Exploring SAR of a new generation of pyrazolo[3,4-*d*]pyrimidines as Fyn tyrosine kinase inhibitors

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Fyn is a cytoplasmic tyrosine kinase (TK) which belongs to Src-family kinases (SFKs). These enzymes play a key role in many phases of cell life, such as differentiation, adhesion and survival. Fyn, analogously to other SFK members, is overexpressed in a number of solid and hematologic malignancies. Furthermore, several studies showed the involvement of Fyn in different central nervous system pathologies, such as Alzheimer's and Parkinson's diseases.[1]

Our group recently performed an interdisciplinary work which, combining molecular modelling studies, synthesis and biological assays, led to the identification of two members of the in-house library of pyrazolo[3,4-*d*]pyrimidines as potent Fyn inhibitors. These compounds possess K_i values of 70 and 95 nM on Fyn, show antiproliferative activity on different cancer cell lines and are active in an *in vitro* Alzheimer's model.[2]

On the basis of these interesting results, we decided to synthesize a new generation of compounds in order to extend structure-activity relationship (SAR) evaluation on this family of inhibitors. In particular, we introduced different decorations on C3 and C6 of the heterocyclic scaffold, while we maintained in N1 and C4 the features giving the best results in the first series of derivatives. Enzymatic assays are still in progress and on the basis of these results we will orient future biological assays and synthesis.

[1] Schenone S, Brullo C, Musumeci F, Biava M, Falchi F, Botta M. *Curr. Med. Chem.* **2011**; 18:2921-42.
[2] Tintori C, La Sala G, Vignaroli G, Botta L, Fallacara AL, Falchi F, Radi M, Zamperini C, Dreassi E, Dello Iacono L, Orioli D, Biamonti G, Garbelli M, Lossani A, Gasparrini F, Tuccinardi T, Laurenzana I, Angelucci A, Maga G, Schenone S, Brullo C, Musumeci F, Desogus A, Crespan E, Botta M. *J. Med. Chem.* **2015**; 58:4590-09.