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Research Article

SYNTHESIS, CYTOTOXIC EVALUATION, *IN SILICO* PHARMACOKINETIC AND QSAR STUDY OF SOME BENZOTHIAZOLE DERIVATIVES

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ABSTRACT

A series of benzothiazole derivatives were synthesized and evaluated for *in vitro* cytotoxic activity against HL-60 and U-937 cell lines and antimicrobial activity against bacterial and fungal strains. The biological evaluation results shows that the dimer exhibits better activity against both cancer cell lines and moderate activity against all microbial strains whereas monomers show significant activity against all microbial strains. *In silico* ADMET study of the compounds revealed that these dimers are free from teratogenicity, irritation and sensitivity properties than monomers. The result recorded for QSAR study shows that the increase in hydrogen bond donor count is conducive for the cytotoxic activity of benzothiazole derivatives against HL-60 cell lines.

Key words: Benzothiazole dimers, cytotoxicity, ADMET, QSAR.

INTRODUCTION

Over recent years, there has been steadily increasing research in the field of anticancer therapy. Many efforts have been directed towards the identification and characterization of novel, potent and selective anticancer ligands. Benzothiazole ring are known to have broad spectrum of biological activities, the prominent of them is the antitumor activity along with antimicrobial[1] and antifungal[2] activities. The 2-amino benzothiazoles are the most important derivative that is extensively studied because of its potent antitumor activity. 2-(4-aminophenyl) benzothiazole (CJM126) (Figure 1) and its analogues comprise a novel mechanistic class of antitumor agents. These ligands come from the related structure polyhydroxylated 2-phenylbenzothiazoles[3-6].

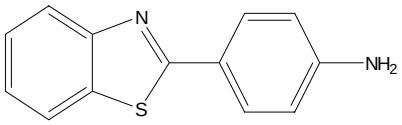


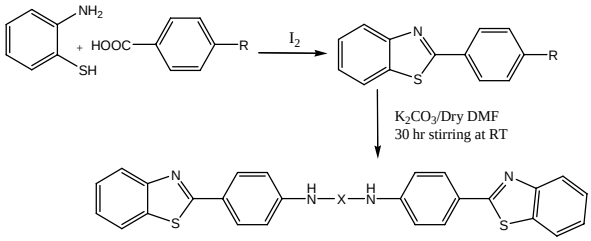
Fig 1: Parent nucleus of 2-(amino phenyl) benzothiazole

Dimers are the molecule, which are having two units of same nucleus and are either directly linked with each other or bridge of some chain. The length of bridge depend on type of bifunctional substituents taken from the bridge and is knows as spacers. Those molecules, which forms adduct with DNA or form covalent bond with DNA, can easily be converted into dimer for increasing activity[7, 8].

The development of potent anticancer molecule is limited by many reasons such as time consumption in synthesis, *in vivo* biological screens and failure of the success rate due to poor absorption, distribution, metabolism, excretion (ADME) and toxicity (T) properties. Therefore it was planned to develop a cost effective method and perform an *in silico* ADMET screening of the designed benzothiazole derivatives. Related to the forgoing, we report herein cost effective synthesis of benzothiazole derivatives and its dimers for antimicrobial and anticancer activity. *In silico* pharmacokinetic and pharmacodynamic study on the compounds also carried out to interpretate the properties in drug action.

CHEMISTRY

Benzothiazole derivatives were synthesized in laboratory with molecular iodine as per the reported procedure. Solvent free condition was found to be the cheapest and effective of all methods for the synthesis of benzothiazole derivatives [9-11]. The dimers were synthesized with DMF and potassium carbonate for 30 hr at room temperature. Dichloromethane and dichloroethane was used as a spacer for the dimer synthesis (Scheme 1).



Scheme 1: Synthetic scheme of Benzothiazole derivatives

EXPERIMENTAL

Material and methods

Reagents, starting materials and solvents were purchased from common commercial suppliers (CDH, S.D. Fine, Loba, E. Merch, Lancaster, etc). The melting points were determined in open capillary method on a Jindal melting point apparatus and are reported uncorrected. C^{13} and H^{1} NMR spectra were recorded on the Bruker NMR using $CDCl_3$, TMS (tetramethyl silane) as an internal standard. The FAB mass spectra were recorded on a JEOL SX 102 Mass Spectrometer/Data System using Argon/Xenon (6KV, 10mA) as the FAB gas, m-nitro benzyl alcohol (NBA) was used as the matrix. IR absorption spectra were recorded on Jasco FT/IR - 470 PLUS, using KBr by diffuse reflectance method. UV-absorption studies were done on Shimadzu Pharmaspec-UV 1700 spectrophotometer to find out λ_{max} of the compounds. The elemental analysis (CHN analysis) was done on a Perkin Elmer CHN rapid analyzer. All the compounds gave satisfactory analysis within ± 0.4% of the theoretical values. The purity and the reactions progress were monitored by thin layer chromatography using silica gel-G on glass plate as stationary phase and different polarity of solvents as mobile phase. Visualization was accomplished with UV light and/or iodine vapour.

Synthesis of benzothiazole dimer

Benzothiazole monomers were synthesized as per the procedure given in literature[3]. For dimer compounds, a mixture of potassium carbonate (4.416 gm, 32 mM), dry DMF (40 ml), 2-(4-amino phenyl) benzothiazole (1.8 gm, 8 mM) (prepared as per literature (8)) and 1,2-dichloromethane (0.256 ml, 4 mM) [for dimer-1] or 1,2-dichloroethane (0.316 ml, 4 mM) [for dimer-2] was stirred at room temperature in a round bottom flask for 30 hr. The mixture was then poured in 80 ml water and extracted with diethyl ether (20 ml x 3). The combined extract was washed with cold water (20 ml x 5), brine solution (20 ml x 4), then the solvent was removed under vacuum

and the product obtained was dried and recrystallized with methanol.

Antimicrobial activity

Antimicrobial activity of the synthesized compounds was done by disc diffusion method in nutrient agar medium[12, 13]. The in vitro screening was carried out using selected microbes like *B. subtilis* (NCIM 2063, Gram positive), *S. epidermitis* (NCIM 2493, Gram positive), *S. aureus* (NCIM 2079, Gram positive), *K. pneumoniae* (NCIM 2957, Gram negative), *P. vulgarism* (NCIM 2027 Gram negative), *E. coli* (NCIM 2063, Gram negative) and fungal strain *C. albicans* (NCIM 347).

***In vitro* cytotoxicity assay in human tumor cell lines**

The compounds were screened in U-937 and HL-60 cell lines by adopting the well-established MTT colorimetric micro culture assay method[14, 15]. Briefly, tumour cells were exposed *in vitro* under sterile cell culture conditions to different concentrations of candidate drug solutions for different time intervals after which, MTT salt solutions was added and incubated further. The cellular reduction of the colorless tetrazolium salts yielded coloured formazan derivatives in proportion to viable cell numbers. The optical density of the reduced formazan derivative was determined in ELISA reader to get the cytotoxicity assay.

***In silico* ADME-toxicity studies**

The Pentium IV work station and Pallas 6.1.1 software were used to calculate and to predict the ADMET properties of the molecules[16]. Chem draw ultra software was used to draw the structure of the compounds to be analyzed and was saved as MDL file. The sketched molecules were undergo calculation of the following properties viz drug likeliness, metabolite, toxicity, etc.

Quantitative structure activity relationship analysis

The QSAR study of the synthesized compounds was done on V-life software and Pentium 4 computer[17]. The compounds were sketched in Chem. Draw software. The lowest energy conformers and physicochemical descriptors were calculated from V-life software (Table 9). The correlation between the activity and the physicochemical descriptors were done by partial least square method.

RESULTS AND DISCUSSION

Benzothiazole derivatives were synthesized by cost effective; iodine catalysed solid phase method (Table 1). The dimers of the benzothiazole derivatives were synthesized by conventional method and its structure was confirmed by analytical method. The physicochemical properties of the compounds were determined and are given in Table 2. Analytical study results (Table 3) shows that the peaks of aliphatic methylene groups in IR and NMR spectra confirm the dimer have been formed from the monomers. Molecular ion peak obtained from the mass spectral analysis confirm the molecular weight of the compounds.

Table 1: Detail of the Benzothiazole derivatives synthesized by iodine catalyst

S. No.		R	Reactant I	Reactant II	Product	Recrystallizing solvent
1.	Monomer 1	OH	2-amino thiophenol	p-hydroxy benzoic acid	2-(4-hydroxyphenyl) benzothiazole	60% methanol
2.	Monomer 2	NH_2	2-amino thiophenol	p-amino benzoic acid	2-(4-aminophenyl) benzothiazole	70% methanol
3.	Monomer 3	OCH_3	2-amino thiophenol	p-methoxy benzoic acid	2-(4-methoxyphenyl) benzothiazole	Chloroform
4.	Monomer 4	H	2-amino thiophenol	Benzoic acid	2-phenyl benzothiazole	70% ethanol
5.	Monomer 5	Cl	2-amino thiophenol	p-chloro benzoic acid	2-(4-chlorophenyl) benzothiazole	70% ethanol
6.	Monomer 6	NO_2	2-amino thiophenol	p-nitro benzoic acid	2-(4-nitrophenyl) benzothiazole	60% ethanol
Synthesis of dimmers						
S. No		**X**	**Reactant (III)**	**Reactant (IV)**	**Product**	**Recrystallizing solvent**
1.	Dimer 1	$-CH_2$	2-(4-aminophenyl) benzothiazole	Dichloromethane	4-(benzo[d]thaizol-2-yl)-N-((4-(benzo[d]thiazol-2-yl)phenyl amino) methyl)benzenamine	Methanol
2.	Dimer 2	$-CH_2CH_2$	2-(4-aminophenyl) benzothiazole	Dichloroethane	4-(benzo[d]thaizol-2-yl)-N-((4-(benzo[d]thiazol-2-yl)phenyl amino) ethyl)benzenamine	Methanol

Table 2: Physicochemical properties of the synthesized compounds

Compounds	Colour	Yield	Melting point (°C)	UV λmax (nm) (methanol)	Rf value
Monomer 1	Light yellow amorphous	95.93%	170-175	335, 240	0.68
Monomer 2	Brown crystalline	87.20%	145-148	350, 237	0.65
Monomer 3	Light yellow amorphous	98.90%	170-173	380, 260	0.44
Monomer 4	Brownish yellow crystalline	97.61%	114-117	340, 231	0.79
Monomer 5	Yellowish amorphous	99.00%	175-179	333, 210	0.62
Monomer 6	Light yellow amorphous	95.30%	170-172	393, 290	0.78
Dimer 1	Greenish Black crystalline	32.46%	270-273	220, 341	0.73
Dimer 2	Greenish Black crystalline	56.81%	220-224	226, 339	0.69

Table 3: Spectroscopic data of synthesized compounds

Compound	Spectral data
Monomer 1	3060 (C-H aromatic stretching), 1308 (C-N stretching); C^{13} NMR: 115-131 (6C) Aromatic, 118-148 (7C) Aromatic benzothiazole
Monomer 2	3468 (N-H stretching), 3059 (C-H aromatic stretching), 1306 (C-N stretching), 1267 (Ar-C-O); C^{13} NMR: 113-132 (6C) Aromatic, 118-148 (7C) Aromatic benzothiazole
Monomer 3	3066 (C-H aromatic stretching), 2835 (C-H stretching of OCH_3), 1303 (C-N stretching), C^{13} NMR: 113-164 (6C) Aromatic, 118-148 (7C) Aromatic benzothiazole, 55.1 (1C), OCH_3.
Monomer 4	3068 (C-H aromatic stretching), 1294 (C-N stretching) Mass Analysis: M^+: 211.
Monomer 5	3061 (C-H aromatic stretching), 1311 (C-N stretching), 1098 (C-Cl stretching) Mass Analysis: M^+: 246.
Monomer 6	3001 (C-H aromatic stretching), 1289 (C-N stretching), 1346 (NO_2 stretching); Mass Analysis: M^+: 257.
Dimer 1	3304 (N-H stretching), 3066 (C-H aromatic stretching), 1307 (C-N stretching), 1152 (C-N stretching). H^1NMR in $CDCl_3$: 3.76 (t, (2H), CH_2), 4.14-4.2 (t, (2H) NH), 6.55-7.14 (m, (8H), CH-Aromatic), 7.17-7.85 (m, (8H), CH-Aromatic benzothiazole); Nitrogen Analysis: 12.06% (12.11%) Mass Analysis: M^+: 464.
Dimer 2	3304 (N-H stretching), 3064 (C-H aromatic stretching), 1306 (C-N stretching), 1164 (C-N stretching). H^1NMR in $CDCl_3$: 2.27 (d, (4H), CH_2CH_2), 4.14-4.2 (t, (2H) NH), 6.55-7.15 (m, (8H), CH-Aromatic), 7.14-7.80 (m, (8H), CH-Aromatic benzothiazole); Nitrogen Analysis : 11.71% (11.15%) Mass Analysis : M^+: 482

s=singlet, d=doublet, t=triplet, q=quartet, bd=bisdoublet, m=multiplet

Antimicrobial activity

Antimicrobial study on benzothiazole derivatives (Table 4) shows that the compounds 1, 2 and 5 (Hydroxyl, amino and chloro) exhibit significant activity against all bacterial and fungal strains. Compound 2 have better activity against *S. aureus, P. vulgaries* and *S. epidermitis*. Compound 5 have considerable activity against *B. subtilis* and *E. coli*. Compound 1 has significant activity against *K. pneumoniae* and *C. albicans*. Other compounds have comparably less activity against all bacterial and fungal strains.

Among all the compounds, monomer 5 has found to be most potent activity against *E.coli* and the monomer 3 (methoxy) and the dimer 1 (methylene) was found to be least potent for *S. epidermitis, S. aureus* and *E. coli*. Compound 2, i.e. 2-(4-aminophenyl) benzothiazole was found to have good potency for all the strains. Previously, it was found that a dimer has more activity than its corresponding monomer but in our case dimer activity has decreased than its corresponding monomers and do not show a significant increase in activity as compared to some other monomers synthesized by bioisosteric principles.

Table 4: Antimicrobial activity of the compounds

Compound no	Zone of inhibition (mm) in 50 µg/ml						
	Strain I	Strain II	Strain III	Strain IV	Strain V	Strain VI	Strain VII*
Monomer 1	12	13	10	12.5	12.5	10	10.5
Monomer 2	13	14	11.5	12	08	12.5	09
Monomer 3	12.5	06	11	07	09	07.5	07
Monomer 4	11.5	11	07.5	10	10	11	10
Monomer 5	11	11	12	20	10	10	08
Monomer 6	08	08.5	09	11.5	07.5	09	09
Dimer 1	06	06.5	07	06	-	-	07
Dimer 2	09	08	09	08	-	-	08
Ethanol	05	05	06.5	05.5	05	04.5	04.5
Ciprofloxacin	20	-	-	-	20	24	-
Ofloxacin	27	23	23	22	26	23	-
Tetracycline	-	22	24	20	-	-	-
Miconazole	-	-	-	-	-	-	22
Amphotericin	-	-	-	-	-	-	17

*40 µg/ml was used for the study. Strain I : *S. aureus,* Strain II : *S. epidermitis,* Strain III: *B. subtilis,* Strain IV : *E. Coli,* Strain V : *K. Pneumoniae,* Strain VI : *P. vulgaries* and Strain VII : *C. albicans*.

Cytotoxic activity

Cytotoxic activity of the compounds was determined in HL-60 and U-937 cell lines by MTT assay techniques. Cisplatin, BCNU, 5-flurouracil and hydroxyurea were taken as reference compounds. It is noteworthy that all the synthesized benzothiazole derivatives exhibited better cytotoxic activity than 5-fluorouracil and hydroxyureas and considerable activity against cisplatin and BCNU. The results obtained are given in Table 5, which shows that the dimer compounds have considerable activity against both the cell lines than the monomers. Except monomer 3 and 4 (methoxy and unsubstituted), all other compounds have significant activity against U-937 lymphoma cell lines and the dimer–1 (methylene) exhibit better activity (1.8 µM) than the reference compounds cisplatin (3.2 µM). The study shows that amino, hydroxyl and chloro group containing compounds have better activity against HL-60 cell lines along with dimers. The nitro group containing compounds have better activity against U-937 cell lines and less activity for HL-60 cell lines. It is worth mentioning that the increase in spacer chain length in dimers reduces the activity and the bioisosteric substituents of the compounds have comparable activity.

***In silico* ADMET study**

The *in silico* pharmacokinetic study on the synthesized molecules (Table 6-8 and Figure 2) shows that the drug likeliness confirms both the dimers are drug like compounds. In order to predict the drug likeliness of the synthesized compounds on the guidelines of Lipinski rule of 5 (Molecular weight >500, Log P>5, HBD>5 and HBA>10), in silico ADME-Toxicity study on the synthesized compounds were carried out using Pallas 3.1.1.2 software. The logP value of the dimers is above 5, but has better activity against cytotoxic cell lines and least activity against microbial strains. Molecular weight of the compounds follows the rule by <500, i.e for monomers molecular weight is in the range of 211-256 and for dimers in the range of 464-478. The dimer compounds are free from teratogenicity, irritation and sensitivity properties. The monomer 6 (nitro derivative) have teratogenicity and irritation. All the compounds have probable mutagenicity. The monomer 2 has irritation property more than other compounds, which are free from irritation.

Table 5: Cytotoxic activity of the benzothiazole derivatives

Compound no	IC_{50} value (μM)	
	Leukemia HL-60	Lymphoma U-937
Monomer 1	22	7.6
Monomer 2	22	10
Monomer 3	124	141
Monomer 4	142	93
Monomer 5	20.4	5.9
Monomer 6	58.6	8.1
Dimer 1	4.3	1.8
Dimer 2	5.2	3.8
Cis-Platinum	7.0	3.2
BCNU	30.5	12.3
5-FU	266.0	4.7
Hydroxyurea		115.0

Table 6: Drug likeliness data of the benzothiazole derivatives

Compound code	Molecular weight	Log P	HBD	HBA	Lipinski score
Monomer 1	227.29	3.26	1	2	0
Monomer 2	226.31	2.78	1	1	0
Monomer 3	241.32	3.71	0	2	0
Monomer 4	211.29	3.64	0	1	0
Monomer 5	245.73	4.25	0	1	0
Monomer 6	256.29	3.52	0	3	0
Dimer 1	464.63	6.36	2	2	1
Dimer 2	478.06	6.17	2	2	1

Table 7: *In silico* toxicity profile of the synthesized compounds

Compound No	Over all toxicity	Oncogene	Mutagenicity	Teratogenicity	Irritation	Sensitivity
Monomer 1	100	100	53	0	53	0
Monomer 2	100	100	53	19	0	29
Monomer 3	100	100	53	19	0	0
Monomer 4	100	100	53	0	0	0
Monomer 5	100	100	53	18	0	0
Monomer 6	100	100	67	29	0	29
Dimer 1	100	100	53	0	0	0
Dimer 2	100	100	53	0	0	0

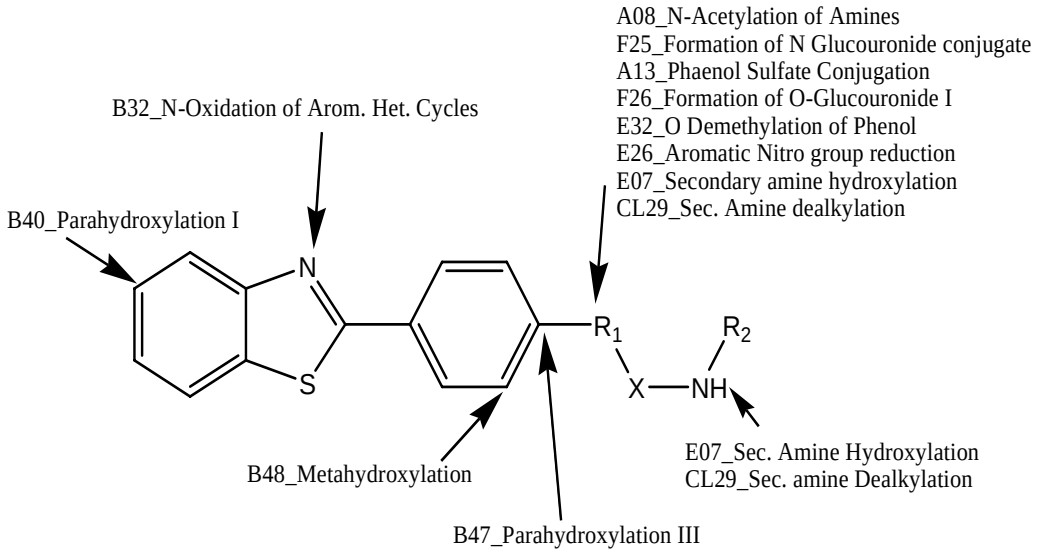


Fig. 2: *In silico* predicted metabolic position of benzothiazole derivatives

Table 8: Metabolic products of benzothiazole derivatives

Name of the metabolite	Compound code and molecular weight							
	M-01	M-02	M-03	M-04	M-05	M-06	D-07	D-08
A08_N Acetylation of amines		268.35						
B32_N Oxidation of Aromatic Heterocycles	244.29	243.32	258.33	228.30	262.74	273.30	481.64	495.65
B40_Parahydroxylation I	243.29	242.31	257.32	227.29	261.73	272.29	480.63	494.66
F25_Formation of N Glucouronide Conjugate		402.45						
A13_Phenol Sulfate conjugation	307.35							
F26_Formation of O Glucouronide Conjugate	402.45							
B47_Parahydroxylation				227.29				
B48_Metahydroxylation				227.29				
E32_O Demethylation of Phenol			227.29					
E26_Aromatic Nitro group reduction						226.31		
E07_Sec. Amine hydroxylation							480.63	494.66
CL29_Sec. Amine hydroxylation								270.37
								226.31

The metabolic studies shows that none of the compounds undergo the toxic metabolic pathways (like acetylated or methylated product), only monomers 1 and 2 undergo second phase metabolism (N-glucouronide, Phenol sulphate and O-glucouronide conjugations).

Quantitative structure activity relationship study

The data set comprising of 8 compounds in benzothiazole derivatives synthesized in our laboratory was taken for study. The structure of the compounds in the series alongwith their corresponding cytotoxic activity values are illustrated in Table 1 and 5. The biological activity was considered as dependent and physicochemical descriptors as independent variables (Table 9). The result obtained from the QSAR analysis is given below.

log1/BA (HL-60 cell lines) = 0.5699 H-Donor Count + 5.1529-Model 1

n = 8, Degree of freedom = 6, r2 = 0.7942, q2 = 0.6536, F test = 23.1480, r2 se = 0.2778, q2 se = 0.3604,

Log1/BA (U-937 cell lines) = 1.2491 chi3Cluster + 4.5223-Model 2

n = 8, Degree of freedom = 6, r2 = 0.5778, q2 = 0.3123, F test = 8.2097, r2 se = 0.4619, q2 se = 0.5895

The correlation coefficient values (r), show that they account for more than 85% of the variance in biological activity. The standard error of estimate is very low demonstrating the accuracy of fit. The mono parametric models having H-donor count descriptor in model 1 and Chi3cluster descriptor in model 2 are positively correlated for the activity.

Model 1 shows that the H-donors atom in the molecule has significantly contributed for activity against HL-60 cell lines. The model has high correlation (r^2=0.7942) and have good predictive power. The Fischer and t-test values of the model represent the significance of the model is exceed the tabulated value by a large margin as desired for a meaningful correlation.

The correlation between U-937 cell lines and physicochemical descriptors exhibit moderate correlation (r^2=0.5778) with Chi3cluster descriptor. The molecular connectivity index of order 3 represents the size of the hydrophobic fragment with three vertices and contains group contribution of all non-hydrogen atoms in the fragment.

The results of the QSAR study suggest presence of hydrophobic moieties in the molecule is conducive for the cytotoxic activity of the benzothiazole derivatives against U-937 cell lines, whereas increase in hydrogen donor count in the molecule favorable for cytotoxic activity against HL-60 cell lines.

Table 9: Log 1/IC50 and calculated descriptors of the synthesized compounds

S. no	Leukemia HL-60	Lymphoma U-937	H-Donor count	chi3cluster
1	5.657577	6	1	0.955342
2	5.657577	6.119186	1	0.955342
3	4.847712	5.031517	0	0.666667
4	4.906578	4.850781	0	0.870791
5	5.69037	6.229148	0	0.955342
6	5.232102	6.091515	0	1.166667
7	6.366532	6.744727	2	1.741582
8	6.283997	6.420216	2	1.741582

CONCLUSION

From the study, it is concluded that the monomers especially, amino and hydroxyl group containing compounds have better activity against bacterial and fungal strains. The dimer compounds have least antimicrobial activity, but have significant cytotoxic activity against HL-60 and U-937 cell lines. Methoxy and unsubstituted 4-(amino phenyl) benzothiazole derivatives have moderate cytotoxic activity. The in silico pharmacokinetic study shows the compounds have better drug likeliness and are free from teratogenicity, irritation and sensitivity. The QSAR study shows that the hydrogen donor count property is important for HL-60 cell lines. The study concluded that the 2-(phenyl) benzothiazole derivatives and its dimers will be significant lead for further investigation of anticancer and antimicrobial agents.

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