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Abstract

$Cu(PPh_3)_3Br$-Catalyzed Synthesis of New Paracetamol–1,2,3-Triazole Molecular Hybrids from Expired Commercial Tablets and Their In Silico Assessment to Study Their Pharmacological Properties †

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Abstract: The 1,2,3-Triazole ring has remarkable importance in medicinal chemistry due to its unique biological properties, such as metabolic stability and ability to form hydrogen bonds. Several biological activities had been reported for this structural nucleus, while paracetamol (acetaminophen) or *N*-(4-hydroxyphenyl)acetamide) is one of the most popular and widely used drugs for the treatment of pain and fever. By applying a molecular hybridization strategy, numerous 1,2,3-triazole-based compounds have been designed, prepared, and studied for pharmacological applications in multiple laboratories around the world. Considering this context, we used expired acetaminophen pills as the starting material for generating new series of functionalized paracetamol–1,2,3-triazole hybrids. Their synthesis consisted of a $Cu(PPh_3)_3Br$-catalyzed 1,3-dipolar cycloaddition reaction of the *O*-propargyl-acetaminophen and several azides prepared from commercially available anilines, following the protocol reported by Filimonov et al. By performing click chemistry and considering green chemistry principles, interesting paracetamol–1,2,3-triazole derivatives were easily prepared in 64–93% yields. Obtained hybrids were subjected to an in silico analysis (Molinspiration, OSIRIS, and DRUDIT), evaluating some physicochemical properties and toxicity risks. According to the predicted biological properties, most of the prepared hybrid molecules exhibited adequate parameters as potential pharmacological agents, presenting high inhibitory activity, low risks of toxicity, and good affinity for various biological targets. This work highlights the recycling of expired drugs and accessibility to new paracetamol-based compounds under green mild reaction conditions (H_2O/*tert*-BuOH mixture, rt) and low catalytic loads (1 mol% $Cu(PPh_3)_3Br$).

Keywords: paracetamol–1,2,3-triazole hybrids; 1,3-dipolar cycloaddition; in silico studies

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