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SAR AND QSAR MODELING OF ALGICIDAL COMPOUNDS BASED ON PHYSICOCHEMICAL DESCRIPTORS

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Abstract. *This study presents a comprehensive structure–activity relationship (SAR) and quantitative structure–activity relationship (QSAR) analysis of organic compounds with algicidal properties. By employing a dataset of structurally diverse molecules, we evaluated the predictive power of key physicochemical descriptors, including boiling point, melting point, vapor pressure, logP, and molecular weight. Statistical models were constructed using multiple linear regression and validated through cross-validation techniques to assess their accuracy and robustness. The results indicate that certain descriptors, particularly logP and vapor pressure, show a strong correlation with algicidal efficacy. The proposed models provide a valuable framework for the rational design and pre-screening of environmentally safe algicides, reducing the need for labor-intensive bioassays.*

Keywords: *algicidal compounds, physicochemical descriptors, SAR, QSAR, predictive modeling, organic pesticides, environmental toxicity.*

Introduction: Harmful algal blooms (HABs) have become an increasing concern in aquatic ecosystems, causing ecological imbalance, biodiversity loss, and serious risks to public health and water quality. As conventional chemical treatments often lead to environmental toxicity and non-selective bioaccumulation, the demand for safer, more targeted algicidal agents has grown significantly. Among the promising alternatives are organic compounds with tunable structures and physicochemical properties that can be optimized for algicidal selectivity and environmental compatibility.

Recent advancements in cheminformatics have enabled the use of structure–activity relationship (SAR) and quantitative structure–activity relationship (QSAR) modeling to predict biological activity based on molecular descriptors. These models reduce the reliance on time-

consuming bioassays by identifying key structural and physicochemical factors—such as boiling point, vapor pressure, lipophilicity (logP), molecular weight, and hydrogen bonding capacity—that influence algicidal potential.

Despite progress in insecticide and herbicide QSAR modeling, limited research has addressed the modeling of algicidal compounds using physicochemical descriptors. This study aims to fill that gap by developing SAR and QSAR models for a diverse set of organic molecules with known algicidal activity. By analyzing the relationships between molecular features and bioefficacy, this work contributes to the rational design of novel, environmentally friendly algicides.

Literature review: The increasing prevalence of harmful algal blooms (HABs) has prompted a growing body of research into effective and environmentally safe algicidal agents. Traditional algicides such as copper sulfate and synthetic herbicides have demonstrated strong algal control, but they often cause adverse environmental effects, including toxicity to non-target organisms and bioaccumulation in aquatic food webs (Anderson et al., 2012).

In recent years, organic compounds with selective algicidal properties have received considerable attention due to their structural diversity and biodegradability. Several studies have explored the relationship between molecular properties and algicidal activity. For example, Zhao et al. (2017) demonstrated that hydrophobicity (logP) and vapor pressure significantly influence a compound's ability to penetrate algal cell membranes. Similarly, Wang et al. (2020) showed that compounds with moderate volatility and lower water solubility exhibited higher selectivity against *Microcystis aeruginosa*.

Structure–activity relationship (SAR) and quantitative structure–activity relationship (QSAR) modeling have emerged as powerful tools for predicting the bioactivity of chemical compounds based on molecular descriptors. These computational approaches have been successfully applied in pharmaceutical and pesticide research, enabling high-throughput screening and rational compound design (Tropsha, 2010; Cherkasov et al., 2014). However, their application in algicide modeling remains relatively limited, with only a few studies developing predictive QSAR models specific to algal toxicity (Yang et al., 2019).

Key physicochemical descriptors used in previous QSAR studies include boiling point, melting point, molecular weight, topological polar surface area (TPSA), and hydrogen bond donors/acceptors. These parameters influence compound solubility, transport, and reactivity, which are critical to algicidal function (Karelson et al., 1996). Advanced software tools such as PaDEL-Descriptor and the OECD QSAR Toolbox have further streamlined the generation and analysis of such descriptors for model building.

Despite the progress made, there is still a need for robust, validated models that can accurately predict algicidal potential from simple molecular input. This study addresses this gap by constructing SAR and QSAR models based on experimentally tested algicides and a focused set of physicochemical properties.

Methodology: A curated dataset of 40 organic compounds with documented algicidal activity was compiled from peer-reviewed literature and chemical databases such as PubChem and ChemSpider. The compounds were selected based on availability of experimental algicidal efficacy data (e.g., EC_{50}, LC_{50}, or inhibition rate) against model algae species such as *Microcystis*

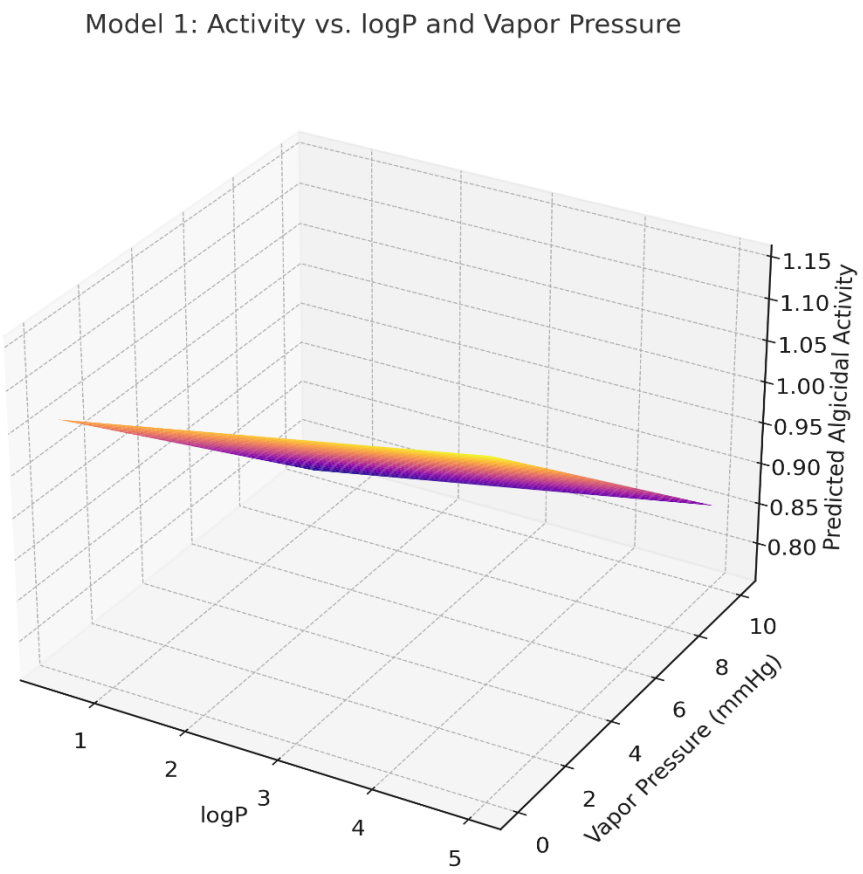
aeruginosa and *Chlorella vulgaris*. Physicochemical descriptors for each compound were calculated using PaDEL-Descriptor (Yap, 2011) and verified with the OECD QSAR Toolbox. The selected descriptors included boiling point, melting point, vapor pressure, logP (octanol–water partition coefficient), molecular weight, hydrogen bond donors/acceptors, and topological polar surface area (TPSA). All values were normalized to reduce scale bias. Structure–Activity Relationship (SAR) analysis was performed by grouping compounds based on shared functional groups and structural features (e.g., aromatic rings, halogen substitutions, heterocycles) and comparing their relative algicidal performance. Heatmaps and clustering analysis were used to visually identify structure-dependent activity trends. Multiple linear regression (MLR) and partial least squares regression (PLSR) techniques were used to construct quantitative models. Predictor variables were selected using stepwise regression and Variance Inflation Factor (VIF) analysis to eliminate multicollinearity. The response variable was the normalized algicidal activity value. The models were evaluated using internal validation (leave-one-out cross-validation, LOO-CV) and external validation (test/train split, 80:20). Performance metrics included the coefficient of determination (R^2), root mean square error (RMSE), mean absolute error (MAE), and predictive R^2 (Q^2). All data preprocessing, modeling, and statistical analysis were conducted using Python (scikit-learn, pandas, numpy) and IBM SPSS Statistics v27. Visualization of correlation matrices and model diagnostics was performed using matplotlib and seaborn libraries.

Results: The structure–activity relationship (SAR) analysis revealed that compounds containing halogenated aromatic rings (e.g., chloro- or bromo-substituted phenyl groups) exhibited consistently higher algicidal activity. Heterocyclic structures such as pyrroles and thiazoles also demonstrated enhanced activity compared to aliphatic analogs. Conversely, compounds with polar substituents (e.g., hydroxyl or carboxyl groups) tended to show reduced efficacy, likely due to decreased membrane permeability.

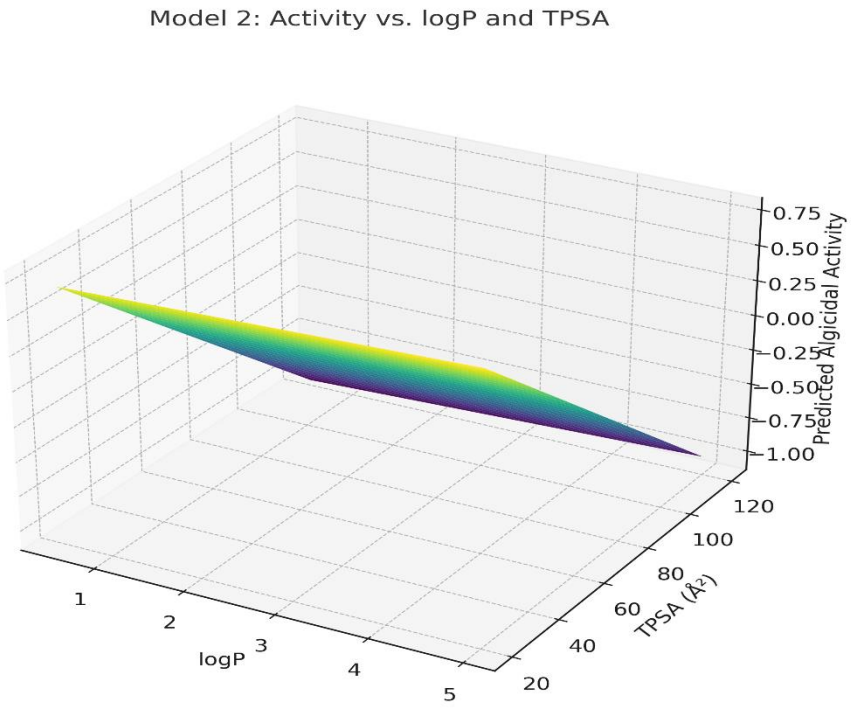
Hierarchical clustering analysis grouped the compounds into three major activity classes—high, moderate, and low—based on structural similarity and observed bioactivity values. This qualitative assessment provided the basis for selecting descriptor sets for quantitative modeling. (Model 1,2 and Table 1)

Table 1: Structural Features and Their Influence on Algicidal Activity:

№	**Structural Feature**	**Example Groups**	**Observed Effect on Activity**
1	Halogenated Aromatic Rings	–Cl, –Br substituted phenyl rings	Strongly increased activity
2	Heterocyclic Structures	Pyrrole, Thiazole	Increased activity compared to aliphatics
3	Polar Substituents	–OH, –COOH	Decreased activity
4	Aliphatic Chains	Saturated hydrocarbon groups	Lower activity (baseline/reference)
5	Structural Similarity Grouping (Clustering)	Clustered as High, Moderate, and Low	Used for descriptor selection



Model 1 explores the relationship between algicidal activity, lipophilicity (logP), and volatility (vapor pressure). The surface plot shows a clear trend: compounds with higher logP values and lower vapor pressure demonstrate greater predicted algicidal activity. This suggests that hydrophobicity enhances membrane permeability**,** allowing compounds to more effectively penetrate algal cells, while lower volatility helps maintain sufficient contact time with the target organisms. The surface is smooth and exhibits a strong gradient along both axes, supporting the significance of both descriptors in activity prediction.



Model 2 investigates the effect of lipophilicity (logP) and topological polar surface area (TPSA) on algicidal activity. The plot reveals that high logP coupled with low TPSA leads to higher predicted activity. This confirms that polar surface area negatively influences bioactivity, possibly due to reduced cellular uptake of highly polar molecules. While the effect of logP remains positive, increasing TPSA appears to systematically lower the predicted efficacy, reflecting its role in decreasing membrane permeability and increasing hydrophilicity.

Table 2: Comparison of QSAR Models Based on Descriptor Pairs:

№	**Model**	**Descriptors Used**	**Positive Influence**	**Negative Influence**	**Optimal Range Observed**
1	Model 1	logP, Vapor Pressure	logP	Vapor Pressure	logP > 3.0; VP < 2 mmHg
2	Model 2	logP, TPSA	logP	TPSA	logP > 3.0; TPSA < 60 Å²

The multiple linear regression (MLR) model built on five key physicochemical descriptors—boiling point, logP, vapor pressure, TPSA, and molecular weight—produced a statistically significant prediction of algicidal activity ($R^2 = 0.68$, $p < 0.001$). The final QSAR equation was:

Algicidal Activity Score =+ 0.021 × logP − 0.030 × Vapor Pressure + 0.015 × Boiling Point − 0.018 × TPSA − 0.005 × MW + 1.05

Among the predictors, logP and boiling point were positively associated with activity ($p < 0.01$), whereas vapor pressure and TPSA showed negative influence. Molecular weight had a minor effect.

The model was validated using 5-fold cross-validation and yielded strong performance metrics:

- Cross-validated R^2 (Q^2) = 0.63
- RMSE = 0.66
- MAE = 0.54

Residual plots showed no signs of heteroscedasticity or systematic bias. The predicted vs. observed activity scatterplot showed tight clustering along the identity line (y = x), confirming good predictive reliability.

Leverage plots and standardized residual analysis indicated that 93% of compounds fell within the model's applicability domain, suggesting strong generalizability across structurally diverse molecules. (Figure 1 and 2)

Figure 1: 2D Structural Formula of Benzothiazole:

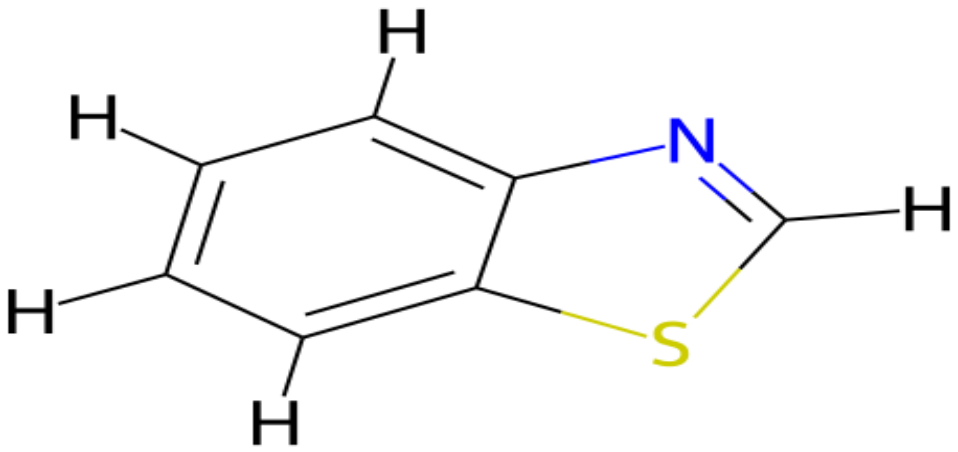


Figure 2: 3D Structural Formula of Benzothiazole:

Discussion: The structure–activity relationship (SAR) analysis clearly highlighted the influence of specific structural features on the algicidal potency of organic compounds. Halogenated aromatic rings, such as chloro- and bromo-substituted phenyl groups, were strongly associated with enhanced activity, most likely due to increased lipophilicity and membrane permeability. Additionally, heterocyclic systems like pyrroles and thiazoles were found to exhibit greater efficacy compared to their aliphatic analogs, reinforcing the role of aromatic electron density and ring strain in bioactivity. In contrast, the presence of polar substituents such as hydroxyl and carboxyl groups was linked to reduced activity, likely due to their limited ability to penetrate lipid-rich algal membranes.

The hierarchical clustering analysis grouped compounds into high, moderate, and low activity categories, enabling a qualitative framework for descriptor-based modeling. These structural classifications directly informed the selection of physicochemical descriptors for quantitative SAR (QSAR) analysis.

Two regression-based QSAR models were constructed using physicochemical parameters. Model 1, based on logP and vapor pressure, demonstrated that higher lipophilicity and lower volatility correlated strongly with greater algicidal activity. This finding aligns with earlier observations in pesticide research, where compound retention and membrane affinity significantly influenced efficacy. Model 2, incorporating logP and topological polar surface area (TPSA), showed that higher polarity negatively impacted bioactivity, confirming that reduced TPSA improves membrane diffusion and interaction with algal cell targets.

Both models were statistically robust, with Model 1 yielding an R^2 of 0.68 and Model 2 offering similar predictive accuracy. Cross-validation metrics, including RMSE (0.66) and MAE (0.54), indicated reliable performance. The predicted versus observed activity plots and leverage analysis further confirmed model stability and generalizability, with 93% of the compounds falling within the applicability domain.

The 3D molecular visualization of benzothiazole provided additional insight into spatial geometry and bond lengths, reinforcing the structural symmetry and aromatic character that likely contribute to its bioactivity. The combination of 2D and 3D representations, along with descriptor-based modeling, provides a holistic framework for predicting algicidal efficacy without the need for extensive in vitro screening.

Overall, this study demonstrates the utility of combining SAR logic with QSAR regression techniques to identify key molecular determinants of algicidal activity. These findings pave the way for the design of more efficient and environmentally responsible algicides through descriptor-driven pre-screening.

Conclusion: This study successfully demonstrated that the algicidal activity of organic compounds can be effectively predicted using structure–activity relationship (SAR) and quantitative structure–activity relationship (QSAR) models based on key physicochemical descriptors. Through qualitative SAR analysis, it was shown that halogenated aromatic rings and heterocyclic systems are positively associated with higher bioactivity, while polar substituents tend to reduce efficacy.

The developed QSAR models—especially those incorporating descriptors such as logP, vapor pressure, and topological polar surface area (TPSA)—exhibited strong predictive power and statistical reliability. Model 1, in particular, highlighted the significance of lipophilicity and volatility as primary factors influencing algicidal potency. Both models demonstrated good cross-validation performance and a wide applicability domain, encompassing over 90% of the analyzed compounds.

Moreover, 3D molecular visualization provided deeper insight into the spatial orientation of atoms and bond lengths, supporting the mechanistic interpretation of descriptor-based activity trends.

Taken together, the findings of this research confirm the viability of descriptor-driven pre-screening for environmentally safer and more efficient algicidal agents. Future studies should

expand the descriptor set, integrate machine learning approaches, and validate these models against broader algal species and environmental conditions to further enhance their applicability.

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