Supporting Information 1

Development of Clickable Photoaffinity Ligands for Metabotropic Glutamate Receptor 2 Based on Two Positive Allosteric Modulator Chemotypes

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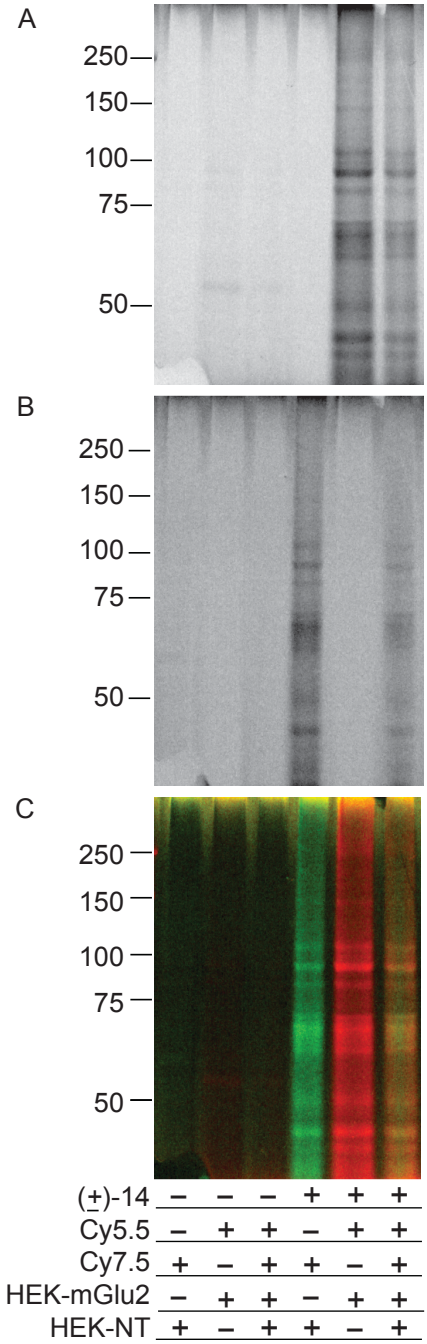
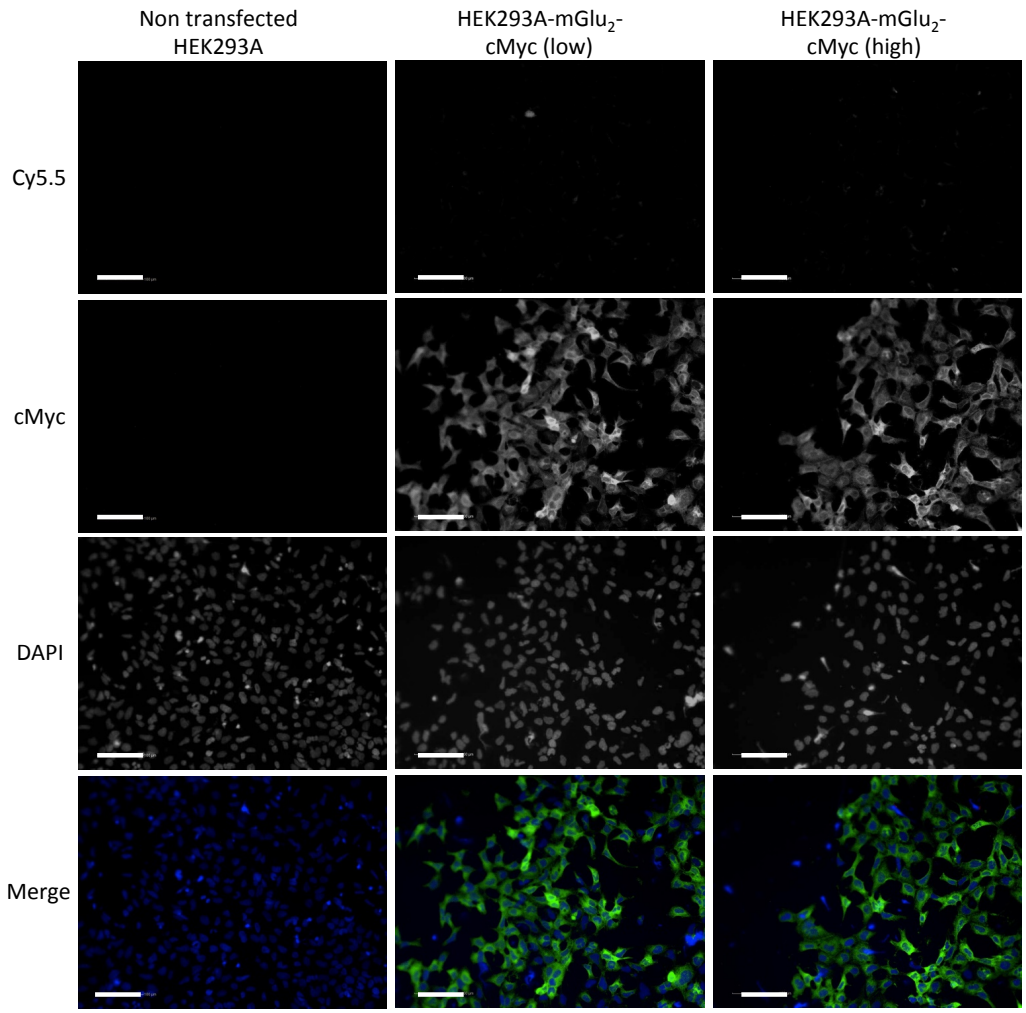
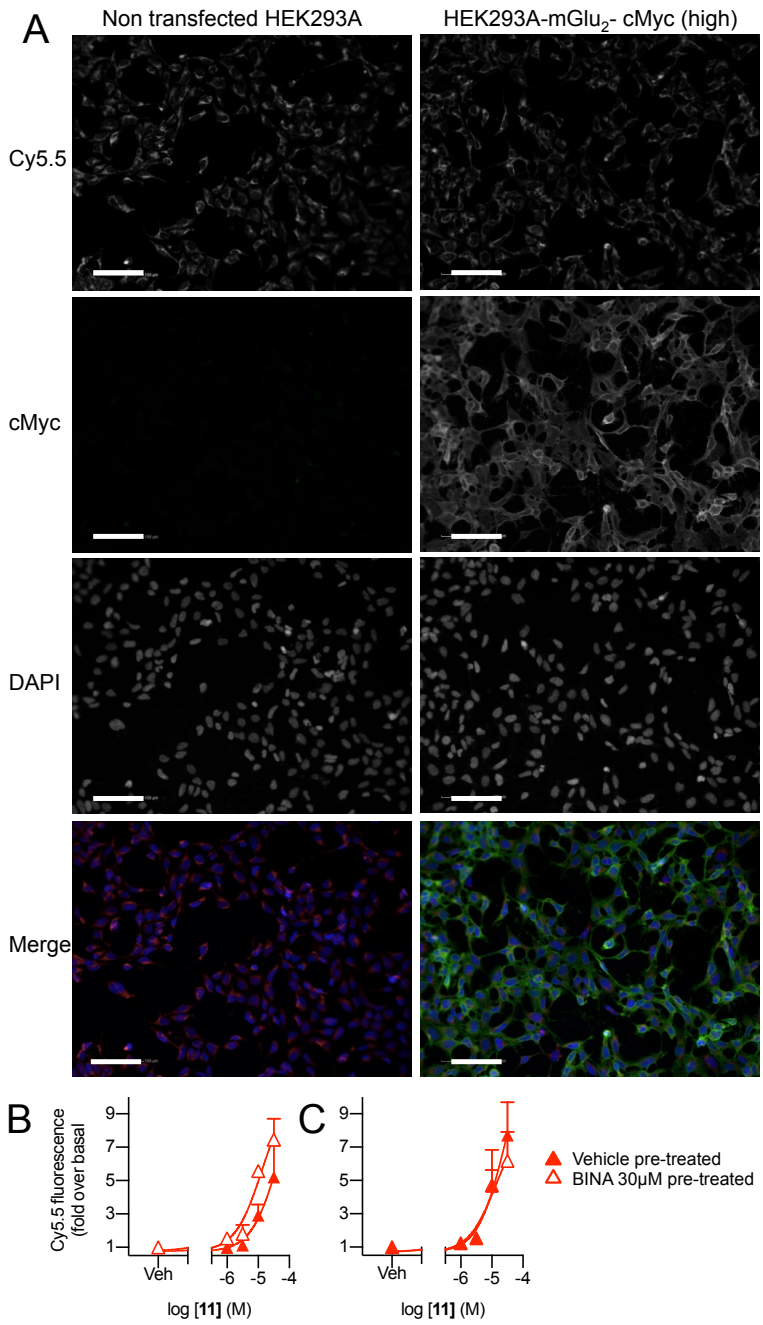
Supplementary Figures:



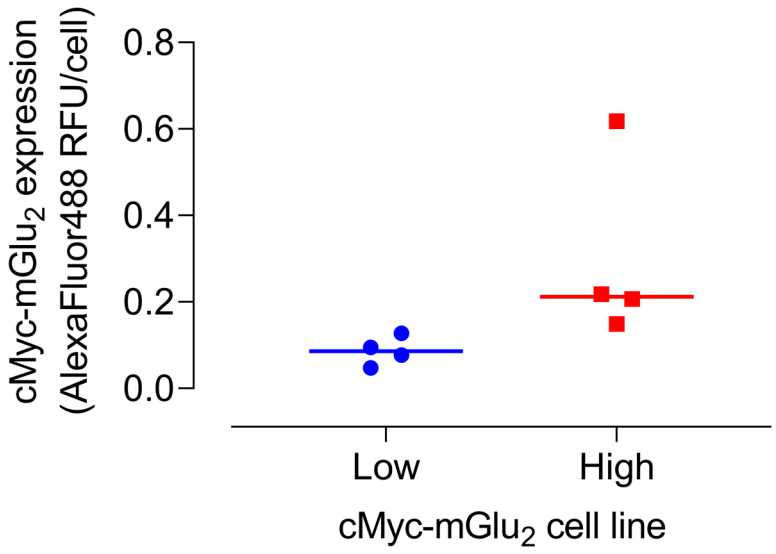
Supplementary Figure 1: Probe-dependent incorporation of azide fluorophores show similar non-specific protein labeling patterns. After labeling with or without 10μM (±)-**14**, HEK293A-cMyc-mGlu$_2$ cells were subjected to click chemistry using Cy5.5 azide (A), whereas non-transfected HEK293A cells were clicked with Cy7.5 azide (B). Lysates from HEK293A-cMyc-mGlu$_2$-high and non-transfected cells were mixed in a 1:1 ratio (lane 6), as can be seen from the merged image (C) the protein labeling overlaps between the two cell lines. In gel fluorescence images are from a single experiment.



Supplementary Figure 2: Cell permeabilization reduces photoaffinity labeling of HEK293A cells with the clickable photoreactive $mGlu_2$ PAM (±)-14. Photoaffinity labeling with (±)-**14** followed by Cy5.5 click chemistry was carried out in whole HEK293A cells followed by cell permeabilization, DAPI counter-staining, and fluorescent antibody labeling of cMyc-tagged $mGlu_2$. (±)-**14** labeling was almost absent in non-transfected HEK293A cells and those expressing cMyc-tagged $mGlu_2$ at low and high levels (HEK293A-$mGlu_2$-cMyc low/high) following cell permeabilization. Representative images after photoaffinity labelling with 10 µM (±)-**14** are shown. Scale bars represent 100 µm. Merge shows Cy5.5 in red, cMyc in green, and DAPI in blue. Refer to Figure 8 in main text for quantification.



Supplementary Figure 3: High levels of non-specific Cy5.5 fluorescence are apparent after photoaffinity labeling of HEK293A cells with clickable photoreactive mGlu$_2$ PAM 11. (**A**) Photoaffinity labeling with **11** followed by Cy5.5 click chemistry was carried out in whole HEK293A cells followed by DAPI counterstaining and fluorescent antibody labeling of cMyc-tagged mGlu$_2$. Representative images after photoaffinity labeling with 10 μM **11** are shown. Scale bars represent 100 μm. Merge shows Cy5.5 in red, cMyc in green, and DAPI in blue. Concentration-dependent labeling was apparent in non-transfected HEK293A cells (**B**) and those expressing cMyc-tagged mGlu$_2$ at high levels (**C**), which is not significantly affected by pretreatment with BINA. Data are mean ± SEM.



Supplementary Figure 4: Relative expression levels of cMyc tagged $mGlu_2$ receptor in cMyc-$mGlu_2$ low- or high-expressing cell lines, as determined by immunocytochemistry. During whole-cell immunofluorescence experiments, HEK293A-cMyc-$mGlu_2$ expression was visualized using fluorescent antibody receptor labeling. Relative expression was then quantified by normalizing relative fluorescence units (RFU) of the goat anti-mouse-AlexaFluor488 secondary antibody to number of cells within the wells of a 96-well plate, determined using brightfield images.

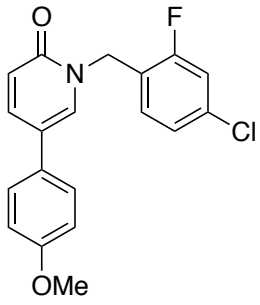
Supplementary Table 1. System-related parameters estimated by fitting the operational model of allosteric to modulation of glutamate concentration-response curves. Associated parameter estimates for the indicated allosteric modulators are found in Table 5 of the main manuscript.

Compound	n[a]	$Log\tau_A$[b]	E_m[c]	basal[d]
1	1.5 ±0.4	0.33 ±0.19	133.8 ±33.1	-0.3 ±0.8
8[d]	n.d.	n.d.	n.d.	n.d.
9	5.6 ±1.9	0.11 ±0.08	137.2 ±24.5	0.01 ±1.3
11	3.6 ±0.6	0.19 ±0.04	117.1 ±6.6	-0.2 ±1.4
BINA ((±)-12)[e]	2.7	0.0001	168	1.6
(±)-13	4.7 ±1.4	0.09 ±0.01	145.6 ±7.3	0.4 ±0.3
(±)-14	3.5 ±0.5	0.05 ±0.03	147.5 ±1.1	4.0 ±2.0
(±)-15	2.7 ±0.5	0.33 ±0.14	137.3 ±32.4	-0.6 ±0.8

[a] transducer function that links receptor occupancy to cellular response measured.
[b] intrinsic efficacy parameter for orthosteric agonist glutamate.
[c] the maximal possible system response, expressed as a percentage of the maximal response to glutamate
[d] basal level of iCa^{2+} mobilization in response to vehicle.
[e] data are the mean of two independent determinations

Supplementary Methods:

General Experimental for Chemical Probe Synthesis. All reactions were performed in a single-neck, flame-dried, round-bottomed flask fitted with rubber septa under a positive pressure of argon, unless otherwise noted. All solvents and chemicals were purchased from Millipore Sigma, Fisher Scientific, or VWR and used without further purification, unless otherwise noted. Air- and moisture-sensitive liquids were transferred via syringe or stainless-steel cannula. Normal flash-column chromatography was performed as described by Still and co-workers.[1] Normal-phase purifications employed Fisher S826-25 silica gel sorbent (70–230 mesh) and eluting solvent mixtures as specified. Analytical thin-layer chromatography (TLC) was performed using TLC Silica Gel 60 F254 plates obtained from EMD Chemicals, Inc. TLC plates were visualized by exposure to ultraviolet light (UV) and/or iodine (I_2) stain. Proportions of solvents used for TLC are by volume. ^{1}H and ^{13}C NMR spectra were recorded on either a Bruker 400 or 500 MHz spectrometer. Chemical shifts for ^{1}H and ^{13}C NMR spectra are reported as parts per million (δ ppm) relative to tetramethylsilane (0.00 ppm) as an internal standard. Coupling constants are measured in hertz (Hz). Infrared (IR) spectra were obtained using a Perkin–Elmer Spectrum RZ I FT-IR spectrophotometer. High-resolution mass spectrometry (HRMS) samples were analyzed at Old Dominion University (Norfolk, VA) by positive ion electrospray on a Bruker 12 Tesla APEX-Qe FTICR-MS with an Apollo II ion source. Combustion analyses of select solid compounds were performed by Atlantic Microlab, Inc. (Norcross, GA) and are within 0.4% of calculated values. Melting point determinations were conducted using a Thomas-Hoover melting point apparatus and are uncorrected. On the basis of ^{1}H and ^{13}C NMR, all compounds were ≥95% pure, unless otherwise noted.



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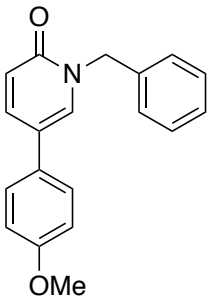

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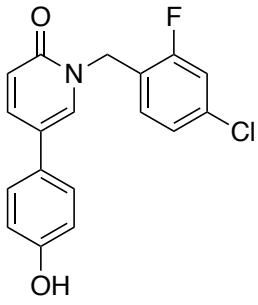

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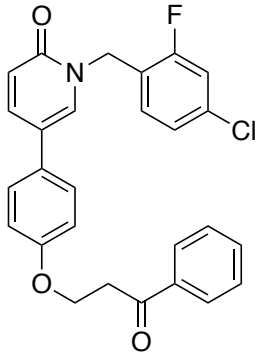
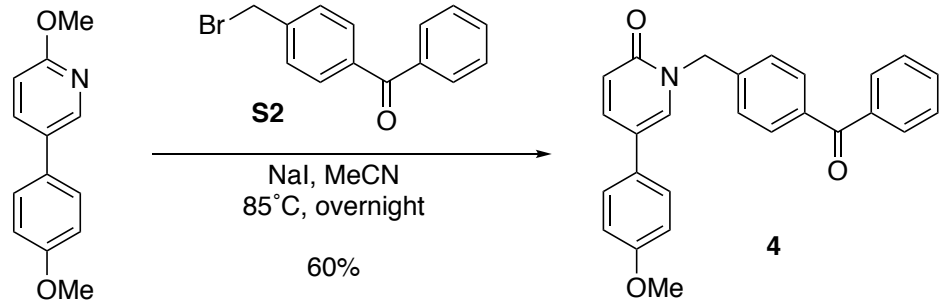


6

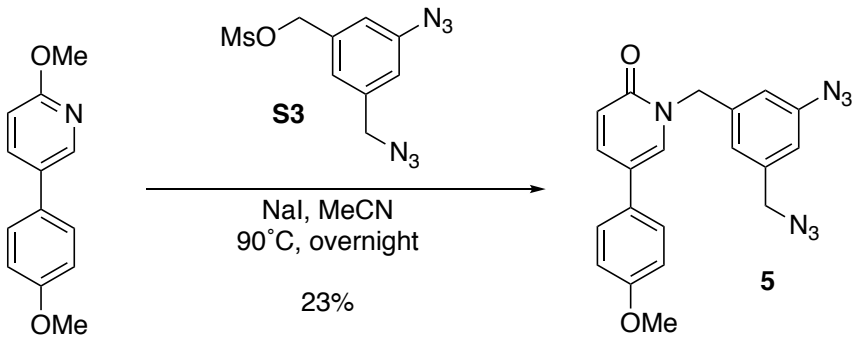
1-(4-Chloro-2-fluorobenzyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (**1**), **1-Benzyl-5-(4-methoxyphenyl)pyridin-2(1*H*)-one** (**2**), **1-(4-Chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyridin-2(1*H*)-one** (**3**), and **1-(4-Chloro-2-fluorobenzyl)-5-(4-(3-oxo-3-phenylpropoxy)phenyl)pyridin-2(1*H*)-one** (**6**) were prepared as previously described.[2]



S1

1-(4-Benzoylbenzyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (**4**). 4-(Bromomethyl)benzophenone (**S2**) (146 mg, 0.53 mmol, 2 equiv) and NaI (79 mg, 0.53 mmol, 2 equiv) were added sequentially to a solution of 2-methoxy-5-(4-methoxyphenyl)pyridine[2] (**S1**) (57 mg, 0.26 mmol, 1 equiv) in MeCN (2.6 mL) at room temperature. The reaction mixture was then refluxed at 85˚C overnight, cooled to room temperature, and concentrated by rotary evaporation. The resulting crude mixture was then dissolved in EtOAc, sequentially washed with H_2O and brine, then dried ($MgSO_4$), filtered, and concentrated by rotary evaporation. The residue obtained was purified by flash column chromatography (SiO_2, 2:8 to 4:6 EtOAc:hexanes) to give 63 mg (60%) of *N*-alkylated benzophenone **4** as a light-brown oil.

R*f* = 0.22 (4:6 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.82 – 7.75 (m, 4H), 7.62 (dd, *J* = 9.4, 2.6 Hz, 1H), 7.57 (d, *J* = 7.5 Hz, 1H), 7.51 – 7.40 (m, 5H), 7.30 (d, *J* = 8.8 Hz, 2H), 6.94 (d, *J* = 8.9 Hz, 2H), 6.73 (d, *J* = 9.4 Hz, 1H), 5.29 (s, 2H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 196.1, 161.8, 159.2, 140.9, 139.8, 137.4, 137.3, 133.7, 132.6, 130.7, 130.1, 128.7, 128.3, 127.7, 127.0, 121.3, 120.6, 114.5, 55.4, 52.2. HRMS calcd for $(C_{26}H_{21}NO_3)Na^+$ 418.1417, found 418.1410.

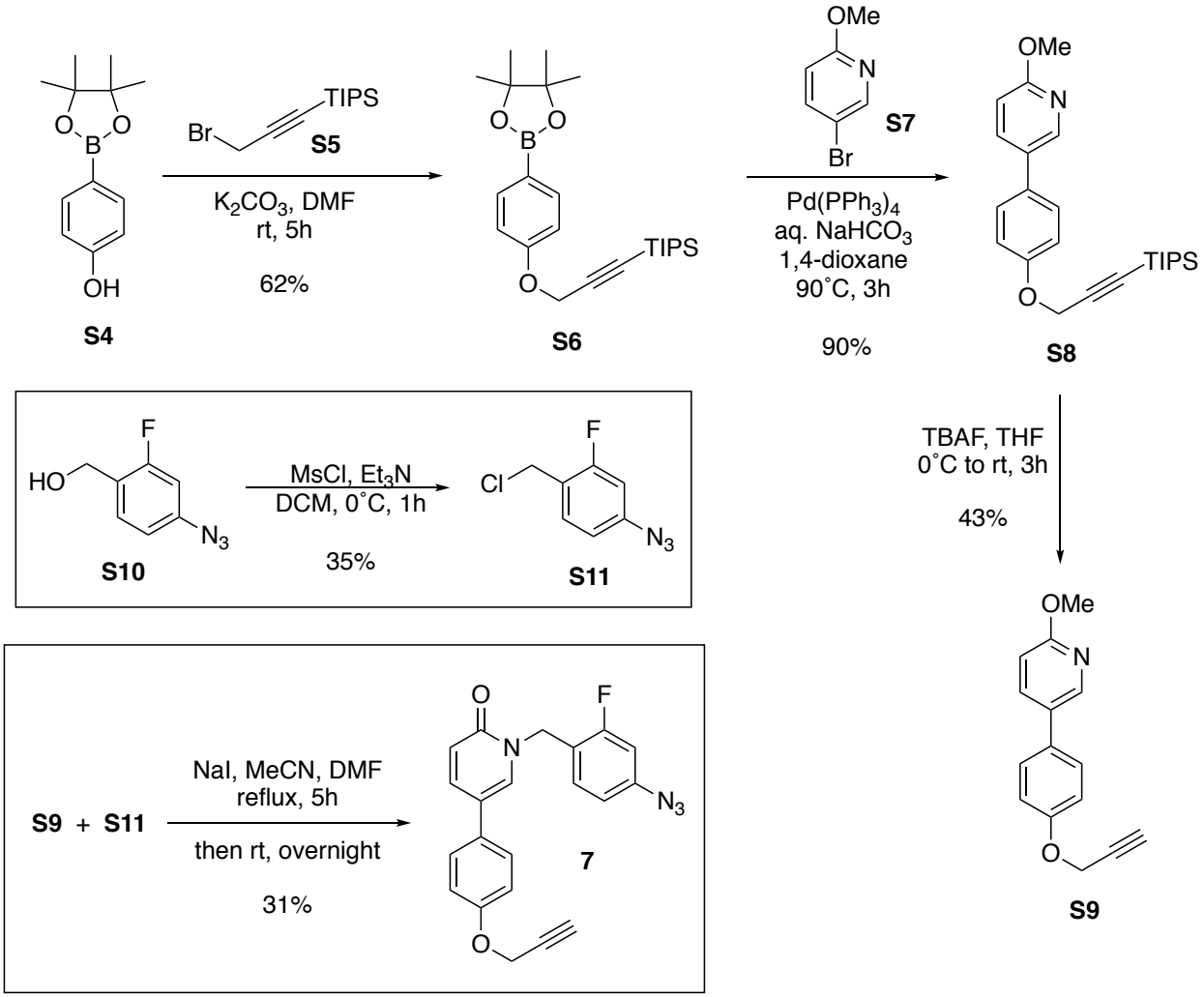


S1

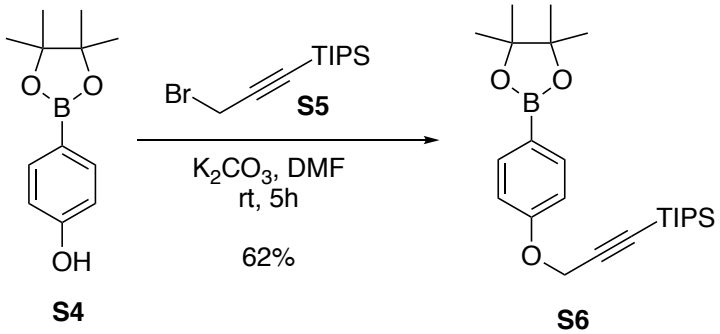
1-(3-Azido-5-(azidomethyl)benzyl)-5-(4-methoxyphenyl)pyridin-2(1*H*)-one (**5**). To 2-methoxy-5-(4-methoxyphenyl)pyridine[2] (**S1**) (17 mg, 0.08 mmol, 1 equiv) and NaI (24 mg, 0.16 mmol, 2 equiv) was added a mixture of 3-azido-5-(azidomethyl)benzyl methanesulfonate[3] (**S3**) (45 mg, 0.16 mmol, 2 equiv) in CH_3CN (4.5 mL). The reaction was then refluxed at 90˚C overnight. The reaction mixture was then cooled to room temperature, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 4:6 EtOAc:hexanes) to give 11 mg of *N*-benzylated derivative **5** as a yellow oil (23%).

*R*f = 0.33 (4:6 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.61 (dd, *J* = 9.5, 2.7 Hz, 1H), 7.39 (dd, *J* = 2.6, 0.7 Hz, 1H), 7.29 (d, *J* = 8.8 Hz, 2H), 7.04 (td, *J* = 1.5, 0.8 Hz, 1H), 6.97 – 6.90 (m, 4H), 6.71 (dd, *J* = 9.5, 0.7 Hz, 1H), 5.18 (s, 2H), 4.34 (s, 2H), 3.83 (s, 3H). ^{13}C NMR

(101 MHz, $CDCl_3$) δ 161.7, 159.2, 141.4, 139.8, 139.1, 138.2, 133.6, 128.7, 127.1, 123.8, 121.3, 120.7, 118.3, 118.0, 114.5, 55.4, 54.1, 51.9. HRMS calcd. for $(C_{20}H_{17}N_7O_2)Na^+$ 410.1336, found 410.1332. IR: azide, 2108 cm^{-1}.



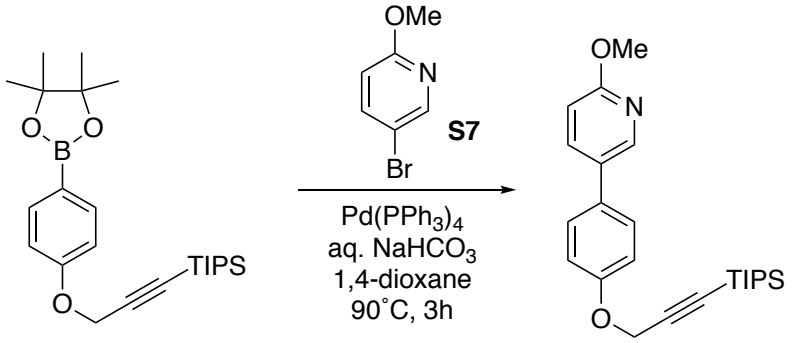
Scheme S1. *Synthesis of mGlu2 PAM clickable photoprobe* ***7****.*



Triisopropyl(3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)prop-1-yn-1-yl)silane (**S6**). A mixture of 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenol (**S4**) (330

mg, 1.5 mmol, 1 equiv), DMF (11 mL), K_2CO_3 (623 mg, 4.5 mmol, 3 equiv), and (3-bromoprop-1-yn-1-yl)triisopropylsilane[4] (**S5**) (578 mg, 2.10 mmol, 1.4 equiv) was stirred at room temperature for 5 hours, then diluted with H_2O and extracted with EtOAc. The organic layer was then separated, washed with brine, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 0:100 to 5:95 EtOAc:hexanes) to afford 388 mg of propargyl ether **S6** as a colorless oil (62%).

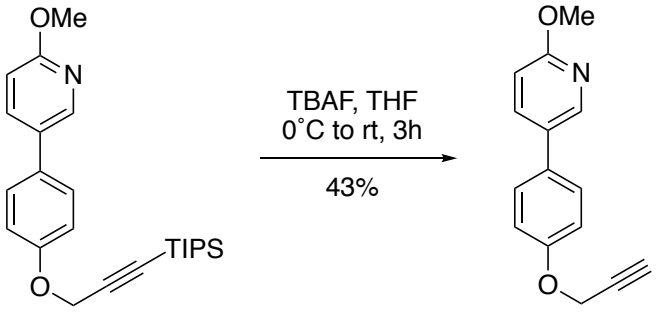
*R*f = 0.41 (1:9 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.74 (d, *J* = 8.7 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.74 (s, 2H), 1.34 (s, 12H), 1.03 (s, 21H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 160.4, 136.3, 136.3, 114.4, 101.8, 89.3, 83.6, 56.6, 24.9, 18.5, 11.1. HRMS calcd for $(C_{24}H_{39}BO_3Si)Na^+$ 437.2654, found 437.2657.



S6 90% **S8**

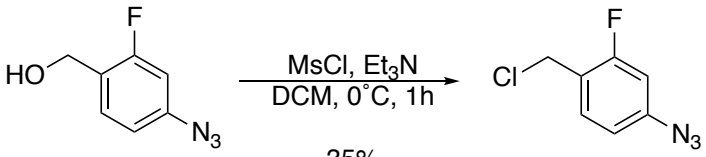
2-Methoxy-5-(4-((3-(triisopropylsilyl)prop-2-yn-1-yl)oxy)phenyl)pyridine (**S8**). A mixture of 2-methoxy-5-bromopyridine (**S7**) (0.023 mL, 0.18 mmol, 1 equiv), boronic pinacol ester **S6** (110 mg, 0.27 mmol, 1.5 equiv), $Pd(PPh_3)_4$ (30 mg, 0.026 mmol, 0.15 equiv), 1,4-dioxane (4 mL), and sat. aq. $NaHCO_3$ solution (1.6 mL) was degassed, then heated at 90˚C for 3 hours. After cooling to room temperature, the mixture was filtered through Celite®, washed sequentially with H_2O and brine, then dried ($MgSO_4$), filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 2:8 EtOAc:hexanes) to provide 70 mg of diaryl product **S8** as a brown oil (90%).

*R*f = 0.47 (1:9 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.33 (dd, *J* = 2.6, 0.8 Hz, 1H), 7.73 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.43 (d, *J* = 8.8 Hz, 2H), 7.08 (d, *J* = 8.8 Hz, 2H), 6.79 (dd, *J* = 8.6, 0.8 Hz, 1H), 4.76 (s, 2H), 3.97 (s, 3H), 1.03 (s, 21H). ^{13}C NMR (101 MHz, Chloroform-*d*) δ 163.2, 157.2, 144.6, 137.2, 131.1, 129.8, 127.6, 115.9, 110.7, 101.8, 89.5, 56.9, 53.5, 18.5, 11.1. HRMS calcd for $(C_{24}H_{33}NO_2Si)Na^+$ 418.2173, found 418.2176.



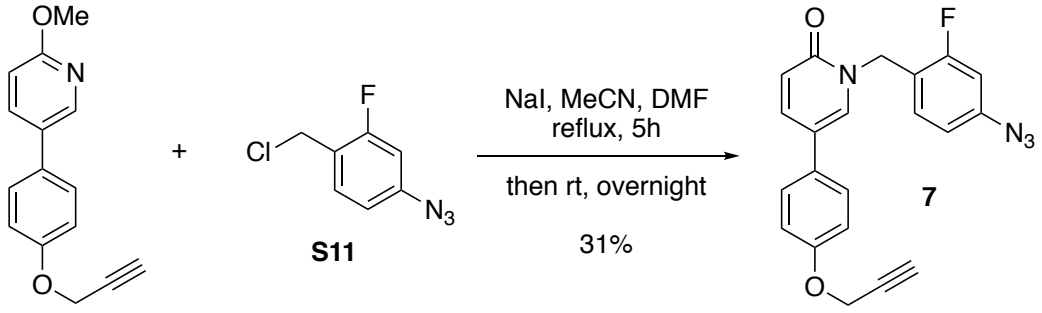
S8 **S9**

2-Methoxy-5-(4-(prop-2-yn-1-yloxy)phenyl)pyridine (**S9**). TBAF (1M in THF, 0.4 mL, 0.4 mmol, 2.1 equiv) was added to a 0˚C mixture of TIPS-protected alkyne **S8** (76 mg, 0.19 mmol, 1 equiv) in THF (3.5 mL). The reaction was then stirred at room temperature for 3 hours, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 5:95 EtOAc:hexanes) to obtain 20 mg of deprotected alkyne **S9** as a white solid (43%).
*R*f = 0.23 (1:9 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.34 (dd, *J* = 2.5, 0.8 Hz, 1H), 7.75 (dd, *J* = 8.6, 2.6 Hz, 1H), 7.47 (d, *J* = 8.9 Hz, 2H), 7.06 (d, *J* = 8.8 Hz, 2H), 6.80 (dd, *J* = 8.6, 0.8 Hz, 1H), 4.74 (d, *J* = 2.4 Hz, 2H), 3.97 (s, 3H), 2.55 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.3, 157.1, 144.6, 137.2, 131.3, 129.6, 127.8, 115.4, 110.7, 78.4, 75.7, 55.8, 53.5. HRMS calcd for $(C_{15}H_{13}NO_2)Na^+$ 262.0838, found 262.0841.



S10 **S11**

4-Azido-1-(chloromethyl)-2-fluorobenzene (**S11**). To a 0˚C mixture of 4-azido-2-fluorobenzyl alcohol[5] (**S10**) (50 mg, 0.31 mmol,1 equiv) in CH_2Cl_2 (2 mL) was added triethylamine (0.1 mL, 0.72 mmol, 2.3 equiv), followed by MsCl (0.03 mL, 0.46 mmol, 1.5 equiv). The reaction mixture was then stirred at 0˚C for 1 hour, followed by quenching with sat. aq. $NaHCO_3$ solution and H_2O. The mixture was then extracted with CH_2Cl_2, washed with brine, then dried ($MgSO_4$), filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 1:10 EtOAc:hexanes) to provide 20 mg of benzyl chloride **S11** (35%) as a relatively unstable compound that was immediately used in the next reaction to produce probe **7**.
*R*f = 0.86 (1:9 MeOH:$CHCl_3$). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.39 (td, *J* = 8.2, 0.3 Hz, 1H), 6.84 (ddd, *J* = 8.3, 2.3, 0.8 Hz, 1H), 6.76 (dd, *J* = 10.4, 2.2 Hz, 1H), 4.60 (d, *J* = 1.1 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.4, 159.9, 142.3, 132.0, 121.3, 115.1, 115.0, 107.0, 106.8, 39.0, 38.9, 29.7. IR: azide, 2115.9 cm^{-1}. HRMS analysis of **S11** was not performed due to its relative instability at room temperature.

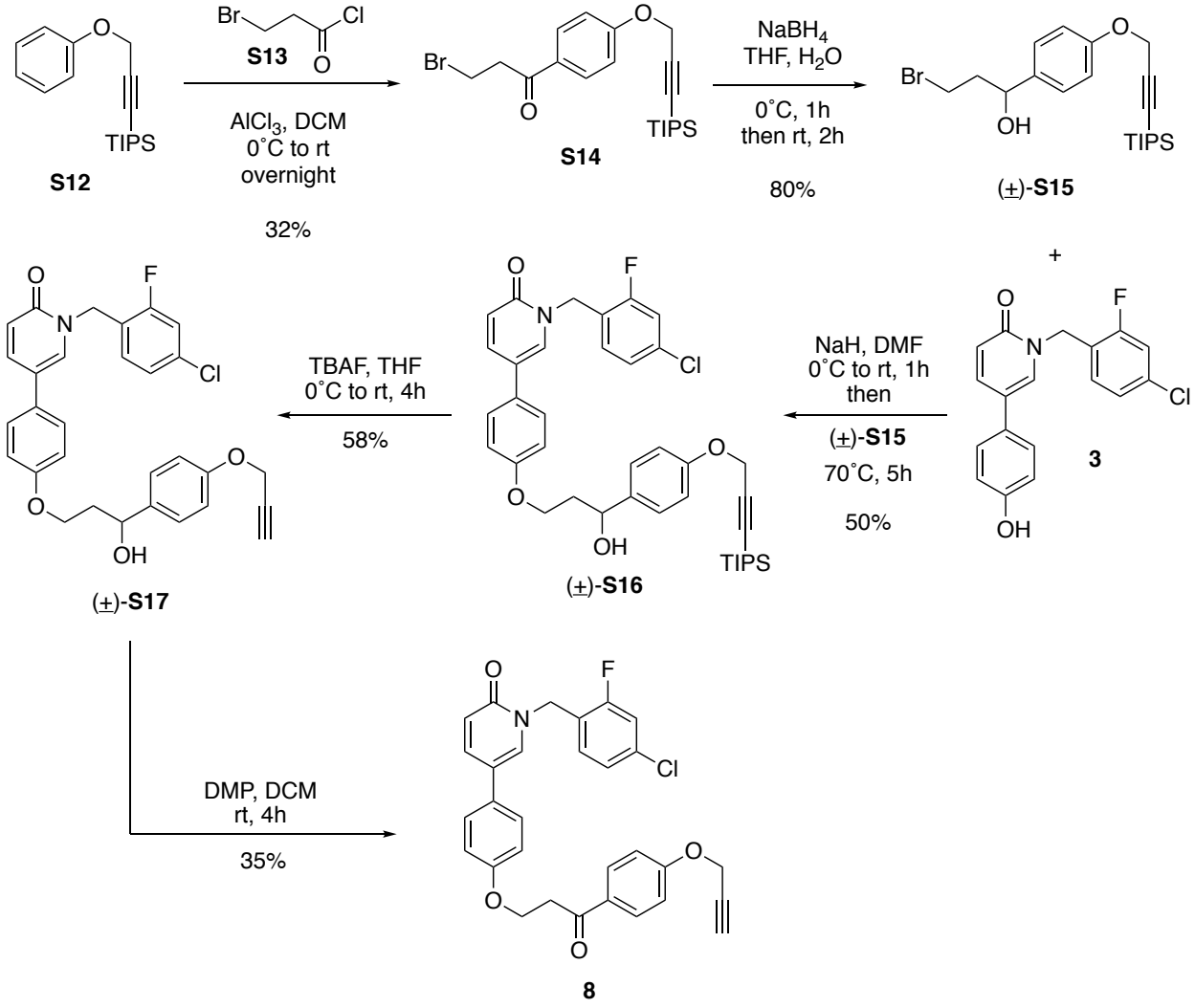


S9 **S11**

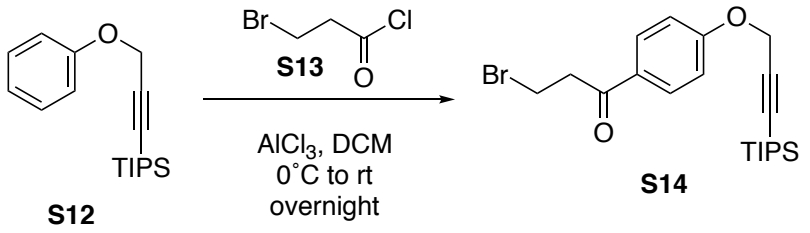
1-(4-Azido-2-fluorobenzyl)-5-(4-(prop-2-yn-1-yloxy)phenyl)pyridin-2(1*H*)-one (**7**). A mixture containing pyridine **S9** (25 mg, 0.10 mmol, 1 equiv), CH_3CN (3 mL), NaI (39 mg, 0.26 mmol, 2.6 equiv), benzyl chloride (**S11**) (19 mg, 0.10 mmol, 1 equiv), and DMF (0.5 mL) was refluxed at 85˚C for 5 hours, followed by stirring at room temperature overnight. The reaction mixture was then concentrated by rotary evaporation and the resulting residue was partitioned between EtOAc and H_2O. The separated EtOAc layer was then sequentially washed with H_2O

and brine, dried (MgSO4), filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 4:6 EtOAc:hexanes) to provide 12 mg of azido-alkyne probe **7** as a yellow oil (31%).

*R*f = 0.69 (4:6 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 7.62 – 7.49 (m, 3H), 7.32 (d, *J* = 8.8 Hz, 2H), 7.03 (d, *J* = 8.8 Hz, 2H), 6.83 (ddd, *J* = 8.2, 2.2, 0.7 Hz, 1H), 6.76 (dd, *J* = 10.6, 2.2 Hz, 1H), 6.66 (dd, *J* = 9.4, 0.7 Hz, 1H), 5.23 – 5.14 (m, 2H), 4.72 (d, *J* = 2.4 Hz, 2H), 2.54 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.8, 160.4, 157.0, 142.1, 139.6, 133.0, 132.9, 127.0, 121.1, 120.2, 119.9, 119.7, 115.5, 115.2, 115.2, 78.3, 75.8, 55.9, 55.9. HRMS calcd for $(C_{21}H_{15}FN_4O_2)Na^+$ 397.1071, found 397.1073. IR: azide, 2117.8 cm^{-1}.

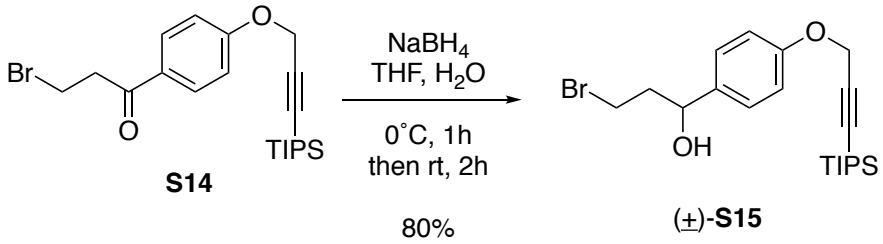


Scheme S2. *Synthesis of mGlu2 PAM clickable photoprobe* ***8****.*



32%

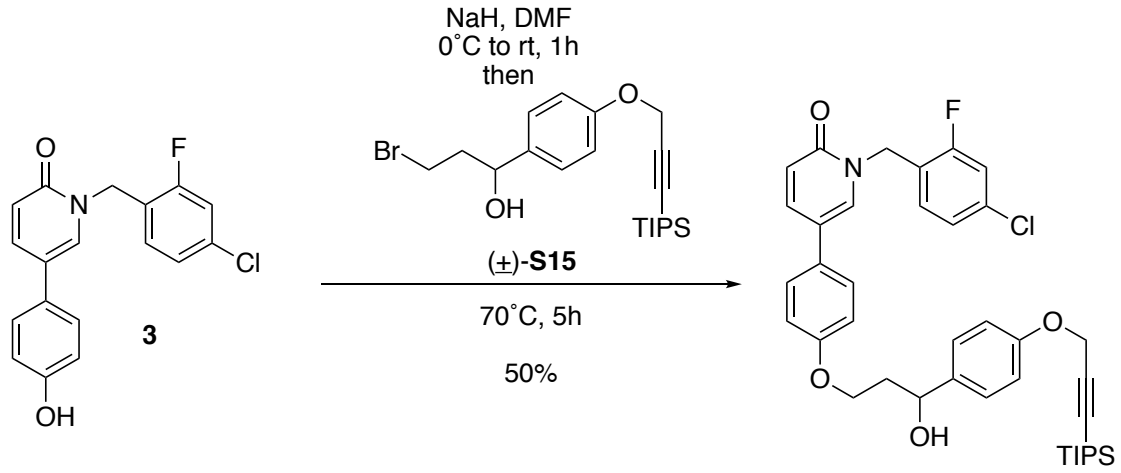
3-Bromo-1-(4-((3-(triisopropylsilyl)prop-2-yn-1-yl)oxy)phenyl)propan-1-one (**S14**). A mixture of triisopropyl(3-phenoxyprop-1-yn-1-yl)silane[6] (**S12**) (410 mg, 1.42 mmol, 1 equiv) and 4-bromopropionyl chloride (**S13**) (0.15 mL, 1.56 mmol, 1.1 equiv) in CH_2Cl_2 (1 mL) was slowly added to a mixture of $AlCl_3$ (282 mg, 2.12 mmol, 1,5 equiv) in CH_2Cl_2 (2 mL) at 0˚C. The resulting brown-black reaction mixture was then warmed to room temperature and stirred overnight. The reaction was then cooled to 0˚C, quenched with ice, and diluted with H_2O and CH_2Cl_2. Potassium sodium tartrate (500 mg) was then added to the mixture followed by vigorous stirring for 30 minutes. The organic layer was then separated, washed with brine, dried ($MgSO_4$), filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 5:95 EtOAc:hexanes) to provide 190 mg of ketone **S14** as a brown oil (32%).
*R*f = 0.6 (1:9 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*; *note:* the ^{1}H NMR spectrum contains slight impurities but the material was acceptable enough to take on further in the synthetic sequence) δ 7.95 (d, *J* = 9.0 Hz, 2H), 6.98 (d, *J* = 8.9 Hz, 2H), 4.62 (s, 2H), 3.74 (td, *J* = 6.9, 0.5 Hz, 2H), 3.53 (td, *J* = 6.9, 0.5 Hz, 2H), 1.06 (d, *J* = 6.3 Hz, 21H). ^{13}C NMR (101 MHz, $CDCl_3$; *note:* the ^{13}C NMR spectrum contains slight impurities but the material was acceptable enough to take on further in the synthetic sequence) δ 195.5, 162.5, 140.4, 130.5, 115.2, 77.2, 71.5, 41.2, 26.0, 18.6, 11.9, 10.6. HRMS calcd. for $(C_{21}H_{31}BrO_2Si)Na^+$ 445.1169, found 445.1172.



80%

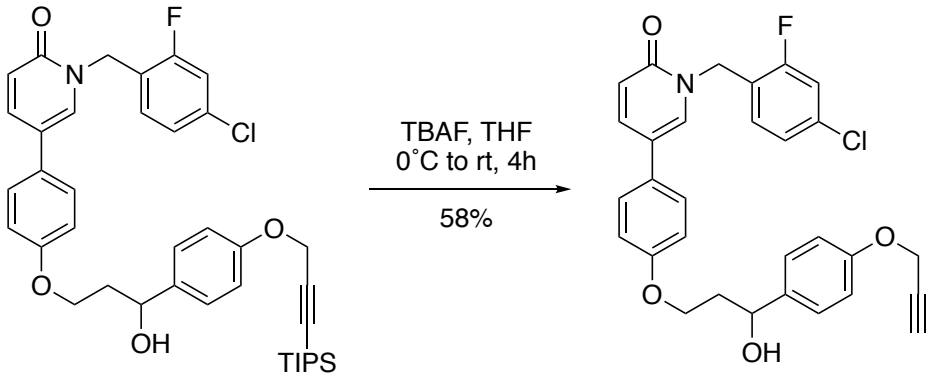
(±)-3-Bromo-1-(4-((3-(triisopropylsilyl)prop-2-yn-1-yl)oxy)phenyl)propan-1-ol ((±)-**S15**). A suspension of ketone **S14** (175 mg, 0.42 mmol, 1 equiv) in THF (3 mL) and H_2O (1mL) was treated with $NaBH_4$ (15 mg, 0.42 mmol, 1 equiv) at 0˚C. The reaction was then stirred at 0˚C for 1 hour, followed by stirring at room temperature for 2 hours. The reaction mixture was then concentrated by rotary evaporation and the residue was partitioned between EtOAc and brine. The organic layer was then separated, dried (MgSO4), filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 1:9 EtOAc:hexanes) to provide to provide 141 mg of benzyl alcohol (±)-**S15** as a colorless oil (80%).
*R*f = 0.25 (1:9 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*; *note:* the ^{1}H NMR spectrum contains impurities but the material was acceptable enough to take on further in the synthetic sequence) δ 7.29 (d, *J* = 8.8 Hz, 2H), 6.92 (d, *J* = 8.7 Hz, 2H), 4.86 (dd, *J* = 8.4, 4.9 Hz, 1H), 4.55 (s, 2H), 3.55 (ddd, *J* = 10.0, 8.0, 6.0 Hz, 1H), 3.38 (dt, *J* = 10.0, 6.2 Hz, 1H), 2.31 (ddt, *J* = 14.3, 8.2, 6.0 Hz, 1H), 2.20 – 2.11 (m, 1H), 2.11 – 2.04 (br s, 1H), 1.06 (d, *J* = 6.2 Hz, 21H). A

^{13}C NMR spectrum was not obtained for this synthetic intermediate due to questionable purity. The ^{1}H NMR spectrum indicated the material was acceptable enough to take on further in the synthetic sequence. HRMS calcd for $(C_{21}H_{33}BrO_2Si)Na^+$ 447.1325, found 447.1329.



(±)-1-(4-Chloro-2-fluorobenzyl)-5-(4-(3-hydroxy-3-(4-((3-(triisopropylsilyl)prop-2-yn-1-yl)oxy)phenyl)propoxy)phenyl)pyridin-2(1*H*)-one ((±)-**S16**). A mixture of phenol **3**[2] (110 mg, 0.33 mmol, 1 equiv) in DMF (3 mL) was added to a suspension of NaH (14.4 mg, 0.6 mmol, 1.8 equiv) in DMF (3 mL) at 0˚C. The mixture was then stirred at room temperature for 1 hour followed by dropwise addition of bromide (±)-**S15** (142 mg, 0.33 mmol, 1 equiv) in DMF (10 mL). The resulting reaction was then stirred at 70˚C for 5 hours, cooled to room temperature, then acidified with 1M aq. HCl and extracted with EtOAc. The separated organic layer was then washed with brine, then dried ($MgSO_4$), filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 6:4 EtOAc:hexanes) to give 119 mg of ether (±)-**S16** as a yellow oil (50%).

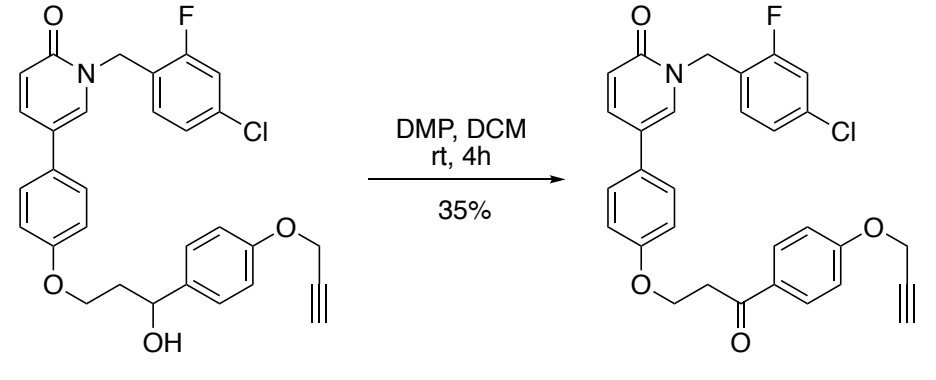
*R*f = 0.38 (6:4 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*; *note:* the ^{1}H NMR spectrum contains impurities but the material was acceptable enough to take on further in the synthetic sequence) δ 7.53 (dd, *J* = 9.4, 1.9 Hz, 1H), 7.49 (s, 1H), 7.44 (t, *J* = 7.8 Hz, 1H), 7.35 – 7.22 (m, 4H), 7.11 (d, *J* = 0.6 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 1H), 6.92 (d, *J* = 8.8 Hz, 3H), 6.60 (d, *J* = 9.3 Hz, 1H), 5.13 (s, 2H), 4.99 – 4.89 (m, 1H), 4.71 (s, 2H), 4.15 (tdt, *J* = 12.8, 9.0, 6.2 Hz, 1H), 4.02 (dq, *J* = 9.3, 6.0 Hz, 1H), 2.31 – 2.07 (m, 2H), 2.03 (br s, 1H), 1.02 (d, *J* = 0.8 Hz, 21H). A ^{13}C NMR spectrum was not obtained for this synthetic intermediate due to questionable purity. The ^{1}H NMR spectrum indicated the material was acceptable enough to take on further in the synthetic sequence. HRMS calcd for $(C_{39}H_{45}ClFNO_4Si)Na^+$ 696.2683, found 696.2686.



(±)-**S16** (±)-**S17**

(±)-1-(4-Chloro-2-fluorobenzyl)-5-(4-(3-hydroxy-3-(4-(prop-2-yn-1-yloxy)phenyl)propoxy)phenyl)pyridin-2(1*H*)-one ((±)-**S17**). A solution of TIPS-protected alkyne (±)-**S16** (100 mg, 0.15 mmol, 1 equiv) in THF (3 mL) was treated with TBAF (1M in THF, 0.33 mL, 0.33 mmol, 2.2 equiv) at 0˚C, then stirred for 4 hours at room temperature. The reaction was then cooled again to 0˚C and TBAF (1M in THF, 0.08 mL, 0.075 mL) was added. The resulting mixture was then concentrated by rotary evaporation and purified by flash column chromatography (SiO_2, 1:1 EtOAc:hexanes) to provide 40 mg of deprotected alkyne (±)-**S17** as an off-white oil (58%).

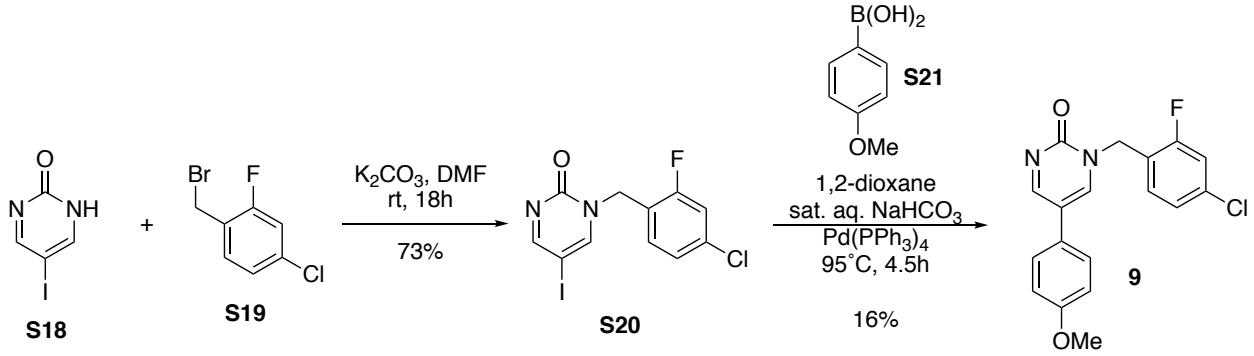
*R*f = 0.27 (6:4 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*; *note:* the spectrum contains trace EtOAc as an impurity) δ 7.56 (ddd, *J* = 9.5, 2.7, 0.9 Hz, 1H), 7.52 – 7.43 (m, 2H), 7.37 – 7.24 (m, 4H), 7.15 – 7.08 (m, 2H), 6.95 (dd, *J* = 13.2, 8.0 Hz, 4H), 6.64 (d, *J* = 9.4 Hz, 1H), 5.17 (s, 2H), 4.97 (dt, *J* = 8.3, 4.0 Hz, 1H), 4.69 (dd, *J* = 2.4, 0.9 Hz, 2H), 4.23 – 4.00 (m, 2H), 2.52 (td, *J* = 2.4, 0.9 Hz, 1H), 2.45 (d, *J* = 3.3 Hz, 1H), 2.34 – 2.09 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 161.8, 158.3, 157.1, 139.7, 137.3, 135.1, 135.0, 132.4, 132.4, 129.0, 127.1, 127.0, 125.0, 121.1, 120.4, 116.4, 116.2, 115.1, 114.9, 78.5, 75.6, 71.4, 65.5, 55.8, 46.2, 38.3. HRMS calcd for $(C_{30}H_{25}ClFNO_4)Na^+$ 540.1348, found 540.1351.



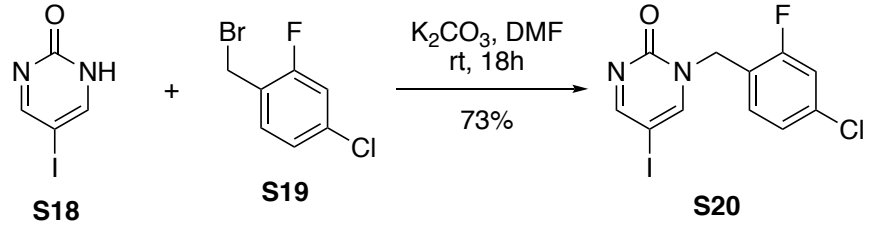
(±)-**S17** **8**

1-(4-Chloro-2-fluorobenzyl)-5-(4-(3-oxo-3-(4-(prop-2-yn-1-yloxy)phenyl)propoxy)phenyl)pyridin-2(1*H*)-one (**8**). To a mixture of benzyl alcohol (±)-**S17** (33 mg, 0.064 mmol, 1 equiv) in CH_2Cl_2 (3 mL) was added DMP (33 mg, 0.077 mmol, 1.2 equiv). The reaction was then stirred for 4 hours at room temperature, followed by dilution with H_2O. The separated organic layer was then washed with brine, dried ($MgSO_4$), filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 3:7 to 1:1 EtOAc:hexanes) to provide 12 mg of ketone **8** as a white solid (58%).

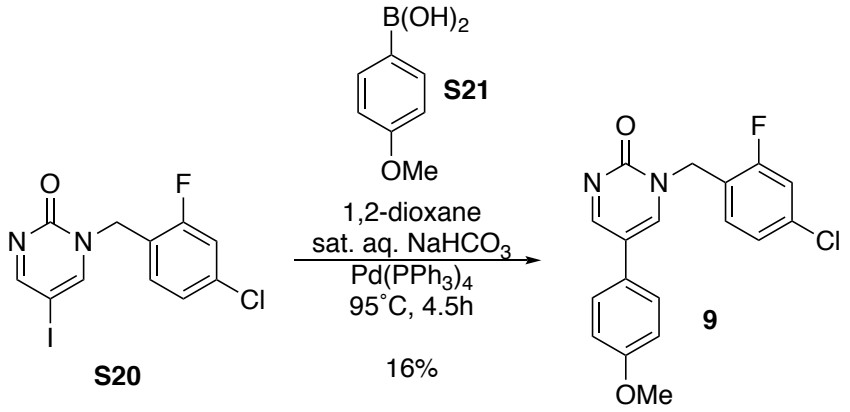
*R*f = 0.46 (6:4 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.01 (d, *J* = 9.0 Hz, 2H), 7.58 (dd, *J* = 9.4, 2.6 Hz, 1H), 7.54 – 7.43 (m, 2H), 7.29 (d, *J* = 8.9 Hz, 2H), 7.15 – 7.09 (m, 2H), 7.05 (d, *J* = 9.0 Hz, 2H), 6.97 (d, *J* = 8.9 Hz, 2H), 6.66 (dd, *J* = 9.4, 0.6 Hz, 1H), 5.18 (s, 2H), 4.78 (d, *J* = 2.4 Hz, 2H), 4.44 (t, *J* = 6.6 Hz, 2H), 3.45 (t, *J* = 6.6 Hz, 2H), 2.57 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 195.9, 162.0, 161.8, 161.5, 159.5, 158.3, 139.7, 135.1, 134.1, 134.1, 132.4, 132.3, 130.6, 130.4, 129.0, 127.0, 125.1, 125.0, 122.0, 121.9, 121.1, 120.5, 116.2, 115.2, 114.7, 77.7, 76.3, 63.5, 55.9, 46.2, 37.8. HRMS calcd for $(C_{30}H_{23}ClFNO_4)Na^+$ 538.1192, found 538.1194. Anal. Calcd. for $C_{30}H_{23}ClFNO_4 \bullet 0.96H_2O$: C, 67.57; H, 4.71; N, 2.63; found C, 67.59; H,4.92; N, 2.54. MP: 203˚C.



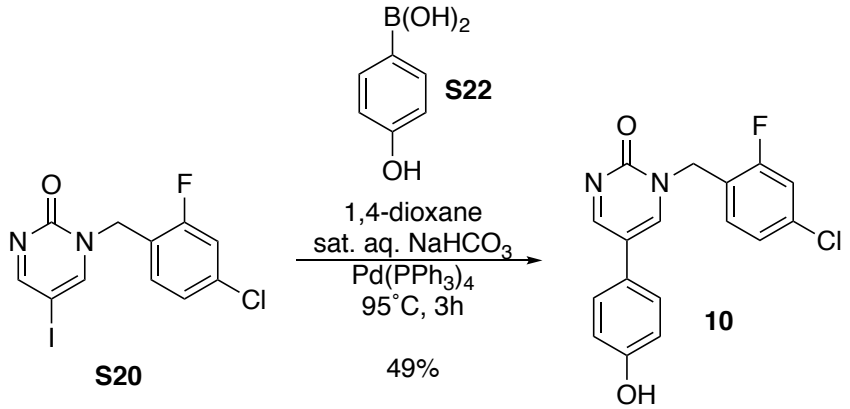
Scheme S3. *Synthesis of mGlu2 PAM photoprobe* ***9****.*



1-(4-Chloro-2-fluorobenzyl)-5-iodopyrimidin-2(1*H*)-one (**S20**). A mixture of 5-iodopyrimidin-2(1*H*)-one (**S18**) (914 mg, 4.12 mmol, 1 equiv), DMF (18 mL), 2-flouro-4-chlorobenzyl bromide (**S19**) (1.1 g, 4.94 mmol, 1.2 equiv), and K_2CO_3 (1.71 g, 12.36 mmol, 3 equiv) was stirred at room temperature for 18 hours, then diluted with H_2O. The resulting precipitate was collected by filtration and dried to provide white solid. Purification by flash column chromatography (SiO_2, 9:1 to 8:2 CH_2Cl_2:hexanes) provided 1.1 g of *N*-benzylated pyrimidin-2(1*H*)-one **S20** as a white solid (73%).
*R*f = 0.39 (EtOAc:hexanes, 1:1). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.59 (d, *J* = 3.1 Hz, 1H), 7.97 (dt, *J* = 3.0, 1.4 Hz, 1H), 7.55 (t, *J* = 7.8 Hz, 1H), 7.15 (ddd, *J* = 10.1, 8.6, 1.4 Hz, 2H), 5.04 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.7, 162.2, 159.7, 154.0, 151.8, 151.8, 136.1, 136.1, 133.2, 133.1, 125.3, 125.3, 119.8, 119.8, 116.6, 116.4, 48.5, 48.5. HRMS calcd. for $(C_{11}H_7ClFIN_2O)Na^+$ 386.9168, found 386.9164.

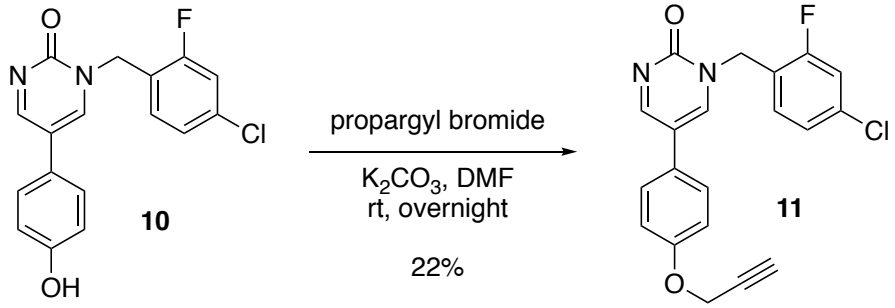


1-(4-Chloro-2-fluorobenzyl)-5-(4-methoxyphenyl)pyrimidin-2(1*H*)-one (**9**). To aryl iodide **S20** (290 mg, 0.80 mmol, 1 equiv) was sequentially added 1,2-dioxane (8 mL), sat. aq. $NaHCO_3$ solution (8 mL), 4-methoxyphenyl boronic acid (**S21**) (204 mg, 1.34 mmol, 1.7 equiv), and $Pd(PPh_3)_4$ (211 mg, 0.18 mmol, 0.23 equiv). The reaction mixture was then purged with argon and heated at 90˚C for 4.5 hours. After cooling to room temperature, the mixture was filtered through Celite® with EtOAc, washed with sat. aq. NH_4Cl solution, then dried ($MgSO_4$), filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 6:4 to 7:3 EtOAc:hexanes) to provide 43 mg of substituted pyrimidone **9** as a yellow solid (16%).
*R*f = 0.09 (1:1 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.81 (d, *J* = 3.3 Hz, 1H), 7.88 (dd, *J* = 3.3, 1.7 Hz, 1H), 7.61 (t, *J* = 8.2 Hz, 1H), 7.31 (d, *J* = 8.8 Hz, 2H), 7.20 – 7.08 (m, 2H), 6.98 (d, *J* = 8.8 Hz, 2H), 5.13 (d, *J* = 1.4 Hz, 2H), 3.84 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 162.2, 159.7, 155.6, 143.9, 143.9, 135.8, 135.7, 133.2, 133.1, 127.1, 125.3, 125.2, 125.2, 120.6, 120.4, 118.7, 116.5, 116.3, 114.8, 55.4, 48.5, 48.5. HRMS calcd for $(C_{18}H_{14}ClFN_2O_2)Na^+$ 367.0620, found 367.0618. Anal. Calcd. for $C_{18}H_{14}ClFN_2O_2$•0.2EtOAc•0.1HCl: C, 61.89; H, 4.28; N, 7.74; Cl, 10.57; F, 5.25; Found C, 62.02; H, 4.20; N, 7.63; Cl, 10.64; F, 5.00. MP: 210˚C.

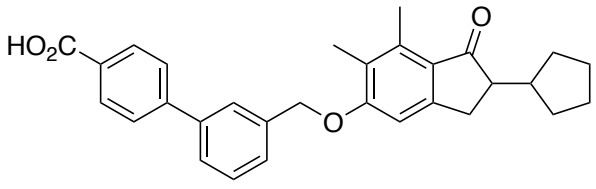


1-(4-Chloro-2-fluorobenzyl)-5-(4-hydroxyphenyl)pyrimidin-2(1*H*)-one (**10**). A mixture of iodide **S20** (394 mg, 1.08 mmol, 1 equiv.), 1,4-dioxane (10 mL), 4-hydroxyphenyl boronic acid (**S22**) (226 mg, 1.64 mmol, 1.5 equiv), sat. aq. $NaHCO_3$ solution (10 mL), and $Pd(PPh_3)_4$ (250 mg, 0.22 mmol, 0.2 equiv.) was purged with argon then heated for 3 hours at 95˚C. The reaction mixture was then cooled to room temperature and filtered through Celite®. The filtrate was then diluted with EtOAc and washed with sat. aq. NH_4Cl solution. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered, concentrated by rotary evaporation. The crude

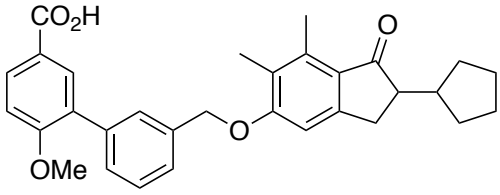
material was then filtered through a short plug of silica gel using CH_2Cl_2 followed by EtOAc, then concentrated by rotary evaporation. The resulting yellow solid was recrystallized in EtOAc to obtain 175 mg of substituted phenol **10** (49%).
*R*f = 0.33 (1:9 MeOH:$CHCl_3$). ^{1}H NMR (400 MHz, DMSO-d_6) δ 9.64 (s, 1H), 8.93 (d, *J* = 3.3 Hz, 1H), 8.60 (d, *J* = 3.3 Hz, 1H), 7.59 – 7.38 (m, 3H), 7.38 – 7.15 (m, 2H), 6.85 (d, *J* = 8.7 Hz, 2H), 5.13 (s, 2H). ^{13}C NMR (101 MHz, DMSO) δ 165.7, 161.9, 159.4, 157.7, 146.3, 133.9, 132.0, 127.3, 125.2, 125.2, 124.1, 117.6, 116.7, 116.4, 116.3, 48.6. HRMS calcd for $(C_{17}H_{12}ClFN_2O_2)Na^+$ 353.0463, found 353.0463.



1-(4-Chloro-2-fluorobenzyl)-5-(4-(prop-2-yn-1-yloxy)phenyl)pyrimidin-2(1*H*)-one (**11**). Propargyl bromide (80% in toluene, 0.07 mL, 1.6 equiv.) was added dropwise to a mixture of phenol **10** (144 mg, 0.44 mmol, 1 equiv) and K_2CO_3 (180 mg, 1.31 mmol, 3 equiv) in DMF (4 mL). The reaction was then stirred at room temperature overnight followed by dilution with EtOAc and H_2O. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 100% EtOAc) to provide 35 mg of propargyl ether **11** as a light-yellow solid (22%).
*R*f = 0.27 (100% EtOAc). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.82 (d, *J* = 3.3 Hz, 1H), 7.88 (dd, *J* = 3.3, 1.6 Hz, 1H), 7.62 (t, *J* = 8.2 Hz, 1H), 7.33 (d, *J* = 8.7 Hz, 2H), 7.22 – 7.10 (m, 2H), 7.06 (d, *J* = 8.7 Hz, 2H), 5.14 (s, 2H), 4.74 (d, *J* = 2.4 Hz, 2H), 2.56 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.6, 159.8, 157.6, 155.6, 144.0, 144.0, 135.8, 133.3, 133.2, 127.2, 126.3, 125.3, 125.3, 120.5, 120.4, 118.5, 116.6, 116.3, 115.8, 78.2, 75.9, 55.9, 48.6, 48.5. HRMS calcd for $(C_{20}H_{14}ClFN_2O_2)Na^+$ 391.0620, found 391.0619. Anal. calcd for $C_{20}H_{14}ClFN_2O_2$•0.2EtOAc: C, 64.65; H, 4.07; N, 7.25; Cl, 9.17; F, 4.92. Found: C, 64.27; H, 4.13; N, 7.14; Cl, 9.44; F, 4.90.

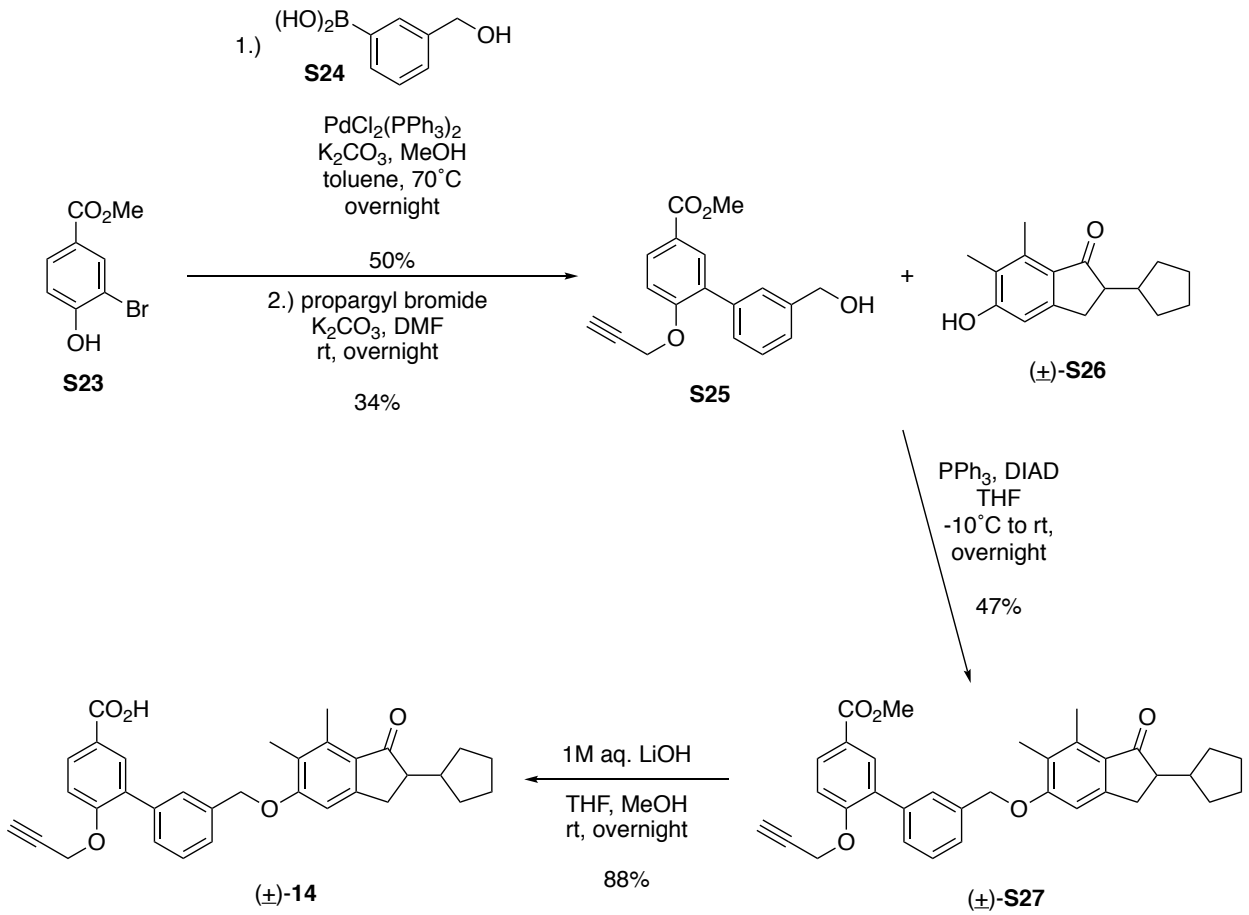


BINA ((±)-**12**)

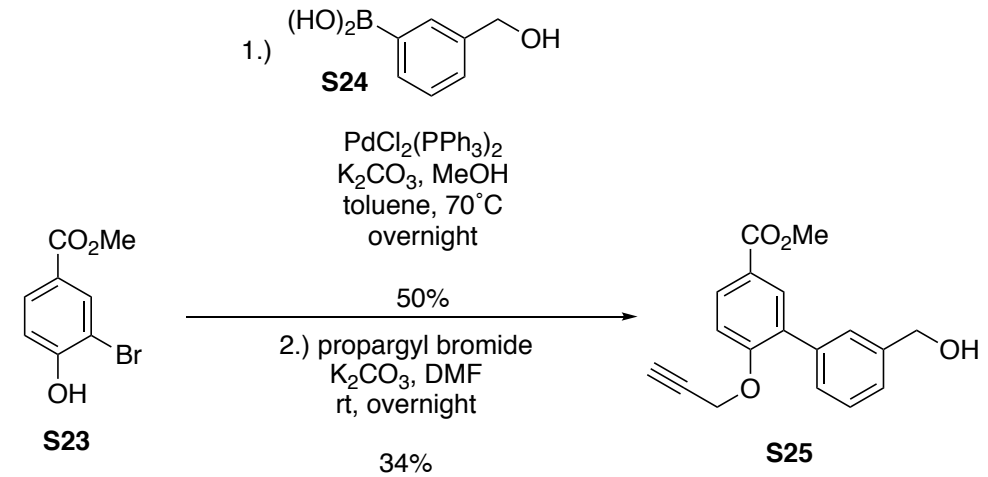


(±)-**13**

BINA ((±)-**12**) was purchased from Hellobio (UK). **(±)-3'-(((2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yl)oxy)methyl)-6-methoxy-[1,1'-biphenyl]-3-carboxylic acid** ((±)-**13**) was prepared as previously described.[7]



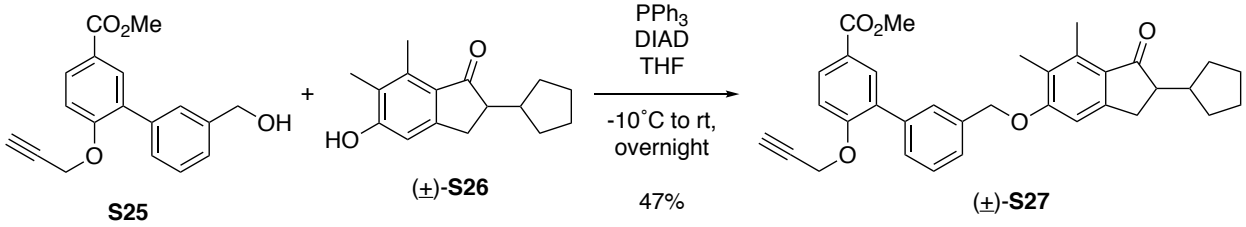
Scheme S4. *Synthesis of mGlu2 PAM clickable photoprobe (±)-**14**.*



Methyl 3'-(hydroxymethyl)-6-(prop-2-yn-1-yloxy)-[1,1'-biphenyl]-3-carboxylate (**S25**). To aryl bromide derivative **S23** (601 mg, 2.60 mmol, 1 equiv.) was sequentially added boronic acid **S24** (474 mg, 3.12 mmol, 1.2 equiv), toluene (7.6 mL), MeOH (1.3 mL), K_2CO_3 (719 mg, 5.19 mmol, 2 equiv), and $PdCl_2(PPh_3)_2$ (182 mg, 0.26 mmol, 0.1 equiv). The reaction mixture was degassed, heated at 70˚C overnight, then cooled to room temperature and filtered over Celite®

rinsing with EtOAc. The filtrate was then sequentially washed with H_2O and brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to provide 333 mg of coupled phenol derivative (50%), which was used immediately without further purification. *R*f = 0.12 (4:6 EtOAc:hexanes). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.30 (s, 1H), 7.95 (d, 1H, *J* = 2.1 Hz), 7.40 (m, 4H), 6.97 (d, 1H, *J* = 8.5 Hz), 4.69 (s, 2H), 3.89 (s, 3H). To a suspension of the coupled phenol derivative (333 mg, 1.29 mmol, 1 equiv) and K_2CO_3 (535 mg, 3.86 mmol, 3 equiv) in DMF (11 mL) was added propargyl bromide (80% in toluene; 0.16 mL) dropwise. The resulting light-yellow colored reaction mixture was then stirred at room temperature overnight, followed by dilution with H_2O and EtOAc. The organic layer was separated and sequentially washed with H_2O and brine, then dried ($MgSO_4$), filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 4:6 EtOAc:hexanes) to provide 129 mg of propargyl ether **S25** as a colorless oil (34%).

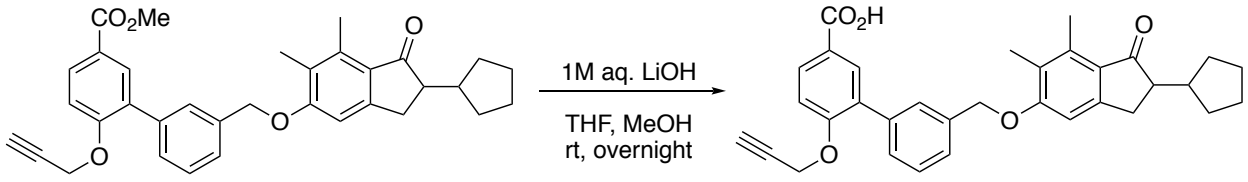
*R*f = 0.65 (1:1 EtOAc:hexanes). ^{1}H NMR (500 MHz, Chloroform-*d*) δ 8.02 (dt, *J* = 3.1, 1.7 Hz, 2H), 7.51 (d, *J* = 1.8 Hz, 1H), 7.46 (dd, *J* = 7.6, 1.7 Hz, 1H), 7.41 (t, *J* = 7.5 Hz, 1H), 7.35 (dd, *J* = 7.5, 1.6 Hz, 1H), 7.14 (d, *J* = 9.1 Hz, 1H), 4.74 (s, 4H), 3.89 (s, 3H), 2.52 (t, *J* = 2.1 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.8, 158.0, 140.9, 137.5, 132.6, 131.0, 130.6, 128.9, 128.3, 128.1, 126.1, 123.6, 112.4, 77.9, 76.2, 65.3, 56.1, 52.1. HRMS calcd for $(C_{18}H_{16}O_4)Na^+$ 319.0941, found 319.0943.



S25 (±)-**S26** (±)-**S27**

(±)-Methyl 3'-(((2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yl)oxy)methyl)-6-(prop-2-yn-1-yloxy)-[1,1'-biphenyl]-3-carboxylate ((±)-**S27**). A mixture of DIAD (89.2 mg, 0.44 mmol, 1.2 equiv) in THF (2 mL) was slowly added to a suspension of phenol (±)-**S26**[8] (90 mg, 0.37 mmol, 1 equiv), Ph_3P (116 mg, 0.44 mmol, 1.2 equiv), and benzyl alcohol derivative **S25** (131 mg, 0.44 mmol, 1.2 equiv) in THF (2 mL) at -10˚C. The reaction mixture was then stirred at room temperature overnight, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 100% CH_2Cl_2) to provide 90 mg of benzyl ether (±)-**S27** as a colorless oil (47%).

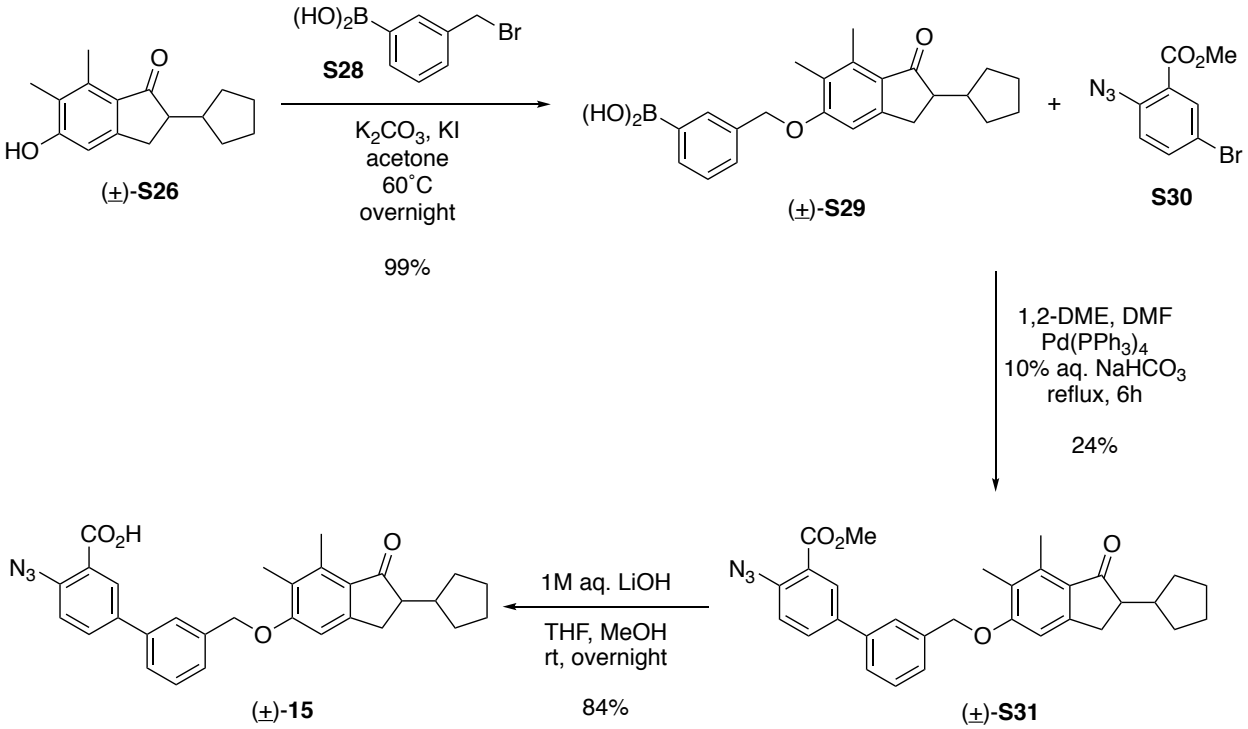
*R*f = 0.8 (100% CH_2Cl_2). ^{1}H NMR (400 MHz, Chloroform-*d*; *note:* the ^{1}H NMR spectrum of this synthetic intermediate contains trace EtOAc as an impurity) δ 8.15 – 7.92 (m, 2H), 7.63 (s, 1H), 7.58 – 7.31 (m, 3H), 7.16 (d, *J* = 8.5 Hz, 1H), 6.80 (s, 1H), 5.18 (s, 2H), 4.74 (d, *J* = 2.4 Hz, 2H), 3.90 (s, 3H), 3.12 – 3.02 (m, 1H), 2.78 – 2.65 (m, 2H), 2.62 (s, 3H), 2.53 (t, *J* = 2.3 Hz, 1H), 2.33 (dtt, *J* = 8.0, 6.0, 3.0 Hz, 1H), 2.22 (s, 3H), 1.92 (ddt, *J* = 11.2, 7.4, 3.7 Hz, 1H), 1.74 – 1.32 (m, 6H), 1.13 – 0.99 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5, 166.7, 161.6, 158.0, 155.0, 138.6, 137.6, 136.3, 132.7, 130.8, 130.6, 129.2, 128.5, 128.3, 128.1, 126.2, 125.7, 123.6, 112.4, 105.6, 77.9, 76.3, 70.0, 56.1, 52.0, 51.2, 41.3, 30.8, 29.7, 28.2, 25.4, 25.2, 14.0, 11.3. HRMS calcd. for $(C_{34}H_{34}O_5)Na^+$ 545.2298, found 545.2291.



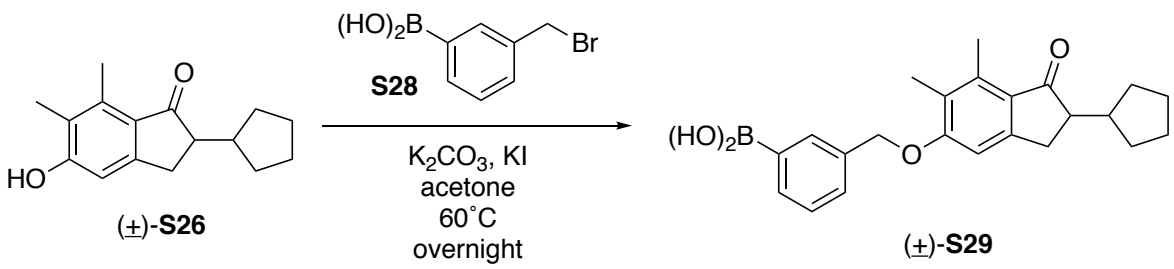
(±)-**S27** (±)-**14**

(±)-3'-(((2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yl)oxy)methyl)-6-(prop-2-yn-1-yloxy)-[1,1'-biphenyl]-3-carboxylic acid ((±)-**14**). A suspension of methyl ester (±)-**S27** (90 mg, 0.17 mmol, 1 equiv) and LiOH (16.5 mg, 0.69 mmol, 4 equiv) in THF (0.4 mL), MeOH (0.2 mL), and H_2O (0.09 mL) was vigorously stirred at room temperature overnight. The resulting clear solution was then acidified with 1M aq. HCl to pH 1, followed by dilution with EtOAc. The EtOAc layer was then separated, washed with brine, dried ($MgSO_4$), filtered, and concentrated by rotary evaporation to provide 77 mg of carboxylic acid (±)-**14** as a white solid (88%).

*R*f = 0.33 (35:60:3:2 EtOAc:hexanes:MeOH:AcOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 12.85 (s, 1H), 7.97 (dd, *J* = 8.6, 2.2 Hz, 1H), 7.88 (d, *J* = 2.2 Hz, 1H), 7.62 (s, 1H), 7.49 (d, *J* = 1.2 Hz, 3H), 7.31 (d, *J* = 8.8 Hz, 1H), 7.07 (s, 1H), 5.28 (s, 2H), 4.92 (d, *J* = 2.5 Hz, 2H), 3.63 (t, *J* = 2.3 Hz, 1H), 3.16 – 3.01 (m, 1H), 2.76 – 2.61 (m, 2H), 2.55 – 2.50 (s, 3H), 2.20 (m, 1H), 2.14 (s, 3H), 1.84 (m, 1H), 1.68 – 1.28 (m, 6H), 1.10 – 0.96 (m, 1H). ^{13}C NMR (101 MHz, DMSO) δ 207.2, 166.9, 161.0, 157.5, 154.9, 137.3, 137.2, 136.8, 131.8, 130.5, 129.8, 128.8, 128.4, 128.2, 127.3, 126.4, 124.7, 124.0, 113.0, 106.4, 78.8, 78.7, 69.5, 56.0, 50.5, 40.8, 30.2, 29.2, 27.8, 25.0, 24.8, 13.4, 11.1. HRMS calcd for $(C_{33}H_{32}O_5)Na^+$ 531.2142, found 531.2134. Anal. calcd for $C_{33}H_{32}O_5$•EtOAc: C, 74.47; H, 6.76. Found: C, 74.28; H, 6.54. MP: 192˚C.

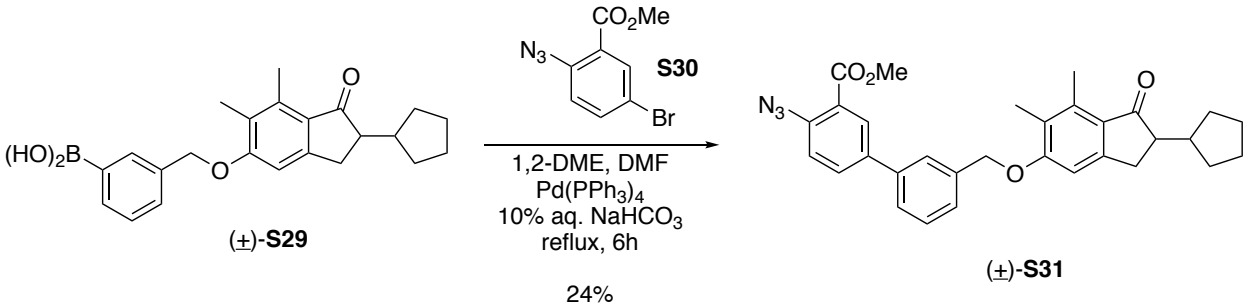


Scheme S5. *Synthesis of mGlu2 PAM clickable photoprobe (±)-**15**.*



99%

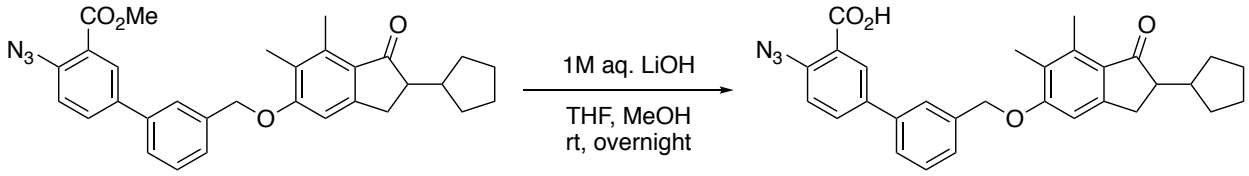
(±)-(3-(((2-Cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yl)oxy)methyl)phenyl)boronic acid ((±)-**S29**). A mixture of phenol (±)-**S26**[8] (500 mg, 2.05 mmol, 1 equiv), K_2CO_3 (1.27 g, 9.21 mmol, 4.5 equiv), KI (68 mg, 0.41 mmol, 0.2 equiv), and boronic acid derivative **S28** (461 mg, 2.15 mmol, 1.1 equiv) in acetone (36 mL) was heated at 60˚C overnight. The reaction mixture was then cooled to room temperature and diluted with EtOAc. The mixture was then sequentially washed with H_2O and brine, dried ($MgSO_4$), filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 1:9 to 3:7 EtOAc:hexanes) to provide 774 mg of benzyl ether (±)-**S29** as a white solid (99%).
*R*f = 0.8 (3:7 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.27 (d, *J* = 6.3 Hz, 1H), 8.15 (d, *J* = 7.2 Hz, 1H), 7.62 (d, *J* = 7.6 Hz, 1H), 7.52 (t, *J* = 7.3 Hz, 1H), 6.77 (s, 1H), 5.11 (s, 2H), 3.18 – 2.94 (m, 1H), 2.83 – 2.46 (m, 5H), 2.43 – 2.09 (m, 4H), 2.01 – 1.80 (m, 1H), 1.78 – 1.45 (m, 5H), 1.38 (td, *J* = 8.6, 7.8, 4.2 Hz, 1H), 1.05 (d, *J* = 10.0 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.7, 161.4, 155.1, 138.8, 136.3, 135.2, 134.0, 131.5, 131.5, 128.4, 128.1, 125.5, 105.4, 69.8, 51.2, 41.3, 30.8, 29.7, 28.2, 25.4, 25.2, 13.9, 11.2. HRMS calcd. for $(C_{23}H_{27}BO_4)Na^+$ 401.1895, found 401.1898. MP: 112˚C.



24%

(±)-Methyl 4-azido-3'-(((2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yl)oxy)methyl)-[1,1'-biphenyl]-3-carboxylate ((±)-**S31**). A mixture of boronic acid (±)-**S29** (74 mg, 0.20 mmol, 1.3 equiv) in 1,2-DME (2 mL) and DMF (1 mL) was added to a solution of aryl bromide **S30**[9] (42 mg, 0.16 mmol, 1 equiv) in 1,2-DME (2 mL) containing $Pd(PPh_3)_4$ (37.9 mg, 0.03 mmol, 0.2 equiv) and 10% aq. $NaHCO_3$ solution (0.32 mL). The resulting reaction mixture was then refluxed for 6 hours in the dark, cooled to room temperature, then filtered through Celite® rinsing with EtOAc. The EtOAc filtrate was then washed with brine, dried ($MgSO_4$), filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 1:9 EtOAc:hexanes) to provide 20 mg of Suzuki-coupled compound (±)-**S31** as a yellow oil (24%). *R*f = 0.39 (2:8 EtOAc:hexanes). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.11 (d, *J* = 2.3 Hz, 1H), 7.77 (dd, *J* = 8.5, 2.3 Hz, 1H), 7.66 (q, *J* = 1.3, 0.8 Hz, 1H), 7.57 (dt, *J* = 7.4, 1.8 Hz, 1H), 7.54 – 7.43 (m, 2H), 7.33 (d, *J* = 8.3 Hz, 1H), 6.80 (s, 1H), 5.20 (s, 2H), 3.95 (s, 3H), 3.14 –

3.02 (m, 1H), 2.79 – 2.67 (m, 2H), 2.63 (s, 3H), 2.37 – 2.27 (m, 1H), 2.22 (s, 3H), 1.92 (q, J = 7.7, 7.2 Hz, 1H), 1.73 – 1.49 (m, 4H), 1.47 – 1.33 (m, 1H), 1.28 – 1.23 (m, 1H), 1.13 – 1.02 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.5, 165.8, 161.4, 155.0, 139.3, 139.3, 138.9, 137.6, 137.3, 131.6, 130.4, 129.4, 128.3, 126.6, 126.6, 125.6, 125.6, 122.9, 120.5, 105.5, 70.0, 52.5, 51.2, 41.3, 30.8, 29.7, 28.2, 25.5, 25.2, 13.9, 11.3. HRMS calcd for $(C_{31}H_{31}N_3O_4)Na^+$ 532.2207, found 532.2210. IR: azide, 2121.2 cm^{-1}.



(±)-**S31** (±)-**15**

(±)-4-Azido-3'-(((2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yl)oxy)methyl)-[1,1'-biphenyl]-3-carboxylic acid ((±)-**15**). A suspension of methyl ester (±)-**S31** (20 mg, 0.04 mmol, 1 equiv) and LiOH (6 mg, 0.24 mmol, 6 equiv) in THF (2 mL), MeOH (1 mL), and H_2O (0.5 mL) was stirred at room temperature overnight in the dark. The reaction was then acidified with 1M aq. HCl to pH 1, followed by dilution with EtOAc. The EtOAc layer was then separated, washed with brine, dried ($MgSO_4$), filtered, concentrated by rotary evaporation, and purified by flash column chromatography (SiO_2, 35:60:3:2 EtOAc:hexanes:MeOH:AcOH) to provide 16 mg of carboxylic acid (±)-**15** as a light-yellow oil (84%).
*R*f = 0.2 (35:60:3:2 EtOAc:hexanes:MeOH:AcOH). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 8.39 (d, J = 2.2 Hz, 1H), 7.90 – 7.78 (m, 1H), 7.67 (s, 1H), 7.58 (d, J = 7.3 Hz, 1H), 7.55 – 7.44 (m, 2H), 7.35 (d, J = 8.3 Hz, 1H), 6.79 (s, 1H), 5.20 (s, 2H), 3.08 (dd, J = 17.8, 8.8 Hz, 1H), 2.78 – 2.67 (m, 2H), 2.63 (s, 3H), 2.40 – 2.28 (m, 1H), 2.22 (s, 3H), 2.00 – 1.86 (m, 1H), 1.71 – 1.46 (m, 5H), 1.40 (qd, J = 9.4, 8.6, 4.5 Hz, 1H), 1.13 – 1.01 (m, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 208.6, 161.5, 155.0, 139.1, 138.9, 138.9, 137.9, 137.7, 137.7, 132.7, 131.9, 129.5, 129.5, 128.2, 126.8, 126.6, 125.7, 125.6, 119.9, 105.5, 69.9, 51.3, 41.3, 30.8, 29.7, 28.1, 25.4, 25.3, 14.0, 11.3. HRMS calcd for $(C_{30}H_{29}N_3O_4)Na^+$ 518.2050, found 518.2053. IR: azide, 2118.4 cm^{-1}. MP: 180˚C.

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