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Substituted Thiazole Analogues as Anti-Tumor Agents

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Abstract : Introduction: Vascular Endothelial Growth Factor receptor (VEGF) is a signal protein produced by cells that stimulates vasculogenesis to create new blood vessels. VEGF family binds to three trans-membrane tyrosine kinase receptors,Dihydrofolate reductase (DHFR) is an enzyme of crucial importance in medicinal chemistry. DHFR catalyzes the reduction 7,8 dihydro-folate to tetrahydrofolate and intimately couples with thymidylate synthase which is a pivotal enzyme that catalysis the reductive methylation of deoxyuridine monophosphate (dUMP) to deoxythymidine monophosphate (dTMP) utilizing N5,N10-methylene tetrahydrofolate as a cofactor which functions as the source of the methyl group. Purpose: Novel substituted Thiazole agents were designed as DHFR and VEGF-TK inhibitors with increased synergistic activity and decreased side effects. Methods: Five series of compounds were designed with a rational that mimic the pharmacophoric features present in the reported active compounds that target DHFR & VEGFR. These molecules were docked against Methotrexate & Sorafenib as controls. An in silico ADMET study was also performed to validate the bioavailability of the newly designed compounds. The in silico molecular docking & ADMET study were also applied to the non-classical antifolates for comparison. The interaction energy comparable to that of MTX for DHFRI and Sorafenib for VEGF-TKI activity were recorded. Results: Compound 5 exhibited the highest interaction energy when docked against Sorafenib, While Compound 9 showed the highest interaction energy when docked against MTX with the perfect binding mode. Comparable results were also obtained for the ADMET study. Most of the compounds showed absorption within (95-99) zone which varies according to the type of substituents. Conclusions: The Substituted Thiazole Analogues could be a suitable template for antitumor drugs that possess enhanced bioavailability and act as DHFR and VEGF-TK inhibitors.

Keywords : anti-tumor agents, DHFR, drug design, molecular modeling, VEGFR-TKIs
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