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PROCEEDINGS ABSTRACT

Novel thiadiazole–thiourea hybrids targeting the vascular endothelial growth factor receptor 2: design, synthesis, characterization, and *in silico* assessment

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A novel series of 1,3,4-thiadiazole-thiourea hybrid derivatives (namely, A-Cl, B-NO_2, C-OH, D-CH_3, and E-OCH_3) was systematically conceived, synthesized, and assessed for their efficacy as inhibitors of the vascular endothelial growth factor receptor 2 (VEGFR-2), thereby aimed at a critical mediator of tumour angiogenesis. The synthetic methodology adopted a convergent two-step strategy. Initially, the key intermediate, 5-amino-1,3,4-thiadiazole-2-thiol, was subjected to *S*-alkylation with a variety of substituted phenacyl bromides (bearing Cl, NO_2, OH, CH_3, and OCH_3) in acetone, at room temperature, affording the corresponding *S*-alkylated intermediates (namely, A–E). Subsequently, the target compounds were proficiently synthesized through the introduction of the thiourea moiety by reacting the amino group of each *S*-alkylated intermediate with 1-isothiocyanato-4-methoxybenzene in acetonitrile under reflux conditions for 24 h. Utilising Fourier transform infrared spectroscopy (FTIR) in conjunction with proton nuclear magnetic resonance (^{1}H-NMR) and carbon-13 nuclear magnetic resonance (^{13}C-NMR) has led to an effective validation of the chemical structures. Subsequently, by using the MOE 2024.06 software, we carried out molecular docking investigations, centring on the VEGFR-2 kinase domain (PDB ID: 4ASD), with sorafenib serving as the reference. The method of docking was confirmed through the effective re-docking of the co-crystallized ligand, resulting in a root mean square deviation (RMSD) measurement of 1.60 Å. Each derivative that was synthesized displayed encouraging binding affinities, with docking scores ranging from -7.94 to -8.64 kcal/mol, which were found to be similar to that of sorafenib (-9.23 kcal/mol). Interestingly, the nitro-substituted derivative (B-NO_2) has risen to the forefront as the most captivating compound, exhibiting a binding affinity (-8.64 kcal/mol) that approached much that of sorafenib. This increased affinity was ascribed to an optimal amalgamation of conserved hydrogen bonding interactions with the critical active site residues ASP_{1046}, LYS_{868}, and GLY_{922}, further augmented by hydrophobic interactions with LEU_{889}, LEU_{1035}, LEU_{840}, ALA_{866}, ILE_{892}, VAL_{899}, VAL_{916}, CYS_{919}, LEU_{1019}, VAL_{898}, and ILE_{1044}. Additionally, the B-NO_2 compound maintained a significant pi–sulfur interaction with CYS_{1045} and a salt bridge interaction with GLU_{885}, further enhancing its binding stability. By using SwissADME for *in silico* ADME (absorption, distribution, metabolism, and excretion) profiling, it was shown that every compound synthesized followed the Lipinski rule of five with no violations, thereby strengthening their qualities as potential drugs. The derivatives exhibited advantageous physicochemical features, comprising acceptable molecular weights

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ranging from 430.57 to 461.54 g/mol, hydrogen bond donor numbers of 2 to 3, and acceptor values from 4 to 6, plus a moderate to high lipophilicity reflected in a consensus log P of 2.79 to 4.12. While all compounds were shown to possess a low gastrointestinal absorption resulting from their relatively elevated topological polar surface area (TPSA; being >161.77 $Å^2$), they exhibited satisfactory bioavailability readings (0.55). More importantly, none of these derivatives exhibited potential PAINS (pan-assay interference compounds) alerts and none are anticipated to penetrate the blood–brain barrier, which is advantageous for minimising the risk of triggering adverse effects associated with the central nervous system. However, the profiling of cytochrome P450 inhibition has suggested possible inhibitions of CYP2C19, CYP2C9, and CYP3A4 from all compounds, while the B-NO_2 and E-OCH_3 ones exerted no inhibition of CYP1A2, thereby emphasizing the necessity for undertaking an assessment of potential drug–drug interactions. In conclusion, we have herein successfully devised and synthesized a novel series of thiadiazole–thiourea derivatives with validated structural integrity; the nitro-substituted derivative B-NO_2 has emerged as a promising candidate for VEGFR-2 inhibition, exhibiting superior binding affinity through optimal molecular interactions within the kinase active site as well as favourable drug-like properties *in silico*, thereby establishing a foundation for its further optimization and development as an anti-angiogenic drug.

Keywords

anticancer; molecular docking; 1,3,4-thiadiazole; thiourea; VEGFR-2

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Conflicts of interest statement

None to declare.

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