



Topological Analysis of NSAID Drugs Using Graph Theory and Linear Regression Models

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ABSTRACT: This paper deals with the topological analysis of quantitative structure–property relationships(QSPR) of nonsteroidal anti-inflammatory drugs(NSAID). Here we consider four different degree based indices such as Randic type lodeg, Randic type hadi, Exponential fraction and Randic type SDI indices. We employ the linear regression models, and data science approaches.

Keywords: NSAID, linear regression model, topological indices.

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1. Introduction

Graph Theory is one of the fundamental mathematical area which can help to solve different critical problems of science and technology. It will also plays a significant role in pharmaceutical research by modeling molecular structures of drugs as graphs. In molecular graphs, atoms are represented as vertices, and bonds between atoms are represented as edges. This mathematical representation helps to analyze molecular properties, predict drug behavior, and optimize drug design. One of the most significant applications of graph theory in chemistry/pharmaceuticals is the use of topological indices. These are the numerical descriptors derived from molecular graphs. These indices form the backbone of Quantitative Structure-Property Relationship (QSPR) and Quantitative Structure-Activity Relationship (QSAR) analyses. These analysis allow researchers to predict the physico-chemical properties of drugs. In this paper we use the topological indices which are defined as follows.

Definition 1.1 Randic type SDI index which is defined as [8]

$$R_{SDI}(G) = \sum_{uv \in E(G)} (d_u)^2 (d_v)^2$$

Definition 1.2 Randic type Lodeg index which is defined as [8]

$$R_L(G) = \sum_{uv \in E(G)} \ln(d_u) \ln(d_v)$$

Definition 1.3 Exponential Fraction index which is defined as [2]

$$EF(G) = \sum_{uv \in E(G)} e^{\frac{d_u}{d_v}}$$

Definition 1.4 Randic type Hadi index which is defined as [8]

$$R_H(G) = \sum_{uv \in E(G)} \frac{1}{2^{d_u+d_v}}$$

Here d_u and d_v represents the degree of the vertices of u and v respectively.

2. Topological Analysis of NSAID Drugs

Leena Rosalind et al., studied the topological nature of NSAID drugs in [1]. Motivated by this we consider ten NSAID drugs such as Ketorolac, Diclofenac, Naproxen, Ibuprofen, Meloxicam, Nabumetone, Indomethacin, Famotidine, Etodolac, and Piroxicam. We use ChemSpider to get the values for these characteristics.

Theorem 2.1 *Exponential fraction, Randic type lodeg, hadi and SDI indices of Ketorolac are 119.7661, 14.693, 0.84375 and 825 respectively.*

Proof: We prove this by edge partition. In Ketorolac, there are 21 edges, in which 3 edges are present in between the vertices of degree 3 and 1. 6 edges connect the vertices of degree 2 each. 6 edges will connect the vertices with degree 2 and 3. Finally 6 edges exist between the vertices of degree 3 each. Thus by the definition of Randic type hadi index

$$\begin{aligned} RH(Ketorolac) &= \frac{3}{2^4} + \frac{6}{2^4} + \frac{6}{2^5} + \frac{6}{2^6} \\ &= 0.84375. \end{aligned}$$

Similar proof can be applied for other indices.

Theorem 2.2 *Exponential fraction, Randic type lodeg, hadi and SDI indices of Diclofenac are 137.94, 12.11, 0.859 and 647 respectively.*

Proof: We prove this by edge partition. In Ketorolac, there are 20 edges, in which 4 edges are present in between the vertices of degree 3 and 1. 5 edges connect the vertices of degree 2 each. 8 edges will connect the vertices with degree 2 and 3. Finally 6 edges exist between the vertices of degree 3 each. Thus by the definition of Randic type hadi index

$$\begin{aligned} RH(Ketorolac) &= \frac{4}{2^4} + \frac{5}{2^4} + \frac{8}{2^5} + \frac{3}{2^6} \\ &= 0.8593. \end{aligned}$$

Theorem 2.3 *Exponential fraction, Randic type lodeg, hadi and SDI indices of Naproxen are 121.57, 11.43, 0.76 and 630 respectively.*

Proof: The edge partition of Naproxen is as follows. There are 18 edges, in which 3 edges are present in between the vertices of degree 3 and 1. 2 edges connect the vertices of degree 2 each. 9 edges will connect the vertices with degree 2 and 3. One edge is there between the vertices of degree 2 and 1. Finally 3 edges exist between the vertices of degree 3 each. Thus by the definition of EF index

$$\begin{aligned} EF(Naproxen) &= e^2 + 3e^3 + 2e + 9e^{\frac{3}{2}} + 3e \\ &= 121.572. \end{aligned}$$

Theorem 2.4 *Exponential fraction, Randic type lodeg, hadi and SDI indices of Ibuprofen are 121.57, 11.43, 0.76 and 630 respectively.*

Proof: The edge partition of Ibuprofen is as follows. There are 15 edges, in which 5 edges are present in between the vertices of degree 3 and 1. 6 edges connect the vertices of degree 2 each. 2 edges will connect the vertices with degree 2 and 3. Finally 2 edges exist between the vertices of degree 3 each. Thus by the definition of EF index

$$\begin{aligned} EF(Ibuprofen) &= 5e^3 + 2e + 2e^{\frac{3}{2}} + 8e \\ &= 131.1373. \end{aligned}$$

Theorem 2.5 *Exponential fraction, Randic type lodeg, hadi and SDI indices of Meloxicam are 257.44, 17.09, 0.90 and 1113 respectively.*

Proof: We prove this by edge partition. In Meloxicam, there are 25 edges, in which 4 edges are present in between the vertices of degree 3 and 1. 4 edges connect the vertices of degree 2 each. 8 edges will connect the vertices with degree 2 and 3. 2 edges will connect the vertices with degree 1 and 4. 2 edges will connect the vertices with degree 3 and 4. Finally 5 edges exist between the vertices of degree 3 each. Thus by the definition of Randic type hadi index

$$\begin{aligned} RH(Meloxicam) &= \frac{4}{2^4} + \frac{2}{2^5} + \frac{4}{2^4} + \frac{8}{2^5} + \frac{5}{2^6} + \frac{2}{2^7} \\ &= 0.9063. \end{aligned}$$

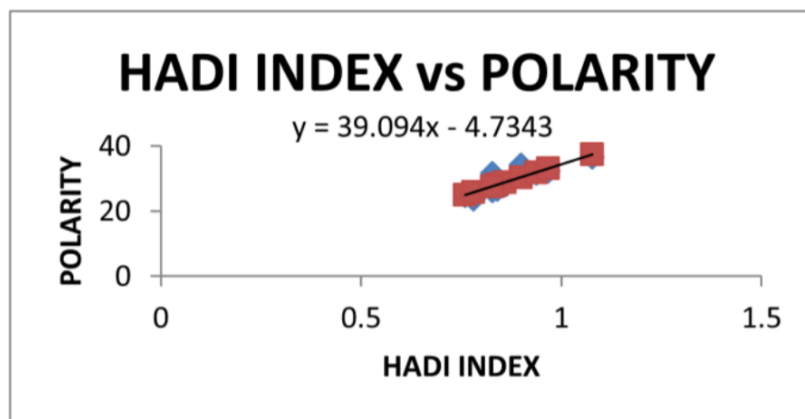
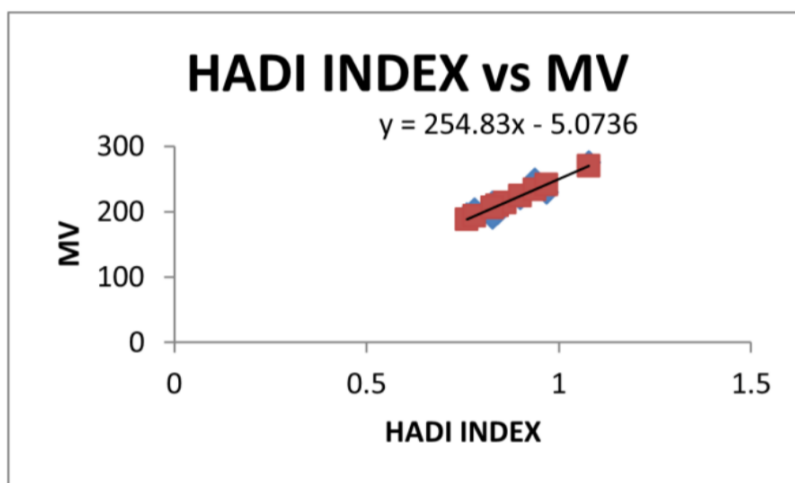
Physical and chemical properties of NSAID are as mentioned below [1].

Table 1: Topological indices of NSAID

Drugs	EF index	Lodeg index	Hadi index	SDI index
Ketorolac	119.76	14.69	0.84	825
Diclofenac	137.94	12.11	0.859	647
Naproxen	121.57	11.43	0.76	630
Ibuprofen	131.13	6.81	0.78	375
Meloxicam	257.44	17.09	0.90	1113
Nabumetone	73.18	10.74	0.828	512
Indomethacin	184.29	18.26	1.078	1060
Famotidine	282.64	9.736	0.828	527
Etodolac	139.38	16.20	0.937	942
Piroxicam	236.54	17.012	0.968	1080

Table 2: Physical and chemical properties of NSAID

Drugs	Pol	C	R	MW	MV
Ketorolac	26.67	376	70.19	83.1	198.2
Diclofenac	27.93	304	75.46	73.1	209.8
Naproxen	24.81	277	64.85	72.1	195.3
Ibuprofen	23.76	203	60.73	62.4	203.3
Meloxicam	34.25	628	88.62	83.5	220.7
Nabumetone	26.17	262	68.43	64.3	213.5
Indomethacin	36.64	506	94.81	83.3	275.6
Famotidine	31.66	469	80.46	100.3	191.7
Etodolac	31.66	400	80.46	84.9	248.3
Piroxicam	32.27	611	87.04	91.3	229.8



3. Linear Regression and Model Evaluation

We use linear regression to quantify relationships between indices and drug efficacy. Model evaluation metrics, such as R-squared and Mean Squared Error, assess model accuracy, guiding feature refinement for predictive robustness. We explain using Hadi index. The following graph represents the Hadi index vs molar volume. The following graph represents the Hadi index vs polarity.

The following graph represents the Hadi index vs refractivity.

4. Regression Model and Correlation with Physicochemical Properties

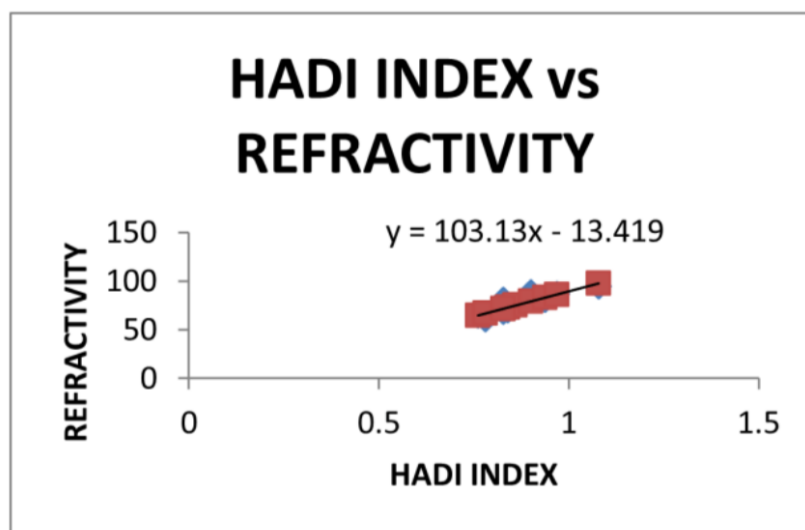
After analyzing the data, the following regression models are established. From Hadi-index we get a good correlation with the physico-chemical properties.

$$\text{Refractivity} = 103.13[\text{HADI}] - 13.419$$

$$\text{Molar volume} = 254.83[\text{HADI}] - 5.0736$$

$$\text{Polarity} = 39.094[\text{HADI}] - 4.7343$$

There is a good correlation between Hadi index and Refractivity of 0.8879. There is a strong correlation between Hadi index and Molar volume of 0.9229. Also, there is a good correlation between Hadi index and Polarity of 0.868.



5. Conclusion

The integration of topological indices into pharmaceutical research exemplifies a paradigm shift in drug discovery, leveraging mathematical abstraction to elucidate intricate molecular interactions. In this current research, we analysed ten NSAID drugs such as Ketorolac, Diclofenac, Naproxen, Ibuprofen, Meloxicam, Nabumetone, Indomethacin, Famotidine, Etodolac, and Piroxicam. It was found that Hadi index is having high correlation with the physico-chemical properties.

Acknowledgments

We the authors would like to thank the anonymous reviewers for your suggestions.

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