

SUPPORTING INFORMATION for

Library docking for Cannabinoid-2 Receptor ligands

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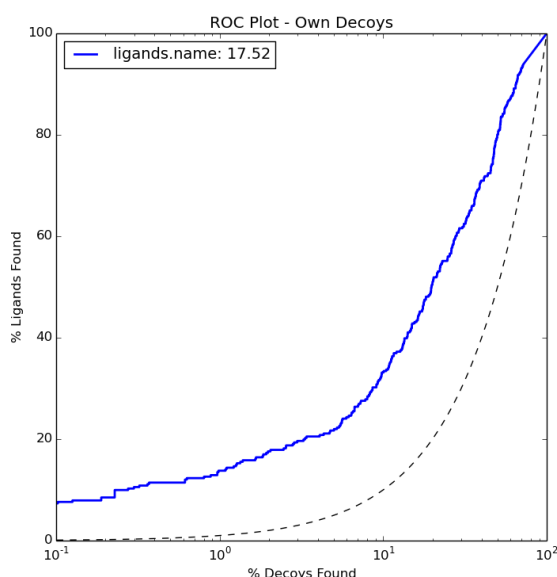


Figure S1. Enrichment (retrieved actives versus decoys) with the optimized CB2 agonist bound structure (6PT0). Actives comprised 34 CB2 ligands from the IUPHAR database. Decoys were property-matched but topologically distinct from ligands. Decoys were obtained from the DUDE-Z database.

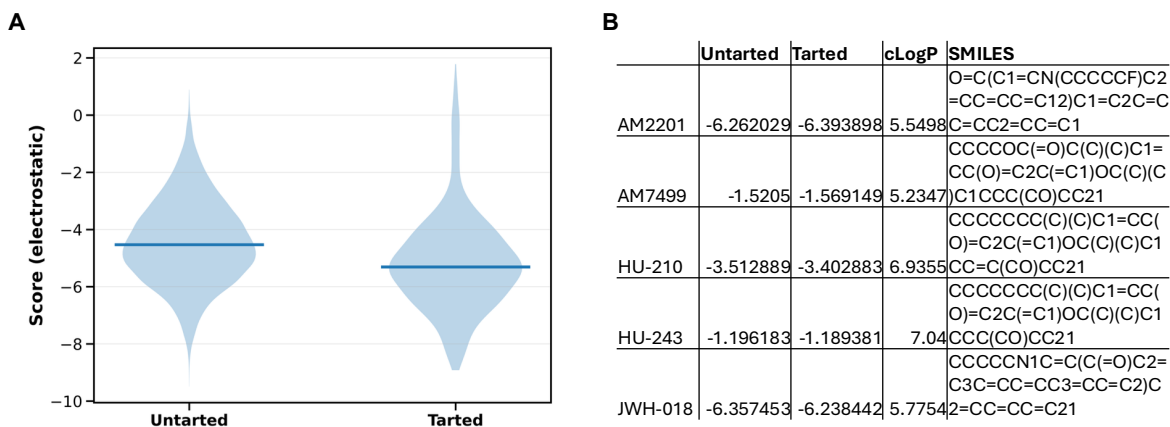


Figure S2. More polar molecules were sought by scaling electrostatic potential grids. A model without scaled electrostatics (“Untarted”) showed worse electrostatic scores than a model with scaled electrostatics (“Tarted”) for IUPHAR CB2 ligands (**A**). For IUPHAR ligands that gave the same pose between these models, less lipophilic ligands (AM2201, AM7499) obtained better electrostatic scores in the “Tarted” model, while more lipophilic ligands (HU-210, HU-243 and JWH-018) showed a worse score (**B**).

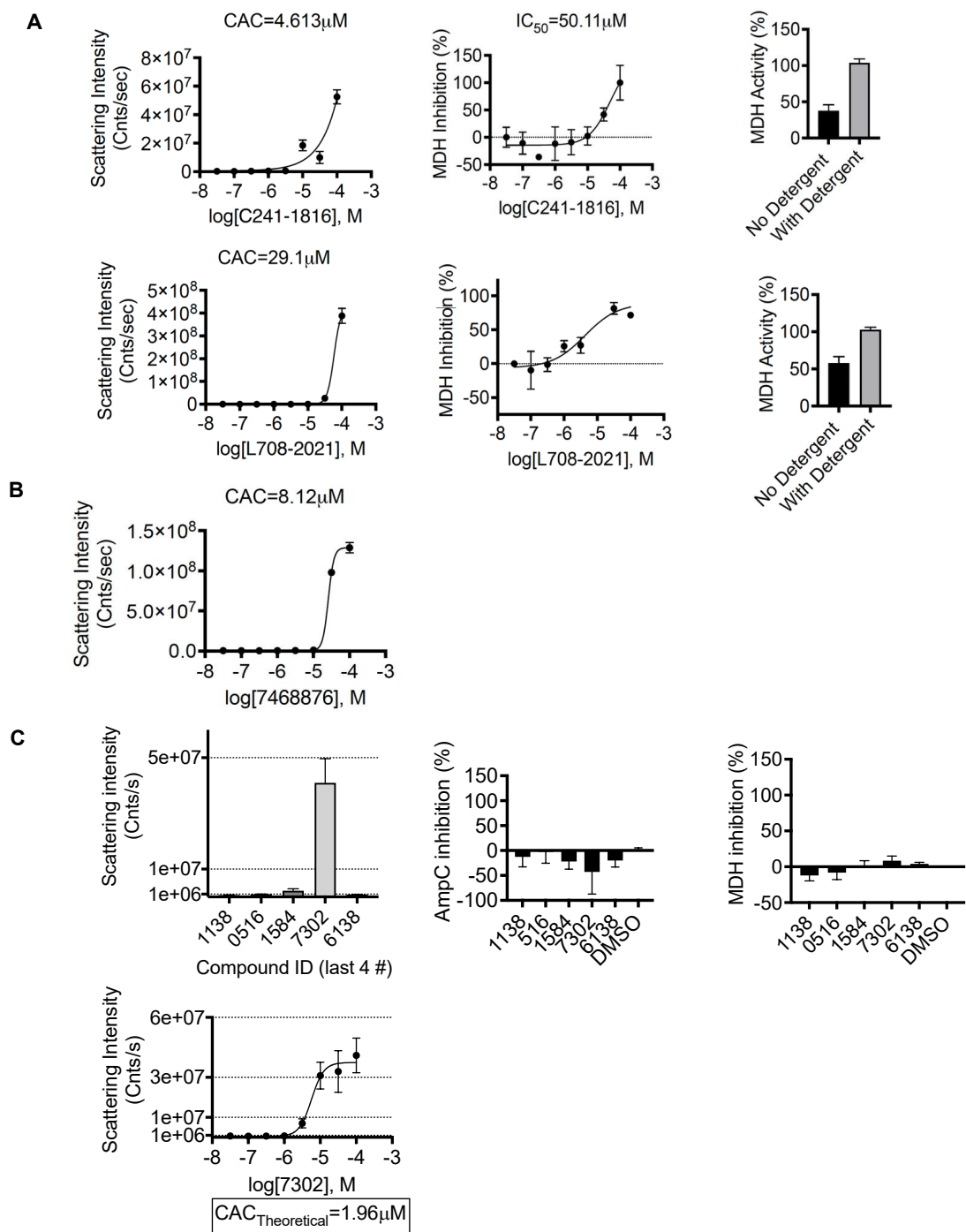


Figure S3. Colloidal aggregation testing on eight in-stock screen hits (at least 30% displacement at 10 μ M). ‘1816 and ‘2021 formed particles and inhibited the counter-enzymes MDH in a detergent dependent manner (**A**). ‘8876 formed particles, but did not inhibit counter-enzymes MDH or AmpC (**B**). ‘1138, ‘0516, ‘1584 and ‘6138 did not form particles, nor inhibited MDH or AmpC. ‘7302 formed particles but did not inhibit MDH or AmpC (**C**).

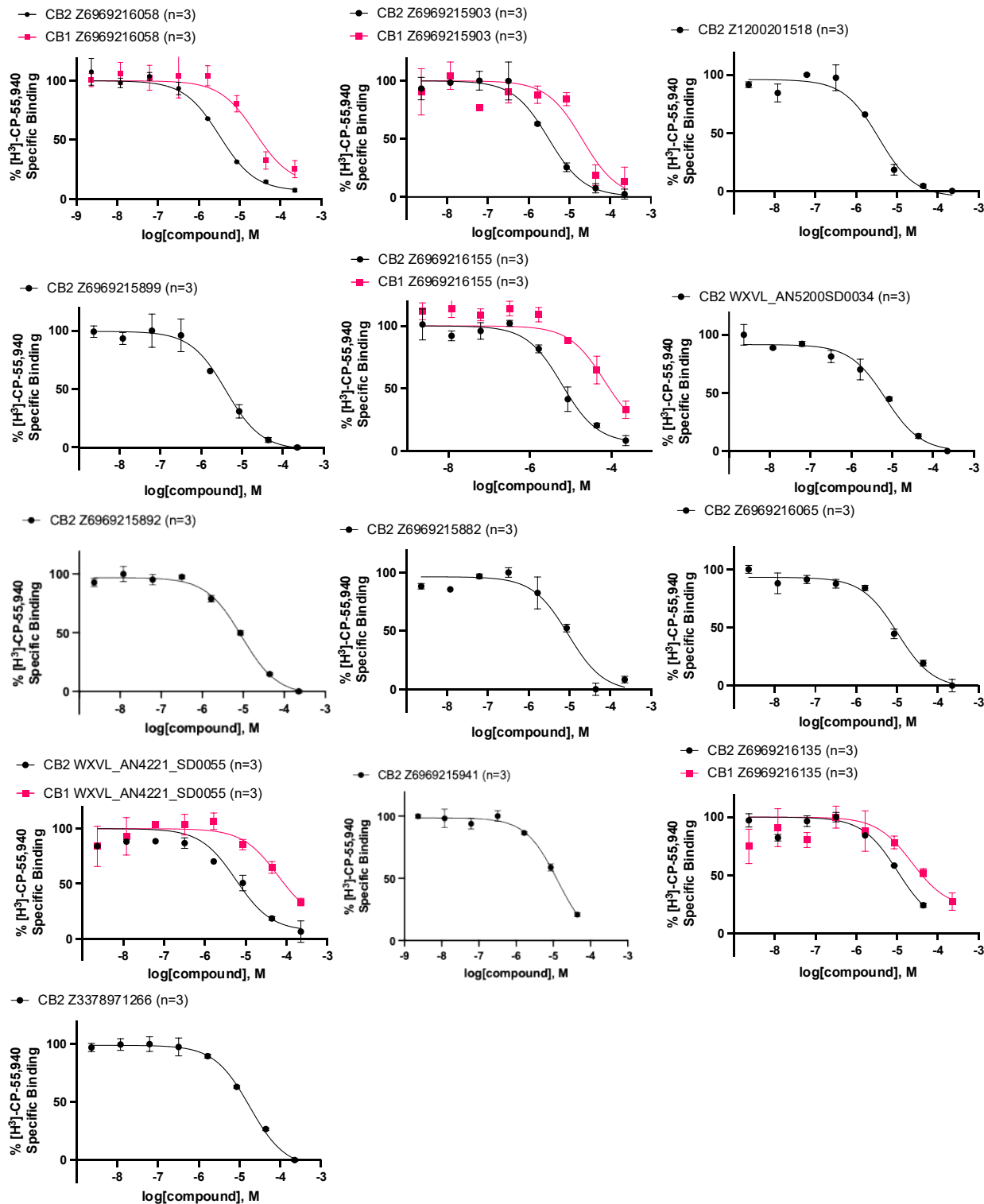


Figure S5. Binding curves of CB2 ligands with K_i 's $<10\ \mu\text{M}$ from a 1.6B library, alongside CB1 curves when tested. K_i values were determined from displacement of $[^3\text{H}]\text{-CP-55,940}$ minus non-specific binding. n = technical repeats, N = independent experiments.

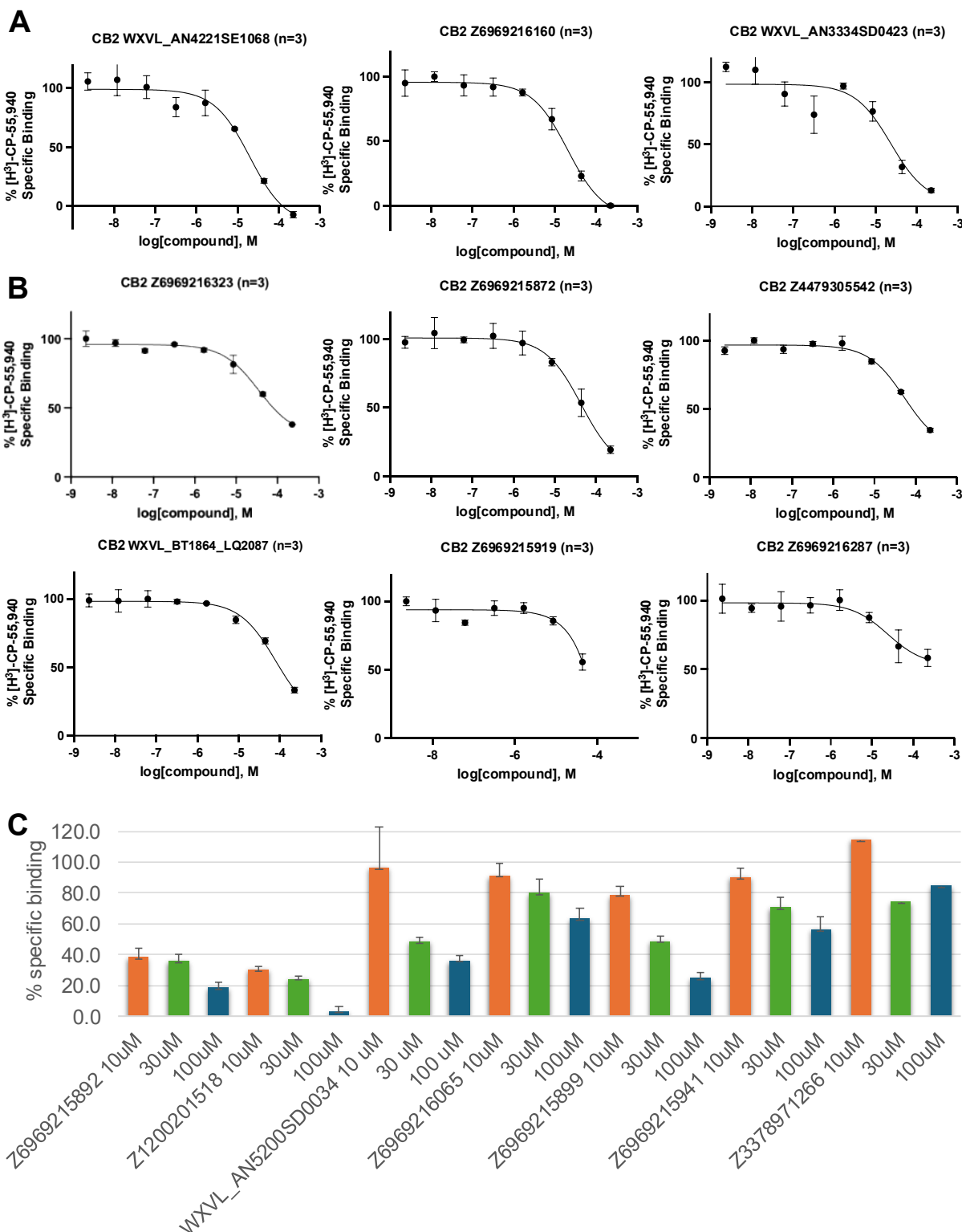


Figure S6. Binding curves of CB2 ligands with $10 \mu\text{M} < K_i$'s $< 15 \mu\text{M}$ (**A**), K_i 's $> 15 \mu\text{M}$ (**B**) and CB1 binding at $10 \mu\text{M}$, $30 \mu\text{M}$ and $100 \mu\text{M}$ of 7 CB2 ligands (**C**) from a 1.6B library. K_i values were determined from displacement of $[^3\text{H}]\text{-CP-55,940}$ minus non-specific binding. n = technical repeats, N = independent experiments.

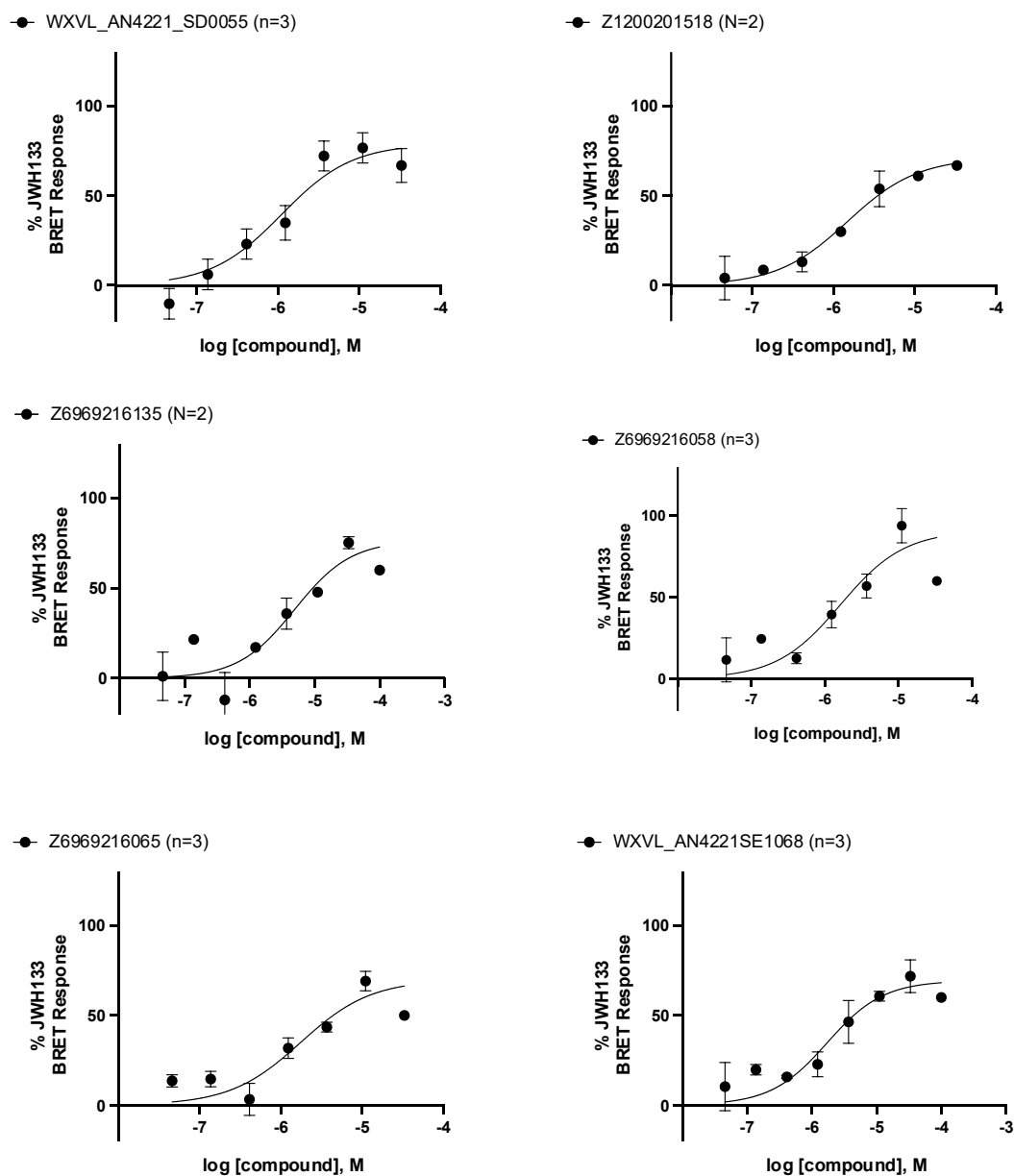


Figure S7. Functional activity of six CB2 agonists from a 1.6B library. Agonism was determined from BRET signals monitoring G_i activation normalized to JWH133 signals. n = technical repeats, N = independent experiments.

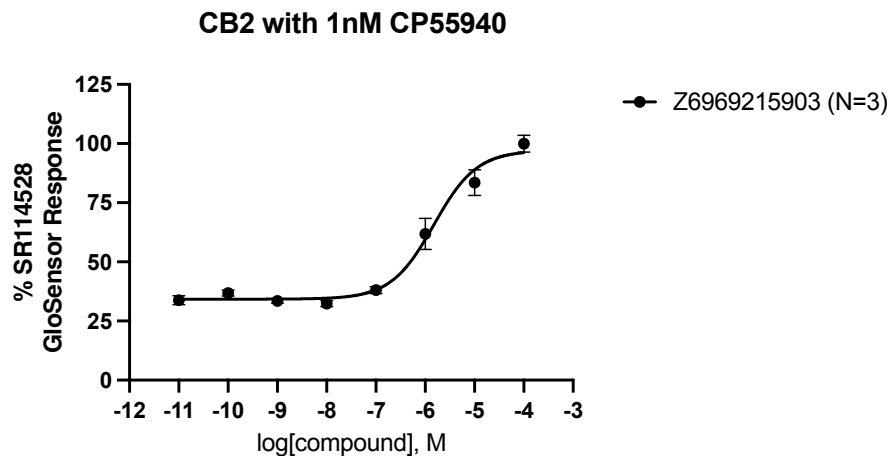


Figure S8. Functional activity of the CB2 inverse agonist from a 1.6B library. Inverse agonism was determined by monitoring cAMP accumulation with GloSensor in the presence of Forskolin and CP-55,940 normalized to SR114528. n = technical repeats, N = independent experiments.

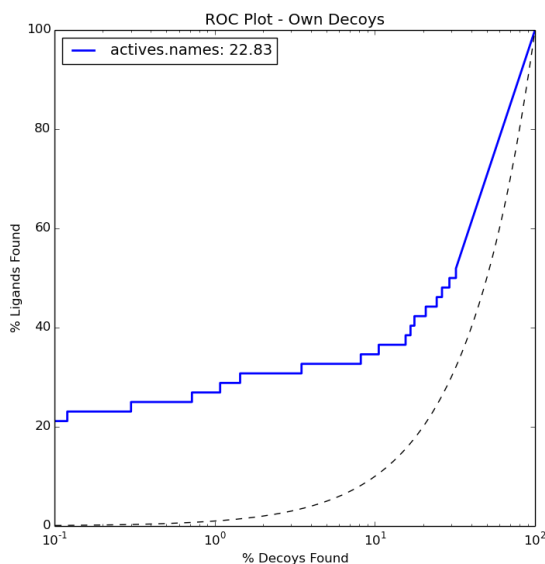


Figure S9. Enrichment (retrieved actives versus decoys) with the optimized CB2 inverse agonist bound structure (5ZTY). Actives comprised 34 CB2 ligands from the IUPHAR database. Decoys were property-matched but topologically distinct from ligands. Decoys were obtained from the DUDE-Z database.

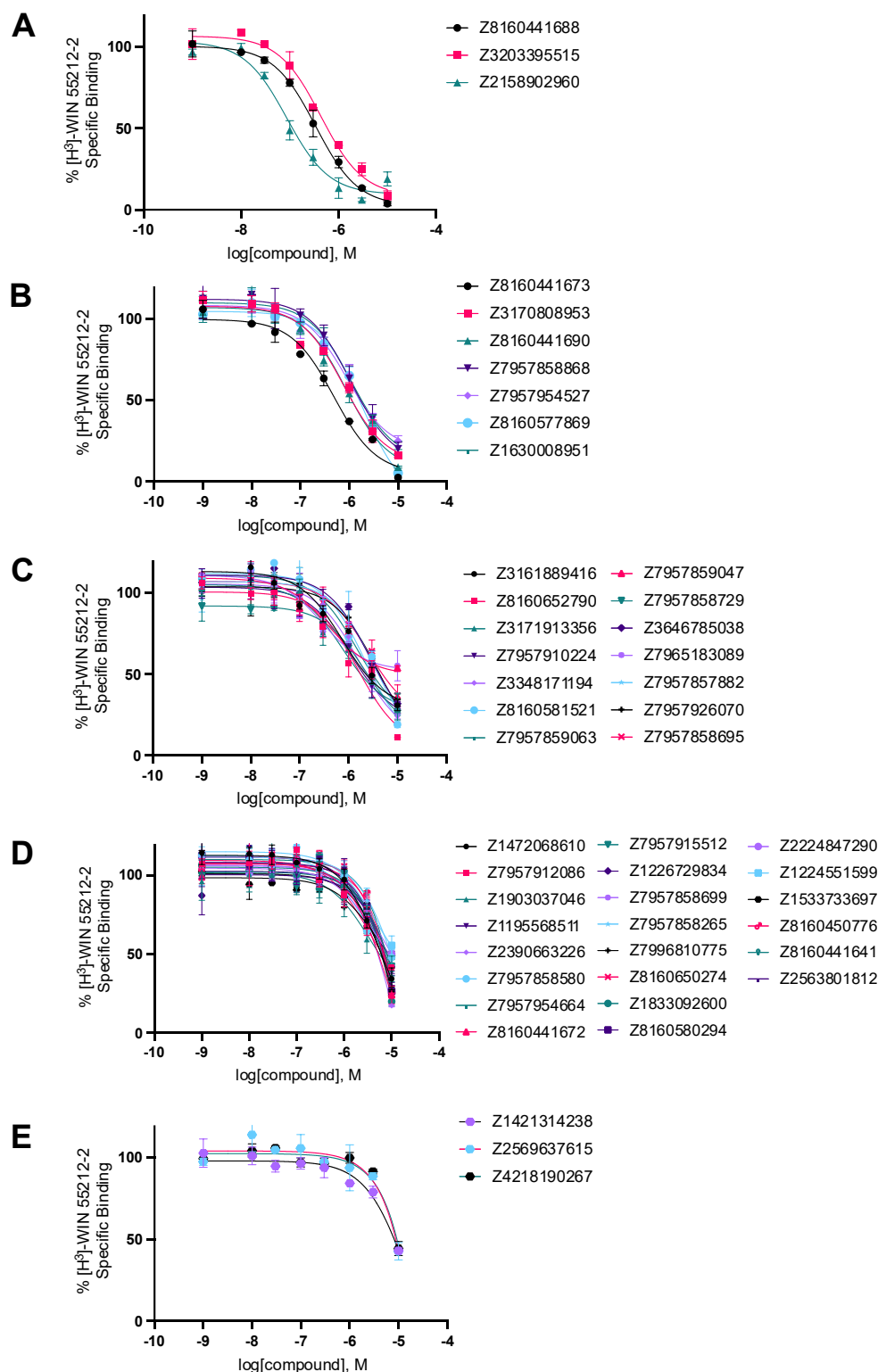


Figure S10. CB2 K_i curves 30 nM - 300 nM (A), 300 nM - 1 μ M (B), 1 μ M - 3 μ M (C), 3 μ M - 10 μ M (D), and 10 μ M - 15 μ M (E) of molecules from the 2.6B screen that showed >30% displacement. All points are from technical duplicates or $n=2$. K_i values were determined from displacement of [3 H]- WIN 55212-2 minus non-specific binding.

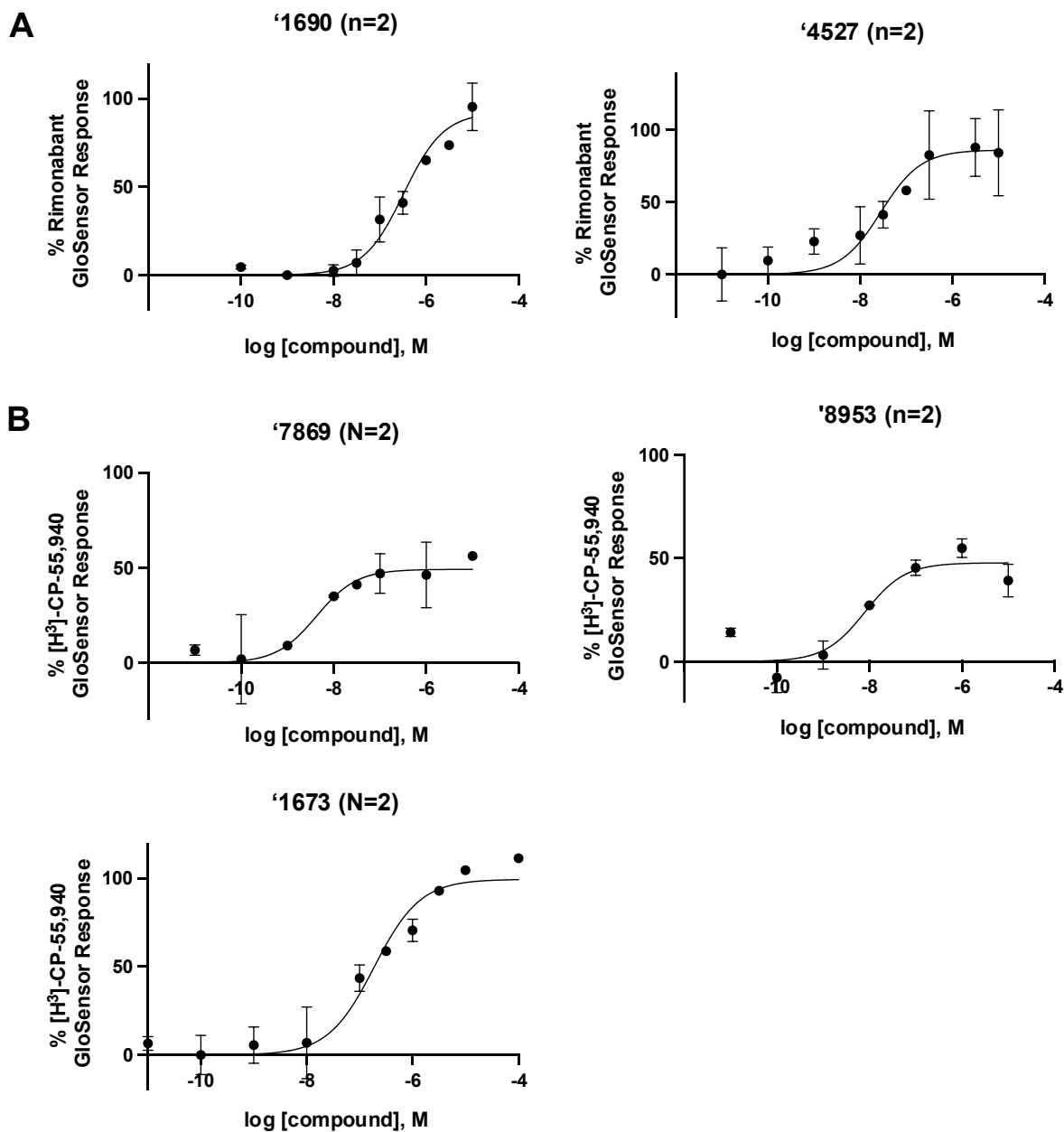


Figure S11. GloSensor curves of 2 inverse agonists (**A**) and 3 agonists (**B**) from the 2.6B screen. Inverse agonism was determined by monitoring cAMP accumulation with GloSensor in the presence of Forskolin and CP-55,940 normalized to Rimonabant. Agonism was determined by monitoring cAMP accumulation with GloSensor in the presence of Forskolin normalized to CP-55,940. n = technical repeats, N = independent experiments.

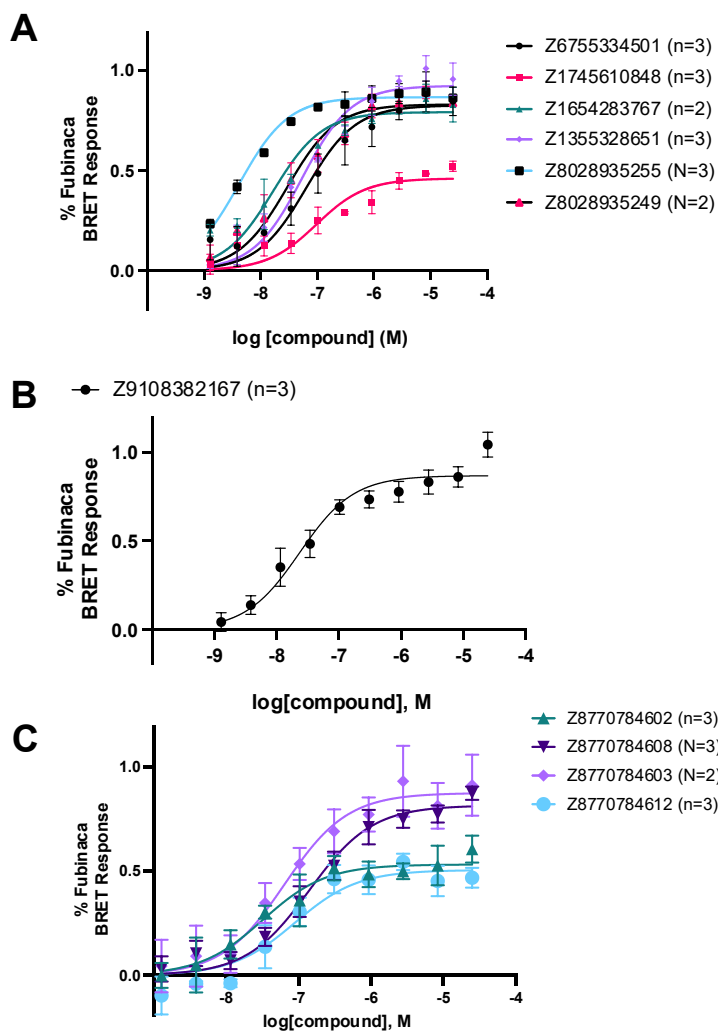


Figure S12. Activity of representative analogs for 3 compounds, ‘6138 from the 7M screen (**A**), ‘1068 from the 1.6B screen (**B**) and ‘7302 from the 7M screen (**C**). Agonism was determined from BRET signals monitoring G_i activation normalized to Fubinaca signals. n = technical repeats, N = independent experiments.

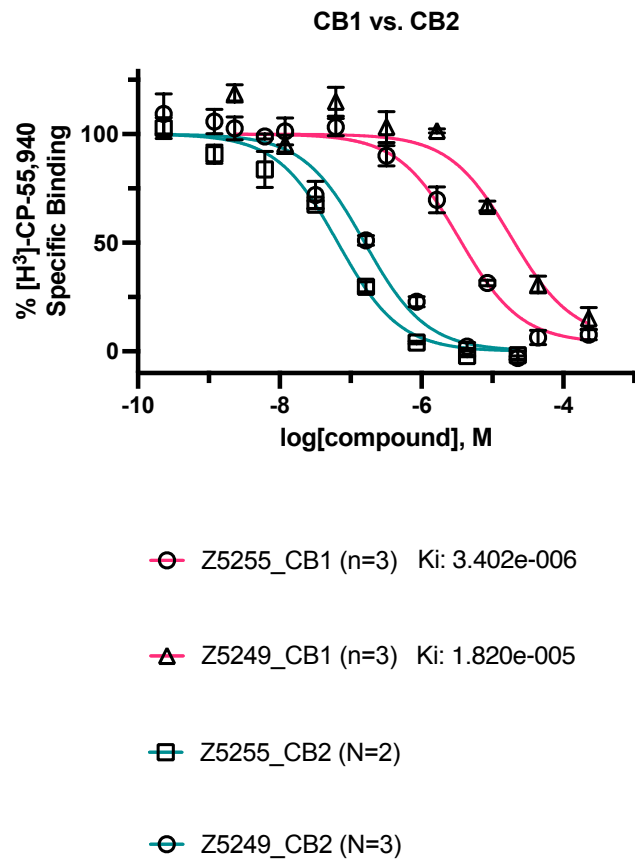


Figure S13. Analogs of ‘6138 from the 7M library screen, ‘5249 has 115-fold selectivity, while ‘5255 has 51-fold selectivity over CB1. K_i values were determined from displacement of [^3H]-CP-55,940 minus non-specific binding. n = technical repeats, N = independent experiments.

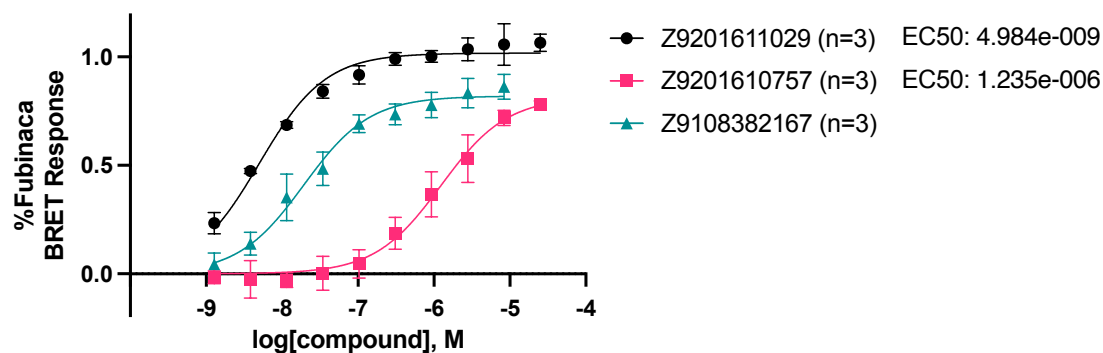


Figure S14. Functional activity of stereochemically purified ‘2167 cis isomers. Agonism was determined from BRET signals monitoring G_i activation normalized to Fubinaca signals. Purification was performed at Enamine. n = technical repeats, N = independent experiments.

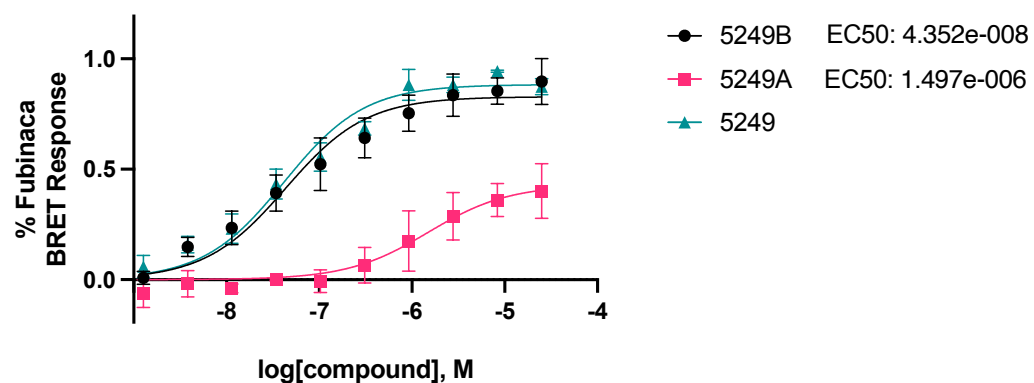


Figure S15. Purified '5249 showed the better isomer being in the same activity range as the racemic mixture. Agonism was determined from BRET signals monitoring G_i activation normalized to Fubinaca signals. Purification was performed at Northeastern University. Data points are from technical triplicates.

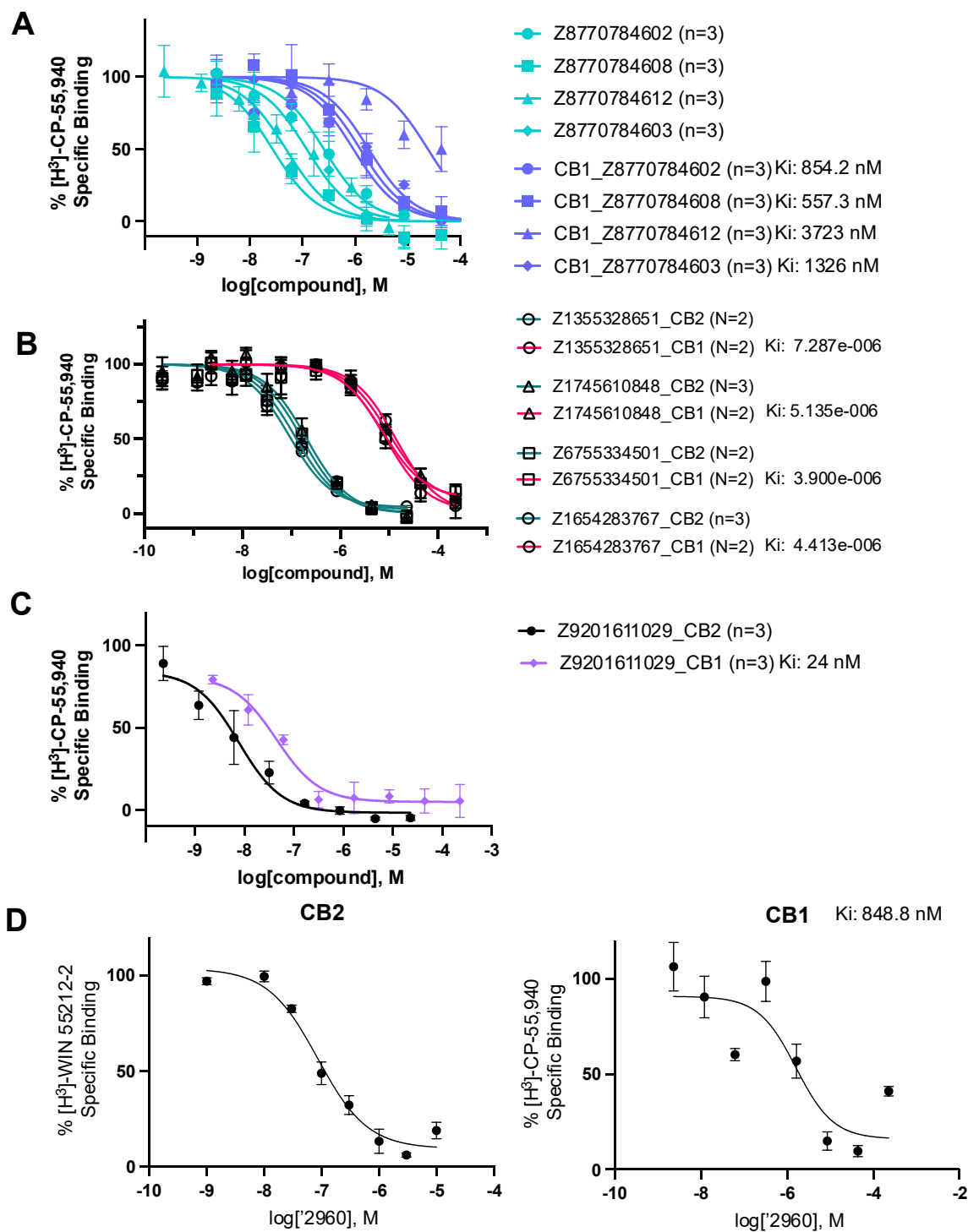


Figure S16. Selectivity over CB1R of discovered compounds <100 nM. K_i values were determined from displacement of [³H]-CP-55,940 or [³H]-WIN 55212-2 minus non-specific binding. n = technical repeats, N = independent experiments.

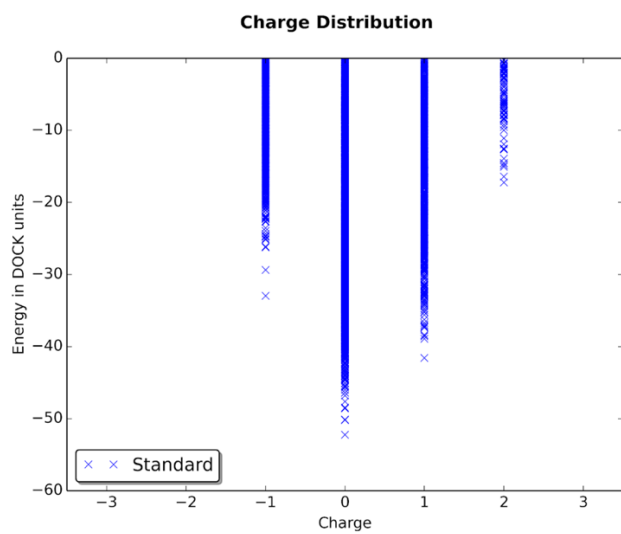


Figure S17. Sanity check of the agonist bound model in retrieving neutral over charged molecules.

Synthetic procedures.

General considerations. All chemicals for the synthesis of the studied compounds were provided by Enamine Ltd. (www.enamine.net). All solvents were treated according to standard methods. ^1H NMR spectra were recorded at 400, 500, or 600 MHz (Varian or Bruker spectrometers). ^1H chemical shifts are calibrated using residual nondeuterated solvent DMSO, $\delta = 2.50$ ppm. Coupling constants are given in Hz. LC/MS analysis was performed utilizing an Agilent 1200 Series LC/MSD system with DAD/ELSD (column Zorbax SB-C18 1.8 μm 4.6x15 mm; solvent A (water, 0.1% formic acid) and solvent B (acetonitrile, 0.1% formic acid); gradient 0% – 100% solvent B, run time, 1.8 min; flow rate, 3 mL/min) and Agilent LC/MSD SL (G6130A) or SL (G6140A) mass spectrometer (APCI mode). All the LC/MS data were obtained using positive/negative mode switching.

Method 1. The synthesis was performed according to a previously published procedure ([dx.doi.org/10.1021/acscombsci.6b00103](https://doi.org/10.1021/acscombsci.6b00103)).

Method 2. A carboxylic acid (100 mg) was dissolved in 0.5 mL of 10% Hydroxybenzotriazole (HOBt) in DMF, followed by the addition of an amine (1 mol equiv to the carboxylic acid) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (1.2 mol equiv to the carboxylic acid). The resulting mixture was shaken for 24 h at room temperature. Then, CHCl_3 (2 mL) was added, and the organic phase was washed with water, dried over sodium sulfate, and evaporated under reduced pressure. The crude was dissolved in 0.5 mL of DMSO and further purified by preparative HPLC.

Method 3. A carboxylic acid (100 mg) was dissolved in 0.5 mL of DMF, followed by the addition of an alcohol (1 mol equiv to the carboxylic acid) and 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC) (1.2 mol equiv to the carboxylic acid) and 4-*N,N*-dimethylaminopyridine (DMAP) (0.05 mol equiv to the carboxylic acid). The resulting mixture was shaken for 24 h at room temperature. Then, CHCl_3 (2 mL) was added, and the organic phase was washed with water, dried over sodium sulfate, and evaporated under reduced pressure. The crude was dissolved in 0.5 mL of DMSO and further purified by preparative HPLC.

Method 4. The synthesis was performed according to the previously published procedure ([dx.doi.org/10.1016/j.tetlet.2010.06.139](https://doi.org/10.1016/j.tetlet.2010.06.139)).

Method 5. The synthesis was performed according to the previously published procedure ([dx.doi.org/10.1007/s11030-021-10218-2](https://doi.org/10.1007/s11030-021-10218-2)).

Method 6. The synthesis was performed according to the previously published procedure ([dx.doi.org/10.1021/co500025f](https://doi.org/10.1021/co500025f)).

Method 7. An amine (50 mg) was dissolved in 0.5 mL of glacial acetic acid in a 4 mL vial. Then sodium acetate (1.1 mol equiv to the amine) and a sulfonyl chloride (1 mol equiv to the amine) were added. The vial was sealed and kept in an ultrasonic bath for 24 h. Then, the crude sample was dissolved in 0.5 mL of DMSO and purified by preparative HPLC.

Method 8. The synthesis was performed according to the previously published procedure ([dx.doi.org/10.1055/s-1984-30909](https://doi.org/10.1055/s-1984-30909) or [dx.doi.org/10.1002/jhet.5570240324](https://doi.org/10.1002/jhet.5570240324)).

Method 9. An amine (100 mg), DIPEA (1.2 mol equivalent to the amine), and DMSO (0.5 mL) were placed into a 4 mL capped glass vial and stirred for 30 min. After the addition of an alkyl halide (1.2 mol equiv to the amine), the vial was stirred for 12 h at room temperature. Then the vial was placed into a thermostat (set to 100°C) for 9 h. After cooling down, the mixture was filtered; the solvent and volatile components were evaporated under reduced pressure to give the crude product. The product was further purified by HPLC.

Spectral description of the synthesized compounds.

5-bromo-8-[5-(2-chloro-2-fluoro-1-methylcyclopropyl)-1,2,4-oxadiazol-3-yl]isoquinoline – Z8160577869 (Method 1).

Yield: 20%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₅H₁₁BrClFN₃O: 382.0; found: 382.0.

3-(4-bromo-2-methoxyphenyl)-5-(2-cyclopropoxyphenyl)-1,2,4-oxadiazole – Z2158902960 (Method 1).

Yield: 29%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₁₆BrN₂O₃: 389.0; found: 389.0.

2-(cyclobutylmethyl)-1-[5-(2-methanesulfonylpropan-2-yl)-1,3,4-oxadiazole-2-carbonyl]piperidine – Z3203395515 (Method 2).

Yield: 16%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₂₈N₃O₄S: 370.2; found: 370.4.

1-[2,5-dimethyl-1-(1,3-thiazol-2-yl)-1H-pyrrol-3-yl]-2-[(2R)-2-ethynyl-2-methylpyrrolidin-1-yl]ethan-1-one trifluoroacetate – Z8160441688 (Method 9).

Yield: 28%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₂₂N₃O₃S: 328.2; found: 328.0.

(2E)-1-(7-fluoro-6-methoxy-1,2,3,4-tetrahydroquinolin-1-yl)-4-(4-methylphenyl)but-2-ene-1,4-dione – Z8160441641 (Method 2).

Yield: 40%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₁H₂₁FN₂O₃: 354.2; found: 354.0.

methyl 2-[5-bromo-1-(2,2-difluoro-4-methylpentanoyl)-2,3-dihydro-1H-indol-3-yl]acetate – Z7957910224 (Method 2).

Yield: 24%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₂₁BrF₂NO₃: 404.1; found: 404.2.

(2-bromo-2-methylcyclopropyl)methyl 6-(4-fluorophenyl)pyridine-2-carboxylate – Z7957954664 (Method 3).

Yield: 33%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₁₆BrFNO₂: 366.0; found: 366.0.

2-[4-(cyclopropylmethyl)-2-methyl-4H-thieno[3,2-b]pyrrol-5-yl]-5-[(2S)-oxolan-2-yl]-1,3,4-oxadiazole – Z3348171194 (Method 4).

Yield: 29%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₂₀N₃O₂S: 330.1; found: 330.1.

5-chloro-1-(6-fluoro-3,4-dihydro-2H-1-benzopyran-2-carbonyl)-3,3-dimethyl-2,3-dihydro-1H-indole – Z7957915512 (Method 2).

Yield: 58%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₂₀ClFNO₂: 360.1; found: 360.0.

(3-cyanothiophen-2-yl)methyl 1-phenyl-5-(propan-2-yl)-1H-pyrazole-3-carboxylate – Z7957858868 (Method 3).

Yield: 29%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₉H₁₈N₃O₂S: 352.1; found: 352.2.

6-bromo-8-methyl-2-{4H,5H,6H,7H-thieno[3,2-c]pyridine-5-carbonyl}imidazo[1,2-a]pyridine – Z8160441672 (Method 2).

Yield: 24%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₆H₁₅BrN₃OS: 376.0; found: 375.9.

1-{bicyclo[4.2.0]octa-3,7-diene-7-carbonyl}-5-chloro-3,3-dimethyl-2,3-dihydro-1H-indole – Z8160580294 (Method 2).

Yield: 14%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₉H₂₁ClNO: 314.1; found: 314.0.

4-(7-fluoro-4-methyl-1-benzofuran-2-carbonyl)-2-methyl-6-(thiophen-3-yl)morpholine – Z8160650274 (Method 2).

Yield: 62%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₉H₁₉FNO₃S: 360.1; found: 360.0.

{4-methyl-2-oxabicyclo[2.2.1]heptan-1-yl}methyl 3-bromo-5-cyclopropoxybenzoate – Z7957954527 (Method 3).

Yield: 18%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₂₂BrO₄: 381.1; found: 381.0.

N-[5-(cyclopropylmethyl)-1,2-oxazol-3-yl]-5-fluoro-2-(propan-2-yloxy)benzamide – Z8160441690 (Method 2).

Yield: 24%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₂₀FN₂O₃: 319.1; found: 319.2.

(3-fluoropyridin-4-yl)methyl 3-methoxy-5-phenylthiophene-2-carboxylate – Z7957858699 (Method 3).

Yield: 27%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₁₅FNO₃S: 344.1; found: 344.0.

(3,5-dimethyl-1,2-oxazol-4-yl)methyl 1-phenyl-5-(propan-2-yl)-1H-pyrazole-3-carboxylate – Z1472068610 (Method 3).

Yield: 42%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₉H₂₂N₃O₃: 340.2; found: 340.2.

(1-ethyl-1H-imidazol-5-yl)methyl 3-methoxy-5-phenylthiophene-2-carboxylate triflate – Z7957858695 (Method 3).

Yield: 29%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₁₉N₂O₃S: 343.1; found: 343.2.

(2-bromo-2-methylcyclopropyl)methyl 3-phenyl-5H,6H,8H-imidazo[4,3-c][1,4]oxazine-1-carboxylate – Z3170808953 (Method 3).

Yield: 22%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₂₀BrN₂O₃: 391.1; found: 391.0.

(1-methylcyclobutyl)methyl 3-phenyl-5H,6H,8H-imidazo[4,3-c][1,4]oxazine-1-carboxylate – Z3161889416 (Method 3).

Yield: 34%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₉H₂₁N₂O₃: 327.2; found: 327.2.

1-(pyridin-3-yl)ethyl 1-phenyl-1H,4H,5H,6H-cyclopenta[c]pyrazole-3-carboxylate – Z1195568511 (Method 3).

Yield: 25%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₂₀N₃O₂: 334.2; found: 334.2.

2-[4-bromo-2-(propan-2-yloxy)phenyl]-5-(2-methyloxolan-2-yl)-1,3,4-oxadiazole – Z2390663226 (Method 4).

Yield: 28%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₆H₂₀BrN₂O₃: 369.1; found: 369.0.

1-(prop-2-en-1-yl)-3-[5-(thiophen-3-yl)-1,3,4-oxadiazol-2-yl]-1H-indole – Z8160441673 (Method 4).

Yield: 30%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₁₄N₃O₂S: 308.1; found: 308.2.

(1-cyanocyclopentyl)methyl 7-methoxy-2-methyl-2,3-dihydro-1-benzofuran-5-carboxylate – Z1630008951 (Method 3).

Yield: 33%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₂₂NO₄: 316.2; found: 316.2.

(5-methylfuran-3-yl)methyl 5-ethyl-1-(2-fluorophenyl)-1H-1,2,4-triazole-3-carboxylate – Z2224847290 (Method 3).

Yield: 23%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₁₇FN₃O₃: 330.1; found: 330.2.

(3-chlorothiophen-2-yl)methyl 5-ethyl-1-phenyl-1H-1,2,4-triazole-3-carboxylate – Z1903037046 (Method 3).

Yield: 46%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₆H₁₅ClN₃O₂S: 348.1; found: 348.0.

1-(3,3-dimethylcyclopentyl) 3-methyl 4,5,6,7-tetrahydro-2-benzothiophene-1,3-dicarboxylate – Z7965183089 (Method 3).

Yield: 24%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M-H] calculated for C₁₈H₂₅O₄S: 335.1; found: 335.2.

5-(1-tert-butyl-1H-1,2,4-triazol-3-yl)-3-cyclopropyl-1-[(3-methylcyclobutyl)methyl]-1H-1,2,4-triazole – Z8160581521 (Method 5).

Yield: 15%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₂₇N₆: 315.2; found: 315.2.

5-(2-benzyl-1,3-thiazol-5-yl)-3-ethyl-1-[(thiolan-3-yl)methyl]-1H-1,2,4-triazole – Z8160652790 (Method 5).

Yield: 16%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₉H₂₃N₄S₂: 371.1; found: 371.0.

1-(3-fluorophenyl)-5-(propan-2-yl)-3-[2-(propan-2-yl)-1,3-oxazolidine-3-carbonyl]-1H-1,2,4-triazole – Z4218190267 (Method 2).

Yield: 26%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₂₄FN₄O₂: 347.2; found: 347.0.

2-ethyl-6-methyl-4-[[5-(2-methylphenyl)-1,2,4-oxadiazol-3-yl]methyl]morpholine triflate – Z1421314238 (Method 3).

Yield: 15%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₂₄N₃O₂: 302.2; found: 302.0.

8-[(5-{7,7-difluoro-2-oxabicyclo[4.1.0]heptan-1-yl}-1,2,4-oxadiazol-3-yl)methyl]quinoline – Z2569637615 (Method 1).

Yield: 17%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₁₆F₂N₃O₂: 344.1; found: 344.0.

2-[5-(oxan-2-yl)-1,3,4-oxadiazol-2-yl]-1-(2,2,2-trifluoroethyl)-1H-indole – Z2563801812 (Method 4).

Yield: 16%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₁₇F₃N₃O₂: 352.1; found: 352.0.

methyl 5-bromo-1-(3-ethynyl-3-fluoroazetidine-1-carbonyl)-2,3-dihydro-1H-indole-3-carboxylate – Z8160450776 (Method 6).

Yield: 18%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₆H₁₅BrFN₂O₃: 381.0; found: 381.0.

(2-chloro-1,3-thiazol-5-yl)methyl 1-(2-fluorophenyl)-1H,4H,5H,6H-cyclopenta[c]pyrazole-3-carboxylate – Z1533733697 (Method 3).

Yield: 25%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₁₄ClFN₃O₂S: 378.1; found: 377.9.

(cyclohex-3-en-1-yl)methyl 5-ethyl-1-phenyl-1H-1,2,4-triazole-3-carboxylate – Z1224551599 (Method 3).

Yield: 27%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₂₂N₃O₂: 312.2; found: 312.2.

8-chloro-4-(3-cyclopentyl-1,2-oxazole-5-carbonyl)-2-methyl-3,4-dihydro-2H-1,4-benzoxazine – Z1833092600 (Method 2).

Yield: 50%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₂₀ClN₂O₃: 347.1; found: 347.0.

3-[[4-(4-fluorophenyl)sulfanyl]methyl]-5-(3-methyl-1-phenyl-1H-pyrazol-5-yl)-1,2,4-oxadiazole – Z7957858265 (Method 1).

Yield: 14%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₉H₁₆FN₄O₂S: 367.1; found: 367.0.

(1S,2R)-2-[3-(5-bromoquinolin-8-yl)-1,2,4-oxadiazol-5-yl]cyclohexan-1-ol – Z7996810775 (Method 1).

Yield: 18%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₁₇BrN₃O₂: 376.0; found: 375.9.

(2-chloro-4-fluorophenyl)methyl 5-ethyl-1-phenyl-1H-1,2,4-triazole-3-carboxylate – Z1226729834 (Method 3).

Yield: 54%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₁₆ClFN₃O₂: 360.1; found: 360.0.

(1-methylcyclopent-3-en-1-yl)methyl 5-ethyl-1-phenyl-1H-1,2,4-triazole-3-carboxylate – Z7957858580 (Method 3).

Yield: 23%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₂₂N₃O₂: 312.2; found: 312.2.

3-bromo-5-{3-cyclopentyl-5-[(oxan-2-yl)methyl]-1H-1,2,4-triazol-1-yl}pyridine – Z7957912086 (Method 5).

Yield: 21%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₂₃BrN₄O: 393.1; found: 393.2.

(1-methylcyclopent-2-en-1-yl)methyl 5-ethyl-1-phenyl-1H-1,2,4-triazole-3-carboxylate – Z7957926070 (Method 3).

Yield: 19%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₂₂N₃O₂: 312.2; found: 312.1.

3-(2H-1,3-benzodioxol-4-yl)-1-(5-chloro-3,3-dimethyl-2,3-dihydro-1H-indol-1-yl)propan-1-one – Z7957857882 (Method 2).

Yield: 54%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₂₁ClNO₃: 358.1; found: 358.2.

(4,5-dihydro-1,2-oxazol-3-yl)methyl 1-(3-fluorophenyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate – Z3646785038 (Method 3).

Yield: 38%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₁₉FN₃O₃: 344.1; found: 344.2.

(4R)-3,4-dihydro-2H-1-benzothiopyran-4-yl 4-ethyl-2-(1H-pyrrol-1-yl)-1,3-thiazole-5-carboxylate – Z7957859047 (Method 3).

Yield: 22%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₉H₁₉N₂O₂S₂: 371.1; found: 371.2.

2-fluoro-2-methylpropyl 1-(4-fluorophenyl)-4,5,6,7-tetrahydro-1H-indazole-3-carboxylate – Z7957858729 (Method 3).

Yield: 30%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₂₁F₂N₂O₂: 335.2; found: 335.2.

(2-fluoro-6-methoxyphenyl)methyl 1-cyclohexyl-5-methyl-1H-pyrazole-3-carboxylate – Z7957859063 (Method 3).

Yield: 35%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₉H₂₄FN₂O₃: 347.2; found: 347.1.

[(1R,5R)-bicyclo[3.1.0]hexan-1-yl]methyl 3-phenyl-5H,6H,8H-imidazo[4,3-c][1,4]oxazine-1-carboxylate – Z3171913356 (Method 3).

Yield: 34%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₂₃N₂O₃: 339.2; found: 339.2.

[2-methyl-4-(trifluoromethyl)furan-3-yl]methyl 2-methanesulfinylbenzoate – Z3378971266 (Method 3).

Yield: 50%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₅H₁₄F₃O₄S: 347.1; found: 347.0.

3-(3-fluoro-2-methoxybenzoyl)-3-azatricyclo[7.3.1.0^{5,13}]trideca-1(13),9,11-triene – Z6969215892 (Method 2).

Yield: 55%; purity, 95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₂₁FNO₂: 326.2; found: 326.1.

methyl 2-(3-chlorophenyl)-2-(1,2,3,4-tetrahydronaphthalene-1-carbonyloxy)acetate – Z1200201518 (Method 3).

Yield: 20%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₂₀ClO₄: 359.1; found: 359.0.

1-{[5-(1-benzothiophen-4-yl)-1,2,4-oxadiazol-3-yl]methyl}-1H-1,3-benzodiazole – Z6969215941 (Method 1).

Yield: 38%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₁₃N₄OS: 333.1; found: 333.0.

[(2R)-1-[(4-chloro-3-methyl-1-benzothiophen-2-yl)sulfonyl]-2,3-dihydro-1H-indol-2-yl]methanol – Z6969216135 (Method 7).

Yield: 45%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₈H₁₇ClNO₃S₂: 394.0; found: 394.0.

5-(3-chloro-1,2-thiazol-5-yl)-1-(1-methyl-1H-pyrazol-3-yl)-3-[(2-methylphenyl)methyl]-1H-1,2,4-triazole – Z6969216058 (Method 5).

Yield: 10%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₁₆ClN₆S: 371.1; found: 371.1.

1-[1-cyclopropyl-3-(pyridin-2-yl)-1H-1,2,4-triazol-5-yl]-5-methylisoquinoline – Z6969216155 (Method 5).

Yield: 24%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₁₈N₅: 328.2; found: 328.2.

4-cyclopropyl-2-[1-(2-methylprop-2-en-1-yl)-3-[(pyridin-3-yl)methyl]-1H-1,2,4-triazol-5-yl]pyridine – Z6969216065 (Method 5).

Yield: 13%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₂₂N₅: 332.2; found: 332.2.

3-[1-(3-chlorophenyl)-3-[(thiophen-2-yl)methyl]-1H-1,2,4-triazol-5-yl]-4-methyl-1,2,5-oxadiazole – Z6969215903 (Method 5).

Yield: 12%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₆H₁₃ClN₅OS: 358.1; found: 357.9.

3-[2-(8-methyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-5-yl)-2-oxoethyl]-1,3-dihydro-2-benzofuran-1-one – Z1745610848 (Method 2).

Yield: 36%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₂₀NO₃S: 354.1; found: 354.0.

3-[2-(7-chloro-2,3,4,5-tetrahydro-1,5-benzothiazepin-5-yl)-2-oxoethyl]-1,3-dihydro-2-benzofuran-1-one – Z1355328651 (Method 2).

Yield: 52%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₉H₁₇ClNO₃S: 374.1; found: 374.2.

3-[2-(7-chloro-2-methyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-5-yl)-2-oxoethyl]-1,3-dihydro-2-benzofuran-1-one – Z6755334501 (Method 2).

Yield: 38%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₁₉ClNO₃S: 388.1; found: 388.0.

3-[2-(7-chloro-3-methyl-2,3,4,5-tetrahydro-1,5-benzothiazepin-5-yl)-2-oxoethyl]-1,3-dihydro-2-benzofuran-1-one – Z1654283767 (Method 2).

Yield: 44%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₁₉ClNO₃S: 388.1; found: 388.0.

3-{2-oxo-2-[7-(trifluoromethyl)-2,3,4,5-tetrahydro-1,5-benzothiazepin-5-yl]ethyl}-1,3-dihydro-2-benzofuran-1-one – Z8028935255 (Method 2).

Yield: 45%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₁₇F₃NO₃S: 408.1; found: 408.0.

3-{2-oxo-2-[7-(trifluoromethyl)-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl]ethyl}-1,3-dihydro-2-benzofuran-1-one – Z8028935249 (Method 2).

Yield: 75%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₁₇F₃NO₄: 392.1; found: 392.0.

3-[2-oxo-2-(7-phenyl-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl)ethyl]-1,3-dihydro-2-benzofuran-1-one – Z8930854171 (Method 2).

Yield: 41%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₅H₂₂NO₄: 400.2; found: 400.2.

3-{2-[7-(5-fluorothiophen-2-yl)-2,3,4,5-tetrahydro-1,5-benzoxazepin-5-yl]-2-oxoethyl}-1,3-dihydro-2-benzofuran-1-one – Z8930854180 (Method 2).

Yield: 32%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₃H₁₉FO₄S: 424.1; found: 424.2.

6-benzyl-3-(2-methoxyphenyl)-[1,2,4]triazolo[3,4-a]phthalazine – Z8144700717 (Method 8).

Yield: 66%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₃H₁₉N₄O: 367.2; found: 367.2.

6-benzyl-3-(2-chloro-6-methoxyphenyl)-[1,2,4]triazolo[3,4-a]phthalazine – Z8770784602 (Method 8).

Yield: 43%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₃H₁₈ClN₄O: 401.1; found: 401.2.

6-benzyl-3-(2-fluoro-6-methoxyphenyl)-[1,2,4]triazolo[3,4-a]phthalazine – Z8770784612 (Method 8).

Yield: 11%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₃H₁₈FN₄O: 385.1; found: 385.4.

6-benzyl-3-(3-chloro-2-methoxyphenyl)-[1,2,4]triazolo[3,4-a]phthalazine – Z8770784603 (Method 8).

Yield: 52%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₃H₁₈ClN₄O: 401.1; found: 401.0.

6-benzyl-3-(4-chloro-2-methoxyphenyl)-[1,2,4]triazolo[3,4-a]phthalazine – Z8770784608 (Method 8).

Yield: 45%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₃H₁₈ClN₄O: 401.1; found: 401.0.

methyl (1S,3aS,6aR)-2-[4-ethyl-3-(morpholine-4-sulfonyl)benzoyl]-octahydrocyclopenta[c]pyrrole-1-carboxylate – Z9108382167 (Method 2).

Yield: 52%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₂H₃₁N₂O₆S: 451.2; found: 451.2.

(1R)-1-[3-(5-{3-bromopyrazolo[1,5-a]pyridin-4-yl}-1,2,4-oxadiazol-3-yl)phenyl]ethan-1-ol – Z6969215882 (Method 1).

Yield: 29%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₇H₁₄BrN₄O₂: 387.0; found: 387.0.

3-(methylsulfonyl)phenyl 3-benzyl-1-methyl-1H-pyrazole-4-carboxylate – Z6969215899 (Method 2).

Yield: 36%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₁₉H₁₉N₂O₂S: 339.1; found: 339.0.

3-[(2,3-dihydro-1-benzofuran-3-yl)methyl]-5-(4-methylfuran-2-yl)-1-(2-methylprop-2-en-1-yl)-1H-1,2,4-triazole – Z6969216160 (Method 5).

Yield: 28%; purity, >95% (assessed by LC/MS).

LC/MS (APSI) m/z [M+H] calculated for C₂₀H₂₂N₃O₂: 336.2; found: 336.2.