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Inverse Sum Indeg Index (Energy) with Applications to Anticancer Drugs

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Abstract: For a simple graph with vertex set $\{v_1, v_2, \ldots, v_n\}$ with degree sequence d_{v_i} of vertex v_i, $i = 1, 2, \ldots, n$, the inverse sum indeg matrix (ISI-matrix) $A_{ISI}(G) = (a_{ij})_{n\times n}$ of G is defined by $a_{ij} = \frac{d_{v_i} d_{v_j}}{d_{v_i} + d_{v_j}}$, if v_i is adjacent to v_j, and zero, otherwise. The multiset of eigenvalues of $A_{ISI}(G)$ is the ISI-spectrum of G and the sum of their absolute values is the ISI-energy of G. In this paper, we modify the two results of (Li, Ye and Broersma, 2022), give the correct characterization of the extremal graphs and thereby obtain better bounds than the already known results. Moreover, we also discuss the QSPR analysis and carry the statistical modelling (linear, logarithmic and quadratic) of the physicochemical properties of anticancer drugs with the ISI-index (energy).

Keywords: adjacency matrix; ISI-matrix; topological indices; correlation; anticancer drugs

MSC: 05C50; 05C90; 05C92

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1. Introduction

Topological indices are the interesting attributes to analyse the physicochemical properties and the characteristics of chemical structures. There are certain important types of topological indices (degree, distance, spectral, and others including their mixed invariants). Here, we consider a degree-based topological index, the ISI-index, and its spectral invariant, the ISI-energy, on anticancer drug molecular structures. Basically, a topological index is generated by converting a molecular structure to a numeric value. Practically, the chemical compounds are taken as a graph where the elements are vertices and the bonds connecting them are edges. The anticancer drugs in this study are considered as chemical compounds, and their underlying graphs are considered. These topological indices and their spectral invariants are utilised in quantitative structure–property relationships (QSPR) studies to determine the bioactivity of chemical compounds. Cancer is a very deadly disease and is a rapid increase of abnormal/dead cells in the body. Carcinogens are the substances that are the cause of cancer. A carcinogen is a chemical substance with certain molecules such as tobacco smoke. It has the property of spreading to other parts of body. Some symptoms of this deadly disease include lumps, abnormal bleeding, prolonger cough, weight loss, anxiety, etc. Some causes of cancer are chewing tobacco, obesity, bad diet, laziness, large intakes of alcohol. Cancer can be cured by several treatments such as surgery, radiotherapy, chemotherapy, hormone therapy, targeted therapy and more. Anticancer drugs are drugs which are used to treat cancer, including alkylates and metabolites. Chemical graph theory is a discipline of mathematical chemistry that deals with the chemical graphs which represent chemical systems. Chemical graph theory defines topological indices on graphs and in particular the chemical structures of alkanes/anticancer drugs. In this work, several chemical graph structures of drugs (see Figure 1) are taken and a QSPR analysis is

carried out on various anticancer drug structures to determine their physical characteristics and chemical reactions along with their ISI-index and ISI-energy (see definitions in the following paragraph). For a similar type of analysis, see [1–6].

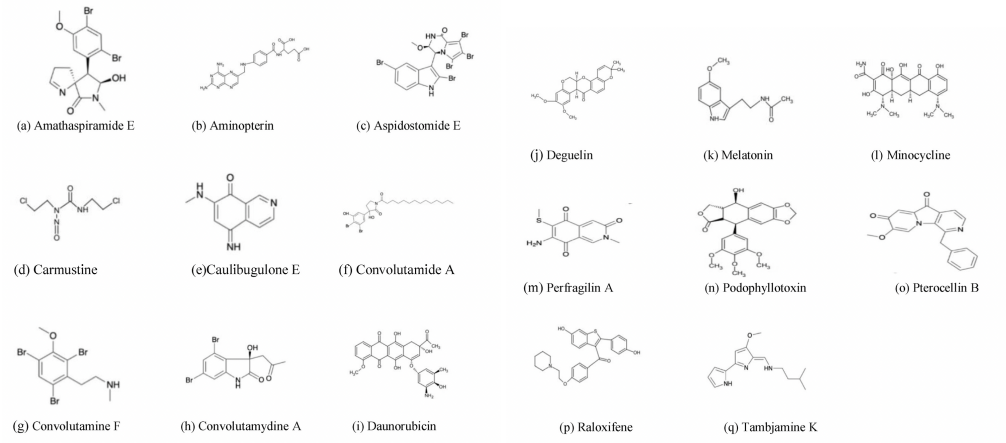

Figure 1. Molecular Structures of Certain Anticancer Drugs.

Let $G = G(V, E)$ be a graph with vertex set $V = \{v_1, v_2, \ldots, v_n\}$ and edge set E. We consider only simple and undirected graphs, unless otherwise stated. The number of elements in V is the *order* n and the number of elements in E is the *size* m of G. By $u \sim v$, we mean a vertex u is adjacent to a vertex v. We denote an edge by uv connecting two vertices u and v. The *neighbourhood* (open neighbourhood) $N(v)$ of $v \in V$ is the set of vertices adjacent to v. The *degree* d_v of a vertex v is the number of elements in the set $N(v)$. A graph G is called *r-regular*, if $d_v = r$ for each v. We denote the complete graph by K_n, the complete bipartite graph by $K_{a,b}$ and the complete q partite graph by $K_{n_1,n_2,\ldots,n_q}$. We follow the standard graph theory notation, and more graph theoretic notations can be found in [7].

The adjacency matrix $A(G)$ of G is a square matrix of order n, with the (i, j)th entry equal to 1, if $v_i \sim v_j$, and 0, otherwise. Clearly, $A(G)$ is a real symmetric matrix and its multiset of eigenvalues is known as the spectrum of G. Let $\lambda_1 \geq \lambda_2 \geq \cdots \geq \lambda_n$ be the eigenvalues of $A(G)$, where the eigenvalue λ_1 is called the spectral radius of G. More about the adjacency matrix $A(G)$ can be seen in [7,8].

The energy [9] of G is defined by

$$\mathcal{E}(G) = \sum_{i=1}^{n} |\lambda_i|.$$

The energy is intensively studied in both mathematics and theoretical chemistry, since it is the trace norm of real symmetric matrices in linear algebra and the total π-electron energy of a molecule in mathematical chemistry, see [10,11]. For more information about the energy of G, including recent developments, see [12–14].

The inverse sum indeg index (shortly ISI-index) [15] is a topological index defined as

$$ISI(G) = \sum_{uv \in E(G)} \frac{d_u d_v}{d_u + d_v}.$$

The ISI-index is a well-studied topological index and it has many applications in quantitative structure–activity or structure–property relationships (QSAR/QSPR) [1,3,4,16].

The inverse sum indeg matrix (ISI-matrix) of a graph G, introduced by Zangi, Ghorbani and Eslampour [17], is a square matrix of order n, and it is defined by

$$A_{ISI}(G) = (a_{ij})_n = \begin{cases} \frac{d_{v_i} d_{v_j}}{d_{v_i} + d_{v_j}} & \text{if } v_i \sim v_j \\ 0 & \text{otherwise.} \end{cases}$$

The ISI-matrix is real and symmetric, and its eigenvalues can be indexed from the largest to the smallest as

$$\tau_1 \geq \tau_2 \geq \cdots \geq \tau_n.$$

The multiset of all eigenvalues of ISI-matrix of G is known as the ISI-spectrum of G, and the largest eigenvalue τ_1 is called the ISI-spectral radius of G. If an eigenvalue τ of ISI-matrix occurs with algebraic multiplicity $k \geq 2$, then we represent it by $\tau^{[k]}$. The ISI-energy of G is defined by

$$\mathcal{E}_{ISI}(G) = \sum_{i=1}^{n} |\tau_i|.$$

Zangi et al. [17] gave basic properties of the ISI-matrix including the bounds for the ISI-energy of graphs. Hafeez and Rashid [18] obtained the ISI-spectrum and ISI-energy of special graphs. They also gave some bounds on the ISI-energy of graphs. Bharali et al. [19] gave some bounds on the ISI-energy and introduced the ISI Estrada index of G. Havare [1] obtained the ISI index and ISI-energy of the molecular graphs of hyaluronic acid–paclitaxel conjugates. For other properties of the ISI-index, ISI-matrix, ISI Laplacian (signless) matrix and other recent results, see [20–22].

In Section 2, we modify the two results of [21], characterize the correct extremal graphs and thereby obtain better results than the already known results. In Section 3, we carry a statistical analysis of various anticancer drugs, give their correlation coefficients with the ISI-index and the ISI-energy along with their applications in quantitative structure–property relationship. We end the article with a conclusion.

2. Inverse Sum Indeg Energy of Graphs

We start with some already known results, which are used in the sequel.

Lemma 1 ([23]). *Let G be a connected graph of order $n \geq 2$. Then, G has exactly two distinct ISI-eigenvalues if and only if G is a complete graph.*

Lemma 2 ([23]). *Let G be a bipartite graph. Then, G has three distinct ISI-eigenvalues if and only if G is a complete bipartite graph.*

The following observation states that G has a symmetric ISI-spectrum towards the origin if G is bipartite.

Remark 1. *Clearly, the ISI-matrix of the bipartite graph G can be written as*

$$ISI(G) = \begin{pmatrix} \mathbf{0} & B \\ B^T & \mathbf{0} \end{pmatrix}.$$

If τ is an eigenvalue of $ISI(G)$ with associated eigenvector $X = (x_1, x_2)^T$, then it is clear that $ISI(G)X = \tau X$. Moreover, it is easy to see that $ISI(G)X' = -\tau X'$, where $X' = (x_1, -x_2)^T$. This implies that the ISI-eigenvalues of a bipartite graph are symmetric about the origin.

Let $\sigma_i, i = 1, 2, \ldots, n$ be the singular values of the $n \times n$ matrix M. The *Frobenius norm* of M is defined by

$$\|M\|_F^2 = \sigma_1^2 + \sigma_2^2 + \cdots + \sigma_n^2.$$

The sum of the squares of the eigenvalues (Frobenius norm of a real symmetric matrix) of the ISI-matrix (Theorem 5, [17]) is

$$\|A_{ISI}(G)\|_F^2 = \sum_{i=1}^{n} \tau_i^2 = 2 \sum_{v_i v_j \in E(G)} \left(\frac{d_{v_i} d_{v_j}}{d_{v_i} + d_{v_j}} \right)^2 = 2R = Tr(A_{ISI}^2(G)), \tag{1}$$

where $R = \sum_{v_iv_j \in E(G)} \left(\frac{d_{v_i} d_{v_j}}{d_{v_i} + d_{v_j}} \right)^2$, and Tr is the trace of the the matrix.

The invariant $R = \sum_{v_iv_j \in E(G)} \left(\frac{d_{v_i} d_{v_j}}{d_{v_i} + d_{v_j}} \right)^2$ is an important parameter related to the ISI-matrix and is repeatedly used in our results. We establish sharp bounds for it.

Proposition 1. *Let G be a connected graph of order $n \geq 2$ with maximum degree Δ and minimum degree δ. Then, the following holds:*

(i)

$$\frac{m\delta^2}{4} \leq R \leq \frac{m\Delta^2}{4},$$

with equality if and only if G is regular.

(ii)

$$R \leq \frac{n\tau_1^2}{2(n-1)},$$

with the equality holding if and only if $G \cong K_n$.

(iii) Let G be a bipartite graph with $p \geq 1$ positive ISI-eigenvalues. Then,

$$R \geq p\tau_1^2,$$

with the equality holding if and only if G is a complete bipartite graph.

Proof. By the definition of R and Lemma 2.2 [20], for any edge $uv \in E(G)$, $\frac{\delta}{2} \leq \frac{d_u d_v}{d_u + d_v} \leq \frac{\Delta}{2}$, with the equality holding if and only if G is regular. Now, part (i) follows.

(ii). Applying the Cauchy–Schwarz inequality to the vector $(\tau_2, \tau_3, \ldots, \tau_n)$, we have

$$\tau_1^2 = 2R - \sum_{i=2}^{n} \tau_i^2 \leq 2R - \frac{1}{n-1} \left(\sum_{i=2}^{n} \tau_i \right)^2 = 2R - \frac{1}{n-1} \tau_1^2, \tag{2}$$

with the equality holding in (2) if and only if $\tau_2 = \tau_3 = \cdots = \tau_n$.

Thus, from the above, it follows that

$$R \leq \frac{n\tau_1^2}{2(n-1)}. \tag{3}$$

Suppose the equality holds in (3). Then, the equality holds in (2), which is possible if and only if $\tau_2 = \tau_3 = \cdots = \tau_n$, that is, G has two distinct ISI-eigenvalues. By Lemma 1, G is a complete graph.

(iii). Using $\tau_1^2 + \tau_2^2 + \cdots + \tau_n^2 = 2R$, the property that G has p positive ISI-eigenvalues and noting that G has a symmetric ISI-spectrum towards the origin (Remark 1), we have

$$2\left(\tau_1^2 + \tau_2^2 + \cdots + \tau_p^2\right) = 2R,$$

which implies that $R \geq p\tau_1^2$, with the equality holding if and only $p = 1$. By Lemma 2, G is a complete bipartite graph. □

The following two results on the ISI-energy of graphs in terms of the size m, the smallest degree δ and the smallest eigenvalue τ_n were given by Li, Ye and Broersma [21], (see Theorems 12 and 14).

Theorem 1 ([21], Theorem 12)**.** *Let G be a connected graph of order $n > 1$ with m edges and minimum degree δ. Then,*

$$\mathcal{E}_{ISI} \geq \delta\sqrt{m},$$

and the equality holds if and only if $G \cong K_{\frac{n}{2},\frac{n}{2}}$.

Theorem 2 ([21], Theorem 14)**.** *Let G be a connected graph of order $n > 1$ with m edges and minimum degree δ. Then,*

$$\mathcal{E}_{ISI} \geq |\tau_n| + \sqrt{m\delta^2 - 3\tau_n^2},$$

and the equality holds if and only if $G \cong K_{\frac{n}{2},\frac{n}{2}}$.

We restate Theorems 1 and 2 in terms of the invariant R and characterize the correct extremal graphs.

Theorem 3. *Let G be a connected graph of order $n \geq 2$. Then,*

$$\mathcal{E}_{ISI} \geq 2\sqrt{R},$$

with the equality holding if and only if G is the complete bipartite graph.

Theorem 4. *Let G be a connected graph of order $n \geq 2$ and τ_n be the smallest ISI-eigenvalue. Then,*

$$\mathcal{E}_{ISI} \geq |\tau_n| + \sqrt{4R - 3\tau_n^2}.$$

The equality holds if and only if G is either a complete bipartite or a complete tripartite graph.

We illustrate the above four theorems with the help of the following examples.

Ex.1 For $G \cong K_{3,5}$, the ISI-spectrum of G is $\{7.26184, 0^{[6]}, -7.26184\}$ and $\mathcal{E}_{ISI}(G) = 14.5237$. Theorem 1 gives $\mathcal{E}_{ISI}(G) \geq 3\sqrt{15} = 11.619$, Theorem 2 gives $\mathcal{E}_{ISI}(G) \geq |-7.26184| + \sqrt{15(3)^2 - 3(-7.26184)^2} = 7.26184 + \sqrt{-23.20296}$, which is imaginary, while Theorem 3 gives $\mathcal{E}_{ISI}(G) = 2\sqrt{(7.26184)^2} = 14.5237$ and Theorem 4 gives $\mathcal{E}_{ISI}(G) = |-7.26184| + \sqrt{4(7.26184)^2 - 3(-7.26184)^2} = 14.5237$.

Ex.2 For $G \cong K_{9,8}$, the ISI-spectrum of G is $\{35.93774, 0^{[15]}, -35.9377\}$ and $\mathcal{E}_{ISI}(G) = 71.8753$. Theorem 1 gives

$$\mathcal{E}_{ISI}(G) \geq 8\sqrt{72} = 67.8823,$$

Theorem 2 gives $\mathcal{E}_{ISI}(G) \geq |35.93774| + \sqrt{72(8)^2 - 3(35.93774)^2} = 63.0199$, Theorem 3 gives $\mathcal{E}_{ISI}(G) = 2\sqrt{(35.93774)^2} = 71.8753$ and Theorem 4 gives $\mathcal{E}_{ISI}(G) = |-35.937744| + \sqrt{4(35.93774)^2 - 3(-35.937744)^2} = 71.87537$.

Ex.3 For $G \cong K_{4,4,4}$, the ISI-spectrum of G is $\{32, 0^{[9]}, (-16)^{[2]}\}$ and $\mathcal{E}_{ISI}(G) = 64$. Theorem 1 gives $\mathcal{E}_{ISI}(G) \geq 8\sqrt{48} = 55.4256$, Theorem 2 gives $\mathcal{E}_{ISI}(G) \geq |-32| + \sqrt{48(8)^2 - 3(-16)^2} = 64$, while $R = 768$ Theorem 3 gives $\mathcal{E}_{ISI}(G) = 2\sqrt{768} = 55.4256$ and Theorem 4 gives $\mathcal{E}_{ISI}(G) = |-16| + \sqrt{4(768) - 3(-16)^2} = 64$.

Ex.4 For $G \cong CS_{5,3}$, the ISI-spectrum of G is $\{20.2893, 0^{[2]}, (-3.5)^{[4]}, -6.28925\}$ and $\mathcal{E}_{ISI}(G) = 40.5785$. Theorem 1 gives $\mathcal{E}_{ISI}(G) \geq 5\sqrt{25} = 25$, Theorem 2 gives $\mathcal{E}_{ISI}(G) \geq |-6.28925| + \sqrt{25(5)^2 - 3(-6.28925)^2} = 28.791$, with $R = 250.104$, Theorem 3 gives $\mathcal{E}_{ISI}(G) = 2\sqrt{250.104} = 31.6294$ and Theorem 4 gives

$$\mathcal{E}_{ISI}(G) = |-6.28925| + \sqrt{4(31.6294) - 3(-6.28925)^2} = 35.9836.$$

Ex.5 The graph obtained from K_ω and the path P_l by adding an edge between any vertex of K_ω and one end vertex of P_l is denoted by $PK_{\omega,l}$. It is known as a *path complete* graph or *kite graph*. The *pineapple* graph $P(\omega, n-\omega)$ is a graph obtained from K_ω by attaching $n-\omega$ pendent vertices at any vertex of K_ω. For $G \cong PK_{3,9}$, the ISI-spectrum of G is

$$\Big\{2.55192, 1.87374, 1.5389, 1.07415, 0.559209, 0.069339, -0.413158, -0.939312, -1,$$
$$-1.43693, -1.81746, -2.06039\Big\},$$

and $\mathcal{E}_{ISI}(G) = 15.3345$. Theorem 1 gives $\mathcal{E}_{ISI}(G) \geq 1\sqrt{12} = 3.4641$, Theorem 2 gives $\mathcal{E}_{ISI}(G) \geq |-2.06039| + \sqrt{12(1)^2 - 3(-2.06039)^2} = 2.06039 + \sqrt{-0.73562}$, which is imaginary. Moreover, $R = 12.7645$, Theorem 3 gives $\mathcal{E}_{ISI}(G) = 2\sqrt{12.7645} = 7.14547$ and Theorem 4 gives

$$\mathcal{E}_{ISI}(G) = |-2.06039| + \sqrt{4(12.7645) - 3(-2.06039)^2} = 8.25088.$$

From Ex. 1 and 2, any complete bipartite graph is extremal for Theorem 3 while the equality holds in Theorem 1, if and only if G is a regular bipartite graph. Moreover, from Ex. 4 and 5, Theorem 3 gives a better bound than Theorem 1. For regular graphs both bounds coincide. Form the above examples, and for irregular graphs, the bound of Theorem 3 is finer than that of Theorem 1. These were the two main reasons for introducing Theorem 3.

From Ex. 3, the equality holds for regular tripartite graphs for Theorem 2 and from Ex. 1 and 2, all bipartite graphs are extremal for Theorem 4, thereby giving large classes of graphs attaining the bound. Further, the lower bound of Theorem 4 is better than the lower bound given by Theorem 2. Moreover, from Ex. 1 and 5, the bound of Theorem 2 is imaginary. These were the reason for Theorem 4.

Next, we prove Theorems 3 and 4. For the sake of completeness, we write complete proofs and correct errors in the summation notation of Theorems 12 and 14 in [21].

Proof of Theorem 3. Since the trace of $A_{ISI}(G)$ is zero and from Equation (1), we have

$$0 = \left(\sum_{i=1}^{n} \tau_i\right)^2 = \sum_{i=1}^{n} \tau_i^2 + 2 \sum_{1 \leq i < j \leq n} \tau_i \tau_j.$$

Thus, it follows that $\sum_{i=1}^{n} \tau_i^2 = -2 \sum_{1 \leq i < j \leq n} \tau_i \tau_j = 2R$. Moreover, from the definition of the ISI-energy and the above information, we have

$$\begin{aligned} \big(\mathcal{E}_{ISI}(G)\big)^2 &= \sum_{i=1}^{n} \tau_i^2 + 2 \sum_{1 \leq i < j \leq n} |\tau_i||\tau_j| \\ &\geq \sum_{i=1}^{n} \tau_i^2 + 2 \left| \sum_{1 \leq i < j \leq n} \tau_i \tau_j \right| \\ &= 2 \sum_{i=1}^{n} \tau_i^2 = 4R. \end{aligned} \tag{4}$$

Therefore, we obtain

$$\mathcal{E}_{ISI}(G) \geq 2\sqrt{R}. \tag{5}$$

If $G \cong K_{a,b}$, $a + b = n$, then the ISI-spectrum (see, [18] Theorem 8) of $K_{a,b}$ is

$$\left\{\frac{(ab)^{\frac{3}{2}}}{n}, 0^{[n-2]}, \frac{(ab)^{\frac{3}{2}}}{n}\right\}.$$

Clearly, $2R = \left(\frac{(ab)^{\frac{3}{2}}}{n}\right)^2 + \left(-\frac{(ab)^{\frac{3}{2}}}{n}\right)^2$ and it implies that $\sqrt{R} = \frac{(ab)^{\frac{3}{2}}}{n}$. Thus, $\mathcal{E}_{ISI}(K_{a,b}) = 2\frac{(ab)^{\frac{3}{2}}}{n} = 2\sqrt{R}$ and the equality holds in (5) for $G \cong K_{a,b}$.

Conversely, if the equality holds in (5), then the equality holds in (4), that is

$$\sum_{1\le i<j\le n}|\tau_i||\tau_j| = \left|\sum_{1\le i<j\le n}\tau_i\tau_j\right|. \tag{6}$$

Since G is connected, by the Perron–Frobenius theorem $\tau_1 > 0$, and we have the following cases:

Case 1. Clearly, $\tau_1 \neq 0$ and $\tau_2 = \tau_3 = \cdots = \tau_n = 0$ satisfies (6), but this cannot happen, since the trace of $A_{ISI}(G)$ is zero.
Case 2. The second option is that the ISI-spectrum $\{\tau_1, \underbrace{0, 0, \ldots, 0}_{n-2}, -\tau_n\}$ satisfies (6). By Lemma 2, $\{\tau_1, \underbrace{0, 0, \ldots, 0, 0}_{n-2}, -\tau_n\}$ is the ISI-spectrum of the complete bipartite graph.
Case 3. If the ISI-spectrum of G is $\{\tau_1, 0, 0, \ldots, 0, -\tau_{n-1}, -\tau_n\}$, then (6) implies that

$$\tau_1\tau_{n-1} + \tau_1\tau_n + \tau_{n-1}\tau_n = |-\tau_1\tau_{n-1} - \tau_1\tau_n + \tau_{n-1}\tau_n|,$$

which cannot happen if $\tau_1 \neq \tau_{n-1} \neq \tau_n$. However, if $\tau_1 \neq \tau_{n-1} = \tau_n$, then $\tau_1 = -2\tau_n$ and from the above we get $\tau_n = 0$, which cannot happen, since G is a connected graph. Similarly, for graphs having more than three nonzero ISI-eigenvalues, (6) cannot hold unless zero is an ISI-eigenvalue of G with multiplicity $n-2$. Thus, the equality holds in (6) and hence in (5), if and only if $G \cong K_{a,b}$. □

Proof of Theorem 4. For the sake of completeness and to modify notation errors in the proof of Theorem 2 (Theorem 14 [21]), we rewrite the proof and correct its equality cases.

Since the sum of the ISI-eigenvalues of G is zero, we have

$$\tau_n^2 = \left(\sum_{i=1}^{n-1}\tau_i\right)^2 = \sum_{i=1}^{n-1}\tau_i^2 + 2\sum_{1\le i<j\le n-1}\tau_i\cdot\tau_j,$$

and

$$\left(\sum_{i=1}^{n-1}|\tau_i|\right)^2 = \sum_{i=1}^{n-1}\tau_i^2 + 2\sum_{1\le i<j\le n-1}|\tau_i|\cdot|\tau_j|.$$

Moreover, by noting that $\tau_1^2 + \tau_2^2 + \cdots + \tau_{n-1}^2 + \tau_n^2 \geq 2\tau_n^2$ always holds with equality if and only if $G \cong K_{a,b}$, we have

$$\begin{aligned}\left(\mathcal{E}_{MS}(G) - |\tau_n|\right)^2 = \left(\sum_{i=1}^{n-1}|\tau_i|\right)^2 &= \sum_{i=1}^{n-1}\tau_i^2 + 2\sum_{1\le i<j\le n-1}|\tau_i|\cdot|\tau_j| \\ &\geq \sum_{i=1}^{n-1}\tau_i^2 + \left|2\sum_{1\le i<j\le n-1}\tau_i\cdot\tau_j\right| \\ &= \sum_{i=1}^{n-1}\tau_i^2 + \left|\tau_n^2 - \sum_{i=1}^{n-1}\tau_i^2\right| = \sum_{i=1}^{n-1}\tau_i^2 + \left|2\tau_n^2 - \sum_{i=1}^{n}\tau_i^2\right| \\ &= 2\sum_{i=1}^{n}\tau_i^2 - 3\tau_n^2 = 4R - 3\tau_n^2.\end{aligned} \tag{7}$$

Thus, we get

$$\mathcal{E}_{ISI}(G) \geq |\tau_n| + \sqrt{4R - 3\tau_n^2}. \tag{8}$$

The equality holds in (8) if and only if the equality holds in (7), that is

$$2\sum_{1\le i<j\le n-1}|\tau_i|\cdot|\tau_j| = \left|2\sum_{1\le i<j\le n-1}\tau_i\cdot\tau_j\right|. \tag{9}$$

Since G is connected, we consider the following possibilities:

The first possibility that satisfies (9) is that $\tau_1 > 0$ and $\tau_2 = \tau_3 = \cdots = \tau_{n-1} = 0$. It follows that $\tau_1 = -\tau_n$, since $\sum_{i=1}^{n} \tau_i = 0$. That is, the ISI-spectrum of G is symmetric towards the origin, so G is bipartite and by Lemma 2, G is the complete bipartite graph.

Conversely, $\mathcal{E}_{ISI}(K_{a,b}) = 2\tau_1 = |\tau_n| + \sqrt{4\tau_1^2 - 3\tau_n^2}$, since $\tau_1 = |\tau_n|$, so the equality holds if and only if $G \cong K_{a,b}$.

The second possibility that satisfies (9) is that $\tau_1 > 0, \tau_2 = \cdots = \tau_{n-2} = 0$, and $-\tau_{n-1} \neq 0$. In this case,

$$2\tau_1\tau_{n-1} = 2\sum_{1\le i<j\le n-1} |\tau_i|\cdot|\tau_j| = \left|2\sum_{1\le i<j\le n-1} \tau_i\cdot\tau_j\right| = |2\tau_1(-\tau_{n-1})| = 2\tau_1\tau_{n-1}.$$

Thus, the ISI-spectrum of G is

$$\Big\{\tau_1, \underbrace{0, 0, \ldots, 0, 0}_{n-3}, -\tau_{n-1}, -\tau_n\Big\}. \tag{10}$$

Next, we show that (10) is the ISI-spectrum of the complete tripartite graph. Let

$$\{u_1, u_2, \ldots, u_{a-1}, u_a, v_1, v_2, \ldots, v_{b-1}, v_b, w_1, w_2, \ldots, w_{c-1}, w_c\},$$

be the vertex labelling of the complete tripartite graph $G \cong K_{a,b,c}, (a+b+c=n)$. With this labelling, $d_{u_i} = b + c = n - a, d_{v_j} = a + c = n - b$, and $d_{w_k} = a + b = n - c$, for $i = 1, 2, \ldots, a$ $j = 1, 2, \ldots, b$ and $k = 1, 2, \ldots, c$. The ISI-matrix of G is

$$A_{ISI}(G) = \begin{pmatrix} \mathbf{0}_a & \frac{d_{u_1}d_{v_1}}{d_{u_1}+d_{v_1}}J_{a\times b} & \frac{d_{u_1}d_{w_3}}{d_{u_1}+d_{w_2}}J_{a\times c} \\ \frac{d_{u_1}d_{v_1}}{d_{u_1}+d_{v_1}}J_{b\times a} & \mathbf{0}_b & \frac{d_{v_1}d_{w_1}}{d_{v_1}+d_{w_1}}J_{b\times c} \\ \frac{d_{u_1}d_{w_1}}{d_{u_1}+d_{w_1}}J_{c\times a} & \frac{d_{v_1}d_{w_1}}{d_{v_1}+d_{w_1}}J_c & \mathbf{0}_{c\times c} \end{pmatrix}, \tag{11}$$

where $\mathbf{0}$ is the zero matrix and J is the matrix of all ones. For $i = 2, 3 \ldots, a$, $J = 2, 3, \ldots, b$ and $k = 2, 3, \ldots, c$, consider the following vectors

$$X_{i-1} = \Big(-1, x_{i2}, x_{i3}, \ldots, x_{ia}, \underbrace{0, 0, \ldots, 0, 0}_{n-a}\Big) \qquad \text{where } x_{il} = \begin{cases} 1 & \text{if } i = l \\ 0 & \text{otherwise} \end{cases},$$

$$Y_{i-1} = \Big(\underbrace{0, 0, \ldots, 0, 0}_{a}, -1, y_{j2}, x_{j3}, \ldots, x_{jb}, \underbrace{0, 0, \ldots, 0, 0}_{c}\Big) \qquad \text{where } y_{il} = \begin{cases} 1 & \text{if } j = l \\ 0 & \text{otherwise} \end{cases},$$

$$Z_{i-1} = \Big(\underbrace{0, 0, \ldots, 0, 0}_{n-c}, -1, z_{k2}, z_{k3}, \ldots, z_{kc}\Big) \qquad \text{where } z_{il} = \begin{cases} 1 & \text{if } k = l \\ 0 & \text{otherwise} \end{cases}.$$

Clearly,

$$A_{ISI}(G)X_1 = \Big(\underbrace{0, 0, \ldots, 0}_{a}, \underbrace{\frac{d_{u_1}d_{v_1}}{d_{u_1}+d_{v_1}} - \frac{d_{u_1}d_{v_1}}{d_{u_1}+d_{v_1}}, \ldots, \frac{d_{u_1}d_{v_1}}{d_{u_1}+d_{v_1}} - \frac{d_{u_1}d_{v_1}}{d_{u_1}+d_{v_1}}}_{b},$$
$$\underbrace{\frac{d_{u_1}d_{w_3}}{d_{u_1}+d_{w_2}} - \frac{d_{u_1}d_{w_3}}{d_{u_1}+d_{w_2}}, \ldots, \frac{d_{u_1}d_{w_3}}{d_{u_1}+d_{w_2}} - \frac{d_{u_1}d_{w_3}}{d_{u_1}+d_{w_2}}}_{c}\Big) = 0X_1.$$

Similarly, $X_2, \ldots, X_{a-1}, Y_1, Y_2, \ldots, Y_{b-1}$ and $Z_1, Z_2, \ldots, Z_{c-1}$ are the eigenvectors corresponding to the eigenvalue zero. Thus, zero is the ISI-eigenvalue of G with multiplicity $n - 3$. The remaining three ISI-eigenvalues of G are the eigenvalues of the following equitable quotient matrix (see, Section 2.3 [8])

$$A_Q = \begin{pmatrix} 0 & b\frac{d_{u_1}d_{v_1}}{d_{u_1}+d_{v_1}} & c\frac{d_{u_1}d_{w_1}}{d_{u_1}+d_{w_1}} \\ a\frac{d_{u_1}d_{v_1}}{d_{u_1}+d_{v_1}} & 0 & c\frac{d_{v_1}d_{w_1}}{d_{v_1}+d_{w_1}} \\ a\frac{d_{u_1}d_{w_1}}{d_{u_1}+d_{w_1}} & b\frac{d_{v_1}d_{w_1}}{d_{v_1}+d_{w_1}} & 0 \end{pmatrix}. \quad (12)$$

The determinant of Matrix (12) is

$$\frac{2abc(a+b)^2(a+c)^2(b+c)^2}{(2a+b+c)(a+2b+c)(a+b+2c)} > 0,$$

and it has one positive eigenvalue τ_1 (Perron–Frobenius theorem) and two negative eigenvalues τ_{n-1}, τ_n, since it has a positive determinant and $Tr(A_Q) = 0$. Conversely, $\mathcal{E}_{ISI}(G) = \tau_1 + |-\tau_{n-1}| + |-\tau_n| = \tau_1 + \tau_{n-1} + \tau_n$ and with $\tau_1 = \tau_{n-1} + \tau_n$, Equation (8) gives $\mathcal{E}_{ISI}(G) = |\tau_n| + \sqrt{2(\tau_1^2 + \tau_{n-1}^2 + \tau_n^2) - 3\tau_n^2} = \tau_n + \sqrt{(\tau_n + 2\tau_{n-1})^2} = \tau_1 + \tau_{n-1} + \tau_n = \mathcal{E}_{ISI}(G)$. Thus, the equality holds if and only if G is the complete tripartite graph. □

3. Regressions Models and Applications to Anticancer Drugs

We carried out a statistical study to compare the correlation of physicochemical properties and the ISI-index (energy) with the chemical structures of anticancer drugs. For the regression models, we considered the most used: linear, logarithmic and quadratic. The picture below displays the molecular structures of various anticancer drugs. Their graph structures can be similarly considered (taking atoms as vertices).

The regression model (linear, logarithmic and quadratic) were

$$P = a + b(ISI/\mathcal{E}_{ISI}), \quad P = a\,ln((ISI/\mathcal{E}_{ISI})) + b, \quad P = (ISI/\mathcal{E}_{ISI})^2 + a(ISI/\mathcal{E}_{ISI}) + b,$$

where a, b are constants, and P is the physical property of an anticancer drug. Now, the different linear models' rounded equations for the ISI-index and the ISI-energy against physical property of anticancer drug were as follows:

$$BP = 12.225ISI + 199.18 \; BP = 10.963\mathcal{E}_{ISI} + 193.25 \; Mp = 4.0977ISI + 88.944$$
$$MP = 3.7228\mathcal{E}_{ISI} + 85.585 \; E = 1.5276ISI + 41.632 \; E = 1.3656\mathcal{E}_{ISI} + 41.12$$
$$MR = 2.2757ISI + 23.916 \; MR = 2.0834\mathcal{E}_{ISI} + 21.351$$

The scattering of anticancer drugs against their physical properties with the ISI-index and the ISI-energy via the linear regression model are given in Figure 2.

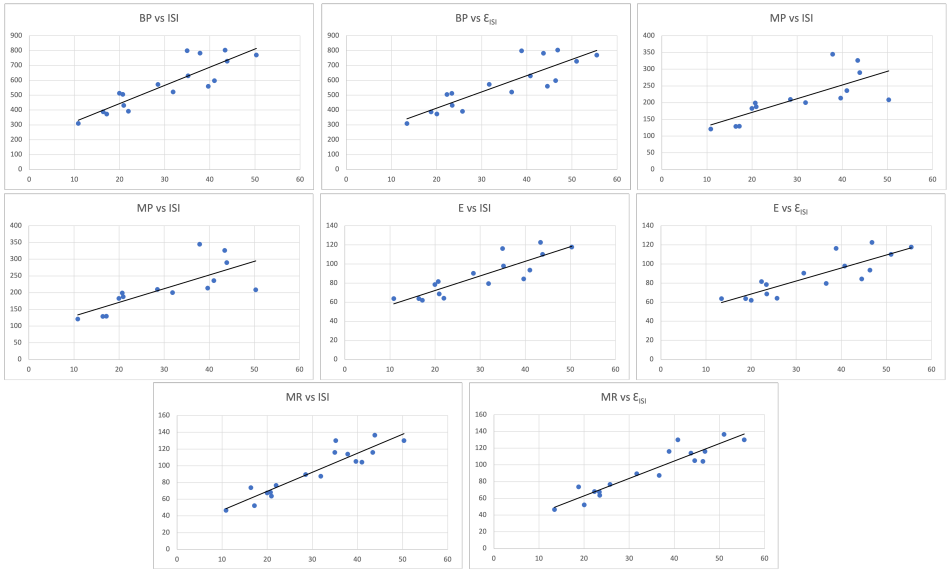

Figure 2. Linear Regression for Physical Property with the ISI-index and $\mathcal{E}_{ISI}$ of Anticancer Drugs.

The different logarithmic model rounded equations for the ISI-index and the ISI-energy against the physical property of anticancer drug were as follows:

$$BP = 329.26ln(ISI) - 527.09, BP = 340.56ln(\mathcal{E}_{ISI}) - 609.11, MP = 114.52ln(ISI) - 166.94$$
$$MP = 119.36ln(\mathcal{E}_{ISI}) - 198.38, E = 40.05ln(ISI) - 45.442, E = 41.45ln(\mathcal{E}_{ISI}) - 55.445$$
$$MR = 60.872ln(ISI) - 109.88, MR = 64.041ln(\mathcal{E}_{ISI}) - 128.78$$

The scattering of anticancer drugs with their physical properties against the ISI-index and the ISI-energy via the logarithmic regression model are given in Figure 3.

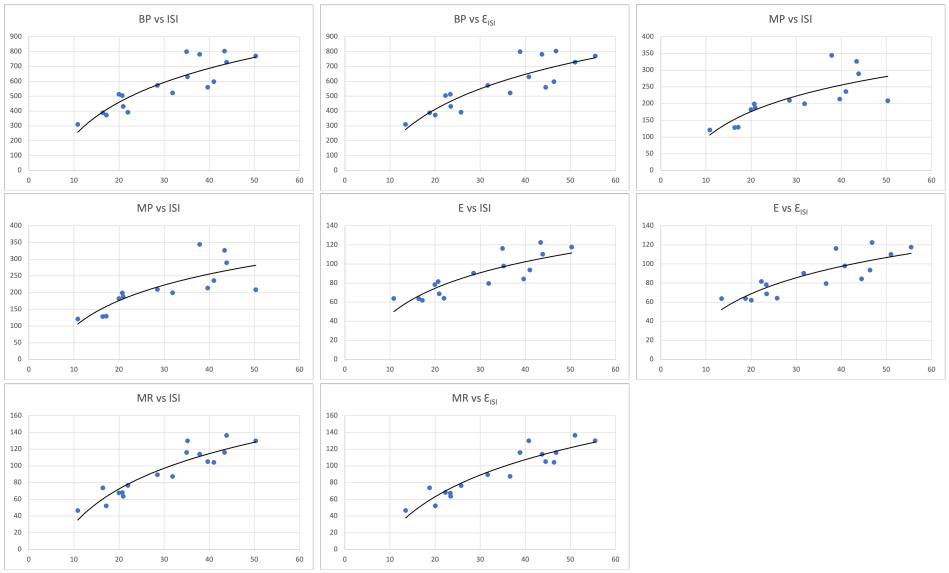

Figure 3. Logarithmic Regression for Physical Property with the ISI-index and $\mathcal{E}_{ISI}$ of Anticancer Drugs.

The different quadratic model rounded equations for the ISI-index and the ISI-energy against physical property of anticancer drug were as follows:

$$BP = -0.1409(ISI)^2 + 20.746ISI + 88.239, \quad BP = -0.1285\mathcal{E}_{ISI}^2 + 19.757\mathcal{E}_{ISI} + 62.688$$
$$MP = -0.1681(ISI)^2 + 14.311ISI - 41.582, \quad MP = -0.1428\mathcal{E}_{ISI}^2 + 13.534\mathcal{E}_{ISI} - 57.478$$
$$E = 0.0044(ISI)^2 + 1.2623ISI + 45.087, \quad E = 0.0015\mathcal{E}_{ISI}^2 + 1.2624\mathcal{E}_{ISI} + 42.653$$
$$MR = -0.0206(ISI)^2 + 3.5246ISI + 7.6566, \quad MR = -0.0132\mathcal{E}_{ISI}^2 + 2.9881\mathcal{E}_{ISI} + 7.9192$$

The graphical representation of anticancer drugs with their physical properties against the ISI-index and the ISI-energy in the quadratic regression model are given in Figure 4.

The following table (Table 1) gives the physical entities along with the ISI-index and the ISI-energy. The BP, MP, E and MR were taken from [5]. The ISI-index and the ISI-energy of these anticancer drugs were calculated by Wolfram Mathematica.

The following tables displays the correlation coefficient of the physicochemical properties of the anticancer drugs with the ISI-index and the ISI-energy.

From Table 2, it can be seen that the ISI-index showed a higher significant correlation when compared with other physicochemical properties, while the ISI-energy showed a better significant correlation than that of the ISI-index when compared with other physicochemical properties.

From Table 3, the coefficient of determination (R^2) was again better for the molar refraction MR; however, R^2 was higher for the ISI-energy than for the ISI-index for the molar refraction of the anticancer drugs.

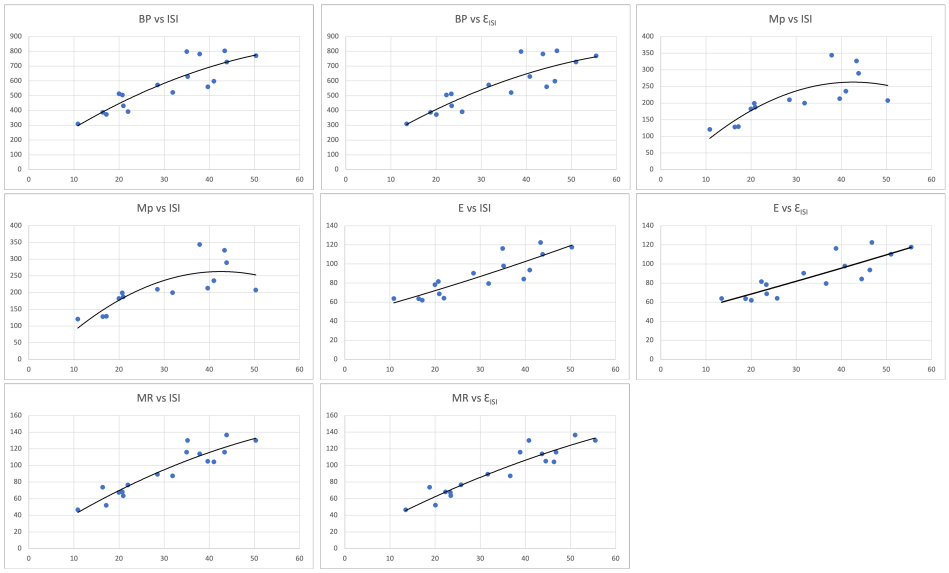

Figure 4. Logarithmic Regression for Physical Property with the ISI-index and $\mathcal{E}_{ISI}$ of Anticancer Drugs.

Table 1. Various Anticancer Drugs with their Physicochemical Properties and the ISI-Index (Energy) of their Chemical Structures.

Drugs	BP	MP	E	MR	$ISI(G)$	$\mathcal{E}_{ISI}(G)$
Amathaspiramide E	572.7	209.72	90.3	89.4	28.5119	31.6741
Aminopterin	782.27	344.45		114	37.85	43.6952
Aspidostomide E	798.8		116.2	116	34.9667	38.8268
Carmustine	309.6	120.99	63.8	46.6	10.85	13.4524
Caulibugulone E	373	129.46	62	52.2	17.1667	20.0501
Convolutamide A	629.9		97.9	130.1	35.1786	40.7735
Convolutamine F	387.7	128.67	63.7	73.8	16.3833	18.7833
Convolutamydine A	504.9	199.2	81.6	68.2	20.7119	22.2929
Daunorubicin	770	208.5	117.6	130	50.2976	55.4943
Deguelin	560.1	213.39	84.3	105.1	39.65	44.5048
Melatonin	512.8	182.51	78.4	67.6	19.9667	23.3733
Minocycline	803.3	326.3	122.5	116	43.3929	46.805
Perfragilin A	431.5	187.62	68.7	63.6	20.9167	23.4653
Podophyllotoxin	597.9	235.86	93.6	104.3	41	46.3479
Pterocellin B	521.6	199.88	79.5	87.4	31.8667	36.6356
Raloxifene	728.2	289.58	110.1	136.6	43.85	51.0142
Tambjamine K	391.7		64.1	76.6	21.9667	25.7574

Table 2. Correlation Coefficients of Anticancer Drugs with the ISI-Index (Energy) of their Chemical Structures.

Invariant	BP	MP	E	MR
$ISI(G)$	0.875742866	0.751128121	0.870072771	0.927336169
$\mathcal{E}_{ISI}(G)$	0.865394398	0.752558075	0.853707593	0.935499557

From Tables 2 and 3 along with the pictures, it can be concluded that the correlations of all the physicochemical properties of anticancer drugs with the ISI-index (energy) were highly significant. Further, the study implied that these anticancer drugs may be considered for designing new drugs using the ISI-index (energy) and other related topological indices. As the regression analysis showed a high correlation of the ISI-index (energy) for these drugs, their combination may be considered for novel drugs.

Table 3. R^2 of Anticancer Drugs with the ISI-Index (Energy) of their Chemical Structures.

Linear regression				
Invariant	BP	MP	E	MR
$ISI(G)$	0.7669	0.7489	0.757	0.86
$\mathcal{E}_{ISI}(G)$	0.7489	0.5663	0.7288	0.8752
Logarithmic regression				
Invariant	BP	MP	E	MR
$ISI(G)$	0.7672	0.6064	0.7141	0.8484
$\mathcal{E}_{ISI}(G)$	0.7553	0.6066	0.6994	0.8642
Quadratic regression				
Invariant	BP	MP	E	MR
$ISI(G)$	0.777	0.6497	0.7576	0.867
$\mathcal{E}_{ISI}(G)$	0.7599	0.6454	0.7289	0.8789

4. Conclusions

This study showed that the physicochemical properties of anticancer drugs can be treated by certain topological indices such as the ISI-index and the ISI-energy in this report. We observed that the physical and chemical properties of anticancer drugs were well correlated with such topological indices. Moreover, this work implied that these anticancer drugs may be utilized for further study by pharmacists and chemists in designing new drugs, using the concept of these topological indices. The more correlated drugs may have a better impact on the treatment of cancer. For a better treatment of cancer, a future study may be carried out by interdisciplinary researchers as a joint venture.

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Conflicts of Interest: The authors declare no conflict of interest.

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