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Novel benzothiazin-piperazin derivatives by peptide-coupling as potential anti-proliferative agents

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ABSTRACT

In an attempt to develop potential and selective anti-proliferative agents, a series of novel benzothiazin-piperazin derivatives **8a-i** and **10a-g** were synthesized by coupling of 2H-1,4-benzothiazin-3(4H)-one with various amines **7a-i** and **9a-g** in excellent yields and evaluated for their *in vitro* anti-proliferative activity against four cancer cell lines, HeLa (cervical), MIAPACA (pancreatic), MDA-MB-231 (breast) and IMR32 (neuroblastoma). *In vitro* inhibitory activity indicated that compounds **8a**, **8d**, **8g**, **10a**, **10b**, **10e**, **10f** were found to be good anti-proliferative agents. Among them the derivatives **8g, 10e** and **10f** were found to be the most active members exhibiting remarkable growth inhibitory activity. Molecular docking was undertaken to investigate the probable binding mode and key active site interactions in HDAC8 and EHMT2 proteins. The docking results are complementary to the experimental results.

Nitrogen-containing heterocycles have always played a major role in the pharmaceutical and agrochemical industries because of their potent physiological properties which have resulted in numerous applications.[1] Benzothiazine derivatives are an important class of natural products possessing a wide range of biological and pharmaceutical activity due to presence of nitrogen and sulphur axis, which is considered to be responsible as one of the structural features to impart their activities.[2, 3] They are widely found in bioorganic and medicinal chemistry with application in drug discovery. Benzothiazole moieties are part of compounds showing numerous biological activities such as antimicrobial,[4-6] anticancer,[7-9] anthelmintic,[10] anti-diabetic[11], antihypertensive[12] and an allosteric muscarine M_1 receptor[13]. They have also found application in industry such as anti-oxidants, vulcanizations accelerators. Various benzothiazoles such as 2-aryl benzothiazole received much attention due to unique structure, and its use as radioactive amyloid imaging agents[14] and anticancer agents.[15] It must be emphasized that combination of benzothiazoles with other heterocyclic is a well known approach to design new drug like molecules, which allows achieving new pharmacological profile, activity and toxicity lowering.

The Piperazines are a broad class of chemical compounds with many important pharmacological properties. This dinitrogen moiety has been an inseparable component of plethora of drugs. Piperazines have the chemical similarity with piperidine, a constituent of piperazine in the black piper plant (*Piper nigrum*). Piperazine was introduced into the medicine as a solvent for uric acid. [16,17] Keeping in view the potential biological activities of benzothiazines and piperazines, it was perceived that if both the heterocyclic moieties are synergized in a single nucleus, the new compounds obtained were likely to possess significant biological activities. Recently, in an on-going program to discover and develop potent new anti-proliferative agents, we have identified several classes of molecules as novel tumor growth inhibitors.[18-22] In an attempt to design new anticancer agents, we discovered novel benzothiazin-piperazin derivatives **8a-i** and **10a-g** to elicit combined antitumor efficacy/cytotoxicity against different cancer cell lines *in vitro*.

Further, we have performed literature search for investigation of enzymatic inhibition of benzothiazinone derivatives for the cancer treatment. Histone-lysine N-methyltransferase 2 (EHMT2, G9a) is a histone modifying enzyme that specifically mono- and dimethylates 'Lys-9' of histone H3 (H3K9me1 and H3K9me2, respectively) in euchromatin.[23] EHMT2 is over expressed in breast, prostate, colon, bladder, ovarian, melanoma, lung, and liver cancers.[24] Methylation of histones play a vital role in epigenetic modification of chromatin that determines gene expression, genomic stability, stem cell maturation, cell lineage development, genetic imprinting, DNA methylation, and cell mitosis.[25] Hence, the dysregulation of EHMT2 plays an important role in the growth regulation of cancer cells and it is considered a promising therapeutic target for various types of cancer.[26] The PUBCHEM assays against EHTM2 inhibition have been reported for several ChEBML compounds (eg. 1574417, 1548773, 589694, 1585706, 1459005, 1460888, 1541342, 1330971, 1481724 and 1539403) having benzothiazinone moiety.[27]