Synthesis, anticancer activity and effects on cell cycle profile and apoptosis of novel thieno[2,3-d]pyrimidine and thieno[3,2-e] triazolo[4,3-c]pyrimidine derivatives.

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Abstract

Motivated by the widely reported anticancer activity of thieno[2,3-d]pyrimidines a series of 24 new 2-substitutedhexahydrocycloocta[4,5] thieno[2,3-d]pyrimidines with different substituents at C-4 position and hexahydrocycloocta[4,5]thieno[3,2-e]-1,2,4-triazolo[4,3-c]pyrimidines were synthesized. The anticancer activity of 17 compounds were evaluated by National Cancer Institute (USA) using a two stage process utilizing 59 different human tumor cell lines representing leukemia, melanoma, cancers of lung, colon, central nervous system (CNS), ovary, kidney, prostate as well as breast. Compound 9c showed broad spectrum potent anticancer activity in nano molar to micro molar range against 56 human tumor cell lines with GI50 less than 10 εM ranging from 0.495 to 5.57 εM, also it is worth mentioning that compound 9c had the marked highest selectivity against the two cell lines T-47D and MDA-MB-468 belonging to breast cancer with GI50 = 0.495 and 0.568 εM respectively, and its effect was further studied on cell cycle progression and induction of apoptosis in the MDA-MB-468 cell line. Results showed that compound 9c induced cell cycle arrest at G2/M phase and also, showed accumulation of cells in pre-G1 phase which may result from, degradation or fragmentation of the genetic materials indicating a possible role of apoptosis in compound 9c-induced cancer cell death and cytotoxicity and verifying this compound as promising selective anticancer lead. Compound 6c was selective against K-562, SR and MOLT-4 cell lines belonging to leukemia showing growth inhibition percentages 86.38, 65.76 and 60.40 at a single dose test, at the same time it showed lethal activity against HOP-92 representing non-small cell lung cancer. Interestingly, leukemia SR, CNS cancer SNB-75 and renal cancer UO-31 cell lines proved to be sensitive to compound 6d with growth inhibition percentages 52.86, 50.94 and 53.99 respectively. Additionally, compound 6d demonstrated lethal activity to HOP-92 belonging non-small cell lung cancer.

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