Supplementary Information

GPCR ontology: development and application of a G protein-coupled receptor pharmacology knowledge framework

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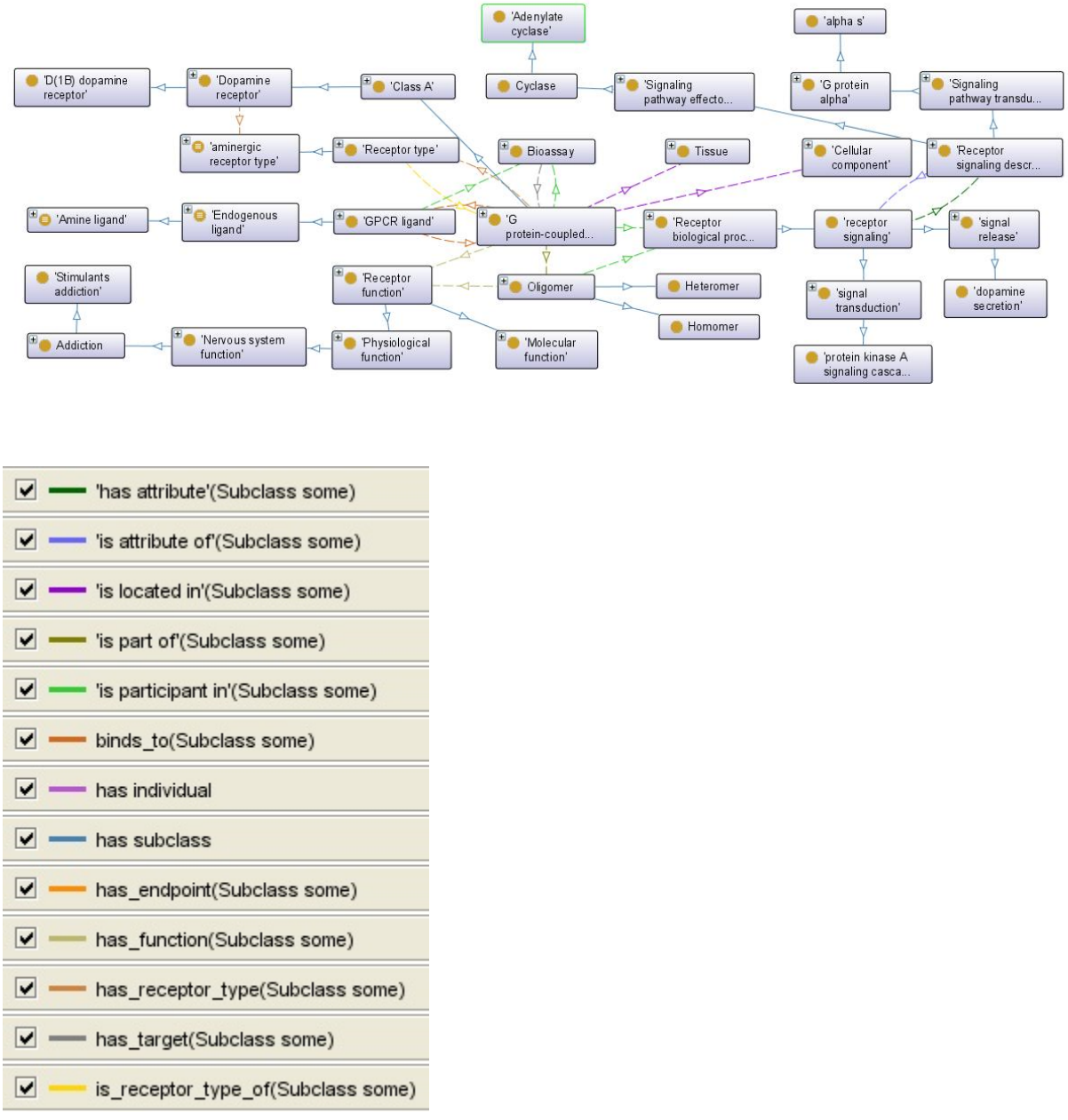
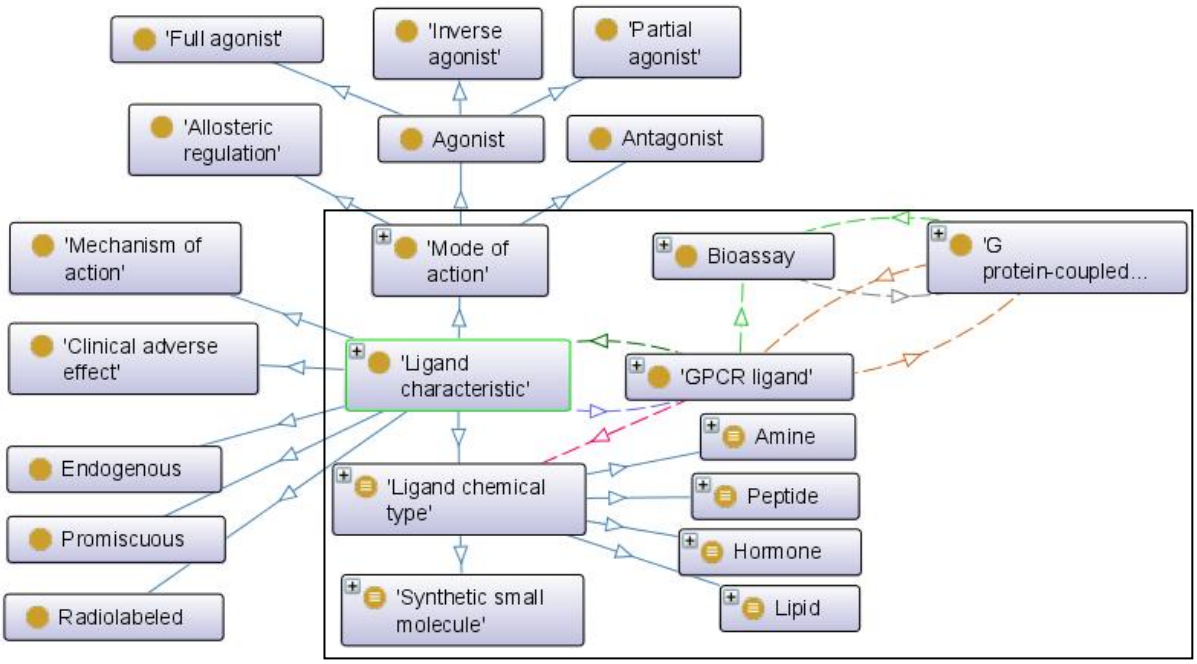
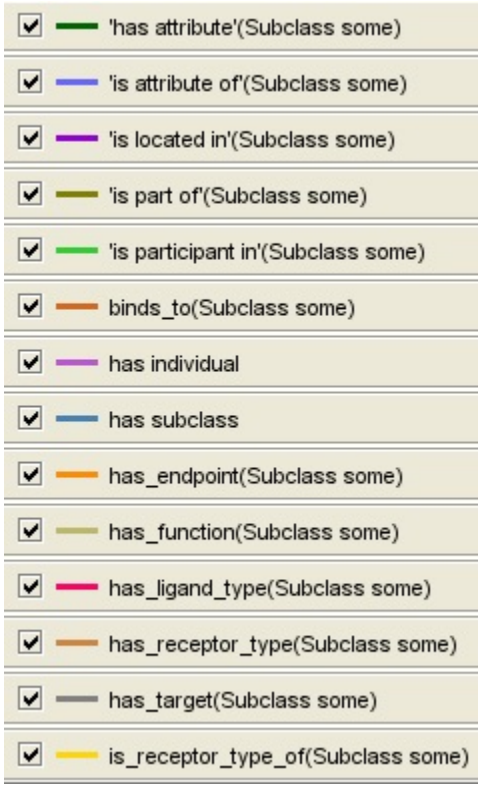
Supplementary Figure 1. Detailed view on parts of the GPCR ontology pertaining to the receptor.

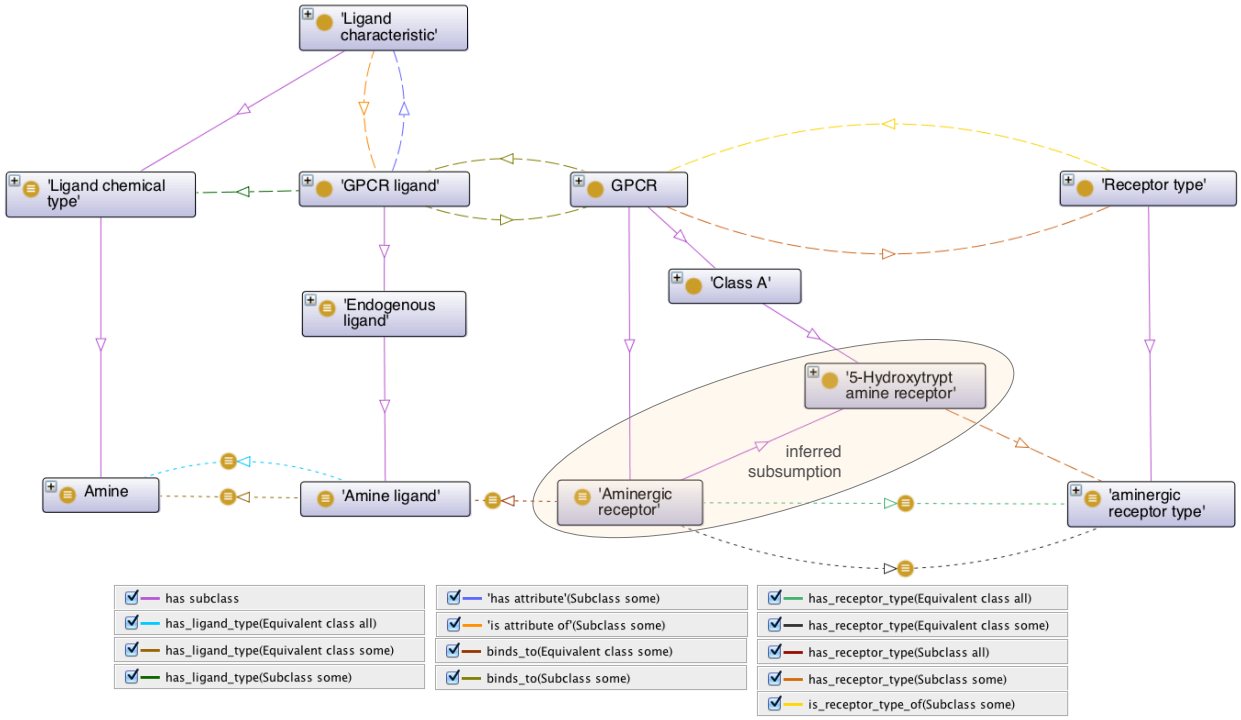


Supplemental Figure 2. Detailed view on parts of the GPCR ontology pertaining to the ligand.

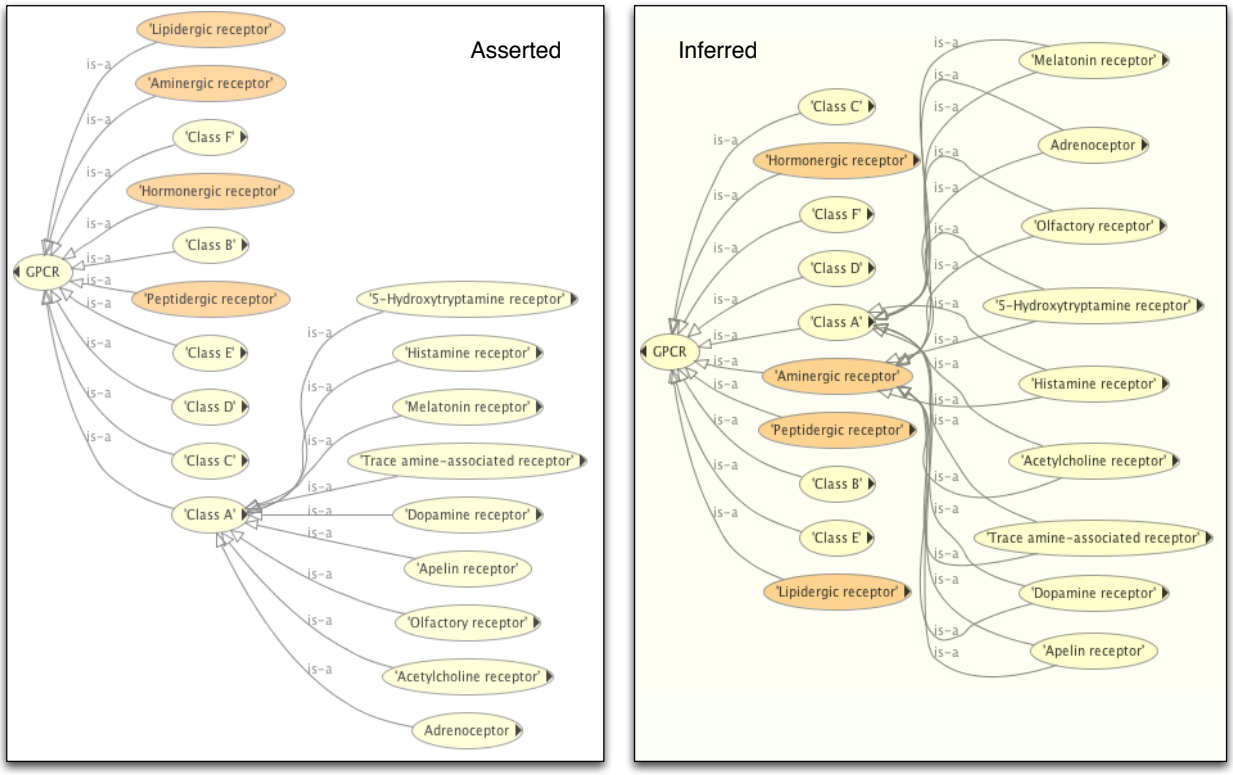




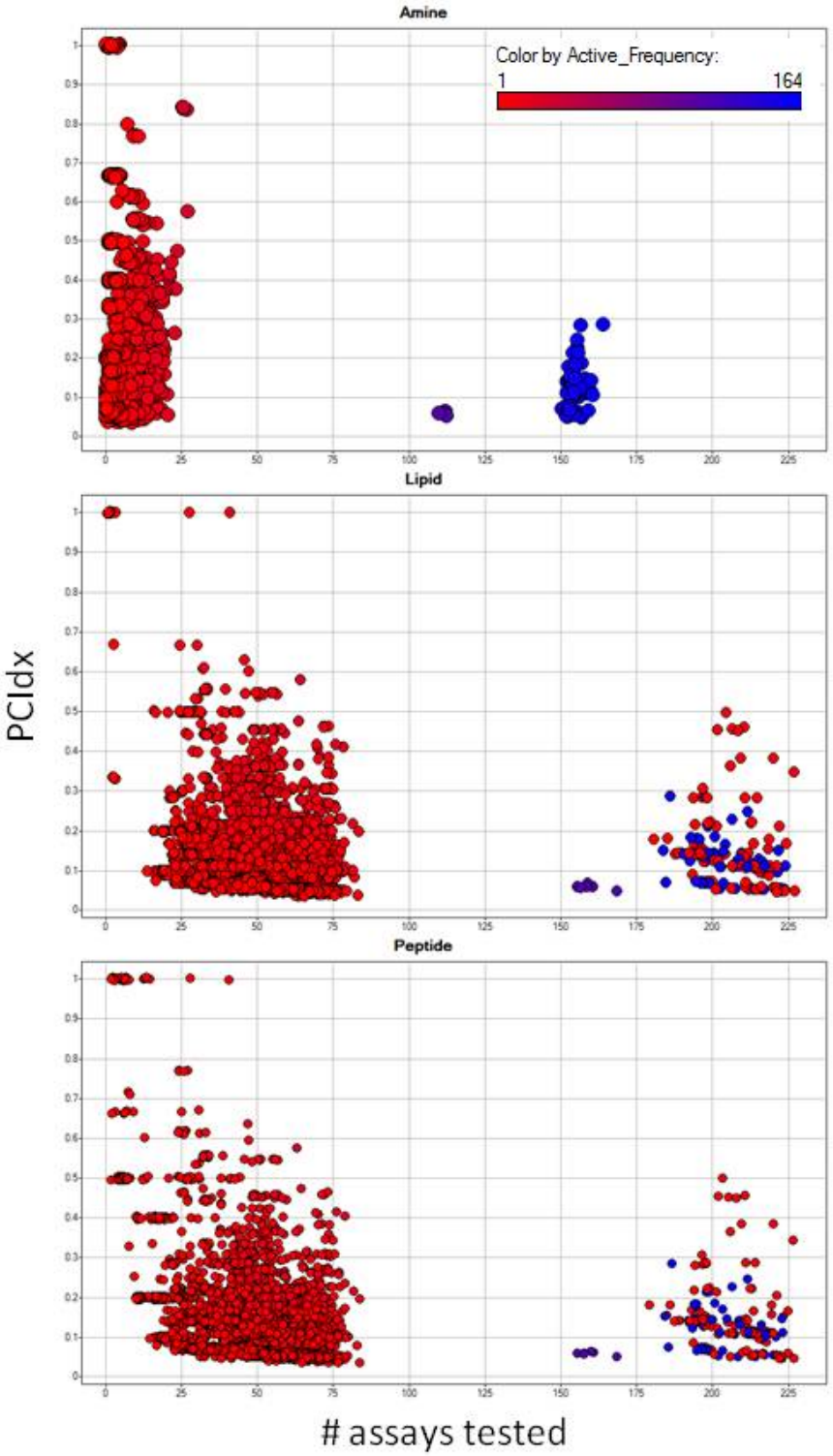
Supplemental Figure 3. Modeling of the relationship of GPCR and GPCR ligand and receptor- and ligand chemical type; aminergic receptor binds to amine ligand; 5-hydroxytryptamine receptor is inferred as subclass of aminergic receptor.



Supplemental Figure 4. Illustration of asserted versus inferred model of an excerpt of the ontology. Aminergic, lipidergic, hormonergic, and peptidergic receptor sub-classes are inferred; example receptor subclasses of aminergic receptor are shown.



Supplementary Figure 5. Compound promiscuity by GPCR type. For each compound the Promiscuity Index vs. number of tested assays is depicted. Color indicates the number of assays in which a compound was active (red, low number; blue, high number of assays tested).There are 17,090 data points for aminergic GPCR type; 15,459 and 15,568 data points for peptidergic and lipidergic GPCR types, respectively.



Supplementary Table 1. An example of details captured during assay annotation.

Screening campaign	"Positive allosteric modulators of the M5 muscarinic receptor"		
AID	2665	2194	2206
Assay Stage	Primary	Confirmatory	Secondary Assay
Relationship	has confirmatory assay 2194 has secondary assay 2206	has primary assay 2665	has primary assay 2665
Assay Measurement Throughput Quality	Single concentration single measurement (e.g. 1x%Inh)	Concentration response multiple replicates (e.g. 3xIC50)	Concentration response multiple replicates (e.g. 3xIC50)
Endpoint	Maximal response	EC50	EC50
Format	Cell-based format	Biochemical format	Cell-based format
Design	Calcium redistribution	Radioligand binding	Calcium redistribution
Detection Technology	Fluorescence intensity	Scintillation counting, filter assay	Fluorescence intensity
Measured Entity	Calcium flux	[3H]-NMS radioactivity	Calcium flux
Meta target	Human M5	Human M5	Rat M1
GPCR Family	Muscarinic	Muscarinic	Muscarinic
Oligomer Component	n/a	n/a	n/a
Receptor Type	Aminergic	Aminergic	Aminergic
Receptor Protein ID	P08912	P08912	P08482
Primary Transduction Mechanism	G_q/G_{11}	G_q/G_{11}	G_q/G_{11}
Primary Effector	Phospholipase C stimulation	Phospholipase C stimulation	Phospholipase C stimulation
Physiological Function	Bronchoconstriction, automaticity of the heart, etc.	Bronchoconstriction, automaticity of the heart, etc.	Modulation of dopaminergic neurotransmission, etc.
Tissue Distribution	CNS, heart, etc.	CNS, heart, etc.	CNS, esophagus, etc.

Supplementary Table 2. Target category of the 407 annotated PubChem assays. Note, 52 summary assays are not included. The abbreviations used for the proteins are: 5-HT, 5-hydroxytryptamine receptor; AGT, angiotensin II receptor; APJ, apelin receptor; AVPR, arginine vasopressin receptor; CCR, C-C chemokine receptor; DRD, dopamine receptor; FPR, formyl peptide receptor; Gal, galanin receptor; GPR30, G protein-coupled estrogen receptor; KOR, kappa opioid receptor; LH, luteinizing hormone receptor; MCH, melanin-concentrating hormone receptor; mGlu, metabotropic glutamate receptor; M, muscarinic; NPS, neuropeptide S receptor; NPY, neuropeptide Y receptor; NP B/W, neuropeptide B/W receptor; NTS, neurotensin receptor; OX, orexin receptor; OT, oxytocin receptor; PTGE, prostaglandin E receptor; RXFP, relaxin receptor; S1P, sphingosine-1-phosphate receptor; TSH, thyroid stimulating hormone receptor; TRH, thyrotropin-releasing hormone receptor. Cdc42, cell division cycle 42; $G_{\alpha q}$, guanine nucleotide binding protein, alpha subunit, q polypeptide.

		GPCR	G protein	RGS	Biological Process
G protein	*Cdc42*		17		
	$G_{\alpha q}$		3		
	GTPases Rac, Rho		14		
RGSs				33	
GPCRs	*5-HT*	10			
	Adrenergic	7			
	AGT	2			
	APJ	6			
	Vasopressin	9			
	Cannabinoid	2			
	CCR	1			
	Opioid	27			
	DRD	12			
	FPR	17			
	GPR30	4			
	GPR35	4			
	GPR55	4			
	Gal	6			
	LH	1			
	MCH	1			
	mGlu	15			
	M	42			
	NPS	9			
	NPY	32			
	NP B/W	2			
	NTS	1			
	OX	4			
	OT	8			
	PTGE	6			
	Relaxin	4			
	S1P	37			
	TSH	7			
	TRH	5			
Biological Process	*Cell death*				3
TOTAL		285	34	33	3

Supplementary Table 3. Detection technology for GPCR, G protein and RGS target-based assays. HTRF, *homogeneous time resolved fluorescence; FRET, fluorescence resonance energy transfer; TR-FRET,* Time-Resolved FRET.

	GPCR	G protein	RGS	total
Chemi-/luminescence	28			28
Filter assay	9			9
Flow cytometry	19	31	24	74
Fluorescence intensity	155	2	5	162
Fluorescence polarization			3	3
FRET	52			52
HTRF	10			10
Lysate based	2			2
Thermal shift			1	1
TR-FRET	12	1		13
Unspecified	1			1
TOTAL	288	34	33	355

Supplementary Table 4. Measured entity for GPCR, G protein and RGS target-based assays. A molecular substance or process measured in PubChem assays reporting GPCR, G protein and RGS as targets.

	GPCR	G protein	RGS	total
[cAMP]	20			20
[IP1]	4	1		5
Acetylcholine	1			1
Arrestin redistribution	33			33
ATP	3			3
Brain penetrance	1			1
Calcium	72	2	5	79
GTP-fluorescent	2	30		32
$G_{\alpha o}$-fluorescent			24	24
Luciferase	23			23
Membrane potential	36		1	37
Peptide-fluorescence	13		3	16
Radioactivity	11			11
Thallium flux	16			16
β-galactosidase	16			16
β-lactamase	38			38
TOTAL	289	33	33	355

Supplementary Table 5. Endpoints of annotated assays and number of compounds screened per assay. Note, some assays report multiple endpoints. AC_{50}, potency, concentration at which compound exhibits half maximal efficacy; B_{max}, amount of drug required to saturate a population of receptors; K_d, dissociation constant; EC_{50}, half maximal effective concentration; IC_{50}, half maximal inhibitory concentration; K_i, absolute inhibition constant; T_m, melting temperature.

	GPCR	G protein	RGS	total
% Activation	41	1		42
% Inhibition	41	3		44
% Response	12	2	13	27
AC_{50}	34		3	37
B_{max}, K_d		5		5
EC_{50}	80	23	14	117
Fold activation	11			11
IC_{50}	49			49
K_i	7			7
Maximal response	31			31
Raw activity	21		2	23
Response	1			1
T_m			1	1
Unspecified	5			5
Number of compounds screened per assay				
#cmpds: 0 - 100	143	24	10	
#cmpds: 101 - 1000	59		6	
#cmpds: 1k - 100k	49	6	9	
#cmpds: 100k - n	34	4	8	

Supplementary Table 6. Mechanism of action. The effect of the compound on the GPCRs, RGS, or G protein target as reported in PubChem.

		GPCR	G protein	RGS	total
activation	*allosteric*	58			58
	competitive	123	29	28	180
	unspecified	94	1	1	96
activation/inhibition		1	1		2
inhibition		12		4	16
saturation binding			3		3
TOTAL		288	34	33	355

Supplementary Table 7. Summary of lead compounds generated for G protein, GPCRs and RGS targets PubChem screening campaigns as reported in NIH MLP Probe Report. (NAM, allosteric agonist; PAM, positive allosteric modulator).

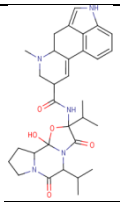
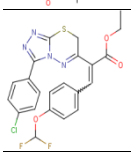
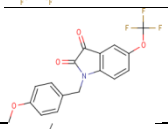
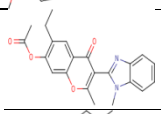
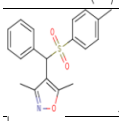
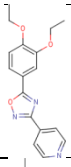
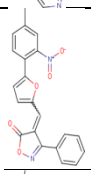
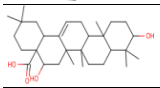
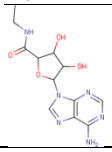
Target Receptor	Probe Efficacy	Probe SID
Cdc42 activated mutant	activator	57578338, 57578337, 57578335
Cdc42 wt	inhibitor	57578341
APJ	agonist	99361200
FPR1	antagonist	24428139, 24702504
GPR30	antagonist	48409542, 48409616
GPR35	antagonist	99309109, 87544496, 87544499
GPR55	agonist	87225724, 87225730, 87225729
GPR55	antagonist	87225762, 87225747, 87225750
GPR7	antagonist	96021160
KOR	agonist	87334039, 87218782
KOR	antagonist	87218794, 88442997
M1	NAM	4248988
M1	PAM	56353039, 99350544, 8528605, 85756541
M4	PAM	85163688
M5	PAM	85285486
mGluR4	PAM	85240643
NPSR	antagonist	56431681, 56431665, 87796314
NPY-Y2	antagonist	22413249, 4242079, 17413392, 17507305
S1P1	agonist	4258673
S1P1	antagonist	24257742
S1P2	agonist	46371210
S1P3	agonist	3714904, 7967985, 864271, 7977380
S1P4	agonist	87544119
S1P4	antagonist	87357351
TSHR	agonist	3714076, 26755506
RGS: RGS4,RGS7,RGS8,RGS12, RGS16, RGS18, RGS19	29 NIH MLP BioAssays; 5289compounds are RGS4 active, 854compounds are RGS7 active, 786compounds are RGS8 active, 1018 compounds are RGS12 active, 875 compounds are RGS16 active, 2compounds are RGS18 active, 111 compounds are RGS19 active, No probes were declared.(Source: PubChem Target-centric BioActivity Service search)	

Supplementary Table 8. A list of screening campaigns targeting GPCRs, G proteins or RGS. Note, some campaigns were combined for analysis and some are not yet annotated.

Campaign	Screening Campaign Name
Campaign 1	Agonists of Neurotensin Receptor type 1 (NTR1)
Campaign 2	Agonists of the 5-Hydroxytryptamine Receptor Subtype 1A (5-HT1A)
Campaign 3	Agonists of the 5-Hydroxytryptamine Receptor Subtype 1E (5-HT1E)
Campaign 4	Agonists of the Galanin receptor 2 (Gal2)
Campaign 5	Agonists of the Neuropeptide Y receptor Y1 (NY1R)
Campaign 6	Agonists of the Neuropeptide Y receptor Y2 (NY2R)
Campaign 7	Agonists of the Oxytocin Receptor (OT)
Campaign 8	Agonists of the Relaxin Receptor RXFP1
Campaign 9	Agonists of the Sphingosine 1-Phosphate Receptor 1 (S1P1)
Campaign 10	Agonists of the Sphingosine 1-Phosphate Receptor 2 (S1P2)
Campaign 11	Agonists of the Sphingosine 1-Phosphate Receptor 3 (S1P3)
Campaign 12	Agonists of the Sphingosine 1-Phosphate Receptor 4 (S1P4)
Campaign 13	Allosteric ligands of the Thyrotropin-releasing hormone receptor, agonist
Campaign 14	Allosteric modulators of D1 Dopamine Receptors
Campaign 15	Antagonists of the 5-Hydroxytryptamine Receptor Subtype 1E (5-HT1E)
Campaign 16	Antagonists of the Chemokine C-C motif receptor 6, CCR6
Campaign 17	Antagonists of the Formyl Peptide Receptor 1 (FPR1)
Campaign 18	Antagonists of the Formyl Peptide Receptor 2 (FPR2)
Campaign 19	Antagonists of the G protein coupled receptor 7 (GPR7)
Campaign 20	Antagonists of the Galanin receptor 2 (Gal2)
Campaign 21	Antagonists of the M1 muscarinic receptor
Campaign 22	Antagonists of the Neuropeptide S Receptor
Campaign 23	Antagonists of the Neuropeptide Y receptor Y1 (NY1R)
Campaign 24	Antagonists of the Neuropeptide Y receptor Y2 (NY2R)
Campaign 25	Antagonists of the Sphingosine 1-Phosphate Receptor 1 (S1P1)
Campaign 26	Antagonists of the Sphingosine 1-Phosphate Receptor 2 (S1P2)
Campaign 27	Antagonists of the Sphingosine 1-Phosphate Receptor 3 (S1P3)
Campaign 28	Antagonists of the Sphingosine 1-Phosphate Receptor 4 (S1P4)
Campaign 29	Compounds affecting Ras and related GTPases
Campaign 30	Compounds affecting the NFAT signaling pathway
Campaign 31	Compounds binding the Estrogen Receptors
Campaign 32	Compounds binding the GPR35, antagonists
Campaign 33	Compounds binding the GPR55, agonists
Campaign 34	Compounds binding the GPR55, antagonists
Campaign 35	Compounds interacting with beta2 adrenergic receptor
Campaign 36	GPCR-mediated thallium flux through GIRK channels
Campaign 37	Inhibitors of platelet dense granule release
Campaign 38	Inhibitors of RGS12 GoLoco Motif Activity
Campaign 39	Late stage dose response (S1P4 agonists in triplicate)
Campaign 40	Late stage dose response counterscreen (Cytotoxicity in quadruplicate)
Campaign 41	Late stage dose response counterscreen (inhibition by S1P4-selective antagonist)
Campaign 42	Late stage dose response counterscreen (S1P1 agonists in triplicate)
Campaign 43	Late stage dose response counterscreen (S1P2 agonists in triplicate)
Campaign 44	Late stage dose response counterscreen (S1P3 agonists in triplicate)
Campaign 45	Late stage dose response counterscreen (S1P5 agonists in triplicate)
Campaign 46	Late stage counterscreen panel assay (Ricerca hit profiling CYP450)
Campaign 47	Ligands of D1 Dopamine Receptors, allosteric agonists
Campaign 48	Ligands of D1 Dopamine Receptors, allosteric antagonists
Campaign 49	Ligands of D1 Dopamine Receptors, allosteric potentiators
Campaign 50	Ligands of D2 Dopamine Receptors, allosteric agonists
Campaign 51	Ligands of D2 Dopamine Receptors, allosteric antagonists
Campaign 52	Ligands of D2 Dopamine Receptors, allosteric potentiators
Campaign 53	Ligands of the Thyroid Stimulating Hormone receptor (TSH)
Campaign 54	Ligands of the Thyroid Stimulating Hormone receptor (TSH), inverse agonist
Campaign 55	Modulators of the metabotropic Glutamate receptor 4 (mGlu4)
Campaign 56	Modulators of the metabotropic Glutamate receptor 8 (mGlu8)
Campaign 57	Modulators of the prostaglandin E2 receptor subtype EP2
Campaign 58	Novel allosteric agonists of the M1 muscarinic receptor
Campaign 59	Novel allosteric antagonists of the M1 muscarinic receptor
Campaign 60	Novel allosteric modulators of the M1 muscarinic receptor
Campaign 61	Novel allosteric modulators of the M4 muscarinic receptor
Campaign 62	Novel allosteric modulators of the M5 muscarinic receptor
Campaign 63	Orexin 1 receptor (OX1) antagonists
Campaign 64	Positive allosteric modulators of the M1 muscarinic receptor
Campaign 65	Potentiators of Oxytocin Receptor (OT)
Campaign 66	Selective ligands of the kappa opioid receptor

Campaign 67	Selective ligands of the kappa opioid receptor, agonists
Campaign 68	Selective ligands of the kappa opioid receptor, agonists and antagonists
Campaign 69	Selective ligands of the kappa opioid receptor, antagonists
Campaign 70	Small molecule agonists of the apelin receptor (APJ)
Campaign 71	Small molecule antagonists of the apelin receptor (APJ)
Campaign 72	Small molecule regulators of the RGS family protein interactions
Campaign 73	Small molecule regulators of the RGS4 protein

Supplementary Table 9. Table 3 expanded to show compound structures.

Classification	SID	Target Symbol	SID Efficacy	Potency (μM)	Structure
Functionally Active	856021	5-HT(1A)	Agonist	EC_{50}=0.018	
	22409370	S1P4R	Antagonist	IC_{50}=0.168	
	85285486	M5R	Allosteric modulator	EC_{50}=1.161	
Target Selective (*, probe)	24428139*	FPR1	Antagonist	K_i=0.3	
	22413249*	NPY-Y2R	Antagonist	IC_{50}=3.917	
	4258673*	S1P1R	Agonist	AC_{50}=0.207	
Unselective OR Artifact (suspected promiscuous)	17415263	M1R	Antagonist	AC_{50}=3.9811	
	85200865	AVPR1A	Agonist	EC_{50}=2.325	
	11532956	RXFP2	Agonist	AC_{50}=0.9742	

SupplementaryTable 10. Promiscuous compounds identified in the GPCR ontology-based flow chart analysis.

SID	Screening Campaign Target	PubChem Outcome
14729216	Angiotensin II receptor type 1 (AGTR-1, AT1)	Active
	Apelin receptor (APJ), antagonists	Active
	Galanin receptor type 2	Active
	Kappa opioid receptor (kappa)	Active
	Muscarinic M1 receptor (M1)	Active
	Neuropeptide S (NPS) receptor	Active
	Neuropeptide Y Y2 (NPY-Y2) receptor, antagonists	Active
	Neuropeptides B/W receptor 1 (NPBWR1)	Active
	Sphingosine 1-phosphate (S1P) receptor 1 (S1P1), antagonists	Active
	Sphingosine 1-phosphate (S1P) receptor 2 (S1P2), antagonists	Active
	Sphingosine 1-phosphate (S1P) receptor 4 (S1P4), antagonists	Active
	Apelin receptor (APJ), agonists	Inactive
	Arginine vasopressin receptor 1A, AVPR1A, V1A	Inactive
	Dopamine D2 receptor	Inactive
	G alpha q	Inactive
	Neuropeptide Y Y1 (NPY-Y1) receptor, agonists	Inactive
	Neuropeptide Y Y1 (NPY-Y1) receptor, antagonists	Inactive
	Neuropeptide Y Y2 (NPY-Y2) receptor, agonists	Inactive
	Neurotensin receptor 1, NTSR1	Inactive
	Oxytocin receptor (OT)	Inactive
	Prostaglandin E receptor 2 (subtype EP2), PTGER2	Inactive
	Ras-related C3 botulinum toxin substrate 1 (Rac1)	Inactive
	Ras-related C3 botulinum toxin substrate 1 activated mutant (Rac_ACT)	Inactive
	Regulators of G protein signaling 16 (RGS16)	Inactive
	Regulators of G protein signaling 4 (RGS4)	Inactive
	Regulators of G protein signaling 7 (RGS7)	Inactive
	Regulators of G protein signaling 8 (RGS8)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 2 (S1P2), agonists	Inactive
	Sphingosine 1-phosphate (S1P) receptor 4 (S1P4), agonists	Inactive
	Thyrotropin-releasing hormone receptor (TRH1)	Inactive
49732444	Arginine vasopressin receptor 1B, AVPR1B, V1B	Active
	Relaxin/insulin-like family peptide receptor 1 (RXFP1)	Active
	Relaxin/insulin-like family peptide receptor 2 (RXFP2)	Active
	Apelin receptor (APJ)	Inactive
	C-C chemokine receptor type 6 (CCR6)	Inactive
	Neuropeptides B/W receptor 1 (NPBWR1)	Inactive
	Neurotensin receptor 1, NTSR1	Inactive
	Thyrotropin-releasing hormone receptor (TRH1)	Inactive
49649489	Arginine vasopressin receptor 1B, AVPR1B, V1B	Active
	Relaxin/insulin-like family peptide receptor 1 (RXFP1)	Active
	Relaxin/insulin-like family peptide receptor 2 (RXFP2)	Active
	Apelin receptor (APJ)	Inactive
	C-C chemokine receptor type 6 (CCR6)	Inactive
	Dopamine D2 receptor	Inactive
	Neuropeptides B/W receptor 1 (NPBWR1)	Inactive
	Thyrotropin-releasing hormone receptor (TRH1)	Inactive
49827544	Arginine vasopressin receptor 1A, AVPR1A, V1A	Active
	G alpha q	Active
	Orexin receptor type 1 (OX1)	Active
	Oxytocin receptor (OT)	Active
	Apelin receptor (APJ)	Inactive
	C-C chemokine receptor type 6 (CCR6)	Inactive
	Dopamine D2 receptor	Inactive
	Neuropeptides B/W receptor 1 (NPBWR1)	Inactive
	Neurotensin receptor 1, NTSR1	Inactive
	Thyrotropin-releasing hormone receptor (TRH1)	Inactive
49679344	Arginine vasopressin receptor 1B, AVPR1B, V1B	Active
	Relaxin/insulin-like family peptide receptor 1 (RXFP1)	Active
	Relaxin/insulin-like family peptide receptor 2 (RXFP2)	Active
	Apelin receptor (APJ)	Inactive
	C-C chemokine receptor type 6 (CCR6)	Inactive
	Dopamine D2 receptor	Inactive
	Neuropeptides B/W receptor 1 (NPBWR1)	Inactive
	Neurotensin receptor 1, NTSR1	Inactive
	Thyrotropin-releasing hormone receptor (TRH1)	Inactive

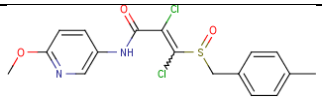
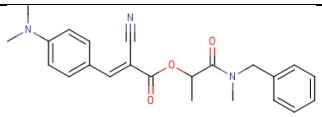
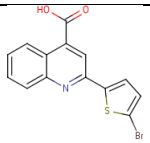
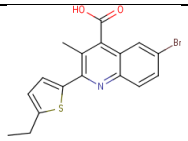
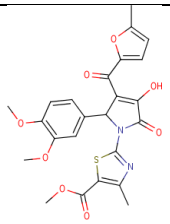
Supplementary Table 11. Global selective compounds identified in the GPCR ontology-based flow chart analysis.

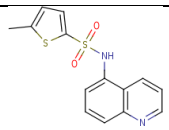
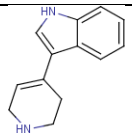
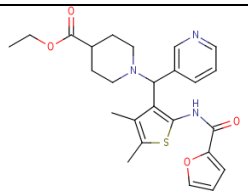
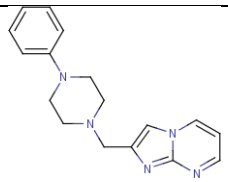
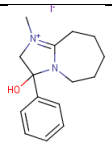
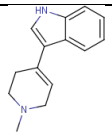
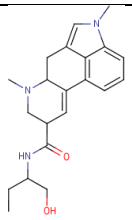
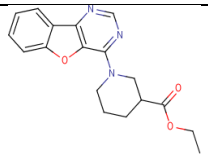
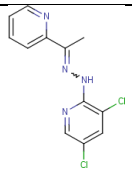
SID	Screening Campaign Target	PubChem Outcome
4244225	5-hydroxytryptamine (serotonin) receptor 1E (5HT1E) agonists	Active
	Regulators of G protein signaling 7 (RGS7)	Active
	Regulators of G protein signaling 4 (RGS4)	Active
	Dopamine D2 receptor, allosteric antagonists	Active
	5-hydroxytryptamine (serotonin) receptor 1A (5HT1A)	Inactive
	5-hydroxytryptamine (serotonin) receptor 1E (5HT1E) antagonist	Inactive
	Apelin receptor (APJ)	Inactive
	Arginine vasopressin receptor 1A, AVPR1A, V1A	Inactive
	Formyl peptide receptor 1 (FPR1)	Inactive
	Formyl peptide receptor 2 (FPR2)	Inactive
	G alpha q	Inactive
	Galanin receptor type 2	Inactive
	Neuropeptide Y Y1 (NPY-Y1) receptor	Inactive
	Neuropeptide Y Y2 (NPY-Y2) receptor	Inactive
	Neuropeptides B/W receptor 1 (NPBWR1)	Inactive
	Neurotensin receptor 1, NTSR1	Inactive
	Orexin receptor type 1 (OX1)	Inactive
	Oxytocin receptor (OT)	Inactive
	Prostaglandin E receptor 2 (subtype EP2), PTGER2	Inactive
	Ras-related C3 botulinum toxin substrate 1 (Rac1)	Inactive
	Ras-related C3 botulinum toxin substrate 1 activated mutant (Rac_ACT)	Inactive
	Regulators of G protein signaling 16 (RGS16)	Inactive
	Regulators of G protein signaling 19 (RGS19)	Inactive
	Regulators of G protein signaling 4 (RGS4)	Inactive
	Regulators of G protein signaling 8 (RGS8)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 1 (S1P1)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 2 (S1P2)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 3 (S1P3)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 4 (S1P4)	Inactive
	Thyrotropin-releasing hormone receptor (TRH1)	Inactive
4251800	5-hydroxytryptamine (serotonin) receptor 1E (5HT1E), agonists	Active
	Neuropeptides B/W receptor 1 (NPBWR1)	Active
	Neuropeptide S (NPS) receptor	Active
	Oxytocin receptor (OT), potentiators	Active
	5-hydroxytryptamine (serotonin) receptor 1A (5HT1A)	Inactive
	5-hydroxytryptamine (serotonin) receptor 1E (5HT1E), agonists	Inactive
	Apelin receptor (APJ)	Inactive
	Arginine vasopressin receptor 1A, AVPR1A, V1A	Inactive
	C-C chemokine receptor type 6 (CCR6)	Inactive
	Dopamine D2 receptor	Inactive
	Formyl peptide receptor 1 (FPR1)	Inactive
	Formyl peptide receptor 2 (FPR2)	Inactive
	G alpha q	Inactive
	Galanin receptor type 2	Inactive
	Neuropeptide Y Y1 (NPY-Y1) receptor	Inactive
	Neuropeptide Y Y2 (NPY-Y2) receptor	Inactive
	Neurotensin receptor 1, NTSR1	Inactive
	Orexin receptor type 1 (OX1)	Inactive
	Oxytocin receptor (OT), agonists	Inactive
	Prostaglandin E receptor 2 (subtype EP2), PTGER2	Inactive
	Ras-related C3 botulinum toxin substrate 1 (Rac1)	Inactive
	Ras-related C3 botulinum toxin substrate 1 activated mutant (Rac_ACT)	Inactive
	Regulators of G protein signaling 16 (RGS16)	Inactive
	Regulators of G protein signaling 4 (RGS4)	Inactive
	Regulators of G protein signaling 7 (RGS7)	Inactive
	Regulators of G protein signaling 8 (RGS8)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 1 (S1P1)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 2 (S1P2)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 3 (S1P3)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 4 (S1P4)	Inactive
	Thyrotropin-releasing hormone receptor (TRH1)	Inactive
7970236	5-hydroxytryptamine (serotonin) receptor 1E (5HT1E), agonists	Active
	Dopamine D2 receptor, allosteric agonists & allosteric antagonists	Active
	5-hydroxytryptamine (serotonin) receptor 1A (5HT1A)	Inactive
	Apelin receptor (APJ)	Inactive

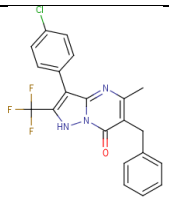
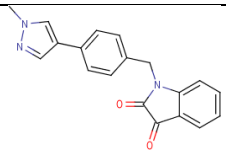
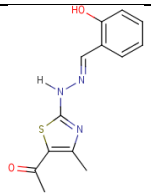
	Arginine vasopressin receptor 1A, AVPR1A, V1A	Inactive
	C-C chemokine receptor type 6 (CCR6)	Inactive
	Formyl peptide receptor 1 (FPR1)	Inactive
	Formyl peptide receptor 2 (FPR2)	Inactive
	G alpha q	Inactive
	Galanin receptor type 2	Inactive
	Neuropeptide Y Y1 (NPY-Y1) receptor	Inactive
	Neuropeptide Y Y2 (NPY-Y2) receptor	Inactive
	Neuropeptides B/W receptor 1 (NPBWR1)	Inactive
	Neurotensin receptor 1, NTSR1	Inactive
	Orexin receptor type 1 (OX1)	Inactive
	Oxytocin receptor (OT)	Inactive
	Prostaglandin E receptor 2 (subtype EP2), PTGER2	Inactive
	Ras-related C3 botulinum toxin substrate 1 (Rac1)	Inactive
	Ras-related C3 botulinum toxin substrate 1 activated mutant (Rac_ACT)	Inactive
	Regulators of G protein signaling 16 (RGS16)	Inactive
	Regulators of G protein signaling 4 (RGS4)	Inactive
	Regulators of G protein signaling 7 (RGS7)	Inactive
	Regulators of G protein signaling 8 (RGS8)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 1 (S1P1)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 2 (S1P2)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 3 (S1P3)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 4 (S1P4)	Inactive
	Thyrotropin-releasing hormone receptor (TRH1)	Inactive
7968332	5-hydroxytryptamine (serotonin) receptor 1E (5HT1E), agonists	Active
	5-hydroxytryptamine (serotonin) receptor 1A (5HT1A), agonists	Inactive
	5-hydroxytryptamine (serotonin) receptor 1A (5HT1A), antagonists	Inactive
	5-hydroxytryptamine (serotonin) receptor 1E (5HT1E), antagonists	Inactive
	Apelin receptor (APJ)	Inactive
	Arginine vasopressin receptor 1A, AVPR1A, V1A	Inactive
	C-C chemokine receptor type 6 (CCR6)	Inactive
	Dopamine D2 receptor	Inactive
	Formyl peptide receptor 1 (FPR1)	Inactive
	Formyl peptide receptor 2 (FPR2)	Inactive
	G alpha q	Inactive
	Galanin receptor type 2	Inactive
	Neuropeptide Y Y1 (NPY-Y1) receptor	Inactive
	Neuropeptide Y Y2 (NPY-Y2) receptor	Inactive
	Neuropeptides B/W receptor 1 (NPBWR1)	Inactive
	Neurotensin receptor 1, NTSR1	Inactive
	Orexin receptor type 1 (OX1)	Inactive
	Oxytocin receptor (OT)	Inactive
	Prostaglandin E receptor 2 (subtype EP2), PTGER2	Inactive
	Ras-related C3 botulinum toxin substrate 1 (Rac1)	Inactive
	Ras-related C3 botulinum toxin substrate 1 activated mutant (Rac_ACT)	Inactive
	Regulators of G protein signaling 16 (RGS16)	Inactive
	Regulators of G protein signaling 4 (RGS4)	Inactive
	Regulators of G protein signaling 7 (RGS7)	Inactive
	Regulators of G protein signaling 8 (RGS8)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 1 (S1P1)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 2 (S1P2)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 3 (S1P3)	Inactive
	Sphingosine 1-phosphate (S1P) receptor 4 (S1P4)	Inactive
	Thyrotropin-releasing hormone receptor (TRH1)	Inactive
4242629	5-hydroxytryptamine (serotonin) receptor 1E (5HT1E), agonists	Active
	Dopamine D2 receptor, allosteric antagonists	Active
	5-hydroxytryptamine (serotonin) receptor 1A (5HT1A), agonists	Inactive
	5-hydroxytryptamine (serotonin) receptor 1A (5HT1A), antagonists	Inactive
	5-hydroxytryptamine (serotonin) receptor 1E (5HT1E), antagonists	Inactive
	Apelin receptor (APJ)	Inactive
	Arginine vasopressin receptor 1A, AVPR1A, V1A	Inactive
	C-C chemokine receptor type 6 (CCR6)	Inactive
	Dopamine D2 receptor, allosteric agonists	Inactive
	Dopamine D2 receptor, allosteric potentiators	Inactive
	Formyl peptide receptor 1 (FPR1)	Inactive
	Formyl peptide receptor 2 (FPR2)	Inactive
	G alpha q	Inactive
	Galanin receptor type 2	Inactive
	Neuropeptide Y Y1 (NPY-Y1) receptor	Inactive

Neuropeptide Y Y2 (NPY-Y2) receptor	Inactive
Neuropeptides B/W receptor 1 (NPBWR1)	Inactive
Neurotensin receptor 1, NTSR1	Inactive
Orexin receptor type 1 (OX1)	Inactive
Oxytocin receptor (OT)	Inactive
Prostaglandin E receptor 2 (subtype EP2), PTGER2	Inactive
Ras-related C3 botulinum toxin substrate 1 (Rac1)	Inactive
Ras-related C3 botulinum toxin substrate 1 activated mutant (Rac_ACT)	Inactive
Regulators of G protein signaling 16 (RGS16)	Inactive
Regulators of G protein signaling 4 (RGS4)	Inactive
Regulators of G protein signaling 7 (RGS7)	Inactive
Regulators of G protein signaling 8 (RGS8)	Inactive
Sphingosine 1-phosphate (S1P) receptor 1 (S1P1)	Inactive
Sphingosine 1-phosphate (S1P) receptor 2 (S1P2)	Inactive
Sphingosine 1-phosphate (S1P) receptor 3 (S1P3)	Inactive
Sphingosine 1-phosphate (S1P) receptor 4 (S1P4)	Inactive
Thyrotropin-releasing hormone receptor (TRH1)	Inactive

Supplementary Table 12. Examples of promiscuous, selective, functionally active compound classification across screening campaigns.

Compound Category	SID	Structure	# of Campaigns	SID is Assay Active (N)	SID is Active (Idx)	SID is Promiscuous (N)	SID is Promiscuous (Idx)	SID is Selective (N)	SID is Selective (Ids)	SID is Functionally Active (N)	SID is Functionally Active (Idx)
Global Promiscuous	14729216		25	39	-0.13	7	0.43	7	-0.43	2	0.00
	49827544		12	15	-0.73	4	1.00	4	-1.00	1	-1.00
	49679344		10	12	-0.67	2	1.00	2	-1.00	0	
	49649489		9	11	-0.64	2	1.00	2	-1.00	0	
	49732444		7	10	-0.40	2	1.00	2	-1.00	0	

	3712888		31	42	-0.57	7	0.43	7	-0.43	2	0.00
Global Selective	4244225		30	44	-0.73	4	-1.00	4	1.00	1	-1.00
	4251800		32	41	-0.76	4	-1.00	4	1.00	2	0.00
	7970236		31	40	-0.80	4	-1.00	4	1.00	1	-1.00
	3714468		29	40	-0.80	4	-1.00	4	1.00	1	-1.00
	7966282		28	36	-0.78	5	-1.00	5	1.00	1	-1.00
Global Functionally Active	855989		28	39	-0.74	3	-1.00	3	1.00	1	1.00
	863325		31	37	-0.89	3	-0.33	3	0.33	2	1.00
	24835397		17	25	-0.76	0		0		1	1.00

	24428974		1	2	1.00	2	-1.00	2	1.00	1	1.00
	85286051		1	0		3	0.33	3	-0.33	1	1.00
	24790058		22	29	-0.86	2	-1.00	2	1.00	2	1.00