SUPPORTING INFORMATION

for

Development of new scaffolds as reversible tissue transglutaminase inhibitors, with improved potency or resistance to glutathione addition

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GSH Incubation Assays

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**Synthetic Methods**

Reference compounds CP4d\(^1\), CP15a\(^2\), CP30a\(^2\) and \(m\)-CP30a\(^2\) \(^3\) were prepared according to published protocols. Coumarin derivative 10 was prepared according to a published protocol\(^4\) and used directly in the synthesis of 11\(^3\). NMR spectra were recorded on Bruker AVANCE 300 and 400 instruments, and coupling constants are given in units of Hertz (Hz). Melting points were recorded for powder compounds on a Stanford Research Systems EZ-Melt.
Scheme S1  Preparation of the Cβ-Alkylated analogues of CP4d

**A) Methylation**

\[
\begin{align*}
&\text{O}_2\text{N}_2\text{C}_\text{O}_2\text{H} \\
&\xrightarrow{(\text{C}_2\text{H}_5\text{O})_2\text{P(O)}\text{CH}_2\text{CO}_2\text{H}, \text{NaH}} \\
&\text{O}_2\text{N}_2\text{C}_\text{O}_2\text{Et} \\
&\xrightarrow{\text{K}_2\text{CO}_3} \\
&\text{MeOH, H}_2\text{O} \\
&\xrightarrow{4 \text{ h}, 65^\circ\text{C}}
\end{align*}
\]

\[
\begin{align*}
&\text{O}_2\text{N}_2\text{C}_\text{O}_2\text{H} \\
&\xrightarrow{(\text{C}_\text{O})_2\text{Cl}, \text{DMF (cat)}} \\
&\text{O}_2\text{N}_2\text{C}_\text{O}_2\text{Cl} \\
&\xrightarrow{\text{benzotriazole, DMAP, Et}_3\text{N}} \\
&\xrightarrow{\text{anhydrous THF}} \\
&\xrightarrow{16 \text{ h}, \text{RT}}
\end{align*}
\]

**B) Isopropylation**

\[
\begin{align*}
&\text{O}_2\text{N}_2\text{C}_\text{O}_2\text{H} \\
&\xrightarrow{(\text{C}_2\text{H}_5\text{O})_2\text{P(O)}\text{CH}_2\text{CO}_2\text{H}, \text{NaH}} \\
&\text{O}_2\text{N}_2\text{C}_\text{O}_2\text{Et} \\
&\xrightarrow{\text{K}_2\text{CO}_3} \\
&\text{MeOH, H}_2\text{O} \\
&\xrightarrow{4 \text{ h}, 65^\circ\text{C}}
\end{align*}
\]

\[
\begin{align*}
&\text{O}_2\text{N}_2\text{C}_\text{O}_2\text{H} \\
&\xrightarrow{(\text{C}_\text{O})_2\text{Cl}, \text{DMF (cat)}} \\
&\text{O}_2\text{N}_2\text{C}_\text{O}_2\text{Cl} \\
&\xrightarrow{\text{benzotriazole, DMAP, Et}_3\text{N}} \\
&\xrightarrow{\text{anhydrous THF}} \\
&\xrightarrow{16 \text{ h}, \text{RT}}
\end{align*}
\]

**General procedure A: Oxidation with TEMPO and PhI(OAc)$_2$**

To a solution of the alcohol (18 or 20, 1.0 equiv) in DCM (0.2 M) were added (diacetoxyiodo)benzene (1.8 equiv) and TEMPO (0.2 equiv), prior to stirring overnight at room temperature. The reaction solution was washed with saturated aqueous sodium bicarbonate and
brine, prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure.

**General procedure B: Oxidation with TEMPO and TCICA**

To a solution of the alcohol (23ab or 25ab, 1.0 equiv) dissolved in acetone (0.2 M) and cooled to 0°C were added trichloroisocyanuric acid (1.05 equiv) and TEMPO (0.01 equiv). The reaction mixture was allowed to gradually warm to room temperature while it was stirred, until TLC analysis showed complete reactant consumption (generally within three hours). The reaction mixture was then filtered over Celite and evaporated under reduced pressure prior to dissolving the crude product in DCM. The organic phase was washed with saturated aqueous sodium bicarbonate and 1 N HCl, prior to being dried over anhydrous magnesium sulfate, filtered and evaporated to dryness.

**General procedure C: Grignard addition with ethynylmagnesium bromide**

To a solution of the aldehyde (19 or 24ab, 1.0 equiv) in anhydrous THF (0.05 M) at -78°C was added ethynylmagnesium bromide (0.5 M in THF, 2.0 equiv), and the resulting reaction solution was allowed to gradually warm to room temperature as it was stirred overnight under nitrogen. The reaction was then quenched with slightly acidic water and the product was extracted with ethyl acetate. The combined organic extracts were washed with brine prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure.
General procedure D: Substituted benzyl azides

A solution of sodium azide in DMSO (0.5 M) was prepared by stirring for 24 hours at room temperature to ensure full dissolution of the salt. The substituted benzyl bromide (1.5 mmol) was dissolved in the solution of sodium azide (1.65 mmol, 3.3 mL) and the resulting reaction solution was stirred at room temperature overnight prior to being quenched with water (5 mL). The product was extracted with diethyl ether (3 x 5 mL), and the combined organic extracts were washed with water (2 x 10 mL) and brine (10 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. Substituted benzyl azides obtained in this manner were verified by \(^1\)H NMR and used without further purification.

General procedure E: Copper-catalysed azide-alkyne cycloaddition

To a solution of propargyl alcohol or ynone (26) (1.0 equiv) in DMF (0.1 M) were added the substituted benzyl azide (1.0 equiv, prepared according to general procedure D) and an aqueous solution (5% v/v) of copper sulfate (0.01 equiv) and sodium L-ascorbate (0.1 equiv). The resulting reaction mixture was stirred at 75°C overnight, prior to being quenched with water. The product was extracted with ethyl acetate, and the combined organic extracts were washed with 0.25 N HCl and brine prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure.

β-methyl-4-nitrocinnamic acid\(^5\) (2)

To a solution of sodium hydride (0.247 g, 10.3 mmol) in anhydrous THF (4 mL) under nitrogen was added triethyl phosphonoacetate (0.882 mL, 4.4 mmol) dropwise over 45 minutes, followed by a solution of 4-nitroacetophenone (4.96 g, 30.0 mmol) in anhydrous THF (5 mL),
prior to stirring the reaction mixture at reflux overnight. The product was extracted with ethyl acetate (30 mL), and the combined organic extracts were washed with brine (3 x 10 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was immediately dissolved in methanol (6 mL) and an aqueous solution of potassium carbonate (0.870 g, 6.3 mmol, 3 mL), and stirred at reflux for 4 hours prior to removal of the methanol by evaporation under reduced pressure. Following the addition of a 1 M solution of NaOH (10 mL), the aqueous phase was washed with ethyl acetate (3 x 8 mL). The aqueous layer was acidified, using 1 M HCl, to pH ~1, and the product was extracted with ethyl acetate (3 x 8 mL). The organic phase was then dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was dissolved in ethyl acetate and precipitated with hexanes, leading to 82 mg of an off-white solid in 9% yield. δH NMR (400 MHz, CDCl$_3$) 11.65 (1 H, br s, CO$_2$H), 8.27 (2 H, d, J=8.9, Ar), 7.65 (2 H, d, J=8.9, Ar), 6.23 (1 H, s, CH$_2$CO$_2$H), 2.63 (3 H, s, CH$_3$). δC NMR (100 MHz, CDCl$_3$) 171.4, 171.2, 155.4, 147.9, 147.8, 127.0, 123.5, 118.9, 20.4, 18.0. m.p. 168-170°C.

1-(1H-benzo[d][1,2,3]triazol-1-yl)-3-(4-nitrophenyl)but-2-en-1-one (3)

A solution of carboxylic acid 2 (150 mg, 0.72 mmol) and oxalyl chloride (0.13 mL, 1.44 mmol) in dichloromethane (10 mL) with a drop of DMF was stirred at reflux for 2 hours prior to being evaporated under reduced pressure. The crude acyl chloride was triturated in hexanes and isolated by filtration, without further purification. A solution of benzotriazole (95 mg, 0.80 mmol), DMAP (18 mg, 0.15 mmol) and triethylamine (0.2 mL, 1.43 mmol) in anhydrous THF (5 mL) was prepared and then added to a solution of the crude intermediate in anhydrous THF (10 mL). The reaction mixture was stirred overnight at room temperature prior
to extraction with ethyl acetate (100 mL). The organic phase was washed with 1 M HCl (3 x 20 mL), saturated aqueous sodium carbonate (3 x 20 mL) and brine (20 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was triturated in a combination of ethyl acetate and acetonitrile prior to being filtered to obtain 93 mg of a yellow solid in an overall yield of 42%. δH NMR (400 MHz, DMSO-d$_6$) 8.36 (6 H, m, Ar), 8.28 (2 H, d, J=8.5, Ar), 8.02 (4 H, d, J=8.5, Ar), 7.82 (2 H, t, J=7.7, benzotriazole), 7.76 (2 H, s, CH-CO), 7.65 (2 H, t, J=7.7, benzotriazole), 2.78 (6 H, s, CH$_3$). δC NMR (100 MHz, DMSO-d$_6$) 162.8, 157.6, 148.1, 147.4, 145.6, 130.9, 130.8, 128.2, 126.6, 124.0, 120.2, 117.8, 114.4, 18.7, 18.6. HRMS (ESI) [C$_{16}$H$_{12}$N$_4$O$_3$+Na]$^+$ calc. 331.08122 Da, obt. 331.08016 Da. m.p. 199-201°C.

(E/Z) ethyl β-isopropyl-4-nitrocinnamoate (4/5)

To a solution of sodium hydride (0.617 g, 25.7 mmol) in anhydrous THF (10 mL) was added triethyl phosphonoacetate (4.48 mL, 22.3 mmol) dropwise over 45 minutes, followed by solution of 2-methyl-1-(4-nitrophenyl)propanone (4.4 g, 22.8 mmol) in anhydrous THF (12 mL). The resulting reaction mixture was stirred at reflux overnight, and the product was extracted with ethyl acetate (75 mL). The organic phase was washed with brine (3 x 25 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was purified by flash column chromatography (95:5 hexanes:ethyl acetate) yielding pure 4, although 5 was still contaminated by the starting material ketone, all in a combined yield of 67%. Product 4 was obtained as 1.311 g of a brown solid, while 5 was obtained as 2.623 g of a yellow oil, and was then used directly in the next step.

4 δH NMR (400 MHz, CDCl$_3$) 8.23 (2 H, dt, J= 8.9, J=2.3, Ar), 7.39 (2 H, dt, J=8.9, J=2.3, Ar), 5.72 (1 H, s, CH-CO$_2$Et), 4.24 (2 H, q, J=7.1, O-CH$_2$), 4.17 (1 H, sept, J=7.0, CH-(CH$_3$)$_2$), 1.33
(3 H, t, J=7.1, O-CH$_2$-CH$_3$), 1.10 (6 H, d, J=7.0, CH-(CH$_3$)$_2$). $\delta$C NMR (100 MHz, CDCl$_3$) 166.0, 164.7, 147.8, 147.7, 129.1, 123.5, 120.2, 60.7, 29.8, 21.7, 14.6. HRMS (ESI) [C$_{14}$H$_{17}$NO$_4$+Na$^+$] calc. 286.10498 Da, obt. 286.10521 Da.

5 $\delta$H NMR (400 MHz, CDCl$_3$) 8.34 (1.2 H, d, J=8.9, ketone), 8.25 (2 H, dt, J=8.8, J=2.0, Ar), 8.12 (1.2 H, d, J=8.9, ketone), 7.28 (2 H, dt, J=8.7, J=2.0, Ar), 5.96 (1 H, s, CH-CO$_2$Et), 4.00 (2 H, q, J=6.9, O-CH$_2$-CH$_3$), 3.56 (0.6 H, sept, J=7.0, ketone), 2.67 (1 H, sept, J=7.1, CH-(CH$_3$)$_2$), 1.27 (3 H, t, J=6.9, O-CH$_2$-CH$_3$), 1.12 (9.6 H, m, ketone and CH-(CH$_3$)$_2$).

(E)-4-methyl-3-(4-nitrophenyl)pent-2-enoic acid (6)

To a solution of ester 4 (1.35 g, 5.1 mmol) in methanol (15 mL) was added dropwise an aqueous solution of potassium carbonate (1.16 g, 8.2 mmol, 4 mL). Following this addition, the reaction mixture was stirred at reflux for 4 hours prior to removal of the organic solvent by evaporation under reduced pressure. The aqueous phase was diluted with water (30 mL) and washed with dichloromethane (3 x 10 mL). After acidifying the aqueous solution to pH ~1 using 1 M HCl, the product was extracted with ethyl acetate (3 x 10 mL), and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure, resulting in 78 mg of a white solid in 65% yield. $\delta$H NMR (300 MHz, CDCl$_3$) 8.24 (2 H, d, J=8.7, Ar), 7.39 (2 H, d, J=8.7, Ar), 5.76 (1 H, s, CH-CO$_2$H), 4.18 (1 H, sept, J=7.2, CH-(CH$_3$)$_2$), 1.10 (6 H, d, J=7.2, CH-(CH$_3$)$_2$). $\delta$C NMR (75 MHz, CDCl$_3$) 171.0, 167.5, 147.5, 146.9, 128.6, 123.2, 119.0, 29.6, 21.2. m.p. 186-188°C.
(Z)-4-methyl-3-(4-nitrophenyl)pent-2-enoic acid (7)

To a solution of ester 5 (2.59 g, 9.8 mmol) in methanol (15 mL) was added dropwise an aqueous solution of potassium carbonate (2.22 g, 16.1 mmol, 7 mL). Following this addition, the reaction mixture was stirred at reflux for 4 hours prior to removal of the organic solvent by evaporation under reduced pressure. The aqueous phase was diluted with water (25 mL) and washed with ethyl acetate (3 x 10 mL). After acidifying the aqueous solution to pH ~1 using 1 M HCl, the product was extracted with ethyl acetate (3 x 10 mL), and the combined organic extracts were dried over anhydrous magnesium sulfate, filtered and evaporated to dryness under reduced pressure, resulting in 1.591 g of an orange solid in 69% yield. δH NMR (300 MHz, CDCl₃) 8.20 (2 H, d, J=8.7, Ar), 7.24 (2 H, d, J=8.7, Ar), 5.91 (1 H, s, CH-COOH), 2.66 (1 H, sept, J=6.8, CH-(CH₃)₂), 1.09 (6 H, d, J=6.8, CH-(CH₃)₂). δC NMR (75 MHz, CDCl₃) 171.3, 166.8, 148.1, 147.5, 129.0, 123.9, 116.9, 38.3, 21.7. m.p. 132-134°C.

(E)-1-(1H-benzo[d][1,2,3]triazol-1-yl)-4-methyl-3-(4-nitrophenyl)pent-2-en-1-one (8)

A solution of carboxylic acid 6 (300 mg, 1.28 mmol) and oxalyl chloride (0.22 mL, 2.60 mmol) in dichloromethane (15 mL) with a drop of DMF was stirred at reflux for 2 hours prior to being evaporated under reduced pressure. The crude product was triturated in hexanes and used without further purification. A solution of benzotriazole (167 mg, 1.40 mmol), DMAP (31 mg, 0.25 mmol) and triethylamine (0.36 mL, 2.55 mmol) in anhydrous THF (10 mL) was prepared, and it was then added to a solution of the crude product in anhydrous THF (20 mL). The reaction mixture was stirred overnight at room temperature prior to extraction with dichloromethane (150 mL). The organic phase was washed with 1 M HCl (3 x 20 mL), saturated aqueous sodium carbonate (3 x 20 mL) and brine (20 mL) prior to being dried over anhydrous
magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was triturated with a combination of ethyl acetate and acetonitrile, prior to being filtered to obtain 306 mg of a cream-coloured solid in overall yield of 71%. δH NMR (400 MHz, DMSO-d$_6$) 8.34 (3 H, m, Ar), 8.27 (1 H, d, J=8.3, benzotriazole), 7.81 (1 H, t, J=7.7, benzotriazole), 7.70 (2 H, d, J=8.8, (p-NO$_2$)Ar), 7.65 (1 H, t, J=8.3, benzotriazole), 7.23 (1 H, s, CH), 4.15 (1 H, sept, J=7.0, CH-(CH$_3$)$_2$), 1.18 (6 H, d, J=7.0, CH-(CH$_3$)$_2$). δC NMR (100 MHz, DMSO-d$_6$) 169.8, 163.5, 148.6, 147.7, 146.8, 132.1, 130.3, 127.9, 124.7, 121.4, 119.5, 115.6, 31.3, 22.3. HRMS (ESI) [C$_{18}$H$_{16}$N$_4$O$_3$+Na]$^+$ calc. 359.11146 Da, obt. 359.11006 Da. m.p. 131-133°C

(Z)-1-(1H-benzo[d][1,2,3]triazol-1-yl)-4-methyl-3-(4-nitrophenyl)pent-2-en-1-one (9)

Compound 9 was prepared according to the same procedure as described above for 8, on the same scale, to obtain 267 mg of a rust-coloured solid in 62% yield. δH NMR (400 MHz, DMSO-d$_6$) 8.26 (3 H, m, Ar), 8.06 (1 H, d, J=8.2, benzotriazole), 7.69 (1 H, t, J=7.5 Hz, benzotriazole), 7.59 (3 H, m, Ar), 7.46 (1 H, s, CH), 2.95 (1 H, sept, J=6.8, CH-(CH$_3$)$_2$), 1.16 (6 H, d, J=6.8, CH-(CH$_3$)$_2$). δC NMR (100 MHz, DMSO-d$_6$) 169.0, 163.1, 147.8, 146.4, 142.9, 131.5, 129.6, 127.4, 124.1, 120.9, 116.0, 115.1, 38.1, 21.5. HRMS (ESI) [C$_{18}$H$_{16}$N$_4$O$_3$+Na]$^+$ calc. 359.11146 Da, obt. 359.10996 Da. m.p. 160-162°C.

3-(1H-benzo[d][1,2,3]triazole-1-carbonyl)-6-nitro-2H-chromen-2-one (11)

Coumarin derivative 10 (600 mg, 2.55 mmol) was dissolved in thionyl chloride (10 mL) and stirred at reflux for 3 hours prior to evaporating to dryness under reduced pressure. The obtained product was triturated in hexanes, affording a yellow solid in 97% yield, which was used without further purification. The crude acyl chloride (300 mg, 1.18 mmol) was combined with benzotriazole (155 mg, 1.30 mmol) in anhydrous dichloromethane (10 mL) and
triethylamine (0.49 mL, 3.54 mmol), and the resulting reaction mixture was stirred overnight prior to being diluted with dichloromethane (30 mL). The organic phase was washed with saturated aqueous sodium carbonate (3 x 15 mL), 1 M HCl (3 x 15 mL) and brine (15 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The crude product was triturated in hexanes prior to being dried under reduced pressure, resulting in 24 mg of a beige powder obtained in 6% yield. δH NMR (300 MHz, DMSO-d$_6$) 8.96 (2 H, m, Ar), 8.59 (1H, dd, J=9.2, 2.8, coumarin), 8.33 (2 H, d, J=9.1, Ar), 7.89 (1 H, t, J=8.2, benzotriazole), 7.80 (1 H, d, J=9.2, coumarin), 7.69 (1 H, t, J=8.2 Hz, benzotriazole). δC NMR (75 MHz, CDCl$_3$) 163.3, 158.9, 157.7, 148.1, 146.8, 145.4, 132.8, 131.8, 130.0, 128.5, 127.3, 124.1, 121.7, 119.6, 119.3, 115.1. HRMS (ESI) [C$_{16}$H$_8$N$_4$O$_5$+Na$^+$] calc. 359.03869 Da, obt. 359.03741 Da. m.p. 213-215°C (dec.)

**Ethyl 3-(4-nitrophenyl)propynoate**$^7$ (12)

To a solution of 1-iodo-4-nitrobenzene (623 mg, 2.50 mmol) and ethyl propynoate (1.02 mL, 10.0 mmol) in degassed THF (10 mL) were added bis(triphenylphospine)palladium(II) dichloride (35 mg, 0.05 mmol), copper(I) iodide (19 mg, 0.10 mmol) and potassium carbonate (691 mg, 5.00 mmol) prior to stirring the reaction mixture at reflux for 5 hours, while adding the aforementioned amounts of palladium complex and copper(I) iodide every two hours. The solvent was then removed by evaporation under reduced pressure and the crude product was dissolved in diethyl ether (40 mL). The organic phase was washed with water (3 x 10 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. Purification by flash column chromatography (1:1 hexane:dichloromethane) afforded 241 mg of the product as a cream-coloured solid in 44% yield. δH NMR (400 MHz, CDCl$_3$) 8.27
(2 H, dt, J=8.9, J=2.0, Ar), 7.77 (2 H, dt, J=8.9, J=2.0, Ar), 4.35 (2 H, q, J=7.1, O-CH$_2$-CH$_3$),
1.39 (3 H, t, J=7.1, O-CH$_2$-CH$_3$). δC NMR (100 MHz, CDCl$_3$) 153.7, 149.0, 134.1, 126.7, 124.2,
84.6, 83.1, 63.0, 14.4. HRMS (ESI) [C$_{11}$H$_9$NO$_4$+H]$^+$ calc. 220.06043 Da, obt. 220.06012 Da.
m.p. 124-126°C.

3-(4-nitrophenyl)propynoic acid$^8$ (13)

To a solution of ester 12 (239 mg, 1.09 mmol) in acetone (5 mL) and water (1 mL) was
added lithium hydroxide (52 mg, 2.17 mmol) prior to stirring the reaction mixture at room
temperature overnight. The reaction was then quenched with water (20 mL) and saturated
aqueous sodium carbonate (5 mL), and the aqueous phase was washed with dichloromethane
(3 x 7 mL). The aqueous phase was then acidified to pH ~1 using 1 M HCl, and the product was
extracted with ethyl acetate (3 x 10 mL). The combined organic extracts were then washed with
brine (10 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated to
dryness. The product was isolated as 188 mg of a cream-coloured solid in 90% yield. δH NMR
(400 MHz, CDCl$_3$) 8.21 (2 H, dt, J=9.0, 2.1, Ar), 7.71 (2H, dt, J=9.0, 2.1, Ar). δC NMR
(100 MHz, CDCl$_3$) 154.8, 149.0, 133.8, 126.6, 123.9, 84.3, 82.3. HRMS (ESI) [C$_9$H$_5$NO$_4$+H]$^+$
calc. 192.02913 Da, obt. 192.02870 Da. m.p. 165-167°C (dec.)

1-(1H-benzo[d][1,2,3]triazol-1-yl)-3-(4-nitrophenyl)prop-2-yn-1-one (14)

A solution of benztotriazole (100 mg, 0.84 mmol) in thionyl chloride (15.3 μL,
0.21 mmol) and anhydrous dichloromethane (10 mL) was stirred for 30 minutes at 25°C prior to
the addition of carboxylic acid 13 (40 mg, 0.21 mmol). The resulting reaction mixture was stirred
for 2 hours prior to washing the formed precipitate with dichloromethane. The organic phase was
washed with 2 M NaOH (3 x 2 mL) and brine (2 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated to dryness. The product was obtained as 31 mg of a beige solid in 51% yield. δH NMR (400 MHz, DMSO-d_6) 8.38 (2 H, d, J=8.9, (p-NO_2)Ar), 8.33 (1 H, d, J=8.3 Hz, benzotriazole), 8.25 (1 H, d, J=8.3 Hz, benzotriazole), 8.12 (2 H, d, J=8.9 Hz, (p-NO_2)Ar), 7.86 (1 H, t, J=7.7, benzotriazole), 7.69 (1 H, t, J=7.7, benzotriazole). δC NMR (75 MHz, DMSO-d_6) 150.7, 150.1, 147.1, 135.8, 132.6, 131.7, 128.5, 125.8, 125.6, 121.7, 115.2, 92.4, 85.4. HRMS (ESI) [C_{15}H_{8}N_{4}O_{3}+H]^+ calc. 293.06692 Da, obt. 293.06681 Da. m.p. 214-216°C (dec.)

( trans-2-(3-nitrophenyl)cyclopropyl)(pyridin-3-yl)methanone (15)

Trimethyloxosulfonium iodide (322 mg, 1.46 mmol) and sodium hydride (35 mg, 1.46 mmol) were dissolved in DMSO (5 mL) and stirred for one hour prior to the addition of substituted azachalcone m-CP30a (300 mg, 1.18 mmol) dissolved separately in DMSO (5 mL). Following this addition, the reaction mixture was stirred at 50°C for one hour prior to being quenched with water (30 mL) and saturated aqueous sodium carbonate (5 mL). The product was extracted with dichloromethane (3 x 15 mL) and the combined organic extracts were washed with water (3 x 10 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (1:1 toluene:ethyl acetate) to obtain 165 mg of an off-white solid in 52% yield. δH NMR (400 MHz, CDCl_3) 9.25 (1 H, d, J=1.4, py), 8.82 (1 H, dd, J=4.7, 1.5, py), 8.28 (1 H, dt, J=8.0, 1.9, py), 8.12 (1 H, dt, J=8.0, 1.3, py), 8.02 (1 H, s, (m-NO_2)Ar), 7.50 (3 H, m, (m-NO_2)Ar), 2.97 (1 H, m, (m-NO_2)Ar-CH), 2.89 (1 H, m, CH-CO), 2.04 (1 H, m, CH_2), 1.71 (1 H, m, CH_2). δC NMR (100 MHz, DMSO-d_6) 197.0, 154.1, 150.0, 149.0, 142.6, 135.8, 133.3, 133.0, 130.0,
124.1, 122.3, 121.1, 29.8, 29.5, 20.2. HRMS (ESI) \([C_{15}H_{12}N_2O_3+H]^+\) calc. 269.09207 Da, obt. 269.09277 Da. m.p. 127-129°C.

\((E)-3-(2-(3-nitrostyryl)oxiran-2-yl)pyridine\) (16)

Trimethylsulfonium iodide (221 mg, 1.10 mmol) and sodium hydride (24 mg, 1.00 mmol) were dissolved in DMSO (7 mL) and stirred at room temperature for one hour prior to the addition of substituted azachalcone \(m\)-CP30a (254 mg, 1.00 mmol) dissolved in DMSO (7 mL) beforehand. Following this addition, the reaction mixture was stirred for a second hour prior to being quenched with water (35 mL) and saturated aqueous sodium carbonate (5 mL). The product was extracted with dichloromethane (3 x 15 mL) and the combined organic extracts were washed with water (3 x 10 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (7:3 dichloromethane:ethyl acetate) to obtain 156 mg of an orange oil in 58% yield. \(\delta^H\) NMR (400 MHz, CDCl\(_3\)) 8.74 (1 H, s, py), 8.62 (1 H, d, J=4.2, py), 8.21 (1 H, s, \((m\text{-NO}_2)\text{Ar}\)), 8.10 (1 H, d, J=8.0, \((m\text{-NO}_2)\text{Ar}\)), 7.79 (1H, d, J=8.0, \((m\text{-NO}_2)\text{Ar}\)), 7.65 (1 H, d, J=7.7, py), 7.49 (1 H, t, J=8.0, \((m\text{-NO}_2)\text{Ar}\)), 7.36 (1H, dd, J=7.7, J=4.2, py), 6.60 (1H, d, J=16.0, C\(_{sp^2}\)H), 6.52 (1 H, d, J=16.0, C\(_{sp^2}\)H), 3.27 (1 H, d, J=5.4, epoxide), 3.17 (1 H, d, J=5.4, epoxide). \(\delta^C\) NMR (100 MHz, CDCl\(_3\)) 150.0, 149.1, 149.0, 137.9, 135.2, 133.8, 132.9, 132.4, 131.6, 130.1, 123.8, 123.2, 121.5, 58.9, 57.5. HRMS (ESI) \([C_{15}H_{12}N_2O_3+H]^+\) calc. 269.09207 Da, obt. 269.09269 Da.
3-(3-nitrophenyl)-5-(pyridin-3-yl)isoxazole (17)

To a solution of N-hydroxy-4-toluenesulfonamide (281 mg, 1.50 mmol) in methanol (1.2 mL) and water (0.2 mL) was added potassium carbonate (222 mg, 1.6 mmol), and to that solution was added a solution of substituted azachalcone \textit{m-CP30a} (50.8 mg, 0.20 mmol) in methanol (0.6 mL) and \textit{N,N}-dimethylformamide (1 mL). The resulting reaction mixture was stirred at 40°C for 24 hours, after which a second portion of potassium carbonate (111 mg, 0.80 mmol) was added and the mixture was stirred at 60°C for an additional 10 hours. The product was extracted with ethyl acetate (40 mL) and the organic phase was washed with water (3 x 10 mL) and brine (10 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The product was precipitated from hexanes to obtain 22 mg of an orange solid in 41% yield. δH NMR (400 MHz, CDCl₃) 8.83 (s, 1 H, py), 8.64 (1 H, d, J=4.4, py), 8.19 (1 H, s, (m-NO₂)Ar), 8.11 (1 H, d, J=7.9, (m-NO₂)Ar), 7.75 (1 H, d, J=7.8, py), 7.61 (1 H, d, J=7.9, (m-NO₂)Ar), 7.44 (1 H, t, J=7.9, (m-NO₂)Ar), 7.34 (1 H, dd, J=7.8, J=4.4, py), 6.45 (1H, s, isoxazole). δC NMR (75 MHz, DMSO-d₆) 168.4, 163.6, 153.0, 149.8, 148.7, 141.6, 134.8, 133.2, 132.9, 130.0, 124.0, 121.2, 119.4, 96.3. HRMS (ESI) [C₁₄H₉N₃O₃+H]⁺ calc. 268.07167 Da, obt. 268.07154 Da. m.p. 152-154°C.

3-(4-nitrophenyl)prop-2-yn-1-ol⁹ (18)

To a solution of 1-iodo-4-nitrobenzene (20.0 mmol, 4.98 g) in anhydrous tetrahydrofuran (60 mL) were added triphenylphosphine (0.40 mmol, 0.105 g), bis(triphenylphosphine)palladium(II) dichloride (0.12 mmol, 84.2 mg), copper(I) iodide (0.40 mmol, 76.2 mg), propargyl alcohol (24.0 mmol, 1.4 mL) and triethylamine (30 mL) prior to stirring under nitrogen overnight at 50°C. The reaction was quenched with water (200 mL),
and the product was extracted with ethyl acetate (3 x 60 mL). The combined organic extracts were washed with saturated aqueous ammonium hydroxide (60 mL), water (60 mL) and brine (60 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (1:1 hexanes:ethyl acetate) to obtain 3.260 g of a dark orange powder in 92% yield. \( R_f 0.42 \) (1:1 hexanes:ethyl acetate). \( \delta H \) NMR (400 MHz, CDCl\(_3\)) 8.20 (2 H, d, J=8.7, Ar), 7.59 (2 H, d, J=8.7, Ar) NMR HRMS (EI) \([C_9H_7NO_3]\) calc. 177.0426 Da, obt. 177.03975 Da. m.p. 95-97°C (dec.).

3-(4-nitrophenyl)propiolaldehyde\(^10\) (19)

Compound 19 was prepared from alcohol 18 (18.40 mmol) according to General Procedure A, and purified by flash column chromatography (9:1 hexanes:ethyl acetate) to obtain 1.708 g of a pale orange powder in 53% yield. \( R_f 0.22 \) (9:1 hexanes:ethyl acetate). \( \delta H \) NMR (400 MHz, CDCl\(_3\)) 9.47 (1 H, s, CHO), 8.29 (2 H, d, J=9.0, Ar), 7.78 (2 H, d, J=9.0, Ar). \( \delta C \) NMR (100 MHz, CDCl\(_3\)) 176.1, 184.8, 133.9, 126.0, 123.9, 90.8, 90.6. HRMS (EI) \([C_9H_5NO_3]\) calc. 175.0269 Da, obt. 175.02434 Da. m.p. 87-89°C (dec.).

1-(4-nitrophenyl)penta-1,4-diyn-3-ol (20)

Compound 20 was prepared from aldehyde 19 (9.75 mmol) according to General Procedure C, and purified by flash column chromatography (7:3 hexanes:ethyl acetate) to obtain 1.275 g of an orange powder in 65% yield. \( R_f 0.24 \) (7:3 hexanes:ethyl acetate). \( \delta H \) NMR (400 MHz, CDCl\(_3\)) 8.22 (2 H, d, J=8.9, Ar), 7.64 (2 H, d, J=8.9, Ar), 5.39 (1 H, s, CHO), 2.68 (1 H, s, Csp-H), 2.36 (1 H, br s, OH). \( \delta C \) NMR (75 MHz, CDCl\(_3\)) 147.6, 132.7, 128.5, 123.6,
1-(4-nitrophenyl)penta-1,4-diyn-3-one (21)

Compound 21 was prepared from alcohol 20 (6.34 mmol) according to General Procedure A, and purified by flash column chromatography (3:7 hexanes:dichloromethane) to obtain 606 mg of a dark orange powder in 48% yield. $R_f$ 0.5 (3:7 hexanes:DCM). $\delta$H NMR (400 MHz, CDCl$_3$) 8.29 (2 H, d, $J$=8.9, Ar), 7.80 (2 H, d, $J$=8.9, Ar), 3.47 (1 H, s, CH).

1-(1-benzyl-1H-1,2,3-triazol-4-yl)-3-(4-nitrophenyl)prop-2-yn-1-one (22a)

Benzyl azide was prepared from benzyl bromide according to General Procedure D. To a solution of ynone 21 (0.50 mmol, 99.6 mg), benzyl azide (0.50 mmol, 66.6 mg) and copper(I) iodide (0.50 mmol, 95.2 mg) in acetonitrile (5 mL) was added $N,N$-diisopropylethylamine (0.50 mmol, 0.09 mL) dropwise prior to stirring overnight at room temperature. The reaction mixture was then diluted with dichloromethane (15 mL) and washed with 1 N HCl (2 x 15 mL), water (15 mL), saturated aqueous ammonium hydroxide (2 x 15 mL), water (15 mL) and brine (2 x 15 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (1:1 hexanes:ethyl acetate) to obtain 42 mg of an off-white powder in 26% yield. $R_f$ 0.33 (1:1 hexanes:ethyl acetate). $\delta$H NMR (400 MHz, DMSO-d$_6$) 9.24 (1 H, s, triazole H), 8.35 (2 H, d, $J$=9.0, Ar), 8.04 (2 H, d, $J$=9.0, Ar), 7.41-7.36 (5 H, m, Ph), 5.73 (2 H, s, CH$_2$). $\delta$C NMR (100 MHz, DMSO-d$_6$) 168.2, 148.4, 146.7, 135.2, 134.2, 130.2, 128.8, 128.3, 127.9, 125.3,
124.0, 89.4, 88.5, 53.2. HRMS (EI) [C$_{18}$H$_{12}$N$_{4}$O$_{3}$] calc. 332.0909 Da, obt. 332.08930 Da. m.p. 154-156°C (dec.).

1-(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)-3-(4-nitrophenyl)prop-2-yn-1-one (22b)

4-Nitrobenzyl azide was prepared from 4-nitrobenzyl bromide according to General Procedure D. To a solution of ynone 21 (1.04 mmol, 0.207 g), 4-nitrobenzyl azide (1.06 mmol, 0.189 g) and copper(I) iodide (1.06 mmol, 0.202 g) in acetonitrile (10 mL) was added N,N-diisopropylethylamine (0.976 mmol, 0.17 mL) dropwise prior to stirring overnight at room temperature. The reaction mixture was then diluted with dichloromethane (30 mL) and washed with 1 N HCl (2 x 30 mL), water (30 mL), saturated aqueous ammonium hydroxide (4 x 30 mL), water (2 x 30 mL) and brine (30 mL) prior to being dried over anhydrous magnesium sulfate, filtered and evaporated under reduced pressure. The product was purified by flash column chromatography (1-5% ethyl acetate in dichloromethane) to obtain 144 mg of a yellow powder in 39% yield. R$_f$ 0.33 (97:3 dichloromethane:ethyl acetate). δH NMR (400 MHz, DMSO-d$_6$, Me$_4$Si) 9.29 (1 H, s, triazole H), 8.35 (2 H, d, J=8.8, Ar), 8.26 (2 H, d, J=8.8 Hz, Ar), 8.04 (2 H, d, J=8.8 Hz, Ar), 7.60 (2 H, d, J=8.8 Hz, Ar), 5.92 (2 H, s, CH$_2$). δC NMR (100 MHz, DMSO-d$_6$, Me$_4$Si) 168.1, 148.5, 147.3, 146.8, 142.4, 134.2, 130.8, 129.1, 125.3, 124.0, 123.9, 89.4, 88.6, 52.3. HRMS (ESI$^+$, MeOH) [C$_{18}$H$_{11}$N$_{5}$O$_{5}$+Na]$^+$ calc. 400.0658 Da, obt. 400.0635 Da. m.p. 190-192°C (dec.)

(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl) methanol$^{11}$ (23a)

4-Nitrobenzyl azide was prepared from 4-nitrobenzyl bromide according to General Procedure D. Compound 23a was prepared from propargyl alcohol (25.00 mmol) and
4-nitrobenzyl azide according to General Procedure E, and obtained in 60% yield (3.498 g) as an orange power. R<sub>f</sub> 0.15 (ethyl acetate). δH NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) 8.26 (2 H, d, J=8.8, Ar), 7.97 (1 H, s, triazole H), 7.59 (2 H, d, J=8.8, Ar), 5.82 (2 H, s, Ar-CH<sub>2</sub>), 4.67 (2 H, s, CH<sub>2</sub>OH). δC NMR (100 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) 150.0, 148.8, 144.6, 129.9, 124.8, 123.6, 56.8, 53.2. HRMS (EI) [C<sub>10</sub>H<sub>10</sub>N<sub>4</sub>O<sub>3</sub>] calc. 234.0753 Da, obt. 234.07401 Da. m.p. 120-123°C.

(1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)methanol<sup>12</sup> (23b)

4-(Trifluoromethyl)benzyl azide was prepared from 4-(trifluoromethyl)benzyl bromide according to General Procedure D. Compound 23b was prepared from propargyl alcohol and 4-(trifluoromethyl)benzyl azide (19.5 mmol) according to General Procedure E, and obtained in 96% yield (4.801 g) as a white powder. R<sub>f</sub> 0.18 (1:1 DCM:ethyl acetate). δH NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) 7.93 (1 H, s, triazole H), 7.73 (2 H, d, J=8.2, Ar), 7.54 (2 H, d, J=8.2, Ar), 5.74 (2 H, s, Ar-CH<sub>2</sub>), 4.66 (2 H, s, CH<sub>2</sub>OH). δC NMR (100 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) 149.0, 141.0, 129.7 (q, J=32.0), 128.6, 125.7 (q, J=3.8), 123.0, 122.4, 55.9, 52.5. δF NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) -63.1. HRMS (ESI<sup>+</sup>) [C<sub>10</sub>H<sub>11</sub>N<sub>3</sub>OF<sub>3</sub>]+, calc. 258.0854 Da, obt. 258.0852 Da. m.p. 99-102°C.

1-(4-nitrobenzyl)-1H-1,2,3-triazole-4-carbaldehyde (24a)

Compound 24a was prepared from alcohol 23a (14.93 mmol) according to General Procedure B, and obtained in 74% yield (2.588 g) as a pale yellow powder. R<sub>f</sub> 0.68 (ethyl acetate). δH NMR (400 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) 10.08 (1 H, s, CHO), 8.78 (1 H, s, triazole H), 8.28 (2 H, d, J=8.8, Ar), 7.68 (2 H, d, J=8.8, Ar), 5.97 (2 H, s, CH<sub>2</sub>). δC NMR (100 MHz, (CD<sub>3</sub>)<sub>2</sub>CO) 185.3, 149.0, 148.9, 143.5, 130.3, 128.2, 124.9, 53.8. HRMS (EI) [C<sub>10</sub>H<sub>8</sub>N<sub>4</sub>O<sub>3</sub>] calc. 232.0596 Da, obt. 232.05772 Da. m.p. 109-111°C (dec.).
1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazole-4-carbaldehyde (24b)

Compound 24b was prepared from alcohol 23b (18.67 mmol) according to General Procedure B, and obtained in 70% yield (3.313 g) as a white powder. Rf 0.82 (1:1 DCM:ethyl acetate). δH NMR (400 MHz, (CD$_3$)$_2$CO) 10.06 (1 H, s, CHO), 8.74 (1 H, s, triazole H), 7.75 (2 H, d, J=8.1, Ar), 7.62 (2 H, d, J=8.1, Ar), 5.90 (2 H, s, CH$_2$). δC NMR (100 MHz, (CD$_3$)$_2$CO) 184.4, 147.9, 139.8, 130.0 (q, J=32.1), 128.9, 127.0, 125.8 (q, J=3.8), 121.6 (q, J=270), 53.1. δF NMR (400 MHz, (CD$_3$)$_2$CO) -63.2. HRMS (ESI$^+$) [C$_{11}$H$_8$N$_3$OF$_3$+Na]$^+$, calc. 278.0517 Da, obt. 278.0486 Da. m.p. 86-88°C (dec.).

1-(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)prop-2-yn-1-ol (25a)

Compound 25a was prepared from aldehyde 24a (11.15 mmol) according to General Procedure C and purified by flash column chromatography (1:2 DCM:ethyl acetate) to obtain 1.584 g of a yellow oil in 55% yield. Rf 0.41 (1:2 DCM:ethyl acetate). δH NMR (400 MHz, (CD$_3$)$_2$CO) 8.27 (2 H, d, J=8.9, Ar), 8.10 (1 H, s, triazole H), 7.62 (2 H, d, J=8.9, Ar), 5.84 (2 H, s, CH$_2$), 5.60 (1 H, s, C$_{sp^3}$H), 3.03 (1 H, s, C$_{sp}$-H). δC NMR (100 MHz, (CD$_3$)$_2$CO) 150.1, 148.8, 144.4, 130.0, 124.8, 123.5, 84.5, 74.4, 57.5, 53.4. HRMS (EI) [C$_{12}$H$_9$N$_4$O$_3$]$^-$ calc. 257.0680 Da, obt. 257.06996 Da.

1-(1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)prop-2-yn-1-ol (25b)

Compound 25b was prepared from aldehyde 24b (12.99 mmol) according to general procedure C and purified by flash column chromatography (3:1 DCM:ethyl acetate) to obtain 1.895 g of a white powder in 52% yield. Rf 0.22 (3:1 DCM:ethyl acetate). δH NMR (400 MHz, (CD$_3$)$_2$CO) 8.08 (1 H, s, triazole H), 7.74 (2 H, d, J=8.1, Ar), 7.58 (2 H, d, J=8.1, Ar), 5.78 (2 H,
s, CH₂), 5.63 (1 H, d, J=2.2, Csp²-H), 5.20 (1 H, br s, OH), 3.02 (1 H, d, J=2.2, Csp-H). δC NMR (100 MHz, (CD₃)₂CO) 150.0, 141.6 (d, J=1.1), 130.7 (q, J=32.1), 129.6, 126.6 (q, J=4.0), 125.2 (q, J=270), 123.3, 84.5, 74.4, 57.5, 53.6. δF NMR (400 MHz, (CD₃)₂CO) -63.1. HRMS (ESI⁺) [C_{13}H_{10}N_{3}OF₃+Na]^+, calc. 304.0674 Da, obt. 304.0674 Da. m.p. 127-135°C.

1-(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)prop-2-yn-1-one (26a)

Compound 26a was prepared from alcohol 25a (6.13 mmol) according to General Procedure B and purified by flash column chromatography (1:1 hexanes:ethyl acetate) to obtain 864 mg of a white powder in 55% yield. Rf 0.30 (1:1 hexanes:ethyl acetate). δH NMR (400 MHz, (CD₃)₂CO) 8.87 (1 H, s, triazole H), 8.28 (2 H, d, J=8.9, Ar), 7.69 (2 H, d, J=8.9, Ar), 5.98 (2 H, s, CH₂), 4.35 (1 H, s, Csp-H). δC NMR (100 MHz, (CD₃)₂CO) 169.7, 148.9, 148.5, 143.3, 130.3, 130.2, 124.9, 82.9, 81.4, 53.8. HRMS (ESI⁺) [C_{12}H_{8}N_{4}O_{3}+Na]^+ calc. 279.0494 Da, obt. 279.0508 Da. m.p. 124-126°C (dec.).

1-(1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)prop-2-yn-1-one (26b)

Compound 26b was prepared from alcohol 25b (6.74 mmol) according to General Procedure B and purified by flash column chromatography (DCM) to obtain 104 mg of a white powder in 6% yield. Rf 0.20 (DCM). δH NMR (400 MHz, (CD₃)₂CO) 8.82 (1 H, s, triazole H), 7.72 (2 H, d, J=8.2, Ar), 7.61 (2 H, d, J=8.2, Ar), 5.88 (2 H, s, CH₂), 4.30 (1 H, s, Csp-H). δC NMR (100 MHz, (CD₃)₂CO), 169.7, 148.5, 140.7 (d, J=1.5), 131.0 (q, J=32.1), 130.1, 129.8, 126.8 (q, J=3.6), 125.2 (q, J=270), 82.8, 81.5, 54.1. δF NMR (400 MHz, (CD₃)₂CO) -63.2. HRMS (ESI⁺) [C_{13}H_{8}N_{3}OF₃+Na]^+ calc. 302.0517 Da, obt. 302.0503 Da. m.p. 115-125°C.
(1-benzyl-1H-1,2,3-triazol-4-yl)(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methanone (27a)

Benzyl azide was prepared from benzyl bromide according to General Procedure D. Compound 27a was prepared from ynone 26a (1.00 mmol) and benzyl azide, according to General Procedure E and purified by flash column chromatography (1:1 DCM:ethyl acetate) to obtain 105 mg of a pale yellow powder in 27% yield. Rf 0.42 (1:1 DCM:ethyl acetate). δH NMR (400 MHz, DMSO-d$_6$) 9.32 (1 H, s, triazole H), 9.23 (s, 1 H, triazole H), 8.25 (2 H, d, J=8.9, Ar), 7.60 (2 H, d, J=8.9, Ar), 7.40-7.33 (5 H, m, Ph), 5.93 (2 H, s, CH$_2$), 5.75 (2 H, s, CH$_2$). δC NMR (100 MHz, DMSO-d$_6$) 175.3, 147.3, 145.2, 142.8, 135.5, 130.8, 130.2, 129.2, 128.8, 128.3, 128.1, 124.0, 53.1, 52.2. Missing one aromatic C due to low solubility. HRMS (ESI$^+$) [C$_{19}$H$_{15}$N$_7$O$_3$+Na]$^+$, calc. 412.1129, obt. 412.1155 Da. m.p. 168-170°C (dec.).

(1-(2-nitrobenzyl)-1H-1,2,3-triazol-4-yl)(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methanone (27b)

2-Nitrobenzyl azide was prepared from 2-nitrobenzyl bromide according to General Procedure D. Compound 27b was prepared from ynone 26a (1.00 mmol) and 2-nitrobenzyl azide according to General Procedure E and purified by flash column chromatography (7:3 DCM:ethyl acetate) to obtain 130 mg of a yellow powder in 30% yield. Rf 0.28 (7:3 DCM:ethyl acetate). δH (400 MHz, DMSO-d$_6$) 9.34 (1 H, s, triazole H), 9.23 (1 H, s, triazole H), 8.25 (2 H, d, J=8.9, (p-NO$_2$)Ar), 8.17 (1 H, dd, J=7.7, J=1.3, Ar), 7.76 (1 H, ddd, J=7.7, J=7.7, J=1.3, Ar), 7.66 (1 H, ddd, J=7.7, J=7.7, J=1.3, Ar), 7.61 (2 H, d, J=8.9, (p-NO$_2$)Ar), 7.17 (1 H, dd, J=7.7, J=1.3, Ar), 6.12 (2 H, s, CH$_2$), 5.94 (2 H, s, CH$_2$). δC (100 MHz, DMSO-d$_6$) 175.2, 147.6, 147.3, 145.2, 145.0, 142.8, 134.5, 131.1, 130.8, 130.3, 129.8, 129.2, 125.2, 124.0, 52.2, 50.3. Missing one
aromatic C due to low solubility. HRMS (ESI$^+$) [C$_{19}$H$_{14}$N$_8$O$_5$+Na]$^+$, calc. 457.0979 Da, obt. 457.0985 Da. m.p. 145-147$^\circ$C (dec.).

(1-(3-nitrobenzyl)-1H-1,2,3-triazol-4-yl)(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methanone (27c)

3-Nitrobenzyl azide was prepared from 3-nitrobenzyl bromide according to General Procedure D. Compound 27c was prepared from ynone 26a (1.00 mmol) and 3-nitrobenzylazide according to General Procedure E and purified by flash column chromatography (7:3 DCM:ethyl acetate) to obtain 117 mg of a pale yellow powder in 27% yield. R$_f$ 0.20 (7:3 DCM:ethyl acetate). $\delta$H NMR (400 MHz, DMSO-d$_6$) 9.34 (1 H, s, triazole H), 9.33 (1 H, s, triazole H), 8.33 (1 H, dd, J=1.8, 1.8, Ar), 8.26-8.21 (3 H, m, Ar), 7.84 (1 H, ddd, J=7.7, 1.3, 1.3, Ar), 7.70 (1 H, dd, J=7.9, 7.9, Ar), 7.60 (2 H, d, J=8.9, (p-NO$_2$)Ar), 5.93 (2 H, s, CH$_2$), 5.92 (2 H, s, CH$_2$). $\delta$C NMR (100 MHz, DMSO-d$_6$) 175.2, 147.8, 147.3, 145.1, 142.7, 137.4, 134.8, 130.7, 130.5, 130.4, 129.1, 123.9, 123.2, 123.0, 52.1, 52.0. Missing one aromatic C due to low solubility. HRMS (ESI$^+$) [C$_{19}$H$_{14}$N$_8$O$_5$+Na]$^+$, calc. 457.0979 Da, obt. 457.0975 Da. m.p. 173-175$^\circ$C (dec.).

bis(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methanone (27d)

4-Nitrobenzyl azide was prepared from 4-nitrobenzyl bromide according to General Procedure D. Compound 27d was prepared from ynone 26a (1.00 mmol) and 4-nitrobenzyl azide according to General Procedure E and purified by flash column chromatography (1:1 DCM:ethyl acetate) as 174 mg of a yellow powder in 40% yield. R$_f$ 0.36 (1:1 DCM:ethyl acetate). $\delta$H (400 MHz, DMSO-d$_6$) 9.33 (2 H, s, triazole H), 8.25 (4 H, d, J=8.9, Ar), 7.61 (4 H, d, J=8.9, Ar), 5.94 (4 H, s, CH$_2$). $\delta$C NMR (100 MHz, DMSO-d$_6$) 175.2, 147.4, 145.2, 142.8, 130.8, 129.2,
(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)(1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)methanone (27e)

4-(Trifluoromethyl)benzyl azide was prepared from 4-(trifluoromethyl)benzyl bromide according to General Procedure D. Compound 27e was prepared from ynone 26a (1.00 mmol) and 4-(trifluoromethyl)benzyl azide according to General Procedure E and purified by flash column chromatography (7:3 DCM:ethyl acetate) to obtain 183 mg of a yellow powder in 40% yield. Rf 0.3 (7:3 DCM:ethyl acetate). δH NMR (400 MHz, DMSO-d6) 9.32 (1 H, s, triazole H), 9.31 (1 H, s, triazole H), 8.25 (2 H, d, J=8.9, (p-NO2)Ar), 7.77 (2 H, d, J=8.1, (p-CF3)Ar), 7.60 (2 H, d, J=8.9, (p-NO2)Ar), 7.57 (2 H, d, J=8.1, (p-CF3)Ar), 5.94 (2 H, s, CH2), 5.80 (2 H, s, CH2). δC NMR (100 MHz, DMSO-d6) 175.2, 147.3, 145.18, 145.15, 142.8, 140.1, 130.8, 130.6, 129.2, 128.8, 125.8 (q, J=4.0), 124.0, 52.4, 52.2. Missing one aromatic C and CF3. δF NMR (400 MHz, (CD3)2CO) -63.2. HRMS (ESI+) [C20H14N7O5F3+Na]+, calc. 480.1002 Da, obt. 480.1025 Da. m.p. 176-178°C (dec.).

(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)(1-(4-(trifluoromethoxy)benzyl)-1H-1,2,3-triazol-4-yl)methanone (27f)

4-(Trifluoromethoxy)benzyl azide was prepared from 4-(trifluoromethoxy)benzyl bromide according to General Procedure D. Compound 27f was prepared from ynone 26a (1.00 mmol) and 4-(trifluoromethoxy)benzyl azide according to General Procedure E and purified by flash column chromatography (2:1 DCM:ethyl acetate) to obtain 175 mg of a white
powder in 37% yield. Rf 0.50 (2:1 DCM:ethyl acetate). δH NMR (400 MHz, DMSO-d6) 9.33 (1 H, s, triazole H), 9.28 (1 H, s, triazole H), 8.25 (2 H, d, J=8.8, (p-NO2)Ar), 7.61 (2 H, d, J=8.8, (p-NO2)Ar), 7.53 (2 H, d, J=8.4, (p-OCF3)Ar), 7.40 (2 H, d, J=8.4, (p-OCF3)Ar), 5.94 (2 H, s, CH2), 5.80 (2 H, s, CH2). δC NMR (100 MHz, DMSO-d6) 175.2, 147.3, 145.1, 145.0, 142.7, 134.9, 130.7, 129.1, 129.0, 121.3, 120.1, 120.0. Missing one aliphatic C and CF3 due to low solubility. δF NMR (400 MHz, DMSO-d6) -56.8. HRMS (ESI+) [C20H14N7O4F3+Na]+, calc. 496.0957 Da, obt. 472.0951 Da. m.p. 167-169°C (dec.).

4-((4-(1-(4-nitrobenzyl)-1H-1,2,3-triazole-4-carbonyl)-1H-1,2,3-triazol-1-y)methyl)benzonitrile (27g)

4-(Azidomethyl)benzonitrile was prepared from 4-(bromomethyl)benzonitrile according to General Procedure D. Compound 27g was prepared from ynone 26a (1.00 mmol) and 4-(azidomethyl)benzonitrile according to General Procedure E and purified by flash column chromatography (6:4 DCM:ethyl acetate) to obtain 108 mg of a pale yellow powder in 26% yield. Rf 0.29 (6:4 DCM:ethyl acetate). δH NMR (400 MHz, DMSO-d6) 9.33 (1 H, s, triazole H), 9.30 (1 H, s, triazole H), 8.25 (2 H, d, J=8.9, (p-NO2)Ar), 7.87 (2 H, d, J=8.4, (p-CN)Ar), 7.61 (2 H, d, J=8.9, (p-NO2)Ar), 7.53 (2 H, d, J=8.4, (p-CN)Ar), 5.94 (2 H, s, CH2), 5.87 (2 H, s, CH2). δC NMR (100 MHz, DMSO-d6), 175.2, 147.3, 145.1, 142.7, 140.8, 132.7, 130.7, 130.6, 129.1, 128.8, 123.9, 118.4, 111.0, 52.4, 52.1. Missing one C due to low solubility. HRMS (ESI+) [C20H14N8O3+Na]+, calc. 437.1081 Da, obt. 437.1093 Da. m.p. 196-198°C (dec.).
(1-(4-methylbenzyl)-1H-1,2,3-triazol-4-yl)(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methanone (27h)

4-Methylbenzyl azide was prepared from 4-methylbenzyl bromide according to General Procedure D. Compound 27h was prepared from ynone 26a (1.00 mmol) and 4-methylbenzyl azide according to General Procedure E and purified by flash column chromatography (7:3 DCM:ethyl acetate) to obtain 157 mg of a yellow powder in 39% yield. Rf 0.34 (7:3 DCM:ethyl acetate). δH NMR (400 MHz, DMSO-d$_6$) 9.32 (1 H, s, triazole H), 9.19 (1 H, s, triazole H), 8.25 (2 H, d, J=8.8, (p-NO$_2$)Ar), 7.60 (2 H, d, J=8.8, (p-NO$_2$)Ar), 7.29 (2 H, d, J=7.9, (p-Me)Ar), 5.93 (2 H, s, CH$_2$), 5.69 (2 H, s, CH$_2$), 2.28 (3 H, s, Me). δC NMR (100 MHz, DMSO-d$_6$) 175.3, 147.3, 145.2, 145.1, 142.8, 137.7, 132.5, 130.8, 130.0, 129.4, 129.2, 128.1, 124.0, 52.9, 52.2, 20.7. HRMS (ESI$^+$) [C$_{20}$H$_{17}$N$_7$O$_3$+Na]$^+$, calc. 426.1285 Da, obt. 426.1296 Da. m.p. 185-187°C (dec.).

(1-(4-methoxybenzyl)-1H-1,2,3-triazol-4-yl)(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methanone (27i)

4-Methoxybenzyl azide was prepared from 4-methoxybenzyl bromide according to General Procedure D. Compound 27i was prepared from ynone 26a (1.00 mmol) and 4-methoxybenzyl azide according to General Procedure E and purified by flash column chromatography (6:4 DCM:ethyl acetate) to obtain 151 mg of a pale yellow powder in 36% yield. Rf 0.47 (1:1 DCM:ethyl acetate). δH NMR (400 MHz, DMSO-d$_6$) 9.32 (1 H, s, triazole H), 9.17 (1 H, s, triazole H), 8.25 (2 H, d, J=8.9, (p-NO$_2$)Ar), 7.60 (2 H, d, J=8.9, (p-NO$_2$)Ar), 7.37 (2 H, d, J=8.8, (p-O-Me)Ar), 6.94 (2 H, d, J=8.8, (p-O-Me)Ar), 5.93 (2 H, s, CH$_2$), 5.66 (2 H, s, CH$_2$), 3.74 (3 H, s, Me). δC NMR (100 MHz, DMSO-d$_6$) 175.2, 159.2, 147.2, 145.1, 145.0,
(1-(4-fluorobenzyl)-1H-1,2,3-triazol-4-yl)(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl) methanone (27j)

4-Fluorobenzyl azide was prepared from 4-fluorobenzyl bromide according to General Procedure D. Compound 27j was prepared from ynone 26a (1.00 mmol) and 4-fluorobenzyl azide according to General Procedure E and purified by flash column chromatography (7:3 DCM:ethyl acetate) to obtain 110 mg of a yellow powder in 27% yield. Rf 0.29 (7:3 DCM:ethyl acetate). δH NMR (400 MHz, DMSO-d$_6$) 9.32 (1 H, s, triazole H), 9.24 (1 H, s, triazole H), 8.25 (2 H, d, J=8.8, (p-NO$_2$)Ar), 7.60 (2 H, d, J=8.8, (p-NO$_2$)Ar), 7.47 (2 H, dd, J=8.9, J=8.9, (p-F)Ar), 7.23 (2 H, dd, J=8.9, J=8.9, (p-F)Ar), 5.93 (2 H, s, CH$_2$), 5.74 (2 H, s, CH$_2$). δC NMR (100 MHz, DMSO-d$_6$) 175.3, 147.3, 145.2, 145.1, 142.8, 131.7, 130.8, 130.5, 130.4, 130.2, 129.2, 124.0, 115.7 (d, J=21.5), 52.3, 51.2. δF NMR (400 MHz, (CD$_3$)$_2$CO) -115.0. HRMS (ESI$^+$) [C$_{19}$H$_{14}$N$_7$O$_3$F+Na]$^+$, calc. 430.1034 Da, obt. 430.1046 Da. m.p. 178-180°C (dec.).

(1-(4-bromobenzyl)-1H-1,2,3-triazol-4-yl)(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl) methanone (27k)

4-Bromobenzyl azide was prepared from 4-bromobenzyl bromide according to General Procedure D. Compound 27k was prepared from ynone 26a (1.00 mmol) and 4-bromobenzyl azide according to General Procedure E and purified by flash column chromatography (7:3 DCM:ethyl acetate) to yield 140 mg of a yellow powder in 30% yield. Rf 0.24 (7:3 DCM:ethyl acetate). δH NMR (400 MHz, DMSO-d$_6$) 9.32 (1 H, s, triazole H), 9.25 (1 H, s, triazole H), 8.25
(2 H, d, J=8.9, (p-NO₂)Ar), 7.603 (2 H, d, J=8.9, (p-NO₂)Ar), 7.596 (2 H, d, J=8.5, (p-Br)Ar), 7.35 (2 H, d, J=8.5, (p-Br)Ar), 5.93 (2 H, s, CH₂), 5.74 (2 H, s, CH₂). δC NMR (100 MHz, DMSO-d₆) 175.8, 147.8, 145.6, 143.3, 135.4, 132.2, 131.3, 130.8, 129.7, 124.4, 122.1, 52.8, 52.7. Missing two aromatic C’s due to low solubility. HRMS (ESI⁺) [C₁₉H₁₄N₇O₃Br+Na]⁺, calc. 490.0239 Da (Br⁷⁹), obt. 490.0215 Da. m.p. 202-204°C (dec.).

(1-(cyclohexylmethyl)-1H-1,2,3-triazol-4-yl)(1-(4-nitrobenzyl)-1H-1,2,3-triazol-4-yl)methanone (27l)

Azidomethylcyclohexane was prepared from bromomethylecyclohexane according to General Procedure D, and used without further purification. Compound 27l was prepared from ynone 26a (1.00 mmol) and azidomethylcyclohexane according to General Procedure E and purified by flash column chromatography (8:2 DCM:ethyl acetate) to obtain 119 mg of a pale yellow powder in 30% yield. Rf 0.25 (8:2 DCM:ethyl acetate). δH NMR (400 MHz, DMSO-d₆) 9.35 (1 H, s, triazole H), 9.09 (1 H, s, triazole H), 8.25 (2 H, d, J=8.8, (p-NO₂)Ar), 7.61 (2 H, d, J=8.8, (p-NO₂)Ar), 5.94 (2 H, s, Ar-CH₂), 4.36 (2 H, d, J=7.2, CH₂-CH), 1.94-1.84 (1 H, m, cy), 1.69-1.65 (2 H, m, cy), 1.62-1.58 (1 H, m, cy), 1.54-1.51 (2 H, m, cy), 1.23-1.09 (3 H, m, cy), 1.03-0.93 (2 H, m, cy). δC NMR (100 MHz, DMSO-d₆) 175.4, 147.3, 145.0, 143.9, 130.9, 130.3, 129.2, 124.0, 53.4, 52.1, 38.0, 29.6, 25.6, 25.0. Missing one aromatic C due to low solubility. HRMS (ESI⁺) [C₁₉H₂₁N₇O₃+Na]⁺, calc. 418.1598 Da, obt. 418.1605 Da. m.p. 169-171°C (dec.)

bis(1-(4-(trifluoromethyl)benzyl)-1H-1,2,3-triazol-4-yl)methanone (27m)

4-(Trifluoromethyl)benzyl azide was prepared from 4-(trifluoromethyl)benzyl bromide according to General Procedure D. Compound 27m was prepared from ynone 26b (0.371 mmol)
and 4-(trifluoromethyl)benzylazide according to General Procedure E and purified by flash column chromatography (8:2 DCM:ethyl acetate) to obtain 103 mg of a white powder in 58% yield. $R_f$ 0.40 (8:2 DCM:ethyl acetate). $\delta$H NMR (400 MHz, DMSO-$d_6$) 9.31 (2 H, s, triazole H), 7.76 (4 H, d, J=8.1, (p-CF$_3$)Ar), 7.58 (4 H, d, J=8.1, (p-CF$_3$)Ar), 5.89 (4 H, s, CH$_2$). $\delta$C NMR (100 MHz, DMSO-$d_6$) 175.3, 145.2, 140.1, 130.6, 128.85 (q, J=31.7), 128.80, 125.7 (q, J=4.0), 124.0 (q, J=270), 52.4. $\delta$F NMR (400 MHz, DMSO-$d_6$) -61.2. HRMS (ESI$^+$) [C$_{21}$H$_{14}$N$_6$O$_6$F$_6$+Na]$^+$, calc. 503.1031 Da, obt. 503.1049 Da. m.p. 203-205°C.

References

3. I. Roy, Ph.D., Université de Montréal, 2014.