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Bioorganic & Medicinal Chemistry 12 (2004) 3695–3701
Bioorganic & Medicinal Chemistry

Topological models for prediction of anti-inflammatory activity of *N*-arylanthranilic acids

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Received 9 February 2004; revised 28 March 2004; accepted 11 April 2004
Available online 25 May 2004

Abstract—Relationship of anti-inflammatory activity of *N*-arylanthranilic acids with distance based Wiener's index, adjacency based Zagreb indices M_1 and M_2, and distance-cum-adjacency based eccentric connectivity index (ECI) was investigated. A dataset comprising of 112 *N*-arylanthranilic acids was selected. The values of all the four indices for each of the 112 compounds were calculated using an in-house computer program. The dataset was divided randomly into training and test sets. The data was analyzed and suitable models were developed after identification the active ranges in the training set. Subsequently, a biological activity was assigned to each of the compound involved in the test set using these models, which was then compared with the reported anti-inflammatory activity. High accuracy of prediction ranging from 83% to 90% was observed using models based upon topological indices.

1. Introduction

Molecular structure is the central theme of chemistry.[1] According to the principle of molecular structure, properties, and behavior of molecules follow from their structures. If one considers nonmetric properties of a molecule, then the molecule can be represented by a (molecular) graph, which is essentially a nonnumerical mathematical object. Measurable properties of a molecule are usually expressed by means of numbers. Hence, to correlate property or activity of a molecule with its topology, one must first convert by an algorithm the information contained in the graph to a numerical characteristic. A scalar numerical descriptor uniquely determined by a molecular graph is named a topological (graph-theoretic) index.[2,3] Next to the famous and widely used Hansch approach,[4] the most developed QSAR/QSPR techniques now involve the calculation of various nonempirical molecular descriptors. Regardless of the descriptors used in the development of QSAR/QSPR models, all of them share in common a basic approach; molecules are represented by vectors constructed in turn by molecular parameters, which are supposed to contain relevant information about molecular structure. Consequent to above, the use of topological indices in QSPR as well as QSAR studies have become of major interest in recent years, and especially the QSPR/QSAR models have become a powerful tool for predicting numerous physicochemical properties and biological activities of organic compounds acting as drugs as well as for molecular design.[5] Topological indices such as molecular connectivity index of Randic,[6] based on vertex adjacency matrix, and the Wiener's index,[7] based on the distance matrix,[8] have received great attention due to their applications in chemistry and drug research.[9–12] A number of other indices have also been proposed and used in structure–activity studies. These include distance based Balaban index[13,14] and Hosoya index,[8] adjacency based Zagreb indices M_1 and M_2,[15–18] and eccentric connectivity index, which is distance-cum-adjacency based.[19–23]

Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for treatment of minor pain and for management of edema and tissue damage resulting from inflammatory joint diseases (arthritis) and other inflammatory diseases. Some primary indications for NSAID therapy include rheumatoid arthritis, osteoarthritis, acute gouty arthritis, ankolysing spondylitis,

Keywords: Topological index; Wiener's index; Eccentric connectivity index; Zagreb indices; *N*-Arylanthranilic acids; Anti-inflammatory agents.
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doi:10.1016/j.bmc.2004.04.012

and dysmenorrhea. The inflammatory process involves a series of events that can be elicited by numerous stimuli (e.g., infectious agents, ischemia, antigen–antibody interactions, and thermal or other physical injuries). Each type of stimulus provokes a characteristic pattern of response that represents a relatively minor variation of inflammation. At microscopic level, the response usually is accompanied by familiar clinical signs of erythema, edema, tenderness (hyperalgesia), and pain.[24] Most of the nonsteroidal anti-inflammatory agents possess analgesic and anti-pyretic properties also. Inhibition of cyclooxygenase (COX), one of the key enzymes in the arachidonic acid cascade,[25] is the main mechanism by which the NSAIDs exert their anti-inflammatory action. 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.[26]

N-Arylanthranilic acids belong to the category of nonsteroidal anti-inflammatory drugs and are amino isosteres of salicylates, 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 dysmeno-rrhea. Fenamates act by blocking the metabolism of arachidonic acid by the enzyme cyclooxygenase. Some fenamates are also known to inhibit arachidonic acid lipoxygenase resulting in decreased synthesis of leukotrines, known mediators involved in inflammatory process.[27] 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.[28] It has 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.

In the present study, relationship of Wiener's index—a distance based topological index, adjacency based Zagreb indices M_1 and M_2, and distance-cum-adjacency based eccentric connectivity index with anti-inflammatory activity of *N*-arylanthranilic acid derivatives has been investigated and suitable models developed for the prediction of anti-inflammatory activity.

2. Calculation of topological indices

Wiener's index: Wiener's number or Wiener's index, W, is the first reported and used topological index in Chemistry. It was invented in 1940s. Wiener index is a useful topological index in structure–property relationship because it is a measure of the compactness of a molecule in terms of its structural characteristics, such as branching and cyclicity. Wiener's index is defined as the sum of the distances between all the pairs of vertices in hydrogen suppressed molecular graph that is

$$W = 1/2\left(\sum_{i=1}^{n} P_{ij}\right)$$

where P_{ij} is the length of the path that contains the least number of edges between vertex i and vertex j in the graph G; n is the maximum possible number of i and j.[1,7,11,14,21,29]

Zagreb indices M_1 and M_2: This pair of indices was introduced in 1972 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 following equations:

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

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

where $d(i)$ is the degree of vertex i and $d(j)$ is the weight of edge i–j.[15–18]

Eccentric connectivity index (ECI): This index was introduced in 1997 by Sharma et al.[19] It is defined as the sum total of the product of eccentricity and degree of each vertex in hydrogen suppressed molecular graph having n total vertices that is

$$\xi^{c} = \sum_{i=1}^{n} (Ei * Vi)$$

For a molecular graph (G), $v_1, v_2 \ldots v_n$ are vertices, the number of first neighbors of a vertex v_i is the degree of this vertex and is denoted by V_i. While, eccentricity E_i of vertex vi, in graph G is the length of shortest path from vi to vertex vj that is farthest from vi ($E_i = \max d(vi, vj); j|G$.[19–23]

3. Model development and analysis

A dataset comprising of 112 *N*-arylanthranilic acids (Fig. 1) was selected.[30] The values of Wiener's index were calculated using an in-house computer program. The dataset was divided randomly into two sets. Compounds having odd serial number were designated as training set and those having even serial number were separated as test set. The data in the training set was analyzed and suitable model developed after identification of active range based on maximization of moving average with respect to active compounds (<35% = inactive, 35–65% = transitional, >65% = active).[31,32] Subsequently, each compound in the test set was assigned a biological activity using this model, which was then compared with the reported anti-inflammatory

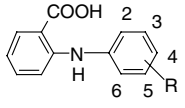

Figure 1. Structure of *N*-arylanthranilic acids.

activity.[33] 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.[30] 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 test compounds with correctly predicted activity to that of total number of test compounds present in the respective range of the proposed models. The overall degree of prediction was obtained from the ratio of total number of test compounds with correctly predicted activity to that of total number of test compounds in active and inactive range. 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 in the test set.

Aforementioned procedure was similarly repeated with ECI and Zagreb indices M_1 and M_2.

4. Results

Four different topological indices viz. Wiener's index, based upon relative interatomic distances, Zagreb indices M_1 and M_2, based upon adjacency or connectivity and eccentric connectivity index, which is both distance-cum-adjacency based, were chosen for model development. The models (Table 2) were developed using the training set of compounds (Table 1) and evaluated using the test set (Table 3). The accuracy of prediction (Table 4) is based upon the compounds in the test set only.

Model based upon Wiener's index:

- This model comprises of four ranges viz. inactive range (<743), lower transitional range (743–899), active range (900–918), and upper transitional range (>918).
- Twenty nine out of thirty three test compounds having Wiener's index values less than 743 were predicted correctly as inactive using the model based upon Wiener's index. The correctly predicted compounds in the inactive range had average MED of $95.22\,mg\,kg^{-1}$.
- Four out of five test compounds having Wiener's index values from 900 to 918 were predicted correctly as active. The correctly predicted active compounds had average MED of $1.52\,mg\,kg^{-1}$.
- Eleven test compounds were found to be in lower transitional range while seven were in upper transitional range.
- The overall predictability of the model using Wiener's index was 86.8%.

Model based upon eccentric connectivity index:

- The model comprises of four ranges viz. inactive range (<296), lower transitional range (296–312), active (313–336), and upper transitional range (>336).
- Twenty nine out of thirty four test compounds having ECI values less than 296 were predicted correctly as inactive using model based upon eccentric connectivity index. The average MED of the correctly predicted compounds in the inactive range was $98.6\,mg\,kg^{-1}$.
- Seven out of eight test compounds having ECI values from 313 to 336 were predicted correctly as active. The correctly predicted active compounds had average MED of only $1.17\,mg\,kg^{-1}$.
- Ten test compounds were found to be in lower transitional range while upper transitional range had only four compounds.
- The overall predictability of the model based upon ECI index was 82.6%.

Model based upon 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).
- Nineteen out of twenty test compounds having M_1 values less than 95 were predicted correctly as inactive using the said model. The correctly predicted compounds had average MED of $87.17\,mg\,kg^{-1}$.
- Five out of seven test compounds having M_1 values from 104 to 108 were predicted correctly as active. The correctly predicted compounds had average MED of only $1.32\,mg\,kg^{-1}$.
- Twenty two and seven test compounds were found to be in lower and upper transitional ranges, respectively.
- The overall predictability of the model using Zagreb index M_1 was 88.88%.

Model based upon Zagreb index M_2:

- The proposed model comprises of four ranges viz. inactive range (<112), lower transitional range (112–120), active range (121–128) and upper transitional range (>128).
- Twenty three out of Twenty five test compounds having M_2 values less than 112 were predicted correctly as inactive using the said model. The correctly predicted compounds had average MED of $90.50\,mg\,kg^{-1}$.
- Five out of six test compounds having M_2 values from 121 to 128 were predicted correctly as active. The correctly predicted compounds had average MED of $1.32\,mg\,kg^{-1}$.
- Seventeen and eight test compounds were found to be in lower and upper transitional ranges, respectively.
- The overall predictability of the model using Zagreb index M_2 was 90.3%.

Table 1. Index values and activity of training set of anti-inflammatory *N*-arylanthranilic acids

Compd no	Substituent(s)	W	ξ^c	M_1	M_2	Reported activity
1	H	447	217	78	88	−
3	3-Cl	528	232	84	95	−
5	2-CH_3	518	230	84	96	−
7	4-CH_3	538	255	84	95	−
9	3-*n*-C_4H_9	877	357	96	108	−
11	3-OC_2H_5	742	310	92	104	−
13	3-*n*-C_3H_7	742	310	92	104	−
15	3-$SO_2N(CH_3)_2$	1074	363	112	130	−
17	3-CN	626	270	88	100	−
19	3-C(=O)CH_3	726	287	94	107	−
21	3-$N(CH_3)_2$	726	287	94	107	−
23	2-F, 3-Cl	602	245	90	104	−
25	2-Cl, 3-CH_3	602	245	90	104	−
27	2-CH_3, 3-NH_2	602	245	90	104	−
29	2,6-Cl_2, 3-C_2H_5	790	296	100	117	+
31	2-NH_2, 3-Cl, 6-CH_3	682	258	96	112	−
33	2-CH_3, 3-Cl, 6-NH_2	682	258	96	112	−
35	2-CH_3, 3-NH_2, 6-Cl	682	258	96	112	−
37	2-Cl, 3,6-$(CH_3)_2$	682	258	96	112	−
39	2,3-Cl_2, 6-CH_3	682	258	96	112	+
41	2,3,6-$(CH_3)_3$	682	258	96	112	−
43	2,6-$(C_2H_5)_2$, 3-NO_2	1126	**343**	114	134	−
45	2,6-Cl_2, 3-$N(CH_3)_2$	900	313	106	124	+
47	2,6-$(CH_3)_2$, 3-C(=O)CH_3	900	313	106	124	+
49	2,6-$(CH_3)_2$, 3-CN	790	296	100	117	+
51	2,6-Cl_2, 3-OC_2H_5	918	336	104	121	+
53	2,6-$(C_2H_5)_2$, 3-$SO_2N(CH_3)_2$	1548	419	132	157	−
55	2,6-Cl_2, 3-CN	790	296	100	117	+
57	2-CH_3, 3-CN	704	283	94	109	−
59	2-Br, 3-CF_3	914	317	108	125	+
61	2-Br, 3-CN	704	283	94	109	+
63	2-CH_3, 3-CF_3	914	317	108	125	+
65	2-CH_3, 3-$N(CH_3)_2$	808	300	100	116	−
67	2,5-Cl_2	604	245	90	103	−
69	3,4-Cl_2	622	270	90	103	−
71	2,4-$(CH_3)_2$	613	268	90	103	−
73	2,6-$(CH_3)_2$	593	243	90	104	−
75	3,5-$(CH_3)_2$	613	247	90	102	−
77	2-Cl, 6-CH_3	593	243	90	104	−
79	2,3,6-Cl_3	682	258	96	112	+
81	2,6-$(CH_3)_2$, 3-Cl	682	258	96	112	+
83	2,3-$(CH_3)_2$, 6-Cl	682	258	96	112	−
85	2,6-$(C_2H_5)_2$, 3-C(=O)CH_3	1126	343	114	134	−
87	2-Cl, 3-$N(CH_3)_2$, 6-CH_3	900	313	106	124	+
89	2,6-Cl_2, 3-$SO_2N(CH_3)_2$	1282	389	124	147	+
91	2,6-$(CH_3)_2$, 3-$SOCH_3$	900	313	106	124	+
93	2,3,5-Cl_3	692	260	96	111	−
95	2,4,5-Cl_3	702	283	96	111	−
97	2,3,5-$(CH_3)_3$	692	260	96	111	−
99	2,4,5-$(CH_3)_3$	702	283	96	111	−
101	2,3-Cl_2, 5-CH_3	692	260	96	111	−
103	2,5-$(CH_3)_2$, 3-Cl	692	260	96	111	+
105	2,3,4,5-Cl_4	793	298	102	120	−
107	2,3,5,6-Cl_4	775	273	102	120	+
109	2,3,4-Cl_3, 6-CH_3	784	296	102	120	−
111	2,3,4,5,6-Cl_5	880	311	108	129	−

−: Inactive compound, +: active compound (compounds having MED mg kg^{-1} less than 2.5), W—Wiener's index, ξ^c—eccentric connectivity index, M_1—Zagreb index M_1 and M_2—Zagreb index M_2.

5. Discussion and conclusions

In contemporary drug research the quantitative structure–activity relationship (QSAR) has become a standard tool in drug design because the inefficient trial and error approach of the past has become prohibitively expensive. Use of topological indices in QSAR has increased during the last decade mainly because their derivation is relatively easy and purely computational. Structure–activity relationship studies employing topological indices use available information on lead compounds in efficient and discriminatory way and exclude

Table 2. Proposed models based on training set of *N*-arylanthranilic acids

Model index	Nature of range in proposed model	Index value
W	Inactive	<743
	Lower transitional	743–899
	Active	900–918
	Upper transitional	>918
ξ^c	Inactive	<296
	Lower transitional	296–312
	Active	313–336
	Upper transitional	>336
M_1	Inactive	<95
	Lower transitional	95–103
	Active	104–108
	Upper transitional	>108
M_2	Inactive	<112
	Upper transitional	112–120
	Active	121–128
	Lower transitional	>128

W—Wiener's index, ξ^c—eccentric connectivity index, M_1—Zagreb index M_1, and M_2–Zagreb index M_2.

excessive unproductive and expensive searches.[34] This is because molecular topology overcomes the inherent problem in structure–activity relationship to quantify chemical structures by translation of chemical structures into numerical descriptors. Topological indices are derived from the information based on connectivity of various atoms within a molecule. Therefore these indices are able to reveal the activity or property related structural and substructural aspects of a molecule. The present study is another attempt, using well-known topological indices, to contribute toward designing of *N*-arylanthranilic acids. In this study a large dataset comprising of 112 anti-inflammatory *N*-arylanthranilic acids[33] was used for development of models. Nonsteroidal 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. Comparative analysis (Table 5) of the developed models and their evaluation using test set of *N*-arylanthranilic acid derivatives reveals that all the four indices used in this study have shown excellent results in terms of predictability. Zagreb indices have shown higher accuracy of prediction but the classification is lower while ECI has comparatively less accuracy but has exhibited much higher classification when compared to the other three indices. Model

Table 3. Cross-validation test with regard to anti-inflammatory activity of *N*-arylanthranilic acids using proposed models based on Wiener's index (W), eccentric connectivity index (ξ^c), and Zagreb indices M_1 and M_2

Compd no	Substituent(s)	W	ξ^c	M_1	M_2	Anti-inflammatory activity				
						Assigned				Reported
						W	ξ^c	M_1	M_2	
2	2-Cl	518	230	84	96	−	−	−	−	−
4	4-Cl	538	255	84	95	−	−	−	−	−
6	3-CH_3	528	232	84	95	−	−	−	−	−
8	3-NH_2	528	232	84	95	−	−	−	−	−
10	3-SCH_3	626	270	88	100	−	−	−	−	−
12	3-OCH_3	626	270	88	100	−	−	−	−	−
14	3-Br	528	232	84	95	−	−	−	−	−
16	3-C_2H_5	626	270	88	100	−	−	−	−	−
18	3-NO_2	726	287	94	107	−	−	−	−	−
20	3-CF_3	828	304	102	116	±	±	±	±	−
22	2,3-Cl_2	602	245	90	104	−	−	−	−	+
24	2-CH_3, 3-Cl	602	245	90	104	−	−	−	−	−
26	2-CH3, 3-NO_2	808	300	100	116	±	±	±	±	−
28	2,3$(CH_3)_2$	602	245	90	104	−	−	−	−	−
30	6-$(CH_3)_2$, 3-NO_2	904	313	108	125	+	+	+	+	+
32	2-NH_3, 3,6-$(CH_3)_2$	682	258	96	112	−	−	±	±	−
34	2-CH_3, 3-NO_2, 6-Cl	900	313	106	124	+	+	+	+	+
36	2,6-$(CH_3)_2$, 3-NH_2	682	258	96	112	−	−	±	±	−
38	2,6-$(CH_3)_2$, 3-N$(CH_3)_2$	900	313	106	112	+	+	+	+	+
40	2,3-Cl_2, 3-OCH_3	790	296	100	117	±	±	±	±	+
42	2,6-$(CH_3)_2$, 3-Br	682	258	96	112	−	−	±	±	+
44	2,6-Cl_2, 3-NH_2	682	258	96	112	−	−	±	±	−
46	2,6-$(CH_3)_2$, 3-C_2H_5	790	296	100	117	±	±	±	±	+
48	2,6-$(CH_3)_2$, 3-N-C_3H_7	918	336	104	121	+	+	+	+	−
50	2-CH_3, 3-OCH_3, 6-Cl	790	296	100	117	±	±	±	±	+
52	2,6-$(CH_3)_2$, 3-SCH_3	790	296	100	117	±	±	±	±	+
54	2,6-Cl_2, 3-CF_3	1012	330	114	133	±	+	±	±	+
56	2-CH_3, 3-$SO_2N(CH_3)_2$, 6-Cl	1282	389	124	147	±	±	±	±	+
58	2,3-Br_2	602	245	90	104	−	−	−	−	−
60	2-CH_3, 3-OCH_3	704	283	94	109	−	−	−	−	−
62	2-CH_3, 2-C_2H_5	704	283	94	109	−	−	−	−	−
64	2-CH_3, 3-$SO_2N(CH_3)_2$	1170	376	118	139	±	±	±	±	−

(*continued on next page*)

Table 3 (*continued*)

Compd no	Substituent(s)	W	ξ^c	M_1	M_2	Anti-inflammatory activity				
						Assigned				Reported
						W	ξ^c	M_1	M_2	
66	2,4-Cl_2	613	268	90	103	−	−	−	−	−
68	2,6-Cl_2	593	243	90	104	−	−	−	−	−
70	3,5-Cl_2	613	247	90	102	−	−	−	−	−
72	2,5-$(CH_3)_2$	604	245	90	103	−	−	−	−	−
74	3,4-$(CH_3)_2$	622	270	90	103	−	−	−	−	−
76	3,5-$(CF_3)_2$	1297	370	126	144	±	±	±	±	−
78	2-CH_3, 6-Cl, 3-$N(CH_3)_2$	900	313	106	124	+	+	+	+	+
80	2,6-Cl_2, 3-CH_3	682	258	96	112	−	−	±	±	+
82	2-CH_3, 3,6-Cl_2	682	258	96	112	−	−	±	±	+
84	2,6-$(CH_3)_2$, 3-$SO_2N(CH_3)_2$	1282	389	124	147	±	±	±	±	+
86	2-$(CH_3)_2$, 3-CF_3	1002	330	116	136	±	+	±	±	+
88	2,6-Cl, 3-CN, 6-CH_3	874	309	108	128	±	±	+	+	+
90	2,6-$(CH_3)_2$, 3-SO_2CH_3	1012	330	114	133	±	+	±	±	+
92	2,3,4-Cl_3	700	283	96	112	−	−	±	±	−
94	2,4,6-Cl_3	692	281	96	111	−	−	±	−	−
96	3,4,5-Cl_3	710	285	96	111	−	−	±	−	−
98	2,4,6-$(CH_3)_3$	682	258	96	112	−	−	±	±	−
100	2-CH_3, 3,5-Cl_2	692	260	96	111	−	−	±	−	+
102	3,5-Cl_2, 4-CH_3	710	285	96	111	−	−	±	−	−
104	2,3-$(CH_3)_2$, 5-Cl	692	260	96	111	−	−	±	−	−
106	2,3,4,6-Cl_4	784	296	102	120	±	±	±	±	−
108	2,3,5,6-$(CH_3)_4$	775	273	102	120	±	−	±	±	−
110	2,4,6-Cl_3, 3-CH_3	784	296	102	120	±	±	±	±	−
112	2,3,5-$(CH_3)_3$, 4,6-Cl_2	880	311	108	129	±	±	+	±	−

−: Inactive compound, +: active compound (MED mg kg^{-1} less than 2.5), ± compound in transitional range.

Table 4. Evaluation of proposed models using test set 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[b] (mg kg^{-1})	
			Total	Correct		Total	Correct
W	Inactive	<743	33	29	87.7	83.81	95.22
	Lower transitional	743–899	11	NA[a]	NA	NA	NA
	Active	900–918	5	4	80	2.46	1.52
	Upper transitional	>918	7	NA	NA	NA	NA
ξ^c	Inactive	<296	34	29	85.3	84.29	98.60
	Lower transitional	296–312	10	NA	NA	NA	NA
	Active	313–336	8	7	87.5	1.80	1.17
	Upper transitional	>336	4	NA	NA	NA	NA
M_1	Inactive	<95	20	19	95.0	82.91	87.17
	Lower transitional	95–103	22	NA	NA	NA	NA
	Active	104–108	7	5	71.4	16.11	1.32
	Upper transitional	>108	7	NA	NA	NA	NA
M_2	Inactive	<112	25	23	92.0	83.40	90.50
	Lower transitional	112–120	17	NA	NA	NA	NA
	Active	121–128	6	5	83.3	2.13	1.32
	Upper transitional	>128	14	NA	NA	NA	NA

[a] NA—Not applicable.
[b] MED—Minimum effective dose.

Table 5. Intermodel comparison

Model index	Percent classification	Accuracy of prediction
W	67.8	86.8
ξ^c	82.1	82.6
M_1	48.2	88.9
M_2	55.3	90.3

based upon Wiener's index has also demonstrated good predictability while its classification lies between those of Zagreb indices and ECI. Amongst the Zagreb indices, M_2 has proven to be better in this study with higher classification and predictability than M_1.

Analysis of the models (Table 2) reveals that 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 is gradual. However if the information available from the compounds in both training and test set is combined the status of this range as transitional range is clarified.

Careful examination of the structure of the compounds in the active ranges indicates that the substitution at position 3 (Fig. 1) is most critical for activity. It can be observed that all the active compounds have bi- or tri-substituted nitrogen, carbon or other atom at position 3. Possibly this type of group is responsible for receptor binding or providing correct shape that fits into the receptor. Larger functional group or straight chain group at this position, as in compound number 53, 56, 64, or 89, leads to loss of activity, which substantiates the above supposition. Further, presence of a similar group at position 5 in addition to the one at position 3 also results in loss of activity as in compound number 76, because this additional group probably causes hindrance in the receptor binding.

Substitution either at positions 2 or at 6, by a small group, is also important for activity. However this substitution is of importance only when the substitution at position 3 is appropriate, while compounds devoid of substitution at 3, for example, compound number 77, are inactive. This relationship suggests that new *N*-aryl-anthranilic acids having similar size, shape, and having index values falling within the active ranges, as reported in these models, but having different functional groups may have similar or improved anti-inflammatory activity. High predictability of the models can easily be exploited to provide lead structures for development of potent therapeutic agents.

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