October 2008 Volume 4 Issue 5

Trade Science Inc.

Organic CHEMISTRY

An Indian Journal

Full Paper

OCAIJ, 4(5), 2008 [339-343]

Quantitative structure toxicity relationship (QSTR) study on a series of aliphatic alcohol derivatives with the help of topological descriptors

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Received: 12th August, 2008 ; Accepted: 17th August, 2008

ABSTRACT

In this present work, we have taken a series of aliphatic alcohol derivatives and developed QSTR models with the help of topological descriptors.The values of topological descriptors are directly obtained by Dragon software. The first set contains amino alcohol derivatives and the correlation coefficient of this set is above 0.80. The second set contains acetylenic and diol derivatives. The correlation coefficient of this set is above 0.83. The third and fourth set contains saturated and unsaturated alcohols respectively. The correlation coefficient of these sets are above 0.80.

KEYWORDS

Alcohols;
Toxicity;
QSTR;
Tetrahymena pyriformis;
Topological.

INTRODUCTION

QSAR has gained importance in the field of pharmacological sciences[1]. QSAR techniques increase the probability of success and reduce the time and cost involvement in the drug discovery process[2-3]. QSAR not only rests on the development of new drug molecules but also exploring the toxicological and ecotoxicological properties of molecules[4]. Hence Quantitative Structure Toxicity Relationship (QSTR) is a predictive tool for preliminary evaluation of the hazards of chemical compounds by using computer-aided models. Recently QSTR studies of small organic molecules have been done[5]. In our present work, we have taken a series of aliphatic alcohol derivatives and developed QSTR models with the help of topological descriptors.

EXPRIMENTAL

The 89 different groups of alcohol derivatives have been chosen with their toxicity values[6-7] in terms of 50% inhibitory growth concentration (IGC50) against Tetrahymena-pyriformis. Experimental determination of toxicological and biochemical as well as human health end points is difficult task. Hence QSTR modeling of the toxicity of compounds on Tetrahymena-pyriformis is vital importance in investigating its toxicity in terms of its inhibitory growth concentration. The values of topological descriptors are directly obtained by Dragon software. The topological descriptor[8-23] are given below:

Information index on molecular size (ISIZ), Total information index of atomic composition (IAC), Mean information index on atomic composition (AAC), First Zagreb index (ZM1), First Zagreb index by valence vertex degrees (ZM1V), Second Zagreb index by valence vertex degrees (ZM2V), Second Zagreb index (ZM2), Second Zagreb index by valence vertex degrees (ZM2V), Quadratic index (Q_{INDEX}), Narumi simple topological index (Snar log), Narumi harmonic topological index (HNar) and Pogliani index (D_Z).

TABLE 1: Amino alcohols and values of topological descriptors with their predicted and observed toxicity of first set

No.	Compounds	IGC_{50}	PT 1	ISIZ	IAC	AAC	ZM1	ZM1V	ZM2	ZM2V	SNar	HNar	Dz
1	2-(Methylamino)ethanol	-1.8202	-1.641	53.30	20.019	1.43	14.0	50.00	12.0	26.00	2.079	1.429	11.5
2	4-Amino-1-butanol	-0.9752	-1.365	69.48	23.433	1.378	18.0	50.00	16.0	28.00	2.773	1.500	13.5
3	2-(Ethylamino)ethanol	-1.6491	-1.463	69.48	23.433	1.378	18.0	54.00	16.0	32.00	2.773	1.500	13.5
4	2-Propylaminoethanol	-1.6842	-1.285	86.43	26.723	1.336	22.0	58.00	20.0	36.00	3.466	1.556	15.5
5	DL-2-Amino-1-pentanol	-	-	-	-	-	-	-	-	-	-	-	-
6	3-Amino-2,2-dimethyl-1-propanol	-0.9246	-0.783	86.43	26.723	1.336	28.0	60.00	28.0	40.00	2.773	1.333	15.5
7	6-Amino-1-hexanol	-0.958	-1.01	104.04	29.929	1.301	26.0	58.00	24.0	36.00	4.159	1.600	17.5
8	DL-2-Amino-1-hexanol	-0.5848	-0.852	104.04	29.929	1.301	28.0	60.00	27.0	41.00	3.871	1.500	17.5
9	DL-2-Amino-3-methyl-1-butanol	-0.5852	-0.872	86.43	26.723	1.336	26.0	58.00	26.0	40.00	2.89	1.355	15.5
10	2-Amino-3,3-dimethyl-butanol	-0.7178	-0.448	104.04	29.929	1.301	34.0	66.00	35.0	49.00	3.178	1.315	17.5
11	2-Amino-3-methyl-1-pentanol	-0.6594	-0.625	104.04	29.929	1.301	30.0	62.00	31.0	45.00	3.584	1.412	17.5
12	2-Amino-4-methyl-pentanol	-0.6191	-0.763	104.04	29.929	1.301	30.0	62.00	29.0	43.00	3.584	1.412	17.5
13	2-(tert-Butylamino)ethanol	------	------	------	------	------	------	------	------	------	------	------	------
14	Diethanolamine	-1.7941	-1.87	75.05	27.005	1.5	22.0	82.00	20.0	44.00	3.466	1.556	16.5
15	1,3-Diamino-2-hydroxy-propane	-1.4275	-1.403	64	24.026	1.502	20.0	60.00	19.0	39.00	2.485	1.385	14
16	N-Methyldiethanol amine	-1.8338	-1.632	92.23	30.523	1.453	28.0	92.00	27.0	53.00	3.871	1.500	18.5
17	3-(Methylamino)-1,2-propanediol	-1.5341	-1.712	75.05	27.005	1.5	24.0	84.00	23.0	49.00	3.178	1.448	16.5
18	Triethanolamine	-1.7488	-1.792	116.09	37.228	1.489	36.0	124.00	36.0	72.00	5.257	1.579	23.5

$IGC_{50-50\%}$ **Inhibitory growth concentration**

TABLE 2: Acectylenic,diols annd values of topological descriptors with their predicted and observed toxicity of second set

No.	Compounds	IGC_{50}	PT1	ISIZ	IAC	AAC	ZM1	ZMV	ZM2	ZM2V	SNar	HNar	Dz
1	3-Butyn-2-ol	-0.402	-0.35	38.05	14.54	1.32	16.00	60.00	14.00	42.00	1.79	1.30	11.0
2	1-Pentyn-3-ol	-1.177	-0.56	53.30	17.69	1.26	20.00	64.00	19.00	47.00	2.48	1.38	13.0
3	2-Pentyn-1-ol	-0.572	-0.56	53.30	17.69	1.26	18.00	66.00	16.00	44.00	2.77	1.50	13.0
4	2-Penten-4-yn-1-ol	-0.554	-0.86	43.02	15.90	1.32	18.00	72.00	16.00	49.00	2.77	1.50	13.0
5	1-Hexyn-3-ol	0.657	-0.41	69.48	20.75	1.22	24.00	68.00	23.00	51.00	3.17	1.44	15.0
6	1-Heptyn-3-ol	-0.265	0.01	86.43	23.76	1.18	28.00	72.00	27.00	55.00	3.87	1.50	17.0
7	4-Heptyn-3-ol	-0.033	0.01	86.43	23.76	1.18	28.00	76.00	27.00	61.00	3.87	1.50	17.0
8	2-Octyn-1-ol	0.194	0.66	104.0	26.73	1.16	30.00	78.00	28.00	56.00	4.85	1.63	19.0
9	4-Methyl-1-pentyn-3-ol	-0.026	-0.41	69.48	20.75	1.22	26.00	70.00	26.00	54.00	2.89	1.35	15.0
10	4-Methyl-1-heptyn-3-ol	0.742	0.66	104.0	26.73	1.16	34.00	78.00	35.00	63.00	4.27	1.45	19.0
11	(±)-1,2-Butanediol	-2.048	-1.89	64.00	20.78	1.29	22.00	70.00	21.00	45.00	2.19	1.28	14.0
12	(±)-1,3-Butanediol	-2.301	-1.89	64.00	20.78	1.29	20.00	68.00	18.00	38.00	2.48	1.38	14.0
13	1,4-Butanediol	-2.236	-1.89	64.00	20.78	1.29	18.00	66.00	16.00	32.00	2.77	1.50	14.0
14	1,2-Pentanediol	-1.626	-1.92	80.71	24.08	1.26	24.00	72.00	23.00	43.00	3.17	1.44	16.0
15	1,5-Pentanediol	-1.934	-1.92	80.71	24.08	1.26	22.00	70.00	20.00	36.00	3.46	1.55	16.0
16	2-Methyl-2,4-pentanediol	-1.953	-1.65	98.10	27.29	1.24	34.00	82.00	32.00	60.00	3.17	1.31	18.0
17	(±)-1,2-Hexanediol	-1.266	-1.65	98.10	27.29	1.24	28.00	76.00	27.00	47.00	3.87	1.50	18.0
18	1,6-Hexanediol	-1.494	-1.65	98.10	27.29	1.24	26.00	74.00	24.00	40.00	4.15	1.60	18.0

$IGC_{50-50\%}$ **Inhibitory growth concentration**

RESULT AND DISCUSSION

The 89 derivatives of alcohol are divided into four sets, according to the nature or bonding of compound and their observed biological toxicity in terms of inhibitory growth concentration (IGC50). The values of various topological descriptors of alcohol derivatives, along their observed biological toxicity are placed in TABLES 1-4. The quantities of descriptors in a number of combinations have been used for MLR analysis and QSTR models. Out of them only 4 QSTR models presented below, have been found to have very high-predicted power. The predicted toxicities of these QSTR models are placed in respective TABLE.

First set

The first set contains 18 amino alcohol derivatives and their observed toxicity in terms of 50% inhibitory

TABLE 3: Halogenated, saturated alcohols and values of various topological descriptors with their predicted and observed toxicity of third set

No.	Compounds	IGC_{50}	PT 1	ISIZ	IAC	AAC	ZM1	ZMV	ZM2	ZM2V	SNar	HNar	Dz
1	2-Bromoethanol	-0.353	-1.262	28.529	14.92	1.658	10.00	33.067	8.00	14.519	1.386	1.333	8.75
2	2-Chloroethanol	-1.534	-1.262	28.529	14.92	1.658	10.00	33.605	8.00	15.556	1.386	1.333	9.33
3	1-Chloro-2-propanol	-1.244	-1.124	43.02	18.613	1.551	16.00	39.605	14.0	25.556	1.792	1.304	11.3
4	3-Chloro-1-propanol	-1.162	-0.966	43.02	18.613	1.551	14.00	37.605	12.0	19.556	2.079	1.429	11.3
5	4-Chloro-1-butanol	-0.532	-0.646	58.603	22.074	1.472	18.00	41.605	16.0	23.556	2.773	1.500	13.3
6	3-Chloro-2,2-dimethyl-1-propanol	-0.856	-0.695	75.059	25.395	1.411	28.00	51.605	28.0	35.556	2.773	1.333	15.3
7	6-Chloro-1-hexanol	-0.353	0.032	92.239	28.623	1.363	26.00	49.605	24.0	31.556	4.159	1.600	17.3
8	8-Chloro-1-octanol	-0.187	0.383	110.039	31.784	1.324	30.00	53.605	28.0	35.556	4.852	1.636	19.3
9	6-Bromo-1-hexanol	0.572	0.032	92.239	28.623	1.363	26.00	49.067	24.0	30.519	4.159	1.600	16.7
10	2,3-Dibromopropanol	-0.926	-0.694	69.487	22.658	1.333	26.00	24.134	26.0	21.556	2.890	1.355	13.5
11	Methyl alcohol	-2.665	-2.356	15.51	7.51	1.252	2.00	26.000	1.00	5.0000	0.000	1.000	5.00
12	Ethyl alcohol	-1.991	-1.996	28.529	11.02	1.224	6.00	30.000	4.00	12.000	0.693	1.200	7.00
13	1-Propanol	-1.746	-1.641	43.02	14.265	1.189	10.00	34.000	8.00	16.000	1.386	1.333	9.00
14	2-Propanol	-1.881	-1.800	43.02	14.265	1.189	12.00	36.000	9.00	21.000	1.099	1.200	9.00
15	1-Butanol	-1.430	-1.282	58.603	17.384	1.159	14.00	38.000	12.0	20.000	2.079	1.429	11.0
16	(±)-2-Butanol	-1.542	-1.441	58.603	17.384	1.159	16.00	40.000	14.0	26.000	1.792	1.304	11.0
17	2-Methyl-1-propanol	-1.372	-1.441	58.603	17.384	1.159	16.00	40.000	14.0	22.000	1.792	1.304	11.0
18	2-Pentanol	-1.159	-1.078	75.059	20.429	1.135	20.00	44.000	18.0	30.000	2.485	1.385	13.0
19	3-Pentanol	-1.243	-1.078	75.059	20.429	1.135	20.00	44.000	19.0	31.000	2.485	1.385	13.0
20	3-Methyl-2-butanol	-0.995	-1.237	75.059	20.429	1.135	22.00	46.000	21.0	33.000	2.197	1.286	13.0
21	tert-Amylalcohol	-1.172	-1.302	75.059	20.429	1.135	24.00	48.000	22.0	30.000	2.079	1.263	13.0
22	2-Methyl-1-butanol	-0.952	-1.078	75.059	20.429	1.135	20.00	44.000	19.0	27.000	2.485	1.385	13.0
23	3-Methyl-1-butanol	-1.035	-1.078	75.059	20.429	1.135	20.00	44.000	18.0	26.000	2.485	1.385	13.0
24	2,2-Dimethyl-1-propanol	-0.870	-1.302	75.059	20.429	1.135	24.00	48.000	22.0	30.000	2.079	1.263	13.0
25	2-Methyl-2-propanol	-1.791	-1.441	58.603	17.384	1.159	16.00	40.000	14.0	22.000	1.792	1.304	11.0
26	1-Hexanol	-0.378	-0.551	92.239	23.426	1.116	22.00	46.000	20.0	28.000	3.466	1.556	15.0
27	3,3-Dimethyl-1-butanol	-0.736	-0.934	92.239	23.426	1.116	28.00	52.000	26.0	34.000	2.773	1.333	15.0
28	4-Methyl-1-pentanol	-0.637	-0.710	92.239	23.426	1.116	24.00	48.000	22.0	30.000	3.178	1.448	15.0
29	1-Heptanol	0.105	-0.182	110.039	26.388	1.099	26.00	50.000	24.0	32.000	4.159	1.600	17.0
30	2,4-Dimethyl-3-pentanol	-0.705	-0.658	110.039	26.388	1.099	32.00	56.000	33.0	45.000	3.296	1.333	17.0

IGC_{50} – 50% Inhibitory growth concentration

growth concentration and are placed in TABLE 1. The values of topological descriptors of this set are presented in the same TABLE. In this set we have done, with the help of topological descriptor fallowed by MLR analysis to evaluate best QSTR model are given below:

PT1=-0.0243715 ZM1V +0.0688246 ZM2-1.24797

rCV^2=0.689306 r^2=0.809635

Equation-PT1 involves ZM1 as first descriptor, ZM1V as second descriptor. Correlation and cross validation coefficients indicate that this model has high degree of predictive power as the value of rCV^2 and r^2 are 0.706862 and 0.808823 respectively. The values of predicted toxicity are listed in TABLE 1.

Second set

This set contains 18 acetylenic and diol derivatives and their observed toxicity in terms of 50% inhibitory growth concentration and are placed in TABLE 2.The values of topological descriptors are also presented in the same table. In this set we have done, with the help of topological descriptor fallowed by MLR analysis to evaluate best QSTR model are presented below:

PT1=0.26422 ISIZ -1.34672 IAC +9.18257

rCV^2=0.754936 r^2=0.839476

Equation-PT1 involves ISIZ as first descriptor,IAC as second descriptor. Correlation and cross validation coefficients indicate that this model has high degree of predictive power as the value of rCV^2 and r^2 are 0.754936 and 0.839476 respectively. The values of predicted toxicity are listed in TABLE 2.

Third set

This set contains halogenated and saturated alcohol derivatives and their observed toxicity in terms of 50% inhibitory growth concentration and are placed in TABLE 3.The values of topological descriptors are presented in TABLE 3. In this set we have done, with the help of topological descriptor fallowed by MLR analysis to evaluate best QSTR model are given below:

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TABLE 4: Unsaturated alcohols and values of topological descriptors with their predicted and observed toxicity of fourth set

No.	Compounds	IGC_{50}	PT1	ISIZ	IAC	AAC	ZM1	ZM1V	ZM2	ZM2V	SNar	HNar	Dz
1	2-Methyl-3-buten-2-ol	-1.3889	-1.147	64.000	19.171	1.198	24.0	56.00	22.0	46.00	2.079	1.263	13
2	4-Pentyn-1-ol	-1.4204	-1.574	53.303	17.693	1.264	18.0	62.00	16.0	38.00	2.773	1.500	13
3	2-Methyl-3-butyn-2-ol	-1.3114	-1.574	53.303	17.693	1.264	24.0	68.00	22.0	56.00	2.079	1.263	13
4	Trans-3-Hexen-1-ol	-0.7772	-0.690	80.711	22.181	1.167	22.0	56.00	20.0	37.00	3.466	1.556	15
5	5-Hexyn-1-ol	-1.2948	-1.176	69.487	20.758	1.221	22.0	66.00	20.0	42.00	3.466	1.556	15
6	3-Methyl-1-pentyn-3-ol	-1.3226	-1.176	69.487	20.758	1.221	28.0	72.00	28.0	62.00	2.773	1.333	15
7	4-Hexen-1-ol	-0.7540	-0.690	80.711	22.181	1.167	22.0	56.00	20.0	36.00	3.466	1.556	15
8	5-Hexen-1-ol	-0.8411	-0.690	80.711	22.181	1.167	22.0	54.00	20.0	34.00	3.466	1.556	15
9	4-Pentyn-2-ol	-1.6324	-1.574	53.303	17.693	1.264	20.0	64.00	18.0	44.00	2.485	1.385	13
10	5-Hexyn-3-ol	-1.4043	-1.176	69.487	20.758	1.221	24.0	68.00	23.0	49.00	3.178	1.448	15
11	3-Heptyn-1-ol	-0.3231	-0.700	86.439	23.768	1.188	26.0	74.00	24.0	52.00	4.159	1.600	17
12	4-Heptyn-2-ol	-0.6160	-0.700	86.439	23.768	1.188	28.0	76.00	26.0	58.00	3.871	1.500	17
13	3-Octyn-1-ol	0.0170	-0.158	104.042	26.739	1.163	30.0	78.00	28.0	56.00	4.852	1.636	19
14	2-Propen-1-ol	-1.9178	-1.788	33.219	12.955	1.295	10.0	42.00	8.0	22.00	1.386	1.333	9
15	2-Buten-1-ol	-1.4719	-1.521	48.106	16.106	1.239	14.0	48.00	12.0	28.00	2.079	1.429	11
16	(±)-3-Buten-2-ol	-1.0529	-1.521	48.106	16.106	1.239	16.0	48.00	14.0	33.00	1.792	1.304	11
17	cis-2-Buten-1,4-diol	-2.1495	-2.057	53.303	19.303	1.379	18.0	76.00	16.0	41.00	2.773	1.500	14
18	cis-2-Penten-1-ol	-1.1052	-1.147	64.000	19.171	1.198	18.0	52.00	16.0	33.00	2.773	1.500	13
19	3-Penten-2-ol	-1.4010	-1.147	64.000	19.171	1.198	20.0	54.00	18.0	39.00	2.485	1.385	13
20	trans-2-Hexen-1-ol	-0.4718	-0.690	80.711	22.181	1.167	22.0	56.00	20.0	37.00	3.466	1.556	15
21	1-Hexen-3-ol	-0.8113	-0.690	80.711	22.181	1.167	24.0	56.00	23.0	42.00	3.178	1.448	15
22	cis-2-Hexen-1-ol	-0.7767	-0.690	80.711	22.181	1.167	22.0	56.00	20.0	37.00	3.466	1.556	15
23	trans-2-Octen-1-ol	0.3654	0.416	116.096	28.096	1.124	30.0	64.00	28.0	45.00	4.852	1.636	19

IGC_{50} – 50% Inhibitory growth concentration

TABLE 5.Combination of topological descriptors of various sets

Set no.	rCV^2	r^2	Descriptors used	DC
1	0.689306	0.809635	ZM1V, ZM2	2
2	0.754936	0.839476	ISIZ, IAC	2
3	0.688462	0.802364	AAC, Snar	2
4	0.861899	0.890835	ISIZ, IAC	2

DC- Number of descriptors used

PT1=0.808332 AAC +0.552603SNar -3.36818

rCV^2=0.688462 r^2=0.802364

Equation-PT1 involves ISIZ as first descriptor, AAC as second descriptor. Correlation and cross validation coefficients indicate that this model has high degree of predictive power as the value of rCV^2 and r^2 are 0.677098 and 0.800768 respectively. The values of predicted toxicity are listed in TABLE 3.

Fourth set

This set contains unsaturated alcohol derivatives and their observed toxicity in terms of 50% inhibitory growth concentration and are placed in TABLE 4.The values of topological descriptors are presented in TABLE 4. In this set we have done, with the help of topological descriptor fallowed by MLR analysis to evaluate best QSTR model are presented below:

PT1=0.0813873 ISIZ -0.299923 IAC-0.606049

rCV^2=0.861899 r^2=0.890835

Equation-PT1 involves ISIZ as first descriptor,IAC as second descriptor. Correlation and cross validation coefficients indicate that this model has high degree of predictive power as the value of rCV^2 and r^2 are 0.677098 and 0.800768 respectively. The values of predicted toxicity are listed in TABLE 4.

CONCLUSION

The quality of prediction of QSTR model is adjudged by the values of cross validation and correlation coefficients. Collectively these values are presented in TABLE 5. The combinations of descriptors providing the various models are included in the same TABLE.

It is clearly indicated that the entire QSTR model from each sets provide high degree of dependability as they have correlation value is above 0.80.

Abbreviations

MW = Molecular Weight ; ΔH_f^0 = Heat of formation ; TE = Total Energy; εHOMO = Energy of Highest Occupied Molecular Orbital; εLUMO = Energy of Lowest Unoccupied Molecular Orbital; χ= Electronegativity ; η= Absolute hardness; ISIZ = Information index on molecular size; IAC = Total information index of atomic composition; AAC = Mean information index on atomic compo-

sition; ZM1= First zagreb index; ZMIV = First zagreb index; ZM2 = Second zagreb index by valence vertex degrees; ZM2V = Second zagreb index; by valence vertex degrees Qindex = Quadratic index; SNar = Narumi simple topological index; HNar = Narumi harmonic topological index ; Dz = Pogliani index.

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