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# ***GPCRs as targets for approved drugs: How many targets and how many drugs?***

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Running Title: How many GPCRs are drug targets?

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Abbreviations:
GPCR: G protein-coupled receptor; FDA: Food and Drug Administration; EMA: European Medicines Agency; PDE: Phosphodiesterase; cAMP: Cyclic adenosine monophosphate; IUPHAR: International Union of Basic and Clinical Pharmacology; VGIC: Voltage-gated ion channels, LGIC: Ligand-gated ion channels

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**Abstract**: Estimates vary regarding the number of G protein-coupled receptors, GPCRs, the largest family of membrane receptors that are targeted by approved drugs and the number of such drugs that target GPCRs. We review current knowledge regarding GPCRs as drug targets by integrating data from public databases (CHEMBL, IUPHAR and DRUGBANK) and from the Broad drug repurposing initiative. To account for discrepancies among these sources, we curated a list of GPCRs currently targeted by approved drugs. As of November 2017, 134 GPCRs are targets for drugs approved in the United States or European Union; 128 GPCRs are targets for drugs listed in the FDA orange book. We estimate that ~700 approved drugs target GPCRs, implying that approximately 35% of approved drugs target GPCRs. GPCRs and GPCR-related proteins, i.e. those upstream or downstream of GPCRs, represent ~17% of all protein targets for approved drugs, with GPCRs themselves accounting for ~12%. As such, GPCRs constitute the largest family of proteins targeted by approved drugs. Drugs that currently target GPCRs and GPCR-related proteins are primarily small molecules and peptides. Since ~100 of the ~360 human endoGPCRs (other than olfactory, taste and visual GPCRs) are orphan receptors (lacking known physiologic agonists), the number of GPCR targets, the number of GPCR-targeted drugs and perhaps the types of drugs will likely increase, thus further expanding this GPCR repertoire and the many roles of GPCR-drugs in therapeutics.

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**Introduction**: G protein-coupled receptors (GPCRs, sometimes termed heptahelical or 7-transmembrane [7-TM] receptors, based on their canonical structure, are the largest family of membrane receptors in humans and numerous other species. In addition, GPCRs are considered the largest family of targets for approved drugs (Allen and Roth, 2011; Rask-Andersen et al, 2014; Santos et al, 2017). Numerous factors contribute to the wide utility of GPCR-targeted drugs, including their druggability, interaction with numerous types of chemical entities, and expression in the plasma membrane, which facilitates molecular interactions in the extracellular milieu. Scientific articles, grant applications and lectures that describe findings related to GPCRs often note the therapeutic utility of GPCRs but differ widely in estimates of their contribution as targets for approved drugs and generally range from ~20 to >50%. To clarify this ambiguity, we reviewed information from three major public databases (see **Methods**). We report here the results of this analysis regarding the identity and number of GPCR targets and drugs that target those GPCRs, as well as GPCR-related proteins upstream (e.g., ligands) and downstream (e.g., phosphodiesterases that degrade cAMP). In addition, we provide information about the types of chemical entities that are GPCR-directed therapeutics and identify inconsistencies among the databases regarding GPCR targets and drugs directed at those targets.

**Materials and Methods**: We assessed information regarding approved drugs, drug targets and if available, ligand-target interactions from three online databases: CHEMBL (Bento et al, 2014), DRUGBANK (Wishart et al, 2007) and IUPHAR (Southan et al, 2016; Alexander et al, 2017). We consolidated data from each source into tables that relate the drugs approved for use in humans to their targets. We obtained a list of all annotated human GPCRs (excluding olfactory and vision receptors) from IUPHAR (Alexander et al, 2017); the genes/proteins on this list were then queried from different sources to identify GPCRs that are drug targets. Approved drugs were cross-checked against those listed by the FDA (fda.gov) and EMA (ema.europa.eu/ema/). As an

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additional source, we used data from the Broad repurposing hub (Corsello et al, 2017), which employed high throughput screening to characterize drug-target interactions of approved drugs, natural products and nutraceuticals along with other entities.

Our analysis yielded a list of currently 'druggable' GPCRs and the drugs that target them. Because of possible database errors in downloadable material, as well as ambiguity of ligand-target interactions in certain sources, we manually curated each druggable GPCR to verify pharmacological interaction of the approved drugs. The primary sources used for cross-checking the data were the aforementioned databases, plus the Drug-gene interactions database (DGIDB.org; Wagner et al, 2015) and GeneCards (genecards.org; Rebhan et al, 1998), along with primary sources cited within those databases.

The resulting list of GPCRs targeted by approved drugs (**Table 1**) includes an example of an approved drug that targets each GPCR. Certain GPCRs (for example, histamine H1) are the targets for multiple drugs. **Supplemental Table 2** lists all such GPCR-targeted drugs. In some cases, we considered families of GPCRs as targets for the same drugs (e.g., multiple P2Y receptors are targets for suramin and multiple S1P receptors as targets for fingolimod). For such examples, we list the GPCRs and approved drugs with the caveat that some of the drug-GPCR interactions are not well defined. In certain cases (e.g., suramin), the approval status of a drug is unclear; we provide details for such drugs in **Table 1** and the accompanying legend.

We thus assembled an integrated list of approved drugs that target GPCRs by combining data from the databases noted above (CHEMBL, IUPHAR and DRUGBANK) and the Broad drug repurposing hub. Due to difficulties in cross-referencing information among the databases (since common identifiers such as Chemical Abstracts Service [CAS] numbers are not provided for drugs listed by all sources), we generated lists of GPCR-related drugs using drug names. We

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considered drugs with multiple derivatives (such as different salts) as duplicates in counting GPCR-related drugs and evaluating overlap/discrepancy among sources. In some cases, the sources list drugs approved in the U.S. and/or Europe but without noting the approving agency. We thus estimated the number of GPCR-targeting drugs based on their approval status, without including information regarding the agencies that have approved such drugs, though the majority of such drugs listed in **Supplemental Table 2** are listed in the FDA orange book.

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## Results

### Section 1. GPCRs that are targets for approved drugs

**Table 1** lists GPCRs that are targets for approved drugs and for each GPCR, we identify an example of an approved drug. We identified 134 GPCRs that are targets for approved drugs; this number represents about one-third of the endo-GPCR family (n= 364, **Supplemental Table 1** and Insel et al, 2015; Alexander et al, 2017) but only ~16% of the ~800 GPCRs (including olfactory receptors) in the human genome. The currently druggable receptors include GPCRs that signal via each class of heterotrimeric GTP (G) proteins (Gs, Gi/o, Gq/11, and G12/13), and are members of each of the major families of GPCRs: Classes A, B, C, Frizzled and Adhesion (**Figure 1**). SMO, of the frizzled class and ADGRG3, an adhesion receptor, are the only GPCRs among these 134 'druggable' receptors without known physiological agonists. A small number of GPCRs interact with approved drugs but lack well-characterized G protein-mediated signaling, for example, GPR35 is targeted by furosemide and bumetanide (Yang et al, 2012), both of which bind this GPCR with similar affinity to SLC12 chloride transporters—considered the primary targets of these drugs (Hebert et al, 2004).

Entries in bold in Table 1 indicate GPCRs considered primary targets for the listed drug, based on affinity and/or functional response (in the majority of cases, both). Entries not in bold indicate GPCRs targeted by approved drugs but for which such an interaction is not likely a primary aspect of the intended therapeutic use of such drugs. Such GPCR-ligand interactions may contribute to side effects. In a number of cases, data are ambiguous regarding precisely which receptors are responsible for mediating the therapeutic efficacy of GPCR-targeted drugs. In such cases, if pharmacological data implicate a strong GPCR-drug affinity, we have bolded such GPCR-drug pairs. An example is the melanocortin receptor family (MC1R – MC5R), which may mediate a number of therapeutic effects of corticotropin/ACTH (Gong, 2014). Similarly, the precise importance of each of the somatostatin receptors (SSTRs) as targets for pasireotide and

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lanreotide is incompletely understood (e.g. Feelders et al, 2012). In total, we thus list 98 GPCRs that are thought to mediate therapeutic effects of approved drugs, with an additional 36 GPCRs that interact with approved drugs and may contribute to therapeutic effects or side effects. We excluded multiple GPCRs as primary targets for molecules with affinity for multiple members within one or more GPCR families. As examples, caffeine and theophylline bind multiple adenosine receptors including ADORA2B, but we do not consider that receptor to be a primary target for any approved drugs. Our rationale is similar for suramin, which binds multiple P2Y receptors.

Different databases/sources identify differing numbers and identities of GPCRs that are targets of approved drugs. **Figure 1A** shows the number of druggable GPCRs identified by each source we used**.** One or more sources identifies 157 GPCRs as a target for approved drugs. Three of the four sources indicate a similar number of GPCRs as druggable but the identities of such receptors are discrepant. CHEMBL identifies fewer GPCRs than the other sources, as we will discuss subsequently. A small number of GPCRs are uniquely identified in each of the four sources (**Figure 1 legend). Supplemental Table 1** lists the 'druggable' GPCRs identified by each source**.**

**Figure 1B** illustrates the primary Gα protein linkage for the 134 GPCRs with approved drugs. In cases where GPCRs couple to multiple Gα's, we counted all such linkages. Approximately two thirds of the targeted receptors couple to either Gs or Gi, thereby highlighting the importance of such GPCRs (and likely, the regulation by cAMP) of current therapeutic agents. By contrast, approved drugs only target 8 GPCRs that signal via G12/13. Two examples are F2R/PAR1, the thrombin receptor, targeted by vorapaxar and SMO, targeted by sonidegib and vismodegib. Such assignments may change as data emerge that identify drugs with signaling bias or activity as allosteric modulators. For example, the benzodiazepine lorazepam, whose anxiolytic action

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results from interaction with $GABA_A$ receptors, also binds to the pH-sensing GPCR GPR68/OGR1 and promotes Gq-mediated signaling (Huang et al, 2015; Pera et al, in press).

The IUPHAR, DRUGBANK and Broad repurposing datasets show relatively good agreement. For example, as shown in **Figure 1C,** IUPHAR and DRUGBANK share in their identification of >80% of GPCRs. The Broad dataset has the largest number of GPCR drug targets, likely resulting from the use of different inclusion criteria compared to the other sources, such as by including a large number of natural products not listed in other sources. However, certain drug-target interactions in the Broad dataset likely do not result from ligand-receptor interaction. For example, that dataset lists GPRC5A as a target of retinoic acid; however, retinoic acid does not bind GPRC5A; instead, retinoic acid regulates its expression (Ye et al, 2009). In the absence of data indicating drug-receptor interaction, we believe one ought not consider a GPCR as a target for an approved drug.

Other discrepancies, in particular between IUPHAR and CHEMBL (**Figure 1D**), appear to result from drugs that have differing affinities in their interaction with multiple targets. The IUPHAR database tends to list all GPCRs with at least moderate affinity for such drugs, whereas the CHEMBL database lists only the 'primary' target. An example is nabilone, an FDA-approved synthetic cannabinoid, which targets CB1 and CB2 receptors but with only slightly higher (~2 fold) affinity for CB1. IUPHAR lists both CB1 and CB2 receptors as drug targets, whereas CHEMBL lists only CB1. Other such discrepancies include B1 and B2 bradykinin receptors, which are targeted by icatibant, for which the B2 receptor has a higher affinity: only B2 is listed as druggable in CHEMBL but both are considered drug targets in IUPHAR. In such cases, we have used IUPHAR's approach, i.e. listing all GPCRs with a reasonable affinity for approved drugs as druggable, while also distinguishing between 'primary' and secondary targets as discussed above. We curated data for each GPCR to ensure availability of pharmacological data for at least one drug approved either in the U.S. (FDA) or Europe (EMA) to define currently druggable

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GPCRs. Of the 134 such GPCRs we curated (**Table 1**), 128 are targets of FDA-approved drugs. Of the remaining GPCRs, for the 4 P2Y receptors (P2YR 1, 2, 6 and 11), suramin is an antagonist but is not formally approved by the FDA, yet it is listed as an essential medicine by the WHO and distributed by the CDC as an anti-parasitic agent. Two other such GPCRs are: HCAR2, a target for acipimox (UK-approved) and HRH3, a target for the antagonist pitolisant (EMA-approved).

**Section 2. FDA-approved drug targets upstream or downstream of GPCRs**



Numerous approved drugs target proteins, such as transporters and enzymes that are proximal (upstream) or distal (downstream) of GPCRs and thereby contribute to GPCR activation and function. Examples include agents that regulate agonist availability by controlling ligand synthesis or transport (e.g., serotonin or norepinephrine reuptake inhibitors) or proteins that regulate concentration of second messengers, for example, inhibitors of phosphodiesterases [PDEs, such as the PDE4 inhibitors roflumilast and apremilast], that hydrolyze cAMP. Calcium is a second messenger for Gq signaling but we have not included proteins that regulate cellular calcium concentrations (such as voltage-gated ion channels [VGIC]) as these proteins generally regulate calcium in contexts independent of GPCR signaling. We also have excluded genes/proteins associated with metabolism (such as in the Krebs cycle) as the primary functions of such proteins are only indirectly related to GPCR signaling. Thus, **Table 2** lists GPCR-related drug targets that are proteins whose function/activity is primarily/largely dependent on GPCRs, and whose targeting directly influences GPCR signaling.

We identified over 50 druggable GPCR-related proteins. Adding these proteins to the list of GPCRs yields >180 targets for approved drugs. Estimates of the total number of druggable genes/proteins vary. For example, Santos et al (2017) recently estimated nearly 700 druggable genes, whereas the three major databases (CHEMBL, IUPHAR and DRUGBANK) each list ~800

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druggable genes. A combined list from those databases yields ~1100 human gene/protein targets for approved drugs. Such estimates lead us to propose that GPCRs and GPCR-related genes together account for ~17% of the genes/proteins currently targeted by approved drugs (**Figure 2**). GPCRs alone represent ~12% of drug targets and hence are the largest family of genes/proteins targeted by approved drugs, followed by VGICs and protein kinases. To verify which of the druggable genes are in different categories, against the ~1100 druggable genes, we queried lists of all genes annotated as protein kinases (from UNIPROT; UniProt Consortium, 2017), VGICs, LGICs (Ligand-gated ion channels) and Transporters (all from IUPHAR; Southan et al, 2016).

**Section 3. Approved drugs that target GPCRs**

Substantial discrepancy exists among the 4 main sources used in this study with respect to the numbers and identities of approved drugs that target GPCRs (**Figure 3A**). A major challenge in comparing these databases is the lack of suitable fields for cross-referencing among sources. DRUGBANK, IUPHAR and CHEMBL do not use the same identifiers for drugs (such as CAS numbers) in downloadable data files. CHEMBL provides a cross-referencing method via the UniChem web API tool (Chambers et al. 2013), however, this still did not allow for thorough cross-referencing, as several compounds are listed in IUPHAR or DRUGBANK but not CHEMBL/UniChem. Thus, it is problematic to readily convert between IUPHAR ligand IDs, CHEMBL IDs and Drugbank IDs, a difficulty also noted by others (e.g. Santos et al, 2017, who also used drug names rather than a universal identifier when compiling data from sources external to their own databases). Compiling drug names among the different sources yields 704 drugs annotated by at least 1 source as targeting one or more of the 134 druggable GPCRs listed in **Section 1**. **Table S2** lists all such drugs, as well as the source that lists them. Of these 704 drugs, 199 are annotated as targeting GPCRs in only a single source, most commonly, in the Broad repurposing hub data or DRUGBANK. Among the 704 drugs, we included ones in DRUGBANK

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for which DRUGBANK provide information on pharmacological interactions or where such data are available in other datasets.

Estimates of the proportion of approved drugs that target GPCRs vary; the CHEMBL and DRUGBANK databases each indicate ~30% of drugs target GPCRs, while the IUPHAR database lists ~38% (**Figure 3B**). Together, the FDA and EMA list ~1950 approved drugs. Using a range of ~500 (conservative estimate) to ~700 GPCR-targeted drugs, we estimate that between ~25% and ~36% of approved drugs target GPCRs, with the upper figure the more likely. As additional studies such as the Broad repurposing initiative (Corsello et al, 2017) characterize GPCR-drug interactions in more detail, we anticipate a growth in this number, as secondary interactions between GPCRs and drugs are defined (Allen and Roth, 2011).

IUPHAR lists more druggable GPCRs than CHEMBL or DRUGBANK but has the smallest number of GPCR-related and overall approved drugs (**Figures 3 A, B**). **Figure 3C** shows the number of GPCR-targeted drugs based on target-ligand interactions annotated by either IUPHAR or CHEMBL; of the 476 such drugs listed in one or both sources, only a portion are common to both (50%). Such discrepancies highlight the need for more detailed and accurate annotation of druggable genes/proteins and the drugs that target them, as well as measures that will facilitate cross-referencing among databases to reconcile such inconsistencies.

Another issue is that different sources categorize/classify types of drugs differently. IUPHAR provides the most detailed breakdown, classifying drugs as either peptides, antibodies, natural products, metabolites or synthetic organics (typically ‘small molecules’). **Figure 3D** shows the classes of GPCR-targeted drugs listed by IUPHAR. Most are synthetic organic molecules. Antibodies represent a novel class of therapeutics for GPCRs. Mogamulizumab, a CCR4 antagonist, is currently the only approved antibody that targets a GPCR although >70 clinical programs on GPCR-antibodies are in progress (Hutchings et al, 2017).

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**Section 4. Which GPCRs are targeted by the most approved drugs?**

Reflective of the discrepancies between databases, the number of drugs that most frequently target GPCRs varies widely among the sources (**Figure 4**). Histamine (HRH1), serotonin, dopamine, opioid and adrenergic receptors are the most frequently targeted GPCRs, in terms of the number of available drugs. DRUGBANK lists a larger number of drugs interacting with many GPCRs, likely because DRUGBANK has the largest number of annotated drugs and drug-target interactions and also has less strict inclusion criteria with respect to. ligand-target binding data in considering a protein target for a given drug. The large number of HRH1 antagonists reflects their frequent use in treating allergic responses (Xie and He, 2005). That multiple members of certain families of GPCRs are druggable raises the possibility that other families of GPCRs, including orphan GPCRs may also become druggable (Huang et al, 2015). **Supplemental Table 3** lists approved drugs that target each GPCR from each major source surveyed.

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**Discussion**:

Our review of information in databases confirms that: a) GPCRs represent the largest family of protein targets for approved drugs and b) GPCRs are the family of protein targets most frequently targeted by approved drugs (**Section 2**). Previous studies (e.g., Santos et al, 2017) have estimated the contribution of GPCRs to the 'druggable genome'. By curating information from public databases, we have identified 134 GPCRs that are targets for currently approved drugs, in particular, FDA-approved drugs. Approximately two-thirds of currently druggable GPCRs regulate cAMP and numerous GPCR-related drug targets influence cAMP signaling (e.g. PDEs, or proteins associated with synthesis/transport of ligands whose receptors regulate cAMP synthesis). The cAMP pathway is thus the most frequently targeted signaling pathway by currently approved therapeutics. It should however be noted that these 'cAMP-regulating' GPCRs and other proteins may also signal via cAMP-independent mechanisms; e.g. Gi-coupled GPCRs may signal via βγ G protein subunits (which regulate a variety of pathways or via β-arrestin. Biased signaling may also influence estimates for how many GPCRs from each signaling category are targets for drugs.

Discrepancies among databases are a concern for both the number of GPCR targets in different sources and of drugs that target GPCRs. We suggest that these problems can be addressed by collaborative, expert review of the content in databases, akin to the approach used by IUPHAR to involve experts to annotate and curate data for drug targets (Alexander et al, 2017). Recent efforts by groups such as the Drug-gene interactions database (Wagner et al, 2015) have sought to consolidate data from different sources into single, searchable datasets. A combination of individually curated and broadly consolidated data may help solve the challenge of developing comprehensive databases with agreed upon data for drugs and drug targets.

With the exception of SMO and ADGRG3, 'orphan' GPCRs (without known physiologic agonists) are not currently drug targets. Certain orphan GPCRs have highly selective patterns of expression

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or activity in normal and disease tissue. Examples include GPRC5A in pancreatic cancer (Jahny et al, 2017), GPR22 in heart disease (Patel and Ostrom, 2008), SMO as part of hedgehog signaling in various cancers (Rimkus et al, 2016), and GPR3 in Alzheimer's disease (Huang et al, 2015b). Such receptors represent a potentially fruitful area for further study and may add to the repertoire of druggable GPCRs and the drugs that target them. In addition, efforts to design new types of GPCR-targeted drugs (e.g., with signaling bias [via G proteins or β-arrestin] and as allosteric modulators), and with new types of therapeutic agents, including antibodies/nanobodies), aptamers, anti-sense oligonucleotides, gene therapies and with ligands delivered in novel ways lead us to predict that GPCRs will continue to play a prominent role as therapeutic targets. Evidence that GPCRs can show differential expression in diseased cells and tissues will likely underlie efforts to design and develop new GPCR-targeted drugs.

Data such as those presented here may allow for more accurate evaluation of interactions and off-target effects of approved drugs with GPCRs (Allen and Roth, 2011; Wacker et al, 2017), as well as providing opportunities for novel repurposing of approved drugs. As noted above, an example is the anti-anxiety drug lorazepam, which is an allosteric modulator of GPR68, a proton-sensing GPCR (Huang et al, 2015). Work from our lab has identified a role for this receptor in pancreatic cancer (Wiley et al, 2017); raising the possibility that lorazepam (or perhaps other benzodiazepines) may be repurposed for this disease. Data such as those presented in this review may thus not only help identify new potential targets for "basic science" studies, but may also reveal novel clinically relevant therapeutic opportunities.

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## Author Contributions

KS co-designed the study, conducted data analysis, compilation of data and co-wrote the manuscript. PAI co-wrote the manuscript, oversaw, and designed the study and edited the manuscript.

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**Supplemental data**

**Supplemental Table 1**
**Supplemental Table 2**
**Supplemental Table 3**

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**References:**

Alexander SPH, Kelly E, Marrion NV, Peters JA, Faccenda E, Harding SD, Pawson AJ, Sharman JL, Southan C, Buneman OP, Cidlowski JA, Christopoulos A, Davenport AP, Fabbro D, Spedding M, Striessnig J, Davies JA; CGTP Collaborators. (2017). The Concise Guide to PHARMACOLOGY 2017/18. Br J Pharmacol. 174 (Suppl 1): S1-S446.

Allen, J.A. and Roth, B.L., 2011. Strategies to discover unexpected targets for drugs active at G protein–coupled receptors. Annual review of pharmacology and toxicology, 51, pp.117-144.

Bento, A.P., Gaulton, A., Hersey, A., Bellis, L.J., Chambers, J., Davies, M., Krüger, F.A., Light, Y., Mak, L., McGlinchey, S. and Nowotka, M., 2014. The ChEMBL bioactivity database: an update. Nucleic acids research, 42(D1), pp.D1083-D1090.

Chambers J, Davies M, Gaulton A, Hersey A, Velankar S, Petryszak R, Hastings J, Bellis L, McGlinchey S, Overington JP. UniChem: a unified chemical structure cross-referencing and identifier tracking system. Journal of cheminformatics. 2013 Dec 1;5(1):3.

Corsello, S.M., Bittker, J.A., Liu, Z., Gould, J., McCarren, P., Hirschman, J.E., Johnston, S.E., Vrcic, A., Wong, B., Khan, M. and Asiedu, J., 2017. The Drug Repurposing Hub: a next-generation drug library and information resource. Nature Medicine, 23(4), pp.405-408.

Feelders RA, Yasothan U, Kirkpatrick P. Pasireotide. Nature Reviews Drug Discovery. 2012 Aug 1;11(8):597-8.

Gong R. Leveraging melanocortin pathways to treat glomerular diseases. Advances in chronic kidney disease. 2014 Mar 31;21(2):134-51.

Hebert, S.C., Mount, D.B. and Gamba, G., 2004. Molecular physiology of cation-coupled Cl− cotransport: the SLC12 family. Pflügers Archiv, 447(5), pp.580-593.

Huang, X.P., Karpiak, J., Kroeze, W.K., Zhu, H., Chen, X., Moy, S.S., Saddoris, K.A., Nikolova, V.D., Farrell, M.S., Wang, S. and Mangano, T.J., 2015. Allosteric ligands for the pharmacologically dark receptors GPR68 and GPR65. Nature, 527(7579), pp.477-483.

Huang, Y., Skwarek-Maruszewska, A., Horré, K., Vandewyer, E., Wolfs, L., Snellinx, A., Saito, T., Radaelli, E., Corthout, N., Colombelli, J. and Lo, A.C., 2015. Loss of GPR3 reduces the amyloid plaque burden and improves memory in Alzheimer's disease mouse models. Science translational medicine, 7(309), pp.309ra164-309ra164.

Hutchings, C.J., Koglin, M., Olson, W.C. and Marshall, F.H., 2017. Opportunities for therapeutic antibodies directed at G-protein-coupled receptors. Nature Reviews Drug Discovery, 16(9), pp.1-24.

Insel, P.A., Wilderman, A., Zambon, A.C., Snead, A.N., Murray, F., Aroonsakool, N., McDonald, D.S., Zhou, S., McCann, T., Zhang, L. and Sriram, K., 2015. G Protein–Coupled Receptor (GPCR) Expression in Native Cells:"Novel" endoGPCRs as Physiologic Regulators and Therapeutic Targets. Molecular pharmacology, 88(1), pp.181-187.

Jahny, E., Yang, H., Liu, B., Jahnke, B., Lademann, F., Knösel, T., Rümmele, P., Grützmann, R., Aust, D.E., Pilarsky, C. and Denz, A., 2017. The G Protein-Coupled Receptor RAI3 Is an Independent Prognostic Factor for Pancreatic Cancer Survival and Regulates Proliferation via STAT3 Phosphorylation. PloS one, 12(1), p.e0170390.

Patel, H.H. and Ostrom, R.S., 2008. An orphan GPCR finds a home in the heart. American Journal of Physiology-Heart and Circulatory Physiology, 295(2), pp.H479-H481.

Pera T, Deshpande DA, Ippolito M, Wang B, Gavrila A, Michael JV, Nayak AP, Tompkins E, Farrell E, Kroeze WK, Roth BL, Panettieri RA Jr, Benovic JL, An SS, Dulin NO, Penn RB. Biased signaling of the proton-sensing receptor OGR1 by benzodiazepines. FASEB J. 2017 Oct 17. pii: fj.201700555R. doi: 10.1096/fj.201700555R. [Epub ahead of print]

Rask-Andersen, M., Masuram, S. and Schiöth, H.B., 2014. The druggable genome: evaluation of drug targets in clinical trials suggests major shifts in molecular class and indication. Annual review of pharmacology and toxicology, 54, pp.9-26.

Rebhan, M., Chalifa-Caspi, V., Prilusky, J. and Lancet, D., 1998. GeneCards: a novel functional genomics compendium with automated data mining and query reformulation support. Bioinformatics (Oxford, England), 14(8), pp.656-664.

Rimkus, T.K., Carpenter, R.L., Qasem, S., Chan, M. and Lo, H.W., 2016. Targeting the sonic hedgehog signaling pathway: review of smoothened and GLI inhibitors. Cancers, 8(2), p.22.

Santos, R., Ursu, O., Gaulton, A., Bento, A.P., Donadi, R.S., Bologa, C.G., Karlsson, A., Al-Lazikani, B., Hersey, A., Oprea, T.I. and Overington, J.P., 2017. A comprehensive map of molecular drug targets. Nature Reviews Drug Discovery, 16(1), pp.19-34.

Southan C, Sharman JL, Benson HE, Faccenda E, Pawson AJ, Alexander SPH, Buneman OP, Davenport AP, McGrath JC, Peters JA, Spedding M, Catterall WA, Fabbro D, Davies JA; NC-IUPHAR. (2016) The IUPHAR/BPS Guide to PHARMACOLOGY in 2016: towards curated quantitative interactions between 1300 protein targets and 6000 ligands. Nucl. Acids Res. 44 (Database Issue): D1054-68.

UniProt Consortium, 2017. UniProt: the universal protein knowledgebase. Nucleic acids research, 45(D1), pp.D158-D169.

Wacker, D., Stevens, R.C. and Roth, B.L., 2017. How ligands illuminate GPCR molecular pharmacology. Cell, 170(3), pp.414-427.

Wagner, A.H., Coffman, A.C., Ainscough, B.J., Spies, N.C., Skidmore, Z.L., Campbell, K.M., Krysiak, K., Pan, D., McMichael, J.F., Eldred, J.M. and Walker, J.R., 2015. DGIdb 2.0: mining clinically relevant drug–gene interactions. Nucleic acids research, 44(D1), pp.D1036-D1044.

Wiley SZ, Sriram K, Liang W, Chang SE, French R, McCann T, Sicklick J, Nishihara H, Lowy AM, Insel PA., 2017. GPR68, a proton-sensing GPCR, mediates interaction of cancer associated fibroblasts and cancer cells. FASEB Journal. In press. (PMID 29092903)

Wishart, D.S., Knox, C., Guo, A.C., Cheng, D., Shrivastava, S., Tzur, D., Gautam, B. and Hassanali, M., 2007. DrugBank: a knowledgebase for drugs, drug actions and drug targets. Nucleic acids research, 36(suppl_1), pp.D901-D906.

Xie, H. and He, S.H., 2005. Roles of histamine and its receptors in allergic and inflammatory bowel diseases. World journal of gastroenterology: WJG, 11(19), p.2851.

Yang, Y., Fu, A., Wu, X. and Reagan, J.D., 2012. GPR35 is a target of the loop diuretic drugs bumetanide and furosemide. Pharmacology, 89(1-2), pp.13-17.

Ye, X., Tao, Q., Wang, Y., Cheng, Y. and Lotan, R., 2009. Mechanisms underlying the induction of the putative human tumor suppressor GPRC5A by retinoic acid. Cancer biology & therapy, 8(10), pp.951-962.

**Footnotes:**

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## Figure Legends

**Figure 1. The number of GPCRs targeted by approved drugs**. **A*)*** *T*he number of GPCRs targeted by approved drugs, based on annotations of GPCR-drug interactions from each of several sources. Also included are the number of commonly listed ("consensus") GPCRs and of GPCRs curated in our analysis. The number of 'druggable' GPCRs uniquely listed in each source is as follows: *IUPHAR, 6; CHEMBL, 3; DRUGBANK, 0; Broad repurposing hub, 24.* **B)** Putative primary Gα protein linkage, based on classification of GPCR signaling by IUPHAR, of the 134 curated GPCRs targeted by approved drugs. Individual GPCRs may couple to multiple G-proteins. **C, D)** Venn diagrams of the overlap between IUPHAR's list of GPCR drug targets and that of CHEMBL and DRUGBANK.

**Figure 2**. **The estimated proportion of genes from different gene families that are targets for approved drugs**. GPCRs comprise the single largest such group. VGICs: Voltage-gated ion channels; LGICs: Ligand-gated ion channels.

**Figure 3**. **The number of GPCR-targeted drugs**. **A**) The number of 'approved' drugs identified in IUPHAR, CHEMB, DRUGBANK and the Broad repurposing hub with the consensus among the 4 sources and each entry combined from the 4 sources**. B)** The percentage of approved drugs that target GPCRs in each database. **C)** Venn diagram showing the relationship between identities of GPCR-related drugs listed in the IUPHAR and CHEMBL databases**. D)** The types of molecules that target GPCRs, based on annotations from IUPHAR (Alexander at al, 2017).

**Figure 4**: **The 15 GPCRs with the most approved drugs and the number of such drugs listed in CHEMBL, DRUGBANK and IUPHAR respectively**.

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**Table 1.** *134 GPCRs have FDA-approved drugs. Exceptions are those marked as *: EMA approved; 1: approved in the UK by the MHRA; 2: suramin is not listed in the FDA's orange book, but is distributed by the CDC and listed as an essential medicine by the WHO. #: GABBR1 and 2 combine to form a single active signaling complex which is activated by baclofen.*

| Gene Name | Example of an approved drug | Gene Name | Example of an approved drug | Gene Name | Example of an approved drug |
|---|---|---|---|---|---|
| ***ACKR3*** | **Plerixafor** | ***F2R*** | **Vorapaxar** | *MLNR* | Erythromycin |
| *ADGRG3* | Beclometasone Dipropionate | *FFAR1* | Rosiglitazone | *MRGPRX1* | Chloroquine |
| ***ADORA1*** | **Adenosine** | *FPR1* | Cyclosporine | ***MTNR1A*** | **Ramelteon** |
| ***ADORA2A*** | **Regadenoson** | ***FSHR*** | **Human Follicle Stimulating Hormone** | ***MTNR1B*** | **Tasimelteon** |
| *ADORA2B* | Theophylline | ***GABBR1 #*** | **Baclofen** | ***NPY4R*** | **Niclosamide** |
| *ADORA3* | Nicardipine | ***GABBR2 #*** | **Baclofen** | ***NTSR2*** | **Levocabastine** |
| ***ADRA1A*** | **Oxymetazoline** | ***GCGR*** | **Glucagon** | ***OPRD1*** | **Naltrexone** |
| ***ADRA1B*** | **Prazosin** | ***GHRHR*** | **Sermorelin** | ***OPRK1*** | **Anileridine** |
| ***ADRA1D*** | **Prazosin** | ***GLP1R*** | **Lixisenatide** | ***OPRM1*** | **Alfentanil** |
| ***ADRA2A*** | **Apraclonidine** | ***GLP2R*** | **Teduglutide** | ***OXTR*** | **Oxytocin** |
| ***ADRA2B*** | **Dexmedetomidine** | ***GNRHR*** | **Abarelix** | *P2RY1* | Suramin 2 |
| ***ADRA2C*** | **Dexmedetomidine** | ***GPBAR1*** | **Deoxycholic Acid** | *P2RY11* | Suramin 2 |
| ***ADRB1*** | **Acebutolol** | ***GPER1*** | **Estradiol** | ***P2RY12*** | **Cangrelor** |
| ***ADRB2*** | **Pindolol** | *GPR143* | Levodopa | *P2RY13* | Cangrelor |
| ***ADRB3*** | **Mirabegron** | *GPR18* | Dronabinol | *P2RY2* | Suramin 2 |
| ***AGTR1*** | **Candesartan** | *GPR35* | Bumetanide | *P2RY6* | Suramin 2 |
| ***AVPR1A*** | **Vasopressin** | *GPR55* | Dronabinol | *PTGDR* | Treprostinil |
| ***AVPR1B*** | **Vasopressin** | *GPR68* | Lorazepam | *PTGDR2* | Indomethacin |
| ***AVPR2*** | **Vasopressin** | *HCAR1* | Sodium Oxybate | ***PTGER1*** | **Prostaglandin E1** |
| *BDKRB1* | Icatibant | ***HCAR2*** | **Acipimox [1]** | ***PTGER2*** | **Prostaglandin E2** |
| ***BDKRB2*** | **Icatibant** | ***HCAR3*** | **Nicotinic Acid** | ***PTGER3*** | **Misoprostol** |
| ***CALCR*** | **Calcitonin** | ***HCRTR1*** | **Suvorexant** | *PTGER4* | Treprostinil |
| ***CASR*** | **Etelcalcetide** | ***HCRTR2*** | **Suvorexant** | ***PTGFR*** | **Latanoprost** |
| ***CCKAR*** | **Ceruletide** | ***HRH1*** | **Cetirizine** | ***PTGIR*** | **Epoprostenol** |
| ***CCKBR*** | **Pentagastrin** | ***HRH2*** | **Betazole** | ***PTH1R*** | **Teriparatide** |
| ***CCR4*** | **Plerixafor** | ***HRH3*** | **Pitolisant *** | *PTH2R* | Teriparatide |
| ***CCR5*** | **Maraviroc** | *HRH4* | Clozapine | ***S1PR1*** | **Fingolimod** |
| ***CHRM1*** | **Biperiden** | ***HTR1A*** | **Vilazodone** | *S1PR2* | Fingolimod |
| ***CHRM2*** | **Propantheline** | ***HTR1B*** | **Frovatriptan** | *S1PR3* | Fingolimod |
| ***CHRM3*** | **Umeclidinium** | ***HTR1D*** | **Frovatriptan** | *S1PR4* | Fingolimod |
| ***CHRM4*** | **Acetylcholine** | *HTR1E* | Asenapine | ***S1PR5*** | **Fingolimod** |
| ***CHRM5*** | **Acetylcholine** | ***HTR1F*** | **Eletriptan** | ***SCTR*** | **Secretin** |
| ***CNR1*** | **Nabilone** | ***HTR2A*** | **Asenapine** | ***SMO*** | **Sonidegib** |
| ***CNR2*** | **Nabilone** | ***HTR2B*** | **Methysergide** | ***SSTR1*** | **Pasireotide** |
| ***CRHR1*** | **Corticorelin Ovine Triflutate** | ***HTR2C*** | **Methysergide** | ***SSTR2*** | **Lanreotide** |
| ***CXCR4*** | **Plerixafor** | ***HTR4*** | **Cisapride** | ***SSTR3*** | **Pasireotide** |
| ***CYSLTR1*** | **Zafirlukast** | *HTR5A* | Ergotamine | *SSTR4* | Octreotide |
| *CYSLTR2* | Zafirlukast | *HTR6* | Amoxapine | ***SSTR5*** | **Lanreotide** |
| ***DRD1*** | **Dopamine** | *HTR7* | Lurasidone | *SUCNR1* | Sodium Succinate |
| ***DRD2*** | **Dopamine** | ***LHCGR*** | **Choriogonadotropin Alfa** | *TAAR1* | Dexamfetamine |
| ***DRD3*** | **Dopamine** | ***MC1R*** | **Corticotropin** | ***TACR1*** | **Aprepitant** |
| ***DRD4*** | **Dopamine** | ***MC2R*** | **Corticotropin** | *TBXA2R* | Iloprost |
| ***DRD5*** | **Dopamine** | ***MC3R*** | **Corticotropin** | ***TRHR*** | **Protirelin** |
| ***EDNRA*** | **Ambrisentan** | ***MC4R*** | **Corticotropin** | ***TSHR*** | **Thyrotropin** |
| ***EDNRB*** | **Bosentan** | ***MC5R*** | **Corticotropin** | | |

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**Table 2.** GPCR-related proteins/genes that are targets for approved drugs.

| Category of proteins/genes | Examples of proteins/genes that are drug targets | Examples of drugs that target these proteins/genes |
|---|---|---|
| Enzymes involved in agonist synthesis | prostaglandin I2 synthase<br>angiotensin I converting enzymes<br>dopamine beta-hydroxylase<br>coagulation Factors (e.g., Factor 10) | Epoprostenol<br>Lisinopril<br>Disulfiram<br>Rivaroxaban |
| Enzymes involved in agonist degradation | monoamine oxidases A and B<br>catechol O-methyltransferase<br>acetylcholinesterase<br>adenosine deaminase<br>dipeptidyl peptidase-4 | Phenelzine<br>Entacapone<br>Neostigmine<br>Pentostatin<br>Sitagliptin |
| Transporters of GPCR agonists | serotonin transporters<br>dopamine Transporters (SLC6A3)<br>ATP Transporters (SLC25A4) | Citalopram<br>Modafinil<br>Clodronic Acid |
| GPCR ligands | C-C motif chemokine ligand 2<br>coagulation factor II, thrombin | Mimosine<br>Vorapaxar |
| Regulators of second messenger signaling | Phosphodiesterases, e.g.<br>PDE1A-C<br>PDE4A-D<br>Rho Kinases (ROCK1-2) | Vinpocetine<br>Roflumilast<br>Fasudil |

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**Figure 1.**

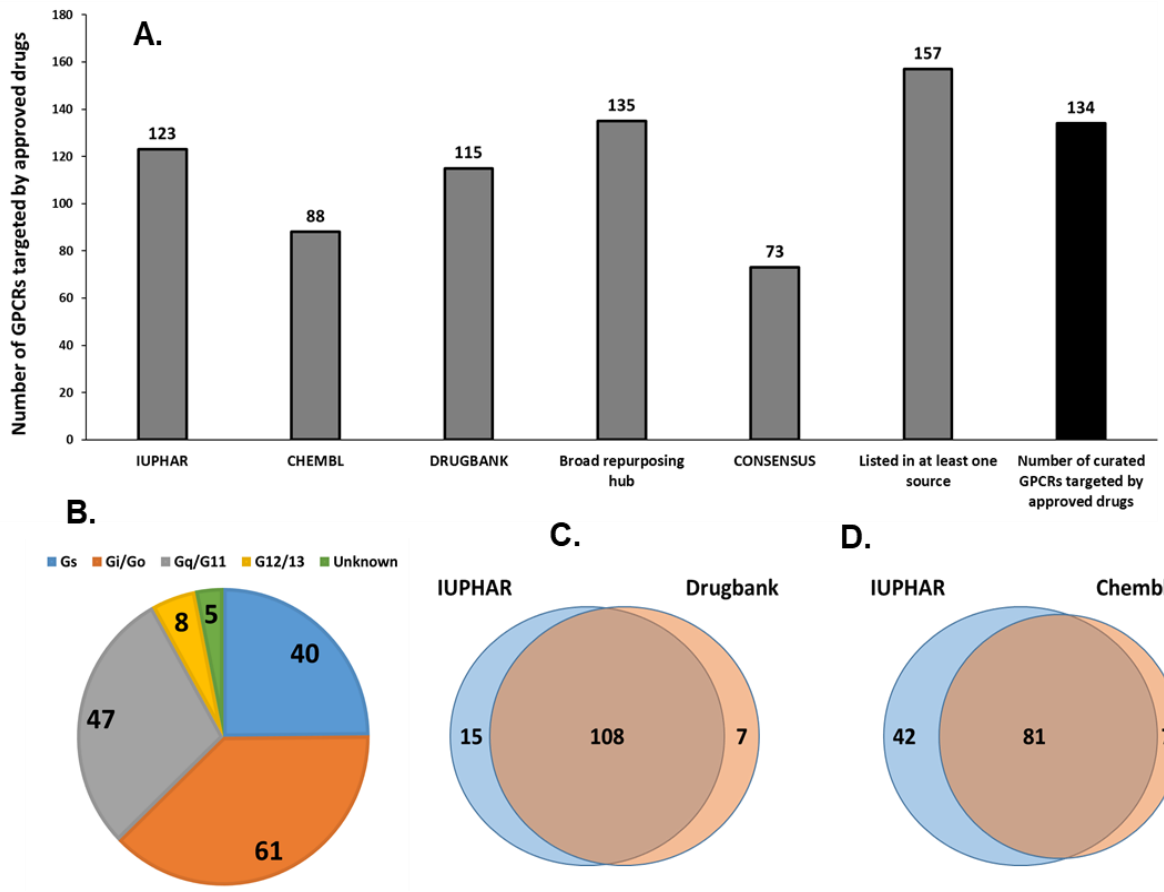

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**Figure 2.**

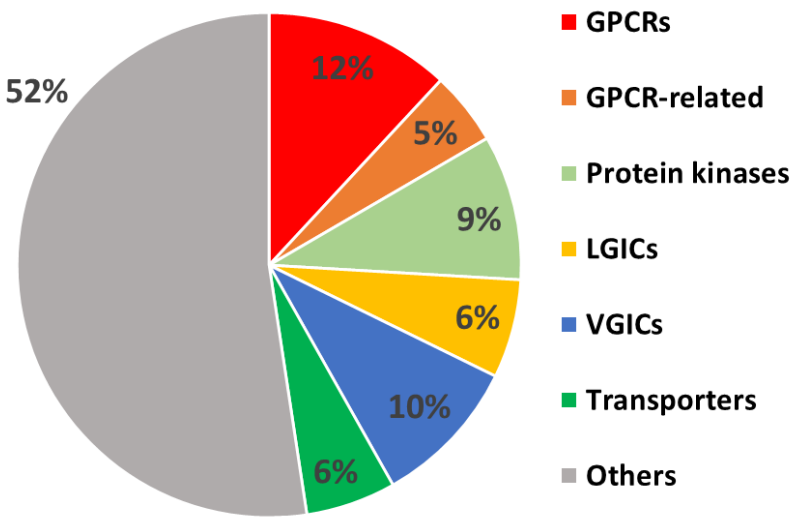

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**Figure 3.**

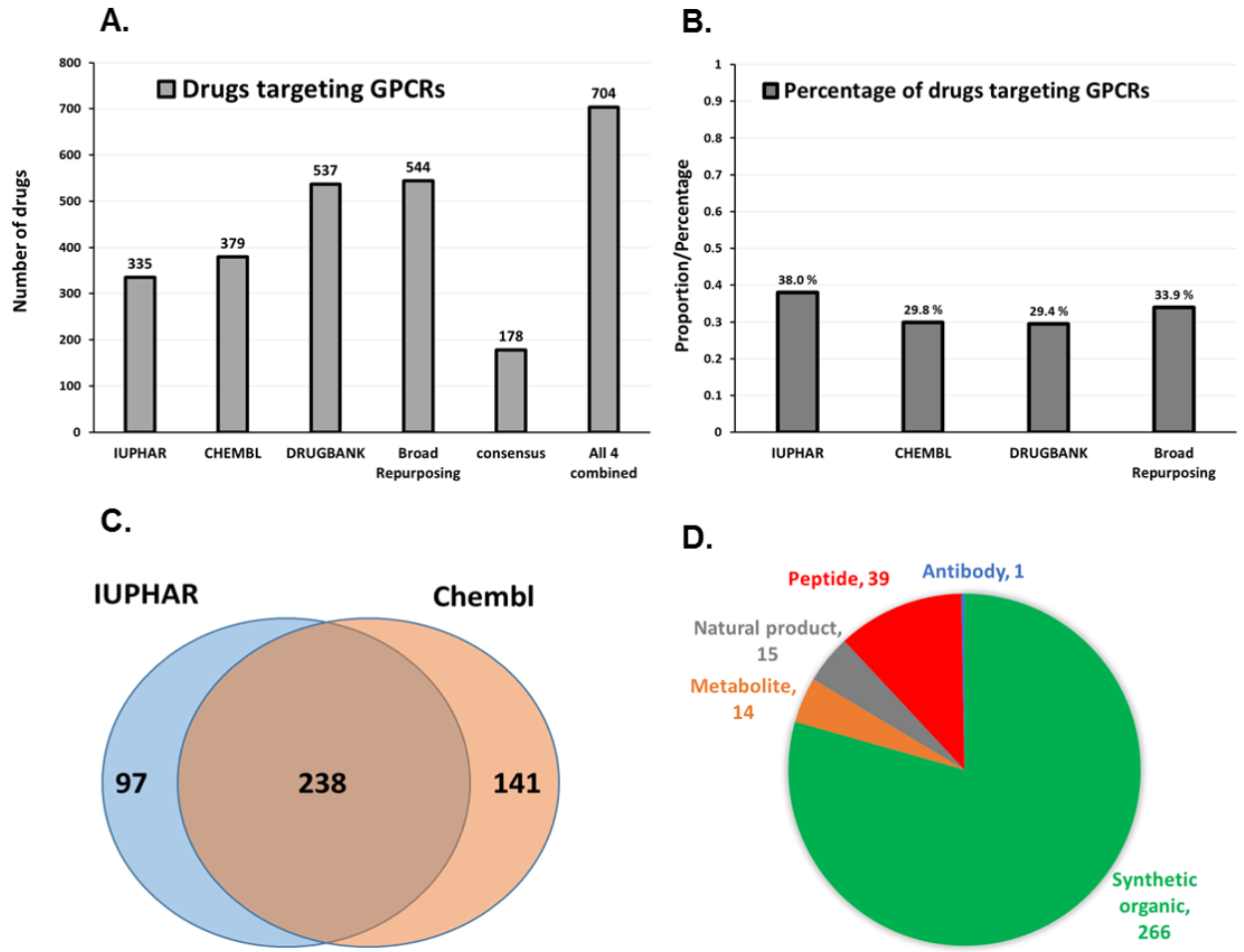

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**Figure 4.**