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Regression Analysis of Topological Indices and Physicochemical Properties of Polymer-Based Anticancer Drugs

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Abstract

The research analyzed the quantitative correlation between topological indices and the physicochemical properties of selected anticancer compounds using regression analysis. Various topological descriptors—such as the First Zagreb Index, Second Zagreb Index, and Forgotten Index were calculated and regressed against key molecular features, including polar surface area, melting point, and molar refractivity. The regression analysis revealed linear correlations between these topological indices and the properties of anticancer drugs, with particularly strong associations observed for degree-based indices. The study demonstrates that graph-theoretical indices can effectively predict molecular behavior, offering valuable insights for evaluating the structure of anticancer agents. Overall, the research presents a computational tool that is both useful and cost-effective for drug discovery and development, providing a practical method for estimating relevant molecular properties without the need for time-consuming experimental procedures. This computational strategy enhances the efficiency of drug design by allowing researchers to forecast properties early in the development process, thereby accelerating the discovery of new therapeutic agents. This work underscores the significance of topological indices in pharmaceutical engineering, particularly in the design and development of anticancer drugs. Use of such indices not only simplifies the drug development process but also deepens the understanding of molecular structures and their efficacy. The findings support the use of topological indices as a foundational element in pharmaceutical research and drug design. Incorporating these indices into the drug design pipeline can substantially improve the predictive accuracy for molecular behavior, leading to more effective and targeted cancer therapies and, ultimately, better patient outcomes in the context of personalized medicine.

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INTRODUCTION

Topological indices on polymers are crucial for understanding their chemical properties and potential applications in various fields, including drug manufacturing and biomedicine. These indices provide a theoretical framework that can enhance the design and efficacy of new pharmaceutical products, particularly in the development of smart polymers for anticancer applications. Recent advancements in the study of topological indices can significantly influence the effectiveness of drug delivery systems utilizing smart polymers. Consequently,

integrating these indices into the design process can lead to more effective and targeted drug delivery solutions, enhancing patient outcomes in cancer treatment. The ongoing research in this area emphasizes the importance of these indices in optimizing drug formulations and improving therapeutic efficacy in cancer therapies. Topological indices have emerged as a pivotal tool in the study of polymers, particularly in relation to their chemical properties and potential applications across various sectors, including drug manufacturing and bio-medicine. These indices offer a theoretical framework that not only aids in the understanding of polymer characteristics but also enhances the design and efficacy of novel pharmaceutical products. This is especially pertinent in the realm of smart polymers, which are increasingly being explored for their applications in anticancer therapies. Recent advancements in the analysis of topological indices have the potential to revolutionize drug delivery systems that utilize these innovative materials. By integrating topological indices into the design process, researchers can develop more effective and targeted drug delivery solutions, ultimately improving patient outcomes in cancer treatment. The ongoing research in this domain underscores the critical role that topological indices play in optimizing drug formulations and enhancing therapeutic efficacy in cancer therapies, marking a significant step forward in the intersection of polymer science and medical innovation.

Degree-based topological indices are numerical values derived from the structure of a molecule, specifically focusing on the degrees of the vertices (atoms) in a graph representation of the molecule. These indices are used to quantify the connectivity and arrangement of atoms within a polymer or other chemical compounds [1]. The degree of a vertex is defined as the number of edges bonds connected to it, and degree-based indices typically incorporate these values to provide insights into the chemical properties and behaviors of the substance. Common examples of degree-based topological indices include the Wiener index, which is based on the distances between pairs of vertices, and the Zagreb indices, which consider the sum of the degrees of the vertices. These indices are particularly useful in polymer science and medicinal chemistry for predicting the biological activity, stability, and reactivity of polymers, aiding in the design of new materials and drug delivery systems.

The paper focuses on QSPR modeling of antiviral drugs like Remdesivir and Favipiravir using degree-based topological descriptors, but it does not specifically address cytomegalovirus drugs or their degree-based topological indices. Moreover, the application of degree-based topological indices extends beyond polymers to various classes of drugs, including anticancer agents, enhancing our understanding of their molecular interactions and therapeutic potential. This broader application underscores the versatility of degree-based topological indices in drug design, particularly for optimizing the efficacy of anticancer therapies and other medicinal compounds. This versatility is crucial, as it allows researchers to tailor drug properties based on specific molecular structures, ultimately leading to improved therapeutic outcomes in cancer treatment. A Study on Degree-Based Topological Indices and M-Polynomial Used in Cancer Treatment," 2024. The integration of degree-based topological indices in drug design not only enhances the understanding of molecular interactions but also facilitates the development of more effective anticancer therapies. This integration can significantly streamline the drug discovery process, enabling the identification of promising candidates more efficiently and effectively. Furthermore, the ongoing exploration of degree-based indices in various drug classes highlights their potential to inform the design of innovative therapeutic agents, ultimately advancing the field of medicinal chemistry. Incorporating degree-based topological indices into the drug development process can lead to significant advancements in the design of targeted therapies, particularly in the realm of anticancer treatments [12]. This approach not only optimizes drug efficacy but also aligns with the growing emphasis on personalized medicine in oncology [3–4]. This alignment with personalized medicine is essential, as it allows for tailored treatment strategies that consider individual patient characteristics and tumor profiles, ultimately improving therapeutic outcomes in oncology.

POLYMER RELATED ANTICANCER DRUGS

Polymer-related anticancer drugs are innovative therapeutic agents that utilize the unique properties of polymers to enhance drug delivery and efficacy in cancer treatment.

Smart Polymers: These are polymers that can respond to specific stimuli such as pH, temperature, or light and are designed to release their drug payloads in a controlled manner, targeting cancer cells more effectively while minimizing side effects on healthy tissues [11].

(i) **Nanoparticle Formulations:** Polymers can be used to create nanoparticles that encapsulate anticancer drugs. This approach improves the solubility of poorly soluble drugs, enhances their stability, and allows for targeted delivery to tumor sites, thus increasing therapeutic efficacy.

(ii) **Polymer-Drug Conjugates:** These involve the covalent attachment of anticancer drugs to polymer carriers. This method can improve the pharmacokinetics of the drug, allowing for prolonged circulation time in the bloodstream and reduced toxicity.

(iii) **Biodegradable Polymers:** Using biodegradable polymers for drug delivery systems ensures that the carrier material is safely broken down in the body after delivering the drug, reducing the risk of long-term toxicity.

Topological Indices in design is the integration of degree-based topological indices in the design of polymeric anticancer drugs can help researchers predict the biological activity and optimize the molecular structure for better therapeutic outcomes [6]. These indices provide insights into the connectivity and arrangement of atoms, which can influence the drug's effectiveness [7]. The Polymer-Based Anticancer Drugs are

- Doxil is a liposomal formulation of doxorubicin that uses a polymeric liposome to enhance delivery to tumors [8].
- Abraxane is a nanoparticle albumin-bound formulation of paclitaxel that improves solubility and delivery [9,10].
- Onivyde is a liposomal formulation of irinotecan used for pancreatic cancer treatment.
- Marqibo is a liposomal formulation of vincristine that is used in certain types of leukemia and lymphoma.

Ongoing research is focused on optimizing polymeric drug formulations through the use of topological indices and other computational methods to enhance the design of targeted therapies for various types of cancer. In summary, polymer-related anticancer drugs represent a promising area of research, leveraging the unique properties of polymers to improve drug delivery, enhance efficacy, and reduce side effects in cancer therapies. The incorporation of topological indices in their design process further enhances the potential for developing innovative therapeutic agents. The continuous exploration of polymer-based drug delivery systems is vital for advancing cancer therapies, as they offer innovative strategies to improve treatment efficacy and patient outcomes. These drugs utilize the unique properties of polymers to enhance drug delivery and efficacy in cancer treatment. The ongoing development of polymer-related anticancer drugs illustrates the potential of innovative drug delivery systems to transform cancer treatment strategies. The continuous innovation in polymer-based drug delivery systems is crucial for addressing the limitations of conventional cancer therapies, ultimately leading to more effective treatments and improved patient outcomes. The advancements in polymer-related anticancer drugs, such as Abraxane, highlight the significance of innovative drug delivery systems in enhancing therapeutic efficacy and patient outcomes in cancer treatment by Hama *et al*., and Miele *et al*. The exploration of polymer-based drug delivery systems continues to be a vital area of research, aiming to overcome the challenges faced by traditional cancer therapies and improve therapeutic efficacy. This ongoing research highlights the transformative potential of polymer-based drug delivery systems in overcoming the limitations of conventional therapies, ultimately paving the way for more effective cancer treatments. The future of cancer treatment lies in the continued development and optimization of polymer-based drug delivery systems, which promise to enhance the precision and efficacy of therapies while minimizing adverse effects. The integration of innovative polymer-based strategies in cancer treatment is essential to address the limitations of conventional therapies, enhancing both efficacy and patient safety. The evolution of polymer-based drug delivery systems exemplifies a

significant shift in cancer treatment paradigms, emphasizing the need for innovative approaches to enhance therapeutic efficacy and patient safety [2]. Moreover, the ongoing research into polymer-drug conjugates and their applications in cancer therapy highlights the potential for these innovative systems to significantly improve treatment outcomes and patient quality of life [5,6]. The future of cancer treatment will increasingly rely on these advanced polymer-based systems to tailor therapies to individual patient needs and improve overall treatment efficacy.

ANTICANCER DRUGS ON TOPOLOGICAL INDICES

Liposomal Delivery System is the Doxil utilizes a lipid-based nanoparticle to encapsulate doxorubicin, enhancing the drug's delivery to tumor sites while minimizing exposure to healthy tissues. The liposomal formulation allows for more targeted delivery of the drug to cancer cells, which improves therapeutic efficacy and reduces side effects associated with traditional doxorubicin administration. Doxil has a longer circulation time in the bloodstream compared to conventional doxorubicin, allowing for sustained drug action and reduced toxicity. The liposomal formulation helps to lower the risk of cardiotoxicity, a common side effect associated with doxorubicin, making it safer for patients, especially those with pre-existing heart conditions. Doxil is commonly used to treat various cancers, including breast cancer, ovarian cancer, and multiple myeloma. Doxorubicin works by intercalatingDNA, inhibiting DNA replication, and inducing apoptosis in cancer cells. Doxil is administered intravenously, and its liposomal nature allows for a more controlled release of the drug. While Doxil is associated with fewer side effects than traditional doxorubicin, potential side effects can still include hand-foot syndrome, nausea, fatigue, and myelosuppression. Overall, Doxil represents a significant advancement in cancer chemotherapy, leveraging the unique properties of liposomal technology to improve drug delivery and patient safety. The innovative design of Doxil exemplifies the critical role of liposomal formulations in enhancing drug delivery efficacy and minimizing adverse effects in cancer therapies by Barenholz, 202 and Martin. Abraxane is a nanoparticle albumin-bound formulation of paclitaxel, designed to enhance the delivery and efficacy of the drug in cancer treatment. Abraxane utilizes a unique nanoparticle technology that binds paclitaxel to albumin, allowing for improved solubility and stability of the drug. The albumin-bound particles facilitate targeted delivery to tumor sites, enhancing the concentration of paclitaxel in cancer tissues while minimizing exposure to healthy cells. Abraxane has a longer circulation time in the bloodstream compared to traditional paclitaxel formulations, which allows for sustained drug action and potentially better therapeutic outcomes. The formulation helps to reduce the risk of hypersensitivity reactions and other side effects commonly associated with conventional paclitaxel, making it safer for patients. Abraxane is approved for the treatment of various cancers, including metastatic breast cancer, non-small cell lung cancer, and pancreatic cancer. Paclitaxel works by inhibiting microtubule depolymerization, which disrupts cell division and induces apoptosis in cancer cells. Abraxane is administered intravenously, and its formulation allows for a more controlled and efficient release of the drug. While Abraxane is associated with fewer side effects than traditional paclitaxel, potential side effects can still include neutropenia, anemia, nausea, fatigue, and peripheral neuropathy.

Abraxane represents a significant advancement in cancer chemotherapy, leveraging innovative nanoparticle technology to improve drug delivery and patient safety. The advancements in polymer-based drug delivery systems, such as Abraxane, demonstrate the potential of innovative formulations to significantly enhance therapeutic efficacy and patient outcomes in cancer treatment. Continued research in this area is essential for overcoming existing limitations in conventional therapies and optimizing treatment strategies. Onivyde is a liposomal formulation of irinotecan, specifically designed for the treatment of pancreatic cancer. Onivyde highlights their potential to enhance the therapeutic index of chemotherapeutic agents, ultimately improving patient outcomes in oncology by Zhang. Paclitaxel has a taxane core structure, which is a bicyclic structure with a four-ring system. It contains various side chains, including a phenylisoserine side chain and an acetyl group, which are crucial for its biological activity.

METHODOLOGY

The molecular structure of anticancer drugs are seen in this section

The anticancer drugs from the Fig. 1 to Fig. 4 were taken from the pubchem. The first zagreb index, second zagreb index and forgotten index values and their physico chemical properties are shown in Table 1.

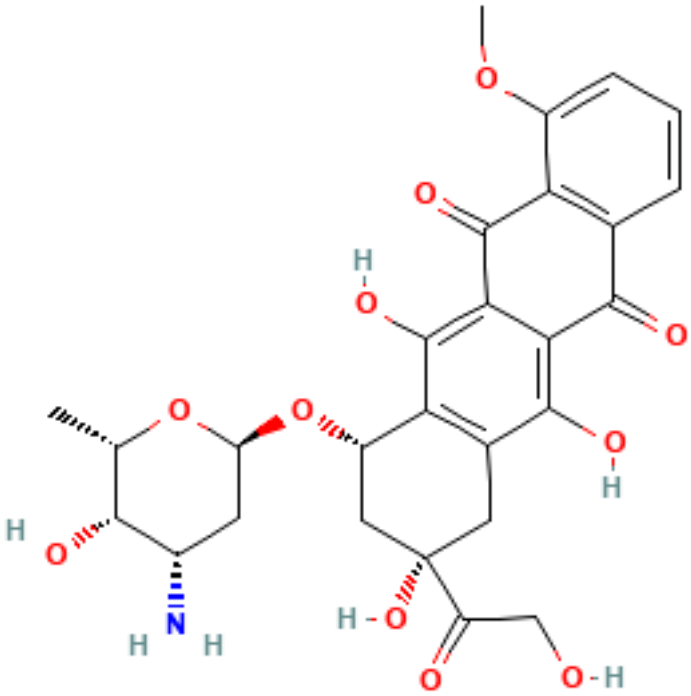

Figure 1. The chemical structure of Doxil

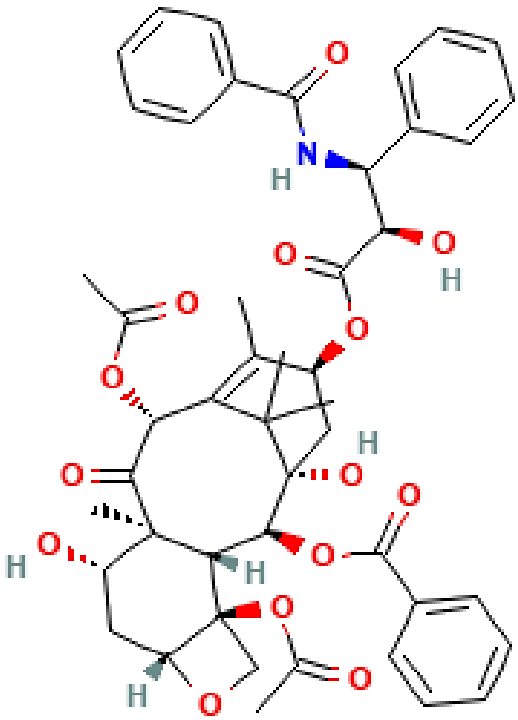

Figure 2. The chemical structure of Abraxane

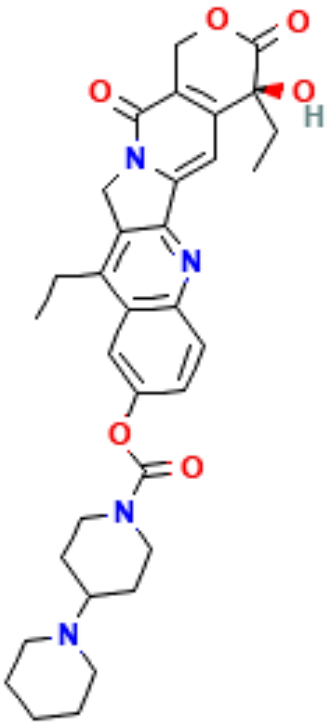

Figure 3. The chemical structure of Onivyde

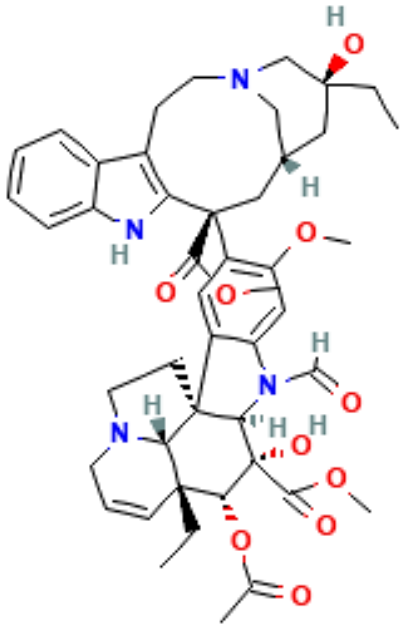

Figure 4. The chemical structure of Marqibo

Table 1. Topological Indices and their physico chemical properties

Drugs	First Zagreb Index	Second Zagreb Index	Forgotten Index	polar surface area	Melting point	Boiling point	Enthalpy of vaporization	Molar refractivity
Doxil	220	275	614	206	229	810	123.5	131.5
Abraxane	362	456	1052	221	213	957.1	146	219.3
Onivyde	246	306	662	116	250	--	--	154.9
Marqibo	381	494	1147	254	218	531	--	221.48

The M polynomial for the anticancer drugs are

(i) $M(Doxil) = 8x^3y + 15x^3y^3 + 12x^3y^2 + 2x^2y^4 + x^4y + x^3y^4 + 2x^2y + 2x^2y^2$

(ii) $M(Abraxane) = 13x^2y^2 + 17x^2y^3 + 9x^3y^3 + 11x^3y + 5x^3y^4 + 6x^4y + 4x^4y^4 + 5x^4y^2$

(iii) $M(Onivyde) = 8x^2y^2 + 21x^2y^3 + 11x^3y^3 + 3x^3y + 2x^2y + 2x^3y^4 + x^4y + x^4y^2$

(iv) $M(Marqibo) = 7x^2y^2 + 18x^2y^3 + 7x^3y^3 + 11x^2y^4 + 9x^3y^4 + 4x^4y + 4x^4y^4$

Using M polynomial, we obtain the first zagreb index, second zagreb index and forgotten index. These values are shown in Table1. The physicochemical and topological indices described provide information regarding the structural complexity, biological behavior and drug-likeness of the anticancer agents. In the Topological Indices, both the Zagreb and Forgotten Indices indicated that Marqibo exhibited the greatest values for the First Zagreb (381), Second Zagreb (494) and Forgotten Index (1147) in displaying greater molecular complexity and branching.

Abraxane performed 2nd to Marqibo with topical complexity but Doxil and Onivyde indicated considerably less values.

Polar Surface Area, while PSA is variable descriptor of drug permeability and bioavailability. Marqibo exhibited the greatest PSA(254 Å²). While Marqibo would indicate lower permeation across cell membranes, it would suggest it would deliver to potential targets. Onivyde however exhibits the lowest PSA(PSA 116 Å²), where passive diffusion could expect low value.

Melting and Boiling Points; Abraxane and Marqibo both exhibited higher boiling points which may correlate with strong intermolecular forces or larger molecular mass. Onivyde exhibited the highest melting point(250°C). Potentially indicating a degree of crystalline stability.

Enthalpy of Vaporization; collectively the data did not display below to address the Enthalpy of Vaporization for Onivyde and Marqibo, however Abraxane exhibited the largest estimated potential value (146 kJ/mol) thereby indicating Abraxane potentially possesses greater degrees of thermal stability, cohesive forces between molecules.

Molar Refractivity (MR); Marqibo exhibited the highest molar refractivity potential (221.48) as this represents larger volume and London Dispersion Forces (becoming stronger). Doxil exhibited the lowest MR(131.5) which suggests this drug is representative of lower volume or less polarizable structure.

Marqibo and Abraxane's higher topological indices and molar refractive index indicate relatively more intricate and bulky structural features, exasperated likely with targeted delivery and controlled or carrier-system release. With relatively less complexity and PSA, Onivyde might provide advantageous permeability and diffusion, which is likely to affect its pharmacokinetic behavior.

The correlation analysis of the anticancer drugs and their physico chemical properties are shown in Table 2.

Table 2. Correlation analysis between topological indices and polar surface area, melting point and molar refractivity

Topological Indices	Polar surface area	Melting Point	Molar refractivity
First Zagreb Index	0.4608	0.5660	0.9879
Second Zagreb Index	0.4838	0.5632	0.9762
Forgotten Index	0.5275	0.6037	0.9660

Of the three topological indices, First Zagreb Index, Second Zagreb Index, and Forgotten Index, the Forgotten Index exhibits the highest overall correlation with the various selected physicochemical

properties. The Forgotten Index has the highest correlation with the Polar Surface Area 0.5275 and the melting Point 0.6037. The First Zagreb Index shows the highest correlation with the Molar Refractivity 0.9879 with the Second Zagreb Index showing a similar association 0.9762 and the Forgotten Index showing a lesser association 0.9660. Hence, the Forgotten Index has shown to be a consistent predictor of multiple physicochemical properties including Polar Surface Area and Melting Point; while the First Zagreb Index was the most predictive of Molar Refractivity.

REGRESSION ANALYSIS ON TOPOLOGICAL INDICES

Regression analysis between the topological indices and properties such as polar surface area, melting point, and molar refractivity is presented in Fig. 5 to Fig.13.

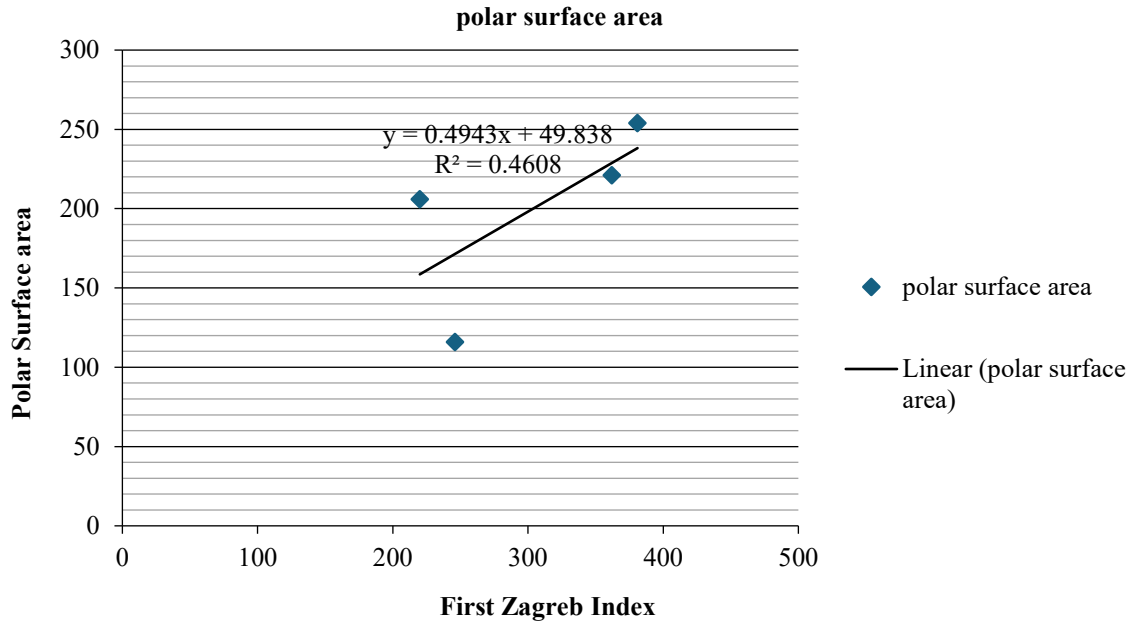

Figure 5. Regression analysis for First zagreb index and Polar surface area

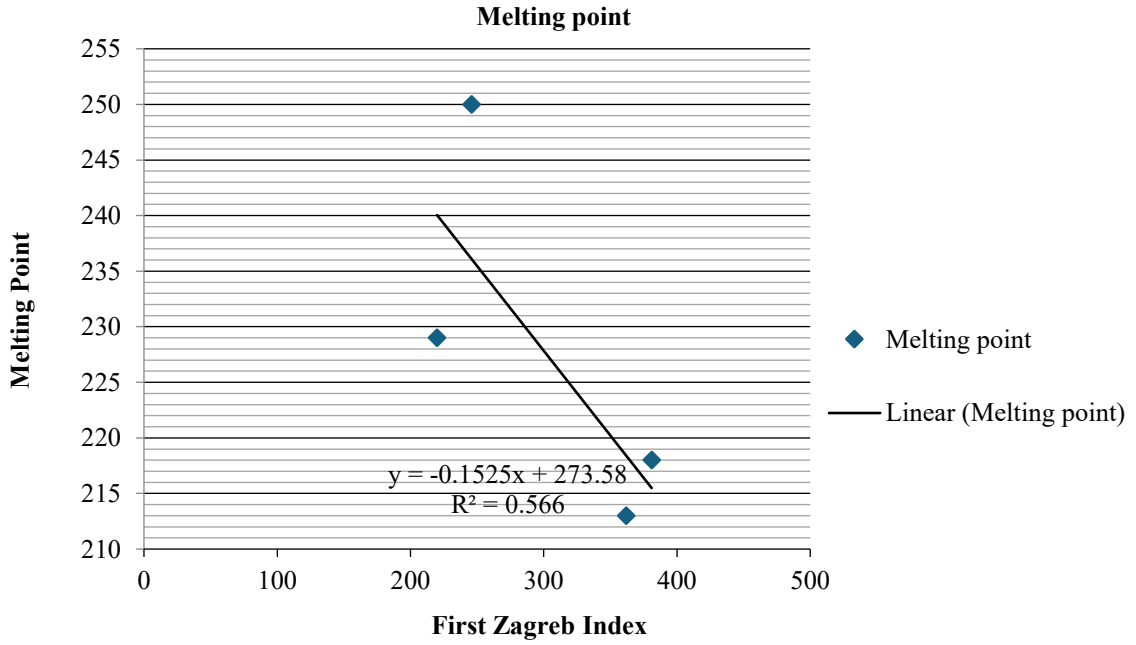

Figure 6. Regression analysis for First zagreb index and melting point

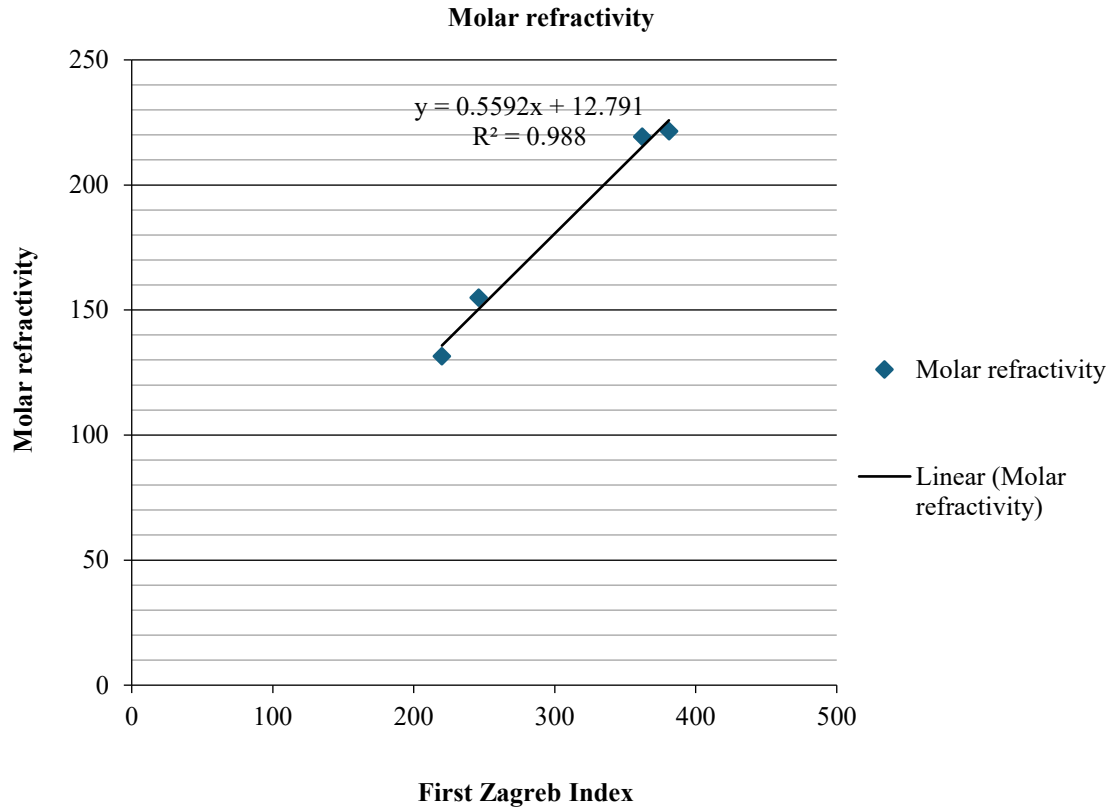

Figure 7. Regression analysis for first zagreb index and molar regractivity

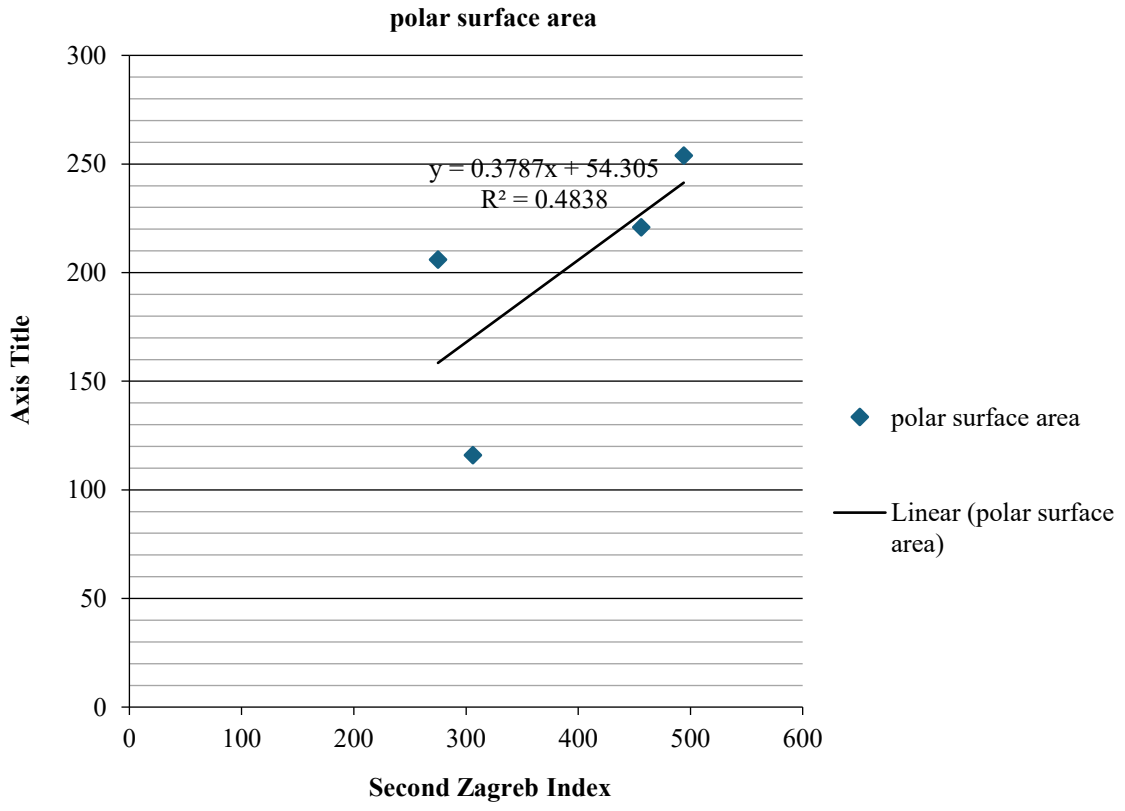

Figure 8. Regression analysis for second zagreb index and polar surface area

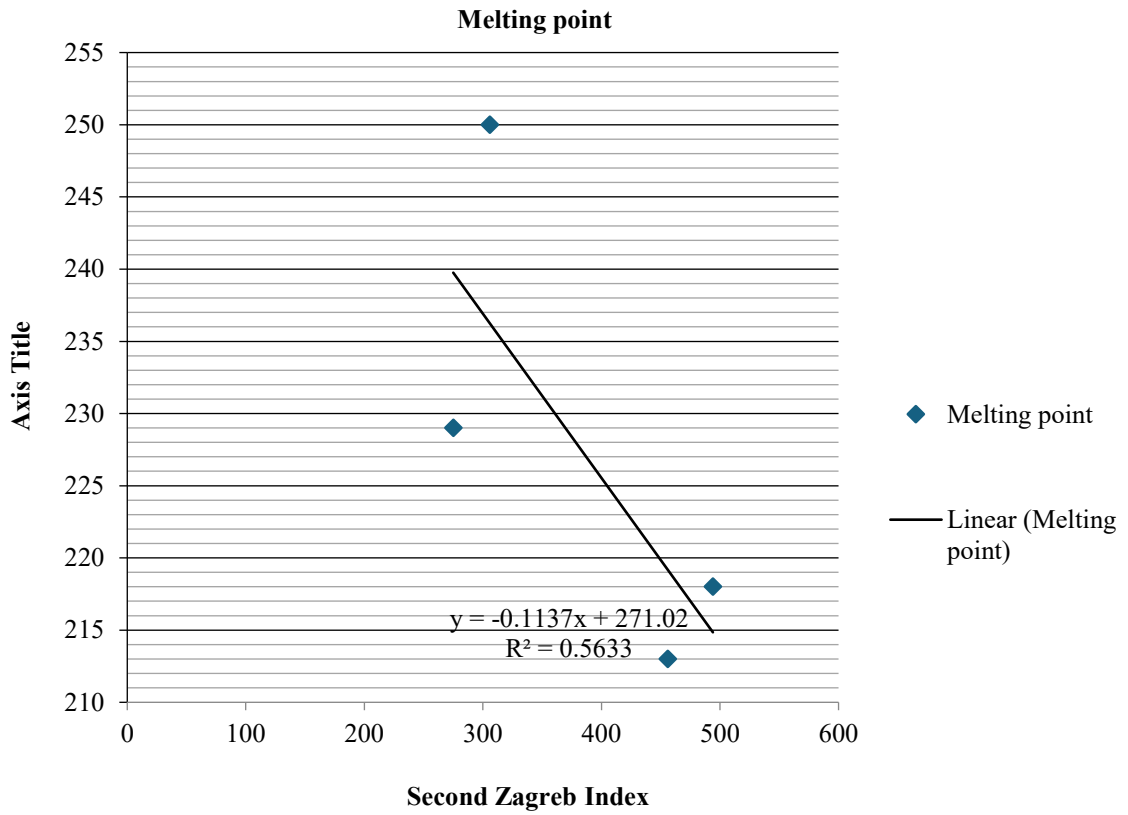

Figure 9. Regression analysis for second zagreb index and melting point

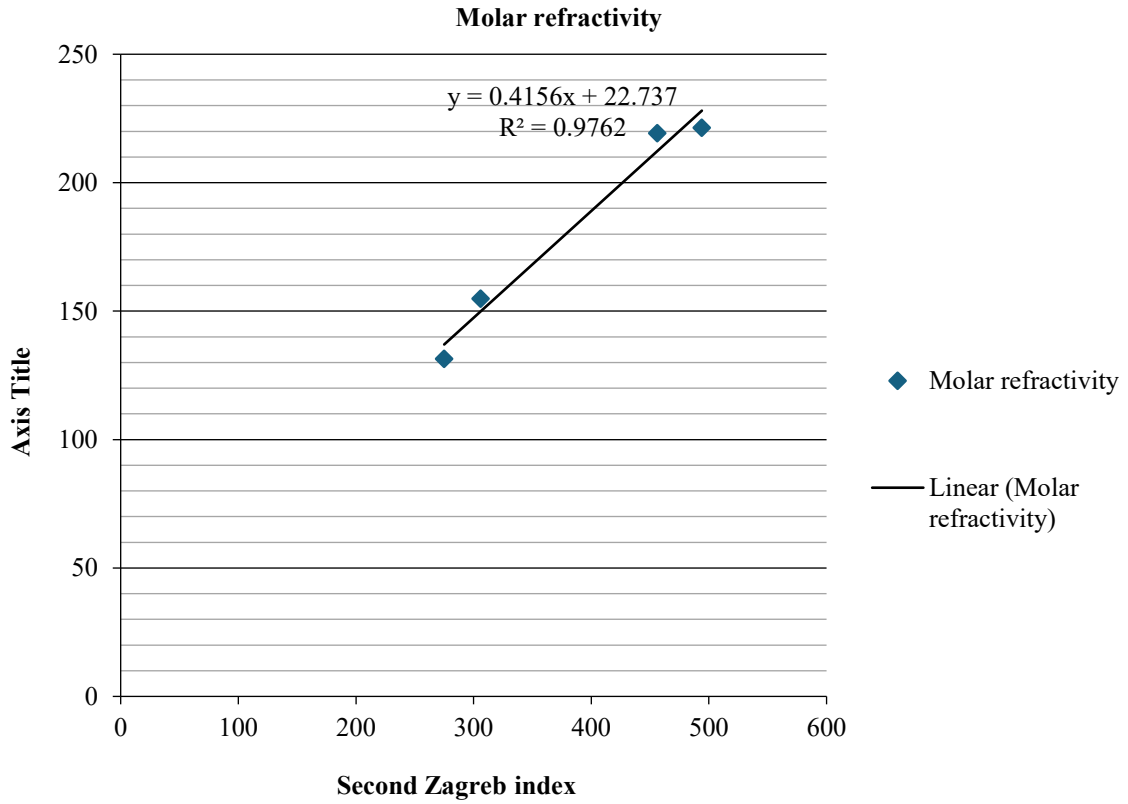

Figure 10. Regression analysis for second zagreb index and molar refractivity

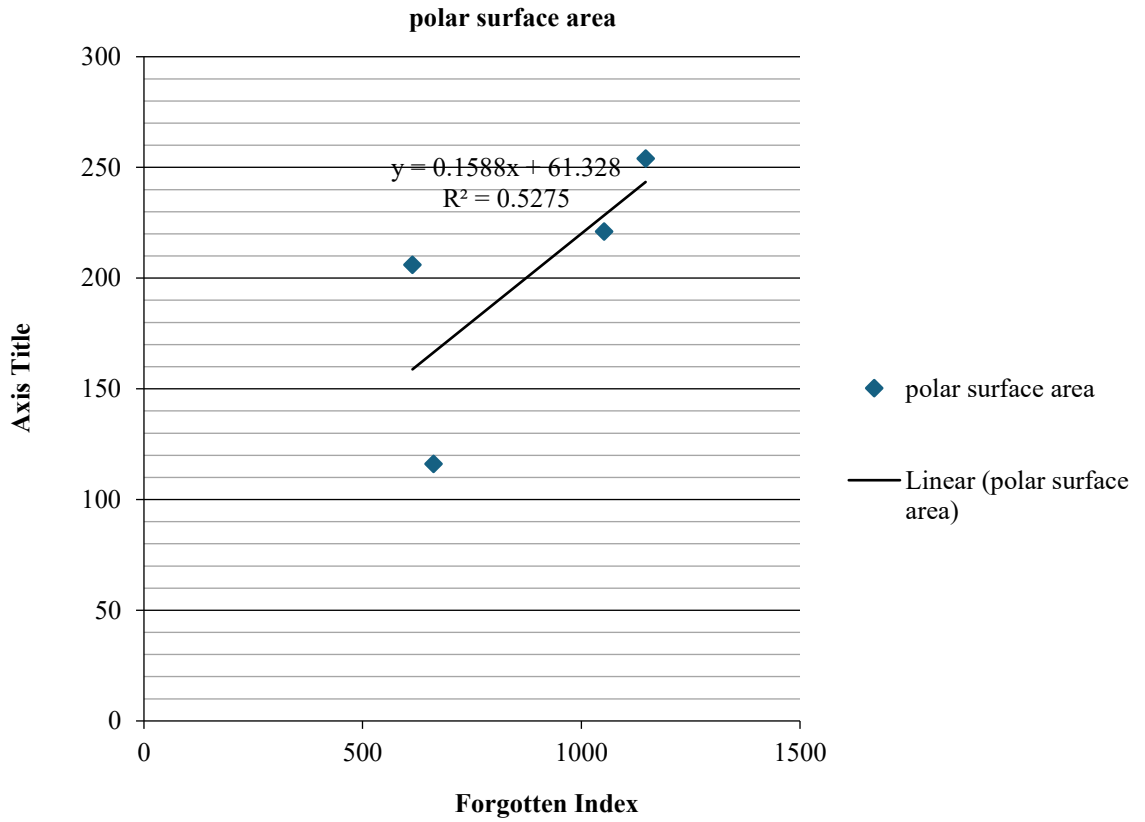

Figure 11. Regression analysis for Forgotten index and polar sruface area

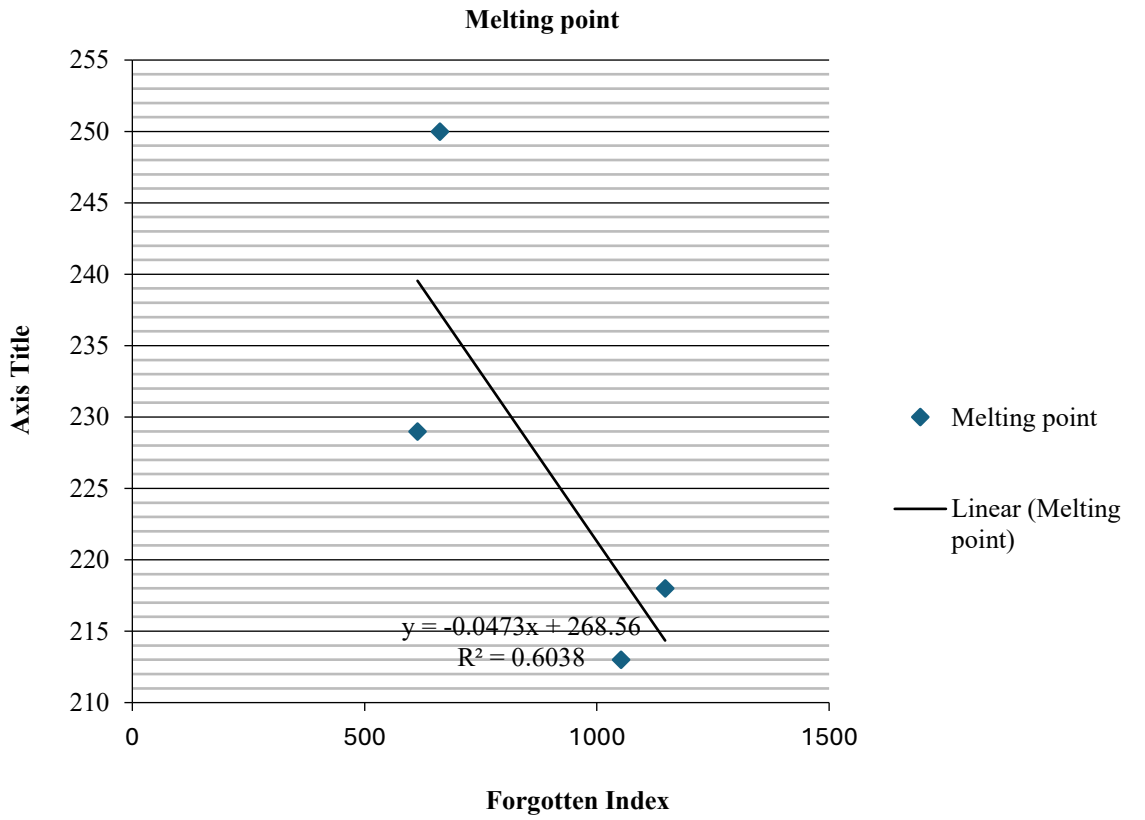

Figure 12. Regression analysis for Forgotten index and melting point

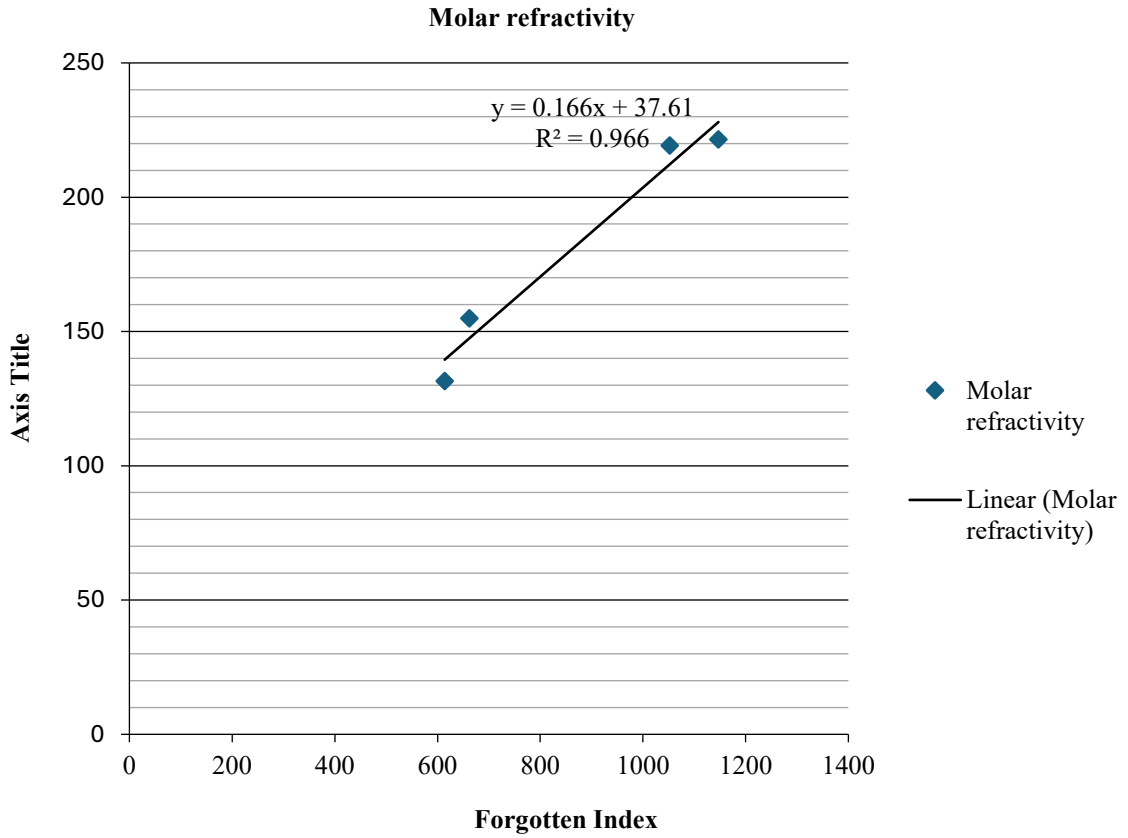

Figure 13. Regression analysis for Forgotten index and molar refractivity

STATISTICAL ANALYSIS

With a positive slope, the parameter y increases when x increases. Moderate sensitivity means that the parameter y decreases as x increases. The comparative study was conducted for the first Zagreb index, polar sruface area, melting point, molar refractivity index. y=0.4943+ 49.838, R^2 = 0.4608 as in Figure 4, y=−0.1525x+273.5, R^2 = 0.5660 in Figure 5 and y=0.5592x+12.791, R^2 = 0.9880 in Figure 6. First Zagreb index with molar refractivity is the best because it has the highest R^2 value (0.988) showing a very strong linear relation between the variables. The best fit, showing a strong linear trend between the topological index and physicochemical properties that correspond. For the second zagreb index, with 'others' being polar surface area robust models were built based upon melting point and molar refractivity. The equation y= 0.4156x + 22.737 , with an R^2 of 0.9762 is the best model suggesting the highest relationship between the topological index and the selected molecular property. Among the three regression models for Forgotten index, the model exhibiting the following equation, y=0.166x+37.61 a R^2 value of 0.9660 represents the best fit suggesting a strong linear relationship between the topological index and the associated physicochemical property.

CONCLUSION

The current study demonstrates a substantive relation between topological indices and physicochemical properties of anticancer drugs. Overall, the regression analysis indicates that the topological indices such as the First Zagreb Index, Second Zagreb Index, Forgotten Index and the molecular descriptors such as polar surface area, melting point, and molar refractivity had significant relationships. The regression models that contained the Forgotten Index were ones that illustrated higher R^2 values - approaching 0.988, showing strong linear relationships. In summary, we believe that topological indices can serve as meaningful predictors for estimating important physicochemical properties of anticancer drugs. Quantitative relationships such as these can provide new avenues of

information for drug design and development and offer a framework for drug evaluation and screening using graph-theoretic methodologies.

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