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Research Article

In-silico Absorption, Distribution, Metabolism, Elimination and Toxicity profile of 9,12,15-Octadecatrienoic acid (ODA) from *Moringa oleifera*

Parvathi K.[1], Kandeepan C.[2], Sabitha M.[2], Senthilkumar N.[3], Ramya S.[4], Boopathi NM.[5], Ramanathan L.[6], Jayakumararaj R.[6]*

[1] *Department of Zoology, Erode Arts and Science College (Autonomous), Erode – 638009, TN, India.*
[2] *PG and Research Department of Zoology, Arulmigu Palaniandavar College of Arts and Culture, Palani – 624601, Dindigul District, TamilNadu, India*
[3] *Institute of Forest Genetics and Tree Breeding (IFGTB), Indian Council of Forestry Research and Education (ICFRE), Coimbatore – 641002, TamilNadu, India*
[4] *PG Department of Zoology, Yadava College (Men), Thiruppalai - 625014, Madurai, TamilNadu, India*
[5] *Centre for Plant Molecular Biology and Biotechnology, Department of Plant Biotechnology, Tamil Nadu Agricultural University, Coimbatore - 641 003, TN, India*
[6] *Department of Botany, Government Arts College, Melur – 625106, Madurai District, TN, India*

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*Address for Correspondence:

Jayakumararaj R., Department of Botany, Government Arts College, Melur – 625106, Madurai District, TN, India

Abstract

9,12,15-Octadecatrienoic acid (ODA) a carboxylic acid composed of 18 carbon atoms and three cis double bonds. ODA is a plant derived essential fatty acid indispensable to the human system. ODA refers to many different structural and conformational isomers, that differ in the position of the double bonds along the backbone and on whether they are in cis ('Z') or trans ('E') conformation. It has been well established that ODA can only be outsourced from food and then converted into eicosa-pentaenoic acid (EPA) and docosa-hexaenoic acid (DHA) in the human system. However, this metabolic process is highly limited and the rate of conversion is influenced by several factors such as dose, gender, and disease. Studies suggest that ODA is associated with reduced risk of fatal ischemic heart disease. Further, higher intake may reduce the risk of sudden death among prevalent myocardial infarction in patients consistent with induced antiarrhythmic effect. ODA significantly reduces blood clots. Traditional usage of ODA is attributed to its cardiovascular-protective, anti-cancer, neuro-protective, anti-osteoporotic, anti-inflammatory, and anti-oxidative properties. Recent pharmacological indicate that ODA has anti-metabolic syndrome, anticancer, anti-inflammatory, anti-oxidant, anti-obesity, neuro-protective, and more specifically involved in the regulation of gut-micro-floral functionalities. Studies, both experimental and clinical trials indicate that ODA has anti-metabolic syndrome effects. In short, ODA is potentially used to treat many diseases, but in-depth ADMET studies are required to firmly re-establish its clinical efficacy and market potential.

Keywords: ADMET; *Moringa oleifera*; Secondary Metabolites; Natural Products (NPs); Bioactive Substances; Octadecatrienoic acid (ODA); Eicosa-Pentaenoic Acid (EPA); Docosa-Hexaenoic Acid (DHA)

INTRODUCTION

Octadecatrienoic acid (ODA), chemically (18:3n-3 or 3n-6) is a carboxylic acid with 18 carbons and three cis double bonds. ODA is present in either cis ('Z') or trans ('E') conformation in the plants. ODA is an essential fatty acid, meaning that human system cannot synthesize ODA and it must be supplied via the diet.[1] ODA in general is in liquid state at room temperature. Table 1 shows physicochemical properties of ODA. It is commonly found in seedoil, beans, walnuts, and leafy vegetables.[2,3] ODA is a precursor of two important long chain omega-3 fatty acids, EPA (eicosa pentaenoic acid, 20:3n-5) and DHA (docosa hexaenoic acid, 22:3n-6), both of them have vital role in the reduced prostate tumor growth,[4] development of brain,[5] cardio-vascular-health,[6] metabolic-inflammatory-response,[7] obesity,[8] diabetics[9] mental disorders[10] etc. Long-chain, n-3 poly-unsaturated fatty acids (PUFAs) of EPA and DHA can be directly supplied by the intake of fish, although very few fish can provide an abundance of these PUFAs.[8,9,10]

Plant-derived n-3 PUFA, ODA, is an important dietary source for EPA and DHA, because of the biochemical conversion of ODA to EPA and EPA to DHA[11]. Although the conversion efficiency is relatively limited in humans (<8% of ODA to EPA and<4% of ODA to DHA), ODA produced by the plants is the only dietary source for the availability of n-3 PUFAs in human system. Metabolism and functional effects of plant-derived omega-3 fatty acids in humans has been studied in detail.[11] Eating foods or taking supplements rich in ODA may not sometime reduce lipid levels in people with hyperlipidemia[12]. This boils down to the fact that there is a growing interest in using ODA for a number of purposes related to health and disease, but there isn't enough reliable information to whether it might be practically helpful.

There are 13 species in the genus *Moringa*, of all *M. oleifera* is the best known and most widely distributed species due to its multifarious uses[13]. *M. oleifera* is native to India, however, cultivated in other regions of the world[14]. It is a deciduous tree with brittle stem, whitish-gray corky bark with branches; leaves pale green, bipinnate/ tri-pinnate with opposite, ovate leaflets[15]. *M. oleifera* recognized as "**The Miracle Tree**" due to its versatile nutraceutical uses[16], all parts of the plant including leaves, roots, pods, seeds, and flowers have been explored for their nutraceutical and pharmaceutical properties[15]. *M. oleifera* has been traditionally used in folk remedies across various indigenous systems of medicine. Pharmacological studies indicate that extracts obtained from the plant have antioxidants[17], anti-diabetic[18], anti-bacterial, anti-fungal[19], and anti-carcinogenic[20] properties. Interestingly, no adverse effects have been reported yet. Though, significant variation in composition of different species exists[21] versatile nature of phytochemicals remains the key aspect of nutrient content. Due to overwhelming nutritive and medicinal use of the plant, it is indicated that *Moringa* can be widely exploited for its nutritionally important phytoconstituents in the development of functional foods, nutraceutical products and therapeutic agents as like similar medicinal plants[22-44]. Aim of this study is to bioprospect ODA from the leaves of MO for its molecular and biological properties to develop ODA as a novel lead in drug discovery.

MATERIALS AND METHODS

The vNN method rests on the premise that compounds with similar structures have similar activities. It is therefore reasonable to weight the contributions of neighbours so that closer neighbours contribute more to the predicted value. The vNN method calculates the similarity distance between molecules in terms of their structure, and uses a distance threshold to define a domain of applicability. This applicability domain ensures that the predictions generated are reliable. vNN models can be built within minutes and require no re-training when new assay information becomes available - an important feature when keeping quantitative structure–activity relationship (QSAR) models up-to-date to maintain their performance levels. The performance characteristics of vNN-based models are comparable, and often superior to, those of other more elaborate model constructs.[45-48] One of the most widely used measures of the similarity distance between two small molecules is the Tanimoto distance, d, which is defined as:

$$d = 1 - \frac{n(P \cap Q)}{n(P) + n(Q) - n(P \cap Q)},$$

where η(P∩Q) is the number of features common to molecules p and q, and η(P) and η(Q) are the total numbers of features for molecules p and q, respectively. The predicted biological activity y is then given by a weighted average across structurally similar neighbours:

$$y = \frac{\sum_{i=1}^{v} y_i e^{-(\frac{d_i}{h})^2}}{\sum_{i=1}^{v} e^{-(\frac{d_i}{h})^2}}, \qquad d_i \le d_0,$$

where d_i denotes the Tanimoto distance between a query molecule for which a prediction is made and a molecule i of the training set; d_0 is a Tanimoto-distance threshold, beyond which two molecules are no longer considered to be sufficiently similar to be included in the average; y_i is the experimentally measured activity of molecule i; v denotes the total number of molecules in the training set that satisfies the condition $d_i \le d_0$; and h is a smoothing factor, which dampens the distance penalty. The values of h and d_0 are determined from cross-validation studies. To identify structurally similar compounds, Accelrys extended-connectivity fingerprints with a diameter of four chemical bonds (ECFP4) was used in the present study,[49] as it has previously been reported to show good overall performance.[48,50,51]

Model Validation

A 10-fold cross-validation (CV) procedure was used to validate new models and to determine the values of the smoothing factor h and Tanimoto distance d_0. In this procedure, the data was randomly divided into 10 sets, and used 9 to develop the model and the 10th to validate it, this process was repeated 10 times, leaving each set of molecules out once. In building new models, the reported averages of the 10-fold CV as the performance measures.

Performance Measures

The following metrics were used to assess model performance. (1) sensitivity measures a model's ability to correctly detect true positives, (2) specificity measures a model's ability to detect true negatives, (3) accuracy measures a model's ability to make correct predictions and (4) kappa compares the probability of correct predictions to the probability of correct predictions by chance (its value ranges from +1 (perfect agreement between model prediction and experiment) to −1 (complete disagreement), with 0 indicating no agreement beyond that expected by chance).

$$\text{sensitivity} = \frac{TP}{TP + FN}$$

$$\text{specificity} = \frac{TN}{FP + TN}$$

$$\text{accuracy} = \frac{TP + TN}{TP + TN + FP + FN}$$

$$\text{kappa} = \frac{\text{accuracy} - Pr(e)}{1 - Pr(e)}$$

where TP, TN, FP, and FN denote the numbers of true positives, true negatives, false positives, and false negatives, respectively. Kappa is a metric for assessing the quality of binary classifiers. Pr (e) is an estimate of the probability of a correct prediction by chance. It is calculated as:

$$Pr(e) = \frac{(TP + FN)(TP + FP) + (FP + TN)(TN + FN)}{(TP + FN + FP + TN)^2}$$

The coverage is the proportion of test molecules with at least one nearest neighbour that meets the similarity criterion. The coverage is a measure of how many test compounds are within the applicability domain of a prediction model.

RESULTS AND DISCUSSION

3D structure, molecular and biological properties of 9,12,15-Octadecatrienoic acid in *M. oleifera*, its physicochemical properties, lipophilicity properties, water solubility properties, pharmacokinetic properties, druglikeness, medicinal chemistry properties, ADMET properties of ODA from *M. oleifera* is provided in Table 1-8 respectively.

Performance measures of vNN models in 10-fold cross validation using a restricted/ unrestricted applicability domain for 9,12,15-Octadecatrienoic acid from *M. oleifera* (Table 9).

ADMET Predictions

The implemented Absorption, Distribution, Metabolism, Excretion and Toxicity (ADMET) prediction models, including their performance measures, have been reported previously.[45] The 15 models cover a diverse set of ADMET endpoints. Some of the models have already been published, including those for Maximum Recommended Therapeutic Dose (MRTD),[46] chemical mutagenicity,[47] human liver microsomal (HLM),[48] Pgp inhibitor/substrates.[49]

Liver Toxicity - DILI: Drug-induced liver injury (DILI) has been one of the most commonly cited reasons for drug withdrawals from the market. This application predicts whether a compound could cause DILI. The dataset of 1,431 compounds was obtained from four sources used by Xu et al.[52] This dataset contains both pharmaceuticals and non-pharmaceuticals; A compound was classified as causing DILI if it was associated with a high risk of DILI and not if there was no such risk.

Liver Toxicity - Cytotoxicity (HepG2): Cytotoxicity is the degree to which a chemical causes damage to cells. A cytotoxicity prediction model was developed, using in vitro data on toxicity against HepG2 cells for 6,000 structurally diverse compounds, collected from ChEMBL. In developing the model, compounds with an $IC_{50} \leq 10$ µM were considered in the in vitro assay as cytotoxic.

Metabolism - HLM: The human liver microsomal (HLM) stability assay is commonly used to identify and exclude compounds that are too rapidly metabolized. For a drug to achieve effective therapeutic concentrations in the body, it cannot be metabolized too rapidly by the liver. Compounds with a half-life of 30 minutes or longer in an HLM assay are considered as stable; otherwise they are considered unstable. HLM data was retrieved from the ChEMBL database, manually curated the data, and classified compounds as stable or unstable based on the reported half-life (T1/2 > 30 min was considered stable, and T1/2 < 30 min unstable. The final dataset contained 3,654 compounds. Of these, 2,313 leads were classified as stable and 1,341 as unstable.[48]

Metabolism - Cytochrome P450 enzyme (CYP) inhibition: CYPs constitute a superfamily of proteins that play an important role in the metabolism and detoxification of xenobiotics. In-vitro data was derived from five main drug-metabolizing CYPs—1A2, 3A4, 2D6, 2C9, and 2C19—to develop CYP inhibition models. CYP inhibitors data was retrieved from PubChem and classified a compound with an $IC_{50} \leq 10$ µM for an enzyme as an inhibitor of the enzyme. Predictions for the following enzymes: CYP1A2, CYP3A4, CYP2D6, CYP2C9, and CYP2C19 have been provided.

Membrane Transporters - BBB: The blood-brain barrier (BBB) is a highly selective barrier that separates the circulating blood from the central nervous system. A vNN-based BBB model was developed, using 352 compounds whose BBB permeability values (logBB) were obtained from the literature respectively.[50,51] The compounds with logBB values of less than –0.3 were classified and greater than +0.3 as BBB non-permeable and permeable.

Membrane Transporters - Pgp Substrates and Inhibitors: P-glycoprotein (Pgp) is an essential cell membrane protein that extracts many foreign substances from the cell. Cancer cells often overexpress Pgp, which increases the efflux of chemotherapeutic agents from the cell and prevents treatment by reducing the effective intracellular concentrations of such agents—a phenomenon known as multidrug resistance. For this reason, identifying compounds that can either be transported out of the cell by Pgp (substrates) or impair Pgp function (inhibitors) is of great interest. A model was developed to predict both Pgp substrates and Pgp inhibitors.[29] The Pgp substrate dataset was collected by Hou and co-workers.[53-55] This dataset consists of measurements of 422 substrates and 400 non-substrates. To generate a large Pgp inhibitor dataset, two datasets were combined,[56,57] and removed duplicates to form a combined dataset consisting of a training set of 1,319 inhibitors and 937 non-inhibitors.

hERG (Cardiotoxicity): The human ether-à-go-go-related gene (hERG) codes for a potassium ion channel involved in the normal cardiac repolarization activity of the heart. Drug-induced blockade of hERG function can cause long QT syndrome, which may result in arrhythmia and death. As much as 282 known hERG blockers were retrieved from the literature and classified compounds with an IC_{50} cut-off value of 10 µM or less as blockers.[54] A set of 404 compounds were collected with IC_{50} values greater than 10 µM from ChEMBL and classified them as non-blockers.

MMP (Mitochondrial Toxicity): Given the fundamental role of mitochondria in cellular energetics and oxidative stress, mitochondrial dysfunction has been implicated in cancer, diabetes, neurodegenerative disorders, and cardiovascular diseases. Largest dataset of chemical-induced changes in mitochondrial membrane potential (MMP) was used based on the assumption that a compound that causes mitochondrial dysfunction is also likely to reduce the MMP. A vNN-based MMP prediction model was developed using 6,261 compounds collected from a previous study that screened a library of 10,000 compounds (~8,300 unique chemicals) at 15 concentrations, each in triplicate, to measure changes in the MMP in HepG2 cells.[55] The study found that 913 compounds decreased the MMP, whereas 5,395 compounds had no effect.

Mutagenicity (Ames test): Mutagens are chemicals that cause abnormal genetic mutations leading to cancer. A common way to assess a chemical's mutagenicity is the Ames test. A prediction model was developed using a literature dataset of 6,512 compounds, of which 3,503 were Ames-positive.

MRTD: The Maximum Recommended Therapeutic Dose (MRTD) is an estimated upper daily dose that is safe. A prediction model was built based on a dataset of MRTD values publically disclosed by the FDA, mostly of single-day oral doses for an average adult with a body weight of 60 kg, for 1,220 compounds (most of which are small organic drugs). Organometallics were excluded, high-molecular weight polymers (>5,000 Da), nonorganic chemicals, mixtures of chemicals, and very small molecules (<100 Da). An external test set of 160 compounds that were collected by the FDA for validation was used in the present study. The total dataset of the model contained 1185 compounds.[46]

CONCLUSION

In the present study ODA from *M. oleifera* was ADMET predicted for functional properties. It has been well established that in the human system, ODA is converted to EPA/ DHA. EPA/ DHA endowed with cardioprotective potentials lowers blood cholesterol level and reduces the risk of heart disease. With limited data, it is not obvious to conclude that ODA of MO is safe as a dietary ingredient as evidence on risks associated with ODA remains inadequate as of now. *In-silico* ADMET prediction data presented in the paper is hopefully expected to assist the process of drug

discovery by rapid design, evaluation, and prioritization of ODA owing to its remarkable biomedical applications.

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Table 1: Structure (3D), molecular and biological properties of 9,12,15-Octadecatrienoic acid in *M. oleifera*

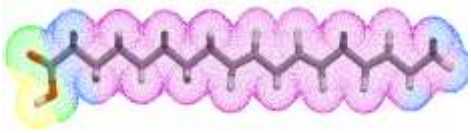
	Molecular Properties	Calculated Values
originalSMILES CCC=CCC=CCC=CCCCCCCCC(=O)O miSMILES: CCC=CCC=CCC=CCCCCCCCC(=O)O 9,12,15-Octadecatrienoic acid 	**miLogP**	5.84
	TPSA	37.30
	Natoms	20
	MW	278.44
	nON	2
	nOHNH	1
	Nviolations	1
	Nrotb	13
	volume	306.47
	Biological Properties	**Bioactivity Scores**
	GPCR ligand	**0.33**
	Ion channel modulator	**0.23**
	Kinase inhibitor	**0.19**
	Nuclear receptor ligand	**0.35**
	Protease inhibitor	**0.13**
	Enzyme inhibitor	**0.42**

Table 2 Physicochemical Properties of Octadecatrienoic Acid

PROPERTY	VALUE
Formula	**C18H30O2**
Molecular weight	278.43 g/mol
Num. heavy atoms	20
Num. arom. heavy atoms	0
Fraction Csp3	0.61
Num. rotatable bonds	13
Num. H-bond acceptors	2
Num. H-bond donors	1
Molar Refractivity	88.99
TPSA	37.30 Å^2

Table 3 Lipophilicity Properties of Octadecatrienoic Acid

PROPERTY	VALUE
Log $P_{o/w}$ (iLOGP)	**3.**36
Log $P_{o/w}$ (XLOGP3)	6.46
Log $P_{o/w}$ (WLOGP)	5.66
Log $P_{o/w}$ (MLOGP)	4.38
Log $P_{o/w}$ (SILICOS-IT)	5.59
Consensus Log $P_{o/w}$	5.09

Table 4 Water Solubility Properties of Octadecatrienoic Acid

PROPERTY	VALUE
Log *S* (ESOL)	-4.78
Solubility	4.64e-03 mg/ml ; 1.67e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-7.04
Solubility	2.55e-05 mg/ml ; 9.16e-08 mol/l
Class	Poorly soluble
Log *S* (SILICOS-IT)	-3.96
Solubility	3.08e-02 mg/ml ; 1.11e-04 mol/l
Class	Soluble

Table 5 Pharmacokinetic Properties of Octadecatrienoic Acid

PROPERTY	VALUE
GI absorption	High
BBB permeant	Yes
P-gp substrate	No
CYP1A2 inhibitor	Yes
CYP2C19 inhibitor	No
CYP2C9 inhibitor	Yes
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-3.41 cm/s

Table 6 Druglikeness Properties of Octadecatrienoic Acid

PROPERTY	VALUE
Lipinski	Yes; 1 violation: MLOGP>4.15
Ghose	No; 1 violation: WLOGP>5.6
Veber	No; 1 violation: Rotors>10
Egan	Yes
Muegge	No; 1 violation: XLOGP3>5
Bioavailability Score	0.85

Table 7 Medicinal Chemistry Properties of Octadecatrienoic Acid

PROPERTY	VALUE
PAINS	0 alert
Brenk	1 alert: isolated_alkene
Leadlikeness	No; 2 violations: Rotors>7, XLOGP3>3.5
Synthetic accessibility	3.03

Table 8 ADMET properties of ODA from *Moringa oleifera*

Property	Model Name	Predicted Value	Unit
Absorption	Water solubility	**-5.787**	Numeric (log mol/L)
Absorption	Caco2 permeability	**1.577**	N (log Papp in 10^{-6} cm/s)
Absorption	Intestinal absorption (human)	**92.836**	Numeric (% Absorbed)
Absorption	Skin Permeability	**-2.722**	Numeric (log Kp)
Absorption	P-glycoprotein substrate	**No**	Categorical (Yes/No)
Absorption	P-glycoprotein I inhibitor	**No**	Categorical (Yes/No)
Absorption	P-glycoprotein II inhibitor	**No**	Categorical (Yes/No)
Distribution	VDss (human)	**-0.617**	Numeric (log L/kg)
Distribution	Fraction unbound (human)	**0.056**	Numeric (Fu)
Distribution	BBB permeability	**-0.115**	Numeric (log BB)
Distribution	CNS permeability	**-1.547**	Numeric (log PS)
Metabolism	CYP2D6 substrate	**No**	Categorical (Yes/No)
Metabolism	CYP3A4 substrate	**Yes**	Categorical (Yes/No)
Metabolism	CYP1A2 inhibitior	**Yes**	Categorical (Yes/No)
Metabolism	CYP2C19 inhibitior	**No**	Categorical (Yes/No)
Metabolism	CYP2C9 inhibitior	**No**	Categorical (Yes/No)
Metabolism	CYP2D6 inhibitior	**No**	Categorical (Yes/No)
Metabolism	CYP3A4 inhibitior	**Yes**	Categorical (Yes/No)
Excretion	Total Clearance	**1.991**	Numeric (log ml/min/kg)
Excretion	Renal OCT2 substrate	**No**	Categorical (Yes/No)
Toxicity	AMES toxicity	**No**	Categorical (Yes/No)
Toxicity	Max. tolerated dose (human)	**-0.84**	Numeric (log mg/kg/day)
Toxicity	hERG I inhibitor	**No**	Categorical (Yes/No)
Toxicity	hERG II inhibitor	**No**	Categorical (Yes/No)
Toxicity	Oral Rat Acute Toxicity (LD50)	**1.441**	Numeric (mol/kg)
Toxicity	Oral Rat Chronic Toxicity (LOAEL)	**3.115**	N (log mg/kg_bw/day)
Toxicity	Hepatotoxicity	**Yes**	Categorical (Yes/No)
Toxicity	Skin Sensitisation	**Yes**	Categorical (Yes/No)
Toxicity	*T.Pyriformis* toxicity	**0.722**	Numeric (log ug/L)
Toxicity	Minnow toxicity	**-1.183**	Numeric (log mM)

Table 9 Performance measures of vNN models in 10-fold cross validation using a restricted/ unrestricted applicability domain for 9,12,15-Octadecatrienoic acid from *M. oleifera*

Model	Data[a]	d_0[b]	h[c]	Accuracy	Sensitivity	Specificity	kappa	R[d]	Coverage
DILI	1427	0.60	0.50	0.71	0.70	0.73	0.42		0.66
		1.00	0.20	0.67	0.62	0.72	0.34		1.00
Cytotox (hep2g)	6097	0.40	0.20	0.84	0.88	0.76	0.64		0.89
		1.00	0.20	0.84	0.73	0.89	0.62		1.00
HLM	3219	0.40	0.20	0.81	0.72	0.87	0.59		0.91
		1.00	0.20	0.81	0.70	0.87	0.57		1.00
CYP1A2	7558	0.50	0.20	0.90	0.70	0.95	0.66		0.75
		1.00	0.20	0.89	0.61	0.95	0.60		1.00
CYP2C9	8072	0.50	0.20	0.91	0.55	0.96	0.54		0.76
		1.00	0.20	0.90	0.44	0.96	0.46		1.00
CYP2C19	8155	0.55	0.20	0.87	0.64	0.93	0.58		0.76
		1.00	0.20	0.86	0.52	0.94	0.50		1.00
CYP2D6	7805	0.50	0.20	0.89	0.61	0.94	0.57		0.75
		1.00	0.20	0.88	0.52	0.95	0.51		1.00
CYP3A4	10373	0.50	0.20	0.88	0.76	0.92	0.68		0.78
		1.00	0.20	0.88	0.69	0.93	0.64		1.00
BBB	353	0.60	0.20	0.90	0.94	0.86	0.80		0.61
		1.00	0.10	0.82	0.88	0.75	0.64		1.00
Pgp Substrate	822	0.60	0.20	0.79	0.80	0.79	0.58		0.66
		1.00	0.20	0.73	0.73	0.74	0.47		1.00
Pgp Inhibitor	2304	0.50	0.20	0.85	0.91	0.73	0.66		0.76
		1.00	0.10	0.81	0.86	0.74	0.61		1.00
hERG	685	0.70	0.70	0.84	0.84	0.83	0.68		0.80
		1.00	0.20	0.82	0.82	0.83	0.64		1.00
MMP	6261	0.50	0.40	0.89	0.64	0.94	0.61		0.69
		1.00	0.20	0.87	0.52	0.94	0.50		1.00
AMES	6512	0.50	0.40	0.82	0.86	0.75	0.62		0.79
		1.00	0.20	0.79	0.82	0.75	0.57		1.00
MRTD[e]	1184	0.60	0.20					0.79	0.69
		1.00	0.20					0.74	1.00

[a]Number of compounds in the dataset; [b]Tanimoto-distance threshold value; [c]Smoothing factor; [d]Pearson's correlation coefficient ; [e]Regression model.