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Synthesis and QSAR Modeling of Novel Benzimidazolo Thiazolidinones, Thiazinones and 5-arylidene-2-imino Thiazolidinones as Antibacterial Agents

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Abstract: A novel series of benzimidazolo thiazolidinones, thiazinones and 5-arylidene-2-imino thiazolidinones were synthesized and evaluated for antibacterial activity. The compounds were synthesized in excellent yield and the structures were characterized on the basis of IR, ^{1}H-NMR and MASS spectral data. Most of the synthesized compounds showed good antibacterial activity against Gram-positive and Gram-negative bacteria. QSAR study was carried out with synthesized compounds using molecular descriptors such as electronic, thermodynamic and steric. Molecular descriptors were used to derive QSAR models between antibacterial activity and structural properties. QSAR study suggested the need of a bulky group to enhance the antibacterial activity in these series of compounds.

Keywords: Antibacterial, Benzimidazole, QSAR, Thiazolidinone, Thiazinone, Iminothiazolidinone.

INTRODUCTION

Benzimidazole nucleus has received much attention of many researchers due to its varied biological activity [1-8]. Benzimidazole nucleus can combined with number of other heterocyclic ring systems for different types of biological activity, like antimicrobial, antinociceptive and proton pump inhibition [9,10]. The other heterocyclic ring systems like thiazolidinone was found in various synthetic pharmaceuticals, displaying a broad spectrum of biological activity such as antimycobacterial [11,12], anti-inflammatory and analgesic [13], antihistaminic [14], antitoxoplasmic gondii [15], antitubercular [16] antioxidant [17] and antiretroviral [18]. The biological significance of benzimidazolo thiazolidin-4-one and thiazinone and their derivatives impelled us to work upon synthesis of these compounds for antibacterial activity. The structural and physicochemical requirement of synthesized compounds for antibacterial activity was explored in QSAR modeling. Calculated molecular descriptors (electronic, steric and thermodynamic) were used to derive QSAR models between antibacterial activity and structural properties. The best model for prediction of antibacterial activity was obtained by applying sequential multiple linear regression (SMLR) analysis. In this study, we reported synthesis and QSAR models of some derivatives of benzimidazolo thiazolidinone and benzimidazolo thiazolidine-4-ones and screened them for antibacterial activity. Consequently, many different protocols were developed that allows synthesis of thiazolidin-4-one skeletons.

CHEMISTRY

The synthesis of benzimidazolo thiazolidin-4-ones (**4a-4f**) is depicted in Scheme **1**. 2-Amino benzimidazoles **(2a-2c)** were prepared by reaction of *o*-phenylenediamine with cynogen bromide in presence of acetonitrile at room temperature. The key intermediate Schiff's bases **(3a-3f)** were synthesized via nucleophilic attack of amine of benzimidazole ring to aromatic aldehydes in good yield. Further, Schiff bases **(3a-3f)** were treated with thioglycolic acid in ethanol under refluxing conditions to afford benzimidazolo thiazolidin-4-ones (**4a-4f**) (Scheme **1**).

In order to prepare the benzimidazolo thiazinones **(5a-5b)** (Scheme **2**), benzimidazole schiff bases (**3a-3b**) were treated with 3-mercapto propionic acid under refluxing temperature with ethanol. Compound **2a** when treated with chloroacetyl chloride in presence of potassium carbonate gave *N*-(1*H*-benzimidazol-2-yl)-2-chloro acetamide **(6a)** in 95% yield as a pale pink solid.

Compound **6a** was treated with KSCN using chloroform as a solvent, afforded product **7a**. The reaction of **7a** with different aromatic aldehydes was used to afford compounds **8a-8l** (Scheme **3**).

Structures of all the compounds were confirmed by IR, ^{1}H-NMR, MASS spectral data and purity by elemental analysis. Physicochemical characteristics of all the synthesized compounds (**4a-f**), (**5a-b**) and (**8a-l**) are given in Table **1**.

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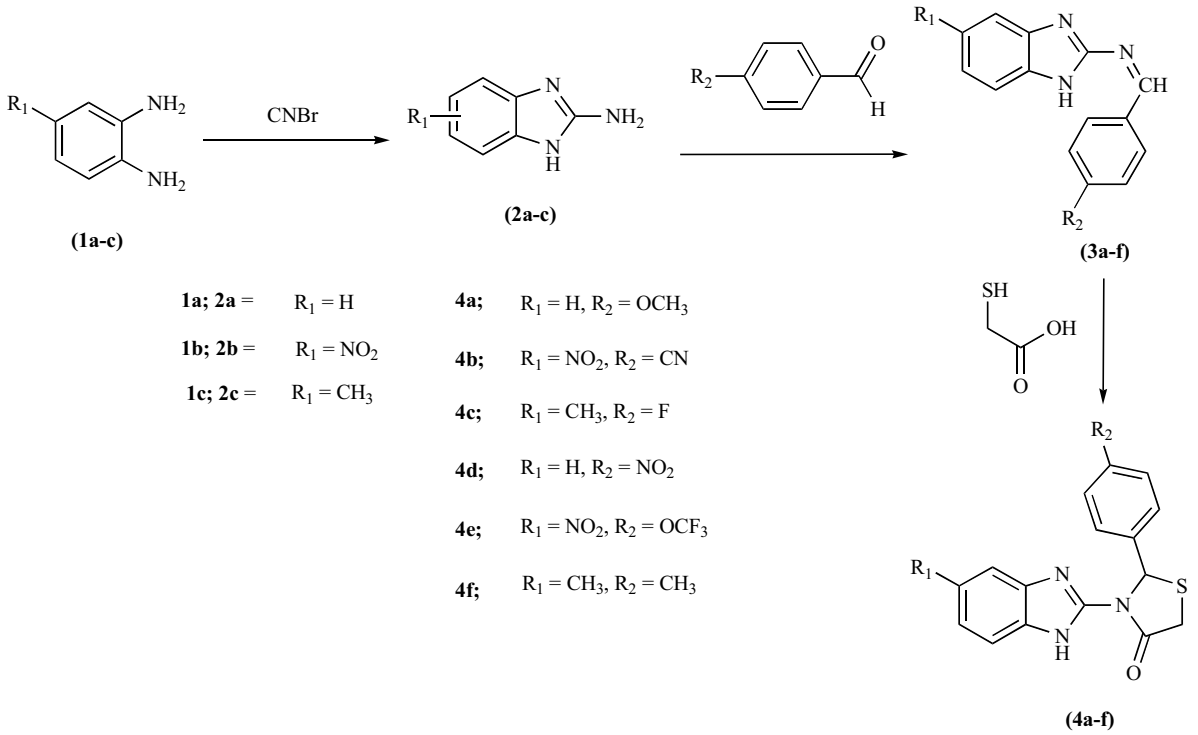
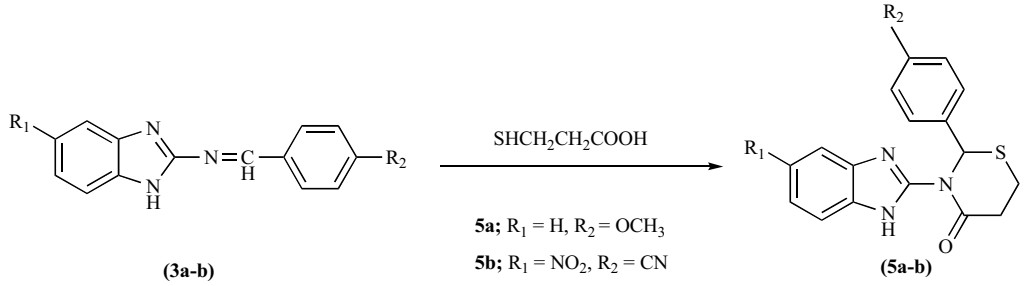
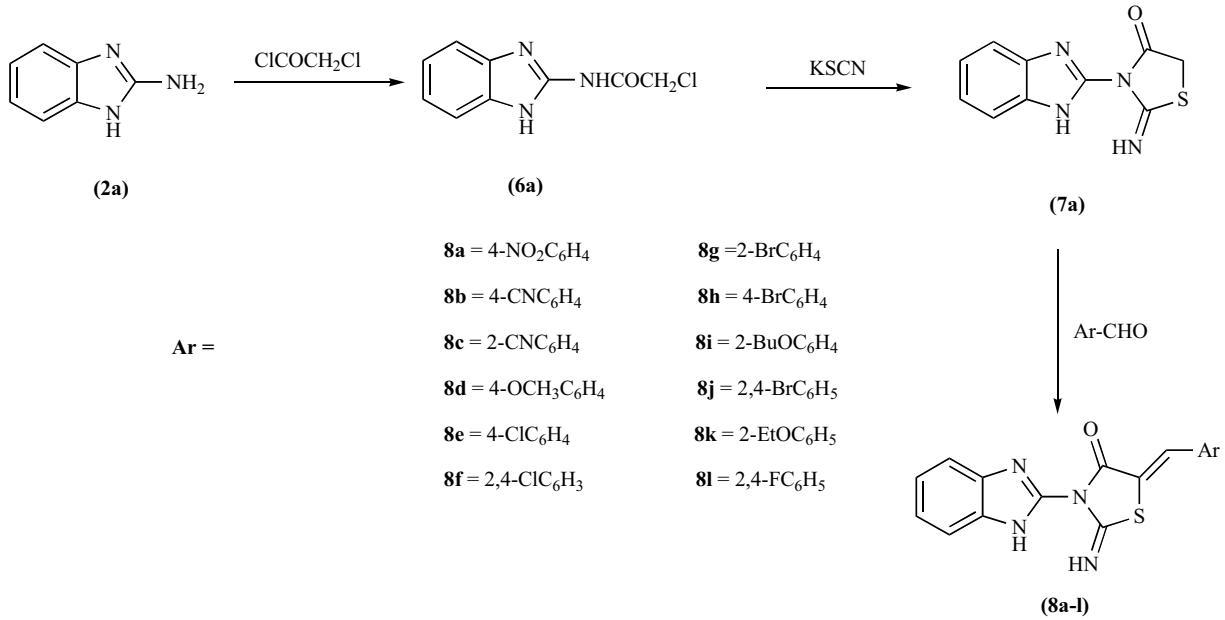


Scheme 1. Synthesis of **4a-4f**.



Scheme 2. Synthesis of **5a** and **5b**.



Scheme 3. Synthesis of **8a-8l**.

Table 1. Physicochemical Characteristics of Synthesized Compounds

Compound	Molecular Formula	Molecular Weight	MP (ºC)	Yield (%)
4a	$C_{17}H_{15}N_3O_2S$	325.38	240-243	69.21
4b	$C_{17}H_{11}N_5O_3S$	365.37	223-225	68.68
4c	$C_{17}H_{14}FN_3OS$	327.38	255-258	63.21
4d	$C_{16}H_{12}N_4O_3S$	340.36	202-205	60.46
4e	$C_{17}H_{11}F_3N_4O_4S$	424.35	220-223	56.56
4f	$C_{18}H_{17}N_3OS$	323.41	220-223	56.78
5a	$C_{18}H_{19}N_3OS$	325.43	123-125	58.67
5b	$C_{18}H_{15}N_5O_2S$	365.41	123-125	55.53
8a	$C_{17}H_{11}N_5O_3S$	365.37	300-302	90.21
8b	$C_{18}H_{11}N_5OS$	345.38	295-297	89.14
8c	$C_{18}H_{11}N_5OS$	345.38	260-262	87.41
8d	$C_{18}H_{14}N_4O_2S$	350.39	295-297	85.65
8e	$C_{17}H_{11}ClN_4OS$	354.81	291-293	83.76
8f	$C_{17}H_{10}Cl_2N_4OS$	389.26	290-292	82.67
8g	$C_{17}H_{11}BrN_4OS$	399.26	295-298	79.89
8h	$C_{17}H_{11}BrN_4OS$	399.26	290-292	75.78
8i	$C_{21}H_{20}N_4O_2S$	392.47	285-288	81.48
8j	$C_{17}H_{10}Br_2N_4OS$	478.16	287-290	88.58
8k	$C_{20}H_{18}N_4O_2S$	378.45	282-285	76.56
8l	$C_{17}H_{10}F_2N_4OS$	356.35	283-285	79.87

BIOLOGICAL STUDIES

All the newly synthesized derivatives were screened for antibacterial activities against *Staphylococcus aureus (*ATCC 6538*)*, *Escherichia coli* (ATCC 25922), *Bacillus subtilis* (ATCC 6033) and *Pseudomonas aeruginosa* (ATCC 27853). Antibacterial activity of all the synthesized compounds were assessed in Mueller-Hinton broth medium. The minimum inhibitory concentration (MIC) was determined by using two fold serial dilution method [19,20] with 96-well microtest plates. Streptomycin, clotrimazole and amphotericin-B were used as reference standards to compare the antibacterial activity. The MIC values were obtained from lowest concentration of test compounds, where tubes remain clear, indicated that bacterial growth was completely inhibited. All the compounds **(4a-4f, 5a-5b** and **8a-8l)** showed activity against Gram-positive and Gram-negative bacteria. Table **2** shows observed antibacterial activities of benzimidazolo thiazolidinones, thiazinones and 5-arylidene-2-imino thiazolidinones against four micro-organism strains. The MIC exhibited by compound **4d** against *B. subtilis* was at 16.45 µg/ml, where as compound **4e** showed MIC at 12.09 µg/ml against *E. coli*. Thiazinone derivatives **(5a, 5b)** exhibited significant antibacterial activity. 5-Arylidene-2-imino-thiazolidinone (**8h)** showed good activity against *E. coli* and *P. aeruginosa* (12.09 µg/ml).

QSAR MODELING

In order to develop QSAR models, data set was subjected to SMLR analysis. QSAR study resulted into several correlation equations between the pIC_{50} values (Table **2**) as the dependent variable and various physicochemical properties (Table **3**) as independent variable. Several statistically significant quadric variant QSAR equations were obtained. The overall quality of QSAR models was indicated by correlation coefficient (r), squared correlation coefficient (r^2), standard deviation (SD) and Fischer ratio values between the variances of calculated and observed activities (F).

QSAR Model for Activity Against *Bacillus subtilis*

pIC_{50} = [5.332 (± 1.157)] +MW [0.003 (± 0.002)] +OV [4.334 (± 0.496)] +DDE [-0.261 (± 0.113)] + DPL_3 [0.051 (± 0.051)] Eq^n 1

where n=14, r=0.907, r^2 = 0.823, SD = 0.125, F=23.436

The statistically significant equation (Eq^n 1) with good correlation coefficient (r = 0.907) and significantly low standard error of estimation (SD = 0.125) was considered as best model for activity against *Bacillus subtilis*. Eq^n 1 explains for 82.3% variance in antibacterial activity with significant F-value ($F_{(4,9)}$ = 23.436). The model was subjected to leave

Table 2. Antibacterial Screening Data (MIC and pIC_{50}) of Benzimidazolo Thiazolidinones, Thiazinones and 5-Arylidene-2-Imino-Thiazolidinones Derivatives

Compound	Minimum Inhibitory Concentration (MIC) µg/ml				pIC_{50}			
	Gram-positive Organisms		Gram-negative Organisms		Gram-positive Organisms		Gram-negative Organisms	
	B. subtilis	*S. aureus*	*E. coli*	*P. aeroginosa*	*B. subtilis*	*S. aureus*	*E. coli*	*P. aeroginosa*
4a	32.56	30.98	29.07	29.07	4.488	4.501	4.537	4.537
4b	32.76	31.89	14.98	14.98	4.485	4.495	4.823	4.825
4c	32.23	32.98	14.98	14.98	4.492	4.482	4.825	4.825
4d	16.45	13.32	13.87	13.87	4.784	4.876	4.858	4.858
4e	16.56	12.98	12.09	12.09	4.781	4.887	4.918	4.918
4f	16.78	15.45	12.98	12.92	4.776	4.812	4.889	4.887
5a	55.34	52.89	12.98	12.98	4.257	4.277	4.887	4.887
5b	57.78	34.92	29.98	29.98	4.239	4.457	4.524	4.524
8a	53.78	34.89	22.98	22.98	4.269	4.458	4.636	4.639
8b	30.12	27.68	24.09	24.09	4.521	4.558	4.612	4.619
8c	57.89	51.23	22.09	22.09	4.237	4.291	4.656	4.656
8d	45.88	44.98	16.78	16.78	4.338	4.347	4.778	4.776
8e	57.89	54.65	52.09	52.09	4.238	4.263	4.284	4.281
8f	30.45	22.98	30.56	30.56	4.517	4.639	4.5149	4.515
8g	51.23	57.68	30.87	30.87	4.291	4.239	4.511	4.511
8h	13.45	8.98	12.09	12.09	4.872	5.047	4.918	4.918
8i	12.89	15.89	31.09	31.09	4.889	4.799	4.508	4.508
8j	32.78	14.98	26.87	26.87	4.485	4.825	4.571	4.571
8k	32.56	30.98	29.07	29.07	4.488	4.509	4.537	4.537
8l	32.76	31.89	14.98	14.98	4.485	4.497	4.825	4.825
Streptomycin	16.25	17.56	18.15	18.12	-	-	-	-
Clotrimazole	19.56	18.25	18.81	22.51	-	-	-	-
Amphotericin-B	13.21	16.89	21.74	21.91	-	-	-	-

Table 3. Physicochemical Properties of Benzimidazolo Thiazolidinones, Thiazinones and 5-Arylidene-2-Imino-Thiazolidinones Analogues Used in QSAR Modeling

Compd	MW (Atomic Mass)	OV	DDE (Kcal/ mol)	SGFE (kJ/ mol)	CAA ($Å^2$)	PMI_X (Grams / Mole $Å^2$)	PMI_Y (Grams / Mole $Å^2$)	N1,4 VDWE (Kcal/ mol)	DPL_3 (Debye)	HOMO (eV)	EE (eV)	LP
4a	325.38	1.476	-8.626	540.99	518.793	2164.4	2350.35	-4.279	-2.963	-8.845	-29097	4.415
4b	365.37	1.459	-9.073	424.84	502.118	1620.48	2247.01	-3.467	-1.673	-8.803	-25343	3.098
4c	327.38	1.486	-9.145	761.25	528.004	1878.77	2419.05	-3.855	-3.292	-8.891	-25588	3.284
4d	340.36	1.499	-9.042	523.07	541.897	1966.83	2356.58	-3.182	-0.886	-8.717	-27149	3.124

Table 3. contd…

Compd	MW (Atomic Mass)	OV	DDE (Kcal/ mol)	SGFE (kJ/ mol)	CAA (Å^2)	PMI_X (Grams / Mole Å^2)	PMI_Y (Grams / Mole Å^2)	N1,4 VDWE (Kcal/ mol)	DPL_3 (Debye)	HOMO (eV)	EE (eV)	LP
4e	424.35	1.508	-8.872	336.55	537.129	1792.42	4205.76	-2.165	-0.604	-9.406	-30797	3.987
4f	323.41	1.53	-9.165	521.86	573.477	2147.81	2724.9	-3.475	-0.754	-8.678	-29092	3.612
5a	325.43	1.494	-6.946	519.39	558.408	1338.47	4123.71	13.818	1.749	-8.641	-29063	3.417
5b	365.41	1.479	-8.046	757.57	542.806	1567.26	3527.87	-2.713	-2.711	-8.552	-27616	3.576
8a	365.37	1.517	-8.046	902.56	561.355	2678.58	3539.18	95.217	-3.54	-7.647	-28645	3.527
8b	345.38	1.555	-6.841	1122.82	554.522	1343.52	4541.03	0.357	-2.506	-8.518	-25694	4.415
8c	345.38	1.532	-7.271	786.41	528.664	1454.81	3928.75	-0.391	0.111	-8.504	-25470	4.257
8d	350.39	1.537	-7.349	884.64	572.093	1363.23	4572.72	3.55	-0.876	-8.095	-27213	4.255
8e	354.81	1.517	-7.251	969.29	550.689	1402.8	4660.48	2.631	-2.059	-8.328	-25242	4.94
8f	389.26	1.539	-6.443	947.73	563.737	1620.39	4801.1	2.427	-2.244	-8.415	-27625	5.5
8g	399.26	1.478	-7.222	995.54	545.203	1921.35	3419.7	2.446	-1.177	-8.369	-25630	5.223
8h	399.26	1.548	-7.303	995.54	558.759	1442.43	6527.49	2.394	-2.385	-8.369	-25154	5.211
8i	392.47	1.591	-7.499	909.9	595.684	2281.36	3637.66	-3.028	1.367	-8.568	-35442	5.214
8j	478.16	1.548	-6.638	1000.23	582.66	2096.89	7021.99	-1.088	-0.421	-8.61	-27434	5.756
8k	378.45	1.591	-7.468	893.06	604.586	1473.36	5833.73	-1.043	0.846	-8.357	-28828	4.31
8l	356.35	1.522	-6.946	519.39	558.408	1338.47	4123.71	13.818	1.749	-8.641	-29063	3.417

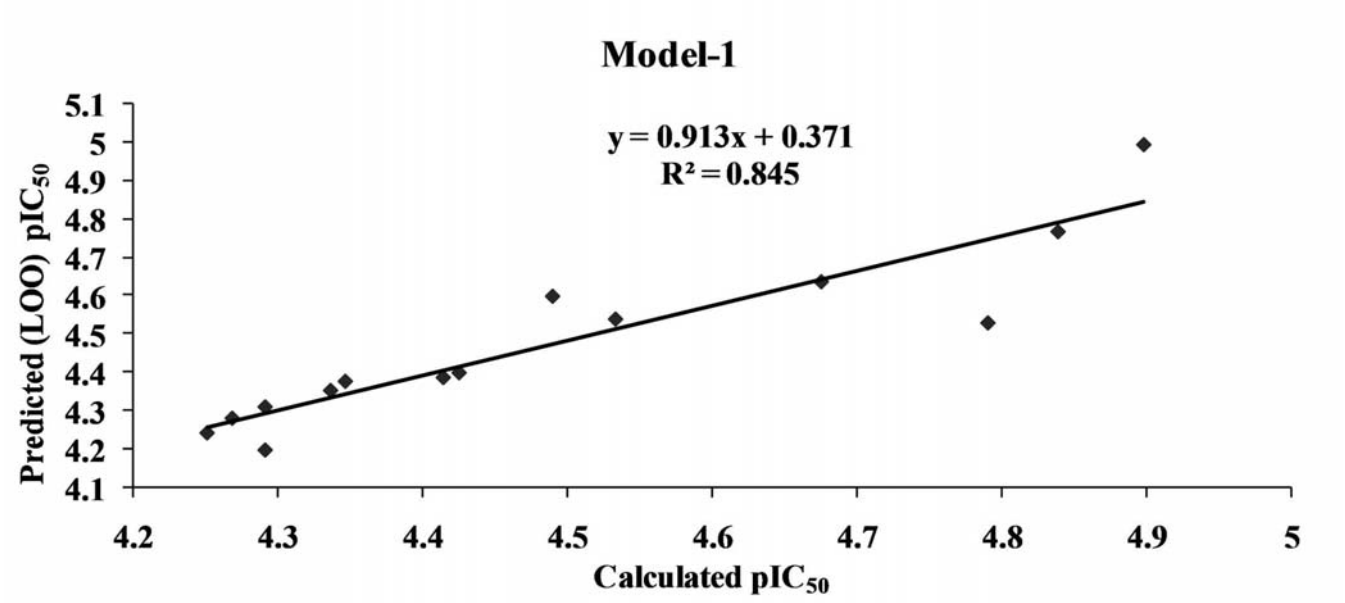


Fig. (1). Plot relating the predicted and calculated activity against *B. subtilis.*

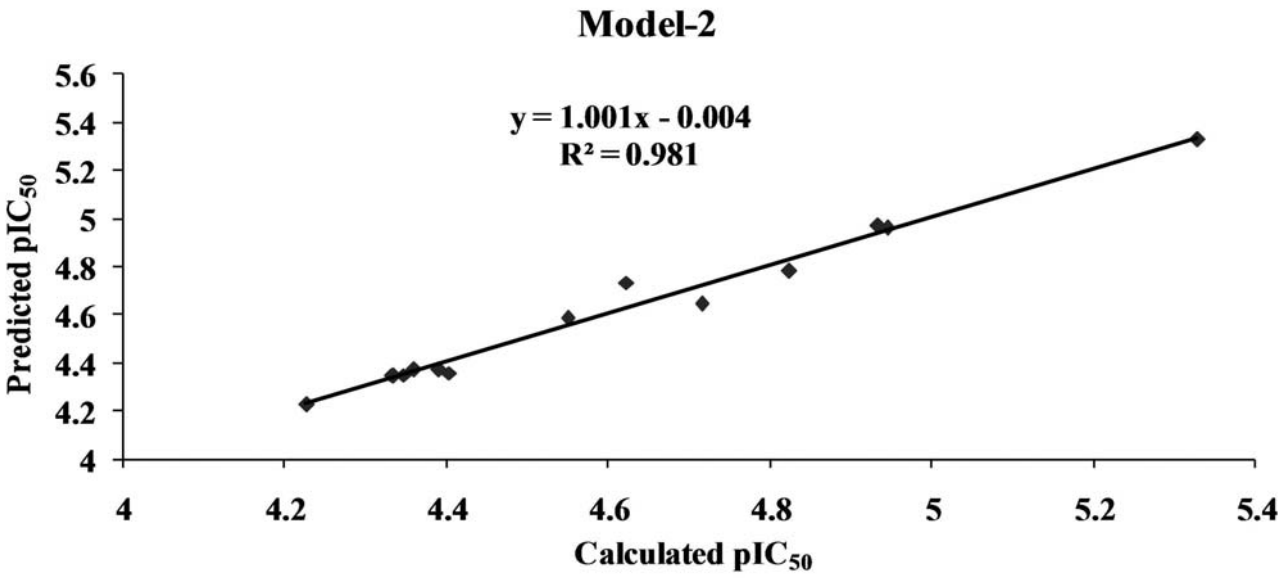


Fig. (2). Plot relating the predicted and calculated activity against *S. aureus*.

one out (LOO) cross validation method (Table **4**, Fig. **1**). Value of cross-validated squared correlation coefficient (Q^2= 0.658), predictive residual sum of square (S_{PRESS}= 0.175) and standard error of predictivity (S_{DEP}= 0.218) suggested good predictive ability for activity against *Bacillus subtilis*. The bootstrapping squared correlation coefficient (r^2_{bs}=0.878) suggested the robustness of the model and contribution of molecular descriptor values of each molecule to the correlation is nearly same. Model's predictive squared correlation coefficient (r^2_{pred}) = 0.587 was in agreement with the accepted criteria. Randomize biological activity data test (Chance < 0.001) revealed that the result were not based on chance correlation (Table **4**). The QSAR study revealed that molecular weight (MW), ovality (OV) and dipole moment on Z-axis (DPL_3) are the principle descriptors for activity against *Bacillus subtilis*. Dipole-dipole energy (DDE) contributed negatively to antibacterial activity. Equation 1 revealed the importance of molecular bulk in term of molecular weight, this is an average molecular mass of compounds and a property of the whole molecule based on the weight of atoms of a certain element type. The coefficient of MW in the equation is positive; hence more bulky molecule may exhibit good antibacterial activity against *B. subtilis*. Ovality is a ratio of the molecular surface area to the minimum surface area (surface area of a sphere having a volume equal to the solvent excluded volume of the molecule) which is a steric parameter, describes more the shape of molecule rather than the bulk of the molecule and can be correlated with the orientation of functional groups [21]. Ovality suggested that a proper orientation of functional groups will improve antibacterial activity of these classes of the compounds. The dipole moment is the most obvious and most widely used quantity to describe the polarity of a molecule indicates the strength and orientation behavior of a molecule in an electrostatic field. DPL_3 is the derivative of the energy with respect to an applied electric field. It measures asymmetry in molecular charge distribution and reported as a vector on Z-axis. The importance of dipole in modulating antibacterial activity may be due to permanent polarization of the electro negativity difference between the atoms.

QSAR Model for Activity Against *Staphylococcus aureus*

pIC_{50} = [3.273 (±0.842)] +SGFE [-0.001 (± 0.0003)] +SAS [1.016(± 0.003)] +PMI_X [0.03 (±0.0001)] +EE [0.124 (± 0.000003)] Eq^n 2

where n = 14, r = 0.972, r^2 =0.946, SD =0.091 F=39. 942

In case of *Staphylococcus aureus* good correlation was shown by the Eq^n 2, explains 94.7% variance in antibacterial activity with significant F-value ($F_{(4,9)}$ =39.942) and significantly low standard error of estimation (SD = 0.091). Internal predictivity of the model-2 was assured with the help of cross-validated constraints like Q^2, S_{PRESS} and S_{DEP} obtained by leave-one-out (LOO) cross validation method (Table **4**, Fig. **2**). Thermodynamic descriptor like standard Gibbs free energy (SGFE) contributed negatively to the activity against *S. aureus*. Reaction's free energy (Gibbs function) is a magnitude which describes the spontaneity of thermal processes, that is, the tendency of molecular systems to associate and/or to react [22]. Free energy property is composed by an enthalpy and entropy contribution. Particularly the entropic term is difficult to handle in QSAR analysis.

Principal moment of inertia-X component (PMI_X) is positively contributed to the activity. PMI_X describes the mass distribution over the molecule on x-component in spatial arrangement, suggesting that an increase in the bulkiness on X-component of molecule for good antibacterial activity. Connolly accessible area (CAA) is locus of centre of a spherical probe (representing the solvent) as it is rolled over the molecular model contributing positively to model. Maximizing electronic energy (EE) of the molecules is helpful in designing of potent antibacterial agents against *S. aureus*.

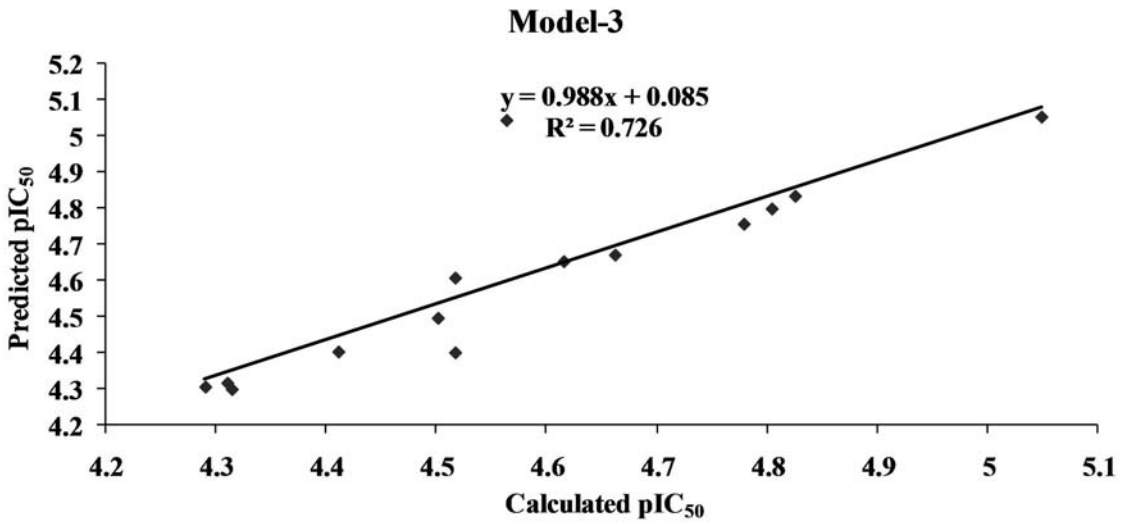


Fig. (3). Plot relating the predicted and calculated activity against *E. coli*.

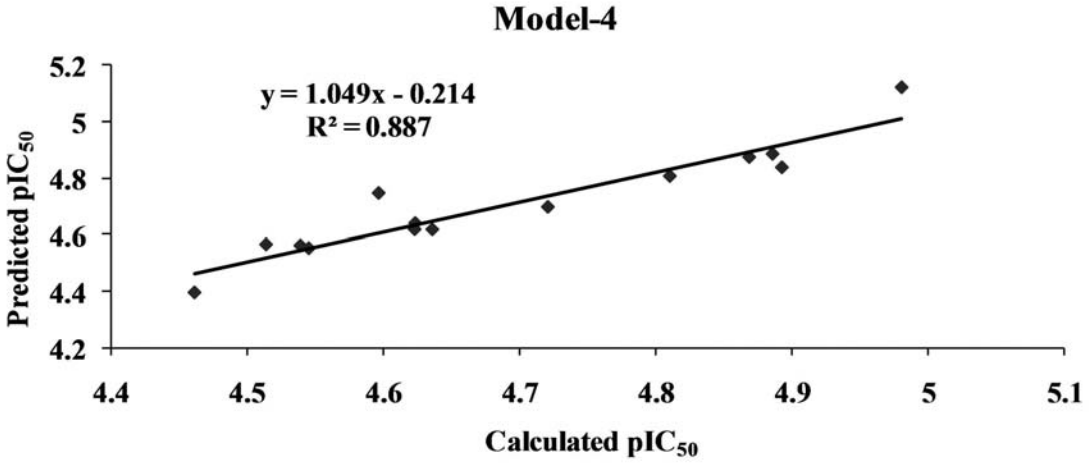


Fig. (4). Plot relating the predicted and calculated activity against *P. aeruginosa*.

QSAR Model for Activity Against *Escherichia coli*

pIC_{50} = [3.898 (±0.692)] +LP [-0.296 (± 0.168)] +PMI_X [0.1026 (±0.0003)] +PMI_Y [0.702 (±0.0001)] + N1,4VDWE [-0.017 (± 0.005)] Eq^n 3

where n =14, r = 0.877, r^2=0.769, SD =0.147, F=27.487

Values of Q^2, S_{PRESS}, S_{DEP}, r^2_{bs} and r^2_{Pred} (Table **4**, Fig. **3**) proved that obtained QSAR model is statistically significant in terms of prediction of activity and shows 76.9% variation in antibacterial activity. Spatial parameters like principal moment of inertia-X component (PMI_X) and principal moment of inertia-Y component (PMI_Y) contributed positively, whereas octanol/water partition coefficients (Log P) and non-1, 4-VDW energy (N 1,4 VDWE) contributed negatively to the equation. PMI_Y describes mass distribution over the molecule on Y-component in spatial arrangement, contributed positively to the activity suggesting an increase in bulkiness on Y-component of molecule for good antibacterial activity. Log P is an important property in describing the affinity of the compounds in terms of their partitioning biological membranes, thus by decreasing lipohilicity by introducing hydrophilic groups would surely lead to give better antibacterial activity. Outer surface of bacterial cell wall is hydrophilic and inner surface is lipophilic in nature, so the compounds for antibacterial activity should possesses good hydrophilic/lipophilic balance. Minimizing non-1, 4 van der Waals energy (N 1,4 VDWE), which is sum of pair wise van der Waal interaction energy terms for atoms separated by more than three chemical bonds, would helpful for designing of better antibacterial agents.

QSAR Model for Activity Against *Pseudomonas aeruginosa*

pIC_{50} = [3.626 (±0.048)] +PMI_Y [1.161 (± 0.045)] +NVDW [-0.115 (±0.017)] + DPL_3 [0.181 (±0.051)] +HOMO [-0.533 (±0.031)] Eq^n 4

where n=14, r=0.861, r^2=0.2741, SD =0.118, F=26.422

The data presented in Table **4** demonstrates that equation 4 (Fig. **4**) is statistically significant.

Table 4. QSAR Statistics of Significant Equations

Eq^n	r^2	SD	F	r^2_{bs}	S_{bs}	Chance	Q^2	S_{PRESS}	S_{DEP}	r^2_{pred}
1	0.823	0.125	23.435	0.878	0.095	<0.001	0.658	0.218	0.175	0.587
2	0.947	0.091	39. 942	0.937	0.045	<0.001	0.871	0.142	0.112	0.446
3	0.769	0.021	27.487	0.832	0.832	<0.001	0.693	0.257	0.206	0.575
4	0.741	0.118	26.422	0.786	0.120	<0.001	0.645	0.172	0.138	0.458

Based on the developed QSAR model, it was observed that the important parameters, which contributes to potentiating activity is spatial descriptor like principal moment of inertia-Y component (PMI_Y) and topological descriptor like dipole moment on z-axis (DPL_3). Both the parameters were contributed positively to the model and on the contrary. It was also observed that electronic descriptor like highest occupied molecular orbital (HOMO) and thermodynamic descriptors like non-1, 4 van der Waals energy (N 1,4 VDWE), contributed negatively to the model. The generated QSAR model (Eq^n 4) indicated that a high value of HOMO energy will decrease the activity. This is some indication of a Lewis base strength particularly if the electrons can be considered as a classical lone pair [23]. It is crucially important in governing molecular reactivity and properties. HOMO descriptor measures the nucleophilicity of a molecule, thus designed analogs with electron-withdrawing substituents would improve antibacterial activity.

CONCLUSION

This study reports synthesis and QSAR modeling of novel benzimidazolo thiazolidinones, thiazinones and 5-arylidene-2-imino-thiazolidinones. Synthesized compounds were evaluated for antibacterial activity against two Gram-positive and two Gram-negative bacteria, and found equipotent as the reference drugs. All the synthesized compounds were characterized by IR, ^{1}H-NMR, MASS and elemental analysis. QSAR models were developed by relating antibacterial activity of synthesized compounds with their physicochemical properties. Satisfactory statistical measures were obtained for all QSAR models. Generally good correlation was observed with the spatial descriptors, especially with principal moment of inertia-X and Y components (PMI_X and PMI_Y), thermodynamic descriptors (Log P, non-1, 4 van der Waals energy and DPL_3) and steric descriptors (ovality and molecular weight). These descriptors can be correlated with the bulk as well as orientation of the functional groups in the parent molecule. QSAR models developed in this work are suitable for the rapid prediction of antibacterial activity of benzimidazolo thiazolidinone, thiazinone and 5-arylidene-2-imino thiazolidinone derivatives.

EXPERIMENTAL

Melting points were determined using Fischer John's melting point apparatus and found uncorrected. For column chromatography, silica gel 60-120 mesh was used. For thin layer chromatography, silica gel 60 F_{254} (Merck) was used. ^{1}H NMR spectra in $CDCl_3$ were recorded at 200 MHz on a Varian Gemini and at 300MHz on a Bruker Avance with TMS as an internal standard (chemical shifts in ppm). ESI-MS spectra were recorded on a Finnigen LCQ Advantage Max. EI-MS mass spectra were measured at 70 eV (EI). IR spectra were taken using Thermo Nicolet Nexus 670 FT-IR and values are given in cm^{-1}.

General Procedure for the Synthesis of 2a-2c

Compounds **2a-2c** were prepared by reacting (2g, 0.018 M) substituted *o*-phenylenediamine **(1a-1c)** in 20 ml methanol and 5M CNBr in 10 ml acetonitrile. CNBr solution (3 ml) was taken in 20 ml of water and added drop wise over 20 minute to substituted *o*-phenylenediamine solution. Reaction mixture was stirred for 12 h at room temperature. Reaction mixture was concentrated under pressure. Compounds were extracted into ethyl acetate, concentrated and purified through column chromatography.

General Procedure for the Synthesis of 3a-3f

A mixture of **2a-2c** (15 mmole) and equimolar concentration of aromatic aldehyde was refluxed at 130°C for 1 day in toluene using the Dean-Stark trap and collected water was removed form the reaction mixture from time to time. The reaction mixture was cooled at room temperature.

General Procedure for Synthesis of 4a-4f

A mixture of **3a-3f** and an equimolar quantity of mercapto acetic acid (thioglycollic acid) were refluxed for 2 days. The reaction mixture was cooled at room temperature; excess of solvent was removed under vacuum and extracted with EtOAc, which was then purified through column chromatography.

3-(1H-benzimidazol-2-yl)-2-(4-methoxyphenyl) thiazolidin-4-one (4a)

IR (cm^{-1}): 1575 (C=C), 3020 (C-H Ar), 3480 (-NH), 1670 (C=O), 650 (C-S), 1140 (C-O); ^{1}H NMR (δ ppm) 11.40 (s, 1H, -NH), 6.60-7.80 (m, 8H, Ar-H), 3.28 (s, 2H, CH_2), 5.90 (s, 1H, CH), 3.60 (s, 3H, $-CH_3$); ESI-MS *m/z* 326 M^++1; Anal.Calcd for $C_{17}H_{15}N_3O_2S$ (325.38) : C, 62.75; H, 4.65; N,12.91; O, 9.83; S, 9.85. Found: C, 62.71; H, 4.60; N, 12.89; O, 9.81; S, 9.81.

4-(3-(5-nitro-1H-benzimidazol-2-yl)-4-oxothiazolidin-2-yl)benzonitrile (4b)

IR (cm^{-1}): 1570 (C=C), 3025 (C-H Ar), 3475 (-NH), 1675 (C=O), 650 (C-S), 2230 (C-N in nitrile), 1550 ($-NO_2$); ^{1}H NMR (δ ppm) 12.20 (s, 1H, -NH), 7.30-8.60 (m, 7H, Ar-H), 3.40 (s, 2H, CH_2), 5.60 (s, 1H, CH); ESI-MS *m/z* 366

M^++1; Anal.Calcd for $C_{17}H_{11}N_5O_3S$ (365.37): C, 55.88; H, 3.03; N, 19.17; O, 13.14; S, 8.78. Found: C, 55.85; H, 3.05; N, 19.15; O, 13.16; S, 8.76.

2-(4-fluorophenyl)-3-(5-methyl-1H-benzimidazol-2-yl) thiazolidin-4-one (4c)

IR (cm^{-1}): 1580 (C=C), 3027 (C-H Ar), 3470 (-NH), 1678 (C=O), 655 (C-S), 835 (C-N), 1130 (-C-F); ^{1}H NMR (δ ppm) 12.40 (s, 1H, -NH), 7.00-7.64 (m, 7H, Ar-H), 3.45 (s, 2H, CH_2), 5.65 (s, 1H, CH), 2.44 (s, 3H, CH_3); ESI-MS *m/z* 328 M^++1; Anal.Calcd for $C_{17}H_{14}FN_3OS$ (327.38): C, 62.37; H, 4.31; N, 12.84; O, 4.89; S, 9.79; F, 5.80. Found: C, 62.35; H, 4.29; N, 12.82; O, 4.85; S, 9.76; F, 5.85.

3-(1H-benzimidazol-2-yl)-2-(4-nitrophenyl) thiazolidin-4-one (4d)

IR (cm^{-1}): 1570 (C=C), 3030 (C-H Ar), 3480 (-NH), 1670 (C=O), 660(C-S), 825 (C-N), 1570 (-NO_2); ^{1}H NMR (δ ppm) 11.60 (s, 1H, -NH), 7.05-8.50(m, 8H, Ar-H), 3.40 (s, 2H, CH_2), 5.40 (s, 1H, CH); ESI-MS *m/z* 341 M^++1; Anal.Calcd for $C_{16}H_{12}N_4O_3S$ (340.36): C,56.46; H, 3.55; N,16.64; O, 14.10; S, 9.42. Found: C, 56.45; H, 3.50; N, 16.60; O, 14.15; S, 9.45.

3-(5-nitro-1H-benzimidazol-2-yl)-2-(4-(trifluoromethoxy) phenyl) thiazolidin-4-one (4e)

IR (cm^{-1}): 1550 (C=C), 3025 (C-H Ar), 3460 (-NH), 1650 (C=O), 680(C-S), 830 (C-N), 1580 (-NO_2),1140 (C-O), 1010 (C-F) ^{1}H NMR (δ ppm) 11.65 (s, 1H, -NH), 7.20-8.40 (m, 7H, Ar-H), 3.80 (s, 2H, CH_2), 5.30 (s, 1H, CH); ESI-MS *m/z* 425 M^++1; Anal.Calcd for $C_{17}H_{11}F_3N_4O_4S$ (424.35): C,48.12; H, 2.61; N,13.20; O, 15.08; S, 7.56; F, 13.43. Found: C, 48.15; H, 2.65; N, 13.25; O, 15.10; S, 7.60; F, 13.45.

3-(5-methyl-1H-benzimidazol-2-yl)-2-p-tolylthiazolidin-4-one (4f)

IR (cm^{-1}): 1560 (C=C), 3020 (C-H Ar), 3440 (-NH), 1630 (C=O), 690(C-S), 2230 (C-N in nitrile), 3050 (CH_3); ^{1}H NMR (δ ppm) 11.40 (s, 1H, -NH), 7.15-8.45 (m, 7H, Ar-H), 3.85 (s, 2H, CH_2), 5.33 (s, 1H, CH), 2.40 (s, 3H, CH_3), 2.10 (s, 3H, CH_3); MS *m/z* 324 M^++1; Anal.Calcd for $C_{18}H_{17}N_3OS$ (323.41): C,66.85; H, 5.30; N,12.99; O, 4.95; S, 9.91; Found: 66.83; H, 5.34; N,13.0; O, 4.93; S, 9.90.

General Procedure for the Synthesis of 5a-5b

A mixture of **3a-3b** and an equimolar quantity of 3-mercapto propionic acid were refluxed for 2 days in distilled benzene. The reaction mixture was cooled at room temperature and excess solvent was removed under vacuum, extracted into EtOAc, which was then purified through column chromatography.

3-(1H-benzimidazol-2-yl)-2-(4-methoxyphenyl)-1,3-thiazinan-4-one (5a)

IR (cm^{-1}): 1560 (C=C), 3015 (C-H Ar), 3460 (-NH), 1670 (C=O), 660(C-S), 835 (C-N), 1130 (C-O) ^{1}H NMR (δ ppm) 12.40 (s, 1H, -NH), 7.10-7.84 (m, 8H, Ar-H), 2.60 (s, 2H, CH_2), 2.65 (s, 2H, CH_2), 5.90 (s, 1H, CH), 3.70 (s, 3H, CH_3); ESI-MS *m/z* 326 M^++1; Anal. Calcd for $C_{18}H_{19}N_3OS$ (325.43): C, 66.43; H, 5.88; N, 12.91; O, 4.92; S, 9.85; Found: C, 66.41; H, 5.85; N, 12.90; O, 4.90; S, 9.82.

4-(3-(5-nitro-1H-benzimidazol-2-yl)-4-oxo-1, 3-thiazinan-2-yl)benzonitrile (5b)

IR (cm^{-1}): 1570 (C=C), 3010 (C-H Ar), 3440 (-NH), 1660 (C=O), 650 (C-S), 2230 (C-N in nitrile), 1550 (-NO_2); ^{1}H NMR (δ ppm) 12.30 (s, 1H, -NH), 7.13-7.87 (m, 7H, Ar-H), 2.65 (s, 2H, CH_2), 2.63 (s, 2H, CH_2), 5.96 (s, 1H, CH); ESI-MS *m/z* 366 M^++1; Anal. Calcd for $C_{18}H_{15}N_5O_2S$ (365.41): C, 59.16, H, 4.14; N, 19.17; O, 8.76; S, 8.78; Found: C, 59.13, H, 4.11; N, 19.13; O, 8.73; S, 8.73.

General Procedure for the Synthesis of 6a

A mixture of **2a** (0.1 mole), chloroacetyl chloride (0.1 mole) and K_2CO_3 was refluxed in chloroform (20 ml) for a period of 6 h. Excess of solvent was removed under vacuum and residue was stirred with water (50 ml). The residue was washed with 5% $NaHCO_3$ and subsequently with water. The crude product is dried and crystallized from methanol to furnish pale brown solid, which was then purified through column chromatography.

General Procedure for the Synthesis of 7a

A mixture of **6a** (0.01 mole), KSCN (0.02 mole) and dry acetone (50 ml) was refluxed for 12 h. Excess of solvent was removed under vacuum and the residue was stirred with water (50 ml). The solid product was filtered, washed with water and dried. The crude product was crystallized from methanol to furnish greenish solid.

General Procedure for the Synthesis of 8a-8l

A mixture of **7a** (0.01 mole), aromatic aldehyde (0.02 mole), anhydrous NaOAc (0.02 mole) was refluxed for 12 h at 120^{o}C in AcOH (30 ml). Reaction mixture was allowed to cool; separated solid was filtered, washed with water, dried and crystallized from ethanol.

3-(1H-benzimidazol-2-yl)-5-benzylidene-2-iminothiazolidin-4-one (8a)

IR (cm^{-1}): 1565 (C=C), 3008 (C-H Ar), 3443 (-NH), 655 (C-S), 1715 (C=O), 1500 (-NO_2); ^{1}H NMR (δ ppm) 12.34 (s, 1H, -NH), 7.12-7.56 (m, 7H, Ar-H), 9.31 (s, 1H, -NH), 6.23 (s, 1H, CH); ESI-MS *m/z* 366 M^++1; Anal. Calcd for $C_{17}H_{11}N_5O_3S$ (365.37): C, 55.88; H, 3.03; N, 19.17; O, 13.14; S, 8.78 Found: C, 55.85; H, 3.01; N, 19.14; O, 13.14; S, 8.75.

4-((3-(1H-benzimidazol-2-yl)-2-imino-4-oxothiazolidin-5-ylidene)methyl)benzonitrile (8b)

IR (cm^{-1}): 1573 (C=C), 3014 (C-H Ar), 3445 (-NH), 653 (C-S), 1715 (C=O), 2240 (C-N in nitrile) ^{1}H NMR (δ ppm) 11.94 (s, 1H, -NH), 7.10-7.25 (m, 7H, Ar-H), 9.33 (s, 1H, -NH), 6.21 (s, 1H, CH); ESI-MS *m/z* 346 M^++1; Anal. Calcd for $C_{18}H_{11}N_5OS$ (345.38): C, 62.60; H, 3.21; N, 20.28; O, 4.63; S, 9.28; Found: C, 62.62; H, 3.19; N, 20.25; O, 4.63; S, 9.26.

2-((3-(1H-benzimidazol-2-yl)-2-imino-4-oxothiazolidin-5-ylidene)methyl)benzonitrile (8c)

mp 260-262 ºC; IR (cm^{-1}); 1578 (C=C), 3020 (C-H Ar), 3450 (-NH), 660 (C-S), 1690 (C=O), 2235 (C-N in nitrile) ^{1}H NMR (δ ppm) 11.92 (s, 1H, -NH), 7.10-7.23 (m, 7H, Ar-H), 9.31 (s, 1H, -NH), 6.23 (s, 1H, CH); ESI-MS *m/z* 346 M^++1; Anal. Calcd for $C_{18}H_{11}N_5OS$ (345.38): C, 62.60; H, 3.21; N, 20.28; O, 4.63; S, 9.28; Found: C, 62.62; H, 3.23; N, 20.26; O, 4.62; S, 9.26.

5-(4-methoxybenzylidene)-3-(1H-benzimidazol-2-yl)-2-iminothiazolidin-4-one (8d)

IR (cm^{-1}): 1573 (C=C), 3014 (C-H Ar), 3445 (-NH), 653 (C-S), 1705 (C=O), 831 (C-N), 2830 (CH_3-O) ^{1}H NMR (δ ppm) 12.12 (s, 1H, -NH), 7.11 -7.19 (m, 7H, Ar-H), 8.78 (s, 1H, -NH), 6.25 (s, 1H, CH); ESI-MS *m/z* 351 M^++1; Anal. Calcd for $C_{18}H_{14}N_4O_2S$ (350.39): C, 61.70; H, 4.03; N, 15.99; O, 9.13; S, 9.15; Found: C, 61.72; H, 4.01; N, 15.96; O, 9.10; S, 9.16.

5-(4-chlorobenzylidene)-3-(1H-benzimidazol-2-yl)-2-iminothiazolidin-4-one (8e)

IR (cm^{-1}): 1555 (C=C), 3018 (C-H Ar), 3460(-NH), 1710 (C=O), 662 (C-S), 831 (C-N), 750 (C-Cl); ^{1}H NMR (δ ppm) 11.94 (s, 1H, -NH), 7.11 -7.21 (m, 7H, Ar-H), 8.75 (s, 1H, -NH), 6.22 (s, 1H, CH); ESI-MS *m/z* 356 M^++1; Anal. Calcd for $C_{17}H_{11}ClN_4OS$ (354.81): C, 57.55; H, 3.12; Cl, 9.99; N, 15.79; O, 4.51; S, 9.04 Found: C, 57.53; H, 3.11; Cl, 9.96; N, 15.76; O, 4.50; S, 9.02.

5-(2,4-dichlorobenzylidene)-3-(1H-benzimidazol-2-yl)-2-iminothiazolidin-4-one (8f)

IR (cm^{-1}): 1550 (C=C), 3023 (C-H Ar), 3440(-NH), 667 (C-S), 1708 (C=O), 824 (C-N), 755 (C-Cl); ^{1}H NMR (δ ppm) 11.91 (s, 1H, -NH), 7.09 -7.18 (m, 6H, Ar H), 8.71 (s, 1H, -NH), 6.20 (s, 1H, CH); ESI-MS *m/z* 390 M^++1; Anal. Calcd for $C_{17}H_{10}Cl_2N_4OS$ (389.26): C, 52.45; H, 2.59; Cl, 18.22; N, 14.39; O, 4.11; S, 8.24 Found: C, 52.43; H, 2.58; Cl, 18.22; N, 14.38; O, 4.08; S, 8.22.

5-(2-bromobenzylidene)-3-(1H-benzimidazol-2-yl)-2-iminothiazolidin-4-one (8g)

IR (cm^{-1}): 1540 (C=C), 3029 (C-H Ar), 3440 (-NH), 662 (C-S), 1713 (C=O), 821 (C-N), 763 (C-Br); ^{1}H NMR (δ ppm) 11.96 (s, 1H, -NH), 7.09 -7.20 (m, 7H, Ar-H), 8.73 (s, 1H, -NH), 6.23 (s, 1H, CH); MS *m/z* 400 M^++1; Anal. Calcd for $C_{17}H_{11}BrN_4OS$ (399.26): C, 51.14; H, 2.78; Br, 20.01; N, 14.03; O, 4.01; S, 8.03 Found: C, 51.12; H, 2.78; Br, 20.03; N, 14.01; O, 4.03; S, 8.02.

5-(4-bromobenzylidene)-3-(1H-benzimidazol-2-yl)-2-iminothiazolidin-4-one (8h)

IR (cm^{-1}): 1536 (C=C), 3016 (C-H Ar), 3443(-NH), 667 (C-S), 1710 (C=O), 828 (C-N), 755 (C-Br); ^{1}H NMR (δ ppm) 11.92 (s, 1H, -NH), 7.11 -7.17 (m, 7H, Ar H), 8.71 (s, 1H, -NH), 6.20 (s, 1H, CH); ESI-MS *m/z* 386 M^++1; Anal. Calcd for $C_{17}H_{11}BrN_4OS$ (399.26): C, 51.14; H, 2.78; Br, 20.01; N, 14.03; O, 4.01; S, 8.03. Found: C, 51.12; H, 2.75; Br, 20.01; N, 14.03; O, 4.02; S, 8.01.

5-(4-butoxybenzylidene)-3-(1H-benzimidazol-2-yl)-2-iminothiazolidin-4-one (8i)

IR (cm^{-1}):1573 (C=C), 3014 (C-H Ar), 3445 (-NH), 653 (C-S), 1705 (C=O), 831 (C-N), 2800 (-CH_3-O), 2970 (-CH_3); ^{1}H NMR (δ ppm) 12.12 (s, 1H, -NH), 7.13 -7.19 (m, 7H, Ar-H), 1.70 (m, 2H, CH_2), 1.6 (m, 2H, CH_2), 0.96 (t, 3H, CH_3), 8.78 (s, 1H, -NH), 3.26 (s, 2H, CH_2), 6.25 (s, 1H, CH); ESI-MS *m/z* 393 M^++1; Anal. Calcd for $C_{21}H_{20}N_4O_2S$ (392.47): C, 64.27; H, 5.14; N, 14.28; O, 8.15; S, 8.17. Found: C, 64.24; H, 5.13; N, 14.25; O, 8.16; S, 8.12.

5-(2,4-dibromobenzylidene)-3-(1H-benzimidazol-2-yl)-2-iminothiazolidin-4-one (8j)

IR (cm^{-1}) 1536 (C=C), 3024 (C-H Ar), 3448(-NH), 675 (C-S), 1710 (C=O), 834 (C-N), 759 (C-Br); ^{1}H NMR (δ ppm) 11.88 (s, 1H, -NH), 7.14 -7.18 (m, 6H, Ar-H), 8.69 (s, 1H, -NH), 6.18 (s, 1H, CH); ESI-MS *m/z* 479 M^++1; Anal. Calcd for $C_{17}H_{10}Br_2N_4OS$ (478.16): C, 42.70; H, 2.11; Br, 33.42; N, 11.72; O, 3.35; S, 6.71. Found: C, 42.72; H, 2.10; Br, 33.41; N, 11.69; O, 3.32; S, 6.73.

5-(2-propoxybenzylidene)-3-(1H-benzimidazol-2-yl)-2-iminothiazolidin-4-one (8k)

IR (cm^{-1}): 1565 (C=C), 3232 (C-H Ar), 3440 (-NH), 640 (C-S), 1700 (C=O), 831 (C-N), 2800 (-CH_3-O); ^{1}H NMR (δ ppm) 12.12 (s, 1H, -NH), 7.10 -7.19 (m, 7H, Ar H), 1.4 (q, 2H, CH_2), 3.5 (t, 3H, CH_3), 8.78 (s, 1H, -NH), 6.25 (s, 1H, CH); ESI-MS *m/z* 379 M^++1; Anal. Calcd for $C_{20}H_{18}N_4O_2S$ (378.45): C, 63.47; H, 4.79; N, 14.80; O, 8.46; S, 8.47. Found: C, 63.44; H, 4.76; N, 14.82; O, 8.47; S, 8.45.

5-(2,4-difluorobenzylidene)-3-(1H-benzimidazol-2-yl)-2-iminothiazolidin-4-one (8l)

IR (cm^{-1}): 1530 (C=C), 3028 (C-H Ar.), 3461(-NH), 670 (C-S), 1710 (C=O), 830 (C-N), 1030 (C-F); ^{1}H NMR (δ ppm) 11.91 (s, 1H, -NH), 7.12 -7.18 (m, 6H, Ar-H), 8.67 (s, 1H, -NH), 6.15 (s, 1H, CH); ESI-MS *m/z* 357 M^++1; Anal. Calcd for $C_{17}H_{10}F_2N_4OS$ (356.35): C, 57.30; H, 2.83; F, 10.66; N, 15.72; O, 4.49; S, 9.00. Found: C, 57.31; H, 2.81; F, 10.64; N, 15.70; O, 4.47; S, 9.02.

Antibacterial Assay

Minimum inhibitory concentration (MIC) was determined by using two fold serial dilution method [19,20] with 96-well microtest plates. For determining antibacterial activity, synthesized compounds and standard drugs were dissolved in redistilled dimethyl sulphoxide (DMSO). Further dilutions were prepared at required quantities of 512, 256, 128, 64, 32, 16, 8, 4, 2 and 1µg/ml, respectively. In order to ensure that solvent has no effect on bacterial growth, a control test was also performed containing broth, supplemented with only DMSO at same dilution used in our experiment. The cultures were obtained in Mueller–Hinton broth for all bacteria after 24 h of incubation at 37ºC. Testing was carried out on Mueller–Hinton broth at pH 7.4 and two fold serial dilution technique was applied. A set of tubes containing only inoculated broth was kept as control. After incubation for 24 h at 37^{o}C, last tube was recorded with no growth of microorganism to represent MIC. Every experiment in anti-

bacterial assay was replicated twice in order to define MIC values.

QSAR Modeling

QSAR modeling was carried out using sequential multiple linear regression (SMLR) method in order to develop QSAR models between antibacterial activity as dependent variables and calculated descriptor values as independent variables. All the calculation to draw molecular descriptor was done on P-IV processor using CS Chem office [24], in order to perform correlation analysis VALSTAT [25] software was used. The structure of benzimidazolo thiazolidinone, thiazinone and 5-arylidene-2-imino-4-thiazolidinone derivatives were drawn in Chem draw and copied to Chem 3D ultra to create 3D model. The structures then subjected to energy minimization using molecular mechanism (MM2) until the root mean square (RMS) gradients value < 0.1 kcal/mol. The energy-minimized molecules were subjected to re-optimization via Austin model-1(AM1) method until the RMS gradient attained a value smaller than 0.001kcal/mol Å using MOPAC. The geometric optimization of the lowest energy structure was carried out eigenvector (EF) routine. The energy-minimized geometry was used for the calculation of descriptor and extended Huckel charges of different atoms. The descriptor values were calculated using "compute properties" module of the program. The total number of descriptor calculated was about 43. Compounds were divided into training set of 14 compounds and test set of 6 compounds for antibacterial activity by straightforward random selection through activity sampling automatically by VALSTAT. The ± data within the parentheses are the standard deviation, associated with the coefficient of descriptors in regression equations. Statistical quality of SMLR equations was judges by parameter like observed squared correlation coefficient (r^2), standard error of estimate (SE), sequential Fischer test (F), bootstrapping squared correlation coefficient (r^2_{bs}), bootstrapping standard deviation (S_{bs}), chance statistics (evaluated as the ratio of the equivalent regression equations to the total number of randomized sets; a chance value of 0.001 corresponds to 0.1% chance of fortuitous correlation), outliers on the basis of Z-score value. The predicted power of equations was validated by cross validated squared correlation coefficient (Q^2) and by predictive squared correlation coefficients (r^2_{pred}). Internal consistency of the model was supported by S_{PRESS} and S_{DEP}, lower values of these parameters describe the better predictability of QSAR model. Bootstrapping analysis was performed for further access of the robustness and statistical confidence.

CONFLICTS OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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