JACOBS PUBLISHERS

OPEN ACCESS

Jacobs Journal of Drug Metabolism and Toxicology

Editorial

Pyrimidine Derivative Compounds as HSP90 Inhibitors in Cancer Treatment

Yusuf TUTAR[1*]

[1]*Cumhuriyet University, Faculty of Pharmacy, Department of Basic Sciences, Biochemistry Division, 58140 Sivas-TURKEY*

**Corresponding author: Dr. Yusuf TUTAR, Cumhuriyet University, Faculty of Pharmacy, Department of Basic Sciences, Biochemistry Division, 58140 Sivas-TURKEY. Tel: +90 346 219 10 10 / 3907 – GSM: +90 506 458 0271. Email: ytutar@cumhuriyet.edu.tr*

Received: 05-01-2015

Accepted: 05-04-2015

Published: 05-05-2015

Pyrimidine scaffold is an important member of bioactive heterocyclic compounds which are also used in the treatment of cancer, infection diseases, diabetes, gastrointestinal diseases, and cardiovascular diseases. Therefore, pyrimidine ring has been significant structure for synthetic organic chemists and drug designers for many years. Pyrimidine derivatives interact with a large number of intracellular targets in human [1,2]. Especially, pyrimidine derivative compounds inhibit Heat Shock Protein 90 (Hsp90) chaperone activity, and interrupt proliferation in cancer cell [2].

Hsp90 is a 90 kDa ATP-dependent chaperone protein and is abundantly expressed in normal eukaryotic cells, however; Hsp90 expression in cancer cells is particularly higher than that of normal cells. Hsp90 is responsible for conformational stability, activation, maturation, and proper folding of the oncogenic client proteins for survival of cancer cells. Therefore, inhibition of Hsp90 was proposed as a cancer drug target at the beginning of the 1990s. Hsp90 N terminal domain (NTD) contains ATP binding site and chaperone activity of Hsp90 depends on ATP hydrolyses energy. Therefore, NTD is also a binding site for many known inhibitors. Pyrimidine derivatives interact with NTD, thus they inhibit binding and hydrolyzes of ATP. BIIB021 (CNF2024), PU-H71, and Debio 0932 are synthetic pyrimidine ring containing new generation Hsp90 inhibitors and their anticancer activities are currently evaluated in clinical trials [3-5]. In our lab, we design and synthesize pyrimidine analogs to develop novel Hsp90 inhibitors in cancer treatment. In order to determine their anticancer potential, we perform cell culture studies with human cancer cell lines. Thermodynamic values of the interaction between the compounds and Hsp90 are determined by molecular docking studies. Furthermore, we perform luciferase refolding and ATPase inhibition assays to determine inhibition degree of Hsp90 chaperone activities. Pyrimidine derivatives are potential candidate for the development of Hsp90 inhibitors in the cancer treatment and they are underway to develop target specific anticancer agents.

References

1. Longley DB, Harkin DP, Johnston PG. 5-fluorouracil: mechanisms of action and clinical strategies. Nat Rev Cancer. 2003, 3(5): 330-338.

2. Torres RJ, Peters GJ, Puig JG. Novel developments in metabolic disorders of purine and pyrimidine metabolism and therapeutic applications of their analogs. Nucleosides Nucleotides Nucleic Acids. 2014, 33(4-6): 165-173.

3. Tutar L, Tutar Y. Heat shock proteins; an overview. Curr Pharm Biotechnol. 2010, 11(2): 216-222.

4. Ozgur A, Tutar Y. Heat shock protein 90 inhibitors in oncology. Curr Proteomics. 2014, 11: 2-16.

5. Koca İ, Gümüş M, Özgür A, Dişli A, Tutar Y. A novel approach to inhibit heat shock response as anticancer strategy by coumarine compounds containing thiazole skeleton. Anticancer Agents Med Chem. 2015, In Press.