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CHEMISTRY ENABLING DRUG DISCOVERY

EFMC
International Symposium on Medicinal Chemistry

Lisbon, Portugal September 7-11, 2014

A Journal of

ChemPubSoc Europe

BOOK OF ABSTRACTS

WILEY-VCH

to increase the binding to the targeted protein kinases as selective allosteric inhibitors. Three different moieties (see Figure 1) were identified: 1) a **polar moiety**, responsible of forming ionic interactions with ATP; 2) a **hydrophobic moiety**, that interacts with a hydrophobic pocket of the kinases; and 3) an **articulation** X, responsible of the curvature of the ligand making the molecule fit very nicely in the allosteric site orientating the polar and hydrophobic moieties. Considering these three moieties we propose novel compounds with several structural modifications in mind (relative orientation, polar moiety, hydrophobic moiety, length of the molecule and nature of the aromatic rings) to confirm their mechanism of action as type III PKIs non-ATP competitive that bind to allosteric sites of MEK.

References:

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[3] A. Kahvedžić, S. M. Nathwani, D. Zisterer, I. Rozas, *J. Med. Chem.* **2013**, *56*, 451–459.
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R039 | New Di(hetero)arylethers and Di(hetero)arylamines in the Thieno[3,2-*b*]pyridine Series: Synthesis, Growth Inhibitory Activity on Human Tumor Cell Lines and Nontumor Cells, Effects on Cell Cycle and on Apoptosis

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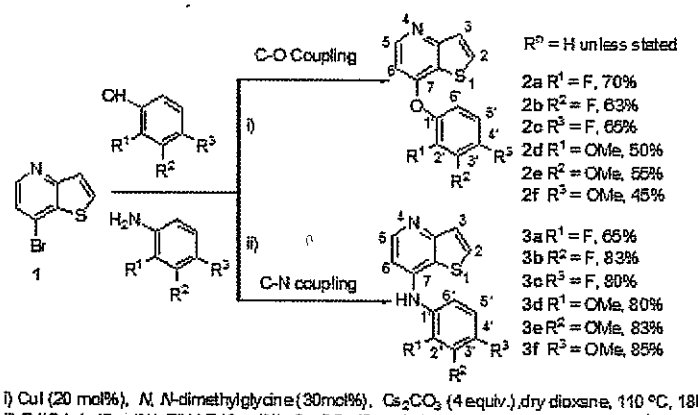
The thienopyridine skeleton has been reported as having interesting biological activities namely antitumor[1,2] and antiangiogenic.[3,4] New fluorinated and methoxylated di(hetero)arylethers and di(hetero)arylamines were prepared functionalizing the 7-position of the thieno[3,2-*b*]pyridine, using copper (C–O) or palladium (C–N) catalyzed couplings, respectively, of the 7-bromo-thieno[3,2-*b*]pyridine (**1**) with *ortho*, *meta* and *para* fluoro or methoxy phenols and anilines (see Scheme).

The compounds obtained were evaluated for their growth inhibitory activity against the human tumor cell lines MCF-7 (breast adenocarcinoma), NCI-H460 (non-small-cell lung cancer), HCT15 (colon carcinoma), HepG2 (hepatocellular carcinoma) and HeLa (cervical carcinoma). The most active compounds, a di(hetero)arylether with a methoxy group in the *meta* position relative to the ether function (**2e**) and two di(hetero)arylamines with a methoxy group either in the *ortho* or in the *meta* position relative to the NH (**3d** and **3e**, respectively), were further tested at their GI_{50} concentrations on NCI-H460 cells causing pronounced alterations in the cell-cycle profile and a strong and significant increase in the apoptosis of these cells (see Figure) after 48 h. The fluorinated and the other methoxylated compounds did not show important activity, presenting high GI_{50} values in all the cell lines tested. Furthermore, the toxicity of the compounds was assessed using porcine liver primary cells (PLP2), established by some of us. Results showed that one of the most active compounds was not toxic to the non-tumor cells at their GI_{50} concentrations showing to be the most promising to be used as antitumor agents.



i) CuI (20 mol%), *N, N*-dimethylglycine (30mol%), Cs_2CO_3 (4 equiv.), dry dioxane, 110 °C, 18h.
ii) $Pd(OAc)_2$ (6mol%), BINAP (8mol%), Cs_2CO_3 (2 equiv.), dry toluene, 100 °C, 2h.

Scheme

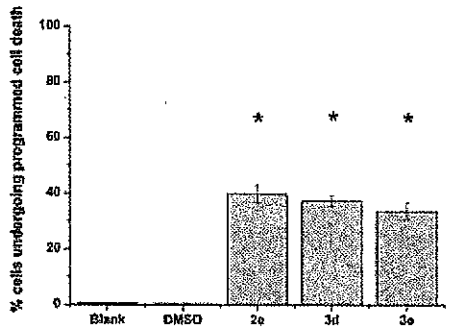


Figure. Analysis of apoptosis (48h) of NCI-H460 cells treated with medium (Blank), DMSO, or the GI_{50} concentrations of compounds 2e, 3d and 3e, * $p < 0.05$