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EDITED BY
Adnan Aslam,
University of Engineering and Technology, Pakistan

REVIEWED BY
Micheal Arockiaraj,
Loyola College, India
Muhammad Kamran Siddiqui,
COMSATS University Islamabad, Pakistan

*CORRESPONDENCE
Ali Raza,
alleerazza786@gmail.com

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Exploring spectrum-based descriptors in pharmacological traits through quantitative structure property (QSPR) analysis

Ali Raza* and Muhammad Mobeen Munir

Department of Mathematics, University of Punjab, Lahore, Pakistan

The study centered on Quantitative Structure Property Relationship (QSPR) analysis with a focus on various graph energies, investigating drugs like Mefloquinone, Sertraline, Niclosamide, Tizoxanide, PHA-690509, Ribavirin, Emricasan, and Sofosbuvir. Employing computational modeling techniques, the research aimed to uncover the correlations between the chemical structures of these medications and their unique properties. The results illuminated the quantitative relationships between structural characteristics and pharmacological traits, advancing our predictive capabilities. This research significantly contributes to medication discovery and design by providing essential insights into the structure-property connections of these medicinal compounds. Notably, certain spectrum-based descriptors, such as positive inertia energy, adjacency energy, arithmetic-geometric energy, first zegrab energy, and the harmonic index, exhibited strong correlation coefficients above 0.999. In contrast, well-known descriptors like the Extended adjacency, Laplacian and signless Laplacian spectral radii, and the first and second Zagreb Estrada indices showed weaker performance. The article emphasizes the application of graph energies and a linear regression model to predict pharmacological features effectively, enhancing the drug discovery process and aiding in targeted drug design by elucidating the relationship between molecular structure and pharmacological characteristics.

KEYWORDS

regression model, graph spectrum, spectral radius, pharmacological traits, correlation coefficient

1 Introduction

QSAR/QSPR techniques offer an efficient means to establish links between the physical and chemical attributes of chemical compounds and their bioactivities [1]. Structure-based topological parameters play a vital role in constructing robust predictive models [2]. Eigenvalues-based topological features have demonstrated a strong association with quantum properties of organic structures. The groundwork for structure-based topological parameters commenced in 1947 with Harold Wiener's introduction of the path number [3], which quantified the sum of distances between all pairs of vertices in a graph.

Fundamentally, the process of converting a molecular graph into a numerical representation relies on unchanging measures known as topological or structural indices. A chemical graph depicts a hydrogen-depleted molecular structure, with bonds

represented by edges and atoms represented by vertices in organic compounds. This field is commonly known as chemical graph theory. These structure descriptors, which remain consistent in terms of structure and topology, enable the establishment of connections with various physical and chemical properties, such as boiling point, enthalpy of vaporization, heat of formation, critical pressure, critical volume, and critical temperature. They also facilitate the development of robust regression models [4]. Particularly noteworthy are the topological descriptors based on spectra, which are highly regarded for their effectiveness in correlating the quantum properties of organic substances. In our current research, our goal is to introduce advanced spectrum-based topological descriptors rooted in graph theory to connect with the quantum properties of numerous substances. Simultaneously, we aim to identify descriptors that warrant the attention of researchers, effectively refining the scope of this field. Our recent work describes the applications of some spectrum descriptors in the field of computer sciences [5, 6].

In the field of chemical graph analysis, a wide array of topological descriptors have been well-established, covering diverse categories such as distance-based descriptors [7], valency/degree-based descriptors [8], eigenvalues-based descriptors [2], and counting-related topological polynomials and descriptors [9]. Notably, spectrum-based topological descriptors stand out due to their exceptional ability to generate highly efficient regression models for an extensive range of physicochemical and quantum properties, including the π-electronic energy. These descriptors are constructed based on eigenvalues derived from specific chemical matrices. The focus of this study centers on a specific subset of spectrum-based topological descriptors, where the chemical matrices in question are dictated by the valencies of vertices within a graph. These descriptors have earned recognition for their outstanding effectiveness in establishing correlations with the total π-electronic energy of polycyclic aromatic hydrocarbons.

The computational complexity associated with the determination of numerous topological descriptors, including the detor index [10], is nontrivial, often falling under the categories of NP-complete or NP-hard problems. Consequently, the computation of these indices for specific sets of chemical or general graphs remains a challenging task of significant relevance. A notable contribution to addressing this challenge was made by Hayat [11], who undertook the task of computing various distance-based topological descriptors for specific infinite families of fullerenes and carbon nanotubes. Additionally, Hayat and her colleagues [12, 13] conducted comprehensive calculations for valency-based descriptors, including the Randic index and the atom-bond connectivity (ABC) index, within specific chemical networks. Moreover, extensive exploration of spectrum-based topological descriptors has been carried out by numerous researchers. For instance, Bozkurt [14] and other researchers explored the Randic matrix and its associated energy in the context of specific graph families. Chen [15] introduced and conducted an in-depth analysis of the ABC matrix and its spectral descriptors, encompassing parameters like the ABC energy and ABC Estrada index. Guo and Gao [16] made significant contributions to the field by introducing and studying the arithmetic-geometric (AG) energy and spectral radius of graphs. In a parallel vein, Jahanbani [17] tackled the computation of the harmonic energy and harmonic Estrada index for specific graph families. For an extensive overview of spectrum-based topological descriptors and their applications in chemistry, Consonni's survey [2] serves as a valuable resource.

In the realm of mathematical modeling, computational techniques wield a substantial influence, encompassing various aspects of graph theory and mathematics as a whole. Pioneering the field, Ashrafi [18, 19] and her collaborative team introduced a computer-driven approach for calculating indices like the Szeged index, PI index, and revised Szeged index within chemical graphs. Building upon Ashrafi's foundational work, Hayat [11] expanded and adapted this approach to encompass a broader range of distance-based indices, extending its application beyond chemical graphs to encompass general graphs. This avenue of research further evolved as Hayat and her colleagues [20] delved into degree-distance-based topological descriptors, including the Gutman index and the Schultz index. Diverging in approach, Darafsheh [21] introduced an algebraic method that leverages the automorphism group of graphs to calculate the Wiener index, Szeged index, and PI index. In a separate research strand, Arockiaraj [22] introduced a computational technique grounded in vertex cuts to compute specific distance-based indices for inorganic structures. Additionally, Ilić and Ilić [23] made significant contributions by providing algorithms for computing specific distance-based topological descriptors. Notably, Ashrafi [24] proposed a computer-based methodology for calculating the energy and Estrada index of chemical graphs, a method that was subsequently extended to encompass general graphs by Hayat and her research team [13]. In the present research work, we introduce a computational approach that builds upon Ashrafi's method [24] and extends it to encompass other spectrum-based descriptors, including the ABC energy and ABC Estrada index. This approach offers the advantage of relatively reduced computational complexity.

The total π-electronic energy, accessible through Huückel molecular orbital (HMO) calculations, provides crucial insights into conjugated molecules [25]. Additionally, the correlation between adjacency energy and π-electronic energy in molecular structures has been highlighted by Gutman [25], while Lucic and others [26] have demonstrated strong correlations between product and sum-connectivity indices and the physiochemical properties of benzenoid hydrocarbons. In a recent publication, Hayat et al. [27, 28] presented novel computational techniques for the computation of spectrum descriptors. Their methodologies incorporated software tools such as HyperChem, Topocluj, and Matlab. In our study, we adopted a distinct approach, exclusively utilizing Matlab algorithms for the computation of these descriptors. Moreover, in our regression analysis, we departed from the conventional use of isomers and instead employed real-life medicines. This deliberate choice aimed to enhance the relevance and applicability of our findings to practical pharmaceutical scenarios. Our utilization of a singular software platform and emphasis on real-world medicinal data contribute to the robustness and practicality of our methodology.

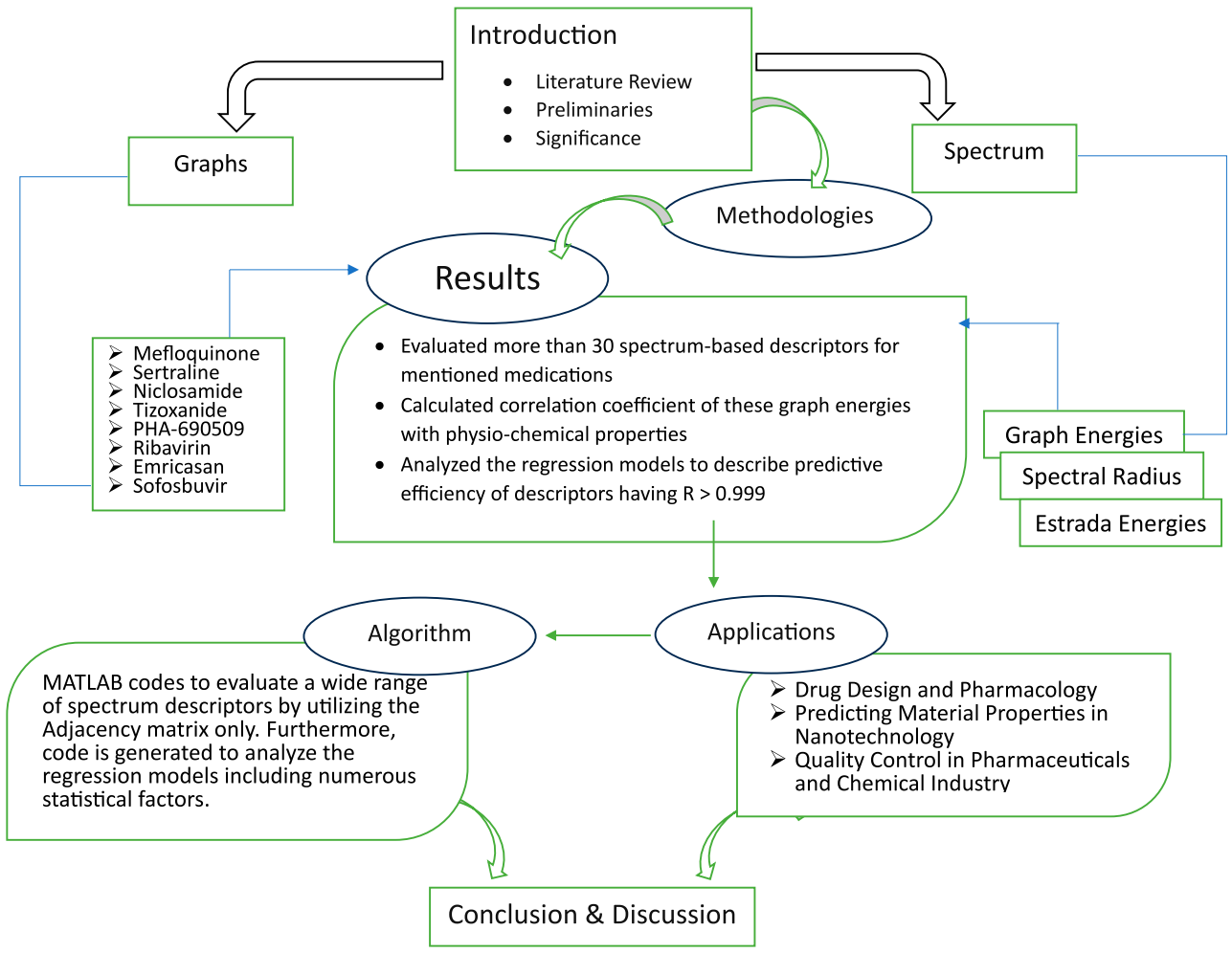

FIGURE 1
Paper structure overview: Navigating the research hierarchy.

2 Graph energies as topological descriptors

In mathematical terms, a graph G is represented as an ordered pair $G = (V, E)$, where $V = V(G)$ is a set of vertices, and $E(G)$ signifies the connections between pairs of vertices known as edges. In a chemical graph, vertices correspond to atoms, and edges represent bonds within the chemical compound. Vertices are considered adjacent if there is an edge connecting them. The degree or valency of a vertex $v \in V(G)$ is the count of adjacent vertices and is denoted as d_v. For organic chemical compounds, the maximum vertex degree is four, as carbon atoms typically have a valency of four. For a more comprehensive understanding of notations and terms related to chemical graph theory, we recommend referring to prior research [29, 30].

Actually, the topological descriptors $\mathcal{TD}$ are real valued functions that transform on different types of graphs and covert them into a real number, finding extensive applications in the field of chemistry [1]. Depending upon vertex valencies, valency- and degree-based topological descriptors have distinctive structures, while distance-based descriptors rely on the distances between vertices in graphs. Examples of valency-based descriptors include the ABC index, the Randić connectivity index, the sum-connectivity index, and Zagreb indices [31–33]. In contrast, the Szeged index, the Balaban index and the Wiener index are comprised by distance-based descriptors among all other invariant [11, 12, 20, 34]. Spectrum-based structural descriptors, on the other hand, base their defining structures on the eigenvalues of matrices generated by graph-theoretic methodologies. These descriptors encompass a wide range of energies from the Laplacian and adjacency energy to the Estrada index and inertia energies. Our research paper's architecture is visualized in Figure 1. In the following subsections, we introduce several well-established eigenvalues-based topological descriptors, whose corresponding chemical matrices are defined based on vertex valencies.

2.1 The adjacency energy

The adjacency matrix, denoted as $\mathcal{A}$, is a fundamental matrix in graph theory. It is an extensively studied graph-related matrix. The adjacency matrix of a connected graph with n vertices, G, is an $n \times n$

symmetric matrix. In this matrix, the entry $(A)_{u,v}$ is defined as 1 if there's an edge between vertices u and v in G, and 0 otherwise. The eigenvalues of $\mathcal{A}$ are denoted as $\beta_1^a \geq \beta_2^a \geq, \ldots, \geq \beta_n^a$. The largest adjacency eigenvalue of a graph G, known as the $\mathcal{A}$-spectral radius, is denoted by $\mathcal{AS}_R$ which is written mathematically as $\mathcal{AS}_R(G) \coloneqq \beta_1^a$. Extensive literature is available on A-spectral radius, with comprehensive coverage in the book by Stevanovic [35]. The $\mathcal{A}djacency$-energy is another extensively studied spectrum-based descriptor, with strong correlations found with chemical compound's physio-chemical properties [25]. The formula to evaluate the adjacency energy is $\mathcal{AD}(G) \coloneqq \sum_{i=1}^{n} |\beta_i^a|$ where β_i^a denotes the eigenvalues obtained by adjacency matrix. In existing literature, a well-known book on graph *Adjacency*-energy is published by Li et al. [36]. Additionally, Gutman's survey provides insights into the results and applications related to graph energy [37].

Estrada introduced another graph parameter related to A-eigenvalues, known as the Estrada index and afterwards, it appeared as a significant invarient as assessing the robustness of networks, describing the topological structure classes and measuring centrality of complex networks including the protein's degree folding [38–41]. The count of positive, negative and zero A-eigenvalues obtained from adjacency matrix of a graph are called the positive inertia index $\mathcal{AIP}$, negative inertia index $\mathcal{AIN}$ and the nullity $\mathcal{AIO}$, respectively have some potential and significant implimentations [42–44].

2.2 Laplacian and signless laplacian matrices

Laplacian matrices are fundamental in graph theory. Given the adjacency matrix $\mathcal{A}(G)$ of an n-vertex graph G and the diagonal matrix $D(G)$ with diagonal entries $d_{u_1}, d_{u_2}, \ldots, d_{u_n}$, the Laplacian matrix of the graph G is defined as:

$$\mathcal{L}(G) = D(G) - \mathcal{A}(G)$$

The eigenvalues of $\mathcal{L}$, denoted as $\beta_1^l \geq \beta_2^l \geq, \ldots, \geq \beta_n^l$, are referred to as $\mathcal{L}$-eigenvalues or Laplacian eigenvalues for a graph G. The Laplacian spectral radius [45] of a graph is defined as the largest $\mathcal{L}$-eigenvalue, which is denoted as $\mathcal{LS}_R = \rho_L(G) \coloneqq \beta_1^l$. Detailed mathematical treatment of the Laplacian spectral radius can be found in Liu et al. [46].

The Laplacian energy [47] is an energy analogue of the Laplacian matrix. For a graph G, it is defined as:

$$\mathcal{LP} = \mathcal{LP}(G) \coloneqq \sum_{i=1}^{n} \left| \beta_i^l - \frac{2m}{n} \right|$$

Zhou and Gutman [48] delved into mathematical properties of the spectral radius obtained by the Laplacian matrix for graphs. Similarly, the Laplacian based Estrada index [49] is:

$$\mathcal{LPE} = \mathcal{LPE}(G) \coloneqq \sum_{i=1}^{n} e^{\beta_i^l}$$

Recent advancements in the mathematical behavior, properties and applications of mentioned index can be found in previous studies [50, 51]. Furthermore, the signless Laplacian matrix is:

$$\mathcal{SL}(G) = D(G) + \mathcal{A}(G)$$

while the eigenvalues of $\mathcal{SL}$ are denoted as $\beta_1^q \geq \beta_2^q \geq, \ldots, \geq \beta_n^q$ and related largest $\mathcal{SL}$-eigenvalue is spectral radius [52] of a graph which can be written as:

$$\mathcal{SL}_R = \mathcal{SL}_R(G) \coloneqq \beta_1^q$$

For in-depth exploration of $\mathcal{SL}_R$-spectral radius in graphs, Fan et al. [53] provide valuable insights. The signless Laplacian energy, introduced by Abreua et al. [54] and denoted as $\mathcal{SLP}$ for a graph G, is defined as:

$$\mathcal{SLP} = \mathcal{SLP}(G) \coloneqq \sum_{i=1}^{n} \left| \beta_i^q - \frac{2m}{n} \right|$$

A connection between the $\mathcal{SLP}$-energy and A-energy for graph families was established by Mojallal et. al [55]. Similarly, signless Laplacian energy for some graph operations and their line graphs was examined by Ganie et al. [56]. Moreover, the Estrada index of this invariant was introduced by Ayyaswamy et al. [57].

$$\mathcal{SLPE} = \mathcal{SLPE}(G) \coloneqq \sum_{i=1}^{n} e^{\beta_i^q}$$

The exploration of mentioned descriptor was done by Ellahi et al. [58] and Nasirie et al. [59] as they evaluated the provided sharp bounds and explored the maximum and minimum values of signless Laplacian Estrada index of graphs with given chromatic numbers.

2.3 The randić matrix

In 2005, Rodríguez [60] introduced the Randić descriptor whose matrix for a graph is obviously a symmetric matrix with order $n \times n$, defined as follows:

$$\mathcal{R}_{u,v} = \begin{cases} \frac{1}{\sqrt{d_u d_v}}, & \text{if uv } \in E(G) \\ 0, & \text{otherwise} \end{cases}$$

Consider the eigenvalues of R are $\beta_1^r \geq \beta_2^r \geq, \ldots, \geq \beta_n^r$, then randic spectral radius, explored by Rodríguez [60], is defined as:

$$\mathcal{HARS}_R = \mathcal{HARS}_R(G) \coloneqq \beta_1^r$$

Utilizing the above definition, Randić energy of graphs was inaugurated by Bozkurt et al. [14] as

$$\mathcal{HAR} = \mathcal{HAR}(G) \coloneqq \sum_{i=1}^{n} |\beta_i^r|$$

Gutman et al. [61] Sorgun et. al [62]. further contributed to explored the chemical significance and mathematical related to the Randić energy.

2.4 The sum-connectivity matrix

In 2010, Trinajstic [63] introduced the concept of sum-connectivity descriptor whose matrix for a graph is obviously a symmetric matrix with order $n \times n$, defined as follows:

$$\mathcal{SMC}_{u,v} = \begin{cases} \frac{1}{\sqrt{d_u + d_v}}, & \text{if uv } \in E(G) \\ 0, & \text{otherwise} \end{cases}$$

Utilizing the eigenvalues of S, denoted as $\beta_1^s \geq \beta_2^s \geq, \ldots, \geq \beta_n^s$, are known as S-eigenvalues of the graph, the spectral radius and energies of $\mathcal{SMC}_{u,v}$ are defined as:

$$\mathcal{SMCS}_R = \mathcal{SMCS}_R(G) \coloneqq \beta_1^s$$
$$\mathcal{SMC} = \mathcal{SMC}(G) \coloneqq \sum_{i=1}^{n} \left|\beta_i^s\right|$$

Recent research by Prakasha et al. [64] has further delved into the properties of the sum-connectivity energy in graphs.

2.5 Zagreb (Z^1) and (Z^2) matrices

Zagreb indices, pivotal in studying π-electronic energies of organic compounds, have led to the development of two important matrices. Rad et al. [65] introduced the first Zagreb matrix Z^1 based on the first Zagreb index. It is an $n \times n$ symmetric matrix, defined as:

$$(\mathcal{Z}G_1)_{u,v} = \begin{cases} d_u + d_v, & \text{if uv } \in E(G) \\ 0, & \text{otherwise} \end{cases}$$

The Z^1-eigenvalues, denoted as $\beta_1^{z^1} \geq \beta_2^{z^1} \geq, \ldots, \geq \beta_n^{z^1}$, correspond to this matrix. Rad et al. [65] studied the spectral radius, energy, and Estrada index associated with the first Zagreb matrix:

$$\mathcal{Z}G_1\mathcal{S}_R = \mathcal{Z}G_1\mathcal{S}_R(G) \coloneqq \beta_1^{z^1}$$
$$\mathcal{Z}G_1 = \mathcal{Z}G_1(G) \coloneqq \sum_{i=1}^{n} \left|\beta_i^{z^1}\right|$$
$$\mathcal{Z}GE_1 = \mathcal{Z}GE_1(G) \coloneqq \sum_{i=1}^{n} e^{\beta_i^{z^1}}$$

In parallel, the second Zagreb matrix Z^2, introduced by Rad et al. [66] and Zhan et al. [67], is based on the second Zagreb index. It is also an $n \times n$ symmetric matrix:

$$(\mathcal{Z}G_2)_{u,v} = \begin{cases} d_u d_v, & \text{if uv } \in E(G) \\ 0, & \text{otherwise} \end{cases}$$

The ZG^2-eigenvalues, $\beta_1^{z^2} \geq \beta_2^{z^2} \geq, \ldots, \geq \beta_n^{z^2}$, are associated with this matrix. Zhan et al. [67] introduced the spectral radius, energy, and Estrada index corresponding to the second Zagreb matrix:

$$\mathcal{Z}G_2\mathcal{S}_R = \mathcal{Z}G_2\mathcal{S}_R(G) \coloneqq \beta_1^{z^2}$$
$$\mathcal{Z}G_2 = \mathcal{Z}G_2(G) \coloneqq \sum_{i=1}^{n} \left|\beta_i^{z^2}\right|$$
$$\mathcal{Z}GE_2 = \mathcal{Z}GE_2(G) \coloneqq \sum_{i=1}^{n} e^{\beta_i^{z^2}}$$

Both matrices have been subjects of in-depth mathematical studies, and Rad et al. [66] contributed essential results on the second Zagreb spectral radius and energy.

2.6 The harmonic matrix

In the realm of graph theory, the harmonic matrix was first introduced by Hosamani et al. in their work [68]. This matrix, denoted as $H(G)$, corresponds to the harmonic index of a graph with n vertices and is defined as an $n \times n$ symmetric matrix:

$$(HAR)_{u,v} = \begin{cases} \frac{2}{d_u + d_v}, & \text{when } uv \in E(G) \\ 0, & \text{otherwise} \end{cases}$$

Now, let's denote the eigenvalues of this harmonic matrix H for a graph G as $\beta_1^h \geq \beta_2^h \geq \ldots \geq \beta_n^h$, which we refer to as H-eigenvalues. Various topological descriptors are defined based on these eigenvalues:

$$\mathcal{HARS}_R(G) \coloneqq \beta_1^h$$
$$\mathcal{HAR}(G) \coloneqq \sum_{i=1}^{n} \left|\beta_i^h\right|$$
$$\mathcal{HARE}(G) \coloneqq \sum_{i=1}^{n} e^{\beta_i^h}$$

In a separate study by Jahanbani et al. [17], some remarkable findings were obtained concerning the harmonic energy and the harmonic Estrada index of graphs.

3 Assessing various physio-chemical properties using spectrum-based topological descriptors' predictive capability

The Molar volume, Polarizability, Molar refractivity, and Complexity are fundamental quantum-theoretic characteristics of chemical compounds, particularly important for drugs targeting infectious diseases. In Section 2, we introduced spectrum-based valency descriptors, and now we are evaluating their ability to predict these physicochemical properties. We use our technique, as discussed in the previous section, to calculate these descriptors for various drugs, namely, Mefloquinone, Sertraline, Niclosamide, Tizoxanide, PHA-690509, Ribavirin, Emricasan, and Sofosbuvir. Details of these all drugs can be found in a file that we have uploaded on the GitHub repository [https://github.com/alleerazza786/DD]. Mefloquine, a quinoline derivative, is widely employed as an antimalarial agent, particularly in regions with chloroquine-resistant strains of *Plasmodium*. It has been shown to be effective in the prevention and treatment of malaria [69].

Sertraline, a selective serotonin reuptake inhibitor (SSRI), is commonly prescribed for the treatment of various mood and anxiety disorders, including major depressive disorder, obsessive-compulsive disorder, and panic disorder [70]. Niclosamide, traditionally used as an anthelmintic agent, has gained attention for its potential in cancer therapy due to its antiproliferative and anticancer properties [71]. Tizoxanide, an active metabolite of nitazoxanide, exhibits broad-spectrum antiparasitic activity and

TABLE 1 The evaluated spectrum based descriptors values, along with numerous medications, provide experimental data for Molar volume, Polarizability and Molar Refractivity.

Spectrum Descriptors	*Mefloquinone*	*Sertraline*	*Niclosamide*	*Tizoxanide*	*PHA690509*	*Ribavirin*	*Emricasan*	*Sofosbuvir*
Molar Volume	273.4	243.9	202.5	161.3	271.6	117.1	410.9	374.6
Polarizability	32.9	34	31.3	26.1	37.4	20.3	51.9	48.9
Molar Refractivity	83	85.8	79	65.7	94.3	51.1	131	123.5
Complexity	483	322	404	336	422	304	934	913
Adjacency Spectral Radius	2.4622	2.4600	2.2388	2.3069	2.3401	2.6908	2.3919	2.4541
Adjacency Energy	26.3539	26.5099	20.7710	21.4563	28.4591	20.7600	42.5579	36.8398
Estrada Adjacency Energy	50.2018	50.2119	40.5938	40.5462	55.5797	44.0513	90.4147	84.4466
Positive Inertia Index	10.001	10.004	8.0011	8.0010	10.0011	8.006	18.0012	13.0011
Negative Inertia Index	10.0001	10.021	9.0013	8.0023	10.0022	7.0001	14.0019	13.0014
Nullity	0.001	0.0002	2.0012	2.0091	3.0011	1.0014	8.0017	10.0034
Laplacian Spectral Radius	5.2244	5.2033	4.7936	4.7363	4.9609	5.7846	5.1489	5.2916
Laplacian Energy	29.2983	28.9349	24.6730	24.4892	32.8888	25.5015	53.2370	48.5145
Estrada Laplacian Energy	602.1296	604.4998	382.4322	400.2298	608.0543	732.4981	950.2364	890.3952
S.Laplacian Spectral Radius	5.2244	5.2033	4.7940	4.8661	4.9687	5.9267	5.1489	5.3757
S.Laplacian Energy	29.2983	28.9349	24.8917	24.8131	33.2040	25.6617	55.2945	51.1602
Estrada S.Laplacian Energy	602.1296	604.4998	392.9649	402.6032	610.4150	746.4629	1077.3568	1129.0853

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TABLE 2 The evaluated spectrum based descriptors values for numerous medications.

Spectrum	Mefloquinone	Sertraline	Niclosamide	Tizoxanide	PHA690509	Ribavirin	Emricasan	Sofosbuvir
$\mathcal{AD}^{*}\mathcal{S}_R$	2.7209	2.6928	2.5450	2.7243	2.7053	3.0499	−3.6806	3.2084
$\mathcal{AD}^{*}$	30.4254	30.0150	24.4965	25.3456	33.9948	26.3699	58.1459	45.9062
$\mathcal{RAN}\mathcal{S}_R$	1.0000	1.0000	1.0000	1.0000	1.0000	1.2181	1.0000	1.0000
$\mathcal{RAN}$	12.0392	12.2463	10.1231	10.6135	13.5366	9.7983	20.6298	16.9179
$\mathcal{SMC}\mathcal{S}_R$	1.0823	1.0865	1.0354	1.0476	1.0579	1.3495	1.0555	1.0698
$\mathcal{SMC}$	12.2997	12.4506	10.0052	10.3909	13.4826	9.9483	19.9824	17.0450
$\mathcal{ABC}\mathcal{S}_R$	1.7185	1.7046	1.5894	1.6460	1.6612	1.9800	1.6983	1.7537
$\mathcal{ABC}$	18.9863	18.9103	15.1331	15.6076	20.6901	15.4918	32.0670	26.9678
$\mathcal{GA}\mathcal{S}_R$	2.4213	2.4347	2.1961	2.2510	2.2869	2.6350	2.3202	2.3667
$\mathcal{GA}$	25.5587	25.7997	20.0561	20.6598	27.3468	19.6853	39.6605	35.1418
$\mathcal{AG}\mathcal{S}_R$	2.5121	2.4904	2.2921	2.3757	2.4050	2.7614	2.4815	2.5758
$\mathcal{AG}$	27.2752	27.3151	21.5986	22.3591	29.7285	22.0231	46.0360	38.8713
$\mathcal{ZG}_1\mathcal{S}_R$	13.3048	13.2110	10.9905	11.4253	11.8705	13.7110	−12.7934	13.4995
$\mathcal{ZG}_1$	123.9316	124.0825	91.2788	93.4447	129.9754	97.7763	198.3214	177.5900
$\mathcal{ZGE}_1$	660293.5	621707.9	70445.7	104249.9	214775.4	960873.8	457275.5	1197102.1
$\mathcal{ZG}_2\mathcal{S}_R$	18.3983	18.2387	13.7948	13.9738	15.4235	20.2580	−17.4564	19.1433
$\mathcal{ZG}_2$	145.0980	146.1781	98.0044	99.2780	144.9343	119.9710	218.9591	209.5050
$\mathcal{ZGE}_2$	99266946	84703925	1001981	1221820	5467443	628892539	39011886	217710904
$\mathcal{HAR}\mathcal{S}_R$	0.9792	0.9824	0.9736	0.9701	0.9715	1.1769	0.9947	0.9736
$\mathcal{HAR}$	11.5663	11.8236	9.6916	10.1541	12.8840	9.1625	18.9149	15.9232
$\mathcal{HARE}$	24.3147	24.4230	22.5695	21.8756	28.0184	19.9063	48.5116	43.0490

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TABLE 3 The correlation coefficient evaluated between pharmacological properties for numerous medications and spectrum based descriptors.

Spectrum Descriptors	Corr.Coef. for Mol.Vol.	Corr.Coef. for Polarizability	Corr.Coef. for Refractivity	Corr.Coef. for Complexity
$\mathcal{AD}$	0.9552	0.9531	0.9528	0.9304
$\mathcal{ADE}$	0.9323	0.9323	0.9322	0.9620
$\mathcal{AIP}$	0.8987	0.8987	0.8983	0.8947
$\mathcal{AIN}$	0.9999	0.9996	0.9998	0.9287
$\mathcal{AIO}$	0.8329	0.8329	0.8328	0.9261
$\mathcal{LP}$	0.9381	0.9381	0.9379	0.9656
$\mathcal{LPE}$	0.6828	0.6828	0.6827	0.7866
$\mathcal{SLP}$	0.9351	0.9351	0.9349	0.9701
$\mathcal{LPE}$	0.7500	0.7500	0.7500	0.8679
$\mathcal{AD}^{*}$	0.9161	0.9161	0.9157	0.9319
$\mathcal{RAN}$	0.9449	0.9449	0.9445	0.9240
$\mathcal{SMC}$	0.9505	0.9505	0.9502	0.9278
$\mathcal{ABC}$	0.9420	0.9420	0.9417	0.9338
$\mathcal{GA}$	0.9639	0.9596	0.9594	0.9264
$\mathcal{AG}$	0.9444	0.9444	0.9441	0.9329
$\mathcal{ZG}_1$	0.9506	0.9430	0.9428	0.9310
$\mathcal{ZGE}_1$	0.1998	0.1998	0.2006	0.3788
$\mathcal{ZG}_2$	0.9073	0.9073	0.9073	0.9103
$\mathcal{HAR}$	0.9514	0.9560	0.9556	0.9218
$\mathcal{HRE}$	0.9503	0.9503	0.9501	0.9718

has been explored for its use in treating parasitic infections such as giardiasis and cryptosporidiosis [72]. PHA-690509 is a potent, selective inhibitor of the cyclin-dependent kinase (CDK2) and has shown promise in preclinical studies for cancer treatment [73]. Ribavirin, a nucleoside analog, has been a key component of antiviral therapy, especially in combination with other drugs, for the treatment of hepatitis C and other viral infections [74]. Emricasan is a caspase inhibitor with potential applications in liver diseases, particularly in the management of liver fibrosis and cirrhosis [75]. Sofosbuvir, a direct-acting antiviral agent, has revolutionized the treatment of hepatitis C and has significantly improved cure rates with fewer side effects [76]. The descriptors displaying the strongest correlation with these properties are recommended for use in quantitative structure and property models. This study enhances the practical utility of these high-performing descriptors in QSAR/QSPR research, building upon prior seminal works [13, 77, 78].

The first algorithm mentioned in Supplementary Appendix S1A section is employed for the assessment of diverse graph energies. Nevertheless, we have provided the methodology for evaluating just three descriptors, such as Laplacian energy, signless Laplacian energy, and extended adjacency energy, as illustrative examples. This section leverages our proposed computational method to calculate commonly occurring spectrum-based topological descriptors and evaluate their effectiveness in correlating Molar volume, Polarizability, Molar refractivity, and Complexity. The intercorrelations between these properties and the spectrum-based descriptors outlined in Section 2 are presented in Tables 1, 2. The first row in the tables represents Molar volume, the second row represents polarizability, the third row represents molar refractivity, and the fourth row represents the complexity of the mentioned drugs. These values are sourced from the reputable chemistry-related website Chem Spider and PubChem. However interested researcher may find these experimental values from the URL [https://github.com/alleerazza786/DD]. The remaining rows contain the graph energies computed using the Matlab algorithm, as discussed in the following section.

We utilize the data in Table 1 and Table 2 to calculate correlation coefficients, which serve as indicators of the efficiency of these spectrum-based descriptors. A simple rule of thumb is that higher correlation coefficients indicate superior performance for a given topological descriptor. Table 3 showcases the correlation coefficients between the physicochemical properties and the spectrum-based structural descriptors. Another Matlab algorithm is mentioned in Supplementary Appendix SA1 section which is utilized for the correlation analysis.

TABLE 4 Most efficient graph energies list along with correlation coefficients.

Priority Position	Spectrum Descriptors	Corr.Coef. for Mol.Vol.	Corr.Coef. for Polarizability	Corr.Coef. for Refractivity
1	Negative Inertia Energy	0.9999	0.9996	0.9998
2	Geometric Arith. Energy	0.9639	0.9596	0.9594
3	Adjacency Energy	0.9552	0.9531	0.9528
4	First Zegrab Energy	0.9506	0.9430	0.9428
5	Harmonic Energy	0.9514	0.9560	0.9556

4 Statistical analysis of evaluated data and regression models

Recently M. Arockiaraj et. al [79, 80]. extensively explores the predictive capabilities of reverse degree and entropy topological indices for drug molecules utilized in blood cancer treatment. This study employs Quantitative Structure Property relationship (QSPR) regression models to assess the effectiveness of these indices. Similarly, their work [81, 82] contributes to our understanding of regression models in the context of drug molecules designed for the latest treatments in combating COVID-19. The research specifically investigates the application of linear and cubic regression models to analyze generalized reverse degree-based topological indices for these crucial drugs. Together, these research studies provide a robust foundation for our current work and contribute valuable insights to the field. Utilizing the similar techniques, In this section, we delve into an in-depth analysis of the results we've obtained in the preceding section. The data found in Table 3 reveals some promising findings regarding spectrum-based descriptors. Notably, descriptors like negative inertia energy, adjacency energy, geometric-arithmetic energy, first zegrab energy, and harmonic energy exhibit exceptionally strong correlation coefficients, surpassing 0.999, which stands out among the rest. Conversely, a set of reputable spectrum-based descriptors, including extended adjacency, Laplacian, signless Laplacian spectral radius, and the second Zagreb Estrada indices, display notably weaker performance with correlation coefficients falling below 0.9. Any spectrum-based topological descriptor with a correlation coefficient below 0.9 is not recommended for incorporation into quantitative structure and property relationship models. Surprisingly, upon examining the data in Table 3, we find that negative inertia $\mathcal{AIN}$ stands out as the most effective spectrum-based descriptor, with correlation coefficients exceeding 0.9999, nearly reaching a perfect correlation of 1, especially in measuring the Molar volume of the mentioned medications. Similarly, $\mathcal{AIN}$ shows extraordinary correlation with Polarizability and Molar Refractivity. However, it is worth noting that none of the descriptors achieve a substantial correlation coefficient with the Complexity of the given drugs, except for the Harmonic Energy, which stands at 0.9718.

Unexpectedly, the Adjacency and geometric-arithmetic energies perform strikingly similarly to the inertia positive energy, with correlation coefficients of 0.9639 and 0.9552, respectively, approaching a perfect correlation of 1. These two spectrum-based topological descriptors undoubtedly rank among the best, justifying their continued use in Quantitative Structure Property relationship models. Following the geometric-arithmetic and adjacency energies, the First zegrab and harmonic energies also exhibit favorable correlation coefficients. These correlation coefficients lead to the formulation of a priority list of the five most promising spectrum-based descriptors for assessing the physical and chemical properties of chemical compounds. You can find this priority list in Table 4.

For these top five spectrum-based descriptors, we carry out a comprehensive regression and correlation analysis. This analysis includes the presentation of regression models, correlation and determination coefficients, and the standard error of fit, along with scatter plots.

We conducted a comprehensive regression analysis for the top two spectrum descriptors, Inertia Positive Energy and Adjacency Energy. This analysis encompasses the derivation of a regression equation and the calculation of various statistical metrics, shedding light on the nature of their relationship. The resulting regression equation provides insight into how changes in these spectrum descriptors influence the target variable. Furthermore, we assessed the precision of the regression model by examining coefficient standard errors. The correlation coefficient (R) quantifies the strength and direction of the relationship between the independent and dependent variables, while the R-squared value offers information about the proportion of variance in the target variable that the model explains. Additionally, we determined the Standard Error of Estimation, which gauges the accuracy of the model's predictions. This in-depth analysis offers a robust understanding of the relationships between Inertia Positive Energy, Adjacency Energy, and the target variable, contributing valuable insights for further investigation and application. The provided data reveals strong linear relationships between the independent variable $\mathcal{AIN}$ and three distinct dependent variables. For molar volume (MV), the regression equation $MV = -175.1091 + 42.1592 \cdot \mathcal{AIN}$ suggests that for every one-unit increase in $\mathcal{AIN}$, MV increases by approximately 42.16 units, with a remarkable correlation coefficient (R) of 0.9999, indicating an almost perfect positive relationship. The high R^2 value (R^2 = 0.9993) reflects the robustness of the model, while the small standard error of the regression (SE_r = 0.4528) signifies the accuracy of predictions. Similarly, polarizability (PL) exhibits a strong positive relationship with $\mathcal{AIN}$ ($PL = -10.1235 + 4.4895 \cdot \mathcal{AIN}$), characterized by a high correlation coefficient (R = 0.9996) and a substantial R^2 value (R^2 = 0.9983). Molar Refractivity (MR) is also strongly influenced by $\mathcal{AIN}$ ($MR = -25.8766 + 11.3589 \cdot \mathcal{AIN}$) with a very high correlation coefficient (R = 0.9998) and a substantial R^2 value

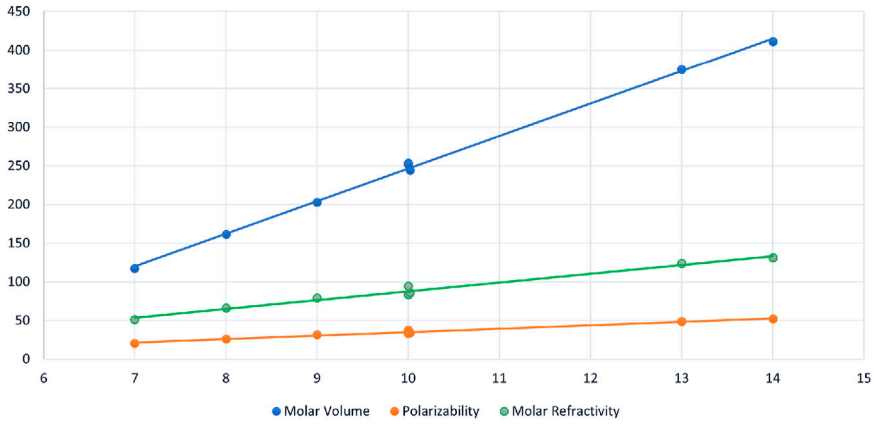

FIGURE 2
Scattered diagram of Inertia Negative Energy $\mathcal{AIN}$ *versus* Molar Volume, Polarizability and Molar Refractivity.

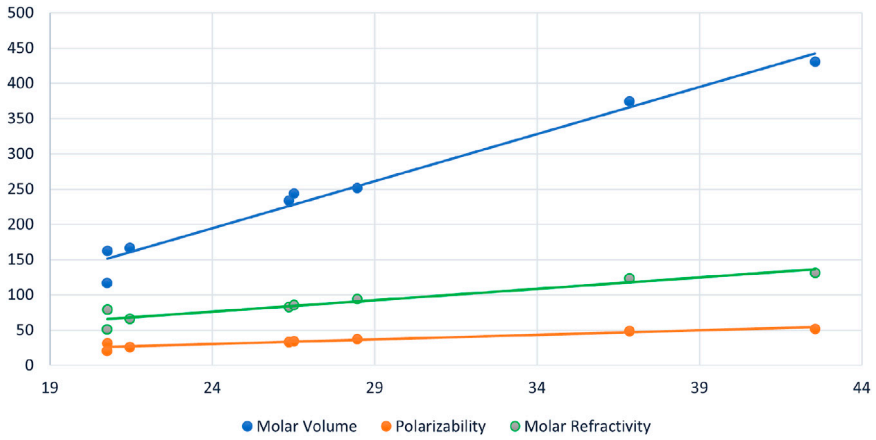

FIGURE 3
Scattered diagram of Geometric Arithmetic Energy $\mathcal{AG}$ *versus* Molar Volume, Polarizability and Molar Refractivity.

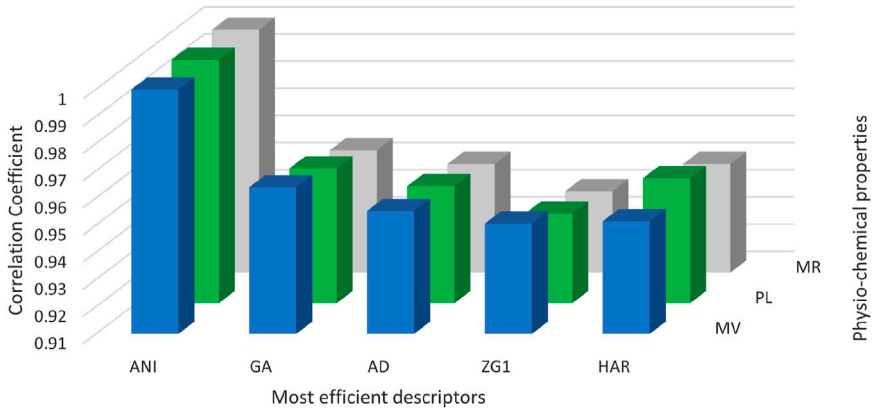

FIGURE 4
Graphical illustration of most efficient graph energies.

(R^2 = 0.9983). These results emphasize the predictive power and reliability of the regression models for *MV*, *PL*, and *MR*, underscoring their potential applications in various fields. The scatter diagram corresponding to the provided regression equation is visually represented in Figure 2.

$MV = -175.1091_{\pm 18.1135} + 42.1592\mathcal{AIN}_{\pm 1.7474}$ $R = 0.9999$ $R^2 = 0.9993$ $SE_r = 0.4528$.

$PL = -10.1235_{\pm 6.2932} + 4.4895\mathcal{AIN}_{\pm 0.6071}$ $R = 0.9996$ $R^2 = 0.9983$ $SE_r = 1.0471$.

$MR = -25.8766_{\pm 1.8695} + 11.3589\mathcal{AIN}_{\pm 0.5309}$ $R = 0.9998$ $R^2 = 0.9983$ $SE_r = 1.5471$.

The data represents regression results for three distinct chemical properties, including molar volume (*MV*), polarizability (*PL*), and molar refractivity (*MR*), each of which is modeled as a function of a common independent variable, denoted as $\mathcal{AD}$. For molar volume (*MV*), the regression equation $MV = 1.4408 \pm 1.8110 + 24.0015 \cdot \mathcal{GA} \pm 0.7747$ demonstrates a positive linear relationship with $\mathcal{GA}$. A one-unit increase in $\mathcal{GA}$ is associated with an increase of approximately 24.0015 units in molar volume. The model exhibits a high correlation coefficient (R = 0.9639), indicating a strong positive relationship between *MV* and $\mathcal{GA}$. The coefficient of determination (R^2 = 0.9456) suggests that the model accounts for a substantial portion of the variance in molar volume, while the standard error of the regression (SE_r = 0.5452) represents the precision of the model's predictions.

Similarly, polarizability (*PL*) is modeled as a linear function of $\mathcal{GA}$, given by $PL = -8.1235 \pm 2.1129 + 1.1489 \cdot \mathcal{GA} \pm 0.3607$. This regression equation reveals a positive relationship between polarizability and $\mathcal{GA}$, with a high correlation coefficient (R = 0.9596). The coefficient of determination (R^2 = 0.8998) indicates that a significant portion of the variation in polarizability can be explained by $\mathcal{GA}$, while the standard error of the regression (SE_r = 0.3047) reflects the accuracy of the model. Molar refractivity (*MR*) is also positively influenced by $\mathcal{GA}$, as evidenced by the regression equation $MR = -5.4876 \pm 0.9018 + 4.3508 \cdot \mathcal{GA} \pm 0.6653$. The strong correlation coefficient (R = 0.9594) signifies a robust positive relationship between *MR* and $\mathcal{GA}$, with a substantial coefficient of determination (R^2 = 0.9083). The standard error of the regression (SE_r = 0.8547) provides insights into the precision of the model's predictions. These regression models offer valuable insights into the relationships between chemical properties (molar volume, polarizability, and molar refractivity) and the independent variable ($\mathcal{GA}$) in the context of the chemical sciences. The scatter diagram corresponding to the provided regression equation is visually represented in Figure 3.

$MV = 1.4408_{\pm 1.8110} + 24.0015\mathcal{GA}_{\pm 0.7747}$ $R = 0.9639$ $R^2 = 0.9456$ $SE_r = 0.5452$.

$PL = -8.1235_{\pm 2.1129} + 1.1489\mathcal{GA}_{\pm 0.3607}$ $R = 0.9596$ $R^2 = 0.8998$ $SE_r = 0.3047$.

$MR = -5.4876_{\pm 0.9018} + 4.3508\mathcal{GA}_{\pm 0.6653}$ $R = 0.9594$ $R^2 = 0.9083$ $SE_r = 0.8547$.

Figure 4 serves as a graphical representation of the data found in Table 3, allowing for a comprehensive comparison of the efficiency of various spectrum-based descriptors. This visual representation offers an insightful examination of the relationships between these descriptors and the properties of interest. Notably, the analysis reveals that among the considered drugs, Positive Inertia Energy stands out as the most efficient descriptor. This conclusion is supported by the observation that Positive Inertia Energy exhibits the highest correlation coefficients when correlated with three essential properties: Molar Volume, Polarizability, and Molar Refractivity. These strong correlations signify a robust association between Positive Inertia Energy and the chemical properties in question, indicating its potential significance in understanding and predicting these properties in the context of the studied drugs. The graphical representation in Figure [Reference] aids in conveying this valuable insight to a broader audience, facilitating a clearer understanding of the relationships between the spectrum-based descriptors and the chemical properties of interest.

5 Conclusuion and discussion

Our research has harnessed the power of spectrum based topological descriptors and linear regression models to forecast the attributes of chemical compounds effectively. This exploration has led to intriguing insights into the correlation coefficients among a multitude of graph energies. Notably, descriptors like negative inertia energy, adjacency energy, geometric-arithmetic energy, first zegrab energy, and harmonic energy have demonstrated remarkably strong correlation coefficients with the physicochemical properties of widely-used medications. Among these correlations, the one between $\mathcal{AIN}$ and molar volume, boasting an impressive R value of 0.999, has stood out. These findings underscore the critical role of judicious index selection and analysis in deciphering and predicting chemical properties, deepening our understanding of the intricate relationships between these attributes and specific variables. We urge fellow researchers to explore the predictive potential of spectrum-based distance descriptors, including the distance energy, the distance Laplacian, and distance signless Laplacian energies, in deciphering the structural behavior of benzenoid hydrocarbons and related compounds, opening promising avenues for further investigation.

Data availability statement

The original contributions presented in the study are included in the article/Supplementary Material, further inquiries can be directed to the corresponding author.

Author contributions

AR: Conceptualization, Data curation, Funding acquisition, Investigation, Methodology, Software, Writing–original draft. MM: Writing–review and editing.

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Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Supplementary material

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fphy.2024.1348407/full#supplementary-material

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