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NEWLY DEVELOPED STATISTICALLY INTENSIVE QSAR MODELS FOR BIOLOGICAL ACTIVITY OF ISATIN DERIVATIVES

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ABSTRACT. The present study introduces a new approach for the quantitative structure-activity relationship (QSAR) issue, which can be called a statistically intensive or condensed QSAR model. This idea was successfully applied to the published data of 32 biologically active molecules derived from 4-(1-aryl-2-oxo-1,2-dihydro-indol-3-ylideneamino)-N-substituted benzene sulfonamides for mixed bacteria and specific bacteria like B.subtilis, E.coli, and S.aureus. The suggested four statistically intensive QSAR (SIQSAR) models possess only two descriptors with excellent statistical parameters, as their values of the square regression coefficient (r^2) and cross-validation (q^2) are lying within the range of 0.967–0.997 and 0.961–0.996, respectively. A zero-one correction term (ZO) reflects the effect of substituents, which was proposed as a second descriptor for two sets of biologically active compounds. In general, the results showed that the biological activity is depended majorly on the topographical properties, and predominated by the field-effect in contrast to an electronic one. The interesting feature of SIQSAR models is their closeness to mathematical methods such as simultaneous linear equation method by eliminating the common inaccuracy and unrealistic statistical treatments. The obtained SIQSAR models were employed for predicting new and efficient biologically active molecules derived from isatin.

Keywords: *QSAR, computational chemistry, isatin derivatives, biological activity, DFT*

INTRODUCTION

Quantitative structure-activity relationship (QSAR) studies can be considered as a powerful tool for scientists, particularly for significant assistance in reducing trial and error [1–6]. Moreover, utilizing QSAR to assess the biological

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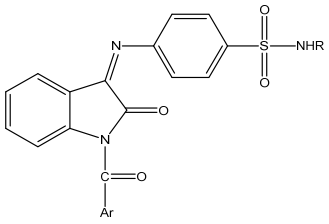
activity, which is termed *in silico* might be considered as parallel to that of experimental *in vivo* and *in vitro,* giving considerable value to this method [2]. At the same time, the background of QSAR is statistical rather than an accurate mathematical method such as simultaneous linear equation method [7]; therefore, researchers who deal with statistical analysis for building up their requested models should consider it attentively. In other words, the statistical treatments always produce results regardless of the correctness and reliability of the provided or input data [8,9]. Furthermore, the outcome of statistical data may be meaningless or without physical meaning, as the statistical calculations are adjusted by researchers in order to give a good correlation coefficient and a lower standard deviation [8–16]. For this reason, the confidence of statistical results depends on the number of both descriptors and observations. Consequently, the decrease in the number of descriptors increases the reliability of the results, while, the decrease in the number of observations makes the results less reliable. Thus, selecting the right descriptors can be considered as a crucial for building up a suitable model.

In general, there are thousands of published articles related to biological activity, using QSAR [17–22]. Most of QSAR studies are dealing with antimicrobial and antifungal activity. No serious efforts have been found for adopting models with statistical significance by reducing the number of descriptors of the suggested model, including physical meaning. In other words, there is always gain combined with loss, as using a few descriptors leads to weak statistical parameters. For instance, the square of the correlation coefficient (r^2) or coefficient of determination cannot exceed 0.937 for two descriptors with 14 observations, and a low value of cross-validation (q^2) up to 0.889 has been found for the same model [23]. Furthermore, the developed model by the QSAR model for biological activity and drug design should be more accurate than that of toxicity.

In the present study, efforts have been made to obtain an intensive QSAR model from already published data for a set of 32 biologically active molecules derived from 4-(1-aryl-2-oxo-1,2-dihydro-indol-3-ylideneamino)-N-substituted benzene sulfonamides (Scheme 1) [24]. To the best of our knowledge, no QSAR models with high statistical and physical significance similar to the model presented here, have been found in the literature.



Scheme 1. The skeleton of isatin derivatives

RESULTS AND DISCUSSION

Table 1 exhibits the estimated properties of isatin derivatives, using HF and PM3 calculations. These descriptors, shown in Table 1, were selected with regard to the dependency between each other, and according to the correlation matrix that was built up for this purpose. The correlation matrix that is built up for filtered properties from the correlation issue is illustrated in Table 2. It is apparent from the data of this table that the properties belong to topography, have the best correlation or dependency with the biological activity of isatin derivatives. Therefore, the models were built up with respect to these parameters. Indeed, the aim of the present study was to solve the QSAR issue, by suggesting an intensive model that is nearly close to accurate mathematical methods with excellent regression parameters. Thus, the first descriptor was selected in accordance with the simple correlation between the biological activities and the adjusted parameters, as exhibited in Table 2. According to the values of correlation coefficient (r), a very good correlation has been observed for those belonging to the topographical properties such as molar refractivity (MR) and Balaban Index (J). However, an additional descriptor must be found in order to enhance the efficiency of the model by supporting physical and statistical significance. It should be noted that the presented training set contains 28 observations, which definitely need multiple descriptors for building up the required model. The aim of this study was to develop an intensive and reliable model that can be used with confidence. Therefore, a second descriptor was added to reinforce the model that already contains the first main topographical parameters, as shown in Table 2. For those of MICec and MICsa, the model of both consists of two descriptors, including cluster count (CCO) together with a molecular topological index (MTI), showing excellent statistical parameters, as demonstrated in Table 3. This phenomenon could indicate that both of these antimicrobial agents (MICec and MICsa) use the same antibacterial mechanism. While for other antimicrobial agents (MICab and MICbs), the first descriptor for both is the molar refractivity (MR), which also belongs to topography. The suggested second descriptor is called zero-one correction term (ZO) that is developed with respect to the chemical structure of the molecule of which depends merely on substituents. This new proposed descriptor boosts the model from a statistical point of view. Indeed, this adopted descriptor has a value of one or zero, which could support the physical impact of the model due to the blind issue of statistical treatments. The new descriptor, ZO depends on the chemical structure of the derivatives, through recognizing the structural effect, according to the residuals of predicted values from the simple regression with MR descriptor. Hence, a value equal to one will be taken only if there is a structural

effect in the substituent. In the presented model, only five observations with the structural effect were detected, where the correction term ZO was included, which takes the value of one in contrast to the value of zero as no correction for the rest of the derivatives. This indicates that only 15.6% of the molecules, including both sets of training and test, have two descriptors in the suggested model, in comparison to only one descriptor for others. However, the structural effect of the correction term includes the field-effect that produced from para chlorine of the aryl group, in addition to the presence of β,β-dinitrogen with respect to the imine group, as compounds 8, 9, 16, and 27, and also in the presence of acetyl groups, as compound 30. In other words, there is a notable field-effect that resulted from the presence of chlorine at the para position of the aryl group, as well as the presence of β,β-dinitrogen, and acetyl groups with regard to the imine group. Indeed, such a phenomenon supports the use of the correct statistical point in understanding the substituent effect on the biological activity of molecules. However, we cannot give a more in-depth explanation about the effects of substituents for the five compounds that required the correction factor.

Table 3 displays the obtained models for antibacterial activity as the MIC for the four types of antimicrobials. We know that the presence of a structural effect like ZO has a negative effect on antibacterial activity. Excellent statistical parameters for these models were found despite the very low number of descriptors that have been used for building up the current models. This clearly announces the achievement in developing the QSAR studies. The interesting values of cross-validation (q^2) as very close to unity, indicate the significant confidence of the developed models, which are very close to reality. It should be noted that the number of descriptors is less than that recommended by the Topliss-Costello rule, with values of r^2 and q^2 better than that recommended by this rule [1]. As mentioned above in the introductory section, the value of q^2 of previous studies cannot exceed 0.889, in contrast to the values of 0.979, 0.996, 0.965, and 0.961 for the current models, despite using lower descriptors and more observations [23]. Furthermore, the already published QSAR model for 28 observations of presented MICab contains one descriptor (molecular connectivity) with r^2 and q^2 equal to 0.702 and 0.639, respectively [24]. Such excellent values of QSAR statistical properties obtained in this study may be due to the considerable confidence that resulted from only two descriptor models of 28 observations. In general, the developed models suggest that field-effect plays a major role in the biological activity of the selected bacteria. This suggestion is raised from that the position of chlorine substituted at the benzene ring of the aryl group, giving a remarkable effect to the biological activity, and indicating the high efficiency of field-effect in contrast to an electronic one.

Table 1. The values of selected descriptors used in the regression analysis in addition to adopted zero-one correction term (all of these theoretical descriptors were estimated, using DFT method, except for those of ε_{HOMO} and ε_{LUMO}, which are calculated, using the PM3 method

No.	CCO	MTI	MR	J	logP	PSA	ε_{HOMO}	ε_{LUMO}	zero-one
Training set									
1	35	29638	128.901	1816557	3.938	117.50	-0.35284	-0.04909	0
2	32	22508	116.888	1359822	2.762	112.98	-0.37258	-0.04478	0
3	36	32686	133.506	2083132	3.994	120.63	-0.37091	-0.04570	0
4	39	40047	142.160	3058009	4.469	139.09	-0.36196	-0.04659	0
5	37	35317	136.793	2414561	4.288	129.86	-0.34764	-0.04929	0
6	35	30276	130.153	1816973	4.092	108.27	-0.33533	-0.04799	0
7	36	31240	133.706	2080770	4.497	117.50	-0.36908	-0.05084	0
8	37	34402	138.311	2377200	4.552	120.63	-0.35199	-0.04802	1
9	40	41982	146.965	3455532	5.027	139.09	-0.35069	-0.05352	1
10	38	37102	141.598	2743970	4.847	129.86	-0.37963	-0.04950	0
11	36	30974	133.706	2054269	4.497	117.50	-0.36876	-0.05171	0
12	33	23616	121.693	1555851	3.321	112.98	-0.36556	-0.04888	0
13	36	31342	133.412	2054706	3.848	120.63	-0.37483	-0.05156	0
14	37	34124	138.311	2348338	4.552	120.63	-0.34627	-0.04443	0
15	35	28285	133.459	1784218	4.991	108.27	-0.34851	-0.04737	0
16	40	41682	146.965	3418784	5.027	139.09	-0.35319	-0.05184	1
17	38	36818	141.598	2712561	4.847	129.86	-0.37089	-0.05041	0
18	36	31644	134.958	2054706	4.65	108.27	-0.36676	-0.04836	0
19	34	26725	121.323	1585232	2.554	126.73	-0.37462	-0.05160	0
20	31	20085	109.310	1169971	1.378	122.21	-0.36489	-0.05191	0
21	34	27058	121.029	1585627	1.905	129.86	-0.36455	-0.05813	0
22	35	29579	125.929	1824777	2.609	129.86	-0.34498	-0.04451	0
23	33	24293	121.076	1366340	3.049	117.50	-0.36043	-0.04876	0
24	38	36464	134.583	2705554	3.084	148.32	-0.35137	-0.05120	0
25	36	32043	129.215	2124021	2.904	139.09	-0.37358	-0.05034	0
26	34	27329	122.575	1585627	2.708	117.50	-0.36543	-0.04631	0
27	36	31610	133.412	2081207	3.848	120.63	-0.37672	-0.05464	1
28	35	28541	133.459	1808479	4.991	108.27	-0.35835	-0.05049	0
Test set									
29	35	29989	128.607	1816973	3.289	120.63	-0.34537	-0.04565	0
30	33	23854	121.693	1579399	3.321	112.98	-0.36266	-0.05132	1
31	34	27032	128.654	1572317	4.433	108.27	-0.37091	-0.04791	0
32	36	31914	134.958	2081207	4.650	108.27	-0.26135	-0.12206	0

Table 2. The correlation matrix of biological activity of mixed antibacterial activity (MICab) specified bacteria like B.subtilis (MICbs), E.coli (MICec), and S.aureus (MICsa) with the selected descriptors

	MICab	**MICbs**	**MICec**	**MICsa**
ε_{HOMO}	0.168	0.152	0.152	0.150
ε_{LUMO}	-0.289	-0.319	-0.167	-0.146
logP	0.616	0.458	0.792	0.811
PSA	0.384	0.325	0.436	0.401
J	0.805	0.664	0.915	0.899
CCO	0.793	0.633	0.946	0.939
MTI	0.772	0.620	0.914	0.905
MR	0.794	0.623	0.964	0.967

Table 3. The suggested statistical intensive models for antimicrobial activity associated with statistical parameters

Eq. no	**Model**	r^2	q^2	***S.E.***
1	*MICab = 0.990 + 0.00318MR + 0.108 ZO*	0.985	0.979	0.007
2	*MICbs = 0.890 + 0.00318 MR + 0.308 ZO*	0.997	0.996	0.007
3	*MICec = 0.268 + 0.0508 CCO - 0.000015 MTI*	0.971	0.965	0.005
4	*MICsa = -0.034 + 0.0512 CCO - 0.000016 MTI*	0.967	0.961	0.006

Figures 1–4 show the linear relationship between estimated and observed antibacterial activity resulted from the application of the suggested models (Table 3) of both training and test sets for MICab, MICbs, MICec, and MICsa, respectively. The relationship of these figures exhibits excellent linearity as the coefficient of determination (r^2) is equal to 0.986, 0.997, 0.963, and 0.959 for MICab, MICbs, MICec, and MICsa, respectively. The residual standard error (*SE*) was calculated using the following equation:

$$SE = \sqrt{\frac{\sum(Y - Y_{est})^2}{n - 2}}$$

where *Y* is the observed MIC, Y_{est} is the estimated MIC and n is the number of observations. The values of *SE* for the training set of 28 observations are quite low, like 0.0073, 0.0073, 0.0053, and 0.0055 for MICab, MICbs, MICec, and MICsa, respectively. Indeed, these excellent values of SE demonstrate the success of the presented intensive models. In contrast, the values of *SE* get higher when the test set is included, as having values of 0.0211, 0.0075, 0.0781and 0.0825 for MICab, MICbs, MICec, and MICsa, respectively, which is generally may be due to the issue of the correction term.

In general, the obtained results are quite significant from both prediction and statistical points, supporting the success of building up a SIQSAR model, as having only two descriptors with 32 observations of the presented types of antimicrobials.

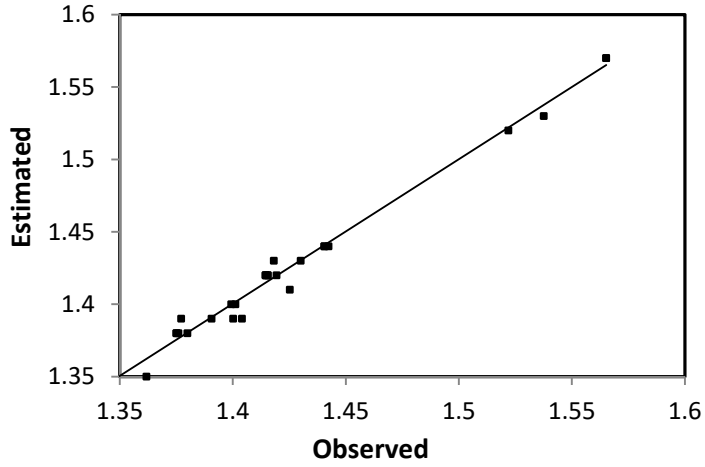


Figure 1. The plot of estimated MICab values versus observed MICab values according to the developed model 1, presented in Table 3.

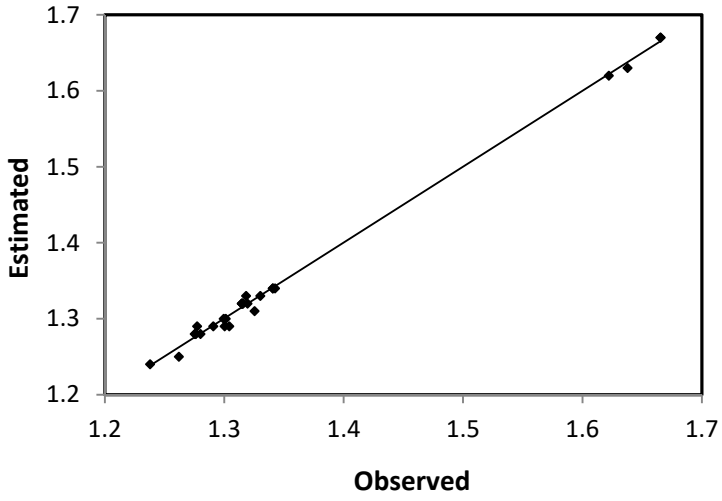


Figure 2. The plot of estimated MICbs values versus observed MICbs values according to the developed model 2, presented in Table 3.

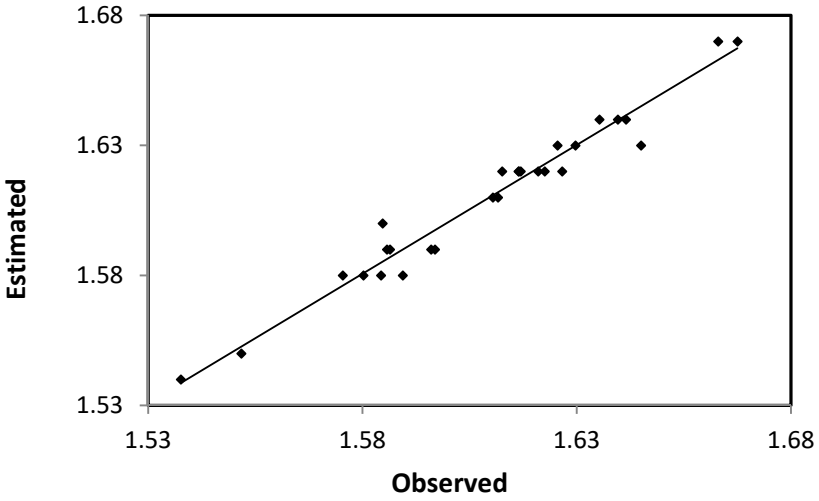


Figure 3. The plot of estimated MICec values versus observed MICec values according to the developed model 3, presented in Table 3.

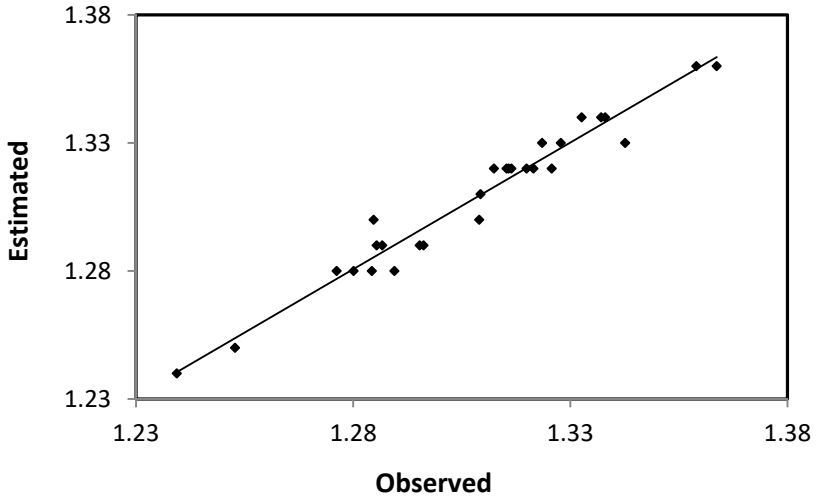


Figure 4. The plot of estimated MICsa values versus observed MICsa values according to the developed model 4, presented in Table 3.

The developed SIQSAR models were also used for predicting new biologically active compounds derived from isatin, as relatively having more efficient activity towards microbial agents. Such a study gives great advantages, particularly, in reducing the difficulty of trial and error. Table 4 shows the resulting predicted molecules in terms of the lowest MIC values together with their theoretically calculated properties. For MICec, no predicted molecule with the highest efficiency has been found, in contrast to that of compound number 29 (MICec =1.29). For other types of antimicrobials, some new derivatives are suggested in Table 4. It should be noted that the selection of the predicted compounds is not limited to the smallest value of MIC, but considerations should also be given to the value of the partition coefficient of the compound between water and octanol (logP). The lower the value of logP is, the more favored is from a pharmaceutical point of view. For MICab, the minimum MIC value is equal to 1.29 (Table 5) with logP equal to 3.289, but the predicted molecule is close to this value with lower logP, such as compounds ***a*** and ***c*** (Table 4). While for MICbs, three predicted derivatives have MIC values equal to 1.211, 1.217, and 1.223, with comparable logP, in contrast to molecule number 20 with MIC value equal to 1.24. Also, for MICsa there are three predicted molecules, possessing MIC values equal to 1.162, 1.185, and 1.189 with lower logP, in comparison with molecule number 20, which has a MIC value equal to 1.24. Thus, it is apparent that the developed SIQSAR models can be considered as a powerful tool for the prediction of new efficient biologically active compounds.

Table 4. The predicted molecules with their calculated properties, acting as antimicrobials using the developed models, presented in Table 3.

	Aryl group	**R group**	**MR**	**CCO**	**MTI**	**logP**	**MICab**	**MICbs**	**MICec**	**MICsa**
a		H	100.929	28	14852	1.667	1.311	1.211	1.467	1.162
b		CH_3	105.753	29	16619	1.506	1.326	1.226	1.491	1.185
c		OH	102.746	29	16153	1.468	1.317	1.217	1.499	1.192
d		NH_2	104.803	29	16386	0.892	1.323	1.223	1.495	1.189
e		-COH	104.718	30	18084	1.264	1.323	1.223	1.521	1.213

CONCLUSIONS

It can be concluded that the present approach of SISQAR for developing QSAR can be considered as a powerful tool for multiple linear regression studies of activated compounds. This can be attributed to the increases in the number of descriptors that decrease the probability of obtaining reliable results. The interesting feature of SIQSAR models can be deduced from eliminating the common inaccuracy and unrealistic statistical treatments, but it is not an accurate method, in contrast to mathematics. The application of the current approach to four sets of biologically active molecules produces excellent statistical parameters, which have not already obtained even using models with more descriptors and fewer observations. The new suggested term of SIQSAR may be attributed to any developed QSAR model of at least 20 observations, and possess one or two descriptors with excellent statistical parameters. Furthermore, the statistical properties that could be obtained from SIQSAR models have more efficiency than that of the best models, according to the Topliss-Costello rule [1]. Finally, this development in solving the QSAR issue shows the potential use of QSAR for drug design and biological activity, which requires more accuracy, in comparison with other related issues such as toxicity and environmental protection.

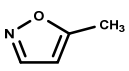
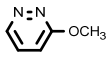
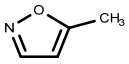
EXPERIMENTAL SECTION

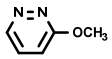
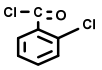
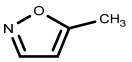
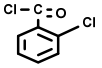
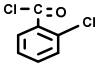
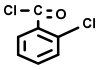
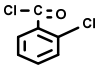
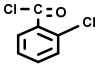
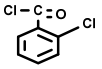
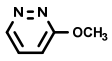
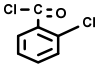
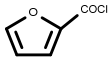
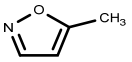
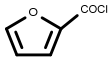
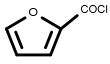
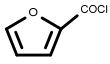
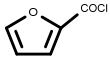
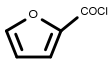
In the current investigation, the biological activity data showed the minimum inhibition concentration (MIC) for a set of thirty-two derivatives of isatin (Scheme 1), adopted from the study of Kumar *et al.* [24]. This set of molecules, as illustrated in Table 5, was subdivided into twenty-eight compounds as a training set, and the rest four were left as a test set. This included the biological activity for the mixed antibacterial activity (MICab) of which was performed against Gram-positive bacteria: S. aureus, B. subtilis, and the Gram-negative bacteria E. coli and some specified bacteria like *B.subtilis* (MICbs), *E.coli* (MICec), and *S.aureus* (MICsa).

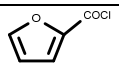
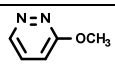
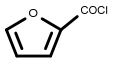
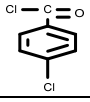
The chemical structures of istain derivatives and their models have been drawn, using two- dimensional Chemdraw ultra version 11.0. Each molecular structure has been transferred to undergo a systematic energy minimization, using Chem 3D-ChemBioOffice software version 16.0.0.82 (level: Ultra). In order to reach the global minima, the optimization was started from molecular mechanics calculations MM2, then MMFF94 methods were used to get a value of smaller than 0.1 kcal/mol of the root mean square (RMS) gradient [10,15]. The minimization process was continued, using

semi-empirical calculations, including Austin Model number 1 (AM1), followed by Parameterized Model number 3 (PM3) methods to reach a negative sign of heat of formation, and a positive sign of frequency. For density functional theory (DFT) calculations, the energy minimizations were continued, using DFT at B3LYP level with a 6-311G (d, p) basis set, until the minimum RMS gradient of 0.1 was reached [10]. The estimations of descriptors were carried out by Gaussian 03w software, using DFT, Hartree–Fock *ab initio* (HF), and PM3 methods (closed-shell MOs), depending on the type of selected descriptor. Statistical analysis for QSAR was performed, using Minitab software release 14.1.

Table 5. The structure of isatin derivatives with their antibacterial activity as minimum inhibitory concentration (MIC, I mol/mL), adopted from Kumar et al. [24].

No. of compound	Aryl Group	R. Groups	MICab	MICbs	MICec	MICsa
Training set						
1			1.39	1.29	1.59	1.29
2			1.35	1.25	1.55	1.25
3			1.40	1.30	1.60	1.30
4			1.44	1.34	1.64	1.34
5			1.41	1.31	1.61	1.31
6			1.39	1.29	1.59	1.29
7			1.42	1.32	1.62	1.32
8			1.53	1.63	1.63	1.33
9			1.57	1.67	1.67	1.36

No. of compound	Aryl Group	R. Groups	MICab	MICbs	MICec	MICsa
10			1.44	1.34	1.64	1.34
11			1.42	1.32	1.62	1.32
12			1.39	1.29	1.59	1.29
13			1.42	1.32	1.62	1.32
14			1.43	1.33	1.63	1.33
15			1.42	1.32	1.62	1.32
16			1.57	1.67	1.67	1.36
17			1.44	1.34	1.64	1.34
18			1.42	1.32	1.62	1.32
19			1.38	1.28	1.58	1.28
20			1.34	1.24	1.54	1.24
21			1.38	1.28	1.58	1.28
22			1.39	1.29	1.59	1.29
23			1.38	1.28	1.58	1.28
24			1.43	1.33	1.63	1.33

No. of compound	Aryl Group	R. Groups	MICab	MICbs	MICec	MICsa
25			1.40	1.30	1.61	1.30
26			1.38	1.28	1.58	1.28
27			1.52	1.62	1.62	1.32
28			1.42	1.32	1.62	1.32
Test set						
29			1.29	1.29	1.29	1.29
30			1.49	1.59	.59	1.29
31			1.39	1.29	1.59	1.29
32			1.42	1.32	1.32	1.62

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