Supplementary Information for

Virtual library docking for cannabinoid-1 receptor agonists with reduced side effects

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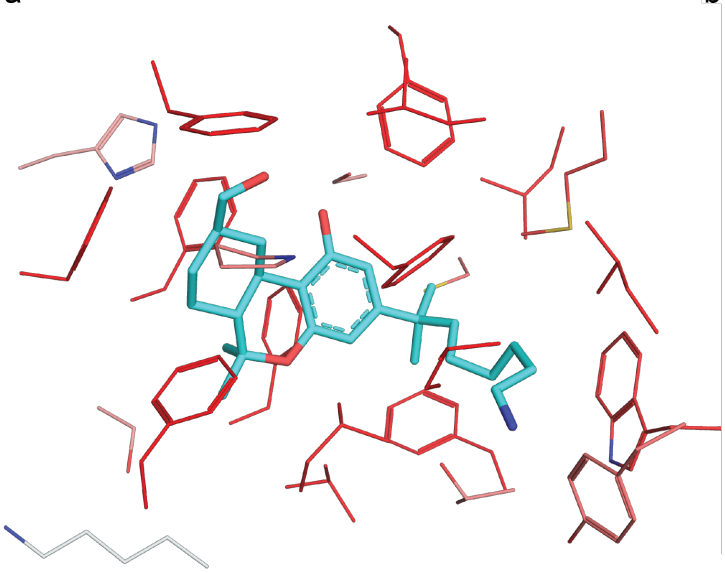
This file includes:

Supplementary Figures

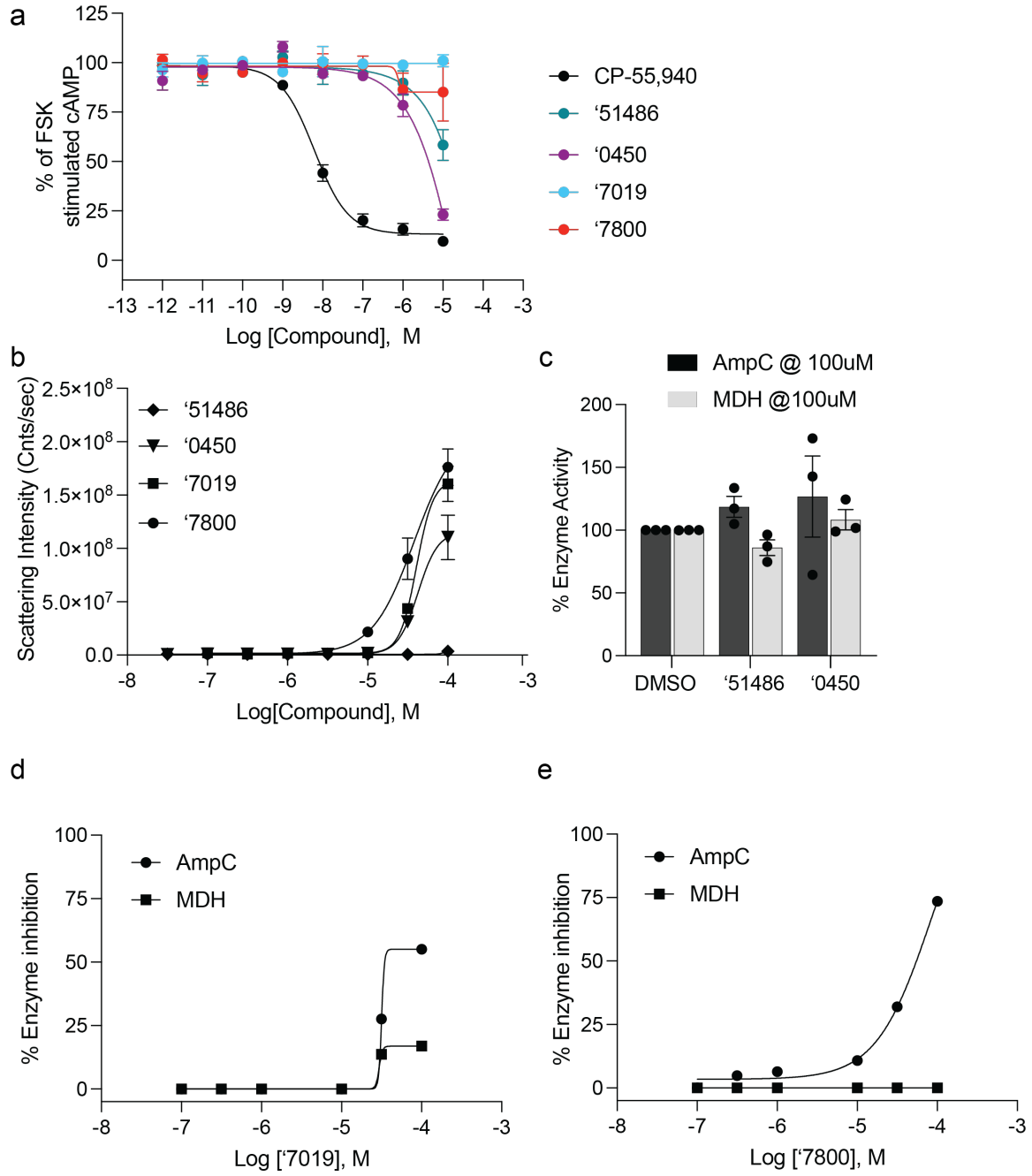
a



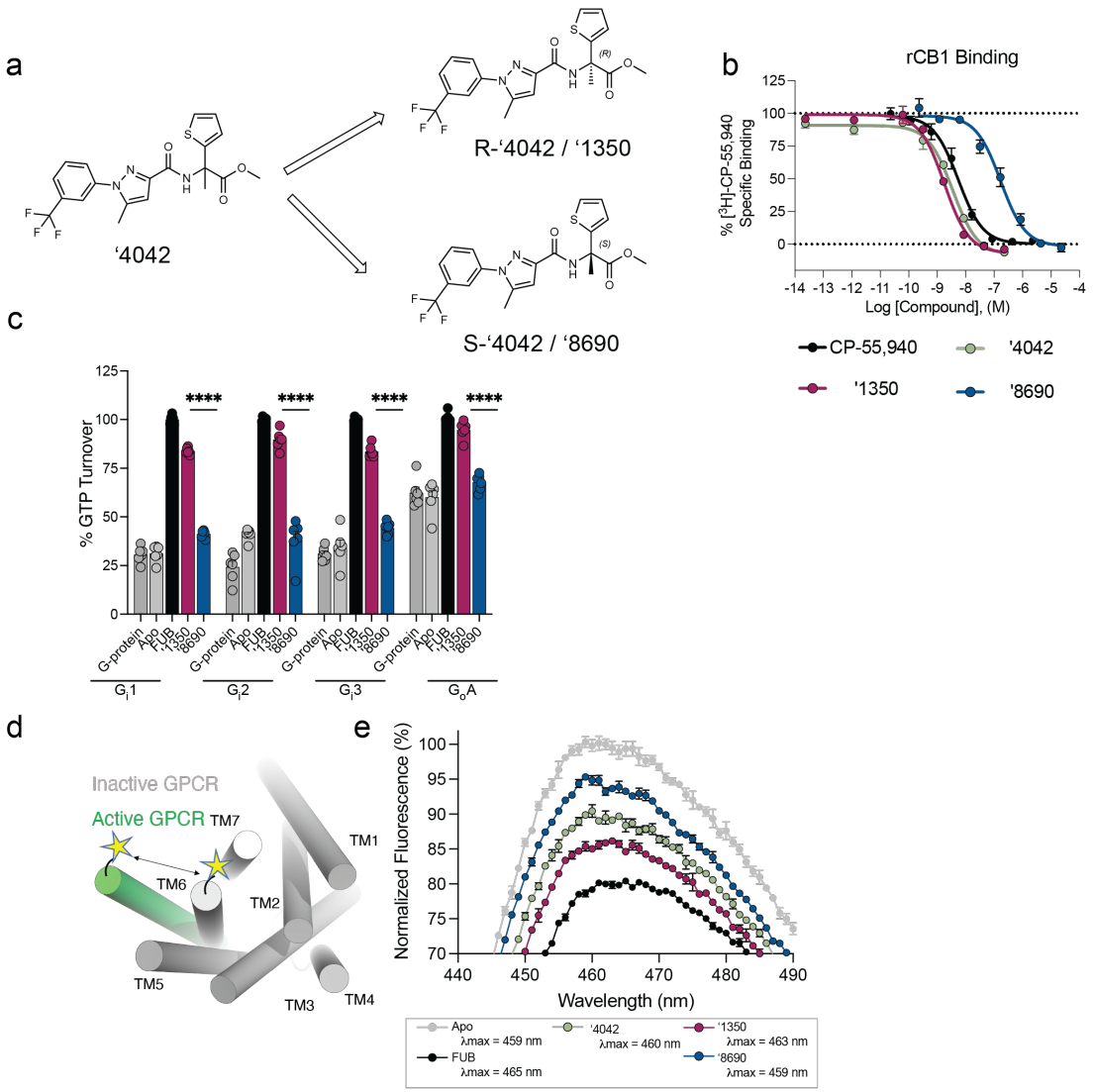
b

Residue Number	Residue Type	Polarity	Kyte & Doolittle Scale [-4.5-4.5]	Eisenberg Scale [-2.5-1.38]
108	PHE	NP	2.80	1.19
170	PHE	NP	2.80	1.19
173	SER	P	-0.80	-0.18
174	PHE	NP	2.80	1.19
177	PHE	NP	2.80	1.19
178	HIS	C/P	-3.20	-0.4
189	PHE	NP	2.80	1.19
192	LYS	C	-3.90	-1.5
193	LEU	NP	3.80	1.06
196	VAL	NP	4.20	1.08
197	THR	P	-0.70	-0.05
200	PHE	NP	2.80	1.19
267	ILE	NP	4.50	1.38
268	PHE	NP	2.80	1.19
269	PRO	NP	-1.60	0.12
271	ILE	NP	4.50	1.38
275	TYR	P	-1.30	0.26
276	LEU	NP	3.80	1.06
279	TRP	NP	-0.90	0.81
359	LEU	NP	3.80	1.06
363	MET	NP	1.90	0.64
379	PHE	NP	2.80	1.19
383	SER	P	-0.80	-0.18
386	CYS	NP	2.50	0.29
		Average	1.59	0.68

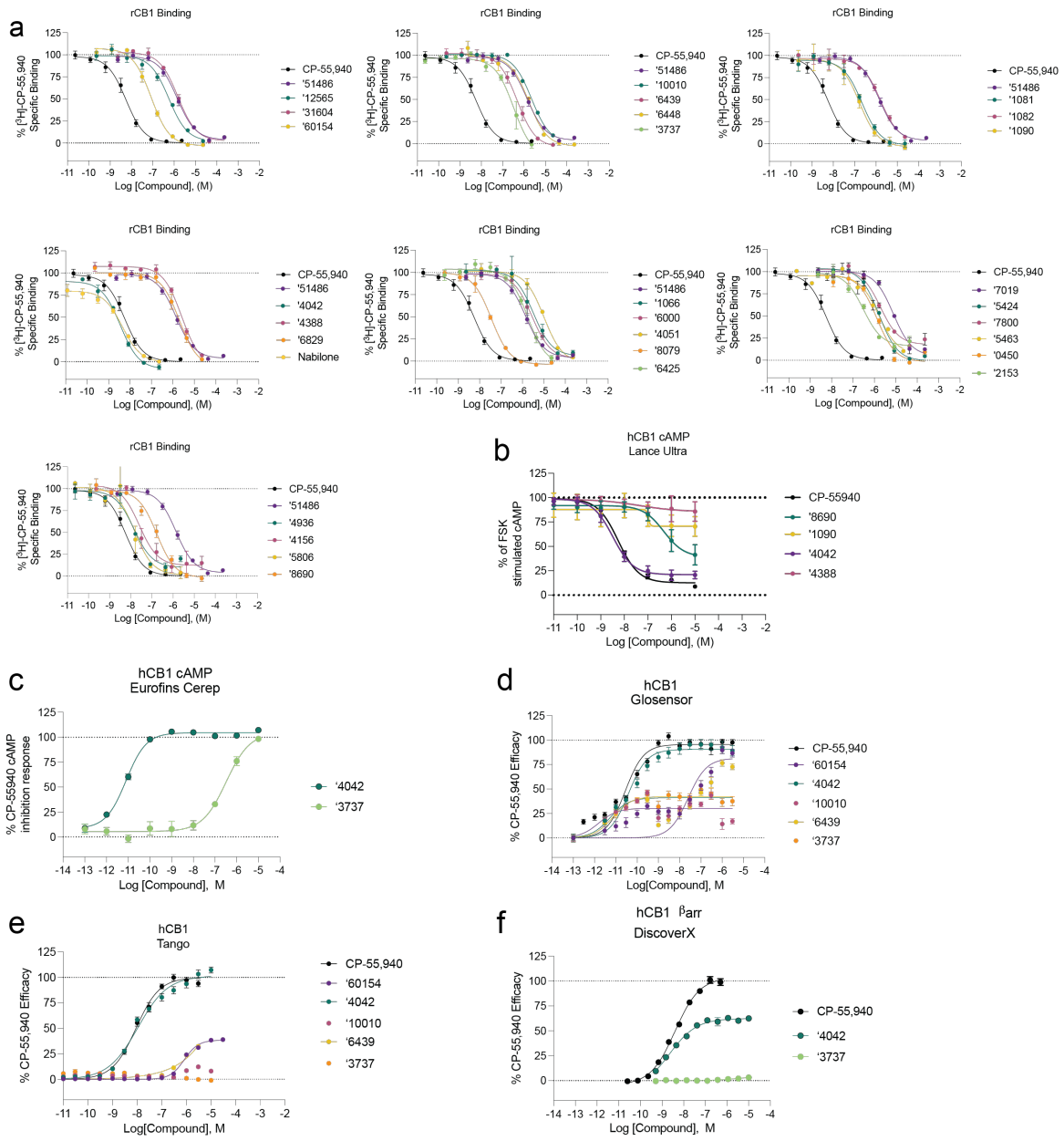
Supplementary Figure 1. Hydrophobicity calculations for the hCB1R orthosteric pocket based on PDB: 5XR8. Residues within 5 Å of AM841 are considered. a. Depiction of the hCB1 orthosteric pocket, colored by the Eisenberg Scale, where darker red colors indicate more hydrophobic residues, and lighter red or gray colors indicate less hydrophobic residues. b. A table of the residues within 5 Å of AM841, with their polarity class (nonpolar (NP), polar (P), or charged (C)), and two hydrophobicity scores indicated.



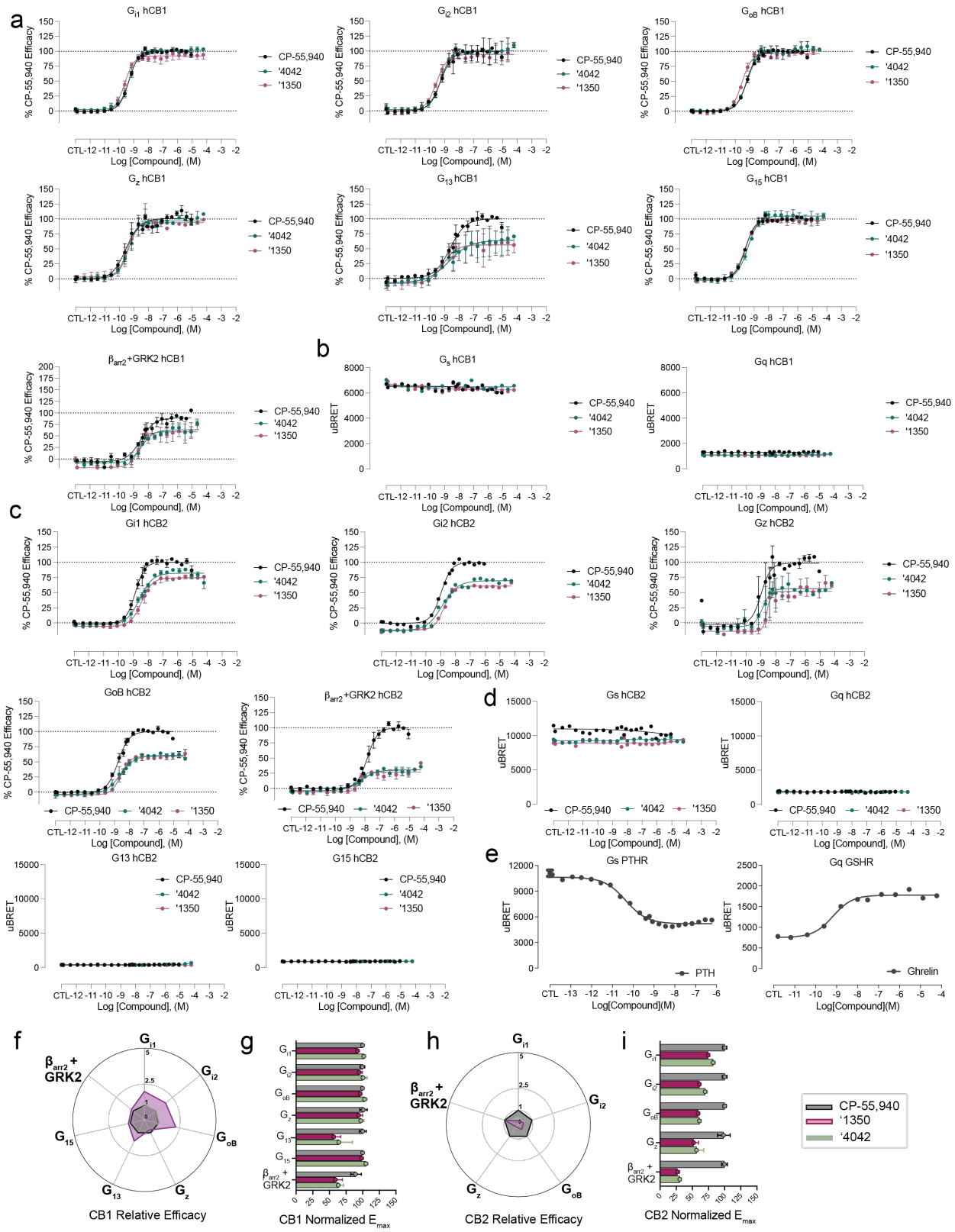
Supplementary Figure 2. Functional measurements for a subset of screening hits. a. Functional cAMP inhibition at hCB1R by the four most potent docking hits. b. Scattering intensity in dynamic light scattering experiments of colloidal aggregation. c. Inhibition of the off-target enzymes MDH and AmpC Beta-lactamase at 100 µM. d. and e. Single-point inhibition of the off-target enzymes MDH and AmpC Beta-lactamase by ‘7019 (D.) and ’7800 (E.). All data represent mean ± SEM of three independent experiments in triplicate except b. which represents one independent experiment in triplicate.



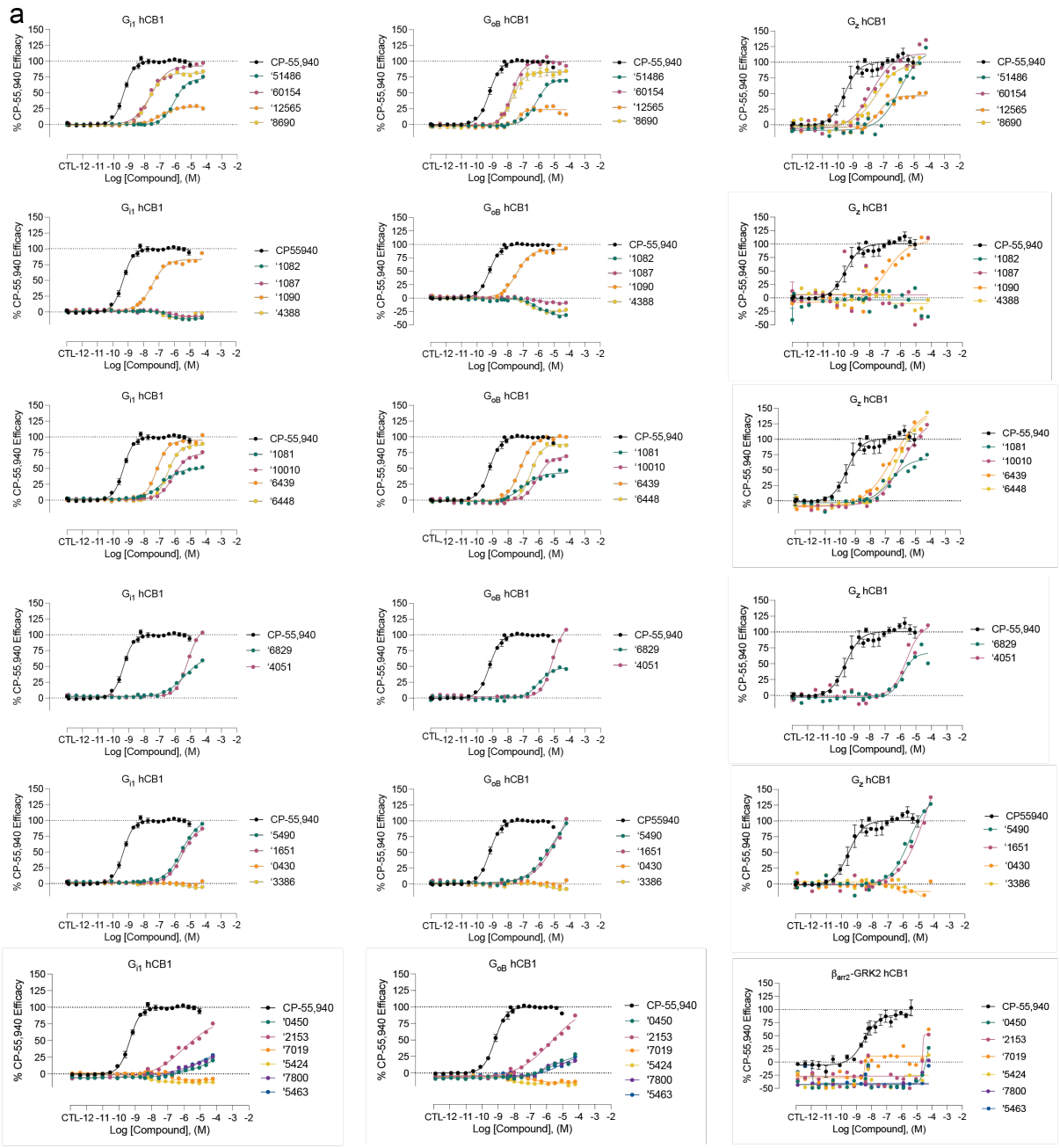
Supplementary Figure 3. Additional pharmacological characterization of '4042 and its enantiomers. a. Chiral column purification led to the separation of two independent enantiomers, '1350 and '8690. '1350 was determined to be *R*-'4042 from the Cryo-EM structure. b. Radioligand competition binding data for '4042, '1350, and '8690 versus CP-55,940. c. GTPase Glo assay characterizing GTP turnover of G proteins $G_{i1\text{-}3/o}$. d. Schematic of the environmentally sensitive fluorophore Monobromobimane (Bimane) which when site-specifically labeled (e.g. on TM6) acts as a conformational reporter. e. Compared to the apo (grey), the spectrum of full agonist MDMB-fubinaca (Fub)-bound CB1 (black) shows a decrease in intensity and a blue-shift in λ_{max} (Apo 459 nm to Fub 465 nm). The bimane spectrum of '8690 (λ_{max} 459 nm, blue) is more similar to apo and the spectrum of '1350 (λ_{max} 463 nm, magenta) is closer to that of Fub. The spectrum of the racemate, '4042 (green) is between '1350 (*R*-'4042) and '8690 (*S*-'4042). All data represent mean ± SEM of three independent experiments in triplicate.



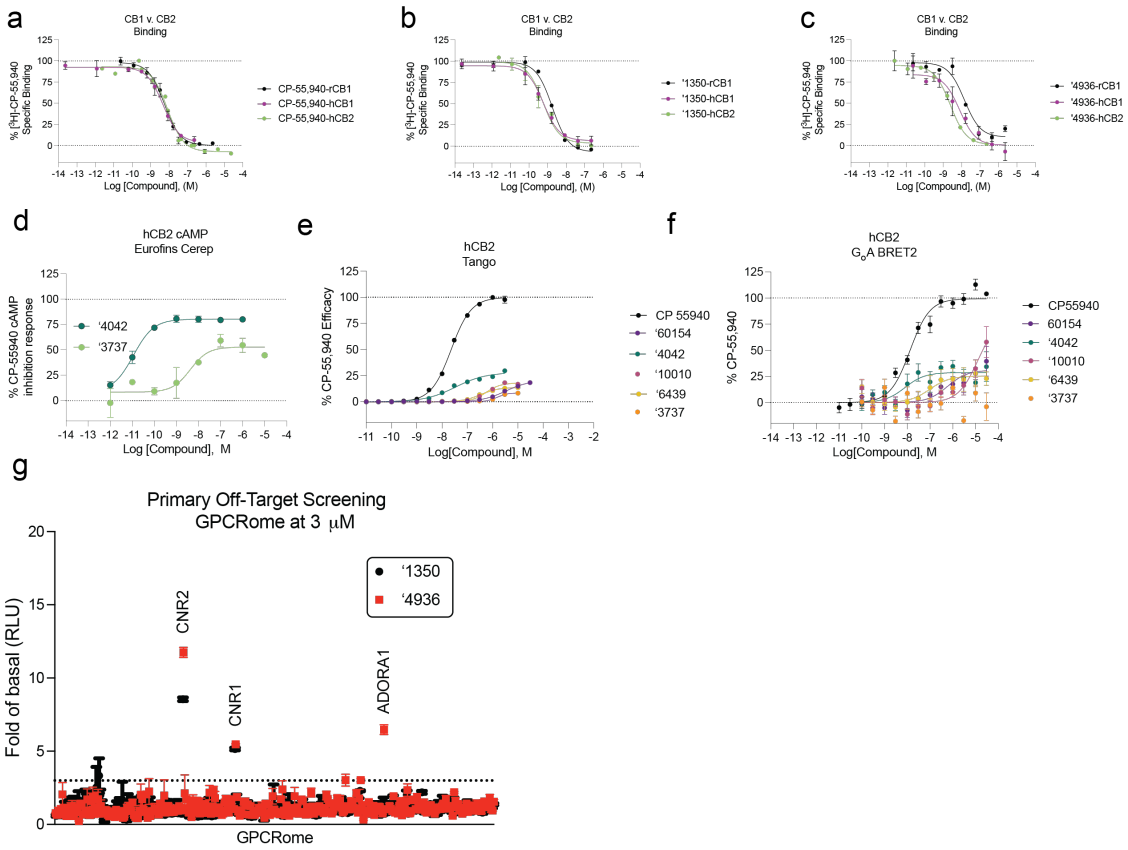
Supplementary Figure 4. CB1 binding and functional data for analogs. a. Competition binding data for primary hits and a subset of their analogs at rCB1. b.-d. Functional cAMP inhibition for a subset of analogs at hCB1 across three separate assays. e.-f. Functional ß$_{arr}$ recruitment for a subset of analogs. All data represent mean ± SEM of at least 2 independent experiments in triplicate except c. and f. which represent one independent experiment in triplicate. Best fit values can be found in Supplementary Table 2.


a
Gi1 hCB1
Gi2 hCB1
GoB hCB1
Gz hCB1
G13 hCB1
G15 hCB1
βarr2+GRK2 hCB1
% CP-55,940 Efficacy
Log [Compound], (M)
CP-55,940
'4042
'1350
b
Gs hCB1
Gq hCB1
uBRET
c
Gi1 hCB2
Gi2 hCB2
Gz hCB2
GoB hCB2
βarr2+GRK2 hCB2
G13 hCB2
G15 hCB2
d
Gs hCB2
Gq hCB2
e
Gs PTHR
PTH
Gq GSHR
Ghrelin
Log[Compound](M)
f
CB1 Relative Efficacy
g
CB1 Normalized Emax
h
CB2 Relative Efficacy
i
CB2 Normalized Emax

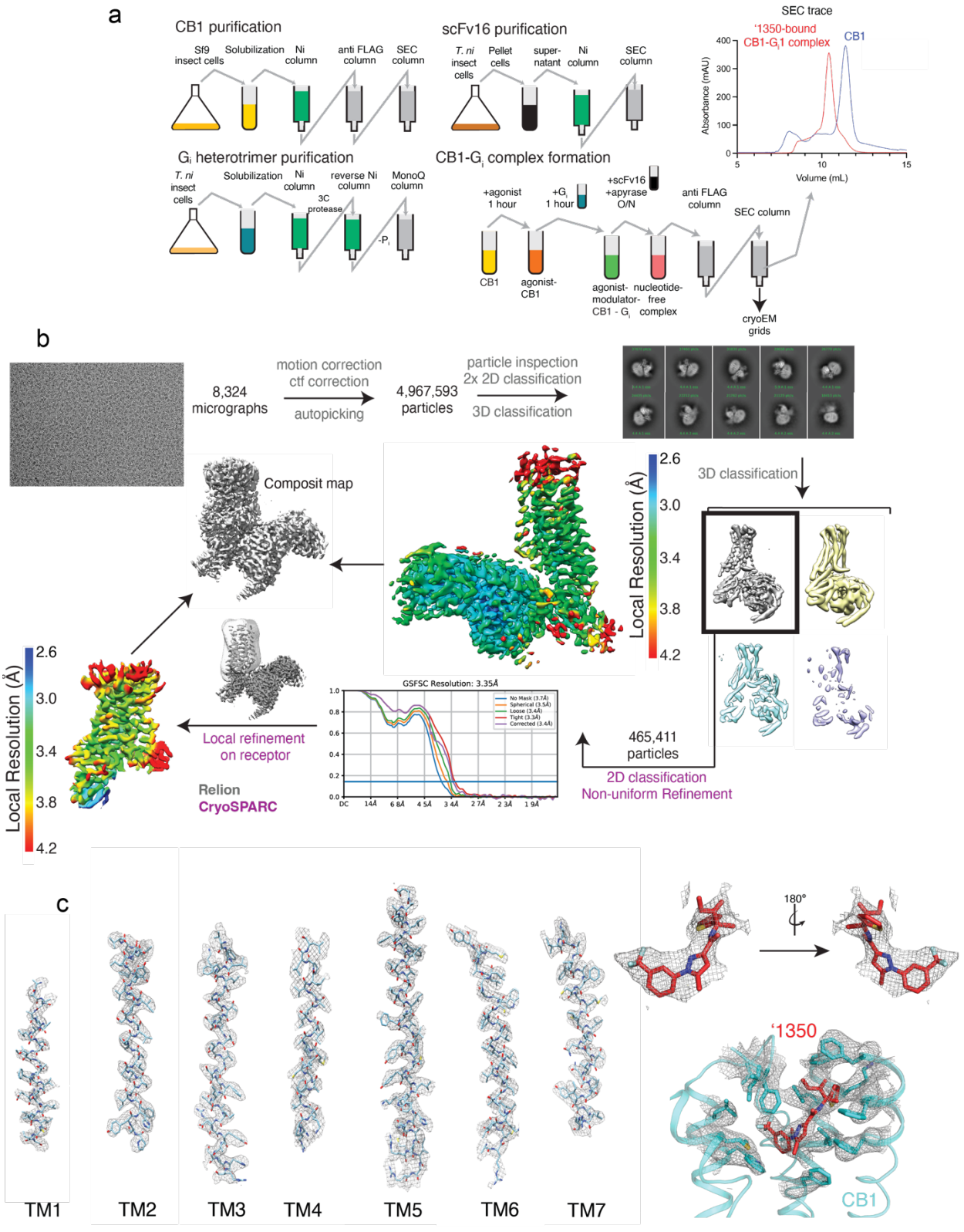
Supplementary Figure 5. hCB1/2 functional data for select analogs in the bioSens-All® platform. If CP-55,940 had no response, data were left unnormalized and raw uBRET was plotted and the values were not included in follow-up analyses. If CP-55,940 had a response, data was normalized to 100% of CP-55,940 activity. The normalized versus unnormalized data is separated by subpanel. a. Normalized activity for select analogs versus a panel of sensors in hCB1-expressing cells. b. Raw BRET activity for select ana- logs versus G_s and G_q in hCB1-expressing cells. c. Normalized activity for select analogs versus a panel of sensors in hCB2-expressing cells. d. Raw BRET activity for select analogs versus G_s, G_q, G_{12}, and G_{15} in hCB2-expressing cells. e. Positive control raw BRET activity for PTHR (activated by PTH) and GSHR (activated by Ghrelin), known Gs and Gq recruiting GPCRs, respectively. f. Relative efficacy ($10^{\Delta\log(Emax/EC50)}$) of '1350 and '4042 compared to CP-55,940 at hCB1. g. Normalized E_{max} from the experiments in f. h. Relative efficacy of '1350 and '4042 compared to CP-55940 at hCB2. i. Normalized E_{max} from the experiments in h. Best fit and relative efficacy values can be found in Supplementary Tables 4, 5, & 7. Data in a.–e. represent mean ± SEM.



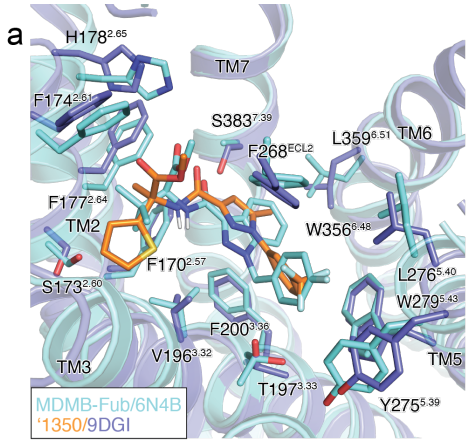
Supplementary Figure 6. hCB1 functional data for select analogs in the bioSens-All® platform. a. Normalized activity for select analogs versus a panel of sensors in hCB1-expressing cells. Best fit values can be found in Supplementary Table 3. Data represent mean ± SEM from two to three experiments.



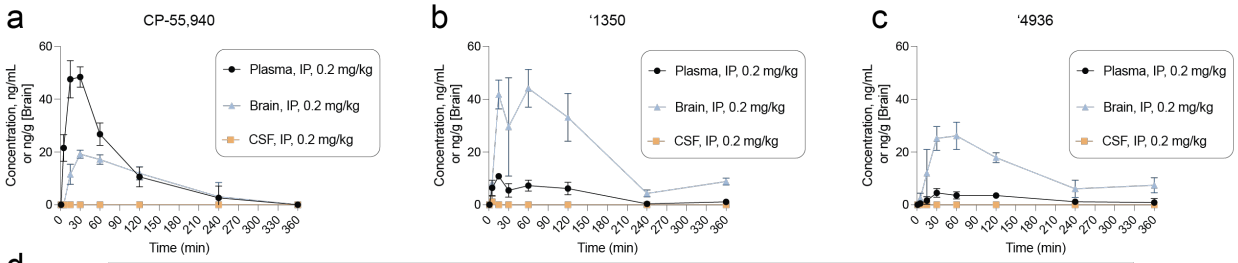
Supplementary Figure 7. Off-target CB2R binding and GPCRome functional data for select analogs. Comparison of (a.) CP-55,940 (rCB1 and hCB2: *n* = 3 experiments in triplicate; hCB1: *n* = 2 experiment in triplicate), (b.) '1350 (rCB1: *n* = 3 experiments in triplicate; hCB1/2: *n* = 2 experiments in triplicate), and (c.) '4936 (all *n* = 2 experiments in triplicate), at CB1 and CB2. d.-f. Functional cAMP inhibition for a subset of analogs at hCB2 across three separate assays. e. TANGO screens against a panel of 320 GPCRs for '1350 and '4936. For d.-g., all data represent mean ± SEM of three independent experiments in triplicate except d. which represents one independent experiment in triplicate and g. which is one independent experiment in quadruplicate. Best fit values can be found in Supplementary Table 6.


a
CB1 purification
Sf9 insect cells
Solubilization
Ni column
anti FLAG column
SEC column
scFv16 purification
T. ni insect cells
Pellet cells
super-natant
Ni column
SEC column
SEC trace
'1350-bound CB1-Gi1 complex
CB1
Absorbance (mAU)
Volume (mL)
Gi heterotrimer purification
T. ni insect cells
Solubilization
Ni column
3C protease
reverse Ni column
MonoQ column
-Pi
CB1-Gi complex formation
+agonist 1 hour
+Gi 1 hour
+scFv16 +apyrase O/N
anti FLAG column
SEC column
CB1
agonist-CB1
agonist-modulator-CB1 - Gi
nucleotide-free complex
cryoEM grids
b
8,324 micrographs
motion correction
ctf correction
autopicking
4,967,593 particles
particle inspection
2x 2D classification
3D classification
Composit map
Local Resolution (Å)
2.6
3.0
3.4
3.8
4.2
3D classification
Local refinement on receptor
GSFSC Resolution: 3.35Å
No Mask (3.7Å)
Spherical (3.5Å)
Loose (3.4Å)
Tight (3.3Å)
Corrected (3.4Å)
465,411 particles
2D classification
Non-uniform Refinement
Relion
CryoSPARC
c
180°
'1350
CB1
TM1
TM2
TM3
TM4
TM5
TM6
TM7

Supplementary Figure 8. Cryo-EM sample preparation and data processing. a. Purification of hCB1, scFv16, the G_i heterotrimer, and complex formation protocols. b. Cryo-EM data processing flow chart of CB1, including particle selection, classifications, and density map reconstruction. c. Density for the transmembranes and around the ligand binding pocket. Details can be found in Supplementary Table 8.

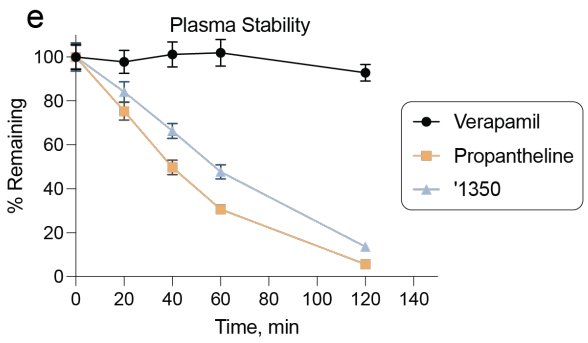


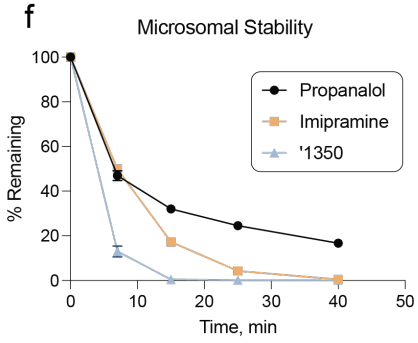
Supplementary Figure 9. Comparison of the '1350-CB1R (PDB: 9DGI) structure to MDMB-Fub-CB1R (PDB: 6N4B). a. '1350 (orange) bound to CB1R (purple compared to MDMB-Fub-CB1R (teal). Similar occupation of the binding pockets by both ligands.

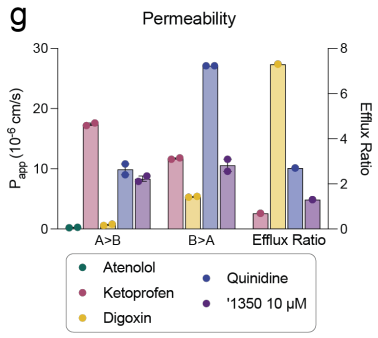


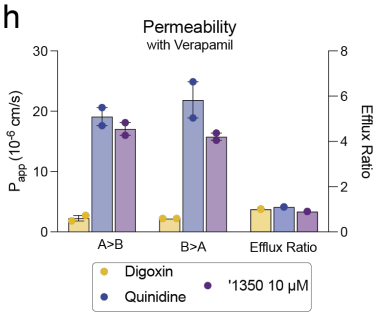
d

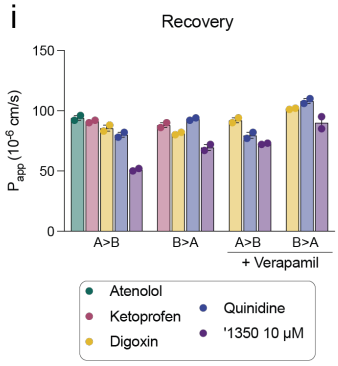
Compound	Compartment	Dose Route	T_{max}, min	C_{max} ng/mL (g)	AUC 0 → tlast ng*min/ml (g)	AUC 0 → inf ng*min/ml (g)	$T_{1/2}$	K_{el}
CP-55,940	Plasma	0.2 mg/kg IP	30	48.4	3360	3990	41.5	0.0167
	Brain		30	19.2	1700	3880	127	0.098
	CSF		ND	BQL	BQL	ND	ND	ND
'1350	Plasma	0.2 mg/kg IP	15	10.8	1440	1510	102	0.0068
	Brain		60	44.1	7720	8180	112	0.0062
	CSF		ND	BQL	BQL	ND	ND	ND
'4936	Plasma	0.2 mg/kg IP	30	4.54	675	865	111	0.006
	Brain		60	26.2	5260	5610	125	0.0055
	CSF		ND	BQL	BQL	ND	ND	ND



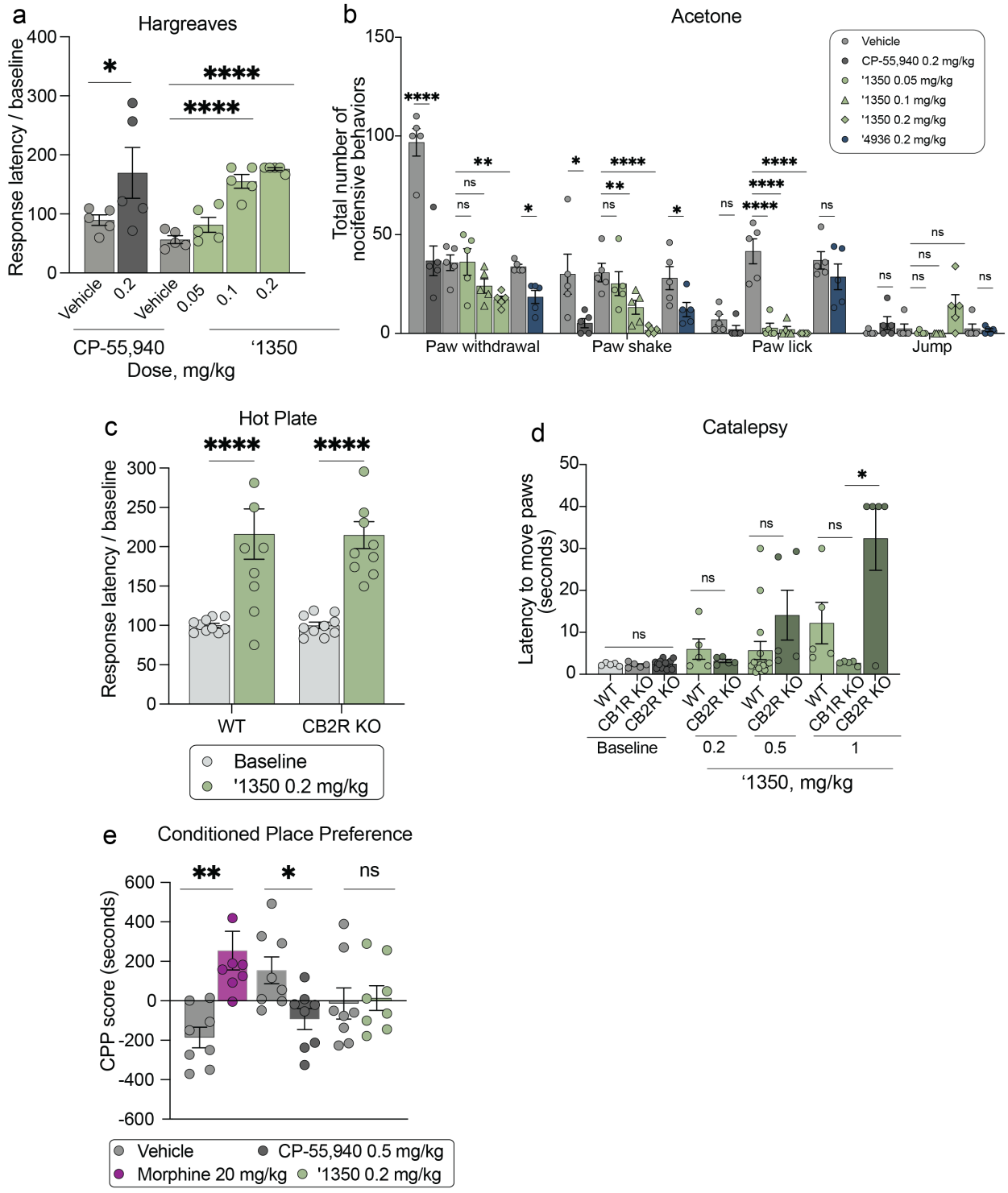








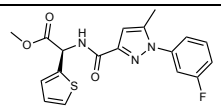
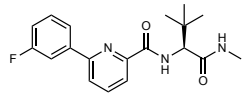
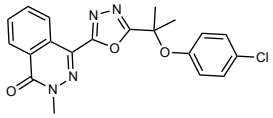
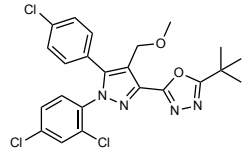
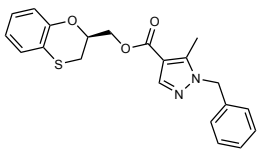
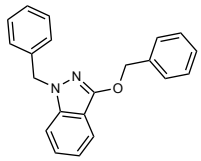
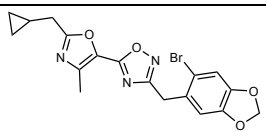
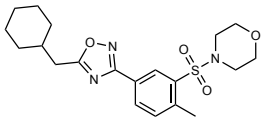
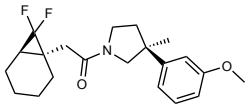
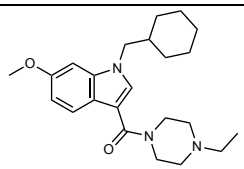
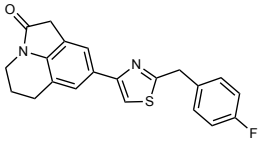
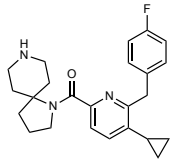
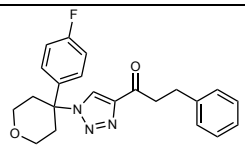
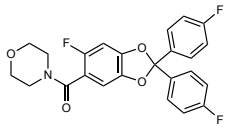
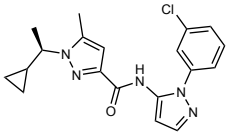
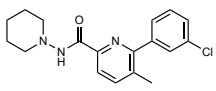
Supplementary Figure 10. Drug Metabolism and pharmacokinetic profiles. Pharmacokinetic profile of CP-55,940 (a.), ‘1350 (b.), ‘4936 (c.) after a single 0.2 mg/kg dose in brain, CSF, and plasma compartments. Data represent mean ± SEM of 3 animals per timepoint. d. Best-fit parameters of the pharmacokinetic data. e. Mouse plasma stability of ‘1350 compared to verapamil (stable) and propantheline (unstable). f. Mouse liver microsome stability of ‘1350 compared to propanalol and imipramine. g. Permeability of ‘1350 and various control molecules to MDRI-MDCKII cells. h. Permeability of ‘1350 and various control molecules to MDRI-MDCKII cells in the presence of the P-gp inhibitor verapamil. i. Recover of various molecules after the permeability assay. All data represent mean ± SEM of three independent animals per timepoint (a.-c.) or two incubations (e.-i).

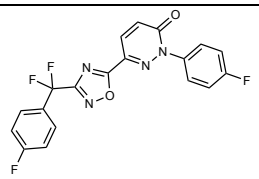
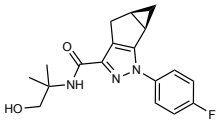

a
Hargreaves
Response latency / baseline
Vehicle
0.2
Vehicle
0.05
0.1
0.2
CP-55,940
'1350
Dose, mg/kg
b
Acetone
Total number of nocifensive behaviors
Vehicle
CP-55,940 0.2 mg/kg
'1350 0.05 mg/kg
'1350 0.1 mg/kg
'1350 0.2 mg/kg
'4936 0.2 mg/kg
Paw withdrawal
Paw shake
Paw lick
Jump
c
Hot Plate
Response latency / baseline
WT
CB2R KO
Baseline
'1350 0.2 mg/kg
d
Catalepsy
Latency to move paws (seconds)
WT
CB1R KO
CB2R KO
Baseline
0.2
0.5
1
'1350, mg/kg
e
Conditioned Place Preference
CPP score (seconds)
Vehicle
CP-55,940 0.5 mg/kg
Morphine 20 mg/kg
'1350 0.2 mg/kg

Supplementary Figure 11. Additional analgesic and side-effect profiles of ‘1350 compared to CP-55.940. a. Hargreaves assay (all n = 5; one-way ANOVA, ‘1350: $F(3, 16) = 37.9$, $P < 0.0001$; two-tailed unpaired t-test, CP-55,940: $t(8) = 1.8$, $P = 0.01$). Asterisks define differences to vehicle after Dunnett’s multiple comparisons post-hoc correction (‘1350) or t-test. b. Acetone test from Fig. 4B broken down by behavior (all n = 5, two-way ANOVAs; ‘1350: behavior x dose interaction: $F(9, 64) = 8.9$, $P < 0.0001$; behavior: $F(3, 64) = 28.5$, $P < 0.0001$; dose: $F(3, 64) = 21.4$, $P < 0.0001$; CP-55,940: behavior x dose interaction: $F(3, 32) = 13.9$, $P < 0.0001$; behavior: $F(3, 32) = 61.02$, $P < 0.0001$; dose: $F(1, 32) = 30.7$, $P < 0.0001$; ‘4936: behavior x dose interaction: $F(3, 32) = 1.59$, $P = 0.21$; behavior: $F(3, 32) = 21.94$, $P < 0.0001$; dose: $F(1, 32) = 12.92$, $P = 0.0011$,Asterisks define differences to vehicle after Dunnett’s (‘1350) or Šídák’s (CP-55,940 and ‘4936) multiple comparisons post-hoc correction; vehicle vs. ‘1350 0.05 mg/kg, withdrawal $P = 0.99$; shake $P = 0.60$; lick $P < 0.0001$; jump $P = 0.97$; 0.1 mg/kg, withdrawal $P = 0.083$; shake $P = 0.005$; lick $P < 0.0001$; jump $P = 0.95$; 0.2 mg/kg, withdrawal $P = 0.0029$; shake $P < 0.0001$; lick $P < 0.0001$; jump $P = 0.09$; vs. CP-55,940, withdrawal $P < 0.0001$; shake $P = 0.01$; lick $P = 0.95$; jump $P = 0.96$; vs. ‘4936, withdrawal $P = 0.04$; shake $P = 0.03$; lick $P = 0.47$; jump $P = 0.99$. c. Wildtype (WT) vs. CB2R knockout (KO) mice (all n = 10; two-way ANOVA; genotype x drug interaction and genotype: $F(1, 36) = 0.002$, $P = 0.96$; drug: $F(1, 36) = 39.8$, $P < 0.0001$; asterisks define differences to baseline after Fisher’s LSD. d. Catalepsy in WT, CB1R, and CB2R KO (all n = 5 except CB2R KO baseline and WT ‘1350 0.5 mg/kg; one-way ANOVAs; baseline: $F(2, 22) = 0.15$, $P = 0.86$; 1 mg/kg: $F(2, 12) = 8.4$, $P = 0.005$, asterisks define differences to vehicle after Dunnett’s multiple comparisons post-hoc correction; two-tailed unpaired t-tests; 0.2 mg/kg: $t(8) = 1.1$, $P = 0.13$; 0.5 mg/kg: $t(18) = 1.7$, $P = 0.17$). e. Conditioned Place Preference (CPP) test (all n = 8; two-tailed unpaired t-tests, morphine: $t(14) = 4.0$, $P = 0.0015$; CP-55,940: $t(14) = 2.9$, $P = 0.01$; ‘1350: $t(14) = 0.28$, $P = 0.78$). For all statistical tests: ns, not significant, *$P < 0.05$, **$P < 0.01$, ***$P < 0.001$, ****$P < 0.0001$. Data represent mean ± SEM; n denotes number of independent animals.

Supplementary Tables

Supplementary Table 1. Binding affinities for hits identified in initial CB1 docking screen.

Compound	Global rank	rCB1 affinity[a] K_i [95% CI] nM pK_i [95% CI]	Tc[b]	Nearest ChEMBL ligand[c]
 ‘51486	117390	731 [552 – 969] 6.14 [6.01 –6.26]	0.30	 CHEMBL4110127
 ‘0450	6582	691 [459 – 1033] 6.16 [5.99 – 6.34]	0.36	 CHEMBL519214
 ‘7800	12210	1007 [615 – 1654] 6.0 [5.78 – 6.21]	0.28	 CHEMBL3116279
 ‘7019	20488	4039 [3027 – 5379] 5.39 [5.27 –5.52]	0.24	 CHEMBL472680
 ‘7218	29322	52.2% [24.79]	0.31	 CHEMBL3347301
 ‘1038	47606	53.6% [2.91]	0.28	 CHEMBL3890211
 ‘7337	24720	57.0% [3.04]	0.29	 CHEMBL259699
 ‘7902	139929	57.1% [0.02]	0.31	 CHEMBL3915046

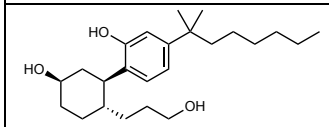
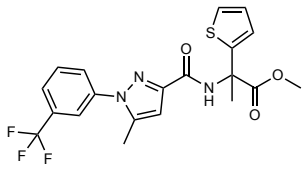
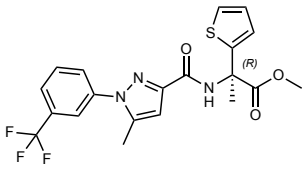
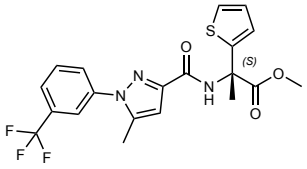
 ‘2443	21964	51.1% [4.87]	0.23	 CHEMBL3354970

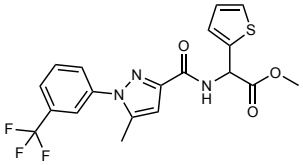
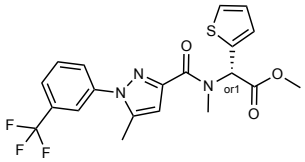
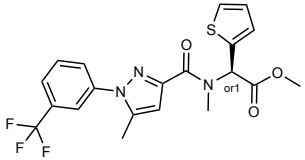
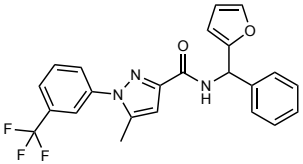
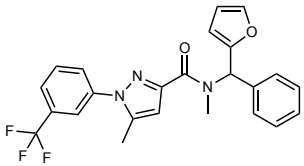
[a]Binding affinity to rCB1 represented as Ki [95% CI] and pKi [95% CI] from three independent experiments in triplicate when measured. Otherwise, % radioligand displacement [S.D] from three replicates in a single-point competition experiment at 10 μM

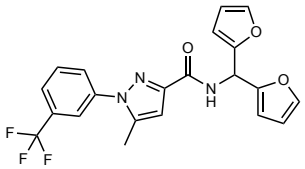
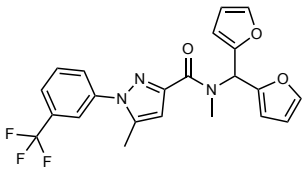
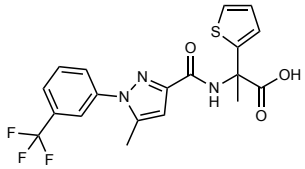
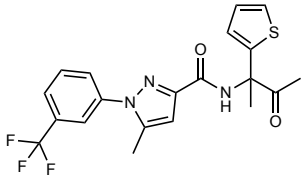
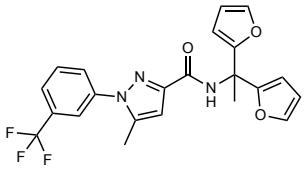
[b]Tanimoto coefficient (Tc) based on ECFP4 fingerprints

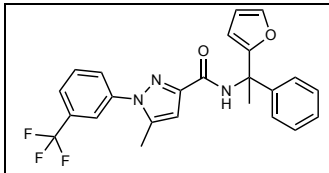
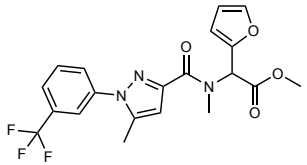
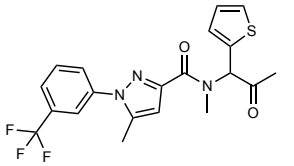
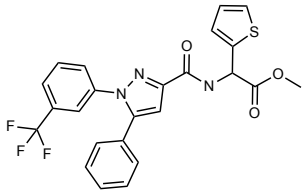
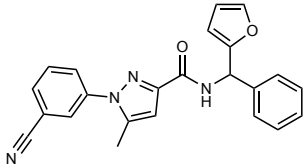
[c]Corresponding ChEMBL ligand with the most similar fingerprint

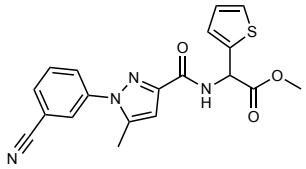
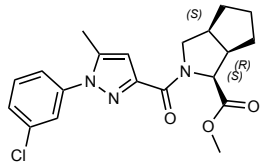
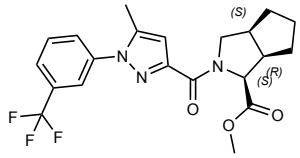
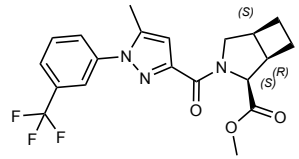
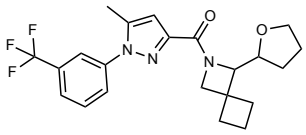
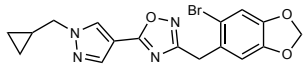
Supplementary Table 2. Binding affinities and functional activities for active analogs at CB1.

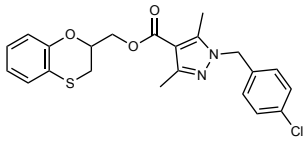
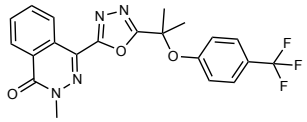
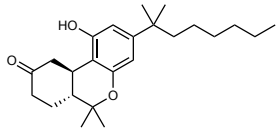
Compound	CB1[a] binding K_i [95% CI] (nM) pK_i [95% CI] E_{max} [SEM]		hCB1 Lance Ultra cAMP EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [SEM]	hCB1 Cerep cAMP EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]	hCB1 Glosensor cAMP EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]	hCB1 Tango ß-arrestin recruitment EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]	hCB1 DiscoverX ß-arrestin recruitment EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]
 CP–55,940	rCB1	2.9 [2.05 – 4.2] 8.5 [8.4 – 8.7] 98% [3.5]	5.5 [4.4 – 6.8] 8.3 [8.2 – 8.4] 86% [2.0]	--	0.028 [0.02 – 0.04] 10.6 [10.5 – 10.7] 96% [93 – 99]	8.9 [7.5 – 10.6] 8.1 [8.0 – 8.1] 100% [96 – 104]	4.0 [3.2 – 4.9] 8.4 [8.3 – 8.5] 108% [99 – 109]
	hCB1	2.5 [1.7 – 3.5] 8.6 [8.5 – 8.8] 88.4% [3.2]					
 ‘4042	1.86 [1.37 – 2.52] 8.7 [8.6 – 8.9] 99% [3.0]		3.3 [1.9 – 5.6] 8.5 [8.3 – 8.7] 78% [78 – 79]	0.008 [0.006 – 0.01] 11.1 [11.0 – 11.2] 96% [102 – 107]	0.039 [2.9 – 5.4] 10.4 [10.3 – 10.5] 91% [87 – 94]	10.7 [8.7 – 13.3] 8.0 [7.9 – 8.1] 102% [98 – 105]	2.3 [2.5 –4.8] 8.7 [8.3 – 9.6] 71% [60 – 65]
 ‘1350	rCB1	0.95 [.74 – 1.2] 9.02 [8.9 – 9.1] 106% [2.9]	1.6 [0.7 – 3.6] 8.8 [8.4 – 9.2] 77% [6.5]	--	--	--	--
	hCB1	0.32 [.17 – .6] 9.5 [9.2 – 9.8] 88% [4.7]					
 ‘8690	90.2 [56.7 – 143] 7.1 [6.9 – 7.3] 100% [4.0]		473 [109 – 1822] 6.3 [5.8 – 7.0] 53% [8.2]	--	--	--	--

 ‘60154	44.3 [33.9 – 58.0] 7.4 [7.2 – 7.5] 110% [2.9]	351 [93] 6.5 [7.0] 67% [13.2]	--	25.2 [16 – 40] 7.6 [7.4 – 7.8] 82% [74 – 189]	819 [718 – 934] 6.1 [6.0 – 6.1] 39% [37 – 40]	--
 ‘1066	1719 [736 – 4048] 5.8 [5.4 – 6.1] 97% [8.0]	--	--	--	--	--
 ‘6000	1455 [943 – 2249] 5.8 [5.7 – 6.0] 96% [4.0]	--	--	--	--	--
 ‘1081	116 [76.3 – 178] 6.9 [6.8 – 7.1] 96% [4.0]	--	--	--	--	--
 ‘1082	850 [488 – 1491] 6.1 [5.8 – 6.3] 94% [5.7]	--	--	--	--	--

 ‘1090	90.8 [42.7 – 192] 7.0 [6.7 – 7.4] 99% [7.13]		N.D.	--	--	--	--
 ‘4388	1360 [998 – 1857] 5.9 [5.7 – 6.0] 113% [4.4]		N.D.	--	--	--	--
 ‘4051	5328 [3774–7507] 5.3 [5.1 – 5.4] 103% [3.8]		--	--	--	--	--
 ‘4156	13.5 [6.3 – 30.1] 7.9 [7.5 – 8.2] 91% [7.5]		--	--	--	--	--
 ‘4936	rCB1	7.5 [3.9 – 14.3] 8.1 [7.9 – 8.4] 88% [6.3]	4.79 [2.4] 8.3 [8.6] 65% [4.5]	--	--	--	--
	hCB1	4.1 [1.2 – 1.5] 8.4 [7.9 – 8.8] 83% [6.5]					

 ‘5806	8.0 [3.0 – 21.8] 8.1 [7.7 – 8.5] 100% [10.5]	--	--	--	--	--
 ‘6425	934 [583 – 1501] 6.0 [5.8 – 6.2] 108% [5.8]	--	--	--	--	--
 ‘6829	1046 [669 – 1643] 6.0 [5.8 – 6.2] 106% [5.8]	--	--	--	--	--
 ‘8079	18.5 [13.8 – 25.0] 7.7 [7.6 – 7.9] 104% [3.0]	--	--	--	--	--
 ‘12565	301 [195 – 462] 6.5 [6.3 – 6.7] 97% [4.0]	--	--	--	--	--

 ‘31604	801 [596 –1,076] 6.1 [6.0 – 6.2] 100% [2.8]	--	--	--	--	--
 ‘10010	1,196 [952 – 1,505] 5.9 [5.8 – 6.0] 101% [2.9]	--	--	N.D	> 10,000	--
 ‘6439	251 [173 – 364] 6.6 [6.4 – 6.8] 106% [3.9]	--	--	N.D.	> 10,000	--
 ‘6448	866 [564 – 1,317] 6.1 [5.9 – 6.3] 103% [4.1]	--	--	--	--	--
 ‘3737	173 [94 – 322] 6.76 [6.5 – 7.03] 112% [8.8]	--	326 [168 – 1044] 6.5 [6.0 – 6.8] 99% [91 – 135]	N.D	> 10,000	> 10,000
 ‘5424	876 [683 – 1123] 6.1 [6.0 – 6.2] 104% [2.6]	--	--	--	--	--

 ‘5463	825 [396 – 1,755] 6.1 [5.8 – 6.4] 88% [6.6]	--	--	--	--	--
 ‘2153	163 [90 – 287] 6.79 [6.5 – 7.0] 82.6% [4.5]	--	--	--	--	--
 Nabilone	2.3 [1.4 – 3.8] 8.6 [8.4 – 8.9] 81% [3.7]	--	--	--	--	--

N.D. = best fit values were not determined due to compound inactivity or poor data quality

-- Not tested

[a]All binding data is rCB1 unless otherwise labeled

Supplementary Table 3. Functional activities for select analogs versus a variety of transducers and hCB1 in the bioSens-All® platform.

Compound		hCB1 G_{i1}	hCB1 G_{oB}	hCB1 G_z
CP–55,940	EC_{50} [95% CI] (nM)	0.46 [0.4 – 0.5]	0.63 [0.6 – 0.7]	0.28 [0.18 – 0.5]
	pEC_{50} [95% CI]	9.3 [9.3 – 9.4]	9.2 [9.2 – 9.3]	9.6 [9.4 – 9.8]
	E_{max} [95% CI]	100 [98 – 102]	100 [99 – 101]	102 [102 – 104]
‘51486	EC_{50} [95% CI] (nM)	849 [745– 947]	711 [579– 873]	1118 [363– 3447]
	pEC_{50} [95% CI]	6.1 [6.0 – 6.1]	6.2 [6.1 – 6.2]	6.0 [5.5 – 6.4]
	E_{max} [95% CI]	73 [70 – 75]	74 [70 – 75]	130 [996 – 163]
‘60154	EC_{50} [95% CI] (nM)	2.5 [1.9 – 3.4]	18.4 [15.8– 21.5]	17.5 [7.5 – 41]
	pEC_{50} [95% CI]	7.6 [7.5 – 7.7]	7.7 [7.7 – 7.8]	7.8 [7.4 – 8.1]
	E_{max} [95% CI]	92 [90 – 94]	100 [98 – 100]	121 [103 – 140]
‘1081	EC_{50} [95% CI] (nM)	150 [116 – 197]	91.7 [55 – 153]	225 [73 – 694]
	pEC_{50} [95% CI]	6.8 [6.7 – 6.9]	7.0 [6.8 – 7.3]	6.7 [6.2 – 7.1]
	E_{max} [95% CI]	49 [48 – 51]	45 [43 –47]	72 [55 –89]
‘1082	EC_{50} [95% CI] (nM)	[a]N.D.	N.D.	N.D.
	pEC_{50} [95% CI]			
	E_{max} [95% CI]			
‘1087	EC_{50} [95% CI] (nM)	N.D.	N.D.	N.D.
	pEC_{50} [95% CI]			
	E_{max} [95% CI]			
‘1090	EC_{50} [95% CI] (nM)	35.6 [28.5 – 45]	37.3 [30 – 47]	126 [45 – 354]
	pEC_{50} [95% CI]	7.5 [7.3 – 7.5]	7.4 [7.3 – 7.5]	6.9 [6.5 – 7.4]
	E_{max} [95% CI]	81 [80 –82]	90 [88 –92]	115 [92 – 137]
‘4388	EC_{50} [95% CI] (nM)	N.D.	N.D.	N.D.
	pEC_{50} [95% CI]			
	E_{max} [95% CI]			
‘6829	EC_{50} [95% CI] (nM)	4056 [2417 – 9228]	1011 [706 – 1449]	1347 [720 – 2522]
	pEC_{50} [95% CI]	5.4 [5.0 – 5.6]	6.0 [5.8 – 6.2]	5.9 [6.0 – 6.2]
	E_{max} [95% CI]	68 [57 – 77]	49 [45 – 53]	70 [57 –83]
‘4051	EC_{50} [95% CI] (nM)	6523 [5770 – 7511]	7988 [6709 – 9511]	2431 [1069 – 5531]
	pEC_{50} [95% CI]	5.2 [5.1 – 5.2]	5.1 [5.0 – 5.2]	5.6 [5.3 – 6.0]
	E_{max} [95% CI]	108 [104 – 113]	115 [106 – 121]	114 [86 –141]
‘12565	EC_{50} [95% CI] (nM)	104 [79 – 138]	44.8 [27 – 73]	54.6 [22.1 – 135]
	pEC_{50} [95% CI]	7.0 [6.9 – 7.1]	7.4 [7.1 – 7.6]	7.3 [6.9 – 7.7]
	E_{max} [95% CI]	28 [27 – 28]	25 [24 –26]	51 [41 – 61]
‘10010	EC_{50} [95% CI] (nM)	814 [717 – 932]	801 [582– 1102]	1396 [506 – 3853]
	pEC_{50} [95% CI]	6.1 [6.0 – 6.1]	6.1 [6.0 – 6.2]	5.9 [5.4 – 6.3]
	E_{max} [95% CI]	74 [70 – 74]	71 [67 – 75]	144 [113 –175]
‘6439	EC_{50} [95% CI] (nM)	65.5 [56.8 – 755]	60.9 [52.9 – 70]	339 [96 – 1195]
	pEC_{50} [95% CI]	7.2 [7.1 – 7.2]	7.2 [7.2 – 7.3]	6.5 [5.9 – 7.0]
	E_{max} [95% CI]	95 [93 – 96]	100 [99 – 101]	162 [125 –199]
‘6448	EC_{50} [95% CI] (nM)	345 [321 – 372]	310 [267 – 360]	728 [381 – 1393]
	pEC_{50} [95% CI]	6.5 [6.4 – 6.5]	6.5 [6.4 – 6.6]	6.1 [5.9 – 6.4]
	E_{max} [95% CI]	87 [86 – 88]	90 [87 – 91]	151 [130 –172]
‘5490	EC_{50} [95% CI] (nM)	2804 [2436 – 3285]	6729 [2678 – 16910]	2470 [998 – 6108]
	pEC_{50} [95% CI]	5.6 [5.5 – 5.6]	5.2 [4.8 – 5.6]	5.6 [5.2 – 6.1]
	E_{max} [95% CI]	98 [94 – 102]	118 [94 – 143]	140 [9109 – 172]
‘1651	EC_{50} [95% CI] (nM)	3026 [2486 – 3822]	19780 [4343 – 90080]	30840 [1133 – 839000]
	pEC_{50} [95% CI]	5.5 [5.4 – 5.6]	4.7 [4.1 – 5.4]	4.5 [3.1– 6.0]
	E_{max} [95% CI]	89 [84 – 94]	152 [94 – 208]	231 [34 – 428]
‘0430	EC_{50} [95% CI] (nM)	N.D.	N.D.	N.D.
	pEC_{50} [95% CI]			
	E_{max} [95% CI]			
‘3386	EC_{50} [95% CI] (nM)	N.D.	N.D.	N.D.

	pEC_{50} [95% CI] E_{max} [95% CI]			
‘7019	EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]	N.D.	N.D.	[b]--
‘5424	EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]	N.D.	N.D.	--
‘7800	EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]	6793 [983] 5.2 [6.0] 34 [24]	597 [398 – 1017] 6.2 [5.9 – 6.4] 21 [20 – 23]	--
‘5463	EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]	4941 [1763 – 26860000] 5.3 [3.4 – 5.8] 31 [24 – 88]	7472 [1125] 5.1 [6.0] 32 [22]	--
‘0450	EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]	56310 [2177] 4.3 [5.7] 49 [26]	2509 5.6 [3.0 – 6.2] 36 [30 – 117]	--
‘2153	EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]	1011 [371 – 6576] 6.0 [5.2 – 6.4] 89 [78 – 118]	2061 [620 – 25390] 5.7 4.6 – 6.2] 109 [91 – 162]	--
‘8690	EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]	19.1 [14.4 – 25.8] 7.72 [7.6 – 7.8] 82 [77 – 85]	18 [14 – 23] 7.8 [7.7 – 7.9] 83 [80 – 87]	33 [15 – 117] 7.5 [6.9 – 7.8] 98 [86 – 121]

[a]N.D. = best fit values were not able to be determined due to compound inactivity or poor data quality
[b]-- Not tested

Supplementary Table 4. Detailed functional activities for select analogs and control versus a variety of transducers and hCB1 in the bioSens-All® platform.

Compound		hCB1 G_{i1}	hCB1 G_{i2}	hCB1 G_{oB}	hCB1 G_z	hCB1 G_{13}	hCB1 G_{15}	hCB1 Barr2 + GRK2
CP–55,940	EC_{50} [95% CI] (nM)	0.46 [0.4 – 0.5]	0.55 [0.4 – 0.7]	0.63 [0.6 – 0.7]	0.28 [0.18 – 0.5]	2.4 [1.65 – 3.4]	0.26 [0.22 – 2.9]	3.1 [1.97 – 4.8]
	pEC_{50} [95% CI]	9.34 [9.3 – 9.4]	9.26 [9.1 – 9.4]	9.20 [9.2 – 9.3]	9.55 [9.4 – 9.8]	8.62 [8.5 – 8.8]	9.59 [9.5 – 9.7]	8.51 [8.3 – 8.7]
	E_{max} [95% CI]	100 [98 – 102]	100 [96 – 103]	100 [98 – 101]	101 [96 – 107]	100 [95 – 105]	100 [98 – 102]	89 [82 – 98]
‘4042	EC_{50} [95% CI] (nM)	0.48 [0.4 – 0.6]	0.56 [0.4 – 0.9]	0.64 [0.5 – 0.8]	0.43 [0.3 – 0.6]	2.1 [0.5 – 9.6]	0.37 [0.28 – 0.49]	3.6 [2.1 – 6.8]
	pEC_{50} [95% CI]	9.32 [9.2 – 9.4]	9.25 [9.0 – 9.5]	9.20 [9.1 – 9.3]	9.37 [9.3 – 9.4]	8.69 [8.0 – 9.3]	9.43 [9.3 – 9.6]	8.44 [8.2 – 8.7]
	E_{max} [95% CI]	102 [100 – 104]	101 [95 – 106]	103 [99 – 106]	97 [93 – 102]	64 [54 – 84]	105 [102 – 108]	72 [71 – 74]
‘1350	EC_{50} [95% CI] (nM)	0.23 [0.18 – 0.3]	0.28 [0.19 – 0.4]	0.29 [0.24 – 0.34]	0.35 [0.22 – 0.53]	0.83 [0.23 – 2.7]	0.22 [0.18 – 0.27]	2.2 [1.1 – 4.4]
	pEC_{50} [95% CI]	9.63 [9.5 – 9.7]	9.54 [9.4 – 9.7]	9.54 [9.5 – 9.6]	9.46 [9.3 – 9.7]	9.08 [8.6 – 9.6]	9.66 [9.6 – 9.8]	8.66 [8.4 – 9.0]
	E_{max} [95% CI]	92 [90 – 95]	95 [90 – 99]	98 [94 – 98]	94 [88 – 100]	56 [48 – 67]	99 [96 – 101]	63 [60 – 72]

Supplementary Table 5. Relative efficacy for ‘4042 and ‘1350 vs. CP-55,940.

Target	Sensor	Compound	Mean log (E_{max}/EC_{50})	SEM log (E_{max}/EC_{50})	Mean Δlog (E_{max}/EC_{50})	SEM Δlog (E_{max}/EC_{50})	t-test to CP-55,940[a]	RE[b]
hCB1	G_{i1}	CP-55,940	9.34	0.07	0.00	0.09		1.00
		'4042	9.33	0.14	-0.01	0.15	$t(5) = 0.15$, $P = 0.9$	0.97
		'1350	9.59	0.06	0.30	0.09	$t(5) = 11.9$, $P < 0.0001$	1.98
	G_{i2}	CP-55,940	9.24	0.13	0.00	0.18		1.00
		'4042	9.25	0.03	0.01	0.13	$t(2) = 0.23$, $P = 0.8$	1.01
		'1350	9.52	0.03	0.28	0.13	$t(2) = 10.6$, $P = 0.009$	1.89
	G_{oB}	CP-55,940	9.19	0.07	0.00	0.10		1.00
		'4042	9.21	0.09	0.02	0.11	$t(5) = 0.25$, $P = 0.8$	1.04
		'1350	9.09	0.44	0.35	0.44	$t(5) = 19.5$, $P < 0.0001$	2.24
	G_z	CP-55,940	9.53	0.23	0.00	0.33		1.00
		'4042	9.32	0.19	-0.21	0.30	$t(4) = 1.1$, $P = 0.3$	0.62
		'1350	9.42	0.22	-0.11	0.32	$t(3) = 0.68$, $P = 0.5$	0.77
	G_{13}	CP-55,940	8.63	0.23	0.00	0.32		1.00
		'4042	8.59	0.25	-0.04	0.33	$t(2) = 0.16$, $P = 0.9$	0.91
		'1350	8.85	0.05	0.22	0.23	$t(2) = 4.5$, $P = 0.046$	1.64
	G_{15}	CP-55,940	9.59	0.02	0.00	0.02		1.00
		'4042	9.46	0.12	-0.13	0.12	$t(2) = 1.09$, $P = 0.38$	0.74
		'1350	9.65	0.06	0.06	0.06	$t(2) = 0.94$, $P = 0.45$	1.14
	$ß_{arr2}$+ GRK2	CP-55,940	8.28	0.25	0.00	0.35		1.00
		'4042	8.19	0.03	-0.09	0.03	$t(3) = 3.77$, $P = 0.03$	0.81
		'1350	8.34	0.08	0.06	0.08	$t(4) = 0.95$, $P = 0.4$	1.16
hCB2	G_{i1}	CP-55,940	8.86	0.12	0.00	0.17		1.00
		'4042	8.49	0.03	-0.20	0.13	$t(2) = 1.0$, $P = 0.4$	0.63
		'1350	8.32	0.10	-0.54	0.16	$t(2) = 5.3$, $P = 0.03$	0.29
	G_{i2}	CP-55,940	8.97	0.00	0.00	0.00		1.00
		'4042	8.74	0.00	-0.23	0.00	[c]--	0.59
		'1350	8.57	0.00	-0.40	0.00	--	0.40
	G_{oB}	CP-55,940	8.76	0.09	0.00	0.13		1.00
		'4042	8.43	0.19	-0.33	0.21	$t(2) = 1.7$, $P = 0.2$	0.47

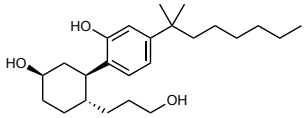
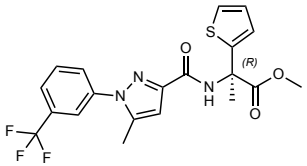
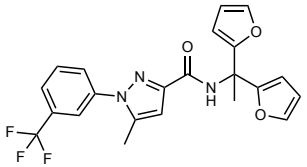
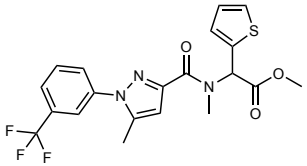
		'1350	8.36	0.01	-0.40	0.09	$t(2) = 33.7$, $P = 0.009$	0.40
	G_z	CP-55,940	8.90	0.39	0.00	0.55		1.00
		'4042	8.48	0.51	-0.42	0.64	$t(2) = 0.8$, $P = 0.5$	0.38
		'1350	8.24	0.23	-0.65	0.45	$t(2) = 2.8$, $P = 0.1$	0.22
	$ß_{arr2}$+ GRK2	CP-55,940	7.83	0.13	0.00	0.18		1.00
		'4042	7.74	0.00	-0.09	0.13	$t(2) = 43.7$, $P = 0.005$	0.82
		'1350	7.79	0.09	-0.04	0.16	$t(2) = 0.41$, $P = 0.7$	0.92

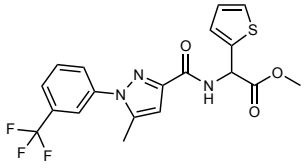
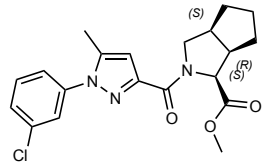
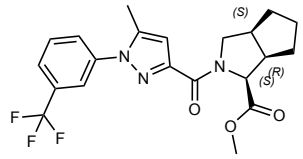
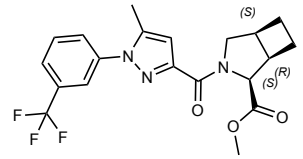
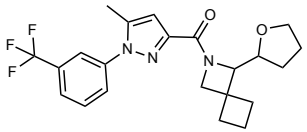
[a]Statistical significance of test compounds vs. CP-55,940 Mean Δlog (E_{max}/EC_{50}) by unpaired two-tailed t-test.

[b]RE, relative efficacy = $10^{\Delta log\ (Emax/EC50)}$

[c]--, not determined

Supplementary Table 6. Binding affinities and functional activities for select active analogs at CB2.

Compound	hCB2 binding EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [SEM]	hCB2 Cerep cAMP EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]	hCB2 BRET2 + GoA EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]	hCB2 Tango ß-arrestin recruitment EC_{50} [95% CI] (nM) pEC_{50} [95% CI] E_{max} [95% CI]
 CP–55,940	4.3 [3.3 – 5.8] 8.4 [8.2 – 8.5] 100% [2.8]	--	13.1 [9.4 – 18.5] 7.9 [7.7 – 8.0] 99% [94 – 105]	22.9 [21.3 – 24.8] 7.6 [7.60 – 7.67] 100% [98 – 102]
 ‘1350	2.9 [1.1 – 7.4] 8.5 [8.1 – 8.9] 73% [5.7]			
 ‘4936	6.7 [2.6 – 14.2] 8.2 [7.8– 8.6] 78% [5.7]			
 ‘4042	[b]--	0.011 [0.002 – 0.02] 10.95 [10.7 – 11.6] 72% [77 – 84]	7.9 [1.6 – 40.6] 8.1 [7.4 – 8.8] 29% [22 – 36]	33.9 [21.7 – 61.5] 7.5 [7.2 – 7.7] 28% [26 – 32]

 ‘60154	--	--	594 [125 – 2813] 6.2 [5.6 – 6.9] 31% [20 – 42]	3341 [2707 – 4371] 5.5 [5.4 – 5.6] 21% [19 – 23]
 10010	--	--	[a]N.D.	556 [506 – 611] 6.3 [6.2 – 6.3] 18% [17 – 19]
 ‘6439	--	--	97.1 [12.6 – 749] 7.0 [6.13 – 67.9] 81% [34 – 128]	338 [282– 415] 6.5 [6.4 – 6.6] 14% [13 – 15]
 ‘6448	--	--	--	--
 ‘3737	--	4.3 [.0004 – 22.6] 8.4 [7.7 – 12.5] 45% [42 – 80%]	N.D.	1500 [1274 – 1805] 5.8 [5.7 – 5.9] 9% [8 – 9]

[a]N.D. = best fit values were not determined due to compound inactivity or poor data quality
[b]-- Not tested

Supplementary Table 7. Functional activities for select analogs and controls versus a variety of transducers and hCB2 in the bioSensAll platform.

Compound		hCB2 G_{i1}	hCB2 G_{i2}	hCB2 G_{oB}	hCB2 G_z	hCB2 Barr2 + GRK2
CP–55,940	EC_{50} [95% CI] (nM)	1.4 [1.1 – 1.7]	1.1 [0.9 – 1.3]	1.7 [1.5 – 2.1]	1.05 [0.6 – 1.9]	14.3 [11.6 – 17.9]
	pEC_{50} [95% CI]	8.87 [8.7 – 8.9]	8.97 [8.9 – 9.1]	8.76 [8.7 – 8.8]	8.98 [8.7 – 9.2]	7.84 [7.8 – 7.9]
	E_{max} [95% CI]	100 [97 – 103]	100 [97 – 104]	100 [98 – 103]	98 [89 – 109]	100 [95 – 104]
‘4042	EC_{50} [95% CI] (nM)	2.7 [2.0 – 3.4]	1.3 [0.9 – 1.7]	2.5 [1.9 – 3.3]	1.36 [0.5 – 3.1]	5.5 [3.5 – 8.7]
	pEC_{50} [95% CI]	8.58 [8.5 – 8.7]	8.90 [8.8 – 9.0]	8.60 [8.5 – 8.7]	8.87 [8.5 – 9.3]	8.26 [8.1 – 8.5]
	E_{max} [95% CI]	82 [79 – 85]	70 [67 – 73]	61 [59 – 63]	56 [47 – 68]	33 [33 – 33]
‘1350	EC_{50} [95% CI] (nM)	3.55 [2.98 – 4.2]	1.6 [1.4 – 1.9]	2.6 [2.15 – 3.1]	2.6 [1.6 – 3.9]	4.2 [2.8 – 6.3]
	pEC_{50} [95% CI]	8.45 [8.4 – 8.5]	8.79 [8.7 – 8.9]	8.58 [8.5 – 8.7]	8.58 [8.4 – 8.8]	8.38 [8.2 – 8.6]
	E_{max} [95% CI]	74 [72 – 77]	61 [59 –63]	59 [57 – 61]	52 [46 – 60]	30 [28 –33]

Supplementary Table 8. Cryo-EM data collection, model refinement, and validation statistics.

Data Collection	**Global Refinement**		
Voltage (kV)	300		
Magnification	96,000		
Total electron dose ($e^-/Å^2$)	56.6		
Defocus range (μm)	-0.7 - -2.0		
Calibrated pixel size (Å)	0.8521		
Micrographs collected	8324		
Data Processing			
Extracted particles	4,967,593		
Particles used for final reconstruction	465,411		
Final map resolution (Å, 0.143 FSC)	3.3		
Map resolution range (Å)	2.6 - 4.2		
Map sharpening B factor ($Å^2$)	175.3		
Model Content			
Initial models used (PDB code)	6N4B ($CB1/G_i$/scFv16)		
Total number of atoms	8,528		
No. of protein residues	1116		
No. of ligands	1		
Model Validation	**$CB1:G_i$**	**CB1 alone**	**$CB1:G_i$ composite**
PDB.	8GAG	9DGI	9EGO
EMDB	EMD-29898	EMD-46828	EMD-47992
CC map vs. model (%) RMSD	69.88	73.64	75.40
Bond lengths (Å) / Bond angles (°)	0.006 / 0.829	0.005/1.265	0.007/1.029
Ramachandran plot statistics			
Favored (%)	87.86	89.49	93.93
Allowed (%)	12.14	10.12	5.97
Outliers (%)	0.0	0.39	0.09
Rotamer outliers (%)	0.0	0.99	0.34
C-beta deviations	0.0	0.0	0.0
Clash score	10.08	1.47	2.79

Supplementary Table 9. Aqueous solubility for lead compound ‘1350.

Compound	PBS solubility, pH 7.4, μM			
	Rep. 1	Rep. 2	Mean	SE
Ondansetron	121	119	120	0.7
‘1350	23	24	23	0.3

Supplementary Table 10. Mouse plasma protein binding for lead compound ‘1350.

Compound	Type of plasma	Conc, μM[a]	Rep.[b]	Area Ratio		% of bound compound	Mean % of bound compound	Recovery %	Stability %
				Buffer	Plasma				
Verapamil	Mouse	1.0	1	3.51E-02	2.87E-01	88	88	91	106
			2	3.54E-02	2.85E-01	88			
‘1350	Mouse	1.0	1	8.97E-04	1.56E-02	94	94*	107	11
			2	9.36E-04	1.69E-02	94			

[a]Concentration
[b]Replicate number
*Parameter should be considered as approximate, compound show low stability in mouse plasma

Supplementary Table 11. Mouse plasma stability for lead compound ‘1350.

Compound	Time, min	Area Ratio		Mean Area Ratio	Mean % Remaining	$T_{1/2}$, min
		Rep. 1	Rep. 2			
Verapamil	0	7.05E-01	6.50E-01	6.77E-01	100	1263*
	20	6.86E-01	6.39E-01	6.63E-01	98	
	40	7.12E-01	6.59E-01	6.85E-01	101	
	60	7.20E-01	6.60E-01	6.90E-01	102	
	120	6.24E-01	6.33E-01	6.29E-01	93	
Propantheline	0	1.09E+00	1.01E+00	1.05E+00	100	28
	20	8.21E-01	7.61E-01	7.91E-01	75	
	40	5.51E-01	4.93E-01	5.22E-01	50	
	60	3.34E-01	3.09E-01	3.22E-01	31	
	120	6.04E-02	5.75E-02	5.90E-02	6	
‘1350	0	2.86E-01	2.61E-01	2.73E-01	100	41
	20	2.37E-01	2.23E-01	2.30E-01	84	
	40	1.86E-01	1.77E-01	1.81E-01	66	
	60	1.24E-01	1.37E-01	1.31E-01	48	
	120	3.73E-02	3.73E-02	3.73E-02	14	

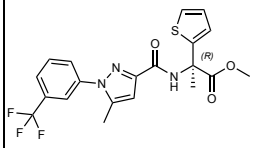
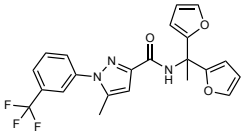
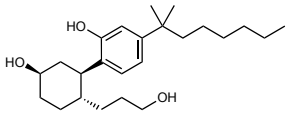
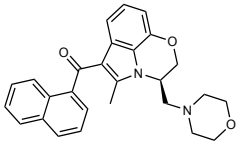
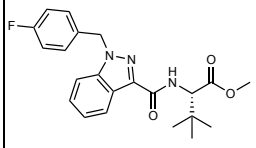
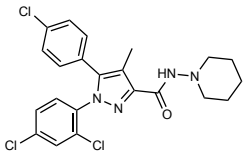
*Parameter should be considered as approximate due to the high stability of the compound

Supplementary Table 12. Mouse microsomal stability for lead compound 1350.

Compound	Time, min	Analyte Peak Area		Mean Analyte Peak Area	Mean % Remaining	R^2	k_{el}, min^{-1}	$t_{1/2}$, min	Cl_{int}, µL/min/mg	Mean % Remaining without cofactor
		Rep. 1	Rep. 2							
Propranolol	0	1.53E-01	1.50E-01	1.51E-01	100	0.894	0.041	16.9	99	100
	7	7.43E-02	6.79E-02	7.11E-02	47					
	15	5.08E-02	4.64E-02	4.86E-02	32					
	25	3.83E-02	3.61E-02	3.72E-02	25					
	40	2.70E-02	2.36E-02	2.53E-02	17		106			
Imipramine	0	1.40E+00	1.41E+00	1.40E+00	100	0.997	0.135	5.1	325	100
	7	7.04E-01	6.98E-01	7.01E-01	50					
	15	2.20E-01	2.67E-01	2.43E-01	17					
	25	5.44E-02	6.58E-02	6.01E-02	4					
	40	6.38E-03	7.22E-03	6.80E-03	0		104			
‘1350	0	9.08E-01	9.27E-01	9.17E-01	100	0.990	0.360*	1.9*	868*	100
	7	9.72E-02	1.42E-01	1.20E-01	13					
	15	3.31E-03	5.15E-03	4.23E-03	0					
	25	1.28E-03	1.67E-03	1.48E-03	0					
	40	1.42E-03	9.18E-04	1.17E-03	0		100			

*Due to rapid degradation of compound, the metabolic stability parameters are considered ambigous

Supplementary Table 13. MPO scores for lead compounds and CB1 controls.

Compound	Structure	Physicochemical properties						MPO Score
		MW[a] (g/mol)	clogP[b]	tPSA[c]	pKa[d]	clogD$_{7.4}$[e]	HBD[f]	
‘1350		437	4.08	73.22	0.07	4.50	1	3.7
‘4936		429	5.08	73.20	0.08	4.37	1	3.3
CP-55,940		377	5.66	60.69	-2.02	5.90	3	3.0
WIN 55-212,2		427	4.60	43.70	6.93	4.35	0	3.7
MDMB-Fub		397	3.54	73.22	-0.85	4.21	1	4.3
Rimonabant		464	5.94	50.16	1.68	5.91	1	3.1

[a]MW = Molecular Weight in g/mol
[b]cLogP = calculated LogP
[c]tPSA = Topological Polar Surface Area
[d]pKa = negative log of the acid dissociation constant
[e]cLogD$_{7.4}$ = calculated log distribution coefficient at pH 7.4
[f]HBD = Hydrogen bond donors

Supplementary Methods

Synthetic procedures.

Method 1. A carboxylic acid (100 mg), 0.7 ml of acetonitrile, a hydrazide (1.1 mol. eq. to the acid), and triethylamine (TEA, 1.1 mol. eq. to the hydrazide) were placed into a 4 ml capped glass vial and the mixture was stirred for 30 min at RT. Then, chloro-N,N,N′,N′-tetramethylformamidinium hexafluorophosphate (1.2 mol. eq. to the acid) was added. If the solution was transparent, the mixture was left for 48 hours at RT as is; otherwise, the vial was placed in the ultrasonic bath and left for 2-3 hours. Then, the mixture was heated in an oven for 6 hours at 100°C. The solvent and volatile components were evaporated under reduced pressure to give the crude product. The product was further purified by HPLC.

Method 2. A carboxylic acid (100 mg), 0.6 ml of DMSO, alcohol (1.1 mol. eq. to the acid), TEA (1.1 mol. eq. to the amine if it is in the form of hydrochloride), and 4-dimethylaminopyridine (DMAP, catalytic amount) were placed into a 4 ml capped glass vial and the mixture was stirred for 15 min at RT. Then, 1,1'-carbonyldiimidazole (CDI, 1.2 mol. eq. to the acid) was added. If the solution was transparent, the mixture was left for 72 hours at RT as is; otherwise, the vial was placed in the ultrasonic bath and left for 2-3 hours. After the reaction is completed, 40 uL of formic acid was added and the mixture was shaken for 15 min at RT. The solvent and volatile components were evaporated under reduced pressure to give the crude product. The product was further purified by HPLC.

Method 3. An amine (100 mg), a carboxylic acid (1.1 mol. eq. to the amine), TEA (1.1 mol. eq. to the amine if it is in the form of hydrochloride), and 0.5 ml of DMSO were placed into a 4 ml capped glass vial and the mixture was stirred for 30 min at RT. Then, 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide (EDC, 1.2 mol. eq. to the amine) was added and the mixture was stirred for 1 hour. If the solution was transparent, the mixture was left overnight at room temperature as is; otherwise, the vial was placed in the ultrasonic bath and left overnight. The solution was filtered, and the solvent and volatile components were evaporated under reduced pressure to give the crude product. The product was further purified by HPLC.

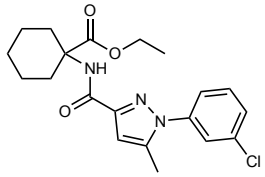
Method 4. A thiourea (100 mg), 0.7 ml of acetonitrile, and an α-halo ketone (1.1 mol. eq. to the acid) were placed into a 4 ml capped glass vial and the mixture was shaken for 30 min at RT. Then, the mixture was heated in an oven for 4 hours at 100°C. The solution was cooled down to RT and 0.2 ml of TEA, C18 molecular sieves, and 2 ml of acetonitrile were added. The mixture was shaken for 15 min at RT and the sieves were filtered off. The solvent and volatile components were evaporated under reduced pressure to give the crude product. The product was further purified by HPLC.

Method 5. The previously published procedure was utilized.[80]

Method 6. An azide (100 mg), an alkyne (1 mol. eq. to the azide), and 0.5 ml of dioxane were placed into a 4 ml capped glass vial and the mixture was stirred for 30 min at RT. Then, the sodium ascorbate (0.1 mol. eq. to the azide) and copper acetate (0.25 mol-% to the azide) were added and the mixture was heated in the oven for 6 hours at 60°C. After completion of the reaction, 2 mL of methanol was added followed by C18 sieves. The vial was shaken for 30 min at RT and the sieves were filtered off. The filtrate was evaporated to give a crude product. The product was further purified by HPLC.

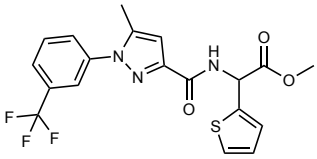
Spectral Description.

ethyl 1-(1-(3-chlorophenyl)-5-methyl-1H-pyrazole-3-carboxamido)cyclohexane-1-carboxylate – '64801, PV-001795007500 (Method 3).



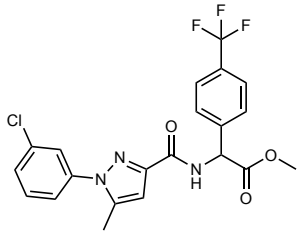
The compound was synthesized from ethyl 1-aminocyclohexane-1-carboxylate hydrochloride (Catalog # EN300-43194, 100 mg, 0.48 mmol) and 1-(3-chlorophenyl)-5-methyl-1H-pyrazole-3-carboxylic acid (Catalog # EN300-127105, 125 mg, 0.53 mmol).
Yield: 55%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.82 (s, 1H), 7.78 (t, J = 2.0 Hz, 1H), 7.64 – 7.51 (m, 2H), 6.64 (d, J = 1.0 Hz, 1H), 4.04 (q, J = 7.1 Hz, 1H), 2.35 (t, J = 2.0 Hz, 3H), 2.08 – 1.98 (m, 2H), 1.78 (ddd, J = 13.8, 10.1, 3.8 Hz, 2H), 1.55 – 1.42 (m, 6H), 1.29 (d, J = 11.6 Hz, 1H), 1.11 (t, J = 7.1 Hz, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 173.9, 161.3, 147.1, 141.6, 140.6, 134.0, 131.3, 128.6, 125.2, 123.9, 108.0, 60.6, 58.5, 32.5, 25.3, 21.7, 14.5, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{25}ClN_3O_3$: 390.2; found: 390.1.

methyl 2-(5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamido)-2-(thiophen-2-yl)acetate – '60154, PV-001796383931 (Method 3).



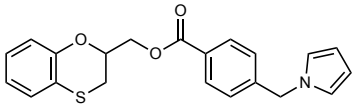
The compound was synthesized from methyl 2-amino-2-(thiophen-2-yl)acetate hydrochloride (Catalog # EN300-60031, 100 mg, 0.48 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 143 mg, 0.53 mmol).
Yield: 66%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.90 (d, J = 7.5 Hz, 1H), 8.00 (d, J = 2.1 Hz, 1H), 7.98 – 7.92 (m, 1H), 7.88 – 7.83 (m, 1H), 7.79 (t, J = 7.9 Hz, 1H), 7.48 (dt, J = 5.1, 1.1 Hz, 1H), 7.15 (dd, J = 3.5, 1.0 Hz, 1H), 7.02 – 6.96 (m, 1H), 6.75 (d, J = 1.0 Hz, 1H), 5.87 (d, J = 7.5 Hz, 1H), 3.68 (s, 3H), 2.37 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 170.4, 163.4, 161.3, 147.8, 146.6, 141.9, 141.6, 139.9, 139.5, 139.0, 138.4, 131.1, 131.0, 130.7, 130.5, 129.8, 129.2, 128.9, 127.6, 127.1, 126.9, 125.4, 125.4, 125.0, 123.2, 122.1, 122.1, 122.0, 121.9, 108.3, 108.1, 53.6, 53.0, 51.9, 12.6, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{19}H_{17}F_3N_3O_3S$: 424.1; found: 424.2.

methyl 2-(1-(3-chlorophenyl)-5-methyl-1H-pyrazole-3-carboxamido)-2-(4-(trifluoromethyl)phenyl)acetate – '14083, PV-001818789715 (Method 3).



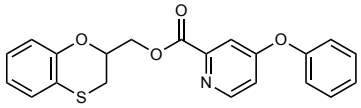
The compound was synthesized from methyl 2-amino-2-[4-(trifluoromethyl)phenyl]acetate hydrochloride (Catalog # EN300-316396, 100 mg, 037 mmol) and 1-(3-chlorophenyl)-5-methyl-1H-pyrazole-3-carboxylic acid (Catalog # EN300-127105, 97 mg, 0.41 mmol).
Yield: 59%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.99 (d, J = 7.5 Hz, 1H), 7.78 – 7.70 (m, 3H), 7.68 (d, J = 7.9 Hz, 2H), 7.64 – 7.52 (m, 3H), 6.69 (s, 1H), 5.81 (d, J = 7.5 Hz, 1H), 3.66 (s, 2H), 2.35 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 170.7, 161.4, 146.4, 142.0, 141.8, 140.5, 134.0, 131.4, 129.5, 129.1, 128.9, 128.8, 125.8, 125.8, 125.7, 125.5, 125.3, 123.9, 123.7, 108.1, 55.9, 53.1, 12.50.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{18}ClF_3N_3O_3$: 452.1; found: 452.0.

(2,3-dihydrobenzo[b][1,4]oxathiin-2-yl)methyl 4-((1H-pyrrol-1-yl)methyl)benzoate – '30177, Z1124220507 (Method 2).



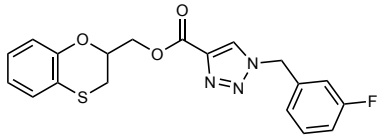
The compound was synthesized from (2,3-dihydro-1,4-benzoxathiin-2-yl)methanol (Catalog # EN300-59707, 100 mg, 0.55 mmol) and 4-[(1H-pyrrol-1-yl)methyl]benzoic acid (Catalog # EN300-69560, 121 mg, 0.6 mmol).
Yield: 26%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 – 7.90 (m, 2H), 7.32 (dd, J = 7.6, 1.7 Hz, 1H), 7.27 (d, J = 8.0 Hz, 2H), 7.18 (td, J = 7.7, 1.7 Hz, 1H), 7.00 (t, J = 7.8 Hz, 2H), 6.80 (q, J = 4.2, 3.2 Hz, 2H), 6.02 (t, J = 2.1 Hz, 2H), 5.44 – 5.36 (m, 1H), 5.19 (s, 2H), 4.52 (dd, J = 13.3, 3.1 Hz, 1H), 4.29 (dd, J = 13.3, 4.3 Hz, 1H), 3.31 – 3.22 (m, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 165.1, 159.3, 145.4, 131.6, 130.1, 128.9, 128.7, 127.7, 126.7, 124.2, 122.3, 121.5, 108.7, 73.0, 73.0, 52.2, 33.4.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{20}NO_3S$: 366.1; found: 366.0.

(2,3-dihydrobenzo[b][1,4]oxathiin-2-yl)methyl 4-phenoxypicolinate – '50267, Z1309468381 (Method 2).



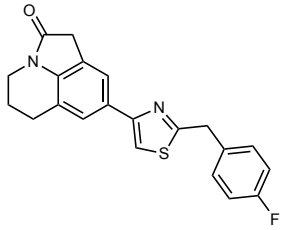
The compound was synthesized from (2,3-dihydro-1,4-benzoxathiin-2-yl)methanol (Catalog # EN300-59707, 100 mg, 0.55 mmol) and 4-phenoxypyridine-2-carboxylic acid hydrochloride (Catalog # EN300-98150, 151 mg, 0.6 mmol).
Yield: 48%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.60 (d, J = 5.5 Hz, 1H), 7.55 – 7.46 (m, 3H), 7.36 – 7.28 (m, 2H), 7.25 – 7.13 (m, 4H), 7.03 – 6.95 (m, 2H), 5.42 (dtd, J = 7.9, 4.7, 3.1 Hz, 1H), 4.55 (dd, J = 13.2, 3.2 Hz, 1H), 4.27 (dd, J = 13.2, 4.4 Hz, 1H), 3.35 – 3.23 (m, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 165.5, 164.0, 159.1, 153.7, 152.2, 149.9, 131.6, 131.1, 128.7, 126.5, 126.4, 124.1, 122.2, 121.2, 115.6, 113.6, 73.8, 72.8, 33.2.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{18}NO_4S$: 380.1; found: 380.0.

(2,3-dihydrobenzo[b][1,4]oxathiin-2-yl)methyl 1-(3-fluorobenzyl)-1H-1,2,3-triazole-4-carboxylate – '23346, Z1415595403 (Method 2).



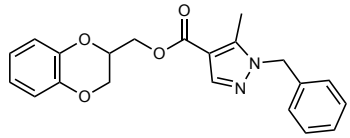
The compound was synthesized from (2,3-dihydro-1,4-benzoxathiin-2-yl)methanol (Catalog # EN300-59707, 100 mg, 0.55 mmol) and 1-[(3-fluorophenyl)methyl]-1H-1,2,3-triazole-4-carboxylic acid (Catalog # EN300-106975, 133 mg, 0.6 mmol).
Yield: 47%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.42 (td, J = 8.0, 6.0 Hz, 1H), 7.33 – 7.26 (m, 1H), 7.22 (dt, J = 9.7, 2.2 Hz, 1H), 7.17 (dq, J = 9.2, 3.4, 2.7 Hz, 3H), 7.02 – 6.96 (m, 2H), 5.69 (s, 2H), 5.43 (dq, J = 8.2, 4.0 Hz, 1H), 4.56 (dd, J = 13.3, 3.2 Hz, 1H), 4.27 (dd, J = 13.3, 4.3 Hz, 1H), 3.32 – 3.23 (m, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 163.4, 161.8, 159.7, 159.0, 139.1, 138.5, 138.5, 131.5, 131.4, 131.4, 130.2, 128.7, 126.4, 124.7, 124.7, 124.1, 122.2, 115.8, 115.6, 115.6, 115.4, 73.0, 72.9, 52.9, 33.2.
LC/MS (APSI) m/z [M+H] calculated for $C_{19}H_{17}FN_3O3S$: 386.1; found: 386.0.

8-(2-(4-fluorobenzyl)thiazol-4-yl)-5,6-dihydro-1H-pyrrolo[3,2,1-ij]quinolin-2(4H)-one – '1038, Z371852066 (Method 4).



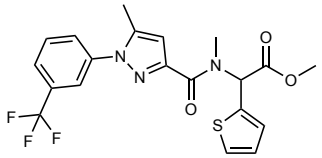
The compound was synthesized from 2-(4-fluorophenyl)ethanethioamide (Catalog # EN300-36372, 100 mg, 0.6 mmol) and 6-(2-chloroacetyl)-1-azatricyclo[6.3.1.0,4,12]dodeca-4(12),5,7-trien-2-one (Catalog # EN300-13775, 162 mg, 0.65 mmol).
Yield: 22%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.74 (s, 1H), 7.68 – 7.63 (m, 2H), 7.40 (ddd, J = 9.5, 6.0, 3.0 Hz, 2H), 7.21 – 7.11 (m, 2H), 4.34 (s, 2H), 3.59 (t, J = 5.8 Hz, 2H), 3.54 (s, 2H), 2.75 (t, J = 6.0 Hz, 2H), 1.91 (p, J = 5.9 Hz, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 173.7, 155.2, 141.4, 134.8, 131.4, 131.3, 128.3, 124.8, 124.1, 120.5, 120.2, 115.9, 115.8, 112.2, 38.8, 38.2, 36.4, 24.3, 21.3.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{18}FN_2OS$: 365.1; found: 365.2.

(2,3-dihydrobenzo[b][1,4]dioxin-2-yl)methyl 1-benzyl-5-methyl-1H-pyrazole-4-carboxylate – '32445, Z419297242 (Method 2).



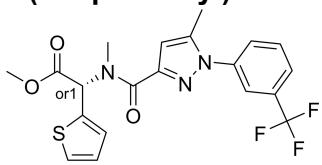
The compound was synthesized from (2,3-dihydro-1,4-benzodioxin-2-yl)methanol (Catalog # EN300-03215, 100 mg, 0.6 mmol) and 1-benzyl-5-methyl-1H-pyrazole-4-carboxylic acid (Catalog # EN300-40120, 143 mmol, 0.66 mmol).
Yield: 30%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.85 (s, 1H), 7.32 (dd, J = 8.2, 6.6 Hz, 2H), 7.31 – 7.23 (m, 1H), 7.14 – 7.09 (m, 2H), 6.91 – 6.77 (m, 4H), 5.36 (s, 2H), 4.50 (ddt, J = 7.0, 4.4, 2.7 Hz, 1H), 4.47 – 4.34 (m, 3H), 4.11 (dd, J = 11.6, 7.0 Hz, 1H), 2.45 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 163.0, 143.8, 143.3, 143.2, 141.0, 136.9, 129.1, 128.1, 127.5, 122.0, 121.8, 117.6, 117.4, 111.2, 71.3, 65.1, 62.3, 52.7, 10.7.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{21}N_2O_4$: 365.1; found: 365.2.

rac-methyl 2-(N,5-dimethyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamido)-2-(thiophen-2-yl)acetate – '3234, Z4971163234 (Method 3).



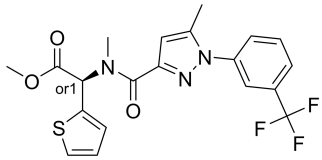
The compound was synthesized from methyl 2-(methylamino)-2-(thiophen-2-yl)acetate hydrochloride (Catalog # EN300-60031, 100 mg, 0.48 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 143 mg,0.53 mmol).
Yield: 68%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 (s, 1H), 7.99 (d, J = 2.0 Hz, 1H), 7.95 (dd, J = 7.9, 2.2 Hz, 1H), 7.89 – 7.83 (m, 1H), 7.79 (t, J = 7.9 Hz, 1H), 7.45 (dd, J = 5.1, 1.3 Hz, 1H), 7.14 (dd, J = 3.7, 1.3 Hz, 1H), 6.96 (dd, J = 5.1, 3.7 Hz, 1H), 6.71 (d, J = 0.9 Hz, 1H), 3.62 (s, 3H), 2.36 (s, 3H), 1.91 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 172.3, 161.0, 146.8, 145.2, 142.0, 139.9, 131.1, 130.7, 130.5, 129.3, 126.9, 126.4, 126.0, 125.5, 125.4, 125.0, 123.2, 122.2, 122.2, 122.2, 108.2, 59.5, 53.1, 25.7, 12.5.
LC/MS (APSI) m/z [M-H] calculated for $C_{20}H_{17}F_3N_3O_3S$: 436.1; found: 436.0.

***rel*-methyl (S)-2-(N,5-dimethyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamido)-2-(thiophen-2-yl)acetate – '6000, Z5199560000 (Method 3).**



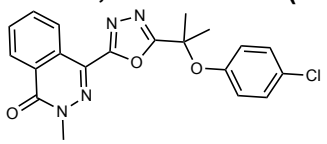
The compound was obtained by a chiral separation of Z4971163234.
Yield: 20%; purity, >95% (assessed by LC/MS).
$[\alpha]^{21}_D$ = 57.7 (c 2.0, CH_3OH).
^{1}H NMR (400 MHz, DMSO-d_6) δ 7.94 (s, 2H), 7.86 – 7.77 (m, 2H), 7.58 (s, 1H), 7.14 (d, J = 17.0 Hz, 1H), 7.04 (s, 1H), 6.72 (d, J = 16.4 Hz, 1H), 6.22 (s, 1H), 3.70 (d, J = 6.6 Hz, 3H), 3.25 (s, 2H), 2.83 (s, 1H), 2.42 (s, 1H), 2.38 (s, 2H).
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{19}F_3N_3O3S$: 438.1; found: 438.2.

***rel*-methyl (R)-2-(N,5-dimethyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamido)-2-(thiophen-2-yl)acetate – '1066, Z5199561066 (Method 3).**



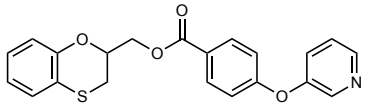
The compound was obtained by a chiral separation of Z4971163234.
Yield: 23%; purity, >95% (assessed by LC/MS).
$[\alpha]^{21}_D$ = -58.6 (c 2.0, CH_3OH).
^{1}H NMR (400 MHz, Chloroform-d) δ 7.84 (s, 1H), 7.73 (s, 1H), 7.71 – 7.58 (m, 3H), 7.25 (dd, J = 5.2, 1.3 Hz, 1H), 7.16 (dd, J = 3.6, 1.3 Hz, 1H), 6.96 (dd, J = 5.2, 3.6 Hz, 1H), 6.72 (s, 1H), 3.76 (s, 3H), 2.35 (s, 3H), 2.16 (s, 3H).
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{19}F_3N_3O_3S$: 438.1; found: 438.2.

4-(5-(2-(4-chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-yl)-2-methylphthalazin-1(2H)-one – '0450, Z685931568 (Method 1).



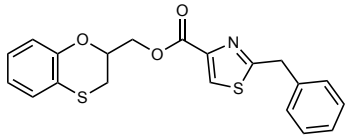
The compound was synthesized from 3-methyl-4-oxo-3,4-dihydrophthalazine-1-carbohydrazide (Catalog # EN300-04897, 112 mg. 0.51 mmol) and 2-(4-chlorophenoxy)-2-methylpropanoic acid (Catalog # EN300-18267, 100 mg, 0.47 mmol).
Yield: 24%; purity, >95% (assessed by LC/MS).
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.93 (d, J = 8.2 Hz, 1H), 8.40 (d, J = 7.8 Hz, 1H), 8.09 (t, J = 7.7 Hz, 1H), 7.99 (t, J = 7.6 Hz, 1H), 7.35 – 7.28 (m, 2H), 6.87 – 6.81 (m, 2H), 3.87 (s, 3H), 1.84 (s, 6H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 168.1, 161.8, 158.8, 153.4, 134.6, 133.0, 130.2, 129.9, 129.8, 128.5, 127.4, 127.3, 126.9, 126.6, 124.1, 123.4, 76.0, 26.0.
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{18}ClN_4O_3$: 397.1; found: 397.2.

(2,3-dihydrobenzo[b][1,4]oxathiin-2-yl)methyl 4-(pyridin-3-yloxy)benzoate – '82778, Z975741758 (Method 2).



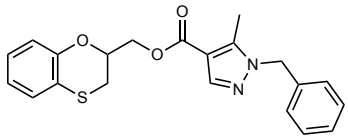
The compound was synthesized from (2,3-dihydro-1,4-benzoxathiin-2-yl)methanol (Catalog # EN300-59707, 100 mg, 0.55 mmol) and 4-(pyridin-3-yloxy)benzoic acid (Catalog # EN300-54901, 130 mg, 0.61 mmol).
Yield: 39%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.48 – 8.41 (m, 2H), 8.06 – 7.98 (m, 2H), 7.58 (ddd, J = 8.3, 2.8, 1.4 Hz, 1H), 7.51 – 7.44 (m, 1H), 7.33 (dd, J = 7.7, 1.7 Hz, 1H), 7.19 (ddd, J = 8.7, 7.3, 1.7 Hz, 1H), 7.17 – 7.10 (m, 2H), 7.05 – 6.97 (m, 2H), 5.41 (dtd, J = 7.6, 4.5, 3.1 Hz, 1H), 4.52 (dd, J = 13.3, 3.1 Hz, 1H), 4.30 (dd, J = 13.2, 4.3 Hz, 1H), 3.35 – 3.23 (m, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 164.7, 161.3, 159.3, 152.3, 146.3, 142.4, 132.4, 131.6, 128.8, 127.7, 126.8, 125.4, 125.0, 124.2, 122.3, 118.2, 73.1, 72.9, 33.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{18}NO_4S$: 380.1; found: 380.0.

(2,3-dihydrobenzo[b][1,4]oxathiin-2-yl)methyl 2-benzylthiazole-4-carboxylate – '86798, Z975742428 (Method 2).



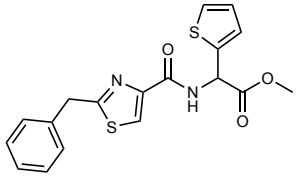
The compound was synthesized from (2,3-dihydro-1,4-benzoxathiin-2-yl)methanol (Catalog # EN300-59707, 100 mg, 0.55 mmol) and 2-benzyl-1,3-thiazole-4-carboxylic acid (Catalog # EN300-38897, 134 mg, 0.61 mmol).
Yield: 32%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.43 (d, J = 1.6 Hz, 1H), 7.38 – 7.23 (m, 6H), 7.21 – 7.13 (m, 1H), 6.99 (td, J = 7.3, 6.9, 1.3 Hz, 2H), 5.44 – 5.36 (m, 1H), 4.57 (dd, J = 13.2, 3.2 Hz, 1H), 4.38 (s, 1H), 4.26 (dd, J = 13.2, 4.3 Hz, 1H), 3.33 – 3.23 (m, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 171.6, 160.3, 159.0, 145.7, 138.2, 131.5, 130.7, 129.5, 129.2, 128.7, 127.6, 126.4, 124.1, 122.2, 73.2, 73.0, 38.9, 33.2.
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{18}NO_3S_2$: 384.1; found: 384.1.

(2,3-dihydrobenzo[b][1,4]oxathiin-2-yl)methyl 1-benzyl-5-methyl-1H-pyrazole-4-carboxylate – '7800, Z975742882 (Method 2).



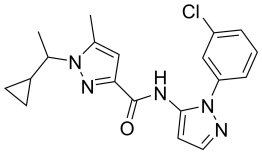
The compound was synthesized from (2,3-dihydro-1,4-benzoxathiin-2-yl)methanol (Catalog # EN300-59707, 100 mg, 0.55 mmol) and 1-benzyl-5-methyl-1H-pyrazole-4-carboxylic acid (Catalog # EN300-40120, 132 mg,0.61 mmol).
Yield: 33%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.86 (s, 1H), 7.36 – 7.23 (m, 5H), 7.18 (ddd, J = 8.6, 7.3, 1.7 Hz, 1H), 7.15 – 7.09 (m, 2H), 7.00 (t, J = 7.6 Hz, 2H), 5.35 (d, J = 19.3 Hz, 3H), 4.46 (dd, J = 13.2, 3.1 Hz, 1H), 4.24 (dd, J = 13.2, 4.5 Hz, 1H), 3.31 – 3.16 (m, 2H).
^{13}C NMR (126 MHz, Chloroform-d) δ 161.9, 158.9, 158.5, 143.3, 140.5, 136.4, 131.1, 128.6, 128.2, 127.6, 127.0, 126.4, 123.7, 121.8, 111.0, 72.7, 71.2, 52.3, 38.9, 33.1, 10.4.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{21}N_2O3S$: 381.1; found: 381.2.

methyl 2-(2-benzylthiazole-4-carboxamido)-2-(thiophen-2-yl)acetate – '61815, Z997021386 (Method 3).



The compound was synthesized from methyl 2-amino-2-(thiophen-2-yl)acetate hydrochloride (Catalog # EN300-60031, 100 mg, 0.48 mmol) and 2-benzyl-1,3-thiazole-4-carboxylic acid (Catalog # EN300-38897, 116 mg, 0.53 mmol).
Yield: 56%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.81 (d, J = 7.4 Hz, 1H), 8.21 (d, J = 1.4 Hz, 1H), 7.50 (dd, J = 5.1, 1.3 Hz, 1H), 7.38 – 7.31 (m, 4H), 7.31 – 7.23 (m, 1H), 7.18 – 7.13 (m, 1H), 7.00 (dd, J = 5.1, 3.5 Hz, 1H), 5.87 (d, J = 7.4 Hz, 1H), 4.38 (s, 2H), 3.69 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 171.6, 170.3, 160.3, 148.8, 139.0, 138.1, 129.5, 129.2, 127.6, 127.6, 127.3, 126.9, 125.7, 53.2, 52.1, 38.9, 7.4.
LC/MS (APSI) m/z [M+H] calculated for $C_{18}H_{17}N_2O_3S_2$: 373.1; found: 373.0.

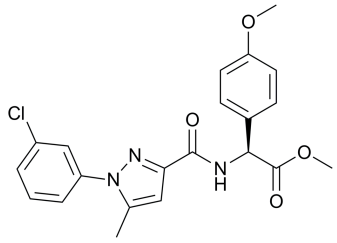
N-(1-(3-chlorophenyl)-1H-pyrazol-5-yl)-1-(1-cyclopropylethyl)-5-methyl-1H-pyrazole-3-carboxamide – 7902, Z1607601216 (Method 3).



The compound was synthesized from 1-(3-chlorophenyl)-1H-pyrazol-5-amine (Catalog # EN300-68701, 100 mg, 0.52 mmol) and 1-(1-cyclopropylethyl)-5-methyl-1H-pyrazole-3-carboxylic acid (Catalog # EN300-124358 111 mg,0.57 mmol).
Yield: 15%; purity, 92% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.88 (s, 1H), 7.74 – 7.66 (m, 2H), 7.58 – 7.53 (m, 1H), 7.49 (t, J = 8.0 Hz, 1H), 7.43 (dt, J = 7.9, 1.3 Hz, 1H), 6.50 – 6.43 (m, 2H), 3.74 (q, J = 7.1, 6.7 Hz, 1H),

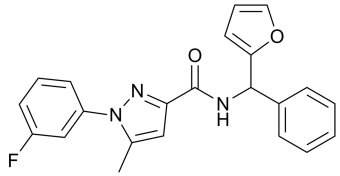
2.24 (s, 3H), 1.47 (d, *J* = 6.7 Hz, 3H), 1.35 (d, *J* = 9.2 Hz, 1H), 0.56 (dp, *J* = 8.3, 4.1 Hz, 1H), 0.32 (dddt, *J* = 35.6, 13.6, 9.2, 4.2 Hz, 3H).
^{13}C NMR (126 MHz, DMSO-d_6) δ 140.3, 139.7, 136.1, 130.8, 127.1, 122.9, 121.8, 105.6, 103.3, 58.5, 20.5, 17.2, 10.6, 3.7, 3.4.
LC/MS (APSI) m/z [M+H] calculated for $C_{19}H_{21}ClN_5O$: 370.1; found: 370.2.

(S)-methyl 2-(1-(3-chlorophenyl)-5-methyl-1H-pyrazole-3-carboxamido)-2-(4-methoxyphenyl)acetate – 69543, Z1607615042 (Method 3).



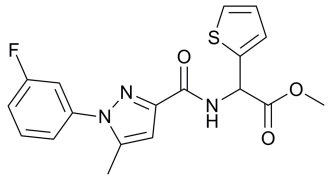
The compound was synthesized from methyl (2S)-2-amino-2-(4-methoxyphenyl)acetate hydrochloride (Catalog # EN300-7466819, 100 mg, 0.43 mmol) and 1-(3-chlorophenyl)-5-methyl-1H-pyrazole-3-carboxylic acid (Catalog # EN300-127105, 112 mg,0.48 mmol).
Yield: 19%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.52 (d, *J* = 7.4 Hz, 1H), 7.75 (t, *J* = 1.9 Hz, 1H), 7.62 – 7.51 (m, 3H), 7.39 – 7.33 (m, 2H), 6.94 – 6.88 (m, 2H), 6.69 (s, 1H), 5.57 (d, *J* = 7.4 Hz, 1H), 3.73 (s, 3H), 3.63 (s, 3H), 2.35 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 171.5, 161.3, 159.6, 146.5, 141.7, 140.6, 134.0, 131.4, 129.7, 129.0, 128.7, 125.2, 123.8, 114.4, 108.1, 55.9, 55.6, 52.8, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{21}ClN_3O_4$: 414.1; found: 414.0.

1-(3-fluorophenyl)-N-(furan-2-yl(phenyl)methyl)-5-methyl-1H-pyrazole-3-carboxamide – 88684, Z1614809888 (Method 3).



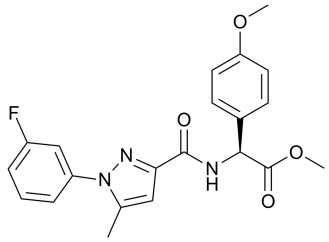
The compound was synthesized from (furan-2-yl)(phenyl)methanamine (Catalog # EN300-14256, 100 mg, 0.58 mmol) and 1-(3-fluorophenyl)-5-methyl-1H-pyrazole-3-carboxylic acid (Catalog # EN300-127391, 140 mg, 0.64 mmol).
Yield: 58%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.94 (d, *J* = 8.9 Hz, 1H), 7.63 – 7.53 (m, 3H), 7.51 – 7.45 (m, 1H), 7.45 – 7.38 (m, 2H), 7.38 – 7.24 (m, 4H), 6.71 (d, *J* = 1.0 Hz, 1H), 6.41 – 6.34 (m, 2H), 6.17 – 6.13 (m, 1H), 2.36 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 163.3, 161.1, 154.6, 146.9, 143.0, 141.5, 140.9, 131.5, 128.8, 127.9, 127.9, 121.2, 121.2, 115.6, 112.8, 110.9, 108.2, 50.6, 12.6.
LC/MS (APSI) m/z [M+H] calculated for $C_{22}H_{19}FN_3O_2$: 376.1; found: 376.2.

methyl 2-(1-(3-fluorophenyl)-5-methyl-1H-pyrazole-3-carboxamido)-2-(thiophen-2-yl)acetate – 51486, Z1615048293 (Method 3).



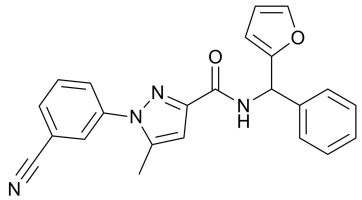
The compound was synthesized from methyl 2-amino-2-(thiophen-2-yl)acetate hydrochloride (Catalog # EN300-60031, 100 mg, 0.48 mmol) and 1-(3-fluorophenyl)-5-methyl-1H-pyrazole-3-carboxylic acid (Catalog # EN300-127391, 117 mg, 0.53 mmol).
Yield: 55%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (d, J = 7.5 Hz, 1H), 7.63 – 7.54 (m, 2H), 7.51 – 7.45 (m, 2H), 7.33 (td, J = 8.6, 2.5 Hz, 1H), 7.15 (d, J = 3.5 Hz, 1H), 6.99 (dd, J = 5.1, 3.5 Hz, 1H), 6.72 (s, 1H), 5.87 (d, J = 7.5 Hz, 1H), 3.68 (s, 3H), 2.36 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 170.4, 161.3, 146.3, 141.8, 139.0, 131.4, 127.6, 126.9, 121.3, 115.7, 112.6, 108.1, 53.1, 51.9, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{18}H_{17}FN_3O_3S$: 374.1; found: 374.0.

methyl (S)-2-(1-(3-fluorophenyl)-5-methyl-1H-pyrazole-3-carboxamido)-2-(4-methoxyphenyl)acetate – 59513, Z1615091760 (Method 3).



The compound was synthesized from methyl (2S)-2-amino-2-(4-methoxyphenyl)acetate hydrochloride (Catalog # EN300-7466819, 100 mg, 0.48 mmol) and 1-(3-fluorophenyl)-5-methyl-1H-pyrazole-3-carboxylic acid (Catalog # EN300-127391, 116 mg, 0.53 mmol).
Yield: 21%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.50 (dd, J = 7.2, 1.5 Hz, 1H), 7.62 – 7.53 (m, 2H), 7.47 (ddd, J = 8.1, 2.5, 1.2 Hz, 1H), 7.41 – 7.29 (m, 3H), 6.95 – 6.88 (m, 2H), 6.69 (d, J = 1.1 Hz, 1H), 5.57 (dd, J = 7.4, 1.3 Hz, 1H), 3.73 (d, J = 1.3 Hz, 3H), 3.63 (d, J = 1.3 Hz, 3H), 2.36 (d, J = 1.3 Hz, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 171.5, 161.3, 159.6, 146.5, 141.7, 131.5, 129.7, 129.0, 121.3, 115.7, 114.4, 112.8, 108.0, 55.8, 55.6, 52.8, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{21}FN_3O_4$: 398.2; found: 398.0.

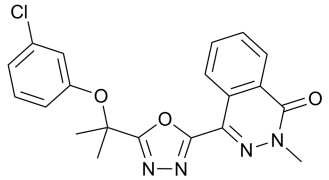
1-(3-cyanophenyl)-N-(furan-2-yl(phenyl)methyl)-5-methyl-1H-pyrazole-3-carboxamide – 12565, Z1627119982 (Method 3).



The compound was synthesized from (furan-2-yl)(phenyl)methanamine hydrochloride (Catalog # EN300-6734468, 100 mg, 0.48 mmol) and 1-(3-cyanophenyl)-5-methyl-1H-pyrazole-3-carboxylic acid (Catalog # EN300-128852, 119 mg, 0.53 mmol).

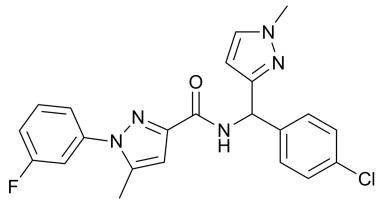
Yield: 51%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.98 (d, J = 8.9 Hz, 1H), 8.20 (t, J = 1.9 Hz, 1H), 8.03 – 7.97 (m, 1H), 7.93 (dt, J = 7.8, 1.3 Hz, 1H), 7.74 (t, J = 8.0 Hz, 1H), 7.61 (d, J = 1.8 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.35 (t, J = 7.6 Hz, 2H), 7.31 – 7.25 (m, 1H), 6.73 (s, 1H), 6.41 – 6.34 (m, 2H), 6.14 (d, J = 3.3 Hz, 1H), 2.38 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 161.0, 154.6, 147.2, 143.0, 141.7, 140.0, 132.3, 131.1, 129.8, 128.8, 128.5, 128.0, 127.8, 118.4, 112.8, 110.9, 108.1, 50.6, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{23}H_{19}N_4O_2$: 383.2; found: 383.1.

4-(5-(2-(3-chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-yl)-2-methylphthalazin-1(2H)-one – 0450_22, Z1664062039 (Method 1).



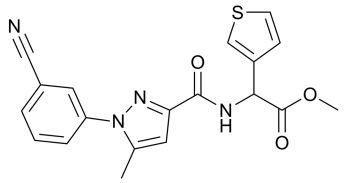
The compound was synthesized from 3-methyl-4-oxo-3,4-dihydrophthalazine-1-carbohydrazide (Catalog # EN300-04897, 112 mg, 0.51 mmol) and 2-(4-chlorophenoxy)-2-methylpropanoic acid (Catalog # EN300-18267, 100 mg, 0.47 mmol).
Yield: 48%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.88 (d, J = 8.2 Hz, 1H), 8.35 (dd, J = 8.0, 1.5 Hz, 1H), 8.05 (ddd, J = 8.4, 7.2, 1.4 Hz, 1H), 7.99 – 7.92 (m, 1H), 7.27 (t, J = 8.1 Hz, 1H), 7.15 (ddd, J = 8.1, 2.1, 0.9 Hz, 1H), 6.95 (t, J = 2.2 Hz, 1H), 6.78 – 6.72 (m, 1H), 3.84 (s, 3H), 1.84 (s, 6H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 168.1, 161.7, 158.8, 155.5, 134.6, 133.8, 133.0, 131.4, 130.2, 127.4, 126.9, 126.6, 124.6, 122.5, 120.8, 76.2, 26.0.
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{18}ClN_4O_3$: 397.1; found: 397.0.

N-((4-chlorophenyl)(1-methyl-1H-pyrazol-3-yl)methyl)-1-(3-fluorophenyl)-5-methyl-1H-pyrazole-3-carboxamide – 17429, Z1686630553 (Method 3).



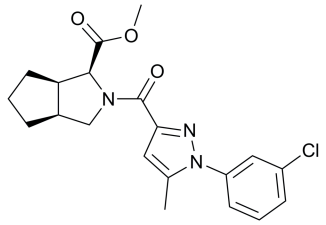
The compound was synthesized from (4-chlorophenyl)(1-methyl-1H-pyrazol-3-yl)methanamine (Catalog # EN300-126692, 100 mg, 0.45 mmol) and 1-(3-fluorophenyl)-5-methyl-1H-pyrazole-3-carboxylic acid (Catalog # EN300-127391, 110 mg, 0.5 mmol).
Yield: 42%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (d, J = 8.4 Hz, 1H), 7.63 – 7.53 (m, 3H), 7.50 – 7.45 (m, 1H), 7.41 – 7.30 (m, 5H), 6.68 (s, 1H), 6.25 (d, J = 8.3 Hz, 1H), 6.18 (d, J = 2.2 Hz, 1H), 3.78 (s, 3H), 2.35 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 160.9, 151.7, 146.9, 141.7, 132.2, 131.5, 129.4, 128.6, 121.4, 115.7, 112.9, 108.0, 104.3, 50.8, 38.9, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{22}H_{20}ClFN_5O$: 424.1; found: 424.2.

methyl 2-(1-(3-cyanophenyl)-5-methyl-1H-pyrazole-3-carboxamido)-2-(thiophen-3-yl)acetate – 31604, Z1711777464 (Method 3).



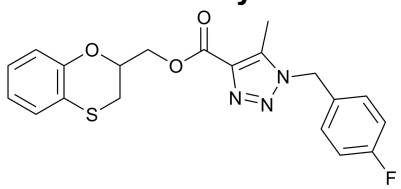
The compound was synthesized from methyl 2-amino-2-(thiophen-3-yl)acetate hydrochloride (Catalog # EN300-140330, 100 mg, 0.48 mmol) and 1-(3-cyanophenyl)-5-methyl-1H-pyrazole-3-carboxylic acid (Catalog # EN300-128852, 120 mg, 0.53 mmol).
Yield: 64%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.70 (d, J = 7.7 Hz, 1H), 8.20 (t, J = 2.0 Hz, 1H), 7.99 (ddd, J = 8.2, 2.3, 1.1 Hz, 1H), 7.94 (dt, J = 7.8, 1.4 Hz, 1H), 7.75 (t, J = 8.0 Hz, 1H), 7.60 – 7.54 (m, 1H), 7.52 (dd, J = 5.0, 2.9 Hz, 1H), 7.19 (dd, J = 5.0, 1.4 Hz, 1H), 6.73 (s, 1H), 5.76 (d, J = 7.7 Hz, 1H), 3.66 (s, 3H), 2.38 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 171.0, 161.3, 146.8, 141.9, 140.0, 137.0, 132.4, 131.2, 129.9, 128.5, 127.9, 127.1, 124.7, 118.4, 112.8, 108.3, 52.9, 52.1, 12.5.
LC/MS (APSI) m/z [M+H] calculated for C19H17N4O3S: 381.1; found: 381.0.

methyl (1S,3aS,6aR)-2-(1-(3-chlorophenyl)-5-methyl-1H-pyrazole-3-carbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylate – 10010, Z1817976028 (Method 3).



The compound was synthesized from methyl rac-methyl (1R,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylate hydrochloride (Catalog # EN300-6491228, 100 mg, 0.49 mmol) and 1-(3-chlorophenyl)-5-methyl-1H-pyrazole-3-carboxylic acid (Catalog # EN300-127105, 127 mg, 0.54 mmol).
Yield: 36%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.62 (q, J = 1.7 Hz, 1H), 7.59 – 7.49 (m, 3H), 6.64 (s, 1H), 5.32 (d, J = 9.2 Hz, 1H), 4.72 (d, J = 8.8 Hz, 1H), 3.63 (d, J = 1.1 Hz, 2H), 3.50 (d, J = 1.2 Hz, 2H), 3.05 (ddd, J = 31.7, 14.3, 8.7 Hz, 1H), 2.80 – 2.74 (m, 1H), 2.64 (td, J = 8.6, 3.6 Hz, 1H), 2.35 (d, J = 12.4 Hz, 3H), 1.69 (tdd, J = 13.9, 10.2, 6.1 Hz, 2H), 1.62 – 1.52 (m, 2H), 1.38 – 1.29 (m, 1H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 172.6, 161.2, 147.9, 134.0, 131.5, 128.7, 124.3, 122.9, 110.3, 64.1, 51.9, 44.3, 41.0, 29.3, 27.8, 26.2, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{23}ClN_3O_3$: 388.1; found: 388.0.

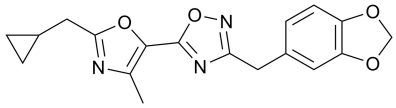
(2,3-dihydrobenzo[b][1,4]oxathiin-2-yl)methyl 1-(4-fluorobenzyl)-5-methyl-1H-1,2,3-triazole-4-carboxylate – 61926, Z1895651057 (Method 2).



The compound was synthesized from methyl (2,3-dihydro-1,4-benzoxathiin-2-yl)methanol (Catalog # EN300-59707, 100 mg, 0.55 mmol) and 1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Catalog # EN300-180745, 142 mg, 0.6 mmol).

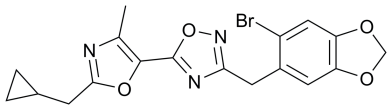
Yield: 28%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.35 – 7.24 (m, 3H), 7.19 (td, *J* = 8.8, 2.5 Hz, 3H), 7.00 (t, *J* = 7.6 Hz, 2H), 5.64 (s, 2H), 5.43 (qd, *J* = 4.5, 2.2 Hz, 1H), 4.48 (dd, *J* = 13.2, 3.1 Hz, 1H), 4.29 (dd, *J* = 13.2, 4.4 Hz, 1H), 3.31 – 3.21 (m, 2H), 2.50 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 160.5, 159.4, 139.5, 136.1, 131.7, 130.2, 128.8, 126.8, 124.2, 122.3, 116.1, 72.6, 50.5, 33.5, 9.4.
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{19}FN_3O_3S$: 400.1; found: 400.2.

3-(benzo[d][1,3]dioxol-5-ylmethyl)-5-(2-(cyclopropylmethyl)-4-methyloxazol-5-yl)-1,2,4-oxadiazole – 97058, Z2156297058 (Method 5).



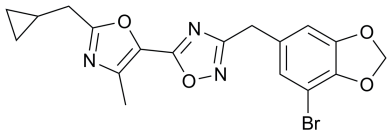
The compound was synthesized from 2-(1,3-dioxaindan-5-yl)acetonitrile (Catalog # EN300-26831, 100 mg, 0.62 mmol) and 2-(cyclopropylmethyl)-4-methyl-1,3-oxazole-5-carboxylic acid (Catalog # EN300-172627, 124 mg, 0.68 mmol).
Yield: 19%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 6.88 (d, *J* = 1.7 Hz, 1H), 6.85 (d, *J* = 7.9 Hz, 1H), 6.78 (dd, *J* = 7.9, 1.8 Hz, 1H), 5.97 (s, 2H), 4.05 (s, 2H), 2.75 (d, *J* = 7.0 Hz, 2H), 2.43 (s, 3H), 1.09 (tq, *J* = 10.2, 3.6, 2.6 Hz, 1H), 0.56 – 0.45 (m, 2H), 0.24 (dt, *J* = 6.1, 4.3 Hz, 2H).
^{13}C NMR (126 MHz, DMSO-d_6) δ 170.1, 167.2, 166.7, 147.8, 146.6, 144.4, 133.2, 129.5, 122.5, 109.8, 108.7, 101.4, 32.4, 31.2, 13.1, 8.7, 4.9.
LC/MS (APSI) m/z [M+H] calculated for $C_{18}H_{18}N_3O_4$: 340.1; found: 340.0.

3-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)-5-(2-(cyclopropylmethyl)-4-methyloxazol-5-yl)-1,2,4-oxadiazole – 7019, Z2157628646 (Method 5).



The compound was synthesized from 2-(6-bromo-1,3-dioxaindan-5-yl)acetonitrile (Catalog # EN300-53536, 100 mg, 0.42 mmol) and 2-(cyclopropylmethyl)-4-methyl-1,3-oxazole-5-carboxylic acid (Catalog # EN300-172627, 83 mg, 0.46 mmol).
Yield: 34%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.21 (d, *J* = 1.5 Hz, 1H), 7.05 (s, 1H), 6.06 (s, 2H), 4.16 (s, 2H), 2.75 (d, *J* = 7.0 Hz, 2H), 2.43 (s, 3H), 1.14 – 1.05 (m, 1H), 0.55 – 0.46 (m, 2H), 0.27 – 0.21 (m, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 169.2, 167.3, 166.7, 148.0, 147.7, 144.5, 133.1, 128.2, 114.9, 112.8, 111.5, 102.5, 32.4, 32.4, 13.1, 8.7, 4.9.
LC/MS (APSI) m/z [M+H] calculated for $C_{18}H_{17}BrN_3O_4$: 420.0; found: 420.0.

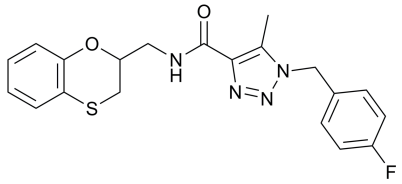
3-((7-bromobenzo[d][1,3]dioxol-5-yl)methyl)-5-(2-(cyclopropylmethyl)-4-methyloxazol-5-yl)-1,2,4-oxadiazole – 53217, Z2157653217 (Method 5).



The compound was synthesized from 2-(7-bromo-1,3-dioxaindan-5-yl)acetonitrile (Catalog # EN300-54744, 100 mg, 0.42 mmol) and 2-(cyclopropylmethyl)-4-methyl-1,3-oxazole-5-carboxylic acid (Catalog # EN300-172627, 83 mg, 0.46 mmol).
Yield: 12%; purity, >95% (assessed by LC/MS).

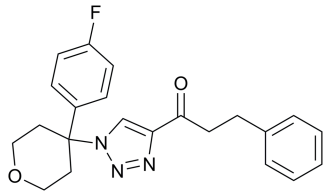
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.02 (d, J = 1.5 Hz, 1H), 6.90 (d, J = 1.5 Hz, 1H), 6.09 (s, 2H), 4.08 (s, 2H), 2.76 (d, J = 7.0 Hz, 2H), 2.43 (s, 3H), 1.14 – 1.01 (m, 1H), 0.55 – 0.46 (m, 2H), 0.27 – 0.21 (m, 2H).
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.3, 166.7, 166.3, 148.0, 144.6, 144.0, 132.6, 130.9, 124.7, 108.8, 101.7, 99.4, 31.9, 30.4, 12.6, 8.2, 4.4.
LC/MS (APSI) m/z [M+H] calculated for $C_{18}H_{17}BrN_3O_4$: 420.0; found: 420.0.

N-((2,3-dihydrobenzo[b][1,4]oxathiin-2-yl)methyl)-1-(4-fluorobenzyl)-5-methyl-1H-1,2,3-triazole-4-carboxamide – 22139, Z2454164835 (Method 3).



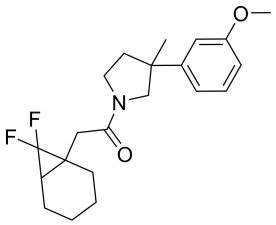
The compound was synthesized from (2,3-dihydro-1,4-benzoxathiin-2-yl)methanamine hydrochloride (Catalog # EN300-258384, 100 mg, 0.46 mmol) and 1-[(4-fluorophenyl)methyl]-5-methyl-1H-1,2,3-triazole-4-carboxylic acid (Catalog # EN300-180745, 120 mg, 0.51 mmol).
Yield: 42%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.68 (t, J = 6.1 Hz, 1H), 7.26 (dd, J = 8.6, 5.6 Hz, 2H), 7.22 – 7.14 (m, 2H), 7.06 (dd, J = 7.7, 1.6 Hz, 1H), 6.97 (tt, J = 7.2, 3.6 Hz, 1H), 6.86 – 6.76 (m, 2H), 5.61 (s, 2H), 4.33 (dtd, J = 8.3, 6.2, 2.0 Hz, 1H), 3.62 (dt, J = 13.7, 6.0 Hz, 1H), 3.53 (dt, J = 13.1, 6.3 Hz, 1H), 3.17 (dd, J = 13.2, 2.1 Hz, 1H), 2.96 (dd, J = 13.3, 8.5 Hz, 1H), 2.46 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 161.7, 151.5, 138.6, 136.6, 130.2, 127.6, 126.1, 121.9, 118.7, 117.8, 116.2, 73.5, 50.3, 42.4, 27.6, 8.8.
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{20}FN_4O_2S$: 399.1; found: 399.0.

1-(1-(4-(4-fluorophenyl)tetrahydro-2H-pyran-4-yl)-1H-1,2,3-triazol-4-yl)-3-phenylpropan-1-one – 7337, Z2527311170 (Method 6).



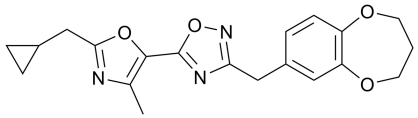
The compound was synthesized from 4-azido-4-(4-fluorophenyl)oxane (Catalog # EN300-71746, 100 mg, 0.45 mmol) and 5-phenylpent-1-yn-3-one (Catalog # EN300-180283, 78 mg, 0.5 mmol).
Yield: 27%; purity, >95% (assessed by LC/MS).
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.97 (s, 1H), 7.30 (dd, J = 8.7, 5.3 Hz, 2H), 7.23 (d, J = 5.2 Hz, 4H), 7.14 (s, 1H), 7.07 (t, J = 8.6 Hz, 2H), 3.82 (d, J = 12.0 Hz, 2H), 3.43 – 3.31 (m, 4H), 3.03 – 2.95 (m, 6H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 193.4, 147.6, 141.5, 139.9, 128.8, 128.7, 127.8, 127.1, 126.4, 116.1, 64.6, 63.4, 41.1, 35.6, 29.5.
LC/MS (APSI) m/z [M+Na] calculated for $C_{22}H_{22}FN_3NaO_2$: 402.2; found: 402.0.

2-(7,7-difluorobicyclo[4.1.0]heptan-1-yl)-1-(3-(3-methoxyphenyl)-3-methylpyrrolidin-1-yl)ethan-1-one – 7218, Z2645906126 (Method 3).



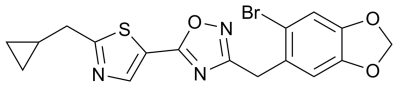
The compound was synthesized from 3-(3-methoxyphenyl)-3-methylpyrrolidine hydrochloride (Catalog # EN300-304264, 100 mg, 0.44 mmol) and 2-{7,7-difluorobicyclo[4.1.0]heptan-1-yl}acetic acid (Catalog # EN300-298624, 92 mg, 0.48 mmol).
Yield: 56%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.23 (tt, J = 7.9, 2.2 Hz, 1H), 6.89 – 6.79 (m, 2H), 6.81 – 6.75 (m, 1H), 3.73 (dd, J = 2.3, 1.5 Hz, 3H), 3.68 – 3.64 (m, 1H), 3.64 – 3.60 (m, 1H), 3.51 (d, J = 9.7 Hz, 1H), 3.42 (q, J = 3.9 Hz, 1H), 3.42 – 3.36 (m, 1H), 2.64 – 2.51 (m, 1H), 2.51 – 2.30 (m, 1H), 2.19 – 2.08 (m, 1H), 2.10 – 1.99 (m, 1H), 1.73 (td, J = 12.8, 5.9 Hz, 1H), 1.60 – 1.52 (m, 1H), 1.38 (dtd, J = 12.6, 8.9, 7.7, 4.7 Hz, 1H), 1.28 (s, 4H), 1.24 (dd, J = 4.5, 2.4 Hz, 3H), 1.18 (tt, J = 14.0, 7.8 Hz, 1H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 159.7, 149.0, 129.8, 118.3, 112.4, 111.8, 55.4, 46.4, 44.4, 38.7, 37.8, 36.0, 27.7, 23.5, 23.0, 21.0.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{28}F_2NO_2$: 364.2; found: 364.2.

5-(2-(cyclopropylmethyl)-4-methyloxazol-5-yl)-3-((3,4-dihydro-2H-benzo[b][1,4]dioxepin-7-yl)methyl)-1,2,4-oxadiazole – 7019_1, Z3555992696 (Method 5).



The compound was synthesized from 2-(3,4-dihydro-2H-1,5-benzodioxepin-7-yl)acetonitrile (Catalog # EN300-1602849, 100 mg, 0.53 mmol) and 2-(cyclopropylmethyl)-4-methyl-1,3-oxazole-5-carboxylic acid (Catalog # EN300-172627, 105 mg, 0.58 mmol).
Yield: 19%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 6.93 – 6.86 (m, 2H), 6.86 (dd, J = 8.2, 2.1 Hz, 1H), 4.11 – 4.01 (m, 6H), 2.75 (d, J = 7.1 Hz, 2H), 2.43 (s, 2H), 2.42 (s, 1H), 2.06 (p, J = 5.5 Hz, 2H), 1.14 – 1.05 (m, 1H), 0.55 – 0.46 (m, 2H), 0.27 – 0.21 (m, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 169.9, 167.2, 166.7, 151.3, 150.4, 144.4, 133.2, 131.0, 124.2, 122.4, 122.1, 70.9, 70.8, 32.4, 32.0, 30.7, 13.1, 8.7, 4.9.
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{22}N_3O_4$: 368.2; found: 368.2.

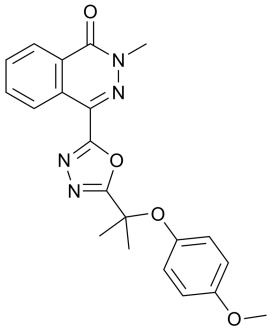
3-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)-5-(2-(cyclopropylmethyl)thiazol-5-yl)-1,2,4-oxadiazole – 7019_analog_11, Z4766160626 (Method 5).



The compound was synthesized from 2-(6-bromo-1,3-dioxaindan-5-yl)acetonitrile (Catalog # EN300-53536, 100 mg, 0.42 mmol) and 2-(cyclopropylmethyl)-1,3-thiazole-5-carboxylic acid (Catalog # EN300-379019, 84 mg, 0.46 mmol).
Yield: 17%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.53 (s, 1H), 7.22 (s, 1H), 7.06 (s, 1H), 6.06 (s, 2H), 4.15 (s, 2H), 2.97 (d, J = 7.1 Hz, 2H), 1.19 – 1.08 (m, 1H), 0.63 – 0.54 (m, 2H), 0.33 (dt, J = 5.9, 2.9 Hz, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 178.0, 169.8, 169.5, 148.0, 147.7, 147.1, 128.1, 120.4, 114.9, 112.8, 111.5, 102.5, 37.7, 32.4, 11.2, 5.3.

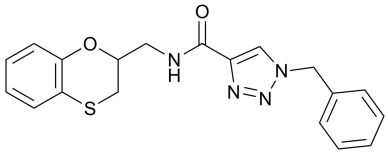
LC/MS (APSI) m/z [M+H] calculated for $C_{17}H_{15}BrN_3O_3S$: 420.0; found: 420.0.

4-(5-(2-(4-methoxyphenoxy)propan-2-yl)-1,3,4-oxadiazol-2-yl)-2-methylphthalazin-1(2H)-one – 9753, Z4877479753 (Method 1).



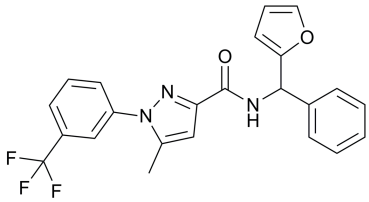
The compound was synthesized from 3-methyl-4-oxo-3,4-dihydrophthalazine-1-carbohydrazide (Catalog # EN300-04897, 114 mg, 0.52 mmol) and 2-(4-methoxyphenoxy)-2-methylpropanoic acid (Catalog # EN300-298355, 100 mg, 0.48 mmol).
Yield: 11%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.87 (d, J = 7.8 Hz, 1H), 8.35 (s, 1H), 8.03 (s, 1H), 7.95 (s, 1H), 6.79 (d, J = 8.3 Hz, 2H), 6.71 (d, J = 9.3 Hz, 2H), 3.85 (s, 3H), 3.66 (s, 3H), 1.79 (s, 6H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 158.8, 156.4, 147.7, 134.6, 133.0, 127.4, 126.9, 126.6, 124.1, 114.8, 75.8, 55.7, 25.9.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{21}N_4O_4$: 393.2; found: 393.0.

1-benzyl-N-((2,3-dihydrobenzo[b][1,4]oxathiin-2-yl)methyl)-1H-1,2,3-triazole-4-carboxamide – 78184, Z4877482092 (Method 3).



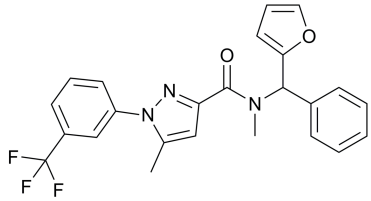
The compound was synthesized from (2,3-dihydro-1,4-benzoxathiin-2-yl)methanamine hydrochloride (Catalog # EN300-258384, 100 mg, 0.46 mmol) and 1-benzyl-1H-1,2,3-triazole-4-carboxylic acid (Catalog # EN300-26964, 103 mg, 0.51 mmol).
Yield: 72%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.75 (t, J = 6.0 Hz, 1H), 8.67 (d, J = 2.7 Hz, 1H), 7.40 – 7.29 (m, 5H), 7.05 (dd, J = 7.8, 1.8 Hz, 1H), 6.97 (td, J = 7.8, 1.8 Hz, 1H), 6.86 – 6.77 (m, 2H), 5.64 (s, 2H), 4.37 – 4.29 (m, 1H), 3.63 (dt, J = 12.6, 6.0 Hz, 1H), 3.52 (dt, J = 13.2, 6.1 Hz, 1H), 3.17 (dd, J = 13.4, 2.3 Hz, 1H), 2.97 (dd, J = 13.2, 8.4 Hz, 1H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 160.5, 151.4, 143.2, 136.1, 129.3, 128.7, 128.5, 127.6, 127.2, 126.1, 121.9, 118.7, 117.7, 73.4, 53.6, 42.6, 27.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{19}H_{19}N_4O_2S$+: 367.1; found: 367.4.

N-(furan-2-yl(phenyl)methyl)-5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamide – 1486_32, Z4967431081 (Method 3).



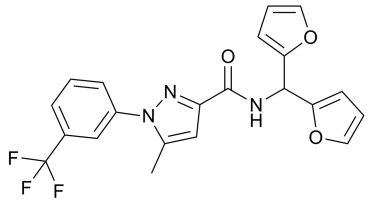
The compound was synthesized from (furan-2-yl)(phenyl)methanamine hydrochloride (Catalog # EN300-6734468, 100 mg, 0.48 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 142 mg, 0.53 mmol).
Yield: 54%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.01 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 2.0 Hz, 1H), 7.98 – 7.93 (m, 1H), 7.87 – 7.82 (m, 1H), 7.78 (t, J = 7.9 Hz, 1H), 7.61 (dd, J = 1.9, 0.9 Hz, 1H), 7.44 – 7.39 (m, 2H), 7.34 (t, J = 7.5 Hz, 2H), 7.31 – 7.24 (m, 1H), 6.74 (d, J = 1.0 Hz, 1H), 6.41 – 6.35 (m, 2H), 6.16 – 6.11 (m, 1H), 2.36 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 161.1, 154.6, 147.2, 143.0, 141.7, 140.4, 140.0, 131.1, 129.2, 128.8, 127.9, 127.9, 125.3, 110.9, 108.3, 108.2, 50.6, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{23}H_{19}F_3N_3O_2$: 426.1; found: 426.2.

N-(furan-2-yl(phenyl)methyl)-N,5-dimethyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamide – 1486_33, Z4967431082 (Method 3).



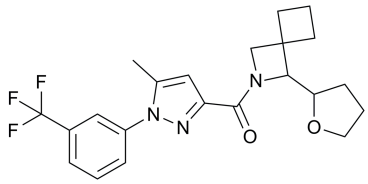
The compound was synthesized from [(furan-2-yl)(phenyl)methyl](methyl)amine (Catalog # EN300-8510002, 100 mg, 0.53 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 159 mg, 0.59 mmol).
Yield: 67%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.95 – 7.89 (m, 1H), 7.89 – 7.79 (m, 1H), 7.79 (s, 1H), 7.79 – 7.66 (m, 2H), 7.38 (dq, J = 13.0, 7.4, 5.5 Hz, 3H), 7.31 (q, J = 7.7 Hz, 1H), 7.23 – 7.17 (m, 2H), 7.04 (s, 1H), 6.69 (d, J = 15.3 Hz, 1H), 6.48 (dt, J = 10.4, 2.6 Hz, 1H), 3.10 (s, 2H), 2.81 (s, 1H), 2.38 (d, J = 8.2 Hz, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 163.7, 152.8, 147.7, 143.8, 140.8, 140.0, 137.7, 131.2, 129.2, 128.4, 128.2, 127.9, 125.0, 121.8, 111.0, 110.2, 110.0, 59.1, 34.0, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{24}H_{21}F_3N_3O_2$: 440.2; found: 440.0.

N-(di(furan-2-yl)methyl)-5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamide – 1486_41, Z4967431090 (Method 3).



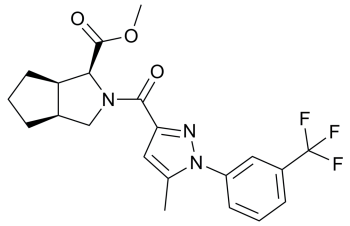
The compound was synthesized from bis(furan-2-yl)methanamine (Catalog # EN300-1258794, 100 mg, 0.61 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 182 mg, 0.67 mmol).
Yield: 54%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.95 (d, J = 8.9 Hz, 1H), 8.00 (s, 1H), 7.95 (d, J = 8.0 Hz, 1H), 7.84 (d, J = 7.8 Hz, 1H), 7.78 (t, J = 7.9 Hz, 1H), 7.62 (d, J = 1.8 Hz, 2H), 6.76 (s, 1H), 6.46 (d, J = 8.8 Hz, 1H), 6.42 (t, J = 2.6 Hz, 2H), 6.32 (d, J = 3.2 Hz, 2H), 2.37 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 161.0, 152.3, 146.9, 143.1, 141.7, 140.0, 131.0, 129.1, 125.3, 123.2, 122.0, 111.0, 108.4, 108.1, 44.8, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{17}F_3N_3O_3$: 416.4; found: 416.1.

(5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)(1-(tetrahydrofuran-2-yl)-2-azaspiro[3.3]heptan-2-yl)methanone – 10010_03, Z5030903737 (Method 3).



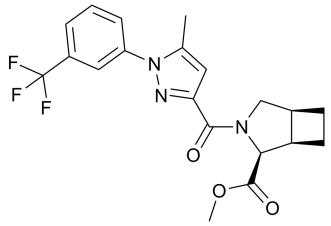
The compound was synthesized from 1-(oxolan-2-yl)-2-azaspiro[3.3]heptane (Catalog # EN300-216770, 100 mg, 0.6 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 178 mg, 0.66 mmol).
Yield: 66%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.92 (d, *J* = 9.4 Hz, 2H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.79 (t, *J* = 7.8 Hz, 1H), 6.63 (s, 1H), 4.41 – 4.28 (m, 1H), 4.06 (d, *J* = 3.4 Hz, 2H), 3.80 (q, *J* = 7.0 Hz, 1H), 3.67 (td, *J* = 16.1, 14.2, 7.2 Hz, 1H), 2.47 – 2.40 (m, 1H), 2.36 (s, 4H), 2.08 (s, 3H), 1.88 (d, *J* = 8.1 Hz, 3H), 1.74 (dq, *J* = 13.2, 7.2, 6.2 Hz, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 163.1 – 163.0 (m), 141.0, 140.1, 131.2, 129.2, 125.2, 121.6, 109.3, 79.0, 71.7, 68.0, 65.6, 42.2, 34.2, 29.5, 28.7, 25.6, 16.5, 12.4.
LC/MS (APSI) m/z [M+H] calculated for $C_{22}H_{25}F_3N_3O_2$: 420.2; found: 420.2.

methyl (1S,3aS,6aR)-2-(5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carbonyl)octahydrocyclopenta[c]pyrrole-1-carboxylate – 10010_01, Z5030906439 (Method 3).



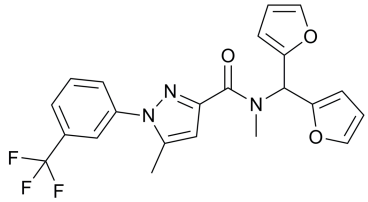
The compound was synthesized from rac-methyl (1R,3aR,6aS)-octahydrocyclopenta[c]pyrrole-1-carboxylate hydrochloride (Catalog # EN300-6491228, 100 mg, 0.49 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 145 mg, 0.54 mmol).
Yield: 64%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 – 7.91 (m, 1H), 7.90 – 7.75 (m, 3H), 6.68 – 6.64 (m, 1H), 5.33 (d, *J* = 9.3 Hz, 1H), 4.44 (dd, *J* = 11.6, 8.7 Hz, 1H), 4.16 (dd, *J* = 12.1, 8.8 Hz, 1H), 3.63 (s, 1H), 3.45 (s, 1H), 3.39 (dd, *J* = 11.7, 8.9 Hz, 1H), 3.12 – 2.98 (m, 1H), 2.89 (p, *J* = 8.3 Hz, 1H), 2.37 (d, *J* = 11.5 Hz, 3H), 1.69 (tdd, *J* = 19.5, 9.5, 5.5 Hz, 2H), 1.64 – 1.52 (m, 2H), 1.49 (dddd, *J* = 15.6, 13.0, 6.8, 3.7 Hz, 1H), 1.38 – 1.29 (m, 1H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 172.6, 161.2, 148.2, 140.9, 140.1, 131.2, 129.3, 125.3, 121.2, 110.4, 110.1, 64.1, 54.3, 51.9, 44.3, 41.0, 29.4, 28.3, 26.2, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{23}F_3N_3O_3$: 422.2; found: 422.1.

methyl (1R,2S,5S)-3-(5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carbonyl)-3-azabicyclo[3.2.0]heptane-2-carboxylate – 10010_02, Z5030906448 (Method 3).



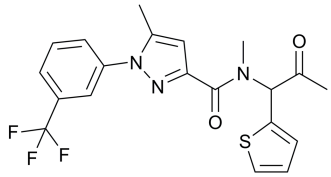
The compound was synthesized from rac-methyl (1R,2S,5S)-3-azabicyclo[3.2.0]heptane-2-carboxylate hydrochloride (Catalog # EN300-1717544, 100 mg, 0.52 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 155 mg, 0.58 mmol).
Yield: 70%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 – 7.91 (m, 1H), 7.90 – 7.75 (m, 3H), 6.69 (s, 1H), 4.20 (dd, *J* = 12.6, 8.9 Hz, 1H), 3.64 (s, 1H), 3.52 (dd, *J* = 12.7, 6.0 Hz, 1H), 3.45 (s, 2H), 3.20 (qd, *J* = 8.6, 5.6 Hz, 1H), 3.03 (d, *J* = 8.1 Hz, 1H), 2.84 (s, 1H), 2.38 (d, *J* = 7.9 Hz, 3H), 2.17 – 2.06 (m, 1H), 2.06 – 1.94 (m, 1H), 1.81 – 1.59 (m, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 172.1, 161.7, 148.3, 140.9, 140.1, 131.2, 129.3, 128.2, 125.3, 121.1, 110.5, 110.2, 65.1, 55.7, 52.0, 42.4, 35.7, 23.9, 21.3, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{21}F_3N_3O_3$: 408.2; found: 408.1.

N-(di(furan-2-yl)methyl)-N,5-dimethyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamide – 1486_43, Z5199554388 (Method 3).



The compound was synthesized from [bis(furan-2-yl)methyl](methyl)amine (Catalog # EN300-2585655, 100 mg, 0.56 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 168 mg, 0.62 mmol).
Yield: 54%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.97 (d, *J* = 7.1 Hz, 1H), 7.94 – 7.86 (m, 2H), 7.79 (dt, *J* = 22.3, 7.8 Hz, 3H), 7.69 (dd, *J* = 14.7, 1.7 Hz, 2H), 6.70 (d, *J* = 5.4 Hz, 1H), 6.51 – 6.41 (m, 2H), 6.37 (d, *J* = 3.3 Hz, 1H), 3.10 (s, 2H), 2.81 (s, 1H), 2.41 (s, 1H), 2.37 (s, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 163.3, 163.3, 162.1, 150.7, 150.2, 147.5, 147.5, 143.8, 143.7, 141.6, 141.2, 140.8, 140.0, 131.2, 131.0, 130.7, 130.4, 129.2, 128.8, 128.6, 125.2, 125.1, 125.0, 123.2, 121.8, 121.7, 111.1, 111.1, 110.6, 110.3, 110.1, 109.7, 107.9, 53.8, 49.7, 33.3, 30.4, 26.0, 12.5, 12.5, 12.3.
LC/MS (APSI) m/z [M-H] calculated for $C_{22}H_{19}F_3N_3O_3$: 430.1; found: 430.2.

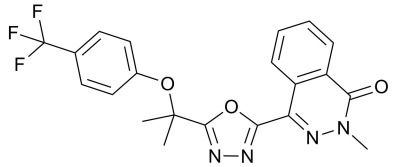
N,5-dimethyl-N-(2-oxo-1-(thiophen-2-yl)propyl)-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamide – 1486_44, Z5204106829 (Method 3).



The compound was synthesized from 1-(methylamino)-1-(thiophen-2-yl)propan-2-one hydrochloride (Catalog # EN300-6869532, 100 mg, 0.59 mmol) and 5-methyl-1-[3-

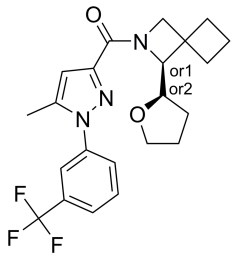
(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 176 mg, 0.65 mmol).
Yield: 22%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.99 – 7.89 (m, 2H), 7.87 – 7.69 (m, 2H), 7.11 (d, J = 3.2 Hz, 1H), 7.08 (d, J = 2.5 Hz, 1H), 7.04 (ddd, J = 12.6, 5.1, 3.5 Hz, 1H), 6.74 – 6.67 (m, 1H), 3.28 (s, 2H), 3.12 (s, 1H), 2.77 (s, 1H), 2.28 (t, J = 2.2 Hz, 1H), 2.14 (d, J = 13.8 Hz, 3H), 1.84 (s, 1H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 203.9, 202.2, 164.7, 163.6, 163.2, 150.6, 147.4, 147.3, 147.1, 141.3, 141.0, 140.4, 140.2, 140.0, 139.6, 136.6, 131.2, 131.1, 130.9, 130.5, 129.4, 129.3, 129.1, 128.9, 128.3, 128.1, 127.8, 127.5, 126.8, 126.5, 125.3, 123.8, 121.9, 121.0, 115.3, 110.7, 110.4, 108.9, 66.1, 65.9, 36.4, 36.2, 31.5, 27.7, 27.4, 17.7, 12.6, 12.4, 12.3.
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{19}F_3N_3O_2S$: 422.1; found: 422.0.

2-methyl-4-(5-(2-(4-(trifluoromethyl)phenoxy)propan-2-yl)-1,3,4-oxadiazol-2-yl)phthalazin-1(2H)-one – 0450_21, Z5468612153 (Method 1).



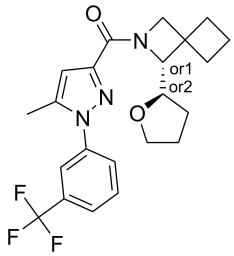
The compound was synthesized from 3-methyl-4-oxo-3,4-dihydrophthalazine-1-carbohydrazide (Catalog # EN300-04897, 97 mg, 0.44 mmol) and 2-methyl-2-[4-(trifluoromethyl)phenoxy]propanoic acid (Catalog # EN300-305386 100 mg, 0.4 mmol).
Yield: 23%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.90 (d, *J* = 8.2 Hz, 1H), 8.36 (dd, *J* = 8.1, 1.4 Hz, 1H), 8.08 – 8.01 (m, 1H), 7.99 – 7.92 (m, 1H), 7.62 (d, *J* = 8.5 Hz, 2H), 7.00 (d, *J* = 8.4 Hz, 2H), 3.82 (s, 3H), 1.88 (s, 6H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 168.0, 161.8, 158.8, 157.9, 134.6, 133.0, 130.1, 127.5, 127.4, 127.4, 127.4, 126.9, 126.6, 121.7, 76.1, 26.1.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{18}F_3N_4O_3$: 431.1; found: 431.0.

***rel*-(5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)((S)-1-((R)-tetrahydrofuran-2-yl)-2-azaspiro[3.3]heptan-2-yl)methanone – EN300-37364332, Z5889661651 (Method 3).**



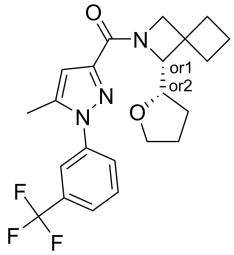
The compound was synthesized from 1-(oxolan-2-yl)-2-azaspiro[3.3]heptane (Catalog # EN300-216770, 100 mg, 0.6 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 178mg, 0.66 mmol) utilizing chiral separation of the mixture.
Yield: 15%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.92 (d, *J* = 9.3 Hz, 2H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.79 (t, *J* = 7.8 Hz, 1H), 6.63 (s, 1H), 4.41 – 4.29 (m, 1H), 4.05 (d, *J* = 3.6 Hz, 2H), 3.82 (d, *J* = 6.9 Hz, 1H), 3.79 (d, *J* = 7.0 Hz, 1H), 3.66 (d, *J* = 7.1 Hz, 2H), 2.36 (s, 3H), 2.07 (d, *J* = 8.1 Hz, 3H), 1.99 (dd, *J* = 13.8, 6.7 Hz, 1H), 1.87 (tq, *J* = 10.9, 5.3 Hz, 3H), 1.82 – 1.69 (m, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 163.0, 147.2, 141.0, 140.1, 131.2, 129.2, 125.2, 121.7, 109.3, 79.0, 71.7, 68.0, 65.6, 42.2, 34.2, 29.5, 25.6, 16.5, 12.4.
LC/MS (APSI) m/z [M+H] calculated for $C_{22}H_{25}F_3N_3O_2$: 420.2; found: 420.2.

***rel*-(5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)((R)-1-((R)-tetrahydrofuran-2-yl)-2-azaspiro[3.3]heptan-2-yl)methanone – EN300-37364334, Z5889670430 (Method 3).**



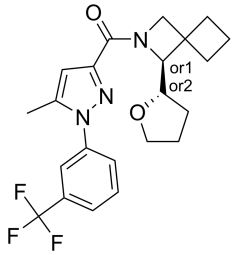
The compound was synthesized from 1-(oxolan-2-yl)-2-azaspiro[3.3]heptane (Catalog # EN300-216770) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239) utilizing chiral separation of the mixture.
Yield: 13%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.92 (d, *J* = 9.2 Hz, 2H), 7.84 (d, *J* = 7.9 Hz, 1H), 7.79 (t, *J* = 7.8 Hz, 1H), 6.63 (s, 1H), 4.39 (d, *J* = 9.8 Hz, 1H), 4.31 (d, *J* = 9.8 Hz, 1H), 4.06 (d, *J* = 3.6 Hz, 2H), 3.80 (q, *J* = 6.9 Hz, 1H), 3.67 (p, *J* = 8.9, 7.2 Hz, 1H), 2.47 – 2.37 (m, 1H), 2.36 (s, 3H), 2.12 – 2.04 (m, 2H), 1.99 (dd, *J* = 13.6, 6.3 Hz, 1H), 1.88 (qd, *J* = 11.4, 10.4, 6.0 Hz, 3H), 1.78 (s, 1H), 1.83 – 1.69 (m, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 163.0, 147.2, 141.0, 140.1, 131.2, 129.2, 125.1 (d, *J* = 32.8 Hz), 121.6, 109.3, 79.0, 71.7, 68.0, 65.6, 42.2, 34.2, 29.5, 25.6, 16.5, 12.4.
LC/MS (APSI) m/z [M+H] calculated for $C_{22}H_{25}F_3N_3O_2$: 420.2; found: 420.2.

***rel*-(5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)((R)-1-((S)-tetrahydrofuran-2-yl)-2-azaspiro[3.3]heptan-2-yl)methanone – EN300-37364335, Z5889673386 (Method 3).**



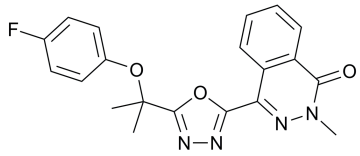
The compound was synthesized from 1-(oxolan-2-yl)-2-azaspiro[3.3]heptane (Catalog # EN300-216770) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239) utilizing chiral separation of the mixture.
Yield: 10%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.92 (d, *J* = 9.9 Hz, 2H), 7.84 (d, *J* = 7.8 Hz, 1H), 7.79 (t, *J* = 7.8 Hz, 1H), 6.63 (s, 1H), 4.34 (q, *J* = 9.5 Hz, 2H), 4.28 – 4.24 (m, 1H), 4.16 (td, *J* = 7.3, 2.4 Hz, 1H), 3.67 (dq, *J* = 32.2, 7.3 Hz, 2H), 2.36 (s, 3H), 2.28 (dt, *J* = 11.8, 8.5 Hz, 1H), 2.15 – 2.03 (m, 3H), 1.90 (ddq, *J* = 18.3, 12.9, 7.3, 5.9 Hz, 2H), 1.73 (q, *J* = 7.1 Hz, 3H), 1.72 – 1.64 (m, 1H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 162.7, 147.3, 141.0, 140.1, 131.2, 129.2, 125.2, 121.6, 109.3, 78.5, 72.6, 68.4, 66.4, 42.6, 34.5, 28.9, 25.8, 16.3, 12.4.
LC/MS (APSI) m/z [M+H] calculated for $C_{22}H_{25}F_3N_3O_2$: 420.2; found: 420.2.

rel-(5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)((S)-1-((S)-tetrahydrofuran-2-yl)-2-azaspiro[3.3]heptan-2-yl)methanone – EN300-37364336, Z5889675490 (Method 3).



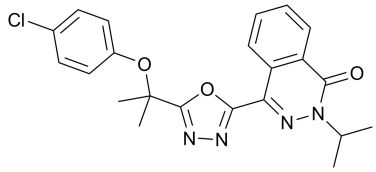
The compound was synthesized from 1-(oxolan-2-yl)-2-azaspiro[3.3]heptane (Catalog # EN300-216770) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239) utilizing chiral separation of the mixture.
Yield: 11%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.92 (d, J = 9.6 Hz, 2H), 7.84 (d, J = 7.9 Hz, 1H), 7.79 (t, J = 7.8 Hz, 1H), 6.63 (s, 1H), 4.36 (d, J = 9.5 Hz, 1H), 4.32 (d, J = 9.5 Hz, 1H), 4.28 – 4.24 (m, 1H), 4.16 (td, J = 7.3, 2.4 Hz, 1H), 3.67 (dq, J = 32.3, 7.3 Hz, 2H), 2.48 (p, J = 1.9 Hz, 3H), 2.28 (d, J = 11.4 Hz, 1H), 2.13 – 2.05 (m, 3H), 1.90 (dq, J = 13.4, 5.5, 4.5 Hz, 2H), 1.72 (dq, J = 12.8, 5.8, 4.7 Hz, 4H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 162.7, 147.3, 141.0, 140.1, 131.2, 129.2, 125.2, 121.6, 109.3, 78.5, 72.6, 68.4, 66.4, 42.6, 34.5, 28.9, 28.6, 25.8, 16.3, 12.4.
LC/MS (APSI) m/z [M+H] calculated for $C_{22}H_{25}F_3N_3O_2$: 420.2; found: 420.2.

4-(5-(2-(4-fluorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-yl)-2-methylphthalazin-1(2H)-one – 31486, Z685931486 (Method 1).



The compound was synthesized from 3-methyl-4-oxo-3,4-dihydrophthalazine-1-carbohydrazide (Catalog # EN300-04897, 121 mg,0.56 mmol) and 2-(4-fluorophenoxy)-2-methylpropanoic acid (Catalog # EN300-11485, 100 mg, 0.51 mmol).
Yield: 14%; purity, >95% (assessed by LC/MS).
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.86 (d, J = 8.2 Hz, 1H), 8.31 (d, J = 7.9 Hz, 1H), 8.01 (t, J = 7.8 Hz, 1H), 7.92 (t, J = 7.7 Hz, 1H), 7.08 (t, J = 8.8 Hz, 2H), 6.87 – 6.79 (m, 2H), 1.81 (s, 9H).
^{13}C NMR (101 MHz, DMSO-d_6) δ 168.1, 161.7, 158.7, 158.0, 150.6, 134.5, 132.9, 130.1, 127.3, 126.8, 126.6, 124.6, 116.6, 76.0, 40.3, 25.9.
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{18}FN_4O_3$: 381.1; found: 381.0.

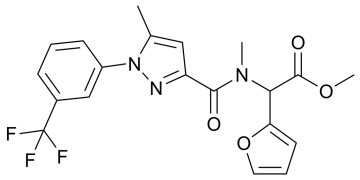
4-(5-(2-(4-chlorophenoxy)propan-2-yl)-1,3,4-oxadiazol-2-yl)-2-isopropylphthalazin-1(2H)-one – 41360, Z685941360 (Method 1).



The compound was synthesized from 4-oxo-3-(propan-2-yl)-3,4-dihydrophthalazine-1-carbohydrazide (Catalog # EN300-05133, 126 mg, 0.51 mmol) and 2-(4-chlorophenoxy)-2-methylpropanoic acid (Catalog # EN300-18267, 100 mg, 0.47 mmol).
Yield: 28%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.83 (s, 1H), 8.39 – 8.35 (m, 1H), 8.04 (s, 1H), 7.95 (s, 1H), 7.31 – 7.26 (m, 2H), 6.90 – 6.84 (m, 2H), 5.31 (s, 1H), 2.49 (s, 2H), 1.85 (s, 5H), 1.37 (s, 5H).

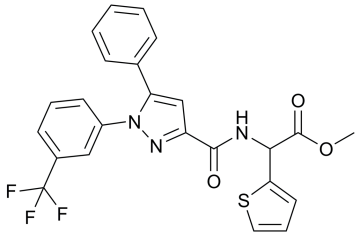
^{13}C NMR (101 MHz, DMSO-d_6) δ 168.0, 161.9, 158.1, 153.5, 134.7, 132.9, 130.2, 129.8, 128.7, 127.4, 127.2, 126.8, 126.4, 124.5, 76.3, 49.7, 26.0, 21.3.
LC/MS (APSI) m/z [M+H] calculated for $C_{22}H_{22}ClN_4O_3$: 425.1; found: 425.0.

methyl 2-(N,5-dimethyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamido)-2-(furan-2-yl)acetate – 1486_46, Z5422676425 (Method 3).



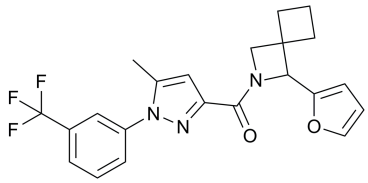
The compound was synthesized from methyl 2-(furan-2-yl)-2-(methylamino)acetate (Catalog # EN300-37160511, 100 mg, 0.59 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 176 mg, 0.65 mmol).
Yield: 27%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.54 (s, 1H), 7.99 (d, *J* = 2.1 Hz, 1H), 7.95 (dd, *J* = 7.8, 2.2 Hz, 1H), 7.87 (d, *J* = 7.8 Hz, 1H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.39 (d, *J* = 5.1 Hz, 1H), 7.07 (d, *J* = 3.5 Hz, 1H), 6.94 (dd, *J* = 5.1, 3.5 Hz, 1H), 6.67 (s, 1H), 2.35 (s, 3H), 1.96 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 169.4, 168.7, 163.9, 148.2, 147.7, 147.3, 144.4, 144.2, 141.0, 139.9, 131.2, 131.2, 131.1, 129.2, 128.5, 125.3, 125.1, 124.8, 121.8, 121.5, 111.7, 111.3, 110.9, 110.4, 108.9, 59.0, 56.0, 53.1, 52.9, 49.5, 35.5, 34.7, 31.3, 21.5, 20.5, 15.1, 12.5, 12.3.
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{19}F_3N_3O_4$: 422.1; found: 422.2.

methyl 2-(5-phenyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamido)-2-(thiophen-2-yl)acetate – 1486_71, Z6314888079 (Method 3).



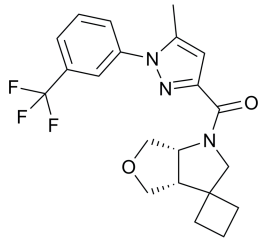
The compound was synthesized from methyl 2-amino-2-(thiophen-2-yl)acetate hydrochloride (Catalog # EN300-60031, 100 mg, 0.48 mmol) and 5-phenyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-37430088, 175 mg, 0.53 mmol).
Yield: 33%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 9.10 (d, *J* = 7.5 Hz, 1H), 7.78 (d, *J* = 7.7 Hz, 1H), 7.75 (d, *J* = 2.1 Hz, 1H), 7.65 (t, *J* = 7.9 Hz, 1H), 7.60 (d, *J* = 8.4 Hz, 1H), 7.50 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.43 – 7.34 (m, 3H), 7.28 (dq, *J* = 4.7, 2.9 Hz, 2H), 7.17 (d, *J* = 3.6 Hz, 1H), 7.11 (s, 1H), 7.00 (dd, *J* = 5.1, 3.5 Hz, 1H), 5.91 (d, *J* = 7.5 Hz, 1H), 3.69 (s, 3H).
^{13}C NMR (126 MHz, DMSO-d_6) δ 169.9, 160.5, 146.6, 144.7, 139.6, 138.4, 130.4, 129.3, 129.0, 128.8, 128.8, 127.2, 126.6, 126.4, 122.1, 108.4, 52.6, 51.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{24}H_{19}F_3N_3O_3S$: 486.1; found: 486.0.

(1-(furan-2-yl)-2-azaspiro[3.3]heptan-2-yl)(5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)methanone – 10_10, Z6314892034 (Method 3).



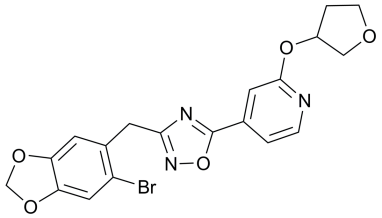
The compound was synthesized from 1-(furan-2-yl)-2-azaspiro[3.3]heptane (Catalog # EN300-244752, 100 mg, 0.61 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 182 mg, 0.67 mmol).
Yield: 26%; purity, 92% (assessed by LC/MS).
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.05 (t, *J* = 6.0 Hz, 1H), 7.95 (s, 1H), 7.92 (d, *J* = 8.0 Hz, 1H), 7.85 (d, *J* = 7.9 Hz, 1H), 7.79 (t, *J* = 7.9 Hz, 1H), 7.55 (d, *J* = 1.8 Hz, 1H), 6.67 (s, 1H), 6.37 (dd, *J* = 3.2, 1.7 Hz, 1H), 6.30 (d, *J* = 3.2 Hz, 1H), 5.67 (d, *J* = 4.7 Hz, 1H), 4.62 (d, *J* = 4.7 Hz, 1H), 3.45 (dd, *J* = 13.6, 6.7 Hz, 1H), 2.36 (s, 3H), 2.06 – 1.91 (m, 2H), 1.84 – 1.80 (m, 1H), 1.81 – 1.73 (m, 1H), 1.61 (tq, *J* = 9.9, 4.6 Hz, 1H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 162.0, 156.4, 147.7, 142.2, 141.8, 140.0, 131.1, 129.1, 125.3, 122.0, 110.5, 108.0, 107.2, 72.2, 46.0, 43.8, 26.6, 25.8, 14.9, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{22}H_{21}F_3N_3O_2$: 416.2; found: 416.0.

(5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazol-3-yl)((3a'S,6a'R)-tetrahydrospiro[cyclobutane-1,3'-furo[3,4-b]pyrrol]-1'(2'H)-yl)methanone – 10_14, Z6314892089 (Method 3).



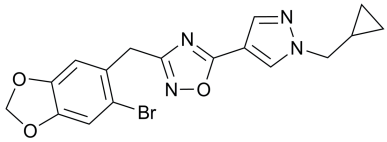
The compound was synthesized from rac-(3'aR,6'aS)-hexahydrospiro[cyclobutane-1,3'-furo[3,4-b]pyrrole] hydrochloride (Catalog # EN300-1425927, 100 mg, 0.53 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 157 mg, 0.58 mmol).
Yield: 31%; purity, >95% (assessed by LC/MS).
^{1}H NMR (600 MHz, DMSO-d_6) δ 7.97 – 7.89 (m, 2H), 7.82 (dt, *J* = 21.6, 8.0 Hz, 2H), 6.68 (d, *J* = 20.5 Hz, 1H), 5.07 (t, *J* = 5.5 Hz, 1H), 4.58 (dd, *J* = 7.4, 4.2 Hz, 1H), 4.28 (d, *J* = 11.5 Hz, 1H), 3.80 (dd, *J* = 9.9, 3.8 Hz, 1H), 3.71 (dddd, *J* = 25.7, 16.8, 9.8, 4.4 Hz, 2H), 3.59 – 3.50 (m, 2H), 2.87 (q, *J* = 7.2 Hz, 1H), 2.81 (td, *J* = 7.8, 5.1 Hz, 1H), 2.38 (d, *J* = 3.4 Hz, 3H), 2.01 – 1.83 (m, 2H), 1.83 – 1.71 (m, 2H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 161.0, 148.4, 140.9, 140.8, 140.1, 131.2, 130.4, 129.1, 128.8, 125.2, 121.7, 121.5, 110.5, 109.9, 77.2, 74.6, 69.8, 69.4, 63.6, 62.5, 58.6, 56.2, 53.5, 51.0, 47.0, 45.0, 40.5, 34.9, 34.7, 26.2, 26.0, 16.1, 15.9, 12.4.
LC/MS (APSI) m/z [M+H] calculated for $C_{21}H_{23}F_3N_3O_2$: 406.2; found: 406.0.

3-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)-5-(2-((tetrahydrofuran-3-yl)oxy)pyridin-4-yl)-1,2,4-oxadiazole – 7019_11, Z1684296820 (Method 5).



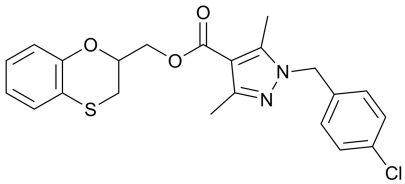
The compound was synthesized from 2-(6-bromo-1,3-dioxaindan-5-yl)acetonitrile (Catalog # EN300-53536, 100 mg, 0.42 mmol) and 2-(oxolan-3-yloxy)pyridine-4-carboxylic acid (Catalog # EN300-122851, 96 mg, 0.46 mmol).
Yield: 27%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.39 (d, J = 5.3 Hz, 1H), 7.56 – 7.51 (m, 1H), 7.31 (s, 1H), 7.21 (d, J = 1.6 Hz, 1H), 7.06 (d, J = 1.5 Hz, 1H), 6.06 (s, 2H), 5.57 – 5.51 (m, 1H), 3.91 (dd, J = 10.4, 4.6 Hz, 1H), 3.85 (q, J = 7.9 Hz, 1H), 3.76 (td, J = 12.9, 11.8, 7.6 Hz, 2H), 3.32 (s, 1H), 2.53 (d, J = 1.5 Hz, 1H), 2.29 – 2.18 (m, 1H), 2.01 (dt, J = 12.8, 5.7 Hz, 1H).
^{13}C NMR (126 MHz, DMSO-d_6) δ 173.2, 169.4, 163.3, 148.8, 147.5, 147.2, 133.2, 127.6, 114.4, 112.3, 111.0, 109.2, 102.0, 76.4, 72.4, 66.3, 32.4, 32.0.
LC/MS (APSI) m/z [M+H] calculated for $C_{19}H_{17}BrN_3O_5$: 446.0; found: 446.0.

3-((6-bromobenzo[d][1,3]dioxol-5-yl)methyl)-5-(1-(cyclopropylmethyl)-1H-pyrazol-4-yl)-1,2,4-oxadiazole – 7019_31, Z5722895424 (Method 5).



The compound was synthesized from 2-(6-bromo-1,3-dioxaindan-5-yl)acetonitrile (Catalog # EN300-53536, 100 mg, 0.42 mmol) and 1-(cyclopropylmethyl)-1H-pyrazole-4-carboxylic acid (Catalog # EN300-305583, 76 mg, 0.46 mmol).
Yield: 31%; purity, >95% (assessed by LC/MS).
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.51 (s, 1H), 7.93 (s, 1H), 7.05 (s, 1H), 6.89 (s, 1H), 6.03 (s, 2H), 4.08 (s, 2H), 4.05 (d, J = 7.2 Hz, 2H), 1.28 (d, J = 31.5 Hz, 1H), 0.59 (d, J = 7.5 Hz, 2H), 0.44 (d, J = 5.2 Hz, 2H).
^{13}C NMR (126 MHz, DMSO-d_6) δ 170.7, 168.6, 147.5, 147.2, 138.6, 131.7, 128.0, 114.3, 112.3, 111.0, 106.2, 102.0, 56.1, 32.0, 11.3, 3.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{17}H_{16}BrN_4O_3$: 405.0; found: 405.0.

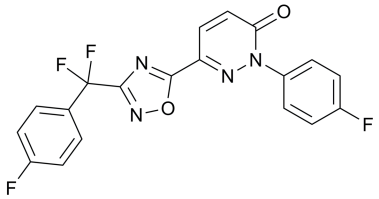
(2,3-dihydrobenzo[b][1,4]oxathiin-2-yl)methyl 1-(4-chlorobenzyl)-3,5-dimethyl-1H-pyrazole-4-carboxylate – 7800_29, Z5722895463 (Method 2).



The compound was synthesized from (2,3-dihydro-1,4-benzoxathiin-2-yl)methanol (Catalog # EN300-59707, 100 mg, 0.55 mmol) and 1-[(4-chlorophenyl)methyl]-3,5-dimethyl-1H-pyrazole-4-carboxylic acid (Catalog # EN300-99633, 145 mg, 0.6 mmol).
Yield: 19%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.42 – 7.36 (m, 2H), 7.34 (dd, J = 7.6, 1.7 Hz, 1H), 7.19 (td, J = 7.7, 1.7 Hz, 1H), 7.14 (d, J = 8.4 Hz, 2H), 7.00 (ddt, J = 10.7, 7.4, 1.5 Hz, 2H), 5.34 (q, J = 3.6 Hz, 1H), 5.28 (s, 2H), 4.39 (dd, J = 13.2, 3.0 Hz, 1H), 4.27 (dd, J = 13.0, 4.6 Hz, 1H), 3.22 – 3.14 (m, 1H), 2.45 (s, 4H), 2.32 (s, 3H).

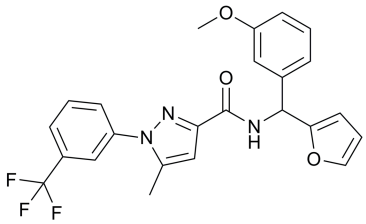
LC/MS (APSI) m/z [M+H] calculated for $C_{22}H_{22}ClN_2O_3S$: 429.1; found: 429.0.

6-(3-(difluoro(4-fluorophenyl)methyl)-1,2,4-oxadiazol-5-yl)-2-(4-fluorophenyl)pyridazin-3(2H)-one – 2443, Z1684426368 (Method 5).



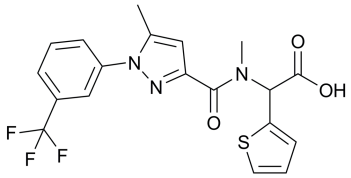
The compound was synthesized from 2,2-difluoro-2-(4-fluorophenyl)acetonitrile (Catalog # EN300-55799, 100 mg, 0.58 mmol) and 1-(4-fluorophenyl)-6-oxo-1,6-dihydropyridazine-3-carboxylic acid (Catalog # EN300-36469, 151 mg, 0.64 mmol).
Yield: 33%; purity, >95% (assessed by LC/MS).
^{1}H NMR (400 MHz, DMSO-d_6) δ 8.10 (d, J = 9.9 Hz, 1H), 7.70 (dt, J = 21.8, 7.5 Hz, 4H), 7.32 (s, 1H), 7.27 (dd, J = 20.9, 8.9 Hz, 4H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 173.3, 166.9, 165.1, 163.4, 163.0, 161.4, 159.1, 137.5, 132.4, 131.7, 129.5, 128.9, 128.6, 116.7.
LC/MS (APSI) m/z [M+H] calculated for $C_{19}H_{11}F_4N_4O_2$: 403.1; found: 403.0.

N-(furan-2-yl(3-methoxyphenyl)methyl)-5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamide – 1486_38, Z4967431087 (Method 3).



The compound was synthesized from (furan-2-yl)(3-methoxyphenyl)methanamine (Catalog # EN300-2209969, 100 mg, 0.49 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 146 mg, 0.54 mmol).
Yield: 34%; purity, >95% (assessed by LC/MS).
^{1}H NMR (400 MHz, Chloroform-d) δ 7.74 (d, J = 21.2 Hz, 2H), 7.67 (d, J = 6.5 Hz, 2H), 7.66 – 7.56 (m, 1H), 7.40 (d, J = 1.8 Hz, 1H), 7.28 (d, J = 15.8 Hz, 1H), 6.98 (d, J = 7.7 Hz, 1H), 6.93 (t, J = 2.2 Hz, 1H), 6.88 – 6.78 (m, 2H), 6.48 (d, J = 8.6 Hz, 1H), 6.37 – 6.31 (m, 1H), 6.24 (d, J = 3.2 Hz, 1H), 3.80 (s, 3H), 2.39 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 161.1, 159.7, 154.6, 147.2, 143.0, 141.9, 140.0, 131.1, 129.9, 129.2, 125.3, 122.1, 120.2, 113.9, 113.2, 110.9, 108.3, 108.1, 55.5, 50.6, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{24}H_{21}F_3N_3O_3$: 456.2; found: 456.2.

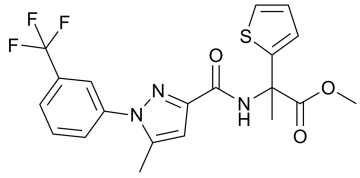
2-(N,5-dimethyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamido)-2-(thiophen-2-yl)acetic acid – 9056, Z5003379056 (Method 3).



The compound was synthesized from 2-(methylamino)-2-(thiophen-2-yl)acetic acid (Catalog # EN300-1259865, 100 mg, 0.58 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 174 mg,0.64 mmol).

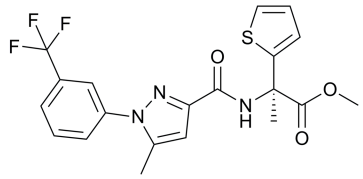
Yield: 35%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 13.27 (s, 1H), 8.54 (s, 1H), 7.99 (d, J = 2.1 Hz, 1H), 7.95 (dd, J = 7.8, 2.1 Hz, 1H), 7.87 (d, J = 7.8 Hz, 1H), 7.80 (t, J = 7.9 Hz, 1H), 7.39 (d, J = 5.0 Hz, 1H), 7.07 (d, J = 3.6 Hz, 1H), 6.94 (dd, J = 5.2, 3.5 Hz, 1H), 6.67 (s, 1H), 2.35 (s, 3H), 1.96 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 160.5, 147.3, 142.1, 139.9, 131.2, 129.5, 126.9, 125.7, 125.5, 122.2, 107.9, 25.0, 12.4.
LC/MS (APSI) m/z [M+H] calculated for $C_{19}H_{17}F_3N_3O_3S$: 424.1; found: 424.0.

methyl 2-(5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamido)-2-(thiophen-2-yl)propanoate – 4042, Z8504214042 (Method 3).



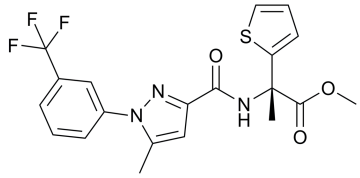
The compound was synthesized from methyl 2-amino-2-(thiophen-2-yl)propanoate hydrochloride (Catalog # EN300-46816185, 100 mg, 0.45 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 134 mg, 0.5 mmol).
Yield: 30%; purity, >95% (assessed by LC/MS).
^{1}H NMR (600 MHz, DMSO-d_6) δ 8.65 (s, 1H), 7.99 (d, J = 2.3 Hz, 1H), 7.95 (d, J = 7.9 Hz, 1H), 7.86 (d, J = 7.8 Hz, 1H), 7.80 (t, J = 7.9 Hz, 1H), 7.45 (dd, J = 5.1, 1.2 Hz, 1H), 7.14 (dd, J = 3.6, 1.3 Hz, 1H), 6.96 (dd, J = 5.1, 3.6 Hz, 1H), 6.71 (s, 1H), 3.62 (s, 3H), 2.36 (s, 3H), 1.92 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 172.3, 161.0, 146.8, 145.2, 142.0, 139.9, 131.1, 130.7, 130.5, 129.3, 125.0, 123.2, 122.2 (2), 108.2, 59.5, 53.1, 40.2, 25.7, 12.5.
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{19}F_3N_3O_3S$: 438.1; found: 438.2.

methyl (R)-2-(5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamido)-2-(thiophen-2-yl)propanoate – 1350, Z8526711350.



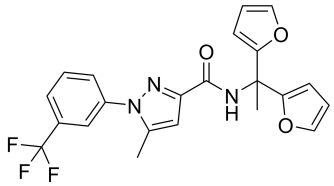
The compound was obtained by a chiral separation of Z8504214042.
Yield: 15%; purity, >95% (assessed by LC/MS).
$[\alpha]^{21}_D$ = -29.1 (*c* 1.0, CH_3OH).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.99 (d, J = 2.0 Hz, 1H), 7.95 (d, J = 8.4 Hz, 1H), 7.86 (d, J = 7.7 Hz, 1H), 7.79 (t, J = 7.9 Hz, 1H), 7.45 (dd, J = 5.1, 1.3 Hz, 1H), 7.14 (dd, J = 3.6, 1.3 Hz, 1H), 6.96 (dd, J = 5.1, 3.6 Hz, 1H), 6.70 (s, 1H), 3.62 (s, 3H), 2.36 (s, 3H), 1.91 (s, 3H).
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{19}F_3N_3O_3S$: 438.1; found: 438.2.

methyl (S)-2-(5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamido)-2-(thiophen-2-yl)propanoate – 8690, Z8526708690.



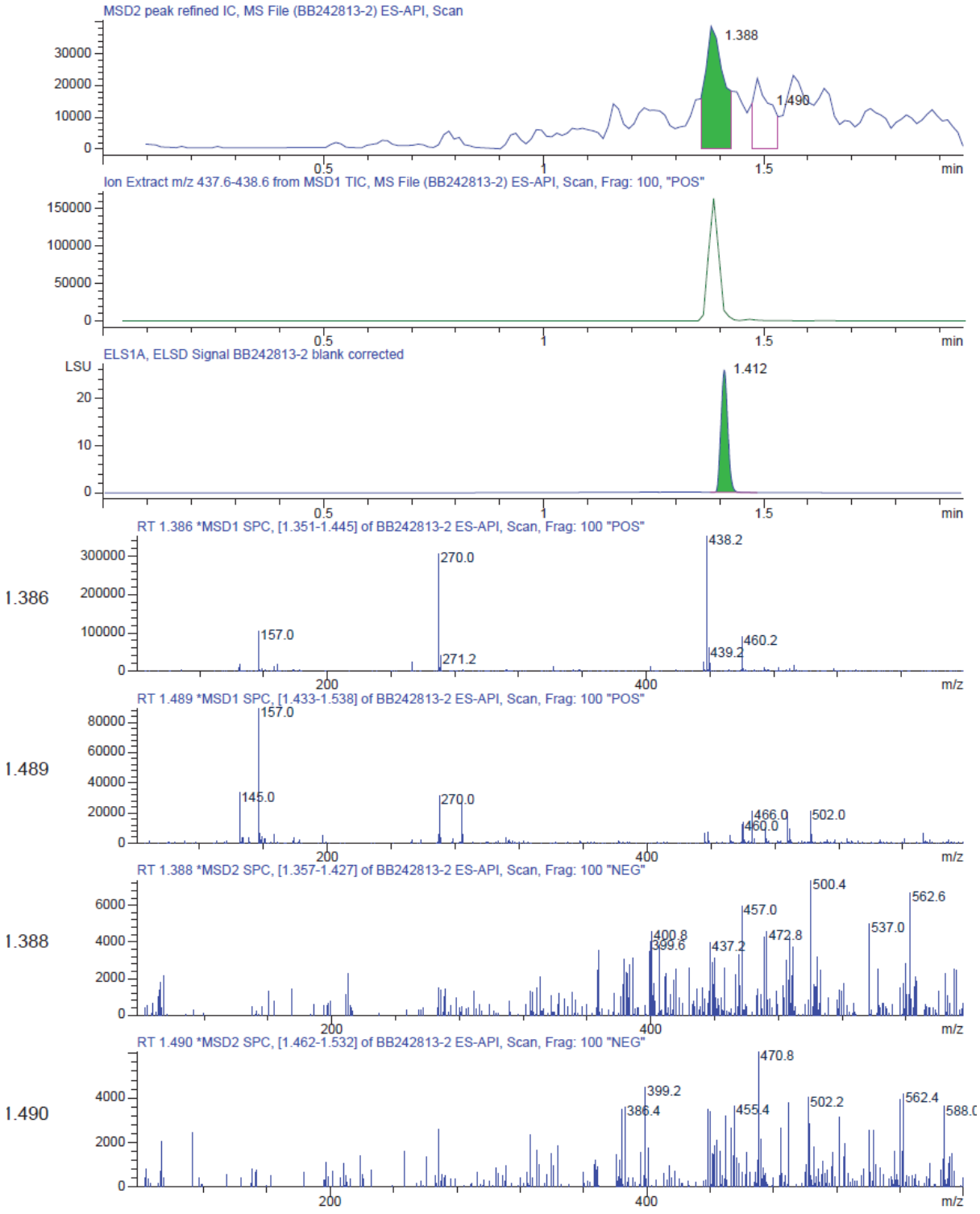
The compound was obtained by a chiral separation of Z8504214042.
Yield: 12%; purity, >95% (assessed by LC/MS).
$[\alpha]^{21}_{D}$ = 27.7 (*c* 2.0, CH_3OH).
^{1}H NMR (500 MHz, DMSO-d_6) δ 8.66 (s, 1H), 7.99 (d, *J* = 2.1 Hz, 1H), 7.95 (d, *J* = 8.1 Hz, 1H), 7.86 (d, *J* = 7.8 Hz, 1H), 7.79 (t, *J* = 7.9 Hz, 1H), 7.45 (dd, *J* = 5.1, 1.3 Hz, 1H), 7.14 (dd, *J* = 3.6, 1.3 Hz, 1H), 6.96 (dd, *J* = 5.1, 3.6 Hz, 1H), 6.70 (s, 1H), 3.62 (s, 3H), 2.36 (s, 3H), 1.92 (s, 3H).
LC/MS (APSI) m/z [M+H] calculated for $C_{20}H_{19}F_3N_3O_3S$: 438.1; found: 438.2.

N-(1,1-di(furan-2-yl)ethyl)-5-methyl-1-(3-(trifluoromethyl)phenyl)-1H-pyrazole-3-carboxamide – Z8703004936 (Method 3).

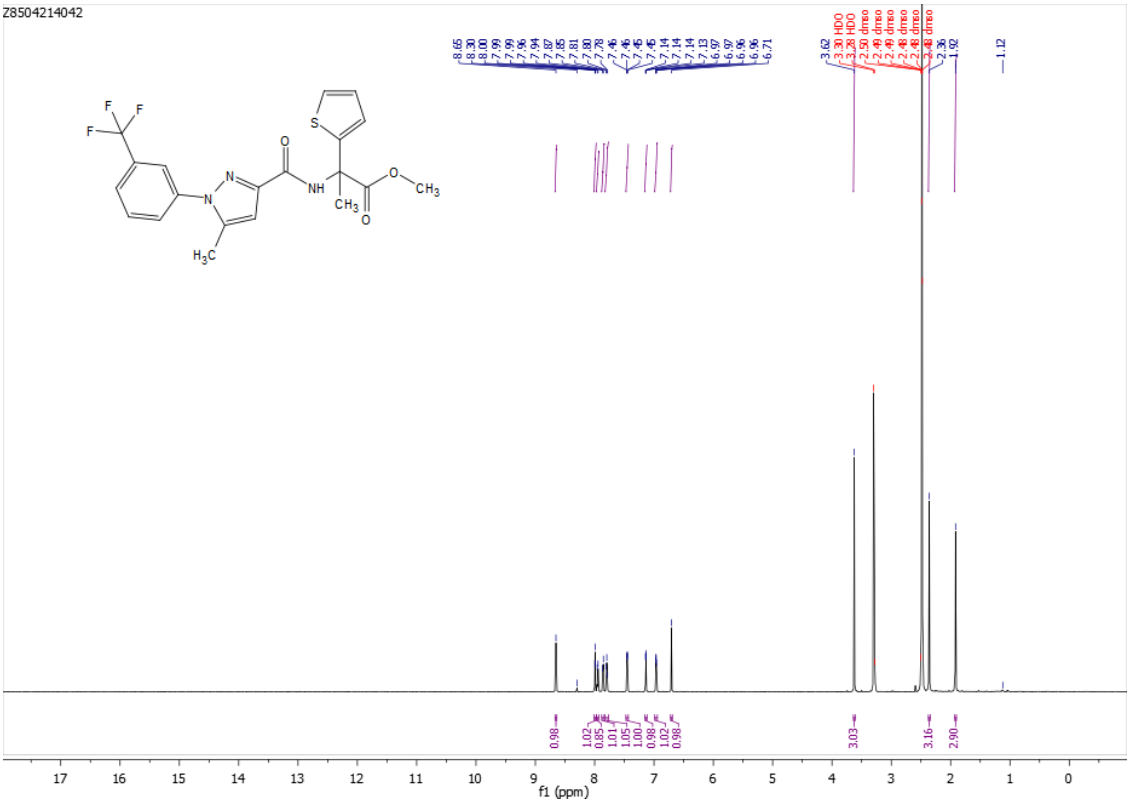


The compound was synthesized from 1,1-bis(furan-2-yl)ethan-1-amine (Catalog # EN300-46161469, 100 mg, 0.56 mmol) and 5-methyl-1-[3-(trifluoromethyl)phenyl]-1H-pyrazole-3-carboxylic acid (Catalog # EN300-260239, 168 mg, 0.62 mmol).
Yield: 28%; purity, >95% (assessed by LC/MS).
^{1}H NMR (500 MHz, DMSO-d_6) δ 7.98 (s, 1H), 7.97 – 7.91 (m, 2H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.79 (t, *J* = 7.9 Hz, 1H), 7.57 (d, *J* = 1.9 Hz, 2H), 6.65 (s, 1H), 6.39 (dd, *J* = 3.2, 1.8 Hz, 2H), 6.22 (d, *J* = 3.3 Hz, 2H), 2.34 (s, 3H), 2.05 (s, 3H).
^{13}C NMR (151 MHz, DMSO-d_6) δ 160.5, 155.5, 147.4, 142.6, 142.1, 139.9, 131.2, 130.7, 129.5, 125.5, 123.2, 122.2, 110.9, 107.9, 106.7, 54.5, 24.2, 12.4.
LC/MS (APSI) m/z [2M+Na] calculated for C44H36F6N6Na1O6: 881.3; found: 881.2.

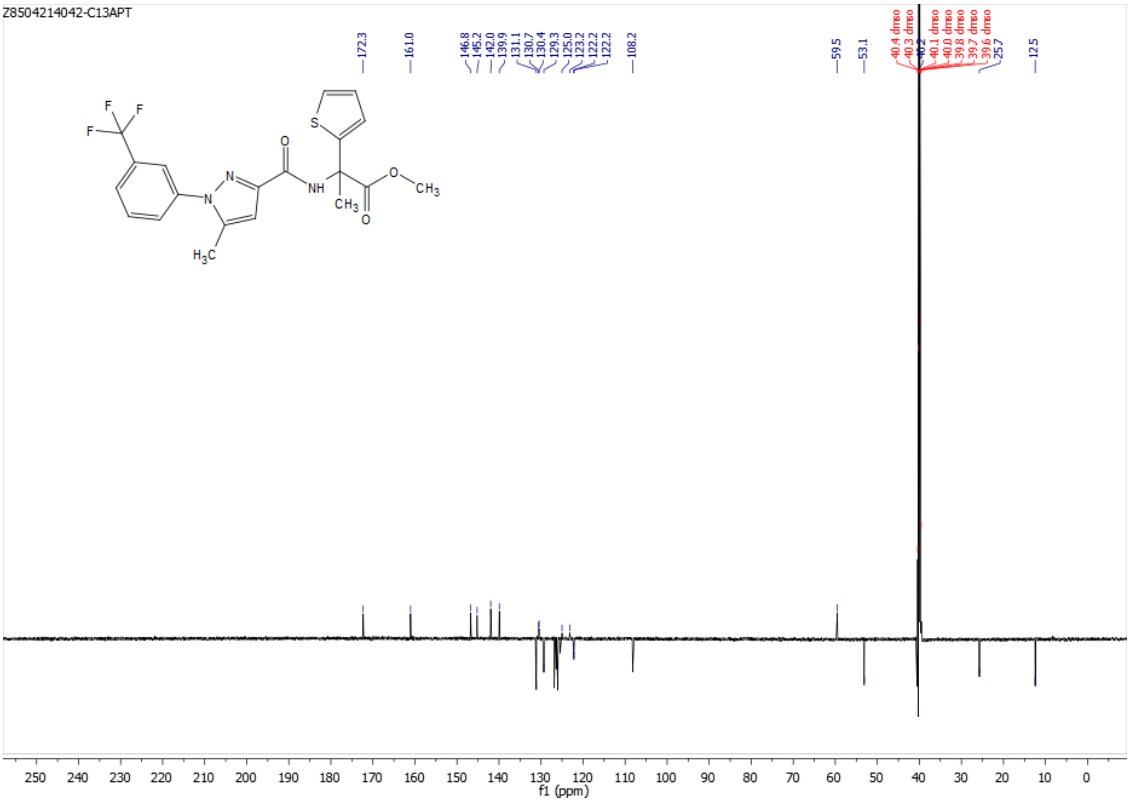
Spectral Data for ‘4042, its enantiomers, and ‘4936.



Z8504214042



Z8504214042



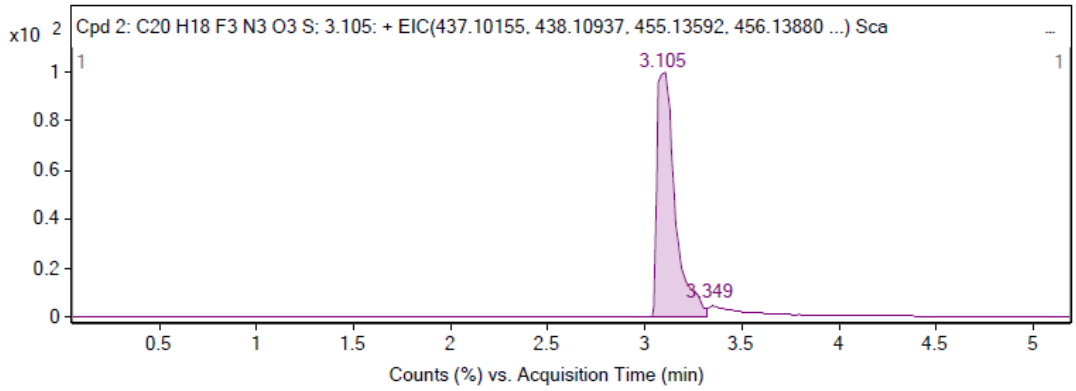
Z8504214042

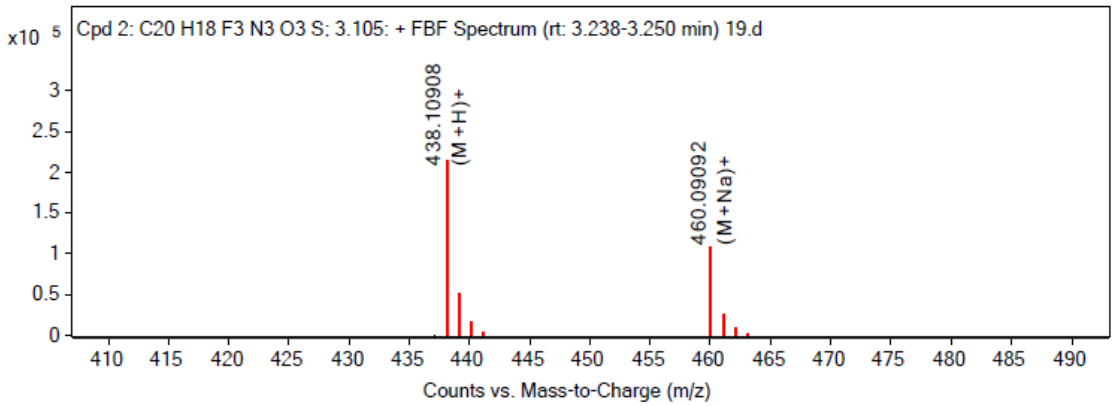
Compound Table

Label	Tgt Score	Mass Error (ppm)	Tgt Formula	Obs. RT	Ref. Mass	Obs. Mass
Cpd 2: C20 H18 F3 N3 O3 S; 3.105	98.89	-0.92	C20 H18 F3 N3 O3 S	3.105	437.1021	437.10169

Obs. *m/z*	Obs. RT	Obs. Mass	Tgt Formula	Tgt Mass	Tgt Mass Error (ppm)	RT Diff.	Find Cpds Algorithm
460.09092	3.105	437.10169	C20 H18 F3 N3 O3 S	437.1021	-0.92	Find By Formula	

Compound Chromatograms

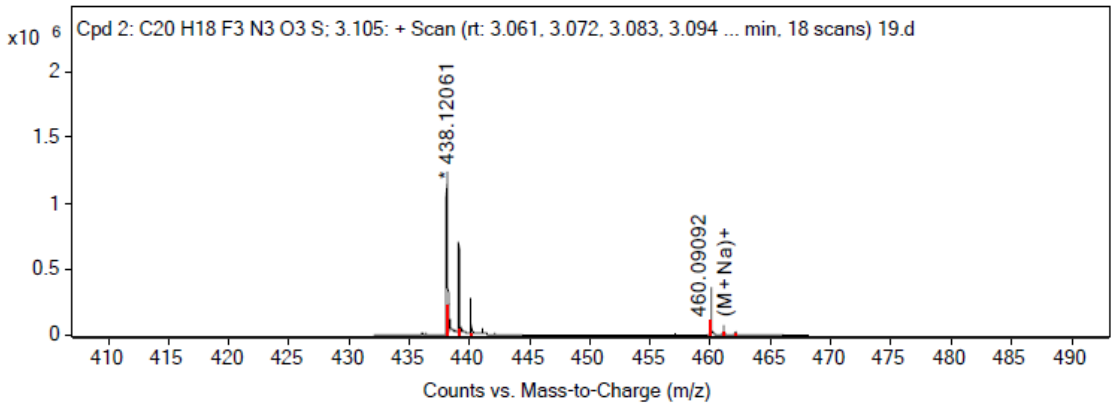




MS Spectrum Peak List

Obs. *m/z*	Charge	Abund	Ion/Isotope
437.09646	1	721.56	M+
438.10908	1	214832.16	(M+H)+
439.11167	1	44635.38	(M+H)+
440.10898	1	14234.8	(M+H)+
441.10958	1	2337.3	(M+H)+
460.09092	1	107890.51	(M+Na)+
461.09352	1	24119.89	(M+Na)+
462.0906	1	7645.8	(M+Na)+
463.09444	1	1390.56	(M+Na)+

MS Zoomed Spectrum



MS Spectrum Peak List

Obs. *m/z*	Charge	Abund	Ion/Isotope	Tgt Mass Error (ppm)
437.09646	1	721.56	M+	11.65
438.10908	1	214832.16	(M+H)+	0.67
438.12061		1248557.22		
439.11167	1	44635.38	(M+H)+	1.52
440.10898	1	14234.8	(M+H)+	0.85
441.10958	1	2337.3	(M+H)+	2.26
460.09092	1	107890.51	(M+Na)+	0.86
461.09352	1	24119.89	(M+Na)+	1.65
462.0906	1	7645.8	(M+Na)+	1.53
463.09444	1	1390.56	(M+Na)+	-4.15

--- End Of Report ---

Z8504214042

Data File: C:\USERS\PUBLIC\DOCUMENTS\CHEMSTATION\1\DATA\2023-05-12_NIGHT\2023-05-12 2023-05-12 17-42-28\BB338254$1_8199_RA->

Sample Name: BB338254$1_8199_RAC

Acq. Operator : SYSTEM Location: 91

Acq. Instrument : HPLC_07

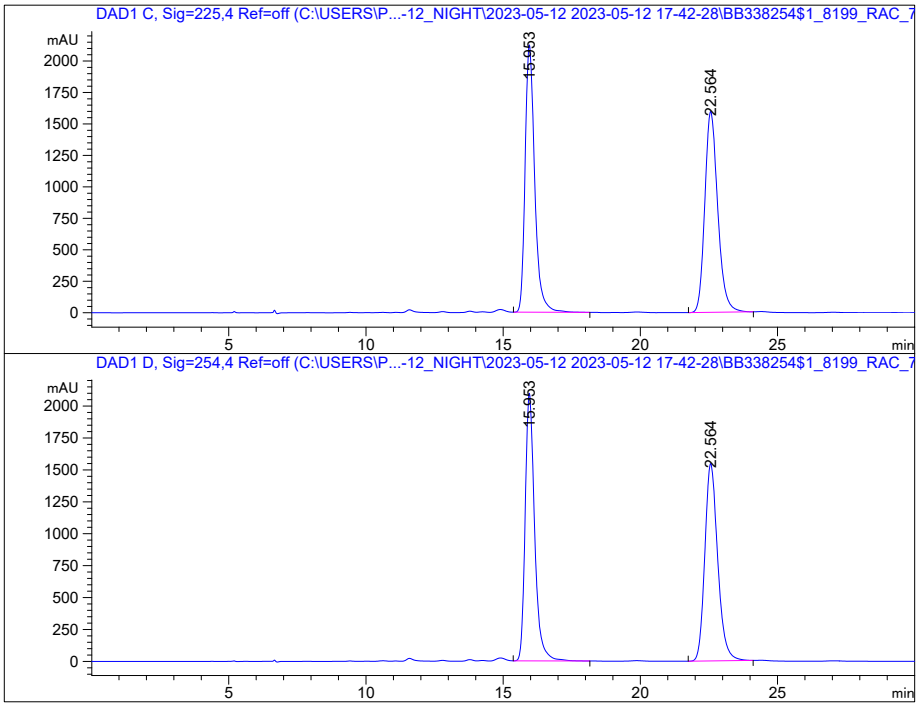
Injection Date : 6:14:56 PM 5/12/2023

Injection Volume: 5 mkl

Column: Chiralpak IC (250x4.6 mm, 5 mkm)--833VJ002-DA181--7

Mobile Phase: Hexane:MeOH:IPA, 70:15:15

Flow Rate: 0.6 ml/min



Signal: DAD1 C, Sig=225,4 Ref=off

RetTime(min)	Area,%	Area	Resolution	Selectivity	30.000
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22.5642	50.33	52220	9.08	1.62	

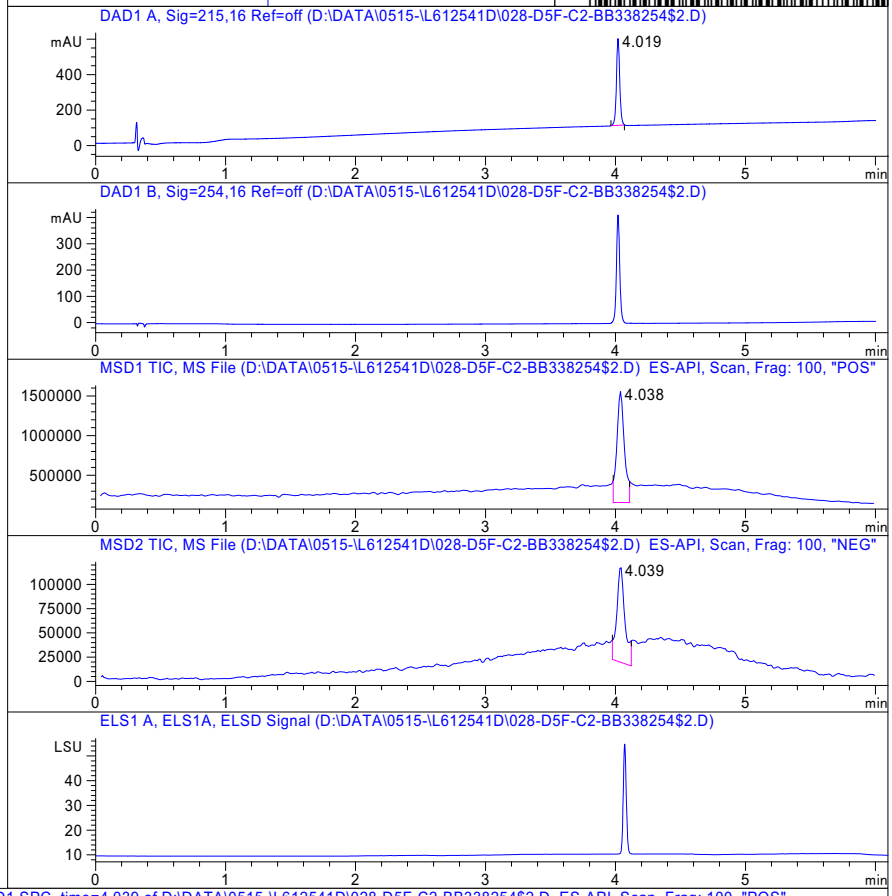
Signal: DAD1 D, Sig=254,4 Ref=off

RetTime(min)	Area,%	Area	Resolution	Selectivity	30.000
15.9532	49.88	50153			
22.5642	50.12	50389	9.17	1.62	

Z8504214042

MaxPeak: 100.00%
Ret_Time: 4.019 min

BB338254$2



Mol Wt 437.44
Exact Mass 437.12

#	Time	Area%
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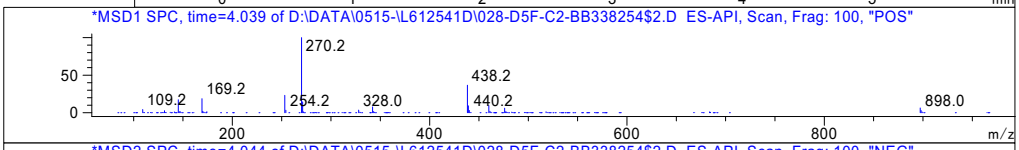
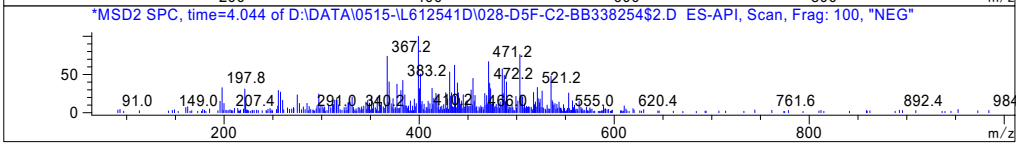
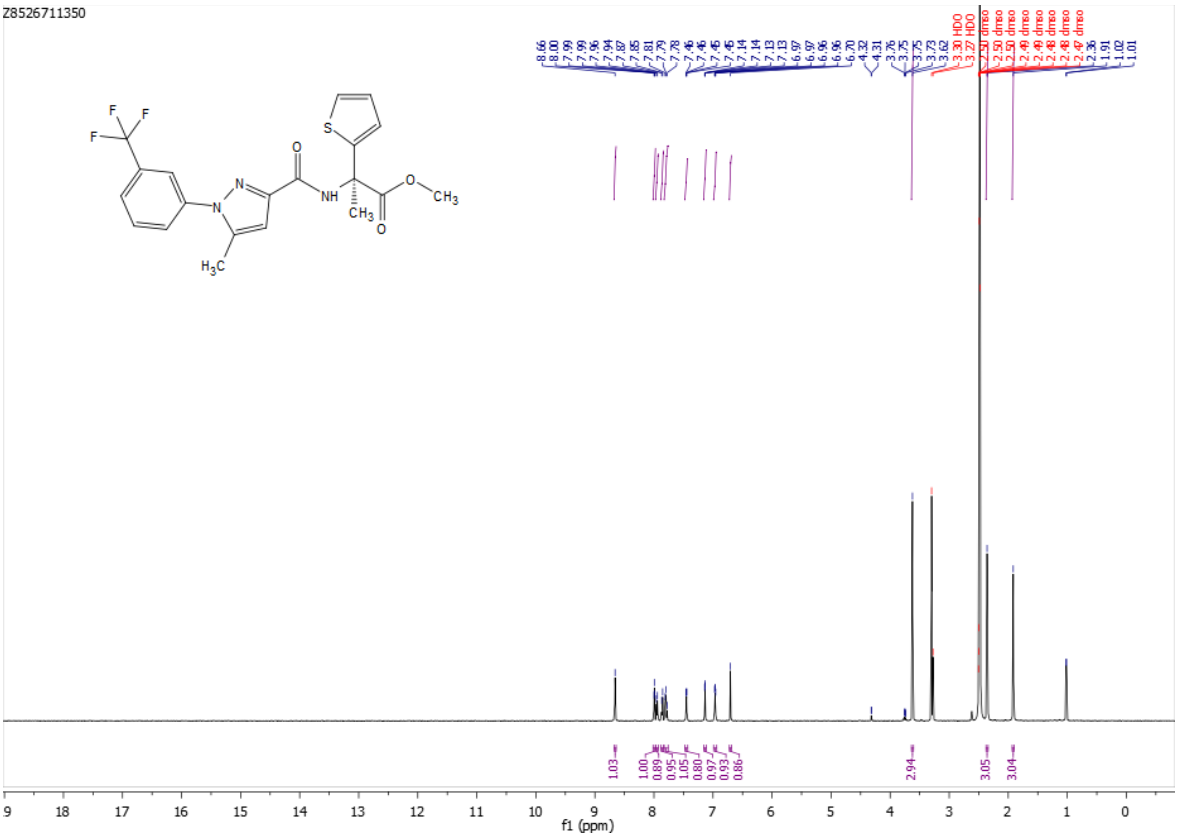
RT 4.038



RT 4.039





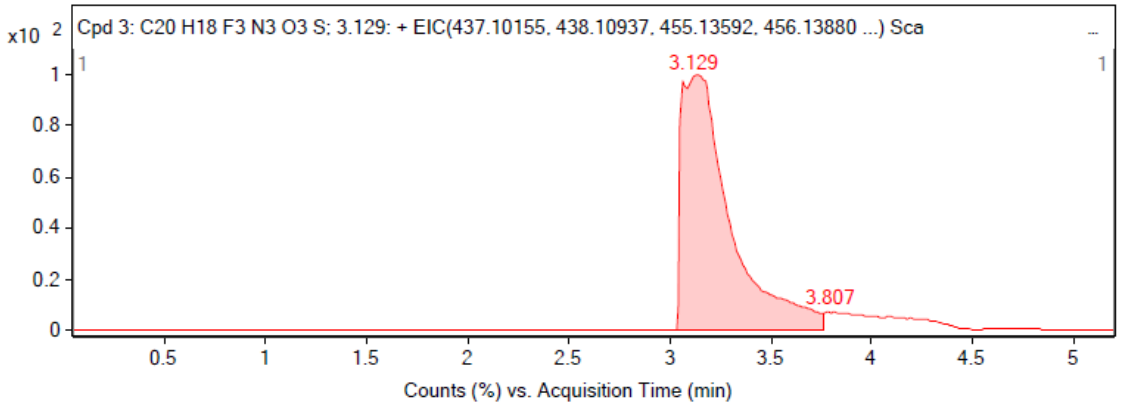
Z8526711350

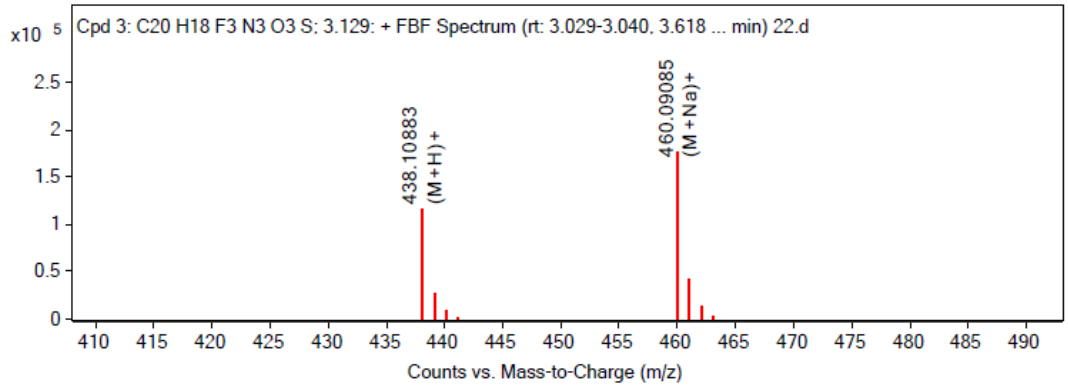
Compound Table

Label	Tgt Score	Mass Error (ppm)	Tgt Formula	Obs. RT	Ref. Mass	Obs. Mass
Cpd 3: C20 H18 F3 N3 O3 S; 3.129	98.44	-1.13	C20 H18 F3 N3 O3 S	3.129	437.1021	437.1016

Obs. *m/z*	Obs. RT	Obs. Mass	Tgt Formula	Tgt Mass	Tgt Mass Error (ppm)	RT Diff.	Find Cpds Algorithm
438.10883	3.129	437.1016	C20 H18 F3 N3 O3 S	437.1021	-1.13	Find By Formula	

Compound Chromatograms

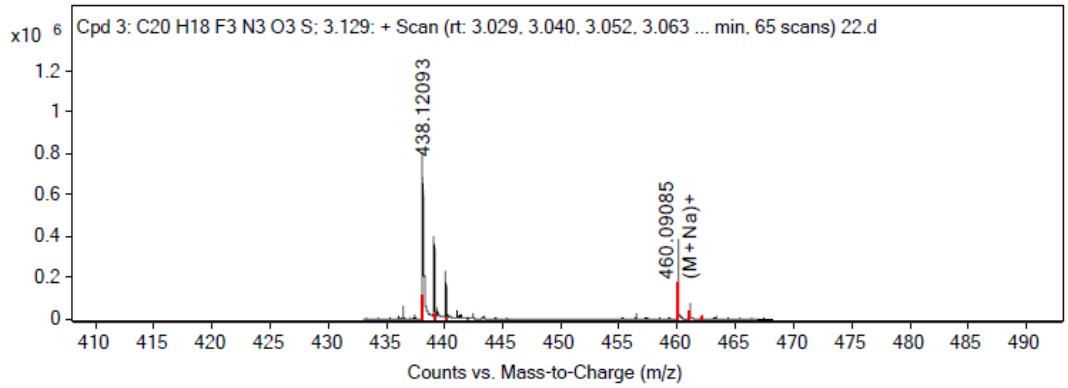




MS Spectrum Peak List

Obs. *m/z*	Charge	Abund	Ion/Isotope
438.10883	1	117409.48	(M+H)+
439.11148	1	26160.09	(M+H)+
440.1095	1	8223.04	(M+H)+
441.10948	1	1344.91	(M+H)+
460.09085	1	177480.36	(M+Na)+
461.09388	1	37935.23	(M+Na)+
462.09065	1	11314.79	(M+Na)+
463.09462	1	1967.56	(M+Na)+

MS Zoomed Spectrum



MS Spectrum Peak List

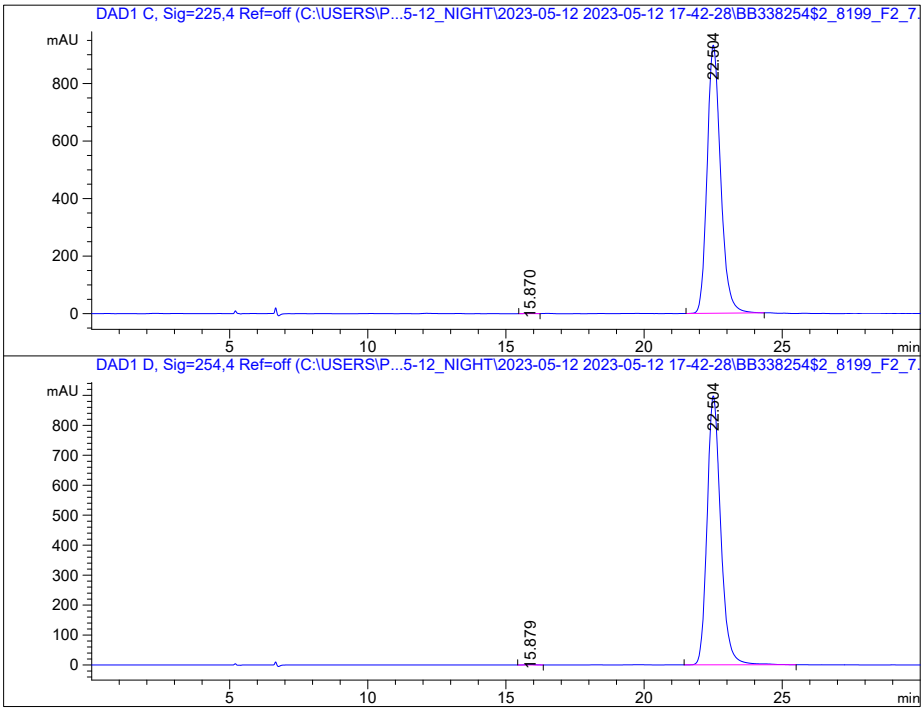
Obs. *m/z*	Charge	Abund	Ion/Isotope	Tgt Mass Error (ppm)
438.10883	1	117409.48	(M+H)+	1.24
438.12093		817354.68		
439.11148	1	26160.09	(M+H)+	1.94
440.1095	1	8223.04	(M+H)+	-0.32
441.10948	1	1344.91	(M+H)+	2.48
460.09085	1	177480.36	(M+Na)+	1.02
461.09388	1	37935.23	(M+Na)+	0.88
462.09065	1	11314.79	(M+Na)+	1.41
463.09462	1	1967.56	(M+Na)+	-4.55

--- End Of Report ---

Z8526711350

Data File: C:\USERS\PUBLIC\DOCUMENTS\CHEMSTATION\1\DATA\2023-05-12_NIGHT\2023-05-12 2023-05-12 17-42-28\BB338254$2_8199_F2->
Sample Name: BB338254$2_8199_F2

Acq. Operator : SYSTEM Location: 93
Acq. Instrument : HPLC_07
Injection Date : 7:17:16 PM 5/12/2023
Injection Volume: 5 mkl
Column: Chiralpak IC (250x4.6 mm, 5 mkm)--833VJ002-DA181--7
Mobile Phase: Hexane:MeOH:IPA, 70:15:15
Flow Rate: 0.6 ml/min



Signal: DAD1 C, Sig=225,4 Ref=off

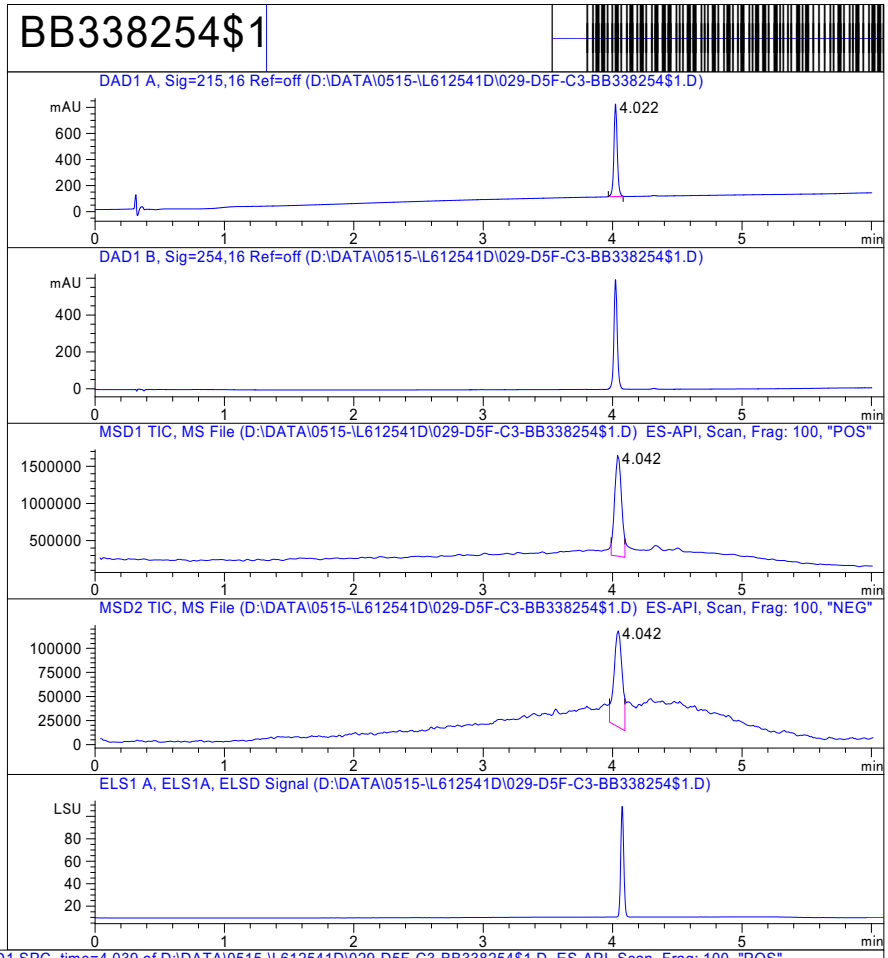
RetTime(min)	Area,%	Area	Resolution	Selectivity	29.997
15.8702	0.11	35			
22.5042	99.89	31614	9.14	1.63	

Signal: DAD1 D, Sig=254,4 Ref=off

RetTime(min)	Area,%	Area	Resolution	Selectivity	29.997
15.8792	0.12	37			
22.5042	99.88	30708	9.02	1.63	

Z8526711350

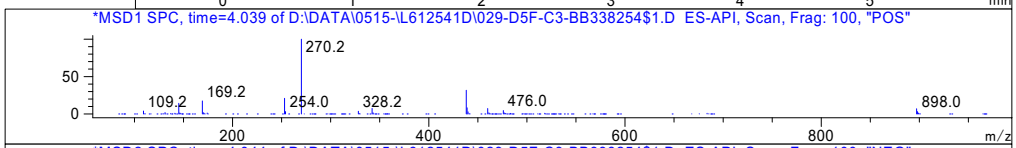
MaxPeak: 100.00%
Ret_Time: 4.022 min



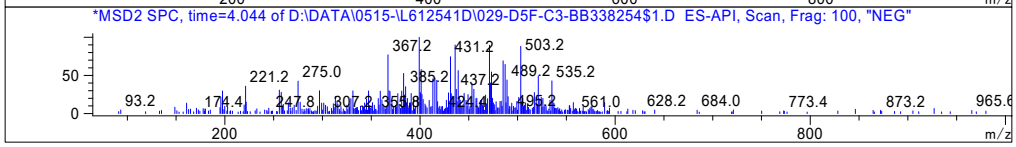
Mol Wt **437.44**
Exact Mass **437.12**

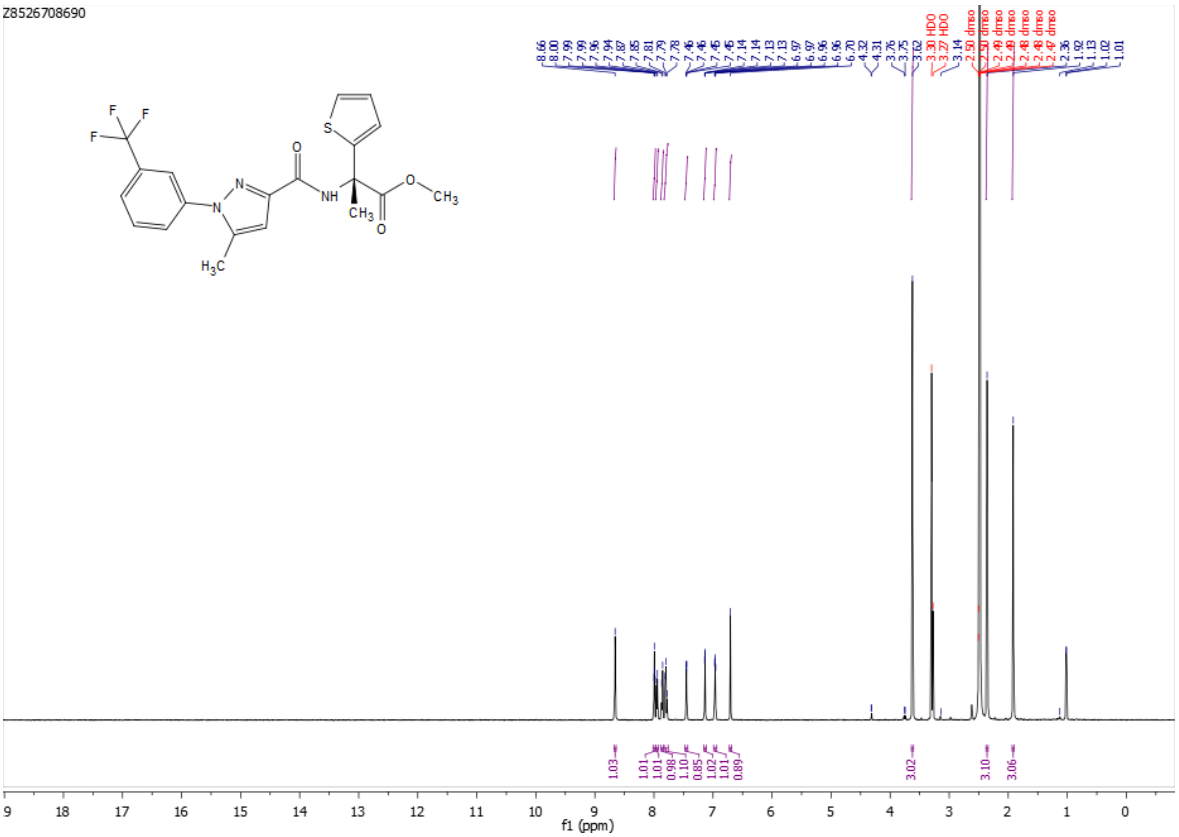
#	Time	Area%
1	4.022	100.00

RT 4.042



RT 4.042





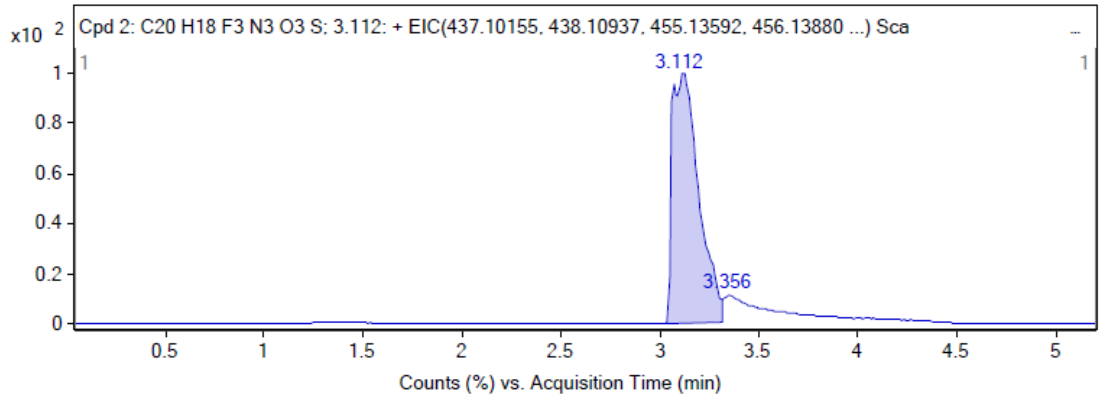
Z8526708690

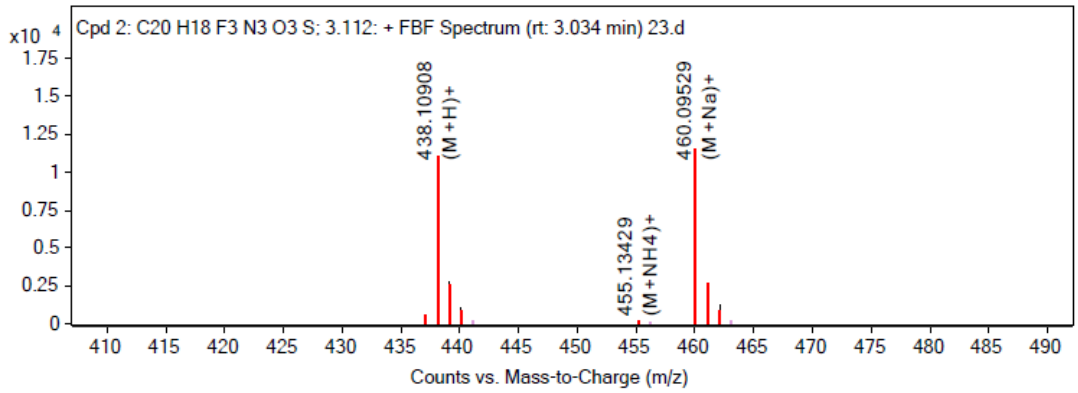
Compound Table

Label	Tgt Score	Mass Error (ppm)	Tgt Formula	Obs. RT	Ref. Mass	Obs. Mass
Cpd 2: C20 H18 F3 N3 O3 S; 3.112	86.33	2.54	C20 H18 F3 N3 O3 S	3.112	437.1021	437.10321

Obs. *m/z*	Obs. RT	Obs. Mass	Tgt Formula	Tgt Mass	Tgt Mass Error (ppm)	RT Diff.	Find Cpds Algorithm
438.10908	3.112	437.10321	C20 H18 F3 N3 O3 S	437.1021	2.54	Find By Formula	

Compound Chromatograms

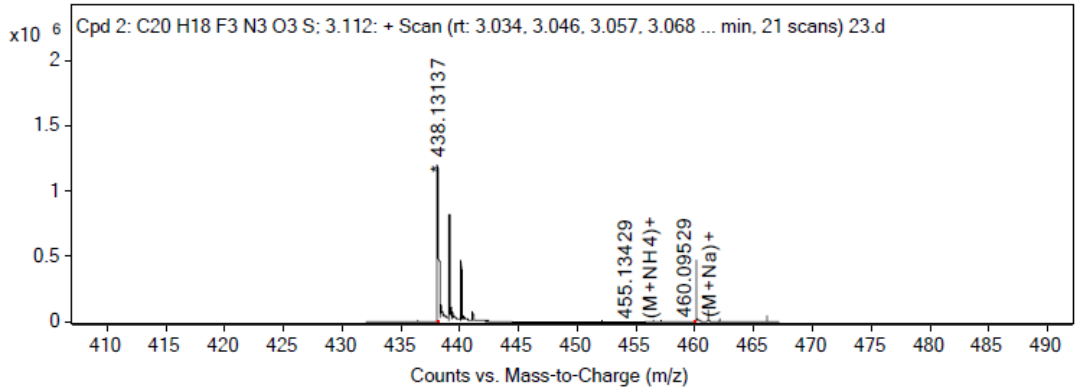




MS Spectrum Peak List

Obs. m/z	Charge	Abund	Ion/Isotope
437.09596	1	614.12	M+
438.10908	1	10678.29	(M+H)+
439.11323	1	2842.31	(M+H)+
440.10169	1	1031.5	(M+H)+
455.13429	1	229.03	(M+NH4)+
460.09529	1	11240.28	(M+Na)+
461.0982	1	2619.27	(M+Na)+
462.08445	1	1270.68	(M+Na)+

MS Zoomed Spectrum



MS Spectrum Peak List

Obs. m/z	Charge	Abund	Ion/Isotope	Tgt Mass Error (ppm)
437.09596	1	614.12	M+	12.78
438.10908	1	10678.29	(M+H)+	0.66
438.13137		1206603.73		
439.11323	1	2842.31	(M+H)+	-2.04
440.10169	1	1031.5	(M+H)+	17.42
455.13429	1	229.03	(M+NH4)+	3.58
460.09529	1	11240.28	(M+Na)+	-8.63
461.0982	1	2619.27	(M+Na)+	-8.5
462.08445	1	1270.68	(M+Na)+	14.83

--- End Of Report ---

Z8526708690

Data File: C:\USERS\PUBLIC\DOCUMENTS\CHEMSTATION\1\DATA\2023-05-12_NIGHT\2023-05-12 2023-05-12 17-42-28\BB338254$1_8199_F1->

Sample Name: BB338254$1_8199_F1

Acq. Operator : SYSTEM Location: 92

Acq. Instrument : HPLC_07

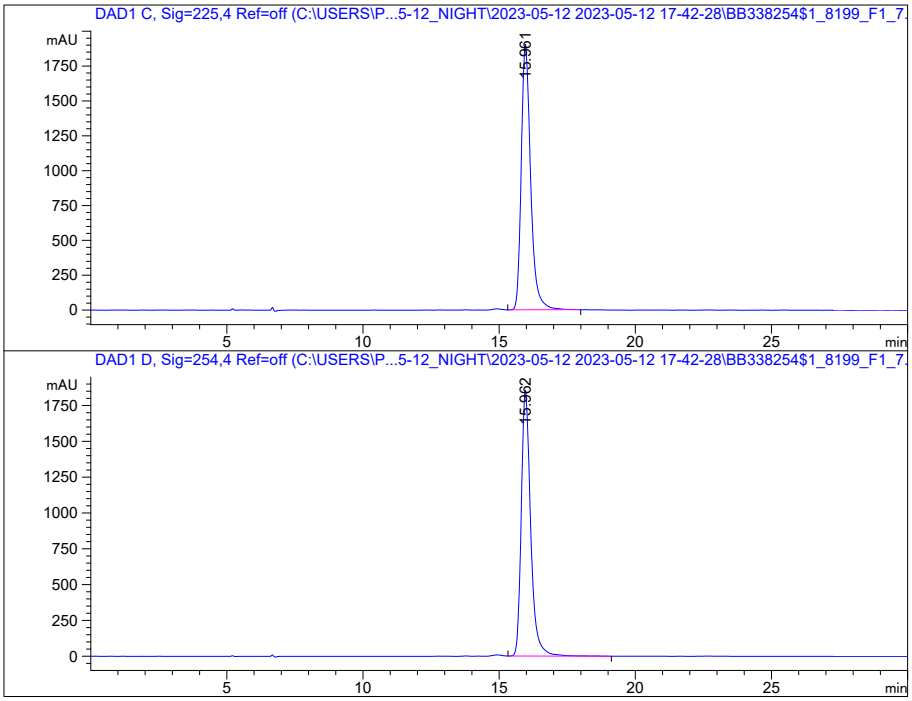
Injection Date : 6:46:10 PM 5/12/2023

Injection Volume: 5 mkl

Column: Chiralpak IC (250x4.6 mm, 5 mkm)--833VJ002-DA181--7

Mobile Phase: Hexane:MeOH:IPA, 70:15:15

Flow Rate: 0.6 ml/min



Signal: DAD1 C, Sig=225,4 Ref=off

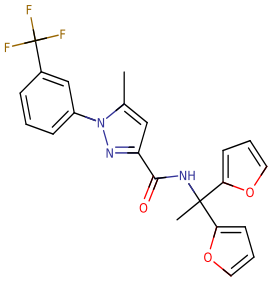
RetTime(min)	Area,%	Area	Resolution	Selectivity	30.001
15.9612	100.00	45699			

Signal: DAD1 D, Sig=254,4 Ref=off

RetTime(min)	Area,%	Area	Resolution	Selectivity	30.001
15.9622	100.00	44470			

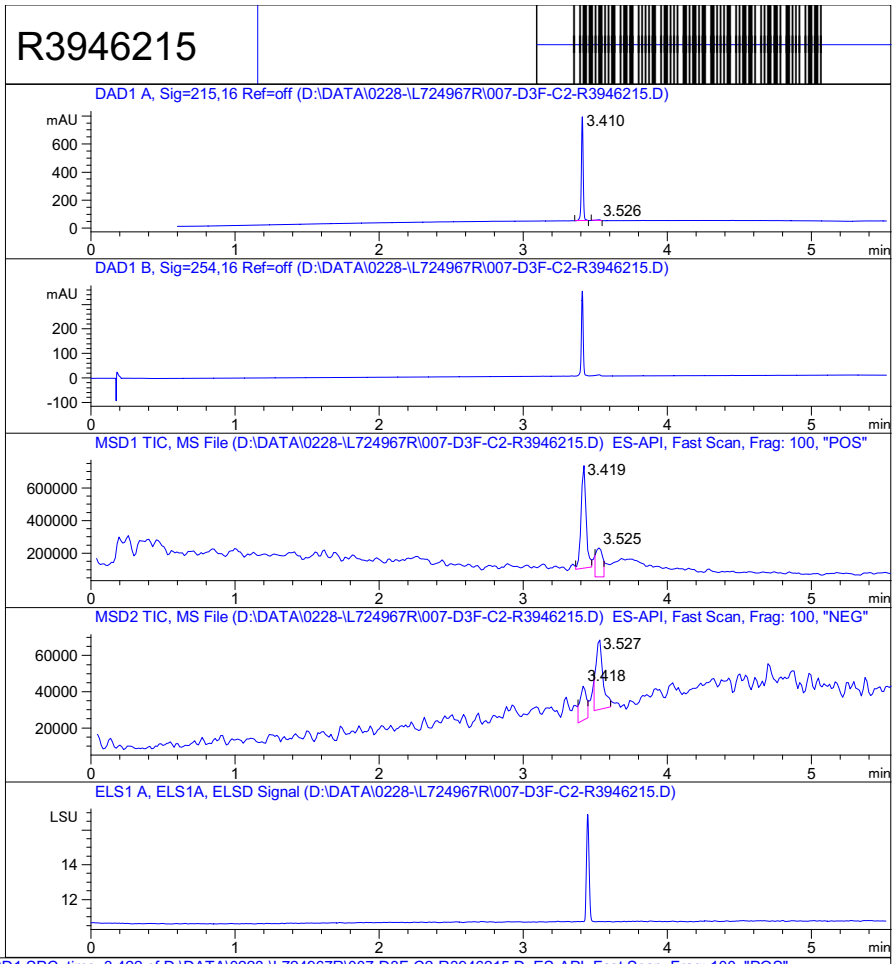
Z8526708690

MaxPeak: 97.90%
Ret_Time: 3.410 min

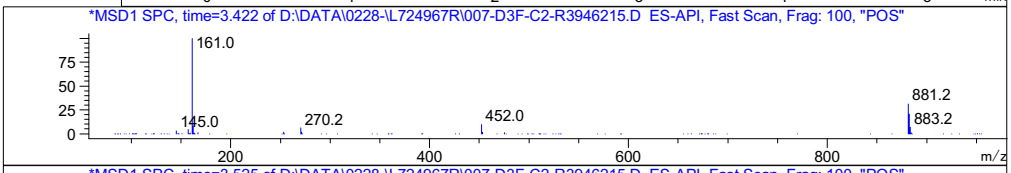


Mol Wt **429.39**
Exact Mass **429.15**

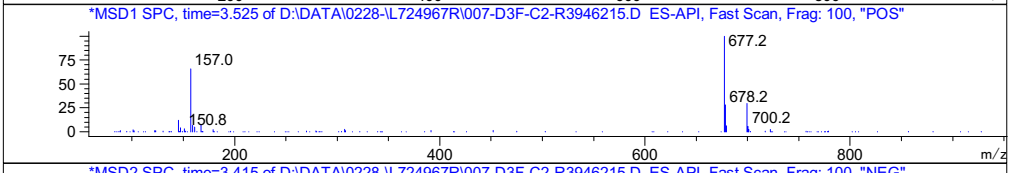
#	Time	Area%
1	3.410	97.90
2	3.526	2.10



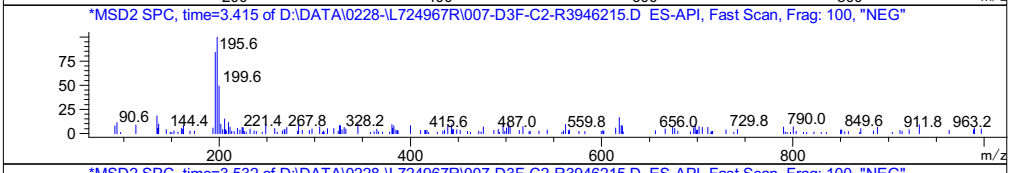
RT 3.419



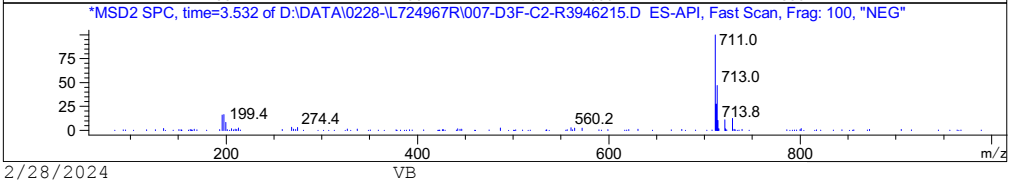
RT 3.525



RT 3.418



RT 3.527



Inj.Date 2/28/2024 VB

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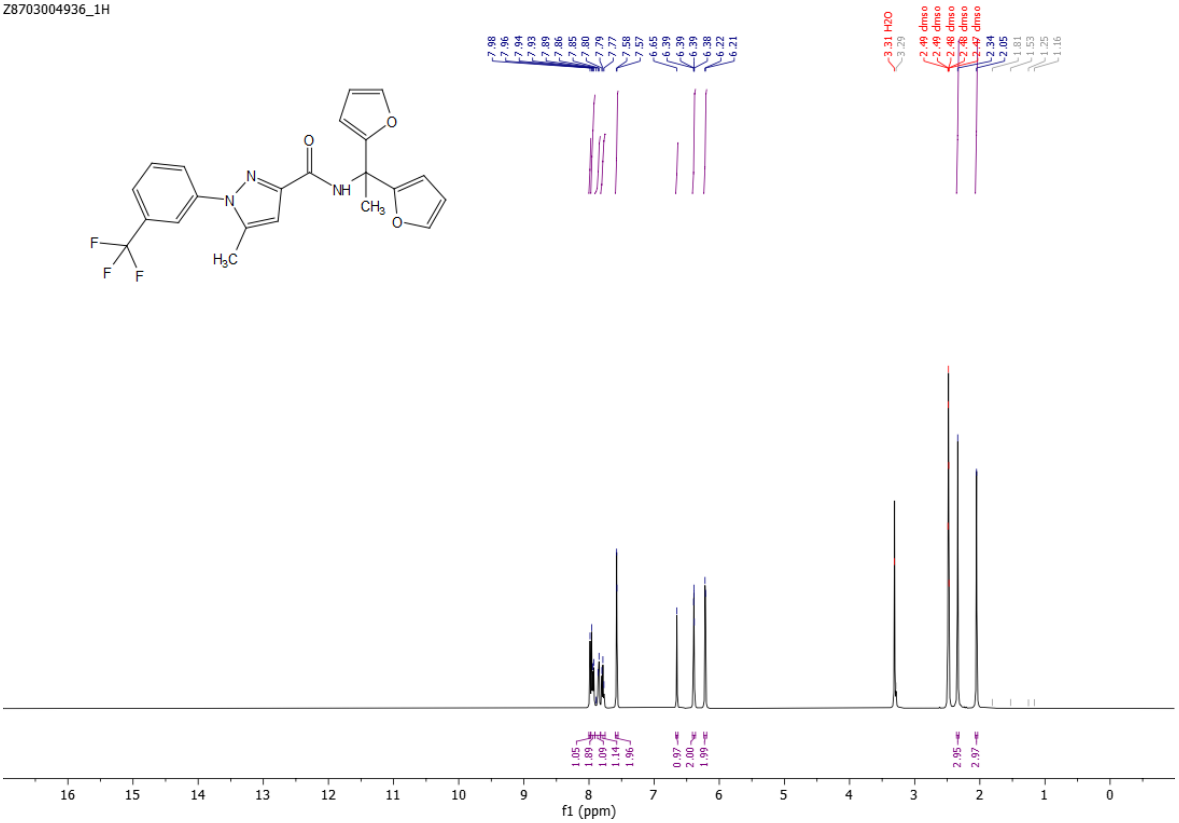
Z8703004936

Z8703004936_1H



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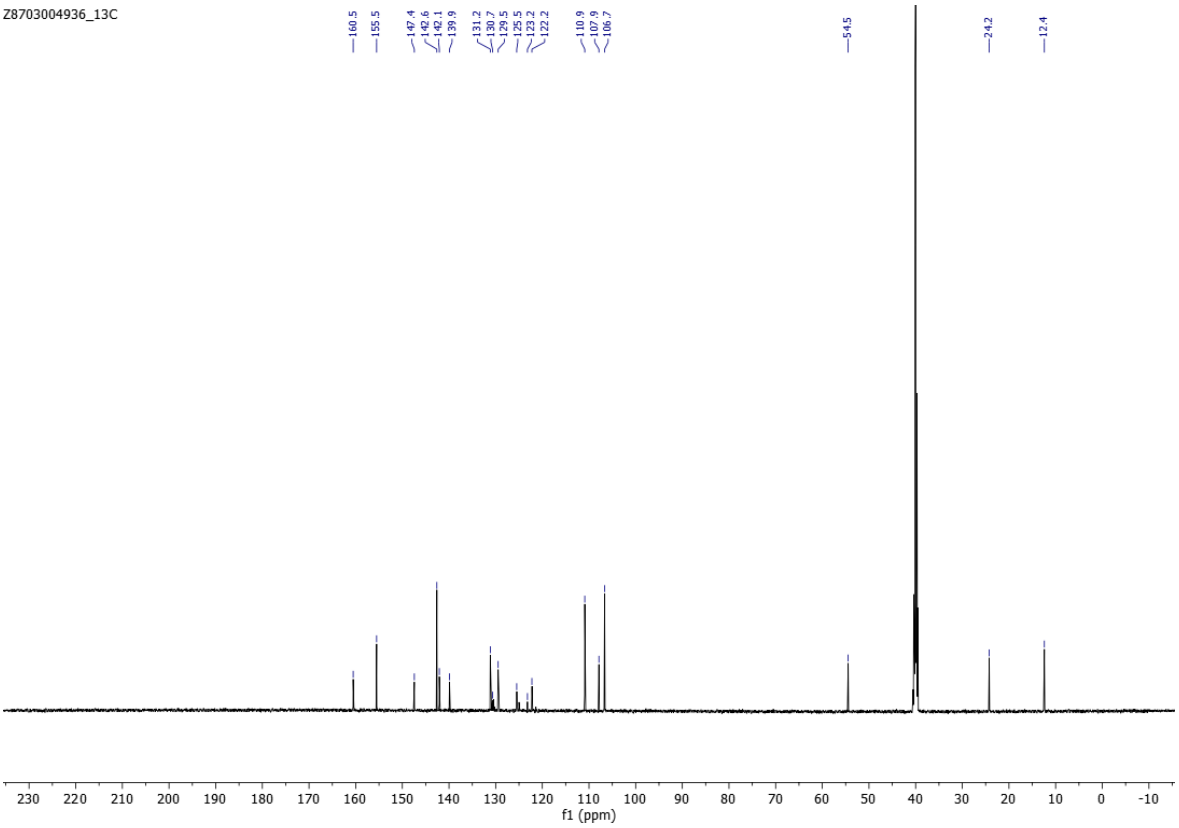

Z8703004936

Supplementary References

80. Tolmachev, A. *et al.* Expanding Synthesizable Space of Disubstituted 1,2,4-Oxadiazoles. *Acs Comb. Sci.* **18**, 616–624 (2016).