Structure−Activity Relationships Comparing *N*-(6-Methylpyridin-yl)-Substituted Aryl Amides to 2-Methyl-6-(substituted-arylethynyl)pyridines or 2-Methyl-4-(substituted-arylethynyl)thiazoles as Novel Metabotropic Glutamate Receptor Subtype 5 Antagonists†

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The metabotropic glutamate receptor subtype 5 (mGluR5) has been implicated in anxiety, depression, pain, mental retardation, and addiction. The potent and selective noncompetitive mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP, **1**) has been a critically important tool used to further elucidate the role of mGluR5 in these CNS disorders. In an effort to provide novel and structurally diverse selective mGluR5 antagonists, we previously described a set of analogues with moderate activity wherein the alkyne bond was replaced with an amide group. In the present report, extended series of both amide and alkyne-based ligands were synthesized. MGluR5 binding and functional data were obtained that identified (1) several novel alkynes with comparable affinities to **1** at mGluR5 (e.g., **10** and **20**–**23**), but (2) most structural variations to the amide template were not well tolerated, although a few potent amides were discovered (e.g., **55** and **56**). Several of these novel analogues show drug-like physical properties (e.g., cLogP range = 2−5) that support their use for in vivo investigation into the role of mGluR5 in CNS disorders.

Introduction

Glutamate is the predominant excitatory neurotransmitter in the brain and mediates its effects through both the ionotropic, i.e., *N*-methyl-D-aspartate (NMDA), α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), and kainate receptors, and eight metabotropic receptors (mGluR 1−8). The metabotropic glutamate receptors are classified into three groups based on protein homology, signal transduction pathways, and pharmacology. Group I consists of the primarily postsynaptic mGluR1 and mGluR5 that are coupled via G_q to phospholipase C. The primarily presynaptically located mGluR2 and 3 in group II and mGluR4, 6, 7, and 8 in group III are coupled to G_i and associated signaling pathways, such as ion channels and inhibition of adenylyl cyclase (for reviews see refs 1−3).[a]

The metabotropic glutamate receptors are members of the family C G-protein coupled receptors (GPCR) that consists of a seven-transmembrane spanning domain protein with a large extracellular N-terminus wherein the orthosteric glutamate binding site resides. The metabotropic glutamate receptor allosteric binding site is located in the transmembrane region of the protein and has been described in detail,[4] and specifically for mGluR5, using the high affinity and selective mGluR5 antagonist 2-methyl-6-(phenylethynyl)pyridine (MPEP, **1**, see ref 5 for recent review).

The therapeutic potential of CNS drug targets is predicted, in part, based on brain localization. The mGluR5s are largely expressed in postsynaptic terminals of the limbic regions and especially in the limbic cortex, hippocampus, amygdala, and basal ganglia, involved in motivational, emotional, and memory processes.[6] Over stimulation of mGluR5 has been implicated in numerous CNS disorders including anxiety, depression, neuropathic pain, drug addiction, and fragile X syndrome.[7] Indeed, the identification of allosteric modulators of mGluR5 that exclusively access the allosteric binding site and hence are exquisitely selective for the mGluR5 subtype has led to an explosion of allosteric mGluR5-targeted drug discovery effort to potentially exploit preclinical discovery into medication development (see refs 5, 8−13 for recent reviews).

Specifically, the localization of mGluR5 in the nucleus accumbens places this receptor system in an area associated with the dopamine family of receptors and the dopamine transporter (DAT). As the dopaminergic system plays a direct and primary role in the reinforcing effects of drugs of abuse such as the psychostimulants cocaine and methamphetamine, significant interest in elucidating a role for mGluR5 in addiction has been ignited. Indeed, experiments with mutant mGluR5 knockout (KO) mice show similar baseline locomotion as compared to wildtype littermates but do not demonstrate dose-dependent locomotor stimulation induced by cocaine. Further, the mGluR5 KO mice do not self-administer cocaine at any dose tested.[14] Likewise, the mGluR5 antagonist **1** dose-dependently decreases cocaine self-administration, but has no effect on food intake, under identical schedules of reinforcement.[14] These studies have been followed with numerous reports investigating the effects of **1** on cocaine self-administration and brain reward function (e.g., refs 15−18) and support further

† Atomic coordinates for compounds **4**, **10**, and **57** have been deposited with the Cambridge Crystallographic Data Centre.

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[a] Abbreviations: mGluR5, metabotropic glutamate receptor subtype 5; NMDA, *N*-methyl-D-aspartate; AMPA, α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid; GPCR, G-protein coupled receptors; DAT, dopamine transporter; mGluR5 KO, metabotropic glutamate receptor subtype 5 knockout.

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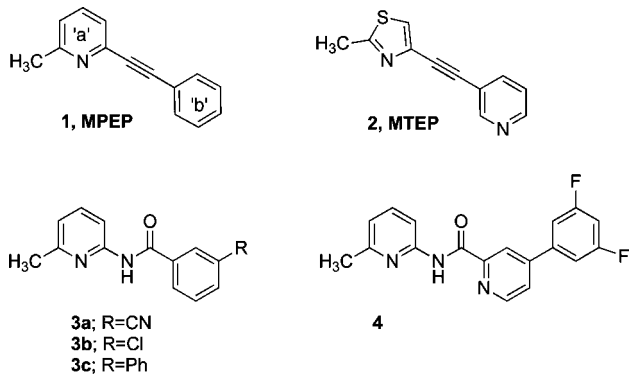


Figure 1. mGluR5 antagonist templates.

investigation into novel mGluR5 antagonists as molecular tools and as potential therapeutic agents for drug addiction.

Acetylenic analogues of the prototypic drug **1** have been largely mined, and the triple bond has proved to be a very important structural motif for high affinity mGluR5 antagonists.[10] In fact, most published mGluR5 structure−activity relationship studies have used this motif as the basis to their drug design and have primarily investigated structural modifications to the appended aryl rings on either side of the alkyne linker.[19−23] Nevertheless, we and others,[24−28] in an attempt to design nonalkynyl mGluR5 antagonists, have discovered several moderately active diarylamides (e.g., **3** and **4** in Figure 1), supporting our hypothesis that the acetylenic linker could be replaced. To further explore SAR and potentially improve binding affinities in the amide series, we attempted to identify critical functional groups for high affinity mGluR5 antagonists in the alkyne series and then incorporate these into the amides. Specifically, a series of alkyne derivatives based on **1**, and the thiazole analogue 2-methyl-4-(pyridin-3-ylethynyl)thiazole (MTEP, **2**, Figure 1) were first prepared to establish optimal pharmacophoric elements on the "b"-ring. On the basis of this series of alkynes (Table 1), optimal "b"-side aryl ring substitutions were incorporated into amides and SAR was compared.

Chemistry. Synthesis of the alkyne series of compounds followed the strategy outlined in Scheme 1. Compounds **7**, **9**, and **11** in this series were reported during the course of our investigation, and these are cited in Table 1. Synthons 2-methyl-4-((trimethylsilanyl)ethynyl)thiazole (**5a**) or 2-methyl-6-((trimethylsilanyl)ethynyl)pyridine (**5b**) were prepared according to literature procedures.[19,29] The phenols were protected as the methoxymethoxy (OMOM) ethers by treating with chloromethylmethyl ether. Thus, compound **5a** or **5b** was coupled with **6**(**a**, **b**, or **c**) or **12**(**a**, **b**, or **c**) under Sonagashira reaction conditions to give the coupling products **7**−**9**, or **13**−**15** in moderate to good yield. The aryl halides **8** and **15** were then converted to **10**, **11**, **16**, and **17** through Suzuki coupling reactions or by palladium-catalyzed coupling with $Zn(CN)_2$. An alternative method to prepare compounds **10** and **11** was to replace the Br (R_1) of 1,3-dibromo-5-fluorobenzene (**6b**) with the pyridinyl or cyano group via Suzuki coupling or by Pd-catalyzed cyanation, respectively, followed by the Sonagashira reaction. However, there were side reactions that typically resulted when **6b** was treated with either 3-pyridinylboronic acid or $Zn(CN)_2$ in the presence of palladium catalyst, especially for the latter reaction, wherein 1,3-dicyano-5-fluorobenzene was always the major product, with only very small quantities of the desired 3-bromo-5-fluorobenzonitrile obtained.

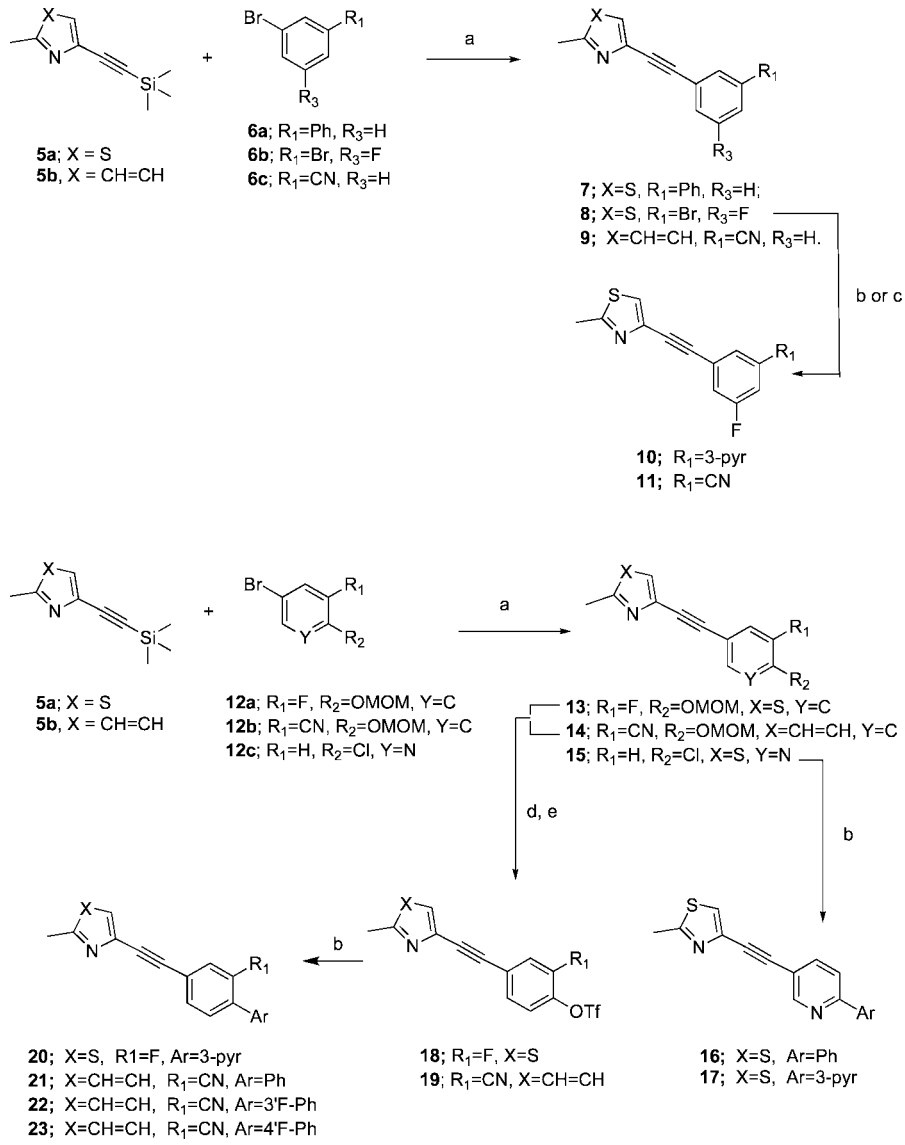
Compounds **13** and **14** were converted to their corresponding triflates **18** and **19** by deprotection of MOMO to the free hydroxyl group under acidic conditions, followed by treatment with trifluoromethanesulfonic anhydride. Noticeably, the deprotection was problematic when R_1 = CN, resulting in hydrolysis under these strong acidic conditions. As a result, the yield of the triflate **19** was low (0−45%), with various amounts of byproduct amide or acid, which were insoluble in both aqueous and organic layers. It was observed that partial hydrolysis of the triflates **18** and **19** to the phenol occurred, in the Suzuki coupling reaction, when strong base such as Na_2CO_3 was employed, resulting in low yields. This problem could be circumvented by using mild base such as KF.

On the basis of previous SAR studies,[24] and concerns regarding in vivo toxicities with the thiazole "a" ring (ref 30 and personal communications with Drs. S. Barak Caine and Roger Spealman), we elected to retain only the 2-methyl-6-pyridyl "a" ring in the amide series. Thus the initial 2-methyl-6-pyridyl amide analogues were prepared according to Schemes 2 and 3 starting with 2-methyl-6-aminopyridine (**24**) using standard amidation methods to give compounds **25**−**29**, **32**−**36**, **42**, and **43**. Addition of aryl substitution to the "b" ring was achieved using Suzuki coupling reactions with a variety of arylboronic acids and the Br-substituted amides (**26**, **35**, **42**, and **43**) to give **30**, **31**, **37**−**41**, and **44**−**47**, respectively.

As the 3-CN substitution on the "b"-ring in the alkyne series was determined to be important for potent activity at mGluR5, a series of similarly substituted amides were designed. To prepare the 3-CN-substituted amide analogues **55**−**59**, a different synthetic strategy was taken starting with 3-bromo-4-hydroxy benzoic acid (**48**) as depicted in Scheme 4. Benzylic protection of both the carboxylic acid and the phenol was achieved using benzyl bromide to give **49**. Displacement of the 3-Br with CN using $Zn(CN)_2$ and $Pd(PPh_3)_4$ gave excellent yields of intermediate **50**. We could take advantage of selective deprotection of the carboxylic acid under basic conditions to give the benzyl protected phenolic carboxylate **51**, which was readily converted to the amide **52** after making the acid chloride of **51** in $SOCl_2$ and then reacting with **24**. Catalytic hydrogenolysis of the benzyl protected phenol was achieved with cyclohexene and 10% Pd/C to give **53**. The triflate **54**, prepared by treating the phenol with trifluoromethanesulfonic anhydride, was then reacted with arylboronic acids, under Suzuki cross-coupling reaction conditions, to give the 4-aryl substituted amides **55**−**59**. Typically, all final products were purified by flash column chromatography, analytically characterized as the free base, and then converted to the HBr or HCl salts for biological testing, unless otherwise described in the Experimental Methods.

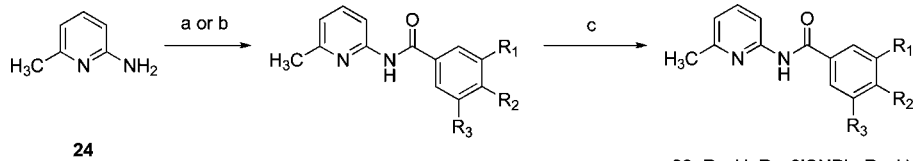
Structure−Activity Relationships. Radioligand binding assays for mGluR5 were performed using [^{3}H]**1** as the radioligand in either membranes from HEK 293-T cells transfected with cloned mGluR5 cDNA or rat brain membranes, as depicted in Table 1 and as previously described.[21] A functional assay using calcium fluorescence was utilized to test compound activity by measuring receptor-induced intracellular release of calcium with a kinetic imaging plate reader that makes simultaneous measurements of calcium levels in each well of a 384-well plate. Cells expressing rat mGluR5 were preincubated with the test compounds for 140 s and then stimulated for 60 s with an EC_{80} concentration of glutamate. In general, mGluR5 binding affinity (K_i) values were comparable to functional potency (IC_{50}) values in the calcium fluorescence assay. The results of these in vitro tests for the alkynes are in Table 1 and for the amides in Table 2, listed according to structural template.

Scheme 1. Synthetic Strategy toward Thiazole and Pyridyl Alkynes[a]



[a] Reagents and conditions: (a) $Pd(PPh_3)_4$, CuI, TBAF, Et_3N; (b) arylboronic acid or (3-pyridin-yl)boronic acid, Na_2CO_3 or KF, DME/H_2O; (c) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 80 °C; (d) aq HCl (6 N), MeOH, 50 °C; (e) $(CF_3SO_2)_2O$, pyridine, CH_2Cl_2.

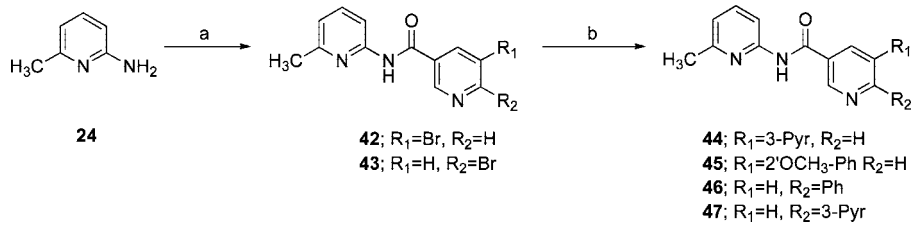
Scheme 2. Synthetic Strategy toward Substituted-Phenylamides[a]



[a] Reagents and conditions: (a) ArCOOH, CDI, pyridine; (b) ArCOCl, pyridine/TEA, dichloromethane, rt, 1−2 h, 50−75%; (c) $ArB(OH)_2$ or 3-pyridyl boronic acid, $Pd(PPh_3)_4$, 2 M aq Na_2CO_3, toluene, 110 °C or DME/H_2O (3:1), 80 °C, overnight, 75−80%.

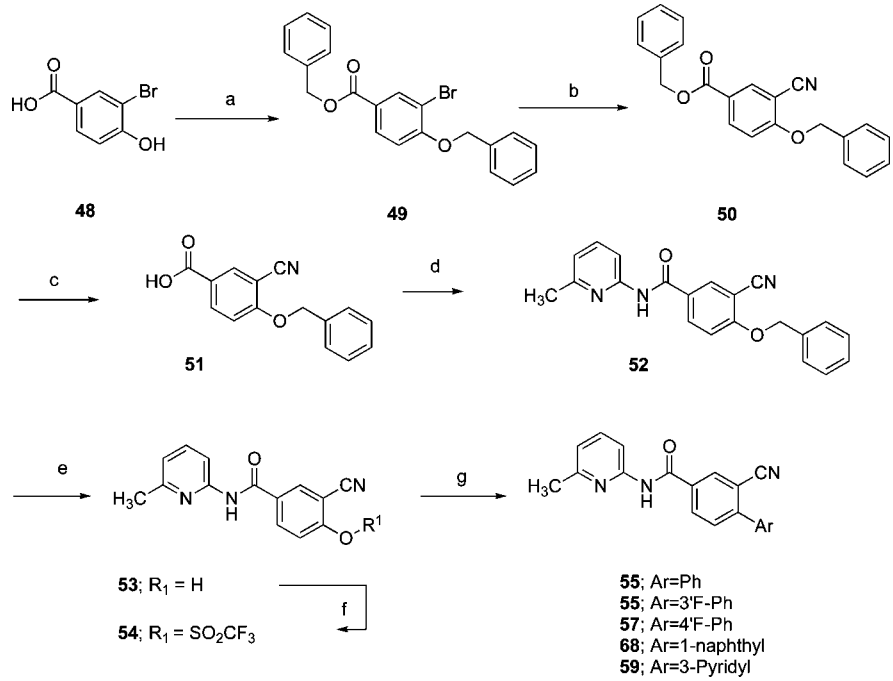
As expected, both thiazole and pyridyl alkynes showed high affinity binding to mGluR5 and were potent antagonists in the functional assay. The compounds based on template A, as compared to their parent compound, **2**, demonstrated tolerability at the 3-position (R_1) in the "b" ring, with the CN analogue, compound **11**, showing subnanomolar affinity and functional

Scheme 3. Synthetic Strategy toward Substituted-Pyridylamides[a]



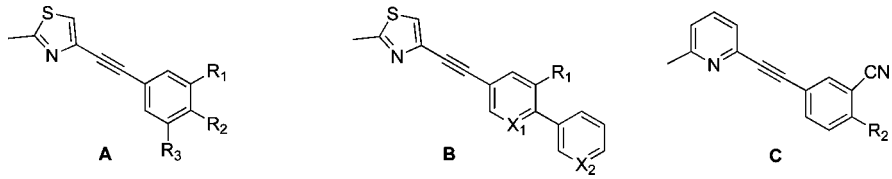
[a] Reagents and conditions: (a) ArCOCl, TEA, dichloromethane, rt, 1−2 h, 85−100%; (b) $ArB(OH)_2$, $Pd(OAc)_2$, 2′-dicyclohexylphosphino-2,6-dimethoxy biphenyl, K_3PO_4, toluene/EtOH, 50% or 3-pyridyl boronic acid, $Pd(PPh_3)_4$, 2 M aq Na_2CO_3, toluene, 110 °C or DME/H_2O (3:1), 80 °C, overnight, 75−80%.

Scheme 4. Synthesis of Substituted 3-Cyano-phenyl Amides[a]



[a] Reagents and conditions: (a) Benzyl bromide, anhydrous K_2CO_3, acetone, reflux, overnight, 99%. (b) $Zn(CN)_2$, $Pd(PPh_3)_4$, 80 °C overnight, DMF, 97%. (c) 4 N NaOH, MeOH, rt, 2 h, 92%. (d) (i) $SOCl_2$, dichloromethane, cat. DMF, reflux, 1 h; (ii) 2-amino-6-methyl pyridine, **24**, TEA, dichloromethane, rt, 1 h, 83%. (e) 10% Pd/C, cyclohexene, ethanol, reflux, 1 h, 87%. (f) trifluoromethanesulfonic anhydride, pyridine, dichloromethane, rt, overnight, 96%. (g) $ArB(OH)_2$, $Pd(PPh_3)_4$, 2 M aq Na_2CO_3, toluene, reflux overnight, 40−50%.

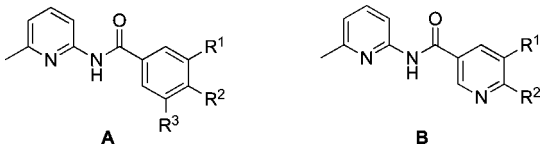
Table 1. In Vitro Data for Alkynyl mGluR5 Antagonists



compd	temp	R_1	R_2	R_3	X_1	X_2	cLogP[g]	mGluR5 binding (K_i, nM)[a]	mGluR function IC_{50} (nM) (Ca^{+2}flux)
1							3.8	13 ± 1[b]	3.54 ± 1.39
2							2.1	NT	13.6 ± 2.09
7[d]	A	Ph	H	H			5.5	10.76 ± 2.8[b]	3.05 ± 0.32
10	A	3-pyr	H	F			4.2	2.7 ± 0.7[b]	4.83 ± 0.60
11[e]	A	CN	H	F			3.2	0.9 ± 0.2[b]	0.813 ± 0.11
16[d]	B	H			N	C	4.2	5.49 ± 1.43[b]	1.21 ± 0.15
17[d]	B	H			N	N	2.8	5.65 ± 1.47[b]	5.24 ± 1.00
20	B	F			C	N	3.0	11.4 ± 3[b]	3.43 ± 0.51
9[f]	C		H				3.2	1.3 ± 0.09[c]	0.415 ± 0.10
21	C		Ph				5.1	4.0 ± 0.6[c]	3.08 ± 0.61
22	C		3′FPh				5.3	17.0 ± 2.2[c]	6.10 ± 1.95
23	C		4′FPh				5.3	3.0 ± 0.5[c]	7.19 ± 1.53

[a] Data provided by NIMH-PDSP. [b] Cloned (ref 21). [c] Rat brain (http://pdsp.med.unc.edu). [d] Compd. previously reported in ref 29. [e] Compd previously reported in ref 33. [f] Compd previously reported in ref 19. [g] Determined using Sybyl 7.2.3, Tripos Inc.

Table 2. In Vitro Data for Amide-Linked mGluR5 Antagonists



compd	temp	R_1	R_2/Ar	R_3	cLogP[e]	mGluR5 binding (K_i, nM)[a]	mGluR5 function IC_{50}(nM) (Ca^{+2}flux)
3a	A	Cl	H	H	3.3	1730 ± 100[c,d]	1870 ± 320
3b	A	CN	H	H	2.1	330 ± 20[c,d]	490 ± 94
3c	A	Ph	H	H	4.4	7300 ± 390[c,d]	NT
4					3.8	43 ± 1.0[f]	98.1 ± 18.9
25	A	H	CN	H	2.1	>10000[b]	NT
26	A	H	Br	H	3.4	>10000[b]	NT
27	A	H	OPh	H	4.6	7290 ± 2190[b]	NT
28	A	H	OBz	H	4.4	>10000[b]	NT
29	A	H	Ph	H	4.4	7000 ± 2120[b]	NT
30	A	H	3′CNPh	H	3.8	>10000[b]	NT
31	A	H	3′ClPh	H	5.1	3330 ± 850[b]	NT
32	A	F	H	F	2.9	7580 ± 2280[b]	NT
33	A	F	F	H	2.8	>10000[b]	NT
34	A	CN	H	F	2.2	65.5 ± 20[c]	21.7 ± 5.41
37	A	3-Pyr	H	F	3.1	702 ± 76[c]	NT
38	A	2′OCH_3Ph	H	F	4.0	>10000[c]	NT
39	A	2′CH_3Ph	H	F	4.8	610 ± 8.0[c]	NT
40	A	F	3-Pyr	H	3.1	7720 ± 1000[c]	>3000
41	A	Cl	3-Pyr	H	3.4	2780 ± 750[c]	>1000
55	A	CN	Ph	H	4.0	9.8 ± 2.1[b]	13.7 ± 2.54
56	A	CN	3′FPh	H	4.1	22 ± 5.3[b]	25.3 ± 1.90
57	A	CN	4′FPh	H	4.1	134 ± 31[c]	4.57 ± 0.38
58	A	CN	1-naphth	H	5.1	72 ± 12[c]	640 ± 32.2
59	A	CN	3-Pyr	H	2.5	2040 ± 340[c]	>1000
44	B	3-Pyr	H		1.8	>10000[c]	NT
45	B	2′OCH_3Ph	H		2.7	4920 ± 134[c]	NT
46	B	H	Ph		3.4	356 ± 41[c]	>3000
47	B	H	3-Pyr		2.0	2480 ± 520[c]	>3000

[a] Data provided by NIMH-PDSP. [b] Cloned (ref 21). [c] Rat brain (http://pdsp.med.unc.edu). [d] Compd previously reported in ref 24. [e] Determined using Sybyl 7.2.3, Tripos Inc. [f] Compd and data reported in ref 25; NT = not tested.

potency across assays. Unfortunately, preliminary in vivo testing of this analogue in rats showed toxicity, which precluded further evaluation (personal communication with Dr. S. Barak Caine). However, replacing the thiazole ring with the 2-methylpyridyl pharmacophore of the parent compound **1** essentially retained the same pharmacological profile and thus this compound or analogues thereof may prove to be better in vivo tools as the 2-methylpyridines, as exemplified by **1** itself, have proven to be well tolerated in laboratory animals. The thiazole analogues with structural template B showed that R_1 need not be CN to have high affinity and functional potency at mGluR5, and further that a pyridyl "b" ring is well tolerated as is aryl substitution in the 6′-position. By allowing the substitution of a bipyridyl system, the lipophilicity of the resulting compound **17** is reduced to give a cLogP = 2.8, which may prove desirable for both water-solubility and blood−brain barrier penetration.

Retaining the 3-CN substituted "b" ring of the compounds with template A and exploring the 4-position (R_2) of the 2-methylpyridyl analogues (template C) also demonstrated potent functional antagonism at mGluR5 and a tolerance for aryl ring substitution in the "b" ring. Although, predictably, this substitution serves to increase lipophilicity with cLogP values >5 for compounds **22** and **23**, which may not be compatible with a "drug-like" profile.[31,32]

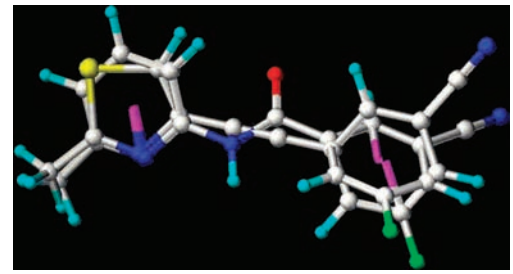


Figure 2. 3D-superimposition of**11** (alkyne) and **34** (amide).

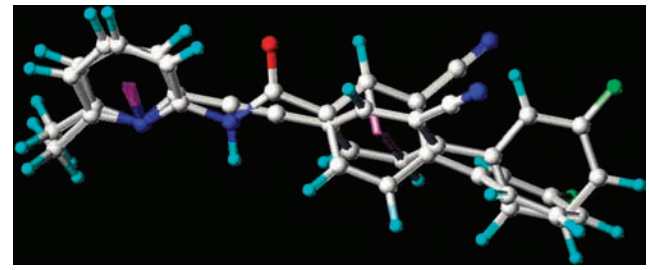


Figure 3. 3D-superimposition of**22** (alkyne) and **56** (amide).

On the basis of these data, we expanded our investigation of amide-linked mGluR5 analogues[24,25] to incorporate pharmacophores from the alkyne series that were deemed important for high affinity binding and functional potency at mGluR5, namely (1) exploring substitutions on the "b" ring that either include the 3-CN group (R_1) and investigate tolerability of substitution at the 4 and 5-positions of the "b" ring or (2) replace the 3-CN group with other substituents, and further (3) replace the aryl "b" ring of the parent compound **1** with the 3-pyridyl "b" ring (template B) to both explore tolerability and attempt to reduce lipophilicity of the analogues by incorporating this heterocycle. Previously we discovered that, in general, the amide linker replacement of the alkyne was poorly tolerated with only a few examples of moderately active mGluR5 antagonists (e.g., **3a**−**3c** and **4**[24,25]). Compounds **25**−**33** were being prepared during the course of those earlier studies, and it was discovered that 4-substitution in the "b" ring was also poorly tolerated despite this substitution being well tolerated in the alkyne series (e.g., **16**, **17**, **20**−**23**). Activity at mGluR5 was gained when the 3-CN and 5-F groups were incorporated into the amides (e.g. **11** vs **34**; Figure 2). However, if the 3-CN group was replaced (**37**−**39**), activity was lost. Indeed, all other substitutions that were attempted proved fatal to mGluR5 activity if the 3-CN group was removed. For example, addition of pyridyl rings on the "b"-side of the alkynes was tolerated at mGluR5 (e.g. **16**, **17**, **20**), whereas this substitution (template B) typically decreased affinity and antagonist potency in the amides (e.g., **59**).

Hence, the final set of compounds all had a 3-CN-substitution in the "b" ring, and these were among the best mGluR5 antagonists in the amide series (**55**−**58**) with the exception of compound **59**. Interestingly, the similarly substituted alkyne **11** and amide **34** align quite well (Figure 2), and yet the alkyne binds with >70-fold higher affinity at mGluR5 than the amide. However, addition of an aryl substitution at R_2 in the amides improved mGluR5 affinity and antagonist potency to give similar potency to the alkyne analogue (e.g., **22** (K_i = 17 nM) vs **56** (K_i = 22 nM); Figure 3).

These compounds are highly specific to mGluR5 as none of the compounds in Table 1 or 2 showed >70% inhibition of PI hydrolysis at a single concentration of 10 μM (data from NIMH-PDSP) in any of the other mGluR subtype functional assays and further evaluation was abandoned. In addition, compounds **10**, **20**, **55**, and **56** were evaluated for hDAT, hSERT, and hNET binding,

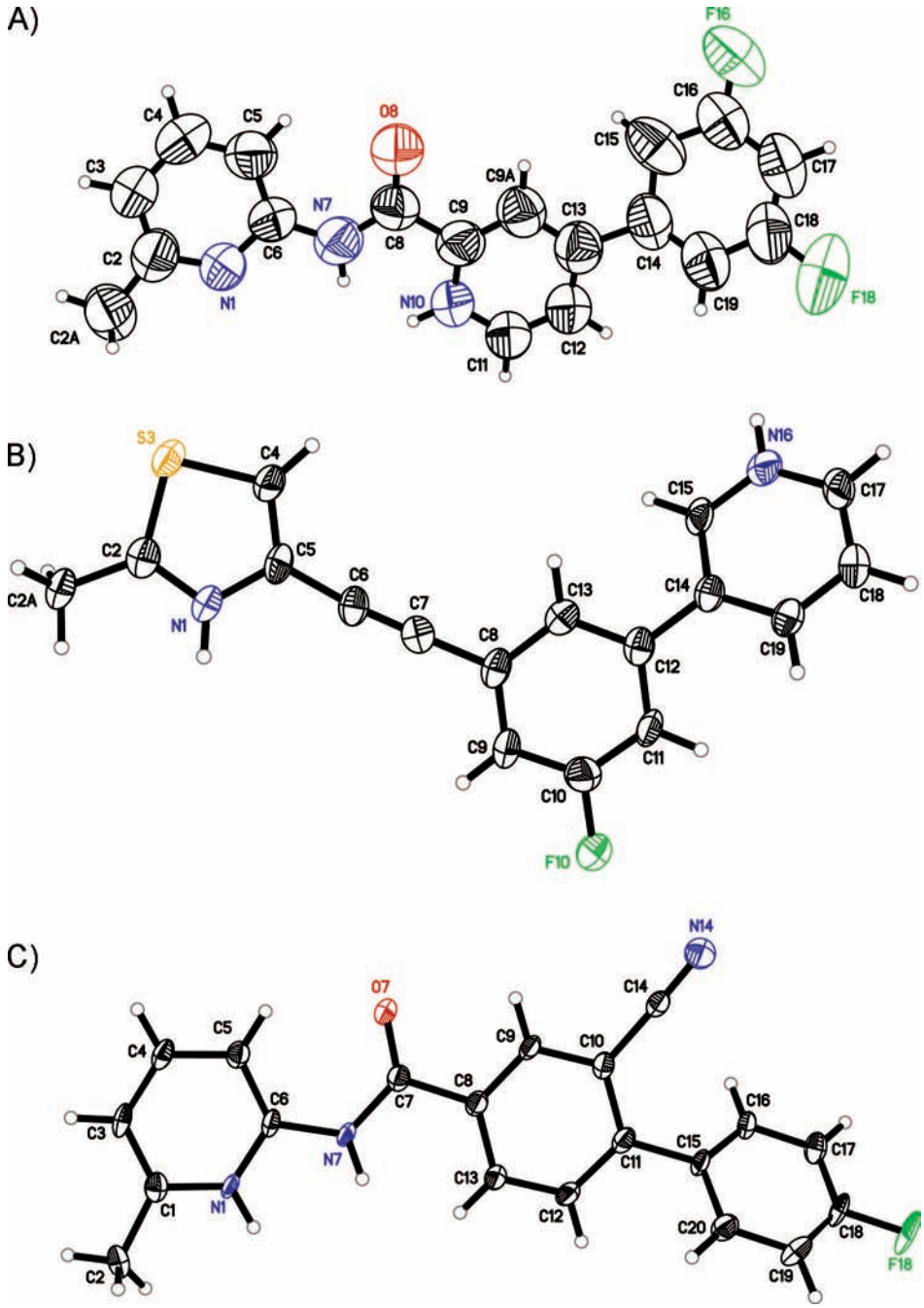


Figure 4. X-ray crystal structures of compounds **4** (A), **10** (B), and **57** (C). For all images, displacement ellipsoids are at the 50% level; for compound **4**, solvent and the counterion are omitted for clarity; for compound **10**, only one of the two molecules in the asymmetric unit is shown and solvent and counterions are omitted for clarity; for compound **57**, the counterion is omitted for clarity.

using [^{125}I]RTI 55 as the radioligand, as well as inhibition of DA, 5-HT, and NE uptake, respectively, in HEK cells. None of the compounds showed significant activity in any of these assays, with K_i values in the 6 to >10 μM range (data from NIDA-ATDP).

X-ray Crystallographic Results and Discussion. Data presented in Tables 1 and 2 revealed that structural differences between the alkynyl- and amido-linked mGluR5 antagonists, although seemingly minor, can have significant impact on binding affinities and functional potencies at mGluR5. The divergence in SAR between the amides and alkynes suggests that the coplanarity of the alkynes is more favored, as described previously.[24−26] Thus, in an effort to collect additional conformational information, representative compounds **4**, **10**, and **57** were analyzed using single-crystal X-ray diffraction and compared (Figure 4A−C). All the bond lengths and angles were within the expected range of values, and as also seen in the energy-minimized molecular models of compound **11** compared to **34** and **22** compared to **56**, respectively, in Figures 2 and 3, the X-ray data confirm similarities in the conformations of the alkynes and amides. However there are subtle differences in the orientation of the aromatic "b" rings, which may access different but overlapping binding sites, potentially affecting potency at mGluR5 that generally favors the alkynes.

Summary

A series of alkynyl analogues of the parent compounds **1** and **2** were synthesized in order to identify optimal substitution on the "b" ring of the molecule for mGluR5 activity. Several very high affinity (K_i = 0.9−11 nM) mGluR5 antagonists were

identified in this series. A second series of amide analogues, based on previously described SAR[24,25] and templates **3b** and **4**, were synthesized and optimal "b" ring substitution, as identified in the alkynyl series, was incorporated. We discovered that only the 3-CN substituent in the "b" ring of both alkynes and amides served to consistently improve mGluR5 binding affinity and functional potency. Other substitutions that also gave high affinity ligands in the alkyne series were not tolerated in the amide series. Likewise, aryl substitutions in the 4-position of the "b" ring (R_2) served to either retain or improve mGluR5 affinity in the amide series, whereas this substitution had no additional positive effect on mGluR5 affinity for the alkynes. This SAR comparison, along with X-ray crystal data, demonstrate that the planar alkyne template is optimal for mGluR5 binding affinity and functional potency but that certain "b" ring substitutions (e.g., 3-CN) can also result in high affinity amide analogues. Likely due to the conformational differences between the alkynes and the amides, other substitutions on the "b" ring of the alkynes did not uniformly improve mGluR5 activity in the amides, and in fact, amides without the 3-CN substitution, in this series, were typically inactive. Nonetheless, cLogP values for most of the novel analogues reported herein are within the 2−5 range, suggesting that the more potent mGluR5 antagonists will be viable in vivo tools. And as several alkynes and amide analogues were identified to be both high affinity and selective mGluR5 antagonists, in vivo evaluation of selected compounds in models of anxiety and drug abuse will continue to provide needed information regarding the potential development of this class of agents as medications for the treatment of addiction and other neuropsychiatric disorders.

Experimental Methods

Reaction conditions and yields were not optimized, and spectroscopic data refer to the free base. Thin-layer chromatography was performed using analytical TLC plates (Analtech Uniplate, 250 μm), and flash chromatography was performed using silica gel (EMD Chemicals, Inc.; 230−400 mesh, 60 Å). ^{1}H and ^{13}C NMR spectra were acquired using a Varian Mercury Plus 400 spectrometer. Chemical shifts are reported in parts-per-million (ppm) and referenced according to deuterated solvent for ^{1}H spectra ($CDCl_3$, 7.26) and ^{13}C spectra ($CDCl_3$, 77.23). Infrared spectra were recorded as a neat film on NaCl plates using a Perkin-Elmer Spectrum RX I FT-IR spectrometer. Gas chromatography−mass spectrometry (GC/MS) data were acquired using an Agilent Technologies (Santa Clara, CA) 6890 GC equipped with an HP-5 MS column (cross-linked 5% PH ME siloxane, 30 m × 0.25 mm i.d. × 0.25 μm film thickness) and a 5973 mass-selective ion detector in electron-impact mode. Ultrapure grade helium was used as the carrier gas at a flow rate of 1.2 mL/min. The injection port and transfer line temperatures were 250 and 280 °C, respectively, and the oven temperature gradient used was as follows: the initial temperature (100 °C) was held for 3 min (0:00−3:00 min) and then increased to 295 at 15.0 °C/min over 13 min (3:00−16:00 min), and finally maintained at 295 °C for 10 min (16:00−26:00 min). Combustion analysis was performed by Atlantic Microlab, Inc. (Norcross, GA) and agrees within 0.4% of calculated values. Melting point determination was conducted using a Thomas−Hoover melting point apparatus and are uncorrected. Anhydrous solvents were purchased from Aldrich (pyridine, acetonitrile, dichloromethane, chloroform ($CHCl_3$), hydrazine) or J. T. Baker (diethyl ether) and were used without further purification, except for tetrahydrofuran, which was freshly distilled from sodium-benzophenone ketyl. All other chemicals and reagents were purchased from Aldrich Chemical Co., Lancaster Synthesis, Inc. (Alfa Aesar), and Combi-Blocks, and used without further purification. The final products were converted into the HBr salts, typically by treating the free base with methanolic HBr followed by precipitation with diethyl ether. The HCl salts were generally made by dissolving the free base in HCl ether solution and then recrystallizing from hot MeOH. On the basis of NMR, GC-MS (where obtainable), and combustion analysis data, all final compounds are >95% pure.

General Procedure A: Protection of Hydroxyl Group as Methoxymethoxy Ether (OMOM). Chloromethyl methyl ether (6 mmol) in dry dichloromethane (2 mL) was added dropwise to an ice-cooled solution of phenol (5 mmol) and *N*-ethyldiisopropylamine (10 mmol) in dichloromethane (10 mL). The mixture was stirred at room temperature for 2 h after the addition. Water (20 mL) was then added, and the two phases were separated. The aqueous layer was extracted with dichloromethane (3 × 20 mL). The combined organic layer was dried (Na_2SO_4) and concentrated. The residue was purified by flash column chromatography.

General Procedure B: Sonagashira Reaction. To the mixture of 2-methyl-4-((trimethylsilanyl)ethynyl)thiazole (**5a**) or 2-methyl-6-((trimethylsilanyl)ethynyl)pyridine (**5b**) (1 equiv), aryl bromide **6a**−**c** (1.2 equiv), CuI (20 mol %),and $Pd(PPh_3)_4$ (5 mol %) in DMF (5 mL DMF/1 mmol scale reaction) was added Bu_4NF (1 eq, 1.0 M solution in THF) dropwise at 80 °C under argon. After the addition, the mixture was stirred at this temperature overnight. The mixture was then filtered through celite, DMF was removed under reduced pressure, and the residue was diluted with H_2O and extracted with EtOAc. The combined organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography to afford the pure product.

General Procedure C: Suzuki Coupling Reaction for Alkynes. To the solution of aryl boronic acid (1.2 equiv), aryl halide, or triflate (1 equiv) and Na_2CO_3 (2 equiv, for halide) or $KF \cdot 2H_2O$ (2 equiv for triflate) in the mixture of solvents DME/H_2O (3/1, 4 mL solvents for 1 mmol scale reaction) was added $Pd(PPh_3)_4$ (5 mol %) under argon. The mixture was warmed to 80 °C for 3−5 h. The solvents were then removed under reduced pressure, and the residue was diluted with water and extracted with EtOAc. The organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by flash column chromatography to afford the pure product.

3-Bromobiphenyl (6a). Prepared from 1,3-dibromobenzene and phenylboronic acid according to general procedure C in 58% yield; purified by column chromatography eluting with hexane/EtOAc (3:1) (white solid). ^{1}H NMR ($CDCl_3$) δ 7.2−7.8 (m, 9H), ppm; GC-MS (EI) *m*/*z* 232(M^+), 234(M^+).

4-Bromo-2-fluoro-1-(methoxymethoxy)benzene (12a). Prepared from 4-bromo-2-fluorophenol according to the general procedure A in 97% yield; purified by column chromatography eluting with hexane/EtOAc (10:1)(clear oil). ^{1}H NMR ($CDCl_3$) δ 3.51 (s, 3H), 5.19 (s, 2H), 7.08 (dd, J = 8.8, 10 Hz, 1H), 7.16−7.20 (m, 1H), 7.25 (dd, J = 2.4, 10 Hz, 1H) ppm; GC-MS (EI) *m*/*z* 234 (M^+), 236 (M^+).

5-Bromo-2-(methoxymethoxy)benzonitrile (12b). Prepared from 4-bromo-2-cyanophenol according to the general procedure A in 91% yield; purified by column chromatography using hexane/EtOAc (10:1) (light-brown solid); mp 67−69 °C. IR (KBr) 2223, 1583, 1256, cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 3.52 (s, 3H), 5.28 (s, 2H), 7.14 (d, J = 9.2 Hz, 1H), 7.61 (dd, J = 2.4, 9.2 Hz, 1H), 7.68 (d, J = 2.4 Hz, 1H) ppm. GC-MS (EI) *m*/*z* 241 (M^+), 243 (M^+).

3-Phenyl-1-(2-methylthiazol-4-ylethynyl)benzene (7). Prepared from **5a** and **6a** according to the general procedure B in 38% yield; purified by column chromatography eluting with hexane/EtOAc (2:1) (brown solid); mp 84−86 °C. IR (KBr, cm^{-1}) 1598 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.40−7.54 (m, 4H), 7.45 (s, 1H), 7.58 (m, 1H), 7.60 (d, J = 1.6 Hz, 1H), 8.04 (t, J = 2.0 Hz, 1H), 8.76 (d, J = 2.0 Hz, 1H), 8.79 (d, J = 2.0 Hz, 1H) ppm. GC-MS (EI) *m*/*z* 275 (M^+). Anal. ($C_{18}H_{13}NS$) for C, H, N.

1-Bromo-3-fluoro-5-(2-methylthiazol-4-ylethynyl)benzene (8). Prepared from **5a** and **6b** according to general procedure B in 57% yield; purified by column chromatography eluting with hexane/EtOAc (2:1) (light-brown solid). ^{1}H NMR ($CDCl_3$) δ 2.74 (s, 3H), 7.19 (ddd, J = 1.6, 2.4, 8.8 Hz, 1H), 7.24 (ddd, J = 1.6, 2.4, 8.8 Hz, 1H), 7.42 (s, 1H), 7.49 (m, 1H) ppm. GC-MS (EI) *m*/*z* 295 (M^+), 297 (M^+).

3-[(6-Methylpyridin-2-yl)ethynyl]benzonitrile (9). Prepared from **5b** and **6c** according to the general procedure B in 48% yield;

purified by column chromatography eluting with hexane/EtOAc (2:1). The free base was converted to its HBr salt and recrystallized from EtOH as a brown solid; mp 189−192 °C (dec). IR (KBr) 2223, 1604 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.60 (s, 3H), 7.17 (d, J = 8.0 Hz, 1H), 7.37 (d, J = 8.0 Hz), 7.49 (t, J = 8.0 Hz, 1H), 7.60 (d, J = 8.0 Hz, 1H), 7.64 (dt, J = 1.6, 8.0 Hz, 1H), 7.81 (dt, J = 1.6, 8.0 Hz, 1H), 7.87 (s, 1H) ppm. GC-MS (EI) m/z 218 (M^+). Anal. ($C_{15}H_{10}N_2 \cdot HBr$) for C, H, N.

1-Fluoro-3-(pyridin-3-yl)-5-(2-methylthiazol-4ylethynyl)benzene (10). Prepared from **8** and 3-pyridineboronic acid according to the general procedure C in 95% yield; purified by column chromatography eluting with hexane/EtOAc (1:1). The free base was converted to the HBr salt and recrystallized from MeOH as a brown solid; mp 175−177 °C (dec). IR (KBr) 1604, 1592 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.29 (d, J = 1.2 Hz, 1H), 7.27 (s, 1H), 7.40 (m, 1H), 7.44 (s, 1H), 7.58 (t, J = 1.2 Hz, 1H), 7.86 (m, 1H), 8.64 (dd, J = 1.2, 5.0 Hz, 1H), 8.84 (d, J = 2.0 Hz, 1H) ppm. GC-MS (EI) m/z 294 (M^+). Anal. ($C_{17}H_{11}N_2FS \cdot 2HBr$) for C, H, N.

3-Fluoro-5-cyano-1-(2-methylthiazol-4-ylethynyl)benzene (11). To a mixture of **8** (200 mg, 0.67 mmol) and $Zn(CN)_2$ (47.6 mg, 0.40 mmol) in DMF (5 mL) was added $Pd(PPh_3)_4$ (39 mg, 5 mol %), and the mixture was heated to 80 °C overnight. DMF was then removed under reduced pressure. The residue was then diluted with H_2O and extracted with EtOAc (3 × 10 mL). The combined organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography eluting with hexane/EtOAc (3:1) to give **11** (110 mg, 68%). The free base was converted to its HBr salt and recrystallized from EtOH as a dark-brown solid; mp 186−189 °C (dec). IR (KBr): 2221, 1605, 1585 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.32−7.36 (m, 1H), 7.45−7.49 (m, 1H), 7.47 (s, 1H), 7.62 (s, 1H) ppm. GC-MS (EI) m/z 242 (M^+). Anal. ($C_{13}H_7N_2FS \cdot HBr$) for C, H, N.

2-Fluoro-1-(methoxymethoxy)-4-(2-methylthiazol-4-ylethynyl)-benzene (13). Prepared from **5a** and **12a** according to the general procedure B in 47% yield; purified by column chromatography eluting with hexane/EtOAc (5:1) (clear oil). IR (neat): 1598, 1272, 1155 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.74 (s, 3H), 3.52 (s, 3H), 5.24 (s, 2H), 7.17 (m, 1H), 7.26−7.30 (m, 2H), 7.36 (s, 1H) ppm. GC-MS (EI) m/z 277 (M^+).

2-(Methoxymethoxy)-5-(6-methylpyridin-2-ylethynyl)benzonitrile (14). Prepared from **5a** and **12b** according to the general procedure B in 53% yield; purified by column chromatography eluting with hexane/EtOAc (3:1) (brown solid); mp 112−114 °C. IR (KBr): 2227, 1583, 1602 (w), 1255 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.59 (s, 3H), 3.54 (S, 3H), 5.32 (S, 2H), 7.14 (d, J = 8.0 Hz, 1H), 7.23 (d, J = 8.8 Hz,1H), 7.34 (d, J = 8.0 Hz, 1H), 7.59 (dd, J = 8.0, 8.0 Hz, 1H), 7.72 (dd, J = 1.6, 8.8 Hz, 1H), 7.78 (d, J = 1.6 Hz, 1H) ppm. GC-MS (EI) m/z 278 (M+).

2-Chloro-5-(2-methylthiazol-4-ylethynyl)pyridine (15). Prepared from **5a** and **12c** according to the general procedure B in 73%; purified by column chromatography eluting with hexane/EtOAc (3:1) (light-yellow solid); mp 139.5−141 °C. ^1H NMR ($CDCl_3$) δ 2.75 (s, 3H), 7.33 (dd, J = 0.8, 8 Hz, 1H), 7.44 (s, 1H), 7.78 (dd, J = 2.4, 8 Hz, 1H), 8.56 (dd, J = 0.8, 2.4 Hz, 1H) ppm. GC-MS (EI) m/z 234 (M^+).

2-Phenyl-5-(2-methylthiazol-4ylethynyl)pyridine (16). Prepared from **15** and phenylboronic acid according to the general procedure C in 80% yield; purified by column chromatography eluting with hexane/EtOAc (7:3); mp 99.5−100.5 °C. The free base was converted to its HBr salt and recrystallized from EtOH as a light-brown solid; mp 188−191 °C (dec). IR (KBr) 1608, 1601 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.40−7.52 (m, 4H), 7.58 (m, 2H), 8.04 (m, 1H), 8.77 (dd, J = 2.2,14.4 Hz, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ 19.5, 85.7, 87.0, 119.9, 123.4, 127.4, 128.7, 129.4, 136.4, 137.1, 147.7, 151.0, 166.2 ppm. GC-MS (EI) m/z 276 (M^+). Anal. ($C_{16}H_{12}N_2S \cdot HBr \cdot H_2O$) for C, H, N.

2-(Pyridin-3-yl)-5-(2-methylthiazol-4ylethynyl)pyridine (17). Prepared from **15** and 3-pyridylboronic acid according to the general procedure C in 73% yield; purified by column chromatography eluting with hexane/EtOAc/Et_3N (2.5:7.5:0.1). The free base was converted to its HBr salt and recrystallized from EtOH as a light-brown solid; mp 224−226 °C (dec). IR (KBr) 1602, 1588 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.42 (m, 1H), 7.47 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.94 (dd, J = 2.0, 8.4 Hz, 1H), 8.35(d, J = 8.0 Hz, 1H), 8.67 (d, J = 2.0 Hz, 1H), 8.88 (s, 1H), 9.22 (d, J = 1.6 Hz, 1H) ppm. GC-MS (EI) m/z 277 (M^+). Anal. ($C_{16}H_{11}N_3S \cdot HBr \cdot 0.5H_2O$) for C, H, N.

2-Fluoro-4-((2-methylthiazol-4-yl)ethynyl)phenyl Trifluoromethanesulfonate (18). To a solution of compound **13** (486 mg, 1.75 mmol) in MeOH (2 mL) was added aq HCl (6 N, 0.6 mL, 3.6 mmol), and the mixture was heated to 50 °C for 3 h. MeOH and H_2O were removed under reduced pressure, and the residue was further dried on high vacuum to afford 2-fluoro-4-[(2-methylthiazol-4-yl)ethynyl]phenol. This crude product was used in the next step without further purification. To a mixture of 2-fluoro-4-((2-methylthiazol-4-yl)ethynyl)phenol and pyridine (0.57 mL, 7.0 mmol) in dry CH_2Cl_2 (5 mL) was added trfluoromethanesulfonic anhydride (0.44 mL, 2.6 mmol) dropwise at 0 °C under argon, and the solution was further stirred at room temperature for 2 h after the addition. The mixture was then diluted with H_2O (10 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 10 mL). The combined organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography eluting with hexane/EtOAc (5:1) to provide the triflate **18** (607 mg) in 95% yield, as a light-yellow solid. ^1H NMR ($CDCl_3$) δ2.75 (s, 3H), 7.29−7.45 (m, 3H), 7.44 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 19.5, 86.0, 86.4, 117.3, 120.7, 120.9, 123.9, 124.8, 128.7, 136.1, 137.0, 152.2, 154.7, 166.4 ppm. GC-MS (EI) m/z 365 (M+).

2-Cyano-4-((6-methylpyridin-2-yl)ethynyl)phenyl Trifluoromethanesulfonate (19). Compound **14** (2.34 g, 8.41 mmol) was dissolved in MeOH (10 mL), and aq HCl (6 N) solution (3 mL, 18 mmol) was added. The mixture was heated to 50 °C. Heating was discontinued after TLC showed most of the starting material disappeared (less than 1 h). MeOH and H_2O were then removed under reduced pressure, and the residue was further dried on high vacuum to afford 2-cyano-4-((6-methylpyridin-2-yl)ethynyl)phenol, which was used in the next step without further purification. To a mixture of 2-cyano-4-((6-methylpyridin-2-yl)ethynyl)phenol and pyridine (2.67 mL, 33 mmol) in dry CH_2Cl_2 (20 mL) was added trfluoromethanesulfonic anhydride (2.12 mL, 12.61 mmol) dropwise, at 0 °C under argon, and the solution was further stirred at room temperature for 2 h after the addition. The mixture was then diluted with H_2O (20 mL). The two layers were separated, and the aqueous layer was extracted with EtOAc (3 × 20 mL). The combined organic layer was dried ($MgSO_4$) and concentrated. The residue was purified by column chromatography eluting with hexane/EtOAc (5:1) to provide product **19** (1.31 g) in 43% yield, as a light-yellow solid. ^1H NMR ($CDCl_3$) δ 2.61 (s, 3H), 7.20 (d, J = 7.6 Hz, 1H), 7.38 (d, J = 7.6 Hz, 1H), 7.50 (d, J = 8.8 Hz, 1H), 7.62 (dd, J = 8.0, 8.0 Hz, 1H), 7.88 (dd, J = 2.4, 8.8 Hz, 1H), 7.95 (d, J = 2.4 Hz, 1H) ppm. GC-MS (EI) m/z 366 (M^+).

1-(Pyridin-3-yl)-2-fluoro-4-(2-methylthiazol-4ylethynyl)benzene (20). Prepared from **18** and 3-pyridylboronic acid according to the general procedure C in 68% yield; purified by column chromatography eluting with hexane/EtOAc (1:1). The free base was converted to its HBr salt and recrystallized from EtOH as a light-brown solid; mp 209.5−211 °C (dec). IR (KBr) 1605, 1599 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.38−7.44 (m, 5H), 7.89 (m, 1H), 8.63 (dd, J = 1.6, 4.8 Hz, 1H), 8.81 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 19.5, 85.4, 87.4, 119.4, 119.7, 123.3, 123.6, 124.6, 126.3, 128.4, 130.6, 131.2, 136.4, 136.6, 149.3, 149.7, 158.3, 160.8, 166.2 ppm. GC/MS (EI) m/z 294 (M^+). Anal. ($C_{17}H_{11}N_2SF \cdot HBr \cdot 0.25H_2O$) for C, H, N.

2-Phenyl-5-(6-methylpyridin-2-ylethynyl)benzonitrile (21). Prepared from **19** and phenylboronic acid according to the general procedure C in 65% yield; purified by column chromatography eluting with hexane/EtOAc (2:1)). The free base was converted to its HBr salt and recrystallized from 2-PrOH as a white solid; mp 188.5−190 °C (dec). IR (KBr) 2234, 1584 cm^{-1}. ^1H NMR ($CDCl_3$) δ 2.61 (s, 3H), 7.17(d, J = 8.0 Hz, 1H), 7.39 (d, J = 7.6 Hz, 1H),

7.45−7.65 (m, 7H), 7.83 (dd, J = 1.6, 8.0 Hz, 1H), 7.97 (d, J = 1.6 Hz) ppm. ^{13}C NMR ($CDCl_3$) δ 24.8, 86.2, 91.4, 111.9, 118.1, 122.6, 123.5, 124.9, 128.9,129.0, 129.3, 130.5, 136.2, 136.8, 137.1, 137.6, 142.5, 145.5, 159.5 ppm. GC-MS (EI) m/z 294 (M^+). Anal. ($C_{21}H_{14}N_2\cdot$HBr) for C, H, N.

2-(3-Fluorophenyl)-5-(6-methylpyridin-2-ylethynyl)benzonitrile (22). Prepared from **19** and 3-fluorophenylboronic acid according to the general procedure C in 70% yield; purified by column chromatography eluting with hexane/EtOAc (2:1)). The free base was converted to its HBr salt and recrystallized from 2-PrOH as a light-yellow solid; mp 183−185 °C (dec). IR (KBr) 2250, 1593 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H), 7.17(m, 2H), 7.27 (m, 1H), 7.36−7.41 (m, 2H), 7.45−7.53 (m, 2H), 7.62 (d, J = 7.6 Hz, 1H), 7.85 (dd, J = 2.0, 8.4 Hz, 1H), 7.98 (d, J = 1.6 Hz, 1H) ppm. ^{13}C NMR($CDCl_3$) δ 24.6, 84.0, 92.7, 107.8, 112.7, 117.0, 120.2, 122.9, 123.7, 124.2, 124.8, 136.6, 137.3, 137.8, 141.2, 149.0, 159.5 ppm. GC-MS (EI) m/z 312 (M^+). Anal. ($C_{21}H_{13}N_2F\cdot$HBr) for C, H, N.

2-(4-Fluorophenyl)-5-(6-methylpyridin-2-ylethynyl)benzonitrile (23). Prepared from **19** and 4-fluorophenylboronic acid according to the general procedure C in 78% yield; purified by column chromatography eluting with hexane/EtOAc (2:1). The free base was converted to its HBr salt and recrystallized from 2-PrOH as a light-brown solid; mp 197−198 °C (dec). IR (KBr): 2226, 1591, 1506 cm^{-1}. ^{1}H NMR ($CDCl_3$) δ 2.61 (s, 3H), 7.15−7.25 (m, 3H), 7.39 (d, J = 7.6 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 7.53−7.58 (m, 2H), 7.62 (dd, J = 8.0, 8.0 Hz, 1H), 7.81 (dd, J = 1.6, 8.0 Hz, 1H), 7.94 (d, J = 1.6 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.8, 86.1, 91.4, 111.9, 116.1, 116.4, 118.0, 122.8, 123.6, 124.9, 130.4, 130.8, 133.7, 136.2, 137.1, 142.0, 144.5, 159.5 ppm. GC-MS (EI) m/z 312 (M^+). Anal. ($C_{21}H_{13}N_2F\cdot$HBr) for C, H, N.

General Procedure D: Synthesis of the Amides. To a solution of aryl carboxylic acid (1 equiv) in anhydrous dichloromethane and catalytic DMF, thionyl chloride (1.1 equiv) was added at 0−5 °C. The reaction was stirred at reflux for 1 h and then evaporated under reduced pressure. The residue was triturated with dichloromethane and evaporated. The acid chloride was then dissolved in dichloromethane and added to a solution of 2-amino 6-methyl pyridine (0.9 equiv) and pyridine or triethylamine (4−8 equiv) in dichloromethane at 0−5 °C. The reaction was then monitored by TLC, and the product was isolated after washing the reaction mixture with saturated aq NaCl solution (×3), dried over anhydrous Na_2SO_4, and evaporated. The residue was further purified by column chromatography.

General Procedure E: Suzuki Coupling Reaction for Amides. To a solution of bromide or triflate (1 equiv) in toluene or DME/H_2O (3:1) was added a solution of aryl boronic acid (1.2 equiv) in EtOH and a 2 M aq Na_2CO_3 solution (2 equiv). The reaction was degassed with argon for 20 min, and $Pd(PPh_3)_4$ (0.03 equiv) was added under an argon atmosphere. The reaction was flushed with additional argon and quickly sealed airtight. The reaction was quenched by filtering through a pad of celite after stirring overnight at 110 or 80 °C, if DME/H_2O was used, until complete conversion of the starting material, as visualized by TLC. The filtrate was evaporated under reduced pressure, and the residue was further purified by column chromatography.

4-Cyano-*N*-(6-methylpyridin-2-yl)-benzamide (25). To a solution of 4-cyano benzoic acid (0.50 g, 3.39 mmol) in pyridine (2 mL), carbonyldiimidazole (CDI, 0.55 g, 3.39 mmol) was added slowly and stirred at room temperature for 1 h. To this reaction mixture 2-amino-6-methyl pyridine (**24**, 0.30 g, 2.77 mmol) was added and stirred at room temperature for 48 h. The reaction mixture was then added to an ice−water mixture with vigorous stirring. The precipitated product was filtered and washed with water. The crude product was further purified by flash chromatography ($CHCl_3$) to give **25** as a white solid. Yield 0.37 g, 56%; mp 132−134 °C. ^{1}HNMR ($CDCl_3$) δ 2.42 (s, 3H), 6.96−6.98 (d, J = 7.6 Hz, 1H), 7.66−7.70 (t, J = 8.0 Hz, 1H), 7.77−7.91 (dt, J = 8.8, 2.0 Hz, 2H), 8.00−8.03 (dt, J = 8.4, 2.0 Hz, 2H), 8.14−8.17 (d, J = 8.4 Hz, 1H), 8.82 (bs, 1H) ppm. ^{13}CNMR ($CDCl_3$) δ 24.13, 111.42, 115.91, 118.1, 120.3, 128.2, 132.8, 138.5, 139.2, 150.5, 157.3, 164.1 ppm. IR (KBr) 3423, 3053, 2232, 1678, 1601 cm^{-1}. GC-MS (EI) m/z 237 (M^+). Anal. ($C_{14}H_{11}N_3O\cdot 0.75H_2O$) C, H, N.

4-Bromo-*N*-(6-methylpyridin-2-yl)-benzamide hydrobromide (26). Prepared as described in the general procedure D where commercially available 4-bromo benzoyl chloride (7.00 g, 31.89 mmol) was used and the product was converted to the HBr salt as white solid. Yield 7.1 g, 75%; mp 252−254 °C. ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 1H), 6.93−6.95 (d, J = 7.2 Hz, 1H), 7.61−7.64 (dt, J = 8.8, 2.4 Hz, 2H), 7.63−7.67 (t, J = 7.6 Hz, 1H), 7.78−7.81 (dt, J = 6.4, 2.8, Hz, 2H), 8.15−8.17 (d, J = 8.4 Hz, 1H), 8.54 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.2, 111.2, 119.9, 127.2, 129.0, 132.3, 133.4, 139.0, 150.8, 157.2, 164.9 ppm. IR (KBr) 3305, 3059, 1679, 1578, 1455 cm^{-1}. GC-MS (EI) m/z 290 (M^+). Anal. ($C_{13}H_{11}BrN_2O\cdot$HBr) C, H, N.

4-Phenoxy-*N*-(6-methylpyridin-2-yl)-benzamide Hydrobromide (27). Prepared as described in the general procedure D using 4-phenoxy benzoic acid (1.00 g, 4.67 mmol). Yield 0.72 g, 51%; HBr salt: white solid; mp 95−96 °C. ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 6.91−6.93 (d, J = 7.6 Hz, 1H), 7.02−7.08 (m, 4H), 7.18−7.26 (m, 1H), 7.38−7.42 (m, 2H), 7.61−7.65 (t, J = 8.0 Hz, 1H), 7.88−7.92 (m, 2H), 8.17−8.19 (d, J = 8.0 Hz, 1H), 8.58 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24,2, 111.2, 118.0, 119.6, 120.3, 124.7, 128.8, 129.5, 130.3, 139.0, 151.1, 155.9, 157.1, 161.4, 165.2 ppm. IR (KBr) 3316, 3063, 1677, 1601, 1455 cm^{-1}. GC-MS (EI) m/z 304 (M^+). Anal. ($C_{19}H_{16}N_2O_2\cdot$HBr) C, H, N.

4-(Benzyloxy)-*N*-(6-methylpyridin-2-yl)-benzamide (28). Prepared as described in the general procedure D using 4-benzyloxy benzoic acid (4.00 g, 17.5 mmol) as white solid. Yield 3.67 g, 66%, mp 125−126 °C. ^{1}H NMR ($CDCl_3$) δ 2.46 (s, 3H), 5.13 (s, 2H), 6.90−6.92 (d, J = 7.2 Hz, 1H), 7.03−7.05 (d, J = 8.8 Hz, 2H), 7.35−7.45 (m, 5H), 7.61−7.65 (t, J = 8.0 Hz, 1H), 7.88−7.90 (d, J = 9.2 Hz, 2H), 8.16−8.18 (d, J = 8.4 Hz, 1H), 8.48 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.3, 70.4, 111.1, 115.1, 119.5, 127.0, 127.8, 128.5, 128.9, 129.4, 136.4, 138.9, 151.2, 157.1, 162.1, 165.3 ppm. IR (KBr) 3415, 3060, 1673, 1600, 1506 cm^{-1}. GC-MS (EI) m/z 318 (M^+). Anal. ($C_{20}H_{18}N_2O_2\cdot 0.25H_2O$) C, H, N.

4-Phenyl-*N*-(6-methylpyridin-2-yl)-benzamide hydrobromide (29). Prepared as described in the general procedure D where commercially available 4-biphenyl carbonyl chloride (2.00 g, 9.2 mmol) was used. Yield 2.38 g, 89%; mp 92−94 °C(white solid). ^{1}H NMR ($CDCl_3$) δ 2.44 (s, 3H), 6.91−6.92 (d, J = 7.2 Hz, 1H), 7.37−7.41 (m, 1H), 7.44−7.48 (m, 2H), 7.60−7.70 (m, 5H), 7.97−8.00 (dt, J = 8.2, 2, Hz, 2H), 8.21−8.23 (d, J = 8.0 Hz, 1H), 8.77 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.2, 111.3, 119.7, 127.5, 127.6, 128.0, 128.4, 129.2, 133.2, 139.0, 140.0, 145.2, 151.1, 157.2, 165.6 ppm. GC-MS (EI) m/z 288 (M^+). Anal. ($C_{19}H_{16}N_2O$.HBr) C, H, N.

4-(3′-Cyano-phenyl)-*N*-(6-methylpyridin-2-yl)-benzamide Hydrobromide (30). Prepared by following the general procedure E using 3-cyano benzene boronic acid (0.20 g, 1.36 mmol) and compound **26** (0.30 g, 1.13 mmol). Yield 0.27 g, 76%; HBr salt: white solid; mp 285 °C (dec). ^{1}H NMR ($CDCl_3$) δ 2.48 (s, 3H), 6.95−9.97 (d, J = 7.2 Hz, 1H), 7.58−7.61 (t, J = 7.6 Hz, 1H), 7.65−7.70 (m, 3H), 7.85−7.87 (dt, J = 8.8, 1.2 Hz, 1H), 7.90−7.91 (t, J = 1.6 Hz, 1H), 8.04−8.07 (dt, J = 8.4, 2.0 Hz, 2H), 8.20−8.22 (d, J = 8.4 Hz, 1H), 8.70 (bs, 1H) ppm. ^{13}CNMR ($CDCl_3$) δ 24.3, 111.3, 113.5, 118.8, 119.9, 127.7, 128.33, 130.1, 131.0, 131.7, 131.8, 134.3, 141.3, 142.7, 150.9, 157.2, 165.2 ppm. IR (KBr) 3378, 3061, 2227, 1686, 1460 cm^{-1}. GC-MS (EI) m/z (M^+) 313. Anal. ($C_{20}H_{15}N_3O$.HBr) C, H, N.

4-(3′-Chloro-phenyl)-*N*-(6-methylpyridin-2-yl)-benzamide Hydrobromide (31). Prepared by following the general procedure E using 3-chloro benzene boronic acid (0.20 g, 1.28 mmol) and compound **26** (0.31 g, 1.06 mmol). Yield 0.27 g, 78%; HBr salt: white solid; mp 258−260 °C. ^{1}H NMR ($CDCl_3$) δ 2.47 (s, 3H), 6.93−6.95 (d, J = 7.6 Hz, 1H), 7.35−7.38 (m, 1H), 7.38−7.42 (t, J = 8.0 Hz, 1H), 7.49−7.52 (dt, J = 7.2, 2.0 Hz, 1H), 7.60−7.61 (m, 1H), 7.64−7.69 (m, 3H), 7.99−8.02 (dt, J = 8.0, 2.4, 2H), 8.20−8.22 (d, J = 8.4 Hz, 1H), 8.63 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.3, 111.2, 119.8, 125.6, 127.6, 127.7, 128.1, 128.4, 130.4, 133.8, 135.1, 139.0, 141.9, 143.7, 151.0, 157.2, 165.3 ppm.

IR (KBr) 3416, 3062, 1677, 1601, 1510 cm^{-1}. GC-MS (EI) *m/z* 322 (M^+). Anal. ($C_{19}H_{15}ClN_2O \cdot HBr$) C, H, N.

3,5-Difluoro-*N*-(6-methylpyridin-2-yl)-benzamide (32). Prepared as described in the general procedure D using 3,5-difluoro benzoic acid (1.0 g, 5.66 mmol). Yield 1.0 g, 45%; mp 129−132 °C (white solid). ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H), 6.95−7.03 (m, 2H), 7.41−7.46 (m, 2H), 7.64−7.68 (t, $J = 8.0$ Hz, 1H), 8.12−8.14 (d, $J = 8.4$ Hz, 1H), 8.56 (bs, 1H) ppm. ^{13}CNMR ($CDCl_3$) δ 24.2, 107.5, 107.8, 108.0, 110.6, 110.7, 110.8, 110.9, 111.3, 120.2, 137.9, 138.0, 139.1, 150.5, 157.3, 162.0, 162.1, 164.5, 164.6 ppm. IR (KBr) 3338, 3074, 1696, 1599, 1580, 1561 cm^{-1}. GC-MS (EI) *m/z* 248 (M^+). Anal. ($C_{13}H_{10}F_2N_2O$) C, H, N.

3,4-Difluoro-*N*-(6-methylpyridin-2-yl)-benzamide (33). Prepared as described in the general procedure D using 3,4-difluoro benzoic acid (1.0 g, 5.66 mmol). Yield 1.10 g, 45%; mp 88−91 °C (white solid). ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H), 6.94−6.96 (d, $J = 7.2$ Hz, 1H), 7.23−7.30 (m, 1H), 7.64−7.69 (m, 2H), 7.77−7.82 (m, 1H), 8.12−8.14 (d, $J = 8.0$ Hz, 1H), 8.55 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.0, 111.1, 117.1, 117.1, 117.3, 117.6, 117,8, 119.8, 123.5, 123.6, 123.6, 123.6, 131.5, 138.9, 149.1, 149.3, 150.4, 151.6, 151.6, 151.7, 151.8, 154.1, 154.2, 157.1, 163.4 ppm IR (KBr) 3338, 3042, 1647, 1601, 1541 cm^{-1}. GC-MS (EI) *m/z* 248 (M^+). Anal. ($C_{13}H_{10}F_2N_2O$) C, H, N.

3-Cyano-5-fluoro-*N*-(6-methylpyridin-2-yl)-benzamide Hydrochloride (34). Prepared as described in the general procedure D using 3-cyano-5-fluorobenzoic acid (900 mg, 5.46 mmol). Yield 407 mg, 100%; HBr salt: white solid; mp 245 −247 °C. ^1H NMR ($CDCl_3$) δ 2.49 (s, 3H), 6.98−7.00 (m, 1H), 7.55−7.57 (m, 1H), 7.67−7.71 (m, 2H), 7.91−7.93 (m, 1H), 8.04 (s, 1H), 8.12−8.14 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.2, 111.3, 120.0, 127.0, 139.3, 167.5 ppm. GC-MS (EI) *m/z* 255 (M^+). Anal. ($C_{14}H_{10}FN_3O \cdot HCl$), C, H, N.

4-Bromo-3-fluoro-*N*-(6-methylpyridin-2-yl)-benzamide (35). Prepared as described in the general procedure D using 4-bromo-3-fluorobenzoic acid (0.87 g, 4.0 mmol) as a yellow solid. Yield 1.0 g, 81%. ^1H NMR ($CDCl_3$) δ 2.45−2.49 (s, 3H), 6.95−6.97 (m, 1H), 7.57−7.74 (m, 4H), 8.13−8.15 (m, 1H) ppm. GC-MS (EI) *m/z* 310 (M^+).

3-Bromo-5-fluoro-*N*-(6-methylpyridin-2-yl)-benzamide (36). Prepared as described in the general procedure D using 3-bromo-5-fluoro benzoic acid (2.0 g, 9.13 mmol) as a white solid. Yield 2.36 g, 83%; mp 189−190 °C. ^1H NMR ($CDCl_3$) δ 2.58 (s, 3H), 7.02−7.04 (d, $J = 8.0$ Hz, 1H), 7.45−7.48 (m, 1H), 7.73−7.80 (m, 2H), 8.08−8.11 (dt, $J = 11.2$, 1.2 Hz, 1H), 8.31−8.33 (d, $J = 8.0$ Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 23.5, 112.2, 114.2, 114.4, 120.4, 122.8, 123.1, 126.8, 126.8, 139.9, 150.8, 156.8 164.1 ppm. GC-MS (EI) *m/z* 309 (M^+).

3-Fluoro-*N*-(6-methylpyridin-2-yl)-5-(pyridin-3-yl)-benzamide (37). Prepared as described in the general procedure E using 3-pyridyl boronic acid (0.18 g, 1.45 mmol) and compound **36** (0.30 g, 0.97 mmol). Yield 0.11 g, 37%; HBr salt: white solid; mp >275 °C. ^1H NMR ($CDCl_3$) δ 2.47 (s, 3H), 6.96−6.98 (d, $J = 7.6$ Hz, 1H), 7.40−7.44 (m, 1H), 7.46−7.50 (m, 1H), 7.65−7.69 (m, 2H), 7.89−7.91 (m, 2H), 8.17−8.19 (d, $J = 8.4$ Hz, 1H), 8.67−8.68 (m, 1H), 8.69 (bs, 1H), 8.87−8.88 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.2, 111.3, 114.1, 114.4, 117.8, 118.0, 120.1, 121.9, 121.9, 124.0, 128.8, 132.3, 134.7, 137.7, 137.7, 139.1, 141.0, 141.1, 148.4, 149.9, 150.6, 157.3, 162.2, 164.2, 164.7 ppm. IR (KBr) 3382, 3063, 1686, 1597, 1554, 1461 cm^{-1}. GC-MS (EI) *m/z* 307 (M^+). Anal. ($C_{18}H_{14}FN_3O.2HBr \cdot 1.5H_2O$) C, H, N.

5-Fluoro-2′-methoxy-*N*-(6-methylpyridin-2-yl)biphenyl-3-carboxamide Hydrobromide (38). To a clean and dry reaction tube, compound **36** (0.20 g, 0.64 mmol), 2-dicyclohexylphosphino-2′,6′-dimethoxy biphenyl (5 mg, 2 mol %), $Pd(OAc)_2$ (1.5 mg, 1 mol %), 2-methoxy benzene boronic acid (0.15 g, 0.9 mmol) powdered potassium phosphate (0.27 g, 1.2 mmol), and degassed toluene/EtOH (3 mL/0.5 mL) were added together and flushed with argon and quickly sealed airtight. The reaction was heated to 100 °C for 2 h and filtered through celite and the filtrate was evaporated. The crude product was passed through silica gel column eluting with chloroform. Yield 0.13 g, 60%; HBr salt: white solid; mp 206−208 °C. ^1H NMR ($CDCl_3$) δ 2.45 (s, 3H), 3.83 (s, 3H), 6.92−6.94 (d, $J = 7.6$ Hz, 1H), 7.00−7.02 (d, $J = 8.4$ Hz, 1H), 7.03−7.07 (td, $J = 1.2$, 7.2 Hz, 1H), 7.31−7.33 (dd, $J = 1.6$, 7.6 Hz, 1H), 7.36−7.40 (m, 1H), 7.44−4.48 (m, 1H), 7.58−7.62 (m, 1H), 7.62−7.66 (t, $J = 8$ Hz, 1H), 7.81−7.82 (t, $J = 1.6$ Hz, 1H), 8.17−8.19 (d, $J = 8.4$ Hz, 1H), 8.56 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.2, 55.8, 111.2, 111.5, 113.1, 113.4, 119.9, 120.5, 120.7, 121.2, 124.0, 124.0, 128.4, 130.0, 130.9, 136.3, 136.4, 139.0, 141.6, 141.7, 150.8, 156.5, 157.2, 161.5, 164.0, 164.7, 164.8 ppm. IR (KBr) 3060, 1678, 1601, 1530, 1455 cm^{-1}. GC-MS (EI) *m/z* 336 (M^+). Anal. ($C_{20}H_{17}FN_2O_2 \cdot HBr$) C, H, N.

5-Fluoro-2′-methyl-*N*-(6-methylpyridin-2-yl)biphenyl-3-carboxamide hydrobromide (39). Prepared from compound **36**, as described above for compound **38**, using 2-methyl benzene boronic acid (0.125 g, 0.9 mmol). Yield 0.14 g, 67%; HBr salt: white solid; mp 207−210 °C. ^1H NMR ($CDCl_3$) δ 2.28 (s, 3H), 2.46 (s, 3H), 6.94−6.96 (d, $J = 7.6$ Hz, 1H), 7.21−7.34 (m, 5H), 7.61−7.62 (d, $J = 2.0$ Hz, 1H), 7.63−7.67 (t, $J = 7.6$ Hz, 1H), 7.64−7.65 (m, 1H), 8.15−8.18 (d, $J = 8.4$ Hz, 1H), 8.48 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 20.3, 24.0, 111.0, 113.0, 113.2, 119.7, 119.8, 120.0, 123.4, 123.4, 126.1, 128.3, 129.5, 130.6, 135.2, 136.4, 136.4, 138.8, 139.5, 144.9, 145.0, 150.5, 157.0, 161.3, 163.8, 164.3 ppm. IR (KBr) 3295, 3063, 1681, 1531, 1455 cm^{-1}. GC-MS (EI) *m/z* 320 (M^+). Anal. ($C_{20}H_{17}FN_2O \cdot HBr$) C, H, N.

3-Fluoro-*N*-(6-methylpyridin-2-yl)-4-(pyridine-3-yl)-benzamide hydrochloride (40). Prepared as described in the general procedure E using pyridin-3-ylboronic acid (0.29 g, 2.41 mmol) and compound **35** (0.62 g, 2.0 mmol). Yield 0.40 g, 65%; HCl salt: white solid; mp 280 °C (dec). ^1H NMR ($CDCl_3$) δ 2.50 (s, 3H), 6.96−6.98 (m, 1H), 7.41−7.44 (m, 1H), 7.57−7.94 (m, 5H), 8.18−8.20 (m, 1H), 8.67 (m, 1H), 8.84 (s, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.3, 111.3, 115.9, 116.1, 120.0, 123.3, 123.4, 123.7, 131.1, 136.6, 139.1, 149.7, 157.3 ppm. GC-MS (EI) *m/z* 307 (M+). Anal. ($C_{18}H_{14}FN_3O \cdot 2HCl \cdot 0.25H_2O$), C, H, N.

3-Chloro-*N*-(6-methylpyridin-2-yl)-4-(pyridine-3-yl)-benzamide Hydrochloride (41). Prepared as described in the general procedure E using pyridin-3-ylboronic acid (431 mg, 3.53 mmol) and 4-bromo-3-chloro-*N*-(6-methylpyridin-2-yl) benzamide (1.04 g, 3.21 mmol), which was prepared using the general procedure D from 4-bromo-3-chlorobenzoic acid (942 mg, 4.0 mmol). Yield 775 mg, 60%; HCl salt: white solid; mp 252−254 °C (dec). ^1H NMR ($CDCl_3$) δ 2.50 (s, 3H), 6.97−6.99 (m, 1H), 7.41−7.50 (m, 2H), 7.66−7.70 (m, 1H), 7.82−7.92 (m, 2H), 8.11−8.20 (m, 2H), 8.70−8.72 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.3, 111.2, 120.1, 125.9, 129.5, 131.9, 133.8, 135.7, 137.0, 139.2, 149.6, 150.0, 157.3, 167.4 ppm. GC-MS (EI) *m/z* 323 (M^+). Anal. ($C_{18}H_{14}ClN_3O \cdot 2HCl \cdot 0.5H_2O$), C, H, N.

5-Bromo-*N*-(6-methylpyridin-2-yl)nicotinamide (42). Prepared as described in the general procedure D using 5-bromo nicotinic acid (3.0 g, 14.8 mmol). Yield 4.43 g, 100%; mp 140−142 °C. ^1H NMR ($CDCl_3$) δ 2.51 (s, 3H), 6.99−7.01 (m, 1H), 7.69−7.71 (m, 1H), 8.16−8.19 (m, 1H), 8.42−8.43 (m, 2H), 8.85−8.86 (m, 2H) ppm. ^{13}C NMR ($CDCl_3$) δ 23.8, 111.9, 114.2, 120.4, 121.2, 131.6, 138.2, 139.7, 146.6, 154.2 ppm. Anal. ($C_{20}H_{18}N_2O_2 \cdot HBr \cdot H_2O$) C, H, N.

6-bromo-*N*-(6-methylpyridin-2-yl)-nicotinamide (43). Prepared as described in the general procedure D using 6-bromonicotinic acid (1.01 g, 5 mmol). Yield 1.24 g, 85%. ^1H NMR ($CDCl_3$) δ 2.47 (s, 3H), 6.97−6.99 (m, 1H), 7.46−7.48 (m, 1H), 7.67−7.69 (m, 1H), 8.11−8.13 (m, 1H), 8.19−8.20 (m, 1H), 8.94−8.95 (m, 1H) ppm.

5-(3′-Pyridyl)-*N*-(6-methylpyridin-2-yl)-nicotinamide hydrobromide (44). Prepared using the general procedure E using 3-pyridyl boronic acid (0.19 g, 1.54 mmol) and compound **42** (0.30 g, 1.0 mmol). Yield 0.19 g, 64%; HBr salt: light-orange solid; mp >275 °C. ^1H NMR ($CDCl_3$) δ 2.48 (s, 3H), 6.97−6.99 (d, $J = 7.6$ Hz, 1H), 7.44−7.48 (m, 1H), 7.67−7.71 (t, $J = 7.6$ Hz, 1H), 7.92−7.95 (m, 1H), 8.17−8.19 (d, $J = 8.0$ Hz, 1H), 8.44−8.45 (t, $J = 2.4$ Hz, 1H), 8.71−8.73 (dd, $J = 1.6$, 3.2 Hz, 1H), 8.83 (bs, 1H), 8.90−8.91 (dd, $J = 0.8$, 1.6 Hz, 1H), 9.02−9.03 (d, $J = 2.0$ Hz, 1H), 9.18−9.19 (d, $J = 2.0$ Hz, 1H) ppm. ^{13}CNMR ($CDCl_3$) δ

24.2, 111.5, 120.3, 124.2, 130.7, 132.6, 134.0, 134.8, 139.2, 147.7, 148.4, 150.2, 150.5, 151.3, 157.4, 163.7 ppm. IR (KBr) 3232, 3055, 1678, 1579, 1457 cm^{-1}. GC-MS (EI) *m/z* 289 (M^+). Anal. ($C_{17}H_{14}N_4O \cdot 3HBr \cdot 1.5H_2O$) C, H, N.

5-(2-Methoxyphenyl)-*N*-(6-methylpyridin-2-yl)-nicotinamide Hydrobromide (45). Prepared as described for the synthesis of compound **38** using 2-methoxy boronic acid (0.15 g, 1.0 mmol) and compound **42** (0.20 g, 0.68 mmol). Yield 0.11 g, 50%; HBr salt: white solid; mp 229−232 °C. ^1H NMR ($CDCl_3$) δ 2.47 (s, 3H), 3.84 (s, 3H), 6.95−6.97 (d, J = 7.2 Hz, 1H), 7.02−7.04 (dd, J = 0.8, 8.4 Hz, 1H), 7.07−7.11 (td, J = 7.6, 1.2 Hz, 1H), 7.33−7.36 (dd, J = 2, 7.2 Hz, 1H), 7.39−7.44 (m 1H), 7.65−7.69 (t, J = 7.6 Hz, 1H), 8.18−8.20 (d, J = 8.0 Hz, 1H), 8.37−8.39 (t, J = 2.4 Hz, 1H), 8.62 (bs, 1H), 8.93−8.94 (d, J = 2.4 Hz, 1H), 9.08−9.09 (d, J = 2.0 Hz, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ24.2, 55.8, 111.3, 111.5, 120.1, 121.4, 126.0, 129.7, 130.4, 130.9, 134.7, 135.9, 139.1, 146.6, 150.6, 153.5, 156.6, 156.8, 157.3, 164.2, 166.5 ppm. GC-MS (EI) *m/z* 319 (M^+). Anal. ($C_{19}H_{17}N_3O_2 \cdot 2HBr \cdot H_2O$) C, H, N.

***N*-(6-Methylpyridin-2-yl)-6-phenylnicotinamide Hydrochloride (46).** Prepared as described in the general procedure E using phenyl boronic acid (146.3 mg, 1.2 mmol) and compound **43** (292 mg, 1 mmol). Yield 250 mg, 87%; HCl salt: white solid; mp 230 °C (dec). ^1H NMR ($CDCl_3$) δ 2.50 (s, 3H), 6.95−6.97 (m, 1H), 7.45−7.53 (m, 3H), 7.64−7.85 (m, 2H), 8.05−8.07 (m, 2H), 8.18−8.20 (m, 1H), 8.27−8.29 (m, 1H), 9.23 (m, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.2, 111.5, 120.1, 127.5, 128.3, 129.2, 130.2, 136.2, 138.4, 139.1, 148.7, 150.7, 157.3, 160.6, 164.1 ppm. GC-MS *m/z* 289 (M+). Anal. ($C_{18}H_{15}N_3O \cdot 2HCl \cdot 0.25H_2O$), C, H, N.

***N*-(6-Methylpyridin-2-yl)-2,3′-bipyridine-5-carboxamide Hydrochloride (47).** Prepared as described in the general procedure E using pyridine-3-ylboronic acid (148 mg, 1.2 mmol) and compound **43** (292 mg, 1 mmol). Yield 200 mg, 69%; HCl salt: white solid; mp 260 °C (dec). ^1H NMR ($CDCl_3$) δ 2.50 (3H, s, CH_3), 6.97−6.99 (1H, m), 7.44−7.47 (1H, m), 7.67−7.71 (1H,m), 7.89−7.91 (1H, m), 8.18−8.21 (1H, m), 8.34−8.42 (2H, m), 8.72 (1H, s), 9.27−9.28 (2H, m) ppm. ^{13}C NMR ($CDCl_3$) δ 24.3, 11.4, 120.1, 120.4, 124.0, 129.0 135.0, 136.5, 139.2, 148.7, 149.0, 150.6, 151.0, 157.3, 158.0, 163.7 ppm. Anal. ($C_{17}H_{14}N_4O \cdot 2HCl \cdot 0.5H_2O$), C, H, N.

Benzyl-4-(benzyloxy)-3-bromobenzoate (49). 3-Bromo, 4-hydroxy benzoic acid (**48**, 15.00 g, 69.0 mmol) was dissolved in 150 mL anhydrous acetone and then stirred at reflux overnight with anhydrous K_2CO_3 (24.0 g, 170 mmol) and benzyl bromide (24.8 g, 17.2 mL, 145 mmol). The reaction mixture was filtered hot, and the filtrate was evaporated under reduced pressure. The clear oil obtained solidified in nearly quantitative yield (29.0 g, 99%), which was used for next reaction without further purification. An analytical sample was purified by flash column chromatography eluting with $CHCl_3$; mp 74−76 °C. ^1H NMR ($CDCl_3$) δ 5.17 (s, 2H), 5.31 (s, 2H), 6.89−6.91 (d, J = 8.8 Hz, 1H), 7.20−7.44 (m, 10H), 7.94−7.97 (m, 1H), 8.27−8.28 (m, 1H) ppm. $^{13}CNMR$ ($CDCl_3$) δ 66.9, 70.9, 112.3, 112.78, 124.0, 126.3, 127.1, 128.3, 128.4, 128.5, 128.8, 128.8, 130.8, 133.2, 135.1, 135.2, 136.1, 158.8, 165.1 ppm. IR (KBr) 3033, 1717, 1598, 1497, 1268 cm^{-1}. GC-MS (EI) *m/z* 396 (M^+).

Benzyl-4-(benzyloxy)-3-cyanobenzoate (50). A solution of compound **49** (4.5 g, 11 mmol) and $Zn(CN)_2$ (0.8 g, 7 mmol) in DMF (20 mL) was stirred at room temperature for 20 min under an argon atmosphere. $Pd(PPh_3)_4$ (0.65 g, 5 mol %) was added, and the solution was heated to 80 °C overnight. The reaction was cooled to room temperature and filtered over celite. The clear solution was evaporated under vacuum to remove DMF. The residue was extracted with $CHCl_3$ (25 mL × 2) from H_2O (50 mL). The organic layer was washed with saturated aq NaCl solution (25 mL × 2), dried over anhydrous Na_2SO_4, and evaporated under reduced pressure. The residue obtained was purified by flash column chromatography eluting with *n*-hexanes/EtOAc (4:1) to obtain a white solid. Yield 3.8 g, 97%; mp 86−88 °C. ^1H NMR ($CDCl_3$) δ 5.26 (s, 2H), 5.34 (s, 2H), 7.02−7.04 (d, J = 9.2 Hz, 1H), 7.31−7.45 (m, 10H), 8.17−8.20 (dd, J = 2.4, 6.4 Hz, 1H), 8.28−8.29 (d, J = 2.0, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 67.3, 71.2, 102.8, 112.7, 115.6, 123.4, 127.2, 128.5, 128.7, 128.8, 129.0, 135.0, 135.7, 135.9, 136.1, 163.5, 164.5 ppm. IR (KBr) 3090, 3034, 2231, 1716, 1607 cm^{-1}. GC-MS (EI) *m/z* 343 (M^+).

4-(Benzyloxy)-3-cyanobenzoic Acid (51). To a solution of compound **50** (3.5 g, 10 mmol) in MeOH (70 mL), aq solution of 4 N NaOH (1.2 g in 7.6 mL H_2O, 30 mmol) was added. The solution was evaporated after stirring at room temperature for 2 h. The residue was dissolved in H_2O, and the insolubles were removed by filtration. The filtrate was neutralized carefully with conc HCl (pH 2) and the precipitated white solid was filtered and washed with cold water and dried in vacuo. Yield 2.4 g, 93%; mp 203−207 °C. ^1H NMR (MeOH-d_4) δ 5.27 (s, 2H), 7.25−7.39 (m, 4H), 7.45−7.46 (m, 2H), 8.16−8.19 (m, 2H) ppm. ^{13}C NMR (MeOH-d_4) δ 70.9, 101.9, 112.8, 115.1, 123.9, 127.2, 128.1, 128.4, 135.3, 135.6, 136.0, 163.5, 166.2 ppm. IR (KBr) 3045, 2230, 1709, 1606, 1502 cm^{-1}.

4-(Benzyloxy)-3-cyano-*N*-(6-methylpyridin-2-yl)-benzamide (52). Prepared by following the general procedure D using compound **51** (2.2 g, 8.7 mmol). The residue was further purified by flash column chromatography eluting with *n*-hexanes/EtOAc (4:1). Yield 2.5 g, 83%; mp 158−160 °C (white solid). ^1H NMR ($CDCl_3$) δ 2.44 (s, 3H), 5.29 (s, 2H), 6.93−6.95 (d, J = 7.6 Hz, 1H), 7.07−7.09 (d, J = 8.8 Hz, 1H), 7.34−7.47 (m, 5H), 7.62−7.66 (t, J = 7.2 Hz, 1H), 8.04−8.06 (dd, J = 2.4, 6.0 Hz, 1H), 8.10−8.12 (d, J = 8.4 Hz, 1H), 8.16−8.17 (d, J = 2.4 Hz, 1H), 8.53 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.2, 71.3, 103.2, 111.2, 113.1, 115.5, 120.0, 127.3, 127.6, 128.8, 129.1, 133.5, 135.0, 139.1, 150.1, 157.3, 162.9, 163.3 ppm. IR (KBr) 3316, 3065, 2925, 2231, 1674, 1577, 1454 cm^{-1}. GC-MS (EI) *m/z* 343 (M^+).

3-Cyano-4-hydroxy-*N*-(6-methylpyridin-2-yl)benzamide (53). To a solution of compound **52** (2.4 g, 7.01 mmol) in anhydrous EtOH (40 mL) and cyclohexene (20 mL), 10% Pd/C (0.49 g) was added slowly. The suspension was refluxed for 1 h and carefully filtered hot through a celite pad. The filtrate was evaporated under reduced pressure to obtain the desired product as white solid. Yield 1.56 g, 87%; mp 268−270 °C. ^1H NMR (DMSO-d_6) δ 2.39 (s, 3H), 6.95−6.97 (d, J = 7.6 Hz, 1H), 7.03−7.05 (d, J = 8.8 Hz., 1H), 7.64−7.67 (t, J = 7.6 Hz, 1H), 7.91−7.93 (d, J = 8.0 Hz, 1H), 8.07−8.10 (dd, J = 2.0, 6.8 Hz, 1H), 8.32−8.33 (d, J = 2.4 Hz, 1H), 10.64 (bs, 1H), 11.81 (bs, 1H) ppm. ^{13}C NMR (DMSO-d_6) δ 24.2, 99.3, 112.24, 116.2, 117.0, 119.7, 125.9, 134.4, 135.5, 139.1, 152.1, 157.2, 163.6, 164.6 ppm.

3-Cyano-4-trifluoromethylsulfonyl-*N*-(6-methylpyridin-2-yl)-benzamide (54). To a solution of the compound **53** (0.95 g, 3.8 mmol) in anhydrous dichloromethane (20 mL) and pyridine (5 mL), trifluoromethanesulfonic anhydride (1.17 g, 0.7 mL, 4.1 mmol) was added at 0 °C. The reaction was further stirred at room temperature overnight, and additional trifluoromethanesulfonic anhydride (0.7 mL) was added and stirred at room temperature for 1 h. The reaction was then washed with brine (25 mL × 2), dried over anhydrous sodium sulfate, and evaporated under reduced pressure. The yellowish oily product was used for next reaction without further purification. Crude yield 1.4 g (96%). GC-MS (EI) *m/z* 385 (M^+).

3-Cyano-4-phenyl-*N*-(6-methylpyridin-2-yl)-benzamide Hydrobromide (55). Prepared by following the general procedure E using phenyl boronic acid (2.02 g, 16.53 mmol) and compound **54** (5.0 g, 13 mmol). Yield 3.5 g, 86%; HBr salt: white solid; mp 238−242 °C. ^1H NMR ($CDCl_3$) δ 2.50 (s, 3H), 6.98−7.00 (d, J = 7.6 Hz, 1H), 7.50−7.56 (m, 3H), 7.60−7.62 (m, 2H), 7.66−7.68 (d, J = 8.4, 1H), 7.67−7.71 (t, J = 7.6 Hz, 1H), 8.16−8.18 (dd, J = 1.6, 6.4 Hz, 2H), 8.34−8.35 (d, J = 1.6 Hz, 1H), 8.50 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.0, 111.1, 112.1, 117.7, 120.0, 128.7, 129.0, 129.5, 130.7, 131.1, 132.8, 133.7, 137.0, 138.9, 148.7, 150.3, 157.2, 163.2 ppm. IR (KBr) 3308, 3063, 2229, 1679, 1602, 1533, 1455 cm^{-1}. GC-MS (EI) *m/z* 313 (M^+); Anal. ($C_{20}H_{15}N_3O \cdot HBr$) C, H, N.

3-Cyano-4-(3′-fluorophenyl)-*N*-(6-methylpyridin-2-yl)-benzamide Hydrobromide (56). Prepared by following the general procedure E using 3-fluorophenyl boronic acid (2.31 g,16.53 mmol) and compound **54** (5.0 g, 13 mmol). Yield 3.8 g, 88%; HBr salt: white solid; mp 266−268 °C. ^1H NMR ($CDCl_3$) δ 2.50 (s, 3H), 6.98−7.00 (d, J = 7.2 Hz, 1H), 7.18−7.23 (m, 1H), 7.28−7.32 (dt, J = 2.4, 9.2

Hz, 1H), 7.39−7.42 (dt, J = 1.2, 8.4 Hz, 1H), 7.49−7.54 (m, 1H), 7.64−7.66 (d, J = 8.0, 1H), 7.67−7.71 (t, J = 7.2 Hz, 1H), 8.16−8.19 (t, J = 7.2 Hz, 1H), 8.17−8.19 (d, J = 8.0 Hz, 1H), 8.35−8.36 (d, J = 2.0 Hz, 1H), 8.51 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.0, 111.1, 112.2, 115.8, 116.0, 116.4, 116.6, 117.4, 117.4, 120.1, 124.6, 124.6, 130.6, 130.6, 130.7, 131.2, 132.9, 134.3, 138.9, 139.0, 147.2, 147.2, 150.2, 157.2, 161.6, 163.0, 164.0 ppm. IR (KBr) 3378, 2231, 1685, 1585.96, 1459.5 60 cm^{-1}. GC-MS (EI) *m/z* 331 (M^+). Anal. ($C_{20}H_{14}FN_3O\cdot HBr$) C, H, N.

3-Cyano-4-(4′-fluorophenyl)-*N*-(6-methylpyridin-2-yl)-benzamide Hydrobromide (57). Prepared by following the general procedure E using 4-fluorobenzene boronic acid (0.2 g, 1.4 mmol) and compound **54** (0.46 g, 1.10 mmol). The crude residue was purified by flash column chromatography, eluting with *n*-hexanes: EtOAc (4:1) to obtain a white solid. Yield 0.20 g, 50%; HBr salt: light-orange solid; mp >275 °C. ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 6.98−7.00 (d, J = 7.2 Hz, 1H), 7.21−7.26 (m, 2H), 7.58−7.61 (m, 2H), 7.63−7.65 (d, J = 8.4 Hz, 1H), 7.67−7.71 (t, J = 7.6 Hz, 1H), 8.16−8.18 (dd, J = 2.0, 6.4 Hz, 2H), 8.33−8.34 (d, J = 1.6 Hz, 1H), 8.51 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.0, 111.1, 112.1, 116.0, 116.2, 117.6, 120.1, 130.5, 130.6, 130.7, 131.2, 132.8, 133.0, 133.0, 133.9, 139.0, 147.6, 150.2, 157.2, 162.3, 163.0, 164.8 ppm. IR (KBr) 3292, 3063, 2923, 2230, 1668, 1602.8, 1455 cm^{-1}. Anal. ($C_{20}H_{14}FN_3O\cdot HBr$) C, H, N.

3-Cyano-*N*-(6-methylpyridin-2-yl)-4-(naphthalen-1-yl)-benzamide (58). Prepared by following the general procedure E using 1-naphthyl boronic acid (0.25 g, 1.4 mmol) and compound **54** (0.46 g, 1.10 mmol). The crude residue was purified by flash column chromatography, eluting with *n*-hexanes:EtOAc (4:1) to obtain a white solid. Yield 0.20 g, 46%; mp158−162 °C. ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 6.96−6.98 (d, J = 7.6 Hz, 1H), 7.44−7.59 (m, 5H), 7.63−7.65 (d, J = 8.4 Hz, 1H), 7.66−7.70 (t, J = 8.0 Hz, 1H), 7.93−9.95 (d, J = 8.4 Hz, 1H), 7.96−7.98 (d, J = 7.6 Hz, 1H), 8.18−8.20 (dd, J = 2.0, 5.6 Hz, 1H), 8.19−8.21 (d, J = 7.6 Hz, 1H), 8.40−8.41 (d, J = 2.0 Hz, 1H), 8.93 (bs, 1H) ppm. ^{13}C NMR ($CDCl_3$) δ 24.0, 111.2, 114.3, 117.1, 120.0, 124,8, 125.2, 126.4, 126.9, 127.5, 128.7, 129.8, 130.6, 131.0, 132.1, 132.3, 133.7, 134.3, 134.7, 139.0, 147.8, 150.4, 157.1, 163.5 ppm. IR (neat, cm^{-1}) 3308, 3061, 2230, 1681, 1603, 1578, 15312 cm^{-1}. Anal. ($C_{24}H_{17}N_3O\cdot HBr$) C, H, N.

3-Cyano-*N*-(6-methylpyridin-2-yl)-4-(pyridine-3-yl)-benzamide Hydrochloride (59). Prepared by following the general procedure E using pyridine-3-ylboronic acid (204 mg, 1.66 mmol) and compound **54** (0.50 g, 1.3 mmol). Yield 74%; HBr salt: white solid; mp 258 °C (dec). ^{1}H NMR ($CDCl_3$) δ 2.50−2.52 (s, 3H), 6.99−7.01 (m, 1H), 7.48−7.51 (m, 1H), 7.68−7.72 (m, 2H), 7.99−8.02 (m, 1H), 8.17−8.26 (m, 2H), 8.41−8.42 (m, 1H), 8.76−8.82 (m, 2H), ppm. ^{13}C NMR ($CDCl_3$) δ 24.3, 111.3, 112.6, 117.5, 120.3, 123.8, 130.8, 131.7, 133.2, 133.3, 134.9, 136.3, 139.3, 145.2, 149.4, 150.4, 150.8, 157.4, ppm. GC−MS (EI) *m/z* 314 (M^+). Anal. ($C_{19}H_{14}N_4O\cdot 2HCl\cdot 0.75H_2O$), C, H, N.

X-ray Crystal Structures of compounds 4, 10, and 57. Single-crystal X-ray diffraction data on compound **4** was collected using Cu Kα radiation and a Bruker Platinum-135 CCD area detector. Single-crystal X-ray diffraction data on compounds **10** and **57** were collected using Mo Kα radiation and a Bruker APEX 2 CCD area detector. The structures was solved by direct methods and refined by full-matrix least-squares on F^2 values using the programs found in the SHELXTL suite (Bruker, SHELXTL v6.10, 2000, Bruker AXS Inc., Madison, WI). Parameters refined included atomic coordinates and anisotropic thermal parameters for all non-hydrogen atoms. Hydrogen atoms on carbons were included using a riding model [coordinate shifts of C applied to H atoms] with C−H distance set at 0.96 Å. Atomic coordinates for these compounds have been deposited with the Cambridge Crystallographic Data Centre (deposition numbers 719936, 719937, and 719938 for compounds **4**, **10**, and **57** respectively). Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge, CB2 1EZ, UK [fax: +44(0)-1223−336033 or e-mail: deposit@ccdc.cam.ac.uk].

4-(3,5-Difluorophenyl)-*N*-(6-methylpyrindin-2-yl)picolinamide Hydrobromide (4). A 0.20 × 0.01 × 0.005 mm^3 crystal of **4** was prepared for data collection coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was placed on a MicroMesh mount *MiTeGen, Ithaca, NY) and transferred immediately to the diffractometer. The crystal was orthorhombic in space group $P2_12_12$ with unit cell dimensions a = 14.2137(5) Å, b = 34.1135(15) Å, and c = 3.8411(2) Å. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 98.3% complete to 67.59° θ (approximately 0.83 Å) with an average redundancy of 4.46.

1-Fluoro-3-(pyridin-3-yl)-5-(2-methylthiazol-4ylethynyl)benzene (10). A 0.32 × 0.15 × 0.04 mm^3 crystal of 10 was prepared for data collection coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was placed on a MicroMesh mount *MiTeGen, Ithaca, NY) and transferred immediately to the cold stream on the diffractometer. The crystal was monoclininc in space group $P2_1$/c with unit cell dimensions a = 22.259(3) Å, b = 16.020(2) Å, c = 10.4700(15) Å, and β = 99.141(5)°. Corrections were applied for Lorentz, polarization, and absorption effects. Data were 98.4% complete to 24.74° θ (approximately 0.75 Å) with an average redundancy of 2.59.

3-Cyano-4-(4′-fluorophenyl)-*N*-(6-methylpyridin-2-yl)-benzamide Hydrobromide (57). A 0.198 × 0.056 × 0.019 mm^3 crystal of **57** was prepared for data collection coating with high viscosity microscope oil (Paratone-N, Hampton Research). The oil-coated crystal was placed on a MicroMesh mount (*MiTeGen, Ithaca, NY) and transferred immediately to the cold stream on the diffractometer. The crystal was monoclinic in space group $P2_1$/a with unit cell dimensions a = 7.2307(16) Å, b = 16.994(4) Å, c = 14.271(3) Å, and β = 90.278(4)°. Corrections were applied for Lorentz, polarization and absorption effects. Data were 99.9% complete to 25.00° θ (approximately 0.75 Å) with an average redundancy of 5.2 for all data from the twinned crystal. Only nonoverlapped reflections from the strong component were used in the final refinement; these data were 82.5% complete to 25.00° θ.

Calcium Fluorescence Assay. HEK 293A cells stably expressing mGluR5 were plated in black-walled, clear-bottomed, poly-D-lysine coated 384-well plates (BD Biosciences, San Jose, CA) in 20 μL of assay medium (DMEM containing 10% dialyzed FBS, 20 mM HEPES, and 1 mM sodium pyruvate) at a density of 20K cells/well. The cells were grown overnight at 37 °C in the presence of 6% CO_2. The next day, medium was removed and the cells incubated with 20 μL of 2 μM Fluo-4, AM (Invitrogen, Carlsbad, CA) prepared as a 2.3 mM stock in DMSO and mixed in a 1:1 ratio with 10% (w/v) pluronic acid F-127 and diluted in assay buffer (Hank's balanced salt solution, 20 mM HEPES, and 2.5 mM Probenecid (Sigma-Aldrich, St. Louis, MO)) for 45 m at 37 °C. Dye was removed, 20 μL ofassay buffer was added, and the plate was incubated for 10 m at room temperature. Ca^{2+} flux was measured using the Functional Drug Screening System (FDSS6000, Hamamatsu, Japan). Compounds were serially diluted 1:3 into 10 point concentration response curves and were transferred to daughter plates using the Echo acoustic plate reformatter (Labcyte, Sunnyvale, CA). Compounds were diluted into assay buffer to a 2× stock using a Thermo Fisher Combi (Thermo Fisher, Waltham, MA), which was applied to cells at t = 3 s. Cells were incubated with the test compounds for 140 s and then stimulated for 60 s with an EC_{80} concentration of glutamate. Data were collected at 1 Hz. Concentration response curves were generated using a four point logistical equation in GraphPad Prism (GraphPad Software, Inc., La Jolla, CA). Subsequent confirmations of concentration response curves were performed using independent serial dilutions of source compounds, and data from experiments generated on multiple days were averaged to generate SEM.

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Supporting Information Available: X-ray crystallographic tables. This material is available free of charge via the Internet at http://pubs.acs.org.

References

(1) Conn, P. J.; Pin, J. P. Pharmacology and functions of metabotropic glutamate receptors. *Annu. Rev. Pharmacol. Toxicol.* **1997**, *37*, 205–237.

(2) Kew, J. N.; Kemp, J. A. Ionotropic and metabotropic glutamate receptor structure and pharmacology. *Psychopharmacology (Berlin).* **2005**, *179* (1), 4–29.

(3) Ritzén, A.; Mathiesen, J. M.; Thomsen, C. Molecular pharmacology and therapeutic prospects of metabotropic glutamate receptor allosteric modulators. *Basic Clin. Pharmacol. Toxicol.* **2005**, *97* (4), 202–213.

(4) Pin, J.-P.; Kniazeff, J.; Liu, J.; Binet, V.; Goudet, C.; Rondard, P.; Prezeau, L. Allosteric functioning of dimeric class C G-protein-coupled receptors. *FEBS J.* **2005**, *272*, 2947–2955.

(5) Gasparini, F.; Bilbe, G.; Gomez-Mancilla, B.; Spooren, W. mGluR5 antagonists: discovery, characterization and drug development. *Curr. Opin. Drug Discovery Dev.* **2008**, *11* (5), 655–665.

(6) Spooren, W.; Ballard, T.; Gasparini, F.; Amalric, M.; Mutel, V.; Schreiber, R. Insight into the function of group I and group II metabotropic glutamate (mGlu) receptors: behavioural characterization and implications for the treatment of CNS disorders. *Behav. Pharmacol.* **2003**, *14* (4), 257–277.

(7) Bear, M. F. Therapeutic Implications of the mGluR5 theory of fragile X mental retardation. *Genes Brain Behav.* **2005**, *4* (6), 393–398.

(8) Nicoletti, F.; Collingridge, G.; Schoepp, D. 2008 Eruptions in metabotropic glutamate receptors. *Neuropharmacology* **2008**, *55*, 391.

(9) Carroll, F. I. Antagonists at metabotropic glutamate receptor subtype 5: structure−activity relationships and therapeutic potential for addiction. *Ann. N.Y. Acad. Sci.* **2008**, *1141*, 221–232.

(10) Jaeschke, G.; Wettstein, J. G.; Nordquist, R. E.; Spooren, W. mGlu5 receptor antagonists and their therapeutic potential. *Expert Opin. Ther. Pat.* **2008**, *18*, 113–142.

(11) Bridges, T. M.; Lindsley, C. W. G-protein-coupled receptors: from classical modes of modulation to allosteric mechanisms. *ACS Chem. Biol.* **2008**, *3* (9), 530–541.

(12) Rodriguez, A. L.; Williams, R. Recent progress in the development of allosteric modulators of mGluR5. *Curr. Opin. Drug Discovery Dev.* **2007**, *10* (6), 715–722.

(13) Conn, P. J.; Lindsley, C. W.; Jones, C. K. Activation of metabotropic glutamate receptors as a novel approach for the treatment of schizophrenia. *Trends Pharmacol. Sci.* **2009**, *30* (1), 25–31.

(14) Chiamulera, C.; Epping-Jordan, M. P.; Zocchi, A.; Marcon, C.; Cottiny, C.; Tacconi, S.; Corsi, M.; Orzi, F.; Conquet, F. Reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice. *Nat. Neurosci.* **2001**, *4* (9), 873–874.

(15) Kenny, P. J.; Boutrel, B.; Gasparini, F.; Koob, G. F.; Markou, A. Metabotropic glutamate 5 receptor blockade may attenuate cocaine self-administration by decreasing brain reward function in rats. *Psychopharmacology (Berlin)* **2005**, *179* (1), 247–254.

(16) Paterson, N. E.; Markou, A. The metabotropic glutamate receptor 5 antagonist MPEP decreased break points for nicotine, cocaine and food in rats. *Psychopharmacology (Berlin)* **2005**, *179* (1), 255–261.

(17) (a) Bäckström, P.; Hyytiä, P. Involvement of AMPA/kainate, NMDA, and mGlu5 receptors in the nucleus accumbens core in cue-induced reinstatement of cocaine seeking in rats. *Psychopharmacology (Berlin)* **2007**, *192* (4), 571–580. (b) Bäckström, P.; Hyytiä, P. Ionotropic and metabotropic glutamate receptor antagonism attenuates cue-induced cocaine seeking. *Neuropsychopharmacology* **2006**, *31* (4), 778–786.

(18) (a) Platt, D. M.; Rowlett, J. K.; Spealman, R. D. Attenuation of cocaine self-administration in squirrel monkeys following repeated administration of the mGluR5 antagonist MPEP: comparison with dizocilpine. *Psychopharmacology (Berlin)* **2008**, *200* (2), 167–176. (b) Lee, B.; Platt, D. M.; Rowlett, J. K.; Adewale, A. S.; Spealman, R. D. Attenuation of behavioral effects of cocaine by the metabotropic glutamate receptor 5 antagonist 2-methyl-6-(phenylethynyl)-pyridine in squirrel monkeys: comparison with dizocilpine. *J. Pharmacol. Exp. Ther.* **2005**, *312* (3), 1232–1240.

(19) (a) Alagille, D.; Baldwin, R. M.; Roth, B. L. l.; Wroblewski, J. T.; Grajkowska, E.; Tamagnan, G. D. Functionalization at position 3 of the phenyl ring of the potent mGluR5 noncompetitive antagonists MPEP. *Bioorg. Med. Chem. Lett.* **2005**, *15* (4), 945–949. (b) Alagille, D.; Baldwin, R. M.; Roth, B. L.; Wroblewski, J. T.; Grajkowska, E.; Tamagnan, G. D. Synthesis and Receptor Assay of Aromatic-Ethynyl-Aromatic Derivatives with Potent mGluR5 Antagonist Activity. *Bioorg. Med. Chem.* **2005**, *13*, 197–209.

(20) (a) Bach, P.; Nilsson, K.; Wållberg, A.; Bauer, U.; Hammerland, L. G.; Peterson, A.; Svensson, T.; Osterlund, K.; Karis, D.; Boije, M.; Wensbo, D. A new series of pyridinyl-alkynes as antagonists of the metabotropic glutamate receptor 5 (mGluR5). *Bioorg. Med. Chem. Lett.* **2006**, *16* (18), 4792–4795. (b) Bach, P.; Nilsson, K.; Svensson, T.; Bauer, U.; Hammerland, L. G.; Peterson, A.; Wållberg, A.; Osterlund, K.; Karis, D.; Boije, M.; Wensbo, D. Structure−activity relationships for the linker in a series of pyridinyl-alkynes that are antagonists of the metabotropic glutamate receptor 5 (mGluR5). *Bioorg. Med. Chem. Lett.* **2006**, *16* (18), 4788–4791.

(21) Iso, Y.; Grajkowska, E.; Wroblewski, J. T.; Davis, J.; Goeders, N. E.; Johnson, K. M.; Sanker, S.; Roth, B. L.; Tueckmantel, W.; Kozikowski, A. P. Synthesis and structure−activity relationships of 3-[(2-methyl-1,3-thiazol-4-yl)ethynyl]pyridine analogues as potent, noncompetitive metabotropic glutamate receptor subtype 5 antagonists; search for cocaine medications. *J. Med. Chem.* **2006**, *49* (3), 1080–1100.

(22) Carroll, F. I.; Kotturi, S. V.; Navarro, H. A.; Mascarella, S. W.; Gilmour, B. P.; Smith, F. L.; Gabra, B. H.; Dewey, W. L. Synthesis and pharmacological evaluation of phenylethynyl[1,2,4]methyltriazines as analogues of 3-methyl-6-(phenylethynyl)pyridine. *J. Med. Chem.* **2007**, *50* (14), 3388–3391.

(23) Micheli, F.; Bertani, B.; Bozzoli, A.; Crippa, L.; Cavanni, P.; Di Fabio, R.; Donati, D.; Marzorati, P.; Merlo, G.; Paio, A.; Perugini, L.; Zarantonello, P. Phenylethynyl-pyrrolo[1,2-*a*]pyrazine: a new potent and selective tool in the mGluR5 antagonists arena. *Bioorg. Med. Chem. Lett.* **2008**, *18* (6), 1804–1809.

(24) Kulkarni, S. S.; Nightingale, B.; Dersch, C. M.; Rothman, R. B.; Newman, A. H. Design and synthesis of noncompetitive metabotropic glutamate receptor subtype 5 antagonists. *Bioorg. Med. Chem. Lett.* **2006**, *16* (13), 3371–3375.

(25) Kulkarni, S. S.; Newman, A. H. Design and synthesis of novel heterobiaryl amides as metabotropic glutamate receptor subtype 5 antagonists. *Bioorg. Med. Chem. Lett.* **2007**, *17* (7), 2074–2079.

(26) Kulkarni, S. S.; Newman, A. H. Discovery of heterobicyclic templates for novel metabotropic glutamate receptor subtype 5 antagonists. *Bioorg. Med. Chem. Lett.* **2007**, *17* (11), 2987–2991.

(27) Bonnefous, C.; Vernier, J. M.; Hutchinson, J. H.; Chung, J.; Reyes-Manalo, G.; Kamenecka, T. Dipyridyl amides: potent metabotropic glutamate subtype 5 (mGlu5) receptor antagonists. *Bioorg. Med. Chem. Lett.* **2005**, *15* (4), 1197–1200.

(28) Ceccarelli, S. M.; Jaeschke, G.; Buettelmann, B.; Huwyler, J.; Kolczewski, S.; Peters, J. U.; Prinssen, E.; Porter, R.; Spooren, W.; Vieira, E. Rational design, synthesis, and structure−activity relationship of benzoxazolones: new potent mglu5 receptor antagonists based on the fenobam structure. *Bioorg. Med. Chem. Lett.* **2007**, *17* (5), 1302–1306.

(29) Cosford, N. D. P.; Tehani, L.; Roppe, J.; Schweiger, E.; Smith, N. D.; Anderson, J.; Bristow, L.; Brodkin, J.; Jiang, X.; McDonald, I.; Rao, S.; Washburn, M.; Varney, M. 3-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]pyridine: A Potent and Highly Selective Metabotropic Glutamate Subtype 5 Receptor Antagonist with Anxiolytic Activity. *J. Med. Chem.* **2003**, *46*, 204–206.

(30) (a) Yang, X.; Chen, W. In vitro microsomal metabolic studies on a selective mGluR5 antagonist MTEP: characterization of in vitro metabolites and identification of a novel thiazole ring opening aldehyde metabolite. *Xenobiotica* **2005**, *35* (8), 797–809. (b) Green, M. D.; Yang, X.; Cramer, M.; King, C. D. In vitro metabolic studies on the selective metabotropic glutamate receptor sub-type 5 (mGluR5) antagonist 3-[(2-methyl-1,3-thiazol-4-yl) ethynyl]-pyridine (MTEP). *Neurosci. Lett.* **2006**, *391* (3), 91–95.

(31) Lipinski, C. A. Drug-like properties and the causes of poor solubility and poor permeability. *J. Pharmacol. Toxicol. Methods* **2000**, *44*, 235–249.

(32) Roppe, J. R.; Wang, B.; Huang, D.; Tehrani, L.; Kamenecka, T.; Schweiger, E. J.; Anderson, J. J.; Brodkin, J.; Jiang, X.; Cramer, M.; Chung, J.; Reyes-Manalo, G.; Munoz, B.; Cosford, N. D. 5-[(2-Methyl-1,3-thiazol-4-yl)ethynyl]-2,3′-bipyridine: a highly potent, orally active metabotropic glutamate subtype 5 (mGlu5) receptor antagonist with anxiolytic activity. *Bioorg. Med. Chem. Lett.* **2004**, *14* (15), 3993–3996.

(33) Hamill, T. G.; Krause, S.; Ryan, C.; Bonnefous, C.; Govek, S.; Seiders, T. J.; Cosford, N. D.; Roppe, J.; Kamenecka, T.; Patel, S.; Gibson, R. E.; Sanabria, S.; Riffel, K.; Eng, W.; King, C.; Yang, X.; Green, M. D.; O'Malley, S. S.; Hargreaves, R.; Burns, H. D. Synthesis, characterization, and first successful monkey imaging studies of metabotropic glutamate receptor subtype 5 (mGluR5) PET radiotracers. *Synapse* **2005**, *56* (4), 205–216.

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