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# A Study of Drug-Like Properties of Regioisomers of Chloroaspirin Using QSAR and Molecular Docking

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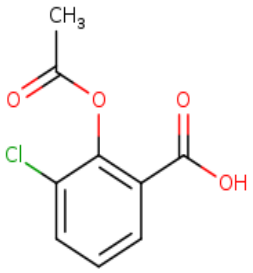
***Abstract*— Chloroaspirin, a chlorinated derivative of aspirin, has drawn interest due to its potential pharmacological applications. There are four regioisomers of chloroaspirin i.e., 3-chloroaspirin, 4-chloroaspirin, 5-chloroaspirin and 6-chloroaspirin. In this study, we evaluate the drug-like properties of all the regioisomers of chloroaspirin using Quantitative Structure-Activity Relationship (QSAR) modeling and molecular docking with cyclooxygenase enzyme-1(COX-1). Various computational approaches are employed to predict physicochemical properties, bioavailability, and interaction with target enzymes. The order of binding affinity of the regioisomers with the enzyme is as '4-chloroaspirin > 3-chloroaspirin > 5-chloroaspirin > 6-chloroaspirin'. Our findings provide insights into the suitability of these regioisomers as potential therapeutic agents.***

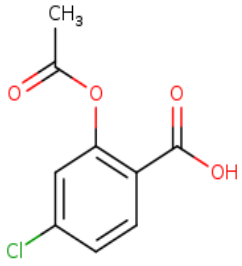
***Keywords: Chloroaspirin, Regioisomers, QSAR, Molecular Docking, ADMET, COX-1, Drug-likeness.***

## I. INTRODUCTION

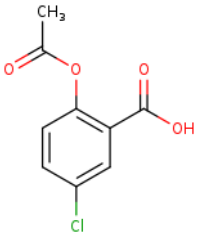
Aspirin (acetylsalicylic acid) is widely used as an anti-inflammatory and antiplatelet agent [1]. Modifications to its structure, such as chlorination, may enhance or alter its biological activity [2]. There are four regioisomers of chloroaspirin i.e. 3-chloroaspirin, 4-chloroaspirin, 5-chloroaspirin and 6-chloroaspirin as represented in scheme-1. This study aims to investigate regioisomeric forms of chloroaspirin through computational modeling to assess their drug-likeness and binding affinity to target proteins COX-1 [3].



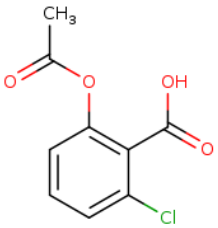

3-Chloroaspirin




4-Chloroaspirin




5-Chloroaspirin




6-Chloroaspirin

**Scheme 1:** Regioisomers of Chloroaspirin

## II. METHODOLOGY

### 2.1. QSAR Analysis:

QSAR models were developed using molecular descriptors, including lipophilicity (LogP), polar surface area (PSA), and hydrogen bond donors/acceptors [4]. The Lipinski's Rule of Five was employed to evaluate drug-like properties [5]. The physicochemical properties, lipophilicity, water solubility, pharmacokinetics, drug likeness, medicinal chemistry of the regioisomers of chloroaspirin were obtained from QSAR model SwissADME (webserver: http://www.swissadme.ch/ ) [6]. These data are reported in Table 1, Table 2, Table 3, Table 4, Table 5 and Table 6.

**Table 1:** Physicochemical Properties of Regioisomers of Chloroaspirin

| Physicochemical parameters | 3-Chloroaspirin | 4-Chloroaspirin | 5-Chloroaspirin | 6-Chloroaspirin |
|---|---|---|---|---|
| Formula | C9H7ClO4 | C9H7ClO4 | C9H7ClO4 | C9H7ClO4 |
| Molecular weight | 214.60 g/mol | 214.60 g/mol | 214.60 g/mol | 214.60 g/mol |
| Num. heavy atoms | 14 | 14 | 14 | 14 |

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| Physicochemical parameters | 3-Chloroaspirin | 4-Chloroaspirin | 5-Chloroaspirin | 6-Chloroaspirin |
|---|---|---|---|---|
| Num. arom. heavy atoms | 6 | 6 | 6 | 6 |
| Fraction Csp3 | 0.11 | 0.11 | 0.11 | 0.11 |
| Num. rotatable bonds | 3 | 3 | 3 | 3 |
| Num. H-bond acceptors | 4 | 4 | 4 | 4 |
| Num. H-bond donors | 1 | 1 | 1 | 1 |
| Molar Refractivity | 49.91 | 49.91 | 49.91 | 49.91 |
| TPSA | 63.60 Å² | 63.60 Å² | 63.60 Å² | 63.60 Å² |

**Table 2:** Lipophilicity Properties of Regioisomers of Chloroaspirin

| Lipophilicity parameters | 3-Chloroaspirin | 4-Chloroaspirin | 5-Chloroaspirin | 6-Chloroaspirin |
|---|---|---|---|---|
| Log $P_{o/w}$ (iLOGP) | 1.41 | 1.60 | 1.73 | 1.45 |
| Log $P_{o/w}$ (XLOGP3) | 1.84 | 1.82 | 1.82 | 1.02 |
| Log $P_{o/w}$ (WLOGP) | 1.96 | 1.96 | 1.96 | 1.96 |
| Log $P_{o/w}$ (MLOGP) | 2.08 | 2.08 | 2.08 | 2.08 |
| Log $P_{o/w}$ (SILICOS-IT) | 1.76 | 1.76 | 1.76 | 1.76 |
| Consensus Log $P_{o/w}$ | 1.81 | 1.85 | 1.87 | 1.66 |

**Table 3:** Water Solubility of Regioisomers of Chloroaspirin

| Water Solubility parameters | 3-Chloroaspirin | 4-Chloroaspirin | 5-Chloroaspirin | 6-Chloroaspirin |
|---|---|---|---|---|
| Log *S* (ESOL) | -2.45 | -2.44 | -2.44 | -1.93 |
| Solubility | 7.63e-01 mg/ml ; 3.56e-03 mol/l | 7.86e-01 mg/ml ; 3.66e-03 mol/l | 7.86e-01 mg/ml ; 3.66e-03 mol/l | 2.51e+00 mg/ml ; 1.17e-02 mol/l |
| Class | Soluble | Soluble | Soluble | Very soluble |
| Log *S* (Ali) | -2.80 | -2.78 | -2.78 | -1.95 |
| Solubility | 3.43e-01 mg/ml ; 1.60e-03 mol/l | 3.60e-01 mg/ml ; 1.68e-03 mol/l | 3.60e-01 mg/ml ; 1.68e-03 mol/l | 2.43e+00 mg/ml ; 1.13e-02 mol/l |
| Class | Soluble | Soluble | Soluble | Very soluble |
| Log *S* (SILICOS-IT) | -2.47 | -2.47 | -2.47 | -2.47 |
| Solubility | 7.25e-01 mg/ml ; 3.38e-03 mol/l | 7.25e-01 mg/ml ; 3.38e-03 mol/l | 7.25e-01 mg/ml ; 3.38e-03 mol/l | 7.25e-01 mg/ml ; 3.38e-03 mol/l |
| Class | Soluble | Soluble | Soluble | Soluble |

**Table 4:** Pharmacokinetics of Regioisomers of Chloroaspirin

| Pharmacokinetics parameters | 3-Chloroaspirin | 4-Chloroaspirin | 5-Chloroaspirin | 6-Chloroaspirin |
|---|---|---|---|---|
| GI absorption | High | High | High | High |
| BBB permeant | Yes | Yes | Yes | Yes |
| P-gp substrate | No | No | No | No |
| CYP1A2 inhibitor | No | No | No | No |
| CYP2C19 inhibitor | No | No | No | No |

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| Pharmacokinetics parameters | 3-Chloroaspirin | 4-Chloroaspirin | 5-Chloroaspirin | 6-Chloroaspirin |
|---|---|---|---|---|
| CYP2C9 inhibitor | No | No | No | No |
| CYP2D6 inhibitor | No | No | No | No |
| CYP3A4 inhibitor | No | No | No | No |
| Log $K_p$ (skin permeation) | -6.30 cm/s | -6.32 cm/s | -6.32 cm/s | -6.88 cm/s |

**Table 5:** Druglikeness of Regioisomers of Chloroaspirin

| Druglikeness Model | 3-Chloroaspirin | 4-Chloroaspirin | 5-Chloroaspirin | 6-Chloroaspirin |
|---|---|---|---|---|
| Lipinski | Yes; 0 violation | Yes; 0 violation | Yes; 0 violation | Yes; 0 violation |
| Ghose | Yes | Yes | Yes | Yes |
| Veber | Yes | Yes | Yes | Yes |
| Egan | Yes | Yes | Yes | Yes |
| Muegge | Yes | Yes | Yes | Yes |
| Bioavailability Score | 0.85 | 0.85 | 0.85 | 0.85 |

**Table 6:** Medicinal Chemistry of Regioisomers of Chloroaspirin

| Medicinal Chemistry | 3-Chloroaspirin | 4-Chloroaspirin | 5-Chloroaspirin | 6-Chloroaspirin |
|---|---|---|---|---|
| PAINS | 0 alert | 0 alert | 0 alert | 0 alert |
| Brenk | 1 alert: phenol_ester | 1 alert: phenol_ester | 1 alert: phenol_ester | 1 alert: phenol_ester |
| Leadlikeness | No; 1 violation: MW<250 | No; 1 violation: MW<250 | No; 1 violation: MW<250 | No; 1 violation: MW<250 |
| Synthetic accessibility | 1.81 | 1.77 | 1.73 | 1.82 |

### 2.2. Molecular Docking:

AutoDock is as an Educational Tool for Drug Discovery [7]. Molecular docking was performed using MGL tools 1.5.7 software with the Auto Grid 4.2.6 and Auto Dock 4.2.6 packages. 'Swiss TargetPrediction' webserver (http://www.swisstargetprediction.ch) was used to predict the target molecule of the product ligand regioisomers of chloroaspirin. COX-1 was the best target suggested. 4awt, stable, high-expression variant of human COX-1was downloaded from PDB (www.rcsb.org). The downloaded structure was processed in Discovery Studio to remove water, heteroatoms and ligands. The processed protein structure was saved as protein pdb file. In the MarvinSkech software 3D structures of regioisomers of chloroaspirin were drawn and saved separately as ligand pdb file. The optimized pdbqt structure of enzyme COX-1 and ligands-regioisomers of chloroaspirin were used in the molecular docking study. Lamarckian genetic algorithm (GA) 4.2 was used in this docking study. Polar hydrogen and Kollman charges were added before starting molecular docking. Auto grid was used to set the grid point. All other parameters were set to the default setting 10 docking runs were carried out. The minimum negative binding energies of docking has been reported in Table-7. The details of docking is provided in supporting information (SI).

**Table-7:** The minimum negative binding energies of docking

| Regioisomers of Chloroaspirin | Binding Energy of Most Stable Conformers with Cox-1 / kcalmol$^{-1}$ |
|---|---|
| 3-Chloroaspirin | -7.14 |
| 4-Chloroaspirin | -7.85 |
| 5-Chloroaspirin | -6.89 |
| 6-Chloroaspirin | -6.80 |

## III. RESULTS AND DISCUSSION

### 3.1. QSAR Analysis Findings:

The calculated molecular descriptors indicate that all regioisomers comply with Lipinski's Rule of Five, suggesting favorable drug-like properties. However, variations in LogP and PSA values influence their solubility and permeability. The SwissADME QSAR model of regioisomers of chloroaspirin has been given in Figure-1

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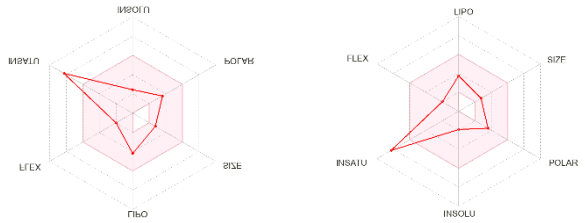
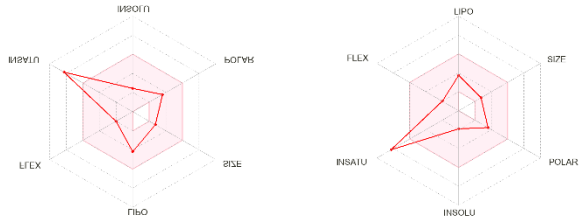
Most regioisomers show acceptable absorption and distribution properties. However, minor differences in metabolism and potential toxicity risks highlight the importance of regioselective modifications.




5-Chloroaspirin 6-Chloroaspirin

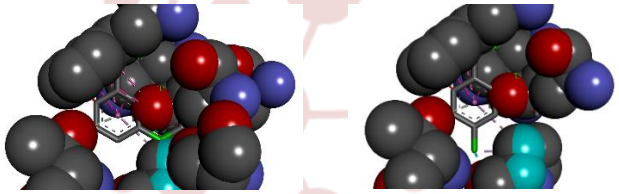



5-Chloroaspirin 6-Chloroaspirin

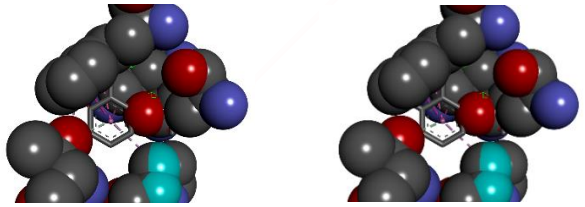
**Figure 1:** QSAR model of regioisomers of chloroaspirin

### 3.2. Molecular Docking Results:

Docking studies revealed that different regioisomers exhibit varying binding affinities to COX-1. Some isomers demonstrate stronger hydrogen bonding and hydrophobic interactions, implying higher potency. 3-D interactions of regioisomers of chloroaspirin with COX-1 has been shown in Figure 2. 2-D interactions of 3-chloroaspirin with COX-1 has been represented in Figure 3. 2-D interactions of 4-chloroaspirin with COX-1 has been represented in Figure 4. 2-D interactions of 5-chloroaspirin with COX-1 has been represented in Figure 5. 2-D interactions of 6-chloroaspirin with COX-1 has been represented in Figure 6.



3-Chloroaspirin Interaction with COX-1 4-Chloroaspirin Interaction with COX-1



5-Chloroaspirin Interaction with COX-1 6-Chloroaspirin Interaction with COX-1

**Figure 2:** 3-D interactions of regioisomers of chloroaspirin with COX-1

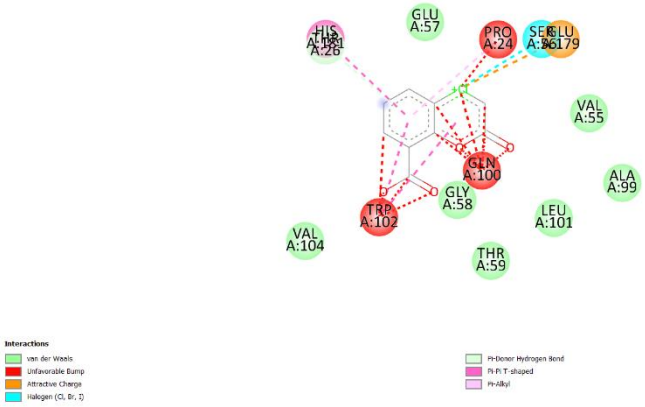



**Figure 3:** 2-D interactions of 3-chloroaspirin with COX-1

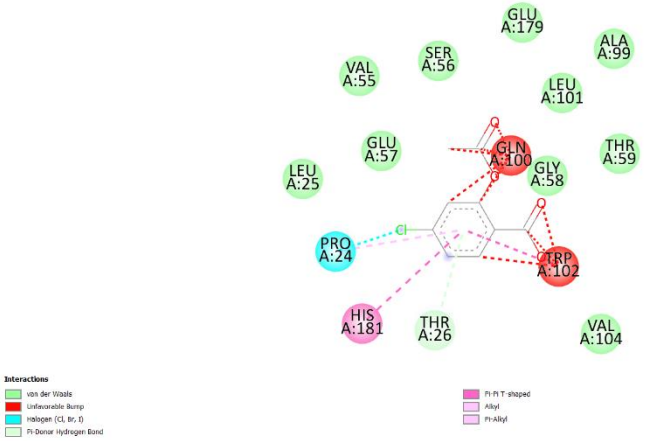



**Figure 4:** 2-D interactions of 4-chloroaspirin with COX-1

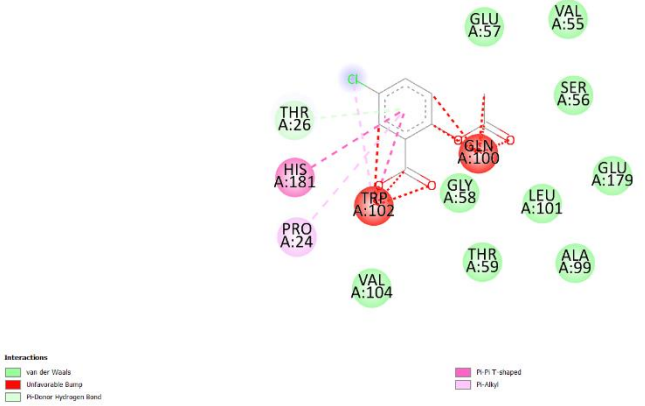



**Figure 5:** 2-D interactions of 5-chloroaspirin with COX-1

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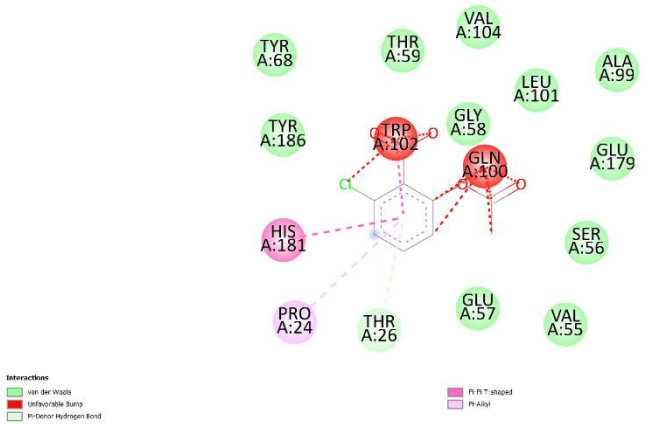


**Figure 6:** 2-D interactions of 6-chloroaspirin with COX-1

The order of binding affinity of the regioisomers with the enzyme is as follows:

4-chloroaspirin > 3-chloroaspirin > 5-chloroaspirin > 6-chloroaspirin

## IV. CONCLUSION

This study provides a comparative evaluation of chloroaspirin regioisomers, revealing their potential as therapeutic candidates. Further experimental validation is recommended to confirm computational findings and explore their biological effects.

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