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QSAR study on inhibition of *E.coli* and *S.enteritidis* by 1,2,4-triazoles

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ABSTRACT

The paper describes a QSAR study on inhibition of *E.coli and S.enteritidis by* 1,2,4-triazoles using some physicochemical descriptors. The 1,2,4-triazole discussed consists of 18 derivatives with N^1-aryl or N^1-heteroaryl substituted rings as well as having aminomethyl or aminoethyl unit. The 20 best models were selected for the discussion. Initial regression analysis indicated that η plays a dominating role in modelling the activity; the physicochemical descriptors: (ST) and (α) are negatively correlated with activity and (η) and (D) are positive correlated in all proposed models (Eq. 1-20). The correlation coefficients in all the cases were found to be 0.82-0.98, and the standard deviation below 0.28. Good cross-validation Q^2 values were obtained (Q^2>0.72). The ratio PRESS/SSY ranges between 0.038-0.317 indicating that all proposed models are reliable QSAR models. The statistically significant result for bacteria inhibitory activity against *S.enteritidis* of choesn triazole derivatives, using eight descriptor have not been obtained.

KEYWORDS

QSAR;
1,2,4-Triazole;
Surface tension;
Index of refraction;
Q^2 values.

INTRODUCTION

The investigation of the quantitative structure activity/property relationships (QSAR/QSPR) of the substances is an important issue in the modern chemistry, biochemistry, medicinal chemistry, as well as in drug discovery[1-6]. This information is composed of mathematical equations relating the chemical structure of compounds to a wide variety of their physical, chemical, biological and technological properties. Once a correlation between structure and activity/property is found, any number of compounds, including those not yet synthesized, can be readily screened on the computer in order to select structure with the desired properties. It is then possible to select the most promising compounds to synthesized and test in the laboratory.

The recent findings that 1,2,4-triazole nucleus is associated with diverse biological activities such as: analgetic, antiasthmatic, diuretic, antihypertensive, antibacterial, antifungal and antiinflammatory properties[7-14], prompt us to synthesise some new 1,2,4-triazole derivatives and to investigate their antibacterial and antifungal activities. Mannich reaction (aminomethylation) of some heterocycles (benzotriazoles, benzimidazoles), formaldehyde and aliphatic and aromatic amines is a well known process[15]. N-hydroxymethyl derivatives of heterocycles under the influence of amines, can also give corresponding Mannich bases[15,16]. It is also known

that some aminomethyl heterocycles possess biological and corrosion-inhibition activity, they can be used as additives in greasy oils as well as photopolymerizing paints for improving adhesion[17-22].

Consequently, spurred by the need of new antimicrobial agents and the fact that many new effective antimicrobial drugs possess heterocyclic rings in their structure, such as 1,2,4-triazole ring, we synthesized and investigated some new 1,2,4-triazole derivatives during the last few years[23-26]. A group of 18 N^1-aryl/heteroarylaminomethyl/ethyl-1,2,4-triazoles was synthesized (SCHEME 1; TABLE 1) by condensation of hydroxymethyl derivative of 1,2,4-triazole and appropriate aromatic/heteroaromatic amines and by reaction of 1,2,4-triazole, acetaldehyde and few aromatic/heteroaromatic amines. All the synthesized compounds were screened for their antibacterial and antifungal activities against *Escherichia coli* and *Salmonella enteritidis*[23].

EXPERIMENTAL

Materials

All the N^1-aryl/heteroarylaminomethyl/ethyl-1,2,4-triazole derivatives (1-18), (SCHEME 1; TABLE 1), used in this study were previously synthesized and reported elsewhere[24]. These compounds are of considerable synthetic interest as substances with potential biological activity. Melting points, time of reaction, yield and elemental analysis of those compounds are given in TABLE 1.

Microbiology

The filter paper disc method[27] was performed in Sabouraud dextrose broth and Mueller Hinton broth. These agar media were inoculated with 0.5 mL of the 24 h liquid cultures containing 10^7 microorganisms/mL. Filter paper discs (5 mm diameter) saturated with each compound solution (1 mg/mL; 5 mg/mL and 10 mg/mL DMSO) were placed on the indicated agar mediums. The incubation time was 24 h at 37^0C. Discs with DMSO were used as control. The diameter of zone inhibition [mm] was measured. The tests were repeated 3 times to confirm the findings.

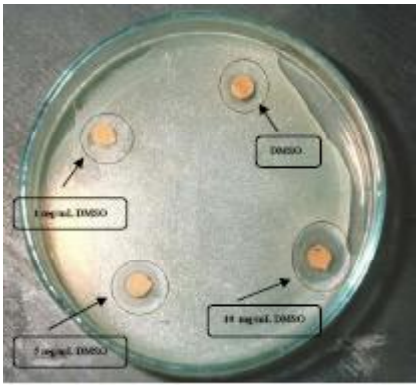
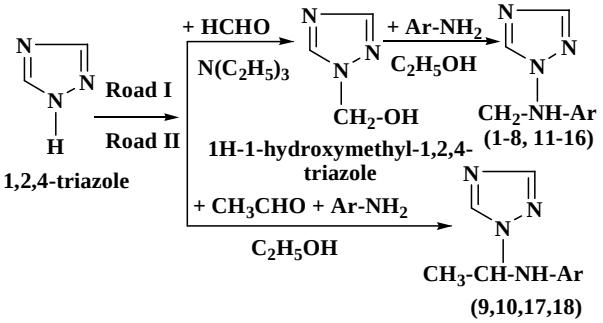


Figure 1: Filter paper discs saturated with compound (10) solution (1 mg/mL; 5 mg/mL and 10 mg/mLDMSO)



SCHEME 1: N^1-aryl/heteroarylaminomethyl/ethyl-1,2,4-triazoles (1-18)

TABLE 1: N^1-aryl/heteroarylaminomethyl/ethyl-1,2,4-triazole derivatives (1-18) used in the present study

	Compound																	
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18
R	H	H	H	H	H	H	H	H	CH_3	CH_3	H	H	H	H	H	H	CH_3	CH_3
Ar	-C_6H_4-$COOC_2H_5$ (p)	-C_6H_4-COOH (p)	-C_6H_4-COOH (o)	-C_6H_4-Cl (p)	-C_6H_4-Br (p)	-C_6H_4-CH_3 (p)	-C_6H_4-C_6H_5 (p)	-C_6N_4-NH-CH_2-	-C_6H_4-$COOC_2H_5$ (p)	-C_6H_4-NO_2 (p)	2-Pyridyl-	4-Methyl-2- pyridyl -	6- Methyl-2- pyridyl -	5-Chloro-2-pyridyl-	2-Pyrimidyl-	1,2,4-Triazole-4-yl	6-Methyl-2-pyridyl-	2-Thiazolyl-

QSAR study for antibacterial activity of *S.enteritidis*

TABLE 2: Experimental obtained zone of inhibition [mm] against: *E.coli* and *S.enteritidis*, and calculated log1/C values

Comp. no:	*E coli*					*S.enteritidis*				
	Zone of inhibition [mm]			MIC[a]	log 1/ C	Zone of inhibition [mm]			MIC[a]	log 1/ C
	1 [mg/mL]	5 [mg/mL]	10[mg/mL]			1[mg/mL]	5 [mg/mL]	10[mg/mL]		
1	6	6	6	4.061E-6	5.391	6	7.5	9.5	4.061E-6	5.391
2	-	-	6	4.583E-5	4.338	6	6	6.5	4.583E-6	5.339
3	-	-	-	-	-	-	-	-	-	-
4	5.5	6	6	4.793 E-6	5.319	6	6	6.5	4.793E-6	5.319
5	6	6	6	3.951E-6	5.403	5.5	5.5	6	3.951E-6	5.403
6	-	-	-	-	-	-	6	7.5	2.656E-5	4.576
7	5.5	5.5	5.5	3.995E-6	5.398	-	6	6	1.998E-5	4.699
8	-	5.5	6.5	1.849E-5	4.732	-	-	6	3.842E-5	4.415
9	6.5	6.5	6.5	3.842E-6	5.415	-	7	7	1.921E-5	4.716
10	7	-	5.5	4.287E-5	4.367	-	-	-	-	-
11	5.5	5.5	6	5.708E-6	5.243	6	6	6.5	5.708E-6	5.244
12	5.5	5.5	6	5.399E-6	5.276	5.5	6	6	5.399E-6	5.267
13	5.5	5.5	6	5.399E-6	5.276	-	-	7.5	5.399E-5	4.267
14	-	-	-	-	-	-	-	-	-	-
15	-	-	-	-	-	-	-	-	-	-
16	-	6	6.5	3.027E-5	4.518	6	6	7	6.055E-6	5.218
17	-	-	-	-	-	-	-	-	-	-
18	-	-	-	-	-	-	-	-	-	-

[a]**Minimum inhibition concentration**

In our work, the chosen model is based on the *in vitro* antimicrobial activity of certain N^1-aryl/heteroaryl aminomethyl/ethyl-1,2,4-triazoles derivatives (1-18), (SCHEME 1), against *Escherichia coli* and *Salmonella enteritidis*, express as zone of inhibition [mm], using 3 concentrations: 1 mg/mL, 5 mg/mL and 10 mg/mL DMSO (TABLE 2). C is the minimum inhibition concentration (MIC) value expressed in molar concentration units (TABLE 2).

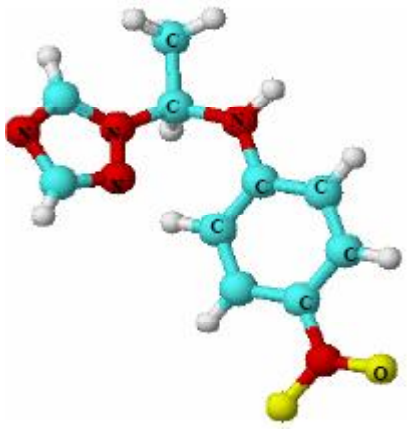


Figure 2: The most active compound (10) against *E.coli*

QSAR analysis

A. Descriptors

To obtain the quantitative effect of the triazole derivatives structural parameters on their biological activities, QSAR analysis with the physicochemical descriptors was operated. The Surface Tension (ST), Molar Refraction (MR), Molar Volumen (MV), Parachor (Pc), Index of Refracttivity (η); Density (D), Polarizability (α) and logP, are the properties that can be calculated for each molecule, Therefore, these data were used to determine the QSAR models. Physicochemical parameters used in this study were calculated using ACD Labs software[28].

Surface tension (ST) or Inter facial tension is the cumulative effect of the different intra and intermolecular forces of two different surfaces. This physicochemical parameter is directly related to parachor (Pc) which in turn is related to molar volume (MV). Thus, we can treat (ST), as a steric parameter. The relationships between (MV), (Pc) and (ST) could be only expressed through the expression for parameter. These three forms are expressed by following equations:

Molar Volumen = MV = MW/d

$Pc = (MW/d)ST^{1/4}$

$Surface\ Tension = ST = (Pc/MV)^4$

Molar Refractivity (MR) is one of the oldest and most successful additive-constitutive physicochemical properties of a compound, which has a strong correlation with the molecular polarizability. Thus, the MR is known to be a measure of the polarizability and is calculated by well-documented Lorentz-Lorenz equa-

tion[30].

Also, the Polarizability (α) of a molecule is in the focus of our research. The electrons and nuclei of a molecule are mobile and free to move to a limited degree. Thus, small charge displacements can take place in polar or non-polar (apolar) molecules in an electric field, and which results in a dipole being introduced into the molecule, in addition to the permanent one that may already exist. Thus, the polarizability of a molecule is a measure of its overall electronic charge distribution that can be distorted by an external electric field[30].

The most common descriptor used in QSAR studies is logP, which is the natural log of the octanol/water partition coefficient:

$$\mathbf{logP = log[drug]_{otanol} - log[drug]_{water}}$$

The octanol/water partition coefficient is measured by placing the compound in a separatory funnel with octanol and water. Octanol and water are immiscible, and the compound under study partitions between the two phases. The concentration of the compound in the two phases and hence the partition coefficient are a measure of the hydrophobic-hydrophilic character of the compound. The more hydrophobic, the larger are P and logP. LogP is a common descriptor in QSAR studies because drugs must often cross membranes. Cell membranes are composed of phospholipids, which have hydrophobic tails that produce a very hydrophobic environment in the middle of the membrane bilayer. In the absence of active membrane transport, more hydrophobic drugs have an easier time getting through a membrane.

B. Multiple linear regression

The mathematical foundation of the quantitative structure-activity relationship is based on the principle of polylinearity. Multiple linear regression is a common method used in QSAR studies. The QSAR equations were obtained by forward stepwise multiple regression techniques the multilinear forms:

$$\mathbf{Log1/C = a_0 + a_1D_1 + a_2D_2 + a_3D_3 + ... + a_nD_n}$$

where D_1, D_2, D_3 and D_n are descriptors, $\eta$is number of descriptors. The intercept (a_0) and regression coefficient of the descriptors were determined using the least squared method.

C. Statistical analysis

The statistical evaluation of the data was performed using Origin program package[31]. To test the quality of the regression equations, the following statistical parameters were used:

- R - Correlation coefficient;
- SD - Standard deviation;
- F-test - Fisher test for singnificance of the equation
- PRESS - Predictive residual error Sum of Squares $PRESS=\Sigma(Y_{pred}-Y_{exp})^2$
- SSY - Sum of squares of deviation of the experimental values from their mean $SSY=\Sigma(Y_{exp}-Y_{mean})^2$
- where Y_{pred}-predicted, Y_{exp}-experimental and Y_{mean}-mean values of the target properties (log1/C) respectively.
- Q^2 – Cross-validation squared correlation coefficient $Q^2=1-PRESS/SSY$

RESULTS AND DISCUSSION

In the earlier part of QSAR study on 1,2,4-triazole were mostly based on the Hansch's approach. In our previous study[32-34], we have shown that some electronic and steric descriptors can be successfully used for this purpose. Literature shows that no QSAR study for N^1-aryl/heteroarylaminomethyl/ethyl-1,2,4-triazole derivatives using physicochemical properties such Surface tension (ST), Molar Refraction (MR), Molar Volume (MV), Parachor (Pc), Index of Refractivity (η); Density (D) and Polarizability (α) have been reported.

In view of this and in persistence to our earlier work, in the present study, an attempt has been made to find structural requirement for inhibition of different bacterial strains using QSAR approach on 1,2,4-triazole derivatives with several steric and one hydrophobic descriptors. The statistical quality of the regression equation was justified by parameters like: R; SD; F-test; Q^2, PRESS, SSY and PRESS/SSY.

After the applying the filter paper disc method[27], the compounds 14, 15, 17 and 18 do not inhibit the growth of the chosen microorganism[23]. From the obtained data, first were calculated MIC values and then the log 1/C values (TABLE 2).

QSAR study for antibacterial activity of *E.coli*

It was important for further analysis to find correlation matrix for used descriptors and their correlation with the activity (TABLE 4). The results (TABLE 4) show that some of them are mutually correlated. Thus,

if a combination of them is present in the regression expression, then the model may suffer from the defect due to collinearly (TABLE 5; Eq. 6, 12 and 20). Data also show that none of the chosen descriptors correlate well with the activity (log1/C). From this we conclude that no single variable model is capable of modelling the activity and that the refereed descriptors can be combined to obtain a statistically significant multiparametric model for modelling the activity.

All physicochemical descriptors (TABLE 3) were selected as independent variable and log1/C as dependent values and stepwise multiple linear regression method was used, with following equations obtained (TABLE 5). Among the several models generated 20 best models were selected for the discussion. The selection was based on the previously mentioned statistical parameters. The statistically significant results for bacteria inhibitory activity against *E.coli* of triazole derivatives, using two to eight descriptors, have been summarized in TABLE 5.

TABLE 3: Physicochemical parameters of triazole derivatives studied ([a] Ref. [28]; [b] Ref. [29])

Comp.	MR[a]	MV[a]	Pc[a]	η[a]	ST[a]	D[a]	α[a]	logP[b]
1	67.92	196.6	518.7	1.607	48.4	1.25	26.29	1.2981
2	58.35	156.0	435.5	1.670	60.6	1.39	23.13	0.4579
3	58.35	156.0	435.5	1.670	60.6	1.39	23.13	1.4690
4	56.64	154.6	414.4	1.653	51.5	1.34	22.45	1.2210
5	59.59	157.9	429.1	1.678	54.5	1.60	23.62	1.4665
6	56.46	160.5	416.7	1.620	45.3	1.17	22.38	1.1238
7	77.14	213.4	562.5	1.642	48.1	1.17	30.58	2.3405
8	76.43	190.1	540.0	1.736	65.0	1.42	30.3	-1.6900
9	72.34	211.8	549.8	1.598	45.3	1.22	28.68	1.7157
10	62.12	166.0	462.2	1.671	60.0	1.40	24.62	1.3895
11	50.48	133.9	366.7	1.677	56.2	1.30	20.01	0.0301
12	54.90	149.2	397.8	1.657	50.5	1.26	21.76	0.5774
13	54.90	149.2	397.8	1.657	50.5	1.26	21.76	0.5774
14	55.08	143.2	395.6	1.695	58.1	1.46	21.83	0.6746
15	48.93	122.5	347.9	1.730	64.9	1.43	19.39	-1.4763
16	43.66	101.1	304.8	1.811	82.5	1.63	17.31	2.1800
17	59.33	164.4	428.9	1.641	46.2	1.23	23.52	0.9950
18	53.50	131.1	370	1.748	62.8	1.48	21.21	0.7441

TABLE 4: Correlation matrix for the chosen parameters (*E. coli*)

	MR	MV	Pc	η	ST	D	α	logP
MR	1.0000							
MV	0.9623	1.0000						
Pc	0.9893	0.9853	1.0000					
η	-0.4721	-0.6806	-0.5652	1.0000				
ST	-0.4542	-0.6419	-0.5139	0.9492	1.0000			
D	-0.4274	-0.5853	-0.4816	0.7913	0.8048	1.0000		
α	0.9992	0.9575	0.9857	-0.4619	-0.4486	-0.4225	1.0000	
logP	-0.12827	0.0086	-0.0624	-0.1709	-0.0827	0.0066	-0.1329	1.0000

TABLE 5: Regression parameters and the quality of correlation of log 1/C with chosen descriptors in multivariate regressions for substituted 1,2,4-triazoles (*E.coli*)

	Equations	R	SD	F
1.	Log1/C=-22.223+0.138MR+0.1014MV-0.0281Pc+18.2188η-0.0754ST+0.968D-0.5268α-0.0912logP	0.9809	0.1614	9.5241
2.	Log1/C=-63.4878-0.2730MR+0.0197MV+0.0544Pc+48.5336η-0.2368ST+0.4802D-0.4494 α	0.9546	0.1530	12.0155
3.	Log1/C=-100.3453-0.8128MR-0.0203MV+0.1190Pc+74.768η-0.3614ST+0.3343D	0.9684	0.1604	12.5385
4.	Log1/C=-108.8421-0.8925MR-0.0322MV+0.1343Pc+81.0781η-0.3899ST	0.9664	0.1509	16.9247
5.	Log1/C=3.1534+0.1239MR+0.0936MV-0.0519Pc+1.2497η	0.9220	0.2099	9.9527
6.	Log1/C=5.3668+0.1379MR+0.0859MV-0.0517Pc	0.9208	0.1980	14.8656
7.	Log1/C=-35.0031+0.0822MV-0.0046Pc+27.4598η-0.1249ST+0.8701D-0.4793α-0.0078logP	0.9807	0.1404	14.3731
8.	Log1/C=-39.8008+0.0459MV+0.0139Pc+31.6324η-0.1559ST+0.5801D-0.5739 α	0.9758	0.1404	16.6112
9.	Log1/C=-11.6469+0.0798MV-0.0296Pc+11.3641η-0.0562ST+0.7259D	0.9441	0.1934	9.8331
10.	Log1/C=-11.1472+0.0749MV-0.0280Pc+11.5855η-0.0528ST	0.9331	0.1953	11.7652
11.	Log1/C=-4.5852+0.1082MV-0.0402Pc+5.8684η	0.8780	0.2435	8.9827
12.	Log1/C=5.51864+0.0634MV-0.02438Pc	0.8264	0.2696	9.6896
13.	Log1/C=-47.8311+0.0411Pc+38.2893η-0.2056ST+0.3076D-0.7609α +0.0453logP	0.9631	0.1728	10.6782
14.	Log1/C=-49.4467+0.0439Pc+39.4211η-0.2109ST+0.3878D-0.8166α	0.9577	0.1688	13.2869
15.	Log1/C=-5.9506-0.0005Pc+9.3916η-0.0885ST+0.3966D	0.8590	0.2779	4.9268
16.	Log1/C=-5.8659-0.0006Pc+9.5839η-0.0854ST	0.8557	0.2631	7.2667
17.	Log1/C=-8.8251+11.4182η-0.0956ST+0.2195D-0.0093α +0.0889logP	0.8898	0.2710	4.4197
18.	Log1/C=-6.3767+9.7716η-0.0904ST+0.3750D-0.0139α	0.8621	0.2751	5.0671
19.	Log1/C=-7.0289+9.8446η-0.0892ST+0.4698D	0.8544	0.2639	7.2095
20.	Log1/C=-7.1208+10.1607η-0.0856ST	0.8499	0.2529	11.6182

Initial regression analysis indicated that out of the 8 molecular descriptors used, (η) in combination with other physicochemical descriptors, plays a dominating role in modelling the activity (the greatest value of regression coefficient of the η). All equation (1-20) shows that the physicochemical descriptors: (ST) and (α) are negatively correlated with activity, which indicates that the activity goes on decreasing with the increasing value of (ST) and (α). The positive coefficients of (η) and (D), in all cases, indicates that the activity goes on increasing with the increase in the magnitude of those descriptors

TABLE 6: Cross-validation parameters, calculated for the proposed models: Q^2, PRESS and PRESS/SSY

Eq.	Parameters	Q^2	PRESS	PRESS/SSY
1.	MR, MV, Pc, η, ST, D, α, logP	0.962	0.078	0.038
2.	MR, MV, Pc, η, ST, D, α	0.954	0.094	0.046
3.	MR, MV, Pc, η, ST, D	0.937	0.129	0.063
4.	MR, MV, Pc, η, ST	0.934	0.137	0.067
5.	MR, MV, Pc, η	0.851	0.308	0.149
6.	MR, MV, Pc	0.848	0.314	0.152
7.	MV, Pc, η, ST, D, α, logP	0.962	0.076	0.038
8.	MV, Pc, η, ST, D, α	0.952	0.099	0.048
9.	MV, Pc, η-, ST, D	0.891	0.224	0.109
10.	MV, Pc, η, ST	0.870	0.267	0.129
11.	MV, Pc, η	0.771	0.473	0.229
12.	MV, Pc	0.683	0.654	0.317
13.	Pc, η, ST, D, α, logP	0.928	0.149	0.072
14.	Pc, η-, ST, D, α	0.917	0.171	0.083
15.	Pc, η, ST, D	0.723	0.541	0.262
16.	Pc, η, ST	0.731	0.554	0.269
17.	η, ST, D, α, logP	0.786	0.440	0.213
18.	η, ST, D, α	0.743	0.529	0.256
19.	η, ST, D	0.730	0.557	0.270
20.	η, ST	0.721	0.576	0.279

The correlation coefficients in all the cases were found to be good (0.82-0.98), and the standard deviation below 0.28 (TABLE 5). An excellent correlation is obtained in Eq 1, 7 and 8, where correlation coefficients R are 0.9809, 0.9807 and 0.9758, (SD = 0.14-0.16).

Validation

We have undergone a cross-validation methodol-

TABLE 7: Comparation of estimated log 1/C values of N^1-aryl/heteroarylaminomethyl/ethyl-1,2,4-triazoles derivatives (1-18), with those reported in TABLE 2. (Residue=difference between observed and estimated log 1/C) (*E.coli*)

Comp.	$Log1/C_{exp.}$	Estimated log 1/C					
		Equation (1)		Equation (2)		Equation (3)	
		$Log1/C_{eq.1}$	Residue	$Log1/C_{eq.2}$	Residue	$Log1/C_{eq.3}$	Residue
1	5.3914	5.3800	0.0113	5.3782	-0.0132	5.2619	-0.1294
2	4.3388	4.3852	-0.0463	4.3209	-0.0178	4.3119	-0.0268
4	5.3194	5.2168	0.1026	5.2237	-0.0956	5.2202	-0.0991
5	5.4034	5.3876	0.0157	5.3850	-0.0183	5.3767	-0.0266
7	5.3985	5.3529	0.0455	5.3782	-0.0202	5.3376	-0.0608
8	4.7328	4.7199	0.0128	4.6951	-0.0376	4.7143	-0.0184
9	5.4156	5.4009	0.0146	5.3716	-0.0439	5.4990	0.0834
10	4.3678	4.3724	-0.0046	4.4670	0.0992	4.5169	0.1491
11	5.2435	5.0462	0.1972	5.0319	-0.2115	5.0535	-0.1899
12	5.2769	5.3886	-0.1117	5.3919	0.1150	5.4025	0.1256
13	5.2769	5.3886	-0.1117	5.3919	0.1150	5.4025	0.1256
16	4.5189	4.5226	-0.0037	4.5277	0.0088	4.5209	0.0020
Comp.	$Log1/C_{exp.}$	Estimated log 1/C					
		Equation (7)		Equation (8)		Equation (13)	
		$Log1/C_{eq.7}$	Residue	$log1/C_{eq.8}$	Residue	$log1/C_{eq.13}$	Residue
1	5.3914	5.3308	0.0605	5.3580	0.0333	5.5065	-0.1151
2	4.3388	4.2253	0.1134	4.3236	0.0151	4.4004	-0.0616
4	5.3194	5.1536	0.1657	5.2082	0.1111	5.2898	0.0295
5	5.4034	5.3325	0.0708	5.3665	0.0368	5.4352	-0.0318
7	5.3985	5.3749	0.0235	5.3834	0.0150	5.4669	-0.0684
8	4.7328	4.4167	0.3160	4.6457	0.0870	4.7740	-0.0412
9	5.4156	5.4023	0.0132	5.2976	0.1179	5.2686	0.1469
10	4.3678	4.3142	0.0535	4.4296	-0.0618	4.5709	-0.2031
11	5.2435	4.8874	0.3560	4.9986	0.2448	5.0723	0.1711
12	5.2769	5.2869	-0.0105	5.3616	-0.0848	5.4375	-0.1607
13	5.2769	5.2869	-0.0105	5.3616	-0.0848	5.4375	-0.1607
16	4.5189	4.4352	0.0836	4.5122	0.0066	4.5050	0.0138

ogy for deciding predictive power of the proposed models (Eq. 1- 20). This is needed because a model with good statistics may not have good predictive potential. The various cross-validation parameters, calculated for the proposed models, are presented in TABLE 6 and are discussed below.

The predictivity of each model was measured by the cross-validated regression coefficient (Q^2) defined as:

$$Q^2=1-\Sigma(Y_{pred}-Y_{exp})^2/\Sigma(Y_{exp}-Y_{mean})^2$$

where Y_{pred}-predicted, Y_{exp}-experimental and Y_{mean}- mean values of the target properties (log1/C) respectively. The calculated Q^2 values are presented in TABLE 6, together with PRESS and PRESS/SSY values.

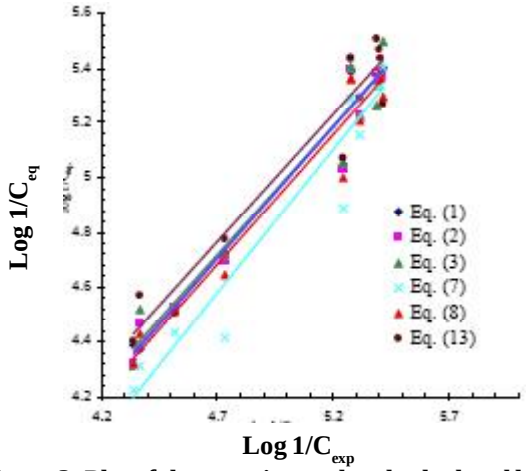


Figure 3: Plot of the experimental and calculated log 1/C values of compounds 1-18 against *E coli*

TABLE 8: Calculated predictive correlation coefficient (R_{pre}^2) for equations: (1); (2); (3); (7); (8) and (13)

Eq.	Correlation: $log1/C_{exp}$ with $log1/C_{eq.}$	Predictive correlation coefficient (R_{pre})	SD
(1)	$Log1/C_{exp.}$ = 0.9617 $log1/C_{eq.(1)}$+ 0.1835	0.9809	0.0867
(2)	$Log1/C_{exp.}$= 0.9537 $log1/C_{eq.(2)}$ + 0.2241	0.9770	0.0945
(3)	$Log1/C_{exp.}$ = 0.9379 $log1/C_{eq.(3)}$ + 0.3088	0.9683	0.1098
(7)	$Log1/C_{exp.}$ = 1.0498 $log1/C_{eq.(7)}$ - 0.3551	0.9677	0.1241
(8)	$Log1/C_{exp.}$ = 0.9472 $log1/C_{eq.(8)}$ + 0.2304	0.9757	0.0966
(13)	$Log1/C_{exp.}$ = 0.9326 $log1/C_{eq.(13)}$ + 0.3808	0.9629	0.1186

Good cross-validation Q^2 values were obtained for all proposed models (Q^2>0.72) suggesting that the models are useful tool for predicting the inhibition of *E.coli*.

PRESS appears to be important cross-validation parameter accounting for a good estimate of the real predictive error of the model. Its value less than SSY indicate that the model predicts better than chance and can be considered statistically significant. In our case (TABLE 6) PRESS<<SSY indicating that all models obtained are statistically significant and are better that chance.

To be reasonable QSAR model, PRESS/SSY should be smaller than 0.4 and the data presented in TABLE 6 indicated that all models proposed are significant. In our case the ratio PRESS/SSY ranges between 0.038-0.317 indicating that all proposed models are reliable QSAR models. There is an increase in predictive power form Eq. (1) to Eq. (20).

Finally, in order to confirm our findings, antimicrobial activity against Escherichia coli (log 1/C) predicted by Eq. (1), (2), (3), (7), (8) and (13) are compared with the corresponding log 1/C values reported in TABLE 2. Such comparison is shown in TABLE 7. Within experimental error, the values agree well. The residual, is the difference between observed and calculated log1/C.

A plot is obtained between the experimental and calculated log 1/C values as shown in Figure 3. Also, we have calculate predictive correlation coefficient (R_{pre}), (TABLE 8), by correlated estimated log1/C values with the experimental once The obtained predictive correlation coefficient (R_{pre}=0.9629÷0.9809) confirm our findings. Calculated predictive correlation coefficient (R_{pre}) and SD for the equations (4); (5); (6); (7); (9); (10); (11); (12); (14); (15); (16); (17); (18); (19) and (20), re given in TABLE 9.

QSAR study for antibacterial activity of *S. enteritidis*

The statistically significant result for bacteria inhibi-

TABLE 9: Calculated predictive correlation coefficient (R_{pre}^2) for equations: (4); (5); (6); (7); (9); (10); (11); (12); (14); (15); (16); (17); (18); (19) and (20)

Eq.	(4)	(5)	(6)	(9)	(10)	(11)	(12)	(14)	(15)	(16)	(17)	(18)	(19)	(20)
R_{pre}	0.9663	0.9221	0.9149	0.9440	0.9330	0.8779	0.8263	0.9577	0.8589	0.8552	0.8868	0.8621	0.8544	0.8490
SD	0.1168	0.1757	0.1833	0.1498	0.1634	0.2174	0.2558	0.1307	0.2326	0.2354	0.2098	0.2301	0.2360	0.2399

tory activity against *S.enteritidis* of choesn N^1-aryl/heteroarylaminomethyl/ethyl-1,2,4-triazole derivatives, using all eight descriptors have not been obtained.

CONCLUSION

Spurred by the need of new antimicrobial agents and the fact that many effective drugs, insecticides and fungicides possess heterocyclic systems in their structure, such as triazole ring, we synthesized some new 1,2,4-triazole derivatives. From the results and discussion made above we conclude that physicochemical properties such Surface tension (ST), Molar Refraction (MR), Molar Volume (MV), Parachor (Pc), Index of Refractivity (η); Density (D) and Polarizability (?) can be used successfully for modelling inhibition of *E.Coli* by triazole derivatives. These results will help medical as well as agriculture chemist in their prediction of increasing activity and thus the synthesis of new triazoles exhibiting better activities then those reported in this paper.

The statistically significant QSAR models for inhibitory activity against *S.enteritidis* of chosen 1,2,4-triazoles, using all descriptors, have not been obtained.

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