Unlocking the Potential of High-Quality Dopamine Transporter Pharmacological Data: Advancing Robust Machine Learning-Based QSAR Modeling

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Abstract

The dopamine transporter (DAT) plays a critical role in the central nervous system and has been implicated in numerous psychiatric disorders. The ligand-based approaches are instrumental to decipher the structure-activity relationship (SAR) of DAT ligands, especially the quantitative SAR (QSAR) modeling. By gathering and analyzing data from literature and databases, we systematically assemble a diverse range of ligands binding to DAT, aiming to discern the general features of DAT ligands and uncover the chemical space for potential novel DAT ligand scaffolds. The aggregation of DAT pharmacological activity data, particularly from databases like ChEMBL, provides a foundation for constructing robust QSAR models. The compilation and meticulous filtering of these data, establishing high-quality training datasets with specific divisions of pharmacological assays and data types, along with the application of QSAR modeling, prove to be a promising strategy for navigating the pertinent chemical space. Through a systematic comparison of DAT QSAR models using training datasets from various ChEMBL releases, we underscore the positive impact of enhanced data set quality and increased data set size on the predictive power of DAT QSAR models.

The dopamine transporter and its inhibitors

Neurotransmitter:sodium symporters (NSSs) transport synaptic neurotransmitters through a Na^+ and Cl^--dependent mechanism back to the presynaptic neuron [1, 2]. Among NSSs, the monoamine transporters include the dopamine, serotonin, and the norepinephrine transporters (DAT, SERT, and NET, respectively) [3]. The cognate substrates of these transporters play key roles in the central nervous system (CNS), responsible for mood, emotion, learning, cognition, memory, sleep, and appetite. Inhibition of these transporters leads to reduced clearance of these neurotransmitters, resulting in prolonged synaptic signaling with higher intensity [3].

Specifically, dopamine is an essential in the brain's reward system [4]. DAT is responsible for regulating the extracellular dopamine levels in the brain, using the energy stored in the Na^+ and Cl^- gradients to symport dopamine back to the neuron [5, 6]. Disrupting the DAT function can lead to several psychiatric disorders, including attention-deficit hyperactivity disorder (ADHD) [7, 8], bipolar disorder [9, 10], and depression [11]. Many psychostimulants, including cocaine and amphetamine, primarily target DAT. Upon entering the human brain, psychostimulants elevate extracellular dopamine levels and can have a highly addictive effect on the individuals consuming the substances, with the possibility of triggering substance use disorders (SUDs). SUDs encompass complex health conditions that include significant impairments of physiological, mental, and social functions due to consumption of substances at high doses and/or frequencies [12]. Specifically, cocaine use disorder (CUD) is characterized by the compulsive consumption of cocaine despite its adverse medical, psychological, and behavioral consequences, was found to affect more than 5 million individuals in 2019 [13]. Notably, cocaine overdose death rates increased nearly 54% from 2019 to 2021 [14]. While users experience a brief sense of intense euphoria when consuming cocaine before the effect wears off, prolonged usage is linked to the development of mental disorders (e.g., depression) and cognitive impairments [13]. Although cocaine acts non-selectively on the three monoamine transporters, substantial evidence indicates that DAT plays a key role in the development of CUD [15, 16].

Many efforts have been spent in past decades toward developing effective medications for CUD; however, there is no approved FDA drugs for CUD. Early efforts in developing therapeutic agents for CUD have centered around cocaine analogues, which have been optimized to possess both higher affinity and improved selectivity for the DAT but decreased stimulatory effects and less abuse liability [3, 17, 18]. It was then discovered that the compounds with decreased stimulatory effects stabilized the DAT in a distinct conformation as compared to cocaine [17, 19]. These compounds were classified as "atypical" DAT inhibitors, distinguishing them from "typical" DAT inhibitors like cocaine [18-20]. Thus, cocaine stabilizes DAT in an outward-facing conformation, whereas atypical inhibitors, such as modafinil and JHW007, favor inward-facing conformations [21-23]. Notable examples of atypical DAT inhibitors include benztropine [17, 24], rimcazole [17], GBR12909 [25], and modafinil analogues [26, 27 , 28].

However, translating these compounds to a human CUD treatment has been challenging [29], while the potential for discovering additional candidate atypical DAT inhibitors based on the well-characterized scaffolds is diminishing. In this work, we provide a comprehensive overview from the cheminformatics perspective in identifying novel DAT inhibitor scaffolds.

Ligand-based versus structure-based drug discovery for the NSSs

Computer-aided drug design (CADD) can be broadly categorized into protein structure-based drug design (SBDD) and ligand-based drug design (LBDD) [30]. SBDD leverages in-depth knowledge of the three-dimensional (3D) structures of the protein targets, allowing the design of small molecules that can interact optimally with the targets [31]. When the high-resolution structures of mammalian NSSs were unavailable, SBDD heavily depended on the qualities of homolog-modeling based computational models of the targets, emphasizing the importance of accurate and reliable molecular modeling approaches [32-36]. LBDD, on the other hand, operates without the 3D structural information of the targets, but relies on the analysis of the known pharmacological information between small molecules (ligands) and their targets. LBDD is

particularly useful when the 3D structure of the target is either unknown or challenging to obtain [37]. Thus, while SBDD provides the target structure-guided precision, LBDD offers ligand-based adaptability, in the quest for new therapeutic agents.

In LBDD, several popular techniques have been employed, with notable examples being pharmacophore modeling and quantitative structure-activity relationship (QSAR) modeling. In pharmacophore modeling, pharmacophore refers to the spatial arrangements of structural and chemical features, usually on a chemical scaffold, that can be extracted from the active compounds of a target. The resulting model can facilitate molecular recognition to effectively identify and characterize new compounds [38-40]. QSAR modeling was first established by Corwin Hansch for its application in the field of virtual drug screening [41]. QSAR modeling focuses on establishing a quantitative relationship between the chemical structures of small compounds and their specific pharmacological activities, by building models that correlate the structural features of compounds with their observed bioactivities. The QSAR method operates on the premise that molecules sharing similar structural or physicochemical properties would demonstrate comparable biological activities [42]. Consequently, the robustness of the QSAR models depends on both the quantity and quality of available pharmacological activity and compound data, much of which have been systematically accumulated and curated in pertinent databases [43]. These models not only provide valuable insights into the essential molecular features contributing to the desired pharmacological effects, but also aid in the design and optimization of novel drug candidates.

The molecular descriptors that QSAR utilizes come in many different forms, including quantitative (molecular shape) and qualitative descriptors (fingerprints) [44], and can range from 2D to 6D [45]. 2D molecular descriptors, which are the most popular, provide information on the connectivity of atoms, properties of chemical bonds, and chemical fingerprints [45]. Many commercial software, such as Mold^2 and DRAGON system, can be used to generate 2D molecular descriptors [46, 47]. 3D descriptors provide physical information, such as surface

properties, molecular volume, and molecular interaction fields [48-50]. A caveat to 3D descriptors is that these additional complexities may not be necessary to improve the predictive power of QSAR models at the expense of the significantly more computational cost, as its performance is sensitive to the accuracy of predicting ligand conformation.

The early pioneering work in QSAR modeling of DAT ligands includes those of the Newman group, in constructing both 2D and 3D QSAR models, which used 2D and 3D descriptors, respectively. Specifically, the 2D QSAR study was carried out with 70 diverse inhibitors of the DAT and produced robust QSAR models, resulting in a $q^2 = 0.85$. These DAT models were then used to search through the National Cancer Institute database, yielding five candidate compounds suitable for testing new DAT scaffolds [51]. A follow-up study was conducted using 3D QSAR methods for the design of new mazindol analogues and to identify molecular interactions for optimal DAT binding. Using comparative molecular field analysis (CoMFA), each compound's steric and electrostatic potential fields were calculated and used as features to generate robust 3D QSAR models [52].

In recent years, there has been extensive applications of machine learning (ML) and deep learning (DL) techniques in the construction of QSAR models [53-55]. These advanced computational techniques offer powerful tools for extracting intricate patterns and relationships from complex data sets, beyond the traditional linear regression based QSAR modeling approaches (see below). By leveraging ML and DL algorithms, significantly enhanced accuracy and predictive capabilities of QSAR models have been achieved [56-60].

Databases containing pharmacological activity information of the DAT

Constructing QSAR models involves consideration of many factors, and one of the initial and pivotal aspects is the collection of available and reliable data from relevant databases. We found that the publicly accessible databases containing pharmacological activity information of the DAT include ChEMBL [61], DrugBank [62], binding database (BindingDB) [63, 64], therapeutic

target database (TTD) [65], psychoactive drug screening program (PDSP) [66], and PubChem [67]. These databases compile data on biomolecules, protein targets, compound characteristics, ADMET properties, binding interactions, functional assays, and more. Typically, these databases are maintained by non-profit organizations and undergo regular updates. While most databases primarily focus on drug-related information and associated targets, BindingDB also offers 3D insights into protein targets and ligands.

To evaluate the available pharmacological data that can be used to construct QSAR models for DAT, we compared pharmacological data of DAT from these databases (data retrieved in December, 2023). Note that in this process, it is essential to consider the number of unique compounds when comparing across databases by removing redundant information. If such information was not found in the database, we employed Morgan fingerprints and Tanimoto similarity measurements to calculate the pairwise similarities to identify the distinct compounds within each database. In addition to human DAT (UniProt ID Q01959), the rattus norvegicus (UniProt ID P23977), bos taurus (UniProt ID P23977), and mus musculus DAT (UniProt ID Q61327) are also included.

- ChEMBL release 33 (May 2023) provides 2,399,743 compounds, 20,334,684 activities, 1,610,596 assays, 15,398 targets, and 88,630 publications [61]. We found 14,102 pharmacological activity data related to DAT, and among them, we identified 7,496 unique compounds, with clear indications of being curated by experts.
- DrugBank Online (version 5.1.10, released 2023-01-04) contains 15,325 drug entries of FDA-approved drugs or experimental drugs going through the FDA approval process [62]. Upon querying for the DAT information in DrugBank, our search revealed 51 drugs specifically targeting DAT. Nevertheless, our comparison of data from other databases and literature suggests that additional drugs listed by DrugBank may also bind to DAT (see **Table S1**).
- BindingDB collects experimental data of protein-small molecule interaction [63, 64]. It provides both 2D- and 3D-information of proteins and ligands. Since its initial launch in the year 2000,

BindingDB has accumulated 2.8 million binding data for more than nine thousand targets and over 1.2 million compounds (released 2023-11-30). Regarding DAT, we found 10,650 pharmacological data points, encompassing 5,724 unique compounds.

- TTD provides information of known therapeutic protein targets and the corresponding drugs [65]. The latest update (2024) includes 3,730 targets and 39,862 drugs. We found 3,578 pharmacological data points directed at DAT. Within that data set, some compound structures are unavailable, making it a challenge to identify unique compounds directly.
- PDSP provides data assessing pharmacological and functional effects at CNS receptors, channels, and transporters [66]. We found 1,234 instances of pharmacological data associated with DAT, which are related to 327 unique compounds.
- PubChem is one of the largest chemical databases of publicly accessible chemicals [67]. There are hundreds of data sources connected to PubChem, containing over 116M compounds, 309M substances, 229M bioactivities, 36M publications and 38M patterns. When focusing on DAT specifically, we found a total of 9,108 pharmacological activities, related to 6,021 distinct compounds. However, the level of expert curation on these DAT activities are not clear.

Among these six databases, ChEMBL is clearly outstanding, as it amasses the largest number of unique compounds and offers an extensive repository of expert-curated bioactivity information. Consequently, it was our primary choice for sieving training data for the development of a robust DAT QSAR model [68]. However, we note that BindingDB is another important resource for DAT pharmacological activity data.

To illustrate the trend of the evolution and the accumulation of DAT pharmacological data over the past four decades, we queried ChEMBL 33 and compiled the retrieved DAT pharmacological activity data along the years (**Fig. 1**, see its legend for query criteria). The first publication curated by ChEMBL on DAT studied amphetamine analogs and tested their inhibition of dopamine uptake in rats [69]. Along the years, the number of relevant publications as well as the pharmacological activity data have been accumulating substantially (**Fig. 1A**,**B**). In

particular, the number of publications had a large spike in 2008 (55 publications), possibly attributed to the availability of the crystal structure of a bacterial NSS homolog, the leucine transporter (LeuT) in 2005 [70]), which allowed homolog modeling of the DAT and other NSSs with a high-resolution experimentally determined structure as the template. Integrated with molecular dynamics simulations and uptake experiments, the LeuT-based homology DAT models have been used to understand the substrate binding mode and the molecular mechanism of inhibitor interactions with DAT [71-74]. Importantly, the LeuT-based homology DAT models have provided valuable guidance to facilitate the drug discovery [36, 75]. However, we did not detect that the publication of the drosophila DAT structure in 2013 [76] resulted in another obvious large accumulation in the relevant publications, although the pharmacological activity data and the number of new unique compounds somewhat increased in 2014 as compared to those in 2013 (**Fig. 1B,C**).

Notably, whereas the number of publications appears to be plateaued in recent years (**Fig. 1A**), between 2008-2010 and 2019-2020, there has been an obvious decline of novel DAT inhibitors being discovered and the associated pharmacological characterizations (**Fig. 1B,C**). Even though there is a noticeable increase of related publications in 2021, the increase of novel DAT ligands was minimal (note that to indicate the delay of ChEMBL data curation, which we found could be more than two years, a dashed line was added to separate the data of year 2021-2023 from early years in **Fig. 1**).

Some of representative DAT ligands specifically and not specifically developed for DAT

When targeting a specific protein, such as DAT, for therapeutic purpose, it is critical the understand the pharmacology beyond the target. Conversely, some high-affinity DAT ligands were not necessarily specifically developed for DAT. To evaluate whether the SAR information accumulated by the field focusing on DAT ligand development can be supplemented by other efforts, we gathered and analyzed a set of representative DAT ligands from both the well-

respected review articles on the DAT inhibitors [21, 22, 77] and DrugBank [62], which collects and curates the compounds that have progressed significantly along the drug development processes. We identified those with relatively high affinities using dopamine as a reference (with either pKi, pIC50, pEC50, or pKd > 5.06) to narrow down to a total of 61 ligands (**Table S1**). Among the 61 ligands, 48 ligands can be found in ChEMBL, but only 46 have recorded DAT pharmacological activity therein. In addition to ChEMBL, 52 ligands can be found in BindingDB, 38 ligands can be found in PDSP, emphasizing the necessity to source the data beyond an individual database. To collect adequate data for **Table S1**, we also had to search the literature extensively.

To characterize the chemical features of these 61 representative DAT ligands, we clustered them based on their chemical structures (see **Fig. 2** legend for the clustering algorithm we employed). Cocaine and eight other DAT ligands were clustered together, and share both a tropane and a phenyl ring. However, a noticeable difference between cocaine and other compounds is the linkage distance between the tropane and phenyl ring. For cocaine, they are separated by a carboxyl group, but for others, they are directly connected. Interestingly, cocaine has the least binding affinity compared to the other compounds in this cluster. Indeed, compared to the affinities at SERT and NET, cocaine is not a DAT selective ligand, while RTI-55, RTI-82, MFZ 2-24, ioflupane I-123 and WIN 35,428 have been used as radiolabeled probes in the binding assays for DAT [78-82]. Among them, we could not found activity data at SERT or NET for RTI-82, MFZ 2-24 and ioflupane I-123, suggesting that these cocaine analogues may have been primary designed for DAT. Altropane is the only DAT selective ligand in this cluster, and has been used as an imaging probe to monitor DAT [83]. Troparil (WIN 35,065-2) is a common inhibitor for the three monoamine transporters, and has exhibited a stronger affinity at DAT compared to that of cocaine [19, 84]. Tesofensine, another common inhibitor for the three transporters, was investigated for its potential applications in obesity-related conditions, Parkinson's disease, and Alzheimer's disease [85].

In the cluster containing methamphetamine, amphetamine, and three other ligands, the common feature among them is a propylbenzene scaffold linked to a protonated amine (**Fig. 2B**). Note that most ligands in this cluster are DAT substrates except for sydnocarb. Amphetamine has been used medically to aid in treating ADHD [86, 87] and in enhancing cognitive functions [88]. Due to the size and structure of amphetamine analogs, they can cross through the blood brain barrier (BBB) [89]. However, it has been found that methamphetamine disrupts the BBB and affects its structural integrity and permeability [90]. Methamphetamine is a recreational psychostimulant drug known for its strong neurotoxic and addictive effects [91]. Methamphetamine use disorder (MUD) exhibits a wide spectrum of adverse outcomes from hallucinatory ideation to self-injurious behaviors [92]. Notably, MUD has been linked to severe cardiac complications [92]. Both methamphetamine and amphetamine function as potent releasers that increase the extracellular concentrations of key neurotransmitters such as dopamine and serotonin in the brain [92, 93]. Sydnocarb functions as a noncompetitive inhibitor of DAT and is used for the treatment of schizophrenia and depression but has been linked to having psychostimulant effects [94, 95].

Dopamine is an endogenous substrate of DAT. It can be clustered together with several benzodioxole compounds, including 3,4-methylenedioxymethamphetamine (MDMA), 3,4-methylenedioxypyrovalerone (MDPV), 3,4-methylenedioxy-N-ethylamphetamine (MDEA), and 3,4-methylenedioxyamphetamine (MDA) (**Fig. 2C**). MDMA, commonly known as “ecstasy”, acts on both DAT and SERT, and can have stimulatory effects and alter perception and induces hallucinatory experiences [96-98]. MDEA, functions as a partial releaser of DAT [99], while MDA has been shown to act as a substrate for all three monoamine NSSs [100]. MDPV, a synthetic cathinone typically seen in “bath salts”, is a psychostimulant drug characterized by its heightened selectivity for DAT and increased potency when compared to that of cocaine [101]. Studies have shown that MDPV is a DAT inhibitor but not a substrate [102], whereas all the other members of this cluster showed at least some substrate properties for DAT [100, 103].

A few well-recognized atypical inhibitors were clustered together including benztropine, JHW-007, vanoxerine, modafinil, GBR-12935, diphenylpyraline, and chlorpheniramine (**Fig. 2D**). In this cluster, diphenylmethane is the common moiety. Among them, modafinil is a therapeutic drug involved in treating excessive sleepiness in narcolepsy patients by increasing extracellular levels of dopamine [27, 104]. Modafinil has two enantiomers (S- and R-modafinil), and it has been shown that the R-enantiomer (also known as armodafinil) has ~3-fold higher affinity than S-enantiomer at DAT [27], while the R-enantiomer is a DAT selective ligand, when comparing the affinities at DAT, SERT and NET [105]. Vanoxerine (GBR12909), a piperazine derivative and another atypical DAT inhibitor, was initially developed as a therapeutic treatment in combatting cocaine addiction, but it was later discontinued due to its heart-related side effects [25, 106]. Diphenylpyraline functions as an antihistamine but has also been shown to inhibit DAT. Previous research suggested a potential for it to reduce the effects of cocaine [107]. Chlorpheniramine is an antihistamine as well and displayed a high affinity for SERT and a relatively low affinity to DAT [108]. In addition to the diphenylmethane moiety, JHW-007 and benztropine also possess a tropane ring. Benztropine, formally used as a drug for Parkinson's disease, share noticeable structural similarities with cocaine. It has been shown to function as an atypical DAT inhibitor and utilized as a pharmacological agent for CUD research [17, 25, 109]. JHW-007 is also an atypical DAT inhibitor and has been demonstrated to possess reduced psychostimulant effects compared to cocaine [110]. Interestingly, except for diphenylpyraline and chlorpheniramine, the other five ligands in cluster D are selective for DAT over SERT and DAT based on the data that we could collect (**Table S1**).

Some known allosteric inhibitors of DAT were clustered in one group (**Fig. 2E**). Specifically, SRI-31142, is a 4-quinazolinamine derivative that could inhibit the actions of cocaine; however, further research is needed to fully explore its therapeutic potential [111]. Three other 4-quinazolinamine analogs, SoRI-9804, SoRI-20040, SoRI-20041, are clustered with SRI-31142, and have been found to be partial inhibitors and allosteric modulators for DAT [112, 113].

While clusters A to E mentioned above have garnered more attentions for their interactions with DAT, the remaining clusters of ligands were mainly developed for use as antidepressants, appetite suppressants, and antipsychotics, which, however, have the off-target effects at DAT. In particular, two clusters of DAT inhibitors were obviously developed to treat depression. They have either tricyclics or bicyclic ring moiety. In the cluster F (**Fig. 2F**), desipramine, nortriptyline, and trimipramine are tricyclic antidepressants (TCAs). Both desipramine and nortriptyline are FDA-approved drugs to treat depression, due to their actions at NET and/or SERT [114], and have been shown to have an inhibiting effect on DAT as well [108]. Trimipramine, has been shown to be a DAT inhibitor but is more potent at SERT [108]. Nomifensine, sertraline, and dasotraline share a bicyclic ring moiety attached to a toluene group (**Fig. 2G**). Sertraline, a selective serotonin reuptake inhibitor (SSRI) that also inhibits DAT, serves as an antidepressant as well [115]. Dasotraline is a dual DAT and NET inhibitor, which is being studied for its therapeutic potential in treating ADHD [116].

Two other clusters also include antidepressants. One cluster shares phenylpiperazine as the common feature (**Fig. 2H**). In this cluster, aripiprazole is an atypical antipsychotic drug that primary target dopamine D2 receptor with a high affinity [117], but can also bind to both DAT and SERT, with only slightly higher affinity at SERT [118, 119]. Nefazodone is an atypical antidepressant and has similar affinities in the three monoamine NSSs [120]. Duloxetine, PAL-287, PAL-1045, and PAL-1046 share a naphthalene moiety and are clustered together (**Fig. 2I**). Duloxetine, a dual NET and SERT inhibitor, has exhibited the potential to serve as an antidepressant based on previous research findings [121], but demonstrated a weaker affinity to DAT [122]. In addition to duloxetine, the other three compounds in cluster I are all substrates. PAL-287 functions as a releaser for DAT, SERT, and NET, and has been shown to suppress the effects of cocaine [123, Rothman, 2012 #86] (**Table S1**). PAL-1045 tends to act as a partial releaser for both DAT and SERT [99, 124], whereas PAL-1046 functions as a full substrate for DAT [99].

Two clusters include appetite suppressants. Phenmetrazine is an anorectic drug used in mid-1900s to promote the release of dopamine in the brain [125] and was clustered together with methylphenidate and PAL-738. All three ligands in this cluster share a toluene moiety either linked to a 3-methylmorpholine moiety or carboxyl group (**Fig. 2K**). However, the phenylacetic acid moiety of methylphenidate, which acts as a typical DAT inhibitor, is common to cocaine, but not to the other two members of this cluster. Although methylphenidate serves as a therapeutic drug for ADHD, it also exhibits psychostimulant effects [126]. PAL-738, on the other hand, serves as a partial releaser for DAT [99]. The next cluster includes mazindol, which is another appetite suppressant, and a triple reuptake inhibitor of DAT, NET, and SERT [127, 128]. It can be clustered together with rimcazole and KM822, and they share a similar tricyclic ring moiety (**Fig. 2J**). Rimcazole has been observed to inhibit the cocaine binding at DAT [129]. KM822 is a noncompetitive inhibitor of DAT and has been shown to reduce the affinity of cocaine to DAT [35].

Ten compounds have distinct scaffolds and are the sole representatives in their own respective clusters in this set of 61 ligands (**Fig. S1**). In particular, bupropion functions as a dual DAT and NET inhibitor and is used for the treatment of ADHD, depression, and smoking cessation [130]. Tamoxifen functions as both a DAT inhibitor with some atypical property without psychostimulant effect and a selective estrogen receptor modulator, which is typically prescribed for the treatment of estrogen related breast cancer [131]. While having a high affinity at SERT, ibogaine operates as a competitive inhibitor of DAT as well, and is a psychostimulant under investigation for its potential to treat SUDs [132].

In summary, while the potential for leveraging the “traditional” DAT inhibitor scaffolds is diminishing, our analysis indicated that ample chemical space can be explored for developing the DAT inhibitors with desired pharmacological profiles. However, the accumulation and availability of large quantity of DAT pharmacological data present both challenges and opportunities.

Curation and filtering the DAT pharmacological data sets

In order to assemble high-quality training data sets for QSAR modeling, adequate understanding and careful curation of the raw data retrieved from the databases are essential. One important issue is to differentiate the half maximal inhibitory concentration (IC50) and inhibition constant (Ki) in measuring the binding potencies of the ligand at a protein target. Whereas Ki can be derived from IC50 based on the Cheng-Prusoff equation, Ki is a more accurate representation of binding affinity than IC50, because IC50 can be influenced by the methods used for measurement [133]. Based on the Cheng-Prusoff equation, Ki values are always expected to be smaller than the IC50 values. However, if the same experimental approaches are employed, the trends of Ki and IC50 should be similar. Additionally, for transporter proteins, we can separate the data according to the assay type, either the radiolabeled inhibitor binding assay (referred to as “binding” below) or uptake inhibition (referred to as “uptake” below), as they represent inhibitory potencies of related but different biological processes [68].

Thus, the DAT pharmacological data retrieved from ChEMBL can be divided into four distinct sets: uptake IC50, uptake Ki, binding IC50, and binding Ki data sets (**Table 1**). Notably, among the four distinct data sets, there are some compounds appeared in more than one set (termed as “overlapping” compounds). By analyzing the trends among these compounds, we validate the points described above. First, in both the uptake pKi versus uptake IC50 and the binding pKi versus binding IC50 plots, we can observe that pKi values have a trend of being larger than IC50s, confirming the deduction from the Cheng-Prusoff equation described above (**Fig. 3C,D**). As expected, there is a strong correlation between uptake and binding pKi values, as well as between uptake and binding IC50 values (**Fig. 3A,B**). However, due to limited available data, it is not conclusive whether uptake pKi or pIC50 values tend to be larger than those of binding (**Fig. 3A,B**).

Hence, it is not advisable to combine either Ki and IC50, or uptake and binding data sets in building the QSAR models of DAT and likely other transporter proteins. As there are more Ki

data than IC50 data in the binding data sets, we mainly focus on using the binding Ki data for DAT QSAR modeling.

ML-based QSAR models using DAT binding data set

Machine learning (ML) and deep learning (DL) have been extensively applied in biological and pharmaceutical research, including protein structure prediction [134, 135], absorption, distribution, metabolism, excretion, and toxicity (ADMET) profiling [136, 137], QSAR modeling [58, 68], de novo drug design [138-140], and the blood–brain barrier (BBB) permeability prediction [141]. With the accumulation of large amount of pharmacological data in the databases such as ChEMBL and the drastic improvement of computation hardware in the recent decade, especially the applications of graphics processing units (GPUs) in scientific computing, ML and DL have risen to become the primary approaches in QSAR modeling, by handling the big data sets as well as the high volume of chemical features that can be generated for each compound.

Among many ML algorithms, XGBoost and RF have gained increasing popularity for their strong prediction performances, relative ease in usage, robustness with adjustable hyperparameters, and interpretability [59, 60, 142]. A comparison of ML- and DL-based QSAR models in the human *ether-à-go-go*- related gene (hERG) indicates that XGBoost provides the best prediction results [143]. XGBoost was found to be an excellent choice for both large and small data sets for QSAR modeling [144]. When utilizing the DAT binding data set, XGBoost-trained models exhibited superior performance [68].

To evaluate impact of the additional data on the quality of the QSAR models, we performed a benchmark analysis of the DAT binding Ki data sets retrieved from different ChEMBL releases. Across the ChEMBL releases from the past five years, we observed a noticeable enhancement in the coefficient of determination (R^2) value from 0.72 to 0.77 (**Table 2**). Similarly, mean square error (MSE), Pearson correlation coefficient, and Spearman's rank correlation

coefficient followed this positive trend, with the latest ChEMBL release yielding the most favorable benchmarks.

Note that while overall volume of the queried data continued to grow from ChEMBL 25 to ChEMBL 33, there was no significant increase in the number of unique compounds within the final training data sets (**Table 1**), which may partially be due to the downward trend of medicinal chemistry efforts on DAT (**Fig. 1**), and potentially on NSSs in general. Notably, there were changes of curation criteria between ChEMBL 25 and ChEMBL 27, resulting in a reduction in the number of inhibitor's Ki and IC50 data sets. These changes in ChEMBL led to an enhancement in the data set's quality, resulting in a 0.02 increase in the R^2 value (**Table 2**). Even though there was only a modest increase of 53 data points in the binding Ki training data set from ChEMBL 27 to ChEMBL 33, this change contributed to an overall benchmark improvement of 0.03 in R^2. Thus, even relatively moderate addition, update, and refinement of data may play a role in enhancing the quality of QSAR models.

While extensive ML/DL efforts have been made on various aspects of the NSSs [43, 145, 146], to our knowledge, no DL-based DAT QSAR research has been published. Because proper applications of DL may require larger data sets, we speculate that there are still not yet enough data points available in the public database to build robust DL-based DAT QSAR models. Indeed, ML-based models can use a small training data to still produce robust predictive QSAR models [147] and have been seen to outperform DL-based models in various cases [148].

Potential applications and challenge

Virtual screening provides a rapid and low-cost compounds screening in the early stage of drug discovery, by searching potential hits from databases [149, 150]. Such techniques have been applied in identifying new compounds in SERT [151-153]. The application of the DAT QSAR model in virtual screening may similarly explore a large compound library and to identify hit compounds and novel scaffolds. In addition, in a medicinal chemistry synthesis campaign, the predicted Ki

of candidate compounds by robust DAT QSAR models can help to prioritize the candidate compounds to be synthesized. The iterative prediction, synthesis, and pharmacological measurements are expected to both improve the quality of the QSAR models and improve the efficiency of synthesis campaign.

The screening process can also involve conducting counter- or synergistic-screening with other targets. In particular, we have established the protocol to screen the ligands for the DAT but against the human ether-a-go-go-related gene (hERG) [68]. The increasing concerns regarding the risks associated with hERG binding have led to a notable surge in the availability of hERG binding affinity data in both public databases and scientific literature. The prediction by the QSAR models can be instrumental in enabling the identification of potential medication candidates characterized by specific attributes, e.g., to aid in pinpointing high-affinity DAT inhibitors with minimal hERG affinity.

At physiological pH of 7.4, dopamine exists predominantly in its cationic form [154]. pH-induced changes between dopamine and DAT could alter their interactions and conformations. Specifically, the protonation of the amine group not only influences the conformation of dopamine but also introduces a positive charge, enhancing the interaction between the bound dopamine and negatively charged residues in DAT, such as Asp79 in the central binding pocket [155]. In comparison, modafinil is not in a charged form when it is bound in DAT [27]. Therefore, considering the proper protonation state of the ligands accordingly should improve the quality of the training data set, by providing a critical chemical context for the models to consider when making bioactivity predictions. However, while different algorithms and software packages are available to predict pKa, such as Epik [156] and MolGpka [157], which may generate decent pKa predictions in water, it is generally a challenging problem to predict the pKa of the ligands in the binding pocket of the target protein.

Conclusion

DAT is a key therapeutic target of SUDs. By collecting and analyzing the representative DAT ligands, we reveal that DAT binds to a variety of compounds, while there is still a large chemical space to be explored for novel DAT ligand scaffolds. The compilation of extensive DAT pharmacological activity data sets, coupled with the power of QSAR modeling, presents a promising avenue for exploring such a space.

Declarations of Competing Interests

No potential conflict of interest was reported by the authors.

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Figures and Figure Legends

Figure 1. Statistics of DAT activity data from ChEMBL33.

The DAT data set was queried and retrieved from entries in a locally installed instance of ChEMBL 33 (May 2023 release). We employed the same query criteria as in our previous study to filter the DAT pharmacological data set [68]. Number of publications on DAT ligands (A), number of related pharmacological activity data (B) and number of unique DAT ligands (C) were plotted along the years. If a compound has <0.999 pairwise similarity to all the other compound in the data set, we consider it as a unique compound. For panel C, the new unique compound in the current year is colored wheat, and the unique compounds found in previous years is in light grey. The total number of publications, pharmacological activity data, and unique compounds are 773, 7815, and 6689 respectively. The data sets in each panel are separated by dash lines between 2020 and 2021, to indicated what we observed that the curation in ChEMBL can be delayed for more than 2 years.

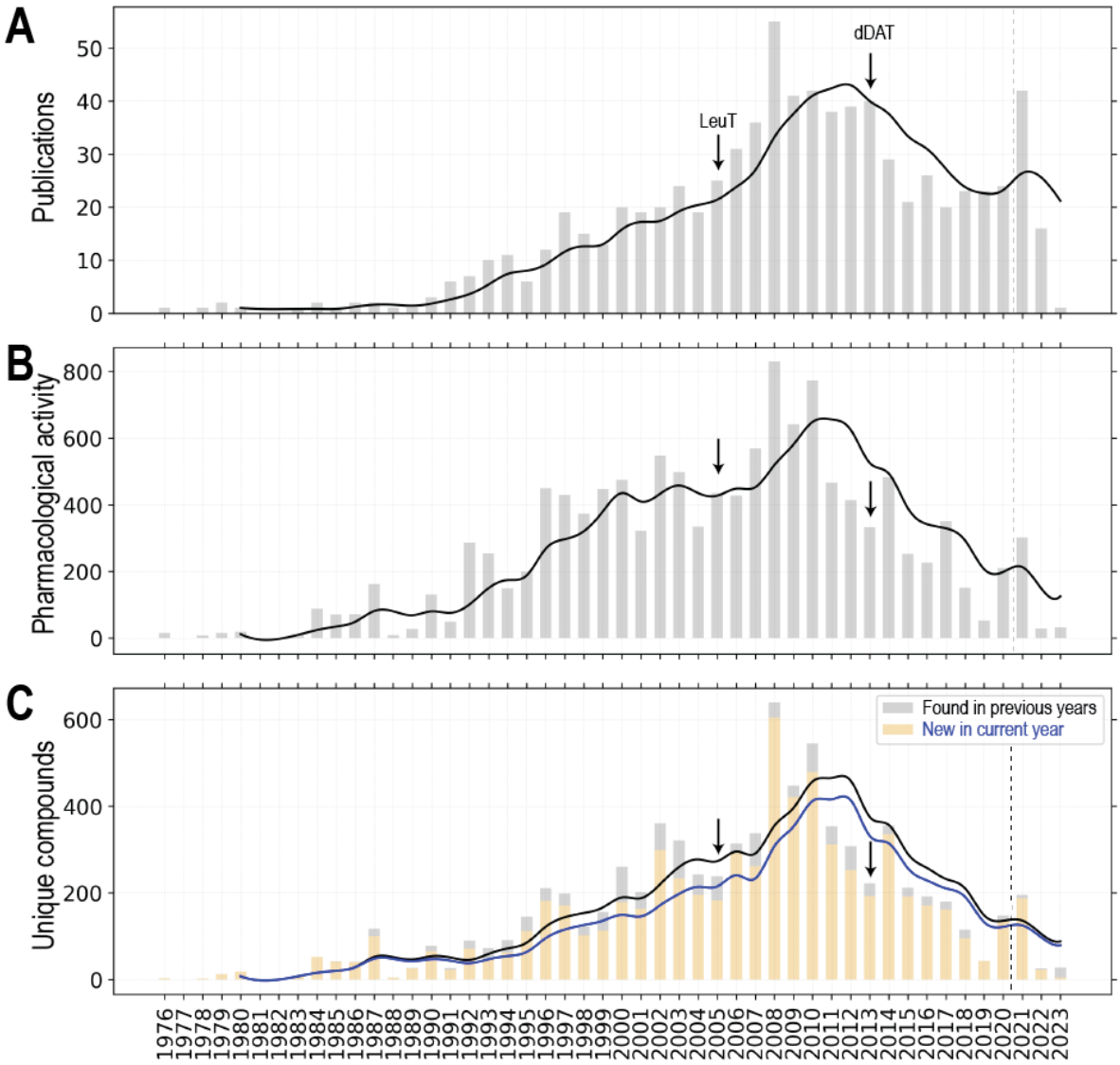


Figure 2. Clustering of representative DAT ligands.

For a total of 61 well-known DAT inhibitors collected from literature [21, 22, 77] and DrugBank [62]. To characterize these DAT ligands, we employed the hierarchical clustering approach implemented in the Schrodinger Maestro suite (version 2023-3). We used linear fingerprints, Tanimoto similarity, and average linkage method. Note that three pairs of compounds (armodafinil and modafinil, methylphenidate and dexmethylphenidate, and amphetamine and dextroamphetamine) are enantiomers and we only use modafinil, methylphenidate, and amphetamine when carrying out the clustering. Some known scaffolds were also used to adjust the final representative clusters. The single-member clusters are shown in **Fig. S1**.

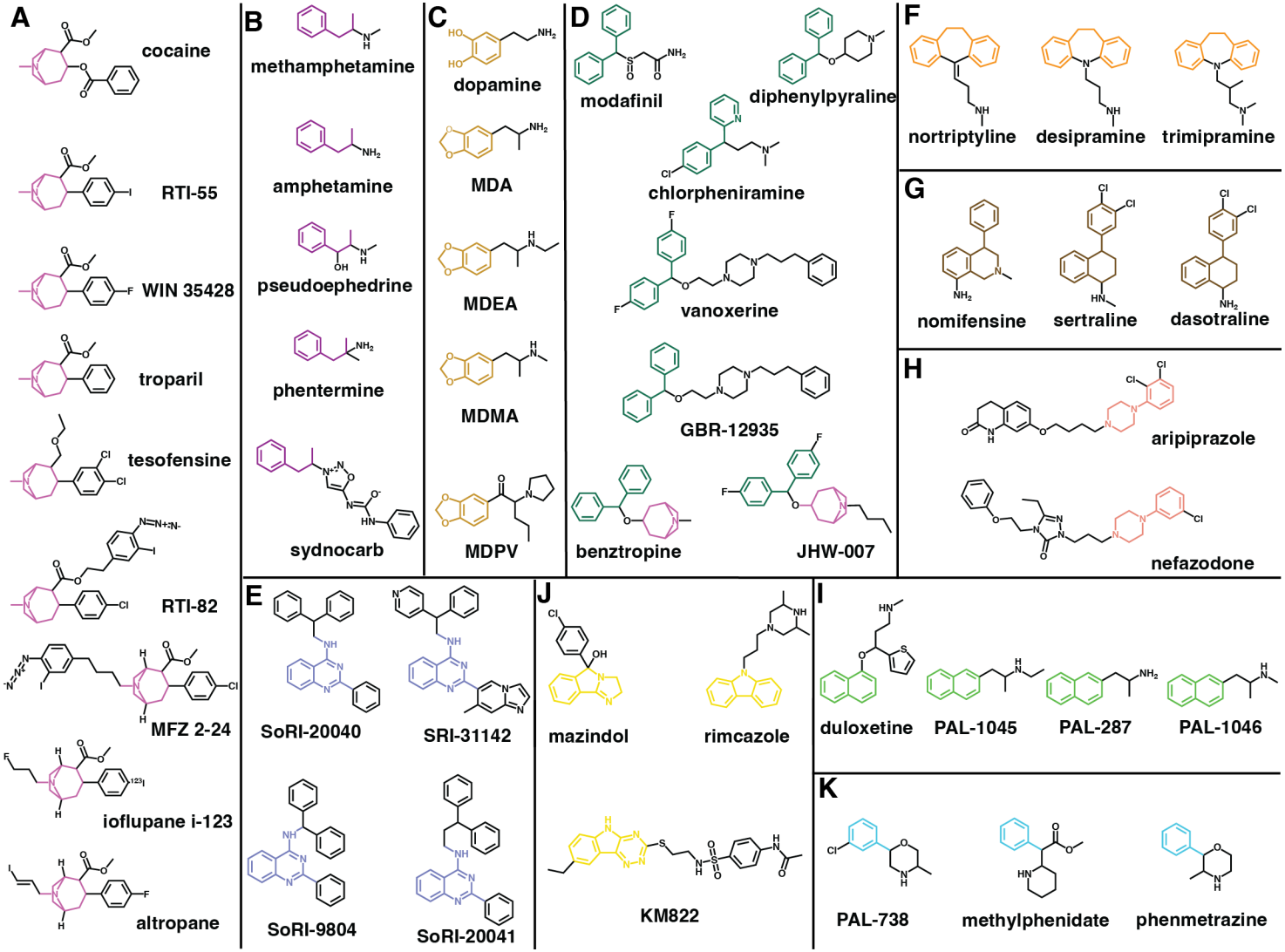

A
cocaine
RTI-55
WIN 35428
troparil
tesofensine
RTI-82
MFZ 2-24
ioflupane i-123
altropane
B
methamphetamine
amphetamine
pseudoephedrine
phentermine
sydnocarb
C
dopamine
MDA
MDEA
MDMA
MDPV
D
modafinil
diphenylpyraline
chlorpheniramine
vanoxerine
GBR-12935
benztropine
JHW-007
F
nortriptyline
desipramine
trimipramine
G
nomifensine
sertraline
dasotraline
H
aripiprazole
nefazodone
E
SoRI-20040
SRI-31142
SoRI-9804
SoRI-20041
J
mazindol
rimcazole
KM822
I
duloxetine
PAL-1045
PAL-287
PAL-1046
K
PAL-738
methylphenidate
phenmetrazine

Figure 3. Comparative analysis of DAT pharmacological data sets with correlation metrics and linear regressions.

The DAT pharmacological data can be divided into four sets, uptake pKi, uptake pIC50, binding pKi, and binding pIC50. The overlapping compounds between different data sets were extracted for comparisons. The correlation of determination (R^2) and the Pearson coefficient correlation (Rp), as well as the number of the overlapping compounds (referred as "overlapping"), are indicated at the top left corner of each panel for the indicated comparisons. The red lines are the linear regressions of the indicated data sets; the black dotted lines are the linear regressions with the slope restrained to 1. Note that slope-restrained regression results were not shown for panels B and D, due to poor goodness-of-fit.

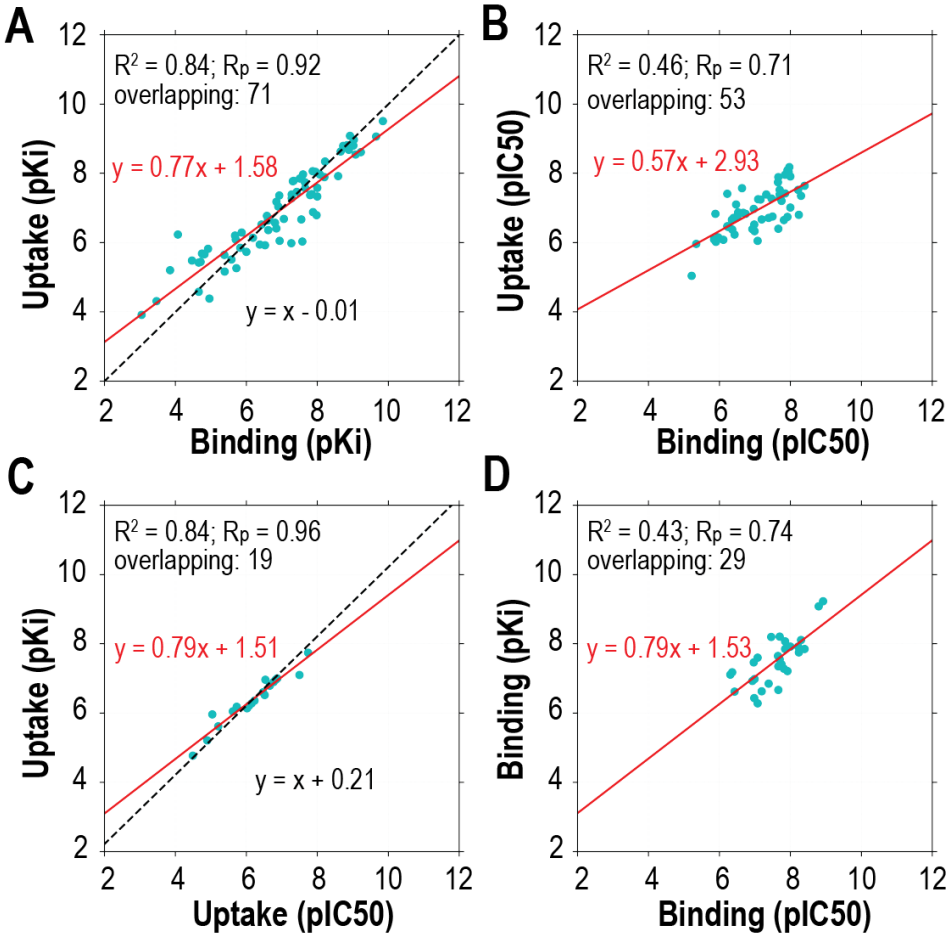


Table 1. Queried pharmacological activity data and training data sets of the DAT ligands from different ChEMBL releases.

version	Release date	queried data	uptake		binding	
			Ki	IC50	Ki	IC50
ChEMBL33	May 2023	14102 (7496)	366 (366)	646 (646)	1166 (1166)	482 (482)
ChEMBL31	Aug 2022	14099 (7470)	366 (366)	646 (646)	1166 (1166)	482 (482)
ChEMBL29	Jul 2021	13915 (7326)	366 (366)	646 (646)	1131 (1131)	482 (482)
ChEMBL27	May 2020	13456 (7049)	366 (366)	606 (606)	1113 (1113)	482 (482)
ChEMBL25	Mar 2019	13273 (6935)	350 (350)	593 (593)	1189 (1189)	556 (556)

The numbers of the unique compounds for each data set are shown in the brackets. Note that although some ChEMBL releases have the same numbers for the final training data sets, the value of pharmacological activity data may be different due to the measurement of the same compounds from new studies collected in new ChEMBL releases.

Table 2. Benchmarks of the DAT QSAR models trained with the XGBoost algorithm

release	binding Ki							
	R^2		MSE		Rp		Rs	
ChEMBL33	0.77	0.03	0.35	0.04	0.88	0.02	0.86	0.02
ChEMBL31	0.77	0.04	0.37	0.06	0.88	0.02	0.86	0.03
ChEMBL29	0.75	0.03	0.42	0.07	0.87	0.02	0.85	0.02
ChEMBL27	0.74	0.03	0.43	0.06	0.86	0.02	0.85	0.02
ChEMBL25	0.72	0.04	0.43	0.08	0.85	0.03	0.85	0.03

We construct 10 distinct QSAR models for each indicated ChEMBL release to mitigate any stochastic effects. For each reported metric, the first value is the average across the 10 QSAR models, which is followed by the standard deviation.

Supplemental Materials

Table S1. The pharmacological activities of some representative DAT ligands

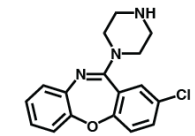
Name[a]	DrugBank ID	DAT (activity)	SERT (activity)	NET (activity)	DAT-SERT (Δactivity)	DAT-NET (Δactivity)	selectivity	cluster ID	Reference (DAT)
vanoxerine[#]	DB03701	10.22	7.62	7.10	2.60	3.12	DAT selective	D	158
RTI-55[#]		9.32	9.42	8.85	-0.10	0.47		A	159
SRI-31142[#]		8.72					DAT only	E	160
Dasotraline	DB12305	8.70	7.85	8.40	0.85	0.30		G	161
MDPV[#]		8.68					DAT only	C	162
GBR-12935[#]		8.43	6.21	6.20	2.22	2.23	DAT selective	D	163
altropane	DB04947	8.18	6.74		1.44			A	83
dextroamphetamine	DB01576	8.18	8.32	8.21	-0.14	-0.03		B	164
nomifensine[#]	DB04821	8.15	6.10	8.42	2.05	-0.27		G	165
benztropine[#]	DB00245	8.10	5.29	5.86	2.81	2.24	DAT selective	D	51
tesofensine	DB06156	8.10	7.96	8.49	0.14	-0.39		A	161
sydnocarb[#]		8.08	5.00	5.82	3.08	2.26	DAT selective	B	166
PAL-1046[#]		8.00					DAT only	I	99
JHW-007[#]		7.98	5.76	5.88	2.22	2.10	DAT selective	D	167
PAL-287[#]		7.90	8.47	7.96	-0.57	-0.06		I	168
RTI-82[#]		7.85					DAT only	A	169
sertraline	DB01104	7.60	10.12	6.80	-2.52	0.80	SERT selective	G	120
ioflupane I-123	DB08824	7.54					DAT only	A	
MFZ 2-24[#]		7.48					DAT only	A	170
mazindol[#]	DB00579	7.35	6.61	9.10	0.74	-1.75	NET selective	J	171
PAL-1045[#]		7.34					DAT only	I	99

PAL-738[#]		7.24					DAT only	K	99
MRS7292[#]		6.90					DAT only	L	172
dexmethylphenidate	DB06701	6.79	8.00	6.69	-1.21	0.10	SERT selective	K	173
WIN 35428[#]		6.77	7.52	5.96	-0.75	0.81		A	174
methylphenidate[#]	DB00422	6.72	5.01	6.66	1.71	0.06		K	175
rimcazole[#]		6.65	6.08	5.67	0.57	0.98		J	176
duloxetine	DB00476	6.62	9.10	8.13	-2.48	-1.51		I	177
troparil[#]		6.59	6.64	6.59	-0.05	0.00		A	174
nefazodone	DB01149	6.44	6.86	6.44	-0.42	0.00		H	120
venlafaxine	DB00285	6.44	8.42	6.86	-1.98	-0.42	SERT selective	L	120
bupropion[#]	DB01156	6.43	4.33	5.16	2.10	1.27	DAT selective	L	51
trodusquemine	DB06333	6.40					DAT only	L	178
diphenylpyraline	DB01146	6.38					DAT only	D	179
methamphetamine[#]	DB01577	6.34	4.50	6.96	1.84	-0.62		B	180
sibutramine	DB01105	6.30	5.96	5.25	0.34	1.05		L	
SoRI-9804[#]		6.28					DAT only	E	181
MDEA[#]	DB01566[*]	6.21					DAT only	C	20
amphetamine[#]	DB00182	6.19	4.41	7.15	1.78	-0.96		B	182
cocaine[#]	DB00907	6.19	6.85	5.80	-0.66	0.39		A	174
chlorpheniramine	DB01114	6.13	7.89	5.31	-1.76	0.82	SERT selective	D	
phenmetrazine[#]	DB00830	6.12					DAT only	K	183
MDMA[#]	DB01454	6.05	6.02	6.46	0.03	-0.41		C	164
nisoxetine[#]	DB09186[*]	5.94	8.85	8.82	-2.91	-2.88		L	184
nortriptyline[#]	DB00540[*]	5.88	8.16	8.50	-2.28	-2.62		F	
tamoxifen[#]	DB00675[*]	5.83	5.91	5.84	-0.08	-0.01		L	
Phentermine	DB00191	5.80	4.86	6.61	0.94	-0.81		B	185
SoRI-20041[#]		5.75					DAT only	E	113
pseudoephedrine	DB00852	5.68					DAT only	B	186

MDA[#]	DB01509[*]	5.62	5.64	6.15	-0.02	-0.53		C	164
desipramine[#]	DB01151[*]	5.52	7.70	9.22	-2.18	-3.70	NET selective	F	187
Aripiprazole	DB01238	5.49	7.50		-2.01			H	188
KM822[#]		5.44					DAT only	J	35
trimipramine	DB00726	5.42	6.83	5.61	-1.41	-0.19	SERT selective	F	108
ibogaine[#]		5.39	6.23		-0.84			L	189
amoxapine	DB00543	5.37	7.24	7.80	-1.87	-2.43		L	108
SoRI-20040[#]		5.27					DAT only	E	181
modafinil[#]	DB00745	5.19	<3.3(N.D.)	4.45		0.74		D	190
armodafinil	DB06413	5.18	3.63	3.77	1.55	1.41	DAT selective	D	105
escitalopram	DB01175	5.09	9.05	4.98	-3.96	0.11	SERT selective	L	191
dopamine[#]	DB00988	5.06	3.00	5.28	2.06	-0.22		C	174

For each DAT ligand, we first attempted to retrieve its pharmacological activity data for DAT, SERT and NET from ChEMBL 33, and then supplemented by literature search. When a compound has pKi, pKd and pIC50 data in ChEMBL, we chose to report either pKi or pKd; then if more than one pKi, pKd, or pIC50 data points are available, we chose to report the highest one. For the ligand that we found having all DAT, SERT, and NET activity data from the same publication in our literature search, we replaced the data retrieved from ChEMBL with the ones from the literature search. Additional information for each compound, include other references we collected can be found on https://github.com/NIDA-IRP-CCMB/QSAR_DAT-hERG. The Δactivity was then calculated to detect the DAT, SERT, and NET selective ligands, with Δactivity >= 1 for one transporter over both the other two transporters. The yellow in reference (DAT) indicates that the entry in ChEMBL has activity data, but no publication record. The grey means the best pKi has been annotation wrongly in ChEMBL, and the second best pKi was used in the table. [#]DAT ligands collected from the well-respected reviews [21, 22, 77]. [*]DAT ligands that can be found in DrugBank, but not listed as targeting DAT in DrugBank.

Figure S1. Single-member clusters



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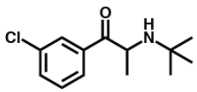
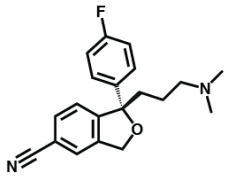
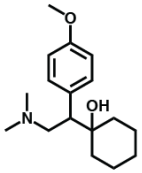


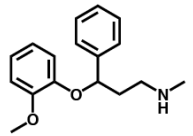
bupropion



escitalopram



venlafaxine



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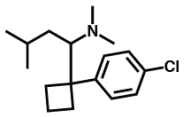

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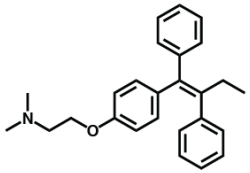

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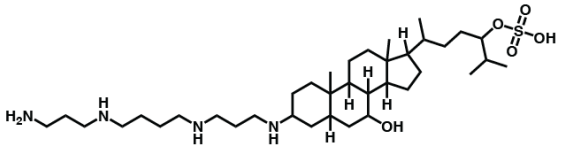
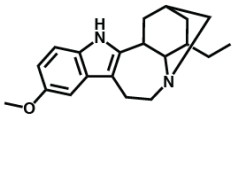
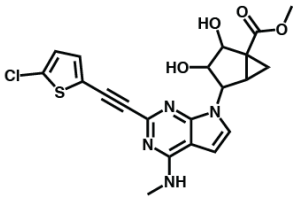


trodusquemine



ibogaine



MRS7292

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