Expedient Construction of Small-Molecule Macroarrays *via* Sequential Palladium- and Copper-Mediated Reactions and *ex situ* Biological Testing

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General experimental information.

Chemical methods. All chemical reagents were purchased from commercial sources (Alfa-Aesar, Sigma-Aldrich, and Acros) and used without further purification. Solvents were purchased from commercial sources (Sigma-Aldrich and J.T. Baker) and used as obtained, with the exception of dichloromethane (CH_2Cl_2), which was distilled over calcium hydride immediately prior to use. Water was purified using a Millipore Analyzer Feed System. Planar cellulose membranes utilized for macroarray construction (Whatman 1Chr and 3MM chromatography paper) were purchased from Fisher Scientific and stored in a dessicator at room temperature (rt; ~23 °C) until ready for use.

Reversed-phase high performance liquid chromatography (RP-HPLC) analyses were performed using a Shimadzu HPLC equipped with a single pump (LC-10Atvp), solvent mixer (FCV-10Alvp), controller (SCL-10Avp), autoinjector (SIL-10AF), and UV diode array detector (SPD-M10Avp). A Shimadzu Premier 25 cm × 4.6 mm C-18 reverse-phase column was used for all analytical HPLC work. Standard RP-HPLC conditions were as follows: flow rate = 1.0 mL/min; mobile phase A = 0.1% trifluoroacetic acid (TFA) in water; mobile phase B = 0.1% TFA in acetonitrile (CH_3CN). Ultraviolet (UV) detection was used in all HPLC analyses. Compound purities were determined by integration of the peaks in HPLC traces at 254 nm.

Electrospray ionization (ESI) MS data for solution-phase intermediates and products were obtained using a Waters (Micromass) LCT™ system. This instrument uses a time-of-flight analyzer. Samples were dissolved in methanol and sprayed with a sample cone voltage of 20. Electron impact (EI) MS data for solution-phase intermediates and products were obtained using a Waters (Micromass) AutoSpec® system. Routine ^1H NMR spectra were recorded in deuterated NMR solvents at 300 MHz on a Varian Mercury-300 spectrometer. Chemical shifts are reported in parts per million (ppm, δ) using corresponding solvents or tetramethylsilane (TMS) as a reference. Couplings are reported in hertz (Hz). UV spectra were recorded using a Varian Cary 50 UV-Vis spectrometer running Cary WinUV software.

LC-MS analyses for macroarray products were performed using a Shimadzu LCMS-2010a equipped with two pumps (LC-10ADvp), controller (SCL-10Avp), autoinjector (SIL-10Advp), UV diode array detector (SPD-M10Avp), and single quadrupole analyzer (by electrospray ionization, ESI). The LC-MS was interfaced with a PC running the Shimadzu LCSolutions software package (Version 2.04 Su2-H2). A Supelco 15 cm × 2.1 mm C-18 wide-pore reversed-phase column was used for all LC-MS work. Standard RP-HPLC conditions for LC-MS analyses were as follows: flow rate = 200 μL/min; mobile phase A = 0.1% formic acid in H_2O; mobile phase B = 0.1% formic acid in CH_3CN.

Macroarray construction specifics. All reactions on planar supports were performed under air. Macroarray reactions subjected to oven heating were performed on a pre-heated bed of sand in a standard drying oven (VWR model # 13OOU). Temperature measurements of planar surfaces were acquired using a non-contact IR thermometer (Craftsman model #82327) with an error of ±2.5%. An Eppendorf pipetteman with a calibrated range between 0.5–10.0 μL was used to "spot" or apply reagents onto planar membranes in a spatially addressed manner using disposable plastic tips. Washing steps were 5 min each at rt unless otherwise noted. After each

washing sequence, the macroarray was dried on a pre-heated sand bath at 60 °C for 5 min.

Initial derivatization of planar cellulose support.

Representative planar cellulose membrane amination protocol. Dots were marked on appropriate sized sheets of Whatman 1Chr paper (Figure S-1, **A**) at distances 1.2 cm apart using a #2 pencil. The sheet was immersed in 100 mL of 10% TFA in CH_2Cl_2 for 20 min in a covered 2.6 L Pyrex dish. This acid wash served as a cellulose pre-activation step, and is believed to increase the surface area of the cellulose available for functionalization. The sheet was washed by adding 60 mL of CH_2Cl_2, allowing it to soak for 5 min, and then decanting the CH_2Cl_2. This process was repeated, after which the membrane was dried on a pre-heated sand bath. The sheet was next immersed in 100 mL of 2.0 M tosyl chloride (TsCl) in pyridine (Pyr) for 5 min at rt. The paper was washed by immersion in two consecutive baths of ethanol (EtOH) and one in CH_2Cl_2 (100 mL), and dried on a sand bath. To install the flexible amine spacer, the tosylated cellulose paper was immersed in 100 mL of neat 4,7,10-trioxa-1,13-tridecanediamine (**B**), and allowed to soak at 60 °C for 15 min (in a drying oven) in a covered Pyrex dish. The amine solution was carefully decanted from the support. The spacer-derivatized support (**C**) was washed by adding then decanting 70 mL portions of *N*,*N*-dimethylformamide (DMF), EtOH, 1.0 N NaOH, H_2O, EtOH (2x), and CH_2Cl_2, and subsequently dried on a sand bath.

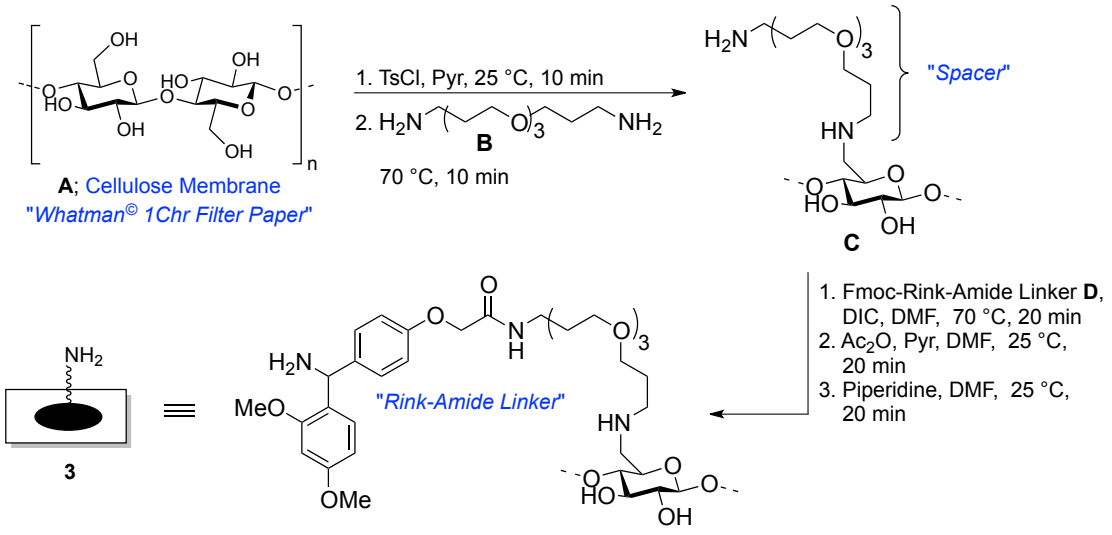


Figure S-1. Initial planar cellulose support modification and Rink-amide linker installation.

Representative Rink-amide linker installation protocol on cellulose support. A Rink-amide linker coupling solution containing 4-[(2,4-dimethoxyphenyl)-(Fmoc-amino)methyl]phenoxy-acetic acid (**D**, 365 mg, 0.676 mmol), *N*-hydroxy-succinimide (HOSu, 78 mg, 0.678 mmol), *N*,*N*'-diisopropylcarbodiimide (DIC, 105 µL, 0.678 mmol), and DMF (1.5 mL) was vortexed and allowed to stand at rt for 30 min. A light precipitate formed, and this was filtered away from the

solution. Aliquots (3.0 μL each) of this activated solution were spotted onto each of the dots of spacer-derivatized support **C** (Figure S-1) using a pipetteman. The sheet was then placed on a sand bath and heated at 60 °C for 15 min. The Rink linker-derivatized support was washed by adding then decanting 70 mL portions of DMF, EtOH (2x), and CH_2Cl_2, and then dried on a sand bath.

Representative acetylation and *N*-Fmoc-deprotection protocol on cellulose support. The *N*-Fmoc-protected, Rink linker-derivatized support from above was immersed in a solution of acetic anhydride (Ac_2O, 30 mL), Pyr (15 mL), and DMF (105 mL) at rt for 20 min. This procedure served to cap any unreacted "spacer" amine on the support. The resulting acetylated support was washed by adding then decanting 70 mL portions of DMF, EtOH (2x), and CH_2Cl_2, and then dried on a sand bath. Next, the *N*-Fmoc group was cleaved by immersing the support in a 20% piperidine/DMF solution at rt for 20 min. The resulting amino support (**3**, Figure S-1) was washed by adding then decanting 70 mL portions of DMF, EtOH (2x), and CH_2Cl_2, and then dried on a sand bath.

Representative UV Fmoc quantitation protocol on cellulose support. A spot (6 mm diameter) was punched from the acetylated, *N*-Fmoc-protected Rink linker-derivatized support using a desktop hole punch and placed in a 4-mL glass vial. DMF (960 μL) was added to the vial, followed by 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU, 40 μL). The mixture was swirled for 30 sec, and then allowed to stand for 15 min. The mixture was swirled again for 30 sec, and then 100 μL of this solution was removed and diluted with DMF (2.0 mL). The solution was swirled again for 30 sec. The absorbance was read at 296 nm in a quartz cuvette (path length = 1 cm). The absorbance value was multiplied by 21 to account for the dilution and divided by the extinction coefficient at 296 nm (ε_{296}= 9500 $M^{-1}cm^{-1}$) to determine the concentration of Fmoc, which is equivalent to the loading of available amine on amino support **3**.

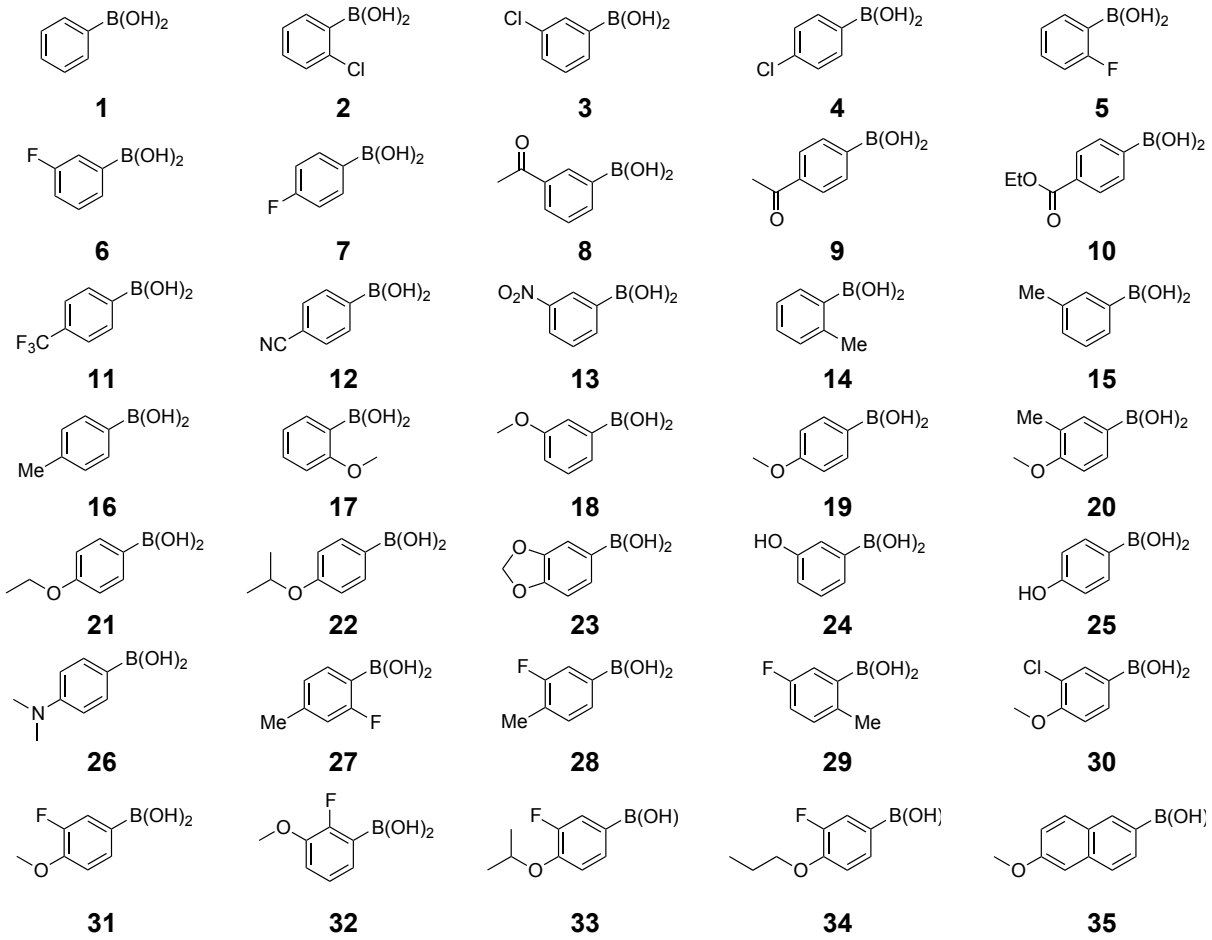
Macroarray construction *via* SPOT synthesis on Rink-amide linker-derivatized support 3.

Representative carbodiimide couplings of initial building blocks on Rink-amide linker-derivatized support (3). Carbodiimide coupling solutions for phenyl-naphthalene macroarray construction (**7a–b**) were prepared by dissolving 6-bromo or 7-bromo-2-naphthalenyloxyacetic acid (**4a** or **4b**, 13.0 mg, 0.046 mmol) and DIC (8.7 μL, 0.055 mmol) in DMF (200 μL). The solutions were allowed to pre-activate at rt for 15 min and then filtered. Aliquots (3.0 μL) of the solutions were pipetted onto the spots of amino support **3**. The support was allowed to sit at rt for 5 min, and then washed by immersion and swirling in 100 mL portions of DMF (2x), EtOH (2x) and CH_2Cl_2. The resulting support was dried on a sand bath. An analogous protocol was used to couple alkynyl acids **8**: **A–D** onto amino support **3** to yield alkyne-loaded support **9** (see below).

Representative Suzuki-Miyaura coupling on bromo-2-naphthalenyloxy-derivatized support 5a–b. Suzuki-Miyaura coupling solutions were prepared by dissolving aryl boronic acids (**6**, 0.25 mmol) and Cs_2CO_3 (32.6 mg, 0.10 mmol) in a pre-mixed solution of NMP:H_2O 9:1 (120 μL). The 35 phenylboronic acid building blocks (**6**: **1–35**) are shown below in Table S-1. Aliquots (3.0 μL) of a freshly prepared 0.166 M solution of $Pd(OAc)_2$ in NMP:H_2O 9:1 were pipetted onto

their designated spots on the bromo-2-naphthalenyloxy-derivatized support **5a–b**. The support was kept at rt for 10 min, after which aliquots (3.0 μL) of the Suzuki-Miyaura coupling solutions were pipetted onto their designated spots. The support was heated on a sand bath at 60 °C for 12 min, and then washed by immersion and swirling in 150 mL portions of DMF (1x), H_2O (1x), DMF (1x), MeOH (1x), hexanes (1x), and CH_2Cl_2 (1x). The resulting phenyl-naphthalene macroarray was dried on a sand bath.

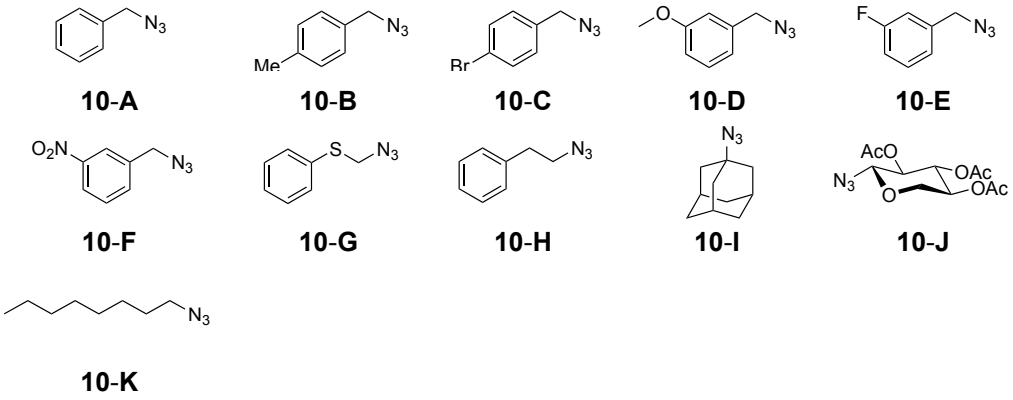
Table S-1. Functionalized aryl boronic acids building blocks (**6**: **1–35**) used in the construction of the phenyl-naphthalenes **7a–b**. Aryl boronic acids were purchased from Sigma-Aldrich and used without further purification.



Representative copper-catalyzed azide-alkyne cycloaddition (CuAAC) protocol on alkyne-derivatized support 9. Azides (**10**: **A–K**, 0.10 mmol) were dissolved in 125 μL of a freshly prepared stock solution consisting of copper (I) iodide (CuI, 1.0 mmol) dissolved in Pyr (17.0 mmol) and 2-acetylpyridine (2-AcPyr, 3.0 mmol). The azide building blocks (**10**: **A–K**) are shown below in Table S-2. Aliquots (3.0 μL) of the azide spotting solutions were pipetted onto their designated spots on the alkyne-loaded support **9**. The support was heated on a sand bath at 60 °C for 12 min, and then washed by immersion and swirling in 150 mL portions of Pyr (2x),

MeOH (1x), DMF (1x), H_2O (1x), MeOH (1x) and CH_2Cl_2 (1x). The resulting 1,4-disubstituted 1,2,3-triazole macroarray was dried on a sand bath.

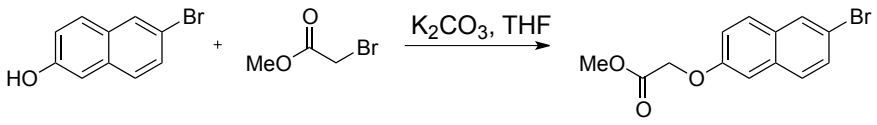
Table S-2. Azide building blocks (**10**: **A–K**) used in the construction of 1,4-disubstituted 1,2,3-triazoles **11**. Azides **10-H**, **10-I** and **10-J** were purchased from Sigma-Aldrich and used without further purification. The remaining azides were synthesized according to the procedures outlined below.



Representative TFA vapor-phase cleavage of macroarray compounds. A 10 mL-portion of TFA was added to the bottom of a glass vacuum dessicator (15 × 20 cm). Spots of macroarrays were punched out and placed in individual 4-mL glass vials. The vials were placed in a Petri dish (12 cm diameter), and the dish was placed on a ceramic shelf in the dessicator. The dessicator was evacuated to 60 mbar for 10 min to produce a TFA vapor atmosphere, and then sealed and allowed to stand for 50 min. The dessicator was opened, and the vials were removed. The cleaved compounds were eluted from the spots with MeOH (1 mL). The eluent was either immediately submitted for HPLC-MS analyses or removed *in vacuo*. Dried product samples were stored at rt for later HPLC analysis and/or biological assays.

Synthesis of initial building blocks and amide-versions of initial building blocks and azides.

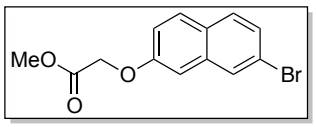
Representative naphthol alkylation with methyl bromoacetate.



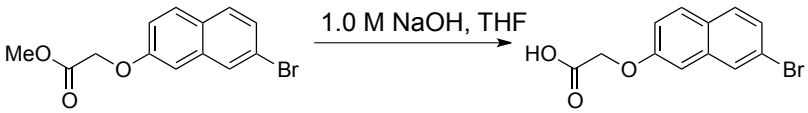
In a 25 mL round-bottom flask, 2-bromo-6-naphthol (500 mg, 2.2 mmol) was dissolved in tetrahydrofuran (THF, 5 mL) at rt. K_2CO_3 (496 mg, 3.6 mmol) and methyl bromoacetate (255 μL, 2.7 mmol) were added to this solution. The reaction mixture was stirred overnight at rt, after which the THF was removed *in vacuo*. The crude product was extracted with H_2O (1 x 30 mL) and ethyl acetate (EtOAc, 3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to afford 615 mg of methyl 2-(6-bromonaphthalen-2-

yloxy)-acetate as a light brown crystalline solid (93% overall yield). ^{1}H NMR (300 MHz, Acetone-*d6*) δ 3.76 (s, 3H), 4.87 (s, 2H), 7.28 (dd, 1H, *J* =2.6, 8.9 Hz), 7.31 (d, 1H, *J* = 2.5 Hz), 7.55 (dd, 1H, *J* = 2.0, 8.7 Hz), 7.75 (d, 1H, *J* = 8.8 Hz), 7.83 (d, 1H, *J* = 9.0 Hz), 8.05 (d, 1H, *J* = 1.9 Hz); ^{13}C NMR (75 MHz, Acetone-*d6*) δ 52.3, 65.8, 108.2, 117.9, 120.7, 129.7, 129.9, 130.5, 131.4, 134.1, 157.5, 169.7; ESI-MS: calculated m/z $[M+Na]^+$ 316.9784, observed m/z 316.9779.

Methyl 2-(7-bromonaphthalen-2-yloxy)-acetate: Synthesis analogous to above; 537 mg of a white crystalline solid (91% overall yield). ^{1}H NMR (300 MHz, Acetone-*d6*) δ 3.77 (s, 3H), 4.87 (s, 2H), 7.24 (m, 2H), 7.45 (dd, 1H, *J* = 2.0, 8.7 Hz), 7.77 (d, 1H, *J* = 8.7 Hz), 7.84 (m, 1H), 7.99 (d, 1H, *J* = 1.5 Hz); ^{13}C NMR (75 MHz, Acetone-*d6*) δ 52.3, 65.7, 107.4, 120.0, 121.1, 127.9, 128.7, 129.7, 130.5, 130.6, 136.8, 157.8, 169.6; ESI-MS: calculated m/z $[M+Na]^+$ 316.9784, observed m/z 316.9773.

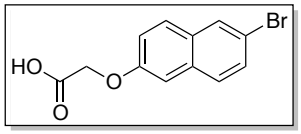


Representative methyl 2-(bromonaphthalen-2-yloxy)-acetate ester hydrolysis.

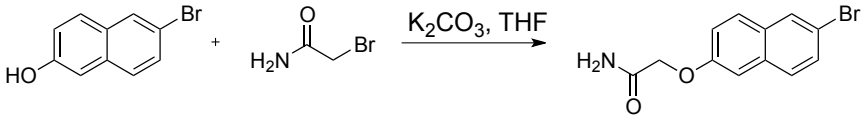


In a 50 mL round-bottom flask, 2-(7-bromonaphthalen-2-yloxy)-acetate (400 mg, 1.4 mmol) was dissolved in THF (5 mL) at rt. The clear solution was cooled to 0 °C using an ice/water bath, and 1.0 M aq. NaOH (5 mL) was added in one portion. The reaction mixture was stirred at 0 °C for 30 min, after which the THF was removed *in vacuo*. The aqueous layer was treated with 6.0 M aq. HCl, upon which a white suspension formed. The suspension was filtered, and the white crystals were washed with H_2O and dried *in vacuo* to afford 374 mg of 7-bromo-2-naphthalenyloxyacetic acid (**4b**) as a white crystalline solid (98% overall yield). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 4.80 (s, 2H), 7.25 (dd, 1H, *J* = 9.0, 2.5 Hz), 7.29 (d, 1H, *J* = 2.4 Hz), 7.47 (dd, 1H, *J* = 8.6, 2.0 Hz), 7.81 (d, 1H, *J* = 9.0 Hz), 7.89 (d, 1H, *J* = 8.8 Hz), 8.06 (d, 1H, *J* = 1.7 Hz), 13.08 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 64.5, 106.4, 119.0, 119.8, 126.7, 127.1, 128.4, 129.5, 129.7, 135.4, 156.4, 169.8; ESI-MS: calculated m/z $[M+Na]^+$ 302.9628, observed m/z 302.9633.

6-bromo-2-naphthalenyloxyacetic acid (4a): Synthesis analogous to above (**4b**); 278 mg of a white crystalline solid (99% overall yield). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 4.78 (s, 2H), 7.26 (dd, 1H, *J* = 8.9, 2.4 Hz), 7.30 (d, 1H, *J* = 2.2 Hz), 7.55 (dd, 1H, *J* = 8.8, 1.9 Hz), 7.76 (d, 1H, *J* = 8.9 Hz), 7.84 (d, 1H, *J* = 9.0 Hz), 8.11 (d, 1H, *J* = 1.5 Hz), 13.31 (bs, 1H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 64.7, 107.1, 116.4, 119.6, 128.6, 128.9, 129.2, 129.3, 129.8, 132.7, 156.1, 170.0; ESI-MS: calculated m/z $[M+Na]^+$ 302.9628, observed m/z 302.9639.

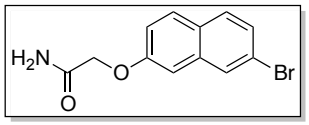


Representative naphthol alkylation with bromo acetamide.

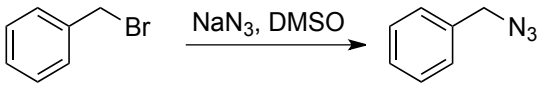


In a 25 mL round-bottom flask, 2-bromo-6-naphthol (350 mg, 1.57 mmol) was dissolved in THF (5 mL) at rt. K_2CO_3 (347 mg, 2.5 mmol) and bromo acetamide (260 mg, 1.9 mmol) were added to the solution. The reaction mixture was stirred overnight at rt, after which the THF was removed *in vacuo*. The crude product was extracted with H_2O (1 x 30 mL) and EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo*. The crude product was recrystallized in a mixture of EtOAc and hexanes to afford 369 mg of 2-(6-bromo-naphthalen-2-yloxy)-acetamide as a white crystalline solid (84% overall yield). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 4.56 (s, 2H), 7.30 (m, 2H), 7.46 (bs, 1H), 7.57 (dd, 1H, J = 2.0, 8.6 Hz), 7.62 (bs, 1H), 7.76 (d, 1H, J = 8.9 Hz), 7.85 (d, 1 H, J = 9.7 Hz) 8.11 (d, 1H, J = 1.8 Hz); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 66.7, 107.2, 116.5, 119.9, 128.6, 129.0, 129.3, 129.4, 129.9, 132.7, 156.0, 169.6; ESI-MS: calculated m/z $[M+Na]^+$ 301.9788, observed m/z 301.9779.

2-(7-bromo-naphthalen-2-yloxy)-acetamide: Synthesis analogous to above; 487 mg of a white crystalline solid (87% overall yield). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 4.55 (s, 2H), 7.30 (m, 2H), 7.46 (m, 2H), 7.63 (bs, 1H), 7.80 (d, 1H, J =8.8 Hz), 7.87 (m, 1H), 8.05 (d, 1H, J = 1.7 Hz); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 66.7, 106.5, 119.3, 119.9, 126.7, 127.2, 128.5, 129.5, 129.8, 135.5, 156.4, 169.6; ESI-MS: calculated m/z $[M+Na]^+$ 301.9788, observed m/z 301.9776.

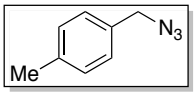


Representative azide building block (10) synthesis.

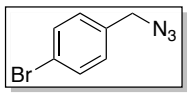


This synthesis was based in part on a previously reported method.[1] In a 25 mL round-bottom flask, benzyl bromide (342 mg, 2.0 mmol) was added to 4.4 mL of a 0.5 M sodium azide (NaN_3) solution in DMSO at rt. The reaction mixture was stirred overnight at rt, followed by quenching with H_2O (30 mL). The mixture was extracted with diethyl ether (Et_2O, 3 x 30 mL), and the combined organic layers were washed with H_2O (3 x 50 mL) and brine (1 x 50 mL). The organic layer was dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to afford 240 mg of benzylazide (**10-A**) as a clear colorless oil (90% yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.37 (s, 2H), 7.42 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.9, 128.3, 128.4, 128.9, 135.5; EI-MS: calculated m/z $[M]^+$ 133.0635, observed m/z 133.0631.

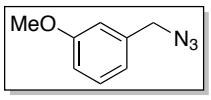
4-Methylbenzyl azide (10-B): Synthesis analogous to above; 268 mg of a clear colorless oil, (91% overall yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.33 (s, 3H), 4.24 (s, 2H), 7.17 (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.2, 54.7, 128.4, 129.6, 132.4, 138.2; EI-MS: calculated m/z $[M]^+$ 147.0791, observed m/z 147.0791.



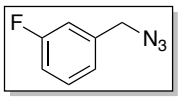
4-Bromobenzyl azide (10-C): Synthesis analogous to above; 407 mg of a clear colorless oil (96% overall yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.28 (s, 2H), 7.17 (m, 2H), 7.49 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.2, 122.5, 129.9, 132.1, 135.6; EI-MS: calculated m/z $[M]^+$ 210.9740, observed m/z 210.9747.



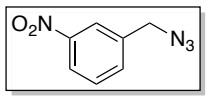
3-Methoxybenzyl azide (10-D): Synthesis analogous to above; 304 mg of a clear colorless oil (93% overall yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 3.90 (S, 3H), 4.29 (s, 2H), 6.87 (m, 3H), 7.28 (t, 1H, J = 7.7 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.9, 55.4, 113.8, 114.0, 120.6, 130.1, 137.1, 160.1; EI-MS: calculated m/z $[M]^+$ 163.0741, observed m/z 173.0746.



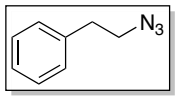
3-Fluorobenzyl azide (10-E): Synthesis analogous to above; 287 mg of a clear colorless oil (95% overall yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.32 (s, 2H), 7.04 (m, 3H), 7.34 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 54.3, 115.3, 123.8, 130.6, 138.1, 161.5, 164.8; EI-MS: calculated m/z $[M]^+$ 151.0541, observed m/z 151.0541.



3-Nitrobenzyl azide (10-F): Synthesis analogous to above; 349 mg of a clear light yellow oil (98% overall yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 4.52 (s, 2H), 7.60 (m, 2H), 8.17 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 53.7, 122.8, 123.1, 129.8, 129.9, 134.0, 137.8, 148.4; EI-MS: calculated m/z $[M]^+$ 178.0486, observed m/z 178.0477.

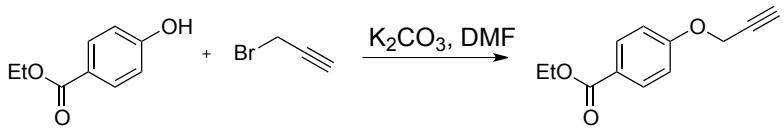


(2-Azidoethyl)benzene (10-H): Synthesis analogous to above; 277 mg of clear colorless oil (94% overall yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.86 (t, 2H, J = 7.3 Hz), 3.47 (t, 2H, J = 7.3 Hz), 7.26 (m, 5H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 35.5, 52.6, 126.9, 128.8, 128.9, 138.2; EI-MS: calculated m/z $[M]^+$ 147.0791, observed m/z 147.0796.



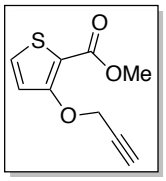
1-Octyl azide (10-K): Synthesis analogous to above; 286 mg of a clear colorless oil (92% overall yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.89 (t, 3H, J = 6.8 Hz), 1.36 (m, 10H), 1.60 (quin, 2H, J = 7.2 Hz), 3.25 (t, 2H, J = 7.0 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.3, 22.8, 26.9, 29.0, 29.3, 29.4, 32.0, 51.7; EI-MS: calculated m/z $[M\text{-}H\text{-}N_2]^+$ 126.1278, observed m/z 126.1284.

Representative *O*-propargylation procedure.

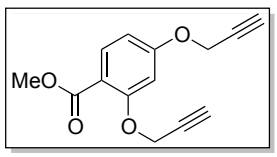


In a 25 mL round-bottom flask, ethyl 4-hydroxy benzoate (831 mg, 5.0 mmol) was dissolved in DMF (5 mL) at rt. K_2CO_3 (1.04 g, 7.5 mmol) and propargylbromide (647 μL, 80% wt solution in toluene, 6.0 mmol) were added to the solution, and the reaction mixture was stirred at 80 °C for 3 h. The mixture was extracted with H_2O (1 x 50 mL) and EtOAc (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, filtered, and the solvent removed *in vacuo* to afford 981 mg of ethyl 4-(2-propynyloxy) benzoate as a white crystalline solid (96% overall yield). ^{1}H NMR (300 MHz, $CDCl_3$) δ 1.37 (t, 3H, *J* = 7.1 Hz), 2.56 (t, 1H, *J* = 2.3 Hz), 4.34 (q, 2H, *J* = 7.1 Hz), 4.73 (d, 2H, *J* = 2.2 Hz), 6.99 (m, 2H), 8.01 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 14.5, 55.9, 60.8, 76.2, 78.0, 114.5, 123.9, 131.6, 161.2, 166.3; EI-MS: calculated m/z $[M]^+$ 204.0781, observed m/z 204.0786.

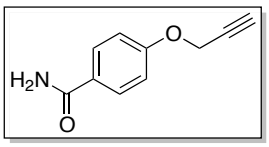
2-Methoxycarbonyl-3-propargyloxythiophene: Synthesis analogous to above; 934 mg of a light brown oil (95% overall yield). ^{1}H NMR (300 MHz, Acetone-*d6*) δ 3.13 (td, 1H, *J* = 2.3, 0.8 Hz), 3.78 (d, 3H, *J* = 0.7 Hz), 4.93 (dd, 2H, *J* = 2.4, 0.8 Hz), 7.14 (dd, 1H, *J* = 5.6, 0.8 Hz), 7.71 (dd, 1H, *J* = 5.5, 0.8 Hz); ^{13}C NMR (75 MHz, Acetone-*d6*) δ 51.8, 59.7, 77.8, 79.5, 96.6, 119.2, 131.7, 160.6, 162.2; EI-MS: calculated m/z $[M]^+$ 196.0189, observed m/z 196.0182.



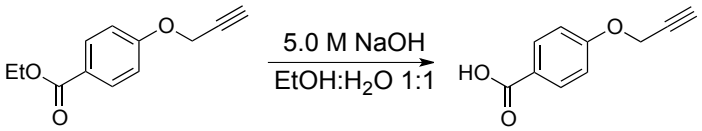
Methyl 2,4-di-(2-propynyloxy) benzoate: Synthesis analogous to above; 1.14 g of a light yellow crystalline solid (93% overall yield). ^{1}H NMR (300 MHz, Acetone-*d6*) δ 3.10 (t, 1H, *J* = 2.4 Hz), δ 3.13 (t, 1H, *J* = 2.4 Hz), δ 3.79 (s, 3H), 4.87 (d, 2H, *J* = 2.4 Hz), 4.88 (d, 2H, *J* = 2.4 Hz), 6.72 (dd, 1H, *J* = 8.7, 2.3 Hz), 6.84 (d, 1H, *J* = 2.3 Hz), 7.79 (d, 1H, *J* = 8.7 Hz); ^{13}C NMR (75 MHz, Acetone-*d6*) δ 51.9, 56.7, 57.4, 77.6, 77.7, 79.1, 79.4, 102.9, 107.7, 115.1, 134.1, 159.8, 162.8, 166.2; ESI-MS: calculated m/z $[M+Na]^+$ 267.0628, observed m/z 267.0626.



4-Propargyloxybenzamide: Synthesis analogous to above; 772 mg of a light yellow crystalline solid (88% overall yield). ^{1}H NMR (300 MHz, Acetone-*d6*) δ 3.11 (t, 1H, *J* = 2.4 Hz), 4.87 (d, 2H, *J* = 2.4 Hz), 6.55 (bs, 1H), 7.06 (m, 2H), 7.34 (bs, 1H), 7.93 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 56.5, 77.4, 79.5, 115.3, 128.5, 130.3, 161.1, 168.5; ESI-MS: calculated m/z $[M+H]^+$ 176.0707, observed m/z 176.0704.

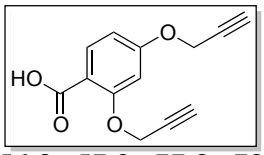


Representative benzoic acid ester hydrolysis.

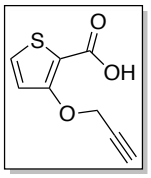


In a 100 mL round-bottom flask, ethyl 4-(2-propynyloxy) benzoate (613 mg, 3.0 mmol) was dissolved in EtOH:H_2O 1:1 (30 mL) at rt and treated with 5.0 M aq. NaOH (60.0 mmol). The reaction mixture was stirred at rt overnight, after which the EtOH was removed *in vacuo*. The aqueous layer was extracted with an additional portion of H_2O (1 x 10 mL) and ether (3 x 20 mL). The aqueous layer was acidified with 6.0 M HCl, and extracted with ether (3 x 20 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo* to afford 513 mg of 4-propargyloxy benzoic acid (**8-A**) as a white crystalline solid (97% overall yield). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 3.61 (t, 1H, *J* = 2.4 Hz), 4.89 (d, 2H, *J* = 2.4 Hz), 7.08 (m, 2H), 7.90 (m, 2H), 12.67 (s, 1H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 55.6, 78.6, 78.7, 114.6, 123.7, 131.2, 160.7, 166.9; ESI-MS: calculated m/z $[M-H]^-$ 175.0400, observed m/z 175.0395.

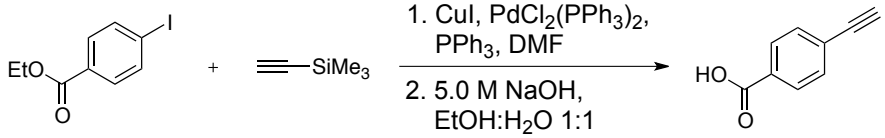
2,4-Dipropargyloxy benzoic acid (8-B): Synthesis analogous to above; 482 mg of a white crystalline solid (95% overall yield). ^{1}H NMR (300 MHz, Acetone-*d6*) δ 3.15 (t, 1H, *J* = 2.4 Hz), 3.18 (t, 1H, *J* = 2.3 Hz), 4.91 (d, 2H, *J* = 2.3 Hz), 5.02 (d, 2H, *J* = 2.6 Hz), 6.79 (dd, 1H, *J* = 8.8, 2.4 Hz), 6.91 (d, 1H, *J* = 2.2 Hz), 7.94 (d, 1 H, *J* = 8.8 Hz); ^{13}C NMR (75 MHz, Acetone-*d6*) δ 56.8, 57.9, 77.8, 78.3, 78.9, 79.1, 102.5, 108.5, 114.2, 135.0, 159.5, 163.2, 165.8; ESI-MS: calculated m/z $[M+Na]^+$ 253.0472, observed m/z 253.0472.



3-Propargyloxy-2-thiophene carboxylic acid (8-C): Synthesis analogous to above; 354 mg of a light brown crystalline solid (97% overall yield). ^{1}H NMR (300 MHz, Acetone-*d6*) δ 3.12 (t, 1H, *J* = 2.4 Hz), 4.94 (d, 2H, *J* = 2.4 Hz), 7.15 (d, 1H, *J* = 5.6 Hz), 7.72 (d, 1H, *J* = 5.6 Hz), 10.00 (bs, 1H); ^{13}C NMR (75 MHz, Acetone-*d6*) δ 59.7, 77.8, 79.4, 112.5, 119.1, 131.9, 160.4, 162.7; ESI-MS: calculated m/z $[M+Na]^+$ 204.9930, observed m/z 204.9923.



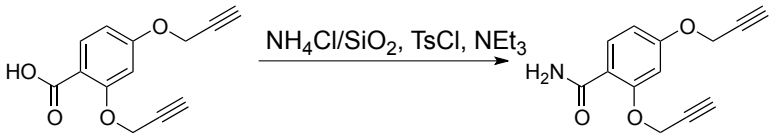
Ethyl 4-trimethylsilanylethynylbenzoate (8-D):



This synthesis was based in part on a previously reported method.[2] A mixture of ethyl 4-iodobenzoate (1.5 g, 5.43 mmol), $PdCl_2(PPh_3)_2$ (0.543 mmol), triphenylphosphine (1.09 mmol), copper (I) iodide (1.09 mmol), and DMF (50 mL) was prepared in a 100-mL three-neck round bottom flask. The flask was purged using five vacuum/N_2 cycles. Next, triethylamine (2.0 mL) and (trimethylsilyl)acetylene (7.16 mmol) were added to the flask under N_2, and the mixture was stirred at rt for 4 h. The reaction was quenched with sat. aq. NH_4Cl (100 mL), and extracted with Et_2O (3 x 75 mL). The combined organic layers were washed with water (2 x 100 mL), brine (1 x

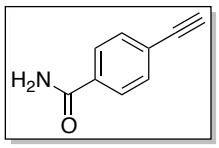
100 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash silica gel column chromatography (CH_2Cl_2:hexanes 1:3) to afford 1.23 g of a light brown crystalline solid. To effect saponification, this solid was dissolved in EtOH:H_2O 1:1 (50 mL) at rt and treated with 5.0 M NaOH (100 mmol). The reaction mixture was stirred at rt overnight, after which the EtOH was removed *in vacuo*. The aqueous layer was extracted with an additional portion of H_2O (1 x 20 mL) and ether (3 x 30 mL). Next, the aqueous layer was acidified with 6.0 M aq. HCl and extracted with ether (3 x 30 mL). The combined organic layers were dried over $MgSO_4$, and concentrated *in vacuo* to afford 732 mg of 4-ethynyl benzoic acid (**8-D**) as a light orange crystalline solid (92% overall yield). ^{1}H NMR (300 MHz, DMSO-*d6*) δ 4.43 (s, 1H), 7.58 (m, 2H), 7.93 (m, 2H), 13.14 (s, 1H); ^{13}C NMR (75 MHz, DMSO-*d6*) δ 82.7, 83.6, 126.0, 129.5, 130.9, 131.9, 166.6; ESI-MS: calculated m/z $[M-H]^-$ 145.0295, observed m/z 145.0297.

Representative procedure for amide synthesis.

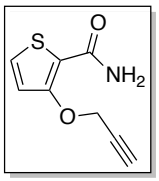


This synthesis was based in part on a previously reported method.[3] A 10-mL test tube was filled with a well-ground mixture of 2,4-dipropargyloxy benzoic acid (115 mg, 0.5 mmol), NH_4Cl/SiO_2 (500 mg 1.0 mmol), and 4-toluenesulfonyl chloride (96 mg, 0.5 mmol). Triethylamine (NEt_3, 279 μL, 2.0 mmol) was added to the tube. The mixture was stirred with a metal spatula for approximately 1 min at rt and then added to EtOAc (30 mL), filtered, and the filtrate was extracted with 0.02 N HCl (2 x 50 mL). The combined aqueous layers were washed with EtOAc (2 x 30 mL). The organic layer was extracted with 1.0 N aq. NaOH (2 x 50 mL), dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The crude product was purified by flash silica gel column chromatography (acetone:hexanes 1:3) to afford 85 mg of 2,4-dipropargyloxybenzamide as a white crystalline solid (74% overall yield). ^{1}H NMR (300 MHz, Acetone-*d6*) δ 3.13 (t, 1H, *J* = 2.4 Hz), 3.20 (t, 1H, *J* = 2.4 Hz), 4.88 (d, 2H, *J* = 2.4 Hz), 5.04 (d, 2H, *J* = 2.6 Hz), 6.59 (bs, 1H), 6.77 (dd, 1H, *J* = 8.9, 2.4 Hz), 6.86 (d, 1H, *J* = 2.2 Hz), 7.52 (bs, 1H), 8.08 (d, 1H, *J* = 8.8 Hz); ^{13}C NMR (75 MHz, Acetone-*d6*) δ 56.7, 57.4, 77.6, 78.2, 79.0, 79.3, 101.7, 108.1, 116.9, 134.5, 158.1, 162.3, 166.2; ESI-MS: calculated m/z $[M+Na]^+$ 252.0632, observed m/z 252.0635.

4-Ethynylbenzamide: Synthesis analogous to above; 57 mg of a white crystalline solid (79% overall yield). ^{1}H NMR (300 MHz, Acetone-*d6*) δ 3.81 (s, 1H), 6.80 (bs, 1H), 7.57 (m, 3H), 7.94 (dt, 2H, *J* = 8.4, 1.8 Hz); ^{13}C NMR (75 MHz, Acetone-*d6*) δ 81.3, 83.6, 126.1, 128.6, 132.8, 135.6, 168.3; ESI-MS: calculated m/z $[M+H]^+$ 146.0601, observed m/z 146.0598.



3-propargyloxy-2-thiophenecarboxamide: Synthesis analogous to above; 62 mg of a white crystalline solid (68% overall yield). ^{1}H NMR (300 MHz, Acetone-*d6*) δ 3.20 (t, 1H, *J* = 2.5 Hz), 5.02 (d, 2H, *J* = 2.5 Hz), 6.61 (bs, 1H), 7.04 (bs, 1H), 7.19 (d, 2H, *J* = 5.5 Hz), 7.63 (d, 2H, *J* = 5.6 Hz); ^{13}C NMR (75 MHz, Acetone-*d6*) δ 59.9, 78.2, 79.2, 118.1, 119.3, 130.0, 155.6, 163.1; ESI-MS: calculated m/z $[M+Na]^{+}$ 204.0090, observed m/z 204.0098.



HPLC calibration curves for initial library building blocks.

Loading 6-bromo and 7-bromo-2-naphthalenyloxyacetic acids (**4a**–**b**) and the alkyne building blocks (**8A**–**D**) onto Rink-linker derivatized amino support **3** and then subsequently cleaving these building blocks off of the support yielded primary amide derivatives. These amides were analyzed by HPLC to quantitate the amount of initial building block loaded onto support **3** and the amount left over after SPOT-synthesis reactions (and therefore, the amount of product formed; see below for more detail). UV calibration curves were constructed for each amide derivative. These calibration curves allowed us to determine the exact amount of product formed, and also ensured the generation of stock solutions for subsequent biological evaluation at an accurate concentration. Notably, we have previously shown that compounds synthesized and quantified by the SPOT-synthesis method result in identical biological readouts as compounds prepared in solution.[4]

Amide versions of each initial building block were synthesized as described above. Stock solutions in CH_3CN were prepared for each amide derivative. Eight dilutions of each stock solution were analyzed by HPLC (see below for specific amounts used), and peak areas at 235 nm were determined by integration. The calibration curves were constructed by plotting the integrated peak area versus compound concentration (see Figures S-2–S-7 below).

- A 2-(6-bromo-naphthalen-2-yloxy)-acetamide stock solution was prepared by dissolving 1.98 mg in 3.00 mL CH_3CN. This stock solution was further diluted as shown below.

Table S-3. Content of 2-(6-bromo-naphthalen-2-yloxy)-acetamide calibration curve solutions.

Solution #	Stock solution used (μL)	CH_3CN used (μL)
1	5	195
2	10	190
3	20	180
4	30	170
5	40	160
6	50	150
7	60	140
8	70	130

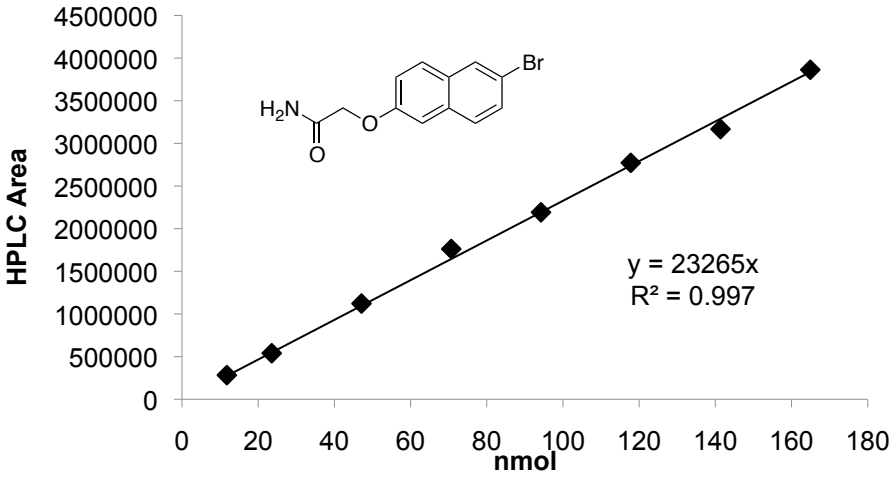


Figure S-2. Calibration curve generated for 2-(6-bromo-naphthalen-2-yloxy)-acetamide by HPLC analysis (UV detection at 235 nm).

- A 2-(7-bromo-naphthalen-2-yloxy)-acetamide stock solution was prepared by dissolving 2.28 mg in 3.00 mL CH_3CN. This stock solution was further diluted as shown below.

Table S-4. Content of 2-(7-bromo-naphthalen-2-yloxy)-acetamide calibration curve solutions.

Solution #	Stock solution used (μL)	CH_3CN used (μL)
1	5	195
2	10	190
3	15	185
4	20	180
5	30	170
6	40	160
7	50	150
8	60	140

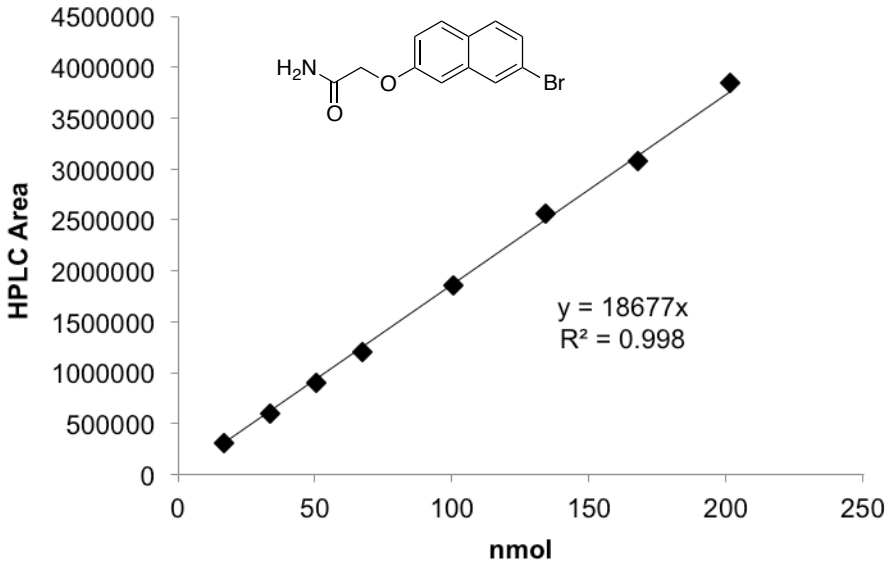


Figure S-3. Calibration curve generated for 2-(7-bromo-naphthalen-2-yloxy)-acetamide by HPLC analysis (UV detection at 235 nm).

- A 4-propargyloxybenzamide stock solution was prepared by dissolving 3.36 mg in 3.00 mL CH_3CN. This stock solution was further diluted as shown below.

Table S-5. Content of 4-propargyloxybenzamide calibration curve solutions.

Solution #	Stock solution used (μL)	CH_3CN used (μL)
1	4	196
2	14	186
3	20	180
4	25	175
5	30	170
6	40	160
7	50	150
8	60	140

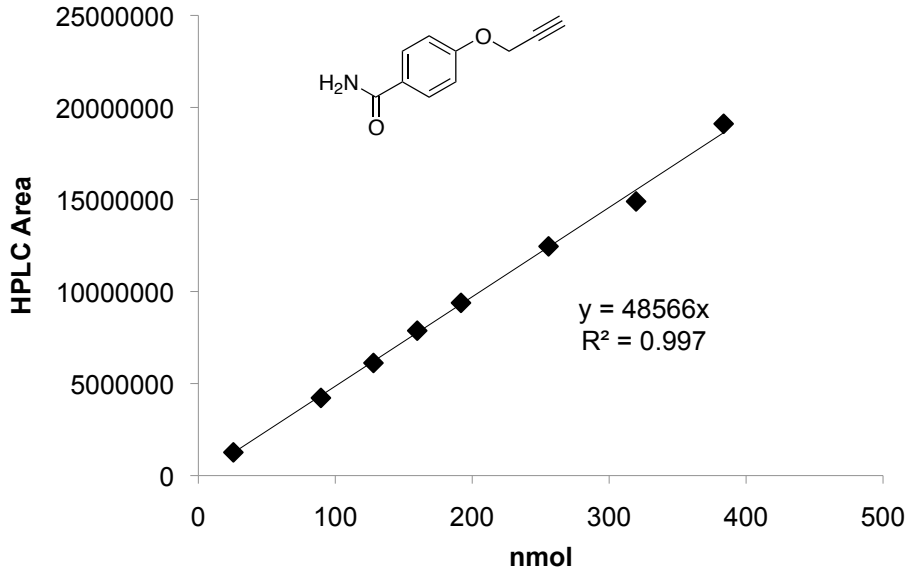


Figure S-4. Calibration curve generated for 4-propargyloxybenzamide by HPLC analysis (UV detection at 235 nm).

- A 3-propargyloxy-2-thiophenecarboxamide stock solution was prepared by dissolving 2.86 mg in 3.00 mL CH_3CN. This stock solution was further diluted as shown below.

Table S-6. Content of 3-propargyloxy-2-thiophenecarboxamide calibration curve solutions.

Solution #	Stock solution used (μL)	CH_3CN used (μL)
1	5	195
2	10	190
3	15	185
4	20	180
5	30	170
6	40	160
7	50	150
8	60	140

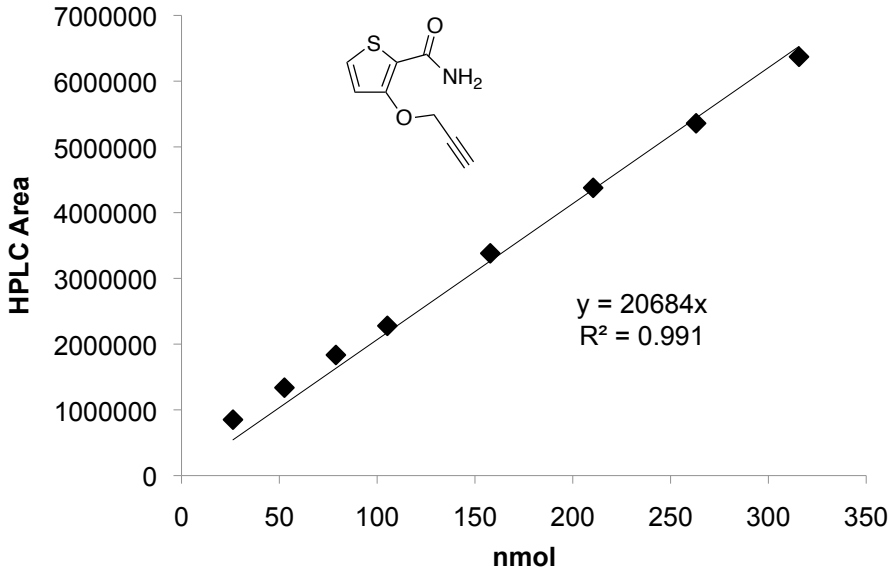


Figure S-5. Calibration curve generated for 3-propargyloxy-2-thiophenecarboxamide by HPLC analysis (UV detection at 235 nm).

- A 4-ethynylbenzamide stock solution was prepared by dissolving 3.02 mg in 3.00 mL CH_3CN. This stock solution was further diluted as shown below.

Table S-7. Content of 4-ethynylbenzamide calibration curve solutions.

Solution #	Stock solution used (μL)	CH_3CN used (μL)
1	5	195
2	10	190
3	15	185
4	20	180
5	30	170
6	35	165
7	40	160
8	45	155

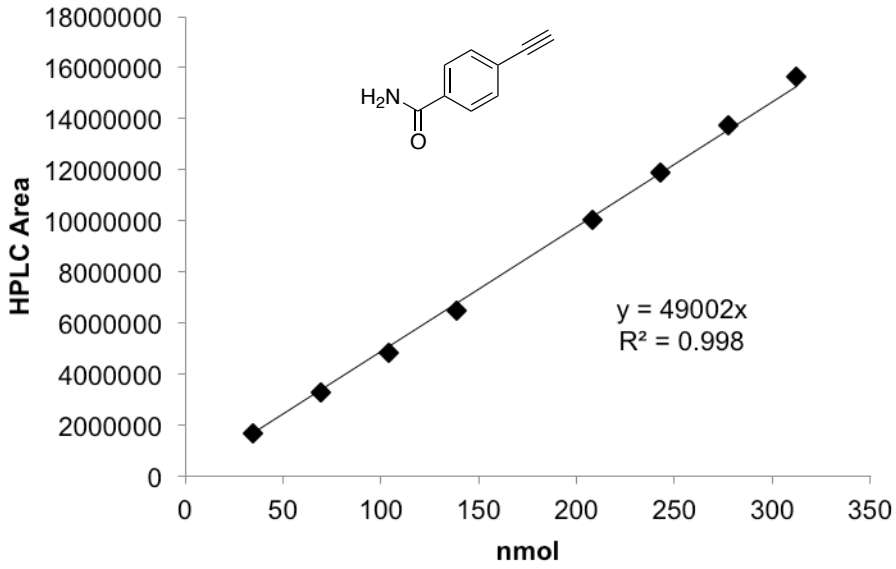


Figure S-6. Calibration curve generated for 4-ethynylbenzamide by HPLC analysis (UV detection at 235 nm).

- A 2,4-dipropargyloxybenzamide stock solution was prepared by dissolving 3.10 mg in 3.00 mL CH_3CN. This stock solution was further diluted as shown below.

Table S-8. Content of 2,4-dipropargyloxybenzamide calibration curve solutions.

Solution #	Stock solution used (μL)	CH_3CN used (μL)
1	4	196
2	10	190
3	18	182
4	20	180
5	25	175
6	35	165
7	45	155
8	55	145

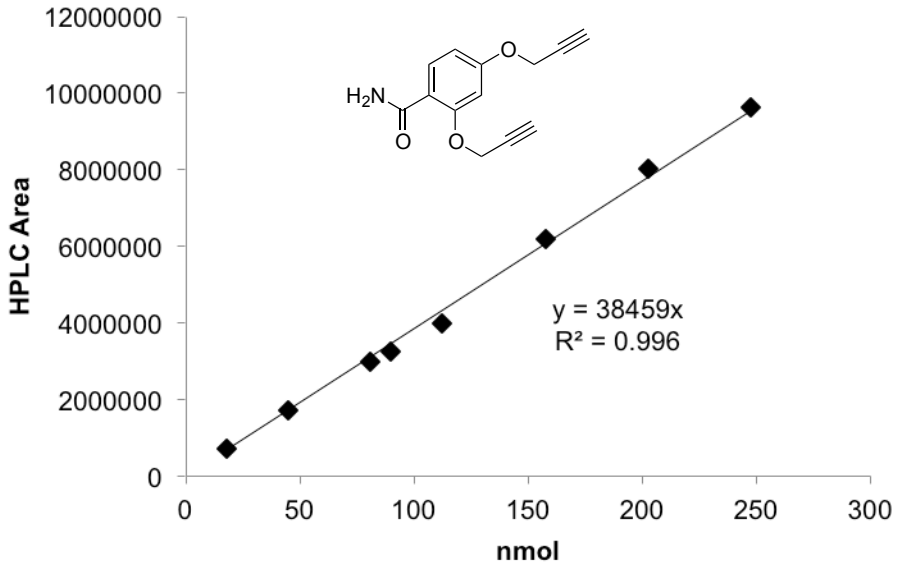


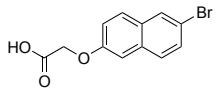
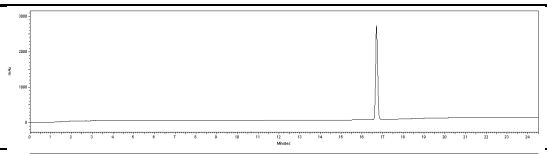
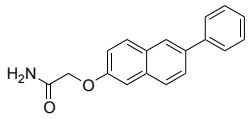
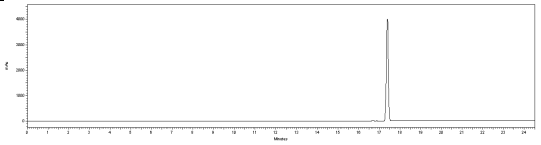
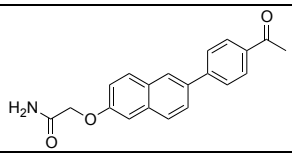
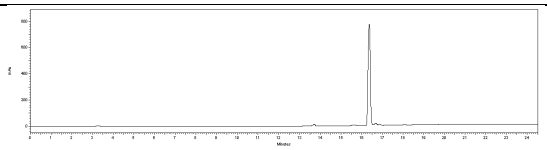
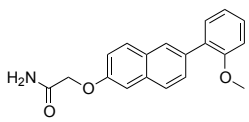
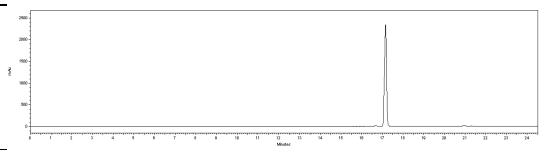
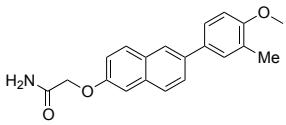
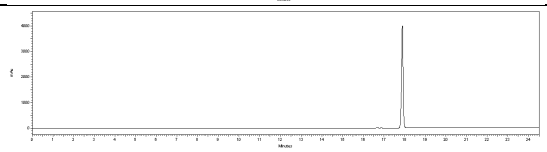
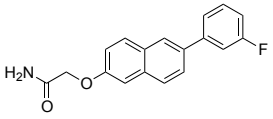
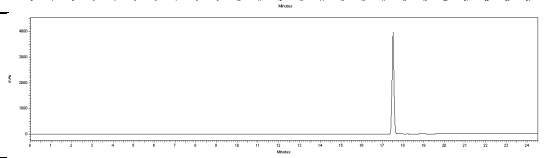
Figure S-7. Calibration curve generated for 2,4-dipropargyloxybenzamide by HPLC analysis (UV detection at 235 nm).

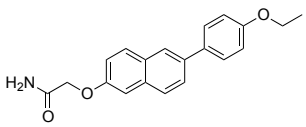
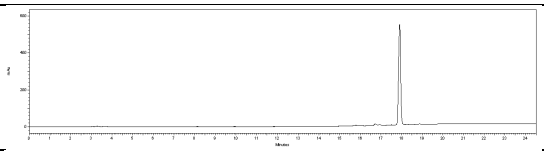
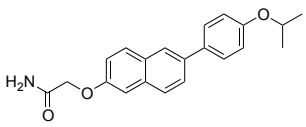
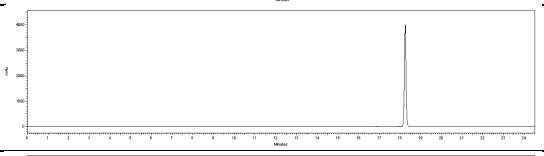
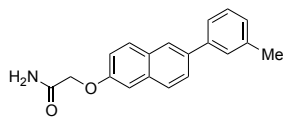
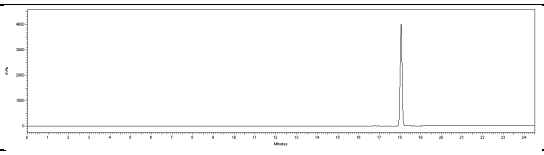
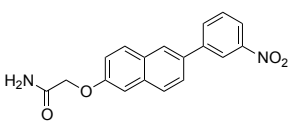
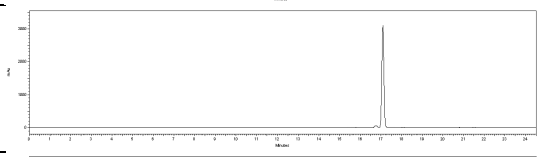
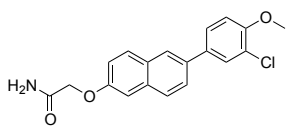
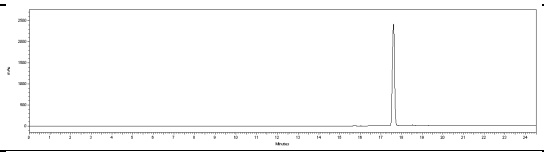
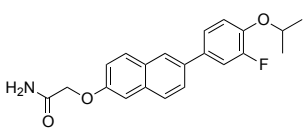
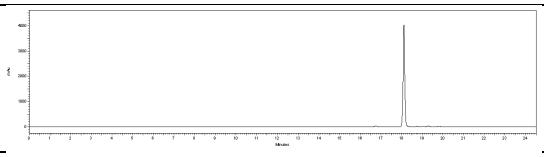
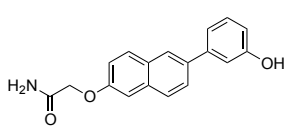
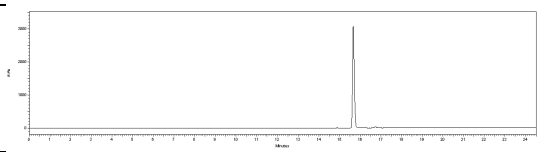
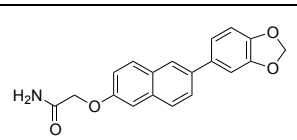
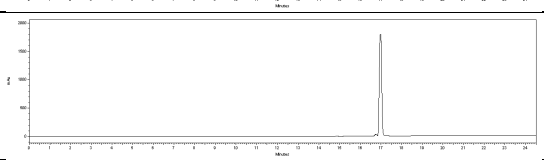
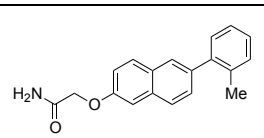
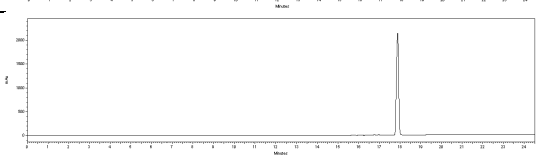
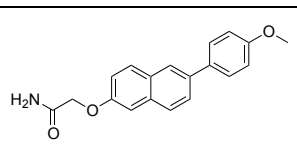
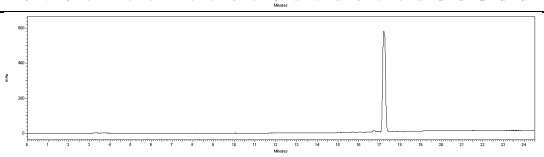
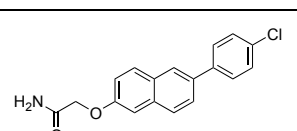
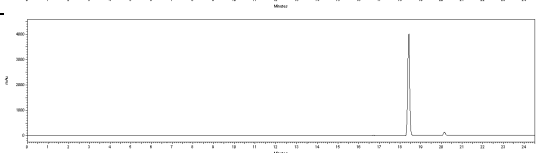
Characterization of 70-member phenyl-naphthalene library (7a-b).

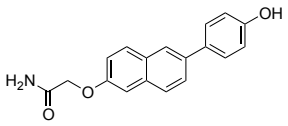
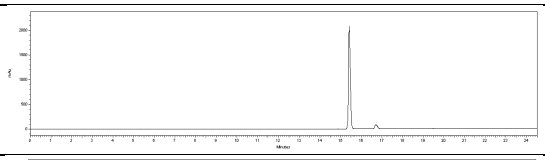
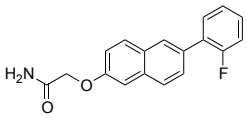
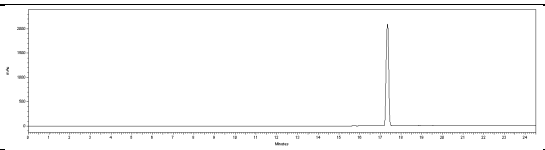
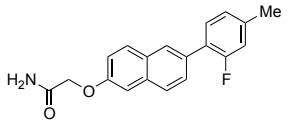
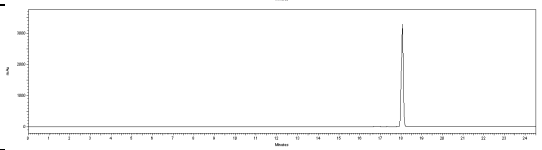
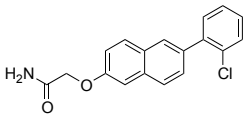
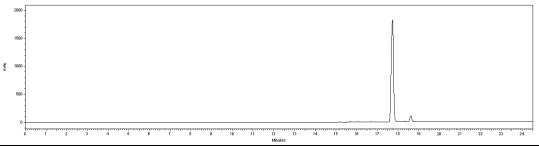
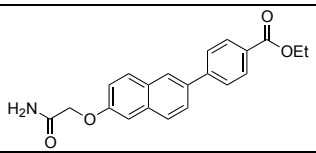
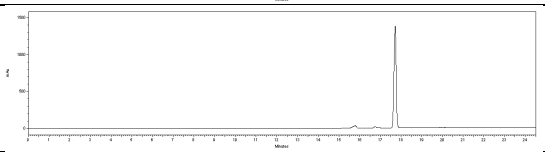
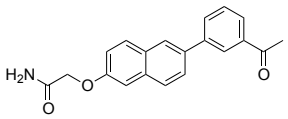
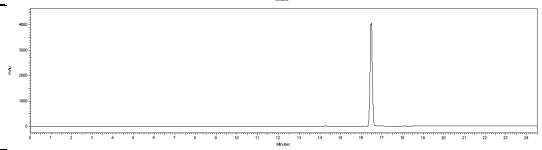
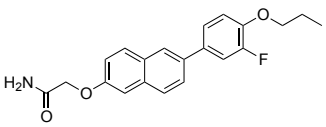
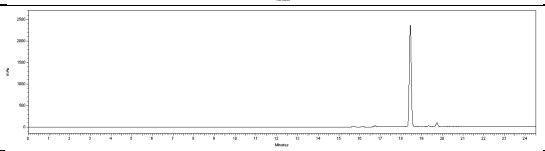
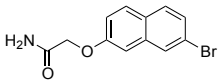
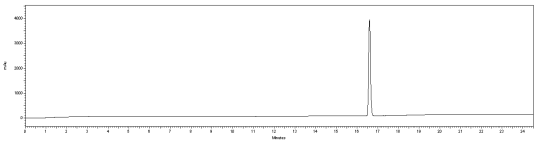
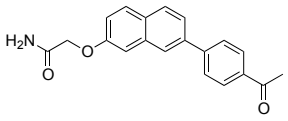
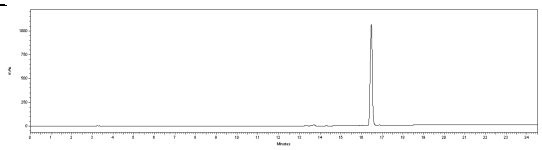
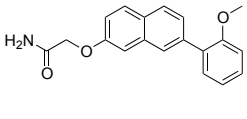
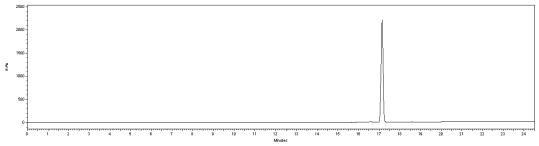
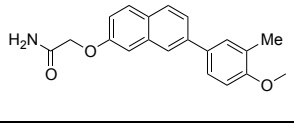
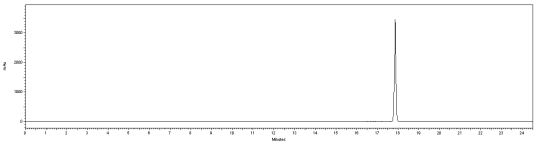
Phenyl-naphthalene library (7a-b) purity, conversion, and HPLC-MS analysis. Forty-six phenyl-naphthalene SPOT-synthesis products (~66% of the entire library) were selected in order to evaluate the Suzuki-Miyaura reaction for conversion and product identity and analyze the phenyl-naphthalene library (**7a-b**) for purity.

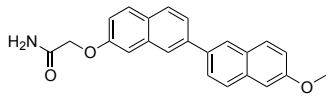
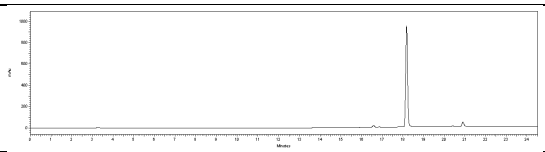
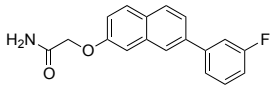
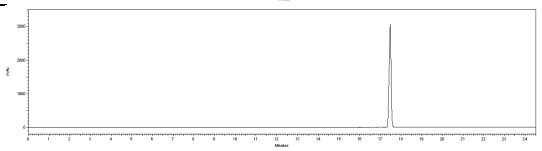
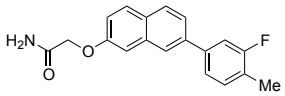
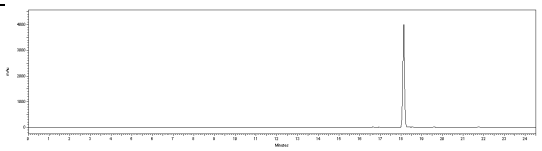
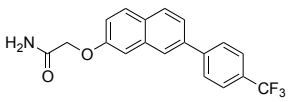
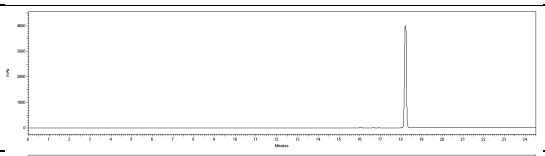
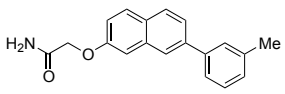
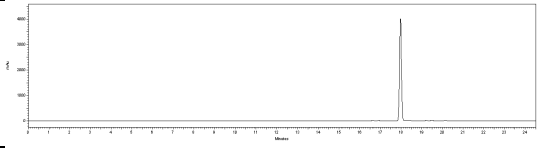
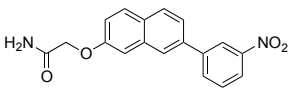
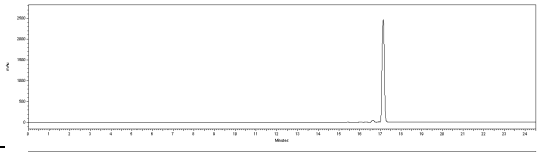
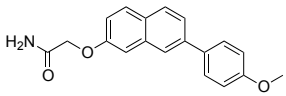
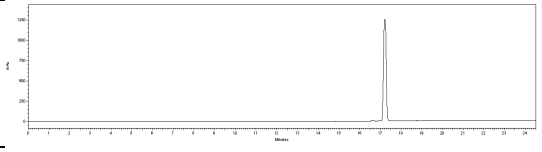
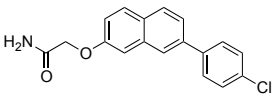
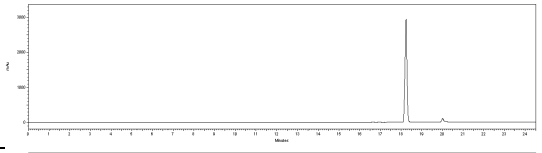
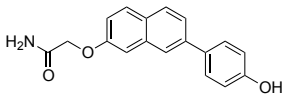
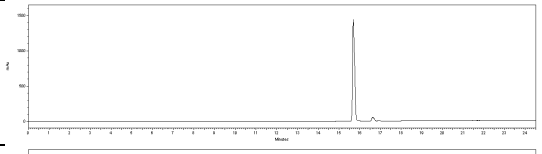
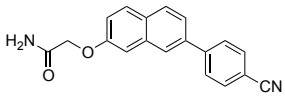
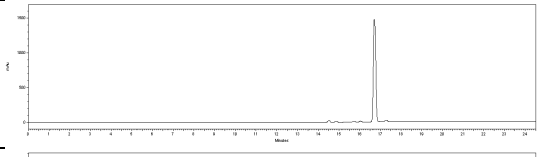
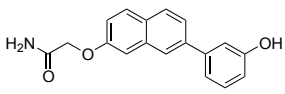
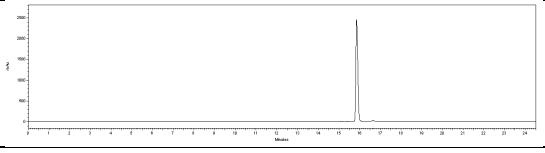
The purities of the 46 phenyl-naphthalenes (**7a-b**) generated from aryl bromide supports **5a-b** were analyzed using HPLC with UV detection at 254 nm. The Suzuki-Miyaura reaction conversions were calculated by comparison of (1) the amount of initial building block that was initially loaded onto Rink-amide linker-derivatized support **3** to (2) the amount of initial building block that was detected in the phenyl-naphthalene **7a-b** products post-cleavage. The two calibration curves shown above in Figures S-2 and S-3 were used for the % conversion calculations and to determine the amount of product formed/per spot. The latter amounts allowed for the generation of stock solutions of known concentrations for biological testing.

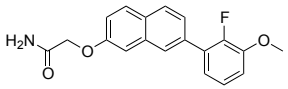
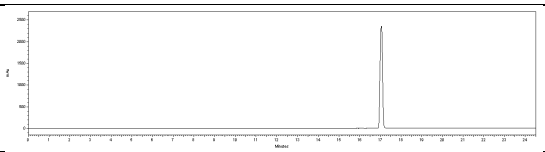
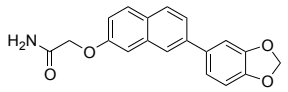
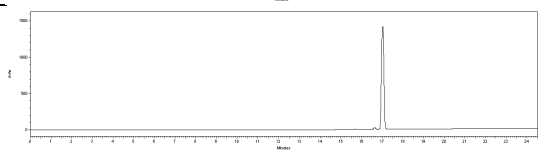
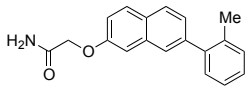
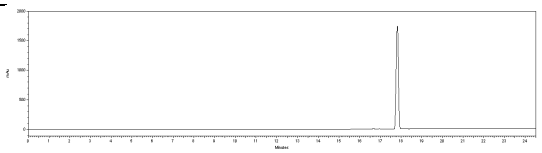
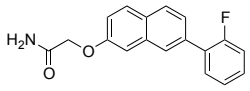
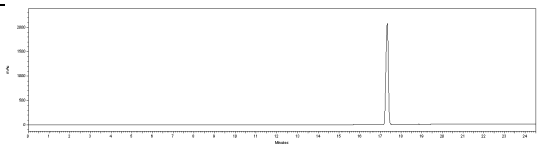
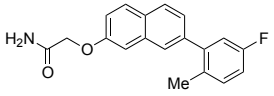
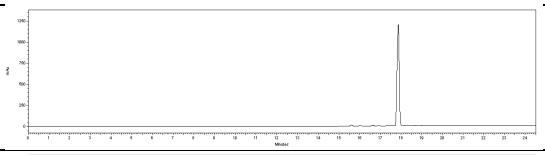
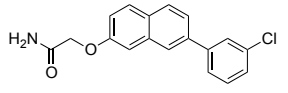
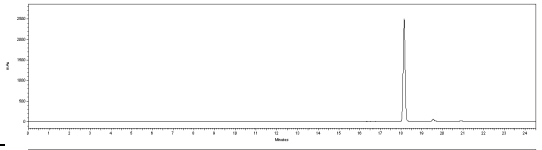
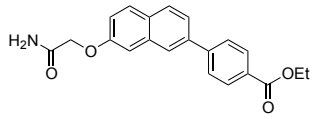
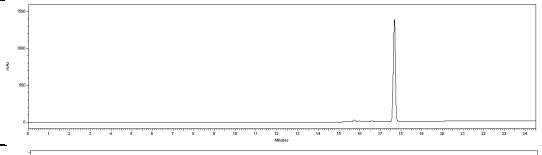
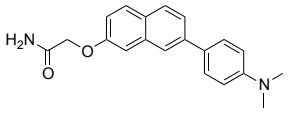
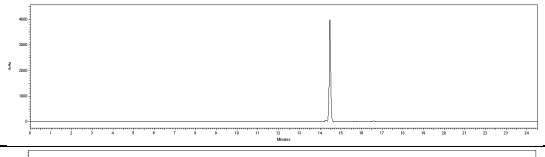
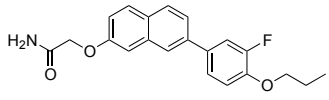
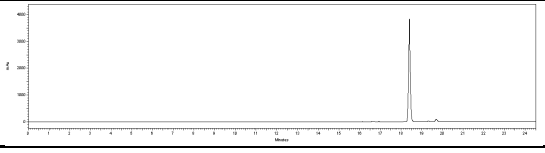
Table S-9. Purity, conversion, and HPLC-MS data for ~66% of phenyl-naphthalene library **7a-b**.

Compound and initial building block loading	% Purity % Conversion Calculated m/z Observed m/z	HPLC chromatogram at 254 nm
 Loading: 100 nmol	>98% - $[M+H]^+$ 280.0 279.9	
	>98% >98% $[M+H]^+$ 278.1 278.1	
	96.4% >98% $[M+H]^+$ 320.1 320.1	
	>98% >98% $[M+H]^+$ 308.1 308.1	
	>98% >98% $[M+H]^+$ 322.1 322.1	
	>98% >98% $[M+H]^+$ 296.1 296.0	

	>98% >98% $[M+H]^+$ 322.1 322.1	
	>98% >98% $[M+H]^+$ 336.2 336.1	
	>98% >98% $[M+H]^+$ 292.1 292.0	
	96.3% >98% $[M+H]^+$ 323.1 323.1	
	>98% >98% $[M+H]^+$ 342.1 342.0	
	96.5% >98% $[M+H]^+$ 354.1 354.1	
	>98% >98% $[M+H]^+$ 294.1 294.0	
	>98% >98% $[M+H]^+$ 322.1 322.1	
	>98% >98% $[M+H]^+$ 292.1 292.0	
	>98% >98% $[M+H]^+$ 308.1 308.1	
	95.9% >98% $[M+H]^+$ 312.1 311.9	

	94.4% 95.3% $[M+H]^+$ 294.1 294.0	
	>98% >98% $[M+H]^+$ 296.1 296.0	
	>98% >98% $[M+H]^+$ 310.1 310.0	
	93.7% >98% $[M+H]^+$ 312.1 311.9	
	95.0% 96.6% $[M+H]^+$ 350.1 350.1	
	>98% >98% $[M+H]^+$ 320.1 320.1	
	94.2% >98% $[M+H]^+$ 354.1 354.1	
 Loading: 115 nmol	>98% - $[M+H]^+$ 280.0 279.9	
	>98% >98% $[M+H]^+$ 320.1 320.1	
	>98% >98% $[M+H]^+$ 308.1 308.0	
	>98% >98% $[M+H]^+$ 322.1 322.1	

	93.5% 97.1% $[M+H]^+$ 358.1 358.1	
	>98% >98% $[M+H]^+$ 296.1 296.0	
	>98% >98% $[M+H]^+$ 310.1 310.0	
	>98% >98% $[M+H]^+$ 346.1 346.0	
	>98% >98% $[M+H]^+$ 292.1 292.1	
	96.8% 97.9% $[M+H]^+$ 323.1 323.1	
	>98% >98% $[M+H]^+$ 308.1 308.1	
	96.7% >98% $[M+H]^+$ 312.1 311.9	
	95.1% 95.5% $[M+H]^+$ 294.1 294.0	
	94.8% 97.1% $[M+H]^+$ 303.1 303.0	
	>98% >98% $[M+H]^+$ 294.1 294.0	

	>98% >98% $[M+H]^+$ 326.1 326.1	
	>98% >98% $[M+H]^+$ 322.1 322.1	
	>98% >98% $[M+H]^+$ 292.1 292.0	
	>98% >98% $[M+H]^+$ 296.1 296.0	
	97.3% >98% $[M+H]^+$ 310.1 310.0	
	97.1% >98% $[M+H]^+$ 312.1 311.9	
	95.2% 97.8% $[M+H]^+$ 350.1 350.1	
	97.2% >98% $[M+H]^+$ 321.2 321.0	
	95.9% >98% $[M+H]^+$ 354.1 354.1	

ICP Pd trace analysis of selected phenyl-naphthalenes.

A set of representative phenyl-naphthalene products (**7a**-**b)** was subjected to Pd trace analysis using inductively coupled plasma (ICP) and an optical emission spectrometer (PerkinElmer Optima 2000 DV). Four phenyl-naphthalene samples (**7a**-**17**, **7a**-**13**, **7b**-**9**, and **7b**-**19**) were analyzed at 340.458 nm (five replicate experiments each), and residual Pd was quantified by

comparison to a Pd standard (Fluka). The averaged ICP Pd data are shown below in Table S-10 and are at the part-per-billion (ppb) level/per spot.

Table S-10. ICP analysis data of selected phenyl-naphthalenes.

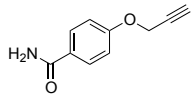
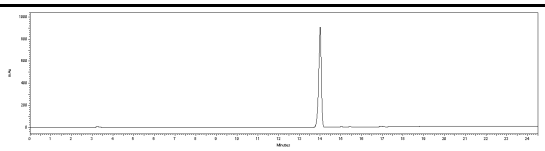
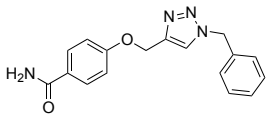
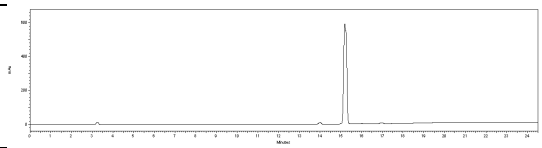
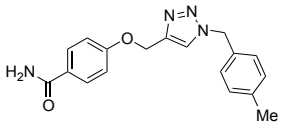
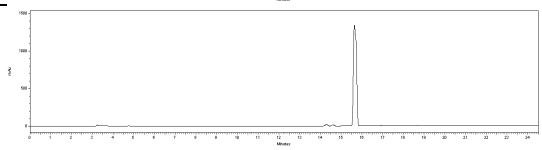
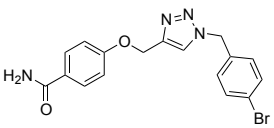
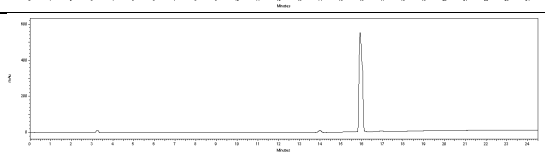
Phenyl-naphthalene	Amount of Pd (ppb)/macroarray spot
7a-17	15
7a-13	16
7b-9	22
7b-19	17

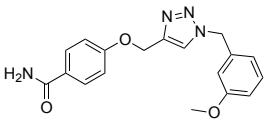
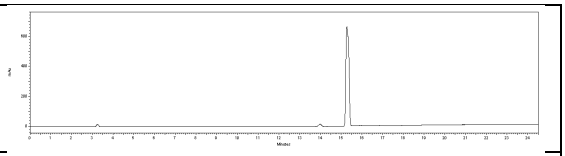
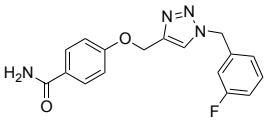
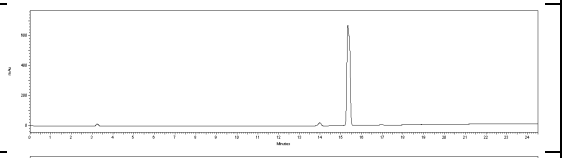
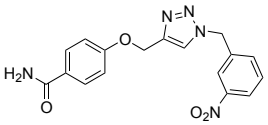
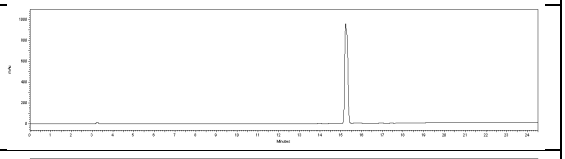
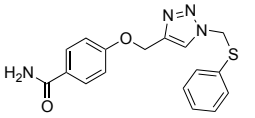
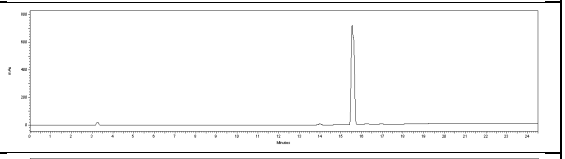
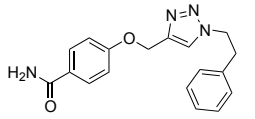
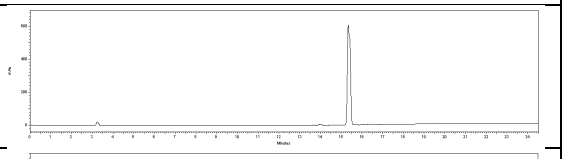
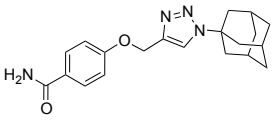
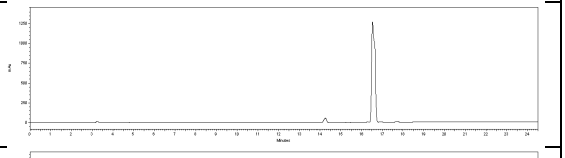
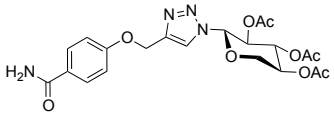
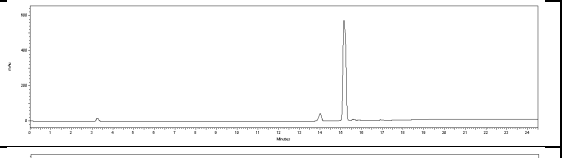
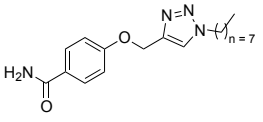
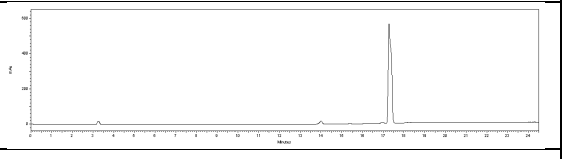
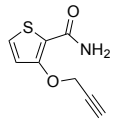
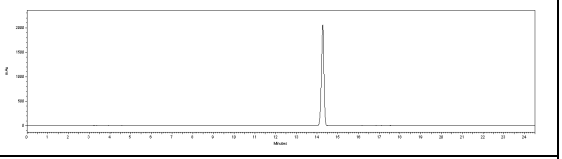
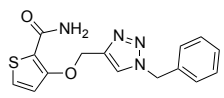
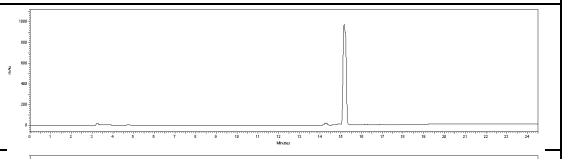
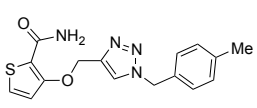
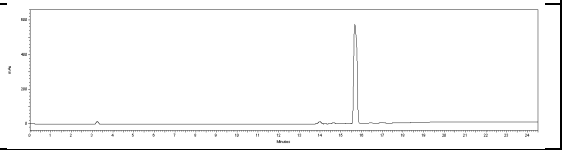
Characterization of 44-member 1,2,3-triazole library (11).

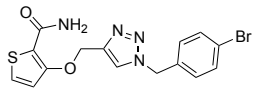
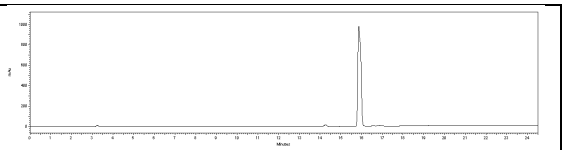
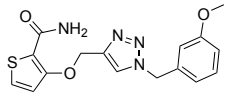
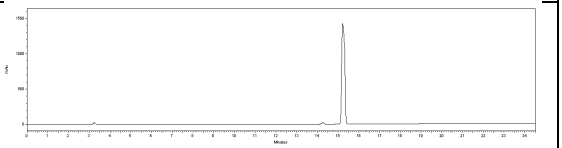
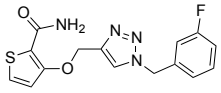
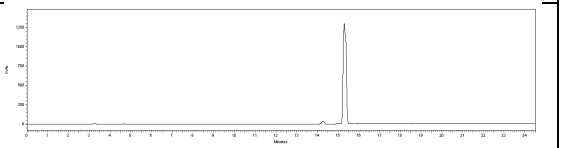
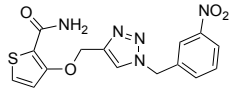
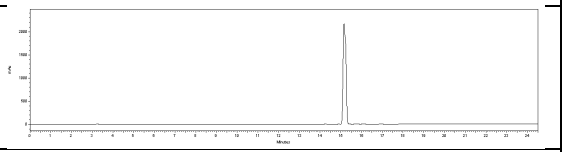
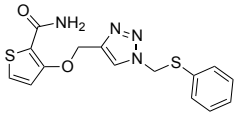
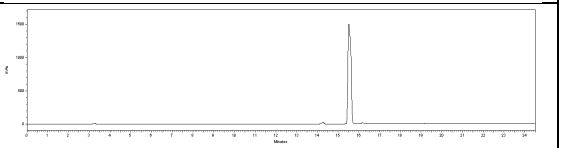
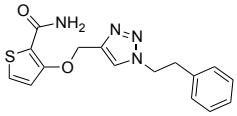
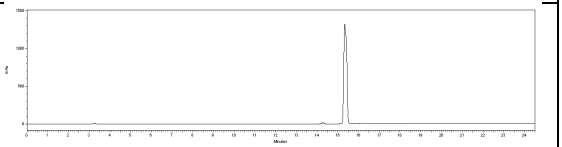
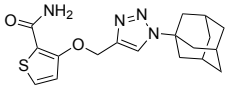
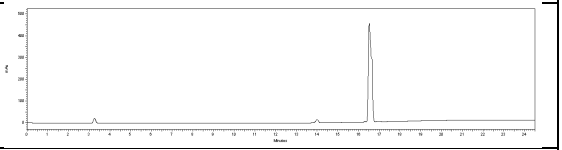
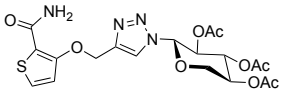
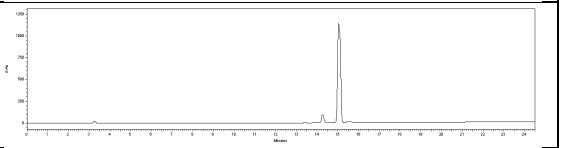
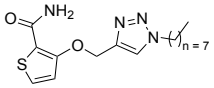
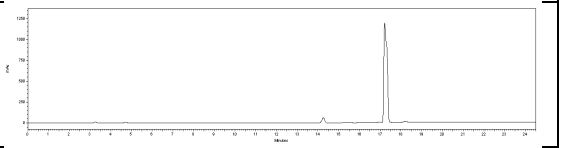
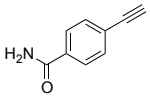
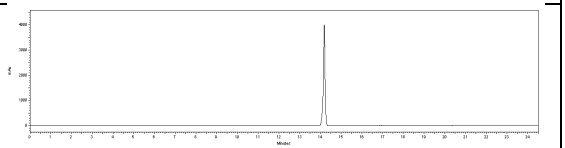
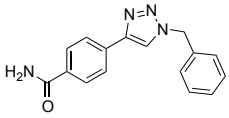
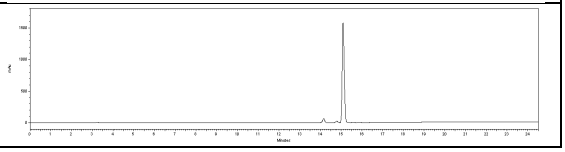
1,2,3-triazole macroarray purity, conversion, and HPLC-MS analysis. The entire 44-member 1,2,3-triazole library (**11**) was analyzed for product purity, conversion, and product identity.

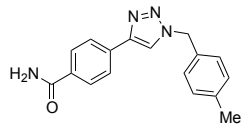
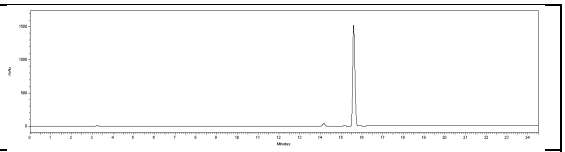
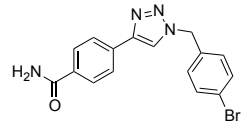
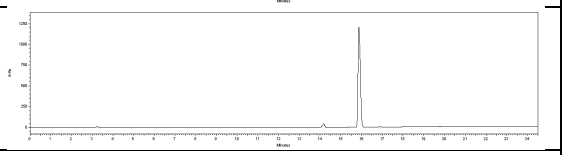
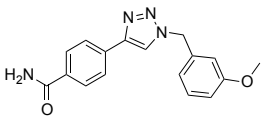
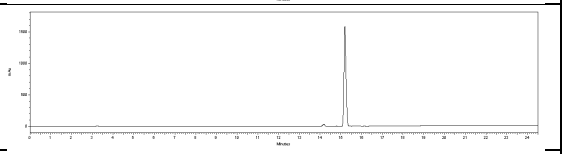
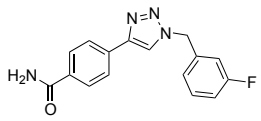
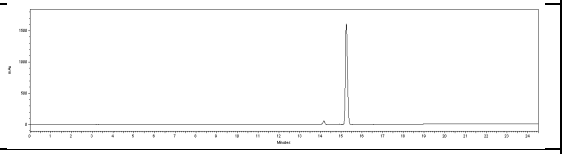
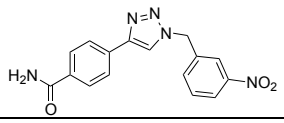
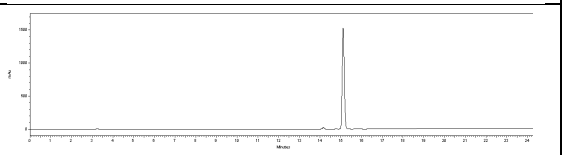
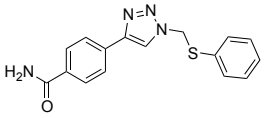
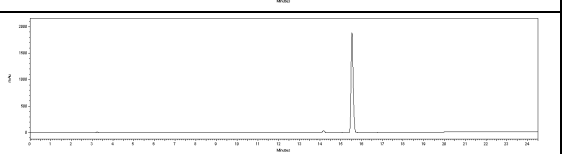
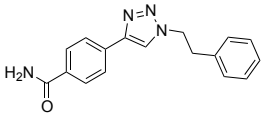
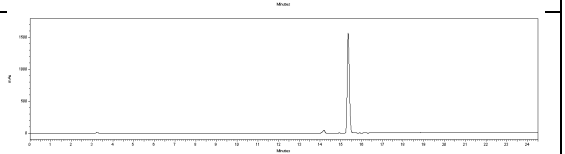
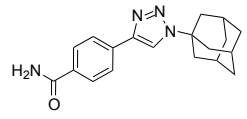
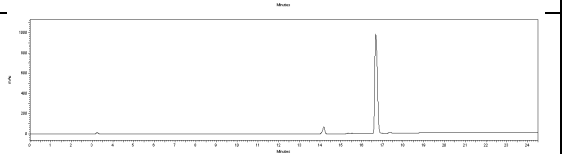
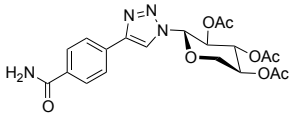
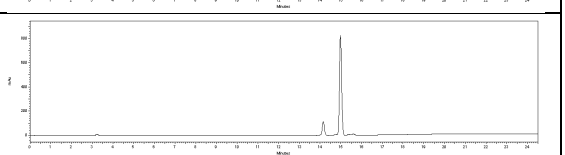
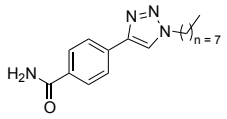
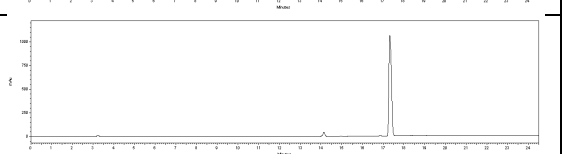
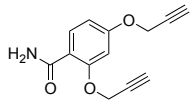
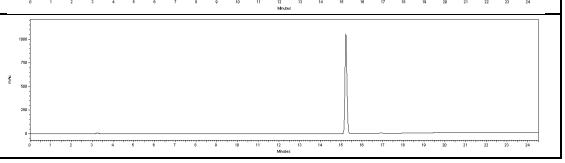
The purities of the 1,2,3-triazoles (**11**) were analyzed using HPLC with UV detection at 254 nm. The CuAAC reaction conversions were calculated by comparison of (1) the amount of initial building block that was loaded onto Rink-amide linker-derivatized support **3** to (2) the amount of initial building block that was detected in the 1,2,3-triazole products (**11**) post-cleavage. The four calibration curves shown above in Figures S-4 to S-7 were used for the % conversion calculations.

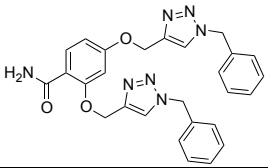
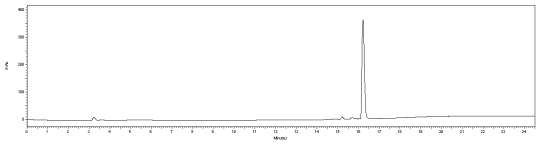
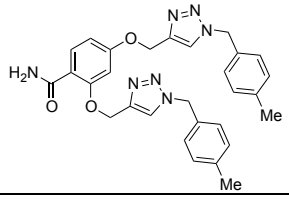
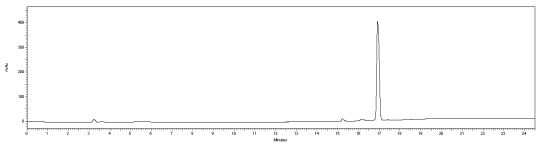
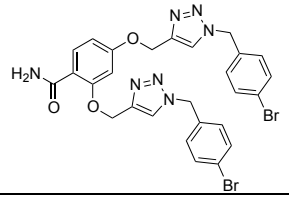
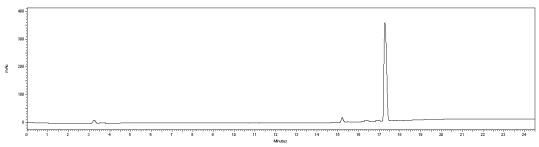
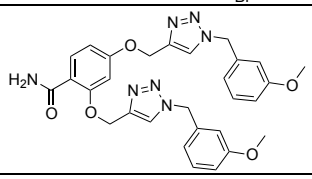
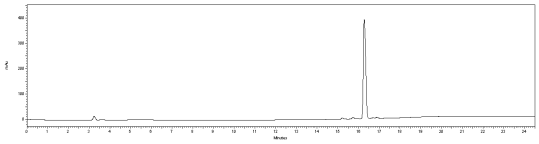
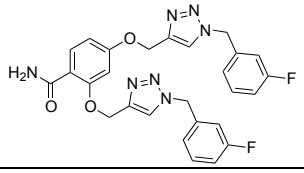
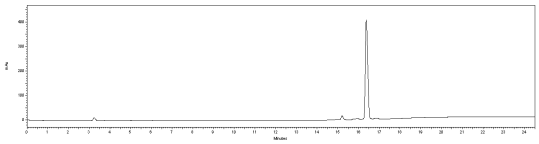
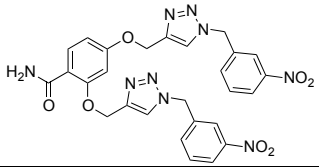
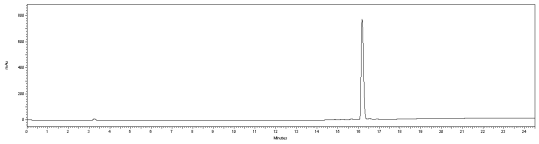
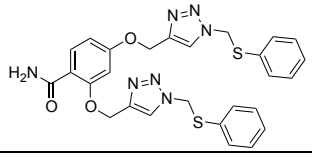
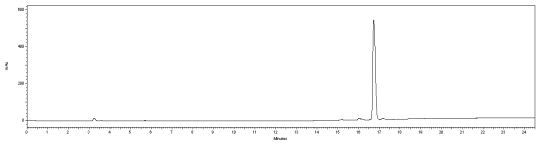
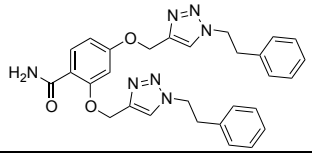
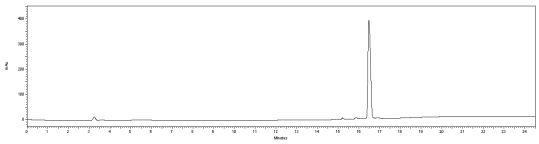
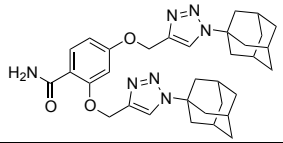
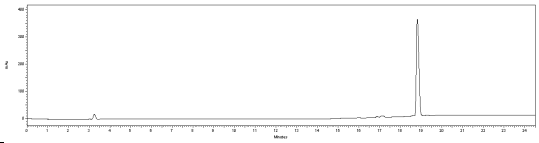
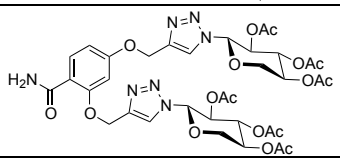
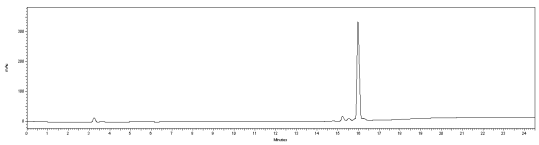
Table S-11. Purity, conversion, and HPLC-MS data for the 1,2,3-triazole library **11**.

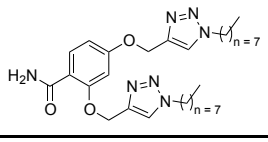
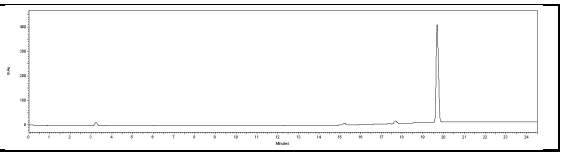
Compound and initial building block loading	% Purity % Conversion Calculated m/z Observed m/z	HPLC chromatogram at 254 nm
 Loading: 257 nmol	>98% - $[M+H]^+$ 176.1 176.0	
	>98% >98% $[M+H]^+$ 309.1 309.1	
	>98% >98% $[M+H]^+$ 323.1 323.1	
	>98% >98% $[M+H]^+$ 387.0 387.0	

	>98% >98% $[M+H]^+$ 387.0 387.0	
	97.4% >98% $[M+H]^+$ 327.1 327.1	
	>98% >98% $[M+H]^+$ 354.1 354.1	
	>98% >98% $[M+H]^+$ 341.1 341.1	
	>98% >98% $[M+H]^+$ 323.1 323.1	
	96.2% 97.1% $[M+H]^+$ 353.2 353.1	
	90.5% 95.3% $[M+H]^+$ 477.2 477.1	
	95.7% 96.9% $[M+H]^+$ 331.2 331.1	
 Loading: 155 nmol	>98% - $[M+H]^+$ 182.0 181.9	
	>98% >98% $[M+H]^+$ 315.1 315.0	
	>98% >98% $[M+H]^+$ 329.1 329.1	

	>98% >98% $[M+H]^+$ 393.0 392.9	
	>98% >98% $[M+H]^+$ 345.1 345.0	
	97.1% 97.8% $[M+H]^+$ 333.1 333.0	
	>98% >98% $[M+H]^+$ 360.1 360.0	
	>98% >98% $[M+H]^+$ 347.1 347.0	
	>98% >98% $[M+H]^+$ 329.1 329.1	
	>98% >98% $[M+H]^+$ 359.2 359.1	
	93.2% 94.8% $[M+H]^+$ 483.1 483.1	
	>98% >98% $[M+H]^+$ 337.2 337.1	
 Loading: 180 nmol	>98% - $[M+H]^+$ 146.1 145.9	
	95.7% 97.5% $[M+H]^+$ 279.1 279.1	

	97.0% >98% $[M+H]^+$ 293.1 293.1	
	96.6% >98% $[M+H]^+$ 357.0 357.0	
	97.9% >98% $[M+H]^+$ 309.1 309.1	
	96.3% 97.8% $[M+H]^+$ 297.1 297.0	
	>98% >98% $[M+H]^+$ 324.1 324.0	
	97.8% >98% $[M+H]^+$ 311.1 310.9	
	96.9% >98% $[M+H]^+$ 293.1 293.0	
	94.3% 97.3% $[M+H]^+$ 323.2 323.1	
	86.2% 93.9% $[M+H]^+$ 447.1 447.1	
	96.5% >98% $[M+H]^+$ 301.2 301.1	
 Loading: 91 nmol	>98% - $[M+H]^+$ 230.1 230.0	

	>98% >98% $[M+H]^+$ 496.2 496.2	
	>98% >98% $[M+H]^+$ 524.2 524.3	
	97.8% >98% $[M+H]^+$ 652.0 652.0	
	>98% >98% $[M+H]^+$ 556.2 556.2	
	96.8% >98% $[M+H]^+$ 532.2 532.2	
	>98% >98% $[M+H]^+$ 586.2 586.2	
	>98% >98% $[M+H]^+$ 560.2 560.1	
	>98% >98% $[M+H]^+$ 524.2 524.2	
	97.5% >98% $[M+H]^+$ 584.3 584.3	
	96.6% >98% $[M+H]^+$ 823.3 823.3	

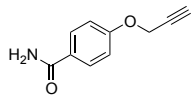
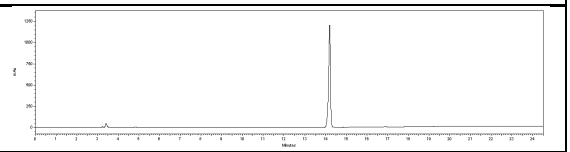
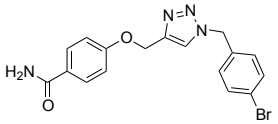
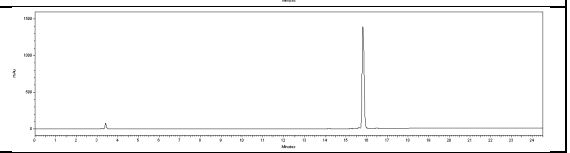
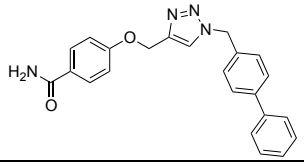
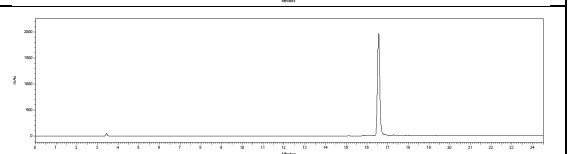
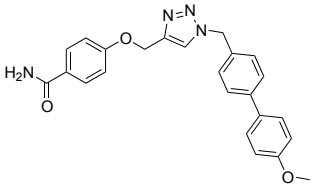
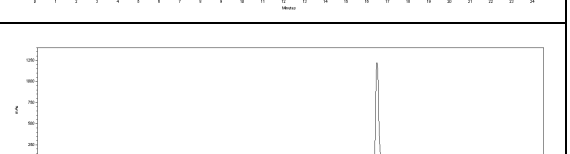
	97.8% >98% $[M+H]^+$ 540.4 540.4	

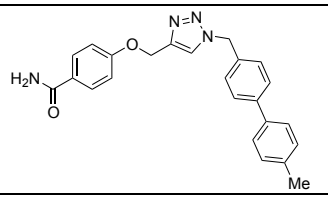
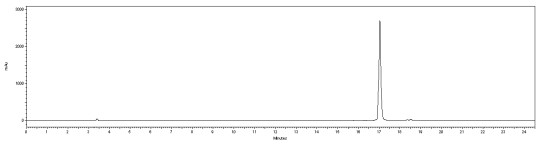
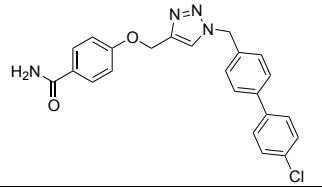
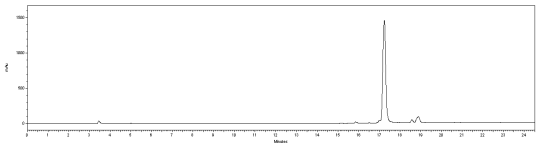
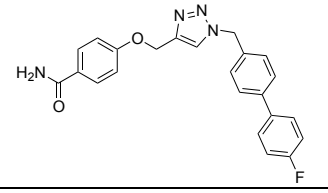
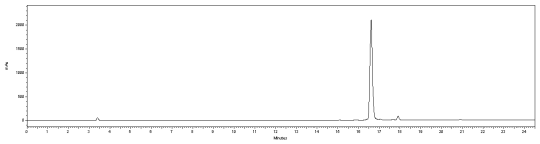
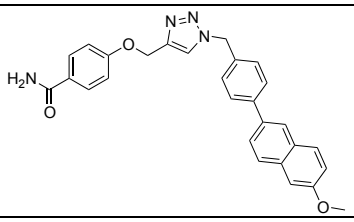
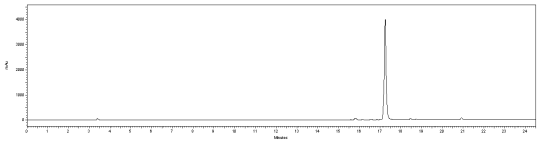
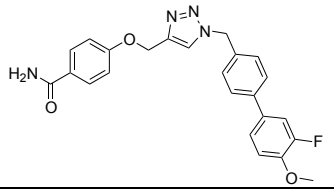
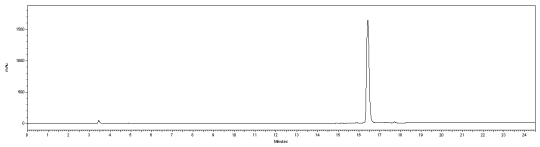
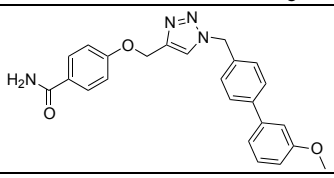
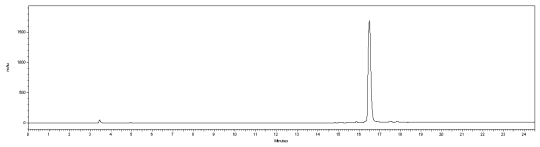
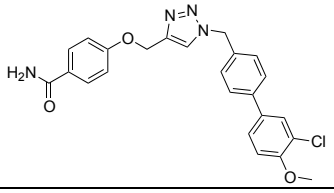
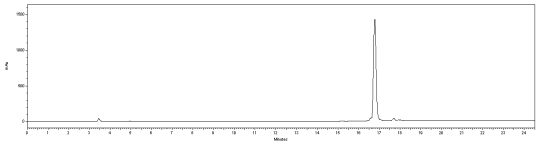
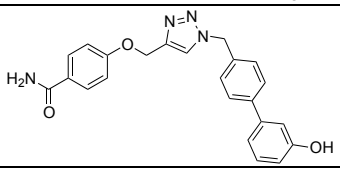
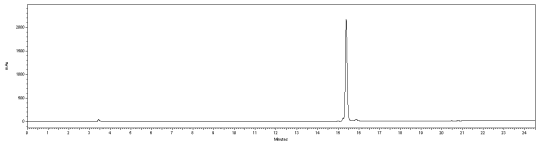
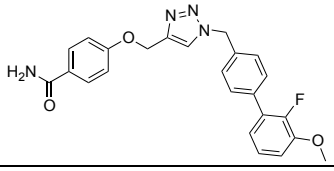
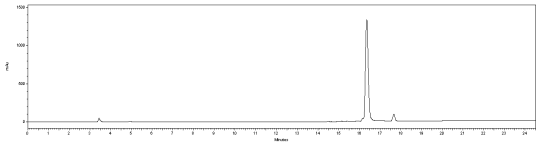
Characterization of 18-member CuAAC/Suzuki-Miyaura library (13).

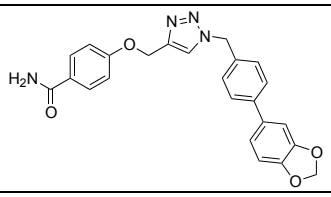
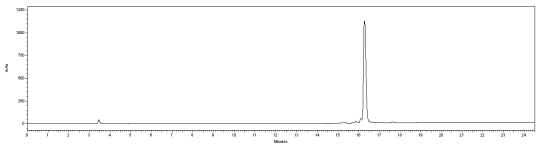
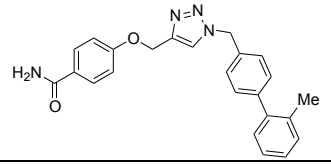
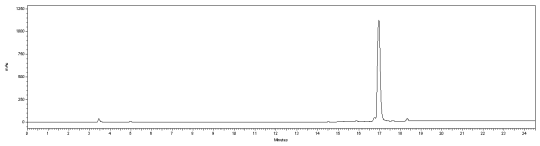
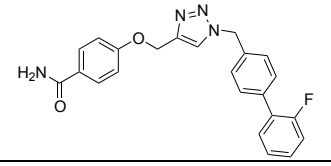
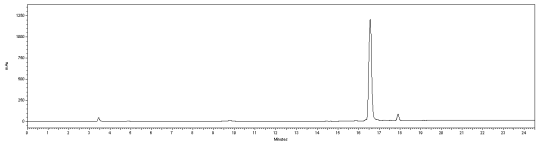
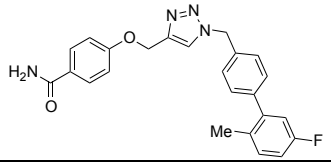
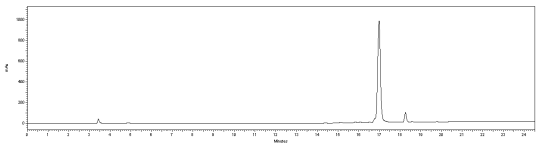
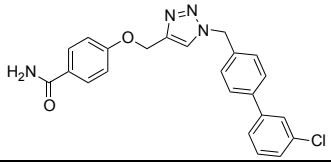
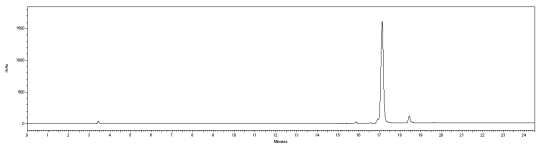
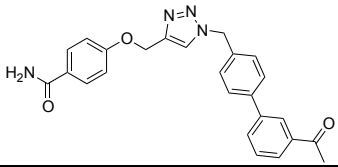
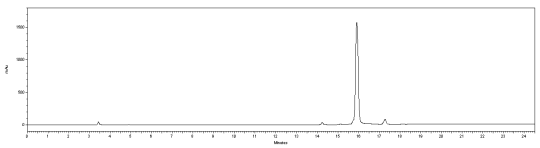
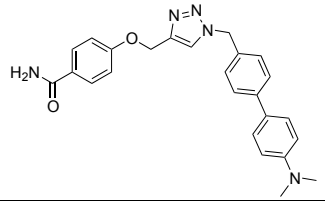
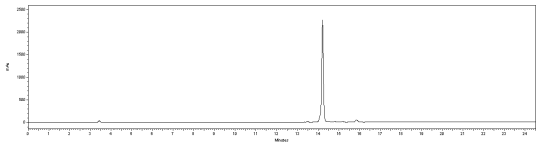
CuAAC/Suzuki-Miyaura macroarray purity, conversion, and HPLC-MS analysis. The entire 18-member CuAAC/Suzuki-Miyaura library (**13**) was analyzed for product purity, conversion, and product identity.

The purities of the CuAAC/Suzuki-Miyaura products (**13**) were analyzed using HPLC with UV detection at 254 nm. The CuAAC reaction conversion was calculated by comparison of (1) the amount of initial building block that was loaded onto Rink linker-derivatized support **3** to (2) the amount of initial building block that was detected in the final products after consecutive CuAAC/Suzuki-Miyaura reactions and cleavage. The calibration curve shown above in Figure S-4 was used for the % conversion calculations for the CuAAC reaction. The integrated area of the cleaved CuAAC product intermediate (from **12**) was compared to its corresponding area after the Suzuki-Miyaura reaction to calculate the Suzuki-Miyaura reaction conversion. Conversions of >98% were observed for the CuAAC reaction and all subsequent Suzuki-Miyaura reactions.

Table S-12. Purity, conversion, and HPLC-MS data for the CuAAC/Suzuki-Miyaura library (**13**).

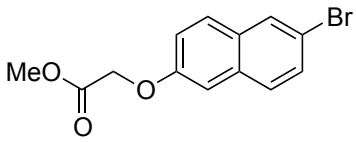
Compound and initial building block loading	% Purity % Conversion Calculated m/z Observed m/z	HPLC chromatogram at 254 nm
 Loading: 110 nmol	>98% - $[M+H]^+$ 176.1 176.0	
	>98% >98% $[M+H]^+$ 387.0 387.0	
	>98% >98% $[M+H]^+$ 385.2 385.1	
	97.7% >98% $[M+H]^+$ 415.2 415.1	

	>98% >98% $[M+H]^+$ 399.2 399.1	
	94.5% >98% $[M+H]^+$ 419.1 419.1	
	97.3% >98% $[M+H]^+$ 403.2 403.1	
	97.9% >98% $[M+H]^+$ 465.2 465.1	
	>98% >98% $[M+H]^+$ 433.2 433.1	
	>98% >98% $[M+H]^+$ 415.2 415.1	
	97.8% >98% $[M+H]^+$ 449.1 449.1	
	>98% >98% $[M+H]^+$ 401.2 401.1	
	96.6% >98% $[M+H]^+$ 433.2 433.1	

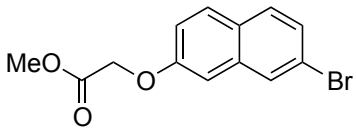
	97.7% >98% $[M+H]^+$ 429.2 429.1	
	97.2% >98% $[M+H]^+$ 399.2 399.1	
	95.4% >98% $[M+H]^+$ 403.2 403.1	
	94.6% >98% $[M+H]^+$ 417.2 417.0	
	95.9% >98% $[M+H]^+$ 419.1 419.1	
	94.5% >98% $[M+H]^+$ 427.2 427.1	
	97.6% >98% $[M+H]^+$ 428.2 428.2	

^{1}H NMR spectra for intermediates and library building blocks.

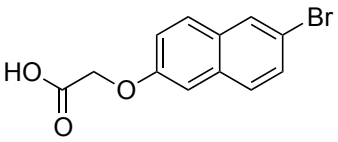
^{1}H NMR, 300 MHz, Acetone-*d6*



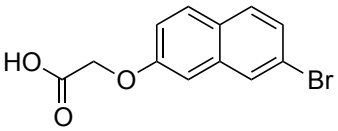
^{1}H NMR, 300 MHz, Acetone-*d6*



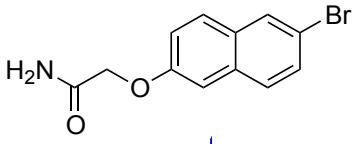
^{1}H NMR, 300 MHz, DMSO-*d6*



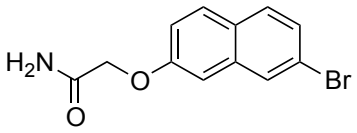
^{1}H NMR, 300 MHz, DMSO-*d6*



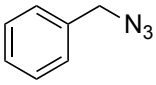
^{1}H NMR, 300 MHz, DMSO-*d6*



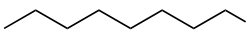
^{1}H NMR, 300 MHz, DMSO-*d6*



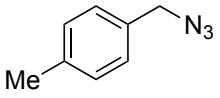
^{1}H NMR, 300 MHz, $CDCl_3$



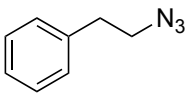
^{1}H NMR, 300 MHz, $CDCl_3$



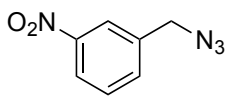
^{1}H NMR, 300 MHz, $CDCl_3$



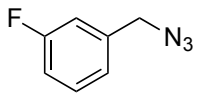
^{1}H NMR, 300 MHz, $CDCl_3$



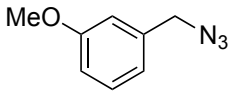
^{1}H NMR, 300 MHz, $CDCl_3$



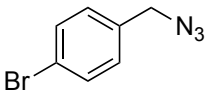
^{1}H NMR, 300 MHz, $CDCl_3$



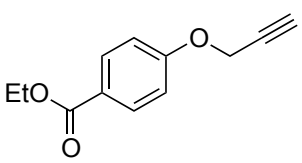
^{1}H NMR, 300 MHz, $CDCl_3$



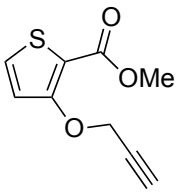
^{1}H NMR, 300 MHz, $CDCl_3$



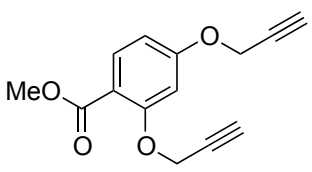
^{1}H NMR, 300 MHz, $CDCl_3$



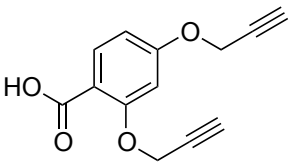
^{1}H NMR, 300 MHz, Acetone-d_6



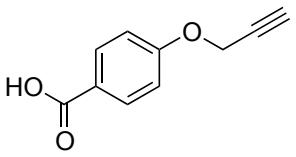
^{1}H NMR, 300 MHz, Acetone-d_6



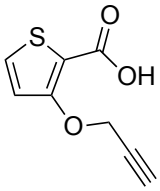
^{1}H NMR, 300 MHz, Acetone-*d6*



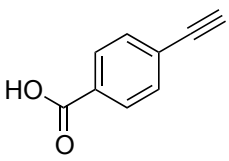
^{1}H NMR, 300 MHz, DMSO-*d6*



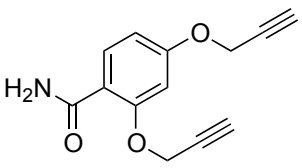
^{1}H NMR, 300 MHz, Acetone-*d6*



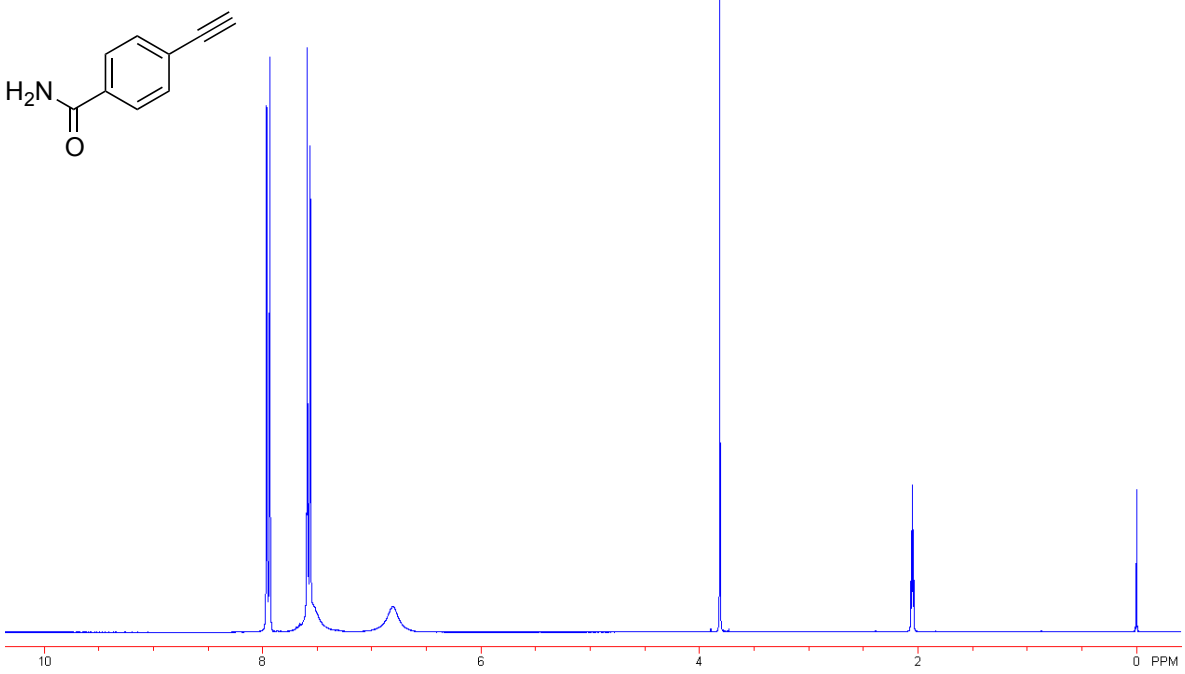
^{1}H NMR, 300 MHz, DMSO-d_6



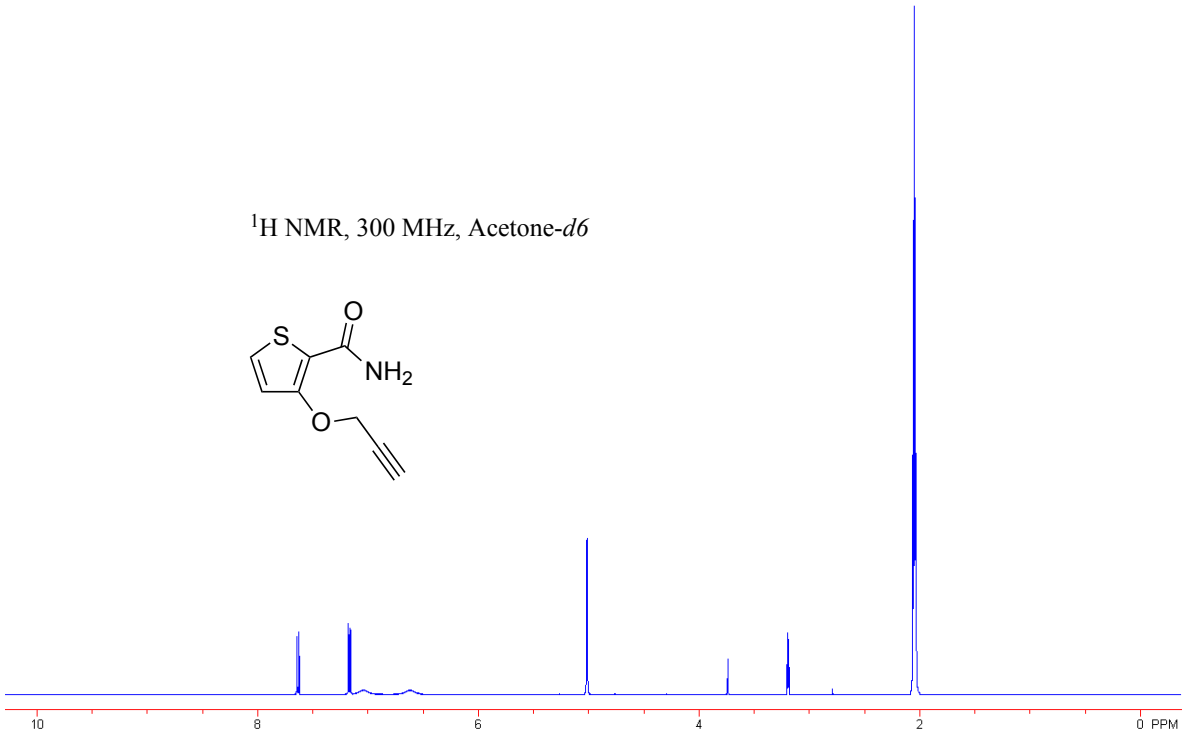
^{1}H NMR, 300 MHz, Acetone-d_6



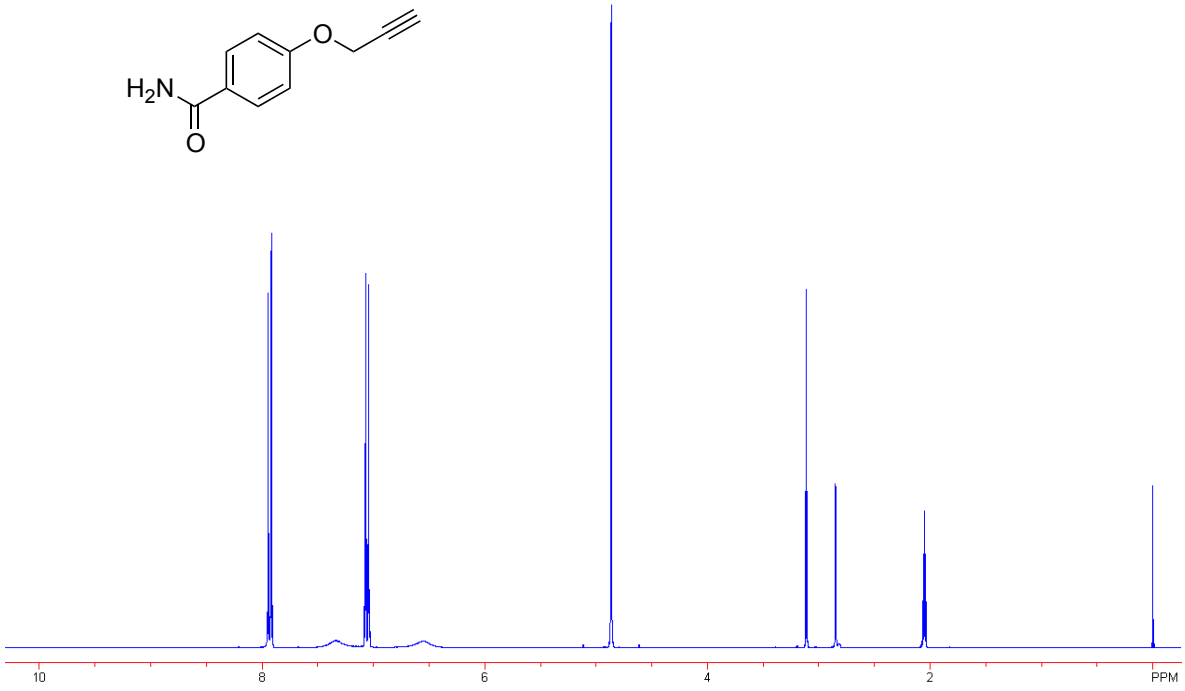
^{1}H NMR, 300 MHz, Acetone-d_6



^{1}H NMR, 300 MHz, Acetone-*d6*



^{1}H NMR, 300 MHz, Acetone-*d6*



Biological evaluation of phenyl naphthalene library (7a–b) in *Vibrio fischeri* LuxR reporter gene assay.

General biological methods. Standard solvents, media, and salts were purchased from commercial sources (Sigma Aldrich) and used as received. *N*-(3-oxo-hexanoyl)-L-homoserine lactone (OHHL; the native QS signal in *V. fischeri*) and *N*-(3-oxo-dodecanoyl)- L-homoserine lactone (OdDHL; a known LuxR inhibitor in *V. fischeri*) were purchased from Sigma Aldrich. *N*-(3-nitrophenylacetanoyl)-L-homoserine lactone (**C14**; a known LuxR agonist in *V. fischeri*) was synthesized according to our previously reported methods.[5,6] Stock solutions of compounds for biological evaluation were prepared in DMSO and stored at -20 °C. Stocks were equilibrated to rt overnight and diluted to the appropriate concentration with DMSO in a polypropylene 96-well microtiter plate (Costar 3879) before each use.

The *V. fischeri* LuxR reporter assays were performed in clear-bottomed, white-walled 96-well microtiter plates (Costar 3610). Absorbance and bioluminescence measurements were obtained using a BioTek Synergy 2 plate reader running Gen 5 1.05 software. Culture cell density was measured according to absorbance at 600 nm (OD_{600}). Bioluminescence was measured according to luminescence at an integration time of 1 sec; sensitivity set to 135, with optics position set to top. Spectroscopic measurements were assessed in 200 μL of media in 96-well microtiter plates (path length ~0.5 cm). Data were analyzed using Microsoft Office Excel 2007 and GraphPad Prism version 5.04. Bioluminescence measurements were normalized to the OD_{600} to account for differences in growth and reported as percent positive control. Reported data represent the average and standard error (STE) of four replicate wells from a single trial; replicate trials gave similar results as the single trials reported here. EC_{50} values were calculated using a sigmoidal curve fit (three parameters) in GraphPad Prism and are reported with a 95% confidence interval.

Strain and media. *V. fischeri* ES114 (Δ-*luxI*) was used for LuxR agonism and antagonism assays (gift of Professor Edward G. Ruby (University of Wisconsin–Madison)), and handled according to literature procedures.[7] OHHL activates bioluminescence in this strain with an EC_{50} of ~2 μM (see Figure S-8), and served as a positive control. All overnight cultures and bioluminescence assays with *V. fischeri* were performed in Luria-Bertani salt (LBS) medium (2% LB medium, 1.5% NaCl, 0.3% glycerol, and 50 mM Tris-HCl) at pH 7.5. Final DMSO concentration per well for all samples was 1.1% with the exception of the sample "Neg Con (no DMSO)" to test for DMSO growth effects *via* OD_{600} measurements. No effects on bacterial growth were observed due to DMSO.

Reporter gene assay protocol. The *V. fischeri* LuxR reporter assay was performed according to our previously reported method with some minor alternations.[5,6] Competitive antagonism assays were performed by testing 2 μM synthetic compound versus 2 μM OHHL (*i.e.*, its EC_{50} value). DMSO solutions of phenyl-naphthalenes (**7a**-**b**) obtained after macroarray cleavage were prepared by adding the appropriate volume of DMSO to obtain a final concentration of 600 μM. These stocks were diluted three-fold with DMSO in a polypropylene microtiter plate to obtain a final concentration of 200 μM. DMSO stocks (1 mM) of the following control compounds were also prepared and diluted five-fold to a final concentration of 200 μM: OdDHL (antagonism control), **C14** (agonism control), and cleaved acetamide-variants of initial building blocks **5a** and **5b**. Aliquots (2 μL) of the final test solutions were added to a microtiter plate. DMSO only was

added to the wells designated "Neg Con (DMSO)"and "Pos Con (2 μM OHHL)" (2.2 and 2.0 μL, respectively).

A freezer stock of *V. fischeri* ES114 was streaked on LBS/agar(1.5%) and incubated at rt for approximately 24 h. Single colonies were selected and used to inoculate LBS medium (5 mL) in a sterile 15 mL culture tube. The culture was grown on a shaker (200 rpm) at rt for approximately 18 h (until OD_{600} = 0.9-1.0). An inoculating culture was prepared from an overnight culture by performing a 10-fold dilution into LBS. Aliquots (200 μL) of the inoculum were added to wells designated as negative controls. OHHL was added from a 2 mM DMSO stock to the remaining inoculum to affect a final concentration of 2 μM OHHL (0.1% DMSO). This secondary inoculum was delivered to the remaining wells. To ensure proper mixing, a 10 μL multi-channel pipette was swirled in each well. Multitier plates were incubated at rt on a 200 rpm shaker until an OD_{600} of 0.35–0.40 (~2–4 h), after which bioluminescence and OD_{600} were measured using a plate reader. Bioluminescence values were divided by the OD_{600} values to normalize for growth. The normalized bioluminescence data are reported as a percentage of that for the positive control (2 μM OHHL) (see Figure S-9).

LuxR agonism assays were performed in largely an analogous manner as the antagonism assays. Phenyl-naphthalenes (**7a**-**b**) and control compounds were tested at 6 μM in the absence of OHHL (note, 100% bioluminescence activation is observed at 6 μM OHHL, Figure S-7). Control stocks (1 mM) were diluted to 600 μM with DMSO; phenyl-naphthalene (**7a**-**b**) stocks (600 μM) required no dilution. Aliquots (2 μL) of the final test solutions were added to microtiter plates. DMSO (2 μL) was added to the "Neg Con (DMSO)" wells and 2 μL of a 600 μM OHHL stock was added to the "Pos Con (6 μM OHHL)" wells. An inoculating culture of *V. fischeri* was prepared as described above. Aliquots (200 μL) of the inoculum were added to wells designated as "Neg Con (no DMSO)". The remaining inoculum was supplemented with DMSO to 0.1% and delivered to the remaining wells. The well contents were mixed, and the plates were incubated to the target OD_{600} as described above. The normalized bioluminescence data are reported as a percentage of that for the positive control (6 μM OHHL) (see Figure S-10).

We note that the results for the control samples in these screens were as expected: negative controls showed no bioluminescence in the absence of an agonist, and positive controls showed activation of bioluminescence with OHHL. The antagonist control (OdDHL) gave approximately 80% inhibition in the antagonism assay screen, and the agonism control (**C14**) gave 100% activation in both the antagonism and agonism screens. It is also important to note that the cleaved initial building blocks **5a** and **5b** showed neither antagonistic nor agonistic bioactivity. None of the tested compounds (or DMSO) were found to have an appreciable effect on bacterial growth over the time course of these assays (data not shown).

The phenyl-naphthalene library showed low antagonistic activity overall (Figure S-9). The only significant antagonist was compound **7a**-**12**, which displayed approximately 50% LuxR inhibition. However, several library compounds displayed agonistic activities in the *antagonism* screen. In general, the phenyl-naphthalene derivatives of type **7b**-**X** were more agonistic relative to type **7a**-**X**. The strongest agonists identified in the antagonism screen include **7b**-**9**, **7b**-**12**, **7b**-**19**, **7b**-**25**, and **7b**-**26**. Interestingly, these compounds contain a *para* substituent on the phenyl group installed *via* the Suzuki-Miyaura reaction. The compounds capable of agonism in the

antagonism assays *failed* to exhibit agonism in the LuxR agonism assay, however (*i.e.*, in the absence on OHHL, Figure S-10). These data suggest that the these compounds require OHHL to display agonistic activities and operate by a different mechanism than other known LuxR agonists based on the AHL scaffold (such as lactone **C14**; see text).

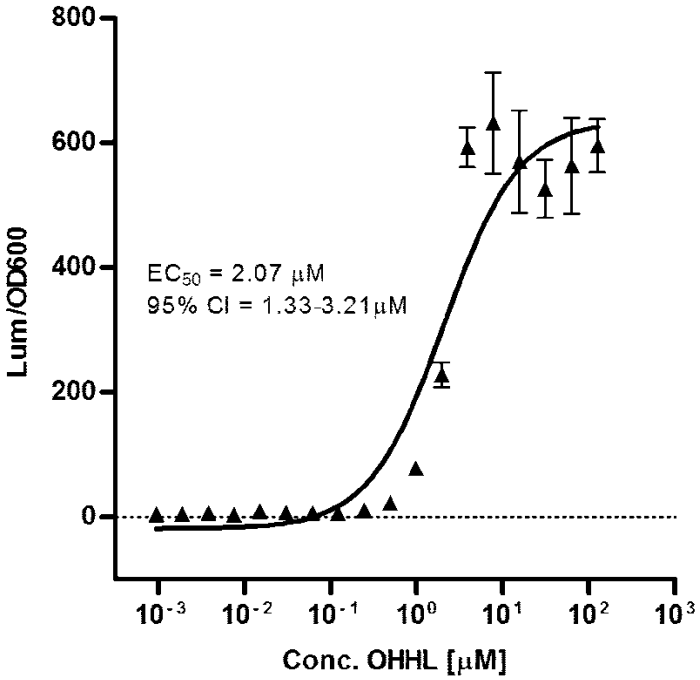


Figure S-8. Dose response curve for OHHL in *V. fischeri* ES114 (Δ-*luxI*). CI = confidence interval.

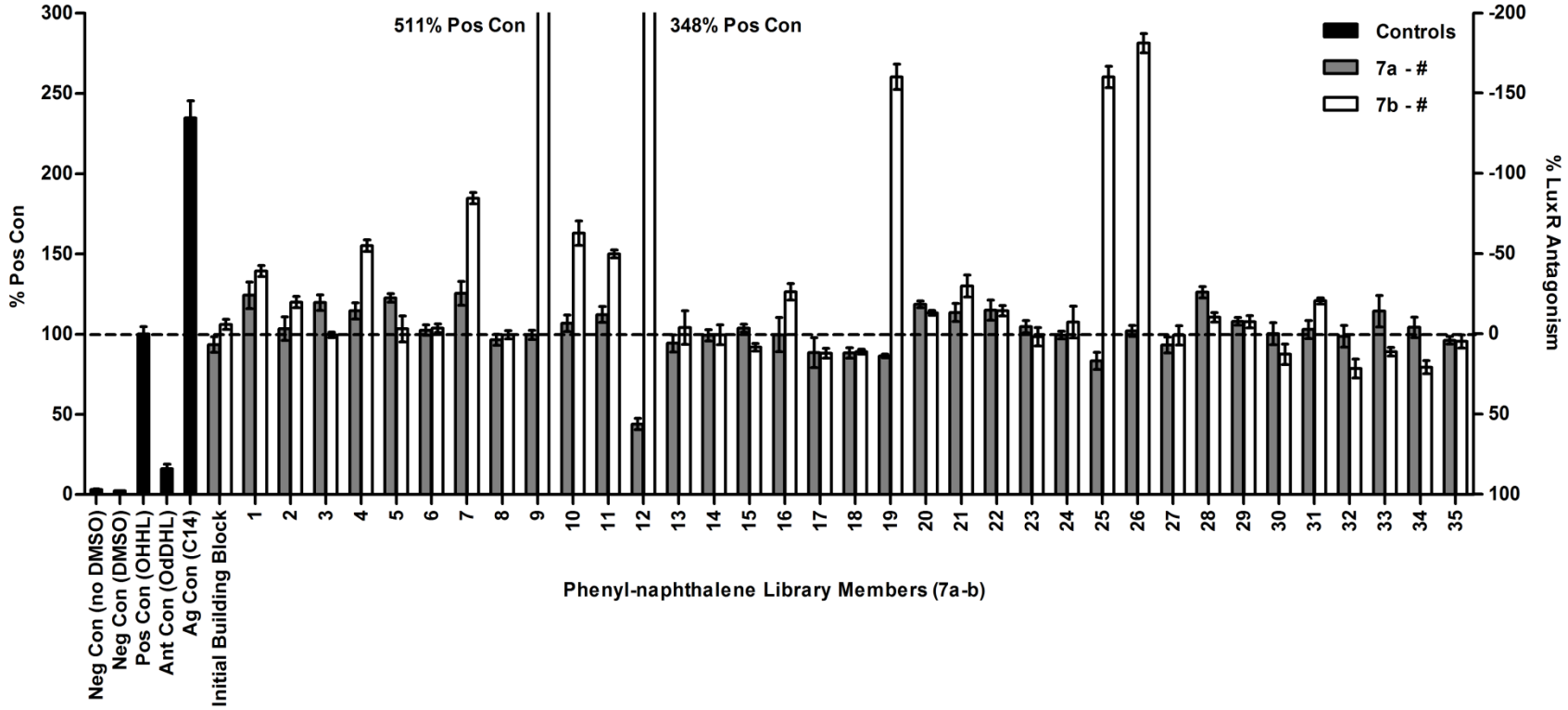


Figure S-9. *V. fischeri* ES114 (Δ-*luxI*) antagonism assay data for phenyl-naphthalenes **7a**-**b**. Assay performed at 1:1 compound:OHHL (at 2 μM each). See assay protocol above for definitions of controls.

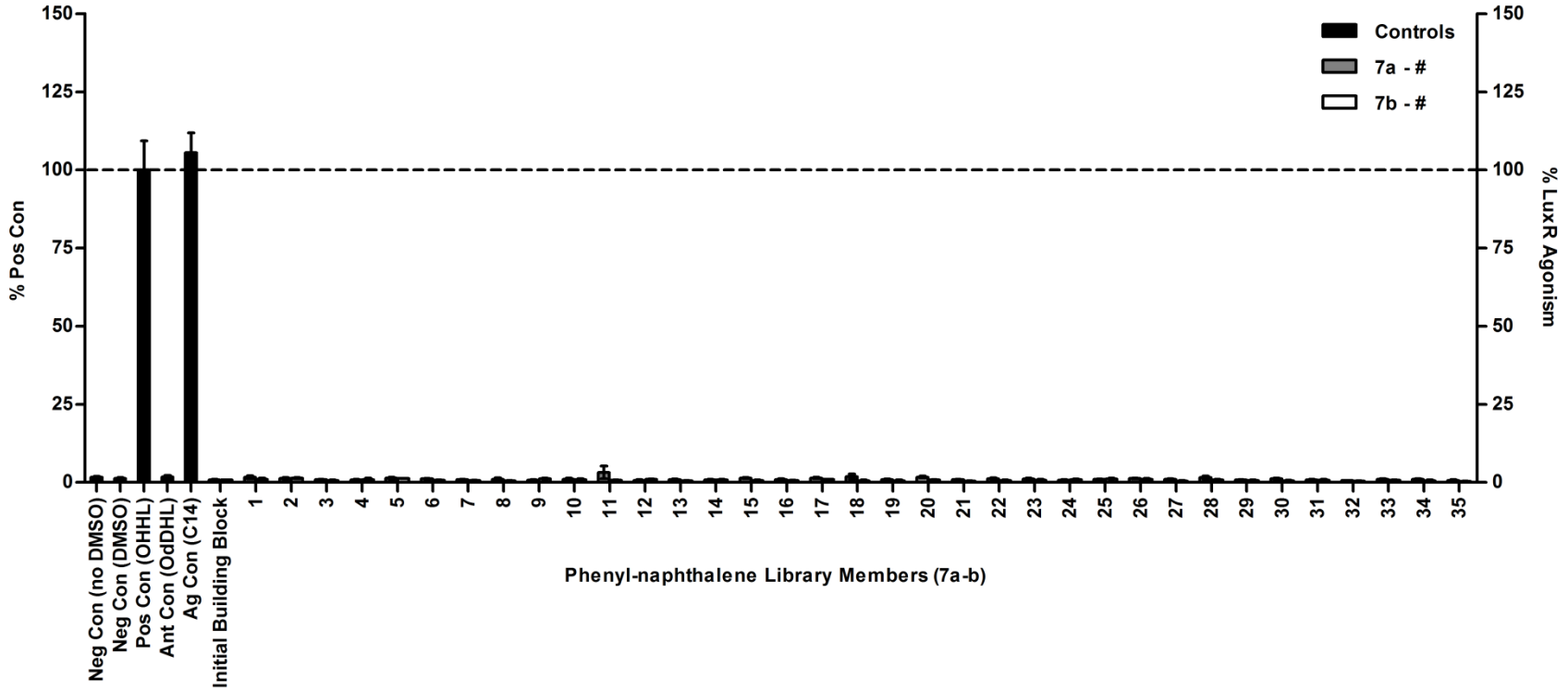


Figure S-10. *V. fischeri* ES114 (Δ-*luxI*) agonism assay data for phenyl-naphthalenes **7a**-**b**. Assay performed at 6 μM compound. See assay protocol above for definitions of controls.

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