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AN ACTIVITY PREDICTION MODEL USING SHAPE-BASED DESCRIPTOR METHOD

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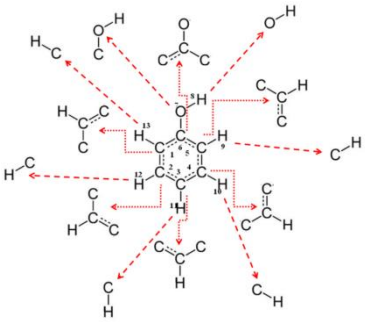
Graphical abstract



Abstract

Similarity searching, the activity of an unknown compound (target) is predicted through the comparison of an unknown compound with a set of known activities of compounds. The known activities of the most similar compounds are assigned to the unknown compound. Different machine learning methods and Multilevel Neighborhoods of Atoms (MNA) structure descriptors have been applied for the activities prediction. In this paper, we introduced a new activity prediction model with Shape-Based Descriptor Method (SBDM) .Experimental results show that SBDM-MNA provides a useful method of using the prior knowledge of target class information (active and inactive compounds) of predicting the activity of orphan compounds. To validate our method, we have applied the SBDM-MNA to different established data sets from literature and compare its performance with the classical MNA descriptor for activity prediction.

Keywords: Bioactive Molecules, Multilevel Neighborhoods of Atoms, Shape-based Descriptors, Activity prediction model

1.0 INTRODUCTION

Due to the similar property principle [1], structurally similar compounds are predicted to exhibit similar properties and biological activities. This principle is exploited for discovery of new drugs with the emergence of an activity prediction technology based on chemical structures. A variety of computational approaches for activity prediction or target has been published over the past several years. For example, Quantitative structure activity relationship (QSAR) [2]–[6] was established on the hypothesis that compounds with similar physicochemical properties and/or structure share similar activities. The effectiveness of the QSAR analysis relies both on selecting the relevant descriptors for modeling the biological activity of interest and on the choice of a good quantitative model that maps the compound descriptors to chemical property or biological activity by means of statistical techniques [3], [4].

In similarity searching strategy, an unknown compound (target) is compared to a set of compounds with known activities. The known activities of the most similar compounds are assigned to the unknown compound. Despite the fact that the target prediction approaches exhibit several successes but some issues still need to be addressed. In many studies, different approaches predict different subset of targets for the same compound [7]–[12].

Some of the popular machine learning methods that have been applied for activity prediction (target) by compound classification are the Binary Kernel Discrimination (BKD) [13], [14], Naïve Bayesian Classifier (NBC) [15], Artificial Neural Networks (ANN) [16]–[18] and the Support Vector Machine (SVM) [19]–[21]. Recently, the Bayesian belief network classifier is used for ligand-based target or activity prediction [22].

In [23], [24], the Multilevel Neighborhoods of Atoms (MNA) structure descriptors were used for prediction.

The MNA of a molecule was generated on the basis of connection table and table of atom types representing the compound. Each particular descriptor has a unique integer number according to the dictionary of the descriptors. The similarity between two molecules is calculated using Tanimoto coefficient and the activity of the unknown molecule is predicted by the activity of the most similar molecule.

Previously, Hentabli *et al*. [25]–[27] developeda new molecular descriptor, Language for Writing Descriptors of Outline Shape of Molecules (LWDOSM) and shape based molecular descriptor (SBDM), that have been inspired by researchers in information retrieval on the use of contour based shape descriptor for image retrieval systems [28] . Shape-based molecular descriptor is a new method used for obtaining the rough description of 2D molecule structure from the 2D outline shape of its 2D diagram. The mentioned descriptor is a textual descriptor that allows rigorous structure specification via a very small and natural grammar. Experiments in ligand-based virtual screening method used SBDM for similarity searching. Experiments with a subset of the MDDR database demonstrated that the SBDM provided an interesting alternative to existing tools for ligand-based virtual screening. It substantially outperformed a conventional Tanimoto-based similarity searching system when the active molecules have a high degree of structural homogeneity. In this paper,we introduce a new tool for activity prediction model using SBDM and MNA. The SBDM-MNA provides a useful method of using the prior knowledge of target class information (active and inactive compounds) to predict the activity of orphan compounds. To validate our method, we applied this SBDM-MNA on different established data sets from literatures and compare its performance with the classical MNA descriptor for activity prediction.

2.0 MATERIALS AND METHODS

The new descriptor SBDM [25], [26] is a textual descriptor that uses printable characters to represent molecules based on their shapes. The outline shape (for the whole molecule) and the internal region (inside molecule rings) are exploited to calculate a rough description of the 2-D structure molecule. The proposed method uses a connection table to extract the information needed to represent the molecule shape. A specific language has been developed to describe the shape features; descriptors written in this language are invariants to scale change and rotation. SBDM is a true language, albeit with a simple vocabulary (atom and bond symbols) and few grammar rules. However, part of the power of the SBDM is that it is highly sensitive to molecular structure changes.

2.1 Multilevel Neighborhoods of Atoms (MNA)

MNA structure descriptors of molecules [23] are generated on the basis of connection table and atom types expressive the compound. Connection table contains data on the covalent bonds in a molecule. Various bond types are not specified (topological approximation). All hydrogen based on valences and partial charges of atoms are taken into account. Atom types are specified according to the data presented in Table 1.

Table 1 Classification of different atom types used in calculation of descriptors

Class name	Elements	Class name	Elements
H	H	C	C
N	N	O	O
F	F	Si	Si
P	P	S	S
Cl	Cl	Ca	Ca
As	As	Se	Se
Br	Br	Li*	Li, Na
B*	B, Re	Mg*	Mg, Mn
Sn*	Sn, Pb	Te*	Te, Po
I*	I, At	Os*	Os, Ir
Sc*	Sc, Ti, Zr	Fe*	Fe, Hf, Ta
Co*	Co, Sb, W	Sr*	Sr, Ba, Ra
Pd*	Pd, Pt, Au	Be*	Be, Zn, Cd, Hg
K*	K, Rb, Cs, Fr	V	V, Cr, Nb, Mo, Tc
Ni*	Ni, Cu, Ge, Ru, Rh, Ag, Bi	In*	In, La, Ce, Pr, Nd, Pm, Sm, Eu
Al*	Al, Ga, Y, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu, Tl	R*	R, He, Ne, Ar, Kr, Xe, Rn, Ac, Th, Pa, U, Np, Pu, Am, Cm, Bk, Cf, Es, Fm, Md, No, Lr, Db, Jl

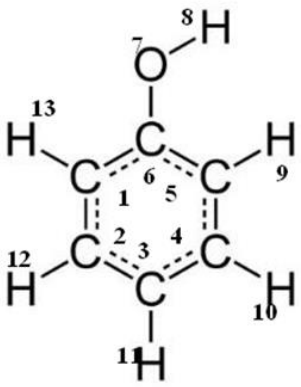
The structure of the molecule is represented as the set of MNA descriptors calculated iteratively. The Zero-level's descriptor is presented by the type of atom according to Table 1 and special dash label if the atom is not included into the cycle. If the atom is included in the cycle, the dash label is absent. The descriptor of the first level includes the atom's zero-level descriptor of its neighboring atoms, sorted lexicographically. This process is continued iteratively covering 2nd, 3rd and nth neighborhood of the atoms.

Examples of structure presentation by zero, first and second levels MNA descriptors for the phenol's molecule are shown in Figure 1.

A set of MNA descriptors for a molecule are generated recursively:

1- The zero-level descriptor is presented by the type of atom. A special mark, "-", is

added to the descriptor of zero level if the atom is not included in the cycle as show in Figure 1.



atom	MNA/0
1	C
2	C
3	C
4	C
5	C
6	C
7	-O
8	-H
9	-H
10	-H
11	-H
12	-H
13	-H

Figure 1 Representation of phenol by the MNA descriptors of the zero level (MNA/0)

2- The descriptor of each successive level is a concatenation of the zero-level descriptor of the atom while enclosed in parentheses is a lexicographically ordered list of descriptors of the previous level of its nearest neighbors as illustrate in Figure 2 below.

atom	MNA/1
1	C(CC-H)
2	C(CC-H)
3	C(CC-H)
4	C(CC-H)
5	C(CC-H)
6	C(CC-O)
7	-O(C-H)
8	-H(-O)
9	-H(C)
10	-H(C)
11	-H(C)
12	-H(C)
13	-H(C)

atom	MNA/2
1	C(C(CC-H)C(CC-O)-H(C))
2	C(C(CC-H)C(CC-H)-H(C))
3	C(C(CC-H)C(CC-H)-H(C))
4	C(C(CC-H)C(CC-H)-H(C))
5	C(C(CC-H)C(CC-O)-H(C))
6	C(C(CC-H)C(CC-H)-O(C-H))
7	-O(C(CC-O)-H(-O))
8	-H(-O(C-H))
9	-H(C(CC-H))
10	-H(C(CC-H))
11	-H(C(CC-H))
12	-H(C(CC-H))
13	-H(C(CC-H))

Figure 2 Representation of phenol by the MNA descriptors of the first and second levels (MAN/1, MNA/2)

2.2 Prediction using MNA

Generally, at some point in the iteration process, the classical MNA descriptor may cover the molecule completely. However, the experiments show that the utilization of MNA descriptors of the first and second levels give best accuracy for property prediction [23]. Such MNA descriptors are generated for each structure from the data set. Each particular descriptor has a unique integer number according to the descriptors' dictionary.

2.3 Calculation of Similarity using MNA

In [23] they modified the Tanimoto coefficient to take into account the different frequencies of descriptors. The similarity between two molecules, A and B, is given by

$$sim(A,B)=\frac{\sum_{i=1}^{M}\min\left[A(i),B(i)\right]}{\sum_{i=1}^{M}A(i)+\sum_{i=1}^{M}B(i)-\sum_{i=1}^{M}\min\left[A(i),B(i)\right]}$$

where A(i) and B(i) are the counts of different frequencies of descriptor in the molecules A and B, respectively, and M is the total number of various descriptors in the dictionary.

3.4 SBDM-MNA

The main idea of the work proposed in this paper is to apply a new hybrid method for biological activities prediction between the Multilevel Neighborhoods of Atoms (MNA) algorithm and the shape based molecular descriptor (SBDM). The process of generating SBDM-MNA of any molecule first starts with applying the MNA first level to decompose the molecule in atoms and their neighboring atoms and then to apply the SBDM descriptor for describing each part from the whole molecule based on the rule of SBDM descriptor as illustrated in Figure 3.

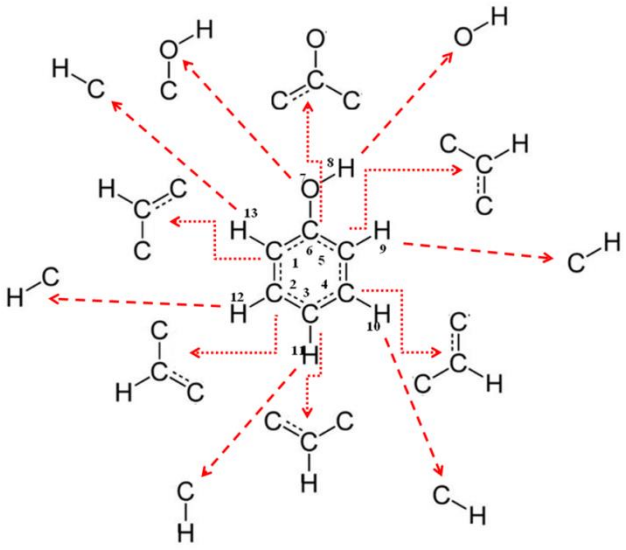


Figure 3 Decompose the molecule in atoms and their neighboring atoms

For each atom extracted using the previous step, we apply the SBDM descriptor to determine the center atom in the part of molecule graph. Then we move in a clockwise direction to the next atom. The bond type and direction of the movement are represented before we visit and represent the next atom. This procedure is repeated until the initial atom is revisited. Once the starting atom is revisited, then the description of the outline shape of the molecule graph is completed as presented in s Figure 4. However, the process of generating the SBDM is composed of a number of specification rules explained next.

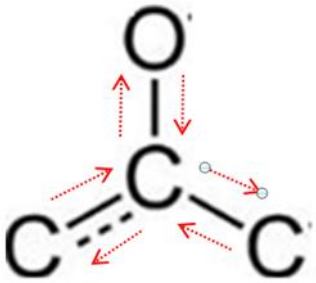
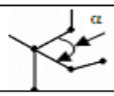
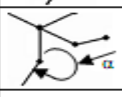
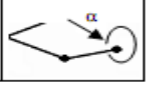


Figure 4 external visiting movements in a 2D graph of the 1st atom

The language used for writing the SBDM descriptor consists of a series of characters and symbols. There are three generic encoding rules corresponding to the specification of atoms, bonds and direction angle. Some of these rules are similar to the rules used in SMILES strings [26] Atoms are represented by their atomic symbols, usually two characters. The second character of the atomic symbol must be entered in lower case. For atomic symbols with just one letter, we add a blank space at the end of each atomic symbol, e.g., "Br", "C1","N "and "O". The single, double, and triple bonds are represented by the symbols "-", "=", and "#", respectively.

The direction of angle of the molecule shape boundary can be calculated using four directions ranging between 0 and 3 based on the value of the angle, as shown in Table 2.

Table 2 Angle directions representation

Angle Degree	Symbols	Example
0 °-90°	0	
91- 180°	1	
181 ° - 270	2	
271 ° - 360 °	3	

By applying the SBDM descriptor for each part of MNA part for the molecule in Figure 2 as show in next Table 3.

Table 3 SBDM-MNA calculation

Atom N	Atom name	SBDM-MNA
1	C	C -0C =3C -2H -3C -2C -3
2	C	C -0C =3C -2H -3C -2C -3
3	C	C -0C =3C -2H -3C -2C -3
4	C	C -0C =3C -2H -3C -2C -3
5	C	C -0C =3C -2H -3C -2C -3
6	C	C -0C =3C -2O -3C -2C -3
7	O	O -0C =3C -2O -3C -2C -3
8	H	O -1H -3
9	H	C -1H -3
10	H	C -1H -3
11	H	C -1H -3
12	H	C -1H -3
13	H	C -1H -3

2.4 Data Sets

We evaluate the quality of our prediction model on different datasets that have been used to validate the classification of molecules based on structure-activity relationship. The three data sets described in Table 4 are taken from [9], [11] literature with compounds classified as active or inactive: cyclooxygenase inhibitors, ligands of the benzodiazepine receptor and ligands of the estrogen receptor (ER). These data sets have been used by literatures for validating prediction models [22], [25], [29].

Table 4 Summary of the different Data Sets

Data set	Number of compounds		Mean similarity	Pairwise
	active	inactive	active	inactive
Cyclooxygenase-2 inhibitors	303	164	0.687	0.690
Benzodiazepine receptor	306	99	0.536	0.538
Estrogen receptor	141	252	0.468	0.456

The last two data sets (Tables 5-6) are taken from [30] and extensively used by many previous studies to validate ligand-based virtual screening approaches [22], [25]–[27], [29], [31], [32]. The data sets MDDR1 and MDDR2 contain 10 each for the homogeneous activity classes and heterogeneous ones.

Tables 4-6 contains activity class, number of molecules/peptides belong to the class, and diversityof classes, which is computed as the mean pair wise Tanimoto similarity calculated across all pairs of molecules/peptides inthe class using ECFC4 (extended connectivity)

Table 5 MDDR Activity Classes for DS1 Data Set

Activity Index	Activity class	Active molecules	Pairwise Similarity
07707	Adenosine agonists A1	207	0.229
07708	adenosine agonists A2	156	0.305
31420	renin inhibitors	1130	0.290
42710	CCK agonists	111	0.361
64100	monocyclic _-lactams	1346	0.336
64200	Cephalosporins	113	0.322
64220	Carbacephems	1051	0.269
64500	Carbapenems	126	0.260
64350	Tribactams	388	0.305
75755	vitamin D analogues	455	0.386

Table 6 MDDR Activity Classes for DS2 Data Set

Activity Index	Activity class	Active molecules	Pairwise Similarity
09249	muscarinic (M1) agonists	900	0.111
12455	NMDAreceptor antagonists	1400	0.098
12464	Nitricoxidesynthaseinhibitor	505	0.102
31281	dopaminehydroxylase inhibitors	106	0.125
43210	aldose reductase inhibitors	957	0.119
71522	reversetranscriptase inhibitors	700	0.103
75721	aromatase inhibitors	636	0.110
78331	cyclooxygenase inhibitors	636	0.108
78348	phospholipase A2 inhibitors	617	0.123
78351	lipoxygenase inhibitors	2111	0.113

Table 7 MUV activity classes for MUV data set

Activity index	Activity class	Active molecules	Pair-wise similarity
466	S1P1 rec. (agonists)	30	0.445
548	PKA (inhibitors)	30	0.430
600	SF1 (inhibitors)	30	0.445
644	Rho-Kinase2 (inhibitors)	30	0.416
652	HIVRT-RNase inhibitors	30	0.398
689	Eph rec. A4 (inhibitors)	30	0.449
692	SF1 (agonists)	30	0.365
712	HSP 90 (inhibitors) 30	30	0.413
713	ERaCoactBind inhibitors	30	0.389
733	ERbCoact.Bind. inhibitors	30	0.352
737	ERCoactBind potentiators	30	0.502
810	FAK (inhibitors)	30	0.425
832	Cathepsin G (inhibitors)	30	0.435
846	FXIa (inhibitors)	30	0.532
852	FXIIa (inhibitors)	30	0.492
858	D1rec.allostericmodulator	30	0.400
859	M1recallosteric inhibitors	30	0.386

The third data set, (MUV) as shown in Table 7, was reported by Rohrer and Baumann [15]. This data set contains 17 activity classes, with each class containing up to 30 actives and 15,000 inactive. The diversity of the class for this dataset shows that it contains high diversity or more heterogeneous activity classes.

2.5 Evaluation Measures

Ten-fold cross-validation was used to validate the results of SBDM-MNA and the SBDM and MNA. In this cross-validation, the data set was split into 10 parts; 9 were used for training and the remaining 1 for testing. This process was repeated 10 times; so all the compounds were used in the test set once. Thus, each activity class was tested against all the others. As in the case of other prediction methods, we used the area under the receiver operating characteristic curve (**AUC**) as quality criterion to quantify the performance of classification algorithms. The **AUC** is given as:

$$\mathbf{AUC}=((\mathbf{sens}+\mathbf{spec}))/2 \quad (2)$$

Where **sens** and **spec** are the sensitivity and specificity respectively, and given as:

$$\mathbf{sens}=\mathbf{tp}/((\mathbf{tp}+\mathbf{fn})) \quad (3)$$

$$\mathbf{spec}=\mathbf{tn}/((\mathbf{tn}+\mathrm{fp}\mathbf{)}) \quad (4)$$

Where **tp**, **tn**, **fp** and **fn** are numbers of true positives, true negatives, false positives, and false negatives, respectively. Where **tp** represents the number of active molecules selected in the active set and **tn** is the number of inactive molecules selected in an inactive set. While **fp** and **fn** represent the number of active molecules selected in inactive set and the number of inactive molecules selected in an active set respectively. An curve describes the trade-off between sensitivity and specificity, where the sensitivity and specificity are defined as the effectiveness of a model to identify positive and negative labels, respectively. The area under the curve (**AUC**) is a measure of the model performance: the closer to 1 the value is, the better the performance of the prediction.

We also used an accuracy (**ACC**) measurement to quantify the performance of the classification models. Accuracy is the overall effectiveness of the model and is calculated as the sum of correct classifications divided by the total number of classifications. This is shown in equation(5) as,

$$\mathbf{ACC}=((tp+tn))/((tp+tn+fp+fn)) \quad (5)$$

3.0 RESULTS AND DISCUSSION

The Shape-Based Descriptor Method (SBDM) was introduced in this study as a new activity prediction approach for unknown compounds. In order to evaluate SBDM's performance, this new approach

was compared with classical MNA on four different datasets. The prediction accuracy as well as the AUC of the prediction models on MDDR1, MDDR2, MUV and the different Dataset are demonstrated in tables' number 8, 9, 10 and 11 respectively.

Table 8 AUC, and Accuracy Rates for the Prediction Models with the MDDR1 Data Set

	MNA		SBDM	
Activity index	**AUC**	**ACC**	**AUC**	**ACC**
7707	96.73	99.40	98.49	99.70
7708	97.69	99.70	98.68	99.80
31420	99.32	99.50	99.15	99.40
42710	94.93	99.50	98.62	99.80
64100	97.83	98.30	99.02	99.20
64200	70.93	96.40	70.28	96.40
64220	98.26	98.80	98.02	98.70
64500	87.39	98.70	95.12	99.50
64350	99.72	99.90	100.00	100.00
75755	59.57	86.80	63.91	88.20
Mean	90.24	97.70	92.13	98.07

Table 9 AUC, and Accuracy Rates for the Prediction Models with the MDDR2 Data Set

	MNA		SBDM	
Activity index	**AUC**	**ACC**	**AUC**	**ACC**
9249	95.41	98.20	96.96	98.80
12455	93.47	96.40	96.71	98.20
12464	84.85	96.60	84.22	96.40
31281	94.75	99.70	93.31	99.60
43210	94.18	97.60	94.41	97.70
71522	86.31	95.80	92.77	97.80
75721	95.41	98.70	96.35	98.90
78331	81.66	94.90	78.35	94.00
78348	81.49	95.00	82.88	95.40
78351	74.67	81.10	78.91	84.30
Mean	88.22	95.40	89.49	96.11

The results of the first dataset MDDR1 are presented in Table 8. These results show that the SBDM offered the highest sensitivity, specificity, AUC, and accuracy values compared to the classical MNA. However, the performance of SBDM was retreated in three activity classes from this dataset (renin inhibitors, Cephalosporins and carbacephems).

Table 10 AUC, and Accuracy Rates for the Prediction Models with the MUV Data Set

	MNA		SBDM	
Activity index	AUC	ACC	AUC	ACC
466	64.00	80.00	66.00	81.10
548	74.00	85.50	70.00	83.30
600	56.00	75.50	56.00	75.50
644	48.00	71.10	54.00	74.40
652	44.00	68.80	50.00	72.20
689	56.00	75.50	54.00	74.40
692	48.00	71.10	44.00	68.80
712	46.00	70.00	50.00	72.20
713	40.00	66.60	42.00	67.70
733	44.00	68.80	44.00	68.80
737	42.00	67.70	44.00	68.80
810	52.00	73.30	50.00	72.20
832	66.00	81.10	70.00	83.30
846	50.00	72.20	48.00	71.10
852	42.00	67.70	44.00	68.80
858	40.00	66.60	42.00	67.70
859	40.00	66.60	46.00	70.00
Mean	50.12	72.24	51.41	72.96

Table 11 AUC, and Accuracy Rates for the Prediction Models with the different Data Sets

	MNA		SBDM	
Activity index	**AUC**	**ACC**	**AUC**	**ACC**
cyclooxygenase-2 inhibitors	95.10	95.30	96.19	96.30
benzodiazepine receptor	91.11	91.20	93.40	93.50
estrogen receptor	89.88	92.10	87.47	90.20
Mean	92.03	92.87	92.35	93.33

The good performance of SBDM approach was not restricted to the first data set since this activity prediction model also perform best for the MDDR2 data sets (Table 7). The results in Table 9 showed that SBDM produced the best performance across seven activity classes in the MDDR2 data set. Nonetheless the performance of SBDM was not satisfying in 3 classes (nitric oxide synthase inhibitors, dopamine hydroxylase inhibitors and cyclooxygenase inhibitors). Since MDDR2 dataset is highly diverse than the previous dataset, the performance of SBDM is considered outstanding.

Despite the fact that MUV dataset includes the most heterogeneous activity classes compared to the previously mentioned datasets (MDDR1 and

MDDR2), SBDM's prediction results were more convenient and applicable than the MNA results which proved the effectiveness of this new prediction method. Additionally, the results presented in table 10 of the different datasets revealed that the SBDM offered the highest AUC, and accuracy values compared to the classical MNA confirming the fact that SBDM is considered as an interesting and promising method for activity prediction.

It was clearly illustrated in Tables 8-11 and in the last row of each table that present the mean of each colonne, the efficiency of SBDM as new prediction method is clearly illustrated in Tables 8-11. While the classical MNA only deals with the short paths in detecting compounds, SBDM's developed features allows it to deal with longer paths along with identifying the bonds types of the molecule and calculating the divergence's angle. SBDM prediction results revealed that it depends on the activity classes of the datasets whether they are highly diverse or not.Thus, it is still important to develop better prediction methods for high diversity activity classes. Therefore, SBDM is presented as a convenient new activity prediction method for target compounds.

4.0 CONCLUSIONS

The main aim of this study is to introduce the Shape-Based Descriptor Method (SBDM) as a new activity prediction approach for the unknown compounds. To test and prove the efficiency of SBDM, it is applied to different dataset and its performance is compared with classical MNA. The results of the experiments revealed that SBDM provides interesting prediction rates with short time calculation for activity prediction. These results also indicate that SBDM is particularly effective for homogeneous datasets rather than structurally heterogeneous ones. Thus, SBDM is presented as a convenient new activity prediction method for target compounds. However, the area the area is still open to develop better prediction methods for high diversity activity classes.

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