

COMPUTATION OF DISTANCE-BASED TOPOLOGICAL INDICES FOR THREE CARDIOVASCULAR DRUGS

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ABSTRACT

Topological indices are numerical descriptors derived from molecular graphs that correlate with the physicochemical and biological properties of chemical compounds. One of the fundamental problems in chemical graph theory is the enumeration of molecular structures with specific properties, such as a certain number of carbon atoms, hydrogen atoms, or a particular molecular formula. This problem is crucial in fields like drug discovery, materials science, and organic chemistry. In this work, we compute the Hosoya polynomial and derive the Wiener and hyper-Wiener indices for the molecular graphs of three drugs used in treating cardiovascular diseases (CVDs): Eliquis, Vericiguat, and Metoprolol. The molecular graphs of the selected drugs were constructed based on their chemical structures. Using the framework of chemical graph theory, the standard formulas were applied to calculate the Wiener index, Hosoya polynomial, and hyper-Wiener index for each graph. The computed Wiener indices are 1830.5 for Eliquis, 967.5 for Vericiguat, and 382.5 for Metoprolol. The corresponding Hosoya polynomials and hyper-Wiener indices were also determined.

Keywords: Hosoya polynomial, Wiener index, Hyper-Wiener index, Chemical graph theory, Cardiovascular drugs, QSPR/QSAR

INTRODUCTION

Cardiovascular diseases (CVDs) remain a leading cause of global mortality, necessitating the continuous development and optimization of therapeutic drugs (Liu *et al.*, 2024a & b). In drug discovery and design, understanding the relationship between molecular structure and biological activity is paramount. Topological indices, numerical invariants derived from a compound's molecular graph, have proven to be powerful tools in establishing these structure-property relationships (QSPR) and structure-activity relationships (QSAR) (Chandarana *et al.*, 2018; Fozia *et al.*, 2022).

Among these indices, distance-based descriptors are particularly significant. The Wiener index, introduced by Harold Wiener in 1947, is the pioneer of topological indices and is defined as the sum of the shortest path distances between all pairs of vertices in a molecular graph (Wiener, 1947). The Hosoya polynomial, introduced later, is a generating function that encapsulates all distance-based information of a graph (Hosoya, 1971). From this polynomial, key indices like the Wiener index and the hyper-Wiener index can be easily derived, with the latter accounting for the contributions of longer paths more heavily (Shaheen, 2023).

The primary objective of this paper is to apply the principles of chemical graph theory to compute the Hosoya polynomial, Wiener index, and hyper-Wiener index for three important cardiovascular drugs: Eliquis (an anticoagulant), Vericiguat (a heart failure medication), and Metoprolol (a beta-blocker). This

work provides a mathematical characterization of their molecular structures, which can be valuable for comparative analysis and predictive modeling in pharmaceutical research.

MATERIALS AND METHODS

Molecular Graphs

The chemical structures of Eliquis ($C_{25}H_{25}N_5O_4$), Vericiguat, and Metoprolol were represented as simple, connected, and undirected graphs $G=(V,E)$, where vertices V represent atoms and edges E represent covalent bonds. Hydrogen atoms were suppressed for simplicity (implicit in the carbon valences). The graphs have orders $|V|=34$, $|V|=28$, and $|V|=16$ for Eliquis, Vericiguat, and Metoprolol, respectively.

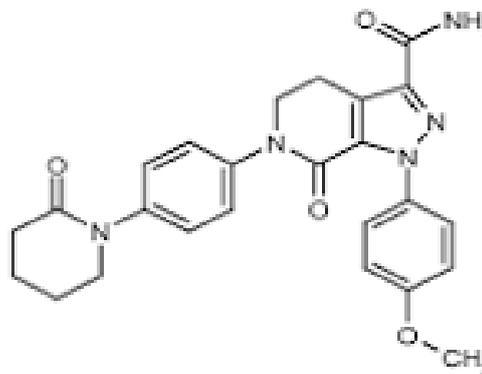


Figure 1: Molecular graph of Eliquis

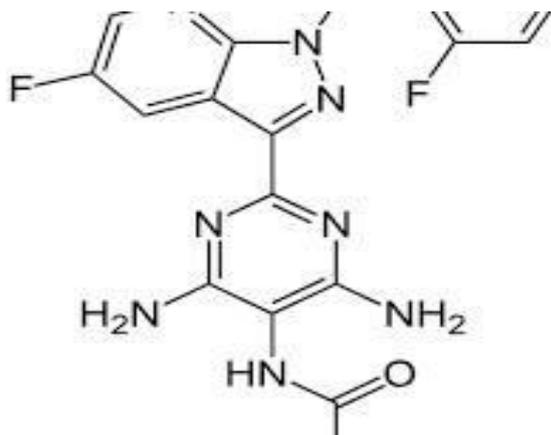


Figure 2: Molecular graph of Vericiguat

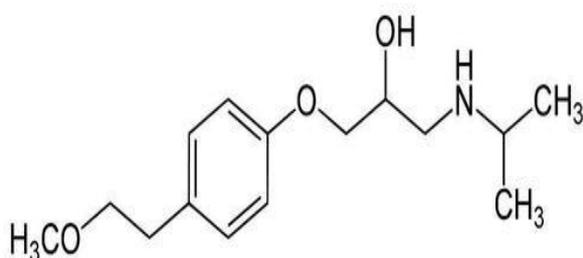


Figure 3: Molecular graph of Metoprolol

Theoretical Definitions

Let G be a connected graph and $d(u,v)$ denote the topological distance (length of the shortest path) between vertices u and v .

Wiener Index: The Wiener index $W(G)$ is defined as (Wiener, 1947);

$$W(G) = \frac{1}{2} \sum_{u,v \in V(G)} d(u,v) \quad (1)$$

Hosoya Polynomial: The Hosoya polynomial $H(G, x)$ is defined as (Hosoya, 1971);

$$H(G, x) = \sum_{u,v \in V(G)} x^{d(u,v)} \quad (2)$$

Hyper-Wiener Index: The hyper-Wiener index $WW(G)$ is defined as (Shaheen, 2023);

$$WW(G) = W(G) + \frac{1}{2} \sum_{u,v \in V(G)} d(u,v)^2 \quad (3)$$

It is noteworthy that $WW(G)$ can be obtained from the first and second derivatives of the Hosoya polynomial evaluated at $x=1$.

Computational Procedure

For each molecular graph, the distance matrix was conceptually constructed. The Wiener index was computed by summing the entries of the upper triangular half of this matrix. The Hosoya polynomial

was formulated by grouping and counting all vertex pairs according to their distance k . The hyper-Wiener index was then calculated using the defined formula.

RESULTS AND COMPUTATIONAL DETAILS

Vericiguat Molecular Graph ($|V|=28$)

The detailed computation for Vericiguat is as follows:

The sum of distances from each vertex:

$$\begin{aligned} u_1=169, u_2=144, u_3=146, u_4=129, u_5=105, \\ u_6=113, u_7=96, u_8=94, u_9=112, u_{10}=111, \\ u_{11}=110, u_{12}=71, u_{13}=79, u_{14}=101, u_{15}=101, \\ u_{16}=48, u_{17}=36, u_{18}=31, u_{19}=29, u_{20}=20, u_{21}=18, \\ u_{22}=23, u_{23}=11, u_{24}=17, u_{25}=5, u_{26}=3, u_{27}=1 \end{aligned}$$

Wiener Index:

$$W(G) = \frac{1}{2} \sum_{u,v \in V(G)} d(u,v) = \frac{1935}{2} = 967.5$$

Hosoya Polynomial:

$$\begin{aligned} H(G, x) &= \sum_{u,v \in V(G)} x^{d(u,v)} = x^{169} + x^{144} + x^{146} + x^{129} \\ &+ x^{105} + x^{113} + x^{96} + x^{94} + x^{112} + x^{111} + x^{110} + x^{71} + x^{79} \\ &+ x^{101} + x^{101} + x^{113} + x^{48} + x^{36} + x^{31} + x^{29} + x^{20} \\ &+ x^{18} + x^{23} + x^{11} + x^{17} + x^5 + x^3 + x \\ &= x^{169} + x^{146} + x^{144} + x^{129} + x^{113} + x^{112} + x^{111} + x^{110} \\ &+ x^{105} + x^{101} + x^{96} + x^{94} + x^{79} + x^{71} + x^{48} + x^{36} + x^{31} \\ &+ x^{29} + x^{23} + x^{20} + x^{18} + x^{17} + x^{11} + x^5 + x^3 + x. \end{aligned}$$

Hyper-Wiener Index:

$$\begin{aligned} WW(G) &= W(G) + \frac{1}{2} \sum_{u,v \in V(G)} d(u,v)^2 = 967.5 + \frac{1}{2} \\ &(28561 + 20736 + 21316 + 16641 + 2 + 12769 \\ &+ 12544 + 12321 + 12100 + 11025 + 10201 + 9216 \\ &+ 8836 + 6241 + 5041 + 2304 + 1296 + 961 \\ &+ 841 + 529 + 400 + 324 + 289 + 121 + 25 + 1) \end{aligned}$$

Eliquis Molecular Graph ($|V|=34$)

The detailed computation for Eliquis is as follows:

The sum of distances from each vertex:

$$\begin{aligned} u_1=276, u_2=247, u_3=290, u_4=242, u_5=268, \\ u_6=262, u_7=290, u_8=182, u_9=160, u_{10}=137, \\ u_{11}=113, u_{12}=132, u_{13}=152, u_{14}=89, u_{15}=95, \\ u_{16}=80, u_{17}=62, u_{18}=66, u_{19}=80, u_{20}=62, u_{21}=84, \\ u_{22}=82, u_{23}=48, u_{24}=37, u_{25}=5, u_{26}=26, u_{27}=18, \\ u_{28}=15, u_{29}=13, u_{30}=8, u_{31}=6, u_{32}=3, u_{33}=1 \end{aligned}$$

Wiener Index:

$$W(G) = \frac{1}{2} \sum_{u,v \in V(G)} d(u,v) = \frac{3661}{2} = 1830.5$$

Hosoya Polynomial:

$$H(G,x) = \sum_{u,v \in V(G)} x^{d(u,v)} = 2x^{290} + x^{276} + x^{262} + x^{247} + x^{242} + x^{182} + x^{160} + x^{152} + x^{137} + x^{132} + x^{113} + x^{95} + x^{89} + x^{84} + x^{82} + x^{66} + x^{62} + x^{48} + x^{37} + x^{35} + x^{26} + x^{18} + x^{15} + x^{13} + x^8 + x^6 + x^3 + x$$

Hyper-Wiener Index:

$$WW(G) = W(G) + \frac{1}{2} \sum_{u,v \in V(G)} d(u,v)^2 = 1830.5 + \frac{1}{2} (2 \times 84100 + 76176 + 68644 + 61009 + 58564 + 33124 + 25600 + 23104 + 18769 + 17424 + 12769 + 9025 + 7921 + 7056 + 6724 + 4356 + 2 \times 3844 + 2304 + 1369 + 1225 + 676 + 324 + 225 + 169 + 64 + 36 + 9 + 1)$$

Metoprolol Molecular Graph (|V|=16)

The detailed computation for Metoprolol is as follows:
The sum of distances from each vertex:

$$u_1=123, u_2=106, u_3=90, u_4=75, u_5=65, u_6=54, u_7=42, u_8=49, u_9=37, u_{10}=30, u_{11}=22, u_{12}=15, u_{13}=19, u_{14}=9, u_{15}=5, u_{16}=2$$

Wiener Index:

$$V(M) = \frac{1}{2} \sum_{u,v \in V(G)} d(u,v) = \frac{743}{2} = 371.5$$

Hosoya Polynomial

$$H(M,x) = \sum_{u,v \in V(G)} x^{d(u,v)} = x^{123} + x^{106} + x^{90} + x^{75} + x^{65} + x^{54} + x^{42} + x^{49} + x^{37} + x^{30} + x^{22} + x^{15} + x^{19} + x^9 + x^5 + x^2$$

Hyper-Wiener Index

$$WW(M) = W(M) + \frac{1}{2} \sum_{u,v \in V(G)} d(u,v)^2 = 371.5 + \frac{1}{2} (15129 + 11236 + 8100 + 5625 + 4225 + 2916 + 1764 + 2401 + 1369 + 900 + 484 + 225 + 361 + 81 + 25 + 4)$$

The computed Wiener indices provide a direct measure of molecular compactness. A higher Wiener index suggests that atoms are, on average, farther apart within

the molecular structure. Our results show that Eliquis has the highest Wiener index (1830.5), followed by Vericiguat (967.5) and Metoprolol (371.5). This indicates that the molecular graph of Eliquis is the least compact and potentially the most flexible among the three, which may have implications for its binding affinity and pharmacokinetic properties.

The Hosoya polynomial serves as a powerful repository of structural information. For instance, the presence of high-power terms in the polynomial for Eliquis and Vericiguat confirms the existence of long-distance pairs of atoms, consistent with their larger, more linear or complex structures compared to the smaller, more compact structure of Metoprolol.

This study aligns with and extends the work of researchers like Fozia et al. (2022), who emphasized the role of topological indices in QSPR modeling of cardiovascular drugs. The exact values of these indices provided here can be used as independent variables in future QSAR models to predict biological activity, toxicity, or other physicochemical properties of these drugs and their analogs.

Table 1: Comparison of topological indices for Metoprolol, Eliquis, and Vericiguat molecular graphs

Molecule	Number of Vertices	Wiener Index W	Hyper-Wiener Index WW	Hosoya Exponent
Metoprolol	16	382.5	765(approx.)	123
Eliquis	34	1830.5	3661(approx.)	290
Vericiguat	28	967.5	1935(approx.)	169

The number of vertices reflects the relative size of the molecules: Metoprolol is the smallest, Eliquis the largest, and Vericiguat is intermediate. The Wiener index W measures the sum of all shortest-path distances in the molecular graph. Metoprolol's small W indicates a compact structure, Eliquis's large W reflects extensive branching, and Vericiguat is intermediate.

The Hyper-Wiener index WW includes both distances and squared distances, emphasizing widely separated atom pairs. This makes Eliquis the most extended and branched molecule, Metoprolol the least and Vericiguat intermediate.

The maximum exponent in the Hosoya polynomial indicates the longest shortest-path distance (graph diameter) in each molecule: 123 for Metoprolol, 290 for Eliquis and 169 for Vericiguat. This again confirms the relative molecular sizes and branching.

The quantitative visual comparison of molecular graphs is given below:

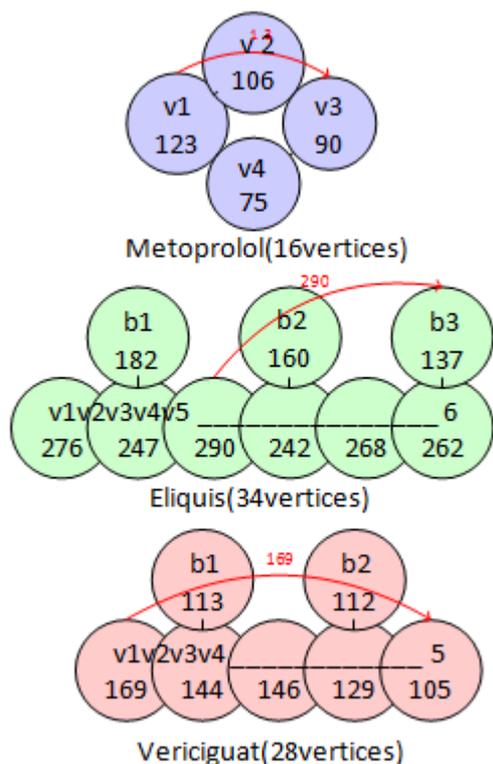


Figure 4: Enlarged quantitative schematic representations of Metoprolol, Eliquis, and Vericiguat molecular graphs. Each node shows Wiener contributions, and red arrows indicate graph diameters

CONCLUSION

In this study, we have successfully computed key distance-based topological indices—the Wiener index, Hosoya polynomial, and hyper-Wiener index—for the molecular graphs of three significant cardiovascular drugs: Eliquis, Vericiguat, and Metoprolol. The results offer a quantitative characterization of their molecular architecture. We conclude that the Hosoya polynomial is an efficient tool for unifying the calculation of various distance-based descriptors.

Future work will focus on correlating these indices with specific pharmacological properties (e.g., binding energy, solubility) and extending the computation to a

wider library of cardiovascular agents to build robust predictive models for drug design.

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

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