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Synthesis and evaluation of anticancer activity of 1-(3-chloro phenyl)-2-piperazinone derivatives as potential farnesyltransferase enzyme inhibitors

S. Ghasemi[1,*], J. Shahbazi[1], S. Sharifi[2], S. Davaran[1], D. Asgari[1]

[1]Department of Medicinal Chemistry, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran
[2]Research Center for Pharmaceutical Nanotechnology, Faculty of Pharmacy, Tabriz University of Medical Sciences, Tabriz, Iran.

Background and Aims: Regulation of cell growth is done by switching between the inactive and the active state of membrane-bound GTP binding proteins (G-proteins). Mutation of the GTP-binding protein Ras that has a key role in cell signaling pathways, can lead to uncontrolled proliferation. 30% of all human cancers are because of mutation of human ras proteins. A CAAX tetrapeptide motif exist at their C-terminal of these G-proteins (C: Cys, A: an aliphatic amino acid, X: Ser, Met, Gln, Ala typically Met). Ras proteins need to suffer a series of modification for their biological functions that they require to be alkylated from cystein amino acid of CAAX. Farnesyltransferase (FTase) as a zinc-containing metalloenzyme identify the CAAX tetrapeptide sequence and add the 15 carbon isoprenoid called farnesyl group from farnesyldiphosphate (FPP) to the thiol of cysteine. The farnesylation is an important step for the biological activity of Ras proteins and is a valuable target for chemotherapy. Peptidomimetics are a class of FTase inhibitors which have a thiol moiety that intract with the FTase zinc atom. Substitution of thiol group by another zinc binding moiety such as an imidazole or other aryl groups made non-thiol, non-peptidic, imidazole or non-imidazole containing inhibitors. More than a decade later, Researchers reported many groups of imidazole containing FTase inhibitors and some of potent ones including L778123, tipifarnib, lonafarnib were tested in clinical trials. Nitrogene in imidazole group in the L778123 structure chelates zinc group. If imidazole group was substituted by small groups, it may show better FTase inhibitor activity and anticancer activity because of more efficient interaction with zinc ion. In this study we report design and synthesis novel anticancer agents using L778123 as a template by substitution of imidazole ring with their bioisoesters and investigation of these compounds on colorectal cell line.

Keywords: Farnesyltransferase; Anticancer; Imidazole containing inhibitors