Chemical Modification of Acetaminophen to Reduce Liver Toxicity and Enhance Drug Efficacy

Each week, **over 60 million individuals consume** acetaminophen for its analgesic (pain relieving) properties in the U.S. alone[1]. Unfortunately, acetaminophen toxicity is a **leading cause of liver transplantation** worldwide[1].

Problem

Acetaminophen Liver Toxicity Mechanism

In the body, acetaminophen oxidizes to NAPQi, a toxic electrophilic species that depletes glutathione (regulatory peptide) and attacks liver proteins, which are nucleophilic by nature[1].

Existing Solutions

- Inaccessible: antidotal therapy is clinically administered[2]
- Impractical: current approaches to modification alter functional groups necessary for pain receptor binding[3], sacrificing drug efficacy

Figure 1. Hepatotoxicity Illustration
Graphic created by student using BioRender, 2024.

Introduction

Acetaminophen Analgesic Mechanism

Acetaminophen metabolizes to AM404, the analgesic form of acetaminophen. AM404 binds to TRPV1 (transient receptor potential vanilloid 1) in the brain and spinal cord[4].

- Non-Opioid
- Non-NSAID
- Standard first-line treatment for pain and fever
- Hydroxyl and amide groups are important for analgesic properties[3]

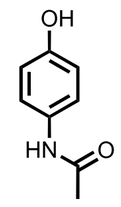


Figure 2. Acetaminophen
Graphic created by student using ChemDraw, 2024.

Computational Analysis of Toxicity

Frontier Molecular Orbital Theory: **HOMO** (highest occupied molecular orbital) of nucleophiles and **LUMO** (lowest unoccupied molecular orbital) of electrophiles overlap in reactions[5,6].

Design NAPQi (oxidized acetaminophen) derivatives in *ChemDraw*

↓

Quantum (DFT) calculations with *Orca 5.0*

↓

Retrieve LUMO values in *Avogadro*

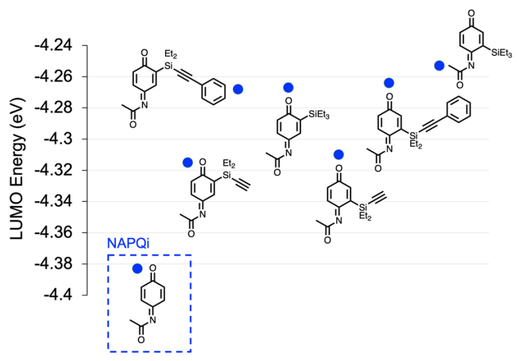


Figure 3. LUMO Energies
Graphic created by student using ChemDraw and Google Drawings, 2024.

Modified derivatives have higher NAPQi (toxic acetaminophen) LUMO energies, which increase the HOMO-LUMO energy gap between NAPQi and nucleophiles, **decreasing electrophilic reactivity** and, thus, **reducing liver toxicity**.

Computational Analysis of Efficacy

Docking predicts how small molecules interact with larger molecules.

Receptor: TRPV1 (PDB: 5irz)
Ligand: AM404 (analgesic form of acetaminophen) derivatives

↓

Dock Prep: add hydrogens & assign charges

↓

Retrieve docking scores in *Autodock Vina*

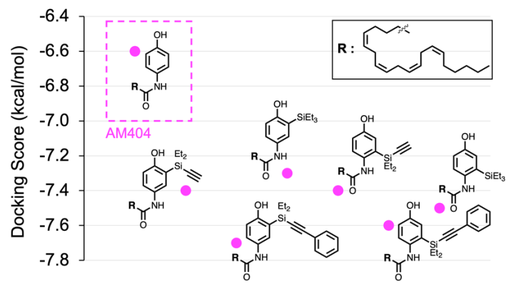
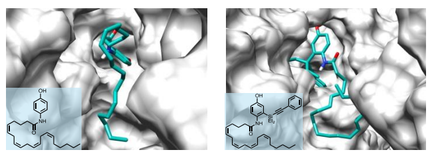


Figure 4. Docking Scores
Graphic created by student using ChemDraw and Google Drawings, 2024.

Docking Modes



Modification lowers docking scores, indicating that AM404 derivatives have a higher affinity to TRPV1 and, thus, **enhanced drug efficacy**.

Figure 5. Docking Modes
Graphic taken by student using UCSF Chimera, 2024.

Synthetic Modification Scheme

*Scheme represents the original idea of student and is a representation of outcomes that were achieved by experimentation. All steps were repeated at least five times.

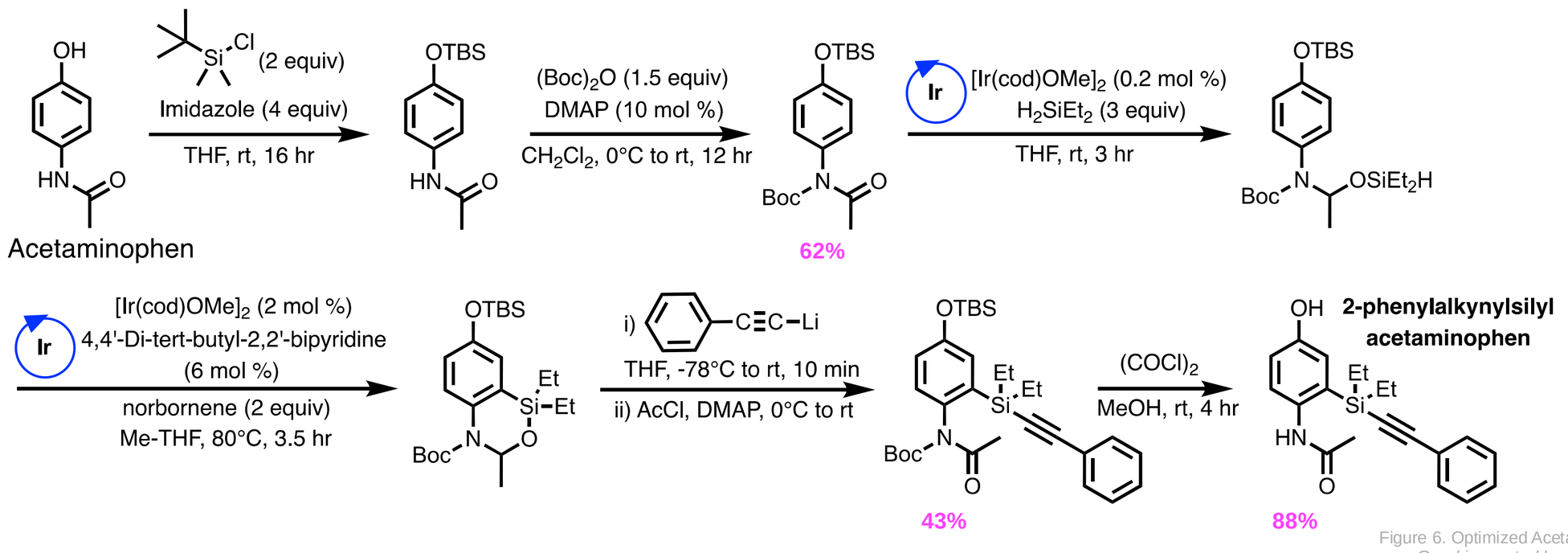
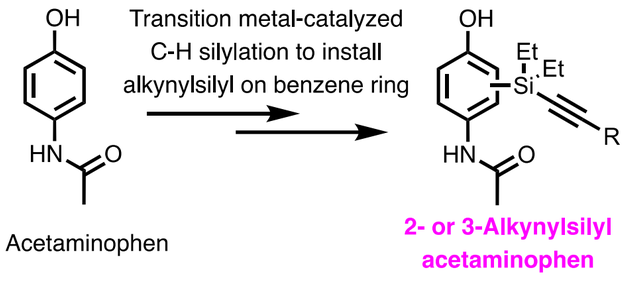


Figure 6. Optimized Acetaminophen ModificationScheme
Graphic created by student using ChemDraw, 2024.

Approach:

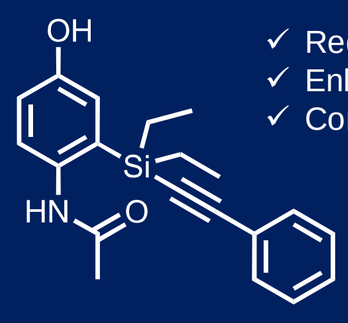
- Benzene-ring has minimal interaction with TRPV1[3], and modifying it could decrease electrophilic reactivity
- Transition metal-catalysts allow for site-selective modification[7]
- Silicon (Si) has no inherent toxicity and can modulate properties of the drug it's placed in[7]



Reduce electrophilic reactivity without sacrificing drug efficacy

Figure 7. Research Purpose
Graphic created by student using ChemDraw, 2024.

2-Phenylalkynylsilyl Acetaminophen



- ✓ Reduced toxicity
- ✓ Enhanced efficacy
- ✓ Complete, optimized synthesis using C-H activation

Figure 8. 2-Phenylalkynylsilyl Acetaminophen
Graphic created by student using ChemDraw, 2024.

- A step towards creating **safer** and **more effective** forms of acetaminophen
- Could overcome acetaminophen's ceiling-effect to develop more effective and safer **alternatives to highly addictive strong analgesics like opioids**, leveraging acetaminophen's non-addictive property[4].

References

[1] Chun, L.J., Tong, M.J., Busuttil, R.W. & Hiatt, J.R. Acetaminophen hepatotoxicity and acute liver failure. *J Clin Gastroenterol* **43**, 342-349 (2009).
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[3] Mallet, C., Desmeules, J., Pegahi, R. & Eschalier, A. An Updated Review on the Metabolite (AM404)-Mediated Central Mechanism of Action of Paracetamol (Acetaminophen): Experimental Evidence and Potential Clinical Impact. *J Pain Res* **16**, 1081-1094 (2023).
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[5] Gould, T., Hashimi, Z., Kronik, L. & Dale, S.G. Single Excitation Energies Obtained from the Ensemble "HOMO-LUMO Gap": Exact Results and Approximations. *J Phys Chem Lett* **13**, 2452-2458 (2022).
[6] Townsend, P.A. & Grayson, M.N. Density Functional Theory in the Prediction of Mutagenicity: A Perspective. *Chem Res Toxicol* **34**, 179-188 (2021).
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