Bioorganic & Medicinal Chemistry Letters 23 (2013) 2134–2139

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry Letters

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

Discovery of biological evaluation of pyrazole/imidazole amides as mGlu5 receptor negative allosteric modulators

Eunhee Chae *, Yong-Je Shin, Eun-Ju Ryu, Mi Kyung Ji, Nahm Ryune Cho, Ki-Ho Lee, Hyun Ji Jeong, Soo-Jin Kim, Yeonjung Choi, Kyung Seok Oh, Chun-Eung Park, Young Soo Yoon

CNS Drug Discovery, Drug Development Center, SK Biopharmaceuticals, Daejeon 305-712, Republic of Korea

ARTICLE INFO

Article history:
Received 25 November 2012
Revised 23 January 2013
Accepted 24 January 2013
Available online 4 February 2013

Keywords:
Ligand-lipophilic efficiency (LipE)
Metabotropic glutamate receptor 5 (mGluR5)
Negative allosteric modulators
Antidepressant
Pyrazole amide
Imidazole amide

ABSTRACT

Development of SAR in a 5-aryl-3-acylpyridinyl-pyrazoles and 1-aryl-4-acylpyridinyl imidazoles series of mGlu5 receptor negative allosteric modulators (mGluR5 NAMs) using a functional cell-based assay is described in this Letter. Analysis of the Ligand-lipophilic efficiency (LipE) of compounds provided new insight for the design of potent mGluR5 negative allosteric modulators with anti-depressant activities.

The metabotropic glutamate receptors (mGluRs) are members of the GPCR-C family and classified into Group I (mGlu1 and mGlu5), Group II (mGlu2 and mGlu3), or Group III (mGlu4, 6, 7, 8). All mGlu receptors have allosteric binding sites which are topologically distinct and less conserved within the subtypes in comparision to glutamate (orthosteric) binding sites.[1] Beyond the classical approach targeting the orthosteric binding site of these receptors, the development of allosteric modulators represents an emerging class of orally available small molecules offering greater selectivity and better modulatory control at disease mediating receptors.[2] In recent years, a number of mGluR5 negative allosteric modulators (NAMs) have reported positive data from clinical studies in psychiatric disorders such as anxiety, depression, pain, migraine, drug abuse and addiction.[3] Since the discovery of the diarylalkynes MPEP, many alkyne-based mGluR5 NAMs have been developed as illustrated in Figure 1. Also, bioisosteric replacement of the ethynyl bond, which keeps the molecular topology and the established SAR within the alkyne series, have been published in recent reviews.[4]

We conducted a high-throughput screening (HTS) with a FLIPR Ca^{2+} mobilization assay in a human mGluR5/HEK293 to find novel mGluR5 NAMs lacking the alkyne moiety which might be relevant to chemical or metabolic liability as reported in the case of ADX10059.[5] With an IC_{50} of 373 nM, 5, 6-dihydro-4*H*-cyclopenta [*d*]isoxazole-3-carboxylic acid (5-chloro-2-hydroxy-phenyl)-amide (HTS hit 1, Fig. 2) was identified as a potential starting point. Conceptually, this scaffold is related to previously reported scaffolds as exemplified in Carboxamide A[6] (Fig. 1). So we could easily perform a preliminary SAR (structure–activity relationship) as described in Figure 2.

Based on prior SAR knowledge for mGluR5 NAMs, the initial focus was centered on a 3-chlorophenyl derivative (**2**), which resulted in the desired direction as demonstrated for *meta*-substitution preference on aryl group in the previous literatures.[3,4] Also, amide N–H is thought to be a key part to target potencies of this series as depicted in compounds **3** and **3a**.[7] It might be a pharmacophoric feature in which a conformational lock is provided by intramolecular hydrogen bonds between proximal amide NH and nitrogen on the pyrazole ring as shown in compound **3**.[8] Compound **4** proved to be inactive and it was assumed that it could not participate in an intramolecular hydrogen bonding interaction or insufficient hydrophobic interaction between target and aromatic ring due to its appropriately constrained structure whereas compound **5** had moderate in vitro potency. Unfortunately, compound **5** was very unstable in rat plasma ($T_{1/2}$ <1 h) and it prompted us to investigate factors that increase in plasma stability, which resulted in compound **6**. The improved rat plasma stability in compound **6** ($T_{1/2}$ >3 h) may stem from steric occlusion of the potentially hydrolysable amide linkage.[9] Furthermore, the introduction of methyl group on the pyrazole ring of compound **6** offered additional beneficial effect in terms of mGluR5 target

* Corresponding author.
E-mail address: Eunhee.chae@sk.com (E. Chae).

0960-894X/$ - see front matter © 2013 Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.bmcl.2013.01.116

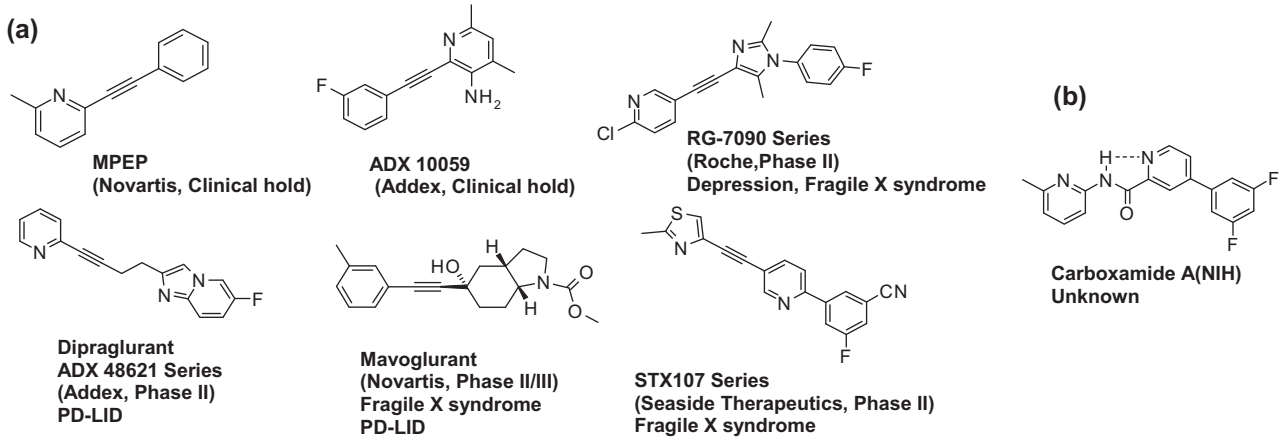


Figure 1. (a) mGluR5 NAMs structural template, (b) a structure of carboxamide A.

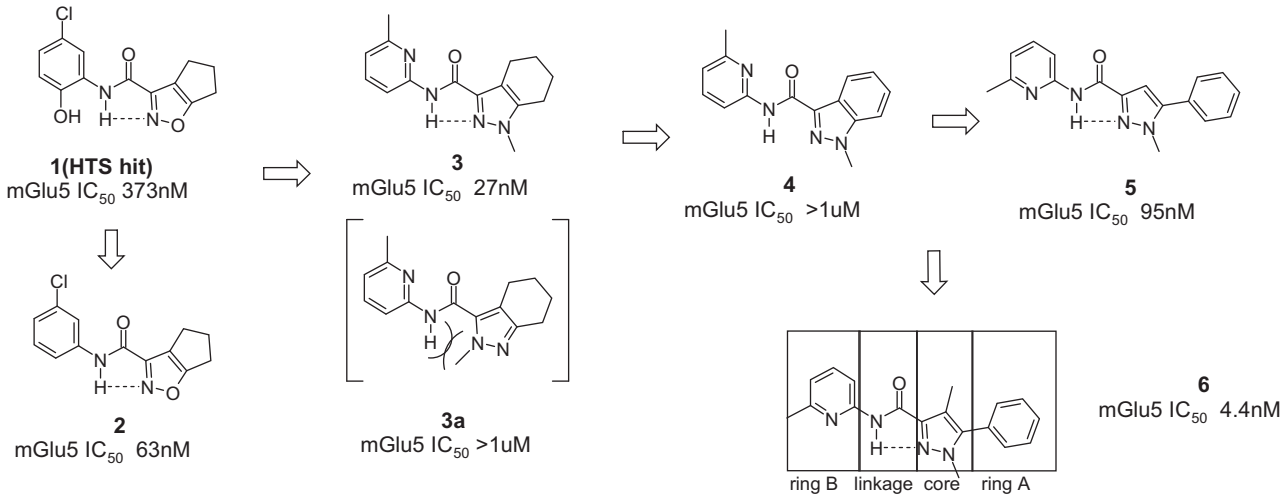


Figure 2. Preliminary exploration from HTS hit **1** to compound **6**.

potency. A pharmacophoric overlay of compound **6** and references (MPEP, RG-7090 series[10] and Carboxamide A[6] in Fig. 3) demonstrated that there is a remarkable similarity between references and compound **6**. In addition, ring A segment of compound **6** is able to mimic in those of RG-7090 series with slightly torsional changes.

Before starting an investment of chemical resources on this template, its overall selectivity profile was checked. Compound **6** was profiled against a battery of in vitro assays including human mGluR1 at the compound concentration of 10 μM. Of 11 receptors screened (Ricerca Biosciences),[11] only weak, but detectable activity

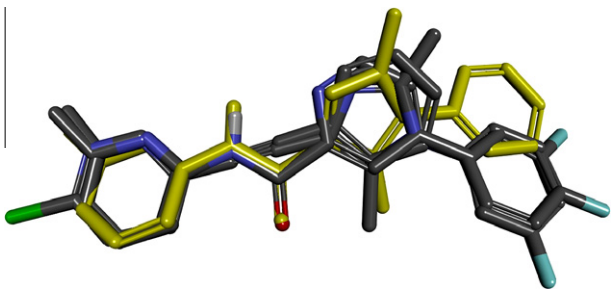
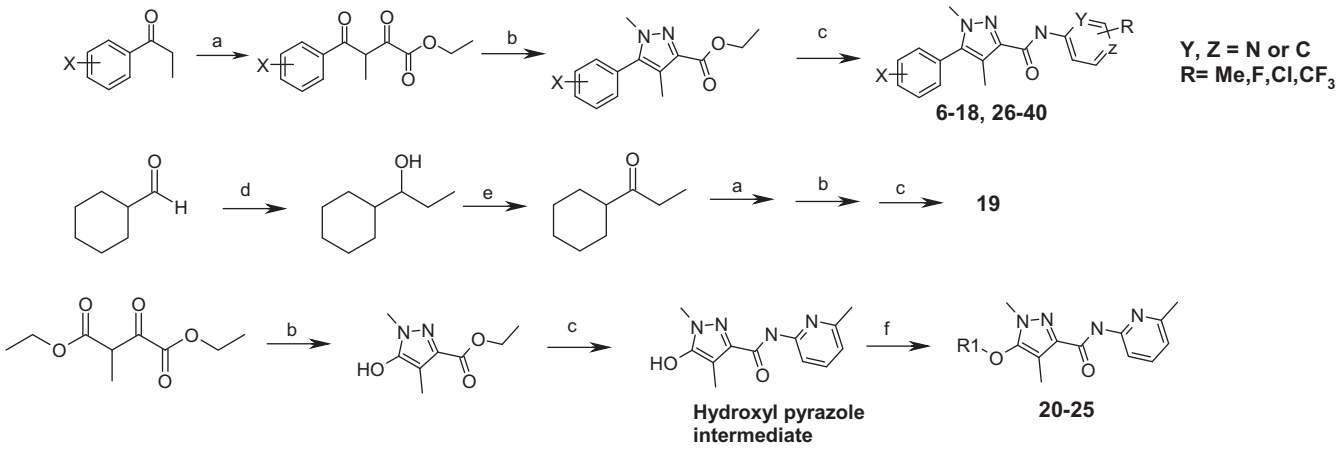


Figure 3. Pharmacophoric alignment with references and compound **6** (Compound **6** is shown in yellow color; references in grey; oxygen in red, nitrogen in blue; chlorine in green, fluorine in turquoise blue).

at the $5HT_{2C}$, dopamine re-uptake transporter (DAT) and noradrenaline re-uptake transporter (NET) (66%, 60% and 63% inh@10 μM, respectively). In order to deliver a candidate compound suitable for in vivo investigation, it was thought to be crucial to balance target potency and lipophilicity. Over the past few years, lipophilic ligand efficiency (LLE or LipE, defined as $p\mathrm{IC}_{50}$–$c\mathrm{Log}P$) concept which correlates potency and lipophilicity has been utilized by medicinal chemists to retrospectively evaluate compounds potencies to properties.[12] LipE is increased when the $p\mathrm{IC}_{50}$ is increased by more than the increase in $c\mathrm{Log}P$. This value of $c\mathrm{Log}P$ is often consistent with reasonable in vivo clearance, solubility and protein binding. An important point to note from LipE concept is that having a design strategy targeting increased LipE values in a series often encounters compounds which have high metabolic clearance even at lower lipophilicity. Thus, we focused a strategy on maximizing LipE values and improving the metabolic stability. These considerations, together with the structural diversity of compound **6** (Three sites of diversity; ring A, B and core ring) encouraged us to consider this series for further development.

The synthesis of this class of compounds was straightforward as shown in Scheme 1. The pyrazole analogs were started with various propiophenones via Claisen condensation to give the corresponding diketo esters. Following cyclization with hydrazine derivatives afforded the corresponding 3-substituted-pyrazole-5-carboxylic acid ethyl esters. Almost all of esters were treated with various anilines in the presence of $AlMe_3$ (2 M solution in



Scheme 1. General preparation of pyrazole analogs. Reagents and conditions: (a) EtO_2CCO_2Et, LiHMDS, THF, −78 °C or EtO_2CCO_2Et, Na, EtOH, −78 °C, 75–83%; (b) MeN–NH_2, acetic acid, EtOH, rt, 80%; (c) $AlMe_3$(2 M solution in toluene), dioxane, 110 °C, various anilines, 20–45%; (d) CH_3CH_2MgBr, THF, −78 °C to rt, 58%; (e) pyridium chlorochromate, CH_2Cl_2, 80%; (f) K_2CO_3, KI, CH_3CN/DMF, R_1Br, reflux or microwave, 100 °C, 10 min, 24–56%.

toluene) to produce their corresponding amides. For the synthesis of the compounds **20–25**, diethyl oxalpropionate with methyl hydrazine were preferably irradiated quickly in a microwave reactor to produce intermediate which was converted to hydroxyl pyrazole. Subsequently, coupling of hyrdoxyl pyrazole with various partners (R_1–X) afforded the target compounds (**20–25**).

Replacement of the amide moiety of compound 6 with –CH_2O–,–CH_2N–, –NC═O–, –NC═ON– produced no active compounds (data not shown). Furthermore, the upper methyl group on the pyrazole ring thought to be optimal for receptor interaction from the result that the larger group such as ethyl, propyl and phenyl group resulted in loss of potency (IC_{50}: 27 nM, 37% inh@2 μM, 26% inh@10 μM, respectively). All functional activities were measured by the ability of the compound to inhibit calcium mobilization caused by an EC_{80} concentration of glutamate in HEK293 cells expressing the human mGlu5 receptor using MTEP as a reference compound.[13]

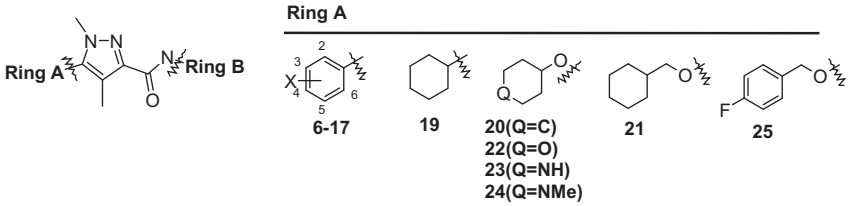
It was observed that ring A analogs yielded comparatively active antagonists as highlighted by the 4-fluoro analog **7**, which is the most potent mGlu5 receptor antagonist (IC_{50} = 1.1 nM) having the highest LipE (6.28) in the series. Small lipophilic substituents (e.g., F, Cl and Me) are more preferred with no dependency on their electronic properties while a larger group such as $N(CH_3)_2$ was not favored for functional potency. Reduction of the aryl ring of compound **6** to cyclohexyl ring analog **19** did not significantly alter affinity. However, oxygen linked compounds **20–25** failed to furnish potent antagonists. Likewise, insertion of one methylene linker into the compound **7** provided analog **25**, which led to a reduction of target potency. In addition, an analog removing aromatic ring had almost no efficacy at the mGluR5 receptor (compound not shown). From these observations, it was hypothesized that a well restrict phenyl group may occupy a hydrophobic pocket in the mGluR5 binding site with a very limited tolerance in this region of the receptor.

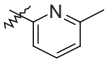
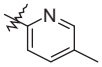
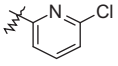
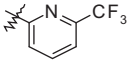
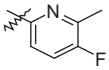
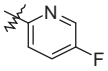
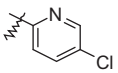
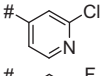
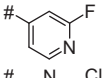
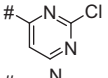
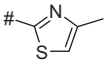
Our initial focus during hit evaluation was also to assess whether the metabolic stability could be increased within this class of compounds while maintaining potency. Aromatic substituents at *para* position on ring A had slight effect on the metabolic stability, which demonstrated that oxidation occurred on aromatic ring A. It was observed that the introduction of an electron withdrawing group such as Cl and CF_3 may help to stabilize the electronic rich phenyl group, thereby improving metabolic stability (**8, 13, 15**). Many of analogs we prepared showed high functional potencies for the mGlu5 receptor and interestingly these analogs proved to be much more stable in the presence of human liver microsomes (HLM) with the exception of di-substituted fluorine analogs (**10–12**). Since our in vivo models are rodent based, we hoped to increase the stability of these molecules to both MLM and RLM by blocking the metabolic sites. Having the optimal substituent as 4-fluoro, we quickly optimized ring B. In terms of target potency, altering the position of the methyl group of compound **7** was still tolerated in potency exemplified in **26** and **27**, whereas it is not the same case in the thiazole ring (**39** and **40**). The metabolic blocking effects were observed in both electron withdrawing group (EWG) and electron donating group (EDG) substituted analogs. However, the magnitude was greater in analogs having EWG in either *meta* or *para* position in all species (**28, 29, 32, 33, 36, and 37**) whereas analogs having EDG such as methyl group did not exert metabolic improvement, which assumed to be involved methyl hydroxylation (**26, 27, and 35**). The most pronounced effect was found in pyrimidine analog **38**, which potentially improved metabolic stabilities in all species. It was thought that as the number of nitrogen atom in the ring increases, the pi-electrons of ring become less energetic, which led to less N-oxidation in pyrimidine ring. At this point, it appeared that the strategy of both blocking metabolic sites and introduction of EWG on ring B through modification of ring A and B would deliver a compound with the desired balance of properties. However, in conjunction with LipE values, it indicated that the introduction of halogens to block metabolic sites had impact for improving the metabolic stability but it rendered compounds having greater *c*Log*P* than the corresponding unsubstituted analog, bringing the lipophilicity higher and LipE values lower.

Next, we investigated core modifications using the preferred aromatic substitution pattern both in ring A and B on the basis of the result of Table 1. The preparation of the imidazole analogs **41–53** is depicted in Scheme 2. The commercially available oxo-esters were reacted with sodium nitrite ($NaNO_2$) to furnish the oximes. Subsequent catalytic reductive acetylation with acetic anhydride afforded the crude compounds, which were cycloaromatized with various anilines in acetonitrile under microwave irradiation to obtain the corresponding imidazole esters. The target compounds **41–53** were obtained from via amidation reactions in the presence of coupling reagent $AlMe_3$ as the same as described in the synthesis of pyrazole analogs.[14]

Representative examples in imidazole analogs are shown in Table 2. Imidazole core replacement rendered compounds **41**–**53**, which were generally less potent than pyrazoles and had a *c*Log*P* values greater than 0.5 unit higher than the corresponding pyrazole analogs, bringing the LipE values lower. The microsomal

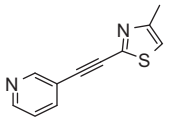
Table 1
Structure–activity relationships for pyrazole analogs **6–40**



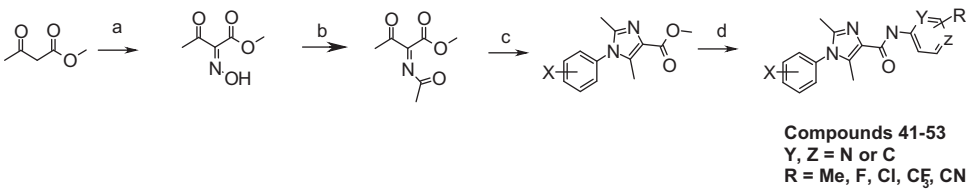
Compound	Ring A	Ring B	mGlu5[a] IC_{50} (nM)	*c*Log*P*[b]	LipE[c]	Metabolic stability $T_{1/2}$ (min)		
						Mice	Rat	Human
6	H		4.4	2.53	6.28	18	34	66
7	4-F		1.1	2.68	5.17	36	56	82
8	4-Cl		3.8	3.25	5.08	64	87	128
9	3-Cl		4.7	3.25	5.62	32	55	122
10	3,4 F_2		4.3	2.75	5.61	42	149	46
11	2,4 F_2		3.7	2.82	4.20	38	76	67
12	3,5 F_2		5.3	2.82	4.80	18	64	32
13	3,4 Cl_2		2.3	3.84	5.25	195	148	107
14	4-Me		5.3	3.03	3.99	45	22	118
15	4-CF_3		38	3.42	5.31	194	>300	>300
16	4-OMe		17	2.46	3.49	71	95	>300
17	4-$N(Me)_2$		645	2.70	6.10			
18	4-Pyridyl		71	1.05	4.52	8	37	42
19	See diagram		25	3.08	4.38	28	8	83
20	See diagram		92	2.66				
21	See diagram		1.3 μM					
22	See diagram		11.6% inh@1 μM					
23	See diagram		5.6% inh@2 μM					
24	See diagram		−7.7% inh@1 μM					
25	See diagram		911	2.54	3.50			
26	4-F		90.8	2.68	4.36	13	67	26
27	4-F		82.3	2.68	4.40	10	119	91
28	4-F		16.4	2.93	4.86	116	108	115
29	4-F		130	3.19	3.69	98	58	269
30	4-F		28	2.86	4.69	99	166	213
31	4-F		195	2.93	3.81	24	143	126
32	4-F		10.3	2.36	5.63	39	>300	>300
33	4-F		184	2.93	3.78	16	219	>300
34	4-F		300.5	2.18	4.34			
35	4-F		94.5	2.68	4.34	84	76	77
36	4-F		56.3	2.93	4.32	>300	161	>300
37	4-F		41.6	2.36	5.02	>300	114	>300
38	4-F		7.1	2.17	5.98	>300	>300	>300
39	4-F		16.4	2.76	5.03	45	61	122

(*continued on next page*)

Table 1 (*continued*)

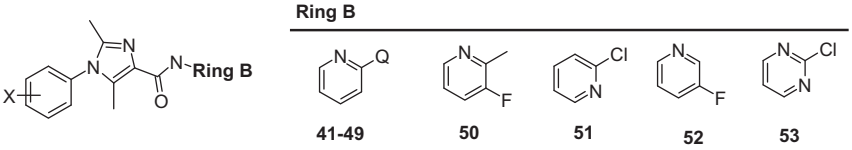
Compound	Ring A	Ring B	mGlu5[a] IC_{50} (nM)	*c*Log*P*[b]	LipE[c]	Metabolic stability $T_{1/2}$ (min)		
						Mice	Rat	Human
40	4-F		2700	2.76				
MTE			12	2.12	5.80	13	60	108

[a] mGluR5 assay data are presented as % inhibition at remarked concentration or IC_{50}. Assay reproducibility was monitored by the use of the mGlu5 negative modulator MTEP (IC_{50} = 12 ± 5 nM).
[b] *c*Log*P* was calculated using ChemBioDraw Ultra version 12.0.
[c] Ligand-lipophilicity efficiency (LipE) = pIC_{50}–*c*Log*P*.



Scheme 2. General preparation of imidazole analogs. Reagents and conditions: (a) $NaNO_2$, H_2O, 4 °C, 2 h, 68%; (b) H_2, Pd/C, 1 atm, Ac_2O, rt, 20 h, 51%; (c) various anilines, TFA, acetonitrile, microwave, 140 °C, 45 min (30–42%); (d) $AlMe_3$ (2 M solution in toluene), dioxane, 110 °C, various anilines, 20–45%.

Table 2
Structure–activity relationships for imidazole analogs **41**–**53**



Compound	X	Ring B	mGlu5[a] IC_{50} (nM)	*c*Log*P*[b]	LipE[c]	Metabolic stability $T_{1/2}$(min)		
						Mice	Rat	Human
41	4-F	Q = Me	13	3.17	4.72	18	106	44
42	3,4-Cl_2		5.8	4.34	3.90	93	134	122
43	3-Cl,4-F		14.5	3.89	3.95	70	87	76
44	4-OMe		147	3.02	3.40			
45	4-CF_3		46.2	3.94	3.40	>300	>300	>300
46	4-Cl		17.1	3.74	4.03	81	59	54
47	4-F	Q = F	24.2	2.86	4.76	37	68	96
48		Q = CF_3	173	3.64	3.12	158	72	196
49		Q = CN	77	2.42	4.69			
50		See diagram	139	3.36	3.50	86	44	60
51		See diagram	62	3.43	3.78	300	94	225
52		See diagram	88.3	2.86	4.19	32	110	>300
53		See diagram	40.4	2.57	4.82	278	165	283

[a] mGlu5 assay data are presented as% inhibition at remarked concentration or IC_{50}. Assay reproducibility was monitored by the use of the mGlu5 negative modulator MTEP (IC_{50} = 12 ± 5 nM).
[b] *c*Log*P* was calculated using ChemBioDraw Ultra version 12.0.
[c] Ligand-lipophilicity efficiency (LipE) = pIC_{50}–*c*Log*P*.

stability pattern is similar to those of pyrazoles. Given the high functional potency of some analogs, we were interested to see if this would translate into in vivo efficacy. To evaluate antidepressant activity of the interesting compounds, several analogs were chosen based on the outcomes of LipE values, target potencies and metabolic stabilities. Antidepressant activity was assessed as percentage decrease in immobility duration in the forced swimming test (FST) and data has been presented as mean ± SEM. The obtained data on the antidepressant activity of the compounds and references (MTEP, ADX48621 series[15]) are given in Table 3. Majority of the synthesized compounds exhibited considerable antidepressant potential as evident from their% decrease of immobility duration values whereas our references was found to be less active than our analogues. Compound **6** was virtually not active at the dose of 10 mg/kg due to low metabolic stability in mice (MLM stability $T_{1/2}$: 18 min), despite its high LipE value. And compound **15** having low LipE value showed weak in vivo efficacy even it had high metabolic stability in mice. Therefore, compounds with low metabolic stabilities and low LipE's were not screened in vivo test. The representative compound 7 in the pyrazole

Table 3
Anti-depressant activities of selected analogs

Compound	mGlu5 IC_{50} (nM)	m-FST [a]
		% Decrease in immobility duration at 10 mg/kg(p.o.)
6	4.4	(53.3 ± 21.5*50 mg/kg, p.o.)
7	1.1	61.1 ± 10.6%*
8	3.8	51.4 ± 8.1%*
10	4.3	58.8 ± 13.7%*
11	3.7	25.7 ± 6.6%*
13	2.3	45.8 ± 7.3%*
14	5.3	30.8 ± 13.4%*
15	38	18.5 ± 6.4*
16	17	14.4 ± 3.4%
28	16.4	12.6 ± 6.2%
32	10.3	36.8 ± 7.1%*
36	56.3	39.1 ± 13.4%*
37	41.6	15.5 ± 6.0%*
38	7.1	31.2 ± 10.0%*
39	16.4	32.8 ± 3.4%*
41	13	52.1 ± 11.8%*
42	5.8	85.2 ± 31.4%*
53	40.4	65.3 ± 17.1%*
MTEP	12	14.0 ± 4.8%
ADX48621 series[b]	20	(44.3 ± 12.2*50 mg/kg, p.o.)

[a] Drugs(10 mg/kg, p.o.) were administered to ICR mice 1 h before the test, and the duration of immobility was measured during 4 min following training for 2 min. Data was expressed in mean ± SEM ($n = 8$) and analyzed by Dunnett's multiple comparisons following one-way ANOVA(*p <0.05).

[b] 6-Fluoro-2-[4-(pyridin-2-yl)but-3-yn-1-yl]imidazo[1,2-*a*]pyridine as shown in Figure 1.

analogues showed potent in vivo efficacy in animal model, which was found to decrease immobility duration as high as 61.1 ± 10.6%. To distinguish antidepressant effect from hyperactivity of animals, compound 7 was conducted in locomotor activity tests in mice. When the compound **7** was administrated intraperitoneally (ip), it showed hypoactivity at a dose range from 1 mg/kg to 30 mg/kg. Therefore, the efficacy in immobility of compound 7 (ED_{50} = 1.1 mg/kg, ip) was not caused by hyperactivity of animal indicating that the locomotor activity fell within the normal range. However, compound **7** demonstrated from moderate bioavailability in mice (F = 31%) to poor in rat (F < 2%). It is likely that its poor solubility (vehicle: 5% DMSO + 5% Cremophore) resulted in insufficient oral exposure especially in rats, which was in agreement with weak activity in rats (10.9%∗ at the dose of 10 mg/kg, ip) against the forced swimming test.

For comparision with pyrazole analogs, imidazole analogues (**41**, 42 and **53**) were chosen and evaluated. The antidepressant efficacy of compound **42** proved to be caused by hyperactivity, that is, false positive results. On the other hand, compound **41** and **53** showed potent antidepressant efficacy without hyperactivities. Taken LipE values and metabolic profiles, compound **53** was further evaluated. Contrary to compound **7**, compound **53** also showed statistically significant efficacious activity in rats with MEDs of 1 mg/kg after oral administration in the forced swimming test. It assumed that imidazole analogs were seemingly more soluble than pyrazoles in our test vehicle, which may contribute to efficacies in rats. In addition, compound **53** showed no appreciable inhibition against CYP1A2, CYP2D6, CYP 2C9, CY2C19 and CYP3A4 at 10 μM and were highly stable in human hepatocytes (Cl_{int} 0.99 μL/min/10^6 cells). The activity of compound **53** in the hERG potassium channel assay was determined to be low (13% at 10 μM) and displayed selectivity over mGluR1 receptor (10% inhibition at 10 μM). A single dose-exposure study in Sprague–Dawley rats revealed that 1 h after an intraperitoneally at a dose of 10 mg/kg, they had moderate plasma and brain concentrations, and a brain/plasma ratio of 1.63 ± 0.39.

In summary, we report a new series of mGluR5 antagonists identified through HTS hit. During preliminary hit-to-lead, the representative pyrazole and imidazole amides have been described and evaluated by monitoring LipE's. In vitro functional potencies were correlated well with our series and their SAR was found to be tractable and majority of the synthesized compounds exhibited considerable anti-depressant potential. However, despite controlled LipE values, some analogs showed weak activities in vivo model, which emphasizes on the importance of initial evaluations of other parameters such as aqueous solubility,metabolic stability, PK/exposure as well as LipE.[16] The continued optimization of this series of mGluR5 NAMs will be to improve physicochemical property by further modification of structural features and will be presented in due course.

References and notes

1. (a) Foord, S. M.; Bonner, T. I.; Neubig, R. R.; Rosser, E. M.; Pin, J. P.; Davenport, A. P.; Spedding, M.; Harmar, A. J. *Pharmacol. Rev.* **2005**, *57*, 279; (b) Behan, D. P.; Chalmers, D. T. *Nat. Rev. Drug Disc.* **2002**, *1*, 599; (c) Topiol, S.; Sabio, M.; Uberti, M. *Neuropharmacology* **2011**, *60*, 93.
2. (a) Kenakin, T. *Trends Pharmacol. Sci.* **2007**, *28*, 407; (b) Christopoulos, A.; Kenakin, T. *Pharmacol. Rev.* **2002**, *54*, 323.
3. (a) Rocher, J. P.; Bonnet, B.; Bolea, C.; Lutjens, R.; Le Poul, E.; Poli, S.; Epping-Jordan, M.; Bessis, A. S.; Ludwig, B.; Mutel, V. *Curr. Top. Med. Chem.* **2011**, *11*, 680; (b) Emmitte, K. A. *ACS Chem. Neurosci.* **2011**, *2*, 411; (c) Chaki, S. *Neuropharmacology* **2013**, *66*, 40; (d) Conn, P. J.; Christopoulos, A.; Lindsley, C. W. *Nat. Rev. Drug Disc.* **2009**, *8*, 41.
4. (a) Burdi, D. F.; Hunt, R.; Fan, L.; Hu, T.; Wang, J.; Guo, Z.; Huang, Z.; Wu, C.; Hardy, L.; Detheux, M.; Orsini, M. A.; Quinton, M. S.; Lew, R.; Spear, K. Y. *J. Med. Chem.* **2010**, *53*, 7107; (b) Lindsley, C. W.; Bates, B. S.; Menon, U. N.; Jadhav, S. B.; Kane, A. S.; Jones, C. K.; Rodriguez, A. L.; Conn, P. J.; Olsen, C. M.; Winder, D. G.; Emmitte, K. A. *ACS Chem. Neurosci.* **2011**, *2*, 471.
5. Development of ADX10059 ended for long-term use. http://www.addexpharma.com/press-releases/press-release-details/article/development-of-adx10059-ended-for-long-term-use/ accessed on October 15, 2010.
6. (a) Newman, A. H. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 2074; (b) WO2008092072.
7. These structures (**3** and **3a**) could be identified by ^{1}H NMR and 2D–^{1}H/^{13}C NMR (HMBC, Hetero nuclear Multiple Bond Correlation). ^{1}H–HMC correlates chemical shifts of protons with carbons separated with two or three bonds. (Compound **3a**: Hydrogen of methyl group on the pyrazole ring crosspeaks with adjacent quaternary and carbonyl carbons, whereas compound **3** displayed the absence of crosspeaks with two carbons).
8. Bonnefous, C.; Vernier, J. M.; Hutchinson, J. H.; Chung, J.; Reyes-Manalo, G.; Kamenecka, T. *Bioorg. Med. Chem. Lett.* **2005**, *15*, 1197.
9. Kerns, E. H; Di, L. In *Drug-Like Properties: Concepts, Structure Design and Methods: from ADME to Toxicity Optimization*; Academic Press: Burlington, Massachusetts, 2008. Chapter 12.

[10]. For information, we refer to following patents (WO2005118568, WO2009024491).

11. Compound **6** has no significant off-target effect regarding to following 11 targets at 10 μM; Monoamine oxidase A, B, adenosine A_{2A}, adrenergic α_{1D}, histamine H_1, muscarinic M_1, M_2, 5-HT_{2C}, transporter for dopamine, norepinephrine, serotonin (DAT, NET, SERT, respectively).
12. (a) Leeson, P. D.; Springthorpe, B. *Nat. Rev. Drug Disc.* **2007**, *6*, 881; (b) Ryckmans, T.; Edwards, M. P.; Horne, V. A.; MonicaCorreia, A.; Owen, D. R.; Thompson, L. R.; Tran, I.; Tutt, M. F.; Young, T. *Bioorg. Med. Chem. Lett.* **2009**, *15*, 4406; (c) Edwards, M. P.; Price, D. A. *Annu. Rep. Med. Chem.* **2010**, *45*, 381; (d) Bembenek, S. D.; Tounge, B. A.; Reynolds, C. H. *Drug Discovery Today* **2009**, *14*, 278; (e) BemHopkins, A. L. *Drug Discovery Today* **2004**, *9*, 430.
13. O'Brian, J.; Lemaire, W.; Chen, T. B.; Chang, R.; Jacobson, M.; Ha, S.; Lindsley, C.; Schaffhauser, H.; Sur, C.; Pettibone, D.; Conn, P.; Williams, D. *Mol. Pharmacol.* **2003**, *64*, 731.
14. Lange, J. H. *Bioorg. Med. Chem. Lett.* **2010**, *1084*, 20. For the synthesis of pyrazole analogs and imidazole analogs, we refer to the following patents (WO2001029007, WO2006087355, respectively).
15. For information, we refer to a following patent (WO2005123703)
16. Gilbert, A. M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 195.