# Understanding The Mode of Action of Resorcinol and its Halogenated Derivatives in Treating Hidradenitis Suppurativa Using Molecular Docking Studies

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## Abstract

This work investigated the mode of action of resorcinol and its 4,6 dihalogenated derivatives in treating a neglected dermatological disease known as Hidradenitis suppurativa (HS). using molecular docking. The studied compounds were docked with the target protein, keratin (PDB ID: 4XIF). Difluoro resorcinol (DFR) had the highest total binding score. The molecular interactions of DFR in the binding pocket of the target protein showed the fluorine atoms formed hydrogen bonds with HIS 901 and HIS 562 amino acids, respectively, and the benzene ring formed a pi-alkyl interaction with LYS 898 amino acid. These molecular interactions are responsible for the high binding score of DFR. The result suggest that DFR might have greater potency in treating HS than resorcinol.

## Introduction

Resorcinol is a white crystalline solid which often exist in both α and β form which are both formed by the crystallization of resorcinol from ethanol and benzene respectively[1]. Resorcinol is a relatively less toxic compound compared to phenol[2]. Hence, its use in the pharmaceutical industry[1]. Halogenated resorcinols are one of the most useful derivatives in resorcinol chemistry. Resorcinol is used in treating Hidradenitis suppurativa, a neglected and rare dermatological disease also known as acne inversa. Its symptoms includes small, painful lumps in skin areas covered by hair such as the armpits and groin. It is caused due to the inflammation and blockage of hair follicles[3]. Drug design and development encourages the adoption of computational techniques in the area of medicinal chemistry in understanding the binding mechanisms of active drugs for a particular ailment[2]. This work employed molecular docking studies to understand the mode of action of resorcinol derivatives in the treatment of Hidradenitis suppurativa.

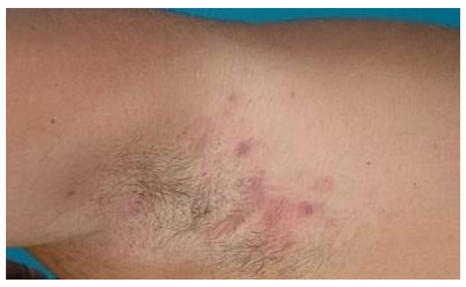

**Fig. 1.** Hidradenitis suppurativa in the armpit of a patient

## Computational Details

### Structure optimization

DFT calculations at the B3LYP/6-311++G (d,p) and B3LYP/6-31G basis set using the GAUSSIAN 09 and Spartan 16 program for the geometry optimization and the electrostatic potential (ESP) map of the studied compounds respectively (Fig. 2) except for the iodine atoms which was done using SDD basis set (Gaussian 09) and LANL2DZ (for Spartan 16) due to its large number of electrons.

### Molecular Docking analysis

CLC drug discovery workbench 3[4] was used to screen the studied compounds with Keratin-7 (PDB ID: 4XIF)[5]. A radius of 13 Å was selected as the binding site using the data from the active site of the PDB site .The molecular interactions in the protein-ligand complex were observed for resorcinol and Difluoro resorcinol (DFR)

## Results

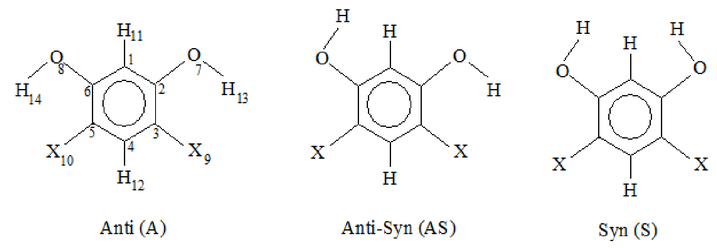


**Fig. 2.** Scheme of the three rotamers of resorcinol where X= H, F, Cl, Br and I

**Table 1.** The relative stabilities (kcal/mol) for the anti-syn(AS), anti(A) and syn(S) conformations of resorcinol derivatives using B3LYP/6-311++G(d,p) basis set

| Form | Resorcinol | DFR | DCR | DBR | DIR |
|---|---|---|---|---|---|
| A | 0.112 | 0.000 | 0.000 | 0.000 | 0.000 |
| AS | 0.000 | 2.818 | 2.873 | 2.954 | 2.208 |
| S | 0.730 | 6.399 | 6.686 | 6.903 | 5.435 |

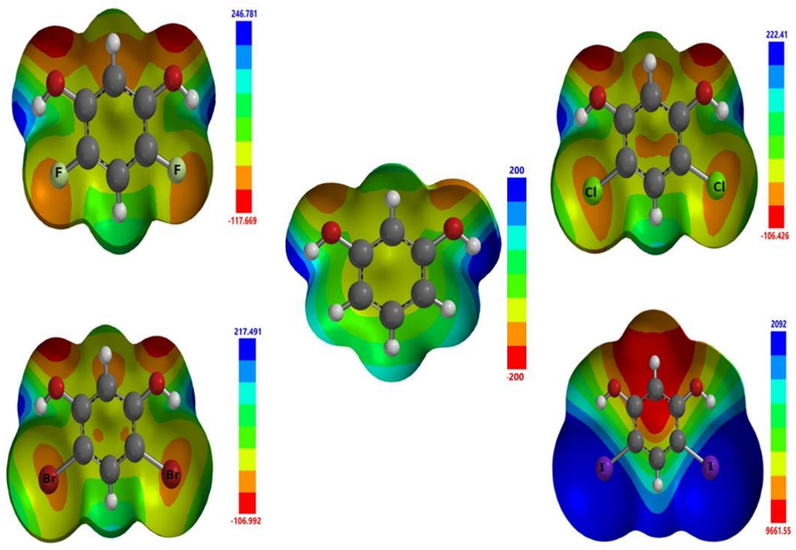

**Fig. 3.** Electrostatic potential maps of the studied compounds in Anti-Anti (AA) form (resorcinol at the center)

**Table 2.** Docking result of resorcinol and its halogenated derivatives with keratin-7.

| Ligand | Mass | HBA | HBD | LogP | HB score | SI score | Total Score |
|---|---|---|---|---|---|---|---|
| Resorcinol | *110.112* | *2* | *2* | *1.098* | *-5.545* | *-27.285* | *-32.830* |
| DFR | *146.093* | *2* | *2* | *1.376* | *-3.806* | *-34.263* | *-38.069* |
| DCR | *178.996* | *2* | *2* | *2.405* | *-5.945* | *-21.282* | *-27.227* |
| DIR | *361.905* | *2* | *2* | *2.307* | *-6.042* | *-19.779* | *-25.822* |
| DBR | *267.904* | *2* | *2* | *2.663* | *-4.000* | *-14.599* | *-18.599* |

## Discussion

The AS form and A form are the most stable structures for resorcinol and its halogenated derivatives respectively (Table 1 and Fig. 2). The ESP maps (Fig. 3) showed that DFR and DIR have the most negative and positive regions respectively. The oxygen atoms of the hydroxyl groups accounts for most of the electronegative regions. The ESP map affirmed that electronegativity decreases down the halogen group. All the studied compounds exhibited a good binding affinity with the target protein by having negative score values. The more negative the binding score the better the binding of the ligand with the target protein. Difluoro resorcinol (DFR) had the best total binding score of -38.069 which is a sum of the Steric Interaction (SI) score and Hydrogen Bond (HB) score (Table 2). The moleclar interactions of resorcinol in the binding pocket (Fig 4.) showed it formed conventional and carbon hydrogen bonds with THR809 and ASN557 and pi-alkyl interaction with LYS898. DFR formed hydrogen bonds via its Fluorine atoms with HIS901 and HIS562 and pi-alkyl interaction with LYS898.

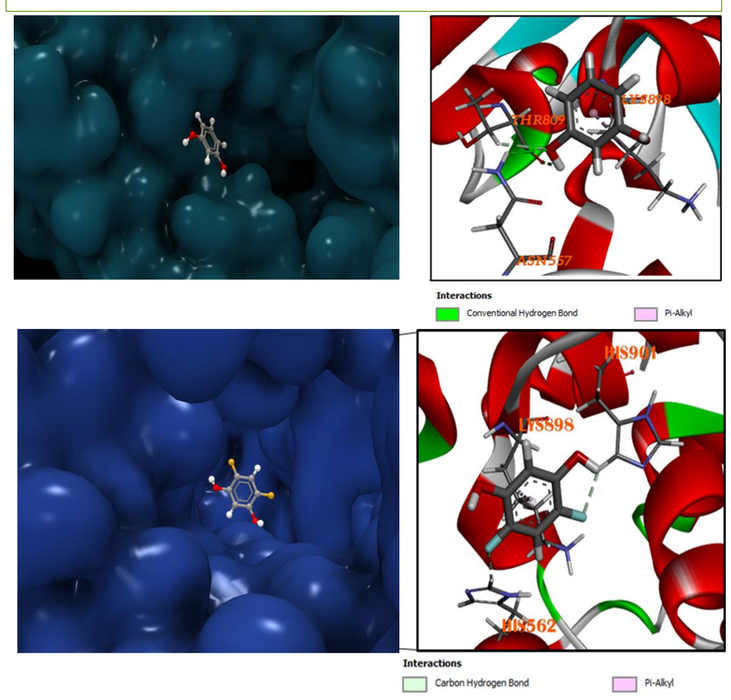


**Fig 4.** Binding mode (left) and Molecular interactions (right) of resorcinol (above) and DFR (below) with keratin-7.

## Conclusions

- All the studied compounds obeyed the Lipinski's rule of five (RO5) for the drug likeness of a molecule.
- The syn form is the least stable amongst all the studied compounds.
- The ESP maps showed the electronegativity trend of the halogenated resorcinols in the order: F>Cl>Br>I . This affirmed the expected trend in the periodic table.
- Both DFR and the resorcinol bind to LYS898 which implied they have similar binding pockets.
- DFR may be more potent than resorcinol in treating Hidradenitis suppurativa due to its high total binding score
- The hydrogen bonds and Pi-alkyl are the molecular interactions responsible for the strong binding of DFR with the target protein.

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## Software Packages used

- **Gaussian 09**
- **Spartan 16**
- **CLC drug discovery workbench 3**

## References

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