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Synthesis of a small library of potential SGK1 inihibitors

Greco C.[*] (1), Musumeci F. (1), Giacchello I. (1), Perrotti N. (2), Alcaro S. (2), Ortuso F. (2) et Schenone S. (1)

(1) Dipartimento di Farmacia, Università di Genova, Viale Benedetto XV 3, 16132 Genova, Italy
(2) Dipartimento di Scienze della Salute, Università "Magna Graecia" di Catanzaro, Viale Europa, 88100 Catanzaro, Italy

The serum- and glucocorticoid-regulated kinase 1 (SGK1) is a serine-threonine kinase which is emerging as an essential and non-redundant target in medicinal chemistry. SGK1 has demonstrated to be involved in cancer development and resistance, and in the metabolic syndrome, a pathological state mainly characterized by hypertension and obesity [1, 2]. Only few SGK1 inhibitors have been reported in the literature to date.

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 agent on different cancer cell lines and also in glioblastoma and hepatocarcinoma xenograft mouse models [3,4]. For this reason we synthesized a new generation of SI113 derivatives, with the aim to find molecules with a higher activity and a better pharmacokinetic profile. We explored the effects of substitutions on N1 phenyl ring, and on C4 and C6 positions. In particular, we inserted polar groups such as the ethanolamino and diethanolamino moieties in C6 to improve the solubility of such molecules.

Synthesis and biological results will be reported in the poster section.

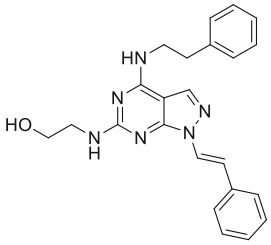

Figure: the SGK1 inhibitor SI113

[1] Bruhn, MA et al. *Growth Factors*, **2010**, 28, 394-408.
[2] Lang, F. et al. *Hormons*, **2013**, 12, 160-71.
[3] Talarico, C. et al. *Oncotarget*, **2015**, 6, 37511-25.
[4] Abbruzzese, C. et al. *Oncotarget*, **2017**, 8, 11043-55.

[*] contact : greco.phd@difar.unige.it