Contents

0.1 4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenol **124** 2

0.2 5-(4-(Hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **125** 2

0.3 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(2-oxo-2-((2-oxotetrahydrofuran-3-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **126** 3

0.4 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrofuran-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **127** 4

0.5 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(6-oxo-6-((2-oxotetrahydrofuran-3-yl)amino)hexyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid **128** 5

0.6 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(2-heptyl-4-oxo-1,4-dihydroquinolin-6-yl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **129** 6

0.7 (*S*)-4-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2-oxotetrahydrofuran-3-yl)butanamide **130** 7

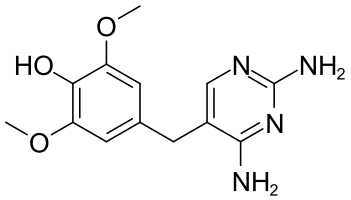
0.8 (*S*)-6-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide **131** 8

0.9 6-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)-2-heptylquinolin-4(1*H*)-one **132** 9

0.10 2-(6-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)hexyl)-3-hydroxyquinolin-4(1*H*)-one **133** 10

go through Cips and check pip C is two peaks not doublet

0.1 4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenol 124



Hydrobromic acid (48 % w/w, aq., 50 ml) was heated to 100 °C. Trimethoprim **99** (5.00 g, 17.2 mmol) was added, and the suspension was stirred for 40 min under Ar. The mixture was removed from the heat, and NaOH (50 % w/w, aq., 15 ml) was added dropwise. The reaction mixture was then cooled slowly to 0 °C, and the resulting crystals were filtered out and washed with cold water. The crystals were then dissolved in hot water (80 ml), neutralized with NH_4OH (sat., aq.) and cooled slowly to 0 °C. The resulting crystals were filtered out, washed with cold water and dried under vacuum. **124** was obtained as pale pink prisms (2.06 g, 7.46 mmol, 43.4 %).

TLC R_f = 0.04 (5 % MeOH/$CHCl_2$)

mp T / °C = 238 (H_2O, decomposes)

IR (neat) ν_{max} / cm^{-1} = 3314.0 (N-H), 3137.4 (N-H), 3045.3 (C-H), 3000.9 (C-H), 2938.1 (C-H), 2838.7 (C-H), 1662.9 (pyrimidine), 1645.2 (pyrimidine), 1626.6 (pyrimidine)

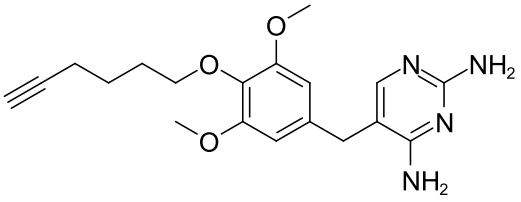
^{1}H NMR (400 MHz, MeOD) δ / ppm = 7.21 (s, 1 H, C<u>H</u>N), 6.54 (s, 2 H, *meta* to OCH_2), 4.87 (br s, 5 H, OH, $NH_2 \times 2$), 3.82 (s, 6 H, O<u>C</u>H_3), 3.63 (s, 2 H, C<u>C</u>H_2C)

^{13}C NMR (101 MHz, MeOD) δ / ppm = 166.4 (CH_2<u>C</u>NH_2), 162.0 (CHN<u>C</u>NH_2), 156.2 (<u>C</u>HNCNH_2), 149.8 (*ipso* to OCH_3), 135.9 (*ipso* to OH), 128.2 (*para* to OH), 111.7 (CH_2<u>C</u>CNH_2), 107.5 (*meta* to OH), 57.0 (O<u>C</u>H_3), 33.9 (C<u>C</u>H_2C)

HRMS (ESI^+) m/z / Da = 277.1295, $[M+H]^+$ found, $[C_{13}H_{17}N_4O_3]^+$ requires 277.1301

The data are consistent with the literature.[?]

0.2 5-(4-(Hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine 125



4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenol **124** (1.00 g, 3.62 mmol, 1 eq.), 6-chloro-1-hexyne **134** (0.524 ml, 0.420 g, 4.34 mmol, 1.2 eq.), Cs_2CO_3 (2.36 g, 7.24 mmol, 2 eq.) and anhydrous DMF (30 ml)

were stirred at 70 °C for 7 h. The solvent was removed under reduced pressure, then CH_2Cl_2 (30 ml) was added and the mixture filtured. The filtrate was concentrated under reduced pressure and purified by column chromatography using a Combiflash (SiO_2, 5 % MeOH/CH_2Cl_2). **125** was obtained as a pale cream amorphous solid (0.253 g, 0.709 mmol, 19.6 %).

TLC R_f = 0.14 (5 % MeOH/CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 3451.4 (alkyne C-H), 3313.4 (N-H), 3136.7 (N-H), 3113.9 (N-H), 2944.2 (C-H), 2839.0 (C-H), 1635.1 (pyrimidine)

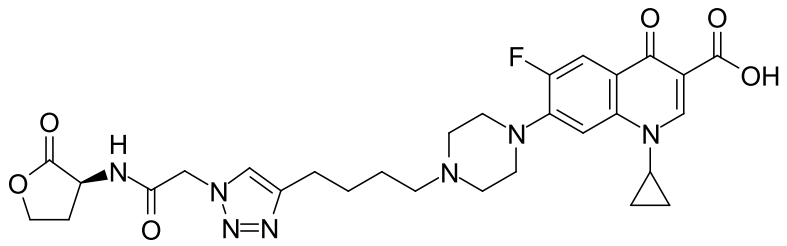
^{1}**H NMR** (400 MHz, MeOD) δ / ppm = 7.77 (s, 1 H, C<u>H</u>N), 6.37 (s, 2 H, *meta* to OCH_2), 4.83 (br s, 2 H, CHNCN<u>H</u>$_2$), 4.63 (br s, 2 H, CH_2CCN<u>H</u>$_2$), 3.95 (t, J = 6.3 Hz, 2 H, C<u>H</u>$_2$O), 3.79 (s, 6 H, OC<u>H</u>$_3$), 3.65 (s, 2 H, CC<u>H</u>$_2$C), 2.28 (td, J = 7.1, 2.6 Hz, 2 H, HC≡CC<u>H</u>$_2$), 1.94 (t, J = 2.7 Hz, 1 H, <u>H</u>C≡C), 1.81 - 1.90 (m, 2 H, C<u>H</u>$_2$$CH_2$O), 1.71 - 1.80 (m, 2 H, C<u>H</u>$_2$$CH_2$$CH_2$O)

^{13}**C NMR** (101 MHz, MeOD) δ / ppm = 162.7 (CH_2C<u>C</u>NH$_2$), 162.0 (CHN<u>C</u>NH$_2$), 156.4 (<u>C</u>HNCNH$_2$), 153.8 (*ipso* to OCH_3), 136.0 (*ipso* to OCH_2), 133.6 (*para* to OCH_2), 106.5 (CH_2<u>C</u>CNH$_2$), 105.0 (*meta* to OCH_2), 84.5 (HC≡<u>C</u>), 72.6 (<u>C</u>H$_2$O), 68.3 (H<u>C</u>≡C), 56.1 (O<u>C</u>H$_3$), 34.7 (C<u>C</u>H$_2$C), 29.1 (<u>C</u>H$_2$$CH_2$O), 24.9 (<u>C</u>H$_2$$CH_2$$CH_2$O), 18.0 (HC≡C<u>C</u>H$_2$)

HRMS (ESI$^+$) m/z / Da = 357.1920, $[M+H]^+$ found, $[C_{19}H_{25}N_4O_3]^+$ requires 357.1927

The compound has not been reported previously.

0.3 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(2-oxo-2-((2-oxotetrahydrofuran-3-yl)amino)ethyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 126



50 % water/*t*-BuOH (2 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 1-cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **135** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-2-azido-*N*-(2-oxotetrahydrofuran-3-yl)acetamide **41** (9.2 mg, 50.0 μmol, 1 eq.). A similarly degassed solution of $CuSO_4 \cdot 5\,H_2O$ (624 μg, 2.5 μmol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (991 μg, 5 μmol, 0.1 eq., 100 mM) in 50 % water/*t*-BuOH (50 μl) was then added. The mixture was stirred at r.t. under argon for 3 h. On observation that the reaction had stalled, the reaction was degassed again, and a further portion of cataylst solution (50 μl) was added. After a further 3 h the reaction mixture was dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-20 % MeOH/CH_2Cl_2 over 15 min). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **126** was obtained as a white amorphous solid (8.8 mg, 14.8 μmol, 29.6 %).

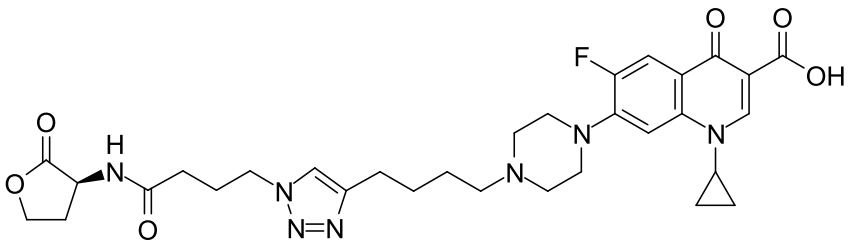
IR (neat) ν_{max} / cm^{-1} = 3266.3 (N-H), 2949.0 (C-H), 2934.8 (C-H), 2827.2 (C-H), 1778.0 (lactone C=O), 1724.9 (carboxylic acid C=O), 1665.0 (amide C=O), 1625.5 (quinolone C=O)

^{1}H NMR (400 MHz, DMSO d_6) δ / ppm = 15.23 (s, 1 H, C(=O)OH), 8.84 (d, J = 7.9 Hz, 1 H, NH), 8.66 (s, 1 H, *ortho* to C(=O)OH), 7.90 (d, J = 13.3 Hz, 1 H, *ortho* to F), 7.82 (s, 1 H, CH=CCH_2), 7.57 (d, J = 7.6 Hz, 1 H, *meta* to F), 5.13 (s, 1 H, C(=O)CHHN), 5.12 (s, 1 H, C(=O)CHHN), 4.64 (ddd, J = 10.9, 9.0, 7.8 Hz, 1 H, CHNH), 4.36 (td, J = 8.9, 1.7 Hz, 1 H, OCHH), 4.23 (ddd, J = 10.6, 8.8, 6.4 Hz, 1 H, OCHH), 3.83 (tt, J = 7.0, 4.0 Hz, 1 H, NCH$(CH_2)_2$), 3.32 (br s, 4 H, $CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 2.67 (t, J = 7.4 Hz, 2 H, CH=CCH_2), 2.58 (br t, J = 5.0 Hz, 4 H, $CH_2CH_2CH_2N(CH_2)CH_2$), 2.42 - 2.49 (m, 1 H, OCH_2CHH), 2.40 (t, J = 7.1 Hz, 1 H, CH=$CCH_2CH_2CH_2CH_2$), 2.17 (dtd, J = 11.7, 10.8, 10.8, 9.0 Hz, 1 H, OCH_2CHH), 1.66 (quin, J = 7.2 Hz, 1 H, CH=CCH_2CH_2), 1.53 (quin, J = 7.2 Hz, 1 H, CH=$CCH_2CH_2CH_2$), 1.28 - 1.35 (m, 1 H, NCH$(CHH)_2$), 1.16 - 1.21 (m, 1 H, NCH$(CHH)_2$)

^{13}C NMR (101 MHz, DMSO d_6) δ / ppm = 176.4 (C(=O)CC(=O)OH), 174.9 (OC(=O)), 166.0 (C(=O)OH), 165.9 (NHC(=O)), 153.1 (d, J = 250.8 Hz, *ipso* to F), 148.0 (CH=CC(=O)OH), 146.6 (CH=CCH_2), 145.3 (d, J = 9.6 Hz, *ipso* to piperazine), 139.2 (*para* to F), 123.4 (CH=CCH_2), 118.5 (d, J = 7.5 Hz, *para* to piperazine), 110.9 (d, J = 23.5 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.4 (d, J = 3.2 Hz, *meta* to C=O and *meta* to F), 65.4 (OCH_2), 57.3 ($CH=CCH_2CH_2CH_2CH_2N$), 52.4 ($CH_2CH_2CH_2N(CH_2)CH_2$), 51.2 ($C(=O)CH_2N$), 49.5 (d, J = 4.3 Hz, $CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 48.2 (CHNH), 35.9 (NCH$(CH_2)_2$), 28.2 (CH_2CHNH), 26.8 ($CH=CCH_2CH_2$), 25.7 ($CH=CCH_2CH_2CH_2$), 24.9 ($CH=CCH_2$), 7.6 (NCH$(CH_2)_2$)

HRMS (ESI$^+$) m/z / Da = 596.2627, $[M+H]^+$ found, $[C_{29}H_{35}FN_7O_6]^+$ requires 596.2633 $[\alpha]_D^{20}$ / $°10^{-1}cm^2g^{-1}$ = -3.5 (c / g(100 mL)$^{-1}$ = 0.0575 , MeOH)

0.4 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(4-oxo-4-((2-oxotetrahydrofuran-3-yl)amino)butyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 127



50 % water/*t*-BuOH (2 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 1-cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **135** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-4-azido-*N*-(2-oxotetrahydrofuran-3-yl)butanamide **46** (10.6 mg, 50.0 μmol, 1 eq.). A similarly degassed solution of $CuSO_4 \cdot 5\,H_2O$ (624 μg, 2.5 μmol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (991 μg, 5 μmol, 0.1 eq., 100 mM) in 50 % water/*t*-BuOH (50 μl) was then added. The mixture was stirred at r.t. under argon for 3 h, then dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-20 % MeOH/CH_2Cl_2 over 15 min). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **127** was obtained as a white amorphous solid (14.6 mg, 23.4 μmol, 46.8 %).

IR (neat) ν_{max} / cm^{-1} = 3286.7 (N-H), 2949.7 (C-H), 2820.6 (C-H), 2778.0 (C-H), 1778.1 (lactone C=O),

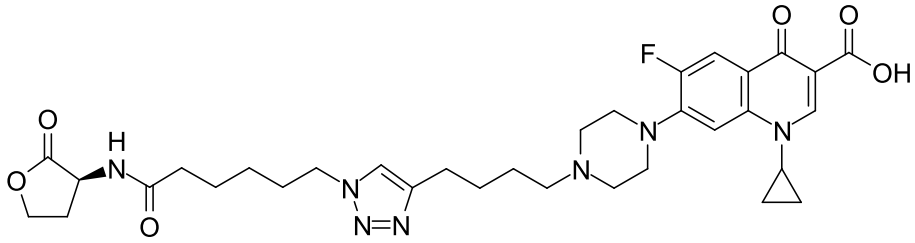
1725.6 (carboxylic acid C=O), 1663.7 (amide C=O), 1625.8 (quinolone C=O)

^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 15.22 (br s, 1 H, C(=O)O<u>H</u>), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.40 (d, J = 8.0 Hz, 1 H, N<u>H</u>), 7.88 (d, J = 13.4 Hz, 1 H, *ortho* to F), 7.85 (s, 1 H, C<u>H</u>=CCH$_2$), 7.55 (d, J = 7.5 Hz, 1 H, *meta* to F), 4.53 (ddd, J = 10.9, 9.0, 8.1 Hz, 1 H, C<u>H</u>NH), 4.33 (td, J = 8.9, 1.8 Hz, 1 H, OC<u>H</u>H), 4.31 (t, J = 7.0 Hz, 2 H, C<u>H$_2$</u>NCH=C), 4.20 (ddd, J = 10.5, 8.8, 6.5 Hz, 1 H, OCH<u>H</u>), 3.82 (tt, J = 6.9, 4.0 Hz, 1 H, NC<u>H</u>(CH$_2$)$_2$), 3.32 (br. t, J = 4.2, 4.2 Hz, 4 H, CH$_2$CH$_2$CH$_2$N(CH$_2$C<u>H$_2$</u>)CH$_2$C<u>H$_2$</u>), 2.64 (t, J = 7.4 Hz, 2 H, CH=CC<u>H$_2$</u>), 2.57 (br. t, J = 5.0, 5.0 Hz, 2 H, CH$_2$CH$_2$CH$_2$N(C<u>H$_2$</u>)C<u>H$_2$</u>), 2.34 - 2.42 (m, 3 H, OCH$_2$C<u>H</u>H and CH=CCH$_2$CH$_2$CH$_2$C<u>H$_2$</u>), 2.09 - 2.19 (m, 3 H, OCH$_2$CH<u>H</u> and C(=O)C<u>H$_2$</u>), 2.02 (quin, J = 7.2 Hz, 2 H, C(=O)CH$_2$C<u>H$_2$</u>), 1.64 (quin, J = 7.6 Hz, 2 H, CH=CCH$_2$C<u>H$_2$</u>), 1.52 (quin, J = 7.2 Hz, 2 H, CH=CCH$_2$CH$_2$C<u>H$_2$</u>), 1.29 - 1.34 (m, 2 H, NCH(C<u>H</u>H)$_2$), 1.15 - 1.21 (m, 2 H, NCH(CH<u>H</u>)$_2$)

^{13}C NMR (126 MHz, DMSO d_6) δ / ppm = 176.3 (<u>C</u>(=O)CC(=O)OH), 175.4 (O<u>C</u>(=O)), 171.2 (NH<u>C</u>(=O)), 166.0 (<u>C</u>(=O)OH), 153.0 (d, J = 248.6 Hz, *ortho* to F), 148.0 (<u>C</u>H=CC(=O)OH), 146.8 (CH=<u>C</u>CH$_2$), 145.2 (d, J = 9.6 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.7 (<u>C</u>H=CCH$_2$), 118.5 (d, J = 7.5 Hz, *para* to piperazine), 110.9 (d, J = 22.4 Hz, *ortho* to C=O and *ortho* to F), 106.7 (<u>C</u>C(=O)OH), 106.3 (d, J = 3.2 Hz, *meta* to C=O and *meta* to F), 65.3 (O<u>C</u>H$_2$), 57.3 (CH=CCH$_2$CH$_2$CH$_2$<u>C</u>H$_2$N), 52.4 (CH$_2$CH$_2$CH$_2$N(<u>C</u>H$_2$)<u>C</u>H$_2$), 49.5 (CH$_2$CH$_2$CH$_2$N(CH$_2$<u>C</u>H$_2$)CH$_2$CH$_2$), 49.4 (CH$_2$CH$_2$CH$_2$N(CH$_2$CH$_2$)CH$_2$<u>C</u>H$_2$), 48.6 (<u>C</u>H$_2$NCH=C), 47.9 (OC(=O)<u>C</u>HNH), 35.9 (N<u>C</u>H(CH$_2$)$_2$), 31.7 (NHC(=O)<u>C</u>H$_2$), 28.2 (<u>C</u>H$_2$CHNH), 26.9 (CH=CCH$_2$<u>C</u>H$_2$), 25.8 (NHC(=O)CH$_2$<u>C</u>H$_2$ and CH=CCH$_2$CH$_2$<u>C</u>H$_2$), 24.9 (CH=C<u>C</u>H$_2$), 7.6 (NCH(<u>C</u>H$_2$)$_2$)

HRMS (ESI$^+$) m/z / Da = 624.2928, [M+H]$^+$ found, [$C_{31}H_{39}FN_7O_6$]$^+$ requires 624.2946 $[\alpha]_D^{20}$ / °10^{-1}cm^{2}g^{-1} = -10.6 (c / g(100 mL)$^{-1}$ = 0.094 , MeOH)

0.5 (*S*)-1-Cyclopropyl-6-fluoro-4-oxo-7-(4-(4-(1-(6-oxo-6-((2-oxotetrahydrofuran-3-yl)amino)hexyl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid 128



50 % water/*t*-BuOH (2 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 1-cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **135** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-6-azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide **47** (12.0 mg, 50.0 μmol, 1 eq.). A similarly degassed solution of $CuSO_4 \cdot 5\,H_2O$ (624 μg, 2.5 μmol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (991 μg, 5 μmol, 0.1 eq., 100 mM) in 50 % water/*t*-BuOH (50 μl) was then added. The mixture was stirred at r.t. under argon for 3 h, then dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-20 % MeOH/CH_2Cl_2 over 15 min) The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **128** was obtained as a white amorphous solid (12.4 mg, 19.0 μmol, 38.0 %).

TLC R_f = 0.30 (30 % MeOH/CH_2Cl_2)

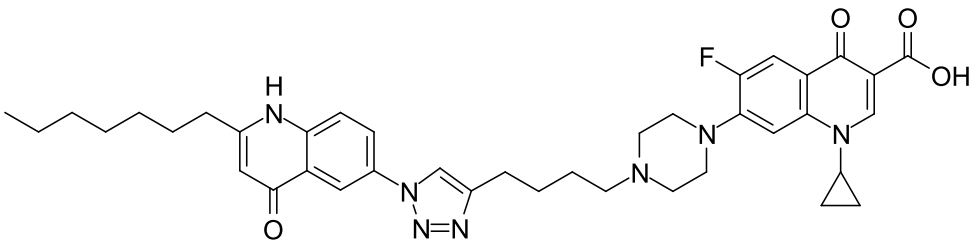
IR (neat) ν_{max} / cm^{-1} = 3301.8 (N-H), 2939.7 (C-H), 2857.5 (C-H), 1784.6 (lactone C=O), 1728.5 (carboxylic acid C=O), 1658.2 (amide C=O), 1625.5 (quinolone C=O)

^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 15.22 (br s, 1 H, C(=O)OH), 8.65 (s, 1 H, *ortho* to C(=O)OH), 8.32 (d, J = 8.0 Hz, 1 H, NH), 7.89 (d, J = 13.3 Hz, 1 H, *ortho* to F), 7.84 (s, 1 H, CH=CCH_2), 7.55 (d, J = 7.6 Hz, 1 H, *meta* to F), 4.51 (ddd, J = 10.9, 9.1, 7.9 Hz, 1 H, CHNH), 4.33 (td, J = 8.8, 1.8 Hz, 1 H, OCHH), 4.28 (t, J = 7.1 Hz, 2 H, CH_2NCH=C), 4.19 (ddd, J = 10.5, 8.7, 6.6 Hz, 1 H, OCHH), 3.82 (tt, J = 7.0, 4.0 Hz, 1 H, NCH$(CH_2)_2$), 3.32 (br t, J = 4.5, 4 H, $CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 2.63 (t, J = 7.5 Hz, 2 H, CH=CCH_2), 2.57 (br t, J = 4.2, 4.2 Hz, 4 H, $CH_2CH_2CH_2N(CH_2)CH_2$), 2.33 - 2.41 (m, 3 H, OCH_2CHH and $CH{=}CCH_2CH_2CH_2CH_2$), 2.06 - 2.16 (m, 3 H, OCH_2CHH and C(=O)CH_2), 1.79 (quin, J = 7.4 Hz, 2 H, C(=O)$CH_2CH_2CH_2CH_2$), 1.63 (quin, J = 7.5 Hz, 2 H, CH=CCH_2CH_2), 1.45 - 1.56 (m, 4 H, C(=O)CH_2CH_2 and CH=$CCH_2CH_2CH_2$), 1.29 - 1.34 (m, 2 H, NCH$(CHH)_2$), 1.19 - 1.25 (m, 2 H, C(=O)$CH_2CH_2CH_2$), 1.15 - 1.19 (m, 2 H, NCH$(CHH)_2$)

^{13}C NMR (126 MHz, DMSO d_6) δ / ppm = 176.4 (C(=O)CC(=O)OH), 175.4 (OC(=O)), 172.1 (NHC(=O)), 166.0 (C(=O)OH), 153.0 (d, J = 250.2 Hz, *ipso* to F), 148.0 (CH=CC(=O)OH), 146.8 (CH=CCH_2), 145.2 (d, J = 9.6 Hz, *ipso* to piperazine), 139.2 (*para* to F), 121.6 (CH=CCH_2), 118.5 (d, J = 8.0 Hz, *para* to piperazine), 110.9 (d, J = 23.5 Hz, *ortho* to C=O and *ortho* to F), 106.7 (CC(=O)OH), 106.3 (d, J = 2.1 Hz, *meta* to C=O and *meta* to F), 65.3 (OCH_2), 57.4 ($CH{=}CCH_2CH_2CH_2CH_2N$), 52.4 ($CH_2CH_2CH_2N(CH_2)CH_2$), 49.5 (d, J = 3.2 Hz, $CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 49.0 ($CH_2$NCH=C), 47.8 (CHNH), 35.9 (NCH$(CH_2)_2$), 34.8 (NHC(=O)CH_2), 29.5 (CH_2CH_2NCH=C), 28.3 (CH_2CHNH), 26.9 (CH=CCH_2CH_2), 25.7 (CH=$CCH_2CH_2CH_2$), 25.4 (NHC(=O)$CH_2CH_2CH_2$), 24.9 (CH=CCH_2), 24.5 (NHC(=O)CH_2CH_2), 7.6 (NCH$(CH_2)_2$)

HRMS (ESI$^+$) m/z / Da = 652.3254, $[M+H]^+$ found, $[C_{33}H_{43}FN_7O_6]^+$ requires 652.3248 $[\alpha]_D^{20}$ / $°10^{-1}cm^2g^{-1}$ = -8.5 (c / g(100 mL)$^{-1}$ = 0.106 , MeOH)

0.6 1-Cyclopropyl-6-fluoro-7-(4-(4-(1-(2-heptyl-4-oxo-1,4-dihydroquinolin-6-yl)-1*H*-1,2,3-triazol-4-yl)butyl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid 129



50 % water/*t*-BuOH (1 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 1-cyclopropyl-6-fluoro-7-(4-(hex-5-yn-1-yl)piperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid **135** (4.1 mg, 10.0 μmol, 1 eq.) and 6-azido-2-heptylquinolin-4(1*H*)-one **26** (2.8 mg, 10.0 μmol, 1 eq.). A similarly degassed solution of $CuSO_4 \cdot 5\,H_2O$ (125 μg, 0.5 μmol, 0.05 eq. 50 mM), THPTA (218 μg, 0.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (198 μg, 1 μmol, 0.1 eq., 100 mM) in 50 % water/*t*-BuOH (10 μl) was then added. The mixture was stirred at r.t. under argon for 1.5 h, then the reaction mixture was evaporated under reduced pressure. The residue was purified by preparatory HPLC (50-100 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 10 ml) and 10 % *i*-PrOH/$CHCl_3$ (10 ml). The organic layer was dried with $MgSO_4$ and evaporated

under reduced pressure. **129** was obtained as a white amorphous solid (8.6 mg, 2.7 μmol, 27.0 %).

IR (neat) ν_{max} / cm^{-1} = 2927.0 (C-H), 2865.5 (C-H), 1715.5 (carboxylic acid C=O), 1631.0 (ciprofloxacin quinolone C=O and HHQ C=O)

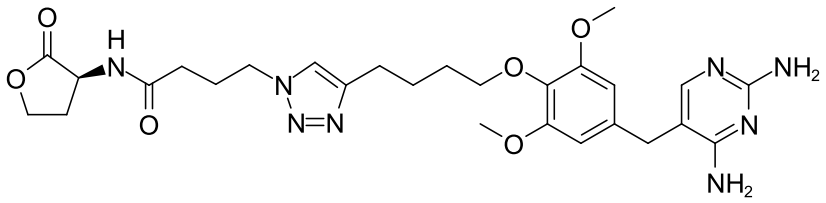
^{1}**H NMR** (500 MHz, DMSO d_6) 15.12 (br s, C(=O)OH), 11.79 (s, 1 H, NH), 8.75 (s, 1 H, NCH=CCH_2), 8.71 (s, 1 H, *ortho* to C(=O)OH), 8.40 (d, J = 2.7 Hz, 1 H, *ortho* to C(=O) and *ortho* to N), 8.18 (dd, J = 8.9, 2.6 Hz, 1 H, *para* to C(=O) and *ortho* to N), 7.99 (d, J = 13.0 Hz, 1 H, *ortho* to F), 7.75 (d, J = 9.0 Hz, 1 H, *meta* to C(=O) and *meta* to N), 7.62 (d, J = 7.8 Hz, 1 H, *meta* to F), 6.02 (s, 1 H, NHC=CHC(=O)), 3.85 (tt, J = 7.0, 4.0 Hz, 1 H, NCH$(CH_2)_2$), 3.23 - 3.30 (m, 6 H, $CH_2N(CH_2CH_2)CH_2CH_2$), 2.82 (t, J = 5.9 Hz, 2 H, NCH=CCH_2), 2.63 (t, J = 7.9 Hz, 2 H, CH_2C=CHC(=O)), 1.76 - 1.81 (m, 4 H, NCH=$CCH_2CH_2CH_2$), 1.70 (quin, J = 7.2 Hz, 2 H, CH_2CH_2C=CHC(=O)), 1.15 - 1.38 (m, 12 H, $CH_3CH_2CH_2CH_2CH_2$, NCH$(CHH)_2$ and NCH$(CHH)_2$), 0.87 (t, J = 6.9 Hz, 3 H, CH_3)

^{13}**C NMR** (126 MHz, DMSO d_6) δ / ppm = 176.4 (C(=O)CC(=O)OH), 176.3 (CHC(=O)), 165.8 (C(=O)OH), 154.3 (CCHC(=O)), 152.9 (d, J = 240.1 Hz, *ipso* to F), 148.3 (CH=CC(=O)OH), 147.5 (NCHCCH_2), 143.3 (d, J = 8.5 Hz, *ortho* to F and *ipso* to N), 139.6 (*ipso* to NH), 139.0 (*para* to F), 132.0 (*para* to NH), 124.9 (*ipso* to C(=O) and *ortho* to NH), 123.6 (*para* to C(=O) and *meta* to NH), 120.5 (NCH=CCH_2), 120.0 (*meta* to C(=O) and *meta* to N), 119.6 (d, J = 9.6 Hz, *ipso* to C(=O) and *para* to N), 115.1 (*ortho* to C(=O) and *ortho* to N), 111.3 (d, J = 28.8 Hz, *ortho* to F and *ortho* to C(=O)), 107.9 (*meta* to F and *meta* to C(=O)), 107.2 (CHC(=O)), 106.9 (CC(=O)OH), 55.4 (CH=$CCH_2CH_2CH_2CH_2N$), 50.6 ($CH_2CH_2CH_2N(CH_2)CH_2$), 46.5 ($CH_2CH_2CH_2N(CH_2CH_2)CH_2CH_2$), 36.0 (NCH$(CH_2)_2$), 33.2 ($CH_2$CNH), 31.2 ($CH_3CH_2CH_2$), 28.3 - 28.5 ($CH_3CH_2CH_2CH_2CH_2CH_2$), 25.6 (CH=$CCH_2CH_2$), 24.4 (CH=$CCH_2$), 22.7 (CH=$CCH_2CH_2CH_2$), 22.0 ($CH_3CH_2$), 13.9 ($CH_3$), 7.6 (NCH$(CH_2)_2$)

^{19}**F NMR** (376.45 MHz, MeOD) δ / ppm = ??

HRMS (ESI$^+$) m/z / Da = 696.3667, $[M+H]^+$ found, $[C_{39}H_{47}FN_7O_4]^+$ requires 696.3668

0.7 (*S*)-4-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2-oxotetrahydrofuran-3-yl)butanamide 130



50 % water/*t*-BuOH (2 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 5-(4-(hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **125** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-4-azido-*N*-(2-oxotetrahydrofuran-3-yl)butanamide **46** (15.9 mg, 75.0 μmol, 1.5 eq.). Similarly degassed solutions of $CuSO_4 \cdot 5\,H_2O$ (624 μg, 2.5 μmol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (991 μg, 5 μmol, 0.1 eq., 100 mM) in water (50 μl) were then added. An extra portion of **46** (10.6 mg, 50.0 μmol, 1 eq.) was added after 4 d. Extra portions of the catalysts were added after 9 d. After 2 weeks, the reaction mixture was extracted with CH_2Cl_2 (6 × 10 ml) then dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-20 % MeOH/CH_2Cl_2).The combined pure fractions were dried

with $MgSO_4$ and evaporated under reduced pressure. **130** was obtained as a pale brown gum (4.8 mg, 8.4 μmol, 16.8 %).

TLC R_f = 0.30 (30 % MeOH/CH_2Cl_2)

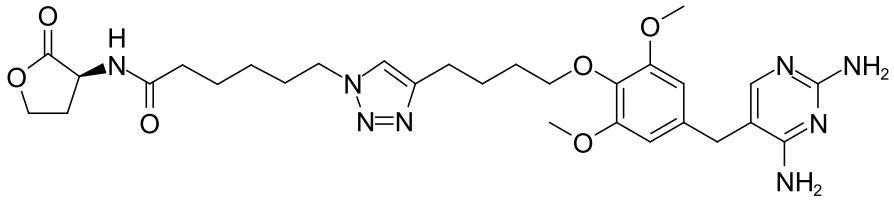
IR (neat) ν_{max} / cm^{-1} = 3340.5 (N-H), 3303.3 (N-H), 3182.5 (N-H), 2933.8 (C-H), 1774.2 (lactone C=O), 1659.7 (amide C=O and pyrimidine)

^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 8.43 (d, J = 8.0 Hz, 1 H, NH), 7.80 (s, 1 H, NCH=CCH_2), 7.46 (s, 1 H, CHN=CNH_2), 6.68 (br s, 2 H, CH_2CCNH_2), 6.53 (s, 2 H, *meta* to CH_2), 6.21 (br s, 2 H, CHN=CNH_2), 4.49 (dt, J = 10.7, 8.6 Hz, 1 H, CHNH), 4.32 (td, J = 8.7, 1.6 Hz, 1 H, CHHOC(=O)), 4.29 (t, J = 6.8 Hz, 2 H, CH_2N), 4.19 (ddd, J = 10.6, 8.7, 6.5 Hz, 1 H, CHHOC(=O)), 3.79 (t, J = 6.2 Hz, 2 H, $CH_2CH_2CH_2O$), 3.68 (s, 6 H, CH_3), 3.53 (br s, 2 H, CCH_2C), 2.63 (t, J = 7.5 Hz, 2 H, CH=CCH_2), 2.37 (dddd, J = 12.2, 8.9, 6.7, 1.8 Hz, 1 H, CHHCHNH), 2.08 - 2.15 (m, 3 H, CHHCHNH and C(=O)CH_2), 2.00 (quin, J = 7.2 Hz, 2 H, CH_2CH_2N), 1.72 (quin, J = 7.3 Hz, 2 H, CH=CCH_2CH_2), 1.61 (quin, J = 6.7 Hz, 2 H, CH_2CH_2O)

^{13}C NMR (126 MHz, DMSO d_6) δ / ppm = 175.8 (OC=O), 171.9 (NHC=O), 163.1 ($CC(NH_2)N$), 159.7 (br s, $NC(NH_2)N$), 153.2 (*ipso* to OCH_3), 150.5 (br s, $CHNC(NH_2)N$), 147.3 (NCH=CCH_2CH_2), 135.2 (*para* to CH_2O), 135.0 (*ipso* to CH_2O), 122.1 (CH=CCH_2CH_2), 107.3 ($CH_2CC(NH_2)$=N), 106.2 (*meta* to CH_2O), 72.3 ($CH_2CH_2CH_2O$), 65.7 (OCH_2CH_2CHNH), 56.2 (OCH_3), 48.9 (CH_2N), 48.3 (CHNH), 32.9 (CCH_2C), 32.0 (C(=O)CH_2), 29.3 ($CH_2CH_2CH_2O$), 28.4 (OCH_2CH_2CHNH), 26.0 (CH_2CH_2N), 25.7 (CH=CCH_2CH_2), 24.9 (CH=CCH_2CH_2)

HRMS (ESI^+) m/z / Da = 569.2834, $[M+H]^+$ found, $[C_{27}H_{37}N_8O_6]^+$ requires 569.2836 $[\alpha]_D^{20}$ / $°10^{-1}cm^2g^{-1}$ = -4.6 (c / g(100 mL)$^{-1}$ = 0.0433 , MeOH)

0.8 (*S*)-6-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide 131



50 % water/*t*-BuOH (2 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 5-(4-(hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **125** (20.6 mg, 50.0 μmol, 1 eq.) and (*S*)-6-azido-*N*-(2-oxotetrahydrofuran-3-yl)hexanamide **47** (18.0 mg, 75.0 μmol, 1.5 eq.). Similarly degassed solutions of $CuSO_4 \cdot 5\,H_2O$ (624 μg, 2.5 μmol, 0.05 eq. 50 mM), THPTA (1.09 mg, 2.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (991 μg, 5 μmol, 0.1 eq., 100 mM) in water (50 μl) were then added. An extra portion of **47** (12.0 mg, 50.0 μmol, 1 eq.) was added after was added after 4 d. Extra portions of the catalysts were added after 9 d. After 2 weeks, the After 2 weeks, the reaction mixture was extracted with CH_2Cl_2 (6 × 10 ml) then dry-loaded onto SiO_2 and purified by column chromatography using a Combiflash (SiO_2, 0-20 % MeOH/CH_2Cl_2).The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **131** was obtained as a clear gum (8.0 mg, 13.4 μmol, 26.8 %).

TLC R_f = 0.35 (30 % MeOH/CH_2Cl_2)

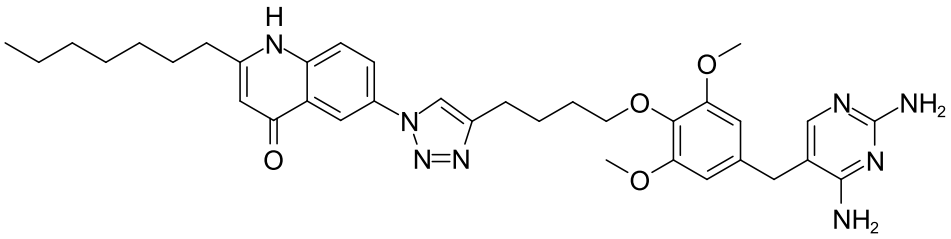
IR (neat) ν_{max} / cm^{-1} = 3336.0 (N-H), 3208.7 (N-H), 2941.1 (C-H), 2869.2 (C-H), 1775.2 (lactone C=O), 1657.3 (amide C=O and pyrimidine)

^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 8.34 (d, J = 8.0 Hz, 1 H, N$\underline{H}$), 7.83 (s, 1 H, NC$\underline{H}$=CCH$_2$), 7.50 (s, 1 H, C$\underline{H}$N=CNH$_2$), 6.54 (s, 2 H, *meta* to CH$_2$), 6.17 (br s, 2 H, CH$_2$CCN$\underline{H}_2$), 5.77 (br s, 2 H, CHN=CN$\underline{H}_2$), 4.51 (ddd, J = 11.0, 9.0, 8.1 Hz, 1 H, C$\underline{H}$NH), 4.33 (td, J = 8.8, 1.9 Hz, 1 H, C$\underline{H}$HOC(=O)), 4.27 (t, J = 7.1 Hz, 2 H, C$\underline{H}_2$N), 4.19 (ddd, J = 10.5, 8.7, 6.5 Hz, 1 H, CH$\underline{H}$OC(=O)), 3.80 (t, J = 6.3 Hz, 2 H, CH$_2$CH$_2$C$\underline{H}_2$O), 3.70 (s, 6 H, C$\underline{H}_3$), 3.52 (s, 2 H, CC$\underline{H}_2$C), 2.64 (t, J = 7.5 Hz, 2 H, CH=CC$\underline{H}_2$), 2.36 (dddd, J = 12.1, 8.9, 6.7, 1.8 Hz, 1 H, C$\underline{H}$HCHNH), 2.06 - 2.16 (m, 3 H, CH$\underline{H}$CHNH and C(=O)C$\underline{H}_2$), 1.78 (quin, J = 7.4 Hz, 2 H, C$\underline{H}_2$CH$_2$N), 1.73 (quin, J = 7.7 Hz, 2 H, CH=CCH$_2$C$\underline{H}_2$), 1.63 (quin, J = 6.8 Hz, 2 H, C$\underline{H}_2$CH$_2$O), 1.52 (quin, J = 7.5 Hz, 2 H, C(=O)CH$_2$C$\underline{H}_2$), 1.17 - 1.27 (m, 2 H, C(=O)CH$_2$CH$_2$C$\underline{H}_2$)

^{13}C NMR (125 MHz, DMSO d_6) δ / ppm = 175.4 (O$\underline{C}$=O), 172.0 (NH$\underline{C}$=O), 162.2 (C$\underline{C}$(NH$_2$)N), 161.8 (N$\underline{C}$(NH$_2$)N), 154.8 ($\underline{C}$HNC(NH$_2$)N), 152.8 (*ipso* to OCH$_3$), 146.7 (CH=$\underline{C}$CH$_2$CH$_2$), 135.5 (*para* to CH$_2$O), 134.8 (*ipso* to CH$_2$O), 121.6 ($\underline{C}$H=CCH$_2$CH$_2$), 105.9 (CH$_2\underline{C}$C(NH$_2$)=N), 105.8 (*meta* to CH$_2$O), 71.9 (CH$_2$CH$_2$ $\underline{C}$H$_2$O), 65.2 (O$\underline{C}$H$_2$CH$_2$CHNH), 55.8 (O$\underline{C}$H$_3$), 49.0 ($\underline{C}$H$_2$N), 47.8 ($\underline{C}$HNH), 34.8 (C(=O)$\underline{C}$H$_2$), 32.9 (C$\underline{C}$H$_2$C), 29.4 ($\underline{C}$H$_2$CH$_2$N), 29.1 (CH$_2\underline{C}$H$_2$CH$_2$O), 28.2 (OCH$_2\underline{C}$H$_2$CHNH), 25.5 (CH=CCH$_2\underline{C}$H$_2$), 25.3 (C(=O)CH$_2$CH$_2$ $\underline{C}$H$_2$), 24.7 (CH=C$\underline{C}$H$_2$CH$_2$), 24.4 (C(=O)CH$_2\underline{C}$H$_2$)

HRMS (ESI$^+$) m/z / Da = 597.3149, $[M+H]^+$ found, $[C_{29}H_{41}N_8O_6]^+$ requires 597.3144 $[\alpha]_D^{20}$ / $°10^{-1}cm^2g^{-1}$ = -3.6 (c / g(100 mL)$^{-1}$ = 0.11 , MeOH)

0.9 6-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)-2-heptylquinolin-4(1*H*)-one 132



50 % water/*t*-BuOH (1 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 5-(4-(hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **125** (3.6 mg, 10.0 μmol, 1 eq.) and 6-azido-2-heptylquinolin-4(1*H*)-one **26** (2.8 mg, 10.0 μmol, 1 eq.). A similarly degassed solution of $CuSO_4 \cdot 5\,H_2O$ (125 μg, 0.5 μmol, 0.05 eq. 50 mM), THPTA (218 μg, 0.5 μmol, 0.05 eq. 50 mM) and sodium ascorbate (198 μg, 1 μmol, 0.1 eq., 100 mM) in water (10 μl) was then added. The mixture was stirred at r.t. under argon for 1.5 h, then evaporated under reduced pressure. The residue was purified by preparatory HPLC (5-100 % acetonitrile/water over 20 min). The combined pure fractions were evaporated under reduced pressure and then partitioned between $NaHCO_3$ (aq., sat., 10 ml) and 10 % *i*-PrOH/$CHCl_3$ (10 ml). The organic layer was dried with $MgSO_4$ and evaporated under reduced pressure. **132** was obtained as a clear gum (2.6 mg, 4.1 μmol, 41.0 %).

TLC R_f = 0.17 (20 % MeOH/CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 2927.7 (C-H), 2855.5 (C-H), 1664.1 (pyrimidine), 1645.4 (pyrimidine and HHQ C=O),

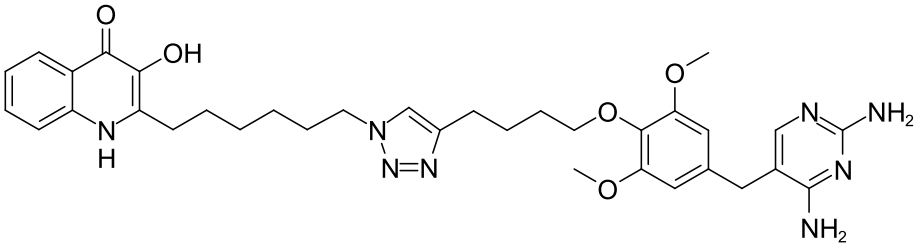
^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 11.80 (s, 1 H, NH), 8.69 (s, 1 H, NCH=CCH_2), 8.41 (d, J = 2.7 Hz, 1 H, *ortho* to C=O), 8.17 (dd, J = 9.0, 2.6 Hz, 1 H, *para* to C=O), 7.73 (d, J = 9.0 Hz, 1 H, ortho to NH), 7.51 (br s, 4 H, NH_2), 7.41 (s, 1 H, CHN=CNH_2), 6.61 (s, 2 H, *meta* to CH_2), 6.02 (d, J = 1.8 Hz, 1 H, C(=O)CH), 3.86 (t, J = 6.3 Hz, 2 H, CH_2O), 3.73 (s, 6 H, OCH_3), 3.57 - 3.62 (m, 2 H, CCH_2C), 2.78 (t, J = 7.5 Hz, 2 H, CH=CCH_2), 2.63 (t, J = 7.3 Hz, 2 H, $HNCCH_2$), 1.85 (quin, J = 7.5 Hz, 2 H, CH=CCH_2CH_2), 1.61 - 1.78 (m, 4 H, $HNCCH_2CH_2$ and CH=$CCH_2CH_2CH_2$), 1.31 - 1.40 (m, 4 H, $HNCCH_2CH_2CH_2CH_2$), 1.25 - 1.31 (m, 4 H, $CH_3CH_2CH_2$), 0.86 (t, J = 7.2 Hz, 3 H, CH_3CH_2)

check all frequencies

^{13}C NMR (125 MHz, DMSO d_6) δ / ppm = 176.4 (C=O), 164.1 ($CC(NH_2)N$), 154.3 (HNC), 154.2 ($NC(NH_2)N$), 153.1 (*ipso* to OCH_3), 148.3 (CH=CCH_2CH_2), 140.2 ($CHNC(NH_2)N$), 139.6 (*ipso* to NH), 135.4 (*ipso* to CH_2O), 132.8 (*para* to CH_2O), 132.1 (*para* to NH), 124.9 (*ipso* to C=O), 123.7 (*para* to C=O), 120.3 ($CH=CCH_2CH_2$), 120.0 (*meta* to C=O and *ortho* to NH), 115.1 (*ortho* to C=O and *meta* to NH), 109.0 ($CH_2CC(NH_2)=N$), 108.0 (C(=O)CH), 106.3 (*meta* to CH_2O), 72.0 ($CH_2CH_2CH_2O$), 56.0 (OCH_3), 33.3 ($HNCCH_2$), 32.1 (CCH_2C), 31.2 ($CH_3CH_2CH_2$), 29.1 (CH_2CH_2O), 28.3 - 28.6 ($CH_3CH_2CH_2CH_2CH_2CH_2$), 25.3 ($CH_2CH_2CH_2O$), 24.7 ($CH=CCH_2$), 22.1 (CH_3CH_2), 14.0 (CH_3CH_2)

HRMS (ESI$^+$) m/z / Da = 641.3557, $[M+H]^+$ found, $[C_{35}H_{45}N_8O_4]^+$ 641.3558

0.10 2-(6-(4-(4-(4-((2,4-Diaminopyrimidin-5-yl)methyl)-2,6-dimethoxyphenoxy)butyl)-1*H*-1,2,3-triazol-1-yl)hexyl)-3-hydroxyquinolin-4(1*H*)-one 133



50 % water/*t*-BuOH (1 ml) was degassed by bubbling N_2 through it. This was then added to a mixture of 5-(4-(hex-5-yn-1-yloxy)-3,5-dimethoxybenzyl)pyrimidine-2,4-diamine **125** (14.2 mg, 39.8 μmol, 1 eq.) and 2-(6-azidohexyl)-3-hydroxyquinolin-4(1H)-one **70** (11.4 mg, 39.8 μmol, 1 eq.). A similarly degassed solution of $CuSO_4 \cdot 5\,H_2O$ (1.25 mg, 5 μmol, 0.125 eq. 50 mM), THPTA (2.18 mg, 5 μmol, 0.125 eq. 50 mM) and sodium ascorbate (1.98 mg, 10 μmol, 0.25 eq., 100 mM) in water (100 μl) was then added. The mixture was stirred at r.t. under argon for 3 h, then MeOH (1 ml) was added and the reaction mixture was dry-loaded onto SiO_2 and purified by column chromatography (SiO_2, 0-20 % MeOH/CH_2Cl_2). The combined pure fractions were dried with $MgSO_4$ and evaporated under reduced pressure. **133** was obtained as a pale brown amorphous solid (4.7 mg, 7.3 μmol, 18.3 %).

TLC R_f = 0.21 (20 % MeOH/CH_2Cl_2)

IR (neat) ν_{max} / cm^{-1} = 2924.8 (C-H), 2853.4 (C-H), 1660.0 (pyrimidine), 1638.8 (pyrimidine and PQS C=O),

^{1}H NMR (500 MHz, DMSO d_6) δ / ppm = 11.53 (br s, 1 H, NH), 8.09 (d, J = 8.0 Hz, 1 H, *ortho* to C=O), 7.83 (s, 1 H, NCH=CCH_2), 7.48 - 7.57 (m, 3 H, *para* to C=O, *ortho* to NH and CHN=CNH_2), 7.21 (ddd, J =

8.0, 6.3, 1.5 Hz, 1 H, *para* to NH), 6.55 (s, 2 H, *meta* to CH_2), 4.28 (t, J = 7.1 Hz, 2 H, $C\underline{H}_2N$), 3.80 (t, J = 6.2 Hz, 2 H, $C\underline{H}_2O$), 3.70 (s, 6 H, $C\underline{H}_3$), 3.53 (d, J = 0.3 Hz, 2 H, $CC\underline{H}_2C$), 2.73 (t, J = 7.5 Hz, 2 H, $HNCC\underline{H}_2$), 2.64 (t, J = 7.4 Hz, 2 H, $CH{=}CC\underline{H}_2$), 1.80 (quin, J = 7.4 Hz, 2 H, $C\underline{H}_2CH_2N$), 1.73 (quin, J = 7.5 Hz, 2 H, $CH{=}CCH_2C\underline{H}_2$), 1.66 (quin, J = 7.2 Hz, 2 H, $HNCCH_2C\underline{H}_2$), 1.62 (quin, J = 6.8 Hz, 2 H, $C\underline{H}_2CH_2O$), 1.33 - 1.40 (m, 2 H, $HNCCH_2CH_2C\underline{H}_2$), 1.27 - 1.32 (m, 2 H, $HNCCH_2CH_2CH_2C\underline{H}_2$)

^{13}C NMR (125 MHz, DMSO d_6) δ / ppm = 168.9 ($\underline{C}{=}O$), 162.5 ($C\underline{C}(NH_2)N$), 162.5 ($N\underline{C}(NH_2)N$), 152.9 ($\underline{C}HNC(NH_2)N$), 152.8 (*ipso* to OCH_3), 146.8 ($CH{=}\underline{C}CH_2CH_2$), 137.7 ($\underline{C}OH$), 137.3 (*para* to OH), 135.4 ($HN\underline{C}$), 135.1 (*para* to CH_2O), 134.8 (*ipso* to CH_2O), 129.9 (*para* to C=O), 124.4 (*ortho* to C=O and *meta* to NH), 122.1 (*ipso* to C=O), 121.5 (*para* to NH), 121.4 ($\underline{C}H{=}CCH_2CH_2$), 117.7 (*meta* to C=O and *ortho* to NH), 106.2 ($CH_2\underline{C}C(NH_2){=}N$), 105.8 (*meta* to CH_2O), 71.9 ($CH_2CH_2\underline{C}H_2O$), 55.8 ($O\underline{C}H_3$), 49.0 ($\underline{C}H_2N$), 32.8 ($C\underline{C}H_2C$), 29.5 ($\underline{C}H_2CH_2N$), 29.0 ($\underline{C}H_2CH_2O$), 28.1 ($HNCCH_2CH_2\underline{C}H_2$), 27.9 ($HNC\underline{C}H_2$), 27.6 ($HNCCH_2\underline{C}H_2$), 25.6 ($\underline{C}H_2CH_2CH_2N$), 25.4 ($\underline{C}H_2CH_2CH_2O$), 24.6 ($CH{=}C\underline{C}H_2CH_2$)

HRMS (ESI$^+$) m/z / Da = 643.3365, $[M+H]^+$ found, $[C_{34}H_{43}N_8O_5]^+$ requires 643.3351