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Group-based quantitative structure and activity relationship on benzothiazole derivatives for development of potent anti-cancer compounds

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ABSTRACT

To develop potent anticancer compounds using benzothiazole scaffolds group-based quantitative structure and activity relationship (GQSAR) analysis was performed on 41 reported benzothiazole derivatives for identification of structural fragments. Benzothiazole dataset was fragmented into two fragments (R1 and R2). GQSAR models were generated using multiple linear regression. GQSAR analysis revealed the presence of hydrophobic groups on R1 will potentiate anticancer activity. The generated models are giving insight into the benzothiazole structural requirements which will be optimized for design of anticancer drugs.

Keywords: Anticancer, fragments, group-based quantitative structure and activity relationship, hydrophilicity, quantitative structure and activity relationship

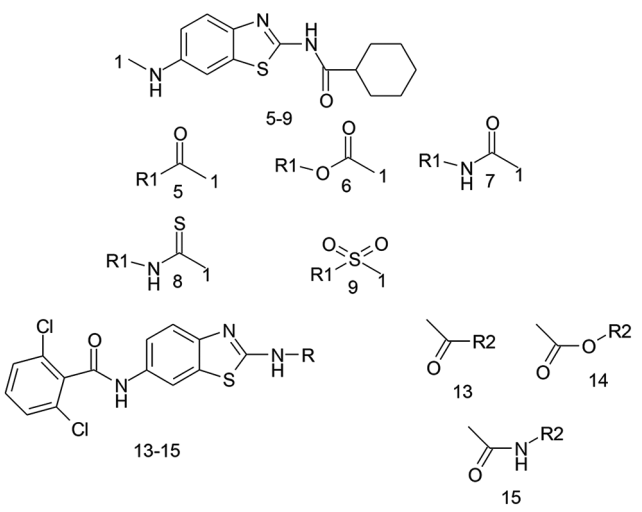
INTRODUCTION

Drug discovery and development process are playing a critical role in human life. Traditional drug development methods such as random screening, molecular modification, and extraction from different sources are utilized in early developments of drug discovery. These traditional methods are lengthy and expensive; to overcome problems associated with these methods rational drug discovery methods come into existence. In recent decades various rational modern drug discovery methods such as fragment-based drug discovery, structure-based drug design, and ligand-based drug design are utilized to develop newer and newer molecules.[1-3] Docking, Pharmacophore, and quantitative structure and activity relationship (QSAR) are the three most utilized methods in the rational drug discovery. QSAR methods are more realistic because there is a correlation between biological activities with structural features in structures. 2D and 3D QSAR methods are the most reported methods in recent decades in number of scientific finding. These two methods correlate contribution of the whole molecule with biological activity, so the requirement of congeneric series is must for these methods. Group-based QSAR (GQSAR) is recently developed methodology of V life sciences where contribution of substituents can be correlated with biological activity. Descriptors in the GQSAR are representative of properties of the molecular fragments, which is an advantage of these methods as the effect of any particular region can be assessed using this GQSAR.[4-8] Benzothiazole is a heterocyclic compound found to show number of important biological activities such as anti-inflammatory, anticancer, and antitubercular. In this present report, a GQSAR analysis on series of benzothiazole derivatives developed by Sugano *et al*. Developed model can be useful for the development of benzothiazole derivatives with selective and specific anticancer properties.

MATERIALS AND METHODS

Data Set Preparation

The molecular set for the study was chosen from literature reported by Sugano *et al*.[9] All 40 structures having benzothiazole derivatives were optimized using Vlife Engine. Merck molecular force field and Gasteiger charges were utilized for minimization of these molecules. Molecular fragments were developed using a common scaffolds with a dummy atom (X) as shown in Figure 1.



Calculation of Descriptors

Optimized fragments were imported into the QSAR module of V life MDS and molecular descriptors were calculated using property calculator. Two hundred and thirty-nine total descriptors were calculated.[10]

Data Selection and Building G-QSAR Model

Toal of 28 and 12 molecules are distributed into training and test set respectively for uniform distribution shown in Table 1. Multiple linear regression method was utilized for the development of the GQSAR model.

Validation of the Developed G-QSAR Model

Developed G-QSAR model was validated for the values for r^2, q^2, pred_r^2, F-test, and standard error.

RESULTS AND DISCUSSION

Good GQSAR model is representative of all the structural properties of the molecules, it should include hydrophilic, steric, and electronic parameters of the molecules. In current communication dataset of the molecules is randomly divided into 70% training set and 30% test set. 10 different GQSAR models were generated 3 out of them are selected on the basis of validation parameters as shown in Table 2.

Interpretation of G-QSAR Model A

The G QSAR model A showed r^2 = 0.81, q^2 = 0.75 and pred_r^2 = 0.70. Critical descriptors are R1-DeltaEpsilonC, R1-XKHydrophilic Area, R2-6 Chain Count. The model can be given by the equation and Figure 2 pEC_{50} = 0.0025–21.8771 (±1.8775) R1-DeltaEpsilonC –0.0169 (±0.0025) R1-XKHydrophilicArea +0.5092 (±0.1015) R2-6 Chain Count.

Coefficient

With *n* = 28, Degree of freedom = 24, Z Score R2 = 6.05, Z Score Q2 = 6.1.

DeltaEpsilonC indicates A measure of contribution of electronegativity which is contributing negatively which shows substitution of aryl ring bearing electron with drawing groups such as nitro and halogen will increase the anticancer activity to the XK Hydrophilic Area is another contributing descriptor which signifies hydrophilic surface area, negative contribution favors substitution of aryl or heteroaryl rings with sufficient lipophilicity to cross cell barrier and reach to cancer cells. R2-R2 6ChainCount indicates six-membered rings in a compound, Positive contribution of this descriptor indicates modification at the R2 amino via aryl and heteroaryl groups will increase the anticancer potential of benzothiazole molecules.

Interpretation of G-QSAR Model B

Model B is another generated GQSAR model with r^2 = 0.71, q^2 = 0.65 and pred_r^2 = 0.72. Descriptors that are contributors for this model are R1-DeltaAlphaB, R1-XKHydrophilic Area, R2-HosoyaIndex. This model B is given by the following equation and Figure 3.

pEC_{50} = 0.0010 + 36.4894 (±4.9507) R1-DeltaAlphaB –0.0111 (±0.0034) R1-XKHydrophilicArea –0.0057 (±0.0021) R2-HosoyaIndex.

Coefficient

With *n* = 28, Degree of freedom = 24, Z Score R2 = 3.09, Z Score Q2 = 2.7.

DeltaAlphaB indicated a measure of count of HBA atoms contributing positively for the biological activity which indicates substitution of hydrogen bond acceptor will potentiate the anticancer activity. XK Hydrophilic Area is another contributing descriptor that signifies hydrophilic surface area, negative contribution favors substitution of aryl or heteroaryl rings. R2-HosoyaIndex signifies the topological index; negative contribution of this descriptor indicates modification at the R2 amino is necessary for improvement in biological activity.

Interpretation of G-QSAR Model C

The G-QSAR model C is third selected GQSAR model with r^2 = 0.74, q^2 = 0.62 and pred_r^2 = 0.71. Descriptors that are contributors for this model are R1-Oxygens Count, R1-XcompDipole, and R2-XAAverageHydrophilicity. The model can be given by the following equation and Figure 4.

pEC_{50} = 00.0012 + 0.4120 (±0.1350) R1-OxygensCount –1.2344 (±0.2245) R1-XcompDipole –11.2324 (±2.5967) R2-XAAverageHydrophilicity.

Coefficient

With *n* = 28, Degree of freedom = 24, Z Score R2 = 7.73, Z Score Q2 = 3.4.

Oxygens Count gives count of oxygen atoms which is contributing positively for the biological activity which indicates substitution of OH will potentiate the anticancer activity of the molecules. XcompDipole is signifies the x component of the dipole moment, negative contribution favors substitution of electron with drawing groups. XAAverageHydrophilicity

Table 1: Derivative under study

Mole. No	R_1	R1	Obs (pEC50 ng/mL)	Pre A (pEC50 ng/mL)	Pre B (pEC50 ng/mL)	Pre C (pEC50 ng/mL)
1.	5a	2-Methylphenyl	0.5	0.5	0.5	0.5
2.	5b	2-Fluorophenyl	0.4	0.4	0.5	0.5
3.	5c	2-Chlorophenyl	0.7	0.4	0.5	0.5
4.	5D	2-Trifluoromethylphenyl	0.7	0.7	0.5	0.5
5.	5e	2-Phenoxyphenyl	0.5	0.4	0.5	0.5
6.	5f	3-Fluorophenyl	0.3	0.4	0.5	0.5
7.	5g	3-Cyanophenyl	0.3	0.4	0.5	0.5
8.	5nb	2,6-Dichlorophenyl	0.8	0.9	0.5	0.5
9.	5ob	2-Fluoro-6-trifluoromethylphenyl	0.6	0.5	0.5	0.5
10.	5q	2-Pentyl	0.4	0.4	0.5	0.5
11.	5t	2-Chloropyridin-3-yl	0.5	0.4	0.5	0.5
12.	5u	2-Methyl-2H-pyrazol-3-yl	0.3	0.4	0.5	0.5
13.	5v	2,5-Dimethyl-2H-pyrazol-3-yl	0.4	0.4	0.5	0.5
14.	5w	1,3,5-Trimethyl-1H-pyrazol-4-yl	0.9	0.8	0.5	0.5
15.	5x	2,4-Dimethylthiazol-5-yl	0.3	0.4	0.5	0.5
16.	6a	Allyl	0.3	0.4	0.5	0.5
17.	6b	Isobutyl	0.3	0.4	0.5	0.5
18.	7a	2,6-Dimethylphenyl	0.3	0.4	0.5	0.5
19.	7b	Phenethyl	0.3	0.4	0.5	0.5
20.	9a	4-Butoxyphenyl	0.3	0.4	0.5	0.5
21.	9b	5-Fluoro-2-methylphenyl	0.3	0.4	0.5	0.5
22.	13a	Cyclobutyl	0.8	0.9	0.7	0.4
23.	13b	Cyclopropyl	0.8	0.9	0.7	0.6
24.	13c	Methyl	0.3	0.2	1.3	0.6
25.	13d	Propyl	1	0.9	1.00	0.6
26.	13e	Isobutyl	0.9	0.8	0.8	0.6
27.	13f	Heptyl	0.4	0.5	0.4	0.6
28.	14a	Methyl	1	1.4	1.9	2.4
29.	14b	Ethyl	2.4	2.3	1.9	2.3
30.	14c	Propyl	2.5	2.6	1.6	2.3
31.	14d	Isopropyl	2.4	2.2	1.7	1.2
32.	14e	Isobutyl	1.8	1.8	1.4	2.3
33.	14f	Methoxyethyl	0.9	0.81	0.6	1.2
34.	14gf	tert-butyl	0.6	0.5	0.6	0.2
35.	14h	Benzyl	0.4	0.5	0.3	0.2
36.	15a	Ethyl	0.6	0.5	0.7	0.7
37.	15b	Isopropyl	0.6	0.7	0.9	0.8
38.	15c	Butyl	0.6	0.6	0.7	0.7
39.	15d	Hexyl	0.4	0.50	0.4	0.5
40.	15e	Benzyl	0.4	0.5	0.2	0.6

Obs: Observed activity, Pre: Predicted activity

signifies the Average hydrophilic value on the vdW surface; negative contribution of this descriptor indicates modification at the R2 amino via lipophilic groups is necessary for improvement biological activity.

Table 2: Developed GQSAR model

Model code	GQSAR model	*n*	Degree of freedom	r^2	q^2	pred_r^2	pred_r^2se
A	pEC_{50}=0.0025–21.8771 (±1.8775) R1-DeltaEpsilonC –0.0169 (±0.0025) R1-XKHydrophilicArea+0.5092 (±0.1015) R2-6ChainCount	28	24	0.81	0.75	0.70	0.3894
B	0.0010+36.4894 (±4.9507) R1-DeltaAlphaB –0.0111 (±0.0034) R1-XKHydrophilicArea-0.0057 (±0.0021) R2-HosoyaIndex	28	24	0.71	0.65	0.72	0.5079
C	00.0012+0.4120 (±0.1350) R1-OxygensCount –1.2344 (±0.2245) R1-XcompDipole –11.2324 (±2.5967) R2-XAAverageHydrophilicity	28	24	0.74	0.62	0.71	0.5987

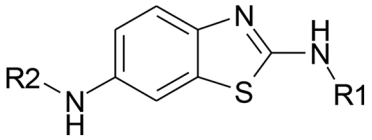


Figure 1: Molecular template utilized for fragmentation pattern

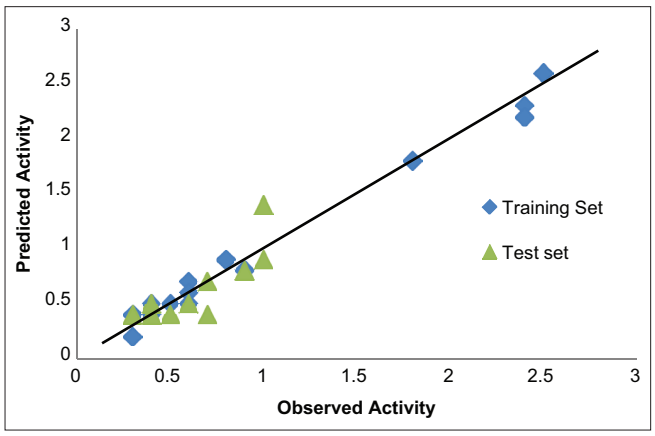


Figure 2: Correlation Plot for group-based quantitative structure and activity relationship Model A

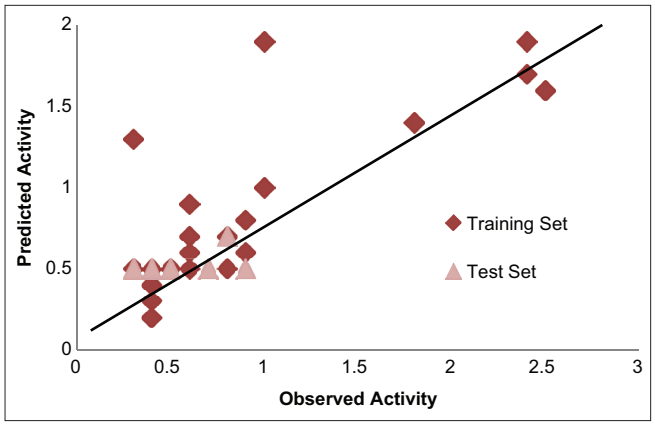


Figure 3: Correlation plot for group-based quantitative structure and activity relationship Model B

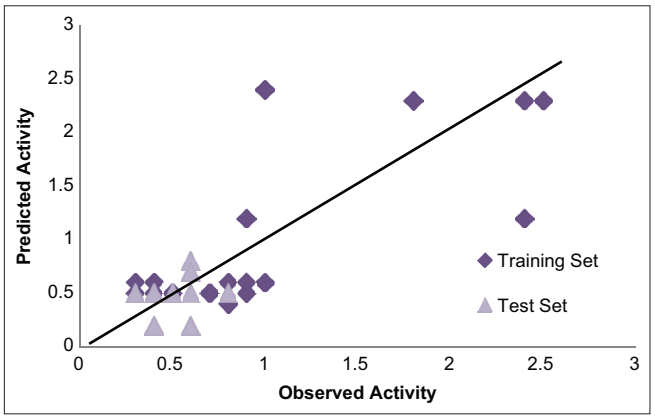


Figure 4: Correlation plot for group-based quantitative structure and activity relationship Model C

CONCLUSION

In this study, a GQSAR model was developed based on 40 benzothiazole derivatives for their anticancer potential. Three different G-QSAR models A, B, and C were generated. Model A was found more significant than all other generated model. The model A generated contained three physicochemical descriptors R1-DeltaEpsilonC, R1-XKHydrophilicArea, R2-6ChainCount. Developed GQSAR equation showed indicated amino fragments are important role in the anticancer potential of the molecules under study. Thus, developed GQSAR model in this study will be a useful tool in for the development of benzothiazole derivatives for anticancer potential.

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