ISSN: 0976-7126

INTERNATIONAL JOURNAL OF PHARMACY & LIFE SCIENCES

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

Shailja Sachan[1*], Santosh Tiwari[2] and Vikash Pandey[2]
1, Department of Chemistry, Govt. New Science College, Rewa, (M.P.) - India
2, Department of Chemistry, A.P.S University, Rewa, (M.P.) - India

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 (POl), Molecular weight (MW) and Molecular volume (MV) and parachore (Pc), The regression analysis of the data employing the multiple regression analysis has indicated that Balban 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 drugs[1].

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 important[2-5].

*** Corresponding Author**

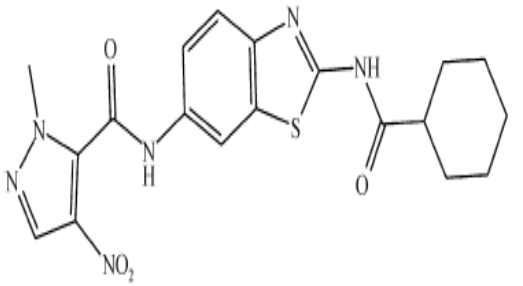
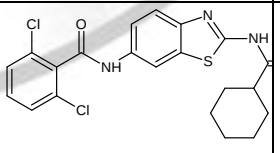


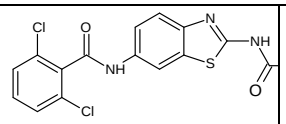
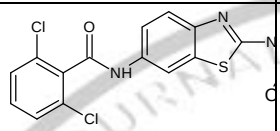
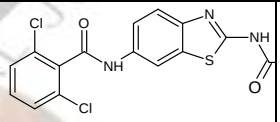
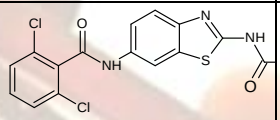
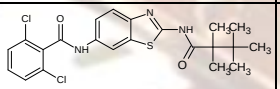
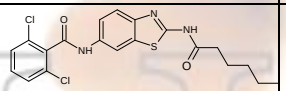
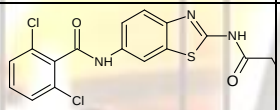
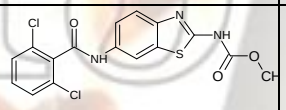
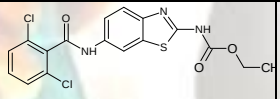
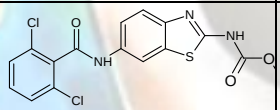
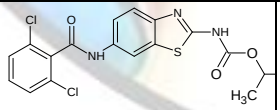
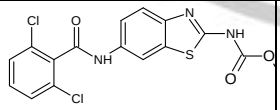
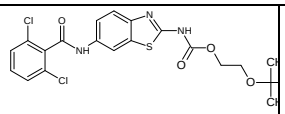
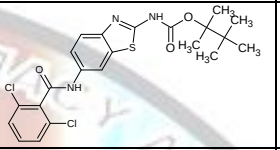
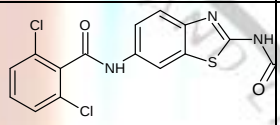
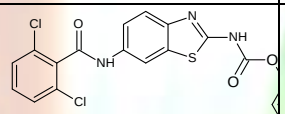
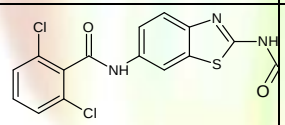
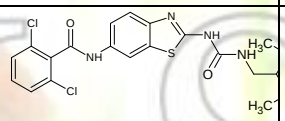
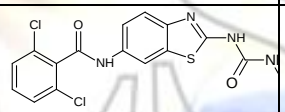
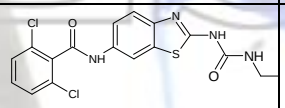
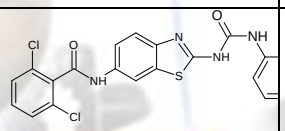
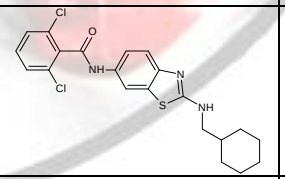
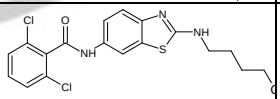
Figure 1 Molecular structural scheme of compound A.

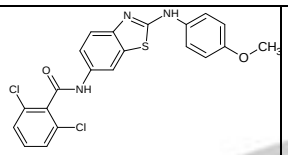
Material and Methods

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

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

25.		6.06

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 procedures[6-9].

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 index[15], Hosoya index,[16] Balaban index , Szeged index etc. are well known. In recent years, topological indices[19] 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 where 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 where attempt 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 significantly 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 model shows 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 type of parameter play important role for the modeling of benzothiazole derivatives as potent anticancer agents 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 confirm 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.

References

1. Gibbs J. B. (2000). Mechanism-based target identification and drug discovery in cancer research. *Science*, **287**: 1969－1973
2. Hayakawa I., Shioya R., Agatsuma T., Furukawa H., Naruto S. and Sugano Y. (2004). 4-Hydroxy-3-methyl-6-phenylbenzofuran-2-carboxylic acid ethyl ester derivatives as potent

anti-tumor agents. *Bioorg Med Chem Lett*, **14**: 455－458
3. Hayakawa I., Shioya R., Agatsuma T., Furukawa H. and Sugano Y. (2004). Thienopyridine and benzofuran derivatives as potent anti-tumor agents possessing different structure-activity relationships. *Bioorg Med Chem Lett*, **14**: 3411－3414
4. Hayakawa I., Shioya R., Agatsuma T. and Sugano Y. (2005). Synthesis and evaluation of 3-methyl-4-oxo-6-phenyl-4, 5, 6, 7-tetrahydrobenzofuran-2-carboxylic acid ethyl ester derivatives as potent antitumor agents. *Chem Pharm Bull*, **53(6)**: 638－640
5. Yoshida M., Hayakawa I., Hayashi N., Agatsuma T., Oda Y., Tanzawa F., Iwasaki S., Koyama K., Furukawa H., Kurakatad S. and Sugano Y. (2005). Synthesis and biological evaluation of benzothiazole derivatives as potent antitumor agents. *Bioorg Med Chem Lett*, **15**: 3328－3332
6. Santos-Filho O. A. and Hopfinger A. J. (2001). A search for sources of drug resistance by the 4D-QSAR analysis of a set of antimalarial dihydrofolate reductase inhibitors. *J Comput Aided Mol Des*, **15**: 1－12
7. Nanbo A. and Nanbo T. (2002). Mechanistic study on *n*-demethylation catalyzed with P450 by quantitative structure activity relationship using electronic properties of 4-substituted *N,N*-dimethylaniline. *Quant Struct Act Relat*, **21**: 613－616
8. Wang X. D., Lin Z. F., Yin D. Q., Liu S. S. and Wang L. S. (2005). 2D/3D-QSAR comparative study on mutagenicity of nitroaromatics. *Sci China Ser B-Chem*, **48(3)**: 246－252
9. Karelson M. and Lobanov V. S. (1996). Quantum-chemical descriptors in QSAR/QSPR studies. *Chem Rev*, **96**: 1027－1044
10. Backer B. (1954). Decrease in intraocular pressure in man by a carbonic anhydrase inhibitor (Diamox). *Am. J. Ophthalmol*, ***37*:** 13.
11. Karelson M. (2000). Molecular Descriptors in QSAR/QSPR, J. Wiley and Sons, New York.
12. Tadeschini R. and Consonni V. (2000). Handbook of Molecular Descriptors, Wiley-VCH, Weinheim.
13. Kier L.B. and Hallk H. (1976). Moleculra connectivity in chemistry & Drug Research, Academic press, New York.
14. Kier L.B. and Hall L.H. (1986).Moleculr activity in structure activity- relationship, Wiley, NewYork.
15. Trinajstic N. (1992). Chemical Graph Theory (2^{nd} ed) CRC Press Boca Raten Florida.
16. Hansch Leo A. (1973). Substitunt constant for correlation analysis in chemistry and biology, Wdey, New York.

Table 3: Obtained QSAR models for the molecules studied against –log EC_{50} isozyme

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

ISSN: 0976-7126

Table 4: Predicted and experimental inhibitory activity –log EC_{50} data of compounds

Comp. No.	-log EC50		
	Actual	Predicted	Residual
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

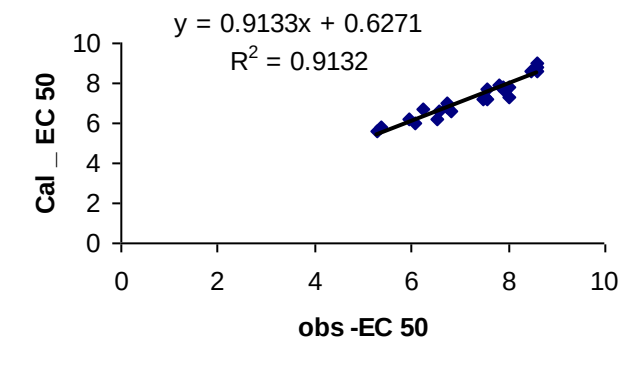


Fig. 2: Plot of observed –log EC_{50} versus calculated –log EC_{50} for the 23 compounds using Eq. 6 excluding two outliers (C3 and C14)