COLLOQUIA ERUDITA 2026; 1: 31–32

PROCEEDINGS ABSTRACT

Design, synthesis, characterization, and *in silico* assessment of novel 1,3,4-thiadiazole–urea derivatives as inhibitors of the vascular endothelial growth factor receptor 2

Noora A. Al-Jubouri, Shaker A. Abdul Hussein, and Hussam W. Al-Humadi

Received: 30 March 2026; Revised: 26 May 2026; Accepted: 17 June 2026; Published: 23 June 2026

A novel series of 1,3,4-thiadiazole–urea hybrid derivatives was conceived, synthesized, and assessed for their efficacy as vascular endothelial growth factor receptor-2 (VEGFR-2) inhibitors, thereby aiming at a critical mediator of tumour angiogenesis. The synthetic methodology adopted a convergent two-step strategy. Initially, the intermediate, 1-(5-mercapto-1,3,4-thiadiazol-2-yl)-3-(*p*-tolyl)urea (TT), was synthesized through a urea-forming reaction that involved the interaction between 5-amino-1,3,4-thiadiazole-2-thiol and *p*-tolyl isocyanate. Subsequently, the target compounds (i.e., TT-Cl, TT-NO_2, TT-OCH_3, TT-OH, and TT-CH_3) were synthesized through an *S*-alkylation of the free thiol moiety with a variety of substituted phenacyl bromides in an aqueous environment. The chemical structures of these novel 1,3,4-thiadiazole–urea hybrid derivatives were validated through the utilization of Fourier transform infrared (FTIR), proton nuclear magnetic resonance (^{1}H-NMR), and carbon-13 nuclear magnetic resonance (^{13}C-NMR) spectroscopy. The molecular docking investigations were executed by employing the Molecular Operating Environment v.2024.06 software and by targeting the VEGFR-2 kinase domain (PDB ID: 4ASD), with sorafenib serving as the reference standard. The docking technique received validation *via* the successful redocking of the reference ligand, culminating in a root mean square deviation (RMSD) of 1.60 Å. Each of the synthesized derivatives exhibited a promising binding affinity, with docking scores varying from -8.24 to -9.319 kcal/mol, which were determined to be comparable to that of sorafenib (-9.23 kcal/mol). Importantly, the nitro-substituted derivative (TT-NO_2) has risen to the forefront as the most captivating compound, as it exhibited a binding affinity (-9.319 kcal/mol) that narrowly outstripped that of sorafenib. This increased affinity was ascribed to an optimal amalgamation of conserved hydrogen bonding interactions with critical active site residues ASP_{1046} and GLU_{885} in a distance of 2.94 Å and 1.82 Å, respectively; these were further augmented by hydrophobic interactions with LEU_{1019}, ILE_{892}, LEU_{889}, VAL_{916}, VAL_{899}, VAL_{848}, and ALA_{866}. Furthermore, the TT-NO_2 derivative exhibited a significant pi–sulfur interaction with CYS_{1045}, thereby further enhancing its binding stability. Subsequently, and after using the SwissADME web tool for the undertaking of an *in silico* ADME (absorption, distribution, metabolism, and excretion) profiling, it was shown that every compound synthesized followed Lipinski's rule of five with no

Al-Jubouri N. A., Abdul Hussein S. A., Al-Humadi H. W.: Design, synthesis, characterization, and *in silico* assessment of novel 1,3,4-thiadiazole–urea derivatives as inhibitors of the vascular endothelial growth factor receptor 2. *Colloq. Erud.* 1: 31–32 (2026).
https://doi.org/10.5281/zenodo.20808354

This proceedings abstract is published in *Colloquia Erudita – Volume 1: Proceedings of the 3rd International Babylon Conference on Clinical and Experimental Pharmacological Research (Hillah; June 29–30, 2026)*; a volume of proceedings edited by Rafal J. Al-Saigh, Argyro Kyriakaki, and Apostolos Zarros.

breaches; a fact that strengthens their qualities as potential drugs. The herein studied derivatives also exhibited advantageous physicochemical features, comprising acceptable molecular weights ranging from 398.50 to 429.47 g/mol, hydrogen bond donor numbers ranging from 2 to 3, and acceptor values from 4 to 6, plus a moderate lipophilicity as reflected in a consensus log P ranging from 2.66 to 3.88. Although all compounds demonstrated low gastrointestinal absorption due to their comparatively high topological polar surface area (TPSA; being >137.52 $Å^2$), they also exhibited adequate bioavailability scores (0.55). Notably, none of these derivatives exhibited potential for PAINS (pan-assay interference compounds) alerts or were forecasted to be able to traverse the blood-brain barrier, which could be a beneficial indicator of their ability to not trigger any central nervous system-related adverse effects. However, findings from the profiling of cytochrome P450 inhibition suggest a possible inhibition of CYP2C19, CYP2C9, and CYP3A4 by all studied compounds, thereby emphasizing the necessity for a further investigation into potential drug–drug interactions. Overall, this study presents our findings on a successfully devised and synthesized novel series of thiadiazole–urea derivatives with validated structural integrity; of these derivatives, the nitro-substituted one (TT-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 of the receptor as well as favourable drug-like properties *in silico*.

Keywords

ADME; cancer; molecular docking; 1,3,4-thiadiazole; VEGFR-2

Acknowledgements

The authors gratefully acknowledge the University of Babylon for providing the facilities to carry out this study. No external funding was received for the undertaking of this study.

Conflicts of interest statement

None to declare.

Affiliation(s)

College of Pharmacy, University of Babylon, Hillah, Iraq *(NAA, HWA)* ▪ Department of Pharmaceutical Chemistry, College of Pharmacy, University of Babylon, Hillah, Iraq *(SAAH)*

Correspondence

Noora A. Al-Jubouri
College of Pharmacy
University of Babylon
Hillah, Iraq
pha155.noora.ali@student.uobabylon.edu.iq