SGK1 AS A NEW TARGET FOR ANTICANCER AGENTS: A HIT-TO-LEAD STUDY

F. Musumeci [1], C. Greco [1], S. Alcaro [2], F. Ortuso [2], N. Perrotti [2], S. Schenone [1]

[1]Department of Pharmacy, University of Genoa, Viale Benedetto XV 3, Genoa, Italy
[2]Department of "Scienze della Salute", University "Magna Graecia" of Catanzaro, Viale Europa, Catanzaro, Italy
francesca.musumeci@unige.it

The serum and glucocorticoid kinase (SGK) is a family of serine/threonine kinases which includes three isoforms, SGK1, SGK2 and SGK3. SGK1 recently appeared as an essential and non-redundant target in cancer therapy, being involved in the development and resistance of human tumours. Furthermore, SGK1 plays a critical role in metabolic syndrome. Nevertheless, only few SGK1 inhibitors have been reported in the literature to date [1].
In this context, we decided to virtually screen our library of pyrazolo[3,4-*d*]pyrimidines, originally synthesized to target the tyrosine kinases Src and Abl, in order to find potential SGK1 inhibitors. This *in silico* study led to the identification of a few promising compounds that have been tested on SGK1 and a small panel of kinases. Among these molecules, SI113 (**Figure 1**) shows an IC_{50} value of 600 nM on SGK1 and results quite selective for this kinase compared with AKT-1, Src and Abl [2]. SI113 possesses pro-apoptotic and anti-proliferative effects in different cancer cell lines, synergizing with radiotherapy in tumor killing [3,4]. Interestingly, SI113 inhibits tumour growth in hepatocarcinoma models *in vitro* and *in vivo*. Moreover, no side effects, e.g. weight loss, diarrhea, dermatitis, or signs of liver failure, appeared in SI113 treated mice [3].
Starting from these exciting results, we decided to start a hit-to-lead study aimed at discovering new SGK1 inhibitors endowed with a better activity than SI113 and a good pharmacokinetic profile. Here, we report an overview of the activity of the hit compound SI113 and an update on the work in progress on this new generation of derivatives **1** (**Figure 1**).

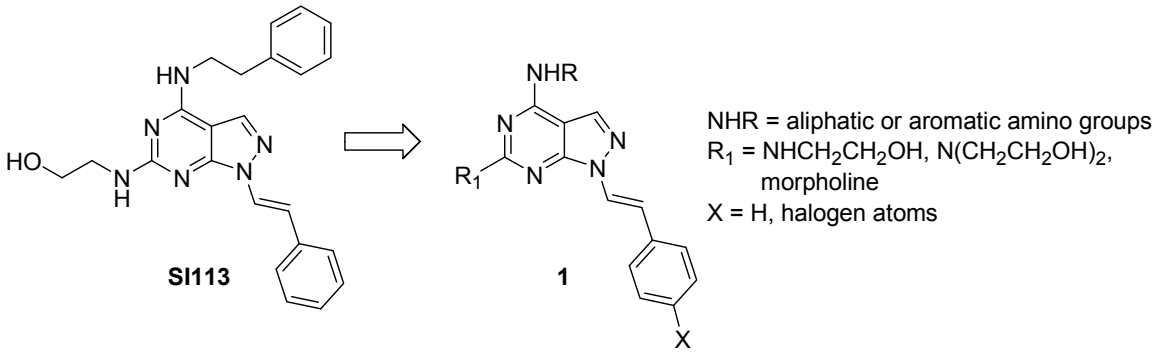

Figure 1 - Structure of the hit compound SI113 and new generation of SGK1 inhibitors 1

References:
[1] F. Lang, J. Voelkl. *Therapeutic potential of serum and glucocorticoid inducible kinase inhibition*. Expert Opin Investig Drugs, 22, 701 (2013).
[2] F. Ortuso, R. Amato, A. Artese, et al. *In silico identification and biological evaluation of novel selective serum/glucocorticoid-inducible kinase 1 inhibitors based on the pyrazolo-pyrimidine scaffold*. J Chem Inf Model 54, 1828 (2014).
[3] C. Talarico, L. D'Antona, D. Scumaci, et al. *Preclinical model in HCC: the SGK1 kinase inhibitor SI113 blocks tumor progression in vitro and in vivo and synergizes with radiotherapy*. Oncotarget, 6, 37511 (2015).
[4] C. Talarico, V. Dattilo, L. D'Antona, et al. *SI113, a SGK1 inhibitor, potentiates the effects of radiotherapy, modulates the response to oxidative stress and induces cytotoxic autophagy in human glioblastoma multiforme cells.* Oncotarget, 7, 15868 (2016).