

# Prediction of Anti-Inflammatory Activity of *N*-Arylanthranilic Acids: Computational Approach Using Refined Zagreb Indices\*\*\*

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Zagreb indices  $M_1$  and  $M_2$  have been refined to significantly reduce their degeneracy. The refined indices are sensitive to both the presence as well as relative position of the heteroatoms and have been termed as Zagreb topochemical indices  $M_1^c$  and  $M_2^c$ . The discriminating power of  $M_1^c$  and  $M_2^c$  was investigated and compared with that of Zagreb indices  $M_1$  and  $M_2$ . Both  $M_1^c$  and  $M_2^c$  exhibited much lower degeneracy without compromising with the discriminating power of  $M_1$  and  $M_2$ . Relationship between the anti-inflammatory activity of *N*-arylanthranilic acids and Zagreb indices and Zagreb topochemical indices was investigated. The values of all the four indices for each of the 112 compounds were calculated using an in-house computer program. The resulting data was analyzed and suitable models were developed after identification of the active ranges. Subsequently, biological activity was assigned to each of the compounds using these models, which was then compared with the reported anti-inflammatory activity. High accuracy of prediction was obtained using models based upon Zagreb indices and Zagreb topochemical indices.

*Keywords*  
topological index  
Zagreb indices  
*N*-arylanthranilic acids  
anti-inflammatory agents  
Zagreb topochemical indices

## INTRODUCTION

*N*-Arylanthranilic acids belong to the category of non-steroidal anti-inflammatory drugs. They are amino isosteres of salicylates and are also known as fenamates. Important molecules of this class include mefenamic acid, flufenamic acid and meclofenamic acid. As an analgesic agent, mefenamic acid has been used to relieve pain arising from rheumatic conditions, soft tissue injuries, other painful musculoskeletal conditions and dysmenorrhea. Fenamates act by blocking the metabolism of arachidonic acid by the enzyme cyclooxygenase (COX), one of

the key enzymes in the arachidonic acid cascade.<sup>1,2</sup> This enzyme bis-oxygenates arachidonic acid to prostaglandin  $G_2$ , which is subsequently degraded to vasoactive and inflammatory mediators such as prostaglandins (PGs), prostacyclin (PGI<sub>2</sub>), and thromboxane-A<sub>2</sub>.<sup>3</sup> Some fenamates also inhibit arachidonic acid lipoxygenase resulting in decreased synthesis of leukotrienes, known mediators involved in inflammatory process.<sup>4</sup> Studies suggest that flufenamic and tolfenamic acids suppress proliferation of human peripheral blood lymphocytes by a mechanism, which involves inhibition of Ca<sup>2+</sup> influx and is not related to inhibition of prostanoid synthesis.<sup>5</sup> It has

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also been reported that substitution of the carboxylic acid functionality of several fenamates with acidic heterocycles provided dual inhibitors of CO and 5-lipoxygenase (5-LO) activities when tested in an intact rat basophilic leukemia (RBL-1) cell line. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a mainstay in the treatment of inflammatory disease and are among the most widely used drugs worldwide. They are anti-inflammatory, antipyretic, and analgesic and are prescribed as first choice for the treatment of rheumatic disorders and, in general, inflammation.<sup>6</sup> The non-steroidal anti-inflammatory drugs (NSAIDs) are widely used for the treatment of minor pain and for the management of edema and tissue damage resulting from inflammatory joint diseases (arthritis) and other inflammatory diseases. The main limitation in using NSAIDs consists in their side-effects, including gastrointestinal ulcerogenic activity and bronchospasm.<sup>6</sup> Since NSAID therapy forms an integral part of treatment of diseases like rheumatoid arthritis, osteoarthritis, acute gouty arthritis, ankylosing spondylitis and dysmenorrhea *etc.*, search for newer, better and more effective agents is always a concern for medicinal chemists.

The finding that structure of a molecule had an important role to play in its biological activity coupled with the need for safer potent drugs to be developed with minimum expenditure, animal sacrifice and time loss led to the genesis of structure-activity relationship (SAR) studies.<sup>7</sup> SAR has been given due recognition in medicinal chemistry and the pharmaceutical industry<sup>8,9</sup> and is one of the indispensable tools of the drug design. Use of topological indices in SAR seems to play an important role in situations where biological activity is determined predominantly by topological architecture of molecular structure, *i.e.* where simple connectivity among neighboring atoms, without considering the chemical nature of atoms or nature of chemical bonding, may be the major determinant of the biological activity of a molecule.<sup>10</sup> When a single number represents a graph invariant, it is known as topological index or topological descriptor. These indices are derived from matrices, like distance matrix and/or adjacency matrix, representing a molecular graph. When the distance or adjacency matrix is weighted corresponding to the heteroatom present within the molecule, the matrix may be termed as chemical distance or chemical adjacency matrix respectively. Indices or descriptors derived from such matrices are known as topochemical indices or descriptors. A number of topological and topochemical indices have received great attention due to their applications in quantitative structure activity relationship (QSAR) studies and drug research.<sup>11–15</sup> Amongst the most important ones are molecular connectivity index of Randić,<sup>16,17</sup> Wiener's index,<sup>18,19</sup> Balaban's indices,<sup>20,21</sup> Hosoya index,<sup>22</sup> Zagreb indices  $M_1$  and  $M_2$ ,<sup>23–26</sup> eccentric connectivity index<sup>27–29</sup> and eccentric adjacency index.<sup>30</sup> Topochemical indices that have been reported

and used for SAR studies include atomic molecular connectivity index,<sup>31</sup> eccentric adjacency topochemical index,<sup>32</sup> Wiener's topochemical index<sup>33</sup> and superadjacency topochemical index<sup>34</sup> *etc.*

In the present study, adjacency based Zagreb indices  $M_1$  and  $M_2$  have been refined and the corresponding Zagreb topochemical indices have been proposed. The discriminating power and degeneracy of the newly proposed Zagreb topochemical indices has been investigated and compared with the original indices. The relationship of these indices with anti-inflammatory activity of *N*-aryl-anthranilic acid derivatives has been investigated and suitable models for the prediction of anti-inflammatory activity have been developed.

*Zagreb Indices  $M_1$  and  $M_2$ .* – This pair of indices was introduced in 1972 (Ref. 35) and were given different names in the literature, such as the Zagreb Group indices, the Zagreb group parameters and most often, the Zagreb indices. These indices are denoted by  $M_1$  and  $M_2$  and are defined as per the Eqs. (1) and (2).

$$M_1 = \sum_{\text{vertices}} d(i)d(i) \quad (1)$$

$$M_2 = \sum_{\text{edges}} d(i)d(j) \quad (2)$$

where  $d(i)$  is the degrees of vertex  $i$  and  $d(i)d(j)$  is the weight of edge  $\{i,j\}$ .

Zagreb indices are referred to in most of the books reporting topological indices and their uses in QSPR and QSAR. They are also included in a number of programs used for the routine computation of topological indices, such as POLLY, OASIS, DRAGON, Cerius, TAM, DISSIM, *etc.* Recently, the Zagreb indices and their variants have been used to study molecular complexity, chirality, *ZE*-isomerism and hetero-systems whilst the overall Zagreb indices exhibited a potential applicability for deriving multi-linear regression models. Zagreb indices have been used by various researchers in their QSPR and QSAR studies. Mathematical properties of Zagreb indices have also been studied.<sup>23</sup>

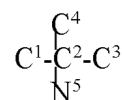
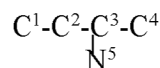
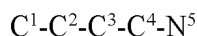
## METHODOLOGY

### *Calculation of Topochemical Indices*

One of the major limitations of Zagreb indices are that they do not consider the presence of heteroatom in a molecule. The new indices are being presented as modifications of the Zagreb indices to overcome this limitation. The refined Zagreb indices have been termed as Zagreb topochemical indices. The newly derived indices are sensitive to both the presence and relative position of heteroatoms. These indices are denoted by  $M_1^c$  and  $M_2^c$ .

*Zagreb Topochemical Index  $M_1^c$ .* – It is defined as the summation of the squares of chemical degrees over all the verti-

Arbitrary Vertex numbering



Adjacency Matrices

	1	2	3	4	5	$V_i$
1	0	1	0	0	0	1
2	1	0	1	0	0	2
3	0	1	0	1	0	2
4	0	0	1	0	1	2
5	0	0	0	1	0	1

	1	2	3	4	5	$V_i$
1	0	1	0	0	0	1
2	1	0	1	0	0	2
3	0	1	0	1	1	3
4	0	0	1	0	0	1
5	0	0	1	0	0	1

	1	2	3	4	5	$V_i$
1	0	1	0	0	0	1
2	1	0	1	1	1	4
3	0	1	0	0	0	1
4	0	1	0	0	0	1
5	0	1	0	0	0	1

Chemical Adjacency Matrices

	1	2	3	4	5	$V_i^c$
1	0	1	0	0	0	1
2	1	0	1	0	0	2
3	0	1	0	1	0	2
4	0	0	1	0	1.167	2.167
5	0	0	0	1	0	1

	1	2	3	4	5	$V_i^c$
1	0	1	0	0	0	1
2	1	0	1	0	0	2
3	0	1	0	1	1.167	3.167
4	0	0	1	0	0	1
5	0	0	1	0	0	1

	1	2	3	4	5	$V_i^c$
1	0	1	0	0	0	1
2	1	0	1	1	1.167	4.167
3	0	1	0	0	0	1
4	0	1	0	0	0	1
5	0	1	0	0	0	1

Zagreb Index  $M_1$ 

$$M_1 = \sum_{\text{vertices}} d(i)d(i) = 14 \quad = 16 \quad = 20$$

Zagreb Topochemical Index  $M_1^c$ 

$$M_1^c(G) = \sum_{i=1}^n (d^c(i))^2 = 14.696 \quad = 17.030 \quad = 21.364$$

Zagreb Index  $M_2$ 

$$M_2 = \sum_{\text{edges}} d(i)d(j) = 12 \quad = 14 \quad = 16$$

Zagreb Topochemical Index  $M_2^c$ 

$$M_2^c(G) = \sum_{ij} (d^c(i)d^c(j)) = 12.501 \quad = 14.668 \quad = 16.668$$

Figure 1. Calculation of Zagreb indices  $M_1$  &  $M_2$  and Zagreb topochemical indices  $M_1^c$  &  $M_2^c$  for three five-member structures with only one nitrogen as heteroatom.

ces in hydrogen suppressed molecular graph. It is expressed by Eq. (3).

$$M_1^c(G) = \sum_{i=1}^n (d^c(i))^2 \quad (3)$$

For hydrogen suppressed molecular graph (G),  $v_1, v_2, \dots, v_n$  are vertices,  $n$  is the number of vertices and the number of first neighbors of a vertex  $v_i$  is the chemical degree of this vertex and is denoted by  $d^c(i)$ .

**Zagreb Topochemical Index  $M_2^c$ .** – It is defined as the summation of chemical weights of all edges in hydrogen suppressed molecular graph. It is expressed by Eq. (4).

$$M_2^c(G) = \sum_{ij} (d^c(i)d^c(j)) \quad (4)$$

where  $d^c(i)d^c(j)$  is the chemical weight of the edge  $\{i, j\}$  in hydrogen suppressed molecular graph in and  $n$  is the number of edges.

The proposed Zagreb topochemical indices  $M_1^c$  &  $M_2^c$  can be easily calculated from the chemical adjacency matrix of hydrogen suppressed molecular structure. Chemical degree for a vertex  $i$  is the sum of entries in a row  $i$  of chemical adjacency matrix. When the adjacency matrix is weighted corresponding to the heteroatom present within the molecule, the matrix may be termed as chemical adjacency matrix. This matrix is obtained by substituting, row elements corresponding to heteroatom, with relative atomic weight with respect to carbon atom. Thus, in this matrix the non-zero row elements of an adjacency matrix represent chemical adjacency between the corresponding vertices in a molecular graph. Calculation of Zagreb indices and Zagreb topochemical indices for three, five-member straight/branched structures, containing only one nitrogen as heteroatom has been exemplified in Figure 1. Discriminating power and degeneracy of Zagreb topochemical indices has been investigated for all possible structures with 3, 4 & 5 vertices with only one nitrogen as heteroatom and compared with that of Zagreb indices (Figure 2 and Table I).

6 6.696 4 4.334	6 6.724 4 4.668	12 13.392 12 13.364	10 10.696 8 8.501	10 11.058 8 8.835	12 13.030 9 9.501	12 13.086 9 10.053
16 17.392 16 17.336	26 28.060 33 35.366	26 28.422 33 36.299	36 39.090 54 58.593	18 19.030 19 19.835	18 19.726 19 20.698	18 19.754 19 21.199
14 14.696 12 12.501	14 15.058 12 13.002	14 15.392 12 13.002	16 17.030 14 14.668	16 17.392 14 15.002	16 16.696 14 14.668	16 17.420 14 15.670
20 21.364 16 16.668	20 21.392 20 21.336	22 23.392 23 24.670	22 23.754 23 25.171	22 23.030 23 23.835	22 23.726 23 24.503	24 25.030 27 28.002
24 26.060 27 29.032	24 26.088 27 29.533	26 27.364 28 29.002	26 28.060 28 30.032	22 23.726 24 25.865	22 24.088 24 26.366	22 23.392 24 25.336
22 22.696 24 24.668	30 32.060 37 39.366	30 32.422 37 40.030	30 31.726 37 39.004	30 32.060 36 38.004	30 32.088 36 39.006	32 34.060 42 44.700
32 33.030 42 43.169	32 34.756 42 45.568	32 34.422 42 45.201	34 34.756 44 46.700	34 36.756 44 47.730	34 35.364 44 45.336	32 34.060 40 42.366
40 42.060 57 59.672	40 42.756 57 61.036	40 43.090 57 61.231	42 44.394 61 64.201	42 45.090 61 65.398	54 56.728 89 93.036	52 55.424 84 89.400
52 55.424 84 89.400	44 45.364 67 68.670	44 47.424 67 72.094	44 46.728 64 67.368	54 57.758 89 94.929	66 70.092 120 127.098	

Figure 2. Values of Zagreb indices  $M_1$  &  $M_2$  and Zagreb topochemical indices  $M_1^c$  &  $M_2^c$  for all possible structures with 3, 4 & 5 vertices with only one nitrogen as heteroatom.

TABLE I. Comparison of discriminating power and degeneracy of the Zagreb indices  $M_1$  &  $M_2$  and the Zagreb topochemical indices  $M_1^c$  &  $M_2^c$ 

Index	DISCRIMINATING POWER									DEGENERACY <sup>(a)</sup>		
	For Three Vertices			For Four Vertices			For Five Vertices			For Vertices		
	Min. Value	Max. Value	Ratio	Min. Value	Max. Value	Ratio	Min. Value	Max. Value	Ratio	Three	Four	Five
$M_1$	6	12	1:2.00	10	36	1:3.60	14	66	1:4.71	1/3	5/11	34/48
$M_1^c$	6.696	13.392	1:2.00	10.696	39.090	1:3.65	14.696	70.092	1:4.77	0/3	0/11	5/48
$M_2$	4	12	1:3.00	8	54	1:6.75	12	120	1:10.00	1/3	5/11	29/48
$M_2^c$	4.334	13.364	1:3.08	8.501	58.593	1:6.89	12.501	127.098	1:10.16	0/3	0/11	3/48

<sup>(a)</sup> Degeneracy = Number of compounds having same value / Total number of compounds having same number of vertices.

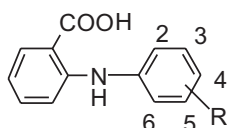


Figure 3. Structure of *N*-Arylanthranilic acids.

### Model Development and Analysis

A dataset comprising of 112 *N*-arylanthranilic acids (Figure 3) was selected.<sup>36,37</sup> The values of Zagreb indices and Zagreb topochemical indices were calculated using an in-house computer program. Resulting data was analyzed and suitable models were developed after identification of the active ranges by maximization of moving average with respect to active compounds (<35 % = inactive, 35–65 % = transitional, >65 % = active).<sup>33,38–40</sup> Subsequently, each compound was assigned a biological activity using these models, which was then compared with the reported anti-inflammatory activity<sup>36</sup> (Table II). The biological activity was reported in terms of minimum effective dose (MED) mg per kg ( $\text{mg kg}^{-1}$ ). In their experiments, compounds were administered by gavage, and their ability to suppress erythema developing in the skin of depilated albino guinea-pigs, 2 h after exposure to UV radiation, was measured on all-or-nothing basis. Compounds, which were significantly more active than vehicle, were administered at half the previous dose, until a dose was reached for which the response was significantly less than that of a reference level of phenylbutazone. This dose was recorded as the MED.<sup>36</sup> The compounds reportedly having MED greater than  $2.5 \text{ mg kg}^{-1}$  were considered as inactive and those having less than or equal to  $2.5 \text{ mg kg}^{-1}$  were considered to be potentially active for the purpose of this study. The percent degree of prediction was calculated from the ratio of number of compounds with correctly predicted activity to that of total number of compounds present in the respective ranges of the proposed models. The overall degree of prediction was obtained from the ratio of total number of compounds with correctly predicted biological activity to that of total number of compounds in the active and inactive ranges. The percent classification was obtained from the ratio of number of compounds present in active and inactive ranges (excluding those in transitional ranges) to the total number of compounds (Table III).

### RESULTS

The discriminating power and degeneracy of the Zagreb topochemical indices was investigated by calculating and analyzing the index values of all possible structures with 3, 4 and 5 vertices with only one nitrogen as heteroatom. Their comparison with Zagreb indices is presented in Table I. These results reveal that the Zagreb topochemical indices have much lower degeneracy when compared to the corresponding topological indices. Further that, with this modification, there has not been any effect on the discriminating power of the Zagreb indices. The relationship of the anti-inflammatory activities of *N*-arylanthranilic acids with the Zagreb indices and Zagreb topochemical indices has been investigated and the results have been presented in Table III. Retrofit analysis of the data in Table II and III reveal the following information with regard to the models based upon various indices.

#### Zagreb Index $M_1$

- This model comprises of four ranges *viz.* inactive range (<95), lower transitional range (95–103), active range (104–108) and upper transitional range (>108).
- 38 out 40 compounds in the inactive range were predicted correctly. The correctly predicted compounds had average MED of  $97.20 \text{ mg kg}^{-1}$ .
- 12 out of 15 compounds in the active range were predicted correctly. The correctly predicted compounds had average MED of only  $1.13 \text{ mg kg}^{-1}$ .
- The active range was ideally bracketed by transitional ranges. The lower transitional range had 43 compounds and the upper transitional range had 14 compounds.
- The overall predictability of the model based upon the Zagreb index  $M_1$  was 90.9 %.

#### Zagreb Topochemical Index $M_1^c$

- This model comprises of four ranges *viz.* inactive range (<113.25), lower transitional range (113.25–129.82), active range (129.83–145.42) and upper transitional range (>145.42).

TABLE II. Relationship of Zagreb indices  $M_1$  and  $M_2$  and the Zagreb topochemical indices  $M_1^c$  and  $M_2^c$  with anti-inflammatory activity of *N*-arylanthranilic acids

Comp. No.	Substituent(s)	$M_1$	$M_1^c$	$M_2$	$M_2^c$	Anti-inflammatory activity <sup>(a)</sup>				
						Assigned				Reported
						$M_1$	$M_1^c$	$M_2$	$M_2^c$	
1	H	78	84.50	88	93.50	-	-	-	-	-
2	2-Cl	84	106.08	96	113.74	-	-	-	-	-
3	3-Cl	84	106.08	95	110.29	-	-	-	-	-
4	4-Cl	84	106.08	95	110.29	-	-	-	-	-
5	2-CH <sub>3</sub>	84	90.50	96	101.67	-	-	-	-	-
6	3-CH <sub>3</sub>	84	90.50	95	100.50	-	-	-	-	-
7	4-CH <sub>3</sub>	84	90.50	95	100.50	-	-	-	-	-
8	3-NH <sub>2</sub>	84	91.53	95	101.34	-	-	-	-	-
9	3-n-C <sub>4</sub> H <sub>9</sub>	96	101.47	108	112.50	±	-	-	-	-
10	3-SCH <sub>3</sub>	88	113.39	100	118.84	-	-	-	-	-
11	3-OC <sub>2</sub> H <sub>5</sub>	92	102.05	104	112.49	-	-	-	-	-
12	3-OCH <sub>3</sub>	88	97.39	100	108.17	-	-	-	-	-
13	3-n-C <sub>3</sub> H <sub>7</sub>	92	98.50	104	109.50	-	-	-	-	-
14	3-Br	84	156.62	95	128.84	-	±	-	-	-
15	3-SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	112	164.37	130	185.95	±	±	±	±	-
16	3-C <sub>2</sub> H <sub>5</sub>	88	94.50	100	105.50	-	-	-	-	-
17	3-CN	88	95.20	100	106.17	-	-	-	-	-
18	3-NO <sub>2</sub>	94	106.69	107	118.34	-	-	-	-	-
19	3-C(=O)CH <sub>3</sub>	94	102.61	107	114.17	-	-	-	-	-
20	3-CF <sub>3</sub>	102	125.55	116	132.00	±	±	±	-	-
21	3-N(CH <sub>3</sub> ) <sub>2</sub>	94	102.25	107	114.67	-	-	-	-	-
22	2,3-Cl <sub>2</sub>	90	127.66	104	139.28	-	±	-	±	+
23	2-F, 3-Cl	90	115.92	104	126.74	-	±	-	-	-
24	2-CH <sub>3</sub> , 3-Cl	90	112.08	104	121.42	-	-	-	-	-
25	2-Cl, 3-CH <sub>3</sub>	90	112.08	104	123.70	-	-	-	-	-
26	2-CH <sub>3</sub> , 3-NO <sub>2</sub>	100	112.69	116	127.67	±	-	±	-	-
27	2-CH <sub>3</sub> , 3-NH <sub>2</sub>	90	97.53	104	110.67	-	-	-	-	-
28	2,3-(CH <sub>3</sub> ) <sub>2</sub>	90	96.50	104	109.67	-	-	-	-	-
29	2,6-Cl <sub>2</sub> , 3-C <sub>2</sub> H <sub>5</sub>	100	137.66	117	148.94	±	+	±	+	+
30	6-(CH <sub>3</sub> ) <sub>2</sub> , 3-NO <sub>2</sub>	108	120.69	125	136.67	+	±	+	±	+
31	2-NH <sub>2</sub> , 3-Cl, 6-CH <sub>3</sub>	96	119.11	112	131.11	±	±	±	-	-
32	2-NH <sub>3</sub> , 3,6-(CH <sub>3</sub> ) <sub>2</sub>	96	103.53	112	119.03	±	-	±	-	-
33	2-CH <sub>3</sub> , 3-Cl, 6-NH <sub>2</sub>	96	119.11	112	130.61	±	±	±	-	-
34	2-CH <sub>3</sub> , 3-NO <sub>2</sub> , 6-Cl	106	134.27	124	147.91	+	+	+	+	+
35	2-CH <sub>3</sub> , 3-NH <sub>2</sub> , 6-Cl	96	119.11	112	130.91	±	±	±	-	-
36	2,6-(CH <sub>3</sub> ) <sub>2</sub> , 3-NH <sub>2</sub>	96	103.53	112	118.84	±	-	±	-	-
37	2-Cl, 3,6-(CH <sub>3</sub> ) <sub>2</sub>	96	118.08	112	131.87	±	±	±	-	-
38	2,6-(CH <sub>3</sub> ) <sub>2</sub> , 3-N(CH <sub>3</sub> ) <sub>2</sub>	106	114.25	112	132.17	+	±	+	-	+
39	2,3-Cl <sub>2</sub> , 6-CH <sub>3</sub>	96	133.66	112	147.45	±	+	±	+	+
40	2,3-Cl <sub>2</sub> , 3-OCH <sub>3</sub>	100	140.55	117	152.59	±	+	±	+	+
41	2,3,6-(CH <sub>3</sub> ) <sub>3</sub>	96	102.50	112	117.84	±	-	±	-	-
42	2,6-(CH <sub>3</sub> ) <sub>2</sub> , 3-Br	96	168.62	112	151.84	±	±	±	+	+
43	2,6-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> , 3-NO <sub>2</sub>	114	126.69	134	145.84	±	±	±	±	-
44	2,6-Cl <sub>2</sub> , 3-NH <sub>2</sub>	96	134.69	112	145.27	±	+	±	±	-
45	2,6-Cl <sub>2</sub> , 3-N(CH <sub>3</sub> ) <sub>2</sub>	106	145.42	124	158.61	+	+	+	+	+
46	2,6-(CH <sub>3</sub> ) <sub>2</sub> , 3-C <sub>2</sub> H <sub>5</sub>	100	106.50	117	122.84	±	-	±	-	+
47	2,6-(CH <sub>3</sub> ) <sub>2</sub> , 3-C(=O)CH <sub>3</sub>	106	114.61	124	131.50	+	±	+	-	+
48	2,6-(CH <sub>3</sub> ) <sub>2</sub> , 3-N-C <sub>3</sub> H <sub>7</sub>	104	110.50	121	126.84	+	-	+	-	-
49	2,6-(CH <sub>3</sub> ) <sub>2</sub> , 3-CN	100	107.20	117	123.50	±	-	±	-	+
50	2-CH <sub>3</sub> , 3-OCH <sub>3</sub> , 6-Cl	100	124.97	117	137.91	±	±	±	±	+
51	2,6-Cl <sub>2</sub> , 3-OC <sub>2</sub> H <sub>5</sub>	104	145.22	121	156.93	+	+	+	+	+
52	2,6-(CH <sub>3</sub> ) <sub>2</sub> , 3-SCH <sub>3</sub>	100	125.39	117	137.84	±	±	±	±	+
53	2,6-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> , 3-SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	132	184.37	157	214.95	±	±	±	±	-
54	2,6-Cl <sub>2</sub> , 3-CF <sub>3</sub>	114	168.71	133	175.44	±	±	±	±	+
55	2,6-Cl <sub>2</sub> , 3-CN	100	138.36	117	149.61	±	+	±	+	+
56	2-CH <sub>3</sub> , 3-SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub> , 6-Cl	124	191.50	147	217.03	±	±	±	±	+



TABLE II. continued

Comp. No.	Substituent(s)	$M_1$	$M_1^c$	$M_2$	$M_2^c$	Anti-inflammatory activity <sup>(a)</sup>				
						Assigned				Reported
						$M_1$	$M_1^c$	$M_2$	$M_2^c$	
57	2-CH <sub>3</sub> , 3-CN	94	101.20	109	115.34	-	-	-	-	-
58	2,3-Br <sub>2</sub>	90	228.73	104	216.40	-	±	-	±	-
59	2-Br, 3-CF <sub>3</sub>	108	197.67	125	181.78	+	±	+	±	+
60	2-CH <sub>3</sub> , 3-OCH <sub>3</sub>	94	103.39	109	117.67	-	-	-	-	-
61	2-Br, 3-CN	94	167.31	109	155.95	-	±	-	+	+
62	2-CH <sub>3</sub> , 2-C <sub>2</sub> H <sub>5</sub>	94	100.50	109	114.67	-	-	-	-	-
63	2-CH <sub>3</sub> , 3-CF <sub>3</sub>	108	131.55	125	141.16	+	+	+	±	+
64	2-CH <sub>3</sub> , 3-SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	118	170.37	139	196.79	±	±	±	±	-
65	2-CH <sub>3</sub> , 3-N(CH <sub>3</sub> ) <sub>2</sub>	100	108.25	116	124.01	±	-	±	-	-
66	2,4-Cl <sub>2</sub>	90	127.66	103	130.53	-	±	-	-	-
67	2,5-Cl <sub>2</sub>	90	127.66	103	133.99	-	±	-	-	-
68	2,6-Cl <sub>2</sub>	90	127.66	104	135.83	-	±	-	-	-
69	3,4-Cl <sub>2</sub>	90	127.66	103	138.83	-	±	-	-	-
70	3,5-Cl <sub>2</sub>	90	127.66	102	127.08	-	±	-	-	-
71	2,4-(CH <sub>3</sub> ) <sub>2</sub>	90	96.50	103	108.67	-	-	-	-	-
72	2,5-(CH <sub>3</sub> ) <sub>2</sub>	90	96.50	103	108.67	-	-	-	-	-
73	2,6-(CH <sub>3</sub> ) <sub>2</sub>	90	96.50	104	109.84	-	-	-	-	-
74	3,4-(CH <sub>3</sub> ) <sub>2</sub>	90	96.50	103	108.50	-	-	-	-	-
75	3,5-(CH <sub>3</sub> ) <sub>2</sub>	90	96.50	102	107.50	-	-	-	-	-
76	3,5-(CF <sub>3</sub> ) <sub>2</sub>	126	166.60	144	170.49	±	±	±	±	-
77	2-Cl, 6-CH <sub>3</sub>	90	112.08	104	121.91	-	-	-	-	-
78	2-CH <sub>3</sub> , 6-Cl, 3-N(CH <sub>3</sub> ) <sub>2</sub>	106	129.84	124	144.25	+	+	+	±	+
79	2,3,6-Cl <sub>3</sub>	96	149.25	112	159.53	±	±	±	+	+
80	2,6-Cl <sub>2</sub> , 3-CH <sub>3</sub>	96	133.66	112	143.94	±	+	±	±	+
81	2,6-(CH <sub>3</sub> ) <sub>2</sub> , 3-Cl	96	118.08	112	129.58	±	±	±	-	+
82	2-CH <sub>3</sub> , 3,6-Cl <sub>2</sub>	96	133.66	112	141.66	±	+	±	±	+
83	2,3-(CH <sub>3</sub> ) <sub>2</sub> , 6-Cl	96	118.08	112	129.91	±	±	±	-	-
84	2,6-(CH <sub>3</sub> ) <sub>2</sub> , 3-SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	124	176.37	147	204.95	±	±	±	±	+
85	2,6-(C <sub>2</sub> H <sub>5</sub> ) <sub>2</sub> , 3-C(=O)CH <sub>3</sub>	114	122.61	134	141.50	±	±	±	±	-
86	2-(CH <sub>3</sub> ) <sub>2</sub> , 3-CF <sub>3</sub>	116	139.55	136	152.33	±	+	±	+	+
87	2-Cl, 3-N(CH <sub>3</sub> ) <sub>2</sub> , 6-CH <sub>3</sub>	106	129.84	124	146.53	+	+	+	+	+
88	2,6-Cl, 3-CN, 6-CH <sub>3</sub>	108	150.28	128	162.74	+	±	+	±	+
89	2,6-Cl <sub>2</sub> , 3-SO <sub>2</sub> N(CH <sub>3</sub> ) <sub>2</sub>	124	207.53	147	234.33	±	±	±	±	+
90	2,6-(CH <sub>3</sub> ) <sub>2</sub> , 3-SO <sub>2</sub> CH <sub>3</sub>	114	157.39	133	182.28	±	±	±	±	+
91	2,6-(CH <sub>3</sub> ) <sub>2</sub> , 3-SOCH <sub>3</sub>	106	139.62	124	156.50	+	+	+	+	+
92	2,3,4-Cl <sub>3</sub>	96	149.25	112	164.82	±	±	±	±	-
93	2,3,5-Cl <sub>3</sub>	96	149.25	111	156.07	±	±	-	+	-
94	2,4,6-Cl <sub>3</sub>	96	149.25	111	150.78	±	±	-	+	-
95	2,4,5-Cl <sub>3</sub>	96	149.25	111	156.07	±	±	-	+	-
96	3,4,5-Cl <sub>3</sub>	96	149.25	111	161.37	±	±	-	±	-
97	2,3,5-(CH <sub>3</sub> ) <sub>3</sub>	96	102.50	111	116.67	±	-	-	-	-
98	2,4,6-(CH <sub>3</sub> ) <sub>3</sub>	96	102.50	112	117.84	±	-	±	-	-
99	2,4,5-(CH <sub>3</sub> ) <sub>3</sub>	96	102.50	111	116.67	±	-	-	-	-
100	2-CH <sub>3</sub> , 3,5-Cl <sub>2</sub>	96	133.66	111	138.21	±	+	-	±	+
101	2,3-Cl <sub>2</sub> , 5-CH <sub>3</sub>	96	133.66	111	146.28	±	+	-	±	-
102	3,5-Cl <sub>2</sub> , 4-CH <sub>3</sub>	96	133.66	111	140.00	±	+	-	±	-
103	2,5-(CH <sub>3</sub> ) <sub>2</sub> , 3-Cl	96	118.08	111	128.42	±	±	-	-	+
104	2,3-(CH <sub>3</sub> ) <sub>2</sub> , 5-Cl	96	118.08	111	126.46	±	±	-	-	-
105	2,3,4,5-Cl <sub>4</sub>	102	170.83	120	190.36	±	±	±	±	-
106	2,3,4,6-Cl <sub>4</sub>	102	170.83	120	185.07	±	±	±	±	-
107	2,3,5,6-Cl <sub>4</sub>	102	170.83	120	185.07	±	±	±	±	+
108	2,3,5,6-(CH <sub>3</sub> ) <sub>4</sub>	102	108.50	120	125.84	±	-	±	-	-
109	2,3,4-Cl <sub>3</sub> , 6-CH <sub>3</sub>	102	155.25	120	172.99	±	±	±	±	-
110	2,4,6-Cl <sub>3</sub> , 3-CH <sub>3</sub>	102	155.25	120	163.69	±	±	±	±	-
111	2,3,4,5,6-Cl <sub>5</sub>	108	192.41	129	219.35	+	±	±	±	-
112	2,3,5-(CH <sub>3</sub> ) <sub>3</sub> , 4,6-Cl <sub>2</sub>	108	145.66	129	162.57	±	±	±	±	-

<sup>(a)</sup> - inactive compound, + active compound (MED mg kg<sup>-1</sup> less than 2.5), ± compound in transitional range where biological activity could not be specifically assigned.

TABLE III. Zagreb topological/topochemical Models for anti-inflammatory activity of *N*-arylanthranilic acids

Model Index	Nature of Range in Proposed Model	Index Value	Number of Compounds falling in the range		Percent Accuracy	Average MED mg kg <sup>-1</sup>		Prediction Accuracy	Percent Classification
			Total	Correct		Total	Correct		
$M_1$	Inactive	<95	40	38	95.0	92.43	97.20	90.9	49.1
	Lower Transitional	95–103	45	N.A.	N.A.	N.A.	N.A.		
	Active	104–108	15	12	80	9.65	1.13		
	Upper Transitional	>108	12	N.A.	N.A.	N.A.	N.A.		
$M_1^c$	Inactive	<114.25	43	41	95.4	99.89	104.72	91.8	54.5
	Lower Transitional	114.25–129.82	23	N.A.	N.A.	N.A.	N.A.		
	Active	129.83–145.42	18	15	83.3	6.88	0.97		
	Upper Transitional	>145.42	28	N.A.	N.A.	N.A.	N.A.		
$M_2$	Inactive	<112	52	48	92.3	93.46	101.10	92.3	58.0
	Lower Transitional	112–120	33	N.A.	N.A.	N.A.	N.A.		
	Active	121–128	13	12	92.3	1.52	1.13		
	Upper Transitional	>128	14	N.A.	N.A.	N.A.	N.A.		
$M_2^c$	Inactive	<135.83	61	55	90.2	77.05	85.34	88.3	68.7
	Upper Transitional	135.83–146.29	14	N.A.	N.A.	N.A.	N.A.		
	Active	146.30–159.53	16	13	81.2	32.24	0.98		
	Lower Transitional	>159.53	21	N.A.	N.A.	N.A.	N.A.		

- 41 out of 43 compounds in the inactive range were predicted correctly. The correctly predicted compounds had average MED of 104.72 mg kg<sup>-1</sup>.

- 15 out of 18 compounds in the active range were predicted correctly. The correctly predicted compounds had average MED of only 0.97 mg kg<sup>-1</sup>.

- The active range was ideally bracketed by transitional ranges. The lower transitional range had 23 compounds and the upper transitional range had 28 compounds.

- The overall predictability of the model based upon the Zagreb index  $M_1$  was 91.8 %.

#### Zagreb Index $M_2$

- This model comprises of four ranges *viz.* inactive range (<112), lower transitional range (112–120), active range (121–128) and upper transitional range (>128)

- 48 out of 52 compounds in the inactive range were predicted correctly. The correctly predicted compounds had average MED of 101.10 mg kg<sup>-1</sup>.

- 12 out of 13 compounds in the active range were predicted correctly. The correctly predicted compounds had average MED of only 1.13 mg kg<sup>-1</sup>.

- The active range was ideally bracketed by transitional ranges. The lower transitional range had 33 compounds and the upper transitional range had 14 compounds.

- The overall predictability of the model based upon the Zagreb index  $M_1$  was 92.3 %.

#### Zagreb Topochemical Index $M_2^c$

- This model comprises of four ranges *viz.* inactive range (<135.83), lower transitional range (135.83–146.29),

active range (146.30–159.53) and upper transitional range (>159.53).

- 55 out of 61 compounds in the inactive range were predicted correctly. The correctly predicted compounds had average MED of 85.34 mg kg<sup>-1</sup>.

- 13 out of 16 compounds in the active range were predicted correctly. The correctly predicted compounds had average MED of only 0.98 mg kg<sup>-1</sup>.

- The active range was ideally bracketed by transitional ranges. The lower transitional range had 14 compounds and the upper transitional range had 21 compounds.

- The overall predictability of the model based upon the Zagreb index  $M_1$  was 88.3 %.

## DISCUSSION AND CONCLUSIONS

One of the current tendencies in chemical and biological investigations is the prediction of physicochemical and biological properties of chemical compounds and drugs from their structures.<sup>41</sup> Use of topological indices is now one of the widely accepted computational tools for prediction of activity/property of compounds. Topological indices are designed by transforming a molecular graph into a number and possess remarkable ability of being able to correlate and predict a wide spectrum of properties for a vast range of molecular species.<sup>42</sup> In the last decade topological indices have played an important role in the development of a number of drugs some of which are now in the market or are going through clinical trials.<sup>43</sup> Although hundreds of topological indices have been derived, still the theoretical chemists are striving to develop, or modify the existing ones into better indices



which have much better applicability. In the present study a pair of very well known and applied topological indices, Zagreb indices have been refined to overcome their limitation of degeneracy. The properties of the refined indices, termed as Zagreb topochemical indices were investigated and compared with the original ones. Analysis of the index values for all possible structures with 3, 4 and 5 vertices with only one nitrogen as heteroatom reveals that the refined indices have much lower degeneracy when compared to the original Zagreb indices. Degeneracy is the measure of ability of an index to differentiate between the relative positions of atoms in a molecule. In case of all possible structures with 3 and 4 vertices, no degeneracy was reported with both the Zagreb topochemical indices, whereas in case of structures with 5 vertices, the degeneracy was reduced from 34/48 to 5/48 for  $M_1$  and 29/48 to 3/48 for  $M_2$ . For all possible structures up to 5 vertices there has not been any adverse effect on the discriminating power of the Zagreb indices. The discriminating power is the ability of an index to convert chemical structures into sufficiently distinct numerical values taking into consideration compactness, branching, and cyclicity. Thus in terms of degeneracy, the Zagreb topochemical indices can be regarded as superior to the Zagreb indices.

Zagreb indices and Zagreb topochemical indices were used for the development of models for prediction of activity of *N*-arylanthranilic acids. The dataset used in this study comprises of 112 anti-inflammatory *N*-arylanthranilic acids.<sup>36</sup> Non-steroidal anti-inflammatory drugs have always been a focus of development because of their wide spread usage in routine and emergency conditions and variety of actions like analgesic, anti-pyretic, anti-inflammatory, anti-rheumatic and anti-gout *etc.* All the four models, developed in this study, have shown excellent results in terms of predictability (Table III). In all these models, the activity lies in a narrow range of index values and the active range is bracketed ideally by two transitional ranges. This indicates the specificity of the active range and that transition from the active range to the inactive range is gradual. There is marginal difference between the overall predictability of each of these models. The model based upon  $M_1^c$  has slightly higher predictability than that based upon  $M_1$ . Although amongst these, the model based upon  $M_2$  has highest overall accuracy of prediction *i.e.* 92.3 %, but the model based upon  $M_2^c$  has much higher classification *i.e.* 68.7 % when compared to the other models (Table III). Therefore the model based upon Zagreb topochemical index  $M_2^c$  may be regarded as better than the models based upon the other three indices. Excellent predictability of the models is indicative of the utility of these models in designing of newer *N*-arylanthranilic acids. These models can be easily exploited to provide lead structures for the development of potent therapeutic agents.

High discriminating power coupled with extremely low degeneracy offer Zagreb topochemical indices vast potential for structure activity/property studies.

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## SAŽETAK

### Predviđanje protuupalnoga djelovanja *N*-arilantranilnih kiselina: Računski pristup temeljen na poboljšanim Zagrebačkim indeksima

Sanjay Bajaj, S. Singh Sambhi i Anil Kumar Madan

Zagrebački indeksi  $M_1$  i  $M_2$  poboljšani su s ciljem smanjivanja njihove degeneracije. Poboljšani Zagrebački indeksi osjetljivi su na prisutnost i relativni položaj heteroatoma u molekuli. Nazvani su Zagrebački topokemijski indeksi i označeni su s  $M_1^c$  i  $M_2^c$ . Ispitan je diskriminatorski potencijal ovih indeksa i uspoređen s onim koji pokazuju izvorni Zagrebački indeksi. Oba poboljšana Zagrebačka indeksa,  $M_1^c$  i  $M_2^c$ , pokazuju znatno nižu degeneraciju od izvornih Zagrebačkih indeksa  $M_1$  i  $M_2$ . Ispitane su relacije između protuupalnoga djelovanja *N*-arilantranilnih kiselina i izvornih Zagrebačkih indeksa i topokemijskih Zagrebačkih indeksa. Vrijednosti indeksa za 112 *N*-arilantranilnih kiselina izračunane su vlastitim programom. Dobiveni su vrlo točni modeli odnosa protuupalnoga djelovanja tih kiselina i njihovih strukturnih parametara izraženih pomoću obiju vrsta Zagrebačkih indeksa, ali je prednost na strani topokemijskih Zagrebačkih indeksa zbog njihove niske degeneracije.