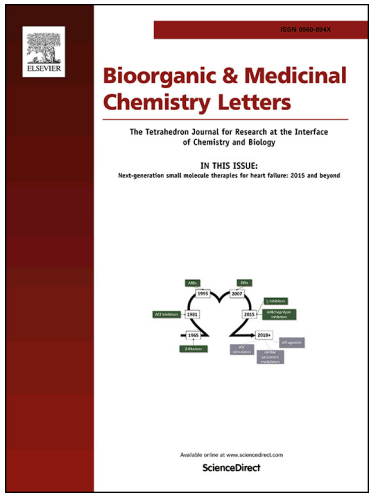
Accepted Manuscript



Efficient optimization of pyrazolo[3,4-*d*]pyrimidines derivatives as c-Src kinase inhibitors in neuroblastoma treatment

Alessio Molinari, Anna Lucia Fallacara, Salvatore Di Maria, Claudio Zamperini, Federica Poggialini, Francesca Musumeci, Silvia Schenone, Adriano Angelucci, Alessandro Colapietro, Emmanuele Crespan, Miroslava Kissova, Giovanni Maga, Maurizio Botta

PII: S0960-894X(18)30755-8
DOI: https://doi.org/10.1016/j.bmcl.2018.09.024
Reference: BMCL 26045

To appear in: *Bioorganic & Medicinal Chemistry Letters*

Received Date: 19 July 2018
Revised Date: 13 September 2018
Accepted Date: 17 September 2018

Please cite this article as: Molinari, A., Fallacara, A.L., Maria, S.D., Zamperini, C., Poggialini, F., Musumeci, F., Schenone, S., Angelucci, A., Colapietro, A., Crespan, E., Kissova, M., Maga, G., Botta, M., Efficient optimization of pyrazolo[3,4-*d*]pyrimidines derivatives as c-Src kinase inhibitors in neuroblastoma treatment, *Bioorganic & Medicinal Chemistry Letters* (2018), doi: https://doi.org/10.1016/j.bmcl.2018.09.024

Bioorganic & Medicinal Chemistry Letters
journal homepage: www.elsevier.com

Efficient optimization of pyrazolo[3,4-*d*]pyrimidines derivatives as c-Src kinase inhibitors in neuroblastoma treatment

Alessio Molinari [a], Anna Lucia Fallacara [a], Salvatore Di Maria [a], Claudio Zamperini [a], Federica Poggialini [a], Francesca Musumeci [b], Silvia Schenone [b], Adriano Angelucci [c], Alessandro Colapietro [c], Emmanuele Crespan [d], Miroslava Kissova [d], Giovanni Maga [d], Maurizio Botta [a,e,f,*].

[a] Dipartimento Biotecnologie, Chimica e Farmacia, Università degli Studi di Siena, Via Aldo Moro 2, 53100 Siena, Italy.
[b] Dipartimento di Farmacia, Università degli Studi di Genova, Viale Benedetto XV 3, Genoa 16132, Italy.
[c] Dipartimento di Scienze Cliniche Applicate e Biotecnologiche, Università dell'Aquila, Via Vetoio, 67100 Coppito, L'Aquila, Italy.
[d] Istituto di Genetica Molecolare, IGM-CNR, Via Abbiategrasso 207, 27100 Pavia, Italy.
[e] Sbarro Institute for Cancer Research and Molecular Medicine, Center for Biotechnology, College of Science and Technology Temple University, BioLife Science Building, Suite 333, 1900 North 12th Street, Philadelphia, PA 19122, United States.
[f] Lead Discovery Siena S.r.l., Via Vittorio Alfieri 31, 53019, Castelnuovo Berardenga, Siena, Italy

ARTICLE INFO

Article history:
Received
Revised
Accepted
Available online

Keywords:
Neuroblastoma
c-Src
pyrazolo[3,4-*d*]pyrimidine

ABSTRACT

The proto-oncogene c-Src is a non-receptor tyrosine kinase which is involved in the regulation of many cellular processes, such as differentiation, adhesion and survival. c-Src hyperactivation has been detected in many tumors, including neuroblastoma (NB), one of the major causes of death from neoplasia in infancy. We already reported a large family of pyrazolo[3,4-*d*]pyrimidines active as c-Src inhibitors. Interestingly, some of these derivatives resulted also active on SH-SY5Y NB cell line. Herein, starting from our previous Free Energy Perturbation/Monte Carlo calculations, we report an optimization study which led to the identification of a new series of derivatives endowed with nanomolar K_i values against c-Src, interesting antiproliferative activity on SH-SY5Y cells and a suitable ADME profile.

The interest in protein kinases has increased in the last two decades with the entry into the market of the first protein kinase inhibitor in 2001. Many studies identified protein tyrosine kinases (TKs) as attractive targets for therapeutic strategies, highlighting the role of different TKs, including c-Src,[1] in cancer. This non-receptor TK belongs to the Src Family Kinase and has been widely reported to be endowed with a strong proto-oncogenic activity.[2] The over-expression or aberrant activation of c-Src was detected in a large variety of human cancers such as breast,[3] prostate,[4] hepatic cancer[5] and neuroblastoma (NB).[6] Furthermore, c-Src was found to stimulate cell proliferation, migration, invasion as well as angiogenesis.[7] A wide number of compounds demonstrating to be active against c-Src were identified as potential therapeutic options in NB treatment.[8] Dasatinib (Figure 1), a potent dual c-Src/Abl inhibitor, is currently being evaluate in Phase II clinical trials for high-risk NB.[9] NB is a rare tumor affecting the sympathetic nervous system. It is the most common extracranial solid tumor in childhood and is one of the major causes of death from neoplasia in infancy.[10] It may occur anywhere along the sympathetic ganglia. Most primary tumors (65%) occur within the abdomen, with at least half of these arising in the adrenal medulla. Even if the treatment of early stage NB patients has shown favorable outcomes, and a substantial improvement in the treatment of certain subsets of patients has been observed, the long-term survival is still less than 40%.[11] Treatment options for this disease include surgery, chemotherapy and radiotherapy.[12] However, severe side effects and poor prognosis characterize the current treatment strategies, that are still far from satisfactory, highlighting the real need of novel therapeutic approaches.

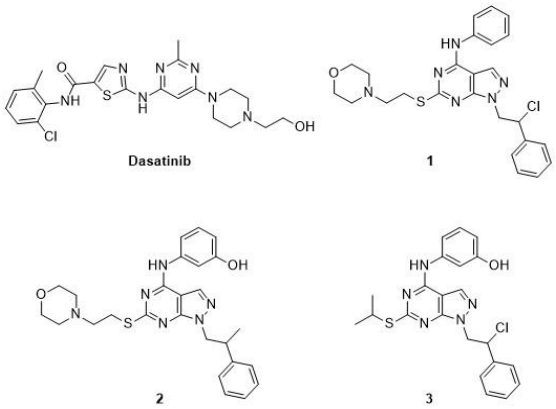


Figure 1. Molecular structures of dasatinib, compounds **1**, **2** and **3**.