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PAPER

Synthesis and evaluation of 1,2,4-methyltriazines as mGluR5 antagonists

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In previous studies we showed that 3-(substituted phenylethynyl)-5-methyl[1,2,4]triazine analogues of MPEP were potent antagonists of glutamate-mediated mobilization of internal calcium in an mGluR5 *in vitro* efficacy assay. In the present study we report the synthesis and evaluation of six 3-(substituted biphenylethynyl)-5-methyl[1,2,4]triazines (**5a–f**), and five 3-(substituted phenoxyphenylethynyl)-5-methyltriazines (**6a–e**). Compound 2-(4-fluorophenyl-5-[2-(5-methyl[1,2,4]triazine-3-yl)ethynyl]benzonitrile (**5f**) with an IC_{50} of 28.2 nM was the most potent analogue.

Introduction

L-Glutamic acid (**1**, glutamate) is a major excitatory neurotransmitter in the central nervous system (CNS) whose excitatory action is modulated by metabotropic glutamate receptors (mGluR). Metabotropic glutamate receptor 5 (mGluR5) has been the subject of great interest over the last several years as a target for the development of pharmacotherapies to treat drug addiction (cocaine, methamphetamine, opioids, nicotine, and alcohol). Chiamulera and co-workers reported that mice lacking the mGluR5 gene did not acquire cocaine self-administration (SA) or exhibit cocaine-induced hyperlocomotor activity at doses that did not affect responding for food.[1] The studies also showed that the selective mGluR5 antagonist MPEP (**2**) decreased cocaine SA in wildtype mice[1] and in rats.[2] Iso and co-workers showed that the more selective mGluR5 antagonist MTEP (**3**), which also displays higher *in vivo* potency, prevented the reinstatement of cocaine SA that can be induced by environmental cues associated with cocaine availability.[3] MPEP (**2**) decreased nicotine SA in rats and mice,[4,5] attenuated cocaine- and morphine-induced CPP in mice,[6,7] and decreased ethanol drinking and ethanol seeking (a relapse model) in rats.[8,9] MPEP (**2**) also attenuated cocaine SA and cocaine-induced reinstatement of drug seeking in squirrel monkeys.[10] MTEP (**3**) dose-dependently inhibited naloxone-induced symptoms of morphine withdrawal without effects on locomotor activity.[11] More recently, Gass and co-workers[12] reported that MTEP (**3**) attenuated the SA of methamphetamine as well as the reinforcing efficacy under a progressive ratio (PR) schedule of reinforcement. These authors also reported that MTEP (**3**) dose dependently prevented cue- and drug-priming induced reinstatement of methamphetamine-seeking behaviour.

In 2004 we reported the synthesis and evaluation of several phenylethynyl[1,2,4]methyltriazine for antagonism of glutamate-mediated mobilization of internal calcium in an mGluR5 *in vitro* assay.[13] In a separate study we found that 3-(4-phenoxyphenylethynyl)-5-methyl[1,2,4]triazine (**4a**) and 3-(3-methylphenylethynyl)-5-methyl[1,2,4]triazine (**4b**) were 41 and 16 times, respectively, more potent than MPEP in reversing morphine tolerance.[14] As a continuation of our earlier research, we report the synthesis and evaluation of six 3-(substituted biphenylethynyl)-5-methyl[1,2,4]triazines (**5a–f**) and five 3-(substituted 4-phenoxyphenylethynyl-5-methyl[1,2,4]triazines (**6a–e**) (see Table 1 for structures).

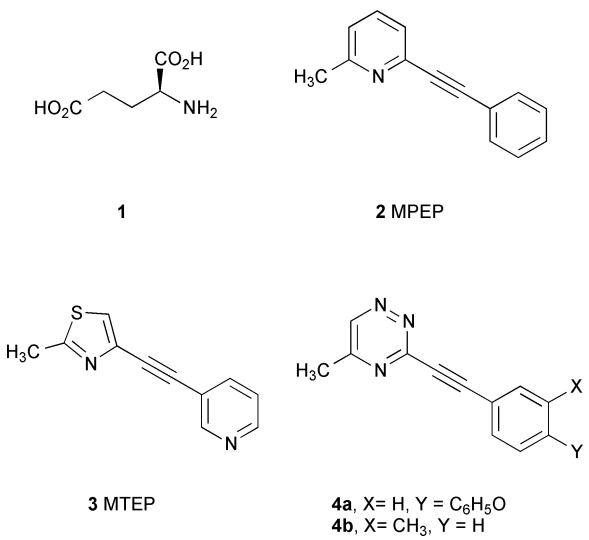

Fig. 1 mGluR5 antagonists.

Chemistry

In order to synthesize the highly functionalized biphenyl analogues **5a–f** and **6a–e**, the substituted biphenyl-alkyne intermediates **12a–c**, **15a–c**, and **20a–e** were synthesized using three different reaction pathways. The first series of biphenyl derivatives synthesized started with 4-hydroxybenzoate (**7**) being iodinated

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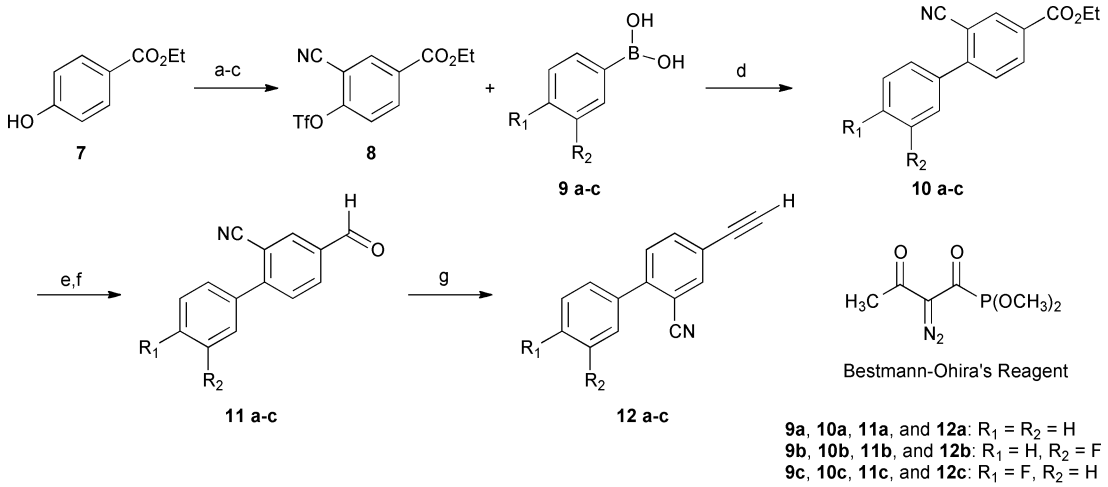
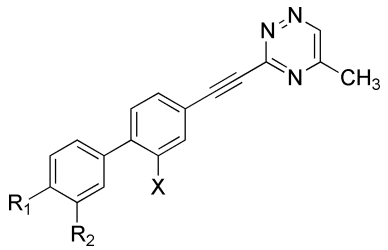


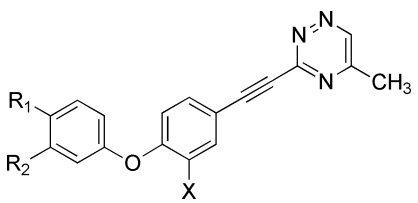
Reagents and conditions: (a) ICl, AcOH, 65 °C, 88% (b) CuCN, DMSO, 100 °C, 61% (c) Tf_2O, Et_3N, DMAP, CH_2Cl_2, 0° C, 84% (d) $Pd(PPh_3)_4$, K_2CO_3, Toluene, 140 °C, 77-89% (e) $LiBH_3$·Pyr, THF, 0° C, 87-89% (f) Dess-Martin Reagent, CH_2Cl_2, 0° C, 88-99% (g) Bestmann-Ohira's reagent, K_2CO_3, MeOH, 90-93%

Scheme 1 Synthesis of cyanobiphenyl analogues.

Table 1 Inhibition of human mGluR5-mediated intracellular calcium mobilization for biphenylethynyltriazine and phenoxyphenylethynyltriazine analogues[a]



Compound	X	R_2	R_1	IC_{50}/nM	*c*Log*P*
MPEP	—	—	—	13.5 ± 0.8	4.21
5a	CH_3	H	H	141± 61	4.91
5b	CH_3	F	H	247 ± 10	5.16
5c	CH_3	H	F	111 ± 16	4.84
5d	CN	H	H	50.0 ± 18.4	3.65
5e	CN	F	H	221 ± 12	3.91
5f	CN	H	F	28.2 ± 9.5	3.59

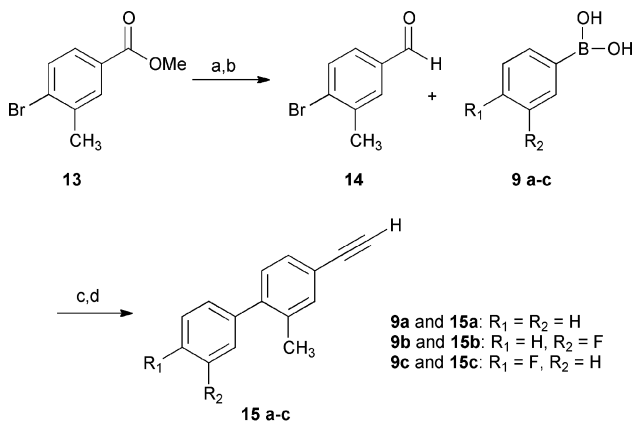


Compound	X	R_2	R_1	IC_{50}/nM	*c*Log*P*
MPEP	—	—	—	13.5 ± 0.8	4.21
6a	CH_3	H	H	1650 ± 374	5.14
6b	CH_3	H	F	1370 ± 323	5.43
6c	CH_3	F	H	1480 ± 89	5.33
6d	CN	H	H	259 ± 110	4.42
6e	CN	F	H	1320 ± 390	4.60

[a] IC_{50} data are listed as average ±SEM of three independent experiments.

with iodine monochloride in acetic acid (Scheme 1).[15] 3-Iodo-4-hydroxybenzoate was converted to **8** using copper cyanide to introduce the cyano groups and trifluoromethanesulfonic anhydride to add the triflate. This triflate **8** was cross-coupled with phenyl boronic acid (**9a**), 3-fluorophenyl boronic acid (**9b**), and 4-fluorophenyl boronic acid (**9c**), to produce the biphenyl compounds **10a–c**. The ester moiety in **10a–c** was reduced with lithium pyrrolidinoborohydride,[16] followed by oxidation of the alcohols to the aldehyde (**11a–c**) using Dess–Martin periodiate.[17] Finally the aldehyde was converted to the alkynes (**12a–c**) using the Bestman–Ohira reagent.[18]

The second series of biphenyl derivatives started with the reduction of methyl 4-bromo-3-methylbenzoate (**13**) with lithium aluminum hydride followed by oxidation to the aldehyde (**14**) using Dess–Martin periodinate (Scheme 2). This aldehyde could then be cross-coupled with the phenylboronic acid (**9a**), 3-fluorophenyl boronic acid (**9b**), and 4-fluorophenyl boronic acid (**9c**) to produce

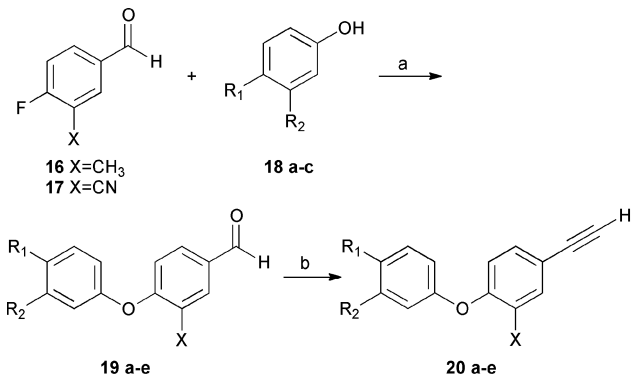


Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C, 94% (b) Dess-Martin Reagent, 0 °C, 81% (c) $Pd(PPh_3)_4$, K_2CO_3, Toluene, 140 °C, 83-96% (d) Bestmann-Ohira's reagent, K_2CO_3, MeOH, 84-97%

Scheme 2 Synthesis of methyl biphenyl analogues.

the desired biphenyl aldehydes. These aldehydes were converted to the alkynes (**15a–c**) using the Bestman–Ohira reagent.

The phenoxy intermediates **20a–e** were synthesized from 4-fluoro-3-methylbenzaldehyde (**16**), and 2-fluoro-5-formylbenzonitrile (**17**) (Scheme 3). Various phenols (**18a–c**) could be coupled with **16** and **17** in acetonitrile using caesium carbonate to give the aldehydes **19a–e**. The aldehydes (**19a–e**) were then converted to the alkynes (**20a–e**) using the Bestman–Ohira reagent.



Reagents and conditions: (a) $CsCO_3$, CH_3CN, 54-66% (b) Bestmann-Ohira's reagent, K_2CO_3, MeOH, 36-87%

Scheme 3 Synthesis of phenoxy acetylene compounds.

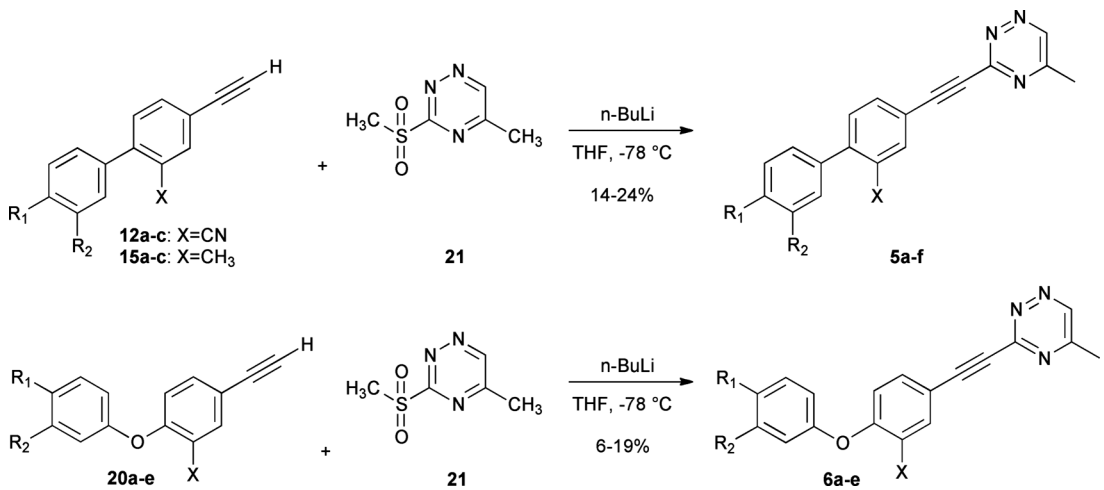
These biphenyl and phenoxy acetylenes **12a–c**, **15a–c**, and **20a–e** were deprotonated with butyl lithium and the corresponding lithium acetylide used to displace the methylsulfonyl group in the 5-methyl-3-sulfonyl[1,2,4]triazine (**21**) to give low to moderate yields of the desired products **5a–f** and **6a–e** (Scheme 4). These low yields were consistent with what has previously been observed for this type of reaction.[13]

In vitro pharmacology

CHO-K1 cells stably transfected with the human mGluR5 were used to determine the effects of MPEP and test compounds on glutamate-stimulated mobilization of internal calcium. Note that we had difficulty with the mGluR5 clone used in our previous study[13] and changed to a different clone for the IC_{50} determinations in the present study. This is the likely reason for the IC_{50} = 13.5 nM compared to 1.5 nM in our previous study. CHO-K1-mGluR5 cells were grown in standard Dulbecco's modified Eagle's medium (DMEM) supplemented with 10% fetal bovine serum, 15 mM Hepes, and 1 × penicillinstreptomycin (Invitrogen, Carlsbad, CA). Cells were plated in black-walled, clear-bottomed 96-well plates in 100 μL growth media and incubated overnight at 37 °C/5% CO_2. The next day the media was removed, and the cells were incubated with Hanks balanced salt solution (HBSS; Invitrogen) containing 20 mM HEPES, 2.74 mM Probenecid (Sigma–Aldrich, St. Louis, MO), and either 2.5 μg mL^{-1} Fluo4-AM dye (75-min incubation; Invitrogen) or Calcium 4 dye from the FLIPR Calcium 4 assay kit (60-min incubation; Molecular Devices Corporation, Sunnyvale, CA) at one-half the recommended dye concentration. For compound concentration–response curves, cells were pretreated in duplicate with vehicle or one of seven different concentrations of test compound or MPEP during the last 15 min of dye incubation. Fluorescence levels in each well before and after the addition of 530 nM glutamate (~EC60) were recorded in a FlexStation3 (Molecular Devices Corporation). The PEAK function of the SoftMax software was used to determine the change in fluorescence. IC_{50} values were calculated from a four-parameter logistic equation fit to the calcium flux concentration-response data using Prism (GraphPad Software, San Diego, CA).

Results and discussion

The six biphenylethynyltriazine analogues **5a–f** and five phenoxyphenylethynyltriazine analogues **6a–e** were synthesized and evaluated for antagonism of glutamate-mediated mobilization of internal calcium in an mGluR5 *in vitro* efficacy assay. The IC_{50} values are listed in Table 1 for **5a–f** and **6a–e**, respectively, along with the IC_{50} values for the standard mGluR5 antagonist



Scheme 4 Synthesis of biphenyl acetylene compounds.

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MPEP. The IC_{50} values for **5a–f** ranged from 28.2 to 247 nM. The highest affinity was observed for analogues with a 4-fluoro substituent (**5c** and **5f**), followed by an unsubstituted aromatic ring (**5a** and **5d**), while the fluorine substituent at the 3 position (**5b** and **5e**) showed the lowest affinity. The results also showed that the cyano substituted analogues (**5d–f**) were favored over those with a methyl group (**5a–c**) at the same position. Analogue **5f** with the IC_{50} value of 28.2 nM was the most potent analogue. Since MPEP has an IC_{50} value of 13.5 nM, **5f** is about one-half as potent as MPEP in this test. However, the *c*Log*P* value for **5f** is 0.62 log units lower than that of MPEP, suggesting that **5f** may have better brain penetration. In our previous studies we found that MPEP was 1.5 times more potent than **4b** in the mGluR5 *in vitro* efficacy assay, yet **4b** was 44 and 16 times more potent than MPEP in blocking the mGluR5 agonist (S)-3,5-DHPG-induced hyperalgesia and morphine antinociceptive tolerance, respectively.[13,14] These results suggest that these two compounds will also have good *in vivo* activity.

In our previous study, we also found that even though **4a** was more than 50 times less potent than MPEP in the mGluR5 *in vitro* efficacy assay, it was 26 and 41 times more potent than MPEP in blocking the mGluR5 agonist (S)-3,5-DHPG-induced hyperalgesia and morphine antinociceptive tolerance, respectively.[13,14] These highly encouraging results led us to synthesize and evaluate the 5-phenoxyphenylethynyltriazine analogues **6a–e**. These analogues were about 10 times less potent than the biphenyl analogues but showed the same trend as the biphenyl analogues where the 3-cyano substituted analogues (**6d** and **6e**) is preferred over the methyl substituted analogues. Compound **6d** with an IC_{50} of 259 nM in the mGluR5 *in vitro* efficacy test was the most potent analogue. Even though **6d** is 19 times less potent than MPEP in this *in vitro* efficacy assay, it is much more potent than **4a** was relative to MPEP.[13]

Conclusions

In summary, six 3-(substituted biphenylethynyl)-5-methyl[1,2,4]triazines (**5a–f**) and five 3-(substituted 4-phenoxyphenylethynyl)-5-methyl[1,2,4]triazines (**6a–e**) were synthesized and evaluated for their ability to antagonize glutamate-mediated mobilization of internal calcium in an mGluR5 *in vitro* efficacy assay. The biphenyl analogues **5a–f** had low nanomolar potency in the assay. Analogue **5f** with an IC_{50} of 28.2 nM was the most potent analogue. Moderate potency was observed for the phenoxy analogues **6a–e**. Analogue **6d** with an IC_{50} of 259 nM was the most potent in the assay. Since the potencies of **5f** and **6d** compare favourably with those of **4a** and **4b**, which had potent activity in antagonising morphine tolerance, these compounds may also have good *in vivo* activity.

Experimental

Commercial reagents and solvents were used as received. All reactions were run under dry N_2 in oven-dried glassware. The $NaHCO_3$ (saturated) used in various procedures refers to saturated aqueous solution. Unless otherwise specified, all organic solvents were anhydrous and used as received. Reactions were monitored by TLC on silica gel GF plates. Preparative separations were performed using flash column chromatography on silica gel (grade 62, 60–200 mesh). Fraction elution was monitored using a hand-held UV lamp. Melting points were uncorrected. ^{1}H NMR and ^{13}C NMR spectra were measured using a Bruker Advance DPX-300 MHz spectrometer in $CDCl_3$ or DMSO-d_6, at 300 and 75 MHz, respectively, and were referenced to internal $(CH_3)_4Si$. Purity of compounds (>95%) was established by elemental analysis. Elemental analysis was conducted by Atlantic Microlab, Norcross, GA. Results were within ± 0.4% of calculated values.

5-Methyl-3-[2-(3-methyl-4-phenylphenyl)ethynyl] [1,2,4]triazine (5a)

To a well-stirred solution of 660 mg (3.43 mmol) 4-ethynyl-2-methylbiphenyl (**15a**) in anhydrous THF at −78 °C was added 1.45 mL (3.68 mmol) 2.5 M solution of BuLi in hexanes, and the mixture was stirred for 1 h. This mixture was transferred by cannulation under N_2 pressure to a well-stirred solution of 540 mg (3.12 mmol) 5-methyl-3-sulfonyl[1,2,4]triazine (**21**) in anhydrous THF at −78 °C. The mixture was stirred at −78 °C for 30 min and slowly allowed to warm to room temperature. After the mixture was stirred for 2 h at room temperature, 25 mL of $NaHCO_3$ (saturated) was added and the organic layers extracted into Et_2O, combined, then dried over anhydrous Na_2SO_4 and concentrated to obtain a dark red oil. Column chromatography on silica gel using EtOAc–hexanes (1 : 1) as the eluent afforded 205 mg (23%) of **5a** as an off-white solid. The analytical sample was recrystallized from $(CH_3)_2CHOH$–heptane (9 : 1): mp 112–114 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 9.05 (s, 1H), 7.64 (s, 1H), 7.57 (d, 1H, J = 3 Hz), 7.34 (m, 6H), 2.63 (s, 3H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$) δ/ppm: 159.2, 154.3, 147.5, 144.1, 140.9, 135.9, 134.6, 130.1, 130.0, 128.9, 128.2, 127.3, 119.5, 92.4, 85.7, 21.7, 20.3. MS (ESI) m/z 286.5 $(M + H)^+$. Elemental calcd C 79.98, H 5.30, N 14.73; found C 79.87, H 5.34, N 14.65.

3-{2-[4-(3-Fluorophenyl)-3-methylphenyl]ethynyl}-5-methyl-[1,2,4]triazine (5b). To a well-stirred solution of 656 mg (3.12 mmol) 4-ethynyl-1-(3-fluorophenyl)-2-methylbenzene (**15b**) in anhydrous THF at −78 °C was added 1.61 mL (3.62 mmol) 2.25 M solution of BuLi in hexanes, and the mixture was stirred for 1 h. This mixture was transferred by cannulation under N_2 pressure to a well-stirred solution of 660 mg (3.43 mmol) 5-methyl-3-sulfonyl[1,2,4]triazine (**21**) in anhydrous THF at −78 °C. The mixture was stirred at −78 °C for 1 h and slowly allowed to warm to room temperature. After the mixture was stirred for 2 h at room temperature, 25 mL of $NaHCO_3$ (saturated) was added and the organic layers extracted into Et_2O, combined, then dried over anhydrous Na_2SO_4 and concentrated to obtain a dark red oil. Column chromatography on silica gel using EtOAc–hexanes (1 : 1) as the eluent afforded 228 mg (24%) of **5b** as an off-white solid: mp 118–119 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 9.06 (s, 1H), 7.64 (s, 1H), 7.58 (d, 1H, J = 9 Hz), 7.39 (m, 1H), 7.25 (d, 1H, J = 9 Hz), 7.08 (m, 3H), 2.63 (s, 3H), 2.29 (s, 3H). ^{13}C NMR ($CDCl_3$) δ/ppm: 164.2, 160.9, 159.2, 154.2, 147.6, 143.0 (d, J_{cf} = 8.25 Hz), 142.6 (d, J_{cf} = 1.5 Hz), 135.8, 134.7, 130.1, 129.8 (d, J_{cf} = 9.75 Hz), 124.7 (d, J_{cf} = 3 Hz), 120.0, 115.9 (d, J_{cf} = 21.75 Hz), 114.2 (d, J_{cf} = 21 Hz), 92.0, 85.9, 21.8, 20.2. MS (ESI) m/z 304.54 $(M + H)^+$. Elemental calcd C 75.23, H 4.65, N 13.85; found C 75.00, H 4.59, N 13.71.

3-{2-[4-(4-Fluorophenyl)-3-methylphenyl]ethynyl}-5-methyl-[1,2,4]triazine (5c). To a well-stirred solution of 656 mg (3.12 mmol) 4-ethynyl-1-(4-fluorophenyl)-2-methylbenzene (**15c**) in anhydrous THF at −78 °C was added 1.61 mL (3.62 mmol) 2.25 M solution of BuLi in hexanes, and the mixture stirred for 1 h. This mixture was transferred by cannulation under N_2 pressure to a well-stirred solution of 660 mg (3.43 mmol) 5-methyl-3-sulfonyl[1,2,4]triazine (**21**) in anhydrous THF at −78 °C. The mixture was stirred at −78 °C for 1 h and slowly allowed to warm to room temperature. After the mixture was stirred for 2 h at room temperature, 25 mL of $NaHCO_3$ (saturated) was added and the organic layers were extracted into Et_2O, combined, then dried over anhydrous Na_2SO_4 and concentrated to obtain a dark red oil. Column chromatography on silica gel using EtOAc–hexanes (1 : 1) as the eluent afforded 137 mg (14%) of **5c** as an off-white solid: mp 117–119 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 9.05 (s, 1H), 7.63 (s, 1H), 7.58 (d, 1H, J = 9 Hz), 7.26 (m, 3H), 7.13 (m, 2H), 2.63 (s, 3H), 2.27 (s, 3H). ^{13}C NMR ($CDCl_3$) δ/ppm: 163.8, 160.6, 159.2, 154.2, 147.5, 142.9, 136.8, 135.9, 134.6, 130.6 (d, J_{cf} = 7.5 Hz), 130.1 (d, J_{cf} = 6 Hz), 119.7, 115.3, 115.0, 92.2, 85.8, 21.8, 20.3. MS (ESI) m/z 304.5 $(M + H)^+$. Elemental calcd C 75.23, H 4.65, N 13.85; found C 74.99, H 4.62, N 13.73.

5-[2-(5-Methyl[1,2,4]triazin-3-yl)ethynyl]-2-phenylbenzonitrile (5d). To a well-stirred solution of 671 mg (3.30 mmol) 5-ethynyl-2-phenylbenzonitrile (**12a**) in anhydrous THF (20 mL) at −78 °C was added 1.40 mL (3.48 mmol) 2.5 M solution of BuLi in hexanes, and the mixture stirred for 1 h. This mixture was transferred by cannulation under N_2 pressure to a well-stirred solution of 519 mg (3.00 mmol) 5-methyl-3-sulfonyl[1,2,4]triazine (**21**) in anhydrous THF (15 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h and slowly allowed to warm to room temperature. After the mixture was stirred for 2 h at room temperature, 25 mL of $NaHCO_3$ (saturated) was added and the organic layers extracted into Et_2O, combined, then dried over anhydrous Na_2SO_4 and concentrated to obtain a dark red oil. Column chromatography on silica gel using EtOAc–hexanes (1 : 1) as the eluent afforded 189 mg (21%) of **5d** as a yellow solid. The analytical sample was recrystallized from ethanol: mp 172–174 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 9.10 (s, 1H), 8.08 (d, 1H, J = 3 Hz), 7.94 (dd, 1H, J = 9 Hz, 3 Hz), 7.58 (m, 6H), 2.65 (s, 3H); ^{13}C NMR ($CDCl_3$) δ/ppm: 159.4, 153.7, 147.9, 146.6, 137.5, 137.2, 136.4, 130.5, 129.4, 128.9, 128.7, 120.8, 117.5, 112.1, 88.7, 87.6, 21.8. MS (ESI) m/z 296.9 $(M + H)^+$. Elemental calcd C 77.01, H 4.08, N 18.91; found C 76.73, H 3.89, N 18.71.

2-(3-Fluorophenyl)-5-[2-(5-methyl[1,2,4]triazin-3-yl)ethynyl]-benzonitrile (5e). To a well-stirred solution of 730 mg (3.30 mmol) 5-ethynyl-2-(3-fluorophenyl)benzonitrile (**12b**) in anhydrous THF (20 mL) at −78 °C was added 1.40 mL (3.48 mmol) 2.5 M solution of BuLi in hexanes, and the mixture stirred for 1 h. This mixture was transferred by cannulation under N_2 pressure to a well-stirred solution of 519 mg (3.00 mmol) 5-methyl-3-sulfonyl[1,2,4]triazine (**21**) in anhydrous THF (15 mL) at -78 °C. The mixture was stirred at −78 °C for 1 h and slowly allowed to warm to room temperature. After the mixture was stirred for 2 h at room temperature, 25 mL of $NaHCO_3$ (saturated) was added and the organic layers were extracted into Et_2O, combined, then dried over anhydrous Na_2SO_4 and concentrated to obtain a dark red oil. Column chromatography on silica gel using EtOAc–hexanes (1 : 1) as the eluent afforded 157 mg (17%) of **5e** as an off-white solid. The analytical sample was recrystallized from ethanol: mp 225–227 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 9.11 (s, 1H), 8.09 (d, 1H, J = 3 Hz), 7.95 (dd, 1H, J = 9 Hz, 3 Hz), 7.57 (d, 1H, J = 9 Hz), 7.49 (m, 1H), 7.38 (d, 1H, J = 9 Hz), 7.29 (m, 1H), 7.17 (m, 1H), 2.65 (s, 3H); ^{13}C NMR ($CDCl_3$) δ/ppm: 164.4, 161.1, 159.4, 153.7, 148.0, 145.1, 139.1 (d, J_{cf} = 8.25 Hz), 137.5, 136.5, 130.6 (d, J_{cf} = 8.25 Hz), 130.4, 124.5 (d, J_{cf} = 3 Hz), 121.4, 117.1, 116.3 (d, J_{cf} = 21 Hz), 115.8 (d, J_{cf} = 23.25 Hz), 112.1, 88.4, 87.9, 21.8. MS (ESI) m/z 315.3 $(M + H)^+$. Elemental calcd C 72.60, H 3.53, N 17.83; found C 72.62, H 3.47, N 17.69.

2-(4-Fluorophenyl)-5-[2-(5-methyl[1,2,4]triazin-3-yl)ethynyl]-benzonitrile (5f). To a well-stirred solution of 730 mg (3.30 mmol) 5-ethynyl-2-(4-fluorophenyl)benzonitrile (**12c**) in anhydrous THF (20 mL) at −78 °C was added 1.40 mL (3.48 mmol) of 2.5 M solution of BuLi in hexanes, and the mixture was stirred for 1 h. This mixture was transferred by cannulation under N_2 pressure to a well-stirred solution of 519 mg (3.00 mmol) 5-methyl-3-sulfonyl[1,2,4]triazine (**21**) in anhydrous THF (15 mL) at −78 °C. The mixture was stirred at −78 °C for 1 h and slowly allowed to warm to room temperature. After the mixture was stirred for 2 h at room temperature, 25 mL of $NaHCO_3$ (saturated) was added and the organic layers were extracted into Et_2O, combined, then dried over anhydrous Na_2SO_4 and concentrated to obtain a dark red oil. Column chromatography on silica gel using EtOAc–hexanes (1 : 1) as the eluent afforded 188 mg (20%) of **5f** as a yellow solid. The analytical sample was recrystallized from ethanol: mp 203–204 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 9.11 (s, 1H), 8.06 (s, 1H), 7.93 (d, 1H, J = 6 Hz), 7.39 (m, 1H), 7.56 (m, 3H), 7.22 (m, 2H), 2.65 (s, 3H). ^{13}C NMR ($CDCl_3$) δ/ppm: 165.1, 161.8, 159.5, 153.7, 148.0, 145.5, 137.5, 136.5, 133.2 (d, J_{cf} = 3.75 Hz), 130.6 (d, J_{cf} = 8.25 Hz), 130.4, 120.9, 117.4, 116.2, 115.9, 112.0, 88.5, 87.8, 21.8. MS (ESI) m/z 315.3 $(M + H)^+$. Elemental calcd C 72.60, H 3.53, N 17.83; found C 72.44, H 3.50, N 17.78.

5-Methyl-3-[2-(3-methyl-4-phenoxyphenyl)ethynyl][1,2,4]triazine (6a). To a well-stirred solution of 481 mg (2.31 mmol) 4-ethynyl-2-methyl-1-phenoxybenzene (**20a**) in anhydrous THF at −78 °C was added 1.0 mL (2.54 mmol) 2.5 M solution of BuLi in hexanes, and the mixture was stirred for 1 h. This mixture was transferred by cannulation under N_2 pressure to a well-stirred solution of 400 mg (2.31 mmol) 5-methyl-3-sulfonyl[1,2,4]triazine (**21**) in anhydrous THF at −78 °C. The mixture was stirred at −78 °C for 30 min and slowly allowed to warm to room temperature. After the mixture was stirred for 2 h at room temperature, 25 mL of $NaHCO_3$ (saturated) was added and the organic layers were extracted into Et_2O, combined, then dried over anhydrous Na_2SO_4 and concentrated to obtain a dark red oil. Column chromatography on silica gel using EtOAc–hexanes (1 : 1) as the eluent afforded 53 mg (8%) of **6a** as a white solid. The analytical sample was recrystallized from ethanol: mp 104–105 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 9.03 (s, 1H), 7.61 (s, 1H), 7.50 (d, J = 9 Hz, 1H), 7.36 (m, 2H), 7.14 (t, J = 8 Hz, 1H), 7.00 (d, J = 8 Hz, 2H), 6.83 (d, J = 8 Hz, 1H) 2.61 (s, 3H), 2.32 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 159.1, 157.2, 156.5, 154.3, 147.4, 135.9, 131.9, 129.9, 129.7, 123.6, 118.8, 117.9, 115.3, 101.6, 92.4, 85.2, 21.8, 16.1; MS (ESI) m/z 302.6 $(M + H)^+$. Elemental calcd C 75.73, H 5.02, N 13.94; found C 75.88, H 4.99, N 13.90.

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3-{2-[4-(4-Fluorophenoxy)-3-methylphenyl]ethynyl}-5-methyl-[1,2,4]triazine (6b). To a well-stirred solution of 523 mg (2.31 mmol) 4-(4-fluorophenoxy)-3-methylbenzaldehyde (**20b**) in anhydrous THF at −78 °C was added 1.0 mL (2.54 mmol) 2.5 M solution of BuLi in hexanes, and the mixture was stirred for 1 h. This mixture was transferred by cannulation under N_2 pressure to a well-stirred solution of 400 mg (2.31 mmol) 5-methyl-3-sulfonyl[1,2,4]triazine (**21**) in anhydrous THF at −78 °C. The mixture was stirred at −78 °C for 30 min and slowly allowed to warm to room temperature. After the mixture was stirred for 2 h at room temperature, 25 mL of $NaHCO_3$ (saturated) was added, and the organic layers were extracted into Et_2O, combined, then dried over anhydrous Na_2SO_4 and concentrated to obtain a dark red oil. Column chromatography on silica gel using EtOAc–hexanes (1 : 1) as the eluent afforded 138 mg (19%) of **6b** as a yellow solid. The analytical sample was recrystallized from ethanol: mp 115–117 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 9.03 (s, 1H), 7.61 (s, 1H), 7.49 (d, J = 8 Hz, 1H), 7.06 (t, J = 8 Hz, 2H), 6.99 (m, 2H), 6.76 (d, J = 9 Hz, 1H), 2.61 (s, 3H), 2.31 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 160.7, 159.1, 157.5, 154.3, 152.2, 147.4, 135.9, 131.9, 129.3, 120.5, 120.4, 117.1, 116.6, 116.3, 115.3, 92.3, 85.2, 21.8, 16.0. MS (ESI) m/z 320.2 $(M + H)^+$. Elemental calcd C 71.46, H 4.42, N 13.16; found C 71.19, H 4.27, N 13.02.

3-{2-[4-(3-Fluorophenoxy)-3-methylphenyl]ethynyl}-5-methyl-[1,2,4]triazine (6c). To a well-stirred solution of 523 mg (2.31 mmol) 4-(3-fluorophenoxy)-3-methylbenzaldehyde (**20c**) in anhydrous THF at −78 °C was added 1.0 mL (2.54 mmol) 2.5 M solution of BuLi in hexanes, and the mixture was stirred for 1 h. This mixture was transferred by cannulation under N_2 pressure to a well-stirred solution of 400 mg (2.31 mmol) 5-methyl-3-sulfonyl[1,2,4]triazine (**21**) in anhydrous THF at −78 °C. The mixture was stirred at −78 °C for 30 min and slowly allowed to warm to room temperature. After the mixture was stirred for 2 h at room temperature, 25 mL of $NaHCO_3$ (saturated) was added, and the organic layers were extracted into Et_2O, combined, then dried over anhydrous Na_2SO_4 and concentrated to obtain a dark red oil. Column chromatography on silica gel using EtOAc–hexanes (1 : 1) as the eluent afforded 63 mg (9%) of **6c** as a yellow solid. The analytical sample was recrystallized from ethanol: mp 110–111 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 9.04 (s, 1H), 7.63 (s, 1H), 7.54 (d, J = 9 Hz, 1H), 7.30 (m, 2H), 6.60–6.92 (m, 4H), 2.62 (s, 3H), 2.27 (s, 3H); ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 165.3, 159.1, 156.1, 154.3, 147.5, 136.0, 132.0, 130.7, 130.6, 130.2, 119.0, 116.4, 113.7, 113.6, 110.4, 110.1, 106.1, 105.8, 91.9, 85.4, 21.8, 15.9. MS (ESI) m/z 320.0 $(M + H)^+$. Elemental calcd C 71.46, H 4.42, N 13.16; found C 71.24, H 4.27, N 13.07.

5-[2-(5-Methyl[1,2,4]triazin-3-yl)ethynyl]-2-phenoxybenzonitrile (6d). To a well-stirred solution of 550 mg (2.51 mmol) 5-ethynyl-2-phenoxybenzonitrile (**20d**) in anhydrous THF at −78 °C was added 1.1 mL (2.76 mmol) 2.5 M solution of BuLi in hexanes, and the mixture was stirred for 1 h. This mixture was transferred by cannulation under N_2 pressure to a well-stirred solution of 434 mg (2.51 mmol) 5-methyl-3-sulfonyl[1,2,4]triazine (**21**) in anhydrous THF at −78 °C. The mixture was stirred at −78 °C for 30 min and slowly allowed to warm to room temperature. After the mixture was stirred for 2 h at room temperature, 25 mL of $NaHCO_3$ (saturated) was added, and the organic layers were extracted into Et_2O, combined, then dried over anhydrous Na_2SO_4, and concentrated to obtain a dark red oil. Column chromatography on silica gel using EtOAc–hexanes (1 : 1) as the eluent afforded 48 mg (6%) of **6d** as a yellow solid. The analytical sample was recrystallized from $(CH_3)_2CHOH$: mp 164–165 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 9.07 (s, 1H), 7.98 (s, 1H), 7.76 (d, J = 9 Hz 1H), 7.46 (t, J = 8 Hz, 2H), 7.29 (t, J = 8 Hz, 1H), 7.15 (d, J = 7 Hz, 2H), 6.86 (d, J = 8 Hz, 1H), 2.63 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 161.0, 159.3, 154.0, 153.8, 147.8, 138.2, 138.0, 130.4, 125.9, 120.6, 116.4, 115.5, 114.7, 104.1, 88.9, 86.4, 21.8. MS (ESI) m/z 313.5 $(M + H)^+$. Elemental calcd C 73.07, H 3.89, N 17.94; found C 73.16, H 3.79, N 17.79.

2-(3-Fluorophenoxy)-5-[2-(5-methyl[1,2,4]triazin-3-yl)ethynyl]-benzonitrile (6e). To a well-stirred solution of 180 mg (0.76 mmol) 5-ethynyl-2-(3-fluorophenoxy)benzonitrile (**20e**) in anhydrous THF at −78 °C was added 0.33 mL (0.82 mmol) 2.5 M solution of BuLi in hexanes, and the mixture was stirred for 1 h. This mixture was transferred by cannulation under N_2 pressure to a well-stirred solution of 0.131 g (0.76 mmol) 5-methyl-3-sulfonyl[1,2,4]triazine (**21**) in anhydrous THF at −78 °C. The mixture was stirred at −78 °C for 30 min and slowly allowed to warm to room temperature. After the mixture was stirred for 2 h at room temperature, 25 mL of $NaHCO_3$ (saturated) was added, and the organic layers were extracted into Et_2O, combined, then dried over anhydrous Na_2SO_4 and concentrated to obtain a dark red oil. Column chromatography on silica gel using EtOAc–hexanes (1 : 1) as the eluent afforded 37 mg (15%) of **6e** as a yellow solid. The analytical sample was recrystallized from ethanol: mp 189–190 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 9.08 (s, 1H), 7.99 (s, 1H), 7.80 (d, J = 9 Hz 1H), 7.41 (m, 1H), 6.90 (m, 4H), 2.63 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 165.2, 161.9, 160.1, 159.4, 155.3, 155.2, 153.8, 147.9, 138.2, 138.1, 131.3, 131.2, 117.0, 116.3, 116.0, 115.9, 114.4, 113.0, 112.8, 108.5, 108.2, 104.6, 88.5, 86.7, 21.8; MS (ESI) m/z 331.2 $(M + H)^+$. Elemental calcd C 69.09, H 3.36, N 16.96; found C 69.20, H 3.24, N 16.87.

Ethyl 4-hydroxy-3-iodobenzoate. Ethyl 4-hydroxybenzoate (**7**, 25.6 g, 0.152 mol) was dissolved in AcOH (50 mL) at 65 °C. A solution of ICl (25.0 g, 0.152 mol) in AcOH (125 mL) was added dropwise, and the mixture was stirred at 65 °C for 6 h. The reaction mixture was added to a mixture of ice-water, filtered, and the resulting solid was washed with water. The solid was dissolved in CH_2Cl_2, dried over Na_2SO_4, filtered, and concentrated to obtain the crude product. Column chromatography on silica using EtOAc–hexanes (1 : 4) as the eluent afforded 39.4 g (88%) of ethyl 4-hydroxy-3-iodobenzoate as a white solid. Spectral data matches previously reported data.[15]

Ethyl 4-hydroxy-3-cyanobenzoate. Ethyl 4-hydroxy-3-iodobenzoate (39.5 g, 0.135 mol) was dissolved in DMSO (110 mL) at 100 °C. Copper(I) cyanide (13.3 g, 0.149 mol) was added, and the mixture was stirred at 100 °C for 24 h. The reaction was cooled to room temperature, added to ice–water, filtered, and the resulting solid washed with water. The solid was dissolved in EtOAc, filtered through Celite, dried over Na_2SO_4, filtered, and concentrated to obtain 15.87 g (61%) of ethyl 4-hydroxy-3-cyanobenzoate as a white solid. Spectral data matches previously reported data.[15]

Ethyl 3-cyano-4-trifluoromethanesulfonyloxybenzoate (8). Ethyl 4-hydroxy-3-cyanobenzoate (15.9 g, 0.083 mol) was

dissolved in CH_2Cl_2 (333 mL) at 0 °C. Triethylamine (12.6 g, 0.124 mol) and DMAP (1.52 g, 0.013 mol) were added, and Tf_2O (35.1 g, 0.125 mol) was added dropwise over 30 min. The reaction mixture was stirred for 2 h, then concentrated to obtain the crude product. Column chromatography on silica using EtOAc–hexanes (1 : 4) as the eluent afforded 22.4 g (84%) of **8** as a white solid. Spectral data matches previously reported data.[15]

Ethyl 3-cyano-4-phenylbenzoate (10a). To a suspension of ethyl 3-cyano-4-trifluoromethanesulfonyloxybenzoate (**8**, 5.10 g, 0.0158 mol) and phenylboronic acid (**9a**, 2.31 g, 0.0189 mol) in toluene (75 mL) was added K_2CO_3 (3.26 g, 0.0237 mol) and $Pd(PPh_3)_4$ (911 mg, 0.79 mmol), and the mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and added to a mixture of EtOAc and water (1 : 1). The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography of the resulting residue on silica gel using Et_2O–hexanes (4 : 1) as the eluent gave 3.51 g (89%) of **10a** as a white solid: mp 64–67 °C.^{1}H NMR ($CDCl_3$) δ/ppm: 8.44 (s, 1H), 8.28 (d, 1H, J = 9 Hz), 7.58 (m, 5H), 4.45 (q, 2H), 1.43 (t, 3H). ^{13}C NMR ($CDCl_3$) δ/ppm: 164.6, 149.2, 137.2, 135.0, 133.6, 130.3, 130.0. 129.4, 128.9, 128.7, 117.9, 111.6, 61.7, 14.3. MS (ESI) m/z 249.2 $(M - H)^+$. Elemental calcd C 76.48, H 5.21, N 5.57; found C 76.22, H 5.13, N 5.41.

Ethyl 3-cyano-4-(3-fluorophenyl)benzoate (10b). To a suspension of ethyl 3-cyano-4-trifluoromethanesulfonyloxy benzoate (**8**, 3.23 g, 0.010 mmol) and 3-fluorophenylboronic acid (**9b**, 1.67 g, 0.012 mol) in toluene (50 mL) was added K_2CO_3 (2.07 g, 0.015 mol) and $Pd(PPh_3)_4$ (578 mg, 0.5 mmol), and the mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and added to a mixture of EtOAc and water (1 : 1). The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography of the resulting residue on silica gel using Et_2O–hexanes (4 : 1) as the eluent gave 2.02 g (77%) of **10b** as a white solid: mp 92–95 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 8.45 (s, 1H), 8.30 (d, 1H, J = 6 Hz), 7.59 (d, 1H, J = 9 Hz), 7.49 (m, 1H), 7.38 (d, 1H, J = 6 Hz), 7.28 (d, 1H, J = 12 Hz), 7.20 (m, 2H), 4.45 (q, 2H), 1.44 (t, 3H). ^{13}C NMR ($CDCl_3$) δ/ppm: 164.4, 161.1, 147.7, 139.2 (d, J_{cf} = 7 Hz), 135.0, 133.7, 130.6, 130.5 (d, J_{cf} = 4.5 Hz), 124.5 (d, J_{cf} = 3 Hz), 117.5, 116.4 (d, J_{cf} = 21 Hz), 115.8 (d, J_{cf} = 22.5 Hz), 111.7, 61.8, 14.3. MS (ESI) m/z 268.3 $(M - H)^+$. Elemental calcd C 71.37, H 4.49, N 5.20; found C 70.98, H 4.55, N 5.24.

Ethyl 3-cyano-4-(4-fluorophenyl)benzoate (10c). To a suspension of ethyl 3-cyano-4-trifluoromethanesulfonyloxy benzoate (**8**, 3.23 g, 0.010 mol) and 4-fluorophenylboronic acid (**9c**, 1.67 g, 0.012 mol) in toluene (50 mL) was added K_2CO_3 (2.07 g, 0.015 mmol) and $Pd(PPh_3)_4$ (578 mg, 0.5 mmol), and the mixture was refluxed for 2 h. The reaction mixture was cooled to room temperature and added into a mixture of EtOAc and water (1 : 1). The organic layer was washed with water and brine, dried on (Na_2SO_4), and concentrated under reduced pressure. Column chromatography of the resulting residue on silica gel using Et_2O–hexanes (4 : 1) as the eluent gave 2.15 g (82%) of **16c** as a white solid: mp 79–81 °C. ^{1}H NMR ($CDCl_3$) δ /ppm: 8.44 (d, 1H, J = 3 Hz), 8.29 (d, 1H, J = 6 Hz), 7.57 (m, 3H), 7.22 (m, 2H), 4.44 (q, 2H), 1.44 (t, 3H). ^{13}C NMR ($CDCl_3$) δ/ppm: 165.2, 164.5, 161.8, 148.1, 135.0, 133.6, 133.2 (d, J_{cf} = 3 Hz), 130.6 (d, J_{cf} = 8.25 Hz), 130.2, 117.4, 116.2. 115.9, 111.6, 61.8, 14.3. MS (ESI) m/z 268.2 $(M - H)^+$. Elemental calcd C 71.37, H 4.49, N 5.20; found C 71.22, H 4.40, N 5.07.

5-Formyl-2-phenylbenzonitrile (11a). Ethyl 3-cyano-4-phenylbenzoate (**10a**, 3.01 g, 0.0119 mol) was dissolved in anhydrous THF (50 mL) and cooled to 0 °C. A 1 M solution of lithium pyrrolidinoborohydride (14.4 mL, 14.4 mmol) was added, and the mixture was stirred for 2 h at room temperature. The reaction mixture was quenched by dropwise addition of 3 N HCl, followed by extraction into Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography of the resulting residue on silica gel using EtOAc–hexanes (2 : 5) as the eluent yielded 2.23 g (89%) of 5-(hydroxymethyl)-2-phenylbenzonitrile as a white solid. The 5-(hydroxymethyl)-2-phenylbenzonitrile (2.23 g, 0.0107 mol) was dissolved in CH_2Cl_2 (100 mL), cooled to 0 °C, and treated with Dess–Martin periodinate (6.78 g, 0.016 mol). After 3 h the reaction mixture was quenched with a mixture of saturated sodium thiosulfate-sodium bicarbonate (1 : 1) and stirred for 30 min. The organic layer was washed with sodium thiosulfate-sodium bicarbonate, brine, dried (Na_2SO_4), and concentrated under reduced pressure. Column chromatography of the resulting residue on silica gel using Et_2O–hexane (2 : 3) as the eluent gave 2.18 g (99%) of **11a** as a white solid: mp 158–161 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 10.08 (s, 1H), 8.27 (d, 1H, J = 3 Hz), 8.15 (dd, 1H, J = 9 Hz, 4.5 Hz), 7.72 (d, 1H, J = 9 Hz), 7.58 (m, 5H). ^{13}C NMR ($CDCl_3$) δ /ppm: 189.7, 150.6, 136.9, 135.2, 132.9, 131.0, 129.7, 128.9, 128.7, 117.6, 112.4. MS (ESI) m/z 206.3 $(M - H)^+$. Elemental calcd C 81.14, H 4.38, N 6.76; found C 80.99, H 4.32, N 6.80.

2-(3-Fluorophenyl)-5-formylbenzonitrile (11b). Ethyl-3-cyano-4-(3-fluorophenyl) benzoate (**10b**, 2.04 g, 0.00758 mol) was dissolved in anhydrous THF (40 mL) and cooled to 0 °C. A 1 M solution of lithium pyrrolidinoborohydride (9.09 mL, 9.09 mmol) was added, and the mixture was stirred for 5 h at room temperature. The reaction mixture was quenched by dropwise addition of 3 N HCl, followed by extraction into Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using EtOAc-hexanes (2 : 3) as the eluent to obtain 1.5 g (87%) of 2-(3-fluorophenyl)-5-(hydroxymethyl)benzonitrile as a white solid. The 2-(3-fluorophenyl)-5-(hydroxymethyl) benzonitrile (1.50 g, 0.0066 mol) was dissolved in CH_2Cl_2 (75 mL), cooled to 0 °C, and treated with Dess–Martin periodinate (4.20 g, 0.009 mol). After 3 h the reaction mixture was quenched with saturated sodium thiosulfate-sodium bicarbonate solution (1 : 1) and stirred for 30 min. The organic layer was washed with sodium thiosulfate-sodium bicarbonate solution, brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using EtOAc–hexanes (2 : 3) as the eluent to obtain 1.4 g (94%) of **11b** as a white solid: mp 150–153 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 10.09 (s, 1H), 8.28 (d, 1H, J = 3 Hz), 8.17 (dd, 1H, J = 9 Hz, 3 Hz), 7.70 (d, 1H, J = 9 Hz), 7.53 (m, 1H), 7.40 (m, 1H), 7.24 (m, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 189.5, 164.4, 161.1, 149.1 (d, J_{cf} = 2.25 Hz), 138.9 (d, J_{cf} = 8.25 Hz), 135.7, 135.2, 133.1, 130.9, 130.7 (d, J_{cf} = 8.25 Hz), 124.5 (d, J_{cf} = 3 Hz), 117.2, 116.7 (d, J_{cf} = 21 Hz), 115.8 (d, J_{cf} = 22.5 Hz),

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112.5. MS (ESI) m/z 224.3 $(M - H)^+$. Elemental calcd C 74.66, H 3.58, N 6.22; found C 74.38, H 3.64, N 5.85.

2-(4-Fluorophenyl)-5-formylbenzonitrile (11c). Ethyl 3-cyano-4-(4-fluorophenyl) benzoate (**10c**, 2.05 g, 0.00761 mol) was dissolved in anhydrous THF (40 mL) and cooled to 0 °C. A 1 M solution of lithium pyrrolidinoborohydride (9.14 mL, 9.14 mmol) was added, and the mixture was stirred for 3 h at room temperature. The reaction mixture was quenched by dropwise addition of 3 N HCl, followed by extraction into Et_2O. The combined organic layers were washed with brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using EtOAc–hexanes (2 : 5) as the eluent to obtain 1.53 g (88%) of 2-(4-fluorophenyl)-5-(hydroxymethyl) benzonitrile as a white solid. 2-(4-Fluorophenyl)-5-(hydroxymethyl)benzonitrile (1.50 g, 0.0066 mol) was dissolved in CH_2Cl_2 (75 mL), cooled to 0 °C, and treated with Dess–Martin periodinate (4.20 g, 0.0099 mol). After 3 h the reaction mixture was quenched with a mixture of saturated sodium thiosulfate-sodium bicarbonate solution (1 : 1) and stirred for 30 min. The organic layer was washed with sodium thiosulfate-sodium bicarbonate solution, brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using EtOAc–hexanes (2 : 3) as the eluent to obtain 1.46 g (98%) of **11c** as a white solid: mp 148–151 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 10.08 (s, 1H), 8.27 (d, 1H, J = 3 Hz), 8.15 (dd, 1H, J = 9 Hz, 4.5 Hz), 7.69 (d, 1H, J = 9 Hz), 7.59 (m, 2H), 7.23 (m, 2H). ^{13}C NMR ($CDCl_3$) δ/ppm: 189.5, 165.3, 161.9, 149.5, 135.4, 135.2, 133.0, 130.9, 130.7 (d, J_{cf} = 9 Hz), 117.4, 116.3, 116.0, 112.4. MS (ESI) m/z 224.3 $(M - H)^+$. Elemental calcd C 74.66, H 3.58, N 6.22; found C 74.41, H 3.60, N 6.17.

5-Ethynyl-2-phenylbenzonitrile (12a). A round-bottom flask equipped with a stirring bar was charged with 5-formyl-2-phenylbenzonitrile (**11a**, 2.29 g, 0.0011 mol), K_2CO_3 (3.05 g, 0.022 mol), and anhydrous MeOH (80 mL). Ohira–Bestmann reagent (2.65 g, 0.00138 mol) was dissolved in 10 mL anhydrous MeOH and added to the reaction mixture at room temperature. Progress of the reaction was monitored by TLC, and when the starting material disappeared, the mixture was diluted with 150 mL Et_2O. The reaction mixture was quenched with 80 mL of a 5% $NaHCO_3$ solution and the organic layer separated. The aqueous layer was extracted twice with 100 mL Et_2O, and the combined organic layers washed with 300 mL brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using EtOAc–hexanes (3 : 7) as the eluent to obtain 2.09 g (93%) of **12a** as a white solid: mp 140–143 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 7.87 (s, 1H), 7.73 (d, 1H, J = 6 Hz), 7.50 (m, 6H), 3.22 (s, 1H). ^{13}C NMR ($CDCl_3$) δ/ppm: 145.5, 137.4, 137.1, 136.1, 130.2, 129.1, 128.8, 128.6, 122.1, 117.8, 111.7, 81.1, 79.9. MS (ESI) m/z 204.5 $(M + H)^+$. Elemental calcd C 88.64, H 4.46, N 6.89; found C 88.88, H 4.41, N 6.76.

5-Ethynyl-2-(3-fluorophenyl)benzonitrile (12b). A round-bottom flask equipped with a stirring bar was charged with 2-(3-fluorophenyl)-5-formylbenzonitrile (**11b**, 1.40 g, 0.00622 mol), K_2CO_3 (1.72 g, 0.0124 mol) and anhydrous MeOH (60 mL). Ohira–Bestmann reagent (1.49 g, 0.0078 mol) was dissolved in 5 mL anhydrous MeOH and added to the reaction mixture at room temperature. Progress of the reaction was monitored by TLC, and when the starting material disappeared, the mixture was diluted with 150 mL Et_2O. The reaction mixture was quenched with 80 mL of a 5% $NaHCO_3$ solution and the organic layer separated. The aqueous layer was extracted twice with 100 mL Et_2O, and the combined organic layers washed with 300 mL brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using EtOAc–hexanes (3 : 7) as the eluent to obtain 1.27 g (93%) of **12b** as a white solid: mp 150–153 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 7.88 (d, 1H, J = 3 Hz), 7.74 (dd, 1H, J = 9 Hz, 3 Hz), 7.48 (m, 2H), 7.35 (d, 1H, J = 6 Hz), 7.17 (m, 2H), 3.24 (s, 1H). ^{13}C NMR ($CDCl_3$) δ/ppm: 164.4, 161.1, 143.9, 139.4 (d, J_{cf} = 7.5 Hz), 137.1, 136.2, 130.5 (d, J_{cf} = 8.25 Hz), 130.1, 124.5 (d, J_{cf} = 2.25 Hz), 122.7, 117.4, 116.2, 115.9 (d, J_{cf} = 2.25 Hz), 115.6, 111.7, 80.9, 80.4. MS (ESI) m/z 222.4 $(M + H)^+$. Elemental calcd C 81.44, H 3.64, N 6.33; found C 81.19, H 3.59, N 6.11.

5-Ethynyl-2-(4-fluorophenyl)benzonitrile (12c). A round-bottomed flask equipped with a stirring bar was charged with 4-(4-fluorophenyl)-3-methylbenzaldehyde (**11c**, 1.46 g, 0.00648 mol), K_2CO_3 (1.79 g, 0.0013 mol), and anhydrous MeOH (60 mL). Ohira–Bestmann reagent (1.55 g, 0.0081 mol) was dissolved in 10 mL anhydrous MeOH and added to the reaction mixture at room temperature. Progress of the reaction was monitored by TLC, and when the starting material disappeared, the mixture was diluted with 150 mL Et_2O. The reaction mixture was quenched with 80 mL of a 5% $NaHCO_3$ solution and the organic layer separated. The aqueous layer was extracted twice with 100 mL Et_2O. The combined organic layers were washed with 300 mL brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using EtOAc–hexanes (1 : 3) as the eluent to obtain 1.29 g (90%) of **12c** as a white solid: mp 151–153 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 7.87 (d, 1H, J = 3 Hz), 7.73 (dd, 1H, J = 9 Hz, 3 Hz), 7.52 (m, 3H), 7.20 (m, 2H), 3.23 (s, 1H). ^{13}C NMR ($CDCl_3$) δ/ppm: 164.5, 161.7, 144.3, 137.0, 136.2, 133.4, 130.5 (d, J_{cf} = 8.25 Hz), 130.1, 122.3, 117.6, 116.0 (d, J_{cf} = 21.75 Hz), 111.7, 81.0, 80.1. MS (ESI) m/z 221.4 $(M + H)^+$. Elemental calcd C 81.44, H 3.64, N 6.33; found C 81.21, H 3.68, N 6.15.

4-Bromo-3-methylbenzaldehyde (14). A solution of 17.0 g (0.0742 mol) of methyl-4-bromo-3-methylbenzoate (**13**) in anhydrous THF at 0 °C was added 3.03 g (0.115 mol) of lithium aluminum hydride slowly over 20 min. The reaction mixture was stirred for 30 min at 0 °C and quenched with 6 M HCl added dropwise until all aluminum salts were dissolved. The product was extracted into EtOAc, dried (Na_2SO_4), and concentrated to obtain (4-bromo-3-methylphenyl)methanol as a brown solid. The crude (4-bromo-3-methylphenyl)methanol (14.0 g, 0.070 mol) was dissolved in CH_2Cl_2 (300 mL) and treated with Dess–Martin periodinate (44.2 g, 0.105 mol). After 1 h the reaction mixture was quenched with a mixture of saturated sodium thiosulfate-sodium bicarbonate solution (1 : 1) and stirred for 30 min. The organic layer was washed with sodium thiosulfate-sodium bicarbonate solution, brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by

column chromatography on silica gel using Et_2O–hexanes (9 : 1) as the eluent to obtain 11.2 g (76% over two steps) of 4-bromo-3-methylbenzaldehyde (**14**) as a colourless oil. Spectral data matches previously reported data.[19]

4-Ethynyl-2-methyl-1-phenylbenzene (15a). To a suspension of 4-bromo-3-methylbenzaldehyde (**14**, 1.99 g, 0.01 mol) and phenyl boronic acid (**9a**, 1.46 g, 12 mmol) in toluene (50 mL) was added K_2CO_3 (2.07 g, 0.015 mol) and $Pd(PPh_3)_4$ (578 mg, 0.5 mmol), and the mixture was refluxed for 24 h. The reaction mixture was poured into a mixture of EtOAc and water (1 : 1). The organic layer was washed with water, brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using EtOAc–hexanes (9 : 1) as the eluent to obtain 1.59 g (81%) of 4-(phenyl)-3-methylbenzaldehyde as a colourless oil. A round-bottom flask equipped with a stirring bar was charged with 4-(phenyl)-3-methylbenzaldehyde (1.59 g, 0.0836 mol), K_2CO_3 (2.31 g, 0.0167 mol), and anhydrous MeOH (70 mL). Ohira–Bestmann reagent (1.77 g, 0.0092 mol) was dissolved in 5 mL anhydrous MeOH and added to the reaction mixture at room temperature. Progress of the reaction was monitored by TLC, and when the starting material disappeared, the mixture was diluted with 150 mL Et_2O. The reaction mixture was quenched with 80 mL of a 5% $NaHCO_3$ solution and the organic layer separated. The aqueous layer was extracted twice with 100 mL Et_2O, and the combined organic layers washed with 300 mL brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using EtOAc–hexanes (9 : 1) as the eluent to obtain 1.48 g (92%) of **15a** as a white solid: mp 47–50 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 7.36 (m, 7H), 7.18 (d, 1H, J = 9 Hz), 3.08 (s, 1H), 2.25 (s, 3H). ^{13}C NMR ($CDCl_3$) δ/ppm: 142.6, 141.2, 135.6, 133.9, 129.8, 129.5, 128.9, 128.2, 127.1, 120.9, 83.7, 20.3. MS (ESI) m/z 191.3 $(M + H)^+$. Elemental calcd C 93.71, H 6.29; found C 93.94, H 6.26.

4-Ethynyl-1-(3-fluorophenyl)-2-methylbenzene (15b). To a suspension of 4-bromo-3-methylbenzaldehyde (**14**, 1.99 g, 0.001 mol) and 3-fluorophenylboronic acid (**9b**, 1.67 g, 0.0012 mol) in toluene (50 mL) was added K_2CO_3 (2.07 g, 0.0015 mol) and $Pd(PPh_3)_4$ (578 mg, 0.5 mmol), and the mixture was refluxed for 24 h. The reaction mixture was poured into a mixture of EtOAc and water (1 : 1). The organic layer was washed with water and brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using Et_2O–hexanes (9 : 1) as the eluent to obtain 2.05 g (96%) of 4-(3-fluorophenyl)-3-methylbenzaldehyde as a yellow oil. A round-bottomed flask equipped with a stirring bar was charged with 4-(3-fluorophenyl)-3-methylbenzaldehyde (2.04 g, 0.00952 mol), K_2CO_3 (2.63 g, 0.019 mol) and anhydrous MeOH (70 mL). Ohira–Bestmann reagent (2.29 g, 0.0119 mol) was dissolved in 5 mL anhydrous MeOH and added to the reaction mixture at room temperature. Progress of the reaction was monitored by TLC, and when the starting material disappeared, the mixture was diluted with 150 mL Et_2O. The reaction mixture was quenched with 80 mL of a 5% $NaHCO_3$ solution and the organic layer separated. The aqueous layer was extracted twice with 100 mL Et_2O, and the combined organic layers washed with 300 mL brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using Et_2O–hexanes (9 : 1) as the eluent to obtain 1.67 g (84%) of **15b** as a yellow oil: bp 150–153 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 7.79 (m, 3H), 7.17 (d, 1H, J = 6 Hz), 7.04 (m, 2H), 3.09 (s, 1H), 2.25 (s, 3H). ^{13}C NMR ($CDCl_3$) δ/ppm: 164.2, 160.9, 143.4 (d, J_{cf} = 7.5 Hz), 141.3, 135.5, 134.1, 129.8, 129.6 (d, J_{cf} = 3.75 Hz), 124.8 (d, J_{cf} = 2.25 Hz), 121.5, 116.0 (d, J_{cf} = 21 Hz), 114.0 (d, J_{cf} = 20.25 Hz), 83.5, 77.5, 20.2. MS (ESI) m/z 209.3 $(M + H)^+$. Elemental calcd C 85.69, H 5.27; found C 85.57, H 5.28.

4-Ethynyl-1-(4-fluorophenyl)-2-methylbenzene (15c). To a suspension of 4-bromo-3-methylbenzaldehyde (**14**, 1.99 g, 0.01 mol) and 4-fluorophenylboronic acid (**9c**, 1.67 g, 0.012 mol) in toluene (50 mL) was added K_2CO_3 (2.07 g, 0.015 mol) and $Pd(PPh_3)_4$ (578 mg, 0.5 mmol), and the mixture was refluxed for 24 h. The reaction mixture was poured into a mixture of EtOAc and water (1 : 1). The organic layer was washed with water, brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using Et_2O–hexanes (9 : 1) as the eluent to obtain 1.78 g (83%) of 4-(4-fluorophenyl)-3-methylbenzaldehyde as a colourless oil. A round-bottomed flask equipped with a stirring bar was charged with 4-(4-fluorophenyl)-3-methylbenzaldehyde (1.79 g, 0.00836 mol), K_2CO_3 (2.31 g, 0.0167 mol) and anhydrous MeOH (70 mL). Ohira–Bestmann reagent (1.77 g, 0.00919 mol) was dissolved in 5 mL anhydrous MeOH and added to the reaction mixture at room temperature. Progress of the reaction was monitored by TLC, and when the starting material disappeared, the mixture was diluted with 150 mL Et_2O. The reaction mixture was quenched with 80 mL of a 5% $NaHCO_3$ solution and the organic layer separated. The aqueous layer was extracted twice with 100 mL Et_2O, and the combined organic layers washed with 300 mL brine, dried (Na_2SO_4), and concentrated under reduced pressure. The resulting residue was purified by column chromatography on silica gel using Et_2O–hexanes (9 : 1) as the eluent to obtain 1.7 g (97%) of **15c** as a white solid: mp 56–58 °C. ^{1}H NMR ($CDCl_3$) δ/ppm: 7.79 (m, 3H), 7.17 (d, 1H, J = 6 Hz), 7.04 (m, 2H), 3.09 (s, 1H), 2.25 (s, 3H). ^{13}C NMR ($CDCl_3$) δ/ppm: 163.7, 160.5, 141.5, 137.1 (d, J_{cf} = 3.75 Hz), 135.6, 133.9, 130.6 (d, J_{cf} = 7.5 Hz), 129.7 (d, J_{cf} = 19.5 Hz), 121.1, 115.1 (d, J_{cf} = 21.75 Hz), 103.2, 101.6, 83.5, 77.1, 20.2. MS (ESI) m/z 209.3 $(M + H)^+$. Elemental calcd C 85.69, H 5.27; found C 85.56, H 5.24.

3-Methyl-4-phenoxybenzaldehyde (19a). To a solution of 4-fluoro-3-methylbenzaldehyde (**16**, 2.03 g, 0.0145 mol) and phenol (**18a**, 1.36 g, 0.0145 mol) in 25 mL DMF was added potassium carbonate (2.01 g, 0.0145mol) and the reaction mixture stirred at 150 °C for 16 h. The reaction mixture was allowed to cool to ambient temperature and poured into ice–water (50 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated to obtain a dark brown oil. Purification by column chromatography on silica gel using EtOAc–hexanes (1 : 9) as the eluent afforded 1.73 g (56%) of **19a** as colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 9.91 (s, 1H), 7.79 (s, 1H), 7.64 (d, J = 8 Hz, 1H), 7.39 (t, J = 8 Hz, 2H), 7.19 (t, J = 8 Hz, 1H), 7.04 (d, J = 8 Hz, 1H), 6.87 (d, J = 8 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 191.0, 161.0, 132.7, 131.5, 130.0, 129.6, 129.5, 124.3, 119.5, 116.9, 16.2. MS (ESI) m/z 213.0 $(M + H)^+$. IR (KBr, cm^{-1}): 3352, 3058, 2355, 1244. Elemental calcd C 73.03, H 4.82; found C 72.37, H 4.68.

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4-(4-Fluorophenoxy)-3-methylbenzaldehyde (19b). To a solution of 4-fluoro-3-methylbenzaldehyde (**16**, 2.03 g, 0.0145 mol) and 4-fluorophenol (**18b**, 1.62 g, 0.0145 mol) in 25 mL DMF was added potassium carbonate (2.01 g, 0.0145 mol), and the reaction mixture stirred at 150 °C for 16 h. The reaction mixture was allowed to cool to ambient temperature and poured into ice-water (50 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated to obtain a dark brown oil. Purification by column chromatography on silica gel using EtOAc–hexanes (1 : 9) as the eluent afforded 2.03 g (61%) of **19b** as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 9.90 (s, 1H), 7.78 (s, 1H), 7.65 (d, J = 8 Hz, 1H), 7.69–7.20 (m, 4H), 6.80 (d, J = 9 Hz, 1H), 2.39 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 190.9, 161.3, 161.0, 157.8, 151.6, 132.7, 131.5, 129.7, 129.2, 121.2, 121.1, 116.8, 116.5, 116.1, 16.2. MS (ESI) m/z 231.4 $(M + H)^+$. IR (KBr, cm^{-1}): 3364, 3066, 2359, 1263. Elemental calcd C 73.03, H 4.82; found C 72.86, H 4.67.

4-(3-Fluorophenoxy)-3-methylbenzaldehyde (19c). To a solution of 4-fluoro-3-methylbenzaldehyde (**16**, 2.03 g, 0.0145 mol) and 3-fluorophenol (**18c**, 1.62 g, 14.5 mmol) in 25 mL DMF was added potassium carbonate (2.01 g, 0.0145 mol) and the reaction mixture stirred at 150 °C for 16 h. The reaction mixture was allowed to cool to ambient temperature and poured into ice-water (50 mL). The aqueous layer was extracted with diethyl ether (2 × 50 mL). The combined organic layer was dried (Na_2SO_4), filtered, and concentrated to obtain a dark brown oil. Purification by column chromatography on silica gel using EtOAc–hexanes (1 : 9) as the eluent afforded 1.8 g (54%) of **19c** as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 9.93 (s, 1H), 7.80 (s, 1H), 7.70 (d, J = 8 Hz, 1H), 7.34 (m, 1H), 6.99–7.01 (m, 4H), 2.36 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 190.9, 165.3, 161.9, 159.9, 157.5, 132.9, 132.3, 130.9, 130.7, 130.0, 129.6, 118.1, 114.5, 114.4, 111.0, 106.9, 106.5, 16.1. MS (ESI) m/z 231.5 $(M + H)^+$. IR (KBr, cm^{-1}): 3367, 3071, 2370, 1211. Elemental calcd C 79.22, H 5.70; found C 78.52, H 5.65.

5-Formyl-2-phenoxybenzonitrile (19d). A suspension of 2-fluoro-5-formylbenzonitrile (**17**, 2.16 g, 0.0145 mol), phenol (**18a**, 1.36 g, 0.145 mol) and caesium carbonate (5.19 g, 0.0159 mol) in acetonitrile (120 mL) was stirred at ambient temperature for 16 h. The reaction mixture was poured into water (100 mL) and extracted with ether (2 × 200 mL). The combined organic layer was washed with brine, dried (Na_2SO_4), filtered, and evaporated. The crude solid was triturated in hexane and dried in vacuum to yield 2.14 g (66%) of **19d** as a cream-coloured solid: mp 107–109 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 9.93 (s, 1H), 8.20 (s, 1H), 7.98 (m, 1H), 7.48 (t, J = 8 Hz, 2H), 7.33 (t, J = 8 Hz, 1H), 7.16 (d, J = 8 Hz, 2H), 6.93 (d, J = 8 Hz, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 186.6, 162.3, 151.7, 134.1, 132.9, 128.9, 128.5, 124.4, 118.8, 113.9, 112.8, 102.0. MS (ESI) m/z 220.1 $(M + H)^+$. Elemental calcd C 75.33, H 4.06, N 6.27; found C 75.30, H 4.00, N 6.35.

2-(3-Fluorophenoxy)-5-formylbenzonitrile (19e). To a solution of 2-fluoro-5-formylbenzonitrile (**17**, 980 mg, 6.58 mmol) and 3-fluorophenol (**18c**, 737 mg, 6.58 mmol) in 20 mL DMF was added potassium carbonate (909 mg, 6.58 mmol), and the reaction mixture stirred at 150 °C for 16 h. The reaction mixture was allowed to cool to ambient temperature, poured into ice–water (50 mL), and stirred vigorously to obtain a precipitate that was collected by filtration. The precipitate was recrystallized from ethanol to yield 967 mg (61%) of **19e** as a brown solid: mp 90–93 °C. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 9.95 (s, 1H), 8.21 (s, 1H), 8.02 (m, 1H), 7.46 (m, 4H), 7.00 (m, 4H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 186.6, 163.4, 161.5, 160.0, 152.9, 152.8, 134.2, 133.2, 129.6, 129.5, 114.6, 114.4, 114.3, 112.6, 111.7, 111.4, 106.9, 106.6, 102.6. MS (ESI) m/z 239.9 $(M - H)^+$. Elemental calcd C 69.71, H 3.34, N 5.81; found C 69.73, H 3.29, N 5.80.

4-Ethynyl-2-methyl-1-phenoxybenzene (20a). To a suspension of potassium carbonate (1.97 g, 0.0142 mol) in anhydrous methanol (100 mL) was added 3-methyl-4-phenoxybenzaldehyde (**19a**, 1.51 g, 0.0071 mol) and Bestmann reagent (1.52 g, 0.0078 mol). The reaction mixture was allowed to stir at ambient temperature under nitrogen blanket for 18 h. The solvent was evaporated in vacuum and the residue redissolved in CH_2Cl_2 (100 mL) and washed with saturated $NaHCO_3$ (saturated) (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, and concentrated. The resulting residue was purified by column chromatography on silica gel using EtOAc–hexanes (1 : 9) as the eluent to obtain 1.29 g (87%) of **20a** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.39 (s, 1H), 7.32 (m, 3H), 7.08 (t, J = 7 Hz, 1H), 6.94 (d, J = 8 Hz, 2H), 6.80 (d, J = 8 Hz, 1H), 3.02 (s, 1H), 2.24 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 157.2, 155.5, 135.2, 131.1, 129.8, 123.0, 119.6, 118.7, 118.1, 117.2, 83.6, 15.9. MS (ESI) m/z 213.1 $(M + H)^+$. IR (KBr, cm^{-1}): 3291, 3039, 2106, 1247. Elemental calcd C 86.51, H 5.81; found C 86.64, H 5.82.

4-Ethynyl-1-(4-fluorophenoxy)-2-methylbenzene (20b). To a suspension of potassium carbonate (2.11 g, 0.0153 mol) in anhydrous methanol (100 mL) was added 4-(4-fluorophenoxy)-3-methylbenzaldehyde (**19b**, 1.76 g, 0.0076 mol) and Ohira–Bestmann reagent (1.62 g, 0.0084 mol). The reaction mixture was allowed to stir at ambient temperature under nitrogen blanket for 18 h. The solvent was evaporated and the residue redissolved in CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (saturated) (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, evaporated, and purified by column chromatography on silica gel using EtOAc–hexanes (1 : 9) as the eluent to obtain 1.29 g (75%) of **20b** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.38 (s, 1H), 7.25 (d, J = 8 Hz, 1H), 7.02 (t, J = 8 Hz, 2H), 6.91 (m, 2H), 6.73 (d, J = 8 Hz, 1H), 3.01 (s, 1H), 2.25 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 160.3, 157.1, 155.9, 152.8, 152.8, 135.2, 131.2, 129.3, 119.8, 119.6, 117.9, 117.1, 116.5, 116.2, 83.3, 15.9. MS (ESI) m/z 249.2 $(M + Na)^+$. IR (KBr, cm^{-1}): 3297, 2924, 2107, 1252. Elemental calcd C 79.63, H 4.90; found C 79.63, H 4.88.

4-Ethynyl-1-(3-fluorophenoxy)-2-methylbenzene (20c). To a suspension of potassium carbonate (1.93 g, 0.014 mol) in anhydrous methanol (100 mL) was added 4-(3-fluorophenoxy)-3-methylbenzaldehyde (**19c**, 1.61 g, 0.007 mol) and Ohira–Bestmann reagent (1.49 g, 0.0077 mol). The reaction mixture was allowed to stir at ambient temperature under nitrogen blanket for 18 h. The solvent was evaporated and the residue redissolved in CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (saturated) (50 mL) and

brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, concentrated, and purified by column chromatography on silica gel using EtOAc–hexanes (1 : 9) as the eluent to obtain 1.37 g (87%) of **20c** as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.41 (s, 1H), 7.30 (m, 2H), 6.87 (d, J = 8 Hz, 1H), 6.63 (m, 3H), 3.04 (s, 1H), 2.21 (s, 3H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 165.3, 161.9, 158.7, 158.6, 154.5, 135.4, 135.2, 131.3, 130.6, 130.5, 130.2, 119.7, 118.1, 116.5, 113.1, 113.0, 109.8, 109.6, 105.4, 105.1, 83.2, 15.9. MS (ESI) m/z 227.0 $(M + H)^+$. IR (KBr, cm^{-1}): 3296, 3073, 2106, 1207. Elemental calcd C 79.63, H 4.90; found C 79.92, H 4.90.

5-Ethynyl-2-phenoxybenzonitrile (20d). To a suspension of potassium carbonate (1.02 g, 0.0074 mol) in anhydrous methanol (60 mL) was added 5-formyl-2-phenoxybenzonitrile (**19d**, 828 mg, 3.71 mmol) and Ohira–Bestmann reagent (792 mg, 3.71 mmol). The reaction mixture was allowed to stir at ambient temperature under nitrogen blanket for 18 h. The solvent was evaporated and the residue redissolved in CH_2Cl_2 (100 mL) and washed with saturated $NaHCO_3$ (saturated) (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, evaporated, and purified by column chromatography on silica gel using EtOAc–hexanes (1 : 9) as the eluent to obtain 610 mg (75%) of **20d** as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.76 (s, 1H), 7.56 (m, 1H), 7.43 (t, J = 8 Hz, 2H), 7.26 (t, J = 8 Hz, 1H), 7.11 (d, J = 7 Hz, 2H), 6.79 (d, J = 9 Hz, 1H), 3.11 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 159.9, 154.4, 137.7, 137.4, 130.3, 125.6, 120.4, 117.0, 116.6, 115.0, 80.9, 78.4. MS (ESI) m/z 220.7 $(M + H)^+$. IR (KBr, cm^{-1}): 3272, 3064, 2230, 1252. Elemental calcd C 82.18, H 4.14, N 6.39; found C 82.15, H 4.11, N 6.34.

5-Ethynyl-2-(3-fluorophenoxy)benzonitrile (20e). To a suspension of potassium carbonate (915 mg, 6.62 mmol) in anhydrous methanol (60 mL) was added 2-(3-fluorophenoxy-5-formylbenzonitrile (**19e**, 600 mg, 2.48 mmol) and Bestmann reagent (708 mg, 3.65 mmol). The reaction mixture was allowed to stir at ambient temperature under nitrogen blanket for 18 h. The solvent was evaporated in vacuum and the residue redissolved in CH_2Cl_2 (100 mL) and washed with $NaHCO_3$ (saturated) (50 mL) and brine (50 mL). The organic layer was dried (Na_2SO_4), filtered, evaporated, and purified by column chromatography on silica gel using EtOAc–hexanes (1 : 9) as the eluent to obtain 210 mg (36%) of **20e** as a colourless oil. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H/ppm: 7.78 (s, 1H), 7.60 (d, J = 8 Hz, 1H), 7.39 (m, 1H), 6.88 (m, 3H), 3.13 (s, 1H). ^{13}C NMR (75.5 MHz, $CDCl_3$) δ_C/ppm: 165.2, 161.9, 158.9, 155.8, 137.8, 137.5, 131.8, 131.1, 117.9, 117.3, 115.6, 115.5, 114.7, 112.6, 112.3, 108.1, 107.8, 104.5, 80.7, 78.8. MS (ESI) m/z 236.3 $(M - H)^+$. IR (KBr, cm^{-1}): 3301, 3079, 2230, 1276. Elemental calcd C 75.94, H 3.40, N 5.90; found C 75.89, H 3.28, N 5.97.

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