Supporting information

Rational design of bisubstrate-type analogs as inhibitors of DNA methyltransferases in cancer cells

Ludovic Halby, Yoann Menon, Elodie Rilova, Dany Pechalrieu, Véronique Masson, Celine Faux, Mohamed Amine Bouhlel, Marie-Hélène David-Cordonnier, Natacha Novosad, Yannick Aussagues, Arnaud Samson, Laurent Lacroix, Fréderic Ausseil, Laurence Fleury, Dominique Guianvarc'h, Clotilde Ferroud and Paola B. Arimondo*

The supporting information contains:

-detailed synthesis procedures;

-detailed biological assays;

-cytotoxicity data;

-Tm melting curves;

-DNase footprinting experiments;

-luciferase reactivation fold data.

Chemistry

All chemicals were from Sigma-Aldrich or Alfa Aesar.

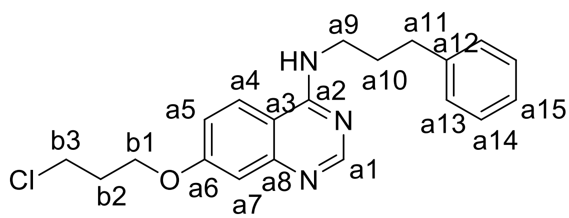
The NMR spectra were recorded on a Bruker Avance II spectrometer equipped with a 13C cryoprobe at 500 MHz for 1H and 125 MHz for 13C; 2D experiments were performed using standard Bruker programs and atoms attribution was performed thanks to 2D correlations. Chemical shifts are given in ppm. Coupling constants J are measured in Hz. Splitting patterns are designed as follows: s, singlet; bs broad singlet; d, doublet; bd broad doublet; t, triplet; brt, broad triplet; dd, doublet of a doublet; m, multiplet; ddd, doublet of a doublet of a doublet; q, quartet; quint, quintet, sext, sextet.

HRMS-ESI were obtained on a Bruker MicroTOF.

Semi preparative HPLC was performed on an apparatus equipped with a VWR International LaPrep pump P110, a VWR LaPrep P314 Dual l absorbance detector and EZChrom software. C18 reversed-phase column (Waters x-bridge, RP-18, 25 ´ 250 mm, 5 µm) were used for semi preparative HPLC with a binary gradient elution (solvent A: H_2O and solvent B: CH_3CN) or (solvent A: H_2O/0.01% TEA and solvent B: CH_3CN/0.01% TEA) or (solvent A: H_2O/0.01% formic acid and solvent B: CH_3CN/0.01% formic acid), a flow rate of 25 mL.min-1 and the chromatogram was monitored at 250 and 320 nm. Fraction purity was verified using reversed-phase HPLC on an X- terra C18 MS column (3.9 100 mm; Waters) with a linear gradient acetonitrile in 0.01% TEA (0 to 95% CH_3CN).

4-(3-phenylpropylamino)-7-(2-chloroethoxy)quinazoline (4)

A solution of **3** (440mg; 2.01mmol) in thionyl chloride (10mL) and a catalytic amount of DMF was boiled for 30min. The solvent was removed and the crude product was dissolved in a solution of phenylpropylamine (570µL; 4.0mmol) in DMF and the mixture was stirred at room temperature for 2h. The mixture was diluted with ethyl acetate and the organic phase was washed with a saturated solution of Na_2CO_3, brine and dried over magnesium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ethyl acetate (0→100% ethyl acetate) in cyclohexane to obtain **4** as a pale brown solid (607mg; 1.70mmol; yield 85%).



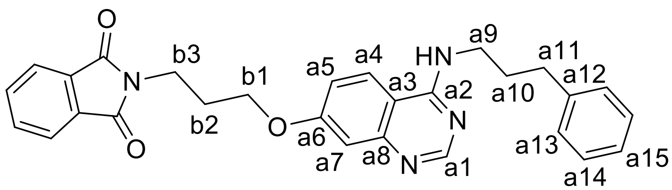
^{1}H NMR (500MHz, $CDCl_3$) δ 8.58 (s, 2H, Ha1), 7.35-7.13 (m, 7H, Ha4 and Ha7 and Ha15 and Ha13 and Ha14), 6.99 (dd, *J*=2.4, 9.0Hz, 1H, Ha5), 5.53 (brs, 1H, HNH), 4.22 (t, *J*=6.0Hz, 2H, Hb1), 3.76 (t, *J*=6.0Hz, 2H, Hb3), 3.70 (q, *J*=7.2Hz, 2H, Ha9), 2.79 (t, *J*=7.2Hz, 2H, Ha11), 2.28 (quint, *J*=6.1Hz, 2H, Ha10), 2.07 (quint, *J*=7.0Hz, 2H, Hb2).

^{13}C NMR (125MHz, $CDCl_3$) δ 162.0 (Ca6), 159.1 (Ca2), 156.1 (Ca1), 151.7 (Ca8), 141.7 (Ca12), 128.8 (Ca13), 128.6 (Ca14), 126.3 (Ca15), 122.0 (Ca4), 117.8 (Ca5), 109.3 (Ca3), 108.1 (Ca7), 64.7 (Cb1), 41.4 (Cb3), 41.3 (Ca9), 33.8 (Ca11), 32.1(Cb2), 30.8 (Ca10).

HRMS-ESI (m/z) calculated for $C_{20}H_{23}N_3ClO$ $[M+H]^+$: 356.1524; Found: 356.1527.

7-((3-phthalimido)propyloxy)-4-((3-phenylpropyl)amino)quinazoline (5)

To a solution of **4** (50mg; 141µmol) in DMF (1mL) was added phthalimide potassium salt and the mixture was heated at 90°C for 6h. The mixture was diluted with ethylacetate and the organic phase was washed with a saturated solution of Na_2CO_3, brine and dried over magnesium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ethylacetate (0→100% ethylacetate) in cyclohexane to obtain **5** as a pale yellow solid (63mg; 138µmol; yield 98%).



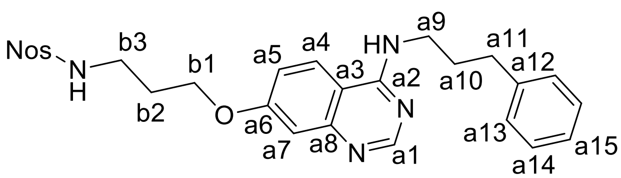
^{1}H NMR (500MHz, CDCl$_3$) δ 8.58 (s, 1H, Ha1), 7.86 (m, 2H, Hphtha), 7.74 (m, 2H, Hphtha), 7.35-7.25 (m, 6H, Ha4 and Ha13 and Ha14 and Ha15), 7.10 (d, *J*=2.5Hz, 1H, Ha7), 6.92 (dd, *J*=2.5, 9.0Hz, 1H, Ha5), 5.47 (brt, *J*=5.1Hz, 1H, HNH), 4.15 (t, *J*=6.3Hz, 2H, Hb1), 3.96 (t, *J*=7.0Hz, 2H, Hb3), 3.72 (q, *J*=6.7Hz, 2H, Ha9), 2.82 (q, *J*=7.3Hz, 2H, Ha11), 2.26 (quint, *J*=6.3Hz, 2H, Hb2), 2.10 (quint, H=7.3Hz, 2H, Ha10).

^{13}C NMR (125MHz, CDCl$_3$) δ 168.3 (Cphtha), 162.0 (Ca6), 159.0 (Ca2), 157.8 (Ca1), 151.3 (Ca8), 141.5 (Ca12), 134.0 (Cphtha), 132.1 (Cphtha), 128.7 (Ca13), 128.4 (Ca14), 126.1 (Ca15), 123.3 (Cphtha), 121.8 (Ca4), 117.9 (Ca5), 109.0 (Ca3), 107.6 (Ca7), 65.7 (Cb1), 41.1 (Ca9), 35.3 (Cb3), 33.7 (Ca11), 30.7 (Ca10), 28.0 (Cb2).

HRMS-ESI (m/z) calculated for $C_{28}H_{27}N_4O_3$ $[M+H]^+$: 467.2078; Found: 467.2078.

7-((2-nitrobenzenesulfonamido)propyloxy)-4-((3-phenylpropyl)amino) quinazoline (6)

To a solution of **5** (60mg; 129µmol) in ethanol (2mL), was added *N*-methylhydrazine (200µL). After stirring at room temperature for 18h, the solvent was removed and the residue was co-evaporated with toluene until the *N*-methylhydrazine was completely eliminated. To the crude product was added a solution of 2-nitrobenzene sulfonyl chloride (71mg; 322mmol) and TEA (54µL; 387µmol). The mixture was stirred at room temperature for 3h, then was diluted with ethyl acetate. The organic phase was washed with saturated Na_2CO_3, with brine and dried over magnesium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of methanol (0→10% MeOH) in dichloromethane to obtain **6** as a pale yellow solid (61mg; 117µmol; yield 91%).



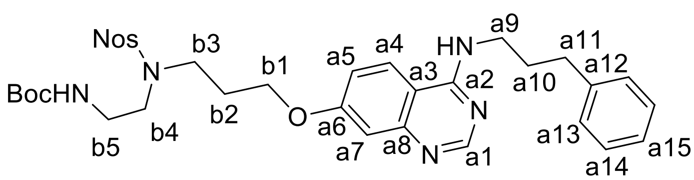
^{1}H NMR (500MHz, $CDCl_3$) δ 8.59 (s, 1H, Ha1), 8.15 (m, 1H, HNos), 7.83 (m, 1H, HNos), 7.69 (m, 2H, HNos), 7.37-7.30 (m, 3H, Ha4 and Ha13), 7.22-7.15 (m, 3H, Ha14 and Ha15), 7.10-7.05 (m, 2H, Ha7 and Ha5), 5.84 (brt, *J*=5.3Hz, 1H, HNH), 5.51 (brt, *J*=5.4Hz, 1H, HNH), 4.13 (t, *J*=3.4Hz, 2H, Hb1), 3.73 (q, *J*=6.3Hz, 2H, Ha9), 3.42 (q, *J*=6.5Hz, Hb3), 2.82 (q, *J*=6.8Hz, 2H, Ha11), 2.17-2.07 (m, 4H, Ha10 and Hb2).

^{13}C NMR (125MHz, $CDCl_3$) δ 161.5 (Ca6), 159.0 (Ca2), 155.9 (Ca1), 151.3 (Ca8), 148.0 (CNos), 141.5 (Ca12), 133.6 (CNos), 133.5 (CNos), 132.8 (CNos), 130.9 (CNos), 128.7 (Ca13), 128.4 (Ca14), 126.2 (Ca15), 125.4 (CNos), 122.0 (Ca4), 117.9 (Ca5), 109.2 (Ca3), 107.6 (Ca7), 66.1 (Cb1), 41.8 (Cb3), 41.2 (Ca9), 33.7 (Ca11), 30.7 (Ca10), 28.9 (Cb2).

HRMS-ESI (m/z) calculated for $C_{29}H_{37}N_8O_4$ $[M+H]^+$: 522.1806; Found: 522.1801.

4-((3-phenylpropyl)amino)-7-(3-(N^1-(Bocaminoethyl)-N^2-(2-nitrobenzenesulfonamido))propyloxy)-4-((3-phenylpropyl)amino)quinazoline (7)

To a solution of **6** (30mg; 57µmol), TEA (60µL; 440µmol), in DMF (0.3mL) was added 2-(*N*-Boc-amino)ethylbromide (20mg; 70µmol). The mixture was stirred at room temperature overnight. The mixture was diluted with ethyl acetate. The organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed by vacuum and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→5% MeOH/NH_3) in dichloromethane to afford crude **7** as a white foam (35mg, 53µmol; yield 92%).



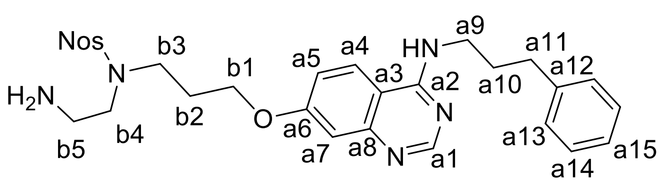
^{1}H NMR (500MHz, DMSO) δ 8.39 (s, 1H, Ha1), 8.14 (d, *J*=9.2Hz, 1H, Ha4), 8.10 (t, *J*=5.5Hz, HNH), 8.05-8.00 (m, 1H, HNos), 7.97-7.92 (m, 1H, HNos), 7.87-7.76 (m, 2H, HNos), 7.33-7.21 (m, 4H, Ha14 and Ha13), 7.21-7.14 (m, 1H, Ha15), 7.00 (dd, *J*=2.5, 9.1Hz, 1H, Ha5), 6.99 (d, *J*=2.5Hz, 1H, Ha7), 5.94 (brt, *J*=5.8Hz, 1H, HNH), 4.07 (t, *J*=4.2Hz, 2H, Hb1), 3.59-3.46 (m, 4H, Ha9 and Hb3), 3.41-3.31 (m, 2H, Hb4), 3.14 (brq, *J*=6.4Hz, 2H, Hb5), 2.05-1.89 (m, 4H, Ha10 and Hb2), 1.36 (s, 9H, HBoc).

^{13}C NMR (125MHz, DMSO) δ 161.8 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 156.0 (CBoc), 151.7 (Ca8), 148.0 (CNos), 142.2 (Ca12), 134.9 (CNos), 132.9 (CNos), 132.0 (CNos), 130.2 (CNos), 128.7 (Ca13), 128.4 (Ca14), 126.2 (Ca15), 124.8 (CNos), 124.7 (Ca4), 117.1 (Ca5), 109.6 (Ca3), 107.8 (Ca7), 78.3 (CBoc), 65.4 (Cb1), 47.3 (Cb4), 45.4 (Ca9), 40.6 (Cb3), 39.3 (Cb5), 33.2 (Ca11), 30.8 (Ca10), 28.6 (CBoc), 27.8 (Cb2).

MS-ESI (m/z) calculated for $C_{33}H_{40}N_6O_{7S}$ $[M+H]^+$: 664.2679; Found: 664.267.

4-((3-phenylpropyl)amino)-7-(3-(N^1-(aminoethyl)-N^2-(2-nitrobenzenesulfonamido))propyloxy)-4-((3-phenylpropyl)amino)quinazoline (8)

A mixture of **7** (35mg; 53µmol) in TFA (0.5 mL) was stirred at room temperature for 0.5h. TFA was removed by vacuum and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→10% MeOH/NH_3) in dichloromethane to afford **8** as a colorless foam (29mg, 51µmol, yield 96%).



^{1}H NMR (500MHz, DMSO) δ 8.38 (s, 1H, Ha1), 8.15 (d, *J*=9.3Hz, 1H, Ha4), 8.10 (brt, *J*=5.5Hz, HNH), 8.07-8.00 (m, 1H, HNos), 7.96-7.93 (m, 1H, HNos), 7.85-7.78 (m, 2H, HNos), 7.30-7.17 (m, 4H, Ha14 and Ha13), 7.20-7.16 (m, 1H, Ha15), 7.06 (dd, *J*=2.6, 8.9Hz, 1H, Ha5), 6.99 (d, *J*=2.3Hz, 1H, Ha7), 4.08 (t, *J*=6.1Hz, 2H, Hb1), 3.57-3.47 (m,4H, Ha9 and Hb3), 3.28 (t, *J*=7.12Hz, Hb4), 2.74-2.65 (m, 4H, Hb5 and Ha11), 2.04-1.90 (m, 4H, Ha10 and Hb2).

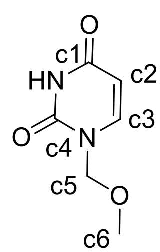
^{13}C NMR (125MHz, DMSO) δ 161.8 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.7 (Ca8), 148.0 (CNos), 142.2 (Ca12), 134.8 (CNos), 132.9 (CNos), 132.2 (CNos), 130.2 (CNos), 128.8 (Ca13), 128.7 (Ca14), 126.2 (Ca15), 124.8 (CNos), 124.7 (Ca4), 117.1 (Ca5), 109.6 (Ca3), 107.8

(Ca7), 78.3 (CBoc), 65.5 (Cb1), 50.8 (Cb4), 45.5 (Ca9), 40.7 (Cb3), 39.4 (Cb5), 33.2 (Ca11), 30.8 (Ca10), 27.8 (Cb2).

MS-ESI (m/z) calculated for $C_{28}H_{32}N_6O_5S$ $[M+H]^+$: 564.2679; Found: 564.22

1-(methoxymethyl)uracil (9)

To a solution of uracil (0.88g; 7.94mmol) in 250 mL of DCM was added N,O-bis(trimethylsilyl)acetamide (4.8mL; 19.4mmol). The mixture was stirred 1h at room temperature. To the reaction mixture was added chloromethylmethyl ether (784µL; 10.32 mmol) and the mixture was stirred 17h at room temperature. The solvent was removed and the residue was purified by silica gel chromatography using the eluent cyclohexane / ethylacetate (7/3) to give **9** (988mg; 7.4mmol; yield 93%) as a white powder.



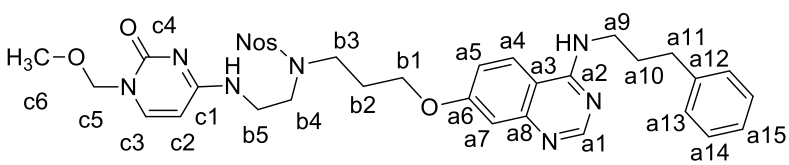
^{1}H NMR (500MHz ; DMSO) δ 11.32 (s, 1H, HNH) , 7.70 (d, *J*=8.0Hz, 1H, Hc3), 5.61 (d, *J*=8.0Hz, 1H, Hc2), 5.02 (s, 2H, Hc5), 3.27 (s, 3H, Hc6).

^{13}C (125MHz, DMSO) δ 164.0 (Cc1), 151.5 (Cc4), 145.4 (Cc3), 101.9 (Cc2), 78.0 (Cc5), 56.4 (C6).

HRMS-ESI(m/z) calculated for $C_6H_8N_2NaO_3$ $[M+Na]^+$: 179.0427 ; Found: 179.0416.

7-(3-N((2-(N^4-(1-methoxymethyl)cytosinyl)ethyl)-N^2-(2-nitrobenzenesulfonamido))propyloxy)-4-((3-phenylpropyl)amino)quinazoline (10)

To a solution of 1,2,4-triazole (56mg; 0.80mmol) and $POCl_3$ (24µL; 0.264mmol) in 0.6mL of acetonitrile at 0°C was added TEA 112µL dropwise. The reaction mixture was stirred at 0°C for 40min then 30min at room temperature. **9** (22mg; 121µmol) was added and the mixture was vigorously stirred at room temperature overnight. The solvent was removed and 1mL of a solution of previously prepared **8** (28mg; 50µmol) was added to the residue. The reaction mixture was stirred 6h at RT. The mixture was diluted with ethyl acetate. The organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→10% $MeOH/NH_3$) in dichloromethane or by reversed phase HPLC using a linear acetonitrile gradient with 0.2% of TEA (0→80% CH_3CN) to afford **10** (19mg; 27µmol, yield 54%) as a white powder.



^{1}H NMR (500MHz, DMSO) δ 8.39 (s, 1H, Ha1), 8.13 (d, *J*=9.5Hz, 1H, Ha4), 8.10-8.07 (m, 2H, HNos and HNH), 7.96-7.89 (m, 1H, HNos and HNH), 7.83-7.76 (m, 2H, HNos), 7.55 (d, *J*=7.4Hz, 1H, Hc3), 7.32-7.22 (m, 4H, Ha14 and Ha13), 7.21-7.16 (m, 1H, Ha15), 7.07 (dd, *J*=2.5, 9.0Hz, 1H, Ha5), 6.98 (d, *J*=2.5Hz, 1H, Ha7), 5.68 (d, *J*=7.4Hz, 1H, Hc2), 5.00 (s, 2H, Hc5), 4.08 (t, *J*=5.9Hz, 2H, Hb1), 3.57-3.47 (m,8H, Hb5, Hb4 , Ha9 and Hb3), 3.24 (s, 3H

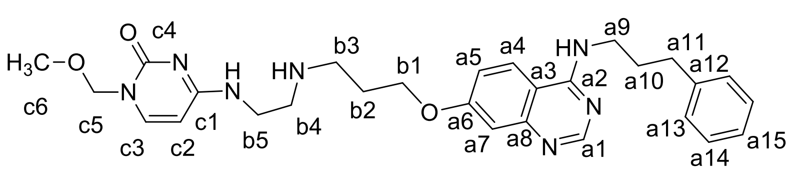
Hc6), 2.69 (t, *J*=77Hz, 4H, Ha11), 2.03 (quint, *J*=6.2Hz, 2H, Hb2), 1.95 (quint, *J*=7.4Hz, 2H, Ha10).

^{13}C NMR (125MHz, DMSO) δ 164.5 (Cc1), 161.8 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 156.0 (Cc4), 151.7 (Ca8), 148.0 (CNos), 145.1 (Cc3), 142.2 (Ca12), 134.9 (CNos), 133.0 (CNos), 131.8 (CNos), 130.5 (CNos), 128.8 (Ca13), 128.7 (Ca14), 126.2 (Ca15), 124.8 (CNos), 124.7 (Ca4), 117.2 (Ca5), 109.6 (Ca3), 107.8 (Ca7), 95.3 (Cc2), 78.9 (Cc5), 65.4 (Cb1), 56.3 (Cc6), 46.5 (Cb4), 45.3 (Ca9), 40.7 (Cb3), 39.1 (Cb5), 33.2 (Ca11), 30.8 (Ca10), 27.8 (Cb2).

MS-ESI (m/z) calculated for $C_{34}H_{38}N_8O_7S$ $[M+H]^+$: 703.27; Found: 703.27.

7-(3-((2-(N^4-(1-methoxymethyl)cytosinyl)ethyl)amino)propyloxy)-4-((3-phenylpropyl)amino)quinazoline (1)

To a solution of **10** (15mg; 21μmol) in acetonitrile (1mL), K_2CO_3 (9mg; 65μmol) and thiophenol (12μL; 120μmol) were added. The mixture was stirred overnight at room temperature then diluted with ethyl acetate. The organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→10% MeOH/NH_3) in dichloromethane or by reversed phase HPLC using a linear acetonitrile gradient with 0.2% of TEA (0→80% CH_3CN) to afford **1** as a white powder (8.0mg; 15.4μmol, yield 73%).



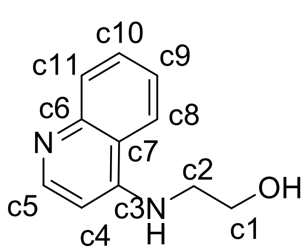
^{1}H NMR (500MHz, DMSO) δ 8.38 (s, 1H, Ha1), 8.15 (d, *J*=9.4 Hz, 1H, Ha4), 8.11 (brt, *J*= 5.4Hz, 2H, HNH), 7.87 (brt, *J*=4.6Hz, 1H, HNH), 7.54 (d, *J*=7.2Hz, 1H, Hc3), 7.32-7.22 (m, 4H, Ha14 and Ha13), 7.21-7.16 (m, 1H, Ha15), 7.10 (dd, *J*=2.7, 9.1Hz, 1H, Ha5), 7.07 (d, *J*=2.5Hz, 1H, Ha7), 5.77 (d, *J*=7.7Hz, 1H, Hc2), 4.99 (s, 2H, Hc5), 4.18 (t, *J*=6.5Hz, 2H, Hb1), 3.52 (brq, *J*=6.5Hz, 2H, Ha9) 3.39 (brq, *J*=5.7Hz, 2H, Hb5), 3.22 (s, 3H Hc6), 2.84-2.76 (m, 4H, Hb4 and Ha9), 2.65 (t, *J*=7.7Hz, 4H, Ha11), 2.03-1.89 (m, 4H, Hb2 and Ha10).

^{13}C NMR (125MHz, DMSO) δ 164.5 (Cc1), 162.0 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 156.0 (Cc4), 151.8 (Ca8), 144.7 (Cc3), 142.2 (Ca12), 128.8 (Ca13), 128.7 (Ca14), 126.2 (Ca15), 124.7 (Ca4), 117.2 (Ca5), 109.6 (Ca3), 107.9 (Ca7), 95.2 (Cc2), 78.9 (Cc5), 66.3 (Cb1), 56.3 (Cc6), 48.3 (Cb4), 40.6 (Ca9), 45.8 (Cb3), 39.5 (Cb5), 33.2 (Ca11), 30.8 (Ca10), 27.8 (Cb2).

HRMS-ESI (m/z) calculated for $C_{28}H_{36}N_8O_3$ $[M+H]^+$: 518,2874; Found: 518,2885.

4-((2-Hydroxyethyl)amino)quinoline (11)

A mixture of 4-chloroquinoline (360mg; 2.21mmol) in ethanolamine (1.5mL; 22mmol) was stirred at 125°C for 4h. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of methanol (0→10% MeOH) in dichloromethane to afford **11** as a white powder (414mg; 2.20mmol; quantitative yield).



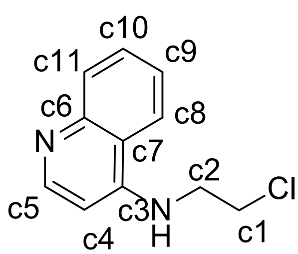
^{1}H NMR (500MHz, $CDCl_3$) δ 8.38 (d, *J*=5.4Hz, 1H, Hc5), 8.19 (dd, *J*=0.9, 8.3Hz, 1H, Hc8), 7.77 (dd, *J*=0.9, 8.3Hz, 1H, Hc11), 7.59 (ddd, *J*=1.3, 6.7, 8.3Hz, 1H, Hc10), 7.40 (ddd, *J*=1.3, 6.7, 8.3Hz, 1H, Hc9), 7.07 (brt, *J*=5.2Hz, 1H, HOH), 6.46 (d, *J*=5.4Hz, 1H, Hc4), 4.83 (brt, *J*=5.5Hz, 1H, HNHc), 3.66 (q, *J*=6.0Hz, 2H, Hc1), 3.35 (q, *J*=5.4Hz, 2H, Hc2).

^{13}C NMR (125MHz, $CDCl_3$) δ 151.1 (Cc5), 150.5 (Cc3), 148.8 (Cc6), 129.5 (Cc8), 129.1 (Cc10), 124.2 (Cc9), 122.1 (Cc11), 119.3 (Cc7), 98.6 (Cc4), 59.3 (Cc1), 45.5 (Cc2).

HRMS-ESI (m/z) calculated for $C_{11}H_{13}N_2O$ $[M+H]^+$: 189.1022; found: 189.1031.

4-((2-chloroethyl)amino)quinoline chlorhydrate (12)

11 (360mg; 1.92mmol) was solubilized in thionyl chloride (3ml). The mixture was flash boiled and the solvent was removed. Toluene was added to remove the residual thionyl chloride by co-evaporation. The residue was triturated in dichloromethane and the solid was filtrated to afford **12** as a white solid (360mg; 1.75mmol; yield 91%).



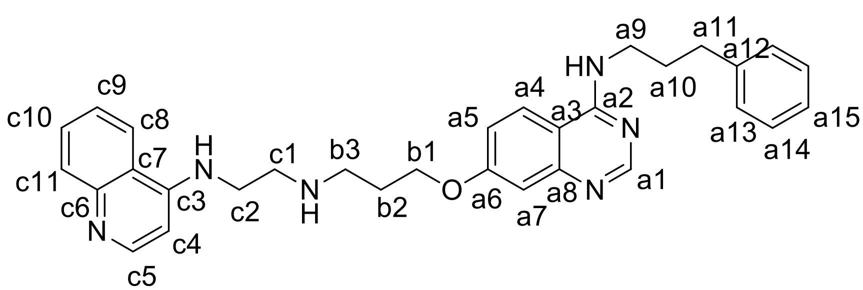
^{1}H NMR (500MHz, $CDCl_3$) δ 8.59 (d, *J*=5.2Hz, 1H, Hc5), 8.00 (dd, *J*=0.7, 8.3Hz, 1H, Hc8), 7.79 (d, *J*=8.3Hz, 1H, Hc11), 7.65 (ddd, *J*=1.3, 7.9, 8.3Hz, 1H, Hc10), 7.45 (ddd, *J*=1.3, 7.0, 8.3Hz, 1H, Hc9), 6.43 (d, *J*=5.3Hz, 1H, Hc4), 5.51 (brs, 1H, HNHc), 3.84 (t, *J*=5.8Hz, 2H, Hc1), 3.70 (q, *J*=5.8Hz, 2H, Hc1).

^{13}C NMR (125MHz, $CDCl_3$) δ 151.0 (Cc5), 148.9 (Cc3), 148.5 (Cc6), 130.0 (Cc8), 129.2 (Cc10), 125.0 (Cc9), 119.3 (Cc11), 118.9 (Cc7), 99.0 (Cc4), 44.4 (Cc2), 42.6 (Cc1).

HRMS-ESI (m/z) calculated for $C_{11}H_{13}N_2Cl$ $[M+H]^+$: 207.0684; found: 207.0678.

7-(3-((2-(quinolin-4-ylamino)ethyl)amino)propyloxy)-4-((3-phenylpropyl) amino)quinazoline (14)

To a solution of **6** (50mg; 96µmol), K_2CO_3 (22mg; 0.160mmol) and a catalytic amount of KI in DMF (1mL) was added **12** (40mg; 288µmol). The mixture was stirred at 65°C overnight then thiophenol (24µL; 240mmol) was added. The mixture was stirred for a day then diluted with ethyl acetate. The organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→10% $MeOH/NH_3$) in dichloromethane or by reversed phase HPLC using a linear acetonitrile gradient with 0.2% of TEA (0→80% CH_3CN) to afford **14** as a white powder (32mg; 0.64mmol, yield 67%).



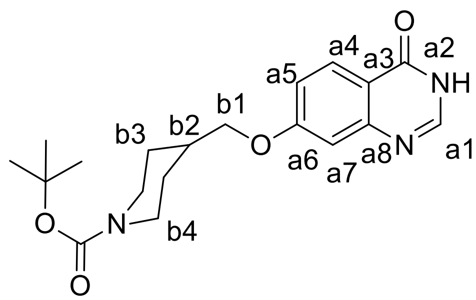
^{1}H NMR ((500MHz, DMSO+MeOD) δ 8.39 (m, 2H, Ha1 and Hc5), 8.19-8.07 (m, 3H, Hc8, HNH and Ha4), 7.76 (dd, *J*=0.9, 8.4Hz, 1H, Hc11), 7.58 (ddd, *J*=1.3, 6.7, 8.2Hz, 1H, Hc10), 7.39 (ddd, *J*=1.3, 6.7, 8.2Hz, 1H, Hc9), 7.43-7.20 (m, 4H, Ha13 and Ha14), 7.17 (brt, *J*= 7.1Hz, Ha15), 7.12-7.04 (m, 3H, Ha7, HNH and Ha5), 6.47 (d, *J*=5.7Hz, 1H, Hc4), 4.17 (t, *J*=6.2Hz, 2H, Hb1), 3.52 (q, *J*=6.9Hz, 2H, Ha9), 3.35 (m, 2H, Hc2), 2.84 (t, *J*= 6.6Hz, 2H, Hc1), 2.73 (t, *J*=6.5Hz, 2H, Hb3), 2.67 (t, *J*=7.4Hz, 2H, Ha11), 2.00-1.83 (m, 4H, Ha10 and Hb2).

^{13}C NMR (125MHz, DMSO+MeOD) δ 162.1 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 151.1 (Cc5), 150.4 (Cc3), 148.7 (Cc6), 142.2 (Ca12), 129.5 (Cc11), 129.1 (Cc10), 128.8 (Ca13), 128.7 (Ca14), 126.2 (Ca15), 124.7 (Ca4), 124.2 (Cc9), 122.0 (Cc8), 119.3 (Cc7), 117.1 (Ca5), 109.5 (Ca3), 107.8 (Ca7), 98.6 (Cc4), 66.9 (Cb1), 48 (Cc1), 46 (Cb3), 43(Cc2), 40.6 (Ca9), 33.1 (Ca11), 30.8 (Ca10), 29.8 (Cb2).

HRMS-ESI (m/z) calculated for $C_{31}H_{35}N_6O$ $[M+H]^+$: 507.2667; found: 507.2666.

7-*O*-((*N*-Boc)piperidin-4-ylmethoxy)quinazolinone (16)

To a mixture of (*N*-Boc)piperidin-4-ylmethanol (1.12g; 5.2mmol) in DMF (2mL) at 0°C under argon was added sodium hydride (125mg, 5.2mmol). The mixture was stirred for 15min at 0°C then **15** (162mg; 1mmol) was added portion wise. The mixture was stirred at 0°C for 10min then at room temperature for 10min, at 60°C for 15min and finally at 110°C for 3h. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over magnesium sulfate and the solvent was removed. The crude product was purified by silica gel flash chromatography using a linear gradient of ethyl acetate (0→100% EtOAc) in cyclohexane to afford **16** as a white powder (241mg; 67µmol; yield 67%).



^{1}H NMR (500MHz, $CDCl_3$) δ 11.50 (s, 1H, HNH), 8.19 (d, 1H, *J*= 8.9, Ha4), 8.7 (s, 1H, Ha1), 7.12-7.07 (m, 2H, Ha7 and Ha5), 4.18 (sb, 2H, Hb4), 3.94 (d, *J*= 6.8, 2H, Hb1), 2.76 (m, 2H, Hb4), 2.03 (m, 1H, Hb2), 1.84 (m, 2H, Hb3), 1.47 (s, 9H, HBoc), 1.38-1.11 (m, 2H, Hb3).

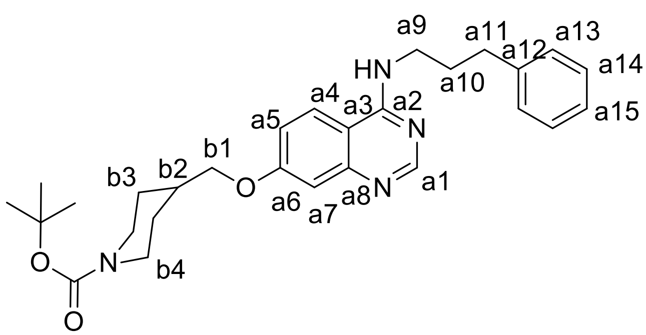
^{13}C NMR (125MHz, $CDCl_3$) δ 164.6 (Ca6), 162.3 (Ca2), 155.2 (CBoc), 151.5 (Ca8), 144.3 (Ca1), 128.3 (Ca4), 118.0 (Ca5), 116.3 (Ca3), 109.4 (Ca7), 79.9 (CBoc), 73.0 (Cb1), 47.0 (Cb4), 36.3 (Cb2), 29.1 (Cb3), 28.8 (CBoc).

HRMS-ESI (m/z) calculated for $C_{19}H_{26}N_3O_4$ $[M+H]^+$: 360.1918; found: 360.1911.

4-((3-phenylpropyl)amino)-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy)) quinazoline (17)

To a solution of 1,2,4-triazole (280mg; 4mmol) and $POCl_3$ (120µl; 1.32mmol) in 3mL of acetonitrile at 0°C was added TEA (560µL) dropwise. The reaction mixture was stirred at 0°C for 40min then 30min at room temperature. **16** (215mg; 0.6mmol) was added and the mixture was vigorously stirred at room temperature overnight. The reaction was followed by TLC using ethyl acetate as eluent. The mixture was refluxed for 1h to reach completion. After complete consumption of the starting material, the solvent was removed and the residue was taken off with ethyl acetate and washed with water and brine, and dried over sodium sulfate. The solvent was removed and the residue was solubilized in DMF (2mL). 3-Phenylpropylamine (130µL;

1.0mmol) and TEA (167µL; 1.2mmol) were added and the mixture was stirred for 3h at room temperature. The mixture was diluted with ethyl acetate and washed with water, brine and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ethyl acetate (0→100% EtOAc) in cyclohexane to afford **17** as a white powder (232mg; 0.49mmol; yield 81%).



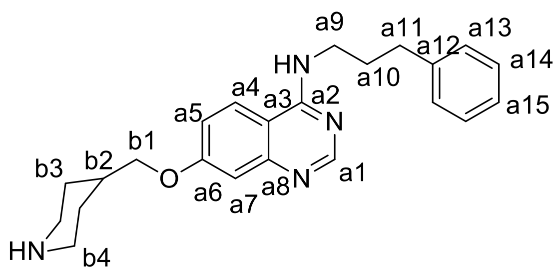
^{1}H NMR (500MHz, CDCl$_3$) δ 8.57 (s, 1H, Ha1), 7.33-7.28 (m, 3H, Ha4 and Ha13), 7.25-7.20 (m, 3H, Ha15 and Ha14), 7.12 (d, *J*=2.6Hz, 1H, Ha7), 7.00 (dd, *J*=2.6, 9.5Hz, 1H, Ha5), 5.44 (brt, *J*=5.2, 1H, HNH), 4.17 (brs, 2H, Hb4eq), 3.92 (d, *J*=6.3Hz, 2H, Hb1), 3.70 (q, *J*=7.2Hz, 2H, Ha9), 2.79 (t, 2H, *J*=7.3Hz, Ha11), 2.75 (brt, *J*=11.2Hz, 2H, Hb4ax), 2.09 (quint, *J*=7.3Hz, 2H, Ha10), 2.01 (m, 1H, Hb2), 1.83 (d, *J*=12.3Hz, 2H, Hb3eq), 1.47 (s, 9H, HBoc), 1.31 (dq, *J*=4.5-12.3Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, CDCl$_3$) δ 162.9 (Ca6), 159.2 (Ca2), 156.1 (Ca1), 155.0 (CBoc), 151.7 (Ca8), 141.7 (Ca12), 128.8 (Ca13), 128.6 (Ca14), 126.3 (Ca15), 122.0 (Ca4) 118.0 (Ca5), 109.1 (Ca3), 108.0 (Ca7), 79.6 (CBoc), 72.6 (Cb1), 43.7(Cb4), 41.3 (Ca9), 36.1 (Cb2), 33.8 (Ca11), 30.9 (Ca10), 29.0 (Cb3), 28.6 (CBoc).

HRMS-ESI (m/z) calculated for $C_{19}H_{26}N_3O_4$ [M+H]$^+$: 477.2860; found: 477.2861.

4-((3-phenylpropyl)amino)-7-*O*-(piperidin-4-ylmethoxy)quinazoline (18)

A mixture of **17** (220mg; 0.46mmol) in TFA was stirred for 1h at room temperature. TFA was removed and the residue was diluted with dichloromethane and the organic phase was washed with saturated Na_2CO_3. The solvent was removed and **18** was obtained as pale blue foam (165mg; 0.44mmol; yield 96%).

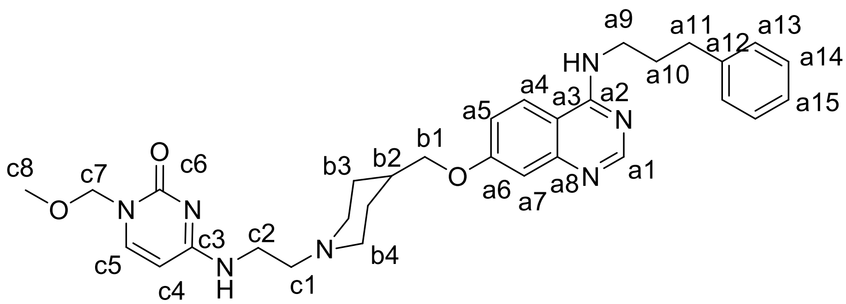


^{1}H NMR (500MHz, DMSO) δ 9.94 (brs, 1H, HNH), 8.79 (s, 1H, Ha1), 8.4 (d, *J*=9.3Hz, 1H, Ha4), 7.43-7.13 (m, 7H, Ha5, Ha7, Ha13, Ha14 and Ha15), 4.06 (d, *J*=6.2Hz, 2H, Hb1), 3.70 (q, *J*=7.2Hz, 2H, Ha9), 3.34 (brd, *J*=12.6Hz, 2H, Hb4eq), 2.94 (brt, *J*=11.5Hz, 2H, Hb4ax), 2.69 (t, *J*=7.3Hz, 2H, Ha11), 2.15 (m, 1H, Hb2), 2.00 (quint, 2H, *J*=7.3Hz, Ha10), 1.95 (brd, 2H, Hb3eq), 1.53 (dq, *J*=4.0-15.0Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 164.5 (Ca6), 160.8 (Ca2), 152.5 (Ca1), 142.3 (Ca8), 141.7 (Ca12), 129.3 (Ca13), 129.2 (Ca14), 127.2 (Ca4),126.7 (Ca15), 119.1 (Ca5), 107.9 (Ca3), 102.6 (Ca7), 72.9 (Cb1), 43.6(Cb4), 42.2(Ca9), 33.8 (Cb2), 33.4 (Ca11), 30.8 (Ca10), 26.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{19}H_{26}N_3O_4$ $[M+H]^+$: 377.2336; found: 377.2303.

1-(methoxymethyl)-*N*^{4}-(2-(4-(((4-((3-phenylpropyl)amino)quinazolin-7-yl)oxy)methyl)piperidin-1-yl)ethyl)cytosine (19)



To a solution of **18** (10mg; 27µmol), TEA (30µL; 0.22mmol), in DMF (0.2mL) was added 2-(*N*-Boc-amino)ethylbromide (10mg; 35µmol). The mixture was stirred at room temperature for 2.5h. The mixture was diluted with ethyl acetate. The organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed and the crude product was immediately solubilized in TFA (0.5mL). The mixture was stirred at room temperature for 0.5h. TFA was removed by vacuum. The residue was solubilized in ammonia 7N in methanol and the solvent was removed to afford crude 4-((3-phenylpropyl)amino)-7-(*O*-((*N*-2-ethylamine)piperidin-4-ylmethoxy))quinazoline that was used without further purification.

To a solution of triazole (28mg; 0.40mmol) and $POCl_3$ (12µL; 0.132mmol) in 0.3 mL of acetonitrile at 0°C was added TEA 56µL dropwise. The reaction mixture was stirred at 0°C for 40min then 30min at room temperature. **9** (10mg; 60µmol) was added and the mixture was vigorously stirred at room temperature overnight. The solvent was removed and 0.5 mL of a solution of previously prepared 4-((3-phenylpropyl)amino)-7-(*O*-((*N*-2-ethylamine)piperidin-4-ylmethoxy))quinazoline was added to the residue. The reaction mixture was stirred 3h at 35°C. The mixture was diluted with ethyl acetate. The organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→10%

$MeOH/NH_3$) in dichloromethane or by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **19** (3.5mg; 6.3µmol, yield 23%) as a white powder.

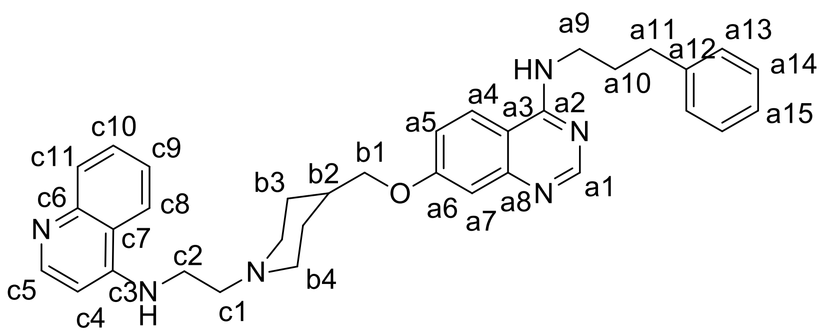
^{1}H NMR (500MHz, $CDCl_3$) δ 8.57 (s, 1H, Ha1), 7.34-7.28 (m, 3H, Ha4 and Ha13), 7.28-7.20 (m, 4H, Ha15, Ha14 and Hc5), 7.11 (d, *J*=2.3Hz, 1H, Ha7), 7.00 (dd, *J*=2.3, 8.9Hz, 1H, Ha5), 5.79 (brt, *J*=4.4Hz, 1H, HNHc), 5.67 (d, *J*=7.3Hz, 1H, Hc4), 5.44 (brt, *J*=5.5, 1H, HNHa), 5.17 (s, 2H, Hc7), 4.85 (brt, *J*=5.1Hz, 1H, HNHc), 3.92 (d, *J*=5.8Hz, 2H,Hb1), 3.70 (q, *J*=7.0Hz, 2H, Ha9), 3.58 (q, *J*=4.9Hz, 2H, Hc2), 3.39 (s, 3H, Hc8), 2.94 (brd, *J*=10.6Hz, 2H, Hb4eq), 2.79 (t, *J*=7.2Hz, Ha11), 2.55 (t, *J*=5.7Hz, 2H, Hc1), 2.11-2.00 (m, 4H,Ha10 and Hb4ax), 1.95-1.79 (m, 3H, Hb2 and Hb3eq), 1.46-1.35 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, $CDCl_3$) δ 163.6 (Cc3), 162.2 (Ca6), 159.0 (Ca2), 157.0 (Cc6), 156.0 (Ca1), 151.6 (Ca8), 142.7 (Cc5), 141.5 (Ca12), 128.6 (Ca13), 128.4 (Ca14), 126.1 (Ca15), 121.8 (Ca4), 117.9 (Ca5), 109.0 (Ca3), 107.8 (Ca7), 95.8 (Cc4), 78.8 (Cc7), 72.7 (Cb1), 56.7 (Cc8), 56.2 (Cc1), 53.0 (Cb4), 41.1 (Ca9), 37.2 (Cc2), 35.6 (Cb2), 33.7 (Ca11), 30.7 (Ca10), 29.0 (Cb3).

HRMS-ESI(m/z) calculated for $C_{31}H_{40}N_7O_3$ $[M+H]^+$: 558.3187; found: 558.3182.

4-((3-phenylpropyl)amino)-7-((1-(2-(quinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (20)

To a solution of **18** (30mg; 80µmol), K_2CO_3 (22mg; 160µmol) and a catalytic amount of KI in DMF (1mL) was added **12** (33mg; 160µmol). The mixture was stirred at 65°C overnight then was diluted with ethyl acetate. The organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→10% MeOH/NH_3) in dichloromethane or by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **20** as a white powder (35mg; 64µmol; 80%).



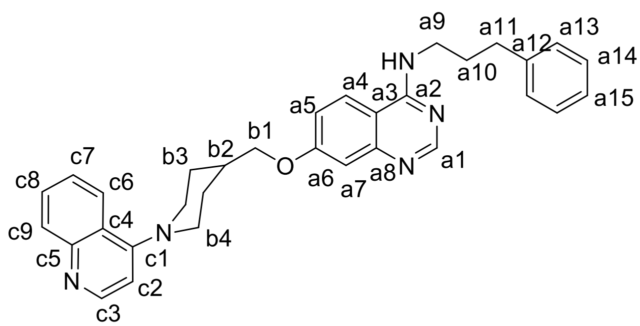
^{1}H NMR (500MHz, $CDCl_3$) δ 8.58 (s, 1H, Ha1), 8.56 (d, *J*=5.4Hz, 1H, Hc5), 7.98 (dd, *J*=0.7, 8.4Hz, 1H, Hc8), 7.76 (dd, *J*=0.7, 8.4Hz, 1H, Hc11), 7.63 (ddd, *J*=1.2, 6.9, 8.2Hz, 1H, Hc10), 7.46 (ddd, *J*=1.2, 6.9, 8.2Hz, 1H, Hc9), 7.34-7.28 (m, 3H, Ha4 and Ha13), 7.25-7.20 (m, 3H, Ha15 and Ha14), 7.13 (d, *J*=2.5Hz, 1H, Ha7), 7.00 (dd, *J*=2.6, 5.1Hz, 1H, 9.1Hz, Ha5), 6.40 (d, *J*=5.1Hz, 1H, Hc4), 5.96 (brt, *J*=4.5Hz, 1H, HNHc), 5.48 (brt, *J*=5.1Hz, 1H, HNHa), 3.96 (d, *J*=6.1Hz, 2H, Hb1), 3.70 (q, *J*=7.2Hz, 2H, Ha9), 3.34 (q, *J*=5.2Hz, 2H, Hc2), 3.00 (brd, *J*=12.0Hz, 2H, Hb4eq), 2.75 (m, 4H, Ha11 and Hc1), 2.14 (dt, *J*=2.1Hz, 2H, Hb4ax), 2.09 (quint, *J*=7.2Hz, 2H, Ha10), 1.94 (m, 1H, Hb2), 1.91 (d, *J*=12.3Hz, 2H, Hb3eq), 1.47 (dq, *J*=3.4, 12.5Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, $CDCl_3$) δ 161.6 (Ca6), 158.4 (Ca2), 155.3 (Ca1), 151.0 (Ca8), 150.5 (Cc5), 149.1 (Cc3), 147.8 (Cc6), 140.9 (Ca12), 129.3 (Cc8), 128.3 (Cc10), 128.0 (Ca13), 127.8 (Ca14), 125.5 (Ca15), 124.0 (Cc9), 121.2 (Ca4), 118.8 (Cc11), 118.3 (Cc7), 117.2 (Ca5), 108.3

(Ca3), 107.2 (Ca7), 98.4 (Cc4), 72.0 (Cb1), 55.3(Cc1), 52.3 (Cb4), 40.5 (Ca9), 38.6 (Cc2), 35.0 (Cb2), 33.0 (Ca11), 30.1 (Ca10), 28.6 (Cb3).

HRMS-ESI (m/z) calculated for $C_{19}H_{26}N_3O_4$ $[M+H]^+$: 547.3180; found: 547.3171.

4-(3-phenylpropylamino)-7-((1-(quinolin-4-yl)piperidin-4-yl)methoxy)quinazoline (21)



To a solution of **18** (20mg; 53µmol), K_2CO_3 (15mg; 106µmol) in DMF (1.5mL) was added **4-chloroquinoline** (17mg; 106µmol). The mixture was stirred at 90°C overnight. **4-chloroquinoline** (40mg; 244µmol) was added and the mixture was stirred at 120°C for 7h. The solvent was removed and the residue was purified by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **21** as a white powder (3.0mg; 6µmol; yield 12%).

^{1}H NMR (500MHz, $CDCl_3$) δ 8.75 (d, *J*=5.2Hz, 1H, Hc3), 8.61 (s, 1H, Ha1), 8.07 (dd, *J*=0.7, 8.4Hz, 1H, Hc6), 8.05 (dd, *J*=0.7, 8.4Hz, 1H, Hc9), 7.68 (ddd, *J*=1.3, 7.0, 8.1Hz, 1H, Hc8), 7.51 (ddd, *J*=1.3, 7.0, 8.1Hz, 1H, Hc7), 7.38-7.31 (m, 3H, Ha4 and Ha13), 7.28-7.23 (m, 3H, Ha15 and Ha14), 7.20 (d, *J*=2.4Hz, 1H, Ha7), 7.08 (dd, *J*=2.5, 1H, 8.8Hz, Ha5), 6.90 (d, *J*=5.1Hz, 1H, Hc2), 5.48 (brt, *J*=5.6Hz, 1H, H_{NHa}), 4.09 (d, *J*=6.1Hz, 2H, Hb1), 3.77-3.68 (m, 4H, Ha9 and Hb4eq), 2.91 (dt, *J*=1.9, 12.1Hz, 2H, Hb4ax), 2.82 (t, *J*=7.4Hz, 2H, Ha11), 2.17-2.06 (m, 5H, Ha10, Hb2 and Hb3eq), 1.82 (dq, *J*=3.5, 12.4Hz, 2H, Hb3ax).

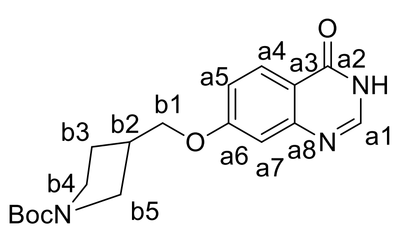
^{13}C NMR (125MHz, $CDCl_3$) δ 162.2 (Ca6), 159.0 (Ca2), 157.5 (Cc1), 156.0 (Ca1), 151.6 (Ca8), 150.8 (Cc3), 149.6 (Cc5), 141.5 (Ca12), 129.9 (Cc6), 129.0 (Cc8), 128.7 (Ca13), 128.4 (Ca14), 126.1 (Ca15), 125.3 (Cc7), 123.7 (Cc9), 123.6 (Cc4), 121.9 (Ca4), 117.9 (Ca5), 109.1 (Ca3), 108.8 (Cc2), 107.9 (Ca7), 72.5 (Cb1), 52.5 (Cb4), 41.2 (Ca9), 35.9 (Cb2), 33.7 (Ca11), 30.7 (Ca10), 29.1 (Cb3).

HRMS-ESI(m/z) calculated for $C_{32}H_{34}N_5O$ $[M+H]^+$: 504.2758; Found: 504.2758.

Compound 22 was synthesized following the same procedure as for **Compound 20**.

7-(*O*-((*N*-Boc)pyrrolin-3-ylmethoxy))quinazolin-4-one (22A)

22A was synthesized from 50mg of **15** (0.30mmol) and 41 mg N-Boc-3-(hydroxymethyl)pyrrolidine *N*-Bocpyrrolidine methanol (0.20mmol). **22A** was obtained as a white powder (40mg; 0.11mmol; yield 57%).



^{1}H NMR (500MHz, DMSO) δ 11.38 (s, 1H, HNH), 8.14 (d, 1H, *J*= 9.0, Ha4), 7.68 (s, 1H, Ha1), 7.14-7.08 (m, 2H, Ha7 and Ha5), 4.11- 4.05 (m, 2H, Hb1), 3.47-3.40 (m, 1H, Hb5), 3.42-3.22 (m, 2H, Hb4), 3.15-3.07 (m, 1H, Hb5), 2.70-2.61 (m, 2H, Ha11 and Hb2), 1.78-1.71 (m, 2H, Hb3), 1.45 (s, 9H, HBoc).

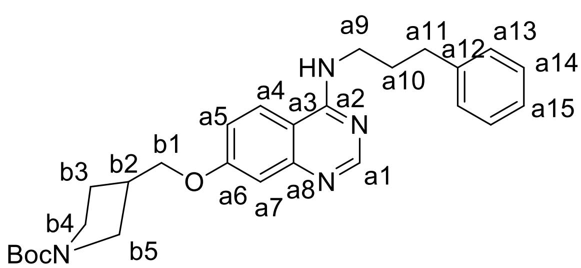
^{13}C NMR (125MHz, DMSO) δ 164.0 (Ca6), 162.1 (Ca2), 155.0 (CBoc), 151.2 (Ca8), 143.9 (Ca1), 128.1 (Ca4), 118.0 (Ca5), 116.1 (Ca3), 109.2 (Ca7), 78.5 and 78.3 (Cb1), 64.0 (CBoc), 49.1 and 48.7 (Cb5), 45.6 and 45.4 (Cb4), 38.4 and 37.4 (Cb2), 28.6 (CBoc), 28.4 and 27.4 (Cb3).

MS-ESI (m/z) calculated for $C_{18}H_{24}N_3O_4$ $[M+H]^+$: 346.17; found: 346.19.

4-((3-phenylpropyl)amino)-7-(*O*-((*N*-Boc)pyrrolidin-4-ylmethoxy))quinazoline (22B)

22B was synthesized from **22A** was synthesized following the same procedure as for Compound **19**.

From 40mg of **22A** (111µmol). **22B** was obtained as a white powder (39mg; 90µmol; yield 77%).



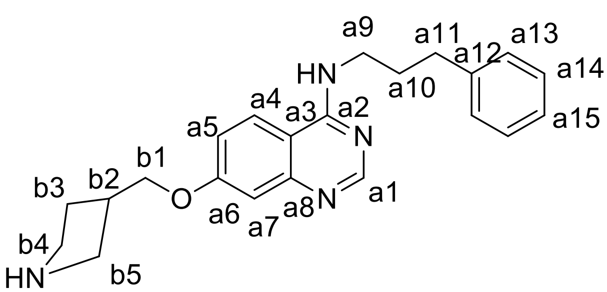
^{1}H NMR (500 MHz, DMSO) δ 8.39 (s, 1H, Ha1), 8.17 (d, *J*=9.1Hz, 1H, Ha4), 8.13 (brt, *J*=5.1 Hz, 1H, HNH), 7.32-7.22 (m, 4H, Ha13 and Ha14), 7.20-7.16 (m, 1H, Ha15), 7.11 (dd, *J*=2.4, 8.7Hz, 1H, Ha5), 7.08 (d, *J*=2.5Hz, 1H, Ha7), 4.16- 4.05 (m, 2H, Hb1), 3.57-3.48 (m, 3H, Ha9 and Hb5), 3.44-3.24 (m, 2H, Hb4), 3.17-3.09 (m, 1H, Hb5), 2.75-2.60 (m, 3H, Ha11 and Hb2), 2.11-2.01 (m, 1H, Hb3), 1.96 (quint, *J*=7.3Hz, 2H, Ha10), 1.80-1.69 (m, 1H, Hb3), 1.41 (s, 9H, HBoc).

^{13}C NMR (125MHz, DMSO) δ 162.0 (Ca6), 159.5 (Ca2), 156.0 (Ca1), 154.0 (CBoc), 151.5 (Ca8), 142.2 (Ca12), 128.8 (Ca14), 128.7 (Ca13), 126.2 (Ca15), 124.8 (Ca4), 117.1 (Ca5), 109.6 (Ca3), 107.9 (Ca7), 78.6 and 78.4 (Cb1), 62.9 (CBoc), 49.0 and 48.7 (Cb5), 45.6 and 45.4 (Cb4), 40.5 (Ca9), 38.3 and 37.4 (Cb2), 33.1 (Ca11), 30.8 (Ca10), 28.6 (CBoc), 28.4 and 27.4 (Cb3).

HRMS-ESI (m/z) calculated for $C_{27}H_{35}N_4O_3$ $[M+H]^+$: 463.2704 $[M+H]^+$; found: 463.2659.

4-((3-phenylpropyl)amino)-7-*O*-(pyrrolidin-3-ylmethoxy)quinazoline (22C)

A mixture of **22B** (100mg; 216µmol) in TFA was stirred for 1h at room temperature. TFA was removed. The residue was diluted with dichloromethane and the organic phase was washed with saturated Na_2CO_3. The solvent was removed and **22C** was obtained as pale blue foam (60mg; 166µmol; yield 76%).



^{1}H NMR (500 MHz ; DMSO) δ 8.38 (s, 1H, Ha1), 8.15 (d, *J*=9.5Hz, 1H, Ha4), 8.09 (brt, *J*=5.7 Hz, 1H, HNH), 7.32-7.22 (m, 4H, Ha13 and Ha14), 7.18 (m, 1H, Ha15), 7.11 (dd, *J*=2.9,9.5Hz, 1H, Ha5), 7.07 (d, *J*=2.1Hz, 1H, Ha7), 4.03- 3.97 (m, 2H, Hb1), 3,56-3.49 (m, 2H, Ha9), 2.93-2.79 (m, 2H, Hb5 and Hb4), 2.76-2.60 (m, 4H, Hb5, Hb4 and Ha11), 2.49-2.41

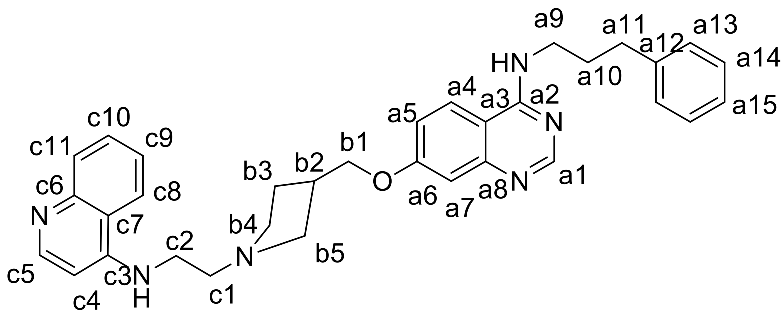
(m, 1H, Hb2), 1.94 (quint, *J*=7.0Hz, 2H, Ha10), 1.90-1.80 (m, 1H, Hb3), 1.50-1.39 (m, 1H, Hb3).

^{13}C NMR (125MHz; DMSO) δ 162.2 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.7 (Ca8), 142.2 (Ca12), 128.8 (Ca14), 128.7 (Ca13), 126.2 (Ca15), 124.7 (Ca4), 117.2 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 71.2 (Cb1), 50.4 (Cb5), 46.7 (Cb4), 40.5 (Ca9), 38.7 (Cb2), 33.2 (Ca11), 31.7 (Ca10), 29.4 (Cb3).

HRMS-ESI (m/z) calculated for $C_{22}H_{27}N_4O_1$ $[M+H]^+$: 363.2180 $[M+H]^+$; found: 363.2195.

4-((3-phenylpropyl)amino)-7-((1-(2-(quinolin-4-ylamino)ethyl)pyrrolidin-3-yl) methoxy)quinazoline (22)

To a solution of **22C** (15mg; 41µmol), K_2CO_3 (11mg; 80µmol) and a catalytic amount of KI in DMF (0.5mL) was added **12** (16mg; 80µmol). The mixture was stirred at 65°C overnight then was diluted with ethyl acetate. The organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→10% $MeOH/NH_3$) in dichloromethane or by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford Compound **22** as a white powder (7mg; 13µmol; yield 31%).



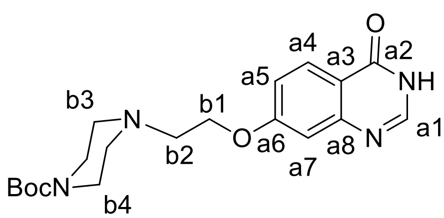
^{1}H NMR (500 MHz, DMSO) δ 8.38 (s, 1H, Ha1), 8.37 (d, *J*= 5.3Hz, 1H, Hc5), 8.16 (d, *J*=7.8Hz, 1H, Hc8), 8.15 (d, *J*=9.2Hz, 1H, Ha4), 8.11 (brt, *J*=5.9 Hz, 1H, HNH), 7.77 (dd, *J*=1.0, 8.2 Hz, 1H, Hc11), 7.59 (ddd, *J*=1.0, 6.8, 8.2Hz, 1H, Hc10), 7.41 (ddd, *J*=1.0, 6.8, 8.1Hz, 1H, Hc9), 7.32-7.22 (m, 4H, Ha13 and Ha14), 7.18 (m, 1H, Ha15), 7.13-7.05 (m, 3H, Ha5, Hc4 and Ha7), 6.47 (d, *J*=5.4Hz, 1H), 4.06- 3.97 (m, 2H, Hb1), 3.46-3.39 (m, 2H, Hc2), 2.93 (q, *J*=6.1Hz, 2H, Ha9), 2.82-2.72 (m, 3H, Hc1 and Hb5), 2.72-2.57 (m, 6H, Hb4, Ha10, Hb2 and Ha11), 2.53-2.43 (m, 1H, Hb5), 1.99-1.86 (m, 1H, Hb3), 1.31-1.24 (m, 1H, Hb3).

^{13}C NMR (125MHz, DMSO) δ 162.0 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.7 (Ca8), 151.1 (Cc5), 150.2 (Cc3), 148.7 (Cc6), 142.2(Ca12), 129.5 (Cc11), 129.1 (Cc10), 128.8 (Ca14), 128.7 (Ca13), 126.2 (Ca15), 124.7 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.1 (Ca5), 109.6 (Ca3), 108.0 (Ca7), 98.67 (Cc4), 71.6 (Cb1), 57.7 (Cc1), 53.8 (Cb4), 41.9 (Cc2), 40.4 (Ca9), 35.9 (Cb2), 33.7 (Ca11), 31.7 (Ca10), 30.8 (Cb3).

HRMS-ESI (m/z) calculated for $C_{33}H_{37}N_6O_1$ $[M+H]^+$: 533.3024 $[M+H]^+$; found: 533.3025.

7-(*O*-2(-(4-((*N*-Boc)piperazin-1-yl)ethoxy)))quinazolin-4-one (23A)

To a mixture of **1-(*N*-Boc)-4-(2-hydroxyethyl)piperazine** (351mg; 1.5mmol) in DMF (6mL) at 0°C under argon was added sodium hydride (183mg; 7.6mmol). The mixture was stirred for 15min at 0°C then **15** (500mg; 3mmol) was added portion wise. The mixture was stirred at 110°C for 4h. The reaction mixture was diluted with ethyl acetate and washed with water and brine. The organic phase was dried over magnesium sulfate and the solvent was removed. The crude product was purified by silica gel flash chromatography using a linear gradient of ethyl acetate (0→100% EtOAc) in cyclohexane to afford **23A** as a white powder (342mg; 91µmol; yield 61%).



^{1}H NMR (500MHz, DMSO) δ 12.10 (brs, 1H, HNH), 8.06 (s, 1H, Ha1), 8.01 (d, *J*=8.5Hz, 1H, Ha4), 7.13-7.09 (m, 2H, Ha5 and Ha7), 4.24 (t, *J*=5.6Hz, 2H, Hb1), 3.33 (m, 4H, Hb4), 2.76 (t, *J*=5.6Hz, 2H, Hb2), 2.45 (t, *J*=4.9Hz, 4H, Hb3), 1.40 (s, 9H, HBoc).

^{13}C NMR (125MHz, DMSO) δ 163.5 (Ca6), 160.7 (Ca2), 154.2 (CBoc), 151.4 (Ca8), 146.4 (Ca1), 127.9 (Ca4), 117.0 (Ca5), 116.4 (Ca3), 109.5 (Ca7), 79.2 (CBoc), 66.3 (Cb1), 56.8 (Cb2), 53.2 (Cb3), 44.1 and 43.1 (Cb4), 28.5 (CBoc).

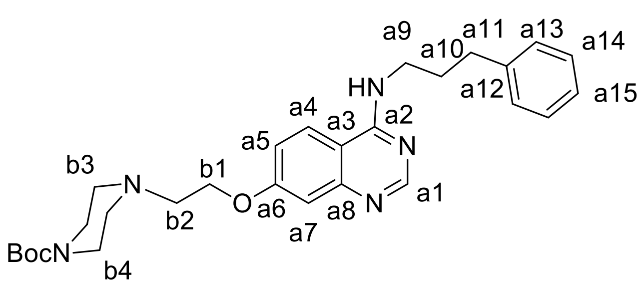
HRMS-ESI (m/z) calculated for $C_{19}H_{27}N_4O_4$ $[M+H]^+$: 375.2027 $[M+H]^+$; found: 375.2029.

4-((3-phenylpropyl)amino)-7-(*O*-2(-(4-((*N*-Boc)piperazin-1-yl)ethoxy))) quinazoline (23)

To a solution of triazole (113mg; 1.6mmol) and $POCl_3$ (48µl; 0.53mmol) in 2 mL of acetonitrile at 0°C was added TEA (228µL) dropwise. The reaction mixture was stirred at 0°C for 40min then 30min at room temperature. **23A** (90mg; 0.24mmol) was added and the mixture was vigorously stirred at room temperature overnight. The solvent was removed and the residue was taken off with ethyl acetate and washed with water and brine, and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of methanol (0→10% MeOH) in dichloromethane to afford the triazolyle derivative of **23B** as a white solid (102mg; 94µmol; yield 39%).

MS-ESI (m/z) calculated for $C_{21}H_{28}N_7O_3$ $[M+H]^+$: 426.22 $[M+H]^+$; found: 426.24.

To a solution of the triazolyle derivative of **23B** (40mg; 94µmol), and TEA (26µL; 188µmol) in DMF (0.5mL) was added 3-phenylpropylamine (25mg; 188µmol) and the mixture was stirred overnight at room temperature. The mixture was diluted with ethyl acetate and washed with water, brine and dried over sodium sulfate. The solvent was removed and the residue was purified by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **23** (25mg, 50µmol, yield 53%) as a white powder.



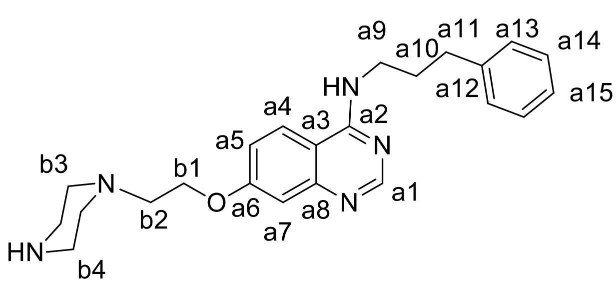
^{1}H NMR (500MHz, DMSO) δ 8.40 (s, 1H, Ha1), 8.13 (d, *J*=9.1Hz, 1H, Ha4), 8.09 (brt, *J*=5.5Hz, 1H, HNHa), 7.34-7.24 (m, 4H, Ha13 and Ha14), 7.20-7.16 (m, 1H, Ha15), 7.13 (dd, *J*=2.5, 9.1Hz, 1H, Ha5), 7.09 (d, *J*=2.5Hz, 1H, Ha7), 4.24 (t, *J*=5.5Hz, 2H, Hb1), 3.51 (q, *J*=6.8Hz, 2H, Ha9), 3.33 (m, 4H, Hb4), 2.80 (t, *J*=5.6Hz, 2H, Hb2), 2.68 (t, *J*=7.6Hz, 2H, Ha11), 2.45 (t, *J*=4.9Hz, 4H, Hb3), 1.96 (quint, *J*=7.6Hz, 2H, Ha10) 1.41 (s, 9H, HBoc).

^{13}C NMR (125MHz, DMSO) δ 165.6 (Ca6), 161.8 (Ca2), 156.2 (Ca1), 154.0 (CBoc), 151.8 (Ca8), 142.2 (Ca12), 128.8 (Ca14), 128.7 (Ca13), 126.2 (Ca15), 124.7 (Ca4), 117.2 (Ca5), 109.6 (Ca3), 108.0 (Ca7), 79.1 (CBoc), 66.1 (Cb1), 56.8 (Cb2), 54.0 (Cb3), 52.8 (Cb3), 45.2 (Cb4), 40.5 (Ca9), 39.7 (Cb4), 33.2 (Ca11), 30.8 (Ca10), 28.7 (CBoc).

HRMS-ESI (m/z) calculated for $C_{28}H_{38}N_5O_3$ $[M+H]^+$: 492.2969 $[M+H]^+$; found: 492.2970.

4-((3-phenylpropyl)amino)-7-(*O*-2-(piperazin-1-yl)ethoxy)))quinazoline (24)

A mixture of **23** (30mg; 61µmol) in TFA was stirred for 1h at room temperature. TFA was removed. The residue was diluted with dichloromethane and the organic phase was washed with saturated Na_2CO_3. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia methanol 7N (0→10% $MeOH/NH_3$) in dichloromethane to afford **24** as a white solid (22mg; 56µmol; yield 92%).



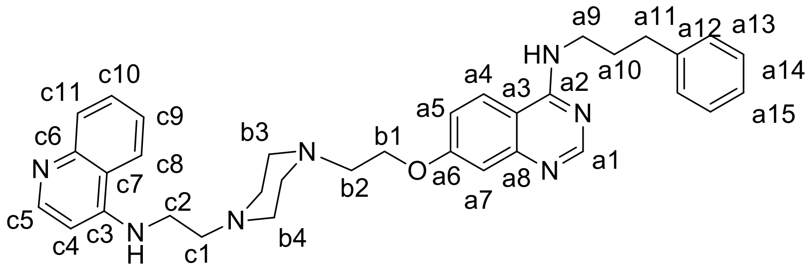
^{1}H NMR (500MHz, DMSO) δ 8.38 (s, 1H, Ha1), 8.14 (d, *J*=9.2Hz, 1H, Ha4), 8.10 (brt, *J*=5.5Hz, 1H, HNHa), 7.33-7.23 (m, 4H, Ha13 and Ha14), 7.22-7.16 (m, 1H, Ha15), 7.11 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.09 (d, *J*=2.6Hz, 1H, Ha7), 4.24 (t, *J*=5.5Hz, 2H, Hb1), 3.51 (q, *J*=6.8Hz, 2H, Ha9), 3.41-3.36 (m, 4H, Hb4), 2.80 (t, *J*=5.5Hz, 2H, Hb2), 2.68 (t, *J*=7.7Hz, 2H, Ha11), 2.52 (m, 2H, Hb3), 2.47 (m, 2H, Hb3), 1.95 (quint, *J*=7.5Hz, 2H, Ha10).

^{13}C NMR (125MHz, DMSO) δ 165.6 (Ca6), 161.8 (Ca2), 156.2 (Ca1), 151.8 (Ca8), 142.2 (Ca12), 128.8 (Ca14), 128.7 (Ca13), 126.2 (Ca15), 124.7 (Ca4), 117.2 (Ca5), 109.6 (Ca3), 108.0 (Ca7), 66.1 (Cb1), 56.8 (Cb2), 54.0 (Cb3), 52.8 (Cb3), 45.2 (Cb4), 40.5 (Ca9), 39.7 (Cb4), 33.2 (Ca11), 30.8 (Ca10).

HRMS-ESI (m/z) calculated for $C_{23}H_{30}N_5O_1$ $[M+H]^+$: 492.2970; found: 492.2969.

N-4-(3-phenylpropylamino)-7-(2-(4-(2-(quinolin-4-ylamino)ethyl)piperazin-1-yl)ethoxy)quinazoline (25)

To a solution **24** (24mg; 61µmol), K_2CO_3 (17mg; 123µmol) and a catalytic amount of KI in DMF (0.3mL) was added **12** (30mg; 123µmol). The mixture was stirred at 65°C overnight. The mixture was diluted with ethyl acetate. The organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→10% MeOH/NH_3) in dichloromethane or by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **25** (5mg; 8.9µmol; yield 15%) as a white powder.



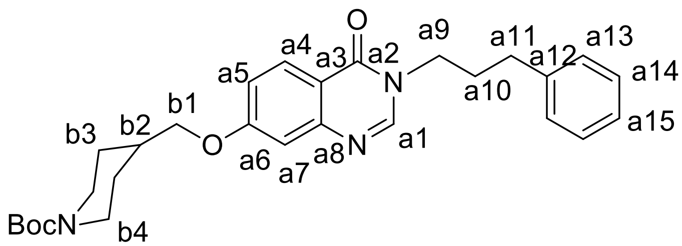
^{1}H NMR (500MHz, DMSO) δ 8.38 (d, *J*=5.3Hz, 1H, Hc5), 8.37 (s, 1H, Ha1), 8.14 (m, 2H, Ha4, Hc8), 8.08 (brt, *J*=5.1Hz, 1H, HNHa), 7.77 (dd, *J*=1.1, 8.4Hz, 1H, Hc11), 7.59 (ddd, *J*=1.1, 6.8, 8.1Hz, 1H, Hc10), 7.41 (ddd, *J*=1.2, 6.9, 8.2Hz, 1H, Hc9), 7.29-7.23 (m, 4H, Ha13, Ha14), 7.18 (m, 1H, Ha15), 7.10 (dd, *J*=2.5, 9.0Hz, 1H, Ha5), 7.07 (d, *J*=2.6Hz, 1H, Ha7), 7.01(brt, *J*=5.3Hz, 1H, HNHc), 6.46 (d, *J*=5.4Hz, 1H, Hc4), 4.20 (t, *J*=5.7Hz, 2H, Hb1), 3.51 (q, *J*=6.7Hz, 2H, Ha9), 3.34 (q, *J*=6.4Hz, 2H, Hc2), 2.74 (t, *J*=5.6Hz, 2H, Hb2), 2.67 (m, 2H, Ha11), 2.61 (t, *J*=7.0Hz, 2H, Hc1), 2.52 (m, 2H, Hb3), 2.45 (m, 2H, Hb4), 1.94 (quint, *J*=7.6Hz, 2H, Ha10).

^{13}C NMR (125MHz, DMSO) δ 161.5 (Ca6), 159.1 (Ca2), 155.7 (Ca1), 151.3 (Ca8), 150.7 (Cc5), 149.8 (Cc3), 148.3 (Cc6), 141.8 (Ca12), 129.1 (Cc11), 128.7 (Cc10), 128.3 (Ca13, Ca14), 125.7 (Ca15), 124.3 (Ca4), 123.9 (Cc9), 121.4 (Cc9), 118.8 (Cc8), 118.8 (Cc7), 116.8 (Ca5), 109.2 (Ca3), 107.6 (Ca7), 98.3 (Cc4), 65.8 (Cb1), 57.3 (Cb2), 56.5 (Cc1), 53.2 (Cb3), 52.8 (Cb4), 40.1 (Ca9 and Cc2), 32.7 (Ca11), 30.4 (Ca10).

HRMS-ESI (m/z) calculated for $C_{34}H_{40}N_7O_1$ $[M+H]^+$: 562.3289; found: 562.3293.

3-(3-phenylpropylamino)-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy))quinazoline (26)

To a solution of **16** (150mg; 42µmol), K_2CO_3 (115mg; 84µmol) in DMF (1.5mL) was added 1-chloro-3-phenylpropane (129mg; 84µmol). The mixture was stirred at 65°C overnight then was diluted with ethyl acetate. The organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed to afford **26** as a white powder (190mg; 40µmol; yield 95%).



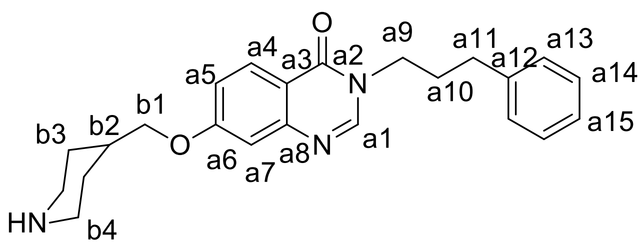
[1]H NMR (500MHz, DMSO) δ 8.31 (s, 1H, Ha1), 8.05 (d, *J*=8.4Hz, 1H, Ha4), 7.31-7.25 (m, 2H Ha13), 7.25-7.20 (m, 2H, Ha14), 7.17 (m, 1H, Ha15), 7.14-7.08 (m, 2H, Ha7 and Ha5), 4.08-3.92 (m, 5H, HNH and Hb1 and Ha9), 2.78 (m, 2H, Hb4ax), 2.74 (t, *J*=8.5Hz, 2H, Ha11), 2.07-1.95 (m, 3H, Hb2 and Ha10), 2.10-2.00 (brd, *J*=11Hz, 2H, Hb3eq), 1.40 (s, 9H, HBoc), 1.26-1.13 (m, 2H, Hb3ax).

[13]C NMR (125MHz, DMSO) δ 163.7 (Ca6), 160.2 (Ca2), 154.3 (CBoc), 150.6 (Ca8), 149.0 (Ca1), 1421.4 (CBoc), 128.8 (Ca13), 128.6 (Ca14), 128.1 (Ca4), 126.3 (Ca15), 117.2 (Ca5), 115.4 (Ca3), 109.2 (Ca7), 78.9 (CBoc), 72.6 (Cb1), 46.1 (Ca9), 45.1 (Cb4), 35.6 (Cb2), 32.6 (Ca11), 30.7 (Ca10), 28.6 (Cb3), 28.5 5 (CBoc).

HRMS-ESI (m/z) calculated for $C_{28}H_{35}N_3NaO_4$ $[M+Na]^+$: 500.2520; Found: 500.2516.

3-(3-phenylpropyl)-7-(piperidin-4-ylmethoxy)quinazolinone (27)

A mixture of **26** (190mg; 40µmol) in TFA was stirred for 1.5h at room temperature. TFA was removed. The solvent was removed and the residue was purified by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **27** as a white powder (124mg; 33µmol; yield 83%).



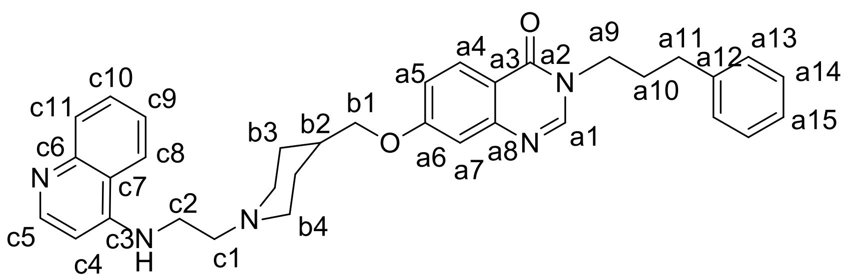
^{1}H NMR (500MHz; CCl_3) δ 8.21 (d, *J*=8.4Hz, 1H, Ha4), 7.93 (s, 1H, Ha1), 7.31-7.28 (m, 2H Ha13), 7.26-7.18 (m, 3H, Ha15 and Ha14), 7.08-7.00 (m, 2H, Ha7 and Ha5), 4.03-3.90 (m, 5H, HNH and Hb1 and Ha9), 3.56 (brd, *J*=9.6Hz, 2H, Hb4eq), 2.96 (m, 2H, Hb4ax), 2.74 (t, *J*=7.5Hz, 2H, Ha11), 2.22-2.10 (m, 3H, Hb2 and Ha10), 2.10-2.00 (m, 2H, Hb3eq), 1.95-1.72 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, CCl_3) δ 163.2 (Ca6), 160.6 (Ca2), 150.2 (Ca8), 147.3 (Ca1), 128.6 (Ca13), 128.4 (Ca4), 128.3 (Ca14), 126.2 (Ca15), 117.2 (Ca5), 115.9 (Ca3), 108.7 (Ca7), 71.6 (Cb1), 46.5 (Ca9), 43.6 (Cb4), 34.1 (Cb2), 32.7 (Ca11), 30.5 (Ca10), 25.6 (Cb3).

HRMS-ESI (m/z) calculated for $C_{23}H_{28}N_3O_2$ $[M+H]^+$: 378.2176; Found: 378.2173.

3-(3-phenylpropyl)-7-((1-(2-(quinolin-4-ylamino)ethyl)piperidin-4-yl) methoxy)quinazolinone (28)

To a solution of **27** (124mg; 0.33mmol), K_2CO_3 (91mg; 0.66mmol) and a catalytic amount of KI in DMF (1.5mL) was added **12** (80mg; 0.33mmol). The mixture was stirred at 65°C overnight. The solvent was removed and the residue was purified by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **28** as a white powder (50mg; 91µmol, yield 28%).

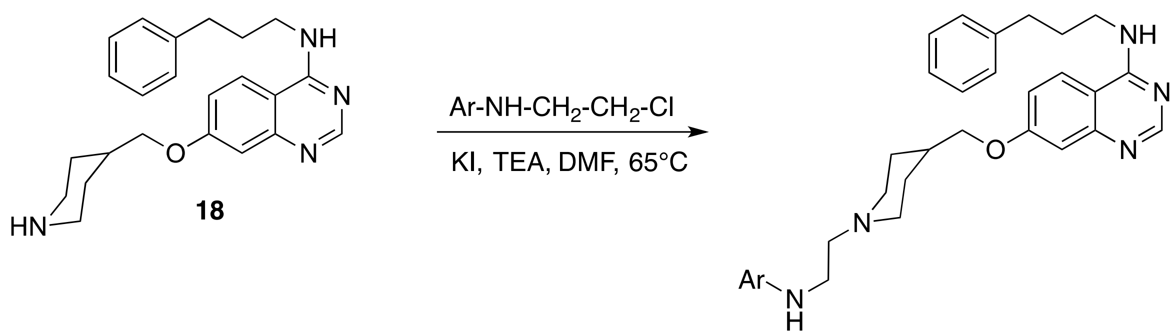


^{1}H NMR (500MHz, DMSO) δ 8.40 (d, *J*=5.5Hz, 1H, Hc5), 8.35 (s, 1H, Ha1), 8.16 (d, 8.4Hz, 1H, Hc8), 8.05 (d, *J*=8.4Hz, 1H, Ha4), 7.79 (dd, *J*=0.7, 8.5Hz, 1H, Hc11), 7.61 (ddd, *J*=1.2, 6.8, 8.2Hz, 1H, Hc10), 7.43 (ddd, *J*=1.2, 6.9, 8.2Hz, 1H, Hc9), 7.31-7.25 (m, 2H, Ha13), 7.25-7.20 (m, 3H, Ha15 and Ha14), 7.14-7.08 (m, 2H, Ha7 and Ha5), 7.04 (brt, *J*=4.9Hz, 1H, HNH), 6.47 (d, *J*=5.4Hz, 1H, Hc4), 4.03-3.95 (m, 5H, HNH and Hb1 and Ha9), 3.40 (m, 2H, Hc2), 3.00 (brd, *J*=11.0Hz, 2H, Hb4eq), 2.68-2.60 (m, 4H, Ha11 and Hc1), 2.10-1.96 (m, 4H, Hb4ax and Ha10), 1.85-1.72 (m, 3H, Hb2 and Hb3eq), 1.37 (dq, *J*=2.6, 11.5Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 163.7 (Ca6), 160.2 (Ca2), 151.2 (Cc5), 150.7 (Ca8), 150.2 (Cc3), 149.0 (Ca1), 148.8 (Cc6), 141.5 (Ca12), 129.5 (Cc11), 129.1 (Cc10), 128.7 (Ca13), 128.6 (Ca14), 128.1 (Ca4), 126.3 (Ca15), 124.3 (Cc9), 121.8 (Cc8), 119.2 (Cc7), 117.2 (Ca5), 115.4 (Ca3), 109.2 (Ca7), 98.7 (Cc4), 72.9 (Cb1), 56.6 (Cc1), 53.4 (Cb4), 46.0 (Ca9), 40.5 (Cc2), 35.7 (Cb2), 32.6 (Ca11), 30.7 (Ca10), 29.2 (Cb3).

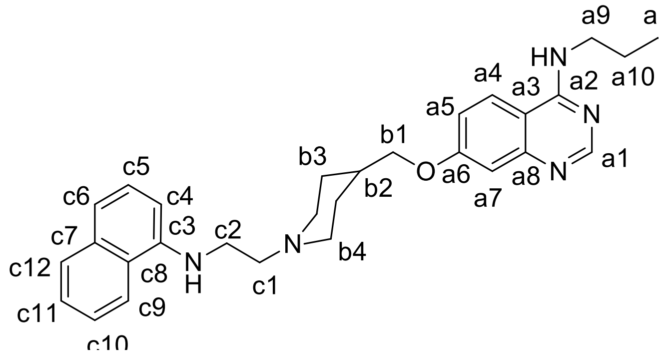
HRMS-ESI (m/z) calculated for $C_{34}H_{38}N_5O_2$ $[M+H]^+$: 548.3020; Found: 548.3026.

General procedure for compounds 29 to 46, 48, 50 and 51:



To a solution of 0.1M of **18**, K_2CO_3 (2eq) and a catalytic amount of KI in DMF was added **the desired chloro-derivative** (2eq). The mixture was stirred at 65°C overnight then was diluted with ethyl acetate. The organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→10% $MeOH/NH_3$) in dichloromethane or by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford compounds **29** to **51.**

7-((1-(2-(naphthalen-1-ylamino)ethyl)piperidin-4-yl)methoxy)-4-(3-phenylpropylamino)quinazoline (29) (18mg; 18µmol; yield 23%) as a white powder from **18** (30mg; 80µmol).



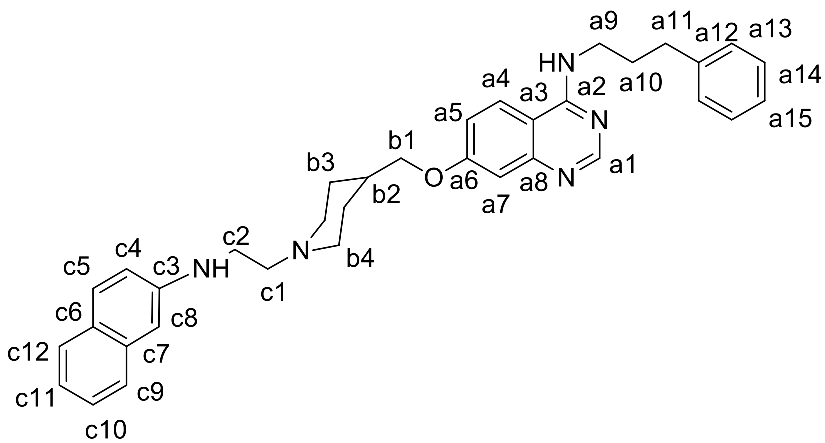
^{1}H NMR (500MHz, DMSO) δ 8.37 (s, 1H, Ha1), 8.15 (d, *J*=9.2Hz, 1H, Ha4), 8.08 (t, *J*=5.5Hz, 1H, HNHa), 8.05 (dd, *J*=1.4, 7.6Hz, 1H, Hc9), 7.75 (brdd, *J*=1.8, 7.5Hz, 1H, Hc12), 7.45-7.39 (m, 2H, Hc10 and Hc11), 7.30-7.21 (m, 6H, Ha13, Ha14 and Hc5), 7.17 (dt, *J*=1.3, 6.8Hz, 1H), 7.14-7.09 (m, 2H, Ha5 and Hc6), 7.05 (d, *J*=2.6Hz, 1H, Ha7), 6.53 (d, *J*=7.6Hz, 1H, Hc4), 5.96 (t, *J*=5.2Hz, 1H, HNHc), 3.97 (d, *J*=5.9Hz, 2H, Hb1), 3.52 (q, *J*=6.9Hz, 2H, Ha9), 3.32 (m, 2H, Hc2), 2.99 (brd, *J*=11.3Hz, 2H, Hb4eq), 2.67 (m, 4H, Ha11 and Hc1), 2.05 (brt, *J*=10.8Hz, 2H, Hb4ax), 1.94 (quint, *J*=7.5Hz, 2H, Ha10), 1.79 (m, 3H, Hb2, Hb3eq), 1.38 (dq, *J*=2.4, 12.1Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 161.7 (Ca6), 159.1 (Ca2), 155.6 (Ca1), 151.4 (Ca8), 144.0 (Cc3), 141.8 (Ca12), 134.0 (Cc7), 128.3 (Ca13 and Ca14), 128.0 (Cc12), 126.9 (Cc5), 125.7 (Ca15), 125.6 (Cc10), 124.3 (Ca4), 124.1 (Cc11), 122.9 (Cc8), 121.2 (Cc9), 116.7 (Ca5), 115.4 (Cc6), 109.1 (Ca3), 107.5 (Ca7), 103.1 (Cc4), 72.3 (Cb1), 56.5 (Cc1), 53.0 (Cb4), 40.8 (Cc2), 40.1 (Ca9), 35.3 (Cb2), 32.7 (Ca11), 30.4 (Ca10), 28.7 (Cb3).

HRMS-ESI (m/z) calculated $C_{35}H_{40}N_5O$ $[M+H]^+$: 546.3228; found: 546.3226.

7-((1-(2-(naphthalen-1-ylamino)ethyl)piperidin-4-yl)methoxy)-4-(3-phenylpropylamino)quinazoline (30)

Compound **30** (14mg; 26µmol; yield 32%) was obtained as a white powder from **18** (30mg; 80µmol)**.**

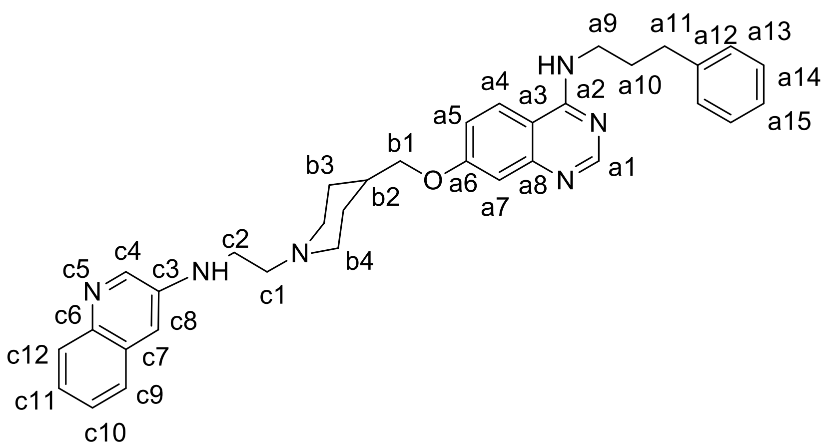


^{1}H NMR (500MHz, DMSO) δ 8.39 (s, 1H, Ha1), 8.16 (d, *J*=9.1Hz, 1H, Ha4), 8.08 (t, *J*=5.4Hz, 1H, HNHa), 7.65-7.57 (m, 2H, Hc5 and Hc9), 7.33-7.22 (m, 5H, Ha13, Ha14 and Hc10), 7.18 (dt, *J*=1.0, 6.7Hz, 1H, Ha15), 7.13-7.09 (m, 2H, Ha5 and Hc11), 7.07 (d, *J*=2.6Hz, 1H, Ha7), 7.02 (dd, *J*=2.2, 8.9Hz, 1H, Hc4), 6.74 (d, *J*=1.9Hz, 1H, Hc8), 5.73 (t, *J*=5.3Hz, 1H, HNHc), 3.98 (d, *J*=6.0Hz, 2H, Hb1), 3.53 (q, *J*=6.9Hz, 2H, Ha9), 3.23 (q, *J*= 6.4Hz, 2H, Hc2), 2.98 (brd, *J*=11.3Hz, 2H, Hb4eq), 2.69 (t, *J*=7.2Hz, 2H, Ha11), 2.59 (t, *J*=6.4Hz, 2H, Hc1), 2.03 (brt, *J*=11.0Hz, 2H, Hb4ax), 1.95 (quint, *J*=7.4Hz, 2H, Ha10), 1.80 (m, 3H, Hb2, Hb3eq), 1.38 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, $CDCl_3$) δ 162.2 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.4 (Ca8), 147.1 (Cc3), 142.2 (Ca12), 135.6 (Cc7), 128.7 (Cc5, Ca13 and Ca14), 127.8 (Cc12), 126.9 (Cc6), 126.4 (Cc10), 126.2 (Ca15), 125.8 (Cc9), 124.7 (Ca4), 121.4 (Cc11), 118.8 (Cc4), 117.2 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 102.7 (Cc8), 72.7 (Cb1), 57.4 (Cc1), 53.6 (Cb4), 41.0 (Cc2), 40.6 (Ca9), 35.8 (Cb2), 33.2 (Ca11), 30.8 (Ca10), 29.0 (Cb3).

HRMS-ESI (m/z) calculated $C_{35}H_{40}N_5O$ $[M+H]^+$: 546.3228 $[M+H]^+$; found: 546.3226.

7-((1-(2-(quinolin-3-ylamino)ethyl)piperidin-4-yl)methoxy)-4-(3-phenylpropyl)quinazoline (31) (15mg; 26µmol; yield 96%) as a white powder from **18** (10mg; 27µmol)**.**

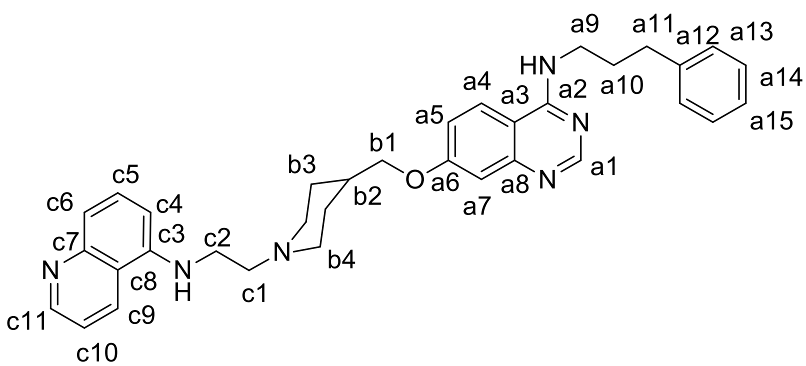


^{1}H NMR (500MHz, DMSO) δ 8.52 (d, *J*=2.8Hz, 1H, Hc4), 8.39 (s, 1H, Ha1), 8.15 (d, *J*=9.1Hz, 1H, Ha4), 8.09 (t, *J*=5.6Hz, 1H, HNHa), 7.78 (d, *J*=8.1Hz, 1H, Hc12), 7.66 (d, *J*=8.1Hz, 1H, Hc9), 7.39 (d, *J*=8.1Hz, 1H, Hc10), 7.34-7.22 (m, 5H, Ha13, Ha14 and Hc11), 7.18 (t, *J*=7.1Hz, 1H, Ha15), 7.11 (dd, *J*=2.4, 9.1Hz, 1H, Ha5), 7.06 (m, 1H, Ha7 and Cc8), 6.12 (t, *J*=5.3Hz, 1H, HNHc), 3.98 (d, *J*=5.7Hz, 2H, Hb1), 3.53 (q, *J*=6.1Hz, 2H, Ha9), 3.24 (q, *J*= 5.9Hz, 2H, Hc2), 2.99 (brd, *J*=11.0Hz, 2H, Hb4eq), 2.68 (t, *J*=7.5Hz, 2H, Ha11), 2.59 (t, *J*=6.6Hz, 2H, Hc1), 2.03 (brt, *J*=11.0Hz, 2H, Hb4ax), 1.95 (quint, *J*=7.5Hz, 2H, Ha10), 1.79 (m, 3H, Hb2, Hb3eq), 1.38 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1(Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 144.2 (Cc4), 143.0 (Cc3), 142.2 (Ca12), 141.2 (Cc6), 130.1 (Cc7), 128.9 (Cc12), 128.7 (Ca13 and Ca14), 126.9 (Cc10), 126.2 (Ca15 and Cc9), 124.7 (Ca4), 124.1 (Cc11), 117.2 (Ca5), 109.5 (Ca3), 107.9 (Ca7 and Cc8), 72.7 (Cb1), 57.1(Cc1), 53.5 (Cb4), 40.7 (Cc2), 40.6 (Ca9), 35.7 (Cb2), 33.1 (Ca11), 30.8 (Ca10), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{34}H_{39}N_6O$ $[M+H]^+$: 547.3180; found: 547.3180.

N-(3-phenylpropyl)-7-((1-(2-(quinolin-5-ylamino)ethyl)piperidin-4-yl)methoxy)quinazolin-4-amine (32) (16mg; 29µmol; yield 73%) as a white powder from **18** (15mg; 40µmol),



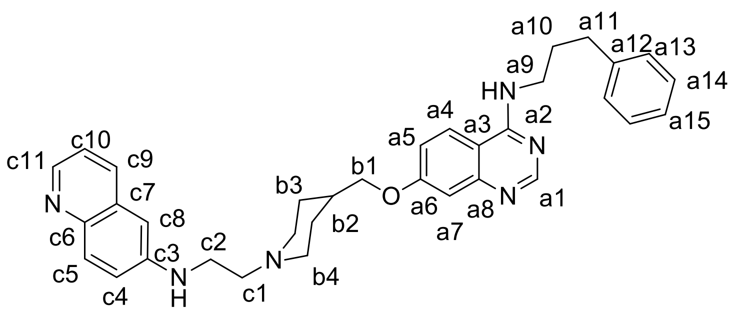
^{1}H NMR (500MHz, CDCl$_3$) δ 8.78 (dd, *J*=1.5, 4.2Hz, 1H, Hc11), 8.53 (d, *J*=8.5Hz, 1H, Hc9), 8.37 (s, 1H, Ha1), 8.14 (d, *J*=9.1Hz, 1H, Ha4), 8.09 (brt, *J*=5.4Hz, 1H, HNHa), 7.50 (t, *J*=8.1Hz, 1H, Hc5), 7.40 (dd, *J*=4.2, 8.5Hz, 1H, Hc10), 7.29-7.16 (m, 6H, Ha13, Ha14, Ha15, Hc6), 7.11 (dd, *J*=2.5, 9.1Hz, 1H, Ha5), 7.04 (d, *J*=2.6Hz, 1H, Ha7), 6.58 (d, *J*=7.8Hz, 1H, Hc4), 6.26 (brt, *J*=5.2Hz, 1H, HNHc), 3.98 (d, *J*=6.0Hz, 2H, Hb1), 3.53 (q, *J*=6.8Hz, 2H, Ha9), 3.33 (m, 2H, Hc2), 3.00 (brd, *J*=11.4Hz, 2H, Hb4eq), 2.66 (m, 4H, Ha11 and Hc1), 2.02

(brt, *J*=11.0Hz, 2H, Hb4ax), 1.94 (quint, *J*=7.7Hz, 2H, Ha10), 1.79 (m, 3H, Hb2, Hb3eq), 1.38 (dq, *J*=3.6, 11.0Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, $CDCl_3$) δ 161.7 (Ca6), 159.1 (Ca2), 155.6 (Ca1), 151.3 (Ca8), 149.8 (Cc11), 148.9 (Cc7), 144.5 (Cc3), 141.8 (Ca12), 130.4 (Cc6), 130.0 (Cc9), 128.3 (Ca13, Ca14), 125.7 (Ca15), 124.3 (Ca4), 119.0 (Cc10), 117.9 (Cc8), 116.7 (Ca5), 116.1 (Cc5), 109.8 (Ca3), 107.5 (Ca7), 103.0 (Cc4), 72.3 (Cb1), 56.5 (Cc1), 53.1 (Cb4), 40.9 (Cc2), 40.1 (Ca9), 35.3 (Cb2), 32.7 (Ca11), 30.4 (Ca10), 28.6 (Cb3).

HRMS-ESI (m/z) calculated for $C_{34}H_{39}N_6O$ $[M+H]^+$: 547.3180; found: 547.3182.

4-((3-phenylpropyl)amino)-7-((1-(2-(quinolin-6-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (33) (14mg; 26μmol; yield 96%) as a white powder from **18** (10mg; 27μmol):



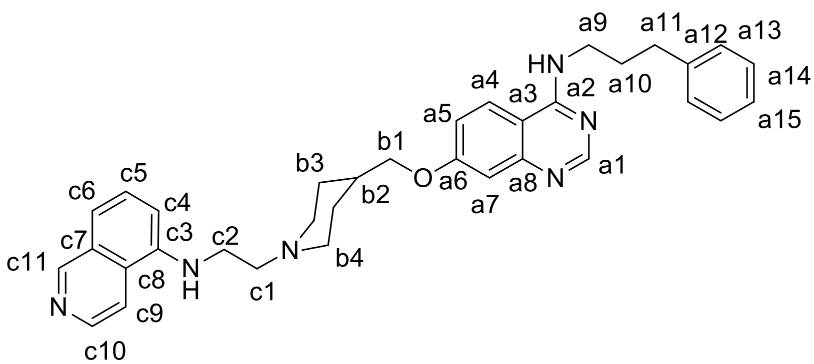
^{1}H NMR (500 MHz, DMSO) δ 8.48 (dd, *J*= 1.63, 4.18Hz, 1H, Hc11), 8.38 (s, 1H, Ha1), 8.15 (d, *J*=9.2Hz, 1H, Ha4), 8.09 (brt, *J*=5.5Hz, 1H, HNH), 7.99 (dd, *J*=0.9, 7.4Hz, 1H, Hc9), 7.70 (d, *J*=9.1Hz, 1H, Hc4), 7.32-7.22 (m, 6H, Ha13, Ha14, Hc5 and Hc10), 7.18 (dt, *J*=1.4, 7.3Hz, 1H, Ha15), 7.12 (dd, *J*=2.5, 9.1Hz, 1H, Ha5), 7.06 (d, *J*=2.6Hz, 1H, Ha7), 6.72 (d, *J*=5.4Hz, H1, Hc8), 5.99 (t, *J*=5.3Hz, 1H, HNH), 3.98 (d, *J*=5.9Hz, 2H, Hb1), 3.53 (q, *J*=6.0Hz, 2H, Ha9), 3.24 (q, *J*=5.9Hz, 2H, Hc2), 2.99 (brd, *J*=11.2Hz, 2H, Ha4eq), 2.68 (t,

J=7.7Hz, 2H, Ha11), 2.59 (t, J=6.7Hz, 2H, Hc1,), 2.03 (brt, J=10.8Hz, 2H, Hb4ax), 1.94 (quint, J=7.4Hz, 2H, Ha10), 1.85-1.75 (m, 3H, Hb3eq and Hb2), 1.45-1.35 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 147.3 (Cc3), 145.4 (Cc11), 142.7 (Cc6), 142.2 (Ca12), 133.6 (Cc9), 130.5 (Cc7), 129.8 (Cc4), 128.8 (Ca14), 128.7 (Ca13), 126.2 (Ca15), 124.7 (Ca4), 122.1 (Cc5), 121.7 (Cc10), 117.2 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 101.6 (Cc8), 72.7 (Cb1), 57.3 (Cc1), 53.6 (Cb4), 41.1 (Cc2), 40.5 (Ca9), 35.7 (Cb2), 33.1 (Ca11), 30.8 (Ca10), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{34}H_{39}N_6O$ $[M+H]^+$: 547.3180; found: 547.3182.

4-(3-phenylpropylamino)-7-((1-(2-(isoquinolin-5-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (**34**) (10mg; 18µmol; yield 67%) as a white powder from **18** (10mg; 27µmol).

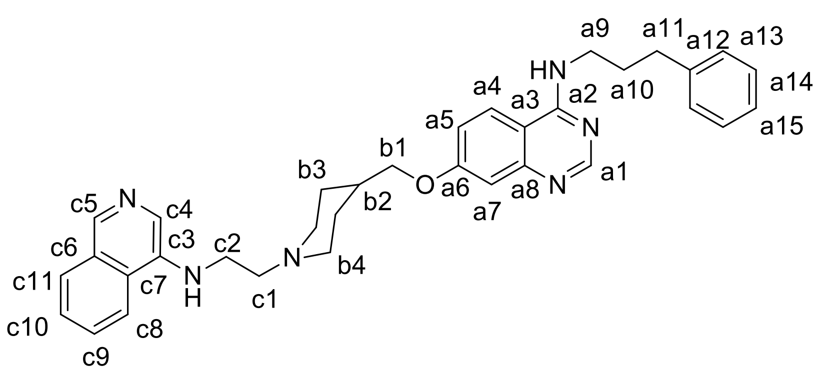


^{1}H NMR (500 MHz, DMSO) δ 8.13 (s, 1H, Hc11), 8.41 (d, J=6.0Hz, 1H, Hc10), 8.38 (s, 1H, Ha1), 8.16 (d, J=9.2Hz, 1H, Ha4), 8.09 (brt, J=5.4Hz, 1H, HNH), 7.97 (d, J=6.0Hz, 1H, Hc9), 7.47 (t, J=7.9Hz, 1H, Hc5), 7.34-7.21 (m, 5H, Ha13, Ha14 and Hc6), 7.18 (dt, J=1.3, 7.2Hz, 1H, Ha15), 7.11 (dd, J=2.5, 9.1Hz, 1H, Ha5), 7.06 (d, J=2.6Hz, 1H, Ha7), 6.74 (d, J=7.7Hz, H1, Hc4), 6.23 (t, J=5.3Hz, 1H, HNH), 3.98 (d, J=5.9Hz, 2H, Hb1), 3.53 (q, *J*=6.6Hz, 2H, Ha9), 3.52 (m, 2H, Hc2), 3.00 (brd, *J*=11.2Hz, 2H, Ha4eq), 2.67-2.61 (m, 4H, Ha11 and Hc1), 2.06 (brt, *J*=10.8Hz, 2H, Hb4ax), 1.95 (quint, *J*=7.4Hz, 2H, Ha10), 1.86-1.75 (m, 3H, Hb3eq and Hb2), 1.45-1.31 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 152.6 (Cc11), 151.8 (Ca8), 143.6 (Cc3), 142.2(Ca12), 141.8 (Cc10), 129.6 (Cc8), 128.9 (Cc5), 128.7 (Ca13 and Ca14), 126.2 (Ca15), 125.8 (Cc7), 124.7 (Ca4), 117.2 (Ca5), 115.1 (Cc9), 114.5 (Cc6), 109.5 (Ca3), 107.9 (Ca7), 106.6 (Cc4), 72.7 (Cb1), 56.9 (Cc1), 53.5 (Cb4), 41.2 (Cc2), 40.6 (Ca9), 35.7 (Cb2), 33.1 (Ca11), 30.8 (Ca10), 29.1 (Cb3).

HRMS-ESI (m/z) calculated for $C_{34}H_{39}N_6O$ $[M+H]^+$: 547.3180; found: 547.3184.

4-(3-phenylpropylamino)-7-((1-(2-(isoquinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (35) (10mg; 18µmol; yield 67%) as a white powder from **18** (10mg; 27µmol).

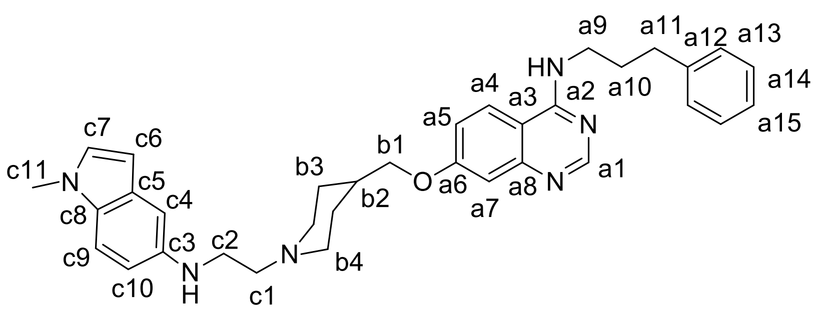


^{1}H NMR (500MHz, DMSO) δ 8.56 (s, 1H, Hc5), 8.38 (s, 1H, Ha1), 8.15 (m, 2H, Ha4 and Hc8), 8.09 (brt, *J*=5.1Hz, 1H, HNHa), 7.96 (dd, *J*=0.7, 8.5Hz, 1H, Hc11), 7.78 (s, 1H, Hc4), 7.69 (ddd, *J*=1.3, 6.9, 8.3Hz, 1H, Hc9), 7.61 (ddd, *J*=0.9, 6.8, 7.9Hz, 1H, Hc10), 7.30-7.23 (m, 4H, Ha13, Ha14), 7.18 (m, 1H, Ha15), 7.13 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.00 (d, *J*=2.6Hz, 1H, Ha7), 6.08 (brt, *J*=5.4Hz, 1H, HNHc), 3.98 (d, *J*=5.9Hz, 2H, Hb1), 3.53 (q, *J*=6.9Hz, 2H, Ha9), 3.37 (q, *J*=6.2Hz, 2H, Hc2), 3.02 (brd, *J*=11.3Hz, 2H, Hb4eq), 2.75 (m, 4H, Ha11 and Hc1), 2.02 (m, 2H, Hb4ax), 1.95 (quint, *J*=7.3Hz, 2H, Ha10), 1.80 (m, 3H, Hb2, Hb3eq and Hb2), 1.38 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 161.7 (Ca6), 159.1 (Ca2), 155.6 (Ca1), 151.4 (Ca8), 141.8 (Ca12), 139.8 (Cc5), 138.2.1 (Cc3), 128.4 (Cc9), 128.3 (Ca13 and Ca14), 128.2 (Cc7), 127.0 (Cc10), 125.7 (Ca15), 125.1 (Cc6), 124.3 (Ca4), 122.3 (Cc4), 116.7 (Ca5), 109.1 (Ca3), 107.5 (Ca7), 72.3 (Cb1), 56.5 (Cc1), 53.1 (Cb4), 40.6 (Cc2), 40.1 (Ca9), 35.3 (Cb2), 32.7 (Ca11), 30.4 (Ca10), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{34}H_{39}N_6O$ $[M+H]^+$: 547.3180; found: 547.3185.

4-(3-phenylpropylamino)-7-((1-(2-((1-methyl-1H-indol-3-yl)amino)ethyl)piperidin-4-yl)methoxy)quinazoline (36) (10mg; 18µmol; yield 67%) as a white powder from **18** (10mg; 27µmol).

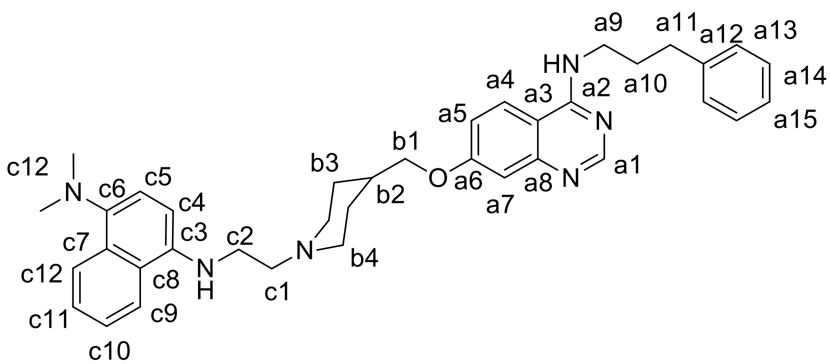


^{1}H NMR (500MHz, DMSO) δ 8.85 (s, 1H, Ha1), 8.41 (d, *J*=9.8Hz, 1H, Ca4), 7.41 (dd, *J*=2.1, 9.3Hz, 1H, Ha5), 7.35-7.16 (m, 8H, Ha7, Ha13, Ha14, Ha15, Hc4 and Hc7), 6.79 (m, 1H, Hc6), 6.65 (brd, *J*=8.7Hz, 1H, Hc9), 6.20 (brd, *J*=2.8Hz, 1H, Hc10), 4.11 (d, *J*=4.8Hz, 2H, Hb1), 3.77-3.66 (m, 5H, Ha9 and Hc11), 3.60 (brd, *J*=11.5Hz, 2H, Hb4eq), 3.46 (t, *J*=6.2Hz, 2H, Hc2), 3.39 (t, *J*=6.2Hz, 2H, Hc1), 3.11 (brd, *J*=11.5Hz, 2H, Hb4ax), 2.70 (t, *J*=7.6Hz, 2H, Ha11), 2.21-2.09 (m, 1H, Hb2), 1.73-1.61 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 164.1 (Ca6), 160.3 (Ca2), 158.3 (Ca8), 151.8 (Ca1), 141.7 (Ca12), 131.4 (Cc3), 129.8 (Cc7), 129.3 (Cc5), 128.8 (Ca13 and Ca14), 126.7 (Cc), 126.3 (Ca15), 118.7 (Ca5), 111.9 (Cc9), 110.6 (Ca7), 107.2 (Ca3), 101.1 (Cc4 and Cc6), 99.4 (Cc10), 72.0 (Cb1), 55.0(Cc1), 51.8 (Cb4), 39.4 (Cc2), 41.7 (Ca9), 32.9 (Cb2 and Cc11), 32.8 (Ca11), 30.2 (Ca10), 25.6 (Cb3).

HRMS-ESI (m/z) calculated for $C_{34}H_{41}N_6O$ $[M+H]^+$: 549.3336; found: 549.3348.

7-((1-(2-(4-dimethylaminonaphthalen-1-ylamino)ethyl)piperidin-4-yl)methoxy)-4-(3-phenylpropylamino)quinazoline (37) (18mg; 18µmol; yield 23%) was obtained as a white powder from **18** (30mg; 80µmol).

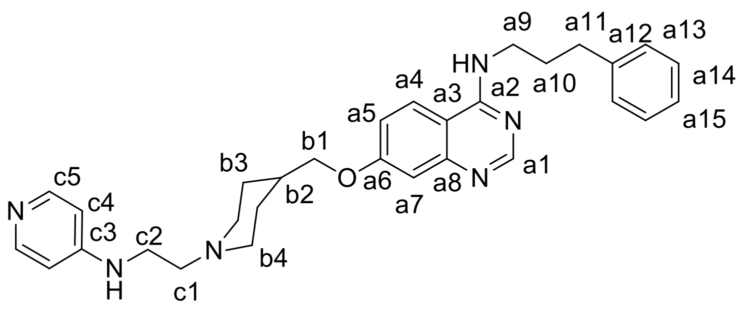


^{1}H NMR (500MHz, DMSO) δ 8.38 (s, 1H, Ha1), 8.15 (d, *J*=9.1Hz, 1H, Ha4), 8.09 (t, *J*=5.3Hz, 1H, HNHa), 8.03 (d, *J*=8.1Hz, 1H, Hc9), 7.50-7.40 (m, 2H, Hc10 and Hc11), 7.32-7.21 (m, 4H, Ha13 and Ha14), 7.18 (dt, *J*=1.3, 7.1Hz, 1Ha15), 7.12 (dd, *J*=2.4, 9.1Hz, 1H, Ha5), 7.05 (m, 2H, Ha7 and Hc5), 6.48 (m, 1H, Hc4), 5.67 (t, *J*=5.0Hz, 1H, HNHc), 3.98 (d, *J*=5.8Hz, 2H, Hb1), 3.53 (q, *J*=6.6Hz, 2H, Ha9), 3.30-3.24 (m, 2H, Hc2), 3.0 (brd, *J*=10.9Hz, 2H, Hb4eq), 2.70 (s, 6H, Hc12), 2.69-2.62 (m, 4H, Ha11 and Hc1), 2.07 (brt, *J*=10.9Hz, 2H, Hb4ax), 1.95 (quint, *J*=7.5Hz, 2H, Ha10), 1.81 (m, 3H, Hb2, Hb3eq), 1.44-1.32 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 161.7 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 142.2 (Ca12), 140.8 (Cc3), 129.8 (Cc7), 128.8 (Ca13 and Ca14), 126.2 (Ca15), 125.6 (Cc11), 124.8 (Cc10), 124.7 (Ca4), 124.6 (Cc8), 124.2 (Cc12), 117.2 (Ca5), 116.1 (Cc5), 109.6 (Ca3), 107.9 (Ca7), 103.1 (Cc4), 103.5 (Cc4), 72.7 (Cb1), 57.1 (Cc1), 53.50 (Cb4), 45.9 (Cc12), 41.5 (Cc2), 40.6 (Ca9), 35.8 (Cb2), 33.2 (Ca11), 30.8 (Ca10), 29.2 (Cb3).

HRMS-ESI (m/z) calculated for $C_{37}H_{45}N_6O$ [M+H]$^+$: 589.3649; found: 589.3655.

4-(3-phenylpropylamino)-7-((1-(2-(pyridin-4-ylamino)ethyl)piperidin-4-yl) methoxy)quinazoline (38) (9.2mg; 19µmol; yield 69%) as a white powder from **18** (10mg; 27µmol).



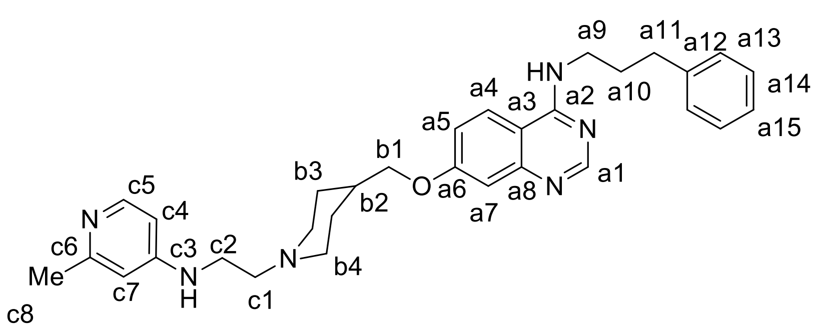
^{1}H NMR (500MHz, $CDCl_3$) δ 8.57 (s, 1H, Ha1), 8.18 (dd, *J*=1.5, 4.8Hz, 2H, Hc5), 7.32-7.28 (m, 3H, Ha4 and Ha13), 7.25-7.20 (m, 3H, Ha15 and Ha14), 7.12 (d, *J*=2.5Hz, 1H, Ha7), 7.00 (dd, *J*=2.5, 9.0Hz, 1H, Ha5), 6.44 (dd, *J*=1.5, 4.8Hz, 2H, Hc4), 5.96 (brt, *J*=5.2, 1H, HNHc), 3.94 (d, *J*=6.0Hz, 2H,Hb1), 3.70 (q, *J*=6.8Hz, 2H, Ha9), 3.19 (q, *J*=5.5Hz, 2H, Hc2), 2.95 (brd, *J*=11.4Hz, 2H, Hb4eq), 2.79 (t, *J*=7.3Hz, Ha11), 2.62 (t, *J*=6.2Hz, 2H, Hc1), 2.09

(quint, *J*=6.8Hz, 2H,Ha10), 2.05 (dt, *J*=2.1, 9.8Hz, 2H, Hb4ax), 1.90 (m, 1H, Hb2), 1.87 (d, *J*=12.2Hz, 2H, Hb3eq), 1.44 (dq, *J*=2.9-12.2Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, $CDCl_3$) δ 162.2 (Ca6), 159.0 (Ca2), 155.9 (Ca1), 153.3 (Cc5), 151.5 (Ca8), 149.9 (Cc3), 141.5 (Ca12), 128.6 (Ca13), 128.4 (Ca14), 126.1 (Ca15), 121.8 (Ca4), 117.9 (Ca5), 109.0 (Ca3), 107.8 (Ca7), 107.6 (Cc4), 72.7 (Cb1), 56.3 (Cc1), 53.0 (Cb4), 41.1 (Ca9), 38.9 (Cc2), 35.6 (Cb2), 33.6 (Ca11), 30.7 (Ca10), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{30}H_{37}N_7O$ $[M+H]^+$: 497.3023; found: 497.3025.

4-(3-phenylpropylamino)-7-((1-(2-(2-methylpyridin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (39) (3.0mg; 5.5µmol; yield 11%) as a white powder from **18** (20mg; 53µmol)

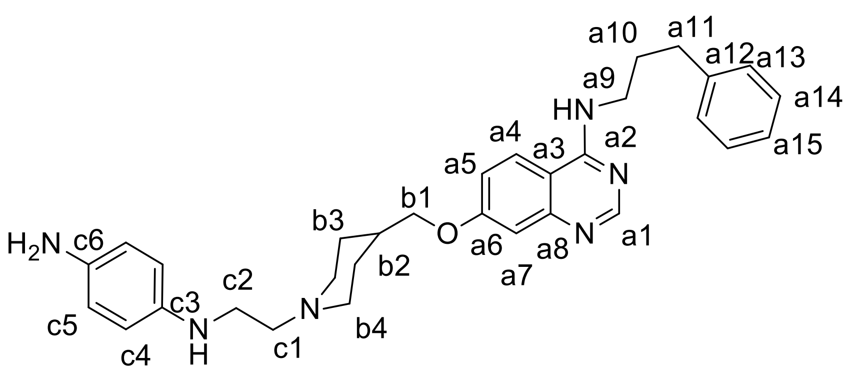


^{1}H NMR (500MHz, DMSO) δ 8.38 (s, 1H, Ha1), 8.15 (d, *J*=9.2Hz, 2H, Ha4), 8.10 (t, *J*=5.4Hz, 1H, HNHa), 7.88 (d, *J*=5.7Hz, 1H, Hc7), 7.33-7.22 (m, 3H, Ha14 and Ha13), 7.18 (t, *J*=7.2Hz, 1H, Ha15), 7.11 (dd, *J*=2.6, 9.1Hz 1H, Ha5), 7.05 (d, *J*=2.6Hz, 1H, Ha7), 6.36 (d, *J*=2.2Hz, 1H, Hc7), 6.33 (dd, *J*=2.2, 5.7Hz, 1H, Hc4), 6.21 (brt, *J*=5.3, 1H, HNHc), 3.97 (d, *J*=5.9Hz, 2H, Hb1), 3.53 (q, *J*=6.6Hz, 2H, Ha9), 3.16 (q, *J*=6.2Hz, 2H, Hc2), 2.94 (brd, *J*=11.1Hz, 2H, Hb4eq), 2.68 (t, *J*=7.7Hz, Ha11), 2.48 (t, *J*=6.8Hz, 2H, Hc1), 2.25 (s, 3H, Hc8), 2.05-1.91 (m, 4H, Hb4ax and Ha10), 1.84-1.73 (m, 3H, Hb2 and Hb3eq), 1.43-1.41 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.5 (Ca2), 157.8 (Cc6), 156.1 (Ca1), 154.3 (Cc3), 151.8 (Ca8), 149.1 (Cc7), 142.2 (Ca12), 128.7 (Ca13 and Ca14), 126.2 (Ca15), 124.7 (Ca4), 117.2 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 106.1 (Cc7), 105.4 (Cc4), 72.7 (Cb1), 57.2 (Cc1), 53.5 (Cb4), 40.5 (Ca9), 39.8 (Cc2), 35.7 (Cb2), 33.1 (Ca11), 30.8 (Ca10), 28.9 (Cb3).

HRMS-ESI (m/z) calculated for $C_{31}H_{39}N_6O$ $[M+H]^+$: 511.3180; found: 511.3181.

4-(3-phenylpropylamino)-7-((1-(2-(anilin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (40) (23mg; 45μmol; yield 21%) as a white powder from **18** (80mg; 212μmol).

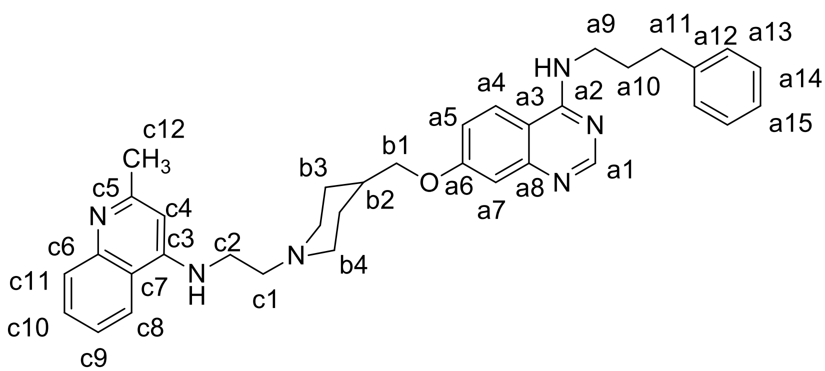


^{1}H NMR (500MHz, DMSO) δ 8.38 (s, 1H, Ha1), 8.15 (d, *J*=9.1Hz, 1H, Ha4), 8.09 (brt, *J*=5.5 Hz, 1H, HNH), 7.32-7.21 (m, 4H, Ha13 and Ha14), 7.17 (t, *J*=7.0Hz, 1H, Ha15), 7.11 (dd, *J*=2.9, 9.2Hz, 1H, Ha5), 7.05 (d, *J*=2.4Hz, 1H, Ha7), 6.45-6.36 (m, 4H, Hc4 and Hc5), 3.97 (d, *J*=5.9Hz, 2H, Hb1), 3.53 (q, *J*=6.2Hz, 2H, Ha9), 3.00 (t, *J*=6.6 Hz, 2H, Hc2), 2.97-2.85 (m, 2H, Hb4eq), 2.68 (t, *J*=8.0Hz, 2H, Ha11), 2.47 (t, *J*=7.1Hz, 2H, Hc1), 2.01-1.90 (m, 2H, Ha10 and Hb4ax), 1.83-1.73 (m, 3H, Hb3eq and Hb2), 1.42-1.29 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.5 (Ca2), 156.0 (Ca1), 151.7 (Ca8), 142.2 (Ca12), 140.7 (Cc3), 139.6 (Cc6), 128.8 (Cca14), 128.7 (Ca13), 126.2 (Ca15), 124.7 (Ca4), 117.2 (Ca5), 115.9 (Cc4), 114.2 (Cc5), 109.5 (Ca3), 107.9 (Ca7), 72.7 (Cb1), 57.8 (Cc1), 53.5 (Cb4), 42.1 (Cc2), 40.5 (Ca9), 35.8 (Cb2), 33.1 (Ca11), 30.8 (Ca10), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{31}H_{39}N_6O$ $[M+H]^+$: 511.3180; found: 511.3180.

7-((1-(2-((2-methylquinolin-4-yl)amino)ethyl)piperidin-4-yl)methoxy)-N-(3-phenylpropyl)quinazolin-4-amine (41) (16mg; 29µmol; yield 72%) as a white powder from **18** (15mg; 40µmol).

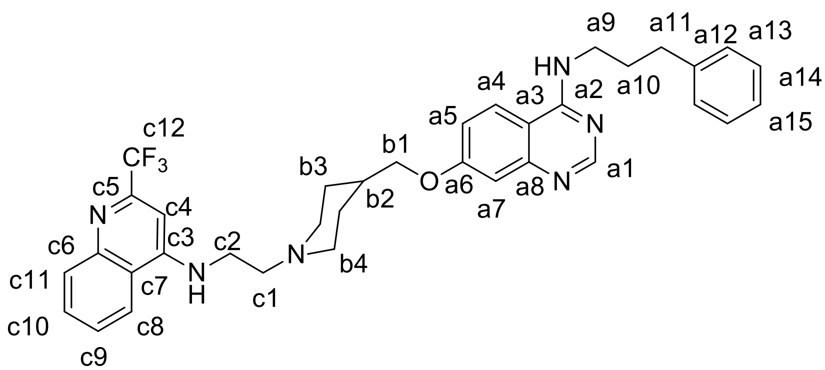


^{1}H NMR (500MHz, DMSO) δ 8.38 (s, 1H, Ha1), 8.16 (d, *J*=9.2Hz, 1H, Ha4), 8.10 (brs, 2H, Hc8 and HNHa), 7.69 (d, *J*= 8.0Hz, 1H, Hc11), 7.55 (d, *J*= 7.6Hz, 1H, Hc10), 7.69 (brt, *J*=7.5, 1H, Hc9), 7.30-7.23 (m, 4H, Ha13 and Ha14), 7.18 (m, 1H, Ha15), 7.11 (dd, *J*=2.4, 9.1Hz, 1H, Ha5), 7.06 (d, *J*=2.4Hz, 1H, Ha7), 6.87 (brt, *J*=5.3Hz, 1H, HNHc), 6.39 (s, 1H, Hc4), 3.98 (d, *J*=5.8Hz, 2H, Hb1), 3.53 (q, *J*=6.7Hz, 2H, Ha9), 3.39 (q, *J*=6.3Hz, 2H, Hc2), 3.00 (brd, *J*=10.9Hz, 2H, Ha4eq), 2.68 (t, *J*=7.6Hz ; 2H, Ha11), 2.64 (t, *J*=6.8Hz, 2H, Hc1), 2.47 (s, 3H, Hc12), 2.06 (brt, *J*=11.7Hz, 2H, Hb4ax), 1.95 (quint, *J*= 7.6Hz, Ha10), 1.80 (m, 3H, Hb3eq

^{13}C NMR (125MHz, DMSO) δ 161.7 (Ca6), 159.1 (Ca2), 158.7 (Cc5), 155.6 (Ca1), 151.4 (Ca8), 149.9 (Cc3), 148.1 (Cc6), 128.6 (Ca10), 128.4 (Cc11), 128.29 (Ca13, Ca14), 125.7 (Ca15), 124.3 (Ca4), 123.5 (Cc9), 121.2 (Cc8), 117.5 (Cc7), 116.7 (Ca5), 109.1 (Ca3), 107.5 (Ca7), 98.2 (Cc4), 72.2 (Cb1), 56.3 (Cc1), 53.1 (Cb4), 40.13 (Cc2), 40.11 (Ca9), 35.3 (Cb2), 32.7 (Ca11), 30.4 (Ca10), 28.6 (Cb3), 25.3 (Cc12).

HRMS-ESI (m/z) calculated for $C_{35}H_{41}N_6O$ $[M+H]^+$: 561.3337; found: 561.3341.

4-(3-phenylpropyl)-7-((1-(2-((2-(trifluoromethyl)quinolin-4-yl)amino)ethyl)piperidin-4-yl)methoxy)quinazoline (42) (21mg; 34µmol; yield 86%) as a white powder from **18** (15mg; 40µmol)

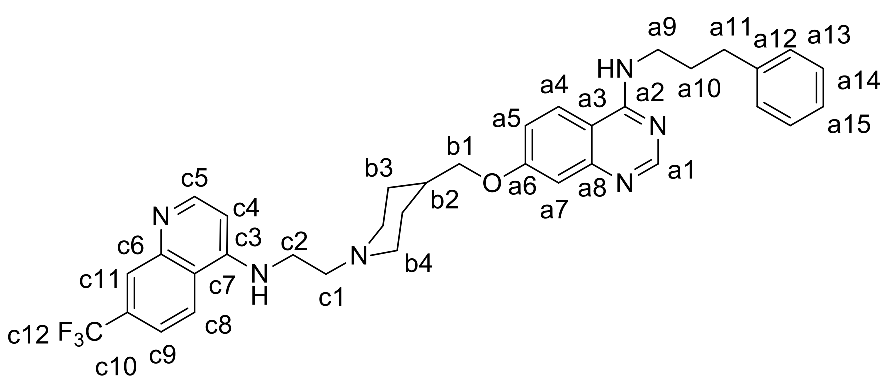


^{1}H NMR (500MHz, DMSO) δ 8.37 (s, 1H, Ha1), 8.29 (d, *J*=8.5Hz, 1H, Hc8), 8.15 (d, *J*=9.2Hz, 1H, Ha4), 8.08 (d, *J*=5.3Hz, 1H, HNHa), 7.90 (dd, *J*=1.0, 8.5Hz, 1H, Hc11), 7.34 (ddd, *J*=1.1, 6.8, 8.0Hz, 1H, Hc10), 7.63 (brt, *J*=5.0Hz, 1H, HNHc), 7.57 (ddd, *J*=1.3, 7.1, 8.2Hz, 1H, Hc9), 7.29-7.22 (m, 4H, Ha13 and Ha14) 7.17 (m, 1H, Ha15), 7.10 (dd, *J*=2.5, 9.1Hz, 1H, Ha5), 7.04 (d, *J*=2.6Hz, 1H, Ha7), 6.81 (s, 1H, Hc4), 3.96 (d, *J*=5.8Hz, 2H, Hb1), 3.51 (m, 4H, Ha9, Hc2), 3.00 (brd, *J*=11.1Hz, 2H, Hb4eq), 2.67 (t, *J*=7.4Hz ; 2H, Ha11), 2.64 (t, *J*=6.7Hz, 2H, Hc1), 2.05 (brt, *J*= 11.4Hz, 2H, Hb4ax), 1.94 (quint, *J*= 7.5Hz, Ha10), 1.78 (m, 3H, Hb3eq and Hb2), 1.36 (dq, *J*=2.0, 12.0Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 161.7 (Ca6), 159.1 (Ca2), 155.7 (Ca1), 152.0 (Cc3), 151.4 (Ca8), 147.5 (q, *J*=32.1Hz, Cc12), 147.1 (Cc6), 141.8 (Ca12), 130.3 (Cc10), 129.5 (Cc11), 128.3 (Ca13, Ca14), 126.0 (Cc9), 125.8 (Ca15), 124.3 (Ca4), 122.1 (q, *J*=274.5Hz, Cc5), 121.8 (Cc8), 118.8 (Cc7), 116.7 (Ca5), 109.1 (Ca3), 107.5 (Ca7), 93.4 (q, *J*=2.6Hz, Cc4), 72.3 (Cb1), 56.3 (Cc1), 53.1 (Cb4), 40.5 (Cc2), 40.1 (Ca9), 35.3 (Cb2), 32.7 (Ca11), 30.4 (Ca10), 28.6 (Cb3).

HRMS-ESI (m/z) calculated $C_{35}H_{38}F_3N_6O$ $[M+H]^+$: 615.3054; found: 615.3059.

4-(3-phenylpropyl)-7-((1-(2-((7-(trifluoromethyl)quinolin-4-yl)amino)ethyl) piperidin-4-yl)methoxy)quinazoline (43) (24mg; 39µmol; yield 98%) as a white powder from **18** (15mg; 40µmol).

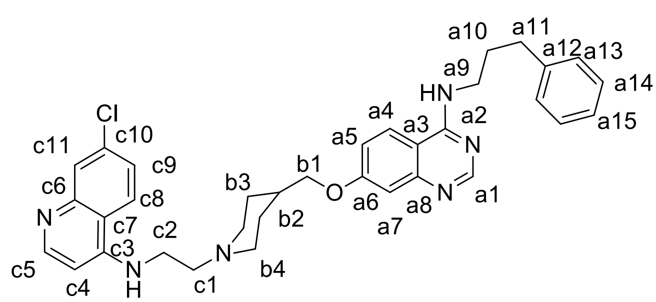


^{1}H NMR (500MHz, DMSO) δ 8.51 (d, *J*=5.4Hz, 1H, Hc5), 8.43 (d, *J*=8.9Hz, 1H, Hc8), 8.37 (s, 1H, Ha1), 8.14 (d, *J*=9.2Hz, 1H, Ha4), 8.10 (brs, 2H, Hc11, HNHa), 7.69 (dd, *J*=1.9, 8.9Hz, 1H, Hc9), 7.35 (brt, *J*=5.2Hz, 1H, HNHc), 7.29-7.22 (m, 4H, Ha13 and Ha14) 7.17 (m, 1H, Ha15), 7.10 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.04 (d, *J*=2.6Hz, 1H, Ha7), 6.61 (d, *J*=5.5Hz, 1H, Hc4), 3.96 (d, *J*=6.0Hz, 2H, Hb1), 3.53 (q, *J*=6.6Hz, 2H, Ha9), 3.42 (q, *J*=6.4Hz, 2H, Hc2), 2.99 (brd, *J*=11.1Hz, 2H, Hb4eq), 2.67 (t, *J*=7.7Hz, 2H, Ha11), 2.63 (t, *J*=6.9Hz, 2H, Hc1), 2.04 (brt, *J*=10.4Hz, 2H, Hb4ax), 1.94 (quint, *J*=7.7Hz, Ha10), 1.78 (m, 3H, Hb3eq and Hb2), 1.44-1.31 (dq, *J*=2.5, 12.4, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 161.7 (Ca6), 159.1 (Ca2), 155.6 (Ca1), 152.3 (Cc5), 151.4 (Ca8), 149.9 (Cc3), 147.5 (Cc6), 141.7 (Ca12), 129.1 (q, *J*=31.9Hz, Cc12), 128.29 (Ca13, Ca14), 126.4 (q, *J*=4.2Hz, Cc11), 125.7 (Ca15), 124.3 (Ca4), 124.2 (q, *J*=274.7Hz, Cc10), 123.8 (Cc8), 120.9 (Cc7), 116.0 (brq, *J*=3.1Hz, Cc9), 116.7 (Ca5), 109.1 (Ca3), 107.5 (Ca7), 99.8 (Cc4), 72.2 (Cb1), 56.0 (Cc1), 53.1 (Cb4), 40.3 (Cc2), 40.1 (Ca9), 35.2 (Cb2), 32.7 (Ca11), 30.4 (Ca10), 28.6 (Cb3).

HRMS-ESI (m/z) calculated $C_{35}H_{38}F_3N_6O$ $[M+H]^+$: 615.3054; found: 615.3062.

4-((3-phenylpropyl)amino)-7-((1-(2-(7-chloroquinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (44) (15mg; 26µmol; yield 97%) from **18** (10mg; 27µmol):

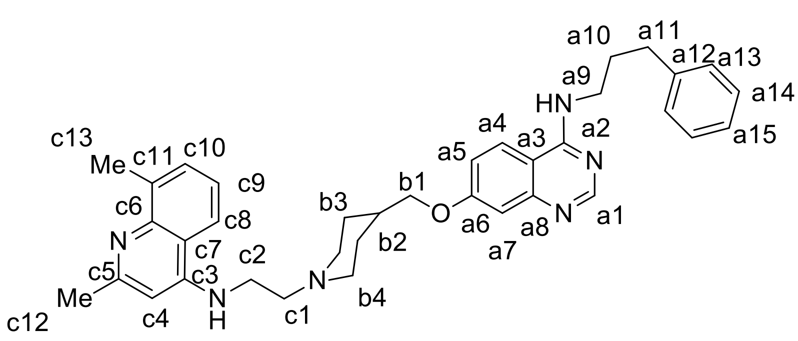


^{1}H NMR (500MHz, DMSO) δ 8.41 (d, *J*= 5.3Hz, 1H, Hc5), 8.38 (s, 1H, Ha1), 8.23 (d, *J*=9.1Hz, 1H, Hc8), 8.15 (d, *J*=9.2Hz, 1H, Ha4), 8.09 (brt, *J*=5.5Hz, 1H, HNH), 7.79 (d, *J*=2.3Hz, 1H, Hc11), 7.46 (dd, *J*=2.2, 7.3, 8.9Hz, 1H, Hc9), 7.32-7.15 (m, 5H, Ha13, Ha14 and Ha15), 7.11 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.05 (d, *J*=2.6Hz, 1H, Ha7), 6.51 (d, *J*=5.4Hz, 1H, Hc4), 3.98 (d, *J*=5.9Hz, 2H, Hb1), 3.53 (q, *J*=6.1Hz, 2H, Ha9), 3.41 (q, *J*=6.5Hz, 2H, Hc2), 3.01 (brd, *J*=11.2Hz, 2H, Ha4eq), 2.68 (t, *J*=7.5Hz ; 2H, Ha11,) 2.62 (t, *J*=7.1Hz, 2H, Hc1,), 2.06 (t, *J*= 11.1Hz, 2H, Hb4ax), 1.95 (q, *J*= 7.5Hz, Ha10), 1.83-1.73 (m, 3H, Hb3eq and Hb2), 1.43-1.31 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 152.4 (Cc5), 151.8 (Ca8), 150.4 (Cc3), 149.5 (Cc6), 142.2 (Ca12), 133.8 (Cc10), 128.8 (Ca14), 128.7 (Ca13), 128.0 (Cc11), 126.2 (Ca15), 124.7 (Ca4), 124.5 (Cc9), 124.4 (Cc8), 117.9 (Cc7), 117.2 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 99.2 (Cc4), 72.7 (Cb1), 56.6 (Cc1), 53.5 (Cb4), 40.7 (Ca9), 40.5 (Cc2), 35.7 (Cb2), 33.1 (Ca11), 30.8 (Ca10), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{34}H_{38}ClN_6O$ [M+H]$^+$: 581.2790; found: 581.2791.

4-(3-phenylpropylamino)-7-((1-(2-((2,8-dimethylquinolin-4-yl)amino)ethyl)piperidin-4-yl)methoxy)quinazoline (45) (23mg, 40µmol, yield 38%) as a white powder from **18** (40mg; 106µmol).

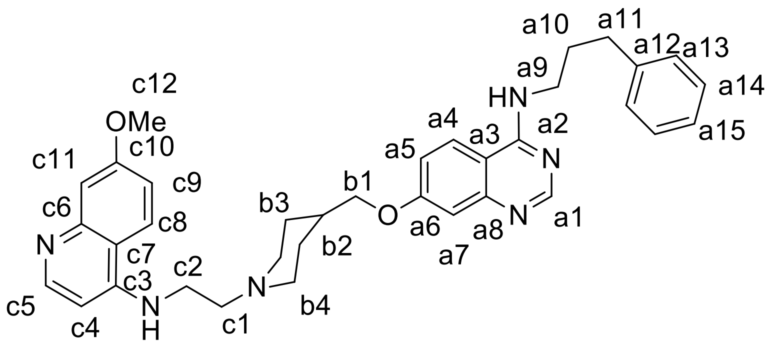


^{1}H NMR (500MHz, DMSO) δ 8.39 (s, 1H, Ha1), 8.16 (d, *J*=9.2Hz, 1H, Ha4), 8.10 (brt, *J*=4.4Hz, 1H, HNH), 7.92 (d, *J*= 8.4Hz, 1H, Hc8), 7.42 (d, *J*=6.9Hz, 1H, Hc10), 7.32-7.21 (m, 5H, Hc9, Ha13 and Ha14), 7.18 (t, *J*=7.1Hz, 1H, Ha15), 7.11 (dd, *J*=2.4, 9.0Hz, 1H, Ha5), 7.06 (d, *J*=2.5Hz, 1H, Ha7), 6.78 (brt, *J*=5.3Hz, 1H, HNH), 6.40 (s, 1H, Hc4), 3.97 (d, *J*=4.7Hz, 2H, Hb1), 3.53 (q, *J*=6.6Hz, 2H, Ha9), 3.41-3.36 (m, 2H, Hc2), 3.00 (brd, *J*=10.2Hz, 2H, Ha4eq), 2.68 (t, *J*=7.7Hz; 2H, Ha11), 2.63 (t, *J*=6.8Hz, 2H, Hc1), 2.60 (s, 3H, Hc13), 2.48 (s,3H, Hc12), 2.04 (brt, *J*=11.2Hz, 2H, Hb4ax), 1.95 (quint, *J*=7.4Hz, Ha10), 1.85-1.73 (m, 3H, Hb3eq and Hb2), 1.44-1.31 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.5(Ca2), 157.9 (Cc5), 156.1 (Ca1), 151.8 (Ca8), 150.6(Cc3), 147.3 (Cc10), 142.2 (Ca12), 135.9 (Cc11), 129.3 (Cc10), 128.7 (Ca14 and Ca13), 126.2 (Ca15), 124.7 (Ca4), 123.0 (Cc9), 119.4 (Cc8), 117.5 (Cc7), 117.2 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 98.6 (Cc4), 72.7 (Cb1), 56.7 (Cc1), 53.5 (Cb4), 40.6 (Cc2), 40.5 (Ca9), 35.7 (Cb2), 33.1 (Ca11), 30.8 (Ca10), 29.1 (Cb3), 26.2 (Cc12), 19.0 (Cc13).

HRMS-ESI (m/z) calculated for $C_{36}H_{43}N_6O$ $[M+H]^+$: 575.3493; found: 575.3494.

4-((3-phenylpropyl)amino)-7-((1-(2-(7-methoxyquinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (46) (43mg; 75µmol; yield 71%) from **18** (40mg; 106µmol):



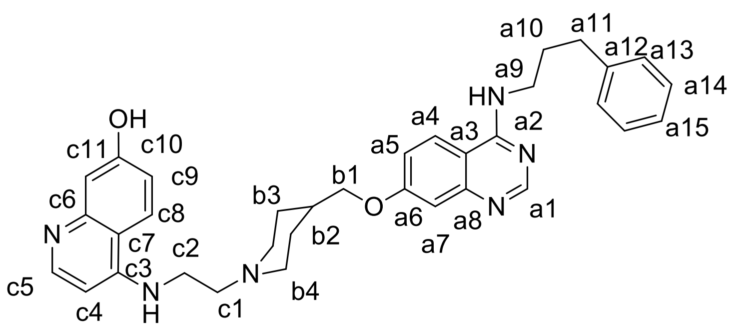
^{1}H NMR (500MHz, DMSO) δ 8.38 (s, 1H, Ha1), 8.32 (d, *J*= 5.3Hz, 1H, Hc5), 8.15 (d, *J*=9.2Hz, 1H, Ha4), 8.10 (brt, *J*=5.4Hz, 1H, HNH), 8.06 (d, *J*=9.1Hz, 1H, Hc8), 7.32-7.22 (m, 4H, Ha13 and Ha14), 7.21-7.15 (m, 2H, Ha15 and Hc11), 7.11 (dd, *J*=2.4, 9.1Hz, 1H, Ha5), 7.08-7.03 (m, 2H, Ha7 and Hc9), 6.96 (brt, *J*=5.2Hz, 1H, HNH), 6.36 (d, *J*=5.5Hz, 1H, Hc4), 3.97 (d, *J*=5.7Hz, 2H, Hb1), 3.87 (s, 3H, Hc12), 3.53 (q, *J*=6.4Hz, 2H, Ha9), 3.41-3.36 (m, 2H, Hc2), 3.00 (brd, *J*=10.9Hz, 2H, Ha4eq), 2.68 (t, *J*=7.7Hz ; 2H, Ha11), 2.61 (t, *J*=6.9Hz, 2H, Hc1), 2.04 (t, *J*=11.1Hz, 2H, Hb4ax), 1.95 (quint, *J*=7.4Hz, Ha10), 1.85-1.73 (m, 3H, Hb3eq and Hb2), 1.44-1.31 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 160.0 (Cc3), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 151.5 (Cc5), 150.6 (Cc10), 150.3 (Cc6), 142.2 (Ca12), 128.8 (Ca14), 128.7 (Ca13), 126.2 (Ca15), 124.7 (Ca4), 123.3 (Cc8), 117.2 (Ca5), 116.0 (Cc9), 113.7 (Cc7), 109.5 (Ca3), 108.3 (Cc11), 107.9 (Ca7), 97.6 (Cc4), 72.7 (Cb1), 56.7 (Cc1), 55.6 (Cc12), 53.5 (Cb4), 40.6 (Cc2), 40.5 (Ca9), 35.7 (Cb2), 33.1 (Ca11), 30.8 (Ca10), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{35}H_{41}N_6O_2$ $[M+H]^+$: 577.3286; found: 577.3296.

4-((3-phenylpropyl)amino)-7-((1-(2-(7-hydroxyquinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (47)

46 (6mg; 10.4µmol) was added to a solution of BBr_3 in DCM 0.5M (0.2mL) and one drop of dioxane. The mixture was stirred at room temperature overnight then quenched with water. The solvent was removed and the residue was purified by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **47** (5mg; 8.9µmol; yield 85%) as a white powder.



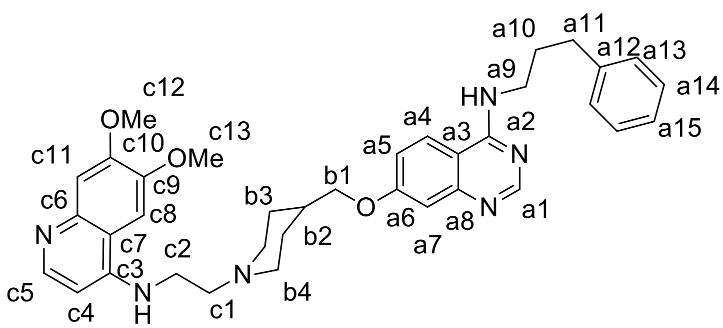
[1]H NMR (500MHz, DMSO) δ 8.38 (s, 1H, Ha1), 8.23 (d, *J*= 5.4Hz, 1H, Hc5), 8.15 (d, *J*=9.2Hz, 1H, Ha4), 8.10 (brt, *J*=5.4Hz, 1H, HNH), 7.94 (d, *J*=9.1Hz, 1H, Hc8), 7.32-7.22 (m, 4H, Ha13 and Ha14), 7.18 (t, *J*=7.2Hz, 1H, Ha15), 7.12 (dd, *J*=2.4, 9.0Hz, 1H, Ha5), 7.06 (d, *J*=2.5Hz, 1H, Ha7), 6.99 (d, *J*=2.25Hz, 1H, Hc11), 6.92 (dd, *J*=2.5, 9.0Hz, 1H, Hc9), 6.80 (brt, *J*=5.4Hz, 1H, HNH), 6.26 (d, *J*=5.4Hz, 1H, Hc4), 3.98 (d, *J*=5.9Hz, 2H, Hb1), 3.53 (q, *J*=6.6Hz, 2H, Ha9), 3.41-3.36 (m, 2H, Hc2), 3.00 (brd, *J*=11.3Hz, 2H, Ha4eq), 2.68 (t, *J*=7.7Hz ; 2H, Ha11), 2.61 (t, *J*=6.9Hz, 2H, Hc1), 2.05 (t, *J*=10.9Hz, 2H, Hb4ax), 1.95 (quint, *J*=7.4Hz, Ha10), 1.85-1.70 (m, 3H, Hb3eq and Hb2), 1.44-1.30 (m, 2H, Hb3ax).

[13]C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.8 (Cc10), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 151.1 (Cc5), 150.8 (Cc3), 150.3 (Cc6), 142.2 (Ca12), 128.8 (Ca14), 128.7 (Ca13), 126.2

(Ca15), 124.7 (Ca4), 123.0 (Cc8), 117.2 (Ca5), 116.5 (Cc9), 112.5 (Cc7), 111.0 (Cc11), 109.5 (Ca3), 107.9 (Ca7), 96.7 (Cc4), 72.7 (Cb1), 56.8 (Cc1), 53.5 (Cb4), 40.6 (Cc2), 40.4 (Ca9), 35.7 (Cb2), 33.2 (Ca11), 30.8 (Ca10), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{34}H_{39}N_6O_2$ $[M+H]^+$: 536.3133 ; found: 536.3123.

4-((3-phenylpropyl)amino)-7-((1-(2-(6,7-dimethoxyquinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (**48)** (9 mg; 15 µmol; yield 56%) from **18** (10mg; 27µmol):



[1]H NMR (500MHz, DMSO) δ 8.37 (s, 1H, Ha1), 8.22 (d, *J*= 5.3Hz, 1H, Hc5), 8.15 (d, *J*=9.3Hz, 1H, Ha4), 8.11 (brt, *J*=5.4Hz, 1H, HNH), 7.45 (s, 1H, Hc8), 7.32-7.21 (m, 4H, Ha13 and Ha14), 7.21-7.15 (m, 2H, Ha15 and Hc11), 7.11 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.05 (d, *J*=2.6Hz, 2H, Ha7), 6.84 (brt, *J*=5.2Hz, 1H, HNH), 6.37 (d, *J*=5.5Hz, 1H, Hc4), 3.98 (d, *J*=5.9Hz, 2H, Hb1), 3.89 (s, 3H, Hc13), 3.87 (s, 3H, Hc12), 3.56-3.49 (m, 2H, Ha9), 3.41-3.36 (m, 2H, Hc2), 3.00 (brd, *J*=10.8Hz, 2H, Ha4eq), 2.68 (t, *J*=7.7Hz ; 2H, Ha11) 2.63 (t, *J*=6.9Hz, 2H, Hc1), 2.06 (t, *J*=10.8Hz, 2H, Hb4ax), 1.95 (quint, *J*=7.4Hz, Ha10), 1.86-1.75 (m, 3H, Hb3eq and Hb2), 1.47-1.32 (m, 2H, Hb3ax).

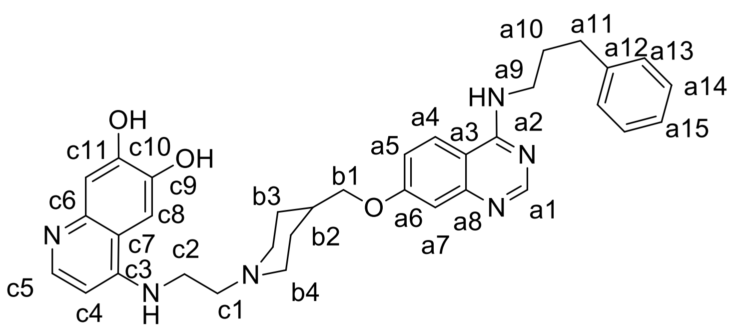
[13]C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.5(Ca2), 156.1 (Ca1), 151.7 (Cc3), 151.5 (Ca8), 149.3 (Cc9), 148.9 (Cc5), 148.0 (Cc10), 145.4 (Cc6), 142.2 (Ca12), 128.8 (Ca14), 128.7

(Ca13), 126.2 (Ca15), 124.7 (Ca4), 117.2 (Ca5), 113.1 (Cc7), 109.5 (Ca3), 108.7 (Cc11), 107.9 (Ca7), 101.1 (Cc8), 97.9 (Cc4), 72.7 (Cb1), 56.9 (Cc1), 56.3 (Cc13), 55.8 (Cc12), 53.6 (Cb4), 40.7 (Cc2), 40.3 (Ca9), 35.7 (Cb2), 33.1 (Ca11), 30.8 (Ca10), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{36}H_{43}N_6O_3$ $[M+H]^+$: 607.3391; found: 607.3391.

4-((3-phenylpropyl)amino)-7-((1-(2-(6,7-dihydroxyquinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (49)

48 (7mg; 12µmol) is added to a solution of BBr_3 in DCM 0.5M (0.2mL) and one drop of dioxane. The mixture was stirred at room temperature overnight. Then the mixture was quenched with water. The solvent was removed and the residue was purified by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **49** (4mg; 6.9µmol; yield 58%) as a white powder.



^{1}H NMR (500MHz, DMSO) δ 8.37 (s, 1H, Ha1), 8.14 (d, *J*=9.1Hz, 1H, Ha4), 8.08 (brt, *J*=5.9Hz, 1H, HNH), 7.95 (m, 1H, Hc5), 7.30-7.310 (m, 5H, Hc?, Ha13 and Ha14), 7.19-7.151 (m, 1H, Ha15), 7.10 (dd, *J*=2.6, 8.8Hz, 1H, Ha5), 7.04 (d, *J*=2.6Hz, 1H, Ha7), 6.26 (d, *J*=6.3Hz, 1H, Hc4), 3.97 (d, *J*=5.9Hz, 2H, Hb1), 3.52 (brq, *J*=6.2Hz, 2H, Ha9), 3.38 (brq,

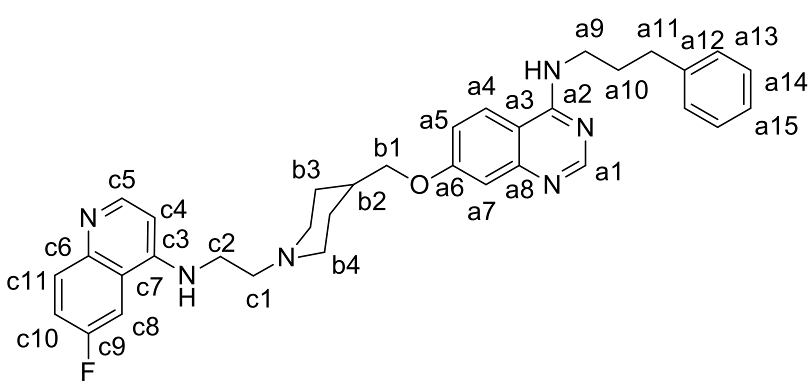
J=3.8Hz, 2H, Hc2), 2.98 (brd, J=11.1Hz, 2H, Ha4eq), 2.67 (t, J=7.7Hz ; 2H, Ha11), 2.59 (t, J=6.8Hz, 2H, Hc1), 2.06 (t, J=10.5Hz, 2H, Hb4ax), 1.93 (quint, J=7.6Hz, Ha10), 1.83-1.73 (m, 3H, Hb3eq and Hb2), 1.42-1.29 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 161.7 (Ca6), 159.1(Ca2), 155.6 (Ca1), 151.3 (Ca8), 141.8 (Ca12), 128.3 (Ca14 and Ca13), 125.7 (Ca15), 124.3 (Ca4), 116.7 (Ca5), 109.1 (Ca3), 107.5 (Ca7), 95.7 (Cc4, observed by HSQC), 72.2 (Cb1), 56.5 (Cc1), 53.0 (Cb4), 40.4 (Cc2), 40.2 (Ca9), 35.3 (Cb2), 32.7 (Ca11), 30.4 (Ca10), 28.6 (Cb3).

NMR signals of Hc11, Hc8, Cc3, Cc5, Cc6, Cc7, Cc8Cc9, Cc10, Cc11 were not observed, presence of the dihydroxyquinoline moiety was confirmed by HRMS and by the presence of the characteristic Hc4 signal and the Hc5 signal as well as by the presence of their correlation on COSY spectra and the presence of a correlation of Hc4 and Cc4 on HSQC spectra.

HRMS-ESI (m/z) calculated for $C_{34}H_{39}N_6O_3$ $[M+H]^+$: 579.3078; found: 579.3081.

4-(3-phenylpropylamino)-7-((1-(2-((6-fluoroquinolin-4-yl)amino)ethyl)piperidin-4-yl)methoxy)- quinazoline 50 (16mg; 28µmol; yield 71%) as a white powder from **18** (15mg; 40µmol).

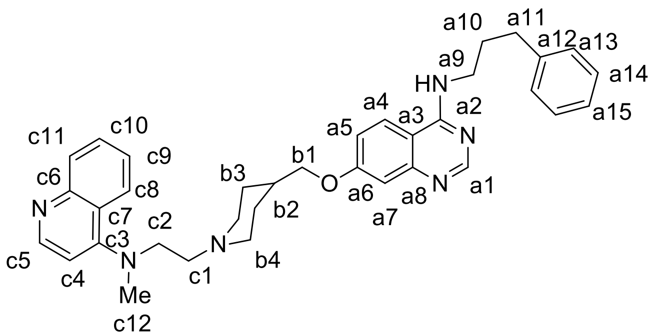


^{1}H NMR (500MHz, DMSO) δ 8.38 (d, *J*=5.3Hz, 1H, Hc5), 8.37 (s, 1H, Ha1), 8.15 (d, *J*=9.0Hz, 1H, Ha4), 8.09 (t, *J*=5.4Hz, 1H, HNHa), 8.02 (dd, *J*=2.8, 11.1Hz, 1H, Hc8), 7.83 (dd, *J*=5.9, 9.2Hz, 1H, Hc11), 7.51 (ddd, *J*=2.9, 8.2, 9.1Hz, 1H, Hc10), 7.28 (m, 2H, Ha14), 7.23 (m, 2H, Ha13), 7.17 (t, *J*=1.5, 7.1Hz, 1H, Ha15), 7.10 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.04 (d, *J*=2.6Hz, 1H, Ha7), 6.99 (brt, *J*=5.3Hz, 1H, HNHc), 6.50 (d, *J*=5.4Hz, 1H, Hc4), 3.97 (d, *J*=5.9Hz, 2H, Hb1), 3.51 (q, *J*=6.0Hz, 2H, Ha9), 3.40 (q, *J*=6.6Hz, 2H, Hc2), 3.00 (brd, *J*=11.2Hz, 2H, Ha4eq), 2.67 (t, *J*=7.6Hz, 2H, Ha11), 2.62 (t, *J*=7.2Hz, 2H, Hc1), 2.04 (brt, *J*=10.7Hz, 2H, Hb4ax), 1.94 (quint, *J*=7.4Hz, Ha10), 1.78 (m, 3H, Hb3eq, Hb2), 1.37 (dq, *J*=2.5, 12.4Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 161.7 (Ca6), 159.5 (Ca2), 158.8 (d, *J*=243.5Hz, Cc9), 155.6 (Ca1), 151.4 (Ca8), 150.3 (d, *J*=2.0Hz, Cc5), 149.6 (d, *J*=4.5Hz, Cc3), 145.7 (Cc6), 141.8 (Ca12), 131.7 (d, *J*=9.4Hz, Cc11), 128.3 (Ca13, Ca14), 125.7 (Ca15), 124.3 (Ca4), 119.2 (d, *J*=8.8Hz, Cc7), 118.2 (d, *J*=25.3Hz, Cc10), 116.7 (Ca5), 109.1 (Ca3), 107.5 (Ca7), 105.6 (d, *J*=23.1Hz, Cc8), 98.5 (Cc4), 72.2 (Cb1), 56.2 (Cc1), 53.1 (Cb4), 40.3 (Cc2), 40.1 (Ca9), 35.2 (Cb2), 32.7 (Ca11), 30.4 (Ca10), 28.6 (Cb3).

HRMS-ESI (m/z) calculated for $C_{35}H_{38}FN_6O$ $[M+H]^+$: 565.3086; found: 565.3097.

4-((3-phenylpropyl)amino)-7-((1-(2-(methyl(quinolin-4-yl)amino)ethyl) piperidin-4-yl)methoxy)quinazoline (51) (13mg; 23μmol; yield 85%) from **18** (10mg; 27μmol):

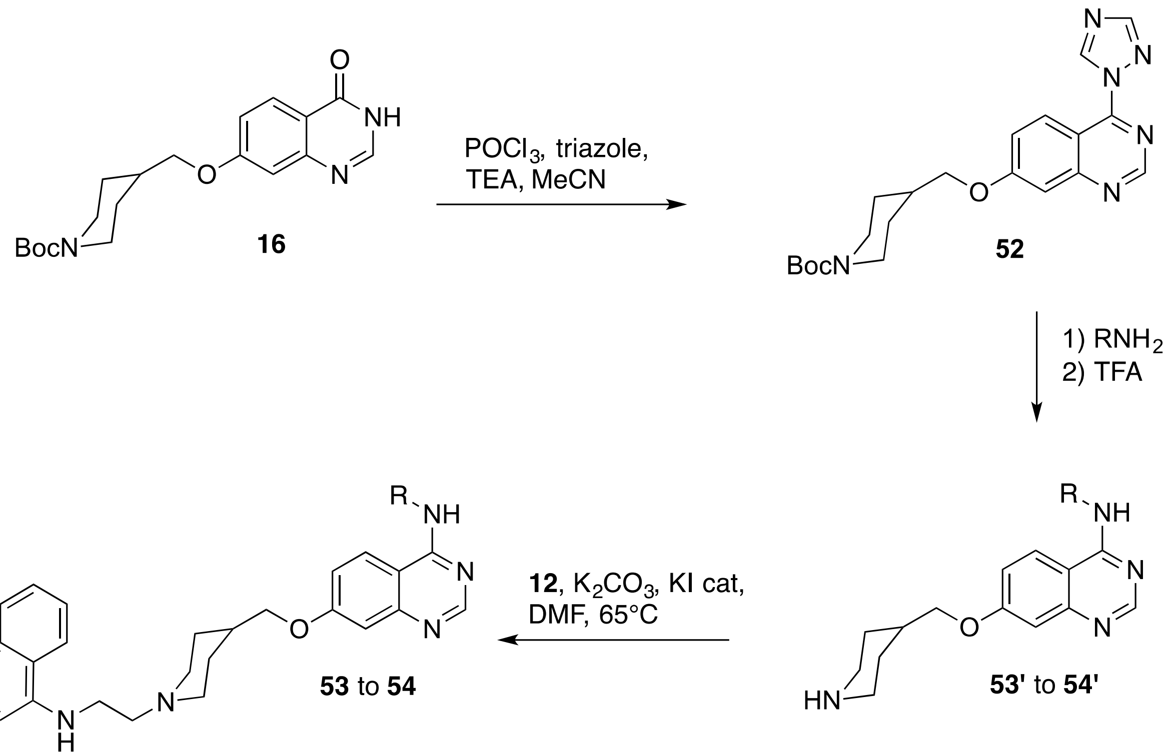


^{1}H NMR (500MHz, DMSO) δ 8.61 (d, *J*= 5.1Hz, 1H, Hc5), 8.38 (s, 1H, Ha1), 8.21 (d, *J*=8.5Hz, 1H, Hc8), 8.15 (d, *J*=9.2Hz, 1H, Ha4), 8.09 (brt, *J*=5.4 Hz, 1H, HNH), 7.91 (dd, *J*=0.7,8.3Hz, 1H, Hc11), 7.66 (t, *J*=7.3Hz, 1H, Hc9), 7.51(t, *J*=7.3Hz, 1H, Hc10), 7.32-7.22 (m, 4H, Ha13 and Ha14), 7.18 (t, *J*=7.3Hz, 1H, Ha15), 7.10 (dd, *J*=2.5, 9.1Hz, 1H, Ha5), 7.04 (d, *J*=2.6Hz, 1H, Ha7), 6.93 (d, *J*=5.4Hz, H1, Hc4), 3.93 (d, *J*=5.9Hz, 2H, Hb1), 3.53 (q, *J*=5.8Hz, 2H, Ha9), 3.40 (t, *J*=6.3Hz, 2H, Hc2), 2.97 (s, 3H, Hc12), 2.85 (brd, *J*=10.7Hz, 2H, Ha4eq), 2.68 (t, *J*=7.7Hz, 2H, Ha11,) 2.64 (t, *J*=6.2Hz, 2H, Hc1,), 2.02-1.88 (m, 4H, Hb4ax and Ha10), 1.79-1.63 (m, 3H, Hb3eq and Hb2), 1.29-1.15 (m, 2H, Hb3ax).

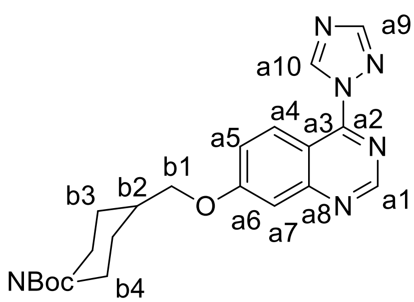
^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.5 (Ca2), 157.1 (Cc3), 156.1 (Ca1), 151.8 (Ca8), 150.8 (Cc5), 149.8 (Cc6), 142.2(Ca12), 129.9 (Cc11), 129.1 (Cc10), 128.8 (Ca14), 128.7 (Ca13), 126.2 (Ca15), 124.9 (Cc9), 124.7 (Ca4), 124.6 (Cc8), 123.1 (Cc7), 117.1 (Ca5), 109.5 (Ca3), 108.8 (Cc4), 107.9 (Ca7), 72.6 (Cb1), 55.9 (Cc1), 54.2 (cc2), 53.6 (Cb4), 40.5 (Ca9), 40.2 (Cc12), 35.6 (Cb2), 33.1 (Ca11), 30.8 (Ca10), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{35}H_{41}N_6O$ $[M+H]^+$: 561.3337; found: 561.3339.

Procedures for compounds 53 and 54.



4-(1H-1,2,4-triazol-1-yl)-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy))quinazoline (52)



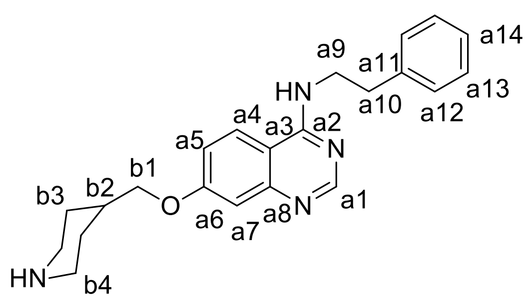
To a solution of triazole (280mg; 4mmol) and $POCl_3$ (120µL; 1.32mmol) in 3mL of acetonitrile at 0°C was added TEA (560µL) dropwise. The reaction mixture was stirred at 0°C for 40min then 30min at room temperature. **16** (215mg; 0.6mmol) was added and the mixture was vigorously stirred at room temperature overnight. The reaction was followed by TLC using ethyl acetate as eluent. After complete consumption of the starting material, the solvent was removed. The residue was taken off with ethyl acetate and washed with water and brine, and dried over sodium sulfate. The solvent was removed to afford **52** as a yellow powder (241mg; 0.59mmol; yield 98%).

^{1}H NMR (500MHz, $CDCl_3$) δ 9.42 (s, 1H, Ha1), 9.25 (d, *J*=9.6Hz, 1H, Ha4), 9.06 (s, 1H, Ha9), 8.28 (s, 1H, Ha10), 7.38-7.33 (m, 2H, Ha5 and Ha7), 4.22 (brs, 2H, Hb4eq), 4.05 (d, *J*=6.3Hz, 2H, Hb1), 2.81 (brt, *J*=13Hz, 2H, Hb4ax), 2.09 (quint, *J*=7.3Hz, 2H, Ha10), 2.11 (m, 1H, Hb2), 1.89 (d, *J*=13.0Hz, 2H, Hb3eq), 1.49 (s, 9H, HBoc), 1.36 (dq, *J*=4.2, 13.0Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, $CDCl_3$) δ 163.8 (Ca6), 156.2 (Ca2), 154.8 (CBoc), 154.0 (Ca9), 153.9 (Ca10), 152.4 (Ca8), 144.9 (Ca1), 128.2 (Ca4), 122.1 (Ca5), 111.0 (Ca3), 107.0 (Ca7), 79.5 (CBoc), 72.8 (Cb1), 43.6 (Cb4), 35.9 (Cb2), 28.8 (Cb3), 28.4 (CBoc).

HRMS-ESI(m/z) calculated for $C_{21}H_{26}N_6O_3Na$ $[M+Na]^+$: 433.1959; found: 433.1960.

4-(2-phenethylamino)-7-(piperidin-4-ylmethoxy)quinazoline (53')



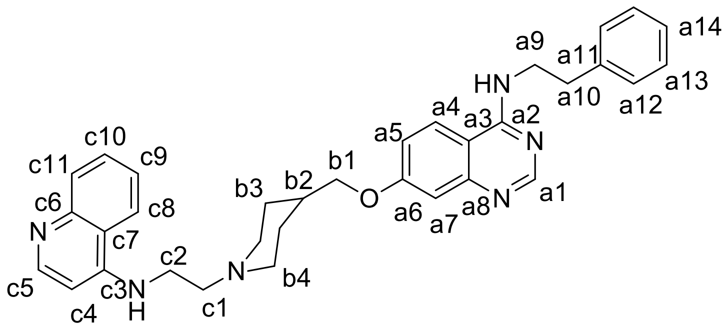
To a solution of the intermediate triazolyl **52** (68mg; 0.16mmol) in DMF was added phenethylamine (23µL; 0.16mmol). The mixture was stirred at 60°C overnight. Ethyl acetate was added and the organic phase was washed with a 10% citric acid solution, water and brine then dried over sodium sulfate. The solvent was removed. The residue was solubilized in TFA and the mixture was stirred for 1.5h at room temperature. TFA was removed and the residue was purified by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **53'** as a white powder (37mg; 0.10mmol; yield 64%).

^{1}H NMR (DMSO) δ 8.41 (s, 1H, Ha1), 8.20 (brt, *J*=5.2Hz, 1H, HNH), 8.10 (d, *J*=9.2Hz, 1H, Ha4), 7.33-7.13 (m, 4H, Ha12 and Ha13), 7.20 (m, 1H,Ha14), 7.10 (dd, *J*=2.5, 9.0Hz, 1H, Ha5), 7.05 (d, *J*=2.5Hz, 1H, Ha7), 3.93 (d, *J*=6.4Hz, 2H, Hb1), 3.72 (m, 2H, Ha9), 3.00-2.93 (m, 4H, Hb4eq and Ha10), 2.48 (m, 2H, Hb4ax), 1.86 (m, 1H, Hb2), 1.95 (brd, *J*=12.0Hz, 2H, Hb3eq), 1.19 (dq, *J*=4.0, 12.0Hz, 2H, Hb3ax).

^{13}C NMR (DMSO) δ 162.2 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 152.8 (Ca8), 140.0 (Ca11), 129.1 (Ca12), 128.8 (Ca13), 126.5 (Ca4),124.6 (Ca14), 117.3 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 73.2 (Cb1), 46.2 (Cb4), 42.6 (Ca9), 36.4 (Cb2), 35.1 (Ca10), 30.1(Cb3).

HRMS-ESI(m/z) calculated for $C_{22}H_{27}N_4O$ $[M+H]^+$: 363.2179; found: 363.2161.

4-(3-phenethylamino)-7-((1-(2-(quinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (53)



To a solution of **53’** (30mg; 0.08mmol), K_2CO_3 (23mg; 0.16mmol) and a catalytic amount of KI in DMF (1.5mL) was added **12** (40mg; 0.16mmol). The mixture was stirred at 65°C overnight. The solvent was removed and the residue was purified by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **53** as a white powder (28mg; 0.05mmol; yield 64%).

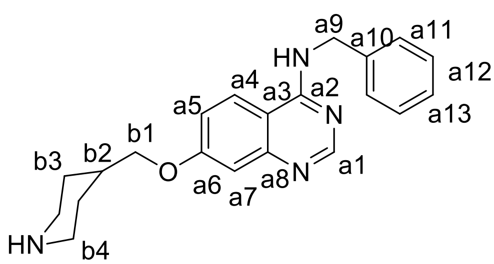
^{1}H NMR (500MHz, $CDCl_3$) δ 8.64 (s, 1H, Ha1), 8.59 (d, *J*=5.6Hz, 1H, Hc5), 8.04 (d, *J*=8.2Hz, 1H, Hc8), 7.80 (d, *J*=0.7, 8.4Hz, 1H, Hc11), 7.68 (ddd, *J*=1.3, 6.9, 8.3Hz, 1H, Hc10), 7.51 (ddd, *J*=1.1, 6.7, 8.3Hz, 1H, Hc9), 7.44 (d, *J*=9.28Hz, 1H, Ha4), 7.38-7.33 (m, 2H, Ha12), 7.31-7.26 (m, 3H, Ha14 and Ha13), 7.18 (d, *J*=2.6Hz, 1H, Ha7), 7.05 (dd, *J*=2.6, 9.0Hz, 1H, Ha5), 6.43 (d, *J*=5.4Hz, 1H, Hc4), 6.15 (brs, 1H, HNHc), 5.60 (brt, *J*=5.7Hz, 1H, HNHa), 4.00 (d, *J*=6.2Hz, 2H, Hb1), 3.70 (dd, *J*=6.7, 12.2Hz, 2H, Ha9), 3.38 (q, *J*=5.2Hz, 2H, Hc2), 3.08-3.00 (m, 4H, Hb4eq and Hc1), 2.83 (t, *J*=6.2Hz, Ha10), 2.18 (dt, *J*=1.3, 11.6Hz, 2H, Hb4ax), 2.09-1.89 (m, 3H, Hb2 and Hb3eq), 1.47 (dq, *J*=3.0,12.5Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, $CDCl_3$) δ 162.2 (Ca6), 159.0 (Ca2), 156.0 (Ca1), 151.7 (Ca8), 150.3 (Cc5), 150.2 (Cc3), 147.5 (Cc6), 138.9 (Ca12), 129.4 (Cc8), 129.1 (Cc10), 128.9 (Ca12), 128.8

(Ca13), 126.6 (Ca14), 124.9 (Cc9), 121.8 (Ca4), 119.5 (Cc11), 118.7 (Cc7), 118.1 (Ca5), 109.2 (Ca3), 107.9 (Ca7), 98.8 (Cc4), 72.6 (Cb1), 55.8 (Cc1), 52.9 (Cb4), 42.1 (Ca9), 39.1 (Cc2), 35.6 (Cb2), 35.3 (Ca10), 29.2 (Cb3).

HRMS-ESI(m/z) calculated for $C_{33}H_{37}N_6O$ $[M+H]^+$: 533.3023; found: 533.3023.

4-(2-benzylamino)-7-(piperidin-4-ylmethoxy)quinazoline (54')



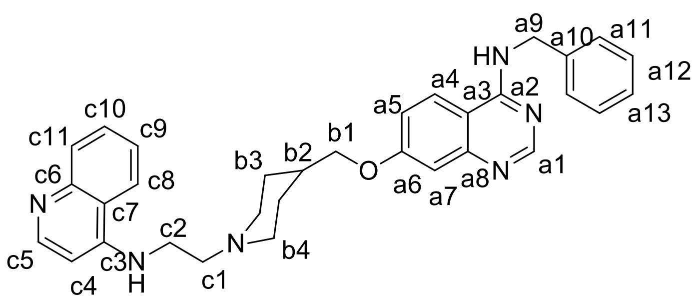
To a solution of the intermediate triazolyl **51** (120mg; 0.29mmol) and TEA (29µL) in DMF was added benzylamine (36µL; 0.32mmol). The mixture was stirred at 90°C overnight. Ethyl acetate was added and the organic phase was washed with a 10% citric acid solution, water and brine then dried over sodium sulfate. The solvent was removed. The residue was solubilized in TFA and the mixture was stirred for 1.5 at room temperature. TFA was removed and the residue was purified by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **53'** as a white powder (50mg; 0.14mmol; yield 50%).

^{1}H NMR (500MHz, DMSO) δ 8.67 (brt, 1H, *J*=6.1Hz, HNH), 8.37 (s, 1H, Ha1), 8.21 (d, *J*=9.2Hz, 1H, Ha4), 7.38-7.18 (m, 5H, Ha11, Ha12 and Ha13), 7.13 (dd, *J*=2.1, 9.1Hz, 1H, Ha5), 7.05 (d, *J*=2.0Hz, 1H, Ha7), 4.76 (d, 2H, *J*=5.7Hz, Ha9), 4.24 (d, *J*=7.4Hz, 2H, Hb1), 4.13-3.93 (m, 2H, Hb4eq), 3.17 (m, 2H, Hb4ax), 2.73 (m, 1H, Hb2), 1.77 (brd, *J*=12.2Hz, 2H, Hb3eq), 1.22 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.8 (Ca6), 158.8 (Ca2), 158.0 (Ca1), 152.8 (Ca8), 141.8 (Ca10), 128.7 (Ca11), 128.1 (Ca13), 127.5 (Ca12), 126.9 (Ca4), 116.4 (Ca5), 109.0 (Ca3), 105.2 (Ca7), 72.7 (Cb1), 44.0 (Cb4), 43.8 (Ca9), 35.9 (Cb2), 28.9 (Cb3).

HRMS-ESI(m/z) calculated for $C_{22}H_{27}N_4O$ $[M+H]^+$: 349.2023; found: 349.2001.

4-(3-benzylamino)-7-((1-(2-(quinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (54)



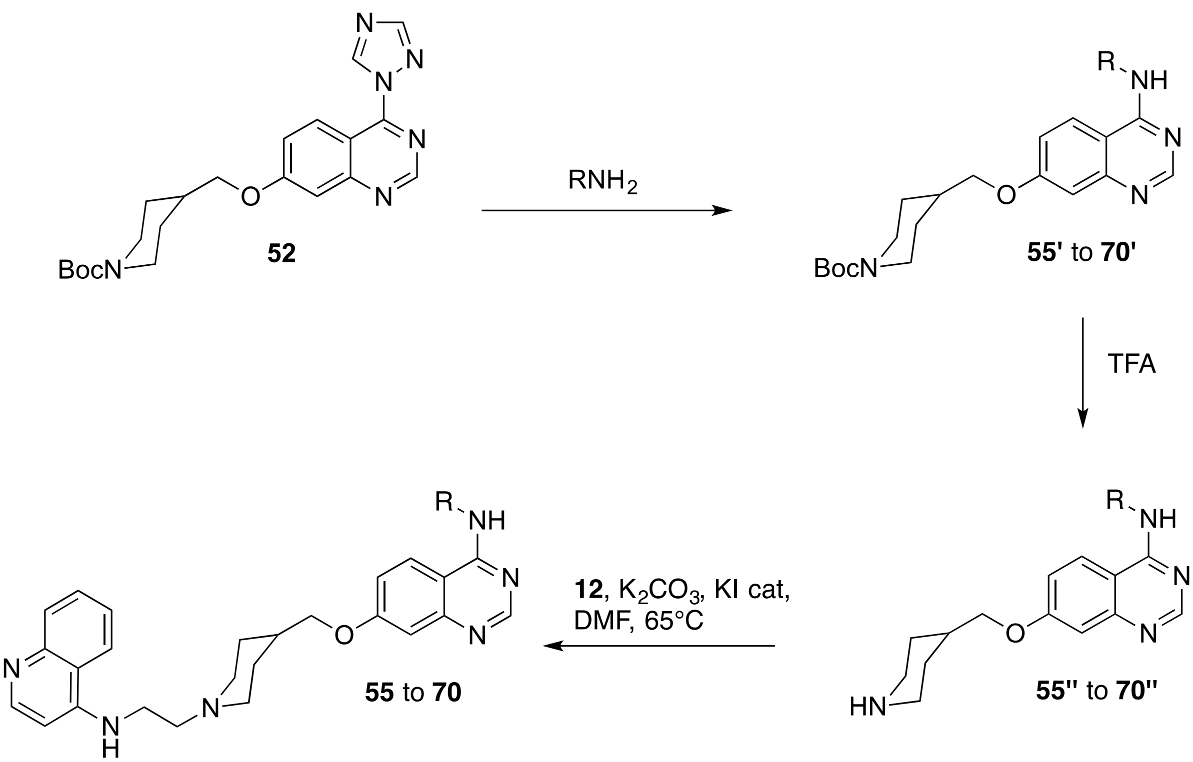
To a solution of **54’** (30mg; 0.086mmol), K_2CO_3 (24mg; 172µmol) and a catalytic amount of KI in DMF (1.5mL) was added **12** (42mg; 0.172mmol). The mixture was stirred at 65°C overnight. The solvent was removed and the residue was purified by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford **53** as a white powder (30mg; 58µmol; yield 68%).

^{1}H NMR (500MHz, $CDCl_3$) δ 8.66 (s, 1H, Ha1), 8.58 (d, *J*=5.1Hz, 1H, Hc5), 8.00 (dd, *J*=0.7, 8.5Hz, 1H, Hc8), 7.79 (dd, *J*=0.7, 8.5Hz, 1H, Hc11), 7.61 (d, *J*=8.9Hz, 1H, Ha4), 7.66 (ddd, *J*=1.4, 6.8, 8.3Hz, 1H, Hc10), 7.48 (ddd, *J*=1.4, 6.8, 8.3Hz, 1H, Hc9), 7.45-7.32 (m, 5H, Ha11 and Ha12 and Ha13), 7.20 (d, *J*=2.4Hz, 1H, Ha7), 7.08 (dd, *J*=2.4, 1H, 9.1Hz, Ha5), 6.42 (d, *J*=5.3Hz, 1H, Hc4), 5.96 (brt, *J*=4.1, 1H, HNHc), 5.87(m, 1H, HNHa), 4.87 (d, *J*=5.2Hz, Ha9), 4.00 (d, *J*=6.1Hz, 2H, Hb1), 3.36 (q, *J*=5.2Hz, 2H, Hc2), 3.03 (brd, *J*=11.7Hz, 2H, Hb4eq), 2.81 (t, *J*=6.0Hz, 2H, Ha11), 2.16 (dt, *J*=1.2, 11.8Hz, 2H, Hb4ax), 2.01-1.89 (m, 3H, Hb2 and Hb3eq), 1.50 (dq, *J*=3.6-12.1Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, $CDCl_3$) δ 162.3 (Ca6), 158.9 (Ca2), 156.0 (Ca1), 151.8 (Ca8), 151.1 (Cc5), 149.8 (Cc3), 148.3 (Cc6), 138.2 (Ca10), 129.8 (Cc8), 129.0 (Cc10), 128.8 (Ca12), 128.0 (Ca11), 127.8 (Ca13), 124.6 (Cc9), 122.0 (Ca4), 119.5 (Cc11), 118.9 (Cc7), 118.1 (Ca5), 109.0 (Ca3), 107.9 (Ca7), 99.0 (Cc4), 72.7 (Cb1), 55.9(Cc1), 52.9 (Cb4), 45.3 (Ca9), 39.2 (Cc2), 35.7 (Cb2), 29.2 (Cb3).

HRMS-ESI(m/z) calculated for $C_{32}H_{35}N_6O$ $[M+H]^+$: 519.2867; Found: 519.2870.

General procedure for compounds 55 to 70.



Step 1:

To a solution of **52** was solubilized in DMF (0.5mL), the desired amine (3eq) and TEA (6eq) were added and the mixture was stirred for 6h at room temperature. The reaction was followed by TLC and if starting material **52** was not completely disappeared the reaction mixture was stirred at 65°C for 3 more hours. The mixture was diluted with ethyl acetate and washed with water, brine and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ethyl acetate (0 → 100% EtOAc) in cyclohexane to afford **55’** to **70’**.

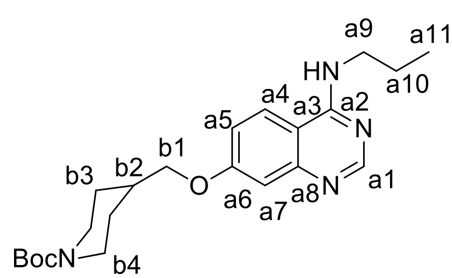
Step 2:

A mixture of the desired compound **55’** to **70’** in TFA was stirred for 1h at room temperature. TFA was removed. The residue was diluted with dichloromethane and the organic phase was washed with saturated Na_2CO_3. The solvent was removed and gave respectively compound **55''** to **70''**.

Step 3:

To a solution of 0.1 M of compound **55''** to **70''** K_2CO_3 (2eq) and a catalytic amount of KI in DMF was added **12** (2eq). The mixture was stirred at 65°C overnight then was diluted with ethyl acetate. The organic phase was washed with water and brine and dried over sodium sulfate. The solvent was removed and the residue was purified by silica gel flash chromatography using a linear gradient of ammonia 1N in methanol (0→10% $MeOH/NH_3$) in dichloromethane or by reversed phase HPLC using a linear acetonitrile gradient with 0.01% of TEA (0→80% CH_3CN) to afford compounds **55** to **70**.

4-propylamino-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy))quinazoline (55') (42mg; 105µmol; yield 75%) from **52** (53mg; 140µmol).

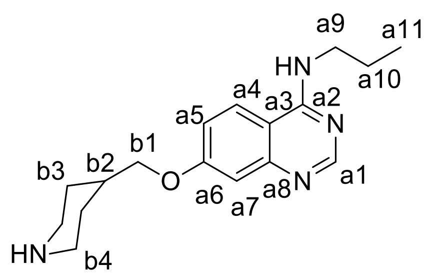


^{1}H NMR (500MHz, CDCl$_3$) δ 8.58 (s, 1H, Ha1), 7.59 (d, *J*=9.0Hz, 1H, Ha4), 7.12 (d, *J*=3.2Hz, 1H, Ha7), 7.04 (dd, *J*=2.4, 9.0Hz, 1H, Ha5), 5.62(brt, *J*=4.8, 1H, HNH), 4.15 (brs, 2H, Hb4eq), 3.92 (d, *J*=6.4Hz, 2H, Hb1), 3.60 (m, 2H, Ha9), 2.75 (m, 2H, Hb4ax), 2.00 (m, 1H, Hb2), 1.82 (d, *J*=10.9Hz, 2H, Hb3eq), 1.74 (sext, *J*=7.5Hz, 2H, Ha10), 1.46 (s, 9H, HBoc), 1.30 (m, 2H, Hb3ax), 1.03 (t, *J*=6.7Hz, 3H, Ha11).

^{13}C NMR (125MHz, $CDCl_3$) δ 162.1 (Ca6), 159.2 (Ca2), 156.0 (Ca1), 154.8 (CBoc),151.6 (Ca8), 121.9 (Ca4), 117.9 (Ca5), 109.1 (Ca3), 107.9 (Ca7), 79.4 (CBoc), 72.4 (Cb1), 43.0 (Cb4), 43.0 (Ca9), 35.9 (Cb2), 28.8 (Cb3), 28.4 (CBoc), 22.7 (Ca10), 11.5 (Ca11).

HRMS-ESI(m/z) calculated for $C_{22}H_{33}N_4O_3$ $[M+H]^+$: 401.2547 ; found: 401.2538.

4-propylamino-7-*O*-(piperidin-4-ylmethoxy)quinazoline (55'') (28mg, 93µmol, yield 90%) from **55'** (42mg, 105µmol).

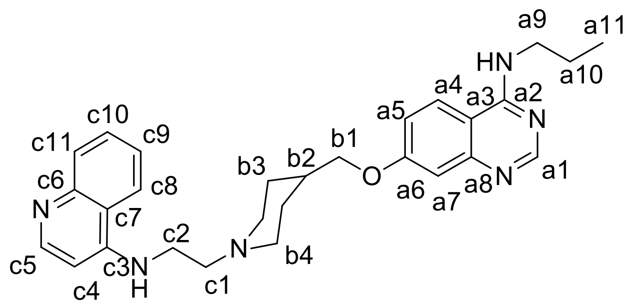


^{1}H NMR (500MHz, DMSO) δ 8.37 (s, 1H, Ha1), 8.14 (d, *J*=9.0Hz, 1H, Ha4), 8.08 (brt, *J*=5.3Hz, 1H, HNH), 7.09 (dd, *J*=2.4, 9.0Hz, 1H, Ha5), 7.04 (d, *J*=2.5Hz, 1H, Ha7), 3.93 (d, *J*=6.2Hz, 2H, Hb1), 3.60 (d, *J*=5.9Hz, 2H, Ha9), 2.95 (brd, *J*=12.1Hz, 2H, Hb4eq), 2.46 (m, 2H, Hb4ax), 1.86 (m, 1H, Hb2), 1.71 (brd, *J*=10.7Hz, 2H, Hb3eq), 1.64 (sext, *J*=7.2Hz, 2H, Ha10), 1.18 (dq, *J*=3.9, 12.5Hz, 2H, Hb3ax), 0.93 (t, *J*=5.7Hz, 3H, Ha11).

^{13}C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 124.7 (Ca4), 117.1 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 73.2 (Cb1), 46.2 (Cb4), 42.6 (Ca9), 36.4 (Cb2), 30.2 (Cb3), 22.4 (Ca10), 11.9 (Ca11).

HRMS-ESI(m/z) calculated for $C_{17}H_{25}N_4O$ $[M+H]^+$: 301.2023; found: 301.2026.

4-propylamino-7-((1-(2-(quinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (55) (12.0mg; 26µmol; yield 78%) from **55’’** (10mg; 33µmol),

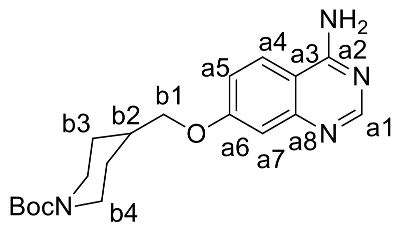


^{1}H NMR (500MHz, DMSO) δ 8.39 (d, *J*=5.3Hz, 1H, Hc5), 8.37 (s, 1H, Ha1), 8.17-8.11 (m, 2H, Ha4 and Hc8), 8.07 (brt, *J*=5.3Hz, 1H, HNH), 7.77 (dd, *J*=1.1, 8.4Hz, 1H, Hc11), 7.60 (ddd, *J*=1.3, 6.9, 8.2Hz, 1H, Hc10), 7.41 (ddd, *J*=1.3, 6.9, 8.2Hz, 1H, Hc9), 7.09 (dd, *J*=2.5, 9.0Hz, 1H, Ha5), 7.04 (m, 1H, Ha7), 6.47 (d, *J*=5.8Hz, 1H, Hc4), 3.96 (d, *J*=5.85Hz, 2H, Hb1), 3.45 (q, *J*=5.8Hz, 2H, Ha9), 3.40 (q, *J*=6.2Hz, 2H, Hc2), 3.00 (brd, *J*=10.1Hz, 2H, Hb4eq), 2.62 (t, *J*=7.1Hz, 2H,Hc1), 2.04 (t, *J*=10.1Hz, 2H, Hb4ax), 1.91 (m, 3H, Hb3eq and Hb2), 1.63 (sext, *J*=7.4Hz, 2H, Ha10),1.36 (dq, *J*=3.0, 12.6Hz, 2H, Hb3ax), 0.91 (t, *J*=7.3Hz, 3H, Ha11)

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 151.2 (Cc5), 150.2 (Cc3), 148.2 (Cc6), 129.5 (Cc11), 129.1 (Cc10), 124.7 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.1 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 56.6 (Cc1), 53.5 (Cb4), 42.6 (Ca9), 40.6 (Cc2), 35.7 (Cb2), 29.0 (Cb3), 22.4 (Ca10), 11.9 (Ca11).

HRMS-ESI(m/z) calculated for $C_{28}H_{35}N_6O$ $[M+H]^+$: 471.2867; found: 471.2876.

4-amino-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy))quinazoline (56'), (38mg; 107µmol; yield 77%) from **52** (53mg; 140µmol).

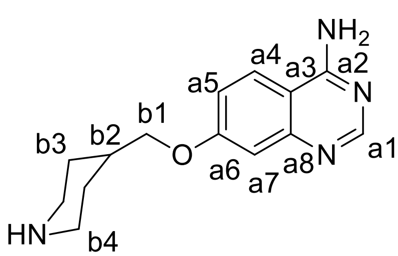


^{1}H NMR (500MHz, DMSO) δ 8.30 (s, 1H, Ha1), 8.0 (d, *J*=8.7Hz, 1H, Ha4), 7.58 (brs, 2H, HNH2), 7.08 (dd, *J*=2.5, 9.1Hz, 1H, Ha5), 7.03 (d, *J*=2.5Hz, 1H, Ha7), 4.15 (m, 4H, Hb4eq and Hb1), 2.75 (m, 2H, Hb4ax), 1.98 (m, 1H, Hb2), 1.78 (d, *J*=10.9Hz, 2H, Hb3eq), 1.40 (s, 9H, HBoc), 1.19 (dq, *J*=5.4, 13.6Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.3 (Ca6), 161.7 (Ca2), 156.4 (Ca1), 154.3 (CBoc), 152.3 (Ca8), 125.6 (Ca4), 117.2 (Ca5), 109.0 (Ca3), 107.6 (Ca7), 79.0 (CBoc), 72.3 (Cb1), 43.9 (Cb4), 35.6 (Cb2), 28.7 (Cb3), 28.5 (CBoc).

HRMS-ESI(m/z) calculated for $C_{19}H_{27}N_4O_3$ $[M+H]^+$: 359.2078; found: 359.2087.

4-amino-7-(piperidin-4-ylmethoxy)quinazoline (56'') (26mg; 101µmol; yield 94%) from **56'** (38mg; 107µmol).

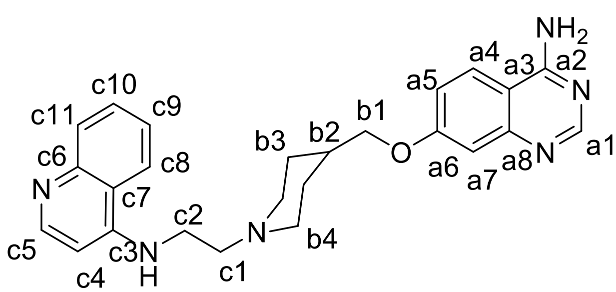


^{1}H NMR (500MHz, DMSO) δ 8.30 (s, 1H, Ha1), 8.10 (d, *J*=9.1Hz, 1H, Ha4), 7.58 (brs, 2H, HNH_2), 7.08 (dd, *J*=2.5, 9.1Hz, 1H, Ha5), 7.03 (d, *J*=2.5Hz, 1H, Ha7), 3.94 (m, 3H, Hb1 and HNH), 2.98 (m, 2H, Hb4eq), 2.48 (m, 2H, Hb4ax), 1.86 (m, 1H, Hb2), 1.71 (brd, *J*=11.2Hz, 2H, Hb3eq), 1.19 (dq, *J*=4.0, 12.3Hz, 2H, Hb3ax),.

^{13}C NMR (125MHz, DMSO) δ 162.4 (Ca6), 161.7 (Ca2), 156.4 (Ca1), 152.6 (Ca8), 125.6 (Ca4), 117.3 (Ca5), 108.9 (Ca3), 107.6 (Ca7), 73.1 (Cb1), 46.0 (Cb4), 36.4 (Cb2), 30.07 (Cb3).

HRHRMS-ESI(m/z) calculated for $C_{11}H_{19}N_4O$ $[M+H]^+$: 259.1553; found: 259.1554.

4-amino-7-((1-(2-(quinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (56) (11.4mg; 27µmol; yield 68%) as a white powder from **56''** (10mg; 0.039mmol).

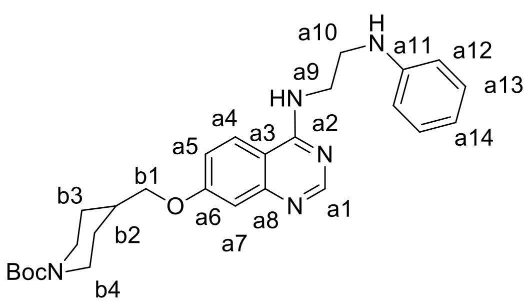


^{1}H NMR (500MHz, DMSO) δ 8.39 (d, *J*=5.5Hz, 1H, Hc5), 8.29 (s, 1H, Ha1), 8.15 (m, 3H, Hc8 and HNH_2), 8.10 (d, *J*=9.0, 1H, Ha4), 7.77 (dd, *J*=1.0Hz, 8.4Hz, 1H, Hc11), 7.60 (ddd, *J*=1.2, 6.8, 8.2Hz, 1H, Hc10), 7.42 (ddd, *J*=1.2, 6.8, 8.2Hz, 1H, Hc9), 7.08 (dd, *J*=2.5, 9.0Hz, 1H, Ha5), 7.06-7.01 (m, 2H, Ha7 and HNH), 6.47 (d, *J*=5.3Hz, 1H, Hc4), 3.97 (d, *J*=5.8Hz, 2H, Hb1), 3.41 (q, *J*=6.4Hz, 2H, Hc2), 3.00 (brd, *J*=11.0Hz, 2H, Hb4eq), 2.62 (t, *J*=6.2Hz, 2H, Hc1), 2.05 (t, *J*=11.9Hz, 2H, Hb4ax), 1.78 (m, 3H, Hb3eq and Hb2), 1.36 (dq, *J*=2.5, 11.9Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.4 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 151.2 (Cc5), 150.2 (Cc3), 148.2 (Cc6), 129.5 (Cc11), 129.1 (Cc10), 124.7 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.1 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 56.6 (Cc1), 53.5 (Cb4), 42.6 (Ca9), 40.6 (Cc2), 35.7 (Cb2), 29.0 (Cb3), 22.4 (Ca10), 11.9 (Ca11).

HRMS-ESI (m/z) calculated for $C_{25}H_{29}N_6O$ $[M+H]^+$: 429.2397; found: 429.2404.

4-(2-(phenylamino)ethylamino)-7-(*O*-((*N*-Boc) piperidin-4-ylmethoxy)) quinazoline (57') (50mg; 105µmol; yield 75%) from **52** (53mg; 140µmol).

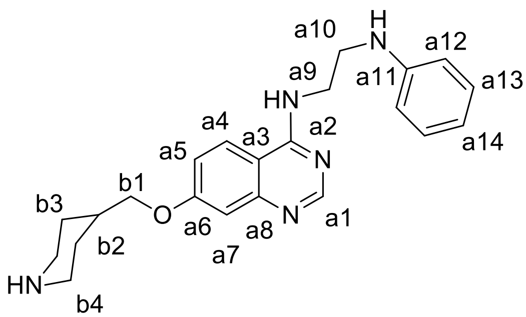


^{1}H NMR (500MHz, DMSO) δ 8.42 (s, 1H, Ha1), 8.21 (brt, *J*=5.6 Hz, 1H, HNH), 8.09 (d, *J*=9.0Hz, 1H, Ha4), 7.15 (dd, *J*=2.7, 9.1 Hz, 1H, Ha5), 7.11-7.05 (m, 3H, Ha7 and Ha13), 6.64 (dd, *J*=0.9, 8.6Hz, 2H, Ha12), 6.53 (dt, *J*=0.9, 7.3Hz, 2H, Ha14), 5.78 (brt, *J*=5.9Hz, HNH), 4.06-3.91 (m, 4H, Hb1 and Hb4eq), 3.67 (q, *J*=6.5Hz, 2H, Ha9), 3.30 (brt, *J*=6.51Hz, 2H, Ha10), 2.85-2.67 (m, 2H, Hb4ax), 2.03-1.93 (m, 1H, Hb2), 1.82-1.75 (m, 2H, Hb3eq), 1.41 (s, 9H, HBoc), 1.26-1.15 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.6 (Ca2), 156.0 (Ca1), 154.3 (CBoc), 151.8 (Ca8), 149,1 (Ca11), 129.4 (Ca13), 124.7 (Ca4), 117.3 (Ca5), 116.0 (Ca14), 112.4 (Ca12), 109.6 (Ca3), 108.0 (Ca7), 79.0 (CBoc), 72.3 (Cb1), 42.3 (Ca10), 40.2 (Ca9), 35.6 (Cb2), 28.7 (Cb3), 28.56 (CBoc).

HRMS-ESI (m/z) calculated for $C_{27}H_{35}N_5O_3$ $[M+H]^+$: 478.2813; found: 478.2819.

4-(2-(phenylamino)ethylamino)-7-*O*-(piperidin-4-ylmethoxy)quinazoline (57'') (38mg; 101µmol; yield 96%) from **57'** (50mg; 105µmol):

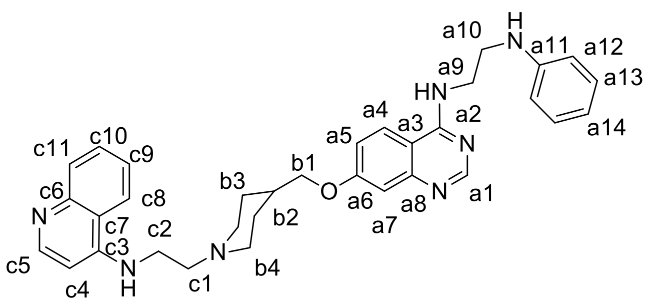


^{1}H NMR (500MHz, DMSO) δ 8.43 (s, 1H, Ha1), 8.21 (brt, *J*=5.8 Hz, 1H, HNH), 8.11 (d, *J*=9.2Hz, 1H, Ha4), 7.12 (dd, *J*=2.6, 9.2 Hz, 1H, Ha5), 7.11-7.05 (m, 3H, Ha7 and Ha13), 6.64 (dd, *J*=0.9, 8.6Hz, 2H, Ha12), 6.53 (dt, *J*=0.9, 7.2Hz, 2H, Ha14), 5.78 (brt, *J*=6.1Hz, HNH), 3.96 (d, *J*=6.4Hz 2H, Hb1), 3.68 (q, *J*=6.5Hz, 2H, Ha9), 3.31 (brt, *J*=6.5Hz, 2H, Ha10), 3.08-2.97 (m, 2H, Hb4eq), 2.62-2.547 (m, 2H, Hb4ax), 1.97-1.86 (m, 1H, Hb2), 1.81-1.72 (m, 2H, Hb3eq), 1.32-1.20 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.6 (Ca2), 156.0 (Ca1), 151.8 (Ca8), 149,1 (Ca11), 129.4 (Ca13), 124.7 (Ca4), 117.3 (Ca5), 116.1 (Ca14), 112.4 (Ca12), 109.5 (Ca3), 108.0 (Ca7), 72.9 (Cb1), 45.6 (Cb4), 42.3 (Ca10), 40.1 (Ca9), 35.8 (Cb2), 29.2 (Cb3).

HRMS-ESI (m/z) calculated for $C_{22}H_{27}N_5O$ $[M+H]^+$: 378.2289; found: 378.2280.

4-(2-(phenylamino)ethylamino)-7-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (57) (11mg; 20μmol; yield 50%) from **57’’** (15mg 40μmol):

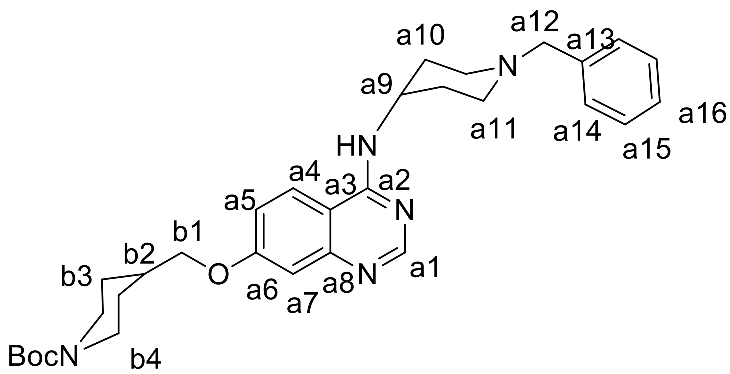


^{1}H NMR (500MHz, DMSO) δ 8.42 (s, 1H, Ha1), 8.40 (d, *J*= 5.2Hz, 1H, Hc5), 8.26 (brt, *J*=5.5 Hz, 1H, HNH), 8.16 (d, *J*=7.9Hz, 1H, Hc8), 8.13 (d, *J*=9.0Hz, 1H, Ha4), 7.78 (dd, *J*=1.0, 8.3 Hz, 1H, Hc11), 7.61 (ddd, *J*=1.0, 6.8, 8.1Hz, 1H, Hc10), 7.42 (ddd, *J*=1.0, 6.9, 7.9Hz, 1H, Hc9), 7.13 (dd, *J*=2.5, 9.0 Hz, 1H, Ha5), 7.11-7.02 (m, 3H, Ha7 and Ha13), 6.64 (d, *J*=7.8Hz, 2H, Ha12), 6.52 (t, *J*=7.3Hz, 2H, Ha14), 6.48 (d, *J*=7.3Hz, 1H, Hc4), 5.81 (brt, *J*=5.8Hz, 1H, HNH), 3.99 (d, *J*=5.8Hz, 2H, Hb1), 3.69 (q, *J*=6.4Hz, 2H, Ha9), 3.41 (q, *J*=6.8 Hz, 2H, Hc2), 3.30 (q, *J*=6.40Hz, 2H, Ha10), 3.05-2.97 (m, 2H, Hb4eq), 2.63 (t, *J*=6.8Hz, 2H, Hc1), 2.05 (t, *J*=6.9 Hz, 2H, Hb4ax), 1.86-1.74 (m, 3H, Hb3eq and Hb2), 1.45-1.32 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.6 (Ca2), 156.0 (Ca1), 151.8 (Ca8), 151.1 (Cc5), 150.2 (Cc3), 149.1(Ca11), 148.7 (Cc6), 129.5 (Cc11), 129.4 (Ca13), 129.1 (Cc10), 124.4 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.3 (Ca5), 116.0 (Ca14), 112.4 (Ca12), 109.6 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 56.6 (Cc1), 53.5 (Cb4), 42.4 (Ca10), 40.5(Hc2), 40.2 (Ca9), 35.7 (Cb2), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{33}H_{38}N_7O$ $[M+H]^+$: 548.3133; found: 548.3140.

4-((*N*-(1-benzylpiperidin-4-yl))amino)-7-(*O*-((*N*-Boc) piperidin-4-ylmethoxy)) quinazoline (58’) (60mg; 113µmol; yield 81%) from **52** (60mg; 140µmol).

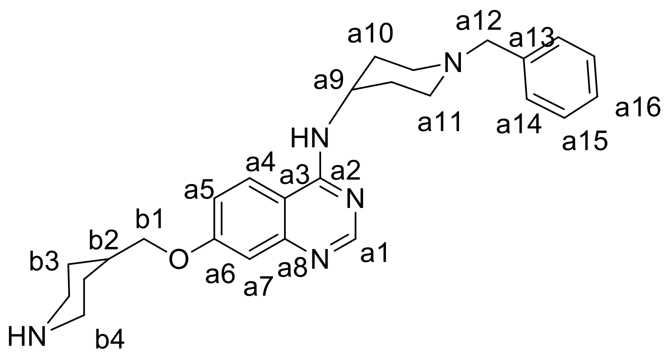


[1]H NMR (500MHz, DMSO) δ 8.36 (s, 1H, Ha1), 8.28 (brs, 1H, HNH), 8.21 (d, *J*=9.2Hz, 1H, Ha4), 7.73 (d, *J*=7.6 Hz, 1H, HNH), 7.37-7.22 (m, 5H, Ha14, Ha15 and Ha16), 7.10 (dd, *J*=2.6, 9.0Hz, 1H, Ha5) , 7.04 (d, *J*=2.7Hz, 1H, Ha7), 4.16- 4.10 (m, 1H, Ha9), 4.06-3.86 (m, 3H, Hb1 and Hb4eq), 3.49 (s, 2H, Ha12), 2.86 (brd, *J*=11.8Hz, 2H, Ha11eq), 2.81-2.67 (m, 2H, Hb4ax), 2.06 (dd, *J*=1.7, 11.8Hz, 2H, Ha11ax), 2.02-1.92 (m, 1H, Hb2), 1.90 (brd, *J*=12.4Hz, 2H, Ha10eq), 1.78 (brd, *J*=13.4Hz, 2H, Hb3eq), 1.64 (dd, *J*=3.6, 12.4Hz, 2H, Ha10ax), 1.41 (s, 9H, HBoc), 1.19 (dd, *J*=4.6, 13.4Hz, 2H, Hb3ax)

[13]C NMR (125MHz, DMSO) δ 162.1 (Ca6), 158.8 (Ca2), 156.0 (Ca1), 154.3 (CBoc), 151.9 (Ca8), 139,2 (Ca13), 129.1 (Ca14), 128.6 (Ca15), 127.3 (Ca16), 124.97 (Ca4), 117.4 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 78.9 (CBoc), 72.3 (Cb1), 62.6 (Ca12), 52.8 (Ca11), 48.2 (Ca9), 35.7 (Cb2), 31.7 (Ca10), 28.7 (Cb3), 28.5 (CBoc).

HRMS-ESI (m/z) calculated for $C_{31}H_{32}N_5O_3$ $[M+H]^+$: 532.3282; found: 532.3296.

4-((*N*-(1-benzylpiperidin-4-yl))amino)-7-*O*-(piperidin-4-ylmethoxy) quinazoline (**58'')** (42mg; 97µmol; yield 86%) from **58'** (55mg; 105µmol).

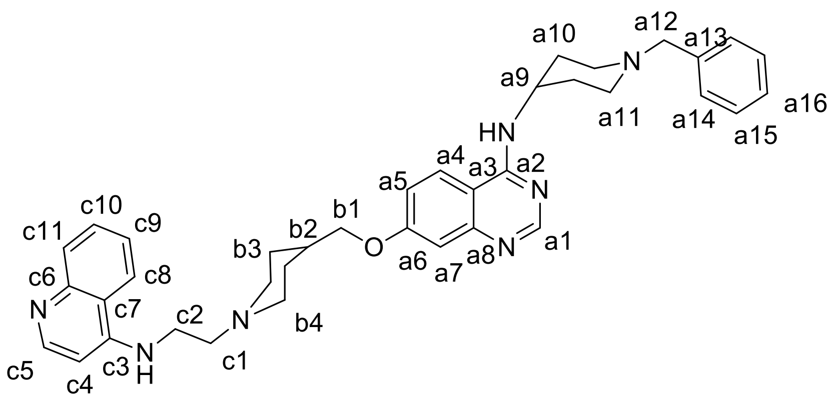


^{1}H NMR (500MHz, DMSO) δ 8.37 (s, 1H, Ha1), 8.28 (brs, 1H, HNH), 8.22 (d, *J*=9.2Hz, 1H, Ha4), 7.74 (d, *J*=7.6 Hz, 1H, HNH), 7.37-7.24 (m, 4H, Ha14 and Ha15), 7.28-7.23 (m, 1H, Ha16), 7.09 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.04 (d, *J*=2.6Hz, 1H, Ha7), 4.20-4.10 (m, 1H, Ha9), 3.95 (d, *J*=6.4Hz, 2H, Hb1), 3.49 (s, 2H, Ha12), 3.01 (brd, *J*=12.2Hz, 2H, Hb4eq), 2.87 (brd, *J*=11.7Hz, 2H, Ha11eq), 2.58 (m, 2H, Hb4ax), 2.06 (dt, *J*=1.5, 11.7Hz, 2H, Ha11ax), 1.94-1.85 (m, 3H, Hb2 and Ha10eq), 1.78 (brd, *J*=10.5Hz, 2H, Hb3eq), 1.65 (ddd, *J*=3.7, 11.7Hz, 2H, Ha10ax), 1.23 (m, 2H, Hb3ax)

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 158.8 (Ca2), 156.0 (Ca1), 151.9 (Ca8), 139,2 (Ca13), 129.1 (Ca14), 128.6 (Ca15), 127.3 (Ca16), 124.9 (Ca4), 117.0 (Ca5), 109.4 (Ca3), 107.9 (Ca7), 72.9 (Cb1), 62.6 (Ca12), 52.8 (Ca11), 48.2 (Ca9), 45.7 (Cb4), 35.9 (Cb2), 31.7 (Ca10), 29.4 (Cb3).

HRMS-ESI (m/z) for $C_{26}H_{34}N_5O$ $[M+H]^+$: 432.2758; found: 432.2753.

4-((N-(1-benzylpiperidin-4-yl))amino)-7-((1-(2-(6,7-dimethoxyquinolin-4-ylamino)ethyl)piperidin-4-yl)methoxy)quinazoline (58) (10mg; 17µmol; yield 48%) from **58’’** (15mg; 35µmol):

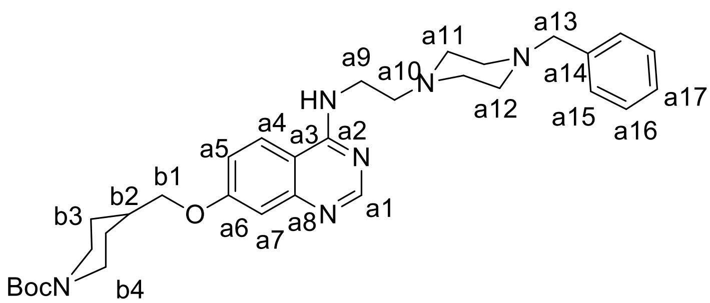


^{1}H NMR (500MHz, DMSO) δ 8.40 (d, *J*= 5.3Hz, 1H, Hc5), 8.37 (s, 1H, Ha1), 8.22 (d, *J*=9.3Hz, 1H, Ha4), 8.16 (dd, *J*=0.9, 7.8Hz, 1H, Hc8), 7.78 (dd, *J*=1.0, 8.4Hz, 1H, Hc11), 7.73 (d, *J*=7.6 Hz, 1H, HNH), 7.60 (ddd, *J*=1.3, 7.3, 8.4Hz, 1H, Hc10), 7.42 (ddd, *J*=1.3, 7.3, 8.4Hz, 1H, Hc9), 7.36-7.29 (m, 4H, Ha14 and Ha15), 7.27-7.23 (m, 1H, Ha16), 7.13-7.05 (m, 3H, Ha5, Hc4 and Ha7), 7.10 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.04 (d, *J*=2.6Hz, 1H, Ha7), 7.02 (brt, *J*=5.3Hz, 1H, HNH), 6.47 (d, *J*=5.4Hz, 1H), 4.20-4.12 (m, 1H, Ha9), 3.97 (d, *J*=5.9Hz, 3H, Hb1), 3.49 (s, 2H, Ha12), 3.41 (q, *J*=6.0,13.0Hz, 2H, Hc2), 3.01 (brd, *J*=11.2Hz, 2H, Ha11eq), 2.87 (brd, *J*=11.7Hz, 2H, Hb4eq), 2.64 (m, 2H, Hc1,), 2.06 (m, 4H, Ha11ax and Hb4ax), 1.94-1.86 (m, 3H, Ha10eq), 1.86-1.74 (m, 2H, Hb2 and Hb3eq), 1.65 (ddd, *J*=3.3, 11.9Hz, 2H, Ha10ax), 1.45-1.31 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 158.8 (Ca2), 156.0 (Ca1), 151.9 (Ca8), 151.1 (Cc5), 150.2 (Cc3), 148.7 (Cc6), 139,2 (Ca13), 129.5 (Cc11), 129.1 (Ca14), 129.1 (Cc10), 128.6 (Ca15), 127.3 (Ca15), 124.9 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.0 (Ca5), 109.5 (Ca3), 107.8 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 62.6 (Ca12), 56.6 (Cc1), 53.6 (Ca11), 52.8 (Cb4), 48.2(Ca9), 40.5 (Cc2), 35.7 (Cb2), 31.7 (Ca10), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{37}H_{43}N_7O$ $[M+H]^+$: 602.3602; found: 602.3603.

4-(2-(4-benzylpiperazin-1-yl)ethyl)-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy)) quinazoline (59') (65mg; 116µmol; yield 95%) as a white powder from **52** (53mg; 120µmol).

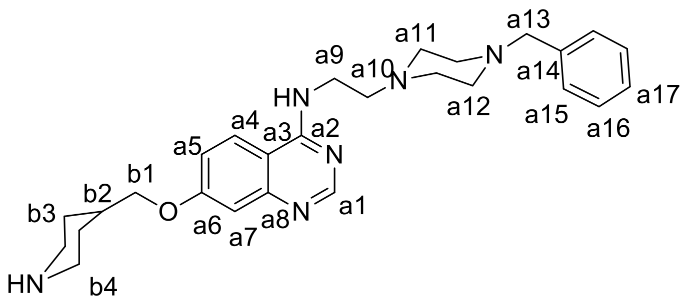


^{1}H NMR (500MHz, DMSO) δ 8.37 (s, 1H, Ha1), 8.10 (d, *J*=8.7Hz, 1H, Ha4), 8.01 (brt, *J*=5.5Hz, 1H, HNH), 7.37-7.22 (m, 5H, Ha15, Ha16 and Ha17), 7.11 (dd, *J*=2.6, 8.4Hz, 1H, Ha5), 7.04 (d, *J*=2.6Hz, 1H, Ha7), 3.98 (d, *J*=6.1Hz, 2H, Hb1), 3.86 (q, *J*=6.8Hz, 2H, Ha9), 3.45 (s, 2H, Ha13), 2.90-2.70 (m, 2H, Hb4eq), 2.56 (t, *J*=6.8Hz, 2H, Ha10), 2.48-2.41 (m, 10H, Hb4ax, Ha11 and Ha12), 2.04-1.93 (m, 1H, Hb2), 1.82-1.73 (m, 2H, Hb3eq), 1.41 (s, 9H, HBoc), 1.27-1.15 (dd, *J*=4.6, 13.4Hz, 2H, Hb3ax)

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 154.3 (CBoc), 151.8 (Ca8), 138,7 (Ca14), 129.2 (Ca15), 128.6 (Ca16), 127.3 (Ca17), 124.7 (Ca4), 117.2 (Ca5), 109.5 (Ca3), 108.0 (Ca7), 79.0 (CBoc), 72.3 (Cb1), 62.5 (Ca13), 57.1 (Ca10), 53.3 (Ca12), 53.1 (Ca11), 38.4(Ca9), 35.7 (Cb2), 28.7 (Cb3), 28.6 (CBoc).

HRMS-ESI (m/z) calculated for $C_{32}H_{44}N_6O_3$ $[M+H]^+$: 561.3548; found: 561.3551.

4-(2-(4-benzylpiperazin-1-yl)ethyl)-7-(piperidin-4-ylmethoxy)) quinazoline (59'') (50mg; 108µmol; yield 93%) from **59**' (65mg; 116µmol).

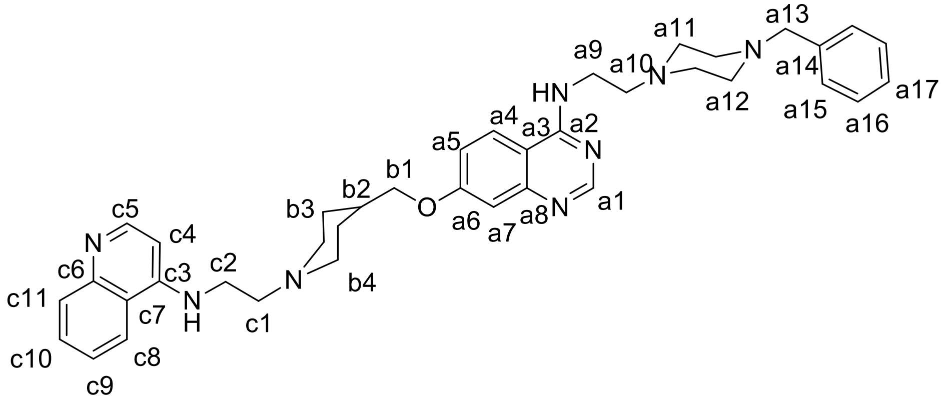


^{1}H NMR (500MHz, DMSO) δ 8.38 (s, 1H, Ha1), 8.10 (d, *J*=9.1Hz, 1H, Ha4), 8.02 (brt, *J*=5.5Hz, 1H, HNH), 7.35-7.28 (m, 4H, Ha15 and Ha16), 7.28-7.22 (m, 1H, Ha17), 7.11 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.06 (d, *J*=2.6Hz, 1H, Ha7), 3.97 (d, *J*=6.5Hz, 2H, Hb1), 3.62 (q, *J*=6.5Hz, 2H, Ha9), 3.45 (s, 2H, Ha13), 3.06 (brd, *J*=12.3Hz, 2H, Hb4eq), 2.64-2.54 (m, 4H, Ha10 and Hb4ax), 2.48-2.29 (m, 8H, Ha11 and Ha12), 1.98-1.86 (m, 1H, Hb2), 1.78 (brd, *J*=10.7Hz, 2H, Hb3eq), 1.32-1.21 (m, 2H, Hb3ax)

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 138,7 (Ca14), 129.2 (Ca15), 128.6 (Ca16), 127.3 (Ca17), 124.6 (Ca4), 117.2 (Ca5), 109.5 (Ca3), 108.0 (Ca7), 72.8 (Cb1), 62.5 (Ca13), 57.1 (Ca10), 53.3 (Ca12), 53.1 (Ca11), 45.4 (Hb4), 38.3 (Ca9), 35.6 (Cb2), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{27}H_{36}N_6O$ $[M+H]^+$: 461.3024; found: 461.3018.

4-(2-(4-benzylpiperazin-1-yl)ethyl)-7-(piperidin-4-ylmethoxy)) quinazoline (59) (21mg; 33µmol; yield 30%) from **59’’** (50mg; 109µmol).

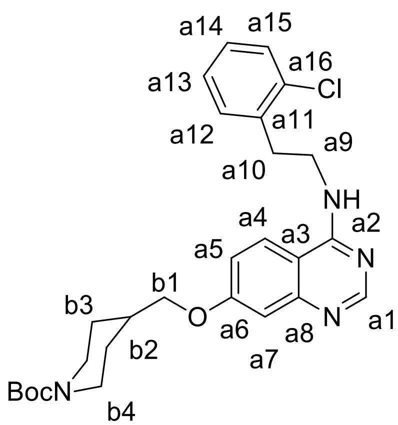


^{1}H NMR (500MHz, DMSO) δ 8.40 (d, *J*= 5.3 Hz, 1H, Hc5), 8.38 (s, 1H, Ha1), 8.17 (d, *J*=7.8 Hz, 1H, Hc8), 8.11 (d, *J*=9.2Hz, 1H, Ha4), 8.05 (brt, *J*=5.5Hz, 1H, HNH), 7.78 (dd, *J*=1.0, 8.4 Hz, 1H, Hc11), 7.61 (m, 1H, Hc10), 7.43 (ddd, *J*=1.3, 6.9, 8.2Hz, 1H, Hc9), 7.34-7.27 (m, 4H, Ha15 and Ha16), 7.27-7.22 (m, 1H, Ha17), 7.12 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.06 (d, *J*=2.6Hz, 1H, Ha7), 6.48 (d, *J*=5.4 Hz, 1H, Hc4), 3.98 (d, *J*=5.9Hz, 2H, Hb1), 3.62 (q, *J*=6.5Hz, 2H, Ha9), 3.45 (s, 2H, Ha13), 3.41 (q, j=6.5Hz, 2H, Hc2), 3.01 (brd, *J*=11.2Hz, 2H, Hb4eq), 2.64 (t, *J*=6.8Hz, 2H, Hc1) , 2.56 (t, *J*=6.8Hz, 2H, Ha10), 2.45-2.29 (m, 8H, Ha11 and Ha12), 2.06 (brt, *J*=10.6Hz, 2H, Hb4ax), 1.86-1.75 (m, 3H, Hb2 and Hb3eq), 1.44-1.32 (m, 2H, Hb3ax)

^{13}C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 151.2 (Cc5), 150.2 (Cc3), 148.7 (Cc6), 138,7 (Ca14), 129.5 (Cc11), 129.2 (Ca15), 129.1 (Cc10), 128.6 (Ca16), 127.3 (Ca17), 127.1 (Ca15), 124.7 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.2 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 62.5 (Ca13), 57.1 (Ca10), 56.6 (Cc1), 53.5 (Cb4), 53.3 (Ca12), 53.1 (Ca11), 45.6 (Cc2), 38.4 (Ca9), 35.7 (Cb2), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{38}H_{47}N_8O$ $[M+H]^+$: 631.3868; found: 631.3867.

4-(2-(2-chlorophenyl)ethylamino)-7-(*O*-((*N*-Boc) piperidin-4-ylmethoxy)) quinazoline (60') (54mg; 0.11mmol; yield 88%) from **52** (60mg; 140μmol).

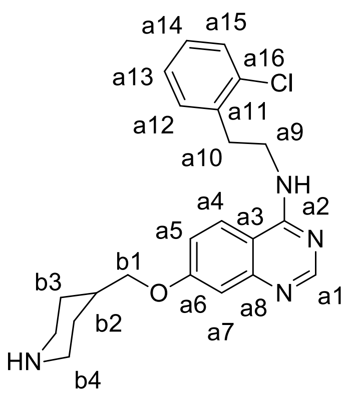


^{1}H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.17 (brt, *J*=5.5 Hz, 1H, HNH), 8.09 (d, *J*=9.3 Hz, 1H, Ha4), 7.36-7.26 (m, 4H, Ha12 and Ha13 and Ha14), 7.11 (dd, *J*=2.7, 9,12 Hz, 1H, Ha5), 7.06 (d, *J*=2.3Hz, 1H, Ha7), 4.04-3.93 (m, 2H, Hb4eq), 3.99 (d, *J*=6.3Hz, 2H, Hb1), 3.75-3.69 (m, 2H, Ha9), 2.95 (brt, *J*=7.3Hz, 2H, Ha10), 2.83-2.68 (m, 2H, Hb4ax), 2.02-1.92 (m, 1H, Hb2), 1.81-1.73 (m, 2H, Hb3eq), 1.41 (s, 9H, HBoc), 1.20 (dq, *J*=3.8, 12.3Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 154.3 (CBoc), 151.8 (Ca8), 139.1 (Ca11), 131.14 (Ca16), 131 (Ca15), 128.7 (Ca13), 128.7 (Ca14), 127.7 (Ca12), 124.6 (Ca4), 117.3 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 78.9 (CBoc), 72.3 (Cb1), 43.3 (Cb4), 42.2 (Ca9), 35.6 (Cb2), 34.3 (Ca10), 28.7 (Cb3), 28.6 (CBoc).

HRMS-ESI (m/z) calculated for $C_{27}H_{34}ClN_4O_3$ $[M+H]^+$: 497.2319; found: 497.2325.

4-(2-(2-chlorophenyl)ethylamino)-7-*O*-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy) (**60’’)** (52mg; 0.13mmol, yield 93%) from **60’** (55mg; 0.11mmol):

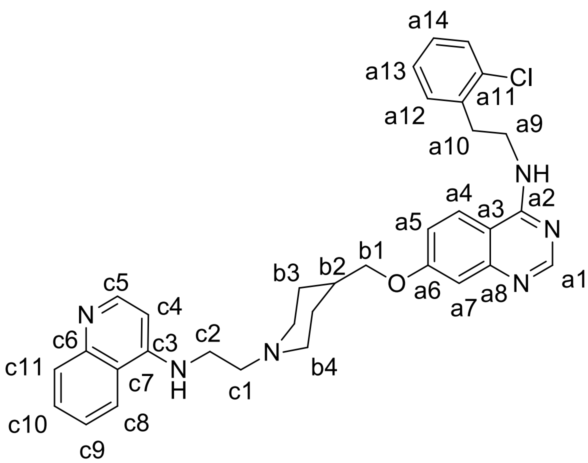


[1]H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.19 (brt, *J*=5.6Hz, 1H, HNH), 8.11 (d, *J*=9.1Hz, 1H, Ha4), 7.37-7.22 (m, 4H, Ha12 and Ha13 and Ha14), 7.10 (dd, *J*=2.7, 9.9Hz, 1H, Ha5), 7.06 (d, *J*=2.5Hz, 1H, Ha7), 3.95 (d, *J*=6.4Hz, 2H, Hb1), 3.75-3.69 (m, 2H, Ha9), 3.07-3.01 (m, 2H, Hb4eq), 2.95 (brt, *J*=7.2Hz, 2H, Ha10), 2.62-2.54 (m, 2H, Hb4ax), 1.97-1.87 (m, 1H, Hb2), 1.82-1.72 (m, 2H, Hb3eq), 1.32-1.20 (m, 2H, Hb3ax).

[13]C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 139.1 (Ca11), 131.1 (Ca16), 131 (Ca15), 128.7 (Ca13), 128.7 (Ca14), 126.6 (Ca12) 126.6 (Ca4), 117.2 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 72.9 (Cb1), 45.5 (Cb4), 42.2 (Ca9), 34.6 (Cb2), 34.3 (Ca10), 29.1 (Cb3).

HRMS-ESI (m/z) calculated for $C_{22}H_{34}ClN_4O$ $[M+H]^+$: 397.1795; found: 397.1791.

4-(2-(2-chlorophenyl)ethylamino)-7-*O*-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (60) (4.0mg; 7.1µmol; yield 29%) from **60’’** (10mg; 25µmol):

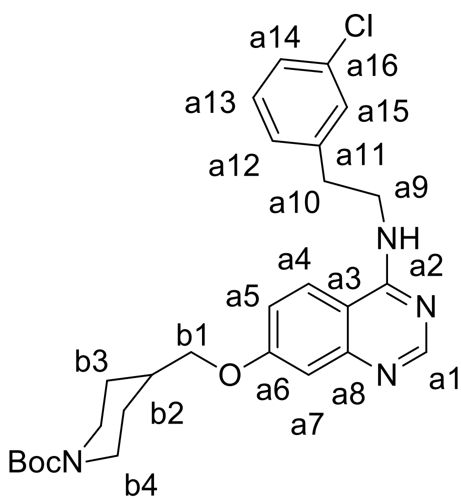


^{1}H NMR (500MHz, DMSO) δ 8.40 (s, 1H, Ha1), 8.39 (d, *J*= 5.8Hz, 1H, Hc5), 8.16 (brt, *J*=5.06Hz, 1H, HNH), 8.15 (d, *J*=8.1Hz, 1H, Hc8), 8.10 (d, *J*=9.03Hz, 1H, Ha4), 7.77 (dd, *J*=0.9, 8.3Hz, 1H, Hc11), 7.60 (m, 1H, Hc10), 7.42 (m, 1H, Hc9), 7.36-7.24 (m, 4H, Ha12and Ha13 and Ha14), 7.11 (dd, *J*=2.47, 9,12Hz, 1H, Ha5), 7.05 (d, *J*=2.61, 1H, Ha7), 7.03 (brt, *J*=5.1 Hz, 1H, HNH), 6.47 (d, *J*=5.3Hz, 1H, Hc4), 3.98 (d, *J*=5.7Hz, 2H, Hb1), 3.77-3.67 (m, 2H, Ha9), 3.44-3.36(m, 2H, Hc2), 3.04-2.97 (m, 2H, Hb4eq), 2.94 (brt, *J*=7.1Hz, 2H, Ha10), 2.63 (t, *J*=6.8Hz, 2H, Hc1), 2.06 (m, 2H, Hb4ax), 1.84-1.74(m, 3H, Hb2 and Hb3eq), 1.44-1.30 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 151.2 (Cc5), 150.2 (Cc3), 148.7 (Cc6), 139.1 (Ca11), 131.14 (Ca16), 131(Ca15), 129.5 (Cc11), 129.1 (Cc10), 128.7 (Ca13), 128.7 (Ca14), 127.9 (Ca12), 124.6 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.3 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 56.6 (Cc1), 53.5 (Cb4), 42.2 (Ca9), 40.5 (Cc2), 35.7 (Cb2), 34.53 (Ca10), 29 (Cb3).

HRMS-ESI (m/z) calculated for $C_{33}H_{36}ClN_6O$ $[M+H]^+$: 567.2639; found: 567.2641.

4-(2-(3-chlorophenyl)ethylamino)-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy)) quinazoline (61') (70mg; 0.14mmol; quantitative yield) from **52** (60mg; 140µmol).

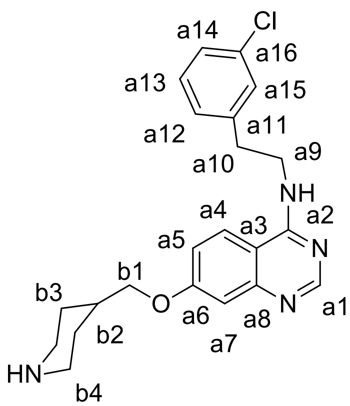


^{1}H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.18 (brt, *J*=5.5Hz, 1H, HNH), 8.10 (d, *J*=9.1Hz, 1H, Ha4), 7.35-7.19 (m, 4H, Ha12 and Ha13 and Ha14), 7.11 (dd, *J*=2.5, 9.1Hz, 1H, Ha5), 7.06 (d, *J*=2.5Hz, 1H, Ha7), 4.03-3.93 (m, 2H, Hb4eq), 3.99 (d, *J*=6.3Hz, 2H, Hb1), 3.77-3.71 (m, 2H, Ha9), 2.97 (brt, *J*=7.0Hz, 2H, Ha10), 2.85-2.68 (m, 2H, Hb4ax), 2.02-1.93 (m, 1H, Hb2), 1.81-1.74 (m, 2H, Hb3eq), 1.41 (s, 9H, HBoc), 1.20 (dq, *J*=4.9, 13.1Hz, 2H, Hb3ax)

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 154.3 (CBoc), 151.8 (Ca8), 142.7 (Ca11), 133.3 (Ca16), 130.5 (Ca15), 129.0 (Ca13), 127.9 (Ca12), 126.5 (Ca14), 124.61 (Ca4), 117.3 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 78.9 (CBoc), 72.3 (Cb1), 42.02 (Ca9), 35.6 (Cb2), 34.5 (Ca10), 28.7 (Cb3), 28.6 (CBoc).

HRMS-ESI (m/z) calculated for $C_{27}H_{34}ClN_4O_3$ $[M+H]^+$: 497.2319; found: 497.2342.

4-(2-(3-chlorophenyl)ethylamino)-7-*O*-(piperidin-4-ylmethoxy)quinazoline (61'') (56mg; 0.14mmol; quantitative yield) from **61'** (69mg; 0.14mmol):

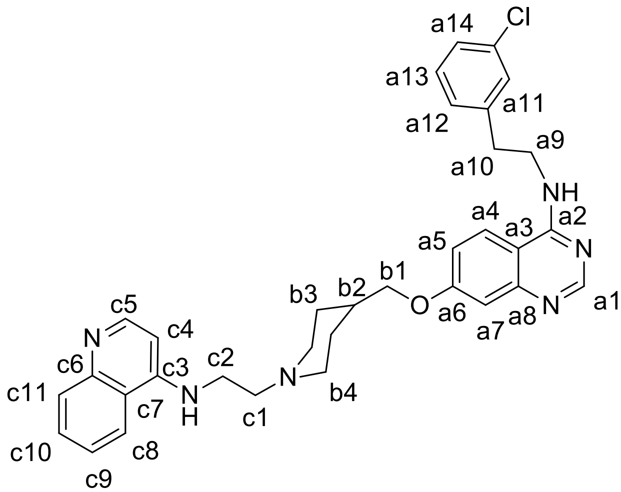


^{1}H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.21 (brt, *J*=5.3Hz, 1H, HNH), 8.12 (d, *J*=9.1 Hz, 1H, Ha4), 7.35-7.20 (m, 4H, Ha12 and Ha13 and Ha14), 7.11 (dd, *J*=2.6, 9,0Hz, 1H, Ha5), 7.07 (d, *J*=2.54Hz, 1H, Ha7), 3.96 (d, *J*=6.4Hz, 2H, Hb1), 3.77-3.71 (m, 2H, Ha9), 3.11-3.06 (m, 2H, Hb4eq) 2.97 (brt, *J*=7.1Hz, 2H, Ha10), 2.68-2.60 (m, 2H, Hb4ax), 2.00-1.89 (m, 1H, Hb2), 1.83-1.74 (m, 2H, Hb3eq), 1.30 (dq, *J*=2.9, 12.2Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 142.7 (Ca11), 133.3 (Ca16), 130.6 (Ca15), 129.0 (Ca13), 127.9 (Ca12), 126.6 (Ca14) 124.7 (Ca4), 117.2 (Ca5), 109.6 (Ca3), 108 (Ca7), 72.7 (Cb1), 45.1 (Cb4), 42 (Ca9), 34.9 (Cb2), 34.5 (Ca10), 28.5 (cb3).

HRMS-ESI (m/z) calculated for $C_{22}H_{25}ClN_4O$ $[M+H]^+$: 397.1795; found: 397.1799.

4-(2-(3-chlorophenyl)ethylamino)-7-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (61) (5.0mg; 8.8µmol; yield 35%) from **61'** (10mg; 25µmol):

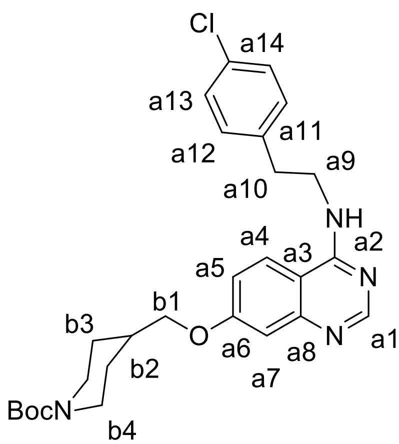


^{1}H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.39 (d, *J*= 5.4Hz, 1H, Hc5) 8.18 (brt, *J*=5.3Hz, 1H, HNH), 8.15 (d, *J*=8.4Hz, 1H, Hc8), 8.10 (d, *J*=9.0Hz, 1H, Ha4), 7.77 (dd, *J*=0.9, 8.4Hz, 1H, Hc11), 7.60(m, 1H, Hc10), 7.42 (m, 1H, Hc9), 7.36-7.18 (m, 4H, Ha12 and Ha13 and Ha14), 7.11 (dd, *J*=2.6, 9.,2Hz, 1H, Ha5), 7.06 (d, *J*=2.5Hz, 1H, Ha7), 7.03 (brt, *J*=5.4Hz, 1H, HNH), 6.47 (d, *J*=5.4Hz, 1H, Hc4), , 3.98 (d, *J*=5.9Hz, 2H, Hb1), 3.79-3.69 (m, 2H, Ha9), 3.44-3.36 (m, 2H, Hc2), 3.00 (m, 2H, Hb4eq), 2.97 (brt, *J*=7.1Hz, 2H, Ha10), 2.63 (t, *J*=6.7Hz, 2H, Hc1), 2.06 (m, 2H, Hb4ax), 1.85-1.72 (m, 3H, Hb2 and Hb3eq), 1.45-1.30 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 151.2 (Cc5), 150.2 (Cc3), 148.7 (Cc6), 142.7 (Ca11), 133.3 (Ca16), 130.6 (Ca15), 129.5 (Cc11), 129.1 (Cc10), 129.0 (Ca13), 127.9 (Ca12), 126.5 (Ca14), 124.6 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.3 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 56.6 (Cc1), 53.6 (Cb4), 42.1 (Ca9), 40.4 (Cc2), 34.5 (Cb2), 34.5 (Ca10), 29 (Cb3)

HRMS-ESI (m/z) calculated for $C_{33}H_{36}ClN_6O$ $[M+H]^+$: 567.2639; found: 567.2644.

4-(2-(4-chlorophenyl)ethylamino)-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy)) quinazoline (62') (93mg; 140µmol; quantitative yield) from **52** (60mg; 140µmol):

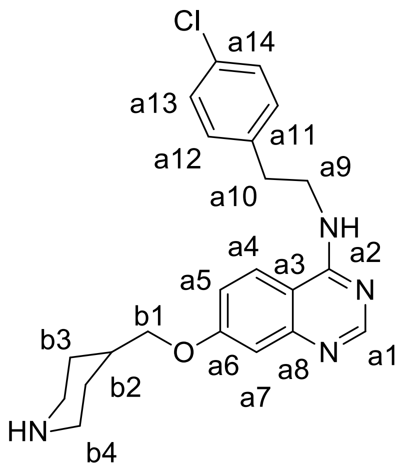


^{1}H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.21 (brt, *J*=5.7Hz, 1H, HNH), 8.10 (d, *J*=9.2Hz, 1H, Ha4), 7.47-7.31 (m, 4H, Ha12 and Ha13 and Ha14), 7.11 (dd, *J*=2.5, 8.9Hz, 1H, Ha5), 7.06 (d, *J*=2.6Hz, 1H, Ha7), 4.03-3.94 (m, 2H, Hb4eq), 3.98 (d, *J*=6.4Hz, 2H, Hb1), 3.80-3.71 (m, 2H, Ha9), 3.09 (brt, *J*=7.4Hz, 2H, Ha10), 2.75-2.60 (m, 2H, Hb4ax), 2.02-1.92 (m, 1H, Hb2), 1.81-1.73 (m, 2H, Hb3eq), 1.41 (s, 9H, HBoc), 1.20 (dq, *J*=3.9, 12.4Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 154.3 (CBoc), 151.8 (Ca8), 138.2 (Ca11), 131.6 (Ca14), 129.6 (Ca12), 127.7 (Ca13), 124.7 (Ca4), 117.3 (Ca5), 109.6 (Ca3), 107.9 (Ca7), 78.9 (CBoc), 72.3 (Cb1), 43.1 (Cb4), 42.4 (Ca9), 35.6 (Cb2), 32.8 (Ca10), 28.7 (Cb3), 28.6 (CBoc).

HRMS-ESI (m/z) calculated for $C_{27}H_{34}ClN_4O_3$ $[M+H]^+$: 497.2319; found: 497.2318.

4-(2-(4-chlorophenyl)ethylamino)-7-*O*-(piperidin-4-ylmethoxy)quinazoline (62'') (50mg; 0.13mmol; yield 93%) from **62'** (70mg; 0.14mmol):

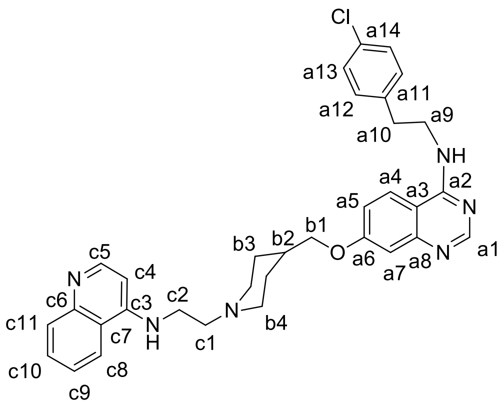


^{1}H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.23 (m, 1H, HNH), 8.11 (d, *J*=9.1Hz, 1H, Ha4), 7.37-7.22 (m, 4H, Ha12 and Ha13 and Ha14), 7.13-7.08 (m, 1H, Ha5), 7.08-7.03 (m, 1H, Ha7), 3.95 (d, *J*=5.9Hz, 2H, Hb1), 3.75-3.69 (m, 2H, Ha9), 3.07-3.01 (m, 2H, Hb4eq) 2.95 (brt, *J*=7.2Hz, 2H, Ha10), 2.62-2.54 (m, 2H, Hb4ax), 1.97-1.87 (m, 1H, Hb2), 1.82-1.72 (m, 2H, Hb3eq), 1.32-1.20 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 139.1 (Ca11), 131.1 (Ca16), 131 (Ca15), 128.7 (Ca13), 128.7 (Ca14), 126.6 (Ca12) 126.6 (Ca4), 117.2 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 72.9 (Cb1), 45.5 (Cb4), 42.2 (Ca9), 34.6 (Cb2), 34.3 (Ca10), 29.1 (Cb3)

HRMS-ESI (m/z) calculated for $C_{22}H_{26}ClN_4O$ $[M+H]^+$: 397.1795; found: 397.1794.

4-(2-(4-chlorophenyl)ethylamino)-7-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (62) (3.0mg; 5.3µmol; yield 21%) from **62'** (10mg; 25µmol):

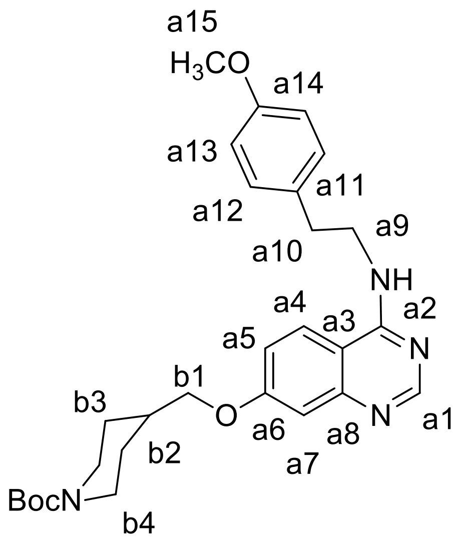


^{1}H NMR (500 MHz, DMSO) δ 8.40 (s, 1H, Ha1), 8.40 (d, *J*=5.3Hz, 1H, Hc5), 8.21 (brt, *J*=5.6Hz, 1H, HNH), 8.16 (dd, *J*=0.9, 8.2Hz, 1H, Hc8), 8.10 (d, *J*=9.3Hz, 1H, Ha4), 7.78 (dd, *J*=1.1, 8.5Hz, 1H, Hc11), 7.61(m, 1H, Hc10), 7.46-7.22 (m, 5H, Hc9 and Ha12 and Ha13), 7.11 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.06 (d, *J*=2.5Hz, 1H, Ha7), 7.03 (brt, *J*=5.3Hz, 1H, HNH), 6.48 (d, *J*=5.5Hz, 1H, Hc4), 3.99 (d, *J*=5.9Hz, 2H, Hb1), 3.80-3.73 (m, 2H, Ha9), 3.41 (q, *J*=6.5Hz, 2H, Hc2), 3.05-2.97 (m, 2H, Hb4eq), 3.09 (brt, *J*=6.9Hz, 2H, Ha10), 2.64 (t, *J*=6.9Hz, 2H, Hc1), 2.11-2.02 (m, 2H, Hb4ax), 1.85-1.76(m, 3H, Hb2 and Hb3eq), 1.38 (dq, *J*=2.5, 12.2Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 151.2 (Cc5), 150.2 (Cc3), 148.7 (Cc6), 137.5 (Ca11), 131.6 (Ca14), 129.6 (Ca12), 129.5 (Cc11), 129.1 (Cc10), 127.7 (Ca13), 124.7 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.3 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 56.6 (Cc1), 53.5 (Cb4), 46.1 (Ca9), 40.6 (Hc2), 35.7 (Cb2), 32.8 (Ca10), 29 (Cb3).

HRMS-ESI (m/z) calculated for $C_{33}H_{36}ClN_6O$ $[M+H]^+$: 567.2639; found: 567.2635.

4-(2-(4-methoxyphenyl)ethylamino)-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy)) quinazoline (63') (49mg; 101µmol; yield 71%) from **52** (60mg; 140µmol).

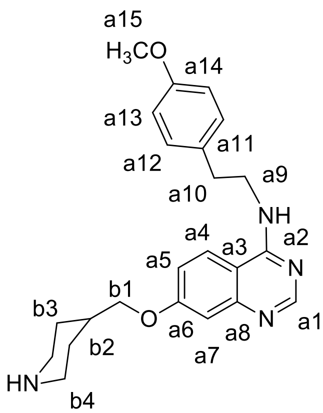


[1]H NMR (500MHz, DMSO) δ 8.42 (s, 1H, Ha1), 8.16 (brt, *J*=5.7Hz, 1H, HNH), 8.10 (d, *J*=9.2 Hz, 1H, Ha4), 7.20-7.15 (m, 2H, Ha12), 6.88-6.83 (m, 2H, Ha13), 7.11 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.06 (d, *J*=2.5Hz, 1H, Ha7), 4.06-3.94 (m, 2H, Hb4eq), 3.99 (d, *J*=6.3Hz, 2H, Hb1), 3.72 (s, 3H, Ha15), 3.71-3.64 (m, 2H, Ha9), 2.88(brt, *J*=7.1Hz, 2H, Ha10), 2.84-2.67 (m, 2H, Hb4ax), 2.04-1.93 (m, 1H, Hb2), 1.83-1.74 (m, 2H, Hb3eq), 1.41 (s, 9H, HBoc), 1.26-1.12 (m, 2H, Hb3ax).

[13]C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 158.1 (Ca14), 156.1 (Ca1), 154.3 (CBoc), 151.8 (Ca8), 144.3 (Ca11), 130.2 (Ca12), 124.6 (Ca4), 117.2 (Ca5), 114.2 (Ca13), 109.6 (Ca3), 107.9 (Ca7), 78.9 (CBoc), 72.3 (Cb1), 55.4 (Ca15), 43.4(Cb4), 42.7 (Ca9), 35.6 (Cb2), 34.2 (Ca10), 28.7 (Cb3), 28.6 (CBoc).

HRMS-ESI (m/z) calculated for $C_{28}H_{37}N_4O_4$ $[M+H]^+$: 493.2814; found: 493.2825.

4-(2-(4-methoxyphenyl)ethylamino)-7-*O*-(piperidin-4-ylmethoxy)quinazoline (63'') (39.0mg; 101µmol; quantitative yield) from **63'** (50mg; 101µmol):

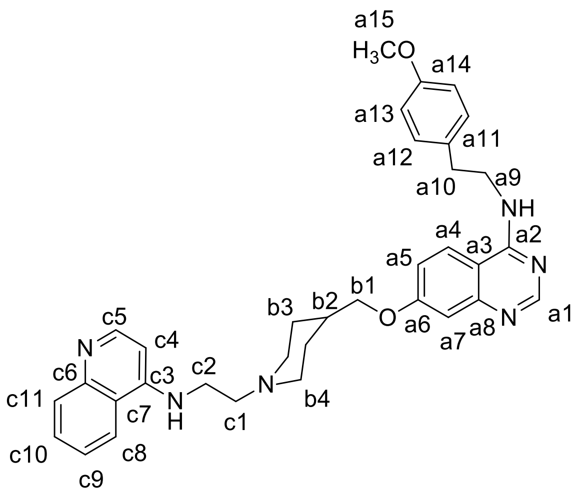


^{1}H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.16 (brt, *J*=5.4Hz, 1H, HNH), 8.11 (d, *J*=9.2Hz, 1H, Ha4), 7.20-7.15 (m, 2H, Ha12), 7.11 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.05 (d, *J*=2.6Hz, 1H, Ha7), 6.88-6.83 (m, 2H, Ha13), 3.94 (d, *J*=6.3Hz, 2H, Hb1), 3.72 (s, 3H, Ha15) 3.71-3.65 (m, 2H, Ha9), 3.01-2.92 (m, 2H, Hb4eq), 2.88 (brt, *J*=7.3Hz, 2H, Ha10), 2.57-2.52 (m, 2H, Hb4ax), 1.92-1.82 (m, 1H, Hb2), 1.76-1.68 (m, 2H, Hb3eq), 1.26-1.14 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 158.1 (Ca14), 156.1 (Ca1), 151.8 (Ca8), 144.3 (Ca11), 130.2 (Ca12), 124.6 (Ca4), 117.2 (Ca5), 114.2 (Ca13), 109.6 (Ca3), 107.9 (Ca7), 72.3 (Cb1), 55.4 (Ca15), 42.7 (Ca9), 35.6 (Cb2), 34.2 (Ca10), 28.7 (Cb3).

HRMS-ESI (m/z) calculated for $C_{23}H_{29}N_4O_2$ $[M+H]^+$: 393.2290; found: 393.2297.

4-(2-(4-methoxyphenyl)ethylamino)-7-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (63) (15mg; 27µmol; yield 71%) from **63''** (15mg; 38µmol):

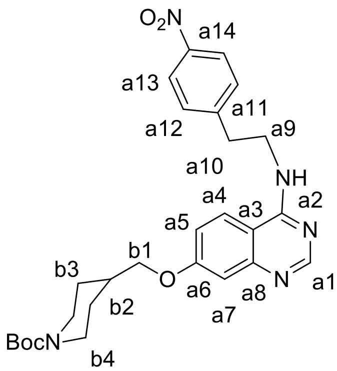


^{1}H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.40 (d, *J*= 5.3Hz, 1H, Hc5), 8.18 (brt, *J*=5.4Hz, 1H, HNH), 8.16 (m, 1H, Hc8), 8.12 (d, *J*=9.2Hz, 1H, Ha4), 7.78 (dd, *J*=0.9, 8.3Hz, 1H, Hc11), 7.61(m, 1H, Hc10), 7.43 (m, 1H, Hc9), 7.20-7.15 (m, 2H, Ha12), 7.12 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.06 (d, *J*=2.6Hz, 1H, Ha7), 7.04 (brt, *J*=5.4Hz, 1H, HNH), 6.88-6.82 (m, 2H, Ha13), 6.48 (d, *J*=5.4Hz, 1H, Hc4), 3.98 (d, *J*=5.9Hz, 2H, Hb1), 3.72 (s, 3H, Ha15), 3.73-3.64 (m, 2H, Ha9), 3.44-3.38 (m, 2H, Hc2), 3.04-2.96 (m, 2H, Hb4eq), 2.89 (brt, *J*=7.1Hz 2H, Ha10), 2.63 (t, *J*=6.8Hz, 2H, Hc1), 2.10-2.01 (m, 2H, Hb4ax), 1.84-1.74(m, 3H, Hb2 and Hb3eq), 1.44-1.31 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.4 (Ca2), 158.1 (Ca14), 156.1 (Ca1), 151.8 (Ca8), 151.2 (Cc5), 150.2 (Cc3), 148.7 (Cc6), 131.8 (Ca11), 130.1 (Ca12), 129.5 (Cc11), 129.1 (Cc10), 124.6 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.2 (Ca5), 114.2 (Ca13), 109.6 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 56.6 (Cc1), 55.4 (Ca15), 53.5 (Cb4), 42.7 (Ca9), 40.6 (Cc2), 35.7 (Cb2), 34.2 (Ca10), 29 (Cb3).

HRMS-ESI (m/z) calculated for $C_{34}H_{39}N_6O_2$ $[M+H]^+$: 563.3134; found: 563.3145.

4(2-(4-nitrophenyl)ethylamino)-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy)) quinazoline (**64’)** (68mg; 132µmol; yield 93%) from **52** (60mg; 140µmol).

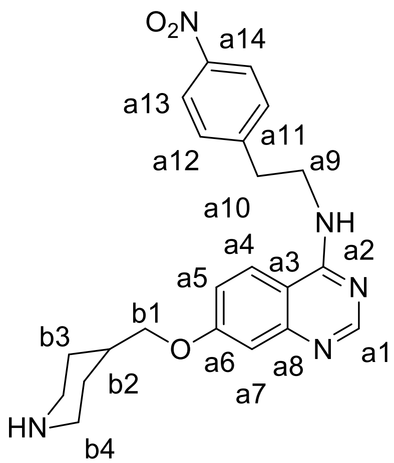


^{1}H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.20 (brt, *J*=5.6Hz, 1H, HNH), 8.18-8.14 (m, 2H, Ha13), 8.12 (d, *J*=9.2Hz, 1H, Ha4), 7.56-7.52 (m, 2H, Ha12), 7.11 (dd, *J*=2.5, 9.0Hz, 1H, Ha5), 7.06 (d, *J*=2.5Hz, 1H, Ha7), 4.06-3.96 (m, 2H, Hb4eq), 3.98 (d, *J*=6.3Hz, 2H, Hb1), 3.74-3.67 (m, 2H, Ha9), 2.94-2.88 (m, 2H, Ha10), 2.88-2.72 (m, 2H, Hb4ax), 2.85 (q, *J*=6.7Hz, 1H, Ha15) 2.02-1.94 (m, 1H, Hb2), 1.81-1.75 (m, 2H, Hb3eq), 1.41 (s, 9H, HBoc), 1.27-1.13 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 154.3 (CBoc), 151.8 (Ca8), 146.5 (Ca11), 137.4 (Ca14), 130.6 (Ca12), 124.7 (Ca4), 123.8 (Ca13), 117.2 (Ca5), 109.6 (Ca3), 107.9 (Ca7), 78.9 (CBoc), 72.3 (Cb1), 43.2 (Cb4), 42.5 (Ca9), 35.6 (Cb2), 34.7 (Ca10), 28.8 (Cb3), 28.6 (CBoc).

HRMS-ESI (m/z) calculated for $C_{27}H_{34}N_5O_5$ $[M+H]^+$: 508.2559; found: 508.2565.

4-(2-(4-nitrophenyl)ethylamino)-7-*O*-(piperidin-4-ylmethoxy)quinazoline (64’’) (51mg; 132µmol; quantitative yield) from **64’** (67mg; 132µmol):

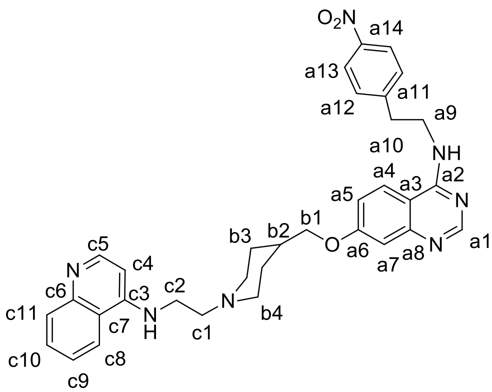


[1]H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.19 (brt, *J*=5.4Hz, 1H, HNH), 8.18-8.14 (m, 2H, Ha13), 8.08 (d, *J*=9.2Hz, 1H, Ha4), 7.57-7.52 (m, 2H, Ha12), 7.11 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.06 (d, *J*=2.6Hz, 1H, Ha7), 3.94 (d, *J*=6.4Hz, 2H, Hb1), 3.83-3.76 (m, 2H, Ha9), 3.11 (brt, *J*=7.2Hz, 2H, Ha10), 3.03-2.97 (m, 2H, Hb4eq), 2.61-2.53 (m, 2H, Hb4ax), 1.94-1.83 (m, 1H, Hb2), 1.77-1.69 (m, 2H, Hb3eq), 1.26-1.16 (m, 2H, Hb3ax).

[13]C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 146.5 (Ca11), 137.4 (Ca14), 130.6 (Ca12), 124.7 (Ca4), 123.8 (Ca13), 117.2 (Ca5), 109.6 (Ca3), 107.9 (Ca7), 72.3 (Cb1), 43.2 (Cb4), 42.5 (Ca9), 35.6 (Cb2), 34.7 (Ca10), 28.8 (Cb3).

HRMS-ESI (m/z) calculated for $C_{22}H_{26}N_5O_3$ $[M+H]^+$: 408.2035; found: 408.2024.

4-(2-(4-nitrophenyl)ethylamino)-7-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (64) (7mg; 12μmol; yield 33%) from **64’’** (15mg; 37μmol):

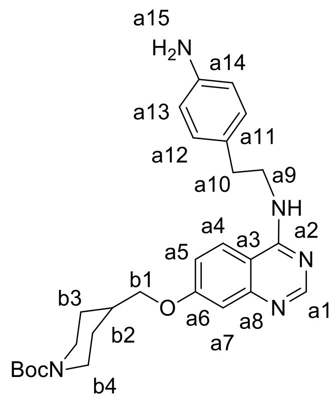


^{1}H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.40 (d, *J*= 5.3Hz, 1H, Hc5), 8.21 (brt, *J*=5.5 Hz, 1H, HNH), 8.18-8.14(m, 3H, Ha13 and Hc8), 8.09 (d, *J*=9.2 Hz, 1H, Ha4), 7.78 (dd, *J*=1.2, 8.4Hz, 1H, Hc11), 7.61 (m, 1H, Hc10), 7.57-7.52 (m, 2H, Ha12), 7.43 (m, 1H, Hc9), 7.12 (dd, *J*=2.73, 9.25Hz, 1H, Ha5), 7.06 (d, *J*=2.6Hz, 1H, Ha7), 7.04 (brt, *J*=5.54Hz, 1H, HNH), 6.48 (d, *J*=5.37Hz, 1H, Hc4), 3.98 (d, *J*=5.9Hz, 2H, Hb1), 3.83-3.77 (m, 2H, Ha9), 3.41 (q, *J*=8.4Hz, 2H, Hc2), 3.12 (brt, *J*=6.9Hz, 2H, Ha10), 3.04-2.97 (m, 2H, Hb4eq), 2.66-2.61 (m, 2H, Hc1), 2.10-2.02 (m, 2H, Hb4ax), 1.84-1.76(m, 3H, Hb2 and Hb3eq), 1.44-1.31 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.4 (Ca2), 156 (Ca1), 151.8 (Ca8), 151.2 (Cc5), 150.2 (Cc3), 148.7 (Cc6), 148.6 (Ca14), 146.5 (Ca11), 130.5 (Ca12), 129.5 (Cc11), 129.1 (Cc10), 123.8 (Ca13), 124.6 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.4 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 56.6 (Cc1), 53.5 (Cb4), 41.9 (Ca9), 40.6 (Cc2), 35.7 (Cb2), 34.8 (Ca10), 29 (Cb3).

HRMS-ESI (m/z) calculated for $C_{33}H_{36}N_7O_3$ $[M+H]^+$: 578.2879; found: 578.2891.

4-(2-(4-aminophenyl)ethylamino)-7-(*O*-((*N*-Boc) piperidin-4-ylmethoxy)) quinazoline (65') (67mg; 140µmol; quantitative yield) from **52** (60mg; 140µmol)



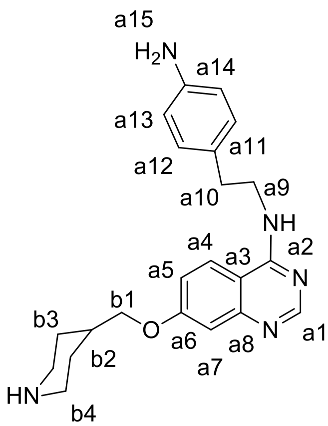
^{1}H NMR (500MHz, DMSO) δ 8.40 (s, 1H, Ha1), 8.14 (brt, *J*=5.5Hz, 1H, HNH), 8.12 (d, *J*=9.3 Hz, 1H, Ha4), 7.10 (dd, *J*=2.6, 9.6Hz, 1H, Ha5), 7.05 (d, *J*=2.5Hz, 1H, Ha7), 6.93-6.88 (m, 2H, Ha12), 6.52-6.47 (m, 2H, Ha13), 4.85 (s, 2H, Ha15), 4.06-3.92 (m, 2H, Hb4eq), 3.99 (d, *J*=6.5Hz, 2H, Hb1), 3.67-3.57 (m, 2H, Ha9), 2.75(brt, *J*=7.5Hz, 2H, Ha10), 2.84-2.68 (m, 2H, Hb4ax), 2.03-1.92 (m, 1H, Hb2), 1.82-1.73 (m, 2H, Hb3eq), 1.41 (s, 9H, HBoc), 1.26-1.14 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 154.3 (CBoc), 151.8 (Ca8), 147.2 (Ca14), 129.6 (Ca12), 129.3 (Ca11), 114.4 (Ca13), 124.7 (Ca4), 117.1 (Ca5), 109.6 (Ca3), 107.9 (Ca7), 78.9 (CBoc), 72.3 (Cb1), 43.1 (Cb4), 42.9 (Ca9), 35.6 (Cb2), 34.4 (Ca10), 28.7 (Cb3), 28.6 (CBoc).

HRMS-ESI (m/z) calculated for $C_{27}H_{36}N_5O_3$ $[M+H]^+$: 478.2818; found: 478.2831.

4-(2-(4-aminophenyl)ethylamino)-7-*O*-(piperidin-4-ylmethoxy)quinazoline (65'')

(34mg; 90µmol; yield 64%) from **65'** (67mg; 140µmol):

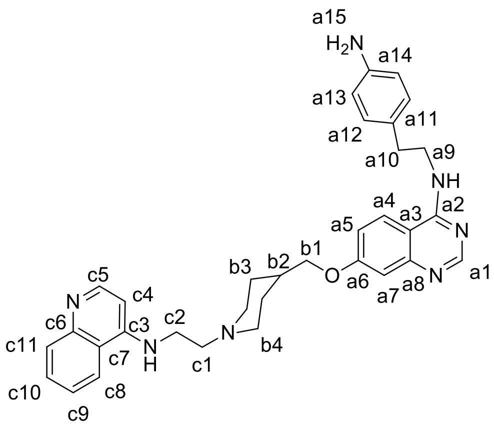


^{1}H NMR (500MHz, DMSO) δ 8.40 (s, 1H, Ha1), 8.13 (brt, *J*=5.7Hz, 1H, HNH), 8.11 (d, *J*=9.6Hz, 1H, Ha4), 7.11 (dd, *J*=2.5, 9.1Hz, 1H, Ha5), 7.04 (d, *J*=2.6Hz, 1H, Ha7), 6.94-6.86 (m, 2H, Ha12), 6.52-6.46 (m, 2H, Ha13), 4.85 (s, 2H, Ha15), 3.94 (d, *J*=6.3Hz, 2H, Hb1), 3.66-3.59 (m, 2H, Ha9), 3.02-2.94 (m, 2H, Hb4eq), 2.76 (brt, *J*=7.3Hz, 2H, Ha10), 2.58-2.52 (m, 2H, Hb4ax), 1.94-1.83 (m, 1H, Hb2), 1.76-1.68 (m, 2H, Hb3eq), 1.26-1.15 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 147.2 (Ca14), 129.6 (Ca12), 129.3 (Ca11), 114.4 (Ca13), 124.7 (Ca4), 117.1 (Ca5), 109.6 (Ca3), 107.9 (Ca7), 72.3 (Cb1), 43.1 (Cb4), 42.9 (Ca9), 35.6 (Cb2), 34.4 (Ca10), 28.7 (Cb3).

HRMS-ESI (m/z) calculated for $C_{22}H_{28}N_5O$ $[M+H]^+$: 378.2293; found: 378.2285.

4-(2-(4-aminophenyl)ethylamino)-7-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (65) (7.0mg; 13µmol; yield 33%) from **65’’** (15mg; 40µmol):

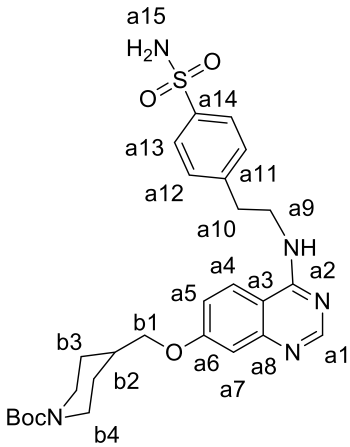


^{1}H NMR (500MHz, DMSO) δ 8.42-8.36 (m, 2H, Ha1 et Hc5), 8.19-8.13 (m, 2H, HNH and Hc8), 8.12 (d, *J*=9.1Hz, 1H, Ha4), 7.78 (dd, *J*=0.9, 8.4Hz, 1H, Hc11), 7.61(m, 1H, Hc10), 7.43 (m, 1H, Hc9), 7.11 (dd, *J*=2.5, 8.9Hz, 1H, Ha5), 7.05 (d, *J*=2.5Hz, 1H, Ha7), 7.04 (brt, *J*=5.3Hz, 1H, HNH), 6.93-6.87 (m, 2H, Ha12), 6.52-6.48 (m, 2H, Ha13), 6.48 (d, *J*=5.4Hz, 1H, Hc4), 4.86 (s, 2H, Ha15), 3.98 (d, *J*=5.9Hz, 2H, Hb1), 3.67-3.58 (m, 2H, Ha9), 3.45-3.38 (m, 2H, Hc2), 3.05-2.97 (m, 2H, Hb4eq), 2.76 (brt, *J*=7.3Hz 2H, Ha10), 2.63 (t, *J*=6.8Hz, 2H, Hc1), 2.11-2.01 (m, 2H, Hb4ax), 1.84-1.75(m, 3H, Hb2 and Hb3eq), 1.45-1.31 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.4 (Ca2), 156.2 (Ca1), 151.8 (Ca8), 151.2 (Cc5), 150.2 (Cc3), 148.7 (Cc6), 147.2 (Ca14), 129.5 (Ca12), 129.5 (Cc11), 129.1 (Cc10), 126.8 (Ca11), 124.7 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.2 (Ca5), 114.4 (Ca13), 109.6 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 56.6 (Cc1), 53.5 (Cb4), 42.9 (Ca9), 40.6 (Cc2), 35.7 (Cb2), 34.4 (Ca10), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{33}H_{38}N_7O$ $[M+H]^+$: 548.3137; found: 548.3142.

4-(2-(4-sulfonamidophenyl)ethylamino)-7-(*O*-((*N*-Boc)piperidin-4-ylmethoxy)) quinazoline (66) (53mg; 98µmol; yield 70%) from **52** (60mg; 140µmol).

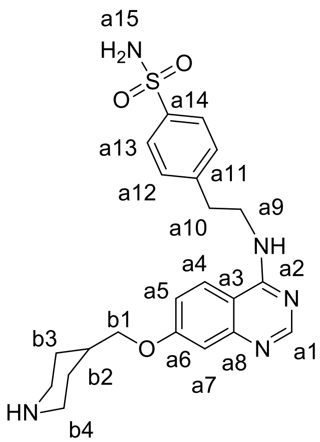


^{1}H NMR (500MHz, DMSO) δ 8.42 (s, 1H, Ha1), 8.21 (brt, *J*=5.8Hz, 1H, HNH), 8.10 (d, *J*=9.1Hz, 1H, Ha4), 7.77-7.73 (m, 2H, Ha13), 7.47-7.43 (m, 2H, Ha12), 7.29 (brs, 2H, Ha15), 7.12 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.07 (d, *J*=2.5Hz, 1H, Ha7), 4.02-3.94 (m, 2H, Hb4eq), 3.99 (d, *J*=6.5Hz, 2H, Hb1), 3.76 (q, *J*=6.5Hz, 2H, Ha9), 3.04 (brt, *J*=7.4Hz, 2H, Ha10), 2.84-2.68 (m, 2H, Hb4ax), 2.02-1.92 (m, 1H, Hb2), 1.81-1.74 (m, 2H, Hb3eq), 1.41 (s, 9H, HBoc), 1.26-1.13 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 154.3 (CBoc), 151.8 (Ca8), 144.3 (Ca11), 142.6 (Ca14), 129.6 (Ca12), 126.2 (Ca13), 124.6 (Ca4), 117.3 (Ca5), 109.6 (Ca3), 107.9 (Ca7), 78.9 (CBoc), 72.3 (Cb1), 42 (Ca9), 35.6 (Cb2), 34.7 (Ca10), 28.7 (Cb3), 28.6 (CBoc).

HRMS-ESI (m/z) calculated for $C_{27}H_{36}N_5O_5S$ $[M+H]^+$: 542.2437; found: 542.2445 .

4-(2-(4-sulfonamidophenyl)ethylamino)-7-*O*-(piperidin-4-ylmethoxy) quinazoline (66’’) (33mg; 75µmol; yield 77%) from **66’** (53mg; 98µmol):

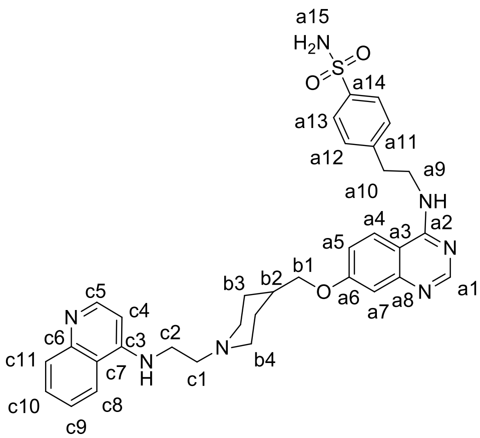


^{1}H NMR (500MHz, DMSO) δ 8.42 (s, 1H, Ha1), 8.21 (brt, *J*=5.4Hz, 1H, HNH), 8.10 (d, *J*=9.1Hz, 1H, Ha4), 7.77-7.72 (m, 2H, Ha13), 7.47-7.42 (m, 2H, Ha12), 7.37-7.21 (brs, 2H, Ha15), 7.11 (dd, *J*=2.4, 9.0Hz, 1H, Ha5), 7.05 (d, *J*=2.5Hz, 1H, Ha7), 3.94 (d, *J*=6.5Hz, 2H, Hb1), 3.79-3.72 (m, 2H, Ha9), 3.04 (brt, *J*=7.1Hz, 2H, Ha10), 2.99-2.92 (m, 2H, Hb4eq), 2.63-2.52 (m, 2H, Hb4ax), 1.93-1.79 (m, 1H, Hb2), 1.76-1.66 (m, 2H, Hb3eq), 1.26-1.12 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 144.3 (Ca11), 142.6 (Ca14), 129.6 (Ca12), 126.2 (Ca13), 124.6 (Ca4), 117.3 (Ca5), 109.6 (Ca3), 107.9 (Ca7), 72.3 (Cb1), 43.2 (Cb4), 42 (Ca9), 35.6 (Cb2), 34.7 (Ca10), 28.7 (Cb3).

HRMS-ESI (m/z) calculated for $C_{22}H_{28}N_5O_3S$ $[M+H]^+$: 397.1795; found: 397.1794.

4-(2-(4-sulfonamidophenyl)ethylamino)-7-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (66) (11mg; 18µmol; yield 52%) from **66’’** (13mg; 34µmol):

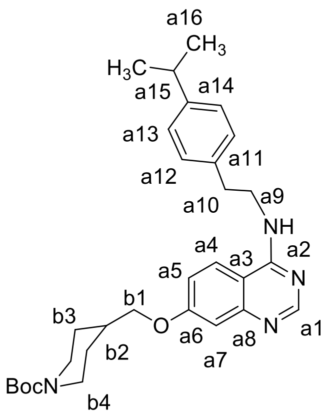


^{1}H NMR (500MHz, DMSO) δ 8.43 (s, 1H, Ha1), 8.40 (d, *J*= 5.3Hz, 1H, Hc5), 8.21 (brt, *J*=5.5Hz, 1H, HNH), 8.16 (dd, *J*=0.8, 8.8Hz, 1H, Hc8), 8.11 (d, *J*=9.1Hz, 1H, Ha4), 7.78 (dd, *J*=1.1, 8.4Hz, 1H, Hc11), 7.76-7.72 (m, 2H, Ha13), 7.61(m, 1H, Hc10), 7.46-7.40 (m, 5H, Hc9, Ha12, Ha15), 7.12 (dd, *J*=2.6, 9.0Hz, 1H, Ha5), 7.07 (d, *J*=2.6Hz, 1H, Ha7), 7.04 (brt, *J*=5.5Hz, 1H, HNH), 6.48 (d, *J*=5.5Hz, 1H, Hc4), 3.99 (d, *J*=5.9Hz, 2H, Hb1), 3.79-3.73 (m, 2H, Ha9), 3.41 (q, *J*=6.4Hz, 2H, Hc2), 3.06-2.97 (m, 4H, Hb4eq, Ha10), 2.64 (t, *J*=7.2Hz, 2H, Hc1), 2.10-2.02 (m, 2H, Hb4ax), 1.84-1.77(m, 3H, Hb2 and Hb3eq), 1.38 (dq, *J*=2.6, 12.1Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 151.2 (Cc5), 150.2 (Cc3), 148.7 (Cc6), 144.1 (Ca11), 142.9 (Ca14), 129.5 (Ca12), 129.5 (Cc11), 129.1 (Cc10), 126.1 (Ca13), 124.6 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.3 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 56.6 (Cc1), 53.5 (Cb4), 42.1 (Ca9), 40.6 (Cc2), 35.7 (Cb2), 34.7 (Ca10), 29 (Cb3).

HRMS-ESI (m/z) calculated for $C_{33}H_{38}N_7O_3S$ $[M+H]^+$: 612.2756; found: 612.2747.

4-(2-(4-isopropylphenyl)ethylamino)-7-*O*-((*N*-Boc)piperidin-4-ylmethoxy)) quinazoline (67') (44mg; 87µmol; yield 62%) from **52** (60mg; 140µmol):

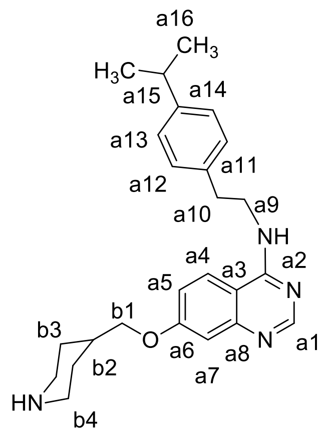


^{1}H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.20 (brt, *J*=5.6Hz, 1H, HNH), 8.10 (d, *J*=9.1Hz, 1H, Ha4), 7.22-7.14 (m, 4H, Ha12 and Ha13), 7.11 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.06 (d, *J*=2.6Hz, 1H, Ha7), 4.0-3.96 (m, 2H, Hb4eq), 3.98 (d, *J*=6.4Hz, 2H, Hb1), 3.70 (q, *J*=5.9Hz, 2H, Ha9), 2.91 (brt, *J*=7.2Hz, 2H, Ha10), 2.85-2.67 (m, 3H, Hb4ax and Ha15), 2.03-1.91 (m, 1H, Hb2), 1.81-1.73 (m, 2H, Hb3eq), 1.41 (s, 9H, HBoc), 1.26-1.13 (m, 8H, Hb3ax and Ha16).

^{13}C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 154.3 (CBoc), 151.7 (Ca8), 146.5 (Ca14), 137.3 (Ca11), 129.6 (Ca12), 129 (Ca13), 124.7 (Ca4), 117.3 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 78.9 (CBoc), 72.3 (Cb1), 43.2 (Cb4), 42.2 (Ca9), 35.6 (Cb2), 34.8 (Ca10), 33.5 (Ca15), 28.8 (Cb3), 28.6 (CBoc), 24.4 (Ca16).

HRMS-ESI (m/z) calculated for $C_{30}H_{41}N_4O_3$ $[M+H]^+$: 505.3178; found: 505.3182.

4-(2-(4-isopropylphenyl)ethylamino)-7-*O*-(piperidin-4-ylmethoxy)quinazoline (67'') (34mg; 80µmol; yield 92%) from **67'** (44mg; 87µmol):

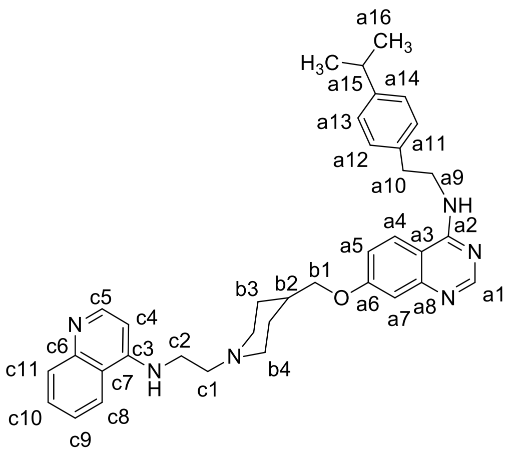


¹H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.20 (brt, *J*=5.7Hz, 1H, HNH), 8.12 (d, *J*=9.2Hz, 1H, Ha4), 7.20-7.13 (m, 4H, Ha12,Ha13), 7.11 (dd, *J*=2.6, 9.0Hz, 1H, Ha5), 7.06 (d, *J*=2.7Hz, 1H, Ha7), 3.95 (d, *J*=6.4Hz, 2H, Hb1), 3.73-3.66 (m, 2H, Ha9), 3.05-2.97 (m, 2H, Hb4eq), 2.91 (brt, *J*=7.2Hz, 2H, Ha10), 2.85 (t, 1H, Ha15), 2.58-2.53 (m, 2H, Hb4ax), 1.95-1.84 (m, 1H, Hb2), 1.78-1.70 (m, 2H, Hb3eq), 1.29-1.10 (m, 8H, Hb3ax and Ha16).

¹³C NMR (125MHz, DMSO) δ 162.1 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 151.7 (Ca8), 146.5 (Ca14), 137.3 (Ca11), 129.6 (Ca12), 129 (Ca13), 124.7 (Ca4), 117.3 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 72.3 (Cb1), 43.2 (Cb4), 42.2 (Ca9), 35.6 (Cb2), 34.8 (Ca10), 33.5 (Ca15), 28.8 (Cb3), 24.4 (Ca16).

HRMS-ESI (m/z) calculated for $C_{25}H_{32}N_4O$ $[M+H]^+$: 405.2654; found: 405.2659.

4-(2-(4-isopropylphenyl)ethylamino)-7-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (67) (1.2mg; 2.0µmol; yield 6%) from **67’’** (15mg; 37µmol):

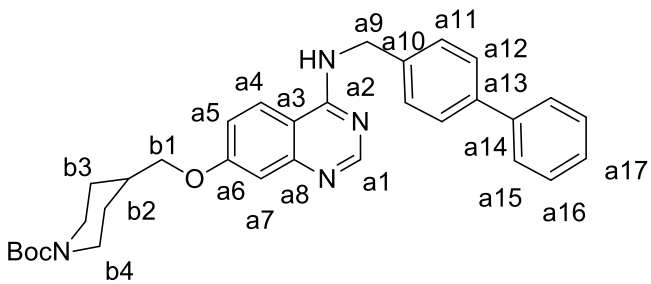


[1]H NMR (500MHz, DMSO) δ 8.41 (s, 1H, Ha1), 8.40 (d, *J*= 5.2Hz, 1H, Hc5), 8.22 (brt, *J*=5.9Hz, 1H, HNH), 8.16 (m, 1H, Hc8), 8.10 (d, *J*=9.3Hz, 1H, Ha4), 7.78 (dd, *J*=1.2, 8.4Hz, 1H, Hc11), 7.61(m, 1H, Hc10), 7.45-7.40 (m, 1H, Hc9), 7.20-7.09 (m, 4H, Ha12, Ha13), 7.12 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.06 (d, *J*=2.2Hz, 1H, Ha7), 7.04 (brt, *J*=5.3Hz, 1H, HNH), 6.48 (d, *J*=5.4Hz, 1H, Hc4), 3.99 (d, *J*=5.8Hz, 2H, Hb1), 3.73-3.68 (m, 2H, Ha9), 3.44-3.38 (m, 2H, Hc2), 3.04-2.98 (m, 2H, Hb4eq), 2.91 (brt, 2H, Ha10), 2.85 (t, 1H, Ha15), 2.66-2.61 (m, 2H, Hc1), 2.10-2.02 (m, 2H, Hb4ax), 1.83-1.77 (m, 3H, Hb2 and Hb3eq), 1.38 (m, 2H, Hb3ax), 1.18 (d, 6H, Ha16).

[13]C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.4 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 151.2 (Cc5), 150.2 (Cc3), 148.7 (Cc6), 146.5 (Ca14), 137.4 (Ca11), 129.5 (Ca12), 129.3 (Ca13), 129.1 (Cc11), 129.1 (Cc10), 124.6 (Ca4), 124.3 (Cc9), 121.9 (Cc8), 119.2 (Cc7), 117.2 (Ca5), 109.6 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 56.6 (Cc1), 53.5 (Cb4), 42.5 (Ca9), 40.6 (Cc2), 35.7 (Cb2), 34.7 (Ca10), 33.5 (Ca15), 29 (Cb3), 24.4 (Ca16).

HRMS-ESI (m/z) calculated for $C_{36}H_{43}N_6O$ $[M+H]^+$: 575.3498; found: 575.3496.

4-([1,1'-biphenyl]-4-ylmethylamino)-7-*O*-((*N*-Boc)piperidin-4-ylmethoxy))quinazoline (68’) (60mg; 114µmol; yield 95%) from **52** (52mg; 120µmol).

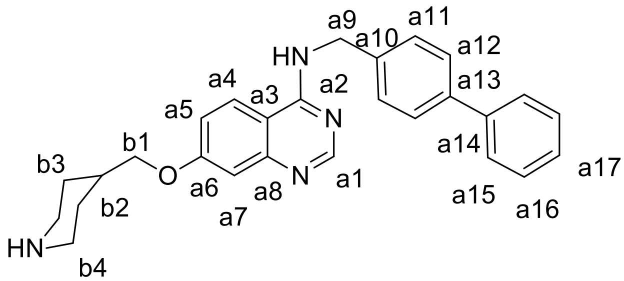


^{1}H NMR (500MHz, DMSO) δ 8.71 (t, *J*=6.0Hz, HNH), 8.40 (s, 1H, Ha1), 8.23 (d, *J*=9.2Hz, 1H, Ha4), 7.68-7.59 (m, 4H, Ha15 and Ha12), 7.49-7.42 (m, 4H, Ha11 and Ha16), 7.39-7.34 (m, 2H, Ha17 and HNH), 7.15 (dd, *J*=2.6, 9.1Hz, 1H, Ha5), 7.10 (d, *J*=2.6Hz, 1H, Ha7), 4.81 (d, *J*=5.9Hz, 2H, Ha9), 4.06-3.93 (m, 2H, Hb1 and Hb4eq), 2.89-2.66 (m, 2H, Hb4ax), 2.05-1.95 (m, 1H, Hb2), 1.84-1.73 (m, 2H, Hb3eq), 1.41 (s, 9H, HBoc), 1.28-1.15 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.3 (Ca6), 159.3 (Ca2), 151.7 (Ca1), 154.4 (CBoc), 151.8 (Ca8), 140.2 (Ca14), 139.8 (Ca13), 137.5 (Ca10), 129.4 (Ca16), 128.6 (Ca11), 128.0 (Ca17), 127.3 (Ca12), 127.1 (Ca15), 124.7 (Ca4), 117.8 (Ca5), 109.7 (Ca3), 107.5 (Ca7), 78.9 (CBoc), 72.5 (Cb1), 44.9 (Ca9), 43.2 (Cb4), 33.3 (Cb2), 28.9 (CBoc), 28.6 (Cb3).

HRMS-ESI(m/z) calculated for $C_{32}H_{37}N_4O_3$ $[M+H]^+$: 525.2860; found: 525.2835

4-([1,1'-biphenyl]-4-ylmethylamino)-7-*O*-(piperidin-4-ylmethoxy)quinazoline (68’’) (48mg; 114µmol; quantitative yield) from **68’** (60mg; 114µmol):



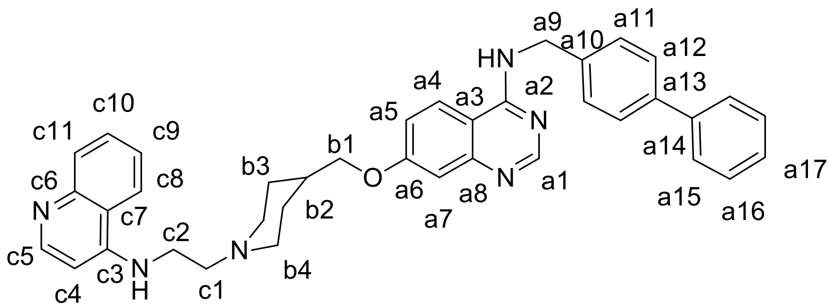
TFA salt

^{1}H NMR (500MHz, DMSO) δ 8.82 (s, 1H, Ha1), 8.63-8.62 (m, 1H, HNH), 8.47 (d, *J*=9.2Hz, 1H, Ha4), 7.69-7.61 (m, 4H, Ha15 and Ha12), 7.54-7.43 (m, 4H, Ha11 and Ha16), 7.42-7.33 (m, 2H, Ha17 and Ha5), 7.29 (d, *J*=2.4Hz, 1H, Ha7), 4.96 (d, *J*=5.8Hz, 2H, Ha9), 4.08 (d, *J*=6.3Hz, 2H, Hb1), 3.35 (m, 4H, Ha9 and Hb4eq), 2.95 (brd, *J*=11.4Hz, 2H, Hb4ax), 2.21-2.10 (m, 1H, Hb2), 2.00-1.91 (m, 2H, Hb3eq), 1.60-1.44 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 164.0 (Ca6), 160.3 (Ca2), 152.6 (Ca1), 156.7 (Ca8), 140.3 (Ca14), 139.8 (Ca13), 137.5 (Ca10), 129.5 (Ca16), 128.6 (Ca11), 128.0 (Ca17), 127.3 (Ca12), 127.1 (Ca15), 126.5 (Ca4), 118.8 (Ca5), 107.7 (Ca3), 102.8 (Ca7), 72.5 (Cb1), 44.7 (Ca9), 43.2 (Cb4), 33.3 (Cb2), 25.6 (Cb3).

HRMS-ESI(m/z) calculated for $C_{27}H_{29}N_4O$ $[M+H]^+$: 425.2336; found: 425.2355

4-([1,1'-biphenyl]-4-ylmethylamino)-7-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (68) (10mg; 17µmol; yield 31%) from **68''** (24mg; 56µmol).

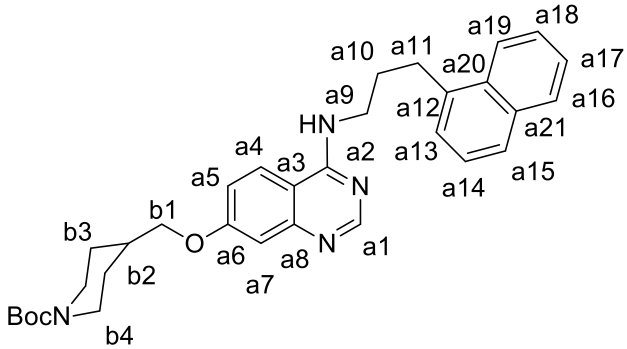


^{1}H NMR (500MHz, $CDCl_3$) δ 8.67 (s, 1H, Ha1), 8.57 (d, *J*=5.3Hz, 1H, Hc5), 8.08 (d, *J*=8.2Hz, 1H, Hc8), 7.81 (dd, *J*=8.2Hz, 1H, Hc11), 7.70 (ddd, *J*=1.2, 6.9, 8.2Hz, 1H, Hc10), 7.46 (ddd, *J*=1.1, 6.8, 8.2Hz, 1H, Hc9), 7.66-7.58 (m, 5H, Ha4 and Ha15 and Ha12), 7.56-7.43 (m, 4H, Ha11 and Ha16), 7.38 (m, 1H, Ha17), 7.20 (d, *J*=2.6Hz, 1H, Ha7), 7.08 (dd, *J*=2.6, 9.2Hz, 1H, Ha5), 6.43 (d, *J*=5.3Hz, 1H, Hc4), 6.40 (brs, 1H, HNH), 5.93 (brt, *J*=5.4Hz, 1H, HNH), 4.92 (d, *J*=5.3Hz, 2H, Ha9), 4.01 (d, *J*=6.0Hz, 2H, Hb1), 3.70 (q, *J*=7.2Hz, 2H, Ha9), 3.41 (brq, *J*=4.3Hz, 2H, Hc2), 3.00 (brd, *J*=11.5Hz, 2H, Hb4eq), 2.84 (t, *J*=5.9Hz, 2H, Hc1), 2.20 (dt, *J*=2.0, 12.0Hz, 2H, Hb4ax), 2.05-1.91 (m, 3H, Hb2 and Hb3eq), 1.52 (dq, *J*=2.4, 12.5Hz, 2H, Hb3ax).

^{13}C NMR (125MHz, $CDCl_3$) δ 162.4 (Ca6), 159.0 (Ca2), 156.0 (Ca1), 151.7 (Ca8), 150.8 (Cc3), 149.2 (Cc5), 146.1 (Cc6), 140.8 (Ca14), 140.6 (Ca13), 137.3 (Ca10), 129.9 (Cc10), 128.8 (Ca16), 128.5 (Ca11), 128.1 (Cc8), 127.6 (Ca12), 127.4 (Ca17), 127.1 (Ca15), 125.2 (Cc9), 122.0 (Ca4), 119.7 (Cc11), 118.4 (Cc7), 118.2 (Ca5), 109.0 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.6 (Cb1), 55.7 (Cc1), 52.9 (Cb4), 45.0 (Ca9), 39.1 (Cc2), 35.6 (Cb2), 29.2 (Cb3).

HRMS-ESI(m/z) calculated for $C_{38}H_{39}N_6O$ $[M+H]^+$: 595.3180; found: 595.3172.

4-(3-(naphtalen-1-yl)propylamino)-7-(*O*-((*N*-Boc) piperidin-4-ylmethoxy)) quinazoline (69') (60mg; 112µmol; 95%) from **52** (52mg; 120µmol).

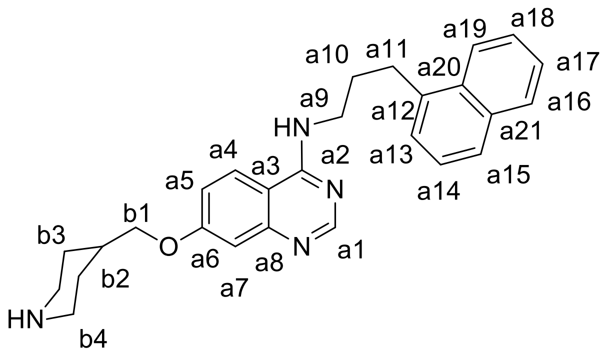


^{1}H NMR (500 MHz ; DMSO) δ ^{1}H NMR (500 MHz ; DMSO) δ 8.39 (s, 1H, Ha1), 8.16 (m, 2H, Ha4 and HNH), 8.10-8.06 (m, 1H, Ha16), 7.94-7.90 (m, 1H, Ha19), 7.80-7.75 (m, 1H, Ha15), 7.53-7.48 (m, 2H, Ha17 and Ha18), 7.46-7.40 (m, 2H, H13 and H14), 7.11 (dd, *J*=2.6, 8.7 Hz, 1H, Ha5), 7.05 (d, *J*=2.6Hz, 1H, Ha7), 8.51 (s, 1H, Ha1), 8.42 (brt, *J*=5.1 Hz, 1H, HNH), 8.14 (d, *J*=9.2 Hz, 1H, Ha19), 8.09 (d, *J*=7.8Hz, 1H, Ha4), 7.76 (dd, *J*=1.8, 6.9Hz, 1H, Ha15), 7.46-7.35 (m, 2H, Ha17 and Ha18), 7.31 (t, *J*=7.9Hz, 1H, Ha13), 7.15 (dd, *J*=2.5, 9.1 Hz, 1H, Ha5), 7.11 (d, *J*=8.1Hz, 1H, Ha14), 7.08 (d, *J*=2.6Hz, 1H, Ha7), 6.71(d, *J*=7.5Hz, 1H, Ha12), 6.45 (brt, *J*=5.1Hz, HNH), 4.05-3.91 (m, 4H, Hb1 and Hb4eq), 3.85 (q, *J*=6.3Hz, 2H, Ha9), 3.51 (brt, *J*=6.1Hz, 2H, Ha10), 2.87-2.67 (m, 2H, Hb4ax), 1.98-1.92 (m, 1H, Hb2), 1.81-1.72 (m, 2H, Hb3eq), 1.25-1.15 (m, 2H, Hb3ax).

^{13}C NMR (125MHz; DMSO) δ 162.2 (Ca6), 159.8 (Ca2), 155.9 (Ca1), 154.3 (Ca8), 151.5 (Ca11), 144.3 (Ca11), 134.5 (Ca21), 128.4 (Ca15), 127.6 (Ca13), 126.1 (Ca17), 124.8 (Ca19), 124.7 (Ca4), 124.5 (Ca18), 123.3 (Ca20), 121.8 (Ca4), 117.4 (Ca5), 115.8 (Ca14), 109.5 (Ca3), 107.8 (Ca7), 103.3 (Ca12), 79.0 (CBoc), 72.1 (Cb1), 46.2 (Cb4), 43.2 (Ca10), 39.4 (Ca9), 35.6 (Cb2), 28.7 (Cb3), 28.6 (CBoc).

HRMS-ESI (m/z) calculated for $C_{32}H_{39}N_4O_3$ $[M+H]^+$: 527.3017; found: 527.3008.

4-(3-(naphtalen-1-yl)propylmino)-7-*O*-(piperidin-4-ylmethoxy)quinazoline (69'') (39mg; 91µmol; 96%) from **69''** (50mg; 95µmol).

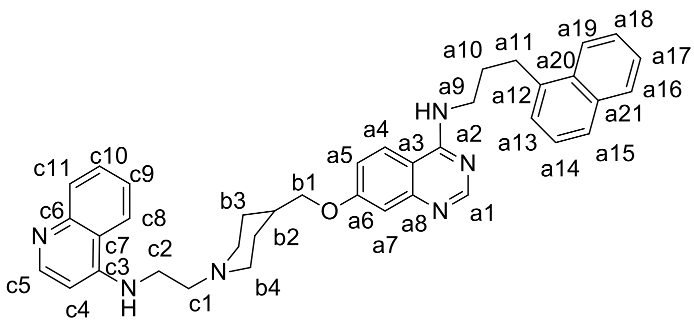


^{1}H NMR (500 MHz ; DMSO) δ 8.39 (s, 1H, Ha1), 8.16 (m, 2H, Ha4 and HNH), 8.10-8.06 (m, 1H, Ha16), 7.94-7.90 (m, 1H, Ha19), 7.80-7.75 (m, 1H, Ha15), 7.53-7.48 (m, 2H, Ha17 and Ha18), 7.46-7.40 (m, 2H, H13 and H14), 7.11 (dd, *J*=2.6, 8.7 Hz, 1H, Ha5), 7.05 (d, *J*=2.6Hz, 1H, Ha7), 3.93 (d, *J*=6.4Hz, 2H, Hb1), 3.63 (q, *J*=6.6Hz, 2H, Ha9), 3.17 (brt, *J*=8.4Hz, 2H, Ha11), 3.00-2.93 (m, 2H, Hb4eq), 2.50-2.44 (m, 2H, Hb4ax), 2.06 (quint, *J*=7.5Hz, 2H, Ha10), 1.91-1.81 (m, 1H, Hb2), 1.75-1.67 (m, 2H, Hb3eq), 1.26-1.14 (m, 2H, Hb3ax).

^{13}C NMR (125MHz; DMSO) δ 162.1 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 138.3 (Ca12), 133.9 (Ca20), 131.8 (Ca21), 129.0 (Ca19), 126.9 (Ca15), 126.3 (Ca17 and Ca18), 126.1 (Ca13 and Ca14), 124.7 (Ca4), 124.1 (Ca16), 117.2 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 73.1 (Cb1), 46.1 (Cb4), 40.8 (Ca9), 36.3 (Cb2), 30.2 (Ca10 and Ca11), 29.9 (Cb3).

HRMS-ESI (m/z) calculated for $C_{27}H_{31}N_4O$ $[M+H]^+$: 427.2492; found: 427.2493

4-(2-(naphthalen-1-yl)propyl)-7-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (69) (10mg; 17µmol; 48%) from **69''** (15mg; 35µmol).

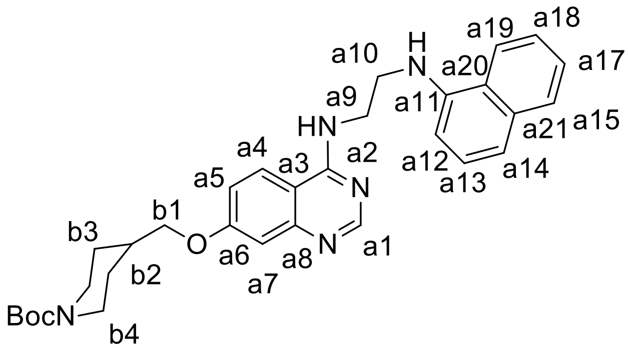


[1]H NMR (500 MHz ; DMSO) δ 8.40 (d, *J*= 5.4Hz, 1H, Hc5), 8.39 (s, 1H, Ha1), 8.20-8.14 (m, 3H, Hc8, Ha4 and HNH), 8.10-8.06 (m, 1H, Ha16), 7.94-7.90 (m, 1H, Ha19), 7.80-7.75 (m, 1H, Hc11 and Ha15), 7.61 (ddd, *J*=1.3, 6.9, 8.6Hz, 1H, Hc10), 7.53-7.49 (m, 2H, Ha17 and Ha18), 7.45-7.39 (m, 3H, Hc9, Ha13 and Ha14), 7.27 (brt, *J*=5.6Hz, 1H, HNH), 7.10 (dd, *J*=2.6, 9.4Hz, 1H, Ha5), 7.04 (d, *J*=2.6Hz, 1H, Ha7), 6.56 (d, *J*=5.3Hz, 1H, Hc4), 4.28-4.21 (m, 2H, Hc1), 4.06-3.98 (m, 2H, Hb4eq), 3.93 (d, *J*=6.3Hz, 2H, Hb1), 3.63 (q, *J*=6.6Hz, 2H, Ha9), 3.44 (q, *J*=5.7Hz, 2H, Hc2), 3.17 (brt, *J*=8.0Hz, 2H, Ha11), 2.12-2.04 (m, 4H, Ha10 and Hb4ax), 1.89-1.75 (m, 1H, Hb2 and Hb3eq), 1.45-1.30 (m, 2H, Hb3ax).

[13]C NMR (125MHz; DMSO) δ 162.1 (Ca6), 159.5 (Ca2), 156.1 (Ca1), 151.8 (Ca8), 151.2 (Cc5), 150.2 (Cc3), 148.7 (Cc6), 138.2 (Ca12), 133.9 (Ca20), 131.8 (Ca21), 129.5 (Cc11), 129.1 (Cc10), 129.0 (Ca19), 126.9 (Ca15), 126.3 (Ca17 and Ca18), 126.1 (Ca13 and Ca14), 124.7 (Ca4), 124.1 (Ca16), 122.0 (Cc9), 119.2 (Cc7), 117.2 (Ca5), 109.5 (Ca3), 107.9 (Ca7), 98.7 (Cc4), 72.7 (Cb1), 63.3 (Cc1), 53.5 (Cb4), 40.8 (Ca9), 40.4 (Cc2), 35.7 (Cb2), 30.2 (Ca10 and Ca11), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{38}H_{41}N_6O$ $[M+H]^+$: 597.3336; found: 597.3333.

4-(2-(naphtylamino)ethylamino)-7-(*O*-((*N*-Boc) piperidin-4-ylmethoxy)) quinazoline (70') (59mg; 112µmol; yield 79%) from **52** (60mg; 140µmol):

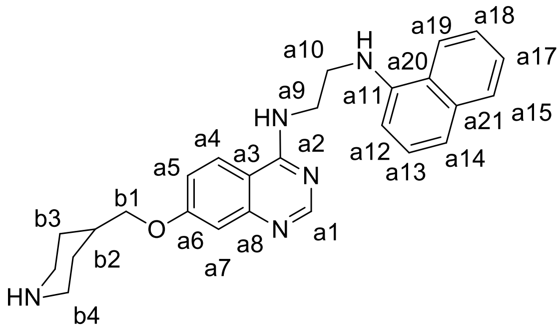


^{1}H NMR (500MHz, DMSO) δ 8.51 (s, 1H, Ha1), 8.42 (brt, *J*=5.1Hz, 1H, HNH), 8.14 (d, *J*=9.2Hz, 1H, Ha19), 8.09 (d, *J*=7.8Hz, 1H, Ha4), 7.76 (dd, *J*=1.8, 6.9Hz, 1H, Ha15), 7.46-7.35 (m, 2H, Ha17 and Ha18), 7.31 (t, *J*=7.9Hz, 1H, Ha13), 7.15 (dd, *J*=2.5, 9.1Hz, 1H, Ha5), 7.11 (d, *J*=8.1Hz, 1H, Ha14), 7.08 (d, *J*=2.6Hz, 1H, Ha7), 6.71(d, *J*=7.5Hz, 1H, Ha12), 6.45 (brt, *J*=5.1Hz, HNH), 4.05-3.91 (m, 4H, Hb1 and Hb4eq), 3.85 (q, *J*=6.3Hz, 2H, Ha9), 3.51 (brt, *J*=6.1Hz, 2H, Ha10), 2.87-2.67 (m, 2H, Hb4ax), 1.98-1.92 (m, 1H, Hb2), 1.81-1.72 (m, 2H, Hb3eq), 1.25-1.15 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.2 (Ca6), 159.8 (Ca2), 155.9 (Ca1), 154.3 (Ca8), 151.5 (Ca11), 144.3 (Ca11), 134.5 (Ca21), 128.4 (Ca15), 127.6 (Ca13), 126.1 (Ca17), 124.8 (Ca19), 124.7 (Ca4), 124.5 (Ca18), 123.3 (Ca20), 121.8 (Ca4), 117.4 (Ca5), 115.8 (Ca14), 109.5 (Ca3), 107.8 (Ca7), 103.3 (Ca12), 79.0 (CBoc), 72.1 (Cb1), 46.2 (Cb4), 43.2 (Ca10), 39.4 (Ca9), 35.6 (Cb2), 28.7 (Cb3), 28.6 (CBoc).

HRMS-ESI (m/z) calculated for $C_{31}H_{38}N_5O_3$ $[M+H]^+$: 528.2969; found: 528.3002.

4-(2-(naphtylamino)ethylamino)-7-*O*-(piperidin-4-ylmethoxy)quinazoline (70'') (47mg; 110µmol; yield 91%) from **70'** (64mg; 121µmol):

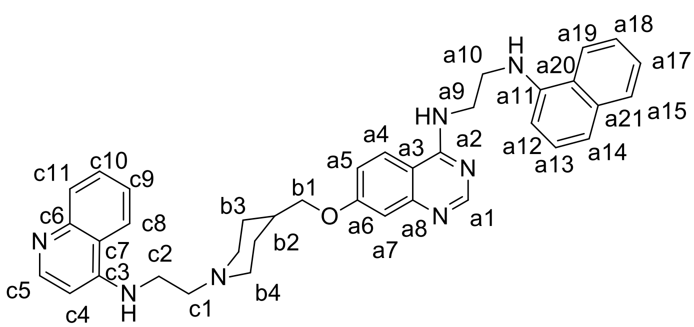


^{1}H NMR (500MHz, DMSO) δ 8.50 (s, 1H, Ha1), 8.38 (brt, *J*=5.05 Hz, 1H, HNH), 8.12 (d, *J*=9.16Hz, 1H, Ha19), 8.11 (d, *J*=7.6Hz, 1H, Ha4), 7.76 (dd, *J*=1.6, 7.1Hz, 1H, Ha15), 7.47-7.38 (m, 2H, Ha17 and Ha18), 7.31 (t, *J*=7.9Hz, 1H, Ha13), 7.15 (dd, *J*=2.8, 9.1Hz, 1H, Ha5), 7.11 (d, *J*=8.4Hz, 1H, Ha14), 7.08 (d, *J*=2.5Hz, 1H, Ha7), 6.71(d, *J*=7.6Hz, 1H, H12), 6.46 (brt, *J*=5.3Hz, 1H, HNH), 3.96 (d, *J*=6.8Hz, 2H, Hb1), 3.85 (q, *J*=6.8Hz, 2H, Ha9), 3.51 (brt, *J*=6.8Hz, 2H, Ha10), 3.07-3.00 (m, 2H, Hb4eq), 2.62-2.54 (m, 2H, Hb4ax), 1.97-1.96 (m, 1H, Hb2), 1.81-1.71 (m, 2H, Hb3eq), 1.31-1.20 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.3 (Ca6), 159.8 (Ca2), 156.0 (Ca1), 151.9 (Ca8), 151.8 (Ca11), 144.3 (Ca11), 134.5 (Ca21), 128.4 (Ca15), 127.3 (Ca13), 126.1 (Ca17), 124.7 (Ca19), 124.5 (Ca4), 124.4 (Ca18), 123.3 (Ca20), 121.9 (Ca4), 117.4 (Ca5), 115.8 (Ca14), 109.5 (Ca3), 108.0 (Ca7), 103.2 (Ca12), 72.9 (Cb1), 45.6 (Cb4), 43.2 (Ca10), 39.7 (Ca9), 35.8 (Cb2), 29.2 (Cb3).

HRMS-ESI (m/z) calculated for $C_{26}H_{30}N_5O$ $[M+H]^+$: 428.2445; found: 428.2610.

4-(2-(naphthalen-1-yl)ethylamino)-7-((1-(2-(quinolin-4-ylamino)ethyl) piperidin-4-yl)methoxy)quinazoline (70) (13mg; 22µmol; 63%) from **70’’** (15mg; 35µmol):



^{1}H NMR (500MHz, DMSO) δ 8.50 (s, 1H, Ha1), 8.40 (d, *J*= 5.3Hz, 1H, Hc5), 8.38 (brt, *J*=5.6Hz, 1H, HNH), 8.16 (d, *J*=7.9Hz, 1H, Hc8), 8.14 (d, *J*=9.4Hz, 1H, Ha19), 8.11 (d, *J*=8.0Hz, 1H, Ha4), 7.79 (d, *J*=8.4Hz, 1H, Hc11), 7.75 (dd, *J*=1.8, 7.5Hz, 1H, Ha15), 7.61(ddd, *J*=0.8, 6.5, 7.7Hz, 1H, Hc10), 7.45-7.38 (m, 3H, Ha17, Hc9 and Ha18), 7.31 (t, *J*=7.9Hz, 1H, Ha13), 7.15 (dd, *J*=2.7, 9.3Hz, 1H, Ha5), 7.11 (d, *J*=7.8Hz, 1H, Ha14), 7.09 (d, *J*=2.6Hz, 1H, Ha7), 7.04 (brt,*J*=5.2Hz, 1H, HNH), 6.70(d, *J*=7.8Hz, 1H, Ha12), 6.48-45 (m, 2H, Hc4 and HNH), 3.99 (d, *J*=5.9Hz, 2H, Hb1), 3.86 (q, *J*=6.0Hz, 2H, Ha9), 3.51 (q, *J*=6.0Hz, 2H, Ha10), 3.41 (q, *J*=6.3Hz, 2H, Hc2), 3.05-2.97 (m, 2H, Hb4eq), 2.66-2.60 (m, 2H, Hc1), 2.10-2.02 (t, *J*=6.9Hz, 2H, Hb4ax), 1.85-1.75 (m, 3H, Hb3eq and Hb2), 1.43-1.31 (m, 2H, Hb3ax).

^{13}C NMR (125MHz, DMSO) δ 162.3 (Ca6), 159.8 (Ca2), 156.0 (Ca1), 151.8 (Ca8), 151.2 (Cc5), 150.2 (Cc3), 148.7 (Cc6), 144.4 (Ca11), 134.5 (Ca21), 129.5 (Cc11), 129.1 (Cc10), 128.4 (Ca15), 127.3 (Ca13), 126.0 (Ca17), 124.7 (Ca19), 124.4 (Ca4), 124.3 (Ca18), 123.3 (Ca20), 121.9 (Ca4), 121.8 (Cc9), 119.2 (Cc7), 117.4 (Ca5), 115.8 (Ca14), 109.5 (Ca3), 108.0 (Ca7), 103.2 (Ca12), 98.7 (Cc4), 72.7 (Cb1), 56.6 (Cc1), 53.5 (Cb4), 43.2 (Ca10), 40.6(Hc2), 39.7 (Ca9), 35.7 (Cb2), 29.0 (Cb3).

HRMS-ESI (m/z) calculated for $C_{37}H_{40}N_7O$ $[M+H]^+$: 598.32893; found: 598.3295.

Biological assays

Enzymatic assays

DNMT3A assay. DNMT3A enzyme inhibition was adapted from the restriction-based fluorescence assay protocol described by (1) and described in (2). Briefly, a 5’-labelled biotin oligonucleotide was hybridized to its complementary strand labelled with 6-carboxyfluorescein at the 3’-end and transferred into a 384-well microplate (black Optiplates; PerkinElmer) pre-coated with avidin. The duplex contains a unique CpG site overlapping with a restriction site of a methylation-sensitive restriction enzyme. The human C-terminal DNMT3A (a.a. 623-908), produced as described, was added to each well (200 ng/well) and mixed with the chemical compounds at the desired concentration and freshly prepared AdoMet (20 mM final concentration) to start the reaction in a total volume of 50 mL. After incubation at 37°C (1h), each well was washed three times with phosphate-buffered saline (PBS) containing 0.05% Tween-20 and NaCl (500 mM) and three more times with phosphate-buffered saline Tween-20 (PBST). Specific fluorescence signals were detected with the methylation-sensitive restriction enzyme HpyCH4IV (New England Biolabs, Ipswich, MA, USA) as described, and measured on a PerkinElmer Envision detector. The percent inhibition was calculated according to Equation (1), where X is the signal determined in the absence of the inhibitor and Y is the signal obtained in the presence of the inhibitor.

Equation (1): $\% \text{ inh.} = [(X-Y)/X] \times 100$

The ligand concentration at which 50% inhibition of enyme activity is observed (EC50) was determined by analysis of a concentration range of the test compounds in triplicates. Nonlinear regression fittings with sigmoidal dose–response (variable slope) were performed with Prism 4.03 (GraphPad Software, Inc., La Jolla, CA, USA).

DNMT1 assay. His-DNMT1 (182 kDa, human) was cloned, expressed and purified as described. The assays were performed as described by (3). The reaction was performed in a total reaction volume of 10 µL in low-volume nonbinding surface (NBS) 384-well microplates (Corning Inc.), containing test compound (up to 1% DMSO), 1 µM of a S-adenosyl-lmethionine (SAM)/[methyl-^{3}H]SAM (3 TBqmmol^{-1}, PerkinElmer) mix in a ratio of 3:1 (isotopic dilution 1*:3), 0.3 µM of biotinylated hemimethylated DNA duplex and 90 nM of DNMT1 in methylation buffer (20 mM HEPES (pH 7.2), 1 mM EDTA, 50 mM KCl, 25 µg/mL of bovine serum albumin). The reaction was incubated at 37°C for 2 h, then an aliquot (8 µL) was transferred into a streptavidin 96- well scintillant-coated FlashPlate (PerkinElmer) containing 20 µM *S*-adenosyl-L-homocysteine (SAH; 190 µL) in 50 mM Tris-HCl (pH 7.4). The FlashPlate was agitated at RT for 1 h, washed three times with 200 µL of 0.05% Tween-20 in 50 mM Tris-HCl (pH 7.4), and read in 200 µL of 50mM Tris-HCl (pH 7.4) on TopCount NXT (PerkinElmer).

The ligand concentration at which 50% inhibition of enyme activity is observed (EC50) was determined by analysis of a concentration range of the test compounds in triplicates. Nonlinear regression fittings with sigmoidal dose–response (variable slope) were performed with Prism 4.03 (GraphPad Software, Inc., La Jolla, CA, USA).

Antiproliferative activity.

KG-1 and Karpas299 human leukemia cells were obtained from the ATCC (USA) and cultivated in RPMI 1640 medium (with HEPES and Glutamine, BE12-115F, Lonza, France) supplemented with, respectively, 20% and 15% foetal calf serum (Lonza, France), at 37°C and under 5% CO_2. To measure the antiproliferative properties of tested molecules, $2x10^4$ cells were seeded at day 0 in a 96-well plate. The compounds to be tested, stored at -20°C as 10^{-2} M stock solution in 100% DMSO, are freshly diluted on day 1 in RPMI 1640 medium, before adding a dose range of 3.2nM to 10µM to the cells. This treatment is repeated on day 2 and 3, and on day 4 cell viability is assessed using the ATPLite kit from Perkin (ATPlite are Step Luminescence Assay System, ref 3016739), following the provider instructions. The raw data are analyzed with GraphPad Prism software (v4.03) to generate EC_{50} values corresponding to the compound concentrations giving 50% reduction in cell viability (using nonlinear regression: sigmoidal dose-response (variable slope)). The values presented are the mean results of at least two independent experiments. The 95% confidence intervals for these EC_{50} values are also indicated.

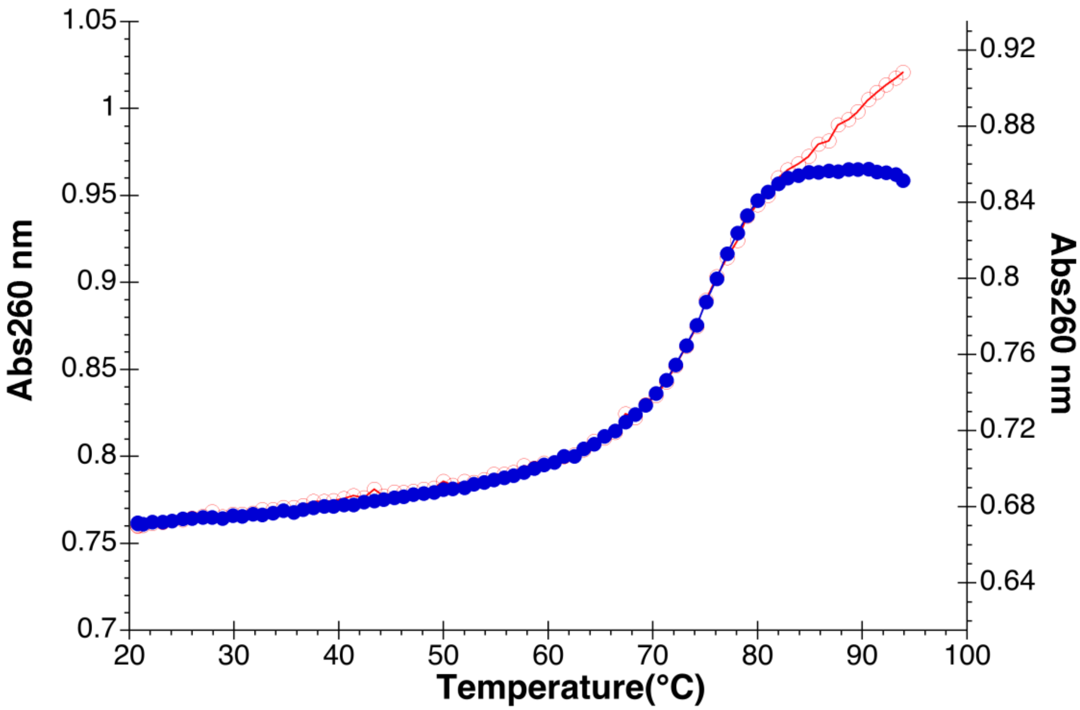
Table S1: Cytotoxicity of compound **20** on cell lines derived from pancreas cancer (PANC-1), metastatic melanoma (WM266-4), glioblastoma (U-87), leukemia (KG-1), lymphoma (Karpas299) and colon (HCT116) and cytotoxicity of compound **68** and **70** on cell lines derived from acute myeloid leukemia (KG-1) and colon carcinoma (HCT116). The mean EC_{50} (μM) ± SE of two to three experiments is reported.

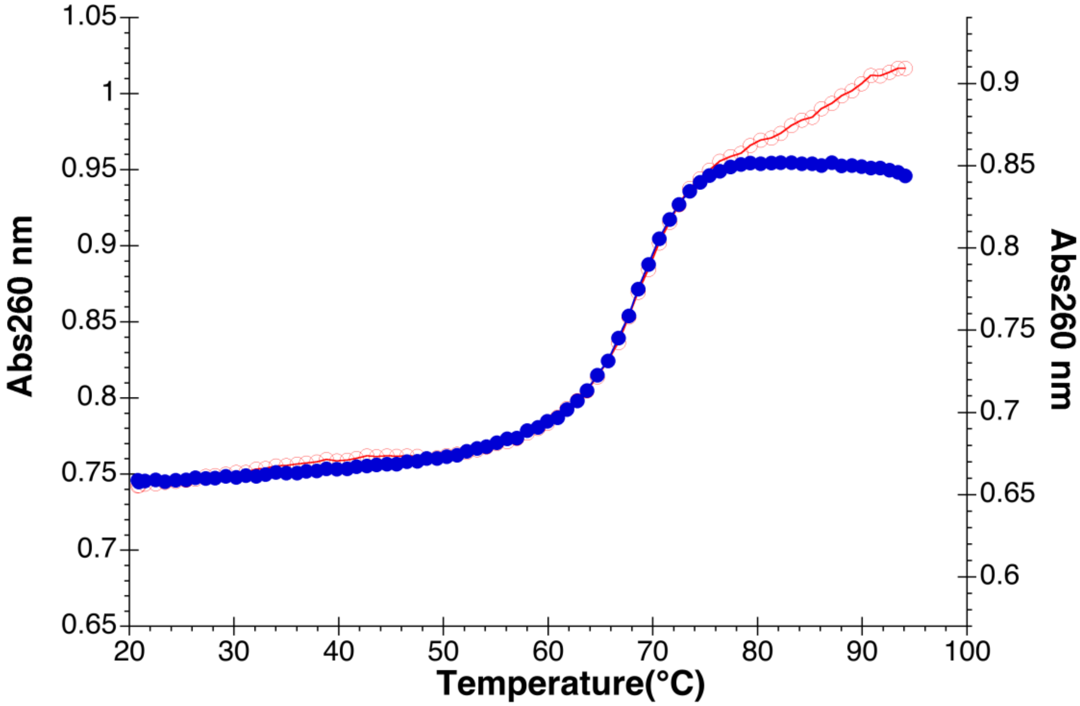
Cpds	**PANC-1**	**WM266-4**	**U-87**	**KG-1**	**Karpas 299**	**HCT116**
20	1.2±0.4	4.0±0.3	0.9±0.1	0.5±0.1	1.8±0.6	0.5±0.2
68	ND	ND	ND	0.4±0.1	ND	0.7±0.1
70	ND	ND	ND	1.3±0.9	ND	0.6±0.3

ND= Not determined

Tm assay

DNA thermal denaturation experiments were conducted as described in (4). Hairpin DNA duplexes hp_2_CG (5'-TATATACGTACGGTGTTTTCACCGTACGTATATA-3') containing 2 CpG sites; hp_1_CG (5'-TATATACGTACTGTGTTTTCACAGTACGTATATA-3') containing 1 CpG site; and hp_0_CG (5'-TATATATGTACTGTGTTTTCACAGTACATATATA-3') containing no CpG site, were used at 2 µM in the absence or in the presence of the inhibitor in the Tm assay buffer (100mM NaCl, Lithium cacodylate 20mM, pH 7.2). The temperature at which 50% of the duplex is denatured Tm was calculated as previously described (4).




Abs260 nm
Temperature(°C)
Abs260 nm

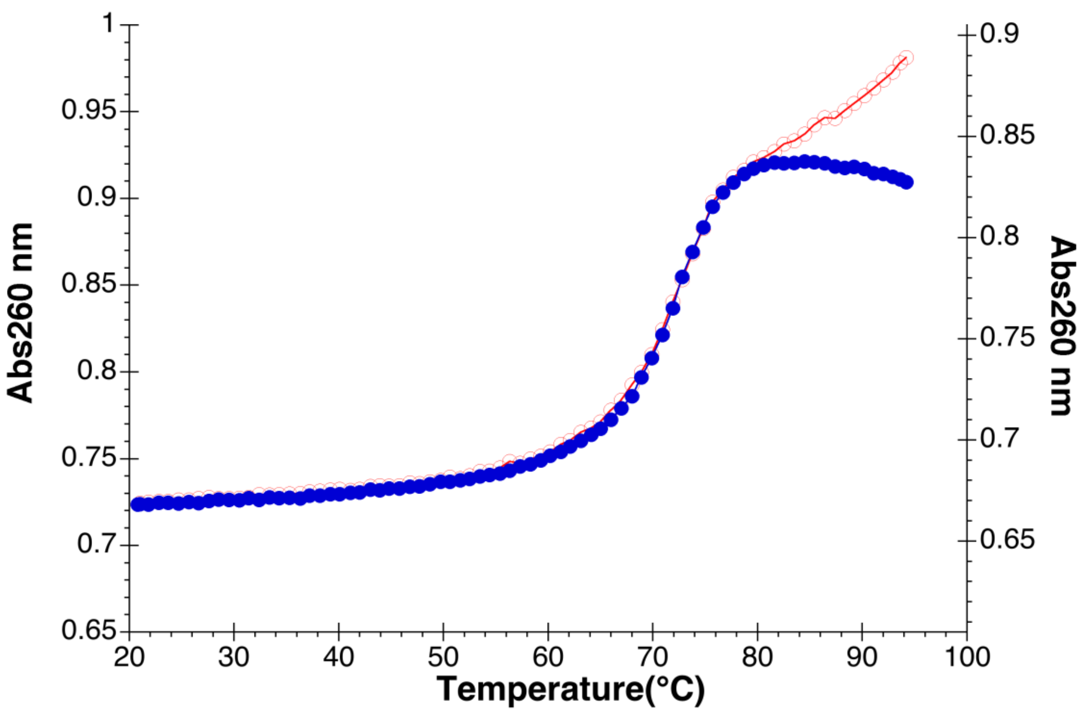

Abs260 nm
Temperature(°C)
Abs260 nm

Figure S1- Melting curves measured at 260nm of 2µM hairpin duplex hp2 (top), hp1 (center) and hpctrl (bottom) in the absence (red circles, left Y axis) and in the presence of 10µM compound **20** (blue circles, right Y axis).

DNase I footprinting

DNase I footprinting experiments were performed essentially as described in Lemster *et al.* (5). Briefly, the 117 and 265bp DNA fragments were obtained from *Eco*RI and *Pvu*II double digestion of the pBS plasmid (Stratagene, La Jolla, CA) and were then 3'-end labeled using α-[^{32}P]-dATP (3000 Ci/mmol, PerkinElmer, France). Increasing concentrations of the compound **20** were incubated with either 117bp or 265bp radiolabeled DNA fragments for 15min at 37°C to ensure equilibrium prior to the addition of 0.001unit/mL of DNase I in appropriate buffer for 3 min of digestion followed by ethanol precipitation. The digested DNAs were subsequently dissolved in 4µL of denaturing loading buffer (80% formamide solution containing tracking dyes), heated 4min at 90°C and chilled 4 min on ice prior to electrophoresis 90min at 65W on a 8% denaturing polyacrylamide gel in TBE buffer. Finally, gels were soaked in 10% acetic acid, dried under vacuum at 80°C on 3MM Whatman paper and revealed using PMI equipment (BioRad). The precise localization of each base was assigned relatively to the guanines sequencing standard (G-track) classically obtained using dimethyl-sulfate (DMS) and piperidine treatment of the same DNA fragment.

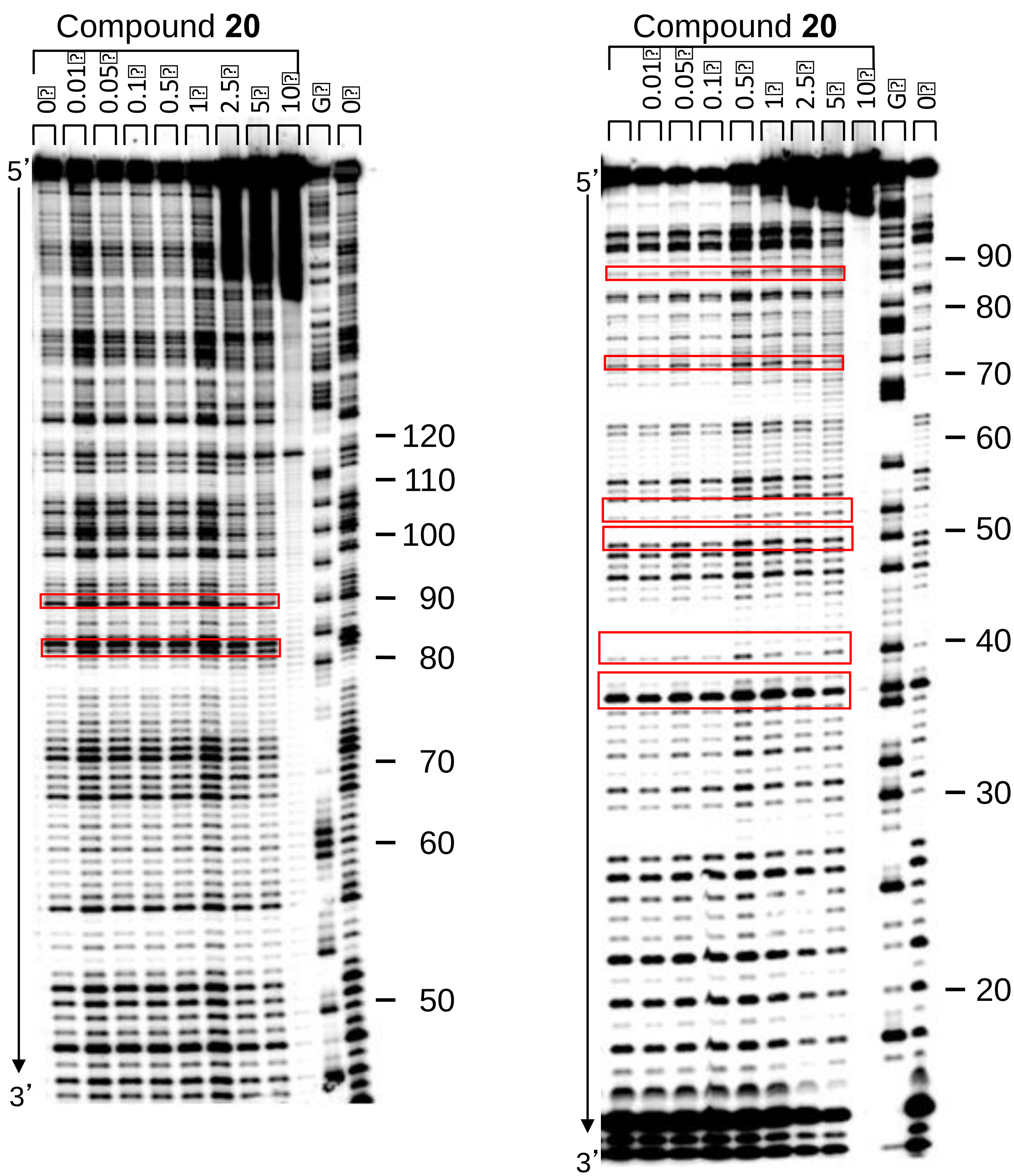


Figure S2: DNase I footprinting gel analysis. 265bp (**left**) or 117bp (**right**) radiolabeled DNA were incubated with increasing concentration (µM) of the compound **20** prior to mild DNase I digestion and separation of the digested fragments on a denaturing 8% polyacrylamide gel. Red boxes localize CpG dinucleotides. G lanes highlights guanines using classic DMS-piperidine treatment.

Luciferase Induction

To generate KG-1-Luc cells, KG-1 cells were stably transfected with the firefly luciferase (Luc+ from pGL3; Promega) reporter gene under the control of the cytomegalovirus (CMV) promoter (from pEGFP-N1; Clontech Laboratories Inc.) that was partially methylated (25 %). KG-1-Luc cells were seeded at 2.10^4 cells per well in a 96-wells plate. After 24 h incubation in the presence of the evaluated compound or solvent (DMSO or water), the luciferase induction was quantified with the Britelite™ assay system (PerkinElmer). The luminescence was measured on an EnVision multilabel plate reader (PerkinElmer), and the data are expressed as the fold induction as compared with the solvent control. The mean of three experiments and the standard error is reported.

Table S2: Reactivation Fold (RF) of the luciferase in the CMV-Luc KG-1 construction. Luminescence was measured after 24h treatment of cells by5azadCand compounds **20**, **29**, **68** and **70**. Luciferase RF was represented as ratio to non-treated cells.

Cpds	**RF of the luciferase gene for concentration (µM)**				
	10	**5**	**3.2**	**1**	**0.1**
5azadC	14.8 ±2.9	15.1 ±3.0	17.3 ±1.2	16.2 ±3.1	9.2 ±2.5
20	2.5 ±1.1	4.7 ±1.3	2.7 ±0.2	0.8 ±0.2	0.9 ±0.2
68	2.1 ±0.2	4.2 ±0.1	5.0 ±0.6	4.1 ±0.3	2.7 ±0.1
70	2.2 ±0.8	4.3 ±0.7	1.4 ±0.2	1.6 ±0.4	1.8 ±0.9
29	0.9 ±0.05	0.9 ±0.03	0.9 ±0.03	0.9 ±0.11	1.2 ±0.24

Nucleosome Occupancy and Methylome Sequencing (NOMe-Seq)

After nuclei extraction, GpC methyltransferase (M.CviPI; New England Biolabs) reactions were done in M.CviPI reaction buffer. GpC methyltransferase treatment was followed by DNA extraction, sodium bisulfite conversion, PCR amplification of the region of interest, cloning, and sequencing of individual clones. KG-1-Luc cells treated with different conditions were centrifuged for 5 min at 500 × g. Cell pellets were washed in ice-cold PBS, resuspended in 1mL of ice-cold nuclei buffer [10mM Tris (pH 7.4), 10mM NaCl, 3mM $MgCl_2$, 0.1mM EDTA, and 0.5% Nonidet P-40, protease inhibitors] per 2×10^6 cells, and incubated on ice for 10 min. Nuclei were recovered by centrifugation at 900×g for 5min, washed twice in nuclei wash buffer [10 mM Tris (pH 7.4), 10mM NaCl, 3mM $MgCl_2$, and 0.1mM EDTA containing protease inhibitors], and resuspended with 200µL in 1× M.CviPI reaction buffer supplemented with 0.3M sucrose, 160µM *S*-adenosyl-L-methionine (AdoMet, New EnglandBiolabs). 100µL of purified genomic DNA were treated with 100 units of M.CviPI for 15 min at 37°C in 200µL final volume. The other part of 100µL of purified genomic DNA were not treated with 100 units of M.CviPI but only incubated for 15min at 37°C to obtain CpG methylation profile on the sequence of interest. Previous publications using locus-specific NOMe-seq have used the minimal amount of M.CviPI that resulted in optimal footprinting of the specific region of interest: 100 units, (6) 200 units, (7) or 200 + 100 units. (8) Reactions were stopped by the addition of an equal volume of stop solution [20nM Tris·HCl (pH 7.9), 600mM NaCl, 1% SDS, 10mM EDTA, and 400µg/mL Proteinase K] and incubated at 55°C overnight. DNA was purified by phenol/chloroform extraction and ethanol precipitation.

Combined Bisulfite Restriction Analysis (COBRA): primer design.

Bisulfite-specific primers with a minimum length of 18bp were designed using Primer 3 program (9). The target sequence of the designed primers contained no CpGs allowing amplification of both un- and hypermethylated DNAs. All primers were tested for their ability to yield high quality sequences and primers that gave rise to an amplicon of the expected size using non-bisulfite treated DNA as a template were discarded, thus ensuring the specificity for bisulfite-converted DNAs.

CDKN2A primers for COBRA :

forward, 5’- GGTTTTTTTAGAGGATTTGAGGGATAGG-3’

reverse, 5’- CTACCTAATTCCAATTCCCCTACAAACTTC 3’

References:

(1) Ceccaldi, A.; Rajavelu, A.; Champion, C.; Rampon, C.; Jurkowska, R.; Jankevicius, G.; Senamaud-Beaufort, C.; Ponger, L.; Gagey, N.; Ali, H. D.; Tost, J.; Vriz, S.; Ros, S.; Dauzonne, D.; Jeltsch, A.; Guianvarc'h, D.; Arimondo, P. B. C5-DNA methyltransferase inhibitors: from screening to effects on zebrafish embryo development. *Chembiochem* **2011,** 12, 1337-1345

(2) Rilova, E.; Erdmann, A.; Gros, C.; Masson, V.; Aussagues, Y.; Poughon-Cassabois, V.; Rajavelu, A.; Jeltsch, A.; Menon, Y.; Novosad, N.; Gregoire, J. M.; Vispe, S.; Schambel, P.; Ausseil, F.; Sautel, F.; Arimondo, P. B.; Cantagrel, F. Design, synthesis and biological evaluation of 4-amino-N- (4-aminophenyl)benzamide analogues of quinoline-based SGI-1027 as inhibitors of DNA methylation. *ChemMedChem* **2014,** 9, 590-601.

(3) Gros, C.; Chauvigne, L.; Poulet, A.; Menon, Y.; Ausseil, F.; Dufau, I.; Arimondo, P. B. Development of a universal radioactive DNA methyltransferase inhibition test for high-throughput screening and mechanistic studies. *Nucleic Acids Res.* **2013,** 41, e185.

(4) J. L Mergny and L. Lacroix. (2003) Analysis of thermal melting curves. *Oligonucleotides.* **13,** 515-537.

(5) T. Lemster, U. Pindur, G. Lenglet, S. Depauw, C. Dassi and M.-H. David-Cordonnier. (2009) Photochemical electrocyclisation of 3-vinylindoles to pyrido[2,3-a]-, pyrido[4,3-a]-, and thieno[2,3-a]-carbazoles: design, synthesis, DNA binding and antitumor cell cytotoxicity. *Eur. J. Med. Chem.* **44**, 3235–3252.

(6) . M. Wolff, H. M. Byun, H. F. Han, S. Sharma, P. W. Nichols, K. D. Siegmund, A. S. Yang, P. A. Jones, G. Liang, *PLoS Genet* **2010**, *6*, e1000917.

(7) a) P. C. Taberlay, T. K. Kelly, C. C. Liu, J. S. You, D. D. De Carvalho, T. B. Miranda, X. J. Zhou, G. Liang, P. A. Jones, *Cell* **2011**, *147*, 1283-1294; b) J. S. You, T. K. Kelly, D. D. De Carvalho, P. C. Taberlay, G. Liang, P. A. Jones, *Proc Natl Acad Sci U S A* **2011**, *108*, 14497-14502.

(8) C. Andreu-Vieyra, J. Lai, B. P. Berman, B. Frenkel, L. Jia, P. A. Jones, G. A. Coetzee, *Mol Cell Biol* **2011**, *31*, 4648-4662.

(9) a) T. Koressaar, M. Remm, *Bioinformatics* **2007**, *23*, 1289-1291; b) A. Untergasser, I. Cutcutache, T. Koressaar, J. Ye, B. C. Faircloth, M. Remm, S. G. Rozen, *Nucleic Acids Res* **2012**, *40*, e115.