Comparison Data Sets for Benchmarking QSAR Methodologies in Lead Optimization

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2D and 3D QSAR techniques are widely used in lead optimization-like processes. A compilation of 40 diverse data sets is described. It is proposed that these can be used as a common benchmark sample for comparisons of QSAR methodologies, primarily in terms of predictive ability. Use of this benchmark set will be useful for both assessment of new methods and for optimization of existing methods.

INTRODUCTION

Lead optimization is a vital component of the drug discovery process in which a chemical showing promise is modified to greatly improve its usefulness as a drug. Computational methods like quantitative structure activity relationships (QSAR) can facilitate this process by elucidating the chemical characteristics that are favorable and unfavorable through statistical analysis of a series of chemicals.[1,2] QSAR methods derive correlations between the properties/descriptors of molecules and their biological activities (e.g., inhibition constants or binding affinities). Since the advent of Free Wilson and Hansch analysis, numerous methods have been published in the literature for structure−activity relationships modeling. These methods can be broadly categorized as two-dimensional (2D-QSAR) or three-dimensional (3D-QSAR) QSARs. 2D-QSAR methods commonly use chemical information derived from connection tables of molecules, molecular holograms, fingerprints, and traditional molecular properties like lipophilicity, polarizability, number of rotatable bonds, and molecular weight. 3D-QSAR methods consider the physicochemical properties of the ligand in their hypothesized bioactive conformations.[3−7]

Some QSAR methods are particularly suited to predict activities of chemically diverse chemicals. Such approaches are particularly useful in the very early stages of drug discovery (e.g., hit identification) or when building reusable general models (e.g., ADMET prediction). Other QSAR approaches are particularly useful for modeling the structure−activity relationship of a relatively small set of structurally similar chemicals. These methods are best suited to aid the lead optimization stage of drug development and are the focus of this paper.

Lead optimization aims to improve the pharmacological characteristics of a small number of lead compounds that have already demonstrated some worth. This typically involves an iterative process of testing a relatively small number of chemical analogues, analysis or results, and selection of new chemicals to test in the next iteration. A number of iterations may be required until a chemical or small set of chemicals meeting the requirements is found. QSAR can aid in the analysis step of each iteration through discovery of the characteristics having the greatest positive and negative influences on the activity of a chemical and prediction of which chemical variations are most likely to improve activity. These predictions are not expected to be perfectly accurate but rather to facilitate the rational section of chemicals for the next iteration of testing that are most likely to have improved activity.

THE NEED FOR THE BENCHMARK DATA SETS

There is an abundance of existing QSAR methodologies that are potentially appropriate to such an application. To date, however, it is very difficult to benchmark their respective performance. This is an important limitation on the development of improved methods and the utilization of the best methods available. A suitable method of benchmarking will allow developers of new methodologies to determine whether their innovation is actually an improvement in terms of predictive ability. In addition to the benefits for new methods, existing methods have many variations (e.g., parameter settings) that can potentially be optimized to improve their overall predictive performance if a reasonable benchmarking approach is available. By clarifying the relative predictive performance this will also make it much easier for users of the technology to make well-informed choices concerning the method to use and the best general set of parameters to use for the method. Currently, this is a difficult choice that is guided mainly by popularity or familiarity of use of a particular methodology or alternatively by trialling multiple methodologies for the specific project. By clarifying the selection of methods and settings it will enable more researchers to make use of the valuable benefits that QSAR can bring into lead optimization-like research projects.

An important step toward improving this situation is to make available a set of data sets that are (i) commonly used to determine predictive performance, (ii) diverse in nature, and (iii) of sufficient sample size to allow accurate estimation and statistical testing of mean differences in predictive ability. A typical report on a new QSAR method will involve the demonstration of the predictive ability in a very small number of data sets. The popular ‘steroids benchmark set’ is a set of steroids with known affinities for human corticosteroid

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binding globulin that has been widely used for validation in the development of different QSAR methods.[8,9] With the exception of this data set[8] the same set of data sets is rarely utilized making comparison difficult. In addition, the use of a single data set or a small number of data sets makes any comparison rather anecdotal in that it is not possible to determine whether the difference observed can be attributed to chance (random error) or not. Every data set (corresponding to a different set of chemical analogues binding to a different target) is different, and the ability of a method to model the data set well will vary from data set to data set. Thus, in order to make a generalization concerning how well the method will work on other data sets in general it is necessary that the sample of data sets used to demonstrate the method is both sufficiently large and representative of typical variation between data sets. If this requirement is met, then statistical tests may be performed to determine the likelihood that the differences in average predictive performance between methods can be attributed to chance or not.

In addition to allowing determination of statistically significant differences on average between methodologies, assessing methodologies using multiple data sets allow for basic analysis of the variability between data sets and potentially prediction of the type of data sets that the methodology will perform best with. For example, as part of a comparison of CoMSIA models generated using different subsets of molecular fields using 23 data sets it was found that although there was a general trend toward a particular set of molecular fields being optimal on average, there was considerable variation between individual data sets in terms of the best performing set of molecular fields. Furthermore, data sets could be clustered into four main groups with different molecular field preference profile.[10] A recent study[11] has also assessed the effect of commonly used empirical and semiempirical partial charge calculation techniques on CoMFA and CoMSIA prediction accuracy using 30 diverse data sets. It was found that on average, 25−40% of the studied data sets showed significant improvement in the predictive ability of CoMFA/CoMSIA models just by changing the partial charge calculation method used to derive the electrostatic field descriptors. The best methods could be determined on average, but there was considerable variation between the best charge calculation methods for individual data sets. As this interdata set variability is better appreciated novel approaches may be developed to predict a priori which methodology is best suited to a particular data set, based on specific chemical characteristics of the data set. Such an exercise will require a large number of data sets to correlate data set characteristics with the performance of the modeling methodology.

Recently, a directory of useful decoys (DUD) with ligands for 40 different targets was collated as benchmarking sets for molecular docking.[12] This set of benchmarks focuses on assessment of computational methods for enriching active chemicals from decoys of similar physical characteristics (e.g. refs 13−16), an approach that is well suited to the lead identification phase of drug discovery. An expanded benchmark for QSAR studies can similarly play an important role in the advancement of methods for lead optimization stage by providing a platform to compare and optimize both currently available and novel technologies.

OVERVIEW OF THE BENCHMARK DATA SETS

Forty diverse data sets suitable for benchmarking of QSAR analysis of lead optimization-like projects were collated. A typical lead optimization project will involve relatively accurate assaying of a relatively limited set of chemicals that will often, but not necessarily, have a common substructure. Thus, suitable data sets require that the chemicals in each data set are relatively similar in overall structure, shape, and chemical properties and will have a quantitative estimate of the biological property measured. Due to the relative similarity in chemical structure within a data set, 3D-QSAR utilizing alignment of the chemical structures is a common analysis approach. This is distinct from the larger and more structurally diverse sets of chemicals that are usually part of hit/lead identification and global ADME modeling. Such data sets are generally better handled by methodologies that can handle diverse chemical structures (e.g., pharmacophore analysis or 2D-QSAR) and are generally outside of the intended scope of the benchmark set presented here.

Each data set is a set of similar chemical structures and some measured chemical property which varies significantly between the chemicals in the set. The data sets were sourced by contacting the authors of recent 3D-QSAR publications or from the Supporting Information. Table 1 provides a brief description of each data set in terms of biological activity, chemical structure, and sample size. Many data sets have a common substructure, and for these a generic structure is presented with regions of variability marked. Some data sets, however, do not have a single or small number of common substructures. These data sets are still relevant for performing QSAR analysis as many QSAR methods are able to deal with modest structural variability as long as there is sufficient similarity in shape, molecular fields, or pharmacophoric features. As an example, the DR data set consists of structurally diverse dopamine antagonists which do not contain a common substructure. In the original study they were aligned using five pharmacophoric features and successfully analyzed using CoMFA and CoMSIA 3D-QSAR techniques. The SMILES chemical structures and related bioactivities of each molecule of each data set are included in Appendix A of the Supporting Information to facilitate future benchmarking of QSAR methodologies. In order to display the chemical variation between each data set, Filter[17] was used to generate a number of molecular properties of interest. Appendix B in the Supporting Information summarizes the descriptor values for each data set.

Based on the mean values of molecular properties for each data set, the data sets were hierarchically clustered using the hclust function in the 'R' statistical environment.[18] The molecular descriptor data were normalized to have a mean of zero and unit variance prior to clustering based on Euclidean distance and Ward (minimum variance) agglomeration. The resulting dendrogram is displayed in Figure 1. Data sets that are most similar in terms of their generic molecular properties are grouped together, and thus the clusters allow a simple overview of the diversity and similarity between data sets. Data sets were clustered mainly into five groups. Data sets with similar profile of molecular properties (e.g., the Steroids-AI and ACE-THERM data sets) are clustered together, whereas data sets with divergent

Table 1. Source Reference(s) and a Brief Description of Each Data Set[a]

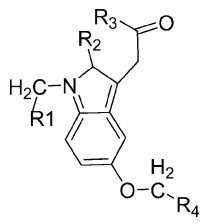
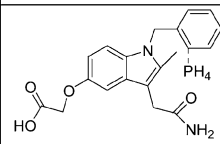
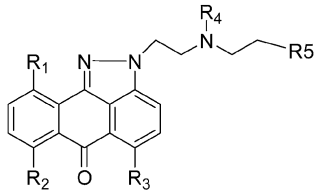
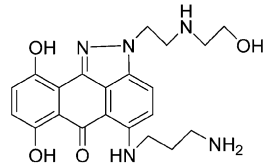
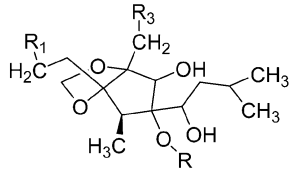
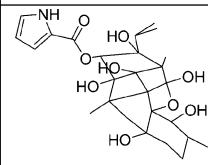
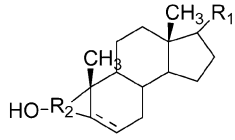
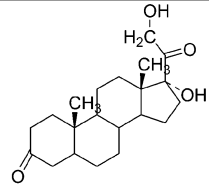
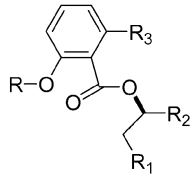
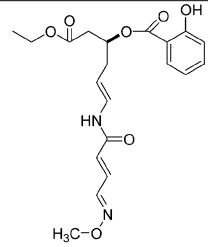
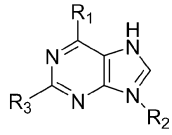
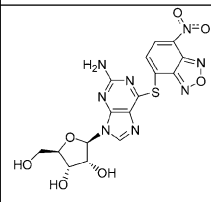
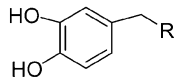
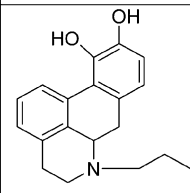
Data Set Abbreviation and Generic Structure(s)	Example Structure(s)	Description of activity	N, Activity Range[#] (number of log units), Molecular Weight Range
PLA2[19] 		Inhibition of phospholipase A2 enzyme	N = 11, Bio_Act: 4.5, Mol_Wt: (308, 442)
APZ[20] 		Anti-cancer activity.	N = 17, Bio_Act: 2.2, Mol_Wt: (299, 543)
RyR[21] 		Binding affinity of ryanoids to the ryanodine receptor	N = 18, Bio_Act: 3.1, Mol_Wt: (401, 674)
STEROIDS[22, 23] 		Binding affinity to the corticosteroid binding globulin (CBG)	N = 21, Bio_Act: 2.9, Mol_Wt: (270, 363)
VATP[24] 		Inhibition of vacuolar type (H+) ATPases	N = 23, Bio_Act: 5.7, Mol_Wt: (332, 805)
TP-II α[25] 		Inhibition of topoisomerase II enzyme	N = 25, Bio_Act: 3.5, Mol_Wt: (206, 686)
D2A[26] 		Binding affinity to dopamine (D_2) receptors	N = 26, Bio_Act: 4.6, Mol_Wt: (154, 296)

Table 1. Continued

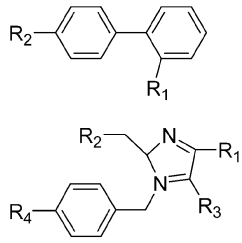
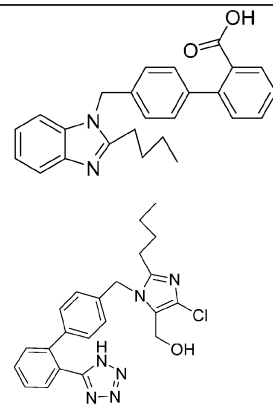
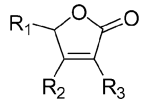
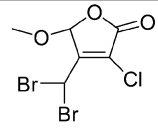
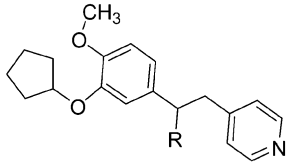
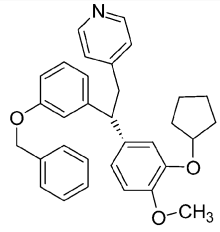
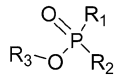
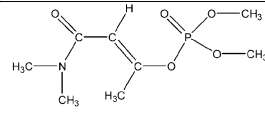
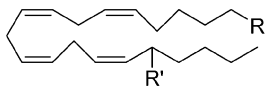
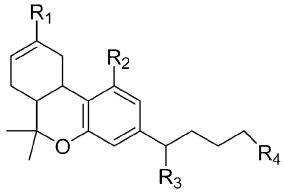
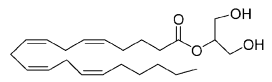
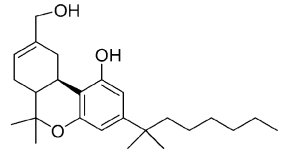
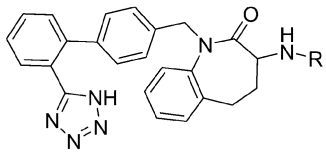
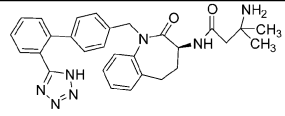
Data Set Abbreviation and Generic Structure(s)	Example Structure(s)	Description of activity	N, Activity Range[#] (number of log units), Molecular Weight Range
ARB[27] 		Inhibition of angiotensin II receptor.	N = 28, Bio_Act: 3.9, Mol_Wt: (361, 483)
MX[28] 		Mutagenic potential of (3-chloro-4-(dichloromethyl)-5-hydroxyl-2(5H)-furanone) wth test strain TA100.	N = 29, Bio_Act: 5.3, Mol_Wt: (114, 351)
PDE[29] 		Inhibition of the phosphodiesterase-IV enzyme.	N = 29, Bio_Act: 2.6, Mol_Wt: (363, 618)
AChE_Tox[30] 		Irreversible inhibition of AChE.	N = 30, Bio_Act: 3.3, Mol_Wt: (141, 381)
CBRA[31]  	 	Binding affinity to the cannabinoid I receptor.	N = 31, Bio_Act: 4, Mol_Wt: (310, 435)
GHS[19] 		Median effective dose for growth hormone secretagogues	N = 31, Bio_Act: 3.5, Mol_Wt: (411, 630)

Table 1. Continued

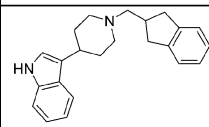
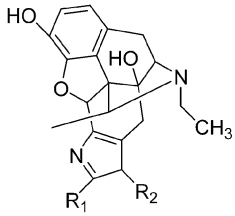
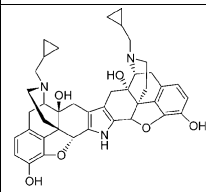
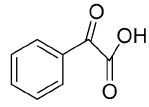
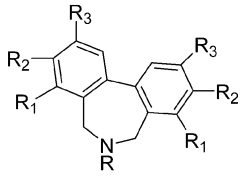
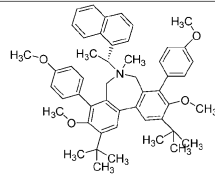
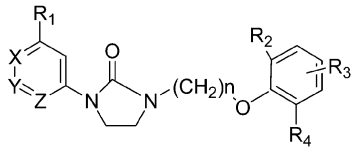
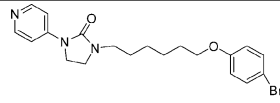
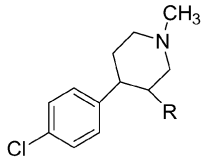
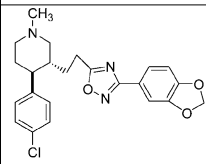
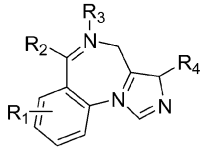
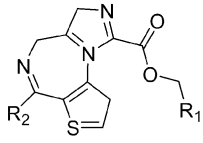
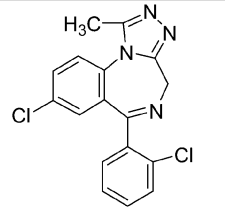
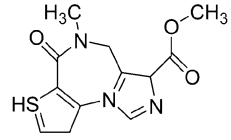
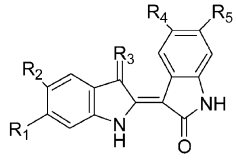
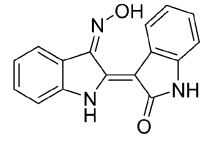
Data Set Abbreviation and Generic Structure(s)	Example Structure(s)	Description of activity	N, Activity Range[a] (number of log units), Molecular Weight Range
DR[32, 33]		Inhibition of dopamine (D_2) receptor	N = 38, Bio_Act: 4.6, Mol_Wt: (309, 411)
KOA[34] 		Inhibition of the kappa opioid receptor.	N = 39, Bio_Act: 2.9, Mol_Wt: (416, 637)
YOPH[35]		Inhibition of Yersinia protein tyrosine phosphatase (YopH)	N = 39, Bio_Act: 4.3, Mol_Wt: (141, 679)
PTC[36] 		Enantiomeric selectivity of phase-transfer asymmetric catalysts	N = 40, Mol_Wt: (294, 1031)
EV71[37-39] 		Inhibition of Enterovirus 71	N = 41, Bio_Act: 4.1, Mol_Wt: (351, 448)
DAT[40] 		Inhibition of dopamine transporters.	N = 42, Bio_Act: 4.0, Mol_Wt: (241, 449)
DIAZEPAM[22, 41]  	 	Binding affinity to benzodiazepine receptor isoforms	N = 42, Bio_Act: 4.1, Mol_Wt: (271, 418)
GSK3B[42] 		Inhibition of glycogen synthase kinase 3	N = 42, Bio_Act: 3.7, Mol_Wt: (262, 445)

Table 1. Continued

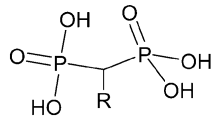
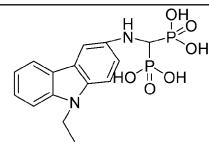
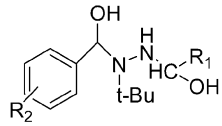
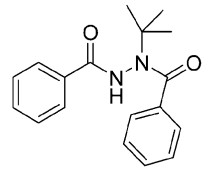
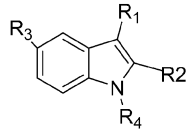
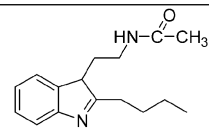
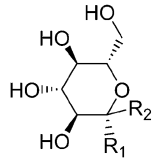
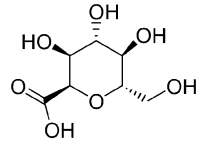
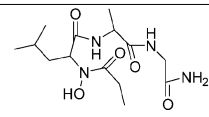
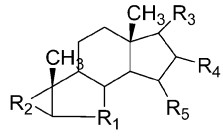
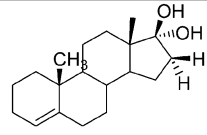
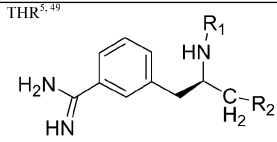
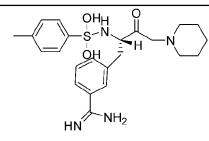
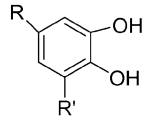
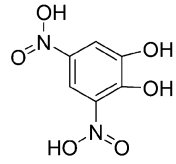
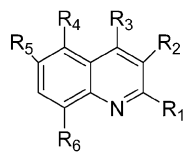
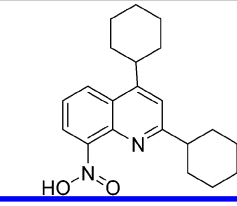
Data Set Abbreviation and Generic Structure(s)	Example Structure(s)	Description of activity	N, Activity Range[#] (number of log units), Molecular Weight Range
TCHK[43] 		Inhibition of *Trypanosoma cruzi* hexokinase enzyme	N = 42, Bio_Act: 2.6, Mol_Wt: (228, 432)
ECR[44] 		Insecticidal activity of ecdysone agonists.	N = 50, Bio_Act: 3.3, Mol_Wt: (290, 457)
MT[45] 		Binding affinity to melatonin receptors	N = 56, Bio_Act: 4.8, Mol_Wt: (292, 669)
GPB[5, 46] 		Inhibition of glycogen phosphorylase b	N = 66, Bio_Act: 5.5, Mol_Wt: (178, 365)
THERM[5, 47]		Inhibition of thermolysin protease.	N = 76, Bio_Act: 9.7, Mol_Wt: (123, 6998)
AI[48] 		Inhibition of steroid aromatase.	N = 78, Bio_Act: 4.5, Mol_Wt: (270, 521)
THR[5, 49] 		Binding affinities towards thrombin enzyme	N = 88, Bio_Act: 4.1, Mol_Wt: (290, 676)
COMT[50] 		Inhibition of catechol-O-methyltransferase.	N = 92, Bio_Act: 3.6, Mol_Wt: (154, 451)
ATA[51] 		Anti-tuberculosis activity.	N = 94, Bio_Act: 4.9, Mol_Wt: (172, 456)

Table 1. Continued

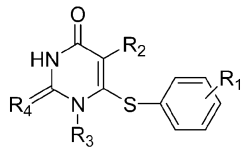
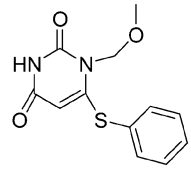
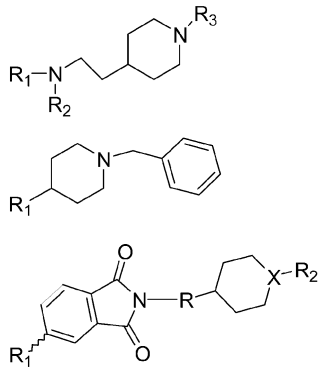
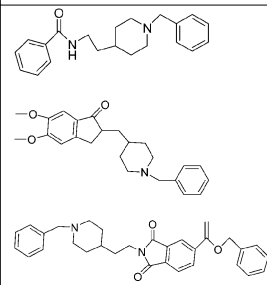
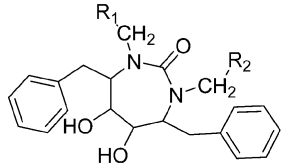
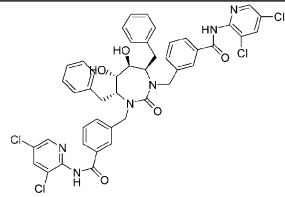
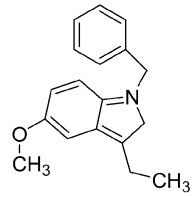
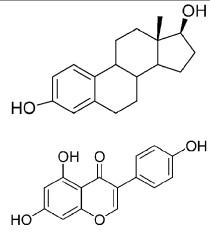
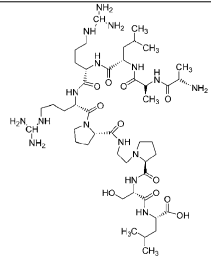
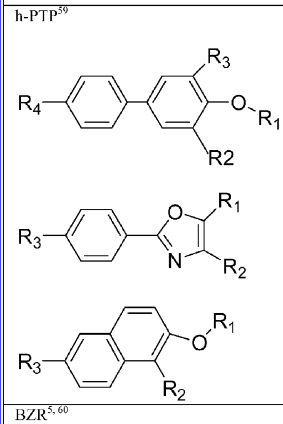
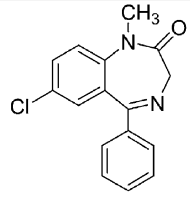
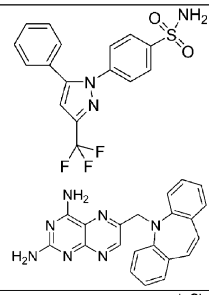
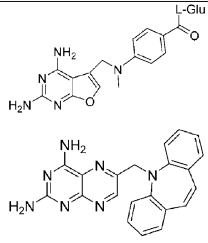
Data Set Abbreviation and Generic Structure(s)	Example Structure(s)	Description of activity	N, Activity Range[#] (number of log units), Molecular Weight Range
HIVRT [52, 53] 		Inhibition of HIV-1 reverse transcriptase	N = 101, Bio_Act: 5.5, Mol_Wt: (262, 473)
AChE[5] 		Inhibition of acetylcholinesterase (AChE).	N = 111, Bio_Act: 5.2, Mol_Wt: (247, 554)
HIVPR[54] 		Inhibition of human immunodeficiency virus protease	N = 113, Bio_Act: 5.9, Mol_Wt: (354, 905)
ACE[5, 47]		Inhibition of angiotensin-converting enzyme.	N = 114, Bio_Act: 7.8, Mol_Wt: (147, 572)
EDC[55, 56]		Relative binding affinity to the Estrogen receptor	N = 123, Bio_Act: 7.1, Mol_Wt: (108, 611)
AMPH1[57, 58]		Binding affinity to the human amphiphysin-1 (hAmph1) SH3 Domain.	N = 130, Bio_Act: 3.5, Mol_Wt: (995, 1359)

Table 1. Continued

Data Set Abbreviation and Generic Structure(s)	Example Structure(s)	Description of activity	N, Activity Range[#] (number of log units), Molecular Weight Range
h-PTP[59]		Inhibition of human protein tyrosine phosphatase 1B	N = 135, Bio_Act: 2.1, Mol_Wt: (314, 813)
BZR[5,60]		Binding affinity to the benzodiazepine receptor.	N = 163, Bio_Act: 3.9, Mol_Wt: (174, 429)
COX2[5]		Inhibition of cyclo-oxygenase-2	N = 322, Bio_Act: 5.0, Mol_Wt: (288, 475)
DHFR[5]		Inhibition of dihydrofolate reductase.	N = 397, Bio_Act: 6.5, Mol_Wt: (174, 520)

[a] The # symbol denotes the following: the active range is defined as the number of log units between the least and most active chemical in the data set.

properties (e.g., AMPH1 and PTC data sets which have higher molecular weight) are clustered separately.

SUGGESTIONS FOR COMPARISONS INVOLVING THE BENCHMARK DATA SETS

An important consideration is to ensure that reproduction of the results of a study based on the benchmark set is as easy as possible for others. Toward this end, it is suggested that all steps undertaken should be explicitly detailed, especially those that are not standard. Additionally, it is commonly possible to use scripts to both automate and document the use of various modeling software (e.g., SPL for Sybyl[22] and python for Open Eye toolkits). If possible, use and inclusion of such scripts as Supporting Information is encouraged to enable simple and accurate reproduction of the approach used.

If the starting point of the comparison is not the SMILES data sets available in the Appendix (e.g., use of prealigned data sets or data sets with partial charges previously calculated), then the source of these data sets should be reported. If any of the data sets used are not publicly available elsewhere, then they should be included as a supplementary file to the publication.

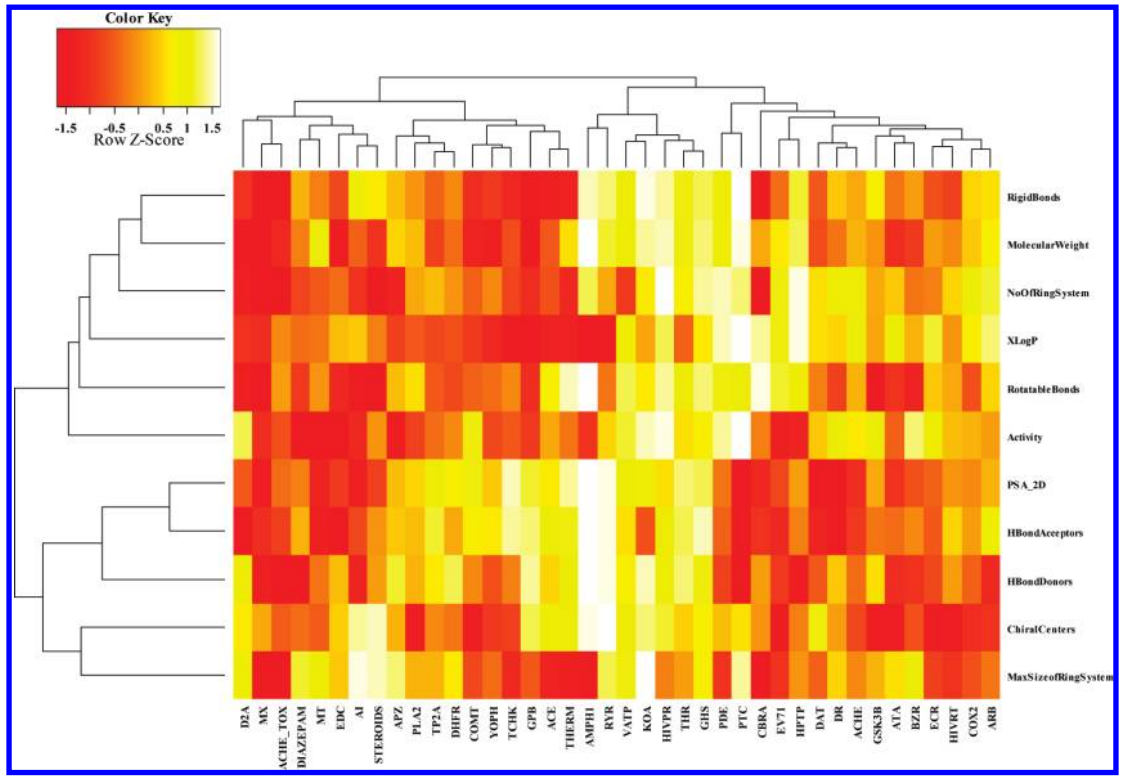


Figure 1. Clustered dendrogram and heat map based on the mean value of simple molecular descriptors for each data set. Data sets that are grouped together are more generally similar in terms of the molecular descriptor profile. Colors in the heat map indicate the relative value (red indicates a low value and yellow/white indicates a high value) of the data set relative to the other data sets in terms of a specific molecular descriptor.

Any data preparation undertaken prior to model training (e.g., 3D structure calculation, data set alignment, and partial charge calculation) should be detailed including both the software and settings used. If significant data preparation is undertaken, then it would be helpful to include the processed data sets as supplementary files to the publication. In this way future comparisons may be able to utilize the processed (e.g., 3D aligned) data sets as a starting point rather than undertake this preliminary work based on the SMILES based chemical structures included with this publication.

Details of the model construction/training training should be included as well as how validation was undertaken. The optimal method of assessing predictive ability is controversial, and thus the most important aspect is that the method used is described well (e.g., how chemicals for the test set were selected, the statistical measures of predictive performance used) and that the results are only directly contrasted to other publications that use a comparable approach (i.e., same data set preparation and validation). It is generally considered best to have measures of predictive performance that separate bias and precision (e.g., mean error and variance of errors). Multiple methods of predictivity assessment (validation) are suggested if possible to make it easier to compare studies and also to get a better feel for the predictive ability.

One very important aspect of assessing model training and validation is that care should be taken not to optimize the model on the method used to assess predictive ability. This is commonly an issue when variable selection procedures are used as part of model development. For each methodology being assessed in the study the predictive performance should be determined only once after all model training has been concluded to avoid biasing the assessment of predictive ability.

LIMITATIONS OF THE BENCHMARK DATA SETS

Although important, prediction is only one aspect of a QSAR model. Another important property for some QSAR methodologies is the intuitive nature of the model and how easy it is for chemists to utilize the model to select chemical changes that are likely to improve activity. Such a property is very difficult to measure objectively and beyond the consideration of the benchmark data sets. Similarly, some QSAR methods are able to give insight into the molecular interactions contributing to the activity (e.g., an understanding of the protein active site that the chemicals bind to). Once again, this is difficult to objectively measure and is beyond the scope considered here.

Validation of predictive ability of a model is a contentious issue, especially with a static set of chemicals. When it is possible to select and test an additional representative set of chemicals subsequent to model construction, this is generally considered to be the best test of a model's prediction ability. In situations such as the benchmark data sets in which the data sets are to be used for both model construction and validation, there are many possible alternatives for how the data are split between these two tasks. It is unlikely that a single method will be used for all comparisons involving the benchmark data sets, and as such an important consideration will be explicitly detailing the steps undertaken so that it may be reproduced by others and thereby allowing comparison.

Although utilizing a range of data sets to compare, optimize, or better understand the performance of the particular methodology is superior in many ways to anecdotal studies based on a single or small number of data sets, the data set benchmarks proposed here are still only a sample of all possible data sets that will potentially be modeled in lead optimization-like projects. Although increasing sample size aids in the reduction of random error in comparisons, it is still possible to both inappropriately analyze the benchmark set and inappropriately interpret results based on the benchmark set.

Additionally, as gaps in the types of data sets included in the benchmark set are subsequently discovered, the benchmark set will need to grow to mitigate these limitations. It is intended that the benchmark set in its current form will allow clearer understanding of the differences in performance on average across data sets between different methodologies and a greater insight into the variability in performance of a methodology between different data sets. This should subsequently lead to a deeper understanding of the data set characteristics that influence the utility of a methodology. For this later aim to be fully achieved the benchmark sets may need to grow further both in size and diversity.

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Supporting Information Available: SMILES chemical structures and related bioactivities of each molecule of each data set (Appendix A) and mean and range values of the selected molecular descriptors for each data set (Appendix B). This material is available free of charge via the Internet at http://pubs.acs.org.

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