P18

SYNTHESIS OF A NEW GENERATION OF PYRAZOLO[3,4-*d*]PYRIMIDINES AS SGK-1 INHIBITORS

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The serum- and glucocorticoid-regulated kinase 1 (SGK1) is a serine-threonine kinase which is emerging as an essential and non-redundant target in cancer therapy. SGK1 also plays critical roles in metabolic syndrome. Only few SGK1 inhibitors have been reported in the literature to date [1].
Our research group synthesized a wide library of 4-amino-substituted pyrazolo[3,4-*d*]pyrimidines active as dual Src/Abl inhibitors, two tyrosine kinases which are involved in many malignancies. Recently, we decided to virtually screen our in house library against SGK1 to evaluate the activity towards this emerging target. The most promising *in silico* compounds have been tested *in vitro* and, among these, SI113 (Figure) showed an IC_{50} value of 600 nM on SGK1 and resulted selective for this kinase compared with AKT-1, Src and Abl. Furthermore, SI113 resulted active *in vitro* as antiproliferative on different cancer cell lines and also in an *in vivo* hepatocellular carcinoma model [2]. A scale-up synthesis for SI113 was then performed with the aim to submit this interesting compound to other *in vitro* and *in vivo* assays.
Starting from the exciting results obtained with this compound, we also decided to synthesize a second generation of derivatives **2** (Figure) in order to find molecules endowed with a higher activity and a better pharmacokinetic profile. Since the N1 phenylvinyl group seems to be essential for the activity on SGK1, we decided to maintain this feature and to explore the effects of substitutions on the N1 side chain phenyl ring, and on C4 and C6 positions. All compounds will be tested on SGK1 by Prof. Perrotti of the University Magna Greacia of Catanzaro. Biological results will be reported in the poster section.

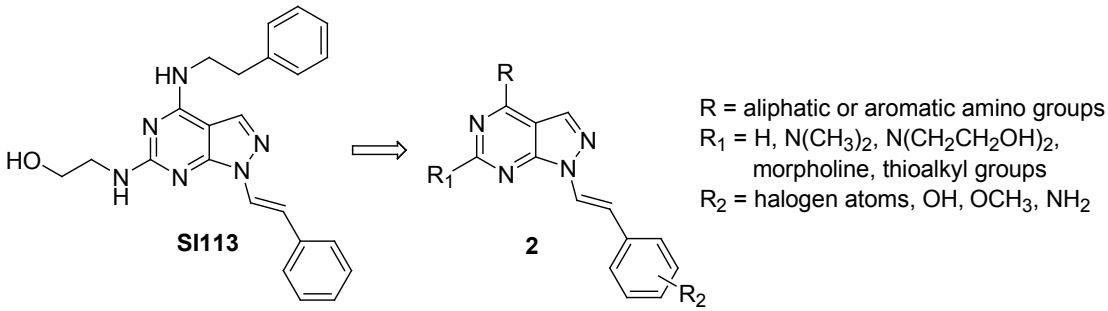

Figure. Structure of lead compound **SI113** and new generation of SGK-1 inhibitors **2**.

References:

[1] Lang, F. *et al*. *Hormons,* **2013***,* 12, 160-71.
[2] Talarico, C. *et al*. *Oncotarget*, **2015**, 6, 37511-25.