Opinion

Is it possible to perform molecular hybridization between acetaminophen and nitric oxide donor molecule?

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Paracetamol (Acetaminophen) belongs to the class of Non-Steroidal Anti-Inflammatory Drugs (NSAIDs), having an analgesic, antipyretic and mild anti-inflammatory action due to a weak inhibitory action on cyclooxygenase isoenzymes, COX-1 and COX-2. These isoenzymes are responsible for the synthesis of prostanoids that have several physiological effects, such as: vasodilation; increased renal blood flow; stimulation of gastric protective mucus production; inhibition of gastric acid secretion responsible for reducing acidity in gastric tissue, among other effects. Despite its beneficial effects, the excessive use of NSAIDs is related to several adverse effects, which can alter the homeostasis of the cardiovascular, renal and gastric system [1].

The selective inhibitors of COX-2, known as COXIBS, were an alternative to control pain without having the adverse effects due to the inhibition of COX-1. Although, several reports related cardiovascular complications with long-term use of COXIBS, suggesting that specific benefit/risk ratio should be considered in the prescription of this drug class [2]. Despite the notorious beneficial effects of anti-inflammatory drugs, their mechanism of action creates an inherent risk with its use, bringing the possibility of proposing hybrid chemical structures that can mitigate adverse effects [3].

The Nurse’s Health [1] analyzed the effect of NSAIDs on 51,630 normotensive nurses aged between 44 and 69 years, pointing that women who have used acetaminophen frequently had a 20% increase in the risk of developing high blood pressure. In hypertensive patients, the long-term use of this drug class can increase up to 6 mmHg arterial pressure mean, interfering with several classes of antihypertensive drugs [4]. In addition to the cardiovascular adverse effects, the mechanism of action of acetaminophen impairs gastric defense mechanisms, providing gastric lesions.

Nitric Oxide (NO) is an intercellular messenger that plays an important role in pathological and physiological regulations. Its antimicrobial, bactericidal, antiviral, vasodilatory and cytoprotective activity are considered fundamental for physiological homeostasis [5-7]. These beneficial effects makes nitric oxide a potential ally in new drugs developments, making molecular structures capable of donating nitric oxide into study targets, such as those derived from furoxan and benzofuroxan.

Nitric oxide donor molecules were capable of decreasing the gastric membrane damage in a group of rodents submitted to ketoprofen therapy associated with nitric oxide donor when compared to the group submitted to ketoprofen only therapy [8]. The association of furoxan or benzofuroxan derivatives with other pharmacological groups as a strategy to enhance their pharmacological effect or mitigate adverse effects has been an interesting and actual strategy. There are reports of molecular hybridization with drugs belonging to the class of β-adrenergic antagonists, H2 antagonists, calcium channel modulators and non-steroidal anti-inflammatory drugs [8].
The hybridization of NSAIDs and nitric oxide donors structures have already been proposed with the objective of making safer NSAIDs [9–11]. Acetaminophen and a nitric oxide donor hybrid have been synthesized using an esterification reaction [12] and a study synthesized a hybrid between acetaminophen and a benzofuroxan derivate [13]. Hybridization of diclofenac and benzofuroxan derivatives have already been proposed too [14].

Therefore, it is feasible to believe that the molecular hybridization of paracetamol, N-(4-hydroxyphenyl) acetamide, with benzofuroxan (6-carboxybenzo [c] [1,2,5] oxadiazole 1-oxide (1)) would promote a considerable reduction in its adverse effects. The formation of the hybrid (4) would be possible with esterification reactions between the carboxylic acids of acetaminophen (3) and benzofuroxan acyl chloride (2), after submitting it to the reaction with acyl chloride (SOCl2), as shown in Figure 1.

![Figure 1: Synthetic route for obtaining the paracetamol hybrid with benzofuroxan.](image)

The reaction between carboxylic acids of acetaminophen (3) and benzofuroxan acyl chloride (2) is possible due to the nucleophilic capability of the acetaminophen hydroxyl group to react with the acyl chloride, a powerful acid. The desterification of the hybrid can be fulfilled by esterases present on the metabolism, allowing both acetaminophen and benzofuroxan to perform their respective roles.

However, increased biochemical markers indicating increase in the oxidative stress in tissues submitted to therapy with nitric oxide donors have already been reported [6]. The association of acetaminophen with nitric oxide donors presented to be less hepatotoxic than acetaminophen isolated [12]. This association didn’t show significant effects on vascular system, despite the nitric oxide vasodilatory effects [12].

The feasibility of synthesizing this hybrid would bring new perspectives on the use of NSAIDs, providing greater safety in pain treatment of patients associated, or not, with other pathologies. The chemistry behind the synthesis of this hybrid is simple, making it achievable. However, the nitric oxide toleration needs to be better understood to grant more reliability and prevent any short or long terms health problems.

Nitric oxide donors may be the solution to prevent the majority cases of acetaminophen intoxications. It is possible to believe that the associations between NSAIDs with nitric oxide donors have the potential to make a revolution in pain treatment, since these associations have shown to be “improved” forms of NSAIDs.

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