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Discovery and SAR of novel mGluR5 non-competitive antagonists not based on an MPEP chemotype

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ABSTRACT

This Letter describes the discovery and SAR of three novel series of mGluR5 non-competitive antagonists/negative allosteric modulators (NAMs) not based on manipulation of an MPEP/MTEP chemotype. This work demonstrates fundamentally new mGluR5 NAM chemotypes with submicromolar potencies, and the first example of a mode of pharmacology 'switch' to provide PAMs with a non-MPEP scaffold.

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Glutamate is the major excitatory transmitter in the central nervous system, exerting its effects through both ionotropic and metabotropic glutamate receptors. The metabotropic glutamate receptors (mGluRs) are members of the GPCR family C, characterized by a large extracellular amino-terminal agonist binding domain. To date, eight mGluRs have been cloned, sequenced and assigned to three groups (Group I: mGluR1 and mGluR5; Group II: mGluR2 and mGluR3; Group III: mGluRs 4, 6–8) based on their sequence homology, pharmacology, and coupling to effector mechanisms.[1] In preclinical models, studies with the non-competitive antagonists MPEP (**1**) and MTEP (**2**) have demonstrated that selective antagonism of mGluR5 has therapeutic potential for chronic disorders such as pain, anxiety, depression, cocaine addiction and Fragile X syndrome.[2]

The vast majority of reported non-competitive mGluR5 antagonists have been designed based on the MPEP (**1**) and MTEP (**2**) scaffolds.[3,4] Many recent efforts have produced diverse heterobicylic analogs **3**,[5,6] along with other directed efforts to replace the acetylinic linker with amides **4**[7] and heterocycles **5**.[8] Other reports describe homologated variants such as **6**[9] and novel heterobiaryls such as **7**.[10] In terms of structural diversity, the thiopyrimidine **8**[11] and fenobam **9**[12] display the greatest departure from the MPEP chemotype; however, all of these scaffolds bear structural and topological similarities to MPEP and/or employed the MPEP/MTEP scaffolds as a basis for ligand design (Fig. 1).[3–10]

In an effort to make a dramatic departure from the MPEP chemotype, we conducted a functional high-throughput mGluR5 antagonist screen to identify novel, non-MPEP chemotypes. We screened a collection of 160,000 compounds and identified 624 mGluR5 antagonists in the primary screen (0.39% hit rate). Following hit verification and generation of full concentration–response-curves for all the primary hits, this effort produced 345 confirmed mGluR5 non-competitive antagonists. In this Letter, we describe the synthesis and SAR of three novel, non-MPEP mGluR5 non-competitive antagonists series **10**, **11** and **12** identified from the functional HTS with submicromolar IC_{50}s, low molecular weight and good clogP values (Fig. 2).

Our attention first focused on lead **10**, a furyl amide of a 2-azaspiro[5.5]undecane core. We employed an iterative parallel synthesis approach,[13] and resynthesized **10** in the context of a 24-member library prepared by standard acylation (24 RCOCls) of commercial 2-azaspiro[5.5]undecane **13** to provide analogs **14**, which were then purified to >98% by prep LC–MS.[14] As shown in Table 1, clear SAR was observed; however, upon resynthesis, lead **10** was a considerably weaker antagonist with an IC_{50} of 1.54 μM (Table 1). We have noted HTS DMSO stocks providing discrepancies with newly synthesized material on several occasions for various programs.[15] While a thienyl analog **14a** proved slightly more potent than **10**, other aryl and heteroaryl congeners were far less potent or inactive. Cyclic alkyl moieties proved the most intriguing in this series, with the cyclohexyl congener **14g** inactive, a cyclopentyl analog **14h** weak (IC_{50} > 10 μM), a cyclobutyl variant **14i** affording submicrolar inhibition (IC_{50} = 820 nM), and further con-

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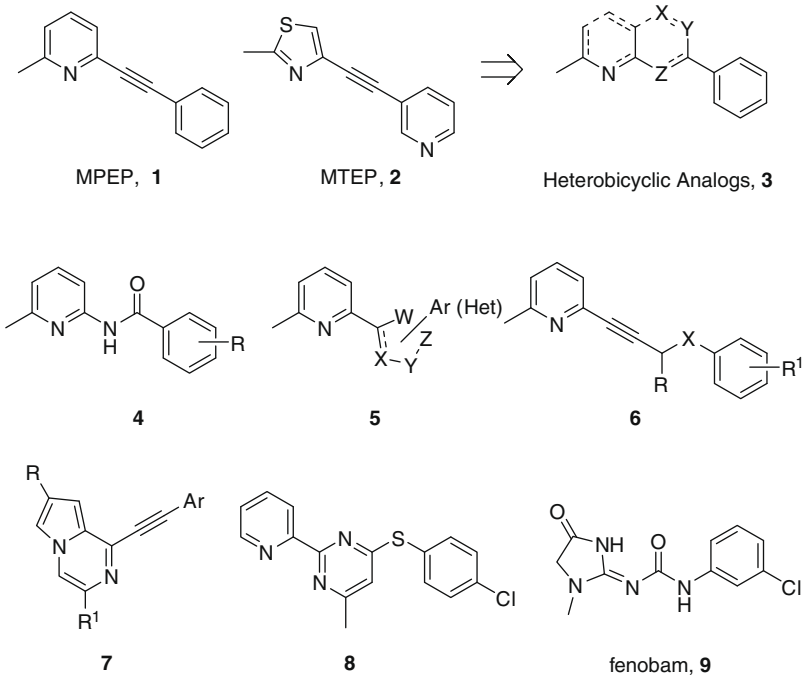


Figure 1. Reported mGluR5 non-competitive antagonists.

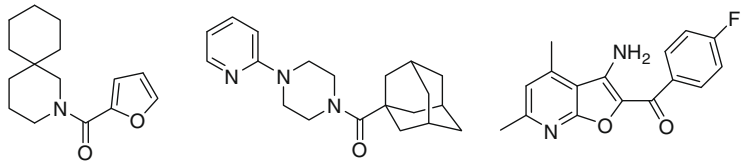


Figure 2. Novel, non-MPEP mGluR5 non-competitive antagonists **10**, **11** and **12** identified from a functional HTS campaign.

traction to a cyclopropyl derivative **14j** provides inhibition comparable to cyclopentyl (IC_{50} > 10 μM). Compound **14i** was further evaluated and found to be selective for mGluR5 (>30 μM vs mGluRs 1 (Group I), 2,3 (Group II) and 4,7,8 (Group III)) and displaced [^{3}H]3-methoxy-5-(2-pyridinylethynyl) pyridine with a K_i of 840 nM—a value in agreement with the IC_{50} (820 nM).

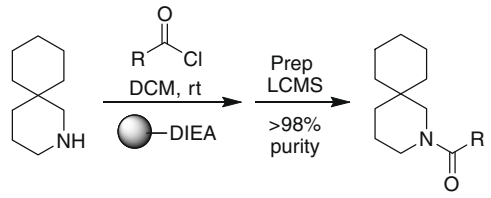
Thus, **14i**, possessing no aryl/heteroaryl features, represents a fundamentally new mGluR5 non-competitive antagonist chemotype that inhibits mGluR5 function by interaction with the MPEP allosteric binding site. Further libraries focused on other spirocyclic systems **15** as well as simple 3,3-dimethyl congeners **16** (Fig. 3). Only analog **17** displayed activity (IC_{50} = 9.9 μM).

Attention was then directed at lead **11**, an adamantyl amide of 2-pyridinylpiperazine. Once again, we employed an iterative parallel synthesis approach,[13] and resynthesized **11** in the context of a 12-member library prepared by standard acylation chemistry of 12 diverse aryl/heteroaryl piperazines **18** and adamantyl chloride **19** to deliver analogs **20**. Upon resynthesis, lead **11** suffered a two-fold loss in potency (IC_{50} = 990 nM) relative to the HTS stock solution (IC_{50} = 414 nM). Solid SAR was noted for this series (Table 2). Moving the pyridine nitrogen from the 2-position (**11**) to the 3-position (**20a**), leads to a >10-fold loss in activity (IC_{50} > 10 μM), and the 4-pyridyl congener (**20b**) loses all mGluR5 inhibitory activity. A thiazole derivative **20c** provided the most potent mGluR5 non-competitive antagonist in the series (IC_{50} = 540 nM). Functionalized aromatic analogs **20d–f** were generally weak to inactive with IC_{50}s ranging from 2.3 μM to >10 μM. **20c** was further evaluated and found to be selective for mGluR5 (>30 μM vs mGluR 2,3 (Group II) and 4,7,8 (Group III) with modest activity at mGluR1 (IC_{50} = 2.3 μM)) and displaced [^{3}H]3-methoxy-5-(2-pyridinylethynyl) pyridine with a K_i of 440 nM—a value in accord with the IC_{50} (540 nM). Thus, **20c** represents a fundamentally new mGluR5 non-competitive antagonist chemotype that inhibits mGluR5 function by interaction with the MPEP allosteric binding site.

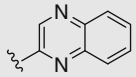
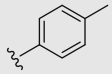
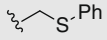
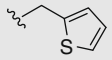
Further libraries focused on replacements for the adamantyl ring system **21–23**, but only moderate micromolar antagonists were discovered (Fig. 4).

Finally, we initiated an optimization campaign on HTS lead **12**, (3-amino-4,6-dimethylfuro[2,3-*b*]pyridine-2-yl)(4-fluorophenyl)-methanone. We again employed an iterative parallel synthesis approach,[13] and resynthesized **12** in the context of a multi-dimensional library prepared according to Scheme 1. Alkylation of a diverse collection of commercial 2-hydroxy-4-methylnicotinonitriles **24** with functionalized α-bromophenyl ketones provides a mixture of O- and N-alkylated products, where upon **25** is easily isolated by column chromatography. Exposure of **25** to K_2CO_3 in DMF at 100 °C under microwave irradiation delivers analogs **26** of HTS lead **12**. Upon resynthesis, lead **12** (IC_{50} = 150 nM, 1.39% Glu Max) was found to possess comparable potency to the HTS stock. **12** was further evaluated and found to be selective for

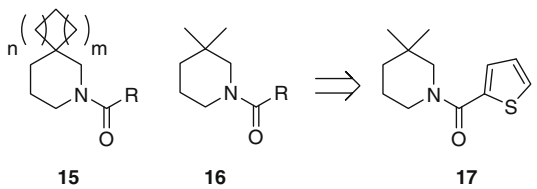
Table 1
Structures and activities of analogs **14**



13 **14**

Compd	R	mGluR5[a] IC_{50} (μM)	% Glu max[b]
10		1.54	2.64
14a		1.18	2.69
14b		>30	ND
14c		5.02	2.39
14d		>10	56.2
14e		5.24	4.23
14f		>10	52.1
14g		>30	ND
14h		>10	26.1
14i		0.82	1.12
14j		>10	40.6

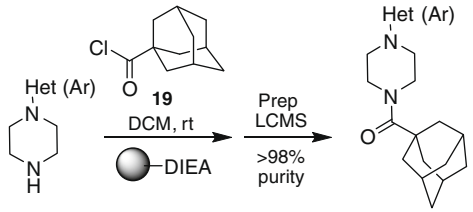
ND, not determined.
[a] IC_{50}s are average of three determinations.
[b] Determined at 30 μM test compound.



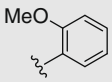
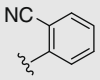
15 **16** **17**

Figure 3. Further analogs of novel mGluR5 antagonist **10**/**14**.

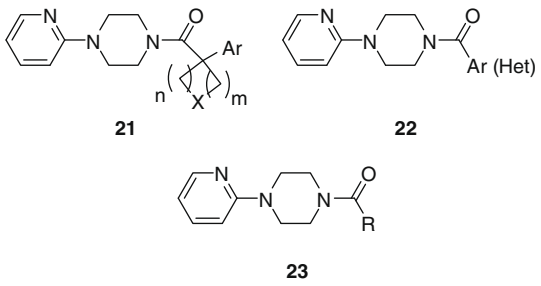
Table 2
Structures and activities of analogs **20**



18 **20**

Compd	R	mGluR5[a] IC_{50} (μM)	%Glu max[b]
11		0.99	3.75
20a		>10	30.2
20b		>30	ND
20c		0.54	1.16
20d		>10	52.0
20e		2.35	3.68
20f		>30	ND

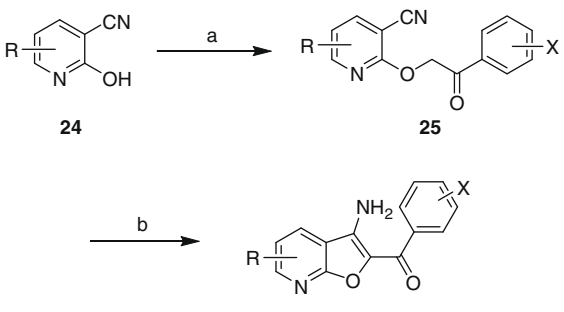
ND, not determined.
[a] IC_{50}s are average of three determinations.
[b] Determined at 30 test compound.



21 **22**

23

Figure 4. Further analogs of novel mGluR5 antagonist **11**/**20**.



24 **25**

26

Scheme 1. Reagents and conditions: (a) (i) NaH, DMF, (ii) 2-bromo-benzophenones, (b) K_2CO_3, DMF, 100 °C, mw, 20 min, 18–56%.

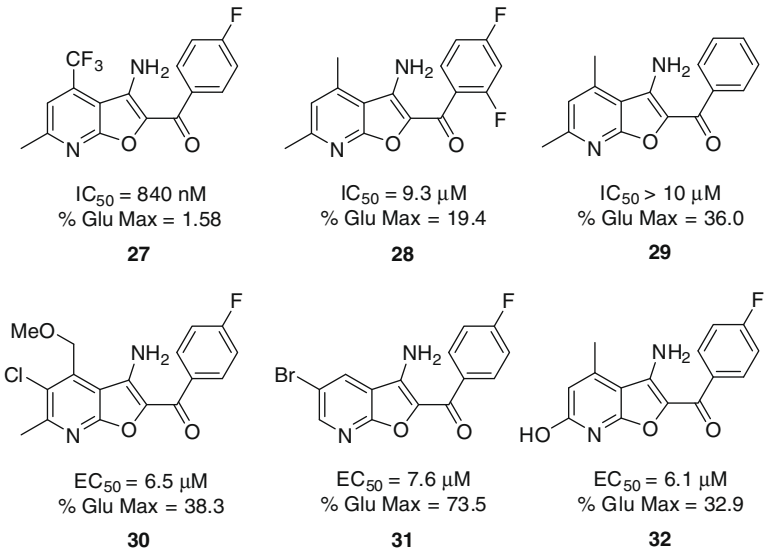


Figure 5. mGluR5 non-competitive antagonists **27–29** and mGluR5 PAMs **30–32** identified by optimization of HTS lead **12**.

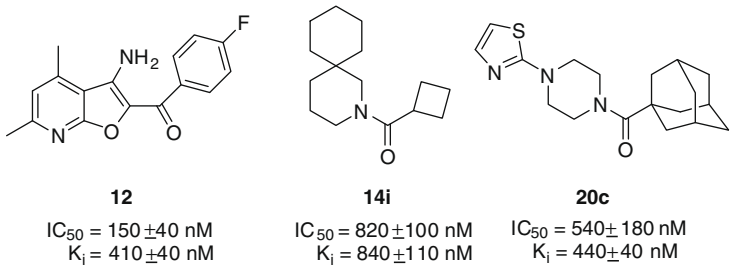


Figure 6. Novel, non-MPEP mGluR5 non-competitive antagonists **12**, **14i** and **20c** that bind at the MPEP allosteric site, but have little or no structural and topological similarity to MPEP.

mGluR5 (>30 μM vs mGluRs 1 (Group I), 2,3 (Group II) and 4,7,8 (Group III)) and displaced [^{3}H]3-methoxy-5-(2-pyridinylethynyl) pyridine with a K_i of 410 nM—a value comparable to the IC_{50} (150 nM). Thus, **12** represents a fundamentally new mGluR5 non-competitive antagonist chemotype that inhibits mGluR5 function by interaction with the MPEP allosteric binding site. Unlike **10** and **11**, SAR for this potent series of mGluR5 non-competitive antagonists was extremely shallow. Out of 36 analogs, only three analogs **27–29** possessed inhibitory activity, and three analogs displayed weak mGluR5 PAM activity **30–32** (Fig. 5). This was the first example of this mode of pharmacology switch within a non-MPEP scaffold, and **30–32** represent another novel mGluR5 PAM scaffold.[16–21] Thus, a functional HTS approach, coupled with iterative parallel synthesis, identified and developed three novel series of potent and selective mGluR5 non-competitive antagonists represented by **12**, **14i** and **20c** that bind at the MPEP allosteric site, but share little or no structural or topological similarities to MPEP (Fig. 6).

In summary, we have identified three novel, non-MPEP series of selective non-competitive mGluR5 antagonists with IC_{50}s ranging from 150 nM to 820 nM for the most potent ligands. These novel mGluR5 ligands bear little or no structural or topological similarity to MPEP and represent fundamentally new mGluR5 antagonist chemotypes. Within series **12**, chemical optimization was able to provide both a potent mGluR5 antagonist **12** (IC_{50} = 150 nM) and **30–32**, weak mGluR5 PAMs (EC_{50}s of 6.1–7.6 μM). This represents the first example of switching modes of pharmacology in a non-MPEP series of mGluR5 ligands. Further studies in this arena are in progress and will be reported in due course.

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