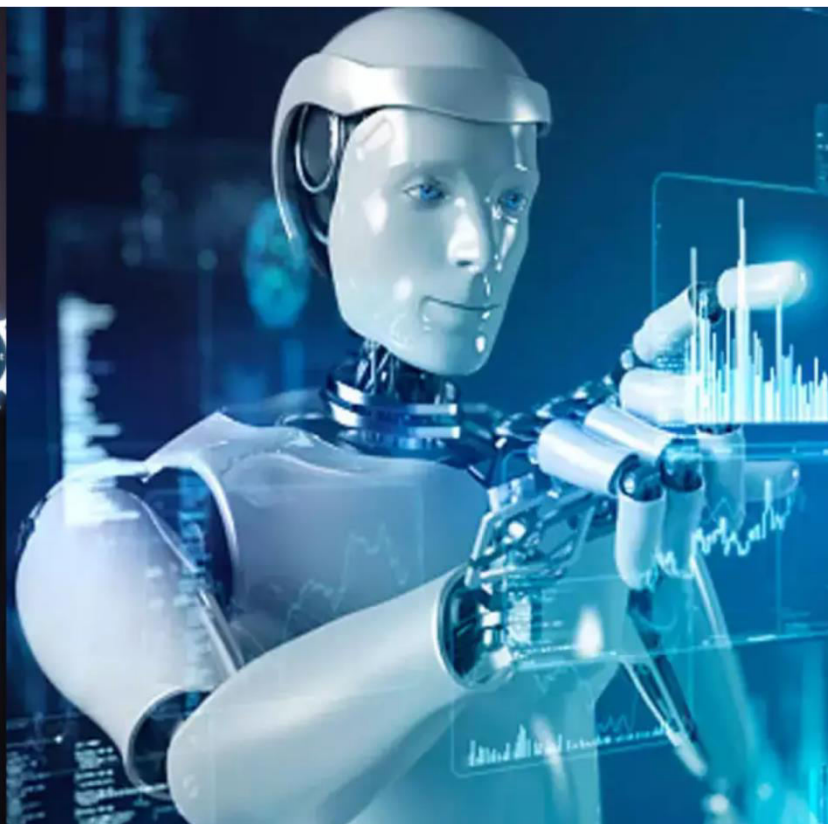




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Computational Design of Transition Metal Complexes as *E. coli* Inhibitors: A QSAR and Virtual Screening Approach

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ABSTRACT: Quantitative structure–activity relationship (QSAR) models have been developed for a data set of 24 transition metal complexes measuring the antibacterial activity against *Escherichia coli*. QSAR models were used to predict the true external compounds without experimental values, with the aim to look for compounds that might have an antibacterial activity against *Escherichia coli* (*E. Coli*). For the virtual screening, 480 untested compounds were theorised by changing the substituents for the ligands. The best predictive model was used to predict the inhibitory activity of transition metal complexes against *Escherichia coli*.

KEYWORDS: QSAR, virtual screening, transition metals, high throughput, validation

I. INTRODUCTION

“Descriptive QSAR” focusses on modelling the existing data, fitting them by using the well-known molecular descriptors for understanding the correlation in terms of mechanism. Such QSAR models are useful for biological end-points (drug design, toxicity, mutagenicity and carcinogenicity). “Predictive QSAR” also named as statistical QSAR has been developed on more heterogenous compounds and focused mainly on validation for new applications. It can be applied to screen and rank more diversified compounds. This QSAR is more useful for big data sets, for experimental tests on compounds that are in silico highlighted as potentially dangerous¹. Prioritizing the predictive QSAR over Descriptive QSAR can be applied to new, not yet synthesized compounds, allowing a Green Chemistry approach to the synthesis of new potentially safer chemicals. A key advantage of predictive QSAR models is their ability to forecast the behaviour of new or hypothetical molecules through mathematical equations. “2D-QSAR” refers specifically to models developed using two-dimensional descriptors, which are favoured for their straightforward mathematical nature, despite limitations such as intercorrelation and insufficient chemical information².

Paper is divided into sections. Section II describes the usefulness of QSAR in identifying compounds which are inhibitors of *E. coli*. Section III describes the experimental work followed by Section IV gives the results obtained in QSAR development and then virtual Screening of 480 compounds. Finally, section V presents conclusion.

II. LITERATURE SURVEY

The cost and time hinderance of traditional drug design has resulted in a list of neglected diseases for which effective drug design, followed by drug resistance, is still a challenge. The evolution of QSAR research has enabled faster, more cost-effective derivatives of drug praziquantel (PZQ) against Schistosomiasis by identifying a lead compound for creating new structural candidates with enhanced biological activity [1]. QSAR modelling for examining toxicity of nitrobenzenes and of the compounds 3,6-disubstituted-11H-benzo[5,6][1,4]thiazino[3,4-a]isoindol-11-ones and natural and synthetic 1,4-benzoxazin-3-ones was established for both antibacterial abilities against *B. subtilis*, *S. epidermidis*, *E. coli* and *P. aeruginosa*, and antifungal abilities against *C. albicans* and *A. niger* [2-4].

QSAR studies have been performed on a series of 24 compounds of imidazole derivatives as novel ORL1 receptor antagonists and on 4-isopropylhydrazones derivatives, reflecting a significant correlation between the experimental and the predicted biological activities [5,6]. QSAR models have explained the modification of wood by the method of acetylation, the correlation of antimicrobial activity of 1,3-disubstituted-1H-naphtho[1,2-c][1,3]oxazines with their topological parameters and in vitro antimicrobial, antiviral and cytotoxic activities [7,8].

The non availability of desired medicines, emergence of antimicrobial resistance, need to save resources has increased the threat of infectious diseases in developing countries. A series of benzylidene hydrazides was synthesized and tested, in vitro, for antibacterial, antifungal and antiviral activities. The use of computational approaches has helped in estimating the activity of different molecules as candidates for drugs before they are synthesized [9,10]. QSAR studies of 31 flavonoids, 4-(1-aryl-5-chloro-2-oxo-1,2-dihydro-indol-3-ylideneamino)-N-substituted benzene sulfonamides and a series of Schiff bases and esters of propionic acid were conducted for antimicrobial and antifungal evaluation. The progress made in the use of QSAR methods has shown that the hydrophobic or lipophilic nature of biologically active molecules are very important [11-14].

A Research explored the application of deep learning methods in ligand-based drug virtual screening, a computational approach to expedite drug discovery by screening potential drug candidates from vast databases. It addressed the increasing reliance on computational methods to reduce the time and cost associated with traditional drug discovery. It compared and analysed various deep learning methods, evaluating their performance on different sized datasets to tackle the challenge of large-scale ligand virtual screening. The study also examines the challenges and future directions in the field, including data complexity and annotation [15].

III. EXPERIMENTAL

MATERIALS AND METHODS:

The synthesis, spectral characterization and antibacterial studies on the complexes of few complexes of Nickel, Manganese, Cobalt and Copper with amide group containing ligands was performed [16-18]. Quantitative Structure-Activity Relationship (QSAR) modelling of these complexes is used to develop predictive models that relate the biological activity of compounds to their molecular properties. By identifying key structural and physicochemical features that influence activity, QSAR models provide valuable insights into drug design and optimization. In this study, a QSAR model was developed to predict the antimicrobial activity of a series of 24 compounds against *Escherichia coli* (*E. coli*). The 24 compounds were synthesized and their biological activity against *E. Coli* was performed. The activity of these compounds was determined based on their Minimum Inhibitory Concentration (MIC), and molecular descriptors were calculated to establish a predictive model. The ChemMaster 1.2 software was used for performing the QSAR modelling process.

GENERAL PROCEDURE:

DATA PREPARATION- Y-VARIABLE TRANSFORMATION

The biological activity, represented as MIC (Molar), was transformed into its logarithmic scale using the equation:

$$pMIC = -\text{Log}(MIC (M))$$

This transformation reduces the variance of the activity values and makes the relationship between the Y-Variable and X-Variables more linear ensuring a more suitable range for regression modelling.

MOLECULAR DESCRIPTORS

A set of fundamental drug-like molecular properties were calculated for each compound. These descriptors were chosen due to their interpretability and relevance to pharmacokinetics and molecular interactions. The selected descriptors include:

- **Molecular Weight (MW):** Total molecular weight of the compound.
- **Heavy Atom Molecular Weight (HAMW):** Sum of atomic weights of non-hydrogen atoms.
- **Hydrogen Bond Donors (HBD):** Number of hydrogen bond donor groups.
- **Hydrogen Bond Acceptors (HBA):** Number of hydrogen bond acceptor groups.
- **LogP:** Octanol-water partition coefficient, a measure of lipophilicity.

- **Rotatable Bonds (RB):** Number of freely rotatable single bonds.

DATASET SPLITTING

The dataset was randomly divided into:

- **Training set (75%, a total of 18 compounds)** – Used to build the model.
- **Test set (25%, a total of 6 compounds)** – Used to evaluate the predictive performance of the model.

MODEL DEVELOPMENT

Multiple Linear Regression (MLR) was chosen as the modelling method due to its simplicity, ease of interpretation, and widespread use in QSAR modelling. The model was constructed using the training set, with pMIC as the dependent variable and molecular descriptors as independent variables.

MODEL VALIDATION

To assess the performance and robustness of the QSAR model, validation metrics were computed for both the training and test sets. The following statistical parameters were evaluated:

- **Coefficient of Determination (R^2):** Measures the proportion of variance explained by the model.
- **Root Mean Squared Error (RMSE):** Represents the average magnitude of prediction errors.
- **Mean Absolute Error (MAE):** Measures the average absolute difference between predicted and actual values.
- **Leave-One-Out Cross-Validation Q^2 ($LOO-Q^2$):** Evaluates the internal predictive ability of the model by systematically omitting one observation at a time and predicting its value. Computed for the training set only as it is an internal validation method.

IV. RESULTS AND DISCUSSION

QSAR MODEL EQUATION

The resulting equation of the QSAR model developed via the MLR method is:

$$pMIC = +0.5438 \times H - \text{Bond Acceptors} + 1.3884 \times H - \text{Bond Donors} \\ - 0.9509 \times \text{Heavy Atoms Molecular Weight} + 0.017 \times \text{LogP} - 0.7942 \times \text{Molecular Weight} \\ + 1.3045 \times \text{Rotatable Bonds} + 4.8791$$

The positive coefficients for H-bond donors (HBD) and H-bond acceptors (HBA) suggest that these properties contribute positively to antimicrobial activity, likely due to their role in molecular interactions with the bacterial target. Conversely, the negative coefficients for heavy atom molecular weight (HAMW) and molecular weight (MW), imply that larger compounds may have reduced activity, possibly due to steric hindrance or lower permeability across bacterial membranes. The slight positive influence of LogP indicates that lipophilicity plays a minor role in activity, while rotatable bonds (RB) show a strong positive contribution, suggesting that increased molecular flexibility may improve target binding.

VALIDATION PARAMETERS FOR THE DEVELOPED QSAR MODEL

The computed validation parameters are displayed in Table 1.

Table 1: The validation parameters of the QSAR model for the training and test set.

Set	R^2	RMSE	MAE	Q^2
Training	0.775	0.067	0.056	0.508
Test	0.643	0.076	0.07	

The developed MLR model demonstrates a reasonable predictive ability, with an R^2 value of 0.775 for the training set, indicating that approximately 77.5% of the variance in pMIC values is explained by the selected molecular descriptors. The test set R^2 of 0.643 suggests that the model retains moderate predictive power on unseen data. The RMSE and MAE values for both sets indicate acceptable prediction errors, with lower values in the training set compared to the test set, as expected.

The experimental vs. predicted pMIC values plot illustrates the model's overall ability to predict the activity of the compounds. Points that are close to the diagonal line indicate good predictions by the model and close values to the experimental activity. Although some deviations are observed, which is common, the overall plot indicates the predicted values are close to experimental values. The plot is shown in Figure 1.

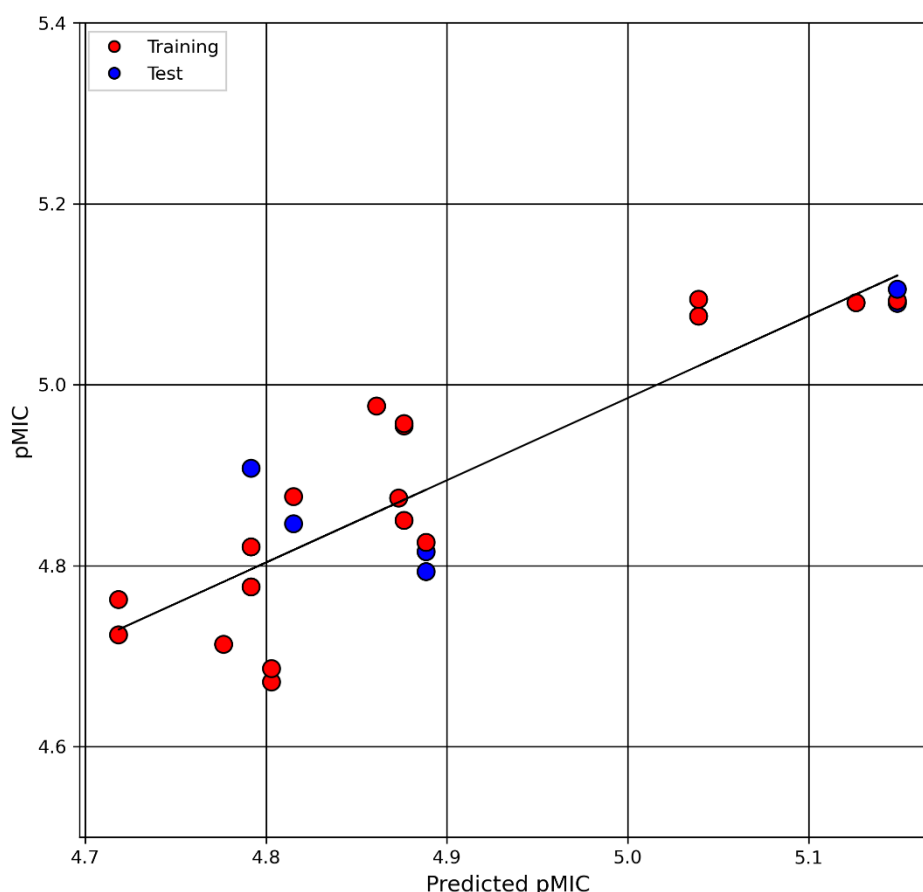


Fig 1. The plot of the experimental activity (pMIC) against the predicted activity (pMIC) by the QSAR model. The red points represent the training set compounds and the blue points represent the test set compounds.

VIRTUAL SCREENING

The developed QSAR model was used to predict the true external compounds without experimental values, with the aim to look for compounds that might have an antibacterial activity against *Escherichia coli* (*E. Coli*). For the virtual screening, 480 untested compounds were theorised by changing the substituents for the ligands. The predictive model was used to predict the inhibitory activity of transition metal complexes against *Escherichia coli*.

Ligand-based drug design is an indirect but highly effective strategy for discovering drug-like compounds. Instead of starting with detailed information about a biological target's structure, this approach focuses on studying molecules already known to interact with the target. By comparison, structure-based drug design draws directly on the three-dimensional structure of the target molecule itself to find or refine potential drug candidates [20].

APPLICABILITY DOMAIN

The applicability domain of our QSAR model was assessed using the leverage approach, ensuring that only predictions for compounds with descriptor values similar to the training set were considered reliable. Compounds falling outside this domain were flagged, and their predicted activities were interpreted with caution.

The top 8 compounds that fall within the applicability domain where activity values ranged from 8 to 20 mg/L where the model prediction can be considered reliable.

V. CONCLUSION

The developed QSAR model successfully predicts the antimicrobial activity of the studied compounds using basic molecular descriptors. The model exhibits good statistical performance and interpretability, making it a useful tool for early-stage drug discovery. Future improvements may include incorporating additional descriptors or non-linear modelling approaches to enhance predictive accuracy. The model can be readily used for performing virtual screening on compounds with unknown MIC values to identify potentially active new E. Coli inhibitors.

From the screening, the top 8 compounds exhibiting the predicted activity between the range of 8 and 20 mg/L were shortlisted as virtual hits. These compounds are summarized in figure 2, which includes their chemical identifiers, predicted activities, and key structural features. Analysis of these top hits revealed a diverse range of metal centers and ligand architectures, suggesting potential for structural novelty in antimicrobial research.

VS- results - E. Coli.sdf

Table	Structure	Molecule Name	cdx.fragmentId	Heavy Atoms Molecular Weight	Molecular Weight	LogP	H-Bond Acceptors	H-Bond Donors	Rotatable Bonds	Predicted Y (Complexes QSAR Model)	MIC (µM)	PPM (mg/L)
1		T0271.cdxml	292.0	571.191	635.703	8.7817	9.0	7.0	3.0	4.8661	13.6113	8.6527
2		T0277.cdxml	254.0	573.183	632.655	9.4354	9.0	5.0	4.0	4.8651	21.6222	13.6794
3		T0229.cdxml	254.0	583.202	651.746	9.6699	9.0	7.0	3.0	4.6001	25.1131	16.3674
4		T0230.cdxml	270.0	583.202	651.746	9.6699	9.0	7.0	3.0	4.6001	25.1131	16.3674
5		T0231.cdxml	280.0	583.202	651.746	9.6699	9.0	7.0	3.0	4.6001	25.1131	16.3674
6		T0269.cdxml	285.0	583.202	651.746	9.6699	9.0	7.0	3.0	4.6001	25.1131	16.3674
7		T0270.cdxml	264.0	583.202	651.746	9.6699	9.0	7.0	3.0	4.6001	25.1131	16.3674
8		T0280.cdxml	254.0	571.187	631.667	8.85	8.0	5.0	4.0	4.4962	31.9007	20.1506

Figure 2- Top compounds- Virtual Screening

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