Coumarins and Neoflavones: Synthesis and HCV NS5B Polymerase Inhibition

Paula de F. de Moraes[1], Raquel A. C. Leão[1], Daniel Brian Nichols[2], Amartya Basu[2], Maksim Chudayeu[2], Tanaji T. Talele[2], Neerja Kaushik-Basu[2], Paulo R. R. Costa[1*]

[1]*Laboratório de Química Bioorgânica, Núcleo de Pesquisas de Produtos Naturais, Centro de Ciências da Saúde, Bloco H, Universidade Federal do Rio de Janeiro, RJ 21941-590, Brazil*
[2]*Department of Biochemistry and Molecular Biology, UMDNJ-New Jersey Medical School, 185 South Orange Avenue, Newark, NJ 07103, USA*

[*] *prrcosta2011@gmail.com*

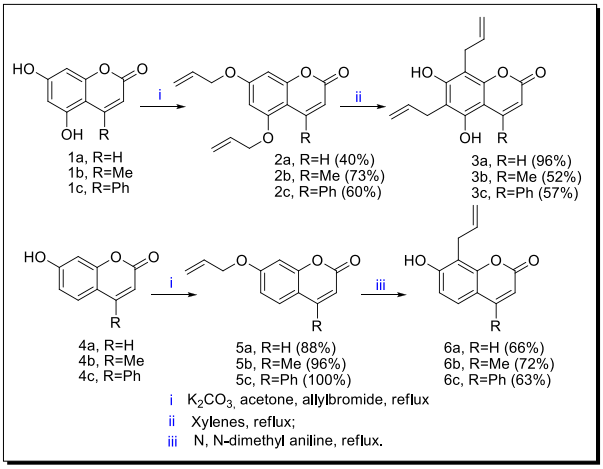
Keywords: antiviral agents, coumarin, neoflavone

INTRODUCTION

Hepatitis C virus (HCV) is the leading cause of malignant chronic liver disease such as fibrosis, cirrhosis and hepatocellular carcinoma.[1] Some years ago we report on the coumestan family of phytoestrogens as a new class of non-nucleoside HCV NS5B polymerase inhibitor.[2] Wedelolactone and LQB-34 were the most potent (Figure 1). However, further efforts to optimize the coumestan scaffold proved discouraging as the synthesis of new derivatives involved multiple steps and expensive chemicals.[2] We therefore sought to explore a trimmed version of coumestans, such as coumarins and neoflavones, which comprise of a bicyclic scaffold as opposed to a tetracyclic one present in LQB-34, as potential HCV NS5B inhibitors.

RESULTS AND DISCUSSION

Eighteen coumarins and neoflavones were prepared through a new zinc-catalyzed hydroarylation of propiolates by phenols.[3] Allyl groups were introduced by *O*-alkylation followed by Claissen rearrangement. These products were investigated as candidate as inhibitors of hepatitis C virus NS5B polymerase[4] (Scheme 1).



Scheme 1. Synthesis of coumarins and neoflavones

Coumarin **3a** was produced in three steps in high chemical yield and proved the most potent of the series, with similar potency to the coumestan LQB-**34** for the inhibition of NS5B polymerase (**Figure 1**).[4]

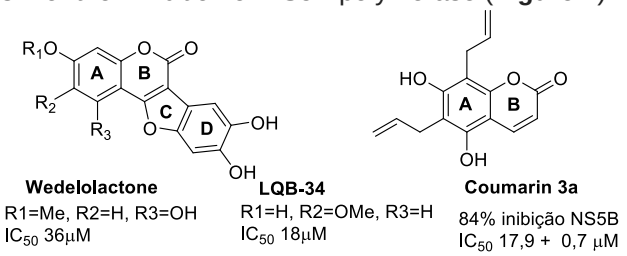


Figure 1. Biological evaluation of coumarin and coumestans

The allyl group at the 6-position of the coumarin ring is stabilized through hydrophobic interactions within **HP-1**, whereas second allyl group at 8-position is anchored within the **HP-2**. The carbonyl oxygen atom of the lactone function in coumarin ring forms a hydrogen bond with the guanidine group of Arg503 (**Figure 2**).

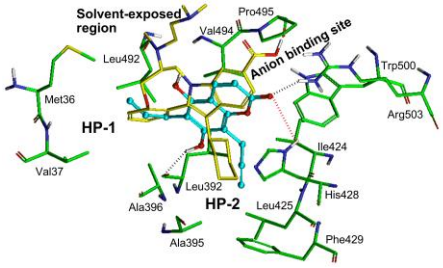


Figure 2: XP-Glide interaction coumarin - receptor

CONCLUSION

Coumarin can be an alternatives to cumestans in the development of novel inhibitors of anti-NS5B. Based on docking studies new synthesis of new derivatives is underway.

ACKNOWLEDGEMENTS

CNPq, FAPERJ e CAPES

REFERENCES

[1] Kaushik-Basu, N., e cols., *Nucleic Acids Res.* **2008**, *36*, 1482.[2] Pocas E.S., e cols., *Bioorg Med Chem.* **2006**, *14*, 7962.[3] Leão R. A. C., e cols., *Synthesis-Stuttgart,* **2011**, *22*, 3692. [4] Nichols D. B., e cols., *Chem. Biol. Drug Design,* **2013**, 81, 607.