2-Phenylalkynylsilyl Acetaminophen as a Less Toxic and More Effective Pain Medication

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Acetaminophen is a widely used non-opioid analgesic and antipyretic medication, with over sixty million weekly consumers in the U.S. alone. Unfortunately, its toxicity is a leading cause of liver transplantation worldwide. NAPQi, the toxic form of acetaminophen produced after oxidizing in the body, is an electrophile that depletes glutathione and eventually attacks liver proteins, which are nucleophilic. Existing approaches to acetaminophen modification to decrease toxicity are impractical as they modify functional groups necessary for acetaminophen's analgesic properties. It was hypothesized that sequential transition metal catalysis, involving precise C-H silylation of acetaminophen's benzene ring, followed by the nucleophilic addition of an alkyne to the silicon center, could decrease acetaminophen toxicity while maintaining its therapeutic effectiveness. The LUMO energy values of acetaminophen analogues were computed through Orca 5.0 and retrieved in Avogadro to assess toxicity. Docking simulations were then performed through AutoDock Vina to analyze the efficacy of acetaminophen analogues by evaluating their binding to TRPV1. An original scheme was developed and optimized to synthesize 2-phenylalkynylsilyl acetaminophen. All acetaminophen analogues had higher LUMO energies than the original compound, indicating reduced nucleophilic reactivity and decreased liver toxicity. They also exhibited enhanced binding to TRPV1, demonstrating improved analgesic efficacy. 2-phenylalkynylsilyl acetaminophen was synthesized through precise C-H silylation via sequential iridium transition metal catalysis, followed by nucleophilic addition of a phenylalkyne. This synthetic approach represents a promising method for developing more potent and less toxic pain medication.

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