentration dependent inhibition of the EC_{80} response to L-glutamate in the presence of test compound.
22. The solubility (μM) was measured from DMSO stock solution of the test compound (300 μL) diluted with 2×200μL, 25 mM potassium phosphate buffer in a titer plate shaker at a speed of 1.8 for 4 h. The supernatant was analyzed by waters acquity UPLC system (column: acquity UPLC BEH C-18, 1.7 μm 2.1 × 50 mm column and PDA detector at 254 nm for quantification) with a gradient (mobile phase A: 2% (w/v) ammonium formate and 20% acetonitrile in water, mobile phase B: 100% acetonitrile) for 2 min.
23. Obach, R. S.; Baxter, J. G.; Liston, T. E.; Silber, B. M.; Jones, B. C.; Macintyre, F.; Rance, D. J.; Wastall, P. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 46. The rat and human maximum liver blood flow corresponds to 20 mL/min and 1.5 L/min, respectively.
24. Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Disc.* **2007**, *6*, 881.
25. A single dose brain and plasma PK of compounds **13n** and **17c** were assessed at 10 mg/kg, po dose in two animals at 1 h. The plasma concentrations were determined using a tandem Agilent 1100 HPLC (Agilent Technologies, Palo Alto, CA) and a TSQ Quantum MS (Thermo Finnigan, San Jose, CA) with Xcalibur software and averaged values are shown. Compound limit of quantification (LOQ) in the brain homogenate and plasma was 2 and 10 ng/mL respectively.