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Development and Testing of Druglike Screening Libraries

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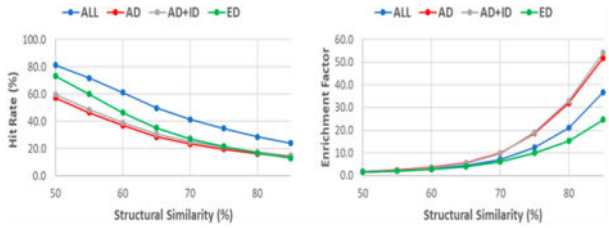
Abstract

Although significant advances in experimental high throughput screening (HTS) have been made for drug lead identification, *in silico* virtual screening (VS) is indispensable owing to its unique advantage over experimental HTS, target-focused, cheap, and efficient, albeit its disadvantage of producing false positive hits. For both experimental HTS and VS, the quality of screening libraries is crucial and determines the outcome of those studies. In this paper, we first reviewed the recent progress on screening library construction. We realized the urgent need for compiling high-quality screening libraries in drug discovery. Then we compiled a set of screening libraries from about 20 million druglike ZINC molecules by running fingerprint-based similarity searches against known drug molecules. Lastly, the screening libraries were objectively evaluated using 5847 external actives covering more than 2000 drug targets. The result of the assessment is very encouraging. For example, with the Tanimoto coefficient being set to 0.75, 36% of external actives were retrieved and the enrichment factor was 13. Additionally, drug target family specific screening libraries were also constructed and evaluated. The druglike screening libraries are available for download from https://mulan.pharmacy.pitt.edu.

Graphical Abstract



1. INTRODUCTION

It is a challenging task to turn a new chemical compound into a real drug. First, a developable drug lead targeting the right protein or nucleic acid receptor must be discovered.

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Supporting Information

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Tables S1–S11 and Figures S1–S4 mentioned in the text (PDF)

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The screening libraries developed in this work are available to download from https://mulan.pharmacy.pitt.edu.

A developable drug lead is then optimized to improve its activity of inhibition, selectivity against other targets, and its absorption, distribution, metabolism, excretion (ADME), and toxicity properties prior to the clinical trials.

Virtual Screening.

In modern drug discovery, high throughput screening is becoming an indispensable approach to identify drug leads. Compared to HTS, virtual screening is another technique which is complementary to experimental HTS. Although frequently produce false positives, VS is widely used because of its unique features, such as drug target-relevant, cheap, and efficient.

Virtual screening is a widely used technique to enrich developable drug leads in computer-aided drug design. A commonly used strategy in VS is the so-called hierarchical screenings,[1,2] in the spirit of achieving both accuracy and efficiency. The basic idea of hierarchical screenings is to apply multiple filters to enrich the hits sequentially, with the efficient filters applied in the early stages and the more advanced and time-consuming filters applied in the later stages. Only the hits of the current screening enter the next round. The most efficient filters include those based on 2D-substructure, molecular fingerprints, and molecular shapes; less efficient filters include pharmacophore models and regular molecular docking; the most advanced filters include molecular docking using accurate scoring functions (such as the Glide extra precision docking scoring function[3]) and free energy-based methods (such as MM/GBSA and MM/PBSA[4–8]). We have successfully applied this strategy to identify drug leads for HIV-1 RT.[1] An alternative screening strategy is parallel screening,[2] where a set of docking screenings are performed in parallel using several complementary methods and the best hits ranked according to each individual method are combined for biological testing.

Virtual Screening Filters.

The VS filters are a key component of VS studies, which can loosely be classified into two categories depending on if the drug target information is used or not. The ligand-based screenings utilize known bioactives to define queries for VS; on the contrary, the structure-based screenings measure how tight a compound interacts with the drug target at the binding site. Molecular docking is the most widely used structure-based filter. Of course, structure-based pharmacophores[9] and *de novo* design[10] also rely on the structure information on protein or nucleic acid targets.[2]

The ligand-based filters, which are typically much cheaper compared to the structure-based ones, include substructures,[11,12] topological indexes,[13] molecular fingerprints,[14] shape[15] and electrostatic[16] properties, and pharmacophore models.[17,19] Li et al. developed a shape-based method called USR (ultrafast shape recognition) to identify potential drug leads. In about 2 s, 93.9 million 3D conformers expanded from 23.1 million purchasable molecules are screened.[19] We recently constructed a set of molecular fingerprint-based artificial neural network (FANN) models for virtual screening of large diverse databases.[20] Using 1361 ligands of cannabinoid receptor 2 as the training set, a FANN-QSAR model was derived and applied to screening a large NCI database to identify novel compounds bound to the CB2 receptor. The screening led to the discovery of several compounds which have CB2 binding affinities ranging from 6.70 nM to 3.75 μM.

Drug likeness is widely used to filter out those compounds unlikely to be drugs. Lipinski's "Rule of 5" is the most famous drug likeness filter ever applied in virtual screening. Other popular molecular properties for characterizing drug likeness include polar surface area (PSA) and polar molecular volume (PMV). It was reported that 90% of orally bioavailable non-CNS drugs had a PSA below 120 $Å^2$, and the criterion was dropped to 80 $Å^2$ for CNS drugs.[21] QSAR models can also serve as a filter in VS.[22–25] A QSAR-based filter is widely applied in the drug lead optimization phase.

Screening Libraries.

Another key component of VS and experimental HTS is the screening library construction. There are two types of screening libraries to be applied in different phases of drug discovery. In the lead-identification phase, one wants the screening compounds structurally diverse so that novel drug leads can be identified; while in the sequential lead-optimization phase, one wants the screening compounds structurally akin to the drug lead to facilitate the construction of the structure–activity relationship. Ideally, the compounds in both kinds of libraries are druglike. Even though the current screening compounds only occupy a very tiny fraction of the entire chemical space which is estimated to be more than 10^{60} molecules, the registered compounds are more than 27 million.[26,27] For example, the ZINC database[28] collects more than 18 million commercially available compounds that satisfy Lipinski's Rule of 5[29] at the time this paper was being written. It is not practical to screen all of them for a drug target both in the *in vitro/in vivo* HTS experiments and in the *in silico* virtual screenings. Therefore, screening compound libraries, which only collect fractions of the total available compounds, must be constructed for either HTS or VS studies. The outcome of an experimental HTS or a VS study strongly depends on the quality of the screening library.

There are a lot of compound libraries which are widely used in VS studies. The following are only some representatives: ZINC database,[28] Pubchem,[30,31] NCI open database,[32] ChemDiv (www.chemdiv.com), Specs (www.specs.net), Chembridge (www.chembridge.com), ChemSpider, ChemNavigator (http://www.chemnavigator.com), etc. Most of the screening libraries collect a great number of compounds. Except for the most efficient filters, it is impractical to screen all the entries.

To construct diverse screening libraries, molecular diversity must be evaluated. A variety of molecular descriptors are applied to define a diversity metric, such as molecular fingerprints,[14] topology index,[13] and physicochemical properties.[33] Recently, Koutsoukas et al. benchmarked a set of 13 molecular descriptors in assessing the diversity of chemical libraries.[34] The descriptor performance was assessed by the coverage of bioactivity space. It was found that Bayes Affinity fingerprints[35] and ECFP4[14] outperform others by retrieving more actives than random sampling.

Diverse screening libraries are then constructed by removing redundancy using a set of algorithms, including the dissimilarity-based method, cell-based method, cluster-based method, and optimization-based method.[36,37] Principal component analysis was routinely applied to decrease the dimensionality of descriptor matrix and to extract the main variation of the descriptor data.[38] We recently developed a Compound Library Acquisition and

Prioritization (CAP) algorithm to construct diverse screening libraries.[37] The CAP algorithm was established using the Euclidean distances of the BCUT[39] chemical space. It was demonstrated that the CAP-selected subsets of an existing in-house screening library have their overall chemical diversities enhanced, as measured by using chemistry-space cell partition statistics and a similarity index.

Schneider et al. applied a self-organizing map (SOM) to construct diverse screening libraries.[40] According to the principle of SOM, "neuron vectors" are positioned in the data space such that the distribution of data points is represented by the distribution of neuron vectors. A training procedure, such as unsupervised learning, is needed to achieve this. SOMs cover diverse fields of drug discovery, such as scaffold-hopping, repurposing, and screening library design. Noeske et al. developed a SOM by using pharmacophore descriptors to map druglike chemical space.[41] Naderi et al. recently presented a graph-based approach for constructing target-focused screening libraries.[42] They developed an exhaustive graph-based search algorithm to conduct virtual new compound syntheses by reconnecting the building blocks according to their connectivity patterns. However, the acquisition of the virtual compounds may be an issue. Sukuru et al. presented an approach based on extended connectivity fingerprints to carry out diversity selection on a per plate basis.[43] They found that a fingerprint-diverse subset of 250 K compounds selected from a 4-fold larger screening deck achieved significantly higher hit rates for most of the screenings. Recently, Horvath et al. described a method of constructing a general-purpose screening library.[38] The work represented a collaborative effort to construct the general-purpose screening library of EU-OPENSCREEN. As this screening is not exclusively targeted at drug discovery, loose compliance to druglikeness criteria was applied during the library construction. Mok and Brenk established a workflow to generate a target-specific screening library.[44] They mined the ChEMBL database to assemble an ion channel-focused screening library.

Application of VS in Drug Discovery.

VS is routinely applied in pharmaceutical industry to identify novel and optimize the known drug leads. Recently, applications of VS to a family of receptors have emerged. Perez-Regidor et al. reviewed the latest effort of applying VS to search novel chemical entities for a set of Toll-like receptor (TLR) modulators, which include TLR2, TLR3, TLR4, TLR7, and TLR8.[45] The TLR family proteins are interesting drug targets as they can recognize a wide variety of pathogens. Senderowitz and Marantz conducted more than 10 docking VS to identify novel compounds targeting GPCRs using the *ab initio* derived GPCR models.[46]

Human histamine H4 receptor (H4R) is a key player in inflammatory responses. Istyastono et al. recently explored the possibilities and challenges of discovering compounds against H4R by performing structure-based virtual screening (SBVS). Of the 37 tested compounds, 9 fragments had affinities between 0.14 and 6.3 μM against the H4R target. They used the area under the ROC curves to evaluate a set of screening studies.[47] Ballester et al. conducted hierarchical virtual screening to discover new molecular scaffolds for antibacterial drug leads.[48] Using the combination of shape-based method for rapid screening and molecular docking for reliable screening, they were able to explore truly large and diverse databases. Fifty new active molecular scaffolds were identified from their VS studies.

Hierarchical VS has been routinely applied in our drug design projects. In the HIV-1 RT project, pharmacophore modeling, molecular docking, and binding free energy calculations using MM-PBSA were applied to identify novel drug leads targeting at the non-nucleoside binding site.[1] In another project, we discovered the first small molecule that inhibits $p18^{INK4C}$ by using the computational chemical genomics screening approach and stem cells specific chemogenomics knowledgebase.[49] $p18^{INK4C}$, a potent negative regulator of human hematopoietic stem cell (HSC) self-renewal, is a member of the cyclin-dependent kinase inhibitory proteins. In the transient receptor potential vanilloid type 1 (TRPVl) project, we developed a five-point pharmacophore model using known antagonists and constructed a homology model for docking-based screening. The *in silico* screenings using both types of filters yielded a set of promising hits and some were confirmed as hTRPV1 antagonists in assay.[50]

Above we briefly reviewed the VS technique with an emphasis on screening library construction. More reviews on VS can be found in other recent publications.[51–54] The reviews on the latest advances of molecular docking can be found elsewhere.[55–58]

As a summary, virtual screening has become a daily practice in modern drug discovery. The screening libraries which collect millions of compounds need to be condensed to be applied in VS studies. Most effort is focused on developing structurally diverse libraries and target-specific libraries. However, general-purpose druglike screening libraries, which have moderate sizes and are suitable for daily virtual screenings of arbitrary drug targets, are under construction. The objective of this work is to construct and evaluate this kind of screening libraries.

In the following, we first justify our effort of applying known drugs to enrich screening compounds by conduct a survey on drug–target interactions. Next, a set of generic and target-specific screening libraries have been compiled using known drugs. Last, the screening libraries have been critically evaluated using an external library of actives. Recommendations on how to use those screening libraries are also discussed.

2. METHODS

Drug–Target Interaction Analysis.

How should a VS be evaluated and how many hits should be selected to do a bioassay? Of course, the answer to this question is target-dependent. We hope to provide some hints to this question by performing a survey of drug–target interactions. A major challenge in drug repositioning is to identify interactions between known drugs and targets. *In silico* prediction of drug–target interaction (DTI) can speed up the process of identifying novel DTIs by providing the most promising DTI candidates to minimize the larger scale expensive and time-consuming experimental work.

In the following, we conducted a survey on DTIs collected by the Drug Bank Database.[59,60] As a unique bioinformatics and cheminformatics resource, the DrugBank database combines detailed drug data with comprehensive drug–target information. The data used in the present study was released on April 1, 2017 (version 5.0.6). The drug–target interaction data were

extracted from the “Drug Target Identifiers” table under the “Protein Identifiers” category on the DrugBank website (https://www.drugbank.ca/releases/latest#protein-identifiers). Other databases that collect DTIs include the TTD (Therapeutic Target Database).[61]

Special attention was paid to some drug target classes, including G-protein coupled receptors (GPCR), ion channels, kinase, and protease, which comprise a large fraction of the targets of the approved and investigational drugs.[62] GPCRs play prominent roles in many physiological processes, which makes them ideal targets to be regulated by small molecule drugs.[63] Owing to the key roles in many bioprocesses that involve rapid changes in cells, ion channels are another type of popular drug targets for pharmacological intervention. Those bioprocesses include cardiac, skeletal, and smooth muscle contraction, T-cell activation, epithelial transport of nutrients and ions, and pancreatic beta-cell insulin release.[64] In many cellular processes, such as cell cycle progression and signal transduction, kinases play a key role.[65] Proteases play an important role in many signaling pathways, and they are the prominent modulators of many diseases, such as cardiovascular disorders and cancer. Proteases are also drug targets for combating many parasites and viruses.[66]

The members of the four prominent target classes were determined using multiple UniProt sources. First, the <keyword> child elements of each protein entry in the UniProt XML file were identified. A protein was determined to be a GPCR if the “id” attribute of a <keyword> element was “KW-0297”. Similarly, the protein belonged to the ion channel family if the “id” attribute was either KW-0107, KW-0407, KW-0631, KW-0851, KW-0869, KW-0894, or KW-1071; the protein belonged to the kinase family if the “id” attribute was either KW-0418, KW-0723, or KW-0829; and the protein was a member of protease family if the “id” attribute was either KW-0031, KW-0064, KW-0121, KW-0224, KW-0482, KW-0645, KW-0720, KW-0788, or KW-0888.

Second, a protein was also recognized as a GPCR if it was listed as a 7- transmembrane G-linked receptor (http://www.uniprot.org/docs/7tmrlist). Similarly, a protein was determined to be a kinase if its name appears in http://www.uniprot.org/docs/pkinfam, or a protease, if its name shows in http://www.uniprot.org/docs/peptidas.

Screening Library Construction.

The screening libraries were compiled from the druglike data set of the ZINC database.[28] In total, 18 855 206 entries were downloaded. All the ZINC entries obey the Lipinski’s Rule of 5 without any violation. Then the FP2 fingerprints were generated using the OpenBabel software.[67] 2D-similarity searches were performed using drug molecules as queries. A ZINC molecule was recognized as a hit when the Tanimoto coefficient between its FP2 fingerprint and any drug molecule’s FP2 fingerprint was equal to or larger than a threshold. A drug molecule belongs to one of the three categories: approved drug (AD, 1596), investigational drug (ID, 486), and experimental drug (ED, 4437). For each drug category, the number in the parentheses is the number of drugs for that category. The numbers of drugs belonging to the four major drug target classes are listed in Table 1. In this work, a series of structural similarity (SS) thresholds, 85, 80, 75, 70, 65, 60, 55, and 50%, were applied to prioritize the screening libraries.

Evaluation of VS Studies.

The success of VS is determined by the ability of VS filters to distinguish actives from inactives through ranking compounds.[68] The ideal performance of VS is that all actives but not one inactive was selected, which is basically impractical. The performance of a VS is evaluated using a set of metrics and statistical parameters including hit rate (HR), enrichment factor (EF), true positive rate (TPR), false positive rate (FPR), false discovery rate (FDR), receiver operator characterization (ROC), and the resulting area under the curve. Other parameters, such as precision, recall, accuracy, F1 score, and Matthews correlation coefficient (MCC) are also applied to evaluate the performance of virtual screenings.[69] The two most important metrics of evaluating the performance of a VS, HR, and EF, are defined below. Hit percentage (HP) is applied to measure how well a VS filter condense a screening library.

$$\mathrm{HR}=\frac{m}{M} \quad (1)$$

$$\mathrm{HP}=\frac{n}{N} \quad (2)$$

$$\mathrm{EF}=\mathrm{HR}/\mathrm{HP}=\frac{m}{M}\times\frac{N}{n} \quad (3)$$

where M is known actives and m is known actives being selected as hits. N and n are total numbers of compounds in a screening library and number of hits, respectively. Unlike HP, HR and EF are calculated using known actives. HR measures the ratio of known actives being selected as hits. EF measures the ratio of the probability of selecting a true active from hits to the probability of selecting a true active randomly from the whole database. With HR and EF, one can calculate the hit rate for a random screening library of the same size: $\mathrm{HR}_{\mathrm{random}} = \mathrm{HR}/\mathrm{EF}$.

Critical Evaluation of the Screening Libraries.

The developed screening libraries were assessed by a set of test data sets of bioactives. All the bioactives, which are more potent than 10 μM against at least one target, were extracted from the target subset of the ZINC database.[28] The entries which are duplicated with any drug molecules were eliminated from the test data sets.

3. RESULTS

Drug–Target Interaction Analysis.

There are 7874 drug entries and 4704 drug targets in the Drug Bank as of May 2017. In total, 20 426 drug–target pairs were collected and 6854 drug entries and 4277 drug targets

were involved. After the further elimination of drugs not having structures, 6248 drugs were left which cover 4046 drug targets. The total number of DTIs drops to 19 057. On average, each drug corresponds to 3.0 drug targets and each drug target corresponds to 4.7 drugs. The total numbers of drugs, targets, and drug–target pairs for the approved, investigational, and experimental drugs are summarized in Table 1.

The total number of approved drugs of the four major drug target classes is 975, which accounts for 61% of all the approved drugs. This percentile slightly drops to 55% in the investigational drugs, and it further drops to 39% in the experimental drugs. It is worthy to point out that the number of ED targeting proteases and kinases dramatically outnumber the numbers of *AD* and ID, reflecting the fact that proteases and kinases are becoming hot drug targets today. It is pointed out that there are some overlaps between the drugs of the four different classes. For the GPCR category, there are 85, 223, and 10 drugs overlapped with the ion channel, protease, and kinase categories, respectively. The numbers of overlapped drugs are 71, 16, and 18 between ion channel/protease, ion channel/kinase, and protease/kinase, respectively. When only approved drugs are considered, the numbers of overlapped drugs are much fewer: there are 77, 3, 7, 6, 7, and 4 drugs overlapped between GPCR/ion channel, GPCR/protease, GPCR/kinase, ion channel/protease, ion channel/kinase, and protease/kinase, correspondingly.

Useful information on the drug discovery trends can be revealed by studying Table 1 and Figure 1. On average every GPCR target has 16.4 drugs, and every ion channel target has 10.1 drugs, both are significantly more than the average of 4.7 for all drug target classes. Interestingly, the number of experimental GPCR drugs, 35, is much smaller than that of investigational GPCR drugs. On the contrary, there are much more experimental than investigational drugs for the protease and kinase drug targets.

The number of targets a drug molecule has is quite different for the approved, investigational, and experimental drugs, as demonstrated in Figure 1A. As to specific target classes, those numbers do not share common patterns at all. The protease and kinase drugs have fewer drug targets than the GPCR and ion channel drugs.

As suggested by Table 1 and Figure 1, a drug molecule is likely associated with many drug targets; therefore, it is a good idea to identify those drug molecules that may interact with the drug target in study. Moreover, more potential drug leads may be identified from screening libraries which collect structurally similar compounds to known drugs. Constructing a set of prioritized druglike screening libraries is the objective of this work.

Screening Library Construction.

It is a dogma that the properties of a molecule are determined by its structure, and as such, similar structures tend to bear similar properties.[70] This similarity principle is the basis of the similarity searches. The higher the similarity between two compounds, the higher the chance the two compounds share the similar bioactivities for a drug target.

The performance of fingerprint-based screenings is summarized in Table 2. The efficiency of a virtual screening, which is measured by HP, strongly depends on the SS threshold. With

the SS threshold of 85%, only less than 1% of entries were selected; while the efficiency is dropped to 50% (only 50% of entries were filtered out) with the SS threshold of 50%. In the following text, we labeled the screening libraries using the threshold; for example, SS85 is the screening library retrieved using the SS threshold of 85%.

With the continually increased computer power, it is practical to screen a database with 200 000 or more entries using regular docking filters. Taking the docking program of Glide as an example,[3] Glide can screen 10 000 to 20 000 molecules for a typical drug target with one CPU core using the standard precision scoring function. As our screening libraries are prioritized, one should always start from SS85, followed by SS80, SS75, and so on.

Besides the general-purpose screening libraries, target class-specific screening libraries were also constructed. It is not a surprise that the screening efficiencies are much higher (smaller HP values) for all four drug target classes (Table 3).

The average and maximum hit numbers of all the fingerprint-based screenings are listed in Tables S1–S4. Studying those tables helps us estimate how many hits we expect to retrieve for a given SS threshold. There are some orphan drug molecules which are not well represented in the ZINC screening library since zero hit was retrieved for them even using a very low SS threshold of 50%. The percentages of zero-hit drugs are listed in Table S5. Other drugs have hits from one to thousands. We allocated the drugs into 17 groups which have hits of 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11–20, 21–50, 51–100, 101–200, 201–500, 501–1000, and 1001 and above. The distributions of drugs among the 17 groups are demonstrated in Figures 2–5 for different SS thresholds. Although the distribution patterns are different from one SS threshold to another and from one drug category to another, the most abundant groups are 11–20, 21–50, and 51–100 hits when SS thresholds are larger than 70%. The distributions of drugs among the 17 groups for SS thresholds of 65, 60, 55, and 50% are demonstrated in Figures S1–S4.

Critical Evaluation of the Screening Libraries.

In total, we collected 5847 bioactives and most of them were tested on human drug targets. Subsets of the bioactives targeting at GPCR, ion channel, kinase, and protease were compiled. Interestingly, only four compounds targeting proteases were left after the removal of the duplicated entries. Details on the composition of the test data sets are provided in Table S6.

Table 4 lists the HR and EF for four drug sets using eight SS thresholds. The relationships between hit rates versus SS thresholds and enrichment factors versus SS thresholds are shown in Figure 6. The overall quality of the screening libraries is satisfactory. For example, the enrichment factors are 36.9, 53.5 and 55.5, 24.8 for SS85 of drug (all drugs), AD (approved drugs), AD_ID (approved and investigational drugs), and ED (experimental drugs), respectively. The corresponding hit rates are 24.1, 14.2, 15.2, and 13.0% for the four SS85 sets. For the drug SS75 set, although EF is dropped to 12.9, HR increases to 36.1%. To seek a balance between HR and EF, we would recommend drug SS75 and AD SS70 (HR = 25.4, EF = 10.7) for virtual screening studies. The HR and EF of the screening libraries

against “Human”, a subset which collects 4078 actives of human drug targets, are listed in Table S7.

The screening performance for specific drug target classes was also investigated (Tables S8–S11). The HR versus SS threshold plots are shown in Figure 7, and the EF vs SS threshold plots are shown in Figure 8. Although the target class-specific screening libraries usually have larger enrichment factors (Figure 8), the hit rates are lower than the general-purpose screening libraries (Figure 7), such as Drug SS75 and *AD* SS70. The striking differences between the general-purpose and target-class-specific screening libraries occur when SS thresholds are larger than 0.8. It is also noted that the patterns of HR ~ SS threshold and EF ~ threshold plots may not be representative for the protease class, as there are only four actives of protease targets left after those overlapping with the known drugs are excluded.

4. DISCUSSION

Drug–Target Interaction Prediction.

The above drug–target interaction analysis was based on the experimentally confirmed drug–target interactions. It is of great interest to identify unknown drug-target interactions. *In silico* prediction of DTI promotes drug repurposing and facilitates us to explore the potential side effects of a drug due to multiple drug–target interactions. DTIs also provide insights about potential drug–drug interactions. Recently, Wen et al. developed a deep-learning-based method to predict drug-target interactions.[71] Using both the extended connectivity fingerprints of drugs and the protein sequence composition (the protein sequence compositions consist of amino acid composition, dipeptide composition, and tripeptide composition) of drug targets as descriptors, they built up a deep-belief-network (DBN) model which outperforms the other state-of-the-art methods. The DBN model can be further applied to predict whether a new target interacts with some existing drugs or whether a drug molecule can bind to some existing targets.

We developed an online tool, TargetHunter, to identify potential drug targets for a chemical compound.[72] The basic idea is to predict ligand–target interactions by comparing a query compound with bioactives for which their drug targets are well documented. The bioactive database TargetHunter explored is ChEMBL,[73] which collects millions of bioactivity data covering more than 8000 drug targets.[72] An algorithm, called TAMOSIC (targets associated with its most similar counterparts) was developed by us to assign the targets which are associated with the compounds most similar to a query compound as the potential drug targets of the query compound.[72] The case studies demonstrated that Target-Hunter was a promising technique for new target identification or repurposing drugs.

Further Development on Screening Library Construction.

Screening library construction plays a critical role in both HTS experiments and virtual screenings. There are two types of screening libraries, diverse screening libraries for drug lead identification and focused libraries for drug lead optimization. The former may not be druglike as they are compiled to maximize the structure diversity or molecular property diversity. The target-focused library using a limit number of known actives might not be able

to cover other potential hits. On the contrary, the druglike data sets constructed in this work have the following advantages. First of all, those screening libraries are druglike as they are enriched by known drugs; second, those screening libraries, although belong to focused libraries, have considerable diversity as they are enriched using all kinds of known drugs. Therefore, the screening libraries developed in this work are general-purpose screening libraries which can be applied in both drug lead identification and optimization for arbitrary drug targets. With our screening libraries, one may identify more actives from VS for the target in study, as the molecules enriched by the drugs of the other drug targets may be potential hits of the drug target in study, as revealed by the complicate DTIs between drugs and drug targets. The advantage of our general-purpose screening libraries is even more obvious for new drug targets for which there are no or only few known actives.

Although the screening libraries constructed in this work are mainly for VS studies, they may provide useful hints on compound library construction for experimental HTS because of the following reasons. First, all the entries of the screening libraries are commercially available; second, the compounds of screening libraries (especially Drug SS80 and the AD SS75) are druglike; last but not least, a compound library for experimental HTS is usually constructed for multiple drug discovery projects.

Certainly, it is worthwhile to continue to improve the enrichment factors of the screening data sets. We plan to further condense the screening data sets by removing those that are least druglike. The drug likeness score of a compound is a function of both molecular properties (aqueous solubility, human oral bio availability, human intestinal absorption, plasma protein binding, and other ADME and pharmacokinetic properties) and druglike fingerprints described by the building blocks of drugs and bioactives. Deng et al. proposed to use biological relevance to assemble screening libraries.[69] The biological relevance score will also become a component of our drug likeness score. We are in the process of developing such a kind of druglike function.

The opposite trend is to include more compounds into the screening libraries. Natural products could be applied as queries to recruit compounds in the ZINC database. Gu et al. found that there was a large portion of overlap in chemical space between FDA-approved drugs and natural products.[74] Therefore, we are planning to compile natural product-like screening libraries.

Wenlock et al. identified the trends in physio chemical properties that likely lead to a drug successful passes through clinical development and go to the market.[75] Those physio chemical properties include aqueous solubility, logP (logarithm of octanol–water partition coefficient), molecular weight, numbers of hydrogen donors and acceptors, and so on. The drug likeness of a compound can be further measured by its ADME properties. Among the many ADME/PK properties, oral bio availability is particularly important for the orally administered drugs[26,76–78]

Besides the molecular properties, molecular scaffolds are widely used to measure the druglike score of a compound. We have developed a brutal-force algorithm to enumerate all the possible building blocks of a given molecule. Druglike scaffolds and fragments were

then identified and assigned drug likeness scores.[26] Bemis and Murcko identified the molecular frameworks that are frequently found in the drug molecules of the Comprehensive Medicinal Chemistry (CMC) database.[79] It is possible to build a drug likeness fingerprint using the results of building block analysis to facilitate screening library construction. We recently performed a large-scale analysis on the interaction of ligand fragments with 20 ammonia acids.[80] First, the small molecule binders of protein targets were extracted and dissected into fragments. Then, LigFrag-RPM, an algorithm matching the preference of ligand fragments and amino acid residues, was developed by comparing the profiles of the interactions between ligand fragments and the 20 proteinogenic amino acid residues. The LigFrag-RMP algorithm could serve as a filter to remove ineligible compounds in the screening libraries for a given protein target. In addition, the recent construction of an allosteric ligand fragment library by us provides promising venue to design functional allosteric modulators for GPCRs.[81]

5. CONCLUSION

In this work, a set of druglike data sets for virtual screenings have been constructed. These data sets have been prioritized and critically evaluated using a large data set of bioactives. Some data sets, particularly drug SS80 and AD SS75 are highly recommended to serve as general purpose screening libraries. These data sets can be used for both drug lead identification and drug lead optimization.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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ABBREVIATIONS USED

AD	approved drugs
AD_ID	approved and investigational drugs
ADME	absorption, distribution, metabolism, excretion
CAP	compound library acquisition and prioritization
DTI	drug–target interaction
ED	experimental drugs
EF	enrichment factor
FANN	fingerprint-based artificial neural network
FDR	false discovery rate

FPR	false positive rate
HR	hit rate
HTS	high throughput screening
HP	hit percentage
GPCR	G-protein coupled receptors
ID	investigational drugs
MCC	Matthews correlation coefficient
MM/GBSA	molecular mechanics/generalized Born surface area
MM/PBSA	molecular mechanics/Poisson–Boltzmann surface area
PMV	polar molecular volume
PSA	polar surface area
QSAR	quantitative structure–activity relationship
ROC	receiver operator characterization
SOM	self-organizing map
SS	structural similarity
TPR	true positive rate
TTD	therapeutic target database
USR	ultrafast shape recognition
VS	virtual screening

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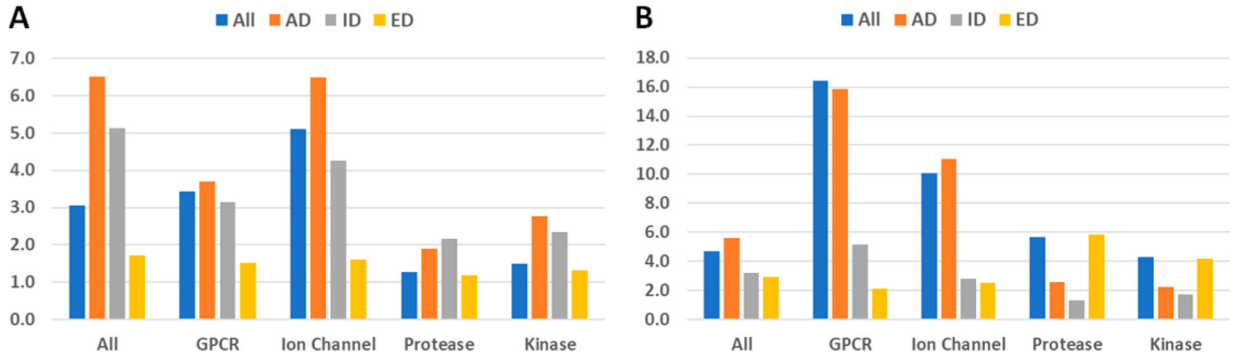

Figure 1.

Summary of drug–target interaction. (A) Number of targets per drug. (B) Number of drugs per target.

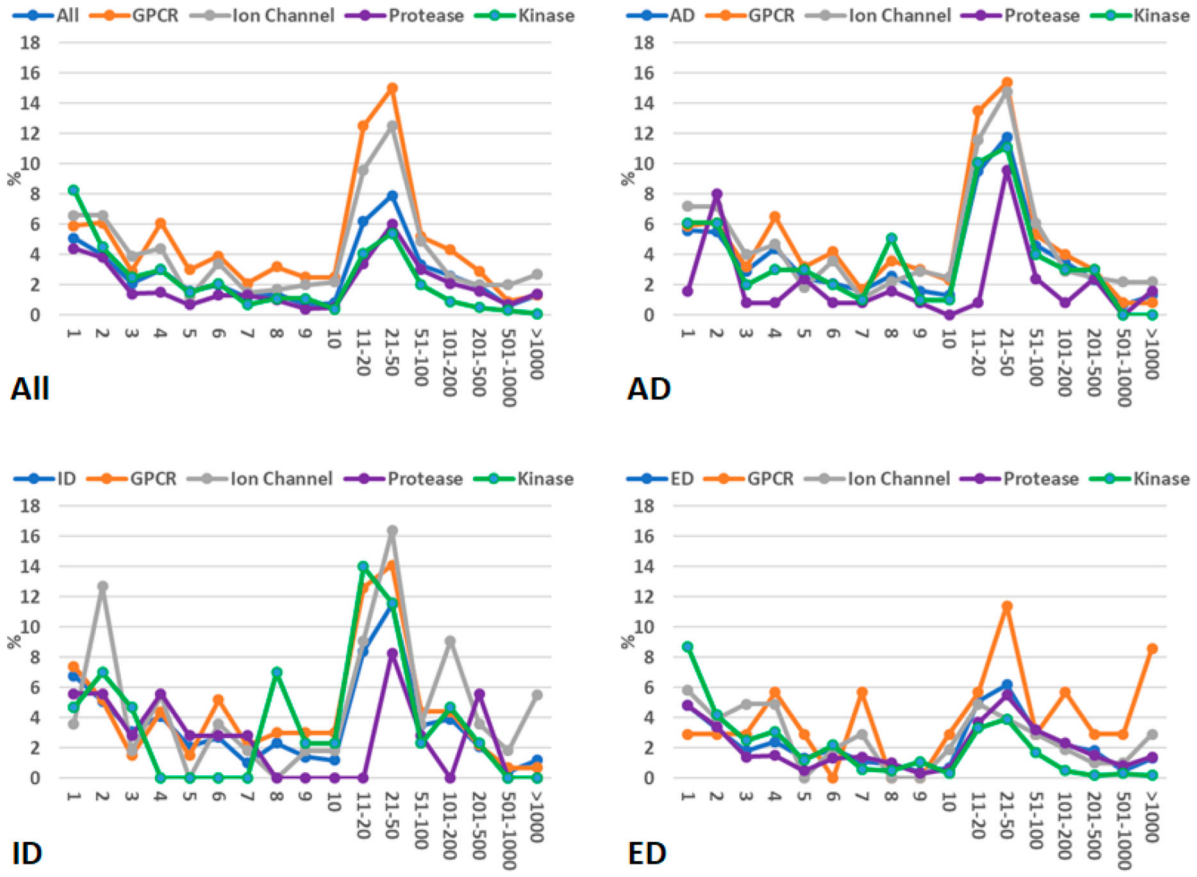

Figure 2.

Distributions of drug molecules (%) in 17 hit number groups. A molecule of the ZINC druglike data set is recognized as a hit if its 2D-similarity score against the query drug molecule is equal to or better than 0.85.

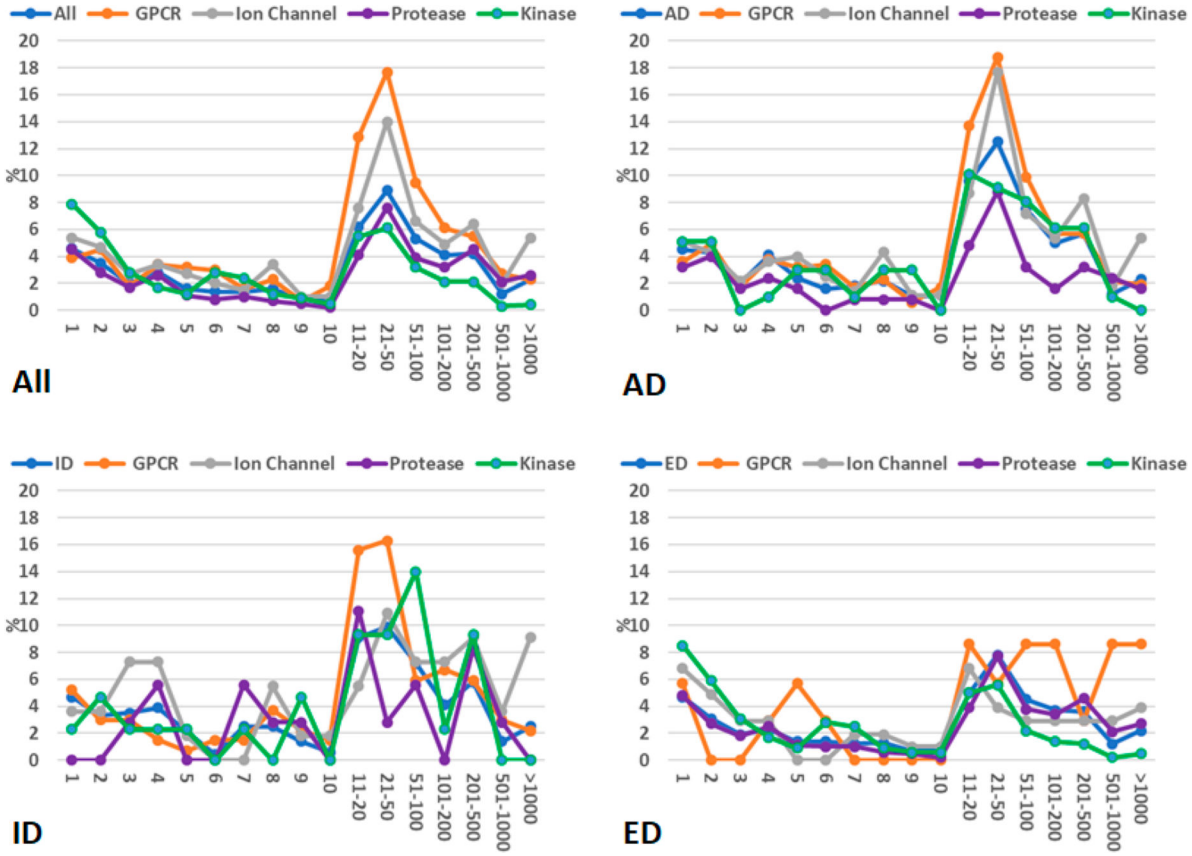

Figure 3.

Distributions of drug molecules (%) in 17 hit number groups. A molecule of the ZINC druglike data set is recognized as a hit if its 2D-similarity score against the query drug molecule is equal to or better than 0.80.

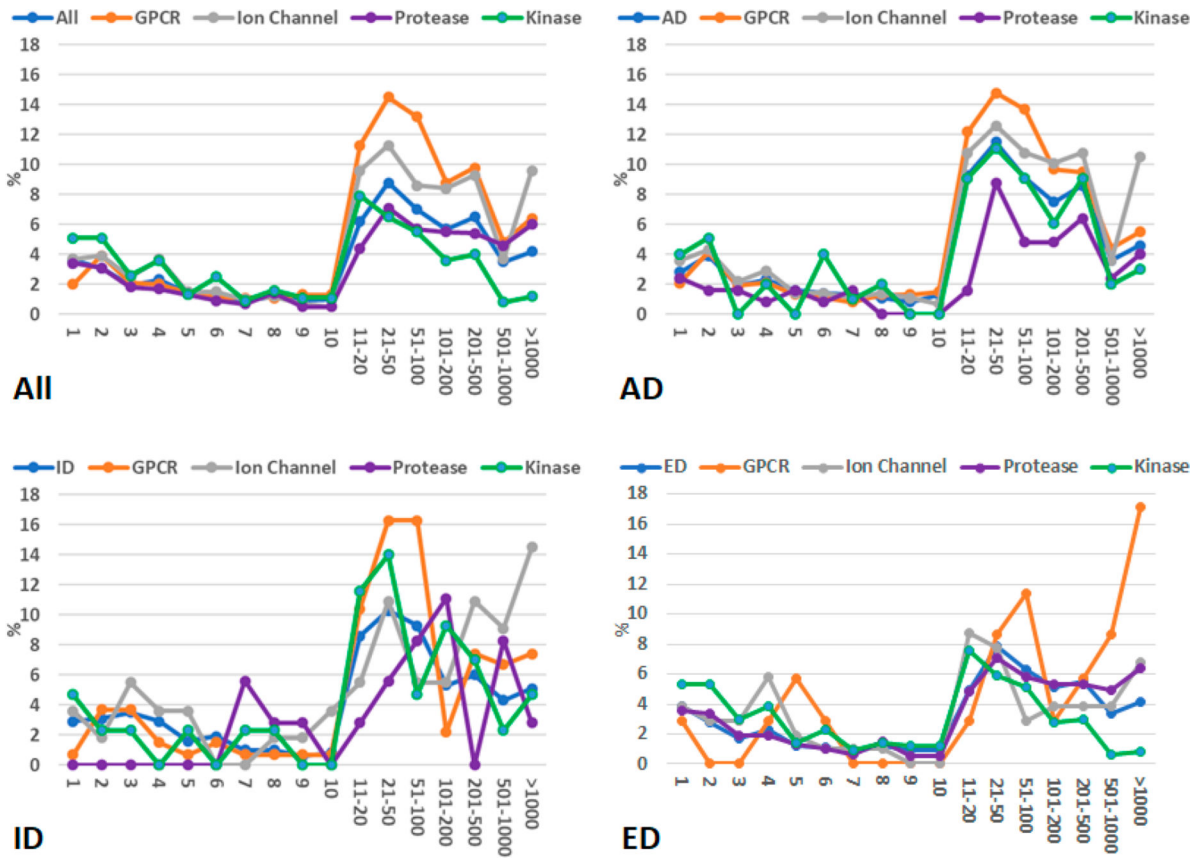

Figure 4.

Distributions of drug molecules (%) in 17 hit number groups. A molecule of the ZINC druglike data set is recognized as a hit if its 2D-similarity score against the query drug molecule is equal to or better than 0.75.

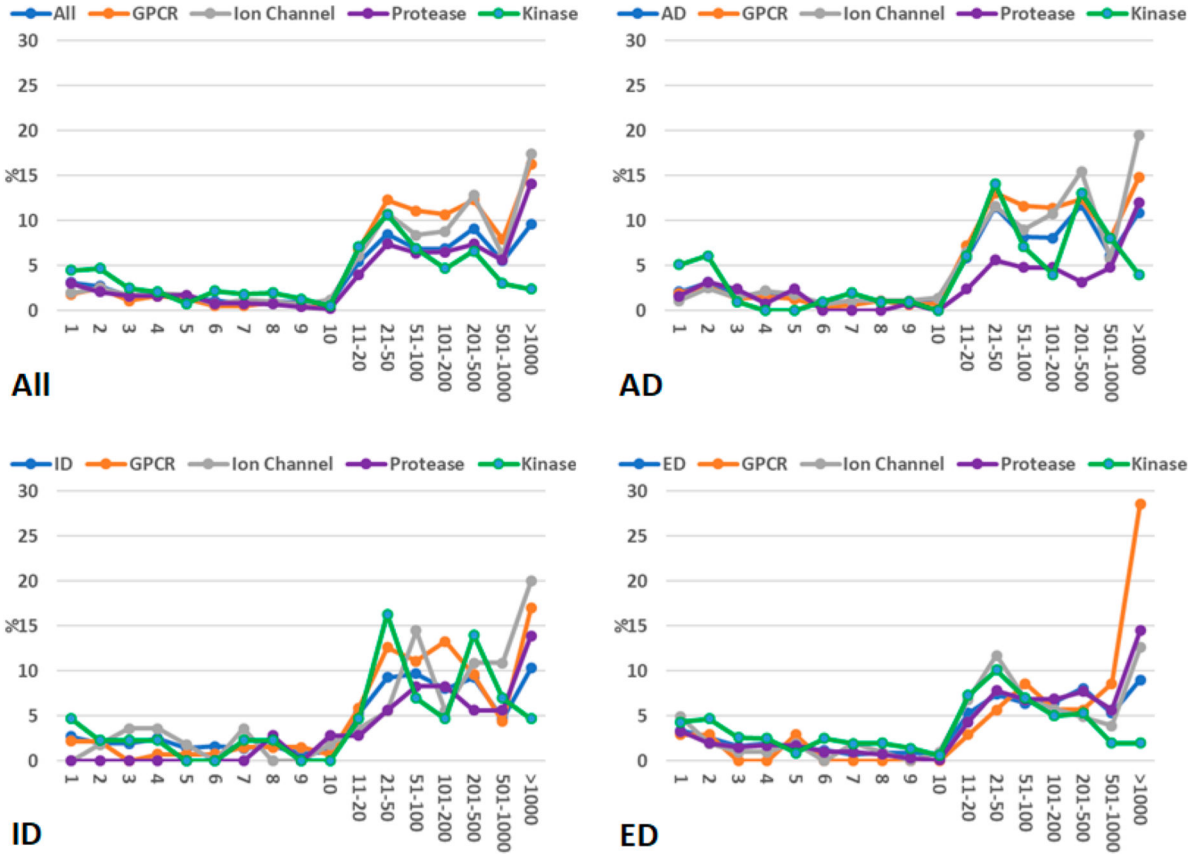

Figure 5.

Distributions of drug molecules (%) in 17 hit number groups. A molecule of the ZINC druglike data set is recognized as a hit if its 2D-similarity score against the query drug molecule is equal to or better than 0.70.

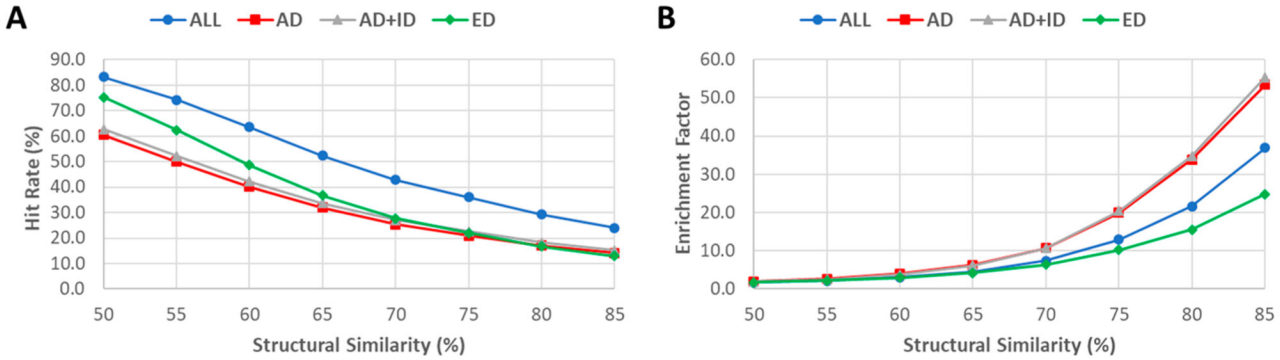

Figure 6.

Performance of virtual screenings for external actives (5847 entries) against screening libraries. (A) Hit rates. (B) Enrichment factors.

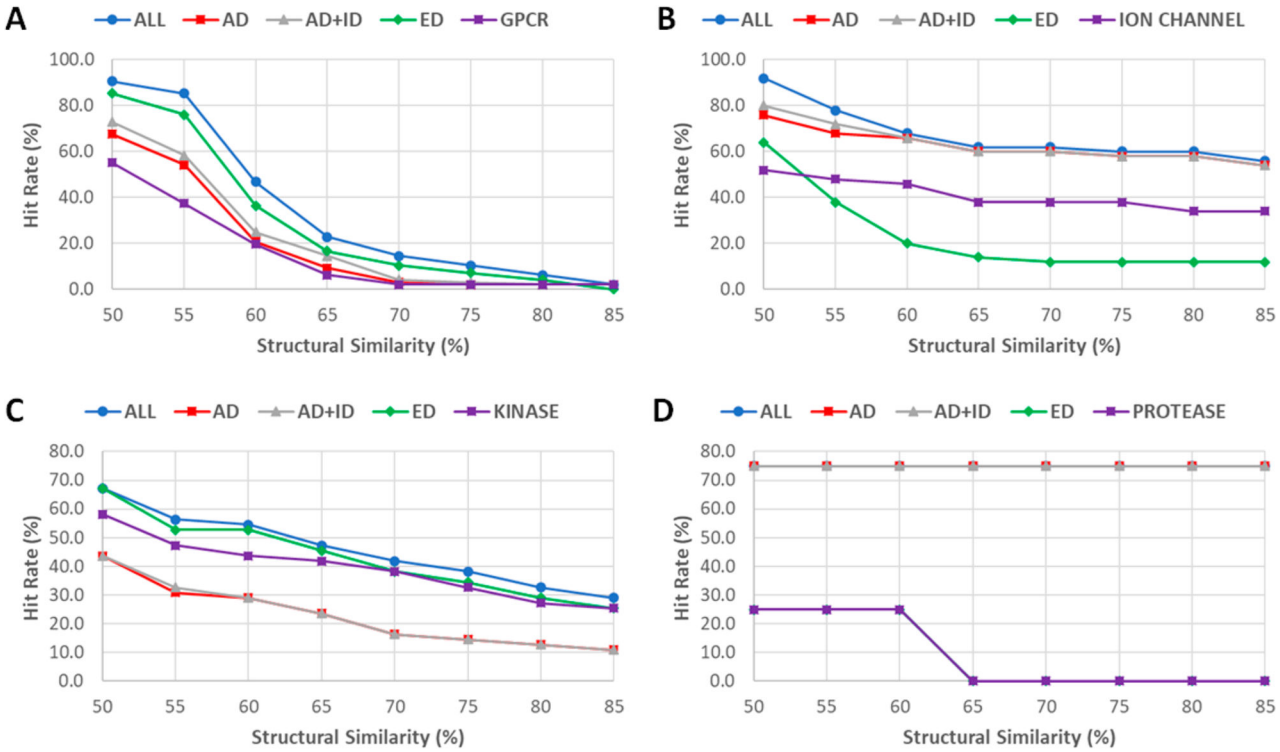

Figure 7.

Hit rates of virtual screenings for external target-specific active sets against general-purpose and target-class-specific screening libraries. (A) GPCR. (B) Ion channel. (C) Kinase. (D) Protease.

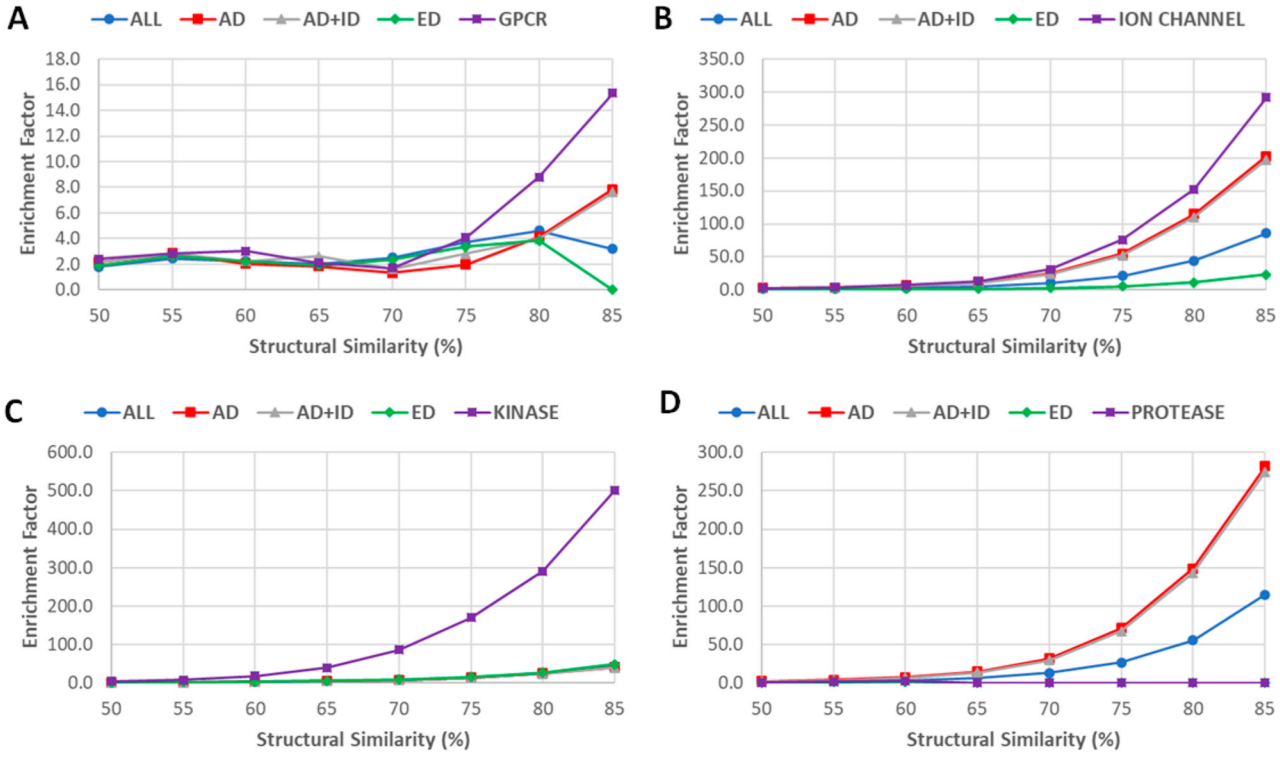

Figure 8.

Enrichment factors of virtual screenings for external target-specific active sets against general-purpose and target-class-specific screening libraries. (A) GPCR. (B) Ion channel. (C) Kinase. (D) Protease.

Table 1.

Summary on the Total Entries of Drugs, Targets, and Drug–Target Pairs for All and Four Major Drug Target Classes

		all	AD	ID	ED
all	no. drugs	6248	1596	486	4437
	no. targets	4046	1858	774	2632
	no. D-T pairs	19057	10387	2492	7679
GPCR	no. drugs	559	474	135	35
	no. targets	117	111	83	25
	no. D-T pairs	1920	1759	426	53
ion channel	no. drugs	407	277	55	103
	no. targets	206	162	84	66
	no. D-T pairs	2075	1794	234	165
protease	no. drugs	1091	125	36	947
	no. targets	246	93	60	193
	no. D-T pairs	1388	237	78	1125
kinase	no. drugs	758	99	43	644
	no. targets	267	124	58	202
	no. D-T pairs	1143	275	101	846

Table 2.

List of the Entry Numbers and Hit Percentages (%) of General-Purpose Druglike Data Sets

	drug		AD		AD_ID		ED	
SS	**no. entries**	**HP**	**no. entries**	**HP**	**no. entries**	**HP**	**no. entries**	**HP**
85	123192	0.7	50220	0.3	51602	0.3	99042	0.5
80	255861	1.4	95044	0.5	99014	0.5	204480	1.1
75	529276	2.8	199205	1.1	210071	1.1	407909	2.2
70	1096003	5.8	448688	2.4	479925	2.5	833300	4.4
65	2165864	11.5	967861	5.1	1051010	5.6	1648630	8.7
60	3949711	20.9	1923581	10.2	2109277	11.2	3098326	16.4
55	6593073	34.9	3570446	18.9	3888542	20.6	5511034	29.2
50	9560618	50.7	5883362	31.2	6288146	33.3	8513983	45.1

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Table 3.

List of the Entry Numbers and Hit Percentages (%) of Target-Specific Druglike Datasets

	GPCR		ion		kinase		protease	
SS	**no. entries**	**HP**	**no. entries**	**HP**	**no. entries**	**HP**	**no. entries**	**HP**
85	25595	0.1	22000	0.1	9573	0.1	40101	0.2
80	44673	0.2	42126	0.2	17677	0.1	84264	0.4
75	96741	0.5	94513	0.5	36471	0.2	177168	0.9
70	231963	1.2	233155	1.2	83746	0.4	376400	2.0
65	557328	3.0	548882	2.9	197394	1.0	801259	4.2
60	1234291	6.5	1169750	6.2	467769	2.5	1661329	8.8
55	2505668	13.3	2363312	12.5	1161054	6.2	3293679	17.5
50	4293284	22.8	4177077	22.1	2676629	14.2	5733633	30.4

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Table 4.

Performance of Druglike Datasets against an External Active Set with 5847 Entries

	drag			AD			AD_ID			ED		
SS	**no. hits**	**HR**	**EF**	**no. hits**	**HR**	**EF**	**no. hits**	**HR**	**EF**	**no. hits**	**HR**	**EF**
85	1409	24.1	36.9	832	14.2	53.5	886	15.2	55.4	761	13.0	24.8
80	1712	29.3	21.6	996	17.0	33.8	1066	18.2	34.7	982	16.8	15.5
75	2109	36.1	12.9	1229	21.0	19.9	1329	22.7	20.4	1289	22.0	10.2
70	2508	42.9	7.4	1486	25.4	10.7	1586	27.1	10.7	1624	27.8	6.3
65	3059	52.3	4.6	1867	31.9	6.2	1975	33.8	6.1	2153	36.8	4.2
60	3715	63.5	3.0	2350	40.2	3.9	2462	42.1	3.8	2843	48.6	3.0
55	4346	74.3	2.1	2926	50.0	2.6	3051	52.2	2.5	3652	62.5	2.1
50	4865	83.2	1.6	3540	60.5	1.9	3671	62.8	1.9	4398	75.2	1.7

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