Supporting Information for;

Dihydroquinazolines as a Novel Class of *Trypanosoma brucei* Trypanothione Reductase Inhibitors: Discovery, Synthesis and Characterization of their Binding Mode by Protein Crystallography.

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1.0 Results and discussion; chemistry.

The supporting information provides more detail on some of the synthetic chemistry described in the main text.

1.1 Synthetic routes to 3,4-dihydroquinazoline analogs.

Refer to the main paper for additional discussion relating to the synthetic schemes outlined below.

Analog 9f.

The N-methyl-ethyl analog (9f) was prepared by demethylation of the corresponding N,N-dimethyl analog (9d) by treatment with 1-chloroethyl chloroformate, followed by carbamate deprotection (Scheme S1).

Scheme S1. Synthesis of 3,4-dihydroquinazoline analog 9f.α

α Reagents and conditions: (i) 1) 1-chloroethyl chloroformate, DCE, 0-80°C, 1 h; 2) MeOH, 65°C, 2 h.

Analog 21.

Synthesis of the alcohol containing analog 21 proved problematic due to over reduction of the 3,4-dihydroquinazoline to the 1,2,3,4-tetrahydroquinazoline 22 (mixture of diastereoisomers) by excess NaBH₄ in the one pot reduction/cyclization reaction (Scheme S2). Therefore, imine 20 was reduced following a modified set of conditions to give dihydroquinazoline 21 in low yield.

Scheme S2. Synthetic route to the preparation of the alcohol-containing analog 21.α

α Reagents and conditions: (i) Ethanolamine, silica-supported TsOH, 150°C, 1.5 h; (ii) NaBH₄, MeOH, 4°C, 48 h.

Analogs 11a-h and 13a-h.

The Boc protected analogs 11a and 13a were prepared using the established methodology as outlined in Schemes 1 and S3. For the synthesis of 11a the intermediate imine 10 was not isolated, but instead reacted on directly in the one pot reduction/cyclization transformation.
Scheme S3. Synthetic route for the preparation of 3,4-dihydroquinazoline amide analogs (11b-h & 13b-h). For details of individual substituents see Table 3.

Reagents and conditions: (i) H$_2$NCH$_2$CH$_2$NHBoc, EtOH, 160°C (MW), 2 h; (ii) 4-(2-amino-ethyl)-1-BOC-piperazine, EtOH, 160°C (MW), 1 h; (iii) NaBH$_4$, EtOH, 78°C, 24 h; (iv) 1) HCl, THF/Dioxane, 25°C, 2.5 h; 2) ClCOR, DMAP, Pyridine, CH$_2$Cl$_2$, 40°C, 16 h.

Analog 15b-d.

The synthesis of R$_6$ halogen analogs 15c and 15d via the general route (Scheme 1) required the preparation of the 2-amino-5-halo-benzophenone starting materials 2c ($R_6$=Br) and 2d ($R_6$=I). Treatment of 2-aminobenzophenone (2b) with N-bromosuccinimide (NBS) in the presence of silica-supported TsOH resulted in bromination at the 5 position exclusively$^1$ giving 2c in good yield. Compound 2d was prepared in an identical fashion by employing NIS. Both 2c and 2d were subsequently converted into 15c and 15d respectively as outlined in Scheme S4. The des-halo analog 15b ($R_6$=H) was similarly prepared from 2b in three steps (Scheme S4).
Scheme S4. Synthetic route for the preparation of 3,4-dihydroquinazoline analogs with differing halogen substitutions at C6 (15b-d).a For details of individual substituents see Table 4.

\[ \text{Reagents and conditions: (i) NBS (for 2c), or NIS (for 2d), silica-supported TsOH, MeCN/Et}_2\text{O, 25°C, 30 min; (ii) AcCl, DMAP, pyridine, CH}_2\text{Cl}_2, 25°C, 16 h; (iii) 1-(2-aminoethyl)piperidine, EtOH, 160°C (MW), 2 h; (iv) NaBH}_4, EtOH, 78°C, 16 h. \]

Analog 18.
The synthesis of the 8-bromo-6-chloro analog 18 required the preparation of 2-amino-3-bromo-5-chlorobenzophenone 2e, which was achieved by bromination of 2-amino-5-chlorobenzophenone (2a) using NBS (Scheme S5). Compound 2e was converted to 18 using the transformations outlined in the general route (Scheme 1, Scheme S5).

Scheme S5. Synthetic route for the preparation of a 3,4-dihydroquinazoline analog containing a bromine at C8 (18).a

\[ \text{Reagents and conditions: (i) NBS, CH}_2\text{Cl}_2, 25°C, 16 h; (ii) AcCl, DMAP, pyridine, CH}_2\text{Cl}_2, 25°C, 16 h; (iii) H}_2\text{N(CH}_2)_3\text{N(CH}_3)_2, EtOH, 160°C (MW), 2 h; (iv) NaBH}_4, EtOH, 78°C, 16 h. \]

Analog 34.
The attempted reduction of 31h (R₄=Bn) did not give the desired dihydroquinazoline 34, but rather resulted in a complex mixture of products containing an E/Z mixture of the olefin derived from elimination of water (37) (Scheme S6).

**Scheme S6.** Attempted synthesis of analog 34 using the shortened synthetic strategy for the preparation of 3,4-dihydroquinazoline analogs substituted at R₄.  

\[
\begin{align*}
\text{Cl} & \quad \text{i} \quad \text{Cl} & \quad \text{CH} & \quad \text{N} & \quad \text{CH} & \quad \text{N} & \quad \text{CH} & \quad \text{N} & \quad \text{Cl} \\
& \quad \text{30} & \quad \text{31h} & \quad \text{37} & \quad \text{34}
\end{align*}
\]

\(^a\) Reagents and conditions: (i) BnMgCl, THF, 0-25°C, 2-4 h; (ii) BF₃·OEt, HSiEt₃, CH₂Cl₂, 25°C, 16 h.

Analog 34 was instead prepared using a modification of the standard route (Scheme 1). The synthesis used the same chemical transformations, but they were performed in a different order (Scheme S7).

**Scheme S7.** Synthetic route for the preparation of a 3,4-dihydroquinazoline analog containing a benzyl substitution at C4 (34).  

\[
\begin{align*}
\text{Cl} & \quad \text{i} \quad \text{Cl} & \quad \text{CH} & \quad \text{N} & \quad \text{CH} & \quad \text{N} & \quad \text{Cl} \\
& \quad \text{26g} & \quad \text{33} & \quad \text{34}
\end{align*}
\]

\(^a\) Reagents and conditions: (i) 1) 1-(2-aminoethyl)piperidine, EtOH, 4Å molecular sieves, 25°C, 10 days; 2) NaBH₄, EtOH, 25°C, 16 h; (ii) 1) AcCl, K₂CO₃, MeCN, 25°C, 16 h; 2) EtOH, 140°C, 4.5 h.

**Analogs 35 and 36.**

The methoxyphenyl analogs (32e & 29d) were converted into the corresponding phenol analogs (35 & 36) by treatment with BBr₃ (Scheme S8).

**Scheme S8.** Synthetic route for the preparation of a 3,4-dihydroquinazoline analogs containing a phenol substitution at C4.  

\[
\begin{align*}
\text{Cl} & \quad \text{i} \quad \text{Cl} & \quad \text{CH} & \quad \text{N} & \quad \text{CH} & \quad \text{N} & \quad \text{Cl} \\
& \quad \text{R=CH₃, R=H 32c} & \quad \text{R=H, R=CH₃ 29d} & \quad \text{R=CH₃, R=H 35} & \quad \text{R=H, R=OH 36}
\end{align*}
\]

\(^a\) Reagents and conditions: (i) BBr₃, CH₂Cl₂, -20°C, 2-3 h.
2.0 Biological Assays.

2.1 Coupled TryR Assay.
A brief description of the coupled TryR employed in this study is given in Figure S1.

Figure S1. The coupled spectrophotometric assay used for measuring TyrR activity in this study. Trypanothione disulfide (T[S]₂) is reduced to trypanothione dithiol (T[SH]₂) by the action of TryR. T[SH]₂ is then non-enzymatically oxidised back to T[S]₂ by 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB, Ellman’s reagent) giving the thionitrobenzoate anion (TNB) which can be monitored at 412 nm.

![Coupled TryR Assay](image)

2.2 Mode of inhibition studies.
The mode of inhibition of the TryR inhibitors was determined by measuring the TryR reaction rate across a 12-point range of T[S]₂ concentrations at three different inhibitor concentrations (and in the absence of inhibitor). See the experimental section of the main paper for a brief description of the protocol used. A representative example of a mode of inhibition study is given in Figure S2.

Figure S2 Kinetic analysis of inhibition of *T. brucei* TryR with respect to trypanothione disulfide.
Panel A: data for analog 1a globally fitted to a linear competitive inhibition model is presented as a Lineweaver-Burke transformation (Kᵢ = 0.92 ± 0.06 μM). Inhibitor concentrations: open circles, closed circles, open squares, closed squares are 0, 1.12, 2.24 and 4.49 μM, respectively. Panel B: data for analog 29a globally fitted to a linear mixed inhibition model (Kᵢ = 0.19 ± 0.01 μM; Kᵢ' =1.5 ± 0.3 μM). Inhibitor concentrations: open circles, closed circles, open squares, closed squares are 0, 0.078, 0.156 and 0.312 μM, respectively.

![Mode of inhibition studies](image)
2.3. Structure activity relationship.

The SAR determined from screening analogs 6a-k, 9a-f, 11a-h, 13a-h, 15c, 16a-f, 18, 19 and 21 (Tables 2-4) is summarized in Figure S3.

**Figure S3.** SAR derived from screening the analogs described in Tables 2-4.
3.0 Results and discussion; protein crystallography.

3.1 Crystal parameters and refinement statistics.

The crystallographic data and refinement statistics of non-liganded TryR and the TryR-ligand complexes is given in Table S1.

Table S1. Crystal parameters and refinement statistics.

| Co-factors /Ligands | - | NADPH | NADPH [SH]$_2$ | 1a | 6a | 11e | 13e | 29a |
|---------------------|---|--------|----------------|----|----|-----|-----|-----|
| Resolution range (Å)| 46.9 – 2.1 | 19.9 – 2.5 | 19.9 – 2.2 | 46.7 – 2.8 | 46.8 – 2.5 | 46.0 – 2.1 | 46.8 – 2.1 | 19.9 – 1.9 |
| Total reflections   | 461328 | 252014 | 389093 | 106275 | 312315 | 521552 | 354504 | 663367 |
| Unique reflections  | 123389 | 69130 | 109888 | 42552 | 72412 | 117749 | 112447 | 160708 |
| Redundancy          | 3.7 | 3.6 | 3.5 | 2.5 | 4.3 | 4.4 | 3.2 | 3.9 |
| Completeness        | 97.7 (78.2) | 93.3 (85.6) | 99.4 (99.3) | 80.5 (79.9) | 96.7 (91.4) | 95.3 (87.7) | 90.2 (79.6) | 99.1 (95.1) |
| I/σI                | 13.8 (3.1) | 14.8 (3.6) | 14.9 (3.4) | 10.8 (4.4) | 9.4 (3.2) | 15.9 (3.2) | 14.5 (3.7) | 9.6 (3.0) |
| R$_{merge}$         | 11.7 (42.9) | 10.9 (39.6) | 11.9 (46.3) | 12.9 (33.1) | 13.7 (42.8) | 12.0 (46.4) | 11.1 (38.5) | 11.2 (32.9) |
| R                   | 15.9 (22.5) | 17.9 (23.0) | 17.2 (20.1) | 16.4 (19.4) | 16.3 (21.2) | 16.8 (21.7) | 16.5 (20.3) | 18.4 (34.2) |
| R$_{free}$          | 20.8 (27.5) | 25.1 (33.3) | 22.6 (26.8) | 21.9 (31.4) | 23.6 (31.7) | 22.9 (26.9) | 23.2 (30.4) | 24.6 (39.4) |
| Reflections used    | 119634 | 68911 | 103837 | 41838 | 71078 | 117205 | 111489 | 152912 |
| Test set            | 6297 | 3627 | 5466 | 2203 | 3741 | 6169 | 5868 | 8048 |
| rmsd bond length    | 0.024 | 0.017 | 0.023 | 0.017 | 0.017 | 0.023 | 0.024 | 0.022 |
| rmsd bond angles    | 1.97 | 1.73 | 1.97 | 1.80 | 1.68 | 1.90 | 1.96 | 1.99 |
| Ramachandran        | Allowed regions (%) | 99.8 | 99.8 | 99.8 | 99.6 | 99.8 | 99.8 | 99.8 |

Note, all of the structures contain FAD.

3.2 Discussion of overall TbTryR structure and comparison to other species and homologs.

The structure of TryR from Trypanosoma cruzi, Crithidia fasciculata and Leishmania infantum are already known, along with the homolog glutathione reductase (GR) from a number of species. Recently, the apo-structure of TryR from Trypanosoma brucei was also described, obtained under different crystallization conditions. A sequence alignment (Figure S4) between the various parasite TryRs shows identities of 82 % between T. brucei and T. cruzi, 70 % between T. brucei and C. fasciculata, 66 % between T. brucei and L. infantum, and around 40 % between TbTryR and human GR. Given the degree of sequence and structural homology with the other TryR structures, only a brief description of the overall structure is presented here. More detailed descriptions of the overall structure including FAD and NADPH binding sites can be found in the previous studies.

As would be expected, when comparing the structure of TbTryR with TryR from T. cruzi, C. fasciculata, and L. infantum, a high level of homology is seen. Overlaying T. brucei apo-TryR (PDB code 2woi) onto TryR from T. cruzi, C. fasciculata and L. infantum gives RMSDs of 0.54 Å.
0.62 Å, and 0.67 Å over 480, 483, and 482 Cα atoms, respectively. The fit with human GR, with its lower sequence identity and various insertions and deletions within the structure, gives an RMSD of 1.1 Å over 438 Cα atoms.

The crystal structure of apo-TryR comprises 1948 residues in 4 subunits (two dimers in the asymmetric unit), 4 FAD molecules, and 1249 waters modelled as oxygen atoms (Figure S5). In all 4 subunits, several residues at the N- and C-termini are missing, probably as a result of flexibility and, in addition, further residues have been modelled as alanines as the electron density for the side chains was not prominent. The N-terminal residues numbered -2, -1 and 0 are remnants of the 6-His tag linker following thrombin cleavage. These are visible in some subunits. The model described was refined to R and Rfree values of 16.3 and 20.8 % respectively. Further model refinement statistics are presented in Table S1. When overlaid, the 4 subunits in the asymmetric unit have RMSDs of 0.38 Å (A and B), 0.46 Å (A and C), 0.43 Å (A and D), 0.27 Å (B and C), 0.28 Å (B and D), 0.30 Å (C and D) over 470 Cα atoms. As with other TryR structures, T. brucei TryR exists as a homodimer, and has approximate dimensions of 100 × 57 × 61 Å. Each disulfide-containing active site is found at the subunit interface. As previously described, the TryR subunit comprises three domains, an FAD binding domain, an NADPH binding domain, and a third domain that contains the inter-subunit interface. The two dimers in the asymmetric unit comprise subunits A and B, and C and D. They come into close proximity via residues in loop β11-θ4 (residues 170-174) and residues 257-260 in β16. No direct hydrogen bonds are made between subunits A and C, but are via a network of water molecules. As each of the two dimer structures is well conserved in the asymmetric unit, dimer AB will be used as representative in the following structural discussion.

A surface area of 3300 Å² is involved in the TbTryR dimer interface, which involves 90 residues and 35 hydrogen bonds, as calculated by the protein interface, surface and assemblies server, PISA. For TbTryR, the secondary structure composition for each subunit consists of 10 α-helices, six 310-helices, and 29 β-strands (Figure S5). The strands together form 7 β-sheets. Three of these are parallel and the other four are anti-parallel (see Figure S5). The functional dimer contains two active sites. Each active site is composed of residues contributed by both subunits in the dimer as will be described later. Cys52 and Cys57 form the redox active disulfide at one end of the large active site cleft near to the isoalloxazine ring of the cofactor FAD.
Figure S4. Sequence alignment of TryR from four trypanosomatid species and human GR, with secondary structure annotation according to TryR from *T. brucei*. Sequence similarities are shaded from black (identical across all sequences) to grey (conserved in at least 2 sequences).
Figure S5. Ribbon diagram of *T. brucei* TryR with secondary structure annotations on subunit A. α-helices are in red, $3_{10}$-helices in green ($\theta$), and β-strands in purple.
3.3 Comparison of \textit{T. brucei} TryR cofactor and substrate binding sites between species.

When comparing the amino acid main chain and side chain positions within the active site of various TryRs, it is evident that they are well conserved. The active site cleft is large, with approximate dimensions of $20 \times 15 \times 15 \text{Å}^3$. Most residues forming the FAD-binding, NADPH-binding, and substrate binding sites are conserved in all species. In the FAD-binding site, the only substitution is Ala46 to Ser47 in \textit{T. cruzi} TryR, which allows one extra hydrogen bond to the adenine ribose of FAD. Phe198 is substituted with Tyr197 in \textit{C. fasciculata} TryR, adding an additional hydrogen bonding interaction with the isoalloxazine ring of FAD. There are no differences in the NADPH-binding sites (see PDB model 2wow). Comparing the active site of TryR from \textit{T. brucei} to that of \textit{T. cruzi}, there are no residue differences within the deep cleft. The important residues interacting with T[S]$_2$ are all conserved. On the periphery of the cleft, there are a few differences. Gly112 is replaced by Glu113, Asn115 by Arg116, Gly342 by Ala342, and Asn402 by Arg402 in the \textit{T. cruzi} enzyme. However, these residues are more than 7 Å from the substrate in \textit{T. cruzi} TryR. The overlay of \textit{T. brucei} TryR with the \textit{T. cruzi} TryR/T[S]$_2$ structure shows that the active site residues are in the same positions and therefore the T[S]$_2$ binding properties of \textit{T. brucei} TryR were expected to be identical to those of the \textit{T. cruzi} enzyme. We have now solved the structure of \textit{T. brucei} TryR in complex with trypanothione dithiol (T[SH]$_2$) (PDB code 2wow) in order to identify any similarities between substrate binding in the two species. The differences are most likely due to \textit{T. cruzi} and \textit{T. brucei} TryR binding trypanothione in the disulfide and dithiol states, respectively.

3.4 Binding of trypanothione in the \textit{Tb}TryR active site.

Structure 2wow shows the product T[SH]$_2$ bound in the active site. Trypanothione disulfide (T[S]$_2$) and NADPH were added to the crystals prior to collection and the structure clearly shows the dithiol form of trypanothione as expected. The flexibility of T[SH]$_2$ hampered the model-building process and one half of the molecule is observed to exist in several different conformations as a result (Figure S6). We have modelled the two most prevalent conformations. The other half of T[SH]$_2$ appears to be bound in a stable conformation. Using the same nomenclature to describe the Glu, Cys, Gly, and Spm moieties as in Bond \textit{et al.},$^8$ γGlu-I interacts with Ser470' OH and Glu467' O$\Sigma$1 [the prime symbol (') denoting a residue from subunit B]. Cys-I forms a mixed disulfide with \textit{T. brucei} TryR Cys52Sγ at a distance of 2.4 Å, and also a hydrogen bond between Cys-I O and Ser14. Gly-I O hydrogen bonds to Tyr110 OH and N1 of Spm binds to Glu18. This half of the Spm moiety forms hydrophobic interactions with the hydrophobic region of TryR created by Trp21 and Met113. The flexible half of T[SH]$_2$ starts halfway along the Spm, pivoting about one of the nitrogen atoms. One conformation closely resembles T[S]$_2$ in the \textit{T. cruzi} TryR structure. Gly-II and Cys-II sit out near the opening of the active site and make no interactions with the enzyme. Glu-II O hydrogen bonds to Glu466'. Glu-II Oε1 makes a water-mediated hydrogen bond to Lys61, whilst Oε2 interacts with Ser464' via a water molecule. In the second modelled conformation, Gly-II and Cys-II again make no bonding interactions with the enzyme. Glu-II Oε1 interacts with Ser395' O and backbone N and Oε2 interacts with Met393' O.
Figure S6. (a) Stick diagram of TbTryR active site with trypanothione bound in two conformations. Trypanothione is shown in yellow with the second conformation in orange. Oxygen atoms are in red, nitrogens in blue, and sulfurs in yellow. Waters are shown as blue spheres and hydrogen bonds as black dotted lines. (b) Trypanothione stick model with nomenclature as found in Bond et al.5
3.5 Comparison to existing ligand bound TryR structures.

Previous structural studies have reported the covalent complex between *T. cruzi* TryR and quinacrine mustard\(^9\) (PDB 1gxf) and the non-covalent interaction between *T. cruzi* TryR and mepacrine\(^10\) (coordinates unavailable) (Figure S6). The covalently bound quinacrine mustard structure is distinct in that two inhibitor molecules bind in the active site, with hydrophobic stacking between each ligand and with the Trp side chain. The acridine moiety of the compound binds in the hydrophobic region created by the conserved Trp, Tyr and Met residues accentuating this region as important when targeting potential inhibitors. Interestingly, this acridine ring stacks against the Trp side chain, whereas the dihydroquinazoline ring of compound 1a sits perpendicular, but a nitrogen atom in both ring systems is positioned such that if protonated, it would hydrogen bond to the nearby Glu18 (Glu19 in the *T. cruzi* structure). In contrast to compounds 1a, 6a, 11e, 13e and 29a where the C6-halogen sits tightly within the active site, the chlorine atom of quinacrine mustard is directed out into solvent some 5.5 Å from the nearest protein atoms. Although limited by the quality of electron density, the published *T. cruzi* TryR-mepacrine structure\(^10\) again highlights the importance of the hydrophobic wall created by the conserved tryptophan and methionine (Trp21 and Met113 in *T. brucei*) in binding the acridine ring. In addition, the alkylamino side chain of mepacrine is proposed to hydrogen bond to the conserved glutamate (Glu18 in *T. brucei*). We have shown that these same residues are essential in the binding of dihydroquinazoline-based inhibitors in *T. brucei* TryR.

**Figure S7.** The structures of mepacrine (quinacrine), quinacrine mustard and 1a (an example of a 3,4-dihydroquinazoline-based inhibitor).
4.0 Experimental section.

4.1 Chemistry.
See the main paper for details of scientific instruments and chemical suppliers used throughout this study.

4.1.1 Synthesis of \textit{N}3-alkyl/benzyl substituted collection (analog 6b-k).
See Scheme 1 for the synthetic route to these analogs. See the main paper for the synthesis of analog 6a.

\textit{(R/S)-6-Chloro-2-methyl-3-phenethyl-4-phenyl-3,4-dihydroquinazoline (6b)}.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme_6b.png}
\end{center}

Prepared in three steps from 3a and 2-phenethylamine following general methods B, C1 and D. The final product was purified by flash column chromatography (MeOH/CH$_2$Cl$_2$ 0:100 $\rightarrow$ 20:80) to give a clear semi-solid (22 mg, 7\% over three steps).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.78-7.74 (m, 1H, ArH), 7.44-7.40 (m, 3H, 3$\times$ArH), 7.34-7.30 (m, 3H, 3$\times$ArH), 7.24-7.21 (m, 3H, 3$\times$ArH), 7.11-7.09 (m, 2H, 2$\times$ArH), 6.76 (d, 1H, $J = 2.0$ Hz, H-5), 5.44 (s, 1H, H-4), 3.76-3.70 (m, 1H, C$_{HH}$H), 3.55-3.49 (m, 1H, CH$_2$H), 2.99-2.89 (m, 2H, CH$_2$), 2.55 (s, 3H, CH$_3$). LRMS (ES+): $m/z$ (%) 361 (100) [\textsuperscript{35}Cl M+H]$^+$, 363 (36) [\textsuperscript{37}Cl M+H]$^+$. HRMS (ES+): calcd for C$_{23}$H$_{22}$ClN$_2$ [M+H]$^+$ 361.1466, found 361.1449 (4.85 ppm).

\textit{(R/S)-6-Chloro-3-(2-methoxybenzyl)-2-methyl-4-phenyl-3,4-dihydroquinazoline (6c)}.

\begin{center}
\includegraphics[width=0.8\textwidth]{scheme_6c.png}
\end{center}

Prepared in three steps from 3a and 2-methoxybenzylamine following general methods B, C1 and D. The final product was purified by triturating from Et$_2$O (45 mg, 22\% over three steps).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.66 (d, 1H, $J = 8.5$ Hz, ArH), 7.47-7.42 (m, 4H, 4$\times$ArH), 7.26-7.21 (m, 3H, 3$\times$ArH), 7.12 (dd, 1H, $J = 7.5$, 1.5 Hz, ArH), 7.04 (ddd, 1H, $J = 7.5$, 7.5, 1.0 Hz, ArH), 6.95 (d, 1H, $J = 8.5$ Hz, ArH), 6.77 (d, 1H, $J = 2.0$ Hz, H-5), 5.51 (s, 1H, H-4), 4.90 (d, 1H, $J = 15.0$ Hz, CH$_2$H), 4.16 (d, 1H, $J = 15.0$ Hz, CH$_2$H), 3.84 (s, 3H, OCH$_3$), 2.87 (s, 3H, CH$_3$). LRMS (ES+): $m/z$ (%) 377 (100) [\textsuperscript{35}Cl M+H]$^+$, 379 (36) [\textsuperscript{37}Cl M+H]$^+$. HRMS (ES+): calcd for C$_{23}$H$_{22}$ClN$_2$O [M+H]$^+$ 377.1415, found 377.1408 (1.82 ppm).

\textit{(R/S)-6-Chloro-3-(2-fluorobenzyl)-2-methyl-4-phenyl-3,4-dihydroquinazoline (6d)}.
Prepared in two steps from 3a and 2-fluorobenzylamine following general methods B, and C2. The final product was purified by flash column chromatography (MeOH/CH$_2$Cl$_2$ 0:100 → 10:90) to give an off-white solid (19 mg, 4% over two steps).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.55-7.42 (m, 8H, 8×ArH), 7.34-7.31 (m, 1H, ArH), 7.31-7.25 (m, 2H, 2×ArH), 6.88 (s, 1H, H-5), 5.50 (s, 1H, H-4), 4.91 (d, 1H, $J$ = 16.5 Hz, CH/H), 4.38 (d, 1H, $J$ = 16.5 Hz, CH/H), 2.50 (s, 3H, CH$_3$). 19F NMR (470 MHz, CDCl$_3$): $\delta$ -117.4 (CF). LRMS (ES+): m/z (%) 365 (100) $[^{35}\text{Cl M+H}]^+$, 367 (33) $[^{37}\text{Cl M+H}]^+$. HRMS (ES+): calcd for C$_{22}$H$_{19}$ClF$_2$N$_2$ [M+H]$^+$ 365.1215, found 365.1213 (0.70 ppm).

(R/S)-6-Chloro-3-(3-chlorobenzyl)-2-methyl-4-phenyl-3,4-dihydroquinazoline (6e).

Prepared in two steps from 3a and 2-fluorobenzylamine following general methods B, and C2. The final product was purified by flash column chromatography (MeOH/CH$_2$Cl$_2$ 0:100 → 10:90) to give a yellow semi-solid (53 mg, 8% over two steps).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.38-7.32 (m, 5H, 5×ArH), 7.29-7.26 (m, 2H, 2×ArH), 7.21 (s, 1H, ArH), 7.14-7.10 (m, 3H, 3×ArH), 6.71 (s, 1H , ArH), 5.32 (s, 1H, H-4), 4.72 (d, 1H, $J$ = 16.5 Hz, CH/H), 4.08 (d, 1H, $J$ = 16.5 Hz, CH/H), 2.31 (s, 3H, CH$_3$). LRMS (ES+): m/z (%) 381 (100) $[^{35}\text{Cl M+H}]^+$, 383 (33) $[^{37}\text{Cl M+H}]^+$. HRMS (ES+): calcd for C$_{22}$H$_{19}$ClF$_2$N$_2$ [M+H]$^+$ 381.0920, found 381.0902 (4.79 ppm).

(R/S)-6-Chloro-2-methyl-4-phenyl-3-(3-(trifluoromethyl)benzyl)-3,4-dihydroquinazoline (6f).

N-(2-benzoyl-4-chlorophenyl)acetamide (3a) (548 mg, 2.0 mmol) and 3-(trifluoromethyl)benzylamine (420 mg, 2.4 mmol) in EtOH (5 mL) were reacted according to method B. The reaction mixture was applied directly to a silica column (EtOAc/hexanes 5:95 → 20:80), to give a mixture of product 4f and 3a. The mixture was dissolved in EtOH (20 mL) and reacted according to method C2. The product was purified by use of a gravity SCX-2 cartridge (Isolute®), followed by flash column chromatography (EtOAc/hexanes 50:50 → 100:0) to give a clear solid (48 mg, 6% over 2 steps).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.59 (d, 1H, $J$ = 7.5 Hz, ArH), 7.51 (dd, 1H, $J$ = 7.5, 7.5 Hz, ArH), 7.45-7.42 (m, 2H, 2×ArH), 7.37-7.30 (m, 3H, 3×ArH), 7.25-7.23 (m, 2H, 2×ArH), 7.14-7.10 (m,
2H, 2×ArH), 6.69 (d, 1H, J = 2.0 Hz, H-5), 5.28 (s, 1H, H-4), 4.77 (d, 1H, J = 16.5 Hz, CHH), 4.17 (d, 1H, J = 16.5 Hz, CHH), 2.31 (s, 3H, CH3). 19F NMR (470 MHz, CDCl3): δ -62.6 (CF3). LRMS (ES+): m/z (%) 415 (100) [35Cl M+H]+, 417 (36) [37Cl M+H]+. HRMS (ES+): calcd for C23H19ClF3N2[M+H]⁺ 415.1183, found 415.1188 (-1.00 ppm).

(R/S)-3-((6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)methyl)-N,N-dimethylaniline (6g).

Prepared in two steps from 3a and 3-(aminomethyl)-N,N-dimethylaniline following general methods B, and C2. The final product was purified by flash column chromatography (MeOH/CH2Cl2 0:100 → 20:80) to give an off-white semi-solid (70 mg, 11% over two steps).

1H NMR (500 MHz, CDCl3): δ 7.38-7.24 (m, 6H, 6×ArH), 7.13-7.09 (m, 2H, 2×ArH), 6.72-6.68 (m, 2H, 2×ArH), 6.61 (d, 1H, J = 7.5 Hz, ArH), 6.52 (s, 1H, Ar H), 5.40 (s, 1H, H-4), 4.76 (d, 1H, J = 16.0 Hz, CHH), 4.04 (d, 1H, J = 16.0 Hz, CHH), 2.94 (s, 6H, N(CH3)2), 2.34 (s, 3H, CH3).

LRMS (ES+): m/z (%) 390 (100) [35Cl M+H]+, 392 (33) [37Cl M+H]+. HRMS (ES+): calcd for C24H25ClN3[M+H]⁺ 390.1732, found 390.1731 (0.22 ppm).

(R/S)-6-Chloro-2-methyl-3-(4-methylbenzyl)-4-phenyl-3,4-dihydroquinazoline (6h).

Prepared in three steps from 3a and 4-methylbenzylamine following general methods B, C1 and D. The final product was purified by triturating from Et2O (40 mg, 15% over three steps).

1H NMR (500 MHz, CDCl3): δ 7.76 (d, 1H, J = 8.5 Hz, ArH), 7.46-7.44 (m, 3H, 3×ArH), 7.27-7.22 (m, 5H, 5×ArH), 7.08-7.06 (m, 2H, 2×ArH), 6.76 (d, 1H, J = 2.0 Hz, H-5), 5.51 (s, 1H, H-4), 4.85 (d, 1H, J = 16.0 Hz, CHH), 4.21 (d, 1H, J = 16.0 Hz, CHH), 2.85 (s, 3H, CH3), 2.40 (s, 3H, ArCH3).

LRMS (ES+): m/z (%) 361 (100) [35Cl M+H]+, 363 (36) [37Cl M+H]+. HRMS (ES+): calcd for C23H22ClN2[M+H]⁺ 361.1466, found 361.1456 (2.65 ppm).

(R/S)-6-Chloro-3-(4-chlorobenzyl)-2-methyl-4-phenyl-3,4-dihydroquinazoline (6i).

Prepared in three steps from 3a and 4-chlorobenzylamine following general methods B, C1 and D. The final product was purified by flash column chromatography (MeOH/CH2Cl2 0:100 → 20:80) to give a clear semi-solid (70 mg, 2.5% over three steps).

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**1H NMR (500 MHz, CDCl₃):** δ 7.37-7.30 (m, 5H, 5×ArH), 7.25-7.23 (m, 2H, 2×ArH), 7.17-7.15 (m, 2H, 2×ArH), 7.13-7.09 (m, 2H, 2×ArH), 6.69-6.68 (m, 1H, ArH), 5.28 (s, 1H, H-4), 4.72 (d, 1H, J = 16.5 Hz, CH₂), 4.06 (d, 1H, J = 16.5 Hz, CH₂), 2.31 (s, 3H, CH₃). LRMS (ES+): m/z (%) 381 (100) [35ClM+H]+, 383 (67) [37Cl37Cl M+H]+. HRMS (ES+): calcd for C_{22}H_{19}Cl₂N₂ [M+H]⁺ 381.0920, found 381.0931 (-2.98 ppm).

**(R/S)-6-Chloro-2-methyl-4-phenyl-3-(4-(trifluoromethyl)benzyl)-3,4-dihydroquinazoline (6j).**

Prepared in two steps from 3a and 4-trifluoromethylbenzylamine following general methods B, and C2. The final product was purified by flash column chromatography (EtOAc/hexane 0:100 → 60:40) to give a white solid (17 mg, 2.5% over two steps).

**1H NMR (500 MHz, CDCl₃):** δ 7.65-7.63 (m, 2H, 2×ArH), 7.38-7.32 (m, 5H, 5×ArH), 7.26-7.24 (m, 2H, 2×ArH), 6.69 (d, 1H, J = 2.0 Hz, H-5), 5.29 (s, 1H, H-4), 4.79 (d, 1H, J = 17.0 Hz, CHH), 4.17 (d, 1H, J = 17.0 Hz, CHH), 2.30 (s, 3H, CH₃). **19F NMR (470 MHz, CDCl₃):** δ -62.6 (CF₃). LRMS (ES+): m/z (%) 415 (100) [35Cl M+H]+, 417 (36) [37Cl M+H]+. HRMS (ES+): calcd for C_{23}H_{19}ClF₃N₂ [M+H]⁺ 415.1183, found 415.1202 (-4.47ppm).

**N-(4-Chloro-2-((ethylimino)(phenyl)methyl)phenyl)acetamide (4k).**

Ethylamine (2.0M solution in MeOH, 1 mL, 2 mmol) was added to a solution of N-(2-benzoyl-4-chlorophenyl)acetamide (3a) (274 mg, 1 mmol) in EtOH (2 mL) and heated to 160°C in a microwave reactor for 1 h. Upon cooling the product crystallised from the crude reaction mixture and was subsequently recovered by filtration and washed with cold EtOH (2×5 mL) to give a white crystalline solid (117 mg, 39%).

**1H NMR (500 MHz, CDCl₃):** δ 13.71 (br s, 1H, NH), 8.71 (d, 1H, J = 9.0 Hz, H-6), 7.52-7.46 (m, 3H, 3×ArH), 7.29 (dd, 1H, J = 9.0, 2.5 Hz, H-5), 7.12-7.10 (m, 2H, 2×ArH), 6.84 (d, 1H, J = 2.5 Hz, H-3), 3.33 (q, 2H, J = 7.0 Hz, CH₂), 2.22 (s, 3H, CH₃), 1.31 (t, 3H, CH₃). **13C NMR (125 MHz, CDCl₃):** δ 170.9 (C), 169.3 (C), 139.2 (C), 135.5 (C), 132.1 (CH), 130.7 (CH), 129.0 (CH), 128.9 (CH), 127.2 (CH), 126.6 (C), 124.2 (C), 121.6 (CH), 48.0 (CH₂), 25.3 (CH₃), 16.5 (CH₃). LRMS (ES+): m/z (%) 301 (100) [35Cl M+H]+, 303 (48) [37Cl M+H]+.

**(R/S)-6-Chloro-3-ethyl-2-methyl-4-phenyl-3,4-dihydroquinazoline (6k).**
Prepared from 4k (105 mg, 0.35 mmol) according to general method C2. The final product was purified by flash column chromatography (MeOH/CH₂Cl₂ 0:100 → 10:90) to give a white solid (40 mg, 40%).

1H NMR (500 MHz, CDCl₃): δ 7.35-7.31 (m, 2H, 2×ArH), 7.30-7.26 (m, 3H, 3×ArH), 7.10-7.06 (m, 2H, 2×ArH), 6.76-6.75 (m, 1H, H-5), 5.48 (s, 1H, H-4), 3.45-3.38 (m, 1H, C¼H), 3.16-3.09 (m, 1H, C¼H), 2.30 (s, 3H, CH₃), 1.15 (dd, 3H, J = 7.5, 7.5 Hz, CH₃). LRMS (ES⁺): m/z (%) 285 (100) [35Cl M+H]+, 287 (33) [37Cl M+H]+. HRMS (ES⁺): calcd for C₁₇H₁₈ClN₂ [M+H]+ 285.1153, found 285.1145 (2.75ppm).

4.1.2 Synthesis of compounds containing a basic N3 substitution (analogs 9b-e).
See Scheme 1 for the synthetic route to these analogs. The synthesis of related analog 9a is described in the main paper.

(R/S)-4-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)morpholine (9b).

Prepared in three steps from 3a and 4-(2-aminoethyl)morpholine following general methods B, C1 and D. The final product was purified by flash column chromatography (MeOH/CH₂Cl₂ 0:100 → 20:80) to give a clear semi-solid (28 mg, 5% over three steps).

1H NMR (500 MHz, CDCl₃): δ 7.35-7.27 (m, 5H, 5×ArH), 7.08 (dd, 1H, J = 8.5, 2.5 Hz, H-7), 7.04 (d, 1H, J = 8.5 Hz, H-8), 6.76 (d, 1H, J = 2.5 Hz, H-5), 5.54 (s, 1H, H-4), 3.68-3.66 (m, 4H, 2×CH₂), 3.46 (ddd, 1H, J = 14.0, 8.0, 6.0 Hz, CH/H), 3.19 (ddd, 1H, J = 14.0, 8.0, 6.0 Hz, CH/H), 2.55 (ddd, 1H, J = 13.0, 8.0, 6.0 Hz, CH/H), 2.46-2.37 (m, 5H, CH/H & 2×CH₂), 2.30 (s, 3H, CH₃). LRMS (ES⁺): m/z (%) 185.5 (15) [35Cl M+2H]⁺, 370 (100) [35Cl M+H]⁺, 372 (38) [37Cl M+H]⁺. HRMS (ES⁺): calcd for C₂₁H₂₅ClN₃O [M+H]⁺ 370.1681, found 370.1664 (4.41 ppm).

(R/S)-6-Chloro-2-methyl-3-(2-(4-methylpiperazin-1-yl)ethyl)-4-phenyl-3,4-dihydroquinazoline (9c).

Prepared in two steps from 3a and 2-(4-methylpiperazin-1-yl)ethylamine following general methods B, and C2. The final product was purified by flash column chromatography (MeOH/CH₂Cl₂ 0:100 → 20:80) to give a clear semi-solid (131 mg, 21% over two steps).

1H NMR (500 MHz, CDCl₃): δ 7.35-7.27 (m, 5H, 5×ArH), 7.08 (dd, 1H, J = 8.5, 2.5 Hz, H-7), 7.06 (d, 1H, J = 8.5 Hz, H-8), 6.76 (d, 1H, J = 2.5 Hz, H-5), 5.56 (s, 1H, H-4), 3.46 (ddd, 1H, J = 14.0, 8.0, 6.0 Hz, CH/H), 3.19 (ddd, 1H, J = 14.0, 8.0, 6.0 Hz, CH/H), 2.60-2.30 (m, 10H, 2×CH₂ & 4×CH), 2.31 (s, 3H, CH₃), 2.28 (s, 3H, CH₃). LRMS (ES⁺): m/z (%) 192 (95) [35Cl M+2H]⁺, 193
(73) $[^{35}\text{Cl} \text{ M+2H}]^{2+}$, 231 (14) $[^{35}\text{Cl} \text{ M+DMSO+2H}]^{2+}$, 383 (100) $[^{35}\text{Cl} \text{ M+H}]^{+}$, 385 (36) $[^{37}\text{Cl} \text{ M+H}]^{+}$. HRMS (ES+): calcd for C$_{22}$H$_{28}$ClN$_{4}$ [M+H]$^+$ 383.1997, found 383.1988 (2.32 ppm).

(R/S)-2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)-N,N-dimethylethanamine (9d).

Prepared in two steps from 3a and N,N-Dimethylthelynediamine following general methods B, and C2. The final product was purified by flash column chromatography (MeOH/CH$_2$Cl$_2$ 0:100 → 20:80) to give a clear semi-solid (280 mg, 17% over two steps).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.31-7.24 (m, 5H, 5×ArH), 7.04 (dd, 1H, $J = 8.5$, 2.5 Hz, H-7), 6.99 (d, 1H, $J = 8.5$ Hz, H-5), 6.72 (d, 1H, $J = 2.5$ Hz, H-5), 5.48 (s, 1H, H-4), 3.41 (ddd, 1H, $J = 14.5$, 9.0, 5.5 Hz, CH$_2$), 3.13 (ddd, 1H, $J = 14.5$, 9.0, 5.5 Hz, CH$_2$), 2.49 (dd, 1H, $J = 12.5$, 9.0, 5.5 Hz, CH$_2$), 2.31 (ddd, 1H, $J = 12.5$, 9.0, 5.5 Hz, CH$_2$), 2.25 (s, 3H, CH$_3$), 2.18 (s, 6H, 2×NCH$_3$). LRMS (ES+): m/z (%) 328 (100) $[^{35}\text{Cl} \text{ M+H}]^{+}$, 330 (35) $[^{37}\text{Cl} \text{ M+H}]^{+}$. HRMS (ES+): calcd for C$_{19}$H$_{23}$ClN$_3$ [M+H]$^+$ 328.1570, found 328.1572 (1.48 ppm).

(R/S)-3-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)-N,N-dimethylpropan-1-amine (9e).

Prepared in two steps from 3a and 3-(dimethylamino)-1-propylamine following general methods B, and C2. The final product was purified by flash column chromatography (0.5M NH$_3$ MeOH/CH$_2$Cl$_2$ 0:100 → 20:80) to give a clear semi-solid (56 mg, 9% over two steps).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.34-7.25 (m, 5H, 5×ArH), 7.07 (dd, 1H, $J = 8.5$, 2.0 Hz, H-7), 7.04 (d, 1H, $J = 8.5$ Hz, H-8), 6.76 (d, 1H, $J = 2.0$ Hz, H-5), 5.48 (s, 1H, H-4), 3.45 (ddd, 1H, $J = 15.0$, 8.5, 6.5 Hz, CH$_2$), 3.09 (ddd, 1H, $J = 15.0$, 8.5, 6.5 Hz, CH$_2$), 2.29 (s, 3H, CH$_3$), 2.28-2.18 (m, 2H, CH$_2$), 2.17 (s, 6H, 2×NCH$_3$), 1.79-1.61 (m, 2H, CH$_2$). LRMS (ES+): m/z (%) 171.5 (68) $[^{35}\text{Cl} \text{ M+2H}]^{2+}$, 172.5 (21) $[^{35}\text{Cl} \text{ M+2H}]^{2+}$, 210.5 (32) $[^{35}\text{Cl} \text{ M+DMSO+2H}]^{2+}$, 211.5 (14) $[^{37}\text{Cl} \text{ M+DMSO+2H}]^{2+}$, 342 (100) $[^{35}\text{Cl} \text{ M+H}]^{+}$, 344 (36) $[^{37}\text{Cl} \text{ M+H}]^{+}$. HRMS (ES+): calcd for C$_{20}$H$_{25}$ClN$_3$ [M+H]$^+$ 342.1723, found 342.1723 (2.45 ppm).

(R/S)-2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)-N-methylethanamine (9f).

1-Chloroethyl chloroformate (28 mg, 0.194 mmol) was added to a solution of (R/S)-2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)-N,N-dimethylethanamine (9d) (51 mg, 0.156 mmol) in anhydrous 1,2-dichloroethane (1 mL) at 0°C. The reaction was stirred for 15 min before being
heated to 80°C for 1 h. Upon cooling aqueous NaOH (1.0 M, 1 mL) was added to the reaction, the layers separated and the aqueous extracted with CH$_2$Cl$_2$ (4×10 mL). The combined organic layers were then dried over MgSO$_4$, filtered and the solvent removed under reduced pressure to give the crude carbamate, which was dissolved in MeOH (10 mL) and heated at 65°C for 2 h. Upon cooling the solvent was removed and the crude product was purified by flash column chromatography (2.0M NH$_3$ in IPA/MeOH/CH$_2$Cl$_2$ 1:0:99 → 1:9:90) to give a brown semi-solid (9 mg, 18%).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.35-7.28 (m, 5H, 5×ArH), 7.10 (dd, 1H, $J = 8.5$, 2.0 Hz, H-7), 7.08 (d, 1H, $J = 8.5$ Hz, H-8), 6.80 (d, 1H, $J = 2.0$ Hz, H-5), 5.50 (s, 1H, H-4), 3.54 (ddd, 1H, $J = 14.5$, 6.5, 6.5 Hz, C$_2$H), 3.24-3.19 (m, 1H, C$_2$H), 2.79-2.75 (m, 2H, CH$_2$), 2.41 (s, 3H, CH$_3$), 2.33 (s, 3H, CH$_3$). LGEMS (ES+): m/z (%) 157.5 (100) $^{35}$Cl M+2H$^+$, 158.5 (35) $^{37}$Cl M+2H$^+$, 314 (73) $^{35}$Cl M+H$,^+$, 316 (23) $^{37}$Cl M+H$. HRMS (ES+): calcld for C$_{18}$H$_{21}$ClN$_3$ [M+H]$^+$ 314.1419, found 314.1410 (-0.43 ppm).

4.1.3 Synthesis of amide analogs (11b,c & e-h).
See Scheme 2 and Scheme S3 for the synthetic route to these analogs. See the main paper for the synthesis of related analogs 11a and 11d.

(R/S)-N-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)acetamide (11b).

Prepared according to method E from tert-butyl 2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethylcarbamate (11a) (120 mg, 0.3 mmol) and acetyl chloride (47 mg, 0.6 mmol). The product was purified by flash column chromatography (0.5M NH$_3$ MeOH/CH$_2$Cl$_2$ 0:100 → 15:85) to give a white solid (16 mg, 16%).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.34-7.27 (m, 5H, 5×ArH), 7.09 (dd, 1H, $J = 8.5$, 2.5 Hz, H-7), 7.03 (d, 1H, $J = 8.5$ Hz, H-8), 6.78 (d, 1H, $J = 2.5$ Hz, H-5), 5.70 (br s, 1H, NH), 5.41 (s, 1H, H-4), 3.56-3.50 (m, 1H, C$_2$H), 3.46-3.40 (m, 1H, C/H), 3.30-3.23 (m, 2H, 2×C$_2$H), 2.26 (s, 3H, CH$_3$), 1.94 (s, 3H, CH$_3$). LRMS (ES+): m/z (%) 342 (100) $^{35}$Cl M+H$,^+$, 344 (37) $^{37}$Cl M+H$,^+$, 316 (23) $^{37}$Cl M+H$. HRMS (ES+): calcld for C$_{19}$H$_{23}$ClN$_3$O [M+H]$^+$ 342.1368, found 342.1369 (-0.43 ppm).

(R/S)-N-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)cyclopropanecarboxamide (11c).

Prepared according to method E from tert-butyl 2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethylcarbamate (11a) (120 mg, 0.3 mmol) and cyclopropane carbonyl chloride (63 mg, 0.6 mmol). The product was purified by flash column chromatography (0.5M NH$_3$ MeOH/CH$_2$Cl$_2$ 0:100 → 10:90) to give a white semi-solid (31 mg, 28%).

$^1$H NMR (500 MHz, CDCl$_3$): $\delta$ 7.28-7.20 (m, 5H, 5×ArH), 7.03 (dd, 1H, $J = 8.5$, 2.5 Hz, H-7), 6.97 (d, 1H, $J = 8.5$ Hz, H-8), 6.71 (d, 1H, $J = 2.5$ Hz, H-5), 5.87 (br s, 1H, NH), 5.35 (s, 1H, H-4), 3.50-
3.45 (m, 1H, CHH), 3.39-3.33 (m, 1H, CHH), 3.28-3.16 (m, 2H, 2×CHH), 2.20 (s, 3H, CH₃), 1.23-1.18 (m, 1H, CH), 0.89-0.86 (m, 2H, 2×CHH), 0.69-0.65 (m, 2H, 2×CHH). LRMS (ES+): m/z (%) 368 (100) [³⁵Cl M+H]+, 370 (33) [³⁷Cl M+H]+. HRMS (ES+): calcd for C₂₁H₂₃ClN₃O [M+H]+ 368.1524, found 368.1512 (3.23 ppm).

*N-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)furan-2-carboxamide (11e).*

Prepared according to method E from tert-butyl 2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethylcarbamate (11a) (120 mg, 0.3 mmol) and 2-furoyl chloride (78 mg, 0.6 mmol). The product was purified by flash column chromatography (0.5M NH₃ MeOH/CH₂Cl₂ 0:100 → 10:90) to give a clear glass (19 mg, 16%).

¹H NMR (500 MHz, CDCl₃): δ 7.40 (dd, 1H, J = 1.5, 0.5 Hz, ArH), 7.34-7.27 (m, 5H, 5×ArH), 7.11-7.08 (m, 2H, 2×ArH), 7.04 (d, 1H, J = 8.5 Hz, H-8), 6.76 (d, 1H, J = 2.5 Hz, H-5), 6.54 (br s, 1H, NH), 5.46 (s, 1H, H-4), 3.63-3.44 (m, 3H, CH₂ & CH₃), 3.40-3.35 (m, 1H, CHH), 2.28 (s, 3H, CH₃). LRMS (ES+): m/z (%) 394 (100) [³⁵Cl M+H]+, 396 (32) [³⁷Cl M+H]+. HRMS (ES+): calcd for C₂₂H₂₁ClN₃O [M+H]+ 394.1317, found 394.1319 (-0.65 ppm).

*N-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)-2-phenylacetamide (11f).*

Prepared according to method E from tert-butyl 2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethylcarbamate (11a) (120 mg, 0.3 mmol) and phenylacetyl chloride (93 mg, 0.6 mmol). The product was purified by flash column chromatography (0.5M NH₃ MeOH/CH₂Cl₂ 0:100 → 10:90) to give a clear glass (36 mg, 29%).

¹H NMR (500 MHz, CDCl₃): δ 7.34-7.25 (m, 6H, 6×ArH), 7.20-7.18 (m, 4H, 4×ArH), 7.09 (dd, 1H, J = 8.5, 2.5 Hz, H-7), 7.03 (d, 1H, J = 8.5 Hz, H-8), 6.71 (d, 1H, J = 2.5 Hz, H-5), 5.58 (br s, 1H, NH), 5.28 (s, 1H, H-4), 3.56 (d, 1H, J = 16 Hz, PhCH₃), 3.51 (d, 1H, J = 16 Hz, PhCH₃), 3.46-3.20 (m, 4H, 2×CH₂), 2.19 (s, 3H, CH₃). LRMS (ES+): m/z (%) 418 (100) [³⁵Cl M+H]+, 420 (37) [³⁷Cl M+H]+. HRMS (ES+): calcd for C₂₅H₂₅ClN₃O [M+H]+ 418.1681, found 418.1669 (2.71 ppm).

*N-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)-2-methoxyacetamide (11g).*

Prepared according to method E from tert-butyl 2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethylcarbamate (11a) (120 mg, 0.3 mmol) and 2-furoyl chloride (78 mg, 0.6 mmol). The product was purified by flash column chromatography (0.5M NH₃ MeOH/CH₂Cl₂ 0:100 → 10:90) to give a clear glass (19 mg, 16%).

¹H NMR (500 MHz, CDCl₃): δ 7.34-7.25 (m, 6H, 6×ArH), 7.20-7.18 (m, 4H, 4×ArH), 7.09 (dd, 1H, J = 8.5, 2.5 Hz, H-7), 7.03 (d, 1H, J = 8.5 Hz, H-8), 6.71 (d, 1H, J = 2.5 Hz, H-5), 5.58 (br s, 1H, NH), 5.28 (s, 1H, H-4), 3.56 (d, 1H, J = 16 Hz, PhCH₃), 3.51 (d, 1H, J = 16 Hz, PhCH₃), 3.46-3.20 (m, 4H, 2×CH₂), 2.19 (s, 3H, CH₃). LRMS (ES+): m/z (%) 418 (100) [³⁵Cl M+H]+, 420 (37) [³⁷Cl M+H]+. HRMS (ES+): calcd for C₂₅H₂₅ClN₃O [M+H]+ 418.1681, found 418.1669 (2.71 ppm).
Prepared according to method E from tert-butyl 2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethylcarbamate (11a) (120 mg, 0.3 mmol) and methoxyacetyl chloride (65 mg, 0.6 mmol). The product was purified by flash column chromatography (0.5M NH₃ MeOH/CH₂Cl₂ 0:100 → 10:90) to give a clear glass (46 mg, 43%).

¹H NMR (500 MHz, CDCl₃): δ 7.37-7.27 (m, 5H, 5×ArH), 7.09 (dd, 1H, J = 8.5, 2.0 Hz, H-7), 7.03 (d, 1H, J = 8.5 Hz, H-8), 6.78 (d, 1H, J = 2.0 Hz, H-5), 6.67 (br s, 1H, NH), 5.45 (s, 1H, H-4), 3.84 (s, 2H, CH₂), 3.55-3.49 (m, 1H, CΗH), 3.43-3.37 (m, 2H, CH₂), 3.35 (s, 3H, CH₃), 3.30-3.25 (m, 1H, CΗH), 2.26 (s, 3H, CH₃). LRMS (ES+): m/z (%) 372 (100) [35Cl M+H]+, 374 (32) [37Cl M+H]+. HRMS (ES+): calcd for C₂₀H₂₃CIN₃O₂ [M+H]+ 372.1473, found 372.1464 (2.37 ppm).

N-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)-2-(dimethylamino)acetamide (11h).

Prepared according to method E from tert-butyl 2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethylcarbamate (11a) (120 mg, 0.3 mmol) and dimethylaminoacetyl chloride hydrochloride (95 mg, 0.6 mmol). The product was purified by flash column chromatography (0.5M NH₃ MeOH/CH₂Cl₂ 0:100 → 15:85) to give a yellow semi-solid (29 mg, 25%).

¹H NMR (500 MHz, CDCl₃): δ 7.37-7.28 (m, 5H, 5×ArH), 7.11 (dd, 1H, J = 8.5, 2.5 Hz, H-7), 7.06 (d, 1H, J = 8.5 Hz, H-8), 6.81 (d, 1H, J = 2.5 Hz, H-5), 5.47 (s, 1H, H-4), 3.60-3.54 (m, 1H, CΗH), 3.44-3.40 (m, 2H, CH₂), 3.32-3.26 (m, 1H, CΗH), 2.93 (s, 2H, CH₂), 2.31 (s, 3H, CH₃), 2.24 (s, 6H, 2×CH₃). LRMS (ES+): m/z (%) 385 (100) [35Cl M+H]+, 387 (36) [37Cl M+H]+. HRMS (ES+): calcd for C₂₁H₂₆CIN₄O [M+H]+ 385.1790, found 385.1786 (0.86 ppm).

4.1.4 Synthesis of piperazine amide analogs (13a-h).
See Scheme 2 and Scheme S3 for the synthetic route to these analogs.

tert-Butyl 4-(2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazine-1-carboxylate (13a).

Prepared in two steps from 3a and 1-Boc-4-(2-aminoethyl)piperazine following general methods B, and C2. The final product was purified by flash column chromatography (0.5M NH₃ MeOH/CH₂Cl₂ 0:100 → 10:90) to give a white solid (1.74 g, 38% over two steps).

¹H NMR (500 MHz, CDCl₃): δ 7.36-7.28 (m, 5H, 5×ArH), 7.09 (dd, 1H, J = 8.5, 2.0 Hz, H-7), 7.03 (d, 1H, J = 8.5 Hz, H-8), 6.76 (d, 1H, J = 2.0 Hz, H-5), 5.55 (s, 1H, H-4), 3.50-3.40 (m, 2×CH₂ & CΗH), 3.23-3.18 (m, 1H, CΗH), 2.58 (ddd, 1H, J = 13.5, 7.5, 6.0 Hz, CΗH), 2.49-2.35 (m, 5H, 2×CH₂ & CΗH), 2.30 (s, 3H, CH₃), 1.46 (s, 9H, 3×CH₃). ¹³C NMR (125 MHz, DMSO-d₆): δ 156.2
(C), 154.7 (C), 143.8 (C), 129.2 (CH), 128.9 (C), 128.5 (CH), 128.4 (CH), 126.6 (CH), 126.1 (C), 126.0 (CH), 125.1 (CH), 79.8 (C), 63.3 (CH), 56.7 (CH), 53.4 (CH<sub>2</sub>), 46.8 (CH<sub>2</sub>), 44.3 & 43.1 (CH<sub>2</sub>), [Note, two peaks due to restricted flexibility of the ring system], 28.4 (CH<sub>3</sub>), 22.5 (CH<sub>3</sub>). [Note, there is one too few aryl quaternary carbon peaks, possibly due to two carbon shifts being identical].

LRMS (ES+): m/z (%) 469 (100) [<sup>35</sup>Cl M+H]<sup>+</sup>, 471 (37) [<sup>37</sup>Cl M+H]<sup>+</sup>. HRMS (ES+): calcd for C<sub>26</sub>H<sub>34</sub>ClN<sub>4</sub>O<sub>2</sub> [M+H]<sup>+</sup> 469.2365, found 469.2352 (2.77 ppm).

(R/S)-1-(4-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazin-1-yl)ethanone (13b).

Prepared according to method E from tert-butyl 4-(2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazine-1-carboxylate (13a) (188 mg, 0.4 mmol) and acetyl chloride (63 mg, 0.8 mmol). The product was purified by flash column chromatography (0.5M NH<sub>3</sub> MeOH/CH<sub>2</sub>Cl<sub>2</sub> 10:90) to give a clear glass (56 mg, 34%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.37-7.28 (m, 5H, 5×ArH), 7.10 (dd, 1H, J = 8.5, 2.5 Hz, H-7), 7.05 (d, 1H, J = 8.5 Hz, H-8), 6.78 (d, 1H, J = 2.5 Hz, H-5), 5.55 (s, 1H, H-4), 3.63-3.58 (m, 2H, CH<sub>2</sub>), 3.52-3.43 (m, 3H, CH<sub>2</sub>), 3.26-3.20 (m, 1H, CH), 2.60 (ddd, 1H, J = 13.5, 7.5, 6.0 Hz, CH), 2.50-2.38 (m, 5H, 2×CH<sub>2</sub>), 2.31 (s, 3H, CH<sub>3</sub>), 2.09 (s, 3H, CH<sub>3</sub>). LRMS (ES+): m/z (%) 411 (100) [<sup>35</sup>Cl M+H]<sup>+</sup>, 413 (33) [<sup>37</sup>Cl M+H]<sup>+</sup>. HRMS (ES+): calcd for C<sub>25</sub>H<sub>30</sub>ClN<sub>4</sub>O [M+H]<sup>+</sup> 411.1946, found 411.1932 (3.42 ppm).

(4-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazin-1-yl)(cyclopropyl)methanone (13c).

Prepared according to method E from tert-butyl 4-(2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazine-1-carboxylate (13a) (188 mg, 0.4 mmol) and cyclopropane chloride (84 mg, 0.8 mmol). The product was purified by flash column chromatography (0.5M NH<sub>3</sub> MeOH/CH<sub>2</sub>Cl<sub>2</sub> 10:90) to give a tan solid (42 mg, 24%).

<sup>1</sup>H NMR (500 MHz, CDCl<sub>3</sub>): δ 7.37-7.29 (m, 5H, 5×ArH), 7.09 (dd, 1H, J = 8.5, 2.5 Hz, H-7), 7.05 (d, 1H, J = 8.5 Hz, H-8), 6.77 (d, 1H, J = 2.5 Hz, H-5), 5.55 (s, 1H, H-4), 3.66-3.62 (m, 4H, 2×CH<sub>2</sub>), 3.49 (ddd, 1H, J = 15.0, 7.5, 6.0 Hz, CH), 3.23 (ddd, 1H, J = 14.5, 7.5, 6.0 Hz, CH), 2.60 (ddd, 1H, J = 14.5, 7.5, 6.0 Hz, CH), 2.50-2.38 (m, 5H, 2×CH<sub>2</sub> & CH), 2.31 (s, 3H, CH<sub>3</sub>), 1.74-1.69 (m, 1H, CH), 1.00-0.97 (m, 2H, 2×CH<sub>2</sub>), 0.79-0.75 (m, 2H, 2×CH<sub>2</sub> & CH). LRMS (ES+): m/z (%) 437 (100) [<sup>35</sup>Cl M+H]<sup>+</sup>, 439 (36) [<sup>37</sup>Cl M+H]<sup>+</sup>. HRMS (ES+): calcd for C<sub>25</sub>H<sub>30</sub>ClN<sub>4</sub>O [M+H]<sup>+</sup> 437.2103, found 437.2094 (2.07 ppm).

(4-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazin-1-yl)(phenyl)methanone (13d).
Prepared according to method E from tert-butyl 4-(2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazine-1-carboxylate (13a) (235 mg, 0.5 mmol) and benzoyl chloride (141 mg, 1.0 mmol). The product was purified by flash column chromatography (MeOH/CH₂Cl₂ 0:100 → 20:80) to give a white solid (86 mg, 36%).

1H NMR (500 MHz, CDCl₃): δ 7.43-7.37 (m, 5H, 5×ArH), 7.35-7.32 (m, 2H, 2×ArH), 7.30-7.27 (m, 3H, 3×ArH), 7.08 (dd, 1H, J = 8.5, 2.0 Hz, H-7), 7.03 (d, 1H, J = 8.5 Hz, H-8), 6.77 (d, 1H, J = 2.0 Hz, H-5), 5.53 (s, 1H, H-4), 3.80-3.71 (m, 2H, CH₂), 3.50-3.37 (m, 3H, CH₂ & C₄H₄), 3.21 (ddd, 1H, J = 14.5, 7.5, 6.5 Hz, C₂H₄), 2.61-2.28 (m, 6H, 2×CH₂), 2.29 (s, 3H, CH₃). 13C NMR (125 MHz, CDCl₃): δ 170.3 (C), 156.5 (C), 143.5 (C), 138.7 (C), 135.5 (C), 129.8 (CH), 129.3 (CH), 129.1 (C), 128.6 (CH), 128.54 (CH), 128.47 (CH), 127.0 (CH), 126.6 (CH), 126.0 (CH), 125.9 (C), 124.7 (CH), 63.2 (CH), 56.3 (CH), 53.9 (CH₂), 53.1 (CH₂), 52.1 (CH₂), [Note, the four carbon atoms in the piperazine ring are non-equivalent due to restricted flexibility in the ring system], 47.6 (CH₂), 42.1 (CH₂), 46.8 (CH₂), 22.1 (CH₃). LRMS (ES+): m/z (%) 473 (100) [35Cl M+H]⁺, 475 (37) [37Cl M+H]⁺. HRMS (ES+): calcd for C₂₈H₃₀ClN₄O [M+H]⁺ 473.2103, found 473.2103 (0.00 ppm).

(R/S)-(4-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazin-1-yl)(furan-2-y1)methanone (13e).

Prepared according to method E from tert-butyl 4-(2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazine-1-carboxylate (13a) (188 mg, 0.4 mmol) and 2-furoyl chloride (104 mg, 0.8 mmol). The product was purified by flash column chromatography (0.5M NH₃ MeOH/CH₂Cl₂ 0:100 → 10:90) to give a tan solid (58 mg, 31%).

1H NMR (500 MHz, CDCl₃): δ 7.46 (dd, 1H, J = 2.0, 0.5 Hz, ArH), 7.35-7.26 (m, 5H, 5×ArH), 7.03 (d, 1H, J = 8.5 Hz, H-8), 6.99 (dd, 1H, J = 3.5, 0.5 Hz, ArH), 6.75 (d, 1H, J = 2.0 Hz, ArH), 6.47 (dd, 1H, J = 3.5, 2.0 Hz, ArH), 5.53 (s, 1H, H-4), 3.86-3.69 (m, 4H, 2×CH₂), 3.47 (ddd, 1H, J = 15.0, 7.5, 6.0 Hz, CH), 3.22 (dd, 1H, J = 15.0, 7.5, 6.0 Hz, CH), 2.58 (ddd, 1H, J = 13.5, 7.5, 6.0 Hz, CH), 2.51-2.42 (m, 5H, CH & 2×CH₂), 2.30 (s, 3H, CH₃). LRMS (ES+): m/z (%) 463 (100) [35Cl M+H]⁺, 465 (36) [37Cl M+H]⁺. HRMS (ES+): calcd for C₂₆H₂₈ClN₄O₂ [M+H]⁺ 463.1895, found 463.1873 (4.88 ppm).

(R/S)-1-(4-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazin-1-yl)-2-phenylethanone (13f).
Prepared according to method E from tert-butyl 4-(2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazine-1-carboxylate (13a) (188 mg, 0.4 mmol) and phenylacetyl chloride (124 mg, 0.8 mmol). The product was purified by flash column chromatography (0.5M NH₃ MeOH/CH₂Cl₂ 0:100 → 10:90) to give an off-white solid (42 mg, 27%).

1H NMR (500 MHz, CDCl₃): δ 7.35-7.32 (m, 10H, 10×ArH), 7.09 (dd, 1H, J = 8.5, 2.5 Hz, H-7), 7.04 (d, 1H, J = 8.5 Hz, H-8), 6.76 (d, 1H, J = 2.5 Hz, H-5), 5.51 (s, 1H, H-4), 3.73 (s, 2H, CH₂), 3.64-3.62 (m, 2H, CH₂), 3.47-3.41 (m, 3H, CH₂ & CH₃), 3.21-3.15 (m, 1H, CH/H), 2.52 (ddd, 1H, J = 13.0, 7.0, 6.0 Hz, CH/H), 2.44-2.33 (m, 3H, CH₂ & CH₃), 2.79 (s, 3H, CH₃), 2.24-2.21 (m, 2H, CH₂). LRMS (ES+): m/z (% 487 (100) [35Cl M+H]+, 489 (43) [37Cl M+H]+. HRMS (ES+): calcd for C₂₉H₂₂ClN₄O [M+H]+ 487.2259, found 487.2243 (3.26 ppm).

(R/S)-1-(4-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazin-1-yl)-2-methoxyethanone (13g).

Prepared according to method E from tert-butyl 4-(2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazine-1-carboxylate (13a) (188 mg, 0.4 mmol) and methoxyacetyl chloride (87 mg, 0.8 mmol). The product was purified by flash column chromatography (0.5M NH₃ MeOH/CH₂Cl₂ 0:100 → 10:90) to give a tan solid (64 mg, 36%).

1H NMR (500 MHz, CDCl₃): δ 7.34-7.26 (m, 5H, 5×ArH), 7.07 (dd, 1H, J = 8.5, 2.0 Hz, H-7), 7.01 (d, 1H, J = 8.5 Hz, H-8), 6.75 (d, 1H, J = 2.0 Hz, H-5), 5.51 (s, 1H, H-4), 4.07 (s, 2H, CH₂), 3.59-3.57 (m, 2H, CH₂), 3.49-3.42 (m, 3H, CH₂ & CH₃), 3.40 (s, 3H, CH₃), 3.20 (ddd, 1H, J = 14.5, 7.5, 6.0 Hz, CH/H), 2.56 (ddd, 1H, J = 13.5, 7.5, 6.0 Hz, CH/H), 2.47-2.34 (m, 5H, 2×CH₂ & CH/H), 2.28 (s, 3H, CH₃). LRMS (ES+): m/z (% 441 (100) [35Cl M+H]+, 443 (33) [37Cl M+H]+. HRMS (ES+): calcd for C₂₉H₂₂ClN₄O [M+H]+ 441.2052, found 441.2055 (-0.73 ppm).

(R/S)-1-(4-(2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazin-1-yl)-2-(dimethylamino)ethanone (13h).

Prepared according to method E from tert-butyl 4-(2-(6-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethyl)piperazine-1-carboxylate (13a) (188 mg, 0.4 mmol) and dimethylaminoacetyl chloride hydrochloride (126 mg, 0.8 mmol). The product was purified by flash column chromatography (0.5M NH₃ MeOH/CH₂Cl₂ 0:100 → 15:85) to give a tan solid (91 mg, 50%).

1H NMR (500 MHz, CDCl₃): δ 7.34-7.26 (m, 5H, 5×ArH), 7.07 (dd, 1H, J = 8.5, 2.5 Hz, H-7), 7.01 (d, 1H, J = 8.5 Hz, H-8), 6.75 (d, 1H, J = 2.5 Hz, H-5), 5.52 (s, 3H, CH₃), 3.58-3.56 (m, 4H, 2×CH₂), 3.46 (ddd, 1H, J = 14.5, 7.5, 6.0 Hz, CH/H), 3.20 (ddd, 1H, J = 14.5, 7.5, 6.0 Hz, CH/H), 3.07 (s, 2H, CH₂), 2.55 (ddd, 1H, J = 13.5, 7.5, 6.0 Hz, CH/H), 2.46-2.33 (m, 5H, CH/H & 2×CH₂), 2.28 (s, 3H, CH₃), 2.45 (s, 6H, 2×CH₃). LRMS (ES+): m/z (% 454 (100) [35Cl M+H]+, 456 (30)
[\textsuperscript{37}Cl M+H]\textsuperscript{+}. HRMS (ES\textsuperscript{+}): calcd for C\textsubscript{25}H\textsubscript{33}ClN\textsubscript{5}O [M+H]\textsuperscript{+} 454.2368, found 454.2350 (4.08 ppm).

4.1.5 Synthesis of an alcohol-containing analog (21).
See Scheme S2 for the synthetic route to analog 21.

(R/S)-2-(6-Chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)ethanol (21).

Tosic acid-derivatised silica gel (0.68 mmol/g, 200 mg) was added to a solution of N-(2-benzoyl-4-chlorophenyl)acetamide (3a) (1.37 g, 5.0 mmol) in ethanolamine (3.02 mL, 50 mmol) and heated to 150°C for 1.5 h. Upon cooling the reaction mixture was filtered, added to EtOAc/water (1:1, 100 mL), the layers separated and the aqueous extracted with EtOAc (3×50 mL). Subsequently the EtOAc layers were combined, dried over MgSO\textsubscript{4}, filtered and the solvent removed under reduced pressure. The resultant crude imine (20) was dissolved in MeOH (100 mL), cooled to 4°C followed by the addition of NaBH\textsubscript{4} (1.51 g, 40 mmol) and the reaction mixture stirred at 4°C for 48 h. The reaction was then added to a solution of NaCl (saturated, 50 mL) and the MeOH removed under reduced pressure. The remaining aqueous layer was extracted with CH\textsubscript{2}Cl\textsubscript{2} (4×50 mL), the CH\textsubscript{2}Cl\textsubscript{2} layers combined, dried over MgSO\textsubscript{4}, filtered and the solvent removed under reduced pressure. The crude product was purified by column chromatography (MeOH/CH\textsubscript{2}Cl\textsubscript{2} 0:100 → 20:80) to give a clear semi-solid (232 mg, 15%).

\textsuperscript{1}H NMR (500 MHz, CDCl\textsubscript{3}): \(\delta\) 7.34-7.26 (m, 3H, 3×Ar), 7.24-7.21 (m, 2H, 2×ArH), 7.04 (dd, 1H, \(J = 8.5, 2.0\) Hz, H-7), 7.01 (d, 1H, \(J = 8.5\) Hz, H-8), 6.55 (d, 1H, \(J = 2.0\) Hz, H-5), 5.43 (s, 1H, H-4), 3.95 (dd, 1H, \(J = 12.0, 8.0, 4.0\) Hz, CH/\(H\)), 3.68 (ddd, 1H, \(J = 12.0, 4.0, 4.0\) Hz, CH/\(H\)), 3.59 (ddd, 1H, \(J = 15.0, 8.0, 4.0\) Hz, CH/\(H\)), 3.09 (dd, 1H, \(J = 15.0, 4.0, 4.0\) Hz, CH/\(H\)), 2.32 (s, 3H, CH\textsubscript{3}). \textsuperscript{13}C NMR (125 MHz, CDCl\textsubscript{3}): \(\delta\) 157.3 (C), 143.4 (C), 138.5 (C), 129.3 (CH), 129.2 (C), 128.5 (CH), 128.2 (CH), 126.8 (CH), 126.3 (CH), 125.8 (C), 124.1 (CH), 62.3 (CH), 58.9 (CH\textsubscript{2}), 50.9 (CH\textsubscript{2}), 22.6 (CH\textsubscript{3}). LRMS (ES\textsuperscript{+}): m/z (%) 301 (100) [\textsuperscript{35}Cl M+H]\textsuperscript{+}, 303 (32) [\textsuperscript{37}Cl M+H]\textsuperscript{+}. HRMS (ES\textsuperscript{+}): calcd for C\textsubscript{17}H\textsubscript{18}ClN\textsubscript{2}O [M+H]\textsuperscript{+} 301.1102, found 301.1105 (-1.04 ppm).

4.1.6 Synthesis of C6 ‘halide’ analogs (15b-d).
See Scheme S4 for the synthetic route to these analogs. See the main paper for the synthesis of related analog 9a.

(R/S)-2-Methyl-4-phenyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (15b).
Prepared in three steps from 2b, acetyl chloride and 1-(2-aminoethyl)piperidine following general methods A, B and C. The final product was purified by flash column chromatography (MeOH/CH₂Cl₂ 0:100 → 20:80) to give a yellow solid (288 mg, 19% over 3 steps).

¹H NMR (500 MHz, CDCl₃): δ 7.30-7.25 (m, 4H, 4×ArH), 7.22-7.18 (m, 1H, ArH), 6.78-6.77 (m, 1H, ArH), 5.57 (s, 1H, H-4), 3.44 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, C₃H), 3.18 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, C₃H), 2.51 (ddd, 1H, J = 13.0, 8.5, 6.0 Hz, C₃H), 2.38-2.28 (m, 8H, C₃H, 2×CH₂), 1.54-1.37 (m, 2H, CH₂). LRMS (ES⁺): m/z (%) 334 (100) [M+H]+. HRMS (ES⁺): calcd for C₂₂H₂₈N₃ [M+H]+ 334.2278, found 334.2262 (4.58 ppm).

(R/S)-6-Bromo-2-methyl-4-phenyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (15c).

Prepared in three steps from 2c, acetyl chloride and 1-(2-aminoethyl)piperidine following general methods A, B and C. The final product was purified by flash column chromatography (MeOH/CH₂Cl₂ 0:100 → 20:80) to give an off-white solid (1.52 g, 20% over 3 steps).

¹H NMR (500 MHz, CDCl₃): δ 7.36-7.28 (m, 5H, 5×ArH), 7.23 (d, 1H, J = 8.5, 2.5 Hz, H-7), 7.02 (d, 1H, J = 8.5 Hz, H-8), 6.92 (d, 1H, J = 2.5 Hz, H-5), 5.57 (s, 1H, H-4), 3.47 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, C₃H), 3.20 (ddd, 1H, J = 13.0, 8.5, 6.0 Hz, C₃H), 2.42-2.32 (m, 8H, C₃H, 2×CH₂, CH₃), 1.58-1.54 (m, 2H, 2×CH₂), 1.46-1.40 (m, 2H, CH₂). LRMS (ES⁺): m/z (%) 206.5 (100) [⁷⁹Br M+2H]+, 207.5 (93) [⁸¹Br M+2H]+. HRMS (ES⁺): calcd for C₂₂H₂₇BrN₃ [M+H]+ 412.1383, found 412.1367 (3.90 ppm).

(2-Amino-5-iodophenyl)(phenyl)methanone (2d).

NIS (4.73 g, 21 mmol) was added to a suspension of 2-aminobenzophenone (3.95 g, 20 mmol) and tosic acid-derivatised silica gel (0.68 mmol/g, 300 mg) in MeCN/Et₂O (1:3, 120 mL). The reaction mixture was stirred for 18 h, filtered, the silica washed with CH₂Cl₂ (50 mL) and the combined filtrate removed under reduced pressure. The crude aryl iodide was purified by flash column chromatography (CH₂Cl₂) to give a yellow solid (2.47 g, 38%).

¹H NMR (500 MHz, CDCl₃): δ 7.71 (d, 1H, J = 2.5 Hz, H-6), 7.63-7.61 (m, 2H, 2×ArH), 7.57-7.54 (m, 1H, ArH), 7.50-7.46 (m, 3H, 3×ArH), 6.53 (d, 1H, J = 9.0 Hz, H-3), 6.12 (br s, 2H, NH₂). ¹³C NMR (125 MHz, CDCl₃): δ 197.8 (C), 150.2 (C), 142.30 (CH), 142.27 (CH), 139.3 (C), 131.6
(CH), 129.2 (CH), 128.4 (CH), 120.3 (C), 119.3 (CH), 75.1 (C). LRMS (ES+): m/z (%) 324 (100) [M+H]+.

(R/S)-6-Iodo-2-methyl-4-phenyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (15d).

Prepared in three steps from 2d, acetyl chloride and 1-(2-aminoethyl)piperidine following general methods A, B and C2. The final product was purified by flash column chromatography (MeOH/CH2Cl2 0:100 → 10:90) to give a clear semi-solid (73 mg, 25% over 3 steps).

1H NMR (500 MHz, CDCl3): δ 7.35 (dd, 1H, J = 8.5, 2.0 Hz, H-7), 7.27-7.19 (m, 5H, Ph), 7.02 (d, 1H, J = 2.0 Hz, H-5), 6.83 (d, 1H, J = 8.5 Hz, H-8), 5.47 (s, 1H, H-4), 3.38 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, CHH), 3.12 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, CHH), 2.44 (ddd, 1H, J = 13.0, 8.5, 6.0 Hz, CHH), 2.34-2.24 (m, 8H, CHH, CH3 & 2×CH2), 1.50-1.45 (m, 2H, CH2). LRMS (ES+): m/z (%) 460 (100) [M+H]+. HRMS (ES+): calcd for C22H27N3 [M+H]+ 460.1244, found 460.1240 (0.83 ppm).

4.1.7 Synthesis of C6 Suzuki array (16b-f).
See Scheme 3 for the synthetic route to these analogs. See the main paper for the synthesis of related analog 16a.

(R/S)-2-Methyl-4-phenyl-3-(2-(piperidin-1-yl)ethyl)-6-(pyridin-4-yl)-3,4-dihydroquinazoline (16b).

Prepared according to method F from 6-bromo-2-methyl-4-phenyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (15c) (82 mg, 0.2 mmol) and 4-pyridylboronic acid (37 mg, 0.3 mmol). The crude product was purified by flash column chromatography (0.5M NH3 MeOH/CH2Cl2 0:100 → 10:90) to give a yellow semi-solid (9 mg, 11%).

1H NMR (500 MHz, CDCl3): δ 8.59-8.55 (m, 2H, 2×ArH), 7.46 (dd, 1H, J = 8.5, 2.0 Hz, ArH), 7.38-7.37 (m, 2H, 2×ArH), 7.35-7.34 (m, 4H, 4×ArH), 7.31-7.28 (m, 2H, 2×ArH), 7.08 (d, 1H, J = 2.5 Hz, H-5), 5.70 (s, 1H, H-4), 3.52 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, CHH), 3.26 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, CHH), 2.57 (ddd, 1H, J = 12.5, 8.5, 6.0 Hz, CHH), 2.46-2.32 (m, 8H, CHH, 2×CH2, CH3), 1.59-1.55 (m, 4H, 2×CH2), 1.46-1.41 (m, 2H, CH2). LRMS (ES+): m/z (%) 206 (17) [M+2H]2+, 411 (100) [M+H]+. HRMS (ES+): calcd for C27H31N4 [M+H]+ 411.2543, found 411.2544 (-0.28 ppm).
(R/S)-6-(Furan-2-yl)-2-methyl-4-phenyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (16c).

Prepared according to method E from 6-bromo-2-methyl-4-phenyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (15c) (82 mg, 0.2 mmol) and 2-furylboronic acid (34 mg, 0.3 mmol). The crude product was purified by flash column chromatography (0.5M NH₃ MeOH/CH₂Cl₂ 0:100 → 10:90) to give a brown semi-solid (34 mg, 43%).

¹H NMR (500 MHz, CDCl₃): δ 7.46 (dd, 1H, J = 8.5, 2.0 Hz, ArH), 7.39 (dd, 1H, J = 1.5, 0.5 Hz, ArH), 7.37-7.32 (m, 4H, 4×ArH), 7.29-7.26 (m, 1H, ArH), 7.14-7.12 (m, 2H, 2×ArH), 6.48 (dd, 1H, J =3.5, 0.5 Hz, ArH), 6.41 (dd, 1H, J = 3.5, 2.0 Hz, ArH), 5.61 (s, 1H, H-4), 3.51 (dd, 1H, J = 15.0, 9.0, 6.0, C/H), 3.24 (dd, 1H, J = 15.0, 9.0, 6.0, C/H), 2.57 (ddd, 1H, J = 13, 9.0, 6.0, C/H), 2.45-2.34 (m, 5H, C/H & 2×CH₂), 2.33 (s, 3H, CH₃), 1.60-1.55 (m, 4H, 2×CH₂), 1.47-1.42 (m, 2H, CH₂). LRMS (ES+): m/z (%) 400 (100) [M+H]+. HRMS (ES+): calcd for C₂₆H₃₀N₃O [M+H]+ 400.2383, found 400.2378 (1.25 ppm).

(R/S)-2-Methyl-4-phenyl-3-(2-(piperidin-1-yl)ethyl)-6-(thiophen-3-yl)-3,4-dihydroquinazoline (16d).

Prepared according to method E from 6-bromo-2-methyl-4-phenyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (15c) (82 mg, 0.2 mmol) and 3-thienylboronic acid (38 mg, 0.3 mmol). The crude product was purified by flash column chromatography (0.5M NH₃ MeOH/CH₂Cl₂ 0:100 → 10:90) to give an orange-brown solid (30 mg, 36%).

¹H NMR (500 MHz, CDCl₃): δ 7.33 (dd, 1H, J = 8.0, 2.0, ArH), 7.28-7.24 (m, 4H, 4×ArH), 7.23-7.19 (m, 4H, 4×ArH), 7.16-7.14 (m, 1H, ArH), 6.95 (d, 1H, J = 2.0 Hz, ArH), 5.57 (s, 1H, H-4), 3.43 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, C/H), 3.18 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, C/H), 2.50 (ddd, 1H, J = 12.5, 8.5, 6.0 Hz, C/H), 2.38-2.27 (m, 8H, C/H, 2×CH₂, CH₃), 1.52-1.48 (m, 4H, 2×CH₂), 1.40-1.34 (m, 2H, CH₂). LRMS (ES+): m/z (%) 416 (100) [M+H]+. HRMS (ES+): calcd for C₂₆H₃₀N₃S [M+H]+ 416.2155, found 416.2139 (3.84 ppm).

(R/S)-2-Methyl-6-(naphthalen-1-yl)-4-phenyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (16e).
Prepared according to method E from 6-bromo-2-methyl-4-phenyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (15c) (82 mg, 0.2 mmol) and 1-Naphthylboronic acid (52 mg, 0.3 mmol). The crude product was purified by flash column chromatography (0.5M NH₃ MeOH/CH₂Cl₂ 0:100 → 10:90) to give a brown solid (39 mg, 42%).

\(^{1}H\) NMR (500 MHz, CDCl₃): δ 7.89-7.80 (m, 3H, 3×ArH), 7.49-7.46 (m, 2H, 2×ArH), 7.38-7.27 (m, 9H, 9×ArH), 6.99 (d, 1H, \(J = 2.0\) Hz, H-5), 5.72 (s, 1H, H-4), 3.55 (ddd, 1H, \(J = 14.5, 8.5, 6.0\) Hz, C₃H), 3.27 (ddd, 1H, \(J = 14.5, 8.5, 6.0\) Hz, C₃H), 2.61 (ddd, 1H, \(J = 13.0, 8.5, 6.0\) Hz, C₃H), 2.48-2.35 (m, 8H, C₄H, 2×CH₂, CH₃), 1.61-1.56 (m, 4H, 2×CH₂), 1.48-1.42 (m, 2H, CH₂). LRMS (ES+): m/z (%) 230 (10) [M+2H]⁺, 460 (100) [M+H]⁺. HRMS (ES+): calcd for C₃₂H₃₄N₃ [M+H]⁺ 460.2747, found 460.2759 (-2.66 ppm).

(R/S)-6-(Benzofuran-2-yl)-2-methyl-4-phenyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (16f).

Prepared according to method E from 6-bromo-2-methyl-4-phenyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (15c) (82 mg, 0.2 mmol) and 2-Benzofuranboronic acid (49 mg, 0.3 mmol). The crude product was purified by flash column chromatography (MeOH/CH₂Cl₂ 0:100 → 10:90) to give a brown solid (47 mg, 52%).

\(^{1}H\) NMR (500 MHz, CDCl₃): δ 7.66 (dd, 1H, \(J = 8.5, 2.0\) Hz, ArH), 7.54-7.52 (m, 1H, ArH), 7.48-7.47 (m, 1H, ArH), 7.41-7.34 (m, 5H, 5×ArH), 7.31-7.28 (m, 1H, ArH), 6.86 (d, 1H, \(J = 0.5\) Hz, ArH), 5.67 (s, 1H, H-4), 3.53 (ddd, 1H, \(J = 14.5, 8.5, 6.0\) Hz, C₃H), 3.27 (ddd, 1H, \(J = 14.5, 8.5, 6.0\) Hz, C₃H), 2.58 (ddd, 1H, \(J = 12.5, 8.5, 6.0\) Hz, C₃H), 2.47-2.34 (m, 8H, C₄H, 2×CH₂ & CH₃), 1.61-1.56 (m, 4H, 2×CH₂), 1.47-1.43 (m, 2H, CH₂). LRMS (ES+): m/z (%) 450 (100) [M+H]⁺. HRMS (ES+): calcd for C₃₀H₂₈N₃O [M+H]⁺ 450.2540, found 450.2554 (-3.07 ppm).

### 4.1.8 Synthesis of C8-bromine substituted analog (18).
See Scheme S5 for the synthetic route to 18.

(2-Amino-3-bromo-5-chlorophenyl)(phenyl)methanone (2e).

NBS (3.74 g, 21 mmol) was added to a solution of 2-amino-5-chlorobenzophenone (2a) (4.63 g, 20 mmol) in CH₂Cl₂ (300 mL) and the solution stirred at 25°C for 16 h before the reaction solvent was removed under reduced pressure. The crude product was purified by flash column chromatography (Et₂O/Hexane 0:100 → 5:95) to give a yellow solid (4.55 g, 73%).

\(^{1}H\) NMR (500 MHz, CDCl₃): δ 7.65-7.57 (m, 4H, 4×ArH), 7.52-7.48 (m, 2H, 2×ArH), 7.42 (d, 1H, \(J = 2.5\) Hz, ArH), 6.61 (br s, 2H, NH₂). \(^{13}C\) NMR (125 MHz, CDCl₃): δ 197.4 (C), 146.5 (C), 138.8
(C), 136.6 (CH), 132.9 (CH), 131.9 (CH), 129.3 (CH), 128.4 (CH), 119.6 (C), 119.2 (C), 111.3 (C). 

LRMS (ES+): m/z (%) 310 (75) [\(^{79}\)Br\(^{35}\)Cl M+H]\(^+\), 312 (100) [\(^{79}\)Br\(^{37}\)Cl & \(^{81}\)Br\(^{35}\)Cl M+H]\(^+\), 314 (25) [\(^{81}\)Br\(^{37}\)Cl M+H]\(^+\). 

(R/S)-3-(6-Bromo-8-chloro-2-methyl-4-phenylquinazolin-3(4H)-yl)-N,N-dimethylpropan-1-amine (18).

![Chemical Structure](image)

Prepared in three steps from 2e, acetyl chloride and 3-(dimethylamino)-1-propylamine following general methods A, B and C\(^2\). The final product was purified by flash column chromatography (0.5M NH\(_3\) in MeOH/CH\(_2\)Cl\(_2\) 0.5:99.5 → 2:98) to give an off-white solid (291 mg, 8% over 3 steps).

\(^1\)H NMR (500 MHz, CDCl\(_3\)): \(\delta\) 7.41 (1H, d, \(J = 2.5\) Hz, ArH), 7.36-7.29 (5H, m, 5×ArH), 6.76 (1H, dd, \(J = 2.5, 1.0\) Hz, ArH), 5.48 (1H, s, C/H), 3.51-3.46 (1H, m, C/H), 3.16-3.10 (1H, m, C/H), 2.37 (3H, s, CH\(_3\)), 2.31-2.20 (8H, m, CH\(_2\) & N(CH\(_3\))\(_2\)). 

\(^13\)C NMR (125 MHz, CDCl\(_3\)): \(\delta\) 157.9 (C), 143.3 (C), 131.6 (C), 129.2 (CH), 128.6 (CH), 128.4 (C), 127.3 (C), 126.5 (CH), 125.5 (CH), 119.5 (C), 62.5 (CH\(_2\)), 46.8 (CH\(_2\)), 45.3 (N(CH\(_3\))\(_2\)), 26.2 (CH\(_2\)), 23.0 (CH\(_3\)). 

LRMS (ES+): m/z (%) 420 (80) [\(^{79}\)Br\(^{35}\)Cl M+H]\(^+\), 422 (100) [\(^{79}\)Br\(^{37}\)Cl & \(^{81}\)Br\(^{35}\)Cl M+H]\(^+\), 424 (24) [\(^{81}\)Br\(^{37}\)Cl M+H]\(^+\). HRMS (ES+): calcd for C\(_{20}\)H\(_{24}\)BrClN\(_3\) [M+H]\(^+\) 420.0837, found 420.0818 (4.47 ppm).

4.1.9 Synthesis of C\(_4\) aryl analogs (29c-f, 31b-d, 32b-g, 34-36).

See Scheme 4 for the synthetic routes to 29c-n. See the main paper for the synthesis of the related analogs 29a and 29b. See Scheme 5 for the synthetic route to 31b-d and 32b-g. See the main paper for the syntheis of the related analogs 31a and 32a. See Schemes S7 and S8 for the synthesis of analogs 34 and 35-36 respectively.

6-Chloro-2-methyl-4H-benzo[d][1,3]oxazin-4-one (24).\(^{11}\)

![Chemical Structure](image)

A solution of 5-chloroanthranilic acid (23) (50 g, 291 mmol) in acetic anhydride (170 mL) was heated to 140°C for 2 h. The reaction mixture was then cooled to 4°C and left for 16 h. The resultant precipitate was collected by filtration, washed with Et\(_2\)O (2×100 mL) and dried under vacuum to give a pale brown solid (46.4 g, 81%), which required no additional purification.

\(^1\)H NMR (500 MHz, DMSO-d\(_6\)): \(\delta\) 8.05 (d, 1H, \(J = 2.5\) Hz, H-5), 7.94 (dd, 1H, \(J = 8.5, 2.5\) Hz, H-7), 7.59 (d, 1H, \(J = 8.5\) Hz, H-8), 2.40 (s, 3H, CH\(_3\)). 

\(^13\)C NMR (125 MHz, DMSO-d\(_6\)): \(\delta\) 160.6 (C), 158.3 (C), 144.9 (C), 136.6 (CH), 132.0 (C), 128.3 (CH), 126.7 (CH), 118.1 (C), 21.0 (CH\(_3\)).
LRMS [NB, MS is recorded on methyl; ester product of ring opening with MeOH] (ES+): m/z (%)
228 (100) $^{35}$Cl M+H$^+$, 230 (31) $^{37}$Cl M+H$^+$, 455 (12) [2M+H]$^+$.

(R/S)-6-Chloro-4-(3-fluorophenyl)-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (29c).

Prepared in four steps from 23, 1-bromo-3-fluorobenzene, acetyl chloride and 1-(2-aminoethyl)piperidine following general methods G, A, B and C2. The final product was purified by reverse phase preparative HPLC to give a yellow semi-solid (19 mg, 3% over 4 steps).

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.32-7.27 (m, 1H, Ar), 7.11-6.95 (m, 5H, 5×Ar), 6.77 (d, 1H, J = 2.5 Hz, H-5), 5.58 (s, 1H, H-4), 3.48 (ddd, 1H, J = 14.0, 8.0, 6.0 Hz, CHH), 3.18-2.30 (m, 8H, C$_2$H$_8$ & 2×CH$_2$), 1.58-1.53 (m, 4H, 2×CH$_2$). $^{19}$F NMR (470 MHz, CDCl$_3$): δ -111.6 (CF). LRMS (ES+): m/z (%) 386 (100) $^{35}$Cl M+H$^+$, 388 (51) $^{37}$Cl M+H$^+$. HRMS (ES+): calcd for C$_{22}$H$_{26}$C$_1$$_1$F$_1$N$_3$ [M+H]$^+$ 386.1794, found 386.1790 (1.05 ppm).

(R/S)-6-Chloro-4-(3-methoxyphenyl)-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (29d).

Prepared in four steps from 23, 1-bromo-3-methoxybenzene, acetyl chloride and 1-(2-aminoethyl)piperidine following general methods G, A, B and C2. The final product was purified by reverse phase preparative HPLC to give a yellow semi-solid (19 mg, 3% over 4 steps).
**1**H NMR (500 MHz, CDCl₃): δ 7.28-7.25 (m, 1H, ArH), 7.09 (dd, 1H, J = 8.5, 2.5 Hz, H-7), 7.03 (d, 1H, J = 8.5 Hz, H-8), 6.92-6.90 (m, 1H, ArH), 6.84-6.82 (m, 2H, 2×ArH), 6.79 (d, 1H, J = 2.5 Hz, H-5), 5.55 (s, 1H, ArH), 3.80 (s, 3H, OCH₃), 3.48 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, C=CH), 3.21 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, C=CH), 2.55 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, C=CH), 2.44-2.33 (m, 5H, C=CH & 2×NCH₂), 1.59-1.55 (m, 4H, 2×CH₂), 1.47-1.42 (m, 2H, CH₂). LRMS (ES⁺): m/z (%) 398 (100) [35Cl M+H]+, 400 (36) [37Cl M+H]+. HRMS (ES⁺): calcd for C₂₃H₂₅N₂ClO [M+H]+ 398.1994, found 398.1985 (2.28 ppm).

(R/S)-6-Chloro-4-(3,4-dichlorophenyl)-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (29e).

![Chemical structure of 29e](image)

Prepared in four steps from 23, 4-bromo-1,2-dichlorobenzene, acetyl chloride and 1-(2-aminomethyl)piperidine following general methods G, A, B and C2. The final product was purified by reverse phase preparative HPLC to give a cream solid (17 mg, 1% over 4 steps).

1H NMR (500 MHz, CDCl₃): δ 7.41 (d, 1H, J = 8.0 Hz, H-5’), 7.36 (d, 1H, J = 2.0 Hz, H-2’), 7.15-7.11 (m, 2H, H-7 & H-6’), 7.04 (d, 1H, J = 8.5 Hz, H-8), 6.75 (d, 1H, J = 2.5 Hz, H-5), 5.58 (s, 1H, H-4), 3.49 (ddd, 1H, J = 15.0, 7.5, 6.0 Hz, C=CH), 3.18-3.12 (m, 1H, C=CH), 2.54 (ddd, 1H, J = 13.0, 7.5, 6.0 Hz, C=CH), 2.44-2.33 (m, 5H, C=CH & 2×CH₂), 2.29 (s, 3H, CH₃), 1.59-1.55 (m, 4H, 2×CH₂), 1.46-1.42 (m, 2H, CH₂). LRMS (ES⁺): m/z (%) 436 (100) [35Cl₂ M+H]+, 438 (97) [35Cl₂ 37Cl M+H]+, 440 (32) [37Cl₂ M+H]+. HRMS (ES⁺): calcd for C₂₂H₂₅Cl₂N₃ [M+H]+ 436.1109, found 436.1093 (3.63 ppm).

6-Chloro-2-methyl-3-(2-(piperidin-1-yl)ethyl)quinazolin-4(3H)-one (30).

1-(2-Aminoethyl)piperidine (3.85 g, 30 mmol) was added to a solution of benzoazinone (24) (4.89 g, 25.0 mmol) in dichloromethane (25 mL) and stirred at 25°C for 16 h. The solvent was then removed under reduced pressure and the resultant oil dissolved in MeCN (5 mL) and heated at 130°C for 20 min in a microwave reactor. The reaction mixture was then stood for 16 h and the resultant precipitate recovered by filtration and washed with cold MeCN (2×25 mL) to give an orange solid, which was further purified by recrystallization from EtOAc/heaxnes to give a white crystalline solid (4.42g, 58%).
1H NMR (500 MHz, CDCl₃): δ 8.19 (d, 1H, J = 2.5 Hz, H-5), 7.63 (dd, 1H, J = 9.0, 2.5 Hz, H-7), 7.54 (d, 1H, J = 9.0 Hz, H-8), 4.20 (t, 2H, J = 7.0 Hz, CH₂), 2.69 (s, 3H, CH₃), 2.63 (t, 2H, J = 7.0 Hz, CH₂), 2.49-2.46 (m, 4H, 2×CH₂), 1.59-1.55 (m, 4H, 2×CH₂), 1.46-1.41 (m, 2H, CH₂).

13C NMR (125 MHz, CDCl₃): δ 161.1 (C), 155.0 (C), 145.8 (C), 134.6 (CH), 132.0 (C), 128.4 (CH), 126.0 (CH), 121.5 (C), 56.9 (CH₃), 42.8 (CH₂), 26.0 (CH₂), 24.1 (CH₂), 23.5 (CH₃).

LRMS (ES+): m/z (%) 306 (100) [35Cl M+H]+, 308 (36) [37Cl M+H]+.

6-Chloro-4-(4-fluorophenyl)-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazolin-4-ol (31b).

Prepared according to general method H using 4-fluorophenylmagnesium bromide. The product was purified by recrystallisation from refluxing MeCN to give a white crystalline solid (412 mg, 51%).

1H NMR (500 MHz, CDCl₃): δ 9.51 (br s, 1H, OH), 7.52-7.47 (m, 2H, AA’BB’), 7.12 (dd, 1H, J = 8.5, 2.0 Hz, H-7), 7.07 (d, 1H, J = 8.5 Hz, H-8), 7.06-7.01 (m, 2H, AA’BB’), 6.76 (d, 1H, J = 2.0 Hz, H-5), 3.47 (ddd, 1H, J = 16.5, 3.5, 1.5 Hz, CH), 3.07 (ddd, 1H, J = 16.5, 11.5, 1.0 Hz, CH), 2.56 (ddd, 1H, J = 13.5, 11.5, 1.5 Hz, CH), 2.49-2.34 (m, 4H, 2×CH₂), 2.34-2.28 (m, 4H, CH₂ & CH₃), 2.17-2.08 (m, 4H, 2×CH₂), 1.55-1.44 (m, 2H, CH₂).

19F NMR (470 MHz, CDCl₃): δ -114.5 (CF).

LRMS (ES+): m/z (%) 402 (100) [35Cl M+H]+, 404 (31) [37Cl M+H]+.

HRMS (ES+): calcd for C₂₂H₂₆Cl₁N₁₃O₁ [M+H]+ 402.1743, found 402.1742 (0.28 ppm).

6-Chloro-4-(4-methoxyphenyl)-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazolin-4-ol (31c).

Prepared according to general method H using 4-methoxyphenylmagnesium bromide. The product was purified by recrystallisation from refluxing MeCN to give a white solid (361 mg, 44%).

1H NMR (500 MHz, CDCl₃): δ 9.37 (br s, 1H, OH), 7.45-7.43 (m, 2H, AA’BB’), 7.14-7.10 (m, 2H, 2×Ar), 6.90-6.88 (m, 2H, AA’BB’), 6.80 (d, 1H, J = 2.0 Hz, H-5), 3.84 (s, 3H, OCH₃), 3.50-3.46 (m, 1H, CH), 3.19-3.14 (m, 1H, CH), 2.61-2.56 (m, 1H, CH), 2.50-2.37 (m, 4H, 2×CH₂), 2.36 (s, 3H, CH₃), 2.32-2.29 (m, 1H, CH), 1.73-1.68 (m, 4H, 2×CH₂), 1.54-1.48 (m, 2H, CH₂). LRMS (ES+): m/z (%) 207.5 (100) [M+2H]⁺, 414 (71) [35Cl M+H⁺], 416 (21) [37Cl M+H⁺]. HRMS (ES+): calcd for C₂₃H₂₇Cl₁N₁₃O₂ [M+H⁺] 414.1943, found 414.1936 (1.57 ppm).

6-Chloro-2-methyl-3-(2-(piperidin-1-yl)ethyl)-4-p-tolyl-3,4-dihydroquinazolin-4-ol (31d).
Prepared according to general method H using 4-methylphenylmagnesium bromide. The product was purified by recrystallisation from refluxing MeCN to give an off-white solid (373 mg, 47%).

\[ \text{H NMR (500 MHz, CDCl} \text{)}: \delta \text{ 9.36 (br s, 1H, OH), 7.40-7.38 (m, 2H, AA’BB’), 7.16-7.13 (m, 2H, AA’BB’), 7.11-7.08 (m, 2H, H-7 & H-8), 6.78-6.77 (m, 1H, H-5), 3.47-3.43 (m, 1H, CHH), 3.14-3.08 (m, 1H, CHH), 2.58-2.53 (m, 1H, CHH), 2.47-2.25 (m, 2×CH}_2, \text{CHH & 2×CH}_3, \text{1.71-1.67 (m, 4H, 2×CH}_2\text{), 1.54-1.43 (m, 2H, CH}_2\text{). LRMS (ES+): m/z (%) 199.5 (59) [^{35}\text{Cl M+2H}]^{2+}, 398 (100) [^{35}\text{Cl M+H}]^+, 400 (41) [^{37}\text{Cl M+H}]^+. HRMS (ES+): calcd for C_{23}H_{29}Cl_1N_3O_1 [M+H]^+ 398.1994, found 398.1978 (3.94 ppm).} \]

(R/S)-6-Chloro-4-(3,4-dimethylphenyl)-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazolin-4-ol (31g).

Prepared according to general method H using 3,4-dimethylphenylmagnesium bromide. The product was purified by recrystallisation from refluxing MeCN to give an off-white solid (205 mg, 25%).

\[ \text{H NMR (500 MHz, CDCl} \text{)}: \delta \text{ 9.32 (br s, 1H, OH), 7.26-7.22 (m, 3H, 3×ArH), 7.11-7.09 (m, 3H, 3×ArH), 6.78-6.77 (m, 1H, ArH), 3.47-3.43 (m, 1H, CHH), 3.16-3.10 (m, 1H, CHH), 2.60-2.54 (m, 1H, CHH), 2.50-2.21 (m, 14H, CH}_2, \text{CHH, 3×CH}_3, \text{1.74-1.66 (m, 4H, 2×CH}_2, \text{1.55-1.43 (m, 2H, CH}_2\text{). LRMS (ES+): m/z (%) 412 (100) [^{35}\text{Cl M+H}]^+, 414 (45) [^{37}\text{Cl M+H}]^+. HRMS (ES+): calcd for C_{24}H_{31}^{^{35}}\text{Cl}_1N_3O_1 [M+H]^+ 412.2150, found 412.2151 (-0.14 ppm).} \]

6-Chloro-4-(4-fluorophenyl)-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (32b).

Prepared according to general method I from 31b (121 mg, 0.3 mmol). The product was purified by preparative HPLC to give a clear semi-solid (17 mg, 15%).

\[ \text{H NMR (500 MHz, CDCl} \text{)}: \delta \text{ 7.30-7.25 (m, 3H, 3×ArH), 7.13-7.09 (m, 1H, ArH), 7.06-7.01 (m, 3H, 3×ArH), 6.75 (s, 1H, H-5), 5.57 (s, 1H, H-4), 3.50-3.44 (m, 1H, CHH), 3.22-3.16 (m, 1H, CHH), 2.57-2.52 (m, 1H, CHH), 2.42-2.33 (m, 5H, CHH & 2×CH}_2, \text{2.29 (s, 3H, CH}_3\text{), 1.60-1.55 (m, 4H, 2×CH}_2, \text{1.47-1.42 (m, 2H, CH}_2\text{). }^1\text{F NMR (470 MHz, CDCl} \text{)}: \delta \text{ -113.6 (CF). LRMS (ES+): m/z (%) 386 (100) [^{35}\text{Cl M+H}]^+, 388 (19) [^{37}\text{Cl M+H}]^+. HRMS (ES+): calcd for C_{22}H_{26}^{^{35}}\text{Cl}_1F_1N_2O_1 [M+H]^+ 386.1794, found 386.1800 (-1.62 ppm).} \]
(R/S)-6-Chloro-4-(4-methoxyphenyl)-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (32c).

Prepared according to general method I from 31c (124 mg, 0.3 mmol). The product was purified by preparative HPLC to give a yellow solid (34 mg, 28%).

1H NMR (500 MHz, CDCl3): 6 7.21-7.18 (m, 2H, AA’BB’), 7.12-7.08 (m, 2H, H-7 & H-8), 6.87-6.84 (m, 2H, AA’BB’), 6.74 (d, 1H, J = 1.0 Hz, H-5), 5.53 (s, 1H, H-4), 3.79 (s, 3H, OCH3), 3.45 (ddd, 1H, J = 14.0, 8.0, 6.0 Hz, CHH), 3.22 (ddd, 1H, J = 14.0, 8.0, 6.0 Hz, CHH), 2.53 (ddd, 1H, J = 14.0, 8.0, 6.0 Hz, CHH), 2.43-2.31 (m, 5H, 5H, CHH & 2xNCH2), 2.18 (s, 3H, CH3), 1.58-1.54 (m, 4H, 2xCH2), 1.46-1.41 (m, 2H, CH2). LRMS (ES+): m/z (%) 398 (100) [35Cl M+H]+, 400 (31) [37Cl M+H]+. HRMS (ES+): calcd for C23H29Cl1N3O1[M+H]+ 398.1994, found 398.1985 (2.12 ppm).

(R/S)-6-Chloro-2-methyl-3-(2-(piperidin-1-yl)ethyl)-4-p-tolyl-3,4-dihydroquinazoline (32d).

Prepared according to general method I from 31d (119 mg, 0.3 mmol). The product was purified by preparative HPLC to give a yellow semi-solid (18 mg, 16%).

1H NMR (500 MHz, CDCl3): 6 7.18-7.15 (m, 2H, AA’BB’), 7.13-7.11 (m, 2H, AA’BB’), 7.06 (dd, 1H, J = 8.5, 2.5 Hz, H-7), 7.00 (d, 1H, J = 8.5 Hz, H-8), 6.74 (d, 1H, J = 2.5 Hz, H-5), 5.50 (s, 1H, H-4), 3.44 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, CHH), 3.17 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, CHH), 2.52 (ddd, 1H, J = 13.0, 8.5, 6.0 Hz, CHH), 2.41-2.31 (m, 8H, CHH, 2xCH2, CH3), 2.26 (s, 3H, CH3), 1.57-1.52 (m, 4H, 2xCH2), 1.44-1.40 (m, 2H, CH2). LRMS (ES+): m/z (%) 382 (100) [35Cl M+H]+, 384 (34) [37Cl M+H]+. HRMS (ES+): calcd for C23H25Cl1N3 [M+H]+ 382.2045, found 382.2037 (2.00 ppm).

(R/S)-6-Chloro-4-(3-chlorophenyl)-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (32e)
Prepared in two steps from 30 and 3-chlorophenylmagnesium bromide following general methods H and I. The product was purified by flash column chromatography (MeOH/CH₂Cl₂ 0:100 → 10:90) to give an off-white solid (51 mg, 13% over two steps).

\(^1\)H NMR (500 MHz, CDCl₃): δ 7.20-7.18 (m, 3H, 3×ArH), 7.11-7.09 (m, 1H, ArH), 7.02 (dd, 1H, J = 8.5, 2.5 Hz, H-7), 6.97 (d, 1H, J = 8.5 Hz, H-8), 6.68 (d, 1H, J = 2.5 Hz, H-5), 5.49 (s, 1H, H-4), 3.40 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, C₃H₃), 3.08 (ddd, 1H, J = 14.5, 8.0, 6.5 Hz, CₓHₓ), 2.48-2.43 (m, 1H, CₓHₓ), 2.34-2.22 (m, 5H, CₓHₓ & 2×CH₂), 2.22 (s, 3H, CH₃), 1.50-1.46 (m, 4H, 2×CH₂), 1.37-1.34 (m, 2H, CH₂). LRMS (ES+): \(m/z\) (%) 402 (100) \([35\text{Cl}]M+H\]^+, 404 (67) \([37\text{Cl}]M+H\]^+. HRMS (ES+): calcd for C₂₂H₂₆Cl₂N₃[M+H]^+ 402.1498, found 402.1580 (4.57 ppm).

\((R/S)-6\)-Chloro-4-(3-methylphenyl)-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (32f)

Prepared in two steps from 30 and 3-methylphenylmagnesium chloride following general methods H and I. The product was purified by preparative HPLC to give a yellow semi-solid (18 mg, 9% over two steps).

\(^1\)H NMR (500 MHz, CDCl₃): δ 7.23-7.20 (m, 1H, ArH), 7.10-7.06 (m, 4H, 4×ArH), 7.02 (d, 1H, J = 8.5 Hz, H-8), 6.76 (d, 1H, J = 2.0 Hz, H-5), 5.51 (s, 1H, H-4), 3.46 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, C₃H₃), 2.53 (ddd, 1H, J = 13.0, 8.5, 6.0 Hz, CₓHₓ), 2.41-2.32 (m, 8H, CₓHₓ, 2×CH₂, CH₃), 2.29 (s, 3H, CH₃), 1.58-1.54 (m, 4H, 2×CH₂), 1.44-1.42 (m, 2H, CH₂). LRMS (ES+): m/z (%) 382 (100) \([35\text{Cl}]M+2H\]²⁺, 384 (35) \([37\text{Cl}]M+H\]^+, 763 (22) \([2\text{[35Cl}M+H]^+\], 765 (15) \([35\text{Cl}M \& 37\text{Cl}M +H]^+\). HRMS (ES+): calcd for C₂₃H₂₉Cl₁N₃[M+H]^+ 382.2045, found 382.2029 (4.13 ppm).

\((R/S)-6\)-Chloro-4-(3,4-dimethylphenyl)-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (32g)

Prepared according to general method I from 31g (103 mg, 0.25 mmol). The product was purified by preparative HPLC, followed by flash column chromatography (MeOH/CH₂Cl₂ 0:100 → 10:90) to give a clear semi-solid (12 mg, 12%).

\(^1\)H NMR (500 MHz, CDCl₃): δ 7.09-7.00 (m, 5H, 5×ArH), 6.75 (s, 1H, ArH), 5.50 (s, 1H, H-4), 3.46 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, C₃H₃), 3.19 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, CₓHₓ), 2.56-2.51 (m, 1H, CₓHₓ), 2.43-2.31 (m, 8H, CHH, 2×CH₂, CH₃), 2.23 (br s, 6H, 2×CH₃), 1.58-1.54 (m, 4H, 2×CH₂), 1.47-1.42 (m, 2H, CH₂). LRMS (ES+): m/z (%) 198.5 (100) \([35\text{Cl}]M+2H\]²⁺, 396 (89) \([37\text{Cl}]M+H\]^+. HRMS (ES+): calcd for C₂₄H₃₁Cl₁N₃[M+H]^+ 396.2201, found 396.2185 (3.98 ppm).
1-(2-Amino-5-chlorophenyl)-2-phenylethanone (26g).

A solution of benzylmagnesium bromide (14 mmol, 2.0M in THF, 7 mL) was slowly added to a solution of nitrile (25) (5.0 mmol, 763 mg) in anhydrous Et₂O (2 mL) at 0°C. The reaction was then allowed to warm to 25°C and subsequently stirred for a further 16 h. The reaction mixture was then cooled to -60°C and the workup was initiated by the addition of HCl (6N, aq., 6 mL). After stirring for 30 min the reaction was diluted with EtOAc (25 mL), the layers separated and the aqueous further extracted with EtOAc (3×25 mL). The combined organic layers were then dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography over silica (EtOAc/hexanes 0:100 → 50:50) to give a yellow solid (466 mg, 38%).

\[ \text{1H NMR (500 MHz, CDCl}_3\text{): } \delta 7.83 \text{ (d, 1H, } J = 2.5 \text{ Hz, H-6\textsuperscript{+}}), 7.40-7.37 \text{ (m, 2H, 2×Ar), 7.32-7.25 (m, 3H, 3×Ar), 7.24 (dd, 1H, } J = 9.0, 2.5 \text{ Hz, H-4\textsuperscript{+}}\text{), 6.63 (d, 1H, } J = 9.0 \text{ Hz, H-3\textsuperscript{+}}\text{), 6.33 (br s, 2H, NH}_2\text{), 4.26 (s, 2H, CH}_2\text{).} \]

\[ \text{13C NMR (125 MHz, CDCl}_3\text{): } \delta 199.1 \text{ (C), 149.3 (C), 134.8 (C), 134.5 (CH), 130.6 (CH), 129.6 (CH), 128.7 (CH), 127.0 (CH), 120.0 (C), 118.9 (CH), 117.9 (C), 46.0 (CH}_2\text{).} \]

LRMS (ES+): m/z (%) 246 (100) [\text{35Cl M+H}], 248 (32) [\text{37Cl M+H}].

4-Chloro-2-(2-phenyl-1-((2-(piperidin-1-yl)ethyl)amino)ethyl)aniline (33).

1-(2-Amino-5-chlorophenyl)-2-phenylethanone (26g) was slowly added to a suspension of ketone 26g (1.75 mmol, 430 mg) and 4 Å molecular sieves in ethanol (4 mL). The reaction was stirred for 10 days before the addition of NaBH₄ (17.5 mmol, 662 mg) in ethanol (10 mL) followed by additional stirring for 16 h. Work up was initiated by the addition of citric acid (10% w/v, aq) and subsequent removal of the ethanol under reduced pressure. The pH of the aqueous layer was then adjusted to 10 followed by extraction with CH₂Cl₂ (4×20 mL). The combined CH₂Cl₂ layers were dried over MgSO₄, filtered and the solvent removed under reduced pressure. The crude product was purified by flash column chromatography over silica (MeOH/CH₂Cl₂ 0:100 → 10:90) to give a cream solid (151 mg, 24%).

\[ \text{1H NMR (300 MHz, CDCl}_3\text{): } \delta 7.25-7.11 \text{ (m, 5H, 5×ArH), 6.91 (dd, 1H, } J = 8.5, 2.5 \text{ Hz, H-5}, 6.85 \text{ (d, 1H, } J = 2.5 \text{ Hz, H-3}), 6.44 \text{ (d, 1H, } J = 8.5 \text{ Hz, H-6}), 3.74 (d, 1H, } J = 9.5 \text{ Hz, CH), 3.06 (dd, 1H, } J = 9.5, 5.0 \text{ Hz, CH}, 2.92 (dd, 1H, } J = 13.5 \text{ Hz, CH, CH}_2\text{), 2.48-2.09 (m, 8H, 4×CH}_2\text{), 1.41-1.22 (m, 6H, 3×CH}_2\text{).} \]

LRMS (ES+): m/z (%) 358 (100) [\text{35Cl M+H}], 360 (41) [\text{37Cl M+H}].

(R/S)-4-Benzyl-6-chloro-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (34).
Acetyl chloride (0.4 mmol, 31 mg) was added to a suspension of 33 (0.4 mmol, 143 mg) and K$_2$CO$_3$ (0.8 mmol, 111 mg) in anhydrous MeCN (5 mL) and stirred at 25°C for 16 h. The resultant amide was separated from unreacted 33 by flash column chromatography (MeOH/CH$_2$Cl$_2$ 0:100 → 10:90), redissolved in EtOH (2.5 mL) and heated to 140°C for 2 h under microwave irradiation. After cooling a portion of the product was purified directly by preparative HPLC to give a yellow semi-solid (18 mg, 12%).

$^1$H NMR (500 MHz, CDCl$_3$): δ 7.29-2.27 (m, 3H, 3×ArH), 7.15 (dd, 1H, $J$ = 8.0, 2.0 Hz, H-7), 7.00 (d, 1H, $J$ = 8.0 Hz, H-8), 6.98-6.96 (m, 2H, 2×ArH), 6.59 (d, 1H, $J$ = 2.0 Hz, H-5), 4.54 (dd, 1H, $J$ = 6.5, 6.5 Hz, H-4), 3.52 (dd, 1H, $J$ = 14.5, 8.5, 6.0 Hz, CH), 2.83 (ddd, 1H, $J$ = 14.5, 8.5, 6.0 Hz, CH), 2.83 (ddd, 2H, $J$ = 13.0, 6.5 Hz, PhCH$_2$), 2.44-2.32 (m, 6H, CH$_2$ & 2×NCH$_2$), 2.19 (s, 3H, CH$_3$), 1.57-1.52 (m, 4H, 2×CH$_2$), 1.46-1.40 (m, 2H, CH$_2$). $^13$C NMR (125 MHz, CDCl$_3$): δ 156.2 (C), 141.5 (C), 136.6 (C), 129.6 (CH), 128.4 (CH), 128.1 (CH), 126.9 (CH), 126.1 (C), 125.0 (CH), 124.2 (CH), 58.4 (CH$_2$), 55.0 (CH$_2$), 48.1 (CH$_2$), 42.2 (CH$_2$), 26.0 (CH$_2$), 24.1 (CH$_2$), 22.2 (CH$_3$) [Note, there is one too few aryl quaternary carbon peaks, possibly due to two carbon shifts being identical]. LRMS (ES+): m/z (%) 382 (100) [$^{35}$Cl M+H]+, 384 (22) [$^{37}$Cl M+H]. HRMS (ES+): calcd for C$_{23}$H$_{29}$Cl$_1$N$_3$ [M+H]$^+$ 382.2045, found 382.2054 (-2.53 ppm).

(R/S)-6-Chloro-4-cyclohexyl-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazoline (29f).
Prepared in four steps from 26f, acetyl chloride and 1-(2-aminoethyl)piperidine following general methods A, B and C1, followed by microwave irradiation at 160°C for 4 h. The final product was purified by flash column chromatography (MeOH/CH₂Cl₂ 0:100 → 15:85) to give a yellow semi-solid (22 mg, 5% over 4 steps).

\[
\begin{align*}
&\text{[Diagram]} \\
\end{align*}
\]

\[
\begin{align*}
^{1}H \text{ NMR (500 MHz, CDCl₃): } & \delta 7.10 (dd, 1H, J = 8.5, 2.5 Hz, H-7), 7.05 (d, 1H, J = 5.0, H-4), 3.68 (ddd, 1H, J = 14.5, 8.5, 6.0 Hz, CHH), 3.20 (ddd, 1H, J = 14.5, 9.0, 5.5 Hz, CHH), 2.41-2.35 (m, 1H, CHH), 2.33-2.24 (m, 5H, 2×CH₂ & CHH), 2.24 (s, 3H, CH₃), 1.69-1.43 (m, 10H, CH, 2×CH₂ & 5×CHH), 1.37-1.32 (m, 2H, CH₂), 1.12-0.91 (m, 4H, 4×CHH), 0.78-0.70 (m, 1H, CHH). \\
^{13}C \text{ NMR (125 MHz, CDCl₃): } & \delta 157.5 (C), 140.5 (C), 128.5 (C), 128.2 (CH), 125.8 (CH), 123.9 (C), 123.3 (CH), 64.4 (CH), 58.2 (CH₂), 55.1 (CH₂), 49.2 (CH₂), 44.7 (CH), 28.8 (CH₂), 27.6 (CH₂), 26.03 (CH₂), 25.98 (CH₂), 25.95 (CH₂), 25.9 (CH₂), 24.1 (CH₂), 21.4 (CH₃). \\
\text{LRMS (ES+): } & m/z (%) 374 (100) [\text{[35Cl M+H]}^+], 376 (80) [\text{[37Cl M+H]}^+]. \\
\text{HRMS (ES+): } & \text{calcd for C}_{22}\text{H}_{33}\text{Cl}_{3}\text{N}_{3}[\text{M+H}]^+ 374.2358, \text{found 374.2346 (3.04 ppm).}
\end{align*}
\]

(R/S)-4-(6-Chloro-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazolin-4-yl)phenol (35).

\[
\begin{align*}
\text{[Diagram]} \\
\end{align*}
\]

BBBr₃ (0.076 mmol, 1.0M solution, 76 µL) was added to a solution of 32c (0.038 mmol, 15 mg) in anhydrous CH₂Cl₂ (1 mL) at -78°C. The reaction was allowed to warm to 0°C over 3 h before workup was initiated by the addition of aqueous NaOH (2.0M, 1 mL). Subsequently the layers were separated and the aqueous extracted with CH₂Cl₂ (3×10 mL). The combined CH₂Cl₂ layers were then dried over MgSO₄, filtered and the solvent removed under reduced pressure. The product was purified by preparative HPLC to give a white solid (2 mg, 13%).

\[
\begin{align*}
^{1}H \text{ NMR (500 MHz, CDCl₃): } & \delta 7.06-7.02 (m, 4H, 4×ArH), 6.82-6.81 (m, 1H, ArH), 6.77-6.74 (m, 2H, AA’BB’), 5.46 (s, 1H, H-4), 3.46 (ddd, 1H, J = 14.5, 8.5, 6.0, CHH), 3.26 (ddd, 1H, J = 14.5, 8.5, 6.0, CHH), 2.53 (ddd, 1H, J = 14.0, 8.5, 6.0, CHH), 2.44-2.34 (m, 5H, CHH & 2×CH₂), 2.26 (s, 3H, CH₃), 1.58-1.54 (m, 4H, 2×CH₂), 1.46-1.41 (m, 2H, CH₂). \\
\text{LRMS (ES+): } & m/z (%) 384 (100) [\text{[35Cl M+H]}^+], 386 (31) [\text{[37Cl M+H]}^+]. \\
\text{HRMS (ES+): } & \text{calcd for C}_{22}\text{H}_{35}\text{Cl}_{3}\text{N}_{3}[\text{M+H}]^+ 384.1837, \text{found 384.1824 (3.35 ppm).}
\end{align*}
\]

(R/S)-3-(6-Chloro-2-methyl-3-(2-(piperidin-1-yl)ethyl)-3,4-dihydroquinazolin-4-yl)phenol (36).
BBR₃ (0.038 mmol, 1.0M solution, 38 µL) was added to a solution of 29d (0.038 mmol, 15 mg) in anhydrous CH₂Cl₂ (1 mL) at -78°C. The reaction was allowed to warm to 0°C over 2 h before workup was initiated by the addition of aqueous NaOH (2.0M, 1 mL). Subsequently the layers were separated and the aqueous extracted with CH₂Cl₂ (4×5 mL). The combined CH₂Cl₂ layers were then dried over MgSO₄, filtered and the solvent removed under reduced pressure. The product was purified by preparative HPLC to give a white solid (5 mg, 34%).

¹H NMR (500 MHz, CDCl₃): δ 7.24 (dd, 1H, J = 8.0, 8.0, H-5'), 6.96-6.85 (m, 4H, 4×ArH), 6.78-6.74 (m, 2H, 2×ArH), 5.51 (s, 1H, H-4), 3.36-3.32 (m, 1H, CHH), 3.27-3.21 (m, 1H, CHH), 2.53-2.47 (m, 1H, CHH), 2.42-2.34 (m, 5H, CHH & 2×CH₂), 1.94 (s, 3H, CH₃), 1.58-1.54 (m 4H, 2×CH₂), 1.46-1.41 (m, 2H, CH₂). ¹³C NMR (125 MHz, CDCl₃): δ 160.2 (C), 156.8 (C), 144.9 (C), 137.7 (C), 129.6 (CH), 129.1 (C), 128.2 (CH), 126.4 (CH), 125.9 (C), 123.3 (CH), 117.8 (CH), 116.9 (CH), 113.7 (CH), 63.1 (CH), 57.1 (CH), 55.1 (CH), 46.3 (CH₂), 26.0 (CH₂), 24.2 (CH₂), 20.4 (CH₂).

LRMS (ES+): m/z (%) 384 (100) [³⁵Cl M+H]⁺, 386 (18) [³⁷Cl M+H]⁺. HRMS (ES+): calcd for C₂₂H₂₃ClN₃O [M+H]⁺ 384.1837, found 384.1829 (2.24 ppm).

5.0 Reference List
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