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ORIGINAL ARTICLE

Polarizability: a promising descriptor to study chemical–biological interactions

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Abstract

Recently, we have defined atomic polarizability, a Conceptual Density Functional Theory (CDFT)-based reactivity descriptor, through an empirical method. Though the method is empirical, it is competent enough to meet the criteria of periodic descriptors and exhibit relativistic effect. Since the atomic data are very accurate, we have applied them to determine molecular polarizability. Molecular polarizability is an electronic parameter and has an impact on chemical–biological interactions. Thus, it plays a pivotal role in explaining such interactions through Structure Activity Relationships (SAR). In the present work, we have explored the application of polarizability in the real field through investigation of chemical–biological interactions in terms of molecular polarizability. A Quantitative Structure–Activity Relationship (QSAR) model is constructed to account for electronic effects owing to polarizability in ligand–substrate interactions. The study involves the prediction of various biological activities in terms of minimum block concentration, relative biological response, inhibitory growth concentration or binding affinity. Superior results are presented for the predicted and observed activities which support the accuracy of the proposed polarizability-QSAR model. Further, the results are considered from a biological viewpoint in order to understand the mechanism of interactions. The study is performed to explore the efficacy of the computational model based on newly proposed polarizability and not to establish the finest QSAR. For future studies, it is suggested that the descriptor polarizability should be contrasted with the use of other drug-like descriptors.

Keywords Polarizability · Conceptual density functional theory (CDFT) · Chemical reactivity descriptor · Quantitative structure–activity relationship (QSAR) · Chemical–biological interactions · Depolarization

Introduction

Polarizability (α) is described as the linear response of electronic charge distribution with respect to an external applied electric field [1, 2]. It is an electronic effect which can be explored further. It is considered as a conversion element between the induced dipole moment (μ) and an applied electric field (ε).

$$\mu = \alpha.\varepsilon \tag{1}$$

As majority of the molecules are asymmetric, polarizability is primarily a three-dimensional tensor. Nevertheless, the average of the tensor's diagonal elements is sufficient for nearly all purposes:

$$\alpha = \alpha = \frac{1}{3}\left(\alpha_{xx} + \alpha_{yy} + \alpha_{zz}\right) \tag{2}$$

Recently, an effective model of atomic polarizability, an important Conceptual Density Functional Theory

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(CDFT)-based descriptor, was proposed by Tandon et al. in terms of absolute radius (r) and electronegativity (χ) [3]:

$$\alpha \propto \frac{r^2}{\chi} \tag{3}$$

The model uses an empirical approach which is simple and integrates relativistic effects. All the *sine qua non* of a periodic descriptor is followed excellently. Additionally, molecular polarizability is computed through property of additivity in their study.

Since the atomic polarizabilities of Tandon et al. are accurate to maintain periodicity trend [3], in the present study we have applied them to determine molecular polarizabilities. Molecular polarizability is an important electronic parameter and has a strong impact on chemical–biological interactions. It plays a crucial role in elucidating such interactions through Structure–Activity Relationships (SAR). In the present work, with the intention of exploring the efficacy of newly proposed polarizability by Tandon et al. in the real field, we have applied it to compute molecular polarizability to study chemical–biological interactions. The study supports validating the model as prescribed by Tandon et al. to compute polarizability in a molecular framework and not to develop the finest Quantitative Structure–Activity Relationship (QSAR). For future prospects, it is suggested that the descriptor polarizability should be contrasted with the use of other drug-like descriptors.

In these contemporary times, computational workers have overlooked the research of twentieth century on the importance of electronic interactions between a receptor and a ligand with the employment of combinatorial chemistry and in silico approaches. Since electronic interactions are a consequence of specific structural features and chemical traits, SAR analyses are indisputably of huge value in the present chemistry and biochemistry. The idea is to use chemical knowledge and perception to alter exploration for compounds with requisite properties into a mathematically quantified and programmed form. When a relationship is accomplished linking structure and activity, a great deal of compounds, inclusive of hypothetical, can be effortlessly analysed by computer in order to select structures with the necessary characters. Thus, it makes the selection of potential compounds simplistic, which can then be developed and examined in the laboratory. Hence, SAR methodology preserves resources and accelerates the route of development of new molecules to be utilized as drugs, anaesthetics, additives and other diverse materials.

Presently, our biodatabase contains a large number of QSAR equations with different parameters to describe distinct electronic effects. However, most of such equations do not encompass polarizability, which plays a crucial role in such relationships. A number of descriptors have been proved to be helpful in relating and accounting for numerous radical reactions [4–6]. These kinds of reactions are imperative in toxic conditions such as smoking or in the case of some environmental chemicals. Employing well-known parameters is the only means to perform comparative QSAR, which is the route towards a science of chemical–biological interactions through which one can approximate the biological activity of compounds that have not been investigated so far. The most essential facet of the theoretical methodology is to realize how living organisms (or their components such as DNA, protein, enzymes, and so on, and organisms ranging from bacteria to human) are affected by chemicals, for which mechanistic chemistry together with biology is crucial, in addition to the proficiency to carry out significant modelling with the 'proper' system. Electronic, hydrophobic and steric interactions constitute the chief interactions, and they must be suitably considered while modelling.

Conventionally, Lorentz–Lorenz equation is defined as [7],

$$\mathrm{MR} = \left(n^2 - \frac{1}{n^2} + 2\right)\frac{\mathrm{MW}}{d} \tag{4}$$

In this equation, n refers to the refractive index, MW indicates the molecular weight and d depicts the density of the substance. The refractive index (MR) is a quantification of the interaction of light with the electrons in a molecule. The term MW/d represents the volume. As there is a minor variation in n, MR depends on MW/d. The initial attempt to apply molecular refractivity in terms of the Lorentz–Lorenz equation to biological processes was made by Pauling and Pressman [8]. Their study was based on hapten antibody interactions, which considered polarizability and involved steric factors [9]. Agin et al. made a remarkable investigation of the ability of diverse chemicals to obstruct the sartorius muscle of the frog incorporating two parameters: α (polarizability) and Ip (ionization potential) [10]. One more case of the minimum blocking concentration of various drugs on frog muscle results from a study by Kamlet and others [11]. In another investigation, Hahin and his coworkers examined the action of alcohols on frog nerves [12]. The pharmacological activities of a number of phenyl alkane p-ω-bis(trialkylammonium) compounds were analysed by Wien and Mason [13]. Minimum blocking concentration to reduce action potential in central nerve cord from American cockroach was evaluated by Nishimura et al. [14]. Recently, García-Jacas et al. explored the aptness of alignment-free geometric molecular descriptors based on N-linear algebraic maps, commonly known as QuBiLS-MIDAS, for extracting structural information of the molecules [15]. A comparison of different QSAR methodologies for investigating their predictive

abilities was also presented by their group [16]. Various studies have been carried out to study the mechanism of different biological activities such as blocking potency, toxicity, anticonvulsant activity, neuromuscular activity, neurophysiological activities, to mention some [17–34]. The history of such works is vast and will not be discussed here.

The mechanism of action of local anaesthetics, narcotics and drugs is in general one of the fundamental difficulties in the study of cell membranes [10]. There are two basic characteristics of this problem, which have puzzled and at the same time fascinated researchers: first of all, there is a broad range of chemical structures, varying from the inert gases to complex molecules, for example tetrodotoxin, which can stop electrical activity reversibly; secondly, a lot more is known about the characteristics of any of these chemical structures than regarding the membrane with which they presumably interact. The foremost complication in earlier times has been the absence of suitable quantitative parameters, mainly those pertaining to active and inactive molecular structures.

Numerous forms of biological activities rest on the pharmacokinetics, circulation and distribution of chemicals within the organism. Such processes are suggested to be greatly controlled by polarizability. Binding of chemicals with body fluids or cells, their passage and various other interactions depend on the polarizability of the chemical as well as the system. However, regardless of its potential, most of the QSAR studies do not employ this elementary parameter. Thus, the objective of this study is to present the potential of Tandon et al.'s polarizability in computing molecular polarizability to use as an electronic interaction parameter for chemical–biological systems and to suggest the probable effects and action mechanism. It is believed that the study of the action mechanism of a variety of molecules would reveal important properties of the biological structures and eventually lead to an understanding of the mechanism of anaesthesia, narcotics, toxicants and other similar chemicals.

Method of computation

The purpose of the present study is to assess the applicability of Tandon et al.'s polarizability [3] in computing molecular polarizability and further exploring its potential in the real field. For this purpose, varied biological activities of different compounds have been modelled using polarizability with the aim of explicating their course of action. In our analysis, we have empirically computed a CDFT-based reactivity descriptor, viz. polarizability (α), for 312 compounds through the property of additivity [35–37] using atomic polarizability data tabulated by Tandon et al. [3]:

$$\alpha_m \approx \sum_i \alpha_i \tag{5}$$

We have determined the molecular polarizabilities for a variety of molecules, viz. anaesthetics, miscellaneous drugs, phenyl-substituted and unsubstituted *n*-alkanols, phenyl alkane *p*-ω-bis(trialkylammonium) compounds, substituted benzyl pyrethroids, miscellaneous aliphatic alcohols and esters and 3-amidinophenylalanine derivatives. The data can be found in Online Resource 1.

The selected compounds have been categorized into seven sets on the basis of their biological activities, viz. minimum concentration of varied anaesthetics required for complete block of excitability in sartorius muscle of the frog, minimum concentration of miscellaneous drugs for blocking electrical activity in frog muscle, minimum blocking concentration of miscellaneous alkanols to reduce action potential of frog nerves by 50%, relative biological response for neuromuscular blocking activity of aromatic bis-quaternary compounds on rabbit phrenic nerve diaphragm, minimum blocking concentration of pyrethroids to suppress action potential of central nerve cord of cockroach, 50% inhibitory growth concentration of miscellaneous aliphatic alcohols and esters to present toxicological activity in *Tetrahymena pyriformis* and binding affinity of 3-amidinophenylalanine derivatives towards thrombin. The biological activity data for these compounds have been taken from literature [10–14, 38, 39]. Regression analysis has been carried out to correlate descriptor values with observed activities to build a scrupulous and realistic QSAR model. In the study, the DFT-based reactivity descriptor, polarizability, is adopted as an independent variable, while log of inverse of minimum blocking concentration (MBC), log of relative biological response (RBR), log of inverse of inhibitory growth concentration (IGC) or log of inverse of binding affinity (K_i) is considered a dependent variable to establish QSAR model to predict the biological activity:

$$\log\left(\frac{1}{\text{MBC}}\right) \text{ or (RBR) or } \left(\frac{1}{\text{IGC}_{50}}\right) = a\alpha + b \tag{6}$$

and

$$\log\left(\frac{1}{K_i}\right) = a\alpha + b\beta + c \tag{7}$$

In these expressions, *log* (1/MBC), (RBR), (1/IGC_{50}) or (1/K_i) implies predicted biological activity, α indicates polarizability of the compound, while 'a', 'b' and 'c' represent constants calculated for respective set of compounds. β signifies the compressibility of the molecule. The total number of compounds in every set (n) is split into training and test set to develop the model and assess its predictive power, respectively. The division is made such that both

the sets contain similar functional group as far as possible. Goodness-of-fit of the developed model is determined by coefficient of determination (R^2), and robustness is evaluated by cross-validation coefficient (using leave-one-out method) (R^2_{CV}). Further, predicted residual error sum of squares and error bar analysis is used to test the uniformity and significance of the data. All the OECD principles have been followed; namely endpoint has been defined, an unambiguous algorithm is developed, applicability domain is defined, measures of goodness-of-fit, robustness and predictivity have been provided and finally, a mechanistic interpretation is also presented. The computations have been carried out using Minitab including the development, testing and validation of the developed regression models [40].

Results and discussion

The study describes the application of Tandon et al.'s polarizability in the real field as a predictor of biological activity for the chosen 312 compounds. Observed activity data (1/MBC or RBR or $1/IGC_{50}$ or $1/K_i$) of the selected compounds are taken as the dependent variable, whereas polarizability (α) is considered as an independent variable in developing the regression models. As mentioned in the above section, the study has been performed by differentiating the selected compounds into seven categories. Discussion for each of the above-mentioned sets is presented in this part.

Complete block of excitability in terms of minimum blocking concentration for sartorius muscle of the frog

The first set of compounds presents the potential of a broad variety of anaesthetics to block the sartorius muscle of the frog. Such blocking is possibly a result of nerve inhibition. The QSAR model obtained for the minimum blocking concentration using polarizability is represented by Eq. (8):

$$\log\left(\frac{1}{\mathrm{MBC}}\right) = (0.019)\alpha - (0.596)$$
$$n = 39, R^2 = 0.950, R^2_{\mathrm{CV}} = 0.938 \quad (8)$$

The predicted and observed biological activities (in mM) of the anaesthetics are presented in Table 1. It is seen that the molecules in the set possess heterogeneity in their chemical structures and yet show a close conformity with Eq. (8). High values of R^2 and R^2_{CV} signify a very impressive correlation between the data sets. Predicted residual error sum of squares and standard error bar analysis presents uniformity and significance of the data. The molecules used in the construction of the model are the different from the ones used for validation purpose. Internal validation by the test set transpires the predictability of the model. It appears that anaesthetics or other simple molecules interact with electrically excitable membranes by a same mechanism. Hence, it is unacceptable to provide a dissimilar and specific interaction mechanism for each and every anaesthetic molecule

Table 1 Minimum concentration of varied anaesthetics required for complete block of excitability in sartorius muscle of the frog (in mM)

S. No	Anaesthetics	Observed *log* 1/MBC[a]	Calculated log 1/MBC
1	Methanol	−0.09	0.12
2	Ethanol[b]	−0.25	0.54
3	Acetone	0.40	0.79
4	2-Propanol[b]	0.45	0.96
5	Propanol	0.60	1.27
6	Urethane[b]	1.00	1.38
7	Ethyl ether[b]	1.07	1.20
8	Butanol	1.22	1.78
9	Antipyrine[b]	1.22	3.54
10	Pyridine[b]	1.23	1.95
11	Chloroform	1.50	0.70
12	Hydroquinone	1.60	1.65
13	Aniline	1.70	1.62
14	Benzyl alcohol[b]	1.70	1.12
15	Acetanilide	1.83	2.41
16	Pentanol[b]	1.80	1.80
17	Phenol	2.00	1.53
18	Toluene	2.00	1.83
19	Benzimidazole	2.19	1.91
20	Hexanol	2.44	2.22
21	Nitrobenzene	2.53	1.70
22	Quinoline[b]	2.70	2.36
23	8-Hydroxyquinoline[b]	2.70	2.63
24	Heptanol[b]	2.80	2.53
25	2-Naphthol	3.00	2.49
26	Methyl anthranilate[b]	3.00	2.69
27	Octanol	3.16	3.05
28	Thymol[b]	3.52	3.21
29	o-Phenanthroline	3.80	3.42
30	Ephedrine[b]	3.80	3.32
31	Procaine	4.67	4.84
32	Xylocaine	4.96	5.14
33	Diphenhydramine	5.80	5.67
34	Tetracaine[b]	5.90	5.68
35	Phenyltoloxamine[b]	6.20	5.67
36	Quinine	6.60	6.92
37	Eserine	6.66	5.55
38	Caramiphen	7.00	6.56
39	Dibucaine[b]	7.20	7.48

[a]Observed data taken from reference [10]. [b]Compounds selected for test set

based on its chemical configuration or structural relations to known biochemical systems. However, in reality, not every molecule behaves as an anaesthetic. The reason for this may be related to polarizability, water (lipid) solubility and other interactions such as hydrogen bonding taking place with molecules. If a group with lower polarizability and higher lipophilicity, for instance, an aromatic ring, is attached to a molecule such as sugar, the newly formed molecule will show anaesthetic action, i.e. block excitability, because it will allow an easy passage of chemicals through membranes which are less polar but more lipophilic. Thus, there will be a greater distribution of the chemicals to hydrophobic regions of the bioorganism consequently demonstrating an anaesthetic or excitability blocking activity, and the minimum blocking concentration will be in accordance with the polarizability of that group. On the other hand, if a polar group enters into an organism, its solubility in water (hydrophilicity) will increase since polarity of water is higher in comparison with lipids and proteins. As a result, there will be a slow passage of chemicals through membranes, which will favour excretion of chemicals out of the organism through various ways like urine, perspiration, etc. Therefore, the tendency to accumulate chemicals in high concentrations will decrease and no or very less anaesthetic action will be observed. The exact course of action of anaesthetics, nevertheless, remains vague. Even though the correlation reported here is fairly remarkable, which lets us predict the minimum blocking concentration of some molecules with significant precision, the theoretical opinions in reference to the involved physical parameters perhaps need to be investigated further.

Blocking of electrical activity in terms of minimum blocking concentration for frog muscle

The second set of compounds presents the ability of miscellaneous drugs to block electrical activity in frog muscle. The QSAR model for computing the minimum blocking concentration using polarizability is given in Eq. (9):

$$\log\left(\frac{1}{\mathrm{MBC}}\right) = (0.023)\alpha - (1.121)$$
$$n = 21, R^2 = 0.977, R^2_{\mathrm{CV}} = 0.968 \quad (9)$$
Outliers : Chloroform, Nitrobenzene

The predicted and observed biological activities (in mM) of the drugs are listed in Table 2. It is noted that the molecules in the given set present a close agreement with Eq. (9). High values of R^2 and R^2_{CV} present the goodness-of-fit and robustness, which in turn suggest a remarkable association amongst the activity data sets. Standard error bar analysis presents uniformity in data, while predicted residual error sum of squares indicates superiority of the model. The molecules used in the construction of the model are the different from the ones used for validation purpose. Internal validation by the test set signifies excellent predictability by the model. From a mechanistic point of view, an increase in the polarizability of drug may result in dipole–dipole or charge–dipole interactions between high-polarity drug molecules and chemicals associated with the electrical conduction of nerve impulses across nerve membranes such as zwitter ionic lecithin and/or ionic acetylcholine. As a result of such interaction, a hindrance is produced in the conduction of nerve impulses. Thus, it follows when interactions take place between extremely polar or charged species; the contribution of polarizability to blocking of electrical activity effect is highest. Undoubtedly, this indicates a definite relationship amongst highly polar solutes and certain molecular entities contributing to the nerve impulse transmission where lecithin and acetylcholine appear probable candidates.

Table 2 Minimum concentration of miscellaneous drugs for blocking electrical activity in frog muscle (in mM)

S. No	Drugs	Observed log 1/MBC[a]	Calculated log 1/MBC
1	Toluene	2.00	2.01
2	Methanol	− 0.09	− 0.06
3	Ethanol[b]	0.25	0.25
4	Propanol	0.60	0.96
5	2-Propanol[b]	0.45	1.14
6	Butanol	1.22	1.47
7	Pentanol[b]	1.80	1.77
8	Hexanol	2.44	2.48
9	Heptanol[b]	2.80	2.79
10	Octanol	3.16	3.50
11	Acetone	0.40	0.75
12	Phenol[b]	2.00	1.45
13	Thymol	3.52	3.68
14	Benzyl alcohol	1.70	2.16
15	Ether	1.07	1.47
16	Chloroform[b,c]	1.50	0.45
17	Aniline	1.70	1.76
18	Nitrobenzene[b,c]	2.53	1.65
19	2-Naphthol	3.00	3.06
20	Pyridine	1.23	1.25
21	Quinoline[b]	2.70	2.46

[a]Observed data taken from reference [11]. [b]Compounds selected for test set. [c]Outliers for Eq. (9)

Reduction in action potential in terms of minimum blocking concentration for frog nerves by 50%

The third set is comprised of a variety of alkanols using which QSAR relationship is constructed for the computation of the minimum blocking concentration to reduce action potential of frogs. The model, displayed by Eq. (10), employs polarizability as a theoretical parameter:

$$\log\left(\frac{1}{\mathrm{MBC}}\right) = (0.021)\alpha - (1.139)$$
$$n = 11,\ R^2 = 0.988,\ R^2_{\mathrm{CV}} = 0.972 \tag{10}$$

The predicted and observed biological activities (in mM) of compounds are arranged in Table 3. An excellent correlation is noted for the selected compounds with Eq. (10). High R^2 and R^2cv values imply a significant relationship between the predicted and observed activities. Predicted residual error sum of squares presents superior predictability by the model. The molecules used in the construction of the model are the different from the ones used for validation purpose. As per error bar analysis, there is a slight variation in the selected data. However, internal validation suggests the good predictability by the model. The variable, viz. polarizability, adopted for the prediction performs a crucial role in binding interactions between membrane proteins and molecules (like alkanols). An increase in alkanol potency with phenyl substitution is represented by Eq. (10). Although the addition of phenyl moiety causes an increase in potency, a decrease can be seen with increasing chain length. This suggests greater efficiency of increase in chain length over addition of phenyl group. The explanation for such behaviour is possibly correlated with polarizability and hydrogen bond acceptor basicity. As the phenyl addition occurs, an increase in the hydrogen bond acceptor basicity of the molecule takes place, which is attributed to the polarization of a specific part of the molecule. Thus, the formation of hydrogen bonds with other donor molecules becomes facile. Since Na^+ channels are known to play a crucial role in mechanism of action potential, obstruction of these channels will result in action potential block. Now, when a high-polarity (and the hydrogen bond acceptor basicity) chemical, *i.e.* alkanol, surrounds the Na^+ channel, there will be an increment in the binding of donor hydrogen bond sites of the Na^+ channel to alkanol molecules, thereby resulting in effective action potential block [41].

Table 3 Minimum blocking concentration of miscellaneous alkanols to reduce action potential of frog nerves by 50% (in mM)

S. No	n-Alkanols	Observed log 1/MBC[a]	Calculated log 1/MBC
1	Methanol	− 0.38	− 0.35
2	Ethanol[b]	0.06	0.11
3	*n*-Propanol	0.63	0.58
4	*n*-Butanol[b]	1.16	1.04
5	*n*-Pentanol	1.70	1.50
6	*n*-Hexanol[b]	2.18	1.97
7	*n*-Heptanol	2.66	2.43
8	Phenol[b]	2.09	1.21
9	Benzyl alcohol	1.70	1.68
10	Phenethyl alcohol[b]	2.00	2.14
11	3-Phenyl-1-propanol	2.51	2.60

[a]Observed data taken from reference [12]. [b]Compounds selected for test set

Neuromuscular blocking activity in terms of relative biological response for phrenic nerve diaphragm of rabbit

The fourth set presents the practicability of polarizability to predict relative biological response for neuromuscular blocking activity on rabbit nerves. The QSAR model obtained for the biological activity is represented by Eq. (11):

$$\log(\mathrm{RBR}) = (0.009)\alpha - (3.681)$$
$$n = 17,\ R^2 = 0.825,\ R^2_{\mathrm{CV}} = 0.780 \tag{11}$$

The predicted and observed biological activities (in mM) of the aromatic bis-quaternary compounds are presented in Table 4. The compounds selected for the investigation are in good accord with Eq. (11). The value of R^2 and R^2_{CV} justifies the dependence of the neuromuscular blocking activity on polarizability. Analysis of error bars presents consistency in the data but predicted residual error sum of squares is high implying average predictability. The molecules used in the construction of the model are different from the ones used for validation purpose. The result of internal validation for predictability of the model is satisfactory. The present phenyl alkane *p*-ω-bis(trialkylammonium) series offers several suitable candidates of pharmacological importance, such as phenyl hexane *p*-ω-bis-(trimethylammonium iodide) and *p*-ω-bis(triethylammonium iodide). It is suggested that the block through such compounds occurs via depolarization, which alters the distribution of electric charge in the nerve cells as it enters or binds to the nerve cell. As a result, the transmission of signals is obstructed due to reversal of charges leading to neuromuscular block. However, there might be a possibility of competitive block too. It has also been observed that the replacement of methyl with ethyl groups in the series, in general, enhanced the neuromuscular blocking property. This may be elucidated by the fact that there is an increase in the polarizability on substitution of methyl with ethyl as indicated by our theoretical values. Accordingly, phenyl hexane p-ω-bis-(triethylammonium iodide) may act as a potential neuromuscular blocking drug.

Table 4 Relative biological response for neuromuscular blocking activity of phenyl alkane *p*-ω-bis(trialkylammonium) compounds to rabbit nerves (in mM)

S. No	Phenyl alkane p-ω-bis(trialkylammonium) compounds[a]	Observed log RBR[b]	Calculated log RBR
1	$(CH_3)_3\ N^+C_6H_4N^+(CH_3)_3$	−1.00	−1.04
2	$(CH_3)_3\ N^+CH_2C_6H_4N^+(CH_3)_3$[c]	−0.70	−1.06
3	$(CH_3)_3\ N^+CH_2CH_2C_6H_4N^+(CH_3)_3$	−0.70	−0.65
4	$CH_3CH_2(CH_3)_2\ N^+CH_2CH_2C_6H_4N^+(CH_3)_2CH_2CH_3$[c]	−0.22	−0.46
5	$(CH_3CH_2)_2(CH_3)N^+CH_2CH_2C_6H_4N^+(CH_3)(CH_2CH_3)_2$	0.40	0.15
6	$(CH_3CH_2)_3\ N^+CH_2CH_2C_6H_4N^+(CH_2CH_3)_3$	0.48	0.55
7	$(CH_3)_3\ N^+(CH_2)_3C_6H_4N^+(CH_3)_3$	−0.70	0.01
8	$CH_3CH_2(CH_3)_2\ N^+(CH_2)_3C_6H_4N^+(CH_3)_2CH_2CH_3$[c]	0.00	−0.92
9	$(CH_3CH_2)_2(CH_3)N^+(CH_2)_3C_6H_4N^+(CH_3)(CH_2CH_3)_2$	0.60	0.35
10	$(CH_3CH_2)_3\ N^+(CH_2)_3C_6H_4N^+(CH_2CH_3)_3$	0.78	0.51
11	$(CH_3)_3\ N^+(CH_2)_4C_6H_4N^+(CH_3)_3$[c]	0.48	-0.46
12	$CH_3CH_2(CH_3)_2\ N^+(CH_2)_4C_6H_4N^+(CH_3)_2CH_2CH_3$	0.18	0.15
13	$(CH_3CH_2)_2(CH_3)N^+(CH_2)_4C_6H_4N^+(CH_3)(CH_2CH_3)_2$	0.70	0.55
14	$(CH_3CH_2)_3\ N^+(CH_2)_4C_6H_4N^+(CH_2CH_3)_3$[c]	1.30	0.73
15	$(CH_3)_3\ N^+(CH_2)_5C_6H_4N^+(CH_3)_3$[c]	0.78	−0.27
16	$(CH_3)_3\ N^+(CH_2)_6C_6H_4N^+(CH_3)_3$	0.70	0.15
17	$(CH_3CH_2)_3\ N^+(CH_2)_6C_6H_4N^+(CH_2CH_3)_3$	1.40	1.34

[a]The anion in all cases is I^-. All substituents on phenyl ring are on 1 and 4 positions. [b]Observed data taken from reference [13]. [c]Compounds selected for test set

Suppression in action potential in terms of minimum blocking concentration for cockroach central nerve cord

In this set, the ability to suppress action potential is analysed using a physicochemical parameter, polarizability, of substituted benzyl pyrethroids in the excised central nerve cord of American cockroach according to Eq. (6). The regression analysis yielded Eq. (12):

$$\log\left(\frac{1}{\mathrm{MBC}}\right) = (0.006)\alpha - (4.523)$$
$$n = 14,\ R^2 = 0.896,\ R^2_{\mathrm{CV}} = 0.836 \qquad (12)$$
$$\text{Outliers}: \ NO_2, SO_2Me$$

The predicted and observed biological activities (in M) of the pyrethroid derivatives are recorded in Table 5. A nice agreement is highlighted by the series of compounds with Eq. (12). The obtained R^2 and R^2_{CV} validate the effective correlation between the two sets of data. Lower values of predicted residual error sum of square and uniformity in error bars imply good predictability by the model. The molecules used in the construction of the model are different from the ones used for validation purpose. Internal validation is also carried out by validating the test set which too transpires the predictability. It is well known that every cell in a living tissue is electrically polarized, *i.e.* maintains a potential difference across its plasma membrane. This potential difference is the effect of an association between ion pumps and ion channels (mainly Na^+ and K^+). When this membrane potential goes through a rapid rise and fall, an action potential is generated which depolarizes the nerve cell following which other nerve cells also get depolarized. Now, when a highly polar pyrethroid enters

Table 5 Minimum blocking concentration of pyrethroids to suppress action potential of central nerve cord of cockroach (in M)

S. No	Substituents	Observed log 1/MBC[a]	Calculated log 1/MBC
1	H	4.61	4.55
2	F[b]	4.39	4.55
3	Br	4.56	4.58
4	CH_3	4.78	4.68
5	C_2H_5[b]	4.80	4.81
6	$CH_2C_6H_5$	5.27	5.26
7	OCH_3	4.83	4.72
8	OC_2H_5[b]	4.84	4.95
9	$OCH(CH_3)_2$	5.11	4.99
10	OC_6H_5[b]	5.67	5.17
11	COC_6H_5	5.32	5.25
12	NO_2[c]	5.00	4.64
13	CN	4.42	4.64
14	SO_2Me[b,c]	4.23	4.89

[a]Observed data taken from reference [14]. [b]Compounds selected for test set. [c]Outliers for Eq. (11)

the living system, it interacts with the Na^+ channel consequently disturbing its mechanism which eventually results in the suppression of action potential. Thus, it is transparent that polarizability plays a very important role in the transmission as well as blocking of nerve impulse.

Toxicological activity in terms of 50% inhibitory growth concentration for *T. pyriformis*

The sixth set of compounds presents the potential of a broad variety of miscellaneous aliphatic alcohols and esters to display toxicological effect in *T. pyriformis*. The QSAR model obtained for the 50% inhibitory growth concentration using polarizability is represented by Eq. (13):

$$\log\left(\frac{1}{\mathrm{IGC}_{50}}\right) = (0.018)\alpha - (3.379)$$
$$n = 122,\ R^2 = 0.845,\ R^2_{\mathrm{CV}} = 0.838 \tag{13}$$

The predicted and observed biological activities (in mg/l) of the miscellaneous aliphatic alcohols and esters are presented in Table 6. It is seen that the molecules in the set possess heterogeneity in their chemical structures and yet show a close conformity with Eq. (13). High values of R^2 and R^2_{CV} signify a very impressive correlation between the data sets. Predicted residual error sum of squares and standard error bar analysis presents uniformity and significance of the data. The molecules used in the construction of the model are different from the ones used for validation purpose. Internal validation by the test set transpires the predictability of the model. It is widely acknowledged that toxicity is a consequence of electronic interactions amongst the atoms/molecules of the toxicant and reactive site. Given that polarizability is a property of electronic distribution, it is assumed to play a major role in understanding diverse interactions including toxic interactions. From the analysis, it is observed that higher polarizability leads to lower toxicological activity. It is also evident that bulky molecules are more toxic as compared to the lower counterparts. Further, other factors such as solubility, medium and concentration also influence the extent of toxicity. Nevertheless, it must be noted that not all molecules are toxic. Although the correlation presented here is quite noteworthy which allows prediction of the inhibitory growth concentration of some alcohols and esters with significant accuracy, the theoretical observations with respect to the involved parameter perhaps require to be probed further.

Table 6 Inhibitory growth concentration of miscellaneous alcohols and esters to inhibit toxicity in *T. pyriformis* by 50% (in mg/l)

S. No	Alcohols and Esters	Observed log $1/\mathrm{IGC}_{50}$[a]	Calculated log $1/\mathrm{IGC}_{50}$
1	(±)-1,2-Butanediol	−2.04	−1.39
2	(±)-1,3-Butanediol	−2.30	−0.99
3	1,2-Pentanediol[b]	−1.62	−0.99
4	1,5-Pentanediol	−1.93	−1.00
5	2-Methyl-2,4-Pentanediol	−1.95	−0.59
6	(±)-1,2-Hexanediol[b]	−1.26	−0.59
7	1,6-Hexanediol	−1.49	−0.60
8	1,2-Decanediol	0.76	0.99
9	1,10-Decanediol[b]	0.22	0.99
10	Methyl alchohol	−2.66	−2.70
11	Ethyl alchohol	−1.99	−2.30
12	2-Propanol[b]	−1.74	-1.90
13	1-Propanol	−1.88	−1.90
14	1-Butanol[b]	−1.43	−1.51
15	(±)-2-Butanol	−1.54	−1.51
16	2-Methyl-1-Propanol	−1.37	−1.51
17	2-Pentanol	−1.15	−1.11
18	3-Pentanol[b]	−1.24	−1.11
19	3-Methyl-2-Butanol	−0.99	−1.11
20	*tert*-Amyl Alcohol[b]	−1.17	−1.11
21	2-Methyl-1-butanol	−0.95	−1.11
22	3-Methyl-1-butanol[b]	−1.03	−1.11
23	2,2-Dimethyl-1-propanol	−0.87	−1.11
24	2-Methyl-2-propanol	−1.79	−1.51
25	1-Hexanol	−0.37	−0.71
26	3,3-Dimethyl-1-butanol[b]	−0.73	−0.71
27	4-Methyl-1-pentanol	−0.63	−0.71
28	1-Heptanol	0.10	−0.31
29	2,4-Dimethyl-3-pentanol[b]	−0.70	−0.31
30	1-Octanol	0.58	0.07
31	2-Octanol[b]	0.00	0.07
32	3-Octanol	0.03	0.07
33	1-Nonanol	0.85	0.47
34	2-Nonanol[b]	0.61	0.47
35	3-Ethyl-2,2-dimethyl-3-pentanol	−0.16	0.47
36	1-Decanol	1.33	0.87
37	(±)-4-Decanol[b]	0.84	0.87
38	3,7-Dimethyl-3-octanol[b]	0.34	−1.27
39	1-Undecanol	1.95	1.27
40	1-Dodecanol	2.16	1.67
41	1-Tridecanol	2.40	2.06
42	2-Methyl-3-buten-2-ol[b]	−1.38	0.87
43	4-Pentyn-1-ol[b]	−1.42	−1.43
44	2-Methyl-3-butyn-2-ol	−1.31	−1.43
45	*trans*-3-Hexen-1-ol	−0.77	−0.87
46	*cis*-3-Hexen-1-ol[b]	−0.80	−0.87
47	5-Hexyn-1-ol	−1.29	−1.04

Table 6 (continued)

S. No	Alcohols and Esters	Observed log $1/IGC_{50}$[a]	Calculated log $1/IGC_{50}$
48	3-Methyl-1-pentyn-3-ol	−1.32	−1.04
49	4-Hexen-1-ol	−0.75	−0.87
50	5-Hexen-1-ol[b]	−0.84	−0.87
51	4-Pentyn-2-ol	−1.63	−1.44
52	5-Hexyn-3-ol	−1.40	−1.04
53	3-Heptyn-1-ol[b]	−0.32	−0.64
54	4-Heptyn-2-ol	−0.61	−0.64
55	3-Octyn-1-ol[b]	0.01	−0.24
56	3-Nonyn-1-ol	0.34	0.15
57	2-Propen-1-ol	−1.91	−2.06
58	2-Buten-1-ol	−1.47	−1.67
59	(±)-3-Buten-2-ol[b]	−1.05	−1.67
60	*cis*-2-Buten -1,4-diol	−2.14	−1.55
61	*cis*-2-Penten-1-ol	−1.10	−1.27
62	3-Penten-2-ol[b]	−1.40	−1.27
63	*trans*-2-Hexen-1-ol	−0.47	−0.87
64	1-Hexen-3-ol[b]	−0.81	−0.87
65	*cis*-2-Hexen-1-ol	−0.77	−0.87
66	*trans*-2-Octen-1-ol	0.36	−0.08
67	3-Butyn-2-ol	−0.40	−1.83
68	1-Pentyn-3-ol[b]	−1.17	−1.27
69	2-Pentyn-1-ol	−0.57	−1.27
70	2-Penten-4-yn-1-ol	−0.55	−1.59
71	1-Heptyn-3-ol[b]	−0.26	−0.64
72	4-Heptyn-3-ol	−0.03	−0.64
73	2-Octyn-1-ol	0.19	−0.24
74	2-Nonyn-1-ol[b]	0.64	0.15
75	2-Decyn-1-ol	0.98	0.54
76	2-Tridecyn-1-ol	2.36	1.74
77	4-Methyl-1-pentyn-3-ol	−0.02	−1.04
78	4-Methyl-1-heptyn-3-ol	0.74	−0.08
79	2-(Methylamino)ethanol	−1.82	−1.70
80	4-Amino-1-butanol	−0.97	−1.31
81	DL-2-Amino-1-pentanol[b]	−0.67	−0.91
82	3-Amino-2,2-dimethyl-1-propanol	−0.92	−0.91
83	6-Amino-1-hexanol	−0.95	−0.51
84	DL-2-Amino-1-hexanol	−0.58	−0.51
85	DL-2-Amino-3-methyl-1-butanol	−0.58	−0.91
86	2-Amino-3,3-dimethyl-1-butanol	−0.71	−0.51
87	2-Amino-3-methyl-1-pentanol[b]	−0.65	−0.51
88	2-Amino-4-methyl-1-pentanol	−0.61	−0.51
89	Diethanolamine	−1.79	−1.19
90	1,3-Diamino-2-propanol	−1.42	−1.50
91	3-(Methylamino)-1,2-propanediol[b]	−1.53	−1.19
92	Ethyl acetate	−1.29	−1.55
93	Propyl acetate	−1.23	−1.16
94	Isopropyl acetate	−1.59	−1.16
95	Butyl acetate[b]	−0.48	−0.76
96	Amyl acetate	0.16	−0.36
97	Hexyl acetate	−0.01	0.03
98	Octyl acetate	1.05	0.83
99	Decyl acetate	1.87	1.62
100	Ethyl propionate	−0.94	−1.16
101	Butyl propionate	0.17	−0.36
102	Isobutyl propionate	−0.69	−0.36
103	Propyl propionate[b]	−0.81	−0.76
104	*tert*-Butyl propionate[b]	−0.40	−0.36
105	Ethyl butyrate	−0.49	−0.76
106	Ethyl isobutyrate[b]	−1.27	−0.76
107	Ethyl valerate	−0.35	−0.36
108	Propyl butyrate[b]	−0.41	−0.36
109	Butyl butyrate	0.51	0.03
110	Propyl valerate	0.01	0.03
111	Amyl propionate	−0.04	0.03
112	Ethyl hexanoate	0.06	0.03
113	Methyl butyrate	−1.24	−1.16
114	Methyl valerate	−0.84	−0.76
115	Methyl hexanoate[b]	−0.56	−0.36
116	Methyl heptanoate	0.10	0.03
117	Methyl octanoate[b]	0.53	0.43
118	Methyl nonanoate	1.04	0.83
119	Methyl decanoate	1.37	1.23
120	Methyl undecanoate	1.42	1.62
121	Methyl formate	−1.49	−2.35
122	*tert*-Butyl formate[b]	−1.37	−1.15

[a]Observed data taken from reference [38]. [b]Molecules selected as test set

Selectivity in terms of binding affinity for the enzyme thrombin

The last set presents the potential of 3-amidinophenylalanine-derived inhibitors to bind with thrombin in order to elucidate their selectivity. The binding affinity data used in this set are taken from reference [39] and are a well-known benchmark data set [42]. The QSAR model developed for the binding affinity using polarizability (α) together with compressibility (β), another important atomic and molecular descriptor [34], is represented by Eq. (14):

$$\log\left(\frac{1}{K_i}\right) = (0.019)\alpha + (0.006)\beta - (0.00001)\alpha\beta - 4.65$$

$$n = 88,\ R^2 = 0.645,\ R^2_{CV} = 0.623$$

Outliers: Compound 53, Compound 58, Compound 69, Compound 88

(14)

Table 7 Binding affinity of 3-amidinophenylalanine derivatives towards thrombin to predict selectivity differences (in mol/l)

S. no	3-Amidinophenylalanine derivatives[a]	Observed log $(1/K_i)$[b]	Calculated log $(1/K_i)$ (including α and β)	Calculated log $(1/K_i)$ (excluding α)
1	Compound 1	8.38	6.90	6.60
2	Compound 2	8.37	6.71	6.38
3	Compound 3	8.30	7.16	6.97
4	Compound 4	8.21	7.13	6.90
5	Compound 5	8.13	7.20	7.09
6	Compound 6	8.06	6.68	7.58
7	Compound 7	7.85	6.65	6.41
8	Compound 8	7.80	6.29	6.06
9	Compound 9	7.77	7.28	6.27
10	Compound 10	7.75	6.65	6.41
11	Compound 11	7.72	7.34	6.97
12	Compound 12	7.68	7.18	6.86
13	Compound 13	7.64	6.80	6.12
14	Compound 14	7.59	7.22	6.60
15	Compound 15	7.59	7.12	7.34
16	Compound 16	7.50	6.76	6.43
17	Compound 17	7.47	7.08	6.99
18	Compound 18	7.43	6.55	6.31
19	Compound 19	7.43	6.26	6.04
20	Compound 20	7.38	6.73	8.00
21	Compound 21	7.38	5.91	5.75
22	Compound 22	7.24	6.42	6.17
23	Compound 23	7.23	6.33	6.10
24	Compound 24	7.19	6.07	5.88
25	Compound 25	7.13	7.18	7.20
26	Compound 26	7.05	6.58	6.34
27	Compound 27	7.02	6.69	6.45
28	Compound 28	6.96	6.54	5.65
29	Compound 29	6.92	6.61	6.37
30	Compound 30	6.92	6.55	6.31
31	Compound 31	6.92	6.73	6.17
32	Compound 32	6.82	6.52	6.27
33	Compound 33	6.82	6.80	6.61
34	Compound 34	6.80	6.55	6.30
35	Compound 35	6.75	6.56	6.31
36	Compound 36	6.70	6.89	6.71
37	Compound 37	6.68	6.88	6.45
38	Compound 38	6.64	6.07	5.88
39	Compound 39	6.64	6.14	6.55
40	Compound 40	6.59	6.28	6.05
41	Compound 41	6.55	5.07	5.20
42	Compound 42	6.55	7.14	7.10
43	Compound 43	6.50	6.59	6.35
44	Compound 44	6.47	6.18	5.96
45	Compound 45	6.47	5.64	5.56
46	Compound 46	6.46	5.37	5.37
47	Compound 47	6.38	6.69	6.45
48	Compound 48	6.30	6.00	5.81
49	Compound 49	6.29	6.95	6.78

Table 7 (continued)

S. no	3-Amidinophenylalanine derivatives[a]	Observed log $(1/K_i)$[b]	Calculated log $(1/K_i)$ (including α and β)	Calculated log $(1/K_i)$ (excluding α)
50	Compound 50	6.24	6.28	6.05
51	Compound 51	6.20	6.41	6.89
52	Compound 52	6.18	6.32	6.09
53	Compound 53[d,e]	6.16	7.29	7.50
54	Compound 54	6.05	5.90	5.80
55	Compound 55	5.96	6.28	6.05
56	Compound 56	5.92	5.46	5.50
57	Compound 57	5.75	5.07	5.83
58	Compound 58[d,e]	5.68	7.14	7.11
59	Compound 59	5.64	5.89	5.90
60	Compound 60	5.54	6.36	6.12
61	Compound 61	5.51	4.95	5.04
62	Compound 62	5.51	5.45	5.75
63	Compound 63	5.24	5.13	5.23
64	Compound 64	5.21	5.69	5.59
65	Compound 65	5.14	4.89	5.43
66	Compound 66	4.89	4.12	4.65
67	Compound 67	4.82	4.19	4.77
68	Compound 68	4.77	5.35	5.05
69	Compound 69[d]	4.57	3.78	4.56
70	Compound 70	4.52	4.85	5.47
71	Compound 71	4.46	4.91	5.15
72	Compound 72	4.36	5.20	5.27
73	Compound 73[c]	8.48	5.32	5.00
74	Compound 74[c]	7.89	5.89	5.74
75	Compound 75[c]	7.59	6.49	6.16
76	Compound 76[c]	7.52	6.44	5.73
77	Compound 77[c]	7.44	6.22	6.00
78	Compound 78[c]	7.28	6.07	5.88
79	Compound 79[c]	7.16	6.29	6.27
80	Compound 80[c]	6.77	6.52	6.62
81	Compound 81[c]	6.59	6.53	5.90
82	Compound 82[c]	6.55	6.72	6.54
83	Compound 83[c]	6.52	7.25	6.27
84	Compound 84[c]	6.28	6.79	6.58
85	Compound 85[c]	6.28	6.69	6.45
86	Compound 86[c]	6.15	7.20	7.25
87	Compound 87[c]	5.42	7.41	6.36
88	Compound 88[c,d,e]	4.75	4.57	4.90

[a]Structures available in Reference [39]. [b]Observed data taken from reference [39]. [c]Compounds selected for test set. [d]Outliers for Eq. (14). [e]Outliers for Eq. (15)

The predicted and observed biological activities (in mol/l) of various 3-amidinophenylalanine-derived inhibitors are presented in Table 7. A more or less acceptable conformity with Eq. (14) is highlighted by the series of compounds. The obtained R^2 and R^2_{CV} are satisfactory for validating the useful correlation between the two sets of data. Lower predicted residual error sum of squares and standard error bar analysis presents reliability and significance of the data to some extent. The molecules used in the construction of the model are different from the ones used for validation purpose. Internal validation by the test set transpires the predictability of the model. It appears that an increase in polarizability leads to an increase in the binding affinity of inhibitors to thrombin, in general.

This is acceptable since higher polarizability favours interaction with potential molecules. Further, it is expected that replacement of simple groups by sterically extensive groups should enhance affinity.

In order to establish the potential of polarizability in explaining chemical–biological interactions, another model has been constructed for the same set which considers only compressibility and excludes polarizability. The model is represented by Eq. (15):

$$\log\left(\frac{1}{K_i}\right) = (0.004)\beta + 1.722$$
$$n = 88,\ R^2 = 0.534,\ R^2_{CV} = 0.508$$
$$\text{Outliers: Compound 53, Compound 58, Compound 88.} \quad (15)$$

The predicted binding affinities (in mol/l) of various 3-amidinophenylalanine-derived inhibitors based on compressibility are also presented in Table 7. The molecules used in the construction of the model are the different from the ones used for validation purpose. On comparing the models based on polarizability/compressibility (Eq. 14) and just compressibility (Eq. 15), it is observed that the polarizability/compressibility-based model is more potent. Comparatively higher values of R^2 and R^2_{CV} are evident for polarizability-dependent model signifying a superior correlation between the data sets than the model excluding it. Further, predicted residual error sum of squares and standard error bar analysis transpires fine uniformity and significance of the data in the case of multi-descriptor model. Similarly, internal validation for the two models also justifies the ability of polarizability to act as a suitable descriptor for chemical–biological interaction modelling. It is recommended that multi-descriptor models are constructed as they offer accurate explanation of the occurring phenomenon due to the incorporation of wide range of effects. For this purpose, reference [43] can be used to calculate a number of descriptors.

A comparison of the predictive potential (R^2_{pred}) of the present polarizability-based MLR methodology with the predictive potentials of 14 QSAR methodologies for thrombin models reported in the literature is presented in Table 8 [15, 16, 42, 44–46]. It is evident from Table 8 that the present MLR model based on polarizability is satisfactory, although not the finest, amongst the data sets considered. However, owing to the simplicity, cost-effectiveness and hastiness of the present model, it is clear that the obtained results are rather useful to get a preview of structure and activity relationships.

The outcomes of this investigation undoubtedly reveal the importance of Tandon et al.'s model of polarizability in the real field. A striking correlation is presented between the predicted and observed biological activities. The reliability and predictability of the newly designed QSAR model are apparent from the statistics for every set. Moreover, it is heartening to note that the predicted biological activities are numerically comparable to those approximated by other complex techniques. Nevertheless, the above QSAR corresponds to only a small fraction of QSARs. An amazing element of our analysis is the diversity of the groups of chemicals studied.

Table 8 Comparison of the predictive potential (R^2_{pred}) of the present polarizability-based methodology for thrombin models with respect to those obtained by 14 QSAR methodologies established in the literature

S. No	QSAR Methodologies	R^2_{pred}
1	MLR model based on polarizability	0.688
2	QuBiLS-MIDAS models based on truncation [16]	0.769
3	QuBiLS-MIDAS models not based on truncation [15]	0.767
4	O3QMFA [44]	0.600
5	COSMOsar3D [44]	0.660
6	O3Q [45]	0.670
7	O3A/O3Q [45]	0.300
8	2D-FPT [46]	0.737
9	CoMFA [42]	0.630
10	COMSIA basic [42]	0.550
11	COMSIA extra [42]	0.630
12	2D [42]	0.040
13	2.5D [42]	0.280
14	EVA [42]	0.110
15	HQSAR [42]	−0.250

Conclusion

A study is performed to investigate the application of recently proposed model of polarizability by Tandon et al. in the real field by determining molecular polarizability through additive property. A comprehensive chemical–biological interaction analysis has been carried out for preferred 312 compounds using molecular polarizability as a predictor to estimate their biological activity. An exceptional resemblance is found between the predicted and observed activities. The usefulness of this descriptor to predict the biological activity is revealed by superior correlations. All the principles of OECD are nicely followed in our study. Therefore, it is clear from the results that Tandon et al.'s polarizability can be suitably implemented as a molecular descriptor in real fields such as biological activity estimation for anaesthetics, narcotics,

neurophysiological and other similar drugs. Species possessing lone pair of electrons offer future prospects for polarizability. Thus, further investigations based on such potent compounds must be carried out as they hold immense significance in this direction. Finally, it is suggested for future explorations that the use of descriptor polarizability should be contrasted with some other drug-like descriptors as well.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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