SUPPORTING INFORMATION

2-Arylamino-6-Ethynylpurines Are Cysteine-Targeting Irreversible Inhibitors of Nek2 Kinase

Christopher J. Matheson, Christopher R. Coxon, Richard Bayliss, Kathy Boxall, Benoit Carbain, Andrew M. Fry, Ian R. Hardcastle, Suzannah J. Harnor, Corine Mas-Droux, David R. Newell, Mark W. Richards, Mangaleswaran Sivaprakasam, David Turner, Roger J. Griffin, Bernard T. Golding and Céline Cano

Contents:

1. Synthesis and Characterisation of Compounds

1.1. General Experimental Details

Chemicals and Solvents

All chemical reagents were purchased from the Aldrich Chemical Company, Apollo Scientific or Alfa Aesar Chemicals and were of the highest available purity. Chemicals were used as supplied with no further treatment. If chemicals used were stated as dry/anhydrous, they were stored in SureSeal™ septum-sealed bottles and removed under an inert nitrogen environment, with the reaction being carried out under the relevant inert atmosphere. Palladium catalysts were stored and measured out under an inert atmosphere.

Chromatography

Reaction monitoring and compound identification was aided using Thin Layer Chromatography (TLC) and Retardation factor (R_f) values. TLC was conducted with Merck aluminium backed Si F_{254}, NH_2 F_{254s} and RP-18 F_{254s} plates. Fluorescent compounds were

visualised under short wave (254 nm) UV irradiation. Compound purification was achieved using medium pressure 'Flash' column chromatography, with the use of Davisil silica 40-60μm as the stationary phase, or Biotage automated chromatography using pre-packed silica cartridges. A Biotage SP4 automated flash purification system was used with UV monitoring at 298 nm and compound collection at 254 nm. Biotage KP-NH cartridges were employed for the separation of secondary, tertiary, and heterocyclic amines; using a primary amine (propyl amine) bonded silica. When stated, compounds were purified *via* semi-preparative HPLC, using an ACE 5 Phenyl 150 x 21.2 mm column using an Agilent 1200 Modular Preparative HPLC system.

Analytical Techniques

All melting points were determined using a Stuart Scientific SMP3 or a Stuart Scientific SMP40 melting point apparatus and are uncorrected. ^{1}H and ^{13}C nuclear magnetic resonance (NMR) spectra were obtained as solutions in deuterated solvents DMSO-d_6, MeOD or $CDCl_3$ using a Bruker Avance III 500 spectrometer recording at 500 MHz. Chemical shifts (δ) are reported in parts per million (ppm) and the spin-multiplicity abbreviated as: s (singlet), d (doublet), t (triplet), q (quartet), quin (quintet), sept (septet), m (multiplet), or br (broad), with coupling constants (*J*) given in Hertz (Hz). Liquid Chromatography – Mass Spectrometry (LC-MS) was carried out on a Micromass Platform LC running in both positive and negative electrospray mode with a PDA 240-400 nm detector using a Waters Symmetry Shield RP18 3 μm, 4.6 x 20 mm column with a flow rate of 3.0 mL/min. Alternatively, a Waters Acquity UPLC system was used, with a Waters SQD ESCi source using an Acquity UPLC BEH C18 1.7 μm, 2.1 x 50 mm column with a flow rate of 0.6 mL/min. The mobile phase used was 0.1% *v/v* formic acid (aq.)/MeCN. Fourier Transform Infrared (FTIR) spectra were obtained using a Bio-Rad FTS 3000MX diamond ATR as a neat sample. Ultraviolet (UV) absorption data were collected using a Hitachi U-2800A spectrophotometer in ethanol. High-resolution mass spectra were performed by the ESPRC UK National Mass Spectrometry Facility, Swansea University, Singleton Park, Swansea, SA2 8PP. The purity of final compounds was assessed by reversed-phase HPLC; all tested compounds were >95% purity. HPLC instrument, Agilent 1200 equipped with a photodiode array detector (190-400 nm). Sample temperature, ambient; injection volume, 5 μL; flow rate, 1 mL/min. 5% to 100% MeCN gradient over 9 min and an isocratic hold at 100% MeCN for 2.5 min, before returning to initial conditions. Mobile phase A = 0.1% ammonia in water or 0.1% formic acid in water, mobile phase B = MeCN. Column: Waters XSELECT CSH C18, 3.5 μm, 4.6 mm × 150 mm or Waters XTerra RP18, 5 μm, 4.6 mm × 150 mm. Column maintained at ambient temperature.

Microwave Assisted Synthesis

When stated, reactions were carried out under microwave irradiation, in sealed vessels, using a Biotage Initiator Sixty with robotic sample bed. Samples were irradiated at 2.45 GHz, able to reach temperatures of 60 - 250 ºC with a rate of heating at 2-5 °C/sec, and pressures of up to 20 bar.

1.2. General Synthetic Procedures

General Procedure A: TFA/TFE coupling of anilines with 2-fluoropurines using conventional heating

TFA (2.5-5.0 equiv.) was added to a solution of the purine substrate (1.0 equiv.) and the required aniline (2.0 equiv.) in TFE (10 mL/mmol). The reaction mixture was heated at reflux for 24 h unless otherwise stated, after which the solution was cooled and evaporated to dryness. The resulting residue was dissolved in EtOAc (10 mL/mmol) and washed with a saturated aqueous solution of $NaHCO_3$ (5 mL/mmol) and brine (5 mL/mmol). The combined aqueous layers were extracted with EtOAc (10 mL/mmol), and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product for chromatographic purification.

General Procedure B: TFA/TFE coupling of anilines with 2-fluoropurines using microwave heating

The purine substrate (1.0 equiv.), the required aniline (2.0 equiv.) and TFA (2.5-5.0 equiv.) were dissolved in TFE (10 mL/mmol) and heated under microwave irradiation at 140 °C for 2 h, unless otherwise stated. Following removal of the solvent *in vacuo*, the resulting residue was dissolved in EtOAc (10 mL/mmol) and washed with a saturated aqueous solution of $NaHCO_3$ (5 mL/mmol) and brine (5 mL/mmol). The combined aqueous layers were extracted with EtOAc (10 mL/mmol), and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo* to give the crude product for chromatographic purification.

General Procedure C: Removal of TIPS-protecting groups using TBAF

TBAF (1.2 equiv.) was added to a solution of the TIPS-protected substrate (1.0 equiv.) in THF (10-20 mL/mmol). The reaction mixture was stirred at RT for 5 min before being concentrated *in vacuo* and the crude residue purified by chromatography to afford the target compound.

General Procedure D: CDI mediated amide coupling reactions

CDI (2.0 equiv.) and DIPEA (2.0 equiv.) were added to a solution of the carboxylic acid substrate (1.0 equiv.) in dry DMF (10 mL/mmol). The mixture was stirred at RT for 1.5 h, at which point the required amine (4.0 equiv.) was added. Following a further 18 h stirring at RT, the solvent was removed *in vacuo* and the resulting residue was purified by chromatography to give the desired product.

General Procedure E: Removal of PMB protecting groups using TFA

The PMB-protected substrate (1.0 equiv.) was dissolved in TFA (10-20 mL/mmol) and the resulting solution was heated at reflux for 24 h, unless stated otherwise. The reaction mixture was evaporated to dryness and the resulting residue was dissolved in EtOAc (20 mL/mmol) and washed with a saturated aqueous solution of $NaHCO_3$ (2 × 10 mL/mmol) and brine (10 mL/mmol). The combined aqueous layers were extracted with EtOAc (20 mL/mmol) and the combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*, and the residue purified by chromatography to give the desired compound.

General Procedure F: Removal of TIPS-protecting groups using KF and 18-crown-6

KF (1.2 equiv.) and 18-crown-6 (0.1 equiv.) were added to a solution of the TIPS-protected substrate (1.0 equiv.) in THF (10 mL/mmol) and the reaction mixture was stirred at RT for 24 h. The solvent was removed *in vacuo* and the crude product was purified by chromatography.

General Procedure G: Removal of TIPS-protecting groups using TBAF followed by removal of TBAF contaminant

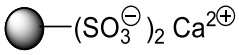
TBAF (1.2 equiv.) was added to a solution of the TIPS-protected substrate (1.0 equiv.) in THF (10-20 mL/mmol). The reaction mixture was stirred at RT for 5 min before being diluted with THF (100-200 mL/mmol) and the TBAF scavenger resin (10 × *w/w*) added. The resulting suspension was agitated at RT for 48 h, before being filtered and the filtrate concentrated *in vacuo*. The resulting residue was purified by chromatography to afford the target compound.

General Procedure H: Sulfonamide synthesis by treatment of trifluoroethyl sulfonate esters with amines

The trifluoroethyl sulfonate ester substrate (1.0 equiv.), the required amine (1.3 equiv.) and DBU (2.0 equiv.) were combined in dry THF (10 mL/mmol) in a sealed vial. The reaction mixture was heated under microwave irradiation at 160 °C for 15 min, before being evaporated to dryness. The resulting residue was dissolved in DCM (10 mL/mmol) and washed with a saturated aqueous solution of $NaHCO_3$ (10 mL/mmol), after which the biphasic mixture was passed through an Isolute® phase separator and the organic phase

was concentrated *in vacuo*. The crude residue was purified *via* chromatography to give the target compound.

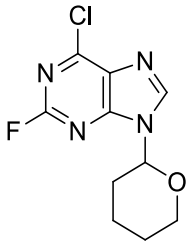
TBAF scavenger resin[5]



Amberlite 15 Ion exchange resin (SO_3H, 100 mL) was loaded into a column and washed with water (400 mL). The column was eluted with sat. calcium hydroxide solution whilst the pH of the eluent was monitored. Once the initially pH neutral eluent became strongly basic, the column was eluted with water until the pH of the eluent returned to neutral. The resin was washed with DCM (300 mL), THF (300 mL) and Et_2O (300 mL), before being removed from the column and dried in a vacuum oven at 40 °C.

1.3. Compound Data

6-Chloro-2-fluoro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (10)[6]

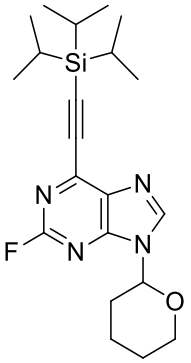


Part 1. To a stirred solution of HBF_4 (48% aqueous, 120 mL) at 0 ºC, was added 2-amino-6-chloropurine (6.0 g, 35.0 mmol). Over 20 min, a solution of $NaNO_2$ (4.9 g, 70.0 mmol) in water (200 mL) was added dropwise, ensuring the temperature remained close to 0 ºC. The pale yellow solution was raised to RT and stirred for 18 h. The resulting solution was neutralised to pH 7 in an ice bath at 0 °C by addition of Na_2CO_3 (6.00 g) in water (200 mL). The crude material was purified by chromatography on silica (10% MeOH/DCM) to afford 6-chloro-2-fluoropurine as a white crystalline solid (4.52 g, 75%); m.p. 171-173 ºC (lit.,[7] m.p. 174 ºC); λ_{max} (EtOH/nm) 393; IR (cm^{-1}) 2964, 2785, 1735, 1581; ^{1}H NMR (500 MHz, DMSO-d_6) 8.60 (1H, s, H-8), 13.9 (1H, s, NH-9); LRMS (ES^+) *m/z* 172.6 $[M+H]^+$.

Part 2. 3,4-Dihydropyran (60 µL, 0.58 mmol) was added dropwise over 10 min to a vigorously stirred solution of 6-chloro-2-fluoropurine (100 mg, 0.58 mmol) and (*rac*)-camphorsulfonic acid (5 mg, 0.02 mmol) in EtOAc (50 mL) at 65 ºC. The temperature was maintained at 65 ºC for 18 h. The resulting bright yellow solution was neutralised to pH 7 by careful addition of aqueous NH_3 solution, until a cloudy suspension persisted. The crude

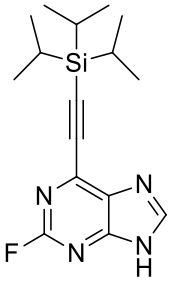
mixture was washed with brine (2 × 30 mL) and the aqueous phase was re-extracted with EtOAc (2 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and purified by chromatography on silica (30% EtOAc/Petrol). The desired compound was isolated as a pale yellow oil which solidified on refrigeration (110 mg, 75%); m.p. 69-70 ºC (lit.[6] m.p. not available); λ_{max} (EtOH/nm) 269; IR (cm^{-1}) 3125, 2954, 2872, 2028, 1577; ^{1}H NMR (300 MHz, DMSO-d_6) 1.60 (2H, m, CH_2), 1.74 (1H, m, CH), 2.01 (2H, m, CH_2), 2.32 (1H, s, CH), 3.71 (1H, t, *J* = 12.0 Hz, CH), 4.01 (1H, d, *J* = 12.0 Hz, CH), 5.64 (1H, d, *J* = 12.0 Hz, CH), 8.25 (1H, s, H-8); LRMS (ES^+) *m/z* 257.7 $[M+H]^+$.

2-Fluoro-9-(tetrahydro-2*H*-pyran-2-yl)-6-((triisopropylsilyl)ethynyl)-9*H*-purine (11)



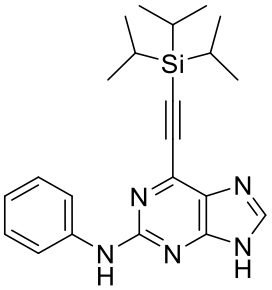
An oxygen-free solution of 6-chloro-2-fluoro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (**10**) (50 mg, 1.95 mmol), bis(triphenylphosphine)palladium (II) chloride (41 mg, 3.00 mol%) and copper iodide (7 mg, 2.00 mol%) in THF (10 mL) was degassed by bubbling nitrogen through the solution in a sealed Biotage microwave vial for 5 min. Triisopropylsilylacetylene (0.50 mL, 2.20 mmol) and triethylamine (0.70 mL, 4.90 mmol) were added to the mixture which was again degassed for 15 min. The solution quickly became dark red and stirring was continued at room temperature for 18 h. The black-brown suspension was filtered through Celite®, eluting with MeOH (3 × 20 mL). The product was purified by chromatography on silica (10% EtOAc/Petrol) and isolated as a viscous yellow oil (78 mg, 99%); λ_{max} (EtOH/nm) 303.5; IR (cm^{-1}) 3433, 2945, 2865, 2705, 1702; ^{1}H NMR (500 MHz, DMSO-d_6) 1.15 (21H, m, $Si(CH(CH_3)_2)_3$) and $Si(CH(CH_3)_2)_3$), 1.60 (2H, m, CH_2), 1.75 (1H, m, CH), 1.99 (2H, m, CH_2), 2.19 (1H, s, CH), 3.74 (1H, t, *J* = 12.0 Hz, CH), 4.16 (1H, d, *J* = 12.0 Hz, CH), 5.69 (1H, d, *J* = 12.0 Hz, CH), 8.30 (1H, s, H-8); LRMS (ES^+) *m/z* 403.4 $[M+H]^+$.

2-Fluoro-6-(2-(triisopropylsilyl)ethynyl)-9*H*-purine (12)



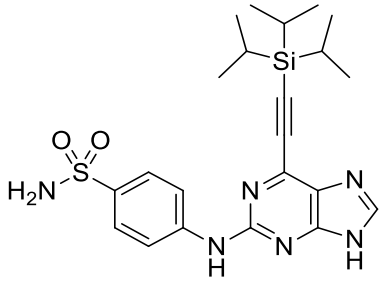
TFA (3 mL) was added to a solution of THP-protected purine **11** (0.644 g, 1.60 mmol) in IPA (15 mL). Water (3 mL) was added and the solution was heated to reflux for 2 h. The mixture was cooled and neutralised (conc. NH_3) before being extracted with EtOAc (3 × 50 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated. The resulting residue was purified by chromatography on silica (30% EtOAc/Petrol) to give the desired product as a pale yellow oil (0.461 g, 91%); R_f 0.25 (7:3 Petrol/EtOAc); λ_{max} (EtOH/nm) 302; IR (cm^{-1}) 2945, 2866, 2361, 2000, 1584; ^{1}H NMR (500 MHz, DMSO-d_6) 1.12-1.21 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 8.68 (1H, s, H-8), 13.89 (1H, br, NH-9); HRMS calcd. for $C_{16}H_{24}FN_4Si$ (ES+) *m*/*z* 319.1749 $[M+H]^+$, found 319.1752.

_N_-Phenyl-6-((triisopropylsilyl)ethynyl)-9*H*-purin-2-amine (13)



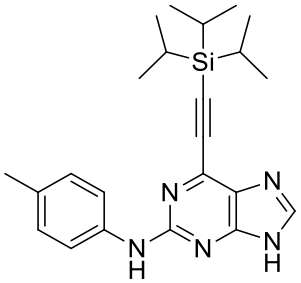
According to **general procedure A**, the title compound was prepared using: 2-fluoro-6-((triisopropylsilyl)ethynyl)-9*H*-purine (**12**) (0.70 g, 2.2 mmol) and aniline (0.40 mL, 4.4 mmol). The compound was isolated after chromatography (silica: 5% MeOH/DCM) followed by reversed phase column chromatography (C18 silica; 25% to 95% MeCN/water + 0.1% HCOOH), as a yellow oil (0.44 g, 47%); λ_{max} (EtOH/nm) 276; IR (cm^{-1}) 3389, 2361, 2021; ^{1}H NMR (500 MHz, $CDCl_3$) 1.13 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 7.02 (1H, t, *J* = 7.5 Hz, H-4'), 7.33 (2H, dd, *J* = 7.4, 7.5 Hz, H-3' and H-5'), 7.80 (2H, d, *J* = 7.4 Hz, H-2' and H-6'), 10.42 (1H, s, NH); LRMS (ES+) *m/z* 392.0 $[M+H]^+$.

4-(6-((Triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)benzenesulfonamide (14)



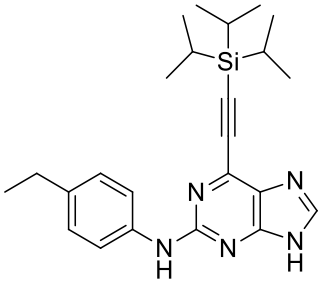
The title compound was synthesised following **general procedure A** using: 2-fluoro-6-((triisopropylsilyl)ethynyl)-9*H*-purine (**12**) (0.156 g, 0.49 mmol) and 4-aminobenzenesulfonamide (0.17 g, 0.98 mmol). The compound was purified using reversed phase column chromatography (C18 silica; 25% to 95% MeCN/water + 0.1% HCOOH), followed by trituration of the resulting oil using DCM, to obtain the product as a yellow solid (70 mg, 30%); m.p.163-165 ºC; λ_{max} (EtOH/nm) 361.0, 291.0, 286.5, 215.5; IR (cm^{-1}) 3327, 2944, 2867, 1569, 1531, 1368, 1149; ^{1}H NMR (500 MHz, DMSO-d_6) 1.15 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 7.17 (2H, s, SO_2NH_2), 7.70 (2H, d, *J* = 9.0 Hz, H-2' and H-6'), 7.95 (2H, d, *J* = 9.0 Hz, H-3' and H-5'), 8.33 (1H, s, H-8); HRMS calcd for $C_{22}H_{31}N_6O_2SSi$ $[M+H]^+$ 471.19874, found 471.19420.

6-(2-(Triisopropylsilyl)ethynyl)-*N*-*p*-tolyl-9*H*-purin-2-amine (15)



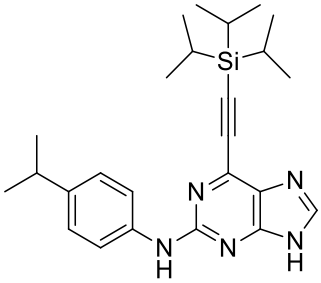
2-Fluoropurine intermediate **12** (0.357 g, 1.12 mmol) and 4-methylaniline (0.241 g, 2.25 mmol) were reacted with TFA (432 µL, 5.61 mmol) in TFE (6 mL) according to **general procedure A**. The resulting crude residue was purified by chromatography on reverse phase silica (19:1 MeOH/H_2O + 0.1% HCOOH) to give the desired compound as a yellow oil (0.215 g, 47%); R_f 0.27 (19:1 MeOH/H_2O + 0.1% HCOOH, C18); λ_{max} (EtOH/nm) 276; IR (cm^{-1}) 2942, 2865, 2361, 2336, 1605; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.22 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.31 (3H, s, CH_3), 7.14 (2H, d, *J* = 8.4 Hz, H-3' and H-5'), 7.74 (2H, d, *J* = 8.4 Hz, H-2' and H-6'), 8.28 (1H, s, H-8), 9.65 (1H, s, NH), 13.11 (1H, br, NH-9); HRMS calcd. for $C_{23}H_{32}N_5Si$ (ES+) *m*/*z* 406.2421 $[M+H]^+$, found 406.2423.

***N*-(4-Ethylphenyl)-6-(2-(triisopropylsilyl)ethynyl)-9*H*-purin-2-amine (16)**



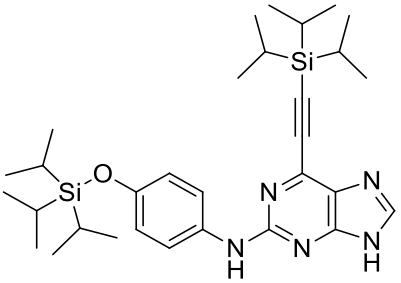
2-Fluoropurine intermediate **12** (0.394 g, 1.24 mmol) and 4-ethylaniline (310 µl, 2.48 mmol) were reacted with TFA (477 µl, 6.19 mmol) in TFE (6 mL) according to **general procedure A**. The resulting residue was purified by chromatography on reverse phase silica (19:1 MeOH/H_2O + 0.1% HCOOH) to give the desired compound as a yellow oil/gum (0.281 g, 54%); R_f 0.27 (19:1 MeOH/H_2O + 0.1% HCOOH, C18); λ_{max} (EtOH/nm) 277; IR (cm^{-1}) 2941, 2865, 2361, 2338, 2160, 1605; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.21 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 1.23 (3H, t, *J* = 7.6 Hz, CH_2CH_3), 2.61 (2H, q, *J* = 7.6 Hz, CH_2CH_3) 7.17 (2H, d, *J* = 8.4 Hz, H-3' and H-5'), 7.75 (2H, d, *J* = 8.4 Hz, H-2' and H-6'), 8.27 (1H, s, H-8), 9.66 (1H, s, NH), 13.11 (1H, br, NH-9); HRMS calcd. for $C_{24}H_{34}N_5Si$ (ES+) *m*/*z* 420.2578 $[M+H]^+$, found 420.2579.

_N_-(4-Isopropylphenyl)-6-(2-(triisopropylsilyl)ethynyl)-9_H_-purin-2-amine (17)



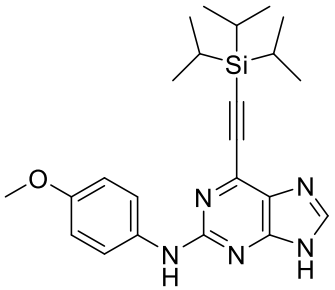
2-Fluoropurine intermediate **12** (0.395 g, 1.24 mmol) and 4-isopropylaniline (353 µL, 2.48 mmol) were reacted with TFA (478 µL, 6.21 mmol) in TFE (6 mL) according to **general procedure A**. The resulting residue was purified by chromatography on reverse phase silica (19:1 MeOH/H_2O + 0.1% HCOOH) to give the desired compound as a yellow oil/gum (0.314 g, 58%); R_f 0.23 (19:1 MeOH/H_2O + 0.1% HCOOH, C18); λ_{max} (EtOH/nm) 277; IR (cm^{-1}) 2956, 2866, 2360, 2157, 1607; ^{1}H NMR (500 MHz, DMSO-d_6) 1.12-1.21 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 1.25 (6H, d, *J* = 7.0 Hz, CH(C*H*$_3$)$_2$), 2.89 (1H, sept, *J* = 7.0 Hz, C*H*$(CH_3)_2$), 7.19 (2H, d, *J* = 8.6 Hz, H-3' and H-5'), 7.74 (2H, d, *J* = 8.6 Hz, H-2' and H-6'), 8.26 (1H, s, H-8), 9.65 (1H, s, NH), 13.10 (1H, br, NH-9); HRMS calcd. for $C_{25}H_{36}N_5Si$ (ES+) *m*/*z* 434.2734 $[M+H]^+$, found 434.2735.

6-((Triisopropylsilyl)ethynyl)-_N_-(4-((triisopropylsilyl)oxy)phenyl)-9_H_-purin-2-amine (18)



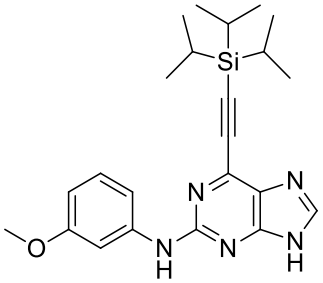
2-Fluoropurine intermediate **12** (0.379 g, 1.19 mmol) and aniline **105** (0.610 g, 2.38 mmol) were reacted with TFA (460 µl, 5.96 mmol) in TFE (8 mL) according to **general procedure A**. Purification by chromatography on silica (7:3 Petrol/EtOAc)) gave the target compound as an orange oil (0.181 g, 0.32 mmol, 27%); R_f 0.44 (7:3 Petrol/EtOAc); λ_{max} (EtOH/nm) 277; IR (cm^{-1}) 2944, 2866, 2367, 2343, 2187, 1607; ^{1}H NMR (500 MHz, DMSO-d_6) 1.08 (18H, d, *J* = 7.3 Hz, OSi(CH(C*H*$_3$)$_2$)$_3$), 1.12-1.24 (24H, m, OSi(C*H*(CH$_3$)$_2$)$_3$ and Si(C*H*(C*H*$_3$)$_2$)$_3$), 6.80 (2H, d, *J* = 9.3 Hz, H-3' and H-5'), 7.64 (2H, d, *J* = 9.3 Hz, H-2' and H-6'), 8.20 (1H, s, H-8), 9.54 (1H, s, NH), 13.01 (1H, br, NH-9); HRMS calcd. for $C_{31}H_{50}N_5OSi_2$ (ES+) *m*/*z* 564.3548 $[M+H]^+$, found 564.3543.

_N_-(4-methoxyphenyl)-6-((triisopropylsilyl)ethynyl)-9_H_-purin-2-amine (19)



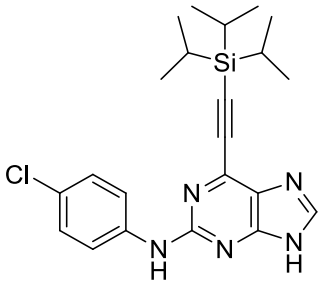
The title compound was prepared according to **general procedure A** using: 2-fluoro-6-((triisopropylsilyl)ethynyl)-9*H*-purine (**12**) (0.20 g, 0.63 mmol) and *para*-anisidine (0.155 g, 1.26 mmol). Purification by chromatography on silica (50% EtOAc/petrol) followed by chromatography on reverse phase silica (25% to 95% MeCN/water + 0.1% HCOOH) gave the compound as a brown glassy solid (0.14 g, 43%); m.p. 101-103 °C; λ_{max} (EtOH) 277.0, 210.0; IR (cm^{-1}) 2943, 2862, 1607, 1574, 1510; ^{1}H NMR (500 MHz, DMSO-d_6) 1.01 (21H, s, Si(C*H*(C*H*$_3$)$_2$)$_3$), 3.59 (3H, s, OCH$_3$), 6.72-6.74 (2H, d, *J* = 10.0 Hz, H-2' and H-6'), 7.52-7.54 (2H, d, *J* = 10.0 Hz, H-3' and H-5'), 8.08 (1H, s, H-8), 9.39 (1H, br s, NH); LRMS (ES$^+$) *m/z* 422.3 $[M+H]^+$.

6-(2-(Triisopropylsilyl)ethynyl)-_N_-(3-methoxyphenyl)-9_H_-purin-2-amine (20)



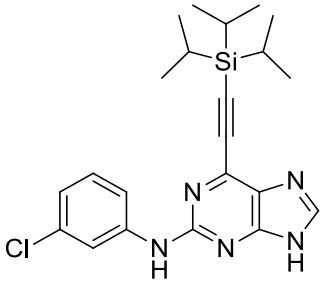
2-Fluoropurine intermediate **12** (0.421 g, 1.32 mmol) and 3-methoxyaniline (298 µL, 2.65 mmol) were reacted with TFA (510 µL, 6.62 mmol) in TFE (6 mL) according to **general procedure A**. Chromatography on reverse phase silica (19:1 MeOH/H_2O + 0.1% HCOOH) afforded the target compound as a yellow oil/gum (0.297 g, 53%); R_f 0.33 (19:1 MeOH/H_2O + 0.1% HCOOH, C18); λ_{max} (EtOH/nm) 274; IR (cm^{-1}) 3147, 2943, 2865, 2360, 1600; ^{1}H NMR (500 MHz, DMSO-d_6) 1.14-1.23 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 3.76 (3H, s, OCH_3), 6.52 (1H, ddd, *J* = 2.3, 2.5 and 8.5 Hz, H-4'), 7.17 (1H, dd, *J* = 8.1 and 8.2 Hz, H-5'), 7.29-7.33 (1H, m, H-6'), 7.64-7.67 (1H, m, H-2'), 8.26 (1H, s, H-8), 9.71 (1H, s, NH), 13.12 (1H, br, NH-9); HRMS calcd. for $C_{23}H_{32}N_5OSi$ (ES+) *m*/*z* 422.2371 $[M+H]^+$, found 422.2372.

6-(2-(Triisopropylsilyl)ethynyl)-*N*-(4-chlorophenyl)-9*H*-purin-2-amine (21)



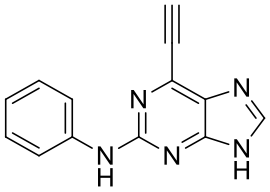
2-Fluoropurine intermediate **12** (0.200 g, 0.62 mmol), 4-chloroaniline (0.161 g, 1.26 mmol), TFA (242 µL, 3.14 mmol) and TFE (6 mL) were reacted according to **general procedure A**. The dried ($MgSO_4$) and concentrated crude material was purified by chromatography on silica (7:3 Petrol/EtOAc) to give the desired product as a yellow oil (0.165 g, 61%); R_f 0.25 (7:3 Petrol/EtOAc); λ_{max} (EtOH/nm) 289; IR (cm^{-1}) 3118, 2945, 2866, 2361, 1541; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.22 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 7.33 (2H, d, *J* = 8.9 Hz, H-2' and H-6'), 7.85 (2H, d, *J* = 8.9 Hz, H-3' and H-5'), 8.27 (1H, s, H-8), 9.91 (1H, s, NH), 13.17 (1H, br, NH-9); LRMS (ES+) *m/z* 426.2 $[M^{35}Cl+H]^+$, 428.2 $[M^{37}Cl+H]^+$.

***N*-(3-Chlorophenyl)-6-(2-(triisopropylsilyl)ethynyl)-9*H*-purin-2-amine (22)**



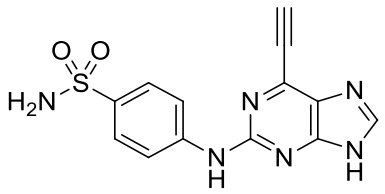
2-Fluoropurine intermediate **12** (0.354 g, 1.11 mmol) and 3-chloroaniline (234 µL, 2.23 mmol) were reacted with TFA (429 µL, 5.57 mmol) in TFE (6 mL) according to **general procedure A**. Purification of the crude residue by chromatography on reverse phase silica (19:1 MeOH/H_2O + 0.1% HCOOH) gave the desired compound as a yellow oil/gum (0.281 g, 59%); R_f 0.27 (19:1 MeOH/H_2O + 0.1% HCOOH, C18); λ_{max} (EtOH/nm) 276; IR (cm^{-1}) 3278, 2944, 2866, 2363, 1596; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.22 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 6.96 (1H, ddd, *J* = 2.0, 2.2 and 8.0 Hz, H-4'), 7.29 (1H, dd, *J* = 8.0 and 8.1 Hz, H-5'), 7.64 (1H, ddd, *J* = 2.0, 2.1 and 8.1 Hz, H-6'), 8.11-8.14 (1H, m, H-2'), 8.30 (1H, s, H-8), 9.96 (1H, s, NH), 13.21 (1H, br, NH-9); HRMS calcd. for $C_{22}H_{29}ClN_5Si$ (ES+) *m*/*z* 426.1875 $[M+H]^+$, found 426.1877.

6-Ethynyl-*N*-phenyl-9*H*-purin-2-amine (23)



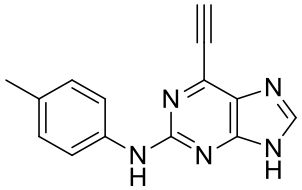
The TIPS-protected purine **13** (0.330 g, 0.84 mmol) and TBAF (1M in THF, 930 µL, 0.93 mmol) were reacted in THF (10 mL) according to **general procedure C**, with purification by chromatography on silica (EtOAc) to give the desired product as a yellow solid (0.201 g, 100%); R_f 0.27 (EtOAc); m.p. 140-160 °C (decomposed); λ_{max} (EtOH/nm) 243; IR (cm^{-1}) 3414, 3111, 3072, 2920, 2110, 1704; ^{1}H NMR (500 MHz, DMSO-d_6) 4.86 (1H, s, C≡CH), 6.91-6.96 (1H, m, H-4'), 7.29 (2H, dd, *J* = 7.6 and 8.0 Hz, H-3' and H-5'), 7.80 (2H, dd, *J* = 2.0 and 8.0 Hz, H-2' and H-6'), 8.30 (1H, s, H-8), 9.70 (1H, s, NH), 13.17 (1H, br, NH-9); HRMS calcd. for $C_{13}H_{10}N_5$ (ES+) *m*/*z* 236.0934 $[M+H]^+$, found 236.0931.

4-(6-Ethynyl-9*H*-purin-2-ylamino)benzenesulfonamide (24)



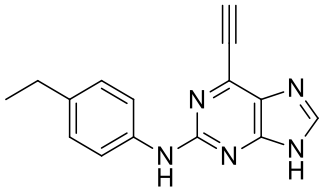
Following **general procedure C**, the title compound was prepared using: TBAF solution (1.0 M in THF, 170 µL, 0.17 mmol) and 4-(6-((triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)benzenesulfonamide (**14**) (50 mg, 0.11 mmol) in THF (3 mL) to complete the deprotection after 5 min. The title compound was purified by chromatography on silica (10% MeOH/DCM) and isolated as a beige solid (18 mg, 50%); m.p. 156-158 ºC; λ_{max} (EtOH/nm) 356.0, 292.5, 215.5; IR (cm^{-1}) 3347, 3255, 2920, 2848, 2118, 1568, 1529, 1477, 1128; ^{1}H NMR (500 MHz, DMSO-d_6) 4.90 (1H, s, C≡C−H), 7.16 (2H, s, SO_2NH_2), 7.17 (2H, d, *J* = 9.0 Hz, H-2' and H-6'), 7.93 (2H, d, *J* = 9.0 Hz, H-3' and H-5'), 8.36 (1H, s, H-8); HRMS calcd for $C_{13}H_{11}N_6O_2S$ $[M+H]^+$ 315.0664, found 315.0687.

6-Ethynyl-*N*-*p*-tolyl-9*H*-purin-2-amine (25)



The TIPS-protected purine **15** (0.208 g, 0.51 mmol) was reacted with TBAF (1M in THF, 770 µL, 0.77 mmol) in THF (5 mL) according to **general procedure C**. Purification by chromatography on silica (1:4 Petrol/EtOAc) afforded the desired compound as a yellow solid (0.102 g, 80%); R_f 0.33 (EtOAc); m.p. 110-120 °C (decomposed); λ_{max} (EtOH/nm) 271; IR (cm^{-1}) 3409, 3268, 2852, 2721, 2110; ^{1}H NMR (500 MHz, DMSO-d_6) 2.26 (3H, s, CH_3), 4.82 (1H, s, C≡CH), 7.10 (2H, d, *J* = 8.4 Hz, H-2’ and H-6’), 7.67 (2H, d, *J* = 8.4 Hz, H-3’ and H-5’), 8.24 (1H, s, H-8), 9.57 (1H, s, NH), 13.09 (1H, br, NH-9); HRMS calcd. for $C_{14}H_{12}N_5$ (ES+) *m*/*z* 250.1087 $[M+H]^+$, found 250.1084.

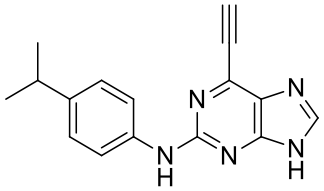
***N*-(4-Ethylphenyl)-6-ethynyl-9*H*-purin-2-amine (26)**



The TIPS-protected purine **16** (0.258 g, 0.61 mmol) was reacted with TBAF (1M in THF, 920 µL, 0.92 mmol) in THF (6 mL) according to **general procedure C**. Purification by

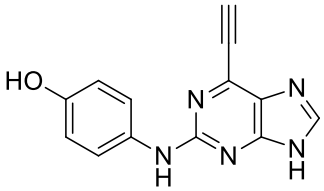
chromatography on silica (1:4 Petrol/EtOAc) gave the desired compound as a yellow solid (0.119 g, 0.45 mmol, 74%); R_f 0.36 (EtOAc); m.p. 120-140 °C (decomposed); λ_{max} (EtOH/nm) 274; IR (cm^{-1}) 3408, 3109, 2961, 2923, 2110, 1748; ^{1}H NMR (500 MHz, DMSO-d_6) 1.17 (3H, t, J = 7.7 Hz, CH_2CH_3), 2.56 (2H, q, J = 7.7 Hz, CH_2CH_3), 4.83 (1H, s, C≡CH), 7.13 (2H, d, J = 8.5 Hz, H-3' and H-5'), 7.68 (2H, d, J = 8.5 Hz, H-2' and H-6'), 8.26 (1H, s, H-8), 9.57 (1H, s, NH), 13.11 (1H, br, NH-9); HRMS calcd. for $C_{15}H_{14}N_5$ (ES+) m/z 264.1246 $[M+H]^+$, found 264.1244.

_N_-(4-Isopropylphenyl)-6-ethynyl-9_H_-purin-2-amine (27)



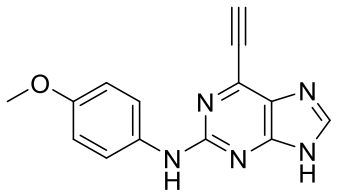
The TIPS-protected purine **17** (0.259 g, 0.60 mmol) was reacted with TBAF (1M in THF, 900 µL, 0.90 mmol) in THF (6 mL) according to **general procedure C**. Purification by chromatography on silica (1:4 Petrol/EtOAc) afforded the target compound as a yellow solid (0.104 g, 0.37 mmol, 62%); R_f 0.40 (EtOAc); m.p. 120-140 °C (decomposed); λ_{max} (EtOH/nm) 277; IR (cm^{-1}) 3408, 3275, 2957, 2814, 2366, 2111; ^{1}H NMR (500 MHz, DMSO-d_6) 0.97 (6H, d, J = 7.1 Hz, $CH(CH_3)_2$), 2.61 (1H, sept, J = 7.1 Hz, $CH(CH_3)_2$), 4.59 (1H, s, C≡CH), 6.92 (2H, d, J = 8.5 Hz, H-3' and H-5'), 7.44 (2H, d, J = 8.5 Hz, H-2' and H-6'), 8.02 (1H, s, H-8), 9.32 (1H, s, NH), 12.88 (1H, br, NH-9); HRMS calcd. for $C_{16}H_{16}N_5$ (ES+) m/z 278.1404 $[M+H]^+$, found 278.1400.

4-(6-Ethynyl-9_H_-purin-2-ylamino)phenol (28)



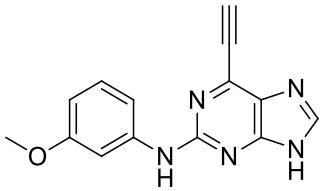
The TIPS-protected purine **18** (0.167 g, 0.30 mmol) was reacted with TBAF (1M in THF, 0.66 mL, 0.66 mmol) in THF (3 mL) according to **general procedure C**. Purification by chromatography on silica (9:1 DCM/MeOH) afforded the desired compound as a beige solid (36 mg, 48%); R_f 0.36 (9:1 DCM/MeOH); m.p. 275-290 °C (decomposed); λ_{max} (EtOH/nm) 274; IR (cm^{-1}) 3391, 3257, 3059, 2921, 2849, 2567, 2114, 1623; ^{1}H NMR (500 MHz, DMSO-d_6) 4.60 (1H, s, C≡CH), 6.51 (2H, d, J = 8.9 Hz, H-2' and H-6'), 7.32 (2H, d, J = 8.9 Hz, H-3' and H-5'), 8.00 (1H, s, H-8), 8.83 (1H, s, NH), 9.12 (1H, s, OH), 12.80 (1H, s, NH-9); HRMS calcd. for $C_{13}H_{10}N_5O$ (ES+) m/z 252.0886 $[M+H]^+$, found 252.0880.

6-Ethynyl-*N*-(4-methoxyphenyl)-9*H*-purin-2-amine (29)



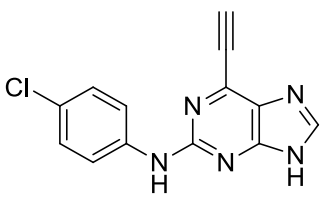
The title compound was prepared according to **general procedure C** using: *N*-phenyl-6-((triisopropylsilyl)ethynyl)-9*H*-purin-2-amine (**19**) (70 mg, 0.17 mmol) and TBAF solution (1.0 M in THF, 0.25 mL, 0.25 mmol) in THF (10 mL). The compound was isolated after purification by chromatography on silica (5% MeOH/DCM) as a dark brown solid (29 mg, 63%); m.p. 129-131 °C; λ_{max} (EtOH/nm) 340.5, 291.0; IR (cm^{-1}) 3347, 2919, 2831, 2108, 1607, 1576; ^{1}H NMR (500 MHz, DMSO-d_6) 4.89 (1H, s, C≡C−H), 3.59 (3H, s, OCH_3), 6.93 (2H, d, *J* = 6.5 Hz, H-2' and H-6'), 7.70 (2H, d, *J* = 6.5 Hz, H-3' and H-5'), 8.26 (1H, s, H-8), 9.51 (1H, br s, NH), 13.09 (1H, br s, NH-9); HRMS calcd for $C_{14}H_{12}N_5O$ $[M+H]^+$ 266.0664, found 266.0687.

6-Ethynyl-*N*-(3-methoxyphenyl)-9*H*-purin-2-amine (30)



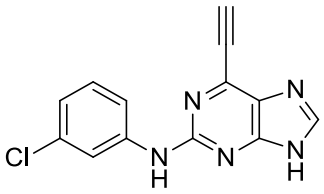
The TIPS-protected purine **20** (0.271 g, 0.64 mmol) was reacted with TBAF (1M in THF, 960 µL, 0.96 mmol) in THF (6 mL) according to **general procedure C**. Purification by chromatography on silica (1:4 Petrol/EtOAc) gave the target compound as a yellow solid (0.119 g, 70%); R_f 0.30 (EtOAc); m.p. 130-150 °C (decomposed); λ_{max} (EtOH/nm) 272; IR (cm^{-1}) 3410, 3264, 3108, 2958, 2868, 2112, 1703; ^{1}H NMR (500 MHz, DMSO-d_6) 3.76 (3H, s, OCH_3), 4.86 (1H, s, C≡CH), 6.53 (1H, ddd, *J* = 2.1 and 8.1 Hz, H-4'), 7.18 (1H, dd, *J* = 8.2 Hz, H-5'), 7.30-7.34 (1H, m, H-6'), 7.59-7.62 (1H, m, H-2'), 8.30 (1H, s, H-8), 9.68 (1H, s, NH), 13.20 (1H, s, NH-9); HRMS calcd. for $C_{14}H_{12}N_5O$ (ES+) *m*/*z* 266.1036 $[M+H]^+$, found 266.1038.

***N*-(4-Chlorophenyl)-6-ethynyl-9*H*-purin-2-amine (31)**



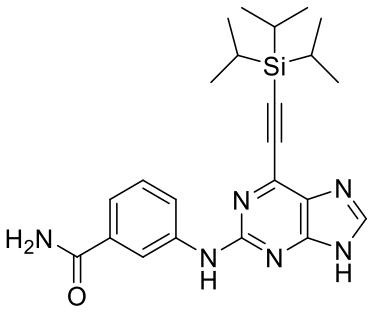
The TIPS-protected purine **21** (0.125 g, 0.29 mmol) and TBAF (1M in THF, 440 µL, 0.44 mmol) were reacted in THF (5 mL) according to **general procedure C**, with purification by chromatography on silica (EtOAc) to give the desired product as a yellow solid (77 mg, 81%); R_f 0.34 (EtOAc); m.p. 180-200 °C (decomposed); λ_{max} (EtOH/nm) 241; IR (cm^{-1}) 3414, 3278, 2921, 2848, 2108, 1576, 1522; ^{1}H NMR (500 MHz, DMSO-d_6) 4.87 (1H, s, C≡CH), 7.34 (2H, d, *J* = 8.9 Hz, H-2' and H-6'), 7.84 (2H, d, *J* = 8.9 Hz, H-3' and H-5'), 8.32 (1H, s, H-8), 9.85 (1H, s, NH), 13.21 (1H, br, NH-9); HRMS calcd. for $C_{13}H_9N_5Cl$ (ES+) *m*/*z* 270.0541 $[M+H]^+$, found 270.0540.

_N_-(3-Chlorophenyl)-6-ethynyl-9_H_-purin-2-amine (32)



The TIPS-protected purine **22** (0.255 g, 0.60 mmol) was reacted with TBAF (1M in THF, 900 µL, 0.90 mmol) in THF (6 mL) according to **general procedure C**. Purification by chromatography on silica (1:4 Petrol/EtOAc) afforded the desired compound as a yellow solid (0.126 g, 78%); R_f 0.35 (EtOAc); m.p. 130-150 °C (decomposed); λ_{max} (EtOH/nm) 273; IR (cm^{-1}) 3407, 3282, 3078, 2926, 2812, 2110, 1706; ^{1}H NMR (500 MHz, DMSO-d_6) 4.93 (1H, s, C≡CH), 7.00 (1H, ddd, *J* = 2.0, 2.1 and 8.0 Hz, H-6'), 7.34 (1H, dd, *J* = 8.0 Hz, H-5'), 7.71 (1H, ddd, *J* = 2.0, 2.1 and 8.1 Hz, H-4'), 8.09 (1H, br, H-2'), 8.37 (1H, s, H-8), 9.97 (1H, s, NH), 13.31 (1H, s, NH-9); HRMS calcd. for $C_{13}H_9ClN_5$ (ES+) *m*/*z* 270.0541 $[M+H]^+$, found 270.0546.

3-(6-(2-(Triisopropylsilyl)ethynyl)-9_H_-purin-2-ylamino)benzamide (33)

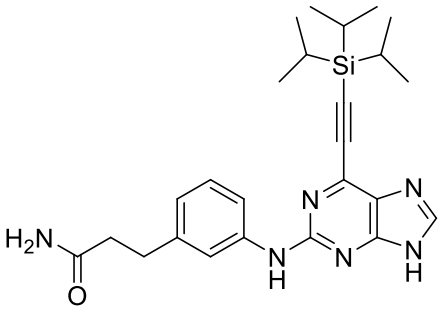


Part 1. 2-Fluoropurine intermediate **12** (0.265 g, 0.83 mmol), aniline **112** (0.428 g, 1.67 mmol) and TFA (320 µL, 4.17 mmol) were reacted in TFE (5 mL) according to **general procedure A**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) followed by normal phase silica (1:1 Petrol/EtOAc) gave the desired compound as a yellow oil (88 mg, 9%); R_f

0.42 (1:1 Petrol/EtOAc); λ_{max} (EtOH/nm) 279, 364; IR (cm^{-1}) 2864, 2159, 1739, 1641; ^1H NMR (500 MHz, DMSO-d_6) 1.13-1.18 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 3.74 (3H, s, OCH_3), 4.40 (2H, d, *J* = 5.9 Hz, CH_2NH), 6.90 (2H, d, *J* = 8.9 Hz, H-3'' and H-5''), 7.27 (2H, d, *J* = 8.9 Hz, H-2'' and H-6''), 7.35 (1H, m, H-5'), 7.41 (1H, m, H-6'), 7.95 (1H, m, H-4'), 8.22-8.25 (2H, m, H-8 and H-2'), 8.89 (1H, t, *J* = 5.9 Hz, CH_2N*H*), 9.83 (1H, s, NH), 13.16 (1H, br, NH-9); HRMS calcd. for $C_{31}H_{39}N_6O_2Si$ (ES+) *m*/*z* 555.2898 $[M+H]^+$, found 555.2893.

Part 2. PMB-carboxamide (82 mg, 0.15 mmol) and TFA (2 mL) were reacted according to **general procedure E** over 24 h. Purification by chromatography on KP-NH silica (9:1 DCM/MeOH) afforded the target compound as a yellow oil (55 mg, 87%); R_f 0.41 (9:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 263, 365; IR (cm^{-1}) 3295, 2964, 2943, 1660; ^1H NMR (500 MHz, DMSO-d_6) 1.14-1.19 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 7.30-7.36 (2H, m, CON*H*H' and H-5'), 7.40-7.42 (1H, m, H-6'), 7.85 (1H, s, CONH*H'*), 7.90-7.93 (1H, m, H-4'), 8.23 (1H, br, H-2'), 8.31 (1H, s, H-8), 9.83 (1H, s, NH); HRMS calcd. for $C_{23}H_{31}N_6OSi$ (ES+) *m*/*z* 435.2323 $[M+H]^+$, found 435.2325.

3-(3-(6-(2-(Triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)phenyl) propanamide (34)

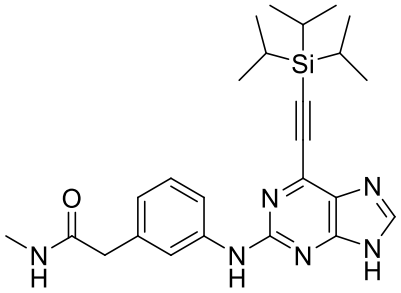


Part 1. 2-Fluoropurine intermediate **12** (0.273 g, 0.86 mmol), aniline **113** (0.490 g, 1.72 mmol) and TFA (330 µL, 4.29 mmol) were reacted in TFE (5 mL) according to **general procedure A**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) gave the target compound as a yellow oil (0.205 g, 41%); R_f 0.35 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 277, 363; IR (cm^{-1}) 3278, 3082, 2944, 2865, 2359, 1644; ^1H NMR (500 MHz, $CDCl_3$) 1.17-1.31 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 2.57 (2H, t, *J* = 7.3 Hz, CH_2CH_2), 2.99 (2H, t, *J* = 7.3 Hz, CH_2CH_2), 3.73 (3H, s, OCH_3), 4.31 (2H, d, *J* = 5.5 Hz, CH_2NH), 6.12 (1H, br, CH_2N*H*), 6.72 (2H, d, *J* = 8.8 Hz, H-3'' and H-5''), 6.82-6.86 (1H, m, H-6'), 7.01 (2H, d, *J* = 8.8 Hz, H-2'' and H-6''), 7.17-7.23 (2H, m, H-4' and H-5'), 7.37 (1H, s, NH), 7.79 (1H, s, H-8), 7.83 (1H, br, H-2'), 11.94 (1H, br, NH-9); HRMS calcd. for $C_{33}H_{43}N_6O_2Si$ (ES+) *m*/*z* 583.3211 $[M+H]^+$, found 583.3212.

Part 2. PMB-carboxamide (0.178 g, 0.31 mmol) and TFA (3 mL) were reacted according to **general procedure E**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH)

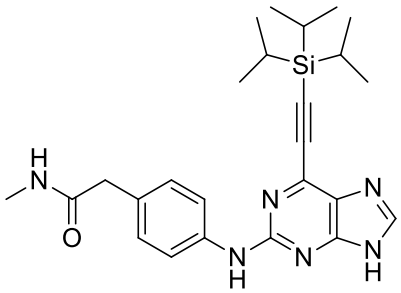
gave the desired compound as a yellow oil (81 mg, 58%); R_f 0.38 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 260, 368; IR (cm^{-1}) 3185, 2942, 2864, 2159, 2030, 1660; ^1H NMR (500 MHz, DMSO-d_6) 1.10-1.23 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.37 (2H, t, *J* = 7.6 Hz, C*H*$_2$CH$_2$), 2.78 (2H, t, *J* = 7.6 Hz, CH$_2$C*H*$_2$), 6.77-6.80 (2H, m, CON*H*H' and H-6'), 7.17 (1H, dd, *J* = 7.8 and 7.9 Hz, H-5'), 7.31 (1H, s, CONH*H*'), 7.61-7.64 (1H, m, H-4'), 7.66-7.69 (1H, m, H-2'), 8.25 (1H, s, H-8), 9.63 (1H, s, NH), 13.08 (1H, br, NH-9); HRMS calcd. for $C_{25}H_{35}N_6OSi$ (ES+) *m*/*z* 463.2636 $[M+H]^+$, found 463.2634.

2-(3-(6-(2-(Triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)phenyl)-*N*-methylacetamide (35)



2-Fluoropurine intermediate **12** (0.127 g, 0.40 mmol), aniline **118** (0.130 g, 0.80 mmol) and TFA (155 µL, 2.00 mmol) were reacted in TFE (2 mL) according to **general procedure A**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) afforded the desired compound as a yellow oil (70 mg, 38%); R_f 0.41 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 264, 368; IR (cm^{-1}) 2942, 2864, 2159, 1641; ^1H NMR (500 MHz, DMSO-d_6) 1.13-1.17 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.59 (3H, d, *J* = 4.6 Hz, NHC*H*$_3$), 3.36 (2H, s, CH$_2$), 6.83-6.85 (1H, m, H-6'), 7.20 (1H, dd, *J* = 7.9 and 7.9 Hz, H-5'), 7.57 (1H, br, H-2'), 7.74-7.77 (1H, m, H-4'), 7.90 (1H, br, N*H*CH$_3$), 8.25 (1H, s, H-8), 9.66 (1H, s, NH), 13.08 (1H, s, NH-9); HRMS calcd. for $C_{25}H_{35}N_6OSi$ (ES+) *m*/*z* 463.2636 $[M+H]^+$, found 463.2640.

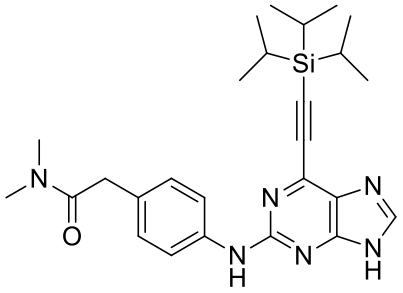
***N*-Methyl-2-(4-((6-((triisopropylsilyl)ethynyl)-9*H*-purin-2-yl)amino)phenyl) acetamide (36)**



2-Fluoropurine **12** (0.200 g, 0.63 mmol), aniline **121** (0.206 g, 1.26 mmol) and TFA (120 µL, 1.57 mmol) were reacted in TFE (6 mL) according to **general procedure B**. Purification by

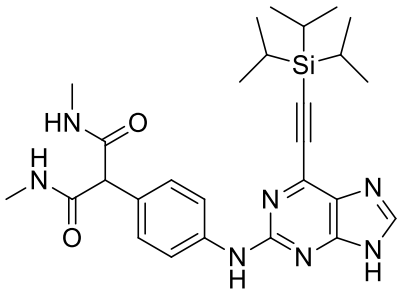
chromatography on KP-NH silica (19:1 DCM/MeOH) afforded the target compound as a yellow oil/gum (0.137 g, 47%); R_f 0.37 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 279, 379; IR (cm^{-1}) 3275, 2942, 2864, 1604, 1573, 1523; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.23 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.58 (3H, d, *J* = 4.7 Hz, NHC*H*$_3$), 3.33 (2H, s, $COCH_2$), 7.15 (2H, d, *J* = 8.6 Hz, H-2'and H-6'), 7.70 (2H, d, *J* = 8.6 Hz, H-3' and H-5'), 7.84 (1H, q, *J* = 4.7 Hz, N*H*CH_3), 8.23 (1H, s, H-8), 9.61 (1H, s, NH), 13.04 (1H, br, NH-9); HRMS calcd. for $C_{25}H_{35}N_6OSi$ (ES+) *m*/*z* 463.2636 $[M+H]^+$, found 463.2631.

_N_,_N_-Dimethyl-2-(4-((6-((triisopropylsilyl)ethynyl)-9_H_-purin-2-yl)amino) phenyl)acetamide (37)



2-Fluoropurine **12** (73 mg, 0.23 mmol), aniline **124** (96 mg, 0.46 mmol) and TFA (45 µL, 0.58 mmol) were reacted in TFE (3 mL) according to **general procedure B**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) gave the desired compound as a yellow oil/gum (69 mg, 61%); R_f 0.32 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 278, 379; IR (cm^{-1}) 3275, 3104, 2941, 2864, 1603, 1570; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.23 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.83 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), 3.62 (2H, s, $COCH_2$), 7.12 (2H, d, *J* = 8.6 Hz, H-2' and H-6'), 7.71 (2H, d, *J* = 8.6 Hz, H-3' and H-5'), 8.22 (1H, s, H-8), 9.60 (1H, s, NH), 13.04 (1H, br, NH-9); HRMS calcd. for $C_{26}H_{37}N_6OSi$ (ES+) *m*/*z* 477.2793 $[M+H]^+$, found 477.2779.

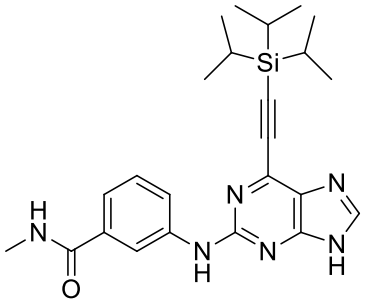
_N_^{1},_N_^{3}-Dimethyl-2-(4-((6-((triisopropylsilyl)ethynyl)-9_H_-purin-2-yl)amino) phenyl)malonamide (38)



2-Fluoropurine **12** (0.198 g, 0.63 mmol), aniline **126** (0.277 g, 1.26 mmol) and TFA (120 µL, 1.57 mmol) were reacted in TFE (6 mL) according to **general procedure B**. Purification by

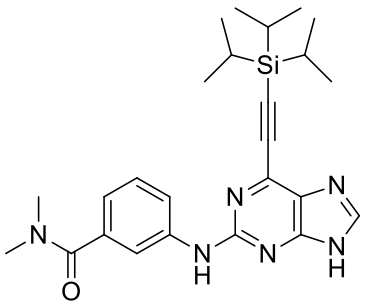
chromatography on KP-NH silica (19:1 DCM/MeOH) gave the desired compound as a yellow oil/gum (0.167 g, 51%); R_f 0.35 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 280, 354; IR (cm^{-1}) 3287, 3085, 2943, 2864, 1663, 1603, 1573, 1521; ^{1}H NMR (500 MHz, DMSO-d_6)) 1.13-1.23 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.62 (6H, d, *J* = 4.7 Hz, (2 x NHC*H*$_3$), 4.28 (1H, s, COC*H*CO), 7.26 (2H, d, *J* = 8.7 Hz, H-2' and H-6'), 7.71 (2H, d, *J* = 8.7 Hz, H-3' and H-5'), 8.02 (2H, q, *J* = 4.7 Hz, 2 x N*H*CH$_3$), 8.23 (1H, s, H-8), 9.68 (1H, s, NH), 13.05 (1H, br, NH-9); HRMS calcd. for $C_{27}H_{38}N_7O_2Si$ (ES+) *m*/*z* 520.2851 $[M+H]^+$, found 520.2847.

_N_-Methyl-3-((6-((triisopropylsilyl)ethynyl)-9_H_-purin-2-yl)amino) benzamide (39)



2-Fluoropurine **12** (0.202 g, 0.63 mmol), aniline **130** (0.190 g, 1.26 mmol) and TFA (120 µL, 1.57 mmol) were reacted in TFE (6 mL) according to **general procedure B** over 3 h. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) gave the target compound as a yellow oil/gum (0.101 g, 37%); R_f 0.30 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 276; IR (cm^{-1}) 3069, 2942, 2865, 2161, 1580; ^{1}H NMR (500 MHz, DMSO-d_6) 1.10-1.25 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.78 (3H, d, *J* = 4.5 Hz, NHC*H*$_3$), 7.32-7.36 (2H, m, H-5' and H-6'), 7.89-7.93 (1H, m, H-4'), 8.19-8.21 (1H, m, H-2'), 8.24 (1H, s, H-8), 8.30 (1H, q, *J* = 4.5 Hz, N*H*CH$_3$), 9.81 (1H, s, NH), 13.14 (1H, br, NH-9); HRMS calcd. for $C_{24}H_{33}N_6OSi$ (ES+) *m*/*z* 449.2480 $[M+H]^+$, found 449.2480.

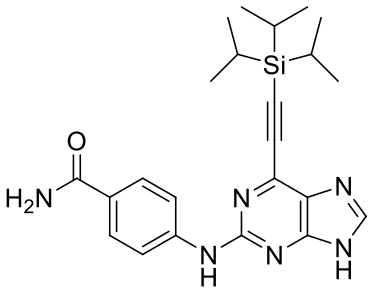
_N_,_N_-Dimethyl-3-((6-((triisopropylsilyl)ethynyl)-9_H_-purin-2-yl)amino) benzamide (40)



2-Fluoropurine **12** (0.121 g, 0.38 mmol), aniline **131** (0.125 g, 0.76 mmol) and TFA (73 µL, 0.95 mmol) were reacted in TFE (4 mL) according to **general procedure B** over 3 h. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) gave the target

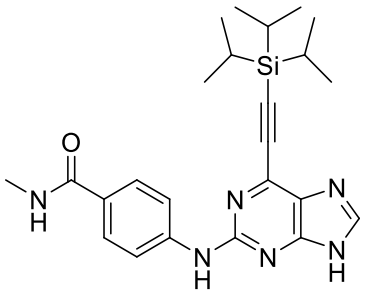
compound as a yellow oil/gum (81 mg, 47%); R_f 0.34 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 228, 317; IR (cm^{-1}) 3079, 2942, 2864, 2057, 1576, 1538; ^1H NMR (500 MHz, DMSO-d_6) 1.13-1.23 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 2.96 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), 6.93 (1H, ddd, *J* = 1.1, 1.2 and 7.7 Hz, H-6'), 7.33 (1H, dd, *J* = 7.7 and 7.9 Hz, H-5'), 7.76-7.80 (1H, m, H-4'), 7.95 (1H, m, H-2'), 8.27 (1H, s, H-8), 9.82 (1H, s, NH), 13.13 (1H, br, NH-9); HRMS calcd. for $C_{25}H_{35}N_6OSi$ (ES+) *m*/*z* 463.2636 $[M+H]^+$, found 463.2632.

4-(6-(2-(Triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)benzamide (41)



2-Fluoropurine intermediate **12** (0.216 g, 0.68 mmol), aniline **119** (0.185 g, 1.36 mmol) and TFA (262 µL, 3.40 mmol) were reacted in TFE (4 mL) according to **general procedure A**. Purification by chromatography on KP-NH silica (9:1 DCM/MeOH) afforded the desired compound as a yellow oil (0.114 g, 38%); R_f 0.29 (9:1 DCM/MeOH); λ_{max} (EtOH/nm) 224, 301, 363; IR (cm^{-1}) 3113, 2942, 2864, 2160, 1653; ^1H NMR (500 MHz, DMSO-d_6) 1.14-1.18 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 7.16 (1H, br, CON*H*H'), 7.79-7.82 (3H, m, CONH*H'*, H-3' and H-5'), 7.89 (2H, d, *J* = 8.9 Hz, H-2' and H-6'), 8.31 (1H, s, H-8), 10.01 (1H, s, NH), 13.17 (1H, br, NH-9); HRMS calcd. for $C_{23}H_{31}N_6OSi$ (ES+) *m*/*z* 435.2323 $[M+H]^+$, found 435.2323.

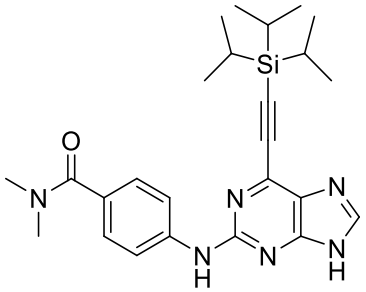
4-(6-(2-(Triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)-*N*-methyl benzamide (42)



2-Fluoropurine intermediate **12** (0.270 g, 0.85 mmol), aniline **120** (0.255 g, 1.70 mmol) and TFA (330 µL, 4.25 mmol) were reacted in TFE (4 mL) according to **general procedure A**. Purification by chromatography on KP-NH silica (9:1 DCM/MeOH) afforded the desired compound as a yellow oil (0.117 g, 31%); R_f 0.51 (9:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm)

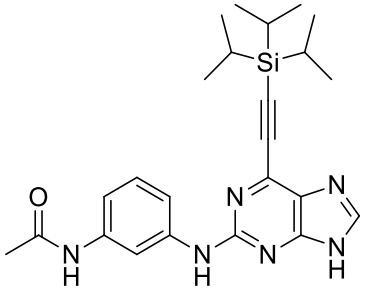
230, 283, 362; IR (cm^{-1}) 3278, 3082, 2942, 2864, 2154, 2027, 1602; ^{1}H NMR (500 MHz, DMSO-d_6) 1.14-1.19 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.78 (3H, d, *J* = 4.6 Hz, NHC*H*$_3$), 7.77 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 7.89 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 8.23 (1H, q, *J* = 4.6 Hz, N*H*CH$_3$), 8.31 (1H, s, H-8), 10.00 (1H, s, NH), 13.19 (1H, br, NH-9); HRMS calcd. for $C_{24}H_{33}N_6OSi$ (ES+) *m*/*z* 449.2480 $[M+H]^+$, found 449.2480.

4-(6-(2-(Triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)-*N*,*N*-dimethyl benzamide (43)



2-Fluoropurine intermediate **12** (0.205 g, 0.64 mmol), aniline **132** (0.210 g, 1.28 mmol) and TFA (248 µL, 3.22 mmol) were reacted in TFE (4 mL) according to **general procedure A**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) afforded the desired compound as a yellow oil (79 mg, 27%); R_f 0.48 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 283, 364; IR (cm^{-1}) 2942, 2862, 2160, 2028, 1601; ^{1}H NMR (500 MHz, DMSO-d_6) 1.14-1.18 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.98 (6H, s, N(CH$_3$)$_2$), 7.36 (2H, d, *J* = 8.5 Hz, H-3' and H-5'), 7.88 (2H, d, *J* = 8.5 Hz, H-2' and H-6'), 8.29 (1H, s, H-8), 9.96 (1H, s, NH), 13.19 (1H, br, NH-9); HRMS calcd. for $C_{25}H_{35}N_6OSi$ (ES+) *m*/*z* 463.2636 $[M+H]^+$, found 463.2641.

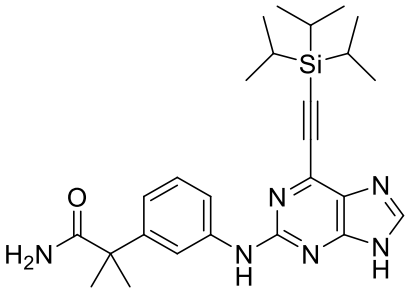
***N*-(3-((6-((Triisopropylsilyl)ethynyl)-9*H*-purin-2-yl)amino)phenyl) acetamide (44)**



2-Fluoropurine **12** (0.230 g, 0.72 mmol), aniline **135** (0.216 g, 1.44 mmol) and TFA (140 µL, 1.80 mmol) were reacted in TFE (7 mL) according to **general procedure B**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) afforded the target compound as a yellow oil/gum (0.200 g, 62%); R_f 0.29 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 276, 375; IR (cm^{-1}) 3109, 2942, 2862, 1667, 1603, 1577, 1534; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.19 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.04 (3H, s, CH$_3$), 7.17 (1H, dd, *J* = 7.9 and 8.0 Hz, H-5'), 7.21-7.25 (1H, m, H-6'), 7.53-7.57 (1H, m, H-4'), 7.76-7.80 (1H, m, H-2'), 8.23 (1H, s, H-8),

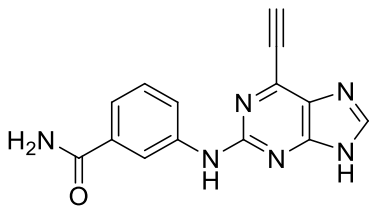
9.65 (1H, s, CONH), 9.85 (1H, s, NH), 13.05 (1H, br, NH-9); HRMS calcd. for $C_{24}H_{33}N_6OSi$ (ES+) *m*/*z* 449.2480 $[M+H]^+$, found 449.2479.

2-(3-(6-(2-(Triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)phenyl)-2-methylpropanamide (45)



2-Fluoropurine intermediate **12** (0.197 g, 0.62 mmol), aniline **140** (0.220 g, 1.24 mmol) and TFA (240 µL, 3.10 mmol) were reacted in TFE (4 mL) according to **general procedure A**. Purification by chromatography on silica (19:1 DCM/MeOH) afforded the desired compound as a yellow oil (0.127 g, 43%); R_f 0.28 (19:1 DCM/MeOH); λ_{max} (EtOH/nm) 270, 368; IR (cm^{-1}) 3094, 2964, 2943, 2162, 1970, 1659; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.19 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 1.45 (6H, s, C(CH$_3$)$_2$), 6.80 (1H, s, CON*H*H'), 6.89 (1H, s, CONH*H*'), 7.04-7.07 (1H, m, H-6'), 7.21 (1H, dd, *J* = 7.9 and 8.1 Hz, H-5'), 7.65-7.69 (1H, m, H-4'), 7.86-7.88 (1H, m, H-2'), 8.25 (1H, s, H-8), 9.65 (1H, s, NH), 13.07 (1H, br, NH-9); HRMS calcd. for $C_{26}H_{37}N_6OSi$ (ES+) *m*/*z* 477.2793 $[M+H]^+$, found 477.2796.

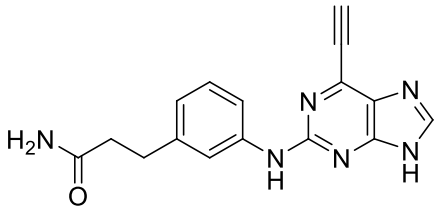
3-(6-Ethynyl-9*H*-purin-2-ylamino)benzamide (46)



TIPS-protected purine **33** (33 mg, 0.076 mmol), KF (22 mg, 0.38 mmol) and 18-crown-6 (3 mg, 0.008 mmol) were reacted in THF (1 mL) according to **general procedure F**. Purification by chromatography on silica (17:3 DCM/MeOH) afforded the desired compound as a yellow solid (20 mg, 94%); R_f 0.38 (17:3 Petrol/EtOAc); m.p. 170-180 °C (decomposed); λ_{max} (EtOH/nm) 274; IR (cm^{-1}) 3254, 3085, 2830, 2775, 2551, 2162, 2117, 1659; ^{1}H NMR (500 MHz, DMSO-d_6) 4.89 (1H, s, C≡CH), 7.35 (1H, s, CON*H*H'), 7.39 (1H, dd, *J* = 7.8 and 7.9 Hz, H-5'), 7.43-7.46 (1H, m, H-6'), 7.90 (1H, s, CONH*H*'), 7.97-7.80 (1H, m, H-4'), 8.20-

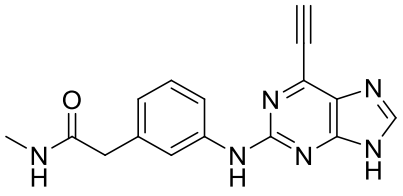
8.23 (1H, m, H-2'), 8.32 (1H, s, H-8), 9.80 (1H, s, NH), 13.21 (1H, br, NH-9); HRMS calcd. for $C_{14}H_{11}N_6O$ (ES+) *m/z* 279.0993 $[M+H]^+$, found 279.0989.

3-(3-(6-Ethynyl-9*H*-purin-2-ylamino)phenyl)propanamide (47)



TIPS-protected purine **34** (45 mg, 0.097 mmol) and TBAF (1M in THF, 106 µL, 0.106 mmol) were reacted in THF (2 mL) according to **general procedure G**. Upon completion of the reaction, the solution was diluted with THF (10 mL) and treated with solid supported TBAF scavenger (0.20 g, 4 x *w/w*) at RT for 18 h. The resin was removed *via* filtration and the solvent removed *in vacuo*. The crude residue was purified by chromatography on silica (17:3 DCM/MeOH) to give the desired compound as a yellow solid (16 mg, 46%); R_f 0.45 (17:3 Petrol/EtOAc); m.p. 135-145 °C (decomposed); λ_{max} (EtOH/nm) 273; IR (cm^{-1}) 3380, 3249, 3093, 2828, 2779, 2160, 2116, 2030, 1653; ^{1}H NMR (500 MHz, DMSO-d_6) 2.37 (2H, t, *J* = 7.6 Hz, COC*H*$_2$CH$_2$), 2.78 (2H, t, *J* = 7.6 Hz, COCH$_2$C*H*$_2$), 4.84 (1H, s, C≡CH), 6.77-6.81 (2H, m, CON*H*H' and H-6'), 7.19 (1H, dd, *J* = 7.9 and 8.0 Hz, H-5'), 7.32 (1H, s, CONH*H'*), 7.57-7.60 (1H, br, H-2'), 7.66-7.69 (1H, m, H-4'), 8.27 (1H, s, H-8), 9.60 (1H, s, NH), 13.13 (1H, br, NH-9); HRMS calcd. for $C_{16}H_{15}N_6O$ (ES+) *m/z* 307.1305 $[M+H]^+$, found 307.1302.

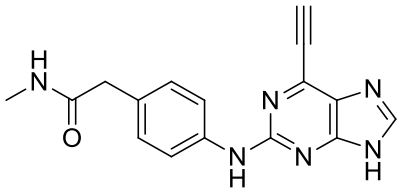
2-(3-(6-Ethynyl-9*H*-purin-2-ylamino)phenyl)-*N*-methylacetamide (48)



TIPS-protected purine **35** (50 mg, 0.11 mmol), KF (31 mg, 0.54 mmol) and 18-crown-6 (3 mg, 0.011 mmol) were reacted in THF (1 mL) according to **general procedure F**. Purification by chromatography on silica (9:1 DCM/MeOH) afforded the desired compound as a yellow solid (24 mg, 73%); R_f 0.41 (9:1 DCM/MeOH); Mp 170-180 °C (decomposed); λ_{max} (EtOH/nm) 274; IR (cm^{-1}) 3270, 3088, 2158, 2025, 1596; ^{1}H NMR (500 MHz, DMSO-d_6) 2.59 (3H, d, *J* = 4.7 Hz, NHC*H*$_3$), 3.36 (2H, s, CH$_2$CO), 4.84 (1H, s, C≡CH), 6.81-6.84 (1H, m, H-6'), 7.21 (1H, dd, *J* = 7.8 and 7.9 Hz, H-5'), 7.52-7.55 (1H, m, H-2'), 7.74-7.77 (1H, m, H-4'), 7.92 (1H, br,

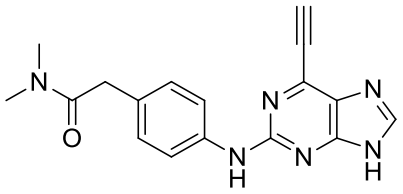
CONH), 8.27 (1H, s, H-8), 9.62 (1H, s, NH), 13.12 (1H, br, NH-9); HRMS calcd. for $C_{16}H_{15}N_6O$ (ES+) *m*/*z* 307.1305 $[M+H]^+$, found 307.1302.

2-(4-((6-Ethynyl-9*H*-purin-2-yl)amino)phenyl)-*N*-methylacetamide (49)



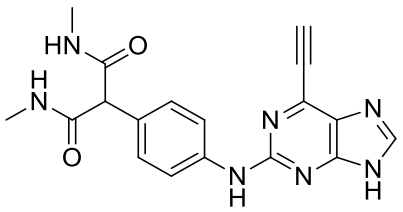
The TIPS-protected purine **36** (0.130 g, 0.28 mmol), TBAF (1M in THF, 0.34 mL, 0.34 mmol) and TBAF scavenger resin (1.30 g, 10 x *w/w*) were reacted in THF (5 mL) according to **general procedure G**. Chromatography on KP-NH silica (9:1 DCM/MeOH) gave the target compound as a yellow solid (50 mg, 58%); R_f 0.26 (9:1 DCM/MeOH, KP-NH); m.p. 140-160 °C (decomposed); λ_{max} (EtOH/nm) 276.0, 371.0; IR (cm^{-1}) 3414, 3092, 2531, 2112, 1611, 1577, 1530; ^{1}H NMR (500 MHz, DMSO-d_6) 2.58 (3H, d, *J* = 4.6 Hz, NHCH_3), 3.33 (2H, s, $COCH_2$), 4.82 (1H, s, C≡CH), 7.16 (2H, d, *J* = 8.5 Hz, H-2' and H-6'), 7.68 (2H, d, *J* = 8.5 Hz, H-3' and H-5'), 7.86 (1H, q, *J* = 4.6 Hz, N*H*CH_3), 8.25 (1H, s, H-8), 9.60 (1H, s, NH), 13.09 (1H, br, NH-9); HRMS calcd. for $C_{16}H_{15}N_6O$ (ES+) *m*/*z* 307.1302 $[M+H]^+$, found 307.1306.

2-(4-((6-Ethynyl-9*H*-purin-2-yl)amino)phenyl)-*N*,*N*-dimethylacetamide (50)



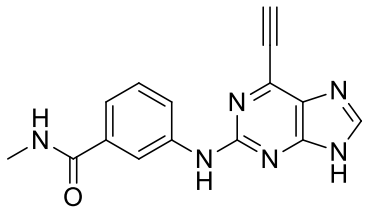
The TIPS-protected purine **37** (56 mg, 0.12 mmol), TBAF (1M in THF, 0.14 mL, 0.14 mmol) and TBAF scavenger resin (0.60 g, 10 x *w/w*) were reacted in THF (5 mL) according to **general procedure G**. Chromatography on KP-NH silica (9:1 DCM/MeOH) afforded the desired compound as a yellow solid (27 mg, 69%); R_f 0.33 (9:1 DCM/MeOH, KP-NH); m.p. 120-130 °C (decomposed); λ_{max} (EtOH/nm) 276.0, 378.0; IR (cm^{-1}) 2932, 2538, 2110, 1607, 1575, 1530; ^{1}H NMR (500 MHz, DMSO-d_6) 2.84 (3H, s, N-CH_3), 3.01 (3H, s, NCH_3), 3.62 (2H, s, $COCH_2$), 4.83 (1H, s, C≡CH), 7.13 (2H, d, *J* = 8.6 Hz, H-2' and H-6'), 7.69 (2H, d, *J* = 8.6 Hz, H-3' and H-5'), 8.26 (1H, s, H-8), 9.60 (1H, s, NH), 13.10 (1H, br, NH-9); HRMS calcd. for $C_{17}H_{17}N_6O$ (ES+) *m*/*z* 321.1458 $[M+H]^+$, found 321.1462.

2-(4-((6-Ethynyl-9*H*-purin-2-yl)amino)phenyl)-*N*^{1},*N*^{3}-dimethylmalonamide (51)



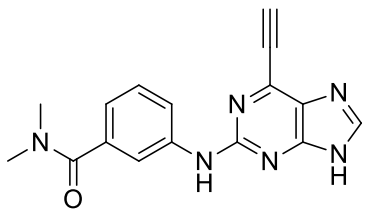
The TIPS-protected purine **38** (0.120 mg, 0.23 mmol), TBAF (1M in THF, 0.28 mL, 0.28 mmol) and TBAF scavenger resin (1.20 g, 10 x *w/w*) were reacted in THF (5 mL) according to **general procedure G**. Purification by chromatography on KP-NH silica (9:1 DCM/MeOH) afforded the target compound as a yellow solid (29 mg, 35%); R_f 0.26 (9:1 DCM/MeOH, KP-NH); m.p. 160-180 °C (decomposed); λ_{max} (EtOH/nm) 277.0, 368.5; IR (cm^{-1}) 3274, 2550, 2160, 2111, 2030, 1660; ^{1}H NMR (500 MHz, DMSO-d_6) 2.61 (6H, d, *J* = 4.6 Hz, 2 x NHC*H*$_3$), 4.28 (1H, s, COC*H*CO), 4.84 (1H, s, C≡CH), 7.27 (2H, d, *J* = 8.7 Hz, H-2' and H-6'), 7.69 (2H, d, *J* = 8.7 Hz, H-3' and H-5'), 8.04 (2H, q, *J* = 4.6 Hz, 2 x N*H*CH_3), 8.28 (1H, s, H-8), 9.65 (1H, s, NH), 13.10 (1H, br, NH-9); HRMS calcd. for $C_{18}H_{18}N_7O_2$ (ES+) *m*/*z* 364.1516 $[M+H]^+$, found 364.1520.

3-((6-Ethynyl-9*H*-purin-2-yl)amino)-*N*-methylbenzamide (52)



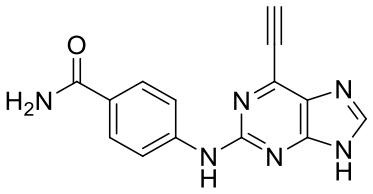
The TIPS-protected purine **39** (72 mg, 0.16 mmol), TBAF (1M in THF, 0.19 mL, 0.19 mmol) and TBAF scavenger resin (0.70 g, 10 x *w/w*) were reacted in THF (5 mL) according to **general procedure G**. Purification by chromatography on KP-NH silica (9:1 DCM/MeOH) gave the target compound as a yellow solid (29 mg, 63%); R_f 0.24 (9:1 DCM/MeOH, KP-NH); m.p. 200-220 °C (decomposed); λ_{max} (EtOH/nm) 274.0, 363.5; IR (cm^{-1}) 3302, 3252, 3113, 1607; ^{1}H NMR (500 MHz, DMSO-d_6) 2.79 (3H, d, *J* = 4.5 Hz, NHC*H*$_3$), 4.86 (1H, s, C≡CH), 7.33-7.39 (2H, m, H-5' and H-6'), 7.92-7.97 (1H, m, H-4'), 8.16-8.18 (1H, m, H-2'), 8.29 (1H, s, H-8), 8.36 (1H, q, *J* = 4.5 Hz, N*H*CH_3), 9.78 (1H, s, NH), 13.20 (1H, br, NH-9); HRMS calcd. for $C_{15}H_{13}N_6O$ (ES+) *m*/*z* 293.1145 $[M+H]^+$, found 293.1149.

3-((6-Ethynyl-9*H*-purin-2-yl)amino)-*N*,*N*-dimethylbenzamide (53)



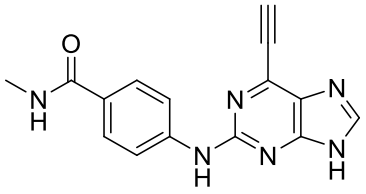
The TIPS-protected purine **40** (52 mg, 0.11 mmol), TBAF (1M in THF, 0.13 mL, 0.13 mmol) and TBAF scavenger resin (0.50 g, 10 x *w/w*) were reacted in THF (5 mL) according to **general procedure G**. Purification by chromatography on KP-NH silica (9:1 DCM/MeOH) gave the target compound as a yellow solid (23 mg, 69%); R_f 0.33 (9:1 DCM/MeOH, KP-NH); m.p. 175-190 °C (decomposed); λ_{max} (EtOH/nm) 274.5, 362.5; IR (cm^{-1}) 3281, 2558, 2160, 2031, 1976, 1575; ^{1}H NMR (500 MHz, DMSO-d_6) 2.96 (3H, s, NCH_3), 3.00 (3H, s, NCH_3), 4.86 (1H, s, C≡CH), 6.94 (1H, ddd, *J* = 1.3, 2.0 and 7.6 Hz, H-6'), 7.34 (1H, dd, *J* = 7.6 and 7.7 Hz, H-5'), 7.80-7.83 (1H, m, H-4'), 7.88 (1H, dd, *J* = 1.3 and 1.4 Hz, H-2'), 8.30 (1H, s, H-8), 9.82 (1H, s, NH), 13.17 (1H, br, NH-9); HRMS calcd. for $C_{16}H_{15}N_6O$ (ES+) *m/z* 307.1302 $[M+H]^+$, found 307.1306.

4-(6-Ethynyl-9*H*-purin-2-ylamino)benzamide (54)



TIPS-protected purine **41** (86 mg, 0.20 mmol), KF (57 mg, 0.99 mmol) and 18-crown-6 (5 mg, 0.020 mmol) were reacted in THF (2 mL) according to **general procedure F**. Purification by chromatography on silica (9:1 DCM/MeOH) afforded the desired compound as a yellow solid (41 mg, 74%); R_f 0.25 (9:1 DCM/MeOH); m.p. 180-190 °C (decomposed); λ_{max} (EtOH/nm) 220, 302; IR (cm^{-1}) 3267, 2164, 2024, 1653, 1602; ^{1}H NMR (500 MHz, DMSO-d_6) 4.89 (1H, s, C≡CH), 7.17 (1H, s, CON*H*H'), 7.70 (1H, s, CONH*H'*), 7.83 (2H, d, *J* = 8.7 Hz, H-2' and H-6'), 7.87 (2H, d, *J* = 8.7 Hz, H-3' and H-5'), 8.35 (1H, s, H-8), 10.00 (1H, s, NH), 13.23 (1H, br, NH-9); HRMS calcd. for $C_{14}H_{11}N_6O$ (ES+) *m/z* 279.0994 $[M+H]^+$, found 279.0989.

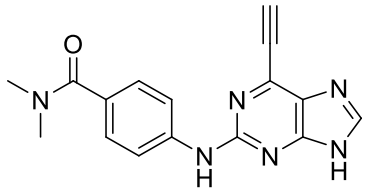
4-(6-Ethynyl-9*H*-purin-2-ylamino)-*N*-methylbenzamide (55)



TIPS-protected purine **42** (0.105 g, 0.23 mmol), KF (67 mg, 1.15 mmol) and 18-crown-6 (6 mg, 0.023 mmol) were reacted in THF (2.5 mL) according to **general procedure F**. Purification by chromatography on silica (9:1 DCM/MeOH) afforded the desired compound as a yellow solid (46 mg, 69%); R_f 0.24 (9:1 DCM/MeOH); m.p. 180-190 °C (decomposed); λ_{max} (EtOH/nm) 221, 301; IR (cm^{-1}) 3275, 3109, 2163, 2111, 2022, 1605; ^{1}H NMR (500 MHz, DMSO-d_6) 2.78 (3H, d, *J* = 4.5 Hz, NHCH_3), 4.89 (1H, s, C≡CH), 7.78 (2H, d, *J* = 8.8 Hz, H-2'

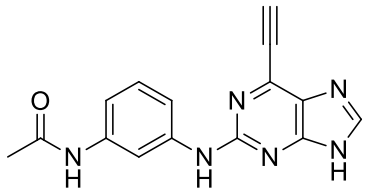
and H-6'), 7.87 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 8.24 (1H, q, *J* = 4.5 Hz, CONH), 8.34 (1H, s, H-8), 9.99 (1H, s, NH), 13.25 (1H, br, NH-9); HRMS calcd. for $C_{15}H_{13}N_6O$ (ES+) *m*/*z* 293.1148 $[M+H]^+$, found 293.1145.

4-(6-Ethynyl-9*H*-purin-2-ylamino)-*N*,*N*-dimethylbenzamide (56)



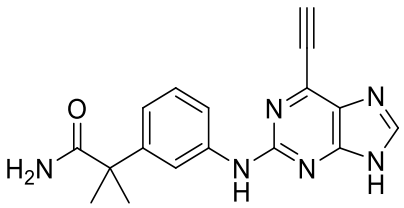
TIPS-protected purine **43** (63 mg, 0.14 mmol), KF (41 mg, 0.70 mmol) and 18-crown-6 (4 mg, 0.014 mmol) were reacted in THF (1.5 mL) according to **general procedure F**. Purification by chromatography on silica (9:1 DCM/MeOH) afforded the desired compound as a yellow solid (27 mg, 63%); R_f 0.29 (9:1 DCM/MeOH); m.p. 190-210 °C (decomposed); λ_{max} (EtOH/nm) 292; IR (cm^{-1}) 3101, 2111, 1599; ^{1}H NMR (500 MHz, DMSO-d_6) 2.98 (6H, s, $N(CH_3)_2$), 4.89 (1H, s, C≡CH), 7.38 (2H, d, *J* = 8.4 Hz, H-2' and H-6'), 7.86 (2H, d, *J* = 8.4 Hz, H-3' and H-5'), 8.33 (1H, s, H-8), 9.95 (1H, s, NH), 13.23 (1H, s, NH-9); HRMS calcd. for $C_{16}H_{15}N_6O$ (ES+) *m*/*z* 307.1302 $[M+H]^+$, found 307.1302.

***N*-(3-((6-Ethynyl-9*H*-purin-2-yl)amino)phenyl)acetamide (57)**



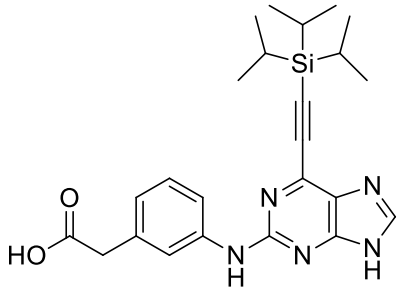
The TIPS-protected purine **44** (0.151 mg, 0.33 mmol), TBAF (1M in THF, 0.40 mL, 0.40 mmol) and TBAF scavenger resin (1.50 g, 10 x *w/w*) were reacted in THF (5 mL) according to **general procedure G**. Purification by chromatography on KP-NH silica (9:1 DCM/MeOH) gave the desired compound as a yellow solid (48 mg, 48%); R_f 0.29 (9:1 DCM/MeOH, KP-NH); m.p. 160-180 °C (decomposed); λ_{max} (EtOH/nm) 251.5, 275.5, 362.0; IR (cm^{-1}) 3266, 2546, 2112, 1668, 1605, 1581, 1536; ^{1}H NMR (500 MHz, DMSO-d_6) 2.04 (3H, s, $COCH_3$), 4.84 (1H, s, C≡CH), 7.19 (1H, dd, *J* = 7.8 and 7.9 Hz, H-5'), 7.24 (1H, m, H-6'), 7.55 (1H, m, H-4'), 7.77 (1H, m, H-2'), 8.27 (1H, s, H-8), 9.63 (1H, s, NH), 9.88 (1H, s, CONH), 13.12 (1H, br, NH-9); HRMS calcd. for $C_{15}H_{13}N_6O$ (ES+) *m*/*z* 293.1145 $[M+H]^+$, found 293.1149.

2-(3-(6-Ethynyl-9*H*-purin-2-ylamino)phenyl)-2-methylpropanamide (58)



TIPS-protected purine **45** (0.108 g, 0.23 mmol), KF (65 mg, 1.13 mmol) and 18-crown-6 (6 mg, 0.023 mmol) were reacted in THF (2.5 mL) according to **general procedure F**. Purification by chromatography on KP-NH silica (9:1 DCM/MeOH) afforded the desired compound as a yellow solid (37 mg, 51%); R_f 0.29 (9:1 DCM/MeOH, KP-NH); m.p. 140-160 °C (decomposed); λ_{max} (EtOH/nm) 274; IR (cm^{-1}) 3270, 2975, 2853, 2155, 1979, 1659, 1599; ^{1}H NMR (500 MHz, DMSO-d_6) 1.45 (6H, s, C(CH_3)$_2$), 4.82 (1H, s, C≡CH), 6.80 (1H, s, CON*H*H'), 6.84 (1H, s, CONH*H'*), 6.90-6.92 (1H, m, H-6'), 7.22 (1H, dd, *J* = 8.1 and 8.2 Hz, H-5'), 7.74-7.76 (2H, m, H-2' and H-4'), 8.27 (1H, s, H-8), 9.60 (1H, s, NH), 13.11 (1H, br, NH-9); HRMS calcd. for $C_{17}H_{17}N_6O$ (ES+) *m*/*z* 321.1463 $[M+H]^+$, found 321.1458.

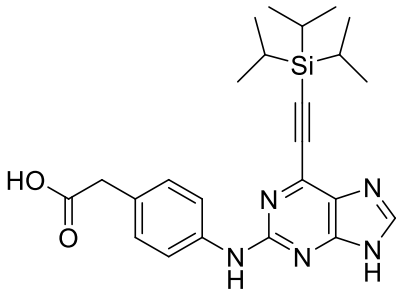
2-(3-(6-(2-(Triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino) phenyl)acetic acid (59)



2-Fluoropurine intermediate **12** (1.06 g, 3.32 mmol) and 3-aminophenyl acetic acid (1.00 g, 6.64 mmol) were reacted with TFA (1.28 mL, 16.6 mmol) in TFE (25 mL) according to **general procedure A**. Upon completion of the reaction, the reaction solvent was removed *in vacuo* and the resultant residue was dissolved in THF (20 mL) and 1M NaOH solution (15 mL). The mixture was stirred at RT for 18 h before the THF was removed *in vacuo*. The aqueous solution was then taken to pH 3 with 4M HCl solution and extracted with EtOAc (3 × 75 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the resulting orange residue was purified by chromatography on silica (9:1 DCM/MeOH) followed by chromatography on reverse phase silica (9:1 MeOH/H_2O + 0.1% HCOOH). The desired product was obtained as an orange oil/gum (0.952 g, 64%); R_f 0.32 (9:1 DCM/MeOH); λ_{max} (EtOH/nm) 275; IR (cm^{-1}) 2972, 2360, 2340, 1977, 1702; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.22 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 3.51 (2H, s, CH_2CO$_2$H), 6.82-6.85 (1H, m, H-6'), 7.22 (1H, dd, *J* = 7.7 and 7.8 Hz, H-5'), 7.65-7.68 (1H, m, H-2'), 7.72-7.76 (1H, m,

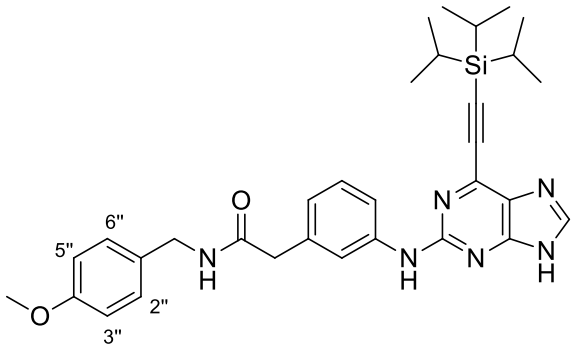
H-4'), 8.25 (1H, s, H-8), 9.71 (1H, s, NH), 12.33 (1H, br, CO_2H), 13.10 (1H, br, NH-9); HRMS calcd. for $C_{24}H_{32}N_5O_2Si$ (ES+) *m*/*z* 450.2320 $[M+H]^+$, found 450.2320.

2-(4-(6-(2-(Triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)phenyl)acetic acid (60)



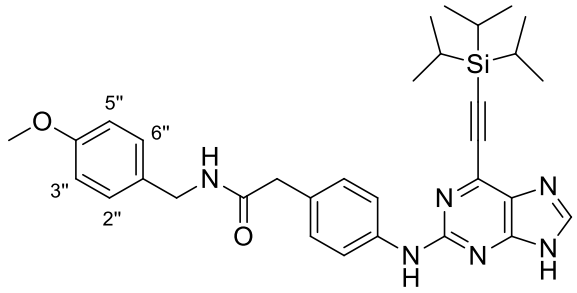
2-Fluoropurine intermediate **12** (0.485 g, 1.53 mmol), (4-aminophenyl)acetic acid (0.460 g, 3.05 mmol) and TFA (588 µL, 7.63 mmol) were reacted in TFE (15 mL) according to **general procedure A**. Upon completion of the reaction, the residue was dissolved in THF (15 mL) and 1M NaOH solution (10 mL). The mixture was stirred at RT for 18 h before the THF was removed *in vacuo*. The aqueous solution was then taken to pH 3 with 4M HCl solution and extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the resulting orange residue was purified by chromatography on reverse phase silica (9:1 MeOH/H_2O + 0.1% HCOOH). The desired product was obtained as an orange oil (0.365 g, 53%); R_f 0.44 (9:1 MeOH/H_2O, 0.1% + HCOOH, C18); λ_{max} (EtOH/nm) 263, 368; IR (cm^{-1}) 2942, 2866, 2540, 2161, 2037, 1636; ^1H NMR (500 MHz, DMSO-d_6) 1.16 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 3.34 (2H, s, CH_2), 7.16 (2H, d, *J* = 8.6 Hz, H-2' and H-6'), 7.73 (2H, d, *J* = 8.6 Hz, H-3' and H-5'), 8.24 (1H, s, H-8), 9.66 (1H, s, NH), 13.10 (1H, br, NH-9); HRMS calcd. for $C_{24}H_{30}N_5O_2Si$ (ES-) *m*/*z* 448.2174 $[M-H]^-$ found 448.2163.

***N*-(4-Methoxybenzyl)-2-(3-(6-(2-(triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)phenyl)acetamide (61)**



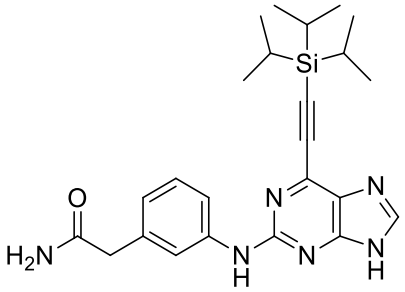
Carboxylic acid **59** (0.193 g, 0.43 mmol), CDI (0.140 g, 0.86 mmol), DIPEA (150 µL, 0.86 mmol) and 4-methoxybenzylamine (223 µL, 1.72 mmol) were reacted in dry DMF (5 mL) according to **general procedure D**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) gave the desired compound as a yellow oil/gum (0.238 g, 99%); R_f 0.48 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 277; IR (cm^{-1}) 2360, 2153, 2120, 1980; ^{1}H NMR (500 MHz, DMSO-d_6) 1.12-1.25 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 3.42 (2H, s, COC*H*$_2$), 3.71 (3H, s, OCH_3), 4.20 (2H, d, *J* = 5.8 Hz, NHC*H*$_2$), 6.85 (2H, d, *J* = 8.8 Hz, H-3'' and H-5''), 6.86-6.91 (1H, m, H-6'), 7.17 (2H, d, *J* = 8.8 Hz, H-2'' and H-6''), 7.20 (1H, dd, *J* = 7.9 and 8.0 Hz, H-5'), 7.59-7.62 (1H, m, H-2'), 7.74-7.78 (1H, m, H-4'), 8.24 (1H, s, H-8), 8.44 (1H, t, *J* = 5.8 Hz, N*H*CH_2), 9.65 (1H, s, NH), 12.06 (1H, br, NH-9); HRMS calcd. for $C_{32}H_{41}N_6O_2Si$ (ES+) *m*/*z* 569.3055 $[M+H]^+$, found 569.3057.

_N_-(4-Methoxybenzyl)-2-(4-(6-(2-(triisopropylsilyl)ethynyl)-9_H_-purin-2-ylamino)phenyl) acetamide (62)



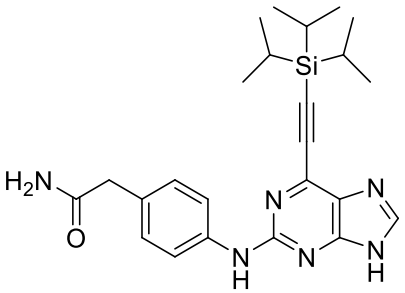
The carboxylic acid **60** (0.160 g, 0.36 mmol), CDI (0.115 g, 0.71 mmol), DIPEA (125 µL, 0.71 mmol) and 4-methoxybenzylamine (185 µL, 1.43 mmol) were reacted in dry DMF (2 mL) according to **general procedure D**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) gave the desired compound as a yellow oil (0.159 g, 78%); R_f 0.48 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 278, 370; IR (cm^{-1}) 3102, 2965, 2943, 2364, 2154, 1646; ^{1}H NMR (500 MHz, $CDCl_3$) 1.14-1.23 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 3.62 (2H, s, CH_2CO), 3.80 (3H, s, OCH_3), 4.41 (2H, d, *J* = 5.8 Hz, C*H*$_2$NH), 6.13 (1H, br, CH_2N*H*), 6.86 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 7.18 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 7.21 (2H, d, *J* = 8.5 Hz, H-3'' and H-5''), 7.56 (2H, d, *J* = 8.5 Hz, H-2'' and H-6''), 8.08 (1H, s, NH), 8.23 (1H, s, H-8); HRMS calcd. for $C_{32}H_{41}N_6O_2Si$ (ES+) *m*/*z* 569.3055 $[M+H]^+$, found 569.3051.

2-(3-(6-(2-(Triisopropylsilyl)ethynyl)-9_H_-purin-2-ylamino)phenyl) acetamide (63)



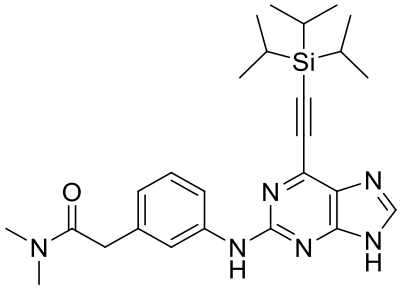
PMB-amide **61** (0.232 g, 0.41 mmol) was reacted in TFA (6 mL) according to **general procedure E** over 72 h. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) gave the desired compound as a yellow oil/gum (0.170 g, 90%); R_f 0.24 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 276; IR (cm^{-1}) 3282, 2965, 2943, 2362, 1669; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.21 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 3.34 (2H, s, COC*H*$_2$), 6.83-6.86 (1H, m, H-6'), 6.88 (1H, s, CON*H*H'), 7.19 (1H, dd, *J* = 8.5 and 8.7 Hz, H-5'), 7.42 (1H, s, CONH*H'*), 7.57-7.60 (1H, m, H-2'), 7.72-7.76 (1H, m, H-4'), 8.23 (1H, s, H-8), 9.65 (1H, s, NH), 13.08 (1H, s, NH-9); HRMS calcd. for $C_{24}H_{33}N_6OSi$ (ES+) *m*/*z* 449.2480 $[M+H]^+$, found 449.2480.

2-(4-(6-(2-(Triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)phenyl) acetamide (64)



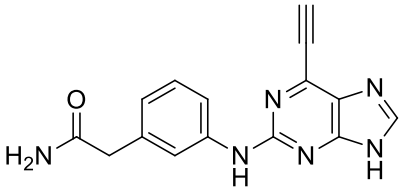
PMB-carboxamide **62** (87 mg, 0.15 mmol) and TFA (2 mL) were reacted according to **general procedure E**. Purification by chromatography on KP-NH silica (9:1 DCM/MeOH) gave the target compound as a yellow oil (60 mg, 87%); R_f 0.37 (9:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 278, 370; IR (cm^{-1}) 3472, 2943, 2865, 2040, 1659; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.23 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 3.31 (2H, s, COCH$_2$), 6.83 (1H, s, CON*H*H'), 7.16 (2H, d, *J* = 8.6 Hz, H-2' and H-6'), 7.38 (1H, s, CONH*H'*), 7.71 (2H, d, *J* = 8.6 Hz, H-3' and H-5'), 8.22 (1H, s, H-8), 9.64 (1H, s, NH), 13.06 (1H, br, NH-9); HRMS calcd. for $C_{24}H_{33}N_6OSi$ (ES+) *m*/*z* 449.2480 $[M+H]^+$, found 449.2480.

2-(3-(6-(2-(Triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)phenyl)-*N*,*N*-dimethylacetamide (65)



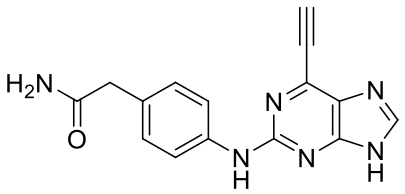
Carboxylic acid **59** (54 mg, 0.12 mmol), CDI (40 mg, 0.24 mmol), DIPEA (125 µL, 0.72 mmol) and dimethylamine hydrochloride (40 mg, 0.48 mmol) were reacted in dry DMF (1 mL) according to **general procedure D**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) gave the desired compound as a yellow oil (51 mg, 92%); R_f 0.38 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 275, 368; IR (cm^{-1}) 3117, 2965, 2943, 2363, 2160, 1711, 1598; ^{1}H NMR (500 MHz, $CDCl_3$) 1.14-1.18 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.96 (3H, s, NCH_3), 3.01 (3H, s, NCH_3), 3.68 (2H, s, CH_2), 6.82-6.85 (1H, m, H-6'), 7.16 (1H, dd, *J* = 7.9 and 8.0 Hz, H-5'), 7.34-7.38 (1H, m, H-4'), 7.61 (1H, s, H-8), 7.65 (1H, br, H-2'), 7.86 (1H, s, NH); HRMS calcd. for $C_{26}H_{37}N_6OSi$ (ES+) *m*/*z* 477.2793 $[M+H]^+$, found 477.2797.

2-(3-(6-Ethynyl-9*H*-purin-2-ylamino)phenyl)acetamide (66)



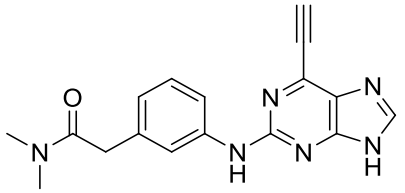
The TIPS-protected purine **63** (0.165 g, 0.37 mmol) was reacted with TBAF (1M in THF, 0.55 mL, 0.55 mmol) in THF (4 mL) according to **general procedure C**. The residue was purified by semi-preparative HPLC (17:3 H_2O/MeCN), to give the desired compound as a yellow solid (0.084 g, 0.28 mmol, 76%); R_f 0.32 (17:3 DCM/MeOH, KP-NH); m.p. 250-270 °C (decomposed); λ_{max} (EtOH/nm) 274; IR (cm^{-1}) 3359, 3170, 2921, 2107, 1658; ^{1}H NMR (500 MHz, DMSO-d_6) 4.76 (1H, s, C≡CH), 6.77-6.81 (1H, m, H-6'), 6.83 (1H, s, CON*H*H'), 7.15 (1H, dd, *J* = 8.0 and 8.1 Hz, H-5'), 7.38 (1H, s, CONH*H'*), 7.47-7.50 (1H, m, H-2'), 7.68-7.73 (1H, m, H-4'), 8.19 (1H, s, H-8), 9.52 (1H, s, NH), 13.06 (1H, s, NH-9); HRMS calcd. for $C_{15}H_{13}N_6O$ (ES+) *m*/*z* 293.1149 $[M+H]^+$, found 293.1145.

2-(4-(6-Ethynyl-9*H*-purin-2-ylamino)phenyl)acetamide (67)



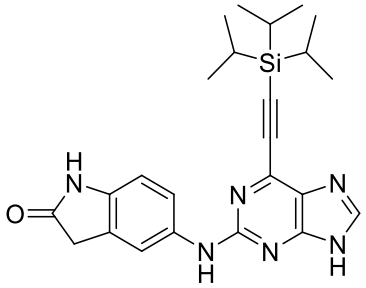
TIPS-protected purine **64** (53 mg, 0.12 mmol) and TBAF (1M in THF, 130 µL, 0.13 mmol) were reacted in THF (2 mL) according to **general procedure G**. Upon completion of the reaction, the solution was diluted with THF (10 mL) and treated with the solid supported TBAF scavenger (0.20 g, 4 x w/w) at RT for 18 h. The resin was removed *via* filtration and the solvent removed *in vacuo*. The crude residue was purified by chromatography on silica (9:1 DCM/MeOH) to give the desired compound as a yellow solid (16 mg, 46%); R_f 0.24 (9:1 DCM/MeOH); m.p. 140-150 °C (decomposed); λ_{max} (EtOH/nm) 275; IR (cm^{-1}) 3375, 3287, 3193, 3127, 2157, 2119, 2030, 1653, 1604; ^{1}H NMR (500 MHz, DMSO-d_6) 3.31 (2H, s, $COCH_2$), 4.84 (1H, s, C≡CH), 6.85 (1H, s, CON*H*H'), 7.17 (2H, d, *J* = 8.6 Hz, H-2' and H-6'), 7.40 (1H, s, CONH*H'*), 7.69 (2H, d, *J* = 8.6 Hz, H-3' and H-5'), 8.27 (1H, s, H-8), 9.62 (1H, s, NH), 13.12 (1H, br, NH-9); HRMS calcd. for $C_{15}H_{13}N_6O$ (ES+) *m*/*z* 293.1148 $[M+H]^+$, found 293.1145.

2-(3-(6-Ethynyl-9*H*-purin-2-ylamino)phenyl)-*N*,*N*-dimethylacetamide (68)



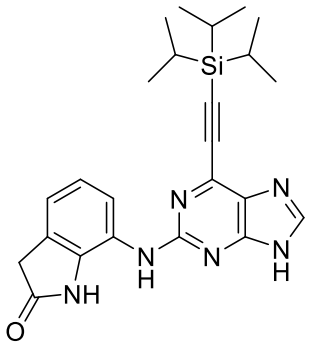
TIPS-protected purine **65** (48 mg, 0.10 mmol) and TBAF (1M in THF, 110 µL, 0.11 mmol) were reacted in THF (2 mL) according to **general procedure C**. Purification by chromatography on silica (9:1 DCM/MeOH) afforded the desired compound as a yellow solid (28 mg, 87%); R_f 0.45 (9:1 DCM/MeOH); m.p. 120-130 °C (decomposed); λ_{max} (EtOH/nm) 274; IR (cm^{-1}) 3084, 2818, 2161, 2110, 2029, 1596; ^{1}H NMR (500 MHz, DMSO-d_6) 2.65 (3H, s, NCH_3), 2.83 (3H, s, NCH_3), 3.45 (2H, s, CH_2CO), 4.65 (1H, s, C≡CH), 6.57-6.60 (1H, m, H-6'), 7.02 (1H, dd, *J* = 7.8 and 8.0 Hz, H-5'), 7.31-7.34 (1H, m, H-2'), 7.54 (1H, ddd, *J* = 1.0, 1.2 and 7.8 Hz, H-4'), 8.08 (1H, s, H-8), 9.44 (1H, s, NH), 12.93 (1H, br, NH-9); HRMS calcd. for $C_{17}H_{17}N_6O$ (ES+) *m*/*z* 321.1462 $[M+H]^+$, found 321.1458.

5-(6-(2-(Triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)indolin-2-one (69)



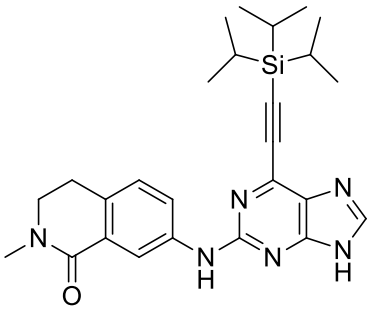
2-Fluoropurine intermediate **12** (0.319 g, 1.00 mmol), 5-amino-1,3-dihydro-2*H*-indol-2-one (0.298 g, 2.01 mmol) and TFA (390 µL, 5.02 mmol) were reacted in TFE (5 mL) according to **general procedure A**. Purification by chromatography on KP-NH silica (17:3 DCM/MeOH) afforded the desired compound as an orange oil (0.143 g, 32%); R_f 0.45 (17:3 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 255, 300, 374; IR (cm^{-1}) 2941, 2864, 2154, 1685; ^{1}H NMR (500 MHz, DMSO-d_6) 1.14-1.19 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 3.47 (2H, s, COCH_2), 6.74 (1H, d, *J* = 8.4 Hz, H-3'), 7.51-7.54 (1H, m, H-4'), 7.72-7.75 (1H, br, H-6'), 8.19 (1H, s, H-8), 9.54 (1H, s, indole NH), 10.23 (1H, s, NH), 13.03 (1H, br, NH-9); HRMS calcd. for $C_{24}H_{31}N_6OSi$ (ES+) *m*/*z* 447.2323 $[M+H]^+$, found 447.2322.

7-(6-(2-(Triisopropylsilyl)ethynyl)-9*H*-purin-2-ylamino)indolin-2-one (70)



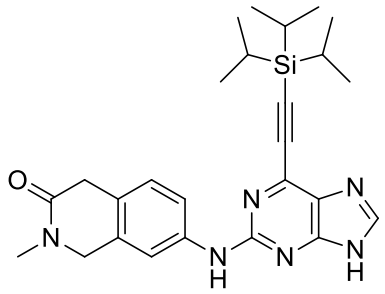
2-Fluoropurine intermediate **12** (0.120 g, 0.37 mmol), aminoindolinone **144** (0.110 g, 0.75 mmol) and TFA (142 µL, 1.85 mmol) were reacted in TFE (4 mL) according to **general procedure A**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) afforded the desired compound as an orange oil (54 mg, 32%); R_f 0.36 (19:1 DCM/MeOH); λ_{max} (EtOH/nm) 255, 359; IR (cm^{-1}) 3351, 3251, 3070, 2943, 2866, 2159, 1704; ^{1}H NMR (500 MHz, DMSO-d_6) 1.14-1.19 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 3.52 (2H, s, CH_2), 6.90-7.00 (2H, m, H-4' and H-5'), 7.58-7.62 (1H, m, H-6'), 8.20 (1H, s, H-8), 9.00 (1H, s, indole NH), 10.08 (1H, s, NH), 13.05 (1H, br, NH-9); HRMS calcd. for $C_{24}H_{31}N_6OSi$ (ES+) *m*/*z* 447.2323 $[M+H]^+$, found 447.2323.

2-Methyl-7-((6-((triisopropylsilyl)ethynyl)-9*H*-purin-2-yl)amino)-3,4-dihydroisoquinolin-1(2*H*)-one (71)



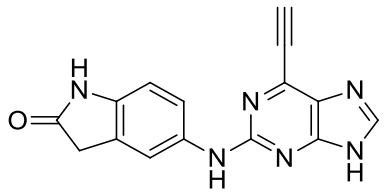
2-Fluoropurine **12** (0.225 g, 0.71 mmol), aniline **149** (0.250 g, 1.41 mmol) and TFA (136 µl, 1.77 mmol) were reacted in TFE (7 mL) according to **general procedure B**. Chromatography on KP-NH silica (19:1 DCM/MeOH) gave the desired product as a yellow oil/gum (0.142 g, 42%); R_f 0.37 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 279; IR (cm^{-1}) 3390, 3136, 2941, 2864, 2167, 1609, 1577, 1538; ^{1}H NMR (500 MHz, DMSO-d_6) 1.12-1.23 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.91 (2H, t, *J* = 6.6 Hz, NCH$_2$C*H*$_2$), 3.04 (3H, s, NCH$_3$), 3.53 (2H, t, *J* = 6.6 Hz, NC*H*$_2$CH$_2$), 7.19 (1H, d, *J* = 8.3 Hz, H-5'), 7.90 (1H, dd, *J* = 2.3 and 8.3 Hz, H-6'), 8.25 (1H, s, H-8), 8.27 (1H, d, *J* = 2.3 Hz, H-8'), 9.77 (1H, s, NH), 13.14 (1H, br, NH-9); HRMS calcd. for $C_{26}H_{35}N_6OSi$ (ES+) *m*/*z* 475.2636 $[M+H]^+$, found 475.2635.

2-Methyl-7-((6-((triisopropylsilyl)ethynyl)-9*H*-purin-2-yl)amino)-1,2-dihydroisoquinolin-3(4*H*)-one (72)



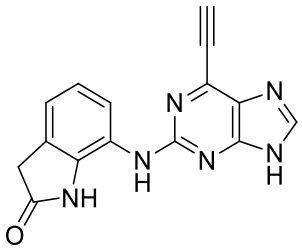
2-Fluoropurine **12** (0.145 g, 0.45 mmol), aniline **152** (0.160 g, 0.91 mmol) and TFA (87 µL, 1.14 mmol) were reacted in TFE (5 mL) according to **general procedure B**. Purification through chromatography on KP-NH silica (19:1 DCM/MeOH) gave the desired compound as a yellow oil/gum (0.138 g, 64%); R_f 0.39 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 277; IR (cm^{-1}) 2943, 2864, 1605, 1577, 1537; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.22 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.98 (3H, s, NCH$_3$), 3.46 (2H, s, COCH$_2$), 4.48 (2H, s, NCH$_2$), 7.10 (1H, d, *J* = 8.4 Hz, H-5'), 7.66 (1H, dd, *J* = 2.1 and 8.4 Hz, H-6'), 7.73-7.77 (1H, m, H-8'), 8.25 (1H, s, H-8), 9.71 (1H, s, NH), 13.08 (1H, br, NH-9); HRMS calcd. for $C_{26}H_{35}N_6OSi$ (ES+) *m*/*z* 475.2636 $[M+H]^+$, found 475.2631.

5-((6-Ethynyl-9*H*-purin-2-yl)amino)indolin-2-one (73)



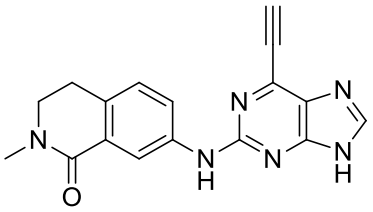
TIPS-protected purine **69** (66 mg, 0.15 mmol), TBAF (1M in THF, 0.18 mL, 0.18 mmol) and TBAF scavenger resin (0.60 g, 10 x *w/w*) were reacted in THF (5 mL) according to **general procedure G**. Purification by chromatography on silica (9:1 DCM/MeOH) gave the desired compound as an orange solid (29 mg, 67%); R_f 0.38 (9:1 DCM/MeOH); m.p. 130-160 °C (decomposed); λ_{max} (EtOH/nm) 285.0, 375.5; IR (cm^{-1}) 2835, 2161, 2112, 2028, 1977, 1668; ^{1}H NMR (500 MHz, DMSO-d_6) 3.48 (2H, s, CH_2), 4.83 (1H, s, C≡CH), 6.74 (1H, d, *J* = 8.4 Hz, H-7'), 7.53 (1H, dd, *J* = 1.4 and 8.4 Hz, H-6'), 7.69-7.71 (1H, m, H-4'), 8.24 (1H, s, H-8), 9.51 (1H, s, lactam-NH), 10.26 (1H, s, NH), 13.08 (1H, br, NH-9); HRMS calcd. for $C_{15}H_{11}N_6O$ (ES+) *m*/*z* 291.0990 $[M+H]^+$, found 291.0989.

7-((6-Ethynyl-9*H*-purin-2-yl)amino)indolin-2-one (74)



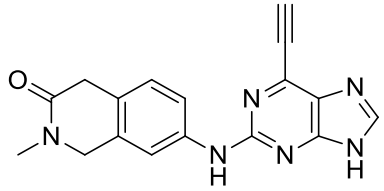
TIPS-protected purine **70** (99 mg, 0.22 mmol), TBAF (1M in THF, 0.27 mL, 0.27 mmol) and TBAF scavenger resin (1.00 g, 10 x *w/w*) were reacted in THF (5 mL) according to **general procedure G**. Purification by chromatography on silica (9:1 DCM/MeOH) afforded the target compound as a pale orange solid (43 mg, 67%); R_f 0.27 (9:1 DCM/MeOH); m.p. 195-225 °C (decomposed); λ_{max} (EtOH/nm) 244.0, 361.0; IR (cm^{-1}) 3248, 2363, 2169, 2013, 1978, 1662; ^{1}H NMR (500 MHz, DMSO-d_6) 3.52 (2H, s, CH_2), 4.81 (1H, s, C≡CH), 6.93 (1H, dd, *J* = 7.4 and 7.7 Hz, H-5'), 6.95-6.98 (1H, m, H-4'), 7.61-7.67 (1H, m, H-6'), 8.23 (1H, s, H-8), 8.96 (1H, s, lactam-NH), 10.11 (1H, s, NH), 13.08 (1H, br, NH-9); HRMS calcd. for $C_{15}H_{11}N_6O$ (ES+) *m*/*z* 291.0990 $[M+H]^+$, found 291.0989.

7-((6-Ethynyl-9*H*-purin-2-yl)amino)-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (75)



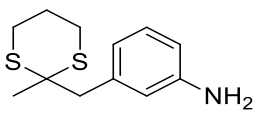
TIPS-protected purine **71** (98 mg, 0.21 mmol), TBAF (1M in THF, 0.25 mL, 0.25 mmol) and TBAF scavenger resin (1.00 g, 10 x *w/w*) were reacted in THF (5 mL) according to **general procedure G**. Purification by chromatography on silica (9:1 DCM/MeOH) gave the target compound as a yellow solid (36 mg, 54%); R_f 0.34 (9:1 DCM/MeOH); m.p. 280-300 °C (decomposed); λ_{max} (EtOH/nm) 276; IR (cm^{-1}) 3117, 2945, 2108, 1641, 1608, 1575, 1540; ^{1}H NMR (500 MHz, DMSO-d_6) 2.92 (2H, t, *J* = 6.6 Hz, NCH_2CH_2), 3.04 (3H, s, NCH_3), 3.54 (2H, t, *J* = 6.6 Hz, NCH_2CH_2), 4.85 (1H, s, C≡CH), 7.20 (1H, d, *J* = 8.3 Hz, H-5'), 7.89 (1H, dd, *J* = 2.3 and 8.3 Hz, H-6'), 8.26 (1H, d, *J* = 2.3 Hz, H-8'), 8.28 (1H, s, H-8), 9.73 (1H, s, NH), 13.2 (1H, br, NH-9); HRMS calcd. for $C_{17}H_{15}N_6O$ (ES+) *m/z* 319.1302 $[M+H]^+$, found 319.1307.

7-((6-Ethynyl-9*H*-purin-2-yl)amino)-2-methyl-1,2-dihydroisoquinolin-3(4*H*)-one (76)



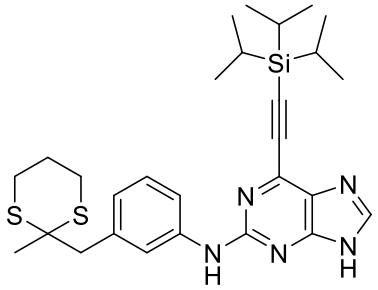
TIPS-protected purine **72** (0.112 g, 0.24 mmol), TBAF (1M in THF, 0.28 mL, 0.28 mmol) and TBAF scavenger resin (1.10 g, 10 x *w/w*) were reacted in THF (5 mL) according to **general procedure G**. Purification by chromatography on silica (9:1 DCM/MeOH) afforded the target compound as a yellow solid (41 mg, 54%); R_f 0.41 (9:1 DCM/MeOH); m.p. 200-220 °C (decomposed); λ_{max} (EtOH/nm) 274.5, 346.5; IR (cm^{-1}) 3292, 3086, 2963, 2774, 2104, 1610, 1551, 1494; ^{1}H NMR (500 MHz, DMSO-d_6) 2.98 (3H, s, NCH_3), 3.46 (2H, s, Ar-CH_2), 4.49 (2H, s, Ar-CH_2), 4.84 (1H, s, C≡CH), 7.11 (1H, d, *J* = 8.5 Hz, H-5'), 7.65-7.71 (2H, m, H-6' and H-8'), 8.28 (1H, s, H-8), 9.69 (1H, s, NH), 13.13 (1H, br, NH-9); HRMS calcd. for $C_{17}H_{15}N_6O$ (ES+) *m/z* 319.1302 $[M+H]^+$, found 319.1301.

3-((2-Methyl-1,3-dithian-2-yl)methyl)aniline (77)



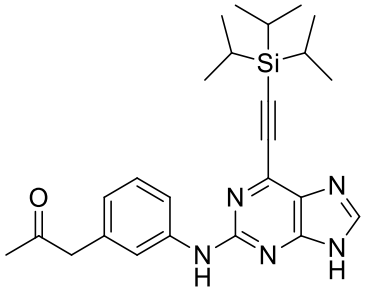
Tin(II) chloride (2.81 g, 14.8 mmol) was added to a mixture of aromatic nitro substrate **154** (1.00 g, 3.71 mmol) in ethanol (40 mL). The reaction mixture was heated at reflux for 1.5 h, after which the solvent was removed *in vacuo*. The resulting residue was dissolved in EtOAc (300 mL) and a saturated aqueous solution of $NaHCO_3$ was added until the aqueous phase was at pH 9-10. The resulting precipitate was removed by filtration through Celite® and the organic phase was collected, washed with brine (100 mL) and evaporated to dryness. Purification by chromatography on silica (7:3 Petrol/EtOAc) gave the desired compound as an off-white solid on cooling (0.760 g, 85%); R_f 0.41 (7:3 Petrol/EtOAc); m.p. 73-75 °C; λ_{max} (EtOH/nm) 235, 291; IR (cm^{-1}) 3444, 3349, 2941, 2913, 1612, 1585; ^{1}H NMR (500 MHz, DMSO-d_6) 1.48 (3H, s, CH_3), 1.80-1.92 (2H, m, $C(SCH_2)_2CH_2$), 2.82-2.99 (4H, m, $C(SCH_2)_2CH_2$), 3.02 (2H, s, Ar-CH_2), 4.94 (2H, s, Ar-NH_2), 6.41 (1H, ddd, *J* = 1.2, 1.6 and 7.6 Hz, H-6), 6.44 (1H, ddd, *J* = 1.2, 2.2 and 7.7 Hz, H-4), 6.46-6.48 (1H, m, H-2), 6.91 (1H, dd, *J* = 7.6 and 7.7 Hz, H-5); HRMS calcd. for $C_{12}H_{18}NS_2$ (ES+) *m*/*z* 240.0875 $[M+H]^+$, found 240.0878.

_N_-(3-((2-methyl-1,3-dithian-2-yl)methyl)phenyl)-6-((triisopropylsilyl)ethynyl)-9_H_-purin-2-amine (78)



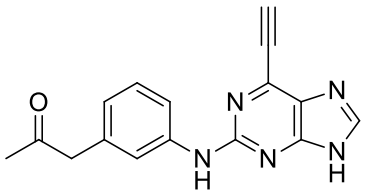
2-Fluoropurine **12** (0.195 g, 0.61 mmol), aniline **77** (0.220 g, 0.92 mmol) and TFA (117 µl, 1.53 mmol) were reacted in TFE (6 mL) according to **general procedure B**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) gave the target compound as a yellow oil/gum (0.182 g, 56%); R_f 0.41 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 276, 379; IR (cm^{-1}) 3072, 2942, 2863, 1595, 1575, 1533; ^{1}H NMR (500 MHz, $CDCl_3$) 1.17-1.26 (21H, m, $Si(CH(CH_3)_2)_3$), 1.58 (3H, s, CH_3), 1.97-2.03 (2H, m, $C(SCH_2)_2CH_2$), 2.87-2.93 (4H, m, $C(SCH_2)_2CH_2$), 3.19 (2H, s, Ar-CH_2), 7.00-7.04 (1H, m, H-6'), 7.28 (1H, dd, *J* = 7.7 and 7.8 Hz, H-5'), 7.38 (1H, s, H-8), 7.39 (1H, s, NH), 7.44-7.47 (1H, m, H-2'), 7.49-7.54 (1H, m, H-4'), 11.80 (1H, s, NH-9); HRMS calcd. for $C_{28}H_{40}N_5S_2Si$ (ES+) *m*/*z* 538.2489 $[M+H]^+$, found 538.2484.

1-(3-((6-((Triisopropylsilyl)ethynyl)-9*H*-purin-2-yl)amino)phenyl)propan-2-one (79)



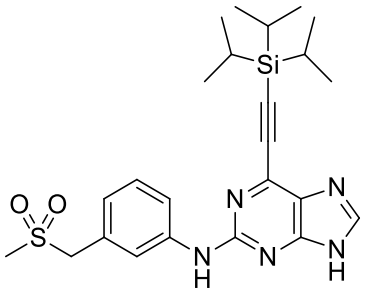
[Bis(trifluoroacetoxy)iodo]benzene (0.158 g, 0.37 mmol) was added to a solution of dithiane protected purine **78** (0.132 g, 0.25 mmol) in MeOH/H_2O (9:1, 25 mL). After stirring at RT for 10 min, the solution was diluted with sat. $NaHCO_3$ solution (30 mL) and the resultant suspension extracted with DCM (2 × 20 mL). The combined organic extracts were dried through a phase separator, evaporated to dryness, and the resultant residue was purified by chromatography on silica (19:1 DCM/MeOH). The desired compound was obtained as a yellow oil/gum (98 mg, 88%); R_f 0.33 (19:1 DCM/MeOH); λ_{max} (EtOH/nm) 277; IR (cm^{-1}) 3402, 2943, 2865, 2363, 2160, 1705, 1597, 1577, 1542; ^{1}H NMR (500 MHz, $CDCl_3$) 1.14-1.25 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.16 (3H, s, CH_3), 3.67 (2H, s, CH_2), 6.85-6.89 (1H, m, H-6'), 7.27 (1H, dd, *J* = 7.7 and 7.9 Hz, H-5'), 7.40-7.45 (2H, m, H-4' and NH), 7.52-7.56 (1H, m, H-2'), 7.70 (1H, s, H-8), 11.44 (1H, br, NH-9); HRMS calcd. for $C_{25}H_{34}N_5OSi$ (ES+) *m*/*z* 448.2527 $[M+H]^+$, found 448.2527.

1-(3-((6-Ethynyl-9*H*-purin-2-yl)amino)phenyl)propan-2-one (80)



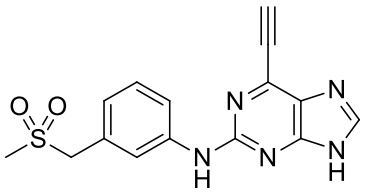
TIPS-protected purine **79** (90 mg, 0.20 mmol), TBAF (1M in THF, 0.24 mL, 0.24 mmol) and TBAF scavenger resin (0.90 g, 10 x *w/w*) were reacted in THF (5 mL) according to **general procedure G**. Purification by chromatography on silica (9:1 DCM/MeOH) gave the desired compound as a yellow solid (43 mg, 70%); R_f 0.43 (9:1 DCM/MeOH); m.p. 90-110 °C (decomposed); λ_{max} (EtOH/nm) 273; IR (cm^{-1}) 3260, 3082, 2964, 2827, 2113, 1705, 1604, 1578, 1537; ^{1}H NMR (500 MHz, DMSO-d_6) 2.15 (3H, s, $COCH_3$), 3.71 (2H, s, $COCH_2$), 4.84 (1H, s, C≡CH), 6.77-6.80 (1H, m, H-6'), 7.24 (1H, dd, *J* = 7.8 and 7.9 Hz, H-5'), 7.52 (1H, dd, *J* = 1.4 and 1.6 Hz, H-2'), 7.75-7.78 (1H, m, H-4'), 8.28 (1H, s, H-8), 9.64 (1H, s, NH), 13.14 (1H, br, NH-9); HRMS calcd. for $C_{16}H_{14}N_5O$ (ES+) *m*/*z* 292.1193 $[M+H]^+$, found 292.1197.

***N*-(3-((Methylsulfonyl)methyl)phenyl)-6-((triisopropylsilyl)ethynyl)-9*H*-purin-2-amine (81)**



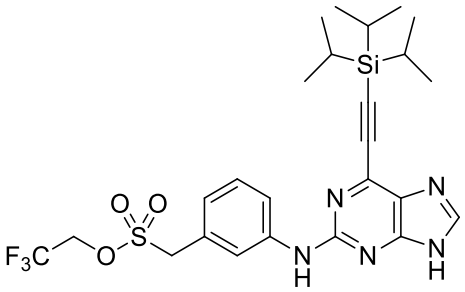
2-Fluoropurine intermediate **12** (0.213 g, 0.67 mmol), aniline **157** (0.248 g, 1.34 mmol) and TFA (130 µL, 1.67 mmol) were reacted in TFE (7 mL) according to **general procedure B**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) gave the target compound as a yellow oil/gum (0.134 g, 42%); R_f 0.36 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 277, 369; IR (cm^{-1}) 3338, 2942, 2864, 1599, 1577, 1539; ^{1}H NMR (500 MHz, DMSO-d_6) 1.11-1.20 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.94 (3H, s, CH_3), 4.40 (2H, s, Ar-CH_2), 6.96-7.01 (1H, m, H-4'), 7.27-7.31 (1H, dd, *J* = 7.9 and 8.1 Hz, H-5'), 7.77-7.80 (1H, m, H-2'), 7.85-7.90 (1H, m, H-6'), 8.26 (1H, s, H-8), 9.79 (1H, s, NH), 13.11 (1H, br, NH-9); HRMS calcd. for $C_{24}H_{34}N_5O_2SSi$ (ES+) *m*/*z* 484.2197 $[M+H]^+$, found 484.2197.

6-Ethynyl-*N*-(3-((methylsulfonyl)methyl)phenyl)-9*H*-purin-2-amine (82)



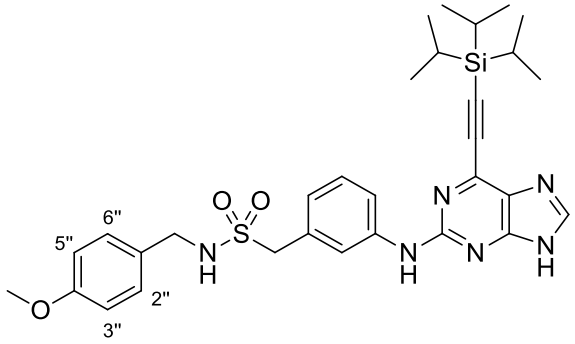
TIPS-protected purine **81** (0.111 g, 0.23 mmol), TBAF (1M in THF, 0.28 mL, 0.28 mmol) and TBAF scavenger resin (1.10 g, 10 x *w/w*) were reacted in THF (5 mL) according to **general procedure G**. Purification by chromatography on silica (9:1 DCM/MeOH) afforded the desired compound as a pale yellow solid (52 mg, 66%); R_f 0.36 (9:1 DCM/MeOH); m.p. 180-200 °C (decomposed); λ_{max} (EtOH/nm) 346.5, 275.0; IR (cm^{-1}) 3330, 3257, 2982, 2919, 2116, 1607, 1548, 1492; ^{1}H NMR (500 MHz, DMSO-d_6) 2.97 (3H, s, SO_2CH_3), 4.43 (2H, s, SO_2CH_2), 4.83 (1H, s, C≡CH), 6.98-7.02 (1H, m, H-4'), 7.32 (1H, dd, *J* = 7.9 and 8.0 Hz, H-5'), 7.69-7.73 (1H, m, H-2'), 7.85-7.89 (1H, m, H-6'), 8.27 (1H, s, H-8), 9.77 (1H, s, NH), 13.11 (1H, br, NH-9); HRMS calcd. for $C_{15}H_{14}N_5O_2S$ (ES+) *m*/*z* 328.0863 $[M+H]^+$, found 328.0868.

2,2,2-Trifluoroethyl (3-((6-((triisopropylsilyl)ethynyl)-9*H*-purin-2-yl)amino)phenyl) methanesulfonate (83)



2-Fluoropurine intermediate **12** (0.416 g, 1.31 mmol) and aniline **160** (0.704 g, 2.62 mmol) were reacted with TFA (504 µL, 6.54 mmol) in TFE (10 mL) according to **general procedure A**. The resulting orange oil was purified by chromatography on reverse phase silica (19:1 MeOH/H_2O + 0.1% HCOOH) followed by chromatography on silica (7:3 Petrol/EtOAc) to give the desired compound as a yellow/orange oil/gum (0.506 g, 68%); R_f 0.34 (9:1 MeOH/H_2O, + 0.1% HCOOH, C18); λ_{max} (EtOH/nm) 368, 277; IR (cm^{-1}) 2950, 2365, 2161, 2011, 1967, 1601; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-2.23 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 4.85 (2H, s, Ar-C*H*$_2$), 4.95 (2H, q, *J* = 8.7 Hz, F_3CC*H*$_2$O), 7.00-7.04 (1H, m, H-6'), 7.34 (1H, dd, *J* = 7.9 and 8.1 Hz, H-5'), 7.74-7.77 (1H, m, H-2'), 7.96-8.00 (1H, m, H-4'), 8.28 (1H, s, H-8), 9.84 (1H, s, NH), 13.12 (1H, br, NH-9); HRMS calcd. for $C_{25}H_{33}F_3N_5O_3SSi$ (ES+) *m*/*z* 568.2020 $[M+H]^+$, found 568.2015.

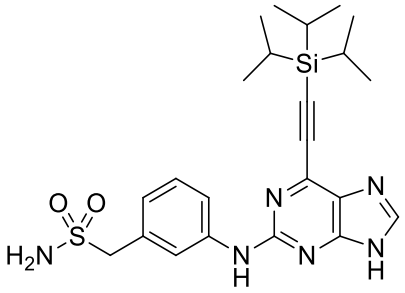
***N*-(4-Methoxybenzyl)-1-(3-((6-((triisopropylsilyl)ethynyl)-9*H*-purin-2-yl)amino)phenyl)methanesulfonamide (84)**



Trifluoroethylsulfonate ester **83** (0.215 g, 0.38 mmol), 4-methoxybenzylamine (64 µl, 0.49 mmol) and DBU (115 µL, 0.76 mmol) were reacted in dry THF (3 mL) according to **general procedure H**. Purification by chromatography on silica (19:1 DCM/MeOH) gave the desired compound as a yellow oil (0.224 g, 97%); R_f 0.44 (19:1 DCM/MeOH); λ_{max} (EtOH/nm) 276; IR (cm^{-1}) 2361, 2341, 2162, 1992, 1969, 1609; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.22 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 3.72 (3H, s, OCH_3), 4.05 (2H, d, *J* = 6.0 Hz, NHC*H*$_2$), 4.23 (2H, s,

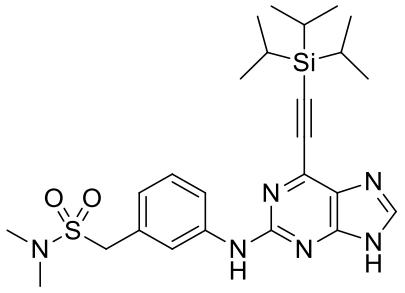
Ar-CH_2), 6.87 (2H, d, *J* = 8.7 Hz, H-3'' and H-5''), 6.91-6.95 (1H, m, H-6'), 7.23 (2H, d, *J* = 8.7 Hz, H-2'' and H-6''), 7.28 (1H, dd, *J* = 8.0 and 8.2 Hz, H-5'), 7.55 (1H, t, *J* = 6.0 Hz, N*H*CH_2), 7.72-7.75 (1H, m, H-2'), 7.87-7.91 (1H, m, H-4'), 8.26 (1H, s, H-8), 9.76 (1H, s, NH), 13.06 (1H, s, NH-9); HRMS calcd. for $C_{31}H_{41}N_6O_3SSi$ (ES+) *m*/*z* 605.2725 $[M+H]^+$, found 605.2723.

(3-((6-((Triisopropylsilyl)ethynyl)-9*H*-purin-2-yl)amino)phenyl) methanesulfonamide (85)



PMB-sulfonamide **84** (0.221 g, 0.37 mmol) was reacted in TFA (6 mL) according to **general procedure E** over 3 h. The crude product was purified by chromatography on KP-NH silica (19:1 DCM/MeOH) to give the desired compound as a yellow oil/gum (0.108 g, 60%); R_f 0.21 (19:1 DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 276; IR (cm^{-1}) 3367, 2943, 2865, 2160, 2021, 1606; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.23 (21H, m, Si(C*H*(CH_3)$_2$)$_3$), 4.21 (2H, s, Ar-CH_2), 6.84 (2H, s, SO_2NH_2), 6.95-6.98 (1H, br, H-6'), 7.13 (1H, dd, *J* = 7.9 and 8.0 Hz, H-5'), 7.68-7.71 (1H, m, H-2'), 7.90 (1H, ddd, *J* = 1.0, 1.9 and 8.0 Hz, H-4'), 8.25 (1H, s, H-8), 9.75 (1H, s, NH), 13.07 (1H, s, NH-9); HRMS calcd. for $C_{23}H_{33}N_6O_2SSi$ (ES+) *m*/*z* 485.2149 $[M+H]^+$, found 485.2147.

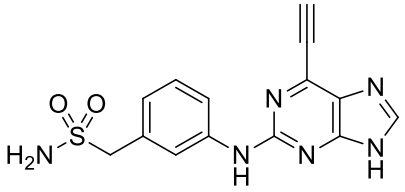
***N*,*N*-Dimethyl-1-(3-((6-((triisopropylsilyl)ethynyl)-9*H*-purin-2-yl)amino)phenyl) methanesulfonamide (86)**



Trifluoroethylsulfonate ester **83** (0.164 g, 0.29 mmol), dimethylamine (2M in THF, 0.29 mL, 0.58 mmol) and DBU (86 µL, 0.58 mmol) were reacted in dry THF (3 mL) according to **general procedure H**. Purification by chromatography on KP-NH silica (19:1 DCM/MeOH) afforded the target compound as a yellow oil/gum (0.148 g, 100%); R_f 0.50 (19:1

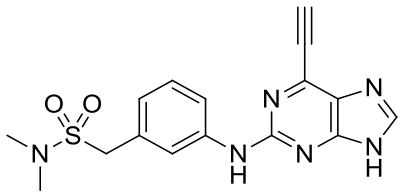
DCM/MeOH, KP-NH); λ_{max} (EtOH/nm) 276, 366; IR (cm^{-1}) 3084, 2942, 2864, 2160, 1599, 1577, 1539; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13-1.23 (21H, m, Si(C*H*(C*H*$_3$)$_2$)$_3$), 2.74 (6H, s, N(CH$_3$)$_2$), 4.34 (2H, s, SO$_2$C*H*$_2$), 6.97-7.01 (1H, m, H-6'), 7.29 (1H, dd, *J* = 7.9 and 8.0 Hz, H-5'), 7.80 (1H, dd, *J* = 1.6 and 1.7 Hz, H-2'), 7.87 (1H, ddd, *J* = 1.0, 1.7 and 8.0 Hz, H-4'), 8.27 (1H, s, H-8), 9.78 (1H, s, NH), 12.25 (1H, br, NH-9); HRMS calcd. for $C_{25}H_{37}N_6O_2SSi$ (ES+) *m*/*z* 513.2462 $[M+H]^+$, found 513.2451.

(3-((6-Ethynyl-9*H*-purin-2-yl)amino)phenyl)methanesulfonamide (87)



The TIPS-protected purine **85** (60 mg, 0.12 mmol), TBAF (1M in THF, 0.15 mL, 0.15 mmol) and the TBAF scavenger resin (0.60 g, 10 x w/w) were reacted in THF (5 mL) according to **general procedure G**. Purification by chromatography on silica (9:1 DCM/MeOH) gave the target compound as a pale yellow solid (23 mg, 58%); R_f 0.29 (9:1 DCM/MeOH); m.p. 190-210 °C (decomposed); λ_{max} (EtOH/nm) 273.5, 359.0; IR (cm^{-1}) 3361, 3248, 2976, 2809, 2707, 2114, 1701, 1610, 1583, 1491; ^{1}H NMR (500 MHz, DMSO-d_6) 4.22 (2H, s, SO$_2$CH$_2$), 4.85 (1H, s, C≡CH), 6.86 (2H, s, SO$_2$NH$_2$), 6.94-6.98 (1H, m, H-6'), 7.30 (1H, dd, *J* = 7.7 and 8.0 Hz, H-5'), 7.64-7.68 (1H, m, H-2'), 7.88-7.92 (1H, m, H-4'), 8.29 (1H, s, H-8), 9.72 (1H, s, NH), 13.13 (1H, br, NH-9); HRMS calcd. for $C_{14}H_{13}N_6O_2S$ (ES+) *m*/*z* 329.0815 $[M+H]^+$, found 329.0821.

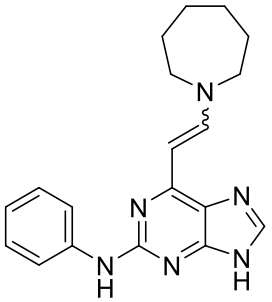
1-(3-((6-Ethynyl-9*H*-purin-2-yl)amino)phenyl)-*N*,*N*-dimethylmethane sulfonamide (88)



The TIPS-protected purine **86** (0.139 g, 0.27 mmol), TBAF (1M in THF, 0.33 mL, 0.33 mmol) and TBAF scavenger resin (1.40 g, 10 x *w/w*) were reacted in THF (5 mL) according to **general procedure G**. Purification by chromatography on silica (9:1 DCM/MeOH) afforded the target compound as a yellow solid (56 mg, 58%); R_f 0.42 (9:1 DCM/MeOH); m.p. 90-110 °C (decomposed); λ_{max} (EtOH/nm) 275, 367; IR (cm^{-1}) 3253, 3126, 2966, 2926, 2852, 2113, 1599, 1580, 1540; ^{1}H NMR (500 MHz, DMSO-d_6) 2.76 (6H, s, N(CH$_3$)$_2$), 4.36 (2H, s, SO$_2$CH$_2$), 4.85 (1H, s, C≡CH), 6.98-7.01 (1H, m, H-6'), 7.31 (1H, dd, *J* = 7.8 and 8.0 Hz, H-

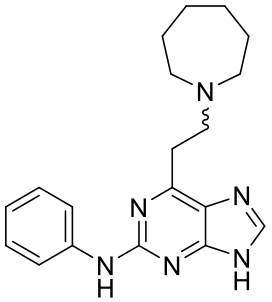
5'), 7.73-7.76 (1H, m, H-2'), 7.84-7.89 (1H, m, H-4'), 8.29 (1H, s, H-8), 9.75 (1H, s, NH), 13.1 (1H, br, NH-9); HRMS calcd. for $C_{16}H_{17}N_6O_2S$ (ES+) *m/z* 357.1128 $[M+H]^+$, found 357.1134.

(*E*)-6-(2-(azepan-1-yl)vinyl)-*N*-phenyl-9*H*-purin-2-amine (89)[8]



A solution of 6-ethynyl-*N*-phenyl-9*H*-purin-2-amine (**23**) (50 mg, 0.21 mmol) and homopiperidine (480 µL, 4.23 mmol) in anhydrous THF (2 mL) was subjected to microwave heating at 100 °C for 10 minutes in a sealed nitrogen flushed microwave vial (2-5 mL capacity). The cooled solution was partitioned between EtOAc (20 mL) and saturated $NaHCO_3$ solution (20 mL). The organic extract was concentrated *in vacuo* to a yellow/orange syrup which was subjected to purification by chromatography on KP-NH silica (9.5:0.5 DCM/MeOH), yielding the title compound as a yellow solid (69 mg, 98%); m.p. 135-137 °C (lit.,[8] m.p. 135-137 ºC); λmax (EtOH/nm) 360, 238, 254; IR (cm^{-1}) 3030, 2921, 2850, 1629, 1559; ^{1}H NMR (500 MHz, $CDCl_3$) 1.49 (4H, m, homopiperidine CH_2), 1.64-1.71 (4H, m, homopiperidine CH_2), 3.28-3.38 (4H, m, homopiperidine CH_2), 5.49-5.52 (1H, d, *J* = 15.0 Hz, C*H*=CH), 6.95-6.99 (1H, t, *J* = 10.5 Hz, H-4'), 7.19 (1H, s, H-8), 7.22-7.26 (2H, dd, *J* = 9.5, 10.5 Hz, H-3' and H-5'), 7.32 (1H, br s, NH), 7.44-7.46 (2H, d, *J* = 9.5 Hz, H-2' and H-6'), 8.23-8.26 (1H, d, *J* = 15.0 Hz, CH=C*H*), 12.89 (1H, br s, NH-9); HRMS calcd for $C_{19}H_{22}N_6$ $[M+H]^+$ 335.1975, found 335.1979.

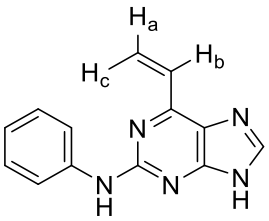
6-(2-(Azepan-1-yl)ethyl)-*N*-phenyl-9*H*-purin-2-amine (90)



To a stirred solution of (*E*)-6-(2-(azepan-1-yl)vinyl)-*N*-phenyl-9*H*-purin-2-amine (**89**) (130 mg, 0.39 mmol) in THF (3 mL) was added sodium cyanoborohydride solution (1 M, in THF, 1.95 mL, 1.95 mmol) followed by TFA (3 µL, 0.04 mmol) *or* HCl (aq) (1 M, 40 µL, 0.04 mmol). Stirring was continued for 2 h (TFA) or 5 h (HCl), after which the solution was partitioned

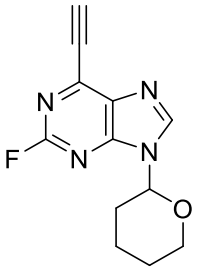
between EtOAc (20 mL) and saturated $NaHCO_3$ solution (10 mL). The organic extract was dried (Na_2SO_4) before purification by chromatography on KP-NH silica (9.5:0.5 DCM/MeOH) to yield a pale yellow solid (41 mg, 30%); m.p. 47-49 °C; λ_{max} (EtOH/nm) 326, 277, 238; IR (cm^{-1}) 2928, 2858, 1582; ^{1}H NMR (500 MHz, DMSO-d_6) 1.32-1.33 (4H, m, homopiperidine CH_2), 1.39-1.40 (4H, m, homopiperidine CH_2), 2.53-2.56 (4H, t, *J* = 5.5 Hz, homopiperidine NCH_2), 2.86-2.91 (2H, t, *J* = 8.0 Hz, CH_2), 2.92-2.98 (2H, t, *J* = 8.0 Hz, CH_2), 6.69-6.72 (1H, t, *J* = 8.5 Hz, H-4'), 7.05-7.08 (2H, dd, *J* = 7.5 and 8.5 Hz, H-3' and H-5'), 7.65-7.66 (2H, d, *J* = 7.5 Hz, H-2' and H-6'), 7.97 (1H, s, H-8), 9.21 (1H, br s, NH); HRMS calcd for $C_{19}H_{25}N_6$ $[M+H]^+$ 337.2135, found 337.2138.

_N_-phenyl-6-vinyl-9_H_-purin-2-amine (92)



m-CPBA (titrated as 62%, 30 mg, 0.108 mmol) was added in one portion to a stirred solution of 6-(2-(azepan-1-yl)ethyl)-*N*-phenyl-9*H*-purin-2-amine (**90**) (30 mg, 0.09 mmol) in anhydrous DCM (2 mL). The colourless solution instantly became bright yellow. After 2 h at room temperature the reaction was diluted with DCM (5 mL) and washed with saturated $NaHCO_3$ solution (4 mL). The crude product was purified by chromatography on silica (9.5:0.5 DCM/MeOH) to yield a yellow solid (6.4 mg, 30%); m.p. 121-123 °C; UV λ_{max} (EtOH) 270, 207; IR (cm^{-1}) 1578, 1532, 1496, 1439, 1392, 1349; ^{1}H NMR (500 MHz, DMSO-d_6) 5.84-5.86 (1H, dd, *J* = 1.5 and 12.5 Hz, alkene H_a), 6.86-6.89 (1H, dd, *J* = 1.5 and 17.5 Hz, alkene H_c), 7.01-7.04 (1H, t, *J* = 8.5 Hz, H-4'), 7.08-7.14 (1H, dd, *J* = 12.5 and 17.5 Hz, alkene H_b), 7.24 (1H, s, H-8), 7.27-7.30 (2H, dd, *J* = 8.5 and 7.5 Hz, H-3' and H-5'), 7.52-7.54 (2H, d, *J* = 7.5 Hz, H-2' and H-6'); HRMS calcd for $C_{13}H_{12}N_5$ $[M+H]^+$ 238.0509, found 238.0511.

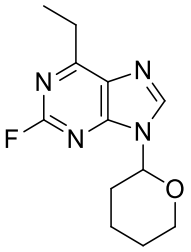
6-Ethynyl-2-fluoro-9-(tetrahydro-2_H_-pyran-2-yl)-9_H_-purine (93)[9]



The TIPS-protected purine **11** (68 mg, 0.169 mmol) and TBAF (1M in THF, 203 μL, 0.203 mmol) were reacted in THF (3 mL) according to **general procedure C**, with purification by

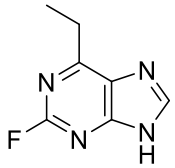
chromatography on silica (15-100% EtOAc/petrol) to give the desired product as an off-white solid (41 mg, 100%); R_f 0.32 (50% EtOAc/petrol); ^{1}H NMR (500 MHz, $CDCl_3$) 1.58-1.63 (1H, m, C*H*), 1.63-1.78 (2H, m, CH_2), 1.90-1.99 (1H, m, C*H*), 1.99-2.06 (1H, m, C*H*), 2.07-2.12 (1H, m, C*H*), 3.68-3.74 (1H, m, C*H*), 3.71 (1H, s, C≡C*H*), 4.09-4.14 (1H, m, C*H*), 5.65 (1H, dd, *J* = 2.6 and 10.8 Hz, NC*H*), 8.26 (1H, s, H-8); LRMS (ES$^+$) *m/z* 247.0 [M+H]$^+$.

6-Ethyl-2-fluoro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (94)



Lindlar's catalyst (10 mg, 20% *w/w*) was suspended in a stirred solution of **93** (50 mg, 0.20 mmol) and quinoline (20 μL, 0.16 mmol) in EtOAc (5 mL) under a balloon of H_2. After 2 h at room temperature the reduction was complete and the suspension was filtered through a plug of Celite, eluting with methanol (30 mL). Volatiles were removed *in vacuo* and the crude residue purified by chromatography on silica (50% EtOAc/petrol). The pure compound was isolated as a colourless oil (50 mg, 99%); λ_{max} (EtOH/nm) 264; IR (cm^{-1}) 2946, 2860, 2364, 2338, 1604; ^{1}H NMR (500 MHz, DMSO-d_6) 1.35 (3H, t, *J* = 7.5 Hz, CH_3), 1.59 (2H, m, tetrahydropyran CH_2), 1.97 (1H, m, tetrahydropyran CH), 1.99 (2H, d, *J* = 10.5 Hz, tetrahydropyran CH_2), 2.50 (1H, m, tetrahydropyran CH), 3.01 (2H, q, *J* = 7.5 Hz, CH_2), 3.73 (1H, m, tetrahydropyran CH), 4.04 (1H, d, *J* = 10.5 Hz, tetrahydropyran CH), 5.69 (1H, d, *J* = 10.5 Hz, tetrahydropyran CH), 8.74 (1H, s, H-8); LRMS (ES$^+$) *m/z* 251.0 [M+H]$^+$.

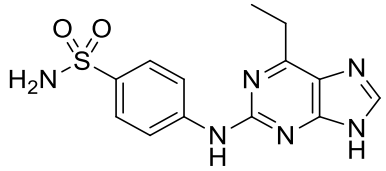
6-Ethyl-2-fluoro-9*H*-purine (95)



TFA (3 mL) was added to a solution of 6-ethyl-2-fluoro-9-(tetrahydro-2*H*-pyran-2-yl)-9*H*-purine (**94**) (0.18 g, 0.72 mmol) in IPA (15 mL). Water (3 mL) was added and the solution was heated to reflux for 2 h. The mixture was cooled and neutralised (conc. NH_3) before being extracted with EtOAc (3 × 50 mL) and the combined organic extracts dried ($MgSO_4$) and concentrated. The resulting residue was purified by chromatography on silica (25% EtOAc/petrol). The compound was isolated as a white solid (0.117 g, 98%); m.p. 146-148 °C; λ_{max} (EtOH/nm) 269; IR (cm^{-1}) 1676, 1616, 1573; ^{1}H NMR (400 MHz, DMSO-d_6) 1.30 (3H, t, *J*

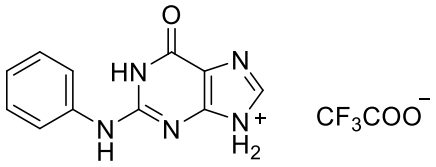
= 7.5 Hz, CH_3), 3.00 (2H, q, *J* = 7.5 Hz, CH_2), 8.17 (1 H, s, H-8); LRMS (ES^+) *m/z* = 167.7 $[M+H]^+$.

4-(6-Ethyl-9*H*-purin-2-ylamino)benzenesulfonamide (96)



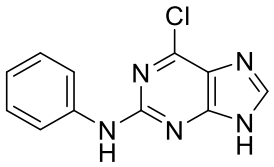
The title compound was synthesised according to **general procedure A** using: 6-ethyl-2-fluoro-9*H*-purine (**95**) (81 mg, 0.49 mmol) and 4-aminobenzenesulfonamide (0.17 g, 0.98 mmol). The compound was isolated after purification by chromatography on silica (50% EtOAc/petrol) as a white solid (33 mg, 21%); m.p. 291-293 ºC; λ_{max} (EtOH/nm) 318, 287, 212; IR (cm^{-1}) 3377, 3060, 2852, 1388, 1158; ^{1}H NMR (500 MHz, DMSO-d_6) 1.35 (3H, t, *J* = 6.0 Hz, CH_3), 3.00 (2H, q, *J* = 6.0 Hz, CH_2), 7.14 (2H, br s, SO_2NH_2), 7.69 (2H, d, *J* = 7.5 Hz, H-2' and H-6'), 7.99 (2H, d, *J* = 7.5 Hz, H-3' and H-5'), 8.17 (1H, s, H-8), 9.89 (1H, br s, NH); HRMS calcd for $C_{13}H_{15}N_6O_2S$ $[M+H]^+$ 319.0971, found 319.0979.

***N*^{2}-Phenylguanine 2,2,2-trifluoroacetate salt (98)**



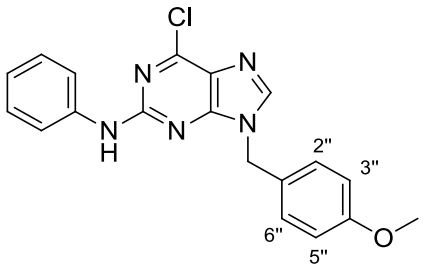
To a suspension of 2-bromohypoxanthine (1.00 g, 4.7 mmol) and aniline (0.9 mL, 9.40 mmol) in TFE (40 mL) was added TFA (1.80 mL, 23.5 mmol). The mixture was heated to reflux under nitrogen for 24 h. The mixture was filtered hot, washed with EtOH (3 × 50 mL/g), and air-dried for 30 min. The filtrate was evaporated *in vacuo* and the solid was recrystallised from EtOH to obtain the title compound as a white solid (1.17 g, 73%); m.p. 229-231 ºC; λ_{max} (EtOH/nm) 272; IR (cm^{-1}) 3332, 3128, 2943, 2756, 2555, 2387, 1678, 1572; ^{1}H NMR (300 MHz, DMSO-d_6) 7.07 (1H, t, *J* = 7.5 Hz, H-4'), 7.36 (2H, dd, *J* = 7.5, 8.0 Hz, H-3' and H-5'), 7.62 (2 H, d, *J* = 8.0 Hz, H-2' and H-6'), 7.94 (1H, s, H-8), 8.46 (1H, br s, NH), 9.00 (1H, br s, NH); HRMS calcd for $C_{11}H_{10}N_5O$ $[M+H]^+$ 228.0881, found 228.0880.

6-Chloro-*N*-phenyl-9*H*-purin-2-amine (99)[10]



N^2-Phenylguanine trifluoroacetate salt (**98**) (2.00 g, 5.87 mmol) and *N*,*N*-diethylaniline (1.9 mL, 11.73 mmol) was suspended in neat $POCl_3$ (30 mL) at room temperature. The reaction mixture was heated at 115 °C for 60 min under a nitrogen atmosphere. The resulting yellow solution was carefully added dropwise on to crushed ice in an ice bath with rapid stirring [CAUTION – VERY EXOTHERMIC]. Once addition was complete and the ice had melted, the homogeneous solution was neutralised to pH 7 by slow addition of NaOH solution (1.0 M), maintaining rapid stirring in an ice bath. The aqueous mixture was extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and purified by chromatography on silica (50% EtOAc/petrol). The title compound was isolated as a white solid (0.67 g, 46%); m.p. 172-174 °C (lit.[10] 155-160 °C); λ_{max} (EtOH/nm) 329, 272; IR (cm^{-1}) 3399, 3289, 1627, 1601, 1571, 1540; ^{1}H NMR (500 MHz, DMSO-d_6) 6.89-6.92 (1H, t, *J* = 7.5 Hz, H-4'), 7.23-7.26 (2H, dd, *J* = 7.4 and 7.5 Hz, H-3' and H-5'), 7.71-7.73 (2H, d, *J* = 7.4 Hz, H-2' and H-6'), 8.20 (1H, s, H-8), 9.81 (1H, br s, NH), 13.20 (1H, br s, NH-9); LRMS (ES^+) *m/z* 246.06 $[M+H]^+$.

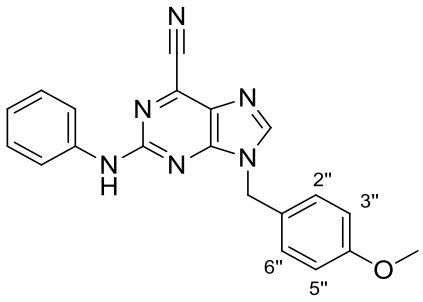
6-Chloro-9-(4-methoxybenzyl)-*N*-phenyl-9*H*-purin-2-amine (100)



4-Methoxybenzylchloride (0.33 mL, 2.43 mmol) was added dropwise to a stirred solution of 6-chloro-*N*-phenyl-9*H*-purin-2-amine (**99**) (0.15 g, 0.6 mmol) and K_2CO_3 (0.25 g, 1.83 mmol) in anhydrous DMF (15 mL). The resulting solution was gently warmed to 60 °C under nitrogen for 18 h. Upon addition of water (50 mL) and brine (6 mL) to the mixture, a white precipitate was observed. The mixture was extracted with DCM (2 × 30 mL) and the combined organics dried (Na_2SO_4). The *N*-9 regioisomer was separated by column chromatography on silica (50% EtOAc/petrol) as a white crystalline solid (114 mg, 52%); m.p. 166-168 °C; λ_{max} (EtOH/nm) 274, 225; IR (cm^{-1}) 3286, 2834, 1599, 1511; ^{1}H NMR (500 MHz, DMSO-d_6) 3.74 (3H, s, OCH_3), 5.35 (2H, s, CH_2), 6.93-6.95 (2H, d, *J* = 9.0 Hz, H-3'' and H-5''), 6.98-7.01 (1H, t, *J* = 8.5 Hz, H-4'), 7.30-7.34 (2H, dd, *J* = 8.0 and 8.5 Hz, H-3' and

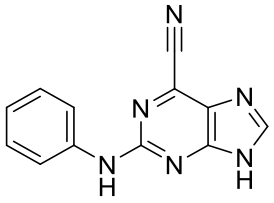
H-5'), 7.35-7.38 (2H, d, *J* = 9.0 Hz, H-2'' and H-6''), 7.76-7.79 (2H, d, *J* = 8.0 Hz, H-2' and H-6'), 8.04 (1H, s, H-8), 9.80 (1H, br s, NH); LRMS (ES^+) *m/z* 365.1 $[M+1]^+$.

6-Cyano-9-(4-methoxybenzyl)-2-(phenylamino)-9*H*-purine-6 (101)



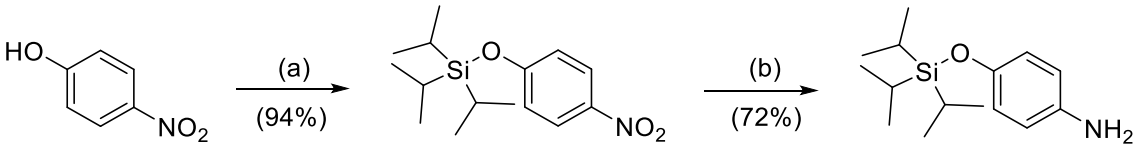
6-Chloro-9-(4-methoxybenzyl)-*N*-phenyl-9*H*-purin-2-amine (**100**) (0.10 g, 0.27 mmol) was suspended in anhydrous MeCN (10 mL) and stirred at room temperature. Addition of tetraethylamonium cyanide (86 mg, 0.55 mmol) followed by DABCO (61 mg, 0.55 mmol) afforded a yellow homogenous solution which was stirred for a further 18 h under nitrogen. Excess cyanide was hydrolysed by addition of aqueous ammonium hydroxide solution (32% v/v, 30 mL) with stirring for an additional 1 h. The crude mixture was partitioned between DCM (20 mL) and brine (20 mL). The organic layer was isolated and dried (Na_2SO_4) before purification by column chromatography on silica (50% EtOAc/petrol). The required compound was obtained as a bright yellow solid (62 mg, 62%); m.p. 242-244 °C; λ_{max} (EtOH) 356, 276; IR (cm^{-1}) 4000, 3470, 3293, 3180, 2258, 1611, 1584, 1511, 1471, 1245; ^{1}H NMR (500 MHz, DMSO-d_6) 3.73 (3H, s, OCH_3), 5.36 (2H, s, CH_2), 6.93-6.95 (2H, dd, *J* = 8.0, 8.5 Hz, H-3' and H-5'), 6.98-7.01 (1H, t, *J* = 8.5 Hz, H-4'), 7.34-7.39 (4H, m, H-2'', H-3'', H-5'' and H-6''), 7.73-7.75 (2H, d, *J* = 8.0 Hz, H-2' and H-6'), 8.66 (1H, s, H-8), 10.11 (1H, br s, NH); LRMS (ES^+) *m/z* 357.2 $[M+H]^+$.

6-Cyano-2-(phenylamino)-9*H*-purine (102)



6-Cyano-9-(4-methoxybenzyl)-2-(phenylamino)-9*H*-purine (**101**) (50 mg, 0.14 mmol) was dissolved in TFA (2 mL). The deep orange solution was heated at 70 °C for 5 h. The reaction mixture was concentrated *in vacuo* and the resulting orange oil was redissolved in EtOAc (2 mL). Residual TFA was neutralised by washing the organic phase with aqueous $NaHCO_3$ (2 × 2 mL). The organic extract was dried (Na_2SO_4) and purified using reversed phase column chromatography on silica (70% MeOH/H_2O + 0.1% HCOOH) to obtain a bright yellow solid (13 mg, 40%); m.p. 247-249 °C (decomposed); λ_{max} (EtOH/nm) 387, 272; IR (cm^{-1}) 3389, 2255, 1601, 1537, 1496, 1396, 1348; ^{1}H NMR (500 MHz, DMSO-d_6) 7.01 (1H, t, *J* = 8.5 Hz, H-4'), 7.34 (2H, dd, *J* = 8.0 and 8.5 Hz, H-3' and H-5'), 7.76 (2H, d, *J* = 8.0 Hz, H-2' and H-6'), 8.52 (1H, s, H-8), 9.99 (1H, br s, NH), 13.60 (1H, br s, NH-9); HRMS calcd for $C_{12}H_8N_6$ $[M+]^+$ 236.0738, found 236.0734.

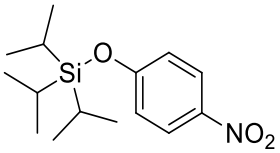
2. Synthesis of Aniline Precursors



103 **104** **105**

Scheme A. *Reagents and conditions:* (a) TIPSCl, imidazole, DCM, RT, 2 h; (b) Zn, AcOH, RT, 2.5 h.

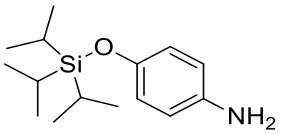
(4-Nitrophenoxy)triisopropylsilane (104)[11]



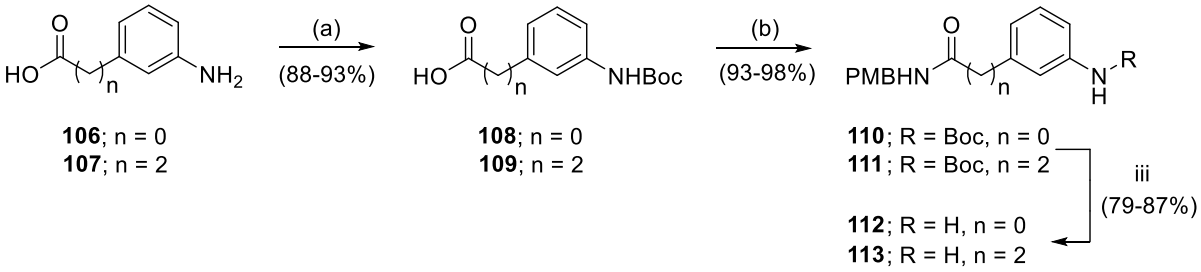
Imidazole (0.735 g, 10.8 mmol) was added to a solution of **103** (0.502 g, 3.60 mmol) in dry DCM (10 mL). Triisopropylsilyl chloride (1.5 mL, 7.20 mmol) was added, and the reaction mixture was stirred at RT for 2 h. The mixture was washed with sat. brine solution (2 × 10 mL) and the combined aqueous washings were extracted with DCM (3 × 10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the resulting residue was purified by chromatography on silica (Petrol). The desired compound was obtained as a colourless oil (0.998 g, 3.38 mmol, 94%); R_f 0.40 (Petrol); λ_{max} (EtOH/nm) 245, 295; IR (cm^{-1}) 2980, 2930, 2156; ^{1}H NMR (500 MHz, DMSO-d_6) 1.13 (18H, d, *J* = 7.6 Hz, Si(CH(CH_3)$_2$)$_3$),

1.38 (3H, sept, *J* = 7.6 Hz, Si(C*H*$(CH_3)_2)_3$), 7.14 (2H, d, *J* = 9.2 Hz, H-2 and H-6), 8.24 (2H, d, *J* = 9.2 Hz, H-3 and H-5); LRMS (ES+) *m*/*z* 296.2 $[M+H]^+$.

4-Triisopropylsilyloxyaniline (105)[12]

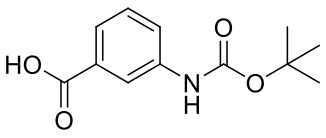


Zinc (0.454 g, 6.94 mmol) was added to a solution of the nitro compound **104** (0.205 g, 0.69 mmol) in acetic acid (10 mL) and the mixture was stirred at RT for 2.5 h. The solvent was removed *in vacuo* and the residue was dissolved in water. The solution was adjusted to pH 8 (conc. NH_3) and extracted with EtOAc (2 × 20 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated, and the residue was purified by chromatography on silica (9:1 Petrol/EtOAc). The desired compound was obtained as an orange oil (0.132 g, 0.50 mmol, 72%); R_f 0.76 (7:3 Petrol/EtOAc); λ_{max} (EtOH/nm) 236, 301; IR (cm^{-1}) 2944, 2866, 1613; ^{1}H NMR (500 MHz, DMSO-d_6) 0.94 (18H, d, *J* = 7.3 Hz, Si(CH(CH_3)$_2$)$_3$), 1.07 (3H, sept, *J* = 7.3 Hz, Si(C*H*$(CH_3)_2)_3$), 4.64 (2H, s, Ar-NH_2), 6.36 (2H, d, *J* = 8.9 Hz, H-2 and H-6), 6.47 (2H, d, *J* = 8.9 Hz, H-3 and H-5); LRMS (ES+) *m*/*z* 266.2 $[M+H]^+$.



Scheme B. *Reagents and conditions:* (a) Boc_2O, 1,4-dioxane, NaOH, H_2O, RT, 18 h; (b) PMB-NH_2, CDI, DIPEA, DMF, RT, 18 h; (c) TFA, DCM, RT, 18 h.

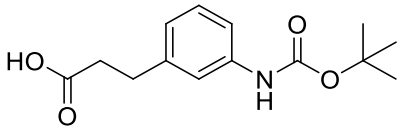
3-((*tert*-Butoxycarbonyl)amino)benzoic acid (108)[13]



3-Aminobenzoic acid **106** (1.00 g, 7.29 mmol) and di-*tert*-butyl dicarbonate (1.75 g, 8.02 mmol) were dissolved in 1,4-dioxane (15 mL), water (7.5 mL) and 0.5 M NaOH (15 mL). The reaction mixture was stirred at RT for 18 h, after which the volume was reduced by half *in vacuo* and the solution taken to pH 3 with 2 M $KHSO_4$ solution. The aqueous mixture was extracted with EtOAc (2 × 70 mL) and the combined organic extracts were dried ($MgSO_4$)

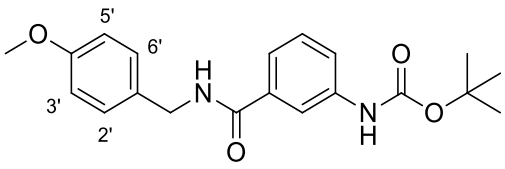
and concentrated in vacuo. The crude residue was purified by chromatography on silica and was obtained as a white waxy solid (1.61 g, 6.77 mmol, 93%); R_f 0.15 (1:1 Petrol/EtOAc); m.p. 183-185 °C (lit.[13] 189-190 °C); λ_{max} (EtOH/nm) 247, 301; IR (cm^{-1}) 3352, 3002, 2971, 1690; ^{1}H NMR (500 MHz, DMSO-d_6) 1.49 (9H, s, $C(CH_3)_3$), 7.37 (1H, dd, *J* = 7.9 and 8.0 Hz, H-5), 7.54 (1H, ddd, *J* = 1.2 and 1.3 and 7.9 Hz, H-6), 7.61-7.65 (1H, m, H-4), 8.13-8.16 (1H, m, H-2), 9.55 (1H, br, Ar-NH), 12.88 (1H, br, COOH); LRMS (ES-) *m*/*z* 236.2 $[M-H]^-$.

3-(3-(*tert*-Butoxycarbonylamino)phenyl)propanoic acid (109)



(3-Aminophenyl)propionic acid **107** (1.00 g, 6.06 mmol) and di-*tert*-butyl dicarbonate (1.45 g, 6.66 mmol) were dissolved in 1,4-dioxane (12 mL), 1 M NaOH (6 mL) and water (6 mL). The reaction mixture was stirred at RT for 18 h, after which the volume was reduced by half *in vacuo* and the solution taken to pH 3 with 2 M $KHSO_4$ solution. The aqueous mixture was extracted with EtOAc (2 × 60 mL) and the combined organic extracts were dried (MgSO4) and concentrated *in vacuo*. The crude residue was purified by chromatography on silica to give the desired product, which was obtained as an off-white waxy solid (1.42 g, 5.35 mmol, 88%); R_f 0.18 (1:1 Petrol/EtOAc); m.p. 120-123 °C; λ_{max} (EtOH/nm) 249, 276; IR (cm^{-1}) 3307, 2927, 1690; ^{1}H NMR (500 MHz, DMSO-d_6) 1.48 (9H, s, $C(CH_3)_3$), 2.50 (2H, t, *J* = 7.7 Hz, $COCH_2CH_2$), 2.76 (2H, t, *J* = 7.7 Hz, $COCH_2CH_2$), 6.81-6.85 (1H, m, H-6), 7.11-7.16 (1H, m, H-5), 7.22-7.26 (1H, m, H-4), 7.34-7.37 (1H, m, H-2), 9.27 (1H, s, Ar-NH), 12.13 (1H, s, COOH); HRMS calcd. for $C_{14}H_{18}NO_4$ (ES-) *m*/*z* 264.1241 $[M-H]^-$, found 264.1233.

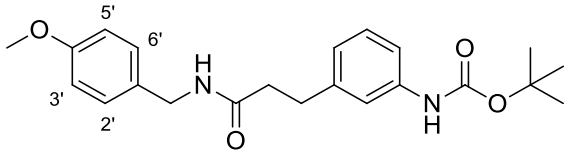
***tert*-Butyl 3-(4-methoxybenzylcarbamoyl)phenyl carbamate (110)**



Carboxylic acid **108** (0.601 g, 2.53 mmol), CDI (0.823 g, 5.07 mmol) and DIPEA (885 µL, 5.07 mmol) were combined in dry DMF (13 mL) and stirred at RT for 1.5 h. 4-methoxybenzylamine (1.31 mL, 10.1 mmol) was added to the mixture. Following a further 18 h stirring at RT, the solvent was removed *in vacuo* and the resulting residue was purified by chromatography on silica (7:3 Petrol/EtOAc). The desired compound was obtained as a

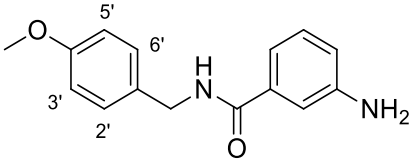
white solid (0.841 g, 2.36 mmol, 93%); R_f 0.27 (7:3 Petrol/EtOAc); m.p. 166-170 °C; λ_{max} (EtOH/nm) 234; IR (cm^{-1}) 3349, 3274, 3062, 2931, 2836, 1697, 1644; ^{1}H NMR (500 MHz, DMSO-d_6) 1.49 (9H, s, $C(CH_3)_3$), 3.74 (3H, s, OCH_3), 4.38 (2H, d, *J* = 6.0 Hz, CH_2NH), 6.89 (2H, d, *J* = 8.4 Hz, H-3' and H-5'), 7.24 (2H, d, *J* = 8.4 Hz, H-2' and H-6'), 7.33 (1H, dd, *J* = 7.9 and 8.1 Hz, H-5), 7.43-7.47 (1H, m, H-4), 7.52-7.56 (1H, m, H-6), 7.98-8.00 (1H, m, H-2), 8.89 (1H, t, *J* = 6.0 Hz, CH_2NH), 9.48 (1H, s, Ar-NH); HRMS calcd. for $C_{20}H_{25}N_2O_4$ (ES+) *m*/*z* 357.1809 $[M+H]^+$, found 357.1812.

tert-Butyl-3-(2-(4-methoxybenzylcarbamoyl)ethyl)phenyl carbamate (111)



Carboxylic acid **109** (0.762 g, 2.87 mmol), CDI (0.932 g, 5.74 mmol) and DIPEA (1.00 mL, 5.74 mmol) were combined in dry DMF (15 mL) and stirred at RT for 1.5 h. 4-methoxybenzylamine (1.50 mL, 11.5 mmol) was added to the mixture. Following a further 18 h stirring at RT, the solvent was removed *in vacuo* and the resulting residue was purified by chromatography on silica (1:1 Petrol/EtOAc) to afford the desired compound as a colourless oil (1.08 g, 2.80 mmol, 98%); R_f 0.48 (1:1 Petrol/EtOAc); λ_{max} (EtOH/nm) 232, 274; IR (cm^{-1}) 3363, 3271, 2971, 2933, 1698, 1643; ^{1}H NMR (500 MHz, DMSO-d_6) 1.47 (9H, s, $C(CH_3)_3$), 2.40 (2H, t, *J* = 7.6 Hz, CH_2CH_2), 2.78 (2H, t, *J* = 7.6 Hz, CH_2CH_2), 3.72 (3H, s, OCH_3), 4.18 (2H, d, *J* = 5.9 Hz, CH_2NH), 6.79-6.83 (1H, m, H-4), 6.84 (2H, d, *J* = 8.4 Hz, H-3' and H-5'), 7.07 (2H, d, *J* = 8.4 Hz, H-2' and H-6'), 7.14 (1H, dd, *J* = 8.1 and 8.2 Hz, H-5), 7.21-7.24 (1H, m, H-6), 7.35-7.38 (1H, m, H-2), 8.25 (1H, t, *J* = 5.9 Hz, CH_2NH), 9.27 (1H, s, Ar-NH); HRMS calcd. for $C_{22}H_{29}N_2O_4$ (ES+) *m*/*z* 385.2122 $[M+H]^+$, found 385.2126.

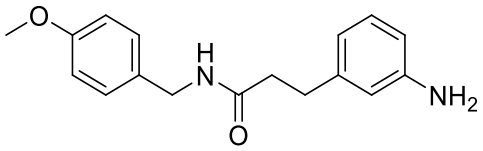
***N*-(4-Methoxybenzyl)-3-aminobenzamide (112)**



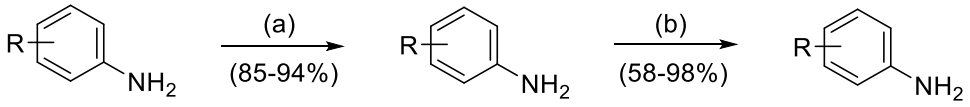
Boc-protected aniline **110** (0.831 g, 2.33 mmol) was treated with TFA (1.80 mL, 23.3 mmol) in DCM (25 mL), which was stirred at RT for 18 h, before diluting with DCM (25 mL). The crude mixture was washed with sat. aqueous $NaHCO_3$ (25 mL). The resulting biphasic

mixture was passed through an Isolute® phase separator, and the organic phase concentrated to dryness. The resulting crude residue was purified by chromatography on silica (1:1 Petrol/EtOAc), giving the target compound as a white waxy solid (0.472 g,1.84 mmol, 79%); R_f 0.30 (1:1 Petrol/EtOAc); m.p. 90-93 °C; λ_{max} (EtOH/nm) 242, 306; IR (cm^{-1}) 3349, 3274, 2972, 2930, 1697, 1643; ^{1}H NMR (500 MHz, DMSO-d_6) 3.73 (3H, s, OCH_3), 4.36 (2H, d, *J* = 6.1 Hz, C*H*$_2$NH), 5.22 (2H, s, Ar-NH_2), 6.89 (1H, ddd, *J* = 2.3 and 2.4 and 7.9 Hz, H-4), 6.88 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 6.97-7.00 (1H, m, H-6), 7.04-7.09 (2H, m, H-2 and H-5), 7.23 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 8.73 (1H, t, *J* = 6.1 Hz, CH_2N*H*); HRMS calcd. for $C_{15}H_{17}N_2O_2$ (ES+) *m*/*z* 257.1285 $[M+H]^+$, found 257.1289.

_N_-(4-Methoxybenzyl)-3-(3-aminophenyl)propanamide (113)



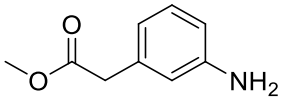
Boc-protected aniline **111** (1.00 g, 2.60 mmol) was treated with TFA (2.00 mL, 26.0 mmol) in DCM (25 mL), which was stirred at RT for 18 h, before diluting with DCM (25 mL). The crude mixture was washed with sat. aqueous $NaHCO_3$ (25 mL). The resulting biphasic mixture was passed through an Isolute® phase separator, and the organic phase concentrated to dryness. The resulting crude residue was purified by chromatography on silica (1:1 Petrol/EtOAc) affording the desired compound as a white solid (0.643 g, 2.26 mmol, 87%); R_f 0.46 (1:1 Petrol/EtOAc); m.p. 88-91 °C; λ_{max} (EtOH/nm) 231, 274; IR (cm^{-1}) 3424, 3337, 3241, 3063, 2945, 2904, 1629; ^{1}H NMR (500 MHz, DMSO-d_6) 2.36 (2H, t, *J* = 7.8 Hz, C*H*$_2$$CH_2$), 2.67 (2H, t, *J* = 7.8 Hz, CH_2C*H*$_2$), 3.73 (3H, s, OCH_3), 4.18 (2H, d, *J* = 5.9 Hz, C*H*$_2$NH), 4.95 (2H, s, Ar-NH_2), 6.33-6.40 (3H, m, H-2, H-4 and H-6), 6.86 (2H, d, *J* = 7.9 Hz, H-3' and H-5'), 6.90 (1H, dd, *J* = 7.4 and 7.5 Hz, H-5), 7.11 (2H, d, *J* = 7.9 Hz, H-2' and H-6'), 8.25 (1H, t, *J* = 5.9 Hz, CH_2N*H*); HRMS calcd. for $C_{17}H_{21}N_2O_2$ (ES+) *m*/*z* 285.1598 $[M+H]^+$, found 285.1603.



114; R = 3-CH_2CO_2H
115; R = 4-CO_2H
116; R = 3-CH_2CO_2Me
117; R = 4-CO_2Me
118; R = 3-$CH_2CONHMe$
119; R = 4-$CONH_2$
120; R = 4-CONHMe

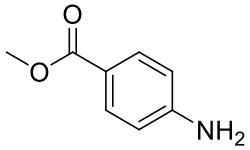
Scheme C: *Reagents and conditions:* (a) $SOCl_2$, MeOH, reflux, 1 h; (b) Aq. RNH_2, RT to 60 °C, 18 h.

Methyl 2-(3-aminophenyl)acetate (116)[14]



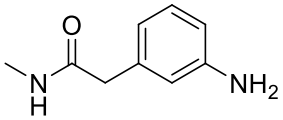
(3-Aminophenyl)acetic acid (1.00 g, 6.62 mmol) and thionyl chloride (970 µL, 13.2 mmol) were combined in dry MeOH (35 mL). The resulting solution was heated at reflux for 1 h, after which the solvent was removed *in vacuo*. The crude residue was purified by chromatography on silica (7:3 Petrol/EtOAc) to give the target compound as a pale yellow oil (0.927 g, 5.61 mmol, 85%); R_f 0.32 (7:3 Petrol/EtOAc); λ_{max} (EtOH/nm) 221, 285; IR (cm^{-1}) 3369, 2952, 1724; ^{1}H NMR (500 MHz, DMSO-d_6) 3.50 (2H, s, CH_2), 3.61 (3H, s, OCH_3), 5.70 (2H, br, Ar-NH_2), 6.45-6.48 (1H, m, H-4), 6.51-6.54 (2H, m, H-2 and H-6), 6.97-7.01 (1H, m, H-5); LRMS (ES+) *m*/*z* 166.2 $[M+H]^+$.

Methyl 4-aminobenzoate (117)[15]



4-Aminobenzoic acid (0.500 g, 3.65 mmol) and thionyl chloride (0.53 mL, 7.29 mmol) were combined in dry methanol (20 mL). The resulting solution was heated at reflux for 1 h, after which the solvent was removed *in vacuo*. The crude residue was purified by chromatography on silica (7:3 Petrol/EtOAc) to afford the desired compound as a white solid (0.520 g, 3.44 mmol, 94%); R_f 0.42 (7:3 Petrol/EtOAc); m.p. 111-114 °C (lit.[5] 109-110 °C); λ_{max} (EtOH/nm) 255, 309; IR (cm^{-1}) 3407, 3336, 3298, 2944, 1681; ^{1}H NMR (500 MHz, DMSO-d_6) 3.74 (3H, s, OCH_3), 5.97 (2H, s, Ar-NH_2), 6.57 (2H, d, *J* = 8.8 Hz, H-3 and H-5), 7.64 (2H, d, *J* = 8.8 Hz, H-2 and H-6); LRMS (ES+) *m*/*z* 152.2 $[M+H]^+$.

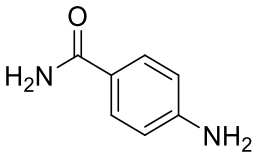
2-(3-Aminophenyl)-*N*-methylacetamide (118)[16]



Methyl ester **116** (0.250 g, 1.51 mmol) was suspended in a concentrated aqueous solution of methylamine (40%, 8 mL) and the resulting mixture was stirred at RT for 24 h. Chromatography on silica (9:1 DCM/MeOH) afforded the desired compound as a pale yellow

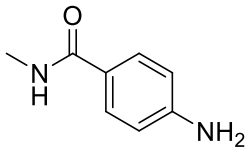
oil (0.233 g, 1.42 mmol, 94%); R_f 0.38 (9:1 DCM/MeOH); λ_{max} (EtOH/nm) 220; IR (cm^{-1}) 3331, 3091, 2943, 1629; ^{1}H NMR (500 MHz, DMSO-d_6) 2.56 (3H, d, J = 4.8 Hz, NHCH_3), 3.20 (2H, s, CH_2), 4.98 (2H, s, Ar-NH_2), 6.37-6.41 (2H, m, H-4 and H-6), 6.42-6.45 (1H, br, H-2), 6.91 (1H, dd, J = 7.7 and 7.9 Hz, H-5), 7.82 (1H, br, NHCH$_3$); LRMS (ES+) m/z 165.2 $[M+H]^+$.

4-Aminobenzamide (119)[17]

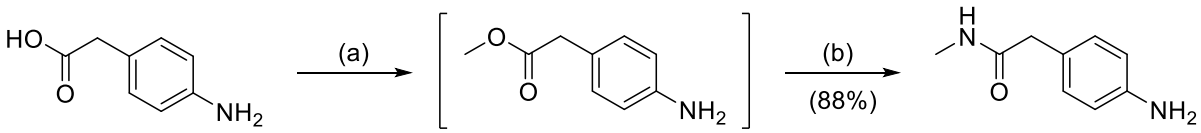


Methyl ester **117** (0.408 g, 2.70 mmol) was dissolved in concentrated ammonium hydroxide (10 mL) and the resulting solution was heated at 60 °C for 18 h. The solvent was removed *in vacuo* and the crude product was purified by chromatography on KP-NH silica (19:1 DCM/MeOH) to give the desired compound as a white solid (0.214 g, 1.57 mmol, 58%); R_f 0.31 (19:1 DCM/MeOH); m.p. 178-181 °C (lit.[17] 175-179 °C); λ_{max} (EtOH/nm) 230, 262; IR (cm^{-1}) 3463, 3317, 3205, 1591; ^{1}H NMR (500 MHz, DMSO-d_6) 5.59 (2H, s, Ar-NH_2), 6.52 (2H, d, J = 8.6 Hz, H-3 and H-5), 6.82 (1H, br, CONHH'), 7.50 (1H, br, CONHH'), 7.58 (2H, d, J = 8.6 Hz, H-2 and H-6); LRMS (ES+) m/z 137.1 $[M+H]^+$.

4-Amino-*N*-methylbenzamide (120)[17]



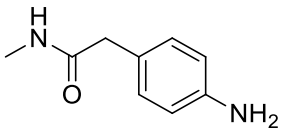
Methyl ester **117** (0.413 g, 2.70 mmol) was suspended in a concentrated aqueous solution of methylamine (40%, 10 mL) and the reaction mixture was stirred at RT for 24 h. The solvent was removed *in vacuo* and the crude residue was purified by chromatography on silica (19:1 DCM/MeOH) to afford the desired compound as a pale yellow solid (0.396 g, 2.64 mmol, 98%); R_f 0.36 (19:1 DCM/MeOH); m.p. 173-176 °C (lit.[17] 178-180 °C); λ_{max} (EtOH/nm) 236, 270; IR (cm^{-1}) 3399, 3336, 3228, 2934, 1627; ^{1}H NMR (500 MHz, DMSO-d_6) 2.72 (3H, d, J = 4.6 Hz, NHCH_3), 5.57 (2H, s, Ar-NH_2), 6.53 (2H, d, J = 8.6 Hz, H-3 and H-5), 7.55 (2H, d, J = 8.6 Hz, H-2 and H-6), 7.94 (1H, br, NHCH$_3$); LRMS (ES+) m/z 151.2 $[M+H]^+$.



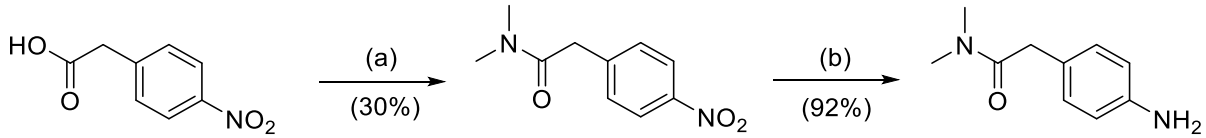
114 **121**

Scheme D. *Reagents and conditions*: (a) $SOCl_2$, MeOH, reflux, 1 h; (b) Aq. $MeNH_2$, RT, 18 h.

2-(4-Aminophenyl)-*N*-methylacetamide (121)[17]



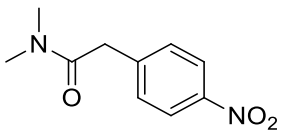
4-Aminophenylacetic acid (0.601 g, 3.97 mmol) and thionyl chloride (0.58 mL, 7.94 mmol) were combined in methanol (20 mL) and heated at reflux for 1 h, after which the solvent was removed *in vacuo*. A concentrated aqueous solution of methylamine (40% aqueous solution, 20 mL) was added to the residue and the reaction mixture was stirred at RT for 24 h. The solvent was removed *in vacuo* and the crude residue was purified by chromatography on silica (19:1 DCM/MeOH), affording the desired product as a pale orange oil (0.573 g, 3.49 mmol, 88%); R_f 0.39 (19:1 DCM/MeOH); λ_{max} (EtOH/nm) 242, 291; IR (cm^{-1}) 3444, 3347, 3308, 3098, 1618, 1556, 1515; ^{1}H NMR (500 MHz, DMSO-d_6) 2.55 (3H, d, *J* = 4.6 Hz, NHCH_3), 3.18 (2H, s, $COCH_2$), 4.89 (2H, s, Ar-NH_2), 6.49 (2H, d, *J* = 8.4 Hz, H-3 and H-5), 6.89 (2H, d, *J* = 8.4 Hz, H-2 and H-6), 7.74 (1H, br, N*H*CH_3); LRMS (ES+) *m*/*z* 165.1 $[M+H]^+$.



122 **123** **124**

Scheme E. *Reagents and conditions:* (a) i) CDI, DIPEA, DMF, RT, 1.5 h, ii) MeRNH, THF, RT, 18 h. (b) Fe, AcOH, 50 °C, 15 min.

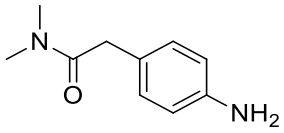
***N*,*N*-Dimethyl-2-(4-nitrophenyl)acetamide (123)[18]**



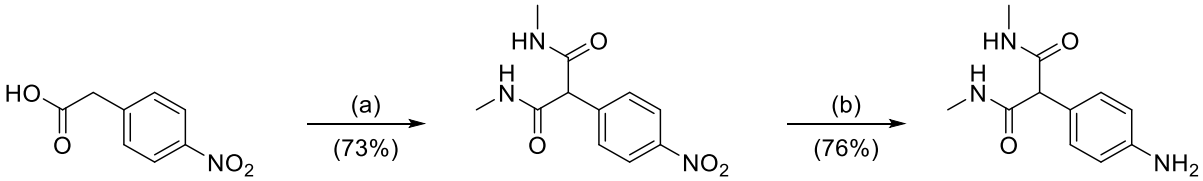
4-Nitrophenylacetic acid (0.600 g, 3.31 mmol), CDI (1.07 g, 6.62 mmol) and DIPEA (1.15 mL, 6.62 mmol) were combined in dry DMF (30 mL) and stirred at RT for 1.5 h. Dimethylamine (2M in THF, 6.60 mL, 13.2 mmol) was added to the mixture and stirring was continued at RT for a further 18 h. The solvent was removed *in vacuo* and the resulting residue was purified by chromatography on silica (7:3 Petrol/EtOAc), affording the target compound as an off-white solid (0.204 g, 0.98 mmol, 30%); R_f 0.38 (7:3 Petrol/EtOAc); m.p. 80-83 °C (lit.[18] 87 °C);

λ_{max} (EtOH/nm) 270; IR (cm^{-1}) 2937, 2449, 1637, 1512; ^{1}H NMR (500 MHz, $CDCl_3$) 3.01 (3H, s, NCH_3), 3.08 (3H, s, NCH_3), 3.83 (2H, s, $COCH_2$), 7.45 (2H, d, *J* = 8.5 Hz, H-2 and H-6), 8.21 (2H, d, *J* = 8.5 Hz, H-3 and H-5); LRMS (ES+) *m*/*z* 209.1 $[M+H]^+$.

2-(4-Aminophenyl)-*N*,*N*-dimethylacetamide (124)[19]



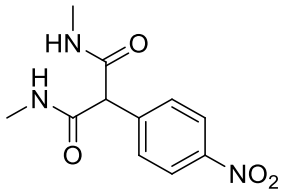
Iron powder (0.355 g, 6.39 mmol) was added to a solution of nitro compound **123** (0.133 g, 0.64 mmol) in acetic acid (6 mL) and the resulting mixture was heated at 50 °C for 15 min, before being filtered through Celite® and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (200 mL) and washed with a sat. aqueous solution of $NaHCO_3$ (2 × 200 mL) and brine (200 mL). The combined aqueous layers were extracted with EtOAc (200 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. Chromatography on silica (9:1 DCM/MeOH) gave the desired compound as a pale red oil (0.105 g, 0.58 mmol, 92%); R_f 0.40 (9:1 DCM/MeOH); λ_{max} (EtOH/nm) 242, 291; IR (cm^{-1}) 3414, 3342, 3230, 2933, 1611, 1515; ^{1}H NMR (500 MHz, DMSO-d_6) 2.81 (3H, s, NCH_3), 2.96 (3H, s, NCH_3), 3.46 (2H, s, $COCH_2$), 4.89 (2H, s, Ar-NH_2), 6.50 (2H, d, *J* = 8.4 Hz, H-3 and H-5), 6.86 (2H, d, *J* = 8.4 Hz, H-2 and H-6); LRMS (ES+) *m*/*z* 179.1 $[M+H]^+$.



122 **125** **126**

Scheme F. *Reagents and conditions:* (a) i) CDI, DIPEA, DMF, RT, 1.5 h, ii) Methylamine, THF, RT, 18 h. (b) Fe, AcOH, 50 °C, 15 min.

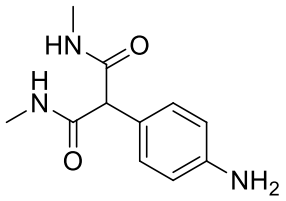
***N*^{1},*N*^{3}-Dimethyl-2-(4-nitrophenyl)malonamide (125)**



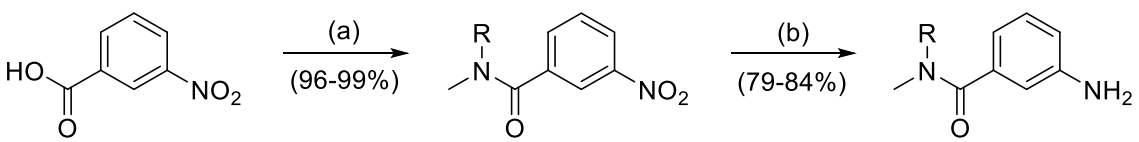
4-Nitrophenylacetic acid (0.598 g, 3.31 mmol), CDI (1.07 g, 6.62 mmol) and DIPEA (1.15 mL, 6.62 mmol) were combined in dry DMF (30 mL) and stirred at RT for 1.5 h. Methylamine (2M in THF, 6.60 mL, 13.2 mmol) was added to the mixture and stirred at RT for a further 18 h.

The solvent was removed *in vacuo* and the resulting residue was purified by chromatography on silica (7:3 Petrol/EtOAc) to give the desired compound as an off-white solid (0.608 g, 2.42 mmol, 73%); R_f 0.33 (7:3 Petrol/EtOAc); m.p. 221-224 °C; λ_{max} (EtOH/nm) 273; IR (cm^{-1}) 3405, 3311, 3111, 2932, 1655, 1512; ^{1}H NMR (500 MHz, DMSO-d_6) 2.62 (6H, d, *J* = 4.6 Hz, 2 x NHC*H*$_3$), 4.57 (1H, s, COC*H*CO), 7.65 (2H, d, *J* = 8.8 Hz, H-2 and H-6), 8.11 (2H, q, *J* = 4.6 Hz, 2 x NH), 8.21 (2H, d, *J* = 8.8 Hz, H-3 and H-5); HRMS calcd. for $C_{11}H_{14}N_3O_4$ (ES+) *m*/*z* 252.0979 $[M+H]^+$, found 252.0983.

2-(4-Aminophenyl)-*N*^{1},*N*^{3}-dimethylmalonamide (126)



Iron powder (1.70 g, 30.5 mmol) was added to a solution of nitro compound **125** (0.593 g, 3.05 mmol) in acetic acid (30 mL). The reaction mixture was heated at 50 °C for 15 min, before being filtered through Celite® and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (200 mL) and washed with a sat. aqueous solution of $NaHCO_3$ (2 × 200 mL) and brine (200 mL). The combined aqueous layers were extracted with EtOAc (200 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. The resulting residue was purified by chromatography on silica (9:1 DCM/MeOH) to give the desired compound as a beige waxy solid (0.380 g, 2.32 mmol, 76%); R_f 0.35 (9:1 DCM/MeOH); m.p. 148-150 °C; λ_{max} (EtOH/nm) 248, 292; IR (cm^{-1}) 3414, 3273, 3100, 2937, 1663, 1650, 1515; ^{1}H NMR (500 MHz, DMSO-d_6) 2.59 (6H, d, *J* = 4.6 Hz, 2 x NHC*H*$_3$), 4.11 (1H, s, COC*H*CO), 5.00 (2H, s, Ar-NH_2), 6.49 (2H, d, *J* = 8.5 Hz, H-3 and H-5), 7.00 (2H, d, *J* = 8.5 Hz, H-2 and H-6), 7.94 (2H, q, *J* = 4.6 Hz, 2 x N*H*CH_3); HRMS calcd. for $C_{11}H_{16}N_3O_2$ (ES+) *m*/*z* 222.1237 $[M+H]^+$, found 222.1239.



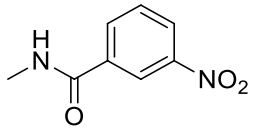
127

128; R = H
129; R = CH_3

130; R = H
131; R = CH_3

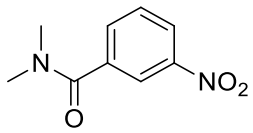
Scheme G: *Reagents and conditions*: (a) R_2-NH, PCl_3, MeCN, MW 150 °C, 5 min; (b) Fe, AcOH, 50 °C, 15 min.

***N*-Methyl-3-nitrobenzamide (128)**[20]



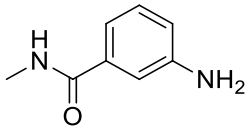
Phosphorus trichloride (288 µL, 3.29 mmol) was added to a solution of 3-nitrobenzoic acid (0.502 g, 2.99 mmol) and methylamine (2M in THF, 3.74 mL, 7.48 mmol) in dry MeCN (15 mL) in a sealed vial. The reaction mixture was heated under microwave irradiation at 150 °C for 5 min, before being concentrated to dryness. The resulting residue was dissolved in DCM (30 mL) and washed with a sat. aqueous solution of $NaHCO_3$ (30 mL). The biphasic mixture was passed through an Isolute® phase separator and the organic phase was concentrated *in vacuo*. Purification by chromatography on silica (7:3 Petrol/EtOAc) gave the desired compound as a beige solid (0.535 g, 2.97 mmol, 99%); R_f 0.33 (7:3 Petrol/EtOAc); m.p. 175-177 °C (lit.[20] 175 °C); λ_{max} (EtOH/nm) 241; IR (cm^{-1}) 3352, 3285, 3093, 1637, 1619, 1559, 1524; ^{1}H NMR (500 MHz, DMSO-d_6) 2.83 (3H, d, *J* = 4.6 Hz, NHCH_3), 7.79 (1H, dd, *J* = 7.9 and 8.0 Hz, H-5), 8.28 (1H, ddd, *J* = 1.0, 1.6 and 7.9 Hz, H-6), 8.38 (1H, ddd, *J* = 1.0, 2.4 and 8.0 Hz, H-4), 8.65-8.68 (1H, m, H-2), 8.84 (1H, br, N*H*CH_3); LRMS (ES+) *m*/*z* 181.1 $[M+H]^+$.

***N*,*N*-Dimethyl-3-nitrobenzamide (129)**[21]



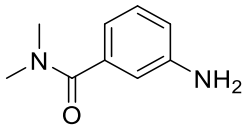
Phosphorus trichloride (288 µl, 3.29 mmol) was added to a solution of 3-nitrobenzoic acid (0.499 g, 2.99 mmol) and dimethylamine (2M in THF, 3.74 mL, 7.48 mmol) in dry MeCN (15 mL) in a sealed vial. The reaction mixture was heated under microwave irradiation at 150 C for 5 min, before being concentrated to dryness. The resulting residue was dissolved in DCM (30 mL) and washed with a sat. aqueous solution of $NaHCO_3$ (30 mL). The biphasic mixture was passed through an Isolute® phase separator and the organic phase was concentrated *in vacuo*. Chromatography on silica (7:3 Petrol/EtOAc) gave the target compound as a beige solid (0.560 g, 2.88 mmol, 96%); R_f 0.36 (7:3 Petrol/EtOAc); m.p. 81-84 °C (lit.[21] 83-84 °C); λ_{max} (EtOH/nm) 243; IR (cm^{-1}) 3083, 2941, 1626, 1527; ^{1}H NMR (500 MHz, $CDCl_3$) 3.03 (3H, s, NCH_3), 3.18 (3H, s, NCH_3), 7.64 (1H, dd, *J* = 7.7 and 8.0 Hz, H-5), 7.80 (1H, ddd, *J* = 1.2, 1.4 and 7.7 Hz, H-6), 8.29-8.33 (2H, m, H-2/H-4); LRMS (ES-) *m*/*z* 195.1 $[M+H]^+$.

3-Amino-*N*-methylbenzamide (130)[22]

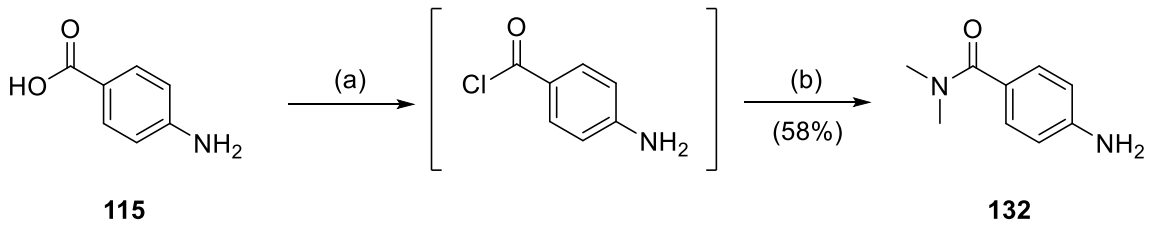


Iron powder (1.30 g, 23.3 mmol) was added to a solution of nitro compound **128** (0.420 g, 2.33 mmol) in acetic acid (20 mL) and was heated at 50 °C for 15 min, before being filtered through Celite® and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (200 mL) and washed with a sat. aqueous solution of $NaHCO_3$ (2 × 200 mL) and brine (200 mL). The combined aqueous layers were extracted with EtOAc (200 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. Purification by chromatography on silica (19:1 DCM/MeOH) gave the desired compound as a beige solid (0.276 g, 1.84 mmol, 79%); R_f 0.38 (19:1 DCM/MeOH); m.p. 98-100 °C (lit.[22] m.p. not available); λ_{max} (EtOH/nm) 217, 313; IR (cm^{-1}) 3465, 3412, 3294, 3221, 1634, 1580, 1547; ^1H NMR (500 MHz, DMSO-d_6) 2.74 (3H, d, *J* = 4.6 Hz, NHCH_3), 5.19 (2H, s, Ar-NH_2), 6.67 (1H, ddd, *J* = 1.0, 2.4 and 7.9 Hz, H-4), 6.92 (1H, ddd, *J* = 1.0, 1.6 and 7.7 Hz, H-6), 7.02 (1H, dd, *J* = 1.6 and 2.4 Hz, H-2), 7.06 (1H, dd, *J* = 7.7 and 7.9 Hz, H-5), 8.15 (1H, q, *J* = 4.6 Hz, N*H*CH_3); LRMS (ES+) *m*/*z* 151.1 $[M+H]^+$.

3-Amino-*N*,*N*-dimethylbenzamide (131)[21]



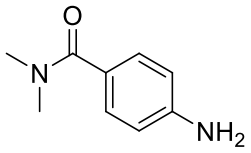
Iron powder (0.57 g, 10.3 mmol) was added to a solution of nitro compound **129** (0.200 g, 1.03 mmol) in acetic acid (10 mL). The reaction mixture was heated at 50 °C for 15 min, before being filtered through Celite® and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (200 mL) and washed with a sat. aqueous solution of $NaHCO_3$ (2 × 200 mL) and brine (200 mL). The combined aqueous layers were extracted with EtOAc (200 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. Purification by chromatography on silica (19:1 DCM/MeOH) gave the target compound as a golden oil (0.142 g, 0.86 mmol, 84%); R_f 0.41 (19:1 DCM/MeOH); λ_{max} (EtOH/nm) 243, 302; IR (cm^{-1}) 3413, 3342, 3232, 2930, 1598, 1579; ^1H NMR (500 MHz, DMSO-d_6) 2.90 (3H, s, NCH_3), 2.94 (3H, s, NCH_3), 5.21 (2H, s, Ar-NH_2), 6.46 (1H, ddd, *J* = 1.1, 1.4 and 7.4 Hz, H-4), 6.54 (1H, dd, *J* = 1.4 and 2.3 Hz, H-2), 6.59 (1H, ddd, *J* = 1.1, 2.3 and 8.0 Hz, H-6), 7.05 (1H, dd, *J* = 7.4 and 8.0 Hz, H-5); LRMS (ES+) *m*/*z* 165.1 $[M+H]^+$.



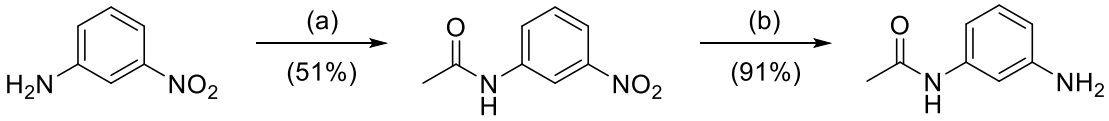
115 **132**

Scheme H. *Reagents and conditions:* (a) $SOCl_2$, DMF, reflux, 1 h; (b) Me_2NH, Et_3N, THF, RT, 18 h.

4-Amino-*N,N*-dimethylbenzamide (132)[23]



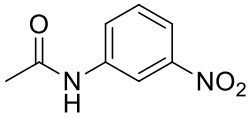
4-Aminobenzoic acid (0.500 g, 3.65 mmol) was dissolved in thionyl chloride (5 mL) and 1 drop of DMF was added. The solution was refluxed for 1 h then concentrated to dryness. Remaining thionyl chloride was removed through addition of toluene (5 mL) and removal of the azeotrope *in vacuo*. The resultant orange residue was suspended in dry THF (4 mL) and triethylamine (530 µL, 3.65 mmol), and dimethylamine (2M in THF, 5.50 mL, 10.9 mmol) was added under nitrogen. The reaction mixture was stirred at RT for 18 h, after which the solvent was removed *in vacuo* and the resultant residue was purified by chromatography on silica (19:1 DCM/MeOH). The desired compound was obtained as an off-white solid (0.348 g, 2.12 mmol, 58%); R_f 0.40 (19:1 DCM/MeOH); m.p. 150-153 °C (lit.[23] 153 °C); λ_{max} (EtOH/nm) 220, 272; IR (cm^{-1}) 3428, 3335, 3236, 2925, 1642; ^{1}H NMR (500 MHz, DMSO-d_6) 2.94 (6H, s, $N(CH_3)_2$), 5.47 (2H, s, Ar-NH_2), 6.54 (2H, d, *J* = 8.6 Hz, H-3 and H-5), 7.14 (2H, d, *J* = 8.6 Hz, H-2 and H-6); LRMS (ES+) *m/z* 165.2 $[M+H]^+$.



133 **134** **135**

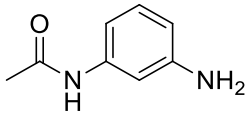
Scheme I: *Reagents and conditions:* (a) Ac_2O, RT, 30 min; (b) Fe, AcOH, 50 °C, 15 min.

***N*-(3-Nitrophenyl)acetamide (134)[24]**

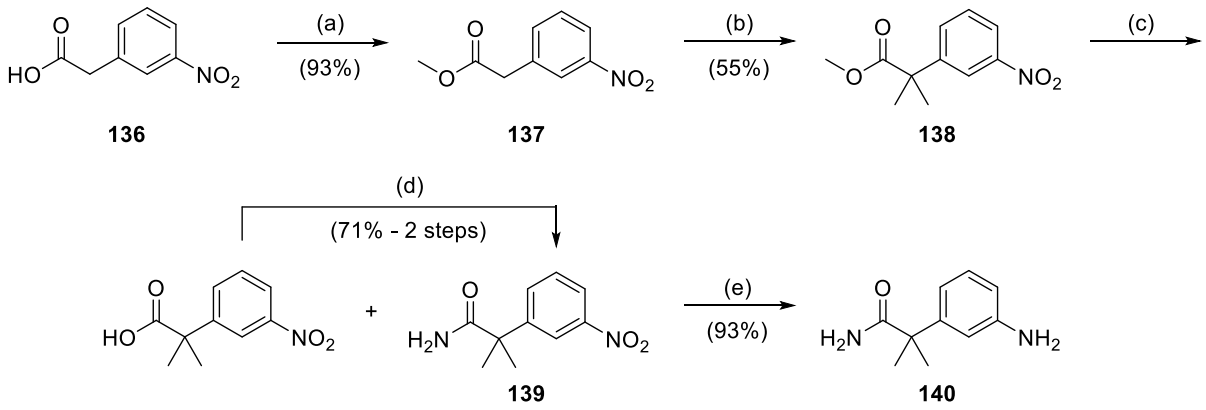


3-Nitroaniline (0.503 g, 3.62 mmol) was added to acetic anhydride at RT. The yellow solution was stirred at RT for 30 mins, over which time a white precipitate formed. Water (20 mL) was added, and the mixture was extracted with DCM (2 × 40 mL). The combined organic extracts were washed with 1M HCl (20 mL), sat. $NaHCO_3$ solution (20 mL) and brine (20 mL). The organic phase was dried ($MgSO_4$) and concentrated *in vacuo*, and the resultant crude was triturated with Et_2O (20 mL). The desired product was obtained as a white solid, collected by filtration (0.334 g, 1.85 mmol, 51%); R_f 0.27 (7:3 Petrol/EtOAc); m.p. 153-156 °C (lit.[24] 152-153 °C); λ_{max} (EtOH/nm) 241, 329; IR (cm^{-1}) 3261, 3193, 3129, 3097, 1672, 1599, 1547, 1526; ^1H NMR (500 MHz, DMSO-d_6) 2.10 (3H, s, CH_3), 7.60 (1H, dd, *J* = 8.2 and 8.3 Hz, H-5), 7.88-7.91 (2H, m, H-4 and H-6), 8.62 (1H, dd, *J* = 2.1 and 2.2 Hz, H-2); LRMS (ES+) *m*/*z* 181.1 $[M+H]^+$.

_N_-(3-Aminophenyl)acetamide (135)[25]

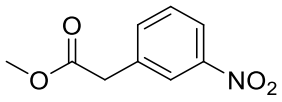


Iron powder (0.845 g, 15.1 mmol) was added to a solution of nitro compound **134** (0.272 g, 1.51 mmol) in acetic acid (15 mL). The reaction mixture was heated at 50 °C for 15 min, before being filtered through Celite® and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (200 mL) and washed with a sat. aqueous solution of $NaHCO_3$ (2 × 200 mL) and brine (200 mL). The combined aqueous layers were extracted with EtOAc (200 mL/mmol) and the combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. Purification by chromatography on silica (9:1 DCM/MeOH) afforded the desired compound as a pale red oil (0.206 g, 1.37 mmol, 91%); R_f 0.46 (9:1 DCM/MeOH); λ_{max} (EtOH/nm) 223, 297; IR (cm^{-1}) 3245, 3074, 2621, 1658, 1608, 1545; ^1H NMR (500 MHz, DMSO-d_6) 1.99 (3H, s, CH_3), 5.01 (2H, s, Ar-NH_2), 6.21-6.25 (1H, m, H-4), 6.63-6.67 (1H, m, H-6), 6.89 (1H, dd, *J* = 7.9 and 8.0 Hz, H-5), 6.92 (1H, dd, *J* = 1.8 and 1.9 Hz, H-2), 9.58 (1H, s, NH); LRMS (ES+) *m*/*z* 151.1 $[M+H]^+$.



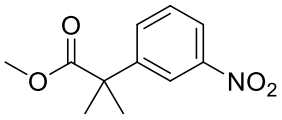
Scheme J: *Reagents and conditions:* (a) $SOCl_2$, MeOH, reflux, 1 h; (b) NaH, MeI, THF, 0 °C to RT, 18 h; (c) Conc. NH_4OH, 60 °C, 18 h; (d) i) $SOCl_2$, DMF, DCM, RT, 15 min, ii) Conc. NH_4OH, THF, RT, 18 h; (e) Pd/C, NH_4HCOO, MeOH, RT, 18 h.

Methyl 2-(3-nitrophenyl)acetate (137)[26]



Thionyl chloride (400 µL, 5.52 mmol) was added to a solution of 3-nitrophenylacetic acid (0.500 g, 2.76 mmol) in methanol (25 mL). The resulting solution was heated at reflux for 1 h, after which the solvent was removed *in vacuo*. The crude product was purified by chromatography on silica (17:3 Petrol/EtOAc) to give the desired compound as a colourless oil (0.501 g, 2.56 mmol, 93%); R_f 0.36 (17:3 Petrol/EtOAc); λ_{max} (EtOH/nm) 272, 320; IR (cm^{-1}) 2985, 2359, 1728, 1530; ^{1}H NMR (500 MHz, DMSO-d_6) 3.65 (3H, s, OCH_3), 3.93 (2H, s, CH_2), 7.64 (1H, dd, *J* = 7.9 and 8.1 Hz, H-5), 7.75-7.78 (1H, m, H-6), 8.15 (1H, ddd, *J* = 0.9, 2.3 and 7.9 Hz, H-4), 8.18-8.21 (1H, m, H-2); LRMS (ES+) *m*/*z* 196.3 $[M+H]^+$.

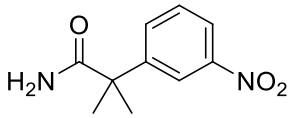
Methyl 2-methyl-2-(3-nitrophenyl)propanoate (138)



Sodium hydride (60% dispersion in mineral oil, 90 mg, 2.25 mmol) was added portion-wise to a solution of **137** (0.200 g, 1.02 mmol) and methyl iodide (160 µL, 2.56 mmol) in dry THF (2 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 20 min, before being warmed to RT and stirred for a further 18 h. The reaction was quenched with acetic acid (1 mL) and the solvent was removed *in vacuo*. The crude residue was purified by chromatography on silica (17:3 Petrol/EtOAc) to give the desired compound as a pale orange oil (0.124 g, 0.56 mmol, 55%); R_f 0.45 (17:3 Petrol/EtOAc); λ_{max} (EtOH/nm) 270, 308; IR (cm^{-1}) 2983, 2954, 2361,

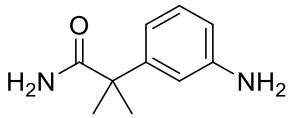
2341, 1730, 1527; ^{1}H NMR (500 MHz, DMSO-d_6) 1.59 (6H, s, C(CH_3)$_2$), 3.63 (3H, s, OCH_3), 7.67 (1H, dd, *J* = 7.9 and 8.1 Hz, H-5), 7.82 (1H, ddd, *J* = 1.0, 1.9 and 7.9 Hz, H-6), 8.12 (1H, dd, *J* = 1.9 and 2.3 Hz, H-2), 8.15 (1H, ddd, *J* = 1.0, 2.3 and 8.1 Hz, H-4);LRMS (ES+) *m*/*z* 224.2 $[M+H]^+$.

2-Methyl-2-(3-nitrophenyl)propanamide (139)



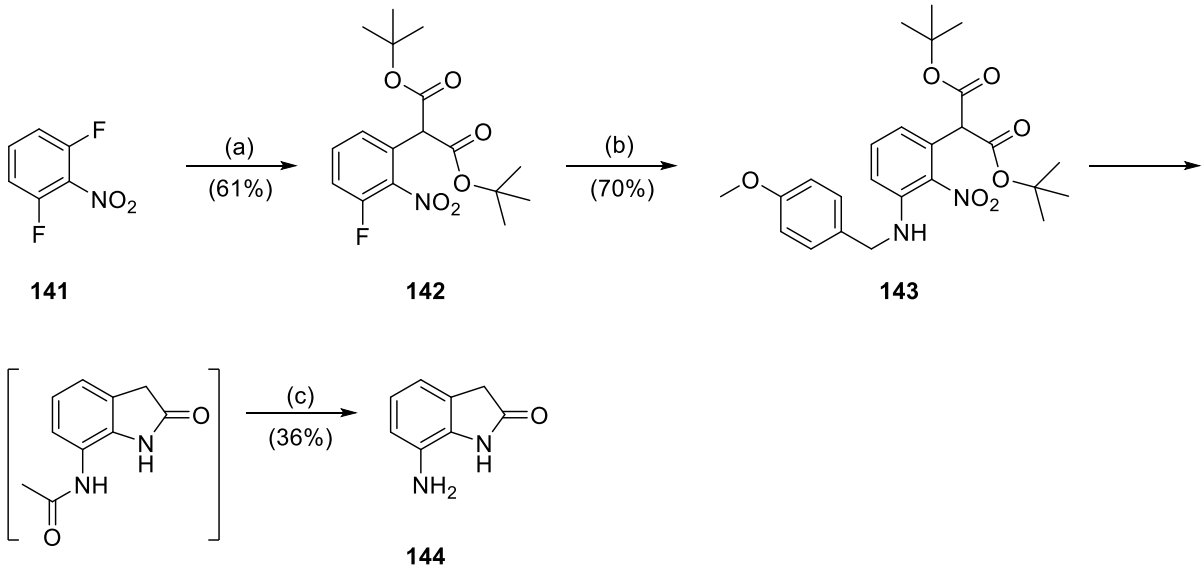
Methyl ester **138** (0.110 g, 0.49 mmol) was dissolved in concentrated ammonium hydroxide (5 mL) and the resultant solution was heated in a sealed vessel at 60 °C for 18 h. The solvent was removed *in vacuo* and the residue was dissolved in dry DCM (5 mL) and treated with thionyl chloride (72 µL, 0.98 mmol) and 1 drop of DMF. The solution was stirred at RT under nitrogen for 15 min, after which point the solvent was removed *in vacuo*. The residue was dissolved in dry THF (5 mL) and the solution was added drop-wise to concentrated ammonium hydroxide (3 mL). The mixture was stirred at RT for 18 h, before the solvent was removed *in vacuo*. The crude residue was purified *via* chromatography on KP-NH silica (7:3 Petrol/EtOAc) to give the desired compound as a white solid (72 mg, 0.35 mmol, 71%); R_f 0.29 (7:3 Petrol/EtOAc, KP-NH); m.p. 116-118 °C; λ_{max} (EtOH/nm) 220, 270; IR (cm^{-1}) 3391, 3208, 2965, 1650, 1535; ^{1}H NMR (500 MHz, DMSO-d_6) 1.51 (6H, s, C(CH_3)$_2$), 7.06 (1H, s, CON*H*H'), 7.11 (1H, s, CONH*H'*), 7.65 (1H, dd, *J* = 8.0 and 8.0 Hz, H-5), 7.81 (1H, ddd, *J* = 1.0, 1.8 and 8.0 Hz, H-6), 8.12 (1H, ddd, *J* = 1.0, 2.3 and 8.0 Hz, H-4), 8.15 (1H, dd, *J* = 1.8 and 2.3 Hz, H-2); HRMS calcd. for $C_{10}H_{13}N_2O_3$ (ES+) *m*/*z* 209.0921 $[M+H]^+$, found 209.0924.

2-(3-Aminophenyl)-2-methylpropanamide (140)



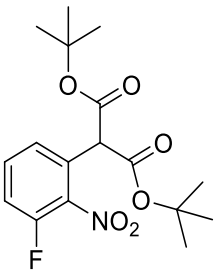
Palladium on carbon (40 mg, 10% w/w) and ammonium formate (1.19 g, 18.8 mmol) were added to a solution of **139** (0.392 g, 1.88 mmol) in methanol (20 mL). The reaction mixture was stirred at RT for 18 h, before being filtered through Celite®. The solvent was removed *in vacuo* and chromatography on silica (19:1 DCM/MeOH) gave the desired compound as an off-white solid (0.311 g, 1.75 mmol, 93%); R_f 0.21 (19:1 DCM/MeOH); m.p. 117-120 °C; λ_{max} (EtOH/nm) 243; IR (cm^{-1}) 3410, 3337, 3172, 2982, 1665; ^{1}H NMR (500 MHz, DMSO-d_6) 1.36 (6H, s, C(CH_3)$_2$), 5.10 (2H, br, Ar-NH_2), 6.40 (1H, ddd, *J* = 0.8, 2.1 and 7.9 Hz, H-6), 6.47-

6.50 (1H, m, H-4), 6.54-6.56 (1H, m, H-2), 6.72 (1H, s, CON*H*H'), 6.78 (1H, s, CONH*H'*), 6.94 (1H, dd, *J* = 7.9 and 8.0 Hz, H-5); HRMS calcd. for $C_{10}H_{15}N_2O$ (ES+) *m*/*z* 179.1179 $[M+H]^+$, found 179.1180.



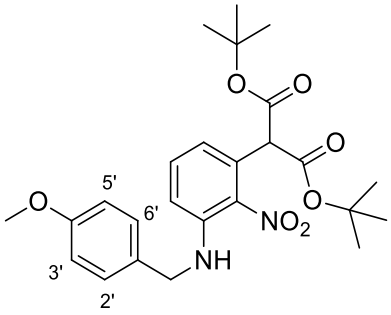
Scheme K: *Reagents and conditions:* (a) Di-*tert*-butylmalonate, K_2CO_3, DMF, 60 °C, 18 h; (b) PMB-NH_2, THF, 80 °C, 18 h; (c) i) Pd/C, NH_4HCOO, AcOH, MW 100 °C, 80 min, ii) AcCl, MeOH, RT, 1 h.

Di-*tert*-butyl 2-(3-fluoro-2-nitrophenyl)malonate (142)[27]



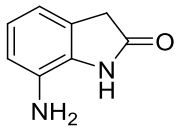
2,6-Difluoronitrobenzene (0.501 g, 3.14 mmol), di-*tert*-butyl malonate (775 µL, 3.46 mmol) and potassium carbonate (0.780 g, 5.65 mmol) were combined in dry DMF (9 mL) and heated at 60 °C for 18 h, after which the reaction mixture was neutralised with 1M HCl, and extracted with Et_2O (3 × 20 mL). The combined organic extracts were dried (Na_2SO_4), concentrated *in vacuo*, and purified *via* chromatography on silica (9:1 Petrol/EtOAc) to give the desired compound as a yellow oil (0.681 g, 1.92 mmol, 61%); R_f 0.56 (9:1 Petrol/EtOAc); λ_{max} (EtOH/nm) 230; IR (cm^{-1}) 2981, 2937, 1727; ^1H NMR (500 MHz, $CDCl_3$) 1.50 (18H, s, $(OC(CH_3)_3)_2$), 4.66 (1H, s, CH), 7.22-7.26 (1H, m, H-4), 7.42-7.45 (1H, m, H-6), 7.50-7.55 (1H, m, H-5); LRMS (ES-) *m*/*z* 354.2 $[M-H]^-$.

Di-*tert*-butyl 2-(3-(4-methoxybenzylamino)-2-nitrophenyl)malonate (143)



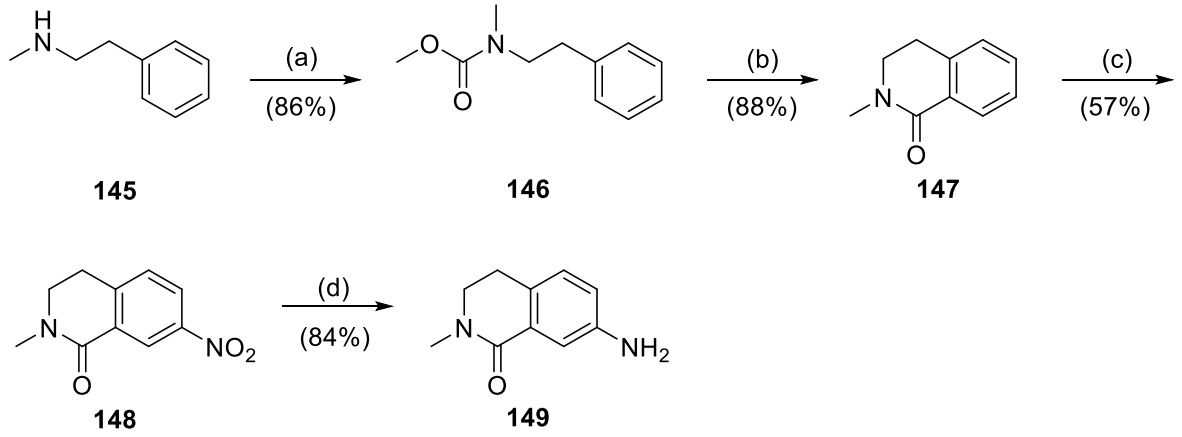
Malonate **142** (0.527 g, 1.48 mmol) was combined with 4-methoxybenzylamine (575 µl, 4.44 mmol) in THF (15 mL). The reaction mixture was heated at 80 °C for 18 h, after which the solvent was removed *in vacuo*. The crude residue was purified *via* chromatography on silica (9:1 Petrol/EtOAc) to give the desired product as a dark orange oil (0.460 g, 1.04 mmol, 70%); R_f 0.25 (9:1 Petrol/EtOAc); λ_{max} (EtOH/nm) 241; IR (cm^{-1}) 3409, 2980, 2360, 1727; ^{1}H NMR (500 MHz, DMSO-d_6) 1.49 (18H, s, $(OC(CH_3)_3)_2$), 3.81 (3H, s, OCH_3), 4.38 (2H, d, *J* = 4.7 Hz, CH_2NH), 4.83 (1H, s, CH), 6.73 (1H, dd, *J* = 1.0 and 7.5 Hz, H-4), 6.80 (1H, dd, *J* = 1.0 and 8.7 Hz, H-6), 6.89 (2H, d, *J* = 8.8 Hz, H-3' and H-5'), 7.25 (2H, d, *J* = 8.8 Hz, H-2' and H-6'), 7.31 (1H, dd, *J* = 7.5 and 8.7 Hz, H-5); HRMS calcd. for $C_{25}H_{33}N_2O_7$ (ES+) *m/z* 473.2282 $[M+H]^+$, found 473.2281.

7-Aminoindolin-2-one (144)[28]



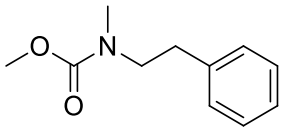
Ammonium formate (1.07 g, 17.0 mmol) and palladium on carbon (0.080 g, 10% w/w) were added to a solution of **143** (0.802 g, 1.70 mmol) in acetic acid (17 mL). The mixture was heated under microwave irradiation at 100 °C for 80 min, then filtered through Celite® and the solvent removed *in vacuo*. The resulting residue was dissolved in EtOAc (30 mL) and washed with sat. $NaHCO_3$ solution (3 × 30 mL). The organic extract was dried (Na_2SO_4) and concentrated, and the crude residue was purified *via* chromatography on silica (9:1 DCM/MeOH) to give the *N*-acetylated product as an off-white solid (0.146 g, 0.77 mmol, crude yield 45%). The solid was suspended in methanol (8 mL) and treated with acetyl chloride (330 µL, 4.62 mmol) at RT for 1 h. The solvent was removed *in vacuo*, the residue partitioned between EtOAc (10 mL) and sat. $NaHCO_3$ solution (10 mL) and the organic extract dried (Na_2SO_4) and concentrated to dryness. Purification by chromatography on silica (1:4 Petrol/EtOAc) gave the desired compound as a beige solid (91 mg, 0.61 mmol, 36%); R_f 0.44 (1:4 Petrol/EtOAc); m.p. 249-251 °C (lit.[18] 247-249 °C); λ_{max} (EtOH/nm) 255; IR (cm^{-1}) 3425, 3363, 3247, 1694; ^{1}H NMR (500 MHz, DMSO-d_6) 3.41 (2H, s, CH_2), 4.81 (2H, s, Ar-

NH_2), 6.47-6.49 (1H, m, H-4), 6.50 (1H, dd, *J* = 1.0 and 8.0 Hz, H-6), 6.69 (1H, ddd, *J* = 8.0 and 8.1 Hz, H-5); LRMS (ES+) *m*/*z* 149.1 $[M+H]^+$.



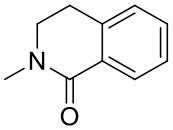
Scheme L: *Reagents and conditions:* (a) $MeCO_2Cl$, K_2CO_3, Et_2O, H_2O, RT, 1 h; (b) Eaton's reagent, MW 120 °C, 15 min; (c) HNO_3, H_2SO_4, 0 °C, 30 min; (d) Fe, AcOH, 50 °C, 15 min.

Methyl methyl(phenethyl) carbamate (146)[29]



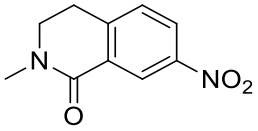
A solution of methyl chloroformate (1.59 mL, 20.6 mmol) in Et_2O (5 mL) was added dropwise over 30 min to the biphasic mixture of *N*-methyl-phenethylamine (2.00 mL, 13.8 mmol) and K_2CO_3 (5.71 g, 41.3 mmol) in Et_2O (20 mL) and water (20 mL). The mixture was stirred at RT for 1 h, before the organic phase was separated and washed with 1M HCl (20 mL), dried ($MgSO_4$) and evaporated to dryness. The crude residue was purified by chromatography on silica (4:1 Petrol/EtOAc) to give the target compound as a colourless liquid (2.44 g, 11.9 mmol, 86%); R_f 0.44 (4:1 Petrol/EtOAc); λ_{max} (EtOH/nm) 259; IR (cm^{-1}) 3027, 2950, 1697; ^1H NMR (500 MHz, DMSO-d_6, 348 K) 2.79 (2H, t, *J* = 7.6 Hz, NCH_2CH_2), 2.80 (3H, s, $N\text{-}CH_3$), 3.45 (2H, t, *J* = 7.6 Hz, NCH_2CH_2), 3.56 (3H, s, OCH_3), 7.19-7.23 (3H, m, H-2,H-4 and H-6), 7.28-7.32 (2H, m, H-3/H-5); LRMS (ES+) *m*/*z* 194.2 $[M+H]^+$.

2-Methyl-3,4-dihydroisoquinolin-1(2*H*)-one (147)[30]



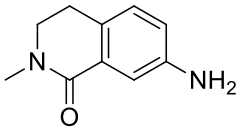
Methyl carbamate **146** (1.77 g, 9.16 mmol) was heated in Eaton's reagent (10 mL) under microwave irradiation conditions at 120 °C for 15 min. The resultant brown oil was dissolved in EtOAc (100 mL) and slowly added to a stirred sat. $NaHCO_3$ solution (100 mL). The organic phase was separated, washed with brine (50 mL), dried ($MgSO_4$) and concentrated *in vacuo*. Chromatography on silica (4:1 Petrol/EtOAc) gave the desired compound as a colourless oil (1.30 g, 8.09 mmol, 88%); R_f 0.26 (4:1 Petrol/EtOAc); λ_{max} (EtOH/nm) 229; IR (cm^{-1}) 2941, 2871, 1641, 1604, 1578; ^1H NMR (500 MHz, $CDCl_3$) 3.02 (2H, t, *J* = 6.7 Hz, NCH_2CH_2), 3.17 (3H, s, $N\text{-}CH_3$), 3.58 (2H, t, *J* = 6.7 Hz, NCH_2CH_2), 7.17-7.20 (1H, m, H-5), 7.34 (1H, ddd, *J* = 1.1, 7.5 and 7.6 Hz, H-7), 7.42 (1H, ddd, *J* = 1.4, 7.4 and 7.5 Hz, H-6), 8.10 (1H, dd, *J* = 1.4 and 7.6 Hz, H-8); LRMS (ES+) *m*/*z* 162.1 $[M+H]^+$.

2-Methyl-7-nitro-3,4-dihydroisoquinolin-1(2*H*)-one (148)



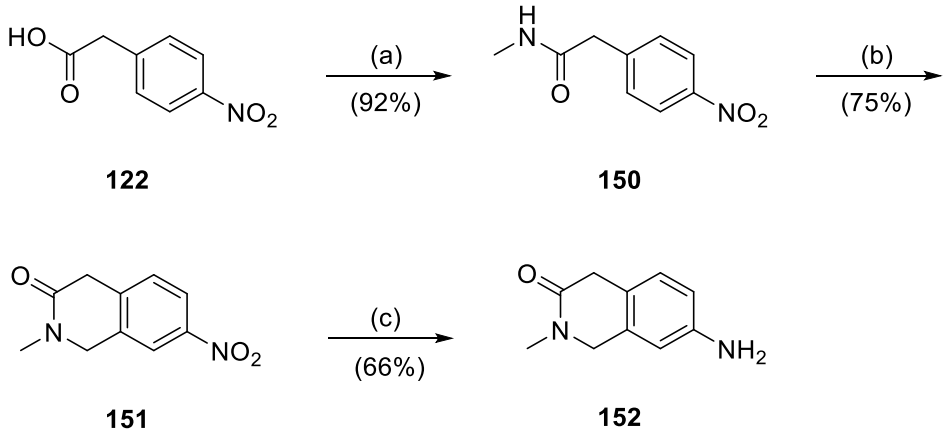
Fuming HNO_3 (42 µL, 1.01 mmol) was added to conc. H_2SO_4 (2 mL) at 0 °C. A solution of isoquinolinone **147** (0.135 g, 0.84 mmol) in conc. H_2SO_4 (0.5 mL) was added dropwise, and the solution was stirred at 0 °C for 30 min. The mixture was poured onto ice water (15 mL) and the resulting precipitate collected by filtration and washed with cold water (5 mL) before being dried in a vacuum oven to give the target compound as a white solid (100 mg, 0.48 mmol, 57%); R_f 0.29 (19:1 DCM/MeOH); m.p. 137-140 °C; λ_{max} (EtOH/nm) 220, 255; IR (cm^{-1}) 2925, 2868, 1647, 1610, 1518; ^1H NMR (500 MHz, DMSO-d_6) 3.07 (3H, s, $N\text{-}CH_3$), 3.14 (2H, t, *J* = 6.7 Hz, NCH_2CH_2), 3.62 (2H, t, *J* = 6.7 Hz, NCH_2CH_2), 7.61 (1H, d, *J* = 8.3 Hz, H-5), 8.31 (1H, dd, *J* = 2.5 and 8.3 Hz, H-6), 8.56 (1H, d, *J* = 2.5 Hz, H-8); HRMS calcd. for $C_{10}H_{11}N_2O_3$ (ES+) *m*/*z* 207.0764 $[M+H]^+$, found 207.0765.

7-Amino-2-methyl-3,4-dihydroisoquinolin-1(2*H*)-one (149)



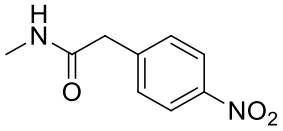
Iron powder (2.56 g, 45.9 mmol) was added to a solution of the nitro compound **148** (0.947 g, 4.59 mmol) in acetic acid (45 mL). The reaction mixture was heated at 50 °C for 15 min, before being filtered through Celite® and the filtrate concentrated *in vacuo*. The residue was

dissolved in EtOAc (200 mL) and washed with a sat. aqueous solution of $NaHCO_3$ (2 × 200 mL) and brine (200 mL). The combined aqueous layers were extracted with EtOAc (200 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. Purification by chromatography on silica (19:1 DCM/MeOH) afforded the desired compound as a pale yellow solid (0.678 g, 3.85 mmol, 84%); R_f 0.24 (19:1 DCM/MeOH); m.p. 131-133 °C; λ_{max} (EtOH/nm) 224, 330; IR (cm^{-1}) 3439, 3359, 3330, 3234, 2931, 1635, 1599, 1576, 1498; ^{1}H NMR (500 MHz, DMSO-d_6) 2.77 (2H, t, *J* = 6.7 Hz, NCH_2CH_2), 2.99 ($N\text{-}CH_3$), 3.45 (2H, t, *J* = 6.7 Hz, NCH_2CH_2), 5.12 (2H, s, $Ar\text{-}NH_2$), 6.66 (1H, dd, *J* = 2.5 and 8.0 Hz, H-6), 6.91 (1H, d, *J* = 8.0 Hz, H-5), 7.15 (1H, d, *J* = 2.5 Hz, H-8); HRMS calcd. for $C_{10}H_{13}N_2O$ (ES+) *m*/*z* 177.1022 $[M+H]^+$, found 177.1021.



Scheme M: *Reagents and conditions*: (a) i) $SOCl_2$, MeOH, reflux, 1 h, ii) Aq. $MeNH_2$, RT, 72 h; (b) $(CH_2O)n$, Eaton's reagent, 80 °C, 6 h; (c) Fe, AcOH, 50 °C, 15 min.

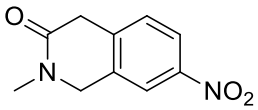
***N*-Methyl-2-(4-nitrophenyl)acetamide (150)**[31]



Thionyl chloride (0.81 mL, 11.0 mmol) was added to a solution of 4-nitrophenylacetic acid (1.00 g, 5.52 mmol) in methanol (50 mL). The resulting solution was heated at reflux for 1 h, after which the solvent was removed *in vacuo*. A concentrated aqueous solution of methylamine (40% aqueous solution, 50 mL) was added to the residue and the reaction mixture was stirred at RT for 72 h. The solvent was removed *in vacuo* and purification by chromatography on silica (19:1 DCM/MeOH) gave the target compound as an off-white solid (0.916 g, 5.08 mmol, 92%); R_f 0.31 (19:1 DCM/MeOH); m.p. 157-160 °C (lit.[31] 159 °C); λ_{max} (EtOH/nm) 271; IR (cm^{-1}) 3260, 3084, 2943, 2844, 1638, 1565, 1505; ^{1}H NMR (500 MHz, DMSO-d_6) 2.60 (3H, d, *J* = 4.7 Hz, $NHCH_3$), 3.58 (2H, s, CH_2), 7.53 (2H, d, *J* = 9.0 Hz, H-2

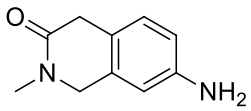
and H-6), 8.09 (1H, br, N*H*CH_3), 8.18 (2H, d, *J* = 9.0 Hz, H-3 and H-5); LRMS (ES+) *m*/*z* 195.2 $[M+H]^+$.

2-Methyl-7-nitro-1,2-dihydroisoquinolin-3(4*H*)-one (151)[32]

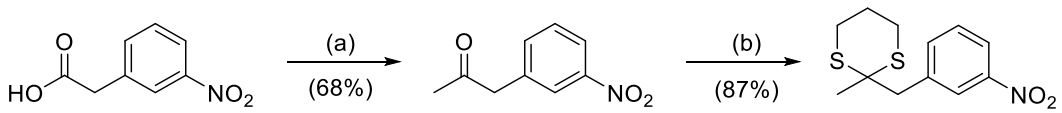


Paraformaldehyde (19 mg, 0.62 mmol) was added to a suspension of **150** (102 mg, 0.51 mmol) in Eaton's reagent (1 mL). The mixture was heated in a sealed vial at 80 °C for 6 h, after which point the brown solution was cooled to RT, diluted with ice water (5 mL) and neutralised with 50% NaOH solution. The resultant suspension was extracted with EtOAc (3 × 10 mL) and the combined organic extracts were dried ($MgSO_4$) and concentrated *in vacuo*. The crude residue was purified by chromatography on silica gel (19:1 DCM/MeOH) to give the target compound as a pale orange solid (78 mg, 0.38 mmol, 75%); R_f 0.30 (19:1 DCM/MeOH); m.p. 151-154 °C; λ_{max} (EtOH/nm) 273; IR (cm^{-1}) 3041, 2875, 1637, 1597, 1500; ^{1}H NMR (500 MHz, DMSO-d_6) 2.98 (3H, s, N-CH_3), 3.70 (2H, s, N-CH_2), 4.64 (2H, s, CH_2), 7.50 (1H, d, *J* = 8.4 Hz, H-5), 8.13 (1H, dd, *J* = 2.3 and 8.4 Hz, H-6), 8.20 (1H, d, *J* = 2.3 Hz, H-8); LRMS (ES+) *m*/*z* 207.1 $[M+H]^+$.

7-Amino-2-methyl-1,2-dihydroisoquinolin-3(4*H*)-one (152)



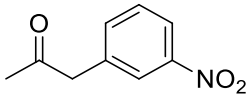
Iron powder (0.943 g, 16.9 mmol) was added to a solution of **151** (0.348 g, 1.69 mmol) in acetic acid (17 mL). The reaction mixture was heated at 50 °C for 15 min, before being filtered through Celite® and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (200 mL) and washed with a sat. aqueous solution of $NaHCO_3$ (2 × 200 mL) and brine (20 mL). The combined aqueous layers were extracted with EtOAc (200 mL) and the combined organic extracts were dried ($MgSO_4$) and evaporated to dryness. Purification *via* chromatography on silica (19:1 DCM/MeOH) gave the desired compound as a pale orange solid (0.196 g, 1.11 mmol, 66%); R_f 0.25 (19:1 DCM/MeOH); m.p. 167-170 °C; λ_{max} (EtOH/nm) 241, 296; IR (cm^{-1}) 3426, 3343, 3241, 3023, 2871, 1612, 1502; ^{1}H NMR (500 MHz, DMSO-d_6) 2.94 (3H, s, N-CH_3), 3.31 (2H, s, CH_2), 4.34 (2H, s, N-CH_2), 4.99 (2H, s, Ar-NH_2), 6.42 (1H, d, *J* = 2.2 Hz, H-8), 6.46 (1H, dd, *J* = 2.2 and 8.0 Hz, H-6), 6.82 (1H, d, *J* = 8.0 Hz, H-5); HRMS calcd. for $C_{10}H_{13}N_2O$ (ES+) *m*/*z* 177.1022 $[M+H]^+$, found 177.1019.



136 **153** **154**

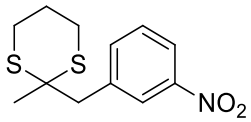
Scheme N: *Reagents and conditions:* (a) Ac_2O, pyridine, reflux, 4 h; (b) 1,3-propanedithiol, $BF_3.Et_2O$, DCM, RT, 18 h; (c) $SnCl_2.H_2O$, EtOH, reflux, 1.5 h.

1-(3-Nitrophenyl)propan-2-one (153)[33]



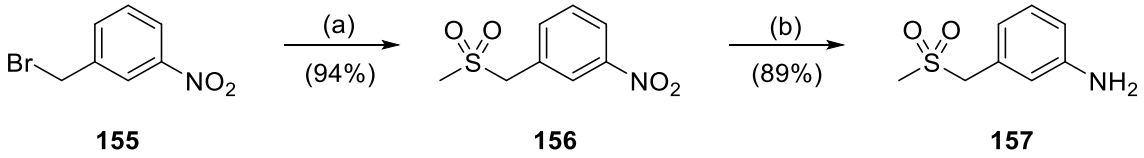
Acetic anhydride (10.4 mL, 110 mmol) was added to a solution of 3-nitrophenylacetic acid (2.00 g, 11.0 mmol) in dry pyridine (4.50 mL, 55.2 mmol). The reaction mixture was heated at reflux under N_2 for 4 h, before being concentrated *in vacuo*. The brown residue was suspended in a mixture of conc. HCl (1 mL) and EtOH (8 mL), and the suspension was heated at reflux for 1 h. The resultant solution was poured onto ice water (50 mL) and the mixture was extracted with EtOAc (3 × 30 mL). The combined organic extracts were dried ($MgSO_4$), concentrated *in vacuo*, and the crude product purified by chromatography on silica (4:1 Petrol/EtOAc). The target compound was obtained as a pale yellow oil which crystallised on standing (1.33 g, 7.43 mmol, 68%); R_f 0.26 (4:1 Petrol/EtOAc); m.p. 62-65 °C (lit.[33] 62 °C); λ_{max} (EtOH/nm) 263; IR (cm^{-1}) 3076, 1719, 1518; ^{1}H NMR (500 MHz, $CDCl_3$) 2.28 (3H, s, CH_3), 3.88 (2H, s, CH_2), 7.53-7.56 (2H, m, H-4 and H-5), 8.07-8.10 (1H, m, H-2), 8.14-8.18 (1H, m, H-6); LRMS (ES-) *m*/*z* 178.1 $[M-H]^-$.

2-Methyl-2-(3-nitrobenzyl)-1,3-dithiane (154)



1,3-Propanedithiol (0.77 mL, 7.70 mmol) and boron trifluoride diethyl etherate (1.58 mL, 12.8 mmol) were added to a solution of **153** (1.15 g, 6.42 mmol) in dry DCM (30 mL) at 0 °C. The solution was stirred under N_2 at RT for 18 h, before being washed with sat. $NaHCO_3$ solution (20 mL). The organic phase was dried through a phase separator, concentrated *in vacuo,* and the crude residue purified *via* chromatography on silica (4:1 Petrol/EtOAc). The desired compound was obtained as an off-white crystalline solid on cooling (1.50 g, 5.56 mmol, 87%); R_f 0.44 (4:1 Petrol/EtOAc); m.p. 75-78 °C; λ_{max} (EtOH/nm) 261; IR (cm^{-1}) 2933, 2907, 1525; ^{1}H NMR (500 MHz, $CDCl_3$) 1.56 (3H, s, CH_3), 1.97-2.11 (2H, m, $C(SCH_2)_2CH_2$), 2.88-3.05

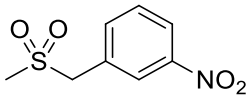
(4H, m, C(SC*H*$_2$)$_2$CH$_2$), 3.37 (2H, s, Ar-CH$_2$), 7.50 (1H, dd, *J* = 7.6 and 7.7 Hz, H-5), 7.61-7.65 (1H, m, H-6), 8.15-8.18 (2H, m, H-2 and H-4); LRMS (ES+) *m*/*z* 270.2 $[M+H]^+$.



155 **156** **157**

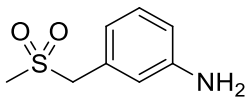
Scheme O: *Reagents and conditions*: (a) NaSO$_2$CH$_3$, EtOH, reflux, 2 h; (b) Fe, AcOH, 50 °C, 15 min.

1-((Methylsulfonyl)methyl)-3-nitrobenzene (156)[34]



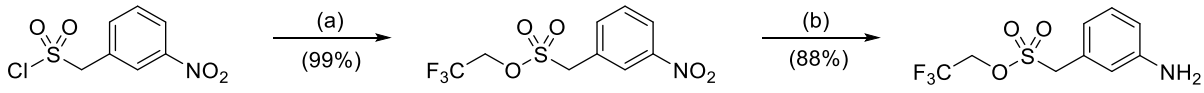
Sodium methanesulfinate (0.306 g, 3.01 mmol) in ethanol (2 mL) was added to a solution of 3-nitrobenzyl bromide (0.502 g, 2.31 mmol) in ethanol (6 mL). The mixture was heated at 80 °C for 2 h, before being cooled and concentrated *in vacuo*. The resultant residue was partitioned between DCM (15 mL) and water (10 mL), and the organic phase was dried through a phase separator. The solvent was removed and the crude residue purified by chromatography on silica (1:1 Petrol/EtOAc) to give the target compound as a white solid (0.467 g, 2.17 mmol, 94%); R_f 0.39 (1:1 Petrol/EtOAc); m.p. 119-121 °C (lit.[34] 105-106 °C); λ_{max} (EtOH/nm) 260; IR (cm^{-1}) 3018, 2989, 2935, 1521; ^{1}H NMR (500 MHz, $CDCl_3$) 2.91 (3H, s, CH$_3$), 4.40 (2H, s, CH$_2$), 7.66 (1H, dd, *J* = 7.6 and 7.7 Hz, H-5), 7.83 (1H, ddd, *J* = 1.3, 1.5 and 7.7 Hz, H-6), 8.29-8.33 (2H, m, H-2 and H-4); LRMS (ES-) *m*/*z* 214.1 $[M-H]^-$.

3-((Methylsulfonyl)methyl)aniline (157)[35]



Iron powder (1.80 g, 32.3 mmol) was added to a solution of **156** (0.695 g, 3.23 mmol) in acetic acid (30 mL). The reaction mixture was heated at 50 °C for 15 min, before being filtered through Celite® and the filtrate concentrated *in vacuo*. The residue was dissolved in EtOAc (200 mL) and washed with a sat. aqueous solution of NaHCO$_3$ (2 × 200 mL) and brine (200 mL). The combined aqueous layers were extracted with EtOAc (200 mL) and the combined organic extracts were dried (MgSO$_4$) and evaporated to dryness. Purification by

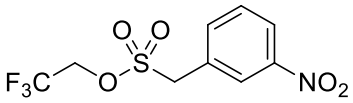
chromatography on silica (9:1 DCM/MeOH) afforded the target compound as an off-white solid (0.532 g, 2.87 mmol, 89%); R_f 0.42 (9:1 DCM/MeOH); m.p. 123-126 °C (lit.[35] 126 °C); λ_{max} (EtOH/nm) 243, 298; IR (cm^{-1}) 3463, 3373, 3221, 3011, 2970, 2930, 1625, 1603; ^1H NMR (500 MHz, DMSO-d_6) 2.87 (3H, s, CH_3), 4.27 (2H, s, CH_2), 5.16 (2H, s, Ar-NH_2), 6.52-6.55 (1H, m, H-6), 6.56 (1H, ddd, *J* = 1.0, 2.2 and 8.0 Hz, H-4), 6.58-6.60 (1H, m, H-2), 7.02 (1H, dd, *J* = 7.8 and 8.0 Hz, H-5); LRMS (ES+) *m/z* 186.1 $[M+H]^+$.



158 **159** **160**

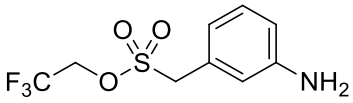
Scheme P: *Reagents and conditions:* (a) TFE, DMAP, Et_3N, RT, 3 h; (b) H_2, Pd/C, TFE, EtOAc, RT, 18 h.

2,2,2-Trifluoroethyl (3-nitrophenyl)methanesulfonate (159)[36]



3-Nitro-α-toluenesulfonyl chloride **158** (1.00 g, 4.24 mmol) was added to a solution of DMAP (0.052 g, 0.42 mmol) and triethylamine (1.77 mL, 12.7 mmol) in TFE (10 mL). The mixture was stirred at RT for 3 h, after which the solvent was removed *in vacuo*. The residue was dissolved in DCM (60 mL) and washed with 0.05 M HCl (60 mL) and water (60 mL), and the organic phase was passed through a phase separator and concentrated. The resulting oil was sonicated with water (5 mL), resulting in the formation of the product as a white precipitate which was collected *via* filtration (1.25 g, 4.19 mmol, 99%); R_f 0.73 (7:3 Petrol/EtOAc); m.p. 89-91 °C (lit.[36] 84-85 °C); λ_{max} (EtOH/nm) 257; IR (cm^{-1}) 2998, 2950, 2160, 1977, 1531; ^1H NMR (500 MHz, DMSO-d_6) 5.00 (2H, q, *J* = 8.4 Hz, F_3CCH_2), 5.19 (2H, s, Ar-CH_2), 7.76 (1H, dd, *J* = 8.0 and 8.2 Hz, H-5), 7.90-7.95 (1H, m, H-6), 8.30 (1H, ddd, *J* = 2.3, 2.4 and 8.2 Hz, H-4), 8.37-8.39 (1H, m, H-2); LRMS (ES-) *m/z* 298.1 $[M-H]^-$.

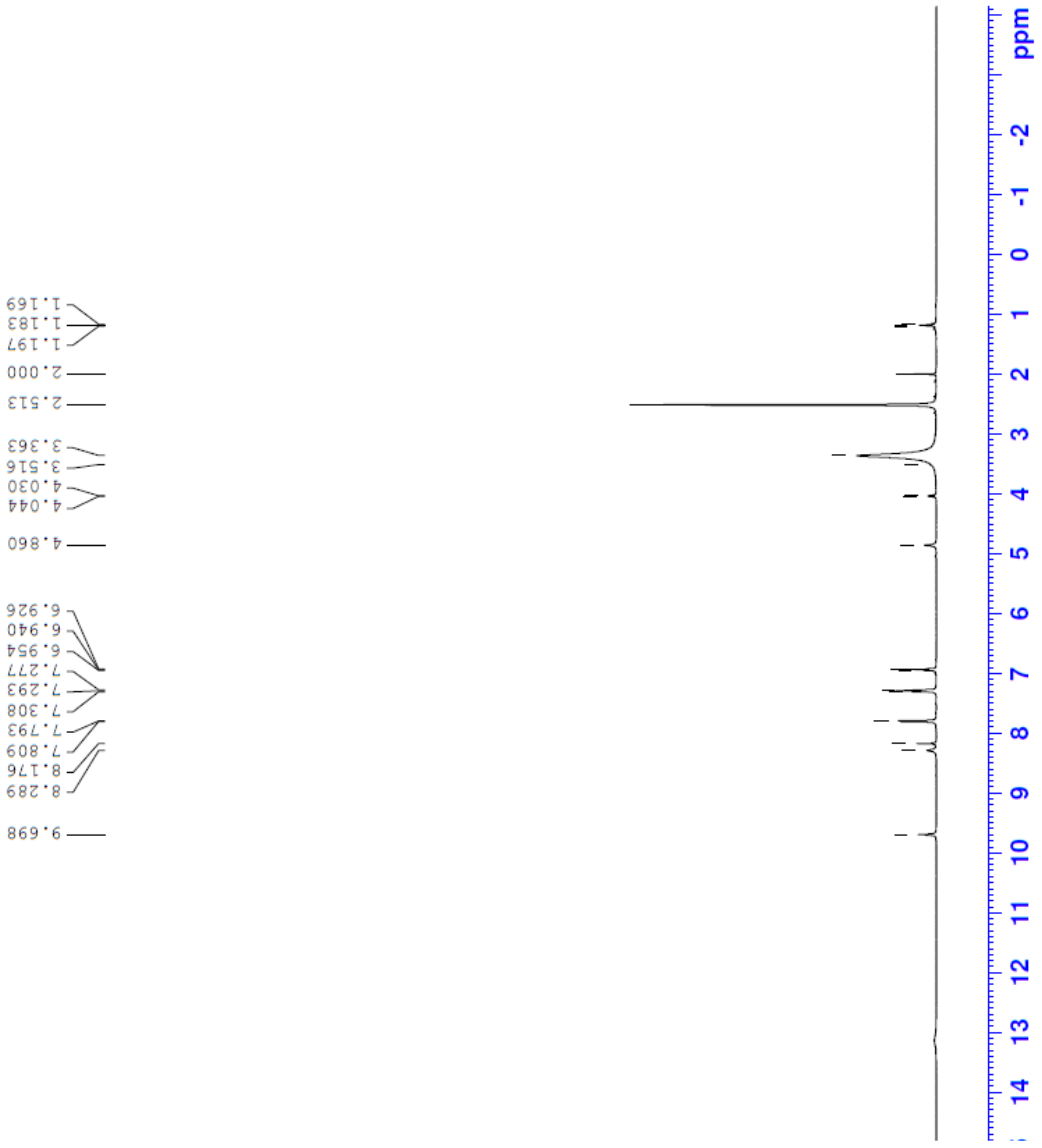
2,2,2-Trifluoroethyl (3-aminophenyl)methanesulfonate (160)[36]



Palladium on carbon (0.30 g, 10% w/w) was added to a solution of **159** (1.00 g, 3.34 mmol) in TFE (10 mL) and EtOAc (3 mL). The mixture was hydrogenated at RT for 18 h before being passed through Celite® and concentrated. The crude oil was purified *via* chromatography on silica (7:3 Petrol/EtOAc) to give an oil, which was triturated with petrol

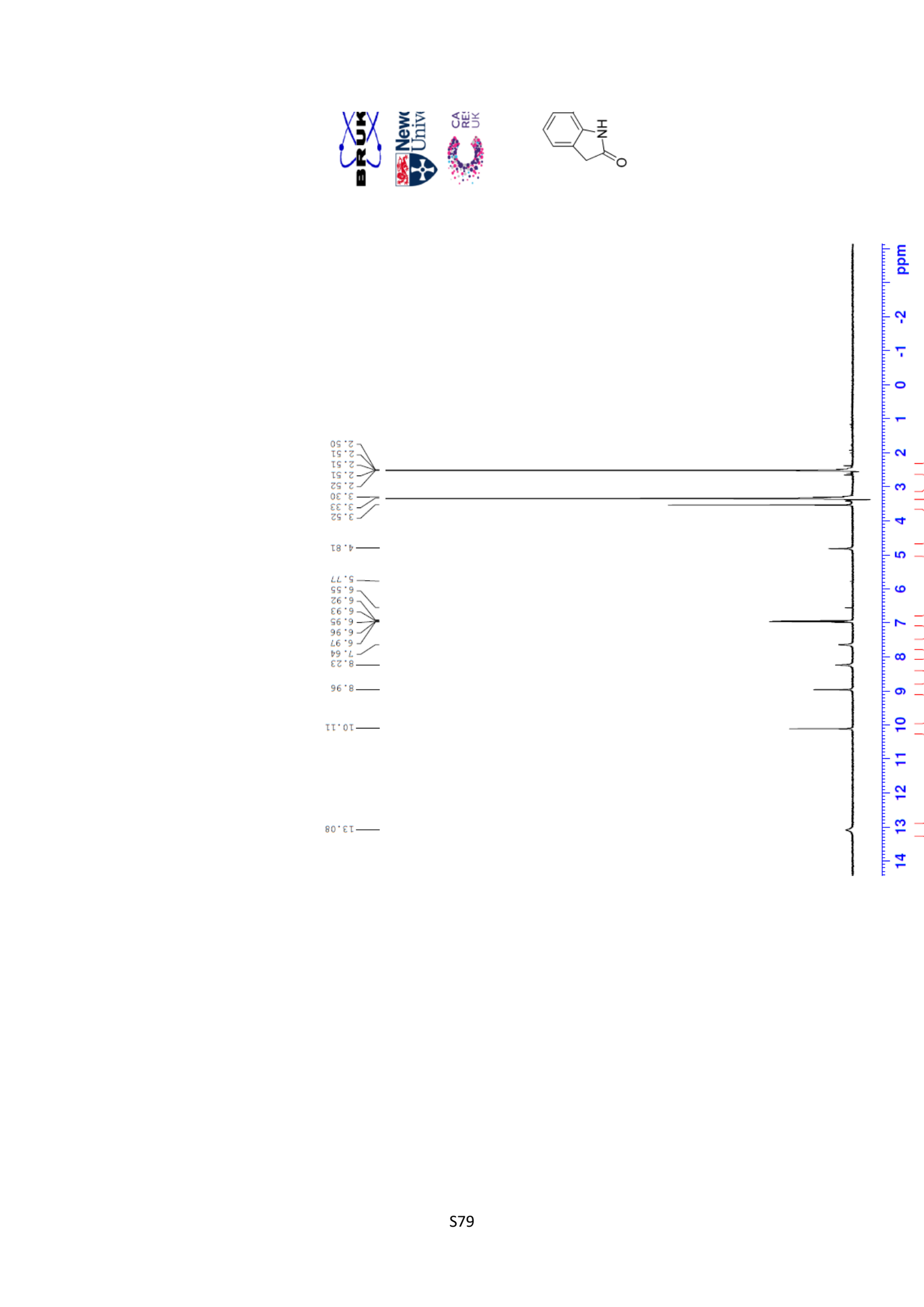
(10 mL) to give the desired compound as a white solid (0.789 g, 2.93 mmol, 88%); R_f 0.36 (7:3 Petrol/EtOAc); m.p. 74-76 °C (lit.[36] 77-78 °C); λ_{max} (EtOH/nm) 243; IR (cm^{-1}) 3502, 3397, 2945, 2359, 1619; ^{1}H NMR (500 MHz, DMSO-d_6) 4.76 (2H, s, Ar-NH_2), 4.95 (2H, q, J = 8.7 Hz, F_3CCH_2O), 5.28 (2H, s, Ar-CH_2), 6.59-6.64 (2H, m, H-4/H-6), 6.65-6.68 (1H, m, H-2), 7.09 (1H, dd, J = 7.7 and 7.9 Hz, H-5); LRMS (ES+) m/z 270.0 $[M+H]^+$.

3. ^{1}H NMR Spectra for Key Compounds



10.093
8.358
7.957
7.953
7.943
7.939
7.934
7.742
7.724
7.152
4.886
3.309
3.177
2.527
2.516
2.513
2.509
2.505
2.502
1.996
1.917
ppm

2.45
2.45
2.45
3.28
4.76
6.79
6.80
6.83
7.13
7.15
7.16
7.38
7.48
7.70
7.72
8.19
9.52
12.94
12.97
13.03
13.06
13.07
13.11
ppm


NH
O
2.50
2.51
2.51
2.51
2.52
3.30
3.33
3.52
4.81
5.77
6.55
6.92
6.93
6.95
6.96
6.97
7.64
8.23
8.96
10.11
13.08
ppm

4. Biological Evaluation

Synthesised inhibitors were evaluated for Nek2 inhibitory activity and counter-screened by Kathy Boxall, Sam Burns, Yvette Newblatt and Maura Westlake under the supervision of Dr. Wynne Aherne in the Analytical Screening and Technology Laboratory of the CR UK Centre for Cancer Therapeutics, The Institute for Cancer Research, Sutton, Surrey, UK, SM2 5NG. The determined inhibitory concentrations are reported as inhibition coefficients for 50% inhibition (IC_{50}) or percentage inhibition as appropriate.

Evaluation of synthesised inhibitors for CDK2/cyclin A3 inhibitory activity was conducted by Lan-Zhen Wang at The Northern Institute for Cancer Research, Paul O'Gorman Building,

Medical School, Newcastle University, Framlington Place, Newcastle upon Tyne, NE2 4HH. Details are given below. Enamine stability studies were undertaken by Huw D. Thomas, also of the above address.

All animal experiments performed were conducted in compliance with the relevant laws and institutional guidelines.

Nek2 Biochemical Assay

Nek2 inhibitory activities were determined using a Caliper EZ Reader II instrument with either a 4 or 12 sipper microfluidic chip (Caliper Life Sciences Ltd, Runcorn, UK).[1] The assay format employs an electrophoretic method which separates a phosphorylated peptide substrate of Nek2 from the non-phosphorylated substrate after incubation in the assay medium for a defined time in the presence of a chemical inhibitor. The separation is based on charge, with the negatively charged phosphopeptide migrating more rapidly towards a positively charged terminal. The extent of phosphorylation is proportional to the extent of functional Nek2 enzymatic activity in the assay solution and its ability to bind ATP to phosphorylate the peptide substrate. The Caliper instrument readout gives an estimate of the proportion of peptide substrate which is phosphorylated by uninhibited Nek2. Therefore, the greater the affinity of an inhibitor for Nek2, the lower the proprotion of phosphopeptide as detected by a fluorescence sensor.

The assay was conducted by 1:4 dilution of a 10 mM stock solution of an inhibitor in DMSO by taking 15 µL of inhibitor solution and adding this to 45 µL of DMSO in the first row of a 384 well polypropylene assay plate (Greiner). Seven further successive 1:3 dilutions were performed by taking 20 µL of the inhibitor solution and adding this to 60 µL of 100% DMSO in the well directly below, to give a 250 µM top concentration in DMSO. The 100% DMSO solutions were each diluted 20-fold by adding 2.5 µL of each well to 47.5 µL of a stock kinase buffer (25 mL, consisting of: stock Cisbio buffer (5 mL), 1,4-dithiothreitol (25 µL, 1 mM), $MgCl_2$ (125 µL, 5 mM solution in water), $Tween_{20}$ (25 µL, 0.1%) and HPLC grade water (20 mL)) to give a top concentration of 125 µM in 5% DMSO. To a second 384 well assay plate was added 4 µL of 5% DMSO solution from each well of the first assay plate to give a top concentration of 50 µM in 2% DMSO after a 1:2.5 dilution. To each well was added Nek2 enzyme (2 µL of 0.28 mg/mL aqueous solution, giving a 4 nM final concentration, PV3360 Invitrogen), substrate ‘peptide-11’ (5-FAM-KKLNRTLSVA-COOH, 2 µL of 1.5 mM aqueous solution, giving a 1 µM final concentration, #760355 Caliper Life Sciences) and finally ATP (2 µL aqueous 10 mM solution, giving a 30 µM final concentration) was added to initiate the

reaction. The plate was immediately sealed and centrifuged for 1 minute to mix all of the reagents before incubation at room temperature for 60 min.[2]

The reaction was stopped after the required time by addition of 90 µL of separation buffer (#760367 Caliper Life Sciences). The amount of peptide 11 phosphorylation was then determined using the Caliper EZ Reader II instrument (1.5 psi, 1750 ΔV). The percentage conversion of substrate protein was measured and the percentage inhibition was thus calculated relative to blank wells, which contained no enzyme and 2% DMSO, and totals wells which contained all reagents and 2% DMSO replacing the inhibitor.

IC_{50} values were determined in duplicate over a range of 8 concentrations using GraphPad Prism 5, employing a non-linear regression fit of log[inhibitor] versus response (% inhibition) with a variable slope equation. It is noteworthy that IC_{50} values presented for the irreversible inhibitor series are the values obtained as above, after 60 minute incubation of the inhibitor with Nek2.

CellTiter-Blue Assay for Growth Inhibition[3]

U2OS human osteosarcoma cells (American Type Culture Collection, Manassas, Virginia, United States) were grown in McCoy's 5A medium supplemented with 1.5 mM L-glutamine, 25 mM HEPES, 2% penicillin/streptomycin (Invitrogen, Paisley, United Kingdom) and 10% fetal bovine serum (Biosera, Ringmer, East Sussex, United Kingdom). MDA-MB-231 human breast cancer cells (American Type Culture Collection, Manassas, Virginia, United States) were grown in RPMI 1640 medium (Invitrogen) supplemented with 2 mM L-glutamine, 25 mM HEPES, 2% penicillin/streptomycin and 10% fetal bovine serum. HeLa cells were grown in Dulbecco's Modified Eagle Medium (D-MEM) (Invitrogen) supplemented with 2% penicillin/streptomycin and 10% fetal bovine serum. All three cell lines were maintained in a humidified atmosphere of 5% CO_2 at 37°C. The medium was aspirated and the cells were washed with PBS (Invitrogen), trypsinized (Internal supply, 0.25% versene trypsin with EDTA), neutralized and counted. Cells were seeded into 384-well clear tissue culture treated microtiter plates (Corning B.V. Life Sciences, Amsterdam, The Netherlands) at 200 cells per well in a 45 µL volume of the respective media. Columns 1 and 24 had no cells added and were plated with 45 µL of media alone. Cells were incubated at 37°C / 5% CO_2. At 24 hours after plating, compounds were three-fold serially diluted in large volume V-shape 384-well microplates (Greiner Bio-One, Stonehouse, Gloucestershire, United Kingdom) using an Evolution plate handling system (PerkinElmer Life Sciences, Waltham, Massachusetts, USA). Then 5 µL of diluted test compounds, Etoposide as positive control (Sigma-Aldrich,

Gillingham, Dorset, United Kingdom), or DMSO at 1% v/v final concentration (Fisher Scientific, Loughborough, Leicestershire, United Kingdom) were added to the wells using a MiniTrack V plate handling system (PerkinElmer Life Sciences). There were four replicates of each compound concentration, 32 replicates of DMSO wells, and 32 replicates of wells containing no cells. Test compounds were screened at final concentrations of 100 µM, 33.33 µM, 11.11 µM, 3.70 µM, 1.23 µM, 0.41 µM, 0.14 µM, and 0.05 µM. Etoposide was screened at final concentrations of 10 µM, 3.33 µM, 1.11 µM, 0.37 µM, 0.12 µM, 0.041 µM, 0.014 µM, and 0.005 µM. After 92 hours, 5 µL of CellTiter-Blue Reagent (Promega, Southampton, United Kingdom) was added to the cells using a Multidrop dispenser (Thermo Electron, Basingstoke, Hants, United Kingdom) and incubated for 4 hours in a humidified atmosphere of 5% CO_2 at 37°C. After the incubation, the plates were placed at room temperature for 40 minutes before fluorescence was recorded ($560_{Ex}/590_{Em}$) on an EnVision 2103 plate reader (PerkinElmer Life Sciences). Data were plotted as percentage of DMSO control against compound concentration using *GraphPad Prism 5* Software. The 50% growth inhibition (GI_{50}) was calculated as the compound concentration required to reduce the cell number by 50% compared with the DMSO control.

CDK2/cyclin A3 Biochemical Assay

Inhibition of human CDK2/Cyclin A3 was assayed as previously described[4] using recombinant CDK2/cyclin A3 (10 µL) with 1 mg/mL histone H1 (150 µL, Sigma type III-S), in the presence of [gamma-^{32}P] ATP (1-5 µL, 3000 Ci/mmol, Cat number NEG002A Perkin Elmer) and cold ATP (13.13 µL, 1 mM) in a final volume of 30 µl. The assay buffer (500 µL total volume) contained Tris-HCl pH 7.5 (50 mM) and $MgCl_2$ (5 mM). The final DMSO concentration in the assay was 1% (V/V), after inhibitors stocks in 100% DMSO were diluted 1:10 in the appropriate assay buffer (3 µl + 27 µl buffer), followed by addition of 3 µl of 10% inhibitor solution to a total assay volume of 30 µl. Therefore, the final DMSO concentration was 1%, final inhibitor concentration was 1/100 of the original stock solution and the final ATP concentration in the assay was 12.5 µM. After incubation for 10 min at 30 ^{o}C, 25 µl aliquots were spotted onto 2.5 cm × 3 cm pieces of Whatman P81 phosphocellulose paper, and after 20 s, the filters were washed five times (> 5 min each time) in 1% phosphoric acid. The dry filters were transferred into 6 ml plastic scintillation vials, 5ml scintillation fluid (Amersham) was added, and the radioactivity was measured using a scintillation counter.

5. Kinase profiling

Table 1: Kinase inhibition following treatment with 1 µM **66** for ProfilerPro® plates. *IC_{50} determination for kinases inhibited >50%.

Enzyme	MAPK APK2	AurA	PKCz	Rsk1	PRAK	Erk1	PKD2	CK1d	Chk1
% inhib.	6	0.078*	9	8	-3	8	3	8	11
Enzyme	ABL	FYN	LYN	Chk2	MET	LCK	SRC	GSK3β	Erk2
% inhib.	39	10	9	13	6	17	22	9	2
Enzyme	PKA	AKT2	INSR	P38α	AKT1	Msk1	Msk2	P38γ	PKD1
% inhib.	1	3	-3	-1	13	6	-6	-1	31
Enzyme	MARK 2	BMX	CSNK 1A1	PKD3	BRSK1	Nek2	PIM1	SGK2	SGK3
% inhib.	27	0.83*	5	26	12	0.088*	18	7	11
Enzyme	ARG	DCAM KL2	Rsk2	Rsk3	BRSK1	PKC-α	PKC-β1	PKC-γ	PKC-δ
% inhib.	32	-2	12	14	5	15	2	29	29
Enzyme	PKC-ε	PKC-η	PKC-θ						
% inhib.	8	17	35						

Table 2: Kinase inhibition data for **23** and **66** and the literature irreversible Nek2 inhibitor **7** from the National Centre for Protein Kinase Profiling, Dundee University.

	Percentage activity at 1 μM Inhibitor					
Kinase	**23**	**k_m**	**66**	**k_m**	**7**	**k_m**
MKK1	95	18	46	2	16	1
MKK2	103	4	75	8	15	0
MKK6	105	2	109	4	54	5
ERK1	102	1	105	13	79	9
ERK2	91	13	92	4	70	3
JNK1	82	6	67	10	85	10
JNK2	96	8	92	3	101	7
JNK3	89	2	111	18	91	6
p38a MAPK	110	7	103	12	106	3
p38b MAPK	85	5	94	2	86	3
p38g MAPK	99	10	100	18	97	6
p38d MAPK	96	3	129	14	105	0
ERK8	86	7	108	2	14	2
RSK1	95	15	84	5	7	0

RSK2	72	2	88	19	16	0
PDK1	87	12	63	1	35	10
PKBa	91	2	116	6	124	18
PKBb	75	27	98	4	110	23
SGK1	103	14	93	16	64	1
S6K1	98	5	102	16	25	2
PKA	90	10	108	0	100	10
ROCK 2	91	6	89	2	23	1
PRK2	103	14	99	6	16	3
PKCa	95	5	108	3	86	2
PKCγ	105	10	98	4	114	5
PKCz	104	7	104	1	94	6
GCK	78	3	71	8	14	1
MINK1	87	6	92	0	13	0
MLK1	54	24	40	11	9	2
MLK3	33	5	29	0	17	2
TAO1	115	13	101	7	95	5
ASK1	96	1	128	10	68	0
TAK1	50	0	37	4	31	16
IRAK1	83	9	92	4	33	6
IRAK4	86	6	85	3	24	1
RIPK2	89	3	93	1	44	1
OSR1	93	4	103	2	84	6
TTK	80	5	92	5	35	4
MPSK1	101	7	92	21	100	6
Src	91	7	100	5	56	10
Lck	110	16	113	1	59	5
CSK	102	12	79	7	82	2
YES1	108	7	92	6	29	3
ABL	87	8	70	16	87	21
BTK	63	11	95	8	87	10
JAK2	75	1	30	0	40	4
SYK	88	14	117	7	83	2
ZAP70	114	9	119	2	88	4
FGF-R1	97	3	74	9	84	17
HER4	61	14	87	10	126	11
IGF-1R	97	6	115	5	59	16
IR	85	17	86	1	9	0
IRR	87	3	92	5	67	1
TrkA	109	7	74	7	31	2
VEG-FR	97	22	64	5	9	1
EPH-A2	105	17	122	2	110	7
EPH-A4	106	15	107	8	105	7
EPH-B1	93	1	95	1	91	14
EPH-B2	106	13	104	15	108	9
EPH-B3	99	2	88	8	122	10

EPH-B4	104	22	108	12	118	11
BRSK1	93	17	110	8	12	3
BRSK2	95	2	103	11	12	0
MELK	93	6	115	1	10	5
NUAK1	72	26	17	3	10	3
CK1d	82	9	91	5	82	27
CK2	93	5	94	13	28	1
DYRK1A	93	2	107	11	3	0
DYRK2	90	4	112	12	6	2
DYRK3	89	6	113	4	6	1
NEK2a	4	1	11	0	9	2
NEK6	101	15	103	10	79	3
IKKb	72	13	118	10	84	1
IKKe	84	0	60	1	14	2
TBK1	91	23	51	7	10	0
PIM1	101	5	108	0	38	4
PIM2	103	15	106	7	95	13
PIM3	92	4	114	12	27	3
SRPK1	75	26	94	5	67	4
EF2K	106	12	107	6	96	4
EIF2AK3	96	6	100	7	96	8
HIPK1	105	29	57	7	32	5
HIPK2	94	8	115	6	22	4
HIPK3	99	15	107	6	29	7
CLK2	77	11	63	3	6	2
PAK2	96	9	102	6	92	19
PAK4	70	7	71	15	44	4
PAK5	93	13	84	6	103	27
PAK6	97	1	102	0	81	2
MST2	79	11	90	5	30	4
MST3	92	4			103	16
MST4	96	4	94	4	41	2
PKD1	104	18	120	13	43	4
STK33	74	9	72	10	34	7
MSK1	87	5	129	20	60	0
MNK1	91	18	110	1	116	45
MNK2	101	4	82	1	71	4
MAPKAP-K2	102	13	78	9	68	3
MAPKAP-K3	89	15	94	3	105	14
PRAK	101	15	103	8	30	5
CAMKKb	101	19	103	4	23	2
CAMK1	95	14	138	18	55	5
SmMLCK	97	15	107	1	9	0
PHK	89	9	126	6	6	2
DAPK1	93	5	85	4	13	1

CHK1	77	18	38	4	15	2
CHK2	73	10	59	4	31	0
GSK3b	87	0	100	10	30	6
CDK2-Cyclin A	83	7	96	10	46	1
PLK1	89	11	115	6	116	3
Aurora A	95	9	69	4	55	1
Aurora B	77	13	67	7	103	2
TLK1	95	5	96	0	90	9
LKB1	100	3	95	11	91	9
AMPK	83	2	60	1	6	0
MARK1	92	10	87	4	14	7
MARK2	93	12	95	3	100	4
MARK3	101	24	96	10	8	1
MARK4	90	3	89	9	27	1
TIE2	100	3	111	1	111	33
BRK	74	1	103	13	117	7
MEKK1	85	7	104	6	105	4
TTBK1	81	21	-	-	86	4
TESK1	89	15	-	-	97	0
WNK1	109	12	-	-	117	4
DDR2					107	11
CDK9-cyclin T1	79	4	-	-	106	4
SIK2	78	12	-	-	63	53
SIK3	88	0	-	-	33	5
TSSK1	79	8	-	-	16	2
CK1y2	83	0	-	-	56	11

6. Crystallographic Analysis

Crystal structures of purine inhibitors co-crystallised with Nek2 were solved by Dr Richard Bayliss and Dr Corine Mas-Droux at the Section of Structural Biology, The Institute for Cancer Research, 237 Fulham Road, London, SW3 6JB. The structures were re-refined and deposited to the PDB by Dr Mark Richards and Dr Richard Bayliss at the Astbury Centre for Structural Molecules Biology at the University of Leeds, Woodhouse Lane, Leeds, LS2 9JT.

To examine the binding mode of ethynylpurines to Nek2 and observe the covalent bond directly, we solved X-ray co-crystal structures of Nek2 with compounds **24** and **66,** and also with the competitively-binding control compounds **96** and **102** (Table 3).

Table 3. Summary of crystallographic analysis.

	24 PDB: 6SGD	**66** PDB: 6SGH	**96** PDB: 6SGI	**102** PDB: 6SGK
Data collection				
Space group	*C*1 2 1	*C*1 2 1	*C*1 2 1	*C*1 2 1
Cell dimensions				
a *b* *c* (Å)	99.67 56.69 73.78	101.02 56.28 74.01	99.39 57.04 78.40	98.73 56.86 73.19
α β γ(°)	90 129.71 90	90 129.46 90	90 133.07 90	90 128.28 90
Resolution	49.75 – 2.00 (2.11 – 2.00)	57.14 - 3.00 (3.16 – 3.00)	38.79 - 2.30 (2.42 – 2.30)	30.76 – 2.00 (2.11 – 2.00)
R_{pim}	0.067 (0.424)	0.104 (0.336)	0.128 (0.731)	0.130 (0.353)
Mean ((I)/sd (I))	8.2 (2.2)	5.1 (2.2)	4.8 (1.1)	4.0 (1.8)
Completeness	99.6 (99.9)	97.3 (98.3)	99.6 (99.2)	98.9 (98.5)
Multiplicity	3.6 (3.7)	2.3 (2.4)	3.0 (2.6)	3.2 (3.2)
Refinement				
Resolution (Å)	30.36 - 2.00	57.14 - 3.00	38.79 - 2.30	28.43 - 2.00
Completeness (%)	99.56	97.16	99.36	98.65
No. reflections	21455	6371	14349	21392
R_{work} / R_{free}	19.77 / 23.38	22.79 / 28.73	21.29 / 26.58	19.54 / 22.27
Mean *B*-factors				
Protein	37.38	47.38	42.51	33.64
Ligand	36.07	40.62	42.48	32.03
Solvent	39.79	34.04	41.98	36.87
r.m.s. deviations				
bond lengths (Å)	0.005	0.003	0.003	0.006
bond angles (°)	0.773	0.654	0.592	0.799
MolProbity analysis				
All-atom clash-score	13.83	12.12	4.73	11.84
Rotamers outliers (%)	0.00	0.00	0.00	0.00
Ramachandran outliers (%)	0.00	0.00	0.00	0.42
Ramachandran favoured (%)	95.34	95.95	96.31	97.88

7. References

1. For more information see: http://www.caliperls.com/products/labchip-systems/ez-reader-ii.htm.
2. Note: for time-dependence experiments reaction was sampled in the Caliper EZ Reader II instrument at different times throughout the duration of the reaction.
3. Cell-based assays conducted and protocol (see experimental section) provided courtesy of Maura Westlake, CR UK Centre for Cancer Therapeutics, ICR, Sutton.
4. C. E. Arris, F. T. Boyle, A. H. Calvert, N. J. Curtin, J. A. Endicott, E. F. Garman, A. E. Gibson, B. T. Golding, S. Grant, R. J. Griffin, P. Jewsbury, L. N. Johnson, A. M. Lawrie, D. R. Newell, M. E. Noble, E. A. Sausville, R. Schultz, W. Yu. Identification of novel purine and pyrimidine cyclin-dependent kinase inhibitors with distinct molecular interactions and tumor cell growth inhibition profiles, *J. Med. Chem.* 2000, **43**, 2797.

5. J. J. Parlow, M. L. Vazquez, D. L. Flynn. A mixed resin bed for the quenching and purification of tetrabutylammonium fluoride mediated desilylating reactions. *Bioorg. Med. Chem. Lett.* 1998**, 8**, 2391.
6. E. Winzeler, N. S. Gray, D. Han, D. Cheng. Compounds and compositions as kinase inhibitors. WO2008094737A2, 2008.
7. N. S. Gray, S. Kwon, P. G. Schultz. Combinatorial synthesis of 2,9-substituted purines. *Tetrahedron Lett*. 1997, **38**, 1161.
8. C. R. Coxon, C. Wong, R. Bayliss, K. Boxall, K. H. Carr, A. M. Fry, I. R. Hardcastle, C. J. Matheson, D. R. Newell, M. Sivaprakasam, H. Thomas, Structure-guided design of purine-based probes for selective Nek2 inhibition. *Oncotarget*, 2017, **8**, 19089.
9. C. R. Coxon, E. Anscombe, S. J. Harnor, M. P. Martin, B. Carbain, B. T. Golding, I. R. Hardcastle, L. K. Harlow, S. Korolchuk, C. J. Matheson, D. R. Newell, Cyclin-dependent kinase (CDK) inhibitors: structure–activity relationships and insights into the CDK-2 selectivity of 6-substituted 2-arylaminopurines. *J. Med. Chem.*, 2017, **60**, 1746.
10. F. Focher, C. Hildebrand, S. Freese, G. Ciarrocchi, T. Noonan, S. Sangalli, N. Brown, S. Spadari, G. Wright, N2-Phenyldeoxyguanosine: A novel selective inhibitor of herpes simplex thymiding kinase. *J. Med. Chem.* 1988, **31**, 1496.
11. J. C. Ellington, E. M. Arnett. Kinetics and thermodynamics of phenolate silylation and alkylation. *J. Amer. Chem. Soc.* 1988**, 110**, 7778.
12. Y. Kondo, S. Kojima, T. Sakamoto. General and facile synthesis of indoles with oxygen-bearing substituents at the benzene moiety. *J. Org. Chem.* 1997**, 62**, 6507.
13. F. Mu, S. L. Coffing, D. J. Riese, R. L. Geahlen, P. Verdier-Pinard, E. Hamel, J. Johnson, M. Cushman. Design, synthesis, and biological evaluation of a series of lavendustin A analogues that inhibit EGFR and Syk tyrosine kinases, as well as tubulin polymerization. *J. Med. Chem.* 2001**, 44**, 441.
14. B. M. Sykes, M. P. Hay, D. Bohinc-Herceg, N. A. Helsby, C. J. O'Connor, W. A. Denny, Leaving group effects in reductively triggered fragmentation of 4-nitrobenzyl carbamates. *J. Chem. Soc., Perkin Trans. 1* 2000, 1601.
15. V. V. Rekha, M. V. Ramani, A. Ratnamala, V. Rupakalpana, G. V. Subbaraju, C. Satyanarayana, C. S. Rao. A simple, efficient, green, cost effective and chemoselective process for the esterification of carboxylic acids. *Org. Proc. Res. Dev.* 2009**, 13**, 769.
16. M. K. Sloss, J. McKenna, W. H. Yoon, S. Norris, D. Robinson, J. Parnes, G. Shelvin. Pyrazole pyrazine amine compounds as kinase inhibitors, composition thereof and methods of treatment therewith. WO2009089042A1, 2009.
17. C. R. Clark, M. J. M. Wells, R. T. Sansom, G. N. Norris, R. C. Dockens, W. R. Ravis. Anticonvulsant activity of some 4-aminobenzamides. *J. Med. Chem.* 1984**, 27**, 779.
18. P. Strazzolini, A. G. Giumanini, A. Runcio, M. Scuccato. Experiments on the chaperon effect in the nitration of aromatics. *J. Org. Chem.* 1998**, 63**, 952.
19. F. H. McMillan, K. A. Kun, C. B. McMillan, J. A. King. Hexamethylene-1,6-bis-t-amines in which part of the six carbon chain is also part of a six-membered ring. *J. Amer. Chem. Soc.* 1956**, 78**, 4077.
20. R. Campbell, C. J. Peterson. N-Nitrobenzamides. I. Synthesis, spectra, and structure. *J. Org. Chem.* 1963**, 28**, 2294.
21. L. M. Jackman, T. E. Kavanagh, R. C. Haddon. Studies in nuclear magnetic resonance—IX. Rotational barriers in substituted N,N-dimethylbenzamides. *Org. Magn. Resonance.* 1969, **1**, 109.
22. R. J. Sorenson. Selective N-Arylation of aminobenzanilides under mild conditions using triarylbismuthanes. *J. Org. Chem.* 2000**, 65**, 7747.

23. H. Wenker. Alkyl- and dialkylamides of p-aminobenzoic acid. *J. Amer. Chem. Soc.* 1938, **60**, 1081.
24. F. B. Mallory, S. P. Varimbi. Furazan oxides. III. An unusual type of aromatic substitution reaction. *J. Org. Chem.* 1963, **28**, 1656.
25. C. l. M. G. dos Santos, T. McCabe, G. W. Watson, P. E. Kruger, T. Gunnlaugsson. The recognition and sensing of anions through “positive allosteric effects” using simple urea−amide receptors. *J. Org. Chem.* 2008, **73**, 9235.
26. T. V. RajanBabu, G. S. Reddy, T. Fukunaga. Nucleophilic addition of silyl enol ethers to aromatic nitro compounds: scope and mechanism of reaction. *J. Amer. Chem. Soc.* 1985, **107**, 5473.
27. I. T. Forbes. A short and efficient synthesis of N-substituted indol-2-ones (oxindoles). *Tetrahedron Lett.* 2001, **42**, 6943.
28. T. Nakashima, I. Suzuki. Ring contraction of 3-hydroxyquinolines to oxindoles with hydrogen peroxide in acetic acid. *Chem. Pharm. Bull.* 1969, **17**, 2293.
29. R. L. Shriner, R. G. Child. The synthesis of N-substituted carbamates. *J. Amer. Chem. Soc.* 1952, **74**, 549.
30. E. Späth, B. L. Manjunath, M. Pailer, H. S. Jois. Synthese und konstitution des psoralens. *Berichte der deutschen chemischen Gesellschaft (A and B Series)* 1936, **69**, 1087.
31. K. J. P. Orton, CXLIII.-Benzoylation of fatty acids in the presence of ammonia. Formation of amides. *J. Chem. Soc., Trans.* 1901, **79**, 1351.
32. L. G. Ulysse, Q. Yang, M. D. McLaws, D. K. Keefe P. R. Guzzo, B. P. Haney. Process development and pilot-scale synthesis of new cyclization conditions of substituted phenylacetamides to tetrahydroisoquinoline-2-ones using Eaton’s reagent. *Org. Proc. Res. Dev.* 2009, **14**, 225.
33. G. Shtacher, S. Dayagi. Iodophenyl derivatives of .alpha.-methyl alanine and isovaline as potential oral cholecystographic agents. *J. Med. Chem.* 1972, **15**, 1174.
34. C. K. Ingold, F. R. Shaw, E. H. Ingold. CXIX.—The nature of the alternating effect in carbon chains. Part XIV. The directive action of groups of the form –CH2·SO2·R in aromatic substitution. *J. Chem. Soc.* 1927, 813.
35. K. Zahn, H. Koch. Acid dyestuffs of the anthraquinone series. DE623883 (C), 1936.
36. C. Wong, R. J. Griffin, I. R. Hardcastle, J. S. Northen, L.-Z. Wang, B. T. Golding. Synthesis of sulfonamide-based kinase inhibitors from sulfonates by exploiting the abrogated SN2 reactivity of 2,2,2-trifluoroethoxysulfonates. *Org. Biomol. Chem.* 2010, **8**, 2457.