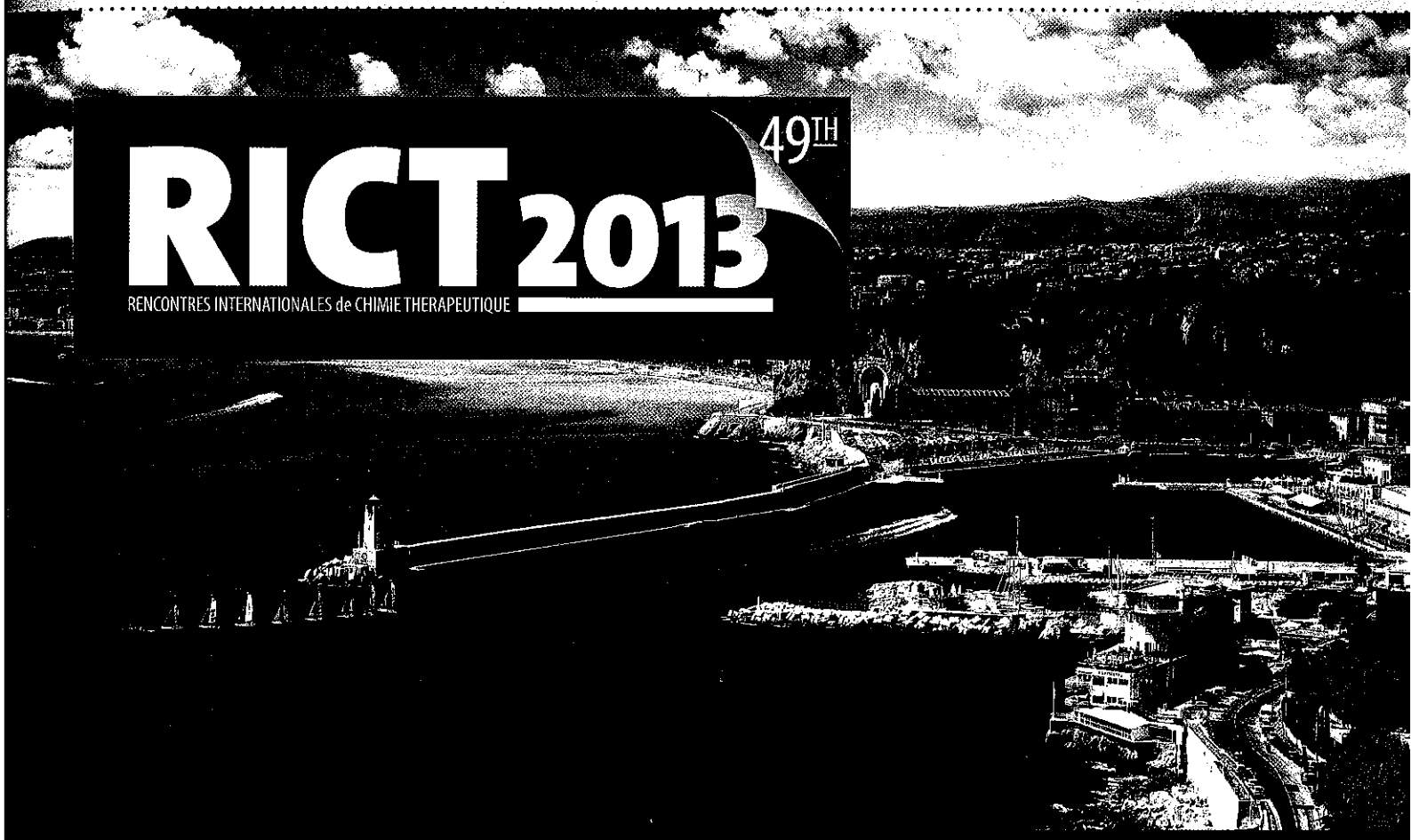
INTERNATIONAL CONFERENCE ON MEDICINAL CHEMISTRY



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49TH

RENCONTRES INTERNATIONALES de CHIMIE THERAPEUTIQUE

DRUG DISCOVERY AND SELECTION

WHEN CHEMICAL BIOLOGY MEETS DRUG DESIGN

JULY 3-5, 2013 | NICE, FRANCE

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NEW DI(HETERO)ARYLTHIOETHERS 1,3-DIARYLUREAS IN THE THIENO[3,2-b]PYRIDINE SERIES AS VEGFR2 TYROSINE KINASE INHIBITORS: DOCKING, SYNTHESIS, ENZYMATIC AND CELLULAR ASSAYS

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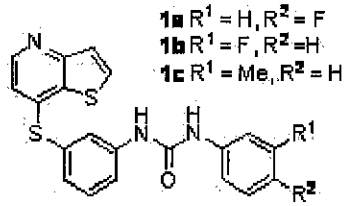
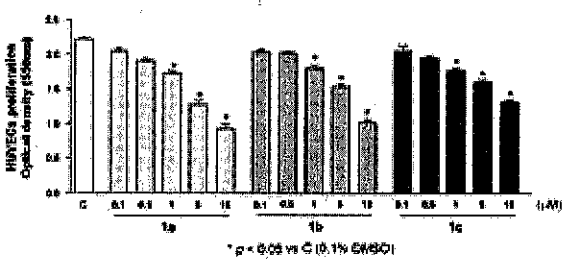
Vascular Endothelial Growth Factor Receptor 2 (VEGFR2) is a tyrosine kinase receptor, expressed primarily in endothelial cells, and is activated by the specific binding of VEGF, produced and released by the tumor, to the VEGFR2 extracellular regulatory domain, undergoing autophosphorylation, triggering signaling pathways leading to endothelial cell proliferation towards the tumor [1]. Small molecules may act as inhibitors by competing for the ATP-binding site of the VEGFR2 intracellular tyrosine kinase domain, thereby preventing the intracellular signaling that leads to angiogenesis [2]. Herein, we report the synthesis using rational design of new 1-aryl-3-[3-thieno[3,2-*b*]pyridin-7-ylthio)phenyl]ureas (**1a-c**) as VEGFR2 tyrosine kinase inhibitors. The compounds presented, with the arylurea in the *meta* position to the thioether and with F or a Me group, showed very low IC_{50} values (11-28 nM) in enzymatic assays as predicted by molecular docking.





To examine the activity of compounds **1** in endothelial cells, VEGF-stimulated (60 ng/mL) Human Umbilical Vein Endothelial Cells (HUVECs) were cultured in M199 medium in the absence (C) or presence of each compound at different concentrations. A remarkable reduction in the proliferation of HUVECs using the BrdU incorporation assay was observed for all compounds at 1 μM, for compound **1a** being observed a higher antiproliferative effect. Further studies are ongoing to examine whether these molecules affect the expression and activity of VEGFR2 and the signaling pathways, using western blotting assays. Given the established role of VEGFR2 in proliferation and migration of endothelial cells, these molecules are promising anti-angiogenic agents that can be used for therapeutic purposes in pathological conditions where angiogenesis is exacerbated, such as cancer.

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References

1) Strawn, L.M. et al. Cancer Res. 1996, 56, 3540-3545.
2) Baka, S.; Clamp, A.R.; Jayson, G.C. Expert Opin. Ther. Targets 2006, 10, 867-876.

PROGRAMME AT A GLANCE

WEDNESDAY JULY 03, 2013	
10:00	Registration
11:30	Reaxys Workshop
14:00	Introductive Remarks
	SESSION 1: Paul Ehrlich Prize-Lecture *Sponsored by Janssen-Cilag*
14:15	**L01** - M. Lazdunski
	SESSION 2: Ion Channels
15:00	**L02** - R. Owen
15:45	**L03** - H. Schirok
16:30	Coffee Break and Exhibition
	SESSION 3: Synergies between Medicinal Chemistry and Biotechnology *Sponsored by Pierre Fabre Reserach Institute*
17:30	**L04** - A. Beck
18:30	Welcome Reception

THURSDAY JULY 04, 2013		
	SESSION 4: Case Study, Immunology & Inflammation	**SESSION 5:** Fragment-based Drug Design
08:45	**L05** - L. Sanière	**L07** - C. Dalvit
09:30	**L06** - W. Haap	**L08** - J. Murray
10:15	Coffee Break, Poster Session (even numbers) and Exhibition	
	SESSION 6: Druggability	**SESSION 7:** ChemoGenomic
10:45	**L09** - P. Leeson	**L11** - S. Helliwell
11:30	**L10** - R. Law	**L12** - J. Brown
12:15	Lunch, Poster Session (even numbers) and Exhibition	
14:00 - 15:30	**CAREER SESSION**	
	SESSION 8: Molecular Networks	
14:15	**L13** - G. Superti-Furga	
	SESSION 9: Case Studies, Anti-infective Agents 1	**SESSION 10:** ChemBioTools
15:00	**L14** - K.H. Altmann	**L16** - M.Morris
15:45	**L15** - J.P. - Surivet	**L17** - D. Bonnaffé
16:30	Coffee Break and Exhibition	
	SESSION 11: Case Studies: Anti-Infective Agents *Sponsored by GlaxoSmithKline*	**SESSION 12:** GPCR
17:00	**L18** - J. Mottram	**L20** - M. Congreve
17:45	**L19** - P. Wyatt	**L21** - N. Tschammer
20:00	Symposium banquet	

FRIDAY JULY 05, 2013	
	SESSION 13: Breaking News
08:30	**L22** - C. Bouix-Peter
09:15	**L23** - I. Lewis
10:00	Coffee Break, Poster Session (odd numbers) and Exhibition
	SESSION 14: Antibody Drug Conjugates *Sponsored by Pierre Fabre Research Institute*
10:30	**L24** - R. Chari
11:15	**L25** - J. Junutula
	SESSION 15: European Lead Factory *Sponsored by ELF Chemistry SMEs: Edelris, Mercachem, Sygnature, Syncom, Taros*
12:00	**L26** - J. Hueser
12:35	Lunch *Sponsored by ELF Chemistry SMEs* Poster Session (odd numbers) and Exhibition
	SESSION 16: Case Studies, Pain & Cancer
14:05	**L27** - R. Foglesong
14:50	**L28** - E. Lingueglia
15:25	**L29** - F. Halley
16:10	Poster Prizes and Conclusive Remarks

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