*Nat. Volatiles & Essent. Oils, 2021; 8(5): 12240-12248*

NVEO
Natural Volatiles & Essential Oils

# Antimicrobial Investigation and Docking Analysis of Quinoline Compounds

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**Abstract**

**Keywords:** Quinoline-8-ol, quniol, quinhydrone, zone of inhibition, biological activity, auto dock and binding energy. The organic compounds quinoline-8-ol, quinol and quinhydrone were subjected to antimicrobial studies against few Gram positive and Gram negative bacteria and fungi. The zone of inhibition towards the microbes was investigated by agar well diffusion method and the compound quinoline-8-ol exhibited lethal zone for the species *Streptococcus* (43 mmml), *Trichophyton* (42 mm/ml), quinol is more resistant towards the organisms like *Bacillus subtilis* (38 mm/ml), *Enterococcus faecalis* (40 mm/ml), *Mucor* (42 mm/ml), *Aspergillus niger* (40 mm/ml) and quinhydrone *Staphylococcus aureus* (40 mm/ml), *Pseudomonas aeruginosa* (38 mm/ml), *Trichophyton* (36 mm/ml) at higher concentrations. Auto dock 4.2.6 was used to perform docking analysis for tiny ligand interactions with macromolecules and the least binding energy; hydrogen atom interactions were reported.

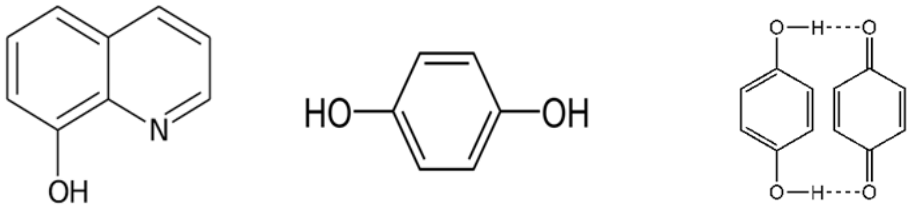
## INTRODUCTION

The compound quinol is originated in the plant food as glucose or its conjugate called as arbutin widely found in fruit pears, beverages, onion and it is hydrolyzed to free benzene-1,4-diol or quinol and absorbed by the intestinal gland[1]. They are active against few bacteria, weed, pests and fungus [2-5]. The multidrug resistance is also shown by few pathogenic strains like *Enterococcus faecium, Streptococcus pneumonia and Staphylococcus aureus*[6]. Various heterocyclic compounds have antitumour[7, 8], analgesic activities[9], anti-inflammatory[10] and antiallergic activity[11]. The derivatives of 1-hydroxy 4-aminoanthraquinones and 9, 10- hydrazones possess antimicrobial activity[12-15] and sedative action[16]. The cigarette smoke is rich in quinol and injuring respiratory tract[17, 18]. Quinhydrone shows antifungal potential against yeast *Saccharomyces cerevisiae*[19]. Quinhydrone is employed as redox electrodes and it is used as an alternative for the glass electrode. Naturally it is found in humic substances comprising of sea water, coal and soil particles. Quinoline-8-ol has extensive biological activities due to its molecular structure.Quinoline-8-ol and the derivatives[20] have extensive antibacterial action against neurodegenerative diseases, inhibitor of tuberculosis, antimalarial agents, Parkinson disease, anti-Human Immuno deficiency virus. The antibacterial and antifungal behavior of the prepared compounds quinol, quinoline-8-ol and quinhydrone are evaluated against few bacteria and fungi like *Streptococcs, Micrococcus, E.coli, Vibrio chlorae, Candida albicans, A. flavus, Trichophyton, Fusarium, Enterococcus faecalis, Salmonella typhi, A. niger, Mucor, Trichoderma* and *Klebsiella pneumonia*. The hydrogen bond interactions, pi-alkyl interactions, aromaticity and many ligand interactions are predicted using docking method. The prepared compounds are employed as the ligand interacts with the macromolecule and the binding sites, binding energy are determined from auto dock tools[21] and Discovery studio visualizer software.

**EXPERIMENTAL:**

**Materials and Methods**

The organic compounds quinoline-8-ol, quinol and quinhydrone (Figure 1) were purchased from Sigma Aldrich of AnalaR grade. The bacteria and fungus were acquired from Eumic analytical Laboratory and Research Institute, Tiruchirappalli. The Hi media nutrient agar slant at $4^0$ C was employed to uphold the bacterial strains.




**(a)** **(b)** **(c)**

**Fig-1: Structure of a. Quinoline-8-ol b. Quinol c. Quinhydrone**

**Spectral Data**

**Quinoline-8-ol:** The carbon hydrogen stretching frequency (3050 $cm^{-1}$), aromatic (-C=C-) stretching at 1572 $cm^{-1}$, 1500$cm^{-1}$, 1460 $cm^{-1}$, -C-O-stretching vibration was observed at 1105 $cm^{-1}$, hydroxy group (phenolic) at 3600 to 2600 $cm^{-1}$, -$CH_2$- assymmetric bending at 1450 $cm^{-1}$, stretching at 2910 $cm^{-1}$, carbon - nitrogen bending vibrations at 1220 and 1020 $cm^{-1}$ and stretching between 1660 $cm^{-1}$.

**Benzene-1, 4-diol:** Benzene-1,4-diol (quinol) proved to have stretching frequency (O-H) at 3300 - 3500 $cm^{-1}$ , aromatic carbon-hydrogen stretching at 3025$cm^{-1}$, double bonded carbon-carbon stretching of alkene at 1660 $cm^{-1}$ and aromatic -C-C- double bond stretching frequency at 1450 and 1502 $cm^{-1}$.

**Quinhydrone:** Strong peak at 3034 $cm^{-1}$ (-C-H), -OH (stretching) group at 3852$cm^{-1}$, -C=O stretching frequency at 1700$cm^{-1}$, bending frequency for -C-H- at 3100 to 3000 $cm^{-1}$, 3640 to 3610 $cm^{-1}$, =C=O at 1760 to 1665 $cm^{-1}$ , benzene ring at 3100 to 300 $cm^{-1}$.

**Selection of Ligand and Macromolecules**

The structures of the protein macromolecule were obtained from the website of protein data bank resource. The protein with ID 7BRA and 5AF1 were collected for studying the bio interaction of ligand and the protein molecules. The compound quinoline-8-ol, quinol and quinhydrone were the ligands. The ligand structures were downloaded from NCBI-PubChem database and the molecule in the SDF mode was converted into charged PDBQT form and saved for docking, using open bable software[22].

**General procedure**

**Anti-bacterial Assay** : Standard agar well diffusion method[23-25] was employed for anti-bacterial assay. On Nutrient agar plates, 0.5 ml ($10^5$ CFU/ml) of diluted inoculums of the test organism was distributed. Different concentrations of plant extracts were filled inside the well (8mm diameter) perforated into the agar medium and incubated at 37°C. The zone of inhibition against the test organism was used to assess the antibacterial activities. The diameter of the zone of inhibition is measured and compared to the standard antibiotics, with the results interpreted. The ingredients used for preparing the culture media includes peptone (5g/l), beef extract (3g/l), agar (15g/l), NaCl (5g/l), yeast extract (1.5g/l) and maintained at neutral pH seven.

**Auto docking Analysis**

The extensive structure and activity of the ligands like quinolin-8-ol, quinol and quinhydrone auto docking was performed for the selected bacteria (*E. coli* and *Candida albicans*) macromolecules in the binding sites using AUTO DOCK 4.2.6 models. All the necessary extension files like autogrid.exe, auto dock.exe, AD4-parameter file, AD 4.1 bound data files were kept in the same folder for docking. The polar hydrogen and the charges were added using Kollman United atom and Gasteiger charges. The AUTOGRID be employed to generate auxiliary programme. The text files were used to save the data regarding the macromolecule, ligand, grid size. The docking results were further analyzed using the Discovery Studio Visualizer of version 3.5, to view the various docked pose of the ligand interactions, aromaticity, hydrogen bonds, charges, ionisability, and hydrophobicity. The runs were repeated to get various docked structures and minimum Root Mean Square Deviations. The strong hydrogen bonding between the ligand the receptor is evaluated. The least binding energy shows that the interactions are instantaneous, rigid and constant.

**RESULTS AND DISCUSSION:**

**Zone of Inhibition of quinoline-8-ol, quinol and quinhydrone**

The antibacterial and antifungal activity of organic compounds dissolved in Dimethyl Sulphoxide $(CH_3)_2SO$ extract on various species is shown in the table1. It is clear from the data that all of the fungus and bacteria are efficient against the antibiotic Gentamicin. The activity is measured by the diameter of a reduce zone that forms around each well, measuring the degree of inhibition. The table 1 data show that the degree of inhibition varies based on the species. The inhibitory zone diameter produced in DMSO extract was determined to be less than, higher than, or equivalent to that of conventional antibiotics against each species.

Table-1: Inhibition zone of the organic compounds

| | $(CH_3)_2SO$ Extract 100 µl added and Zone of inhibition (mm/ml) | | | | | |
|---|---|---|---|---|---|---|
| Quinoline-8-ol | Microorganisms | 25 µl | 50 µl | 75 µl | 100 µl | Control Gentamicin antibiotic disc |
| | *Streptococcus* | 36 | 38 | 40 | 43 | 20 |
| | *Micrococcus* | 34 | 36 | 38 | 42 | 20 |
| | *E.coli* | 30 | 34 | 36 | 38 | 18 |
| | *Vibrio cholerae* | 30 | 34 | 36 | 38 | 18 |
| | *Candida albicans* | 34 | 36 | 38 | 40 | 20 |
| | *A.flavus* | 34 | 36 | 38 | 40 | 20 |
| | *Trichophyton* | 36 | 38 | 40 | 42 | 20 |
| | *Fusarium* | 36 | 38 | 40 | 42 | 20 |
| Quinol | *Bacillus subtilis* | 25 | 30 | 34 | 38 | 20 |
| | *Enterococcus faecalis* | 28 | 34 | 36 | 40 | 18 |
| | *E.coli* | 25 | 30 | 34 | 38 | 18 |
| | *Salmonella typhi* | 20 | 22 | 24 | 26 | 20 |
| | *Candida albicans* | 30 | 34 | 37 | 40 | 20 |

| | | | | | | |
|---|---|---|---|---|---|---|
| | *A.niger* | 30 | 34 | 36 | 40 | 20 |
| | *Mucor* | 30 | 35 | 38 | 42 | 20 |
| | *Trichoderma* | 20 | 22 | 25 | 28 | 20 |
| Quinhydrone | *Staphylococcus aureus* | 26 | 26 | 36 | 40 | 20 |
| | *Streptococcus* | 22 | 25 | 28 | 32 | 20 |
| | *Pseudomonas aeruginosa* | 28 | 32 | 36 | 38 | 20 |
| | *Klebsiella pneumoniae* | 22 | 25 | 29 | 32 | 23 |
| | *Candida albicans* | 20 | 24 | 28 | 30 | 22 |
| | *A.flavus* | 23 | 26 | 30 | 34 | 20 |
| | *Trichophyton* | 24 | 28 | 32 | 36 | 20 |
| | *Fusarium* | 22 | 26 | 30 | 32 | 20 |

The compound quinoline-8-ol or 8-hydroxyquinoline showed lethal zone for the species Streptococcus (43 mmml), Trichophyton (42 mm/ml) at higher concentrations. For the species, Bacillus subtilis (38 mm/ml), E.coli (38 mm/ml), Salmonella typhi (26 mm/ml), Candida albicans (40 mm/ml), A.niger(40 mm/ml), Mucor (42 mm/ml), Trichoderma (28 mm/ml) was observed for the compound quinol. The bacteria Staphylococcus aureus (40 mm/ml), Klebsiella pneumoniae (32 mm/ml), A.flavus (34 mm/ml), Trichophyton (36 mm/ml), Fusarium (32 mm/ml) showed activity against the compound quinhydrone.

The external membrane of cell walls of gram-negative bacteria consist of lipoprotein, lipid bilayer, and lipopolysaccharide. The cell membrane is comparable to the lipid (bilayer).

Furthermore, gram-negative bacteria have periplasmic space, which contains a range of enzymes such as protease, nuclease, and detoxifying enzymes, all of which are important in bacterial antidrug resistance. The chemical compounds were more active to extinguish the progress of the microorganisms and hence proved to be more resistant.

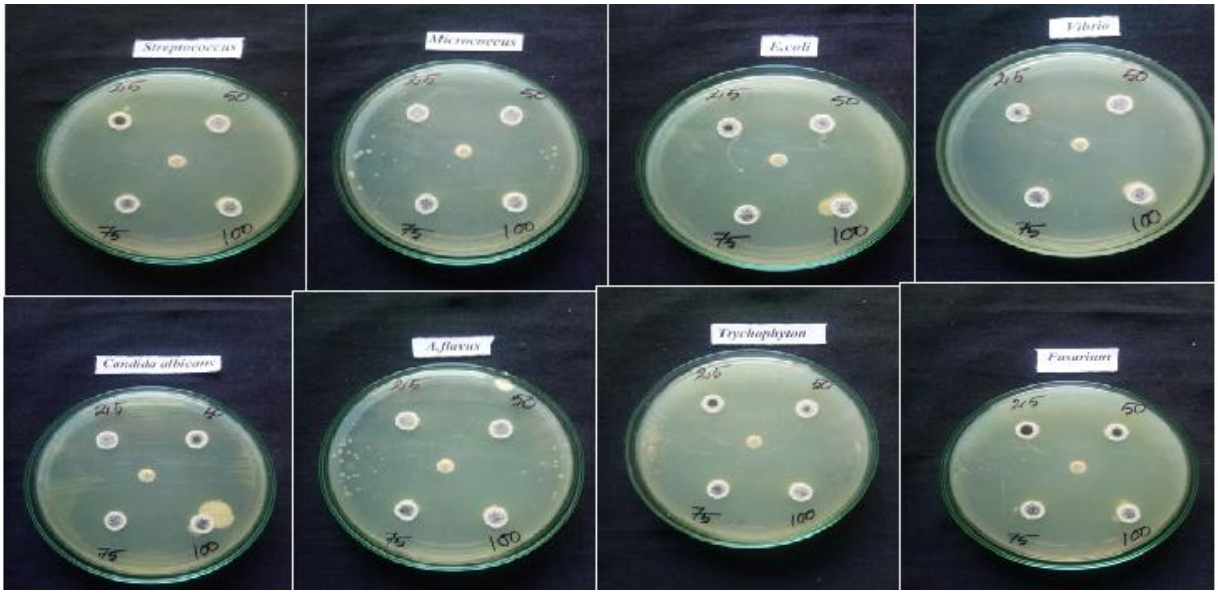



**Fig-2: Inhibition of quinoline-8-ol**

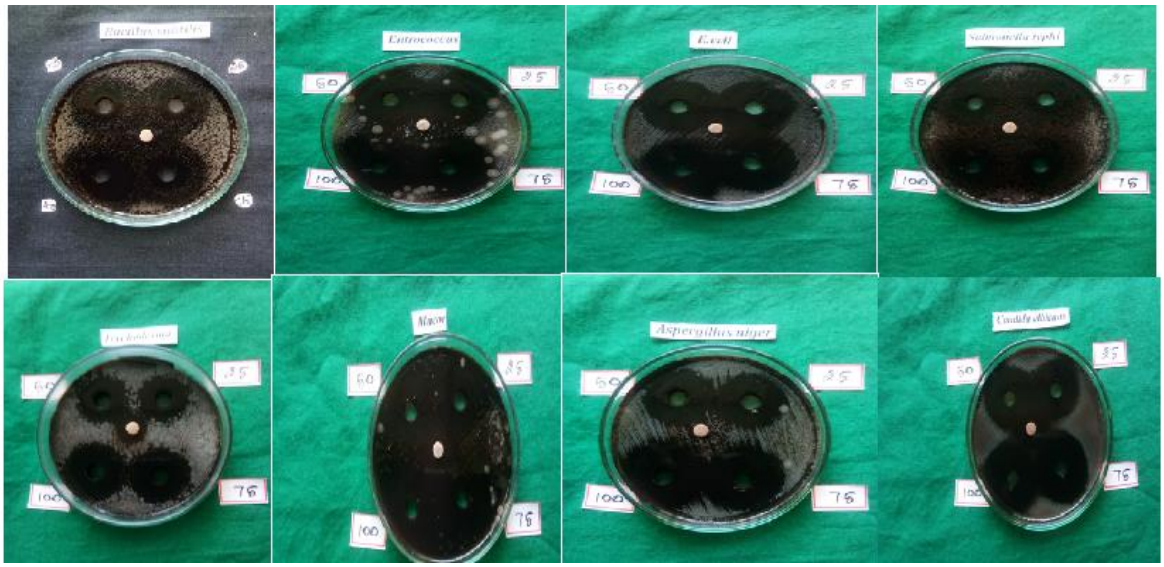


**Fig-3: Inhibition of quinol**

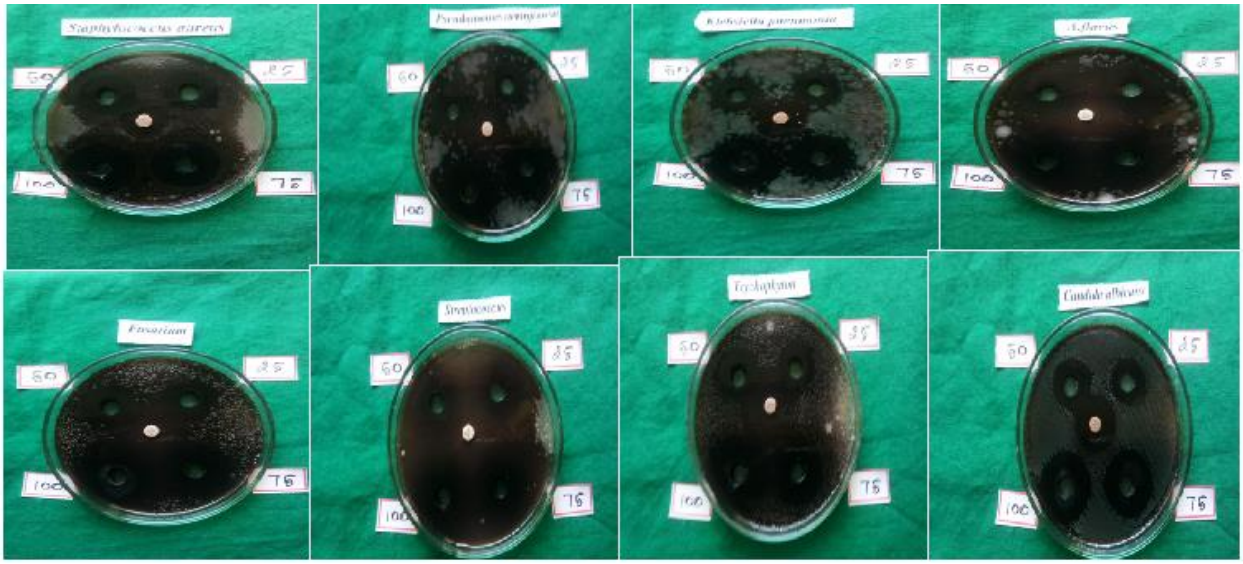


**Fig-4: Inhibition of quinydrone**

**Molecular Docking**

The docking result of quinoline-8-ol depicts the interactions between the aminoacid chain GLY319, GLN347, TYR326, PRO350, HIS343, GLU342, SER346 (Figure 5). The hydrogen bond interaction is between GLY338, -C-H bond interactions in ILE268, GLY319, conventional hydrogen bond interactions in LEU339, attractive charge between ARG283, alkyl interactions in LYS416. The minimum binding energy is -6.35 Kcal/mol, torsional energy and internal energy is 0.3 and -0.32Kcal/mol. The docking results of quinoline-8-ol with 7BRA macromolecule represent the interactions between the amino acid chain VAL447, ALA58, LEU448, PRO441. The hydrogen bond between PRO441, LEU339, (Figure 6) the binding energy is -7.53 Kcal/mol.

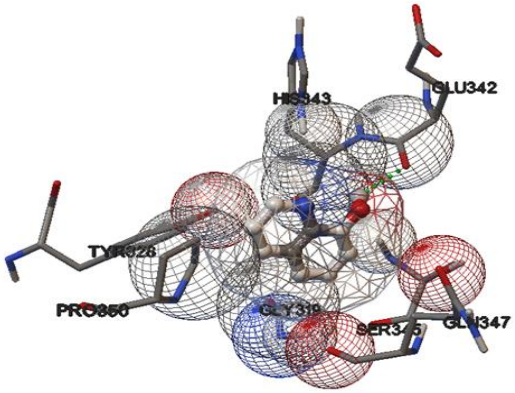



**Fig-5 : The wire structure of interactions of ligand with 7BRA macromolecule**

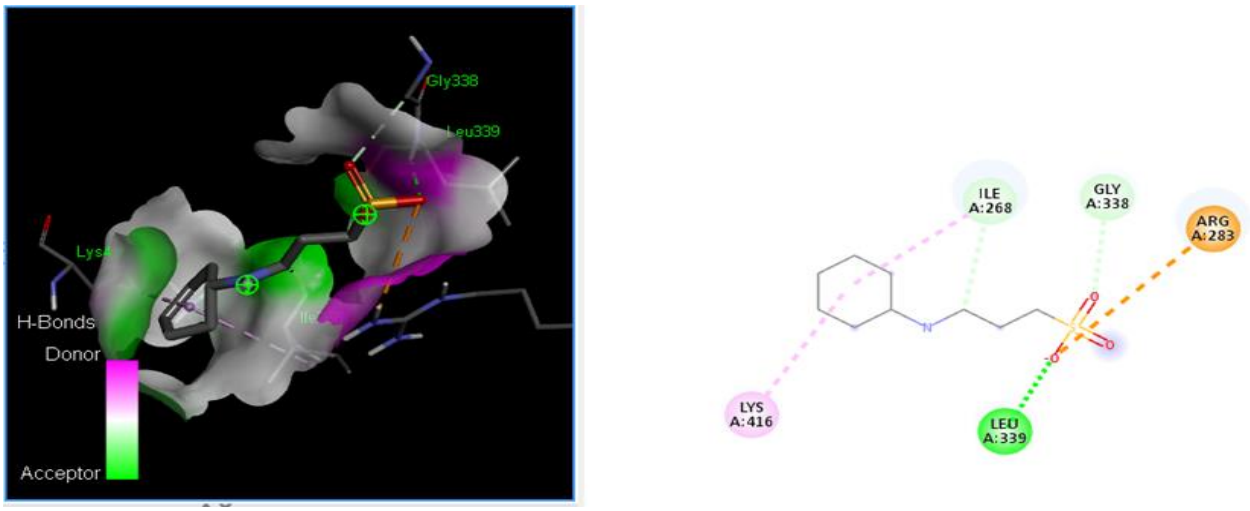



**Fig-6 : The 3D and 2D pictures of interactions of ligand with 7BRA macromolecule**

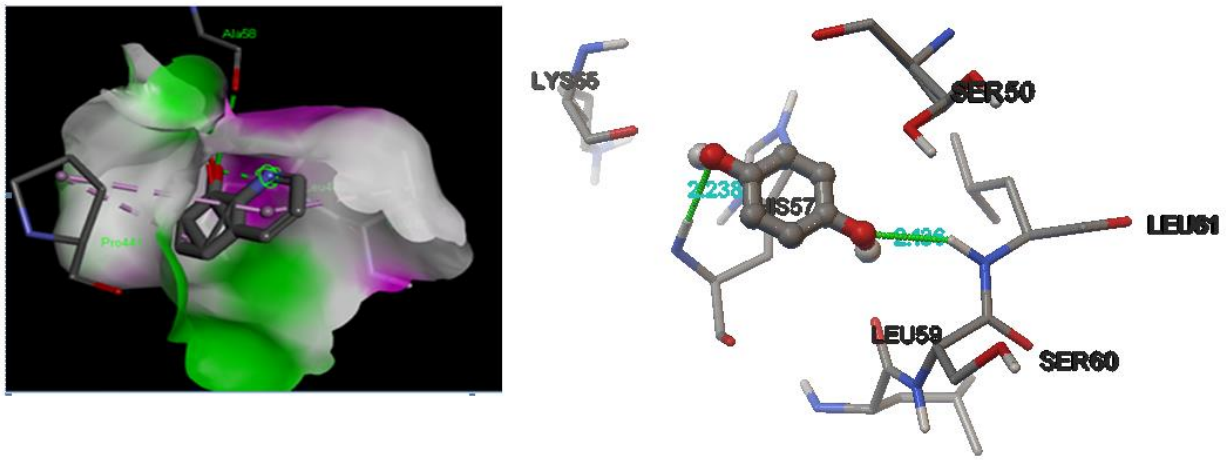



**Fig-7: Two Hydrogen atom bonds for the 5AF1 macro molecule**

The ligand quinol bind with the macromolecule 5AF1 exhibits two hydrogen atoms in bonds through the residue HIS57, LEU61, SER60 (Figure 7). The binding energy is -5.17 Kcal/mol, intermolecular energy is -5.77 Kcal/mol, torsional energy 0.6 Kcal/mol respectively. The protein 7BRA exhibits hydrogen bond contact with GLN347, SER345 residue, binding energy is -6.34 Kcal/mol, intermolecular and internal energy is -6.94 Kcal/mol, 0.41 Kcal/mol, torsional energy is 0.41 respectively.

The quinhydrone ligand bind with the 5AF1 macro molecule and exhibits pi donor hydrogen bond through HIS220, SER60, conventional hydrogen bond with LEW59, LEU61, LYS55, HIS57, SER50, pi alkyl interaction with HIS220, HIS57 as shown in the figure 8. The same ligand has the bonded with the residue with energy -4.87 Kcal/mole, intermolecular energy -5.46 Kcal/mol and torsional energy 0.6 Kcal/mol.

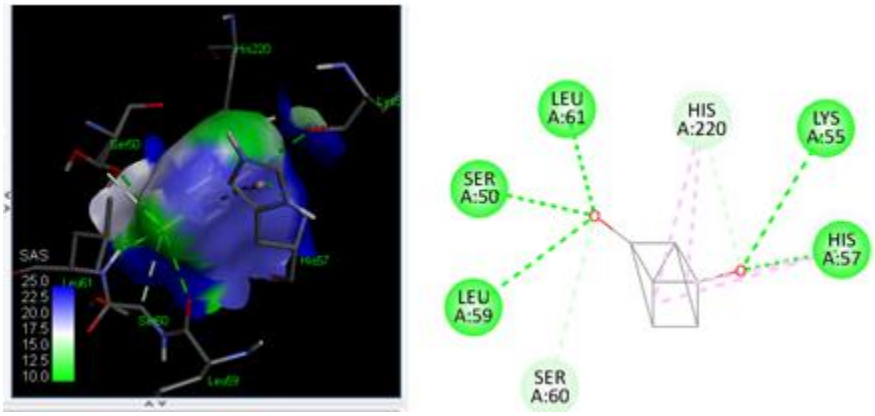



**Fig-8: The Quinhydrone ligand interaction with 5AF1 macromolecule**

**CONCLUSION**

The current investigation provides a basis for the treatment of pathogenic microorganisms using quinol, quinoline-8-ol and quinhydrone . They hydroxyl groups, hetero cyclic nitrogen atom imparts more potential towards Gram-positive, Gram-negative bacteria and few fungi. The computer assisted molecular docking predicts the ligand interactions, the hydrogen bond interactions at various poses of macromolecule and the natural activities of quinoline compounds are efficiently determined.

**ACKNOWLEDGEMENT:**

The authors are grateful to the President of Nehru Memorial College and all the people for supporting to carry the work in a successful manner. The authors are also grateful for the free software providers of AUTO DOCK, Discovery Studio Visualizer and PyMOL.

**REFERENCES:**

1. McDonald T. A, Holland N. T, Skibola C, Duramad P and Smith M. T. Hypothesis: phenol and hydroquinone derived mainly from diet and gastrointestinal flora activity are causal factors in leukemia, *Leukemia*. 2001: 15(1); 10–20.
2. Khambay B. P. S, Jewess P. The potential of natural naphthoquinones as the basis for a new class of pest control agents. Crop Prot. 2000: 19(1); 597–601

3. Sasaki K, Abe H, Yoshizaki F. In Vitro antifungal activity of naphthoquinone derivatives. *Biol. Pharm. Bull.* 2002: 25(5); 669– 670.
4. Binutu O. A, Adesogan K. E, Okogun J. I. Antibacterial and antifungal compounds from Kigelia pinnata. *Planta Med.* 1996: 62 (4); 352–353.
5. Reichman L. B. Multidrug Resistance in the World: The Present Situation. Chemotherapy. 1996: 42 (3); 2-9.
6. Lipsitch M, Samore M. H. Antimicrobial use and antimicrobial resistance: a population perspective. Emerg Infect Dis. 2002: 8(4); 347-354.
7. McFadyen M.C.E, Melvin W.T, Murray G.I. Cytochrome P450 enzymes: novel options for cancer therapeutics*. Mol. Cancer Ther*. 2004: 3 (3); 363-371.
8. Starcevic K, Caleta I, Cincic D, Kaitner B, Kralj M, Ester K, Karminski-Zamola G. Synthesis, crystal structure determination and antiproliferative evaluation of novel benzazoyl benzamides. *Heterocycle*s.2006: 68 (11); 2243-2246.
9. Baell J.B, Forsyth S.A, Gable R.W, Norton R.S, Mulder R.J. Design and synthesis of type-III mimetics of u-conotoxin GVIA. *J.Comput. Aided. Mol. Des*. 2002: 15 (12); 1119-1136.
10. Ban M, Taguchi H, Katsushima T, Takahash M, Shinoda K, Watanabe A, Tominaga T. Novel antiallergic and antiinflammatory agents. Part II: synthesis and pharmacology of TYB-2285 and its related compounds. *Bioorg. Med.Chem*. 1998: 6 (7); 1069-1076.
11. Katsuura K. Directed ortho metalation reactions. Synthesis of the naturally-occurring benz [a]anthraquinones X-14881 C and ochromycinone. *Tetrahedron Lett*., 1985: 26(1); 9-12.
12. Albuquerque L. L. D. A bianthraquinone and 4'-O-methyl-ent-gallocatechin fromCassia trachypus. *Phytochem*., 1992: 31(1); 259-261.
13. Abdanne W. and Endale M. Recent advances in the synthesis of biologically and pharmaceutically active quinoline and its analogues: Review. *Royal Society of Chemistry Advances.* 2020: 10; 20784–20793.
14. Gabriella da Rosa Monte Machado, Denise Diedrich, Thaís Carine Ruaro, Aline Rigon Zimmer, Mário Lettieri Teixeira, Luís Flávio de Oliveira, Mickael Jean, Pierre Van de Weghe, Saulo Fernandes de Andrade, Simone Cristina Baggio Gnoatto and Alexandre Meneghello Fuentefria. Quinolines derivatives as promising new antifungal candidates for the treatment of candidiasis and dermatophytosis. *Brazilian Journal of Microbiology*. 2020: 51;1691–1701.
15. Bloomer L. Preparation of functionalized juglone acetates and juglones via 1,4-dimethoxynaphthalene derivatives: synthesis of anthraquinones related to rhein and aloe-emodin*. J. Org. Chem*., 1993: 58(27); 7906-7912.
16. Holt P. G. and Keast D. Environmentally-induced changes in immunological function: Acute and chronic effects of inhalation of tobacco smoke and other atmospheric contaminants in man and experimental animals. *Bacteriol. Rev*. 1977: 41(1); 205- 216.
17. Jin Myung Choi, Young-Chang Cho, Won Jea Cho, Tae Sung Kim1, and Bok Yun Kang, Hydroquinone, a Major Component in Cigarette Smoke, Reduces IFN-γ Production in Antigen-Primed Lymphocytes. *Arch Pharm Res.*2008: 31(3); 337-341.
18. Xiangyu Wang, Jian Shi, Zhaozheng Li, Ling Li, Rui Zhang, Yang Bai, Junmei Li,
19. Fang Liang and Yiting Tang. An 8-Hydroxy-Quinoline Derivative Protects Against

20. Lipopolysaccharide-Induced Lethality in Endotoxemia by Inhibiting HMGB1-Mediated Caspase-11 Signaling. Frontiers in Pharmacology. 2021: 12; 1-11.
21. Nataša Curcic, Aleksandra Velicanski, Dragoljub Cvetkovic, Filis Morina, Sonja Veljovic Jovanovic and Dejana Pankovic, *Fresenius Environmental Bulletin*, **22,** 6(2013).
22. Ketan B Patel and Kiran S Nimavat, Synthesis, Characterization and Comparative Microbial Screening of Some 5-AlkoxyMethyl-8-Quinolinol. *Res. J. Pharm. Biol. Chem. Sci.*2012: 3(3); 838-844.
23. C. H. Tseng, C. W. Tung, S. I. Peng, Y. L. Chen, C. C. Tzeng and C. M. Cheng, Discovery of Pyrazolo[4,3-c]quinolines Derivatives as Potential Anti-Inflammatory Agents through Inhibiting of NO Production*, Molecules,* 2018: 23(5); 1036.
24. G. Swapna, D. Rakesh and M. Estari, In-silico Molecular Docking Analysis of Andrographolide Derived from Andrographis paniculata as Potential Anti-Hiv Agent Targeting Hiv-1 Reverse Transcriptase, *Rasayan J. Chem.* 2020: 13(4); 2588-2594
25. Perez C, Paul M, Bazerque P. Antibiotic assay by agar- well diffusion method. Society for Biology and Experimental Medicine. 1990: 15(1); 113 -115.
26. Bauer A. W, Kirby W. M. Sherris J. C. Turck M. Antibiotic susceptibility testing by a standardized single disk method. *American Journal of Clinical Pathology*. 1966: 45(4); 493–496.
27. Blazevic D. J. Koepcke M. H. Matsen J. M. Quality control testing with disk antibiotic susceptibility test of Bauer-Kirby-Sherris-Turck. *American Journal of Clinical Pathology*. 1972: 57(5); 592–597.