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PEER-REVIEW REPORT

Name of journal: *World Journal of Gastrointestinal Oncology*

Manuscript NO: 83001

Title: BZD9 benzimidazole analogue hampers colorectal tumor progression by impeding angiogenesis

Provenance and peer review: Invited Manuscript; Externally peer reviewed

Peer-review model: Single blind

Reviewer's code: 05560107
Position: Peer Reviewer
Academic degree: PhD
Professional title: Academic Editor, Associate Professor, Director, Doctor
Reviewer's Country/Territory: China
Author's Country/Territory: Malaysia

Manuscript submission date: 2023-01-03

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-01-26 05:56

Reviewer performed review: 2023-02-06 03:30

Review time: 10 Days and 21 Hours

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Scientific significance of the conclusion in this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No scientific significance
Language quality	[Y] Grade A: Priority publishing [ ] Grade B: Minor language polishing [ ] Grade C: A great deal of language polishing [ ] Grade D: Rejection
Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

General comments for the author Enhanced angiogenesis is a cancer hallmark and critical for colorectal cancer (CRC) invasion and metastasis. Anti-angiogenic drugs and chemotherapy represent a standard of care for treating metastatic CRC. However, drug resistance to CRC is common in clinical practice, and the search for new drugs has been the focus of research. In this manuscript, the authors investigated the the anti-angiogenic potential of BZD9L1 on endothelial cells (EC) in vitro, ex vivo and in HCT116 CRC xenograft in vivo models. The conclusion showed that anti-angiogenic potential of BZD9L1 to reduce CRC tumor progression. Overall, this study is interesting and innovative, but it needs to be revised before it can be published. Major concerns: 1. “Novelty” BZD9L1 has not been reported to inhibit angiogenesis. Therefore, this study is innovative. 2. “Value of findings” The existing experimental data support the value of further development of BZD9L1, so this study has a guiding significance for peers. 3. “Experimental design” Overall, the experimental design of this research is reasonable, but there are several problems, the author must improve. First, EA.hy926 is a fusion cell. Although some studies have pointed out that it has certain vascular endothelial

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properties, our team found that EA.hy926 basically does not have the ability of vascular endothelial cells to form tubes in vitro and most of the surface markers of vascular endothelial cells have been lost. Therefore, I believe that the authors should use vascular endothelial cells from human CRC tissue isolated or human umbilical vein endothelial cells to supplement the in vitro toxicity and tubular experiments. Second, because BZD9L1 itself has cytotoxic effects, it is reasonable to inhibit the tumorigenesis of CRC cells in vivo. To highlight the potential anti-angiogenic effect of BZD9L1, the authors should further examine the number and status of CD31-positive vessels in the xenografts tissue by IHC. Third, the authors need to consider whether to add VEGFA to rescue in some in vitro experiments. Minor concerns: 1. The chart is clear and the language is smooth. There are almost no minor concerns.

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Reviewer's code: 05744019
Position: Editorial Board
Academic degree: PhD
Professional title: Professor
Reviewer's Country/Territory: China
Author's Country/Territory: Malaysia

Manuscript submission date: 2023-01-03

Reviewer chosen by: AI Technique

Reviewer accepted review: 2023-01-26 02:42

Reviewer performed review: 2023-02-07 04:03

Review time: 12 Days and 1 Hour

Scientific quality	[ ] Grade A: Excellent [Y] Grade B: Very good [ ] Grade C: Good [ ] Grade D: Fair [ ] Grade E: Do not publish
Novelty of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No novelty
Creativity or innovation of this manuscript	[ ] Grade A: Excellent [Y] Grade B: Good [ ] Grade C: Fair [ ] Grade D: No creativity or innovation

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Conclusion	[ ] Accept (High priority) [ ] Accept (General priority) [Y] Minor revision [ ] Major revision [ ] Rejection
Re-review	[Y] Yes [ ] No
Peer-reviewer statements	Peer-Review: [Y] Anonymous [ ] Onymous
	Conflicts-of-Interest: [ ] Yes [Y] No

SPECIFIC COMMENTS TO AUTHORS

This manuscript "BZD9L1 benzimidazole analogue hampers colorectal tumor progression by impeding angiogenesis" was well designed and showed good results. The results found that BZD9L1showed its anti-angiogenic potential in CRC tumor and inhibited CRC tumor growth in in vitro and in vivo. In Fig.2, A and B are mislabeled, and the authors should detected the protein expression of intercellular adhesion molecule 1 (ICAM-1, VE-cadherin and ITGA5) and SIRT1/2, besides QPCR analysis. In animal experiments, the methods only described that "The treatments were injected intraperitoneally at a maximum volume of 250μl every three days", and how many times to inject BZD9L1. The discussion part is mainly about the repeated description of the results, which are relatively shallow and need to be modified. For example, the mechanism, clinical application and combined treatment strategy such as oncolytic virus (doi: 10.3390/biomedicines8120593) of BZD9L1 against colon cancer need to be further discussed. There are some language and grammar errors through the manuscript. Please correct them carefully.