Journal of Exploratory Research in Pharmacology **2026** vol. 11(3) | e00003
DOI: 10.14218/JERP.2026.00003

Letter to the Editor

Proposal on Future Drug Development of Novel 1,2,3-Triazole-Urea Hybrids

Shumeng Shen[1], Wenhao Wang[2*] and Zhengwei Huang[1*]

[1]*State Key Laboratory of Bioactive Molecules and Druggability Assessment, Guangdong Basic Research Center of Excellence for Natural Bioactive Molecules and Discovery of Innovative Drugs, College of Pharmacy, Jinan University, Guangzhou, Guangdong, China;* [2]*School of Pharmaceutical Sciences, Sun Yat-sen University, Guangzhou, Guangdong, China*

Received: February 03, 2026 | **Revised:** March 03, 2026 | **Accepted:** April 07, 2026 | **Published online:** April 28, 2026

Dear Editors,

We have carefully read the paper by Gao *et al*.[1] with interest. In this paper, the authors designed and evaluated a new series of triazole-urea hybrid compounds for anti-cancer potential. It is proposed in the article that most compounds exhibited potent, concentration- and time-dependent, selective antiproliferative activity against hepatocellular carcinoma Huh-7 cells, with negligible cytotoxicity toward normal hepatocytes L02. Further investigations revealed that compound 3c induced apoptosis, autophagy, and DNA damage in Huh-7 cells, thereby exerting anti-hepatocellular carcinoma effects. *In vivo* acute toxicity studies demonstrated a high maximum tolerated dose and favorable safety profile. These findings highlight the selective anti-liver cancer efficacy and favorable *in vivo* safety of these triazole-urea hybrids, particularly compound 3c, underscoring their strong potential as promising therapeutic candidates for hepatocellular carcinoma.

Although this study has demonstrated that novel 1,2,3-triazole-urea hybrids exhibit significant selective toxicity toward Huh-7 hepatocellular carcinoma cells while showing no notable effects on normal hepatocytes L02, the underlying mechanism of this selectivity remains incompletely elucidated. To this end, we present several perspectives on the clinical translation and highlight key concerns of these compounds. We contend that an insufficient understanding of the underlying selective mechanism may hinder their clinical translation prospects. Accordingly, we propose that this selective effect may be attributable to deficiencies in the DNA damage response pathway, coupled with heightened sensitivity of the apoptosis and autophagy pathways in tumor cells. Studies have shown that p53 mutation in hepatocellular carcinoma is associated with the DNA damage repair pathway.[2] Huh-7 cells are known to be a typical p53-mutant cell line, which may possess inherent defects in their DNA damage repair machinery. By employing techniques such as qPCR, Western blot, or immunofluorescence, it is possible to examine the differential expression of potential drug targets—such as key proteins involved in DNA damage repair, apoptosis, or autophagy—between Huh-7 and L02 cells. Such a comparative analysis would help elucidate why these compounds selectively target cancer cells.

In parallel with the aforementioned mechanistic studies, the clinical translation of these compounds faces a key challenge—drug solubility. Currently, *in vivo* experiments for these compounds rely on dimethyl sulfoxide as a solvent. However, progression toward clinical application necessitates addressing the critical issue of druggability, with enhancing solubility representing the foremost challenge. Novel 1,2,3-triazole-urea hybrids possess an extended conjugated framework that promotes hydrophobic interactions through synergistic π–π stacking. A nanocrystal-based solubilization strategy is therefore proposed, wherein a combination of top-down and bottom-up techniques can be employed to facilitate drug self-assembly into nanocrystals. In nanomedicine drug delivery systems, nanocrystals represent one of the key strategies to enhance the bioavailability of poorly water-soluble drugs. For instance,[3] the nanocrystal-based formulation of telmisartan has been reported to markedly improve its pharmaceutical properties, resulting in a 53-fold increase in aqueous solubility, accelerated *in vitro* drug release, and a 2.2-fold enhancement in *in vivo* bioavailability. If the self-assembly driving force is insufficient, the addition of stabilizers such as Tween 80 may be considered to promote nanocrystal formation and ensure uniformity. Importantly, several nanocrystal-based formulations, including Rapamune®, Tricor®, and Emend®, have received Food and Drug Administration approval and are commercially available,[4] underscoring the safety and translational viability of this approach. Thus, the application of nanocrystal technology to novel 1,2,3-triazole-urea hybrids holds considerable potential for eliminating dimethyl sulfoxide dependency, optimizing drug delivery, and improving patient compliance, thereby supporting promising prospects for clinical translation. Nonetheless, the clinical translation of this strategy still faces challenges: nanocrystals are prone to precipitation during storage or in physiological environments, leading to inconsistent particle size and content uniformity. Furthermore, issues such as the

***Correspondence to:** Zhengwei Huang, State Key Laboratory of Bioactive Molecules and Druggability Assessment, Guangdong Basic Research Center of Excellence for Natural Bioactive Molecules and Discovery of Innovative Drugs, College of Pharmacy, Jinan University, 855 East Xingye Dadao, Panyu District, Guangzhou, Guangdong 510006, China. ORCID: https://orcid.org/0000-0003-2351-7347. Tel: +86-13580481121, E-mail: huangzhengw@jnu.edu.cn; Wenhao Wang, State Key Laboratory of Bioactive Molecules and Druggability Assessment, Guangdong Basic Research Center of Excellence for Natural Bioactive Molecules and Discovery of Innovative Drugs, School of Pharmaceutical Sciences, Sun Yat-sen University, 132 East Waihuan Road, Guangzhou, Guangdong 510632, China. ORCID: https://orcid.org/0000-0002-7015-9047. Tel: +86-18813298353, E-mail: wangwh37@mail2.sysu.edu.cn

How to cite this article: Shen S, Wang W, Huang Z. Proposal on Future Drug Development of Novel 1,2,3-Triazole-Urea Hybrids. *J Explor Res Pharmacol* 2026;11(3):e00003. doi: 10.14218/JERP.2026.00003.

scalability of the manufacturing process, batch-to-batch reproducibility, *in vivo* biodistribution, and potential immunogenicity require systematic investigation.

This study analyzed the potential molecular mechanisms underlying the selective killing of liver cancer cells by novel compounds and addressed their solubility and delivery challenges through the introduction of nanocrystal technology. These considerations provide a theoretical foundation and a feasible formulation pathway for the precision design and clinical translation of targeted anticancer drugs. In conclusion, we congratulate the authors on their valuable contribution to research on novel 1,2,3-triazole-urea hybrids.

Acknowledgments

None.

Funding

This work was supported by the Science and Technology Projects in Guangzhou, under grant No. 202102070001.

Conflict of interest

Prof. Zhengwei Huang is an editorial board member of *Journal of Exploratory Research in Pharmacology*. The authors have no conflicts of interest to declare.

Author contributions

Research concept and design (SSM), data acquisition (SSM), manuscript writing (SSM), critical revision of the manuscript for important intellectual content (WWH), administrative, technical, or material support (HZW), and research supervision (HZW). All authors have made significant contributions to this study and have approved the final manuscript.

References

[1] Gao E, Zhang H, Guo Y, Wang X, Mao L, Peng L, *et al*. Design, Synthesis and Antiproliferative Activity Studies of Novel 1,2,3-Triazole-Urea Hybrids. Drug Des Devel Ther 2025;19:9481–9499. doi:10.2147/DDDT.S536920, PMID:41147003.

[2] Ma J, Tang D, Cui G, Zhang X, Wang X, Li Y, *et al*. The molecular characteristics of DNA damage and repair related to P53 mutation for predicting the recurrence and immunotherapy response in hepatocellular carcinoma. Sci Rep 2025;15(1):14939. doi:10.1038/s41598-025-99853-5, PMID:40301641.

[3] Kshirsagar R, Bule P, Kandula JS, Kundu S, Pullapanthula R, Sahu BD, *et al*. Unveiling the potential of telmisartan in breast cancer using nanocrystal approach: Formulation, optimization, in vitro, and in vivo pharmacokinetic evaluation. J Drug Deliv Sci Technol 2026;115(Pt 2):107693. doi:10.1016/j.jddst.2025.107693.

[4] Bobo D, Robinson KJ, Islam J, Thurecht KJ, Corrie SR. Nanoparticle-Based Medicines: A Review of FDA-Approved Materials and Clinical Trials to Date. Pharm Res 2016;33(10):2373–2387. doi:10.1007/s11095-016-1958-5, PMID:27299311.