International Journal of Multidisciplinary Research and Development
Online ISSN: 2349-4182, Print ISSN: 2349-5979
Impact Factor: RJIF 5.72
Received: 12-11-2018; Accepted: 13-12-2018
www.allsubjectjournal.com
Volume 5; Issue 12; December 2018; Page No. 148-151

QSAR and docking study of some benzothiazole derivatives as anthelmintics

FA Omer [1], Hiba H Mahgoub[2*], AEM Saeed[3]
[1-3] Department of Chemistry, College of Science, Sudan university of Science and Technology, Sudan

Abstract
Modeling studies using QSAR and molecular docking methods were performed on a set of benzothiazole derivatives previously studied as effective anthelmintic agents, the method of multiple linear regression (MLR) was explored to build the QSAR model, the model tested showed high performance towards its predictability, having the squared correlation coefficient r^2 = 0.8004, correlation coefficient r = 0.8946 and cross-validated squared correlation coefficient Q^2 = 0.6597. The predicted model was confirmed by validation method: leave-one-out (LOO) cross validation. The molecular docking study of compounds on 5e0o as the protein target helps to understand and predict the binding modes with the binding sites.

Keywords: benzothiazoles, anthelmintics, QSAR, molecular docking, 5e0o

1. Introduction
Nitrogen-and sulfur-containing heterocycles play an important role, not only for life science, but also in many other industrial fields related to special and fine chemistry. Benzothiazoles are bicyclic ring comprise a class of therapeutic compounds that show a wide range of biological activities [1]. The ring system in which benzene ring is fused to the 4, 5-positions of thiazole ring is designated as benzothiazole and it is a weak base, completely planar. The various positions on the ring are numbered in the manner indicated, with the sulfur having priority over other family members as shown in Fig.1.

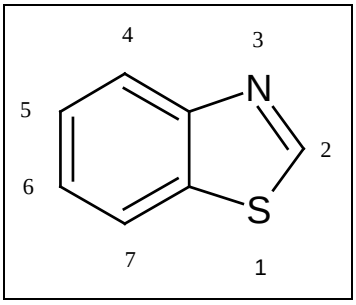


Fig 1: structure of benzothiazole

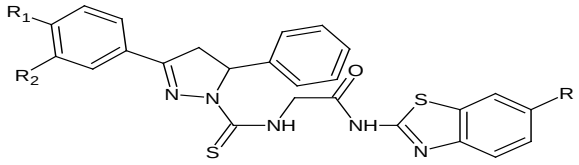
benzothiazole ring is present in various marine or terrestrial natural compounds, which have useful biological properties [2] and widely found in bioorganic and medicinal chemistry with application in drug discovery. They show numerous biological activities such as anticancer [3], antimicrobial [4], anticonvulsant [5], antiviral, antitubercular [6], antimalarial, antihelmintic [7], analgesic, antiinflammtor [8], anti-diabetic [9] anti-oxidant, and fungicidal activities. Recently, benzothiazole derivatives have been evaluated as potential amyloid-binding diagnostic agents in neurodegenerative disease [10], selective fatty acid amide hydrolase inhibitors [11], inhibitors of stearoyl-coenzyme A δ-9 desaturase and histamine H2 antagonists. They are also useful as appetite depressants [12], intermediates for dyes [13], plant protectants, imaging agents for -amyloid plaques, and photographic sensitizers, and in polymer chemistry [14]. Various benzothiazoles such as 2-aminobenzothiazole received much attention due to unique structure and its uses, it is one of privileged structure in medicinal chemistry and reported cytotoxic effects. It must be emphasized that combination of 2-aminobenzothiazoles with other heterocyclic is a well-known approach to design new drug like molecules, which allows achieving new pharmacological profile, action, and toxicity lowering.
Quantitative structure activity relationships (QSAR) studies are tools which quantitatively correlates the variations in biological activity with the properties or molecular structures, is one of the most effective approaches for designing new chemical identities and understanding the action mechanisms of drugs [15].
In the present work, quantitative structure activity relationship study was performed to obtain a QSAR model, which was used to predict the anthelmintic activity against earthworms for a set of benzothiazole derivatives, in addition of docking studies using 5e0o protein.

2. Materials and methods
2.1. QSAR study
A total of nine benzothiazole derivatives reported by Srividya Girija [16] was used in QSAR study. These compounds were synthesized and evaluated for anthelmintic activity on earthworms.
The biological activity was reported as the mean lethal time in (min), values were converted to negative logarithmic in (min), values and structures can be found in Table1.
ACD/ChemSketch v 14.01 software (Copyright 1994-2013 Advanced Chemistry Development, Inc.) was used to drawing the studied compounds, molecular modeling was performed using the Molecular Operating Environment software package

(MOE, v2009.10; Chemical Computing Group Inc.)

Table 1: Biological activities and structures of benzothiazole derivatives obtained by Srividya Girija [16].

Compound	R	R_1	R_2	MIN	pMIN
1	H	H	H	60	-1.778
2	Cl	H	H	57	-1.756
3	OCH_3	OCH_3	H	55	-1.740
4	$N(CH_3)_2$	H	H	49	-1.690
5	CH_3	H	H	53	-1.724
6	Cl	H	OCH_3	46	-1.663
7	OCH_3	OCH_3	OCH_3	51	-1.708
8	$N(CH_3)_2$	H	OCH_3	50	-1.699
9	CH_3	H	OCH_3	48	-1.681



2.1.1. Molecular descriptors

Total of seven molecular descriptors were calculated for each molecule namely, ionization potential (IP), sum of atomic polarizabilities (S-ap), total polar surface area (T-psa), density (D), molar refractivity (MR), molecular weight (M.w), and log octanol/water partition coefficient(logP(o/w)), these descriptors were calculated using MOE program and listed in Table 2. To select the optimal subset of physicochemical properties, highly correlated chemical descriptors were excluded through correlation matrix.

Table 2: Values of molecular descriptors calculated for data set.

Compd	IP	S-ap	T-psa	D	MR	M.w	LogP(o/w)
1	8.7297	70.1047	167.8027	1.0783	13.5750	471.6090	5.4640
2	8.6892	71.6179	170.2334	1.1174	14.0804	506.0540	6.0930
3	8.7105	76.2918	160.0634	1.0522	14.4767	499.6630	6.0970
4	8.6623	73.1982	145.5473	1.0662	14.0265	485.6360	5.7990
5	8.6527	73.1982	145.9206	1.0635	14.0265	485.6360	5.7990
6	8.8326	74.7114	140.0760	1.1042	14.5339	520.0810	6.4280
7	8.5914	79.3854	167.6477	1.0489	14.9296	513.6900	6.4300
8	8.6454	76.2918	164.9123	1.0555	14.4767	499.6630	6.1340
9	8.6348	76.2918	148.6652	1.0547	14.4767	499.6630	6.1340

The QSAR model equation was derived by using MLR statistical method where the independent variables molecular descriptors and dependent variable (pMIN) (Equation 1). The statistical quality of the regression equations was justified by statistical parameters such as the root mean square error (RMSE), correlation coefficient (r), squared correlation coefficient (r^2), standard error of estimate (s) and F-test value (ratio between the variances of observed and calculated activities, F). Calculation of statistical parameters was carried out by using statistical program SPSS version 24.

pMIN = -1.78623 + 0.06646 * logP(o/w) – 0.00211 * T-psa (1)

Table 3: Statistical parameters used for statistical quality of model.

r	r^2	Q^2	s	F	RMSE	*P* value
0.8946	0.8004	0.6597	0.0178	28.165	0.0157	0.001

Table 4: Experimental, predicted pMIN and cross validation for data set.

Compd	$pMIN_{exp.}$	$pMIN_{pred.}$	Residuals	$CV_{pred.}$	Residuals
1	-1.778	-1.7771	-0.0009	-1.7757	-0.0023
2	-1.756	-1.7405	-0.0155	-1.7342	-0.0218
3	-1.740	-1.7188	-0.0212	-1.7157	-0.0243
4	-1.690	-1.7079	0.0179	-1.7164	0.0264
5	-1.724	-1.7087	-0.0153	-1.7018	-0.0222
6	-1.663	-1.6546	-0.0084	-1.6452	-0.0178
7	-1.708	-1.7126	0.0046	-1.7163	0.0083
8	-1.699	-1.7265	0.0275	-1.7329	0.0339
9	-1.681	-1.6922	0.0112	-1.6947	0.0137

2.1.2. Validation of QSAR model

The predictive powers of the equations were validated by the leave-one-out (LOO) cross-validation method (CV). The cross validated squared correlation coefficient (Q2) was considered for the validation of this model (Table 3). The developed QSAR model equation showed a relationship between predicted pMIN values and correlated two chemical descriptors. The observed activities and those calculated by QSAR model (Equation 1) for data set were presented in Table 4.

2.2. Molecular docking

Molecular docking study is a technique to determine the interactions between two molecules ligand and receptor, and to find the best orientation of ligand that would form a complex with overall minimum energy. The protein file (PDB ID: 5e0o) selected for this purpose obtained from Protein Data Bank and further optimized and minimized to obtain a low energy and structural correct target protein.

3. Results and discussion

3.1. QSAR studies

The resulted QSAR model equation showed a high square of the correlation coefficient (r^2 = 0.8004) and low root mean square error (RMSE = 0.0157), all other statistical parameters calculated to justified the statistical quality of model were in acceptable range Table 3. The predictive ability of QSAR model was validated through leave one out cross validated (Q^2=0.6597).

Two molecular descriptor logP(o/w) and total polar surface area (T-psa) were correlated with anthelmintic activity, it is evident from the equation (1) that logP(o/w) is positively correlated, that mean the biological activity increases when the value is positively increased. Meanwhile, the descriptor (T-psa) negatively correlated with anthelmintic activity, that mean the biological activity decreases when the value of this descriptor is increase. Figure 1 and 2 show the correlation plots of the experimental versus predicted pMIN values for

data set, cross-validation against anthelmintic activity respectively.

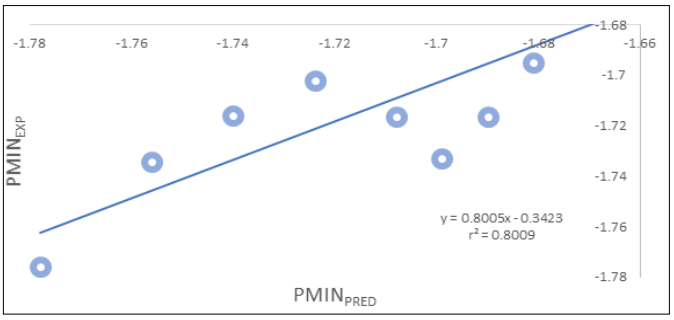


Fig 1: Predicted versus experimental pMIN values of data set.

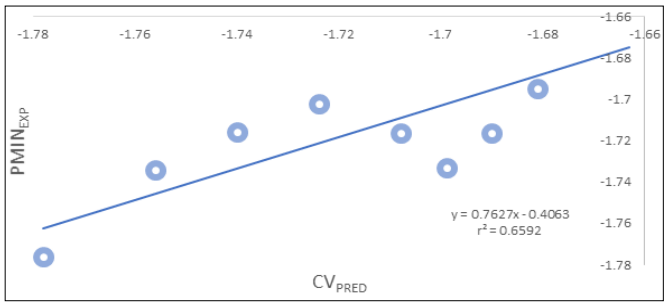


Fig 2: Predicted versus experimental pMIN values of cross validation.

3.2. Docking study

5e0o Brugia malayi Trehalose-6 Phosphate Phosphatase in complex with PEG at the active site, trehalose-phosphatase protein Catalyzes the hydrolysis of trehalose 6-phosphate to trehalose and phosphate; prevents the accumulation of toxic levels of trehalose 6-phosphate. Molecular docking was performed for benzothiazole compounds (1-9), and some selected compounds on the active site using the Molecular Operating Environment software package (MOE, v2009.10; Chemical Computing Group Inc.). Molecular docking show that all benzothiazole compounds (1-9) were capable of forming interaction between Arg 337 with phenyl ring, and interactions between Trp280 with phenyl ring, and the other set of compound mention by (A1-A6) show different type of interactions listed in Table 5. The energy score (S) of the complexes between benzothiazole compounds (1-9) and active site of protein, and selected compounds (A1-A6) and active site of same protein are listed in Table 5.

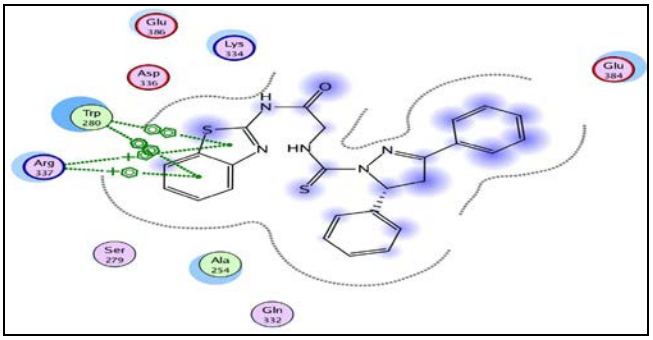


Fig 3: 2D molecular docking model of compound **1** with 5e0o

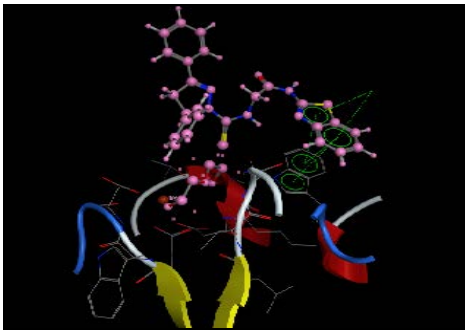


Fig 4: 3D molecular docking model of compound **1** with 5e0o

Table 5: The energy score, amino acid, and type of interaction

Compnd	S (kcal/mol)	Amino acid interaction	Type of interaction
1	-26.7361	Trp 280 Arg 337	Aren-aren Aren-cation
2	-25.9602	Trp 280 Arg 337	Aren-aren Aren-cation
3	-26.4041	Trp 280 Arg 337	Aren-aren Aren-cation
4	-25.7414	Trp 280 Arg 337	Aren-aren Aren-cation
5	-25.7073	Trp 280 Arg 337	Aren-aren Aren-cation
6	-26.2492	Trp 280 Arg 337	Aren-aren Aren-cation
7	-27.9727	Trp 280 Arg 337	Aren-aren Aren-cation
8	-26.1736	Trp 280 Arg 337	Aren-aren Aren-cation
9	-26.1538	Trp 280 Arg 337	Aren-aren Aren-cation
A1	-16.4133	Asp 213 Asp 424	Metal complex (Mg) Metal complex (Mg)
A2	-16.0674	Asp 213 Asp 424	Metal complex (Mg) Metal complex (Mg)
A3	-16.6592	Trp 280 Arg 337	Aren - aren Aren-cation
A4	-17.9935	Asp 213 Asp 424 Lys 334	Metal complex (Mg) Metal complex (Mg) Aren-cation
A5	-18.2089	Asp 213 Asp 424 Lys 334	Metal complex (Mg) Metal complex (Mg) Aren-cation
A6	-21.7207	Trp 280 Arg 424 Lys 334	Aren-aren Aren-cation Aren-cation

4. Conclusion

In this work, a QSAR study was developed, the developed model shows the structural requirements affecting the anthelmintic activity, through the identification of the best fit molecular descriptors in the models, validation indicate that the built QSAR model was satisfactory. The QSAR model developed in this study can provide a useful tool to predict the activity of new compounds and also to design new compounds with high activity.

The molecular docking study of (1-9) and (A1-A6) compounds has been done for the better understanding of the ligand-receptor interaction and the results confirmed that these compounds have a potential anthelmintic activity.

5. References

1. Gulati S, Wakode S, Kaur A, Anand K. Synthesis, biological activity and recent advancement of benzothiazoles: a classical review. World Journal of Pharmacy and Pharmaceutical Sciences. 2017; 6(6):1842-1869.
2. Mariappan G, Prabhat P, Sutharson L, Banerjee J, Patangia U, Nath S. Synthesis and antidiabetic evaluation of benzothiazole derivatives. Journal of the Korean Chemical Society. 2012; 56(2):251-256.
3. Kini S, Swain S, Gandhi A. Synthesis and evaluation of novel benzothiazole derivates against Human Cervical Cancer cell lines. Ind J Pharm Sci, 2007, 46-50.
4. Singh M, Singh SK, Gangwar M, Nath G, Singh SK. Design, synthesis and mode of action of some benzothiazole derivatives bearing an amide moiety as antibacterial agents. RSC advances. 2014; 4(36):19013-19023.
5. Siddiqui N, Pandeya SN, Khan SA, Stables J, Rana A, Alam M, Arshad MF, Bhat MA. Synthesis and anticonvulsant activity of sulfonamide derivatives-hydrophobic domain. Bioorganic & medicinal chemistry letters. 2007; 17(1): 255-259.
6. Palmer PJ, Trigg RB, Warrington JV. Benzothiazolines as antituberculous agents. Journal of Medicinal Chemistry. 1971; 14(3):248-251.
7. Shaista A, Amrita P. Benzothiazole – a magic molecule. IJPSR. 2017; 8(12):4909-4929.
8. Gurupadayya BM, Manohara YN, Gopal M. Synthesis and biological activities of some 2H-3-(6'-fluoro-7'-substituted -2'- benzothiazolyl)-3, 4-dihydro-1, 3-benzoxazines. Indian journal of heterocyclic chemistry. 2005; 15(2):113-116.
9. Rezki N. A green ultrasound synthesis, characterization and antibacterial evaluation of 1, 4-disubstituted 1, 2, 3-triazoles tethering bioactive benzothiazole nucleus. Molecules. 2016; 21(4):505.
10. Henriksen G, Hauser AI, Westwell AD, Yousefi BH, Schwaiger M, Drzezga A, Wester HJ. Metabolically Stabilized Benzothiazoles for Imaging of Amyloid Plaques. Journal of Medicinal Chemistry. 2007; 50(6):1087-1089.
11. Wang X, Sarris K, Kage K, Zhang D, Brown SP, Kolasa T, Surowy C, *et al.* Synthesis and evaluation of benzothiazole-based analogues as novel, potent, and selective fatty acid amide hydrolase inhibitors. Journal of medicinal chemistry. 2008; 52(1):170-180.
12. Rana A, Siddiqui N, Khan SA, Ehtaishamul Haque S, Bhat MA. N-{[(6-Substituted-1, 3-benzothiazole-2-yl) amino] carbonothioyl} - 2/4 -substituted benzamides: Synthesis and pharmacological evaluation. European Journal of Medicinal Chemistry. 2008; 43(5):1114-1122.
13. Okoh OA, Bisby RH, Lawrence CL, Rolph CE, Smith RB. Promising near-infrared non-targeted probes: benzothiazole heptamethine cyanine dyes. Journal of Sulfur Chemistry. 2013; 35(1):42-56.
14. Kokelenberg H, Marvel CS. Polymers containing anthraquinone units: Benzimidazole and benzothiazole polymers. Journal of Polymer Science Part A-1: Polymer Chemistry. 1970; 8(11):3199-3209.
15. Liao SY, Chen JC, Qian L, Shen Y, Zheng KC. Studies and Molecular Design of Phenanthrene-based Tylophorine Derivatives with Anticancer Activity. QSAR & Combinatorial Science. 2008; 27(3):280-288.
16. SrividyaGirija PV, Tejaswi K, Saritajyostna T. Synthesis, characterization and anthelmintic activity of some novel benzothiazole derivatives. J Pharm Res. 2017; 6(11):192-196.