Elenco B, (8)

Synthesis of new pyrazolo[3,4-*d*]pyrimidines 6-alkyl substituted Bcr-Abl tyrosine kinase inhibitors

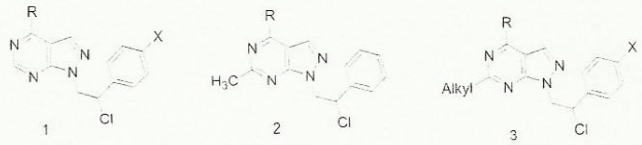
F. Musumeci[a] , S. Schenone[a], C. Brullo[a], O. Bruno[a], M. Botta[b]

[a] *Dipartimento di Scienze Farmaceutiche, Università di Genova, V.le Benedetto XV 3, Genoa, Italy*
[b] *Dipartimento Farmaco Chimico Tecnologico, Università di Siena, Via A. Moro, Siena, Italy*

francesca.musumeci@unige.it

Chronic myelogenous leukemia (CML) is a disease characterized by the presence of the Philadelphia chromosome, which results from a reciprocal translocation between chromosomes 9 and 22. This translocation fuses the breakpoint cluster region (Bcr) and the Abl genes, forming the Bcr-Abl oncogene, that encodes a constitutively active cytoplasmatic tyrosine kinase (TK) Bcr-Abl, present in > 90% of CML. The finding that Bcr-Abl is the cause of the leukemic phenotype and that the tyrosine kinase activity of Abl is fundamental for Bcr-Abl-mediated transformation, made this kinase an important target for the development of specific therapies. Imatinib mesylate, approved by FDA in 2001, became within a few years of its discovery the first line therapy generally well tolerated for the treatment of CML; nevertheless primary refractoriness and acquired resistance to this drug are observed frequently in patients in the accelerated phase or blast crisis. For these reasons overcoming resistance to Imatinib remains a major challenge for successful treatment of CML particularly in the advanced phases.

In this context we previously synthesized a new series of pyrazolo[3,4-*d*]pyrimidines 4-amino-substituted **1** and **2**, derived from our family of dual Src Abl TK inhibitors[1,2,3]. In derivatives **1** we inserted in the N1 side chain an alogen atom, whereas in compounds **2** we introduced in position 6 of the pyrazolo-pyrimidine nucleus a methyl group. Some of the new molecules showed to be potent Abl inhibitors in enzymatic cell free assays, with IC_{50} values in the low nanomolar range. In order to obtain more potent derivatives and to extend SAR, we synthesized compound **3**, bearing C6 alkyl groups and an alogen atom on the para position of the N1 phenyl ring. In position 4, compound **3** presented the same amino substituents resulted more active in the previous derivatives **1** and **2**.



R = Amines
X = H, F, Cl

X = F, Cl

Synthesis, some biological results and SAR consideration will be reported in the poster session.

[1] Manetti, F.; Locatelli, G.A.; Maga, G.; Schenone, S.; et al. *J. Med. Chem.* **2006**, *49*, 3278-3286.
[2] Carraro, F.; Naldini, A.; Pucci, A.; Locatelli, G.A.; Maga, G.; Schenone, S.; et al. *J. Med. Chem.* **2006**, 49, 1549-1561.
[3] Falchi, F.; Manetti, F.; Carraro, F.; Naldini, A.; Maga, G.; Crespan, E.; Schenone, S.; Botta, M.; et al. *ChemMedChem.* **2009**, *4*, 976-987.