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A Computational QSPR Study of Neurotransmitters using Distance-Based Topological Descriptors

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Abstract

Neurotransmitter systems are central to neuronal communication and play a pivotal role in the regulation of cognitive, emotional, and motor functions, while their dysfunction is closely associated with numerous neuropsychiatric and neurodegenerative disorders. In this work, graph-theoretic methodologies are employed to systematically investigate the structural characteristics of neurotransmitter-related molecular networks through the computation of the Mostar, Padmakar-Ivan, Szeged, and geometric-arithmetic indices. These topological descriptors quantitatively capture molecular symmetry, connectivity, and distance-based features, thereby enabling a rigorous assessment of structural heterogeneity, balance, and spatial organization.

Furthermore, the computed topological indices are utilized to construct regression models for the prediction of key physicochemical properties, including molecular weight, polar surface area, structural complexity, solubility, and melting point. The predictive capability and reliability of the proposed models are evaluated using multiple graphical diagnostics, such as line plots, bar charts, violin plots, and scatter plots, providing a comprehensive validation of the developed structure-property relationships.

Keywords: Neurotransmitter, topological index, physicochemical properties, neuropsychiatric disorders

1 Introduction

Neurotransmitters are essential biomolecules that mediate synaptic transmission by facilitating the propagation of action potentials across neuronal and non-neuronal synapses. They regulate critical physiological processes, including motor coordination, cognition, emotional behavior, and neural circuit development through precise control of synaptic connectivity and plasticity [1]. Among them, dopamine acts through G-protein-coupled receptors and serves dual roles: as a central neuromodulator influencing executive function and as a peripheral immunomodulator regulating T-cell activation and cytokine signaling, expanding its functional reach beyond the central nervous system (CNS) [2].

Recent advances in therapeutic delivery have led to the development of reactive oxygen species (ROS)-responsive nanocarriers that enable targeted delivery of neuromodulator conjugated drugs to injured spinal cord regions. These nanodrugs modulate inhibitory neuronal networks and attenuate oxidative stress, resulting in neuroprotection and enhanced functional recovery post-injury [3]. In the context of neurodegenerative diseases such as Alzheimer’s disease (AD), metabolic dysregulation in astrocytes disrupts the glutamate GABA-glutamine cycle, leading to impaired neurotransmitter clearance and excitotoxicity. Restoration of astrocytic metabolic functions may ameliorate synaptic dysfunction and neuronal loss [4].

Environmental neurotoxins, particularly organophosphates and carbamates, inhibit acetylcholinesterase (AChE), resulting in excessive synaptic acetylcholine accumulation. AChE-based electrochemical biosensors, enhanced through enzyme immobilization and nanomaterial integration, offer high specificity and sensitivity for detecting neurotoxic pesticides and neurotransmitters in both clinical and ecological settings [5]. Parallel to this, artificial synaptic devices capable of simulating excitatory and inhibitory postsynaptic potentials (EPSPs/IPSPs) have been engineered using electrochemical reaction systems, demonstrating their applicability in neuromorphic computing architectures [6].

Detection technologies have also advanced the monitoring of neuromodulators such as serotonin (5-HT), with optical and electrochemical biosensors employing nanostructured electrodes achieving ultralow detection limits and real-time, in vivo analysis [7]. Neurotransmitters, classified as canonical (e.g., amino acids, monoamines, purines) or noncanonical (e.g., exosomes, D-aspartic acid, steroids), influence neurodevelopment and neuroplasticity. Dysregulation in their homeostasis is strongly correlated with numerous neuropathological conditions, reinforcing the necessity for accurate detection and therapeutic targeting [8].

Catecholamines, including dopamine, L-DOPA, and noradrenaline, also function as endogenous antioxidants by scavenging free radicals. Their radical-trapping efficiency is modulated by pH, ionization state, and the biophysical characteristics of the surrounding lipid matrix, suggesting a protective role in oxidative stress-mediated pathologies [9]. Quantum chemical simulations, using density functional theory (DFT) and ab initio molecular dynamics (AIMD), have elucidated the solvation effects and energetic profiles of neurotrans-

mitters in polar solvents. These insights reveal the role of solvent-mediated noncovalent interactions in conformational stabilization and electron delocalization [10].

Endothelial cells, traditionally not regarded as neurotransmitter-releasing units, have been shown to release dopamine and 6-nitrodopamine (6-ND), which modulate vascular tone and cardiac output via antagonism of D2-like receptors and 1-adrenoceptor interaction, suggesting an alternative, non-neuronal control mechanism of cardiovascular regulation [11]. Clinically, the use of low-dose dopamine as a nephroprotective adjunct to diuretic therapy in acute decompensated heart failure has yielded inconclusive results, with no significant differences observed in renal biomarkers or neurohormonal indices across treatment groups [12].

Acetylcholine (ACh) and oxytocin (OXT), both neuromodulators, exhibit dynamic temporal interplay across sleep-wake states. ACh levels surge during REM sleep and active wakefulness, promoting cortical gamma oscillations and circuit synchronization, whereas OXT lags and diminishes during these transitions, indicating differential roles in brain state regulation and social behavior modulation [13]. In neurodevelopmental disorders such as autism spectrum disorder (ASD), neurotransmitter dysregulation—particularly involving serotonin, dopamine, glutamate, and GABA—has been implicated in synaptic dysfunction. Computational modeling integrating neurochemical and genetic data improves ASD diagnosis and provides mechanistic insights for targeted interventions [14].

Finally, a high-resolution, spatiotemporal map of oxytocin receptor (OXTR) expression in the mouse brain across six postnatal stages has revealed distinct regional and cell-type specific patterns. Notably, glutamatergic and GABAergic populations in the ventral dentate gyrus and basal forebrain show high *Oxtr* mRNA expression, offering new avenues for exploring oxytocin’s role in neurodevelopment and social behavior [15, 16].

The utility of topological indices (TIs) extends beyond biological neurotransmission into quantitative structure-property relationship (QSPR) modeling for drug molecules. Degree-based indices derived from M-polynomials have been used to construct linear and quadratic regression models predicting physicochemical parameters—such as boiling point, polarizability, molar volume, and surface tension of beta-blocker drugs used in cardiovascular therapy. The harmonic index and modified Zagreb indices have emerged as reliable predictors across different properties [17, 18].

Graphical descriptors have also been applied to benzenoid hydrocarbons (BHs), where temperature-based topological indices demonstrated strong correlation with thermodynamic properties like entropy and heat capacity. The quadratic regression models developed here outperform existing indices, offering statistical robustness (correlation coefficients ≥ 0.9) and promoting a more systematic approach to index development [19]. Similarly, graph-theoretical frameworks have been used to derive reduced reverse (RR) degree-based indices for nanostructures such as graphyne and graphdiyne nanoribbons, revealing their potential for predicting molecular reactivity and contributing to advancements in sustainable electronics and catalysis [20].

In oncology, especially blood cancer, topological modeling enables early prediction of

biological efficacy and pharmacokinetics. By analyzing reverse degree and entropy indices of anti-leukemia agents, researchers have proposed QSPR models that highlight key molecular properties contributing to drug performance, improving over traditional degree-based descriptors [21]. The same approach has been extended to antiviral therapies against SARS-CoV-2. Degree-based indices, including Nirmala and inverse Nirmala types, along with neighborhood degree sum-based descriptors, have been employed to build multivariate regression models that accurately correlate with pharmacokinetic and physicochemical profiles of drugs such as Remdesivir and Molnupiravir [22].

Furthermore, topological descriptors have been employed in the prediction of drug toxicity and efficacy for blood cancer treatments using edge-partitioned graphs. Degree-based indices of drugs such as daunorubicin and glasdegib were used to derive QSPR models that reliably forecast properties like boiling point, flash point, and molecular complexity, indicating the strong potential of these techniques in targeted drug design [23, 24]. Temperature-based graphical indices have also evolved, with newly defined reduced reciprocal product-connectivity temperature (RRPT) and geometric-arithmetic temperature (GAT) indices offering superior predictive power for thermodynamic descriptors-such as boiling point and standard enthalpy of formation of polycyclic aromatic hydrocarbons (PAHs). These indices demonstrate statistical superiority over existing temperature indices and offer further applicability in modeling nanostructured systems like silicon carbide nanotubes [25]. A huge literature is mentioned in [26–31].

2 Materials and method

First, to evaluate distance-based topological descriptors, the chemical structures along with their experimental physicochemical properties of the neurotransmitters obtained from the public repository Pubchem, are transformed into their corresponding molecular graphs, in which atoms are represented as vertices and chemical bonds as edges. Throughout this study, n_u and n_v denote the numbers of vertices that are closer to vertex u than to vertex v , and closer to vertex v than to vertex u , respectively. These quantities constitute the fundamental components for computing the considered distance based topological indices.

Subsequently, the computed topological descriptors are utilized as independent variables to establish regression models within a QSPR framework for predicting key physicochemical properties, including molecular weight, polar surface area, structural complexity, solubility, and melting point. The predictive performance, robustness, and reliability of the proposed models are systematically examined using diverse graphical diagnostics, such as line plots, bar charts, violin plots, and scatter plots, thereby enabling a clear and comprehensive interpretation of the obtained results.

Doslic introduced the concept of the Mostar descriptor (Mo) to analyze structural complexity, particularly for deriving lower bounds in tricyclic graphs [32]. Additionally, the Mostar descriptor has been employed to estimate the deviation of Tribonacci cubes from distance balance [33].

$$Mo(G) = \sum_{uv \in E(G)} |n_u - n_v| \quad (1)$$

The Padmakar–Ivan descriptor (PI) is a distance based topological descriptor that has been computed for various classes of graphs, including lexicographic product graphs and perfect graphs [34,35].

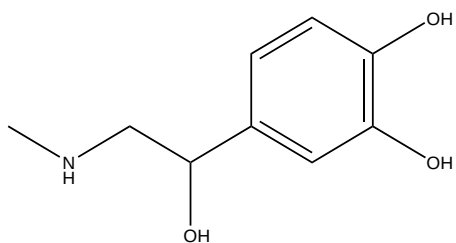
$$PI(G) = \sum_{uv \in E(G)} (n_u + n_v) \quad (2)$$

Another distance based topological descriptor used to analyze graph structures is the Szeged descriptor (Sz). In [36], the authors compute Sz for hollow hexagonal graphs, whereas [37] studies extremal unicyclic graphs to determine a modified Szeged descriptor. The Szeged descriptor of a graph G is defined as:

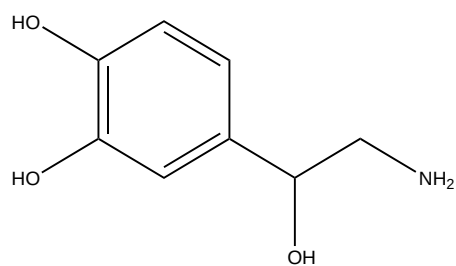
$$Sz(G) = \sum_{uv \in E(G)} n_u \cdot n_v, \quad (3)$$

Building on distance based topological descriptors, Gutman introduced the geometric–arithmetic descriptor (GA). Rodriguez [38] computed its values for certain graphs, while [39] derived two variants of the GA descriptor for benzenoid structures. The GA descriptor of a graph G is defined as:

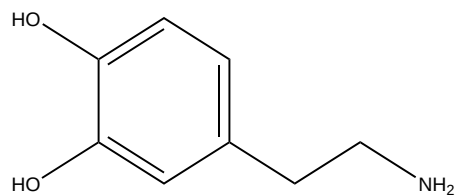
$$GA(G) = \sum_{uv \in E(G)} \frac{2\sqrt{n_u n_v}}{n_u + n_v}, \quad (4)$$



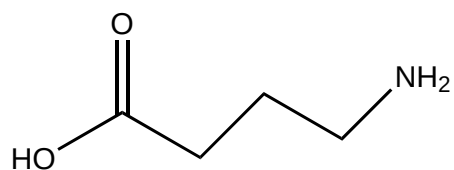
(a) Chemical structure of Adrenaline



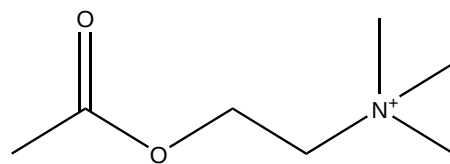
(b) Chemical structure of Noradrenaline



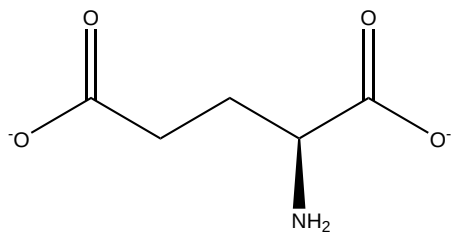
(c) Chemical structure of Dopamine



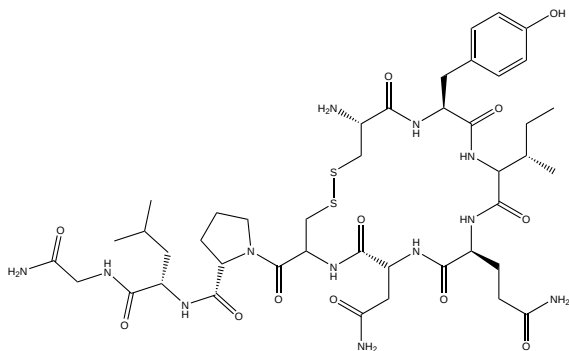
(d) Chemical structure of GABA



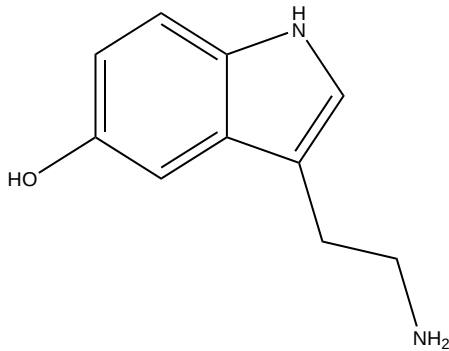
(e) Chemical structure of Acetylcholine



(f) Chemical structure of Glutamate



(a) Chemical structure of Oxytocin



(b) Chemical structure of Serotonin

3 Results and discussion

In this section, the aforementioned topological indices are systematically computed for a representative set of neurotransmitters, namely Adrenaline (Ad) (Fig. 1a), Noradrenaline (No) (Fig. 1b), Dopamine (Do) (Fig. 1c), (GABA) (Fig. 1d), Acetylcholine (Ac) (Fig. 1e), Glutamate (Gl) (Fig. 1f), Oxytocin (Ox) (Fig. 2a), and Serotonin (Se) (Fig. 2b). The numerical values of the calculated descriptors are summarized in Table 1, while their overall distributional behavior and relative trends across the studied neurotransmitters are illustrated in Fig. 4. These results provide an initial quantitative characterization of the structural and distance-based features inherent to the considered molecular graphs.

Subsequently, the computed topological descriptors are employed to develop regression models for the prediction of key physicochemical properties, including molecular weight (MW), polar surface area (PSA), structural complexity (C), solubility (S), and melting point (MP). The predicted values obtained using the Mostar index are reported in Tables 2 and 3 and graphically represented in Figs. 5 and 6. Similarly, predictions based on the Padmakar-Ivan (PI) index are presented in Tables 4 and 5 and visualized in Figs. 7 and 8, while those derived from the Szeged index are summarized in Tables 6 and 7 and depicted in Figs. 9 and 10. Finally, the regression outcomes based on the geometric–arithmetic (GA) index are documented in Tables 8 and 9 and illustrated in Figs. 11 and 12. A comprehensive comparative analysis is then conducted to systematically evaluate and contrast the predictive performance, robustness, and reliability of all developed models.

3.1 Results for Adrenaline

The chemical structure of adrenaline, depicted in Fig. 1a, comprises 13 atoms interconnected through chemical bonds. Its corresponding molecular graph is constructed by mapping atoms to vertices and bonds to edges, as illustrated in Fig. 3. Based on this graphical representation, pairwise distance relationships between adjacent vertex pairs are systemat-

ically evaluated to compute the distance based topological descriptors, namely the Mostar (Mo), Padmakar–Ivan (PI), Szeged (Sz), and geometric-arithmetic (GA) indices.

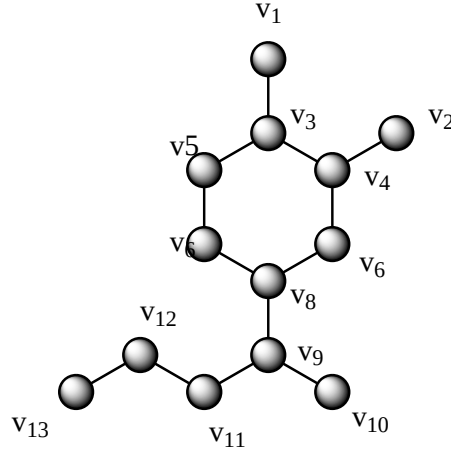


Figure 3: Graphical structure of Adrenaline(G_1)

• Mostar descriptor

In the molecular graph G_1 , vertices are connected through edges of degree types $(1, 2)$, $(1, 3)$, $(2, 2)$, $(2, 3)$, and $(3, 3)$. For each adjacent vertex pair (u, v) , the quantities n_u and n_v denote the numbers of vertices closer to u than to v , and closer to v than to u , respectively. For example, for the edge (v_1, v_3) of type $(1, 3)$, we obtain $n_{v_1} = 0$ and $n_{v_3} = 11$, yielding $|n_{v_1} - n_{v_3}| = 11$. Similarly, for the adjacent pair (v_3, v_4) , we have $n_{v_3} = 3$ and $n_{v_4} = 8$, which gives $|3 - 8| = 5$. Repeating this procedure for all edges and summing the absolute differences according to Eq. 1, the Mostar descriptor of G_1 is obtained as

$$Mo(G_1) = 85.$$

• Padmakar–Ivan descriptor

The Padmakar–Ivan index is computed using the same edge partition of G_1 . For each edge (u, v) , the contribution is given by $n_u + n_v$. As an illustration, the edge of type $(1, 3)$ connecting v_2 and v_4 yields $n_{v_2} = 0$ and $n_{v_4} = 11$, giving a contribution of 11. Likewise, for the edge between v_3 and v_4 , $n_{v_3} = 3$ and $n_{v_4} = 8$, resulting in a contribution of 11. By evaluating all edges in this manner and summing the contributions using Eq. 2, the Padmakar–Ivan descriptor of G_1 is computed as

$$PI(G_1) = 143.$$

• Szeged descriptor

To determine the Szeged index, each edge $e = (u, v)$ of G_1 contributes the product $n_u n_v$. For instance, for the $(3, 3)$ -type edge (v_8, v_9) , we find $n_{v_8} = 7$ and $n_{v_9} = 4$, giving a contribution of 28. Similarly, for the $(2, 3)$ -type edge (v_9, v_{11}) , the values $n_{v_9} = 9$ and $n_{v_{11}} = 2$ yield a contribution of 18. Summing all such products over the edge set according to Eq. 3, the Szeged descriptor is obtained as

$$Sz(G_1) = 216.$$

• Geometric–arithmetic descriptor

The geometric–arithmetic index of G_1 is evaluated by considering, for each edge (u, v) , the contribution

$$\frac{2\sqrt{n_u n_v}}{n_u + n_v},$$

which reflects the balance between vertex-distance partitions. For example, the $(3, 3)$ -type edge (v_8, v_9) with $n_{v_8} = 7$ and $n_{v_9} = 4$ contributes 0.96, while the $(2, 3)$ -type edge (v_9, v_{11}) with $n_{v_9} = 9$ and $n_{v_{11}} = 2$ contributes 0.77. By systematically computing and summing these contributions for all edges using Eq. 4, the geometric–arithmetic descriptor of G_1 is obtained as

$$GA(G_1) = 7.93.$$

The same computational protocol is applied to all remaining neurotransmitters, and the resulting topological descriptor values are summarized in Table 1. A detailed account of the underlying methodology and theoretical background can be found in [40].

Table 1: Topological descriptors for neurotransmitters

Neurotransmitter	Mo	PI	Sz	GA
Adrenaline	85	143	216	7.93
Noradrenaline	68	120	168	7.26
Dopamine	49	99	130	7.32
Oxytocin	3288	4688	30510	34.56
GABA	20	30	16	2.75
Acetylcholine	48	72	58	3.80
Glutamate	50	72	55	3.70
Serotonin	80	140	215	10.07

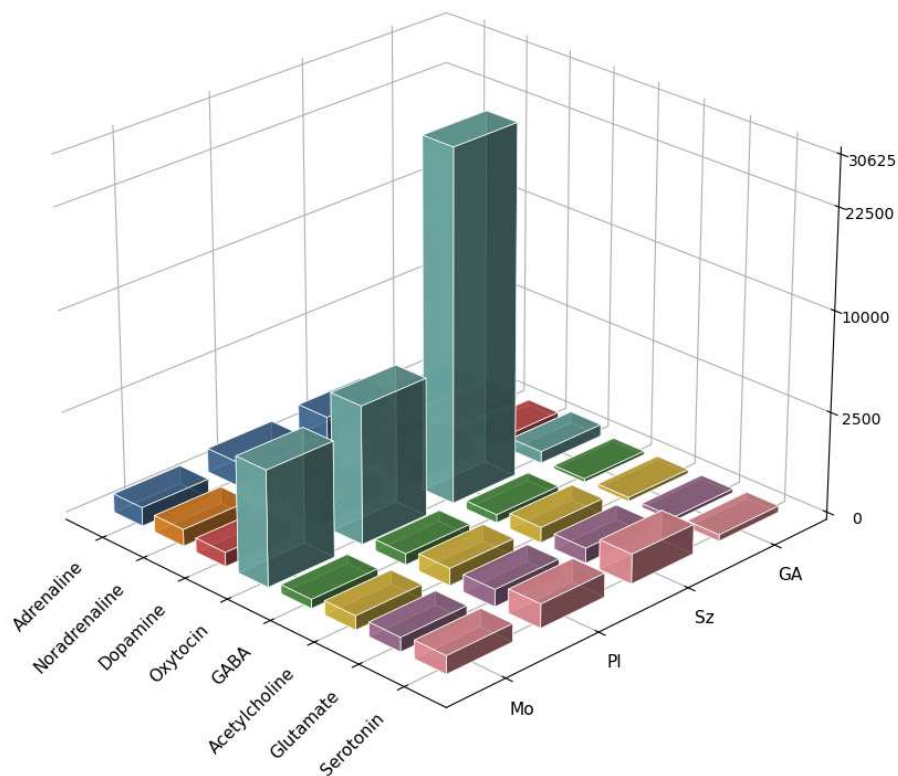


Figure 4: 3D plot of topological descriptors

Regression models

Regression polynomial models will be constructed for the distance based topological descriptors, namely the Mostar (Mo), Padmakar-Ivan (PI), Szeged (Sz), and geometric-arithmetic (GA) descriptors. These regression models will subsequently be employed to predict essential physicochemical properties, including molecular weight (MW), polar surface area (PSA), structural complexity (C), solubility (S), and melting point (MP).

Results of mostar index

$$\begin{aligned}
MW_{\text{Mo}}(x) &= 3.79944 \times 10^{-11}x^6 - 1.28638 \times 10^{-7}x^5 + 1.2205 \times 10^{-5}x^4 \\
&\quad + 3.20527 \times 10^{-7}x^3 + 5.99595 \times 10^{-9}x^2 - 3.30665 \times 10^{-8}x + 108.881 \\
PSA_{\text{Mo}}(x) &= 1.38041 \times 10^{-11}x^6 - 4.66191 \times 10^{-8}x^5 + 4.04767 \times 10^{-6}x^4 \\
&\quad + 1.063 \times 10^{-7}x^3 + 1.98852 \times 10^{-9}x^2 - 1.09663 \times 10^{-8}x + 57.1866 \\
C_{\text{Mo}}(x) &= 4.68014 \times 10^{-11}x^6 - 1.58323 \times 10^{-7}x^5 + 1.45994 \times 10^{-5}x^4 \\
&\quad + 3.83408 \times 10^{-7}x^3 + 7.17225 \times 10^{-9}x^2 - 3.95536 \times 10^{-8}x + 76.2186 \\
S_{\text{Mo}}(x) &= 1.02125 \times 10^{-9}x^6 - 3.43038 \times 10^{-6}x^5 + 2.38432 \times 10^{-4}x^4 \\
&\quad + 6.26183 \times 10^{-6}x^3 + 1.17138 \times 10^{-7}x^2 - 6.46002 \times 10^{-7}x + 1686.91 \\
MP_{\text{Mo}}(x) &= -9.60112 \times 10^{-11}x^6 + 3.22959 \times 10^{-7}x^5 - 2.39178 \times 10^{-5}x^4 \\
&\quad - 6.28139 \times 10^{-7}x^3 - 1.17504 \times 10^{-8}x^2 + 6.48017 \times 10^{-8}x + 211.066
\end{aligned}$$

Table 2: Actual vs predicted values of MW, PSA, and C based on Mo

NT	MW			PSA			C		
	Actual	Predicted	Error	Actual	Predicted	Error	Actual	Predicted	Error
Ad	183.20	189.74	-6.54	72.7	66.90	5.80	154.0	153.71	0.29
No	169.18	186.67	-17.49	86.7	77.35	9.35	142.0	162.93	-20.93
Do	153.18	143.47	9.71	66.5	67.56	-1.06	119.0	116.35	2.65
Ox	1007.20	1007.19	0.01	450.0	450.00	0.00	1870.0	1870.01	-0.01
GABA	103.12	110.43	-7.31	63.3	57.69	5.61	62.7	78.05	-15.35
Ac	146.21	141.39	4.82	26.3	66.98	-40.68	115.0	113.99	1.01
Gl	147.13	145.60	1.53	101.0	68.15	32.85	145.0	118.77	26.23
Se	212.67	197.40	15.27	62.0	73.89	-11.89	174.0	167.88	6.12

Table 3: Actual vs predicted values of S and MP based on Mo

NT	S			MP		
	Actual	Predicted	Error	Actual	Predicted	Error
Ad	0.1000	-698.56	698.66	412	358.93	53.07
No	50.0000	1900.30	-1850.30	217	159.54	57.46
Do	600.0000	2107.29	-1507.29	128	163.01	-35.01
Ox	55.0000	55.01	-0.01	192	192.00	-0.00
GABA	0.0012	1714.19	-1714.19	203	208.26	-5.26
Ac	500.0000	2091.71	-1591.71	148	165.15	-17.15
Gl	8570.0000	2121.85	6448.15	205	160.93	44.07
Se	0.0319	483.33	-483.30	167	264.18	-97.18

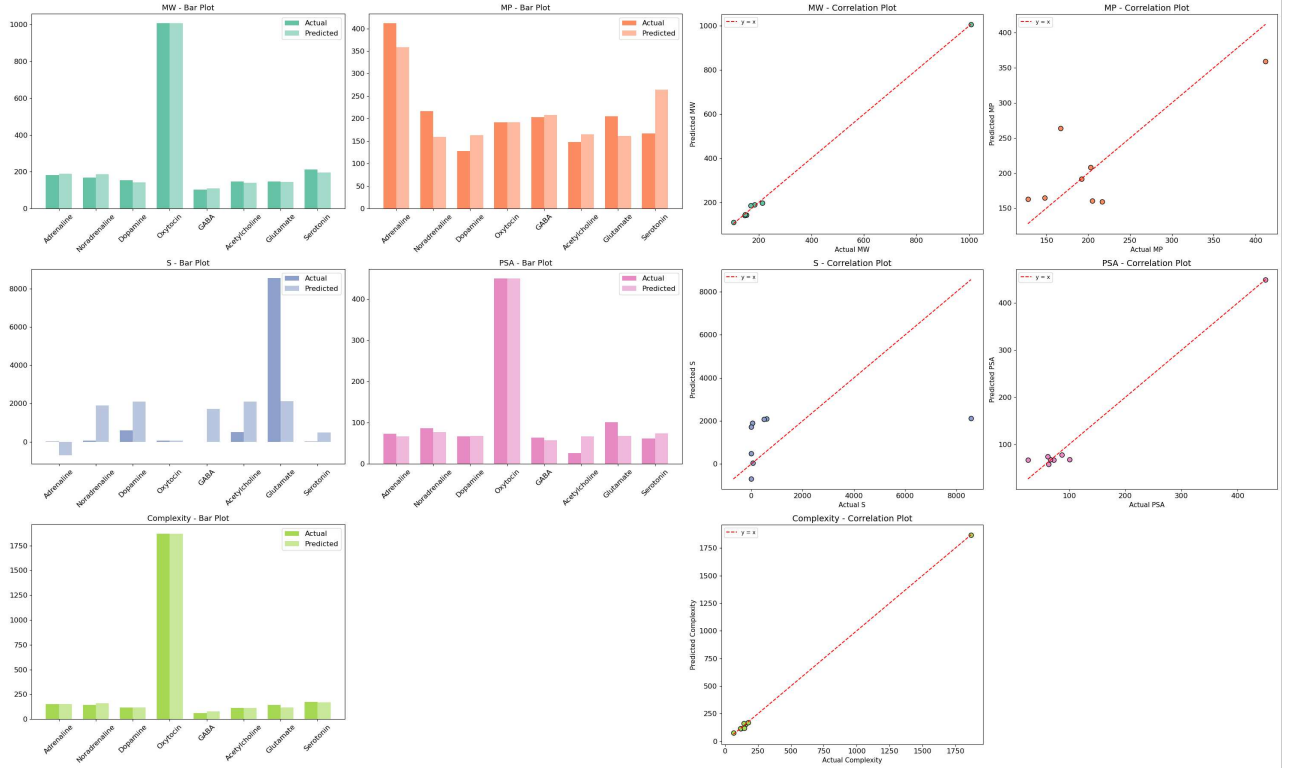


Figure 5: Bar and scatter plots based on Mo

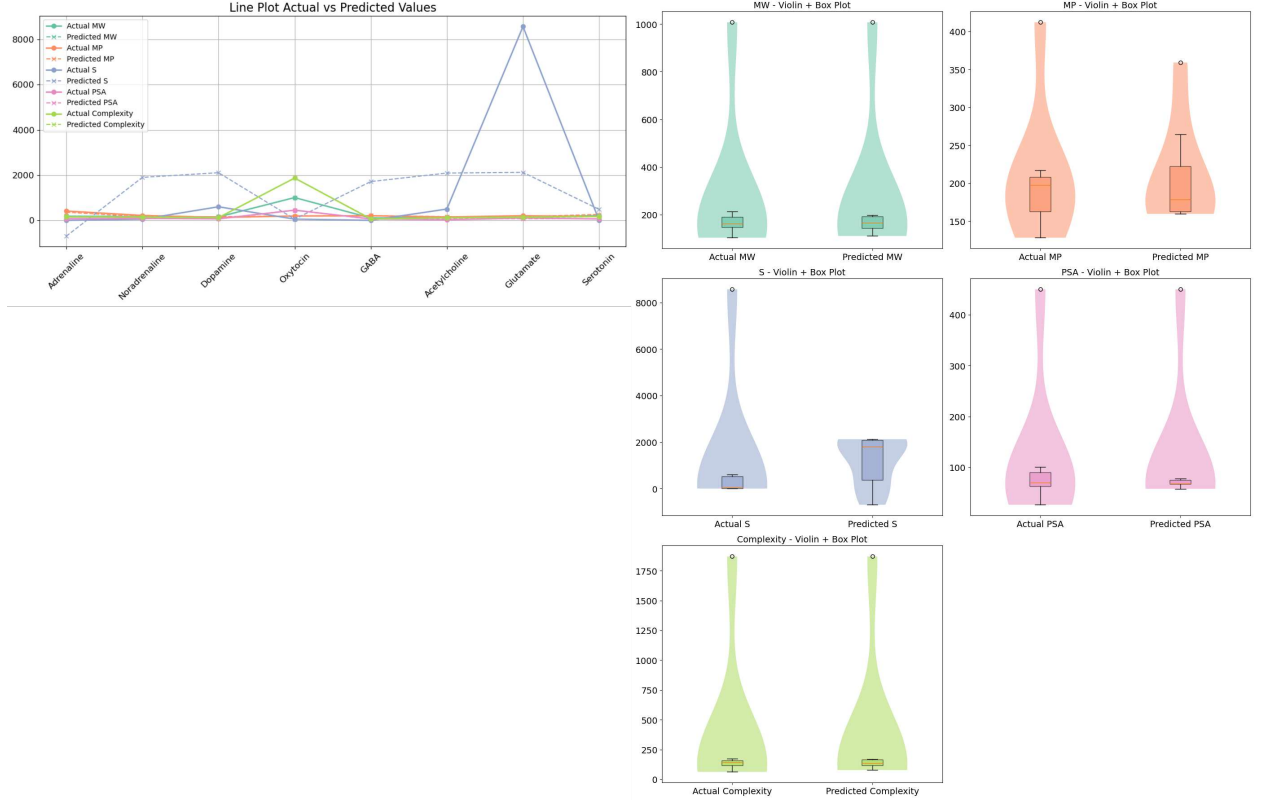


Figure 6: Line and violin plots based on Mo

Results of PI index

$$\begin{aligned}
 MW_{PI}(x) &= 1.04138 \times 10^{-12}x^6 - 5.07063 \times 10^{-9}x^5 + 8.84413 \times 10^{-7}x^4 \\
 &\quad + 1.37178 \times 10^{-8}x^3 + 1.50888 \times 10^{-10}x^2 + 1.06657 \times 10^{-9}x + 119.616 \\
 PSA_{PI}(x) &= 6.44201 \times 10^{-13}x^6 - 3.11681 \times 10^{-9}x^5 + 4.53784 \times 10^{-7}x^4 \\
 &\quad + 7.03851 \times 10^{-9}x^3 + 7.74199 \times 10^{-11}x^2 + 5.47251 \times 10^{-10}x + 58.8831 \\
 CPI(x) &= 1.2043 \times 10^{-12}x^6 - 5.85414 \times 10^{-9}x^5 + 9.76942 \times 10^{-7}x^4 \\
 &\quad + 1.5153 \times 10^{-8}x^3 + 1.66675 \times 10^{-10}x^2 + 1.17815 \times 10^{-9}x + 91.8051 \\
 SPI(x) &= -2.27533 \times 10^{-11}x^6 + 1.11526 \times 10^{-7}x^5 - 2.27794 \times 10^{-5}x^4 \\
 &\quad - 3.53321 \times 10^{-7}x^3 - 3.88633 \times 10^{-9}x^2 - 2.74707 \times 10^{-8}x + 2811.24 \\
 MP_{PI}(x) &= -4.21743 \times 10^{-12}x^6 + 2.0314 \times 10^{-8}x^5 - 2.54405 \times 10^{-6}x^4 \\
 &\quad - 3.94602 \times 10^{-8}x^3 - 4.34042 \times 10^{-10}x^2 - 3.06808 \times 10^{-9}x + 204.68
 \end{aligned}$$

Table 4: Actual vs predicted values of MW, PSA, and C based on PI

NT	MW			PSA			C		
	Actual	Predicted	Error	Actual	Predicted	Error	Actual	Predicted	Error
Ad	183.20	195.18	-11.98	72.7	67.79	4.91	154.0	160.61	-6.61
No	169.18	179.97	-10.79	86.7	77.36	9.34	142.0	152.34	-10.34
Do	153.18	157.35	-4.17	66.5	73.45	-6.95	119.0	131.13	-12.13
Ox	1007.20	1007.20	-0.00	450.0	450.00	0.00	1870.0	1870.00	0.00
GABA	103.12	120.21	-17.09	63.3	59.18	4.12	62.7	92.46	-29.76
Ac	146.21	133.72	12.49	26.3	65.14	-38.84	115.0	106.91	8.09
Gl	147.13	133.72	13.41	101.0	65.14	35.86	145.0	106.91	38.09
Se	212.67	194.54	18.13	62.0	70.45	-8.45	174.0	161.37	12.63

Table 5: Actual vs predicted values of S and MP based on PI

NT	S			MP		
	Actual	Predicted	Error	Actual	Predicted	Error
Ad	0.1000	-240.85	240.95	412	319.39	92.61
No	50.0000	794.29	-744.29	217	169.96	47.04
Do	600.0000	1661.90	-1061.90	128	149.47	-21.47
Ox	55.0000	55.00	-0.00	192	192.00	-0.00
GABA	0.0012	2795.47	-2795.47	203	203.11	-0.11
Ac	500.0000	2411.56	-1911.56	148	175.02	-27.02
Gl	8570.0000	2411.56	6158.44	205	175.02	29.98
Se	0.0319	-113.81	113.84	167	288.03	-121.03

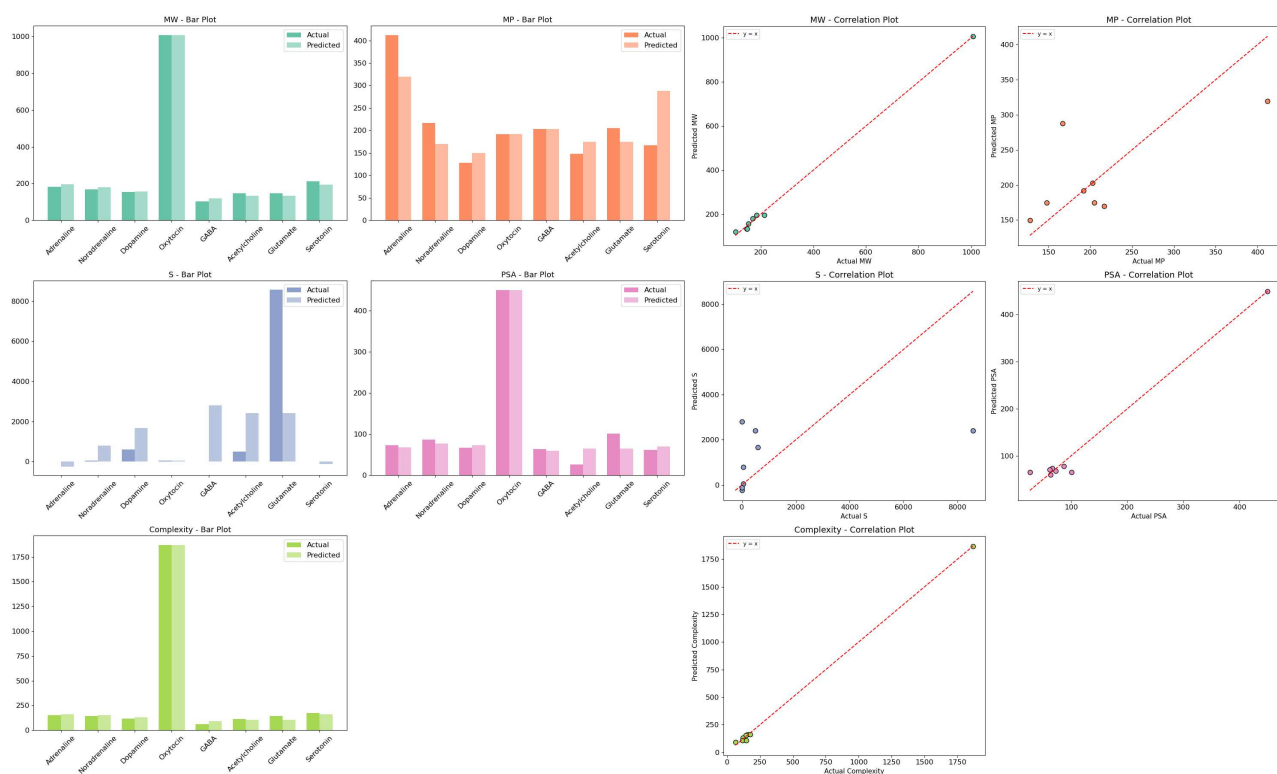


Figure 7: Bar and scatter plots based on PI

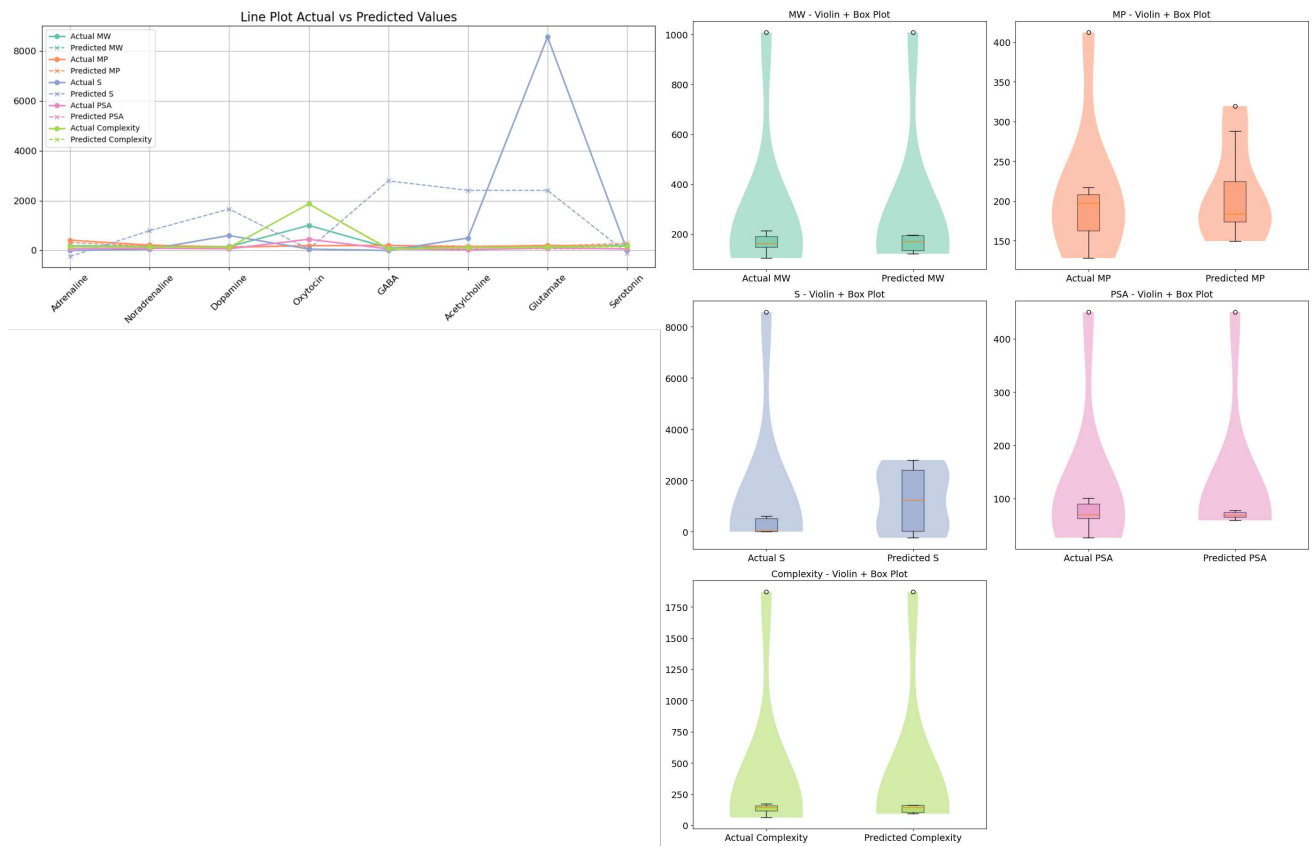


Figure 8: Line and violin plots based on PI

Results of Szeged index

$$\begin{aligned}
MW_{Sz}(x) &= 1.05129 \times 10^{-24}x^6 + 3.44571 \times 10^{-29}x^5 + 1.12937 \times 10^{-33}x^4 \\
&\quad + 3.70164 \times 10^{-38}x^3 + 1.21323 \times 10^{-42}x^2 - 3.67342 \times 10^{-40}x + 159.241 \\
PSA_{Sz}(x) &= 4.73155 \times 10^{-25}x^6 + 1.55082 \times 10^{-29}x^5 + 5.08299 \times 10^{-34}x^4 \\
&\quad + 1.66601 \times 10^{-38}x^3 + 5.46041 \times 10^{-43}x^2 - 9.18355 \times 10^{-41}x + 68.3571 \\
C_{Sz}(x) &= 2.15693 \times 10^{-24}x^6 + 7.06957 \times 10^{-29}x^5 + 2.31713 \times 10^{-33}x^4 \\
&\quad + 7.59467 \times 10^{-38}x^3 + 2.48918 \times 10^{-42}x^2 - 7.34684 \times 10^{-40}x + 130.243 \\
S_{Sz}(x) &= -1.65337 \times 10^{-24}x^6 - 5.4191 \times 10^{-29}x^5 - 1.77617 \times 10^{-33}x^4 \\
&\quad - 5.8216 \times 10^{-38}x^3 - 1.90805 \times 10^{-42}x^2 + 3.67342 \times 10^{-40}x + 1388.59 \\
MP_{Sz}(x) &= -2.40873 \times 10^{-26}x^6 - 7.89488 \times 10^{-31}x^5 - 2.58764 \times 10^{-35}x^4 \\
&\quad - 8.48127 \times 10^{-40}x^3 - 2.77977 \times 10^{-44}x^2 + 5.73972 \times 10^{-42}x + 211.429
\end{aligned}$$

Table 6: Actual vs predicted values of MW, PSA, and C based on Sz

NT	MW			PSA			C		
	Actual	Predicted	Error	Actual	Predicted	Error	Actual	Predicted	Error
Ad	183.20	159.24	23.96	72.7	68.36	4.34	154.0	130.24	23.76
No	169.18	159.24	9.94	86.7	68.36	18.34	142.0	130.24	11.76
Do	153.18	159.24	-6.06	66.5	68.36	-1.86	119.0	130.24	-11.24
Ox	1007.20	1007.20	-0.00	450.0	450.00	-0.00	1870.0	1870.00	-0.00
GABA	103.12	159.24	-56.12	63.3	68.36	-5.06	62.7	130.24	-67.54
Ac	146.21	159.24	-13.03	26.3	68.36	-42.06	115.0	130.24	-15.24
Gl	147.13	159.24	-12.11	101.0	68.36	32.64	145.0	130.24	14.76
Se	212.67	159.24	53.43	62.0	68.36	-6.36	174.0	130.24	43.76

Table 7: Actual vs predicted values of S and MP based on Sz

NT	S			MP		
	Actual	Predicted	Error	Actual	Predicted	Error
Ad	0.1000	1388.59	-1388.49	412	211.43	200.57
No	50.0000	1388.59	-1338.59	217	211.43	5.57
Do	600.0000	1388.59	-788.59	128	211.43	-83.43
Ox	55.0000	55.00	0.00	192	192.00	-0.00
GABA	0.0012	1388.59	-1388.59	203	211.43	-8.43
Ac	500.0000	1388.59	-888.59	148	211.43	-63.43
Gl	8570.0000	1388.59	7181.41	205	211.43	-6.43
Se	0.0319	1388.59	-1388.56	167	211.43	-44.43

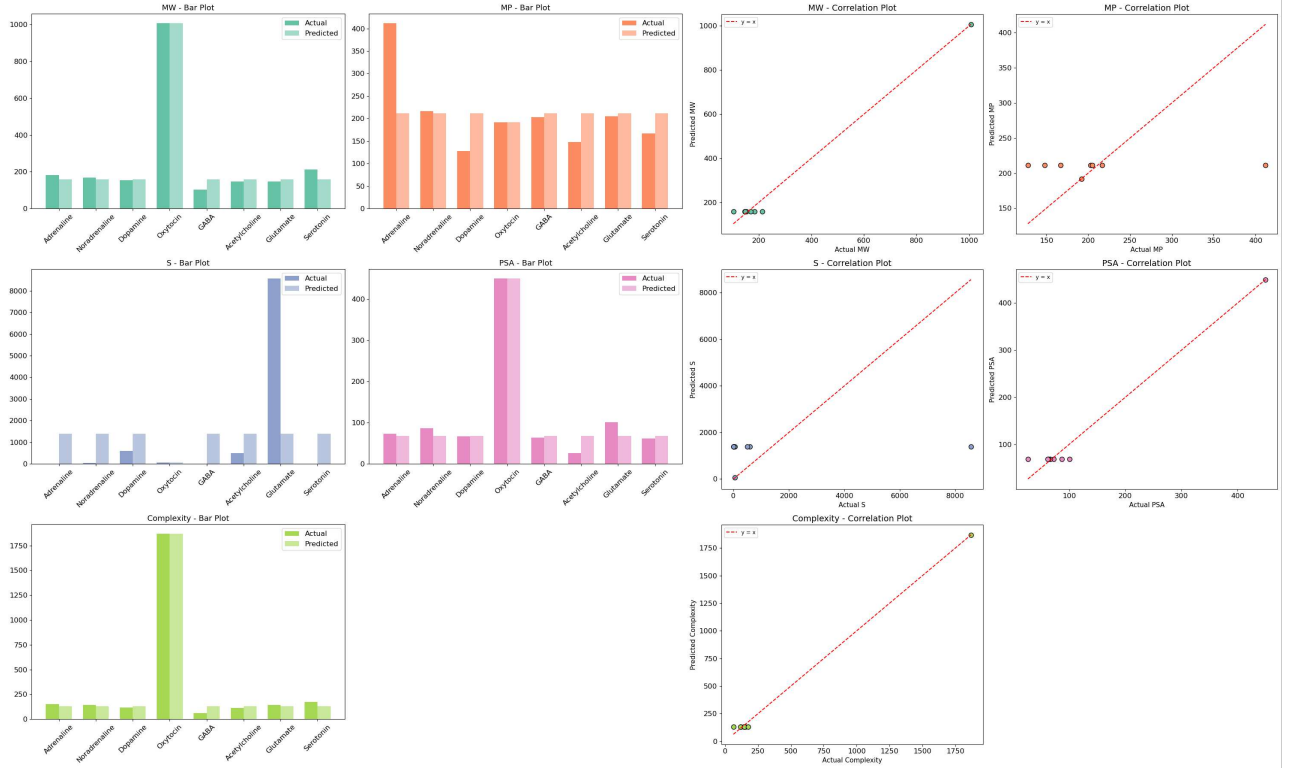


Figure 9: Bar and scatter plots based on Sz

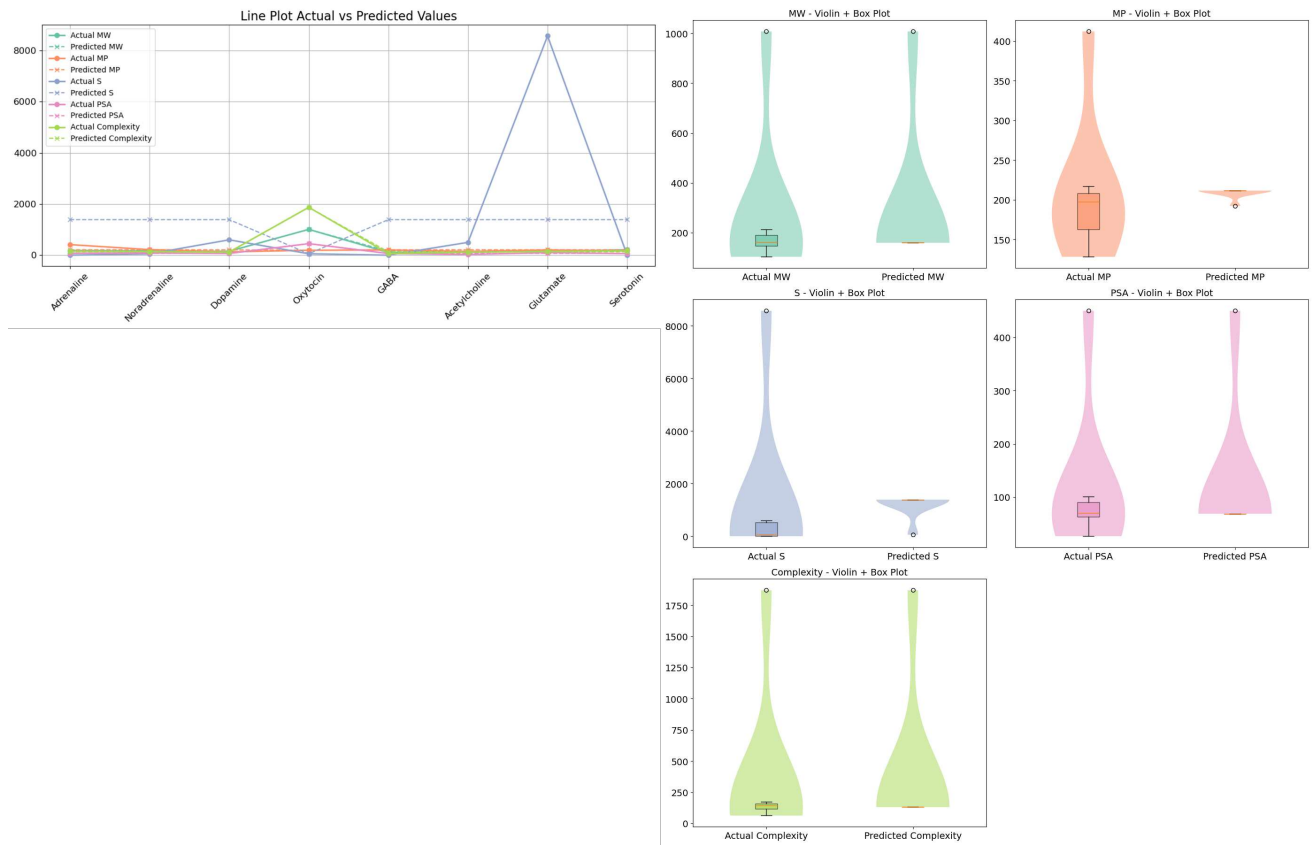


Figure 10: Line and violin plots based on Sz

Results of geometric-arithmetic index

$$\begin{aligned}
MW_{GA}(x) &= 0.00274037x^6 - 0.157223x^5 + 2.58203x^4 - 14.8292x^3 \\
&\quad + 4.0167x^2 + 213.534x - 330.141 \\
PSA_{GA}(x) &= -0.244696x^6 + 16.2283x^5 - 362.8x^4 + 3796.38x^3 \\
&\quad - 20128.7x^2 + 51678.7x - 50480.3 \\
C_{GA}(x) &= -0.0946127x^6 + 6.31102x^5 - 142.476x^4 + 1509.27x^3 \\
&\quad - 8117.54x^2 + 21190.7x - 21014.1 \\
S_{GA}(x) &= -28.2438x^6 + 1875.07x^5 - 41996.2x^4 + 440576x^3 \\
&\quad - 2.34374 \times 10^6 x^2 + 6.0418 \times 10^6 x - 5.9339 \times 10^6 \\
MP_{GA}(x) &= -0.0583157x^6 + 4.16098x^5 - 103.583x^4 + 1203.11x^3 \\
&\quad - 6962.6x^2 + 19071.7x - 19315.1
\end{aligned}$$

Table 8: Actual vs predicted values of MW, PSA, and C based on GA

NT	MW			PSA			C		
	Actual	Predicted	Error	Actual	Predicted	Error	Actual	Predicted	Error
Ad	183.20	182.51	0.69	72.7	71.48	1.22	154.0	152.86	1.14
No	169.18	160.67	8.51	86.7	71.66	15.04	142.0	127.91	14.09
Do	153.18	162.31	-9.13	66.5	82.63	-16.13	119.0	134.12	-15.12
Ox	1007.20	1007.20	-0.00	450.0	450.00	0.00	1870.0	1869.99	0.01
GABA	103.12	103.18	-0.06	63.3	63.40	-0.10	62.7	62.80	-0.10
Ac	146.21	147.64	-1.43	26.3	28.83	-2.53	115.0	117.37	-2.37
Gl	147.13	145.70	1.43	101.0	98.47	2.53	145.0	142.63	2.37
Se	212.67	212.68	-0.01	62.0	62.02	-0.02	174.0	174.02	-0.02

Table 9: Actual vs predicted values of S and MP based on GA

NT	S			MP		
	Actual	Predicted	Error	Actual	Predicted	Error
Ad	0.1000	-28.18	28.28	412	407.55	4.45
No	50.0000	-295.32	345.32	217	162.32	54.68
Do	600.0000	970.10	-370.10	128	186.68	-58.68
Ox	55.0000	56.36	-1.36	192	192.01	-0.01
GABA	0.0012	2.18	-2.18	203	203.38	-0.38
Ac	500.0000	557.86	-57.86	148	157.20	-9.20
Gl	8570.0000	8511.81	58.19	205	195.80	9.20
Se	0.0319	0.30	-0.27	167	167.08	-0.08

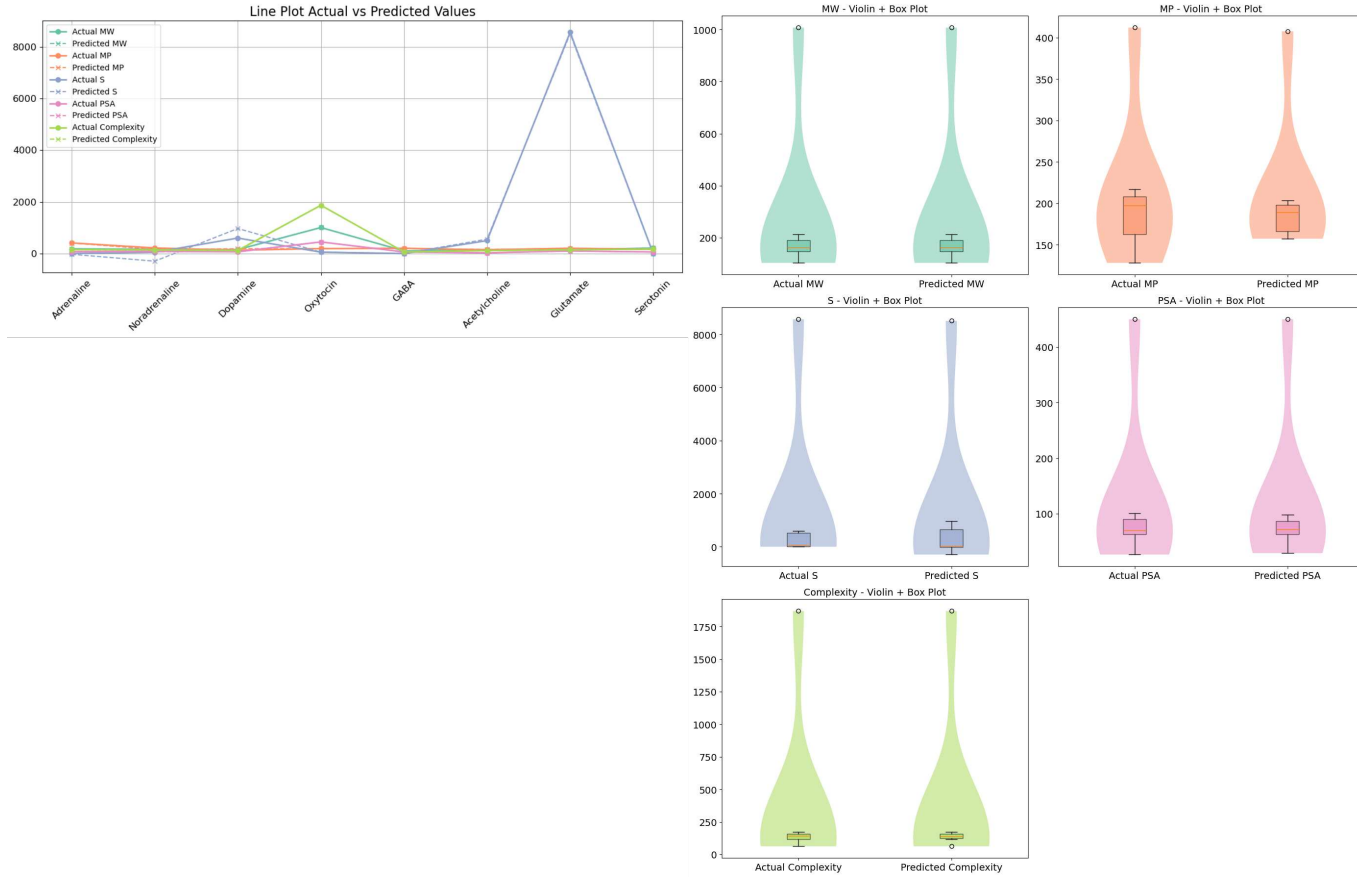


Figure 11: Line plot of actual vs predicted values

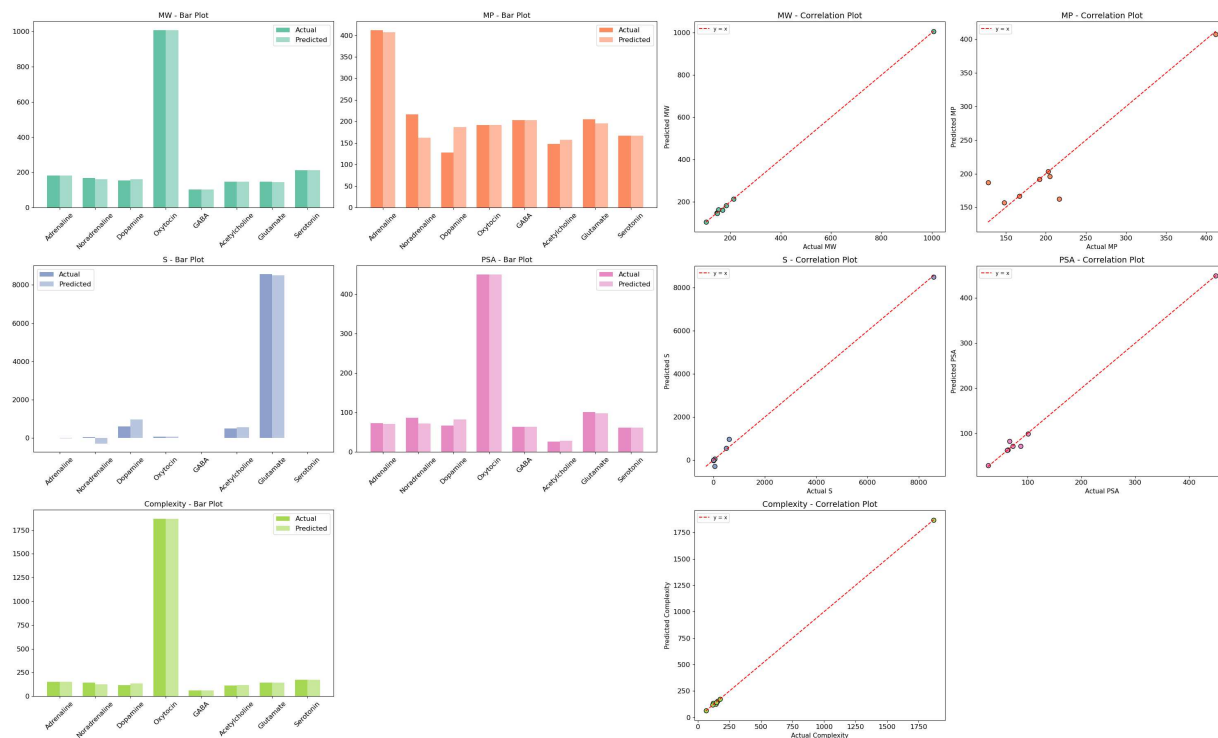


Figure 12: Bar plot of actual vs predicted values

3.2 Comparative analysis of regression models

A comprehensive comparison of the regression models constructed using the Mostar (Mo), PI, Szeged (Sz), and Geometric–Arithmetic (GA) descriptors reveals clear differences in their predictive reliability across physicochemical properties. For molecular weight (MW), polar surface area (PSA), and complexity (C), the GA-based models consistently exhibit the smallest absolute errors for the majority of compounds, with near-exact predictions observed for Oxytocin and Serotonin, and minimal deviations for Adrenaline, GABA, Acetylcholine, and Glutamate. In contrast, the Sz-based models show systematic bias, producing almost constant predicted values for several compounds, which leads to large deviations, particularly for MW and C. The PI and Mo-based models demonstrate moderate performance for MW and PSA but display noticeable inconsistencies for complexity, especially in structurally diverse molecules. These trends indicate that GA, by integrating both degree information and edge contributions in a balanced manner, captures molecular size, surface characteristics, and structural intricacy more effectively than Mo, PI, or Sz descriptors.

For solubility (S) and melting point (MP), all models struggle due to the highly non-linear and environment-sensitive nature of these properties; however, GA again provides the most stable predictions, yielding relatively small errors for Oxytocin, GABA, Acetyl-

choline, Glutamate, and Serotonin, while maintaining acceptable deviations for the remaining compounds. In comparison, Mo, PI, and Sz-based models often generate physically unrealistic or excessively large predicted values for solubility, reflecting overfitting and limited generalization. Overall, the GA-based regression model emerges as the most robust and transferable framework among the tested descriptors, offering superior accuracy and consistency across multiple physicochemical endpoints. These findings highlight the future potential of GA-driven QSPR models in rational drug design, virtual screening, and early-stage optimization, where reliable multi-property prediction is crucial. The demonstrated robustness further suggests that integrating GA descriptors with advanced machine learning or hybrid modeling strategies could significantly enhance predictive performance for complex biological and pharmaceutical datasets.

4 Conclusion

This study establishes a rigorous graph-theoretic QSPR framework for modeling the physicochemical behavior of neurotransmitter molecules by leveraging distance-based topological indices. The comparative analysis unequivocally demonstrates that the geometric-arithmetic (GA) descriptor possesses superior descriptive and predictive capacity relative to the Mostar, Padmakar-Ivan, and Szeged indices. The GA-based regression models exhibit enhanced goodness of fit, reduced residual dispersion, and improved error stability across molecular weight, polar surface area, structural complexity, solubility, and melting point, underscoring their robustness and generalizability. The consistent accuracy of GA models across structurally diverse neurotransmitters reflects their ability to effectively encode both local connectivity patterns and global molecular topology, which are critical determinants of structure–property relationships.

From a broader perspective, the findings highlight the strong predictive power and transferability of topological index-driven regression models in molecular informatics. The demonstrated robustness of the GA-based models supports their applicability in high throughput virtual screening, rational molecular design, and early stage optimization of neuroactive compounds, where reliable multi-parameter prediction is essential. Moreover, the integration of graph theoretic descriptors with advanced statistical learning or hybrid machine learning paradigms offers a promising pathway toward developing next generation predictive models with enhanced accuracy, interpretability, and scalability for complex biochemical and pharmaceutical systems.

Declarations

Author Contribution

H.M.F., Z.U.H., K.A., M.F.N. conducted Writing – original draft, Visualization, Validation, Software, Methodology, Investigation, Formal analysis, Data curation, Concep-

tualization. P.R., A.L. and S.M. worked on Writing – review & editing, Visualization, Validation, Resources, Data curation, Conceptualization.

Declaration of competing interest

The authors have no conflict of interest to disclose.

Data availability statements

All the data used to finding the results is taken from public repository, PubChem <https://pubchem.ncbi.nlm.nih.gov/>.

Funding statement

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Ethical statement

This article does not contain any studies with human or animals.

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References

- [1] Sheffler, Z. M., Reddy, V., & Pillarisetty, L. S. (2023). Physiology, neurotransmitters. In StatPearls [Internet]. StatPearls Publishing. 1
- [2] Franco, R., Reyes-Resina, I., & Navarro, G. (2021). Dopamine in health and disease: Much more than a neurotransmitter. *Biomedicines*, 9(2), 109. 1
- [3] Zuo, Y., Ye, J., Cai, W., Guo, B., Chen, X., Lin, L., & Wang, X. (2023). Controlled delivery of a neurotransmitter–agonist conjugate for functional recovery after severe spinal cord injury. *Nature Nanotechnology*, 18(10), 1230-1240. 1
- [4] Andersen, J. V., Schousboe, A., & Verkhratsky, A. (2022). Astrocyte energy and neurotransmitter metabolism in Alzheimer’s disease: integration of the glutamate/GABA-glutamine cycle. *Progress in neurobiology*, 217, 102331. 1

- [5] Rajagopalan, V., Venkataraman, S., Rajendran, D. S., Kumar, V. V., Kumar, V. V., & Rangasamy, G. (2023). Acetylcholinesterase biosensors for electrochemical detection of neurotoxic pesticides and acetylcholine neurotransmitter: A literature review. *Environmental Research*, 227, 115724. 1
- [6] Kim, D., & Lee, J. S. (2022). Neurotransmitter-induced excitatory and inhibitory functions in artificial synapses. *Advanced Functional Materials*, 32(21), 2200497. 1
- [7] Chavan, S. G., Rathod, P. R., Koyappayil, A., Hwang, S., & Lee, M. H. (2025). Recent advances of electrochemical and optical point-of-care biosensors for detecting neurotransmitter serotonin biomarkers. *Biosensors and Bioelectronics*, 267, 116743. 1
- [8] Teleanu, R. I., Niculescu, A. G., Roza, E., Vladăcenco, O., Grumezescu, A. M., & Teleanu, D. M. (2022). Neurotransmitters—key factors in neurological and neurodegenerative disorders of the central nervous system. *International journal of molecular sciences*, 23(11), 5954. 1
- [9] Jodko-Piorecka, K., Sikora, B., Kluzek, M., Przybylski, P., & Litwinienko, G. (2021). Antiradical activity of dopamine, L-DOPA, adrenaline, and noradrenaline in water/methanol and in liposomal systems. *The Journal of Organic Chemistry*, 87(3), 1791-1804. 1
- [10] Thomas, R., Pooventhiran, T., Bakht, M. A., Alzahrani, A. Y., & Salem, M. A. (2022). Study of interaction between different solvents and neurotransmitters dopamine, l-adrenaline, and l-noradrenaline using LED, QTAIM and AIMD. *Journal of Molecular Liquids*, 368, 120708. 1
- [11] Zatz, R., & De Nucci, G. (2024). Endothelium-derived dopamine and 6-nitrodopamine in the cardiovascular system. *Physiology*, 39(1), 44-59. 1
- [12] Kourek, C., Xanthopoulos, A., Giamouzis, G., Parisis, C., Briasoulis, A., Magouliotis, D. E., & Skoularigis, J. (2024). Neurohormonal Effects of Intravenous Dopamine in Patients with Acute Heart Failure. *Journal of Clinical Medicine*, 13(19), 5667. 1
- [13] Zhang, Y., Karadas, M., Liu, J., Gu, X., Voroslakos, M., Li, Y., & Buzsáki, G. (2024). Interaction of acetylcholine and oxytocin neuromodulation in the hippocampus. *Neuron*, 112(11), 1862-1875. 1
- [14] Bamicha, V., Pergantis, P., Skianis, C., & Drigas, A. (2025). Computational Neuroscience's Influence on Autism Neuro-Transmission Research: Mapping Serotonin, Dopamine, GABA, and Glutamate. *Biomedicines*, 13(6), 1420. 1
- [15] Li, H., Li, Y., Wang, T., Li, S., Liu, H., Ning, S., & Wu, H. (2024). Spatiotemporal Mapping of the Oxytocin Receptor at Single-Cell Resolution in the Postnatally Developing Mouse Brain. *Neuroscience Bulletin*, 1-19. 1

- [16] Fraz, H. M., Ali, K., & Nadeem, M. F. (2025). Entropy measures of silicon nanotubes using degree based topological indices. *Physica Scripta*, 100(1), 015202. 1
- [17] Fraz, H. M., Ali, K., Nadeem, M. F., Ali, N., & Tolasa, F. T. (2025). Predictive modeling of copper iodide properties using graph-theoretical descriptors. *Scientific Reports*, 15(1), 39878. 1
- [18] Hasani, M., & Ghods, M. (2024). Topological indices and QSPR analysis of some chemical structures applied for the treatment of heart patients. *International Journal of Quantum Chemistry*, 124(1), e27234. 1
- [19] Hayat, S., Khan, A., Ali, K., & Liu, J. B. (2024). Structure-property modeling for thermodynamic properties of benzenoid hydrocarbons by temperature-based topological indices. *Ain Shams Engineering Journal*, 15(3), 102586. 1
- [20] Zaman, S., Hakami, K. H., Rasheed, S., & Agama, F. T. (2024). Reduced reverse degree-based topological indices of graphyne and graphdiyne nanoribbons with applications in chemical analysis. *Scientific Reports*, 14(1), 547. 1
- [21] Arockiaraj, M., Greeni, A. B., & Kalaam, A. A. (2024). Comparative analysis of reverse degree and entropy topological indices for drug molecules in blood cancer treatment through QSPR regression models. *Polycyclic Aromatic Compounds*, 44(9), 6024-6041. 1
- [22] Das, S., Rai, S., & Kumar, V. (2024). On topological indices of Molnupiravir and its QSPR modelling with some other antiviral drugs to treat COVID-19 patients. *Journal of Mathematical Chemistry*, 62(10), 2581-2624. 1
- [23] Zaman, S., Yaqoob, H. S. A., Ullah, A., & Sheikh, M. (2024). QSPR analysis of some novel drugs used in blood cancer treatment via degree based topological indices and regression models. *Polycyclic Aromatic Compounds*, 44(4), 2458-2474. 1
- [24] Abid, M., Fraz, H. M., Ali, K., & Nadeem, M. F. (2025). Predictive modeling of physicochemical properties of anticancer drugs using distance-based topological descriptors. *Physica Scripta*, 100(8), 085004. 1
- [25] Hayat, S., Alanazi, S. J., & Liu, J. B. (2024). Two novel temperature-based topological indices with strong potential to predict physicochemical properties of polycyclic aromatic hydrocarbons with applications to silicon carbide nanotubes. *Physica Scripta*, 99(5), 055027. 1
- [26] Zhang, X., Bajwa, Z. S., Zaman, S., Munawar, S., & Li, D. (2024). The study of curve fitting models to analyze some degree-based topological indices of certain anti-cancer treatment. *Chemical Papers*, 78(2), 1055-1068. 1
- [27] Arockiaraj, M., Campena, F. J. H., Greeni, A. B., Ghani, M. U., Gajavalli, S., Tchier, F., & Jan, A. Z. (2024). QSPR analysis of distance-based structural indices for drug compounds in tuberculosis treatment. *Heliyon*, 10(2). 1

- [28] Sardar, M. S., & Hakami, K. H. (2024). QSPR analysis of some Alzheimer's compounds via topological indices and regression models. *Journal of Chemistry*, 2024(1), 5520607. 1
- [29] Fraz, H.M., Ali, K., Nadeem, M.F., Wang, M., Mallik, S. (2026). QSPR modeling of anti-COVID drugs using distance-based topological indices. *Next Research*, 102368:12, 2026, doi: 10.1016/j.nexres.2026.102368. 1
- [30] Fraz, H. M., Ali, N., Alshammari, F. S., Tolasa, F. T., Smerat, A., & Olana, J. A. (2026). Spectral Energy and QSPR Investigation of Selected Antiviral Compounds Using Graph-Theoretical Descriptors of Antiviral Drugs Targeting SARS-CoV-2. *ChemistrySelect*, 11(33), e74333. 1
- [31] Fraz, H. M., Ali, K., Nadeem, M. F., Ali, N., & Tolasa, F. T. (2025). Predictive modeling of copper iodide properties using graph-theoretical descriptors. *Scientific Reports*, 15(1), 39878. 1
- [32] Wang, H., & Liu, M. (2023). The Upper Bound of the Edge Mostar Index with Respect to Bicyclic Graphs. *Mathematics*, 11(11), 2506. 2
- [33] Wang, Y., & Niu, M. (2025). The Mostar index of Tribonacci cubes. *Discrete Mathematics*, 348(2), 114281. 2
- [34] Kavaskar, T., & Vinothkumar, K. (2024). Padmakar-Ivan index of some families of graphs. *Discrete Mathematics, Algorithms and Applications*, 16(05), 2350064. 2
- [35] Chithrabhanu, M. S., & Somasundaram, K. (2022). Padmakar-Ivan index of some types of perfect graphs. *Discrete Math. Lett*, 9, 92-99. 2
- [36] Lopera, C., & Cruz, R. (2023). Szeged index of hollow hexagons. *International Journal of Quantum Chemistry*, 123(23), e27231. 2
- [37] He, S., Geng, Q., & Hao, R. X. (2023). The extremal unicyclic graphs with given diameter and minimum edge revised Szeged index. *AIMS Mathematics*, 8(11), 26301-26327. 2
- [38] Rodriguez, J. M., Sánchez, J. L., Sigarreta, J. M., & Tourís, E. (2021). Bounds on the arithmetic-geometric index. *Symmetry*, 13(4), 689. 2
- [39] Loghman, A., & Saheli, M. (2023). Computing two types of geometric-arithmetic indices of some benzenoid graphs. *Journal of Discrete Mathematics and Its Applications*, 8(3), 171-175. 2
- [40] Fraz, H. M., Ali, K., & Nadeem, M. F. (2024). Computational analysis of antiviral drugs using topological descriptors. *Computers in Biology and Medicine*, 175, 108529. 3.1