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Supplementary Materials for

Drug discovery for psychiatric disorders using high-content single-cell screening of signaling network responses ex vivo

Santiago G. Lago, Jakub Tomasik, Geertje F. van Rees, Hannah Steeb, David A. Cox, Nitin Rustogi, Jordan M. Ramsey, Joshua A. Bishop, Tracey Petryshen, Stephen J. Haggarty, Javier Vázquez-Bourgon, Sergi Papiol, Paula Suarez-Pinilla, Benedicto Crespo-Facorro, Nico J. van Beveren, Sabine Bahn*

*Corresponding author. Email: sb209@cam.ac.uk

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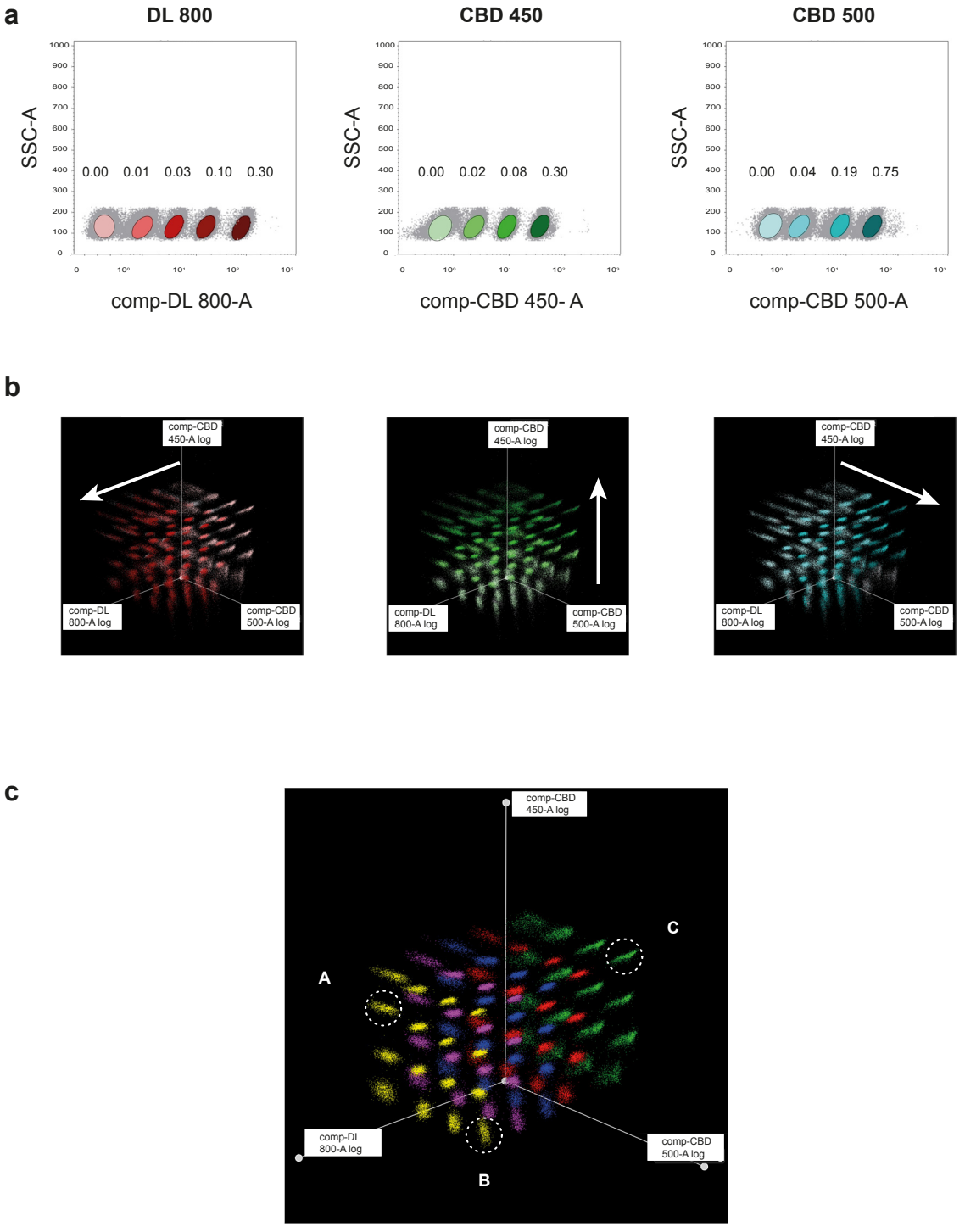
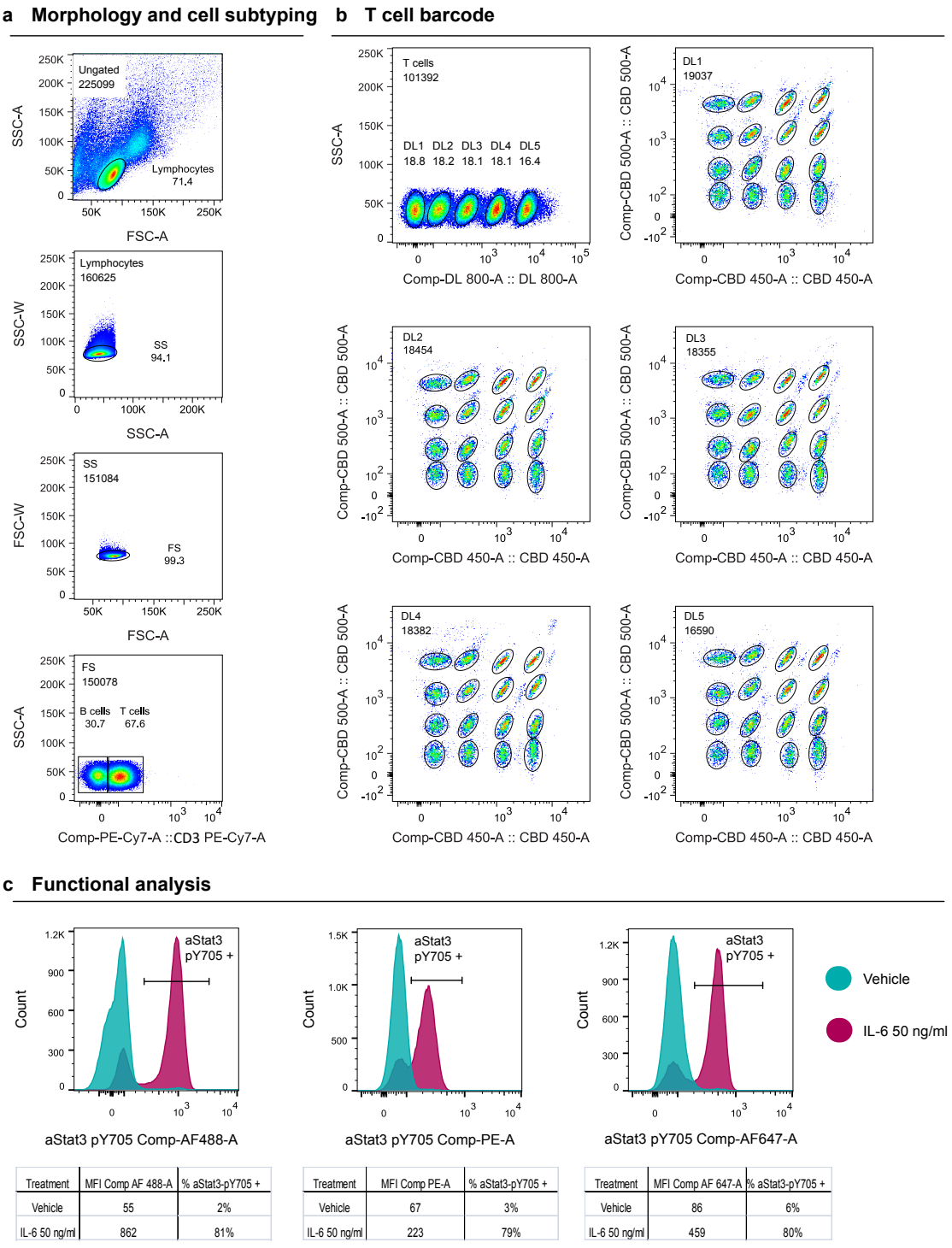


Fig. S1. Construction of a three-dimensional fluorescent cell barcoding matrix for multiplexing of 80 cellular treatments. (**a**) Peripheral blood mononuclear cells (PBMCs) in each treatment (ligand or vehicle) well of a 96 well plate were stained with different intensities of each of three fluorescent barcoding dyes (DL 800, CBD 450 and CBD 500). (**b**) Combination of the three dyes produced the 80 population barcoding matrix in which the contribution of each dye can be visualized as a distinct fluorescence intensity gradient along the x, y and z axes. The 80 populations were then pooled and stained for intracellular signaling epitopes. (**c**) Three dimensional deconvolution of the 80 barcoded populations as individual ligand or vehicle treatments, for example A = staurosporine, B = calyculin and C = vehicle. Data represents one PBMC sample.



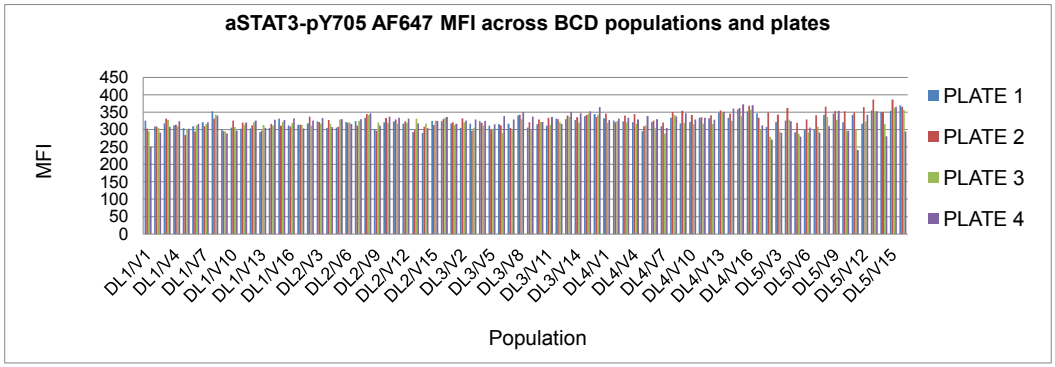
Treatment	MFI Comp AF 488-A	% aStat3-pY705 +
Vehicle	55	2%
IL-6 50 ng/ml	862	81%

Treatment	MFI Comp PE-A	% aStat3-pY705 +
Vehicle	67	3%
IL-6 50 ng/ml	223	79%

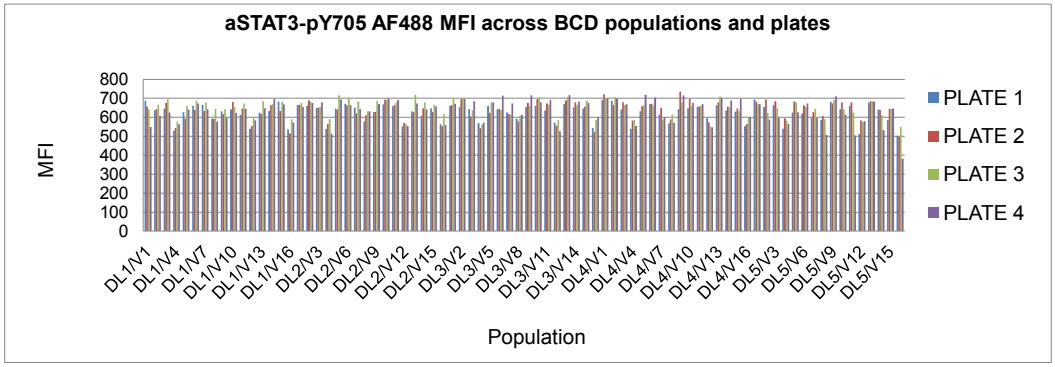
Treatment	MFI Comp AF 647-A	% aStat3-pY705 +
Vehicle	86	6%
IL-6 50 ng/ml	459	80%

Fig. S2. Gating strategies for the functional analysis of 80 barcoded T cell populations. (**a**) Viable cells were gated (FSC-A vs. SSC-A), followed by single cell discrimination (SSC-A vs. SSC-W and FSC-A vs. FSC-W) and T cell subtyping using anti-CD3 PE-Cy7. Population labeled 'B cells' refers to $CD3^-$ cells, comprised largely of B and natural killer (NK) cells. (**b**) 80 populations, each corresponding to a different ligand or vehicle condition, were resolved within the T lymphocyte gate following fluorescent cell barcoding using DL800, CBD 450 and CBD 500 dyes. T cells were gated first for DL800 populations (DL1-5) and subsequently for CBD 450 vs. CBD 500 populations (16 populations). (**c**) Within each barcoded T cell population, functional analysis of intracellular signaling epitopes (n=78) was conducted across AF 488, PE and AF 647 channels. Induction of Stat3 (pY705) phosphorylation in response to 15 min stimulation with IL-6 50 ng/ml is shown as an example. Data represents one peripheral blood mononuclear cell (PBMC) sample. Cell counts are shown for parent gates in the top left hand corner of each dot plot and % frequencies of cells are shown next to gate names. MFI = median fluorescence intensity.

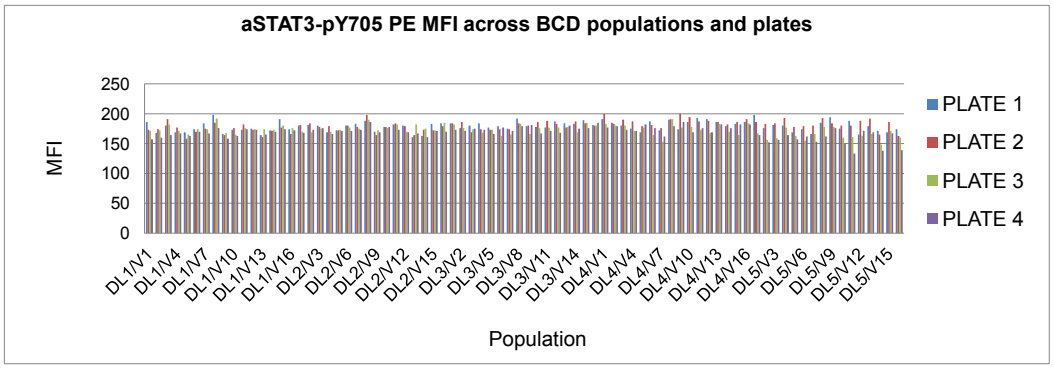
a



b



c



d

Antibody	PLATE 1	PLATE 2	PLATE 3	PLATE 4	Mean
aSTAT3-pY705 AF647	5	7	5	8	6
aSTAT3-pY705 AF488	8	8	7	10	8
aSTAT3-pY705 PE	5	5	5	6	5

Fig. S3. MFIs and CVs across 80 barcoded T cell populations for each functional fluorescence channel. 80 wells in four different plates were treated with IL-6 50 ng/ml for 15 min. Each plate was barcoded separately and the pooled sample from each plate was stained with anti-STAT3 (pY705) AF 647 (**a**), anti-STAT3 (pY705) AF488 (**b**) and anti-STAT3 (pY705) PE (**c**). (**d**) The %CVs for each plate and the mean are shown for each functional channel. Data represents one PBMC sample.

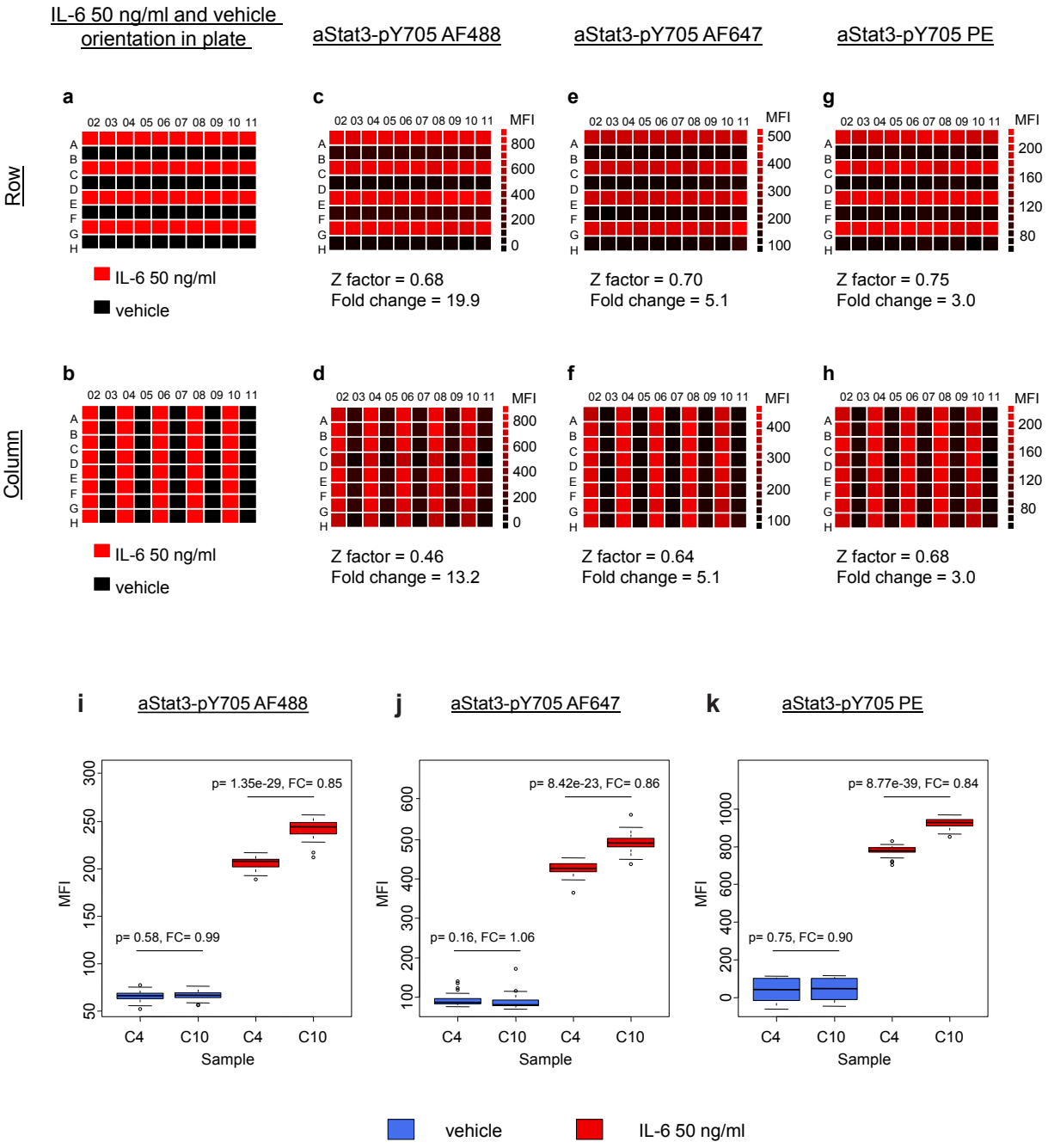


Fig. S4. *Z* factor analyses across 80 barcoded T cell populations for each functional fluorescence channel. Peripheral blood mononuclear cells (PBMCs) were treated for 15 min with IL-6 50 ng/ml or vehide arranged alternately in rows (**a**) or columns (**b**). Mean MFIs (median fluorescence intensities) of two PBMC donors for each barcode population were used to calculate the Z factor and fold change for each orientation after staining with anti-Stat3 (pY705) AF 488 (**c**, **d**), anti-Stat3 (pY705) AF 647 (**e**, **f**) and anti-Stat3 (pY705) PE (**g**, **h**). Differences in Stat3 (pY705) phosphorylation between PBMC donors (C4 and C10) are significant ($p<0.05$, t test) following IL-6 50 ng/ml stimulation but not in vehicle condition across anti-Stat3 (pY705) AF 488 (**i**), anti-Stat3 (pY705) AF 647 (**j**) and anti-Stat3 (pY705) PE (**k**).

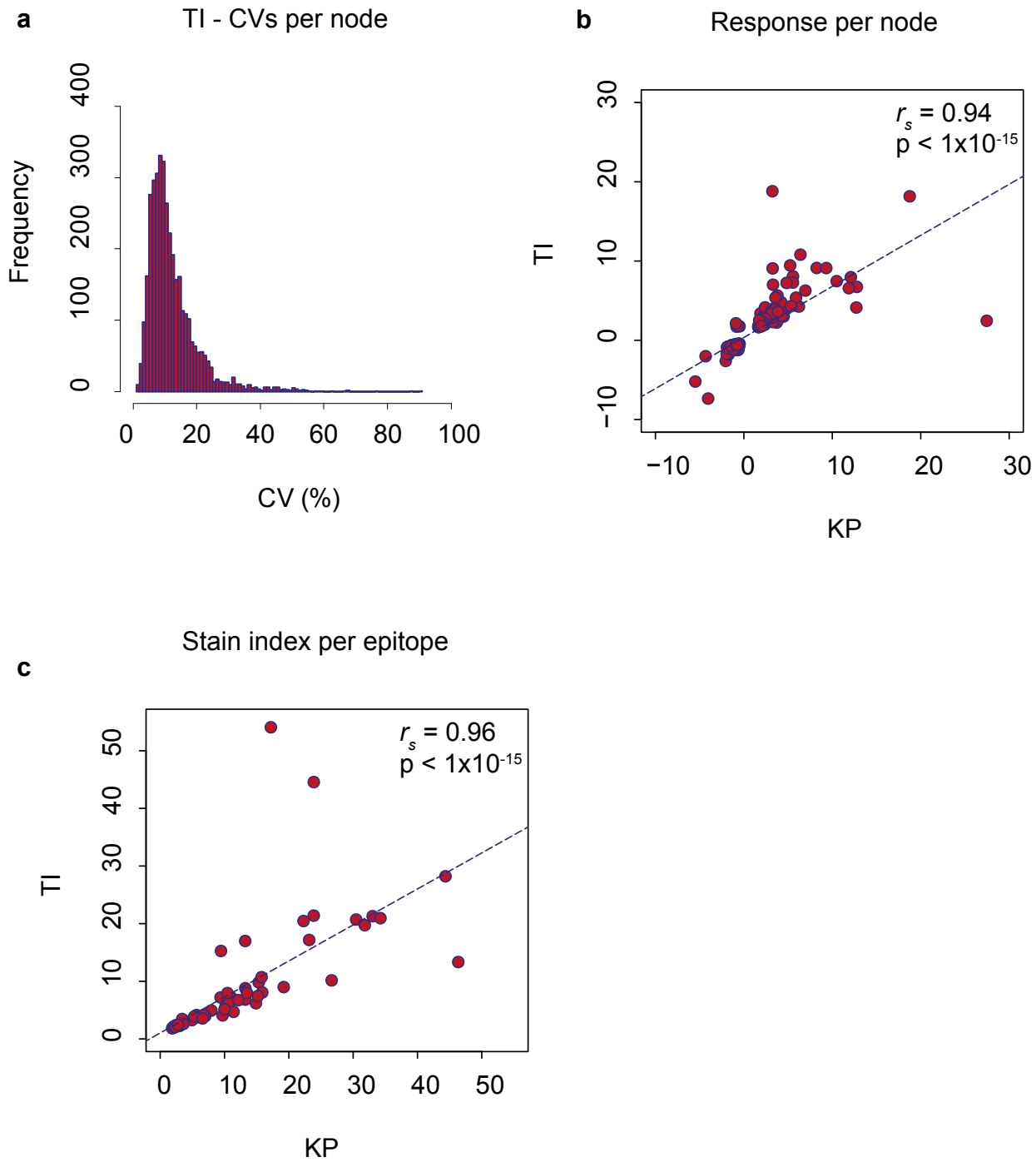


Fig. S5. Reproducibility across time and independent PBMC cohorts. (**a**) CVs for each T cell signaling node (ligand-epitope combination) in the same quality control PBMC sample from a healthy donor measured across six days in the drug target identification (TI) study. (**b**) Spearman's rank correlation of fold change signaling responses (n=197 nodes) in healthy control PBMC donors for nodes which were active in the kinetic profiling (KP) at 30 min (n=8 donors) and validated in the same direction in the TI study (n=12 donors). Three nodes (Akt (pT308)/calyculin, S6 (pS235/pS236)/calyculin, S6 (pS235/pS236)/PMA-ionomycin) with fold changes above 40 were removed from (b) for representation, however r_s and p values are reported for full data set. (**c**) Spearman's rank correlation of stain indices between the KP and TI studies (n=66 epitopes).

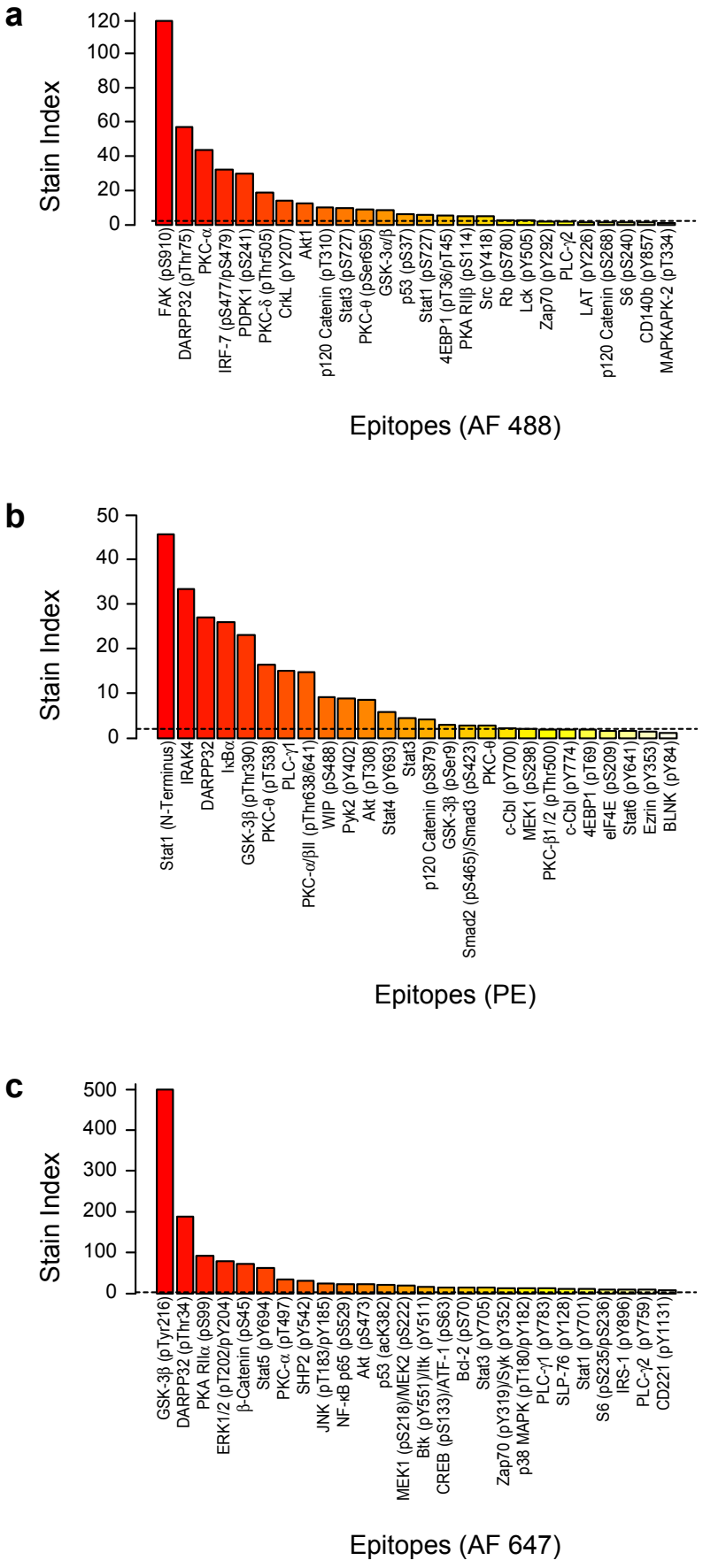


Fig. S6. Stain indices of antibody clones against T cell signaling epitopes used in the KP experiments. Shows the median MFI of the stained samples/median MFI of the unstained samples in the vehicle condition across eight peripheral blood mononuclear cell (PBMC) donors for each epitope. Stain indices are ranked per functional fluorescence detection channel as labeled with a representative fluorochrome: Alexa Fluor 488 (AF 488) (**a**), phycoerythrin (PE) (**b**) and Alexa Fluor 647 (AF 647) (**c**). Dotted line marks threshold stain index of two. MFI = median fluorescence intensity.

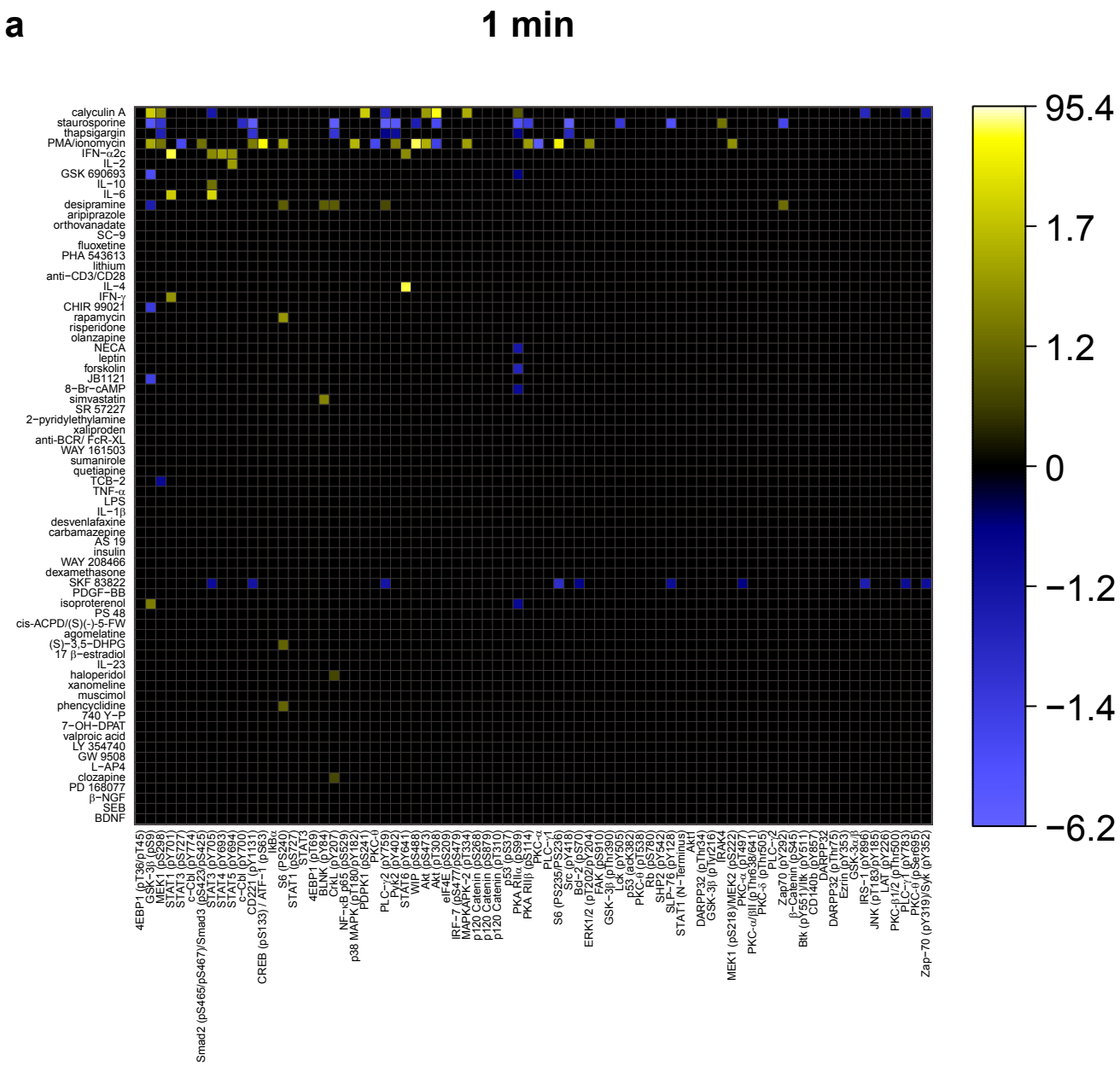


Fig. S7. Kinetic induction of cell signaling responses across the ligand and epitope array (*n* = 5460 nodes; i.e., ligand-epitope combinations). Responses in T cells to 70 diverse functional ligands (y axes) were measured at 78 intracellular signaling epitopes (x axes) following 1 min (**a**), 5 min (**b**), 15 min (**c**) or 30 min (**d**) ligand incubation times. Legend shows fold change in epitope expression, calculated as median MFI of the ligand treatment/median MFI of the vehicle treatment across eight peripheral blood mononuclear cell (PBMC) donors, with labels distributed evenly across the quantile range for negative and positive fold changes separately. For downregulated epitopes, the legend shows -1/fold change. For each epitope only ligands which showed significant responses (permuted P<0.05, Wilcoxon rank-sum test) with a minimum fold change of 10%, relative to the vehicle, are shown. Ligands and epitopes are ranked in terms of the number of significantly responding nodes at 30 min time point. MFI = median fluorescence intensity.

b **5 min**

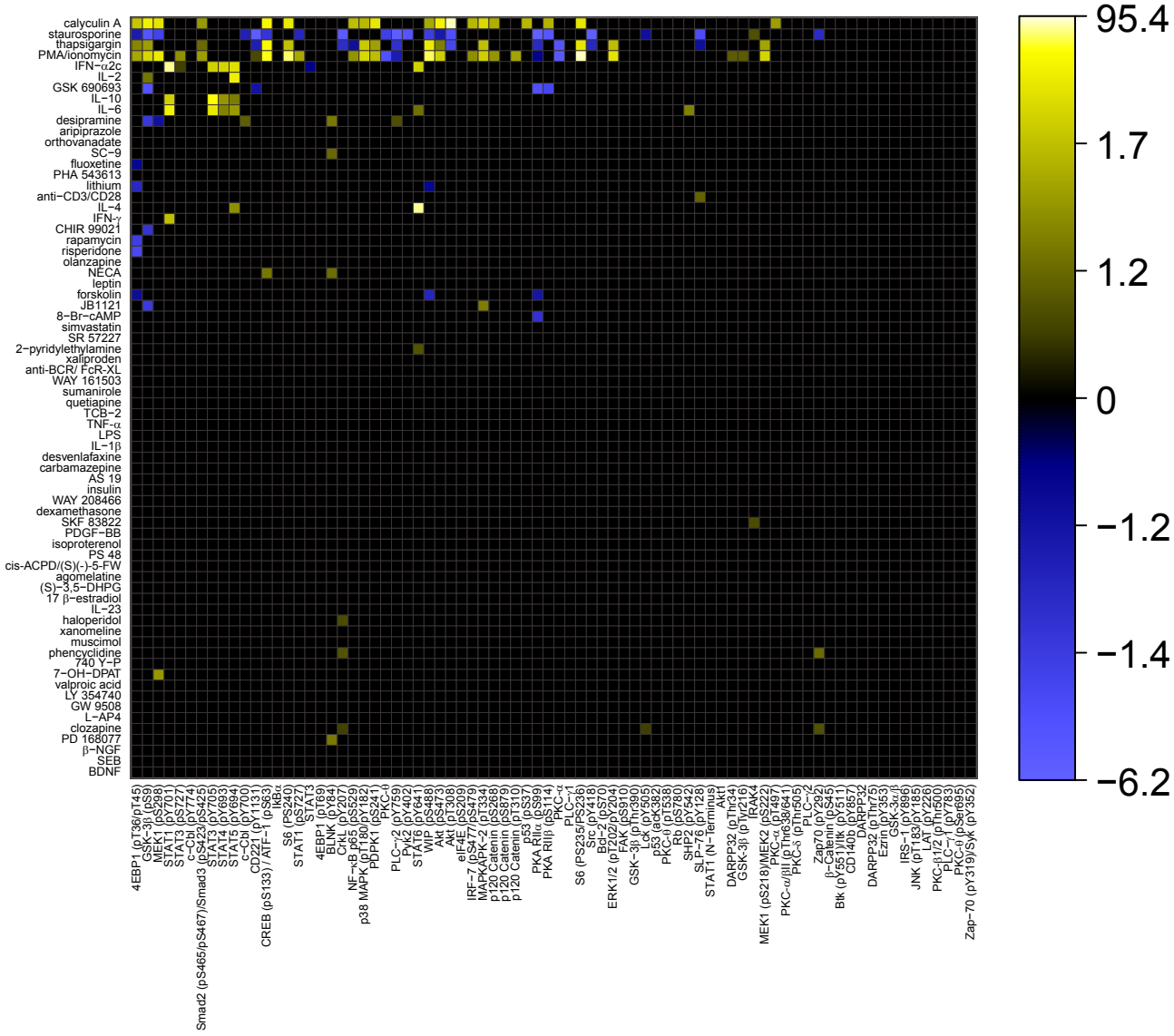


Fig. S7 Kinetic induction of cell signaling responses across the ligand and epitope array (n=5460 nodes, i.e. ligand-epitope combinations) - continued.

c **15 min**

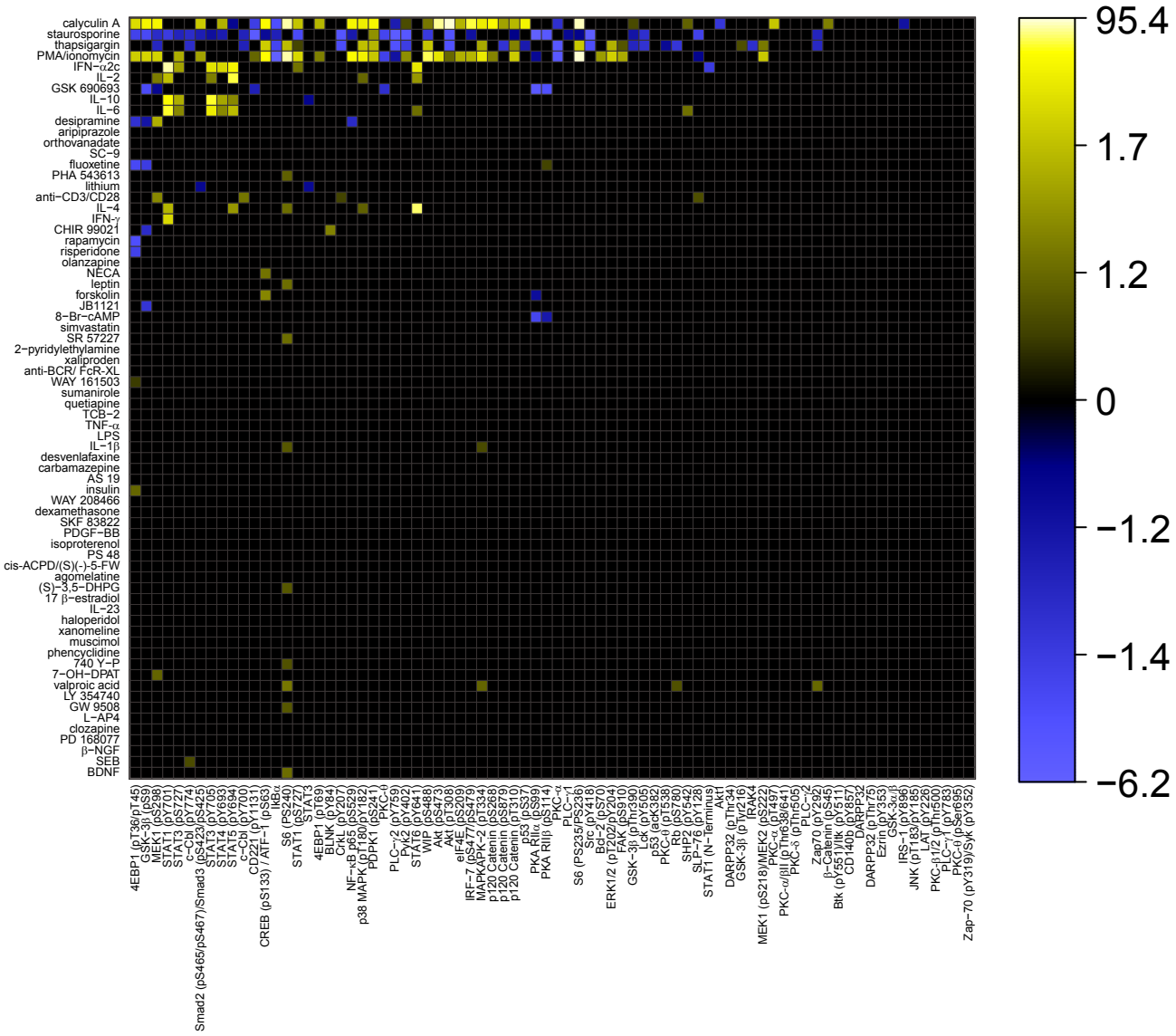


Fig. S7 Kinetic induction of cell signaling responses across the ligand and epitope array (n=5460 nodes, i.e. ligand-epitope combinations) - continued.

d **30 min**

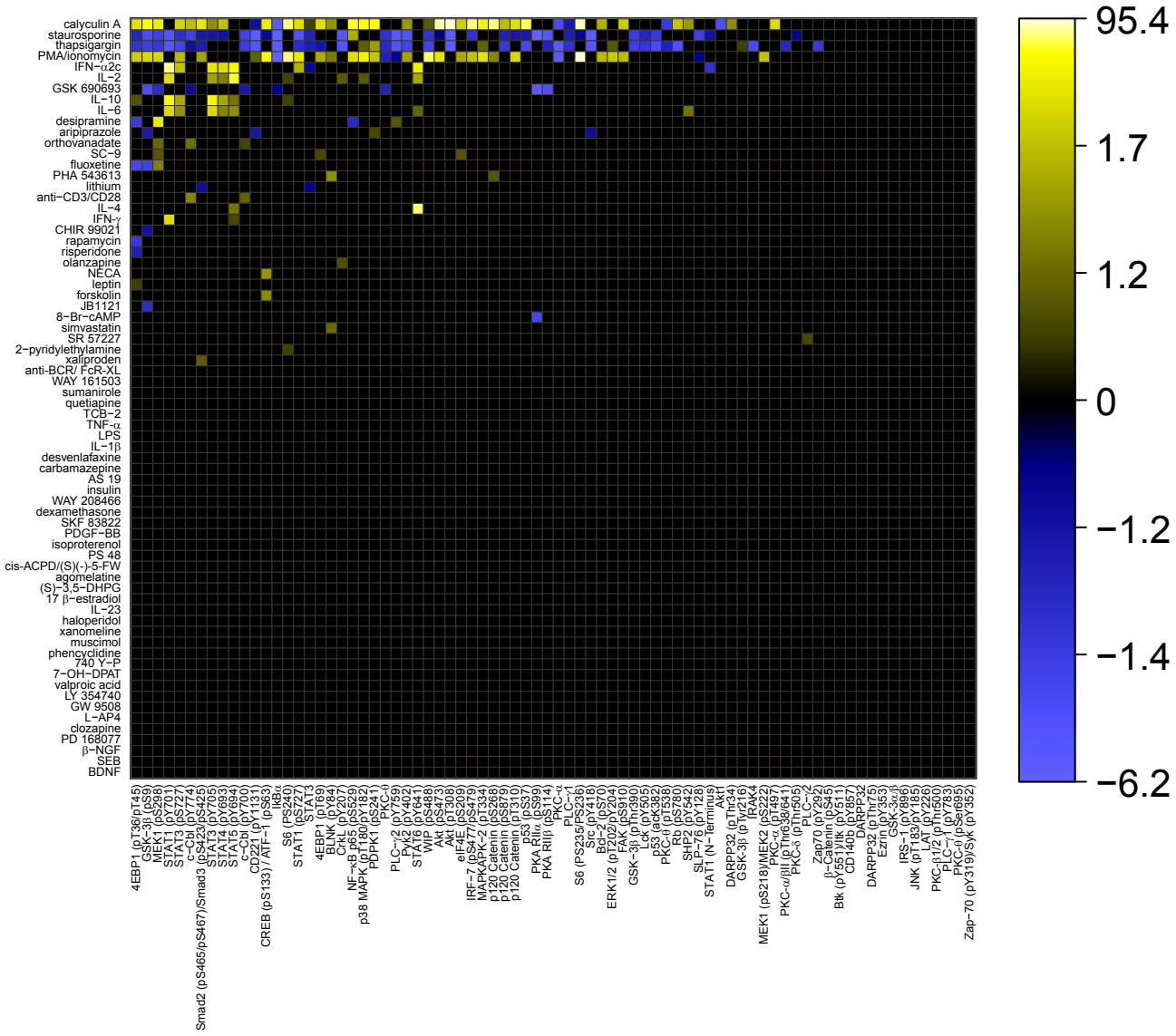


Fig. S7 Kinetic induction of cell signaling responses across the ligand and epitope array (n=5460 nodes, i.e. ligand-epitope combinations) - continued.

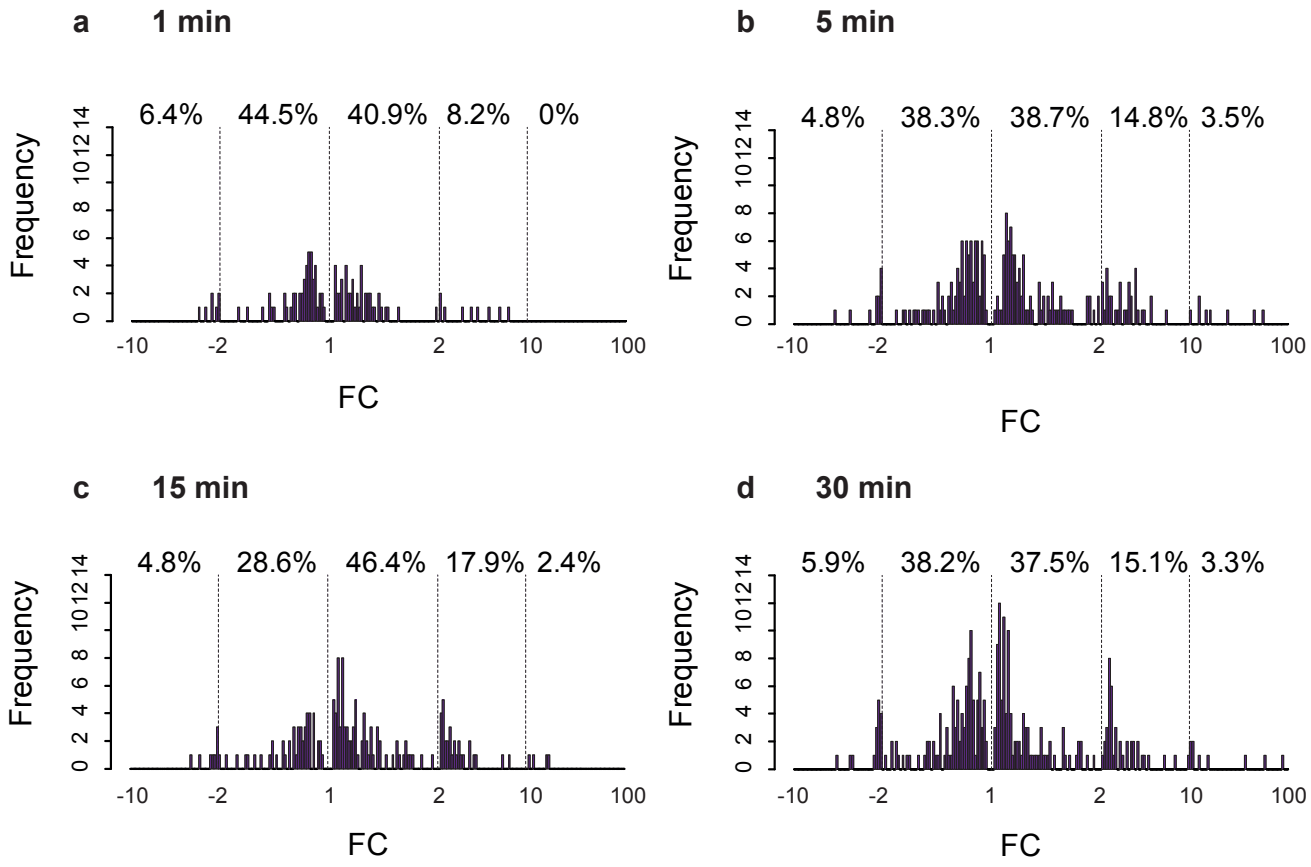


Fig. S8. Distribution of FCs for T cell signaling responses across time points. The proportion of responses (%) in each fold change (FC) interval is shown for 1 min (**a**), 5 min (**b**), 15 min (**c**) and 30 min (**d**) time points. The data is binned in different increments for each FC interval as follows: -10 to -2 (0.2), -2 to 2 (0.05), 2 to 10 (0.2) and 10 to 100 (2). Only significant responses (permuted P<0.05, Wilcoxon rank-sum test) with a minimum fold change of 10%, relative to the vehicle, are shown. Data represents median responses of eight peripheral blood mononuclear cell (PBMC) donors.

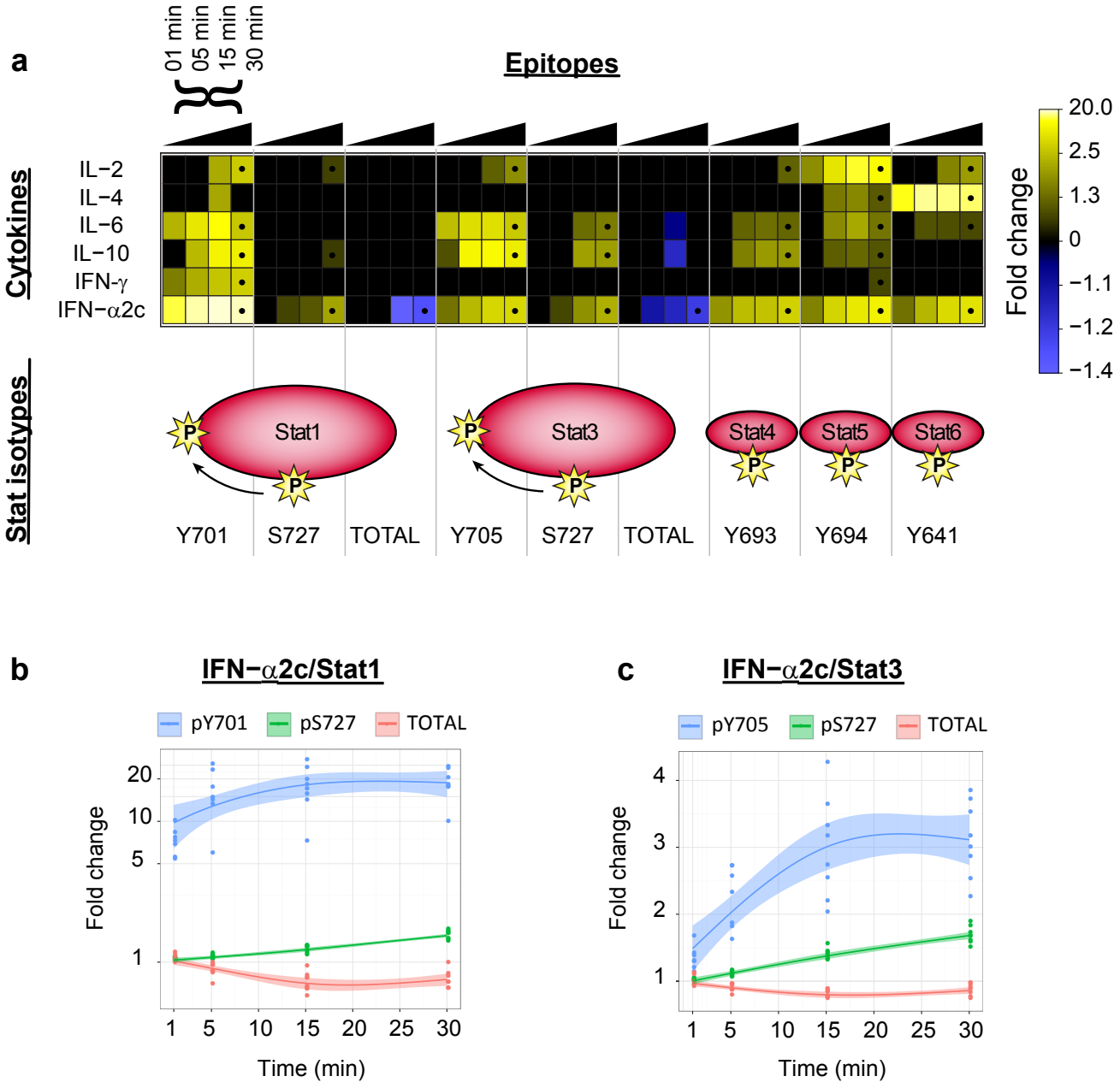


Fig. S9. Dynamic regulation of JAK/STAT T cell signaling across time course. (**a**) Specific responses across Stat isotypes were observed for different cytokines. Kinetic induction of phosphorylation at activation sites (Stat1 (pY701), Stat3 (pY705), Stat4 (pY693), Stat5 (pY694) and Stat6 (pY641)) and regulatory sites (Stat1 (pS727) and Stat3 (pS727)) was followed by decreases in total protein epitope availability (Stat1 and Stat3). Black dots at 30 min time points represent replication in independent peripheral blood mononuclear cell (PBMC) cohort (n=12). Arrows represent regulatory activity between sites. Legend shows fold change in epitope expression, calculated as median MFI of the ligand treatment/median MFI of the vehicle treatment, with labels distributed evenly across the quantile range for negative and positive fold changes separately. For downregulated epitopes, the legend shows -1/fold change. Only significant responses (permuted P<0.05, Wilcoxon rank-sum test) are shown. Dynamic regulation of all three sites on Stat1 (**b**) and Stat3 (**c**) in response to IFN-α2c. All data represents median across eight PBMC donors. MFI = median fluorescence intensity.

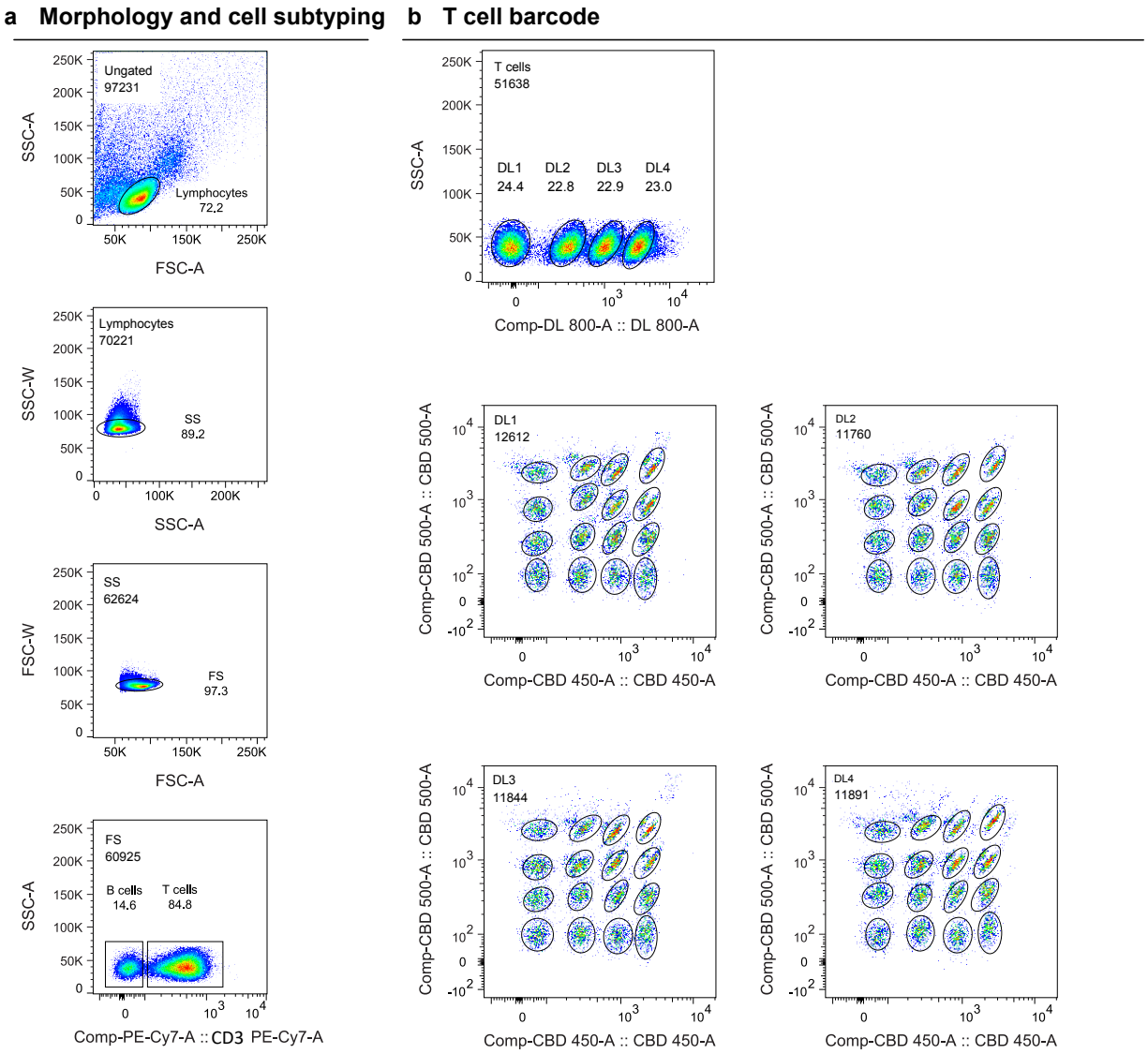


Fig. S10. Gating strategies for the functional analysis of 64 barcoded T cell populations. (**a**) Viable cells were gated (FSC-A vs. SSC-A), followed by single cell discrimination (SSC-A vs. SSC-W and FSC-A vs. FSC-W) and T cell subtyping using anti-CD3 PE-Cy7. Population labeled 'B cells' refers to $CD3^-$ cells, comprised largely of B and natural killer (NK) cells. (**b**) 64 populations, each corresponding to a different ligand or vehicle condition, were resolved within the T lymphocyte gate following fluorescent cell barcoding using DL800, CBD 450 and CBD 500 dyes. T cells were gated first for DL800 populations (DL1-4) and subsequently for CBD 450 vs. CBD 500 populations (16 populations). Within each barcoded T cell population, functional analysis of intracellular signaling epitopes (n=66) was conducted across AF 488, PE and AF 647 channels. Data represents one peripheral blood mononuclear cell (PBMC) sample. Cell counts are shown for parent gates in the top left hand corner of each dot plot and % frequencies of cells are shown next to gate names.

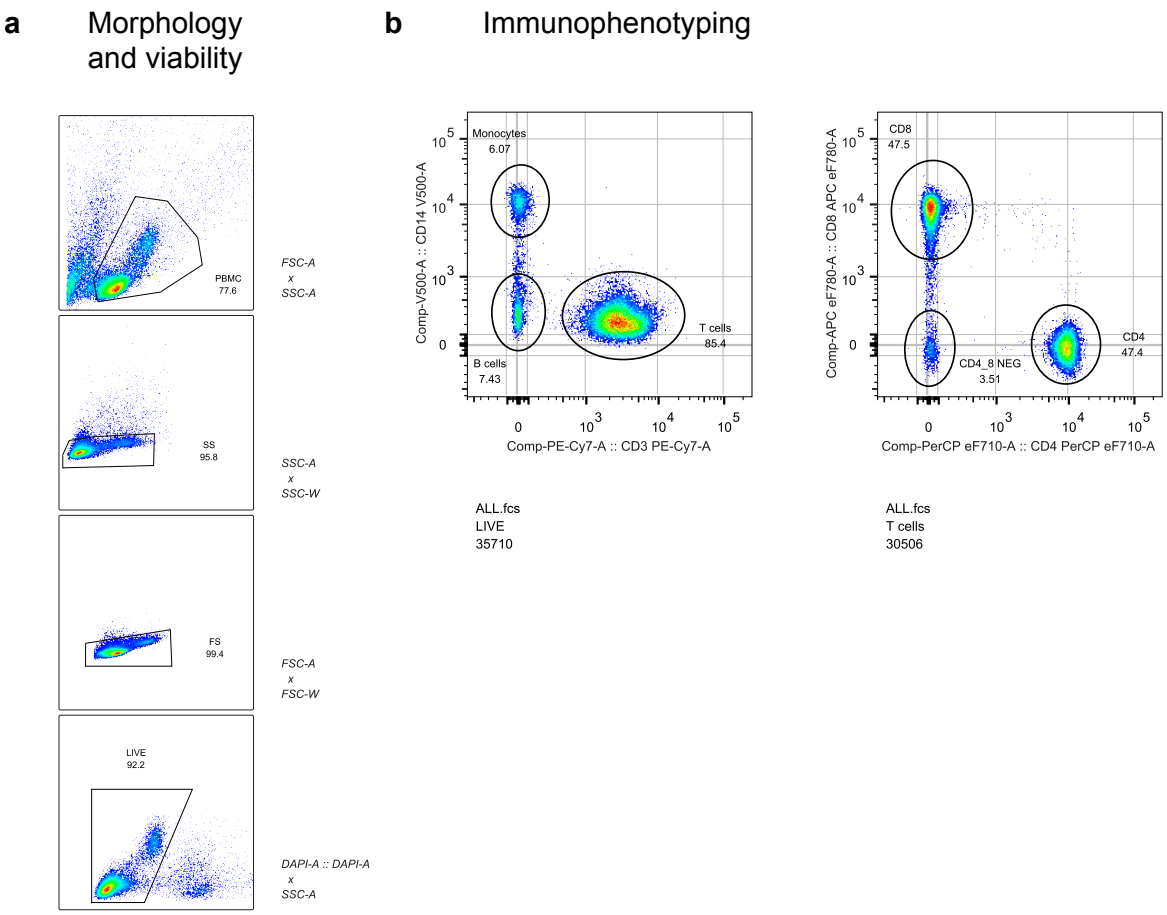
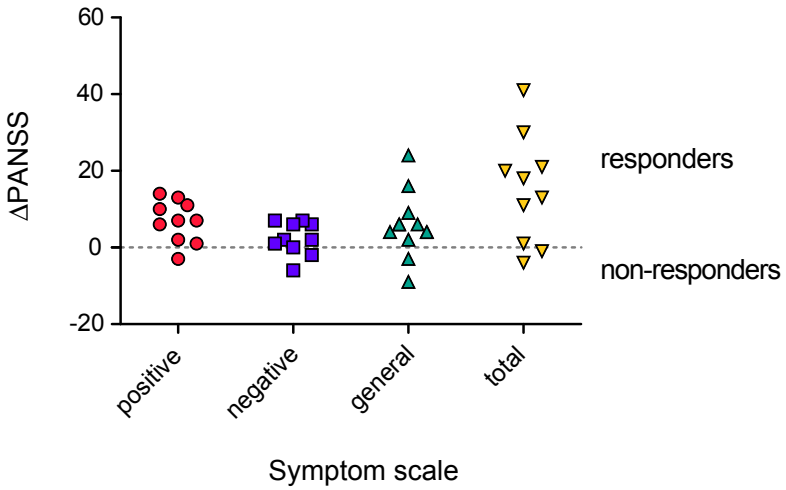


Fig. S11. Gating strategy for cell viability and immunophenotyping. (**a**) PBMCs were gated (FSC-A vs. SSC-A), followed by single cell discrimination (SSC-A vs. SSC-W and FSC-A vs. FSC-W) and viability measurement (DAPI-A vs. SSC-A). (**b**) Within the live cell gate, relative proportions of T, $CD3^-$ (largely B and natural killer (NK) cells; labeled 'B cells') and monocytic cells were quantified using anti-CD3 PE-Cy7 and anti-CD14 V500. Within the T cell gate, relative proportions of $CD4^+$, $CD8^+$ and $CD4^-/CD8^-$ cells were quantified using anti-CD4 PerCP-eF710 and anti-CD8 APC-eF780. Cell counts are shown for parent gates below each dot plot and % frequencies of cells are shown next to gate names.



PANSS	positive	negative	general	total
Before treatment	20.5 ± 5.3	22.1 ± 5.4	39.6 ± 6.0	82.2 ± 13.9
After treatment	13.7 ± 4.8	19.8 ± 5.1	33.7 ± 8.6	67.2 ± 15.4
Δ	6.8 ± 5.5	2.3 ± 4.3	5.9 ± 9.2	15.0 ± 14.2

Fig. S12 Clinical response to antipsychotic treatment with olanzapine in schizophrenia patients at 6 weeks. Ten out of the initial twelve drug-naïve schizophrenia patients were measured after 6 weeks of treatment with atypical antipsychotic medication olanzapine. 70% of these patients were classed as responders showing overall improvements in psychopathological symptoms, as measured by total Positive and Negative Syndrome Scale (PANSS) scores, relative to before treatment initiation. Concurrently, symptom improvements for these patients were also observed for positive, negative and general psychopathology PANSS subscales. Table shows mean values ± standard deviation. ΔPANSS refers to PANSS before treatment - PANSS after treatment, with positive values indicating symptom improvement.

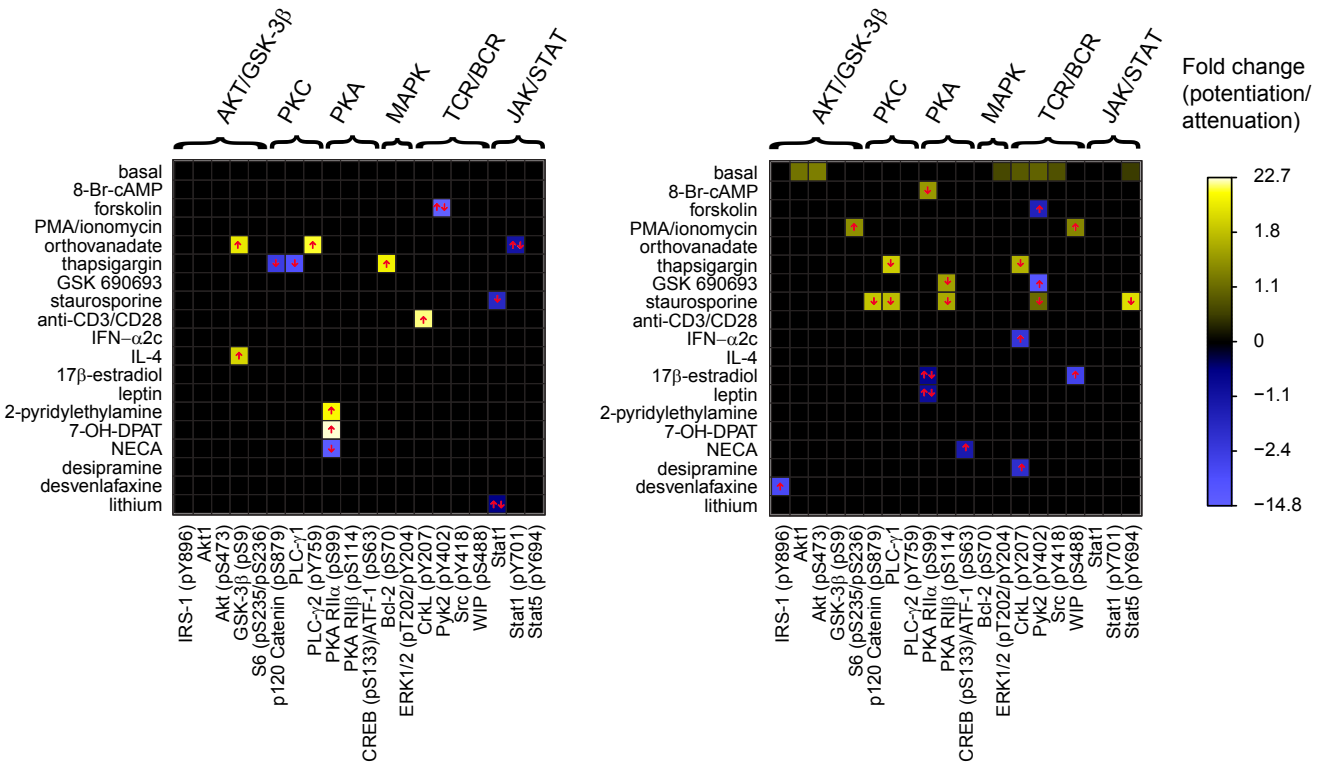


Fig. S13. Altered T cell signaling nodes (ligand-epitope combinations) in pretreatment SCZ versus control and pretreatment versus posttreatment SCZ comparisons. Shows significant differences between clinical groups, in either SCZ T0 (drug-naïve) vs. CTRL (**a**) or SCZ T0 (drug-naïve) vs. SCZ T6 (6 weeks of treatment with olanzapine) (**b**) comparisons, for cell signaling epitope expression under basal conditions or in response to ligand exposure. Significantly altered basal epitopes were defined as those with permuted '*P value*' in the vehicle condition <0.05 (ANCOVA) and a minimum '*Stain index*' (median MFI of the stained samples/median MFI of the unstained samples for the vehicle condition in the CTRL group) of 2. Terms in '*italics*' represent column headings in **Tables S6** and **S7** for referencing of absolute values. Significantly altered ligand responses were defined as nodes for which there was a significant interaction between clinical group status and the response to ligand ('*P interaction*'<0.05, two-way ANCOVA). Only nodes which displayed a significant '*Ligand response*', defined as median MFI of the ligand treatment/median MFI of the vehicle treatment (permuted P<0.05, Wilcoxon rank-sum test; minimum fold change 10%), after adjusting for background fluorescence, in either clinical group, and a minimum '*Stain index*' of 2, were analyzed. The arrows (↓ ↑) denote the direction of the '*Ligand response*' relative to vehicle. A single arrow represents a similar ligand response direction in both clinical groups and double arrows represent different directions of ligand response in each clinical group. The legend shows relative '*Potentiation* (yellow) or *attenuation* (blue) *fold change*' for the epitope expression under basal condition or in response to ligand, calculated as described in **Tables S6** and **S7**, with labels distributed evenly across the quantile range for negative and positive fold changes separately. Total peripheral blood mononuclear cell sample numbers in each group include CTRL (n=12), SCZ T0 (n=12) and SCZ T6 (n=10). MFI = median fluorescence intensity.

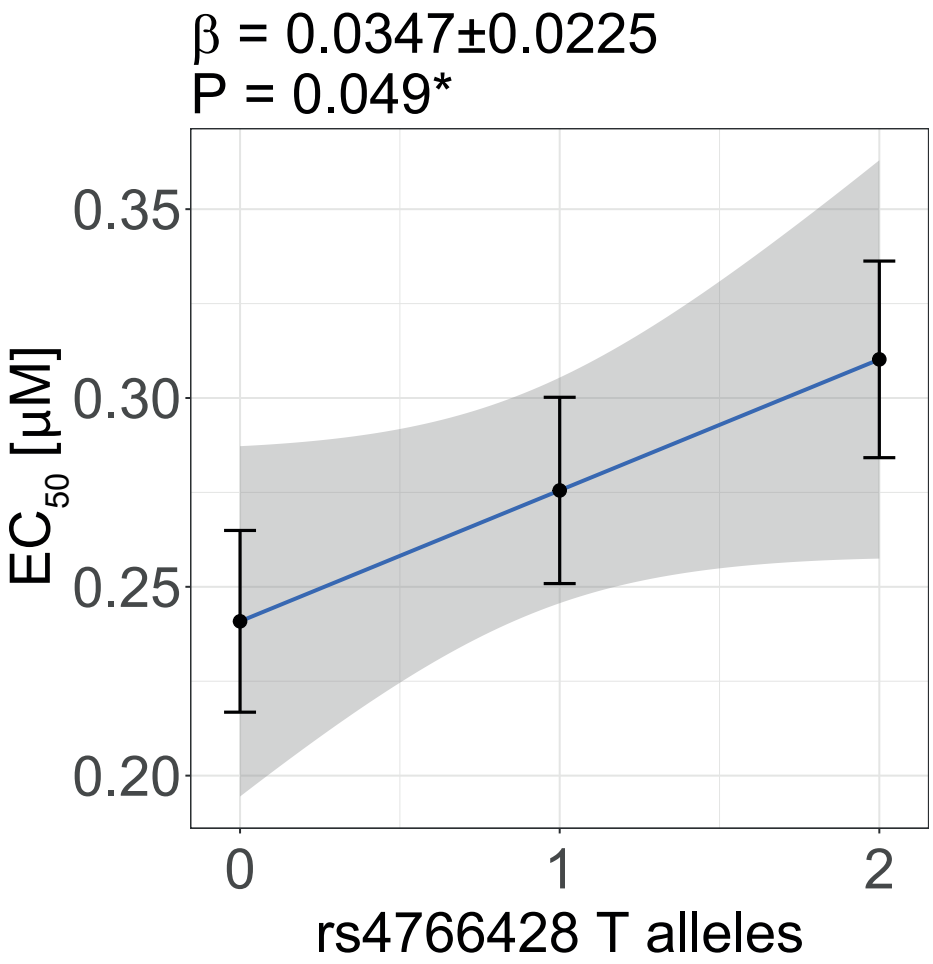


Fig. S14. Association between the drug target response to thapsigargin at PLC-γ1 in SCZ and the genome-wide significant SCZ risk SNP rs4766428 in the *ATP2A2* gene. X axis shows the number of schizophrenia risk alleles (T) and Y axis shows half-maximal effective concentration (EC_{50}) of the thapsigargin/PLC-γ1 response in 30 recent-onset drug-naïve schizophrenia patients (**Table S10** and **Fig. 7**). Data was analyzed using fixed effects linear regression adjusted for age, gender and body mass index. One-tailed P value was obtained by permutation testing (N=1000 permutations). Error bars represent standard error of the mean. Sample size by genotype: n_{CC} = 10, n_{CT} = 13, n_{TT} = 7. * P < 0.05.

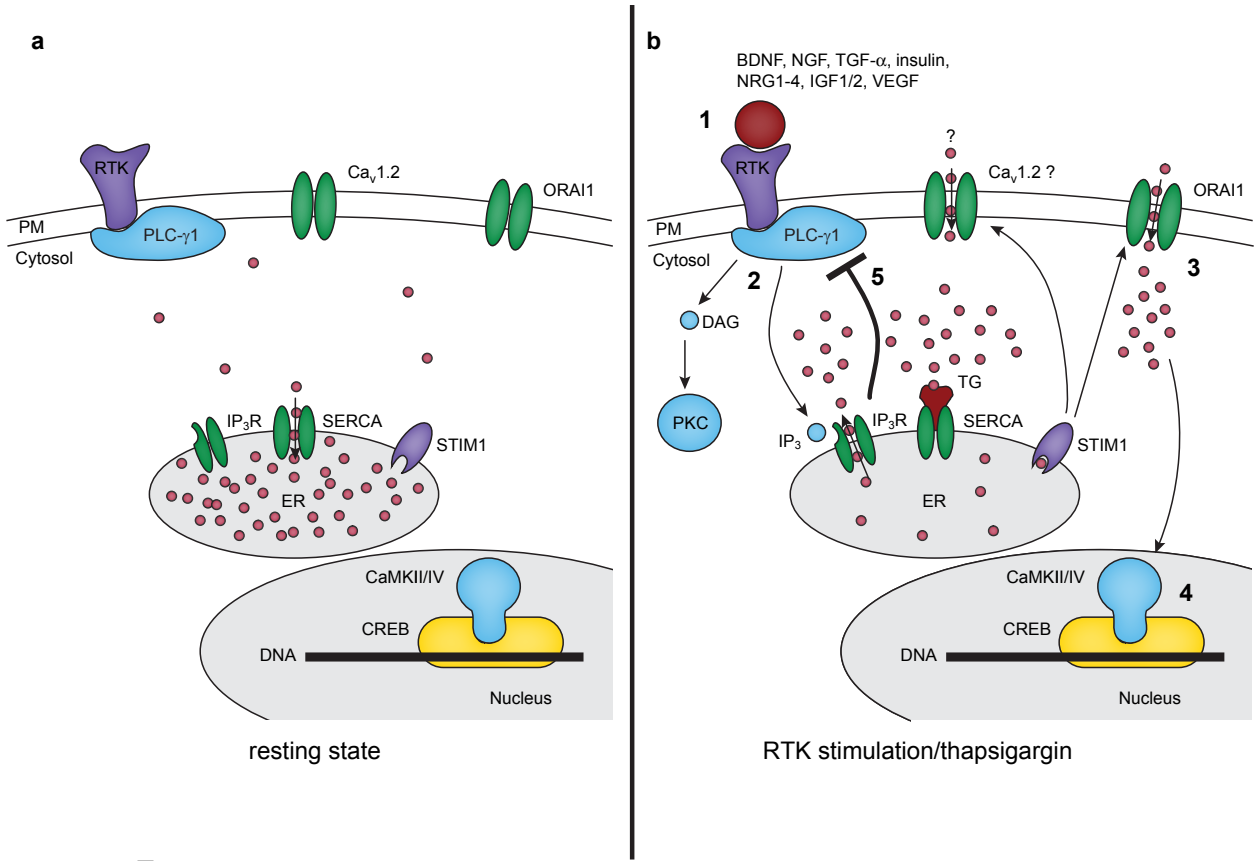


Fig. S15. Normal regulatory response at PLC-γ1 to calcium release from the endoplasmic reticulum and hypothetical mechanism of action in SCZ, based on the altered response to thapsigargin at PLC-γ1 in T cells from patients with SCZ. (**a**) In resting cells, low calcium concentration is maintained in the cytosol (~100nM), relative to the endoplasmic reticulum (ER; ~0.5 mM) and extracellular space (~1 mM), by active calcium transporter sarco-endoplasmic reticulum Ca^{2+}-ATPase, SERCA (including schizophrenia-associated ATP2A2 (SERCA2), **Fig. S14**). (**b**) 1) Receptor tyrosine kinase (RTK) ligand activation by cytokines, hormones or growth factors (selected examples shown) activates PLC-γ1. 2) PLC-γ1 catalyzes the degradation of phosphatidylinositol 4,5-biphosphate into intracellular second messengers, inositol 1,4,5-triphosphate (IP_3) and 1,2 diacylglycerol (DAG), which induce the release of calcium stored in the ER, via IP_3 receptors (IP_3Rs), and the activation of protein kinase C (PKC), respectively. Analogous depletion of ER calcium stores is achieved by SERCA blockade using TG. 3) Reduction of ER calcium is sensed by stromal interaction molecule 1 (STIM1), which subsequently promotes the influx of extracellular calcium via the ORAI1 plasma membrane (PM) channel. 4) Elevated cytosolic calcium activates gene transcription via Ca^{2+}/calmodulin-dependent protein kinase II/IV (CaMKII/IV) and transcription factor cAMP response element-binding protein (CREB). 5) Elevated cytosolic calcium causes the downregulation or sequestration of PLC-γ1 to desensitize RTK signal transduction. We hypothesize that in schizophrenia, either the initial calcium flux from the ER or the negative feedback regulation of PLC-γ1 is disrupted and restored by clinical treatment with olanzapine for 6 weeks. However, further mechanistic studies are required to test this hypothesis. Voltage gated calcium channels (e.g. L-type Cav1.2) are included based on repeated association to schizophrenia in GWAS studies (CACNA1C, CACNB2 and CACNA1I). Their contribution to the altered TG/PLC-γ1 response and reported interactions with STIM1 remain to be defined.

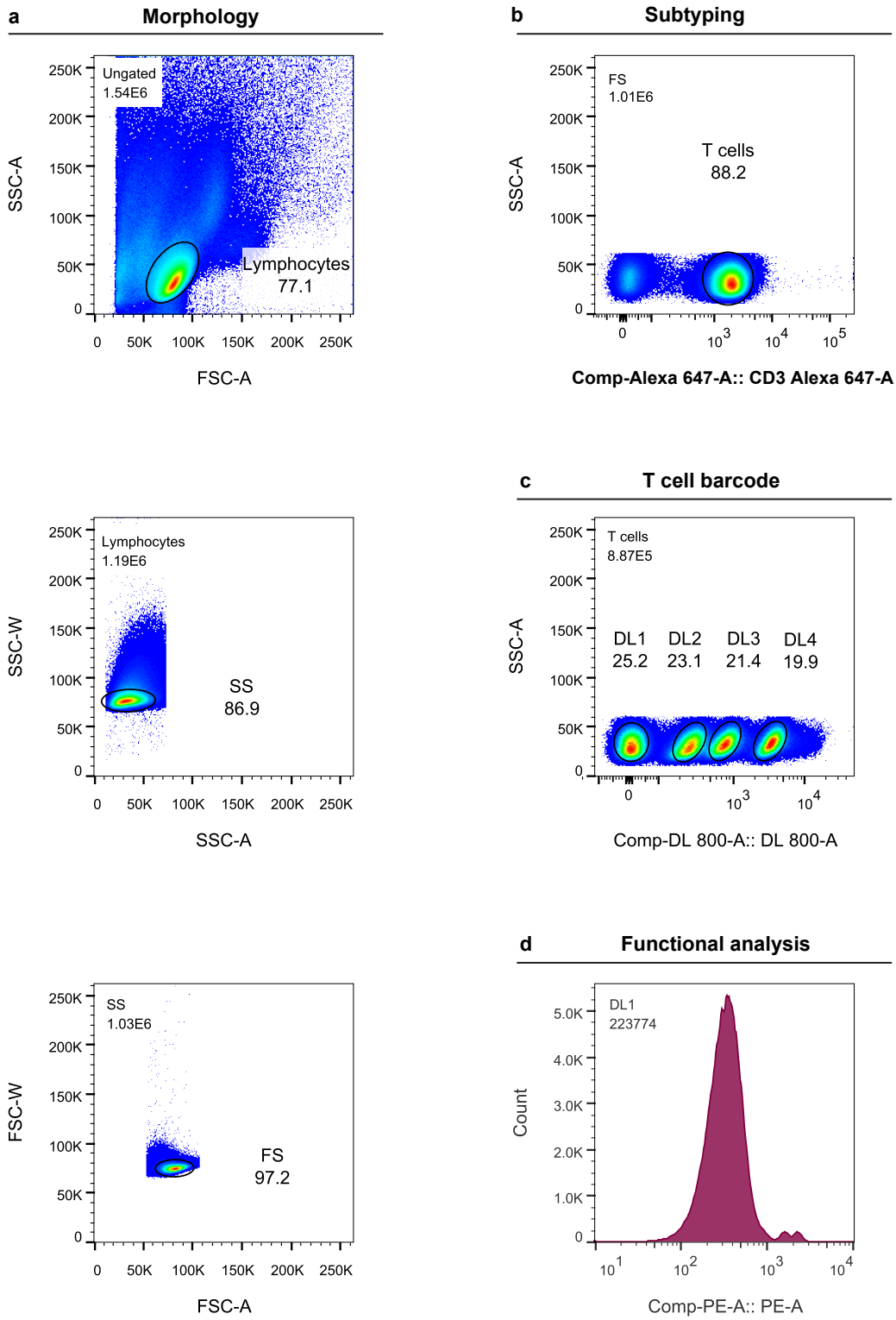


Fig. S16. Gating strategies for the functional analysis of PLC-γ1 expression in four barcoded T cell populations. (**a**) Viable cells were gated (FSC-A vs. SSC-A), followed by single cell discrimination (SSC-A vs. SSC-W and FSC-A vs. FSC-W). (**b**) T cell subtyping using anti-CD3 APC. (**c**) Four populations, each corresponding to a different stimulation condition (thapsigargin or vehicle) and compound condition (compound or negative control), were resolved within the T lymphocyte gate following fluorescent cell barcoding using DL 800 (DL1-4). (**d**) Within each barcoded T cell population functional analysis of intracellular signaling epitope PLC-γ1 expression was conducted using anti-human PLC-γ1 PE. Data represents one peripheral blood mononuclear cell (PBMC) sample. Cell counts are shown for parent gates in the top left hand corner of each dot plot and % frequencies of cells are shown next to gate names.

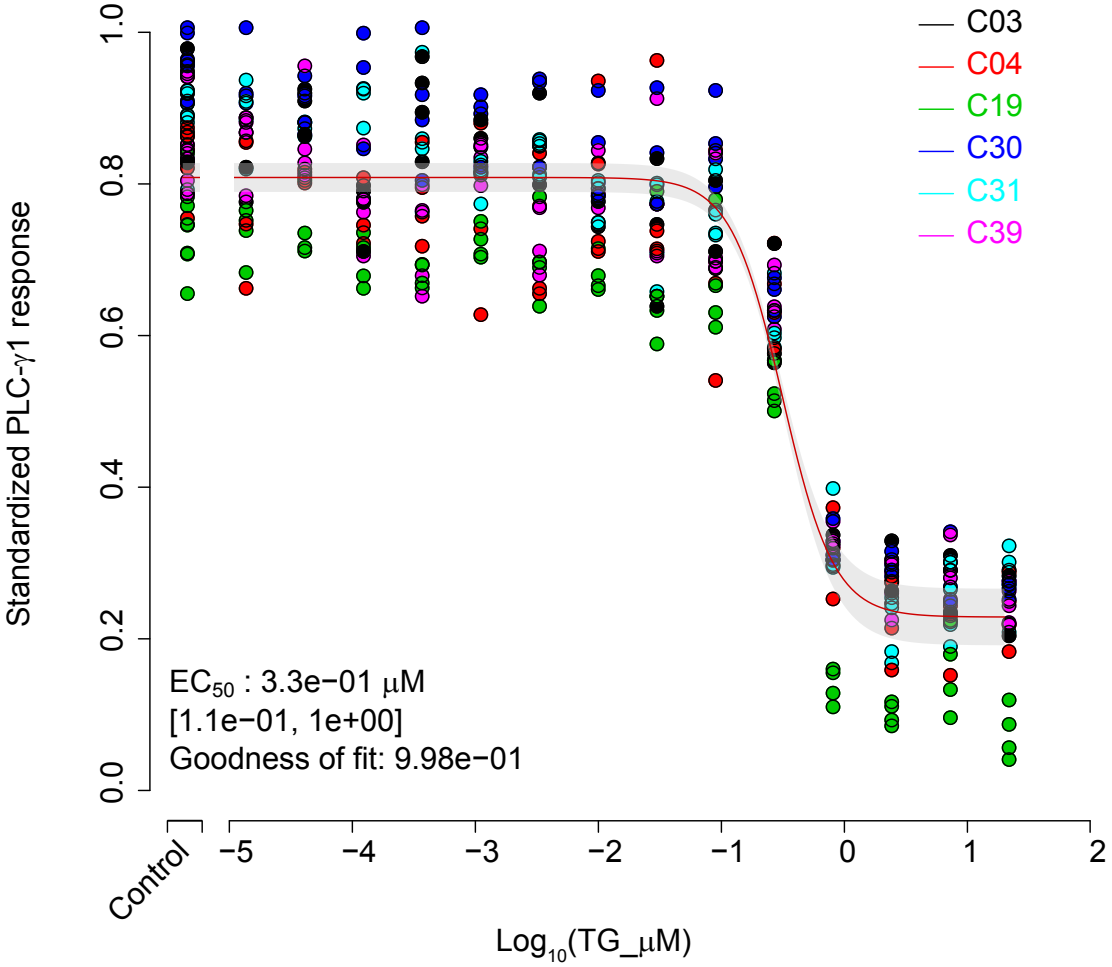


Fig. S17. Thapsigargin dose response at PLC-γ1. TG provokes a dose-dependent decrease in PLC-γ1 expression. Y axis represents the median fluorescence intensity standardized as a proportion of minimum and maximum values. TG stimulation circa the EC_{50} concentration (0.5 μM) determined from 4-parameter logistic curve (red) was used as a background condition for the extended US Food and Drug Administration (FDA)-approved library screen. Data represents six healthy control (C) peripheral blood mononuclear cell (PBMC) samples colored by donor.

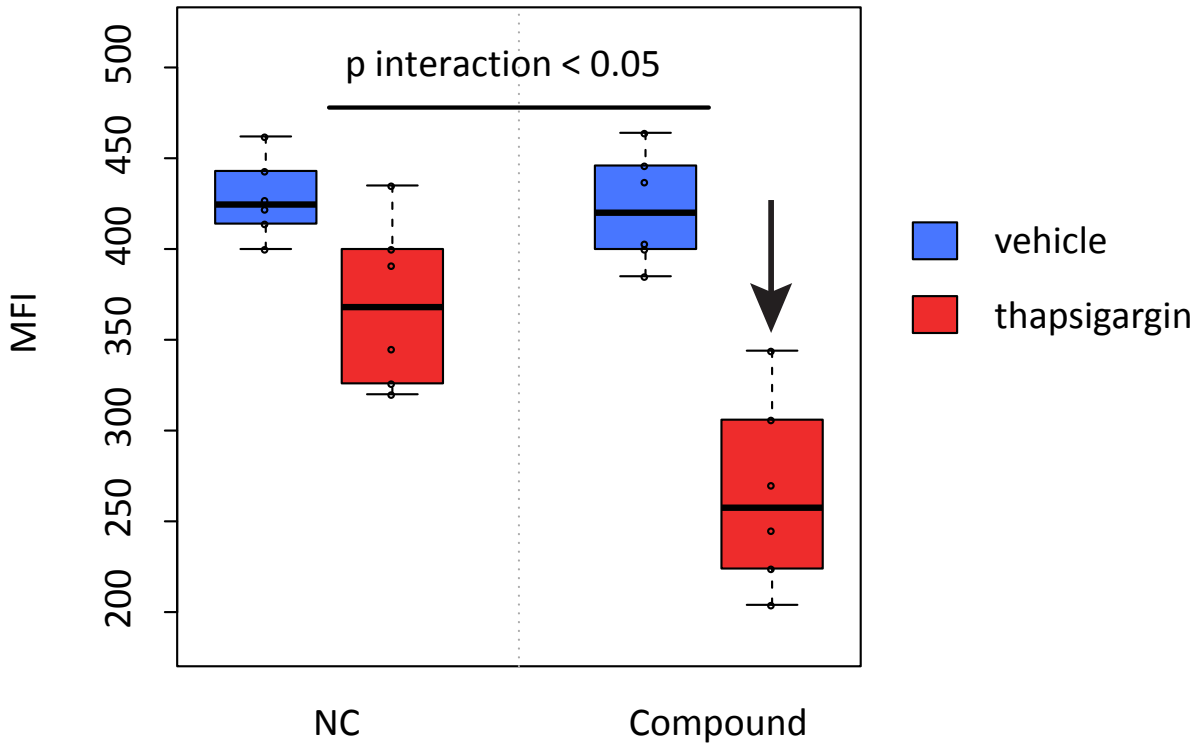


Fig. S18. Selective potentiation of PLC-γ1 response in the presence of thapsigargin. Compounds from the extended US Food and Drug Administration (FDA)-approved library were initially identified based on their interaction with the response to TG at PLC-γ1 independently of the direction of change (p interaction < 0.05, two-way ANOVA). Subsequently, these hits were refined to compounds which showed the desired directionality (decrease in PLC-γ1, arrow) specifically in the TG condition and were not active in the vehicle condition (post-hoc ANOVA tests). In other words, these compounds had no intrinsic activity but were capable of potentiating the PLC-γ1 response when co-administered with TG. Figure shows representative compound screened in six peripheral blood mononuclear cell (PBMC) samples. Compounds were at 20 µM final concentration, unless otherwise stated in **Table S8**, in DMSO 0.2%. Negative control (NC) = DMSO 0.2%. TG was at 0.5 µM, DMSO 0.01%. Vehicle = DMSO 0.01%. MFI = median fluorescence intensity.

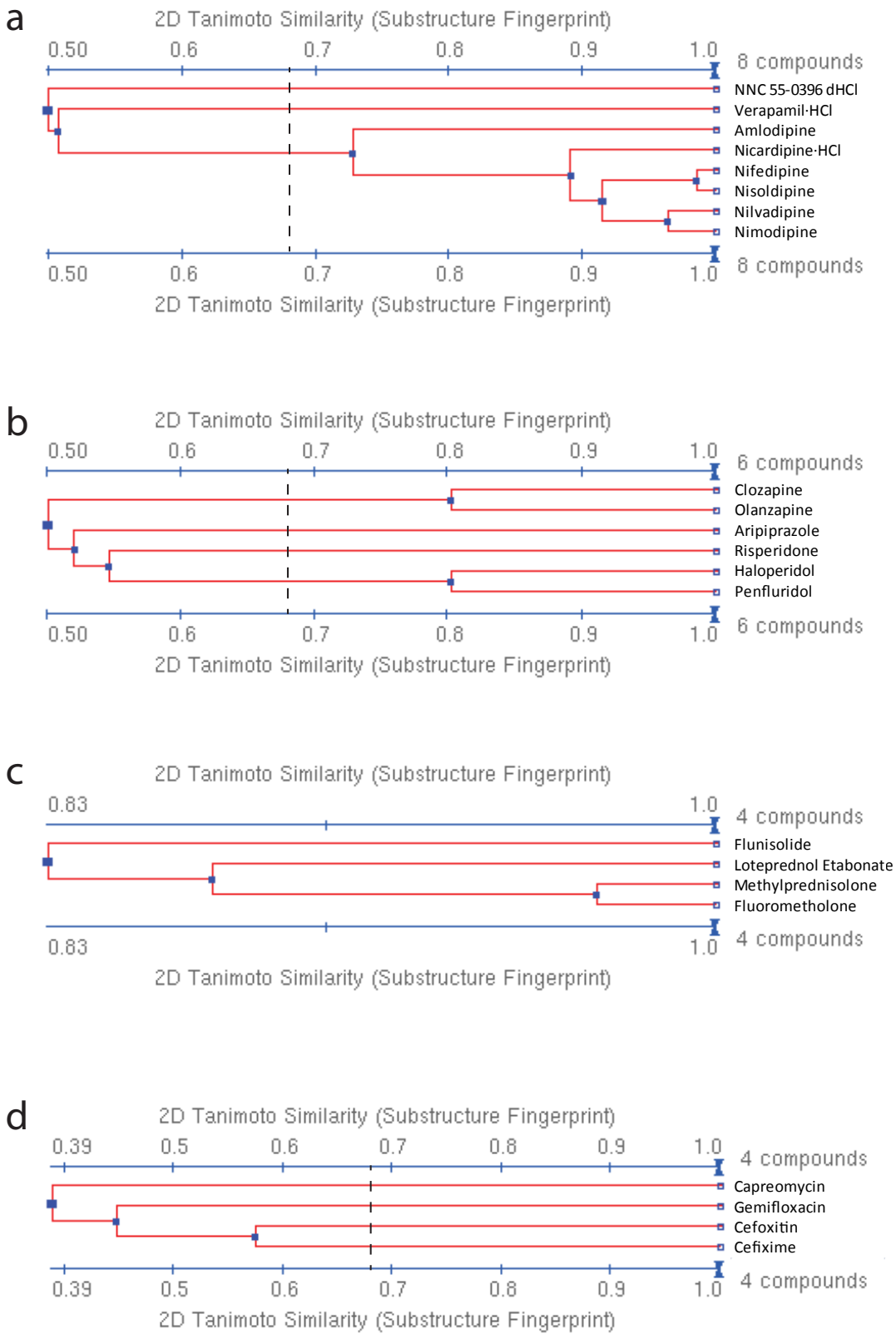
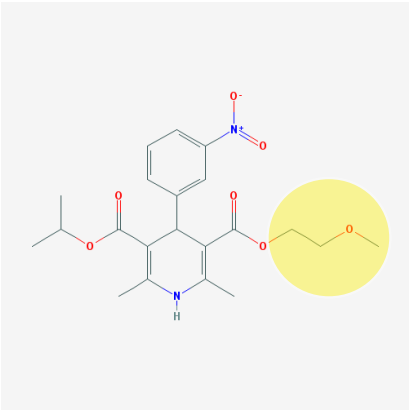
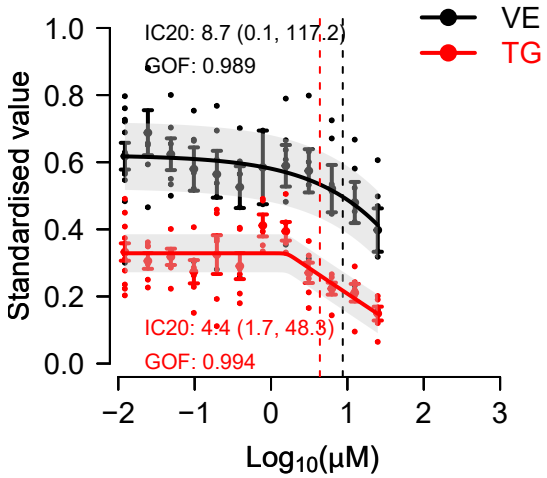


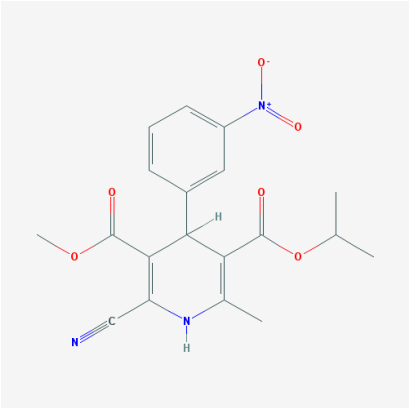
Fig. S19. Tanimoto structural similarity clustering of calcium channel blocker, antipsychotic, corticosteroid, and antibiotic compounds used in PLC-γ1 dose-response validation and selectivity testing. Compounds are clustered according to 2D structural Tanimoto similarity using Single Linkage algorithm (PubChem). This grouping hierarchy is used to define the representation order of compounds in each class in **Fig. 5**. A 2D similarity score of 0.68 (dashed line) is statistically significant at the 95% confidence interval (Kim et al., 2012).

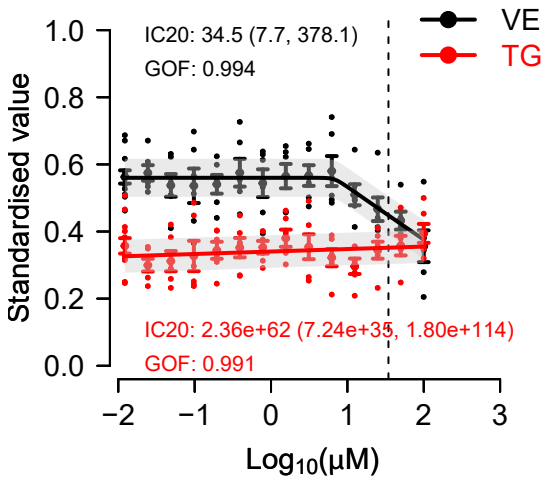
Nimodipine



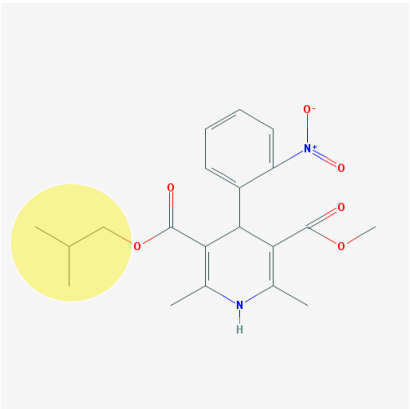


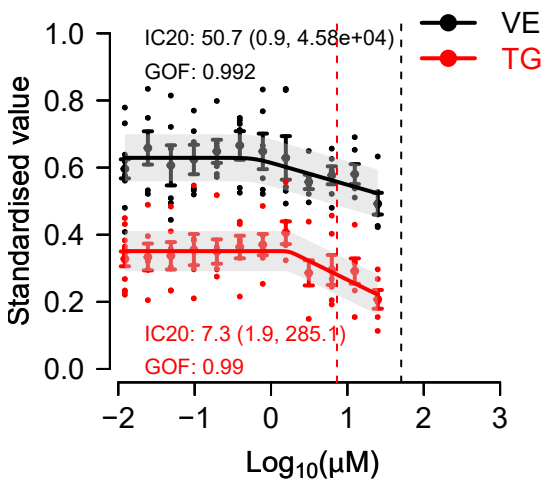
Nilvadipine



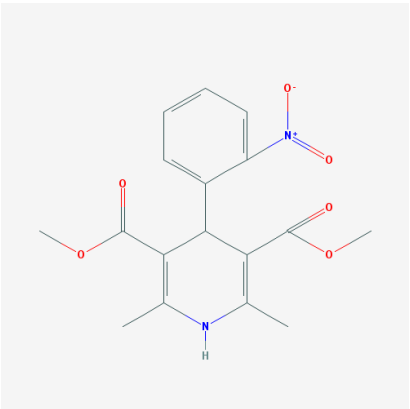


Nisoldipine





Nifedipine



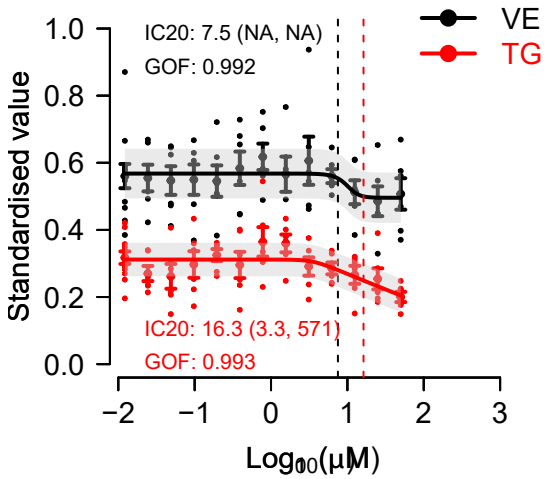
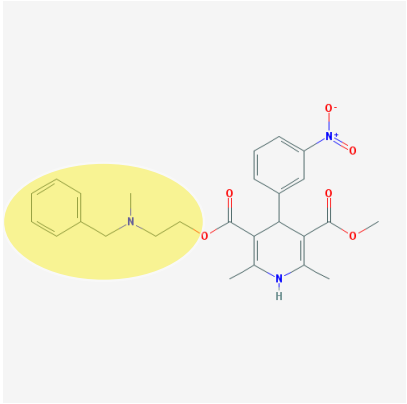
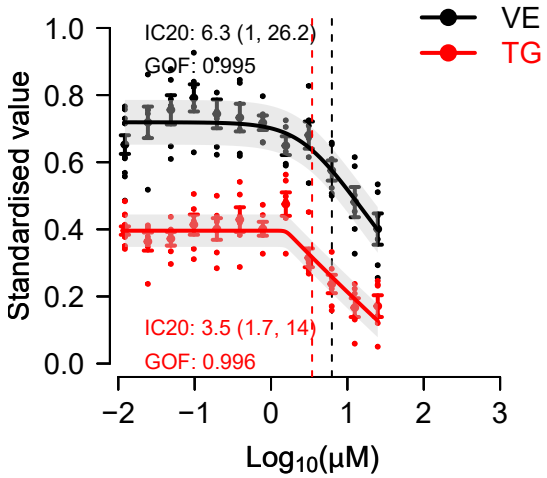


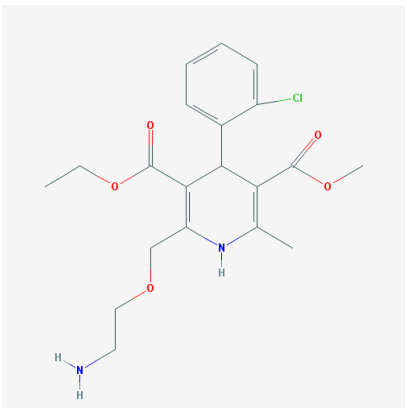
Fig. S20 Validation and selectivity testing of calcium channel blocker, antipsychotic, corticosteroid, antibiotic and other drug classes at phospholipase C (PLC)−γ1.

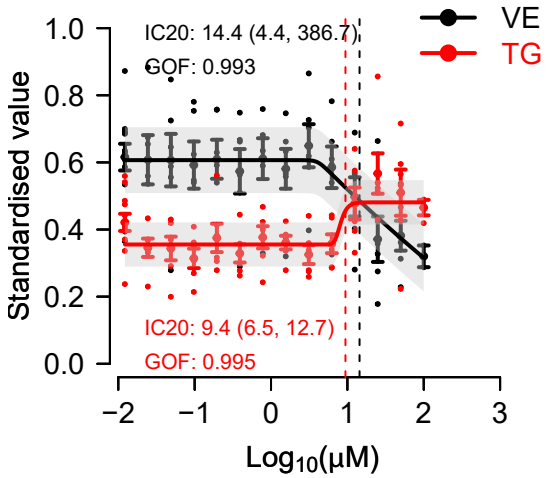
Nicardipine



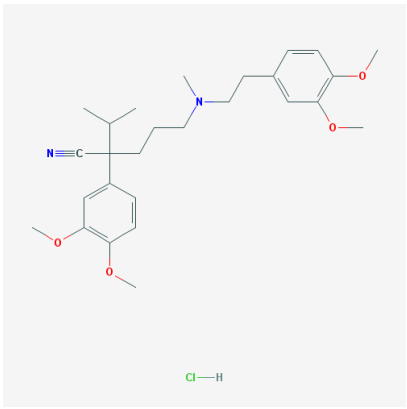


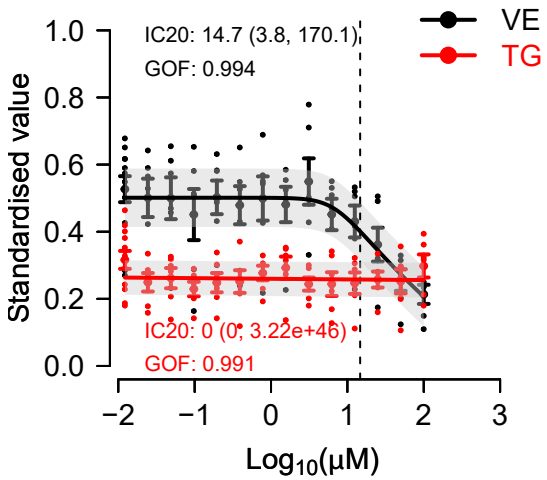
Amlodipine



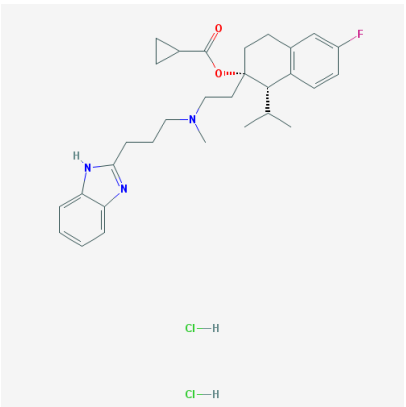


Verapamil





NNC 55−0396



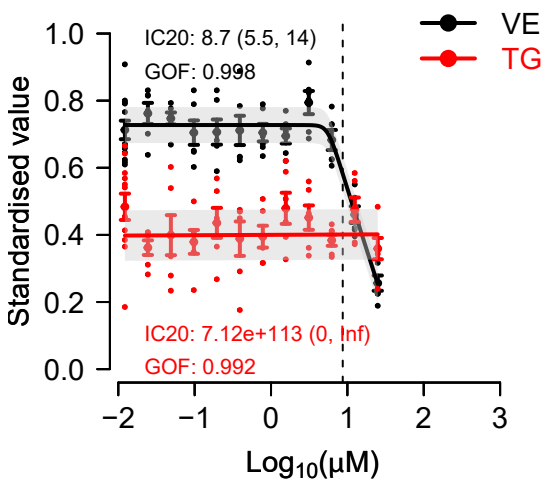
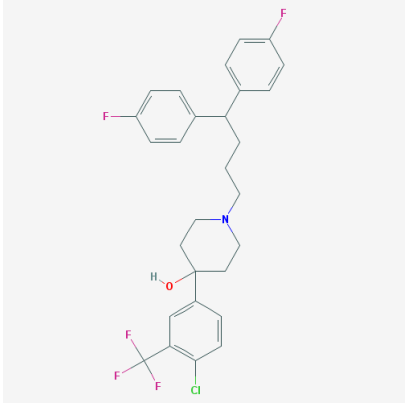
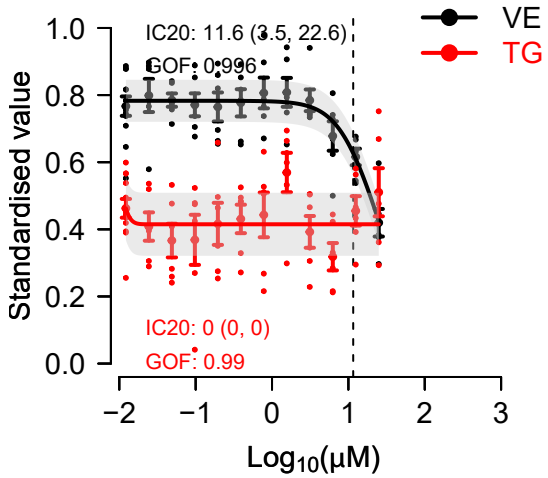


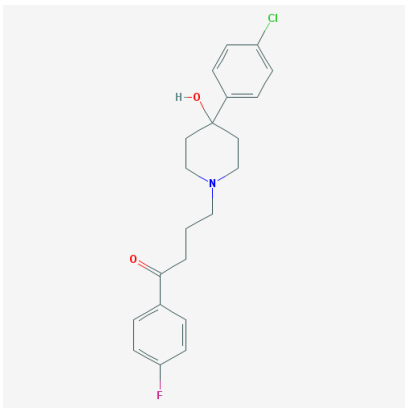
Fig. S20 Validation and selectivity testing of calcium channel blocker, antipsychotic, corticosteroid, antibiotic and other drug classes at phospholipase C (PLC)−γ1 - continued.

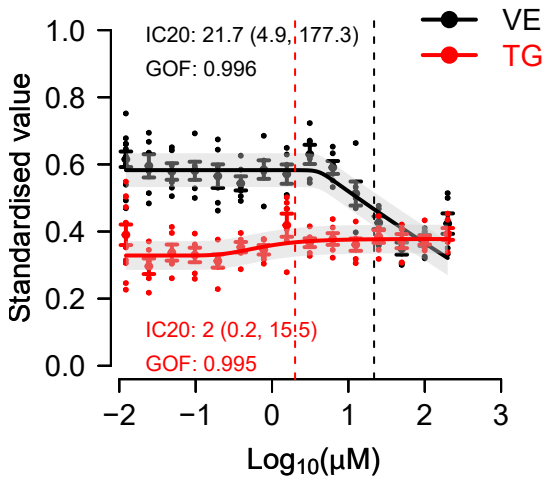
Penfluridol



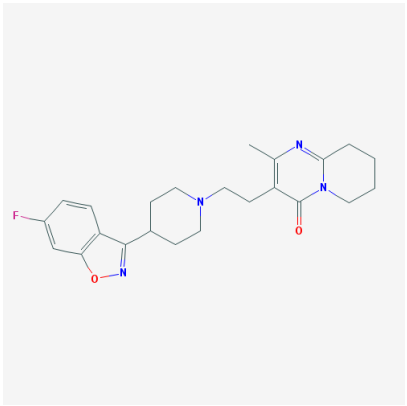


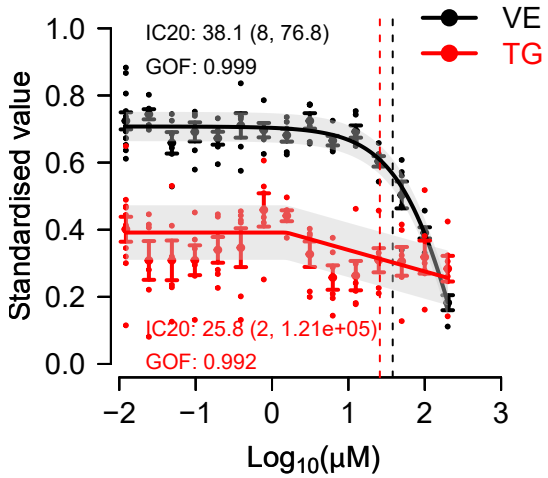
Haloperidol



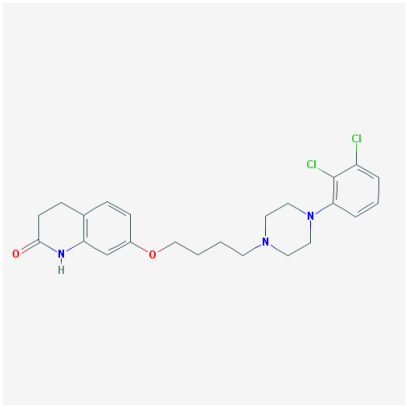


Risperidone





Aripiprazole



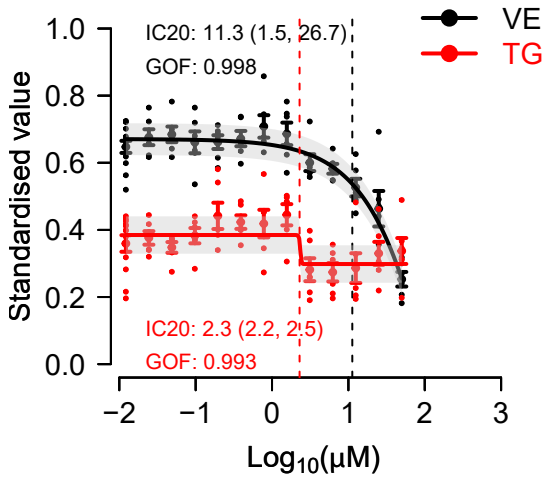
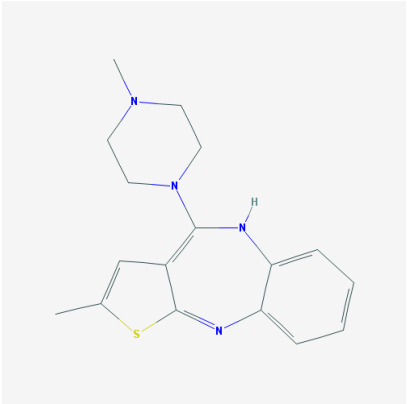
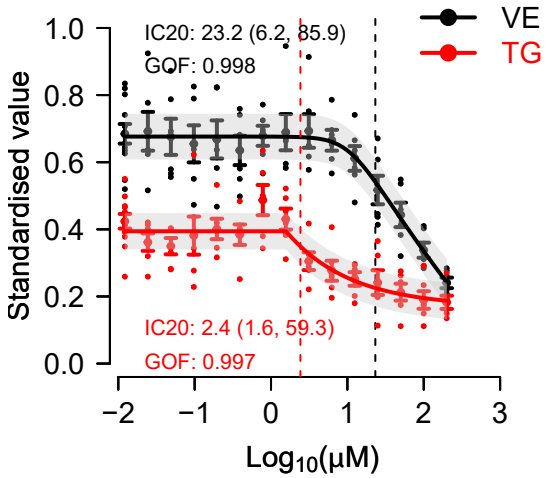


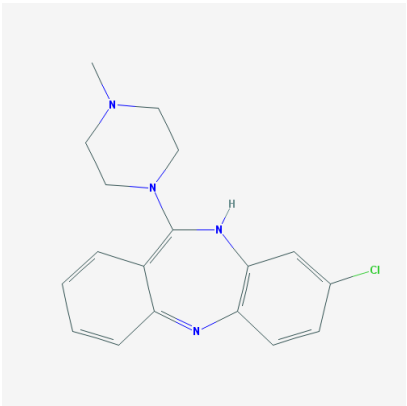
Fig. S20 Validation and selectivity testing of calcium channel blocker, antipsychotic, corticosteroid, antibiotic and other drug classes at phospholipase C (PLC)−γ1 - continued.

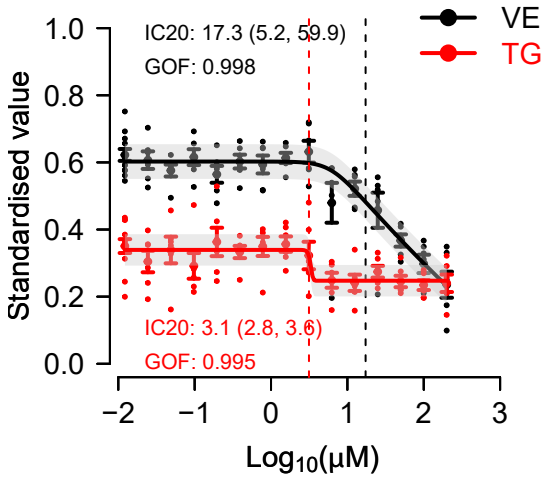
Olanzapine



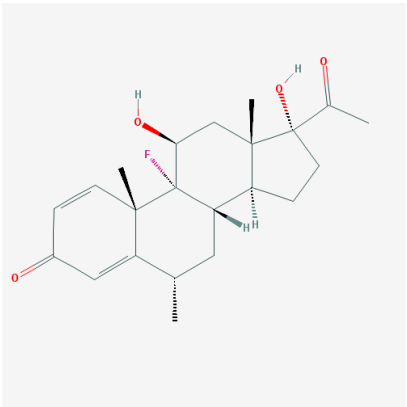


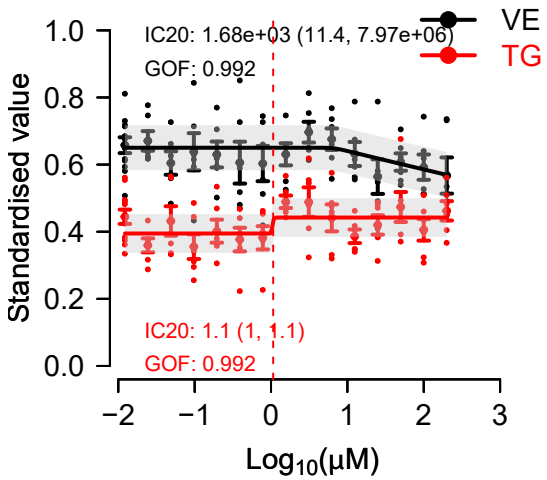
Clozapine



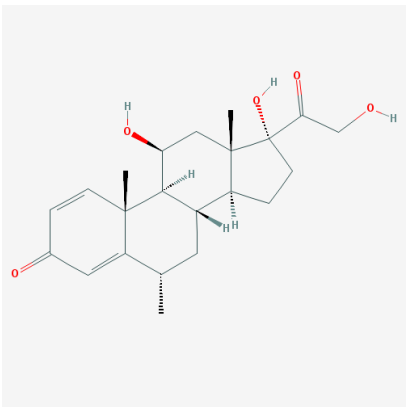


Fluorometholone





Methylprednisolone



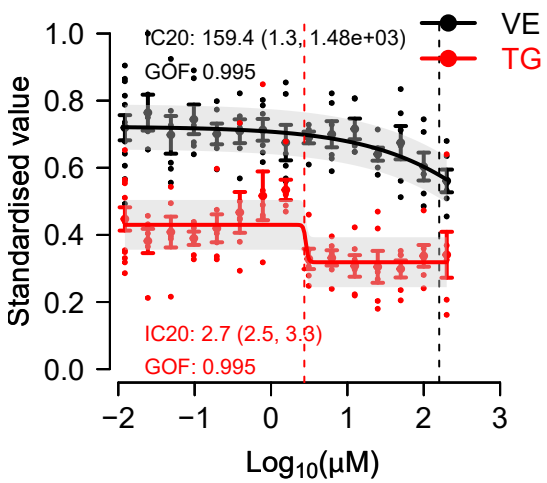
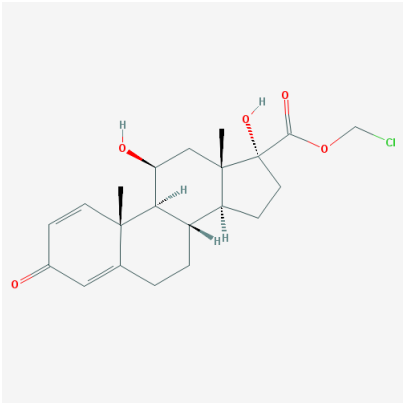
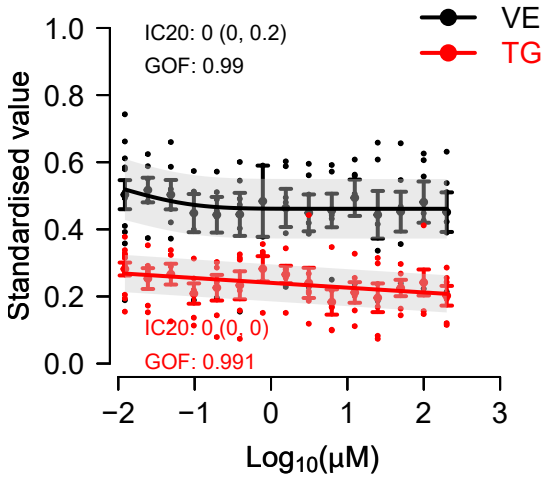


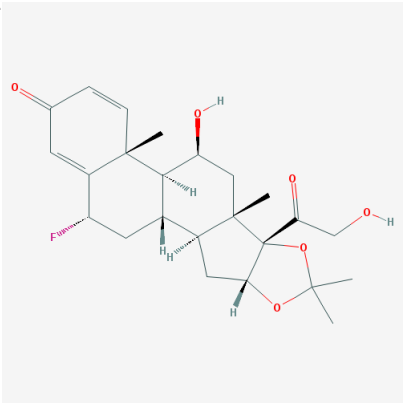
Fig. S20 Validation and selectivity testing of calcium channel blocker, antipsychotic, corticosteroid, antibiotic and other drug classes at phospholipase C (PLC)−γ1 - continued.

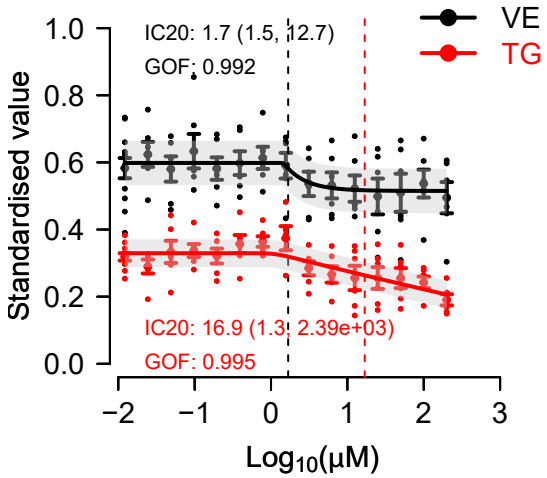
Loteprednol



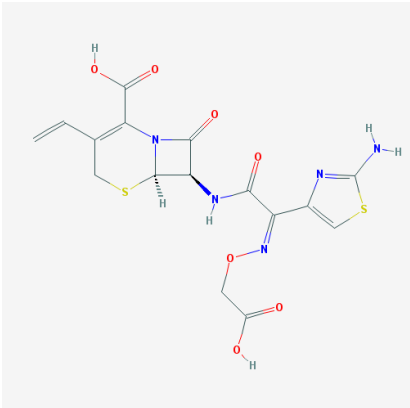


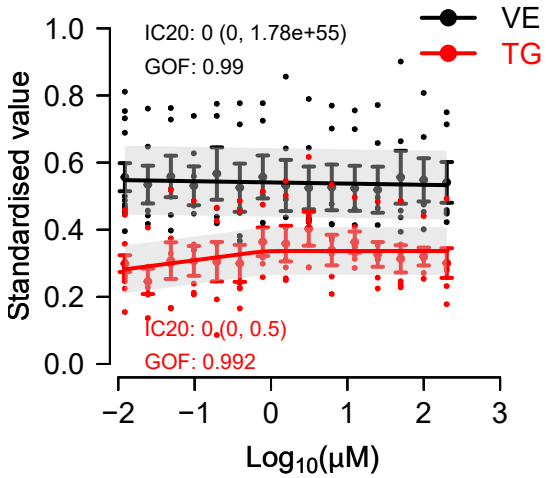
Flunisolide



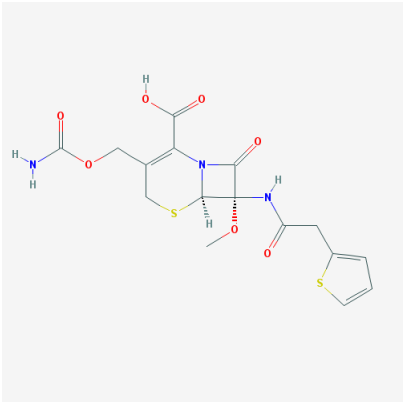


Cefixime





Cefoxitin



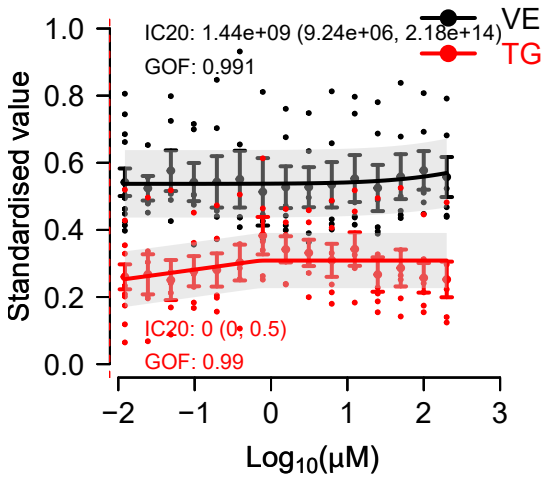
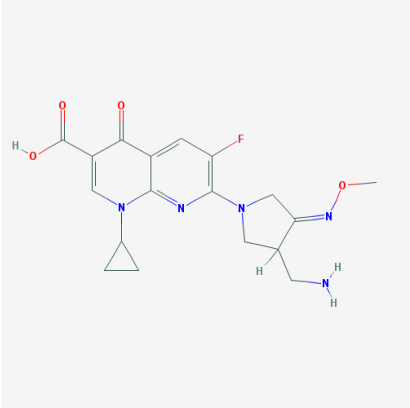
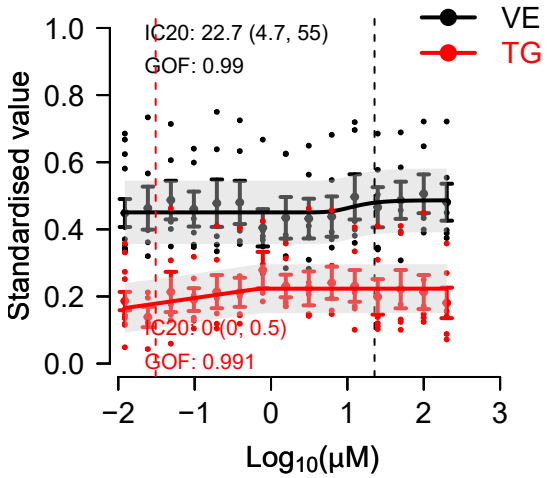


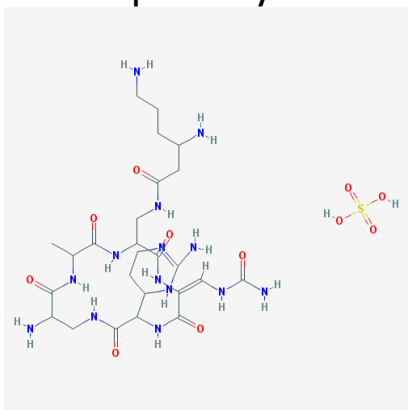
Fig. S20 Validation and selectivity testing of calcium channel blocker, antipsychotic, corticosteroid, antibiotic and other drug classes at phospholipase C (PLC)−γ1 - continued.

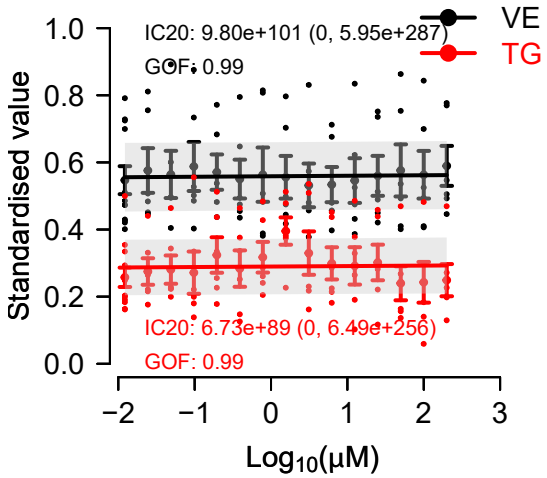
Gemifloxacin



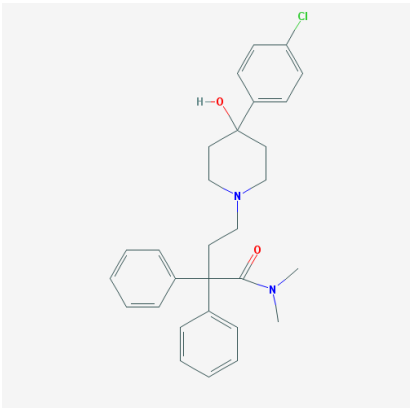


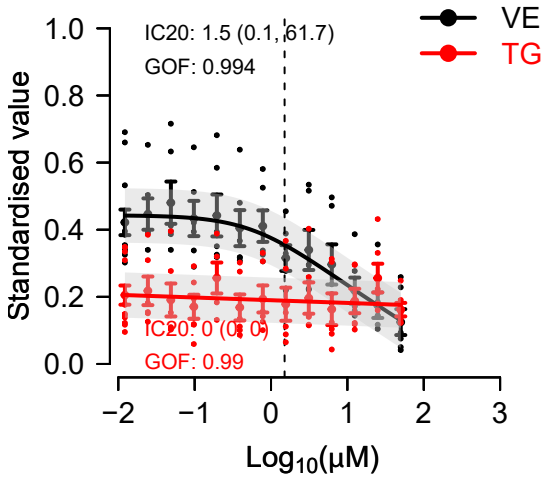
Capreomycin



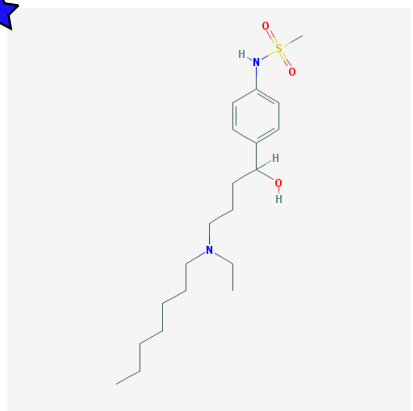


Loperamide





Ibutilide



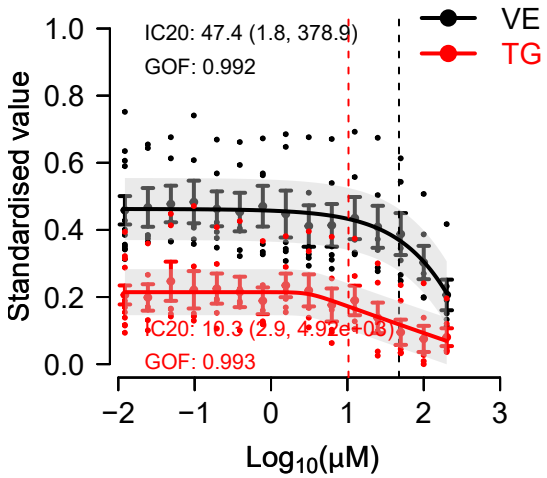


Fig. S20 Validation and selectivity testing of calcium channel blocker, antipsychotic, corticosteroid, antibiotic and other drug classes at phospholipase C (PLC)−γ1 - continued.

Fig. S20. Validation and selectivity testing of calcium channel blocker, antipsychotic, corticosteroid, antibiotic, and other drug classes at PLC-γ1. Compounds for which at least one class member selectively potentiated the PLC-γ1 response in the presence of thapsigargin (TG) in the extended US Food and Drug Administration (FDA)-approved library screen (depicted in the "Validation and selectivity testing" panel in **Fig. 5D**; **Fig. S19**), were explored using a 14-point two-fold dose response of the compound (0.024-200 μM, DMSO 0.2%) in vehicle (VE; DMSO 0.01%; black color) and TG (0.5 μM, DMSO 0.01%; red color) conditions. The lowest plotted concentration represents the negative control condition (DMSO 0.2%). Y axes represent the median fluorescence intensity standardized as a proportion of minimum and maximum values. The difference between the lowest potentiation concentration of the TG and vehicle curves defined by the respective IC20 values (red and black vertical dashed lines, respectively) represents the putative therapeutic window for selective potentiation in the presence of TG relative to vehicle. Compounds which showed the putative therapeutic window of selective potentiation, in addition to flunisolide which selectively potentiated the TG/PLC-γ1 response at higher concentrations, were chosen for the final repurposing stage (potentiation testing; **Fig. 5C**) and are marked with a blue asterisk. Yellow circles indicate structural moieties which differentiate compounds with a selective therapeutic window compared to non-selective or inactive class relatives. Compounds are ordered according to structural similarity within each class using Tanimoto coefficient clustering (**Fig. S19**). Data represents 6 peripheral blood mononuclear cell (PBMC) samples (dots), standard error (vertical bars) and fitted 5-parameter logistic curves (solid lines). GOF = weighted goodness-of-fit; IC20 = 20% maximal inhibitory concentration (95% confidence intervals). Chemical structures are taken from PubChem.

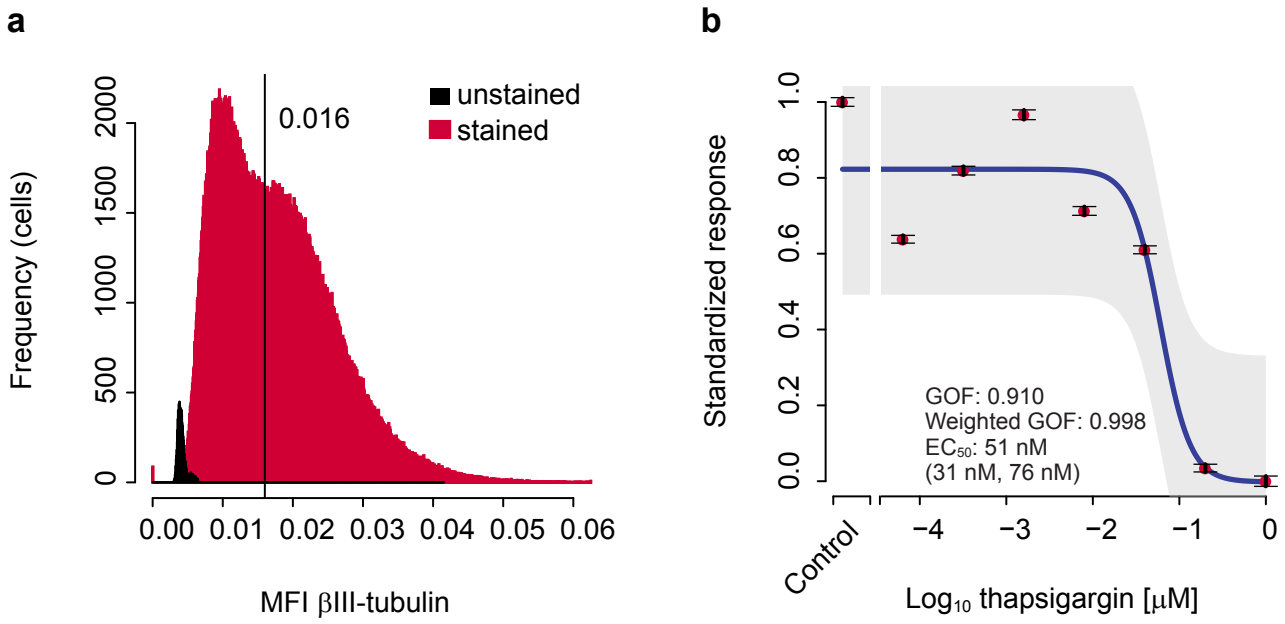


Fig. S21. Validation of top drug candidates in the SH-SY5Y neuronal cell line. (**a**) Distribution of βIII-tubulin staining in SH-SY5Y cells. Represents 10,170 cells in the unstained condition and 752,736 cells in the stained condition, from 3 replicate experiments imaged using wide-field microscopy (20x magnification). Vertical line denotes the 0.016 mean fluorescence intensity (MFI) threshold used to define βIII-tubulin-positive SH-SY5Y neurons. (**b**) Thapsigargin/PLC-γ1 dose response curve in βIII-tubulin-positive SH-SY5Y neurons after 30 min stimulation. Shown are mean, standard error and fitted 4-parameter logistic curve with 95% confidence intervals. Each data point represents on average 10,816 cells from 3 replicate experiments imaged using wide-field microscopy (20x magnification). Y axis shows PLC-γ1 levels standardized to the mean control level (0 μM thapsigargin). GOF – goodness of fit.

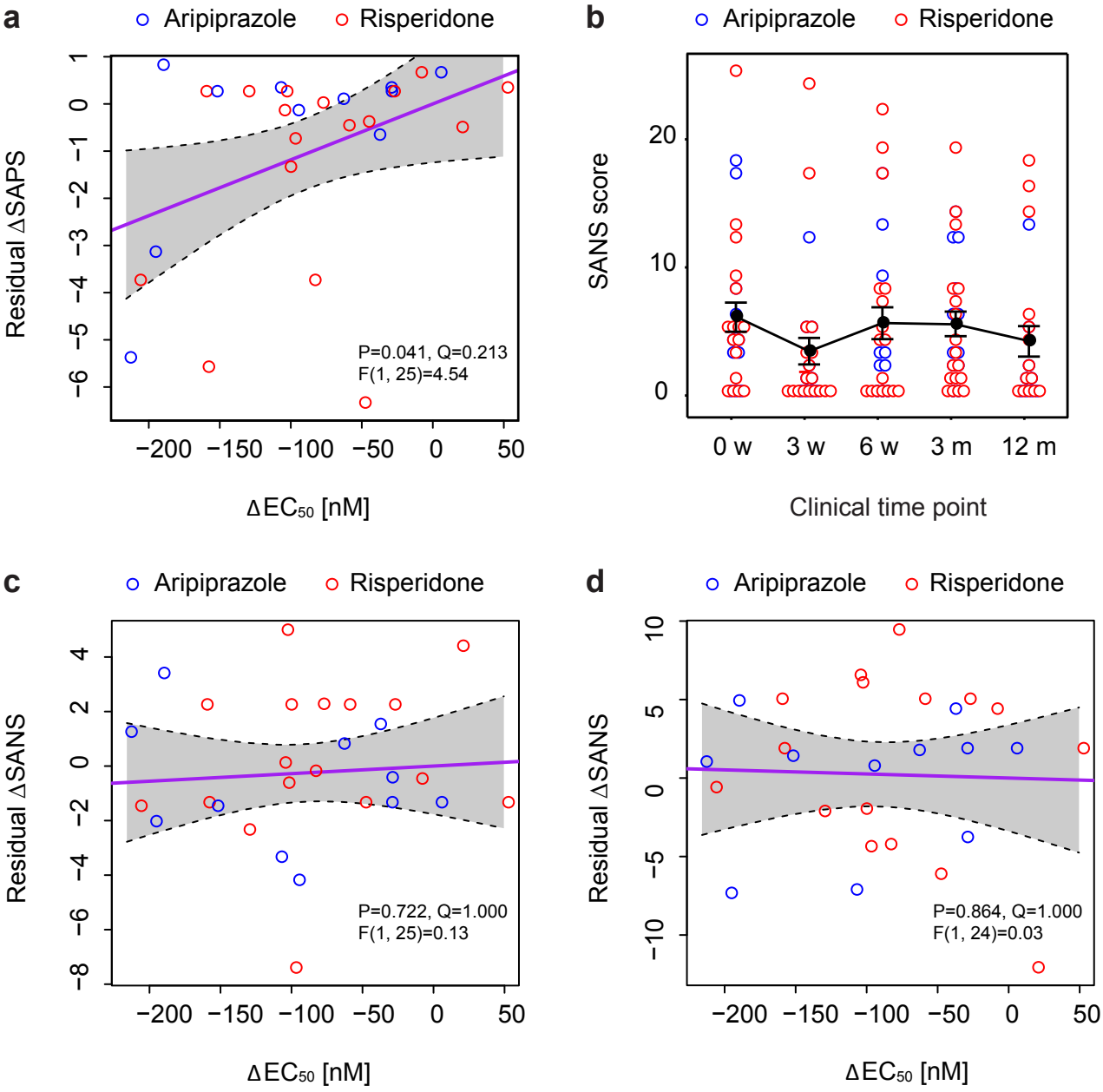


Fig. S22. Correlation of ex vivo drug-target activity with in vivo efficacy in the CV study. (**a**) Correlation between the *ex vivo* efficacy of the two antipsychotic medications (aripiprazole and risperidone) identified in the screening phase (**Fig. 5**), measured as the shift in EC_{50} (ΔEC_{50}) of the thapsigargin/PLC-γ1 response, in peripheral blood mononuclear cells from individual drug-naïve schizophrenia patients and the *in vivo* efficacy in ameliorating positive symptoms (ΔSAPS, Scale for the Assessment of Positive Symptoms) after 6 weeks of clinical treatment in the same patients. Linear regression model with 95% confidence intervals, adjusted for covariates selected in stepwise procedure using Bayesian Information Criterion. Total n=12 and 18 samples for aripiprazole and risperidone treatments, respectively. (**b**) Longitudinal clinical assessment of the *in vivo* efficacy of aripiprazole and risperidone on schizophrenia symptoms assessed using the Scale for the Assessment of Negative Symptoms (SANS) in the same schizophrenia patients between 0 weeks (w) and 12 months (m) of treatment. Patients remained on the same treatment at least until the three month time point. (**c**) Correlation between drug-induced thapsigargin/PLC-γ1 ΔEC_{50} *ex vivo* and *in vivo* drug efficacy on negative symptoms (ΔSANS) in the same patients after 3 weeks and (**d**) 6 weeks of treatment.

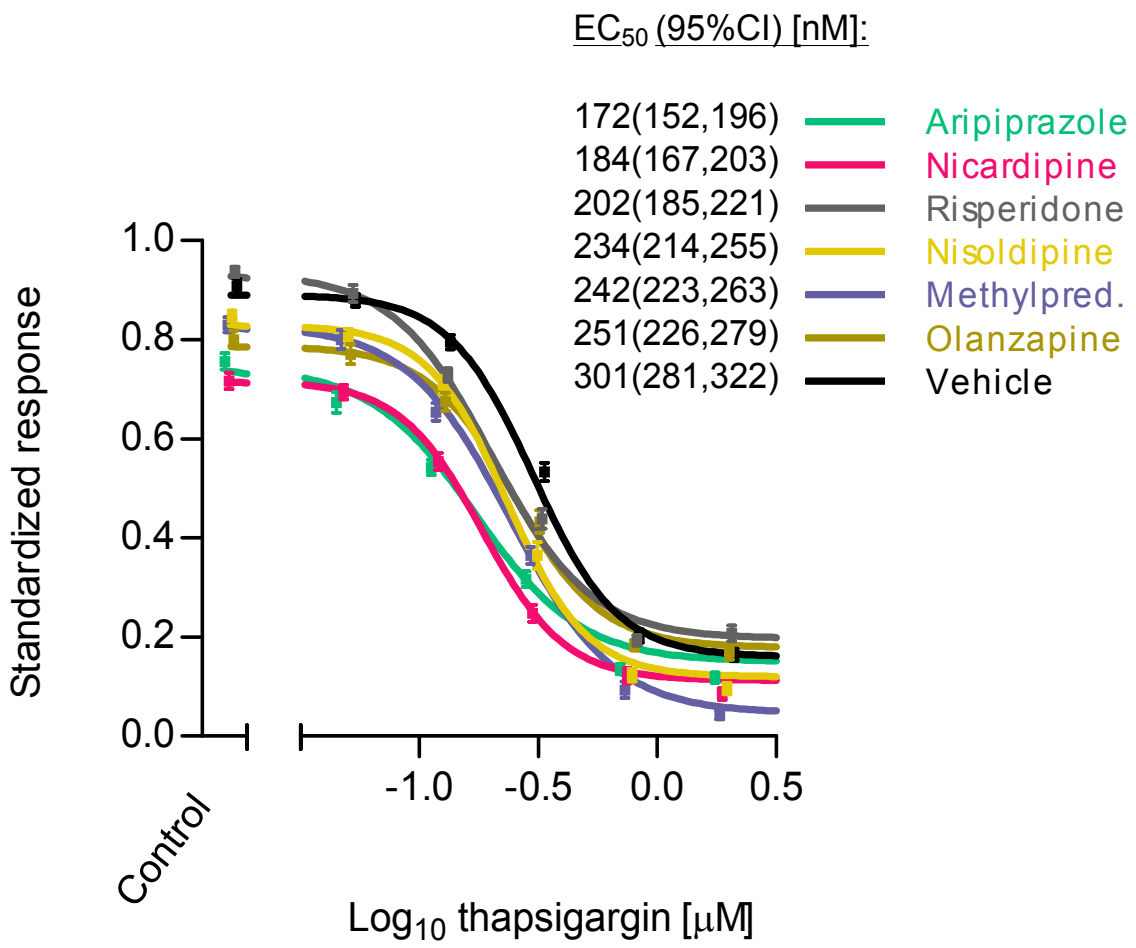


Fig. S23. Potentiation of thapsigargin/PLC-γ1 dose response at 30 min by top drug candidates from the screening phase at 10 μM concentration in PBMCs from drug-naïve patients with SCZ. Shows mean data from 30 patients (points) with standard error of the mean (vertical bars) and fitted 4-parameter logistic curves. Y axis represents the median fluorescence intensity standardized as a proportion of minimum and maximum values. Legend shows the EC_{50} values with 95% confidence intervals (CI). Methylprednisolone is abbreviated as Methylpred.

Table S1. Antibodies used to detect intracellular cell signaling epitopes and PBMC subtypes. Antibodies are grouped by class, in terms of which cell signaling pathways they are ascribed to, and then ordered alphabetically. Kinetic profiling (KP), drug target identification (TI) and drug repurposing (DR) columns denote the studies for which the antibodies were used. Rabbit (R), Mouse (Ms), protein kinase B (AKT), interleukin-1 receptor/toll-like receptor (IL1R/TLR), Janus kinase/signal transducer and activator of transcription (JAK/STAT), mitogen-activated protein kinase (MAPK), protein kinase A (PKA), protein kinase C (PKC), T cell receptor/B cell receptor (TCR/BCR).

Epitopes	Clone	Isotype	Gene	Class	Fluoro-chrome	KP	TI	DR	Supplier
4EBP1 (pT36/pT45)	M31-16	Ms IgG_1, κ	EIF4EBP1	AKT	AF 488	KP	TI		BD Biosciences
4EBP1 (pT69)	M34-273	Ms IgG_1, κ	EIF4EBP1	AKT	PE	KP	TI		BD Biosciences
Akt (pS473)	M89-61	Ms IgG_1, κ	AKT1	AKT	AF 647	KP	TI		BD Biosciences
Akt (pT308)	J1-223.371	Ms IgG_1, κ	AKT1	AKT	PE	KP	TI		BD Biosciences
Akt1	55/PKBa/Akt	Ms IgG_1, κ	AKT1	AKT	AF 488	KP	TI		BD Biosciences
β-Catenin (pS45)	K63-363	Ms IgG_1, κ	CTNNB1	AKT	AF 647	KP	TI		BD Biosciences
CD221 (pY1131)	K74-218	Ms IgG_1, κ	IGF1R	AKT	AF 647	KP	TI		BD Biosciences
eIF4E (pS209)	J77-925	Ms IgG_1, κ	EIF4E	AKT	PE	KP	TI		BD Biosciences
Ezrin (pY353)	I66-386	Ms IgG_1	EZR	AKT	PE	KP	TI		BD Biosciences
FAK (pS910)	K73-480	Ms IgG_{2b}, κ	PTK2	AKT	AF 488	KP			BD Biosciences
GSK-3α/β	4G-1E	Ms IgG_1	GSK3B	AKT	FITC	KP	TI		Merck Millipore
GSK-3β (pSer9)	D85E12	R IgG	GSK3B	AKT	PE	KP	TI		Cell Signaling Technology
GSK-3β (pThr390)	polyclonal	R IgG	GSK3B	AKT	PE	KP	TI		Bioss
GSK-3β (pTyr216)	polyclonal	R IgG	GSK3B	AKT	AF 647	KP			Bioss
IRS-1 (pY896)	K9-211	Ms IgG_{2a}, κ	IRS1	AKT	AF 647	KP	TI		BD Biosciences
PDPK1 (pS241)	J66-653.44.17	Ms IgG_1, κ	PDPK1	AKT	AF 488	KP	TI		BD Biosciences
S6 (pS235/pS236)	N7-548	Ms IgG_1, κ	RP26	AKT	AF 647	KP	TI		BD Biosciences
S6 (pS240)	N4-41	Ms IgG_1, κ	RPS6	AKT	AF 488	KP	TI		BD Biosciences
IκBα	25/IkBa/MAD-3	Ms IgG_1	NFKBIA	IL1R/ TLR	PE	KP	TI		BD Biosciences
IRAK4	L29-525	Ms IgG_1, κ	IRAK4	IL1R/ TLR	PE	KP			BD Biosciences
IRF-7 (pS477/pS479)	K47-671	Ms IgG_1, κ	IRF7	IL1R/ TLR	AF 488	KP	TI		BD Biosciences
NF-κB p65 (pS529)	K10-895.12.50	Ms IgG_{2b}, κ	RELA	IL1R/ TLR	AF 647	KP	TI		BD Biosciences
Stat1 (N-Terminus)	1/Stat1	Ms IgG_1	STAT1	JAK/ STAT	PE	KP	TI		BD Biosciences
Stat1 (pS727)	K51-856	Ms IgG_1, κ	STAT1	JAK/ STAT	AF 488	KP	TI		BD Biosciences
Stat1 (pY701)	4a	Ms IgG_{2a}	STAT1	JAK/ STAT	AF 647	KP	TI		BD Biosciences
Stat3	M59-50	Ms IgG1, λ	STAT3	JAK/ STAT	PE	KP	TI		BD Biosciences
Stat3 (pS727)	49/p-Stat3	Ms IgG_1	STAT3	JAK/ STAT	AF 488	KP	TI		BD Biosciences
Stat3 (pY705)	4/P-STAT3	Ms IgG_{2a}, κ	STAT3	JAK/ STAT	AF 647	KP	TI		BD Biosciences
Stat4 (pY693)	38/p-Stat4	Ms IgG_{2b}	STAT4	JAK/ STAT	PE	KP	TI		BD Biosciences
Stat5 (pY694)	47/Stat5(pY694)	Ms IgG_1, κ	STAT5A, STAT5B	JAK/ STAT	AF 647	KP	TI		BD Biosciences
Stat6 (pY641)	18/P-Stat6	Ms IgG_{2a}	STAT6	JAK/ STAT	PE	KP	TI		BD Biosciences
Bcl-2 (pS70)	N46-467	Ms IgG_1	BCL2	MAPK	AF 647	KP	TI		BD Biosciences
ERK1/2 (pT202/pY204)	20A	Ms IgG_1	MAPK1, MAPK3	MAPK	AF 647	KP	TI		BD Biosciences
JNK (pT183/pY185)	N9-66	Ms IgG_1, κ	MAPK8	MAPK	AF 647	KP			BD Biosciences
MAPKAPK-2 (pT334)	P24-694	Ms IgG_1, κ	MAPKAPK	MAPK	AF 488	KP	TI		BD Biosciences
MEK1 (pS218)/MEK2 (pS222)	O24-836	Ms IgG_1, κ	MAP2K1, MAP2K2	MAPK	AF 647	KP	TI		BD Biosciences
MEK1 (pS298)	J114-64	Ms IgG_1, κ	MAP2K1	MAPK	PE	KP	TI		BD Biosciences
p38 MAPK (pT180/pY182)	36/p38 (pT180/pY182)	Ms IgG_1, κ	MAPK14, MAPK13, MAPK12	MAPK	AF 647	KP	TI		BD Biosciences
p53 (acK382)	L82-51	Ms IgG_1, κ	TP53	MAPK	AF 647	KP	TI		BD Biosciences
p53 (pS37)	J159-641.79	Ms IgG_1, κ	TP53	MAPK	AF 488	KP	TI		BD Biosciences
CD140b (pY857)	J24-618	Ms IgG_1, κ	PDGFRB	Other	AF 488	KP	TI		BD Biosciences
Rb (pS780)	J146-35	Ms IgG_1, κ	RB1	Other	AF 488	KP	TI		BD Biosciences
Smad2 (pS465/pS467)/Smad3 (pS423/pS425)	O72-670	Ms IgG_1, κ	SMAD2	Other	PE	KP	TI		BD Biosciences
CREB (pS133)/ATF-1 (pS63)	J151-21	Ms IgG_1, κ	CREB1	PKA	AF 647	KP	TI		BD Biosciences
DARPP32	polyclonal	R IgG	PPP1R1B	PKA	PE	KP			Bioss
DARPP32 (pThr34)	polyclonal	R IgG	PPP1R1B	PKA	AF 647	KP			Bioss
DARPP32 (pThr75)	polyclonal	R IgG	PPP1R1B	PKA	AF 488	KP			Bioss
PKA RIIα (pS99)	I65-856.286	Ms IgG_1, κ	PRKAR2A	PKA	AF 647	KP	TI		BD Biosciences
PKA RIIβ (pS114)	47/PKA	Ms IgG_1	PRKAR2B	PKA	AF 488	KP	TI		BD Biosciences
p120 Catenin (pS268)	9a.390	Ms IgG_{2b}, κ	CTNND1	PKC	AF 488	KP	TI		BD Biosciences
p120 Catenin (pS879)	K114-1011	Ms IgG_1, κ	CTNND1	PKC	PE	KP	TI		BD Biosciences
p120 Catenin (pT310)	22/p120 (pT310)	Ms IgG_1, κ	CTNND1	PKC	AF 488	KP	TI		BD Biosciences
PKC-α	3/PKCα	Ms IgG_{2b}	PRKCA	PKC	AF 488	KP	TI		BD Biosciences
PKC-α (pT497)	K14-984	Ms IgG_1, κ	PRKCA	PKC	AF 647	KP	TI		BD Biosciences
PKC-α/βII (pThr638/641)	polyclonal	R IgG	PRKCA, PRKCB	PKC	PE	KP			Bioss
PKC-β1/2 (pThr500)	polyclonal	R IgG	PRKCB	PKC	PE	KP			Bioss
PKC-δ (pThr505)	polyclonal	R IgG	PRKCD	PKC	AF 488	KP			Bioss
PKC-θ	27/PKCθ	Ms IgG2a, κ	PRKCQ	PKC	PE	KP	TI		BD Biosciences
PKC-θ (pT538)	polyclonal	R IgG	PRKCQ	PKC	PE	KP	TI		Bioss
PKC-θ (pSer695)	polyclonal	R IgG	PRKCQ	PKC	AF 488	KP			Bioss
PLC-γ1	10/PLCgamma	Ms IgG_1	PLCG1	PKC	PE	KP	TI	DR	BD Biosciences
PLC-γ1 (pY783)	27/PLC	Ms IgG_1	PLCG1	PKC	AF 647	KP	TI		BD Biosciences
PLC-γ2	K86-1161	Ms IgG_1, κ	PLCG2	PKC	AF 488	KP	TI		BD Biosciences
PLC-γ2 (pY759)	K86-689.37	Ms IgG_1, κ	PLCG2	PKC	AF 647	KP	TI		BD Biosciences
BLNK (pY84)	J117-1278	Ms IgG_{2b}, κ	BLNK	TCR/ BCR	PE	KP	TI		BD Biosciences
Btk (pY551)/Itk (pY511)	24a/BTK (Y551)	Ms IgG_1	BTK	TCR/ BCR	AF 647	KP			BD Biosciences
c-Cbl (pY700)	47/c-Cbl	Ms IgG_1	CBL	TCR/ BCR	PE	KP	TI		BD Biosciences
c-Cbl (pY774)	29/c-Cbl	Ms IgG_1	CBL	TCR/ BCR	PE	KP	TI		BD Biosciences
CrkL (pY207)	K30-391.50.80	Ms IgG_{2a}, κ	CRKL	TCR/ BCR	AF 488	KP	TI		BD Biosciences
LAT (pY226)	J96-1238.58.93	Ms IgG_1, κ	LAT	TCR/ BCR	AF 488	KP	TI		BD Biosciences
Lck (pY505)	4/LCK-Y505	Ms IgG_1	LCK	TCR/ BCR	AF 488	KP	TI		BD Biosciences
Pyk2 (pY402)	L68-1256.272	Ms IgG_{2b}, κ	PTK2B	TCR/ BCR	PE	KP	TI		BD Biosciences
SHP2 (pY542)	L99-921	Ms IgG_1, κ	PTPN11	TCR/ BCR	AF 647	KP	TI		BD Biosciences
SLP-76 (pY128)	J141-668.36.58	Ms IgG_1, κ	LCP2	TCR/ BCR	AF 647	KP	TI		BD Biosciences
Src (pY418)	K98-37	Ms IgG_1, κ	SRC	TCR/ BCR	AF 488	KP	TI		BD Biosciences
WIP (pS488)	K32-824	Ms IgG_1, κ	WIPF1	TCR/ BCR	PE	KP	TI		BD Biosciences
Zap70 (pY292)	J34-602	Ms IgG_1, κ	ZAP70	TCR/ BCR	AF 488	KP	TI		BD Biosciences
Zap70 (pY319)/Syk (pY352)	17A/P-ZAP70	Ms IgG_1	SYK, ZAP70	TCR/ BCR	AF 647	KP	TI		BD Biosciences
CD3	UCHT1	Ms IgG1, κ	CD3E	Subtyping	PE Cy7	KP	TI		eBioscience
CD3	UCHT1	Ms IgG1, κ	CD3E	Subtyping	APC			DR	eBioscience
CD4	SK3	Ms IgG1, κ	CD4	Subtyping	PerCP-eF710		TI		eBioscience
CD8a	SK1	Ms IgG1, κ	CD8A	Subtyping	APC-eF780		TI		eBioscience

Table S2 Ligands used to stimulate/alter cell signaling dynamics in peripheral blood mononuclear cells (PBMCs). Ligands are ordered by class and then alphabetically. Kinetic profiling (KP), drug target identification (TI) and drug repurposing (DR) columns denote the studies for which the ligands were used. The antibodies in anti-CD3/CD28 and anti-CD3/CD28-XL stimulant cocktails are anti-human mouse monoclonal antibodies for which the clone is specified in brackets. The antibodies in anti-BCR/FcR-XL and anti-BCR/FcR-XL + CD40L stimulant cocktails are anti-human goat polyclonal antibodies. Receptor (R) subtypes and enzyme isotypes quoted represent those for which the ligand displays significantly higher binding affinity (K_i) or in vitro-potency (EC_{50}) relative to other subtypes/isotypes. *recombinant human protein.

Ligands	Abbreviation	Function	Class	Assay conc.	Conc. unit	KP	TI	DR	CAS number	Supplier
anti-IgG/ anti-IgM/ anti-Igλ/ anti-Igκ	anti-BCR/FcR-XL	B cell R (BCR)/ Fc R cross-linker agonist	Antigen receptor ligand	2/ 2/ 2/ 4	ug/ml	KP	TI		NA	Sigma (3)/ ab-online
anti-IgG/ anti-IgM/ anti-Igλ/ anti-Igκ// MegaCD40L	anti-BCR/FcR-XL // CD40L	B cell R (BCR)/ Fc R cross-linker agonist// CD40 agonist	Antigen receptor ligand	2/ 2/ 2/ 4// 0.25	ug/ml				NA	Sigma (3)/ ab-online/ Enzo
anti-CD3 (HIT3a)/ anti-CD28 (CD28.2)	anti-CD3/ CD28	T cell R (TCR)/ CD28 agonist	Antigen receptor ligand	0.5/ 0.5	ug/ml	KP	TI		NA	eBioscience (2)
anti-CD3 (OKT3)-biotin/ anti-CD28 (CD28.2)-biotin/ NeutrAvidin	anti-CD3/ CD28-XL	T cell R (TCR)/ CD28 cross-linker agonist	Antigen receptor ligand	2.5/ 2.5/ 12.5	ug/ml				NA	eBioscience (2)/ Life Technologies
lipopolysaccharides *Escherichia coli* 055:B5	LPS	toll-like R 4 (TLR4) agonist	Antigen receptor ligand	0.1	ug/ml	KP	TI		NA	Sigma
staphylococcal enterotoxin B *Staphylococcus aureus*	SEB	T cell R (TCR) agonist	Antigen receptor ligand	1	ug/ml	KP	TI		NA	Sigma
(S)-3,5-DHPG	(S)-3,5-DHPG	metabotropic glutamate 1/5 (mGlu1/5) R agonist	CNS ligand	10	uM	KP			162870-29-3	Tocris
2-pyridylethylamine dihydrochloride	2-pyridylethylamine	histamine 1 (H1) R agonist	CNS ligand	10	uM	KP	TI		3343-39-3	Tocris
7-hydroxy-DPAT hydrobromide	7-OH-DPAT	dopamine 3 (D3) R agonist	CNS ligand	10	uM	KP	TI		74938-11-7	Tocris
agomelatine	agomelatine	melatonin 1/2 (MT1/2) R agonist	CNS ligand	10	uM	KP	TI		138112-76-2	abcam
AS 19	AS 19	5-hydroxytryptamine 7 (5-HT7) R agonist	CNS ligand	10	uM	KP	TI		1000578-26-6	Tocris
cis-ACPD// (S)-(-)-5-fluorowillardiine	cis-ACPD// (S)(-)-5-FW	N-methyl-D-aspartate (NMDA) R agonist, mGlu2/3 R agonist // α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid (AMPA) R agonist	CNS ligand	10// 10	uM	KP			477331-06-9	Tocris (2)
isoproterenol hydrochloride	isoproterenol	β-adreno (β-A) R agonist	CNS ligand	10	uM	KP	TI		51-30-9	Tocris
L-AP4	L-AP4	metabotropic glutamate 4/6/7/8 (mGlu4/6/7/8) R agonist	CNS ligand	10	uM	KP			23052-81-5	Tocris
LY 354740 hydrate	LY 354740	metabotropic glutamate 2/3 (mGlu2/3) R agonist	CNS ligand	10	uM	KP			176199-48-7	Tocris
muscimol	muscimol	γ-Aminobutyric acid A (GABA-A) R agonist	CNS ligand	10	uM	KP			2763-96-4	Tocris
NECA	NECA	adenosine 1/2A/3 (A1/2A/3) R agonist	CNS ligand	10	uM	KP	TI		35920-39-9	Tocris
PD 168077 maleate	PD 168077	dopamine 4 (D4) R agonist	CNS ligand	10	uM	KP			630117-19-0	Tocris
PHA 543613 hydrochloride	PHA 543613	α-7 nicotinic acetylcholine receptor (α-7nACh) R agonist	CNS ligand	10	uM	KP	TI		478149-53-0	Tocris
phencyclidine hydrochloride	phencyclidine	N-methyl-D-aspartate (NMDA) R antagonist, σ R agonist	CNS ligand	10	uM	KP	TI		956-90-1	Sigma
SKF 83822 hydrobromide	SKF 83822	dopamine 1/5 (D1/5) R agonist	CNS ligand	10	uM	KP	TI		74115-08-5	Tocris
SR 57227 hydrochloride	SR 57227	5-hydroxytryptamine 3 (5-HT3) R agonist	CNS ligand	10	uM	KP	TI		77145-61-0	Tocris
sumanirole maleate	sumanirole	dopamine 2 (D2) R agonist	CNS ligand	10	uM	KP	TI		179386-43-7	Tocris
TCB-2	TCB-2	5-hydroxytryptamine 2A (5-HT2A) R agonist	CNS ligand	10	uM	KP	TI		912342-28-0	Tocris
WAY 161503 hydrochloride	WAY 161503	5-hydroxytryptamine 2C (5-HT2C) R agonist	CNS ligand	10	uM	KP			75704-24-4	Tocris
WAY 208466 dihydrochloride	WAY 208466	5-hydroxytryptamine 6 (5-HT6) R agonist	CNS ligand	10	uM	KP			633304-27-5	Tocris
xaliproden hydrochloride	xaliproden	5-hydroxytryptamine 1A (5-HT1A) R agonist	CNS ligand	10	uM	KP	TI		90494-79-4	Tocris
xanomeline oxalate	xanomeline	muscarinic 1 (M1) R agonist	CNS ligand	10	uM	KP	TI		141064-23-5	Tocris
interferon-α2c*	IFN-α2c	interferon α/β (IFNα/β) R agonist	Cytokine	0.1	ug/ml	KP	TI		NA	eBioscience
interferon-γ*	IFN-γ	interferon γ (IFNγ) R agonist	Cytokine	0.1	ug/ml	KP	TI		NA	eBioscience
interleukin-10 *	IL-10	interleukin-10 (IL-10) R agonist	Cytokine	0.1	ug/ml	KP	TI		NA	eBioscience
interleukin-1β *	IL-1β	interleukin-1β (IL-1β) R agonist	Cytokine	0.1	ug/ml	KP	TI		NA	eBioscience
interleukin-2 *	IL-2	interleukin-2 (IL-2) R agonist	Cytokine	0.1	ug/ml	KP	TI		NA	eBioscience
interleukin-23 *	IL-23	interleukin-23 (IL-23) R agonist	Cytokine	0.1	ug/ml	KP	TI		NA	eBioscience
interleukin-4 *	IL-4	interleukin-4 (IL-4) R agonist	Cytokine	0.1	ug/ml	KP	TI		NA	eBioscience
interleukin-6 *	IL-6	interleukin-6 (IL-6) R agonist	Cytokine	0.1	ug/ml	KP	TI		NA	eBioscience
tumor necrosis factor-α *	TNF-α	tumor necrosis factor (TNF) R agonist	Cytokine	0.1	ug/ml	KP	TI		NA	eBioscience

Ligands	Abbreviation	Function	Class	Assay conc.	Conc. unit	KP	TI	DR	CAS number	Supplier
17 β-estradiol	17 β-estradiol	Oestrogen (E) R agonist	Hormone/ growth factor	10	uM	KP	TI		50-28-2	Sigma
brain derived neurotrophic factor *	BDNF	tyrosine receptor kinase B (TrkB) R agonist	Hormone/ growth factor	0.1	ug/ml	KP	TI		NA	eBioscience
dexamethasone	dexamethasone	glucocorticoid (G) R agonist	Hormone/ growth factor	10	uM	KP	TI		50-02-2	Sigma
insulin*	insulin	insulin (I) R agonist	Hormone/ growth factor	0.1	uM	KP	TI		NA	Sigma
leptin*	leptin	leptin (LEP) R agonist	Hormone/ growth factor	1	ug/ml	KP	TI		NA	R&D Systems
platelet-derived growth factor-BB *	PDGF-BB	fibroblast proliferation agonist	Hormone/ growth factor	0.1	ug/ml	KP			NA	eBioscience
β-nerve growth factor*	β-NGF	tropomyosin receptor kinase A (TrkA) agonist	Hormone/ growth factor	0.1	ug/ml	KP			NA	Life Technologies
aripiprazole	aripiprazole	dopamine 2 (D2) R and 5-HT1A R partial agonist, 5-HT2A R antagonist	Neuropsychiatric treatment	10	uM	KP	TI		129722-12-9	abcam
carbamazepine	carbamazepine	voltage-gated sodium channel inhibitor	Neuropsychiatric treatment	10	uM	KP			298-46-4	Sigma
clozapine	clozapine	5-hydroxytryptamine 2A/2C (5-HT2A/2C) R and dopamine 4 (D4) R antagonist	Neuropsychiatric treatment	10	uM	KP	TI		5786-21-0	Tocris
desipramine hydrochloride	desipramine	noradrenaline (NA) reuptake inhibitor	Neuropsychiatric treatment	10	uM	KP	TI		58-28-6	Sigma
desvenlafaxine succinate	desvenlafaxine	5-hydroxytryptamine (5HT) reuptake inhibitor	Neuropsychiatric treatment	10	uM	KP	TI		386750-22-7	Tocris
fluoxetine hydrochloride	fluoxetine	5-hydroxytryptamine (5HT) reuptake inhibitor	Neuropsychiatric treatment	10	uM	KP	TI		56296-78-7	Tocris
haloperidol	haloperidol	dopamine 2/3 (D2/3) R inverse agonist	Neuropsychiatric treatment	10	uM	KP	TI		52-86-8	Sigma
lithium chloride	lithium	glycogen synthase kinase-3β (GSK-3β) inhibitor	Neuropsychiatric treatment	10000	uM	KP	TI		7447-41-8	Sigma
olanzapine	olanzapine	5-hydroxytryptamine 2A (5-HT2A) R and dopamine 1-5 (D1-5) R antagonist	Neuropsychiatric treatment	10	uM	KP	TI		132539-06-1	Tocris
quetiapine hemifumarate	quetiapine	5-hydroxytryptamine 2A (5-HT2A) R and dopamine 2/3 (D2/3) R antagonist	Neuropsychiatric treatment	10	uM	KP			111974-72-2	Tocris
risperidone	risperidone	5-hydroxytryptamine 2A (5-HT2A) R and dopamine 2-4 (D2-4) R antagonist	Neuropsychiatric treatment	10	uM	KP	TI		106266-06-2	Tocris
sodium valproic acid	valproic acid	sodium channel and histone deacetylase inhibitor	Neuropsychiatric treatment	1000	uM	KP	TI		1069-66-5	Sigma
740 Y-P	740 Y-P	Phosphatidylinositol-4,5-bisphosphate 3-kinase activator	Positive control - activator	3	uM	KP			1236188-16-1	Tocris
sodium 8-bromo-cAMP	8-Br-cAMP	protein kinase A activator	Positive control - activator	700	uM	KP	TI		76939-46-3	Tocris
calyculin A	calyculin A	protein phosphatase 1/2A (PP1/2A) inhibitor	Positive control - activator	1	uM	KP	TI		101932-71-2	Tocris
forskolin	forskolin	adenylyl cyclase activator	Positive control - activator	10	uM	KP	TI		66575-29-9	Tocris
GW 9508	GW 9508	free fatty acid receptor 1 (FFA1) R agonist	Positive control - activator	10	uM	KP			885101-89-3	Tocris
sodium orthovanadate	orthovanadate	protein tyrosine phosphatase (PTPase), alkaline phosphatase (ALPase) and adenosine triphosphatase (ATPase) inhibitor	Positive control - activator	150	uM	KP	TI		13721-39-6	Tocris
phorbol 12-myristate 13-acetate/ calcium ionomycin *Streptomyces conglobatus*	PMA/ ionomycin	protein kinase C (PKC) activator / extracellular calciuim ionophore	Positive control - activator	0.1/ 1	uM	KP	TI		56092-82-1	Tocris/ Sigma
PS 48	PS 48	Phosphoinositide-dependent protein kinase-1 (PDK1) activator	Positive control - activator	10	uM	KP	TI		1180676-32-7	Tocris
SC-9	SC-9	protein kinase C (PKC) activator	Positive control - activator	10	uM	KP	TI		102649-78-5	Tocris
simvastatin	simvastatin	3-hydroxy-3-methyl-glutaryl-CoA reductase (HMGCR) inhibitor	Positive control - activator	10	uM	KP	TI		79902-63-9	Tocris
thapsigargin	thapsigargin	sarco-endoplasmic reticulum Ca2+-ATPase inhibitor	Positive control - activator	1	uM	KP	TI	DR	67526-95-8	Tocris
CHIR-99021	CHIR-99021	glycogen synthase kinase-3β (GSK-3β) inhibitor	Positive control - inhibitor	10	uM	KP	TI		252917-06-9	Collaborator
GSK 690693	GSK 690693	protein kinase B (AKT) inhibitor	Positive control - inhibitor	10	uM	KP	TI		937174-76-0	Tocris
JB1121	JB1121	glycogen synthase kinase-3β (GSK-3β) inhibitor	Positive control - inhibitor	10	uM	KP	TI			Collaborator
rapamycin	rapamycin	mammalian target of rapamycin (mTOR) inhibitor	Positive control - inhibitor	5	uM	KP	TI		53123-88-9	Tocris
staurosporine	staurosporine	protein kinase inhibitor	Positive control - inhibitor	5	uM	KP	TI		62996-74-1	Enzo

Table S2 Ligands used to stimulate/alter cell signaling dynamics in peripheral blood mononuclear cells (PBMCs) - continued.

Table S3. Activity of ligands across the time course. Shows the number of significant responses (permuted P<0.05, Wilcoxon rank-sum test) with a minimum fold change of 10% relative to the vehicle, across 1, 5, 15 and 30 min time points. Ligands are ranked in descending order of activity at 30 min. Data represents eight peripheral blood mononuclear cell (PBMC) donors.

Ligand	01 min	05 min	15 min	30 min
calyculin A	12	19	35	41
staurosporine	16	21	33	38
thapsigargin	7	22	31	38
PMA/ionomycin	19	27	33	32
IFN-α2c	5	7	8	9
GSK 690693	2	4	6	8
IL-2	1	2	6	8
IL-10	1	4	6	7
IL-6	2	6	7	7
aripiprazole	0	0	0	4
desipramine hydrochloride	6	5	4	4
fluoxetine	0	1	3	3
SC-9	0	1	0	3
sodium orthovanadate	0	0	0	3
anti-CD3/CD28	0	1	4	2
IFN-γ	1	1	1	2
IL-4	1	2	5	2
lithium chloride	0	2	2	2
PHA 543613 hydrochloride	0	0	1	2
2-pyridylethylamine dihydrochloride	0	1	0	1
8-bromo-cAMP	1	1	2	1
forskolin	1	3	2	1
leptin	0	0	1	1
NECA	1	2	1	1
olanzapine	0	0	0	1
rapamycin	1	1	1	1
risperidone	0	1	1	1
simvastatin	1	0	0	1
SJH 6 (JB1121)	1	2	1	1
SJH1 (CHIR-99021)	1	1	2	1
SR 57227 hydrochloride	0	0	1	1
xaliproden hydrochloride	0	0	0	1
(S)-3,5-DHPG	1	0	1	0
17 β-estradiol	0	0	0	0
740 Y-P	0	0	1	0
7-hydroxy-DPAT hydrobromide	0	1	1	0
agomelatine	0	0	0	0
AS 19	0	0	0	0
BCR stim	0	0	0	0
BDNF	0	0	1	0
beta-NGF	0	0	0	0
carbamazepine	0	0	0	0
cis-ACPD/(S)-(-)-5-fluorowillardiine	0	0	0	0
clozapine	1	3	0	0
desvenlafaxin succinate (WY 45233)	0	0	0	0
dexamethasone	0	0	0	0
GW 9508	0	0	1	0
haloperidol	1	1	0	0
IL-1β	0	0	2	0
IL-23	0	0	0	0
insulin	0	0	1	0
isoproterenol hydrochloride	2	0	0	0
L-AP4	0	0	0	0
LPS	0	0	0	0
LY 354740 hydrate	0	0	0	0
muscimol	0	0	0	0
PD 168077 maleate	0	1	0	0
PDGF-BB	0	0	0	0
phencyclidine hydrochloride	1	2	0	0
PS 48	0	0	0	0
quetiapine	0	0	0	0
SEB	0	0	1	0
SKF 83822 hydrobromide	10	1	0	0
sumanirole maleate	0	0	0	0
TCB-2	1	0	0	0
TNF-α	0	0	0	0
valproic acid	0	0	4	0
WAY 161503 hydrochloride	0	0	1	0
WAY 208466 dihydrochloride	0	0	0	0
xanomeline oxalate	0	0	0	0
Total	97	146	211	228

Table S4. Activity of epitopes across the time course. Shows the number of significant response (permuted P<0.05, Wilcoxon rank-sum test) with a minimum fold change of 10% relative to the vehicle, across 1, 5, 15 and 30 min time points. Epitopes are ranked in descending order of activity at 30 min. Data represents eight peripheral blood mononuclear cell (PBMC) donors.

Epitope	01 min	05 min	15 min	30 min
4EBP1 (pT36/pT45)	0	9	9	10
GSK-3β (pSer9)	8	9	8	9
MEK1 (pS298)	5	5	9	9
Stat1 (pY701)	3	4	7	7
Stat3 (pS727)	1	2	5	7
c-Cbl (pY774)	0	0	3	6
Smad2 (pS465/pS467)/Smad3 (pS423/pS425)	1	3	4	6
Stat3 (pY705)	5	3	5	6
Stat4 (pY693)	1	3	5	6
Stat5 (pY694)	2	5	6	6
c-Cbl (pY700)	1	2	3	5
CD221 (pY1131)	4	4	4	5
CREB (pS133)/ATF-1 (pS63)	1	5	6	5
IκBα	0	0	4	5
S6 (pS240)	5	3	13	5
Stat1 (pS727)	0	2	5	5
Stat3	0	1	2	5
4EBP1 (pT69)	0	0	2	4
BLNK (pY84)	2	4	1	4
CrkL (pY207)	5	5	3	4
NF-κB p65 (pS529)	0	3	4	4
p38 MAPK (pT180/pY182)	1	3	5	4
PDPK1 (pS241)	1	3	4	4
PKC-θ	1	2	3	4
PLC-γ2 (pY759)	5	4	4	4
Pyk2 (pY402)	3	1	4	4
Stat6 (pY641)	2	4	4	4
WIP (pS488)	2	6	4	4
Akt (pS473)	2	4	2	3
Akt (pT308)	3	3	4	3
eIF4E (pS209)	0	0	2	3
IRF-7 (pS477/pS479)	0	2	3	3
MAPKAPK-2 (pT334)	2	4	5	3
p120 Catenin (pS268)	0	2	2	3
p120 Catenin (pS879)	0	0	2	3
p120 Catenin (pT310)	0	1	4	3
p53 (pS37)	0	1	2	3
PKA RIIα (pS99)	8	6	5	3
PKA RIIβ (pS114)	2	3	4	3
PKC-α	1	2	3	3
PLC-γ1	0	0	1	3
S6 (pS235/pS236)	2	3	4	3
Src (pY418)	2	2	2	3
Bcl-2 (pS70)	1	0	1	2
ERK1/2 (pT202/pY204)	1	2	2	2
FAK (pS910)	0	0	2	2
GSK-3β (pThr390)	0	0	3	2
Lck (pY505)	1	2	2	2
p53 (acK382)	0	0	0	2
PKC-θ (pT538)	0	0	1	2
Rb (pS780)	0	0	2	2
SHP2 (pY542)	0	1	2	2
SLP-76 (pY128)	2	3	3	2
Stat1 (N-Terminus)	0	0	1	2
Akt1	0	0	1	1
DARPP32 (pThr34)	0	1	0	1
GSK-3β (pTyr216)	0	1	1	1
IRAK4	1	2	1	1
MEK1 (pS218)/MEK2 (pS222)	1	2	2	1
PKC-α (pT497)	1	1	1	1
PKC-α/βII (pThr638/641)	0	0	0	1
PKC-δ (pThr505)	0	0	0	1
PLC-γ2	0	0	0	1
Zap70 (pY292)	2	3	3	1
β-Catenin (pS45)	0	0	1	0
Btk (pY551)/Itk (pY511)	0	0	0	0
CD140b (pY857)	0	0	0	0
DARPP32	0	0	0	0
DARPP32 (pThr75)	0	0	0	0
Ezrin (pY353)	0	0	0	0
GSK-3α/β	0	0	0	0
IRS-1 (pY896)	2	0	1	0
JNK (pT183/pY185)	0	0	0	0
LAT (pY226)	0	0	0	0
PKC-β1/2 (pThr500)	0	0	0	0
PLC-γ1 (pY783)	2	0	0	0
PKC-θ (pSer695)	0	0	0	0
Zap70 (pY319)/Syk (pY352)	2	0	0	0
Total	97	146	211	228

Table S5. Demographic characteristics and matching of PBMC donors used in the TI study. Matching was achieved for male drug-naïve schizophrenia (SCZ) vs. male control (CTRL) samples for all demographic variables except smoking and alcohol consumption. Statistical tests included Wilcoxon rank-sum test (*) and Fisher's exact test (**). Table shows mean values ± standard deviation.

	SCZ	CTRL	$p_{SCZ-CTRL}$
N	12	12	na
Age (years)*	26.4 ± 6.2	27.0 ± 6.5	1.000
Gender (male/female)	12/0	12/0	na
BMI (kg/m^2)*	24.0 ± 4.8	23.5 ± 1.6	0.419
Ethnicity (white/other)**	8/4	11/1	0.317
Smoking (y/n)**	8/4	2/10	**0.036**
Cannabis (y/n)**	2/10	4/8	0.640
Alcohol (y/n)**	4/8	11/1	**0.009**
Blood pressure systolic (mmHg)*	131.3 ± 11.0	124.8 ± 14.0	0.203
Blood pressure diastolic (mmHg)*	78.4 ± 10.3	76.7 ± 9.2	0.908
Hip (cm)*	95.9 ± 9.5	92.5 ± 5.7	0.435
Waist (cm)*	86.8 ± 10.5	88.2 ± 5.6	0.339

Table S6 Altered ligand responses at T cell signaling epitopes in healthy control vs. pre-treatment schizophrenia (CTRL vs. T0) and pre- vs. post-treatment schizophrenia (T0 vs. T6) comparisons. Shows ranked nodes (individual ligand-epitope combinations) for which there was a significant interaction between group status and the response to ligand ('*P interaction*'<0.05, two-way ANCOVA; terms in '*italics*' represent column headings) in either of the group comparisons CTRL vs. T0 (drug-naïve) or T0 (drug-naïve) vs. T6 (6 weeks of treatment with olanzapine). Clinical groups in the first column are assigned as 'reference' or 'comparison' groups, respectively, for interpretation of each row in subsequent columns. The number of peripheral blood mononuclear cell (PBMC) samples ('*n*') in each comparison group is cited in columns 4-7. Column '*Covariates*' lists variables included in the ANCOVA model by the stepwise covariate selection algorithm using the Bayesian Information Criterion. Column '*Q value*' shows '*P value*' adjusted for multiple comparisons. '*Ligand response*' represents median MFI of the ligand treatment/median MFI of the vehicle treatment within the respective clinical group. Only nodes which displayed a significant '*Ligand response*' (permuted P<0.05, Wilcoxon rank-sum test; min. fold change 10%), after adjusting for background fluorescence, in either clinical group, were analyzed. '*Response direction*' refers to the increase (↑) or decrease (↓) in epitope expression evoked by the ligand. Arrows in both directions (↑↓) indicate responses in different directions in the reference and comparison groups. '*Response ratio*' represents (1-'*Ligand response in the comparison group*')/(1-'*Ligand response in the reference group*'). For the majority of responses, this represents a means of expressing the relative potentiation or attenuation of response independently of its direction. This is expressed in the following column as '*Potentiation/attenuation fold change*' ('*Response ratio*' converted to -1/'*Response ratio*' for response ratios between 0 and 1), whereby a positive value represents potentiation and a negative value represents attenuation or reversal of response. '*Stain index*' refers to the median MFI of the stained samples/median MFI of the unstained samples for the vehicle condition in the CTRL group. Only nodes which displayed a minimum '*Stain index*' of 2 were analyzed. The '*CD4/CD8 correlation*' statistics reflect the Spearman's rank-order correlation P value and correlation coefficient (ρ) between ligand responses in individual samples and the respective CD4/CD8 cell type ratios in the immunophenotyping test. Total PBMC sample numbers in each group include CTRL (n=12), T0 (n=12) and T6 (n=10). MFI = median fluorescence intensity.

Reference vs. comparison group	Epitope	Ligand	n reference group (vehicle)	n reference group (ligand)	n comp. group (vehicle)	n comp. group (ligand)	Covariates	P interaction	Q interaction	Ligand response (reference group)	Ligand response (comp. group)	Response direction (across groups)	Response ratio (comp./ reference group)	Potentiation/ attenuation fold change (comp vs. reference)	Stain index	CD4/CD8 correlation P	CD4/CD8 correlation ρ
CTRL vs. T0	PLC-gamma 1	thapsigargin	9	9	11	10	age	0.0001	0.018	0.80	0.92	↓	0.38	-2.61	7.2	0.875	-0.04
CTRL vs. T0	PKA RII alpha (pS99)	NECA	10	10	11	10	-	0.003	0.259	0.80	0.94	↓	0.29	-3.43	65.4	0.247	0.27
CTRL vs. T0	Stat1 (N-Terminus)	staurosporine	9	9	12	10	age	0.011	0.626	0.62	0.82	↓	0.47	-2.15	12.5	0.369	-0.22
CTRL vs. T0	GSK-3 beta (pSer9)	IL-4	10	8	10	8	-	0.013	0.674	1.05	1.13	↑	2.41	2.41	2.3	0.338	-0.26
CTRL vs. T0	Bcl-2 (pS70)	thapsigargin	11	10	11	10	-	0.014	0.711	1.02	1.14	↑	6.60	6.60	8.9	0.750	-0.08
CTRL vs. T0	Pyk2 (pY402)	forskolin	11	9	12	10	BMI	0.019	0.805	0.99	1.13	↑↓	-14.75	-14.75	3.2	0.710	-0.09
CTRL vs. T0	PLC-gamma 2 (pY759)	sodium orthovanadate	11	8	10	10	age, BMI	0.021	0.831	1.01	1.11	↑	8.87	8.87	4.9	0.748	-0.08
CTRL vs. T0	GSK-3 beta (pSer9)	sodium orthovanadate	10	9	10	8	-	0.031	0.935	1.04	1.17	↑	3.87	3.87	2.3	0.060	0.47
CTRL vs. T0	Stat1 (N-Terminus)	lithium chloride	9	9	12	11	age	0.031	0.935	0.73	1.04	↑↓	-0.16	-0.16	12.5	0.672	0.10
CTRL vs. T0	PKA RII alpha (pS99)	2-pyridylethylamine	10	10	11	9	age	0.032	0.936	1.01	1.12	↑	8.69	8.69	65.4	0.302	0.25
CTRL vs. T0	CrkL (pY207)	anti-CD3/CD28	9	9	11	9	age, BMI	0.036	0.955	1.01	1.11	↑	18.59	18.59	5.3	0.129	0.37
CTRL vs. T0	Stat1 (pY701)	sodium orthovanadate	9	9	12	9	age, BMI	0.036	0.956	1.12	0.87	↑↓	-1.08	-1.08	3.8	0.503	0.17
CTRL vs. T0	p120 Catenin (pS879)	thapsigargin	10	10	12	12	age	0.044	0.979	0.80	0.92	↓	0.42	-2.37	2.4	0.956	0.01
CTRL vs. T0	PKA RII alpha (pS99)	7-OH-DPAT	10	11	11	10	age	0.046	0.982	1.01	1.20	↑	22.66	22.66	65.4	0.496	0.16
T0 vs. T6	CREB (pS133) / ATF-1 (pS63)	NECA	12	11	9	9	age	0.002	0.046	1.46	1.24	↑	0.53	-1.90	9.8	0.262	0.26
T0 vs. T6	Pyk2 (pY402)	forskolin	12	10	10	9	-	0.004	0.092	1.13	1.06	↑	0.48	-2.07	3.2	0.815	-0.06
T0 vs. T6	CrkL (pY207)	desipramine	11	10	10	10	BMI	0.006	0.121	1.11	1.05	↑	0.44	-2.26	5.3	0.276	0.26
T0 vs. T6	Pyk2 (pY402)	GSK 690693	12	10	10	10	-	0.007	0.148	1.16	1.06	↑	0.38	-2.62	3.2	0.203	-0.30
T0 vs. T6	WIP (pS488)	PMA/ionomycin	10	9	9	9	age	0.007	0.155	8.55	9.95	↑	1.18	1.18	4.3	0.754	-0.08
T0 vs. T6	Stat5 (pY694)	staurosporine	9	8	10	10	BMI	0.008	0.170	0.96	0.89	↓	2.87	2.87	35.8	0.418	0.20
T0 vs. T6	PKA RII beta (pS114)	staurosporine	11	10	10	10	age	0.009	0.182	0.70	0.60	↓	1.32	1.32	3.0	0.992	0.00
T0 vs. T6	PKA RII alpha (pS99)	leptin	11	10	10	10	-	0.009	0.191	1.12	0.96	↑↓	-0.35	-0.35	65.4	0.482	0.17
T0 vs. T6	Pyk2 (pY402)	staurosporine	12	11	10	9	BMI	0.010	0.216	0.53	0.49	↓	1.10	1.10	3.2	0.045	0.46
T0 vs. T6	PLC-gamma 1	thapsigargin	11	10	10	10	-	0.017	0.340	0.92	0.82	↓	2.33	2.33	7.2	0.654	-0.11
T0 vs. T6	PKA RII alpha (pS99)	17 beta-estradiol	11	10	10	10	age	0.019	0.387	1.12	0.96	↑↓	-0.32	-0.32	65.4	0.920	-0.02
T0 vs. T6	CrkL (pY207)	IFN-alpha 2c	11	9	10	9	-	0.020	0.409	1.16	1.07	↑	0.44	-2.28	5.3	0.843	0.05
T0 vs. T6	p120 Catenin (pS879)	staurosporine	12	11	9	9	-	0.022	0.443	0.92	0.82	↓	2.19	2.19	2.4	0.750	-0.08
T0 vs. T6	WIP (pS488)	17 beta-estradiol	10	9	9	9	-	0.035	0.638	1.15	1.06	↑	0.42	-2.40	4.3	0.967	0.01
T0 vs. T6	IRS-1 (pY896)	desvenlafaxin	11	11	8	8	-	0.037	0.655	1.15	1.06	↑	0.40	-2.52	5.1	0.546	0.15
T0 vs. T6	PKA RII beta (pS114)	GSK 690693	11	10	10	9	age	0.038	0.666	0.73	0.65	↓	1.31	1.31	3.0	0.471	-0.18
T0 vs. T6	PLC-gamma 1	staurosporine	11	9	10	9	-	0.040	0.677	0.84	0.74	↓	1.57	1.57	7.2	0.503	0.17
T0 vs. T6	CrkL (pY207)	thapsigargin	11	10	10	10	BMI	0.040	0.686	0.83	0.73	↓	1.54	1.54	5.3	0.255	-0.27
T0 vs. T6	PKA RII alpha (pS99)	8-bromo-cAMP	11	9	10	9	-	0.043	0.716	0.67	0.58	↓	1.28	1.28	65.4	0.339	0.24
T0 vs. T6	S6 (pS235/pS236)	PMA/ionomycin	10	9	9	9	-	0.048	0.771	98.19	121.14	↑	1.24	1.24	5.4	0.120	-0.38

Table S7. Altered basal expression of T cell signaling epitopes in pretreatment versus posttreatment SCZ comparison. No significant differences in basal epitope expression were detected in the healthy control vs. pre-treatment schizophrenia (CTRL vs. T0) comparison. Shows ranked epitopes which displayed a significant association between clinical group status and epitope expression ('*P value*'<0.05, ANCOVA; terms in '*italics*' represent column headings) in the T0 (drug-naïve schizophrenia) vs. T6 (6 weeks of treatment with olanzapine) comparison. The clinical groups were assigned as '*reference*' or '*comparison*' for interpretation of subsequent columns. Sample size of each group is shown in columns labeled '*n*'. Column '*Covariates*' lists variables included in the ANCOVA model by the stepwise covariate selection algorithm using Bayesian Information Criterion. The '*Expression ratio*' refers to the median epitope MFI for the vehicle condition in the comparison vs. reference group. Column '*Q value*' shows '*P value*' adjusted for multiple comparisons. '*Stain index*' refers to the median MFI of the stained samples/median MFI of the unstained samples for the vehicle condition measured in the CTRL group. Only nodes which displayed a minimum '*Stain index*' of 2 were analyzed. The '*CD4/CD8 correlation*' statistics reflect the Spearman's rank-order correlation P value and correlation coefficient (ρ) between MFIs of individual samples and the respective CD4/CD8 cell subtype ratios in the immunophenotyping test. Total peripheral blood mononuclear cell sample numbers in each group included CTRL (n=12), T0 (n=12) and T6 (n=10). MFI = median fluorescence intensity.

Reference vs. comparison group	Epitope	Ligand	n reference group	n comparison group	Covariates	Expression ratio (comp./ reference group)	P value	Q value	Stain index	CD4/CD8 correlation P	CD4/CD8 correlation ρ
T0 vs. T6	Akt (pS473)	null	11	10	-	1.14	0.006	0.233	16.3	0.244	0.27
T0 vs. T6	Akt1	null	11	10	-	1.12	0.008	0.275	16.1	0.276	-0.25
T0 vs. T6	CrkL (pY207)	null	11	10	-	1.07	0.016	0.469	5.3	0.756	-0.07
T0 vs. T6	Pyk2 (pY402)	null	12	10	age	1.07	0.021	0.564	3.2	0.836	-0.05
T0 vs. T6	Src (pY418)	null	12	10	-	1.07	0.029	0.662	3.3	0.146	-0.32
T0 vs. T6	Stat5 (pY694)	null	9	10	BMI	1.05	0.042	0.787	35.8	0.311	-0.25
T0 vs. T6	ERK1/2 (pT202/pY204)	null	12	10	-	1.05	0.046	0.814	34.7	0.162	-0.31

Table S8. Extended FDA-approved compound library. Source refers to the original compound library. The majority come from the FDA-approved drug library v.2.0 Enzo Life Sciences (FDA). Compounds from collaborators include those labeled: Broad Institute (BI), John's Hopkins University/McMaster University (JH/M), Royal Holloway University (RH). Positive controls and neutraceuticals are included in those labeled Cambridge Centre for Neuropsychiatric Research library (CCNR). Assay concentration is shown in µM for small molecule drugs and µg/ml for biologicals.

ID	Source	Ligand	Assay conc.
1	FDA	(±) Isoproterenol·HCl	20
2	FDA	(±)-Atenolol	20
3	FDA	(S)-Timolol Maleate	20
4	FDA	4-Aminosalicylic Acid	20
5	FDA	Abacavir Sulfate	20
6	FDA	Acamprosate	20
7	FDA	Acarbose	20
8	FDA	Acebutolol·HCl	20
9	FDA	Acetaminophen	20
10	FDA	Acetazolamide	20
11	FDA	Acetohexamide	20
12	FDA	Acetohydroxamic Acid	20
13	FDA	Acetylcholine Chloride	20
14	FDA	Acetylcysteine	20
15	FDA	Acitretin	20
16	FDA	Acrivastine	4
17	FDA	Acyclovir (Acycloguanosine) Zovirax	20
18	FDA	Adapalene	20
19	FDA	Adefovir Dipivoxil	20
20	FDA	Adenosine	20
21	FDA	Albendazole	20
22	FDA	Alendronate·Na Trihydrate	20
23	FDA	Alfuzosin	20
24	FDA	Alitretinoin	20
25	FDA	Allopurinol	20
26	FDA	Almotriptan	20
27	FDA	Alosetron·HCl	20
28	FDA	Alprostadil	20
29	FDA	Altretamine	20
30	FDA	Amantadine·HCl	20
31	FDA	Ambrisentan	20
32	FDA	Amcinonide	20
33	FDA	Amifostine	20
34	FDA	Amikacin Disulfate	20
35	FDA	Amiloride·HCl·2H2O	20
36	FDA	Aminocaproic Acid	20
37	FDA	Aminohippurate·Na	20
38	FDA	Aminolevulinic Acid·HCl	20
39	FDA	Aminophylline	20
40	FDA	Amiodarone·HCl	20
41	FDA	Amitriptyline·HCl	20
42	FDA	Amlexanox	20
43	FDA	Amlodipine	20
44	FDA	Amoxapine	20
45	FDA	Amoxicillin	20
46	FDA	Amphotericin B	20
47	FDA	Ampicillin Trihydrate	20
48	FDA	Amrinone	20
49	FDA	Anagrelide	20
50	FDA	Anastrozole	20
51	FDA	Apomorphine·HCl Hemihydrate	20
52	FDA	Aprepitant	20
53	FDA	Argatroban	20
54	FDA	Aripiprazole	20
55	FDA	Arsenic Trioxide	20
56	FDA	Artemether	20
57	FDA	Articaine·HCl	20
58	FDA	Asenapine Maleate	20
59	FDA	Aspirin (Acetylsalicylic Acid)	20
60	FDA	Atazanavir	20
61	FDA	Atomoxetine·HCl	20
62	FDA	Atorvastatin Calcium	20
63	FDA	Atovaquone	20
64	FDA	Atracurium Besylate	20
65	FDA	Atropine Sulfate Monohydrate	20
66	FDA	Auranofin	20
67	FDA	Azacitidine	20
68	FDA	Azathioprine	20
69	FDA	Azelaic Acid	20
70	FDA	Azelastine·HCl	20
71	FDA	Azithromycin	20
72	FDA	Aztreonam	20
73	FDA	Bacitracin	20
74	FDA	Baclofen	20
75	FDA	Balsalazide	20
76	FDA	Beclomethasone Dipropionate	20
77	FDA	Benazepril·HCl	20
78	FDA	Bendamustine·HCl	20
79	FDA	Bendroflumethiazide	20
80	FDA	Benztropine Mesylate	20
81	FDA	Betaine	20
82	FDA	Betamethasone	20
83	FDA	Betaxolol·HCl	20
84	FDA	Bethanechol Chloride	20
85	FDA	Bexarotene	20
86	FDA	Bicalutamide	20
87	FDA	Bimatoprost	20
88	FDA	Biperiden·HCl	20
89	FDA	Bisacodyl	20
90	FDA	Bisoprolol Fumarate	20
91	FDA	Bleomycin Sulfate	20
92	FDA	Bortezomib	20
93	FDA	Bosentan	20
94	FDA	Brimonidine	20
95	FDA	Bromfenac	20
96	FDA	Bromocriptine Mesylate	20
97	FDA	Brompheniramine Maleate	20
98	FDA	Budesonide	20
99	FDA	Bumetanide	20
100	FDA	Bupivacaine·HCl	20
101	FDA	Bupropion	20
102	FDA	Buspirone·HCl	20
103	FDA	Busulfan	20
104	FDA	Butenafine·HCl	20
105	FDA	Butoconazole Nitrate	20
106	FDA	Butorphanol-(+)-Tartrate (Schedule Iv)	20
107	FDA	Cabergoline	20
108	FDA	Caffeine	20
109	FDA	Calcipotriene	20
110	FDA	Calcitriol	20
111	FDA	Candesartan	20
112	FDA	Capecitabine	20
113	FDA	Capreomycin Sulfate	20

114	FDA	Capsaicin	20
115	FDA	Captopril	20
116	FDA	Carbachol (Carbamylcholine) Chloride	20
117	FDA	Carbamazepine	20
118	FDA	Carbidopa	20
119	FDA	Carbinoxamine Maleate	20
120	FDA	Carboplatin	20
121	FDA	Carglumic Acid	20
122	FDA	Carmustine	20
123	FDA	Carvedilol	20
124	FDA	Cefaclor	20
125	FDA	Cefadroxil	20
126	FDA	Cefazolin·Na	20
127	FDA	Cefdinir	20
128	FDA	Cefditoren Pivoxil	20
129	FDA	Cefepime·HCl Hydrate	20
130	FDA	Cefixime	20
131	FDA	Cefotaxime Acid	20
132	FDA	Cefotetan Disodium	20
133	FDA	Cefoxitin·Na	20
134	FDA	Cefpodoxime Proxetil	20
135	FDA	Cefprozil	20
136	FDA	Ceftazidime	20
137	FDA	Ceftibuten	20
138	FDA	Ceftizoxim·Na	20
139	FDA	Ceftriaxone·Na	20
140	FDA	Cefuroxime Axetil	20
141	FDA	Cefuroxime·Na	20
142	FDA	Celecoxib	20
143	FDA	Cephalexin Monohydrate	20
144	FDA	Cetirizine 2HCl	20
145	FDA	Chenodiol (Chenodeoxycholic Acid)	20
146	FDA	Chlorambucil	20
147	FDA	Chloramphenicol	20
148	FDA	Chlorhexidine Dihydrochloride	20
149	FDA	Chloroquine Diphosphate	20
150	FDA	Chlorothiazide	20
151	FDA	Chlorpheniramine Maleate	20
152	FDA	Chlorpromazine·HCl	20
153	FDA	Chlorpropamide	20
154	FDA	Chlorthalidone	20
155	FDA	Chlorzoxazone	20
156	FDA	Ciclesonide	20
157	FDA	Ciclopirox	20
158	FDA	Cidofovir	20
159	FDA	Cilastatin·Na	20
160	FDA	Cilostazol	20
161	FDA	Cimetidine	20
162	FDA	Cinacalcet·HCl	20
163	FDA	Ciprofloxacin	20
164	FDA	Cisatracurium Besylate	20
165	FDA	Cisplatin (Cis-Diamineplatinum(Ii) Dichloride)	20
166	FDA	Citalopram·HBr	20
167	FDA	Cladribine	20
168	FDA	Clarithromycin	20
169	FDA	Clavulanate Potassium	20
170	FDA	Clemastine Fumarate	20
171	FDA	Clindamycin Palmitate·HCl	20
172	FDA	Clindamycin·HCl	20
173	FDA	Clobazam	20
174	FDA	Clobetasol Propionate	20
175	FDA	Clofarabine	20
176	FDA	Clofazimine	20
177	FDA	Clomiphene Citrate	20
178	FDA	Clomipramine·HCl	20
179	FDA	Clonazepam	20
180	FDA	Clonidine·HCl	20
181	FDA	Clopidogrel Hydrogen Sulfate	20
182	FDA	Clotrimazole	20
183	FDA	Cloxacillin·Na	20
184	FDA	Clozapine	20
185	FDA	Colchicine	20
186	FDA	Colistimethate·Na	20
187	FDA	Colistin Sulfate	20
188	FDA	Cortisone Acetate	20
189	FDA	Cromolyn·Na (Disodium Cromoglycate)	20
190	FDA	Crotamiton	20
191	FDA	Cyclobenzaprine·HCl	20
192	FDA	Cyclopentolate	20
193	FDA	Cyclophosphamide (Free Base)	20
194	FDA	Cycloserine	20
195	FDA	Cyclosporine A	20
196	FDA	Cyproheptadine·HCl Sesquihydrate	20
197	FDA	Cysteamine·HCl	20
198	FDA	Cytarabine	20
199	FDA	Dacarbazine	20
200	FDA	Dactinomycin (= Actinomycin D)	20
201	FDA	Dalfampridine (4-Aminopyridine)	20
202	FDA	Danazol	20
203	FDA	Dantrolene·Na	20
204	FDA	Dapsone	20
205	FDA	Daptomycin	20
206	FDA	Darifenacin·HBr	20
207	FDA	Darunavir	20
208	FDA	Dasatinib	20
209	FDA	Daunorubicin·HCl	20
210	FDA	Decitabine	20
211	FDA	Deferasirox	20
212	FDA	Deferoxamine Mesylate	20
213	FDA	Delavirdine Mesylate	20
214	FDA	Demeclocycline·HCl	20
215	FDA	Desipramine·HCl	20
216	FDA	Desloratadine	20
217	FDA	Desogestrel	20
218	FDA	Desonide	20
219	FDA	Desoximetasone	20
220	FDA	Desvenlafaxine Succinate Hydrate	20
221	FDA	Dexamethasone	20
222	FDA	Dexchlorpheniramine Maleate	20
223	FDA	Dexmedetomidine·HCl	20
224	FDA	Dexrazoxane	20
225	FDA	Dextromethorphan	20
226	FDA	Diatrizoate Meglumine	20
227	FDA	Diazepam	20
228	FDA	Diazoxide	20
229	FDA	Diclofenac·Na Salt	20
230	FDA	Dicloxacillin·Na Salt Monohydrate	20
231	FDA	Dicyclomine·HCl	20
232	FDA	Didanosine	20
233	FDA	Dienogest	20
234	FDA	Diflunisal	20
235	FDA	Difluprednate	20
236	FDA	Digoxin	20
237	FDA	Dihydroergotamine Mesylate	20
238	FDA	Diltiazem·HCl	20
239	FDA	Dimenhydrinate	20

240	FDA	Dinoprostone	20
241	FDA	Diphenhydramine·HCl	20
242	FDA	Dipyridamole	20
243	FDA	Disopyramide	20
244	FDA	Disulfiram	20
245	FDA	Dobutamine·HCl	20
246	FDA	Docetaxel (Taxotere)	20
247	FDA	Dofetilide	20
248	FDA	Dolasetron	20
249	FDA	Donepezil·HCl	20
250	FDA	Dopamine·HCl	20
251	FDA	Doripenem	20
252	FDA	Dorzolamide·HCl	20
253	FDA	Doxapram·HCl	20
254	FDA	Doxazosin Mesylate	20
255	FDA	Doxepin·HCl	20
256	FDA	Doxorubicin·HCl	20
257	FDA	Doxycycline Monohydrate	20
258	FDA	Droperidol	20
259	FDA	Drospirenone	20
260	FDA	Duloxetine·HCl	20
261	FDA	Dutasteride	20
262	FDA	Dyphylline	20
263	FDA	Econazole Nitrate	20
264	FDA	Efavirenz	20
265	FDA	Eflornithine·HCl	20
266	FDA	Emtricitabine	20
267	FDA	Enalapril	20
268	FDA	Enalaprilat Maleate	20
269	FDA	Entacapone	20
270	FDA	Epinastine·HCl	20
271	FDA	Epinephrine (L-(-)-Epinephrine-(+)-Bitartrate)	20
272	FDA	Epirubicin·HCl	20
273	FDA	Eplerenone	20
274	FDA	Eprosartan Mesylate	20
275	FDA	Eptifibatide	20
276	FDA	Ergotamine Tartrate	20
277	FDA	Erlotinib	20
278	FDA	Erythromycin	20
279	FDA	Escitalopram	20
280	FDA	Esmolol	20
281	FDA	Esomeprazole Potassium	20
282	FDA	Estradiol	20
283	FDA	Estramustine Phosphate·Na	20
284	FDA	Estrone	20
285	FDA	Estropipate	20
286	FDA	Eszopiclone	20
287	FDA	Ethacrynic Acid	20
288	FDA	Ethambutol Dihydrochloride	20
289	FDA	Ethinyl Estradiol	20
290	FDA	Ethionamide	20
291	FDA	Ethosuximide	20
292	FDA	Etidronate Disodium	20
293	FDA	Etodolac	20
294	FDA	Etomidate	20
295	FDA	Etonogestrel	20
296	FDA	Etoposide	20
297	FDA	Everolimus	20
298	FDA	Exemestane	20
299	FDA	Ezetimibe	20
300	FDA	Famciclovir	20
301	FDA	Famotidine	20
302	FDA	Febuxostat	20
303	FDA	Felbamate	20
304	FDA	Felodipine	20
305	FDA	Fenofibrate	20
306	FDA	Fenoldopam Mesylate	20
307	FDA	Fenoprofen Calcium	20
308	FDA	Fexofenadine·HCl	20
309	FDA	Finasteride	20
310	FDA	Fingolimod	20
311	FDA	Flavoxate·HCl	20
312	FDA	Flecainide Acetate	20
313	FDA	Floxuridine	20
314	FDA	Fluconazole	20
315	FDA	Flucytosine	20
316	FDA	Fludarabine Phosphate	20
317	FDA	Fludrocortisone Acetate	20
318	FDA	Flumazenil	20
319	FDA	Flunisolide	20
320	FDA	Fluocinolone Acetonide	20
321	FDA	Fluocinonide	20
322	FDA	Fluorometholone	20
323	FDA	Fluorouracil (5-Fluorouracil)	20
324	FDA	Fluoxetine·HCl	20
325	FDA	Fluphenazine·HCl	20
326	FDA	Flurandrenolide	20
327	FDA	Flurbiprofen	20
328	FDA	Flutamide	20
329	FDA	Fluticasone Propionate	20
330	FDA	Fluvastatin·Na	20
331	FDA	Fluvoxamine Maleate	20
332	FDA	Fomepizole	20
333	FDA	Formoterol	20
334	FDA	Foscarnet·Na (Sodium Phosphonoformate Tribasic Hexahydrate)	20
335	FDA	Fosfomycin Calcium	20
336	FDA	Fosinopril·Na	20
337	FDA	Fosphenytoin·Na Pentahydrate	20
338	FDA	Fulvestrant	20
339	FDA	Furosemide	20
340	FDA	Gabapentin	20
341	FDA	Galantamine·HBr	20
342	FDA	Ganciclovir	20
343	FDA	Gatifloxacin	20
344	FDA	Gefitinib	20
345	FDA	Gemcitabine·HCl	20
346	FDA	Gemfibrozil	20
347	FDA	Gemifloxacin	20
348	FDA	Gentamycin Sulfate	20
349	FDA	Glimepiride	20
350	FDA	Glipizide	20
351	FDA	Glyburide	20
352	FDA	Glycopyrrolate Iodide	20
353	FDA	Goserelin Acetate	20
354	FDA	Granisetron·HCl	20
355	FDA	Griseofulvin	20
356	FDA	Guanabenz Acetate	20
357	FDA	Guanfacine·HCl	20
358	FDA	Guanidine·HCl	20
359	FDA	Halcinonide	20
360	FDA	Halobetasol Propionate	20
361	FDA	Haloperidol	20
362	FDA	Hexachlorophene	20
363	FDA	Homatropine Methylbromide	20
364	FDA	Hydralazine·HCl	20
365	FDA	Hydrochlorothiazide	20
366	FDA	Hydrocortisone	20
367	FDA	Hydrocortisone Acetate	20
368	FDA	Hydroflumethiazide	20
369	FDA	Hydroxocobalamin·HCl	20
370	FDA	Hydroxychloroquine Sulfate	20

371	FDA	Hydroxyurea	20
372	FDA	Hydroxyzine Dihydrochloride	20
373	FDA	Ibandronate·Na Monohydrate	20
374	FDA	Ibuprofen	20
375	FDA	Ibutilide Fumarate	20
376	FDA	Idarubicin·HCl	20
377	FDA	Idoxuridine	20
378	FDA	Ifosfamide	20
379	FDA	Iloperidone	20
380	FDA	Imatinib Mesylate	20
381	FDA	Imipenem	20
382	FDA	Imipramine·HCl	20
383	FDA	Imiquimod	20
384	FDA	Indapamide	20
385	FDA	Indinavir	20
386	FDA	Indomethacin	20
387	FDA	Ipratropium·Br	20
388	FDA	Irbesartan	20
389	FDA	Irinotecan·HCl	20
390	FDA	Isocarboxazid	20
391	FDA	Isoniazid	20
392	FDA	Isosorbide Dinitrate	20
393	FDA	Isotretinoin (13-Cis-Retinoic Acid)	20
394	FDA	Isradipine	20
395	FDA	Itraconazole	20
396	FDA	Ivermectin	20
397	FDA	Kanamycin Sulfate	20
398	FDA	Ketoconazole	20
399	FDA	Ketoprofen	20
400	FDA	Ketorolac Tromethamine	20
401	FDA	Ketotifen Fumarate	20
402	FDA	Labetalol·HCl	20
403	FDA	Lacosamide	20
404	FDA	Lactulose	20
405	FDA	Lamivudine	20
406	FDA	Lamotrigine	20
407	FDA	Lansoprazole	20
408	FDA	Lapatinib Ditosylate	20
409	FDA	L-Ascorbic Acid	20
410	FDA	Latanoprost	20
411	FDA	Leflunomide	20
412	FDA	Lenalidomide	20
413	FDA	Letrozole	20
414	FDA	Leucovorin Calcium Pentahydrate	20
415	FDA	Levalbuterol·HCl	20
416	FDA	Levetiracetam	20
417	FDA	Levobunolol·HCl	20
418	FDA	Levocarnitine	20
419	FDA	Levocetirizine Dihydrochloride	20
420	FDA	Levofloxacin·HCl	20
421	FDA	Levonorgestrel	20
422	FDA	Levothyroxine·Na	20
423	FDA	Lidocaine·HCl·H2O	20
424	FDA	Lincomycin·HCl	20
425	FDA	Lindane	20
426	FDA	Linezolid	20
427	FDA	Liothyronine·Na	20
428	FDA	Lisinopril·2H2O	20
429	FDA	Lomustine	20
430	FDA	Loperamide·HCl	20
431	FDA	Lopinavir	20
432	FDA	Loratadine	20
433	FDA	Lorazepam	20
434	FDA	Losartan Potassium	20
435	FDA	Loteprednol Etabonate	20
436	FDA	Lovastatin	20
437	FDA	Loxapine Succinate	20
438	FDA	Mafenide·HCl	20
439	FDA	Malathion	20
440	FDA	Mannitol	20
441	FDA	Maprotiline·HCl	20
442	FDA	Maraviroc	20
443	FDA	Mebendazole	20
444	FDA	Mechlorethamine·HCl	20
445	FDA	Meclizine Dihydrochloride	20
446	FDA	Meclofenamate·Na	20
447	FDA	Medroxyprogesterone Acetate	20
448	FDA	Mefenamic Acid	20
449	FDA	Mefloquine·HCl	20
450	FDA	Megestrol Acetate	20
451	FDA	Meloxicam	20
452	FDA	Melphalan	20
453	FDA	Memantine·HCl	20
454	FDA	Mepenzolate Bromide	20
455	FDA	Mepivacaine·HCl	20
456	FDA	Meprobamate (Schedule Iv)	20
457	FDA	Mequinol	20
458	FDA	Mercaptopurine Hydrate	20
459	FDA	Meropenem	20
460	FDA	Mesalamine (5-Aminosalicylic Acid)	20
461	FDA	Mesna	20
462	FDA	Mestranol	20
463	FDA	Metaproterenol Hemisulfate (Orciprenaline)	20
464	FDA	Metaraminol Bitartrate	20
465	FDA	Metaxalone	20
466	FDA	Metformin·HCl	20
467	FDA	Methacholine Chloride	20
468	FDA	Methazolamide	20
469	FDA	Methenamine Hippurate	20
470	FDA	Methimazole	20
471	FDA	Methocarbamol	20
472	FDA	Methotrexate	20
473	FDA	Methoxsalen (Xanthotoxin)	20
474	FDA	Methscopolamine Bromide ((−)-Scopolamine Methyl Bromide)	20
475	FDA	Methsuximide	20
476	FDA	Methyclothiazide	20
477	FDA	Methyl Aminolevulinate·HCl	20
478	FDA	Methyldopa Sesquihydrate (L-A-Methyl-Dopa Sesquihyrate)	20
479	FDA	Methylergonovine Maleate	20
480	FDA	Methylprednisolone	20
481	FDA	Metoclopramide·HCl	20
482	FDA	Metolazone	20
483	FDA	Metoprolol Tartrate	20
484	FDA	Metronidazole	20
485	FDA	Metyrapone	20
486	FDA	Mexiletine·HCl	20
487	FDA	Micafungin	20
488	FDA	Miconazole	20
489	FDA	Midodrine·HCl	20
490	FDA	Mifepristone	20
491	FDA	Miglitol	20
492	FDA	Miglustat (N-Butyldeoxynojirimycin·HCl)	20
493	FDA	Milnacipran·HCl	20
494	FDA	Milrinone	20
495	FDA	Minocycline	20
496	FDA	Minoxidil	20
497	FDA	Mirtazapine	20

498	FDA	Misoprostol	20
499	FDA	Mitomycin C	20
500	FDA	Mitotane	20
501	FDA	Mitoxantrone·HCl	20
502	FDA	Modafinil (Schedule Iv)	20
503	FDA	Moexipril·HCl	20
504	FDA	Mometasone Furoate	20
505	FDA	Montelukast·Na	20
506	FDA	Moxifloxacin·HCl	20
507	FDA	Mupirocin	20
508	FDA	Mycophenolate Mofetil	20
509	FDA	Mycophenolic Acid	20
510	FDA	Nabumetone	20
511	FDA	Nadolol	20
512	FDA	Nafcillin·Na	20
513	FDA	Naftifine·HCl	20
514	FDA	Nalbuphine·HCl Dihydrate	20
515	FDA	Naloxone·HCl	20
516	FDA	Naltrexone·HCl	20
517	FDA	Naphazoline·HCl	20
518	FDA	Naproxen	20
519	FDA	Naratriptan·HCl	20
520	FDA	Natamycin	20
521	FDA	Nateglinide	20
522	FDA	Nebivolol·HCl	20
523	FDA	Nefazodone·HCl	20
524	FDA	Nelarabine	20
525	FDA	Nelfinavir Mesylate	20
526	FDA	Neomycin Sulfate	20
527	FDA	Nepafenac	20
528	FDA	Nevirapine	20
529	FDA	Niacin (Known As Vitamin B3, Nicotinic Acid And Vitamin Pp)	20
530	FDA	Nicardipine·HCl	20
531	FDA	Nicotine	20
532	FDA	Nifedipine	20
533	FDA	Nilotinib	20
534	FDA	Nilutamide	20
535	FDA	Nimodipine	20
536	FDA	Nisoldipine	20
537	FDA	Nitazoxanide	20
538	FDA	Nitisinone	20
539	FDA	Nitrofurantoin	20
540	FDA	Nizatidine	20
541	FDA	Norepinephrine Bitartrate Monohydrate	20
542	FDA	Norethindrone	20
543	FDA	Norfloxacin	20
544	FDA	Nortriptyline·HCl	20
545	FDA	Nystatin	20
546	FDA	Ofloxacin	20
547	FDA	Olanzapine	20
548	FDA	Olmesartan	20
549	FDA	Olopatadine	20
550	FDA	Olsalazine·Na	20
551	FDA	Omeprazole	20
552	FDA	Ondansetron	20
553	FDA	Orlistat (Tetrahydrolipstatin)	20
554	FDA	Orphenadrine Citrate	20
555	FDA	Oseltamivir Phosphate	20
556	FDA	Oxacillin·Na	20
557	FDA	Oxaliplatin	20
558	FDA	Oxaprozin	20
559	FDA	Oxazepam	20
560	FDA	Oxcarbazepine	20
561	FDA	Oxiconazole Nitrate	20
562	FDA	Oxtriphylline	20
563	FDA	Oxybutynin Chloride	20
564	FDA	Oxytetracycline·HCl	20
565	FDA	Paclitaxel (Taxol)	20
566	FDA	Paliperidone	20
567	FDA	Palonosetron·HCl	20
568	FDA	Pamidronate Disodium Pentahydrate (Pamidronic Acid)	20
569	FDA	Pancuronium·2Br	20
570	FDA	Pantoprazole	20
571	FDA	Paromomycin Sulfate	20
572	FDA	Paroxetine·HCl	20
573	FDA	Pazopanib·HCl	20
574	FDA	Pemetrexed Disodium	20
575	FDA	Pemirolast Potassium	20
576	FDA	Penciclovir	20
577	FDA	Penicillamine (D-Penicillamine)	20
578	FDA	Penicillin G Potassium (Benzylpenicillin)	20
579	FDA	Penicillin V Potassium	20
580	FDA	Pentamidine Isethionate	20
581	FDA	Pentostatin	20
582	FDA	Pentoxifylline	20
583	FDA	Perindopril Erbumine	20
584	FDA	Permethrin	20
585	FDA	Perphenazine	20
586	FDA	Phenelzine Sulfate	20
587	FDA	Phenoxybenzamine·HCl	20
588	FDA	Phentolamine·HCl	20
589	FDA	Phenylephrine	20
590	FDA	Phenytoin	20
591	FDA	Phytonadione	20
592	FDA	Pilocarpine·HCl	20
593	FDA	Pimecrolimus	20
594	FDA	Pimozide	20
595	FDA	Pindolol	20
596	FDA	Pioglitazone·HCl	20
597	FDA	Piperacillin	20
598	FDA	Piroxicam	20
599	FDA	Pitavastatin Calcium	20
600	FDA	Podofilox	20
601	FDA	Posaconazole	20
602	FDA	Pralidoxime Chloride	20
603	FDA	Pramipexole Dihydrochloride Monohydrate	20
604	FDA	Prasugrel	20
605	FDA	Pravastatin·Na	20
606	FDA	Praziquantel	20
607	FDA	Prazosin·HCl	20
608	FDA	Prednisolone	20
609	FDA	Prednisone	20
610	FDA	Pregabalin	20
611	FDA	Prilocaine·HCl	20
612	FDA	Primaquine Phosphate	20
613	FDA	Primidone	20
614	FDA	Probenecid	20
615	FDA	Procainamide·HCl	20
616	FDA	Procarbazine·HCl	20
617	FDA	Progesterone	20
618	FDA	Promethazine·HCl	20
619	FDA	Propafenone·HCl	20
620	FDA	Proparacaine·HCl	20
621	FDA	Propofol	20
622	FDA	Propranolol·HCl	20
623	FDA	Propylthiouracil	20
624	FDA	Protriptyline·HCl	20
625	FDA	Pyrazinamide	20
626	FDA	Pyridostigmine Bromide	20

627	FDA	Pyrimethamine	20
628	FDA	Quetiapine Fumarate	20
629	FDA	Quinapril·HCl	20
630	FDA	Quinidine·HCl·H2O	20
631	FDA	Quinine·HCl·H2O	20
632	FDA	Rabeprazole·Na	20
633	FDA	Raloxifene·HCl	20
634	FDA	Raltegravir	20
635	FDA	Ramelteon	20
636	FDA	Ramipril	20
637	FDA	Ranitidine·HCl	20
638	FDA	Ranolazine·2HCl	20
639	FDA	Rasagiline Mesylate	20
640	FDA	Regadenoson	20
641	FDA	Repaglinide	20
642	FDA	Reserpine	20
643	FDA	Ribavirin	20
644	FDA	Rifabutin	20
645	FDA	Rifampin (Rifampicin)	20
646	FDA	Rifapentine	20
647	FDA	Rifaximin	20
648	FDA	Riluzole·HCl	20
649	FDA	Rimantadine·HCl	20
650	FDA	Risperidone	20
651	FDA	Risredonic Acid	20
652	FDA	Ritonavir	20
653	FDA	Rivastigmine Tartrate	20
654	FDA	Rizatriptan Benzoate	20
655	FDA	Rocuronium Bromide	20
656	FDA	Ropinirole·HCl	20
657	FDA	Ropivacaine·HCl Monohydrate	20
658	FDA	Rosiglitazone	20
659	FDA	Rosuvastatin Calcium	20
660	FDA	Rufinamide	20
661	FDA	Salbutamol Hemisulfate	20
662	FDA	Salmeterol	20
663	FDA	Saquinavir Mesylate	20
664	FDA	Scopolamine·HBr	20
665	FDA	Selegiline·HCl	20
666	FDA	Sertaconazole	20
667	FDA	Sertraline·HCl	20
668	FDA	Sildenafil Citrate	20
669	FDA	Silver Sulfadiazine	20
670	FDA	Simvastatin	20
671	FDA	Sirolimus (Rapamycin)	20
672	FDA	Sitagliptin Phosphate	20
673	FDA	Sodium Phenylbutyrate	20
674	FDA	Sorafenib Tosylate	20
675	FDA	Sotalol·HCl	20
676	FDA	Spectinomycin·HCl Pentahydrate	20
677	FDA	Spironolactone	20
678	FDA	Stavudine	20
679	FDA	Streptomycin Sulfate	20
680	FDA	Streptozocin	20
681	FDA	Succinylcholine Chloride·2H2O	20
682	FDA	Sulconazole Nitrate	20
683	FDA	Sulfacetamide·Na	20
684	FDA	Sulfadiazine	20
685	FDA	Sulfamethoxazole	20
686	FDA	Sulfanilamide	20
687	FDA	Sulfasalazine	20
688	FDA	Sulindac	20
689	FDA	Sumatriptan Succinate	20
690	FDA	Sunitinib Malate	20
691	FDA	Tacrine·HCl	20
692	FDA	Tacrolimus (Fk506)	20
693	FDA	Tadalafil	20
694	FDA	Tamoxifen Citrate	20
695	FDA	Tamsulosin·HCl	20
696	FDA	Tazarotene	20
697	FDA	Telbivudine	20
698	FDA	Telithromycin	20
699	FDA	Telmisartan	20
700	FDA	Temazepam	20
701	FDA	Temozolomide	20
702	FDA	Temsirolimus	20
703	FDA	Teniposide	20
704	FDA	Tenofovir	20
705	FDA	Terazosin·HCl	20
706	FDA	Terbinafine·HCl	20
707	FDA	Terbutaline Hemisulfate	20
708	FDA	Terconazole	20
709	FDA	Testosterone Enanthate	20
710	FDA	Tetrabenazine	20
711	FDA	Tetracycline	20
712	FDA	Tetrahydrozoline·HCl	20
713	FDA	Thalidomide	20
714	FDA	Theophylline	20
715	FDA	Thioguanine (6-Thioguanine)	20
716	FDA	Thioridazine·HCl	20
717	FDA	Thiotepa	20
718	FDA	Tiagabine·HCl	20
719	FDA	Ticlopidine·HCl	20
720	FDA	Tigecycline	20
721	FDA	Tiludronate Disodium	20
722	FDA	Tinidazole	20
723	FDA	Tiopronin	20
724	FDA	Tiotropium Bromide Monohydrate	20
725	FDA	Tirofiban·HCl	20
726	FDA	Tizanidine·HCl	20
727	FDA	Tobramycin	20
728	FDA	Tolazamide	20
729	FDA	Tolbutamide	20
730	FDA	Tolcapone	20
731	FDA	Tolmetin·Na	20
732	FDA	Tolterodine Tartrate	20
733	FDA	Tolvaptan	20
734	FDA	Topiramate	20
735	FDA	Topotecan·HCl	20
736	FDA	Toremifene Base	20
737	FDA	Torsemide	20
738	FDA	Tramadol·HCl	20
739	FDA	Trandolapril	20
740	FDA	Tranexamic Acid	20
741	FDA	Tranylcypromine Hemisulfate	20
742	FDA	Travoprost	20
743	FDA	Trazodone·HCl	20
744	FDA	Tretinoin	20
745	FDA	Triamcinolone Acetonide	20
746	FDA	Triamterene	20
747	FDA	Triazolam	20
748	FDA	Trientine Dihydrochloride	20
749	FDA	Trifluoperazine·HCl	20
750	FDA	Trihexyphenidyl·HCl	20
751	FDA	Trimethadione	20
752	FDA	Trimethobenzamide·HCl	20
753	FDA	Trimethoprim	20
754	FDA	Trimipramine Maleate	20
755	FDA	Triptorelin Acetate	20
756	FDA	Tropicamide	20
757	FDA	Trospium Chloride	20
758	FDA	Ursodiol	20

759	FDA	Valacyclovir·HCl	20
760	FDA	Valganciclovir·HCl	20
761	FDA	Valproate·Na	20
762	FDA	Valproic Acid	20
763	FDA	Valsartan	20
764	FDA	Vancomycin·HCl	20
765	FDA	Vardenafil	20
766	FDA	Varenicline Tartrate	20
767	FDA	Vecuronium Bromide	20
768	FDA	Venlafaxine·HCl	20
769	FDA	Verapamil·HCl	20
770	FDA	Vigabatrin	20
771	FDA	Vinblastine Sulfate	20
772	FDA	Vincristine Sulfate	20
773	FDA	Vinorelbine	20
774	FDA	Voriconazole	20
775	FDA	Vorinostat	20
776	FDA	Warfarin·Na	20
777	FDA	Zafirlukast	20
778	FDA	Zalcitabine (2',3'-Dideoxycytidine)	20
779	FDA	Zaleplon	20
780	FDA	Zanamivir	20
781	FDA	Zidovudine (3'-Azido-3'-Deoxythymidine)	20
782	FDA	Zileuton	20
783	FDA	Ziprasidone	20
784	FDA	Zoledronic Acid Monohydrate	20
785	FDA	Zolmitriptan	20
786	FDA	Zonisamide	20
787	BI	BRD_1 (TV062569)	20
788	BI	BRD_10 (TV062581)	20
789	BI	BRD_11 (TV062567)	20
790	BI	BRD_12 (TV062568)	20
791	BI	BRD_13 (TV062203)	20
792	BI	BRD_14 (TV062240)	20
793	BI	BRD_15 (TV062245)	20
794	BI	BRD_16 (TV062246)	20
795	BI	BRD_17 (TV062582)	20
796	BI	BRD_18 (TV062192)	20
797	BI	BRD_19 (TV062193)	20
798	BI	BRD_2 (TV062570)	20
799	BI	BRD_20 (TV062194)	20
800	BI	BRD_21 (TV062195)	20
801	BI	BRD_22 (TV062196)	20
802	BI	BRD_23 (TV062197)	20
803	BI	BRD_24 (TV062202)	20
804	BI	BRD_25 (TV062207)	20
805	BI	BRD_26 (TV062208)	20
806	BI	BRD_27 (TV062209)	20
807	BI	BRD_28 (TV062200)	20
808	BI	BRD_29 (TV062201)	20
809	BI	BRD_3 (TV062572)	20
810	BI	BRD_30 (TV062198)	20
811	BI	BRD_31 (TV062199)	20
812	BI	BRD_4 (TV062573)	20
813	BI	BRD_5 (TV062574)	20
814	BI	BRD_6 (TV062577)	20
815	BI	BRD_7 (TV062578)	20
816	BI	BRD_8 (TV062579)	20
817	BI	BRD_9 (TV062580)	20
818	BI	CHIR-99021	20
819	BI	SJH2	20
820	BI	SJH3	20
821	BI	SJH4	20
822	BI	SJH5	20
823	BI	JB1121	20
824	JH/ M	5C10	20
825	JH/ M	78-3	20
826	JH/ M	86-1	20
827	JH/ M	86-2	20
828	JH/ M	86-3	20
829	JH/ M	87-1	20
830	JH/ M	87-2	20
831	JH/ M	87-3	20
832	JH/ M	87-4	20
833	JH/ M	90-2	20
834	JH/ M	90-3	20
835	JH/ M	90-4	20
836	JH/ M	90-5	20
837	JH/ M	CPH2-102	20
838	JH/ M	CPH2-103	20
839	JH/ M	CPH2-128	20
840	JH/ M	CPH2-141	20
841	JH/ M	CPH2-48	20
842	JH/ M	CPH2-49	20
843	JH/ M	CPH2-52	20
844	JH/ M	CPH2-53	20
845	JH/ M	CPH2-56	20
846	JH/ M	CPH3-27	20
847	JH/ M	CPH6-60	20
848	JH/ M	FTY720 HCL	20
849	JH/ M	JDG3-82	20
850	JH/ M	JGD-13W(3f)	20
851	JH/ M	JGD3-142	20
852	JH/ M	JGD3-143	20
853	JH/ M	JGD4-11Y (3e)	20
854	JH/ M	JGD4-12W(3c)	20
855	JH/ M	JGD4-13Y(3d)	20
856	JH/ M	JGD4-20W	20
857	JH/ M	Toxo-0027	20
858	JH/ M	Toxo-0028	20
859	RH	RW_121	3000
860	RH	RW_26	3000
861	RH	RW_43	3000
862	RH	RW_44	3000
863	RH	RW_54	3000
864	RH	RW_60	3000
865	RH	RW17	3000
866	CCNR	2-pirydylethylamine	20
867	CCNR	7-hydroxy-DPAT	20
868	CCNR	8-bromo-cAMP	1400
869	CCNR	agomelatine	20
870	CCNR	AICAR (+ GW501516 0.1uM)	20
871	CCNR	anti-CD3/CD28	0.006
872	CCNR	AS19	20
873	CCNR	BCR stim	0.056
874	CCNR	BDNF	0.008
875	CCNR	calyculin	2
876	CCNR	clozapine	20
877	CCNR	cucurbitacin I	20
878	CCNR	Curcumin	20
879	CCNR	fenobam	20
880	CCNR	forskolin	20
881	CCNR	FPL 64176	0.2
882	CCNR	FPL 64176	2
883	CCNR	FPL 64176	20
884	CCNR	GSK690693	20
885	CCNR	GW7647	20
886	CCNR	haloperidol	20
887	CCNR	idebenone	20
888	CCNR	IFN-α2c	0.01
889	CCNR	IFN-γ	0.012
890	CCNR	IL-10	0.01
891	CCNR	IL-1β	0.012

892	CCNR	IL-2	0.014
893	CCNR	IL-23	0.004
894	CCNR	IL-4	0.014
895	CCNR	IL-6	0.008
896	CCNR	insulin	0.2
897	CCNR	isoproterenol	20
898	CCNR	KT 5720	0.8
899	CCNR	leptin	0.126
900	CCNR	LPS	0.0002
901	CCNR	LY-294,002 hydrochloride	20
902	CCNR	m-3M3FBS	0.2
903	CCNR	m-3M3FBS	2
904	CCNR	m-3M3FBS	20
905	CCNR	NECA	20
906	CCNR	Nefiracetam	0.2
907	CCNR	Nefiracetam	2
908	CCNR	Nefiracetam	20
909	CCNR	NNC 55-0396 dHCl	0.2
910	CCNR	NNC 55-0396 dHCl	2
911	CCNR	NNC 55-0396 dHCl	20
912	CCNR	olanzapine	20
913	CCNR	orthovanadate	300
914	CCNR	PCP	20
915	CCNR	Penfluridol	0.2
916	CCNR	Penfluridol	2
917	CCNR	Penfluridol	20
918	CCNR	PHA543613	20
919	CCNR	PMA/ionomycin	2
920	CCNR	PS48	20
921	CCNR	resveratrol	20
922	CCNR	risperidone	20
923	CCNR	ryanodine	0.2
924	CCNR	ryanodine	2
925	CCNR	ryanodine	20
926	CCNR	SB 239063	10
927	CCNR	SB202190	20
928	CCNR	SC9	20
929	CCNR	SEB	0.07
930	CCNR	SKF83822	20
931	CCNR	SR57227	20
932	CCNR	staurosporine	10
933	CCNR	sumanirole	20
934	CCNR	TCB-2	20
935	CCNR	TC-G 24	20
936	CCNR	thapsigargin	2
937	CCNR	TNF-α	0.01
938	CCNR	trolox	20
939	CCNR	U0126	20
940	CCNR	U73122	0.2
941	CCNR	U73122	2
942	CCNR	U73122	20
943	CCNR	Vitamin D3 solution	0.2
944	CCNR	WHI-P 154	20
945	CCNR	xaliproden	20
946	CCNR	xanomeline	20

Table S9 Extended US Food and Drug Administration (FDA)-approved library screening of compounds which selectively potentiate the phospholipase C (PLC)–γ1 response in the presence of 0.5 µM thapsigargin (TG). Compounds depicted in the "Extended FDA library screening" panel of **Figure 5D** (listed in **Table S8**) which significantly interacted with the TG/PLC-γ1 response (p permuted interaction<0.05, two-way ANOVA; n=102 compounds; **Figure 5B**) were refined to compounds which showed the desired directionality (decrease in PLC-γ1; **Figure S18**) specifically in the TG condition and were not active in the vehicle (VEH) condition (post-hoc ANOVA tests; n=22 compounds). In other words, these compounds had no intrinsic activity but were capable of potentiating the PLC-γ1 response when co-administered with TG. The compounds are ranked with respect to their permuted p values for interaction. The number of peripheral blood mononuclear cell (PBMC) samples in each comparison group is shown in columns 2-5. *'Potentiation factor' (*calculated as (1 - mean PLC-γ1 MFI in TG-drug condition/mean PLC-γ1 MFI in vehicle-drug condition)/(1 - mean PLC-γ1 MFI in TG-negative control condition/mean PLC-γ1 MFI in vehicle-negative control condition)) represents a factor by which the PLC-γ1 response to TG was enhanced by the drug relative to the untreated condition. Concentration of the compounds is given in **Table S8**. MFI = median fluorescence intensity.

Compound	n VEH_NC	n VEH_drug	n TG_NC	n TG_drug	p perm interaction	Potentiation factor	Chemical class
Nisoldipine	12	12	11	11	0.0002	3.1	Dihydropyridine
Tretinoin	6	6	6	6	0.0031	4.1	Retinoid
Fenofibrate	12	12	12	12	0.0032	2.5	Fibrate
Triamterene	6	6	6	6	0.0033	4.1	Thiazide
Triamcinolone Acetonide	6	6	6	6	0.007	4.2	Steroid
Methylprednisolone	12	12	12	12	0.0086	1.5	Steroid
Olanzapine	12	12	11	12	0.0087	2.9	Thienobenzodiazepine
Cefotetan Disodium	6	6	6	6	0.009	2.0	Cephalosporin
Testosterone Enanthate	6	6	6	6	0.0127	2.9	Steroid
Finasteride	12	12	12	12	0.0141	2.5	Steroid
Cefixime	6	6	6	6	0.0179	2.1	Cephalosporin
Tiopronin	6	6	6	6	0.0187	3.6	Thiol
Gemifloxacin	6	6	6	6	0.0238	2.3	Quinolone
Cefoxitin·Na	6	6	6	6	0.0263	2.1	Cephalosporin
Tazarotene	6	6	6	6	0.0294	2.4	Retinoid
Cephalexin Monohydrate	6	6	6	6	0.0308	2.5	Cephalosporin
Fluorometholone	6	6	6	6	0.0348	1.8	Steroid
Flunisolide	6	6	6	6	0.04	1.5	Steroid
Ethacrynic Acid	12	12	12	12	0.046	1.8	Phenoxyacetic acid
Cefepime·HCl Hydrate	12	12	11	12	0.0462	2.6	Cephalosporin
Tirofiban·HCl	6	6	6	6	0.049	3.6	Phenylpropanoic acid
Albendazole	12	12	12	12	0.0493	1.6	Benzimidazole

Table S10. Demographic characteristics and matching of PBMC donors used in the CV study. Matching was achieved for drug-naïve schizophrenia patients treated with aripiprazole and risperidone for all demographic variables except body mass index (BMI). Statistical tests included Wilcoxon rank-sum test (*) and Fisher's exact test (**). Table shows mean values ± standard deviation. Percentage of missing data is shown in the last column ('*Missing (%)*'). SAPS – Scale for the Assessment of Positive Symptoms score; SANS – Scale for the Assessment of Negative Symptoms score; w – week; m – month; y – yes; n – no.

	Aripiprazole	Risperidone	p	Missing (%)
N	12	18	na	
Age (years)*	28.60 ± 9.01	33.19 ± 10.46	0.290	-
Gender (male/female)**	8/4	12/6	1.000	-
BMI (kg/m^2)*	23.70 ± 7.68	25.32 ± 4.89	**0.043**	10.0
Cannabis (y/n)**	5/7	6/12	0.712	-
Smoking (y/n)**	8/4	8/10	0.284	-
Alcohol (y/n)**	7/5	8/10	0.710	-
SAPS*	15.67 ± 4.25	14.94 ± 4.15	0.651	-
SAPS_3w*	3.82 ± 4.26	4.00 ± 3.81	0.703	6.7
SAPS_6w*	0.82 ± 1.66	1.47 ± 2.32	0.426	6.7
SAPS_3m*	1.00 ± 1.95	0.53 ± 1.37	0.512	6.7
SAPS_12m*	0.89 ± 1.83	0.29 ± 1.07	0.307	23.3
SANS*	5.67 ± 6.05	5.82 ± 6.37	0.840	3.3
SANS_3w*	2.64 ± 3.64	3.39 ± 6.56	0.653	3.3
SANS_6w*	4.82 ± 5.71	5.59 ± 7.24	0.981	6.7
SANS_3m*	5.67 ± 4.87	4.94 ± 5.61	0.536	-
SANS_12m*	2.44 ± 4.28	4.79 ± 6.44	0.397	23.3

Table S11. Prediction of in vivo response to treatment from ex vivo treatment activity. Clinical *in vivo* response was measured by change in the Scale for the Assessment of Positive Symptoms score (ΔSAPS) and change in the Scale for the Assessment of Negative Symptoms score (ΔSANS) after 3 weeks (3w), 6 weeks (6w) and 3 months (3m) of stable antipsychotic treatment with aripiprazole (total n=12) and risperidone (total n=18). *Ex vivo* response was measured as a shift in EC_{50} of the thapsigargin/PLC-γ1 dose response by the respective treatment drug, relative to vehicle, in T cells from individual patients. Results from linear regression model (10,000 permutations). Relevant covariates were selected from basal symptom score, treatment drug, age, gender and body mass index (BMI) in a stepwise procedure using Bayesian Information Criterion.

Response	N	F value	Covariates	P value	Q value
ΔSAPS_3w	28	14.01	SAPS_0w, gender, BMI	0.001	0.007
ΔSAPS_6w	28	4.54	SAPS_0w	0.041	0.213
ΔSAPS_3m	28	1.81	SAPS_0w	0.197	0.706
ΔSANS_3w	28	0.13	SANS_0w	0.722	1.000
ΔSANS_3m	29	0.07	SANS_0w	0.782	1.000
ΔSANS_6w	27	0.03	SANS_0w	0.864	1.000