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

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Recent genetic and pharmacological studies have suggested that the metabotropic glutamate receptor subtype 5 (mGluR5) may represent a druggable target in identifying new therapeutics for the treatment of various central nervous system disorders including drug abuse. In particular, considerable attention in the mGluR5 field has been devoted to identifying ligands that bind to the allosteric modulatory site, distinct from the site for the primary agonist glutamate. Both 2-methyl-6-(phenylethynyl)pyridine (MPEP) and its analogue 3-[(2-methyl-4-thiazolyl)ethynyl]pyridine (MTEP) have been shown to be selective and potent noncompetitive antagonists of mGluR5. Because of results presented in this study showing that MTEP prevents the reinstatement of cocaine self-administration caused by the presentation of environmental cues previously associated with cocaine availability, we have prepared a series of analogues of MTEP with the aim of gaining a better understanding of the structural features relevant to its antagonist potency and with the ultimate aim of investigating the effects of such compounds in blunting the self-administration of cocaine. These efforts have led to the identification of compounds showing higher potency as mGluR5 antagonists than either MPEP or MTEP. Two compounds **19** and **59** exhibited functional activity as mGluR5 antagonists that are 490 and 230 times, respectively, better than that of MTEP.

Introduction

While many efforts have focused on the discovery of cocaine medication by designing drugs that act on the dopamine transporter (DAT), less research has been directed to manipulation of metabotropic glutamate receptor in controlling chemical addictions. The metabotropic glutamate receptors (mGluRs) constitute a family of seven-transmembrane domain, G protein-coupled receptors and are characterized by the presence of large, extracellular, N-terminal agonist-binding domains.[1] mGluRs cloned from mammalian tissues can be subdivided into three groups based on sequence homology, pharmacology, and intracellular signal transduction. Group I consists of mGluR1 and mGluR5 which stimulate phospholipase C, leading to phosphoinositide hydrolysis and formation of two intracellular second messengers: inositol triphosphate (IP_3), which induces intracellular Ca^{2+} release, and diacylglycerol (DAG), which can stimulate protein kinase C activity. Group II (mGluR2 and mGluR3) and group III (mGluR4, mGluR6, mGluR7, and mGluR8) are negatively coupled to adenylate cyclase. Therefore, their activation decreases intracellular cAMP levels. In addition, many mGluR subtypes have been shown to induce either direct or indirect modulation of various ion channels. As a group, mGluRs mediate multiple modulatory actions in the central nervous system, ranging from the control of neuronal excitability, participation in mechanisms of neurotoxicity, and neuroprotection to the modulation of gene expression, learning, memory, and expression of various behaviors. In particular, recent evidence points to the role that one of the group I receptors, mGluR5, may play in cocaine addiction.

Group I mGluRs are characterized by a distinct pharmacology and can be activated by a group-selective agonist (*S*)-3,5-dihydroxyphenylglycine (DHPG),[2] as well as the mGluR5-selective agonist 2-chloro-5-hydroxyphenylglycine (CHPG). The existing competitive antagonists include 4-carboxy-3-hydroxyphenylglycine (4C3HPG), *RS*-1-aminoindan-1,5-dicarboxylic acid (AIDA), and LY-367385, which show some selectivity for mGluR1, but none are selective for mGluR5. More selective are compounds acting as noncompetitive antagonists of group I mGluRs. These include 7-hydroximinocyclopropa[*b*]chromene-1a-carboxylic acid ethyl ester (CPCCOEt),[3] which is selective for mGluR1, as well as 2-methyl-6-(phenylethynyl)pyridine (MPEP)[4] and its analogue, 3-[(2-methyl-4-thiazolyl)ethynyl]-pyridine (MTEP),[5] which are selective for mGluR5. These compounds bind to amino acid residues located in the transmembrane domain of the group I mGluRs and inhibit receptor activity without interfering with the binding of the primary agonist (glutamate). Studies from several laboratories have indicated that modifications of the MPEP and MTEP molecules lead to a number of compounds which selectively inhibit mGluR5 with potencies in the low nanomolar range.[4−6]

MPEP has been suggested to bind to amino acid residues located in the transmembrane region of the third and sixth

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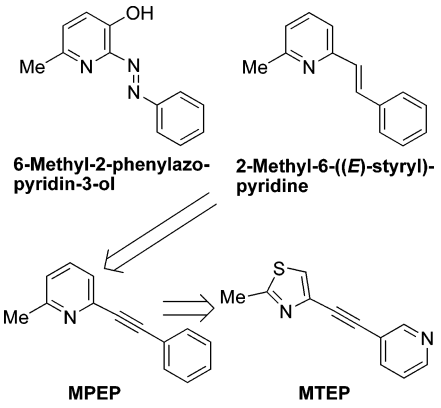
transmembrane heptahelical domain of mGluR5.[7] Interestingly, in the absence of the extracellular glutamate binding portion of mGluR5, MPEP has been shown to act as an inverse agonist at this site. Recent studies have provided evidence for the existence of a full pharmacological spectrum of drugs that act at this transmembrane site, including positive, negative, and neutral modulators.[7c] Thus, it is possible that the design of MPEP- or MTEP-based ligands could yield chemical entities capable of fine-tuning the activity of this important modulatory site.

The expression pattern of mGluR5 suggests a possible role in the effects of drugs of abuse. mGluR5 is highly expressed in both the intrinsic and efferent projection neurons in the nucleus accumbens and striatum, brain regions associated with the behavioral effects of psychostimulant drugs. Perhaps the most compelling study pointing to mGluR5 as a potential drug target is one that demonstrated that the reinforcing and locomotor stimulant effects of cocaine are absent in mGluR5 null mutant mice.[8] Importantly, this effect appears to be mediated downstream of cocaine's effect on dopaminergic neurons as there was no difference between the wild type (WT) and null mutant regarding cocaine-induced dopamine (DA) release in the ventral striatum. It is important to note that acquisition of a food reinforced task was not different between WT and null mutant mice. Also relevant to this research is that MPEP, a selective mGluR5 noncompetitive antagonist, blocked cocaine self-administration by about 50% in C57BI/6J mice.

Although the precise mechanism is unknown, it is quite possible that the effect of mGluR5 antagonism is mediated on striatal GABAergic output neurons that receive both dopaminergic ventral tegmental area neurons and glutamatergic input from the frontal cortex.[9] It is known that cocaine increases both extracellular DA and glutamate levels in the nucleus accumbens (NAc)[10] and that these effects are enhanced with repeated administration.[11] Activation of DA and mGluR5 in the NAc[12] consequent to cocaine-induced DA and glutamate release could act synergistically via their respective second messenger systems. For example, acute administration of amphetamine has been demonstrated to increase striatal phosphorylation of CREB, Elk-1, and ERK1/2 in a manner that was blocked by MPEP.[13]

Other studies supporting this approach include the demonstration that MPEP dose-dependently reduced cocaine conditioned place preference, while having no effect on place preference for other drugs including nicotine and morphine.[14] Importantly, and in opposition to the place preference data, MPEP has been reported to inhibit nicotine self-administration in both rats and mice, while having no effect on food maintained responding.[15] Further, MPEP has been demonstrated to significantly inhibit both acquisition and expression of conditioned place preference to morphine in mice.[16]

These data suggest that MPEP may have inhibitory effects on drug reward mechanisms in general, but they also point out that subtle differences may exist between different methods of evaluating drug effects on reward mechanism. These data also suggest the value of using different models of drug reinforcement in the evaluation of the therapeutic potential of drugs to be used in drug addiction. One of the major problems in maintaining abstinence from cocaine is that cocaine addicts often relapse because environmental cues previously associated with cocaine use can precipitate drug seeking and subsequent cocaine self-administration, which in turn, causes further drug seeking. For this reason it is important to understand the mechanisms underlying the association between such environmental cues and drug seeking. Therefore the current study also included experiments designed to evaluate the potential of MTEP to disrupt this association.



MPEP
Ca^{2+} Flux in human mGluR5, IC_{50} = 2 nM
K_i for rat mGluR5 binding = 12 nM
log D; 3.5

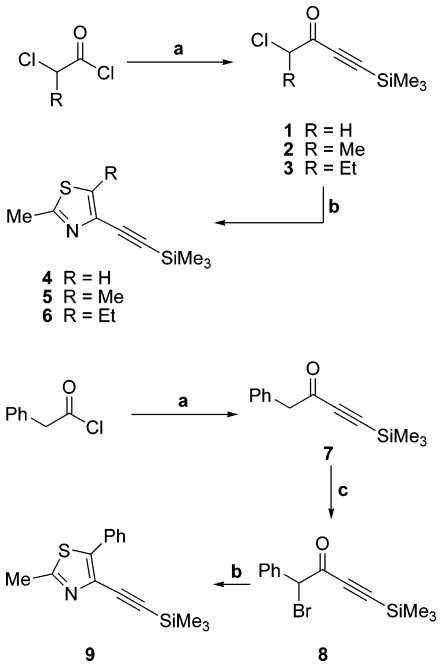
MTEP
Ca^{2+} Flux in human mGluR5, IC_{50} = 5 nM
K_i for rat mGluR5 binding = 16 nM
log D; 2.1

Figure 1. mGluR5 antagonists.[5]

The development of the present class of noncompetitive mGluR5 antagonists[17] began with the discovery through random screening of a lead compound, 6-methyl-2-(phenylazo)pyridin-3-ol and its structural modification to the analogue, 2-methyl-6-((*E*)-styryl)pyridine, by Cosford and co-workers.[18] Both compounds are high-nanomolar (IC_{50} = 0.37 and 0.29 μM, respectively) antagonists of the increase in intracellular [Ca^{2+}] evoked by glutamate (at EC_{80}) at recombinant human mGluR5a, but not mGluR1b or other mGluR subtypes. In addition, 2-methyl-6-((*E*)-styryl)pyridine is a weak (EC_{50} = 26.4 μM) agonist at human mGluR4a. No activity (either agonist or antagonist) was encountered for either compound at a selection of human α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA), kainate, and *N*-methyl-D-aspartate (NMDA) receptors. Replacement of the C═C double bond in 2-methyl-6-((*E*)-styryl)pyridine with a triple bond resulted in 2-methyl-6-(phenylethynyl)pyridine (MPEP)[4] which exhibited a dramatically improved mGluR5 antagonist activity (Figure 1). In the case of the other mGluRs, the only other activity observed for MPEP is very weak antagonism at mGluR6 (20% depression of forskolin-stimulated cAMP level at 100 μM). Additionally, it has been reported that MPEP exhibits weak antagonism at NMDA receptors.[19] No activity was observed at several other subtypes of ionotropic glutamate receptors.[4]

Various SAR studies have been reported on MPEP by several research groups.[4,6c,6e,6g,6i,6j] including the synthesis of compounds in which the pyridine ring was replaced by a thiazole ring. As these later compounds suffered from poor water solubility, the benzene ring of these thiazole analogues was replaced by a pyridine ring. Of the compounds tested, only the 3-pyridyl isomer, namely 3-[(2-methyl-4-thiazolyl)ethynyl]pyridine (MTEP),[5] exhibited satisfactory potency. Like MPEP, MTEP is highly selective for mGluR5 vs other mGluRs; its antagonism at NMDA receptors is strongly reduced although not completely abolished, and no activity is observed at other ionotropic glutamate receptors. Taken together, these data make MTEP a desirable lead compound for further structural modifications.

Scheme 1. Key Intermediates **4**−**6** and **9**[a]



[a] Reagents and conditions: (a) bis(trimethylsilyl)acetylene, $AlCl_3$, CH_2Cl_2, 0 °C, 2 h and then 25 °C, 1 h; (b) thioacetamide, DMF, 25 °C, 17 h (and then 85 °C, 1.5 h for preparation of **5**, **6**, and **9**); (c) bromine, CCl_4, 0 °C, 10 min.

Synthetic Methods

On the basis of the structure−activity relationship (SAR) information that was available at the time we undertook the present synthetic efforts, we chose to further explore the SAR of MTEP in order to identify the best possible candidates for use in our drug abuse studies. To begin our work, we first prepared four different 2-methyl-5-substituted-4-(trimethylsilanylethynyl)thiazole derivatives **4**, **5**, **6**, and **9**. These four compounds serve as key intermediates in the synthesis of the MTEP analogues and were synthesized as shown in Scheme 1. These intermediates **4**−**6** were obtained in a manner similar to that reported in the synthesis of MTEP.[5] However, we found that it was not necessary to purify compounds **1**−**3** and obtained **4**−**6** efficiently by simply employing the crude starting materials. In the case of **9** having an aromatic substituent at the 5-position of the thazole ring, the benzylic chlorine atom in the requisite 2-aryl-2-chloroacetyl chloride staring material is probably too labile to survive the subsequent $AlCl_3$-promoted condensation reaction with bis(trimethylsilyl)acetylene. Accordingly, α-halogenation was postponed until after this step. Thus, after the $AlCl_3$-promoted condensation of benzoyl chloride with bis(trimethylsilyl)acetylene, **7** was successfully brominated at its benzylic position using bromine to give **8**. Crude **8** was then immediately subjected to the thiazole ring forming reaction with thioacetamide to furnish the key intermediate **9** in good yield.

Next, using a one-pot modified Sonogashira coupling reaction, the in situ desilylation of key intermediates **4**−**6** and **9** with tetrabutylammonium fluoride (TBAF) and subsequent palladium catalyzed cross-coupling reaction with the appropriate aryl or heteroaryl halide was carried out in a manner similar to that reported for the synthesis of certain thiazole derivatives of MTEP.[5,6g]

In Table 1, we present a list of the aryl and heteroaryl halides that were reacted with **4**−**6** and **9** as substrates, together with two different sets of reaction conditions that were employed in the modified Sonogashira coupling reaction, and the respective yields obtained for the coupling products.

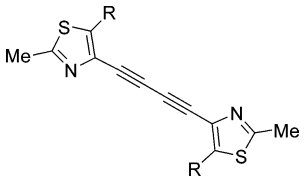
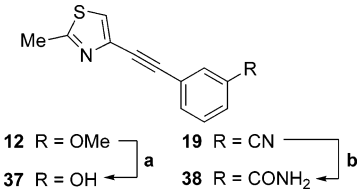


Figure 2. Structure of the dimer formed in the homo-coupling reaction.

Scheme 2[a]



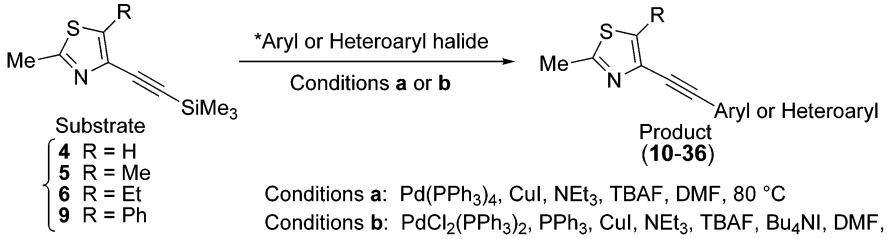
[a] Reagents and conditions: (a) BBr_3, CH_2Cl_2, rt; (b) H_2O_2, aqueous NaOH, EtOH, 60 °C.

All of the aryl or heteroaryl halides used in these reactions were available commercially, with the exception of *N*-(3-iodophenyl)acetamide, which was obtained by acetylation of 3-iodoaniline with acetyl chloride in the presence of triethylamine. For the most part, these reactions proceeded in good yield, although several took place in <40% yield. In these cases the products of homo-coupling were observed. The competition between the desired cross-coupling reaction pathway and the undesired homo-coupling reaction that takes place in the modified Sonogashira coupling reaction is likely dependent on the reactivity of the aryl or heteroaryl halide that is used (Figure 2). The more reactive aryl iodides are the preferred partners for obtaining the products of the cross-coupling reaction. For the preparation of the MTEP analogues **37** and **38**, the methoxy group of **12** and the cyano group of **19** were converted to the corresponding hydroxy or amide groups, respectively, using standard conditions as shown in Scheme 2.[20]

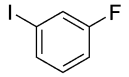
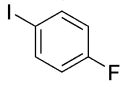
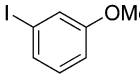
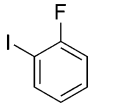
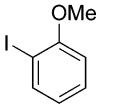
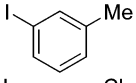
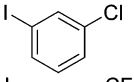
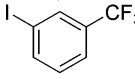
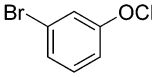
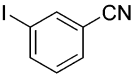
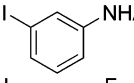
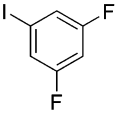
Next, we carried out modifications at the 2-position of the thiazole ring of MTEP and also prepared analogues in which its pyridine ring was replaced by a 3-fluorophenyl group as shown in Schemes 3 and 4. The key intermediate **39** was readily synthesized using the same method as in Scheme 1 by simply using thiourea in place of thioacetamide. Intermediate **39** was then subjected to the modified Sonogashira coupling reaction to give two types of 2-aminothiazole derivatives, namely **40** and **41**. Analogue **41** contains the 3-pyridyl moiety common to MTEP while **40** contains a 3-fluorophenyl group in place of MTEP's pyridyl group. The MTEP analogue **10** bearing a 3-fluorophenyl moiety is known to be more potent as an mGluR5 antagonist than MTEP (Table 2). The amine analogues **42**−**45** comprised of amide, urea, and carbamate groups were obtained by reaction of **41** with the corresponding acid chloride, isocyanate, or chloroformate, respectively, in the presence of an appropriate base (Scheme 3).

Other modifications at the 2-position of thiazole ring were brought about through the bromide **46**, which was obtained from **40** through the Sandmeyer reaction as detailed in Scheme 4. Accordingly, the amine **40** was reacted with *tert*-butyl nitrite and cupric bromide,[21] and the resulting bromide was then subjected to the Suzuki, Sonogashira, or Stille cross-coupling reactions. The Suzuki coupling reaction of **46** with 3,5-difluorophenylboronic acid, the Sonogashira coupling reaction of **46** with trimethylsilylacetylene or propargyl alcohol, and the Stille coupling reaction of **46** with tributyl(vinyl)tin proceeded

Table 1. Preparation of MTEP Analogues Using the Modified Sonogashira Coupling Reaction via an in Situ Desilylation Reaction



Conditions **a**: $Pd(PPh_3)_4$, CuI, NEt_3, TBAF, DMF, 80 °C
Conditions **b**: $PdCl_2(PPh_3)_2$, PPh_3, CuI, NEt_3, TBAF, Bu_4NI, DMF, 80 °C

Substrate	*halide	Conditions	Product	Yield (%)
4		**b**	**10**	62
4		**b**	**11**	68
4		**a**	**12**	78
4		**a**	**13**	71
4		**a**	**14**	67
4		**a**	**15**	72
4		**a**	**16**	82
4		**a**	**17**	79
4		**a**	**18**	29
4		**a**	**19**	80
4		**a**	**20**	78
4		**a**	**21**	73

Substrate	*halide	Conditions	Product	Yield (%)
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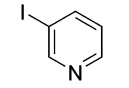
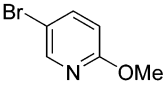
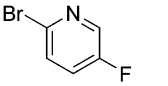
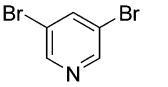
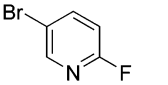
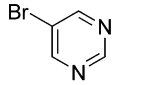
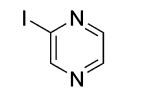
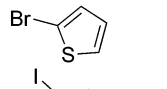
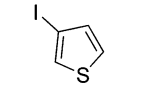
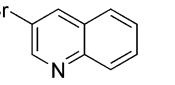
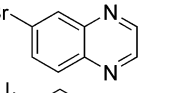
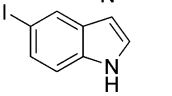
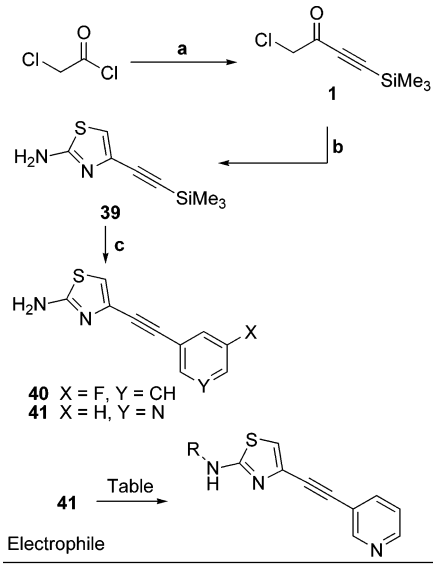
5		**b**	**23**	55
6		**b**	**24**	51
9		**a**	**25**	52
4		**a**	**26**	68
4		**a**	**27**	66
4		**a**	**28**	76
4		**a**	**29**	41
4		**a**	**30**	51
4		**a**	**31**	61
4		**a**	**32**	28
4		**a**	**33**	80
4		**a**	**34**	52
4		**a**	**35**	38
4		**a**	**36**	35

in the presence of the appropriate palladium catalyst and base to give the coupling products **47**, **48**, **49**, and **51**, respectively. Unfortunately, we found that **51** was too unstable to be isolated in pure form, as it apparently polymerized during evaporation to remove water after reverse-phase HPLC purification. Intermediate **48** was desilylated by the usual method using TBAF to furnish the terminal acetylene derivative **50**.

We next carried out modifications at the 5-position of pyridine ring using the bromide **28** as shown in Scheme 5. We were able to successfully convert the bromo group to an aryl or alkynyl group using the Suzuki or Sonogashira coupling reaction to afford **52**−**55**. Compound **54** was desilylated as above using TBAF to give the terminal acetylene derivative **56**. This acetylene **56** was converted to the *trans*-vinylstannane **57** by hydrostannylation using tributyltin hydride and 2,2′-azobis(2-methylpropionitrile) (AIBN) under heating, followed by Sn−Si conversion using butyllithium and chlorotrimethylsilane and finally desilylation with 1 N hydrochloric acid to give the terminal olefin derivative **59**.[22] Attempts to bring about the direction alkylation of bromide **28** using various organometalic reagents such as cuprates or Grignard reagents with zinc chloride and palladium catalysts were unsuccessful.

To explore the effect of modifications at the 6-position of the pyridine ring, we used the 6-methoxypyridine derivative **26** as the starting material as displayed in Scheme 6. At the beginning of this study, efforts were made to cleave the methoxy group of **26** using standard demethylation protocols consisting of BBr_3 (CH_2Cl_2, 0 °C to room temperature) or HBr in acetic acid at room temperature in order to obtain the key pyridone **61**. However, all of these typical demethylation methods resulted

Scheme 3. Modifications at the 2-Position of the Thiazole Ring (Synthesis of Amino Analogues)[a]



Acid chloride, isocyanate, or chloroformate	Base	Product (R)	Yield (%)
AcCl	NEt_3	Ac (**42**)	89
BzCl	NEt_3	Bz (**43**)	92
2,4-F_2-Ph-NCO	DMAP (cat.)	CONH−2,4-F_2-Ph (**44**)	72
MeOCOCl	NEt_3	CO_2Me (**45**)	82

[a] Reagents and conditions: (a) bis(trimethylsilyl)acetylene, $AlCl_3$, CH_2Cl_2, 0 °C, 2 h and then 25 °C, 1 h; (b) thiourea, DMF, 25 °C, 17 h; (c) $Pd(PPh_3)_4$, CuI, NEt_3, TBAF, DMF, 80 °C.

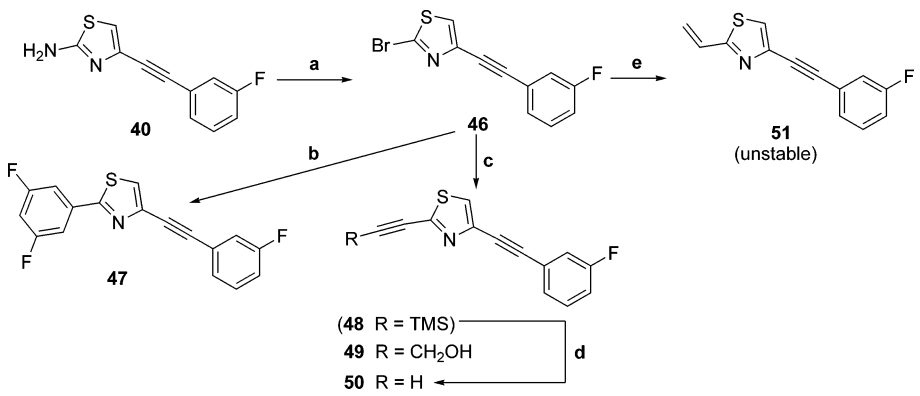
in no reaction. When the demethylation reaction was carried out under more vigorous conditions involving an excess of HBr in AcOH with heating, the bromoolefin derivative **60** was generated as a result of both hydrobromination of the alkyne tether together with demethylation of the methoxy group. Dehydrobromination of the bromoolefin **60** by potassium hydroxide in refluxing methanol[23] proceeded in good yield to provide the desired pyridone **61**. Conversion of **61** to its mesylate **62**, chloride **63**, or triflate **64** was performed by standard methods. Triflate **64** was subjected to the Suzuki or Sonogashira coupling reaction followed by desilylation as above to give the aryl pyridine derivative **65** or the terminal acetylene derivative **66**, respectively. As in the case of modification at the 5-position of the pyridine ring, we planed to synthesize the terminal olefin derivative **68** via the *trans*-vinylstannane intermediate **67**. However, the hydrostannylation reaction of **66** was complicated and failed to furnish the expected intermediate **67**. We therefore attempted to prepare **68** directly from **64** by carrying out a Stille coupling reaction with tributyl(vinyl)tin and a palladium catalyst. This reaction proceeded smoothly to furnish the terminal olefin derivative **68**.

To explore modifications at the 2-position of the pyridine ring, we first prepared 3-iodo-2-methoxypyridine (**69**) according to a literature procedure (Scheme 7).[24] Crude compound **69** was then subjected to the modified Sonogashira coupling reaction involving in situ desilylation with TBAF as described above to successfully furnish the 2-methoxypyridine derivative **70**. Intermediate **70** was then transformed to its mesylate **73**, chloride **74**, and triflate **75** via the pyridone **72** in the same fashion as described for the MTEP analogues modified at the 6-position. Again, the terminal acetylene **77** was obtained from the triflate **75** by the Sonogashira coupling reaction followed by desilylation.

It is also possible to modify the tether that links the two (hetero)aryl rings. While many possibilities can be envisioned, we explored only two such modifications as shown in Scheme 8. In one case the acetylene is replaced by a *trans*-olefin unit, while in the other case the tether is replaced by an amide group. The starting material compound **4**, was first desylilated with TBAF, and the resulting unstable and volatile intermediate **78** was immediately subjected to hydrostannylation by heating with tributyltin hydride and AIBN to give the *trans*-vinylstannane **79**. The vinylstannane **79** was successfully converted in turn to the desired *trans*-olefin analogue **80** of MTEP by the Stille coupling reaction with 3-iodopyridine. The amide analogues **81** and **82** were readily available from 2-methyl-thiazole-4-carboxylic acid by preparation of an activated acid derivative using EDC or by reaction with thionyl chloride to generate the acid chloride followed by coupling with the appropriate amine.

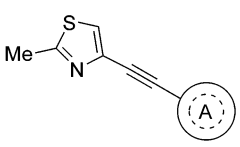
Finally, the preparation of oxazole analogues of MTEP is summarized in Scheme 9. 2-Methyl-oxazole-4-carboxaldehyde (**85**) was prepared according to a literature procedure.[25] Thus, the oxazoline **83** was obtained by reaction of DL-serine methyl ester hydrochloride with ethyl acetimidate hydrochloride, and the intermediate oxazoline **83** was then directly subjected to oxidation using cupric bromide[26] to afford the oxazole **84**. The methyl ester **84** was reduced with lithium aluminum hydride in ether at −78 °C for 30 min to give the expected aldehyde **85**, which was immediately subjected to a Wittig reaction with

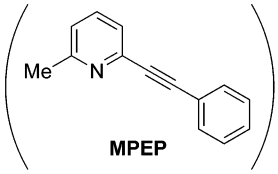
Scheme 4. Modifications at the 2-Position of the Thiazole Ring Starting from Amine **40**[a]

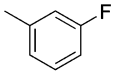
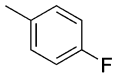
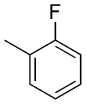
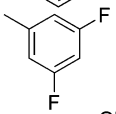
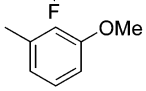
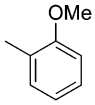
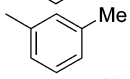
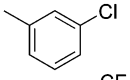
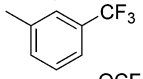
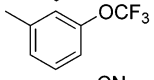
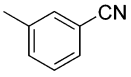
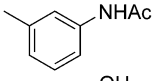
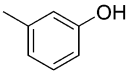
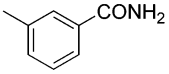


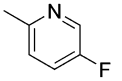
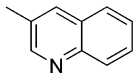
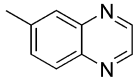
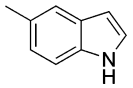
[a] Reagents and conditions: (a) *t*-BuONO, $CuBr_2$, MeCN, 80 °C, 15 min; (b) 3,5-difluorophenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3 (2 M aqueous solution), DME, 85 °C, 15 h; (c) trimethylsilylacetylene or propargyl alcohol, $Pd(PPh_3)_4$, CuI, NEt_3, DMF, 85 °C, 1.5−3 h; (d) TBAF, THF, rt, 10 min; (e) tributyl(vinyl)tin, $PdCl_2(PPh_3)_2$, LiCl, DMF, 85 °C, 15 h.

Table 2. SAR of the Pyridine Moiety of MTEP





	A (Aryl)	IC_{50}[a] (mean ± SEM, nM)
10		23 ± 1.2
11		2966 ± 115
13		140 ± 47
21		25.3 ± 6.7
12		49.0 ± 4
14		36.3 ± 7.2
15		82.6 ± 20.7
16		129 ± 18
17		413 ± 177
18		266 ± 80
19		0.94 ± 0.18
20		2020 ± 158
37		654 ± 42
38		1000 ± 210

	A (Heteroaryl)	IC_{50}[a] (mean ± SEM, nM)
MPEP		39 ± 8.4
22 (MTEP)		462 ± 112
27		1093 ± 33
30		946 ± 129
31		1830 ± 310
32		475 ± 137
33		337 ± 176
34		>10000
35		>10000
36		>10000

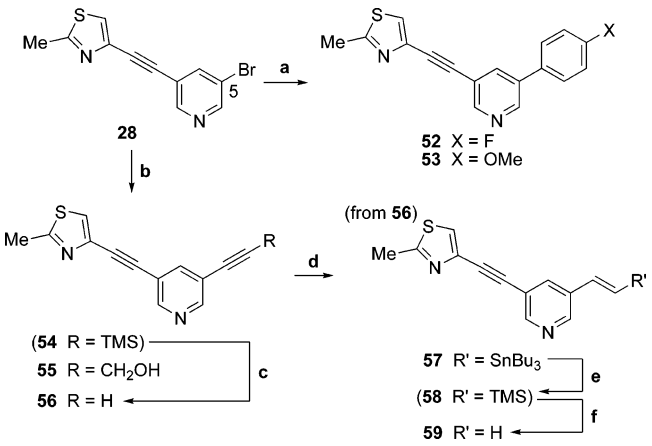
[a] IC_{50} values are expressed as mean ± SE, $n = 6$. IC_{50} values represent the ability of compounds containing various aryl or heteroaryl groups (A) to inhibit agonist-induced phosphoinositide hydrolysis.

carbon tetrabromide and triphenylphosphine to furnish the dibromoolefin **86** in good yield. We next explored the application of a procedure previously reported by Nicolaou in the synthesis of thiazolyl acetylene derivatives.[27] After dehydrobromination of the dibromoolefin **86** was performed by reaction with 1 equiv of sodium bis(trimethylsilyl)amide and lithiation was brought about using 1 equiv of MeLi, the intermediate acetylide **87** was trapped with chlorotrimethylsilane to afford the key intermediate 2-methyl-4-(trimethylsilylethynyl)oxazole (**88**) in good yield. The above modified Sonogashira coupling reaction involving in situ desilylation with TBAF using **88** as a substrate once again proved successful, and we could procure the oxazole analogues **89** and **90** in good yield. The details of the synthesis of these oxazole analogues have been reported separately.[28]

Results and Discussion

Behavioral Experiments. All rats learned to self-administer cocaine according to the established criteria in an average of 12.11 (±6.19) sessions. All animals met the criteria for successful baseline responding in an average of 8.25 (±1.9) sessions. All animals met the criteria for successful extinction in an average of 5.85 (±2.78) sessions. The mean baseline responses for cocaine prior to extinction was 157 ± 13 (baseline control, not shown in Figure 3) and was reduced to 14.3 ± 1.1 under extinction (9.1% of baseline, Figure 3). Cue-induced reinstatement increased the response number to about 40% of baseline cocaine responding, Rats were pretreated with MPEP (5 or 10 mg/kg), MTEP (5 or 10 mg/kg), or vehicle 30 min before reinstatement testing to determine the effects of the drugs on the ability of conditioned environmental stimuli to reinstate

Scheme 5. Modifications at the 5-Position of the Pyridine Ring[a]



[a] Reagents and conditions: (a) 4-fluorophenylboronic acid or 4-methoxyphenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3 (2 M aqueous solution), DME or DMF, 85 °C, 16−22 h; (b) trimethylsilylacetylene or propargyl alcohol, $Pd(PPh_3)_4$, CuI, NEt_3, DMF, 75 °C, 17 h; (c) TBAF, THF, rt, 10 min; (d) Bu_3SnH, AIBN, toluene, 90 °C, 14 h; (e) BuLi, Me_3SiCl, THF, −15 °C to rt; (f) 1 N HCl, THF, rt, 20 min.

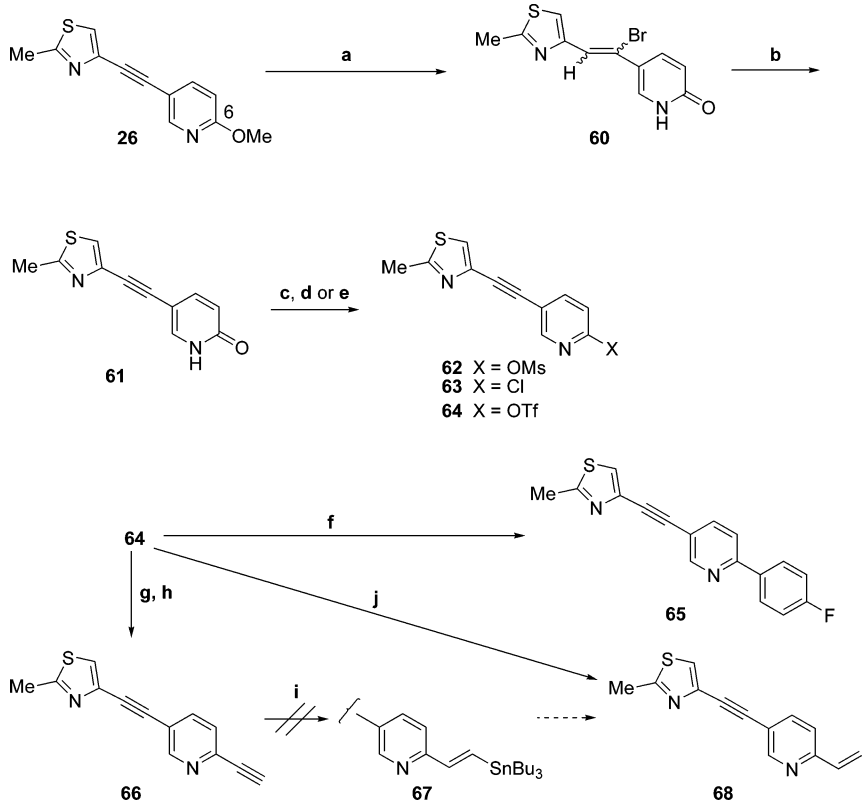
extinguished cocaine-seeking behavior. A one-way ANOVA indicated a significant effect of the treatment conditions on responding on the active lever $F(4,19) = 40.45$; $p < 0.0001$, with responding on the active lever following vehicle pretreatment during reinstatement significantly higher than responding during extinction.

Tukey's post hoc test shows a significant difference between vehicle and 10 mg/kg MTEP ($p < 0.01$). None of the other treatments showed a significant decrease in responding when compared to vehicle (Figure 3). Responding on the inactive lever was also affected by 10 mg/kg MTEP treatment during reinstatement with a $p < 0.05$. None of the other treatments had a significant effect on responding on the inactive lever.

That MPEP was without a significant effect in this study was somewhat surprising in view of several studies that have shown positive effects with MPEP on various aspects of nicotine or cocaine self-administration.[16,29] In the present study, this discrepancy is most likely due to the small number of rats in both the 5 and 10 mg/kg groups (as both doses appeared to have a partial, though not significant, effect). Another potential cause for the greater effect of MTEP relative to MPEP is that the ED_{50} for MTEP for receptor occupancy in vivo is about one-half that of MPEP.[30] Similarly, MTEP has about the same mGluR5 occupancy as MPEP at a 3-fold lower dose in rats (although the reverse is true in mice[30]). Thus, it is quite possible that subtle differences in absorption, distribution, metabolism, and elimination of these two drugs in different rat strains also could have played a role. Most importantly, these data demonstrate that MTEP has the ability to prevent reinstatement of cocaine seeking by environmental cues associated with cocaine availability. However, MTEP is not without behaviorally important side-effects,[31] and it will be important to thoroughly investigate other compounds (e.g., **19** and **59**, see below) that could lead to the development of clinically useful drugs for the treatment of cocaine and, perhaps, drug addiction in general.

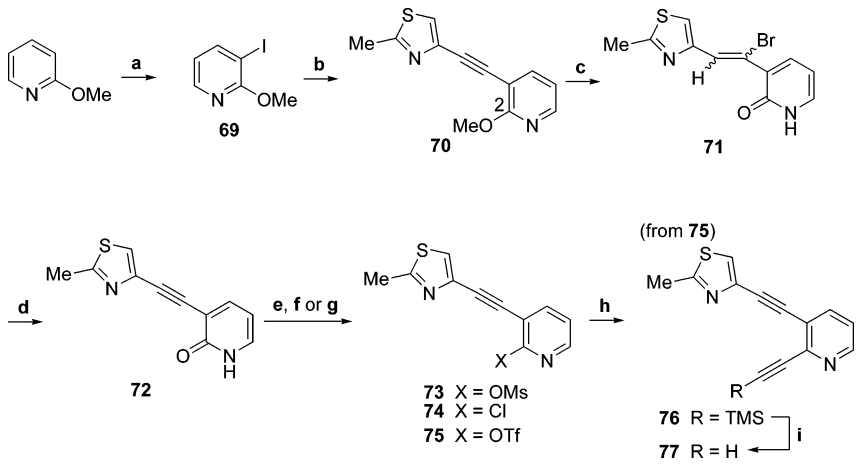
Pharmacological Experiments and SAR. To assess the activity of the newly synthesized MTEP analogues prepared in this study, we tested them in a functional assay which measures agonist-induced phosphoinositide hydrolysis using CHO cells which stably express mGluR5. The CHO cell line expressing these receptors has been created previously, and these assay methods have now become fairly routine.[32] Concentration−

Scheme 6. Modifications at the 6-Position of the Pyridine Ring[a]



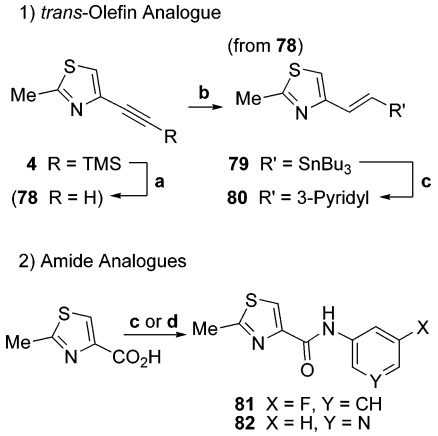
[a] Reagents and conditions: (a) 30% HBr in AcOH, 80 °C, 7.5 h; (b) KOH, MeOH, reflux, 1 h; (c) MsCl, NEt_3, CH_2Cl_2, rt; (d) $POCl_3$, 120 °C, 1.5 h; (e) Tf_2O, NEt_3, CH_2Cl_2, 0 °C; (f) 4-fluorophenylboronic acid, $Pd(PPh_3)_4$, K_2CO_3 (2 M aqueous solution), DME, 80 °C, 18 h; (g) trimethylsilylacetylene, $Pd(PPh_3)_4$, CuI, NEt_3, DMF, 85 °C, 2 h; (h) TBAF, THF, rt, 10 min; (i) Bu_3SnH, AIBN, toluene, 90 °C; (j) tributyl(vinyl)tin, $Pd(PPh_3)_4$, DMF, 85 °C, 15 h.

Scheme 7. Modifications at the 2-Position of the Pyridine Ring[a]



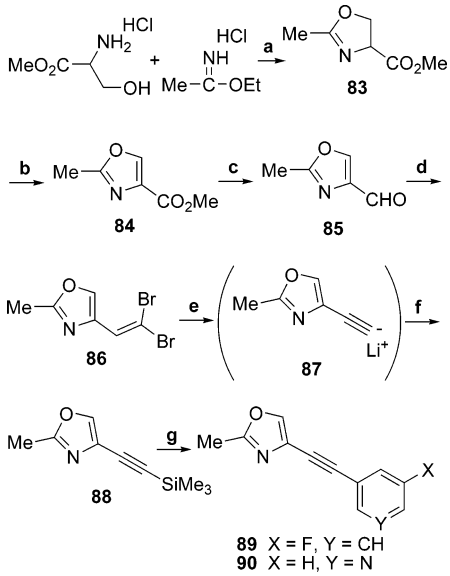
[a] Reagents and conditions: (a) i. LiMe, *i*-Pr_2NH, THF, 0 °C, 3 h; ii. I_2, THF, −60 °C, 30 min; (b) **4**, $Pd(PPh_3)_4$, CuI, NEt_3, TBAF, DMF, 80 °C, 15 h; (c) 30% HBr in AcOH, 80 °C, 6 h; (d) KOH, MeOH, reflux, 1 h; (e) MsCl, NEt_3, CH_2Cl_2, rt; (f) $POCl_3$, 120 °C, 1.5 h; (g) Tf_2O, NEt_3, CH_2Cl_2, 0 °C; (h) trimethylsilylacetylene, $Pd(PPh_3)_4$, CuI, NEt_3, DMF, 85 °C, 4 h; (i) TBAF, THF, rt, 10 min.

Scheme 8. Modifications of the Tether[a]



[a] Reagents and conditions: (a) TBAF, THF, rt, 10 min; (b) Bu_3SnH, AIBN, toluene, 90 °C, 1 h; (c) 3-iodopyridine, $PdCl_2(PPh_3)_2$, LiCl, CuI, DMF, 80 °C, 1.5 h; (c) 3-fluoroaniline, EDC, HOBt, NEt_3, CH_2Cl_2, rt, 18 h; (d) i. $SOCl_2$, DMF, toluene, 105 °C, 80 min; ii. 3-aminopyridine, CH_2Cl_2, rt, 10 min.

Scheme 9. Synthesis of Oxazole Analogues of MTEP[a]



[a] Reagents and conditions: (a) NEt_3, CH_2Cl_2, rt, 16 h; (b) $CuBr_2$, DBU, hexamethylenetetramine, THF, rt, 2 h; (c) $LiAlH_4$, Et_2O, −78 °C, 30 min; (d) CBr_4, PPh_3, CH_2Cl_2, 0 °C, 20 min; (e) NaHMDS, then MeLi, THF, −78 °C; (f) Me_3SiCl, THF, −78 °C to rt; (g) 1-fluoro-3-iodobenzene or 3-iodopyridine, $Pd(PPh_3)_4$, CuI, Et_3N, Bu_4NF, DMF, 85 °C, 13 h.

response curves were performed using seven concentrations of the drug with a total of six separate experiments being conducted on active compounds. All IC_{50} values reported in Tables 2−6 represent means ± SEM.

The activities of compounds which contain various aryl or heteroaryl groups in place of the 3-pyridinyl found in MTEP are shown in Table 2. In general, the derivatives having a 3-substituted aryl group attached to the ethynyl group (**10**, **12**) are more potent than other aryl derivatives. On the other hand, the derivatives having a 4-substituted aryl group (**11**) are less potent. The analogue containing a 3,5-disubstituted aryl group (**21**) shows a potency that is comparable to that of the corresponding monosubstituted derivative (**10**). Overall, it is clear that small, electron-withdrawing groups like CN or F located at the 3-position of the aryl ring increase the potency of these compounds as mGluR5 antagonists (**19**, **10**). On the other hand, introduction of polar groups such as NHAc, $CONH_2$, or OH clearly results in a decrease in activity. In particular, we point out that compound **19**, which has a cyano group at the 3-position in aryl ring, is the most potent of the 58 compounds reported in this article. Compound **19** has an IC_{50} value of 0.94 nM, and it is therefore 490-fold more potent than MTEP. Unfortunately, few of the heteroaryl derivatives including the fused ring derivatives (found in the right column of Table 2) that we have synthesized are very potent in comparison to MTEP. Both the pyrimidine derivative (**30**) and the pyrazine derivative (**31**) containing two nitrogen atoms in the heteroaryl ring are less potent than MTEP. Only the two thiazole derivatives **32** and **33** reveal mGluR5 antagonist potencies comparable to MTEP. The loss of potency for the fused ring compounds may be due to the inability of the antagonist binding site to accommodate these bulkier structures.

Next, we investigated the effects of substituents on the thiazole ring in modulating mGluR5 antagonist activity (section 1 of Table 3). As the substituents located on the 5-position of the thiazole ring became bulkier, compound potency decreased, suggesting some limitations in the size of the binding pocket. In the case of analogue **25** having the largest substituent, a phenyl group, no detectable activity was measured.

The derivatives chemically modified at the 2-position of the thiazole ring basically showed reduced activities compared to

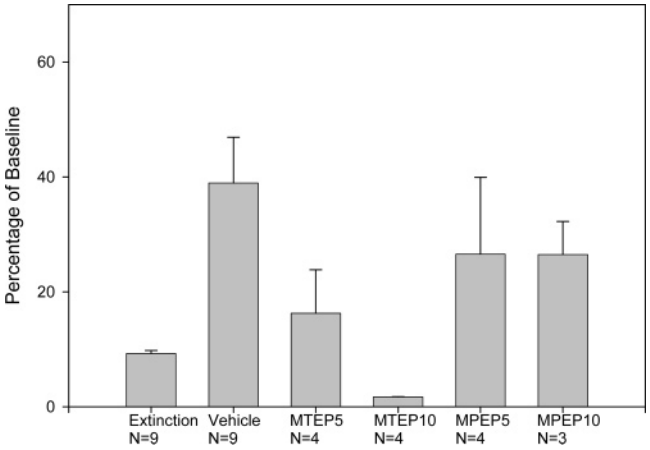


Figure 3. Effect of MTEP on cue-induced reinstatement of cocaine self-administration. Responses are shown as a percentage of the baseline.

the lead structures MTEP and **10** (sections 2 and 3 of Table 3). For both sets of the aminothiazole bearing analogues of MTEP and the analogues of **10**, their functional activity appears to relate to steric factors as opposed to substituent polarity. For those derivatives containing larger substitutents as found in **43**−**45**, **47**, and **49**, little or no activity was found.

The activities of MTEP analogues bearing a substituent at the 2-, 5-, or 6-positions of the 3-pyridyl group of MTEP are shown in Table 4. On the whole, the MTEP analogues substituted at the 5-position of the 3-pyridyl moiety are more potent as mGluR5 antagonists than those compounds containing substituents at the 2- or 6-positions of the 3-pyridyl moiety.

All substituents introduced at the 5-position of 3-pyridyl moiety led to an increase in functional potency as compared to MTEP (section 1 of Table 4). The analogues (**56** and **59**) possessing a sterically small, unsaturated group such as vinyl or ethynyl at this position showed very potent activities. In particular, compound **59** is the second most potent mGluR5 antagonist of all newly synthesized compounds reported herein. Its IC_{50} value is 2 nM, which translates into a 230-fold increase in potency relative to the activity measured for MTEP.

On the other hand, the MTEP analogues substituted at the 6-position of the 3-pyridyl moiety were generally less active than other members of this series (section 2 of Table 4). Of some interest, however, is the activity displayed by the 4-flurophenyl analogue **65**, which shows an IC_{50} value of 10 nM. This is somewhat surprising in light of the poor activity shown by the ethynyl and vinyl analogues **66** and **68**, and we therefore plan to explore this modification further.

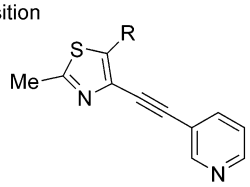
In the case of the analogues substituted at the 2-position (section 3 of Table 4), the 2-chloro compound was found to be the most active with an IC_{50} of 45 nM. Both the methoxy and ethynyl bearing compounds were less active than this chloro compound. On the other hand, analogue **73** having a strongly electron-withdrawing group mesyloxy group at the 2-postion failed to show activity.

The activities of the derivatives that have been chemically modified in the tether connecting the thiazole ring and aryl or heteroaryl ring are shown in Table 5. The analogue **80** having a *trans*-vinyl group as the tether in place of the ethynyl group in MTEP showed 10-fold less activity than MTEP. For the amide analogues **81** and **82** of MTEP and the fluorophenyl compound **10**, no activity was detectable.

For reasons relating to the anticipated toxicological effects of the thiazole ring versus the oxazole ring system, we were hopeful that the oxazole analogues of MTEP and **10** would retain good mGluR5 activity (Table 6). However, again neither of these compounds showed detectable activity. The lack of activity is somewhat surprising, as the overall change in structure brought about by replacing sulfur in the thiazole ring by oxygen is small. Apparently, the differences caused by the presence of the smaller, more electron withdrawing oxygen are sufficient to prevent interaction of these oxazole analogues with the allosteric binding site present in the intracellular domain of mGluR5. These findings will undoubtedly be of value to probe through molecular modeling studies.

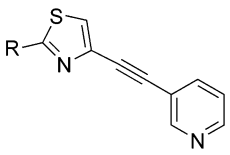
Table 3. Effects of Substituents on the Thiazole Ring

1) 5-Position



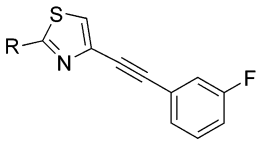
	R	IC_{50}[a] (mean ± SEM, nM)
22 (MTEP)	H	462 ± 112
23	Me	698 ± 62
24	Et	1243 ± 80
25	Ph	>10000

2) 2-Position (Amino Analogues of MTEP)



	R	IC_{50}[a] (mean ± SEM, nM)
22 (MTEP)	Me	462 ± 112
41	NH_2	789 ± 118
42	NHAc	1920 ± 370
43	NHBz	>10000
44	NHCONH−2,4-F_2-Ph	>10000
45	$NHCO_2Me$	>10000

3) 2-Position (Analogues of **10**)

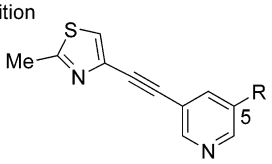


	R	IC_{50}[a] (mean ± SEM, nM)
10	Me	23.0 ± 1.2
40	NH_2	78.6 ± 22.7
46	Br	526 ± 62
47	3,5-F_2-Ph	>10000
49	C≡C−CH_2OH	>10000
50	C≡CH	2920 ± 2480

[a] IC_{50} values are expressed as mean ± SE, $n = 6$. IC_{50} values represent the ability of compounds containing various aryl or heteroaryl groups (A) to inhibit agonist-induced phosphoinositide hydrolysis.

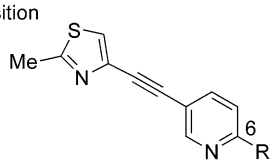
Table 4. Effects of Substituents on the Pyridine Ring

1) 5-Position



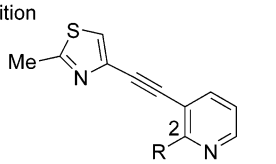
	R	IC_{50}[a] (mean ± SEM, nM)
22 (MTEP)	H	462 ± 112
28	Br	60 ± 5
52	4-F-Ph	162 ± 13
53	4-MeO-Ph	225 ± 17
55	C≡C−CH_2OH	68.6 ± 13.4
56	C≡CH	19.2 ± 4.5
59	HC=CH_2	2.01 ± 0.46

2) 6-Position



	R	IC_{50}[a] (mean ± SEM, nM)
22 (MTEP)	H	462 ± 112
26	OMe	426 ± 16
29	F	833 ± 36
62	OMs	2340 ± 1470
63	Cl	>10000
65	4-F-Ph	10.2 ± 2.0
66	C≡CH	2950 ± 130
68	HC=CH_2	>10000

3) 2-Position



	R	IC_{50}[a] (mean ± SEM, nM)
22 (MTEP)	H	462 ± 112
70	OMe	228 ± 77
73	OMs	>10000
74	Cl	45.5 ± 8.0
77	C≡CH	192 ± 48

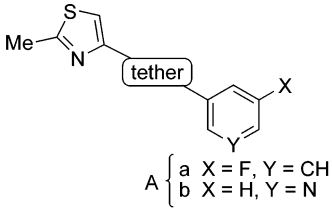
[a] IC_{50} values are expressed as mean ± SE, $n = 6$. IC_{50} values represent the ability of compounds containing various aryl or heteroaryl groups (A) to inhibit agonist-induced phosphoinositide hydrolysis.

To further confirm the activity of the two most potent compounds identified from the present SAR study, the binding affinities of analogues **19** and **59** at the **cloned** mGluR5 were measured. The binding studies were conducted using radiolabeled [3H]-MPEP and transiently transfected 293-T cells transfected with cloned mGluR5 cDNA. As is apparent from Table 7, the K_i values obtained for binding to the cloned mGluR5 correlate well with the IC_{50} values obtained from the rat mGluR5 antagonist assay.

Conclusion

The present work delineates the chemical synthesis of a total of 58 MTEP analogues in which chemical modifications have been made to each of the three regions of the lead molecule. In general, we found that modifications to the thiazole moiety of MTEP including its replacement by an oxazole group resulted in a decrease in functional activity. Likewise, in the few cases studied, replacement of the acetylenic tether by either a *trans*-

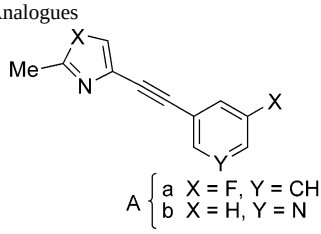
Table 5. Modification of the Tether



	tether	A	IC_{50}[a] (mean ± SEM, nM)
22 (MTEP)	C≡C	b	462 ± 112
80	HC=CH (*trans*)	b	3090 ± 930
82	CONH	b	>10000
10	C≡C	a	23 ± 1.2
81	CONH	a	>10000

[a] IC_{50} values are expressed as mean ± SE, $n = 6$. IC_{50} values represent the ability of compounds containing various aryl or heteroaryl groups (A) to inhibit agonist-induced phosphoinositide hydrolysis.

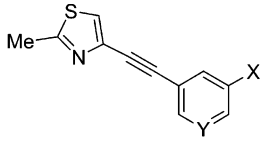
Table 6. Oxazole Analogues



	X	A	IC_{50}[a] (mean ± SEM, nM)
22 (MTEP)	S	b	462 ± 112
90	O	b	>10000
10	S	a	23 ± 1.2
89	O	a	>10000

[a] IC_{50} values are expressed as mean ± SE, $n = 6$. IC_{50} values represent the ability of compounds containing various aryl or heteroaryl groups (A) to inhibit agonist-induced phosphoinositide hydrolysis.

Table 7. In Vitro Cloned mGluR5 Binding Affinity Data for Potent mGluR5 Antagonists **19** and **59**



19 X = CN, Y = CH
59 X = vinyl, Y = N

	Rat Brain Membranes (Ki[a] nM)	Cloned mGluR5
19	0.25	0.37
59	0.71	1.003

[a] K_i values are expressed as nM. K_i values are analyzed by the displacement by the test compounds (**19**, **59**) of [3H]-MPEP from cloned mGluR5 and represent the binding affinity of compounds (**19**, **59**) to the cloned mGluR5.

olefin or an amide was also not promising. This SAR information thus suggests that the (2-methyl-1,3-thiazol-4-yl)ethynyl group represents one of the best part structures valuable to achieving mGluR5 antagonist activity. Further detailed chemical modifications of the 3-pyridyl moiety in MTEP including its replacement by a variety of aryl and heteroaryl groups possessing various substituents located at different positions resulted in several promising compounds. We found that when relatively small groups such as vinyl or cyano were introduced into the positions meta to the ethynyl group in either the pyridyl ring of MTEP or the phenyl ring of its fluorophenyl analogue **10**, large enhancements in compound potency could be achieved. Among the compounds synthesized and tested in this study, analogues **19** and **59** were found to be 490- and 230-fold more potent as mGluR5 antagonists than MTEP. Moreover, the binding affinities measured for these analogues using human mGluR5 from cortical tissues correlated well with the antagonist potencies measured using rat mGluR5. As our behavioral data clearly demonstrate that MTEP has the ability to prevent reinstatement of cocaine seeking by environmental cues associated with cocaine availability, the identification of other MTEP analogues that exhibit appropriate ADME and safety parameters should be pursued in the quest for medications for drug addiction. The SAR information available from the present research will be used to guide our efforts in identifying other noncompetitive mGluR5 antagonists for study in cocaine self-administration experiments in rodents.

Experimental Section

Behavioral Methods. Subjects. Adult male Wistar rats ($n = 9$, Harlan Sprague Dawley) 80 to 100 days old at the start of the experiments were used. Rats were tested for reinstatement following pretreatment with MTEP, MPEP, and vehicle. All rats were housed singly in cages equipped with a laminar flow unit and air filter in a temperature- and humidity-controlled, AAALAC-accredited animal care facility on a reversed 12 h light/dark cycle (lights on at 18:00 h) with free access to water. Rats were also allowed free access to food until their free-feeding body weights increased to approximately 380−400 g. These rats were subsequently maintained at 85 to 90% of their free-feeding body weights by supplemental post-session feeding (Purina Rat Chow) throughout the course of the experiments. All procedures were approved by the LSUHSC Institutional Animal Care and Use Committee and were carried out in accordance with the NIH "Principles of laboratory animal care" (NIH publication No. 85-23).

Once the targeted weight was reached, rats ($n = 9$) were injected with sterile penicillin G procaine suspension (75,000 units, i.m.), and immediately thereafter they were implanted with chronic indwelling jugular catheters under pentobarbital anesthesia (50 mg/kg, i.p.) with methylatropine nitrate pretreatment (10 mg/kg, i.p.) using previously reported procedures.[33]

Apparatus. Standard plastic and stainless steel operant conditioning chambers contained within sound-attenuating enclosures (Med-Associates, Inc.) were used to run the behavioral experiments. Each experimental chamber was equipped with two response levers (Med-Associates, Inc.) mounted on either side of the chamber with a stimulus light located above each lever. A food pellet dispenser was located between the two levers, and the lever on the right was designated the "inactive" lever for the self-administration experiments. The chambers were also equipped with a house light and tone generator (Piezo, 66 decibels) to produce a compound stimulus that was paired with each cocaine infusion. The enclosures contained an exhaust fan that supplied ventilation and white noise to mask extraneous sounds.

Self-Administration Training. Rats were trained to self-administer cocaine by pressing one of the response levers under a fixed-ratio 4 (FR4) schedule of reinforcement during daily 2 h sessions conducted 5 days per week as previously described.[33c] Completion of the FR4 schedule resulted in an intravenous infusion of cocaine (0.25 mg/kg/infusion delivered in 200 μL 0.9% NaCl delivered over 5.6 s) and the concurrent presentation of the house light and tone compound stimulus. The criterion for "stable responding" under the FR4 schedule of reinforcement was a minimum of 10 days of exposure to this schedule that included 3 consecutive days when responding varied by less than 10%. Responses on the inactive lever were counted but resulted in no programmed consequences at any time.

Extinction Training. Once stable responding under the FR4 schedule of self-administration was observed according to the criteria described above, extinction training began. During extinction, responding on either lever produced no programmed consequences, and no cocaine or cocaine-associated cues were delivered. Successful extinction was determined individually for each rat instead of exposing all rats to a predefined number of extinction sessions.[33c] The rats were exposed to extinction training until responding on the active lever decreased to below 20% of baseline responding (i.e., average responding during the last 3 days of cocaine self-administration) for at least 3 consecutive days. Responding was not completely extinguished to allow for the possibility of cue-induced reinstatement.

Reinstatement Testing. Once responding on the active lever was successfully extinguished according to the criteria described above, reinstatement testing commenced. Rats were placed into the chambers, and each response on the active lever resulted in a 5.6 s presentation of the conditioned cue (the paired house light and tone compound stimulus). Responses on the inactive lever were counted but resulted in no scheduled consequences. Rats were randomly pretreated (30 min) with either an i.p. injection of the vehicle (5% emulphor in saline) or one of the two test drugs (MTEP or MPEP) at a dose of either 5 or 10 mg/kg. Following the reinstatement test, the rats were re-trained to self-administer cocaine for a minimum of 5 days until stable self-administration was observed as described above. These rats once again underwent extinction training, and when the criteria for successful extinction were met, they were once again tested for reinstatement with the contingent presentation of the conditioned reinforcer. Prior to this second test, the rats were pretreated with a compound (i.e., MPEP, MTEP or vehicle) different than the one that they had received during the first test.

Drugs. Cocaine HCl was obtained from the National Institute on Drug Abuse (Research Triangle Park, NC) and was dissolved in bacteriostatic, heparinized 0.9% saline. Cocaine was self-administered at a dose of 0.25 mg/kg/infusion and was delivered in a 200 μL volume over 5.6 s. MTEP and MPEP were suspended in 5% emulphor in 0.9% saline. Two rats were previously exposed to oxazepam (10 mg/ kg, i.p.) and CP 154,526 (20 mg/kg, i.p.).

Data Analysis. Data collected included the number of cocaine infusions during self-administration and the number of responses on the active and inactive levers during self-administration, extinction, and reinstatement testing. Significance of the differences between the various treatments was determined with a one-way analysis of variance with the treatment administration during reinstatement (i.e., vehicle, MTEP 5, MTEP 10, MPEP 5, or MPEP 10) and subject as the variables. Tukey's all pairwise multiple comparison procedures were then used to isolate differences between groups.

Biological Evaluation. Phosphoinositide Hydrolysis Assay.[34] Recombinant cDNA for mGluR5a was stably transfected and expressed in Chinese hamster ovary (CHO) cells.[35] Cultured in 96-well plates, the receptor-expressing cells were incubated with 0.75 μCi *myo*-[^{3}H]inositol to label the cell membrane phosphoinositides. Incubations with test compounds were carried out for 45 min at 37 °C in Locke's buffer (156 mM NaCl, 5.6 mM KCl, 3.6 mM $NaHCO_3$, 1 mM $MgCl_2$, 1.3 mM $CaCl_2$, 5.6 mM glucose, and 20 mM HEPES, pH 7.4) containing 20 mM LiCl, which blocks the degradation of inositol phosphates (IPs). The reaction was terminated by aspiration and addition of 0.1 M HCl. IPs were extracted with 0.1 M HCl. [^{3}H]IPs were separated by anion exchange

chromatography and determined in duplicate by a liquid scintillation counter (LKB, Uppsala, Sweden) as previously described.[36]

Data were normalized to the maximal response induced by 1 mM glutamate for mGluR5. IC_{50} of the title compounds was determined from the concentration−response curves using seven concentrations in four to six separated experiments; values were determined by fitting the normalized data to the logistic equation by nonlinear regression using Sigma Plot (SPSS Science, Chicago, IL).

Binding Assay for Cloned mGluR5. Radioligand binding assays were performed essentially as previously detailed[6g] with the following modifications: membranes from HEK293-T cells transfected (FuGENE6 transfection Reagent, Roche.) with cloned mGluR5 cDNA and rat brain membranes were used. The binding assays were conducted in a total volume of 500 μL (50 mM Tris-Cl, 0.9% NaCl, pH = 7.4) using 3.0 nM [^{3}H]-MPEP and various concentrations of the unlabeled ligands in 96-well plates. The plates were incubated at 20 °C for 90 min. The membranes were harvested in polyethyleneimine-pretreated Whatman GF/C filters, dried, incubated overnight with scintillation cocktail (Ecoscint A), and counted in a scintillation counter. Nonspecific binding was determined using 10 μM MPEP, which was typically < 5% of total binding. Data were analyzed using GraphPad Prizm V4.1.

General Chemistry Methods. All solvents and reagents were used as obtained from commercial sources unless otherwise indicated. All starting materials were also obtained from commercial sources. All reactions were carried out under a positive pressure of nitrogen. Glassware for water-sensitive reactions was dried in an oven at 120 °C overnight. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were recorded on an Avance 300 Bruker instrument operating at 300 MHz for ^{1}H and 75 MHz for ^{13}C. Deuterated chloroform (99.8% D) or methanol (99.8% D) was used as solvents. Chemical shifts values (δ) are expressed in ppm downfield from tetramethylsilane as internal standard, and coupling constants (J) in Hertz. Exact masses were determined on a Micromass Q-TOF time-of-flight mass spectrometer using positive mode electrospray ionization. Anhydrous solvents were purchased from Aldrich Chemical Co. Organic solutions were dried over anhydrous magnesium sulfate ($MgSO_4$). Flash chromatography was performed on silica gel Fluka Art. No. 60738. Analytical thin-layer chromatography (TLC) was performed on Merck TLC glass plates precoated with silica gel 60 F254 (detection by UV illumination at 254 nm and with iodine vapors). Analytical HPLC was performed using a Shimadzu LC-10AD system, equipped with a SPD-10A variable wavelength detector set at 254 nm. The HPLC data of tested compounds including the chromatographic conditions can be seen in the Supporting Information.

2-Methyl-4-(trimethylsilylethynyl)thiazole (4). Aluminum trichloride ($AlCl_3$) (9.31 g, 70.0 mmol) was suspended in CH_2Cl_2 (70 mL) and cooled in an ice bath. Bis(trimethylsilyl)acetylene (15.7 mL, 70.0 mmol) and chloroacetyl chloride (5.6 mL, 70.0 mmol) were combined in CH_2Cl_2 (120 mL), and this solution was added to the $AlCl_3$ suspension dropwise from an addition funnel over 1 h. The dark brownish-red solution was stirred at 0 °C for 45 min, and the ice bath was removed. After 50 min at room temperature, the reaction was cooled to 0 °C and quenched by slow addition of 1.0 N HCl (175 mL). After the acidic solution was extracted with diethyl ether (2 × 350 mL), the combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give crude 1-chloro-4-trimethylsilyl-3-butyn-2-one (**1**). This crude compound **1** was dissolved in DMF (120 mL), and thioacetamide (6.31 g, 84.0 mmol) was added in one portion. The mixture was allowed to stir for 17 h at room temperature. The mixture was diluted with EtOAc (600 mL), washed with 0.1 N HCl (300 mL) and H_2O (2 × 300 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 10:1 to give **4** (9.40 g, 69%); ^{1}H NMR ($CDCl_3$) δ 0.25 (s, 9H), 2.70 (s, 3H), 7.32 (s, 1H).

2,5-Dimethyl-4-(trimethylsilylethynyl)thiazole (5). Aluminum trichloride ($AlCl_3$) (2.67 g, 20.0 mmol) was suspended in CH_2Cl_2 (20 mL) and cooled in an ice bath. Bis(trimethylsilyl)acetylene (4.48 mL, 20.0 mmol) and 2-chloropropionyl chloride (1.95 mL, 20.0 mmol) were combined in CH_2Cl_2 (40 mL), and this solution was added to the $AlCl_3$ suspension dropwise from an addition funnel over 40 min. The dark brownish-red solution was stirred at 0 °C for 30 min, and the ice bath was removed. After 50 min at room temperature, the reaction was cooled to 0 °C and quenched by slow addition of 1.0 N HCl (50 mL). After the acidic solution was extracted with diethyl ether (2 × 100 mL), the combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give crude 4-chloro-1-trimethylsilyl-1-pentyn-3-one (**2**). This crude compound **2** was dissolved in DMF (40 mL), and thioacetamide (1.80 g, 24.0 mmol) was added in one portion. The mixture was allowed to stir for 20 h at room temperature and then for 1.5 h at 85 °C. The mixture was diluted with EtOAc (250 mL), washed with 0.1 N HCl (120 mL) and H_2O (2 × 120 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 20:1 to give **5** (1.80 g, 43%); ^{1}H NMR ($CDCl_3$) δ 0.26 (s, 9H), 2.49 (s, 3H), 2.63 (s, 3H).

5-Ethyl-2-methyl-4-(trimethylsilylethynyl)thiazole (6). Aluminum trichloride ($AlCl_3$) (4.00 g, 30.0 mmol) was suspended in CH_2Cl_2 (30 mL) and cooled in an ice bath. Bis(trimethylsilyl)-acetylene (6.80 mL, 30 mmol) and 2-chlorobutyryl chloride (4.23 g, 30 mmol) were combined in CH_2Cl_2 (60 mL), and this solution was added to the $AlCl_3$ suspension dropwise from an addition funnel over 40 min. The dark brownish-red solution was stirred at 0 °C for 30 min, and the ice bath was removed. After 50 min at room temperature, the reaction was cooled to 0 °C and quenched by slow addition of 1 N HCl (75 mL). After the acidic solution was extracted with diethyl ether (2 × 150 mL), the combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give crude 4-chloro-1-trimethylsilyl-1-hexyn-3-one (**3**). This crude compound **3** was dissolved in DMF (60 mL), and thioacetamide (2.70 g, 36.0 mmol) was added in one portion. The mixture was allowed to stir for 20 h at room temperature and then for 1.5 h at 85 °C. The mixture was diluted with EtOAc (300 mL), washed with 0.1 N HCl (150 mL) and H_2O (2 × 150 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 40:1 to give **6** (2.21 g, 33%); ^{1}H NMR ($CDCl_3$) δ 0.26 (s, 9H), 1.29 (t, J = 7.5 Hz, 3H), 2.64 (s, 3H), 2.90 (q, J = 7.5 Hz, 2H).

1-Phenyl-4-trimethylsilyl-3-butyn-2-one (7). Aluminum trichloride ($AlCl_3$) (6.67 g, 50.0 mmol) was suspended in CH_2Cl_2 (50 mL) and cooled in an ice bath. Bis(trimethylsilyl)acetylene (11.3 mL, 50 mmol) and phenylacetyl chloride (6.62 mL, 50 mmol) were combined in CH_2Cl_2 (100 mL), and this solution was added to the $AlCl_3$ suspension dropwise from an addition funnel over 40 min. The dark brownish-red solution was stirred at 0 °C for 30 min, and the ice bath was removed. After 50 min at room temperature, the reaction was cooled to 0 °C and quenched by slow addition of 1.0 N HCl (125 mL). After the acidic solution was extracted with diethyl ether (2 × 250 mL), the combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexane to give **7** (7.68 g, 71%); ^{1}H NMR ($CDCl_3$) δ 0.21 (s, 9H), 3.85 (s, 2H), 7.24−7.38 (m, 5H).

2-Methyl-5-phenyl-4-(trimethylsilylethynyl)thiazole (9). Compound **7** (1.08 g, 5.0 mmol) was dissolved in CCl_4 (30 mL) and cooled in an ice bath. Bromine (0.26 mL, 5.0 mmol) was added to the above solution dropwise over 10 min. The reaction mixture was partitioned between CH_2Cl_2 (50 mL) and saturated aqueous $NaHCO_3$ (40 mL). The organic layer was washed with H_2O (30 mL) and brine (30 mL), dried over $MgSO_4$, and evaporated in vacuo to give crude 1-bromo-1-phenyl-4-trimethylsilyl-3-butyn-2-one (**8**). This crude compound **8** was dissolved in DMF (10 mL), and thioacetamide (451 mg, 6.0 mmol) was added in one portion. The mixture was allowed to stir for 14 h at room temperature and then for 1.5 h at 85 °C. The mixture was diluted with EtOAc (60 mL), washed with 0.1 N HCl (30 mL) and H_2O (2 × 30 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 30:1 to give **9** (570 mg, 42%); ^{1}H NMR ($CDCl_3$) δ 0.27 (s, 9H), 2.70 (s, 3H), 7.34−7.45 (m, 3H), 7.86 (d, J = 7.0 Hz, 2H).

General Procedure for the Modified Sonogashira Coupling Reaction Involving an in Situ Desilylation Reaction. Conditions a. 2-Methyl-4-(trimethylsilylethynyl)thiazole (**4**) as a substrate and the corresponding aryl or heteroaryl halide (1.1 equiv) were combined in a flask containing deoxygenated DMF. To this mixture were added $Pd(PPh_3)_4$ (0.05 equiv), CuI (0.1 equiv), and triethylamine (1.2 equiv). The mixture was warmed to 85 °C, and a solution of Bu_4NF (1.0 M in THF) (1.1 equiv) was then added dropwise over 15 min. TLC analysis demonstrated the reaction to be complete after Bu_4NF addition. The reaction mixture was filtered through Celite and partitioned between EtOAc and 0.1 N HCl. The organic layer was washed twice with H_2O, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a hexanes−EtOAc solvent system to give the corresponding product.

4-(3-Methoxyphenylethynyl)-2-methylthiazole (12). Hexanes−EtOAc 7:1 for elution; yield 78%. ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 3.83 (s, 3H), 6.93 (d, J = 7.9 Hz, 1H), 7.11 (s, 1H), 7.17 (d, J = 7.6 Hz, 1H), 7.27 (t, J = 7.9 Hz, 1H), 7.39 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.5, 55.6, 83.7, 89.1, 115.7, 116.8, 122.8, 123.8, 124.6, 129.8, 137.2, 159.7, 166.0. MS (ESI) m/z 230.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 230.0639; calcd mass $(C_{13}H_{11}NOS + H)^+$, 230.0640.

4-(2-Fluorophenylethynyl)-2-methylthiazole (13). Hexanes−EtOAc 7:1 for elution; yield 71%. ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.12 (t, J = 8.6 Hz, 1H), 7.15 (t, J = 6.9 Hz, 1H), 7.29−7.39 (m, 1H), 7.44 (s, 1H), 7.56 (t, J = 6.6 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 82.6, 88.7, 111.6 (d, $^2J_{CF}$ = 15.6 Hz), 116.0 (d, $^2J_{CF}$ = 20.7 Hz), 123.3, 124.4 (d, $^4J_{CF}$ = 3.7 Hz), 130.8 (d, $^3J_{CF}$ = 7.9 Hz), 132.5 (m), 134.0, 163.2 (d, $^1J_{CF}$ = 252.6 Hz), 166.2. MS (ESI) m/z 218.4 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 218.0436; calcd mass $(C_{12}H_8FNS + H)^+$, 218.0440.

4-(2-Methoxyphenylethynyl)-2-methylthiazole (14). Hexanes−EtOAc 5:1 for elution; yield 67%. ^{1}H NMR ($CDCl_3$) δ 2.74 (s, 3H), 3.90 (s, 3H), 6.91 (t, J = 8.0 Hz, 1H), 6.93 (t, J = 7.5 Hz, 1H), 7.32 (t, J = 7.7 Hz, 1H), 7.38 (s, 1H), 7.53 (d, J = 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 56.2, 85.7, 87.7, 111.0, 112.1, 120.8, 122.4, 130.5, 134.1, 137.6, 160.6, 165.8. MS (ESI) m/z 230.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 230.0639; calcd mass $(C_{13}H_{11}NOS + H)^+$, 230.0640.

2-Methyl-4-(*m*-tolylethynyl)thiazole (15). Hexanes−EtOAc 8:1 for elution; yield 72%. ^{1}H NMR ($CDCl_3$) δ 2.36 (s, 3H), 2.76 (s, 3H), 7.15−7.29 (m, 2H), 7.37 (s, 1H), 7.40 (br s, 2H). ^{13}C NMR ($CDCl_3$) δ 19.7, 21.6, 83.5, 89.4, 122.4, 122.7, 128.7, 129.2, 130.0, 132.7, 137.4, 138.4, 166.0. MS (ESI) m/z 214.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 214.0697; calcd mass $(C_{13}H_{11}NS + H)^+$, 214.0690.

4-(3-Chlorophenylethynyl)-2-methylthiazole (16). Hexanes−EtOAc 7:1 for elution; yield 82%. ^{1}H NMR ($CDCl_3$) δ 2.74 (s, 3H), 7.28 (d, J = 7.5 Hz, 1H), 7.31 (t, J = 7.8 Hz, 1H), 7.39 (s, 1H), 7.43 (d, J = 7.2 Hz, 1H), 7.54 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 85.0, 87.7, 123.2, 124.6, 129.3, 130.0, 130.2, 131.9, 134.6, 136.9, 166.3. MS (ESI) m/z 234.1 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 234.0136; calcd mass $(C_{12}H_8ClNS + H)^+$, 234.0144.

2-Methyl-4-[[3-(trifluoromethyl)phenyl]ethynyl]thiazole (17). Hexanes−EtOAc 7:1 for elution; yield 79%. ^{1}H NMR ($CDCl_3$) δ 2.75 (s, 3H), 7.42 (s, 1H), 7.48 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 7.6 Hz, 1H), 7.72 (d, J = 7.5 Hz, 1H), 7.83 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 85.3, 87.6, 123.4, 123.9, 124.1 (q, $^1J_{CF}$ = 272.4 Hz) 125.5 (q, $^3J_{CF}$ = 3.6 Hz), 128.9 (q, $^3J_{CF}$ = 3.9 Hz), 129.3, 131.4 (q, $^2J_{CF}$ = 32.8 Hz), 135.1, 136.7, 166.4. MS (ESI) m/z 268.4 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 268.0404; calcd mass $(C_{13}H_8F_3NS + H)^+$, 268.0408.

2-Methyl-4-[[3-(trifluoromethoxy)phenyl]ethynyl]thiazole (18). Hexanes−EtOAc 7:1 for elution; yield 29%. ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 7.22 (d, J = 8.0 Hz, 1H), 7.39 (t, J = 7.7 Hz, 1H), 7.43 (br s, 2H), 7.50 (d, J = 7.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 85.1, 87.6, 119.1, 121.8, 123.4, 124.4, 124.8, 130.3, 130.5, 136.8, 149.4, 166.4. MS (ESI) m/z 284.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 284.0352; calcd mass $(C_{13}H_8F_3NOS + H)^+$, 284.0357.

3-[(2-Methyl-4-thiazolyl)ethynyl]benzonitrile (19). Hexanes−EtOAc 5:1 for elution; yield 80%. ^{1}H NMR ($CDCl_3$) δ 2.69 (s, 3H), 7.40 (s, 1H), 7.41 (t, J = 7.9 Hz, 1H), 7.56 (d, J = 7.7 Hz, 1H), 7.70 (d, J = 7.8 Hz, 1H), 7.75 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 86.2, 86.6, 113.3, 118.3, 124.0, 124.5, 129.8, 132.1, 135.3, 136.1, 136.4, 166.5. MS (ESI) m/z 225.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 225.0491; calcd mass $(C_{13}H_8N_2S + H)^+$, 225.0486.

***N*-[3-[(2-Methyl-4-thiazolyl)ethynyl]phenyl]acetamide (20).** The starting material, *N*-(3-iodophenyl)acetamide, was obtained quantitatively by reaction of 3-iodoaniline with acetyl chloride in the presence of triethylamine. Compound **20**: hexanes−EtOAc 1:2 for elution; yield 78%. ^{1}H NMR ($CDCl_3$) δ 2.15 (s, 3H), 2.72 (s, 3H), 7.22 (br s, 2H), 7.36 (s, 1H), 7.54 (br s, 1H), 7.69 (br s, 1H), 8.33 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 24.9, 83.8, 89.0, 120.9, 122.9, 123.3, 123.3, 127.8, 129.4, 137.1, 138.7, 166.2, 169.4. MS (ESI) m/z 257.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 257.0751; calcd mass $(C_{14}H_{12}N_2OS + H)^+$, 257.0749.

4-(3,5-Difluorophenylethynyl)-2-methylthiazole (21). Hexanes−EtOAc 7:1 for elution; yield 73%. ^{1}H NMR ($CDCl_3$) δ 2.74 (s, 3H), 6.81 (tt, J_1 = 8.9 Hz, J_2 = 1.9 Hz, 1H), 7.05 (d, J = 6.0 Hz, 2H), 7.42 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 85.7, 86.8 (t, $^4J_{CF}$ = 4.0 Hz), 105.2 (t, $^2J_{CF}$ = 25.4 Hz), 115.0 (dd, $^2J_{CF}$ = 17.8 Hz, $^4J_{CF}$ = 8.7 Hz), 123.8, 125.6 (t, $^3J_{CF}$ = 11.8 Hz), 136.5, 163.1 (dd, $^1J_{CF}$ = 249.2 Hz, $^3J_{CF}$ = 13.4 Hz), 166.4. MS (ESI) m/z 236.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + Na)^+$, 258.0169; calcd mass $(C_{12}H_7F_2NS + Na)^+$, 258.0165.

3-[(2-Methyl-4-thiazolyl)ethynyl]pyridine (MTEP) (22). Hexanes−EtOAc 1:2 for elution; yield 52%. ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.30 (dd, J_1 = 7.4 Hz, J_2 = 3.7 Hz, 1H), 7.45 (s, 1H), 7.85 (d, J = 7.6 Hz, 1H), 8.58 (d, J = 3.8 Hz, 1H), 8.80 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 85.8, 87.0, 120.2, 123.5, 123.5, 136.7, 139.0, 149.3, 152.8, 166.4. MS (ESI) m/z 201.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 201.0478; calcd mass $(C_{11}H_8N_2S + H)^+$, 201.0486.

3-[(2-Methyl-5-phenyl-4-thiazolyl)ethynyl]pyridine (25). Hexanes−EtOAc 2:3 for elution; yield 52%. ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.28−7.33 (m, 1H), 7.38−7.51 (m, 3H), 7.79−7.87 (m, 3H), 8.57 (d, J = 4.0 Hz, 1H), 8.77 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.8, 88.1, 88.2, 120.4, 120.4, 123.5, 128.6, 128.6, 129.2, 129.2, 129.3, 131.3, 138.8, 142.4, 149.2, 152.7, 164.4. MS (ESI) m/z 277.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 277.0800; calcd mass $(C_{17}H_{12}N_2S + H)^+$, 277.0799.

2-Methoxy-5-[(2-methyl-4-thiazolyl)ethynyl]pyridine (26). Hexanes−EtOAc 3:1 for elution; yield 68%. ^{1}H NMR ($CDCl_3$) δ 2.75 (s, 3H), 3.96 (s, 3H), 6.73 (d, J = 8.6 Hz, 1H), 7.37 (s, 1H), 7.71 (dd, J_1 = 8.6 Hz, J_2 = 2.1 Hz, 1H), 8.38 (d, J = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 54.1, 85.2, 86.1, 111.2, 112.7, 122.5, 137.1, 141.6, 150.7, 164.0, 166.1. MS (ESI) m/z 231.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 231.0595; calcd mass $(C_{12}H_{10}N_2OS + H)^+$, 231.0592.

5-Fluoro-2-[(2-methyl-4-thiazolyl)ethynyl]pyridine (27). Hexanes−EtOAc 2:1 for elution; yield 66%. ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.42 (td, J_1 = 8.3 Hz, J_2 = 2.7 Hz, 1H), 7.52 (s, 1H), 7.59 (dd, J_1 = 8.6 Hz, J_2 = 4.4 Hz, 1H), 8.49 (d, J = 2.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 83.3, 87.3, 123.6 (d, $^2J_{CF}$ = 19.0 Hz), 124.5, 128.7 (d, $^3J_{CF}$ = 4.8 Hz), 136.3, 139.1 (t, $^2J_{CF}$ = 24.5 Hz), 139.4, 159.1 (d, $^1J_{CF}$ = 260.1 Hz), 166.3. MS (ESI) m/z 219.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + Na)^+$, 241.0206; calcd mass $(C_{11}H_7FN_2S + Na)^+$, 241.0212.

3-Bromo-5-[(2-methyl-4-thiazolyl)ethynyl]pyridine (28). Hexanes−EtOAc 4:1 for elution; yield 76%. ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 7.47 (s, 1H), 7.99 (br t, J = 1.7 Hz, 1H), 8.64 (d, J = 1.8 Hz, 1H), 8.70 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 84.3, 88.4, 120.5, 121.5, 124.2, 136.2, 141.1, 150.4, 150.6, 166.5. MS (ESI) m/z 279.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 278.9593; calcd mass $(C_{11}H_7BrN_2S + H)^+$, 278.9592.

2-Fluoro-5-[(2-methyl-4-thiazolyl)ethynyl]pyridine (29). Hexanes−EtOAc 3:1 for elution; yield 41% ^{1}H NMR ($CDCl_3$) δ 2.77

(s, 3H), 6.96 (dd, $J_1 = 8.4$ Hz, $J_2 = 2.7$ Hz, 1H), 7.44 (s, 1H), 7.94 (td, $J_t = 8.0$ Hz, $J_d = 2.1$ Hz, 1H), 8.44 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 84.5, 86.9, 109.9 (d, $^2J_{CF} = 38.1$ Hz), 118.0 (d, $^4J_{CF} = 4.8$ Hz), 123.6, 136.5, 144.1 (d, $^3J_{CF} = 8.3$ Hz), 151.2 (d, $^3J_{CF} = 15.5$ Hz), 163.2 (d, $^1J_{CF} = 243.0$ Hz), 166.5. MS (ESI) *m/z* 219.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 219.0387; calcd mass ($C_{11}H_7FN_2S$ + H)$^+$, 219.0392.

5-[(2-Methyl-4-thiazolyl)ethynyl]pyrimidine (30). Hexanes−EtOAc 1:1 for elution; yield 51%. ^{1}H NMR ($CDCl_3$) δ 2.78 (s, 3H), 7.51 (s, 1H), 8.90 (s, 2H), 9.18 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 82.2, 90.7, 119.7, 124.5, 136.0, 157.3, 159.1, 159.1, 166.7. MS (ESI) *m/z* 202.3 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 202.0432; calcd mass ($C_{10}H_7N_3S$ + H)$^+$, 202.0439.

2-[(2-Methyl-4-thiazolyl)ethynyl]pyrazine (31). Hexanes−EtOAc 1:1 for elution; yield 61%. ^{1}H NMR ($CDCl_3$) δ 2.74 (s, 3H), 7.55 (s, 1H), 8.49 (s, 1H), 8.57 (s, 1H), 8.77 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 85.5, 87.4, 125.6, 135.9, 140.2, 143.5, 144.9, 148.2, 166.6. MS (ESI) *m/z* 202.3 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 202.0438; calcd mass ($C_{10}H_7N_3S$ + H)$^+$, 202.0439.

2-Methyl-4-(2-thienylethynyl)thiazole (32). Hexanes−EtOAc 5:1 for elution; yield 28%. ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.03 (dd, $J_1 = 5.0$ Hz, $J_2 = 3.8$ Hz, 1H), 7.33 (d, $J = 5.0$ Hz, 1H), 7.34 (d, $J = 3.3$ Hz, 1H), 7.39 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 82.4, 86.3, 122.6, 127.5, 128.2, 133.1, 137.3, 147.0, 167.0. MS (ESI) *m/z* 206.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 206.0105; calcd mass ($C_{10}H_7NS_2$ + H)$^+$, 206.0098.

2-Methyl-4-(3-thienylethynyl)thiazole (33). Hexanes−EtOAc 5:1 for elution; yield 80%. ^{1}H NMR ($CDCl_3$) δ 2.72 (s, 3H), 7.21 (d, $J = 4.5$ Hz, 1H), 7.29 (d, $J = 4.5$ Hz, 1H), 7.33 (s, 1H), 7.56 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 83.4, 84.5, 121.9, 122.3, 125.8, 129.9, 130.3, 137.3, 166.1. MS (ESI) *m/z* 206.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + Na)$^+$, 227.9914; calcd mass ($C_{10}H_7NS_2$ + Na)$^+$, 227.9918.

3-[(2-Methyl-4-thiazolyl)ethynyl]quinoline (34). Hexanes−EtOAc 2:1 for elution; yield 52%. ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.46 (s, 1H), 7.57 (t, $J = 7.4$ Hz, 1H), 7.73 (t, $J = 7.7$ Hz, 1H), 7.78 (t, $J = 7.4$ Hz, 1H), 8.09 (d, $J = 8.4$ Hz, 1H), 8.33 (s, 1H), 9.02 (d, $J = 1.9$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 86.5, 87.0, 117.1, 123.5, 127.5, 127.8, 128.1, 129.8, 130.7, 136.8, 139.1, 147.4, 152.4, 166.4. MS (ESI) *m/z* 251.3 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 251.0640; calcd mass ($C_{15}H_{10}N_2S$ + H)$^+$, 251.0643.

6-[(2-Methyl-4-thiazolyl)ethynyl]quinoxaline (35). Hexanes−EtOAc 2:3 for elution; yield 38%. ^{1}H NMR ($CDCl_3$) δ 2.79 (s, 3H), 7.51 (s, 1H), 7.91 (dd, $J_1 = 8.7$ Hz, $J_2 = 1.7$ Hz, 1H), 8.10 (d, $J = 8.7$ Hz, 1H), 8.32 (d, $J = 1.4$ Hz, 1H), 8.85 (d, $J = 1.6$ Hz, 1H), 8.89 (d, $J = 1.6$ Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 86.7, 88.2, 123.8, 125.0, 130.1, 133.1, 133.2, 136.8, 143.2, 143.3, 145.7, 146.2, 166.5. MS (ESI) *m/z* 252.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 252.0600; calcd mass ($C_{14}H_9N_3S$ + H)$^+$, 252.0595.

5-[(2-Methyl-4-thiazolyl)ethynyl]-1*H*-indole (36). Hexanes−EtOAc 3:1 for elution; yield 35%. ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 6.58 (s, 1H), 7.31−7.49 (m, 3H), 7.35 (s, 1H), 7.91 (s, 1H), 8.24 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 81.5, 83.6, 103.5, 112.0, 114.8, 121.5, 125.4, 125.4, 126.2, 128.1, 136.6, 142.1, 165.1. MS (ESI) *m/z* 239.3 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 239.0646; calcd mass ($C_{14}H_{10}N_2S$ + H)$^+$, 239.0643.

Conditions b. 2-Methyl-5-substituted-4-(trimethylsilylethynyl)-thiazole (**4**, **5**, or **6**) as a substrate and the corresponding aryl or heteroaryl halide (1.1 equiv) were combined in a flask containing deoxygenated DMF. To this mixture were added $(PPh_3)_2PdCl_2$ (0.1 equiv), PPh_3 (0.1 equiv), CuI (0.1 equiv), Bu_4NI (1.1 equiv), and triethylamine (1.2 equiv). The mixture was warmed to 85 °C, and a solution of Bu_4NF (1.0 M in THF) (1.1 equiv) was then added dropwise over 15 min. TLC analysis demonstrated the reaction to be complete after Bu_4NF addition. The reaction mixture was filtered through Celite and partitioned between EtOAc and 0.1 N HCl. The organic layer was washed twice with H_2O, dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with a hexanes−EtOAc solvent system to give the corresponding product.

4-(3-Fluorophenylethynyl)-2-methylthiazole (10). Hexanes−EtOAc 8:1 for elution; yield 62%. ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.04−7.12 (m, 1H), 7.24−7.38 (m, 3H), 7.42 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 84.7, 87.9, 116.4 (d, $^2J_{CF} = 21.1$ Hz), 118.9 (d, $^2J_{CF} = 23.0$ Hz), 123.2, 124.7 (d, $^3J_{CF} = 9.4$ Hz), 128.0 (d, $^4J_{CF} = 3.0$ Hz), 130.4 (d, $^3J_{CF} = 8.7$ Hz), 136.9, 162.7 (d, $^1J_{CF} = 246.7$ Hz), 166.3. MS (ESI) *m/z* 218.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 218.0442; calcd mass ($C_{12}H_8FNS$ + H)$^+$, 218.0440.

4-(4-Fluorophenylethynyl)-2-methylthiazole (11). Hexanes−EtOAc 8:1 for elution; yield 68%. ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 7.06 (t, $J = 8.6$ Hz, 2H), 7.38 (s, 1H), 7.55 (td, $J_1 = 7.0$ Hz, $J_2 = 3.1$ Hz, 2H). ^{13}C NMR ($CDCl_3$) δ 19.6, 83.5, 88.1, 116.1 (d, $^2J_{CF} = 22.2$ Hz), 119.0 (d, $^4J_{CF} = 3.5$ Hz), 122.6, 134.1 (d, $^3J_{CF} = 8.4$ Hz), 137.2, 163.1 (d, $^1J_{CF} = 250.2$ Hz), 166.2. MS (ESI) *m/z* 218.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + Na)$^+$, 240.0258; calcd mass ($C_{12}H_8FNS$ + Na)$^+$, 240.0259.

3-[(2,5-Dimethyl-4-thiazolyl)ethynyl]pyridine (23). Hexanes−EtOAc 3:2 for elution; yield 55%. ^{1}H NMR ($CDCl_3$) δ 2.57 (s, 3H), 2.68 (s, 3H), 7.30 (dd, $J_1 = 8.0$ Hz, $J_2 = 5.1$ Hz, 1H), 7.84 (d, $J = 7.9$ Hz, 1H), 8.57 (d, $J = 4.1$ Hz, 1H), 8.80 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 12.8, 19.7, 86.5, 88.4, 120.5, 123.4, 134.1, 138.7, 138.8, 149.1, 152.6, 163.4. MS (ESI) *m/z* 215.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 215.0638; calcd mass ($C_{12}H_{10}N_2S$ + H)$^+$, 215.0643.

3-[(5-Ethyl-2-methyl-4-thiazolyl)ethynyl]pyridine (24). Hexanes−EtOAc 3:2 for elution; yield 51%. ^{1}H NMR ($CDCl_3$) δ 1.35 (t, $J = 7.5$ Hz, 3H), 2.69 (s, 3H), 2.99 (q, $J = 7.5$ Hz, 2H), 7.30 (dd, $J_1 = 7.9$ Hz, $J_2 = 4.0$ Hz, 1H), 7.84 (d, $J = 7.8$ Hz, 1H), 8.58 (d, $J = 4.0$ Hz, 1H), 8.79 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 16.4, 19.7, 21.3, 86.5, 88.3, 120.6, 123.5, 132.7, 138.8, 146.5, 149.1, 152.6, 163.3. MS (ESI) *m/z* 229.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 229.0797; calcd mass ($C_{13}H_{12}N_2S$ + H)$^+$, 229.0799.

3-[(2-Methyl-4-thiazolyl)ethynyl]phenol (37). Compound **12** (122 mg, 0.53 mmol) was dissolved in CH_2Cl_2 (5 mL) and cooled in an ice bath. A solution of BBr_3 (1.0 M in CH_2Cl_2) (0.64 mL, 0.64 mmol) was added dropwise. The reaction mixture was allowed to stir for 4 h at room temperature and partitioned between EtOAc (20 mL) and saturated aqueous $NaHCO_3$ (10 mL). The organic layer was washed with H_2O (2 × 10 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 3:1 to give **37** (34.4 mg, 30%); ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 6.89 (d, $J = 7.8$ Hz, 1H), 7.08 (d, $J = 7.5$ Hz, 1H), 7.21 (t, $J = 7.7$ Hz, 1H), 7.21 (s, 1H), 7.37 (d, $J = 8.1$ Hz, 1H), 7.38 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.4, 82.9, 89.9, 117.2, 119.0, 122.7, 123.5, 124.4, 130.0, 137.0, 156.6, 166.9. MS (ESI) *m/z* 216.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 216.0484; calcd mass ($C_{12}H_9NOS$ + H)$^+$, 216.0483.

3-[(2-Methyl-4-thiazolyl)ethynyl]benzamide (38). To a solution of **19** (38.5 mg, 0.17 mmol) in ethanol (7 mL) were added a solution of H_2O_2 (35% in H_2O) (42 μL, 0.51 mmol) and 6.0 N aqueous NaOH (34 μL, 0.20 mmol), and the reaction mixture was allowed to stir for 40 min at 60 °C. After the mixture was partitioned between EtOAc (50 mL) and 0.1 N HCl (25 mL), the organic layer was washed with H_2O (25 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc to give **38** (35 mg, 85%); ^{1}H NMR (CD_3OD) δ 2.74 (s, 3H), 7.52 (t, $J = 7.7$ Hz, 1H), 7.71 (s, 1H), 7.72 (d, $J = 7.8$ Hz, 1H), 7.91 (t, $J = 7.7$ Hz, 1H), 8.07 (s, 1H). ^{13}C NMR (CD_3OD) δ 17.7, 83.7, 87.8, 123.1, 123.7, 123.7, 128.0, 129.0, 130.8, 134.6, 136.3, 167.6, 170.2. MS (ESI) *m/z* 243.3 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 243.0600; calcd mass ($C_{13}H_{10}N_2OS$ + H)$^+$, 243.0592.

4-(Trimethylsilylethynyl)-2-thiazolylamine (39). $AlCl_3$ (5.2 g, 39.0 mmol) was suspended in CH_2Cl_2 (40 mL) and cooled in an ice bath. Bis(trimethylsilyl)acetylene (8.8 mL, 39.0 mmol) and chloroacetyl chloride (3.1 mL, 39.0 mmol) were combined in CH_2Cl_2 (80 mL), and this solution was added to the above $AlCl_3$

suspension dropwise from an addition funnel over 50 min. The dark brownish-red solution was stirred at 0 °C for 30 min, and the ice bath was removed. After 50 min at room temperature, the reaction was cooled to 0 °C and quenched by slow addition of 1.0 N HCl (100 mL). After the acidic solution was extracted with diethyl ether (2 × 200 mL), the combined organic layers were dried over $MgSO_4$ and evaporated in vacuo to give crude 1-chloro-4-trimethylsilyl-3-butyn-2-one (**1**). This crude compound **1** was dissolved in DMF (80 mL), and thiourea (3.56 g, 46.8 mmol) was added in one portion. The mixture was allowed to stir for 20 h at room temperature, diluted with EtOAc (300 mL), washed with 0.1 N HCl (170 mL) and H_2O (2 × 170 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 3:1 to give **39** (4.13 g, 54%); ^{1}H NMR ($CDCl_3$) δ 0.25 (s, 9H), 4.92 (br s, 2H), 6.77 (s, 1H).

4-(3-Fluorophenylethynyl)-2-thiazolylamine (40) and 4-(3-Pyridylethynyl)-2-thiazolylamine (41). Compounds **40** and **41** were obtained by the reaction of **39** with 1-fluoro-3-iodobenzene or 3-iodopyridine, respectively, using the above "condition a" in the General Procedure for the Modified Sonogashira Coupling Reaction. The reaction mixture was partitioned between EtOAc and H_2O instead of 0.1 N HCl at the final work up in the synthesis of **41**.

Compound 40. Hexanes−EtOAc 2:1 for elution; yield 72%. ^{1}H NMR ($CDCl_3$) δ 5.03 (br s, 2H), 6.84 (s, 1H), 7.04−7.11 (m, 1H), 7.21−7.34 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 85.1, 87.2 (d, $^4J_{CF}$ = 3.5 Hz), 114.1, 116.3 (d, $^2J_{CF}$ = 21.2 Hz), 118.8 (d, $^2J_{CF}$ = 22.9 Hz), 124.8 (d, $^3J_{CF}$ = 9.6 Hz), 128.0 (d, $^4J_{CF}$ = 2.9 Hz), 130.4 (d, $^3J_{CF}$ = 8.7 Hz), 133.0, 162.7 (d, $^1J_{CF}$ = 246.7 Hz), 167.3. MS (ESI) *m*/*z* 219.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 219.0397; calcd mass $(C_{11}H_7FN_2S + H)^+$, 219.0392.

Compound 41. Hexanes−EtOAc 1:2 for elution; yield 60%. ^{1}H NMR ($CDCl_3$) δ 5.00 (br s, 2H), 6.88 (s, 1H), 7.30 (dd, J_1 = 8.0 Hz, J_2 = 3.8 Hz, 1H), 7.82 (d, J = 7.9 Hz, 1H), 8.57 (d, J = 3.8 Hz, 1H), 8.78 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 85.1, 87.5, 114.6, 120.3, 123.4, 132.9, 138.9, 149.2, 152.7, 167.1. MS (ESI) *m*/*z* 202.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 202.0440; calcd mass $(C_{10}H_7N_3S + H)^+$, 202.0439.

***N*-[4-(3-Pyridylethynyl)-2-thiazolyl]acetamide (42).** To a solution of **41** (20.1 mg, 0.10 mmol) in CH_2Cl_2 (5 mL) were added under ice cooling acetyl chloride (8 μL, 0.11 mmol) and triethylamine (17 μL, 0.12 mmol), and the reaction mixture was allowed to stir for 10 min at the same temperature. After the mixture was partitioned between EtOAc (20 mL) and saturated aqueous $NaHCO_3$ (10 mL), the organic layer was washed with H_2O (10 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 1:2 to give **42** (21.7 mg, 89%); ^{1}H NMR ($CDCl_3$) δ 2.35 (s, 3H), 7.30 (s, 1H), 7.32 (dd, J_1 = 7.8 Hz, J_2 = 3.8 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 8.60 (d, J = 4.1 Hz, 1H), 8.84 (s, 1H), 10.15 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 23.7, 82.2, 85.5, 119.4, 123.6, 129.3, 131.4, 139.0, 149.3, 152.7, 160.0, 168.8. MS (ESI) *m*/*z* 244.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 244.0539; calcd mass $(C_{12}H_9N_3OS + H)^+$, 244.0545.

***N*-[4-(3-Pyridylethynyl)-2-thiazolyl]benzamide (43).** To a solution of **41** (12.0 mg, 60 μmol) in CH_2Cl_2 (5 mL) were added benzoyl chloride (8 μL, 66 μmol) and triethylamine (10 μL, 72 μmol), and the reaction mixture was allowed to stir for 20 min at room temperature. After the mixture was partitioned between EtOAc (20 mL) and 0.1 N HCl (10 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 1:1 to give **43** (16.9 mg, 92%); ^{1}H NMR ($CDCl_3$) δ 7.31 (dd, J_1 = 7.5 Hz, J_2 = 3.8 Hz, 1H), 7.33 (s, 1H), 7.53−7.64 (m, 3H), 7.83 (d, J = 7.2 Hz, 1H), 7.96 (d, J = 7.3 Hz, 2H), 8.58 (d, J = 3.8 Hz, 1H), 8.81 (s, 1H), 9.82 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 86.3, 91.3, 119.4, 123.2, 124.9, 128.1, 128.1, 129.5, 129.5, 131.9, 132.1, 133.6, 139.0, 149.2, 152.7, 159.0, 166.0. MS (ESI) *m*/*z* 306.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + Na)^+$, 328.0521; calcd mass $(C_{17}H_{11}N_3OS + Na)^+$, 328.0521.

1-(2,4-Difluorophenyl)-3-[4-(3-pyridylethynyl)-2-thiazolyl]-urea (44). To a solution of **41** (20.1 mg, 0.10 mmol) in THF (5 mL) were added 2,4-difluorophenyl isocyanate (16 μL, 0.13 mmol) and 4-(dimethylamino)pyridine (1.2 mg, 10 μmol), and the reaction mixture was allowed to stir for 16 h at room temperature. After the mixture was partitioned between EtOAc (30 mL) and 0.1 N HCl (15 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL) and H_2O (15 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 1:1 to give **44** (26.3 mg, 72%); ^{1}H NMR (CD_3OD) δ 6.86 (t, J = 8.5 Hz, 2H), 7.16 (s, 1H), 7.32 (dd, J_1 = 7.5 Hz, J_2 = 3.8 Hz, 1H), 7.83 (d, J = 7.5 Hz, 1H), 8.04−8.15 (m, 1H), 8.52 (d, J = 3.8 Hz, 1H), 8.70 (s, 1H). ^{13}C NMR (CD_3OD) δ 86.1, 89.9, 105.4 (t, $^2J_{CF}$ = 25.2 Hz), 114.5 (dd, $^2J_{CF}$ = 18.3 Hz, $^4J_{CF}$ = 7.7 Hz), 119.1, 120.9 (dd, $^2J_{CF}$ = 18.1 Hz, $^4J_{CF}$ = 8.1 Hz), 123.0, 123.8 (t, $^3J_{CF}$ = 12.9 Hz), 124.6, 133.3, 139.0, 149.2, 152.7, 155.6 (dd, $^1J_{CF}$ = 248.5 Hz, $^3J_{CF}$ = 13.1 Hz), 158.0, 159.3 (dd, $^1J_{CF}$ = 251.2 Hz, $^3J_{CF}$ = 12.9 Hz), 166.6. MS (ESI) *m*/*z* 357.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 357.0623; calcd mass $(C_{17}H_{10}F_2N_4OS + H)^+$, 357.0622.

[4-(3-Pyridylethynyl)-2-thiazolyl]carbamic Acid Methyl Ester (45). To a solution of **41** (12.0 mg, 60 μmol) in CH_2Cl_2 (5 mL) were added methyl chloroformate (6 μL, 72 μmol) and triethylamine (13 μL, 90 μmol), and the reaction mixture was allowed to stir for 10 min at room temperature. After the mixture was partitioned between EtOAc (20 mL) and 0.1 N HCl (10 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (10 mL) and H_2O (10 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 1:1 to give **45** (12.8 mg, 82%); ^{1}H NMR ($CDCl_3$) δ 3.90 (s, 3H), 7.24 (s, 1H), 7.31 (dd, J_1 = 7.8 Hz, J_2 = 3.8 Hz, 1H), 7.85 (d, J = 7.7 Hz, 1H), 8.59 (d, J = 3.9 Hz, 1H), 8.73 (br s, 1H), 8.84 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 53.9, 86.7, 87.9, 118.7, 123.7, 130.0, 132.2, 139.0, 149.0, 153.0, 159.7, 165.0. MS (ESI) *m*/*z* 260.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + Na)^+$, 282.0316; calcd mass $(C_{12}H_9N_3O_2S + Na)^+$, 282.0313.

2-Bromo-4-(3-fluorophenylethynyl)thiazole (46). To a solution of **40** (310 mg, 1.42 mmol) in acetonitrile (20 mL) were added *tert*-butyl nitrite (0.21 mL, 1.56 mmol) and copper(II) bromide (349 mg, 1.56 mmol), and the reaction mixture was allowed to stir for 15 min at 85 °C. After the mixture was concentrated under reduced pressure, the concentrate was partitioned between diethyl ether (30 mL) and H_2O (15 mL). After the mixture was filtered through Celite, the organic layer was washed with brine (15 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 20:1 to give **46** (343 mg, 86%); ^{1}H NMR ($CDCl_3$) δ 7.08−7.16 (m, 2H), 7.27−7.39 (m, 3H). ^{13}C NMR ($CDCl_3$) δ 82.2, 93.2, 115.1, 117.1 (d, $^2J_{CF}$ = 21.3 Hz), 119.1 (d, $^2J_{CF}$ = 23.2 Hz), 123.2 (d, $^3J_{CF}$ = 9.1 Hz), 128.3, 130.9 (d, $^3J_{CF}$ = 8.5 Hz), 136.8 (d, $^4J_{CF}$ = 2.8 Hz), 138.5, 162.9 (d, $^1J_{CF}$ = 246.1 Hz). MS (ESI) *m*/*z* 282.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 281.9389; calcd mass $(C_{11}H_5BrFNS + H)^+$, 281.9388.

2-(3,5-Difluorophenyl)-4-(3-fluorophenylethynyl)thiazole (47). Compound **46** (64 mg, 0.23 mmol) and 3,5-difluorophenylboronic acid (40 mg, 0.25 mmol) were combined in a flask containing deoxygenated ethylene glycol dimethyl ether (DME) (10 mL). To this mixture were added $Pd(PPh_3)_4$ (13 mg, 0.012 mmol) and 2.0 M aqueous solution of K_2CO_3 (115 μL, 0.23 mmol). The mixture was allowed to stir for 15 h at 85 °C, filtered through Celite, and partitioned between EtOAc (60 mL) and 0.1 N HCl (30 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (30 mL) and H_2O (30 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 20:1 to give **47** (42.8 mg, 59%); ^{1}H NMR ($CDCl_3$) δ 6.94 (t, J = 8.5 Hz, 1H), 7.13 (t, J = 7.7 Hz, 1H), 7.32−7.48 (m, 6H). ^{13}C NMR ($CDCl_3$) δ 82.6, 92.9, 106.5 (t, $^2J_{CF}$ = 25.4 Hz), 109.8 (dd, $^2J_{CF}$ = 18.2 Hz, $^4J_{CF}$ = 9.1 Hz), 115.3, 117.0 (d, $^2J_{CF}$ = 21.3 Hz), 119.1 (d, $^2J_{CF}$ = 23.2 Hz), 124.1 (d, $^3J_{CF}$ = 9.4 Hz), 128.3 (d, $^4J_{CF}$ = 3.2 Hz), 130.5 (d, $^3J_{CF}$ = 8.6 Hz), 135.6 (t, $^3J_{CF}$ = 10.0 Hz), 139.9, 162.7 (d, $^1J_{CF}$ = 247.3 Hz), 163.7 (dd,

$^1J_{CF}$ = 250.4 Hz, $^3J_{CF}$ = 12.7 Hz), 165.3. MS (ESI) *m/z* 338.3 (M + Na)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 316.0415; calcd mass ($C_{17}H_8F_3NS$ + H)$^+$, 316.0408.

3-[4-(3-Fluorophenylethynyl)-2-thiazolyl]-2-propyn-1-ol (49). Compound **46** (50 mg, 0.18 mmol) and propargyl alcohol (13 μL, 0.22 mmol) were combined in a flask containing deoxygenated DMF (8 mL). To this mixture were added $Pd(PPh_3)_4$ (10.4 mg, 9 μmol), CuI (3.4 mg, 18 μmol), and triethylamine (30 μL, 0.22 mmol). The mixture was allowed to stir for 1.5 h at 85 °C, filtered through Celite, and partitioned between EtOAc (50 mL) and 0.1 N HCl (25 mL). The organic layer was washed with H_2O (2 × 25 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 2:1 to give **49** (17.1 mg, 37%); ^{1}H NMR ($CDCl_3$) δ 1.79 (br, 1H), 4.57 (s, 2H), 7.07−7.14 (m, 1H), 7.24−7.38 (m, 3H), 7.55 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 51.7, 78.4, 83.7, 88.6, 93.4, 116.8 (d, $^2J_{CF}$ = 21.3 Hz), 119.0 (d, $^2J_{CF}$ = 23.1 Hz), 124.3 (d, $^3J_{CF}$ = 9.5 Hz), 124.7, 128.1 (d, $^4J_{CF}$ = 3.0 Hz), 130.5 (d, $^3J_{CF}$ = 8.6 Hz), 138.2, 148.2, 162.7 (d, $^1J_{CF}$ = 246.9 Hz). MS (ESI) *m/z* 258.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 258.0386; calcd mass ($C_{14}H_8FNOS$ + H)$^+$, 258.0389.

2-Ethynyl-4-(3-fluorophenylethynyl)thiazole (50). Compound **46** (50 mg, 0.18 mmol) and trimethylsilylacetylene (30 μL, 0.22 mmol) were combined in a flask containing deoxygenated DMF (8 mL). To this mixture were added $Pd(PPh_3)_4$ (10.4 mg, 9 μmol), CuI (3.4 mg, 18 μmol), and triethylamine (30 μL, 0.22 mmol). The mixture was allowed to stir for 3 h at 85 °C, filtered through Celite, and partitioned between EtOAc (60 mL) and 0.1 N HCl (30 mL). The organic layer was washed with H_2O (2 × 30 mL), dried over $MgSO_4$, and evaporated in vacuo to give crude 4-(3-fluorophenylethynyl)-2-(trimethylsilylethynyl)thiazole (**48**). This crude compound **48** was dissolved in THF (10 mL), then tetrabutylammonium fluoride solution (1.0 M in THF) (0.18 mL, 0.18 mmol) was added. After being stirred for 10 min at room temperature, the mixture was partitioned between EtOAc (60 mL) and 0.1 N HCl (30 mL). The organic layer was washed with H_2O (2 × 30 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 7:1 to give **50** (20.9 mg, 51%); ^{1}H NMR ($CDCl_3$) δ 3.52 (s, 1H), 7.05−7.14 (m, 1H), 7.32−7.37 (m, 1H), 7.43−7.52 (m, 1H), 7.56 (s, 1H), 7.74 (dd, J_1 = 13.9 Hz, J_2 = 7.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 79.5, 80.9, 83.3, 87.5, 115.2 (d, $^2J_{CF}$ = 21.1 Hz), 117.0 (d, $^2J_{CF}$ = 23.2 Hz), 119.3 (d, $^3J_{CF}$ = 9.4 Hz), 124.7, 128.3 (d, $^4J_{CF}$ = 2.9 Hz), 130.5 (d, $^3J_{CF}$ = 8.5 Hz), 135.2, 138.4, 164.0 (d, $^1J_{CF}$ = 249.4 Hz). MS (ESI) *m/z* 228.3 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 228.0278; calcd mass ($C_{13}H_6FNS$ + H)$^+$, 228.0283.

3-(4-Fluorophenyl)-5-[(2-methyl-4-thiazolyl)ethynyl]pyridine (52). Compound **28** (90 mg, 0.32 mmol) and 4-fluorophenylboronic acid (49 mg, 0.35 mmol) were combined in a flask containing deoxygenated DME (15 mL). To this mixture were added $Pd(PPh_3)_4$ (37 mg, 32 μmol) and 2.0 M aqueous solution of K_2CO_3 (0.16 mL, 0.32 mmol). The mixture was allowed to stir for 16 h at 85 °C, filtered through Celite, and partitioned between EtOAc (60 mL) and 0.1 N HCl (30 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (30 mL) and H_2O (30 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 3:2 to give **52** (28.3 mg, 30%); ^{1}H NMR ($CDCl_3$) δ 2.80 (s, 3H), 7.21 (t, *J* = 8.5 Hz, 2H), 7.47 (s, 1H), 7.57 (td, J_1 = 6.8 Hz, J_2 = 3.0 Hz, 2H), 8.02 (s, 1H), 8.77 (s, 2H). ^{13}C NMR ($CDCl_3$) δ 19.7, 85.7, 87.4, 116.6 (d, $^2J_{CF}$ = 21.7 Hz), 123.6, 129.3 (d, $^3J_{CF}$ = 8.2 Hz), 133.4, 133.4, 135.6 (d, $^4J_{CF}$ = 2.9 Hz), 136.6, 137.1, 147.7, 151.2, 163.5 (d, $^1J_{CF}$ = 248.2 Hz), 166.5. MS (ESI) *m/z* 295.3 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 295.0707; calcd mass ($C_{17}H_{11}FN_2S$ + H)$^+$, 295.0705.

3-(4-Methoxyphenyl)-5-[(2-methyl-4-thiazolyl)ethynyl]pyridine (53). Compound **28** (53 mg, 0.19 mmol) and 4-methoxyphenylboronic acid (32 mg, 0.21 mmol) were combined in a flask containing deoxygenated DMF (10 mL). To this mixture were added $Pd(PPh_3)_4$ (22 mg, 19 μmol) and 1.0 M aqueous solution of K_2CO_3 (0.19 mL, 0.19 mmol). The mixture was allowed to stir for 24 h at 90 °C, filtered through Celite, and partitioned between EtOAc (60 mL) and 0.1 N HCl (30 mL). The organic layer was washed with H_2O (2 × 30 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 2:1 to give **53** (18.6 mg, 32%); ^{1}H NMR ($CDCl_3$) δ 2.78 (s, 3H), 3.89 (s, 3H), 7.04 (d, *J* = 8.4 Hz, 2H), 7.46 (s, 1H), 7.54 (d, *J* = 8.4 Hz, 2H), 8.02 (s, 1H), 8.72 (s, 1H), 8.77 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 55.8, 82.2, 86.9, 115.1, 117.1, 123.5, 128.6, 129.6, 136.2, 136.8, 147.6, 150.6, 152.0, 160.5, 167.0. MS (ESI) *m/z* 307.3 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 307.0902; calcd mass ($C_{18}H_{14}N_2OS$ + H)$^+$, 307.0905.

3-[5-[(2-Methyl-4-thiazolyl)ethynyl]-3-pyridyl]-2-propyn-1-ol (55). Compound **28** (36 mg, 0.13 mmol) and propargyl alcohol (9 μL, 0.16 mmol) were combined in a flask containing deoxygenated DMF (5 mL). To this mixture were added $Pd(PPh_3)_4$ (14.9 mg, 13 μmol), CuI (2.5 mg, 13 μmol), and triethylamine (25 μL, 0.16 mmol). The mixture was allowed to stir for 22 h at 85 °C, filtered through Celite, and partitioned between EtOAc (50 mL) and 0.1 N HCl (25 mL). The organic layer was washed with H_2O (2 × 25 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 1:1 to give **55** (11.9 mg, 36%); ^{1}H NMR ($CDCl_3$) δ 1.83 (d, *J* = 6.1 Hz, 1H), 2.77 (s, 3H), 4.55 (d, *J* = 6.2 Hz, 2H), 7.47 (s, 1H), 7.87 (t, *J* = 1.8 Hz, 1H), 8.63 (d, *J* = 1.7 Hz, 1H), 8.71 (d, *J* = 1.8 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 51.8, 82.2, 85.0, 87.3, 88.9, 115.0, 117.0, 124.0, 141.2, 142.5, 151.6, 151.6, 167.0. MS (ESI) *m/z* 255.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 255.0598; calcd mass ($C_{14}H_{10}N_2OS$ + H)$^+$, 255.0592.

3-Ethynyl-5-[(2-methyl-4-thiazolyl)ethynyl]pyridine (56). Compound **28** (42 mg, 0.15 mmol) and trimethylsilylacetylene (26 μL, 0.18 mmol) were combined in a flask containing deoxygenated DMF (5 mL). To this mixture were added $Pd(PPh_3)_4$ (17.5 mg, 15 μmol), CuI (2.9 mg, 15 μmol), and triethylamine (25 μL, 0.18 mmol). The mixture was allowed to stir for 16 h at 75 °C, filtered through Celite, and partitioned between EtOAc (50 mL) and 0.1 N HCl (25 mL). The organic layer was washed with H_2O (2 × 25 mL), dried over $MgSO_4$, and evaporated in vacuo to give crude 3-[(2-methyl-4-thiazolyl)ethynyl]-5-(trimethylsilylethynyl)-pyridine (**54**). This crude compound **54** was dissolved in THF (5 mL), then tetrabutylammonium fluoride solution (1.0 M in THF) (0.15 mL, 0.15 mmol) was added. After being stirred for 10 min at room temperature, the mixture was partitioned between EtOAc (50 mL) and 0.1 N HCl (25 mL). The organic layer was washed with H_2O (2 × 25 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 3:1 to give **56** (26.2 mg, 78%); ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 3.26 (s, 1H), 7.47 (s, 1H), 7.92 (t, *J* = 1.8 Hz, 1H), 8.66 (d, *J* = 1.7 Hz, 1H), 8.74 (d, *J* = 1.7 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 79.9, 81.8, 84.8, 87.8, 119.4, 119.8, 124.0, 136.4, 141.7, 151.9, 152.1, 166.5. MS (ESI) *m/z* 225.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 225.0489; calcd mass ($C_{13}H_8N_2S$ + H)$^+$, 225.0486.

3-[(2-Methyl-4-thiazolyl)ethynyl]-5-[2-(tributylstannyl)vinyl]-pyridine (57). To a solution of **56** (160 mg, 0.71 mmol) in toluene (20 mL) were added tributyltin hydride (0.19 mL, 0.71 mmol) and 2,2′-azobis(isobutyronitrile) (AIBN) (12 mg, 71 μmol), and the reaction mixture was allowed to stir for 14 h at 90 °C. After the solvent was removed under reduced pressure, the residue was chromatographed on silica gel eluting with hexanes−EtOAc 4:1 to give **57** (129 mg, 35%); ^{1}H NMR ($CDCl_3$) δ 0.89 (t, *J* = 7.1 Hz, 9H), 0.92−1.13 (m, 6H), 1.32 (sextet, *J* = 7.2 Hz, 6H), 1.42−1.58 (m, 6H), 2.77 (s, 3H), 5.58 (s, 1H), 6.09 (s, 1H), 7.44 (s, 1H), 7.62 (s, 1H), 8.35 (s, 1H), 8.62 (s, 1H).

3-[(2-Methyl-4-thiazolyl)ethynyl]-5-vinylpyridine (59). Compound **57** (82 mg, 0.16 mmol) was dissolved in THF (10 mL) and cooled at −15 °C. A solution of butyllithium (2.5 M in hexanes) (77 μL, 0.19 mmol) was added dropwise to the above solution, and the reaction mixture was stirred for 10 min at −15 °C. After chlorotrimethylsilane (50 μL, 0.4 mmol) was added dropwise, the mixture was stirred at −15 °C for 30 min, at 0 °C for 30 min, then

at room temperature for 30 min and partitioned between EtOAc (50 mL) and H_2O (25 mL) with addition of saturated aqueous $NaHCO_3$ so as to neutralize the acid present in the mixture. The organic layer was washed with brine (25 mL), dried over $MgSO_4$, and evaporated in vacuo to give crude 3-[(2-methyl-4-thiazolyl)-ethynyl]-5-[2-(trimethylsilyl)vinyl]pyridine (**58**). This crude compound **58** was dissolved in THF (2 mL), and 1.0 N HCl (1 mL) was added. After being stirred for 20 min at room temperature, the mixture was partitioned between EtOAc (30 mL) and diluted aqueous $NaHCO_3$ (15 mL). The organic layer was washed with H_2O (15 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 2:1 to give **59** (18.8 mg, 52%); ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 5.46 (d, J = 11.0 Hz, 1H), 5.88 (d, J = 17.6 Hz, 1H), 6.71 (dd, J_1 = 17.6 Hz, J_2 = 11.0 Hz, 1H), 7.45 (s, 1H), 7.91 (s, 1H), 8.58 (s, 1H), 8.68 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 85.8, 87.1, 117.7, 117.7, 123.5, 133.0, 133.0, 135.6, 136.7, 147.8, 151.5, 166.4. MS (ESI) m/z 227.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + Na)^+$, 249.0461; calcd mass $(C_{13}H_{10}N_2S + Na)^+$, 249.0463.

Bromoolefin 60. Compound **26** (430 mg, 1.87 mmol) and a solution of hydrogen bromide (33 wt % in acetic acid) (3.0 mL, excess) were combined in a flask. The mixture was allowed to stir for 14 h at 80 °C in the sealed flask and was carefully poured into ice-cold saturated aqueous $NaHCO_3$ (30 mL). The mixture was extracted with EtOAc (2 × 50 mL), and the combined organic layers were washed with H_2O (2 × 40 mL), dried over $MgSO_4$, and evaporated in vacuo to give **60**, which was used in the following step without further purification (500 mg, 90%); ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 6.60 (d, J = 9.4 Hz, 1H), 7.36 (s, 1H), 7.59 (d, J = 9.4 Hz, 1H), 7.66 (s, 1H), 8.13 (s, 1H), 12.3 (br s, 1H).

5-[(2-Methyl-4-thiazolyl)ethynyl]-1*H*-pyridin-2-one (61). To a solution of **60** (500 mg, 1.68 mmol) in methanol (60 mL) was added KOH (236 mg, 4.2 mmol), and the reaction mixture was allowed to reflux for 1 h. After the solution was concentrated under reduced pressure to 10 mL, the concentrate was partitioned between EtOAc (60 mL) and 0.1 N HCl (30 mL). The aqueous layer was saturated with NaCl and extracted again with EtOAc (50 mL), and the combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc−MeOH 30:1 to give **61** (129 mg, 94%); ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 6.60 (d, J = 9.4 Hz, 1H), 7.36 (s, 1H), 7.59 (d, J = 9.4 Hz, 1H), 7.66 (s, 1H), 12.7 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 84.6, 84.7, 103.2, 120.9, 122.7, 136.8, 138.8, 144.1, 164.4, 166.5.

Methanesulfonic Acid 5-[(2-Methyl-4-thiazolyl)ethynyl]-2-pyridyl Ester (62). To a solution of **61** (30 mg, 0.13 mmol) in CH_2Cl_2 (15 mL) cooled in an ice bath were added triethylamine (23 μL, 0.16 mmol) and methanesulfonyl chloride (12 μL, 0.14 mmol), and the reaction mixture was stirred for 10 min at room temperature. After the mixture was partitioned between CH_2Cl_2 (20 mL) and 0.1 N HCl (15 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL) and H_2O (15 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 2:1 to give **62** (38 mg, quant); ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 3.54 (s, 3H), 7.13 (d, J = 8.3 Hz, 1H), 7.47 (s, 1H), 7.96 (dd, J_1 = 8.3 Hz, J_2 = 2.0 Hz, 1H), 8.52 (d, J = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 41.3, 84.3, 87.9, 115.7, 119.5, 124.0, 136.3, 143.4, 151.1, 156.9, 166.6. MS (ESI) m/z 295.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 295.0219; calcd mass $(C_{12}H_{10}N_2O_3S_2 + H)^+$, 295.0211.

2-Chloro-5-[(2-methyl-4-thiazolyl)ethynyl]pyridine (63). Compound **61** (70 mg, 0.32 mmol) and $POCl_3$ (2.0 mL, excess) were combined in a flask, and the mixture was allowed to stir for 1.5 h at 120 °C. After quenching by addition of ice, the mixture was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (20 mL). The organic layer was washed with H_2O (20 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 3:1 to give **63** (46.6 mg, 62%); ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 7.35 (d, J = 8.3 Hz, 1H), 7.46 (s, 1H), 7.80 (dd, J_1 = 8.2 Hz, J_2 = 2.0 Hz, 1H), 8.58 (d, J = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 84.6, 88.1, 119.0, 123.8, 124.4, 136.4, 141.4, 151.3, 152.6, 166.6. MS (ESI) m/z 235.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 235.0101; calcd mass $(C_{11}H_7ClN_2S + H)^+$, 235.0097.

Trifluoromethanesulfonic Acid 5-[(2-Methyl-4-thiazolyl)ethynyl]-2-pyridyl Ester (64). To a solution of **61** (50 mg, 0.23 mmol) in CH_2Cl_2 (18 mL) cooled in an ice bath were added triethylamine (38 μL, 0.28 mmol) and trifluoromethanesulfonic anhydride (43 μL, 0.25 mmol), and the reaction mixture was stirred for 10 min at the same temperature. After the mixture was partitioned between CH_2Cl_2 (20 mL) and 0.1 N HCl (15 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL) and H_2O (15 mL), dried over $MgSO_4$, and evaporated in vacuo to give compound **64**, which was used in the following step without further purification (80 mg, quant); ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 7.17 (d, J = 8.5 Hz, 1H), 7.46 (s, 1H), 7.91 (dd, J_1 = 8.1 Hz, J_2 = 2.0 Hz, 1H), 8.57 (d, J = 1.5 Hz, 1H).

2-(4-Fluorophenyl)-5-[(2-methyl-4-thiazolyl)ethynyl]pyridine (65). Compound **64**, which was freshly prepared from compound **61** (50 mg, 0.23 mmol) according to the above method, and 4-fluorophenylboronic acid (35 mg, 0.25 mmol) were combined in a flask containing deoxygenated DME (15 mL). To this mixture were added $Pd(PPh_3)_4$ (27 mg, 23 μmol) and 2.0 M aqueous solution of K_2CO_3 (0.12 mL, 0.24 mmol). The mixture was allowed to stir for 18 h at 80 °C, filtered through Celite, and partitioned between EtOAc (50 mL) and 0.1 N HCl (25 mL). The organic layer was washed with saturated aqueous $NaHCO_3$ (25 mL) and H_2O (25 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 3:1 to give **65** (21 mg, 31%); ^{1}H NMR ($CDCl_3$) δ 2.82 (s, 3H), 7.22−7.27 (m, 2H), 7.56 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.93 (dd, J_1 = 8.3 Hz, J_2 = 2.2 Hz, 2H), 8.17 (d, J = 8.3 Hz, 1H), 9.03 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 87.2, 91.9, 117.0 (d, $^2J_{CF}$ = 21.4 Hz), 122.0, 125.0, 129.4 (d, $^3J_{CF}$ = 8.1 Hz), 131.8, 135.4, 139.8 (d, $^4J_{CF}$ = 2.8 Hz), 146.5, 153.7, 157.3, 162.3 (d, $^1J_{CF}$ = 252.3 Hz), 166.7. MS (ESI) m/z 295.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 295.0710; calcd mass $(C_{17}H_{11}FN_2S + H)^+$, 295.0705.

3-Ethynyl-5-[(2-methyl-4-thiazolyl)ethynyl]pyridine (66). Compound **64**, which was freshly prepared from compound **61** (80 mg, 0.37 mmol) according to the above method, and trimethylsilylacetylene (63 μL, 0.44 mmol) were combined in a flask containing deoxygenated DMF (10 mL). To this mixture were added $Pd(PPh_3)_4$ (43 mg, 37 μmol), CuI (7 mg, 37 μmol), and triethylamine (62 μL, 0.44 mmol). The mixture was allowed to stir for 16 h at 75 °C, filtered through Celite, and partitioned between EtOAc (60 mL) and 0.1 N HCl (30 mL). The organic layer was washed with H_2O (2 × 30 mL), dried over $MgSO_4$, and evaporated in vacuo. To a solution of the residue in THF (10 mL) was added tetrabutylammonium fluoride solution (1.0 M in THF) (0.37 mL, 0.37 mmol). After being stirred for 10 min at room temperature, the mixture was partitioned between EtOAc (60 mL) and 0.1 N HCl (30 mL). The organic layer was washed with H_2O (2 × 30 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 3:1 to give **66** (44 mg, 53%); ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 3.28 (s, 1H), 7.47 (s, 1H), 7.49 (s, 1H), 7.81 (dd, J_1 = 8.0 Hz, J_2 = 1.8 Hz, 1H), 8.77 (d, J = 1.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 79.5, 82.9, 85.5, 88.9, 119.9, 123.9, 127.2, 136.5, 139.0, 141.6, 152.9, 166.5. MS (ESI) m/z 225.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 225.0484; calcd mass $(C_{13}H_8N_2S + H)^+$, 225.0486.

5-[(2-Methyl-4-thiazolyl)ethynyl]-2-vinylpyridine (68). Compound **64**, which was freshly prepared from compound **61** (40 mg, 0.19 mmol) according to the above method, and tributyl(vinyl)tin (59 μL, 0.20 mmol) were combined in a flask containing deoxygenated DMF (10 mL). To this mixture was added $Pd(PPh_3)_4$ (11 mg, 10 μmol). The mixture was allowed to stir for 15 h at 85 °C, filtered through Celite, and partitioned between EtOAc (60 mL) and aqueous KF (30 mL). The organic layer was washed with 0.1 N HCl (30 mL) and H_2O (2 × 30 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 5:2 to give **68** (12.6 mg, 30%);

^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 5.56 (d, J = 10.9 Hz, 1H), 6.26 (d, J = 17.5 Hz, 1H), 6.84 (dd, J_1 = 17.4 Hz, J_2 = 10.7 Hz, 1H), 7.35 (d, J = 8.1 Hz, 1H), 7.44 (s, 1H), 7.81 (d, J = 6.7 Hz, 1H), 8.76 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 86.2, 87.4, 118.6, 119.9, 121.0, 123.3, 136.7, 139.4, 142.0, 152.5, 155.1, 167.0. MS (ESI) *m/z* 227.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 227.0647; calcd mass $(C_{13}H_{10}N_2S + H)^+$, 227.0643.

3-Iodo-2-methoxypyridine (69).[24] A solution of methyllithium (1.6 M in diethyl ether) (60 mL, 96 mmol) was added dropwise to THF (80 mL) cooled to −40 °C. 2-Methoxypyridine (5.57 mL, 53.4 mmol) and isopropylamine (0.16 mL, 1.14 mmol) were successively added dropwise to this solution, and the reaction mixture was stirred for 3 h at 0 °C. After the mixture was cooled below −40 °C again, a THF solution (50 mL) of iodine (14.9 g, 58.7 mmol) was added dropwise from an addition funnel over 30 min below −40 °C. The reaction mixture was stirred at −60 °C for 30 min and treated successively with concentrated HCl (50 mL) and sodium thiosulfate (25 g, 100 mmol) in H_2O (200 mL). After basification with K_2CO_3, the mixture was saturated with NaCl and extracted with diethyl ether (2 × 500 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. The precipitated solid was removed by filtration, and the filtrate was evaporated in vacuo to give crude product **69** (6.76 g), which was used in subsequent reactions without purification.

2-Methoxy-3-[(2-methyl-4-thiazolyl)ethynyl]pyridine (70). Compound **4** (650 mg, 3.3 mmol) and crude compound **69** (2 g) were combined in a flask containing deoxygenated DMF (15 mL). To this mixture were added $Pd(PPh_3)_4$ (191 mg, 0.17 mmol), CuI (63 mg, 0.33 mmol), and triethylamine (0.55 mL, 4.0 mmol). The mixture was warmed to 85 °C, and Bu_4NF (863 mg, 3.3 mmol) was then added dropwise over 15 min. The reaction mixture was allowed to stir for 15 h at 85 °C, filtered through Celite, and partitioned between EtOAc (100 mL) and 0.1 N HCl (50 mL). The organic layer was washed with H_2O (2 × 50 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 5:2 to give **70** (312 mg, 41%); ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 4.05 (s, 3H), 6.90 (dd, J_1 = 7.2 Hz, J_2 = 5.1 Hz, 1H), 7.44 (s, 1H), 7.80 (d, J = 5.9 Hz, 1H), 8.16 (d, J = 3.5 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 54.4, 84.0, 88.9, 107.1, 116.8, 123.1, 137.1, 142.2, 147.1, 164.1, 166.1. MS (ESI) *m/z* 231.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 231.0592; calcd mass $(C_{12}H_{10}N_2OS + H)^+$, 231.0592.

Bromoolefin 71. Compound **70** (150 mg, 0.65 mmol) and hydrogen bromide solution (33 wt % in acetic acid) (2.0 mL, excess) were combined in a flask. After the mixture was allowed to stir for 6 h at 80 °C in the sealed flask, it was carefully poured into ice-cold saturated aqueous $NaHCO_3$ (20 mL). The mixture was extracted with EtOAc (2 × 40 mL), and the combined organic layers were washed with H_2O (2 × 40 mL), dried over $MgSO_4$, and evaporated in vacuo to give the intermediate **71**, which was used in the following step without further purification (193 mg, quant); ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 6.38 (t, J = 6.9 Hz, 1H), 7.40 (d, J = 6.1 Hz, 1H), 7.93 (d, J = 7.1 Hz, 1H), 8.09 (s, 1H), 8.34 (s, 1H), 11.8 (br s, 1H).

3-[(2-Methyl-4-thiazolyl)ethynyl]-1*H*-pyridin-2-one (72). To a solution of **70** (193 mg, 0.65 mmol) in methanol (25 mL) was added KOH (91 mg, 1.6 mmol), and the reaction mixture was allowed to reflux for 1 h. After the solution was concentrated under reduced pressure to 4 mL, the concentrate was partitioned between EtOAc (30 mL) and 0.1 N HCl (15 mL). The aqueous layer was saturated with NaCl and extracted again with EtOAc (30 mL), and the combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc−MeOH 20:1 to give **72** (103 mg, 73%); ^{1}H NMR ($CDCl_3$) δ 2.74 (s, 3H), 6.34 (t, J = 6.7 Hz, 1H), 7.46 (s, 1H), 7.54 (d, J = 5.6 Hz, 1H), 7.78 (d, J = 6.5 Hz, 1H), 13.6 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.6, 84.5, 89.3, 107.5, 115.4, 123.3, 135.9, 137.0, 145.5, 164.8, 166.1.

Methanesulfonic Acid 3-[(2-Methyl-4-thiazolyl)ethynyl]-2-pyridyl Ester (73). To a solution of **72** (10 mg, 46 μmol) in CH_2Cl_2 (3 mL) cooled in an ice bath were added triethylamine (8 μL, 55 μmol) and methanesulfonyl chloride (4 μL, 51 μmol), and the reaction mixture was stirred for 10 min at room temperature. After the mixture was partitioned between CH_2Cl_2 (10 mL) and 0.1 N HCl (7 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (7 mL) and H_2O (7 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 1:1 to give **73** (13 mg, quant); ^{1}H NMR ($CDCl_3$) δ 2.76 (s, 3H), 3.58 (s, 3H), 7.30 (dd, J_1 = 6.9 Hz, J_2 = 3.1 Hz, 1H), 7.55 (s, 1H), 7.99 (d, J = 7.2 Hz, 1H), 8.31 (d, J = 3.3 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 41.6, 81.6, 91.3, 112.5, 122.7, 124.8, 136.4, 143.3, 147.4, 157.5, 166.4. MS (ESI) *m/z* 295.1 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 295.0208; calcd mass $(C_{12}H_{10}N_2O_3S_2 + H)^+$, 295.0211.

2-Chloro-3-[(2-methyl-4-thiazolyl)ethynyl]pyridine (74). Compound **72** (15 mg, 69 μmol) and $POCl_3$ (1.5 mL, excess) were combined in a flask, and the mixture was allowed to stir for 1.5 h at 120 °C. After quenching by addition of ice, the mixture was partitioned between EtOAc (30 mL) and saturated aqueous $NaHCO_3$ (15 mL). The organic layer was washed with H_2O (15 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 2:1 to give **74** (9.7 mg, 59%); ^{1}H NMR ($CDCl_3$) δ 2.78 (s, 3H), 7.26 (dd, J_1 = 5.0 Hz, J_2 = 2.7 Hz, 1H), 7.51 (s, 1H), 7.91 (d, J = 7.5 Hz, 1H), 8.38 (d, J = 3.2 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 83.9, 91.0, 120.4, 122.3, 124.3, 136.4, 141.9, 149.0, 152.8, 166.5. MS (ESI) *m/z* 235.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 235.0092; calcd mass $(C_{11}H_7ClN_2S + H)^+$, 235.0097.

Trifluoromethanesulfonic Acid 5-[(2-Methyl-4-thiazolyl)ethynyl]-2-pyridyl Ester (75). To a solution of **61** (28 mg, 0.13 mmol) in CH_2Cl_2 (10 mL) cooled in an ice bath, triethylamine (22 μL, 0.16 mmol) and trifluoromethanesulfonic anhydride (24 μL, 0.14 mmol) were added, and the reaction mixture was stirred for 10 min at the same temperature. After the mixture was partitioned between CH_2Cl_2 (15 mL) and 0.1 N HCl (15 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL) and H_2O (15 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 2:1 to give **75** (36 mg, 80%); ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 7.41 (dd, J_1 = 7.3 Hz, J_2 = 5.0 Hz, 1H), 7.57 (s, 1H), 8.04 (d, J = 7.0 Hz, 1H), 8.36 (d, J = 3.4 Hz, 1H).

3-[(2-Methyl-4-thiazolyl)ethynyl]-2-(trimethylsilylethynyl)pyridine (76). Compound **75** (20 mg, 58 μmol) and trimethylsilylacetylene (10 μL, 70 μmol) were combined in a flask containing deoxygenated DMF (5 mL). To this mixture were added $Pd(PPh_3)_4$ (6.8 mg, 6 μmol), CuI (1.2 mg, 6 μmol), and triethylamine (98 μL, 70 μmol). The mixture was allowed to stir for 4 h at 85 °C, filtered through Celite, and partitioned between EtOAc (30 mL) and 0.1 N HCl (15 mL). The organic layer was washed with H_2O (2 × 15 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 2:1 to give **76** (8.3 mg, 49%); ^{1}H NMR ($CDCl_3$) δ 0.31 (s, 9H), 2.77 (s, 3H), 7.41 (dd, J_1 = 7.2 Hz, J_2 = 4.3 Hz, 1H), 7.43 (s, 1H), 7.85 (d, J = 7.9 Hz, 1H), 8.54 (d, J = 3.6 Hz, 1H).

2-Ethynyl-3-[(2-methyl-4-thiazolyl)ethynyl]pyridine (77). Compound **76** (6.0 mg, 20 μmol) was dissolved in THF (3 mL), then tetrabutylammonium fluoride solution (1.0 M in THF) (20 μL, 20 μmol) was added. After being stirred for 10 min at room temperature, the mixture was partitioned between EtOAc (25 mL) and 0.1 N HCl (10 mL). The organic layer was washed with H_2O (2 × 10 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 3:2 to give **77** (4.4 mg, 98%); ^{1}H NMR ($CDCl_3$) δ 2.77 (s, 3H), 3.45 (s, 1H), 7.29 (dd, J_1 = 6.8 Hz, J_2 = 4.2 Hz, 1H), 7.49 (s, 1H), 7.88 (d, J = 7.7 Hz, 1H), 8.56 (d, J = 4.1 Hz, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 81.5, 81.8, 85.1, 90.3, 123.1, 123.1, 124.1, 136.7, 139.6, 144.3, 149.4, 166.4. MS (ESI) *m/z* 225.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 225.0490; calcd mass $(C_{13}H_8N_2S + H)^+$, 225.0486.

2-Methyl-4-[2-(tributylstannyl)vinyl]thiazole (79). Compound **4** (586 mg, 3.0 mmol) was dissolved in THF (6 mL), then tetrabutylammonium fluoride solution (1.0 M in THF) (3.0 mL,

3.0 mmol) was added. After being stirred for 10 min at room temperature, the mixture was partitioned between diethyl ether (50 mL) and H_2O (20 mL). The organic layer was washed with H_2O (20 mL), dried over $MgSO_4$, and evaporated carefully under slightly reduced pressure. The volatile residue consisting of intermediate **78** was immediately dissolved in toluene (15 mL), tributyltin hydride (0.81 mL, 3.0 mmol) and AIBN (20 mg, 0.12 mmol) were added, and the reaction mixture was allowed to stir for 1 h at 90 °C. After the solvent was removed under reduced pressure, the residue was chromatographed on silica gel eluting with hexane to give **79** (385 mg, 31%); ^{1}H NMR ($CDCl_3$) δ 0.88 (t, J = 7.5 Hz, 9H), 0.92 (q, J = 8.7 Hz, 6H), 1.30 (sextet, J = 7.0 Hz, 6H), 1.48 (sextet, J = 7.3 Hz, 6H), 2.69 (s, 3H), 6.39 (d, J = 13.1 Hz, 1H), 6.83 (s, 1H), 7.32 (d, J = 13.3 Hz, 1H).

***(E)*-3-[2-(2-Methyl-4-thiazolyl)vinyl]pyridine (80).** Compound **79** (41.4 mg, 0.10 mmol) and 3-iodopyridine (19 mg, 0.12 mmol) were combined in a flask containing deoxygenated DMF (5 mL). To this mixture were added $PdCl_2(PPh_3)_2$ (7.0 mg, 10 μmol), CuI (1.9 mg, 10 μmol), and LiCl (4 mg, 0.10 mmol). After the mixture was allowed to stir for 1.5 h at 80 °C, it was filtered through Celite, then partitioned between EtOAc (30 mL) and aqueous KF (15 mL). The organic layer was washed with 0.1 N HCl (15 mL) and H_2O (2 × 15 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 1:2 to give **80** (6.5 mg, 32%); ^{1}H NMR ($CDCl_3$) δ 2.64 (s, 3H), 6.53 (d, J = 12.6 Hz, 1H), 6.78 (d, J = 12.5 Hz, 1H), 7.14 (s, 1H), 7.64−7.73 (m, 1H), 8.32 (d, J = 7.1 Hz, 1H), 8.66 (s, 1H), 9.14 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.7, 119.8, 122.4, 132.5, 133.3, 133.8, 137.5, 146.5, 148.6, 152.3, 164.7. MS (ESI) m/z 203.3 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 203.0647; calcd mass ($C_{11}H_{10}N_2S$ + H)$^+$, 203.0643.

2-Methylthiazole-4-carboxylic Acid 3-Fluorophenylamide (81). To a solution of 2-methylthiazole-4-carboxylic acid (49 mg, 0.34 mmol) in CH_2Cl_2 (5 mL) were added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC·HCl) (72 mg, 0.37 mmol), 1-hydroxybenzotriazole (HOBt) (51 mg, 0.37 mmol), and triethylamine (95 μL, 0.68 mmol), and the reaction mixture was stirred for 18 h at room temperature. After the mixture was partitioned between EtOAc (30 mL) and 0.1 N HCl (15 mL), the organic layer was washed with saturated aqueous $NaHCO_3$ (15 mL) and H_2O (15 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 4:1 to give **81** (58.6 mg, 73%); ^{1}H NMR ($CDCl_3$) δ 2.75 (s, 3H), 6.84 (t, J = 7.1 Hz, 1H), 7.27−7.38 (m, 1H), 7.33 (s, 1H), 7.71 (d, J = 10.8 Hz, 1H), 8.06 (s, 1H), 9.26 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.5, 107.5 (d, $^2J_{CF}$ = 26.3 Hz), 111.4 (d, $^2J_{CF}$ = 21.4 Hz), 115.4 (d, $^4J_{CF}$ = 2.9 Hz), 124.4, 130.5 (d, $^3J_{CF}$ = 9.3 Hz), 139.7 (d, $^3J_{CF}$ = 11.0 Hz), 149.8, 159.3, 163.5 (d, $^1J_{CF}$ = 244.7 Hz), 166.7. MS (ESI) m/z 237.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + Na)$^+$, 259.0323; calcd mass ($C_{11}H_9FN_2OS$ + Na)$^+$, 259.0318.

2-Methylthiazole-4-carboxylic Acid 3-Pyridylamide (82). To a suspension of 2-methylthiazole-4-carboxylic acid (49 mg, 0.34 mmol) in toluene (10 mL) were added thionyl chloride (73 μL, 1.0 mmol) and DMF (5 μL, 65 μmol), and the reaction mixture was allowed to stir for 80 min at 105 °C. The reaction mixture was evaporated in vacuo, and the residue was dissolved again in CH_2Cl_2 (10 mL). After 3-aminopyridine (64 mg, 0.68 mmol) was added to this solution, the mixture was stirred for 10 min at room temperature. The mixture was partitioned between EtOAc (50 mL) and saturated aqueous $NaHCO_3$ (15 mL), and the aqueous layer was saturated with NaCl and extracted again with EtOAc (50 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel eluting with EtOAc to give **82** (45.5 mg, 61%); ^{1}H NMR ($CDCl_3$) δ 2.74 (s, 3H), 7.30 (dd, J_1 = 7.5 Hz, J_2 = 4.6 Hz, 1H), 8.06 (s, 1H), 8.32 (d, J = 8.0 Hz, 1H), 8.38 (s, 1H), 8.77 (s, 1H), 9.27 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 19.5, 124.1, 124.7, 127.1, 135.0, 141.6, 145.7, 149.5, 159.7, 166.8. MS (ESI) m/z 220.2 (M + H)$^+$. HRMS (positive mode) obsd mass (M + H)$^+$, 220.0548; calcd mass ($C_{10}H_9N_3OS$ + H)$^+$, 220.0545.

2-Methyloxazole-4-carboxylic Acid Methyl Ester (84).[25] To a stirred suspension of ethyl acetimidate hydrochloride (6.18 g, 50 mmol) and DL-serine methyl ester hydrochloride (7.78 g, 50 mmol) in CH_2Cl_2 (100 mL) was added dropwise over 25 min a solution of triethylamine (15 mL, 108 mmol) in CH_2Cl_2 (35 mL). After 16 h the solids were removed by filtration and washed with ether. The filtrate was concentrated, and the resulting solid residue was washed several times with ether. The combined organic extracts were concentrated to give crude 4,5-dihydro-2-methyloxazole-4-carboxylic acid methyl ester (**83**) as yellow oil. Hexamethylenetetramine (17.5 g, 125 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (18.7 mL, 125 mmol) were added to a stirred suspension of $CuBr_2$ (27.9 g, 125 mmol) at 0 °C. After 20 min, the above crude compound **83** was added, and the reaction mixture was stirred at room temperature for 2 h. The solvent was removed in vacuo, and the residue was partitioned between EtOAc (150 mL) and saturated aqueous NH_4Cl:saturated aqueous NH_4OH (1:1, 100 mL). The aqueous layer was extracted with EtOAc (150 mL), and the combined organic layers were washed with saturated aqueous NH_4Cl:saturated aqueous NH_4OH (1:1, 100 mL), 10% citric acid (100 mL), saturated aqueous $NaHCO_3$ (100 mL), and brine, then dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 3:2 to give **84** (4.09 g, 58%); ^{1}H NMR ($CDCl_3$) δ 2.54 (s, 3H), 3.93 (s, 3H), 8.16 (s, 1H).

2-Methyloxazole-4-carboxaldehyde (85). $LiAlH_4$ solution (1.0 M in THF) (31.9 mL, 31.9 mmol) was added to a solution of **84** in diethyl ether (200 mL) at −78 °C. After 30 min, a saturated aqueous solution of sodium acetate (100 mL) was added, and the mixture was extracted with diethyl ether (2 × 100 mL). The combined organic layers were dried over $MgSO_4$ and evaporated carefully under slightly reduced pressure (caution: compound **85** readily sublimes). The residue was chromatographed on silica gel eluting with hexanes−EtOAc 2:1 to give **85** (994 mg, 42%); ^{1}H NMR ($CDCl_3$) δ 2.56 (s, 3H), 8.19 (s, 1H), 9.92 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.0, 141.2, 145.6, 163.4, 184.0.

4-(2,2-Dibromovinyl)-2-methyloxazole (86). To a solution of CBr_4 (2.88 g, 8.68 mmol) in CH_2Cl_2 (10 mL) cooled in an ice bath was added dropwise a solution of triphenylphosphine (4.53 g, 17.4 mmol) in CH_2Cl_2 (10 mL), and the reaction mixture was stirred for 10 min at the same temperature. A solution of **85** (241 mg, 2.17 mmol) in CH_2Cl_2 (10 mL) was added dropwise to the reaction mixture with continued cooling, and the mixture was stirred for 20 min at the same temperature. After addition of H_2O (20 mL), the mixture was extracted with CH_2Cl_2 (40 mL), and the organic layer was washed with saturated aqueous $NaHCO_3$ (20 mL) and saturated aqueous NH_4Cl (20 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 6:1 to give **86** (500 mg, 86%); ^{1}H NMR ($CDCl_3$) δ 2.45 (s, 3H), 7.35 (s, 1H), 8.13 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.1, 90.8, 129.3, 137.0, 137.8, 161.2.

2-Methyl-4-(trimethylsilylethynyl)oxazole (88). To a solution of **86** (258 mg, 0.97 mmol) in THF (10 mL) cooled at −78 °C was added sodium hexamethyldisilazide (NaHMDS) solution (1.0 M in THF) (0.97 mL, 0.97 mmol) dropwise over 3 min. The mixture was stirred for 45 min at −78 °C, then methyllithium solution (1.6 M in diethyl ether) (1.21 mL, 1.94 mmol) was added dropwise over 6 min. After a further 75 min, chlorotrimethylsilane (0.62 mL, 4.9 mmol) was added dropwise, and the reaction mixture was stirred at −78 °C for 3 h. Then, the mixture was allowed to slowly warm to room temperature over 100 min. After addition of saturated aqueous NH_4Cl (20 mL), the mixture was extracted with diethyl ether (2 × 30 mL), and the combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 25:1 to give **88** (146 mg, 84%); ^{1}H NMR ($CDCl_3$) δ 0.25 (s, 9H), 2.46 (s, 3H), 7.68 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 0.1, 14.2, 94.7, 98.9, 124.1, 141.8, 161.8.

4-[(3-Fluorophenyl)ethynyl]-2-methyloxazole (89). Compound **88** (43 mg, 0.24 mmol) and 1-fluoro-3-iodobenzene (31 μL, 0.26 mmol) were combined in a flask containing deoxygenated DMF

(5 mL). To this mixture, was added $Pd(PPh_3)_4$ (14 mg, 12 μmol), CuI (4.6 mg, 24 μmol), and triethylamine (40 μL, 0.29 mmol). The mixture was warmed to 85 °C, and Bu_4NF (63 mg, 0.24 mmol) was then added dropwise over 15 min. The reaction mixture was allowed to stir for 13 h at 85 °C, filtered through Celite, and partitioned between EtOAc (40 mL) and 0.1 N HCl (15 mL). The organic layer was washed with H_2O (2 × 15 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 7:1 to give **89** (41 mg, 85%); ^{1}H NMR ($CDCl_3$) δ 2.50 (s, 3H), 7.03−7.12 (m, 1H), 7.22 (d, J = 8.8 Hz, 1H), 7.29−7.35 (m, 1H), 7.31 (s, 1H), 7.77 (s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.2, 80.5, 91.4, 116.5 (d, $^2J_{CF}$ = 21.2 Hz), 118.7 (d, $^2J_{CF}$ = 22.9 Hz), 123.8, 124.7 (d, $^3J_{CF}$ = 9.4 Hz), 127.9 (d, $^4J_{CF}$ = 3.1 Hz), 130.4 (d, $^3J_{CF}$ = 8.6 Hz), 141.6, 162.2, 162.7 (d, $^1J_{CF}$ = 246.8 Hz). MS (ESI) *m*/*z* 202.3 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 202.0661; calcd mass $(C_{12}H_8FNO + H)^+$, 202.0668.

3-[(2-Methyl-4-oxazolyl)ethynyl]pyridine (90). Compound **88** (43 mg, 0.24 mmol) and 3-iodopyridine (42 mg, 0.26 mmol) were combined in a flask containing deoxygenated DMF (5 mL). To this mixture were added $Pd(PPh_3)_4$ (14 mg, 12 μmmol), CuI (4.6 mg, 24 μmol), and triethylamine (40 μL, 0.29 mmol). The mixture was warmed to 85 °C, and Bu_4NF (63 mg, 0.24 mmol) was then added dropwise over 15 min. The reaction mixture was allowed to stir for 13 h at 85 °C, filtered through Celite, and partitioned between EtOAc (40 mL) and 0.1 N HCl (15 mL). The organic layer was washed with H_2O (2 × 15 mL), dried over $MgSO_4$, and evaporated in vacuo. The residue was chromatographed on silica gel eluting with hexanes−EtOAc 1:2 to give **90** (23 mg, 52%); ^{1}H NMR ($CDCl_3$) δ 2.51 (s, 3H), 7.31 (t, J = 9.0 Hz, 1H), 7.80 (s, 1H), 7.81 (d, J = 9.0 Hz, 1H), 8.58 (br s, 1H), 8.78 (br s, 1H). ^{13}C NMR ($CDCl_3$) δ 14.3, 83.0, 89.4, 123.2, 123.5, 123.7, 138.8, 141.8, 149.3, 152.6, 162.3. MS (ESI) *m*/*z* 185.2 $(M + H)^+$. HRMS (positive mode) obsd mass $(M + H)^+$, 185.0709; calcd mass $(C_{11}H_8N_2O + H)^+$, 185.0715.

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Supporting Information Available: HPLC, HRMS, and elemental analysis data for compounds in Tables 2−5. This material is available free of charge via the Internet at http://pubs.acs.org.

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