

# Physicochemical Properties of Natural Based Products versus Synthetic Chemicals

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**Abstract:** The majority of the currently used cosmetics and drugs are natural products-based compounds or their derivatives. This could add weight to the argument that natural based products are inherently better tolerated in the body than synthetic chemicals and have higher chance to be approved as new drugs. The present study was undertaken to analyze a natural product database compared to synthetic chemicals and to search for discriminative physicochemical properties that may probably help in differentiating between natural and synthetic compounds. We have formulated rules to assess the natural likeness of chemicals and thereby discriminate between natural-based and synthetic chemicals. A Mathews Correlation Coefficient of 0.5 was obtained; nearly 81% of natural-based products and 68% of synthetic chemicals were precisely classified using this filter. The property criteria for drug-likeness and lead-likeness are more pronounced in natural products rather than synthetic ones. The fraction of synthetic chemicals which are natural-like could have higher chance to be successful drug.

**Keywords:** Natural product, natural-likeness, drug-likeness, *in silico* prediction model, chemo-informatics.

## INTRODUCTION

Natural product-based medicines, particularly, herbal-based drugs represented about 80 percent of all drugs in use by 1990 [1-3]. They represented the main source of leads for the development of new drugs for centuries [4-6]. During the past couple of decades, after the introduction of high throughput synthesis and combinatorial chemistry, natural products became less significant source of drugs and leads. Although global expenditure on drug research has doubled since 1991, the number of new drug entities approved annually decreased by 50% or even more [7, 8]. To change this situation, the players in the pharmaceutical industry shifted their interest back to natural or natural-based products [9-15]. It becomes commonly accepted that natural based products are inherently better tolerated in the body and have innate advantages for drug discovery and development over synthetic chemicals [16-19].

Although computational methods are well established in drug discovery and molecular design [20-22], their application in the field of natural products is still in its infancy. During the last decade we have seen an increased interest in the application of *in silico* tools in the natural product-based drug discovery in order to accelerate identification of bioactive natural-based products, maximize their efficacy and minimize potential side effects. Computer assisted approaches [23], such as docking [24-27], pharmacophore

modeling [28-30] and virtual screening [31-34] have been carried out and reported related to the field of bioactive natural products. In order to introduce the natural products features into the design of drug candidates, the discriminative features of natural products need to be unraveled. Most scientific reports utilized structural features and substructures for scoring natural likeness of products [35-38]. However, the utility of ranges-based filters which is composed of 2D physicochemical descriptors in modeling could give sometimes less discriminative models but guarantee finding new chemical entities in higher rates [39, 40]. The present study aims to introduce a new highly efficient rules-based filter to assess the natural likeness of chemicals utilizing physicochemical properties and thereby differentiates between natural-based and synthetic chemicals.

## MATERIALS AND METHODS

A natural products database of commercially available natural products and natural product derivatives was downloaded from ZINC database (ZINC natural products <http://zinc.docking.org/catalog/npd.in>). Other twenty thousands synthetic compounds were selected from ZINC database of commercially available chemicals (<http://zinc.docking.org/subset1/>). All selected synthetic chemical are drug like according to Lipinski rules of five and have entire diversity of Tanimoto < 0.7. In this study we seek a method that could provide simple rules to be utilized for differentiation between natural based and synthetic chemicals. For this purpose we have utilized 2D descriptors that were computed by MOE 2008.10. MOE is an integrated drug discovery software package with tools for chemoinformatics, bioinformat-

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ics, molecular modeling and visualization. It was developed by Chemical Computing Group, Inc. Montreal, Canada.

The decision, which set of relevant descriptors to use for differentiating between natural based and synthetic chemicals, is crucial. We sought after the most significant set of descriptors from which guidelines for natural likeness could be extracted. The selection has been performed automatically as following: all descriptors were evaluated separately and the best discriminative descriptor was chosen to be the core. The second descriptor to be added to the core was selected from the rest descriptors while giving the best performance in discrimination. The process continued until we have an efficient rules-of-thumb filter.

We aim to construct a filter consisting of ranges of few descriptors that can differentiate well between natural based and synthetic chemicals. For this purpose, descriptors' ranges were optimized simultaneously in exhaustive search, by maximizing a function (Matthews' Correlation Coefficient, MCC) [41] that considers each of the four possible outcomes for any chemical – Positive, Negative, False Positive and False Negative. Higher MCC means better distinction.

The division process of databases into training set and test set was performed by a random choice with 50% of the natural-based/ synthetic chemicals, while the remaining (50% of the databases) was used as a test set.

The need for a combinatorial optimization of descriptors' ranges dictates the requirement to transform descriptor values into discrete ones. Some descriptors already have a discrete character, i.e., the numbers of Oxygen atoms, H-bond acceptors etc, while others, such as molecular weight, VDW surface area, etc., are continuous. The transformation to discrete character was limited to give 50 values for upper and lower limit ranges each.

A set of rules is constructed by picking lower limit and upper limit for each descriptor. Each set has two values for each descriptor, constituting the range which is considered to be the “correct” one (by that set of descriptors) for natural likeness. The “correctness” of this set is measured by its MCC value, described below. The constructed set of rules is applied to the natural based chemicals in the training sets to calculate the value of the scoring function, its Matthews Correlation Coefficient (MCC) (equation 1).

$$MCC = \frac{(PN) - (P_f N_f)}{\sqrt{(N + N_f)(N + P_f)(P + N_f)(P + P_f)}} \quad (1)$$

Where, P and N are the percentages of true positive and true negative predictions while  $P_f$  and  $N_f$  are the percentages of false positives and false negatives, respectively. True positives are natural based chemicals that are identified as natural-like chemicals. False positives are synthetic chemicals that are identified as natural-like chemicals. False negatives are natural based chemicals identified as synthetic-like chemicals, and true negatives are synthetic chemicals, identified as synthetic-like chemicals. The possible values for MCC range between -1.0 and 1.0 (1.0 for a perfect prediction and -1.0 for a completely erroneous prediction).

An exhaustive search is performed for all combinations (more than one hundred million options) and the resulting sets of rules are sorted based on their MCC score. The best set of rules is presented.

## RESULTS AND DISCUSSION

Results obtained from the present study indicate that 98.4% of chemicals in the natural products database obey Lipinski rule of 5 [42] and 85.6% obey Oprea lead-like rule [43]. An analysis of 2245 drugs were used in order to formulate the Lipinski rule of 5, which indicates that orally bio available drug-like molecules are likely to have  $\leq 5$  H-bond donors,  $\leq 10$  H-bond acceptors,  $\leq 500$  molecular weight and  $\leq 5 \log P$ . However, an analysis of 96 drugs and leads from which they were derived, were utilized to extract the Oprea rules for lead likeness, stating that lead molecules are more likely to have  $\leq 450$  molecular weight, between -3.5 and 4.5  $\log P$ ,  $\leq 4$  rings,  $\leq 10$  non-terminal single bonds,  $\leq 5$  hydrogen bond donors and  $\leq 8$  hydrogen bond acceptors. Drug like or lead like molecules should have less than 2 violations – descriptor's value that is out of the range. Fig. (2) shows the number of violation for drug-likeness and lead-likeness in natural products database. Fig. (2a) demonstrates that 98.8% of the compounds had less than 2 violations to Lipinski rule of 5, with 87.3% having no violation. Fig. (2b) shows that more than 85% of the natural products had less than 2 violations to Oprea lead-likeness, with 65.8% having no violation. These findings indicate that the property criteria for drug-likeness and lead-likeness are highly pronounced in natural products. The distribution for the individual properties of the natural products is shown in Fig. (1). The molecular weight, H-bond donors, H-bond acceptors and  $\log P$  (o/w) distributions peak at 300-400 dalton, 0, 4 and 2-3 units of  $\log P$  respectively.

Bajorath and his co-workers [37] proposed several sets of descriptors for distinguishing between natural products and synthetic molecules. Four out of the six proposed models composed only of 2D physicochemical descriptors while the two others include structural elements. We have utilized those sets of descriptors as well as the four descriptors of Lipinski to construct a discriminative filter able to distinguish between natural and synthetic molecules by optimization ranges. Out of Bajorath proposed models, Model 5 (M5) composed of 8 descriptors gave the best result compared to the other sets in that group. As shown in Table 1, it has a Matthews' Correlation Coefficient of 0.36, retaining 79% of the natural products and 56% of the synthetic molecules.

A new discriminative filter between natural products and synthetic chemicals was constructed as described in the method section. In order to ensure non-redundant information in the features utilized for model construction, correlation between descriptors in natural products database were computed by WEKA (<http://www.cs.waikato.ac.nz/ml/weka/>) and stored into a matrix, see Table 2. The values of the correlation coefficient are constricted into the interval [-1, 1], correlation coefficient equal 1 corresponding to perfectly correlated features while coefficient of -1 corresponding to perfectly uncorrelated features. As shown in Table 2,

**Table 1. Filters for Differentiating between Natural Products and Synthetic Molecules**

Model	MCC	True Natural Products	True Synthetic Molecules
Lipinski descriptors <sup>1</sup>	0.27	78	48
M1 <sup>2</sup>	0.28	89	34
M2 <sup>3</sup>	0	100	0
M3 <sup>4</sup>	0.34	69	65
M5 <sup>5</sup>	0.36	79	56
<b>Our model<sup>6</sup></b>	<b>0.5</b>	<b>81</b>	<b>68</b>

1: Molecular Weight, Hydrogen Bond Acceptors, Hydrogen Bond Donors and calculated logP(o/w).

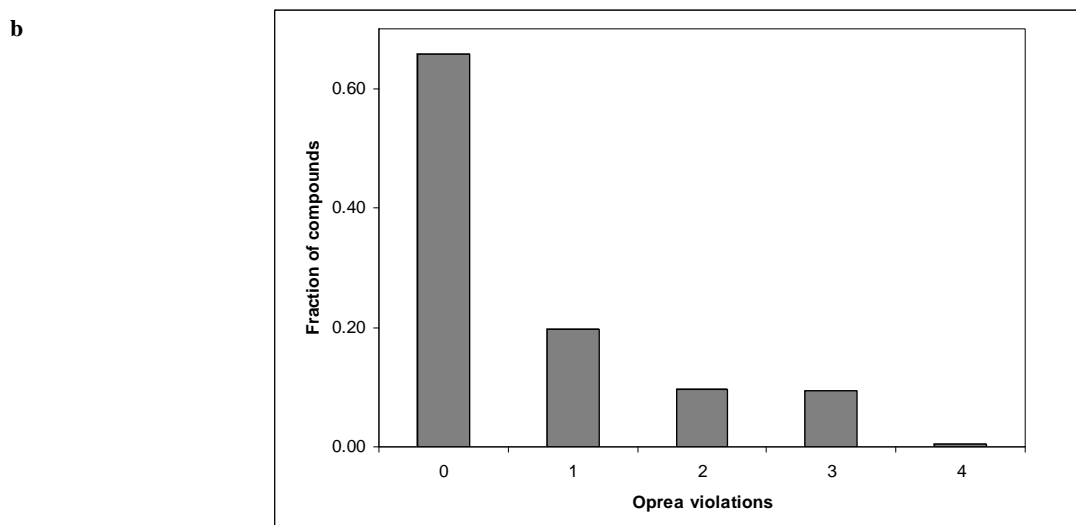
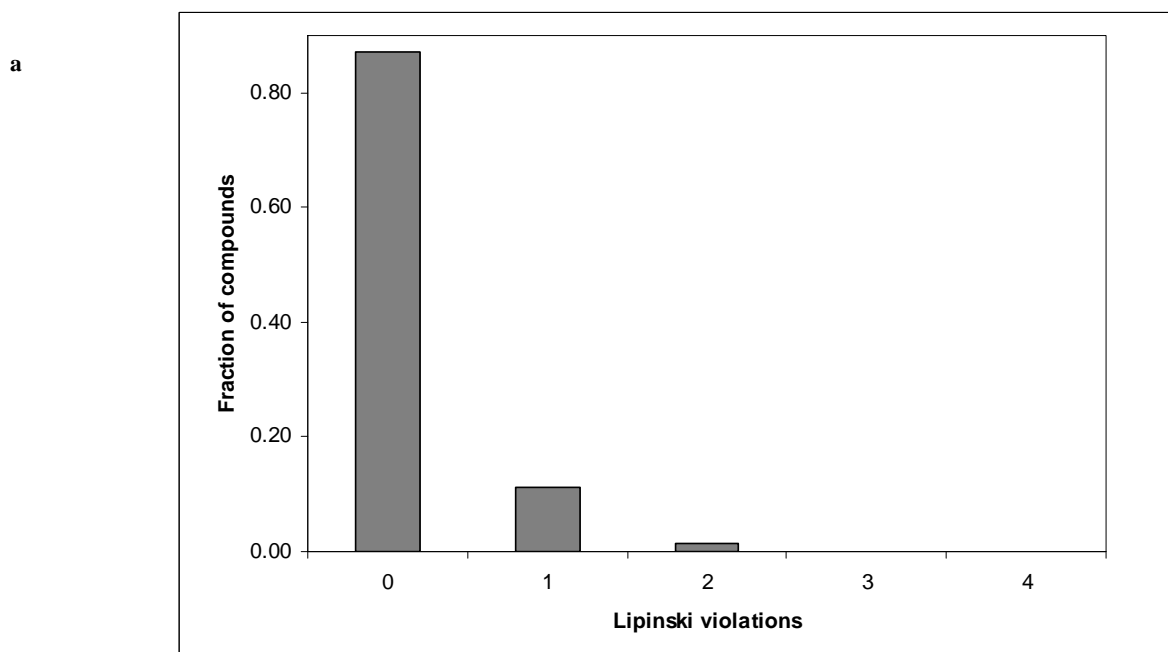
2: petitjean, PEOE\_VSA\_+2, b\_double, PEOE\_VSA\_-5, PEOE\_VSA\_+3, radius and vsa\_other

3: PC+, PC-, RPC+, RPC-, Fcharge, a\_nI, a\_nP, a\_nBr, b\_triple, vsa\_acid, vsa\_base

4: b\_IrotR, VadjEq, a\_ICM, PEOE\_RPC-, VdistEq, VdistMa, PEOE\_RPC+ and VAdjMa

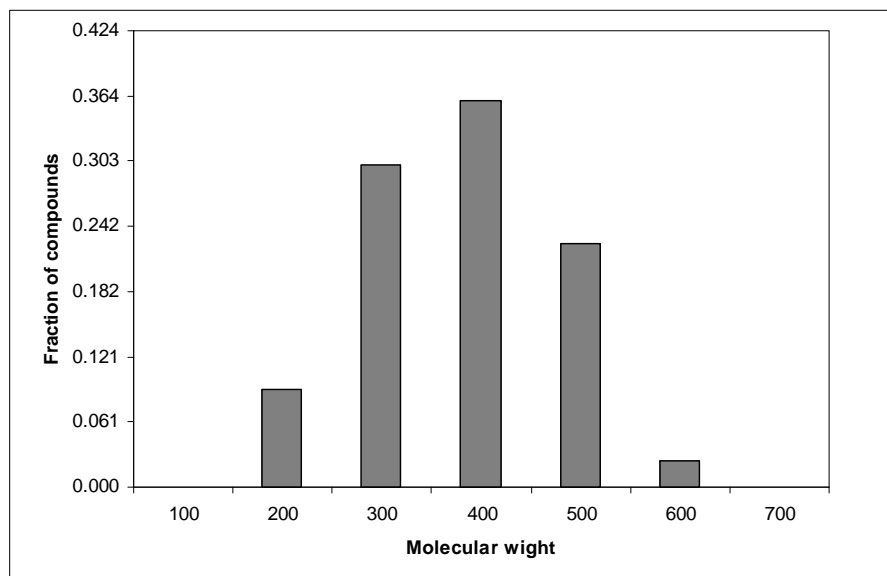
5: a\_ICM, bpol, chi0v\_C, b\_double, chi1v, a\_nH, b\_single and b\_ar

6: KierFlex, a\_nN, chiral\_u, KierFlex and vsa\_acid

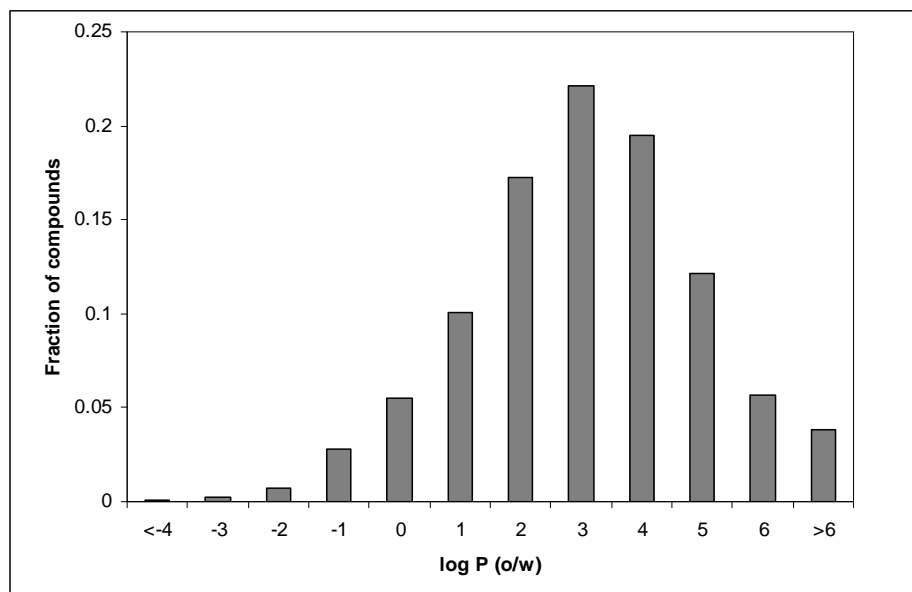


**Fig. (1).** Histograms of **a)** Lipinski violations for drug-likeness and **b)** Oprea violations for lead-likeness. Drug like or lead like could bear up to 1 violation.

a



b



c

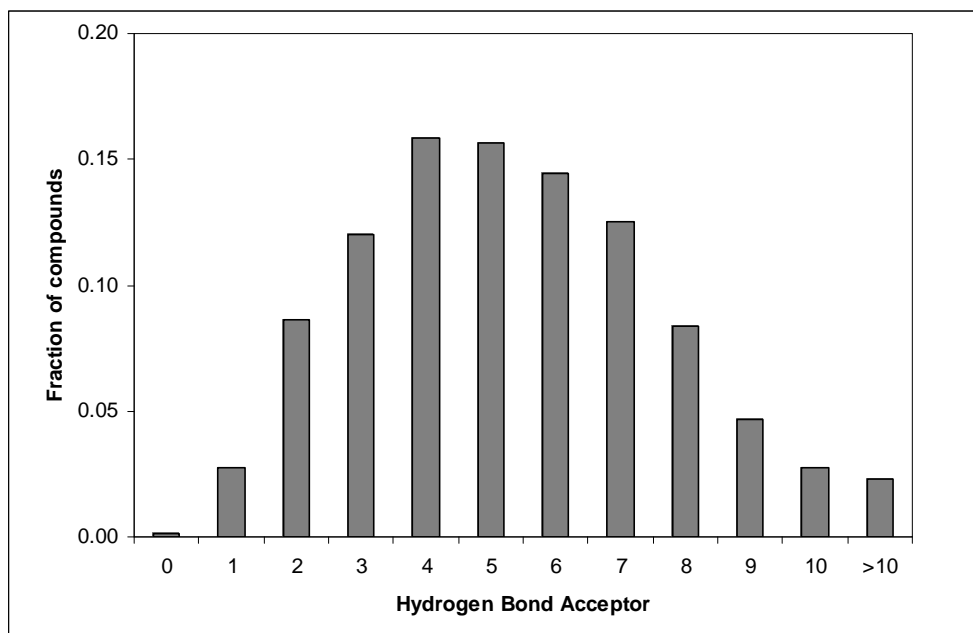
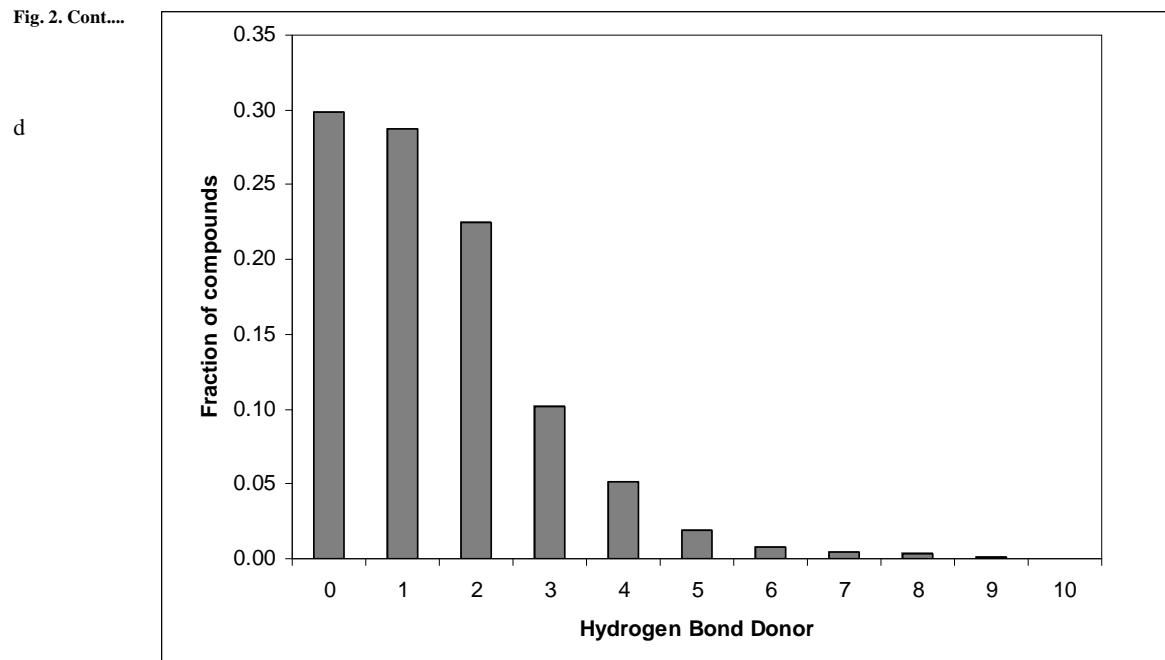


Fig. 2. Cont....



**Fig. (2).** Histograms of four physicochemical properties of compounds from the natural products database (NPD) showing **a)** molecular weight, **b)** logP(o/w), **c)** hydrogen bond acceptors and **d)** hydrogen bond donors. These selected descriptors are related to oral bioavailability and drug likeness. The physicochemical profile of the NPD molecules was computed by MOE 2008.10.

**Table 2. Correlation Matrix for Natural Products**

Descriptor	KierFlex	Q_VSA_HYD	a_nN	chiral_u	vsa_acid
KierFlex	1	0.175	-0.217	0.14	0.187
Q_VSA_HYD	0.175	1	-0.4	0.066	-0.252
a_nN	-0.217	-0.4	1	-0.239	-0.14
chiral_u	0.14	0.066	-0.239	1	-0.038
vsa_acid	0.187	-0.252	-0.14	-0.038	1

the correlation matrix of our model descriptors for the natural products sample contains only elements  $\leq 0.4$  (in absolute values).

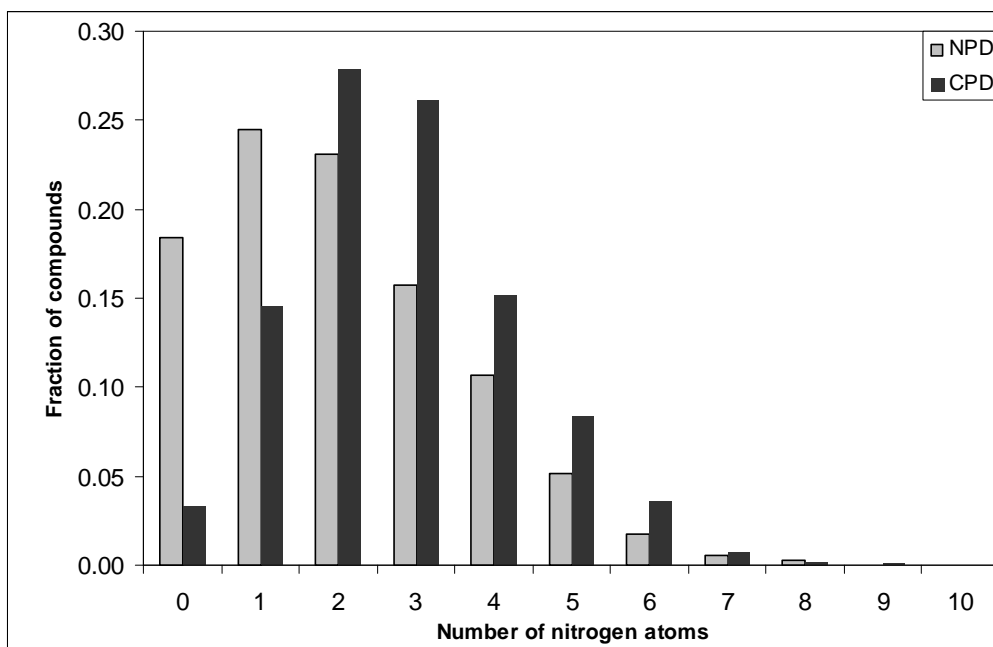
The property distribution of the proposed five discriminative descriptors for both the natural products database (NPD) and synthetic products database (CPD), are shown in Fig. (3). The histograms showing 3a) number of nitrogen atoms ( $a_{nN}$ ), 3b) total hydrophobic Vander Waals area ( $Q_{VSA\_Hyd}$ ), 3c) number of unconstrained chiral centers ( $chiral\_u$ ), 3d) KierFlex – molecular flexibility index (KierFlex) and 3e) sum of VDW surface area of acidic atoms ( $vsa\_acid$ ). x- axis label is the upper limit of binned data, e.g., 6 in KierFlex histogram is equivalent to 3-6. The enrichment factors (fraction of natural products/ fraction of synthetic chemicals) equal 5.8, 3.2, 5, 2.8 and 1.9 for  $a_{nN}=0$ ;  $KierFlex \leq 3$ ;  $chiral\_u \geq 3$ ;  $KierFlex \leq 160$  and  $vsa\_acid > 27$  respectively. Distribution histogram 3a shows that number of nitrogen atoms peaks at 1 in natural products and at 2 in synthetic chemicals. As well, sum of VDW surface area of acidic atoms is higher in synthetic chemicals

compared to natural products. As shown in Fig. (3b), it peaks at 220 in natural products and at 280 in synthetic chemicals.

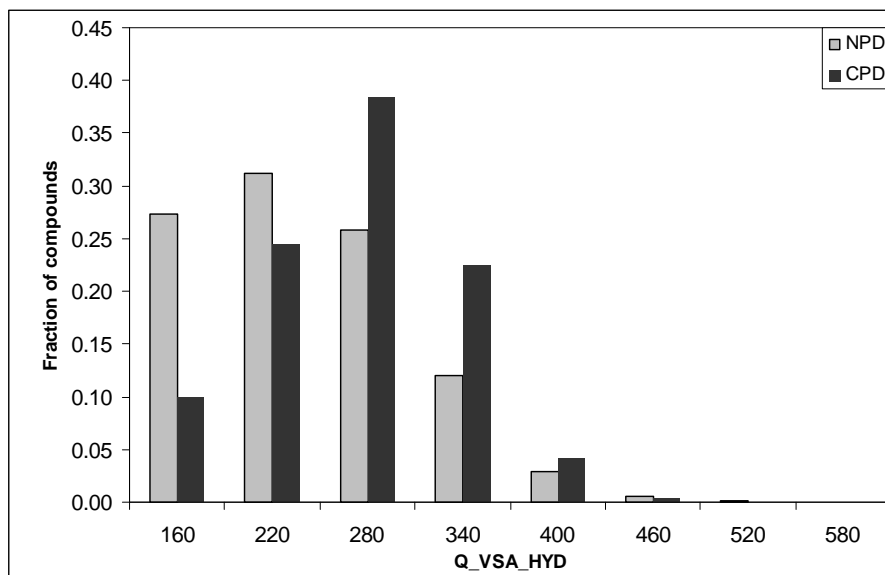
Two thousands natural products and two thousands synthetic chemicals were selected randomly from the pool 5 times (assuring that the molecules in the new set have not been selected before for the previous sets). Table 3 lists the performance of the model on the different sets and as shown, the proposed model is highly robust.

Our natural likeness rules states that synthetic chemicals are more likely to have up to 1 violation while natural-based products having more than 1 violation to the following rules:  $a_{nN} \geq 2$ ,  $160 \leq Q_{VSA\_Hyd} \leq 548$ ,  $chiral\_u < 3$ ,  $3 \leq KierFlex \leq 28$  and  $vsa\_acid \leq 27$ . These extracted rules are useful for separating natural-based chemicals from synthetic ones. Mathews Correlation Coefficient of 0.5 is attained; nearly 81% of natural-based products and 68% of synthetic chemicals were correctly classified with this filter. In Fig. (4) we present some known natural-based drugs that are predicted as natural chemicals according to our proposed model. One

a



b



c

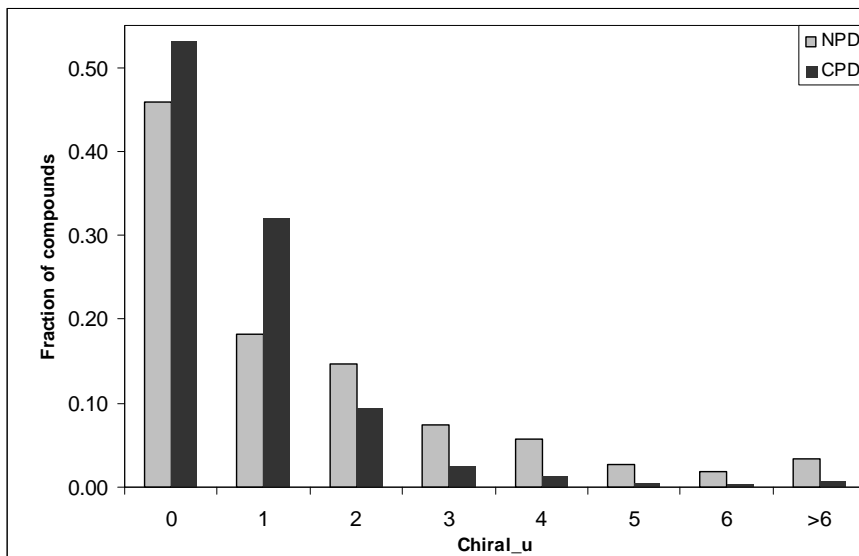
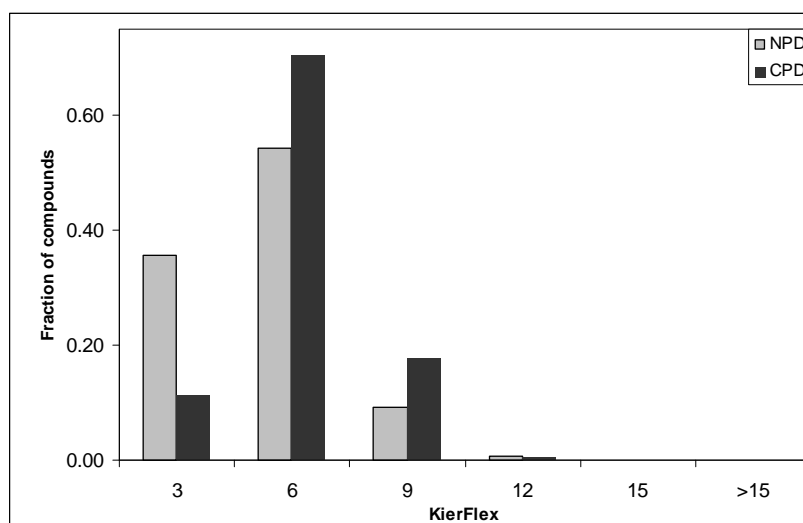
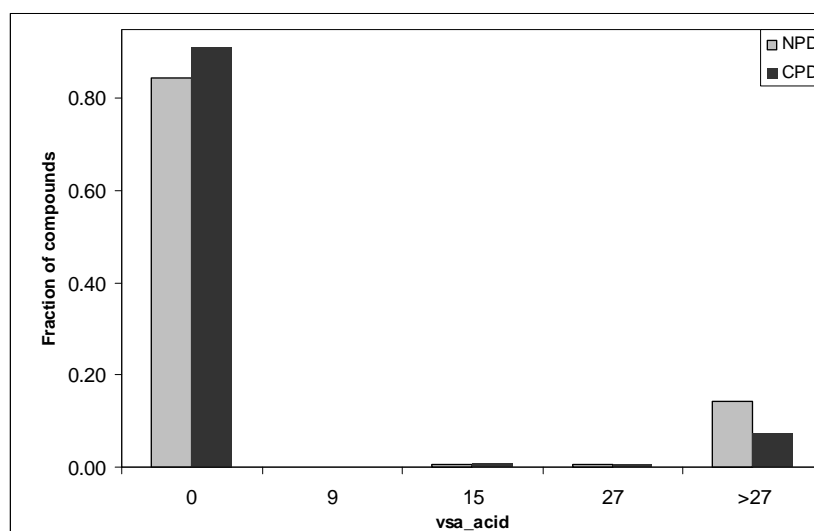


Fig. 3. Cont....

d



e



**Fig. (3).** Comparison of property distribution of five discriminative descriptors for the two data sets (NPD – natural products database, colored Gray and CPD – synthetic products database, colored black). The histograms showing **a)** number of nitrogen atoms, **b)** total hydrophobic Vander Waals area, **c)** number of unconstrained chiral centers, **d)** KierFlex – molecular flexibility index and **e)** sum of VDW surface area of acidic atoms. x- axis label is the upper limit of binned data, e.g., 6 in KierFlex histogram is equivalent to 3-6.

**Table 3. Robustness of the Proposed Model**

Partition Number	Natural%	Synthetic%	MCC
1	80.8	68.1	0.5
2	81.7	68.6	0.51
3	80.5	67.3	0.49
4	81.2	67.3	0.5
5	80.7	68.3	0.5

of the earliest success stories in developing a drug from a natural product was aspirin. It is chemically similar to Salicin which is a natural chemical produced from willow barks. Topiramate is a sulfamate derivative of the naturally occurring sugar D-fructose. Dydrogesterone molecular structure is almost identical to that of natural progesterone. Citric

acid is a weak organic acid, and it is a natural chemical exists in a variety of fruits and vegetables. Tretinoin is the acid form of vitamin A. Pilocarpine is a parasympathomimetic alkaloid obtained from the leaves of tropical American shrubs from the genus *Pilocarpus*. Geraniol is a monoterpenoid and an alcohol considered as the primary part

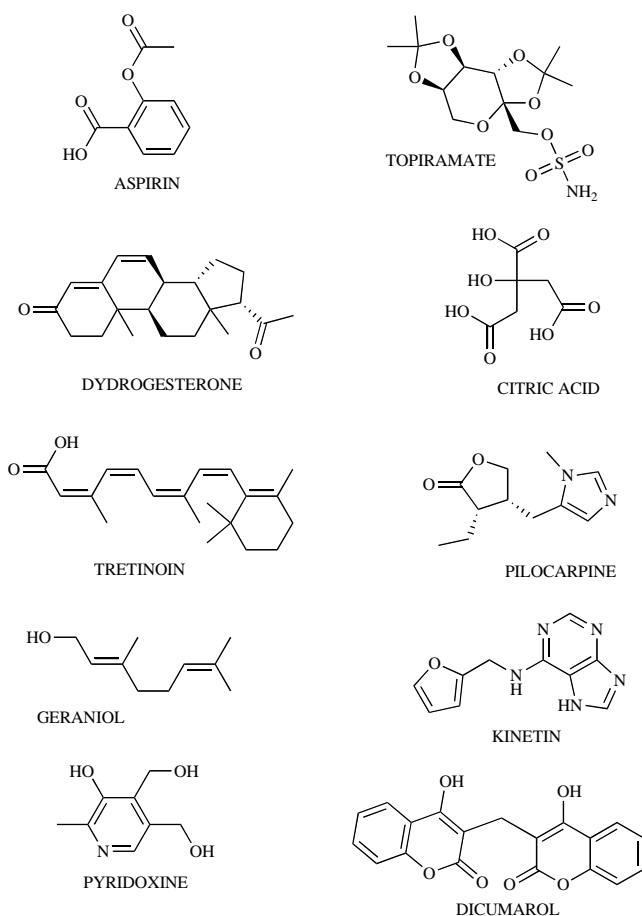


Fig. (4). Natural-based drugs.

of rose oil, palmarosa oil, and citronella oil. Kinetin is a kind of cytokinin, a class of plant hormone that promotes cell division. Pyridoxine is a vitamin B6 and the dragon fruit from South East Asia is a very good source for it. Dicumarol is a natural chemical substance of combined plant and fungal origin. It is a derivative of coumarin, a substance made by plants and transformed by a number of species of fungi into dicoumarol. Some of these drugs such as Aspirin, Pyridoxine and Dicumarol belong to the top-selling prescribed drugs.

### CONCLUDING REMARKS

A highly efficient rules based model for natural- likeness of chemicals has been unraveled and could be incorporated into virtual screening process of large chemical databases as well as in library design of natural like chemicals. As well, since natural based products are inherently better tolerated in the body than synthetic chemicals and have higher chance to be approved as new drugs, selection of natural-like drug candidates is justified. Our model for natural likeness proposed herein states that synthetic chemicals are more likely to have up to 1 violation while natural-based products having more than 1 violation to the following rules: Number of nitrogen atoms  $\geq 2$ , total hydrophobic Vander Waals area ranges between 160 and 548, number of unconstrained chiral centers is less than 3, molecular flexibility index (KierFlex) ranges between 3 and 28, while sum of VDW surface area of acidic atoms is up to 27.

This model attained Mathews Correlation Coefficient of 0.5; nearly 81% of natural-based products and 68% of synthetic chemicals were correctly classified. The model is highly robust when was run on 5 different sets of natural products and synthetic chemicals.

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### ABBREVIATIONS

NPD = Natural Products Database  
 MCC = Matthews' Correlation Coefficient

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