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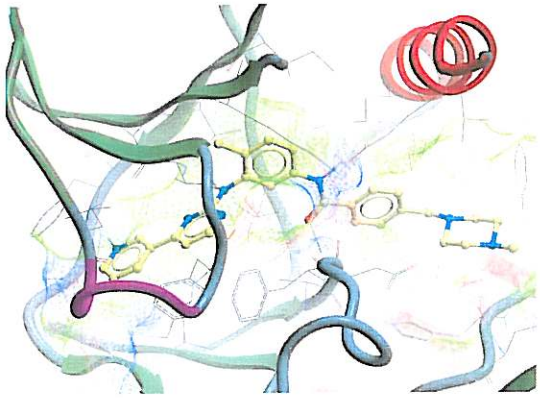
2nd National Meeting on Medicinal Chemistry

28 a 30 Novembro 2010
COIMBRA, PORTUGAL

LIVRO DE RESUMOS
ABSTRACT BOOK



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P21

ANTI-PROLIFERATIVE ACTIVITY OF THIENO[3,2-*B*]PYRIDINE DERIVATIVES IN TUMORAL AND PRIMARY HEPATIC CELL LINES

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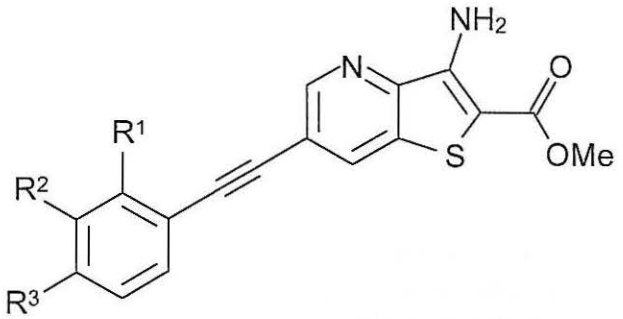
Hepatocellular carcinoma (HCC) is the fifth most frequent human cancer worldwide, with the highest frequency in countries where hepatitis B and C are endemic and food is contaminated by Aflatoxin B1. HCC incidence is on the rise in Europe and United States, due to the increased incidence of hepatitis C virus infection, cirrhosis related to type II diabetes, and non-alcoholic steatohepatitis. For these reasons there is a need for more therapies with pharmacological agents to help the improvement of the prognosis of patients with HCC. In this study ten methyl 3-amino-6-(arylethynyl)thieno[3,2-*b*]pyridine-2-carboxylates [1] were investigated for their anti-proliferative activity in the HEPG2 hepatocellular carcinoma cell line using the sulforhodamine assay. In order to investigate the liver cytotoxicity of the compounds, the same assay was applied using a primary liver cells culture prepared from fresh pig hepatocytes (liver biopsy). This assay is very important as mammalian hepatocytes still represent an obligatory step in the evaluation of toxic compounds that lead to the production of various metabolites, which are the ultimate cause of toxicity.



1 $R^1=R^2=R^3=H$
2 $R^1=NH_2$, $R^2=R^3=H$
3 $R^1=R^3=H$, $R^2=NH_2$
4 $R^1=R^2=H$, $R^3=NH_2$
5 $R^1=OMe$, $R^2=R^3=H$
6 $R^1=R^3=H$, $R^2=OMe$
7 $R^1=R^2=H$, $R^3=OMe$
8 $R^1=F$, $R^2=R^3=H$
9 $R^1=R^2=H$, $R^3=F$
10 $R^1=R^2=H$, $R^3=N(Me)_2$

Among the compounds studied, compound **3** with an amino group in the *meta* position showed the best anti-proliferative activity against HEPG2 cells (IC_{50} = 1.2 µM). Curiously, compounds **4** and **2**, with the amino group on the *para* or *ortho* position showed moderated (IC_{50} = 26 µM) and no activity (IC_{50} > 125 µM), respectively. It should be highlighted that the three compounds did not show cytotoxicity (IC_{50} > 125 µM) in the primary hepatic cell line used. This comparison shows that, not only the presence of the amino group is important, but also its relative position. This work shows that these thieno[3,2*b*]pyridine derivatives are promising new pharmacological agents against HCC, not presenting cytotoxicity in the primary liver cells.

[1]- Calhelha RC, Queiroz M-JRP *Tetrahedron Lett.* **2010**, *51*, 281-283.

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