Ligand-Protein Binding of Cantharidin and Norcantharidin on HSF1: A Docking Study

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Ligand-Protein Binding of Cantharidin and Norcantharidin on HSF1: A Docking Study

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Overview

- Cantharidin has been shown to display anti-tumor properties through inhibitory activity on heat shock factor 1 protein (HSF1)\(^1\).
- In the same study, norcantharidin displayed no inhibitory activity on the same protein.
- No literature on a binding site or binding strength is available at the time of this study.
- Our goal is to present potential binding sites and strengths for cantharidin and norcantharidin on HSF1 (PDB ID: 5HDG).
- Another goal is to supply binding energies to explain the inhibitory/non-inhibitory activity of cantharidin/norcantharidin on 5HDG.

Methods

- Docking simulations through AutoDock 4.2\(^\circ\).
- Ligand structure files generated using Avogadro/ORCA.
- Water molecules stripped from 5HDG, Gasteiger charges added
- AutoGrid with 0.425 Ångstrom spacing, failed dockings increased from 10 to 25.
- Small GridBox in pocket, high AutoDock simulations
- Ligand-protein renderings were done using the Chimera\(^4\).

Table 1: Summary of ligand-protein docking simulations in AutoDock.

<table>
<thead>
<tr>
<th>Protein</th>
<th>Ligand</th>
<th>Pocket</th>
<th>Binding Energy kcal · mol(^{-1})</th>
</tr>
</thead>
<tbody>
<tr>
<td>5HDG</td>
<td>Cantharidin</td>
<td>P1</td>
<td>-4.75</td>
</tr>
<tr>
<td>5HDG</td>
<td>Cantharidin</td>
<td>P2</td>
<td>-4.65</td>
</tr>
<tr>
<td>5HDG</td>
<td>Norcantharidin</td>
<td>P1</td>
<td>-4.46</td>
</tr>
<tr>
<td>5HDG</td>
<td>Norcantharidin</td>
<td>P2</td>
<td>-4.09</td>
</tr>
</tbody>
</table>

Conclusions

- Regardless of binding site, cantharidin consistently binds stronger to HSF1 than norcantharidin.
- Computational investigation reinforced the experimental evidence of cantharidin inhibitory activity on HSF1.
- Two potential binding sites (P1 and P2) were put forth for cantharidin and norcantharidin on 5HDG.

Future Work

- Further studies forthcoming using GROMACS to account for protein structure changes and thus more accurate binding free energy.
- Increase number of ligands screened to determine most effective inhibitor of HSF1 while considering possible toxicities.
- Synthesis of such ligands.
- More explicitly account for solvent interactions.

References

[3] Molecular graphics and analyses performed with UCSF Chimera, developed by the Resource for Biocomputing, Visualization, and Informatics at the University of California, San Francisco, with support from NIH P41-GM103311