3º Encontro Nacional de Química Terapêutica

3rd Portuguese Meeting on Medicinal Chemistry
1st Portuguese-Spanish-Brazilian Meeting on Medicinal Chemistry.

SOCIEDADE PORTUGUESA DE QUÍMICA

Synthesis, growth inhibitory activity on human tumor cell lines and evaluation of the hepatotoxicity of di(hetero)arylethers and di(hetero)arylamines in the thieno[3,2-*b*]pyridine series

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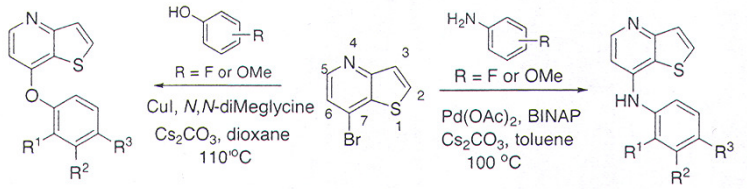
Thienopyridine skeleton has been reported as having interesting biological activity, namely antitumor[1] and antiangiogenic[2] activities.

Herein we describe the synthesis of di(hetero)arylethers **1a-f** and di(hetero)arylamines **2a-f** functionalizing the 7-position of the thieno[3,2-*b*]pyridine in good to high yields, using copper (C-O) or palladium (C-N) catalyzed couplings, like presented below.



1a R^1 = F, R^2 = R^3 = H; 69%
1b R^1 = R^3 = H; R^2 = F; 63%
1c R^1 = R^2 H; R^3 = F; 65%
1d R^1 = OMe, R^2 = R^3 = H; 45%
1e R^1 = R^3 = H; R^2 = OMe; 50%
1f R^1 = R^2 H; R^3 = OMe; 45%

2a R^1 = F, R^2 = R^3 =H; 75%
2b R^1 = R^3 = H; R^2 = F; 70%
2c R^1 = R^2 = H; R^3 = F; 73%
2d R^1 = OMe, R^2 = R^3 = H; 80%
2e R^1 = R^3 = H; R^2 =OMe ; 83%
2f R^1 = R^2 = H; R^3 = OMe; 54%

The growth inhibitory activity of the di(hetero)arylethers **1a-f** and di(hetero)arylamines **2a-f** was evaluated against five human tumor cell lines (breast- MCF-7, non-small cell lung- NCI-H460, colon- HCT15- hepatocellular- HepG2 and cervical- HeLa carcinomes), using the sulforhodamine B assay. Furthermore, the hepatotoxicity of compounds was studied using a porcine liver primary cell culture (PLP2). The most promising compounds were shown to be the methoxy derivatives **1e** and **2e**, presenting GI_{50} values comparable with ellipticine (control) without hepatotoxicity. For these compounds more studies are needed to find out their mechanisms of action.

Acknowledgments: To the Foundation for the Science and Technology (FCT–Portugal) for financial support through the NMR Portuguese network (Bruker 400 Avance III-Univ Minho). To FCT and FEDER-COMPETE/QREN/EU for financial support through the research unities PEst-C/QUI/UI686/2011 and PEst-OE/AGR/UI0690/2011, the research project PTDC/QUI-QUI/111060/2009 and the post-Doctoral grant attributed to R.C.C. (SFRH/BPD/68344/2010) also financed by POPH and FSE.

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