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# QSAR study of 8-Hydroxyquinoline and its Chloro derivatives as antimicrobial agents

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**ABSTRACT**
*8-Hydroxyquinoline (8-HQ) is an important heterocyclic framework in organic and analytical chemistry because of the properties of chromophores and is used to distinguish various metal ions and anions. However, due to its considerable biological activity, this part has attracted the interest of medicinal chemists for the past two decades. Synthetic modification of 8-hydroxyquinoline is being investigated on a massive scale in order to generate more potent target-based broad range beneficial molecules for the treatment of a variety of life-threatening diseases, including cancer, HIV, neurological disorders, and others.The antimicrobial activity of 8HQ, as well as its derivatives, had been examined. A monochloro (5-Chloro 8HQ) and Dichloro (5,7-dichloro 8HQ) revealed supreme anti-bacterial activity. The QSAR study can help in designing new compounds which can be 8HQ-based anti-microbial activity.*
**KEYWORDS** 8-hydroxyquinoline, mono chloro-8HQ, dichloro-8HQ, antimicrobial activity, QSAR.

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## INTRODUCTION

*Staphylococcus aureus* infection has been considered a worldwide health threat for decades, with clinical signs ranging from simple skin infection to severe septicemia. Penicillin has been shown to be an effective therapy for numerous gram-positive bacterial infections. The drug, however, is ineffective against S. aureus due to its ability to produce penicillinase enzyme. Penicillinase-stable penicillins (such as methicillin and oxacillin) have been created to tackle resistance as a result of this situation. Unfortunately, a methicillin-resistant strain known as methicillin-resistant S. aureus (MRSA) arose after only a few years of clinical usage.[1] The mechanism of methicillin resistance has been discovered as a shift in the target penicillin-binding protein (PBP) to PBP 2a or PBP 2'. MRSA has also been reported to be resistant to a variety of other antibiotics, including macrolide, lincosamide, and streptogramin.[2] As a result, the only effective treatment for MRSA infection is vancomycin. However, vancomycin-intermediate S. aureus (VISA) and vancomycin-resistant S. aureus (VRSA) have developed a long-term resistance to the antibiotic vancomycin.[3] Despite the introduction of new treatments to combat MRSA infections, such as linezolid, quinupristin-dalfopristin, daptomycin, and tigecycline, resistant strains continue to arise.[4] As a result of this situation, the development of novel, effective antimicrobial drugs have become a key priority. Medication repositioning (the discovery of novel pharmacological activity in existing drugs/bioactive compounds) has long been recognized as a time-saving medication development technique.[5] Antioxidant and anticancer properties of 8HQ derivatives have been reported, as well as multi-antimicrobial activity against bacteria, amoeba, malaria, fungi, and virus.[6,7] Surprisingly, 8HQ compounds have been shown to have antibacterial efficacy against methicillin-susceptible S. aureus (MSSA) and methicillin-resistant S. aureus (MRSA) isolates.[8]

The mechanisms underlying their antibacterial activity, however, remain unknown. The quantitative structure-activity relationship (QSAR) is an in-silico tool for accelerating the time-consuming and difficult process of drug discovery. The discovery of potent bioactive compounds is aided by QSAR modeling, which reveals a relationship between important chemical traits and/or qualities required for desirable biological activities and pharmacokinetic parameters.[9] For a wide spectrum of chemicals and bioactivities, the success of QSAR application has been established. As previously stated, 8HQ and derivatives have been studied as potential drug repositioning molecules for the development of innovative antimicrobial medications. In order to further research, 8HQ and its derivatives were investigated as novel potential medicines against MRSA infection and as antioxidants. QSAR is an in-silico

method for speeding up and simplifying the arduous and time-consuming process of drug development. The discovery of potent bioactive compounds is aided by QSAR modeling, which reveals a relationship between important chemical traits and/or qualities required for desirable biological activities and pharmacokinetic parameters. [10-11]

## MATERIAL AND METHODS

### Bacterial strains

Staphylococcus aureus Bacteria was used for antimicrobial and antioxidant activity.

2.2- Tested compounds and reagents:

8-Hydroxyquinoline (8HQ), cloxyquin (5-Cl-8HQ), 5,7-dichloro-8HQ (5,7-diCl-8HQ), and 5-amino-8HQ (5-NH2-8HQ) were purchased.

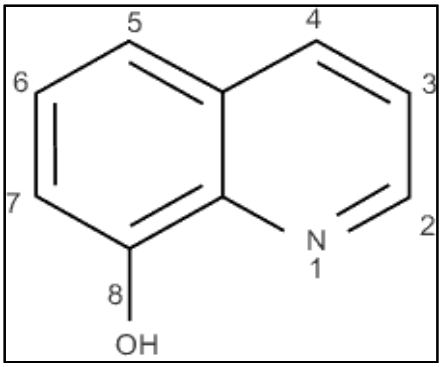


**FIGURE -1 Chemical structures of 8HQ**

### Antimicrobial activity

The antimicrobial activity of compounds was investigated using the agar dilution method. The tested compound was completely dissolved in DMSO, the solution was mixed systematically with the sterile Mueller Hinton (MH) broth. The tested microorganisms with the standard strains were injected on each compound in agar and were incubated at 350C for at least 24 hr. The minimum inhibitory concentration (MIC) of the tested compounds against the microorganisms was evaluated. Minimum bactericidal concentrations (MBC) were performed using the microdilution method [12]. The lowest concentration at which bacteria cannot grow the following subculture on the MH agar plate was used to determine the MBC value of each chemical.

### QSAR analysis

### Data set

Chemical structures of the tested compounds together with their experimental antimicrobial activities were used as data sets for QSAR modeling.

### Descriptor generation

A compound's chemical structure is a key to its characteristics and biological activities. These features are defined by a collection of numerical numbers known as descriptor values that are produced from the computational process. Initially, molecular structures were drawn by GaussView [13] and were geometrically improved at the semi-empirical level using Austin Model 1 followed by density functional theory (DFT) calculation using Becke's three-parameter hybrid method and the Lee-Yang–Parr correlation functional (B3LYP) together with the 6–31 g(d) basis using Gaussian 09 [14]. The improved output structures were exposed to the construct of 13 quantum chemical descriptors i.e., the total energy (Etotal) of the molecule, the highest occupied molecular orbital energy (EHOMO), the lowest unoccupied molecular orbital energy (ELUMO), the total dipole moment (μ) of the molecule, the electron affinity (EA), the ionization potential (IP), the energy difference of HOMO and LUMO (HOMO–LUMO Gap), the Mulliken electronegativity (χ), the hardness (η), the softness (S), electrophilicity (ω), the electrophilic index (ωi ), and the mean absolute atomic charge (Qm).

### Descriptors selection

Among a large set of descriptors obtained from the calculation, a set of useful ones were selected for further model building.

### Generation of training and testing sets

The data set was divided into two subsets: the training and testing (the leave-one-out cross-validation; LOO-CV) sets. The training set was used to build the QSAR models, whereas LOO-CV was used to validate the models. LOO-CV method was finalized apart from one sample from the entire data set to be used as a

testing set, and the remaining n − 1 sample was used as a training set to construct the model. This process has incessantly occurred until all of the samples in the data set were used as the testing set [15].

## RESULTSAND DISCUSSION

### Antimicrobial activity

Antimicrobial activities of compounds against *Staphylococcus aureus*, tested by the agar dilution method. Results showed that 8HQ and cloxyquin displayed a high antimicrobial activity with the MIC range of ≤6.90–110.20 μM and ≤5.58–44.55 μM, respectively. Cloxyquin exerted the lowest MIC value whereas 8HQ had a wider range of MIC values.

In contrast to *Staphylococcus aureus*, 8HQ and its derivatives with substituents halogen (at 5- and 7-positions) on the 8HQ scaffold showed antibacterial action. 8HQ (MIC50 ≤6.90 M) and cloxyquin (MIC50 ≤5.58 M) both showed strong antibacterial activity. As shown by the lowest atomic polarizabilities, the most powerful chloro-8HQ molecule with 5-Cl substitution may have a sufficient size and lipophilic feature that is required for interacting with the lipophilic site of action. A less polarised lipophilic chloro group at the 5-position is responsible for the most effective antibacterial agent.

**TABLE -1 MIC values (μM) and cytotoxicity (IC50, μM) of 8HQ and derivatives:**

| Compounds | MIC range | MIC50 | MIC90 | Cytotoxicity |
|---|---|---|---|---|
| 8HQ | ≤6.90–110.20 | ≤6.90 | 13.79 | 6.28 |
| 5-Cl-8HQ | ≤5.58–44.55 | ≤5.58 | 44.58 | 81.75 |
| 5,7-dichloro-8HQ | 18.69–74.75 | 37.37 | 37.37 | 27.98 |

## REFERENCES


1. Anighoro, A., Bajorath, J., & Rastelli, G. (2004). Polypharmacology. Challenges and opportunities in drug discovery. Journal of Medicinal Chemistry, 57: 7874–7887.
2. Balouiri, M., Sadiki, M., & Ibnsouda, S. K.(2016).Methods for in vitro evaluating antimicrobial activity; A review. Journal of Pharmaceutical Analysis, 6: 71–79.
3. Bareggi, S. R., & Umberto, C. (2012). Clioquinol: Review of its mechanisms of action and clinical uses in neurodegenerative disorders. CNS Neuroscience & Therapeutics, 18: 41–46.
4. Boda, S. K., Pandit, S., Garai, A., Pal, D., & Basu, B. (2016). Bacterial siderophore mimicking iron complexes as DNA targeting antimicrobials. RSC Advances, 6: 39245–39260.
5. Chan, S. H., Chui, C. H., Chan, S. W., Kok, S. H. L., Chan, D., Tsoi, M. Y. T., Tang, J. C. O. (2013). Synthesis of 8-hydroxyquinoline derivatives as novel antitumor agents. ACS Medicinal Chemistry Letters, 4: 170–174.
6. Chan-on, W., Huyen, N. T. B., Songtawee, N., Suwanjang, W., Prachayasittikul, S., & Prachayasittikul, V. (2015). Quinoline-based clioquinol and nitroxoline exhibit anticancer activity inducing FoxM1 inhibition in cholangiocarcinoma cells. Drug Design, Development, and Therapy, 9: 2033–2047.
7. Chauhan, D., Hati, S., Priyadarshini, R., & Sen, S. (2019). Transcriptome analysis predicts mode of action of benzimidazole molecules against Staphylococcus aureus UAMS-1. Drug Development Research, 80: 490–503.
8. Cherdtrakulkiat, R., Boonpangrak, S., Pingaew, R., Prachayasittikul, S., Ruchirawat, S., & Prachayasittikul, V. (2015). Bioactive triterpenoids, antimicrobial, antioxidant and cytotoxic activities of Eclipta prostrata Linn. Journal of Applied Pharmaceutical Science, 5: 46–50.
9. Cherdtrakulkiat, R., Boonpangrak, S., Sinthupoom, N., Prachayasittikul, S., Ruchirawat, S., & Prachayasittikul, V. Derivatives (halogen, nitro and amino) of 8-hydroxyquinoline with highly potent antimicrobial and antioxidant activities. Biochemistry and Biophysics Reports, 6: (2016),135–141.
10. Cosimi, R. A., Beik, N., Kubiak, D. W., & Johnson, J. A. Ceftaroline for severe methicillin-resistant Staphylococcus aureus infections: A systematic review. Open Forum Infectious Diseases, 4: (2017), 1–7.
11. Erzincan, P., Saçan, M. T., Yuce Dursun, B., Danış,, O., Demir, S., Erdem, S. S., Ogan, A. QSAR models forantioxidant activity of new coumarin derivatives. SAR QSAR Environ Res., 26: (2015), 721–737.
12. Frisch, M.J., Trucks, G.W., Schlegel, H.B., Scuseria, G.E., Robb, M.A., Cheeseman, J.R. Gaussian, Inc., Wallingford, CT, USA, A.02: (2009).
13. Hongmanee, P., Rukseree, K., Buabut, B., Somsri, B., & Palittapongarnpim, P. (2007). In vitro activities of cloxyquin (5-chloroquinolin-8-ol) against Mycobacterium tuberculosis. Antimicrobial Agents and Chemotherapy, 51: 1105–1106.
14. Kumar, K., & Chopra, S. (2013). New drugs for methicillin-resistant Staphylococcus aureus: an update. The Journal of Antimicrobial Chemotherapy, 68: 1465–1470.
15. Lawung, R., Cherdtrakulkiat, R., Nabu, S., Prachayasittikul, S., Israngkura Na Ayudhya, C., & Prachayasittikul, V. (2018). Repositioning of 8-hydroxyquinoline derivatives as a new promising candidate for combating multidrug-resistant *Neisseria gonorrhoeae*. EXCLI Journal, 17: 840–846.



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