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Original Scientific Paper

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.[1,2] 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_2), and thromboxane-A_2.[3] Some fenamates also inhibit arachidonic acid lipoxygenase resulting in decreased synthesis of leukotrines, known mediators involved in inflammatory process.[4] Studies suggest that flufenamic and tolfenamic acids suppress proliferation of human peripheral blood lymphocytes by a mechanism, which involves inhibition of Ca^{2+} influx and is not related to inhibition of prostanoid synthesis.[5] 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.[6] 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.[6] Since NSAID therapy forms an integral part of treatment of diseases like rheumatoid arthritis, osteoarthritis, acute gouty arthritis, ankolysing 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.[7] SAR has been given due recognition in medicinal chemistry and the pharmaceutical industry[8,9] 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.[10] 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 form 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.[11–15] Amongst the most important ones are molecular connectivity index of Randić,[16,17] Wiener's index,[18,19] Balaban's indices,[20,21] Hosoya index,[22] Zagreb indices M_1 and M_2,[23–26] eccentric connectivity index[27–29] and eccentric adjacency index.[30] Topochemical indices that have been reported and used for SAR studies include atomic molecular connectivity index,[31] eccentric adjacency topochemical index,[32] Wiener's topochemical index[33] and superadjacency topochemical index[34] *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*-arylanthranilic 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).

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

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

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.[23]

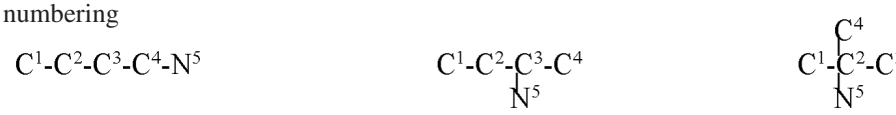
METHODOLOGY

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

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

Zagreb Topochemical Index M_1^c

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

Zagreb Index M_2

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

Zagreb Topochemical Index M_2^c

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

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

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).

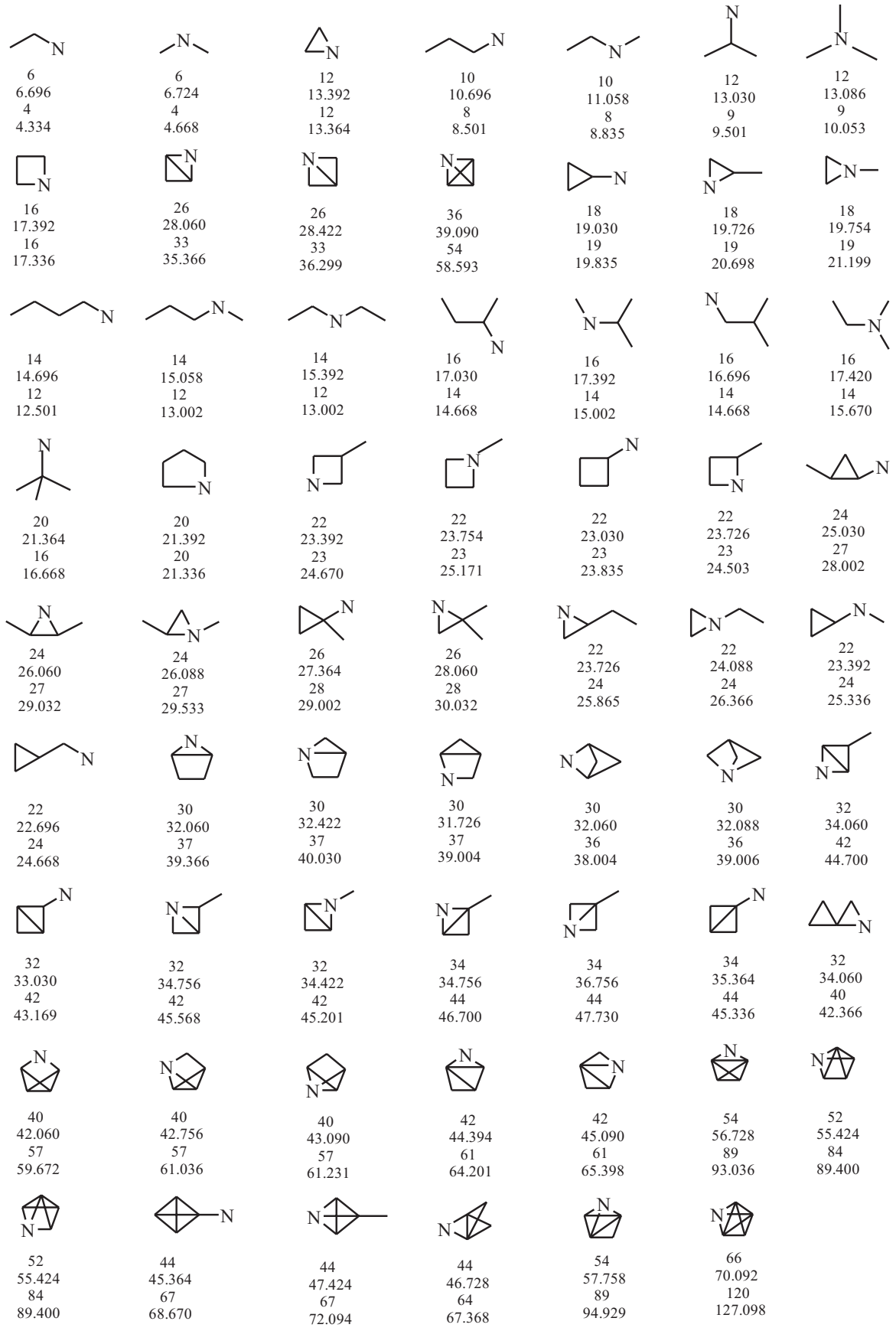


Figure 2. Values of Zagreb indices M_1 & M_2 and Zagreb topochemical indices M_1^c & M_2^c for all possible structures with 3, 4 & 5 vertices with only one nitrogen as heteroatom.

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[(a)]		
	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

[(a)] Degeneracy = Number of compounds having same value / Total number of compounds having same number of vertices.

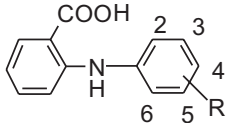


Figure 3. Structure of *N*-Arylanthranilic acids.

Model Development and Analysis

A dataset comprising of 112 *N*-arylanthranilic acids (Figure 3) was selected.[36,37] 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).[33,38–40] Subsequently, each compound was assigned a biological activity using these models, which was then compared with the reported anti-inflammatory activity[36] (Table II). The biological activity was reported in terms of minimum effective dose (MED) mg *per* kg (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.[36] The compounds reportedly having MED greater than 2.5 mg kg^{-1} were considered as inactive and those having less than or equal to 2.5 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 form 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 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 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[a]				
						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_3	84	90.50	96	101.67	–	–	–	–	–
6	3-CH_3	84	90.50	95	100.50	–	–	–	–	–
7	4-CH_3	84	90.50	95	100.50	–	–	–	–	–
8	3-NH_2	84	91.53	95	101.34	–	–	–	–	–
9	3-n-C_4H_9	96	101.47	108	112.50	±	–	–	–	–
10	3-SCH_3	88	113.39	100	118.84	–	–	–	–	–
11	3-OC_2H_5	92	102.05	104	112.49	–	–	–	–	–
12	3-OCH_3	88	97.39	100	108.17	–	–	–	–	–
13	3-n-C_3H_7	92	98.50	104	109.50	–	–	–	–	–
14	3-Br	84	156.62	95	128.84	–	±	–	–	–
15	3-$SO_2N(CH_3)_2$	112	164.37	130	185.95	±	±	±	±	–
16	3-C_2H_5	88	94.50	100	105.50	–	–	–	–	–
17	3-CN	88	95.20	100	106.17	–	–	–	–	–
18	3-NO_2	94	106.69	107	118.34	–	–	–	–	–
19	3-C(=O)CH_3	94	102.61	107	114.17	–	–	–	–	–
20	3-CF_3	102	125.55	116	132.00	±	±	±	–	–
21	3-$N(CH_3)_2$	94	102.25	107	114.67	–	–	–	–	–
22	2,3-Cl_2	90	127.66	104	139.28	–	±	–	±	+
23	2-F, 3-Cl	90	115.92	104	126.74	–	±	–	–	–
24	2-CH_3, 3-Cl	90	112.08	104	121.42	–	–	–	–	–
25	2-Cl, 3-CH_3	90	112.08	104	123.70	–	–	–	–	–
26	2-CH_3, 3-NO_2	100	112.69	116	127.67	±	–	±	–	–
27	2-CH_3, 3-NH_2	90	97.53	104	110.67	–	–	–	–	–
28	2,3-$(CH_3)_2$	90	96.50	104	109.67	–	–	–	–	–
29	2,6-Cl_2, 3-C_2H_5	100	137.66	117	148.94	±	+	±	+	+
30	6-$(CH_3)_2$, 3-NO_2	108	120.69	125	136.67	+	±	+	±	+
31	2-NH_2, 3-Cl, 6-CH_3	96	119.11	112	131.11	±	±	±	–	–
32	2-NH_3, 3,6-$(CH_3)_2$	96	103.53	112	119.03	±	–	±	–	–
33	2-CH_3, 3-Cl, 6-NH_2	96	119.11	112	130.61	±	±	±	–	–
34	2-CH_3, 3-NO_2, 6-Cl	106	134.27	124	147.91	+	+	+	+	+
35	2-CH_3, 3-NH_2, 6-Cl	96	119.11	112	130.91	±	±	±	–	–
36	2,6-$(CH_3)_2$, 3-NH_2	96	103.53	112	118.84	±	–	±	–	–
37	2-Cl, 3,6-$(CH_3)_2$	96	118.08	112	131.87	±	±	±	–	–
38	2,6-$(CH_3)_2$, 3-$N(CH_3)_2$	106	114.25	112	132.17	+	±	+	–	+
39	2,3-Cl_2, 6-CH_3	96	133.66	112	147.45	±	+	±	+	+
40	2,3-Cl_2, 3-OCH_3	100	140.55	117	152.59	±	+	±	+	+
41	2,3,6-$(CH_3)_3$	96	102.50	112	117.84	±	–	±	–	–
42	2,6-$(CH_3)_2$, 3-Br	96	168.62	112	151.84	±	±	±	+	+
43	2,6-$(C_2H_5)_2$, 3-NO_2	114	126.69	134	145.84	±	±	±	±	–
44	2,6-Cl_2, 3-NH_2	96	134.69	112	145.27	±	+	±	±	–
45	2,6-Cl_2, 3-$N(CH_3)_2$	106	145.42	124	158.61	+	+	+	+	+
46	2,6-$(CH_3)_2$, 3-C_2H_5	100	106.50	117	122.84	±	–	±	–	+
47	2,6-$(CH_3)_2$, 3-C(=O)CH_3	106	114.61	124	131.50	+	±	+	–	+
48	2,6-$(CH_3)_2$, 3-N-C_3H_7	104	110.50	121	126.84	+	–	+	–	–
49	2,6-$(CH_3)_2$, 3-CN	100	107.20	117	123.50	±	–	±	–	+
50	2-CH_3, 3-OCH_3, 6-Cl	100	124.97	117	137.91	±	±	±	±	+
51	2,6-Cl_2, 3-OC_2H_5	104	145.22	121	156.93	+	+	+	+	+
52	2,6-$(CH_3)_2$, 3-SCH_3	100	125.39	117	137.84	±	±	±	±	+
53	2,6-$(C_2H_5)_2$, 3-$SO_2N(CH_3)_2$	132	184.37	157	214.95	±	±	±	±	–
54	2,6-Cl_2, 3-CF_3	114	168.71	133	175.44	±	±	±	±	+
55	2,6-Cl_2, 3-CN	100	138.36	117	149.61	±	+	±	+	+
56	2-CH_3, 3-$SO_2N(CH_3)_2$, 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[a]				
						Assigned				Reported
						M_1	M_1^c	M_2	M_2^c	
57	2-CH_3, 3-CN	94	101.20	109	115.34	–	–	–	–	–
58	2,3-Br_2	90	228.73	104	216.40	–	±	–	±	–
59	2-Br, 3-CF_3	108	197.67	125	181.78	+	±	+	±	+
60	2-CH_3, 3-OCH_3	94	103.39	109	117.67	–	–	–	–	–
61	2-Br, 3-CN	94	167.31	109	155.95	–	±	–	+	+
62	2-CH_3, 2-C_2H_5	94	100.50	109	114.67	–	–	–	–	–
63	2-CH_3, 3-CF_3	108	131.55	125	141.16	+	+	+	±	+
64	2-CH_3, 3-$SO_2N(CH_3)_2$	118	170.37	139	196.79	±	±	±	±	–
65	2-CH_3, 3-$N(CH_3)_2$	100	108.25	116	124.01	±	–	±	–	–
66	2,4-Cl_2	90	127.66	103	130.53	–	±	–	–	–
67	2,5-Cl_2	90	127.66	103	133.99	–	±	–	–	–
68	2,6-Cl_2	90	127.66	104	135.83	–	±	–	–	–
69	3,4-Cl_2	90	127.66	103	138.83	–	±	–	–	–
70	3,5-Cl_2	90	127.66	102	127.08	–	±	–	–	–
71	2,4-$(CH_3)_2$	90	96.50	103	108.67	–	–	–	–	–
72	2,5-$(CH_3)_2$	90	96.50	103	108.67	–	–	–	–	–
73	2,6-$(CH_3)_2$	90	96.50	104	109.84	–	–	–	–	–
74	3,4-$(CH_3)_2$	90	96.50	103	108.50	–	–	–	–	–
75	3,5-$(CH_3)_2$	90	96.50	102	107.50	–	–	–	–	–
76	3,5-$(CF_3)_2$	126	166.60	144	170.49	±	±	±	±	–
77	2-Cl, 6-CH_3	90	112.08	104	121.91	–	–	–	–	–
78	2-CH_3, 6-Cl, 3-$N(CH_3)_2$	106	129.84	124	144.25	+	+	+	±	+
79	2,3,6-Cl_3	96	149.25	112	159.53	±	±	±	+	+
80	2,6-Cl_2, 3-CH_3	96	133.66	112	143.94	±	+	±	±	+
81	2,6-$(CH_3)_2$, 3-Cl	96	118.08	112	129.58	±	±	±	–	+
82	2-CH_3, 3,6-Cl_2	96	133.66	112	141.66	±	+	±	±	+
83	2,3-$(CH_3)_2$, 6-Cl	96	118.08	112	129.91	±	±	±	–	–
84	2,6-$(CH_3)_2$, 3-$SO_2N(CH_3)_2$	124	176.37	147	204.95	±	±	±	±	+
85	2,6-$(C_2H_5)_2$, 3-C(=O)CH_3	114	122.61	134	141.50	±	±	±	±	–
86	2-$(CH_3)_2$, 3-CF_3	116	139.55	136	152.33	±	+	±	+	+
87	2-Cl, 3-$N(CH_3)_2$, 6-CH_3	106	129.84	124	146.53	+	+	+	+	+
88	2,6-Cl, 3-CN, 6-CH_3	108	150.28	128	162.74	+	±	+	±	+
89	2,6-Cl_2, 3-$SO_2N(CH_3)_2$	124	207.53	147	234.33	±	±	±	±	+
90	2,6-$(CH_3)_2$, 3-SO_2CH_3	114	157.39	133	182.28	±	±	±	±	+
91	2,6-$(CH_3)_2$, 3-$SOCH_3$	106	139.62	124	156.50	+	+	+	+	+
92	2,3,4-Cl_3	96	149.25	112	164.82	±	±	±	±	–
93	2,3,5-Cl_3	96	149.25	111	156.07	±	±	–	+	–
94	2,4,6-Cl_3	96	149.25	111	150.78	±	±	–	+	–
95	2,4,5-Cl_3	96	149.25	111	156.07	±	±	–	+	–
96	3,4,5-Cl_3	96	149.25	111	161.37	±	±	–	±	–
97	2,3,5-$(CH_3)_3$	96	102.50	111	116.67	±	–	–	–	–
98	2,4,6-$(CH_3)_3$	96	102.50	112	117.84	±	–	±	–	–
99	2,4,5-$(CH_3)_3$	96	102.50	111	116.67	±	–	–	–	–
100	2-CH_3, 3,5-Cl_2	96	133.66	111	138.21	±	+	–	±	+
101	2,3-Cl_2, 5-CH_3	96	133.66	111	146.28	±	+	–	±	–
102	3,5-Cl_2, 4-CH_3	96	133.66	111	140.00	±	+	–	±	–
103	2,5-$(CH_3)_2$, 3-Cl	96	118.08	111	128.42	±	±	–	–	+
104	2,3-$(CH_3)_2$, 5-Cl	96	118.08	111	126.46	±	±	–	–	–
105	2,3,4,5-Cl_4	102	170.83	120	190.36	±	±	±	±	–
106	2,3,4,6-Cl_4	102	170.83	120	185.07	±	±	±	±	–
107	2,3,5,6-Cl_4	102	170.83	120	185.07	±	±	±	±	+
108	2,3,5,6-$(CH_3)_4$	102	108.50	120	125.84	±	–	±	–	–
109	2,3,4-Cl_3, 6-CH_3	102	155.25	120	172.99	±	±	±	±	–
110	2,4,6-Cl_3, 3-CH_3	102	155.25	120	163.69	±	±	±	±	–
111	2,3,4,5,6-Cl_5	108	192.41	129	219.35	+	±	±	±	–
112	2,3,5-$(CH_3)_3$, 4,6-Cl_2	108	145.66	129	162.57	±	±	±	±	–

[a] – inactive compound, + active compound (MED mg kg^{-1} 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^{-1}		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 43 compounds in the inactive range were predicted correctly. The correctly predicted compounds had average MED of 104.72 mg kg^{-1}.

• 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^{-1}.

• 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 52 compounds in the inactive range were predicted correctly. The correctly predicted compounds had average MED of 101.10 mg kg^{-1}.

• 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^{-1}.

• 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 61 compounds in the inactive range were predicted correctly. The correctly predicted compounds had average MED of 85.34 mg kg^{-1}.

• 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^{-1}.

• 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.[41] 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 vide spectrum of properties for a vast range of molecular species.[42] 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.[43] 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.[36] 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

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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 parametera izraženih pomoću obiju vrsta Zagrebačkih indeksa, ali je prednost na strani topokemijskih Zagrebačkih indeksa zbog njihove niske degeneracije.