Synthesis of pyrazolo[3,4-d]pyrimidine derivatives active in a preclinical glioblastoma model

Francesca Musumeci,[a] Monica Sanna,[a*] Andrea Desogus,[a] Chiara Brullo,[a] Cristina Tintori,[b] Maurizio Botta,[b] Paola Indovina,[c] Antonio Giordano,[c] and Silvia Schenone[a]

[a]*Dipartimento di Farmacia, Università degli Studi di Genova*
Viale Benedetto XV, 3, 16132 Genova, Italy
[b]*Dipartimento di Biotecnologie, Chimica e Farmacia, Università degli Studi di Siena*
Via Aldo Moro 2, 53100 Siena, Italy
[c]*Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, College of Science and Technology, Temple University, Philadelphia, Pennsylvania*

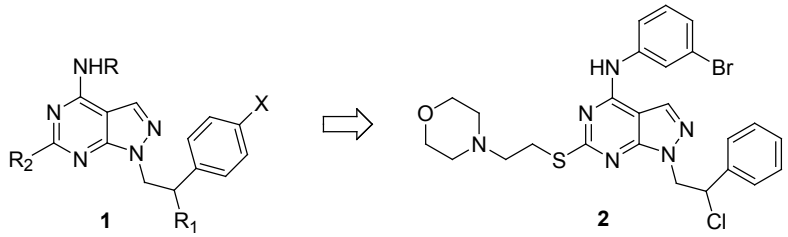
**sanna@difar.unige.it*

Glioblastoma (GB) is the most common and aggressive primary tumor of the central nervous system. The current standard of care for GB consists of surgical resection, followed by radiotherapy combined with temozolomide chemotherapy. Recent studies showed that Src family kinases (SFKs) could represent promising molecular targets for GB therapy.[1]

In this context, our group synthesized a library of pyrazolo[3,4-*d*]pyrimidines **1** (in the **Figure**) active as SFK inhibitors endowed with antiproliferative and proapoptotic properties on several tumor cell lines.[2,3]

We decided to investigate if some compounds of our library are also active on GB cell lines. Furthermore, we synthesized new selective Src inhibitors, with the aim of obtaining more potent agents toward GB. This work led to the identification of compound **2** (in the **Figure**), which shows a K_i of 40 nM on Src and good ADME properties. In cell assays, **2** has a significant antiproliferative activity both against U87 GB and multidrug resistant (MDR) U87-TxR cell lines. An enhanced apoptosis has been also observed. On the basis of these promising results, compound **2** was selected as a candidate for *in vivo* preclinical studies. Very interestingly, after 60 days of treatment with 50 mg/kg of **2**, a 50% reduction was observed in U87 cell xenograft tumors in mice. A 80% reduction was observed when the treatment was combined with radiotherapy. Moreover, mice did not shown any sign of distress or weight loss.

All together this data suggest compound **2** as a promising lead for GB therapy.



R = aliphatic or aromatic amino groups
R_1 = H, CH_3, Cl
R_2 = H, alkyl and thioalkyl groups
X = H, F, Cl, Br

Figure. General structure of our library of pyrazolo[3,4-*d*]pyrimidines **1** and structure of compound **2**, the lead candidate for GB therapy.

References

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