SUPPORTING INFORMATION

Development and Optimization of Piperidyl-1,2,3-Triazole Ureas as Selective Chemical Probes of Endocannabinoid Biosynthesis

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I. EXPERIMENTAL SECTION

Analysis of SILAC samples by LC-MS/MS. Samples were analyzed by multidimensional liquid chromatography tandem mass spectrometry (MudPIT) using an Agilent 1200-series quaternary pump and Thermo Scientific LTQ-Orbitrap ion trap mass spectrometer. Peptides were eluted in a 5-step MudPIT experiment using 0%, 25%, 50%, 80%, and 100% salt bumps of 500 mM aqueous ammonium acetate and data were collected in data-dependent acquisition mode with dynamic exclusion turned on (20 s, repeat of 1). Specifically, one full MS (MS1) scan (400-1800 m/z) was followed by 30 MS2 scans of the most abundant ions. The MS2 spectra data were extracted from the raw file using RAW Xtractor (version 1.9.9.2; publicly available at http://fields.scripps.edu/downloads.php). MS2 spectra data were searched using the ProLuCID algorithm (available through IP2-Integrated Proteomics Pipeline http://goldfish.scripps.edu/ip2.jsp) against the latest version of the mouse UniProt database concatenated with the reversed database for assessment of false-discovery rates. ProLucid searches allowed for static modification of cysteine residues (+57.02146 due to alkylation), methionine oxidation (+15.9949), mass shifts of labeled amino acids (+10.0083 R, +8.0142 K) and no enzyme specificity. The resulting MS2 spectra matches were assembled into protein identifications and filtered using DTASelect (version 2.0) using the --modstat, --mass, and --trypstat options (applies different statistical models for the analysis of high resolution masses, peptide digestion state, and methionine oxidation state respectively). Ratios of heavy/light (test compound/DMSO) peaks were calculated using in-house software (CIMAGE) and normalized at the peptide level to the average ratio of all non-serine hydrolase peptides. Reported ratios represent the mean of all unique, quantified peptides per protein and do not include peptides that were >3 standard deviations from the median peptide value. Proteins with less than three peptides per protein ID were not included in the analysis.

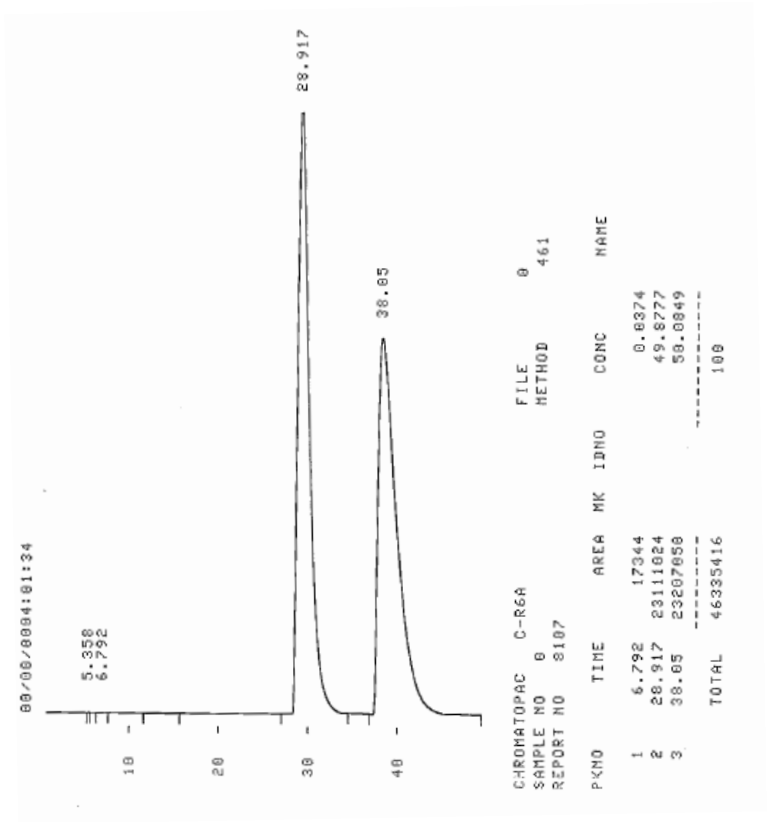
Synthetic Methods. All chemicals and reagents were purchased from the following vendors: Sigma-Aldrich, Acros, Fisher, Fluka, Maybridge, Combi-Blocks, BioBlocks, ChemExper, Capot Chemicals, or Matrix Scientific and used without further purification unless noted otherwise. Dry solvents were obtained by passing commercially available pre-dried, oxygen-free formulations through activated alumina columns. All reactions were performed under a nitrogen atmosphere using oven-dried glassware except where noted. Flash chromatography was carried out using 230-400 mesh silica gel. Reactions were monitored by analytical thin-layer chromatography (TLC) on precoated, glass backed silica gel 60 F_{254} plates. Reactions were purified either by pTLC, also on silica gel 60 F_{254} plates or by flash chromatography on 40-60 MYM mesh silica gel as specified. ^{1}H-NMR and spectra were recorded in $CDCl_3$ on a Varian Mercury-300 spectrometer, a Varian Inova-400, or a Bruker DRX-600 spectrometer, and were referenced to trimethylsilane (TMS). Chemical shifts were reported in ppm relative to TMS and *J* values were reported in Hz. High resolution mass spectrometry (HRMS) experiments were performed at The Scripps Research Institute Mass Spectrometry Core on an Agilent mass spectrometer using electrospray ionization-time of flight (ESI-TOF).

Analysis of Compound Purity by LC/MS. Compound purity was determined by LC/MS on an Agilent 1100 series LC-MSD SL instrument with UV detection at 254 nm. Chromatographic separation was performed using a Phenomenex Gemini C18 column (5 µm, 50 mm x 4.6 mm). Mobile phases A and B were composed of H_2O (0.1% formic acid) and CH_3CN (0.1% formic

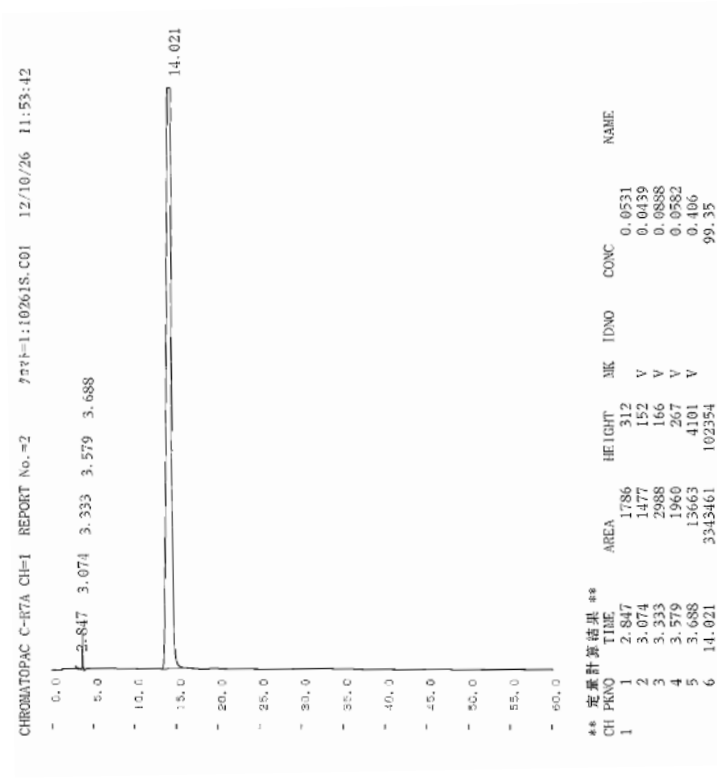
acid), respectively. Using a constant flow rate of 0.5 ml/min, the mobile phase was as follows: 1.0 min, 10% B; 2.0 min, 10-98% B (linear gradient); 5.0 min, 98% B; 2.0 min, 10% B. All final compounds were determined to be ≥95% pure by this method.

Chiral separation of compound 2. Racemic compound **2** was separated into its enantiomers using a 20 X 250 cm Daicel Chiralcel OD-H column eluting with 20% isopropylalcohol in hexane (20:80 IPA/Hex) with a flow rate of 9.9 ml/min. Two peaks were collected and analyzed on a Daicel Chiralcel OD-H column (4.6 X 250 mm, 20:80 IPA/Hex, flow rate of 1 ml/min) to yield its enantiomers as follows: **(-)-2a** as peak 1, 28.9 min, [α]$_D$ -72.7^o (c0.55, $CHCl_3$), e.e. > 99%; **(+)-2b** as peak 2, 38.1 min, [α]$_D$ +70.9^o (c0.55, $CHCl_3$), e.e. >99%.

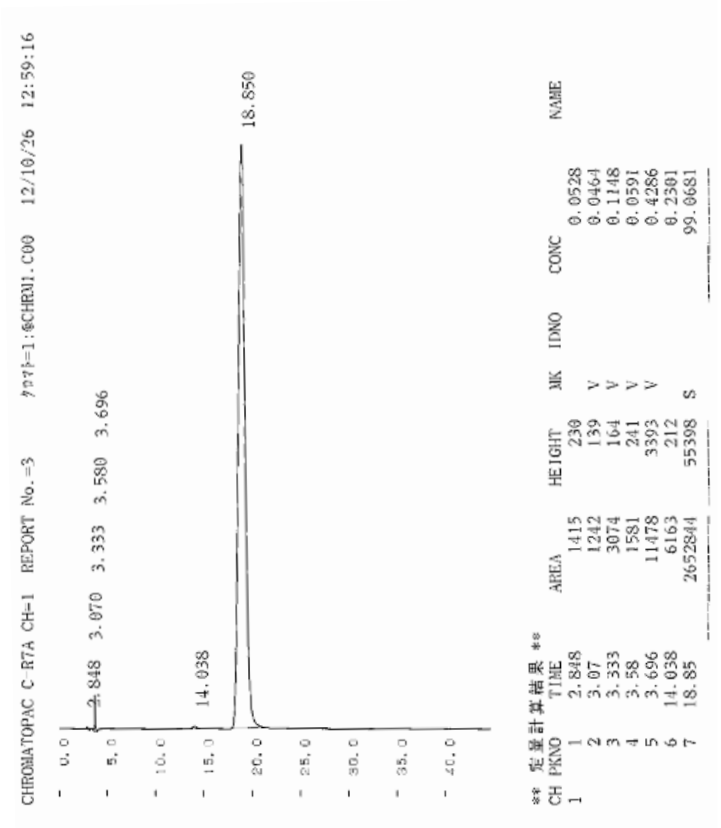
Chiral separation of compound **2**:



Chiral analysis for each fraction:



Peak 1 = 14.0 min
e.e. >99%
$[\alpha]_D$ -22.7° (c 0.55, $CHCl_3$)



Peak 2 = 18.9 min
e.e. >99%
$[\alpha]_D$ +20.9° (c 0.55, $CHCl_3$)

(2-Benzylpiperidin-1-yl)(4-(4-bromophenyl)-1*H*-1,2,3-triazol-1-yl)methanone (2). **2** was prepared and characterized as previously reported.[1]

(2-Benzylpiperidin-1-yl)(4-(4-bromophenyl)-2*H*-1,2,3-triazol-2-yl)methanone (3). **3** was prepared and characterized as previously reported.[1]

(2-Benzylpiperidin-1-yl)(4-(4-(trifluoromethoxy)phenyl)-1H-1,2,3-triazol-1-yl)methanone (5). General procedure A. A solution of 2-benzyl piperidine (23 mg, 0.13 mmol) in THF (1 mL) was treated with iPr_2NEt (68 µL, 0.39 mmol, 3.0 equiv) and triphosgene (20 mg, 0.067 mmol, 0.5 equiv), and the reaction mixture was stirred for 30 min at 4 ºC. The mixture was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The intermediate was dissolved in THF (20 mL), and iPr_2NEt (68 µL, 0.39 mmol, 3.0 equiv), DMAP (16 mg, 0.13 mmol, 1.0 equiv) and 4-(4-trifluoromethoxyphenyl)-1H-1,2,3-triazole[2] (**4,** 30 mg, 0.13 mmol, 1.0 equiv) were added to the solution. The mixture was stirred for 2 hr at 60 ºC and poured into saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. pTLC (ethyl acetate:hexane=1:4) afforded **5** (12 mg, 0.028 mmol, 21%) as a top spot.
Compound 1: ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.72-7.54 (m, 2H), 7.45-6.89 (m, 7H), 5.29 (br, 1H), 4.34 (brd, 1H, *J* = 13.5 Hz), 3.42-3.10 (m, 2H), 2.67 (br, 1H), 2.04-1.60 (m, 6H). ^{13}C NMR ($CDCl_3$, 150 MHz) δ 150.07, 145.98, 138.82, 130.02, 129.57, 129.33, 128.01, 127.44, 122.28, 121.53, 121.32 (q, *J* = 257.5 Hz, O*C*F_3), 58.29, 41.82, 37.51, 29.74, 26.17, 19.72. HRMS calculated for $C_{22}H_{22}F_3N_4O_2$ $[M+H]^+$ 431.1689, found 431.1691.

(2-Benzylpiperidin-1-yl)(4-bromo-1H-pyrazol-1-yl)methanone (6). A solution of 2-benzyl piperidine (50 mg, 0.29 mmol) in THF (2 mL) was treated with iPr_2NEt (0.15 mL, 0.86 mmol, 3.0 equiv) and triphosgene (42 mg, 0.14 mmol, 0.5 equiv), and the reaction mixture was stirred for 30 min at 4 ºC. The mixture was poured into H_2O and extracted ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The intermediate was dissolved in THF (3 mL), and iPr_2NEt (0.15 mL, 0.86 mmol, 3.0 equiv), DMAP (35 mg, 0.29 mmol, 1.0 equiv) and 4-bromo-1H-pyrazole (43 mg, 0.29 mmol, 1.0 equiv) were added to the solution. The mixture was stirred for 2 hr at 60 ºC and poured into saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Silica gel chromatography (ethyl acetate:hexane=1:5) afforded **6** (80 mg, 0.23 mmol, 81%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.56 (br, 1H), 7.52 (s, 1H), 7.30-7.05 (m, 5H), 4.86 (br, 1H), 4.28 (m, 1H), 3.23 (td, 1H, *J* = 13.3, 2.8 Hz), 3.14 (dd, 1H, *J* = 13.3, 8.0 Hz), 2.81 (dd, 1H, *J* = 13.3, 8.0 Hz), 1.85-1.55 (m, 6H). HRMS calculated for $C_{16}H_{19}BrN_3O$ $[M+H]^+$ 348.0706, found 348.0699.

(2-Benzylpiperidin-1-yl)(4-bromo-1H-imidazol-1-yl)methanone (7). A solution of 2-benzyl piperidine (50 mg, 0.29 mmol) in THF (2 mL) was treated with iPr_2NEt (0.15 mL, 0.86 mmol, 3.0 equiv) and triphosgene (42 mg, 0.14 mmol, 0.5 equiv), and the reaction mixture was stirred for 30 min at 4 ºC. The mixture was poured into H_2O and extracted ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The intermediate was dissolved in THF (3 mL), and iPr_2NEt (0.15 mL, 0.86 mmol, 3.0

equiv), DMAP (35 mg, 0.29 mmol, 1.0 equiv) and 4-bromo-1H-imidazole (43 mg, 0.29 mmol, 1.0 equiv) were added to the solution. The mixture was stirred for 2 hr at 60 ºC and poured into saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Silica gel chromatography (ethyl acetate:hexane=1:1) afforded **7** (75 mg, 0.22 mmol, 76%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.33-7.05 (m, 6H), 6.65 (s, 1H), 4.40 (br, 1H), 3.85 (m, 1H), 3.26 (m, 1H), 3.13 (dd, 1H, *J* = 13.6, 9.8 Hz), 2.77 (m, 1H), 1.87-1.48 (m, 6H). HRMS calculated for $C_{16}H_{19}BrN_3O$ $[M+H]^+$ 348.0706, found 348.0709.

(2-Benzylpiperidin-1-yl)(4-(4-(trifluoromethoxy)phenyl)-1H-pyrazol-1-yl)methanone (8). A solution of **6** (25 mg, 0.072 mmol) in dioxane (2 mL) and H_2O (0.1 mL) was treated with 4-trifluoromethoxyphenyl boronic acid (22 mg, 0.11 mmol, 1.5 equiv), K_2CO_3 (30 mg, 0.22 mmol, 3.0 equiv) and $PdCl_2$(dppf) (10.5 mg, 0.014 mmol, 0.2 equiv), and the reaction mixture was stirred for 2 hr at 80 ºC under N_2. The mixture was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by pTLC (ethyl acetate:hexane=1:5) to afford **8** (10 mg, 0.023 mmol, 32%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (br, 1H), 7.83 (s, 1H), 7.46 (d, 2H, *J* = 8.3 Hz), 7.30-7.06 (m, 7H), 4.95 (br, 1H), 4.35 (m, 1H), 3.33-3.10 (m, 2H), 2.85 (m, 1H), 1.88-1.60 (m, 6H). HRMS calculated for $C_{23}H_{23}F_3N_3O_2$ $[M+H]^+$ 430.1737, found 430.1735.

(2-Benzylpiperidin-1-yl)(4-(4-(trifluoromethoxy)phenyl)-1H-imidazol-1-yl)methanone (9). A solution of **7** (25 mg, 0.072 mmol) in dioxane (2 mL) and H_2O (0.1 mL) was treated with 4-trifluoromethoxyphenyl boronic acid (22 mg, 0.11 mmol, 1.5 equiv), K_2CO_3 (30 mg, 0.22 mmol, 3.0 equiv) and $PdCl_2$(dppf) (10.5 mg, 0.014 mmol, 0.2 equiv), and the reaction mixture was stirred for 2 hr at 80 ºC under N_2. The mixture was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by pTLC (ethyl acetate:hexane=1:2) to afford **8** (7 mg, 0.016 mmol, 23%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.71 (d, 2H, *J* = 7.6 Hz), 7.38 (s, 1H), 7.34-7.10 (m, 7H), 6.90 (s, 1H), 4.50 (br, 1H), 3.91 (m, 1H), 3.37-3.13 (m, 2H), 2.80 (dd, 1H, *J* = 13.7, 6.0 Hz), 1.88-1.36 (m, 6H). HRMS calculated for $C_{23}H_{23}F_3N_3O_2$ $[M+H]^+$ 430.1737, found 430.1742.

(2-Benzylpiperidin-1-yl)(4-(3,5-difluorophenyl)-1H-1,2,3-triazol-1-yl)methanone (10). A solution of 2-benzyl piperidine (30 mg, 0.17 mmol) in THF (2 mL) was treated with iPr_2NEt (66 µL, 0.51 mmol, 3.0 equiv) and triphosgene (50 mg, 0.17 mmol, 1 equiv), and the reaction mixture was stirred for 30 min at 4 ºC. The mixture was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The intermediate was dissolved in THF (5 ml), and iPr_2NEt (66 µl, 0.51 mmol, 3.0 equiv), DMAP (21 mg, 0.17 mmol, 1.0 equiv) and 4-(4-trifluoromethoxyphenyl)-1H-1,2,3-triazole[2] (31 mg, 0.17 mmol, 1.0 equiv) were added to the solution. The mixture was stirred for 2 hr at 60 ºC and poured into saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. pTLC (ethyl acetate:hexane=1:5) afforded **10** (3 mg, 0.008 mmol, 5%) as a top spot.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37-7.28 (m, 2H), 6.91 (s, 2H), 6.74 (tt, 2H, *J* = 8.8, 2.5 Hz), 4.72 (s, 2H), 4.27 (d, 2H, *J* = 13.8 Hz), 3.29 (s, 2H), 3.15 (s, 2H), 2.58 (s, 1H), 1.53 (d, 4H, *J* = 9.0 Hz). HRMS calculated for $C_{21}H_{21}F_2N_4O$ $[M+H]^+$ 383.1678, found 383.1672.

(4-([1,1'-Biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(2-benzylpiperidin-1-yl)methanone (11). **11** was prepared and characterized as previously reported.[1]

(2-Benzylpiperidin-1-yl)(4-(3-bromophenyl)-1H-1,2,3-triazol-1-yl)methanone (12). A solution of 2-benzyl piperidine (50 mg, 0.29 mmol) in THF (2 mL) was treated with iPr_2NEt (0.15 mL, 0.87 mmol, 3.0 equiv) and triphosgene (42 mg, 0.14 mmol, 0.5 equiv), and the reaction mixture was stirred for 30 min at 4 ºC. The mixture was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The intermediate was dissolved in THF (3 mL), and iPr_2NEt (0.15 mL, 0.87 mmol, 3.0 equiv), DMAP (35 mg, 0.29 mmol, 1.0 equiv) and 4-(3-bromophenyl)-1H-1,2,3-triazole[3] (60 mg, 0.29 mmol, 1.0 equiv) were added to the solution. The mixture was stirred for 2 hr at 60 ºC and poured into saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography (ethyl acetate:hexane=1:6) afforded **12** (30 mg, 0.071 mmol, 25%) as a top spot.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.98 (s, 1H), 7.71 (m, 1H), 7.49 (m, 1H), 7.41-6.82 (m, 6H), 4.80 (br, 1H), 4.32 (d, 1H, *J* = 13.5 Hz), 3.40-2.50 (m, 3H), 2.01-1.55 (m, 6H). HRMS calculated for $C_{21}H_{22}BrN_4O$ $[M+H]^+$ 425.0971, found 425.0979.

(2-Benzylpiperidin-1-yl)(4-(2-bromophenyl)-1H-1,2,3-triazol-1-yl)methanone (13). A solution of 2-benzyl piperidine (50 mg, 0.29 mmol) in THF (2 mL) was treated with iPr_2NEt (0.15 mL, 0.87 mmol, 3.0 equiv) and triphosgene (42 mg, 0.14 mmol, 0.5 equiv), and the reaction mixture was stirred for 30 min at 4 ºC. The mixture was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The intermediate was dissolved in THF (3 mL), and iPr_2NEt (0.15 mL, 0.87 mmol, 3.0 equiv), DMAP (35 mg, 0.29 mmol, 1.0 equiv) and 4-(2-bromophenyl)-1H-1,2,3-triazole[3] (60 mg, 0.29 mmol, 1.0 equiv) were added to the solution. The mixture was stirred for 2 hr at 60 ºC and poured into saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography (ethyl acetate:hexane=1:6) afforded **13** (35 mg, 0.083 mmol, 29%) as a top spot.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.09 (d, 1H, *J* = 8.2 Hz), 7.70 (d, 1H, *J* = 8.2 Hz), 7.43 (t, 1H, *J* = 8.2 Hz), 7.32-6.70 (m, 6H), 4.87 (br, 1H), 4.32 (d, 1H, *J* = 13.5 Hz), 3.45-2.52 (m, 3H), 2.00-1.55 (m, 6H). HRMS calculated for $C_{21}H_{22}BrN_4O$ $[M+H]^+$ 425.0971, found 425.0976.

(4-([1,1'-Biphenyl]-3-yl)-1H-1,2,3-triazol-1-yl)(2-benzylpiperidin-1-yl)methanone (14). A solution of **12** (12 mg, 0.028 mmol) in dioxane (1 mL) and H_2O (0.1 mL) was treated with phenylboronic acid (5.2 mg, 0.042 mmol, 1.5 equiv), K_2CO_3 (12 mg, 0.084 mmol, 3.0 equiv) and $PdCl_2$(dppf) (4.0 mg, 0.0056 mmol, 0.2 equiv), and the reaction mixture was stirred for 2 hr at 80 ºC under N_2. The mixture was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced

pressure. The residue was purified by pTLC (ethyl acetate:hexane:CH_2Cl_2=1:6:1) to afford **14** (4 mg, 0.009 mmol, 33%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.05 (s, 1H), 7.80-6.90 (m, 13H), 4.84 (br, 1H), 4.36 (brd, 1H, *J* = 12.9 Hz), 3.45-2.50 (m, 3H), 2.05-1.65 (m, 6H). HRMS calculated for $C_{27}H_{27}N_4O$ $[M+H]^+$ 423.2179, found 423.2175.

(4-([1,1'-Biphenyl]-2-yl)-1H-1,2,3-triazol-1-yl)(2-benzylpiperidin-1-yl)methanone (15). Prepared as described for **14** using **13** (12 mg, 0.028 mmol), phenylboronic acid (5.2 mg, 0.042 mmol, 1.5 equiv), K_2CO_3 (12 mg, 0.084 mmol, 3.0 equiv) and $PdCl_2$(dppf) (4 mg, 0.0056 mmol, 0.2 equiv) in dioxane (1 mL) and H_2O (0.1 mL) yielding **13** (3 mg, 0.007 mmol, 25%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.07 (d, 1H, *J* = 8.0 Hz), 7.50-6.50 (m, 13H), 4.73 (m, 1H), 4.18 (m, 1H), 3.30-2.62 (m, 3H), 1.85-1.35 (m, 6H). HRMS calculated for $C_{27}H_{27}N_4O$ $[M+H]^+$ 423.2179, found 423.2183.

(2-Benzylpiperidin-1-yl)(4-bromo-1H-1,2,3-triazol-1-yl)methanone (17). A solution of 2-benzyl piperidine (118 mg, 0.68 mmol) in THF (5 mL) was treated with iPr_2NEt (0.36 mL, 2.0 mmol, 3.0 equiv) and triphosgene (100 mg, 0.34 mmol, 0.5 equiv), and the reaction mixture was stirred for 30 min at 4 ºC. The mixture was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The intermediate was dissolved in THF (5 mL), and iPr_2NEt (0.36 mL, 2.04 mmol, 3.0 equiv), DMAP (83 mg, 0.68 mmol, 1.0 equiv) and 4-bromo-1H-1,2,3-triazole (**16**, 100 mg, 0.68 mmol, 1.0 equiv) were added to the solution. The mixture was stirred for 2 hr at 60 ºC and poured into saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography (ethyl acetate:hexane=1:5) afforded **17** (140 mg, 0.40 mmol, 59%) as a mixture of N1-carbamoyl (1,4 regioisomer) and N2-carbamoyl (2,4-regioisomer) triazole ureas. This mixture was taken forward to prepare **19**, which was purified as the 1,4-regioisomer.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.30-6.88 (m, 5H), 4.72 (br, 1H), 4.28 (br, 1H), 3.38-2.50 (m, 3H), 2.01-1.59 (m, 6H). HRMS calculated for $C_{15}H_{18}BrN_4O$ $[M+H]^+$ 349.0658, found 349.0662.

(2-Benzylpiperidin-1-yl)(4-(4-(piperidine-1-carbonyl)phenyl)-1H-1,2,3-triazol-1-yl)methanone (19). Prepared as described for **8** using **17** (33 mg, 0.095 mmol), (4-(piperidine-1-carbonyl)phenyl)boronic acid (33 mg, 0.14 mmol, 1.5 equiv), K_2CO_3 (39 mg, 0.29 mmol, 3.0 equiv) and $PdCl_2$(dppf) (14 mg, 0.019 mmol, 0.2 equiv) in dioxane (2 mL) and H_2O (0.1 mL) yielding **19** (5 mg, 0.011 mmol, 12%) as a top spot.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 2H), 7.48 (d, 2H, *J* = 8.5 Hz), 7.43-6.90 (m, 5H), 4.82 (br, 1H), 4.35 (brd, 1H, *J* = 13.7 Hz), 3.80-2.55 (m, 7H), 2.00-1.45 (m, 12H). HRMS calculated for $C_{27}H_{32}N_5O_2$ $[M+H]^+$ 458.255, found 458.2558.

(2-Benzylpiperidin-1-yl)(4-(4'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)methanone (20). Prepared as described for **8** using **2** (15 mg, 0.035 mmol), (4-(trifluoromethoxy)phenyl)boronic acid (11 mg, 0.053 mmol, 1.5 equiv), K_2CO_3 (14 mg, 0.105 mmol, 3.0 equiv) and $PdCl_2$(dppf) (5 mg, 0.007 mmol, 0.2 equiv) in dioxane (2 mL) and H_2O (0.1 mL) yielding **20** (5 mg, 0.010 mmol, 28%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (br, 2H), 7.70-7.60 (m, 4H), 7.50-6.80 (m, 7H), 4.85 (br, 1H), 4.32 (brd, 1H, *J* = 13.0 Hz), 3.40-2.56 (m, 3H), 2.10-1.58 (m, 6H). HRMS calculated for $C_{28}H_{26}F_3N_4O_2$ $[M+H]^+$ 507.2002, found 507.2006.

(4-(4-(Benzo[d][1,3]dioxol-5-yl)phenyl)-1H-1,2,3-triazol-1-yl)(2-benzylpiperidin-1-yl)methanone (21). Prepared as described for **8** using **2** (30 mg, 0.071 mmol), (3,4-methylenedioxy)phenylboronic acid (18 mg, 0.11 mmol, 1.5 equiv), K_2CO_3 (29 mg, 0.21 mmol, 3.0 equiv) and $Pd(Ph_3P)_4$ (16 mg, 0.014 mmol, 0.2 equiv) in dioxane (2 mL) and H_2O (0.2 mL) yielding **21** (15 mg, 0.032 mmol, 46%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (br, 2H), 7.60 (d, 2H, *J* = 8.1 Hz), 7.50-6.88 (m, 8H), 6.02 (s, 2H), 4.85 (br, 1H), 4.37 (brd, 1H, *J* = 13.9 Hz), 3.42-2.50 (m, 3H), 2.02-1.65 (m, 6H). HRMS calculated for $C_{28}H_{27}N_4O_3$ $[M+H]^+$ 467.2078, found 467.2080.

(2-Benzylpiperidin-1-yl)(4-(3'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)methanone (22). Prepared as described for **8** using **2** (30 mg, 0.071 mmol), (3-(hydroxymethyl)phenyl)boronic acid (17 mg, 0.11 mmol, 1.5 equiv), K_2CO_3 (29 mg, 0.21 mmol, 3.0 equiv) and $PdCl_2$(dppf) (10 mg, 0.014 mmol, 0.2 equiv) in dioxane (2 mL) and H_2O (0.1 mL) yielding **22** (14 mg, 0.031 mmol, 44%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.80 (m, 2H), 7.68 (d, 2H, *J* = 8.6 Hz), 7.65 (s, 1H), 7.57 (d, 1H, *J* = 7.5 Hz), 7.46 (t, 1H, *J* = 7.5 Hz), 7.37 (d, 1H, *J* = 7.5 Hz), 7.34-6.90 (m, 5H), 4.84 (m, 1H), 4.79 (s, 2H), 4.35 (brd, 1H, *J* = 13.9 Hz), 3.49-2.52 (m, 3H), 2.03-1.65 (m, 6H). HRMS calculated for $C_{28}H_{29}N_4O_2$ $[M+H]^+$ 453.2285, found 453.2290.

(2-Benzylpiperidin-1-yl)(4-(4'-(piperidine-1-carbonyl)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)methanone (23). Prepared as described for **8** using **2** (30 mg, 0.071 mmol), (4-(piperidine-1-carbonyl)phenyl)boronic acid (25 mg, 0.11 mmol, 1.5 equiv), K_2CO_3 (29 mg, 0.21 mmol, 3.0 equiv) and $PdCl_2$(dppf) (10 mg, 0.014 mmol, 0.2 equiv) in dioxane (2 mL) and H_2O (0.1 mL) yielding **23** (22 mg, 0.041 mmol, 58%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.88 (m, 2H), 7.70-7.63 (m, 4H), 7.48 (d, 2H, *J* = 8.4 Hz), 7.26-6.90 (m, 5H), 4.85 (br, 1H), 4.36 (brd, 1H, *J* = 13.7 Hz), 3.80-2.55 (m, 7H), 2.02-1.48 (m, 12H). HRMS calculated for $C_{33}H_{36}N_5O_2$ $[M+H]^+$ 534.2863, found 534.2863.

(2-Benzylpiperidin-1-yl)(4-(4'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)methanone (24). Prepared as described for **8** using **2** (10 mg, 0.024 mmol), (4-(trifluoromethyl)phenyl)boronic acid (7 mg, 0.035 mmol, 1.5 equiv), K_2CO_3 (10 mg, 0.072 mmol, 3.0 equiv) and $PdCl_2$(dppf) (3.4 mg, 0.005 mmol, 0.2 equiv) in dioxane (1 mL) and H_2O (0.1 mL) yielding **24** (3 mg, 0.006 mmol, 26%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90 (m, 2H), 7.77-7.66 (m, 6H), 7.30-6.92 (m, 5H), 4.85 (br, 1H), 4.36 (brd, 1H, *J* = 13.0 Hz), 3.42-2.57 (m, 3H), 2.07-1.61 (m, 6H). HRMS calculated for $C_{28}H_{26}F_3N_4O$ $[M+H]^+$ 491.2053, found 491.2048.

(2-Benzylpiperidin-1-yl)(4-(3'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)methanone (25). Prepared as described for **8** using **2** (30 mg, 0.071 mmol), (3-(trifluoromethyl)phenyl)boronic acid (20 mg, 0.11 mmol, 1.5 equiv), K_2CO_3 (29 mg, 0.21 mmol, 3.0 equiv) and $PdCl_2$(dppf) (10 mg, 0.014 mmol, 0.2 equiv) in dioxane (2 mL) and H_2O (0.1 mL) yielding **25** (16 mg, 0.033 mmol, 46%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.95-7.79 (m, 4H), 7.70 (d, 2H, *J* = 8.0 Hz), 7.65-7.55 (m, 2H), 7.50-6.92 (m, 5H), 4.85 (br, 1H), 4.37 (brd, 1H, *J* = 13.4 Hz), 3.42-2.49 (m, 3H), 2.05-1.65 (m, 6H). HRMS calculated for $C_{28}H_{26}F_3N_4O$ $[M+H]^+$ 491.2053, found 491.2055.

(2-Benzylpiperidin-1-yl)(4-(2'-(trifluoromethyl)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)methanone (26). Prepared as described for **8** using **2** (30 mg, 0.071 mmol), (2-(trifluoromethyl)phenyl)boronic acid (20 mg, 0.11 mmol, 1.5 equiv), K_2CO_3 (29 mg, 0.21 mmol, 3.0 equiv) and $PdCl_2$(dppf) (10 mg, 0.014 mmol, 0.2 equiv) in dioxane (2 mL) and H_2O (0.1 mL) yielding **25** (18 mg, 0.037 mmol, 52%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.90-7.74 (m, 3H), 7.63-7.35 (m, 5H), 7.33-6.93 (m, 5H), 4.85 (br, 1H), 4.36 (brd, 1H, *J* = 13.8 Hz), 3.41-2.50 (m, 3H), 2.05-1.63 (m, 6H). HRMS calculated for $C_{28}H_{26}F_3N_4O$ $[M+H]^+$ 491.2053, found 491.2051.

(2-Benzylpiperidin-1-yl)(4-(2'-methoxy-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)methanone (27).
27 was prepared and characterized as previously reported.[1]

(2-Benzylpiperidin-1-yl)(4-(2'-(trifluoromethoxy)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)methanone (28). Prepared as described for **8** using **2** (10 mg, 0.024 mmol), (2-(trifluoromethoxy)phenyl)boronic acid (6 mg, 0.029 mmol, 1.2 equiv), K_2CO_3 (10 mg, 0.072 mmol, 3.0 equiv) and $Pd(Ph_3P)_4$ (6 mg, 0.005 mmol, 0.2 equiv) in dioxane (1 mL) and H_2O (0.1 mL) yielding **28** (3 mg, 0.006 mmol, 25%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.86 (br, 2H), 7.55 (d, 2H, *J* = 8.4 Hz), 7.50-7.35 (m, 4H), 7.30-6.92 (m, 5H), 4.85 (br, 1H), 4.36 (brd, 1H, *J* = 13.3 Hz), 3.42-2.58 (m, 3H), 2.06-1.63 (m, 6H). HRMS calculated for $C_{28}H_{26}F_3N_4O_2$ $[M+H]^+$ 507.2002, found 507.2006.

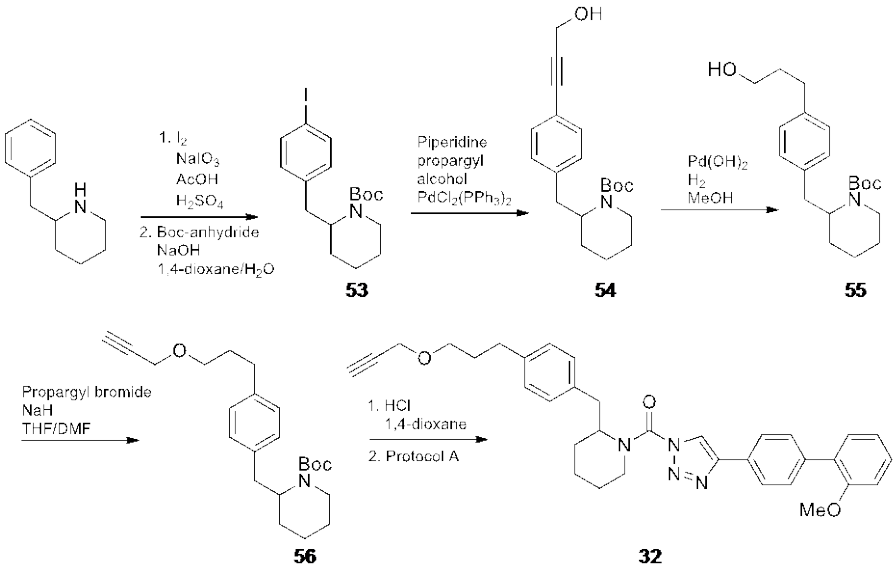
(2-Benzylpiperidin-1-yl)(4-(2'-(hydroxymethyl)-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)methanone (29). Prepared as described for **8** using **2** (10 mg, 0.024 mmol), (2-(hydroxymethyl)phenyl)boronic acid (6 mg, 0.039 mmol, 1.6 equiv), K_2CO_3 (10 mg, 0.072 mmol, 3.0 equiv) and $Pd(Ph_3P)_4$ (6 mg, 0.005 mmol, 0.2 equiv) in dioxane (1 mL) and H_2O (0.1 mL) yielding **29** (4 mg, 0.009 mmol, 38%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.84 (m, 2H), 7.61-6.90 (m, 11H), 4.85 (m, 1H), 4.66 (s, 2H), 4.35 (brd, 1H, *J* = 13.2 Hz), 3.45-2.60 (m, 3H), 2.00-1.60 (m, 6H). HRMS calculated for $C_{28}H_{29}N_4O_2$ $[M+H]^+$ 453.2285, found 453.2283.

(2-Benzylpiperidin-1-yl)(4-(2'-chloro-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)methanone (30). Prepared as described for **8** using **2** (10 mg, 0.024 mmol), (2-chlorophenyl)boronic acid (6 mg, 0.038 mmol, 1.6 equiv), K_2CO_3 (10 mg, 0.072 mmol, 3.0 equiv) and $Pd(Ph_3P)_4$ (6 mg, 0.005 mmol, 0.2 equiv) in dioxane (1 mL) and H_2O (0.1 mL) yielding **30** (3 mg, 0.007 mmol, 28%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 7.85 (m, 2H), 7.56-6.90 (m, 11H), 4.85 (m, 1H), 4.35 (brd, 1H, *J* = 13.2 Hz), 3.42-2.58 (m, 3H), 2.05-1.60 (m, 6H). HRMS calculated for $C_{27}H_{26}ClN_4O$ $[M+H]^+$ 457.179, found 457.1788.

(2-Benzylpiperidin-1-yl)(4-(2'-methyl-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)methanone (31). Prepared as described for **8** using **2** (10 mg, 0.024 mmol), (2-methylphenyl)boronic acid (6

mg, 0.039 mmol, 1.6 equiv), K_2CO_3 (10 mg, 0.072 mmol, 3.0 equiv) and $Pd(Ph_3P)_4$ (6 mg, 0.005 mmol, 0.2 equiv) in dioxane (1 mL) and H_2O (0.1 mL) yielding **31** (3 mg, 0.007 mmol, 28%). ^1H NMR ($CDCl_3$, 300 MHz) δ 7.83 (m, 2H), 7.43-6.90 (m, 11H), 4.86 (m, 1H), 4.35 (brd, 1H, *J* = 14.4 Hz), 3.40-2.55 (m, 3H), 2.31 (s, 3H), 2.05-1.60 (m, 6H). HRMS calculated for $C_{28}H_{29}N_4O$ $[M+H]^+$ 437.2336, found 437.2335.

(4-(2'-Methoxy-[1,1'-biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)(2-(4-(3-(prop-2-yn-1-yloxy)propyl)benzyl)piperidin-1-yl)methanone (32).



A solution of 2-benzylpiperidine (480 mg, 2.74 mmol) in acetic acid (5 mL) and sulfuric acid (0.4 mL) was treated with iodine (348 mg, 1.37 mmol) and sodium iodate (108 mg, 0.55 mmol) and the mixture was stirred at 70 °C for 20 hr. Sodium periodate (586 mg, 2.74 mmol) was then added in two portions and the reaction was stirred for 2 hr. The reaction was then diluted with ethyl acetate and neutralized with 2N NaOH. The organics were washed with a saturated aqueous solution of $NaHCO_3$, dried over Na_2SO_4, and the solvent was evaporated to yield 664 mg of crude 2-(4-iodobenzyl)piperidine.

The crude products from the previous step (664 mg) were dissolved in H_2O (2.75 mL) and 1,4-dioxane (2.75 mL) and treated with 1 N NaOH (2.5 mL). The reaction was brought to 0 °C and treated with Boc-anhydride (529 mg, 2.4 mmol) and was allowed to stir for 3 hr at 25 °C. The reaction was then diluted with 1 N HCl and extracted with ethyl acetate. The organics were dried over Na_2SO_4, and the solvent was evaporated. The product was purified by pTLC (6:1 Hexanes/Ethyl acetate) to yield **53** (620 mg, 1.54 mmol, 56% over two steps).
^1H NMR ($CDCl_3$, 400 MHz) δ 7.63 (d, *J* = 8.2 Hz, 2H), 6.91 (d, *J* = 8.2 Hz, 2H), 4.37 (br s, 1H), 4.05 (br s, 1H), 2.84 (m, 2H), 2.69 (dd, *J* = 13.2, 8.0 Hz, 1H), 1.70 – 1.37 (m, 6H), 1.32 (s, 9H). MS calculated for $C_{17}H_{24}INO_2$ $[M+H]^+$ 402.1, found 402.3.

Compound **53** (159 mg, 0.4 mmol) in a 2 dram vial was treated with piperidine (0.3 mL) and propargyl alcohol (22 mg, 0.4 mmol). $PdCl_2(PPh_3)_2$ (15 mg) was then added and the vial was capped and the reaction stirred at 90 °C for 30 min. The reaction was diluted with ethyl acetate

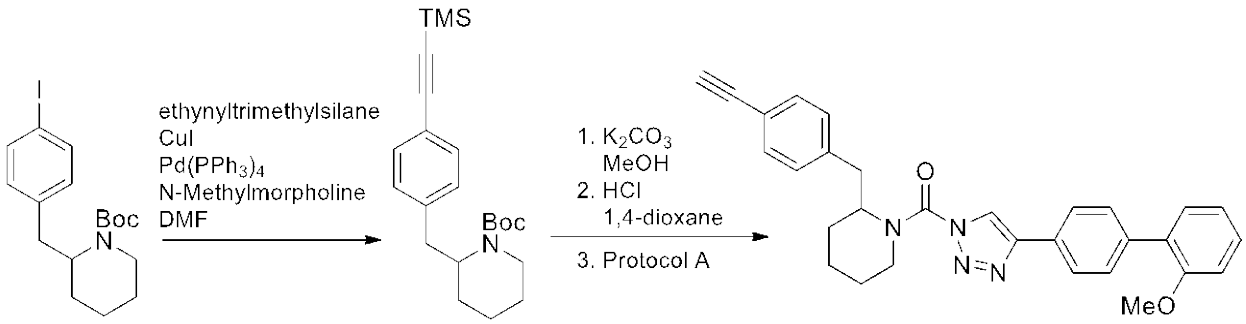
and washed with 1 N aqueous HCl. The organics were dried over Na_2SO_4, and the solvent was evaporated. The product was purified by silica column (3:1 Hexanes/Ethyl acetate) to yield **54** (125 mg, 0.38 mmol, 96%).
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.33 (d, *J* = 7.9 Hz, 2H), 7.11 (d, *J* = 7.9 Hz, 2H), 4.47 (s, 2H), 4.39 (s, 1H), 4.05 (br s, 1H), 2.88 (dd, *J* = 13.4, 9.5 Hz, 2H), 2.72 (dd, *J* = 13.2, 8.0 Hz, 1H), 2.27 (br s, 1H), 1.71 – 1.37 (m, 6H), 1.32 (s, 9H). MS calculated for $C_{20}H_{27}NO_3$ $[M+H]^+$ 330.2, found 330.3.

Compound **54** (125 mg, 0.38 mmols) was dissolved in methanol (5 mL) and treated with $Pd(OH)_2$ on carbon (30 mg), followed by treatment with H_2 gas (balloon). The reaction was stirred for 10 hr and then filtered over Celite and the solvent removed. The product was purified by pTLC (3:1 Hexanes/Ethyl acetate) to yield **55** (71 mg, 0.21 mmol, 56% yield).
^{1}H NMR ($CDCl_3$, 500 MHz) δ 7.10 (s, 4H), 4.39 (br s, 1H), 4.05 (br s, 1H), 3.66 (t, *J* = 6.4 Hz, 2H), 3.47 (s, 2H), 2.88 (ddd, *J* = 26.2, 13.4, 8.9 Hz, 2H), 2.73 (dd, *J* = 13.4, 8.1 Hz, 1H), 2.66 (t, *J* = 7.8 Hz, 2H), 1.92 – 1.79 (m, 2H), 1.81 – 1.38 (m, 6H), 1.33 (s, 9H). MS calculated for $C_{20}H_{31}NO_3$ $[M+H]^+$ 334.2, found 334.3.

Compound **55** (71 mg, 0.21 mmol) was dissolved in anhydrous THF (0.8 mL) and DMF (0.2 mL) and was brought to 0 °C. The reaction was then treated with NaH (12.8 mg of 60% dispersion in mineral oil, 0.32 mmol). The reaction was stirred for 30 min at 0 °C and was treated with propargyl bromide (63 mg of 80% solution in toluene, 0.43 mmol). The reaction was stirred for 3 hr, diluted with ethyl acetate and washed with H_2O. The organics were dried over Na_2SO_4, and the solvent was evaporated. The product was purified by pTLC (6:1 hexanes/ethyl acetate) to yield **56** (48 mg, 0.13 mmol, 60% yield).
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.09 (s, 4H), 4.39 (br s, 1H), 4.14 (d, *J* = 2.3 Hz, 2H), 4.04 (br s, 1H), 3.53 (t, *J* = 6.4 Hz, 2H), 2.98 – 2.80 (m, 2H), 2.79 – 2.62 (m, 3H), 2.42 (t, *J* = 2.4 Hz, 1H), 1.94 – 1.84 (m, 2H), 1.71 – 1.37 (m, 6H), 1.33 (s, 9H). MS calculated for $C_{23}H_{33}NO_3$ $[M+H]^+$ 372.2, found 372.2.

Compound **56** was then treated with 4 N HCl in 1,4-dioxane (3 mL) and stirred for 3 hr at 25 °C. The solvent was removed by a stream of N_2 to yield 40 mg 2-(4-(3-(prop-2-yn-1-yloxy)propyl)benzyl)piperidine hydrochloride, which was then reacted with 4-(2'-methoxy-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole (33 mg, 0.13 mmols) according to general procedure A to yield **32** (22 mg, 0.03 mmol, 30% yield). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.89 – 7.77 (m, 2H), 7.63 (d, 2H, *J* = 8.3 Hz), 7.58 – 7.40 (m, 1H), 7.35 (m, 2H), 7.20 – 6.78 (m, 6H), 4.86 (br s, 1H), 4.36 (br s, 1H), 4.12 (d, 2H, *J* = 2.4 Hz), 3.84 (s, 3H), 3.49 (t, 2H, *J* = 6.3 Hz), 3.35 (t, 1H, *J* = 12.5 Hz), 3.18 (s, 1H), 2.65 (t, 2H, *J* = 7.7 Hz), 2.39 (t, 1H, *J* = 2.3 Hz), 2.03 – 1.63 (m, 8H). HRMS calculated for $C_{34}H_{37}N_4O_3$ $[M+H]^+$ 549.2864, found 549.2863.

(2-(4-Ethynylbenzyl)piperidin-1-yl)(4-(2'-methoxy-[1,1'-biphenyl]-4-yl)-1*H*-1,2,3-triazol-1-yl)methanone (33).



57 **33**

Compound **53** (154 mg, 0.38 mmol) was dissolved in DMF (1 mL) and N-methylmorpholine (0.2 mL). The reaction was then treated with ethynyltrimethylsilane (150 mg, 1.5 mmol), $Pd(PPh_3)_4$ (44 mg, 0.04 mmol), and CuI (0.03 mmol, 6 mg) and stirred at 80 °C for 3 hr. The reaction was cooled to room temperature, diluted with ethyl acetate, and washed with 1 N aqueous HCl and saturated aqueous $NaHCO_3$. The organics were dried over Na_2SO_4, and the solvent was evaporated. The product was purified by pTLC (3:1 hexanes/ethyl acetate) to yield **57** (128 mg, 0.34 mmol, 90% yield).
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.37 (d, *J* = 8.1 Hz, 2H), 7.11 (d, *J* = 7.8 Hz, 2H), 4.39 (br s, 1H), 4.04 (br s, 1H), 2.95 – 2.65 (m, 3H), 1.73 – 1.40 (m, 6H), 1.36 (s, 9H), 0.24 (d, *J* = 2.0 Hz, 9H). MS calculated for $C_{22}H_{33}NO_2Si$ $[M+H]^+$ 372.2, found 372.3.

Compound **57** (55 mg, 0.15 mmol) was dissolved in methanol (3 mL), treated with K_2CO_3 (80 mg, 0.56 mmol), and stirred at room temperature for 3 hr. The reaction was then diluted with ethyl acetate and washed with H_2O. The organics were dried over Na_2SO_4, and the solvent was evaporated. The crude product was then treated with 4 N HCl in 1,4-dioxane (3 mL) and stirred for 2 hr. The solvent was evaporated under a stream of N_2 to give crude 2-(4-ethynylbenzyl)piperidine hydrochloride, which was then reacted with 4-(2'-methoxy-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazole (33 mg, 0.13 mmols) according to general procedure A to yield **33** (17 mg, 0.035 mmol, 27% yield).
^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.06 (d, 1H, *J* = 3.9 Hz), 7.89 (dd, 2H, *J* = 9.7, 5.7 Hz), 7.64 (t, 3H, *J* = 7.8 Hz), 7.57 (d, 1H, *J* = 7.3 Hz), 7.44 – 7.28 (m, 3H), 7.10 – 6.84 (m, 3H), 4.88 (br s, 1H), 4.38 (br s, 1H), 3.84 (s, 3H), 3.29 (d, 2H, *J* = 31.9 Hz), 3.08 (s, 1H), 2.01 – 1.48 (m, 6H), 1.36 (d, 1H, *J* = 6.2 Hz). HRMS calculated for $C_{30}H_{29}N_4O_2$ $[M+H]^+$ 477.2285, found 477.2283.

N-Isobutyl-N-phenethyl-4-(4-(trifluoromethoxy)phenyl)-1H-1,2,3-triazole-1-carboxamide (35).
A solution of phenylethanamine (100 mg, 0.83 mmol) in THF (8.3 ml) was treated with isobutyraldehyde (54 mg, 0.74 mmol, 0.9 equiv) and $NaBH(OAc)_3$ (250 mg, 1.16 mmol, 1.4 equiv), and the reaction mixture was stirred at room temperature for 2 hr or until the reaction was complete. The mixture was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (DCM/MeOH = 9:1) to afford 2-methyl-*N*-phenethylpropan-1-amine,[4] which (10 mg, 0.056 mmol) was reacted with **4** (13 mg, 0.056 mmol, 1 equiv) to yield compound **35** (2 mg, 0.005 mmol, 9%) following general procedure A.

^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.85 (s, 4H), 7.31 (d, 3H, *J* = 8.2), 7.09 (s, 2H), 4.06 (s, 2H), 3.62 (s, 2H), 3.44 (d, 2H, *J* = 7.8), 3.04 (s, 1H), 2.92 (s, 2H), 1.42 (s, 2H), 1.03 (d, 6H, *J* = 6.6 Hz). HRMS calculated for $C_{22}H_{24}F_3N_4O_2$ $[M+H]^+$ 433.1846, found 433.1845

N-(Furan-2-ylmethyl)-N-phenethyl-4-(4-(trifluoromethoxy)phenyl)-1H-1,2,3-triazole-1-carboxamide (36).
A solution of phenylethanamine (100 mg, 0.83 mmol) in THF (8.3 mL) was treated with furan-2-carbaldehyde (71 mg, 0.74 mmol. 0.9 equiv) and $NaBH(OAc)_3$ (250 mg, 1.16 mmol, 1.4 equiv), and the reaction mixture was stirred at room temperature for 2 hr or until the reaction was complete. The mixture was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The residue was purified by silica gel chromatography (DCM/MeOH = 9:1) to afford *N*-(furan-2-ylmethyl)-2-phenylethanamine (10 mg, 0.049 mmol, 6%).
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.39 (s, 1H), 7.27-7.24 (m, 2H), 7.20-7.15 (m, 3H), 6.33-6.32 (m, 1H), 6.22-6.21 (m, 1H), 3.73 (s, 2H), 2.85-2.81 (m, 2H), 2.72-2.68 (m, 2H).

N-(furan-2-ylmethyl)-2-phenylethanamine (10 mg, 0.049 mmol) was then reacted with **4** (11 mg, 0.049 mmol, 1 equiv) to yield compound **36** (4 mg, 0.009 mmol, 18%) following general procedure A.
^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.91 (d, 2H, *J* = 11.2), 7.32 (d, 3H, *J* = 8.3 Hz), 7.14 (s, 7H), 6.40 (m, 2H), 4.05 (s, 1H), 3.81 (s, 1H), 2.98 (t, 2H, *J* = 7.5 Hz), 2.17 (s, 1H). HRMS calculated for $C_{23}H_{20}F_3N_4O_3$ $[M+H]^+$ 457.1482, found 457.1480.

***Tert*-butyl (5-(*N*-phenethyl-4-(4-(trifluoromethoxy)phenyl)-1*H*-1,2,3-triazole-1-carboxamido)pentyl)carbamate (37).**
37 was prepared and characterized as previously reported.[1]

5,5-Difluoro-7,9-dimethyl-3-(3-oxo-3-((5-(*N*-phenethyl-4-(4-(trifluoromethoxy)phenyl)-1*H*-1,2,3-triazole-1-carboxamido)pentyl)amino)propyl)-5*H*-dipyrrolo[1,2-*c*:2',1'-*f*][1,3,2]diazaborinin-4-ium-5-uide (38).
38 was prepared and characterized as previously reported.[1]

(4-(4-Bromophenyl)-1H-1,2,3-triazol-1-yl)(2-phenylpiperidin-1-yl)methanone (42).
42 was prepared and characterized as previously reported.[1]

(3-Benzylpiperidin-1-yl)(4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)methanone (43). A solution of 3-benzyl piperidine hydrochloride (34 mg, 0.16 mmol) in THF (2 mL) was treated with iPr_2NEt (0.084 mL, 0.48 mmol, 3.0 equiv) and triphosgene (24 mg, 0.079 mmol, 0.5 equiv), and the reaction mixture was stirred for 30 min at 4 ºC. The mixture was poured into H_2O and extracted with ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The intermediate was dissolved in THF (3 mL), and iPr_2NEt (0.084 mL, 0.48 mmol, 3.0 equiv), DMAP (20 mg, 0.16 mmol, 1.0 equiv) and 4-(4-bromophenyl)-1H-1,2,3-triazole[5] (36 mg, 0.16 mmol, 1.0 equiv) were added to the solution. The mixture was stirred for 2 hr at 60 ºC and poured into saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with H_2O and brine, dried over Na_2SO_4 and

concentrated under reduced pressure. Recrystallization from ethyl acetate and hexane (1:5) afforded **43** (22 mg, 0.052 mmol, 32%) as a top spot.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 1H), 7.74 (d, 2H, *J* = 8.5 Hz), 7.59 (d, 2H, *J* = 8.5 Hz), 7.31-7.05 (m, 5H), 4.36 (m, 2H), 3.30-2.38 (m, 4H), 2.10-1.60 (m, 4H), 1.29 (m, 1H). HRMS calculated for $C_{21}H_{22}BrN_4O$ $[M+H]^+$ 425.0971, found 425.0967.

(4-Benzylpiperidin-1-yl)(4-(4-bromophenyl)-1H-1,2,3-triazol-1-yl)methanone (44). A solution of 4-benzyl piperidine (28 mg, 0.16 mmol) in THF (2 mL) was treated with iPr_2NEt (0.084 mL, 0.48 mmol, 3.0 equiv) and triphosgene (24 mg, 0.079 mmol, 0.5 equiv), and the reaction mixture was stirred for 30 min at 4 ºC. The mixture was poured into H_2O and extracted ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The intermediate was dissolved in THF (3 mL), and iPr_2NEt (0.084 mL, 0.48 mmol, 3.0 equiv), DMAP (20 mg, 0.16 mmol, 1.0 equiv) and 4-(4-bromophenyl)-1H-1,2,3-triazole[5] (36 mg, 0.16 mmol, 1.0 equiv) were added to the solution. The mixture was stirred for 2 hr at 60 ºC and poured into saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Recrystallization from ethyl acetate and hexane (1:5) afforded **44** (22 mg, 0.052 mmol, 32%) as a top spot.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.32 (s, 1H), 7.75 (d, 2H, *J* = 8.5 Hz), 7.58 (d, 2H, *J* = 8.5 Hz), 7.33-7.13 (m, 5H), 4.51 (br, 2H), 3.21-2.93 (m, 2H), 2.62 (d, 2H, *J* = 7.0 Hz), 1.94-1.72 (m, 3H), 1.46 (m, 2H). HRMS calculated for $C_{21}H_{22}BrN_4O$ $[M+H]^+$ 425.0971, found 425.0980.

(4-(4-Bromophenyl)-1H-1,2,3-triazol-1-yl)(2-phenethylpiperidin-1-yl)methanone (45). A solution of 2-phenethyl piperidine (36 mg, 0.16 mmol) in THF (2 mL) was treated with iPr_2NEt (0.084 ml, 0.48 mmol, 3.0 equiv) and triphosgene (24 mg, 0.079 mmol, 0.5 equiv), and the reaction mixture was stirred for 30 min at 4 ºC. The mixture was poured into H_2O and extracted ethyl acetate. The organic layer was washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. The intermediate was dissolved in THF (3 mL), and iPr_2NEt (0.084 mL, 0.48 mmol, 3.0 equiv), DMAP (20 mg, 0.16 mmol, 1.0 equiv) and 4-(4-bromophenyl)-1H-1,2,3-triazole[5] (36 mg, 0.16 mmol, 1.0 equiv) were added to the solution. The mixture was stirred for 2 hr at 60 ºC and poured into saturated aqueous NH_4Cl solution. The mixture was extracted with ethyl acetate, washed with H_2O and brine, dried over Na_2SO_4 and concentrated under reduced pressure. Chromatography (ethyl acetate:hexane=1:5) afforded **45** (25 mg, 0.057 mmol, 36%) as a top spot.
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.27 (br, 1H), 7.74 (d, 2H, *J* = 8.5 Hz), 7.59 (d, 2H, *J* = 8.5 Hz), 7.30-7.10 (m, 5H), 4.73 (m, 1H), 4.31 (brd, 1H, *J* = 14.0 Hz), 3.24 (br, 1H), 2.66 (br, 2H), 2.25 (m, 1H), 2.00-1.65 (m, 7H). HRMS calculated for $C_{22}H_{24}BrN_4O$ $[M+H]^+$ 439.1128, found 439.1134.

(4-(2'-Methoxy-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)(2-phenylpiperidin-1-yl)methanone (46). Prepared as described for **8** using **42** (10 mg, 0.024 mmol), (2-methoxyphenyl)boronic acid (6 mg, 0.039 mmol, 1.6 equiv), K_2CO_3 (10 mg, 0.072 mmol, 3.0 equiv) and $PdCl_2$(dppf) (4 mg, 0.005 mmol, 0.2 equiv) in dioxane (1 mL) and H_2O (0.1 mL) yielding **46** (4 mg, 0.009 mmol, 38%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.42 (s, 1H), 7.92 (d, 2H, *J* = 8.3 Hz), 7.64 (d, 2H, *J* = 8.3 Hz), 7.43-7.26 (m, 7H), 7.07-7.00 (m, 2H), 5.94 (br, 1H), 4.39 (brd, 1H, *J* = 13.6 Hz), 3.84 (s, 3H),

3.19 (m, 1H), 2.53 (brd, 1H, *J* = 14.0 Hz), 2.16 (m, 1H), 1.92-1.64 (m, 4H). HRMS calculated for $C_{27}H_{27}N_4O_2$ $[M+H]^+$ 439.2128, found 439.2122.

(3-Benzylpiperidin-1-yl)(4-(2'-methoxy-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)methanone (47). Prepared as described for **8** using **43** (10 mg, 0.023 mmol), (2-methoxyphenyl)boronic acid (6 mg, 0.039 mmol, 1.6 equiv), K_2CO_3 (10 mg, 0.072 mmol, 3.0 equiv) and $PdCl_2$(dppf) (4 mg, 0.005 mmol, 0.2 equiv) in dioxane (1 mL) and H_2O (0.1 mL) yielding **47** (3 mg, 0.007 mmol, 29%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.33 (s, 1H), 7.91 (d, 2H, *J* = 8.4 Hz), 7.64 (d, 2H, *J* = 8.4 Hz), 7.38-7.10 (m, 7H), 7.08-7.00 (m, 2H), 4.40 (br, 1H), 3.84 (s, 3H), 3.31-2.40 (m, 5H), 2.12-1.60 (m, 4H). HRMS calculated for $C_{28}H_{29}N_4O_2$ $[M+H]^+$ 453.2285, found 453.2282.

(4-(2'-Methoxy-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)(2-phenethylpiperidin-1-yl)methanone (48). Prepared as described for **8** using **45** (10 mg, 0.024 mmol), (2-methoxyphenyl)boronic acid (6 mg, 0.039 mmol, 1.6 equiv), K_2CO_3 (10 mg, 0.072 mmol, 3.0 equiv) and $PdCl_2$(dppf) (4 mg, 0.005 mmol, 0.2 equiv) in dioxane (1 mL) and H_2O (0.1 mL) yielding **47** (4 mg, 0.009 mmol, 38%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.30 (s, 1H), 7.91 (d, 2H, *J* = 8.4 Hz), 7.64 (d, 2H, *J* = 8.4 Hz), 7.38-7.32 (m, 2H), 7.30-7.12 (m, 5H), 7.07-7.00 (m, 2H), 4.76 (br, 1H), 3.84 (s, 3H), 4.34 (brd, 1H, *J* = 13.4 Hz), 3.30-2.49 (m, 3H), 2.28 (m, 1H), 2.00-1.65 (m, 7H). HRMS calculated for $C_{29}H_{31}N_4O_2$ $[M+H]^+$ 467.2441, found 467.2441.

(4-Benzylpiperidin-1-yl)(4-(2'-methoxy-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)methanone (49). Prepared as described for **8** using **44** (10 mg, 0.024 mmol), (2-methoxyphenyl)boronic acid (6 mg, 0.039 mmol, 1.6 equiv), K_2CO_3 (10 mg, 0.072 mmol, 3.0 equiv) and $PdCl_2$(dppf) (4 mg, 0.005 mmol, 0.2 equiv) in dioxane (1 mL) and H_2O (0.1 mL) yielding **48** (2 mg, 0.004 mmol, 19%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.34 (s, 1H), 7.91 (d, 2H, *J* = 8.1 Hz), 7.64 (d, 2H, *J* = 8.1 Hz), 7.38-7.14 (m, 7H), 7.08-7.00 (m, 2H), 4.53 (m, 2H), 3.84 (s, 3H), 3.20-2.90 (m, 2H), 2.63 (d, 2H, *J* = 7.0 Hz), 1.94-1.74 (m, 3H), 1.55-1.38 (m, 2H). HRMS calculated for $C_{28}H_{29}N_4O_2$ $[M+H]^+$ 453.2285, found 453.2279.

(4-([1,1'-Biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)(2-phenylpiperidin-1-yl)methanone (50). Prepared as described for **8** using **42** (10 mg, 0.024 mmol), phenylboronic acid (6 mg, 0.049 mmol, 2.0 equiv), K_2CO_3 (10 mg, 0.072 mmol, 3.0 equiv) and $PdCl_2$(dppf) (4 mg, 0.005 mmol, 0.2 equiv) in dioxane (1 mL) and H_2O (0.1 mL) yielding **50** (5 mg, 0.012 mmol, 50%).
^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.44 (s, 1H), 7.96 (d, 2H, *J* = 8.4 Hz), 7.70 (d, 2H, *J* = 8.4 Hz), 7.66-7.63 (m, 2H), 7.48-7.26 (m, 8H), 5.29 (br, 1H), 4.38 (brd, 1H, *J* = 13.7 Hz), 3.19 (m, 1H), 2,54 (brd, 1H, *J* = 14.3 Hz), 2.16 (m, 1H), 1.92-1.63 (m, 4H). HRMS calculated for $C_{26}H_{25}N_4O$ $[M+H]^+$ 409.2023, found 409.2020.

(4-([1,1'-Biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)(2-phenethylpiperidin-1-yl)methanone (51). Prepared as described for **8** using **45** (10 mg, 0.023 mmol), phenylboronic acid (6 mg, 0.049 mmol, 2.1 equiv), K_2CO_3 (10 mg, 0.072 mmol, 3.0 equiv) and $PdCl_2$(dppf) (4 mg, 0.005 mmol, 0.2 equiv) in dioxane (1 mL) and H_2O (0.1 mL) yielding **51** (3 mg, 0.007 mmol, 30%).

^{1}H NMR ($CDCl_3$, 300 MHz) δ 8.31 (s, 1H), 7.95 (d, 2H, *J* = 8.3 Hz), 7.70 (d, 2H, *J* = 8.3 Hz), 7.65 (d, 2H, *J* = 7.3 Hz), 4.76 (br, 1H), 4.34 (brd, 1H, *J* = 13.6 Hz), 3.30-2.40 (m, 3H), 2.27 (m, 1H), 2.00-1.60 (m, 7H). HRMS calculated for $C_{28}H_{29}N_4O$ $[M+H]^+$ 437.2336, found 437.2330.

(4-(4'-Methoxy-[1,1'-biphenyl]-4-yl)-1H-1,2,3-triazol-1-yl)(2-phenylpiperidin-1-yl)methanone (52).

52 was prepared and characterized as previously described.[1]

II. SUPPLEMENTARY FIGURES

Supplementary Figure 1. Mechanism of serine hydrolase inhibition by 1,2,3-triazole ureas.

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