Exploring a Tetrahydroquinoline Antimalarial Hit from the Medicines for Malaria Pathogen Box and Identification of its Mode of Resistance as PfeEF2

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Supporting Information

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Biological Experimental Methods:

In vitro P.falciparum viability assay, 3D7 strain (compounds 1-34 and 36)

Cultures of the widely-used malaria reference strain of chloroquine-sensitive Plasmodium falciparum strain 3D7 were maintained in a 5% suspension of A+ human red blood cells (obtained from East of Scotland Blood Transfusion Service, Ninewells Hospital, Dundee) cultured in RPMI 1640 medium (pH 7.3) supplemented with 0.5% Albumax II (Gibco Life Technologies, San Diego, CA), 12 mM sodium bicarbonate, 0.2 mM hypoxanthine, and 20 mg/L gentamicin at 37 °C, in a humidified atmosphere of 1% O₂, 3% CO₂ with a balance of nitrogen. Growth inhibition was quantified using a fluorescence assay utilising the binding of SYBR Green I to double stranded DNA, which emits a fluorescent signal at 528 nm after excitation at 485 nm. The assay was performed in 384 well format as previously published (https://pubmed.ncbi.nlm.nih.gov/15105138/). All assays were performed in duplicate.

In vitro P.falciparum viability assay, 3D7 strain (compound 35)

P. falciparum 3D7 (From BEI resource) lactate dehydrogenase (Pf-LDH) growth inhibition assay was carried out as described in the following paper (F. J. Gamo, L. M. Sanz, J. Vidal, C. de Cozar, E. Alvarez, J. L. Lavandera, D. E. Vanderwall, D. V. Green, V. Kumar, S. Hasan, J. R. Brown, C. E. Peishoff, L. R. Cardon, J. F. Garcia-Bustos, Nature 2010, 465, 305-310) with minor modification in the culture state of inoculum (10-15% parasitaemia with ≥80% rings).

Data were normalized to percent growth inhibition with respect to positive (0.2% DMSO as 0% inhibition) and negative (mixture of 100 mM Chloroquine and 100 mM Atovaquone as 100% inhibition) controls.

In vitro P.falciparum viability assay, NF54

In vitro activity against erythrocytic stages of P. falciparum using the chloroquine-sensitive NF54 strain was determined with a ³H-hypoxanthine incorporation assay. Test compounds were dissolved in DMSO at 10 mg/mL and added to parasite cultures incubated in RPMI 1640 medium without hypoxanthine, supplemented with HEPES (5.94 g/L, NaHCO₃ (2.1 g/L), neomycin (100 U/mL), and Albumax (5 g/L). Cultures were maintained at 2.5% hematocrit (0.3% parasitemia) using A+ human red blood cells. Serial drug dilutions of 11 3-fold dilution steps (covering a range from 100–0.002 μg/mL) were prepared. The 96-well plates were incubated in a humidified atmosphere at 37 °C; 4% CO₂, 3% O₂, 93% N₂. After 48 h, 0.05 mL of ³H-hypoxanthine (=0.5 μCi) was added to each well. The plates were incubated for another 24 h under the same conditions. Plates were harvested with a Betaplate cell harvester (Wallac,
Zurich, Switzerland). The red blood cells were transferred onto glass fiber filters and washed with distilled water. The dried filters were inserted into a plastic foil with 10 mL of scintillation fluid and counted in a Betaplate liquid scintillation counter. IC\textsubscript{50} values were determined from sigmoidal inhibition curves by linear regression using Microsoft Excel. Chloroquine (Sigma C6628) was used as a control.

\textit{P. berghei liver stage assay.}

3000 HepG2-CD81 cells per well in 5 µL of screening medium were seeded into 1,536 well plates containing 50 nL of test and control compounds diluted into DMSO. Approximately 24 h later, ~1,000 \textit{P. berghei} sporozoites \textit{(P. berghei ANKA GFP-Luc-SM\textsubscript{contra})} in screening media were added to each well and centrifuged at 330g for 3 min. Cells were incubated for 48 h at 37 °C. Next, 2 µL of luciferin reagent (Promega BrightGlo) was added to each well and luciferase activity was detected using a Perkin Elmer Envision plate reader. IC\textsubscript{50} values were determined in CDD vault (https://www.collaborativedrug.com/) (normalized to maximum and minimum inhibition levels for the positive (atovaquone, 0.25 µM) and negative (DMSO) control wells.

\textit{P. falciparum} gametocyte stage V sexual stage assay

Gametocyte stages V were diluted to 0.50% gametocytemia and 1.25% hematocrit into complete media for the two step protocol (TSSA) or 0.5%–0.75% gametocytemia and 1.25% hematocrit into serum-free SALSSA screening media (RPMI 1640, gentamicin 0.05 mg/mL, hypoxanthine 0.014 mg/mL, HEPES 38.4 mM, sodium bicarbonate 0.2% [w/v], D-glucose 0.2% [w/v], sodium hydroxide 3.4 mM and 0.4% [w/v] AlbuMAX II). Cultures were dispensed (40 mL versus 10 mL) into 384 or 1,536-well plates containing 50 nL or 2.5 nL of compound (final concentration of 1.25 to 12.5 mM) using a MultiFlo dispenser. Plates were incubated at 37 °C for 72 h under low-oxygen conditions. For SaLSSA 3 mL (1,536 well) or 10 mL (384 well) of 2.5 mM MitoTracker Red CMXRos and 0.13% saponin solution (w/v) in screening media was added to each well, and plates were incubated for 60–120 min at 37 °C. For 384-well TSSA, 5 mL MitoTracker Red CMXRos (5 mM) in screening media was added to each well. After 20 min at 37 °C, 5 mL was transferred from the assay plate to a new 384-well imaging plate, that already contained 40 mL MitoTracker Red CMXRos (500 nm) in serum-free screening media. For both TSSA and SaLSSA, plates were imaged after 30 min incubation.

\textit{Parasite Reduction Ratio Assay}

\textit{In vitro} parasite reduction ratio (PRR) assay with \textit{Plasmodium falciparum} (GSK). The \textit{in vitro} PRR assay was conducted as previously described (L. M. Sanz, B. Crespo, C. De-Cózar, X. C. Ding, J. L. Llergo, J. N. Burrows, J. F. Garcia-Bustos, F. J. Gamo, F.J. \textit{PLoS ONE}. 2012, 7, e30949). Briefly,
0.5% parasitemia 3D7 *P. falciparum* parasites (≥80% ring-stage population) at 2% hematocrit were exposed to compounds for 120 h at a concentration corresponding to 10 x EC₅₀. Drug was renewed daily over the entire treatment period. Samples of parasites were taken from the treated culture at intervals (24, 48, 72, 96 and 120 h time points), drug was washed out and drug-free parasites were cultured in 96-well plates by adding fresh erythrocytes and new culture media. The number of viable parasites was determined by the serial dilution technique. Four independent serial dilutions were done with each sample to correct for experimental dilution variation.

The following reagent was obtained through BEI Resources, NIAID, NIH: *Plasmodium falciparum*, Strain 3D7A, MRA-151, contributed by David Walliker.

The human biological samples were sourced ethically and their research use was in accord with the terms of the informed consents under an IRB/EC approved protocol and all animal studies were ethically reviewed and carried out in accordance with European Directive 2010/63/EEC and the GSK Policy on the Care, Welfare and Treatment of Animals.

**In Vitro Resistance Selection Studies**

*P. falciparum* Dd2 (clone B2) parasites were expanded to triplicate flasks of 10⁹ parasites each and selections started at 1.5% parasitemia and 3% hematocrit with 2.0 µM MMV692140, corresponding to three times the IC₅₀ of this compound in 72 hour growth inhibition assays. All three flasks yielded recrudescence on day 17. Parasite clones were generated by limiting dilution and subjected to 72 hour dose-response assays with MMV692140 or the PfeEF2 inhibitor M5717 (earlier known as DDD107498).

**Whole-genome sequence analysis**

Whole-genome sequencing was performed using a TruSeq DNA LT Sample Prep Kit and multiplexed on a MiSeq flow cell to generate 300 bp paired-end reads. Sequences were aligned to the *Pf* 3D7 reference genome using the Burrow-Wheeler Alignment (BWA version 0.7.17) (see PlasmoDB-48_Pfalciparum3D7; https://plasmodb.org/plasmo/app/downloads/release-48/Pfalciparum3D7/fasta/). PCR duplicates and unmapped reads were filtered out using Samtools (version 1.13) and Picard MarkDuplicates (GATK version 4.2.2). Base quality scores were recalibrated using GATK BaseRecalibrator (GATK version 4.2.2). GATK HaplotypeCaller (GATK version 4.2.2) was used to identify all possible single nucleotide variants (SNVs) in test parasite lines filtered based on quality scores (variant quality as function of depth QD > 1.5, mapping quality > 40, min base quality score > 18, read depth > 5) to obtain high quality single nucleotide polymorphisms (SNPs) that were annotated using SnpEff version 4.3t ⁶. BIC-Seq version 1.1.2 ⁷ was used to screen for copy number variants.
(CNVs) against the parental strain using the Bayesian statistical model. No CNVs were found. SNPs were visually inspected and confirmed using Integrative Genome Viewer (IGV). Comparative SNP analyses between the MMV692140 treated Dd2-B2 samples A3, D3, and G12 and the Dd2-B2 parental strain were performed to generate the final list of SNPs (Supplementary Tables 1 and 2).

**Table S1.** Whole-genome sequencing metrics for MMV692140-selected *P. falciparum* clones.

|                      | MMV692140-selected clones |        |        |
|----------------------|---------------------------|--------|--------|
| **Sample names**     |                           | A3     | D3     | G12    |
| **Total reads**      |                           | 5,782,144 | 4,599,012 | 4,249,339 |
| **# Mapped reads**   |                           | 5,299,182 | 4,141,599 | 3,875,875 |
| **Duplication rate** |                           | 2.53%  | 2.20%  | 1.93%  |
| **General error rate** |                         | 1.7%  | 1.7%  | 1.7%  |
| **Mean mapping quality (Phred)** |                       | 56.5  | 56.5  | 56.4  |
| **Depth of coverage** |                           | mean  | 53.3  | 41.7  | 39.1  |
|                      |                           | SD    | 37.5  | 30.9  | 28.0  |
| **% of PF genome with > x no. reads** |     | 1X    | 96.4  | 96.3  | 96.3  |
|                      |                           | 5X    | 94.8  | 94.5  | 94.4  |
|                      |                           | 10X   | 93.5  | 92.5  | 92.3  |
|                      |                           | 30X   | 82.3  | 74.0  | 71.0  |

**Table S2.** List of single nucleotide polymorphisms found in MMV692140-selected clones.

| CHROM         | POS   | REF | ALT | AMINO ACID CHANGE | CODON CHANGE | GENE NAME                                  | EFFECT / IMPACT                      |
|---------------|-------|-----|-----|-------------------|--------------|--------------------------------------------|--------------------------------------|
| Pf3D7_14_v3   | 2092421 | T   | C   | L507S             | tTa/tCa      | PF3D7_1451100 (elongation factor 2)        | NON SYN CODING / MODERATE             |
| Pf3D7_14_v3   | 2093057 | A   | G   | Y719C             | tAt/tGt      | PF3D7_1451100 (elongation factor 2)        | NON SYN CODING / MODERATE             |
| Pf3D7_14_v3   | 2093211 | C   | A   | F770L             | tCt/tA       | PF3D7_1451100 (elongation factor 2)        | NON SYN CODING / MODERATE             |
Safety pharmacology Experimental Methods:

*In vitro cytotoxicity assay with mammalian HepG2 cells*

HepG2 cells were cultured in DMEM supplemented with Sodium Pyruvate (1 mM), HEPES (10 mM) and 10% FBS. HepG2 cells were sub-cultured in growth media (DMEM + 10% FBS) 48 hours prior to cell plating. Cells were plated in 384-well clear bottom culture plates with a cell count of 2000 cells per well in 50 µL of media and incubated for 24 hours in a CO₂ incubator so that 30-40 % of confluency was obtained on the day of treatment with test compounds. After 24 hours of incubation media was discarded carefully and 45 µL of fresh media was added to each well. The cells were treated with either 5 µL of vehicle (5% DMSO) or the desired concentration of the test compound and incubated at 37 °C for 72 hours. The final DMSO concentration in cell plate was 0.5%. In the positive control wells (100% inhibition) cells were treated with 5 µL of 1% triton (final assay conc. 0.1%). Following incubation for 72 hours, 25 µL of media was discarded from the cell plate and 25 µL of Cell Titer Glo reagent was added. Following addition of reagent, the plate was incubated for 15 minutes at 25 °C in a thermomixer with shaking (300 rpm) to develop the luminescent signal. Luminescence was measured (Spectramax M5). Data was analyzed using standard methodology. Doxorubicin was used as the reference standard.

**Measurement of hERG binding**

Affinity for the hERG (human ether-a-go-go-related-gene) ion channel was evaluated using a Predictor™ hERG Fluorescence Polarization Assay kit (Invitrogen, Catalog no: PV5365). The test compound (10 µM) was incubated at ambient temperature for 4 hours with hERG membrane and red fluorescent hERG channel ligand (provided in the kit). A DMSO concentration of 1% was maintained in all wells. Fluorescence polarization was measured at an emission wavelength of 595 nm with the excitation of 531 nm using a microplate reader (Envision, Perkin Elmer). E-4031 was used as the reference inhibitor. Inhibition for test compounds was calculated considering the mP values of E-4031 (30 µM) as 100% inhibition and vehicle control as 0% inhibition.
**Metabolic stability study using human liver microsomes**

A solution of the test compounds in phosphate buffer solution (1 μM) was incubated in pooled human liver microsomes (0.5 mg/mL) for 0, 5, 20, 30, 45 and 60 minutes at 37 °C in the presence and absence of NADPH regeneration system. The reaction was terminated with the addition of ice-cold acetonitrile containing system suitability standard at designated time points. The sample was centrifuged (4200 rpm) for 20 minutes at 20 °C and the supernatant was half diluted in water and then analysed by means of LC-MS/MS. % Parent compound remaining, half-life (T1/2) and clearance (CLint,app) were calculated using standard methodology. The experiment was carried out in duplicate. Verapamil, diltiazem, phenacetin and imipramine were used as reference standards.

**Metabolic stability study using mice liver microsomes**

A mixture of mouse liver microsomes (0.4 mg/mL protein) and test compound (1 μM) was preincubated at 37 °C for 5 min, then NADPH was added to the mixture. The time course concentration (0, 5, 20, 30, 45 and 60 minutes) of the test compound was determined by LC-MS/MS. The reaction was terminated with the addition of ice-cold acetonitrile containing system suitability standard at designated time points. The sample was centrifuged (4200 rpm) for 20 minutes at 20 °C and the supernatant was half diluted in water and then analysed by means of LC-MS/MS. % Parent compound remaining, half-life (T1/2) and apparent intrinsic clearance (μL/min/mg protein) were calculated using standard methodology. The experiment was carried out in duplicate. Atenolol, propranolol, diclofenac and verapamil were used as reference standards.

**Caco-2 permeability assay (apical to basal and/or basal to apical)**

Caco-2 cells were seeded at a density of 18.75 × 10³ cells/well were plated in 96 well inserts and media (DMEM, FBS 10%, Transferrin 10 μg/ml) changed at every 48 h for the entire growth period. Permeability assay (both Apical to Basal and Basal to Apical) was conducted at 5 μM concentration and 2 h incubation. Acceptor and initial donor samples were analyzed by LC-MS/MS. Cell layer integrity was assessed by Lucifer yellow permeation study.

**Mouse Plasma Protein Binding by Equilibrium Dialysis**

Protein binding in mouse plasma was assessed using rapid equilibrium dialysis. Mouse plasma was spiked with test compound at 1 μM and added to the chamber of the RED device (Pierce, Cat no 89809), isotonic sodium phosphate buffer was added to outer chamber of the RED device and the plate was incubated 6 h at 37 °C with shaking. At completion Aliquots of the buffer and matrix were quenched
by adding 160 µL ice cold acetonitrile mixture followed by vigorous shaking and centrifugation at 4200 rpm for 20 min at 20 °C. Quenched solutions were filtered before analysis by LC/MS/MS.

**LogD, pH 7.4**

The LogD, pH 7.4 assay was performed using a miniaturized shake flask method. A solution of a pre-saturated mixture of 1-octanol and phosphate buffered saline (PBS) (1:1, v/v) and the test compound (75 µM) was incubated at 25 °C with constant shaking (850 rpm) for 2 hours with The organic and aqueous phases were separated, and samples of each phase transferred to plate for dilution. The organic phase was diluted to 1000-fold and the aqueous phase was diluted 20-fold. The samples were quantitated using LC-MS/MS. The experiment was carried out in duplicate. Propranolol, amitriptyline and midazolam were used as reference standards.

**Solubility in phosphate buffered saline (PBS) pH 7.4**

The solubility assay was performed using a miniaturized shake flask method. A solution of phosphate buffered saline (PBS) and the test compound (200 µM) was incubated at 25 °C with constant shaking (600 rpm) for 2 hours. The samples were filtered using a multiscreen solubility filter plate. The filtrate was half diluted in acetonitrile. A five-point linearity curve was prepared in PBS:Acetonitrile (1:1, v/v) at 200, 150, 75, 25 and 2.5 µM. Blank, linearity and test samples (n = 2) were transferred to a UV readable plate and the plate was scanned for absorbance. Best fit calibration curves were constructed using the calibration standards and used to determine the test sample solubility. The experiment was carried out in duplicate. Diethylstilbestrol, haloperidol and sodium diclofenac were used as reference standards.

**In Vivo Pharmacokinetics in Rats**

Compound 2 was administered to male Sprague Dawley rats (200-350 g) intravenously (i.v.) at 1 mg/kg body weight or orally (p.o.) at 5 mg/kg body weight (n=3/route of administration). 250 µl of blood samples were collected through were catheterized in jugular vein puncture at 0.83, 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h post-dose following intravenous administration and 0.25, 0.5, 1, 2, 4, 6, 8 and 24 h following oral administration. Plasma was separated by centrifugation at 6000 rpm for 5 min at 4 ± 2 °C within 30 min of scheduled time and stored at -60 °C until assayed. The compound concentrations in plasma were determined by LC-MS/MS analysis. Pharmacokinetic parameters [including AUC_{(0-t)last} and AUC_{(0-infinity)}] were calculated by non-compartmental analysis using Phoenix WinNonlin software (version 6.3).
The Mean PK parameters for MMV692140 are summarized below:

| Route/Dose | $T_{\text{max}}^a$ (h) | $C_0/C_{\text{max}}$ (ng/mL) | AUC_{\text{last}} (ng.h/mL) | AUC_{\text{inf}} (ng.h/mL) | CL (mL/min/kg) | V_{ss} (L/kg) | $T_{1/2}$ (h) | % F$^b$ |
|------------|-----------------|-----------------|-----------------|-----------------|----------------|----------------|-------------|----------|
| MMV692140  | IV/1            | NA              | ± 298           | ± 8.86          | ± 8.99         | ± 0.579        | ± 0.159     | ± 0.481   | <1       |
| PO/5       | 0.5             | 10.2            | 5.8             | NR              | NA             | NA             | NR          | <1       |

$^a$ $T_{\text{max}}$ presented as median (min-max), NA-not applicable, NR: not reportable due to inadequate elimination phase, $^b$ Nominal doses and AUC_{\text{last}} were used for calculation of bioavailability

Plasma concentration-time data for MMV692140

| Analyte     | Route | Dose (mg/kg) | Rat No. | Time (h) | Plasma Concentrations (ng/mL) |
|-------------|-------|--------------|---------|----------|-------------------------------|
|             |       |              |         | 0.083    | 0.25 | 0.5 | 1 | 2 | 4 | 6 | 8 | 24    |
| MMV692140   | IV    | 1 mg/kg      | Rj8875  | 1180     | 450 | 216 | 68.9 | 20.2 | 3.96 | 2.14 | 1.00 | BLQ |
|             |       |              | Rj8876  | 1150     | 429 | 221 | 86.3 | 26.1 | 5.05 | 1.97 | BLQ | BLQ |
|             |       |              | Rj8877  | 1400     | 465 | 182 | 56.2 | 15.3 | 3.50 | 2.02 | BLQ | BLQ |
|             |       |              | Mean    | 1250     | 448 | 206 | 70.5 | 20.5 | 4.17 | 2.04 | 0.333 | 0.00 |
|             |       |              | SD      | 133      | 18.1 | 21.2 | 15.1 | 5.41 | 0.796 | 0.0874 | 0.577 | 0.00 |
|             |       |              | CV%     | 11       | 0.4 | 10 | 21 | 26 | 19 | 0.4 | 173 | NA |
|             | PO    | 5 mg/kg      | Rj8878  | 5.49     | 3.4 | 2.4 | 1.0 | 1.03 | 1.49 | -    |
|             |       |              | Rj8879  | 5.49     | 3.4 | 2.4 | 1.0 | 1.03 | 1.49 | -    |
|             |       |              | Rj8880  | 5.49     | 3.4 | 2.4 | 1.0 | 1.03 | 1.49 | -    |

BLQ (Below limit of quantification 1.0 ng/mL); NA-Not applicable
## Profile of MMV692140 (compound 2)

|                           | Activity of MMV692140 | MMV Validated Hit Criteria |
|---------------------------|------------------------|-----------------------------|
| **MW/HBD/HBA**            | 388/0/5                | 500/<5/<10                  |
| *P. falciparum* 3D7, IC$_{50}$ | 1.8 µM                | < 1.0 µM                    |
| *P. falciparum* NF54, IC$_{50}$ | 0.6 µM                | < 1.0 µM                    |
| Liver stage, *P. berghei*, IC$_{50}$ | 0.09 µM            | Measured                    |
| Sexual stage, GamV, IC$_{50}$ | 2.0 µM                | Measured                    |
| Parasite Reduction Ratio  | Slow rate              | Measured                    |
| Mam. Cytotoxicity, Hep G2, IC$_{50}$ | 40 µM               | >10 fold window             |
| hERG, IC$_{50}$           | 10.6 µM                | Measured                    |
| Hu Mics/Mouse Mics        | >578/>578 µL/min/mg    | No Criteria                 |
| CaCo2, (A to B/B to A)    | 17.5/26 10$^\circ$ cm/sec | Measured                  |
| Mouse PPB                 | 10% free               | Measured                    |
| Log D                     | 3.3                    | <5                          |
| Solubility                | 7 µM                   | >10 µM                      |
| Rat PK, Cl/F              | 32.7 mL/min/Kg/<1%     | No Criteria                 |
## Chemistry Experimental

**General Information:** Reagents and solvents received from commercial suppliers were used without further purification. Reactions were conducted under an inert atmosphere of dry nitrogen in oven dried glassware. Column chromatography was carried out using silica gel (100-200 mesh and 230-400 mesh) from Chromatochem Products. Flash column chromatography was performed using instrument CombiFlash NEXTGEN 100 from Teledyne Isco and using pre-packed column from Phenomenex India (particle size 0.040-0.060 mm). LC-MS Purity was determined by Shimadzu Prominence LC-20AD Binary pump, Shimadzu SIL-HTC autosampler and Applied biosystem API-2000 triple quadruple mass spectrometer equipped with ESI source. GCMS experiments were carried out on Agilent 6890 series GC coupled with 5973N series mass selective detector, with HP-5MS capillary column. The 1H NMR spectra were recorded on a Bruker Ultrashield 400MH/5mm instrument on a Bruker Avance II. All compounds used for biological testing were assayed for HPLC-purity by long gradient HPLC using PDA/DAD detector. All were determined to have purity in excess of 95%.

### Abbreviations:

| Abbreviation | Name |
|--------------|------|
| DIPEA        | N,N-Diisopropylethylamine |
| DMSO         | Dimethylsulphoxide |
| EtOAc        | Ethyl acetate |
| HATU         | Hexafluorophosphate azabenzotriazole tetramethyl uranium |
| DMF          | Dimethylformamide |
| DIPEA        | N,N-Diisopropylethylamine |
| T₃P          | Propylphosphonic anhydride |
| THF          | Tetrahydrofuran |
| HOBT         | Hydroxybenzotriazole |
| EDC HCl      | 1-Ethyl-3-(3-dimethylaminopropyl)carbodiimide hydrochloride |
| DMAP         | 4-Dimethylaminopyridine |
| TBAB         | Tetrabutylammonium bromide |
| BrettPhos Pd G3 | (2-Di-cyclohexylphosphino-3,6-dimethoxy-2’4’,6’-triisopropyl-1,1’-biphenyl)-2-(2’-amino-1,1’-biphenyl)palladium(II) methanesulfonate methanesulfonate |
| Pd₂(dba)₃    | Tris(dibenzylideneacetone)dipalladium(0) |
Synthesis of compounds 3, 4, 6, 8, 9, 11, 12, 14 and 14:

Method-A: Synthesis of compounds 3, 6 and 14:
DIPEA (2.5 eq.) was added to a stirred solution of 1-(piperidine-4-carbonyl)-1,2,3,4-tetrahydroquinoline (1 eq.) and N-aryl-5-chloro-1H-tetrazole (1.1 eq.) in n-butanol at 0 °C. The reaction mixture was allowed to attain rt and was then stirred overnight. The reaction mixture was concentrated and purified to afford the desired targets as solids.

(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-pyridin-4-yl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (3), 15% yield.

LC-MS m/z: 390 [M + H]+. 1H NMR (400 MHz, DMSO-d6): δ 8.45 (d, J = 4.2 Hz, 2H), 7.76 (d, J = 4.2 Hz, 2H), 7.37 (br s, 1H), 7.18-7.11 (m, 3H), 3.68 (br s, 2H), 3.43(d, J = 12.2 Hz, 2H), 3.06 (m, 1H), 2.92 (m, 2H), 2.69 (m, 2H), 1.87 (br s, 2H), 1.87-1.70 (m, 4H).

(1-(1-(3-Chlorophenyl)-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (6), 3% yield.

LC-MS m/z: 423 [M + H]+. 1H NMR (400 MHz, DMSO-d6): δ 7.83 (s, 1H), 7.67 (s, 3H), 7.35 (br s, 1H), 7.22-7.07 (m, 3H), 3.67 (br s, 2H), 3.42 (d, J = 11.9 Hz, 2H), 3.03 (m, 1H), 2.88 (m, 2H), 2.68 (m, 2H), 1.86 (br s, 2H), 1.78-1.60 (m, 4H).

(1-(1-(4-Chlorophenyl)-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (14), 42% yield.
LC-MS m/z: 423 [M + H]+. 1H NMR (400 MHz, CDCl3): δ 7.58 (d, J = 8.6 Hz, 2H), 7.51 (d, J = 8.6 Hz, 2H), 7.22-7.12 (m, 4H), 3.77 (t, J = 6.6 Hz, 2H), 3.53 (d, J = 11.7 Hz, 2H), 3.03 (m, 1H), 2.80 (m, 2H), 2.69 (m, 2H), 1.95 (m, 4H), 1.69 (m, 2H).

Method-B: Synthesis of compounds 4, 5, 10, 11, 12, and 13;

DIPEA (2.5 eq.) was added to a stirred solution of 1-(piperidine-4-carbonyl)-1,2,3,4-tetrahydroquinoline (1 eq.) and N-aryl-5-chloro-1H-tetrazole (1.1 eq.) in n-butanol at 0 °C. The solution was allowed to attain rt during 20 min and was then heated in a sealed tube at 130 °C for 16 h. The reaction mixture was then concentrated, EtOAc was added to the residue and the organic solution was washed with water, brine, dried over Na2SO4 and concentrated to get a residue which was purified by column chromatography to afford the desired targets as solids.

(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-(pyridin-3-yl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (4), 27% yield.

LC-MS m/z: 390 [M + H]+. 1H NMR (400 MHz, DMSO-d6): δ 8.90 (d, J = 2.2 Hz, 1H), 8.77 (d, J = 4.8 Hz, 1H), 8.15 (d, J = 8.2 Hz, 1H), 7.70 (dd, J = 8.1, 4.8 Hz, 1H), 7.35 (br s, 1H), 7.22-7.06 (m, 3H), 3.67 (t, J = 6.3 Hz, 2H), 3.41 (d, J = 12.9 Hz, 2H), 3.04 (m, 1H), 2.89 (m, 2H), 2.68 (t, J = 6.5 Hz, 2H), 1.86 (m, 2H), 1.75-1.60 (m, 4H).

(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-(4-fluorophenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (5), 57% yield.
LC-MS m/z: 407 [M + H]^+. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 7.72 (dd, \(J = 8.9, 8.9\) Hz, 2H), 7.49 (t, \(J = 8.8\) Hz, 2H), 7.40-7.26 (br s, 1H), 7.21-3.06 (m, 3H), 3.67 (t, \(J = 6.3\) Hz, 2H), 3.42 (d, \(J = 12.6\) Hz, 2H), 3.03 (m, 1H), 2.84 (m, 2H), 2.68 (m, 2H), 1.83 (m, 2H), 1.73-1.58 (m, 4H).

\textbf{4-(5-(4-(1,2,3,4-Tetrahydroquinoline-1-carbonyl)piperidin-1-yl)-1H-tetrazol-1-yl)benzonitrile (10)}, 34\% yield.

LC-MS m/z: 414 [M + H]^+. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 8.14 (d, \(J = 8.5\) Hz, 2H), 7.91 (d, \(J = 8.5\) Hz, 2H), 7.41-7.30 (br s, 1H), 7.22-3.07 (m, 3H), 3.67 (t, \(J = 6.3\) Hz, 2H), 3.40 (d, \(J = 12.6\) Hz, 2H), 3.04 (m, 1H), 2.89 (m, 2H), 2.68 (t, \(J = 6.6\) Hz, 2H), 1.86 (m, 2H), 1.80-1.60 (m, 4H).

(3,4-Dihydroquinolin-1(2\(H\))-yl)(1-(1-(2-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (11), 26\% yield.

LC-MS m/z: 457 [M + H]^+. \(^1\)H NMR (400 MHz, DMSO-\(d_6\)): \(\delta\) 8.08 (d, \(J = 7.8\) Hz, 1H), 7.97 (t, \(J = 7.4\) Hz, 1H), 7.89, (t, \(J = 7.9\) Hz, 1H), 7.86 (t, \(J = 7.9\) Hz, 1H), 7.32 (br s, 1H), 7.20-7.06 (m, 3H), 3.64 (t, \(J = 6.3\) Hz, 2H), 3.42 (d, \(J = 12.7\) Hz, 2H), 3.01 (m, 1H), 2.88 (m, 2H), 2.65 (t, \(J = 6.5\) Hz, 2H), 1.84 (m, 2H), 1.65-1.40 (m, 4H).

\textbf{3-(5-(4-(1,2,3,4-Tetrahydroquinoline-1-carbonyl)piperidin-1-yl)-1H-tetrazol-1-yl)benzonitrile (12)}, 22\% yield.
LC-MS m/z: 414 [M + H]+. 1H NMR (400 MHz, DMSO-d6): δ 8.24 (s, 1H), 8.07 (d, J = 7.8 Hz, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.85 (t, J = 8.0 Hz, 1H), 7.36 (br s, 1H), 7.22-7.08 (m, 3H), 3.67 (t, J = 6.0 Hz, 2H), 3.40 (d, J = 13.2 Hz, 2H), 3.06 (m, 1H), 2.89 (m, 2H), 2.68 (t, J = 6.2 Hz, 2H), 1.86 (m, 2H), 1.76-1.60 (m, 4H).

(1-(1-(2-Chlorophenyl)-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (13), 10% yield.

![Structure](image)

LC-MS m/z: 423 [M + H]+. 1H NMR (400 MHz, DMSO-d6): δ 7.80 (t, J = 7.5 Hz, 2H), 7.67 (t, J = 7.4 Hz, 1H), 7.62 (t, J = 7.8 Hz, 1H), 7.33 (br s, 1H), 7.20-7.06 (m, 3H), 3.70 (t, J = 6.3 Hz, 2H), 3.46 (d, J = 13.7 Hz, 2H), 3.03 (m, 1H), 2.90 (m, 2H), 2.67 (t, J = 6.5 Hz, 2H), 1.84 (m, 2H), 1.69-1.56 (m, 4H).

tert-Butyl 4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carboxylate.

![Structure](image)

HATU (17.13 g, 45.05 mmol) was added to a stirred solution of 1-(tert-butoxycarbonyl)piperidine-4-carboxylic acid (5.68 g, 24.8 mmol) in DMF (30 mL) at rt. The mixture was stirred for 30 min, then DIPEA (12.13 mL, 69.77 mmol) and tetrahydroquinoline (3.00 g, 22.5 mmol) was added. The mixture was stirred for an additional 16 h at rt and EtOAc was then added. The organic extract was washed with cold water, saturated sodium bicarbonate solution, dried over Na2SO4 and concentrated. The residue was purified by column chromatography using 25% EtOAc in hexane as eluent to obtain tert-butyl 4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carboxylate (5.96 g, 77%) as a yellow solid. LC-MS m/z: 345 [M + H]+. 1H NMR (400 MHz, CDCl3): δ 7.25-7.14 (m, 4H), 4.09 (br s, 2H), 3.77 (t, J = 6.4 Hz, 2H), 2.98 (m, 1H), 2.69 (m, 2H), 2.60 (br s, 2H), 1.95 (t, J = 6.6 Hz, 2H), 1.80-1.74 (m, 2H), 1.62-1.58 (m, 2H), 1.43 (s, 9H).

1-(Piperidine-4-carbonyl)-1,2,3,4-tetrahydroquinoline.
A solution of 4 M HCl in dioxane (10 mL) was added to tert-butyl 4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carboxylate (1.50 g, 4.36 mmol) at 0 °C. The reaction mixture was stirred at rt for 2 h, then the volatiles were removed under reduced pressure and the residue was partitioned between a saturated aqueous NaHCO₃ solution and CH₂Cl₂. The organic extract was washed with brine, dried over Na₂SO₄ and concentrated to afford crude 1-(piperidine-4-carbonyl)-1,2,3,4-tetrahydroquinoline (0.70 g) which was used without further purification. LC-MS m/z: 245 [M + H]⁺. ¹H NMR (400 MHz, CDCl₃): δ 7.25-7.13 (m, 4H), 3.77 (t, J = 6.6 Hz, 2H), 3.08 (m, 2H), 2.98 (m, 1H), 2.69 (t, J = 6.3 Hz, 2H), 1.93 (t, J = 6.6 Hz, 2H), 1.79-1.70 (m, 7H).

**Synthesis of substituted N-aryl-5-chloro-1H-tetrazole derivatives:**

**Synthesis of 4-(5-chloro-1H-tetrazol-1-yl)pyridine.**

![Chemical structure of 4-(5-chloro-1H-tetrazol-1-yl)pyridine]

4-Isothiocyanatopyridine.

1,4-diazabicyclo[2.2.2]octane (4.77 g, 42.50 mmol) was added to a stirred solution of 4-aminopyridine (2.00 g, 21.3 mmol) in THF (20 mL) at rt, followed by a drop wise addition of CS₂ (6.42 mL, 106.3 mmol). The resulting reaction mixture was stirred at rt overnight, then FeCl₃·6H₂O (11.5 g, 42.5 mmol) in water (40 mL) was added. After stirring an additional 2 h, the reaction mixture was partitioned between EtOAc and water, the organic extract was washed with brine, dried over anhydrous Na₂SO₄ and concentrated to afford 4-isothiocyanatopyridine as an orange solid (1.80 g, 62%) that was used without further purification. LC-MS m/z: 136.9 [M + H]⁺.

**1-Chloro-N-(pyridin-4-yl)methanecarbonimidoyl chloride**
A solution of 4-isothiocyanatopyridine (500 mg, 5.31 mmol) in CCl₄ (10 mL) was purged with Cl₂ at 0-5 °C for 30 min. The solution was stirred at rt overnight, then concentrated to afford 1-chloro-N-(pyridin-4-yl)methanecarbonimidoyl chloride as a brown solid (800 mg) which was used without further purification. LC-MS: m/z = 174.9 [M + H]+.

4-(5-Chloro-1H-1,2,3,4-tetrazol-1-yl)pyridine.

A solution of sodium azide (178 mg, 2.74 mmol) and tetrabutylammonium bromide (147 mg, 0.460 mmol) in water (2 mL) was added to a solution of 1-chloro-N-(pyridin-4-yl)methanecarbonimidoyl chloride (800 mg, 4.57 mmol) in toluene. The mixture was left to stir at rt for 3 h, then extracted with toluene, dried over anhydrous Na₂SO₄, concentrated to afford a crude residue, which was purified by column chromatography using 70% EtOAc in hexane as eluent to afford 4-(5-chloro-1H-1,2,3,4-tetrazol-1-yl)pyridine as a brown solid (205 mg, 25%) that was used directly in next step.

Synthesis of 5-chloro-1-(4-fluorophenyl)-1H-tetrazole.

1-Fluoro-4-isothiocyanatobenzene.

Triethylamine (2.26 mL, 16.2 mmol) was added to a stirred solution of 4-fluoroaniline (600 mg, 5.40 mmol) in dry CH₂Cl₂ (20 mL), at rt for 5 min. Then the reaction mixture was cooled to 0 °C and CS₂ (1.95 mL, 32.4 mmol) was added dropwise to the solution. The resulting mixture was warmed to rt and
stirred at this temperature for 20 h. Then the reaction mixture was again cooled to 0 °C and a 50% solution of T3P in EtOAc (6.17 mL, 9.72 mmol) was added and the mixture was allowed to stir at rt for 3 h. Then the reaction mixture was diluted with water (50 mL) and extracted with EtOAc. The organic layer was washed with 1 M aqueous HCl, water, brine, dried over Na2SO4 and concentrated to get a crude which was purified by chromatography using hexane as eluent to afford 1-fluoro-4-isothiocyanatobenzene (500 mg, 60%) as gummy liquid which was used without further purification. GC-MS: m/z = 174.9 [M]+ 153. 1H NMR (400 MHz, DMSO-d6): δ 7.52 (d, J = 8.9 Hz, 1H), 7.51 (d, J = 12.3 Hz, 1H), 7.31 (dd, J = 11.9, 8.8 Hz, 2H).

(4-Fluorophenyl)carbonimidic dichloride.

A stirred solution of 1-fluoro-4-isothiocyanatobenzene (500 mg, 3.27 mmol) in CCl4 (15 mL) was purged with Cl2 at 0 °C for 30 min and then left to stir at rt for 18 h. After consumption of starting material, the volatiles were removed to get crude (4-fluorophenyl)carbonimidic dichloride (500 mg, 80%) as a brown solid which was used without further purification.

5-Chloro-1-(4-fluorophenyl)-1H-tetrazole.

A solution of sodium azide (102 mg, 1.57 mmol) and tetrabutylammonium bromide (84 mg, 0.26 mmol) was added to (4-fluorophenyl)carbonimidic dichloride (500 mg, 2.60 mmol) in toluene (3 mL), followed by the addition of 2 mL water. The reaction mixture was then stirred at rt for 3 h. After consumption of starting material, the mixture was concentrated and the reaction residue was diluted with water (10 mL) and EtOAc (10 mL). The organic layer was isolated and the aqueous layer was extracted with EtOAc (2 x 10 mL). The combined organic extracts were washed with water (10 mL), brine (10 mL) and dried to get a crude which was purified by chromatography using 20% EtOAc in hexane as eluent to afford 5-chloro-1-(4-fluorophenyl)-1H-tetrazole as brown gummy solid. 1H NMR (400 MHz, DMSO-d6): δ 7.86-7.79 (m, 2H), 7.55 (t, J = 8.8 Hz, 2H).

Synthesis of 5-chloro-1-(4-fluorophenyl)-1H-tetrazole.
N-(3-Chlorophenyl)formamide.

A solution of acetic anhydride (2.89 mL, 30.6 mmol) and formic acid (1.42 mL, 37.6 mmol) was heated for 2 h at 60 °C. After the solution was cooled to rt, a solution of 3-chloroaniline (1.50 g, 11.8 mmol) in THF (7.5 mL) was added dropwise in such a way that the reaction temperature did not exceed 40 °C. After completion of the reaction, the reaction mixture was concentrated, co-distilled with CH₂Cl₂ to afford crude N-(3-chlorophenyl)formamide (1.83 g, 92.8%) as an off white solid, which was used without further purification.

(3-Chlorophenyl)carbonimidic dichloride.

SO₂Cl₂ (0.364 mL, 4.50 mmol) was added dropwise to a stirred solution of N-(3-chlorophenyl)formamide (500 mg, 3.21 mmol) in SOCl₂ (1.47 mL, 20.25 mmol) at 0 °C. The reaction mixture was stirred at rt for 1 h, followed by heating at 50 °C overnight. The reaction mixture was then concentrated and co-distilled with CH₂Cl₂ twice to afford crude (3-chlorophenyl)carbonimidic dichloride (680 mg) as a light yellow gum which was used without further purification.

5-Chloro-1-(3-chlorophenyl)-1H-tetrazole.
A solution of sodium azide (112 mg, 1.73 mmol) and tetrabutylammonium bromide (92.8 mg, 0.288 mmol) in water (1.3 mL) was added to a stirred solution of (3-chlorophenyl)carbonimidic dichloride (600 mg, 2.88 mmol) in toluene (4.5 mL). The mixture was stirred at rt for 3 h, then the organic layer was separated, the aqueous layer was extracted with toluene, the combined organic extracts were dried and concentrated to afford crude 5-chloro-1-(3-chlorophenyl)-1H-tetrazole (620 mg), which was used without further purification.

**Synthesis of 3-(5-chloro-1H-tetrazol-1-yl)pyridine.**

![Reaction Scheme](attachment:image.png)

Pyridin-3-ylcarbonimidic dichloride.

A stirred solution of 3-isothiocyanatopyridine (500 mg, 3.67 mmol) in CCl₄ (20 mL) was purged with Cl₂ at 0-5 °C for 30 min and then left to stir at rt overnight. After consumption of starting material, the solution was concentrated to get crude pyridin-3-ylcarbonimidic dichloride as brown solid which was used without further purification.

3-(5-Chloro-1H-tetrazol-1-yl)pyridine.

![Reaction Scheme](attachment:image.png)

A solution of sodium azide (112 mg, 1.73 mmol) and tetrabutylammonium bromide (92.8 mg, 0.288 mmol) in water (1.3 mL) was added to a stirred solution of (pyridin-3-yl)carbonimidic dichloride (500 mg, 2.87 mmol) in toluene and water (1:1, 4.5 mL). The mixture was stirred at rt for 18 h, then the organic layer was separated, the aqueous layer was extracted with toluene, the combined organic extracts were dried and concentrated to afford crude 3-(5-chloro-1H-tetrazol-1-yl)pyridine (620 mg), which was used without further purification. $^1$H NMR (400 MHz, DMSO-d₆): δ 8.98 (d, $J = 2.1$ Hz, 1H), 8.87 (d, $J = 4.4$ Hz, 1H), 8.27 (d, $J = 8.2$ Hz, 1H), 7.76 (dd, $J = 8.1, 4.8$ Hz, 1H).
Synthesis of 3-(5-chloro-1H-tetrazol-1-yl)benzonitrile.

\[
\begin{align*}
\text{NH}_2 & \quad \text{Ac}_2\text{O}, \text{HCO}_2\text{H} \quad \text{ThF/50 °C/16h} \quad \begin{array}{c}
\text{H} \\
\text{O} \\
\text{Cl} \\
\text{N}
\end{array} \\
\text{CN} & \quad \text{Cl} \\
\text{CN} & \quad \text{NaN}_3, \text{TBAB} \\
\text{CN} & \quad \text{toluene/H}_2\text{O} \\
\text{CN} & \quad \text{25 °C/16h}
\end{align*}
\]

N-(3-Cyanophenyl)formamide.

A stirred solution of acetic anhydride (3.12 mL, 33.0 mmol) and formic acid (1.53 mL, 40.6 mmol) was heated for 2 h at 60 °C. The solution was then cooled to rt and a solution of 3-aminobenzonitrile (1.60 g, 13.6 mmol) in THF (20 mL) was added to the reaction mixture dropwise in such a way that the reaction temperature did not exceed 40 °C, then the reaction mixture was stirred overnight at 50 °C. After completion of the reaction, the reaction mixture was concentrated and co-distilled with CH\(_2\)Cl\(_2\) twice to get N-(3-cyanophenyl)formamide as a crude (1.70 g) which was used without further purification.

(3-Cyanophenyl)carbonimidic dichloride.

SO\(_2\)Cl\(_2\) (1.25 mL, 15.4 mmol) was added dropwise to a stirred solution of N-(3-cyanophenyl)formamide (1.50 g, 10.3 mmol) in SOCl\(_2\) (4.47 mL, 61.6 mmol) at 0 °C. The reaction mixture was stirred at rt for 1 h, followed by heating at 50 °C overnight. The reaction mixture was then concentrated and co-distilled with CH\(_2\)Cl\(_2\) twice to afford crude (3-cyanophenyl)carbonimidic dichloride (1.80 g) as a light yellow gum which was used without further purification.

3-(5-Chloro-1H-tetrazol-1-yl)benzonitrile.
A solution of sodium azide (355 mg, 5.46 mmol) and tetrabutylammonium bromide (293 mg, 0.909 mmol) in water (4 mL) was added to a stirred solution of (3-cyanophenyl)carbonimidic dichloride (1.80 g, 9.10 mmol) in toluene and water (1:1, 20 mL). The mixture was stirred at rt for 16 h, then the organic layer was separated and the aqueous layer was extracted with toluene. The combined organic extracts were dried, filtered and concentrated. The residue was purified by column chromatography using 10% EtOAc in hexane as eluent to afford 3-(5-chloro-1H-tetrazol-1-yl)benzonitrile (280 mg, 10% after three steps). $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 8.35 (s, 1H), 8.19 (d, $J = 7.7$ Hz, 1H), 8.14 (d, $J = 8.1$ Hz, 1H), 7.9 (dd, $J = 7.9$, 7.9 Hz, 1H).

**Synthesis of 5-chloro-1-(2-chlorophenyl)-1H-tetrazole.**

\[
\begin{align*}
\text{Cl} & \quad \text{NH}_2 \\
& \underset{\text{Ac}_2\text{O}, \text{HCO}_2\text{H}}{\text{H}} \quad \underset{\text{SO}_2\text{Cl}_2}{\text{Cl}} \quad \underset{\text{NaN}_3, \text{TBAB}}{\text{Cl}} \\
& \underset{\text{THF/65 °C/15h}}{\text{Cl}} \quad \underset{\text{SO}_2\text{Cl}_2}{\text{Cl}} \quad \underset{\text{toluene/H}_2\text{O}}{\text{Cl}} \\
& \underset{\text{60 °C/16h}}{\text{Cl}} \quad \underset{\text{25 °C/16h}}{\text{Cl}} \\
\end{align*}
\]

**N-(2-Chlorophenyl)formamide.**

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

A stirred solution of acetic anhydride (3.14 g, 30.7 mmol) and formic acid (1.74 g, 30.8 mmol) was heated at 60 °C for 2 h. The solution was then cooled to rt and a solution of 2-chloroaniline (1.50 g, 11.8 mmol) in THF (20 mL) was added to the reaction mixture dropwise in such a way that the reaction temperature did not exceed 40 °C, then the reaction mixture was stirred at 50 °C overnight. After completion of the reaction, the reaction mixture was concentrated and co-distilled with CH$_2$Cl$_2$ twice to get crude N-(2-chlorophenyl)formamide (1.71 g, 88%) which was used without further purification. $^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 9.86 (s, 1H), 8.35 (s, 1H), 8.10 (d, $J = 8.0$ Hz, 1H), 7.50 (d, $J = 8.1$ Hz, 1H), 7.3 (t, $J = 7.6$ Hz, 1H), 7.2 (t, $J = 7.6$ Hz, 1H).

**(2-Chlorophenyl)carbonimidic dichloride.**
SO$_2$Cl$_2$ (1.22 mL, 15.0 mmol) was added dropwise to a stirred solution of N-(2-chlorophenyl)formamide (1.56 g, 10.0 mmol) in SOCl$_2$ (4.40 mL, 60.2 mmol) at 0 °C. The reaction mixture was then stirred at rt for 1 h, followed by heating at 50 °C overnight. The reaction mixture was concentrated and co-distilled with CH$_2$Cl$_2$ twice to afford crude (2-chlorophenyl)carbonimidic dichloride (1.80 g) as a light yellow gum which was used without further purification.

5-Chloro-1-(2-chlorophenyl)-1H-tetrazole.

A solution of sodium azide (339 mg, 5.22 mmol) and tetrabutylammonium bromide (280 mg, 0.87 mmol) in water (4 mL) was added to a stirred solution of crude (2-chlorophenyl)carbonimidic dichloride (1.80 g, 8.70 mmol) in toluene and water (1:1, 20 mL). The mixture was stirred at rt for 16 h, then the organic layer was separated and the aqueous layer was extracted with toluene. The combined organic extracts were dried, filtered and concentrated. The crude product was purified by column chromatography using 30% EtOAc in hexane as eluent to afford 5-chloro-1-(2-chlorophenyl)-1H-tetrazole (600 mg, 32% after two steps). LC-MS m/z: 215.0 [M + H]$^+$. $^1$H NMR (400 MHz, DMSO-d$_6$): δ 7.95 (d, $J = 7.8$ Hz, 1H), 7.89 (d, $J = 8.1$ Hz, 1H), 7.79 (t, $J = 7.8$ Hz, 1H), 7.70 (t, $J = 7.7$ Hz, 1H).

Synthesis of 4-(5-chloro-1H-tetrazol-1-yl)benzonitrile.

N-(4-Cyanophenyl)formamide.
A stirred solution of acetic anhydride (3.12 mL, 33.0 mmol) and formic acid (1.53 mL, 40.6 mmol) was heated for 2 h at 60 °C. The solution was then cooled to rt and a solution of 4-aminobenzonitrile (1.50 g, 12.0 mmol) in THF (20 mL) was added to the reaction mixture dropwise in such a way that the reaction temperature did not exceed 40 °C. After stirring at 50 °C overnight, the solution was concentrated and co-distilled with CH₂Cl₂ twice to get N-(4-cyanophenyl)formamide as a crude (1.70 g) which was used without further purification. LC-MS m/z: 147.0 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 10.64 (s, 1H), 8.37 (s, 1H), 7.80-7.75 (m, 4H).

(4-Cyanophenyl)carbonimidic dichloride.

SO₂Cl₂ (1.25 mL, 15.4 mmol) was added dropwise to a stirred solution of N-(4-cyanophenyl)formamide (1.50 g, 10.3 mmol) in SOCl₂ (4.47 mL, 61.6 mmol) at 0 °C. The reaction mixture was then stirred for 1 h at rt, followed by heating at 50 °C overnight. The solution was then concentrated and co-distilled with CH₂Cl₂ twice to afford crude (4-cyanophenyl)carbonimidic dichloride (1.80 g) as a light yellow gum which was used without further purification. ¹H NMR (400 MHz, DMSO-d₆): δ 7.93 (d, J = 8.4, 2H), 7.25 (d, J = 8.6, 2H).

4-(5-Chloro-1H-tetrazol-1-yl)benzonitrile.

A solution of sodium azide (355 mg, 5.46 mmol) and tetrabutylammonium bromide (293 mg, 0.909 mmol) in water (4 mL) was added to a stirred solution of crude (4-cyanophenyl)carbonimidic dichloride (1.80 g, 9.09 mmol) in toluene and water (1:1, 20 mL). The mixture was then stirred for 16 h at rt, then the organic layer was separated and the aqueous layer was extracted with toluene. The combined organic
extracts were dried, filtered and concentrated. The crude product was purified by column chromatography using 10% EtOAc in hexane as eluents to get 4-(5-chloro-1H-tetrazol-1-yl)benzonitrile (620 mg, 24% after three steps). $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.21 (d, $J$ = 8.5 Hz, 2H), 8.01 (d, $J$ = 8.5 Hz, 2H).

**Synthesis of 5-chloro-1-(2-(trifluoromethyl)phenyl)-1H-tetrazole.**

A stirred solution of acetic anhydride (2.44 mL, 25.8 mmol) and formic acid (1.20 mL, 31.8 mmol) was heated for 2 h at 60 °C. The solution was then cooled to rt and a solution of 2-(trifluoromethyl)aniline (1.60 g, 9.94 mmol) in THF (20 mL) was added to the reaction mixture dropwise in such a way that the reaction temperature did not exceed 40 °C. After stirring at 50 °C overnight the reaction mixture was concentrated and co-distilled with CH$_2$Cl$_2$ twice to get crude N-(2-(trifluoromethyl)phenyl)formamide (1.60 g, 85%) which was used without further purification. $^1$H NMR (400 MHz, DMSO-$d_6$): $\delta$ 9.80 (s, 1H), 8.34 (s, 1H), 7.88 (d, $J$ = 8.0 Hz, 1H), 7.73 (d, $J$ = 7.8 Hz, 1H), 7.73 (t, $J$ = 7.6 Hz, 1H), 7.40 (t, $J$ = 7.6 Hz, 1H).

**N-(2-(Trifluoromethyl)phenyl)formamide.**

SO$_2$Cl$_2$ (1.02 mL, 12.7 mmol) was added dropwise to a stirred solution of N-(2-(trifluoromethyl)phenyl)formamide (1.60 g, 8.47 mmol) in SOCl$_2$ (3.68 mL, 50.8 mmol) at 0 °C. The reaction mixture was allowed to warm to rt for 1 h, followed by heating at 50 °C overnight. The reaction mixture was then concentrated and co-distilled with CH$_2$Cl$_2$ twice to afford crude (2-(trifluoromethyl)phenyl)carbonimidic dichloride (1.80 g) which was used without further purification.
\textsuperscript{1}H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.79 (d, $J = 7.8$ Hz, 1H), 7.75 (t, $J = 7.8$ Hz, 1H), 7.45 (t, $J = 7.6$ Hz, 1H), 7.25 (d, $J = 7.9$ Hz, 1H).

5-Chloro-1-(2-(trifluoromethyl)phenyl)-1H-tetrazole.

A solution of sodium azide (291 mg, 4.48 mmol) and tetrabutylammonium bromide (241 mg, 0.747 mmol) in water (4 mL) was added to a stirred solution of (2-(trifluoromethyl)phenyl)carbonimidic dichloride (1.80 g, 7.47 mmol) in toluene and water (1:1, 20 mL). The mixture was stirred for 16 h at rt, then the organic layer was separated and the aqueous layer was extracted with toluene. The combined organic extracts were dried, filtered and concentrated. The crude product was purified by column chromatography using 30% EtOAc in hexane as eluents to afford 5-chloro-1-(2-(trifluoromethyl)phenyl)-1H-tetrazole (620 mg, 33% after two steps). 249.1 [M + H]$^+$. \textsuperscript{1}H NMR (400 MHz, DMSO-$d_6$): $\delta$ 8.16 (d, $J = 7.6$ Hz, 1H), 8.10-8.05 (m, 2H), 8.01 (t, $J = 7.3$ Hz, 1H).

(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-(4-(trifluoromethoxy)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (9).

K$_2$CO$_3$ (145 mg, 1.06 mmol) was added to a solution of 5-tosyl-1-(4-(trifluoromethoxy)phenyl)-1H-tetrazole (135 mg, 0.352 mmol) and (3,4-dihydroquinolin-1(2H)-yl)(piperidin-4-yl)methanone (171.6 mg, 0.703 mmol) in CH$_3$CN (10 mL) at rt. The reaction mixture was stirred at 60 °C for 24 h, then filtered, washed with CH$_3$CN and concentrated. Preparative TLC of the residue using EtOAc as developing solvent gave 9 (10.0 mg, 6%) as brown sticky solid. LC-MS m/z: 473 [M + H]$^+$. \textsuperscript{1}H NMR (400 MHz, DMSO-$d_6$): $\delta$ 7.82 (d, $J = 8.8$ Hz, 2H), 7.65 (d, $J = 8.6$ Hz, 2H), 7.40-7.30 (br s, 1H), 7.22-7.06 (m, 3H), 3.67 (t, $J = 6.2$ Hz, 2H), 3.41 (d, $J = 12.7$ Hz, 2H), 3.03 (m, 1H), 2.87 (m, 2H), 2.68 (t, $J = 6.4$ Hz, 2H), 1.86 (m, 2H), 1.76-1.60 (m, 4H).
Synthesis of 5-chloro-1-(2-(trifluoromethyl)phenyl)-1H-tetrazole.

\[
\text{NH}_2 \quad \xrightarrow{(i) \text{NaNO}_2/\text{HCl}(6 \text{ M aq})/\text{THF}} \quad \text{N}_3 \quad \xrightarrow{(ii) \text{NaN_3H}_2\text{O}(100^\circ\text{C} \times 72 \text{ h})} \quad \text{p-toluenesulfonyl cyanide} \quad \text{100}^\circ\text{C} / 72 \text{ h} \quad \text{1H-tetrazole} \quad \text{OCF}_3 \quad \text{OCF}_3
\]

1-Azido-4-(trifluoromethoxy)benzene.

An ice cooled solution of 2.7M NaNO₂ in water (136 mg NaNO₂ in 0.8 mL water) was added dropwise to a stirred mixture of 4-(trifluoromethoxy)aniline (350 mg, 1.98 mmol), 6 M aqueous HCl (3 mL) and THF (5 mL), maintaining the temperature between 0-5 °C. After the mixture was stirred for an additional 10 min at 0 °C, an ice cold solution of 3.2 M NaN₃ in water (154 mg NaN₃ in 0.8 mL) was added dropwise. The mixture was then allowed to attain room temperature over 1 h and the reaction mixture was extracted with EtOAc. The organic extract was dried over Na₂SO₄, filtered and concentrated to afford crude 1-azido-4-(trifluoromethoxy)benzene (360 mg, 90%) as an off white solid which was used without further purification. ¹H NMR (400 MHz, DMSO-d₆): δ 7.41 (d, J = 8.4, 2H), 7.24 (d, J = 8.4, 2H).

5-Tosyl-1-(4-(trifluoromethoxy)phenyl)-1H-tetrazole.

1-azido-4-(trifluoromethoxy)benzene (895 mg, 4.41 mmol) and p-toluenesulfonyl cyanide (798 mg, 4.41 mmol) was heated in a sealed tube at 100 °C for 3 days. After cooling to room temperature, the residue was dissolved in minimal CH₂CL₂ and purified by column chromatography using 10% EtOAc in hexane as eluent to afford 5-tosyl-1-(4-(trifluoromethoxy)phenyl)-1H-tetrazole (320 mg, 19%) as an off white solid. LC-MS m/z: 385 [M + H]⁺.
(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (7).

\[
\begin{align*}
\text{N} & \text{N} \\
\text{Cl} & \text{OMe} \\
\text{Cl} & \text{O} \\
\text{Cl} & \text{N} \\
\text{Cl} & \text{N} \\
\end{align*}
\]

DIPEA (0.5 mL, excess) was added dropwise to a stirred solution of 1-(3-chloro-4-methoxyphenyl)-5-tosyl-1H-tetrazole (250 mg, 1.03 mmol) and (3,4-dihydroquinolin-1(2H)-yl)(piperidin-4-yl)methanone (250 mg, 1.03 mmol) in n-butanol (6 mL) in a sealed tube at 0°C. After the solution had been stirred for 10 min at 0°C it was allowed to attain rt during 20 min and was then heated at 130°C for 16 h. The solution was concentrated and the residue was diluted with EtOAc, washed with water, brine, dried over Na₂SO₄ and concentrated under reduced pressure. Residue was purified by column chromatography using 70% EtOAc in hexane as eluent to afford (1-(1-(3-chloro-4-methoxyphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (210 mg, 45%) as a white solid. LC-MS m/z: 453 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 7.81 (d, J = 2.4 Hz, 1H), 7.61 (d, d, J = 4.4, 2.5 Hz, 1H), 7.37 (d, J = 8.9 Hz, 1H), 7.41-7.29 (br s, 1H), 7.22-7.07 (m, 3H), 3.95 (s, 3H), 3.67 (t, J = 6.3 Hz, 2H), 3.45 (d, J = 12.6 Hz, 2H), 3.03 (m, 1H), 2.85 (m, 2H), 2.68 (t, J = 6.4 Hz, 2H), 1.86 (m, 2H), 1.75-1.60 (m, 4H).

(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (7).
A solution of (1-(1-(3-chloro-4-methoxyphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (120 mg, 0.265 mmol) in methanol (10 mL) was purged with argon for 20 min, then Pd-C (10%, 50% moist; 100 mg) was added at rt and the mixture was purged again with argon for 5 min. The reaction mixture was then stirred under hydrogen at balloon pressure for 15 h at rt. Upon completion of the reaction, the mixture was filtered through the bed of Celite and concentrated. The residue was triturated with ether-pentane to afford 7 (98 mg, 88%) as a white solid. LC-MS m/z: 419 [M + H]+. 1H NMR (400 MHz, DMSO-d6): δ 7.55 (d, J = 8.8 Hz, 2H), 7.42-7.28 (br s, 1H), 7.13 (d, J = 11.6 Hz, 2H) 7.22-7.05 (m, 3H), 3.94 (s, 3H), 3.66 (t, J = 6.3 Hz, 2H), 3.44 (d, J = 12.8 Hz, 2H), 3.02 (m, 1H), 2.82 (m, 2H), 2.68 (t, J = 6.6 Hz, 2H), 1.85 (m, 2H), 1.73-1.57 (m, 4H).

Synthesis of 5-chloro-1-(3-chloro-4-methoxyphenyl)-1H-tetrazole.

(3-Chloro-4-methoxyphenyl)carbonimidic dichloride.

A stirred solution of 1-isothiocyanato-4-methoxybenzene (4.00 g, 24.2 mmol) in CCl4 (40 mL), was purged with Cl2 at 0-5 °C for 30 min. The reaction mixture was stirred at rt overnight, concentrated to afford crude (3-chloro-4-methoxyphenyl)carbonimidic dichloride (4.10 g) which was used without further purification.

5-Chloro-1-(3-chloro-4-methoxyphenyl)-1H-tetrazole.
A solution of sodium azide (1.95 g, 30.1 mmol) and tetrabutylammonium bromide (383 mg, 1.19 mmol) in water (10 mL) was added to a solution of (3-chloro-4-methoxyphenyl)carbonimidic dichloride (4.00 g, 16.77 mmol) in toluene and water (2:1, 60 mL). After stirring at rt for 16 h the organic layer was separated off and the aqueous layer was extracted with toluene. The combined organic extracts were dried over Na$_2$SO$_4$, filtered and concentrated. The crude product was purified by column chromatography using 10% EtOAc in hexane as eluent to afford 5-chloro-1-(3-chloro-4-methoxyphenyl)-1H-tetrazole (2.1 g, 35%, after two steps). $^1$H NMR (400 MHz, CDCl$_3$): δ 7.60 (d, $J = 2.6$ Hz, 1H), 7.45 (dd, $J = 8.8$, 2.6 Hz, 1H), 7.10 (d, $J = 8.9$ Hz, 1H), 3.99 (s, 3H).

(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-(o-tolyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (8).

DIPEA (0.5 mL, excess) was added dropwise to a stirred solution of 5-chloro-1-(2-chloro-6-methylphenyl)-1H-tetrazole (180 mg, 0.923 mmol) and (3,4-dihydroquinolin-1(2H)-yl)(piperidin-4-yl)methanone (225.2 mg, 0.923 mmol) in n-butanol (6 mL) at 0 °C. After the solution had been stirred for 10 min at 0 °C, it was allowed to attain rt during 20 min and was then heated at 130 °C for 16 h. The solution was then concentrated and the residue was diluted with EtOAc, washed with water, brine, dried over Na$_2$SO$_4$ and then concentrated. Residue was purified by column chromatography using 70% EtOAc in hexane as eluent to afford 1-(1-(2-Chloro-6-methylphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (130 mg, 35%) as a white solid. LC-MS m/z: 437 [M + H]$^+$. $^1$H NMR (400 MHz, DMSO-d$_6$): δ 7.66 (s, 1H), 7.58-7.50 (m, 2H), 7.41-7.27 (br s, 1H), 7.22-7.06 (m, 3H), 3.65 (t, $J = 6.3$ Hz, 2H), 3.42 (d, $J = 12.4$ Hz, 2H), 3.01 (m, 1H), 2.88 (m, 2H), 2.67 (t, $J = 6.5$ Hz, 2H), 2.08 (s, 3H), 1.85 (m, 2H), 1.70-1.52 (m, 4H).

(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-(o-tolyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (8).
A solution of (1-(1-(2-chloro-6-methylphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (180 mg, 0.41 mmol) in methanol (10 mL) was purged with argon for 20 min, then Pd-C (10%, 50% moist; 100 mg) was added at rt and the mixture was purged again with argon for 5 min. The reaction mixture was stirred under hydrogen at balloon pressure for 16 h at rt. Upon completion of the reaction, the mixture was filtered through Celite and concentrated. The residue was triturated with ether-pentane to afford 8 (120 mg, 73%) as a light yellow solid. LC-MS m/z: 403 [M + H]+. 1H NMR (400 MHz, DMSO-d6): δ 7.58-7.40 (m, 4H), 7.38-7.27 (br s, 1H), 7.22-7.06 (m, 3H), 3.65 (t, J = 6.4 Hz, 2H), 3.42 (d, J = 12.5 Hz, 2H), 3.00 (m, 1H), 2.86 (m, 2H), 2.67 (t, J = 6.5 Hz, 2H), 2.07 (s, 3H), 1.84 (m, 2H), 1.67-1.50 (m, 4H).

**Synthesis of 5-chloro-1-(2-chloro-6-methylphenyl)-1H-tetrazole.**

![Synthesis diagram]

1-Isocyanato-2-methylbenzene.

A stirred solution of acetic anhydride (3.49 g, 34.2 mmol) and formic acid (1.94 g, 42.1 mmol) was heated for 2 h at 60 °C. The solution was cooled to rt and a solution of o-toluidine (1.50 g, 13.99 mmol) in THF (20 mL) was added to the reaction mixture dropwise in such a way that the reaction temperature did not exceed 40 °C. The reaction mixture was stirred at 50 °C overnight then concentrated and co-distilled with CH2Cl2 twice to get crude 1-isocyanato-2-methylbenzene which was used without further purification.

(2-Chloro-6-methylphenyl)carbimimic dichloride.
SO\textsubscript{2}Cl\textsubscript{2} (1.40 mL, 17.3 mmol) was added dropwise to a stirred solution of 1-isocyanato-2-methylbenzene (1.56 g, 11.5 mmol) in SO\textsubscript{2}Cl\textsubscript{2} (5.01 mL, 69.1 mmol) at 0 °C. The reaction mixture was stirred at rt for 1 h and heated at 50 °C overnight. The reaction mixture was then concentrated and co-distilled with CH\textsubscript{2}Cl\textsubscript{2} twice to afford crude (2-chloro-6-methylphenyl)carbonimidic dichloride as light yellow gummy liquid which was used without further purification. \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}): δ 7.41 (s, 1H), 7.32 (d, \(J = 8.8\) Hz, 1H), 6.99 (d, \(J = 8.4\) Hz, 1H), 2.11 (s, 3H).

5-Chloro-1-(2-chloro-6-methylphenyl)-1H-tetrazole.

A solution of sodium azide (375 mg, 5.78 mmol) and tetrabutylammonium bromide (310 mg, 0.963 mmol) in water (4 mL) was added to a solution of crude (2-chloro-6-methylphenyl)carbonimidic dichloride (1.80 g, 9.63 mmol) in toluene and water (1:1, 20 mL). The mixture was stirred at rt for 16 h, then the organic layer was separated and the aqueous layer was extracted with toluene. The combined organic extracts were dried, filtered and concentrated. The crude product was purified by column chromatography using 10% EtOAc in hexane as eluent to afford 5-chloro-1-(2-chloro-6-methylphenyl)-1H-tetrazole (200 mg, 11%, after three consecutive steps). \textsuperscript{1}H NMR (400 MHz, DMSO-d\textsubscript{6}): δ 7.73 (s, 1H), 7.72 (d, \(J = 7.5\) Hz, 1H), 7.60 (d, \(J = 8.5\) Hz, 1H), 2.07 (s, 3H).

Synthesis of compounds 15-26;

Method-A: Synthesis of compounds 16, 17, 18, 20, 21, 23, 24, 25 and 26;

DIPEA (3 eq.) and T\textsubscript{3}P (2 eq.) was added to a solution of 1-(1-phenyl-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (1 eq.) and amine (1 eq.) in THF, followed by stirring for 16 h at rt. The solution was
concentrated under reduced pressure and the residue was diluted with EtOAc, washed with brine, dried over Na$_2$SO$_4$ and concentrated. Residue was purified by column chromatography to afford the target compounds.

(7-Methoxy-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone) (16), 6.8% yield.

\[
\text{LC-MS } m/z: 419 [M + H]^+.
\]
$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.70-7.55 (m, 5H), 7.08 (d, $J = 7.9$ Hz, 1H), 6.94 (br s, 1H), 6.70 (d, $J = 7.9$ Hz, 1H), 6.70 (br s, 2H), 3.70 (s, 3H), 3.65 (br s, 2H), 3.43 (d, $J = 11.8$ Hz, 2H), 3.07 (m, 1H), 2.88 (m, 2H), 2.61 (m, 2H), 1.83 (t, $J = 6.1$ Hz, 2H), 1.76-1.60 (m, 4H).

(5-Chloro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (17), 22% yield.

\[
\text{LC-MS } m/z: 423 [M + H]^+.
\]
$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.69-7.55 (m, 5H), 7.42-7.33 (br s, 1H), 7.25 (d, $J = 8.2$ Hz, 1H), 7.19 (t, $J = 7.8$ Hz, 1H), 3.69 (br s, 2H), 3.43 (d, $J = 12.7$ Hz, 2H), 3.03 (m, 1H), 2.89 (m, 2H), 2.74 (t, $J = 6.4$ Hz, 2H), 1.90 (m, 2H), 1.75-1.60 (m, 4H).

(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (18), 76% yield.

\[
\text{LC-MS } m/z: 391 [M + H]^+.
\]
$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.73-7.55 (m, 5H), 7.04 (m, 1H), 6.95-6.80 (m, 2H), 4.24 (s, 2H), 3.88 (s, 2H), 3.46 (d, $J = 12.4$ Hz, 2H), 3.10 (m, 1H), 2.95 (m, 2H), 1.77-1.60 (m, 4H).
(6-Chloro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (20), 44% yield.

LC-MS m/z: 423 [M + H]+. 1H NMR (400 MHz, DMSO-d6): δ 7.70-7.55 (m, 5H), 7.43 (br s, 1H), 7.27 (s, 1H), 7.19 (d, J = 7.4 Hz, 1H), 3.67 (s, 2H), 3.43 (d, J = 12.0 Hz, 2H), 3.01 (m, 1H), 2.90 (m, 2H), 2.70 (m, 2H), 1.85 (t, J = 6.0 Hz, 2H), 1.75-1.55 (m, 4H).

(6-Methoxy-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (21), 56% yield.

LC-MS m/z: 419 [M + H]+. 1H NMR (400 MHz, DMSO-d6): δ 7.72-7.55 (m, 5H), 7.19 (d, J = 7.7 Hz, 1H), 6.75 (m, 2H), 3.72 (s, 3H), 3.63 (m, 2H), 3.40 (m, 2H), 2.97 (m, 2H), 2.80 (m, 1H), 2.63 (m, 2H), 1.82 (m, 2H), 1.75-1.50 (m, 4H).

(7-Chloro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (23), 34% yield.

LC-MS m/z: 423 [M + H]+. 1H NMR (400 MHz, DMSO-d6): δ 7.75-7.55 (m, 6H), 7.19 (d, J = 7.7 Hz, 1H), 7.12 (d, J = 6.9 Hz, 1H), 3.70 (br s, 2H), 3.45 (d, J = 12.2 Hz, 2H), 3.04 (m, 1H), 2.94 (m, 2H), 2.69 (m, 2H), 1.86 (t, J = 5.9 Hz, 2H), 1.75-1.60 (m, 4H).

(3,4-Dihydro-1,5-naphthyridin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (24), 53% yield.
(3,4-Dihydro-1,6-naphthyridin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (25), 48% yield.

(5-Methoxy-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (26), 6.5% yield.

Method-B: Synthesis 1-(1-(1-Phenyl-1H-tetrazol-5-yl)piperidine-4-carbonyl)-1,2,3,4-tetrahydroquinoline-6-carbonitrile (19), 44% yield.
N-methyl morpholine (0.24 mL, 2.22 mmol) was added to a stirred solution of 1-(1-phenyl-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (605 mg, 2.22 mmol) in THF (15 mL) at rt. The reaction mixture was cooled to -15 °C and isobutyl chloroformate (0.29 mL, 2.22 mmol) was added dropwise to the solution which was then stirred for 15 min at -15 °C, followed by addition of 1,2,3,4-tetrahydroquinoline-6-carbonitrile (350 mg, 2.22 mmol). The reaction mixture was stirred at rt overnight, then partitioned between EtOAc and water, the organic extract was washed with brine, dried over Na₂SO₄, concentrated and finally purified by column chromatography (SiO₂ 100-200, 5% methanol in dichloromethane) to afford 19 (400 mg, 44%). LC-MS m/z: 414 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 7.75-7.55 (m, 8H), 3.63 (s, 2H), 3.44 (d, J = 11.1 Hz, 2H), 3.04 (br s, 1H), 2.94 (m, 2H), 2.74 (s, 2H), 1.87 (m, 2H), 1.75-1.60 (m, 4H).

Method-C: (3,4-Dihydro-1,8-naphthyridin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (15), 62% yield.

HOBT (1.2 eq.) was added to a stirred solution of 1-(1-phenyl-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (306 mg, 1.12 mmol), triethylamine (0.78 mL, 5.60 mmol) and EDC.HCl (322 mg, 1.68 mmol), in CH₂Cl₂ (7 mL), followed by addition of 1,2,3,4-tetrahydro-1,8-naphthyridine (150 mg, 1.12 mmol). The mixture was stirred at rt overnight, concentrated and partitioned between EtOAc and water. The organic extracts were washed with brine, dried over Na₂SO₄, concentrated and finally purified by column chromatography to afford 15 (270 mg, 62%). LC-MS m/z: 390 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 8.19 (d, J = 3.6 Hz, 1H), 7.72-7.53 (m, 6H), 7.13 (dd, J = 6.0, 5.0 Hz, 1H), 3.71 (t, J = 5.9 Hz, 2H), 3.52-3.38 (m, 3H), 2.82 (t, J = 11.5 Hz, 2H), 2.74 (t, J = 6.4 Hz, 2H), 1.82 (m, 2H), 1.78-1.60 (m, 4H).

Synthesis of 1-(1-phenyl-1H-tetrazol-5-yl)piperidine-4-carboxylic acid.
Ethyl 1-(1-phenyl-1H-tetrazol-5-yl)piperidine-4-carboxylate.

\[
\text{N} \quad \text{N} \\
\text{N} \quad \text{N} \\
\text{N} \quad \text{N} \\
\text{O} \quad \text{Et} \\
\]

DIPEA (16.7 mL, 95.1 mmol) was added dropwise to a stirred solution of ethyl piperidine-4-carboxylate (6.00 g, 38.2 mmol) and 5-chloro-1-phenyl-1H-tetrazole (7.58 g, 42.0 mmol) in n-butanol (60.0 mL) at 0 °C. The reaction mixture was stirred for 10 min, followed by heating for 16 h at 110 °C. The reaction mixture was then concentrated, the residue was partitioned between EtOAc and water. The organic extract was washed with brine, dried over anhydrous Na$_2$SO$_4$, concentrated and purified by column chromatography using 40% EtOAc in hexane as eluent to afford ethyl 1-(1-phenyl-1H-tetrazol-5-yl)piperidine-4-carboxylate (9.0 g, 78%) as a white solid. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.62–7.43 (m, 5H), 4.17–4.08 (m, 2H), 3.53 (dt, $J=13.0$, 3.6 Hz, 2H), 2.94 (td, $J=12.1$, 2.7 Hz, 2H), 2.45 (m, 1H), 1.91 (dd, $J=13.7$, 3.4 Hz, 2H), 1.83–1.67 (m, 2H), 1.23 (t, $J=7.1$ Hz, 3H).

1-(1-Phenyl-1H-tetrazol-5-yl)piperidine-4-carboxylic acid.

\[
\text{N} \quad \text{N} \\
\text{N} \quad \text{N} \\
\text{N} \quad \text{N} \\
\text{O} \quad \text{O} \\
\]

LiOH·H$_2$O (3.80 g, 89.7 mmol) was added portion wise to a stirred solution of ethyl 1-(1-phenyl-1H-tetrazol-5-yl)piperidine-4-carboxylate (9.00 g, 29.9 mmol) in THF·H$_2$O (1:1, 90 mL) at 0 °C. After stirring for 16 h at rt the mixture was concentrated and the residue was dissolved in water (5.0 mL) and washed with diethyl ether (10.0 mL). The aqueous solution was acidified using 1 M HCl solution (pH ~3–4) and extracted with EtOAc. The organic extracts were washed with brine, dried over Na$_2$SO$_4$, concentrated and finally triturated with hexane to afford 1-(1-phenyl-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (8.0 g, 98%) as a white solid. $^1$H NMR (400 MHz, DMSO-d$_6$): δ 12.30 (s, 1H) 7.70–7.55 (m, 5H), 3.40 (d, $J=13.8$, 2H), 2.94 (t, $J=11.3$ Hz, 2H), 2.43 (m, 1H), 1.78 (d, $J=11.3$ Hz, 2H), 1.66-1.51 (m, 2H).

1-(1-(1-Phenyl-1H-tetrazol-5-yl)piperidine-4-carbonyl)-1,2,3,4-tetrahydroquinoline-7-carbonitrile (22).
(7-Bromo-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone.

Triethylamine (1.54 mL, 11.0 mmol) and 2-chloro-1-methylpyridinium iodide (842 mg, 3.30 mmol) was added to a solution of 1-(1-phenyl-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (600 mg, 2.20 mmol) and 7-bromo-1,2,3,4-tetrahydroquinoline (513 mg, 2.42 mmol) in CH₂Cl₂ (15 mL). The reaction mixture was stirred at rt for 3 h, then concentrated to afford a crude residue which was purified by column chromatography to afford (7-bromo-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone which was used without further purification (308 mg, 30%).

1-(1-(1-Phenyl-1H-tetrazol-5-yl)piperidine-4-carbonyl)-1,2,3,4-tetrahydroquinoline-7-carbonitrile (22).

A solution of (7-bromo-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (280 mg, 0.60 mmol) and Zn(CN)₂ in dioxane (3 mL) was purged with argon for 10 min, then Pd(PPh₃)₄ (69.3 mg, 0.06 mmol) was added and the mixture was heated at 120 °C in a microwave reactor for 1 h. The reaction mixture was then filtered, concentrated and the residue was purified by column chromatography to afford 22 (90 mg, 36%) as a solid. LC-MS m/z: 414 [M + H]+. ¹H NMR (400 MHz, DMSO-d₆): δ 7.97 (s, 1H), 7.71-7.55 (m, 5H), 7.50 (d, J = 7.0, 1H), 7.37 (d, J = 7.7, 1H), 3.73 (s, 2H), 3.45 (d, J = 11.9 Hz, 2H), 3.15-2.90 (m, 3H), 2.80 (m, 2H), 1.88 (t, J = 5.9 Hz, 2H), 1.80-1.60 (m, 4H).

(2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)(1-(1-(4-fluorophenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (30).
tert-Butyl 4-(3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)piperidine-1-carboxylate.

DIPEA (1.0 mL, 5.7 mmol) was added to a stirred solution of 1-({tert-butoxycarbonyl)piperidine-4-carboxylic acid (460 mg, 2.00 mmol), 3,4-dihydro-2H-benzo[b][1,4]oxazine (270 mg, 2.00 mmol) and HATU (114 mg, 3.00 mmol) in dry DMF (10 mL). The reaction mixture was stirred for 38 h at rt, then partitioned between water and EtOAc, the organic extracts were washed with water, saturated NaHCO₃ solution, brine, dried over anhydrous Na₂SO₄, filtered and concentrated. The residue was purified by column chromatography using 40% EtOAc in hexane as eluent to afford tert-butyl 4-(7-bromo-1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carboxylate (300 mg, 45%) which was used without further purification.

(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(piperidin-4-yl)methanone.

A solution of 4M HCl in dioxane (20 mL) was added to tert-butyl 4-(3,4-dihydro-2H-benzo[b][1,4]oxazine-4-carbonyl)piperidine-1-carboxylate (300 mg, 0.867 mmol) in diethyl ether (6 mL) and the reaction mixture was stirred for 2 h at rt. After completion of the reaction the mixture was neutralized with aqueous 1M NaOH solution and extracted with EtOAc. The combined organic extracts were washed with water, dried over anhydrous Na₂SO₄ and concentrated to get crude (2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)(piperidin-4-yl)methanone (120 mg, 56%) as a light brown solid, which was used without further purification.

(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(1-(1-(4-fluorophenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (30).
DIPEA (0.49 mL, 2.77 mmol) was added to a stirred solution of 5-chloro-1-(4-fluorophenyl)-1H-tetrazole (90 mg, 0.45 mmol) and (2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)(piperidin-4-yl)methanone (120 mg, 0.49 mmol) in n-butanol (5 mL) at 0 °C and the solution was then stirred at 130 °C for 16 h. The reaction mixture was then concentrated and purified by column chromatography using 80% EtOAc in hexane as eluent to afford 30 (45 mg, 24%). LC-MS m/z: 409 [M + H]+. 1H NMR (400 MHz, DMSO-d6): δ 7.78-7.71 (m, 3H), 7.50 (t, J = 8.6, 2H), 7.04 (br s, 1H), 6.87 (d, J = 8.4 Hz, 2H), 4.24 (s, 2H), 3.88 (s, 2H) 3.45 (d, J = 12.7 Hz, 2H), 3.10 (m, 1H), 2.95 (m, 2H), 1.80-1.60 (m, 4H).

(5-Chloro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (31).

Ethyl 1-(1-(3-chloro-4-methoxyphenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylate.

DIPEA (0.492 mL, 2.77 mmol) was added to a stirred solution of 5-chloro-1-(3-chloro-4-methoxyphenyl)-1H-tetrazole (80.0 mg, 0.328 mmol) and ethyl piperidine-4-carboxylate (56.6 mg, 0.361 mmol) in n-butanol (5 mL) in a sealed tube at 0 °C and then stirred at 130 °C for 16 h. The reaction mixture was then concentrated and purified by column chromatography using 50% EtOAc in hexane as eluent to afford ethyl 1-(1-(3-chloro-4-methoxyphenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylate (52 mg, 43%). LC-MS m/z: 366 [M + H]+. 1H NMR (400 MHz, CDCl3): δ 7.64 (d, J = 2.5 Hz, 1H), 7.47 (dd, J = 8.8, 2.5 Hz, 1H), 7.05 (d, J = 8.8 Hz, 1H), 4.14 (q, J = 7.1 Hz, 2H), 3.97 (s, 3H).
3.54 (dt, J = 13.0, 3.5 Hz, 2H) 2.97 (t, J = 12.7 Hz, 2H), 2.47 (m, 1H), 1.99-1.90 (m, 2H), 1.85-1.72 (m, 2H), 1.25 (t, J = 7.2 Hz, 3H).

**Ethyl 1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylate.**

A mixture of ethyl 1-(1-(3-chloro-4-methoxyphenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylate (50 mg, 0.137 mmol) and Pd-C (10% moist) in methanol (5 mL) was hydrogenated at rt under balloon pressure. Upon completion of the reaction, the mixture was filtered through Celite and concentrated to afford crude ethyl 1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylate (37 mg, 81%) as a white solid which was used without further purification. LC-MS m/z: 332 [M + H]+.

**1-(1-(4-Methoxyphenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylic acid.**

LiOH.H2O (11.7 mg, 0.279 mmol) was added to a stirred solution of ethyl 1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylate (37 mg, 0.112 mmol) in MeOH-THF-water (1:1:1, 6 mL) at rt. The mixture was stirred at rt for 3 hr and then diluted with water and EtOAc. The aqueous layer was separated, acidified with 1 M HCl and extracted with EtOAc. The combined organic extracts were washed with brine, dried over anhydrous Na2SO4 and concentrated to afford crude 1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (30 mg, 88%) which was used without further purification. LC-MS m/z: 304 [M + H]+.

(5-Chloro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (31).
N-methyl morpholine (200 mg, 1.98 mmol) was added to a stirred solution of 1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (150 mg, 0.495 mmol) in THF (5 mL) at rt. The reaction mixture was then cooled to -15 °C and isobutyl chloroformate (0.097 mL, 0.743 mmol) was added dropwise to the mixture. The solution was then stirred for 15 min at -15 °C followed by the addition of 5-chloro-1,2,3,4-tetrahydroquinoline (83.66 mg, 0.495 mmol). The reaction mixture was stirred at rt overnight, then extracted with EtOAc. The organic extract was washed with water, brine, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by column chromatography (SiO₂, 100-200 mesh) using 5% methanol in CH₂Cl₂ as eluent to afford 31 (15 mg, 7%) as an off white solid. LC-MS m/z: 453 [M + H]+. 

1H NMR (400 MHz, DMSO-d₆): δ 7.55 (d, J = 8.8 Hz, 2H), 7.37 (br s, 1H), 7.26 (d, J = 7.8 Hz, 1H), 7.20 (d, J = 8.0 Hz, 1H), 7.16 (d, J = 8.7 Hz, 2H), 3.84 (s, 3H), 3.69 (t, J = 5.4 Hz, 2H), 3.45 (d, J = 12.4 Hz, 2H), 3.03 (m, 1H), 2.87 (m, 2H), 2.74 (t, J = 6.8 Hz, 2H), 1.89 (t, J = 5.8 Hz, 2H), 1.72-1.60 (m, 4H).

(8-Chloro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)(1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (32).

SO₂Cl₂ (0.011 mL, 0.139 mmol) was added to a stirred solution of 1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (35.0 mg, 0.116 mmol) and pyridine (0.026 mL, 0.289 mmol) in CH₂Cl₂ (4.0 mL) under nitrogen atmosphere at rt. The reaction mixture was stirred for 30 min, followed by addition of 8-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine (21.0 mg, 0.127 mmol) in CH₂Cl₂ (1 mL), Et₃N (0.019 mL, 0.37 mmol) and a catalytic amount of DMAP. The reaction mixture was stirred for an additional 16 h, then washed with 1 M HCl, water, dried over anhydrous Na₂SO₄ and concentrated. The residue was purified by preparative TLC using 70% EtOAc in hexane as eluent to afford 32 (15 mg, 30%) as a white solid. LC-MS m/z: 455 [M + H]+. 1H NMR (400 MHz, DMSO-d₆): δ 7.52 (br d, J = 8.7 Hz, 3H), 7.19 (d, J = 7.7, 2H), 7.14 (d, J = 8.8 Hz, 2H), 6.86 (d, J = 8.1 Hz, 1H),
4.33 (m, 2H), 3.88 (m, 2H) 3.81 (s, 3H), 3.46 (d, $J_{12.3 \text{ Hz}}$, 2H), 3.07 (m, 1H), 2.92 (t, $J_{12.2 \text{ Hz}}$, 2H), 1.75-1.55 (m, 4H).

(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-isopropyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (27).

2-isothiocyanatopropane (0.14 g, 1.39 mmol) was added to a solution of 1-[(piperidin-4-yl)carbonyl]-1,2,3,4-tetrahydroquinoline (0.34 g, 1.39 mmol) in CH$_2$Cl$_2$ and the mixture was stirred for 16 h at rt. The reaction mixture was then concentrated to afford a crude residue which was purified by silica column chromatography using 30-50% EtOAc in hexane as eluent to afford N-isopropyl-4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carbothioamide (0.17 g, 35%) as a solid which was used without further purification

(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-isopropyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (27).

Sodium azide (0.067 g, 1.043 mmol), HgCl$_2$ (0.103 g, 0.383 mmol) and triethylamine (0.14 mL, 1.04 mmol) was added to a stirred solution of N-isopropyl-4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carbothioamide (0.120 g, 0.348 mmol) in CH$_2$Cl$_2$ (5 mL) at 0 °C. The mixture was stirred for 2 h at rt, then partitioned between EtOAc and water. The organic extracts were concentrated to obtain a residue, which was purified by silica column chromatography using 30-50% EtOAc in hexane as eluents to afford 27 (0.50 g, 50%) as a white solid. LC-MS m/z: 455 [M + H]$^+$

$^1$H NMR (400 MHz, DMSO-d$_6$): $\delta$ 7.40 (br s, 1H), 7.18 (m, 2H), 7.13 (m, 1H), 4.57 (m, 1H), 3.71 (t, $J_{6.3 \text{ Hz}}$, 2H), 3.41 (d, $J_{12.2 \text{ Hz}}$, 2H), 3.07 (m, 1H), 2.89 (m, 2H), 2.71 (t, $J_{6.7 \text{ Hz}}$, 2H), 1.94-1.70 (m, 6H), 1.45 (d, $J_{6.6 \text{ Hz}}$, 6H).
Synthesis of compound 28, (3,4-dihydroquinolin-1(2H)-yl)(1-(1-isopropyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone.

Isothiocyanatocyclopentane.

CS₂ (10.0 mL, 169.2 mmol) was added to a stirred solution of cyclopentylamine (1.00 g, 16.9 mmol) in absolute ethanol (12 mL), followed by the addition of triethylamine (2.60 mL, 18.6 mmol) to the reaction mixture. After stirring for 30 min at rt, the reaction mixture was cooled on ice and di-tert-butyl dicarbonate (3.80 mL, 16.92 mmol) and a catalytic amount of DMAP in ethanol (5 mL) was added. The mixture was stirred at rt overnight, then concentrated to afford crude isothiocyanatocyclopentane (177 mg) which was used without further purification.

N-Cyclopentyl-4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carbothioamide.

Isothiocyanatocyclopentane (0.177 g, 1.39 mmol) was added to a stirred solution of (3,4-dihydroquinolin-1(2H)-yl)(piperidin-4-yl)methanone (0.34 g, 1.39 mmol) in CH₂Cl₂ (20 mL). The mixture was stirred at rt for 16 h, then concentrated and the residue was purified by silica column chromatography using 30-50% EtOAc in hexane as eluents to afford N-cyclopentyl-4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carbothioamide (0.32 g, 80% over 2 steps) as a solid. LC-MS m/z: 372 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 7.36 (br s, 1H), 7.30-7.05 (m, 4H), 4.61 (d, J = 9.8 Hz, 1H), 3.68 (s, 2H), 3.11 (m, 1H), 2.89 (m, 2H), 2.87 (m, 2H), 2.69 (m, 2H), 1.88 (m, 4H), 1.73-1.40 (m, 10H).

(1-(1-cyclopentyl-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (28).

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Sodium azide (0.063 g, 0.97 mmol), HgCl₂ (0.096 g, 0.356 mmol) and triethylamine (0.135 mL, 0.97 mmol) was added to a stirred solution of N-cyclopentyl-4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carbothioamide (0.12 g, 0.32 mmol) in DMF (5 mL) at 0 °C. The mixture was stirred for 2 h at rt, then partitioned between EtOAc and water. The organic extracts were concentrated to obtain a residue, which was purified by silica column chromatography using 30-50% EtOAc in hexane as eluent to afford 28 (0.80 g, 65%) as a white solid. LC-MS m/z: 381 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆): δ 7.39 (br s, 1H), 7.20 (m, 2H), 7.13 (d, J = 7.1 Hz, 1H), 4.73 (m, 1H), 3.71 (t, J = 6.2 Hz, 2H), 3.45 (d, J = 12.4 Hz, 2H), 3.08 (m, 1H), 2.89 (m, 2H), 2.71 (t, J = 6.6 Hz, 2H), 2.14 (m, 2H), 1.97-1.64 (m, 12H).

(1-(1-Cyclohexyl-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (29).

N-Cyclohexyl-4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carbothioamide.

Cyclohexyl isothiocyanate (0.139 g, 0.98 mmol) was added to a stirred solution of (3,4-dihydroquinolin-1(2H)-yl)(piperidin-4-yl)methanone (0.24 g, 0.98 mmol) in CH₂Cl₂ (20 mL). The mixture was stirred for 16h at rt and then concentrated. The residual crude was purified by silica column chromatography using 30-50% EtOAc in hexane as eluents to afford N-cyclohexyl-4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carbothioamide (0.33 g, 87%) as a solid which was used directly in next step.

(1-(1-Cyclohexyl-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (29).
Sodium azide (0.066 g, 1.01 mmol), HgCl$_2$ (0.101 g, 0.371 mmol) and triethylamine (0.14 mL, 1.01 mmol) was added to a stirred solution of N-cyclohexyl-4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carbothioamide (0.13 g, 0.34 mmol) in DMF (5 mL) at 0 °C. The mixture was stirred at rt for 2 h, then partitioned between EtOAc and water. The organic extracts were concentrated to obtain a residue which was purified by column chromatography using 30-50% EtOAc in hexane as eluents to afford 29 (0.60 g, 45%) as a white solid. LC-MS m/z: 395 [M + H$^+$]. $^1$H NMR (400 MHz, DMSO-d$_6$): δ 7.39 (br s, 1H), 7.20 (m, 2H), 7.12 (m, 1H), 4.15 (m, 1H), 3.71 (t, $J=6.2$ Hz, 2H), 3.40 (d, $J=12.3$ Hz, 2H), 3.08 (m, 1H), 2.90 (m, 2H), 2.71 (t, $J=6.6$ Hz, 2H), 1.97 (d, $J=11.2$ Hz, 2H), 1.93-1.71 (m, 10H), 1.67 (d, $J=13.0$ Hz, 1H), 1.45 (q, $J=12.8$ Hz, 2H), 1.26 (m, 1H).

Synthesis of (5-chloro-3,4-dihydroquinolin-1(2H)-yl)-(1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (33), (8-chloro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)(1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (34) and (3,4-dihydroquinolin-1(2H)-yl)(1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (35):

Synthesis of 1-(4-bromophenyl)-5-(methylsulfonyl)-1H-tetrazole.

1-Bromo-4-isothiocyanatobenzene.
Triethylamine (4.05 mL, 29.07 mmol) and CS$_2$ (17.53 mL, 290.7 mmol) was added to a stirred solution of 4-bromoaniline (5 g, 29.07 mmol) in THF (60 mL) at 0 °C. Then the reaction mixture was stirred at rt for 1 h, then concentrated. The residual crude was purified by silica column chromatography using 10% EtOAc in hexane as eluent to afford 1-bromo-4-isothiocyanatobenzene (2.0 g, 32%) as an off white solid. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.46 (d, $J = 8.6$ Hz, 2H), 7.08 (d, $J = 8.6$ Hz, 2H).

1-(4-Bromophenyl)-1,4-dihydro-5H-tetrazole-5-thione.

A solution of 1-bromo-4-isothiocyanatobenzene 2 (200 mg, 0.93 mmol) and sodium azide (120.9 mg, 1.86 mmol) in water (10 mL) was heated under reflux for 4 h. The cooled solution filtered and acidified to pH 3.0 with concentrated HCl. The white solid obtained was filtered off, washed with cold water, and dried under vacuum to give crude 1-(4-bromophenyl)-1,4-dihydro-5H-tetrazole-5-thione as a white solid (205 mg, 86%), which was used without further purification. $^1$H NMR (400 MHz, CDCl$_3$): δ 7.91 (d, $J = 8.5$ Hz, 2H), 7.75 (br s, 1H), 7.69 (d, $J = 8.8$ Hz, 2H).

1-(4-Bromophenyl)-5-(methylthio)-1H-tetrazole.

Dimethyl sulphate (1.294 g, 10.27 mmol), NaOH (448 mg, 11.21 mmol), and TBAB (301 mg, 0.934 mmol) were added to a stirred solution of 1-(4-bromophenyl)-1,4-dihydro-5H-tetrazole-5-thione (2.4 g, 9.34 mmol) in H$_2$O-CH$_2$Cl$_2$ (1:1, 70 mL) at 25 °C. The mixture was stirred at rt for 18 h, then the organic layer was separated, the aqueous layer was extracted with toluene. The combined organic extracts were dried over Na$_2$SO$_4$ and concentrated. The crude product was purified by column chromatography using 30% ethyl acetate in hexane as eluent to afford 1-(4-Bromophenyl)-5-(methylthio)-1H-tetrazole (2.2 g,
87%) as an off white solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.91 (d, J = 8.8 \text{ Hz}, 2H), 7.46 (d, J = 8.6 \text{ Hz}, 2H), 2.83 (s, 3H)\).

1-(4-Bromophenyl)-5-(methylsulfonyl)-1\(H\)-tetrazole.

\(\text{H}_2\text{O}_2\) (30\%, 5.20 mL, 46.0 mmol) was added to a stirred solution of 1-(4-bromophenyl)-5-(methylthio)-1\(H\)-tetrazole (2.50 g, 9.19 mmol) in acetic acid (10 mL) at rt. The solution was stirred at 70 °C for 24 h, then poured into cold water and extracted with ethyl acetate. The combined organic extracts were dried over Na\(_2\)SO\(_4\), filtered and concentrated. The crude product was purified by column chromatography using 30\% ethyl acetate in hexane as eluent to afford 1-(4-bromophenyl)-5-(methylsulfonyl)-1\(H\)-tetrazole (900 mg, 32\%) as an off white solid. \(^1\)H NMR (400 MHz, acetone-d\(_6\)): \(\delta 7.90 (d, J = 8.7 \text{ Hz}, 2H), 7.76 (d, J = 8.8 \text{ Hz}, 2H), 3.66 (s, 3H)\).

Ethyl 1-(1-(4-bromophenyl)-1\(H\)-tetrazol-5-yl)piperidine-4-carboxylate.

A mixture of 1-(4-Bromophenyl)-5-(methylsulfonyl)-1\(H\)-tetrazole (2.50 g, 8.21 mmol) & ethyl piperidine-4-carboxylate (8.86 mL, 57.49 mmol) was heated at 120 °C in a sealed tube for 16h. After completion, the reaction was quenched with water and extracted by ethyl acetate. The crude product was purified by column chromatography using 70\% ethyl acetate in hexane as eluent to afford ethyl 1-(1-(4-bromophenyl)-1\(H\)-tetrazol-5-yl)piperidine-4-carboxylate (1.7 g, 54\%) as an off white solid. \(^1\)H NMR (400 MHz, CDCl\(_3\)): \(\delta 7.68 (d, J = 8.8 \text{ Hz}, 2H), 7.52 (d, J = 8.6 \text{ Hz}, 2H), 4.14 (q, J = 7.2 \text{ Hz}, 2H), 3.53 (dt, J = 13.0, 3.6 \text{ Hz}, 2H), 2.97 (td, J = 12.4, 2.7 \text{ Hz}, 2H), 2.47 (m, 1H), 1.95 (dd, J = 13.7, 3.3 \text{ Hz}, 2H), 1.85-1.73 (m, 2H), 1.25 (t, J = 7.1 \text{ Hz}, 3H).

Ethyl 1-(1-(4-pyrrolidin-1-yl)phenyl)-1\(H\)-tetrazol-5-yl)piperidine-4-carboxylate.
A solution of ethyl 1-(1-(4-bromophenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylate (350 mg, 0.921 mmol), sodium-tert-butoxide (265.3 mg, 2.76 mmol) and pyrrolidine (130.8 mg, 1.84 mmol) in dioxane (3 mL) in a microwave vial was purged with argon for 15 min, then BrettPhos Pd G3 (41.72 mg, 0.046 mmol) and Pd$_2$(dba)$_3$ (42.13 mg, 0.046 mmol) were added and the mixture was heated at 120 °C in a microwave reactor for 1 h. The reaction mixture was then filtered, concentrated and the residue was purified by column chromatography using 80% ethyl acetate in hexane as eluent to afford ethyl 1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylate (165 mg, 48%) as off white solid.

$^1$H NMR (400 MHz, CDCl$_3$): δ 7.32 (d, $J = 8.9$ Hz, 2H), 6.58 (d, $J = 8.9$ Hz, 2H), 4.13 (q, $J = 7.1$ Hz, 2H), 3.60 (dt, $J = 13.1$, 3.4 Hz, 2H), 3.33 (m, 4H), 2.91 (td, $J = 12.6$, 4.0 Hz, 2H), 2.43 (m, 1H), 2.05 (m, 4H), 1.90 (dd, $J = 13.6$, 3.2 Hz, 2H), 1.79-1.70 (m, 2H), 1.24 (t, $J = 7.1$ Hz, 3H)

1-(1-(4-(Pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylic acid.

LiOH·H$_2$O (13.62 mg, 0.324 mmol) was added to a stirred solution of ethyl 1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylate (60 mg, 0.162 mmol) in THF-water (3:2, 5 mL) at 25 °C. The mixture was stirred at 25 °C for 3 h and then diluted with water and ethyl acetate. The aqueous layer was separated, acidified with 1M HCl and extracted with ethyl acetate. The combined organic extracts were washed with brine, dried over anhydrous Na$_2$SO$_4$ and concentrated to afford crude 1-(1-(4-(Pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (35 mg, 63%) as off white solid which was used without further purification.

$^1$H NMR (400 MHz, DMSO-d$_6$): δ 12.27 (s, 1H), 7.34 (d, $J = 8.7$ Hz, 2H), 6.66 (d, $J = 8.7$ Hz, 2H), 3.46 (d, $J = 12.9$ Hz, 2H), 3.29 (m, 4H), 2.90 (t, $J = 11.5$ Hz, 2H), 2.42 (m, 1H), 1.98 (m, 4H), 1.77 (d, $J = 11.3$ Hz, 2H), 1.60-1.48(m, 2H).

(5-chloro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (33),
To a stirred solution of 1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (40.0 mg, 0.117 mmol) in pyridine (1 mL) was added T3P (0.267 mL, 133.7 mg, 50% in ethyl acetate) at 25 °C. The mixture was stirred at rt for 5 minutes and then 5-chloro-1,2,3,4-tetrahydroquinoline (19.53 mg, 0.117 mmol) in pyridine (1 mL) was added. The resulting mixture was stirred at 25 °C for 16 h. After completion of the reaction the mixture was concentrated and the crude product was purified by preparative HPLC to afford (5-Chloro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (12 mg, 21%) as white solid. LC-MS m/z: 492 [M + H]+. 1H NMR (400 MHz, 100 °C, DMSO-d6): δ 7.37 (m, 1H), 7.31 (d, J = 12.4 Hz, 2H), 7.25-7.12 (m, 2H), 6.69 (d, J = 12.4 Hz, 2H), 3.70 (m, 2H), 3.55 (d, J = 13.2 Hz, 2H), 3.2 (br s, 4H), 3.04 (m, 1H), 2.95 (t, J = 10.8 Hz, 2H), 2.77 (t, J = 6.8 Hz, 2H), 2.01 (br s, 4H), 1.93 (t, J = 6.0 Hz, 2H), 1.68 (br s, 4H).

\((8\text{-chloro-2,3-dihydro-}4\text{H-benzo[}b][1,4]\text{]oxazin-4-yl})\(1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (34)

To a stirred solution of 1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (40.0 mg, 0.117 mmol) in pyridine (1 mL) was added T3P (0.267 mL, 133.7 mg, 50% in ethyl acetate). The mixture was stirred at 25 °C for 5 minutes and then 8-chloro-3,4-dihydro-2H-benzo[b][1,4]oxazine (19.76 mg, 0.117 mmol) in pyridine (1mL) was added. The resulting mixture was stirred at RT for 48 h. After completion of the reaction the mixture was concentrated and the crude product was purified by preparative HPLC to afford (8-Chloro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)(1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (15 mg, 26%) as white solid. LC-MS m/z: 494 [M + H]+. 1H NMR (400 MHz, DMSO-d6): δ 7.63 (d, J = 8.0 Hz, 1H), 7.33 (d, J = 8.8 Hz, 2H), 7.18 (d, J = 8.0 Hz, 1H), 6.87 (t, J = 8.4 Hz, 1H), 6.69 (d, J = 8.8 Hz, 2H), 4.46 (m, 2H), 3.92 (m, 2H), 3.57 (d, J = 12.8 Hz, 2H), 3.32 (m, 3H), 2.01 (br s, 4H), 1.72 (br s, 4H), 1.27 (br s, 4H).
To a stirred solution of 1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (150 mg, 0.437 mmol) in pyridine (3 mL) was added T3P (1.03 mL, 501.4 mg, 1.575 mmol, 50% in ethyl acetate). The mixture was stirred at 25 °C for 1 h and then 1,2,3,4-tetrahydroquinoline (58.20 mg, 0.437 mmol) in pyridine (1 mL) was added. The resulting mixture was stirred at RT for 20 h. After completion of the reaction, volatiles were removed and the resultant crude product was purified by preparative HPLC to afford (3,4-dihydroquinolin-1(2H)-yl)(1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (35, 35 mg, 19%) as a brown solid. LC-MS m/z: 458 [M + H]+. 1H NMR (400 MHz, 100 °C, DMSO-d6): δ 7.35 (d, J = 8.0 Hz, 1H), 7.31 (d, J = 8.4 Hz, 2H), 7.18 (m, 2H), 7.16 (m, 1H), 6.68 (d, J = 8.8 Hz, 2H), 3.68 (d, J = 8.4 Hz, 2H), 3.54 (d, J = 13.2 Hz, 2H), 3.31 (br s, 4H), 2.85 (t, J = 11.2 Hz, 2H), 2.69 (t, J = 6.8 Hz, 2H), 2.01 (s, 4H), 1.89 (m, 2H), 1.78-1.60 (m, 5H).

**Synthesis of (5-fluoro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (36),**

To a stirred solution of 1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylic acid (60 mg, 0.175 mmol) and 5-fluo-1,2,3,4-tetrahydroquinoline (26.44 mg, 0.175 mmol) in dry CH2Cl2 (3 mL) at 0°C was added POCl3 (26.82 mg, 0.175 mmol). The mixture was stirred at 0 °C for 1 h and
then then at room temperature for 3h. After completion of the reaction, the crude reaction mixture was diluted with CH₂Cl₂ and the organic layer was separated, washed with brine, dried over Na₂SO₄ and concentrated to get crude which was purified by preparative HPLC to afford 5-fluoro-1-(1-[4-(pyrrolidin-1-yl)phenyl]-1,2,3,4-tetrazol-5-yl)piperidine-4-carbonyl)-3,4-dihydro-2H-quinoline (36) (11 mg, 13%) as a white solid. LC-MS m/z: 476 [M + H]⁺. ¹H NMR (400 MHz, DMSO-d₆):  δ 7.34 (d, J = 8.6 Hz, 2H), 7.28 (m, 1H), 7.18 (q, J = 7.6 Hz, 1H), 6.96 (t, J = 8.8 Hz, 1H), 6.66 (d, J = 8.8 Hz, 2H), 3.70 (t, J = 5.7 Hz, 2H), 3.51 (d, J = 12.5 Hz, 2H), 3.30-3.24 (m, 4H), 3.05 (m, 1H), 2.86 (m, 2H), 2.70 (t, J = 6.8 Hz, 2H), 1.98 (br s, 4H), 1.87 (m, 2H), 1.65 (br s, 4H).

Synthesis of 5-fluoro-1,2,3,4-tetrahydroquinoline.

3-(2-fluorophenyl)propan-1-ol

To a cooled solution of 3-(2-fluorophenyl)propanoic acid (1.0 g, 5.95 mmol) in THF (25 mL) under an argon atmosphere was added lithium aluminum hydride (451.6 mg, 11.9 mmol) portion wise at 0 °C. The reaction mixture was allowed to reach at rt. After 3h, the mixture was quenched at 0 °C with a 1.0 M NaOH solution (2 mL) and water (2 mL). The reaction mixture was diluted with water (50 mL) and filtered through a pad of celite, washed with ethyl acetate (2 x 25 mL). The filtrate was extracted with ethyl acetate (3 x 25 mL). The combined organic layers were washed with water, brine and dried over Na₂SO₄. Filtration and evaporation of the solvents afforded 3-(2-fluorophenyl)propan-1-ol (880 mg, 96%) as crude which was used in the next step without further purification. ¹H NMR (400 MHz, CDCl₃):  δ 7.23–7.13 (m, 1H) 7.18 (d, J = 7.6 Hz, 1H), 7.05 (t, J = 7.6 Hz, 1H), 7.00 (t, J = 9.2 Hz, 1H), 3.67 (t, J = 6.4 Hz, 2H), 2.74 (t, J = 7.6 Hz, 2H), 1.86 (m, 2H).

tert-butyl (3-(2-fluorophenyl)propyl)(tosyloxy)carbamate
To a stirred solution of triphenylphosphine (1.021 g, 3.894 mmol) in anhydrous THF (15 mL) at 0 °C was added DIAD (7876 mg; 3.89 mmol). After stirring for 0.5h, a solution of 3-(2-fluorophenyl)propan-1-ol (500 mg, 3.245 mmol) and tert-butyl tosylxycarbamate (TsONHBoc) (1.12 g, 3.89 mmol) in anhydrous THF (10 mL) was added. After stirring at 0 °C for 2h, the reaction was allowed to warm to rt and stirring was continued for 1h. After completion of reaction, volatiles were removed under reduced pressure and the residue was purified by flash column chromatography using 10% ethyl acetate in hexane as eluent to afford tert-butyl (3-(2-fluorophenyl)propyl)(tosyloxy)carbamate (1.0 g, 73%) as an off white gummy solid. 

1H NMR (400 MHz, CDCl3): δ 7.84 (d, J = 8.1 Hz, 2H), 7.32 (d, J = 7.7 Hz, 2H), 7.16 (br s, 2H), 7.04 (t, J = 6.9 Hz, 1H), 6.98 (t, J = 9.1 Hz, 1H), 3.62 (br s, 2H), 2.61 (m, 2H), 2.43 (s, 3H), 1.93 (br s, 2H), 1.21 (s, 9H).

5-fluoro-1,2,3,4-tetrahydroquinoline

Hexafluoro-2-propanol (25 mL), FeSO4·7H2O (49.20 mg, 0.177 mmol) and TFA (0.542 mL, 7.084 mmol) were added to a stirred solution of tert-butyl (3-(2-fluorophenyl)propyl)(tosyloxy)carbamate (1.5 g, 3.54 mmol) in a 20 mL reaction vial. The mixture was stirred at rt for 4 h, then the reaction was quenched with an aqueous 1 M NaOH solution (50 mL). The aqueous layer was extracted with EtOAc (2 x 50 mL). The combined organic layers were washed with brine, dried over Na2SO4, and concentrated under reduced pressure. The residue was purified by flash column chromatography using 10% ethyl acetate in hexane as eluent to get 5-fluoro-1,2,3,4-tetrahydroquinoline (180 mg, 34%) as off white gummy solid. 

1H NMR (400 MHz, CDCl3): δ 6.88 (d, J = 6.9 Hz, 1H), 6.32 (d, J = 8.7 Hz, 1H), 6.24 (d, J = 8.0 Hz, 1H), 3.27 (t, J = 5.4 Hz, 2H), 2.71 (t, J = 6.4 Hz, 2H), 1.92 (m, 2H).
(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-(pyridin-4-yl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (3),
(1-(1-(3-Chlorophenyl)-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (6).
(1-(1-(4-Chlorophenyl)-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (14),

\[
\begin{array}{c}
\text{Cl} \\
\text{N} \quad \text{N} \\
\text{N} \quad \text{N}
\end{array}
\]
(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-(pyridin-3-yl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (4),
(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-(4-fluorophenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (5),
4-(5-(4-(1,2,3,4-Tetrahydroquinoline-1-carbonyl)piperidin-1-yl)-1H-tetrazol-1-yl)benzonitrile (10).
(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-(2-(trifluoromethyl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (11),

\[
\text{\includegraphics{image.png}}
\]
3-(5-(4-(1,2,3,4-Tetrahydroquinoline-1-carbonyl)piperidin-1-yl)-1H-tetrazol-1-yl)benzonitrile (12),

![Chemical structure of 3-(5-(4-(1,2,3,4-Tetrahydroquinoline-1-carbonyl)piperidin-1-yl)-1H-tetrazol-1-yl)benzonitrile (12).]
(1-(1-(2-Chlorophenyl)-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (13),
*tert*-Butyl 4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carboxylate.
1-(Piperidine-4-carbonyl)-1,2,3,4-tetrahydroquinoline.
1-Fluoro-4-isothiocyanatobenzene.
5-Chloro-1-(4-fluorophenyl)-1H-tetrazole.
3-(5-Chloro-1H-tetrazol-1-yl)pyridine.
3-(5-Chloro-1H-tetrazol-1-yl)benzonitrile.
N-(2-Chlorophenyl)formamide.
5-Chloro-1-(2-chlorophenyl)-1H-tetrazole.
N-(4-Cyanophenyl)formamide.
4-(5-Chloro-1H-tetrazol-1-yl)benzonitrile.
N-(2-(Trifluoromethyl)phenyl)formamide.
(2-(Trifluoromethyl)phenyl)carbonimidic dichloride.

\[
\begin{align*}
&\text{Cl} \quad \text{Cl} \\
&\text{F}_3\text{C} \quad \text{C} \\
&\text{H} \quad \text{H}
\end{align*}
\]
5-Chloro-1-(2-(trifluoromethyl)phenyl)-1H-tetrazole.
(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-(4-(trifluoromethoxy)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (9).
1-Azido-4-(trifluoromethoxy)benzene.
(1-(1-(3-Chloro-4-methoxyphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone.
(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (7).
5-Chloro-1-(3-chloro-4-methoxyphenyl)-1H-tetrazole.
(1-(1-(2-Chloro-6-methylphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone.
(3,4-Dihydroquinolin-1(2H)-yl)(1-(o-tolyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (8).
(2-Chloro-6-methylphenyl)carbonimidic dichloride.
5-Chloro-1-(2-chloro-6-methylphenyl)-1H-tetrazole.
(7-Methoxy-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone) (16).
(5-Chloro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (17),

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\text{N=N}
\]

\[
\text{N=N}
\]

\[
\text{O} \quad \text{Cl}
\]

\[
\text{N} \quad \text{N} \quad \text{O}
\]

CHEMBIOTEK, A TCG Lifesciences Private Limited

CR302-9846-33-P-1 IN DMSO

TCGLS/ARD/NMR01/K01

Kolkata

\[
7.1 \quad 7.2 \quad 7.3 \quad 7.4 \quad 7.5 \quad 7.6 \quad 7.7 \quad 7.8
\]

ppm

1.07
1.04
1.06
1.19
4.00

1.6651
1.8907
1.9040
2.5000
2.6695
2.7269
2.7431
2.7591
2.8946
3.0305
3.3179
3.4162
3.4479
3.6865

11 10 9 8 7 6 5 4 3 2 1 0 ppm
(2,3-Dihydro-4H-benzo[b][1,4]oxazine-4-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (18),
(6-Chloro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (20),

\[
\text{N=N} \quad \text{N=N} \\
\quad \text{O} \\
\quad \text{Cl}
\]

CHEMBIOTEK, A TCG Lifesciences Private Limited
Kolkata

CR302-9846-17-P IN DMSO

TCGLS/ARD/NMR01/K01

7.2 7.4 7.6 7.8 ppm

12 11 10 9 8 7 6 5 4 3 2 1 ppm
(6-Methoxy-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (21),

\[
\text{N=N} \quad \text{N} \quad \text{N} \\
\text{O} \quad \text{O} \\
\text{OMe}
\]
(7-Chloro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (23),

![Chemical Structure](image-url)
(3,4-Dihydro-1,5-naphthyridin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (24),
(3,4-Dihydro-1,6-naphthyridin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (25),
(5-Methoxy-3,4-dihydroquinolin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (26),
1-(1-(1-Phenyl-1H-tetrazol-5-yl)piperidine-4-carbonyl)-1,2,3,4-tetrahydroquinoline-6-carbonitrile (19),
(3,4-Dihydro-1,8-naphthyridin-1(2H)-yl)(1-(1-phenyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (15),
Ethyl 1-(1-phenyl-1H-tetrazol-5-yl)piperidine-4-carboxylate.
1-(1-Phenyl-1H-tetrazol-5-yl)piperidine-4-carboxylic acid.
1-(1-(1-Phenyl-1H-tetrazol-5-yl)piperidine-4-carbonyl)-1,2,3,4-tetrahydroquinoline-7-carbonitrile (22).
(2,3-Dihydro-4H-benzo[b][1,4]oxazin-4-yl)(1-(1-(4-fluorophenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (30).
Ethyl 1-(1-(3-chloro-4-methoxyphenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylate.
(5-Chloro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (31).
(8-Chloro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)(1-(1-(4-methoxyphenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (32).
(3,4-Dihydroquinolin-1(2H)-yl)(1-(1-isopropyl-1H-tetrazol-5-yl)piperidin-4-yl)methanone (27).
N-Cyclopentyl-4-(1,2,3,4-tetrahydroquinoline-1-carbonyl)piperidine-1-carbothioamide.
(1-(1-cyclopentyl-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (28).
(1-(1-Cyclohexyl-1H-tetrazol-5-yl)piperidin-4-yl)(3,4-dihydroquinolin-1(2H)-yl)methanone (29).
1-Bromo-4-isothiocyanatobenzene.
1-(4-Bromophenyl)-1,4-dihydro-5H-tetrazole-5-thione.
1-(4-Bromophenyl)-5-(methylthio)-1H-tetrazole.
1-(4-Bromophenyl)-5-(methylsulfonyl)-1H-tetrazole.
Ethyl 1-(1-(4-bromophenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylate.
Ethyl 1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-carboxylate.
1-(1-(4-(Pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidine-4-carboxylic acid.
(5-Chloro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (33),
(8-Chloro-2,3-dihydro-4H-benzo[b][1,4]oxazin-4-yl)(1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (34),
TCG Lifesciences Private Limited
Kolkata

CR302-16404-94-F1 IN DMSO AT 20 DEG C

TCGLS/ARD/NMR03/K76

PC                 1.00
GB                    0
LB                 0.30 Hz
SSB                   0
WDW                  EM
SF          400.1700039 MHz
SI                16384

Processing parameters
P1                 8.00 usec
P0                 2.67 usec
NUC1                 1H
SFO1        400.1724710 MHz
TD0                   1
D1           0.00000000 sec
TE                295.5 K
DE                18.11 usec
DW               62.400 usec
RG                 19.9
AQ            1.4998964 sec
FIDRES         0.666735 Hz
SWH            8012.820 Hz
DS                    0
NS                  128
SOLVENT            DMSO
TD                24036
PULPROG            zg30
PROBHD   Z163739_0162 (
INSTRUM           spect
Time              17.31 h
Date_          20210806

Acquisition Parameters
PROCNO                1
EXPNO                10
NAME     CR302

Current Data Parameters

TCG Lifesciences Private Limited
Kolkata
(3,4-dihydroquinolin-1(2H)-yl)(1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (35),

![Chemical structure](image)
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CR302-17085-64-F IN DMSO AT 100 DEG C

TCGLS/ARD/NMR03/K76

CR302-17085-64-F IN DMSO AT 20 DEG C

ANALYSED BY - Ayan Kundu
Synthesis of (5-fluoro-3,4-dihydroquinolin-1(2H)-yl)(1-(1-(4-(pyrrolidin-1-yl)phenyl)-1H-tetrazol-5-yl)piperidin-4-yl)methanone (36),
Current Data Parameters

NAME     CR302-17940-18-F
EXPNO                10
PROCNO                1
F2 - Acquisition Parameters
Date_          20220228
Time              15.23 h
INSTRUM           spect
PROBHD   Z163739_0162 (PULPROG            zg30
TD                24036
SOLVENT            DMSO
NS                    8
DS                    0
SWH            8012.820 Hz
FIDRES         0.666735 Hz
AQ            1.4998465 sec
RG                22.68
DW               62.400 usec
DE                18.11 usec
TE                297.2 K
D1           1.00000000 sec
TD0                   1
SFO1        400.1724710 MHz
NUC1                 1H
P0                 2.67 usec
P1                 8.00 usec
PLW1        21.75399971 W
F2 - Processing parameters
SI                16384
SF          400.1700032 MHz
WDW                  EM
SSB                   0
LB                 0.30 Hz
GB                    0
PC                 1.00
TCG Lifesciences Pvt. Limited

**Kolkata**

- **PC**                 1.00
- **LB**                 0.30 Hz
- **SSB**                   0
- **WDW**                  EM
- **SF**          400.1700034 MHz
- **SI**                16384
- **PLW1**        21.75399971 W
- **P1**                 8.00 usec
- **NUC1**                 1H
- **SFO1**        400.1724710 MHz
- **TD0**                   1
- **D1**                    0 sec
- **TE**                299.4 K
- **DE**                18.11 usec
- **DW**               62.400 usec
- **AQ**            1.4998465 sec
- **FIDRES**         0.666735 Hz
- **SWH**            8012.820 Hz
- **DS**                    0
- **NS**                   32
- **SOLVENT**            DMSO
- **TD**                24036
- **PULPROG**            zg30
- **PROBHD**   Z163739_0162
- **INSTRUM**           spect
- **Time**              20.10 h
- **Date_**          20220228

**F2 - Acquisition Parameters**

- **PROCNO**                1
- **EXPNO**                10
- **NAME**     CR302-17940-18-F

**Current Data Parameters**

- **LB**                 0.30 Hz
- **SSB**                   0
- **WDW**                  EM
- **SF**          400.1700034 MHz
- **SI**                16384
- **PLW1**        21.75399971 W
- **P1**                 8.00 usec
- **P0**                 2.67 usec
- **NUC1**                 1H
- **SFO1**        400.1724710 MHz
- **TD0**                   1
- **TE**                371.6 K
- **DE**                18.11 usec
- **DW**               62.400 usec
- **RG**                93.07
- **AQ**            1.4998465 sec
- **FIDRES**         0.666735 Hz
- **SWH**            8012.820 Hz
- **DS**                    0
- **NS**                   32
- **TD**                24036
- **PULPROG**            zg30
- **PROBHD**   Z163739_0162
- **INSTRUM**           spect
- **Time**              21.25 h
- **Date_**          20220228

**F2 - Processing parameters**

- **PROCNO**                1
- **EXPNO**                11
- **NAME**     CR302-17940-18-F

**Current Data Parameters**

- **LB**                 0.30 Hz
- **SSB**                   0
- **WDW**                  EM
- **SF**          400.1700034 MHz
- **SI**                16384
- **PLW1**        21.75399971 W
- **P1**                 8.00 usec
- **P0**                 2.67 usec
- **NUC1**                 1H
- **SFO1**        400.1724710 MHz
- **TD0**                   1
- **DE**                18.11 usec
- **DW**               62.400 usec
- **RG**                93.07
- **AQ**            1.4998465 sec
- **FIDRES**         0.666735 Hz
- **SWH**            8012.820 Hz
- **DS**                    0
- **SOLVENT**            DMSO
- **PULPROG**            zg30
- **PROBHD**   Z163739_0162
- **INSTRUM**           spect
- **Time**              20.10 h
- **Date_**          20220228

TCG Lifesciences Pvt. Limited

**Kolkata**

- **PC**                 1.00
- **GB**                    0
- **LB**                 0.30 Hz
- **SSB**                   0
- **WDW**                  EM
- **SF**          400.1700034 MHz
- **SI**                16384
- **PLW1**        21.75399971 W
- **P1**                 8.00 usec
- **P0**                 2.67 usec
- **NUC1**                 1H
- **SFO1**        400.1724710 MHz
- **TD0**                   1
- **TE**                371.6 K
- **DE**                18.11 usec
- **DW**               62.400 usec
- **RG**                93.07
- **AQ**            1.4998465 sec
- **FIDRES**         0.666735 Hz
- **SWH**            8012.820 Hz
- **DS**                    0
- **NS**                   32
- **TD**                24036
- **PULPROG**            zg30
- **PROBHD**   Z163739_0162
- **INSTRUM**           spect
- **Time**              20.10 h
- **Date_**          20220228

**F2 - Acquisition Parameters**

- **PROCNO**                1
- **EXPNO**                11
- **NAME**     CR302-17940-18-F

**Current Data Parameters**

- **LB**                 0.30 Hz
- **SSB**                   0
- **WDW**                  EM
- **SF**          400.1700034 MHz
- **SI**                16384
- **PLW1**        21.75399971 W
- **P1**                 8.00 usec
- **P0**                 2.67 usec
- **NUC1**                 1H
- **SFO1**        400.1724710 MHz
- **D1**                    0 sec
- **TE**                371.6 K
- **DE**                18.11 usec
- **DW**               62.400 usec
- **RG**                93.07
- **AQ**            1.4998465 sec
- **FIDRES**         0.666735 Hz
- **SWH**            8012.820 Hz
- **DS**                    0
- **SOLVENT**            DMSO
- **PULPROG**            zg30
- **PROBHD**   Z163739_0162
- **INSTRUM**           spect
- **Time**              21.25 h
- **Date_**          20220228

**F2 - Processing parameters**

- **PROCNO**                1
- **EXPNO**                11
- **NAME**     CR302-17940-18-F
3-(2-fluorophenyl)propan-1-ol
**tert-butyl (3-(2-fluorophenyl)propyl)(tosyloxy)carbamate**

![NMR spectrum of tert-butyl (3-(2-fluorophenyl)propyl)(tosyloxy)carbamate](image)

**Current Data Parameters**

**NAME**: CR302-17085-73-P  
**EXPNO**: 10  
**PROCNO**: 1  

**F2 - Acquisition Parameters**

**Date**: 20220120  
**Time**: 17.10 h  
**INSTRUM**: spect  
**PROBHD**: Z8246_0048 (PH)  
**PULPROG**: zg30  
**TD**: 24036  
**SOLVENT**: CDCl₃  
**NS**: 8  
**DS**: 0  
**SWH**: 8012.820 Hz  
**FIDRES**: 0.666735 Hz  
**AQ**: 1.4998465 sec  
**RG**: 181  
**DW**: 62.400 usec  
**DE**: 6.50 usec  
**TE**: 300.0 K  
**D1**: 1.00000000 sec  
**TD0**: 1  
**SFO1**: 400.1024006 MHz  
**NUC1**: 1H  
**P0**: 6.00 usec  
**P1**: 18.00 usec  
**PLW1**: 10.00000000 W

**F2 - Processing parameters**

**SI**: 16384  
**SF**: 400.1000144 MHz  
**WDW**: EM  
**SSB**: 0  
**LB**: 0 Hz  
**GB**: 0  
**PC**: 1.00

**Analysed By**: Souvik De
5-fluoro-1,2,3,4-tetrahydroquinoline