



Synthesis and Optimization of Benzyldiene-Digoxigenin Derivatives with Modified Sugar Moieties for Pharmacological Applications

Erick C. Oliveira(G)^{1*}, Gustavo F. F. Lima(PG)¹, Jefferson L. Princival(PQ)², Leandro A. O. Barbosa(PQ)³, José A. F. P. Villar (PQ)¹.

¹Laboratório de Síntese Orgânica e Nano Estruturas, ²Laboratório de Catálise Orgânica, ³Laboratório de Bioquímica Celular, Universidade Federal de São João del Rei, campus Centro-Oeste Dona Lindu, Divinópolis, MG, CEP: 35.501-296. Brasil.

*erickecardosooliveira01@gmail.com

Abstract

This work reports the synthesis of new benzyldiene digoxigenin derivatives by replacing the original sugar moiety with different monosaccharides. Digoxin was hydrolyzed to obtain digoxigenin, which was then glycosylated with L-rhamnose and D-galactose using the Koenigs-Knorr reaction. The resulting derivatives were further transformed into benzyldiene compounds, with potential applications in pharmacological and biochemical studies.

Keywords: digoxin, benzyldiene, Na/K-ATPase, Koenigs-Knorr.

Introduction

Digoxin is a cardiac glycoside derived from *Digitalis lanata* and is one of the oldest used medicaments in cardiology. It has been heavily employed when treating a number of heart problems, including congestive heart failure, atrial fibrillation or flutter, and certain cardiac arrhythmias[1]. The basic structure of cardiotonic steroids consists of a steroid backbone with a cis/trans/cis configuration and a lactone moiety at position 17 β , also known as the aglycone. In addition, these compounds frequently have sugar attached at position 3 β of the steroidal nucleus. On the other hand, Ouabain is a cardiac glycoside isolated naturally from *Strophanthus gratus*. Compounds Digoxin(1) and Ouabain(2) inhibits the Na/K-ATPase membrane pump, resulting in an increase in intracellular sodium and calcium concentrations and the difference between 1 and 2 consisting of a glycosylated steroid core L-rhamnose (ouabain) or trisaccharide (digoxin)[2].

Experimental

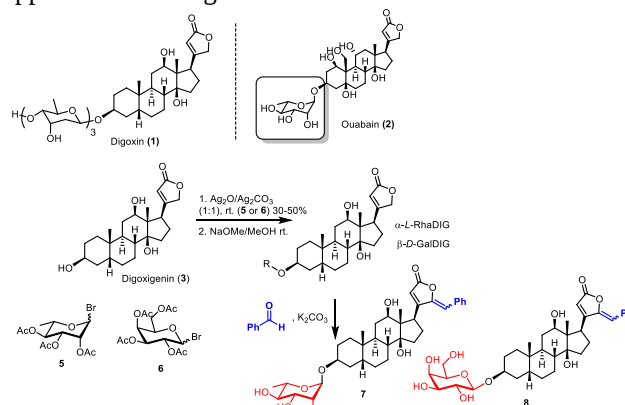
All compounds were synthesized on a laboratory scale (<1 g) using standard techniques in organic synthesis. Purification was performed by column chromatography or recrystallization. All reagents were commercially obtained with high purity. The synthesized compounds were characterized by spectroscopic and spectrometric techniques NMR 400 MHz ¹H and ¹³C, IR-FTIR, and MS-ESI.

Results and Discussion

Digoxigenin was efficiently obtained from digoxin via acid hydrolysis, achieving a high yield of 80%. Per-O-acetylated L-rhamnose and D-galactose were successfully synthesized and subsequently employed in Koenigs-Knorr glycosylation reactions with digoxigenin, affording the corresponding acetylated glycosides. Subsequent deacetylation furnished the final glycosylated digoxigenin derivatives, α -L-RhaDIG and β -D-GalDIG, in good purity.

These glycosylated derivatives were then subjected to a vinylogous aldol condensation, yielding the corresponding

benzyldiene analogues. The overall synthetic route proved to be efficient, reproducible, and suitable for structural diversification (Scheme 1). Optimization of both the glycosylation and condensation steps is currently underway to enable scale-up and to support future biological evaluations



Scheme 1. Synthesis of sugar-digoxigenin derivatives and benzyldienes.

Conclusion

In conclusion, α -L-RhaDIG and β -D-GalDIG were efficiently synthesized and fully characterized. Ongoing efforts are focused on optimizing both the glycosylation and vinylogous aldol reactions to enable the preparation of novel benzyldiene derivatives on a gram scale.

Acknowledgements

FAPEMIG, CAPES, CNPq, UFSJ, FINEP, LCACCO-UFSJ.

References

1. Prassas I, Diamandis EP. Novel therapeutic applications of cardiac glycosides. *Nat Rev Drug Discov* 2008; 7: 926-35.
2. NEWMAN, R.A. et al. Cardiac Glycosides as Novel Cancer Therapeutic Agents. *Molecular Interventions*, v. 8, n. 1, p. 36-49, 1 fev. 2008.