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QSPR Modeling of Non-Steroidal Anti-Inflammatory Drugs Using Contra Harmonic Index

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Abstract

This study analyses Contra Harmonic Index (*CHI*), a graph-theoretical descriptor, in Quantitative Structure-Property Relationship (QSPR) modeling to predict properties of some Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) which include diclofenac, ibuprofen, celecoxib, indomethacin, mefenamic acid, etodolac and sulindac. It was found that *CHI* relates with molecular weight, complexity, refractivity, polarizablity and polar surface area. These results help us understand that *CHI* can be used as a potential topological descriptor which aids in drug design.

AMS 2010 Classifications: 05C07, 05C90

Keywords and phrases: Contra Harmonic index, QSPR analysis, NSAID, molecular weight, complexity, refractivity, polarizablity, polar surface area

1. Introduction

Ever since the introduction of Wiener index in 1947 by Harold Wiener[2], several topological indices have been introduced, aiding in predicting different characteristics of chemical compounds. S. Ragavi and R. Sridevi introduced Contra Harmonic index of graphs in [8]. Contra Harmonic Index of networks are studied in [1]. Gnanaraj et al. analysed topological indices in some NSAIDs [7] and analysis of different classes of drugs are done in [3], [5] and [11]. Throughout the study, molecular graph imply hydrogen depleted graphs of the chemical structures.

The Contra Harmonic Index (CHI) captures molecular topology by weighting vertex degrees in a graph representation of chemical structures. Here we analyse how *CHI* can be used to predict physiochemical properties of NSAIDs. Non-Steroidal Anti-Inflammatory Drugs (NSAIDs) are among the most widely used therapeutic agents globally, valued for their analgesic, anti-inflammatory, and antipyretic properties. These drugs are essential for managing pain, reducing inflammation in conditions like arthritis and preventing cardiovascular events through platelet inhibition. Beyond medicine, NSAIDs serve as research tools for studying inflammatory pathways and hence useful in clinical practice and biomedical research.

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Definition 1.1 [8]**:** Contra Harmonic index of a graph G is defined as sum of the term $\frac{d(u)^2+d(v)^2}{d(u)+d(v)}$ over all edges uv of graph G.

$$CHI(G) = \sum_{uv \in E(G)} \frac{d(u)^2 + d(v)^2}{d(u) + d(v)}$$

2. Contra Harmonic Index of NSAIDs

Theorem 2.1. *Contra Harmonic index of Diclofenac is* 49.8.

Proof. Let N_1 be the molecular graph of Diclofenac

Table 2.1. Edge partition of N_1 based on degree of vertices

(d_u, d_v)	Number of adjacent pair of vertices u, v
(1,3)	4
(2,2)	5
(2,3)	8
(3,3)	3

$$CHI(N_1) = \sum_{u_i u_j \in E(N_1)} \frac{d(u_i)^2 + d(u_j)^2}{d(u_i) + d(u_j)}$$

$$= 4\left[\frac{1^2+3^2}{1+3}\right] + 5\left[\frac{2^2+2^2}{2+2}\right] + 8\left[\frac{3^2+2^2}{3+2}\right] + 3\left[\frac{3^2+4^2}{3+4}\right]$$

Therefore, $CH(N_1)$=49.8

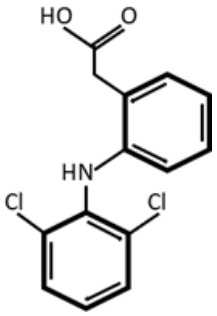

Figure 2.1. Molecular graph of Diclofenac

Theorem 2.2. *Contra Harmonic index of Ibuprofen is* 38.1.

Proof. Let N_2 be the molecular graph of Ibuprofen

Table 2.2. Edge partition of N_2 based on degree of vertices

(d_u, d_v)	Number of adjacent pair of vertices u, v
$(1,3)$	5
$(2,2)$	2
$(2,3)$	6
$(3,3)$	2

$$CHI(N_2) = \sum_{u_i u_j \in E(N_2)} \frac{d(u_i)^2 + d(u_j)^2}{d(u_i) + d(u_j)}$$

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$$= 5\left[\frac{1^2+3^2}{1+3}\right] + 2\left[\frac{2^2+2^2}{2+2}\right] + 6\left[\frac{3^2+2^2}{3+2}\right] + 2\left[\frac{3^2+3^2}{3+3}\right]$$

Therefore, $CHI(N_2)$= 38.1

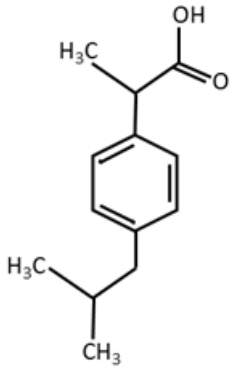


Figure 2.2. Molecular graph of Ibuprofen

Theorem 2.3. *Contra Harmonic index of Naproxen is* 45.56.

Proof. Let N_3 be the molecular graph of Naproxen

Table 2.3. Edge partition of N_3 based on degree of vertices

(d_u, d_v)	**Number of adjacent pair of vertices u, v**
$(1,2)$	1
$(1,3)$	3
$(2,2)$	2
$(2,3)$	9
$(3,3)$	3

$$CH(N_3) = \sum_{u_i u_j \in E(N_3)} \frac{d(u_i)^2 + d(u_j)^2}{d(u_i) + d(u_j)}$$

$$= 1\left[\frac{1^2+2^2}{1+2}\right] + 3\left[\frac{1^2+3^2}{1+3}\right] + 2\left[\frac{2^2+2^2}{2+2}\right] + 9\left[\frac{3^2+2^2}{3+2}\right] + 3\left[\frac{3^2+3^2}{3+3}\right]$$

Therefore, $CH(N_3)$= 45.56

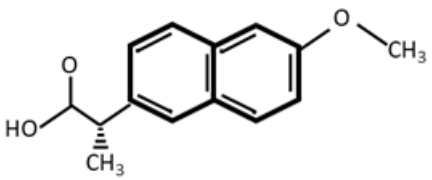


Figure 2.3. Molecular graph of Naproxen

Theorem 2.4. *Contra Harmonic index of Celecoxib is* 78.24.

Proof. Let N_4 be the molecular graph of Gliclazide

Table 2.4. Edge partition of N_4 based on degree of vertices

(d_u, d_v)	**Number of adjacent pair of vertices u, v**
(1,3)	1

(1,4)	6
(2,2)	4
(2,3)	12
(3,3)	3
(3,4)	2

$$CHI(N_4) = \sum_{u_i u_j \in E(N_4)} \frac{d(u_i)^2 + d(u_j)^2}{d(u_i) + d(u_j)}$$

$$= 1\left[\frac{1^2+3^2}{1+3}\right] + 6\left[\frac{1^2+4^2}{1+4}\right] + 4\left[\frac{2^2+2^2}{2+2}\right] + 12\left[\frac{3^2+2^2}{3+2}\right] + 3\left[\frac{3^2+3^2}{3+3}\right] + 2\left[\frac{3^2+4^2}{3+4}\right]$$

Therefore, $CHI(N_4)$= 78.24

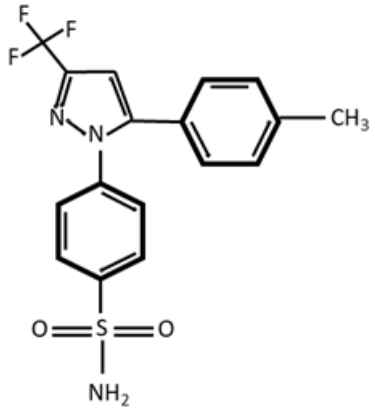


Figure 2.4. Molecular graph of Celecoxib

Theorem 2.5. *Contra Harmonic index of Indomethacin is* 69.76.

Proof. Let N_5 be the molecular graph of Indomethacin

Table 2.5. Edge partition of N_5 based on degree of vertices

(d_u, d_v)	**Number of adjacent pair of vertices u, v**
(1,2)	1
(1,3)	5
(2,2)	3
(2,3)	11
(3,3)	7

$$CHI(N_5) = \sum_{u_i u_j \in E(N_5)} \frac{d(u_i)^2 + d(u_j)^2}{d(u_i) + d(u_j)}$$

$$= 1\left[\frac{1^2+2^2}{1+2}\right] + 5\left[\frac{1^2+3^2}{1+3}\right] + 3\left[\frac{2^2+2^2}{2+2}\right] + 11\left[\frac{3^2+2^2}{3+2}\right] + 7\left[\frac{3^2+3^2}{3+3}\right]$$

Therefore, $CHI(N_5)$=69.76

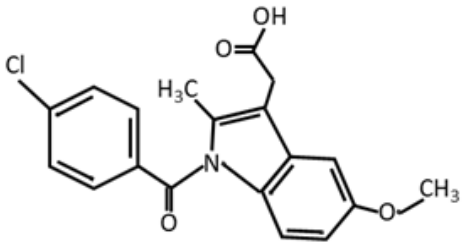


Figure 2.5. Molecular graph of Indomethacin

Theorem 2.6. *Contra Harmonic index of Mefenamic acid is* 47.6.

Proof. Let N_6 be the molecular graph of Furosemide

Table 2.6. Edge partition of N_6 based on degree of vertices

(d_u, d_v)	**Number of adjacent pair of vertices u, v**
(1,3)	4
(2,2)	5
(2,3)	6
(3,3)	4

$$CHI(N_6) = \sum_{u_i u_j \in E(N_6)} \frac{d(u_i)^2 + d(u_j)^2}{d(u_i) + d(u_j)}$$

$$= 4\left[\frac{1^2+3^2}{1+3}\right] + 5\left[\frac{2^2+2^2}{2+2}\right] + 6\left[\frac{3^2+2^2}{3+2}\right] + 4\left[\frac{3^2+3^2}{3+3}\right]$$

Therefore, $CHI(N_6)$= 47.6

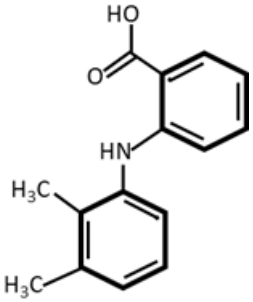


Figure 2.6. Molecular graph of Mefenamic Acid

Theorem 2.7. *Contra Harmonic index of Etodolac is* 60.10.

Proof. Let N_7 be the molecular graph of Etodolac

Table 2.7. Edge partition of N_7 based on degree of vertices

(d_u, d_v)	**Number of adjacent pair of vertices u, v**
(1,2)	2
(1,3)	2
(2,2)	4
(2,3)	7

(2,4)	3
(3,3)	4
(3,4)	1

$$CHI(N_7) = \sum_{u_i u_j \in E(N_7)} \frac{d(u_i)^2 + d(u_j)^2}{d(u_i) + d(u_j)}$$
$$= 2\left[\frac{1^2+2^2}{1+2}\right] + 2\left[\frac{1^2+3^2}{1+3}\right] + 4\left[\frac{2^2+2^2}{2+2}\right] + 7\left[\frac{3^2+2^2}{3+2}\right] + 3\left[\frac{2^2+4^2}{3+4}\right] + 4\left[\frac{3^2+3^2}{3+4}\right] + 1\left[\frac{3^2+4^2}{3+4}\right]$$

Therefore, $CHI(N_7)$= 60.10

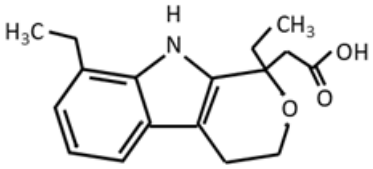


Figure 2.7. Molecular graph of Etodolac

Theorem 2.8. *Contra Harmonic index of Sulindac is* 70.2.

Proof. Let N_8 be the molecular graph of Sulindac

Table 2.8. Edge partition of N_8 based on degree of vertices

(d_u, d_v)	**Number of adjacent pair of vertices u, v**
(1,3)	6
(2,2)	3
(2,3)	12
(3,3)	6

$$CHI(N_8) = \sum_{u_i u_j \in E(N_8)} \frac{d(u_i)^2 + d(u_j)^2}{d(u_i) + d(u_j)}$$
$$= 6\left[\frac{1^2+3^2}{1+3}\right] + 3\left[\frac{2^2+2^2}{2+2}\right] + 12\left[\frac{3^2+2^2}{3+2}\right] + 6\left[\frac{3^2+3^2}{3+3}\right]$$

Therefore, $CHI(N_8)$= 70.2

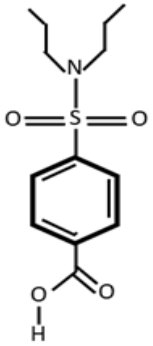


Figure 2.8. Molecular graph of Sulindac

3. QSPR Analysis of Sulfonamides

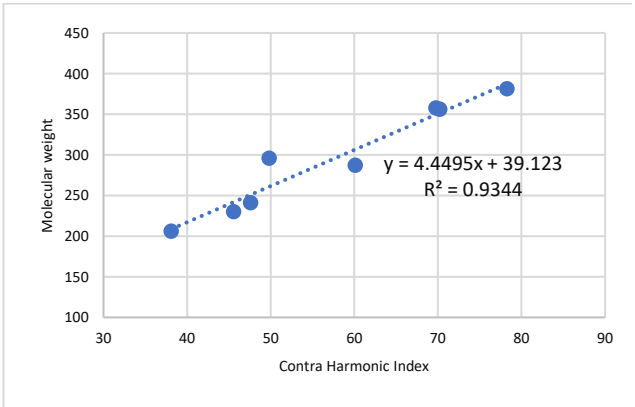
This section explores the quantitative structure-property relationships (QSPR) of NSAIDs using the Contra Harmonic index. The experimental datasets for NSAIDs include molecular weight and complexity from PubChem[10], refractivity, polar surface area and polarizability from DrugBank[6]. These properties were selected to assess CHI's ability to predict steric bulk, electronic distribution and bioavailability, offering insights into drug design and pharmacokinetic optimization. By correlating CHI with these experimentally derived properties, this study aims to establish reliable QSPR models that link molecular structure with drug-like behavior, facilitating the rational design of improved pharmaceuticals.

Table 2.9. The molecular properties of NSAIDs

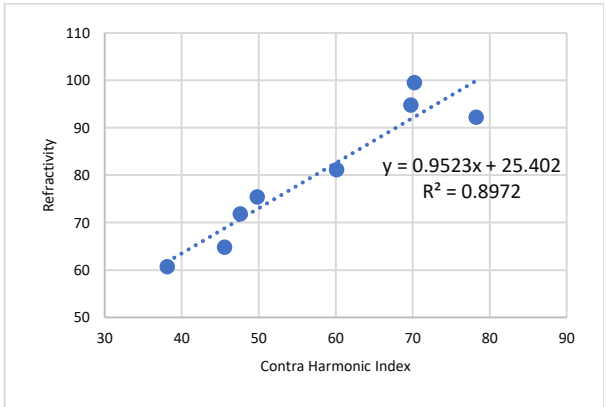
NSAID	Molecular Weight	Refractivity	Polarizablity	Polar Surface Area	Complexity
Diclofenac	296.1	75.46	27.93	49.3	304
Ibuprofen	206.28	60.73	23.76	37.3	203
Naproxen	230.26	64.85	24.81	46.5	277
Celecoxib	381.4	92.23	35.2	86.4	577
Indomethacin	357.8	94.81	36.64	68.5	506
Mefenamic acid	241.29	71.88	26.22	49.33	292
Etodolac	287.36	81.16	31.94	62.32	399
Sulindac	356.41	99.56	37.21	73.6	616

Table 2.10. The statistical measures of the molecular properties

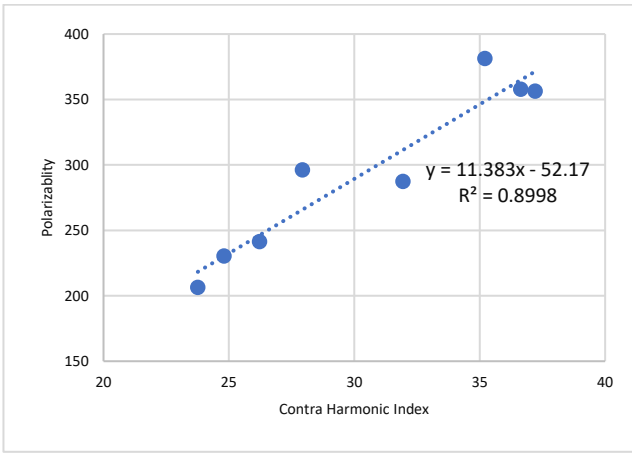
Molecular Properties	Correlation Coefficient R	R-squared	Standard Error	F-statistic	p-value
Molecular Weight	.967	.934	18.166	85.472	9.05×10^{-5}
Refractivity	.947	.897	4.968	52.356	3.54×10^{-4}
Polarizablity	.956	.914	1.729	64.094	2.03×10^{-4}
Polar Surface Area	.989	.979	2.538	285.764	2.74×10^{-6}
Complexity	.969	.939	40.916	91.936	7.36×10^{-5}



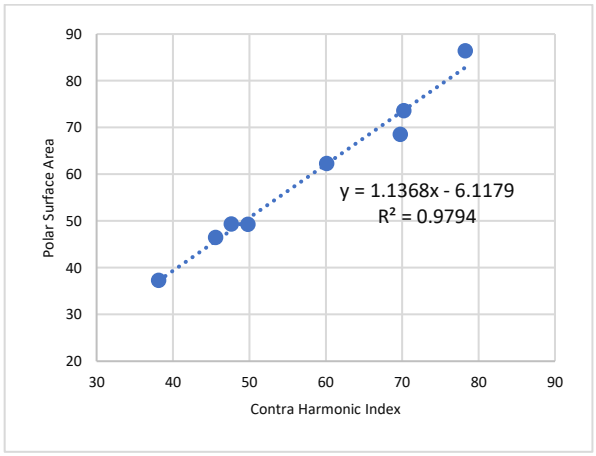
a) Correlation chart of CH and molecular weight



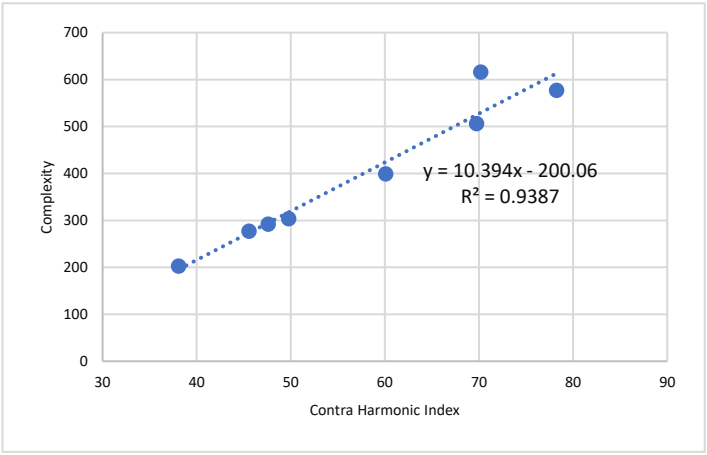
b) Correlation chart of CH and refractivity



c) Correlation chart of CH and polarizablity



d) Correlation chart of CH and polar surface area



e) Correlation chart of CH and complexity

Figure 2.9. Linear Regression model correlating CHI with molecular properties of NSAIDs

From Table 2.10 and Figure 2.9, the Contra Harmonic index demonstrates remarkable predictive capability for the following key molecular properties of NSAIDs, as evidenced by the strong statistical correlations.

- The CHI strongly correlates with polar surface area, a critical parameter for membrane permeablity and oral absorption. The minimal standard error confirms CHI's reliability in estimating PSA.
- CHI accurately predicts molecular weight, complexity and polarizability, all with $R^2 > 0.9$ and high significance ($p - value < 10^{-4}$). Hence CHI can be effectively used to predict these significant properties of the molecules.
- CHI shows a consistent correlation with refractivity and hence assist in estimating the concentration and hence crucial for quality control in pharmaceuticals.

4. Conclusion

The potency of these correlations suggests that CHI could replace experimental measurements for preliminary screening of compounds in drug discovery and materials science. Ultimately, CHI's versatility makes it an essential tool for accelerating molecular design in fields ranging from drug discovery to sustainable energy solutions.

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