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Synthesis of 2-arylmethylthio-4-benzyl-5-methylimidazoles as Anti-metastatic Drug Candidates Through the Inhibition of STAT3-SH2 Pathway

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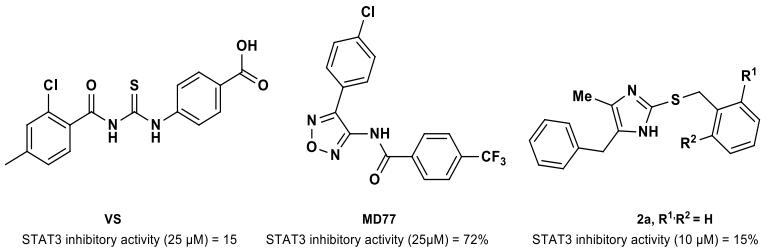
Abstract

The intrinsic inflammatory signal transducers and activators of transcriptions (STATs) are latent cytoplasmic transcription factors that can be activated in response to signals by extracellular ligands such as cytokines, growth factors, and hormones. STAT3 is well-established as a critical molecular abnormality in the biological processes leading to cancer development. Based on the structure-based pharmacophore model constructed by poli et al [1], we synthesized 2-arylmethylthio-4-benzyl-5-methylimidazoles and screened them for their anticancer activity. Among the synthesized compounds, 2a and 2d showed the highest activity in suppressing cancer cells and inducing apoptosis. Also, 2a and 2d exhibited marked inhibition of STAT3 transcriptional activity than the reference compounds VS1 and Md77 with an inhibitory activity up to 89 and 82% respectively at 10 µM. We further confirmed that the phosphorylation of STAT3 which was inhibited by 2a and 2d treatment. In vitro, wound-healing and transwell-invasion assays revealed that the newly synthesized compounds 2a and 2d have strong suppressive ability on the migration and invasion of 4T1 breast cancer cells. Modeling studies strongly explain the high potency of 2a and 2d toward the STAT3-SH2 domain. Notably, the binding mode of 2a is comparable to that of phosphorylated Tyr705, since it involves the same pocket in which pTyr705 is inserted when the two STAT3 subunits are assembled in the dimer. These astonishing results clearly indicate that 2a and 2d may serve as promising lead compounds as anti-metastatic STAT3-SH2 inhibitors.

Key words

Imidazole, anticancer, STAT3-inhibitor, antimetastatic, pTyr705, docking



Recent Publications

1. Poli, G., Gelain, A., Porta, F., Asai, A., Martinelli, A., and Tuccinardi, T., Identification of a new STAT3 dimerization inhibitor through a pharmacophore-based

virtual screening approach. J. Enz. Inhib. Med. Chem., 3: 1011–1017, (2016).

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Biography: Botros Y. Beshay is a young researcher who is currently an lecturer of Medicinal Chemistry, college of pharmacy, AAST. He has started his academic career as an Organic Chemistry demonstrator at Faculty of Pharmacy, Sinai University since 2009.He has obtained his Master degree in Pharmaceutical Chemistry in May 2016, from the Faculty of Pharmacy, Suez Canal University, Egypt. He is currently a PhD candidate at faculty of Pharmacy, Alexandria University since September 2016.He graduated at Jun. 2008 from Faculty of Pharmacy, Asyut University with a general grade “excellent with honor and ranked 19th”He is interested in Drug design and discovery fields where he has Designed novel ligands with promising biological activity as anticancer, antibacterial, antifungal and anti HIV agents using different molecular modelling techniques. He has a good experience on handling with different drug design software such as Discovery Studio, SYBYL, MOE, GOLD, PYMOL and Autodock