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Structure-Based Optimization of Benzothiazole Derivatives as Potent Anticancer Agents: A QSAR/QSPR Approach

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Abstract

The development of novel therapeutic agents for the treatment of cancer is of vital importance since the currently available chemotherapeutic agents only provide palliative cure. QSAR of a series of benzothiazole derivative showing a potent and selective cytotoxicity against tumorigenic cell line has been studied by regression analysis which is done firstly with topological indices, later inhibitory activity is correlated with physico-chemical properties. Further investigation has attempted for still better model by combining topological as well as physicochemical parameter together. QSAR studies of the Benzothiazole is attempted using the Wiener Index (w), Polarizability (POI), Molecular weight (MW) and Molecular volume (MV) and parachore (Pc), The regression analysis of the data employing the multiple regression analysis has indicated that Balaban index is most suitable index for this purpose

Key-Words: QSAR, Benzothiazole, Molecular modeling, Regression analysis.

Introduction

Cancer is the leading disease-related cause of death of the human population in some areas of the world, and it is predicted to continue to become the leading cause of death within the coming years. Chemotherapy, or the use of chemical agents to destroy cancer cells, is a mainstay in the treatment of malignancies. A major advantage of chemotherapy is its ability to treat widespread or metastatic cancers, whereas surgery and radiation therapies are limited to treating cancers that are confined to specific areas. The chemotherapy has aroused many researchers' interests and a great deal of current efforts has been focusing on the design and development of varied anticancer drugs¹.

In order to discover more potent benzothiazole derivatives (Fig. 1) that possess a remarkable *in vivo* inhibitory effect on tumor growth, the structural modification and optimization of lead compounds are very important²⁻⁵.

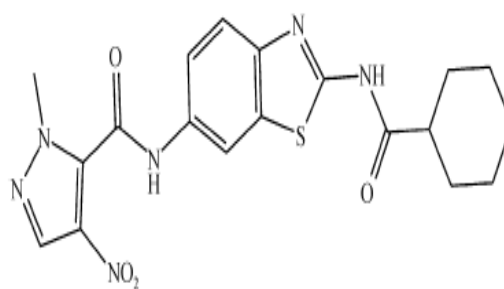


Figure 1 Molecular structural scheme of compound A.

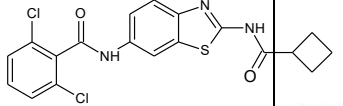
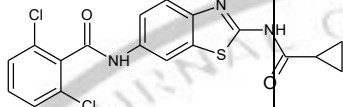
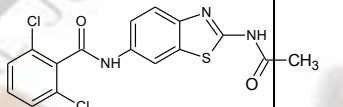
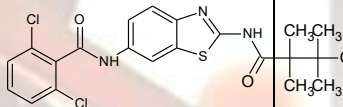
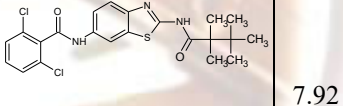
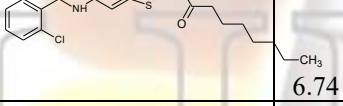
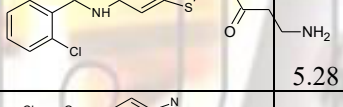
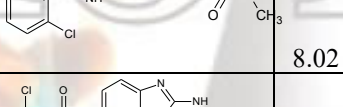
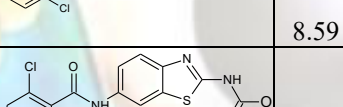
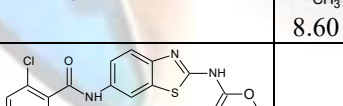
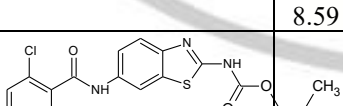
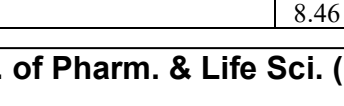
Material and Methods

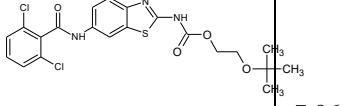
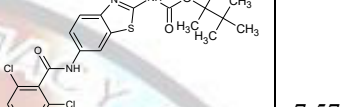
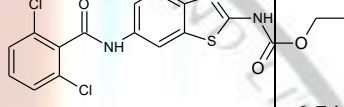
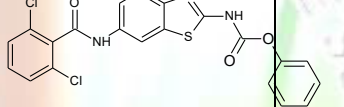
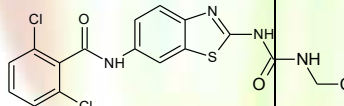
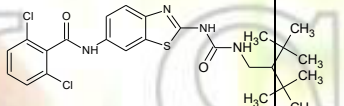
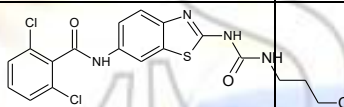
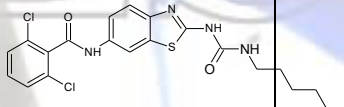
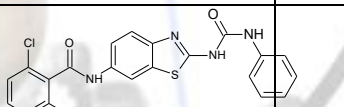
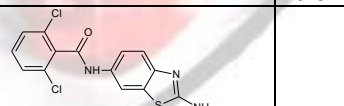
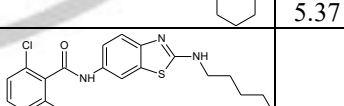
The substitutions are given below in table 1.

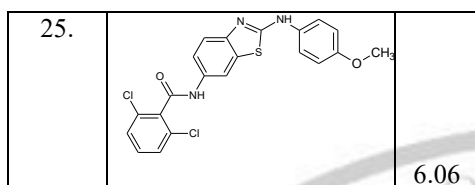
Table 1: The list of compounds studied and their observed $-\log EC_{50}$ values

No.	Structure	$-\log EC_{50}$
1.		7.82

* Corresponding Author

2.		7.89
3.		7.89
4.		6.22
5.		8.00
6.		7.92
7.		6.74
8.		5.28
9.		8.02
10.		8.59
11.		8.60
12.		8.59
13.		8.46

14.		7.96
15.		7.57
16.		6.74
17.		5.96
18.		7.49
19.		7.52
20.		7.55
21.		6.54
22.		6.82
23.		5.37
24.		6.57



Results and Conclusion

QSAR analysis is one of the most effective approaches for optimizing lead compounds and designing new drugs. Excellent QSAR models can aid in understanding the mechanism of the action of drugs and may save the cost and time in the course of developing a new drug when compared with empirical procedures⁶⁻⁹.

Two basic kinds of molecular descriptions are used in QSAR. One of them involves parameters that bear relation to free energy and usually represent some of the important physicochemical properties of the molecules (Hansch approach)¹⁰. Another category of molecular descriptor is the topological index which is produced directly from molecular structure^{10,11} (topological approach). Among many topological indices that have been proposed since the Wiener in 1945, the Randic connectivity index¹⁵, Hosoya index,¹⁶ Balaban index, Szeged index etc. are well known. In recent years, topological indices¹⁹ have gained attention in explaining biological activities and physical and chemical properties of organic compounds. The calculated values of all 25 substituents of various topological and physicochemical parameters are given below in table 2. Multiple regression analysis for correlating experimental anticancer activity of benzothiazole derivatives ($-\log EC_{50}$) and calculated molecular descriptors were carried out by using NCSS software.

Table 2: Calculated descriptors and data of compounds studied

S.No.	MW	MV	PC	Den	Xeq	Pol
1	448.36	304.6	891.1	1.47	2.389	47.6
2	420.31	269.1	810.9	1.56	2.416	43.9
3	406.28	251.4	770.9	1.615	2.433	42.1
4	380.24	242.1	703.5	1.57	2.451	39.3
5	408.3	275.1	783	1.48	2.414	43
6	422.32	292	820.2	1.44	2.4	44.8
7	464.4	341.1	942.2	1.36	2.478	50.3
8	409.28	262.2	772.3	1.56	2.351	42.5
9	396.24	248.4	723.1	1.59	2.451	40.02
10	410.27	264.9	762.9	1.54	2.45	41.8
11	424.3	281.4	802.7	1.5	2.432	43.6
12	424.3	281.8	800.1	1.5	2.432	43.6
13	438.32	298.3	839.9	1.46	2.416	45.5
14	440.3	287.8	822.4	1.52	2.449	44.3

15	438.32	298	837.6	1.47	2.416	45.5
16	453.89	295.6	874.4	1.53	2.438	48.5
17	439.87	280.4	834.8	1.568	2.455	46.7
18	404.87	270.4	790.1	1.497	2.398	43.23
19	423.31	284.3	808.4	1.488	2.417	44.4
20	437.34	300.4	850.8	1.455	2.403	46.2
21	465.39	333.4	930.3	1.39	2.38	49.9
22	452.913	298.1	882.7	1.519	2.475	49.2
23	434.38	310.9	871.3	1.39	2.361	47.6
24	408.34	294.5	817.8	1.38	2.368	44.8
25	429.31	298.3	829.8	1.43	2.365	46

Several multiple regressions were attempted using correlation matrix from the programme and the best result are considered and discussed in developing QSAR modeling of benzothiazole as anticancer agents. Any significant mono-parametric correlation is not obtained in this study. Very small values of correlation suggest that instead of mono-parametric correlation one should go for multi-parametric modeling. Regression analysis study has been performed on the data set and the obtained significant results have been reported. Some important models are discussed here in given below table 3.

In the above model change in statistics is observed. The variance of 92% suggests that as compared to the four parametric models the present model is much better. These models show that topological parameter such as Xeq while physicochemical parameter such as Pol., Parachor, MW and MV are responsible for the modeling of these compounds, both types of parameter play an important role for the modeling of benzothiazole derivatives as potent anticancer agents and transcriptase inhibitors.

In order to obtain further support in favour of our result we have also estimated the activity of compounds and found that the estimated values are very close to experimental activity. The residue, i.e., the difference between the experimental and estimated values confirms these feelings.

The final support in our favour is obtained by plotting the estimated activity against the experimental activity and such a plot showed is the best suitable model for modeling of benzothiazole derivative used in present study.

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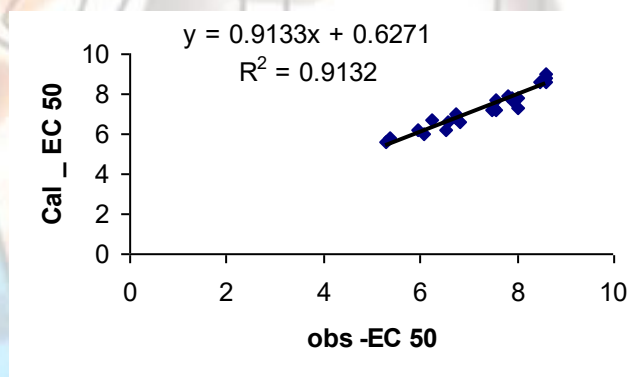
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Table 3: Obtained QSAR models for the molecules studied against –log EC₅₀ isozyme

No.	Equation	Statistical Characteristics
1.	$-\log EC_{50} = 4.1982 - 0.6130 \text{ Pol} + 0.0717 \text{ PC}$	N=25, R² = 0.3754, R²A = 0.3187, F-ratio = 6.612
2.	$-\log EC_{50} = 7.7057 - 1.0826 \text{ Pol} + 0.0511 \text{ MW} + 3.0046 \text{ PC}$	N=25, R² = 0.4610, R²A = 0.3840, F-ratio = 5.987
3.	$-\log EC_{50} = 10.9708 - 1.1143 \text{ Pol} + 8.9191 \text{ Xeq} + 0.0324 \text{ MW} + 0.0402 \text{ PC}$	N=25, R² = 0.5346, R²A = 0.4654, F-ratio = 5.744
4.	$-\log EC_{50} = -8.4578 - 1.0570 \text{ Pol} + 9.2499 \text{ Xeq} + 0.0324 \text{ MW} + 0.0368 \text{ PC} + 1.8567 \text{ IR}$	N=25, R² = 0.5365, R²A = 0.4145, F-ratio = 4.398
5.	$-\log EC_{50} = 87.5264 - 75.0541 \text{ Den} - 1.3354 \text{ Pol} + 17.0296 \text{ Xeq} + 0.2451 \text{ MW} - 4.0829 \text{ MV} + 0.0745 \text{ PC}$	N=25, R² = 0.7772, R²A = 0.6928, F-ratio = 10.465
6.	$-\log EC_{50} = 113.376 - 97.066 \text{ Den} - 1.537 \text{ Pol} + 19.064 \text{ Xeq} + 0.342 \text{ MW} - 0.502 \text{ MV} + 7.242 \text{ PC}$	N=23, R² = 0.9132, R²A = 0.8806, F-ratio = 28.051 (Comp.3 and Comp.14 are outlier)

Table 4: Predicted and experimental inhibitory activity –log EC₅₀ data of compounds

Comp. No.	-log EC ₅₀		Residual
	Actual	Predicted	
1	7.82	7.913	-0.093
2	7.89	7.814	0.076
3	6.22	6.663	-0.443
4	8	7.781	0.219
5	7.92	7.628	0.292
6	6.74	6.984	-0.244
7	5.28	5.625	-0.345
8	8.02	7.342	0.678
9	8.59	8.831	-0.241
10	8.6	8.994	-0.394
11	8.59	8.605	-0.015
12	8.46	8.65	-0.19
13	7.57	7.663	-0.093
14	6.74	6.844	-0.104
15	5.96	6.22	-0.26
16	7.49	7.175	0.315
17	7.52	7.261	0.259
18	7.55	7.21	0.34
19	6.54	6.164	0.376
20	6.82	6.552	0.268
21	5.37	5.763	-0.393
22	6.57	6.63	-0.06
23	6.06	6.007	0.053

Fig. 2: Plot of observed –log EC₅₀ versus calculated –log EC₅₀ for the 23 compounds using Eq. 6 excluding two outliers (C3 and C14)