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Design and synthesis of novel thioethers derived from 1,5-diphenyl-6-thioxo-6,7-dihydro-1H-pyrazolo[3,4-d]pyrimidin-4(5H)-ones as antiangiogenic agents

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Abstract:

Background: In attempts to discover new antiangiogenic entities, a novel series of thioethers derived from 6-thioxo-6,7-dihydro-1H-pyrazolo[3,4-d]pyrimidine-4(5H)ones was considered and designed. Methods: Virtual screening was carried out through docking of the compounds into the vascular endothelial growth factor and matrix metalloproteinase-9 binding sites. Molecular docking studies were performed using Lamarckian Genetic Algorithm. Compounds possessing lowest ligand-protein pairwise interaction energies were synthesized and screened for their antiproliferative activities against five cancer cell lines namely MHCC97H (liver), MDA-MB 231 (Breast), Colo205 (Co-lon), A549 (lung), A498 (kidney) and IC50 values were determined for the most potent compounds. Additionally, they were tested for their antiangiogenic activities by testing their ability to inhibit Human Umbilical Vein Endothelial Cell (HUVEC), cord formation and migration in response to chemoattractant. Results: Three compounds 2a, 2b and 5b showed significant antiangiogenic activities. The allyl thioether 2b was the most active with chemotaxis activity data nearly comparable to that of the positive control, TNP-470. Additionally, 2a, 2b and 5b, contrary to TNP-470, interfered with the migration of HUVECs in response to vascular endothelial growth factor rather than endothelial cells proliferation or cord formation. Compounds 2a, 2b and 5b were also investigated for their inhibitory effects on MMPs to investigate the relationship between their angiogenic activity and MMPs. Results revealed that compound 2b was the most effective MMP-9 inhibitor in this series. Additionally, compound 2b reduced the expression levels

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of VEGF and pERK1/2. Conclusion: Our results suggest that compound 2b is considered as a promising antiangiogenic agent by targeting VEGF and MMP-9. © 2019 Bentham Science Publishers.

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