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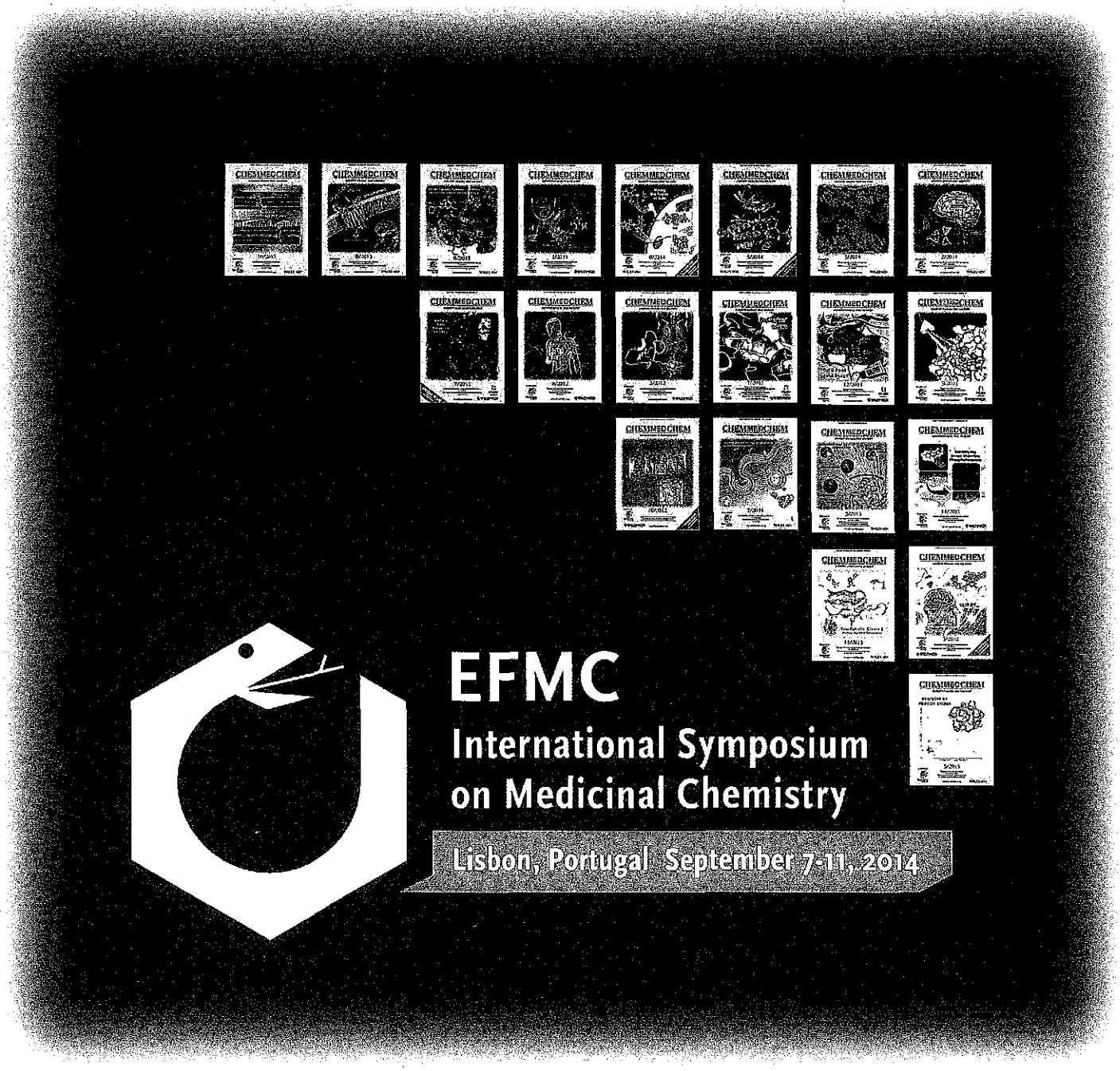

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BOOK OF ABSTRACTS

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R026 | Synthesis, Molecular Docking and Biological Evaluation of New 1-Aryl-3-[3-(thieno[3,2-*b*]pyridin-7-ylthio)phenyl]ureas as Potent Type II VEGFR-2 Tyrosine Kinase Inhibitors

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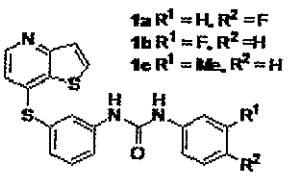
The vascular endothelial growth factor receptor 2 (VEGFR-2) is a tyrosine kinase receptor, expressed primarily in endothelial cells, and is activated by the specific binding of VEGF to the VEGFR-2 extracellular regulatory domain. Once activated, VEGFR-2 undergoes autophosphorylation, triggering signaling pathways leading to endothelial cell proliferation and subsequent angiogenesis.[1] Small molecules may act as inhibitors by competing for the ATP-binding site of the VEGFR-2 intracellular tyrosine kinase domain, thereby preventing the intracellular signaling that leads to angiogenesis.[2]

Here, we present the synthesis of new 1-aryl-3-[3-(thieno[3,2-*b*]pyridin-7-ylthio)phenyl]ureas **1a–c**, as potent type II VEGFR-2 inhibitors based on molecular docking (Figure A) and biological evaluation including enzymatic assays using the VEGFR-2 tyrosine kinase domain (IC_{50}=10–28 nM) and studies in human umbilical vein endothelial cells (HUVECs). The latter included cell viability (MTS), proliferation (BrdU) and Western blot for total and phosphorylated VEGFR-2 (Figure B).

The predicted docked poses were analyzed in detail and a plausible explanation for compounds **1** potency was obtained based on the simultaneous presence of a S-linker and the arylurea moiety in the *meta* position as a new substitution pattern for the type II VEGFR-2 inhibitors. These chemical features place the thieno[3,2-*b*]pyridine and the terminal aryl ring in close superimposition to a pyrrolo[3,2-*d*]pyrimidine derivative. The presence of hydrofobic substituents (F and Me) in the terminal aryl ring is also important. For these compounds a significant inhibition in HUVECs proliferation upon VEGF stimulation was observed at low concentrations (0.5–1.0 μM) without affecting cell viability. Western-blot analysis demonstrated that compounds **1** significantly inhibited the VEGFR-2 phosphorylation at 1.0 μM, thus confirming their anti-angiogenic potential.



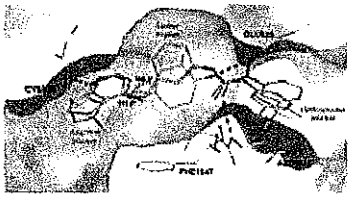


Fig. A. Docking pose superimposition at the VEGFR-2 kinase binding site for compounds **1a** and **1c** with a known type II inhibitor (pyrrolo[3,2-d]pyrimidine derivative)

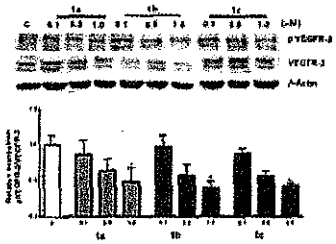


Fig. B. Western blot for total and phosphorylated VEGFR-2. *$p < 0.05$ vs control (DMSO).

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R027 | Novel Pyrimido-Oxazepinones as Potent and Selective mTOR Inhibitors

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Mammalian target of rapamycin (mTOR), a 289 kDa serine/threonine kinase of the phosphoinositide 3-kinase-like kinase family, is a central regulator of cell growth and proliferation. Mutations and dysregulation of the PI3K/mTOR pathway (amplification of RTKs, loss of