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Can BDDCS illuminate targets in drug design?

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The fact that pharmacokinetic (PK) properties of drugs influence their interaction with protein targets is a principle known for decades. The same cannot be said for the opposite, namely that targets influence the PK properties of drugs. Evidence confirming this possibility is introduced here for the first time, as we show that certain protein families have a clear preference for drugs with specific PK properties. We investigate this by cross-referencing 'druggable target' annotations for >1000 US Food and Drug Administration (FDA)-approved drugs with their PK profile, as defined by the Biopharmaceutics Drug Disposition Classification System (BDDCS) criteria, and then examine the BDDCS preference for several major target protein families and therapeutic categories. Our findings suggest a novel way to conduct drug discovery by focusing PK profiles at the very early stage of target selection.

Introduction

The advance of computational procedures and their integration with improving experimental technologies have resulted in more effective risk mitigation and improved patient safety. However, the process of developing new chemical entities (NCEs) continues to include sequential steps that span several refinement cycles over multiple years. When the lead NCEs fail to meet the anticipated target properties needed for progression to the next development step, either the cycle undergoes another iteration or the project is closed. For example, lead identification and optimization remain sequential steps [1], and are often separated from target identification and validation [2]. This lack of integration between cycle steps, particularly at the level of data, information, and knowledge transfer, impacts both the costs and time of drug discovery projects. One way to improve integration is to introduce an additional identification-optimization criterion by incorporating BDDCS criteria in early drug discovery by cross-referencing BDDCS with drug target information. The BDDCS [3] can be used to estimate PK properties [4] and to forecast drug disposition [5] issues for small-molecule NCEs based on aqueous solubility (as defined by FDA criteria) and extent of metabolism [6] (Fig. 1). Its usefulness, when combined with the 'rule of 5' physicochemical property criteria for drugs [7], was discussed recently elsewhere [8]. Categorizing drugs into four BDDCS classes is an effective, easy-to-interpret tool for mapping PK properties and their relationships with other events, such as transporters effects, drug–drug interaction (DDI) risk, and so on [9,10]. The BDDCS methodology and its relevance in early drug discovery are summarized in Box 1.

Here, we report cross-referencing BDDCS categories for >1000 FDA-approved drugs to their mode-of-action (MoA) protein ('MoA_protein') targets [11], as well as other targets that might be responsible for off-target effects. DrugCentral [12], the online drug compendium, was used to extract data for major protein families, particularly those that have been extensively explored and are considered 'druggable' [13]. BDDCS classes, attributed to each drug, were assigned to the corresponding annotated MoA and off-target proteins and, thus, for the associated protein families. This mapping revealed that certain protein families have

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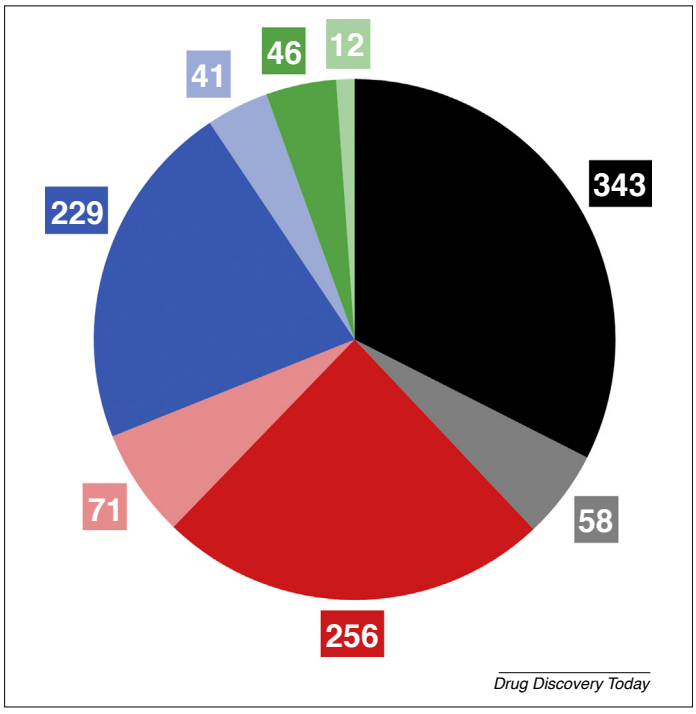

FIGURE 1

Biopharmaceutics Drug Disposition Classification System (BDDCS) drug count in the original Benet's collection (darker color) and in the Hosey's collection (lighter color). Class 1, 2, 3, and 4 are depicted in black, red, blue, and green, respectively. The four BDDCS classes are as follows: Class 1, high-solubility/high-metabolism; Class 2, low-solubility/high-metabolism; Class 3, high-solubility/low-metabolism; and Class 4, low-solubility/low-metabolism.

higher preference for a specific BDDCS class. This information could be used to better understand the influence that drug targets might exert on defining the PK properties of NCEs. In the case of protein families that exhibit a clear BDDCS-class bias, these observations can reduce the sampling space to only chemicals that match specific PK properties, potentially streamlining the lead identification and optimization process. Although the influence of PK properties on drug–target interactions (i.e., pharmacodynamics; PD) has been widely studied, here we show that some protein drug target categories have themselves a specific preference for drugs with certain PK profiles. Thus, PD also influences PK. We further discuss BDDCS and target druggability integration in more detail for specific protein families in the context of anatomic, therapeutic and chemical (ATC) classification codes and subcellular compartment location of proteins. To further verify differences in BDDCS class–MoA target category preference, we applied the Pearson's chi-squared test to each data sample discussed in this work (Figs 2–6g). For most of the examples, $P < 0.05$, suggesting that target preferences for a given BDDCS category are not aleatory (see Table S1 in the supplemental information online).

BDDCS overview

For this study, we combined a collection of >900 drugs [3], with an additional 175 drugs [4]. BDDCS Class 0 drugs were not included in this study. The number of drugs belonging to each of the four BDDCS classes is summarized in Fig. 1. During the 5-year gap that separates the two collections, there has been a 28% increase in BDDCS Class 2 drugs, compared with 17% and 18% increase for Class 1 and 3, respectively. Surprisingly, the overall under-represented Class 4 drugs also increased by 26% compared with the 2011 collection. Temporal aspects (e.g., separating the collection into pre-1998 and post-1997 by drug approval date) are also discussed below.

Druggable targets according to BDDCS

Analysis of major protein families

We examined the distribution of protein drug targets for those drugs that already have a BDDCS class annotation ('BDDCS_drug') by focusing on six major target families: G-protein-coupled receptors (GPCRs), ion channels, kinases, nuclear hormone receptors, enzymes and transporters. Here, enzymes and transporters relate to the MoA, not to the mechanism of drug disposition. We only considered those drug–protein pairs for which both MoA_protein and BDDCS_drug annotations were already present (i.e., known BDDCS_drug–MoA_protein

BOX 1

The Biopharmaceutics Drug Disposition Classification SystemBDDCS is an adaption of an FDA classification system based on the extent of intestinal permeability and solubility of the highest approved dose strength over a pH range of 1–6.4 to facilitate the waiver of *in vivo* bioequivalence studies for generic drugs and newly developed formulations of drugs previously approved by the regulatory agencies [6]. BDDCS was developed to predict drug disposition of NCEs in humans, including the major route of elimination, the relative importance of enzymes and transporters in the elimination process, and, thus, the ability to predict relevant drug–drug interactions (DDIs), the drug distribution into the brain, and the potential for toxicity, such as drug-induced liver injury (DILI) [10]. The BDDCS classification is based on the rate of membrane permeability, which distinguishes with remarkable accuracy NCEs that will be primarily eliminated by metabolism versus renal and biliary excretion of unchanged drug, and a simple 0.3 mg/ml solubility cut-off to distinguish high and low-solubility NCEs over the pH range 1–6.8, given that the highest approved dose strength will not be known early in drug development [3].

In the BDDCS system, with their high permeability rate (extensively metabolized), highly soluble Class 1 NCEs can be expected to be extensively absorbed from the gastrointestinal tract, primarily eliminated by metabolism, transporter effects will be clinically insignificant, the NCE will readily pass into the brain, and DILI potential will be low and well predicted by preclinical animal studies. BDDCS Class 2 will show a high membrane permeability rate, poorly soluble NCEs will also be highly absorbed and primarily eliminated by metabolism, but transporter effects can be rate limiting and cannot be ignored. DILI is primarily seen with BDDCS Class 2 NCEs and preclinical animal and *in vitro* studies might not be predictive. These NCEs, if substrates for efflux transporters, will not exhibit extensive central effects. BDDCS Class 3 and 4 NCEs will exhibit poor membrane permeability rate and will require transporters to achieve druggable PK characteristics. They will be primarily eliminated unchanged in the urine and bile, and metabolic DDIs will not be a major source of concern.

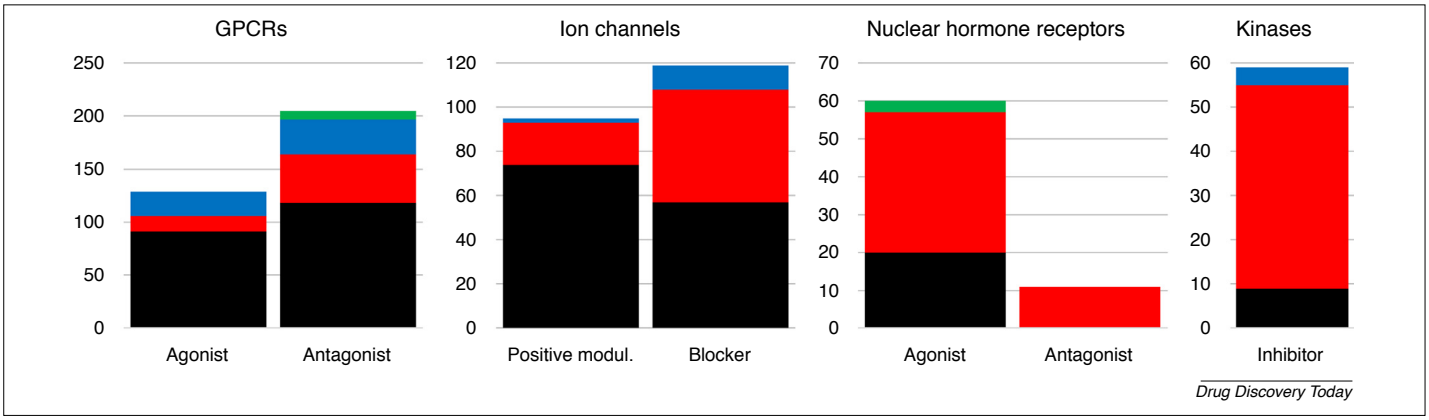

FIGURE 2

Biopharmaceutics Drug Disposition Classification System (BDDCS) class distributions for the major target families. On each plot, the vertical axis reports the number of drug–target annotations and the horizontal axis displays the mode of action (MoA). Classes 1, 2, 3, and 4 are depicted in black, red, blue, and green, respectively.

pairs). MoA proteins were grouped by the most frequently annotated mechanism of action (e.g., agonist, antagonist, etc.) of the associated drugs, and displayed with one of four colors, depending on the BDDCS class of the corresponding drugs. The result of this analysis for GPCRs, ion channels, nuclear hormone receptors, and kinases is summarized in Fig. 2. The numbers on the vertical axis are drug–target annotation counts, rather than drug counts or protein counts. Supporting data are provided in Table S2 in the supplemental information online.

Uneven class distributions, which emerge when comparing GPCRs and ion channels against kinases and nuclear receptors, allow us to make some observations regarding drug lipophilicity and protein subcellular location. For GPCRs and ion channels, BDDCS Class 1 drugs (high solubility, high metabolism) dominate, whereas nuclear hormone receptors and kinases appear to be targeted mostly by BDDCS Class 2 (low solubility, high metabolism) drugs (see Box 1 for additional details on BDDCS). The data suggest that certain 'druggable' target families have a clear preference for a specific BDDCS class and, according to Pearson's chi-squared test, these preferences are statistically significant ($P = 2.2*10^{-16}$, Chi-squared = 147.62; see also Table S1 in the supplemental information online).

In our opinion, these differences can primarily be explained by the subcellular location of these proteins: GPCRs and ion channels are located primarily on the cell membrane, and appear to be better targeted by highly soluble, BDDCS Class 1 drugs. By contrast, kinases and nuclear receptors have an intracellular location and are targeted by the less soluble, more lipophilic Class 2 drugs (i.e., drugs that are required to cross the cell membrane to exert their therapeutic action). This observation does not imply that low solubility is the most important MoA of the drug–target interaction where kinases and nuclear receptors are concerned. Indeed, additional aspects need to be considered with respect to the specific hydrophilicity/hydrophobicity profile of the binding site of the individual target. Nevertheless, in accordance with these findings, it appears prudent to incorporate FDA solubility as one of the design factors when developing NCEs for these target families.

Analysis of protein subfamilies

With respect to enzymes and transporters, BDDCS classes are more evenly distributed (data not shown), which is not surprising: Transporter active site(s) can be reached by both hydrophilic (from extracellular space or cytoplasm) and lipophilic (through the lipid bilayer) drugs [14]. Concerning enzymes, their mechanistic, substrate, and cellular location diversity (compared with kinases) is greater and, therefore, BDDCS categories show less specificity. Given that we did not find a clear BDDCS class preference for enzymes or transporters, we interrogated more specific protein subfamilies, as summarized in Fig. 3. Instances where the count of BDDCS_drug–MoA_protein was <5 were excluded for clarity. Supporting data are provided in Tables S3 and S4 in the supplemental information online.

Only poorly metabolized (designated here as low-metabolism) drugs are annotated as carbonic anhydrase (CAs) inhibitors (seven BDDCS Class 3 and four BDDCS Class 4 drugs; see also Fig. 3a and Tables S1 and S3 in the supplemental information online). In terms of cellular compartment location, seven CAs are cytosolic and four are membrane associated. With respect to our observations, Class 3 and Class 4 drugs target both cytosolic (CA1, CA2, and CA7) and membrane-associated (CA4 and CA12) proteins. Low-metabolism drugs (BDDCS Class 3 and 4) are expected to have a low passive permeability [3] (Box 1). Hence, they are likely to access membrane-bound proteins, but not cytosolic proteins, by passive diffusion only. This might explain why membrane-bound CAs are targeted by low-metabolism drugs. How do Class 3 and 4 drugs reach cytosolic CAs? We hypothesize that, to overcome their low passive permeability, uptake transporters might be involved. However, the only evidence to support this hypothesis is a study in which two CAs inhibitors, methazolamide and acetazolamide, Class 3 and Class 4 drugs, respectively, were reported to have an affinity with two organic anion transporter proteins (OAT1 and OAT3) [15].

Most drugs targeting solute carrier 6A (SLC6A) transporters are BDDCS Class 1 (high metabolism, high solubility; see Fig. 3b, and Tables S1 and S3 in the supplemental information online). SLC6A transporter family proteins, which are involved in, for

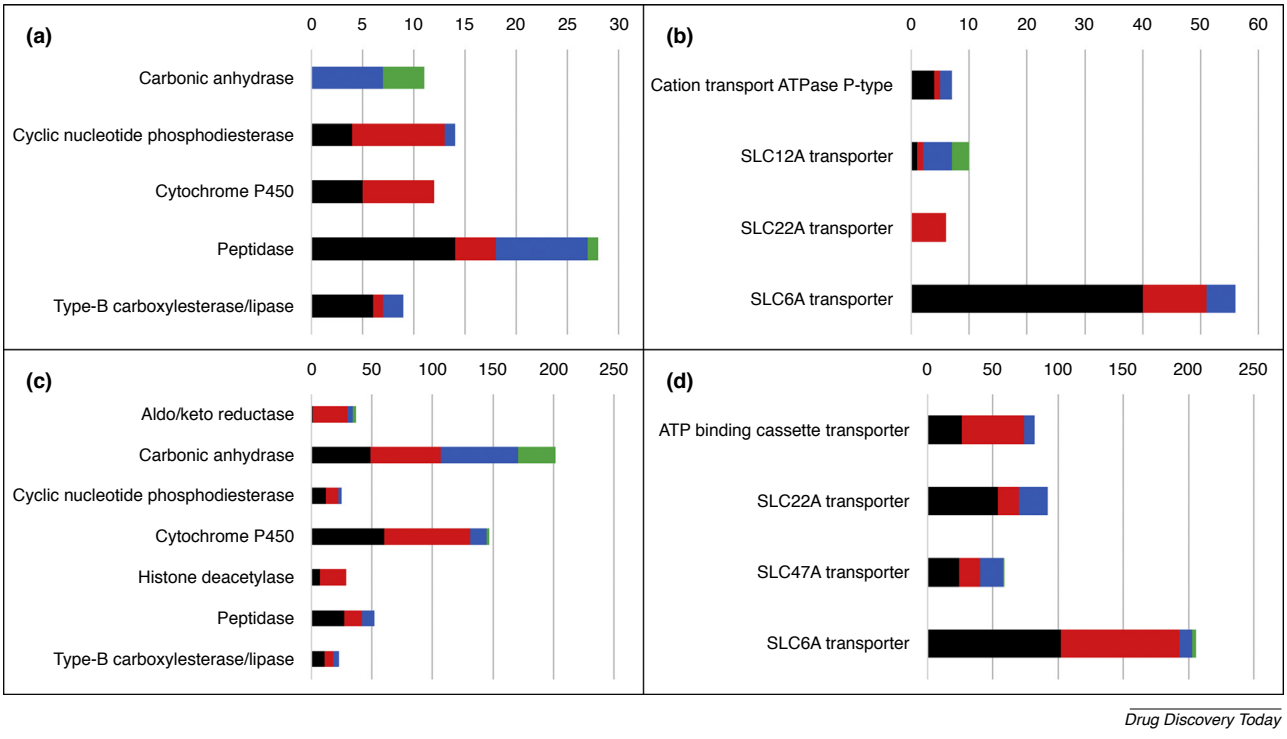

FIGURE 3

Biopharmaceutics Drug Disposition Classification System (BDDCS) class distributions for enzymes and transporters subfamilies. **(a)** Drug–target records with annotated mode of action (MoA) for enzymes. **(b)** Drug–target records with annotated MoA for transporters. **(c)** Drug–target records without annotated MoA for enzymes. **(d)** Drug–target records without annotated MoA for transporters. On each plot, the horizontal axis reports the number of drugs and the vertical axis displays the subfamily name. Classes 1, 2, 3, and 4 are depicted in black, red, blue, and green respectively.

example, transporting GABA and monoamine (dopamine, serotonin, and norepinephrine) neurotransmitters, are expressed on both pre- and postsynaptic membranes in the central nervous system (CNS) and act as neurotransmitter reuptake pumps. These are well-characterized drug targets for several neurological and psychiatric disorders, such as Parkinson's disease, epilepsy, and depression [16]. Preference for BDDCS Class 1 drugs could be explained by the requirement that SLC6A drugs should be active at the synaptic interface, which is similar to the extracellular matrix, and possibly by the lack of clinical effect of efflux transporters on these drugs. Efflux transporters represent a major xenobiotic elimination route for chemicals that pass the blood–brain barrier, but do not influence Class 1 drugs, probably because of transporter saturation effects caused by the high degree of passive permeability and solubility of Class 1 drugs. According to our interpretation, drugs belonging to all other BDDCS categories, which do not exhibit the same permeability as Class 1 drugs, could more effectively be removed from the brain and, therefore, would not be able to achieve a meaningful blockade on SLC6A transporters. The fact that BDDCS Class 1 drugs are optimal for reaching CNS targets has been noted previously [17].

To compare BDDCS class relevance when examining clinical and *in vitro* data, we explored situations where a clear mechanism of action was not reported [11] for both enzymes (Fig. 3c, and Tables S1 and S4 in the supplemental information online) and transporters (Fig. 3d, and Table S4 in the supplemental information online). For carbonic anhydrases, 'non-MoA' records show a relatively even distribution of BDDCS classes. The fact that only BDDCS Classes 3 and 4 have a known MoA (Fig. 3a) might be illustrative of the situation in which measured *in vitro* activity might not be relevant *in vivo* [18]. We can reach similar conclusions for SLC6A transporters, because the dominance of Class 1 drugs, which is relevant for MoA, shifts towards an even Class 1–Class 2 distribution where *in vitro* data are concerned. Therefore, it appears prudent to conclude that situations where a specific BDDCS/MoA category is dominant can inform the likelihood of clinical success for NCE development.

In Fig. 3b, we also show that SLC12A transporter inhibitors are preferentially targeted by BDDCS Classes 3 and 4 (i.e., low metabolism drugs), similar to CAs. SLC12A transporters are expressed on renal cell membranes and are relevant in renal diseases [19]. According to its definition, 'low extent of metabolism' often implies that a high fraction of the drug is excreted unchanged in the urine (i.e., renal clearance has a major role in their elimination). In this case, the drugs reach the organ where their intended drug targets are specifically expressed. In another example, SLC22A transporter inhibitors show preference for BDDCS Class 2 drugs. SLC22A are organic anion transporters expressed mainly in kidneys [20]. SLC22A12 (URAT1), which is expressed on the apical membrane of the proximal tubular cells, mediates the reabsorption of urate from primary urine into plasma. However, an abnormally high plasma level of urate, or hyperuricemia, causes

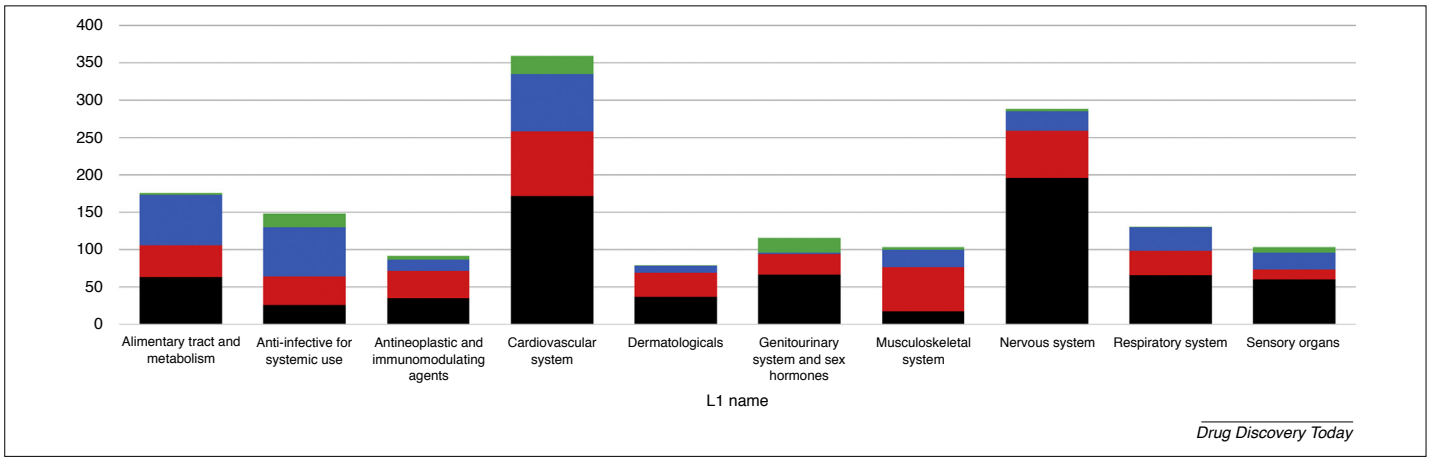

FIGURE 4

Biopharmaceutics Drug Disposition Classification System (BDDCS) drug distributions for each anatomic, therapeutic, and chemical (ATC) Level 1. Classes 1, 2, 3 and 4 are depicted in black, red, blue, and green, respectively.

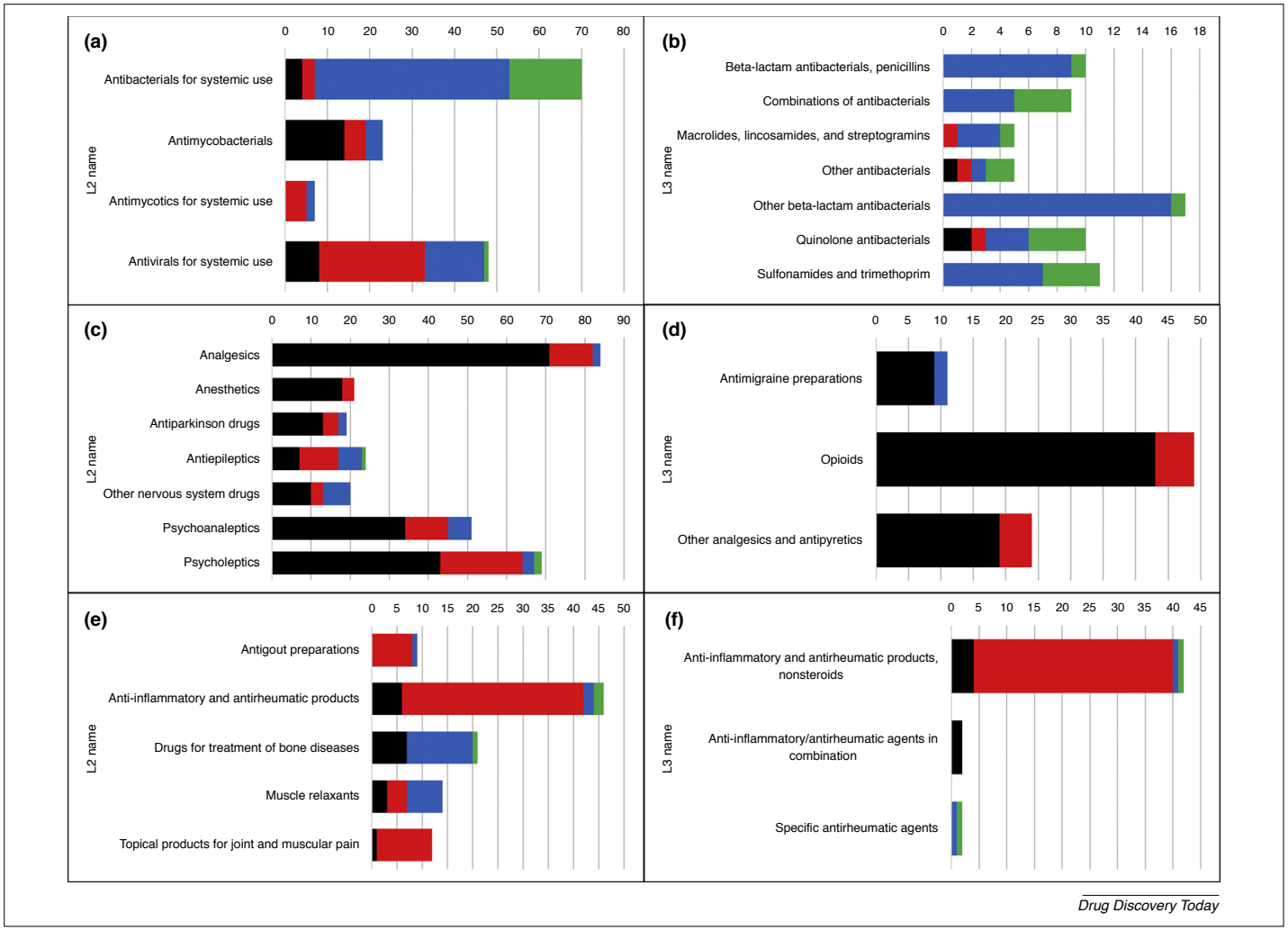

FIGURE 5

Biopharmaceutics Drug Disposition Classification System (BDDCS) distribution plots for: anti-infectives for systemic use drugs, **(a)** anatomic, therapeutic, and chemical (ATC) Level 2 and **(b)** ATC Level 3; nervous system drugs, **(c)** ATC Level 2 and **(d)** ATC Level 3; musculoskeletal system drugs, **(e)** ATC Level 2 and **(f)** ATC Level 3. On each plot, the number of drugs is reported. Classes 1, 2, 3, and 4 are depicted in black, red, blue, and green, respectively.

gout. The Class 2 drug lesinurad is approved to treat gout by specifically blocking the URAT1 transporter. The SLC22A transporters preference for Class 2 low solubility drugs (Fig. 3b) over Class 1 and 3 high-solubility drugs (Fig. 3d) could be explained by the location of these target: high metabolism, low-solubility drugs (Class 2) might have an optimal PK profile, in contrast to Class 1 drugs, which undergo hepatic clearance, or Class 3 drugs, which require basolateral uptake to reach URAT1 or might involve drug–drug interactions.

Temporal analysis

Using the date of first launch for each drug, we examined the influence of temporal trends on the distribution of BDDCS_drug–MoA_protein pairs for GPCRs, ion channels, kinases, and nuclear hormone receptors (Table S5 and Figs S1 and S2 in the supplemental information online). We separated the data into 'drugs approved before 1998' or 'drugs approved after 1997' based on the year (1997) when the 'rule of 5' landmark paper [7,21] was first published, as previously detailed [22]. All oncology drugs that act as kinase inhibitors (except one) were approved after 1997. Most (53) BDDCS_drug–nuclear hormone receptor pairs are for drugs approved before 1998, compared with 23 after 1997. Therefore, we discuss GPCRs (234 pre-1998 and 90 post-1997) and ion channels (170 pre-1998 and 46 post-1997), respectively. Although BDDCS Class 1 drugs remain the dominant category overall for both GPCRs and ion channels, there is a slight increase in BDDCS Class 2 drugs for GPCR antagonists launched after 1997 (Fig. S1 in the supplemental information online), and a net increase in BDDCS Class 3 drugs for both GPCR agonists and ion channel positive modulators and blockers launched after 1997 (Figs S1 and S2 in the supplemental information online), respectively. BDDCS Class 1 drugs are less dominant in post-1997 drugs, both for GPCRs and Ion Channels. However, 'high-solubility' drugs (Class 1 and 3) remain dominant in the second time period (60 out of 90 BDDCS–GPCR drug pairs; and 33 out of 46 BDDCS–ion channel drug pairs, respectively).

Therapeutic categories according to BDDCS

To further explore the relationship between drug categories and BDDCS classes, we cross-referenced BDDCS-annotated drugs with ATC codes extracted from DrugCentral. The ATC Classification System classifies each drug based on five different levels [23]. Briefly, the first ATC level is the anatomical component (organ or system of the human body) in which the drug acts; the second level indicates the therapeutic purpose; the third level describes pharmacological action; the fourth level is the

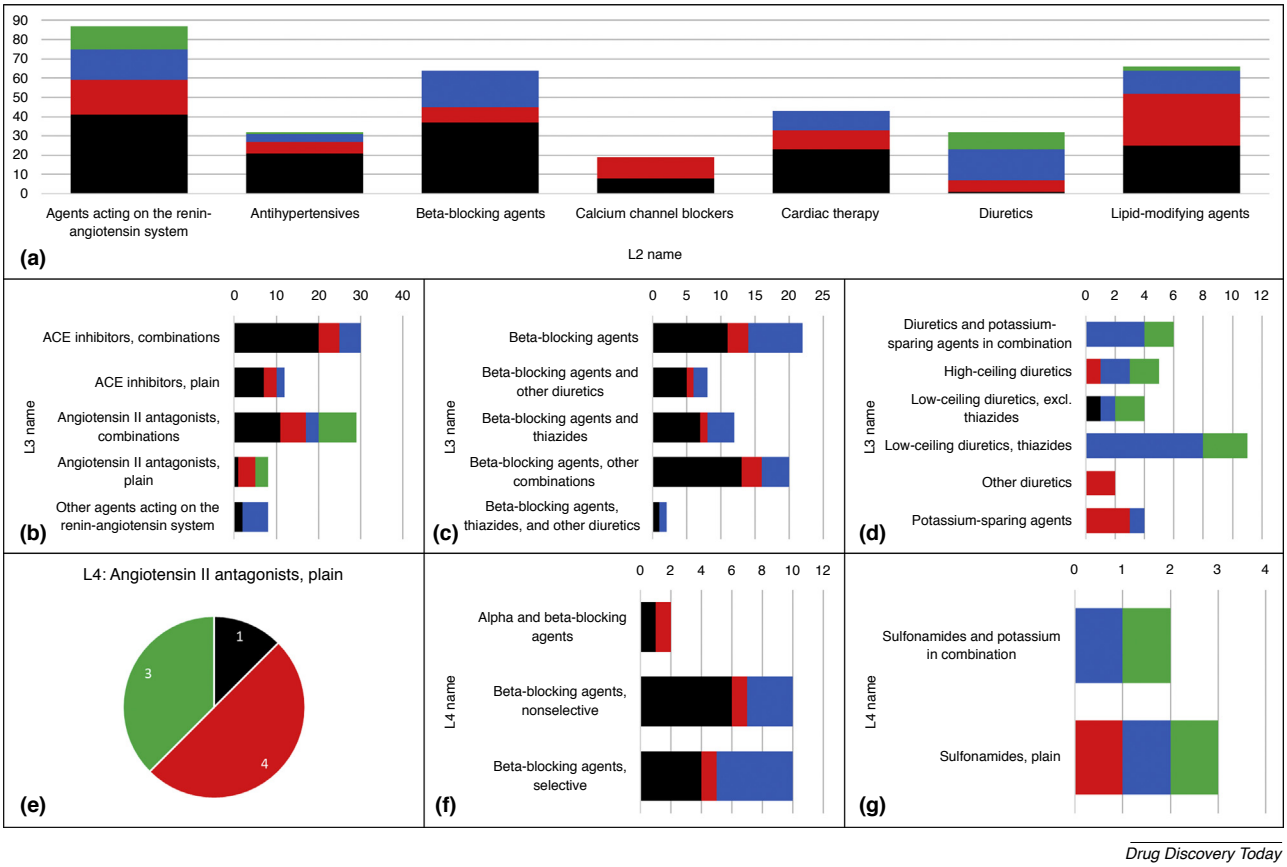

FIGURE 6

Biopharmaceutics Drug Disposition Classification System distribution for cardiovascular system drugs, as classified by anatomic, therapeutic and chemical (ATC) levels. **(a)** BDDCS distribution at ATC Level 2 for cardiovascular system drugs. **(b)** Level 3 distributions for agents acting on the renin-angiotensin system. **(c)** Level 3 distributions for beta-blocking agents. **(d)** Level 3 distributions for diuretics. **(e)** Pie chart of the unique ATC Level 4 code of angiotensin II antagonists. **(f)** Level 4 distributions for beta blocking agents (same name as for Level 3). **(g)** Level 3 distributions of high-ceiling diuretics. On each plot, the number of drugs is reported. Classes 1, 2, 3 and 4 are depicted in black, red, blue, and green, respectively.

chemical class of the drug in question; and the fifth level is the actual substance. A drug can have multiple ATC codes when it has multiple therapeutic uses. This can either refer to a different posology or to a different administration route. Examining the distribution of BDDCS classes from a pharmacological point of view, as summarized by ATC codes, can provide additional information regarding the BDDCS_drug–MoA_protein relationships, particularly if specific pharmacological subcategories appear to have a dominant BDDCS class. Thus, such information could be used to guide the drug discovery process for cases involving that specific pharmacology by focusing on a specific BDDCS class, or at least on a specific PK category, during the early stages of the process.

Drug counts, grouped by BDDCS, for each ATC Level 1 group are shown in Fig. 4. We excluded groups with <50 drugs for simplicity. Figure 4 suggests that certain BDDCS classes have a preference for specific anatomic components or organs; some of these are expected (e.g., Class 1 for CNS drugs), whereas others are not (e.g., Class 2 drugs for the musculoskeletal system). This begs the question whether this preference is conserved for lower ATC levels.

To address this issue, we focused on those cases showing an uneven distribution among BDDCS classes. Most 'anti-infectives for systemic use' drugs are low metabolism (Classes 3 and 4). By expanding ATC Level 1 into Level 2 (Fig. 5a), Classes 3 and 4 pertain mostly to antibacterials (antibiotics), whereas most antivirals are BDDCS Class 2, and some are Class 3. As we expand into ATC Level 3 (Fig. 5b), both Class 3 and 4 continue to be present in each subcategory. When developing new antibiotics, it appears prudent to give preference to molecules exhibiting BDDCS Class 3 properties, because there are significantly fewer Class 4 drugs, which suggests that the approval process would be more problematic. Their low extent of metabolism could be explained by the fact that many such antibacterials inhibit the formation of crosslinks between bacterial cell wall peptides by blocking DD-transpeptidase, an enzyme that is accessible from the periplasm [24]. Regarding antivirals, BDDCS class assignment might be influenced by the life-cycle stage of the targeted virus. Before viral entry, cell membrane proteins would be targeted (BDDCS Class 3), whereas cytoplasmic proteins or nucleic acids would be targeted at later stages (BDDCS Classes 1 and 2).

CNS-acting drugs are typically high metabolism (Class 1 or 2), and often high solubility as well (Class 1 only). As stated earlier, BDDCS Class 1 drugs have high brain permeability, which makes them ideal for CNS targets. Class 1 drug preference is also conserved over pharmacological subcategories (Fig. 5c,d). Musculoskeletal system drugs are equally interesting, because anti-inflammatory drugs are prevalently Class 2 (Fig. 5e,f). These drugs mainly target cyclooxygenases 1 (PTGS1) and 2 (PTGS2), which have intracellular locations on the Golgi apparatus and endoplasmic reticulum, and in mitochondria, respectively.

Contrary to the previous examples, drugs acting on the cardiovascular system have a more even BDDCS distribution. At the ATC Level 2, there are cases where high solubility (Class 1 and 3) prevails (e.g., for beta blocking agents) and where low metabolism prevails (e.g., for diuretics; Class 3 and 4). There is no clear separation for agents acting on the renin-angiotensin system (Fig. 6a). For beta-blockers and diuretics, ATC Level 3

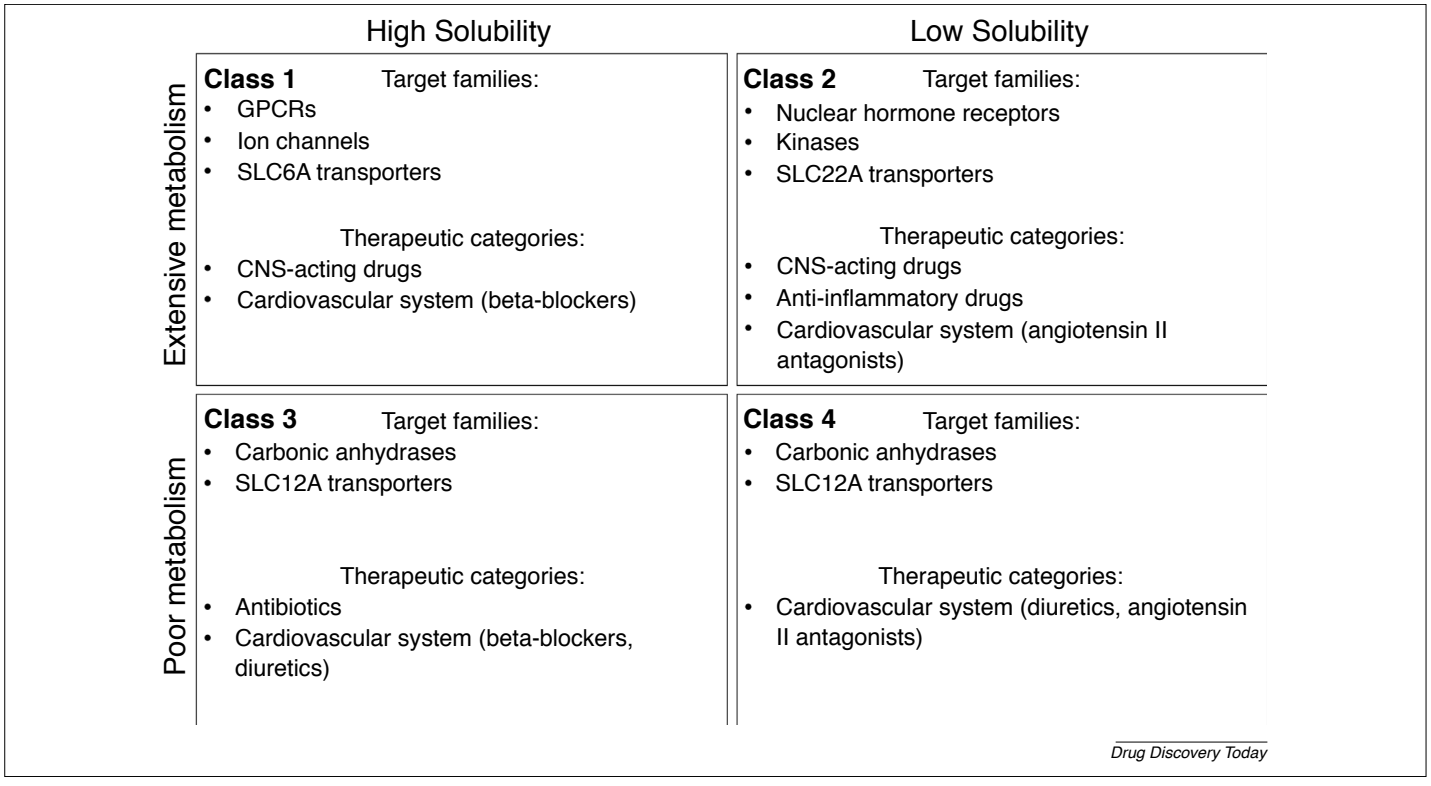

FIGURE 7

Biopharmaceutics Drug Disposition Classification System (BDDCS) class preference for certain protein families and therapeutic categories. Abbreviations: CNS, central nervous system; GPCR, G-protein-coupled receptor; SCL, solute carrier.

(Fig. 6c,d) and Level 4 (Fig. 6f,g) do not provide additional information, because the prevailing classes have a similar distribution. However, ATC Level 3 provides additional information for renin-angiotensin system inhibitors (Fig. 6b). Yet, there are some categories for which even Level 4 shows a nearly equal BDDCS class distribution. Angiotensin receptor AT1 blockers are such an example (Fig. 6e): Class 2 drugs are irbesartan, losartan potassium, tasosartan, and telmisartan, whereas Class 4 drugs are candesartan cilexetil, eprosartan, and valsartan; olmesartan medoximil is Class 1. This finding is in agreement with the different PK profiles for these drugs [25].

Concluding remarks and future directions

Here, we examined the relationship between BDDCS categories for >1000 drugs and their annotated MoA protein targets. The BDDCS distribution shows clear specificity for certain 'druggable' target families or subfamilies, as well as for specific pharmacological (ATC) drug categories. These results can often be rationalized in terms of protein tissue or compartment location. Although this work is primarily descriptive (i.e., lacking a complete exploration across all proteins and pharmacological categories), there appears to be clear evidence that certain protein families are preferentially targeted by one, sometimes two BDDCS classes. The evidence is supported by Pearson's chi-squared tests (Table S1 in the supplemental information online). The preference for Class 1 drugs of GPCRs and ion channels, as opposed to the preference for Class 2 drugs of kinases and nuclear receptors, might be indicative of the way these target families 'select' drugs with different solubility and hydrophobicity. The requirement for high FDA solubility, further substantiated by the temporal analysis, is clearly shown for GPCR- and ion channel-acting drugs. Furthermore, CAs and SLC12A transporters are preferentially targeted by low metabolism drugs (Class 3 and 4), whereas Class 1 drugs are better suited to target SLC6A transporters and Class 2 drugs are better SLC22A transporters, respectively. The ATC drug classification system can also be used to show that, for certain therapeutic categories, a BDDCS Class is dominant. These findings are summarized in Fig. 7.

We believe that the concepts introduced here could lead to the development of an integrated 'discovery' and 'optimization' system that supports parallel property optimization that might significantly influence the drug design process. Indeed, these findings might help medicinal chemists by giving preference on lead series, or scaffolds, that meet specific PK profiles at the step of hit identification, and certainly lead optimization. To make this type of analysis available to the scientific community, we plan to create a web-app that medicinal chemists could use to study the BDDCS distribution for protein families or therapeutic drug categories of interest. The analysis described here could be extended in several ways. Future efforts could aim to explore in more detail the location of protein targets and how BDDCS classes are distributed. Furthermore, the influence of the nature of the protein (drug target) binding sites on the BDDCS–target preferences described herein could be examined by pharmacophore analyses of the known (e.g., X-ray crystallography) binding pockets for drugs with BDDCS–MoA target annotations.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.drudis.2019.09.021.

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