**Synthesis of new Benzylidene digoxin and ouabain derivatives: Preliminary evaluation of the NaK activity.**

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The general structure of cardiac glycosides, such as Digoxin and Ouabain, is characterized by four fused rings with a specific arrangement (the B/C ring is trans, while the C/D and A/B rings are mostly cis). Considering this privileged structure, employing these natural compounds as building blocks for new molecules is a strategy to explore different effects on Na/K-ATPase. The most potent inhibitors of Na/K-ATPase have an unsaturated lactone ring (five or six-membered) attached to the C17 position and a sugar moiety at C3. The requirement of a lactone ring for the inhibition of Na,K-ATPase is a strategy for developing new compounds. However, a critical disadvantage of these compounds (CS) is their narrow therapeutic index and the resulting risk of toxicity, which can lead to life-threatening heart arrhythmias. This drawback hinders the development of new compounds. Therefore, our goal in chemical modifications was to introduce an aromatic group into the lactone ring of digoxin to create steric hindrance at the binding site of Na,K-ATPase and to remove the sugar moiety from the synthesized benzylidenes. In the first step we have synthesized 3 new benzylidenes starting from Digoxin, Digitoxigenin and Ouabain by a stereoselective vinylogous aldol reaction. All compounds were characterized on the basis of extensive analyses of mass spectrometry and NMR. Preliminary activity of the Na,K,Pump was evaluated. We used a membrane fraction prepared from kidney tissue of Wistar rats and incubated it at concentrations of 1 nM, 10 nM, 100 nM, 1 μM, and 10 μM. No inhibitory effect on the alpha-1 isoform was observed, which aligns with our expectations. In conclusion, we have synthesized three new benzylidene derivatives, and further investigations on Na,K-ATPase are underway.