

Supporting Information

Discovery of a PCAF Bromodomain Chemical Probe

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I.I Solvents and reagents

All solvents were purchased from commercial sources and used without purification (HPLC or analytical grade). Anhydrous solvents were purchased from Acros Organics stored under a nitrogen atmosphere with activated molecular sieves. Standard vacuum line techniques were used and glassware was flame dried prior to use. Deionised water was sourced using an Elga DV 25 system. Organic solvents were dried during workup using anhydrous Na_2SO_4 .

I.II Purification and chromatography

Thin Layer Chromatography (TLC) was carried out using aluminium plates coated with 60 F_{254} silica gel. Plates were visualised using UV light (254 or 365 nm) or staining with Ninhydrin (1 M, EtOH) or 1% aq. KMnO_4 . Normal-phase silica gel chromatography was carried out using Biotage Isolera One flash column chromatography system (LPLC). Reverse-phase high pressure liquid chromatography (RP-HPLC) was performed using a Waters system equipped with a Waters 2545 Binary Gradient Module, a SecurityGuard™ ULTRA cartridges for EVO-C18 UHPLC HPLC, Kinetex 5 μM EVO C18 100 Å 100 x 3.0 mm column and a Waters SQ Detector 2 using the stated eluent system.

I.II Characterisation

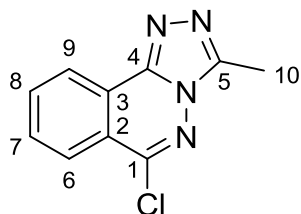
Infrared spectroscopy was carried out with a Thermo Scientific Nicolet iS5 FT-IR spectrometer fitted with an iD7-ATR accessory, selected absorption maxima (ν_{max}) recorded in wavenumbers (cm^{-1}). NMR spectra were recorded using a Bruker Avance 400 MHz spectrometer using the deuterated solvent stated. Chemical shifts (δ) quoted in parts per million (ppm) and referenced to the residual solvent peak. Multiplicities are denoted as s- singlet, d- doublet, t- triplet, q- quartet and quin- quintet and derivatives thereof (br denotes a broad resonance peak). Coupling constants recorded as Hz and round to the nearest 0.1 Hz. Two-dimensional NMR experiments (COSY, HSQC, HMBC) were used to aid the assignment of ^1H and ^{13}C spectra. Low Resolution mass spectra were recorded on a Waters SQ Detector 2 (LC-MS). High Resolution Mass Spectrometry (HRMS) was recorded using an Agilent 6530 QTOF. Melting points were obtained using a Stuart SMP40 apparatus and are reported uncorrected in $^{\circ}\text{C}$. Optical rotations were recorded using a Perkin Elmer 341 polarimeter; absolute optical rotations are quoted as $[\alpha]_{\text{D}}^T$ at 23 $^{\circ}\text{C}$, concentration (c) is reported as g/100 mL. Enantiomeric excesses were determined by HPLC analysis on an Agilent 1200 series instrument using chiral stationary phase columns. The same instrument was used in the separation of enantiomers using the stated semipreparative chiral stationary phase column. Compound names were generated using ChemBioDraw Ultra v14 systematic naming. Atom numbering in structures is purely for the purposes of assignment and does not reflect IUPAC numbering conventions.

II.

Practical Experimental

II.I Synthetic Procedures

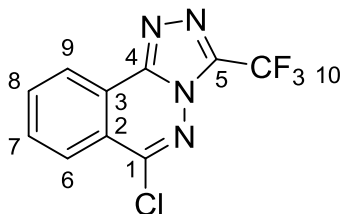
6-chloro-3-methyl-[1,2,4]triazolo[3,4-a]phthalazine (5)



To a stirred solution of 1,4-dichlorophthalazine (18.4 g, 92 mmol, 1 eq) in DMF (anhydrous) (95 mL, 0.97 M) was added acetohydrazide (12.84 g, 139 mmol, 1.5 eq). The solution was stirred at 120 °C with a reflux condenser attached for 24 h after which TLC/LCMS analysis confirmed consumption of the starting material. The reaction mixture was cooled to 4 °C for 2 h after which an off white precipitate had formed. The precipitate was filtered off, washed with EA and dried under vacuum to afford **5** (12.478 g, 57.1 mmol, 61.7%) as an off white solid.

Mpt: 142.0-144.0 °C; ν_{\max} (cm^{-1}) 3401, 3000, 2870, 1659, 1256, 1003, 767; **$^1\text{H-NMR}$ (400MHz, CDCl_3):** δ_{H} 8.69 (d, J = 7.8 Hz, 1H, H -6), 8.27 (d, J = 8.1 Hz, 1H, H -9), 8.01 (t, J = 8.1, 1H, H -8), 7.87 (t, J = 7.8, 1H, H -7); **$^{13}\text{C-NMR}$ (100 MHz CDCl_3):** δ_{C} 149.8 (C-1), 147.8 (C-4), 142.3 (C-5), 134.8 (C-8), 131.2 (C-7), 127.5 (C-6), 124.1 (C-2), 123.6 (C-6), 122.0 (C-3), 9.8 (C-10); **LR-ESI-MS:** $\text{C}_{10}\text{H}_8\text{ClN}_4$ $[\text{M}+\text{H}]^+$ m/z found 219.27, calcd 219.04; **HR-ESI-MS:** $\text{C}_{10}\text{H}_8\text{ClN}_4$ $[\text{M}+\text{H}]^+$ m/z found 219.0467, calcd 219.0437.

6-chloro-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-a]phthalazine (6)



79 (860 mg, 4.42 mmol, 1 eq) was dissolved in TFA (2 mL, 26.5 mmol, 6 eq) at room temperature and stirred at 100 °C under an inert atmosphere (N_2) for 2 h. The reaction mixture was then cooled and concentrated to dryness to give a crude pink solid. The crude material was then dissolved in EA and washed with NaHCO_3 sat. solution (x 3). The organic layer was then washed with brine and dried over Na_2SO_4 before being concentrated and purified by Isolera Biotage LPLC (DCM/MeOH 90:10) to give **6** (519 mg, 1.903 mmol, 43%) as an off white crystalline solid.

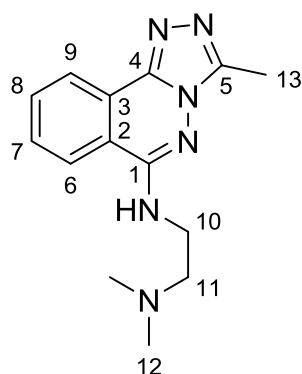
Mpt: 170.7-172.7 °C; ν_{\max} (cm^{-1}) 1498, 1448, 1123, 1018, 962, 774, 643, 504; **$^{19}\text{F-NMR}$ (376 MHz, CDCl_3):** δ_{F} -63.55; **$^1\text{H-NMR}$ (400MHz, CDCl_3):** δ_{H} 8.79 (dd, 1H, J = 7.9, 0.5 Hz, H -9), 8.37 (d, 1H, J = 8.3 Hz, H -6), 7.83 (td, 1H, J = 7.7, 1.1 Hz, H -8), 8.01 (m, 1H, H -7); **$^{13}\text{C-NMR}$ (100MHz CDCl_3):** δ_{C} 152.3 (C-1), 144.3 (C-4), 140.2 (q, J = 42.5 Hz, C-5), 135.5 (C-8), 132.6 (C-7), 127.8 (C-9), 124.2 (C-3), 123.0 (C-6), 122.6 (C-2), 117.6 (q, J = 271.4 Hz, C-10); **LR-ESI-MS:** $\text{C}_{10}\text{H}_5\text{F}_3\text{N}_4$ $[\text{M}+\text{H}]^+$ m/z found 272.9, calcd 273.0; **HR-ESI-MS:** $\text{C}_{10}\text{H}_5\text{F}_3\text{N}_4$ $[\text{M}+\text{H}]^+$ m/z found 273.0172, calcd 273.0155.

General Procedure A

To a stirred solution of **5** (1 eq) in EtOH (0.46 M, anhydrous) was added amine (2 eq), KI (0.1 eq) and conc. HCl (0.05 eq). The reaction mixture was then stirred at reflux for 72 h before being cooled to 4 °C at which point any precipitate formed was filtered off and washed with EA/ H_2O before drying to give the desired product. In the absence of precipitated product, the reaction mixture was

concentrated to dryness and purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to furnish the desired compound.

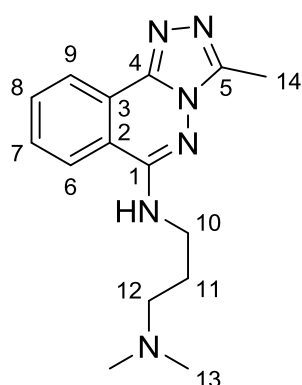
***N*₁,*N*₁-dimethyl-*N*₂-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)ethane-1,2-diamine (7)**



5 (100 mg, 0.457 mmol, 1 eq) and *N*₁,*N*₁-dimethylethane-1,2-diamine (81 mg, 0.915 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **7** (52 mg, 0.192 mmol 41.9%) as a white solid.

Mpt: 225.9-227.9 °C; **v_{max} (cm⁻¹)** 3227, 1566, 1519, 702; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_{H} 8.34 (dd, 1H, *J* = 7.9, 0.9 Hz, *H*-9), 8.25 (d, 1H, *J* = 8.2 Hz, *H*-6), 7.88 (m, 1H, *H*-8), 7.78 (m, 1H, *H*-7), 7.50 (m, 1H, NH), 3.50 (m, 2H, *H*-10), 2.57 (t, 2H, *J* = 6.9 Hz, *H*-11), 2.54 (s, 3H, *H*-13), 2.22 (s, 6H, *H*-12); **¹³C-NMR (100 MHz, DMSO-*d*⁶):** δ_{C} 151.1 (*C*-1), 145.9 (*C*-4), 141.1 (*C*-5), 132.8 (*C*-8), 130.1 (*C*-7), 124.1 (*C*-9), 123.3 (*C*-3), 122.5 (*C*-6), 118.2 (*C*-2), 57.0 (*C*-10), 45.3 (*C*-11; *C*-12), 9.3 (*C*-13); **LR-ESI-MS:** C₁₄H₁₉N₆ [M+H]⁺ *m/z* found 271.4, calcd 271.2; **HR-ESI-MS:** C₁₄H₁₉N₆ [M+H]⁺ *m/z* found 271.1682, calcd 271.1671.

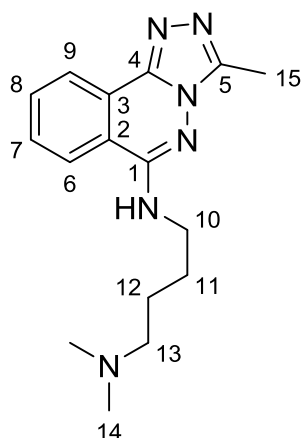
***N*₁,*N*₁-dimethyl-*N*₃-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)propane-1,3-diamine (8)**



5 (200 mg, 0.915 mmol, 1 eq) and *N*₁,*N*₁-dimethylpropane-1,3-diamine (187 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **8** (174 mg, 0.613 mmol 67%) as a white solid.

Mpt: 118.5-120.5 °C; **v_{max} (cm⁻¹)** 3229, 2777, 1565, 1513, 1369, 1266, 1160, 783; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_{H} 8.35 (dd, 1H, *J* = 7.9, 0.9 Hz, *H*-9), 8.23 (d, 1H, *J* = 8.1 Hz, *H*-6), 7.89 (m, 1H, *H*-8), 7.79 (td, 1H, *J* = 7.7, 1.3 Hz, *H*-7), 7.73 (m, 1H, NH), 3.43 (m, 2H, *H*-10), 2.54 (s, 3H, *H*-14), 2.34 (t, 2H, *H*-12), 2.17 (s, 6H, *H*-13), 1.84 (m, 2H, *H*-11); **¹³C-NMR (100 MHz, DMSO-*d*⁶):** δ_{C} 151.2 (*C*-1), 145.9 (*C*-4), 141.1 (*C*-5), 132.7 (*C*-8), 130.1 (*C*-7), 124.0 (*C*-9), 123.3 (*C*-3), 122.4 (*C*-6), 118.3 (*C*-2), 57.3 (*C*-10), 45.2 (*C*-12; *C*-13), 25.6 (*C*-11), 9.3 (*C*-14); **LR-ESI-MS:** C₁₅H₂₁N₆ [M+H]⁺ *m/z* found 285.2, calcd 285.2; **HR-ESI-MS:** C₁₅H₂₁N₆ [M+H]⁺ *m/z* found 285.1845, calcd 285.1828.

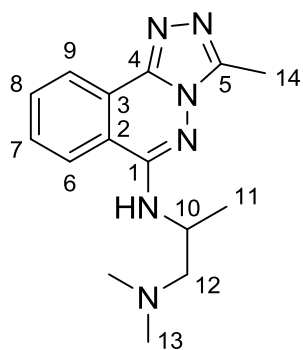
***N*₁,*N*₁-dimethyl-*N*₄-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)butane-1,4-diamine (9)**



5 (200 mg, 0.915 mmol, 1 eq) and *N*₁,*N*₁-dimethylbutane-1,4-diamine (213 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **9** (225 mg, 0.755 mmol 83%) as a white waxy solid.

Mpt: 158.3-160.3 °C; **v_{max} (cm⁻¹)** 3261, 2865, 1591, 1512, 1476, 654; **¹H-NMR (400MHz, DMSO-*d*⁶)**: δ_{H} 8.35 (dd, *J* = 7.9, 0.9 Hz, 1H, *H*-9), 8.30 (d, *J* = 8 Hz, 1H, *H*-6), 7.89 (m, 1H *H*-8), 7.79 (td, *J* = 7.9, 1.3 Hz, 1H *H*-7), 7.61 (t, *J* = 5.2 Hz, 1H, NH) 3.41 (m, 2H, *H*-10), 2.55 (s, 3H, *H*-15), 2.26 (m, 2H, *H*-13), 2.12 (s, 6H, *H*-14), 1.71 (quin, *J* = 7.3 Hz, 2H, *H*-11), 1.51 (quin, *J* = 7.3 Hz, 2H, *H*-12); **¹³C-NMR (100 MHz DMSO-*d*⁶)**: δ_{C} 151.2 (C-1), 145.9 (C-4), 141.1 (C-5), 132.7 (C-8), 130.1 (C-7), 124.2 (C-9), 123.3 (C-3), 122.4 (C-6), 118.3 (C-2), 58.7 (C-13), 45.0 (C-14), 41.2 (C-10), 25.7 (C-11), 24.7 (C-12), 9.3 (C-15); **LR-ESI-MS**: C₁₆H₂₃N₆ [M+H]⁺ *m/z* found 299.3, calcd 299.2; **HR-ESI-MS**: C₁₆H₂₃N₆ [M+H]⁺ *m/z* found 299.2011, calcd 299.1984.

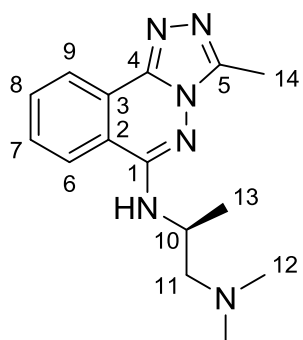
***N*₁,*N*₁-dimethyl-*N*₂-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)propane-1,2-diamine (11)**



5 (200 mg, 0.915 mmol, 1 eq) and *N*₁,*N*₁-dimethylpropane-1,2-diamine (187 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **11** (72 mg, 0.254 mmol 27.8%) as a white solid.

Mpt: 142.3-144.3 °C; **v_{max} (cm⁻¹)** 3247, 2773, 1509, 1454, 1033, 699; **¹H-NMR (400MHz, DMSO-*d*⁶)**: δ_{H} 8.37 (d, 2H, *J* = 8.3 Hz, *H*-6; *H*-9), 7.91 (m, 1H, *H*-8), 7.81 (m, 1H, *H*-7), 7.18 (d, 1H, *J* = 7.5 Hz, NH), 4.28 (m, 1H, *H*-10), 2.58 (m, 1H, *H*-12''), 2.56 (s, 3H, *H*-14), 2.27 (m, 1H, *H*-12'), 2.23 (s, 6H, *H*-13), 1.3 (d, 3H, *J* = 6.5 Hz, *H*-11); **¹³C-NMR (100 MHz, DMSO-*d*⁶)**: δ_{C} 150.6 (C-1), 145.9 (C-4), 141.0 (C-5), 132.8 (C-8), 130.0 (C-7), 124.3 (C-9), 123.4 (C-3), 122.4 (C-6), 118.2 (C-2), 64.0 (C-10), 45.6 (C-13), 44.8 (C-12), 18.4 (C-11), 9.3 (C-14); **LR-ESI-MS**: C₁₅H₂₁N₆ [M+H]⁺ *m/z* found 285.2, calcd 285.2; **HR-ESI-MS**: C₁₅H₂₁N₆ [M+H]⁺ *m/z* found 285.1850, calcd 285.1828.

(*S*)-*N*₁,*N*₁-dimethyl-*N*₂-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)propane-1,2-diamine ((*S*)-11)

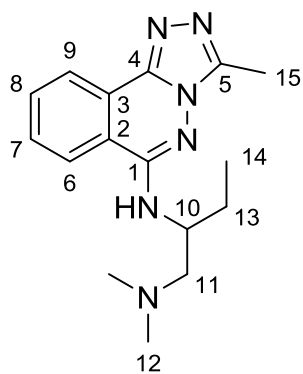


5 (300 mg, 1.372 mmol, 1 eq) and (*S*)-*N*₁,*N*₁-dimethylpropane-1,2-diamine (280 mg, 2.74 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give (***S***)-**11** (86 mg, 0.303 mmol 22.1%) as a white solid.

Mpt: 147.4-149.4 °C; **v_{max} (cm⁻¹)** 3293, 2974, 2951, 2772, 1690, 1407, 1463, 1032, 700; **¹H-NMR (400MHz, DMSO-*d*⁶)**: δ_{H} 8.37 (d, *J* = 8.3 Hz, 2H, *H*-9; *H*-6), 7.91 (m, 1H, *H*-8), 7.81 (m, 1H, *H*-7), 7.17 (d, *J* = 7.3 Hz, NH), 4.27 (spt, *J* = 6.8 Hz, 1H, *H*-10), 2.56 (m, 1H, *H*-11''), 2.55 (s, 3H, *H*-14), 2.27 (m, 1H, *H*-11'), 2.22 (s, 6H, *H*-12), 1.3 (d, *J* = 6.5 Hz, 3H, *H*-13); **¹³C-NMR (100 MHz DMSO-*d*⁶)**: δ_{C} 150.6 (C-1), 145.9 (C-4), 141.0

(C-5), 132.8 (C-8), 130.0 (C-7), 124.3 (C-9), 123.4 (C-3), 122.5 (C-6), 118.2 (C-2), 64.1 (C-11), 45.6 (C-10), 44.8 (C-12), 18.5 (C-13), 9.3 (C-14); **LR-ESI-MS**: $C_{15}H_{21}N_6$ $[M+H]^+$ m/z found 285.3, calcd 285.2; **HR-ESI-MS**: $C_{15}H_{21}N_6$ $[M+H]^+$ m/z found 285.1829, calcd 285.1828.

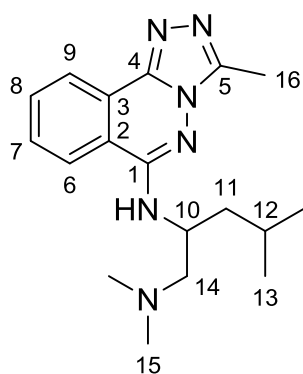
***N*₁,*N*₁-dimethyl-*N*₂-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)butane-1,2-diamine (12)**



5 (400 mg, 1.829 mmol, 1 eq) and *N*₁,*N*₁-dimethylbutane-1,2-diamine (425 mg, 3.66 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **12** (185 mg, 0.621 mmol 33.9%) as a white solid.

Mpt: 153.5-155.5 °C; ν_{\max} (cm⁻¹) 3246, 2928, 2756, 1599, 1458, 1391, 1190; **¹H-NMR (400MHz, DMSO-*d*⁶)**: δ_H 8.43 (d, J = 8.2 Hz, 1H, *H*-9), 8.37 (d, J = 7.8 Hz, 1H, *H*-6), 7.92 (m, 1H, *H*-8), 7.81 (m, 1H, *H*-7), 7.11 (d, J = 7.8 Hz, 1H, NH), 4.14 (m, 1H, *H*-10), 2.55 (m, 1H, *H*-11''), 2.54 (s, 3H, *H*-15), 2.30 (m, 1H, *H*-11'), 2.22 (s, 6H, *H*-12), 1.81 (m, 1H, *H*-13''), 1.62 (m, 1H, *H*-13'), 0.94 (m, 3H, *H*-14); **¹³C-NMR (100 MHz, DMSO-*d*⁶)**: δ_C 151.2 (C-1), 145.9 (C-4), 141.0 (C-5), 132.7 (C-8), 130.0 (C-7), 124.3 (C-9), 123.3 (C-3), 122.5 (C-6), 118.3 (C-2), 62.7 (C-11), 50.6 (C-10), 45.7 (C-12), 25.1 (C-13), 10.8 (C-14), 9.3 (C-15); **LR-ESI-MS**: $C_{16}H_{23}N_6$ $[M+H]^+$ m/z found 299.2, calcd 299.2; **HR-ESI-MS**: $C_{16}H_{23}N_6$ $[M+H]^+$ m/z found 299.2001, calcd 299.1984.

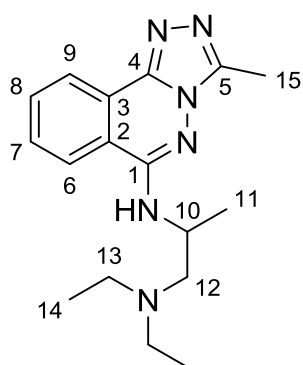
***N*₁,*N*₁-4-trimethyl-*N*₂-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)pentane-1,2-diamine (13)**



5 (300 mg, 1.372 mmol, 1 eq) and *N*₁,*N*₁,4-trimethylpentane-1,2-diamine (297 mg, 2.06 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **13** (183 mg, 0.561 mmol 40.9%) as a white solid.

Mpt: 172.4-174.4 °C; ν_{\max} (cm⁻¹) 3242, 2951, 2758, 1457, 1394, 1166, 1026; **¹H-NMR (400MHz, CDCl₃)**: δ_H 8.55 (dd, J = 7.9, 0.7 Hz, 1H, *H*-9), 7.85 (d, J = 8.2 Hz, 1H, *H*-6), 7.80 (m, 1H, *H*-8), 7.68 (m, 1H, *H*-7), 5.97 (d, J = 4.3 Hz, 1H, NH), 4.17 (m, 1H, *H*-10), 2.69 (s, 3H, *H*-16), 2.66 (m, 1H, *H*-14''), 2.51 (m, 1H, *H*-14'), 2.33 (s, 6H, *H*-15), 1.84 (m, 2H, *H*-11''; *H*-12), 1.40 (m, 1H, *H*-11'), 1.04 (d, J = 6.4 Hz, 3H, *H*-13''), 0.97 (d, J = 6.5 Hz, 3H, *H*-13'); **¹³C-NMR (100 MHz CDCl₃)**: δ_C 151.1 (C-1), 147.2 (C-4), 142.0 (C-5), 132.4 (C-8), 129.9 (C-7), 124.2 (C-9), 123.6 (C-3), 122.7 (C-6), 118.8 (C-2), 62.9 (C-14), 47.5 (C-10), 45.6 (C-15), 42.6 (C-11), 25.1 (C-12), 23.3 (C-13''), 22.6 (C-13'), 9.9 (C-16); **LR-ESI-MS**: $C_{18}H_{27}N_6$ $[M+H]^+$ m/z found 327.4, calcd 327.2; **HR-ESI-MS**: $C_{18}H_{27}N_6$ $[M+H]^+$ m/z found 327.2319, calcd 327.2297.

***N*₁,*N*₁-diethyl-*N*₂-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)propane-1,2-diamine (**14**)**

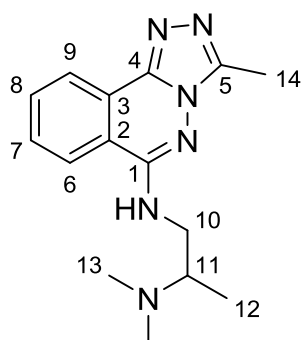


5 (400 mg, 1.829 mmol, 1 eq) and *N*₁,*N*₁-diethylpropane-1,2-diamine (477 mg, 0.571 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **14** (178 mg, 0.571 mmol 31.2%) as a white solid.

Mpt: 167.9-169.9 °C; **v**_{max} (cm⁻¹) 3243, 3070, 2965, 2930, 1592, 1293, 699; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_H 8.36 (m, 2H, *H*-6; *H*-9), 7.90 (m, 1H, *H*-8), 7.81 (m, 1H, *H*-7), 7.15 (s, 1H, NH), 4.21 (m, 1H, *H*-10), 2.63 (m, 5H, *H*-12''; *H*-13), 2.54 (s, 3H, *H*-15), 2.38 (m, 1H, *H*-12'), 1.32 (d, 3H, *J*= 6.5

Hz, *H*-11), 0.97 (s, 6H, *H*-14); **¹³C-NMR (100 MHz, DMSO-*d*⁶):** δ_C 150.7 (C-1), 145.9 (C-4), 141.0 (C-5), 132.7 (C-8), 130.0 (C-7), 124.3 (C-9), 123.4 (C-3), 122.4 (C-6), 118.3 (C-2), 57.7 (C-10), 47.2 (C-13), 45.5 (C-12), 18.3 (C-11), 12.0 (C-14), 9.3 (C-15); **LR-ESI-MS:** C₁₇H₂₅N₆ [M+H]⁺ *m/z* found 313.3, cald 313.2; **HR-ESI-MS:** C₁₇H₂₅N₆ [M+H]⁺ *m/z* found 313.2164, cald 313.2141.

***N*₂,*N*₂-dimethyl-*N*₁-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)propane-1,2-diamine (**15**)**

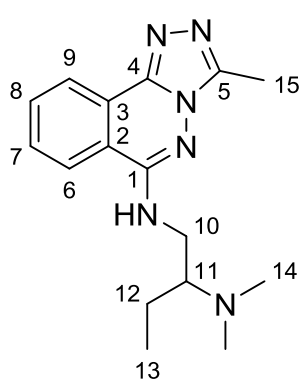


5 (200 mg, 0.915 mmol, 1 eq) and *N*₂,*N*₂-dimethylpropane-1,2-diamine (187 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **15** (45 mg, 0.159 mmol 17.3%) as a white solid.

Mpt: 227.1-229.1 °C; **v**_{max} (cm⁻¹) 3237, 3084, 2962, 1595, 1514, 770, 697; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_H 8.36 (d, 1H, *J*= 7.8 Hz, *H*-9), 8.29 (d, 1H, *J*= 8.1 Hz, *H*-6), 7.91 (m, 1H, *H*-8), 7.81 (m, 1H, *H*-7), 7.48 (t, 1H, *J*= 4.8 Hz,

NH), 3.56 (dd, 1H, *J*= 12.9, 6.3 Hz, *H*-10''), 3.23 (dt, 1H, *J*= 13.1, 6.4 Hz, *H*-10'), 3.02 (m, 1H, *H*-11), 2.55 (s, 3H, *H*-14), 2.26 (s, 6H, *H*-12), 1.00 (d, 1H, *J*= 6.6 Hz, *H*-12); **¹³C-NMR (100 MHz, DMSO-*d*⁶):** δ_C 151.1 (C-1), 146.0 (C-4), 141.0 (C-5), 132.8 (C-8), 130.2 (C-7), 124.1 (C-9), 123.3 (C-3), 122.5 (C-6), 118.2 (C-2), 56.6 (C-11), 43.9 (C-10), 40.4 (C-13), 12.3 (C-12), 9.3 (C-14); **LR-ESI-MS:** C₁₅H₂₁N₆ [M+H]⁺ *m/z* found 285.2, cald 285.2; **HR-ESI-MS:** C₁₅H₂₁N₆ [M+H]⁺ *m/z* found 285.1841, cald 285.1828.

***N*₂,*N*₂-dimethyl-*N*₁-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)butane-1,2-diamine (**16**)**

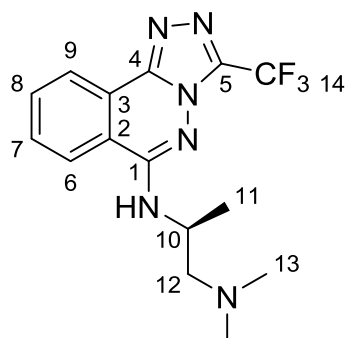


5 (200 mg, 0.915 mmol, 1 eq) and *N*₂,*N*₂-dimethylbutane-1,2-diamine (213 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **16** (36 mg, 0.122 mmol 13.3%) as a white solid.

Mpt: 211.5-213.5 °C; **v**_{max} (cm⁻¹) 3227, 2927, 2776, 1510, 1451, 994, 698; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_H 8.37 (dd, 1H, *J*= 7.9, 0.9 Hz, *H*-9), 8.30 (d, 1H, *J*= 8.2 Hz, *H*-6), 7.91 (m, 1H, *H*-8), 7.81 (m, 1H, *H*-7), 7.52 (m, 1H, NH), 3.57 (m, 1H, *H*-11), 3.29 (m, 1H, *H*-10''), 2.82 (m, 1H, *H*-10'), 2.55 (s,

3H, *H*-15), 2.31 (s, 6H, *H*-14), 1.45 (m, 2H, *H*-12), 0.94 (t, 3H, *J* = 7.4 Hz, *H*-13); ¹³C-NMR (100 MHz, DMSO-*d*⁶): δ_c 150.9 (C-1), 145.9 (C-4), 141.1 (C-5), 132.8 (C-8), 130.2 (C-7), 124.1 (C-9), 123.3 (C-3), 122.5 (C-6), 118.3 (C-2), 62.7 (C-11), 40.5 (C-10), 40.2 (C-14), 20.9 (C-12), 11.5 (C-13), 9.3 (C-15); LR-ESI-MS: C₁₆H₂₃N₆ [M+H]⁺ *m/z* found 299.4, calcd 299.2; HR-ESI-MS: C₁₆H₂₃N₆ [M+H]⁺ *m/z* found 299.1990, calcd 299.1984.

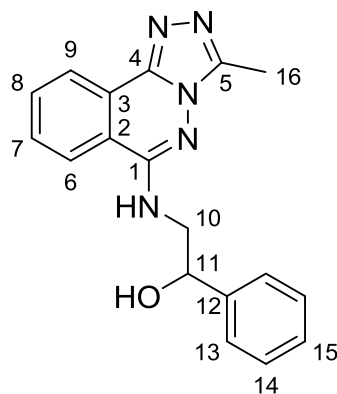
(*S*)-*N*₁,*N*₁-dimethyl-*N*2-(3-(trifluoromethyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)propane-1,2-diamine ((*S*)-17)



79 (85 mg, 0.312 mmol, 1 eq) and (*S*)-*N*₁,*N*₁-dimethylpropane-1,2-diamine (48 mg, 0.468 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give (**S**)-**17** (67 mg, 0.199 mmol, 64%) as a white solid.

Mpt: 129.5-131.5 °C; *v*_{max} (cm⁻¹) 3272, 2978, 1501, 1420, 1218, 1033, 979, 720; ¹⁹F-NMR (376 MHz, CDCl₃): δ_F -64.17; ¹H-NMR (400MHz, CDCl₃): δ_H 8.49 (dd, 1H, *J* = 8.1, 1 Hz, *H*-9), 7.90 (m, 2H, *H*-6; *H*-8), 7.82 (m, 1H, *H*-7), 6.52 (br-s, 1H, NH), 4.01 (m, 1H, *H*-10), 2.68 (m, 1H, *H*-12''), 2.42 (dd, 1H, *J* = 12.3, 4.9 Hz, *H*-12'), 2.33 (s, 6H, *H*-13), 1.41 (d, 3H, *J* = 6.1 Hz, *H*-11); ¹³C-NMR (100MHz CDCl₃): δ_c 152.2 (C-1), 143.9 (C-4), 139.9 (q, *J* = 40.3 Hz, C-5), 132.9 (C-8), 131.3 (C-7), 124.3 (C-9), 123.1 (C-3), 122.9 (C-6), 119.2 (C-2), 118.6 (q, *J* = 270.0 Hz, C-14), 63.9 (C-10), 45.3 (C-13), 45.2 (C-12), 18.1 (C-11); LR-ESI-MS: C₁₅H₁₈F₃N₆ [M+H]⁺ *m/z* found 339.1, calcd 339.2; HR-ESI-MS: C₁₅H₁₈F₃N₆ [M+H]⁺ *m/z* found 339.1553, calcd 339.1545.

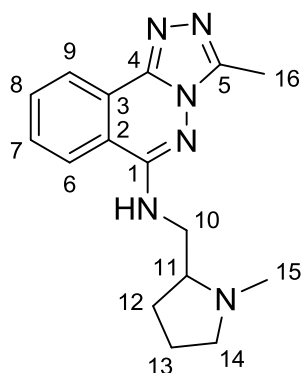
2-((3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)amino)-1-phenylethan-1-ol (96**)**



5 (10 g, 45.7 mmol, 1 eq) and 2-amino-1-phenylethan-1-ol (12.55 g, 91 mmol, 2 eq) were reacted according to general procedure **A**. After cooling to 4 °C a precipitate had formed which was washed according to **A** to give **96** as a white solid (9.6585 g, 30.2 mmol 66.1%).

Mpt: 172.1-174.1 °C; *v*_{max} (cm⁻¹) 3309, 3061, 1515, 1265, 1052, 759, 699, 558; ¹H-NMR (400MHz, DMSO-*d*⁶): δ_H 8.37 (m, 2H, *H*-6; *H*-9), 7.92 (m, 1H, *H*-8), 7.84 (m, 2H, *H*-7; NH), 7.46 (d, *J* = 7.3 Hz, 2H, *H*-13), 7.35 (m, 2H, *H*-14), 7.25 (m, 1H, *H*-15), 5.55 (d, *J* = 4.3 Hz, 1H, OH), 5.12 (dt, *J* = 8.2, 4, 4 Hz, 1H,

3-methyl-*N*-((1-methylpyrrolidin-2-yl)methyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-amine (97)



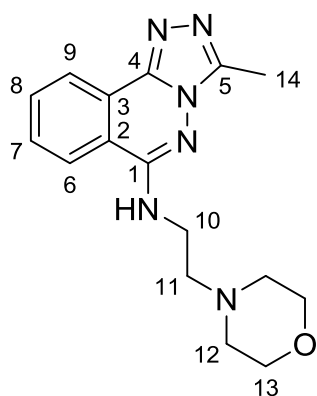
5 (200 mg, 0.915 mmol, 1 eq) and (1-methylpyrrolidin-2-yl)methanamine (209 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **97** (221 mg, 0.746 mmol 82%) as an off white powder.

Mpt: 248.6-250.6 °C; ν_{\max} (cm⁻¹) 3223, 3078, 2964, 2934, 2768, 1452, 698;

¹H-NMR (400MHz, DMSO-*d*⁶): δ_{H} 8.34 (m, 2H, *H*-9; *H*-6), 7.92 (t, *J* = 7.2 Hz, 1H, *H*-8), 7.82 (t, *J* = 7.2 Hz, 1H, *H*-7), 7.63 (s, 1H, NH), 3.68 (m, 1H, *H*-10'), 3.23 (m, 1H, *H*-10''), 3.17 (m, 1H, *H*-11), 2.98 (m, 2H, *H*-14), 2.56 (s, 3H, *H*-16), 2.41 (m, 3H, *H*-15), 2.16 (m, 1H, *H*-13'), 1.92 (m, 1H, *H*-12'), 1.66 (m, 2H, *H*-12''; *H*-13'');

¹³C-NMR (100 MHz DMSO-*d*⁶): δ_{C} 151.2 (*C*-1), 145.9 (*C*-4), 141.1 (*C*-5), 132.8 (*C*-8), 130.2 (*C*-7), 124.1 (*C*-9), 123.3 (*C*-3), 122.5 (*C*-6), 118.2 (*C*-2), 63.1 (*C*-10), 56.9 (*C*-11), 45.1 (*C*-14), 40.9 (*C*-15), 29.6 (*C*-12), 22.4 (*C*-13), 9.3 (*C*-16); **LR-ESI-MS:** C₁₆H₂₁N₆ [M+H]⁺ *m/z* found 297.4, calcd 297.2; **HR-ESI-MS:** C₁₆H₂₁N₆ [M+H]⁺ *m/z* found 297.1852, calcd 297.1828.

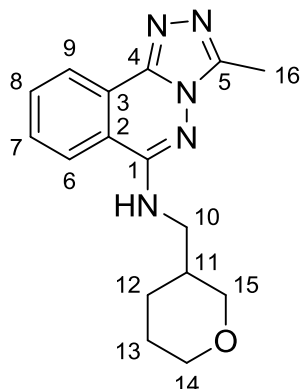
3-methyl-*N*-(2-morpholinoethyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-amine (98)



5 (200 mg, 0.915 mmol, 1 eq) and 2-morpholinoethan-1-amine (238 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. After cooling to 4 °C a precipitate had formed which was washed according to **A** to give **98** (58 mg, 0.185 mmol, 20.3%) as an off white powder.

Mpt: 169.7-171.7 °C; ν_{\max} (cm⁻¹) 3219, 3071, 2946, 1594, 1552, 1112, 771; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_{H} 8.36 (d, *J* = 8.6 Hz, 1H, *H*-9), 8.26 (d, *J* = 8.1 Hz, 1H, *H*-6), 7.90 (t, *J* = 7.2 Hz, 1H, *H*-8), 7.80 (m, 1H, *H*-7), 7.56 (t, *J* = 5.3 Hz, 1H, NH), 3.58 (m, 6H, *H*-10; *H*-13), 2.64 (t, *J* = 7 Hz, 2H, *H*-11), 2.55 (s, 3H, *H*-14), 2.48 (m, 4H, *H*-12); **¹³C-NMR (100 MHz DMSO-*d*⁶):** δ_{C} 151.1 (*C*-1), 146.0 (*C*-4), 141.1 (*C*-5), 132.8 (*C*-8), 130.2 (*C*-7), 124.1 (*C*-9), 123.3 (*C*-3), 122.5 (*C*-6), 118.2 (*C*-2), 66.3 (*C*-13), 56.3 (*C*-12), 53.4 (*C*-11), 38.4 (*C*-10), 9.3 (*C*-14); **LR-ESI-MS:** C₁₆H₂₁N₆O [M+H]⁺ *m/z* found 313.4, calcd 313.2; **HR-ESI-MS:** C₁₆H₂₁N₆O [M+H]⁺ *m/z* found 313.1812, calcd 313.1777.

3-methyl-*N*-((tetrahydro-2H-pyran-3-yl)methyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-amine (99)

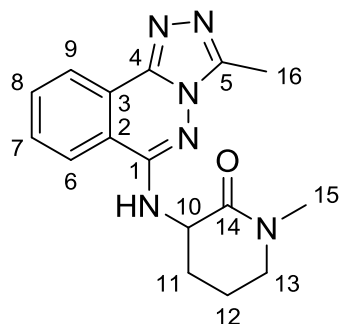


5 (100 mg, 0.457 mmol, 1 eq) and (tetrahydro-2H-pyran-3-yl)methanamine (105 mg, 0.915 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **99** (41 mg, 0.138 mmol 30.1%) as an off white powder.

Mpt: 156.6-158.6 °C; ν_{\max} (cm⁻¹) 3250, 3923, 2849, 1567, 1483, 770; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_{H} 8.35 (t, *J* = 8.6 Hz, 2H, *H*-6; *H*-9), 7.9 (m, 1H,

H-8), 7.8 (m, 1H, *H*-7), 7.6 (t, *J* = 5.3 Hz, 1H, *NH*), 3.87 (m, 1H, *H*-15''), 3.72 (m, 1H, *H*-15'), 3.33 (m, 1H, *H*-14''), 3.21 (m, 1H, *H*-14'), 2.55 (s, 3H, *H*-16), 2.09 (m, 1H, *H*-13''), 1.84 (m, 1H, *H*-13'), 1.61 (m, 1H, *H*-12''), 1.49 (m, 1H, *H*-12'), 1.33 (m, 1H, *H*-11); ¹³C-NMR (100 MHz DMSO-*d*⁶): δ_c 151.3 (C-1), 146.0 (C-4), 141.1 (C-5), 132.7 (C-8), 130.1 (C-7), 124.2 (C-9), 123.3 (C-3), 122.4 (C-6), 118.2 (C-2), 70.9 (C-15), 67.5 (C-14), 54.9 (C-10), 34.8 (C-11), 27.4 (C-12), 24.9 (C-13), 9.3 (C-16); LR-ESI-MS: C₁₉H₂₀N₂O [M+H]⁺ *m/z* found 298.4, calcd 298.2; HR-ESI-MS: C₁₉H₂₀N₂O [M+H]⁺ *m/z* found 298.1703, calcd 298.1668.

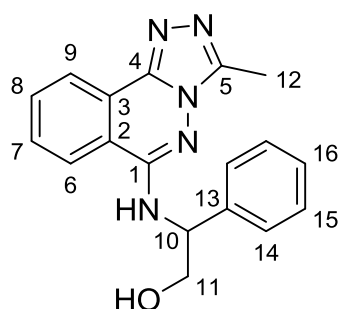
1-methyl-3-((3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)amino)piperidin-2-one (50)



5 (100 mg, 0.457 mmol, 1 eq) and 3-amino-1-methylpiperidin-2-one (117 mg, 0.915 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **50** (53 mg, 0.172 mmol 37.5%) as a white solid.

Mpt: 229.5–231.5 °C; **v**_{max} (cm⁻¹) 3259, 3077, 2941, 1595, 1504, 1270, 658; ¹H-NMR (400MHz, DMSO-*d*⁶): δ_H 8.34 (d, *J* = 7.2 Hz, 1H, *H*-6), 8.28 (d, *J* = 8.2 Hz, 1H, *H*-9), 7.99 (d, *J* = 7.3 Hz, 1H, *NH*), 7.87 (t, *J* = 7.6 Hz, 1H, *H*-8), 7.76 (m, 1H, *H*-7), 4.36 (dt, *J* = 11.2, 6.6 Hz, 1H, *H*-10), 3.43 (m, 1H, *H*-13''), 3.37 (s, 3H, *H*-15), 3.35 (m, 1H, *H*-13'), 2.89 (s, 3H, *H*-16), 2.22 (m, 1H, *H*-12''), 2.09 (m, 1H, *H*-12'), 1.92 (m, 2H, *H*-11); ¹³C-NMR (100 MHz DMSO-*d*⁶): δ_c 168.4 (C-14), 150.3 (C-1), 145.8 (C-4), 141.0 (C-5), 132.8 (C-8), 130.1 (C-7), 124.2 (C-9), 123.3 (C-3), 122.4 (C-6), 118.2 (C-2), 51.8 (C-10), 49.5 (C-15), 34.4 (C-13), 26.5 (C-11), 21.3 (C-12), 9.3 (C-16); LR-ESI-MS: C₁₆H₁₉N₆O [M+H]⁺ *m/z* found 311.4, calcd 311.2; HR-ESI-MS: C₁₆H₁₉N₆O [M+H]⁺ *m/z* found 311.1663, calcd 311.1620.

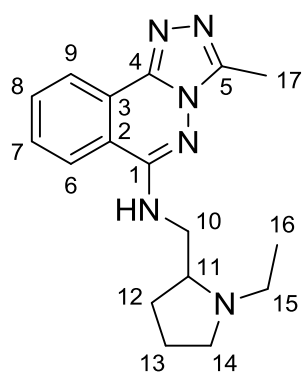
2-((3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)amino)-2-phenylethan-1-ol (51)



5 (100 mg, 0.457 mmol, 1 eq) and 2-amino-2-phenylethan-1-ol (125 mg, 0.915 mmol, 2 eq) were reacted according to general procedure **A**. After cooling to 4 °C a precipitate had formed which was washed according to **A** to give **51** (43 mg, 0.133 mmol, 29%).

Mpt: 171.3–173.3 °C; **v**_{max} (cm⁻¹) 3215, 2924, 1544, 1474, 1036, 760, 773; ¹H-NMR (400MHz, DMSO-*d*⁶): δ_H 8.56 (d, *J* = 7.9 Hz, 1H, *H*-6), 8.36 (d, *J* = 8.9 Hz, 1H, *H*-9), 7.88 (m, 3H, *NH*; *H*-8 & *H*-7), 7.49 (d, *J* = 7.2 Hz, 2H, *H*-14), 7.31 (t, *J* = 7.5 Hz, 2H, *H*-15), 7.21 (m, 1H, *H*-16), 5.12 (m, 1H, *H*-10), 5.04 (t, *J* = 5.8 Hz, 1H, *OH*), 3.91 (ddd, *J* = 11.1, 8.4, 5.7 Hz, 1H, *H*-11''), 3.73 (dt, *J* = 11.1, 5.5 Hz, 1H, *H*-11'), 2.45 (s, 3H, *H*-12); ¹³C-NMR (100 MHz DMSO-*d*⁶): δ_c 150.7 (C-1), 145.9 (C-4), 141.4 (C-5), 140.9 (C-13), 132.9 (C-8), 130.1 (C-7), 128.0 (C-15), 127.3 (C-14), 126.9 (C-16), 124.6 (C-6), 123.3 (C-3), 122.5 (C-9), 118.2 (C-2), 64.5 (C-10), 58.3 (C-11), 9.2 (C-12); LR-ESI-MS: C₁₈H₁₈N₅O [M+H]⁺ *m/z* found 320.4, calcd 320.2; HR-ESI-MS: C₁₈H₁₈N₅O [M+H]⁺ *m/z* found 320.1530, calcd 320.1511.

***N*-((1-ethylpyrrolidin-2-yl)methyl)-3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-amine (52)**

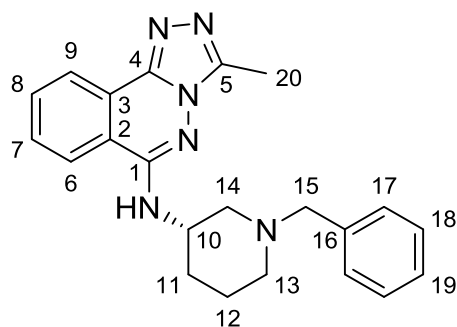


5 (200 mg, 0.915 mmol, 1 eq) and (1-ethylpyrrolidin-2-yl)methanamine (235 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **52** (138 mg, 0.445 mmol 48.6%) as a yellow solid.

Mpt: 219.4-221.4 °C; **v_{max} (cm⁻¹)** 3227, 3070, 2960, 2772, 1482, 779; **¹H-NMR (400MHz, DMSO-*d*⁶)**: δ_H 8.36 (d, *J* = 7.8 Hz, 1H, *H*-9), 8.3 (d, *J* = 8.1 Hz, 1H, *H*-6), 7.9 (m, 1H, *H*-8), 7.8 (m, 1H, *H*-7), 7.67 (m, 1H, NH), 4.11 (s, 1H, *H*-10''), 3.63 (m, 1H, *H*-10'), 3.17 (m, 2H, *H*-15), 3.07 (m, 1H, *H*-11),

2.99 (m, 1H, *H*-14''), 2.91 (m, 1H, *H*-14'), 2.54 (s, 3H, *H*-17), 2.38 (m, 1H, *H*-12''), 2.18 (m, 1H, *H*-12'), 1.85 (m, 1H, *H*-13''), 1.68 (m, 1H, *H*-13'), 1.09 (t, *J* = 7.2 Hz, 3H, *H*-16); **¹³C-NMR (100 MHz CDCl₃)**: δ_C 151.2 (C-1), 145.9 (C-4), 141.1 (C-5), 132.8 (C-8), 130.2 (C-7), 124.1 (C-9), 123.3 (C-3), 122.5 (C-6), 118.2 (C-2), 61.2 (C-11), 53.3 (C-14), 48.6 (C-15), 48.3 (C-10), 29.1 (C-12), 22.5 (C-13), 13.8 (C-16), 9.3 (C-17); **LR-ESI-MS**: C₁₇H₂₃N₆ [M+H]⁺ *m/z* found 311.4, calcd 311.2; **HR-ESI-MS**: C₁₇H₂₃N₆ [M+H]⁺ *m/z* found 311.2000, calcd 311.1984.

***(S)*-N-(1-benzylpiperidin-3-yl)-3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-amine (56)**

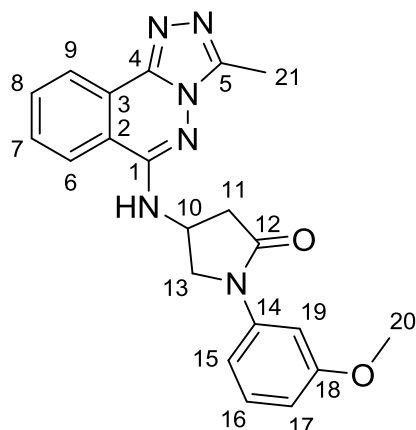


5 (400 mg, 1.829 mmol, 1 eq) and (*S*)-1-benzylpiperidin-3-amine (522 mg, 2.74 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **56** (200 mg, 0.537 mmol 29.4%) as a yellow solid.

Mpt: 132.6-134.6 °C; **v_{max} (cm⁻¹)** 3336, 2930, 2795, 1590, 1513; **¹H-NMR (400MHz, DMSO-*d*⁶)**: δ_H 8.34 (m, 2H, *H*-9; *H*-6), 7.88 (m, 1H, *H*-8), 7.78 (td, *J* = 7.7, 1.3 Hz, 1H, *H*-8), 7.31 (m, 4H, *H*-17; *H*-18), 7.21 (m, 1H, *H*-19), 7.12 (d, *J* = 7.3 Hz, 1H, NH), 4.05 (m, 1H, *H*-10), 3.62 (d, *J* = 13.3 Hz, 1H, *H*-15''), 3.39 (d, *J* = 13.3 Hz, 1H, *H*-15'), 3.16 (m, 1H, *H*-14''), 2.81 (m, 1H, *H*-14'), 2.43 (s, 3H, *H*-20), 2.02 (m, 2H, *H*-13), 1.86 (t, *J* = 10 Hz, 1H, *H*-12''), 1.74 (m, 1H, *H*-11''), 1.62 (m, 1H, *H*-11'), 1.5 (m, 1H, *H*-12');

¹³C-NMR (100 MHz, DMSO-*d*⁶): δ_C 150.4 (C-1), 145.9 (C-4), 141.0 (C-5), 138.5 (C-16), 132.8 (C-8), 130.0 (C-7), 128.7 (C-17), 128.1 (C-18), 126.8 (C-19), 124.4 (C-9), 123.3 (C-3), 122.4 (C-6), 118.1 (C-2), 62.1 (C-15), 56.9 (C-14), 53.6 (C-13), 48.3 (C-10), 29.5 (C-11), 24.1 (C-12), 9.2 (C-20); **LR-ESI-MS**: C₂₂H₂₅N₆ [M+H]⁺ *m/z* found 373.3, calcd 373.2; **HR-ESI-MS**: C₂₂H₂₅N₆ [M+H]⁺ *m/z* found 373.2173, calcd 373.2141.

1-(3-methoxyphenyl)-4-((3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino)pyrrolidin-2-one (57)

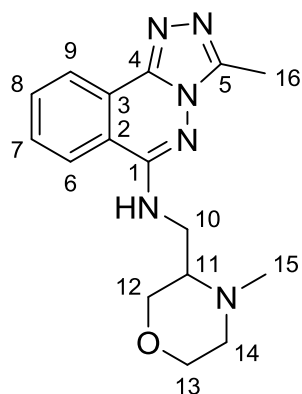


5 (400 mg, 1.829 mmol, 1 eq) and 4-amino-1-(3-methoxyphenyl)pyrrolidin-2-one (566 mg, 2.74 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **57** (61 mg, 0.157 mmol 8.6%) as a brown solid.

Mpt: 249.9-251.1 °C; **v_{max}** (cm⁻¹) 3250, 2929, 1697, 1592, 1498, 1317, 1212, 1043, 765, 701; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_H 8.34 (m, 2H, *H*-6; *H*-9), 7.88 (m, 2H, *H*-7; *H*-8), 7.76 (m, 1H, NH), 7.74 (m, 1H, *H*-19), 7.26 (m, 1H, *H*-16), 7.20 (m, 1H, *H*-15), 6.71 (dt, 1H, *J* = 8, 1.2 Hz, *H*-17), 4.67 (s, 1H, *H*-10), 4.30 (dd, 1H, *J* =

10.4, 7.1 Hz, *H*-13''), 3.97 (dd, 1H, *J* = 10.5, 3.2 Hz, *H*-13'), 3.73 (s, 3H, *H*-20), 3.10 (dd, 1H, *J* = 17.4, 8.4 Hz, *H*-11''), 2.81 (dd, 1H, *J* = 17.5, 3.9 Hz, *H*-11'), 2.55 (s, 3H, *H*-21); **¹³C-NMR (100 MHz, DMSO-*d*⁶):** δ_C 172.17 (C-12), 159.4 (C-18), 150.6 (C-1), 146.1 (C-4), 141.0 (C-5), 140.5 (C-14), 132.8 (C-8), 129.9 (C-7), 129.4 (C-19), 124.4 (C-9), 123.3 (C-3), 122.4 (C-6), 118.1 (C-2), 111.6 (C-16), 109.2 (C-15), 105.6 (C-17), 55.1 (C-20), 53.9 (C-10), 44.1 (C-11), 38.6 (C-13), 9.3 (C-21); **LR-ESI-MS:** C₂₁H₂₁N₆O₂ [M+H]⁺ *m/z* found 389.2, calcd 389.1; **HR-ESI-MS:** C₂₁H₂₁N₆O₂ [M+H]⁺ *m/z* found 389.1742, calcd 389.1726.

3-methyl-N-((4-methylmorpholin-3-yl)methyl)-[1,2,4]triazolo[3,4-a]phthalazin-6-amine (58)

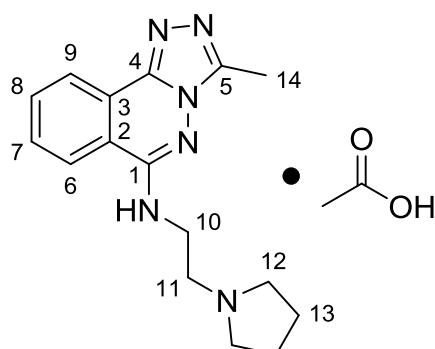


5 (200 mg, 0.915 mmol, 1 eq) and (4-methylmorpholin-3-yl)methanamine (238 mg, 1.829 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **58** (97 mg, 0.310 mmol 33.9%) as a white solid.

Mpt: 172.7-174.7 °C; **v_{max}** (cm⁻¹) 3224, 3069, 2924, 2857, 2792, 1565, 1513, 1124, 699; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_H 8.36 (d, 1H, *J* = 7.7 Hz, *H*-9), 8.29 (d, 1H, *J* = 8.1 Hz, *H*-6), 7.91 (t, 1H, *J* = 7.6 Hz, *H*-8), 7.80 (m, 1H, *H*-7), 7.61 (t, 1H, *J* = 5.4 Hz, NH), 3.80 (m, 2H, *H*-12''; *H*-13''), 3.66 (m, 1H, *H*-12'), 3.52 (m, 1H, *H*-13'), 3.33 (m, 1H, *H*-10''), 3.19 (m, 1H, *H*-10'), 2.66

(m, 1H, *H*-11), 2.56 (s, 3H, *H*-16), 2.51 (m, 1H, *H*-14''), 2.40 (s, 3H, *H*-15), 2.21 (m, 1H, *H*-14'); **¹³C-NMR (100 MHz, DMSO-*d*⁶):** δ_C 151.1 (C-1), 145.9 (C-4), 141.1 (C-5), 132.9 (C-8), 130.2 (C-7), 124.2 (C-9), 123.3 (C-3), 122.5 (C-6), 118.2 (C-2), 69.6 (C-12), 66.2 (C-13), 60.3 (C-11), 54.4 (C-14), 42.8 (C-10), 39.5 (C-15), 9.3 (C-16); **LR-ESI-MS:** C₁₆H₂₁N₆O [M+H]⁺ *m/z* found 313.2, calcd 313.2; **HR-ESI-MS:** C₁₆H₂₁N₆O [M+H]⁺ *m/z* found 313.1797, calcd 313.1777.

3-methyl-*N*-(2-(pyrrolidin-1-yl)ethyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-amine acetate (**59**)

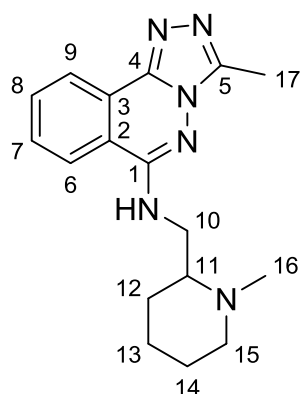


5 (200 mg, 0.915 mmol, 1 eq) and 2-(pyrrolidin-1-yl)ethan-1-amine (209 mg, 1.829 mmol, 1.5 eq) were reacted according to general procedure **A**. After cooling to 4 °C a precipitate had formed which was washed according to **A** and then co-evaporated with AcOH to give **59** as an AcOH salt (101 mg, 0.283 mmol, 31%).

Mpt: 172.4-174.4 °C; ν_{max} (cm^{-1}) 3449, 3261, 2693, 2615, 1516, 701; $^1\text{H-NMR}$ (400MHz, $\text{MeOD-}d^4$): δ_{H} 8.33 (d, 1H, $J=7.9$ Hz, $H-9$), 8.18 (d, 1H, $J=8.2$ Hz, $H-6$), 7.89 (m, 1H, $H-8$),

7.81 (m, 1H, $H-7$), 3.96 (t, 2H, $J=5.9$ Hz, $H-10$), 3.69 (t, 2H, $J=5.9$ Hz, $H-11$), 3.50 (br s, 4H, $H-12$), 2.64 (s, 3H, $H-14$), 2.16 (s, 4H, $H-13$); $^{13}\text{C-NMR}$ (100 MHz, $\text{MeOD-}d^4$): δ_{C} 152.1 (C-1), 147.2 (C-4), 141.8 (C-5), 132.9 (C-8), 130.8 (C-7), 123.8 (C-9), 122.7 (C-3), 122.6 (C-6), 118.6 (C-2), 54.1 (C-12), 52.9 (C-11), 37.7 (C-10), 22.6 (C-13), 8.1 (C-14); **LR-ESI-MS:** $\text{C}_{16}\text{H}_{21}\text{N}_6$ $[\text{M}+\text{H}]^+$ m/z found 297.2, calcd 297.2; **HR-ESI-MS:** $\text{C}_{16}\text{H}_{21}\text{N}_6$ $[\text{M}+\text{H}]^+$ m/z found 297.1852, calcd 297.1828.

3-methyl-*N*-((1-methylpiperidin-2-yl)methyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-amine (**60**)

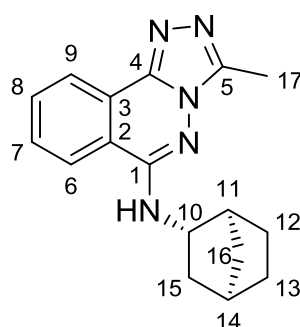


5 (200 mg, 0.915 mmol, 1 eq) and (1-methylpiperidin-2-yl)methanamine (235 mg, 1.829 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/ NH_3 9:1:0.5) to give **60** (147 mg, 0.475 mmol 51.9%) as a white solid.

Mpt: 171.6-173.6 °C; ν_{max} (cm^{-1}) 3231, 3071, 2928, 1565, 1511, 1267, 698; $^1\text{H-NMR}$ (400MHz, $\text{DMSO-}d^6$): δ_{H} 8.37 (dd, 1H, $J=7.9, 1$ Hz, $H-9$), 8.31 (d, 1H, $J=8.2$ Hz, $H-6$), 7.91 (m, 1H, $H-8$), 7.81 (td, 1H, $J=7.8, 1.3$ Hz, $H-7$), 7.56 (t, 1H, $J=5$ Hz, NH), 4.11 (s, 1H, $H-11$), 3.79 (m, 1H, $H-10''$), 3.26 (m, 1H, $H-10'$), 2.80 (d, 1H, $J=11.2$ Hz, $H-12''$), 2.55 (s, 3H, $H-17$), 2.38 (s, 3H, $H-16$), 2.09 (m, 1H, $H-12'$), 1.8-1.1 (m, 6H, $H-13$; $H-14$; $H-15$); $^{13}\text{C-NMR}$ (100 MHz, $\text{DMSO-}d^6$): δ_{C} 151.1 (C-1), 145.9 (C-4), 141.1 (C-5), 132.8 (C-8), 130.2 (C-7), 124.1 (C-9), 123.3 (C-3), 122.5 (C-6), 118.2 (C-2), 61.4 (C-11), 56.1 (C-15), 54.9 (C-10), 48.6 (C-16), 43.8 (C-12), 25.1 (C-14), 23.3 (C-13), 9.3 (C-17);

LR-ESI-MS: $\text{C}_{17}\text{H}_{23}\text{N}_6$ $[\text{M}+\text{H}]^+$ m/z found 311.4, calcd 311.2; **HR-ESI-MS:** $\text{C}_{17}\text{H}_{23}\text{N}_6$ $[\text{M}+\text{H}]^+$ m/z found 311.2006, calcd 311.1984.

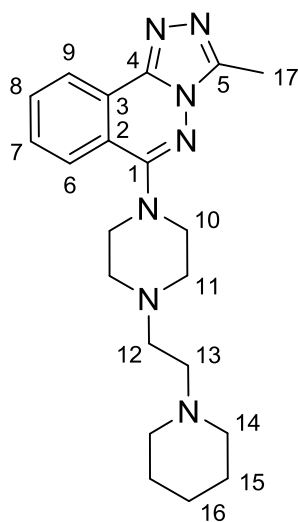
N-((1*S**, 2*S**, 4*R**)-bicyclo[2.2.1]heptan-2-yl)-3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-amine (**61**)



5 (100 mg, 0.457 mmol, 1 eq) and *rac*-(1*S*,2*S*,4*R*)-bicyclo[2.2.1]heptan-2-amine (102 mg, 0.915 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/ NH_3 9:1:0.5) to give **61** (20 mg, 0.068 mmol 14.9%) as a white crystalline solid.

Mpt: 256.2-258.2 °C; ν_{max} (cm^{-1}) 3273, 2944, 1502, 769; $^1\text{H-NMR}$ (400MHz, $\text{DMSO-}d^6$): δ_{H} 8.48 (d, 1H, $J=8.2$ Hz, $H-9$), 8.35 (dd, 1H, $J=7.9$,

0.8 Hz, *H*-6), 7.89 (m, 1H, *H*-8), 7.79 (m, 1H, *H*-7), 7.13 (d, 1H, *J* = 5.5 Hz, *NH*), 3.75 (m, 1H, *H*-10), 2.55 (s, 3H, *H*-17), 2.46 (m, 1H, *H*-11), 2.27 (m, 1H, *H*-14), 1.8-1.4 (m, 5H, *H*-12''; *H*-15; *H*-16), 1.3-1.1 (m, 3H, *H*-12'; *H*-13); **¹³C-NMR (100 MHz, DMSO-*d*⁶)**: δ_c 150.5 (C-1), 145.9 (C-4), 140.9 (C-5), 132.6 (C-8), 129.9 (C-7), 124.6 (C-9), 123.3 (C-3), 122.3 (C-6), 118.3 (C-2), 55.2 (C-10), 40.6 (C-15), 38.5 (C-12), 35.2 (C-14), 35.1 (C-11), 28.1 (C-13), 26.3 (C-16), 9.2 (C-17); **LR-ESI-MS**: C₁₇H₂₀N₅ [M+H]⁺ *m/z* found 294.4, calcd 294.2; **HR-ESI-MS**: C₁₇H₂₀N₅ [M+H]⁺ *m/z* found 294.1744, calcd 294.1719.



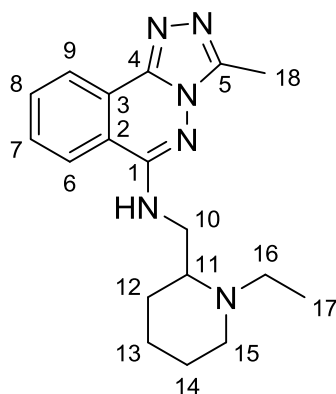
3-methyl-6-(4-(2-(piperidin-1-yl)ethyl)piperazin-1-yl)-[1,2,4]triazolo[3,4-a]phthalazine (62)

5 (200 mg, 0.915 mmol, 1 eq) and 1-(2-(piperidin-1-yl)ethyl)piperazine (361 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **62** (180 mg, 0.475 mmol 51.9%) as a white solid.

Mpt: 228.6-230.6 °C; **ν_{\max} (cm⁻¹)** 3254, 2932, 2643, 2550, 1654, 1477, 989, 792; **¹H-NMR (400MHz, CDCl₃)**: δ_H 8.60 (d, 1H, *J* = 7.7 Hz, *H*-9), 8.00 (d, 1H, *J* = 8.2 Hz, *H*-6), 7.84 (t, 1H, *J* = 7.3 Hz, *H*-8), 7.72 (m, 1H, *H*-7), 3.42 (br-s, 4H, *H*-10), 2.94 (br-s, 6H, *H*-11; *H*-12; *H*-13), 2.82 (br-s, 4H, *H*-14), 1.92 (br-s, 4H, *H*-15), 1.60 (br-s, 2H, *H*-16); **¹³C-NMR (100**

MHz, CDCl₃): δ_c 157.5 (C-1), 147.6 (C-4), 142.5 (C-5), 132.9 (C-8), 129.9 (C-7), 126.3 (C-9), 125.0 (C-3), 123.8 (C-6), 119.9 (C-2), 54.5 (C-10), 52.9 (C-11), 51.1 (C-12; C-13), 26.9 (C-14), 23.8 (C-15), 22.9 (C-16); **LR-ESI-MS**: C₂₁H₃₀N₇ [M+H]⁺ *m/z* found 380.3, calcd 380.3; **HR-ESI-MS**: C₂₁H₃₀N₇ [M+H]⁺ *m/z* found 380.2583, calcd 380.2563.

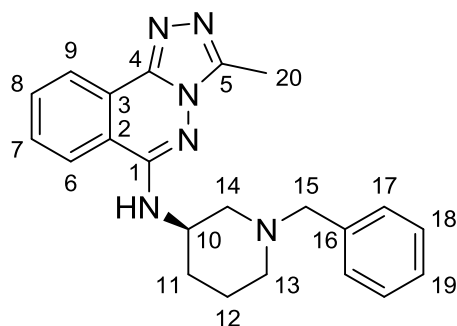
N-((1-ethylpiperidin-2-yl)methyl)-3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-amine (63)



5 (200 mg, 0.915 mmol, 1 eq) and (1-ethylpiperidin-2-yl)methanamine (260 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **63** (99 mg, 0.307 mmol 33.6%) as a white solid.

Mpt: 169.0-171.0 °C; **ν_{\max} (cm⁻¹)** 3250, 2946, 2660, 1510, 1339, 1212, 627, 573; **¹H-NMR (400MHz, DMSO-*d*⁶)**: δ_H 8.46 (d, 1H, *J* = 8.1 Hz, *H*-9), 8.37 (d, 1H, *J* = 7.7 Hz, *H*-6), 8.23 (m, 1H, *NH*), 7.92 (t, 1H, *J* = 7.5 Hz, *H*-8), 7.81 (m, 1H, *H*-7), 4.01 (m, 1H, *H*-11), 3.95-3.5 (m, 2H, *H*-10), 3.44 (m, 1H, *H*-15''), 3.07 (m, 1H, *H*-15'), 2.56 (s, 3H, *H*-18), 2.06 (m, 1H, *H*-12''), 2.0-1.7 (m, 4H, *H*-12'; *H*-14''; *H*-16), 1.49 (m, 1H, *H*-13''), 1.29 (m, 3H, *H*-13'; *H*-17); **¹³C-NMR (100 MHz, DMSO-*d*⁶)**: δ_c 151.1 (C-1), 146.1 (C-4), 141.1 (C-5), 133.1 (C-8), 130.3 (C-7), 124.5 (C-9), 123.4 (C-3), 122.5 (C-6), 118.1 (C-2), 58.9 (C-11), 50.7 (C-11), 47.2 (C-15), 42.1 (C-16), 27.2 (C-12), 22.2 (C-14), 21.4 (C-13), 9.5 (C-18), 7.8 (C-17); **LR-ESI-MS**: C₁₈H₂₅N₆ [M+H]⁺ *m/z* found 325.3, calcd 325.2; **HR-ESI-MS**: C₁₈H₂₅N₆ [M+H]⁺ *m/z* found 325.2160, calcd 325.2141.

(R)-N-(1-benzylpiperidin-3-yl)-3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-amine (64)

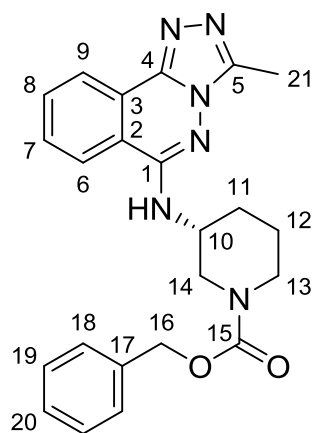


5 (400 mg, 1.829 mmol, 1 eq) and (R)-1-benzylpiperidin-3-amine (522 mg, 2.74 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **64** (153 mg, 0.411 mmol 22.5%) as a white solid.

Mpt: 122.5-124.5 °C; **v_{max}** (cm⁻¹) 3344, 2930, 2802, 1528, 1512, 1158, 733, 658; **¹H-NMR (400MHz, DMSO-*d*⁶)**: δ_{H} 8.34

(m, 2H, *H*-6; *H*-9), 7.89 (m, 1H, *H*-8), 7.78 (td, 1H, *J*= 7.7, 1.3 Hz, *H*-7), 7.31 (m, 4H, *H*-17; *H*-18), 7.23 (m, 1H, *H*-19), 7.13 (d, 1H, *J*= 7.3 Hz, NH), 4.09 (m, 1H, *H*-10), 3.63 (d, 1H, *J*= 13.3 Hz, *H*-15''), 3.40 (d, 1H, *J*= 13.3 Hz, *H*-15'), 3.18 (d, 1H, *J*= 7.7 Hz, *H*-14''), 2.82 (d, 1H, *J*= 11 Hz, *H*-14'), 2.44 (s, 3H, *H*-20), 2.02 (m, 2H, *H*-13), 1.86 (m, 1H, *H*-12''), 1.74 (m, 1H, *H*-11''), 1.62 (m, 1H, *H*-11'), 1.5 (m, 1H, *H*-12'); **¹³C-NMR (100 MHz, DMSO-*d*⁶)**: δ_{C} 150.4 (C-1), 145.9 (C-4), 141.0 (C-5), 138.5 (C-16), 132.8 (C-8), 130.0 (C-7), 128.7 (C-17), 128.1 (C-18), 126.8 (C-19), 124.4 (C-9), 123.3 (C-3), 122.4 (C-6), 118.1 (C-2), 62.1 (C-15), 56.9 (C-14), 53.6 (C-13), 48.3 (C-10), 29.5 (C-11), 24.1 (C-12), 9.2 (C-20); **LR-ESI-MS**: C₂₂H₂₄N₆ [M+H]⁺ *m/z* found 373.3, calcd 373.2; **HR-ESI-MS**: C₂₂H₂₄N₆ [M+H]⁺ *m/z* found 373.2173, calcd 373.2141.

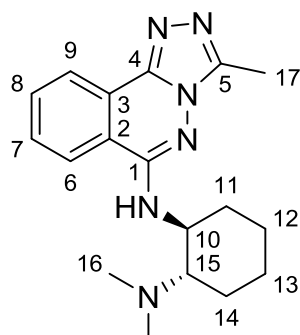
benzyl (R)-3-((3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino)piperidine-1-carboxylate (65)



5 (300 mg, 1.372 mmol, 1 eq) and benzyl (R)-3-aminopiperidine-1-carboxylate (482 mg, 2.058 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **65** (93 mg, 0.223 mmol 16.3%) as a white solid.

Mpt: 172.2-174.2 °C; **v_{max}** (cm⁻¹) 3277, 2925, 2851, 1678, 1509, 1258, 1231, 696; **¹H-NMR (VT) (400MHz, 343 K, DMSO-*d*⁶)**: δ_{H} 8.38 (m, 2H, *H*-6; *H*-9), 7.91 (td, 1H, *J*= 7.6, 1.1 Hz, *H*-8), 7.79 (ddd, 1H, *J*= 8.3, 7.2, 1.4 Hz, *H*-7), 7.27 (s, 5H, *H*-18; *H*-19, *H*-20), 6.99 (d, 1H, *J*= 6.3 Hz, NH), 5.07 (s, 2H, *H*-16), 4.34 (m, 1H, *H*-14''), 4.02 (m, 1H, *H*-10), 3.85 (m, 1H, *H*-14'), 3.08 (m, 2H, *H*-13), 3.03 (s, 3H, *H*-21), 2.15 (m, 1H, *H*-11''), 1.82 (m, 2H, *H*-11'; *H*-12''), 1.55 (m, 1H, *H*-12'); **¹³C-NMR (100 MHz, DMSO-*d*⁶)**: δ_{C} 154.5 (C-15), 150.5 (C-1), 146.0 (C-4), 141.0 (C-5), 136.9 (C-17), 132.9 (C-8), 130.0 (C-7), 128.2 (C-18), 127.7 (C-19), 127.1 (C-20), 124.6 (C-9), 123.4 (C-3), 122.4 (C-6), 118.1 (C-2), 66.2 (C-16), 47.8 (C-14), 43.8 (C-10), 29.3 (C-13), 26.3 (C-11; C-12), 9.1 (C-21); **LR-ESI-MS**: C₂₃H₂₅N₆O₂ [M+H]⁺ *m/z* found 417.2, calcd 417.2; **HR-ESI-MS**: C₂₃H₂₅N₆O₂ [M+H]⁺ *m/z* found 417.2064, calcd 417.2039.

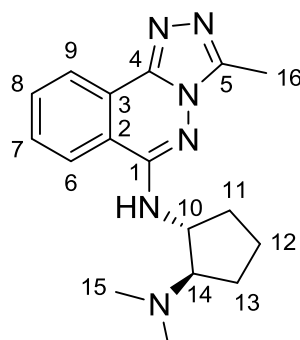
(1*S*, 2*S*)-*N*₁,*N*₁-dimethyl-*N*₂-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)cyclohexane-1,2-diamine (66)



5 (300 mg, 1.372 mmol, 1 eq) and (1*S*,2*S*)-*N*₁,*N*₁-dimethylcyclohexane-1,2-diamine (390 mg, 2.74 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **66** (245 mg, 0.755 mmol 55%) as a white solid.

Mpt: 183.0-185.0 °C; **v_{max} (cm⁻¹)** 3306, 2993, 1592, 1498, 791; **¹H-NMR (400MHz, DMSO-*d*⁶)**: δ_H 8.37 (dd, 1H, *J* = 7.9, 1.0 Hz, *H*-9), 8.29 (d, 1H, *J* = 8.1 Hz, *H*-6), 7.94 (m, 1H, *H*-8), 7.81 (m, 1H, *H*-7), 7.03 (d, 1H, *J* = 6.5 Hz, NH), 3.92 (m, 1H, *H*-10), 2.65 (m, 1H, *H*-15), 2.55 (s, 3H, *H*-17), 2.32 (m, 1H, *H*-11''), 2.20 (s, 6H, *H*-16), 1.85 (m, 1H, *H*-11'), 1.81 (m, 1H, *H*-14''), 1.70 (m, 1H, *H*-14'), 1.28 (m, 4H, *H*-12; *H*-13); **¹³C-NMR (100 MHz, DMSO-*d*⁶)**: δ_C 150.8 (C-1), 145.9 (C-4), 141.0 (C-5), 132.7 (C-8), 130.2 (C-7), 124.1 (C-9), 123.4 (C-3), 122.5 (C-6), 118.4 (C-2), 65.5 (C-15), 51.7 (C-10), 40.0 (C-16), 31.8 (C-11), 25.0 (C-12), 24.7 (C-14), 22.2 (C-13), 9.3 (C-17); **LR-ESI-MS**: C₁₈H₂₅N₆ [M+H]⁺ *m/z* found 325.2, cald 325.2; **HR-ESI-MS**: C₁₈H₂₅N₆ [M+H]⁺ *m/z* found 325.2160, cald 325.2141.

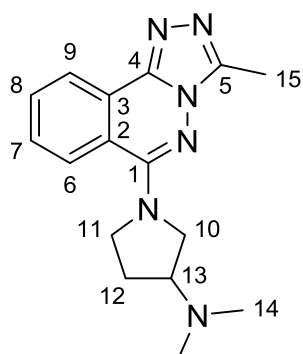
(1*R, 2*R**)-*N*₁,*N*₁-dimethyl-*N*₂-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)cyclopentane-1,2-diamine (67)**



5 (300 mg, 1.372 mmol, 1 eq) and *rac*-(1*R*,2*R*)-*N*₁,*N*₁-dimethylcyclopentane-1,2-diamine (264 mg, 2.058 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **67** (120 mg, 0.387 mmol 28%) as a white solid.

Mpt: 178.3-180.3 °C; **v_{max} (cm⁻¹)** 3231, 2948, 1593, 1392, 1174, 769, 589; **¹H-NMR (400MHz, DMSO-*d*⁶)**: δ_H 8.43 (d, 1H, *J* = 8.1 Hz, *H*-9), 8.36 (dd, 1H, *J* = 7.9, 0.9 Hz, *H*-6), 7.91 (m, 1H, *H*-8), 7.80 (td, 1H, *J* = 7.8, 1.3 Hz, *H*-7), 7.35 (d, 1H, *J* = 7.6 Hz, NH), 4.35 (m, 1H, *H*-10), 2.91 (q, 1H, *J* = 7.1 Hz, *H*-14), 2.56 (s, 3H, *H*-16), 2.19 (s, 6H, *H*-15), 2.13 (m, 1H, *H*-11''), 1.81 (m, 1H, *H*-13''), 1.60 (m, 4H, *H*-11'; *H*-12; *H*-13'); **¹³C-NMR (100 MHz, DMSO-*d*⁶)**: δ_C 150.6 (C-1), 146.0 (C-4), 141.0 (C-5), 132.7 (C-8), 130.0 (C-7), 124.4 (C-9), 123.3 (C-3), 122.4 (C-6), 118.3 (C-2), 71.0 (C-14), 54.5 (C-10), 42.8 (C-15), 31.6 (C-11), 27.2 (C-13), 22.0 (C-12), 9.3 (C-16); **LR-ESI-MS**: C₁₇H₂₃N₆ [M+H]⁺ *m/z* found 311.2, cald 311.2; **HR-ESI-MS**: C₁₇H₂₃N₆ [M+H]⁺ *m/z* found 311.2006, cald 311.1984.

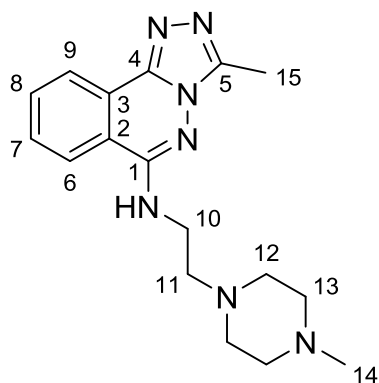
N,N-dimethyl-1-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)pyrrolidin-3-amine (**68**)



5 (200 mg, 0.915 mmol, 1 eq) and *N,N*-dimethylpyrrolidin-3-amine (209 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **68** (246 mg, 0.831 mmol 91%) as a white solid.

Mpt: 141.1-143.1 °C; ν_{max} (cm⁻¹) 3380, 2864, 2785, 1681, 1493, 1420, 799, 704; ¹H-NMR (400MHz, CDCl₃): δ_{H} 8.55 (dd, 1H, *J* = 7.9, 1.0 Hz, *H*-9), 8.09 (d, 1H, *J* = 8.3 Hz, *H*-6), 7.77 (m, 1H, *H*-8), 7.65 (ddd, 1H, *J* = 8.4, 7.2, 1.3 Hz, *H*-7), 3.92 (m, 1H, *H*-13), 3.84-3.69 (m, 3H, *H*-10; *H*-11''), 2.86 (m, 1H, *H*-11'), 2.66 (s, 3H, *H*-15), 2.35 (s, 6H, *H*-14), 2.22 (m, 1H, *H*-12''), 1.97 (m, 1H, *H*-12'); ¹³C-NMR (100 MHz, CDCl₃): δ_{C} 154.3 (C-1), 147.1 (C-4), 142.2 (C-5), 132.1 (C-8), 129.3 (C-7), 126.5 (C-9), 125.0 (C-3), 123.5 (C-6), 120.1 (C-2), 65.4 (C-13), 55.8 (C-10), 50.3 (C-11), 44.3 (C-14), 30.2 (C-12), 9.7 (C-15); **LR-ESI-MS:** C₁₆H₂₁N₆ [M+H]⁺ *m/z* found 297.2, calcd 297.2; **HR-ESI-MS:** C₁₆H₂₁N₆ [M+H]⁺ *m/z* found 297.1850, calcd 297.1828.

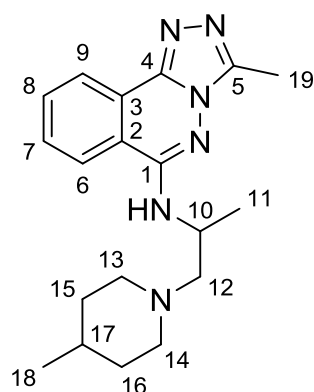
3-methyl-*N*-(2-(4-methylpiperazin-1-yl)ethyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-amine (**69**)



5 (200 mg, 0.915 mmol, 1 eq) and 2-(4-methylpiperazin-1-yl)ethan-1-amine (262 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **69** (189 mg, 0.582 mmol 63.6%) as an off white solid.

Mpt: 120.5-122.5 °C; ν_{max} (cm⁻¹) 3223, 2938, 2802, 1566, 1390, 1269, 1145, 1006, 770, 698; ¹H-NMR (400MHz, CDCl₃): δ_{H} 8.55 (d, 1H, *J* = 7.9 Hz, *H*-9), 7.78 (m, 2H, *H*-8; *H*-6), 7.68 (m, 1H, *H*-7), 6.19 (s, 1H, NH), 3.56 (m, 2H, *H*-10), 2.77 (t, 2H, *J* = 6 Hz, *H*-11), 2.66 (s, 3H, *H*-15), 2.61 (m, 4H, *H*-12), 2.50 (m, 4H, *H*-13), 2.31 (s, 3H, *H*-14); ¹³C-NMR (100 MHz, CDCl₃): δ_{C} 151.0 (C-1), 147.1 (C-4), 141.9 (C-5), 132.3 (C-8), 129.9 (C-7), 124.1 (C-9), 123.6 (C-3), 122.3 (C-6), 118.4 (C-2), 55.5 (C-10), 55.2 (C-12), 52.6 (C-13), 45.9 (C-11), 37.8 (C-14), 9.7 (C-15); **LR-ESI-MS:** C₁₇H₂₄N₇ [M+H]⁺ *m/z* found 326.2, calcd 326.2; **HR-ESI-MS:** C₁₇H₂₄N₇ [M+H]⁺ *m/z* found 326.2114, calcd 326.2093.

3-methyl-*N*-(1-(4-methylpiperidin-1-yl)propan-2-yl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-amine (**70**)

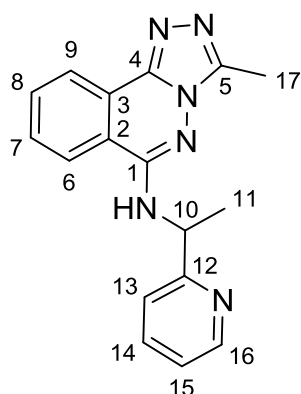


5 (200 mg, 0.915 mmol, 1 eq) and 2-(4-methylpiperazin-1-yl)ethan-1-amine (286 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **70** (40 mg, 0.117 mmol 12.8%) as an off white solid.

Mpt: 128.6-130.6 °C; ν_{max} (cm⁻¹) 3249, 2919, 1507, 1083, 699; ¹H-NMR (400MHz, DMSO-*d*⁶): δ_{H} 8.36 (m, 2H, *H*-6; *H*-9), 7.9 (m, 1H, *H*-8), 7.8 (m, 1H, *H*-7), 7.16 (d, 1H, *J* = 6.7 Hz, NH), 4.28 (m, 1H, *H*-10), 3.00 (d, 1H, *J* = 9.8 Hz, *H*-12''), 2.84 (m, 1H, *H*-12'), 2.59 (m, 1H, *H*-13''), 2.54 (s, 3H, *H*-

19), 2.30 (m, 1H, 13'), 1.97 (m, 2H, *H*-14), 1.52 (t, 2H, *J* = 15 Hz, *H*-15), 1.30 (d, 3H, *H*-11), 1.27 (m, 1H, *H*-17), 1.06 (m, 2H, *H*-16), 0.82 (d, 3H, *J* = 6.4 Hz, *H*-18); **¹³C-NMR (100 MHz, DMSO-*d*⁶)**: δ_c 150.7 (C-1), 145.9 (C-4), 141.0 (C-5), 132.7 (C-8), 130.0 (C-7), 124.3 (C-9), 123.4 (C-3), 122.4 (C-6), 118.3 (C-2), 63.1 (C-12), 54.2 (C-13), 53.5 (C-14), 44.4 (C-10), 34.0 (C-15), 30.3 (C-16), 26.3 (C-17), 21.8 (C-18), 18.5 (C-11), 9.2 (C-19); **LR-ESI-MS**: C₁₉H₂₇N₆ [M+H]⁺ *m/z* found 339.2, calcd 339.2; **HR-ESI-MS**: C₁₉H₂₇N₆ [M+H]⁺ *m/z* found 339.2320, calcd 339.2297.

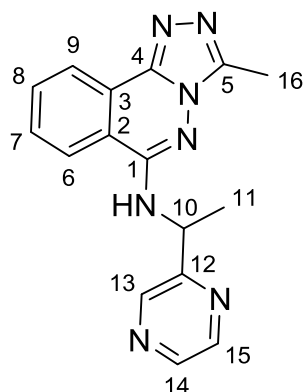
3-methyl-*N*-(1-(pyridin-2-yl)ethyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-amine (71)



5 (300 mg, 1.372 mmol, 1 eq) and 1-(pyridin-2-yl)ethan-1-amine (335 mg, 2.74 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **71** (172 mg, 0.567 mmol 41.4%) as an off white solid.

Mpt: 143.5-145.5 °C; *v*_{max} (cm⁻¹) 3266, 1591, 1475, 1376, 1164, 698; **¹H-NMR (400MHz, CDCl₃)**: δ_H 8.60 (d, 1H, *J* = 4.6 Hz, *H*-16), 8.53 (d, 1H, *J* = 7.8 Hz, *H*-9), 7.94 (d, 1H, *J* = 8.2 Hz, *H*-6), 7.74 (m, 2H, *H*-14; *H*-8), 7.64 (m, 1H, *H*-7), 7.41 (d, 1H, *J* = 7.8 Hz, *H*-13), 7.25 (m, 1H, *H*-15), 7.15 (d, 1H, *J* = 6 Hz, *NH*), 5.29 (quin, 1H, *J* = 6.5 Hz, *H*-10), 2.65 (s, 3H, *H*-17), 1.69 (d, 3H, *J* = 6.6 Hz, *H*-11); **¹³C-NMR (100 MHz, CDCl₃)**: δ_c 161.3 (C-12), 150.0 (C-1), 148.6 (C-16), 147.0 (C-4), 141.9 (C-5), 137.0 (C-14), 132.4 (C-8), 129.9 (C-7), 124.1 (C-9), 123.6 (C-3), 122.7 (C-13), 122.4 (C-6), 121.6 (C-15), 118.5 (C-2), 51.5 (C-10), 21.8 (C-11), 9.7 (C-17); **LR-ESI-MS**: C₁₇H₁₇N₆ [M+H]⁺ *m/z* found 305.2, calcd 305.2; **HR-ESI-MS**: C₁₇H₁₇N₆ [M+H]⁺ *m/z* found 305.1556, calcd 305.1515.

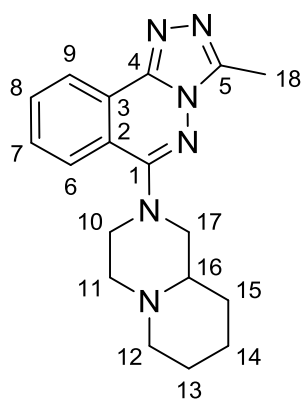
3-methyl-*N*-(1-(pyrazin-2-yl)ethyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-amine (72)



5 (300 mg, 1.372 mmol, 1 eq) and 1-(pyrazin-2-yl)ethan-1-amine (338 mg, 2.74 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **72** (66 mg, 0.215 mmol 15.6%) as an off white solid.

Mpt: 172.9-174.9 °C; *v*_{max} (cm⁻¹) 3201, 3057, 1513, 1407, 1141, 701, 629, 604; **¹H-NMR (400MHz, CDCl₃)**: δ_H 8.78 (d, 1H, *J* = 1.3 Hz, *H*-13), 8.59 (d, 1H, *J* = 7.3 Hz, *H*-9), 8.55 (m, 1H, *H*-15), 8.52 (m, 1H, *H*-15), 7.97 (d, 1H, *H*-6), 7.82 (m, 1H, *H*-8), 7.73 (m, 1H, *H*-7), 6.59 (d, 1H, *NH*), 5.40 (quin, 1H, *J* = 6.7 Hz, *H*-10), 2.64 (s, 3H, *H*-16), 1.75 (d, 3H, *J* = 6.7 Hz, *H*-11); **¹³C-NMR (100 MHz, CDCl₃)**: δ_c 157.2 (C-12), 150.0 (C-1), 147.1 (C-4), 143.9 (C-15), 143.8 (C-14), 143.5 (C-12), 141.7 (C-5), 132.8 (C-8), 130.3 (C-7), 124.0 (C-9; C-3), 122.6 (C-6), 118.3 (C-2), 49.9 (C-10), 21.6 (C-11), 9.7 (C-16); **LR-ESI-MS**: C₁₆H₁₆N₇ [M+H]⁺ *m/z* found 306.1, calcd 306.1; **HR-ESI-MS**: C₁₆H₁₆N₇ [M+H]⁺ *m/z* found 306.1509, calcd 306.1467.

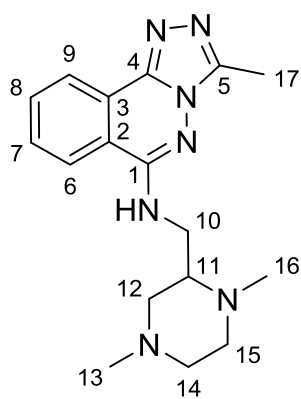
3-methyl-6-(octahydro-2H-pyrido[1,2-a]pyrazin-2-yl)-[1,2,4]triazolo[3,4-a]phthalazine (73)



5 (200 mg, 0.915 mmol, 1 eq) and octahydro-2H-pyrido[1,2-a]pyrazine (257 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **73** (228 mg, 0.709 mmol 78%) as an off white solid.

Mpt: 128.7-130.7 °C; ν_{max} (cm⁻¹) 2929, 2807, 1510, 1345, 1259, 1124, 748; **¹H-NMR (400MHz, CDCl₃):** δ_{H} 8.60 (dd, 1H, *J* = 7.9, 0.6 Hz, *H*-9), 8.01 (d, 1H, *J* = 8.2 Hz, *H*-6), 7.83 (m, 1H, *H*-8), 7.71 (m, 1H, *H*-7), 3.70 (dd, 1H, *J* = 12.6, 2 Hz, *H*-17''), 3.57 (d, 1H, *J* = 12.6 Hz, *H*-17'), 3.37 (m, 1H, *H*-16), 2.98 (m, 3H, *H*-11; *H*-10''), 2.74 (s, 3H, *H*-18), 2.64 (m, 1H, *H*-10'), 2.30 (m, 2H, *H*-12), 1.69 (m, 6H, *H*-13; *H*-14, *H*-15); **¹³C-NMR (100 MHz, CDCl₃):** δ_{C} 157.2 (C-1), 147.7 (C-4), 142.4 (C-5), 132.8 (C-8), 129.8 (C-7), 126.3 (C-9), 125.1 (C-3), 123.8 (C-6), 120.0 (C-2), 61.1 (C-16), 56.6 (C-17), 55.6 (C-11), 54.4 (C-10), 50.8 (C-12), 29.2 (C-15), 25.2 (C-13), 23.7 (C-14), 9.8 (C-18); **LR-ESI-MS:** C₁₈H₂₃N₆ [M+H]⁺ *m/z* found 323.2, calcd 323.2; **HR-ESI-MS:** C₁₈H₂₃N₆ [M+H]⁺ *m/z* found 323.2007, calcd 323.1984.

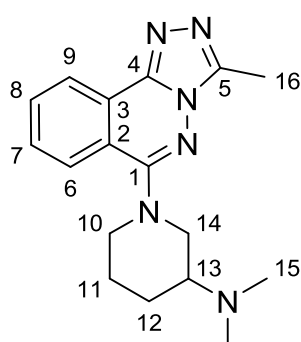
N-((1,4-dimethylpiperazin-2-yl)methyl)-3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-amine (74)



5 (200 mg, 0.915 mmol, 1 eq) and (1,4-dimethylpiperazin-2-yl)methanamine (262 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **74** (89 mg, 0.273 mmol 29.9%) as an off white solid.

Mpt: 251.6-253.6 °C; ν_{max} (cm⁻¹) 3226, 3064, 2794, 1512, 1265, 1166, 697; **¹H-NMR (400MHz, CDCl₃):** δ_{H} 8.56 (m, 1H, *H*-9), 7.80 (m, 2H, *H*-6; *H*-8), 7.69 (m, 1H, *H*-7), 6.43 (m, 1H, NH), 3.66 (m, 1H, *H*-10''), 3.58 (m, 1H, *H*-10'), 2.94 (dt, 1H, *J* = 11.6, 3 Hz, *H*-15''), 2.81 (m, 2H, *H*-12''; *H*-14''), 2.69 (m, 1H, *H*-15'), 2.68 (s, 3H, *H*-17), 2.53 (td, 1H, *J* = 10.9, 2.8 Hz, *H*-11), 2.41 (s, 3H, *H*-16), 2.36 (m, 2H, *H*-12'; *H*-14'), 2.29 (s, 3H, *H*-13); **¹³C-NMR (100 MHz, CDCl₃):** δ_{C} 151.1 (C-1), 147.2 (C-4), 142.0 (C-5), 132.4 (C-8), 129.9 (C-7), 124.1 (C-9), 123.7 (C-3), 122.4 (C-6), 118.5 (C-2), 59.2 (C-11), 58.4 (C-12), 54.7 (C-14), 45.9 (C-13; C-16), 42.1 (C-15), 41.5 (C-10), 9.8 (C-17); **LR-ESI-MS:** C₁₇H₂₄N₇ [M+H]⁺ *m/z* found 326.2, calcd 326.2; **HR-ESI-MS:** C₁₇H₂₄N₇ [M+H]⁺ *m/z* found 326.2121, calcd 326.2093.

N,N-dimethyl-1-(3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)piperidin-3-amine (75)

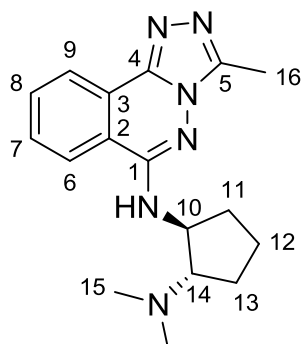


5 (200 mg, 0.915 mmol, 1 eq) and *N,N*-dimethylpiperidin-3-amine (235 mg, 1.829 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **75** (227 mg, 0.730 mmol 80%) as an off white solid.

Mpt: 139.7-141.7 °C; ν_{max} (cm⁻¹) 2932, 2825, 1383, 1252, 703; **¹H-NMR (400MHz, CDCl₃):** δ_{H} 8.58 (dd, 1H, *J* = 7.9, 0.7 Hz, *H*-9), 8.00 (d, 1H, *J* = 8.1

Hz, *H*-6), 7.82 (m, 1H, *H*-8), 7.71 (m, 1H, *H*-7), 3.97 (m, 1H, *H*-14''), 3.7 (m, 1H, *H*-14'), 2.92 (m, 3H, *H*-10; *H*-13), 2.72 (s, 3H, *H*-16), 2.46 (s, 6H, *H*-15), 2.19 (m, 1H, *H*-12''), 1.98 (m, 1H, *H*-12'), 1.86 (m, 1H, *H*-11''), 1.56 (dd, 1H, *J* = 11.2, 4.1 Hz, *H*-11'); ¹³C-NMR (100 MHz, CDCl₃): δ_c 157.8 (C-1), 147.6 (C-4), 142.5 (C-5), 132.8 (C-8), 129.9 (C-7), 126.4 (C-9), 125.0 (C-3), 123.7 (C-6), 120.3 (C-2), 61.1 (C-13), 53.8 (C-14), 52.1 (C-10), 41.9 (C-15), 27.0 (C-12), 24.4 (C-11), 9.8 (C-16); LR-ESI-MS: C₁₇H₂₃N₆ [M+H]⁺ *m/z* found 311.3, calcd 311.2; HR-ESI-MS: C₁₇H₂₃N₆ [M+H]⁺ *m/z* found 311.2000, calcd 311.1984.

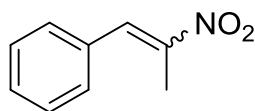
(1*S*, 2*S*)-*N*₁,*N*₁-dimethyl-*N*₂-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)cyclopentane-1,2-diamine (76)



5 (200 mg, 0.915 mmol, 1 eq) and (1*S*,2*S*)-*N*₁,*N*₁-dimethylcyclopentane-1,2-diamine, 2HCl (276 mg, 1.372 mmol, 1.5 eq) were reacted according to general procedure **A** with added DIPEA (478 μL, 2.74 mmol, 3 eq). The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **76** (48 mg, 0.155 mmol 16.9%) as an off white solid.

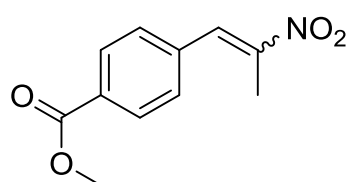
Mpt: 211.0-213.0 °C; **v_{max}** (cm⁻¹) 3238, 2954, 1561, 1551, 1264, 699; ¹H-NMR (400 MHz, DMSO-*d*⁶): δ_H 8.38 (m, 2H, *H*-9; *H*-6), 7.91 (t, 1H, *J* = 7.6 Hz, *H*-8), 7.80 (m, 1H, *H*-7), 7.37 (d, 1H, *J* = 7.6 Hz, NH), 4.34 (quin, 1H, *J* = 6.9 Hz, *H*-10), 2.92 (q, 1H, *J* = 7.3 Hz, *H*-14), 2.56 (s, 3H, *H*-16), 2.19 (s, 6H, *H*-15), 2.10 (m, 1H, *H*-11''), 1.83 (m, 1H, *H*-13''), 1.60 (m, 4H, *H*-11'; *H*-12; *H*-13'); ¹³C-NMR (100 MHz, DMSO-*d*⁶): δ_c 151.0 (C-1), 146.5 (C-4), 141.4 (C-5), 133.2 (C-8), 130.6 (C-7), 124.7 (C-9), 123.4 (C-3), 122.9 (C-6), 118.7 (C-2), 71.3 (C-14), 54.7 (C-10), 43.0 (C-15), 31.9 (C-11), 27.5 (C-13), 22.3 (C-12), 9.6 (C-16); LR-ESI-MS: C₁₇H₂₃N₆ [M+H]⁺ *m/z* found 311.3, calcd 311.2; HR-ESI-MS: C₁₇H₂₃N₆ [M+H]⁺ *m/z* found 311.1996, calcd 311.1984.

***E/Z*-(2-nitroprop-1-en-1-yl)benzene (18)**



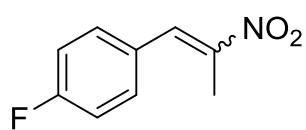
A solution of benzaldehyde (20 g, 188 mmol, 1 eq) and ammonium acetate (2.91 g, 37.7 mmol, 0.2 eq) in nitroethane (314 mL, 0.6 M) was stirred at 110 °C for 48 h. After reaction completion the mixture was cooled to 4 °C and washed with cold CH before being filtered off and dried to give *E/Z*-**18** as a 1:1 mixture (19.266 g, 118 mmol, 62.7%) which was submitted to the following step without further purification.

methyl *E/Z*-(2-nitroprop-1-en-1-yl)benzoate (19)



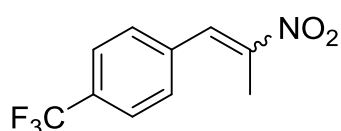
A solution of methyl 4-formylbenzoate (5.31 g, 32.3 mmol, 1 eq) and ammonium acetate (0.499 g, 6.47 mmol, 0.2 eq) in nitroethane (54 mL, 0.6 M) was stirred at 110 °C for 6 days. After reaction completion the mixture was cooled to 4 °C and washed with cold CH before being filtered off and dried to give *E/Z*-**19** (6.554 g, 29.6 mmol, 92%) which was submitted to the following step without further purification.

***E/Z*-1-fluoro-4-(2-nitroprop-1-en-1-yl)benzene (20)**



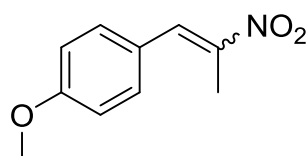
A solution of 4-fluorobenzaldehyde (20 g, 161 mmol, 1 eq) and ammonium acetate (2.484 g, 32.2 mmol, 0.2 eq) in nitroethane (269 mL, 0.6 M) was stirred at 110 °C for 24 h. After reaction completion the mixture was cooled to 4 °C and washed with cold CH before being filtered off and dried to give *E/Z*-**20** (14.95 g, 83 mmol, 51.2%) which was submitted to the following step without further purification.

***E/Z*-1-(2-nitroprop-1-en-1-yl)-4-(trifluoromethyl)benzene (21)**



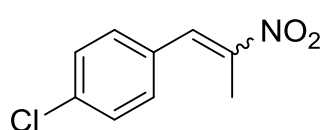
A solution of 4-(trifluoromethyl)benzaldehyde (8 g, 45.9 mmol, 1 eq) and ammonium acetate (0.708 g, 9.19 mmol, 0.2 eq) in nitroethane (77 mL, 0.6 M) was stirred at 110 °C for 4 days. After reaction completion the mixture was cooled to 4 °C and washed with cold CH before being filtered off and dried to give *E/Z*-**21** (10.62 g, 45.9 mmol, 100%) which was submitted to the following step without further purification.

***E/Z*-1-methoxy-4-(2-nitroprop-1-en-1-yl)benzene (22)**



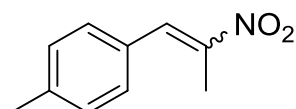
A solution of 4-methoxybenzaldehyde (10 g, 73.4 mmol, 1 eq) and ammonium acetate (1.132 g, 14.69 mmol, 0.2 eq) in nitroethane (122 mL, 0.6 M) was stirred at 110 °C for 3 days. After reaction completion the mixture was cooled to 4 °C and washed with cold CH before being filtered off and dried to give *E/Z*-**22** (14.19 g, 73.4 mmol, 100%) which was submitted to the following step without further purification.

***E/Z*-1-chloro-4-(2-nitroprop-1-en-1-yl)benzene (23)**



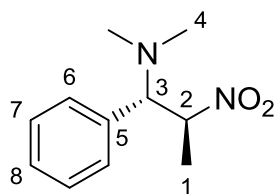
A solution of 4-chlorobenzaldehyde (10 g, 71.1 mmol, 1 eq) and ammonium acetate (1.097 g, 14.23 mmol, 0.2 eq) in nitroethane (119 mL, 0.6 M) was stirred at 110 °C for 4 days. After reaction completion the mixture was cooled to 4 °C and washed with cold CH before being filtered off and dried to give *E/Z*-**23** (14.06 g, 71.1 mmol, 100%) which was submitted to the following step without further purification.

***E/Z*-1-methyl-4-(2-nitroprop-1-en-1-yl)benzene (24)**



A solution of 4-methylbenzaldehyde (10 g, 83 mmol, 1 eq) and ammonium acetate (1.283 g, 16.65 mmol, 0.2 eq) in nitroethane (139 mL, 0.6 M) was stirred at 110 °C for 16 h. After reaction completion the mixture was cooled to 4 °C and washed with cold CH before being filtered off and dried to give *E/Z*-**24** (14.75 g, 83 mmol, 100%) which was submitted to the following step without further purification.

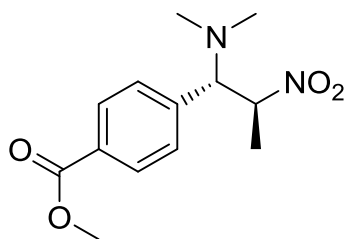
(1S*, 2S*)-N,N-dimethyl-2-nitro-1-phenylpropan-1-amine (25)



To a stirred solution of *E/Z*-**18** (1 g, 6.13 mmol, 1 eq) in THF (15 mL, anhydrous) was added Dimethylamine 2M (in THF) (15 mL, 30.6 mmol, 5 eq) at room temperature and the solution was allowed to stir for 16 h. After reaction completion the solution was concentrated to a yellow crystalline crude material which was immediately submitted to a purification by Isolera Biotage LPLC (CH/EA 90:10 to CH/EA 2:8) to give **25** (1.0219 g, >33:1 dr, 70.5%) as a unstable white waxy solid.

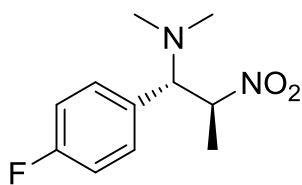
ν_{\max} (cm⁻¹) 2975, 2944, 2835, 2791, 1556, 1451, 1353, 873, 705, 614; ¹H-NMR (400 MHz, CDCl₃): δ_{H} 7.39 (m, 3H, *H*-7; *H*-8), 7.11 (m, 1H, *H*-6), 5.23 (dq, 1H, *J* = 11.1, 6.6 Hz, *H*-2), 4.01 (d, 1H, *J* = 11 Hz, *H*-3), 2.15 (s, 6H, *H*-4), 1.34 (d, 1H, *J* = 6.6 Hz, *H*-1); ¹³C-NMR (100 MHz, CDCl₃): δ_{C} 131.0 (C-5), 129.2 (C-6), 128.3 (C-7), 128.2 (C-8), 83.7 (C-2), 72.3 (C-3), 40.9 (C-4), 17.2 (C-1); LR-ESI-MS: C₁₁H₁₇N₂O₂ [M+H]⁺ *m/z* found 209.1, calcd 209.1. HR-ESI-MS: C₁₁H₁₇N₂O₂ [M+H]⁺ *m/z* found 209.0879, calcd 209.1290.

methyl 4-((1S*, 2S*)-1-(dimethylamino)-2-nitropropyl)benzoate (26)



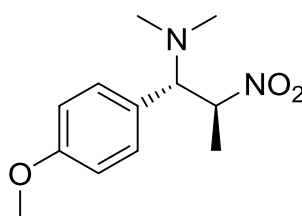
To a stirred solution of *E/Z*-**19** (1.133 g, 5.12 mmol, 1 eq) in THF (10 mL, anhydrous) was added Dimethylamine 2M (in THF) (12.8 mL, 25.6 mmol, 5 eq) at room temperature and the solution was allowed to stir for 16 h. After reaction completion the solution was concentrated to give **26** (1.364 g, 5.12 mmol, 12:1 dr, 100%) as an unstable red crude material which was immediately submitted to the next step without further purification.

(1S*, 2S*)-1-(4-fluorophenyl)-N,N-dimethyl-2-nitropropan-1-amine (27)



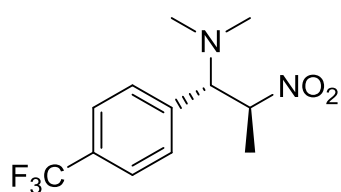
To a stirred solution of *E/Z*-**20** (5 g, 27.6 mmol, 1 eq) in THF (20 mL, anhydrous) was added Dimethylamine 2M (in THF) (69 mL, 138 mmol, 5 eq) at room temperature and the solution was allowed to stir for 16 h. After reaction completion the solution was concentrated to give **27** (6.24 g, 27.6 mmol, 15:1 dr, 100%) as an unstable yellow crystalline crude material which was immediately submitted to the next step without further purification.

(1S*, 2S*)-1-(4-methoxyphenyl)-N,N-dimethyl-2-nitropropan-1-amine (28)



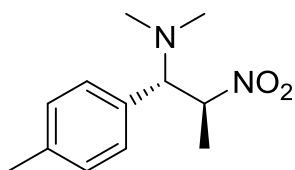
To a stirred solution of *E/Z*-**22** (14.19 g, 73.4 mmol, 1 eq) in THF (30 mL, anhydrous) was added Dimethylamine 2M (in THF) (184 mL, 367 mmol, 5 eq) at room temperature and the solution was allowed to stir for 48 h. After reaction completion the solution was concentrated to give **28** (17.5 g, 73.4 mmol, 7.5:1 dr, 100%) as an unstable red solid which was immediately submitted to the next step without further purification.

(1S*, 2S*)-N,N-dimethyl-2-nitro-1-(4-(trifluoromethyl)phenyl)propan-1-amine (29)



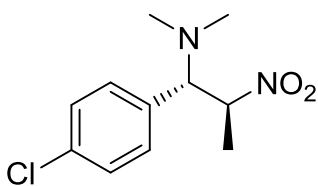
To a stirred solution of *E/Z*-**21** (10.62 g, 45.9 mmol, 1 eq) in THF (30 mL, anhydrous) was added Dimethylamine 2M (in THF) (115 mL, 230 mmol, 5 eq) at room temperature and the solution was allowed to stir for 16 h. After reaction completion the solution was concentrated to give **29** (12.69 g, 45.9 mmol, 6.8:1 dr, 100%) as an unstable red solid which was immediately submitted to the next step without further purification.

(1S*, 2S*)-N,N-dimethyl-2-nitro-1-(p-tolyl)propan-1-amine (30)



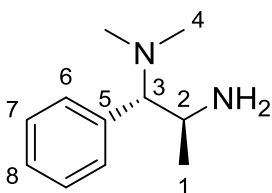
To a stirred solution of *E/Z*-**24** (14.75 g, 83 mmol, 1 eq) in THF (30 mL, anhydrous) was added Dimethylamine 2M (in THF) (208 mL, 291 mmol, 5 eq) at room temperature and the solution was allowed to stir for 16 h. After reaction completion the solution was concentrated to give **30** (18.5 g, 83 mmol, 13:1 dr, 100%) as an unstable dark red solid which was immediately submitted to the next step without further purification.

(1S*, 2S*)-1-(4-chlorophenyl)-N,N-dimethyl-2-nitropropan-1-amine (31)



To a stirred solution of *E/Z*-**23** (14.06 g, 71.1 mmol, 1 eq) in THF (30 mL, anhydrous) was added Dimethylamine 2M (in THF) (178 mL, 249 mmol, 5 eq) at room temperature and the solution was allowed to stir for 16 h. After reaction completion the solution was concentrated to give **31** (17.27 g, 71.1 mmol, 4.6:1 dr, 100%) as an unstable dark red solid which was immediately submitted to the next step without further purification.

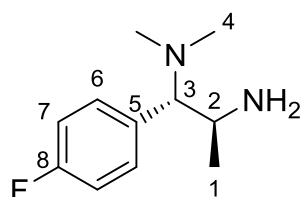
(1S*, 2S*)-N,N₁-dimethyl-1-phenylpropane-1,2-diamine (32)



To a degassed stirred solution of **25** (4.2127 g, 20.23 mmol, 1 eq) in MeOH (101 mL, 0.2 M, anhydrous) was added Pd/C (10%) (0.42 g, 0.195 eq) and atmosphere was exchanged with H₂ gas (x3). The reaction mixture was stirred under a H₂ atmosphere (double balloon, 1 bar) for 5 h. Upon reaction completion the mixture was filtered through celite, followed by filtration through a sintered frit to afford a crude oil after drying. The oily residue was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **32** (0.4 g, 2.244 mmol, single diastereomer, 11% over two steps) as a colourless oil.

ν_{max} (cm⁻¹) 2963, 2780, 1581, 1452, 1375, 753, 704; ¹H-NMR (400 MHz, CDCl₃): δ_{H} 7.46 (m, 2H, *H*-7, *H*-8), 7.26 (m, 2H, *H*-6), 3.56 (m, 1H, *H*-2), 3.19 (d, 1H, *J* = 9.5 Hz, *H*-3), 2.28 (s, 6H, *H*-4), 1.03 (d, 3H, *J* = 6.2 Hz, *H*-1); ¹³C-NMR (100 MHz DMSO-*d*⁶): δ_{C} 135.3 (C-5), 129.4 (C-6), 127.6 (C-7), 126.8 (C-8), 79.2 (C-3), 45.2 (C-2), 40.9 (C-4), 20.4 (C-1); LR-ESI-MS: C₁₁H₁₉N₂ [M+H]⁺ *m/z* found 179.2, calcd 179.2; HR-ESI-MS: C₁₁H₁₉N₂ [M+H]⁺ *m/z* found 179.1549, calcd 179.1548.

(1S*, 2S*)-1-(4-fluorophenyl)-N₁,N₁-dimethylpropane-1,2-diamine (33)

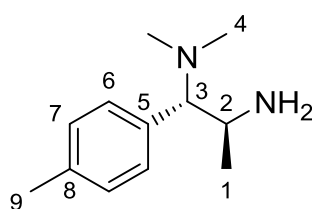


To a degassed stirred solution of **27** (6.24 g, 27.6 mmol, 1 eq) in MeOH (68.9 mL, 0.4 M, anhydrous) was added Pd/C (10%) (0.646 g, 0.22 eq) and atmosphere was exchanged with H₂ gas (x3). The reaction mixture was stirred under a H₂ atmosphere (double balloon, 1 bar) for 16 h. Upon reaction completion the mixture was filtered through celite, followed by filtration through a sintered frit to afford a yellow crude oil after drying.

The oily residue was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **33** (0.569 g, 2.90 mmol, single diastereomer, 10.5% over two steps) as a colourless oil.

v_{max} (cm⁻¹) 2827, 1599, 1506, 1222, 846; **¹⁹F-{H}-NMR (376 MHz, CDCl₃)**: **δ_F** -115.77; **¹H-{F}-NMR (400 MHz, CDCl₃)**: **δ_H** 7.08 (d, 2H, *J* = 8.7 Hz, *H*-7), 7.02 (d, 2H, *J* = 8.7 Hz, *H*-6), 3.36 (dq, 1H, *J* = 9.8, 6.2 Hz, *H*-2), 3.03 (d, 1H, *J* = 9.2 Hz, *H*-3), 2.11 (s, 6H, *H*-4), 0.86 (d, 3H, *J* = 6.2 Hz, *H*-1); **¹³C-NMR (100 MHz CDCl₃)**: **δ_C** 162.0 (d, *J* = 245 Hz, C-8), 131.0 (d, *J* = 3.7 Hz, C-5), 130.8 (d, *J* = 8.1 Hz, C-6), 114.6 (d, *J* = 20.5 Hz, C-7), 76.2 (C-3), 46.0 (C-2), 41.1 (C-4), 20.4 (C-1); **LR-ESI-MS**: C₁₁H₁₈FN₂ [M+H]⁺ *m/z* found 197.2, cald 197.2; **HR-ESI-MS**: C₁₁H₁₇FN₂Na [M+Na]⁺ *m/z* found 219.1363, cald 219.1273.

(1S*, 2S*)-N₁,N₁-dimethyl-1-(p-tolyl)propane-1,2-diamine (34)

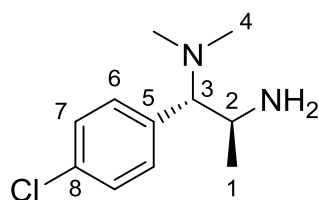


To a degassed stirred solution of **30** (1 g, 4.50 mmol, 1 eq) in MeOH (30 mL, 0.15 M, anhydrous) was added Pd/C (10%) (0.144 g, 0.3 eq) and atmosphere was exchanged with H₂ gas (x3). The reaction mixture was stirred under a H₂ atmosphere (double balloon, 1 bar) for 16 h. Upon reaction completion the mixture was filtered through celite, followed by filtration through a sintered frit to afford a yellow crude oil after drying.

The oily residue was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **34** (0.153 g, 0.796 mmol, single diastereomer, 17.7% over two steps) as a white waxy solid.

v_{max} (cm⁻¹) 3283, 2973, 2867, 1599, 1451, 1016, 801, 591; **¹H-NMR (400 MHz, CDCl₃)**: **δ_H** 7.14 (d, 2H, *J* = 7.8 Hz, *H*-6), 6.99 (d, 2H, *J* = 8.1 Hz, *H*-7), 3.38 (dq, 1H, *J* = 9.7, 6.3 Hz, *H*-2), 3.01 (d, 1H, *J* = 9.8 Hz, *H*-3), 2.35 (s, 3H, *H*-9), 2.11 (s, 6H, *H*-4), 0.87 (d, 3H, *J* = 6.2 Hz, *H*-1); **¹³C-NMR (100 MHz CDCl₃)**: **δ_C** 136.6 (C-5), 132.0 (C-8), 129.4 (C-6), 128.4 (C-7), 76.5 (C-3), 45.8 (C-2), 41.2 (C-4), 21.0 (C-9), 20.4 (C-1); **LR-ESI-MS**: C₁₂H₂₁N₂ [M+H]⁺ *m/z* found 193.3, cald 193.2; **HR-ESI-MS**: C₁₂H₂₁N₂ [M+H]⁺ *m/z* found 193.1706, cald 193.1705.

(1S*, 2S*)-1-(4-chlorophenyl)-N₁,N₁-dimethylpropane-1,2-diamine (35)



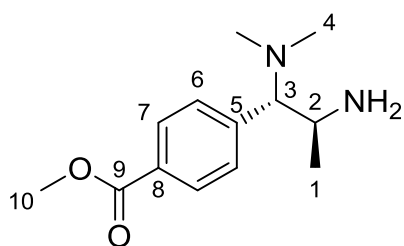
Under an inert atmosphere (N₂) Raney Ni (2400) (0.234 g, 0.3 eq) was activated by washings with H₂O (x3) and then MeOH (x3, anhydrous) before a degassed solution of **31** (3.22 g, 13.27 mmol, 1 eq) in MeOH (66 mL, 0.2 M, anhydrous) was added. The reaction vessel atmosphere was then exchanged with H₂ gas (x3). The reaction mixture was stirred under a H₂ atmosphere (double balloon, 1 bar) for 16 h. Upon reaction

completion the mixture was filtered through celite, followed by filtration through a sintered frit to afford a colourless crude oil after drying. The oily residue was purified by Isolera Biotage LPLC

(DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **35** (0.691 g, 3.25 mmol, single diastereomer, 24.48% over three steps) as a colourless oil.

ν_{max} (cm⁻¹) 2933, 2864, 2825, 2780, 1592, 1488, 1452, 1090, 1012, 842, 802, 701; ¹H-NMR (400 MHz, CDCl₃): δ_{H} 7.30 (d, 2H, *J* = 8.6 Hz, *H*-7), 7.03 (d, 2H, *J* = 8.3 Hz, *H*-6), 3.36 (dq, 1H, *J* = 9.6, 6.3 Hz, *H*-2), 3.02 (d, 1H, *J* = 9.7 Hz, *H*-3), 2.10 (s, 6H, *H*-4), 0.86 (d, 3H, *J* = 6.2 Hz, *H*-1); ¹³C-NMR (100 MHz CDCl₃): δ_{C} 133.6 (C-8), 132.9 (C-5), 130.7 (C-6), 127.9 (C-7), 76.2 (C-3), 45.8 (C-2), 41.1 (C-4), 20.3 (C-1); LR-ESI-MS: C₁₁H₁₈ClN₂ [M+H]⁺ *m/z* found 213.2, calcd 213.1; HR-ESI-MS: C₁₁H₁₈ClN₂ [M+H]⁺ *m/z* found 213.0792, calcd 213.1159.

methyl 4-((1*S**, 2*S**)-2-amino-1-(dimethylamino)propyl)benzoate (**36**)

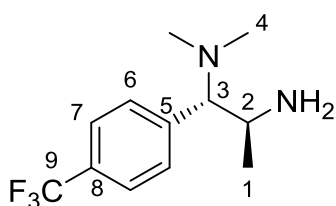


Under an inert atmosphere (N₂) Raney Ni (2400) (0.066 g, 0.3 eq) was activated by washings with H₂O (x3) and then MeOH (x3, anhydrous) before a degassed solution of **26** (1 g, 3.76 mmol, 1 eq) in MeOH (38 mL, 0.1 M, anhydrous) was added. The reaction vessel atmosphere was then exchanged with H₂ gas (x3). The reaction mixture was stirred under a H₂ atmosphere (double balloon, 1 bar) for 3 h. Upon reaction completion the mixture

was filtered through celite, followed by filtration through a sintered frit to afford a colourless crude oil after drying. The oily residue was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **36** (0.251 g, 1.062 mmol, single diastereomer, 28.3% over three steps) as a colourless oil.

ν_{max} (cm⁻¹) 2950, 2826, 2782, 1716, 1435, 1311, 765; ¹H-NMR (400 MHz, CDCl₃): δ_{H} 8.01 (d, 2H, *J* = 8.1 Hz, *H*-7), 7.18 (d, 2H, *J* = 8.3 Hz, *H*-6), 3.92 (s, 3H, *H*-10), 3.42 (dq, 1H, *J* = 9.7, 6.3 Hz, *H*-2), 3.10 (d, 1H, *J* = 9.7 Hz, *H*-3), 2.13 (s, 6H, *H*-4), 0.87 (d, 3H, *J* = 6.4 Hz, *H*-1); ¹³C-NMR (100 MHz CDCl₃): δ_{C} 167.0 (C-9), 140.7 (C-5), 129.4 (C-7), 129.1 (C-8), 129.0 (C-6), 52.1 (C-3), 45.7 (C-2), 41.2 (C-4), 20.3 (C-1); LR-ESI-MS: C₁₃H₂₁N₂O₂ [M+H]⁺ *m/z* found 237.2, calcd 237.2; HR-ESI-MS: C₁₃H₂₁N₂O₂ [M+H]⁺ *m/z* found 237.1560, calcd 237.1603.

(1*S**, 2*S**)-*N*₁,*N*₁-dimethyl-1-(4-(trifluoromethyl)phenyl)propane-1,2-diamine (**37**)



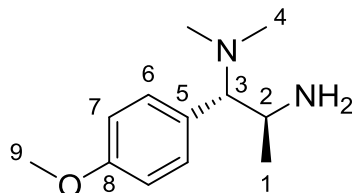
To a degassed stirred solution of **29** (2.486 g, 9 mmol, 1 eq) in MeOH (60 mL, 0.15 M, anhydrous) was added Pd/C (10%) (0.287 g, 0.3 eq) and atmosphere was exchanged with H₂ gas (x3). The reaction mixture was stirred under a H₂ atmosphere (double balloon, 1 bar) for 16 h. Upon reaction completion the mixture was filtered through celite,

followed by filtration through a sintered frit to afford a colourless crude oil after drying. The oily residue was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **37** (0.153 g, 0.796 mmol, single diastereomer, 14.2% over three steps) as a colourless oil.

ν_{max} (cm⁻¹) 3222, 2936, 2785, 1670, 1163, 1032, 850; ¹⁹F-{¹H}-NMR (376 MHz, CDCl₃): δ_{F} -62.44; ¹H-NMR (400 MHz, CDCl₃): δ_{H} 7.60 (d, 2H, *J* = 8.1 Hz, *H*-7), 7.23 (d, 2H, *J* = 8.1 Hz, *H*-6), 3.42 (dq, 1H, *J* = 9.6, 6.3 Hz, *H*-2), 3.12 (d, 1H, *J* = 9.7 Hz, *H*-3), 2.13 (s, 6H, *H*-4), 0.87 (d, 3H, *J* = 6.2 Hz, *H*-1); ¹³C-NMR (100 MHz CDCl₃): δ_{C} 139.6 (C-5), 129.7 (C-7; C-6), 124.7 (q, *J* = 3.7 Hz, C-9), 76.5 (C-3), 45.7 (C-2), 41.2 (C-

4), 20.3 (C-1); **LR-ESI-MS**: $C_{12}H_{18}F_3N_2$ $[M+H]^+$ m/z found 247.1, calcd 247.1; **HR-ESI-MS**: $C_{12}H_{18}F_3N_2$ $[M+H]^+$ m/z found 247.1428, calcd 247.1422.

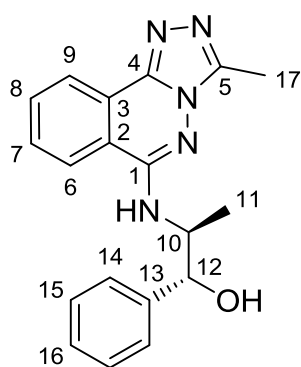
(1S*, 2S*)-1-(4-methoxyphenyl)-N₁,N₁-dimethylpropane-1,2-diamine (38)



To a degassed stirred solution of **30** (2.556 g, 10.73 mmol, 1 eq) in MeOH (72 mL, 0.15 M, anhydrous) was added Pd/C (10%) (0.342 g, 0.3 eq) and atmosphere was exchanged with H₂ gas (x3). The reaction mixture was stirred under a H₂ atmosphere (double balloon, 1 bar) for 16 h. Upon reaction completion the mixture was filtered through celite, followed by filtration through a sintered frit to afford a colourless crude oil after drying. The oily residue was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **38** (0.334 g, 1.603 mmol, single diastereomer, 15% over three steps) as a colourless oil.

ν_{\max} (cm⁻¹) 2931, 2825, 1608, 1509, 1246, 1030, 840, 808, 593; **¹H-NMR (400 MHz, CDCl₃)**: δ_H 7.02 (d, 2H, J = 8.7 Hz, *H*-6), 6.87 (d, 2H, J = 8.7 Hz, *H*-7), 3.81 (s, 3H, *H*-9), 3.35 (dq, 1H, J = 9.7, 6.2 Hz, *H*-2), 2.99 (d, 1H, J = 9.7 Hz, *H*-3), 2.10 (s, 6H, *H*-4), 0.87 (d, 3H, J = 6.2 Hz, *H*-1); **¹³C-NMR (100 MHz CDCl₃)**: δ_C 158.6 (C-8), 130.5 (C-6), 127.3 (C-5), 113.0 (C-7), 76.2 (C-3), 55.1 (C-9), 46.0 (C-2), 41.2 (C-4), 20.4 (C-1); **LR-ESI-MS**: $C_{12}H_{21}N_2O$ $[M+H]^+$ m/z found 209.2, calcd 209.2; **HR-ESI-MS**: $C_{12}H_{21}N_2O$ $[M+H]^+$ m/z found 209.1295, calcd 209.1654.

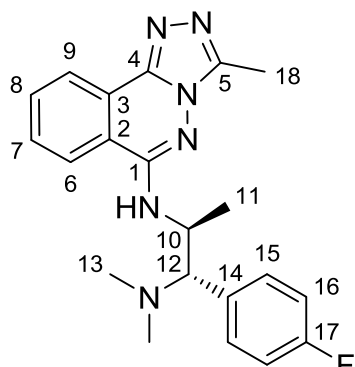
(1R, 2S)-2-((3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino)-1-phenylpropan-1-ol (77)



5 (1 g, 0.915 mmol, 1 eq) and (1R,2S)-(-)-Norephedrine (1.037 g, 6.86 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10) to give **77** (0.413 g, 1.239 mmol, 27.1%) as a white solid.

Mpt: 239.6-241.6 °C; ν_{\max} (cm⁻¹) 3640, 3277, 2972, 1514, 1000, 701; **¹H-NMR (400 MHz, CDCl₃)**: δ_H 8.47 (d, 1H, J = 8.2 Hz, *H*-9), 8.35 (d, 1H, J = 7.9 Hz, *H*-6), 7.89 (m, 1H, *H*-8), 7.81 (m, 1H, *H*-7), 7.49 (d, 2H, J = 7.3 Hz, *H*-14), 7.31 (m, 3H, *H*-15; NH), 7.18 (m, 1H, *H*-16), 5.45 (d, 1H, J = 4.8 Hz, OH), 5.07 (m, 1H, *H*-12), 4.32 (m, 1H, *H*-10), 1.17 (d, 3H, J = 6.7 Hz, *H*-11); **¹³C-NMR (100 MHz, DMSO-*d*⁶)**: δ_C 150.4 (C-1), 146.0 (C-13), 143.9 (C-4), 141.0 (C-5), 132.7 (C-8), 130.0 (C-7), 127.8 (C-14), 126.5 (C-16), 125.9 (C-15), 124.6 (C-9), 123.3 (C-3), 122.4 (C-6), 118.3 (C-2), 72.1 (C-12), 53.0 (C-10), 13.2 (C-11), 9.4 (C-17); **LR-ESI-MS**: $C_{19}H_{20}N_5O$ $[M+H]^+$ m/z found 334.2, calcd 334.2; **HR-ESI-MS**: $C_{19}H_{20}N_5O$ $[M+H]^+$ m/z found 334.1711, calcd 334.1668.

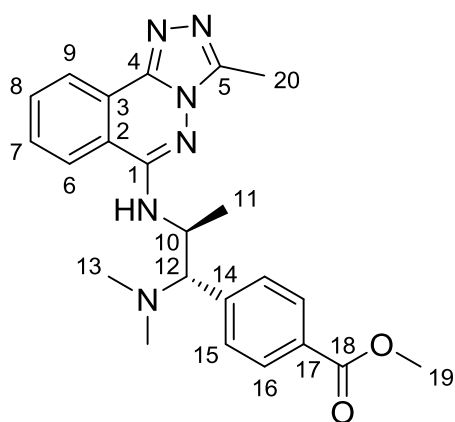
(1S*, 2S*)-1-(4-fluorophenyl)-N₁,N₁-dimethyl-N₂-(3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)propane-1,2-diamine (39)



5 (365 mg, 1.669 mmol, 1 eq) and **33** (491 mg, 2.504 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10) to give **39** (206 mg, 0.545 mmol, 32.7%) as an off white solid.

Mpt: 239.8-241.8 °C; ν_{\max} (cm⁻¹) 3453, 2953, 2814, 2773, 1593, 1500, 1246, 1028, 547, 695, 656, 446; ¹⁹F-{¹H}-NMR (376 MHz, CDCl₃): δ_F -115.67; ¹H-{¹F}-NMR (400 MHz, DMSO-*d*⁶): δ_H 8.40 (d, 1H, *J* = 7.7 Hz, *H*-9), 8.28 (d, 1H, *J* = 8.2 Hz, *H*-6), 7.94 (t, 1H, *J* = 7.7 Hz, *H*-8), 7.82 (m, 1H, *H*-7), 7.27 (d, 2H, *J* = 8.7 Hz, *H*-16), 7.18, (d, 2H, *J* = 7.2 Hz, *H*-15), 7.01 (d, 1H, *J* = 5.7 Hz, NH), 4.70 (m, 1H, *H*-10), 3.72 (d, 1H, *J* = 8.2 Hz, *H*-12), 2.62 (s, 3H, *H*-18), 2.13 (s, 6H, *H*-13), 1.10 (d, 3H, *J* = 6.2 Hz, *H*-11); ¹³C-NMR (100 MHz, DMSO-*d*⁶): δ_C 161.5 (d, *J* = 242.1 Hz, C-17), 150.6 (C-1), 146.1 (C-4), 141.1 (C-5), 132.9 (C-8), 132.3 (C-14), 131.1 (d, *J* = 8.1 Hz, C-15), 130.2 (C-7), 124.2 (C-9), 123.4 (C-3), 122.6 (C-6), 118.3 (C-2), 114.5 (d, *J* = 21.3 Hz, C-16), 70.7 (C-12), 46.2 (C-10), 42.0 (C-13), 16.0 (C-11), 9.4 (C-18); **LR-ESI-MS:** C₂₁H₂₄FN₆ [M+H]⁺ *m/z* found 379.3, cald 379.2; **HR-ESI-MS:** C₂₁H₂₄FN₆ [M+H]⁺ *m/z* found 379.2070, cald 379.2046.

methyl 4-((1S*, 2S*)-1-(dimethylamino)-2-((3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino)propyl)benzoate (40)

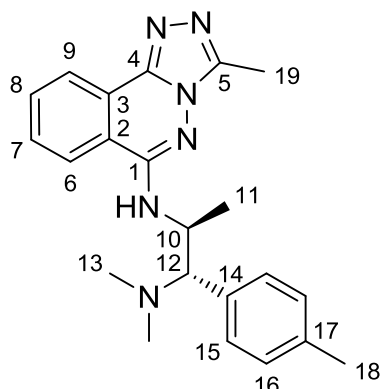


5 (156 mg, 0.713 mmol, 1 eq) and **36** (253 mg, 1.07 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **40** (83 mg, 0.198 mmol 27.8%) as a white solid.

Mpt: 254.3-256.3 °C; ν_{\max} (cm⁻¹) 3256, 2926, 2775, 1722, 1593, 1432, 1101, 1019, 670, 659, 542; ¹H-NMR (400MHz, DMSO-*d*⁶): δ_H 8.40 (d, 1H, *J* = 7.9 Hz, *H*-9), 8.29 (d, 1H, *J* = 8.2 Hz, *H*-6), 7.94 (m, 3H, *H*-8; *H*-16), 7.81 (m, 1H, *H*-7), 7.36 (d, 2H, *J* = 8.3 Hz, *H*-15), 7.01 (d, 1H, *J* = 5.7 Hz, NH), 4.78 (m, 1H, *H*-10), 3.85 (s, 3H, *H*-19), 3.79 (d, 1H, *J* = 7.7 Hz, *H*-12), 2.62

(s, 3H, *H*-20), 2.15 (s, 6H, *H*-13), 1.10 (d, 3H, *J* = 6.6 Hz, *H*-11); ¹³C-NMR (100 MHz DMSO-*d*⁶): δ_C 166.3 (C-18), 150.6 (C-1), 146.1 (C-4), 142.3 (C-14), 141.1 (C-5), 132.9 (C-8), 130.2 (C-7), 129.7 (C-16), 128.6 (C-15), 128.6 (C-17), 124.2 (C-9), 123.5 (C-3), 122.6 (C-6), 118.3 (C-2), 71.1 (C-12), 52.1 (C-19), 46.5 (C-10), 42.3 (C-13), 15.8 (C-11), 9.4 (C-20); **LR-ESI-MS:** C₂₃H₂₇N₆O₂ [M+H]⁺ *m/z* found 419.4, cald 419.2; **HR-ESI-MS:** C₂₃H₂₇N₆O₂ [M+H]⁺ *m/z* found 419.2233, cald 419.2195.

(1S*, 2S*)-N₁,N₁-dimethyl-N₂-(3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-1-(p-tolyl)propane-1,2-diamine (41)

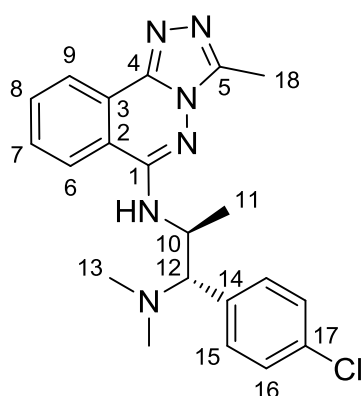


5 (75 mg, 0.343 mmol, 1 eq) and **34** (99 mg, 0.515 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **41** (43 mg, 0.115 mmol 33.4%) as a white solid.

Mpt: 189.6-191.6 °C; **v_{max} (cm⁻¹)** 3257, 2926, 2772, 1508, 1306, 1265, 1027, 802, 699; **¹H-NMR (400MHz, CDCl₃):** δ _H 8.61 (d, 1H, *J* = 7.9 Hz, *H*-9), 7.84 (m, 2H, *H*-6; *H*-8), 7.74 (m, 1H, *H*-7), 7.26 (m, 2H, *H*-15), 7.21 (d, 2H, *J* = 7.7 Hz, *H*-16), 6.86 (s, 1H, NH), 4.34 (m, 1H, *H*-10), 3.66 (m, 1H, *H*-12), 2.74 (s, 3H, *H*-18), 2.41 (s, 3H, *H*-18),

2.21 (s, 6H, *H*-13), 1.26 (d, 3H, *J* = 6 Hz, *H*-11); **¹³C-NMR (100 MHz, CDCl₃):** δ _C 151.4 (C-1), 147.3 (C-4), 142.0 (C-5), 136.0 (C-14), 132.4 (C-8), 130.0 (C-15), 129.7 (C-7), 128.4 (C-16), 124.3 (C-9), 123.8 (C-3), 122.8 (C-6), 119.2 (C-2), 73.0 (C-12), 47.2 (C-10), 40.8 (C-13), 21.1 (C-18), 17.6 (C-11), 9.8 (C-19); **LR-ESI-MS:** C₂₂H₂₇N₆ [M+H]⁺ *m/z* found 375.3, calcd 375.3; **HR-ESI-MS:** C₂₂H₂₇N₆ [M+H]⁺ *m/z* found 375.2315, calcd 375.2297.

(1S*, 2S*)-1-(4-chlorophenyl)-N₁,N₁-dimethyl-N₂-(3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)propane-1,2-diamine (42)

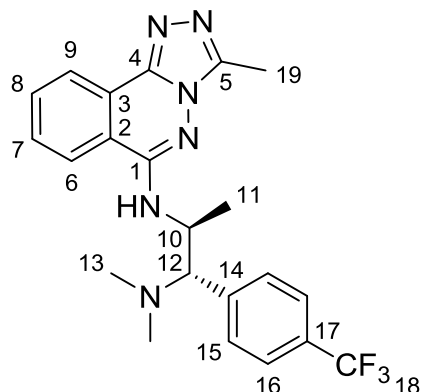


5 (410 mg, 1.875 mmol, 1 eq) and **35** (598 mg, 2.81 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **42** (43 mg, 0.115 mmol 33.4%) as a white solid.

Mpt: 158.8-160.8 °C; **v_{max} (cm⁻¹)** 3272, 2924, 1593, 1497, 1455, 1262, 1051, 696, 552, 461; **¹H-NMR (400 MHz, CDCl₃):** δ _H 8.63 (d, 1H, *J* = 7.8 Hz, *H*-9), 7.83 (m, 2H, *H*-6; *H*-8), 7.75 (m, 1H, *H*-7), 7.41 (d, 2H, *J* = 8.3 Hz, *H*-16), 7.21 (d, 2H, *J* = 8.4 Hz, *H*-15), 6.68 (s, 1H, NH), 4.30 (m, 1H, *H*-10), 3.61 (d, 1H, *J* = 10.1 Hz, *H*-12), 2.73 (s, 3H, *H*-18),

2.15 (s, 6H, *H*-13), 1.25 (d, 3H, *J* = 6 Hz, *H*-11); **¹³C-NMR (100 MHz CDCl₃):** δ _C 151.2 (C-1), 147.3 (C-4), 142.0 (C-5), 133.9 (C-8), 132.5 (C-14), 132.0 (C-17), 130.9 (C-16), 130.0 (C-7), 128.4 (C-15), 124.3 (C-9), 123.8 (C-3), 122.5 (C-6), 119.1 (C-2), 72.7 (C-12), 47.1 (C-10), 40.9 (C-13), 17.4 (C-11), 9.8 (C-18); **LR-ESI-MS:** C₂₁H₂₄ClN₆ [M+H]⁺ *m/z* found 395.3, calcd 395.2; **HR-ESI-MS:** C₂₁H₂₄ClN₆ [M+H]⁺ *m/z* found 395.1773, calcd 395.1751.

(1*S, 2*S**)-*N*₁,*N*₁-dimethyl-*N*₂-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)-1-(4-(trifluoromethyl)phenyl)propane-1,2-diamine (**43**)**

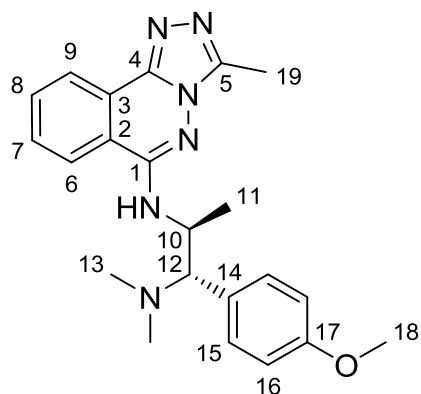


5 (170 mg, 0.778 mmol, 1 eq) and **37** (287 mg, 1.166 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **43** (53 mg, 0.124 mmol, 16%) as a white solid.

Mpt: 143.6–145.6 °C; **v_{max}** (cm⁻¹) 3286, 2958, 2820, 1505, 1320, 1066, 699, 617; **¹⁹F-NMR** (376 MHz, CDCl₃): **δ_F** -62.53; **¹H-NMR** (400 MHz, CDCl₃): **δ_H** 8.64 (d, 1H, *J* = 7.9 Hz, *H*-9), 7.87 (m, 1H, *H*-8), 7.81 (m, 1H, *H*-6), 7.75 (m, 1H, *H*-7), 7.70 (d, 2H, *J* = 8.1 Hz, *H*-16), 7.41 (d, 2H, *J* = 8.1 Hz, *H*-15), 6.62 (s, 1H, *NH*), 4.39 (m,

1H, *H*-10), 3.71 (d, 1H, *J* = 10.3 Hz, *H*-12), 2.74 (s, 3H, *H*-18), 2.21 (s, 6H, *H*-13), 1.26 (d, 3H, *J* = 6 Hz, *H*-11); **¹³C-NMR** (100 MHz CDCl₃): **δ_C** 151.2 (C-1), 147.3 (C-4), 142.0 (C-5), 137.8 (C-14), 132.5 (C-8), 130.0 (q, *J* = 36.7 Hz, C-17), 129.9 (C-7), 125.1 (q, *J* = 3.7 Hz, C-16), 124.4 (C-9), 124.1 (q, *J* = 105.6 Hz, C-18), 123.9 (C-3), 122.7 (C-15), 122.5 (C-6), 119.1 (C-2), 72.9 (C-12), 47.1 (C-10), 40.9 (C-13), 17.4 (C-11), 9.8 (C-19); **LR-ESI-MS:** C₂₂H₂₄F₃N₆ [M+H]⁺ *m/z* found 429.2, calcd 429.2; **HR-ESI-MS:** C₂₂H₂₄F₃N₆ [M+H]⁺ *m/z* found 429.2061, calcd 429.2015.

(1*S, 2*S**)-1-(4-methoxyphenyl)-*N*₁,*N*₁-dimethyl-*N*₂-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)propane-1,2-diamine (**44**)**

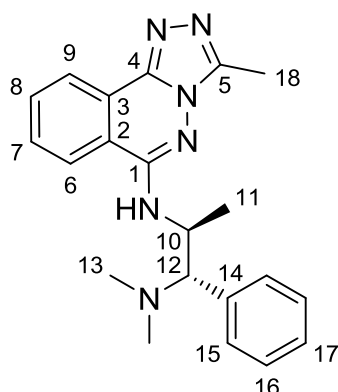


5 (234 mg, 1.07 mmol, 1 eq) and **38** (334 mg, 1.605 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **44** (330 mg, 1.07 mmol, 79%) as a white solid.

Mpt: 171.9–173.9 °C; **v_{max}** (cm⁻¹) 3318, 2929, 2778, 1509, 1263, 1177, 1028, 769; **¹H-NMR** (400 MHz, CDCl₃): **δ_H** 8.63 (d, 1H, *J* = 7.6 Hz, *H*-9), 7.84 (m, 2H, *H*-6; *H*-8), 7.75 (m, 1H, *H*-7), 7.20 (d, 2H, *J* = 8.3 Hz, *H*-15), 6.98 (d, 2H, *J* = 8.6 Hz, *H*-16), 6.85 (s, 1H, *NH*), 4.28 (m, 1H, *H*-10), 3.86 (s, 3H, *H*-18), 3.57 (d, 2H, *J* = 9.8

Hz, *H*-12), 2.74 (s, 3H, *H*-19), 2.17 (s, 6H, *H*-13), 1.26 (d, 3H, *J* = 6 Hz, *H*-11); **¹³C-NMR** (100 MHz, CDCl₃): **δ_C** 159.3 (C-17), 151.4 (C-1), 147.3 (C-4), 142.0 (C-5), 132.4 (C-8), 130.7 (C-14), 130.0 (C-7), 125.4 (C-15), 124.3 (C-9), 123.8 (C-3), 122.6 (C-6), 119.3 (C-2), 113.5 (C-16), 72.7 (C-10), 55.2 (C-18), 47.4 (C-12), 40.8 (C-13), 17.5 (C-11), 9.8 (C-19); **LR-ESI-MS:** C₂₂H₂₇N₆O [M+H]⁺ *m/z* found 391.4, calcd 391.2; **HR-ESI-MS:** C₂₂H₂₇N₆O [M+H]⁺ *m/z* found 391.2262, calcd 391.2246.

(1S*, 2S*)-N₁,N₁-dimethyl-N₂-(3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)-1-phenylpropane-1,2-diamine (45)



5 (110 mg, 0.503 mmol, 1 eq) and **93** (135 mg, 0.755 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **45** (34 mg, 0.095 mmol, 18.9%) as a white solid.

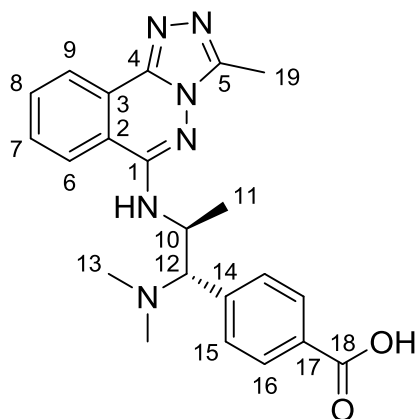
The *racemic* mixture **45** (16 mg) was resolved by preparative chiral HPLC (Chiralpak®OG, CH/IPA 85:15, λ 220 nm, 3 mL/min) to give both enantiomers of **45** which were analysed by analytical chiral HPLC to ascertain optical purity:

L-45 (2.8 mg, Chiralpak®OG CH/IPA 9:1, 1 mL/min, R_t= 43.88 min, 90% *ee*) [α]_D²⁰ -0.068 (0.5 c in CHCl₃)

D-45 (5.8 mg, Chiralpak®OG CH/IPA 9:1, 1 mL/min, R_t= 37.13 min, 99% *ee*) [α]_D²⁰ +0.117 (0.5 c in CHCl₃)

Mpt: 182.7-184.7 °C; **v_{max} (cm⁻¹)** 3242, 3078, 2929, 2771, 1510, 1148, 753, 698, 546; **¹H-NMR (400 MHz, DMSO-*d*⁶):** δ_H 8.41 (d, 1H, *J*= 7.7 Hz, *H*-9), 8.29 (d, 1H, *H*-6), 7.94 (m, 1H, *H*-8), 7.83 (m, 1H, *H*-7), 7.37 (m, 3H, *H*-15; *H*-17), 7.24 (d, 2H, *J*= 7.0 Hz, *H*-16), 7.08 (d, 1H, *J*= 5.9 Hz, NH), 4.71 (m, 1H, *H*-10), 3.72 (d, 1H, *J*= 8.6 Hz, *H*-12), 2.62 (s, 3H, *H*-18), 2.12 (s, 6H, *H*-13), 1.11 (d, 3H, *J*= 6.4 Hz, *H*-11); **¹³C-NMR (100 MHz, DMSO-*d*⁶):** δ_C 150.7 (C-1), 146.1 (C-4), 141.1 (C-5), 135.7 (C-14), 132.9 (C-8), 130.2 (C-7), 129.4 (C-15), 127.8 (C-16), 127.3 (C-17), 124.1 (C-9), 123.4 (C-3), 122.5 (C-6), 118.3 (C-2), 71.6 (C-12), 46.5 (C-10), 41.8 (C-13), 16.5 (C-11), 9.4 (C-18); **LR-ESI-MS:** C₂₁H₂₅N₆ [M+H]⁺ *m/z* found 361.3, calcd 361.2; **HR-ESI-MS:** C₂₁H₂₅N₆ [M+H]⁺ *m/z* found 361.2161, calcd 361.2141.

4-((1S*, 2S*)-1-(dimethylamino)-2-((3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino)propyl)benzoic acid (78)

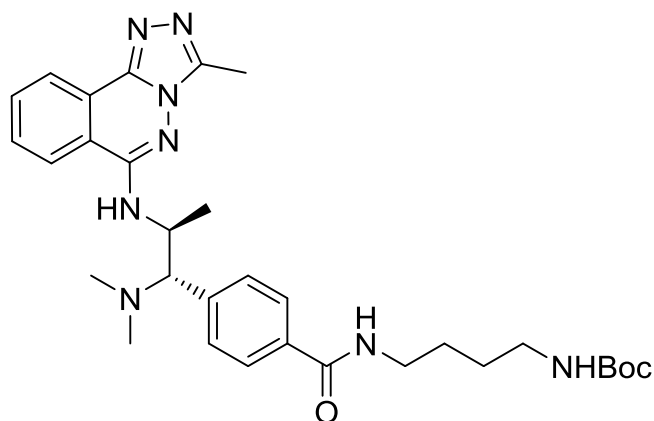


To a stirred solution of **40** (38 mg, 0.091 mmol, 1 eq) in THF/H₂O (908 μL, 2:1, 0.1 M) was added LiOH.H₂O (33 mg, 1.362 mmol, 15 eq) portion wise and allowed to stir for 16 h. Upon reaction completion the mixture was carefully quenched with 1N HCl (1.3 mL, 1.362 mmol, 15 eq) and concentrated down to dryness. The crude material was suspended in DCM/MeOH (9:1, 50 mL) and sonicated prior to being filtered through a sintered frit. The filtrate was concentrated down to give **78** (39 mg, 0.097 mmol, *quant.*) as a white solid.

Mpt: 256.3-258.3 °C; **v_{max} (cm⁻¹)** 3276, 2918, 1698, 1515, 1268, 1116, 700; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_H 8.42 (m, 2H, *H*-9; *H*-9), 8.05 (d, 1H, *J*= 7.9 Hz, *H*-16), 7.97 (t, 1H, *J*= 7.6 Hz, *H*-8), 7.85 (t, 1H, *J*= 7.7 Hz, *H*-7), 7.64 (m, 3H, *H*-15, NH), 5.15 (br-s, 1H, *H*-12), 4.85 (br-s, 1H, *H*-10), 4.78 (m, 1H, *H*-10), 3.85 (s, 3H, *H*-19), 3.79 (d, 1H, *J*= 7.7 Hz, *H*-12), 2.68 (m, 9H, *H*-13; *H*-19), 1.18 (d, 3H, *J*= 6.5 Hz, *H*-11); **¹³C-NMR (100MHz, DMSO-*d*⁶):** δ_C 170.3 (C-18), 150.9 (C-1), 146.1 (C-4), 141.1 (C-5), 136.6 (C-14), 132.8 (C-8), 130.3 (C-7),

128.7 (C-16), 128.4 (C-15), 124.5 (C-9), 123.4 (C-3), 122.5 (C-6), 118.5 (C-2), 71.5 (C-12), 46.6 (C-10), 41.7 (C-13), 16.8 (C-11), 9.5 (C-19); **LR-ESI-MS**: $C_{22}H_{25}N_6O_2$ $[M+H]^+$ m/z found 405.3, calcd 405.2; **HR-ESI-MS**: $C_{22}H_{25}N_6O_2$ $[M+H]^+$ m/z found 405.2067, calcd 405.2039.

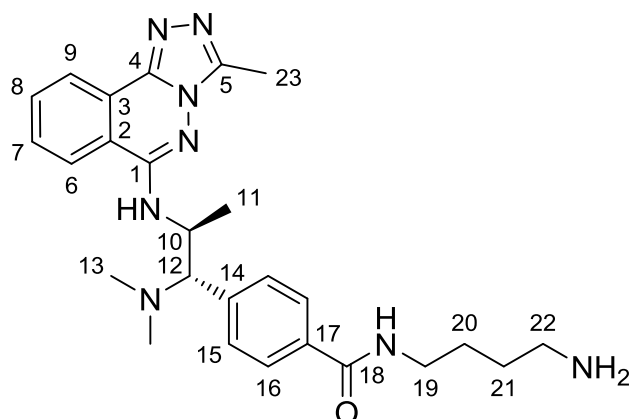
tert-butyl (4-(4-((1S*, 2S*)-1-(dimethylamino)-2-((3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino)propyl)benzamido)butyl)carbamate (79)



To a stirred solution of **78** (24 mg, 0.059 mmol, 1 eq) in DMF (1.1 mL, 0.05 M, anhydrous) under an inert atmosphere (N_2) was added TEA (19 μ L, 0.142 mmol, 2.4 eq) and HATU (27 mg, 0.071 mmol, 1.2 eq). The solution was allowed to stir for 10 min before tert-butyl (4-aminobutyl)carbamate (12.5 μ L, 0.065 mmol, 1.1 eq) was added. The reaction mixture was allowed to stir for 16 h before being concentrated to dryness and flushed through a silica pad with

DCM/MeOH (9:1) to remove impurities and **79** was submitted to the next step without further purification.

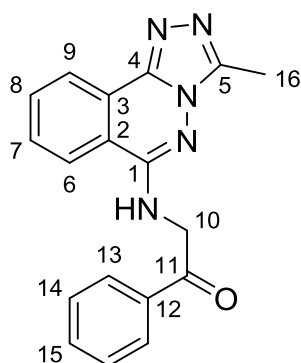
N-(4-aminobutyl)-4-((1S*, 2S*)-1-(dimethylamino)-2-((3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino)propyl)benzamide (80)



To a stirred solution of **79** (408 mg, 0.710 mmol, 1 eq) in DCM (35 mL, 0.02 M anhydrous) was added TFA (1.4 mL, 17.75 mmol, 25 eq). The reaction mixture was allowed to stir for 16 h at room temperature before being concentrated down to dryness. The crude residue was dissolved in MeOH and purified by SC-X ion exchange chromatography (MeOH to 7N NH_3 in MeOH) to give **80** (150 mg, 0.317 mmol, 45%) as a yellow oil.

ν_{max} (cm^{-1}) 2941, 1670, 1637, 1527, 1420, 1171, 1018, 704; **1H -NMR (400MHz, DMSO- d_6)**: δ_H 8.71 (m, 1H, CONH), 8.45 (m, 1H, H-9), 8.37 (m, 1H, H-6), 8.01 (m, 3H, H-18; H-16), 7.91 (m, 1H, H-7), 7.74 (m, 2H, H-15), 7.60 (m, 1H, NH), 5.17 (m, 1H, H-10), 4.77 (m, 1H, H-12), 3.32 (d, 2H, J = 5.5 Hz, H-19), 2.90 (m, 2H, H-22), 2.71 (s, 3H, H-23), 2.54 (s, 6H, H-13), 1.59 (m, 4H, H-20; H-21), 1.13 (d, 3H, J = 6.4 Hz, H-11); **^{13}C -NMR (100MHz DMSO- d_6)**: δ_C 165.4 (C-18), 158.2 (C-, 157.9 (C-, 151.0 (C-1), 146.4 (C-4), 141.1 (C-5), 136.6 (C-14), 132.8 (C-8), 130.9 (C-7), 130.2 (C-16), 127.7 (C-15), 123.3 (C-9), 118.5 (C-3), 118.1 (C-6), 115.1 (C-2), 71.5 (C-12), 43.1 (C-10), 40.4 (C-13), 38.7 (C-22), 38.6 (C-19), 26.2 (C-20), 24.6 (C-21), 17.116.8 (C-11), 9.5 (C-23); **LR-ESI-MS**: $C_{26}H_{35}N_8O$ $[M+H]^+$ m/z found 475.3, calcd 475.3; **HR-ESI-MS**: $C_{26}H_{35}N_8O$ $[M+H]^+$ m/z found 475.2390, calcd 475.2934.

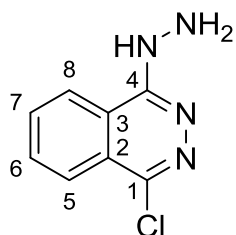
2-((3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino)-1-phenylethan-1-one (81)



To a stirred solution of **96** (2 g, 6.26 mmol, 1 eq) in DMF (42 mL, 0.15 M, anhydrous) was added Pyridinium Dichromate (11.78 g, 31.3 mmol, 5 eq) portion wise under an inert atmosphere (N_2). The reaction mixture was stirred at room temperature for 48 h after which ice was added to the reaction mixture. A brown precipitate formed which was filtered off and dissolved in $CHCl_3/MeOH$ (9:1). The mixture was then filtered through a celite plug to give ketone **81** (1.017 g, 3.20 mmol, 51%) as an off white solid.

Mpt: 156.6-158.6 °C; ν_{max} (cm^{-1}) 3220, 3074, 2919, 1701, 1571, 1473, 1002, 965, 667; 1H -NMR (400MHz, $DMSO-d_6$): δ_H 8.40 (d, 2H, J = 8.2 Hz, H -13), 8.28 (t, 1H, J = 5.6 Hz, NH), 8.10 (m, 2H, H -6; H -9), 7.96 (m, 1H, H -8), 7.88 (m, 1H, H -7), 7.69 (m, 1H, H -15), 7.59 (t, 1H, J = 7.9 Hz, H -14), 4.90 (d, 1H, J = 5.6 Hz, H -10), 2.25 (s, 3H, H -16); ^{13}C -NMR (100MHz, $DMSO-d_6$): δ_C 196.3 (C-11), 151.0 (C-1), 145.8 (C-4), 141.1 (C-5), 135.8 (C-12), 133.4 (C-15), 133.1 (C-8), 130.3 (C-7), 128.8 (C-13), 127.8 (C-14), 124.3 (C-9), 123.3 (C-3), 122.5 (C-6), 118.0 (C-2), 79.2 (C-10), 8.9 (C-16); **LR-ESI-MS:** $C_{18}H_{16}N_5O$ $[M+H]^+$ m/z found 318.3, calcd 318.1; **HR-ESI-MS:** $C_{18}H_{16}N_5O$ $[M+H]^+$ m/z found 318.1387, calcd 318.1355.

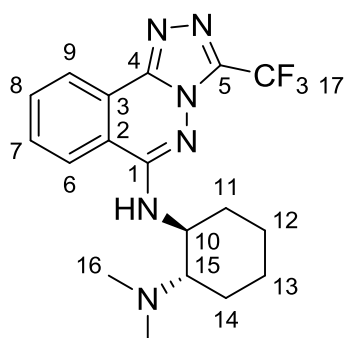
1-chloro-4-hydrazinylphthalazine (82)



To a stirred solution of 1,4-dichlorophthalazine **4** (884 mg, 4.44 mmol, 1 eq) in EtOH (22 mL, 0.2 M) was added hydrazine.monohydrate (1.637 mL, 33.8 mmol, 7.6 eq) and the reaction mixture was warmed to 120 °C. After 10 mins the reaction mixture completely precipitated out to a yellow solid. The reaction mixture was cooled and filtered to give a yellow solid which was washed with cold Et_2O (25 mL x 3) and dried to give **82** (862 mg, 4.43 mmol, *quant.*) as a yellow solid.

Mpt: 174.5-176.5 °C; ν_{max} (cm^{-1}) 3240, 3157, 2944, 1640, 1515, 1420, 1294, 1102, 988, 757; 1H -NMR (400MHz, $DMSO-d_6$): δ_H 8.25 (m, 1H, H -8), 7.92 (m, 3H, H -5; H -6; H -7); ^{13}C -NMR (100MHz $DMSO-d_6$): δ_C 132.6 (C-6, C-7), 124.7 (C-2), 124.5 (C-5), 122.5 (C-3, C-8); **LR-ESI-MS:** $C_8H_8ClN_4$ $[M+H]^+$ m/z found 195.0, calcd 195.0; **HR-ESI-MS:** $C_8H_8ClN_4$ $[M+H]^+$ m/z found 195.0096, calcd 195.0437.

(1S, 2S)-*N*₁,*N*₁-dimethyl-*N*₂-(3-(trifluoromethyl)-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)cyclohexane-1,2-diamine (83)

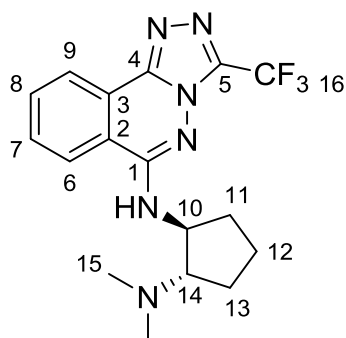


6 (300 mg, 1.1 mmol, 1 eq) and (1S,2S)-*N*₁,*N*₁-dimethylcyclohexane-1,2-diamine (313 mg, 2.201 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/ NH_3 9:1:0.5) to give **83** (194 mg, 0.514 mmol 47%) as a white solid.

Mpt: 216.6-218.6 °C; ν_{max} (cm^{-1}) 3312, 2939, 2864, 1530, 1477, 1125, 1024, 991, 735; ^{19}F -NMR (376 MHz, $CDCl_3$): δ_F -64.22; 1H -NMR (400MHz, $CDCl_3$): δ_H 8.60 (dd, 1H, J = 7.9, 0.7 Hz, H -9), 8.06 (d, 1H, J = 7.9 Hz, H -6), 7.86 (m, 1H, H -8), 7.79 (m, 1H, H -7), 7.07 (br-s, 1H, NH),

3.67 (t, 1H, $J = 10.5$ Hz, $H-10$), 2.87 (m, 2H, $H-11''$; $H-15$), 2.41 (s, 6H, $H-16$), 1.99 (m, 2H, $H-14$), 1.81 (d, 1H, $J = 11$ Hz, $H-11'$), 1.35 (m, 4H, $H-12$; $H-13$); $^{13}\text{C-NMR}$ (100MHz CDCl_3): δ_{C} 152.4 (C-1), 143.9 (C-4), 139.6 (q, $J = 40.4$ Hz, C-5), 132.9 (C-8), 131.3 (C-7), 124.0 (C-9), 123.5 (C-3), 122.9 (C-6), 119.3 (C-2), 118.7 (q, $J = 270.7$ Hz, C-17), 66.4 (C-15), 53.1 (C-10), 39.8 (C-16), 31.0 (C-11), 25.2 (C-14), 24.3 (C-13), 21.4 (C-12); **LR-ESI-MS**: $\text{C}_{18}\text{H}_{22}\text{F}_3\text{N}_6$ $[\text{M}+\text{H}]^+$ m/z found 379.2, calcd 379.2; **HR-ESI-MS**: $\text{C}_{18}\text{H}_{22}\text{F}_3\text{N}_6$ $[\text{M}+\text{H}]^+$ m/z found 379.1913, calcd 379.1858.

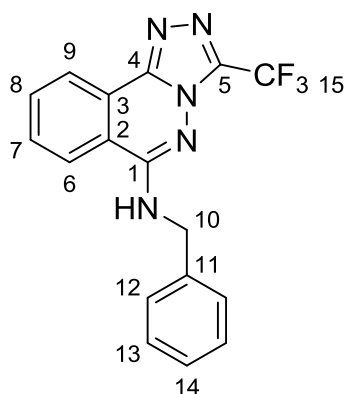
(1S*, 2S*)- N_1,N_1 -dimethyl- N_2 -(3-(trifluoromethyl)-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)cyclopentane-1,2-diamine (84)



6 (300 mg, 1.1 mmol, 1 eq) and (1S*,2S*)- N_1,N_1 -dimethylcyclopentane-1,2-diamine (212 mg, 1.651 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/ NH_3 9:1:0.5) to give **84** (306 mg, 0.84 mmol, 76%) as a white solid.

Mpt: 191.1-193.1 °C; ν_{max} (cm^{-1}) 3483, 3303, 2945, 2775, 1567, 1459, 1184, 1146, 979, 703; $^{19}\text{F-NMR}$ (376 MHz, $\text{DMSO}-d_6$): δ_{F} -63.12; $^1\text{H-NMR}$ (400MHz, $\text{DMSO}-d_6$): δ_{H} 8.53 (d, 1H, $J = 7.8$ Hz, $H-9$), 8.49 (dd, 1H, $J = 7.8, 1.2$ Hz, $H-6$), 8.01 (m, 1H, $H-8$), 7.95 (m, 1H, $H-7$), 7.77 (d, 1H, $J = 7.7$ Hz, NH), 4.31 (m, 1H, $H-10$), 2.97 (m, 1H, $H-14$), 2.18 (s, 6H, $H-15$), 2.08 (m, 1H, $H-11''$), 1.83 (m, 1H, $H-13''$), 1.61 (m, 1H, $H-11'$; $H-13'$; $H-12$); $^{13}\text{C-NMR}$ (100MHz $\text{DMSO}-d_6$): δ_{C} 151.9 (C-1), 143.7 (C-4), 138.2 (q, $J = 39.6$ Hz, C-5), 133.3 (C-8), 131.6 (C-7), 124.6 (C-9), 123.2 (C-3), 122.1 (C-6), 118.9 (C-2), 118.7 (q, $J = 269.2$ Hz, C-16), 70.7 (C-10), 54.6 (C-14), 42.5 (C-15), 31.3 (C-11), 26.9 (C-13), 22.0 (C-12); **LR-ESI-MS**: $\text{C}_{17}\text{H}_{20}\text{F}_3\text{N}_6$ $[\text{M}+\text{H}]^+$ m/z found 365.3, calcd 365.2; **HR-ESI-MS**: $\text{C}_{17}\text{H}_{20}\text{F}_3\text{N}_6$ $[\text{M}+\text{H}]^+$ m/z found 365.1742, calcd 365.1702.

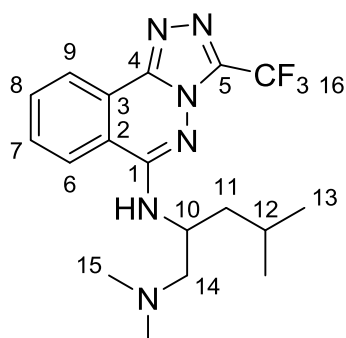
N -benzyl-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-a]phthalazin-6-amine (85)



6 (200 mg, 0.734 mmol, 1 eq) and benzylamine (157 mg, 1.467 mmol, 2 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10) to give **85** (134 mg, 0.391 mmol, 53%) as a white solid.

Mpt: 166.8-168.8 °C; ν_{max} (cm^{-1}) 3888, 1562, 1527, 1289, 1116, 1023, 973, 721, 699, 516; $^{19}\text{F-NMR}$ (376 MHz, CDCl_3): δ_{F} -64.07; $^1\text{H-NMR}$ (400MHz, CDCl_3): δ_{H} 8.70 (d, 1H, $J = 7.9$ Hz, $H-9$), 7.92 (ddd, 1H, $J = 8.1, 5.3, 3$ Hz, $H-6$), 7.81 (m, 2H, $H-8, H-7$), 7.49 (d, 2H, $J = 7.2$ Hz, $H-12$), 7.38 (m, 3H, $H-13; H-14$), 5.61 (br-s, 1H, NH), 4.73 (d, 2H, $J = 5.1$ Hz, $H-10$); $^{13}\text{C-NMR}$ (100MHz CDCl_3): δ_{C} 151.5 (C-1), 143.9 (C-11), 137.4 (C-4), 133.2 (C-8), 131.3 (C-7), 128.9 (C-12), 128.6 (C-13), 128.1 (C-14), 126.5 (C-14), 124.6 (C-9), 123.3 (C-3), 122.2 (C-6), 118.6 (q, $J = 269.2$ Hz, C-15), 118.5 (C-2), 46.5 (C-10); **LR-ESI-MS**: $\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}_5$ $[\text{M}+\text{H}]^+$ m/z found 344.1, calcd 344.1; **HR-ESI-MS**: $\text{C}_{17}\text{H}_{13}\text{F}_3\text{N}_5$ $[\text{M}+\text{H}]^+$ m/z found 344.1142, calcd 344.1123.

***N*₁,*N*₁,4-trimethyl-*N*₂-(3-(trifluoromethyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)pentane-1,2-diamine (86)**

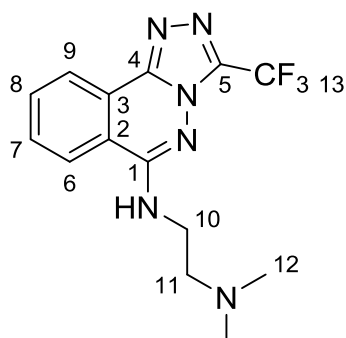


6 (300 mg, 1.1 mmol, 1 eq) and *N*₁,*N*₁,4-trimethylpentane-1,2-diamine (238 mg, 1.651 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **86** (108 mg, 0.283 mmol, 26%) as a white solid.

Mpt: 218.5-220.5 °C; **v_{max}** (cm⁻¹) 3286, 2957, 2821, 1552, 1493, 1148, 1044, 979, 709, 703; **¹⁹F-NMR (376 MHz, DMSO-*d*⁶):** δ_F -63.29; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_H 8.49 (m, 2H, *H*-9; *H*-6), 8.01 (m, 1H, *H*-8), 7.95 (m, 1H, *H*-7), 7.95 (m, 1H, *H*-7), 7.55 (d, 1H, *J* = 8.4 Hz, NH),

4.42 (m, 1H, *H*-10), 2.51 (m, 1H, *H*-14''), 2.28 (dd, 1H, *J* = 11.8, 6.8 Hz, *H*-14'), 2.18 (s, 6H, *H*-15), 1.66 (m, 2H, *H*-11''; *H*-12), 1.48 (m, 1H, *H*-11'), 0.85 (d, 6H, *J* = 7.1 Hz, *H*-13); **¹³C-NMR (100MHz DMSO-*d*⁶):** δ_C 152.5 (C-1), 143.6 (C-4), 138.1 (q, *J* = 40.3 Hz, C-5), 133.4 (C-8), 131.6 (C-7), 124.5 (C-9), 123.3 (C-3), 122.2 (C-6), 118.7 (C-2), 118.7 (q, *J* = 270 Hz, C-16), 63.5 (C-10), 47.0 (C-14), 45.4 (C-15), 41.6 (C-11), 24.5 (C-12), 23.2 (C-13''), 21.7 (C-13'); **LR-ESI-MS:** C₁₈H₂₄F₃N₆ [M+H]⁺ *m/z* found 381.3, calcd 381.2; **HR-ESI-MS:** C₁₈H₂₄F₃N₆ [M+H]⁺ *m/z* found 381.2061, calcd 381.2015.

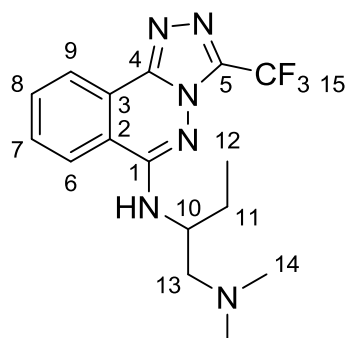
***N*₁,*N*₁-dimethyl-*N*₂-(3-(trifluoromethyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)ethane-1,2-diamine (87)**



6 (300 mg, 1.1 mmol, 1 eq) and *N*₁,*N*₁-dimethylethane-1,2-diamine (146 mg, 1.651 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **87** (339 mg, 1.046 mmol, 95%) as a white solid.

Mpt: 166.1-168.1 °C; **v_{max}** (cm⁻¹) 3380, 2948, 2768, 1551, 1499, 1140, 1035, 979, 720, 693; **¹⁹F-NMR (376 MHz, CDCl₃):** δ_F -64.19; **¹H-NMR (400MHz, CDCl₃):** δ_H 8.64 (d, 1H, *J* = 7.9 Hz, *H*-9), 7.90 (m, 2H, *H*-6; *H*-8), 7.82 (m, 1H, *H*-7), 6.50 (br-s, 1H, NH), 3.61 (m, 2H, *H*-10), 2.75 (t, 2H, *J* = 5.8 Hz, *H*-11), 2.39 (s, 6H, *H*-12); **¹³C-NMR (100MHz CDCl₃):** δ_C 152.1 (C-1), 144.0 (C-4), 139.8 (q, *J* = 41.1 Hz, C-5), 133.0 (C-8), 131.3 (C-7), 124.3 (C-9), 123.0 (C-3), 122.8 (C-6), 118.8 (C-2), 118.6 (q, *J* = 270.0 Hz, C-16), 56.8 (C-10), 45.0 (C-11), 38.6 (C-12); **LR-ESI-MS:** C₁₄H₁₆F₃N₆ [M+H]⁺ *m/z* found 325.3, calcd 325.1; **HR-ESI-MS:** C₁₄H₁₆F₃N₆ [M+H]⁺ *m/z* found 325.1396, calcd 325.1389.

***N*₁,*N*₁-dimethyl-*N*₂-(3-(trifluoromethyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)butane-1,2-diamine (88)**

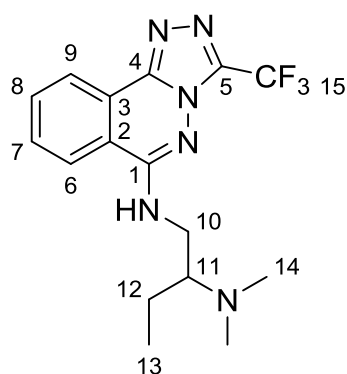


6 (300 mg, 1.1 mmol, 1 eq) and *N*₁,*N*₁-dimethylbutane-1,2-diamine (166 mg, 1.431 mmol, 1.3 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **88** (299 mg, 0.849 mmol, 77%) as a white solid.

Mpt: 175.1-177.1 °C; **v_{max}** (cm⁻¹) 3298, 2937, 2821, 2773, 1554, 1492, 1287, 1136, 978, 781; **¹⁹F-NMR (376 MHz, DMSO-*d*⁶):** δ_F -63.35; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_H 8.49 (d, 1H, *J* = 8.1 Hz, *H*-9), 8.44 (d, 1H,

J = 7.7 Hz, *H*-6), 7.95 (m, 1H, *H*-8), 7.89 (m, 1H, *H*-7), 7.49 (d, 1H, *J* = 7.8 Hz, NH), 4.11 (m, 1H, *H*-10), 2.54 (m, 1H, *H*-13''), 2.26 (m, 1H, *H*-13'), 2.15 (s, 6H, *H*-14), 1.76 (m, 1H, *H*-11''), 1.61 (m, 1H, *H*-11'), 0.91 (t, 3H, *J* = 7.3 Hz, *H*-12); **¹³C-NMR (100MHz, DMSO-*d*⁶):** δ_C 152.5 (C-1), 143.6 (C-4), 138.1 (q, *J* = 39.6 Hz, C-5), 133.2 (C-8), 131.4 (C-7), 124.5 (C-9), 123.1 (C-3), 122.1 (C-6), 118.7 (C-2), 118.7 (q, *J* = 271.43 Hz, C-15), 62.5 (C-10), 54.8 (C-13), 50.9 (C-11), 45.4 (C-14), 25.0 (C-11), 10.6 (C-12); **LR-ESI-MS:** C₁₆H₂₀F₃N₆ [M+H]⁺ *m/z* found 353.2, calcd 353.2; **HR-ESI-MS:** C₁₆H₂₀F₃N₆ [M+H]⁺ *m/z* found 353.1731, calcd 353.1702.

***N*₂,*N*₂-dimethyl-*N*₁-(3-(trifluoromethyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)butane-1,2-diamine (89)**

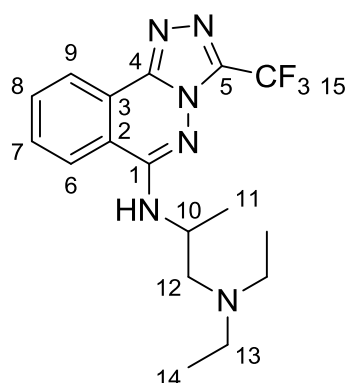


6 (300 mg, 1.1 mmol, 1 eq) and *N*₂,*N*₂-dimethylbutane-1,2-diamine (192 mg, 1.651 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **89** (247 mg, 0.702 mmol, 64%) as a white solid.

Mpt: 130.2-132.2 °C; **v_{max}** (cm⁻¹) 3263, 2930, 1565, 1501, 1454, 1178, 1074, 980, 770, 719; **¹⁹F-NMR (376 MHz, DMSO-*d*⁶):** δ_F -63.20; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_H 8.48 (d, 1H, *J* = 7.6 Hz, *H*-9), 8.36 (d, 1H, *J* = 7.9 Hz, *H*-6), 8.03 (m, 1H, *H*-8), 7.89 (m, 2H, NH; *H*-7), 7.49 (d, 1H,

J = 7.8 Hz, NH), 4.23 (m, 1H, *H*-10''), 3.32 (m, 1H, *H*-10'), 2.78 (m, 1H, *H*-11), 2.25 (s, 6H, *H*-14), 1.52 (m, 1H, *H*-12''), 1.31 (m, 2H, *H*-12'), 0.88 (t, 3H, *J* = 7.3 Hz, *H*-13); **¹³C-NMR (100MHz DMSO-*d*⁶):** δ_C 152.6 (C-1), 144.0 (C-4), 138.4 (q, *J* = 39.6 Hz, C-5), 133.6 (C-8), 132.0 (C-7), 124.5 (C-9), 123.5 (C-3), 122.3 (C-6), 119.1 (C-2), 118.9 (q, *J* = 269.20 Hz, C-15), 62.6 (C-10), 55.0 (C-11), 48.8 (C-14), 21.1 (C-12), 11.6 (C-13); **LR-ESI-MS:** C₁₆H₂₀F₃N₆ [M+H]⁺ *m/z* found 353.3, calcd 353.2; **HR-ESI-MS:** C₁₆H₂₀F₃N₆ [M+H]⁺ *m/z* found 353.1722, calcd 353.1702.

***N*₁,*N*₁-diethyl-*N*₂-(3-(trifluoromethyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)propane-1,2-diamine (90)**

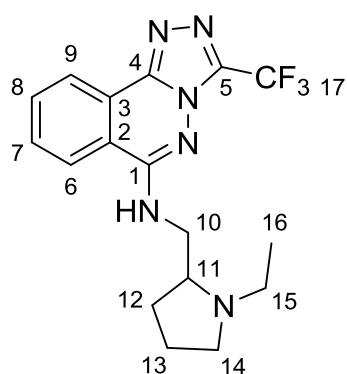


6 (300 mg, 1.1 mmol, 1 eq) and *N*₁,*N*₁-diethylpropane-1,2-diamine (215 mg, 1.651 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **90** (171 mg, 0.467 mmol, 42%) as a white solid.

Mpt: 121.1-123.1 °C; **v_{max} (cm⁻¹)** 3341, 2970, 2809, 1552, 1492, 1177, 1142, 703, 467; **¹⁹F-NMR (376 MHz, DMSO-*d*⁶):** δ_F -63.16; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_H 8.47 (m, 2H, *H*-9; *H*-6), 8.00 (m, 1H, *H*-8), 7.94 (m, 1H, *H*-7), 6.52 (d, 1H, *J* = 7.7 Hz, *NH*), 4.19 (m, 1H, *H*-10),

2.59 (m, 1H, *H*-12''), 2.40 (m, 1H, *H*-12'), 1.31 (d, 3H, *J* = 6.5 Hz, *H*-11), 0.93 (t, 6H, *J* = 7.1 Hz, *H*-14); **¹³C-NMR (100MHz DMSO-*d*⁶):** δ_C 152.0 (*C*-1), 143.7 (*C*-4), 138.1 (q, *J* = 39.61 Hz, *C*-5), 133.3 (*C*-8), 131.5 (*C*-7), 124.4 (*C*-9), 123.2 (*C*-3), 122.2 (*C*-6), 118.8 (*C*-2), 118.7 (q, *J* = 269.2 Hz, *C*-15), 57.7 (*C*-10), 47.1 (*C*-12), 45.8 (*C*-13), 18.0 (*C*-11), 12.0 (*C*-14); **LR-ESI-MS:** C₁₇H₂₂F₃N₆ [M+H]⁺ *m/z* found 367.3, cald 367.2; **HR-ESI-MS:** C₁₇H₂₂F₃N₆ [M+H]⁺ *m/z* found 367.1884, cald 367.1858.

***N*-((1-ethylpyrrolidin-2-yl)methyl)-3-(trifluoromethyl)-[1,2,4]triazolo[3,4-*a*]phthalazin-6-amine (91)**

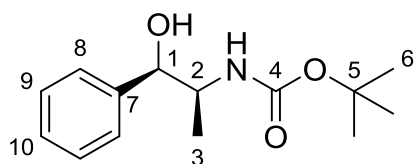


6 (300 mg, 1.1 mmol, 1 eq) and (1-ethylpyrrolidin-2-yl)methanamine (212 mg, 1.651 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **91** (336 mg, 0.929 mmol, 84%) as a white solid.

Mpt: 166.1-168.1 °C; **v_{max} (cm⁻¹)** 3404, 2932, 2800, 1562, 1497, 1526, 1137, 976, 401; **¹⁹F-NMR (376 MHz, CDCl₃):** δ_F -64.18; **¹H-NMR (400MHz, CDCl₃):** δ_H 8.66 (d, 1H, *J* = 7.8 Hz, *H*-9), 7.90 (m, 1H, *H*-8), 7.83 (m, 2H, *H*-6; *H*-7), 6.62 (br-s, 1H, *NH*), 3.69 (ddd, 1H, *J* = 13.6, 6.8,

2.5 Hz, *H*-10''), 3.47 (m, 1H, *H*-10'), 3.34 (dt, 1H, *J* = 9.2, 4.7 Hz, *H*-11), 2.89 (m, 2H, *H*-14), 2.35 (m, 2H, *H*-15), 2.03 (m, 1H, *H*-12''), 1.79 (m, 3H, *H*-12'; *H*-13), 1.16 (t, 3H, *J* = 7.2 Hz, *H*-16); **¹³C-NMR (100MHz CDCl₃):** δ_C 152.4 (*C*-1), 144.0 (*C*-4), 139.8 (q, *J* = 41.1 Hz, *C*-5), 132.9 (*C*-8), 131.4 (*C*-7), 124.3 (*C*-9), 123.1 (*C*-3), 122.5 (*C*-6), 119.0 (*C*-2), 118.6 (q, *J* = 268.5 Hz, *C*-15), 61.8 (*C*-11), 53.5 (*C*-14), 48.0 (*C*-15), 42.1 (*C*-10), 28.8 (*C*-12), 23.0 (*C*-13), 13.9 (*C*-16); **LR-ESI-MS:** C₁₇H₂₂F₃N₆ [M+H]⁺ *m/z* found 365.3, cald 365.2; **HR-ESI-MS:** C₁₇H₂₂F₃N₆ [M+H]⁺ *m/z* found 365.1773, cald 365.1702.

tert-butyl ((1*R*,2*S*)-1-hydroxy-1-phenylpropan-2-yl)carbamate (**92**)



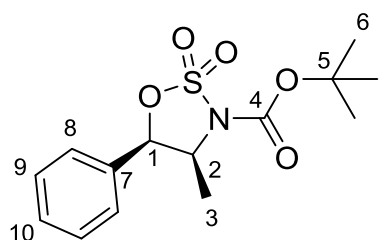
(1*R*,2*S*)-(-)-Norephedrine (4.02 g, 26.6 mmol, 1 eq) was dissolved in CH₂Cl₂ (89 mL, 0.3 M, anhydrous) under an inert atmosphere (N₂). DIPEA (6.95 mL, 39.9 mmol, 1.5 eq) was then added dropwise before the solution was cooled to 0 °C and Boc₂O (9.16 mL, 39.9 mmol, 1.5 eq) was added dropwise. The

solution was allowed to stir at ambient temperature for 16 h. The reaction mixture was then concentrated to dryness and the crude material was purified by Isolera Biotage LPLC (DCM/MeOH 1:0 then DCM/MeOH 9:1) to give **92** (3.374 g, 13.42 mmol, 51%) as a white solid.

Mpt: 88.9-90.9 °C; **v_{max} (cm⁻¹)** 3358, 2984, 1679, 1523, 1448, 1160, 1013, 856, 697; **¹H-NMR (400MHz, CDCl₃):** δ_H 7.23 (m, 5H, *H*-8, *H*-9, *H*-10), 4.78 (br-s, 1H, *H*-1), 4.60 (br-s, 1H, *NH*), 3.94 (br-s, 1H, *OH*), 3.33 (br-s, 1H, *H*-2), 1.40 (s, 9H, *H*-6), 0.92 (d, 3H, *J*= 6.8 Hz, *H*-3) **¹³C-NMR (100MHz CDCl₃):** δ_C 156.4 (*C*-4), 140.8 (*C*-7), 128.1 (*C*-8), 127.4 (*C*-9), 126.3 (*C*-10), 79.8 (*C*-1), 51.9 (*C*-2), 28.4 (*C*-6), 14.8 (*C*-3);

LR-ESI-MS: C₁₄H₂₂NO₃ [M+H]⁺ *m/z* found 252.1, calcd 252.2; **HR-ESI-MS:** C₁₄H₂₁NNaO₃ [M+Na]⁺ *m/z* found 274.1432, calcd 274.1419.

tert-butyl (4*S*,5*R*)-4-methyl-5-phenyl-1,2,3-oxathiazolidine-3-carboxylate 2,2-dioxide (**47**)



Part one:

92 (1.033g, 4.11 mmol, 1.0 eq) was dissolved in MeCN (10 mL, anhydrous) under an inert atmosphere (N₂). The solution was then added dropwise to a solution of SOCl₂ (373 μL, 5.14 mmol, 1.25 eq) in MeCN (10 mL, anhydrous, 0.2 M final concentration) with stirring at -40 °C. After 10 mins of stirring Pyridine (1.324 mL,

16.44 mmol, 4 eq) was then added and the mixture was stirred at -40 °C for 1 h. The mixture was then warmed to 0 °C and stirred for 1 h before H₂O (15 mL) and EtOAc (15 mL) were added. The layers were separated and the organic layers were washed with 1*N* HCl (30 mL). The combined aqueous phases were extracted with EtOAc (x3) before the organic layers were combined and washed with sat. NaHCO₃ (x1), brine and then dried over Na₂SO₄ before being concentrated to a brown oil.

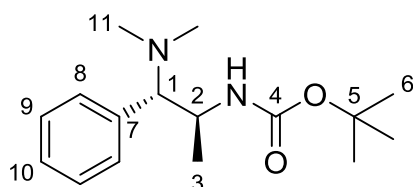
Part two:

The residue was taken up in MeCN (20 mL) and cooled to 0 °C. The mixture then had RuCl₃·3H₂O (20 mg, 0.041 mmol, 2 mol%), NaIO₄ (1.319 g, 6.17 mmol, 1.5 eq) and H₂O (20 mL) added sequentially before being stirred vigorously for 1 h. The mixture was then diluted with H₂O (20 mL) and Et₂O (20 mL) before the layers were separated and the organic layer was washed successively with H₂O until the brown/black colour had been completely removed. The solution was dried over Na₂SO₄ and concentrated to a residue which was triturated out of cyclohexane to give **47** (0.628 g, 2.00 mmol, 49%) as an off white solid.

Mpt: 111.3-113.3 °C; **v_{max} (cm⁻¹)** 2990, 1731, 1364, 1327, 1184, 1159, 801, 697, 629; **¹H-NMR (400MHz, CDCl₃):** δ_H 7.43 (m, 3H, *H*-8, *H*-10), 7.33 (m, 2H, *H*-9), 5.97 (d, 1H, *J*= 5.3 Hz, *H*-1), 4.58 (dq,

^1H , $J = 6.7, 5.5$ Hz, $H-2$), 1.58 (s, 9H, $H-6$), 1.09 (d, 3H, $J = 6.6$ Hz, $H-3$) **^{13}C -NMR (100MHz CDCl_3)**: δ_{C} 148.4 (C-4), 131.3 (C-7), 129.4 (C-8), 128.9 (C-9), 125.4 (C-10), 85.5 (C-1), 82.3 (C-5), 58.6 (C-2), 27.9 (C-6), 14.2 (C-3); **LR-ESI-MS**: $\text{C}_{14}\text{H}_{23}\text{N}_2\text{O}_5\text{S}$ $[\text{M}+\text{NH}_4]^+$ m/z found 313.1, calcd 313.1; **HR-ESI-MS**: $\text{C}_{14}\text{H}_{19}\text{NNaO}_5\text{S}$ $[\text{M}+\text{Na}]^+$ m/z found 336.0883, calcd 336.0882.

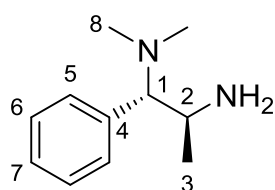
tert-butyl ((1S,2S)-1-(dimethylamino)-1-phenylpropan-2-yl)carbamate (48**)**



47 (0.627 g, 2.00 mmol, 1.0 eq) was dissolved in THF (2 mL, anhydrous) under an inert atmosphere (N_2) in a sealed tube. Dimethylamine (3 mL, 6.00 mmol, 3 eq, 2 M) was then added dropwise at room temperature and the mixture was allowed to stir at 80 °C for 16 h. The mixture was then concentrated down to dryness and purified by Isolera Biotage LPLC (CH/EA 9:1 then CH/EA 2:8) to give **48** (0.396 g, 1.422 mmol, 71%) as a white solid.

Mpt: 83.4-85.4 °C; ν_{max} (cm^{-1}) 3373, 2974, 1698, 1485, 1345, 1163, 1060, 863, 703; **^1H -NMR (400MHz, CDCl_3)**: δ_{H} 7.33 (m, 3H, $H-9, H-10$), 7.19 (m, 2H, $H-8$), 4.97 (s, 1H, NH), 4.02 (m, 1H, $H-2$), 3.21 (d, 1H, $J = 8.6$ Hz, $H-1$), 2.14 (s, 6H, $\text{N}(\text{CH}_3)_2$), 1.48 (s, 9H, $H-6$), 1.02 (d, 3H, $H-3$); **^{13}C -NMR (100MHz CDCl_3)**: δ_{C} 156.0 (C-1), 135.3 (C-7), 129.5 (C-8), 127.9 (C-9), 127.5 (C-10), 79.0 (C-1), 73.7 (C-5), 46.4 (C-2), 41.9 (C-11), 28.5 (C-6), 17.4 (C-3); **LR-ESI-MS**: $\text{C}_{16}\text{H}_{27}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ m/z found 279.0, calcd 279.2; **HR-ESI-MS**: $\text{C}_{16}\text{H}_{27}\text{N}_2\text{O}_2$ $[\text{M}+\text{H}]^+$ m/z found 279.2060, calcd 279.2073.

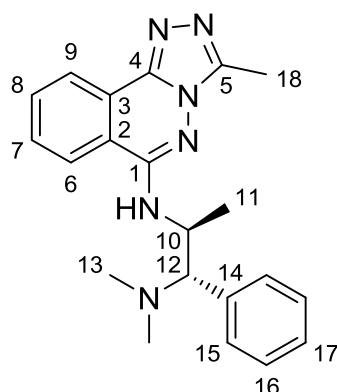
((1S,2S)- N_1,N_1 -dimethyl-1-phenylpropane-1,2-diamine (93**))**



47 (0.396 g, 1.422 mmol, 1.0 eq) was dissolved in CH_2Cl_2 (3.56 mL, 0.4 M, anhydrous) under an inert atmosphere (N_2). TFA (1.09 mL, 14.22 mmol, 10 eq) was then added dropwise before the mixture was allowed to stir for 2 h. The mixture was then concentrated to dryness before being redissolved in a minimal amount of MeOH and purified by a Flash SC-X column eluting with MeOH then 7N in MeOH to give **93** (0.266 g, 1.492 mmol, *quant.*) as a colourless oil.

^1H -NMR (400MHz, CDCl_3): δ_{H} 7.46 (m, 2H, $H-7, H-8$), 7.27 (m, 2H, $H-6$), 3.56 (m, 1H, $H-2$), 3.19 (d, 1H, $J = 9.7$ Hz, $H-3$), 2.31 (s, 6H, $H-4$), 1.03 (d, 3H, $J = 6.2$ Hz, $H-1$); **^{13}C -NMR (100MHz CDCl_3)**: δ_{C} 130.9 (C-5), 129.4 (C-6), 128.3 (C-7), 71.6 (C-1), 46.9 (C-2), 40.6 (C-8), 16.2 (C-3); **LR-ESI-MS**: $\text{C}_{11}\text{H}_{19}\text{N}_2$ $[\text{M}+\text{H}]^+$ m/z found 179.2, calcd 179.2; *Data in agreement with that found for 32.*

(1*S*, 2*S*)-*N*₁,*N*₁-dimethyl-*N*₂-(3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazin-6-yl)-1-phenylpropane-1,2-diamine (*L*-Moses)

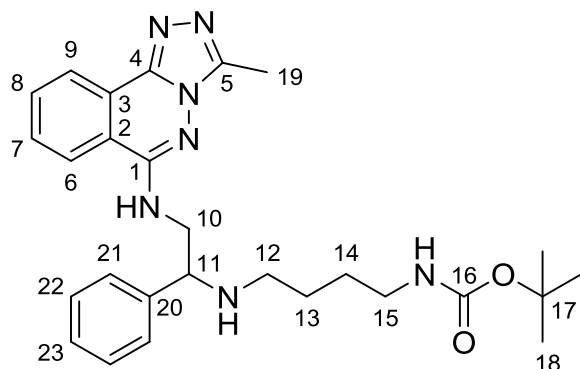


5 (35 mg, 0.160 mmol, 1 eq) and **93** (43 mg, 0.240 mmol, 1.5 eq) were reacted according to general procedure **A**. The crude material was purified by Isolera Biotage LPLC (DCM/MeOH 90:10 then DCM/MeOH/NH₃ 9:1:0.5) to give **L-Moses** (17 mg, 0.047 mmol, 29.5%) as a white solid.

L-Moses (Chiralpak® OG CH/IPA 8:2, 1 mL/min, *R*_t = 14.60 min, >99% ee)

¹H-NMR (400 MHz, DMSO-*d*⁶): δ_{H} 8.40 (d, 1H, *J* = 7.8 Hz, *H*-9), 8.28 (d, 1H, *J* = 8.3 Hz, *H*-6), 7.93 (m, 1H, *H*-8), 7.82 (m, 1H, *H*-7), 7.37 (m, 3H, *H*-15; *H*-17), 7.22 (d, 2H, *J* = 7.2 Hz, *H*-16), 7.07 (d, 1H, *J* = 5.7 Hz, NH), 4.70 (m, 1H, *H*-10), 3.71 (d, 1H, *J* = 8.6 Hz, *H*-12), 2.61 (s, 3H, *H*-18), 2.11 (s, 6H, *H*-13), 1.11 (d, 3H, *J* = 6.4 Hz, *H*-11); **¹³C-NMR (100 MHz, DMSO-*d*⁶):** δ_{C} 150.7 (C-1), 146.1 (C-4), 141.1 (C-5), 135.7 (C-14), 132.8 (C-8), 130.3 (C-7), 129.4 (C-15), 127.8 (C-16), 127.3 (C-17), 124.1 (C-9), 123.4 (C-3), 122.6 (C-6), 118.4 (C-2), 71.7 (C-12), 46.6 (C-10), 41.8 (C-13), 16.5 (C-11), 9.4 (C-18); **LR-ESI-MS:** C₂₁H₂₅N₆ [M+H]⁺ *m/z* found 361.3, calcd 361.2; Data in agreement with that found for **74**.

6-chloro-3-methyl-[1,2,4]triazolo[3,4-*a*]phthalazine (94**)**

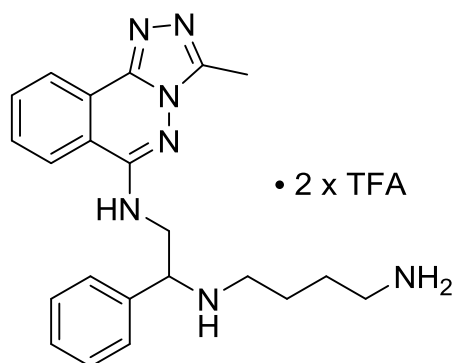


81 (163 mg, 0.514 mmol, 1 eq) was solubilised in CHCl₃/MeOH (5.14 mL, 2:1) under a N₂ atmosphere. tert-butyl (4-aminobutyl)carbamate (484 mg, 491 μ L, 2.57 mmol, 5 eq) was then added to the solution followed by 8 drops of AcOH. NaB(CN)H₃ (38.7 mg, 0.616 mmol, 1.2 eq) was then added and the solution was warmed to 65 °C and allowed to stir for 24 h. Following completion the reaction mixture was concentrated to dryness and the crude material

was purified by Isolera Biotage LPLC (DCM/MeOH 90:10) to give **94** (25 mg, 0.051 mmol, 9.9%) as a white powder.

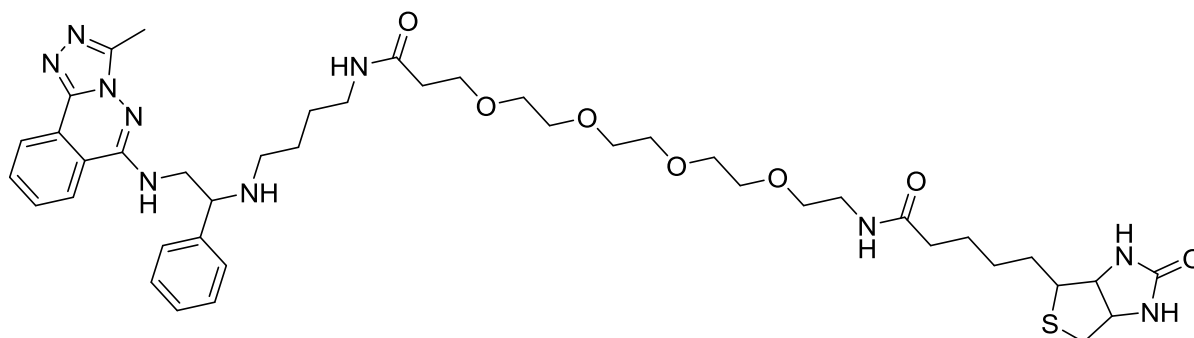
Mpt: 212.3-214.3 °C; **ν_{max} (cm⁻¹):** 3309, 3217, 3067, 2927, 1678, 1515, 1250, 669; **¹H-NMR (400MHz, DMSO-*d*⁶):** δ_{H} 8.37 (d, *J* = 8.7 Hz, 1H, *H*-9), 8.27 (d, *J* = 8.2 Hz, 1H, *H*-6), 7.91 (m, 1H, *H*-8), 7.81 (m, 1H, *H*-7), 7.74 (s, 1H, NHBoc), 7.74 (d, *J* = 7.3 Hz, 2H, *H*-21), 7.33 (t, *J* = 7.5 Hz, 2H, *H*-22), 7.23 (m, 1H, *H*-23), 6.73 (s, 1H, C-11-NH-C-12), 4.15 (s, 1H, *H*-11), 3.62 (s, 1H, *H*-10''), 3.46 (s, 1H, *H*-10'), 2.84 (m, 2H, *H*-15), 2.59 (s, 3H, *H*-19), 2.36 (s, 2H, *H*-12), 1.35 (m, 4H, *H*-13/*H*-14), 1.33 (s, 9H); **¹³C-NMR (100 MHz DMSO-*d*⁶):** δ_{C} 155.5, 151.1, 146.0, 141.1, 132.8, 130.1, 128.2, 127.1, 124.1, 123.3, 122.5, 118.2, 77.2, 60.6, 48.5, 47.0, 28.2, 27.4, 26.9, 9.3; **LR-ESI-MS:** C₂₇H₃₆N₇O₂ [M+H]⁺ *m/z* found 490.6, calcd 490.3; **HR-ESI-MS:** C₂₇H₃₆N₇O₂ [M+H]⁺ *m/z* found 490.2962, calcd 490.2930.

***N*-1-(2-((3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino)-1-phenylethyl)butane-1,4-diamine, 2TFA (95)**



To a stirred solution of **94** (55 mg, 0.112 mmol, 1 eq) in DCM (anhydrous) (1.1 mL, 0.1 M) at room temperature was added TFA (215 μ L, 2.81 mmol, 25 eq) and allowed to stir for 16 h. Upon reaction completion the reaction mixture was concentrated down to dryness to afford **95** 2xTFA salt which was submitted to the next step without further purification (66 mg, 0.108 mmol, 96%).

***N*-(4-((2-((3-methyl-[1,2,4]triazolo[3,4-a]phthalazin-6-yl)amino)-1-phenylethyl)amino)butyl)-1-(5-(2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)pentanamido)-3,6,9,12-tetraoxapentadecan-15-amide (46)**



To a stirred solution of **95** (2.5 mg, 6.42 μ mol, 1 eq) in DCM (642 μ L, 0.01 M, anhydrous) was added 2,5-dioxopyrrolidin-1-yl 17-oxo-21-(2-oxohexahydro-1H-thieno[3,4-d]imidazol-4-yl)-4,7,10,13-tetraoxa-16-azahenicosanoate (3.8 mg, 6.42 μ mol, 1 eq). The reaction mixture was stirred for 16 h after which TLC/LCMS analysis confirmed reaction completion. The reaction mixture was concentrated down to dryness and purified via HPLC (pH 8, MeCN:H₂O) to afford **46** (2.3 mg, 2.66 μ mol, 41.5%) as a white solid.

LR-ESI-MS: C₄₃H₆₃N₁₀O₇S [M+H]⁺ *m/z* found 864.1, calcd 863.4. **ELSD-LCMS** 96% purity.

Human bromodomains were cloned, expressed and purified as previously described.^[1]

Thermal melting points were recorded using an Mx3005p Real Time PCR Machine (Stratagene). Subject proteins were buffered in 10 mM HEPES at pH 7.5, 500 mM NaCl and assayed in a 96-well plate at a final concentration of 2 μ M in 20 μ L volume. Compounds were then added to a final concentration of 10 μ M. SPYRO Orange (Molecular Probes) was used as a fluorescent probe at a dilution of 1:1000. Excitation and emission filters for the SPYRO-Orange dye were set to 465 nm and 590 nm, respectively. The temperature was raised with a step of 3 $^{\circ}$ C/min from 25 $^{\circ}$ C to 96 $^{\circ}$ C and fluorescence readings were taken at each interval. Data was analysed as previously described.^[2]

Supplemental Table 1.

Compound	PCAF ΔT_m (°C) [†]	GCN5L2 ΔT_m (°C) [†]
(S)- 11	+5.4 ± 0.1	+3.7 ± 0.2

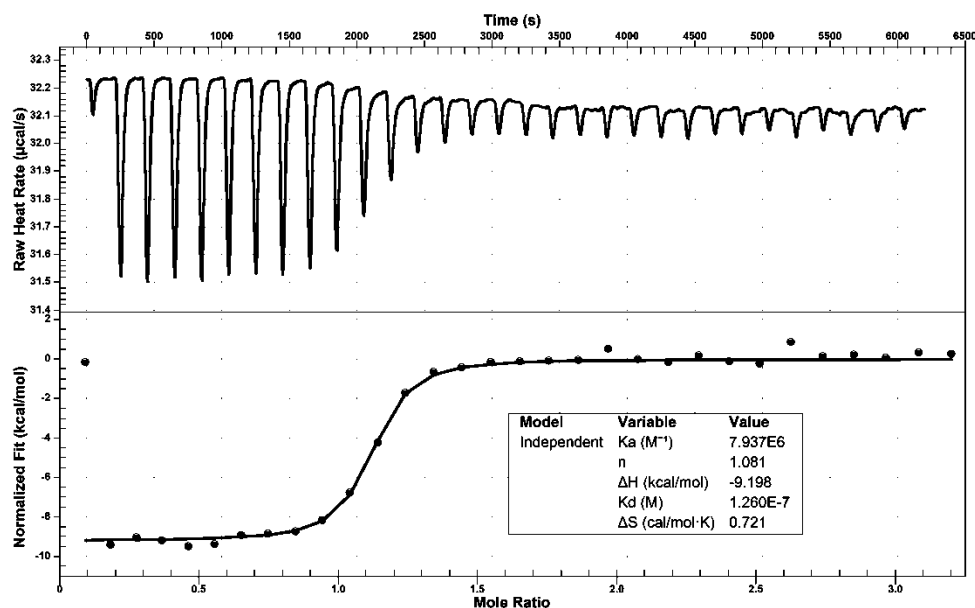
[†]Mean ΔT_m ± SEM (number of measurements = 2). Compound concentration: 10 μM

Supplemental Table 2. DSF results of selected compounds against PCAF and GCN5

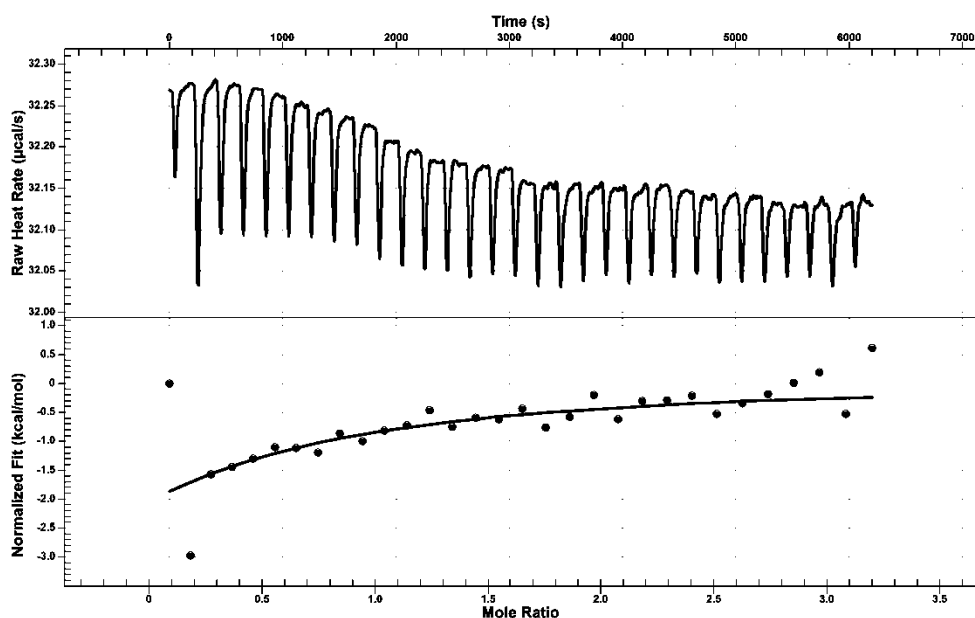
Compound (10 μ M)	PCAF ΔT_m ($^{\circ}$ C)	GCN5L2 ΔT_m ($^{\circ}$ C)
9	0.9	0.3
11	5.6	2.5
(S)- 11	7.4	4.0
12	3.3	1.1
13	0.9	1.1
14	0	0
15	4.6	1.0
(S)- 17	0.7	0.2
50	1.1	0.1
51	1.0	0
56	0.6	0.1
57	0.4	0.1
58	2.7	0.4
59	3.7	0.7
60	2.9	1.1
61	0.5	0
62	0.2	0.3
63	0.2	0
64	1.1	0.5
66	0.6	0.1
67	0.7	0.3
68	0.8	0.1
69	0.9	0
70	0	0.1
73	0.5	0.2
75	0.4	0.2
76	7.3	2.4
77	0.3	0.2
39	8.3	4.4
40	9.6	6.3
41	7.8	4.3
42	6.2	2.7
43	9.1	7.2
44	10.3	6.8
45	7.9	5.0
81	1.0	0.3
83	0.8	0
84	0.7	0.2
85	3.7	0.9
86	0.02	0.2
88	0.4	0.1
89	0.4	0.2
90	0.4	0.1
91	0.1	0.1
94	0	0.2
97	2.8	0.9
98	0.7	0.2
99	3.8	1.5

Isothermal Titration Calorimetry (ITC)

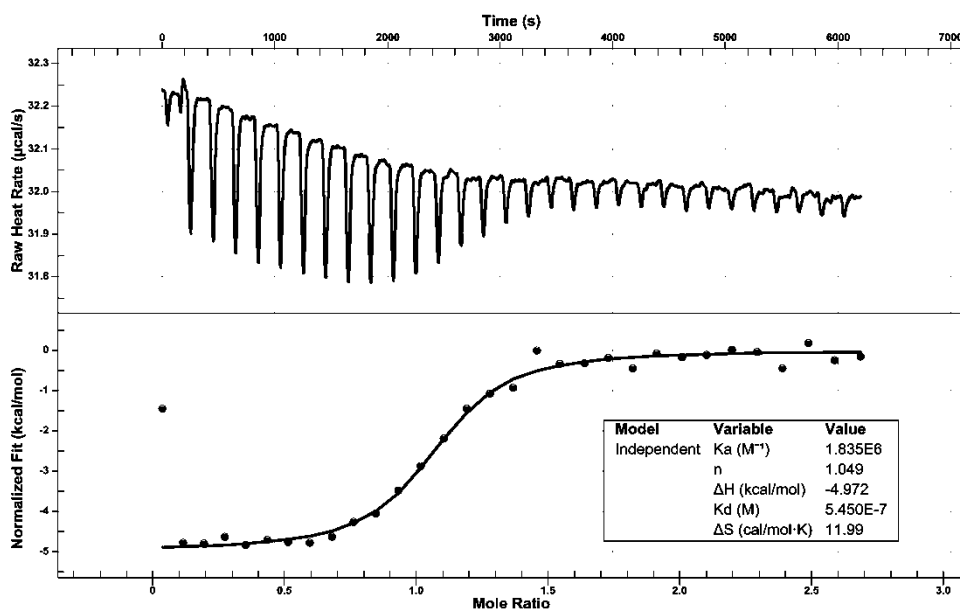
Experiments were carried out on a Nano-ITC Standard Volume Instrument (TA Instruments). All experiments were carried out at 25 °C in 20 mM HEPES pH 7.5, 150 mM NaCl, 0.5 mM TCEP and 5% glycerol. Protein solutions were buffer exchanged by gel filtration. The titrations were conducted using an initial injection of 2 μ L followed by 32 injections of 8 μ L. Background dilution heat was subtracted from each experiment. Thermodynamic parameters were calculated using $\Delta G = \Delta H - T \Delta S = -RT \ln K_D$, where $K_D = 1/K_B$. ΔG , ΔH and ΔS are changes in free energy, enthalpy and entropy respectively. Independent single site binding models were employed in data analysis.



Supplemental Figure 2. ITC trace of *L*-Moses and PCAF Brd



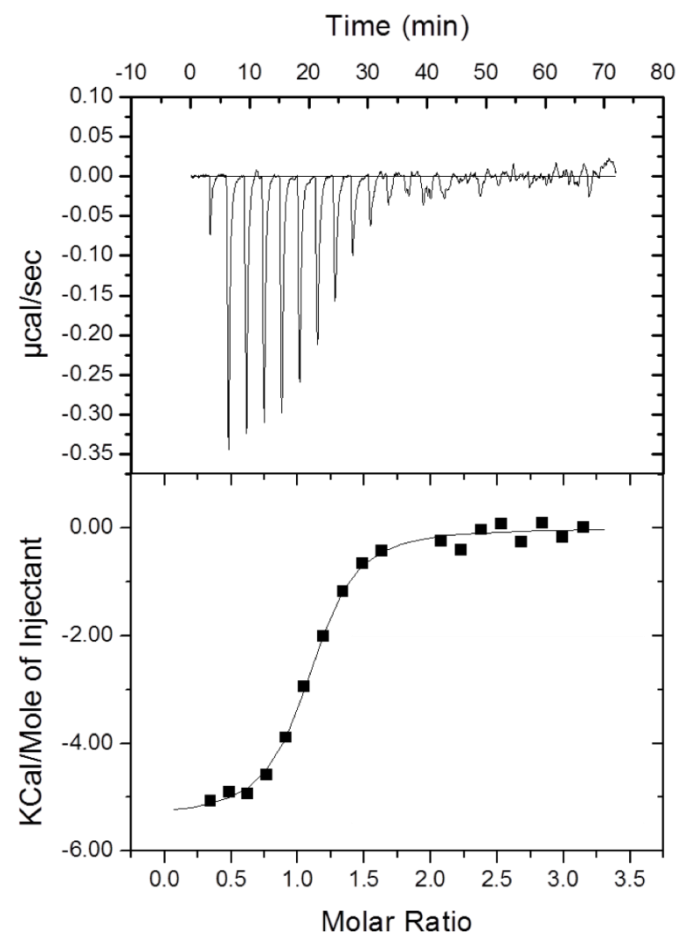
Supplemental Figure 3. ITC trace of *D*-Moses and PCAF Brd



Supplemental Figure 4. ITC trace of **L-Moses** and **HGCN5 Brd**

ITC *PfGCN5*

The binding of compound to the bromodomain of *PfGCN5* was assessed using isothermal titration calorimetry. The assay was performed at 25 °C using a VP-ITC instrument (MicroCal, Northampton, MA, USA) with 0.2 mM recombinant *PfGCN5* and 0.01 mM **L-Moses**, both in a buffer of 20 mM HEPES, 100 mM NaCl, pH 7.5. The experimental data were fitted to a theoretical titration curve using the software package Origin (MicroCal), resulting in a calculated K_D of $(2.8 \pm 0.4) \times 10^{-7}$ M.



Supplemental Figure 5. ITC trace of *L-Moses* and *PfGCN5* Brd

Supplemental Table 3. Binding affinity of selected compounds (ITC).

Compound	PCAF K _D (μM) [†]	
7	7.98	±0.65
8	>30	-
9	>30	-
11	0.298	±0.039
(S)-11	0.284	±0.029
12	1.76	±0.23
13	>30	-
14	>30	-
15	7.30	±1.1
16	6.90	±1.4
(S)-17	>30	-
56	>30	-
57	>30	-
59	4.30	±0.31
60	1.13	±0.24
62	>30	-
64	>30	-
65	>30	-
66	>30	-
67	0.321	±0.039
68	>30	-
69	>30	-
70	>30	-
71	2.3	±0.93
72	>30	-
73	>30	-
75	>30	-
76	0.168	±0.023
39	0.195	±0.040
40	0.133	±0.015
41	0.160	±0.054
42	0.223	±0.078
43	0.163	±0.117
44	0.179	±0.048
45	0.168	±0.027
83	>30	-
84	>30	-
85	>30	-
86	>30	-
87	>30	-
88	>30	-
89	>30	-
90	>30	-
91	>30	-
97	18.2	±0.13
L-45/L-Moses	0.126	±0.015
L-45/D-Moses	>30	-

[†] Compound concentration: 30 μM, Protein concentration: 280-320 μM.

NanoLuciferase Bioluminescent Resonance Energy Transfer (NanoBRET) Assay

Methods

HEK293 cell (8×10^5) were plated in each well of a 6-well plate and co-transfected with Histone H3.3-HaloTag (NM_002107) and a NanoLuciferase fusion of the isolated bromodomain of PCAF. Twenty hours post-transfection, cells were collected, washed with PBS, and exchanged into media containing phenol red-free DMEM and 4% FBS in the absence (control sample) or the presence (experimental sample) of 100 nM NanoBRET 618 fluorescent ligand (Promega). Cell density was adjusted to 2×10^5 cells/ml and then re-plated in a 96-well assay white plate (Corning Costar #3917). Compounds were then added directly to media at final concentrations 5 μ M or an equivalent amount of DMSO as a vehicle control, and the plates were incubated for 18 h at 37 °C in the presence of 5% CO₂. NanoBRET Nano-Glo substrate (Promega) was added to both control and experimental samples at a final concentration of 10 μ M. Readings were performed within 5 minutes using a Glo-MAX Discover instrument (Promega) equipped with 450/8 nm bandpass and 600 nm longpass filters with a 0.3 sec reading setting. A corrected BRET ratio was calculated and is defined as the ratio of the emission at 600 nm/450 nm for experimental samples (i.e. those treated with NanoBRET fluorescent ligand) subtracted by and the emission at 600 nm/450 nm for control samples (not treated with NanoBRET fluorescent ligand). BRET ratios are expressed as milliBRET units (mBU), where 1 mBU corresponds to the corrected BRET ratio multiplied by 1000.

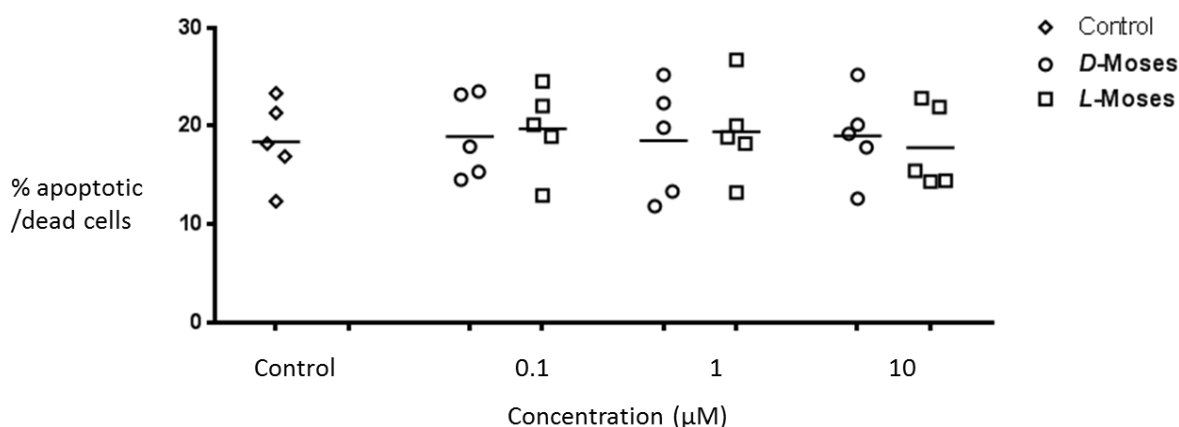
In vitro Metabolism Studies

Metabolic stability studies were carried out exposing nominated compounds to samples of liver microsomes. Compounds were analysed by LC-MS for loss of compound at 0, 5, 15, 30 and 45 minute time points. The rate of metabolic degradation of compounds was used to calculate CL_{int}, SE CL_{int}, t_{1/2} (summarised in supplemental table 2.)

Supplemental Table 4. *In vitro* metabolic stability of compounds **DL-45/DL-Moses** and **39**

Compound	Metbolic Stability (Human)				Metbolic Stability (Mouse)				
	CL _{int} (μL/min/mg protein)	SE CL _{int}	t _{1/2}	n	CL _{int} (μL/min/mg protein)	SE CL _{int}	t _{1/2}	n	
45/DL-Moses	35	2.2	40	5	37	2.6	38	5	
39	29	2.0	48	5	21	1.3	65	5	

Cytotoxicity Studies



Supplemental Figure 6. Cytotoxicity studies on PMBC cells of **L-Moses** and **D-Moses**

Toxicity of **D-Moses** and **L-Moses** were tested on peripheral blood mononuclear cells (PBMC) obtained from 5 healthy donors. PBMC were cultured either with **D-Moses** or **L-Moses** at concentrations of 0.1, 1 and 10 μM or with a control (DMSO) for 24 hours. Viability of PBMC were then checked using LIVE/DEAD Fixable Aqua Dead Cell Stain Kit (ThermoFisher Scientific).

High Throughput Time Resolved Fluorescence Assay (HTRF)

HTRF assay was carried out using a Cisbio Epigenous kit B (62BDBPEH) using the standard assay protocol with GST-PCAF_{BRD}.^[3] Final assay concentrations: GST-PCAF_{BRD} (20 nM), SA-XL665 (62.5 nM), α-GST donor (62.5 nM), compound **46** (500 nM). K_i was calculated using the Cheng-Prusoff equation with a value of 400 nM for the K_D of compound **46**.

Crystallography

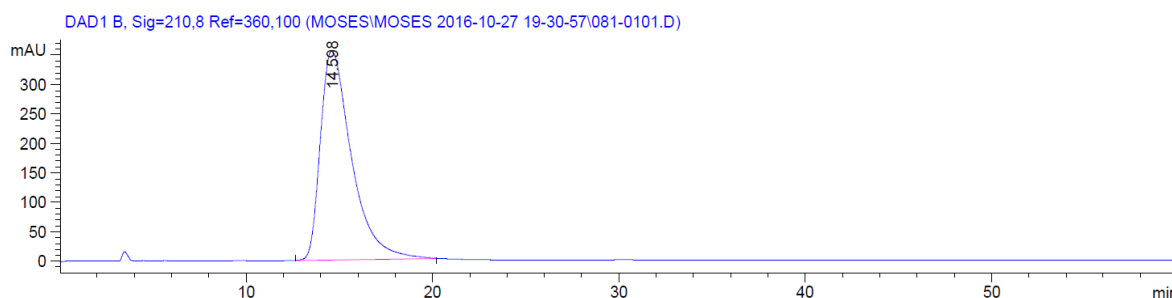
Recombinant PfGCN5 (bromodomain only) was expressed in *E. coli* and purified using a previously described system^[4]. The protein crystallized with the compound **L-45** at 293 K in 0.1M CaCl₂, 30% PEG 8k, 0.2 M NH₄SO₄. The concentrations of the protein sample and the compound were 10 mg/ml and 2 mM, respectively.

X-ray diffraction data for the crystal was collected at 100 K at the beamline 08ID-1 of the Canadian Macromolecular Crystallography Facility. The dataset was processed using the HKL-2000 suite^[5], and the structure solved using Phaser^[6], a component of the CCP4 suite^[7] with molecular replacement model 4QNS. Iterative model building using the graphics program COOT^[8], the refinement program Buster-TNT^[9] and the validation tools of MOLPROBITY^[10] led to a model with a working R value of 0.185 and a R-free value of 0.236 over a resolution range between 37.5-2.10 Å, with excellent stereochemistry.

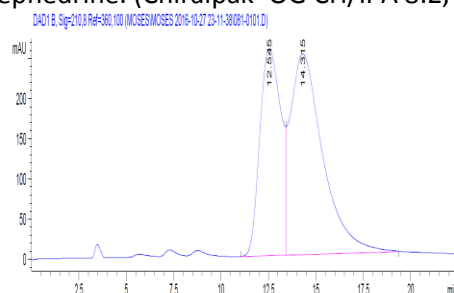
Supplemental Table 4. Crystallography data and refinement statistics

PDB Code		5TPX
Data collection		
Space group		P42 ₁ 2
Cell dimensions		
<i>a</i> , <i>b</i> , <i>c</i> (Å)		75.00 75.00 49.62
<i>α</i> , <i>β</i> , <i>γ</i> (°)		90.0, 90.0, 90.0
Resolution (Å) (highest resolution shell)		37.50-2.10 (2.14-2.10)
Measured reflections		65686
Unique reflections		8411
<i>R</i> _{meas} (%)		10.0(72.5)
<i>I</i> / <i>σI</i>		20.6 (2.2)
Completeness(%)		96.0(89.0)
Redundancy		7.8(7.8)
Refinement		
Resolution (Å)		37.5-2.1
No. reflections (test set)		8368(390)
<i>R</i> _{work} / <i>R</i> _{free} (%)		18.5/23.6
No. atoms		
Protein		870
Water		66
Heterogen		43
Average B-factors (Å²)		
Protein	45.06	
Water	49.12	
Heterogen	54.5	
Geometry (RMSD)		
Bond lengths (Å)		0.010
Bond angles (°)		0.67
Ramachandran plot % residues		
Favored		100.0
Additional allowed		0.0
Disallowed		0

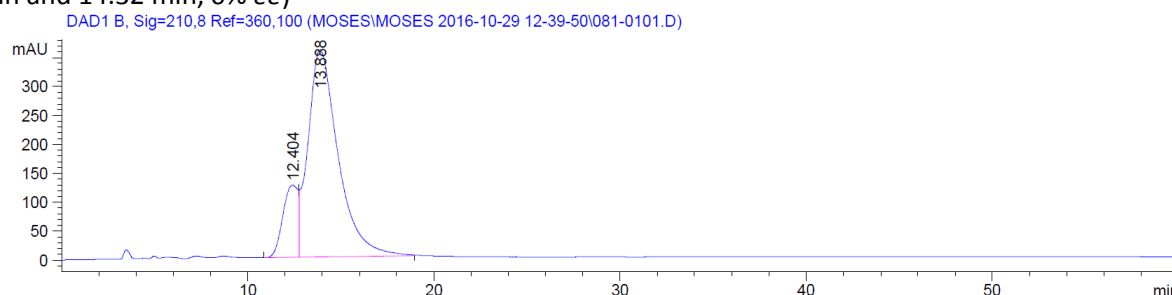
Chiral HPLC Traces



Supplemental Figure 7. HPLC trace of **L-45/L-Moses** after asymmetric synthesis from (1*R*,2*S*)-(-)-Norephedrine. (Chiralpak®OG CH/IPA 8:2, 1 mL/min, R_t = 14.59 min, >99% *ee*)



Supplemental Figure 8. HPLC trace of **45/DL-Moses**. Chiralpak®OG CH/IPA 8:2, 1 mL/min, R_t = 12.54 min and 14.32 min, 0% *ee*)



Supplemental Figure 9. HPLC trace of **L-45/L-Moses** spiked with ~15% **45/DL-Moses**. Chiralpak®OG CH/IPA 8:2, 1 mL/min, R_t = 12.40 min and 13.88 min, 70% *ee*)

Supplemental References

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