Synthesis and Antiviral (HCV) Evaluation of 5-Carba-pterocarpens

Talita de A. Fernandes[1] (PQ), Dinesh Manvar[2] (PQ), Jorge L. O. Domingos[3] (PQ), Erdenechimeg Baljinnyam[2] (PQ), Amartya Basu[2] (PQ), Rupa Guhamazumder[2] (PQ), Neerja Kaushik-Basu*[2] (PQ), Paulo R. R. Costa*[1] (PQ)

[1]Universidade Federal do Rio de Janeiro; [2]Rutgers-The State University of New Jersey; [3]Universidade do Estado do Rio de Janeiro

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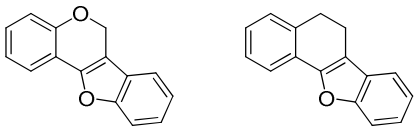
Introduction

Pterocarpens belong to the isoflavonoids class of natural products and display a wide variety of activities, including antibacterial and affinity to estrogenic receptors (ER). The corresponding carba-analog, an isostere with the substitution of the oxygen atom by the methylene group, also shows affinity to ER.[1]



Pterocarpen 5-Carba-Pterocarpen

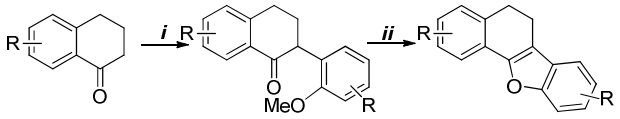
Figure 1. Natural product structure and its analog

Hepatitis C virus (HCV), a major human pathogen and causative agent of parenteral non-A, non-B hepatitis, is often associated with the development of malignant chronic disease, including steatosis, liver cirrhosis and hepatocellular carcinoma. HCV infection is estimated to be around five times more prevalent than HIV-1, with over 200 million cases globally. There is no vaccine against HCV or any effective therapy broadly targeting all genotypes of HCV.

Based on our previous studies with coumestan and coumarins,[2] we report in this work the synthesis and the evaluation of anti-HCV activity of the 5-carba-pterocarpens.

Results and Discussion

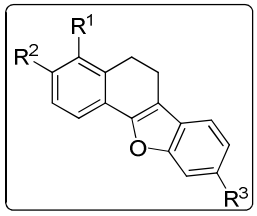
The work started with the preparation of 5-carba-pterocarpens, through the sequence of α-arylation of tetralones followed by the demethylation and cyclization catalyzed by BBr_3 (Scheme 1).[3]



Scheme 1. *Conditions:* ***i****- ArBr (1.2Eq),* Pd_2dba_3 *(2.5mol%),* tBu_3BF_4 *(0,1Eq.) KOH (2.5Eq), Dioxane/water, 80W, 100°C, 40min;* ***ii****-* BBr_3 *(5 Eq.), DCM, 0°C, 1h*

Under these conditions the 5-carba-pterocarpens were obtained in good to excellent yields (60-85%).

The anti-HCV activity was accessed by the inhibition of cell proliferation in Huh7/Rep-Feo1b and Huh7.5-FGR-JC1-Rluc2A replicon reporter cells, derived from two different HCV genotypes, and the compounds were also evaluated as HCV NS5B inhibitors. Their toxicity was determined in non-infected Huh7.5 parental cells. The results are shown in Figure 2.



LQB358 (R^1=H;R^2=OMe;R^3=OH)
a-19.9 μM
b-1.5 μM

LQB359 (R^1=H;R^2=R^3=OH)
a-12.39 μM
b-1.9 μM

LQB360 (R^1=OH;R^2=H;R^3=OH)
a-5.9 μM
b-2.4 μM

LQB361 (R^1=OH;R^2=R^3=H)
a- --
b-4.5 μM

LQB362 (R^1=H;R^2=OMe;R^3=H)
a-20.3 μM
b-4.2 μM

Figure 2. Values of EC_{50} (Replicon reporter cells: a- Huh7/Rep-Feo1b; b- Huh7.5-FGR-JC1-Rluc2Ab)

The compounds tested were more active on replicon reporter cell Huh7.5-FGR-JC1-Rluc2A and LQB360 was active on both replicon reporter cells. The compounds showed a moderate inhibition of NS5B enzyme, ranging from 25-37%, at 50μM.

Conclusions

The 5-carbapterocapens were obtained in 2 steps and good yields with the synthetic approach used. Some of these compounds showed anti-HCV, with moderate inhibitory action on H5SB enzyme, indicating that another mechanism of action must be operating. Other derivatives and the corresponding pterocarpens are under preparation, to study the activity and the possible mechanism of action.

Aknowledgements

FAPERJ, CAPES, CNPq

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