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PHYSICOCHEMICAL PROPERTIES OF ANTIPSYCHOTIC DRUGS FOR SCHIZOPHRENIA: A QSPR STUDY BASED ON DEGREE-BASED TOPOLOGICAL INDICES

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ABSTRACT
A chronic psychiatric disorder characterized by disturbances in perception, thinking, emotions, and behaviour, Schizophrenia requires long-term treatment with antipsychotic drugs whose effectiveness depends on several physicochemical properties. Quantitative Structure-Property Relationship (QSPR) analysis provides an efficient framework to investigate the relationship between molecular structure and such properties. In this study, the degree-based topological index $VL(G)$and its derived variants $\sqrt{VL(G)}$, $[VL(G)]^2$, $\frac{1}{VL(G)}$, and $\frac{1}{\sqrt{VL(G)}}$ are applied to thirteen antipsychotic drugs prescribed for schizophrenia. Correlation and regression analyses are performed to examine their relationships with eight physicochemical properties, namely boiling point, melting point, enthalpy, flash point, molar refractivity, complexity, molecular weight, and refractivity. The results reveal that three of the considered indices exhibit strong correlations and satisfactory predictive performance for the selected physicochemical parameters, indicating their potential applicability in estimating molecular characteristics of antipsychotic drugs.

Keywords: QSPR, Degree-based topological indices, Physicochemical properties, Antipsychotic drugs, Schizophrenia.

I. Introduction
Schizophrenia represents a complex psychiatric condition that affects perception, cognition, emotions, and behavioural responses [1,2,3,4]. Individuals suffering from this disorder often experience disturbances in thinking patterns and social functioning, making long-term pharmacological treatment necessary [5,6]. Antipsychotic medications are commonly used to control these symptoms; however, their therapeutic effectiveness depends on several physicochemical characteristics of the drug molecules [7,8]. Properties such as molecular weight, stability, refractivity, and other structural attributes influence drug absorption, distribution, and biological activity [10,11]. Therefore, understanding the relationship between molecular structure and these physicochemical parameters is important for improving the performance of antipsychotic drugs [1,12].
Quantitative Structure-Property Relationship (QSPR) methods provide a mathematical approach for investigating the relationship between molecular structure and physicochemical properties of chemical compounds [13,14]. In this framework, molecules are represented as graphs in which atoms are modelled as vertices and bonds as edges [15,16]. Numerical descriptors derived from such graphs, known as topological indices, summarize structural features of molecules in quantitative form [17–19]. These indices have been widely used to estimate and predict physicochemical and pharmacological properties of various chemical compounds [9].
In recent years, numerous degree-based topological indices have been proposed and successfully applied in modelling physicochemical properties of chemical and pharmaceutical compounds [1,15]. These indices reflect the connectivity patterns of molecular graphs and often exhibit strong

relationships with different molecular parameters [20,21]. Nevertheless, the applicability of several recently introduced indices to pharmaceutical compounds has not been extensively examined. In particular, the predictive capability of the degree-based index *VL(G)* and its associated transformations for estimating physicochemical properties of antipsychotic drugs remains relatively unexplored. Motivated by this observation, the present study investigates the effectiveness of *VL(G)* and its derived forms in establishing correlation and regression models for selected physicochemical properties of antipsychotic drugs prescribed for schizophrenia [1].

1.1 Definition

Let G be a simple, connected molecular graph in chemical graph theory. *V(G)* denotes the set of vertices, and $E(G)$denotes the set of edges; $d(u)$ represents the degree of a vertex u in G. *VL(G)* is defined as

$$VL(G) = \frac{1}{2}\sum_{uv\epsilon E[G]} \quad [d(u) + d(v) + d(u)d(v)]$$

II. Materials and Methods

2.1. Degree-based molecular descriptors in QSPR studies

In the present study, the degree-based index $VL(G)$and its transformations $\sqrt{VL(G)}$, $[VL(G)]^2$, $1/VL(G)$, and $1/\sqrt{VL(G)}$ are used as structural descriptors. These indices are computed for thirteen antipsychotic drugs used in the treatment of Schizophrenia, namely chlorpromazine, trifluoperazine, thioridazine, thiothixene, haloperidol, ziprasidone, loxapine, quetiapine, aripiprazole, clozapine, risperidone, olanzapine, and sertindole.

Eight physicochemical parameters-boiling point (BP), melting point (MP), enthalpy(E), flash point (FP), molar refractivity (MR), complexity(C), molecular weight (MW), and refractivity(R), are considered to examine the association between the chosen indices and the corresponding parameters of the drug molecules.

2.2. Linear Regression Analysis

To study the relationship among the calculated topological descriptors and the selected structural and chemical features, correlation and linear regression analyses are performed. In this analysis, the physicochemical parameters are treated as dependent variables, while the topological indices are considered independent variables.

The relationship between a structural and chemical features and a topological descriptor is expressed through the linear regression model

$$Y = i + jX$$

where Y ddenotes the physicochemical property, X denotes the corresponding topological index, and i and j represent the intercept and slope of the regression line, respectively. The parameters are estimated using the least-squares method.

The strength of the relationship between variables is examined with statistical measures, including R, R^2 which indicate the robustness and forecasting ability of the established models.

2.3 Data Collection

The chemical structures of the selected antipsychotic drugs for schizophrenia are illustrated in Figure 1. The physicochemical properties of these compounds were collected from reliable chemical databases and relevant literature sources. Some of the data were obtained from previously published studies, while the remaining values were retrieved from established chemical databases. The compiled dataset, including physicochemical parameters for each selected compound, is presented in Table 1. These physicochemical properties served as the input data for the correlation analysis and the development of linear QSPR regression models.

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Table 1: Physical and chemical attributes of therapeutic agents for schizophrenia

Drugs	BP (°C)	MP (°C)	E (kJ/mol)	FP (°C)	MR (cm^3)	C	MW (g/mol)	R (cm^3)
chlorpromazine	450.1	60	70.9	226	92.8	339	355.33	93.76
trifluoperazine	506	242	77.6	259.8	108.2	510	480.4	110.98
thioridazine	515.665	73	78.8	265.7	112.8	432	370.6	113.52
thiothixene	599	114	89.2	316.1	126.5	711	443.62	137.85
haloperidol	529	151.5	84.6	273.8	101	451	375.9	102.59
clozapine	489.2	183	75.5	249.6	93.7	446	326.8	97.36
ziprasidone	554.8	213	83.6	289.3	114.1	573	412.936	116.72
loxapine	458.6	109	71.9	231.1	92.1	450	327.81	95.11
quetiapine	556.5	172	88.2	290.4	110.2	496	383.51	114.09
aripiprazole	646.2	139	95.3	344.6	120.3	559	448.4	124.34
risperidone	572.4	170	85.8	300	111.7	731	410.5	111.7
olanzapine	476	195	74	241.7	92.2	432	312.432	107.17
sertindole	592.1	97.5	92.0	311.9	130.2	780	440.94	131.0

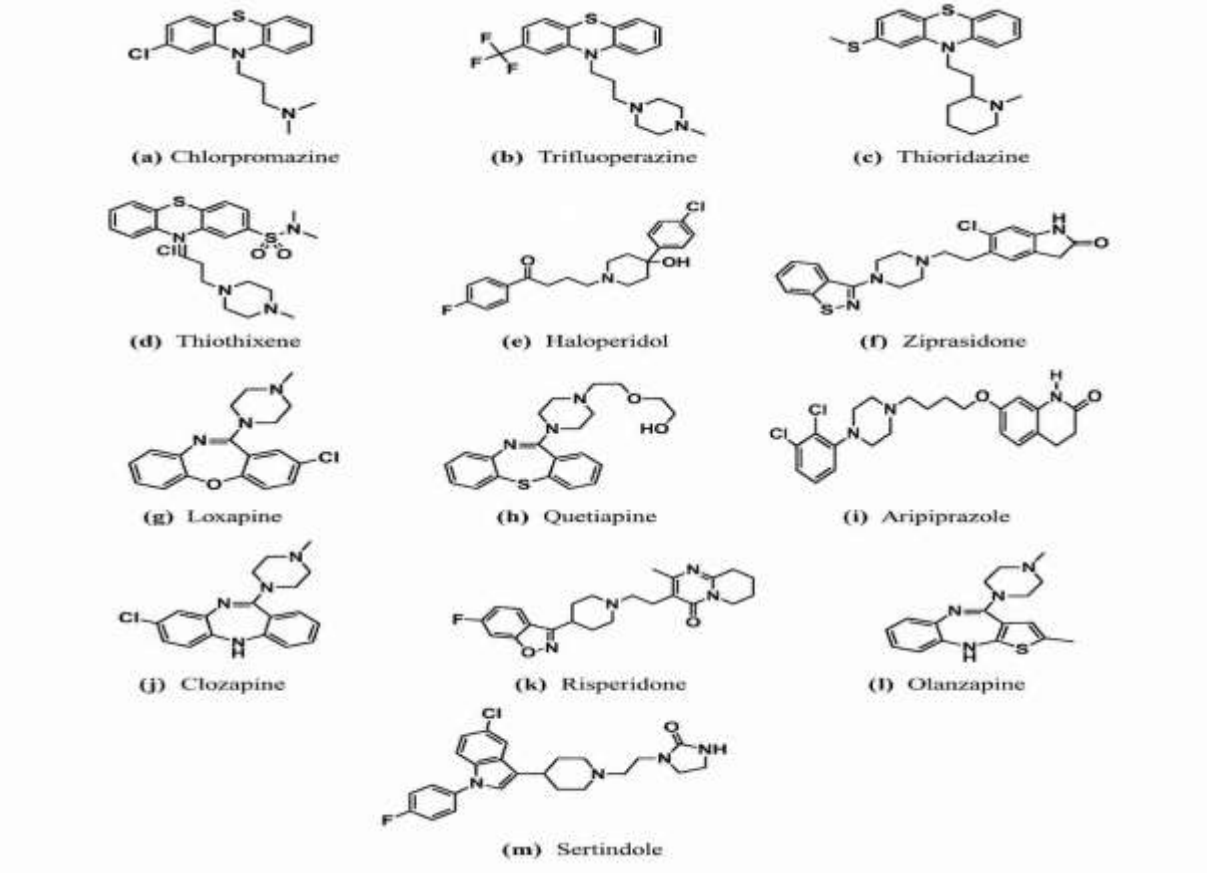

Figure 1: Chemical structures of Antipsychotic Drugs for Schizophrenia

III. Results and Discussion

In this section, the computed molecular descriptors and the selected structural and chemical features of the considered medications are analyzed through correlation and regression techniques. The aim of the analysis is to examine the extent to which the degree-based index VL(G) and its transformations can describe the physicochemical characteristics of the selected antipsychotic drugs.

The computed values of VL(G) and its derived descriptors for the thirteen schizophrenia drugs are presented in Table 2. These descriptor values are subsequently compared with the corresponding selected physicochemical parameters and the correlation coefficients between them are summarized in Table 3.

Correlation analysis is carried out to measure the strength of the relationship between each molecular descriptor and the selected physicochemical properties. Subsequently, linear regression models are developed by employing the calculated topological descriptors as independent variables and the physicochemical properties as dependent variables. The resulting regression equations provide a quantitative description of the relationship between molecular structure and the selected physicochemical parameters. The performance of the regression models is evaluated using statistical measures including the correlation coefficient (R), coefficient of determination (R^2), F-statistic, and p-value.

Table 2: Topological descriptors associated with medications for schizophrenia

Drugs	*VL(G)*	$\sqrt{VL(G)}$	$[VL(G)]^2$	$\frac{1}{VL(G)}$	$\frac{1}{\sqrt{VL(G)}}$
chlorpromazine	121	11	14641	0.008264463	0.090909091
trifluoperazine	165.5	12.86468033	27390.25	0.006042296	0.077732207
thioridazine	147	12.12435565	21609	0.006802721	0.08247861
thiothixene	182	13.49073756	33124	0.005494505	0.074124932
haloperidol	144	12	20736	0.006944444	0.083333333
clozapine	138	11.74734012	19044	0.007246377	0.085125653
ziprasidone	171.5	13.09580085	29412.25	0.005830904	0.076360355
loxapine	138	11.74734012	19044	0.007246377	0.085125653
quetiapine	152	12.32882801	23104	0.006578947	0.081110711
aripiprazole	167	12.92284798	27889	0.005988024	0.077382323
risperidone	183	13.52774926	33489	0.005464481	0.073922127
olanzapine	134	11.5758369	17956	0.007462687	0.086386843
sertindole	186.5	13.65650028	34782.25	0.00536193	0.073225203

Table 3: Correlation of various physicochemical parameters with topological indices

TI/Properties	*VL(G)*	$\sqrt{VL(G)}$	$[VL(G)]^2$	$\frac{1}{VL(G)}$	$\frac{1}{\sqrt{VL(G)}}$
BP	**0.819456506**	**0.82315426**	**0.809978115**	-0.829177477	-0.828084212
MP	0.18803822	0.202205476	0.159859027	-0.244356151	-0.230424478
E	0.775343469	0.779577181	0.765210321	-0.788017462	-0.785987985
FP	**0.819354421**	**0.823052927**	**0.80987569**	-0.829080676	-0.827985532
MR	**0.885911116**	**0.885547953**	**0.884204315**	-0.87877337	-0.882038827
C	**0.949027557**	**0.942582349**	**0.959858388**	-0.918829821	-0.927500238

MW	**0.809725577**	**0.810971191**	**0.803818424**	-0.806909529	-0.809629733
R	**0.835263713**	**0.835072167**	**0.833555609**	-0.829651379	-0.832314179

3.1 Regression equation and Statistical evaluation of the linear QSPR model for topological descriptors

The correlation coefficient (R) indicates the strength of the relationship between the topological descriptor and the physicochemical property, while the coefficient of determination (R^2) represents the proportion of variation explained by the regression model. The F-statistic and p-value are used to evaluate the statistical significance of the fitted model. The resulting regression equations and corresponding statistical parameters for the selected physicochemical properties are presented below.

3.1.1 VL(G) with Physio-chemical properties

To evaluate the predictive capability of the topological descriptor VL(G), simple linear regression analysis was performed between VL(G) and the eight selected physicochemical properties of schizophrenia drugs. The corresponding scatter plots with best-fit regression lines are presented in Figure 2, illustrating the relationships between VL(G) and selected physicochemical properties. As shown in Figure 2, VL(G) exhibits strong positive linear relationships with BP, E, FP, MR, C, MW, and R, whereas MP shows only a weak linear relationship.

$$BP = 177.6551 + 2.2843\ VL(G)\ ; R^2 = 0.67, F(1,11) = 22.49, p < 0.001.$$
$$MP = 71.4556 + 0.4878\ VL(G)\ ; R^2 = 0.035, F(1,11) = 0.40, p = 0.538.$$
$$E = 36.8774 + 0.2897\ VL(G)\ ; R^2 = 0.60, F(1,11) = 16.58, p = 0.002.$$
$$FP = 61.1997 + 1.3818\ VL(G)\ ; R^2 = 0.67, F(1,11) = 22.47, p < 0.001.$$
$$MR = 22.7614 + 0.5469\ VL(G)\ ; R^2 = 0.78, F(1,11) = 40.12, p < 0.001.$$
$$C = -405.2330 + 6.0005\ VL(G)\ ; R^2 = 0.90, F(1,11) = 99.72, p < 0.001.$$
$$MW = 75.3780 + 2.0248\ VL(G)\ ; R^2 = 0.66, F(1,11) = 20.94, p < 0.001.$$
$$R = 75.3780 + 2.0248\ VL(G)\ ; R^2 = 0.66, F(1,11) = 20.94, p < 0.001.$$

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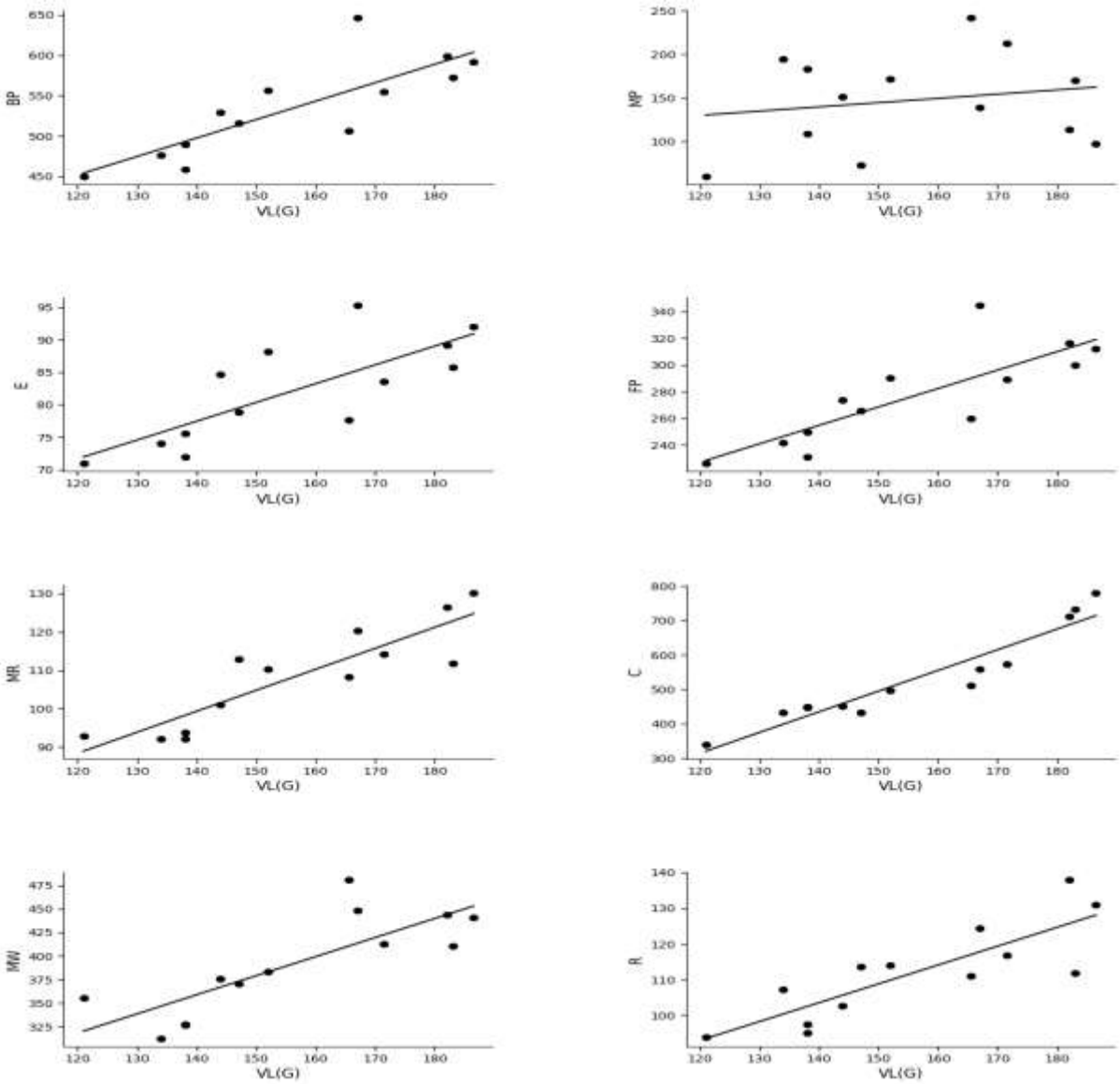

Figure 2: Scatter plots with linear regression best-fit lines illustrating the relationship among VL(G) and the eight physicochemical properties.

3.1.2 $\sqrt{\mathrm{VL(G)}}$ with Physicochemical Properties

To further investigate the predictive performance of the transformed topological descriptor, $\sqrt{\mathrm{VL(G)}}$, simple linear regression analysis was carried out between $\sqrt{\mathrm{VL(G)}}$ and the eight selected physicochemical properties of schizophrenia drugs. The corresponding scatter plots with best-fit regression lines are presented in Figure 3, illustrating the relationships between $\sqrt{\mathrm{VL(G)}}$ and selected physicochemical properties. As shown in Figure 3, $\sqrt{\mathrm{VL(G)}}$ exhibits strong positive linear relationships with BP, E, FP, MR, C, MW, and R, whereas MP shows only a weak linear association, indicating that the transformed descriptor retains good predictive capability for QSPR analysis.

$BP = -178.0345 + 57.1317\ [\sqrt{VL(G)}]$; $R^2 = .68, F(1,11) = 23.12, p < .001.$

$MP = -15.232 + 13.0614\ [\sqrt{VL(G)}]$; $R^2 = .041, F(1,11) = 0.47, p = .508.$

$E = -8.3203 + 7.2529\ [\sqrt{VL(G)}]$; $R^2 = .61, F(1,11) = 17.04, p = .002.$

$FP = -153.962 + 34.5597[\sqrt{VL(G)}]$; $R^2 = .68, F(1,11) = 23.1, p < .001.$

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$MR = -61.5576 + 13.6107\ [\sqrt{VL(G)}]$; $R^2 = .78, F(1,11) = 39.97, p < .001.$

$C = -1318.5072 + 148.3853\ [\sqrt{VL(G)}]$; $R^2 = .89, F(1,11) = 87.62, p < .001.$

$MW = -238.0259 + 50.49\ [\sqrt{VL(G)}]$; $R^2 = .66, F(1,11) = 21.13, p < .001.$

$R = -52.0075 + 13.1556\ [\sqrt{VL(G)}]$; $R^2 = .7, F(1,11) = 25.35, p < .001.$

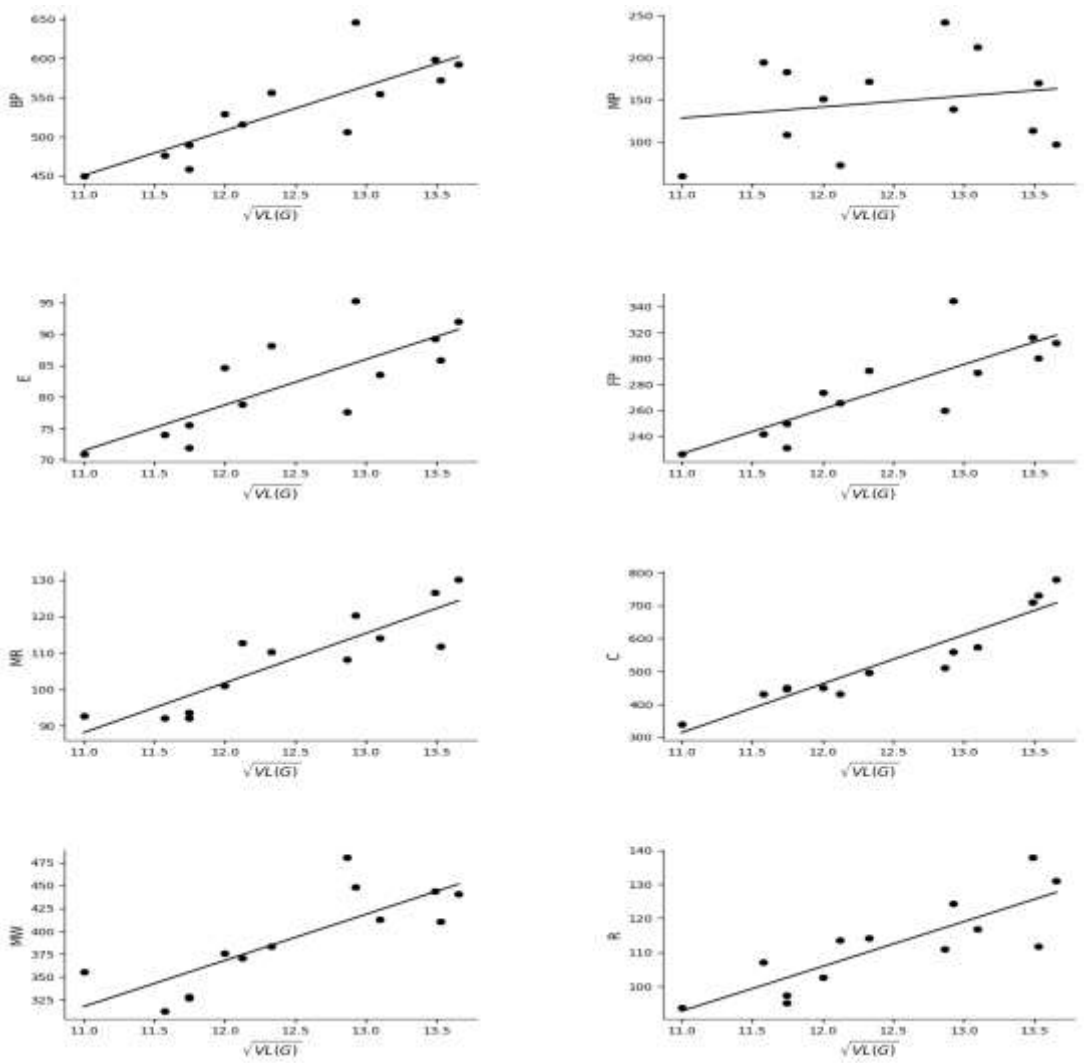

Figure 3: Scatter plots with linear regression best-fit lines illustrating the relationship among $\sqrt{\mathrm{VL(G)}}$ and the eight physicochemical properties

3.1.3 $[\mathbf{VL(G)}]^2$ with Physicochemical Properties

The predictive performance of the squared topological descriptor, $[\mathrm{VL(G)}]^2$, was further investigated by developing linear regression models with eight physicochemical properties of schizophrenia drugs. The corresponding scatter plots with best-fit regression lines are presented in Figure 4, illustrating the relationships between $[\mathrm{VL(G)}]^2$ and the selected properties. The regression results indicate that $[\mathrm{VL(G)}]^2$ exhibits strong predictive capability for most of the considered properties, particularly complexity (C), molar refractivity (MR), refractivity (R), boiling point (BP), flash point (FP), and molecular weight (MW), whereas melting point (MP) shows only a weak linear relationship.

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$BP = 355.526 + 0.007212\ [VL(G)]^2$; $R^2 = .66, F(1,11) = 20.98, p < .001.$
$MP = 114.7827 + 0.001325\ [VL(G)]^2$; $R^2 = .026, F(1,11) = 0.29, p = .602.$
$E = 59.4714 + 0.0009133\ [VL(G)]^2$; $R^2 = .59, F(1,11) = 15.54, p = .002.$
$FP = 168.7963 + 0.004362\ [VL(G)]^2$; $R^2 = .66, F(1,11) = 20.97, p < .001.$
$MR = 64.9275 + 0.001743\ [VL(G)]^2$; $R^2 = .78, F(1,11) = 39.42, p < .001.$
$C = 51.0845 + 0.01938\ [VL(G)]^2$; $R^2 = .92, F(1,11) = 128.82, p < .001.$
$MW = 232.3531 + 0.00642\ [VL(G)]^2$; $R^2 = .65, F(1,11) = 20.08, p < .001.$
$R = 70.261 + 0.001685\ [VL(G)]^2$; $R^2 = .69, F(1,11) = 25.04, p < .001.$

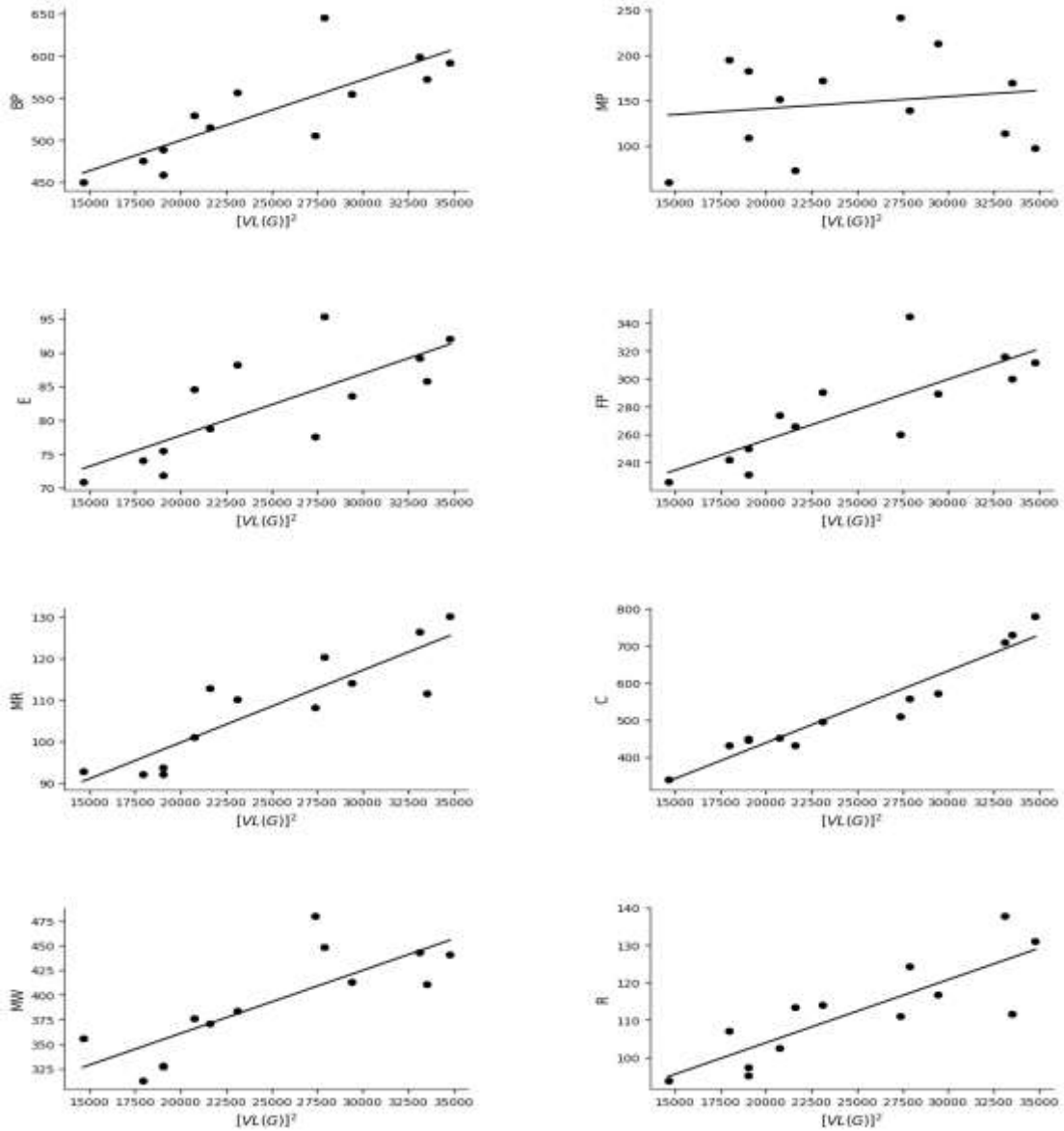

Figure 4: Scatter plots with linear regression best-fit lines illustrating the relationship among $[\mathrm{VL(G)}]^2$and the eight physicochemical properties.

Note: The transformed topological indices $1/\mathrm{VL}(G)$and $1/\sqrt{\mathrm{VL}(G)}$exhibit negative correlations with the selected physicochemical properties of the antipsychotic drugs for schizophrenia (Table 3). Therefore, regression models were not developed for these descriptors. The observed negative

correlations indicate inverse relationships between the descriptors and the physicochemical properties, making them less suitable for reliable predictive QSPR modeling in the present study.

IV. CONCLUSION

In this work, the degree-based topological index $VL(G)$and its derived forms $\sqrt{VL(G)}$, $[VL(G)]^2$, $1/VL(G)$, and $1/\sqrt{VL(G)}$ were analyzed to examine their ability to describe selected physicochemical properties of thirteen antipsychotic drugs prescribed for schizophrenia. Correlation and linear regression analyses were carried out to evaluate the relationships between these indices and eight physicochemical parameters: boiling point, melting point, enthalpy, flash point, molar refractivity, complexity, molecular weight, and refractivity.

The correlation analysis indicates that several of the considered indices exhibit strong associations with specific physicochemical properties. Among all descriptors, the highest positive correlation is observed between the squared index $[VL(G)]^2$and molecular complexity with a correlation coefficient of $R = 0.9598$. The basic index $VL(G)$also shows a strong relationship with complexity ($R = 0.9490$). Significant correlations are further observed with refractivity, where $VL(G)$gives $R = 0.8859$. Boiling point and flash point also demonstrate notable relationships with the indices, particularly with $\sqrt{VL(G)}$, which shows correlations of $R = 0.8231$for boiling point and $R = 0.8230$ for flash point. Molecular weight exhibits moderate correlations ($R \approx 0.81$), whereas melting point shows comparatively weaker relationships ($R \approx 0.20$).

The strong correlation between $[VL(G)]^2$and molecular complexity indicates that this index effectively reflects structural characteristics related to atomic connectivity within the studied antipsychotic drugs. Such results demonstrate that the considered topological descriptors provide reliable structural information useful for estimating several physicochemical properties through QSPR analysis.

Overall, the study confirms that $VL(G)$ and its derived forms, particularly $[VL(G)]^2$, serve as effective structural descriptors in QSPR modelling. These indices contribute to the analysis and estimation of physicochemical characteristics of antipsychotic drugs and substantiate the application of degree-based topological indices in computational studies related to pharmaceutical compounds.

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