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Topological Modelling of Analgesia

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Abstract—Analgesic activity (log IC) of a large series of 97 analgesics was modelled topologically using a series of distance-based topological indices. The results show that analgesic activity (log IC) exhibit inter familial correlation and these can only be modelled by splitting 97 analgesics into five different categories. The regression analyses of the data show that the Wiener (W)-, Branching (B)- and first-order connectivity (χ)- indices are the better topological indices for modelling the activity (log IC), and that W index gave the excellent results.

Introduction

Analgesics are the drugs which relieve pain by acting on the central nervous system (CNS) and reduce pain without causing loss of consciousness. Because of potential to relieve pain, they play an important role in medical therapy.[1] The dose required to produce analgesia usually does not alter the functions of CNS.[2] That is, analgesia produced is not accompanied by slurred speech or motor in coordination. They modify the emotional reaction to pain and raise the pain threshold.

Narcotic and opioid analgesics are the most potent and clinically useful agents causing depression of CNS. The analgesia is thought to involve activation of μ-receptors largely at supraspinal sites and κ-receptors largely within the spinal cord.[3] These receptors function by exerting inhibitory modulation of synaptic transmission in both the CNS and myenteric plexus.

Like inflammation, analgesia also is a feeling. However, our earlier study[4,5] showed that anti-inflammation can be successfully modelled using topological indices. Likewise, we believe that we can use topological indices for modelling analgesia as well. This was, therefore, the primary aim of our present investigation. The results as discussed below show that the topological indices can be used for modelling analgesia.

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Randic[6] has emphasized the importance of graph recognition in QSAR/QSPR studies, and pointed out that chemical graphs can belong to families in the same way that plants belong to Genera. Consequently, the compounds exhibit 'familial' behaviour and correlate according to the family to which they belong. As a result of this the heterogeneous collection of compounds splits into two or more categories depending upon the family to which they belong. The set of analgesics used by us is also a heterogeneous set of different types of analgesic compounds, some are narcotic, some are opioid, and some non-opioid. Hence, it is observed in the present case that better and statistically significant models are only obtained by splitting the set of 97 analgesics into different categories. Like Randic,[6] we also believe that obtained 'interfamilial' correlations should be viewed as a viable additional new technique in the growing armory of data reduction technique[7] applicable to heterogeneous systems such as one in the present study.

Results and Discussion

In the present study, we have used a pool of distance-based topological indices, namely information theoretic index (Id),[8] Wiener index (W),[9] first-order connectivity (χ) index,[10,11] Balaban index (J),[12] Szeged index (Sz),[13,14] Branching index (B) and RB (logRB) index[10] for modelling analgesic activity (log IC). The calculations of these indices are reported in the literature,[10] and a brief account is given in the Experimental section. The

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Table 1. Molecular descripters (topological indices) Id, W, B, X, J, Sz, log RB and analgesic activity log IC calculated for 97 analgesics

Compd	Name of the analgesic	Id	W	B	χ	J	Sz	log RB	log IC
1	Acetanilide	−2.3265	156.0000	5.2152	5.2152	2.3206	228.0000	49.7028	2.2600
2	Aniline	−2.1391	88.0000	4.3045	4.3045	2.2284	142.0000	27.6625	2.1500
3	Antipyrine	−2.5746	284.0000	6.6984	6.6984	2.0049	414.0000	90.7187	2.7800
4	Aminopyrine	−2.6743	394.0000	7.4592	7.4592	2.1454	560.0000	126.0151	3.6800
5	Anileridine	−3.2795	2304.0000	13.5477	13.5477	1.4696	3513.0000	597.3932	3.5000
6	Aminopropylon	−3.0401	1142.0000	10.7686	10.7686	2.1220	1434.0000	338.2793	3.0000
7	2-Amino, 4-Picoline	−2.2245	117.0000	4.6984	4.6984	2.3199	186.0000	37.2374	1.7100
8	Alcofenac	−2.7072	497.0000	7.6682	7.6682	2.2734	688.0000	147.1579	1.7100
9	Alminoprofen	−3.0330	1120.0000	10.5797	10.5797	1.5298	1719.0000	316.8177	1.3900
10	Aminochlorothenoxazin	−2.8695	692.0000	9.2062	9.2062	2.0230	1202.0000	210.1250	2.9200
11	Apazone	−2.9541	789.0000	9.9296	9.9296	1.9617	1171.0000	248.1835	3.9500
12	Alphacetyl methadole	−3.4521	1436.0000	12.4128	12.4128	2.4322	1850.0000	440.7966	13.0000
13	Alpha prodine	−2.8741	648.0000	9.0814	9.0814	2.1547	982.0000	203.2601	5.0000
14	Bemidone	−2.8741	776.0000	9.5925	9.5925	2.0845	1169.0000	237.8106	1.5000
15	Betacetyl methadole	−3.1864	1436.0000	12.4128	12.4128	2.4322	1850.0000	440.7966	2.3000
16	Benorylate	−3.1074	1495.0000	11.3799	11.3799	1.8025	2124.0000	407.7732	2.4700
17	Benzdamine	−2.9485	137.0000	11.2372	11.2372	1.4953	1846.0000	363.6399	1.4300
18	Benziperylon	−3.2234	1626.0000	12.7204	12.7204	1.4512	2449.0000	465.8112	0.8400
19	Benozaprofen	−3.0331	1120.0000	10.5797	10.5797	1.5298	1719.0000	316.8177	1.0500
20	Bufexamac	−2.8322	743.0000	8.6682	8.6682	2.1461	983.0000	207.8544	1.4200
21	Codeine	−3.1830	940.0000	11.2019	11.2019	1.6177	2224.0000	297.6836	8.0400
22	Chlorthenoxazine	−2.6475	344.0000	7.2364	7.2364	2.0262	640.0000	109.3376	2.7400
23	p-chlorobonzohydrazide	−2.5456	312.0000	6.5197	6.5197	2.4059	432.0000	97.4319	1.6200
24	5-Chloro salicyclic acid	−2.4845	240.0000	6.1851	6.1851	2.5373	352.0000	77.2238	3.6200
25	1(*p*-Chlorophenyl)propylamine	−2.4845	250.0000	6.1471	6.1471	2.4118	358.0000	79.1495	0.9000
26	*p*-Chloro porpiophenone	−2.3264	160.0000	5.2364	5.2364	2.2677	244.0000	50.4470	1.0300
27	3-Chloro salicylic acid	−2.4844	236.0000	6.2019	6.2019	2.5829	344.0000	76.3075	2.8300
28	Cinchophen	−2.9567	766.0000	9.7920	9.7920	1.7012	1409.0000	234.5918	0.9900
29	Dioxaphetyl butyrate	−3.2206	1549.0000	12.7432	12.7432	1.7829	2170.0000	457.8582	0.2500
30	2′,4′-Dimethyl acetophenone	−2.3096	150.0000	5.1091	5.1091	2.4372	236.0000	48.0526	1.8200
31	2′,4′-Dichloro benzyl alcohol	−2.3265	158.0000	5.2364	5.2364	2.3117	244.0000	50.0393	2.6700
32	4′,4′-Dichloro phthallic acid	−2.6745	416.0000	7.5064	7.5064	2.7466	590.0000	132.7405	1.4100
33	3′4′-Dimethyl acetophenone	−2.3028	152.0000	5.1091	5.1091	2.3956	240.0000	48.4988	0.7800
34	Dipanone	−3.2513	1489.0000	12.6807	12.6807	1.8560	2110.0000	446.8885	0.8000
35	Dihydromorphinone	−3.0342	820.0000	10.6639	10.6639	1.6359	1995.0000	262.5535	0.1700
36	Dihydrocodeinone	−3.0342	824.0000	10.6639	10.6639	1.6279	2007.0000	263.1413	1.2800
37	Dihydrocodeine	−1.5065	940.0000	11.2019	11.2019	1.6177	2224.0000	297.6838	1.3400
38	Dihydrodesoxymorphine-D	−2.9965	730.0000	10.2532	10.2532	1.6139	1812.0000	233.6256	0.0800
39	Dextromoramide	−3.3300	1939.0000	14.2252	14.2252	1.6575	2694.0000	576.3300	13.0000
40	Ethoheptazine	−2.8870	659.0000	9.1606	9.1606	2.0999	918.0000	205.6603	1.0000
41	Ethenzamide	−2.5636	301.0000	6.6639	6.6639	2.5238	415.0000	95.8835	2.6400
42	Epirzole	−2.7647	431.0000	7.7407	7.7407	1.9465	617.0000	134.4794	3.7100
43	Fertiazac	−3.0901	1198.0000	11.1690	11.1690	1.6309	1719.0000	348.6794	−0.9100
44	Flurbiprofen	−2.8826	736.0000	9.1302	9.1302	1.8649	1150.0000	217.2921	1.2100
45	Fenoprofen	−2.8955	760.0000	9.2027	9.2027	1.7890	1132.0000	222.4367	1.3400
46	Feprazone	−3.1234	1257.0000	11.5922	11.5922	1.7710	1751.0000	373.9607	1.2200
47	Flufenamic acid	−3.0065	1180.0000	10.3247	10.3247	1.7797	1810.0000	326.0737	0.5300
48	Heterocodeine	−3.1830	940.0000	11.2019	11.2019	1.6177	2224.0000	297.6838	0.4800
49	Hexalgon	−3.1792	1376.0000	12.2700	12.2700	1.7933	1970.0000	411.1584	0.5000
50	α-Isomorphine	−3.1830	940.0000	11.2019	11.2019	1.6177	2224.0000	297.6838	0.8000
51	β-Isomorphine	−3.1830	954.0000	11.1850	11.1850	1.5932	2264.0000	300.1360	7.0900
52	Isomethadone	−3.0661	1030.0000	11.0290	11.0290	2.3724	1390.0000	322.3319	0.6500
53	Indomethacin	−3.1889	1594.0000	12.4559	12.4559	1.7582	2355.0000	460.4667	1.0800
54	Ibuprofen	−2.6911	487.0000	7.5409	7.5409	2.3088	676.0000	145.0069	1.2100
55	Isoxicam	−2.8479	493.0000	8.5924	8.5924	1.9847	1111.0000	160.6700	3.3700
56	Isonixin	−3.4424	775.0000	9.4304	9.4304	2.0459	1144.0000	236.4924	1.8900
57	Ketoprofen	−2.9882	842.0000	9.6302	9.6302	1.8835	1244.0000	248.1457	0.6800
58	Ketobemidone	−2.8741	656.0000	9.1194	9.1194	2.1251	1024.0000	204.3667	6.2000
59	Ketorolac	−2.9448	809.0000	9.7196	9.7196	1.6228	1124.0000	240.2649	2.0700
60	Methyl-2 acetamide acrylate	−2.2673	160.0000	5.0021	5.0021	3.9004	160.0000	51.4946	3.2100
61	*p*-Methyl propiophenone	−2.2124	160.0000	5.2364	5.2364	2.2677	244.0000	50.4447	1.2100
62	Methyl-2 methyl-3-furan carboxylate	−2.2241	121.0000	4.6984	4.6984	2.2617	136.0000	38.2591	2.9200
63	Methyl salicylate	−2.4195	201.0000	5.7364	5.7364	2.3588	290.0000	64.0653	2.6200
64	Mefenamic acid	−2.8826	676.0000	9.1471	9.1471	2.0326	1012.0000	208.4772	1.1600
65	Meclofenamic acid	−2.9243	866.0000	9.9684	9.9684	2.1292	1288.0000	265.3557	0.5700
66	Metofoline	−2.9001	1382.0000	11.6177	11.6177	1.5827	2321.0000	390.8643	0.2200
67	Morazone	−3.2825	2045.0000	13.5754	13.5754	1.4038	3078.0000	563.9540	2.5400
68	Morphine	−3.1830	940.0000	11.2019	11.2019	1.6177	2224.0000	297.6838	0.7500
69	Metopon	−3.0643	906.0000	11.0258	11.0258	1.6767	2176.0000	290.3745	0.0700
70	Methadone	−3.0652	1044.0000	11.0189	11.0189	2.3328	1404.0000	325.1784	1.0000

(continued on next page)

Table 1 (*continued*)

Compd	Name of the analgesic	Id	W	B	χ	J	Sz	log RB	log IC
71	Meperidine	−2.8295	568.0000	8.6875	8.6875	2.0999	871.0000	178.2034	1.0000
72	Niflumic acid	−3.0065	1036.0000	10.3416	10.3416	2.0307	1522.0000	307.1054	0.8900
73	Normethadone	−3.1411	944.0000	10.6082	10.6082	2.2674	1286.0000	293.8302	0.4400
74	Oxyphenbutazone	−3.1670	1433.0000	12.1682	12.1682	1.7511	2047.0000	418.2098	2.0800
75	Paracetamol	−2.4844	260.0000	6.1471	6.1471	2.3170	380.0000	80.8722	2.4500
76	Phenacetin	−2.5636	331.0000	6.6471	6.6471	2.2780	475.0000	100.9465	2.4300
77	Phenol	−2.0465	64.0000	3.9319	3.9319	2.1250	109.0000	19.6969	2.2600
78	Phenylbutazone	−3.0901	1109.0000	11.2364	11.2364	1.7787	1571.0000	334.1000	1.8800
79	Pheneridine	−3.1791	1626.0000	12.2163	12.2163	1.5077	2484.0000	44.7812	2.6000
80	Pirprofen	−2.8387	676.0000	8.7027	8.7027	1.7314	949.0000	196.0041	1.1700
81	Piroxacam	−3.6039	1344.0000	11.8911	11.8911	1.8351	2234.0000	401.9088	2.5400
82	Propylphenazone	−2.7642	492.0000	8.1639	8.1639	2.0548	676.0000	154.0631	3.1400
83	Prolidine	−2.8153	555.0000	8.5982	8.5982	2.1573	732.0000	175.6742	0.3000
84	Propoxyphene	−3.1536	1364.0000	11.9752	11.9752	2.2686	1760.0000	411.9212	0.2100
85	Ramifenazone	−2.8564	656.0000	8.9473	8.9473	2.1272	876.0000	203.6894	3.3800
86	Sulfadiazine	−2.9162	830.0000	9.4256	9.4256	1.9200	1235.0000	244.6573	1.1800
87	Salicylic acid	−2.4195	194.0000	5.7912	5.7912	2.4591	283.0000	62.4558	2.8300
88	Salsalate	−2.9882	942.0000	10.1682	10.1682	1.9365	1336.0000	278.7045	2.5900
89	Sulindac	−3.1891	1717.0000	12.3631	12.3631	1.6236	2535.0000	477.3157	0.9500
90	Trimeperidine	−2.9162	732.0000	9.4920	9.4920	2.2173	1110.0000	229.5978	7.5000
91	Tolmetin	−2.9243	861.0000	9.5241	9.5241	1.8616	1133.0000	250.2536	1.4400
92	Tenoxicam	−3.0976	1202.0000	11.3911	11.3911	1.8252	1802.0000	362.2767	1.8200
93	Tiaprofenic acid	−2.8975	801.0000	9.2027	9.2027	1.7091	1026.0000	228.2642	−0.4400
94	Vanillic acid	−2.5643	307.0000	6.7231	6.7231	2.4741	450.0000	96.7388	2.9300
95	Ximinol	−3.1926	1700.0000	12.5108	12.5108	2.0111	1973.0000	479.4294	0.2400
96	Zomepirac	−2.9118	952.0000	9.9349	9.9349	1.9500	1244.0000	278.4474	1.6100
97	Oxycodone	−3.1089	1025.0000	11.5805	11.5805	1.6676	2662.0000	325.9950	1.3400

Id, information topological index; W, Wiener index; B, branching index; χ, first-order connectivity index; J, Balaban index; Sz, Szeged index; log RB, Branching index; log IC, analgesic activity.

Table 2. Correlation matrix

	log IC	Id	W	B	χ	J	Sz	log RB
log IC	1.00000							
Id	−0.08727	1.00000						
W	0.05863	−0.77880	1.00000					
B	0.04418	−0.84710	0.92527	1.00000				
χ	0.04418	−0.84710	0.92527	1.00000	1.00000			
J	0.12662	−0.52501	−0.58480	−0.66678	−0.66678	1.00000		
Sz	0.03074	−0.75546	0.90548	0.94382	0.94382	−0.73465	1.00000	
log RB	0.05917	−0.78249	0.92217	0.93564	0.93564	−0.57954	0.89193	1.00000

calculated values of these indices, as shown in Table 1, show that their magnitude depends upon the size, shape, extends of branching present in the 97 analgesics used in the present investigation.

It has been demonstrated in the literature[15,16] that log IC can be successfully used to predict analgesic activity. We have, therefore, adopted these values from the literature.[15,16]

The correlation matrix for seven descriptors and the analgesic activity (log IC) is listed in Table 2. It shows that all the topological indices, except Balaban index (J), are highly correlated. It means that they are not independent variables for the other one(s). This correlation matrix also shows that none of the topological indices correlates significantly with the analgesic activity (log IC). Further study showed that no simple or multiparametric regressions gave any statistically significant model. This is obvious, as the heterogeneous set of 97 analgesics contains several types (families) of analgesic compounds. Earlier[17,18] also, we obtain statistically significant results only after splitting the data into different categories.

The aforementioned results, therefore, show that the analgesic activity (log IC) depends upon the type (family) of compounds used. In view of this, when we have plotted graphs (not shown here) for the heterogeneous set of compounds between a particular topological index and log IC, then we observed that 97 analgesic compounds split into five different categories (Table 3). That is, 97 compounds may be divided into five categories, targeting different descriptors (families). Hence, we have carried out modelling of analgesic activity (log IC) independently under these five categories using all the seven topological indices mentioned above.

Table 3. Splitting of 97 analgesics into five categories (families)

Category (family)	Analgesics	Total
a	1, 3, 4, 5, 8, 16, 17, 22, 26, 27, 29, 31, 32, 35, 36, 38, 46, 47, 58, 63, 66, 68, 70, 71, 72, 85, 86, 87, 94, 100, 103, 107	32
b	9, 11, 13, 28, 30, 37, 44, 61, 98	9
c	6, 23, 34, 39, 48, 55, 60, 75, 76, 96, 102, 108	12
d	10, 20, 21, 24, 40, 43, 51, 52, 54, 57, 59, 65, 74, 77, 78, 79, 81, 83, 84, 89, 105, 106, 110	23
e	7, 18, 25, 33, 41, 42, 45, 49, 50, 64, 67, 73, 80, 88, 92, 93, 95, 99, 101, 104, 109	21

One will argue that such a practice may not be a good strategy for QSAR analysis and that the topological indices used in the present study may not be good descriptors for QSAR analysis for these compounds. The alternative is to go for multiple regression analysis. However, no combination of the topological indices resulted into statistically significant multi-parametric model. Since, the compounds present in this heterogeneous set of 97 analgesics belong to different families (types or categories), we can only use indicator parameters representing a particular family and then carry out multiple regression analysis. However, such a familial behaviour undertaken for multiple analgesics is equivalent to split the data into five different family (categories). Such familial behaviour is reported by Randic[15] as well as by us[16–18] in the earlier studies.

The results as recorded in Tables 4 and 5 show that out of the seven topological indices used, only Wiener (W)-, Branching (B)-, and first-order connectivity (χ) indices along with information-theoretic index (Id) are important. Also, that the results obtained using B and χ indices are similar. Therefore, out of the pool of seven topological indices only three indices, namely W, χ (or B), and Id are more important in modelling analgesic activity of the compounds used.

The data presented in Table 5 also show that:

(i) The information theoretic index (Id) is capable of modelling analgesic activity (log IC) of the compounds belonging to category 'a' and 'b' only;

(ii) The indices W, B and χ can be used successfully for modelling analgesics belonging to all the five categories; that is W/B/χ can model the activity of all the 97 compounds successfully;

(iii) The Balaban index (J) is the worse topological index for modelling the activity (log IC). It fails to give any statistically significant model. Furthermore, regression expressions for modelling the analgesic activity (log IC) of compound belonging to categories 'a', 'd' and 'e' are such that the coefficient of J was considerably smaller than its standard deviation in the respective regression expressions. Such models are not allowed statistically. Hence, this shows that J is the useless topological index for this purpose;

(iv) Correlation matrix (Table 2) has shown that W and Sz indices are highly correlated. It means that like W, the Szeged index (Sz) should have been capable of modelling analgesic activity of all the 97 compounds. Instead, the results (Table 5) show that Sz can do so only with the compounds belonging to categories 'a', 'b' and 'c'.

Table 4. Regression expressions for the different series (a, b, c, d, e) based on Id, W, B, χ, J, Sz and log RB indices[a]

Based on Id	
1a.	log IC = −6.0142 (±0.7980) Id−11.9839
1b.	log IC = −13.7032 (±2.2090) Id−34.8918
1c.	log IC = −6.4878 (±2.9010) Id−19.7745
1d.	log IC = −5.3235 (±1.7157) Id−15.3836
1e.	log IC = −0.5930 (±0.3568) Id−0.2056
Based on W	
2a.	log IC = 0.0077 ($\pm 4.6662\times10^{-4}$) W + 0.7475
2b.	log IC = 0.0073 ($\pm 4.1971\times10^{-4}$) W−1.5865
2c.	log IC = 0.0035 ($\pm 4.1253\times10^{-4}$) W−4.8136
2d.	log IC = 0.0031 ($\pm 2.8965\times10^{-4}$) W−2.3307
2e.	log IC = 0.0026 ($\pm 4.5122\times10^{-4}$) W−0.6573
Based on B	
3a.	log IC = 0.8397 (±0.1287) B−2.3632
3b.	log IC = 1.4837 (±0.1614) B−9.4634
3c.	log IC = 1.4619 (±0.2543) B−17.3766
3d.	log IC = 0.7716 (±0.1421) B−7.4420
3e.	log IC = 0.4274 (±0.1192) B−2.6456
Based on χ	
4a.	log IC = 0.8397 (±0.1287) χ−2.3632
4b.	log IC = 1.4837 (±0.1614) χ−9.4634
4c.	log IC = 1.4619 (±0.2543) χ−17.3766
4d.	log IC = 0.7716 (±0.1421) χ−7.4420
4e.	log IC = 0.4274 (±0.1192) χ−2.6456
Based on J	
5a.	log IC = −0.8903 (±1.1190) J + 5.5093
5b.	log IC = −9.6166 (±2.7133) J + 24.6249
5c.	log IC = −2.2618 (±1.2774) J + 4.7405
5d.	log IC = 0.1327 (±0.6134) J + 0.7545
5e.	log IC = −0.1902 (±0.7879) J + 1.8820
Based on Sz	
6a.	log IC = 0.0029 ($\pm 5.1066\times10^{-4}$) Sz + 1.6262
6b.	log IC = 0.0052 ($\pm 4.4793\times10^{-4}$) Sz−1.6405
6c.	log IC = 0.0021 ($\pm 2.2280\times10^{-4}$) Sz−3.9834
6d.	log IC = 8.5590×10^{-4} ($\pm 3.9102\times10^{-4}$) Sz−0.5500
6e.	log IC = 6.4494×10^{-4} (±3.1354) Sz + 0.6900
Based on log RB	
7a.	log IC = 0.0187 (±0.0027) log RB + 1.2038
7b.	log IC = 0.0249 (±0.0014) log RB−1.7445
7c.	log IC = 0.0156 (±0.0019) log RB−6.3226
7d.	log IC = 0.0027 (±0.0022) log RB + 0.1885
7e.	log IC = 0.0085 (±0.0016) log RB−0.6080

[a]The detail statics is given in Table 5. For *n* values refer Table 3.

(v) Like Sz, the topological index log RB also correlates highly with W, however, unlike Sz, log RB is slightly better index as it is only incapable of modelling the activity (log IC) of the compounds belonging to category 'd'.

The regression equations[19,20] for the five splitted categories (Table 3) using each of the seven topological indices are presented in Table 4 and their regression

parameters and quality of correlations are presented in Table 5.

The regression parameters and the quality of regressions as shown in Table 5 can be used to investigate relative potential of Id, W, B, χ, J, Sz and log RB indices in modelling the analgesic activity (log IC) of the compounds used in the present investigation. The data (Table 5) show that the Wiener index (W) is the most appropriate index for this purpose. Using W index, excellent models are obtained for all the five categories. These models are found as:

$$\text{2a. } \log \text{IC} = 0.0077\ (\pm\ 4.6662 \times 10^{-4})\ \text{W} + 0.7475$$
$$n = 32,\quad Se = 0.7974,\quad R = 0.9487,$$
$$F = 269.869,\quad Q = 1.1897 \tag{1}$$

$$\text{2b. } \log \text{IC} = 0.0073\ (\pm\ 4.1971 \times 10^{-4})\ \text{W} -\ 1.5865$$
$$n = 09,\quad Se = 0.6021,\quad R = 0.9888,$$
$$F = 306.672,\quad Q = 1.6423 \tag{2}$$

$$\text{2c. } \log \text{IC} = 0.0035\ (\pm\ 4.1253 \times 10^{-4})\ \text{W} -\ 4.8136$$
$$n = 12,\quad Se = 0.4220,\quad R = 0.9375,$$
$$F = 72.577,\quad Q = 2.2216 \tag{3}$$

$$\text{2d. } \log \text{IC} = 0.0031\ (\pm\ 2.8965 \times 10^{-4})\ \text{W} -\ 2.3307$$
$$n = 23,\quad Se = 0.3261,\quad R = 0.9190,$$
$$F = 114.169,\quad Q = 2.8182 \tag{4}$$

$$\text{2e. } \log \text{IC} = 0.0026\ (\pm\ 4.5122 \times 10^{-4})\ \text{W} -\ 0.6573,$$
$$n = 21,\quad Se = 0.3862,\quad R = 0.7998,$$
$$F = 33.734,\quad Q = 2.0709 \tag{5}$$

In order to support our findings we have estimated the analgesic activity (log IC) for the compounds belonging to all the five categories mentioned earlier and compared them with the observed activity. Such a comparison is shown in the Tables 6 and 7. The residue, that is, difference between the observed and the calculated activity

Table 5. Regression models proposed for topological modelling of analgesic activity (log IC)[a]

Model no.	Parameter used	Splitted correlation (category or family)	Se	R	F	P	Q
1.	Id	1a	1.4821	−0.8089	56.796	2.110×10^{-8}	−0.5458
		1b	1.5811	−0.9198	38.481	4.438×10^{-4}	−0.5817
		1c	0.9900	−0.5774	5.002	0.0493	−0.5832
		1d	0.6850	−0.5607	9.628	5.387×10^{-3}	−0.8185
		1e	0.6012	−0.3563	2.762	0.1129	−0.5926
2	W	2a	0.7974	0.9487	269.869	0.0000	1.1897
		2b	0.6021	0.9888	306.672	4.874×10^{-7}	1.6423
		2c	0.4220	0.9375	72.577	6.760×10^{-6}	2.2216
		2d	0.3261	0.9190	114.169	5.998×10^{-10}	2.8182
		2e	0.3862	0.7998	33.734	1.353×10^{-5}	2.0709
3	B	3a	1.6212	0.7658	42.544	3.268×10^{-7}	0.4724
		3b	1.1531	0.9582	78.515	4.720×10^{-5}	0.8310
		3c	0.5844	0.8762	33.056	1.853×10^{-4}	1.4993
		3d	0.5336	0.7642	29.482	2.189×10^{-5}	1.4322
		3e	0.4968	0.6354	12.867	1.966×10^{-3}	1.2790
4	χ	4a	1.6212	0.7658	42.544	3.268×10^{-7}	0.4724
		4b	1.1531	0.9582	78.515	4.720×10^{-5}	0.8310
		4c	0.5844	0.8762	33.056	1.853×10^{-4}	1.4993
		4d	0.5336	0.7642	29.482	2.189×10^{-5}	1.4322
		4e	0.4968	0.6354	12.867	1.966×10^{-3}	1.2790
5	J	5a	2.4949	−0.1437	0.633	0.4325	−0.0576
		5b	2.4108	−0.8013	12.562	9.416×10^{-3}	−0.3324
		5c	1.0580	−0.4886	3.135	0.1070	−0.4618
		5d	0.8263	0.0472	0.047	0.8308	0.0571
		5e	0.6424	−0.0553	0.058	0.8119	−0.0861
6	Sz	6a	1.7405	0.7234	32.938	2.896×10^{-6}	0.4150
		6b	0.9014	0.9747	132.936	8.311×10^{-6}	1.0813
		6c	0.3979	0.9446	82.881	3.732×10^{-6}	2.3740
		6d	0.7465	0.4310	4.791	0.0400	0.5774
		6e	0.5819	0.4268	4.231	0.0537	0.7335
7	log RB	7a	1.5678	0.7831	47.568	1.173×10^{-7}	0.4995
		7b	0.6032	0.9887	305.431	4.943×10^{-7}	1.6391
		7c	0.4371	0.9328	66.964	9.652×10^{-6}	2.1341
		7d	0.7988	0.2599	1.521	0.2311	0.3254
		7e	0.4140	0.7656	26.903	5.247×10^{-5}	1.8493

[a]For n values see Table 3.

Table 6. Found and estimated log IC for the 97 analgesics compounds

Compd	Name of compound	log IC observed	log IC estimated from							
			Id		W		B		χ	
			Est.	Res.	Est.	Res.	Est.	Res.	Est.	Res.
1	Acetanilide	2.2600	2.0080	0.2518	1.9430	0.3167	2.0160	0.2439	2.0160	0.2439
2	Aniline	2.1500	0.8810	1.2689	1.4220	0.7279	1.2510	0.8986	1.2510	0.8986
3	Antipyrine	2.7800	3.5000	−0.7203	2.9240	−0.1445	3.2620	−0.4816	3.2620	−0.4816
4	Aminopyrine	3.6800	4.1000	−0.4202	3.7680	−0.0877	3.9000	−0.2205	3.9000	−0.2205
5	Anileridine	3.5000	1.5020	1.9979	3.2840	0.2163	2.4280	1.0716	2.4280	1.0716
6	Aminopropylon	3.0000	1.5970	1.4030	2.3360	0.6644	1.9570	1.0430	1.9570	1.0430
7	2 Amino, 4-Picoline	1.7100	1.3940	0.3155	1.6440	0.0656	1.5820	0.1279	1.5820	0.1279
8	Alcofenac	1.7100	2.2050	−0.4954	2.0660	−0.3564	1.9140	−0.2040	1.9140	−0.2040
9	Alminoprofen	1.3900	0.7630	0.6274	1.1360	0.2544	0.7210	0.6690	0.7210	0.6690
10	Aminochlorothenoxazin	2.9200	4.4290	−1.5094	3.5000	−0.5796	4.1960	−1.2760	4.1960	−1.2760
11	Apazone	3.9500	5.5890	−1.6387	4.2130	−0.2626	5.2690	−1.3192	5.2690	−1.3192
12	Alphacetyl methadole	13.0000	8.7780	4.2222	11.7550	1.2449	8.0600	4.9399	8.0600	4.9399
13	Alpha prodine	5.0000	5.3020	−0.3015	5.7150	−0.7147	5.2630	−0.2626	5.2630	−0.2626
14	Bemidone	1.5000	1.4990	0.0014	1.3760	0.1236	1.4540	0.0457	1.4540	0.0457
15	Betacetyl methadole	2.3000	1.5790	0.7208	2.1140	0.1864	2.1350	0.1647	2.1350	0.1647
16	Benorylate	2.4700	1.1590	1.3113	2.2960	0.1738	1.3380	1.1316	1.3380	1.1316
17	Benzdamine	1.4300	5.7490	−4.3191	1.7980	−0.3677	7.0730	−5.6429	7.0730	−5.6429
18	Benziperylon	0.8400	1.1380	−0.2982	0.9010	−0.0609	1.2190	−0.3790	1.2190	−0.3790
19	Benozaprofen	1.0500	0.7630	0.2869	1.1360	−0.0856	0.7210	0.3290	0.7210	0.3290
20	Butexamac	1.4200	1.4740	−0.0538	1.2900	0.1301	1.0590	0.3607	1.0590	0.3607
21	Codeine	8.0400	7.1590	0.8809	7.9530	0.0870	7.0430	0.9967	7.0430	0.9967
22	Chlorthenoxazine	2.7400	3.9390	−1.1988	3.3840	−0.6444	3.7130	−0.9733	3.7130	−0.9733
23	*p*-Chlorobonzohydrazide	1.6200	-9.02510^{-3}	1.6290	0.7070	0.9134	0.2100	1.4100	0.2100	1.4100
24	5-Chloro salicyclic acid	3.6200	2.9580	0.6615	2.5870	1.0328	2.8310	0.7895	2.8310	0.7895
25	1 (*p*-Chlorophenyl) propylamine	0.9000	−0.8460	1.7463	0.2510	0.6491	−0.3430	1.2429	−0.3430	1.2429
26	*p*-Chloro porpiophenone	1.0300	2.0080	−0.9782	1.9740	−0.9440	2.0340	−1.0039	2.0340	−1.0039
27	3-Chloro salicylic acid	2.8300	2.9580	−0.1279	2.5570	0.2734	2.8450	−0.0147	2.8450	−0.0147
28	Cinchophen	0.9900	1.5480	−0.5576	1.3500	−0.3602	1.5400	−0.5496	1.5400	−0.5496
29	Dioxaphetyl butyrate	0.2500	1.1200	−0.8700	0.6300	−0.3803	1.2520	−1.0023	1.2520	−1.0023
30	2′,4′ Dimethyl acetophenone	1.8200	1.9070	−0.0866	1.8970	−0.0773	1.9270	−0.1070	1.9270	−0.1070
31	2′,4′ Dichloro benzyl alcohol	2.6700	2.0080	0.6618	1.9590	0.7113	2.0340	0.6361	2.0340	0.6361
32	4′,5′ Dichloro phthallic acid	1.4100	1.7570	−0.3473	1.4710	−0.0610	1.6740	−0.2640	1.6740	−0.2640
33	3′,4′ Dimethyl acetophenone	0.7800	1.8660	−1.0857	1.9130	−1.1327	1.9270	−1.1470	1.9270	−1.1470
34	Dipanone	0.8000	1.3190	−0.5192	0.4190	0.3806	1.1610	−0.3610	1.1610	−0.3610
35	Dihydromorphinone	0.1700	0.7690	−0.5992	0.2070	−0.0371	0.7860	−0.6159	0.7860	−0.6159
36	Dihydrocodeinone	1.2800	1.5940	−0.3136	1.5020	−0.2222	1.9120	−0.6322	1.9120	−0.6322
37	Dihydrocodeine	1.3400	0.6880	0.6523	1.8060	−0.4662	2.1420	−0.8022	2.1420	−0.8022
38	Dihydrodesoxymorphine-D	0.0800	0.5680	−0.4883	−0.0710	0.1514	0.4690	−0.3891	0.4690	−0.3891
39	Dextromoramide	13.0000	10.7400	2.2603	12.6650	0.3351	11.6430	1.3573	11.6430	1.3573
40	Ethoheptazine	1.0000	1.5060	−0.5063	1.0700	−0.6980	1.2700	−0.2697	1.2700	−0.2697
41	Ethenzamide	2.6400	3.4340	−0.7942	3.0550	−0.4148	3.2330	−0.5926	3.2330	−0.5926
42	Epirzole	3.7100	4.6440	−0.9336	4.0510	−0.3413	4.1370	−0.4268	4.1370	−0.4268
43	Fertiazac	−0.9100	0.2730	−1.1833	−0.6030	−0.3067	−1.0490	0.1388	−1.0490	0.1388
44	Flurbiprofen	1.2100	1.5040	−0.2937	1.2720	−0.6160	1.2570	−0.0467	1.2570	−0.0467
45	Fenoprofen	1.3400	1.5110	−0.1713	1.3340	0.0055	1.2880	0.0523	1.2880	0.0523
46	Feprazone	1.2200	1.2440	−0.0238	1.5600	−0.3396	1.5020	−0.2822	1.5020	−0.2822
47	Flufenamic acid	0.5300	0.6220	−0.9150	1.3210	−0.7913	0.5240	0.0058	0.5240	0.0058
48	Heterocedeine	0.4800	1.5610	−1.0809	0.5790	−0.0985	1.2010	−0.7110	1.2010	−0.7110
49	Hexalgon	0.5000	0.8510	−0.3514	0.0220	0.4777	0.5610	−0.0607	0.5610	−0.0607
50	α-Isomorphine	0.8000	1.5610	−0.7609	0.5790	0.2215	1.2010	−0.4010	1.2010	−0.4010
51	β-Isomorphine	7.0900	7.1590	−0.0691	8.0600	−0.9703	7.0290	−0.0609	7.0290	−0.0609
52	Isomethadone	0.6500	0.9390	−0.2888	0.8570	−0.2070	1.0680	−0.4176	1.0680	−0.4176
53	Indomethacin	1.0800	0.9140	0.1657	0.7880	0.2916	0.8320	0.2476	0.8320	0.2476
54	Ibuprofen	1.2100	1.9850	−0.7748	1.9930	−0.7829	1.7250	−0.5151	1.7250	−0.5151
55	Isoxicam	3.3700	5.1440	−1.7740	4.5270	−1.1566	4.8520	−1.4820	4.8520	−1.4820
56	Isonixin	1.8900	1.8360	0.0544	1.3740	0.5162	1.3850	0.5050	1.3850	0.5050
57	Ketoprofen	0.6800	0.5240	0.1559	0.2750	0.4048	−0.0120	0.6916	−0.0120	0.6916
58	Ketobemidone	6.2000	5.3020	0.8984	5.7760	0.4240	5.2950	0.9055	5.2950	0.9055
59	Ketorolac	2.0700	1.5410	0.5295	1.4630	0.6071	1.5090	0.5614	1.5090	0.5614
60	Methyl-2 acetamide acrylate	3.2100	1.6520	1.5578	1.9740	1.2360	1.8370	1.3728	1.8370	1.3728
61	*p*-Methyl propiophenone	1.2100	1.3220	−0.1120	1.9740	−0.7640	2.0340	−0.8239	2.0340	−0.8239
62	Methyl-2 methyl-3-furan carboxylate	2.9200	1.3920	1.5276	1.6750	1.2450	1.5820	1.3379	1.5820	1.3379
63	Methyl salicylate	2.6200	2.5680	0.0525	2.2880	0.3317	2.4540	0.1663	2.4540	0.1663
64	Mefenamic acid	1.1600	1.5040	−0.3437	1.1140	0.0457	1.2640	−0.1039	1.2640	−0.1039
65	Meclofenamic acid	0.5700	0.1840	0.3861	0.3490	0.2205	0.2490	0.3207	0.2490	0.3207
66	Metofoline	0.2200	−0.9590	1.1793	0.0430	0.1767	−0.3930	0.6129	−0.3930	0.6129
67	Morazone	2.5400	1.5220	1.0184	2.3730	0.1666	2.4690	0.0711	2.4690	0.0711
68	Morphine	0.7500	1.5610	−0.8109	0.5790	0.1715	1.2010	−0.4510	1.2010	−0.4510
69	Metopon	0.0700	0.9290	−0.8592	0.4730	−0.4033	1.0650	−0.9952	1.0650	−0.9952

(continued on next page)

Table 6 (*continued*)

Compd	Name of compound	log IC observed	log IC estimated from							
			Id		W		B		χ	
			Est.	Res.	Est.	Res.	Est.	Res.	Est.	Res.
70	Methadone	1.0000	0.9340	0.0660	0.9000	0.9960	1.0600	−0.0599	1.0600	−0.0599
71	Meperidine	1.0000	1.4720	−0.4722	0.8310	0.1687	1.0680	−0.0675	1.0680	−0.0675
72	Niflumic acid	0.8900	0.6220	0.2685	0.8760	0.0144	0.5370	0.3528	0.5370	0.3528
73	Normethadone	0.4400	1.3380	−0.8981	0.5910	−0.1509	0.7430	−0.3030	0.7430	−0.3030
74	Oxyphenbutazone	2.0800	1.4760	0.6041	2.1040	−0.0243	1.9470	0.1334	1.9470	0.1334
75	Paracetamol	2.4500	2.9580	−0.5079	2.7410	−0.2905	2.7990	−0.3486	2.7990	−0.3486
76	Phenacetin	2.4300	3.4340	−1.0042	3.2850	−0.8548	3.2180	−0.7885	3.2180	−0.7885
77	Phenol	2.2600	0.3240	1.9358	1.2380	1.0219	0.9380	1.3216	0.9380	1.3216
78	Phenylbutazone	1.8800	1.6270	0.2533	2.2490	−0.3691	2.1570	−0.2769	2.1570	−0.2769
79	Pheneridine	2.6000	1.5400	1.0596	2.7020	−0.1016	1.9840	0.6163	1.9840	0.6163
80	Pirprofen	1.1700	1.4780	−0.3076	1.1140	0.0557	1.0740	0.0960	1.0740	0.0960
81	Piroxacam	2.5400	1.9310	0.6086	2.8650	−0.3250	2.4370	0.1032	2.4370	0.1032
82	Propylphenazone	3.1400	4.6410	−1.5006	4.5190	−1.3789	4.4920	−1.3522	4.4920	−1.3522
83	Prolidine	0.3000	1.4640	−1.1637	0.7970	−0.4972	1.0290	−0.7293	1.0290	−0.7293
84	Propoxyphene	0.2100	0.6850	−0.4753	−0.0200	0.2299	0.1300	0.0803	0.1300	0.0803
85	Ramifenazone	3.3800	4.2500	−0.8699	3.2350	0.1450	3.8120	−0.4318	3.8120	−0.4318
86	Sulfadiazine	1.1800	1.5240	−0.3436	1.5180	−0.3379	1.3830	−0.2030	1.3830	−0.2030
87	Salicylic acid	2.8300	2.5680	0.2625	2.2350	0.5954	2.5000	0.3302	2.5000	0.3302
88	Salsalate	2.5900	1.5660	1.0237	1.8110	0.7786	1.7000	0.8896	1.7000	0.8896
89	Sulindac	0.9500	0.9160	0.0344	1.2210	−0.2707	0.6970	0.2533	0.6970	0.2533
90	Trimeperidine	7.5000	5.5550	1.9452	6.3590	1.1414	5.6070	1.8925	5.6070	1.8925
91	Tolmetin	1.4400	1.5280	−0.0884	1.5990	−0.1591	1.4250	0.0149	1.4250	0.0149
92	Tenoxicam	1.8200	1.1060	0.7135	1.3890	0.4306	1.3470	0.4730	1.3470	0.4730
93	Tiaprofenic acid	−0.4400	0.0320	−0.4717	0.1480	−0.5883	−0.3410	−0.0985	−0.3410	−0.0985
94	Vanillic acid	2.9300	3.4380	−0.5084	3.1010	−0.1708	3.2820	−0.3523	3.2820	−0.3523
95	Ximinol	0.2400	0.9380	−0.6983	1.1610	−0.9209	0.9130	−0.6726	0.9130	−0.6726
96	Zomepirac	1.6100	1.5210	0.0890	1.8380	−0.2276	1.6010	0.0094	1.6010	0.0094
97	Oxycodone	1.3400	1.1670	0.1733	0.8420	0.4984	1.4930	−0.1532	1.4930	−0.1532

Table 7. Found and estimated log IC for the 97 analgesics compounds

Compd	Name of compound	log IC observed	log IC estimated from					
			J		Sz		log RB	
			Est.	Res.	Est.	Res.	Est.	Res.
1	Acetanilide	2.260	3.4430	−1.1833	2.2940	−0.0345	2.1310	0.1288
2	Aniline	2.1500	3.5250	−1.3754	2.0420	0.1076	1.7200	0.4301
3	Antipyrine	2.7800	3.7240	−0.9443	2.8400	−0.0596	2.8960	−0.1165
4	Aminopyrine	3.6800	3.5990	0.0807	3.2670	0.4125	3.5550	0.1250
5	Anileridine	3.5000	1.4160	2.0836	3.3080	0.1916	3.0080	0.4916
6	Aminopropylon	3.0000	1.4780	1.5216	1.6150	1.3852	2.2720	0.7281
7	2 Amino, 4-Picoline	1.7100	3.4440	−1.7340	2.1710	−0.4614	1.8990	−0.1886
8	Alcofenac	1.7100	2.7620	−1.0523	1.9130	−0.2027	1.9190	−0.2088
9	Alminoprofen	1.3900	0.9570	0.4325	0.9210	0.4687	1.0300	0.3599
10	Aminochlorothenoxazin	2.9200	5.1710	−2.2509	4.5670	−1.6473	3.4860	−0.5664
11	Apazone	3.9500	5.7600	−1.8097	4.4070	−0.4572	4.4340	−0.4838
12	Alphacetyl methadole	13.0000	3.3440	9.6561	7.0480	5.9519	9.4280	3.5717
13	Alpha prodine	5.0000	3.5910	1.4090	4.5040	0.4958	4.9960	0.0037
14	Bemidone	1.5000	1.4860	0.0144	1.4440	0.0561	1.4170	0.0834
15	Betacetyl methadole	2.3000	1.0770	1.2227	1.0330	1.2666	1.3600	0.9405
16	Benorylate	2.4700	0.9940	1.4763	1.2680	1.2021	1.2720	1.1982
17	Benzdamine	1.4300	4.1780	−2.7481	7.0360	−5.6064	7.9890	−6.5587
18	Benziperylon	0.8400	1.4580	−0.6180	1.1000	−0.2599	0.9530	−0.1132
19	Benozaprofen	1.0500	0.9570	0.0925	0.9210	0.1287	1.0300	−0.0199
20	Butexamac	1.4200	1.4740	−0.0538	1.3240	0.0960	1.1620	0.2584
21	Codeine	8.0400	4.0690	3.9709	8.1440	−0.1042	6.7580	1.2820
22	Chlorthenoxazine	2.7400	3.7050	−0.9654	3.5020	−0.7619	3.2440	−0.5039
23	*p*-Chlorobonzohydrazide	1.6200	1.4880	0.1318	0.5910	1.0294	0.6810	0.9390
24	5-Chloro salicyclic acid	3.6200	3.2500	0.3697	2.6580	0.9621	2.6450	0.9753
25	1 (*p*-Chlorophenyl) propylamine	0.9000	1.4310	−0.5313	0.2080	0.6916	0.2260	0.6742
26	*p*-Chloro porpiophenone	1.0300	3.4900	−2.4604	2.3410	−1.3114	2.1450	−1.1151
27	3-Chloro salicylic acid	2.8300	3.2100	−0.3798	2.6340	0.1956	2.6280	0.2024
28	Cinchophen	0.9900	1.5580	−0.5685	1.5990	−0.6087	1.3890	−0.3992

(continued on next page)

Table 7 (*continued*)

Compd	Name of compound	log IC observed	log IC estimated from					
			J		Sz		log RB	
			Est.	Res.	Est.	Res.	Est.	Res.
29	Dioxaphetyl butyrate	0.2500	0.7080	−0.4578	0.5210	−0.2708	0.8290	−0.5790
30	2′,4′ Dimethyl acetophenone	1.8200	3.3400	−1.5195	2.3180	−0.4979	2.1000	−0.2804
31	2′,4′ Dichloro benzyl alcohol	2.6700	3.4510	−0.7812	2.3410	0.3286	2.1370	0.5325
32	4′,5′ Dichloro phthallic acid	1.4100	−1.7880	3.1982	1.4070	0.0034	1.5600	−0.1499
33	3′,4′ Dimethyl acetophenone	0.7800	3.3760	−2.5965	2.3300	−1.5496	2.1090	−1.3287
34	Dipanone	0.8000	0.5430	0.2574	0.3960	0.4038	0.6580	0.1424
35	Dihydromorphinone	0.1700	0.9720	−0.8016	1.1570	−0.9875	0.8860	−0.7160
36	Dihydrocodeinone	1.2800	1.5720	−0.2924	1.9840	−0.7044	1.6320	−0.3522
37	Dihydrocodeine	1.3400	1.5740	−0.2343	2.1240	−0.7843	1.9260	−0.5863
38	Dihydrodesoxymorphine-D	0.0800	0.9690	−0.8886	1.0010	−0.9209	0.8090	−0.7291
39	Dextromoramide	13.0000	8.6850	4.3148	12.2730	0.7271	12.6030	0.3972
40	Ethoheptazine	1.0000	1.4830	−0.4826	1.2820	−0.2820	1.1430	−0.1429
41	Ethenzamide	2.6400	3.2620	−0.6224	2.8430	−0.2025	2.9930	−0.3528
42	Epirzole	3.7100	3.7760	−0.0664	3.4350	0.2755	3.7130	−0.0030
43	Fertiazac	−0.9100	1.0520	−1.9617	−0.4150	−0.4946	−0.8760	−0.0336
44	Flurbiprofen	1.2100	1.5270	−0.3173	1.4320	−0.2217	1.2420	−0.0319
45	Fenoprofen	1.3400	1.5420	−0.2018	1.4200	−0.0800	1.2860	0.0543
46	Feprazone	1.2200	0.9890	0.2305	0.9490	0.2714	1.1820	0.0381
47	Flufenamic acid	0.5300	0.9910	−0.4607	0.9990	−0.4691	1.0550	−0.5247
48	Heterocedeine	0.4800	0.9690	−0.4891	1.3530	−0.8735	0.9790	−0.4993
49	Hexalgon	0.5000	0.6840	−0.1843	0.1060	0.3944	0.1000	0.4005
50	α-Isomorphine	0.8000	0.9690	−0.1691	1.3530	−0.5535	0.9790	−0.1793
51	β-Isomorphine	7.0900	4.0910	2.9991	8.2610	−1.1715	6.8040	0.2862
52	Isomethadone	0.6500	1.0690	−0.4193	0.6400	0.0103	1.0450	−0.3948
53	Indomethacin	1.0800	0.7640	0.3162	0.9050	0.1752	0.8700	0.2103
54	Ibuprofen	1.2100	2.4220	−1.2122	1.8510	−0.6407	1.8650	−0.6553
55	Isoxicam	3.3700	3.7420	−0.3723	4.8820	−1.5123	4.2020	−0.8316
56	Isonixin	1.8900	1.4930	0.3971	1.4280	0.4622	1.4050	0.4846
57	Ketoprofen	0.6800	1.0040	−0.3244	0.5150	0.1653	0.8480	−0.1677
58	Ketobemidone	6.2000	3.6170	2.5827	4.6270	1.5727	5.0170	1.1831
59	Ketorolac	2.0700	1.5730	0.4966	1.4150	0.6551	1.4370	0.6325
60	Methyl-2 acetamide acrylate	3.2100	2.0370	1.1732	2.0950	1.1148	2.1650	1.0454
61	*p*-Methyl propiophenone	1.2100	3.4900	−2.2804	2.3410	−1.1314	2.1450	−0.9350
62	Methyl-2 methyl-3-furan carboxylate	2.9200	3.4960	−0.5757	2.0250	0.8952	1.9180	1.0023
63	Methyl salicylate	2.6200	3.4090	−0.7893	2.4760	0.1438	2.3990	0.2206
64	Mefenamic acid	1.1600	1.4950	−0.3354	1.3430	−0.1827	1.1670	−0.0069
65	Meclofenamic acid	0.5700	1.0370	−0.4670	0.5520	0.0176	0.8930	−0.3234
66	Metofoline	0.2200	1.1610	−0.9408	0.8340	−0.6142	−0.2170	0.4374
67	Morazone	2.5400	1.5650	−0.9746	2.4050	0.1345	2.4860	0.0539
68	Morphine	0.7500	0.9690	−0.2191	1.3530	−0.6035	0.9790	−0.2293
69	Metopon	0.0700	0.9770	−0.9070	1.3120	−1.2424	0.9600	−0.8899
70	Methadone	1.0000	1.0640	−0.0641	0.6520	0.3484	1.0520	−0.0523
71	Meperidine	1.0000	1.4830	−0.4826	1.2520	−0.2517	0.9090	0.0909
72	Niflumic acid	0.8900	1.0240	−0.1340	0.7530	0.1374	1.0040	−0.1143
73	Normethadone	0.4400	1.0550	−0.6154	0.5510	−0.1106	0.9690	−0.5291
74	Oxyphenbutazone	2.0800	0.9870	1.0932	1.2020	0.8780	1.2990	0.7805
75	Paracetamol	2.4500	3.4470	−0.9965	2.7400	−0.2899	2.7130	−0.2627
76	Phenacetin	2.4300	3.4810	−1.0512	3.0180	−0.5884	3.0870	−0.6573
77	Phenol	2.2600	3.6170	−1.3574	1.9460	0.3143	1.5710	0.6887
78	Phenylbutazone	1.8800	1.5440	0.3363	1.7030	0.1768	2.2360	−0.3563
79	Pheneridine	2.6000	0.9550	1.6454	1.5760	1.0240	0.3070	2.2926
80	Pirprofen	1.1700	1.5530	−0.3827	1.3020	−0.1320	1.0610	0.1093
81	Piroxacam	2.5400	1.5330	1.0070	2.1310	0.4092	2.8140	−0.2736
82	Propylphenazone	3.1400	3.6800	−0.5399	3.6070	−0.4674	4.0780	−0.9383
83	Prolidine	0.3000	1.4720	−1.1717	1.1620	−0.8621	0.8880	−0.5876
84	Propoxyphene	0.2100	−0.3910	0.6007	−0.3300	0.5403	0.1110	0.0985
85	Ramifenazone	3.3800	4.1680	−0.7883	2.8840	0.4964	3.3260	0.0538
86	Sulfadiazine	1.1800	1.5170	−0.3368	1.4860	−0.3065	1.4750	−0.2949
87	Salicylic acid	2.8300	3.3200	−0.4900	2.4560	0.3743	2.3690	0.4609
88	Salsalate	2.5900	1.5140	1.0763	1.5520	1.0384	1.7650	0.8253
89	Sulindac	0.9500	1.0680	−0.1181	1.2780	−0.3284	1.1330	−0.1829
90	Trimeperidine	7.5000	3.5350	3.9647	4.8790	2.6206	5.4880	2.0123
91	Tolmetin	1.4400	1.5280	−0.0880	1.4210	0.0193	1.5230	−0.0825
92	Tenoxicam	1.8200	0.9970	0.8233	0.9920	0.8277	1.1510	0.6691
93	Tiaprofenic acid	−0.4400	0.9810	−1.4213	0.3280	−0.7681	0.7950	−1.2349
94	Vanillic acid	2.9300	3.3070	−0.3766	2.9450	−0.0151	3.0090	−0.0788
95	Ximinol	0.2400	0.1920	0.0483	0.1120	0.1281	1.1660	−0.9259
96	Zomepirac	1.6100	1.5110	0.0988	1.4920	0.1177	1.7630	−0.1525
97	Oxycodone	1.3400	0.9760	0.3642	1.5570	−0.2172	1.0550	0.2855

(log IC) (Tables 6 and 7), also shows that the Wiener index (W) is the best index among all the seven topological indices used in the present study.

In order to finally confirm our findings we have estimated predictive correlation coefficient from the plots of the observed against the calculated activity (Figs 1–7).

The next suitable index is the Id index. The predictive potential of the indices used follow in the following sequence:

$$W > Id > logRB > B \sim \chi > Sz > J$$

It is interesting to record that though all these indices are highly linearly correlated (Table 2) their predictive

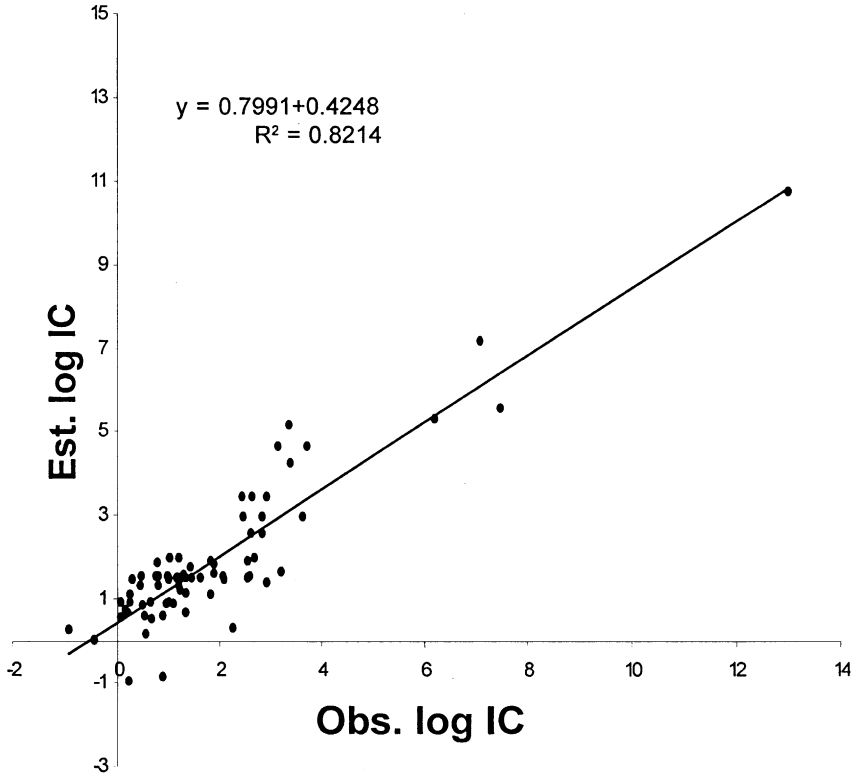

Figure 1. Correlation of observed log IC against estimated log IC using Id index.

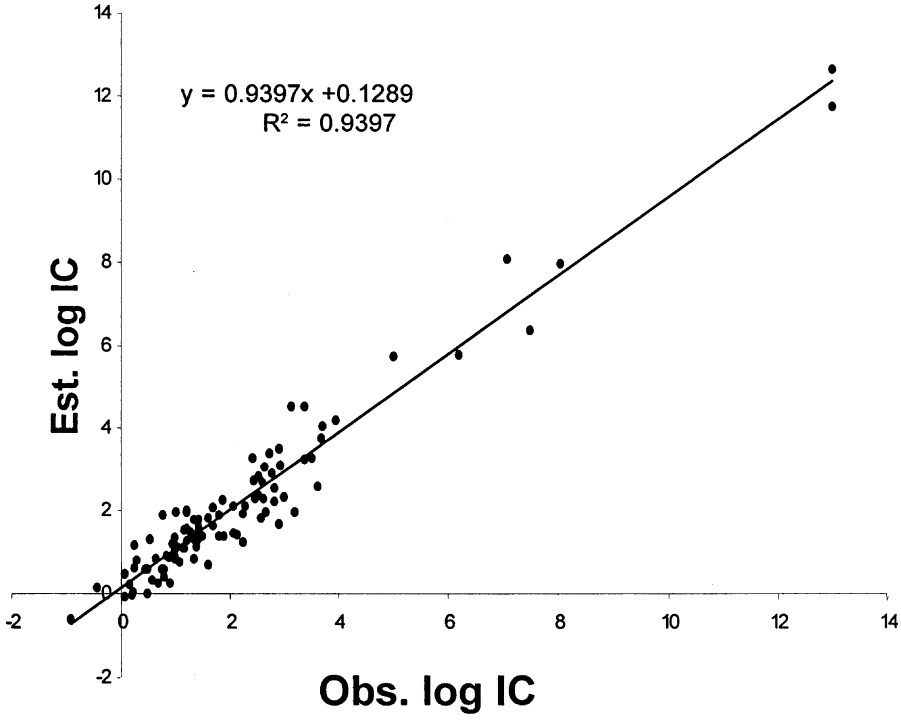

Figure 2. Correlation of observed log IC against estimated log IC using W index.

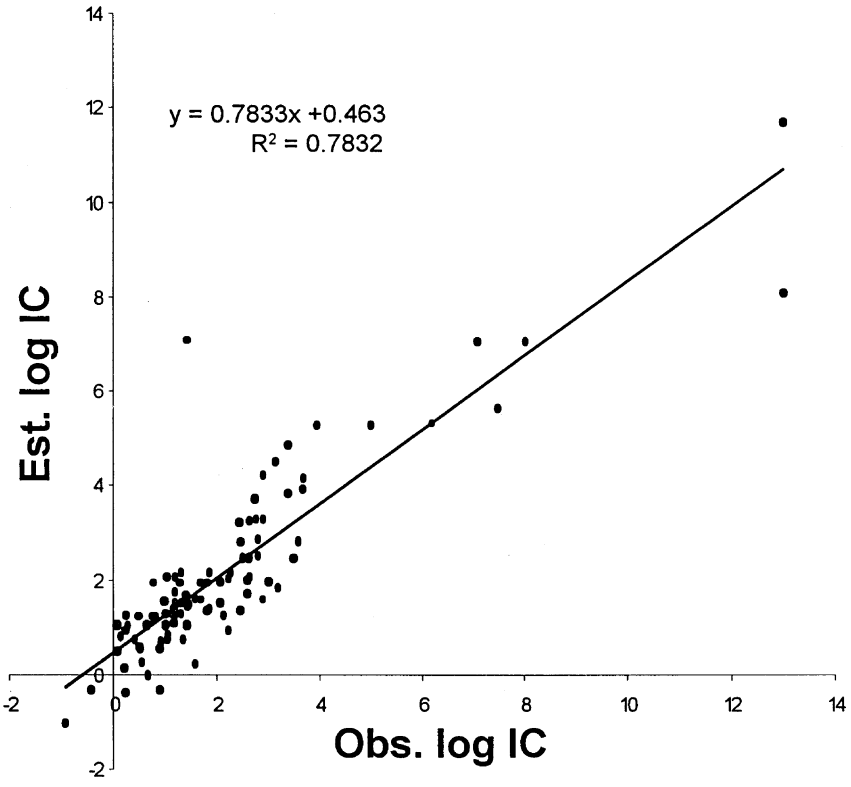

Figure 3. Correlation of observed log IC against estimated log IC using B index.

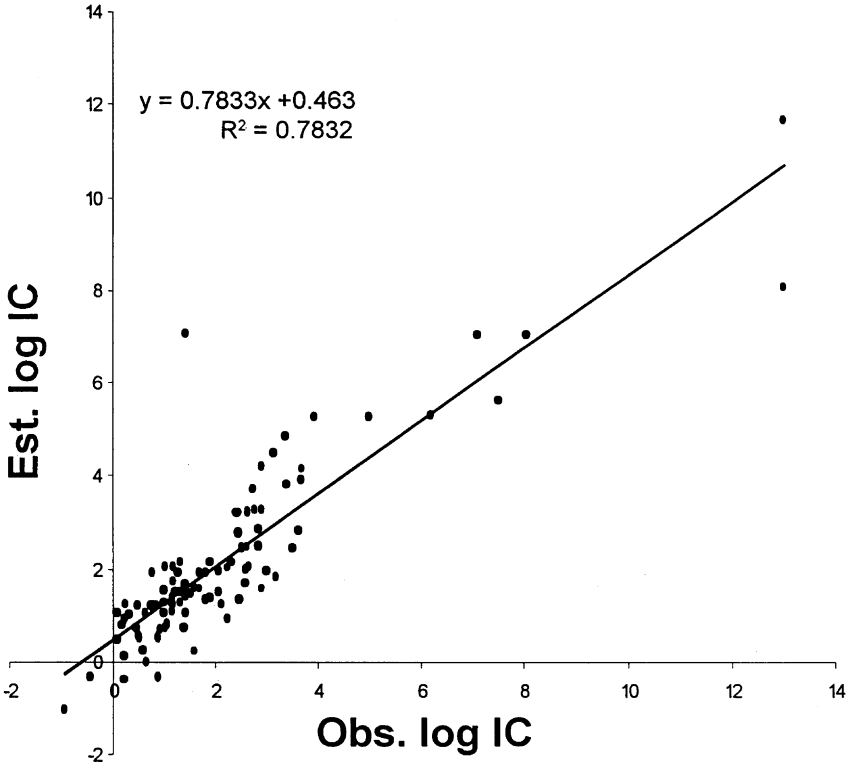

Figure 4. Correlation of observed log IC against estimated log IC using χ index.

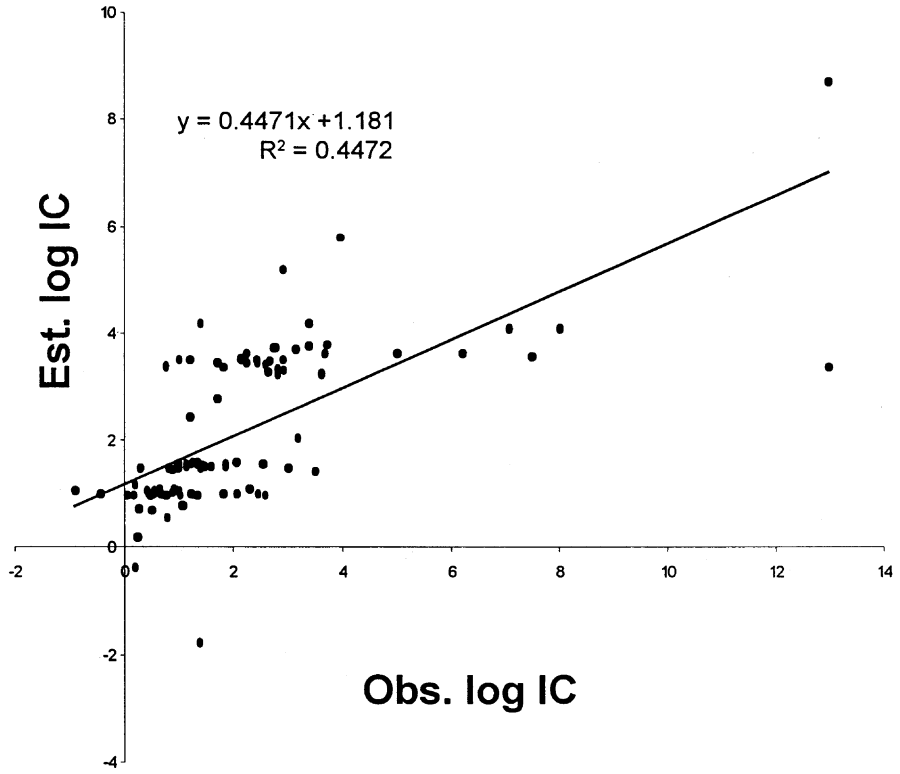

Figure 5. Correlation of observed log IC against estimated log IC using J index.

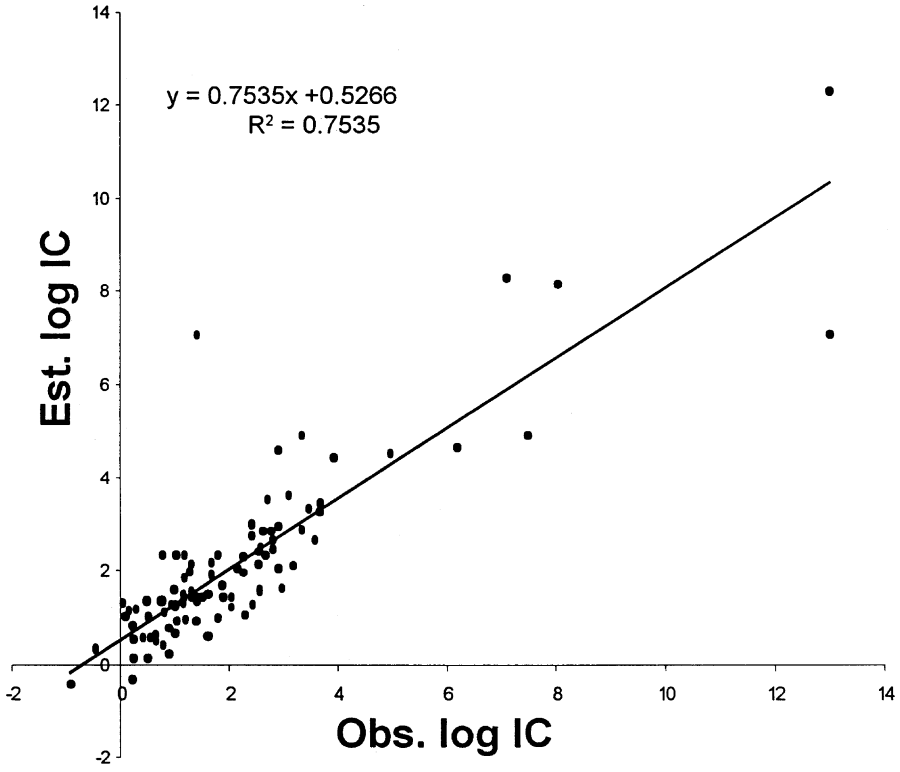

Figure 6. Correlation of observed log IC against estimated log IC using Sz index.

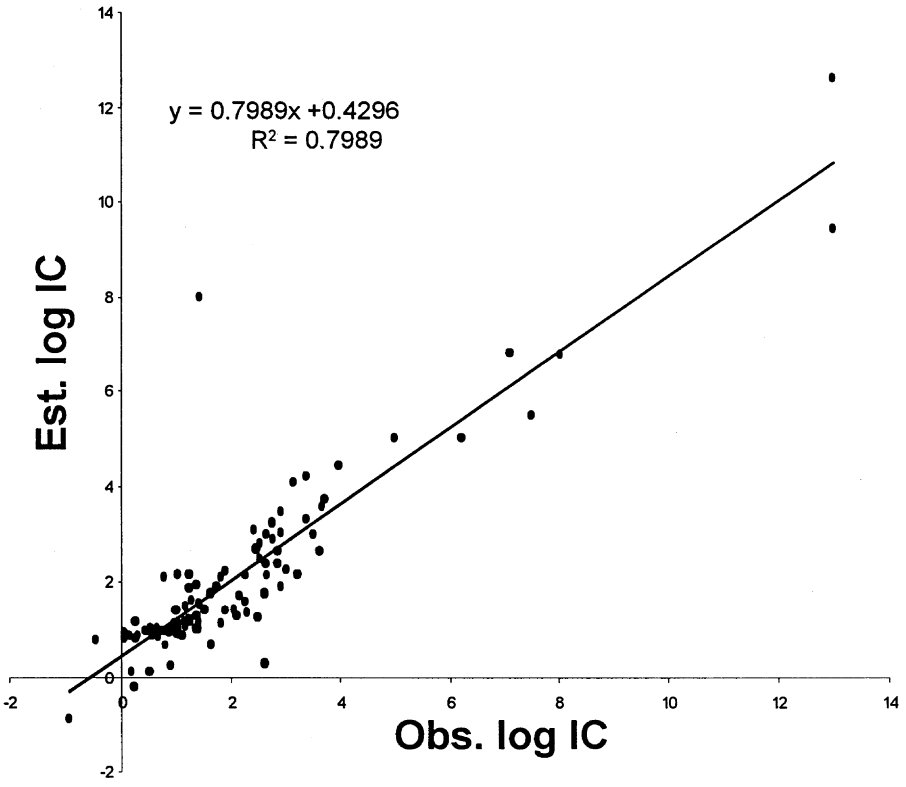

Figure 7. Correlation of observed log IC against estimated log IC using RB index.

potentials are quite different and may be attributed to their differential information contents.

The R^2 values were found as: 0.8214, 0.9397, 0.7832, 0.7832, 0.4472, 0.7535, and 0.7989 respectively when Id, W, B, χ, J, Sz and logRB were used for modelling the analgesic activity (log IC) of 97 compounds. These R^2 values show that J index is useless, while B and χ have similar potential.

The highest predictive correlation coefficient is obtained in that the Wiener index (W) is used as the correlating parameter.

It is interesting to record that compared to Wiener index (W), the compounds belonging to this category 'b' are better modelled by B, χ, Sz and log RB indices. Furthermore, the modelling ability of B and χ indices is found to be the same. Out of the four indices, Sz and log RB gave the best results for the compounds of the category 'b'. The corresponding models are found as:

$$\text{6b. } \log \text{IC} = 0.0052\ (\pm 4.4793 \times 10^{-4})\ \text{Sz} - 1.6405,$$
$$n = 9,\ \ Se = 0.9014,\ \ R = 0.9747,$$
$$F = 132.936,\ \ Q = 1.0813 \tag{6}$$

$$\text{7b. } \log \text{IC} = 0.0249\ (\pm\ 0.0014)\ \log \text{RB} - 1.7445$$
$$n = 9,\ \ Se = 0.6032,\ \ R = 0.9887,$$
$$F = 305.431,\ \ Q = 1.6391 \tag{7}$$

Also, that the compounds belonging to category 'c' are best modelled by Sz and logRB. These indices are found better than W index for this purpose. The models are found as under:

$$\text{6c. } \log \text{IC} = 0.0021\ (\pm 2.2800 \times 10^{-4})\ \text{Sz} - 3.9834$$
$$n = 12,\ \ Se = 0.3679,\ \ R = 0.9446,$$
$$F = 82.881,\ \ Q = 2.3740 \tag{8}$$

$$\text{7c. } \log IC = 0.0156\ (\pm 0.0019)\ \log RB - 6.3226$$
$$n = 12,\ \ Se = 0.4371,\ \ R = 0.9328, \tag{9}$$
$$F = 66.964,\ \ Q = 2.1341$$

In general, the activity (log IC) of any molecule is explained by three effects: (i) electrostatic effect which expresses the electrostatic interactions between drug and target molecules; (ii) steric effect which shows very weak or non-electrostatic interaction without any chemical bond, that is van der Waals interactive and so on; and (iii) transfer effect which implies many problems associated with the process through which the drug molecules meets with the target. Out of all probability W index is capable of exhibiting activity due to steric effect; as W depends upon the size, shape and branching effect.

The sign of the regression coefficient is important because it can contribute to the understanding of the drug-action mechanism and/or give us the useful information about the drug design. In Table 4, the signs of

the coefficient of descriptors: W, B, χ, Sz and log RB are positive. It means that these quantities should be large for good potency of the drug.

Conclusions

The aforementioned results and discussion show that the analgesic activity (log IC) can be modelled successfully using distance-based topological indices, and that the Wiener index (W) is the most appropriate index for this purpose. This means that the analgesic activity (log IC) is a function of size, shape and branching of the compounds used in the present study. Furthermore, drug-action mechanism can be inferred from the sign of the coefficient of topological index present in the proposed model.

Experimental

Analgesic activity (log IC)

The analgesic activity IC as expressed in terms of log IC are adopted from the literature[15,16]

Topological indices

All the topological indices (W, B, χ, J, Sz and log RB) were calculated from the carbon-hydrogen suppressed molecular graph.

Wiener Index (W)[9]

The Wiener index (W)[9] is the oldest and widely used topological index. It is based on the vertex distances of the respective molecular graph and is defined as:

$$\mathrm{W} = \mathrm{W}(G) = 1/2\sum_{i=1}^{n}\sum_{j=1}^{n} d(v_i,\ v_j \mid G) \tag{10}$$

where G is the graph having v_1, v_2, v_3, …, v_n as its vertices; d(v_i v_j) stands for the distances (shortest) between the vertices v_i and v_j.

Szeged index (Sz)[13,14]

Let e be an edge of the molecular graphs G; let $n_1(e|G)$ be the number of vertices of G lying closer to one ned of e; let $n_2(e|G)$ be the number of vertices of G lying closer to the another end of e. Then, the Szeged index (Sz) is defined[13,14] as:

$$\mathrm{Sz} = \mathrm{Sz(G)} = \sum_{e} n_1(e \mid G) n_2(e \mid G) \tag{11}$$

The summation gives over all the edges of graph G.

Connectivity index (χ)[11]

The connectivity index $\chi = \chi(G)$ of a graph G is defined as:

$$\chi = \chi(G) = \sum_{ij} (\mathrm{d}_i,\ \mathrm{d}_j) - 5 \tag{12}$$

where d_i is the valency of a vertex i, equal to number of bond connected to the atom i in G, representing the graph of a compound. Meaning of d_j is analogous.

Balaban index (J)[12]

The Balaban index,[12] $J = J(G)$ was introduced by Balaban as the average distance sum connectivity index. It is defined as:

$$J = J(g) = \frac{M}{\mu + 1}\sum_{e} (d_i d_j)^{-0.5} \tag{13}$$

where M is the number of edges of G; μ is the cyclomatic number of G; d_i is the distance sums where $i = 1, 2, \ldots, N$. The cyclomatic number (μ) is the minimum number of edges, that must be removed from the cyclic graph G in order to transform it into the related acyclic graph.

Information theoretic index (Id)[8]

Bonchev and Trinajstic[8] applied information theory to the problem of characterizing molecular structure. The information content of the system i with N elements is defined by the following relationship:

$$\mathrm{Id} = N\log_2 N - \sum_{j=1}^{n} N_j \log_2 N_j \tag{14}$$

where n is the number of different sets of elements; N_j is the number of elements in the jth set of elements and the summation is over all sets of elements. Logarithm is taken at the base 2 for measuring information contents in bytes.

Branching indices B and log RB[10]

The Branching indices B and logRB were calculated using the software provided by Lukovits.

Statistical analysis

All the statistics were performed by least-square regression program and the maximum R^2 method is adopted[19,20]

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