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Pyrazolo[3,4-*d*]pyrimidines as tyrosine kinase inhibitors: synthesis and biological evaluation

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Tyrosine kinases (TKs) are a large class of enzymes which play a key role in many phases of cell life, such as differentiation, adhesion and survival. These proteins are overexpressed and/or hyperactivated in a variety of tumor cells and their inhibition has been widely recognized as a successfully strategy in cancer therapy. So far, more then twenty TK inhibitors have been approved for clinical use. Most of them are small molecule ATP competitive inhibitors endowed with a heterocyclic scaffold [1]. In particular, the pyrazolo[3,4-*d*]pyrimidine nucleus, an isostere of adenine, has gained importance in the search for TK inhibitors, as confirmed by the recent approval of Btk TK inhibitor ibrutinib for the treatment of mantle cell lymphoma [2].

In this context, our research group synthesized a wide library of 4-amino-substituted pyrazolo[3,4-*d*]pyrimidines active as ATP-competitive inhibitors of Bcr-Abl and/or Src, two cytoplasmic TKs involved in solid and haematological cancers. These kinases show high structural homology, but the introduction of a different substitution pattern on the scaffold allowed us to obtain either selective inhibitors or dual inhibitors. Both selective and dual (or multitargeted) inhibitors are important in drug discovery, since the former can reduce the risk of side effects, and the latter can be more effective in multifactorial pathologies such as cancer. Interestingly, several in-house compounds resulted active in *in vivo* tumor models [3,4].

Starting from this solid background, we decided to synthesize a new generation of derivatives in order to discover potent selective or multikinase inhibitors. To achieve this goal, we differently decorated the N1 and C6 positions of the pyrazolo[3,4-*d*]pyrimidine scaffold, and introduced an anilino derivative in C4, since the presence of this substituent was often related to a good activity profile in previous generation compounds. The molecules are currently being tested on a panel of kinases, i.e. Bcr-Abl, Src and Fyn (another cytoplasmic TK belonging to the same family of Src). Interestingly, we have already identified a selective Fyn inhibitor, which possesses an ID_{50} value of 384 nM in an enzymatic assay. Synthesis and available biological data will be reported in the poster section.

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[4] Vignaroli G. et al. *J. Med. Chem.* **2017**, *60*, 6305-6320.

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