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Cross-Pharmacology Analysis of G Protein-Coupled Receptors

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Abstract

The degree of applicability of chemogenomic approaches to protein families depends on the accuracy and completeness of pharmacological data and the corresponding level of pharmacological similarity observed among their protein members. The recent public domain availability of pharmacological data for thousands of small molecules on 204 G protein-coupled receptors (GPCRs) provides a firm basis for an in-depth cross-pharmacology analysis of this superfamily. The number of protein targets included in the cross-pharmacology profile of the different GPCRs changes significantly upon varying the ligand similarity and binding affinity criteria. However, with the exception of muscarinic receptors, aminergic GPCRs distinguish themselves from the rest of the members in the family by their remarkably high levels of pharmacological similarity among them. Clusters of non-GPCR targets related by cross-pharmacology with particular GPCRs are identified and the implications for unwanted side-effects, as well as for repurposing opportunities, discussed.

Keywords

GPCR network; ligand similarity; target profile; adverse effects; drug repositioning

Introduction

G protein-coupled receptors (GPCRs) are extremely versatile signaling proteins involved in many physiological processes [1]. Because of that, they are highly relevant in a wide range of therapeutic indications and thus they constitute a target superfamily of utmost importance in drug discovery [2]. Sequence analyses have recognised over 800 GPCRs in the human genome, of which approximately 50% of them are expected to exert their biological function in response to endogenous small molecules [3]. At present, ligands have been identified for the majority of these GPCRs but there remain more than 100 orphan GPCRs for which endogenous ligands have yet to be assigned [4]. Complementing phylogenetic relationships with a deeper understanding of the patterns observed in the interaction profile of small molecules across GPCRs may become a useful deorphanisation strategy [5].

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In recent years, the capacity to screen large chemical libraries on multiple GPCRs has increased dramatically and, most importantly, in many cases the bioactivity data generated has become available in the public domain [6]. In addition, several informatics efforts aiming at extracting and storing chemical structures for which pharmacological data have been reported in bibliographic sources have contributed significantly to expand our knowledge base on ligand-GPCR interactions [7]. Collectively, these data have enabled the characterisation of the property space relevant for GPCR activity [8,9] and for identifying the presence of privileged substructures in GPCR ligands [10-12]. This information can be exploited in the design of GPCR-directed chemical libraries with optimal coverage across its members [13]. Furthermore, these data have revealed that active GPCR ligands tend to have exceptionally high levels of target promiscuity, in particular for class A aminergic GPCRs [14-17], making chemogenomic strategies especially adequate to GPCR drug discovery [18-23].

The broad target promiscuity observed for GPCR ligands is a reflection of the inherent similarity among the transmembrane binding cavities of GPCRs [18,22]. The idea that closely related targets will bind similar ligands has led to the concept of pharmacological similarity, commonly referred to as cross-pharmacology [24]. In this respect, GPCRs are recognised to have levels of cross-pharmacology significantly above those observed within other protein families [17]. For example, based on a large set of screening data available from proprietary and commercial sources, Paolini *et al.* [25] identified among the most intense cross-pharmacology relationships those within and between class A aminergic and peptidic GPCRs. Using a much smaller set of pharmacological data from both public and commercial sources, Gregori-Puigjané and Mestres [15] revealed that aminergic GPCRs had particularly intense pharmacological similarities with opioid receptors but also with two non-GPCR proteins, namely, sigma-1 and NMDA. The identification of cross-pharmacology signals among proteins can be naturally exploited to predict putative novel targets for drugs but also to anticipate potential adverse drug reactions. Under this premise, Keiser *et al.* [26,27] identified several novel drug-GPCR interactions that were then successfully confirmed experimentally and Garcia-Serna and Mestres [28] used recently comparative pharmacology to predict the likely side-effect profile of GPCR drugs.

The current main limitation of cross-pharmacology analyses of proteins is that coverage of both chemical space and pharmacological data along target space are largely incomplete [29]. As new data are collected, they may modulate the levels of cross-pharmacology perceived previously but may reveal also new cross-pharmacology relationships for GPCRs. The recent explosion of publicly available pharmacological data calls for an up-to-date in-depth cross-pharmacology analysis of GPCRs.

Reference Framework

When performing pharmacological similarity analyses of target families, one should keep in mind that the final perception of the cross-pharmacology between two targets depends on the reference framework used [30]. This comprises three aspects: the number and diversity of ligands for which pharmacological data is known, the molecular descriptors used to represent ligands mathematically and the index to assess their similarity, and the chemical similarity and biological activity criteria set.

Chemogenomic Databases

The construction of chemical libraries annotated with pharmacological data opened an avenue to performing family-wide cross-pharmacology analyses of protein targets. Private initiatives, such as BioPrint [31], Wombat [32], and MDL Drug Data Report (MDDR) [33], were pioneering in this respect. Therefore, most of the cross-pharmacology analyses

reported to date were based either on internal proprietary data [25] or on those commercial databases [15, 23-26]. However, recent efforts on delivering publicly available well-crated chemogenomic databases have finally opened cross-pharmacology analyses to the entire scientific community. The list of available public databases is in constant growth and it currently includes GLIDA [34], PDSP [35], BindingDB [36], lUPHARdb [37], PubChem [38], ChEMBLdb [39], hGPCR-lig [40], and DrugBank [41]. The cross-pharmacology analysis of GPCRs performed by Gregori-Puigjané and Mestres [15] made use of BindingDB and the recent work by van der Horst *et al.* [23] was based on GLIDA, PDSP, and ChEMBLdb. As databases are continuously updated, Table 1 contains a summary of the number of ligands, GPCRs, and ligand-GPCR interaction data collected from the latest releases of seven public sources. A total of 196,074 unique interactions between 93,068 ligands and 204 GPCRs were compiled, of which 180 are human GPCRs sharing at least one bioactive ligand with another GPCR (list provided as Supplementary Material). Among the pharmacological data available, affinity data (pK_i) were extracted from five public sources, namely, ChEMBLdb, PDSP, IUPHARdb, BindingDB, and PubChem, and represent 48.3%, 81.9%, and 54.9% of the total number of unique ligands, GPCRs, and interactions, respectively. With the exception of PDSP, the other four sources contain also an important number of additional functional data (pIC_{50} and pEC_{50}) that together represent an additional 41.7%, 12.6%, and 36.9% of the total number of unique ligands, GPCRs, and interactions, respectively. Finally, two public sources, namely, hGPCR-lig and DrugBank, do not contain quantitative pharmacological data but contribute to expand GPCR space with additional non-numeric bioactivity annotations. It ought to be clarified that if a ligand had different values of the same interaction type for exactly the same target interaction (either within the same database or across databases), an average interaction value was assigned. A systematic analysis of the variations found in compounds with multiple interaction data of the same type for the same target revealed an average standard deviation of ca. 0.5 log units, irrespective of the value range.

Molecular Descriptors

Similarity assessment between ligands requires that chemical structures are encoded using some sort of mathematical descriptors. The choice of a particular type of molecular descriptor may ultimately have a subtle influence on our perception of the cross-pharmacology between targets. Interestingly, recent cross-pharmacology analyses of GPCRs have been performed on essentially different types of molecular descriptors. Hert *et al.* [24] and Keiser *et al.* [26] used up to six types of topological fingerprints, including 2048-bit Daylight [42], 988-bit Unity [43], 166-bit MDL keys [44], 1024-bit ECFP4 [45], 1024-bit FCFP4 [45], 1200-bit CATS [46], and one type of three-dimensional structural fingerprint, FEPOPS [47]. In contrast, van der Horst *et al.* [23] utilised frequencies of substructures present in bioactive ligands [48], whereas Gregori-Puigjané and Mestres [15] employed a reduced set of 10 feature-based topological Shannon entropy descriptors (SHED) [49]. The latter will be applied here in the cross-pharmacology analysis of GPCRs based on the most updated publicly available chemogenomic databases (*vide infra*). In addition, the (dis)similarity index used on the particular selection of molecular descriptors may have also an effect on the final perception of the cross-pharmacology between targets. In this respect, while Hert *et al.* [24] and Keiser *et al.* [26] relied on the use of Tanimoto coefficients to assess ligand similarity, van der Horst *et al.* [23] applied Pearson correlation coefficients and Gregori-Puigjané and Mestres [15] used a Euclidean distances. The cross-pharmacology analysis of GPCRs presented here (*vide infra*) will describe ligands with SHED and will use Euclidean distances to assess their (dis)similarity.

Cross-Pharmacology

The number of similar bioactive ligands between two targets determines its level of cross-pharmacology. However, the exact definition of both *similar* and *bioactive* needs to be specified, as those criteria will have a direct impact on the strength of the cross-pharmacology signals detected. In this respect, Paolini *et al.* [25] took the similarity criteria to the limit of identity and used an activity window instead of a threshold to decide whether a compound is shared between two targets only if itself has less than an n log difference in potency. In contrast, Keiser *et al.* [26] considered that two compounds contribute to the cross-pharmacology of a pair of targets if the similarity between their Daylight fingerprints is above a Tanimoto coefficient of 0.57 and both have at least 10 μM affinity for their respective targets, the same bioactivity cut-off applied also by Gregori-Puigjané and Mestres [15] and van der Horst *et al.* [23]. However, a systematic study of the effect that similarity and bioactivity criteria have on the cross-pharmacology between targets is still missing.

Cross-Pharmacology Profiles and Scores

The cross-pharmacology profile of a given target is defined here as the list of targets having at least one similar bioactive ligand. For each one of the 180 human GPCRs (provided as Supplementary Material), two cross-pharmacology profiles were derived: one within GPCRs (internal) and another one within non-GPCRs (external). The concept of Shannon entropy [50] is then applied to determine the variability in the number of similar bioactive ligands in a cross-pharmacology profile. Within this approach, the entropy, S, of a total number of similar bioactive ligands, L, shared with a certain number of targets, T, is given by

$$S = -\sum_{i=1}^{T} \rho_i \cdot \ln \rho_i \; ; \quad \rho_i = l_i / L$$

where p_i and l_i are, respectively, the probability and the number of similar bioactive ligands at each target i of the cross-pharmacology profile. The values of S range between 0, reflecting the situation of all similar bioactive ligands being concentrated in a single target, and a maximum number, $S_{max} = \ln T$, reflecting the situation of a uniformly distributed population of similar bioactive ligands among multiple targets. In order to have a more intuitive measure that can be linearly related to the situation of full uniform occupancy, entropy values are transformed into projected entropy values, $E = e^S$. Correspondingly, E values provide a measure of the expected maximum uniform occupancy from the corresponding S value. Now, for any given ligand population $L > 0$, the values of E can vary from 1, reflecting the situation of zero entropy in which the population is totally concentrated in a single target, to T, reflecting the situation of maximum entropy in which the population is uniformly distributed among all targets. In the limit case of $L = 0$, then E will be assigned to $E = 0$. This E value will be used here as a cross-pharmacology score. The bias, B, in the distribution of the ligand population is given by $1 - E/T$.

To illustrate the different concepts, Fig. (1) depicts the internal and external cross-pharmacology profiles for the adenosine 2B receptor (ADORA2B) when taking a distance threshold of 0.2 (ligands between two targets are considered similar if their SHED Euclidean distance is less than or equal to 0.2) and a bioactivity threshold of 7.0 (ligands between two targets are considered bioactive if their similar ligands have pK_i, pIC_{50}, or pEC_{50} values larger than or equal to 7.0 for both targets). The internal cross-pharmacology profile Fig. (1a) is composed of 1,487 similar bioactive ligands distributed across 16 GPCR targets. As can be observed, the distribution is highly biased ($B_i = 0.76$) towards the three other adenosine receptor subtypes, as reflected by a cross-pharmacology score close to 3 ($E_i =$

3.81). In comparison, the external cross-pharmacology profile Fig. (1b) contains only 60 similar bioactive ligands distributed across 16 non-GPCR targets. Whereas the maximum number of similar bioactive ligands with a GPCR target (adenosine 2A receptor) was 563, the corresponding number with a non-GPCR target (the ion channel Gamma-aminobutyric acid receptor subunit alpha-1) is 24, which gives a good impression of the significantly different degree of internal and external cross-pharmacology. In comparison with the internal profile, the external cross-pharmacology profile is less biased (B_e = 0.46) and the population of similar bioactive ligands is more evenly distributed across the targets (E_e = 8.68). This type of analysis was performed for the 180 human GPCR targets covered in this work.

Cross-Pharmacology Analysis

In an attempt to address the issue of how different similarity and bioactivity criteria affect the cross-pharmacology of targets, variations in the cross-pharmacology profiles of all GPCR targets were studied through systematic scanning of distance (d) and bioactivity ($pAct$) criteria. Seven distance criteria were applied. The tightest one (d=0.0) considered cross-pharmacology only when a "descriptor collision" between ligands bioactive to any two targets occurred. Note here that descriptor collision does not strictly correspond to structural identity since some atomic mutations may ultimately lead to exactly the same feature-pair distribution [49]. A distance window of $d \leq t$ allows for contributing to the cross-pharmacology of targets all bioactive ligands within a Euclidean distance smaller than or equal to a given threshold t. Based on previous validation studies [15], threshold t values ranged from 0.1 to a maximum of 0.6, in intervals of 0.1. Five bioactivity criteria were applied, with bioactivity windows of $pAct \geq t$, threshold t values ranging from 5 (10 μM) to 9 (1 nM), in intervals of 1 log unit (using the negative log scale). In total, all cross-pharmacology profiles obtained from the thirty-five combinations of distance and bioactivity thresholds were explored.

As an illustrative example, changes in the cross-pharmacology perception of the histamine HI receptor (H1R) upon varying distance and bioactivity thresholds are shown in Fig. (2). Two main effects, reproduced in the cross-pharmacology profiles of the other GPCRs, are worth discussing. First, as the bioactivity threshold is set towards higher potency ($pAct$ from 5 to 9), the cross-pharmacology scores (E_i and E_e) decrease significantly, meaning that fewer GPCRs, but also fewer non-GPCR targets, are related to H1R by cross-pharmacology. Notably, the level of cross-pharmacology of H1R with other GPCRs is, under all $pAct$ thresholds, clearly higher than with non-GPCR targets. In this particular case, when the bioactivity threshold changes from $pAct \geq 6.0$ to $pAct \geq 7.0$, the cross-pharmacology relative to non-GPCR targets is severely reduced, whereas the cross-pharmacology relative to GPCR remains largely unaffected. This is most indicative of the fact that as one moves towards more stringent bioactivity criteria, the probability of hitting any unwanted non-GPCR target decreases significantly. Second, as the distance threshold is enlarged to allow for similar compounds to be considered, both internal and external cross-pharmacology scores increase steadily. As can be observed, the H1R cross-pharmacology profile shrinks from 150 targets for the most relaxed criteria ($d \leq 0.2$ and $pAct \geq 5.0$) to just 19 targets for the most stringent criteria (d = 0.0 and $pAct \geq 9.0$). In this respect, more stringent criteria are likely to highlight potent promiscuous GPCR antagonists for which, more often than not, H1R antagonism is an unwanted side effect (drowsiness), for centrally acting H1R antagonists, rather than the therapeutic effect in itself (antiallergic), for peripherally acting H1R blockers [51].

Having explored the effects of the various distance and bioactivity criteria on the final perception of the cross-pharmacology of targets, the relationship between the degree of

internal and external cross-pharmacology (as measured by $E_i - E_e$) and the number of ligands considered to evaluate the respective cross-pharmacology scores (as measured by $L_i - L_e$) was revised. The results under two essentially different sets of criteria are illustrated in Fig. (3). Using a set of rather stringent criteria ($d = 0.0$ and $pAct \geq 8.0$), it is observed that class A aminergic GPCRs clearly differentiate from the rest of GPCRs Fig. (3a). On one hand, they show a comparably large bias towards wider cross-pharmacology among GPCRs than among non-GPCR targets, with 57% of class A aminergic GPCRs having $E_i - E_e \geq 5.0$ compared to the 5% and 0% of peptidic and other GPCRs, respectively. On the other hand, they also are amongst the ones showing the largest differences in the amount of ligands shared with GPCRs relative to non-GPCR targets, with 65% of class A aminergic GPCRs having $L_i - L_e \geq 500$ compared to the 6% and 0% of peptidic and other GPCRs, respectively. In particular, the histamine H1 receptor is the aminergic GPCR with the largest difference between internal and external cross-pharmacology ($E_i - E_e = 24.0$) and the adrenoceptor α_{1A} is the one with the largest difference between the amount of ligands shared with GPCRs and non-GPCRs ($L_i - L_e = 2{,}729$). Of mention is the case of muscarinic receptors (CHRMs), the only aminergic GPCRs showing negative values for the difference in cross-pharmacology scores. Close inspection of their cross-pharmacology profiles reveals that, unlike the rest of aminergic GPCRs, this is caused by the relatively low strength of the cross-pharmacology outside their own subfamily, very much in agreement with the results from recent clustering analyses of GPCR binding site sequences [22,23] and the difficulties for obtaining subtype selective compounds via an orthosteric mechanism [52].

The use of more relaxed criteria ($d \leq 0.2$ and $pAct \geq 6.0$) offers a different view of the cross-pharmacology of GPCRs discussed above Fig. (3b). The most significant change is the clear spread by some non-aminergic GPCRs towards larger negative values of the difference between internal and external cross-pharmacology scores, reflecting wider cross-pharmacology profiles for non-GPCR targets. Among them, cholecystokinin (CCKs), adenosine (ADORs) and cannabinoid (CNRs) receptors are the ones being most affected. In all cases, this is due to the fact that, while their external cross-pharmacology has expanded when similar low-potent ligands have been included in the analysis, their internal cross-pharmacology has remained mainly concentrated within the members of each subfamily. Remarkably, inclusion of similar low-potent ligands in the analysis had little effect on the cross-pharmacology of aminergic GPCRs perceived under more stringent criteria Fig. (3a) and, apart from the already noted odd muscarinic receptors, they all keep on appearing well discriminated from the rest of GPCRs in a similar region of the picture.

To summarise in a more illustrative manner some of the results obtained from the cross-pharmacology analysis of GPCRs, a cross-pharmacology network was constructed Fig. (4). The use of stringent criteria ($d \leq 0.2$ and $pAct \geq 9.0$) allowed for focussing on some of the strongest cross-pharmacology relationships identified. The central network in Fig. (4) contains GPCR targets that are linked if they share highly potent similar ligands. As can be observed, this network is composed mainly of class A aminergic GPCRs. Muscarinic receptors are however notably absent in this network, due to their previously noted inbreeding cross-pharmacology. The only non-aminergic GPCRs present in the central network are the sigma-1 receptor and all opioid and adenosine receptors.

Also added in Fig. (4) is a related network composed solely of non-GPCR targets, namely, sodium-dependent serotonin transporter (SLC6A4, also referred to as SERT or 5HTT), nischarin (NISCH), monoamine oxidases (MAOA and MAOB) and phenylethanolamine N-methyltransferase (PNMT). Targets in this network are linked because they share highly potent similar ligands with GPCR targets and, in particular, they all share ligands with the adrenoceptor α_{2C}. SERT is likely to be linked to α_{2C} due to the cross-link with the sodium-dependent noradrenaline transporter (SLC6A2, also referred to as NET); nischarin appears

to be a functional imidazoline I1 receptor [53] and related to α_{2C} antagonists that have an antihypertensive effect (e.g., moxonidine and tolazoline); MAO enzymes are known to have a catabolic role in adrenergic pathways; and PNMT is also acknowledged to have an anabolic role in adrenergic pathways (epinephrine biosynthesis). Therefore, this cluster appears to be organised around ligands with antihypertensive and antidepressive indications, which substantiates the need for stronger scrutiny with respect to unwanted side-effects but also to repurposing opportunities. This provides a good representative example of the potential implications that cross-pharmacology analyses can have for GPCR drug discovery.

Conclusions

Perhaps the main lesson learned from all the pharmacological similarity studies reported thus far is that cross-pharmacology analyses are context-sensitive, as they depend on the amount, quality, and type of pharmacological data available, the molecular descriptors used, and the similarity and bioactivity criteria applied. With respect to data, one ought to consider that in many instances the data available may reflect in part that pharmacological testing of GPCR ligands outside the realm of its own family is more the exception rather than the norm and thus, any conclusions drawn should be taken with caution and balanced with regards to data completeness [29]. With respect to descriptors, one should be warned by the different artifacts that may arise from the use of any type of mathematical representation of ligands and that can partly distort the perception of cross-pharmacology for certain (or all) targets. Finally, with respect to criteria, stringent similarity and bioactivity thresholds offer a highly focused view of cross-pharmacology, often centered in a sub-family of receptors (e.g., class A amine GPCRs). This type of analysis could be used in prophetic patents, in particular when one lacks the resources to perform extended coverage for multiple receptor types. On the other hand, more relaxed criteria (lower similarity and bioactivity thresholds) highlight out-of-target-class potential interactions, which may indeed prove relevant in the context of adverse events or drug repurposing, as well as a potential platform for lead hopping.

Major technical advancements have allowed recently the determination of the first high-resolution X-ray crystal structures of GPCRs and in the not so distant future representative structures of key subfamily members are expected to become available [54]. With this structural information in hand, the different cross-pharmacology relationships between GPCRs observed at present indirectly from pharmacological similarity analysis of bioactive ligands are likely to be rationally explained through comparative analyses of binding site structures [55], opening an avenue for the design of safer, more efficacious, GPCR ligands with customised pharmacological profiles [56].

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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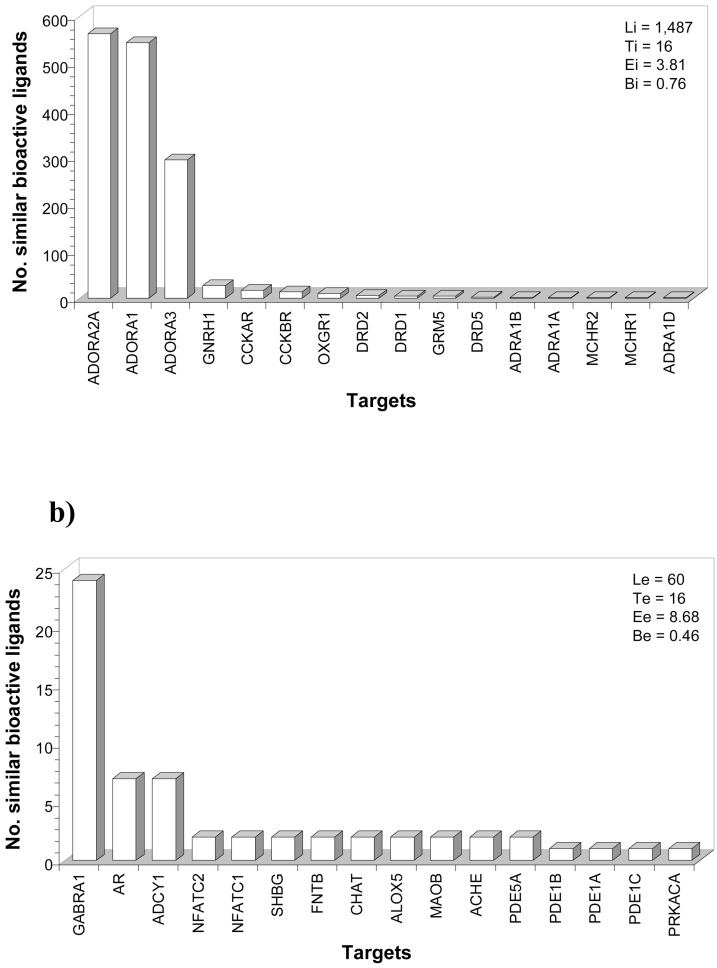

Figure 1.

Cross-pharmacology profiles among **(a)** GPCR and **(b)** non-GPCR targets for the adenosine 2B receptor (ADORA2B). All numerical bioactivity data available (pK_i, pIC_{50}, and pEC_{50}) were considered and the criteria for shared ligands were set to $d \leq 0.2$ and $pAct \geq 7.0$. See text for the definition of the different parameters (L_i, T_i, E_i, B_i and L_e, T_e, E_e, B_e). Description of gene names is available as Supplementary Material.

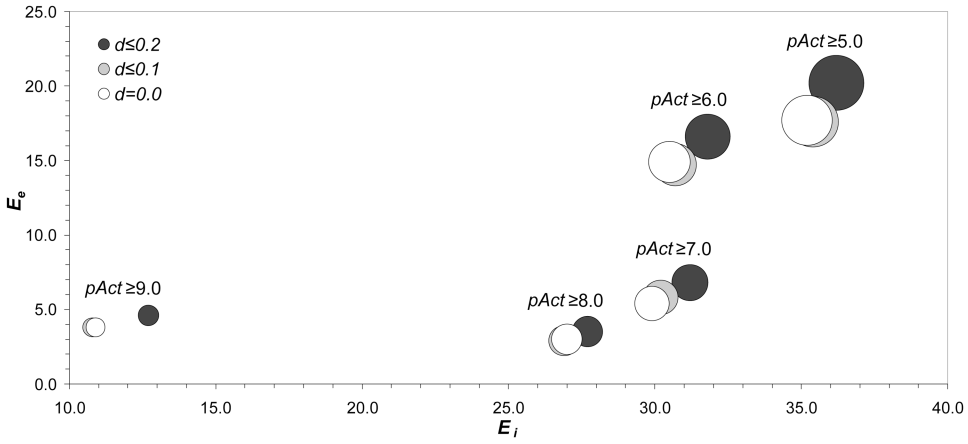

Figure 2.

Changes in the internal, E_i, and external, E_e, cross-pharmacology scores for the histamine H1 receptor (H1R) upon varying distance and bioactivity thresholds. Size of circles reflect the relative number of targets involved in the cross-pharmacology profile of H1R.

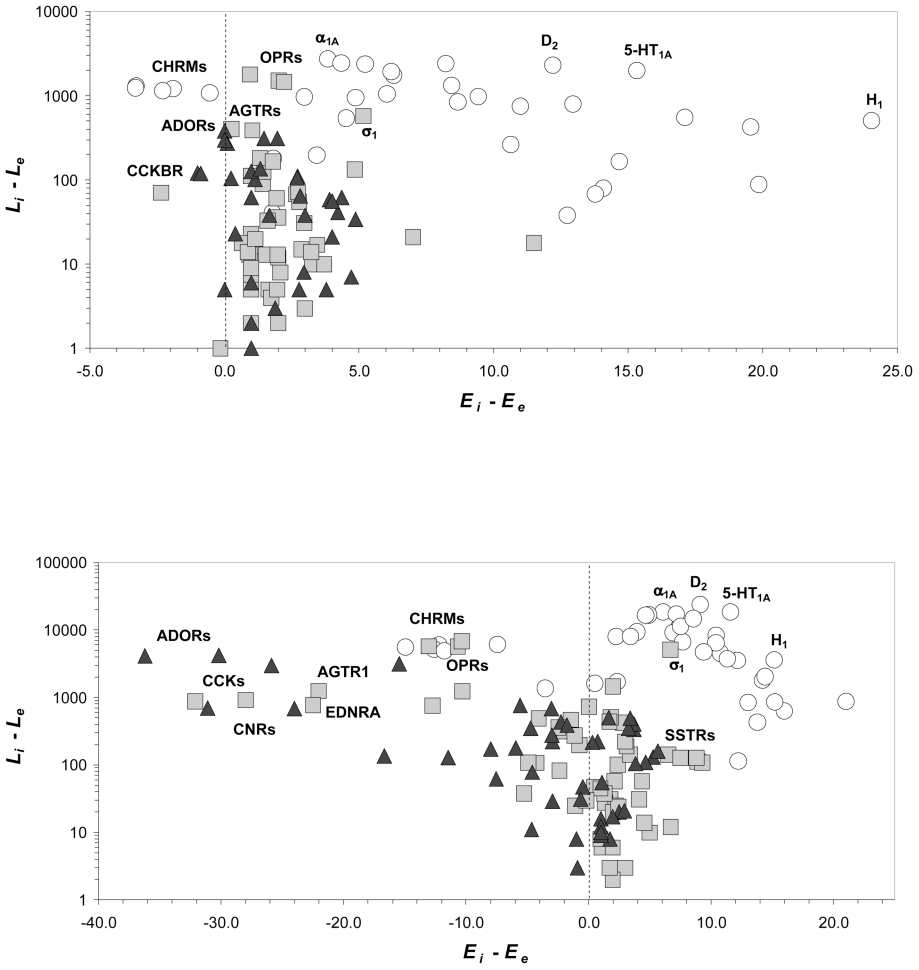

Figure 3.

Difference between GPCR and non-GPCR cross-pharmacology, $E_i - E_e$, versus difference in the number of ligands considered to evaluate the respective cross-pharmacology scores, $L_i - L_e$, under two sets of criteria: **(a)** $d = 0.0$ and $pAct \geq 8.0$ and **(b)** $d \leq 0.2$ and $pAct \geq 6.0$. Description of gene names and subfamily abbreviations is available as Supplementary Material, ○: aminergic GPCRs, □: peptidic GPCRs, Δ: other GPCRs.

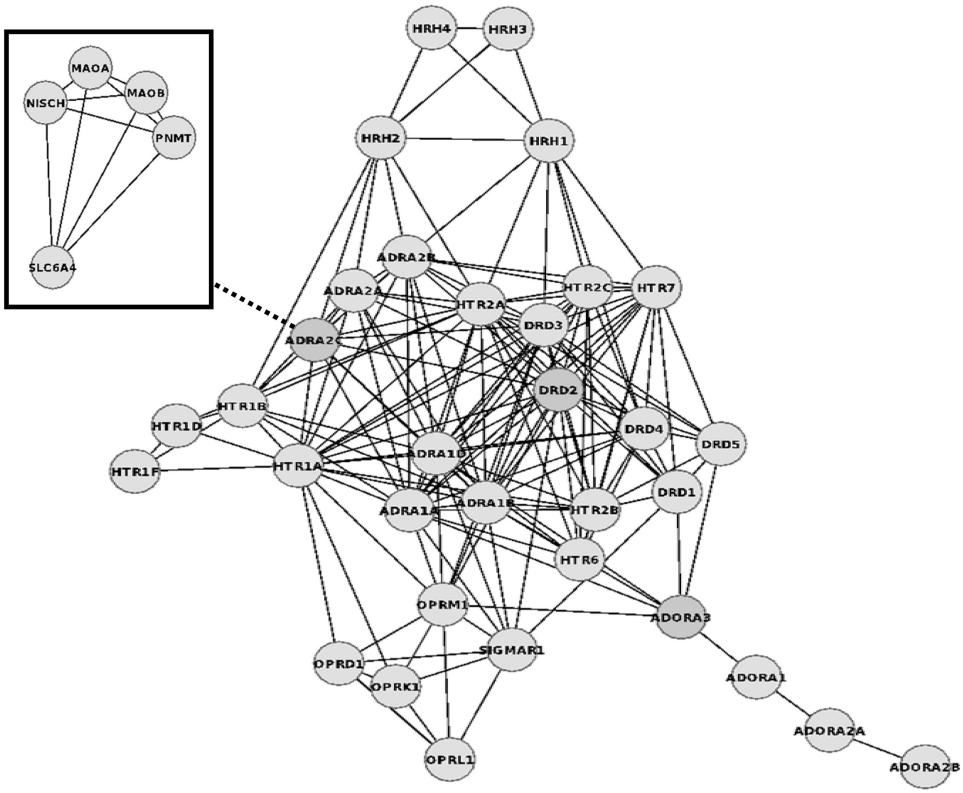

Figure 4.

Cross-pharmacology network between GPCR targets and a cluster of non-GPCR targets connected by cross-pharmacology to GPCRs. GPCR targets linked share ligands under the criteria of $d \leq 0.2$ and $pAct \geq 9.0$; non-GPCR targets linked share ligands under the same criteria with the adrenoceptor α_{2C} (marked with a dashed line). Description of gene names is available as Supplementary Material.

Table 1

Number of Ligands Interacting with GPCR Targets According to Bioactivity Data and Annotations Available from Public Sources

Database	No. Ligands	No. GPCRs	No. Interactions
Affinity Data (pKi)			
ChEMBLdb	43,440	151	98,820
PDSP	1,667	127	9,309
IUPHARdb	514	74	1,625
BindingDB	464	30	855
PubChem	16	2	16
Total unique	*44,960*	*167*	*107,638*
Additional Functional Data (pIC50, pECSO)			
ChEMBLdb	38,261	166	71,405
IUPHARdb	144	46	203
BindingDB	201	7	259
PubChem	140	7	213
Total unique	*38,531*	*172*	*71,800*
Cumulative unique	*77,123*	*191*	*170,511*
Additional Bioactivity Annotations			
hGPCR-lig	18,581	152	29,450
DrugBank	380	97	827
Total unique	*18,821*	*167*	*30,053*
Cumulative unique	*93,068*	*204*	*196,074*