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Synthesis and receptor assay of aromatic–ethynyl–aromatic derivatives with potent mGluR5 antagonist activity

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Abstract—Noncompetitive antagonists of the human metabotropic glutamate receptor subtype 5 (mGluR5) have been implicated as potential therapeutics for the treatment of a variety of nervous system disorders, including pain, anxiety, and drug addiction. To discover novel noncompetitive antagonists to the mGluR5, we initiated an SAR study around the known lead compounds MPEP and M-MPEP. Our results pointed out the critical role of the *para* position of the two aromatic rings, which leads to inactive products and permitted the discovery of potent mGluR5 antagonists (e.g., **16**, **25**, **28**, **34** IC_{50} = 13.5, 11.9, 21, 15 nM, respectively).

1. Introduction

L-Glutamate is the principal excitatory neurotransmitter in the central nervous system (CNS), and regulates a variety of neuronal activities through interacting with specific receptors. The heterogeneous family of glutamate receptors can be divided into two major types: ionotropic (iGluR) and metabotropic (mGluR). The iGluR groups are glutamate-gate cation channels and can be subdivided into *N*-methyl-D-aspartate (NMDA) receptors for NMDA and non-NMDA receptors for kainite and α-amino-3-hydroxy-5-methyl-4-isoxazole propionic acid (AMPA).[1] mGluRs are members of the superfamily 3 of G-protein coupled receptors and possess a unique structure with a large extracellular N-terminus domain involved in glutamate recognition.[2,3] mGluRs comprise a family of eight subtypes that are activated by glutamate and can modulate fast excitatory responses evoked by glutamatergic stimulation of ionotropic receptors.[4] The eight mGluR subtypes are subdivided into three groups based principally on sequence homology but also on signal transduction pathway and agonist selectivity. Group I mGluRs are selectively activated by dihydroxyphenylglycine (DHPG) and initiate cell responses through $G_{q/11}$ protein coupling to phospholipase C and stimulation of phosphoinositide hydrolysis. In contrast, group II and III mGluRs are negatively coupled via G_i/G_o to adenylyl cyclase and reduce forskolin stimulated increases in cAMP in recombinant expression systems. Group II receptors can be stimulated by (2*S*, 2′*R*,3′*R*)-2-(2′,3′-dicarboxycyclopropyl)glycine and (+)-2-aminobicyclo[3.1.0]hexane-2,6-dicarboxylate monohydrate (LY354740), and group III receptors are selectively stimulated by L-(+)-2-amino-4-phosphonobutyric acid and (*R*,*S*)-4-phosphonophenylglicine.[5] Recent studies have suggested that mGluRs represent the candidate receptors for acid homocysteine metabolites.[6] These findings suggest that some of the pathogenic actions attributed to hyperhomocysteinemia may be due, in part, to activation of mGluRs. Compared to the thoroughly investigated roles of the ionotropic receptors, functional studies on mGluR have just emerged in recent years. Group I mGluRs (including the mGluR1 and mGluR5 subtypes) exhibit a regional pattern of expression in the CNS suggesting distinct functional roles for each receptor.[7] For example, expression of

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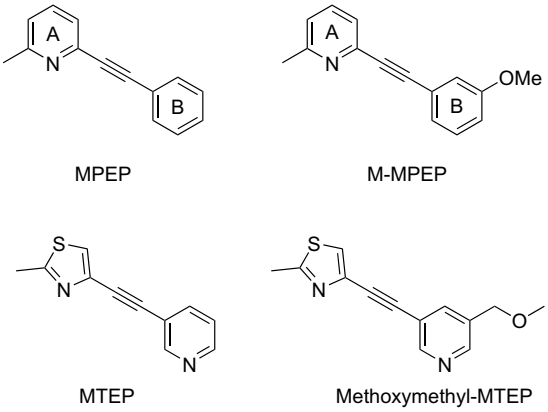
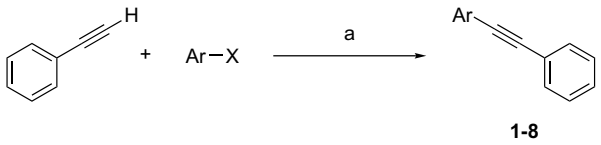


Figure 1.



Scheme 1. Reagents and conditions: (a) aryl halide, $PdCl_2(PPh_3)_2$, CuI, Et_3N, room temp.

mGluR5 is high-to-moderate in frontal cortex, caudate putamen, nucleus accumbens, olfactory tubercle, hippocampus, and dorsal surface of the spinal cord, whereas low levels of expression are observed in cerebellum.[8,9] In contrast, mGluR1 is present in high density in the cerebellum and low-to-moderate expression is found in frontal cortex, caudate putamen, nucleus accumbens, and olfactory tubercle.[9] Given the high level of expression of mGluR5 in the limbic forebrain, these receptors are positioned to play key roles in emotional and behavioral processing. Some selective noncompetitive mGluR5 antagonists have been developed in recent years,[10,11] all derived from the lead compounds MPEP and M-MPEP (Fig. 1), where the pyridine ring is arbitrarily designated A and the phenyl ring is designated B. More recently, Cosford et al. successfully replaced the A-ring of MPEP by a methylthiazole moiety, leading to interesting compounds such as MTEP (Fig. 1) and its methoxymethyl analogue.[12,13]

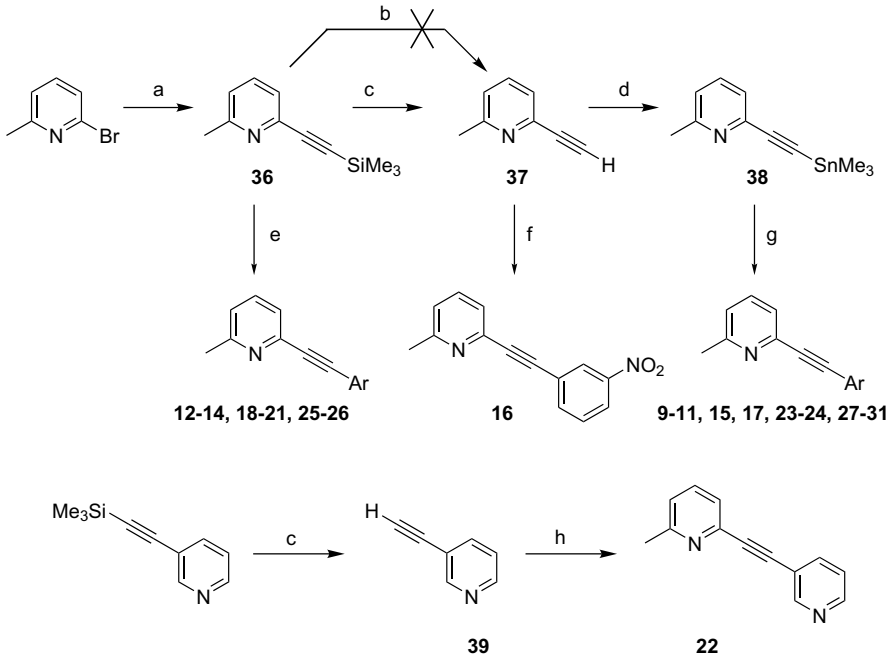
Evaluation of MPEP in animal models of mood disorders, including depression and anxiety[14–16] and drug addiction,[17] reinforce the growing evidence for the role of mGluR5 in these pathologies and the potential therapeutic application of specific and potent mGluR5 noncompetitive antagonists. Unfortunately, the high lipophilicity and poor blood–brain barrier penetration of both MPEP and M-MPEP limit their application for therapeutic purposes. A number of analogs have been claimed in patent applications, but specific receptor activity has not been reported for most of them. The design of mGluR5 antagonists is limited by the lack of robust published structure–activity relationships (SAR). We therefore initiated investigation of mGluR5 antagonists with the goal to clarify and extend the structural requirements of the known mGluR5 antagonists with a simple and rational SAR. This paper reports the first results of studies examining the effect of modification around the known inhibitors MPEP and M-MPEP.

2. Chemistry

Preparation of arylalkynyl derivatives is well described in the literature and proceeding through different methods, starting in 1963 with the Castro–Stephens[18] protocol; the scope has been extended with the introduction of palladium catalyzed coupling, reviewed in 2003 by Negishi and Anastasia.[19] The simple ring A positional isomers **2**–**4** were prepared by Sonogashira cross coupling between phenylacetylene and commercially available bromopyridines. Using the same methodology, compounds **6**–**8** and **1** were obtained starting from the corresponding bromopyridine or 3-iodotoluene (Scheme 1).

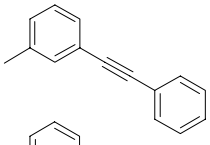
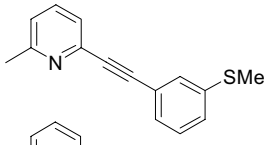
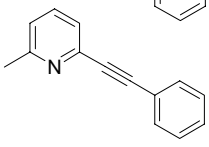
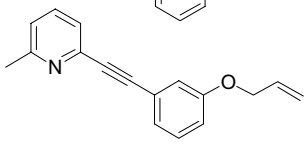
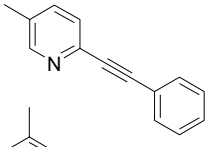
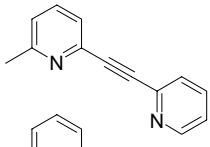
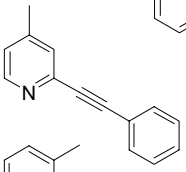
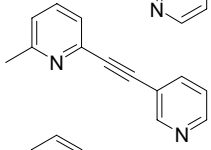
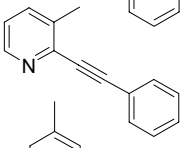
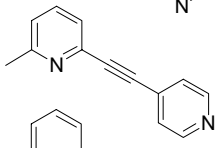
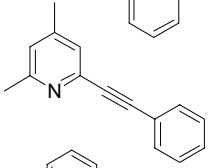
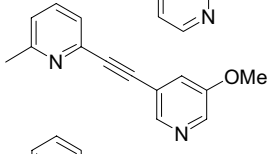
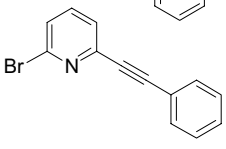
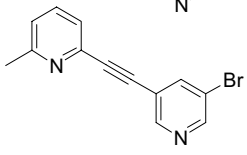
Compounds **9**–**11**, **15**, **17**, **23**, **24**, **27**–**31** were obtained by Migita–Kosugi–Stille cross coupling starting from the tributyltin alkyne key intermediate **38** (Scheme 2, Table 1). This cross coupling reaction is used frequently with activated alkynes, with which the reaction proceeds under mild conditions without cuprous iodide in higher yield than obtained under Sonogashira conditions.[20] Thus, treatment of 2-bromo-6-methylpyridine with trimethylsilylacetylene under Sonogashira conditions afforded silyl acetylene **36** (Scheme 2). Interestingly, removal of the trimethylsilyl group by treatment with tetrabutylammonium fluoride led to degradation. Desilylation to acetylene **37** was readily accomplished with KOH in methanol. Treatment of **37** with dimethylaminotrimethyltin led to the key stannyl intermediate **38** in quantitative yield (Scheme 2).

Reaction of 3-bromopyridine with stannyl acetylene **38** did not lead to the desired pyridinoacetylene **22** but to the homocoupling product. Compound **22** was successfully obtained by cross coupling between 2-bromo-6-methylpyridine and 3-ethynylpyridine **39**, which was synthesized by desilylation of 3-trimethylsilylethynyl pyridine under basic conditions (Scheme 2, Table 1). Compounds **12**–**14**, **18**–**21**, **25**, **26** were obtained using a modified Sonogashira reaction involving the in situ desilylation of silyl acetylene **36** using tetrabutylammonium fluoride and subsequent palladium cross coupling with the appropriate aryl or heteroaryl halide (Scheme 2). Nitro compound **16** was synthesized with a classic Sonogashira reaction between ethynylpyridine **37** and 3-iodo-nitrobenzene (Scheme 2, Table 1). Treatment of 3,5-dibromopyridine by sodium methoxide provided 3-methoxy-5-bromopyridine **40**, which was subsequently converted to silyl acetylene **41** using Sonogashira coupling. Compounds **32**–**35** were obtained by the same modified Sonogashira method used for **12**–**14**, **18**–**21**, **25**, **26**, starting from the trimethylsilylethynyl intermediates **41** or **42**[13] and the appropriated aryl or heteroaryl halide (Scheme 3, Table 1).



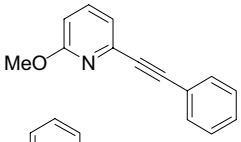
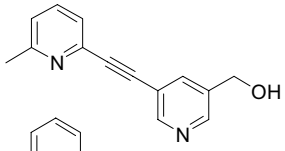
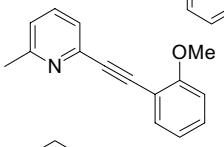
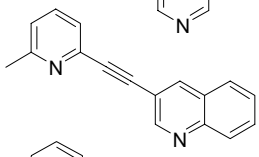
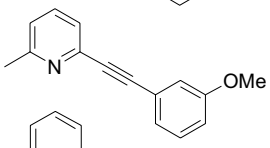
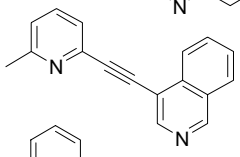
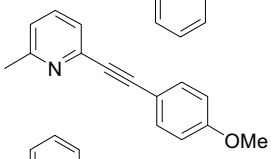
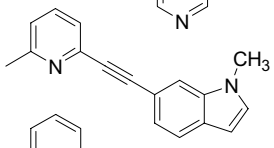
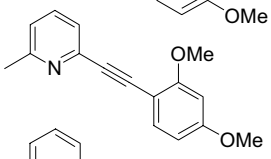
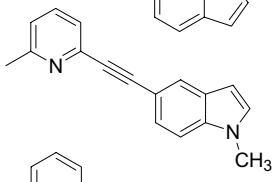
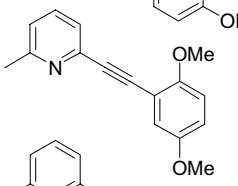
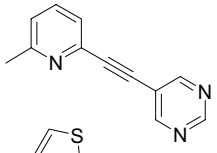
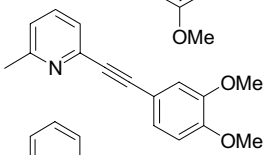
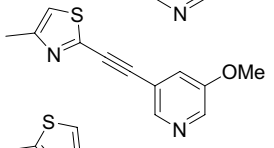
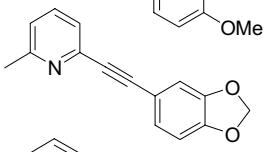
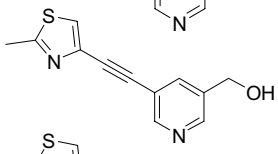
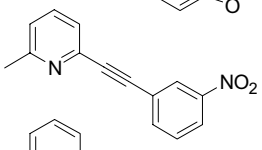
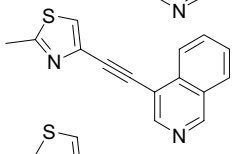
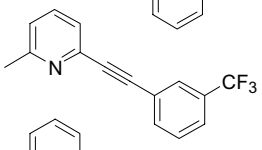
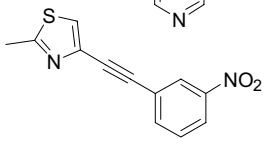
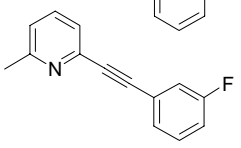
Scheme 2. Reagents and conditions: (a) (trimethylsilyl)acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, room temp; (b) *n*-Bu_4NF, THF, rt; (c) KOH, MeOH, room temp; (d) (dimethylamino)trimethyltin, room temp; (e) aryl bromide, $PdCl_2(PPh_3)_2$, CuI, Et_3N, Bu_4NF, DMF, 70 °C; (f) 1-iodo-3-nitrobenzene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, room temp; (g) aryl bromide, $Pd(PPh_3)_4$, DMF, 110 °C; (h) 2-bromo-6-methylpyridine, $PdCl_2(PPh_3)_2$, CuI, Et_3N, 90 °C.

Table 1. Structures of reported compounds

Compound	Structure	Yield[a] %	Compound	Structure	Yield[a] %
1		78	**19**		44
2 MPEP		64	**20**		60
3		81	**21**		65
4		73	**22**		35
5		33	**23**		70
6		64	**24**		68
7		62	**25**		49

(*continued on next page*)

Table 1 (*continued*)

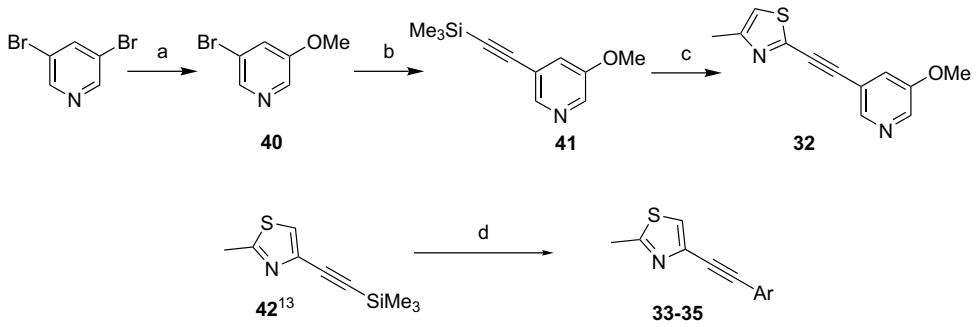
Compound	Structure	Yield[a] %	Compound	Structure	Yield[a] %
8		48	**26**		65
9		47	**27**		82
10 M-MPEP		60	**28**		87
11		45	**29**		65
12		28	**30**		75
13		34	**31**		90
14		23	**32**		58
15		81	**33**		81
16		47	**34**		59
17		61	**35**		76
18		31			

[a] Yields were calculated from isolated compounds and are not optimized.

3. Biological evaluation

3.1. Phosphoinositide hydrolysis assays (mGluR1, 5, and 8)

Recombinant cDNAs for mGluR1a and mGluR5a (group I) were stably transfected and expressed in Chinese hamster ovary (CHO) cells.[21] The native mGluR8 (group III) is not naturally coupled to phospholipase C; however, in this study mGluR8 was stably expressed in CHO cell line that expressed a chimeric G protein, $G\alpha_{qi9}$, and experimentally allowed a positive coupling of mGluR8 to phospholipase C.[22] 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



Scheme 3. Reagents and conditions: (a) MeONa, MeOH, 130 °C sealed tube; (b) (trimethylsilyl)acetylene, $PdCl_2(PPh_3)_2$, CuI, Et_3N, room temp; (c) 2-iodo-4-methyl-thiazole, $PdCl_2(PPh_3)_2$, CuI, Bu_4NF, Et_3N, 60 °C; (d) aryl bromide, $PdCl_2(PPh_3)_2$, CuI, Et_3N, Bu_4NF, DMF, 70 °C.

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.[23]

Data were normalized to the maximal response induced by 1 mM glutamate for mGluR5 and mGluR1, or by 0.1 mM AP4 for mGluR8. 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 SigmaPlot (SPSS Science, Chicago, IL). For mGluR1 and mGluR8, percent of inhibition was determined at a single concentration of 10 μM in duplicate experiments.

3.2. Cyclic AMP assay

Cyclic AMP-coupled receptors mGluR2 (group II) and mGluR6 (group III) were stably expressed in CHO cells, whereas mGluR4 (group III) was stably expressed in baby hamster kidney cells.[21] Receptor-mediated inhibition of the forskolin-induced elevation of cyclic AMP formation was described previously.[21] In brief, the receptor-expressing cells, cultured in 96-well culture plates, were preincubated for 10 min at 37 °C in Locke's medium containing 300 μM isobutylmethylxanthine, which inhibits the activity of phosphodiesterases to prevent the degradation of cAMP. Then, 5 μM forskolin was added without or with the test compounds, and the incubation was continued for 10 min. After incubation, the medium was rapidly aspirated. cAMP was extracted with 0.1 M HCl and measured by radioimmunoassay using magnetic Amerlex RIA kit (Amersham Biosciences Inc.). Percent of inhibition was determined at a single concentration of 10 μM in duplicate experiments.

4. Results and discussion

The known noncompetitive antagonists of mGluR5 (MPEP and M-MPEP) are characterized by two aromatic rings linked by an ethynyl spacer. Ring A (Fig. 1) is a pyridine substituted by a methyl group in position 6 and linked to the ethynyl group in position 2. Ring B is a phenyl moiety in which the introduction of a methoxy group in position 3 increases the activity. We first envisaged modification in the A-ring of MPEP to better understand the SAR of this structure. The presence of a nitrogen in the 2-position of ring A is indispensable for antagonists activity as illustrated by the lack of activity of the carbocyclic aromatic analog of MPEP (**1**, Table 2). Moving the 6-methyl group of MPEP to the

Table 2. mGluR5 IC_{50} values of selected compounds using IP hydrolysis assay

Compound	IC_{50} (mean ± SEM, nM)[a]
1	1105 ± 584
2 MPEP	24 ± 4.1
3	NA
4	91 ± 20
5	63 ± 16
6	61 ± 39
7	663 ± 128
8	1961 ± 210
9	60 ± 18
10 M-MPEP	8 ± 2
11	497 ± 261
12	274 ± 34
13	82 ± 10
14	808 ± 141
15	625 ± 510
16	13.5 ± 6.7
17	354 ± 263
18	33.4 ± 5.4
19	208 ± 32
20	293 ± 37
21	184 ± 112
22	55.9 ± 19.8
23	94 ± 37
24	22 ± 0.14
25	11.9 ± 4.6
26	242 ± 50
27	235 ± 71
28	21 ± 6.7
29	1840 ± 180
30	547 ± 280
31	173 ± 38
32	11.3 ± 3.2
33	428 ± 238
34	19.7 ± 5.5
35	15 ± 2

[a] IP hydrolysis assay is described under *Biological evaluation*.[25] Concentration–response curves were performed using seven concentrations in four to six separated experiments. All values represent means ± SEM.

other three positions, as in **3**–**5**, led to a reduction of the in vitro potency at mGluR5 (Table 2). This loss of activity is presumably due to an unfavorable interaction between the methyl group and the receptor and not just due to the loss of the 6-methyl moiety as illustrated by the dimethyl analogue **6**, which displayed the same range of inhibition as the 4-methyl analog **4**. The 5-isomer **3** was inactive; in keeping with preliminary experiments indicating total loss of activity when position 5 of the pyridine was substituted (unpublished results). Replacement of the 6-methyl by a bromine as in **7** or a methoxy moiety as in **8** dramatically decreased the activity. We then modified the structure of ring B, starting by moving the methoxy moiety of M-MPEP. Moving the methoxy moiety from position 3 to position 2 (**9**) decreased the activity and moving to position 4 (**11**) led to essential loss of activity. Of the diether analogues **12**–**15**, only the 2,5-dimethoxy derivative **13** retained moderate antagonist activity; the other dimethoxy (**12** and **14**) and the methylenedioxy derivative **15** showed very poor activity (Table 2). These results suggest the critical role of substitution at the 4-position (**11**–**12**, **14**–**15** vs **10** and **13**), since substitution at this position led to inactive compounds. We then examined other substituents to replace the 3-methoxy moiety of M-MPEP (**16**–**20**, Table 2). The greatest mGluR5 activity was seen with the 3-nitro and 3-fluoro analogs **16** and **18** (IC_{50} = 13.5 and 33.4 nM, respectively). Passing from M-MPEP to the thiomethoxy analog **19** reduced the activity 26-fold. The same range of reduction in activity was observed with the allyl ether (**20**) and the trifluoromethyl analogue (**18**). Both MPEP and M-MPEP are lipophilic, with high distribution coefficients (log *D* 3.5 and 3.0, respectively). Cosford et al.[12] described compounds with a pyridine as the B-ring, which decreased the lipophilicity. We thus decided to replace the B-ring in the present series by a pyridine. The three B-ring pyridine isomers **21**–**23** were all less potent than the corresponding carbocyclic analogs, although the 3-pyridinyl isomer **22** was the most active of this series. Functionalization of position 3 of **22** with methoxy or bromo led to active compounds **24** and **25** (IC_{50} = 22 and 11.9 nM, respectively). We then extended the concept by replacing ring B by other heteroaromatic rings. The 3-quinoline (**27**) and 4-isoquinoline (**28**) derivatives exhibited totally different biological profiles: whereas **27** had low potency, **28** showed antagonist activity with an IC_{50} = 22 nM. The two indole analogues **29** and **30** presented very low activity. We hypothesize that the loss of activity of **27**, **29**, and **30** is caused by the steric hindrance in the *para* position (relative to the ethynyl substituent) as previously considered for the mono and dimethoxy analogs. Introduction of a pyrimidine ring (**31**) also led to a reduction of activity (IC_{50} 173 nM).

To conclude this work, we replaced ring A by a methylthiazole moiety as in MTEP, choosing as B-ring the best pharmacophoric elements deduced previously. Methoxy (**32**), benzo (**34**), and nitro (**35**) but not alcohol **33** presented potent antagonist activity comparable to that observed with the analogous 3-pyridyl derivatives (**35** vs **16**, **34** vs **28**, **32** vs **24**, and **33** vs **26**). To identify off-target activities, compounds **2**, **10**, **16**, **18**, **22**, **24**, **25**, **28**, **32**, **34**, and **35** were profiled against others mGluR subtypes. Experiments were performed at a single drug concentration of 10 μM on mGluR1, mGluR5, mGluR2, mGluR4, mGluR6, and mGluR8. All compounds exerted a similar antagonist effect on mGluR5 (101–134% inhibition) and were inactive (less than 25% inhibition) at the other mGluR subtypes.

5. Conclusion

This exploration of a series of diaryl acetylene derivatives as mGluR5 noncompetitive antagonists permitted the discrimination of two critical positions (*para* ring A and B) that led to inactive compounds, possibly as a result of steric hindrance to ligand–receptor binding. Six candidates (**16**, **25**, **28**, **32**, **34**, and **35**) were identified as potent and selective ligands, with a promising pharmacological profile warranting further investigation.

6. Experimental

Melting points were determined using a Thomas–Hoover melting point apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were recorded on a U400 or U500 Varian FT-NMR spectrometer. Chemical shifts (δ) are reported in parts per million (ppm) downfield from tetramethylsilane external as external lock. Low resolution mass spectra were performed by the Mass Spectrometry Laboratory of the University of Illinois. Elemental analysis were performed by Atlantic Microlab, Norcross, GA 30091. Reaction progress was monitored by analytical thin layer chromatography on 0.25 mm Merck F-254 silica gel aluminum plates, visualizing with Dragendorff's reagent or quenching of UV illumination at 254 nm. Flash chromatography[24] was performed using 230–400 mesh silica gel and eluent indicated in the procedure. All reactions were performed under a dry (Drierite) argon atmosphere. Unless otherwise specified, reagents and solvents used in this study were obtained from commercial sources and were used without further purification. Et_3N was dried with NaOH pellets and distilled from and stored over 3 Å molecular sieves.

6.1. General procedure for synthesis of compounds 1–8

To a solution of aryl halide (2.9 mmol) in 10 mL of degassed Et_3N was added successively CuI (55 mg, 0.29 mmol), phenylacetylene (350 μL, 3.19 mmol), and *trans*-dichlorobis(triphenylphosphine)palladium (204 mg, 0.29 mmol). The mixture was stirred at rt overnight, then the black solution was hydrolyzed with 10 mL of H_2O and extracted with EtOAc (3 × 10 mL). The organic layer was washed with saturated NaCl (3 × 10 mL) and were dried over anhydrous Na_2SO_4, and evaporated to dryness on a rotary evaporator. Flash column chromatography yielded the corresponding compounds **1**–**8**. HCl salts **2**–**8** were prepared by adding 2 M HCl/Et_2O to a solution of free base in Et_2O and isolated by suction filtration.

6.1.1. 1-Methyl-3-phenylethynyl-benzene (1). Chromatography (hexane), yield 78%, colorless oil. ^{1}H NMR ($CDCl_3$) δ ppm: 2.47 (s, 3H, CH_3); 7.26 (d, 1H, $J = 7.6$ Hz, CHAr); 7.36 (t, 1H, $J = 7.6$ Hz, CHAr); 7.44–7.46 (m, 3H, CHAr); 7.49–7.52 (m, 2H, CHAr); 7.67–7.70 (m, 2H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 21.7 (1C, CH_3); 89.6 (1C, C≡C); 90.2 (1C, C≡C); 123.6 (1C, Cq); 123.9 (1C, Cq); 128.7 (1C, CHAr); 128.8 (1C, CHAr); 128.9 (2C, CHAr); 129.2 (1C, CHAr); 129.7 (1C, CHAr); 132.1 (2C, CHAr); 132.7 (1C, CHAr); 138.5 (1C, Cq). MS (EI) *m/z* 192.1 (M). Anal. ($C_{15}H_{12}$) C, H.

6.1.2. 6-Methyl-2-phenylethynylpyridine, MPEP (2). Chromatography (hexane/EtOAc 8/2), yield 64%, yellow oil. ^{1}H NMR ($CDCl_3$) δ ppm: 2.33 (s, 3H, CH_3); 6.62 (dd, 1H, $J = 8.5$; 0.8 Hz, CHAr); 7.13 (dd, 1H, $J = 7.2$; 0.8 Hz, CHAr); 7.29–7.34 (m, 3H, CHAr); 7.46 (dd, 1H, $J = 8.5$; 7.2 Hz, CHAr); 7.54–7.58 (m, 2H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 19.0 (1C, OCH_3); 88.6 (1C, C≡C); 88.9 (1C, C≡C); 122.1 (C, Cq); 123.1 (1C, CHAr); 128.3 (2C, CHAr); 128.8 (1C, CHAr); 132.1 (2C, CHAr); 138.4 (1C, CHAr); 140.3 (1C, Cq); 141.2 (1C, Cq); 149.8 (1C, CHAr). HCl salt mp 145–146 °C. Anal. ($C_{14}H_{11}N{\cdot}HCl{\cdot}0.2H_2O$) C, H, N.

6.1.3. 5-Methyl-2-phenylethynylpyridine (3). Chromatography (hexane/EtOAc 8/2), yield 81%, yellow solid, mp 80–82 °C. ^{1}H NMR ($CDCl_3$) δ ppm: 2.31 (s, 3H, CH_3); 7.31–7.45 (m, 5H, CHAr); 7.56–7.58 (m, 2H, CHAr); 8.42 (s, 1H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 18.8 (1C, CH_3); 88.9 (1C, C≡C); 89.0 (1C, C≡C); 122.8 (1C, Cq); 127.0 (1C, CHAr); 128.7 (2C, CHAr); 129.1 (1C, CHAr); 132.3 (2C, CHAr); 133.1 (1C, Cq); 137.0 (1C, CHAr); 140.9 (1C, Cq); 150.9 (1C, CHAr). HCl salt mp 148–150 °C. Anal. ($C_{14}H_{11}N{\cdot}HCl{\cdot}0.2H_2O$) C, H, N.

6.1.4. 4-Methyl-2-phenylethynylpyridine (4). Chromatography (hexane/EtOAc 8/2), yield 73%, yellow oil. ^{1}H NMR ($CDCl_3$) δ ppm: 2.16 (s, 3H, CH_3); 6.88 (d, 1H, $J = 4.5$ Hz, CHAr); 7.19–7.22 (m, 4H, CHAr); 7.45–7.48 (m, 2H, CHAr); 8.31 (d, 1H, $J = 4.5$ Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 21.1 (1C, CH_3), 89.1 (1C, C≡C); 89.2 (1C, C≡C); 122.7 (1C, Cq); 124.2 (1C, CHAr); 128.3 (1C, CHAr); 128.7 (2C, CHAr); 129.2 (1C, CHAr); 132.3 (2C, CHAr); 143.4 (1C, Cq); 147.7 (1C, Cq); 150.0 (1C, CHAr). HCl salt mp 155–157 °C. Anal. ($C_{14}H_{11}N{\cdot}HCl$) C, H, N.

6.1.5. 3-Methyl-2-phenylethynylpyridine (5). Chromatography (hexane/EtOAc 8/2), yield 33%, yellow oil. ^{1}H NMR ($CDCl_3$) δ ppm: 2.34 (s, 3H, CH_3); 6.96 (dd, 1H, $J = 8.0$; 5.0 Hz, CHAr), 7.19–7.22 (m, 3H, CHAr); 7.33 (dd, 1H, $J = 8.0$; 0.8 Hz, CHAr); 7.47–7.49 (m, 2H, CHAr); 8.30 (dd, 1H, $J = 5.0$; 0.8 Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 19.7 (1C, CH_3); 87.9 (1C, C≡C); 93.3 (1C, C≡C); 122.8 (1C, Cq); 123.0 (1C, CHAr); 128.7 (2C, CHAr); 129.2 (1C, CHAr); 132.2 (2C, CHAr); 136.2 (1C, Cq); 137.3 (1C, CHAr); 143.3 (1C, Cq); 147.6 (1C, CHAr). HCl salt mp 150–152 °C. Anal. ($C_{14}H_{11}N{\cdot}HCl{\cdot}0.2H_2O$) C, H, N.

6.1.6. 2,4-Dimethyl-6-phenylethynylpyridine (6). Chromatography (hexane/EtOAc 9/1), yield 64%, yellow oil. ^{1}H NMR ($CDCl_3$) δ ppm: 2.26 (s, 3H, CH_3); 2.51 (s, 3H, CH_3); 6.89 (s, 1H, CHAr); 7.16 (s, 1H, CHAr); 7.30–7.33 (m, 3H, CHAr); 7.57–7.60 (m, 2H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 20.7 (1C, CH_3); 24.4 (1C, CH_3); 88.3 (1C, C≡C); 89.0 (1C, C≡C); 122.4 (1C, Cq); 123.6 (1C, CHAr); 125.3 (1C, CHAr); 128.3 (2C, CHAr); 128.7 (1C, CHAr); 132.0 (2C, CHAr); 142.3 (1C, Cq); 147.4 (1C, Cq); 158.5 (1C, Cq). HCl salt mp 160–162 °C. MS (EI) *m/z* 207.1 (M). Anal. ($C_{15}H_{13}N{\cdot}HCl$) C, H, N.

6.1.7. 2-Bromo-6-phenylethynylpyridine (7). Chromatography (hexane/EtOAc 8/2), yield 62%, of white solid. ^{1}H NMR ($CDCl_3$) δ ppm: 2.25–2.29 (m, 3H, CHAr); 2.34–2.36 (m, 2H, CHAr); 2.43 (d, 1H, $J = 7.7$ Hz, CHAr); 2.48–2.49 (m, 2H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 87.9 (1C, C≡C); 91.2 (1C, C≡C); 122.1 (1C, Cq); 126.4 (1C, CHAr); 127.8 (1C, CHAr); 128.8 (2C, CHAr); 129.7 (1C, CHAr); 132.5 (2C, CHAr); 138.8 (1C, CHAr); 142.1 (1C, Cq); 144.2 (1C, Cq). HCl salt mp 138–140 °C. Anal. ($C_{13}H_8BrN{\cdot}HCl{\cdot}0.1H_2O$) C, H, N.

6.1.8. 2-Methoxy-6-phenylethynylpyrylpyridine (8). Chromatography (hexane/EtOAc 95/5), yield 45%, yellow oil. ^{1}H NMR ($CDCl_3$) δ ppm: 3.96 (s, 3H, OCH_3); 6.68 (dd, 1H, $J = 8.5$; 0.8 Hz, CHAr); 7.11 (dd, 1H, $J = 7.2$; 0.8 Hz, CHAr); 7.30–7.33 (m, 3H, CHAr); 7.48 (dd, 1H, $J = 8.5$; 7.2 Hz, CHAr); 7.56–7.58 (m, 2H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 53.5 (1C, OCH_3); 88.5 (1C, C≡C); 88.9 (1C, C≡C); 111.0 (1C, CHAr); 120.7 (1C, CHAr); 122.4 (C, Cq); 128.3 (2C, CHAr); 128.8 (1C, CHAr); 131.9 (2C, CHAr); 138.4 (1C, CHAr); 140.3 (1C, Cq); 163.8 (1C, Cq). HCl salt mp 114–116 °C. MS (EI) *m/z* 209.1 (M). Anal. ($C_{14}H_{11}NO{\cdot}HCl{\cdot}0.8H_2O$) C, H, N.

6.2. 2-Methyl-6-trimethylsilylethynylpyridine (36)

To a solution of 2-bromo-6-methylpyridine (3 g, 17.4 mmol) in 50 mL of degassed Et_3N was added trimethylsilylacetylene (2.70 mL, 19.1 mmol), CuI (331 mg, 1.74 mmol), and *trans*-dichlorobis(triphenylphosphine)palladium (1.22 g, 1.74 mmol). The resulting solution was stirred at rt over night under N_2 atmosphere. Then the black solution was hydrolyzed with 30 mL of H_2O and extracted with Et_2O (3×30 mL). Purification of the residue by column chromatography (hexane/Et_2O 9/1) yielded 2.35 g (71%) of **36** as a brown oil. ^{1}H NMR (CD_2Cl_2) δ ppm: 0.08 (s, 9H, CH_3); 2.30 (s, 3H, CH_3); 6.89 (dd, 1H, $J = 7.6$; 0.5 Hz, CHAr); 7.05 (dd, 1H, $J = 7.6$; 0.5 Hz, CHAr); 7.32 (t, 1H, $J = 7.5$ Hz, CHAr). ^{13}C NMR (CD_2Cl_2) δ ppm: 0.0 (3C, CH_3); 24.7 (1C, CH_3); 94.0 (1C, C≡C); 104.7 (1C, C≡C); 123.1 (1C, CHAr); 124.8 (1C, CHAr); 136.7 (1C, CHAr); 142.6 (1C, Cq); 159.4 (1C, Cq).

6.3. 2-Ethynyl-6-methylpyridine (37)

To a solution of KOH (2.41 g, 43.0 mmol) in 50 mL of MeOH was added **36** (4.05 g, 21.5 mmol) dissolved in

5 mL of methanol. The resulting solution was stirred at rt for 2 h. Then 50 mL of H_2O was added and the resulting mixture was extracted with EtOAc (3 × 30 mL). Purification of the residue by column chromatography (hexane/Et_2O 9/1) yielded 1.86 g (74%) of **37** as a colorless oil. ^{1}H NMR ($CDCl_3$) δ ppm: 2.05 (s, 3H, CH_3); 2.72 (s, 2H, C≡C-H); 6.63 (d, 1H, J = 7.2 Hz, CHAr); 6.78 (d, 1H, J = 7.2 Hz, CHAr); 7.04 (td, 1H, J = 7.2; 0.8 Hz, CHAr).

6.4. 2-Methyl-6-trimethylstannylethynylpyridine (38)

Under N_2 atmosphere was added (dimethylamino)trimethyltin (2.1 mL, 12.3 mmol) to **37** (1.38 g, 11.8 mmol). The resulting solution was stirred at rt for 2 h. Evaporation of the crude mixture under high vacuum (1 mmHg) afforded the desired compound **38** as an oil, 4.1 g (quantitative yield). ^{1}H NMR ($CDCl_3$) δ ppm: 0.00 (s, 9H, $3CH_3$); 2.16 (s, 3H, CH_3); 6.67 (d, 1H, J = 8.0 Hz, CHAr); 6.88 (d, 1H, J = 8.0 Hz, CHAr); 7.12 (t, 1H, J = 8.0 Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: −7.4 (3C, $3CH_3$); 24.8 (1C, CH_3); 94.4 (1C, C≡C); 108.0 (1C, C≡C); 122.6 (1C, CHAr); 124.4 (1C, CHAr); 136.4 (1C, CHAr); 142.8 (1C, Cq); 158.8 (1C, Cq).

6.5. General procedure for the synthesis of compounds 9–11, 15, 17, 23, 24, 27–31

To a solution of **38** (500 mg, 1.79 mmol) in 15 mL degassed *N*,*N*-dimethylformamide was added successively the appropriate aryl bromide (1.97 mmol) and etrakis(triphenylphosphine)palladium (207 mg, 0.18 mmol). The resulting mixture was warmed to 110 °C and stirred at this temperature for 4 h. After cooling, 10 mL of H_2O was added and the resulting solution was extracted with EtO_2 (4 × 10 mL). The organic layer was washed with saturated NaCl (3 × 10 mL), dried over Na_2SO_4, and evaporated. Purification of the residue by column chromatography yielded the corresponding compounds **9**–**11**, **15**, **17**, **23**, **24**, **27**–**31**.

6.5.1. 2-(2-Methoxyphenylethynyl)-6-methylpyridine (9). Chromatography (hexane/EtOAc 7/3), yield 47%, brown oil. ^{1}H NMR ($CDCl_3$) δ ppm: 2.51 (s, 3H, CH_3); 3.83 (s, 3H, OCH_3); 6.83 (d, 1H, J = 8.4 Hz, CHAr); 6.87 (td, 1H, J = 7.6; 0.8 Hz, CHAr); 7.01 (dd, 1H, J = 7.6; 0.4 Hz, CHAr); 7.26 (td, 1H, J = 8.4; 2.0 Hz, CHAr); 7.31 (d, 1H, J = 7.6; 0.8 Hz, CHAr); 7.47 (t, 1H, J = 7.6 Hz, CHAr); 7.51 (dd, 1H, J = 7.6; 2.0 Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 24.8 (1C, CH_3); 56.0 (1C, OCH_3); 85.7 (1C, C≡C); 93.1 (1C, C≡C); 110.9 (1C, CHAr); 111.8 (1C, Cq); 120.7 (1C, CHAr); 122.7 (1C, CHAr); 124.6 (1C, CHAr); 130.7 (1C, CHAr); 134.1 (1C, CHAr); 136.6 (1C, CHAr); 143.1 (1C, Cq); 159.0 (1C, Cq); 160.6 (1C, Cq). HCl salt mp 166–168 °C. MS (EI) *m*/*z* 223.1 (M). Anal. ($C_{15}H_{13}NO$·HCl) C, H, N.

6.5.2. 2-(3-Methoxy-phenylethynyl)-6-methylpyridine (10, M-MPEP). Chromatography (toluene/Et_2O 9/1), yield 60%, yellow oil. HCl salt mp 180–182 °C. ^{1}H NMR (MeOH-d_4) δ ppm: 2.84 (s, 3H, CH_3); 3.86 (s, 3H, CH_3); 5.01 (br s, 1H, NH^+); 7.13 (dd, 1H, J = 8.4; 2.8 Hz, CHAr); 7.28 (d, 1H, J = 1.2 Hz, CHAr); 7.31 (dd, 1H, J = 7.6; 1.2 Hz, CHAr); 7.41 (t, 1H, J = 8.0 Hz, CHAr); 7.88 (d, 1H, J = 7.6 Hz, CHAr); 8.03 (d, 1H, J = 7.6 Hz, CHAr); 8.47 (t, 1H, J = 8.0 Hz, CHAr). ^{13}C NMR (MeOH-d_4) δ ppm: 20.4 (1C, CH_3); 56.5 (1C, CH_3); 81.5 (1C, C≡C); 101.9 (1C, C≡C); 118.8 (1C, CHAr); 119.1 (1C, CHAr); 122.2 (1C, Cq); 126.3 (1C, CHAr); 128.6 (1C, CHAr); 129.3 (1C, CHAr); 131.7 (1C, CHAr), 136.4 (1C, Cq); 147.6 (1C, CHAr); 157.3 (1C, Cq); 161.6 (1C, Cq). Anal. ($C_{15}H_{13}NO$·HCl) C, H, N.

6.5.3. 2-(4-Methoxyphenylethynyl)-6-methylpyridine (11). Chromatography (hexane/EtOAc 8/2), yield 45%, brown oil. ^{1}H NMR ($CDCl_3$) δ ppm: 2.44 (s, 3H, CH_3); 3.65 (s, 3H, OCH_3); 6.74 (d, 2H, J = 9.2 Hz, CHAr); 7.92 (d, 1H, J = 8.0 Hz, CHAr); 7.18 (d, 1H, J = 8.0 Hz, CHAr); 7.38 (t, 1H, J = 8.0 Hz, CHAr); 7.41 (d, 2H, J = 9.2 Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 25.2 (1C, CH_3); 55.8 (1C, OCH_3); 88.4 (1C, C≡C); 89.7 (1C, C≡C); 114.6 (2C, CHAr); 115.0 (1C, Cq); 122.9 (1C, CHAr); 124.7 (1C, CHAr); 134.2 (2C, CHAr); 137.0 (1C, CHAr); 143.5 (1C, CHAr); 159.4 (1C, Cq); 160.7 (1C, Cq). HCl salt mp 148–150 °C. MS (EI) *m*/*z* 223.2 (M). Anal. ($C_{15}H_{13}NO$·HCl) C, H, N.

6.5.4. 2-Benzo[1,3]dioxol-5-ylethynyl-6-methylpyridine (15). Chromatography (hexane/EtOAc 8/2), yield 81%, brown solid; mp 79–80 °C. ^{1}H NMR ($CDCl_3$) δ ppm: 2.47 (s, 3H, CH_3); 5.88 (s, 2H, OCH_2O); 6.68 (d, 1H, J = 8.0 HZ, CHAr); 6.94 (d, 1H, J = 2.0 Hz, CHAr); 6.98 (dd, 1H, J = 8.0; 0.8 Hz, CHAr); 7.04 (dd, 1H, J = 8.0; 2.0 Hz, CHAr); 7.21 (dd, 1H, J = 8.0; 0.8 Hz, CHAr); 7.43 (t, 1H, J = 8.0 Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 24.8 (1C, CH_3); 87.7 (1C, C≡C); 89.2 (1C, C≡C); 101.7 (1C, OCH_2O); 108.8 (1C, CHAr); 112.1 (1C, CHAr); 115.9 (1C, Cq); 122.7 (1C, CHAr); 124.5 (1C, CHAr); 127.2 (1C, CHAr); 136.6 (1C, CHAr); 134.0 (1C, Cq); 147.7 (1C, Cq); 148.7 (1C, Cq); 159.1 (1C, Cq). Hydrochloride mp 212–215 °C. MS (EI) *m*/*z* 237.1 (M). Anal. ($C_{15}H_{11}NO_2$·HCl) C, H, N.

6.5.5. 2-Methyl-6-(3-trifluoromethylphenylethynyl)pyridine (17). Chromatography (hexane/Et_2O 7/3), yield 61%, yellow oil. ^{1}H NMR ($CDCl_3$) δ ppm: 2.45 (s, 3H, CH_3); 6.98 (dd, 1H, J = 8.0; 0.4 Hz, CHAr); 7.23 (dd, 1H, J = 8.0; 0.4 Hz, CHAr); 7.33 (t, 1H, J = 8.0 Hz, CHAr); 7.43 (t, 1H, J = 8.0 Hz, CHAr); 7.46 (d, 1H, J = 8.0 Hz, CHAr); 7.62 (d, 1H, J = 8.0 Hz, CHAr); 7.74 (s, 1H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 24.7 (1C, CH_3); 87.1 (1C, C≡C); 90.5 (1C, C≡C); 123.3 (1C, CHAr); 123.7 (1C, Cq); 124.8 (1C, CHAr); 125.5 (1C, Cq); 129.2 (2C, CHAr); 135.3 (1C, CHAr); 136.7 (2C, CHAr); 142.3 (1C, Cq); 159.4 (1C, Cq). Hydrochloride mp 108–110 °C. MS (EI) *m*/*z* 261 (M). Anal. ($C_{15}H_{11}F_3N$·HCl·0.5H_2O) C, H, N.

6.5.6. 2-Methyl-6-pyridin-4-ylethynylpyridine (23). Chromatography (ether/hexane 7/3), yield 70%, brown oil. ^{1}H NMR (MeOH-d_4) δ ppm: 3.11 (s, 3H, CH_3); 5.59 (t, 1H, J = 6.8 Hz, CHAr); 6.07 (d, 2H, J = 5.4 Hz, CHAr); 6.57 (d, 1H, J = 6.8 Hz); 7.07 (d, 2H, J = 5.4 Hz, CHAr); 7.14

(d, 1H, $J = 6.8$ Hz, CHAr). ^{13}C NMR (MeOH-d_4) δ ppm: 23.0 (1C, CH_3); 83.1 (1C, C≡C); 98.5 (1C, C≡C); 119.6 (1C, CHAr); 123.8 (1C, Cq); 125.1 (1C, CHAr); 127.1 (2C, CHAr); 138.3 (1C, CHAr); 141.5 (2C, CHAr); 144.6 (1C, Cq); 158.8 (1C, Cq). Hydrochloride mp 125–130 °C (dec). MS (EI) *m/z* 194.1 (M). Anal. ($C_{13}H_{10}N_2$·2HCl·H_2O) C, H, N.

6.5.7. 3-(6-Methylpyridin-2-ylethynyl)-5-methoxypyridine (24). Chromatography (ether/hexane 7/3), yield 68%, white solid; mp 91–93 °C. ^{1}H NMR ($CDCl_3$) δ ppm: 2.47 (s, 3H, CH_3); 3.73 (s, 3H, OCH_3); 7.01–7.03 (m, 2H, CHAr); 7.26 (s, 1H, CHAr); 7.44–7.48 (m, 1H, CHAr); 8.17 (s, 1H, CHAr); 8.32 (s, 1H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 24.9 (1C, CH_3); 55.9 (1C, OCH_3); 85.3 (1C, C≡C); 92.0 (1C, C≡C); 120.0 (1C, Cq); 122.7 (1C, CHAr); 123.4 (1C, CHAr); 124.8 (1C, CHAr); 136.8 (1C, CHAr); 138.4 (1C, CHAr); 142.2 (1C, Cq); 145.0 (1C, CHAr); 155.3 (1C, Cq); 159.4 (1C, Cq). Hydrochloride mp 168 °C (dec). Anal. ($C_{14}H_{13}N_2O$·2HCl) C, H, N.

6.5.8. 3-(6-Methylpyridin-2-ylethynyl)quinoline (27). Chromatography (hexane/Et_2O 4/6), yield 82%, yellow solid; mp 70–72 °C. ^{1}H NMR ($CDCl_3$) δ ppm: 2.49 (s, 3H, CH_3); 7.62 (td, 1H, $J = 8.0$; 1.5 Hz, CHAr); 7.68 (d, 1H, $J = 8.0$ Hz, CHAr); 7.99 (d, 1H, $J = 8.0$ Hz, CHAr); 8.26 (d, 1H, $J = 1.2$ Hz, CHAr); 7.02 (d, 1H, $J = 8.0$ Hz, CHAr); 7.30 (d, 1H, $J = 8.0$ Hz, CHAr); 7.45 (td, 1H, $J = 8.0$; 1.5 Hz, CHAr); 7.48 (t, 1H, $J = 8.0$ Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 24.99 (1C, CH_3); 86.2 (1C, C≡C); 92.2 (1C, C≡C); 116.9 (1C, Cq); 123.4 (1C, CHAr); 124.9 (1C, CHAr); 127.4 (1C, Cq); 127.7 (1C, CHAr); 128.1 (1C, CHAr); 129.7 (1C, CHAr); 130.8 (1C, CHAr); 136.8 (1C, CHAr); 139.5 (1C, CHAr); 142.4 (1C, Cq); 147.4 (1C, Cq); 152.4 (1C, CHAr); 159.5 (1C, Cq). Hydrochloride mp 174–176 °C. Anal. ($C_{17}H_{12}N_2$·2HCl) C, H, N.

6.5.9. 4-(6-Methylpyridin-2-ylethynyl)isoquinoline (28). Chromatography (hexane/Et_2O 4/6), yield 87%, yellow oil. ^{1}H NMR ($CDCl_3$) δ ppm: 2.51 (s, CH_3); 7.04 (d, 1H, $J = 8.0$ Hz, CHAr); 7.36 (d, 1H, $J = 8.0$ Hz, CHAr); 7.50 (t, 1H, $J = 8.0$ Hz, CHAr); 7.55 (dd, 1H, $J = 8.0$; 1.2 Hz, CHAr); 7.68 (td, 1H, $J = 8.0$; 1.2 Hz, CHAr); 8.26 (d, 1H, $J = 8.0$ Hz, CHAr); 8.72 (s, 1H, CHAr); 9.09 (s, 1H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 23.9 (1C, CH_3); 83.1 (1C, C≡C); 95.3 (1C, C≡C); 114.5 (1C, Cq); 122.4 (1C, CHAr); 124.0 (1C, CHAr); 124.5 (1C, CHAr); 127.0 (1C, Cq); 127.2 (1C, CHAr); 127.4 (1C, CHAr); 130.6 (1C, CHAr); 134.9 (1C, Cq); 135.8 (1C, CHAr); 141.5 (1C, Cq); 146.3 (1C, CHAr); 151.7 (1C, CHAr); 158.5 (1C, Cq). Hydrochloride mp 184–186 °C. Anal. ($C_{17}H_{12}N_2$·2HCl·0.75H_2O) C, H, N.

6.5.10. 1-Methyl-6-(6-methylpyridin-2-ylethynyl)-1*H*-indole (29). Chromatography (hexane/Et_2O 4/6), yield 65%, yellow solid; mp 161–163 °C. ^{1}H NMR ($CDCl_3$) δ ppm: 2.46 (s, 3H, CH_3); 3.58 (s, 3O, NCH_3); 6.34 (d, 1H, $J = 3.2$ Hz, CHAr); 6.91 (d, 1H, $J = 8.0$ Hz, CHAr); 6.94 (d, 1H, $J = 3.2$ Hz, CHAr); 7.21 (d, 1H, $J = 7.6$ Hz, CHAr); 7.23 (dd, 1H, $J = 8.0$; 1.2 Hz, CHAr); 7.38 (t, 1H, $J = 7.6$ Hz, CHAr); 7.45 (d, 1H, $J = 8.0$ Hz, CHAr); 7.49 (s, 1H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 24.9 (1C, CH_3); 33.1 (1C, NCH_3); 88.0 (1C, C≡C); 91.4 (1C, C≡C); 101.7 (1C, CHAr); 114.0 (1C, CHAr); 115.1 (1C, Cq); 121.1 (1C, CHAr); 122.4 (1C, CHAr); 123.6 (1C, CHAr); 124.5 (1C, CHAr); 129.4 (1C, Cq); 131.0 (1C, CHAr); 136.5 (1C, Cq); 136.7 (1C, CHAr); 143.6 (1C, Cq); 159.1 (1C, Cq). Hydrochloride mp 154–156 °C. HRMS obsd, *m/z* 246.1163, calcd, *m/z* 264.1156. Anal. ($C_{17}H_{14}N_2$·HCl·1/3H_2O) C, H, N.

6.5.11. 1-Methyl-5-(6-methylpyridin-2-ylethynyl)-1*H*-indole (30). Chromatography (hexane/EtOAc 8/2), yield 75%, yellow solid; mp 98–99 °C. ^{1}H NMR ($CDCl_3$) δ ppm: 2.50 (s, 3H, CH_3); 3.67 (s, 3H, NCH_3); 6.39 (d, 1H, $J = 2.8$ Hz, CHAr); 7.96–7.98 (m, 2H, CHAr); 7.18 (d, 1H, $J = 8.4$ Hz, CHAr); 7.26 (d, 1H, $J = 7.6$ Hz, CHAr); 7.38 (dd, 1H, $J = 8.4$; 1.2 Hz, CHAr); 7.45 (t, 1H, $J = 8.4$ Hz, CHAr); 7.81 (s, 1H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 24.9 (1C, CH_3); 33.2 (1C, NCH_3); 87.2 (1C, C≡C); 91.6 (1C, C≡C); 101.8 (1C, CHAr); 109.7 (1C, CHAr); 113.2 (1C, CHAr); 122.4 (1C, CHAr); 124.5 (1C, CHAr); 125.9 (1C, CHAr); 126.0 (1C, CHAr); 128.6 (1C, Cq); 130.3 (1C, CHAr); 136.7 (1C, CHAr); 137.0 (1C, Cq); 143.7 (1C, Cq); 159.1 (1C, Cq). Hydrochloride mp 182–184 °C. Anal. ($C_{17}H_{14}N_2$·HCl·1/3H_2O) C, H, N.

6.5.12. 5-(6-Methylpyridin-2-ylethynyl)pyrimidine (31). Chromatography (hexane/Et_2O 7/3), yield 90%, yellow solid; mp 109–111 °C. ^{1}H NMR ($CDCl_3$) δ ppm: 2.52 (s, 3H, CH_3); 7.11 (d, 1H, $J = 8.0$ Hz, CHAr); 7.32 (d, 1H, $J = 8.4$ Hz, CHAr); 7.54 (t, 1H, $J = 8.4$ Hz, CHAr); 8.85 (s, 2H, CHAr); 9.09 (s, 1H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 24.9 (1C, CH_3); 81.8 (1C, C≡C); 95.6 (1C, C≡C); 119.5 (1C, Cq); 124.0 (1C, CHAr); 125.0 (1C, CHAr); 137.0 (1C, CHAr); 141.6 (1C, Cq); 157.5 (1C, CHAr); 159.4 (2C, CHAr); 159.7 (1C, Cq). Hydrochloride mp 164–166 °C. MS (EI) *m/z* 195.1 (M). Anal. ($C_{12}H_9N_3$·HCl·0.5H_2O) C, H, N.

6.6. General procedure for the synthesis of compounds 12–14, 18–21, 25, 26

To a solution of **36** (1 g, 5.32 mmol) in 15 mL degassed *N*,*N*-dimethylformamide was added successively the appropriate aryl bromide (6.96 mmol), CuI (110 mg, 0.57 mmol), Et_3N (2.95 mL, 21.2 mmol), and *trans*-dichlorobis(triphenylphosphine)palladium (204 mg, 0.29 mmol). The resulting mixture was warmed to 70 °C, Bu_4NF (5.85 mL, 5.85 mmol) was added dropwise, and the reaction was stirred at this temperature overnight. After cooling, 10 mL of H_2O was added and the resulting solution was extracted with EtOAc (4 × 10 mL). The organic layer was washed with saturated NaCl (3 × 10 mL), dried over Na_2SO_4, and evaporated. Purification of the residue by column chromatography yielded the corresponding compounds **12–14**, **18–21**, **25**, **26**.

6.6.1. 2-(2,4-Dimethoxy-phenylethynyl)-6-methylpyridine (12). Chromatography (hexane/Et_2O 3/7), yield 28%, yellow oil. ^{1}H NMR (CD_2Cl_2) δ ppm: 2.40 (s, 3H, CH_3); 3.67 (s, 3H, CH_3); 3.76 (s, 3H, CH_3); 6.35–6.37

(m, 2H, CHAr); 6.93 (d, 1H, $J = 8.0$ Hz, CHAr); 7.16 (d, 1H, $J = 8.0$ Hz, CHAr); 7.32 (d, 1H, $J = 8.0$ Hz, CHAr); 7.40 (t, 1H, $J = 8.0$ Hz, CHAr). ^{13}C NMR (CD_2Cl_2) δ ppm: 25.0 (1C, CH_3); 56.2 (1C, OCH_3); 56.5 (1C, OCH_3); 86.2 (1C, C≡C); 92.4 (1C, C≡C); 99.0 (1C, CHAr); 104.6 (1C, Cq); 105.9 (1C, CHAr); 122.8 (1C, CHAr); 124.6 (1C, CHAr); 135.4 (1C, CHAr); 136.9 (1C, CHAr); 143.8 (1C, Cq); 159.6 (1C, Cq); 162.5 (1C, Cq); 162.7 (1C, Cq). Hydrochloride mp 142–144 °C. MS (EI) *m/z* 253.1 (M). Anal. ($C_{16}H_{15}NO_2 \cdot HCl \cdot 1/3H_2O$) C, H, N.

6.6.2. 2-(2,5-Dimethoxy-phenylethynyl)-6-methylpyridine (13). Chromatography (hexane/Et_2O 3/7), yield 34%, yellow oil. ^{1}H NMR (CD_2Cl_2) δ ppm: 2.43 (s, 3H, CH_3); 3.65 (s, 3H, CH_3); 3.75 (s, 3H, CH_3); 7.74–7.80 (m, 2H, CHAr); 6.97–6.99 (m, 2H, CHAr); 7.22 (d, 1H, $J = 8.0$ Hz, CHAr); 7.44 (t, 1H, $J = 8.0$ Hz, CHAr). ^{13}C NMR (CD_2Cl_2) δ ppm: 25.0 (1C, CH_3); 56.5 (1C, OCH_3); 57.0 (1C, OCH_3); 85.7 (1C, C≡C); 93.5 (1C, C≡C); 112.6 (1C, Cq); 112.7 (1C, CHAr); 117.2 (1C, CHAr); 119.0 (1C, CHAr); 123.2 (1C, CHAr); 124.9 (1C, CHAr); 137.0 (1C, CHAr); 143.3 (1C, Cq); 145.0 (1C, Cq); 155.7 (1C, Cq); 159.8 (1C, Cq). Hydrochloride mp 162–164 °C. MS (EI) *m/z* 253.1 (M). Anal. ($C_{16}H_{15}NO_2 \cdot HCl \cdot 0.5H_2O$) C, H, N.

6.6.3. 2-(3,4-Dimethoxy-phenylethynyl)-6-methylpyridine (14). Chromatography (hexane/Et_2O 3/7), yield 23%, yellow oil. ^{1}H NMR (CD_2Cl_2) δ ppm: 2.41 (s, 3H, CH_3); 3.73 (s, 3H, CH_3); 3.74 (s, 3H, CH_3); 6.74 (d, 1H, $J = 8.0$ Hz, CHAr); 6.97–6.98 (m, 2H, CHAr); 7.07 (dd, 1H, $J = 8.0$; 2.0 Hz, CHAr); 7.20 (d, 1H, $J = 8.0$ Hz, CHAr); 7.44 (t, 1H, $J = 8.0$ Hz, CHAr). ^{13}C NMR (CD_2Cl_2) δ ppm: 25.0 (1C, CH_3); 56.5 (1C, OCH_3); 56.6 (1C, OCH_3); 88.4 (1C, C≡C); 89.4 (1C, C≡C); 112.0 (1C, CHAr); 115.0 (1C, Cq); 115.5 (1C, CHAr); 123.0 (1C, CHAr); 124.7 (1C, CHAr); 126.0 (1C, CHAr); 137.0 (1C, CHAr); 143.5 (1C, Cq); 149.7 (1C, Cq); 151.0 (1C, Cq); 159.7 (1C, Cq). Hydrochloride mp 172–176 °C (dec). MS (EI) *m/z* 253.1 (M). Anal. ($C_{16}H_{15}NO_2 \cdot HCl \cdot 0.25H_2O$) C, H, N.

6.6.4. 2-(3-Fluoro-phenylethynyl)-6-methylpyridine (18). Chromatography (hexane/EtOAc 9/1), yield 31%, yellow oil. Hydrochloride mp 158–160 °C. ^{1}H NMR (MeOH-d_4) δ ppm: 2.87 (s, 3H, CH_3); 5.06 (br s, 1H, N^+H); 7.33–7.37 (m, 1H, CHAr); 7.52–7.61 (m, 3H, CHAr); 7.94 (d, 1H, $J = 8.5$ Hz, CHAr); 8.09 (d, 1H, $J = 8.5$ Hz, CHAr); 8.51 (t, 1H, $J = 8.5$ Hz, CHAr). ^{13}C NMR (MeOH-d_4) δ ppm: 20.4 (1C, CH_3); 82.2 (1C, C≡C); 99.2 (1C, C≡C); 120.0 (d, 1C, $J = 21.5$ Hz, CHAr); 120.5 (d, 1C, $J = 23.3$ Hz, CHAr); 123.2 (d, 1C, $J = 8.5$ Hz, Cq); 129.0 (1C, CHAr); 129.5 (1C, CHAr); 130.2 (d, 1C, $J = 3.3$ Hz, CHAr); 132.7 (d, 1C, $J = 8.1$ Hz, CHAr); 136.0 (1C, Cq); 147.7 (1C, CHAr); 157.6 (1C, Cq); 164.2 (d, 1C, $J = 245$ Hz, Cq). MS (EI) *m/z* 211.1 (M). Anal. ($C_{14}H_{10}FN \cdot HCl$) C, H, N.

6.6.5. 2-Methyl-6-(3-methylthiophenylethynyl)pyridine (19). Chromatography (hexane/EtOAc 8/2), yield 44%, yellow oil. ^{1}H NMR ($CDCl_3$) δ ppm: 2.47 (s, 3H, CH_3); 2.57 (s, 3H, SCH_3); 7.08 (d, 1H, $J = 8.0$ Hz, CHAr); 7.21–7.24 (m, 2H, CHAr); 7.32–7.36 (m, 2H, CHAr); 7.46 (s, 1H, CHAr); 7.53 (t, 1H, $J = 7.5$ Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 15.5 (1C, SCH_3); 24.5 (1C, CH_3); 88.2 (1C, C≡C); 89.1 (1C, C≡C); 122.7 (1C, CHAr); 123.0 (1C, Cq); 124.4 (1C, CHAr); 127.0 (1C, CHAr); 128.5 (1C, CHAr); 128.6 (1C, CHAr); 129.1 (1C, CHAr); 136.3 (1C, CHAr); 139.0 (1C, Cq); 142.4 (C, Cq); 158.9 (1C, Cq). Hydrochloride mp 132–134 °C. MS (EI) *m/z* 239.2 (M). Anal. ($C_{15}H_{13}NS \cdot HCl$) C, H, N.

6.6.6. 2-(3-Allyloxy-phenylethynyl)-6-methylpyridine (20). Chromatography (hexane/Et_2O 6/4), yield 60%, yellow oil. ^{1}H NMR ($CDCl_3$) δ ppm: 2.56 (s, 3H, CH_3); 4.51 (t, 1H, $J = 1.5$ Hz, CH_{2a}); 4.20 (t, 1H, $J = 1.5$ Hz, CH_{2b}); 2.27 (dq, 1H, $J = 10.5$; 2.0 Hz, CH_a); 5.40 (dq, 1H, $J = 16.5$; 1.5 Hz, CH_b); 6.03 (dqint, 1H, $J = 21.0$; 5.0 Hz, CH); 6.92 (ddd, 1H, $J = 8.0$; 2.5; 1.0 Hz, CHAr); 7.07 (d, 1H, $J = 8.0$ Hz, CHAr); 7.14 (dd, 1H, $J = 3.0$; 1.5 Hz, CHAr); 7.19 (dt, 1H, $J = 7.5$; 1.0 Hz, CHAr); 7.23 (t, 1H, $J = 8.0$ Hz, CHAr); 7.33 (d, 1H, $J = 8.5$ Hz, CHAr); 7.52 (t, 1H, $J = 8.0$ Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 24.6 (1C, CH_3); 68.7 (1C, CH_2); 88.6 (1C, C≡C); 88.7 (1C, C≡C); 116.3 (1C, CHAr); 117.5 (1C, CHAr); 117.7 (1C, CH_2allyl); 122.6 (1C, CHAr); 123.3 (1C, Cq); 124.4 (1C, CHAr); 124.7 (1C, CHAr); 129.4 (1C, CHAr); 132.9 (1C, CHAr); 136.3 (C, CHallyl); 142.5 (1C, Cq); 158.2 (1C, Cq); 158.9 (1C, Cq). Hydrochloride mp 120–122 °C. MS (EI) *m/z* 249.1 (M). Anal. ($C_{17}H_{15}NO \cdot HCl \cdot 1/5H_2O$) C, H, N.

6.6.7. 2-Methyl-6-pyridin-2-ylethynylpyridine (21). Chromatography (hexane/Et_2O 3/7), yield 65%, brown oil. ^{1}H NMR ($CDCl_3$) δ ppm: 2.57 (s, 3H, CH_3); 7.14 (d, 1H, $J = 6.0$ Hz, CHAr); 7.40 (ddd, 1H, $J = 6.0$; 4.8; 0.8 Hz, CHAr); 7.43 (d, 1H, $J = 6.0$ Hz, CHAr); 7.58 (t, 1H, $J = 6.0$ Hz); 7.88 (dt, 1H, $J = 6.0$; 0.8 Hz, CHAr); 8.57 (td, 1H, $J = 6.8$; 1.2 Hz, CHAr); 8.63 (dt, 1H, $J = 2.8$; 0.8 Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 24.8 (1C, CH_3); 87.7 (1C, C≡C); 88.4 (1C, C≡C); 123.5 (1C, CHAr); 123.6 (1C, CHAr); 125.2 (1C, CHAr); 127.9 (1C, CHAr); 136.5 (1C, CHAr); 136.7 (1C, CHAr); 142.0 (1C, Cq); 142.9 (1C, Cq); 150.3 (1C, CHAr); 159.3 (1C, Cq). Hydrochloride mp 102–104 °C. MS (EI) *m/z* 195.1 (M+1). Anal. ($C_{13}H_{10}N_2 \cdot 2HCl \cdot 0.5H_2O$) C, H, N.

6.6.8. 3-(6-Methylpyridin-2-ylethynyl)-5-bromopyridine (25). Chromatography (hexane/Et_2O 4/6), yield 49%, brown solid. ^{1}H NMR ($CDCl_3$) δ ppm: 2.60 (s, 3H, CH_3); 7.17 (d, 1H, $J = 8.0$ Hz, CHAr); 7.37 (d, 1H, $J = 8.0$ Hz, CHAr); 7.60 (t, 1H, $J = 8.0$ Hz, CHAr); 8.02 (s, 1H, CHAr); 8.63 (s, 1H, CHAr); 8.72 (s, 1H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 25.0 (1C, CH_3); 83.8 (1C, C≡C); 93.4 (1C, C≡C); 120.4 (1C, Cq); 121.4 (1C, Cq); 123.8 (1C, CHAr); 125.0 (1C, CHAr); 136.9 (1C, CHAr); 141.4 (1C, CHAr); 141.9 (1C, Cq); 150.6 (1C, CHAr); 150.9 (1C, CHAr); 159.7 (1C, Cq). Hydrochloride mp 174–176 °C. MS (EI) *m/z* 272.0 and 274.0 (M, ^{79}Br and ^{81}Br). Anal. ($C_{12}H_9BrN_2 \cdot 2HCl$) C, H, N.

6.6.9. [5-(6-Methylpyridin-2-ylethynyl)-pyridin-3-yl]-methanol (26). Chromatography (EtOAc/Et_2O 3/7), yield 65%, brown oil. ^1H NMR ($CDCl_3$) δ ppm: 2.57 (s, 3H, CH_3); 4.76 (s, 2H, CH_2); 5.43 (br s, 1H, OH); 7.15 (d, 1H, $J = 8.0$ Hz, CHAr); 7.35 (d, 1H, $J = 8.0$ Hz, CHAr); 7.59 (t, 1H, $J = 8.0$ Hz, CHAr); 7.88 (t, 1H, $J = 2.0$ Hz, CHAr); 8.50 (d, 1H, $J = 2.0$ Hz, CHAr); 8.60 (d, 1H, $J = 2.0$ Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 24.3 (1C, CH_3); 61.4 (1C, CH_2); 85.4 (1C, C≡C); 91.6 (1C, C≡C); 119.1 (1C, Cq); 123.3 (1C, CHAr); 124.7 (1C, CHAr); 136.8 (1C, CHAr); 136.9 (1C, Cq); 137.5 (1C, CHAr); 141.7 (1C, Cq); 147.6 (1C, CHAr); 150.8 (1C, CHAr); 159.0 (1C, Cq). Hydrochloride mp 164–166 °C. MS (EI) *m/z* 224.1 (M). Anal. ($C_{14}H_{12}N_2O{\cdot}2HCl{\cdot}H_2O$) C, H, N.

6.7. 2-Methyl-6-(3-nitro-phenylethynyl)-pyridine (16)

To a solution of **37** (165 mg, 1.41 mmol) in 10 mL of degassed Et_3N was added 1-iodo-3-nitrobenzene (386 mg, 1.55 mmol), CuI (26 mg, 0.14 mmol), and *trans*-dichlorobis(triphenylphosphine)palladium (99 mg, 0.14 mmol). The resulting solution was stirred at rt for 3 h under N_2 atmosphere, then the black solution was hydrolyzed with 10 mL of H_2O and extracted with EtOAc (3 × 10 mL). The organic layer was washed with saturated NaCl (3 × 20 mL), dried over Na_2SO_4, and evaporated. Purification of the residue by column chromatography (SiO_2/hexane/EtOAc 8/2) yield 47% of **16** as a brown solid; mp 103–105 °C. ^1H NMR ($CDCl_3$) δ ppm: 2.60 (s, 3H, CH_3); 7.17 (d, 1H, $J = 7.6$ Hz, CHAr); 7.40 (d, 1H, $J = 7.6$ Hz, CHAr); 7.55 (t, 1H, $J = 8.0$ Hz, CHAr); 7.62 (t, 1H, $J = 8.0$ Hz); 7.90 (d, 1H, $J = 8.0$ Hz, CHAr); 8.21 (dd, $J = 8.4$; 1.8 Hz, CHAr); 8.45 (t, 1H, $J = 1.8$ Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 25.0 (1C, CH_3); 86.2 (1C, CC); 91.4 (1C, C≡C); 123.7 (1C, CHAr); 123.9 (1C, CHAr); 124.6 (1C, Cq); 125.0 (1C, CHAr); 127.2 (1C, CHAr); 129.8 (1C, CHAr); 136.9 (1C, CHAr); 138.0 (1C, CHAr); 142.1 (1C, Cq); 148.4 (1C, Cq); 159.6 (1C, Cq). Hydrochloride mp 162–165 °C. MS (EI) *m/z* 238.1 (M). Anal. ($C_{14}H_{10}N_2O_2{\cdot}HCl$) C, H, N.

6.8. Synthesis of 3-ethynylpyridine (39)

To a solution of KOH (1.28 g, 22.8 mmol) in 20 mL of MeOH was added commercial 3-trimethylsilylethynylpyridine (2.00 g, 11.4 mmol) dissolved in 5 mL of methanol. The resulting solution was stirred at rt for 2 h. Then 20 mL of H_2O was added and the resulting mixture was extracted with EtOAc (3 × 10 mL). The organic layer was washed with saturated NaCl (3 × 20 mL), dried over Na_2SO_4, and evaporated. Purification of the residue by column chromatography (hexane/Et_2O 7/3) yielded 760 mg (65%) of **39** as a white solid, mp 34–35. ^1H NMR ($CDCl_3$) δ ppm: 3.32 (s, 1H, C≡CH); 7.24 (ddd, 1H, $J = 8.0$; 5.0; 0.8 Hz CHAr); 7.76 (dt, 1H, $J = 8.0$; 1.6 Hz, CHAr); 8.55 (dd, 1H, $J = 5.0$; 1.6 Hz, CHAr); 8.73 (d, 1H, $J = 1.6$ Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 80.3 (1C, C≡C); 80.9 (1C, C≡CH); 119.2 (1C, Cq); 122.9 (1C, CHAr); 139.0 (1C, CHAr); 149.0 (2C, CHAr); 152.7 (1C, CHAr).

6.9. 2-Methyl-6-pyridin-3-ylethynylpyridine (22)

To a solution of **39** (300 mg, 2.91 mmol) in 10 mL of degassed Et_3N was added successively CuI (55 mg, 0.29 mmol), 2-bromo-6-methylpyridine (551 μg, 3.20 mmol), and *trans*-dichlorobis(triphenylphosphine)palladium (204 mg, 0.29 mmol). The mixture was stirred at 90 °C for 6 h, then the black solution was hydrolyzed with 10 mL of H_2O and extracted with EtOAc (3 × 10 mL). Purification of the residue by column chromatography (Et_2O/hexane 8/2) yielded 160 mg (35%) of **29** as a yellow oil. ^1H NMR ($CDCl_3$) δ ppm: 2.58 (s, 3H, CH_3); 7.14 (d, 1H, $J = 8.0$ Hz, CHAr); 7.40 (ddd, 1H, $J = 8.0$; 5.8; 0.8 Hz, CHAr); 7.38 (d, 1H, $J = 8.0$ Hz, CHAr); 7.58 (t, 1H, $J = 8.0$ Hz); 7.88 (dt, 1H, $J = 8.0$; 2.0 Hz, CHAr); 8.57 (dd, 1H, $J = 5.8$; 2.0 Hz, CHAr); 8.83 (dd, 1H, $J = 2.0$; 0.8 Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 24.8 (1C, CH_3); 85.4 (1C, C≡C); 92.2 (1C, CC); 119.9 (1C, Cq); 123.4 (1C, CHAr); 123.5 (1C, CHAr); 124.8 (1C, CHAr); 136.8 (1C, CHAr); 139.2 (1C, CHAr); 142.1 (1C, Cq); 149.3 (1C, CHAr); 152.7 (1C, CHAr); 159.4 (1C, Cq). Hydrochloride mp 164–166 °C. MS (EI) *m/z* 194.1 (M). Anal. ($C_{13}H_{10}N_2{\cdot}2HCl$) C, H, N.

6.10. 3-Bromo-5-methoxy-pyridine (40)

In 10 mL of MeOH was added by portion Na metal (854 mg, 37.1 mmol) and the resulting mixture was stirred at rt until complete reaction. Then 3,6-dibromopyridine (4.40 g, 18.5 mmol) was added and the solution was heated at 130 °C in a sealed tube for 24 h. After cooling the reaction was poured into 50 mL of H_2O and extracted twice with 30 mL of EtOAc. The organic layer was washed with saturated NaCl (3 × 20 mL), dried over Na_2SO_4, and evaporated. Purification of the residue by column chromatography (hexane/EtOAc 7/3) yielded 3.21 g (92%) of **40** as a white solid, mp 33–34 °C. ^1H NMR ($CDCl_3$) δ ppm: 3.68 (s, 3H, OCH_3); 7.18 (t, 1H, $J = 2.4$ Hz, CHAr); 8.08 (d, 1H, $J = 2.4$ Hz, CHAr); 8.12 (d, 1H, $J = 2.4$ Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 56.1 (1C, OCH_3); 120.6 (1C, Cq); 123.4 (1C, CHAr); 136.4 (1C, CHAr); 143.1 (1C, CHAr); 156.3 (1C, Cq).

6.11. 3-Methoxy-5-trimethylsilanylethynylpyridine (41)

To a solution of **40** (3 g, 16.1 mmol) in 30 mL of degassed Et_3N was added trimethylsilylacetylene (2.51 mL, 17.7 mmol), CuI (306 mg, 1.61 mmol), and *trans*-dichlorobis(triphenylphosphine)palladium (1.11 g, 1.61 mmol). The resulting solution was stirred at rt for 5 h under N_2 atmosphere. Then the black solution was hydrolyzed with 30 mL of H_2O and extracted with EtOAc (3 × 30 mL). Purification of the residue by column chromatography (hexane/EtOAc 8/2) yielded 2.88g (88%) of **40** as a brown oil. ^1H NMR ($CDCl_3$) δ ppm: 0.00 (s, 9H, $Si(CH_3)_3$); 3.56 (s, 3H, OCH_3); 6.97 (s, 1H, CHAr); 8.11 (br s, 1H, CHAr); 8.23 (br s, 1H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: −0.1 (3C, $Si(CH_3)_3$); 55.7 (1C, OCH_3); 98.2 (2C, 2C≡C); 101.8 (1C, Cq); 122.3 (1C, CHAr); 123.2 (1C, Cq); 137.5 (1C, CHAr); 144.7 (1C, CHAr).

6.12. 3-Methoxy-5-(4-methyl-thiazol-2-ylethynyl)-pyridine (32)

To a solution of **40** (661 mg, 4.96 mmol) in 15 mL degassed Et_3N was added successively 2-iodo-4-methyl-thiazole (1 g, 4.52 mmol), CuI (85 mg, 0.45 mmol), and *trans*-dichlorobis(triphenylphosphine)palladium (317 mg, 0.45 mmol). The resulting mixture was warmed to 60 °C, Bu_4NF (5.85 mL, 5.85 mmol) was added drop-wise, and the reaction was stirred at this temperature overnight. After cooling, 10 mL of H_2O was added and the resulting solution was extracted with EtOAc (4 × 10 mL). The organic layer was washed with saturated NaCl (3 × 10 mL), dried over Na_2SO_4, and evaporated. Purification of the residue by column chromatography (hexane/Et_2O 1/1) yielded 590 mg of 32 as a brown solid; mp 88–90 °C. ^1H NMR ($CDCl_3$) δ ppm: 2.36 (s, 3H, CH_3); 3.73 (s, 3H, OCH_3); 6.87 (s, 1H, CHAr); 7.21 (s, 1H, CHAr); 8.19 (s, 1H, CHAr); 8.29 (s, 1H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 17.3 (1C, CH_3); 55.8 (1C, OCH_3); 85.6 (1C, C≡C); 89.9 (1C, C≡C); 116.5 (1C, CHAr); 119.1 (1C, Cq); 122.3 (1C, CHAr); 138.8 (1C, CHAr); 144.7 (1C, CHAr); 147.1 (1C, Cq); 154.3 (1C, Cq); 155.3 (1C, Cq). Hydrochloride mp 149–150 °C. MS (EI) *m/z* 230.0 (M). Anal. ($C_{12}H_{10}N_2OS$·HCl) C, H, N.

6.13. General procedure for the synthesis of compounds 33–35

To a solution of **42**[10] (500 mg, 2.55 mmol) in 15 mL degassed *NN*-dimethylformamide was added successively the appropriate aryl bromide (2.80 mmol), CuI (48 mg, 0.25 mmol), Et_3N (1.42 mL, 10.2 mmol), and *trans*-dichlorobis(triphenylphosphine)palladium (89 mg, 0.12 mmol). The resulting mixture was warmed to 70 °C, Bu_4NF (2.80 mL, 2.80 mmol) was added drop-wise, and the reaction was stirred at this temperature overnight. After cooling, 10 mL of H_2O was added and the resulting solution was extracted with EtOAc (4 × 10 mL). The organic layer was washed with saturated NaCl (3 × 10 mL), dried over Na_2SO_4, and evaporated. Purification of the residue by column chromatography yielded the corresponding compounds **33**–**35**.

6.13.1. [5-(2-Methyl-thiazol-4-ylethynyl)-pyridin-3-yl]-methanol (33). Chromatography (EtOAc/Et_2O 3/7), yield 81%, yellow oil. ^1H NMR ($CDCl_3$) δ ppm: 2.71 (s, 3H, CH_3); 4.71 (d, 2H, J = 5.5 Hz, CH_2); 5.39 (br s, 1H, OH); 7.44 (s, 1H, CHAr); 7.84 (s, 1H, CHAr); 8.47 (d, 1H, J = 1.5 Hz, CHAr); 8.56 (d, 1H, J = 1.5 Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 19.1 (1C, CH_3); 61.3 (1C, CH_2); 85.4 (1C, C≡C); 86.5 (1C, C≡C); 119.4 (1C, Cq); 123.4 (1C, CHAr); 135.9 (1C, Cq); 137.0 (1C, Cq); 137.2 (1C, CHAr); 147.3 (1C, CHAr); 150.5 (1C, CHAr); 166.2 (1C, Cq). Hydrochloride mp 159–163 °C. MS (EI) *m/z* 230.2 (M). Anal. ($C_{12}H_{10}N_2OS$·HCl·0.5H_2O) C, H, N.

6.13.2. 4-(2-Methyl-thiazol-4-ylethynyl)-isoquinoline (34). Chromatography (hexane/Et_2O 4/6), yield 59%, colorless oil. ^1H NMR ($CDCl_3$) δ ppm: 2.77 (s, 3H, CH_3); 7.51 (s, 1H, CHAr); 7.65 (t, 1H, J = 7.0 Hz, CHAr); 7.79 (td, 1H, J = 7.0; 1.0 Hz, CHAr); 7.99 (d, 1H, J = 8.5 Hz, CHAr); 8.35 (d, 1H, J = 8.5 Hz, CHAr); 8.80 (s, 1H, CHAr); 9.21 (s, 1H, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 19.3 (1C, CH_3); 84.0 (1C, C≡C); 90.6 (1C, C≡C); 115.2 (1C, Cq); 123.1 (1C, CHAr); 125.2 (1C, CHAr); 127.7 (1C, Cq); 127.9 (1C, CHAr); 128.0 (1C, CHAr); 131.2 (1C, CHAr); 135.4 (1C, Cq); 136.6 (1C, Cq); 146.8 (1C, CHAr); 152.3 (1C, CHAr); 166.0 (1C, Cq). Hydrochloride mp 188–192 °C (dec). MS (EI) *m/z* 250.0 (M). Anal. ($C_{15}H_{10}N_2S$·2HCl) C, H, N.

6.13.3. 2-Methyl-4-(3-nitro-phenylethynyl)-thiazole (35). Chromatography (hexane/Et_2O 6/4), yield 76%, yellow solid; mp 107–109 °C. ^1H NMR ($CDCl_3$) δ ppm: 2.75 (s, 3H, CH_3); 7.46 (s, 1H, CHAr); 7.53 (t, 1H, J = 7.5 Hz, CHAr); 7.84 (dt, 1H, J = 7.5; 1.5 Hz, CHAr); 8.19 (ddd, 1H, J = 8.5; 2.5; 1.5 Hz, CHAr); 8.39 (t, 1H, J = 2.5 Hz, CHAr). ^{13}C NMR ($CDCl_3$) δ ppm: 19.2 (1C, CH_3); 85.9 (1C, C≡C); 86.2 (1C, C≡C); 123.2 (1C, CHAr); 123.6 (1C, CHAr); 124.3 (1C, Cq); 126.5 (1C, CHAr); 129.4 (1C, CHAr); 135.9 (1C, Cq); 137.2 (1C, CHAr); 148.1 (1C, Cq); 166.1 (1C, Cq). Hydrochloride mp 140–142 °C. MS (EI) *m/z* 244.1 (M). Anal. ($C_{12}H_8N_2O_2S$·0.9HCl) C, H, N.

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Supplementary data

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