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QSAR Studies of Thiazolidinone Derivatives as Antimicrobial Agents

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ABSTRACT

QSAR (Quantitative Structure–Activity Relationship) relate biological activity data along with the physiochemical and structural properties of a group of compounds. In general, most of the medicinal compounds involve heterocyclic compounds containing nitrogen and sulphur especially thiazolidinones they possess a broad spectrum antimicrobial activity. In the present study, we have carried out the QSAR studies of antimicrobial thiazolidinones using Hansch analysis. The results of QSAR studies indicated that the antimicrobial activity of thiazolidinones are mainly governed by the topological parameters, kiers 3rd order alpha shape index ($\kappa\alpha_3$) and second order valence connectivity index ($^2\chi^v$) along with the lipophilic parameter, log of octanol water partition coefficient (log P).

Keywords: Thiazolidinone, antibacterial, antifungal, QSAR

INTRODUCTION

QSAR (Quantitative Structure–Activity Relationship) relate biological activity data along with the physiochemical and structural properties of a group of compounds. It has been regularly used to figure out biological activities of novel compounds and to create compounds with preferred properties [1]. The fundamental assumption in QSAR studies is that the molecular structures maintain association with their activities [2]. The advancements in computer hardware and software now allow the molecular properties of molecules to be easily estimated without the need to synthesize the molecules in question using QSAR model [3].

During past decades, the frequency of systemic illness has raised significantly together with the number of invasive, opportunistic microbial species carrying infection [4]. Antimicrobial resistance is one of the major public health problems especially in developing countries where relatively easy availability and higher consumption of medicines have lead to disproportionately higher incidence of inappropriate use of antibiotics and greater levels of resistance compared to developed countries [5]. The appearance of resistant microorganisms, one of the two by mutations or the acquisition of mobile genetic elements carrying resistance genes, may take place irrespective of the occurrence of antibacterial agents [6] which necessitates the search for novel antimicrobial agents.

The great amplification in the field of medicinal research is that the assorted heterocyclic compounds have participated much to the progress of medicine. Half of the medications involves heterocyclic compounds containing nitrogen and sulphur as they possess a broad spectrum of biological activity [7]. Compounds together with thiazolidinone moiety have been found to exhibit a wide range of biological activities like antibacterial, antifungal, anti-inflammatory [8], antitubercular, antihistaminic, anti-HIV, antiviral and antimycobacterial [9]. Thiazolidinone possess antibacterial activity due to the presence of β-lactam ring with sulphur atom in it which prevents the biosynthesis of the peptidoglycan polymer essential for the formation of cell wall of bacteria [10].

Prompted by the afore findings and in continuation of our work, related to correlation of biological activities with the structure of the molecule using Hansch analysis [11], in the present study we here in report the QSAR studies of antimicrobial thiazolidinones synthesized by various researchers [12-18].

MATERIALS AND METHODS

Data Set

A dataset of 48 substituted thiazolidinone derivatives has been selected form reported works ([8-9],[12-18]) and is given in Table 1. The biological activity reported in minimum inhibitory concentration (MIC in µg/ml) was converted to pMIC values for eliminating much clustering, rendering it more suitable for QSAR study given in Table 2.

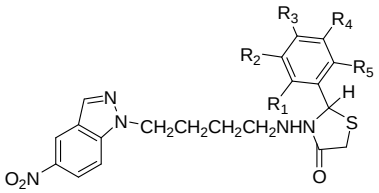
Descriptor generation

The next step in developing a model is generation of the numerical description of the molecular structures. The structures of substituted thiazolidinones were sketched and energy minimized. The energy minimized structures were used to calculate the molecular descriptors like hydrophobic, geometric, electronic and topological characters using the software TSAR 3.3 for windows. The values of descriptors selected for MLR model are presented in Table 3.

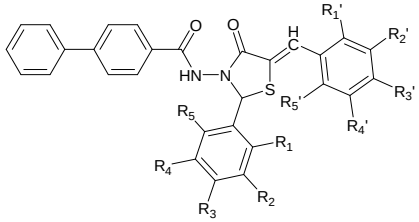
Pearson correlation analysis

Since there was large number of descriptors for each compound, we used Pearson's correlation matrix as a qualitative model (Table 4), in order to select the suitable descriptors for MLR analysis. This technique was adopted for choosing a suitable set of generated descriptors for developing a multiple linear regression model. The best generated MLR model was used to prepare a calibration model, which predicts the antimicrobial activity of thiazolidinone derivatives.

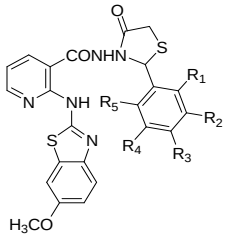
TABLE 1: Molecular structures of thiazolidinones selected for QSAR studies



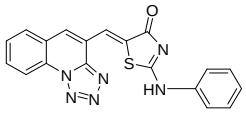
Rajput *et al.*, 2013 (**1-6**)



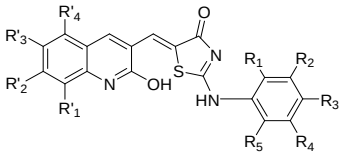
Deep *et al*., 2014 (**7-9**)



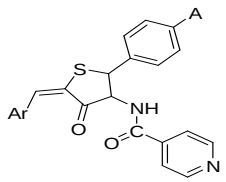
Patel *et al.*, 2010 (**10-11**)



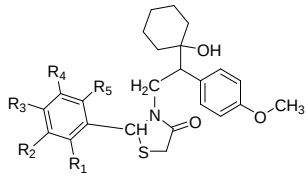
Adhikari *et al.*, 2012 (**12**)



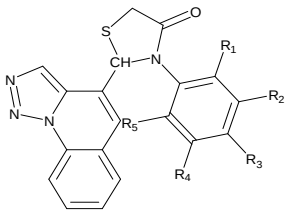
Adhikari *et al*., 2012 (**13-14**)



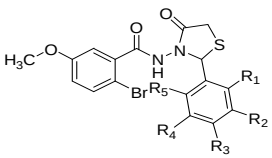
Mudgal *et al.*, 2011 (**15-21**)



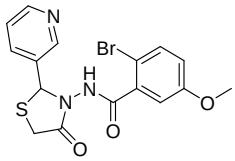
Kortiwala *et al.*, 2015 (**22**)



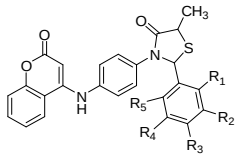
Mistry *et al*., 2010 (**23-29**)



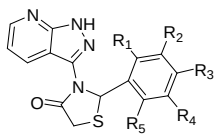
Nandagokula *et al*., 2013 (**30-33, 35-38**)



Nandagokula *et al*., 2013 **(34)**

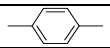
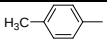
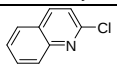


Kumari *et al.,* 2010 (**39-42**)



Kundariya *et al.,* 2014 (**43-48**)

S. No.	Ar	A	R_1	R_2	R_3	R_4	R_5	R'_1	R'_2	R'_3	R'_4	R'_5
1	--	--	2-Cl	H	H	H	H	--	--	--	--	--
2	--	--	H	3-Cl	H	H	H	--	--	--	--	--
3	--	--	H	3-Br	H	H	H	--	--	--	--	--
4	--	--	H	H	4-Br	H	H	--	--	--	--	--
5	--	--	2-NO_2	H	H	H	H	--	--	--	--	--
6	--	--	H	H	4-NO_2	H	H	--	--	--	--	--
7	--	--	H	H	H	H	H	--	--	--	--	--
8	--	--	H	3-Br	H	H	H	H	H	4-Cl	H	H
9	--	--	H	3-Br	H	H	H	H	3-Br	H	H	H
10	--	--	2-Cl	H	H	H	H	--	--	--	--	--
11	--	--	H	H	4-Cl	H	H	--	--	--	--	--

S. No.	Ar	A	R_1	R_2	R_3	R_4	R_5	R'_1	R'_2	R'_3	R'_4	R'_5
13	--	--	H	H	H	H	H	H	H	H	H	H
14	--	--	H	H	4-CH_3	H	H	H	H	H	H	H
15			--	--	--	--	--	--	--	--	--	--
16			--	--	--	--	--	--	--	--	--	--
17			--	--	--	--	--	--	--	--	--	--
18	—H	—Cl	--	--	--	--	--	--	--	--	--	--
19		—Cl	--	--	--	--	--	--	--	--	--	--
20		—Cl	--	--	--	--	--	--	--	--	--	--
21		—Cl	--	--	--	--	--	--	--	--	--	--
22	--	--	H	H	4-CH_3	H	H	--	--	--	--	--
23	--	--	2-NO_2	H	H	H	H	--	--	--	--	--
24	--	--	H	3-NO_2	H	H	H	--	--	--	--	--
25	--	--	H	H	4-NO_2	H	H	--	--	--	--	--
26	--	--	2-Cl	H	H	H	H	--	--	--	--	--
27	--	--	H	3-Cl	H	H	H	--	--	--	--	--
28	--	--	H	H	4-Cl	H	H	--	--	--	--	--
29	--	--	H	H	4-F	H	H	--	--	--	--	--
30	--	--	H	3-Cl	H	H	H	--	--	--	--	--
31	--	--	H	H	4-Cl	H	H	--	--	--	--	--
32	--	--	2-Cl	H	H	H	H	--	--	--	--	--
33	--	--	H	H	4-CH_3	H	H	--	--	--	--	--
35	--	--	H	H	4-F	H	H	--	--	--	--	--
36	--	--	2-OH	H	H	H	H	--	--	--	--	--
37	--	--	H	H	4-OH	H	H	--	--	--	--	--
38	--	--	H	3-OCH_3	4-OH	H	H	--	--	--	--	--
39	 Phenyl	--	--	--	--	--	--	--	--	--	--	--
40	 *p*-Xylene	--	--	--	--	--	--	--	--	--	--	--
41	 Benzaldehyde	--	--	--	--	--	--	--	--	--	--	--
42	 2-chloroquinoline	--	--	--	--	--	--	--	--	--	--	--
43	--	--	2-OH	H	H	H	H	--	--	--	--	--
44	--	--	H	3-NO_2	H	H	H	--	--	--	--	--
45	--	--	H	H	4-OH	H	H	--	--	--	--	--
46	--	--	H	3-OCH_3	4-OH	H	H	--	--	--	--	--
47	--	--	H	H	H	H	H	--	--	--	--	--
48	--	--	H	H	4-OCH_3	H	H	--	--	--	--	--

Multiple linear regression

We have applied multiple linear regression technique to develop the QSAR models to predict the antimicrobial activity of substituted thiazolidinone derivatives selected for the present study. MLR is the classical approach to regression problems in QSARs. MLR assumes the predictor variables, normally called X, to be mathematically independent (orthogonal). Mathematical independence means that the rank of X is K (the number of X-variables). A limitation of MLR is the sensitivity to correlated descriptors. One practical workaround is to use long and lean data matrices-matrices where the number of compounds substantially exceeds the number of chemical descriptors-where interrelatedness among variables usually drops. It has been recommended that the ratio of compounds to variables should be at least 5. MLR is satisfactorily applied in QSAR studies if the main problem of the selection of variables is faced and solved. MLR is usually used to fit the regression model (Eq. 1), which models a response variable, y, as a linear combination of the X-variables, with the coefficients b. The deviations between the data (y) and the model (Xb) are called residuals, and are denoted by e:

$$y = Xb + e \qquad \text{Eq. 1}$$

For many response variables (columns in the response matrix Y), regression normally forms one model for each of the M y-variables, that is, M separate models [19].

Cross validation

The models were cross-validated by the 'leave one out' method where a model is produced with N -1 compounds and the N^{th} compound is predicted. Each compound is excluded from the model derivation and predicted in turn. A sign of the performance of the model is obtained from the cross-validated (or predictive q^2) method, which is express as (Eq. 2),

$$q^2 = (SD - PRESS / SD) \qquad \text{Eq. 2}$$

Where, SD is the sum of squares deviation for each activity from the mean. PRESS (predictive sum-of-squares) is the sum of the squared difference between the actual and that of the expected values when the compound is removed from the fitting process. The model with high q^2 value is said to have high predictability [20].

RESULTS AND DISCUSSION

In the present study, we have performed the quantitative structure activity relationship study of 48 substituted thiazolidinone derivatives by conventional Hansch's analysis using the linear free energy relationship model (LFER) described by Hansch and Fujita [21]. In this approach, structural features of drug molecules were quantified in terms of different parameters and these structural features were correlated to quantified biological activity through equation using regression analysis. Biological activity data determined as MIC values was first transformed into pMIC values (i.e. –log MIC) and used as dependent variable in QSAR study. Data is represented in Table 2.

The different molecular descriptors (independent variables) like log of octanol–water partition coefficient (log P), molar refractivity (MR), Kier's molecular connectivity ($^0\chi$, $^0\chi^v$, $^1\chi$, $^1\chi^v$, $^2\chi$, $^2\chi^v$) and shape (κ_1, $\kappa\alpha_1$, $\kappa\alpha_2$, $\kappa\alpha_3$) topological indices, Randic topological index (R), Balaban topological index (J), Wiener topological index (W), Total energy (Te), energies of highest occupied molecular orbital (HOMO) and lowest unoccupied molecular orbital (LUMO), dipole moment (μ) and electronic energy (Ele. E) [22], [23], [24], [25], [26] and [27] were calculated for thiazolidinone derivatives and the values of selected descriptors are presented in Table 3.

Preliminary analysis was carried out in terms of correlation analysis. A correlation matrix constructed for antimicrobial activity of thiazolidinones against *E. coli* is presented in Table 4. The correlation different parameters against antibacterial and antifungal activity of thiazolidinone derivatives are presented in Table 5.

In general, high colinearity ($r > 0.8$) was observed between different parameters. The high interrelationship was observed between $^1\chi$ and R ($r = 1.000$) and low interrelationship was observed between HOMO and $^0\chi^v$ ($r = 0.003$). The correlation matrix indicated the predominance of topological parameter $\kappa\alpha_3$ ($r = 0.667$, Table 4, Eq. 1) in describing the antimicrobial activity of thiazolidinone derivatives.

Table 2: Antimicrobial activity of thiazolidinone derivatives in µM/ml

Comp. No.	$pMIC_{ec}$	$pMIC_{sa}$	$pMIC_{ca}$
1	2.25	2.65	2.65
2	1.95	2.25	1.95
3	2.69	2.29	2.29
4	1.99	1.99	2.29
5	2.66	2.66	1.66
6	2.26	2.26	1.66
7	1.87	1.87	2.17
8	1.66	1.96	1.96
9	2.00	2.30	2.60
10	0.71	0.71	0.01
11	0.01	0.41	-0.29
12	1.35	1.00	1.37
13	1.26	1.03	1.26
14	1.34	1.00	1.34
15	2.83	3.13	3.13
16	3.13	2.82	3.44
17	2.88	2.88	3.18
18	2.44	2.44	3.04
19	2.54	2.84	3.14
20	2.83	2.83	3.45
21	3.18	3.18	3.18
22	0.23	-0.07	-0.37
23	0.89	0.59	0.29
24	0.89	0.42	-0.01
25	0.59	0.89	0.20
26	0.28	0.41	0.18
27	0.28	0.58	-0.02
28	0.41	0.41	-0.12
29	0.86	0.56	0.26
30	1.55	1.55	2.45
31	1.55	1.55	1.55
32	1.55	1.85	1.85
33	1.53	1.83	1.83
34	1.82	1.82	1.82
35	1.83	1.53	1.83
36	1.53	1.83	2.13
37	1.83	1.53	1.83
38	1.56	1.86	1.56
39	0.03	0.03	-0.27
40	0.34	0.34	0.25
41	0.36	-0.04	0.06
42	0.41	0.31	0.31
43	-0.51	-0.20	-0.51
44	0.23	-0.17	-0.47
45	0.19	0.19	-0.20
46	0.14	0.53	-0.47
47	-0.53	0.68	-0.53
48	-0.19	0.51	-0.49

Table 3. Values for selected descriptors used in regression analysis

Comp.	log p	MR	$^{0}\chi$	$^{0}\chi^{v}$	$^{1}\chi$	$^{1}\chi^{v}$	$^{2}\chi$	$^{2}\chi^{v}$	$\kappa\alpha_1$	$\kappa\alpha_2$	$\kappa\alpha_3$	R	J	W	Te	LUMO	HOMO	μ
1.	3.52	111.52	21.14	15.95	14.48	8.95	13.26	6.70	20.20	8.34	4.14	14.48	1.10	2847.00	-5095.29	-3.77	-8.69	22.36
2.	3.52	111.52	21.14	15.95	14.47	8.95	13.36	6.70	20.20	8.34	4.28	14.47	1.09	2870.00	-5099.87	-2.37	-9.61	12.04
3.	3.80	114.34	21.14	16.75	14.47	9.35	13.36	7.10	20.39	8.46	4.35	14.47	1.09	2870.00	-5079.39	-2.38	-9.62	11.93
4.	3.80	114.34	21.14	16.75	14.47	9.35	13.35	7.10	20.39	8.46	4.35	14.47	1.08	2893.00	-5074.06	-4.04	-8.13	2.93
5.	2.96	114.04	22.72	16.02	15.39	8.94	14.19	6.58	21.42	8.74	4.33	15.39	1.13	3339.00	-5566.26	-3.52	-8.97	11.82
6.	2.96	114.04	22.72	16.02	15.38	8.94	14.24	6.58	21.42	8.74	4.47	15.38	1.09	3477.00	-5567.71	-3.62	-9.86	4.65
7.	2.95	129.52	23.33	17.50	16.69	10.07	14.61	7.21	20.44	8.96	4.32	16.69	1.08	3707.00	-4902.90	-4.77	-8.80	3.54
8.	4.63	142.87	25.07	20.70	17.47	11.67	15.86	8.81	23.24	10.00	5.13	17.47	1.09	4321.00	-5636.41	-2.99	-8.76	7.39
9.	4.90	145.69	25.07	21.50	17.47	12.07	15.87	9.21	23.42	10.12	5.20	17.47	1.10	4292.00	-5613.32	-4.45	-7.99	22.19
10.	5.43	133.56	23.66	18.74	16.53	10.96	14.91	8.31	23.00	9.85	4.76	16.53	1.11	3654.00	-5669.16	-3.23	-8.90	9.29
11.	5.43	133.56	23.66	18.74	16.51	10.96	15.00	8.31	23.00	9.85	4.89	16.51	1.10	3708.00	-5666.39	-2.98	-9.01	6.42
12.	1.75	103.25	18.22	13.88	13.28	8.16	12.01	6.04	16.80	6.99	3.22	13.28	1.08	1922.00	-4152.92	-3.36	-9.66	4.55
13.	1.71	93.47	17.23	12.95	12.19	7.54	11.06	5.54	15.61	6.54	3.32	12.19	1.16	1623.00	-3856.74	-3.48	-6.98	5.74
14.	4.81	103.42	18.10	13.45	12.58	7.79	11.70	5.79	16.43	6.70	3.51	12.58	1.17	1806.00	-3983.86	-3.29	-5.59	4.41
15.	3.68	126.72	21.79	15.90	15.02	8.94	13.45	6.48	20.00	8.61	4.34	15.02	1.29	2744.00	-4688.70	-3.57	-9.19	4.85
16.	2.29	119.24	21.09	15.30	14.52	8.60	13.10	6.27	19.43	8.23	4.12	14.52	1.30	2499.00	-4756.29	-3.54	-9.14	5.86
17.	3.96	141.90	24.24	17.34	16.33	9.61	14.97	7.04	22.51	9.44	4.90	16.33	1.28	3629.00	-5146.93	-3.55	-6.70	6.32
18.	2.07	80.95	15.53	12.14	10.65	6.86	9.51	4.95	14.76	6.30	3.21	10.65	1.45	1083.00	-3724.20	-3.40	-8.95	5.16
19.	2.36	109.06	20.22	15.64	14.11	8.86	12.55	6.52	18.83	8.24	4.17	14.11	1.29	2260.00	-4607.00	-3.46	-8.98	3.08
20.	1.35	101.50	19.51	15.05	13.61	8.52	12.20	6.30	18.25	7.86	3.95	13.61	1.30	2041.00	-4672.11	-3.12	-8.98	6.82
21.	3.06	114.32	21.09	16.84	14.51	9.46	13.18	7.12	20.15	8.70	4.56	14.51	1.28	2505.00	-4981.01	-3.10	-6.13	8.85
22.	5.08	125.48	21.14	15.52	14.50	8.86	13.15	6.48	18.49	7.27	3.50	14.50	1.41	2360.00	-4435.90	-2.55	-8.99	6.37
23.	1.99	101.52	19.25	14.20	13.65	8.28	12.52	6.10	17.11	6.55	2.67	13.65	1.22	1821.00	-4666.88	-3.21	-9.73	3.40
24.	1.99	101.52	19.25	14.20	13.63	8.28	12.59	6.10	17.11	6.55	2.75	13.63	1.17	1878.00	-4671.90	-3.25	-8.87	12.53
25.	1.99	101.52	19.25	14.20	13.63	8.28	12.58	6.10	17.11	6.55	2.75	13.63	1.16	1935.00	-4672.08	-3.30	-8.94	12.59
26.	2.56	99.00	17.67	14.13	12.74	8.28	11.59	6.22	15.93	6.16	2.48	12.74	1.20	1489.00	-4197.64	-2.77	-9.60	3.71
27.	2.56	99.00	17.67	14.13	12.72	8.28	11.69	6.22	15.93	6.16	2.57	12.72	1.18	1508.00	-4200.61	-3.37	-9.03	5.80
28.	2.56	99.00	17.67	14.13	12.72	8.28	11.68	6.22	15.93	6.16	2.57	12.72	1.18	1527.00	-4196.42	-2.65	-9.43	5.03
29.	2.18	94.41	17.67	13.31	12.72	7.88	11.68	5.81	15.60	5.96	2.47	12.72	1.18	1527.00	-4307.71	-2.76	-9.50	5.84
30.	4.22	102.73	17.97	15.11	11.99	8.33	10.86	6.29	17.64	7.37	3.75	11.99	1.47	1509.00	-4446.42	-2.54	-9.20	4.62
31.	4.22	102.73	17.97	15.11	11.99	8.33	10.84	6.29	17.64	7.37	3.75	11.99	1.46	1527.00	-4446.27	-2.44	-8.67	4.90
32.	4.22	102.73	17.97	15.11	12.01	8.33	10.75	6.29	17.64	7.37	3.60	12.01	1.49	1491.00	-4447.38	-2.41	-9.34	4.70
33.	4.14	104.02	17.97	14.41	11.99	7.98	10.84	5.95	17.14	7.05	3.55	11.99	1.46	1527.00	-4193.32	-2.66	-5.25	6.66
34.	2.32	96.60	17.10	13.86	11.60	7.68	10.22	5.66	16.71	7.18	3.54	11.60	1.46	1350.00	-4152.06	-2.90	-9.14	4.27
35.	3.82	98.53	17.97	14.29	11.99	7.92	10.84	5.89	17.29	7.14	3.61	11.99	1.46	1527.00	-4558.94	-2.75	-8.95	4.30
36.	3.27	99.94	17.97	14.32	12.01	7.93	10.75	5.90	17.16	7.06	3.41	12.01	1.49	1491.00	-4392.37	-2.67	-5.67	2.55
37.	3.27	99.94	17.97	14.32	11.99	7.93	10.84	5.90	17.16	7.06	3.56	11.99	1.46	1527.00	-4392.95	-2.66	-5.53	3.94
38.	3.14	107.19	19.55	15.23	12.94	8.34	11.54	6.21	18.94	7.81	3.81	12.94	1.48	1877.00	-4840.43	-2.70	-5.86	5.56
39.	4.92	123.55	21.37	15.91	15.10	9.23	13.77	6.83	18.50	7.38	3.38	15.10	1.05	2846.00	-4736.49	-2.85	-8.96	5.48
40.	5.21	129.44	22.24	16.41	15.49	9.48	14.39	7.08	19.31	7.55	3.55	15.49	1.06	3126.00	-4860.47	-3.40	-8.63	9.49
41.	4.67	130.70	22.95	16.82	16.05	9.68	14.49	7.19	20.07	8.00	3.59	16.05	1.07	3338.00	-5186.62	-2.73	-8.23	3.29
42.	5.90	143.66	24.81	19.05	17.47	11.02	16.29	8.35	22.06	8.66	3.95	17.47	0.96	4238.00	-5698.79	-3.39	-8.55	11.57
43.	0.60	79.77	15.10	11.40	10.75	6.71	9.67	4.91	13.50	5.24	2.16	10.75	1.39	966.00	-3556.37	-3.25	-9.80	6.53
44.	1.35	86.23	16.68	12.25	11.65	7.10	10.68	5.19	15.15	5.91	2.58	11.65	1.34	1267.00	-4090.08	-2.93	-6.46	1.90
45.	0.60	79.77	15.10	11.40	10.74	6.71	9.77	4.91	13.50	5.24	2.25	10.74	1.35	996.00	-3561.61	-3.40	-8.97	5.26
46.	2.25	92.41	16.68	12.30	11.69	7.12	10.46	5.22	15.21	5.95	2.51	11.69	1.35	1265.00	-4010.26	-3.40	-8.95	6.08
47.	1.21	78.45	14.23	10.99	10.34	6.51	9.14	4.71	12.67	5.05	2.07	10.34	1.36	861.00	-3238.60	-3.09	-8.63	5.75
48.	2.64	90.59	15.81	11.90	11.28	6.92	9.93	5.01	14.38	5.77	2.42	11.28	1.33	1153.00	-3679.86	-2.90	-9.09	12.75

Table 4: Correlation matrix for antibacterial activity of thiazolidinones derivatives against *E. coli*

	$pMIC_{ec}$	log p	MR	$^0\chi$	$^0\chi^v$	$^1\chi$	$^1\chi^v$	$^2\chi$	$^2\chi^v$	$\kappa\alpha_1$	$\kappa\alpha_2$	$\kappa\alpha_3$	R	J	W	te	LUMO	HOMO	μ
$pMIC_{ec}$	1.000																		
log p	0.059	1.000																	
MR	0.262	0.776	1.000																
$^0\chi$	0.350	0.680	0.965	1.000															
$^0\chi^v$	0.349	0.738	0.938	0.941	1.000														
$^1\chi$	0.259	0.627	0.953	0.986	0.919	1.000													
$^1\chi^v$	0.244	0.721	0.940	0.940	0.988	0.942	1.000												
$^2\chi$	0.244	0.632	0.942	0.981	0.908	0.995	0.932	1.000											
$^2\chi^v$	0.230	0.736	0.921	0.918	0.986	0.917	0.996	0.912	1.000										
$\kappa\alpha_1$	0.465	0.694	0.922	0.967	0.954	0.924	0.929	0.917	0.918	1.000									
$\kappa\alpha_2$	0.556	0.649	0.882	0.920	0.935	0.870	0.899	0.849	0.887	0.979	1.000								
$\kappa\alpha_3$	0.667	0.623	0.798	0.834	0.866	0.761	0.806	0.740	0.797	0.924	0.973	1.000							
R	0.259	0.627	0.953	0.986	0.919	1.000	0.942	0.995	0.917	0.924	0.870	0.761	1.000						
J	0.067	-0.288	-0.551	-0.626	-0.524	-0.717	-0.608	-0.747	-0.598	-0.514	-0.426	-0.302	-0.717	1.000					
W	0.293	0.649	0.940	0.981	0.925	0.980	0.935	0.976	0.913	0.943	0.901	0.815	0.980	-0.700	1.000				
Te	-0.382	-0.641	-0.858	-0.941	-0.914	-0.906	-0.900	-0.911	-0.895	-0.964	-0.908	-0.823	-0.906	0.570	-0.914	1.000			
LUMO	-0.211	0.108	-0.282	-0.343	-0.255	-0.396	-0.284	-0.377	-0.242	-0.271	-0.296	-0.258	-0.396	0.422	-0.410	0.217	1.000		
HOMO	0.162	0.155	0.020	-0.029	0.003	-0.098	-0.047	-0.096	-0.039	0.012	0.042	0.134	-0.098	0.292	-0.069	0.059	0.052	1.000	
μ	0.101	0.207	0.300	0.347	0.366	0.355	0.370	0.373	0.381	0.351	0.310	0.266	0.355	-0.381	0.385	-0.374	-0.253	-0.115	1.000

LR-model for antibacterial activity of thiazolidinones against E. coli

$pMIC_{ec} = 0.816\ \kappa\alpha_3 - 1.607$ Eq. 1

n = 48 r = 0.667 $q^2 = 0.388$ S = 0.771 F = 36.887

Here and thereafter, n: number of data points, r: correlation coefficient, q^2: cross validated r^2: obtained by leave one out method, s: standard error of the estimate and F: Fischer statistics.

Table 5: Correlation of various molecular descriptors with antibacterial and antifungal activity of thiazolidinone derivatives

Parameters	$pMIC_{ec}$	$pMIC_{sa}$	$pMIC_{ca}$
log p	0.059	0.038	0.082
MR	0.262	0.230	0.243
$^0\chi$	0.350	0.309	0.288
$^0\chi^v$	0.349	0.334	0.339
$^1\chi$	0.259	0.218	0.198
$^1\chi^v$	0.244	0.227	0.231
$^2\chi$	0.244	0.193	0.173
$^2\chi^v$	0.230	0.214	0.220
$\kappa\alpha_1$	0.465	0.441	0.407
$\kappa\alpha_2$	0.556	0.549	0.523
$\kappa\alpha_3$	0.667	0.659	0.649
R	0.259	0.218	0.198
J	0.067	0.119	0.148
W	0.293	0.271	0.242
te	-0.382	-0.339	-0.289
LUMO	-0.211	-0.237	-0.221
HOMO	0.162	0.146	0.202
μ	0.101	0.175	0.071

The addition of topological parameter, second order valence connectivity index $^2\chi^v$ to kiers alpha shape index improved the correlation from 0.667 to 0.833 and also improved the insignificant q^2 value ($q^2 = 0.388$, Eq. 1) to significant one ($q^2 = 0.644$, Eq. 2).

MLR-model for antibacterial activity of thiazolidinones against E. coli

$pMIC_{ec} = -0.851\ ^2\chi^V + 1.6236\ \kappa\alpha_3 - 0.949$ Eq. 2

n = 48 r = 0.833 $q^2 = 0.644$ S = 0.578 F = 51.251

Further the addition of lipophilic parameter log P, to the parameters in Eq. 2 improved the correlation value to the maximum (r = 0.866, Eq. 3).

MLR-model for antibacterial activity of thiazolidinones against E. coli

$pMIC_{ec}$ = -0.268 log P - 0.615 $^2\chi^V$ + 1.666 $\kappa\alpha_3$ + 0.143 Eq.3

n = 48 r = 0.866 q^2 = 0.697 S = 0.529 F = 44.096

The cross-validation of Eq. 3 was subsequently checked by employing ''leave one out'' (LOO) method. The $q^2 > 0.5$ qualifies a QSAR model to be a valid one [28]. In equation 3, q^2 is more than 0.5, which shows that the developed model is a valid one. As the observed and predicted values are close to each other, the QSAR model for antibacterial activity against *E. coli* is a valid one (Table 6, Fig. 1) [29]. To determine the existence of the systemic error in the model development we have plotted pMICec observed against pMICec residual values (Fig. 2). The propagation of residuals on both sides of zero indicated that there is no systemic error in the development of QSAR model [30].

As in case of *E. coli*, the kiers 3rd order alpha shape index contributed significantly to the antibacterial activity of thiazolidinones against *S. aureus* (Table 5, Eq. 4).

LR-model for antibacterial activity of thiazolidinones against S. aureus

$pMIC_{sa}$ = 0.792 $\kappa\alpha 3$ – 1.474 Eq. 4

n = 48 r = 0.658 q^2 = 0.384 S = 0.766 F = 35.249

The addition of topological parameter, second order valence connectivity index, $^2\chi^v$, to the kiers alpha shape index improved the correlation from 0.658 to 0.836 (Eq. 5) and further addition of the lipophilic parameter log P to $^2\chi^V$ and $\kappa\alpha_3$ improved the correlation significantly (Eq. 6). The validity of Eq. 6 is evidenced by its high q^2 value (q^2 = 0.714) and well the low residual values depicted by Table 6.

MLR-models for antibacterial activity of thiazolidinones against S. aureus

$pMIC_{sa}$ = -0.864 $^2\chi^V$ + 1.612 $\kappa\alpha_3$ + 1.1216 Eq. 5

n = 48 r = 0.836 q^2 = 0.653 S = 0.564 F = 52.503

$pMIC_{sa}$ = -0.279 log P - 0.618 $^2\chi^V$ + 1.656 $\kappa\alpha_3$ + 0.281 Eq.6

n = 48 r = 0.873 q^2 = 0.714 S = 0.508 F = 47.015

The antifungal activity of thiazolidinones against *C. albicans* is also governed by kiers 3rd order alpha shape index (Table 5, Eq. 7).

LR-model for antifungal activity of thiazolidinones against C. albicans

$pMIC_{ca}$ = 0.999 $\kappa\alpha_3$ – 2.329 Eq. 7

n = 48 r = 0.648 q^2 = 0.368 S = 0.993 F = 33.420

The addition of topological parameter, Wiener index (W) to the kiers alpha shape index improved the correlation (Eq. 8) and further addition of the lipophilic parameter log P to W and $\kappa\alpha_3$ improved the correlation significantly (Eq. 9). The validity of Eq. 9 is evidenced by its q^2 value (q^2 = 0.681) and well the low residual values depicted in Table 6 in case of *C. albicans*.

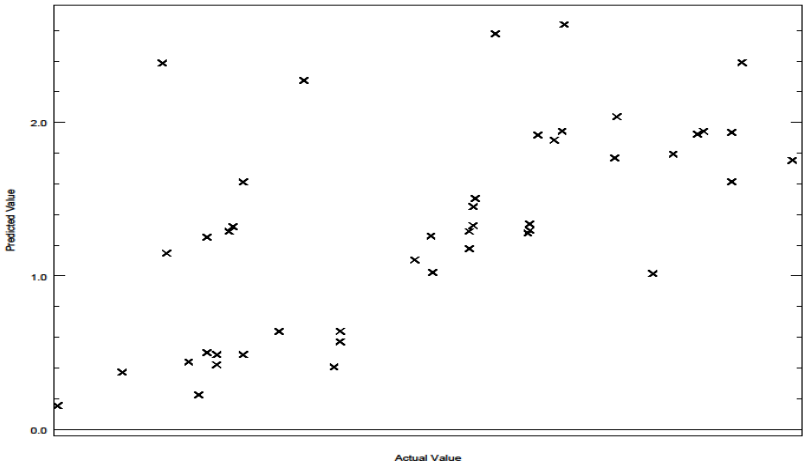


Figure 1. Comparison of observed and predicted activity of antibacterial activity of thiazolidinones using Eq. 3

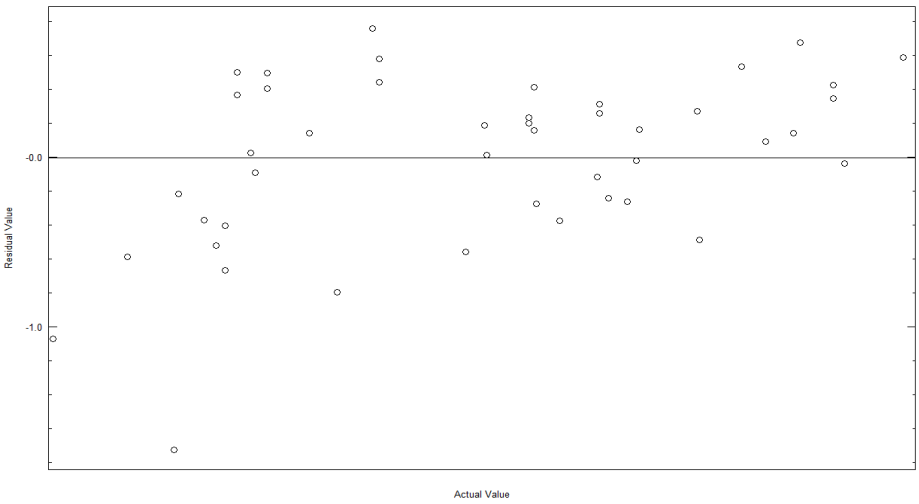


Figure 2. Comparison of observed and residual activity of antibacterial activity of thiazolidinones using Eq. 3

MLR-model for antifungal activity of thiazolidinones against C. albicans

$pMIC_{ca}$ = 2.0696 $\kappa\alpha_3$ - 0.001 W – 3.645 Eq. 8

n = 48 r = 0.815 q^2 = 0.618 S = 0.763 F = 44.647

$pMIC_{ca}$ = -0.351 log P + 2.226 $\kappa\alpha_3$ - 0.0009 W – 3.536 Eq.9

n = 48 r = 0.859 q^2 = 0.681 S = 0.682 F = 41.355

Summarizingly, from the developed equations 1-9, it was evident that the antimicrobial activity of thiazolidinones are mainly governed by the topological parameters, kiers 3rd order alpha shape index ($\kappa\alpha_3$) and second order valence connectivity index ($^2\chi^v$) along with the lipophilic parameter, log of octanol water partition coefficient (log P).

According to Kier, the shape of a molecule may be partitioned into attributes, each describable by the count of bonds of various path lengths. The basis for devising a relative index of shape is given by the relationship of the number of path of length *l* in the molecule *i*, ^lP_i, to some reference values based on molecules with a given number of atoms, *n*, in which the values of ^lP are maximum and minimum, $^lP_{max}$ and $^lP_{min}$ [31]. The modified kappa shape indices are given by:

$\kappa\alpha_1 = (n + \alpha)(n + \alpha - 1)^2/(^1P_i + \alpha)^2$

$\kappa\alpha_2 = (n + \alpha - 1)(n + \alpha - 2)^2/(^2P_i + \alpha)^2$

$\kappa\alpha_3 = (n + \alpha - 1)(n + \alpha -3)^2/(^3P_i + \alpha)^2$ n is odd

$\kappa\alpha_3 = (n + \alpha - 3)(n + \alpha -2)2/(^3P_i + \alpha)^2$ n is even.

The molecular connectivity index, an adjacency based topological index proposed by Randic is denoted by χ and is defined as sum over all the edges (ij) as per following equation

$$\chi = \sum_{i=1} (V_i V_j)^{-1/2}$$

Where V_i and V_j are the degrees of adjacent vertices i and j and n is the number of vertices in a hydrogen suppressed molecular structure [32]. The topological index, χ signifies the degree of branching, connectivity of atoms and unsaturation in the molecule which accounts for variation in activity [33].

Table 6. Observed, predicted and residual antimicrobial activities of thiazolidinones

Comp.	$pMIC_{ec}$			$pMIC_{sa}$			$pMIC_{ca}$		
	Obs.	Pre. (Eq. 3)	Res.	Obs.	Pre. (Eq. 6)	Res.	Obs.	Pre. (Eq. 9)	Res.
1.	2.25	1.97	0.28	2.65	2.01	0.64	2.65	1.82	0.83
2.	1.95	2.21	-0.26	2.25	2.25	0.00	1.95	2.11	-0.16
3.	2.69	2.01	0.68	2.29	2.04	0.25	2.29	2.17	0.12
4.	1.99	2.01	-0.02	1.99	2.04	-0.05	2.29	2.15	0.14
5.	2.66	2.51	0.15	2.66	2.56	0.10	1.66	1.99	-0.33
6.	2.26	2.75	-0.49	2.26	2.79	-0.53	1.66	2.17	-0.51
7.	1.87	2.11	-0.24	1.87	2.15	-0.28	2.17	1.63	0.54
8.	1.66	2.03	-0.37	1.96	2.04	-0.08	1.96	2.29	-0.33
9.	2.00	1.83	0.17	2.30	1.84	0.46	2.60	2.38	0.22
10.	0.71	1.50	-0.79	0.71	1.51	-0.80	0.01	1.78	-1.77
11.	0.01	1.73	-1.72	0.41	1.74	-1.33	-0.29	2.04	-2.33
12.	1.35	1.33	0.02	1.00	1.40	-0.40	1.37	1.26	0.11
13.	1.26	1.82	-0.56	1.03	1.89	-0.86	1.26	1.77	-0.51
14.	1.34	1.15	0.19	1.00	1.18	-0.18	1.34	0.93	0.41
15.	2.83	2.40	0.43	3.13	2.44	0.69	3.13	2.31	0.82
16.	3.13	2.54	0.59	2.82	2.59	0.23	3.44	2.53	0.91
17.	2.88	2.91	-0.03	2.88	2.94	-0.06	3.18	2.64	0.54
18.	2.44	1.90	0.54	2.44	1.97	0.47	3.04	1.89	1.15
19.	2.54	2.44	0.10	2.84	2.50	0.34	3.14	2.83	0.31
20.	2.83	2.48	0.35	2.83	2.54	0.29	3.45	2.90	0.55
21.	3.18	2.54	0.64	3.18	2.58	0.60	3.18	3.24	-0.06
22.	0.23	0.63	-0.40	-0.07	0.66	-0.73	-0.37	0.31	-0.68
23.	0.89	0.30	0.59	0.59	0.37	0.22	0.29	0.03	0.26
24.	0.89	0.44	0.45	0.42	0.51	-0.09	-0.01	0.16	-0.17
25.	0.59	0.44	0.15	0.89	0.51	0.38	0.20	0.11	0.09
26.	0.28	-0.23	0.51	0.41	-0.16	0.57	0.18	-0.27	0.45
27.	0.28	-0.09	0.37	0.58	-0.03	0.61	-0.02	-0.11	0.09
28.	0.41	-0.09	0.50	0.41	-0.03	0.44	-0.12	-0.13	0.01
29.	0.86	0.10	0.76	0.56	0.17	0.39	0.26	-0.21	0.47
30.	1.55	1.39	0.16	1.55	1.42	0.13	2.45	1.94	0.51
31.	1.55	1.39	0.16	1.55	1.42	0.13	1.55	1.92	-0.37
32.	1.55	1.13	0.42	1.85	1.17	0.68	1.85	1.61	0.24
33.	1.53	1.29	0.24	1.83	1.33	0.50	1.83	1.51	0.32
34	1.82	1.93	-0.11	1.82	2.00	-0.18	1.82	2.28	-0.46
35.	1.83	1.51	0.32	1.53	1.55	-0.02	1.83	1.75	0.08
36.	1.53	1.32	0.21	1.83	1.37	0.46	2.13	1.54	0.59
37.	1.83	1.56	0.27	1.53	1.61	-0.08	1.83	1.83	0.00
38.	1.56	1.83	-0.27	1.86	1.88	-0.02	1.56	2.12	-0.56
39.	0.03	0.25	-0.22	0.03	0.28	-0.25	-0.27	-0.37	0.10
40.	0.34	0.31	0.03	0.34	0.33	0.01	0.25	-0.34	0.59
41.	0.36	0.45	-0.09	-0.04	0.48	-0.52	0.06	-0.26	0.32
42.	0.41	0.00	0.41	0.31	0.01	0.30	0.31	-0.73	1.04
43.	-0.51	0.56	-1.07	-0.20	0.65	-0.85	-0.51	0.17	-0.68
44.	0.23	0.90	-0.67	-0.17	0.98	-1.15	-0.47	0.57	-1.04
45.	0.19	0.71	-0.52	0.19	0.80	-0.61	-0.20	0.34	-0.54
46.	0.14	0.51	-0.37	0.53	0.58	-0.05	-0.47	0.09	-0.56
47.	-0.53	0.38	-0.91	0.68	0.47	0.21	-0.53	-0.14	-0.39
48.	-0.19	0.39	-0.58	0.51	0.46	0.05	-0.49	-0.13	-0.36

Log P is the logarithm of the ratio of the concentrations of the un-ionized solute in two solvents, which is calculated according to following equation, where o is octanol and w is un-ionized water.

log P o/w = log ([solute o] / [solute w])

The hydrophobic effect is the major driving force for the binding of drugs to their receptor targets in pharmacodynamics, and is based on the log P contribution of each atom. Each atom in a molecule contributes to the log P by the amount of its atomic parameter multiplied by the degree of exposure to the surrounding solvent [34].

CONCLUSION

In conclusion, in the present study, we have performed the quantitative structure activity relationship study of antimicrobial substituted thiazolidinone derivatives by Hansch's analysis. The QSAR models developed indicated that the antimicrobial activity of thiazolidinones are mainly governed by the topological parameters, kiers 3rd order alpha shape index ($\kappa\alpha_3$) and second order valence connectivity index ($^2\chi^v$) along with the lipophilic parameter, log of octanol water partition coefficient (log P).

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