



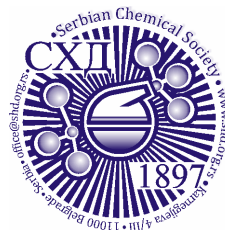
## ACCEPTED MANUSCRIPT

This is an early electronic version of an as-received manuscript that has been accepted for publication in the Journal of the Serbian Chemical Society but has not yet been subjected to the editing process and publishing procedure applied by the JSCS Editorial Office.

Please cite this article as K. N. Mishra, H. C. Upadhyay, and P. Verma, *J. Serb. Chem. Soc.* (2024) <https://doi.org/10.2298/JSC240330094M>

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*J. Serb. Chem. Soc.* **00(0)** 1-14 (2024)  
JSCS-12871

## Monte Carlo optimization-based QSAR modeling of *Staphylococcus aureus* inhibitory activity of coumarin-1,2,3-triazole hybrids

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(Received 30 March; revised 22 September; accepted 12 November 2024)

**Abstract:** In this study, 51 coumarin-1,2,3-triazole hybrids with known minimum inhibitory concentration (MIC) values against *Staphylococcus aureus* were used for the generation of a Monte Carlo based optimized QSAR model on CORrelations And Logic (CORAL) software. The entire dataset was divided into four different sets, namely the training set (Tr), the invisible training set (iTr), the calibration set (C), and the validation set (V) of three random splits. For each split, five models were generated using various combinations of SMILES, graphs, and hybrid optimal descriptors with various connectivity indices. Finally, fifteen models were obtained from three random, non-identical splits. For the best model from each split, the correlation coefficient ( $r^2$ ) ranged from 0.9672 to 0.8693, while the cross-validated correlation coefficient ( $Q^2$ ) ranged from 0.9478 to 0.8250. The mean absolute error (MAE) for the best models was less than 0.065. Additionally, favorable values of the index of ideality of correlation (IIC) and correlation intensity index (CII) were reported, justifying the robustness, reliability, and predictive potential of the developed models. Further, good and bad fingerprints were estimated based on correlation weights for structural attributes.

**Keywords:** CORAL software; antibacterial; structural attributes; index of ideality of correlation; correlation intensity index.

### INTRODUCTION

Natural products have played a crucial role in the discovery of drugs for almost all types of diseases.<sup>1</sup> The natural products as such and their semisynthetic analogs contribute more than half of the approved drugs of today.<sup>2,3</sup> Because of safety and compatibility, natural products are and will be at the center of the drug discovery process.<sup>4</sup> Traditional drug discovery methods often rely on trial-and-error approaches, which are time-consuming and resource-intensive.<sup>5</sup> However, due to

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<https://doi.org/10.2298/JSC240330094M>

dependence on several factors, it is not possible to estimate exactly, but on average, the development of a single drug from a new chemical entity may cost up to \$1 billion over twelve to fifteen years.<sup>5,6</sup> While natural products continue to inspire drug discovery efforts, there is a growing recognition of the need for innovative approaches that integrate advances in computational biology, synthetic chemistry, and biotechnology to overcome the limitations of traditional drug discovery.<sup>7,8</sup> By leveraging interdisciplinary approaches and cutting-edge technologies, researchers can harness the potential of natural resources more effectively and develop novel therapeutics with improved efficacy, safety, and sustainability.<sup>9</sup> Computer-aided drug design (CADD) has emerged as a powerful tool in the field of pharmaceutical research that utilizes computational methods to facilitate the discovery and development of new drugs.<sup>10</sup> The CADD approach integrates principles from various disciplines, such as chemistry, biology, and computer science, to expedite the drug discovery process.<sup>11,12</sup> CADD-based rational drug design approaches, viz., virtual screening by docking simulations, quantitative structure-activity relationship (QSAR) studies for lead optimization and prediction of bioactivities, and in silico prediction of physicochemical characteristics of molecules in terms of absorption, distribution, metabolism, and toxicity, help the researchers prioritize the most promising candidates for further experimental validation, significantly reducing the time and cost associated with traditional screening methods.<sup>10</sup>

QSAR studies play a pivotal role in drug discovery and development by enabling the rational design, optimization, and selection of potential drug candidates. QSAR models provide valuable insights into the relationship between the chemical structure of compounds and their biological activities.<sup>13</sup> QSAR modeling utilizes computational techniques to analyze the structural features of molecules and predict their pharmacological properties, thus facilitating the identification of potential drug candidates.<sup>10</sup> The application of QSAR studies is poised to revolutionize the drug discovery process, driving innovation and accelerating the development of new therapeutic agents to address unmet medical needs.<sup>10</sup> The most popular classic approach to QSAR modeling utilizes descriptors of molecular structure by using a simplified molecular input line entry system (SMILES) to correlate with the biological activity reported in wet lab experiments.<sup>14</sup> These models are formulated as a training set (for defining the model) and a test set or validation set (for checking the model with compounds of an external validation) and are often associated with one or more drawbacks.<sup>14</sup> A developed model must be robust enough to have high predictive power.<sup>14</sup> To validate a QSAR as scientifically legitimate and so enable its regulatory approval, the Organization for Economic Cooperation and Development (OECD) has proposed five guidelines.<sup>15</sup> For any QSAR model, "appropriate measures of goodness-of-fit, robustness, and predictivity" must be established, according to Principle 4 of OECD.<sup>15</sup> It highlights the necessity for both the QSAR model's

external validation (predictivity) and internal validation (as demonstrated by robustness and goodness-of-fit). The key to determining the trustworthiness of predictions is to determine whether the built models can be used with any confidence on new sets of data by using validation procedures.<sup>13,15</sup> The CORrelations And Logic (CORAL), a freeware software for QSAR modelling uses the standardized SMILES-based optimal descriptors.<sup>16</sup> CORAL generates random models based on the Monte Carlo approach, and from a probabilistic perspective, the algorithms employed in CORAL can provide some answers to the limitations of classic QSAR modeling issues.<sup>16</sup> If the statistical quality of the model can be replicated in a series of attempts to create the model for both the training and validation sets, then a random model may be a reasonable predictor for an endpoint.<sup>16,17</sup> Following this logic, CORAL allows random splits to build a robust QSAR model. One can utilize the balance of correlations that is provided by the CORAL in addition to the conventional scheme that was previously dealt with.<sup>16,17</sup> The division of the training set into a calibration set and a sub-training/invisible training set is the fundamental concept of the balancing of correlations.<sup>16</sup> The calibration set serves as the basis for the initial validation of the model the preliminary check assists in preventing overtraining. An additional measure to enhance predictability has involved analyzing the balance of correlations with optimal slopes.<sup>16</sup> If the values of the cluster's slopes on the internal training and calibration sets are as close to each other as possible, the plot of the experimental versus calculated endpoint values will be perfect.<sup>16,18</sup>

Coumarins (2H-1-benzopyran-2-one) are a varied class of naturally occurring pharmacophores with a wide range of bioactivities, viz., anti-inflammatory, antioxidant, antinociceptive, hepatoprotective, antithrombotic, antiviral, antimicrobial, antituberculosis, anticancer, antidepressant, antihyperlipidemic, anti-Alzheimer, anticholinesterase, and antiviral activities.<sup>19,20</sup> On the other hand, triazoles are five-membered heterocyclic compounds containing three nitrogen atoms that exist in two isomeric forms: 1,2,3-triazoles and 1,2,4-triazoles.<sup>21,22</sup> Commonly found in both natural and synthetic leads, 1,2,3-triazoles have a wide range of biological actions, including antitubercular, anticancer, antibacterial, and antifungal properties.<sup>21,22</sup> Being enriched with electronegative nitrogen atoms that can interact in a variety of ways with biological targets, the 1,2,3-triazole ring system has emerged as a versatile and intriguing scaffold in medicinal chemistry, offering a myriad of pharmacological effects that contribute to its significance in drug discovery.<sup>21,22</sup> In recent attempts to synthesize multitargeting 'hybrid molecules' there are enough reports on different Coumarin-1,2,3-triazole-based molecular hybrids synthesized by coupling the coumarin to 1,2,3-triazole as pharmacologically active segments, either in the presence or absence of tethering agents (spacer/linker).<sup>21,22</sup> Additionally, enough SAR has been identified in numerous series of potentially active coumarin hybrids with antibacterial,

anticancer, antitubercular, antifungal, anti-Alzheimer, antidiabetic, antidepressant, and antithrombotic properties that have been synthesized.<sup>21,22</sup>

In the given frame of context, from our recently published review encompassing the antibacterial coumarin-1,2,3-triazole hybrids, we collected data on coumarin-1,2,3-triazole hybrids with known activity against *Staphylococcus aureus* in terms of MIC values.<sup>21</sup> The collected data was used for the development of Monte Carlo optimization-based predictive QSAR modeling of *S. aureus* inhibitory activity of Coumarin-1,2,3-triazole hybrids.

## EXPERIMENTAL

### Data collection

A total of 51 coumarin-1,2,3-triazole derivatives showing minimum inhibitory concentration (MIC) values in the range of 0.4 to 75 µg/mL against *S. aureus* were retrieved from earlier published reports.<sup>21,23-30</sup> The molecular structures were drawn by using ChemDraw v22, saved in '.cdxml' format, and then converted to Simplified molecular-input line-entry system (SMILES) by using Optical Structure Recognition (OSRA) online tool (<https://cactus.nci.nih.gov/cgi-bin/osra/index.cgi>). The input files for building the QSAR models corresponding to SMILES of the derivatives along with their pMIC values were saved as text (.txt) (also see Table S-I of supplementary material).

### Descriptor Calculation

Three types of descriptors (i) SMILES-based, (ii) graph-based, and (iii) hybrid descriptors, which are combinations of SMILES and graphs, were calculated using CORAL (CORrelation And Logic) software (<http://www.insilico.eu/coral>).<sup>17</sup>

*SMILES-based descriptors*: The optimal SMILES based descriptor were calculated as follows:

$${}^{\text{SMILES}}\text{DCW}(T, N_{\text{epoch}}) = \alpha \sum \text{CW}(S_k) + \beta \sum \text{CW}(SS_k) + \gamma \sum \text{CW}(SSS_k) + \delta \text{CW}(\text{PAIR}) + x \text{CW}(\text{BOND}) + y \text{CW}(\text{NOSP}) + z \text{CW}(\text{HALO}) + m \text{CW}(\text{HARD}) \quad (1)$$

Where T is the threshold used to classify molecular features into rare (noise) and active based on their frequency, and  $N_{\text{epoch}}$  is the number of iterations of the optimization process. CW represents the correlation weight for the above-mentioned eight types of structural attributes.  $S_k$ ,  $SS_k$ , and  $SSS_k$  are local SMILES attributes as representations of molecular fragments. PAIR, BOND, NOSP, and HALO are global SMILES attributes, while the HARD index represents the association of BOND, NOSP, and HALO attributes. The coefficients  $\alpha$ ,  $\beta$ ,  $\gamma$ ,  $\delta$ ,  $x$ ,  $y$ ,  $z$ , and  $m$  are assigned binary values only, i.e., 0 if the attribute is not used in building the model or 1 if the attribute is used in building the model.  $S_k$  represents the sole SMILES element (e.g., Cl..., C..., N...),  $SS_k$  denotes the combination of two SMILES elements connected with each other, and they can be represented as C1... (... =... O..., etc.  $SSS_k$  stands for the combination of the three SMILES elements, represented as C... C... (... C... #... N..., etc. PAIR denotes the simultaneous presence of two SMILES atom compounds during descriptor calculation. The index BOND is related to the presence of three categories of chemical bonds i.e., '=' double bond, '#' triple bond, and '@@' stereospecific chemical bond. NOSP indicates the presence or absence of nitrogen, oxygen, sulfur, and phosphorous atoms. The index HALO is related to the presence or absence of only three halogen atoms i.e., fluorine, chlorine, and bromine.

*Graph-based descriptors:* In CORAL, three types of graph-based descriptors, namely HSG (hydrogen-suppressed graph), HFG (hydrogen-filled graph), and GAO (graph of atomic orbitals), with many invariants, are available. The optimal graph-based descriptors are calculated as follows:

$$\text{GraphDCW}(T, N_{\text{epoch}}) = \sum \text{CW}(A_k) + \alpha \sum \text{CW}({}^0\text{EC}_k) + \beta \sum \text{CW}({}^1\text{EC}_k) + \gamma \sum \text{CW}({}^2\text{EC}_k) + \delta \sum \text{CW}({}^3\text{EC}_k) \quad (2)$$

Where CW is the correlation weight of the invariants of the molecular graph. The indexes  $A_k$  is the correlation weight of atomic elements, and  ${}^0\text{EC}_k$ ,  ${}^1\text{EC}_k$ ,  ${}^2\text{EC}_k$ , and  ${}^3\text{EC}_k$  are the Morgan extended connectivity for each vertex in the molecular graph of the zero, first, second, and third order, respectively. The coefficients  $\alpha$ ,  $\beta$ ,  $\gamma$ , and  $\delta$  belong to invariants of molecular graphs, which can take up only binary values, i.e., 0 if not used or 1 if used in model building.

*Hybrid descriptors:* Hybrid descriptors are the combination of SMILES-based and graph-based descriptors and are calculated as follows:

$$\text{HybridDCW}(T, N_{\text{epoch}}) = \text{GraphDCW}(T, N_{\text{epoch}}) + \text{SMILESDCW}(T, N_{\text{epoch}}) \quad (3)$$

#### Monte Carlo optimization

A three-step process was chosen for the generation of a Monte Carlo-based optimized model. As required in the input format of CORAL software, the very first step entails preparing SMILES attributes from the molecular structures in various splits. The optimization of T and  $N_{\text{epoch}}$  values for each model independently is the second step. Here,  $N_{\text{epoch}}$  is the number of iterations in the Monte Carlo optimization, and T is the number of thresholds for classifying the molecular characteristics taken from the SMILES. Herein, values 1-4 of T and 15-60 of  $N_{\text{epoch}}$  were considered the most preferable combination.<sup>31</sup> The third and final step belongs to the calculation of descriptors (SMILES, graph, and hybrid) and optimization of correlation weights (CW) using the balance correlation scheme of the Monte Carlo algorithm.<sup>32</sup> The entire dataset was divided into four different sets, namely the training set (Tr), the invisible training set (iTr), the calibration set (C), and the validation set (V) of three random splits. The distribution of compounds in training and various sets of three random splits have been provided in Table S-II of the supplementary material. For each split, five models were generated using various combinations of SMILES, graphs, and hybrid optimal descriptors with various connectivity indices. Finally, fifteen models were obtained from three random non-identical splits.

#### Mechanistic interpretation

Correlation weights (CW) for structural attributes (SAKs), i.e., descriptors for SMILES, hybrids, and fragments of local symmetry, were obtained in several probes of the Monte Carlo optimization for the best models (M4, M10, and M11). Structural attributes were classified into four types: promoters of increase, promoters of decrease, undefined, and blocked. Those SAKs whose CW are positive indicate that these attributes of the derivatives of coumarin are promoters of an increase in MIC. SAKs with negative CW are responsible for decreasing the MIC of the derivatives. SAKs having both positive and negative correlation weights fall in the undefined category, and all the attributes, where CW shows null values, fall under the blocked category.

## RESULTS AND DISCUSSION

Several earlier published reports on the antibacterial activity of coumarin-1,2,3-triazole hybrids have been compiled in a review by our group.<sup>21</sup> These reports comprise a preliminary screening of the antibacterial activity of the

synthesized hybrid molecules against various Gram-positive and Gram-negative bacterial strains. The results of most of the preliminary screening have been published in terms of either zone of inhibition or MIC values. We collected the coumarin-1,2,3-triazole hybrids with antibacterial activities tested against *S. aureus* presented in MIC for the current study.<sup>21</sup> The descriptors of 51 molecules with known MICs were calculated using CORAL software, which calculates SMILES-based, graph-based, and hybrid descriptors, which are combinations of SMILES and graph-based descriptors. The literature reports highlight the outstanding forecasting capability of QSAR models on SMILES-based optimal descriptors as calculated by CORAL.<sup>16,33</sup> Using the Monte Carlo optimization method, the CORAL software allows the user to build QSAR models as a mathematical function of descriptors (also known as correlation weights of fragments of quasi-SMILES) with biological activity.<sup>16</sup> The entire dataset was divided into four different sets, namely the training set (Tr), the invisible training set (iTr), the calibration set (C), and the validation set (V) of three random non-identical splits: Split 1 (Tr = 16 compounds, iTr = 14 compounds, C = 11 compounds, and V = 10 compounds); Split 2 (Tr = 15 compounds, iTr = 14 compounds, C = 11 compounds, and V = 11 compounds); and Split 3 (Tr = 11 compounds, iTr = 15 compounds, C = 14 compounds, and V = 11 compounds) (also see table S2). Each set aimed to solve an individual task. The training set aims to find the maximum correlation coefficient between endpoint and descriptor for compounds present. The invisible training set is aimed at finding out whether the correlation is satisfactory for similar substances that are not involved in the training set. The calibration set identifies the starting point of overtraining. For each split, five models were generated using various combinations of SMILES, Graph, and hybrid optimal descriptors with various connectivity indices. Finally, fifteen models were generated after the search for the best preferable threshold value and  $N_{\text{epoch}}$  value for Monte Carlo optimization. The statistical parameters, correlation coefficient ( $r^2$ ), cross-validated correlation coefficient ( $Q^2$ ), standard error of estimation (s), Fischer ratio (F), mean absolute error (MAE), index of ideality of correlation (IIC), and correlation intensity index (CII), were calculated to evaluate the predictive potential of each model (Table I).



TABLE I: Various models for *S. aureus* inhibitory activity by using Monte Carlo optimization

No.	Splits	Parameter	T, N		n	r <sup>2</sup>	Q <sup>2</sup>	IIC	CII	s	MAE	F
M1	1	SMILES	1, 40	Tr	16	0.4147	0.1668	0.5008	0.7502	0.455	0.347	10
				iTr	14	0.9052	0.8791	0.4884	0.9264	0.510	0.343	115
				C	11	0.7681	0.6661	0.8762	0.8670	0.362	0.284	30
				V	10	0.8036	0.7118	0.1263	0.8281	0.535	0.355	33
M2	1	SMILES and HSG with 0 ECK	1, 25	Tr	16	0.9062	0.8655	0.9519	0.9312	0.182	0.137	165
				iTr	14	0.9009	0.8741	0.7171	0.9272	0.479	0.389	109
				C	11	0.7638	0.6257	0.8736	0.8526	0.309	0.246	29
				V	10	0.2453	-0.5510	0.1673	0.3575	0.897	0.493	3
M3	1	SMILES and HSG with 1 ECK	1, 50	Tr	16	0.8467	0.7969	0.7157	0.8887	0.233	0.188	77
				iTr	14	0.8470	0.8167	0.8623	0.8694	0.362	0.304	66
				C	11	0.8959	0.8539	0.9465	0.9194	0.231	0.178	77
				V	10	0.2455	-0.2148	0.1270	0.5582	0.969	0.610	3
M4	1	SMILES and HFG with 0 ECK	1, 40	Tr	16	0.8738	0.8250	0.7270	0.9184	0.211	0.161	97
				iTr	14	0.8819	0.8493	0.9371	0.9177	0.473	0.353	90
				C	11	0.8732	0.8114	0.9343	0.9066	0.221	0.188	62
				V	10	0.3808	0.0753	0.3603	0.5537	0.766	0.482	5
M5	1	SMILES and HFG with 1 ECK	1, 45	Tr	16	0.8871	0.8462	0.7325	0.9097	0.200	0.155	110
				iTr	14	0.8793	0.8515	0.6968	0.8947	0.414	0.354	87
				C	11	0.6791	0.4856	0.8239	0.8121	0.340	0.272	19
				V	10	0.4852	0.2614	0.1450	0.5698	0.580	0.360	8
M6	2	SMILES	1, 30	Tr	15	0.8593	0.8258	0.6180	0.8861	0.288	0.226	79
				iTr	14	0.8711	0.8339	0.3429	0.9105	0.286	0.223	81
				C	11	0.6806	0.4677	0.8248	0.7768	0.434	0.301	19
				V	11	0.6524	0.2616	0.4050	0.7163	0.419	0.249	17
M7	2	SMILES and HSG with 0 ECK	1, 70	Tr	15	0.8447	0.8099	0.6127	0.8804	0.303	0.230	71
				iTr	14	0.8773	0.8443	0.2638	0.9136	0.250	0.181	86
				C	11	0.7032	0.5015	0.8384	0.8000	0.426	0.279	21
				V	11	0.6121	0.4713	0.5489	0.7854	0.415	0.299	14
M8	2	SMILES and HSG with 1 ECK	1, 40	Tr	15	0.8519	0.8210	0.8076	0.8772	0.296	0.236	75
				iTr	14	0.8973	0.8661	0.5188	0.9334	0.305	0.254	105
				C	11	0.7634	0.6097	0.8735	0.8201	0.284	0.207	29
				V	11	0.4633	0.1582	0.0625	0.6474	0.771	0.534	8
M9	2	SMILES and HFG with 0 ECK	2, 25	Tr	15	0.8416	0.8015	0.6116	0.8806	0.306	0.246	69
				iTr	14	0.8852	0.8598	0.4471	0.9171	0.302	0.237	93
				C	11	0.6644	0.4191	0.8149	0.8271	0.438	0.334	18
				V	11	0.6085	0.4633	0.2208	0.7015	0.801	0.572	14
M10	2	SMILES and HFG with 1 ECK	1, 40	Tr	15	0.8693	0.8399	0.6216	0.9011	0.278	0.222	86
				iTr	14	0.8923	0.8602	0.0793	0.9248	0.294	0.219	99
				C	11	0.7627	0.5970	0.8733	0.8364	0.330	0.240	29
				V	11	0.6788	0.3623	0.5865	0.7518	0.511	0.381	19
M11	3	SMILES	1, 70	Tr	11	0.9672	0.9478	0.8195	0.9687	0.087	0.065	265
				iTr	15	0.8475	0.8045	0.5932	0.8851	0.624	0.489	72
				C	14	0.8889	0.8500	0.9428	0.9397	0.355	0.275	96
				V	11	0.2995	-0.0298	0.5029	0.6025	0.737	0.563	4
M12	3	SMILES and HSG	1, 33	Tr	11	0.9579	0.9282	0.8156	0.9632	0.099	0.079	205
				iTr	15	0.8301	0.7703	0.5334	0.8923	0.576	0.456	64

<i>M1</i> 3	with 0 Eck	C	14	0.8099	0.7314	0.8998	0.9394	0.420	0.326	51	
			V	11	0.3844	0.0716	0.5218	0.6268	0.891	0.750	6
	SMILES and HSG with 1 Eck	3, 15	Tr	11	0.8739	0.7521	0.5341	0.8810	0.171	0.128	62
			iTr	15	0.7665	0.6942	0.5871	0.8499	0.543	0.418	43
		1, 23	C	14	0.7612	0.6833	0.8725	0.8876	0.500	0.415	38
			V	11	0.3552	-0.2766	0.3893	0.5673	0.688	0.474	5
<i>M1</i> 4	SMILES and HFG with 0 Eck	3	Tr	11	0.9302	0.8892	0.8037	0.9414	0.127	0.093	120
				iTr	15	0.8668	0.8322	0.5049	0.8942	0.761	0.535
	SMILES and HFG with 1 Eck	1, 23	C	14	0.8469	0.7822	0.9195	0.9543	0.440	0.347	66
			V	11	0.3105	-0.0192	0.2676	0.6277	0.706	0.545	4
		3, 75	Tr	11	0.8928	0.7935	0.7874	0.9286	0.158	0.130	75
			iTr	15	0.7843	0.7114	0.4777	0.8490	0.436	0.317	47
<i>M1</i> 5	SMILES and HFG with 1 Eck	3	Tr	14	0.6740	0.5633	0.8205	0.8872	0.567	0.483	25
				V	11	0.3723	0.0122	0.2434	0.5971	0.649	0.462

T: Threshold, N:  $N_{\text{epoch}}$ /Number of iterations, n: Number of compounds in set,  $r^2$ : Correlation coefficient, s: Standard error of estimation, MAE: Mean absolute error, F: Fischer ration, Tr: Training set, iTr: Invisible training set, C: calibration set, V: Validation set

A developed QSAR model must, as always, be sufficiently robust to be able to forecast new molecular characteristics in an impartial, reliable, and precise way.<sup>9,14</sup> The so-called five OECD principles, which are internationally defined, are (i) a defined endpoint; (ii) an unambiguous algorithm; (iii) a defined domain of applicability; (iv) suitable measures of robustness, predictivity, and goodness-of-fit; and (v) a mechanistic interpretation, if feasible.<sup>15,34</sup> Considering OECD principles, the best models with higher predictive potential for each split are presented in Figure 1, and their equations are depicted below:

*Split 1:*

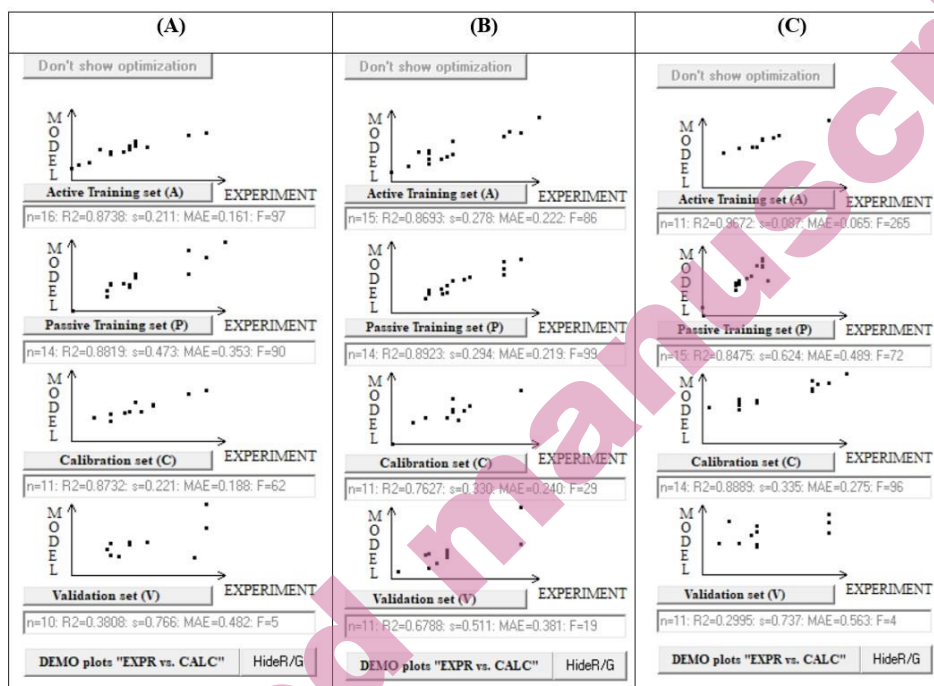
$$\text{pMIC} = -4.1880389 (\pm 0.1069537) + 0.1795520 (\pm 0.0063400) * \text{DCW} (1,40) \quad (\mathbf{M4})$$

*Split 2:*

$$\text{pMIC} = -4.4055993 (\pm 0.0701103) + 0.1119546 (\pm 0.0022489) * \text{DCW} (1,40) \quad (\mathbf{M10})$$

*Split 3:*

$$\text{pMIC} = -5.1755729 (\pm 0.1209286) + 0.1698881 (\pm 0.0045733) * \text{DCW} (1,70) \quad (\mathbf{M11})$$



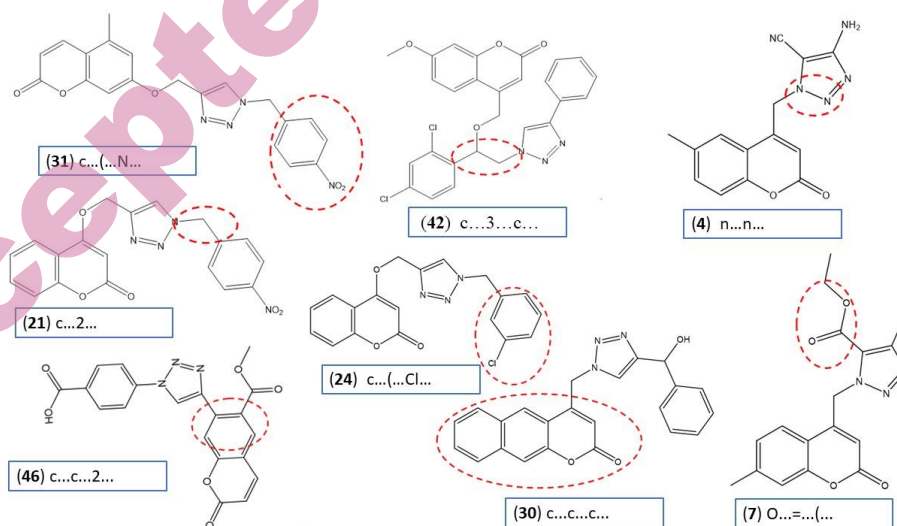
**Fig. 1.** Monte Carlo Optimization based on best QSAR models from each split: M4 from split 1 (A), M10 from split 2 (B), and M11 from split 3 (C).

The problem of overtraining in prediction models can be calculated by using the newly introduced parameters Index of Ideality of Correlation (IIC) and Correlation Intensity Index (CII), which increase the predictive potential of the model.<sup>18,35</sup> The IIC is based on the correlation coefficient and mean absolute error, while the CII indicates the statistical quality of linear regression models with a unique ability since it is a measure that is sensitive both to the value of the correlation coefficient and to the value of the mean absolute error (MAE).<sup>35</sup> Both IIC and CII can expose the drawbacks of the predictive model usually seen with others. Favorable statistical parameters are obtained for all the models from each split.

#### *Mechanistic interpretation*

Correlation weights (CW) for structural attributes (SAKs) were estimated for both SMILES and hybrid descriptors using CORAL software. Structural attributes were classified into four types: promoters of increased activity, i.e., good fingerprints (stable positive values), promoters of decreased activity, i.e., bad fingerprints (stable negative values), undefined, and blocked. SAKs having both positive and negative correlation weights fall in the undefined category, while all the attributes, where CW shows null values, fall under the blocked category. The

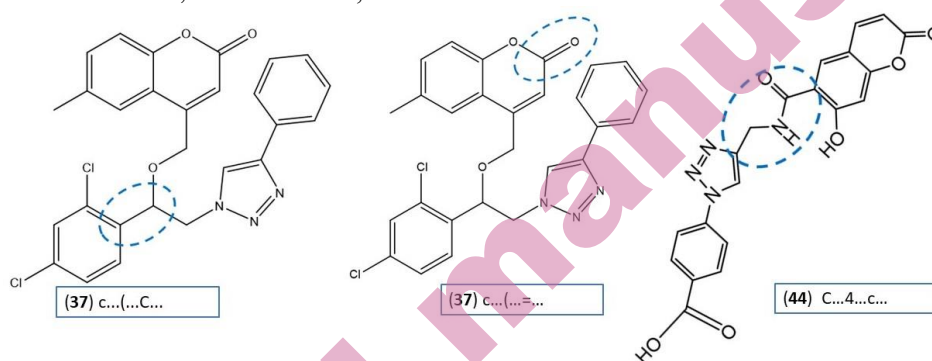
data on CW for each structural attribute, which were obtained in several probes of the Monte Carlo optimization for the best models (M4, M10, and M11), are shown in supplemental Table S-III. The structural attributes of coumarin-1,2,3-triazole hybrids responsible for the increase in MIC value (Figure 2) were c...3...c... (i.e. presence of two aromatic cycles at three bond distances as can be seen in compound **42**), c...2..... (i.e. presence of aromatic cycle followed by two bonds as can be seen in compounds **21**, and **22**), c...c...c... (i.e. presence of three fused aromatic cycles as can be seen in compound **30**), c...c...2... (i.e. presence of branching on adjacent aromatic cycle as seen in compound **46**), n...n.....(i.e. presence of adjacent Nitrogen atoms as in the compound **4**), O...=...(i.e. presence of Oxygen with double bonds as seen in the compound **7**), c...(Cl... (i.e. presence of aromatic cycle and Chlorine atom with branching as seen in compound **24**), and c...(N... (i.e. presence of aromatic cycle and Nitrogen atom with branching in between as can be seen in compound **31**). On the other hand, among the hybrid descriptor correlation weights of Morgan's extended connectivity, the promoters responsible for the crucial increase in the inhibitory activity of the derivatives were found to be "EC0-O...1...", "EC1-C...6...", "EC1-C...9...", "EC1-N...5...", "EC1-Cl...6...", "EC1-O...4...", "EC1-N...2...", and "EC1-N...8..." of the model. "BOND10000000" constitutes the presence of a double bond is very important for compound's activity.



**Fig. 2.** Good fingerprints causing the increase in activity against *S. aureus*

The structural attributes of coumarin-1,2,3-triazole hybrids responsible for the decrease in MIC value (bad fingerprints, Figure 3) obtained from M4, M10, and M11 among SMILES descriptors were found to be c...(=...(i.e. presence of

branching between aromatic carbon and double bonding as in compound **37**), c...4...c...(i.e., the presence of two aromatic cycles separated by four bonds as shown in compound **44**), and c...(C...(i.e., the presence of branching between aromatic ring and aliphatic carbon as in compound **37**). On the other hand, among hybrid descriptors correlation weights of Morgans extended connectivity the promoters responsible for the decrease of activity of the derivatives were found to be EC0-C...2..., EC1-C...10....



**Fig. 3.** Bad fingerprints causing the decrease in activity against *S. aureus*

It can be seen that promoters of the decrease effect are not very much affected by the Morgans' extended connectivity in comparison to the promoters of the increase. BOND11000000 (presence of a triple bond in the compound) and HALO00000000 (absence of a halogen atom) are detrimental to the inhibitory activity of bacteria.

#### CONCLUSION

New 2D-QSAR models with good prediction ability were developed and validated for the prediction of the antibacterial activity of coumarin-1,2,3-triazole hybrids against *S. aureus* using the Monte Carlo optimization method. The consideration of additional statistical parameters such as the index of ideality of correlation and correlation intensity index gave clear insight into the improved predictability in all the QSAR models. Overall, among all the developed models, M-11 may be considered best based on statistical parameters. The study provides a significant analysis of the important structural fingerprints required to be a potentially active substrate against *S. aureus*. Overall, the models will help design novel chemical entities with the coumarin-1,2,3-triazole moiety for the development of potent antibacterial drugs against *S. aureus*.

## SUPPLEMENTARY MATERIAL

Additional data are available electronically at the pages of journal website: <https://www.shd-pub.org.rs/index.php/JSCS/article/view/12871>, or from the corresponding author on request.

*Acknowledgements:* The authors thank the Director, of Rajkiya Engineering College, Sonbhadra, for his constant encouragement and for providing all types of facilities for this study. The financial support by the Council of Science and Technology Uttar Pradesh (Project No. 3027) is duly acknowledged.

## ИЗВОД

QSAR МОДЕЛОВАЊЕ ИНХИБИТОРНЕ АКТИВНОСТИ ХИБРИДА КУМАРИН-1,2,3-ТРИАЗОЛА НА *STAPHYLOCOCCUS AUREUS*, БАЗИРАНО НА МОНТЕ КАРЛО ОПТИМИЗАЦИЈИ

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У овој студији су 51 кумарински-1,2,3-триазолски хибрид са познатим минималним вредностима инхибирајућих концентрација (MIC) према *Staphylococcus aureus* искоришћени за генерисање, на Монте Карло заснованом, оптимизованог QSAR модела на CORrelations And Logic (CORAL) софтверу. Целокупан скуп података је подељен на четири различита скупа података, наиме скуп за увежбавање (Tr), невидљиви скуп за увежбавање (iTr), скуп за калибрисање (C), и скуп за валидацију (V) из три случајне поделе. За сваку поделу, било је генерисано пет модела користећи различите комбинације SMILES-а, графова, и хибридних оптималних дескриптора са различитим индексима повезаности, петнаест модела је добијено из три насумичне неидентичне поделе. За најбољи модел из сваке поделе, корелациони коефицијент ( $r^2$ ) ишао је од 0,9672 до 0,8693, док унакрсно валидирани коефицијенти корелације ( $Q^2$ ) ишли су од 0,9478 до 0,8250. Просечна апсолутна грешка (MAE) за најбоље моделе хе била мања од 0,065. Додатно, саопштене су пожељне вредности индекса идеалности корелације (IC) и индекс интензитета корелације (CII), потврђујући робустност, поузданост и потенцијал предвиђања развијених модела. Надаље, процењени су добри и лоши отисци прстију на основу корелационих тежина структурних атрибута.

(Примљено 30. март; ревидирано 22. септембра; прихваћено 12. новембра 2024.)

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