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OPEN PEER REVIEW

Synthesis and Bioactivity Investigation of Novel 2-({2-[(Dialkylamino) Methyl] Quinazolin-4-one-3-yl} Methyl) Benzonitrile Derivatives as Dipeptidyl Peptidase-4 Inhibitory Agent

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About this report

This open peer review (OPR) report shows the public comments made on this article during peer review, by the reviewers, the associate editor and the editor-in-chief, for every revision round, together with the authors' replies. Comments appear only with the consent of the people who wrote them. Reviewers who chose to sign their report are named; the others are shown as "Referee". Comments are edited for language only, and confidential remarks to the editors are not included.

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1 Original submission

1 comment · 30 Jan 2024

Referee 1 Reviewer

MAJOR REVISION 30 Jan 2024

You have submitted an interesting manuscript and made an interesting novel set of compounds. But in order to publish the article, it is necessary to provide some additional data.

First, you need to add docking results to your data. Docking scores must be considered and the relationship between them and clinical results should be investigated thoroughly.

Secondly, you should definitely increase the number of compounds beyond the current number in order to get better results in the discussion and conclusion sections.

Thirdly, you have not used mass spectrum and elemental analysis data, which we suggest adding.

Fourth, the language of the article should be improved. Grammatical and spelling errors should be corrected.

Fifth, the chemical data must be added in the form of Chemdraw files, featuring the exact chemical structure of the newly developed compounds. The chemical structure of the novel compounds must be added to Table 1.

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Revision 1

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

REPLY TO THE REVIEWERS

Reviewer 1:

No.	**Reviewers' Comments:**	**Reply/Answer:**
	The study was interesting. However, it is recommended to correct the following:	Thank you for your comments and suggestions. The following are my responses to your comments and suggestions:
1	Docking studies are strongly recommended for this study. Also, a comparison of the docking and evaluation results could be done.	The docking studies of the compounds and sitagliptin have been done. The results of the docking simulation between the compounds and sitagliptin were compared. We also compared them to the result of the docking simulation of the lead compound reported earlier.
2	Please add a figure in the background section to show your lead compounds and how you design your molecules.	A figure in the background section has been added, as **Figure 1** in the revised version of the manuscript.
3	The quality of the scheme should be improved.	The quality of the scheme has been improved. In the revised manuscript, the schema is marked as **Figure 2.**
4	The caption of the figure should be the same number as the body of the manuscript. The caption is Figure 2, but in the body, it is Figure 1.	Its typo has been corrected. There are six figures in the revised manuscript now.
5	In the results and discussion, you should discuss your evaluation results more.	In the results and discussion of the revised manuscript, we have added the evaluation of the results of structure confirmation, the in vitro DPP-4 inhibitory activity test compared to sitagliptin as the reference standard, and the activity of the lead compound as reported in the literature. Additionally, we add the results and discussion of a docking simulation study of the compounds compared to sitagliptin. The result is also compared to the reported result by literature on the docking simulation of the lead compound.
6	The methods section should be classified into three headings, such as the results section: 1- chemistry, 2.	In the revised manuscript, the methods have been classified into 3.1. Chemistry, 3.2. DPP-4 inhibitory Activity Assay, and 3.3. In silico study

	DPP-4 inhibitory Activity Assay, and 3. Anti-inflammatory Activity Assay.	
7	Please pay attention to the italic style of some words or letters; in vivo, in vitro, para, etc. should be written in italics.	In the revised manuscript, the typo has been corrected
8	In section 4.2, the IC50 range should be written from the smallest to largest values. (The synthesized compounds exhibited good DPP-4 inhibitory activity with the IC50 of 6.78-1.46 µM).	In the revised manuscript, the IC50 range has been written from the smallest to largest values. The title compounds exhibited good inhibition against DPP-4 enzyme activity (IC_{50}: 1.4621 to 6.7805 µM).
9	To use an abbreviation, such as DPP-4, write out the term or phrase on first use, followed by the abbreviation in parentheses.	In the revised manuscript, each abbreviation has been preceded by the term or phrase on first use. - Dipeptidyl Peptidase-4 (DPP-4) inhibition - the DPP-4 inhibitory activity
10	Also, please answer these questions: Why the diclofenac concentration is in logarithmic values in Figure 1B?	Figure 1B: The inhibition (%) of heat-induced protein denaturation versus log concentration (µM) curve of diclofenac sodium. The figure has been deleted because, in this manuscript, we do not report the anti-inflammatory of the compounds anymore. The title of the manuscript to br changed to "**Synthesis and Bioactivity Investigation of Novel 2-({2-[(Dialkylamino)methyl]quinazolin-4-one-3-yl}methyl)benzonitrile Derivatives as Dipeptidyl Peptidase-4 Inhibitory Agent".**
11	Why did you perform an anti-inflammatory test for these compounds? Please specify the reason you have performed this test.	In order to focus on the objective of this study, which is the evaluation of the DPP-4 inhibitory activity of the compounds, we do not report the evaluation of the anti-inflammatory of the compounds anymore in this manuscript.

Reviewer 2:

No	Reviewers' Comments:	Respons

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	You have submitted an interesting manuscript, made an interesting novel set of compounds. But in order to publish the article, it is necessary to provide some additional data.	Thank you for your comments and suggestions. The following are my responses to your comments and suggestions:
1	You need to add docking results to your data. Docking scores must be considered, and the relationship between them and clinical results should be investigated thoroughly.	The docking studies of the compounds and sitagliptin have been done. The results of the docking simulation between the compounds and sitagliptin were compared. We also compared them to the result of the docking simulation of the lead compound reported earlier. The relationship between docking simulation and in vitro DPP-4 activity results has been investigated thoroughly.
2	You should definitely increase the number of compounds from this amount in order to get better results in the discussion and conclusion sections.	Thank you for your suggestion to increase the number of compounds. I agree that the results and discussion would be better. However, we are constrained from doing so because the funding for this study is no longer available, so we regretfully cannot fulfill your suggestion.
3	You have not used the data of mass spectrum and elemental analysis, which we suggest to be added.	We did not conduct the elemental analysis (CHNO). However, the target molecules (the tested molecule) have been completed with HR-MS data. We believe that the HR-MS data and the complementary IR, 1H-NMR, and 13C-NMR data provide more than enough evidence to confirm the structure.
4	The writing language of the article should be improved. Grammatical and spelling errors should be corrected.	The writing language of the revised manuscript has been improved. Grammatical and spelling errors have been corrected.
5	The chemical data must be added as ChemDraw files featuring the exact chemical structure of the newly developed compounds. The chemical structure of the novel compounds must be added to the Table 1.	The chemical structure of the novel compounds has been added to the Table 1.

2 Revision 1

2 comments · 28 Dec 2024 – 31 Dec 2024

Referee 1 Reviewer

ACCEPT 28 Dec 2024

All of my comments were addressed. The manuscript is ready to publish. Congratulations.

Associate Editor

MINOR REVISION 31 Dec 2024

Dear Author
Thank you for submitting your valuable work "Synthesis and Bioactivity of Novel 2-({2-[(Dialkylamino)methyl]quinazolin-4-one-3-yl}methyl)benzonitrile Derivatives as Dipeptidyl Peptidase-4 Inhibitory Agent" to the IJPR. The answers are acceptable, but the reviewers have some additional comments, and your manuscript needs minor revision. Please make the required corrections before publication in the IJPR.

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Revision 2

AUTHORS' RESPONSE TO REVIEWERS

Authors' reply to reviewers

The next pages contain the authors' point-by-point reply to the comments of this revision round, as submitted with the revised manuscript. It is published as the authors wrote it.

REPLY TO THE REVIEWERS

Reviewer 1:

No.	Reviewers' Comments:	Response
	All of my comments were addressed. The manuscript is ready to publish. Congratulations	Thank you for your suggestions to help improve my manuscript for publication.

Reviewer 2:

The manuscript 145406 entitled " Synthesis and Bioactivity of Novel 2-({2-[(Dialkylamino)methyl] quinazolin-4-one-3yl}methyl) benzonitrile Derivatives as Dipeptidyl Peptidase-4 Inhibitory Agent" was about synthesis and biological evaluation of six 4-oxo-3,4-dihydroquinazoline derivatives as DPP-4 inhibitors.

No.	Reviewers' Comments:	Response
	My comments are as follow:	Thank you for your comments and suggestions. The following are my responses to your comments and suggestions:
1	The introduction is very short. It is recommended to improve the introduction by providing more context and background information.	The introduction has been revised to provide more background information (page 2).
2	Additionally, I noticed that the number of compounds discussed in the manuscript is relatively limited.	The compounds studied were only six. However, the six vary in physical, chemical, and steric properties, resulting in variations in activity and orientation in molecular docking simulations. The results of this work can be valuable input for further research.
3	What does @ stand for? "mixtures of synthesized compound solutions (@ 25 µL) at various"	The symbol of @ stands for “each.” The symbol “@” has been removed because, without @, it can be understood that the volume of solutions added to each well.

Reviewer 3:

No.	Reviewers' Comments:	Respons
	As mentioned in the last review, the	Thank you for your review.

	previous comments were applied to the manuscript.	

Reviewer Assistant Comments:

No.	Reviewers' Comments:	Response
	These comments were generated by AI based on your manuscript. **Please review them and consider incorporating the suggestions to enhance your article.**	Thank you. The comment has been to be considered to enhance my article by giving responses as follows:
	Major Comments: The discussion could be expanded to include more context on the significance of the findings and potential future research directions.	The discussion has been expanded by adding information about the results of in-silico studies. The study's results might be valuable for designing and developing DPP-4 inhibitor agents with excellent and selective activity.
	Minor Comments: • The abstract is well-structured and provides a comprehensive overview of the study. • Consider providing more detailed information on the in silico methods used for molecular docking.	• Thanks for the comments. • Thank you for your suggestion. Unfortunately, I cannot provide further details about the in silico method used for molecular docking, as it is a commonly utilized technique. Readers can refer to the literature I have cited for more information.

3 Revision 2

0 comments

No public comments in this round.