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باللغة الانجليزية: (٧)

Novel antiproliferative agents bearing substituted thieno[2,3-*d*]pyrimidine scaffold as dual VEGFR-2 and BRAF kinases inhibitors and apoptosis inducers; design, synthesis and molecular docking

A series of novel thieno[2,3-*d*]pyrimidine derivatives was designed and synthesized based on multitarget directed drug design strategy. All the newly synthesized compounds were evaluated for their antiproliferative activity in the National Cancer Institute (NCI) against a panel of 60 tumor cell lines. Compounds **4a** and **4b** showed a significant antiproliferative activity at 10 µM dose, and were accordingly evaluated at five dose concentrations. They showed potent and broad-spectrum antiproliferative activity, with GI_{50} values in the micromolar range of 1.44–6.93 µM and 1.66–5.82 µM, respectively. They also showed TGI values in the cytostatic range of 3.49–97.3 µM and 3.33–77.3 µM respectively. These two compounds potently inhibited VEGFR-2 with IC_{50} = 0.111 and 0.049 µM, $BRAF^{V600E}$ with IC_{50} = 0.089 and 0.063 µM and $BRAF^{WT}$ IC_{50} = 0.071 and 0.05 µM, in comparison to sorafenib IC_{50} values of 0.031, 0.035 and 0.021 µM against VEGFR-2, $BRAF^{V600E}$ and $BRAF^{WT}$, respectively. Compounds **4a** and **4b** showed also potent down-regulation of total VEGFR-2 and phosphorylated VEGFR-2. In addition, the HUVECs migratory potential was greatly reduced resulting in significantly disrupted wound healing patterns after treatment with compounds **4a** and **4b** for 72 h. Furthermore, Compounds **4a** and **4b** induced apoptosis by 22.82- and 25.81-fold increase in the total apoptosis percentage in breast cancer MCF7 cell line. This apoptotic activity was supported by an increase in the level of apoptotic caspase-9 by 6.17- and 9.07-fold, respectively. Moreover, the cell cycle analysis showed that compounds **4a** and **4b** arrested the cell cycle mainly in the G1 and G1/S phases, respectively. The molecular modeling studies were performed to assess the binding pattern and affinity of derivatives **4a** and **4b** toward the VEGFR-2 and BRAF active sites.