Supporting Information
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Intramolecular ring-opening of oxetanes: Access to functionalised hydroxymethyl 2,3-Dihydroimidazo[1,2-c]quinazolines

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Supporting Information

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General Considerations

$^1$H NMR spectra were recorded on a Bruker AV400 or AV500 spectrometer at 400 MHz or 500 MHz respectively and referenced to residual solvent. $^{13}$C NMR spectra were recorded at 101 MHz. Chemical shifts ($\delta$ in ppm) were referenced to residual solvent peaks (DMSO at $\delta$H 2.50 ppm and $\delta$C at 39.52 ppm). $J$ values are given in Hz and s, d, t, q, dd, ddd and m are abbreviations corresponding to singlet, doublet, triplet, quartet, doublet of doublets, doublet of doublets of doublets and multiplet respectively.

Low resolution mass spectra were recorded by UPLC methods on reverse-phase C18 silica with detection by Electrospray Mass Spectrometry using positive or negative ion electrospray (ESI+ or ESI-) and by UV absorbance recording a wavelength range of 220-320 nm. Analytical UPLC was performed on CSH C18 reverse-phase silica, using a Waters XSelect CSH C18 column with dimensions 2.1 x 50mm and particle size 1.7 micron. Gradient analysis was employed using decreasingly polar mixtures as eluent, for example decreasingly polar mixtures of water (containing 0.1% formic acid or 0.1% ammonia) as solvent A and acetonitrile as solvent B.

High resolution mass spectra were recorded on Thermo Scientific and Fusion Orbitrap MS using positive or negative ion electrospray (ESI+ or ESI-).

Normal phase flash column chromatography was carried out using ultra performance Interchim puriflash 50 µm silica columns and carried out using Teledyne ISCO CombiFlash Lumen system. Reverse phase column chromatography was carried out using preparative HPLC (Waters XSelect CSH C18 ODB column, 5µ silica, 30 mm diameter, 100 mm length) Interchim 4250 system.

Starting materials, reagents and solvents were bought from Sigma-Aldrich or Fluorochem and were used without further purification.
Experimental Procedures

Ethyl 4-chloroquinazoline-6-carboxylate (1a)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{HN} & \quad \text{NH}
\end{align*}
\]

\[
\begin{align*}
\text{SOCl}_2 & \quad \text{DMF, 90°C, 3h} \\
\text{O} & \quad \text{O} \\
\text{HN} & \quad \text{NH}
\end{align*}
\]

To a stirred solution of ethyl 4-hydroxyquinazoline-6-carboxylate (100 mg, 0.46 mmol) in thionyl chloride (2 mL) at 25°C under nitrogen was added DMF (0.2 mL) and the reaction mixture was heated to 90°C for 3 hours. The resulting mixture was evaporated to dryness and the residue was azeotroped with excess toluene to afford ethyl 4-chloroquinazoline-6-carboxylate (108 mg, 100%), which was used without further purification. LCMS: m/z ES⁺ [M+H]⁺ = 233.4.*

4-Chloro-6-nitroquinazoline (1b)

\[
\begin{align*}
\text{O}_2\text{N} & \quad \text{O} \\
\text{HN} & \quad \text{NH}
\end{align*}
\]

\[
\begin{align*}
\text{SOCl}_2 & \quad \text{DMF, 90°C, 3h} \\
\text{O}_2\text{N} & \quad \text{O} \\
\text{HN} & \quad \text{NH}
\end{align*}
\]

To a stirred solution of 6-nitroquinazolin-4-ol (500 mg, 2.62 mmol) in thionyl chloride (10 mL) at 25°C under nitrogen was added DMF (0.2 mL) and the reaction mixture was heated to 90°C for 3 hours. The resulting mixture was evaporated to dryness and the residue was azeotroped with excess toluene to afford 4-chloro-6-nitroquinazoline which was used without further purification. LCMS: m/z ES⁺ [M+H]⁺ = 206.1.*

4-Chloro-6-methoxyquinazoline (1c)

\[
\begin{align*}
\text{O} & \quad \text{O} \\
\text{HN} & \quad \text{NH}
\end{align*}
\]

\[
\begin{align*}
\text{SOCl}_2 & \quad \text{DMF, 90°C, 3h} \\
\text{O} & \quad \text{O} \\
\text{HN} & \quad \text{NH}
\end{align*}
\]
To a stirred solution of 6-methoxyquinazolin-4-ol (500 mg, 2.84 mmol) in thionyl chloride (10 mL) at 25°C under nitrogen was added DMF (0.2 mL) and the reaction mixture was heated to 90°C for 3 hours. The resulting mixture was evaporated to dryness and the residue was azeotroped with excess toluene to afford 4-chloro-6-methoxyquinazoline which was used without further purification. **LCMS:** m/z ES+ [M+H]+ = 192.1.*

*Final compound analysed by methanol quench and LCMS analysis.

4-Chloro-6-iodoquinazoline (1d)

![Chemical structure of 4-Chloro-6-iodoquinazoline (1d)]

To a stirred solution of 6-iodoquinazolin-4-ol (500 mg, 1.84 mmol) in thionyl chloride (7 mL) at 25°C under nitrogen was added DMF (0.2 mL) and the reaction mixture was heated to 90°C for 3 hours. The resulting mixture was evaporated to dryness and the residue was azeotroped with excess toluene to afford 4-chloro-6-iodoquinazoline which was used without further purification. **LCMS:** m/z ES+ [M+H]+ = 287.1.*

Ethyl 4-[(3-methyloxetan-3-yl)amino]quinazoline-6-carboxylate (3a)

![Chemical structure of Ethyl 4-[(3-methyloxetan-3-yl)amino]quinazoline-6-carboxylate (3a)]

3-Methyloxetan-3-amine (0.051 mL, 0.57 mmol) was added to ethyl 4-chloroquinazoline-6-carboxylate (108 mg, 0.46 mmol) and potassium carbonate (126 mg, 0.91 mmol) in acetonitrile (5 mL) at 0°C under nitrogen for 30 minutes and then heated to 50°C for 24 hours. The reaction mixture was then cooled to 25°C and the solvent evaporated followed by dilution with EtOAc (20 mL). The organic layer was washed with water (2x 20 mL), saturated brine (15 mL) and dried over a phase separating cartridge. The solvent was removed under reduced pressure to afford crude ethyl 4-[(3-methyloxetan-3-yl)amino]quinazoline-6-carboxylate (120 mg, 92% yield) as a brown oil. **1H NMR** (400 MHz; DMSO-d6) δ 1.38 (3H, t, J = 7.1 Hz, CH3CH2), 1.74 (3H, s, Me), 4.40 (2H, q, J = 7.1 Hz, CH3CH2), 4.48 (2H, d, J = 6.6 Hz, CH2O), 4.83 (2H, d, J = 6.6 Hz, CH2O), 7.18 (2H, s, Me), 7.40 (2H, d, J = 7.1 Hz, CH3CH2).
N-(3-Methyloxetan-3-yl)-6-nitroquinazolin-4-amine (3b)

\begin{align*}
\text{3-Methyloxetan-3-amine} (0.291 \text{ mL, } 3.27 \text{ mmol}) \text{ was added to 4-chloro-6-nitroquinazoline (548 mg, 2.61 mmol) and potassium carbonate (723 mg, 5.23 mmol) in acetonitrile (10 mL) at 25°C under nitrogen. The mixture was heated to 50°C for 24 hours. The reaction mixture was then cooled to 25°C and the solvent evaporated followed by dilution with EtOAc (20 mL). The organic layer was washed with water (2 x 20 mL), saturated brine (15 mL) and dried over a phase separating cartridge. The solvent was removed under reduced pressure to afford crude material as a yellow solid, which was purified by flash silica chromatography, elution gradient 0-10% MeOH in DCM. Pure fractions were evaporated to dryness to afford N-(3-methyloxetan-3-yl)-6-nitroquinazolin-4-amine (406 mg, 59% yield) as a yellow solid.} \\
\text{\textbf{1H NMR} (400 MHz; DMSO-d6) } \delta 1.74 \text{ (3H, s, Me), 4.50 (2H, d, J = 6.7 Hz, CH}_2\text{O), 4.84 (2H, d, J = 6.7 Hz, CH}_2\text{O), 7.83 (1H, d, J = 9.1 Hz, Ar-H), 8.48 (1H, dd, J = 2.5, 9.1 Hz, Ar-H), 8.55 (1H, s, Ar-H), 9.27 (1H, br s, NH), 9.33 (1H, d, J = 2.5 Hz, Ar-H); 13C NMR (101 MHz, DMSO, 30°C) } \delta 22.55 \text{ (CH}_3\text{), 54.47 \text{ (C), 80.56 (2x CH}_2\text{), 114.05, 120.60 (CH), 126.29 (CH), 129.22 (CH), 144.01 (C), 152.72 (C), 157.63 (C), 158.76 (C); HRMS m/z calcd for C}_{12}\text{H}_{12}\text{N}_4\text{O}_3 \text{ [M+H]}^+ = 261.0909, \text{ found [M+H]}^+ = 261.0985, \text{ [M–NO}_2\text{]}^+ = 215.1052.}\n\end{align*}

6-Methoxy-N-(3-methyloxetan-3-yl)quinazolin-4-amine (3c)

Please see 4c

6-Iodo-N-(3-methyloxetan-3-yl)quinazolin-4-amine (3d)

Please see 4d
6-Methyl-N-(3-methyloxetan-3-yl)quinazolin-4-amine (3e)

3-methyloxetan-3-amine (0.315 mL, 3.55 mmol) was added to 4-chloro-6-methylquinazoline (506.6 mg, 2.84 mmol) and potassium carbonate (784 mg, 5.67 mmol) in acetonitrile (10 mL) at 25°C under nitrogen. The resulting suspension was stirred at 90°C and the reaction mixture was stirred for a further 48 hours. The reaction mixture was concentrated and used without further purification.

7-Bromo-6-chloro-N-(3-methyloxetan-3-yl)quinazolin-4-amine (3f)

3-methyloxetan-3-amine (0.370 mL, 4.16 mmol) was added to 7-bromo-4,6-dichloroquinazoline (771 mg, 2.77 mmol) and potassium carbonate (767 mg, 5.55 mmol) in acetonitrile (27 mL) at 25°C under nitrogen. The resulting slurry was stirred at 50°C for 48 hours. The reaction mixture was concentrated and diluted with water (50 mL). The precipitate was collected by filtration, washed with water (25 mL) and dried under vacuum to afford 7-bromo-6-chloro-N-(3-methyloxetan-3-yl)quinazolin-4-amine (713 mg, 78% yield) as a cream solid.

**1H NMR** (400 MHz; DMSO-d6) \( \delta \) 1.72 (3H, s, Me), 4.48 (2H, d, J = 6.3 Hz, CH2O), 4.80 (2H, d, J = 6.3 Hz, CH2O), 8.10 (1H, s, Ar-H), 8.45 (1H, s, Ar-H), 8.59 (1H, s, Ar-H), 8.79 (1H, br s, NH).

**13C NMR** (126 MHz, DMSO-d6, 27°C) \( \delta \) 23.09 (CH3), 54.83 (C), 81.16 (2x CH2), 115.46 (C-Br), 124.82 (C-Br), 126.77 (C), 130.28 (CH), 132.84 (CH), 149.06 (C) 156.42 (CH), 157.58 (C).

**HRMS** m/z calcld for C12H11BrClN3O [M+H]+ = 326.9774, found [M+H]+ = 327.9853.
A solution of ethyl 4-((3-methyloxetan-3-yl)amino)quinazoline-6-carboxylate (109 mg, 0.38 mmol) in methanol (15 mL) was stirred at 70°C for 16 hours. The solvent was removed and the crude product was purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM. Pure fractions were evaporated to dryness to afford ethyl 2-(hydroxymethyl)-2-methyl-2,3-dihydroimidazo[1,2-c]quinazoline-9-carboxylate (67.7 mg, 62% yield) as a beige solid. 

$^{1}$H NMR (400 MHz; DMSO-d$_6$) $\delta$ 1.22 (3H, s, Me), 1.34 (3H, t, J = 7.1 Hz, CH$_3$CH$_2$), 3.34 (1H, dd, J = 6.2, 10.8 Hz, CH$_2$O), 3.41 (1H, dd, J = 5.1, 10.8 Hz), 3.73 and 4.12 (1H, d, J = 10.7 Hz and 1H, d, J = 10.7 Hz, CH$_2$), 4.33 (2H, q, J = 7.1 Hz, CH$_3$CH$_2$), 4.94 (1H, t, J = 5.7 Hz, OH), 7.45 (1H, d, J = 8.5 Hz, Ar-H), 8.02 (1H, s, Ar-H), 8.06 (1H, dd, J = 2.1, 8.5 Hz, Ar-H), 8.42 (1H, d, J = 2.1, Ar-H); $^{13}$C NMR (101 MHz, DMSO-d$_6$) $\delta$ 14.13 (CH$_3$H$_3$CH$_2$), 24.43 (CH$_3$), 53.73 (CH$_2$), 60.89 (CH$_2$CH$_3$), 67.74 (CH$_2$O), 71.09 (C), 118.32(C), 126.31 (CH), 126.75 (C), 126.94 (CH), 132.65 (CH), 146.72 (CH), 149.95 (C), 150.61 (C), 164.77 (CO$_2$Et); HRMS m/z calcd for C$_{15}$H$_{17}$N$_3$O$_3$ [M+H]$^+$ = 288.1270, found [M+H]$^+$ = 288.1338, [M–C$_2$H$_5$]$^+$ = 260.1031.

N-(3-methyloxetan-3-yl)-6-nitroquinazolin-4-amine (309 mg, 1.19 mmol) was suspended in methanol (5 mL) and sealed into a microwave tube. The reaction was heated to 100°C for 2.5 hours and cooled to 25°C. The reaction mixture was diluted with methanol (25 mL) and the precipitate was collected by filtration, washed with methanol (25 mL) and dried under vacuum to afford (2-methyl-9-nitro-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (288 mg, 93% yield) as a yellow solid. 

$^{1}$H NMR (400 MHz; DMSO-d$_6$) $\delta$ 1.24 (3H, s, Me), 3.36 (1H, dd, J = 5.9, 10.9 Hz, CH$_2$O), 3.44 (1H, dd, J = 5.9, 10.9 Hz, CH$_2$O), 3.77 and 4.15 (1H, d, J = 10.9 Hz and 1H, d, J = 10.9 Hz and 1H, d, J = 10.9 Hz, CH$_2$), 5.00 (1H, t, J = 5.9 Hz, OH), 7.53 (1H, d, J = 8.9 Hz, Ar-H), 8.10 (1H, s, Ar-H), 8.32 (1H, d, J = 2.7, 8.9 Hz, Ar-H), 8.56 (1H, d, J = 2.7 Hz, Ar-H); $^{13}$C NMR (101 MHz, DMSO-d$_6$, 30°C) $\delta$ 24.27 (CH$_3$), 53.81 (CH$_2$), 67.66 (CH$_2$O), 71.42 (C), 118.32 (C), 120.54 (CH), 127.07 (CH), 127.93 (CH), 144.18 (C), 147.86 (CH), 150.12 (C), 151.49 (C); HRMS m/z calcd for C$_{12}$H$_{12}$N$_4$O$_3$ [M+H]$^+$ = 261.0909, found [M+H]$^+$ = 261.0988, [M–NO$_2$]$^+$ = 215.1053.
(9-Methoxy-2-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (4c)

3-Methyloxetan-3-amine (0.315 mL, 3.55 mmol) was added to 4-chloro-6-methoxyquinazoline (552 mg, 2.84 mmol) and potassium carbonate (784 mg, 5.67 mmol) in acetonitrile (10 mL) at 25°C under nitrogen. The resulting suspension was heated to 90°C for 72 hours. The reaction mixture was concentrated to afford crude product which was purified by preparative HPLC (Waters XSelect CSH C18 ODB column, 5µ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing by volume 1% NH₄OH (28-30% in H₂O)) and acetonitrile as eluents. Fractions containing the desired compound were evaporated to dryness to afford (9-methoxy-2-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (15 mg, 31% yield) as a grey solid.

1H NMR (500 MHz; DMSO-d₆) δ 1.21 (3H, s, Me), 3.34 (2H, br dd, CH₂O), 3.68 and 4.08 (1H, d, J = 10.5 and 1H, d, J = 10.5 Hz, CH₂), 3.81 (3H, s, OMe), 4.86 (1H, br s, OH), 7.18 (1H, dd, J = 3.0, 8.8, Ar-H), 7.26 (1H, d, J = 3.0, Ar-H), 7.36 (1H, d, J = 8.8 Hz, Ar-H), 7.85 (1H, s, Ar-H); 13C NMR (101 MHz, DMSO-d₆, 30°C) δ 24.73 (CH₃), 53.94 (CH₂), 55.47 (CH₂O), 67.85 (OMe), 70.68 (C), 105.70 (CH), 119.18 (C), 121.39 (CH), 128.28 (CH), 140.50 (CH), 142.73 (C), 151.21 (C), 157.22 (C); HRMS m/z calcd for C₁₃H₁₅N₃O₂ [M+H]+ = 246.1164, found [M+H]+ = 246.1236.

(9-Iodo-2-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (4d)

3-Methyloxetan-3-amine (0.204 mL, 2.30 mmol) was added to 4-chloro-6-iodoquinazoline (534 mg, 1.84 mmol) and potassium carbonate (508 mg, 3.68 mmol) in acetonitrile (10 mL) at 25°C under nitrogen. The resulting suspension was heated to 90°C for 48 hours. The reaction mixture was concentrated onto silica and purified by flash silica chromatography, elution gradient 0 to 10% MeOH in DCM. Pure fractions were evaporated to dryness to afford (9-iodo-2-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (14 mg, 32% yield) as a white solid.

1H NMR (400 MHz; DMSO-d₆) δ 1.20 (3H, s, Me), 3.33 (1H, dd, J = 6.0, 9.5 Hz, CH₂O), 3.37 (1H, dd, J = 5.1, 10.6 Hz, CH₂O) 3.70 and 4.09 (1H, d, J = 10.6 Hz and 1H, d, J = 10.6 Hz, CH₂), 4.85 (1H, t, J = 5.1 Hz, OH), 7.18 (1H, d, J = 8.5 Hz, Ar-H), 7.87 (1H, d, J = 2.1, 8.5 Hz, Ar-H), 7.97 (1H, s, Ar-H), 8.13 (1H, d, J = 2.1 Hz, Ar-H); 13C NMR (101 MHz, DMSO, 30°C) δ 24.99 (CH₃), 54.28 (CH₂), 68.29 (CH₂O), 71.45 (C), 90.93 (C), 120.94 (C), 129.32 (CH), 133.56 (C), 140.50 (CH), 142.73 (C), 151.21 (C), 157.22 (C).
141.51 (CH), 145.91 (CH), 146.33 (C), 150.30 (C); HRMS m/z calcd for C_{12}H_{12}IN_{3}O [M+H]^+ = 342.0025, found [M+H]^+ = 342.0094, [M–I]^+ = 215.1057.

(2,9-dimethyl-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (4e)

6-Methyl-N-(3-methyloxetan-3-yl)quinazolin-4-amine (500 mg, 1.33 mmol) was suspended in methanol (2 mL) and sealed into a microwave tube. The reaction was heated to 100°C for 2 hours in the microwave reactor, cooled to 25°C, concentrated onto silica and purified by flash silica chromatography, elution gradient 0 to 10% methanol in DCM. Fractions containing crude product were evaporated to dryness to afford a pale yellow gum. The crude product was purified by preparative HPLC (Waters XSelect CSH C18 ODB column, 5µ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing by volume 1% NH₄OH (28-30% in H₂O)) and acetonitrile as eluents. Fractions containing the desired compound were evaporated to dryness to afford (2,9-dimethyl-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (62.0 mg, 20% yield) as a white solid. ¹H NMR (400 MHz; DMSO-d₆) δ 1.20 (3H, s, Me), 2.34 (3H, s, Ar-Me), 3.33 (1H, d, J = 10.7 Hz, CH₂O), 3.39 (1H, d, J = 10.7 Hz, CH₂O), 3.68 and 4.09 (1H, d, J = 10.5 Hz and 1H, d, J = 10.5 Hz, CH₂), 4.99 (1H, br s, OH), 7.27 (1H, d, J = 8.2 Hz, Ar-H), 7.37 (1H, dd, J = 2.1, 8.2 Hz, Ar-H), 7.67 (1H, d, J = 2.1 Hz, CH), 7.88 (1H, s, Ar-H); ¹³C NMR (101 MHz, DMSO-d₆, 30°C) δ 20.58 (CH₃), 24.67 (CH₃), 53.74 (CH₂), 67.84 (CH₂O), 70.66 (C), 118.18 (C), 124.56 (CH), 126.43 (CH), 133.58 (CH), 135.52 (C), 143.89 (CH), 144.16 (C), 151.19 (C); HRMS m/z calcd for C_{13}H_{15}N_{3}O [M+H]^+ = 230.1215, found [M+H]^+ = 230.1285.

(8-Bromo-9-chloro-2-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (4f)

A suspension of 7-bromo-6-chloro-N-(3-methyloxetan-3-yl)quinazolin-4-amine (100 mg, 0.30 mmol) in methanol (15 mL) was heated to 70°C for 16 hours. The reaction was cooled to 25°C and filtered under vacuum. The filtrate was concentrated to afford (8-bromo-9-chloro-2-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (35 mg, 35% yield) as a cream
solid.\textsuperscript{1}H NMR (400 MHz; DMSO-d6) $\delta$ 1.21 (3H, s, Me), 3.35 (2H, br dd, CH$_2$O), 3.70 and 4.09 (1H, d, J = 10.7 Hz and 1H, d, J = 10.7 Hz, CH$_2$), 4.83 (1H, t, J = 5.7 Hz, OH), 7.79 (1H, s, Ar-H), 7.94 (1H, s, Ar-H), 7.99 (1H, s, Ar-H); \textsuperscript{13}C NMR (101 MHz, DMSO-d6, 30°C) $\delta$ 24.88 (CH$_3$), 54.27 (CH$_2$), 68.22 (CH$_2$O), 71.71 (C), 119.59 (C), 126.11 (CH), 126.28 (CH), 130.56 (CH), 131.92 (C), 146.74 (CH), 146.86 (C), 150.20 (C); HRMS $m/z$ calcd for C$_{12}$H$_{11}$BrClN$_3$O [M+H]$^+$ = 327.9774, found [M+H]$^+$ = 327.9848, [M–OH]$^+$ = 311.9720.

7-Bromo-6-chloro-N-(oxetan-3-yl)quinazolin-4-amine (6)

![Chemical structure of 7-Bromo-6-chloro-N-(oxetan-3-yl)quinazolin-4-amine (6)]

Triethylamine (0.5 mL, 3.58 mmol) was added dropwise to 7-bromo-4,6-dichloroquinazoline (498 mg, 1.79 mmol) and oxetan-3-amine (0.157 mL, 2.24 mmol) in MeCN (6 mL) at 25°C. The resulting suspension was stirred at 40°C for 3.5 hours. The reaction mixture was concentrated and diluted with water (25 mL). The precipitate was collected by filtration, washed with water (3 x 15 mL) and dried under vacuum to afford 7-bromo-6-chloro-N-(oxetan-3-yl)quinazolin-4-amine (531 mg, 94 % yield) as a cream solid.\textsuperscript{1}H NMR (400 MHz; DMSO-d6) $\delta$ 4.65 (2H, t, J = 6.9 Hz, CH$_2$), 4.88 (2H, t, J = 6.9 Hz, CH$_2$), 5.17 (1H, m, CH), 8.11 (1H, s, Ar-H), 8.47 (1H, s, Ar-H), 8.70 (1H, s, Ar-H), 8.95 (1H, d, J = 5.2 Hz, NH); \textsuperscript{13}C NMR (101 MHz, DMSO-d6, 30°C) $\delta$ 46.12 (CH), 76.56 (2x CH$_2$), 114.70 (C), 124.37 (CH), 126.37 (C), 129.87 (C), 132.28 (CH), 148.57 (C), 156.16 (CH), 157.82 (C); HRMS $m/z$ calcd for C$_{11}$H$_9$BrClN$_3$O [M+H]$^+$ = 313.9618, found [M+H]$^+$ = 313.9691.

(8-Bromo-9-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (7)

![Chemical structure of (8-Bromo-9-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (7)]

7-Bromo-6-chloro-N-(oxetan-3-yl)quinazolin-4-amine (2.2 g, 6.99 mmol) was suspended in methanol (15 mL) and sealed into a microwave tube. The reaction was heated to 100°C for 9 hours and cooled to 25°C. The precipitate was collected by filtration, washed with methanol (50 mL) and dried under vacuum to afford (8-bromo-9-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (1.54 g, 70% yield) as an off-white solid. \textsuperscript{1}H NMR (400 MHz; DMSO-d6) $\delta$ 1.21 (3H, s, Me), 3.35 (2H, br dd, CH$_2$O), 3.70 and 4.09 (1H, d, J = 10.7 Hz and 1H, d, J = 10.7 Hz, CH$_2$), 4.83 (1H, t, J = 5.7 Hz, OH), 7.79 (1H, s, Ar-H), 7.94 (1H, s, Ar-H), 7.99 (1H, s, Ar-H); \textsuperscript{13}C NMR (101 MHz, DMSO-d6, 30°C) $\delta$ 24.88 (CH$_3$), 54.27 (CH$_2$), 68.22 (CH$_2$O), 71.71 (C), 119.59 (C), 126.11 (CH), 126.28 (CH), 130.56 (CH), 131.92 (C), 146.74 (CH), 146.86 (C), 150.20 (C); HRMS $m/z$ calcd for C$_{12}$H$_{11}$BrClN$_3$O [M+H]$^+$ = 327.9774, found [M+H]$^+$ = 327.9848, [M–OH]$^+$ = 311.9720.
DMSO-d6) δ 3.52 (2H, ddt, CH2O), 3.98 and 4.13 (1H, dd and 1H, t, CH2), 4.27 (1H, m, CH), 4.83 (1H, t, OH), 7.77 (1H, s, Ar-H), 7.94 (1H, s, Ar-H), 8.01 (1H, s, Ar-H); 13C NMR (101 MHz, DMSO-d6, 30°C) δ 48.60 (CH2), 63.45 (CH2O), 66.90 (CH), 119.03 (C), 125.48 (CH), 125.92 (C), 130.09 (C), 131.45 (CH), 146.29 (C), 146.38 (CH), 151.16 (C); HRMS m/z calcd for C11H9BrClN3O [M+H]+ = 313.9618, found [M+H]+ = 313.9693.

8-Bromo-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)-9-chloro-2,3-dihydroimidazo[1,2-c]quinazoline (8)

TBDMSCl, Imidazole
DMF, 25°C, 4h

..tert-Butylchlorodimethylsilane (34 mg, 0.23 mmol) was added to (8-bromo-9-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (47 mg, 0.15 mmol) and 1H-imidazole (25 mg, 0.38 mmol) in DMF (1 mL) at 25°C under nitrogen. The resulting suspension was stirred at 25°C for 4 hours. The reaction mixture was diluted with EtOAc (20 mL), and washed sequentially with water (2 x 15 mL) and saturated brine (15 mL). The organic layer was dried with a phase separating cartridge, filtered and evaporated to afford crude product. The crude product was purified by flash silica chromatography, elution gradient 0 to 100% EtOAc in heptane. Pure fractions were evaporated to dryness to afford 8-bromo-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)-9-chloro-2,3-dihydroimidazo[1,2-c]quinazoline (63 mg, 98% yield) as a white solid. 1H NMR (400 MHz; DMSO-d6) δ -0.03 (3H, s, Si-Me), 0.04 (3H, s, Si-Me), 0.77 (9H, s, Si-t-Bu), 3.64 (1H, dd, J = 5.0, 10.3 Hz, CH2O), 3.74 (1H, dd, J = 3.7, 10.3 Hz, CH2O), 3.97 and 4.14 (1H, dd, J = 6.4, 10.7 Hz and 1H, t, J = 10.7 Hz, CH2), 4.30 (1H, m, CH), 7.80 (1H, s, Ar-H), 7.94 (1H, s, Ar-H), 8.03 (1H, s, Ar-H); 13C NMR (101 MHz, DMSO-d6, 30°C) δ -5.36 (2x Si-CH3), 17.75 (C), 25.56 (3x t-Bu-CH3), 48.44 (CH2), 65.06 (CH2O), 66.44 (CH), 119.04 (C), 125.33 (C), 125.94 (CH), 130.08 (C), 131.52 (CH), 146.28 (CH), 146.32 (C), 151.32 (C).

8-Bromo-2-({[tert-butyl(dimethyl)silyl]oxy}methyl)-9-chloroimidazo[1,2-c]quinazoline (9)

KMnO4, SiO2
MeCN, 25°C, 18h
Potassium permanganate (73 mg, 0.47 mmol) was added to 8-bromo-2-((tert-butyl(dimethyl)silyloxy)methyl)-9-chloro-2,3-dihydroimidazo[1,2-c]quinazoline (100 mg, 0.23 mmol) and silica gel 60 (400 mg) in MeCN (5 mL) at 25°C under nitrogen. The resulting mixture was stirred at 25°C for 18 hours. The reaction mixture was filtered through celite and washed with DCM (50 mL). The filtrate was evaporated to afford crude product which was purified by flash silica chromatography, elution gradient 0 to 50% EtOAc in heptane. Pure fractions were evaporated to dryness to afford 8-bromo-2-((tert-butyl(dimethyl)silyloxy)methyl)-9-chloroimidazo[1,2-c]quinazoline (52 mg, 52% yield) as a white solid. 

\[ \text{1H NMR (400 MHz; DMSO-d6)} \delta 0.13 (6H, s, SiMe}_2\), 0.93 (9H, s, Si-\text{-t-Bu}), 4.86 (2H, s, CHO), 7.97 (1H, s, Ar-H), 8.31 (1H, s, Ar-H), 8.44 (1H, s, Ar-H), 9.30 (1H, s, Ar-H). \]

\[ \text{13C NMR (126 MHz, DMSO-d6, 27°C)} \delta -4.79 (2x CH}_3\), 18.52 (C), 26.32 (3x CH}_3\), 60.21 (CH), 111.62 (CH), 119.73 (C), 120.36 (C), 123.12 (CH), 133.19 (C), 133.48 (CH), 140.25 (C), 140.33 (CH), 140.77 (C), 147.23 (C). \]

\[ \text{HRMS m/z calcd for C}_{17}\text{H}_{21}\text{BrClN}_3\text{OSi} \ [\text{M+H}]^+ = 425.3206, \text{ found [M+H]}^+ = 426.0392. \]

\( \text{(8-Bromo-9-chloroimidazo[1,2-c]quinazolin-2-yl)methanol (10)} \)

\[ \text{8-Bromo-2-((tert-butyl(dimethyl)silyloxy)methyl)-9-chloroimidazo[1,2-c]quinazoline (50 mg, 0.12 mmol) in THF (5 mL) at 25°C under nitrogen. The resulting solution was stirred for 15 minutes and evaporated to dryness. The residue was extracted into EtOAc (50 mL) and washed sequentially with water (50 mL) and saturated brine (25 mL). The organic layer was dried with a phase separating cartridge, filtered and evaporated to afford crude product. The crude product was purified by preparative HPLC (Waters XSelect CSH C18 ODB column, 5μ silica, 30 mm diameter, 100 mm length), using increasingly polar mixtures of water (containing by volume 1% NH}_3\text{OH (28-30% in H}_2\text{O)) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford (8-bromo-9-chloroimidazo[1,2-c]quinazolin-2-yl)methanol (19 mg, 28% yield) as a white solid. } \]

\[ \text{1H NMR (400 MHz; DMSO-d6)} \delta 4.66 (2H, d, J = 0.8 Hz, CH}_2\), 7.94 (1H, s, Ar-H), 8.31 (1H, s, Ar-H), 8.45 (1H, s, Ar-H), 9.29 (1H, s, Ar-H). \text{OH unobserved. \text{13C NMR (126 MHz, DMSO, 27°C)} \delta 56.21 (CH}, 109.41 (CH), 117.57 (C), 120.96 (C), 121.17 (CH), 131.15 (C), 131.33 (CH), 138.12 (C), 138.60 (CH), 146.23 (C), 159.37 (C). \]

\[ \text{HRMS m/z calcd for C}_{11}\text{H}_{7}\text{BrClN}_3\text{O} \ [\text{M+H}]^+ = 310.9461, \text{ found [M+H]}^+ = 311.9538. \]
General procedure for one-pot process (4b, c)

1 (b,c) + 2 → 4 (b,c)

4-Chloro-quinazoline 1 (100 mg), 3-methyloxetan-3-amine 2 (1.2 equivalents) and N-ethyl-N-isopropylpropan-2-amine (2 equivalents) were dissolved in MeCN (3 mL) and sealed in a microwave tube. The reaction was purged with nitrogen for 1 minute and then heated to 150°C for 4 hours in the microwave reactor and cooled to 25°C. The reaction was evaporated to dryness and purified by preparative HPLC (Waters XSelect CSH C18 ODB column, 5µ silica, 30 mm diameter, 100 mm length), using decreasingly polar mixtures of water (containing 1% NH₃) and MeCN as eluents. Fractions containing the desired compound were evaporated to dryness to afford product 4.

NMR Spectra

¹H NMR
$^{13}$C NMR
Pure product
Carbon: DMSO (apt/baspin3.Spl5.chem 21)

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LCMS Data

Ethyl 4-chloroquinazoline-6-carboxylate (1a)

Sample Report:

4-Chloro-6-nitroquinazoline (1b)

Sample Report:
4-Chloro-6-methoxyquinazoline (1c)

Sample Report:

- UV Detector: TIC Smooth (Mn. 3x3)

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4-Chloro-6-iodoquinazoline (1d)

Sample Report:

- UV Detector: TIC Smooth (Mn. 3x3)

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HRMS Data

N-(3-Methyloxetan-3-yl)-6-nitroquinazolin-4-amine (3b)

Exact Mass = 260.

7-Bromo-6-chloro-N-(3-methyloxetan-3-yl)quinazolin-4-amine (3f)

Exact Mass = 326.
**Ethyl 2-(hydroxymethyl)-2-methyl-2,3-dihydroimidazo[1,2-c]quinazoline-9-carboxylate (4a).**

Exact Mass = 287.

**Exact mass = 260.**

(2-methyl-9-nitro-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (4b).

**Exact mass = 260.**
(9-Methoxy-2-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (4c)

Exact mass = 245.

(9-Iodo-2-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (4d)

Exact mass = 341.
(2,9-dimethyl-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (4e)
Exact mass = 229.

(8-Bromo-9-chloro-2-methyl-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (4f)
Exact mass = 326.
7-bromo-6-chloro-N-(oxetan-3-yl)quinazolin-4-amine (6)

Exact mass = 312.

(8-Bromo-9-chloro-2,3-dihydroimidazo[1,2-c]quinazolin-2-yl)methanol (7)

Exact mass = 312.
8-Bromo-2-\{\{\text{tert-butyl(dimethyl)silyl}oxy\}\text{methyl}\}-9-chlorimidazo[1,2-c]quinazoline (9)

Exact Mass = 425.

(8-Bromo-9-chlorimidazo[1,2-c]quinazolin-2-yl) methanol (10)

Exact Mass = 310.
One-pot process LCMS data

Reference LCMS of 3b reaction mixture from fully characterised sample in experimental.

LCMS of Table 5 Entry 1b to 3b (3b one-pot process at 50°C).
Reference LCMS of 4b from fully characterised sample in experimental.

LCMS Table 5 Entry 1b to 4b (4b one-pot process at 150°C).
Quantum Mechanics (QM) calculations

QM calculations were run using Jaguar, embedded within Schrodinger’s Maestro package (version 2018-4). Initial structures for the reactant and products were generated via a molecular mechanics-based minimization protocol, before being optimized at the B3-LYP level of theory using a 6-31G*** basis set.

The transition states were found using the AutoTS module in Jaguar. Once again, the B3-LYP level of theory was used alongside the 6-31G*** basis set.