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OPEN PEER REVIEW

Design, Synthesis, Anticonvulsant Evaluation, and Molecular Docking Studies of New $GABA_A$ Agonist Derivatives

Mansur Nassiri Koopaei, Parsa Moghimirad, Ebrahim Saeedian Moghadam, Nasrin Nassiri Koopaei, Massoud Amanlou, Tahmineh Akbarzadeh, Mohammad Sharifzadeh, Mohsen Amini

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Contents

1 **Original submission** Referee 1, Referee 2, Samira Shafiee, Referee 3 2
2 **Revision 1** 5
Authors' reply to reviewers 6
Reviewer and editor comments 8

1 Original submission

4 comments · 13 Nov 2024 – 10 Dec 2024

Referee 1 Reviewer

ACCEPT 13 Nov 2024

The manuscript is qualified for publication in IJPR. In my opinion, all of the required data are present.

Referee 2 Reviewer

REJECT 30 Nov 2024

Dear Author
The subject of the manuscript "Synthesis and Evaluation of Anticonvulsant Effects of New GABAA Agonist Derivatives" is interesting, but the authors should introduce a series of compounds with similarities in their design to present their work as well as possible. The diversity of the designed compounds is not suitable and not interesting. Also, the number of synthesized compounds is not enough. In this regard, the SAR of the designed compounds is poorly written and unacceptable. A docking study is needed to show the virtual efficacy of the designed compounds. Also, the title of the manuscript is not suitable for presenting the contents. In my opinion, this manuscript is not good enough to be accepted by IJPR.

Samira Shafiee Reviewer

MINOR REVISION 6 Dec 2024

Dear Associate Editor and Authors;

After thoroughly reviewing the submitted research paper, I have identified several critical areas that require minor revisions to enhance the manuscript's clarity, coherence, and scholarly impact.

1. The title should be changed as it must succinctly summarize the content and focus of the study, making it clear to readers what they can expect from the paper. The authors said in the abstract that the GABA agonist derivatives were designed, synthesized, and
screened for the treatment of seizures. They also mentioned that molecular docking studies were carried out; however, they did not reflect this clearly in the title, so I recommend changing it to "Design, synthesis, anticonvulsant evaluation, and molecular docking studies of new GABAA agonist derivatives".

2. There are several grammatical errors in this work. This is typified by statements like:

• pg 3 line 4 - ' Molecular docking studies was carried out to check the styles of
interactions with GABAA receptor and the synthesized derivatives.'
• pg 3 line 1 -' In this study, a new series of GABA agonist derivatives were designed, synthesized, and were screened for treatment of seizure in animal model.'

• pg 3 line 6 -' Docking outcomes showed that compound 3c with highest
anticonvulsant effects has the lowest binding energy.'

• pg 16 line 293-'ANOVA demonstrated that derivative 3c was most potent compound showed most protective effect'.

Unfortunately, the entire work has these types of issues. So, please correct them.

3. The source of supply for the compound "1-methyl-1H-indazole-3-carbonyl chloride" is not mentioned in the materials section. If it was synthesized in previous studies, please give a reference for that.
4. The section "General procedure for the synthesis of compounds 1c, 1d, 2a, 3c, 4b, 5 & 6b" and the relevant

sections do not contain numbering formats.
5. Although the background suggests some rationale for the research, more detail on the significance of the study could improve clarity.
6. The objectives are described but not explicitly mentioned. A clear statement of the specific aims of the study should be provided in the introduction.
7. Pg 6 line 73- Confusion arises from the statement 'A mixture of 1-methyl-1H-indazole-3-carbonyl chloride 1a (2 mmol) was dissolved in acetonitrile'. This is not correct: if you are mixing, then there should be more than one compound. If there is only one compound (1-methyl-1H-indazole-3-carbonyl chloride 1a), then you cannot say ' A mixture'.
8. Details on the animal model used should include species, number of subjects, and selection criteria. Please provide comprehensive details on the methods, including participant selection, variables measured, and statistical analyses.
9. Definitions of the outcomes (e.g., seizure symptoms) and how they were measured should be provided.
10. Specific results, including statistical significance and effect size, should be provided in the results.
11. Key changes in Statistical analysis
• The phrase "declared as" should be changed to "presented as" for better clarity.
• "Assessment of variance" should be changed to "analysis of variance" (standard terminology).
• "Anti-seizures activity" should be revised to "anti-seizure activity" for consistency with common scientific terminology.

12. To improve clarity, explicitly connecting the statistical results to Figure 2 might be helpful. For instance:
• "As shown in Figure 2, compound 3c exhibited the most significant protective effect against PTZ-induced convulsions, as indicated by the latency time and statistical analysis (*P < 0.05)."
This way, the statistical analysis and the figure complement each other and provide a comprehensive understanding of the results.
• The quality of Figure 2 is not good. In general, the figure is blurred.

13. Please specify a section for 'Conclusion'.

Kind regards

Referee 3 Reviewer

MAJOR REVISION 10 Dec 2024

Overall Summary and Evaluation:
The manuscript describes the synthesis and biological evaluation of several GABA agonist derivatives. Among these, compound 3c exhibited the highest anticonvulsant effects. The authors confirmed the involvement of GABA receptor-mediated anticonvulsant effects using the flumazenil test. Overall, the synthesis is well described, the yields are good, and the animal studies demonstrate the efficacy of these compounds. However, the manuscript contains numerous grammatical errors, necessitating English editing (e.g., page 3, line 9, etc.). Additionally, the modeling results do not align with the animal data. For instance, compound 3c doesn't show the lowest binding energy in the docking studies, and the mortality rate is missing.

Specific Comments:
Abstract:
• Page 3, line 9: The phrase "with at least mortality" should be revised to "with the lowest mortality rate."
Introduction:
• Page 3, line 18: "Epilepsy is the fourth most common disease in the world that is categorized under neurological diseases." should be revised to "Epilepsy is the fourth most common neurological disease in the world."

• Page 3, line 20: “Seizures contain among the symptoms that are seen due to abnormal electrical activity of the brain…” should be revised to “Seizures are the result of abnormal electrical activity in the brain.”
• Page 3, line 25: “The result excessive neuronal excitability is the formation of a special area in the brain that is named as epileptic centre.” should be revised to “Excessive neuronal excitability causes the formation of epileptic centers in specific regions of the brain.”
• Page 3, line 28: Please write the full names of abbreviations when they first appear in the text, such as PTZ, GABA, and CNS.
• Page 4, line 32: The word “energy” is not appropriate in this context. Please replace it with “flow.”
• Page 4, line 38: Zonisamide and tiagabine have been available for at least 20 years; they are not recently approved medicines.
• Page 4, line 41: The word “Tiadabine” is a spelling error and should be corrected.
• Page 4, line 42: Both pharmacophores are seen in tiagabine, but zonisamide contains only the aryl group. Therefore, the generalization to both is incorrect. Additionally, how did you design the rest of the scaffold (linker part)? Please provide a more detailed rationale for designing this series.
Experimental (Docking Methodology, Page 10):
• Could you elaborate on your homology modeling approach? How did you validate the model?
Results and Discussion:
• Page 15, Table 1: Please specify whether log P was calculated or experimentally measured.
• Page 16, line 288: The mortality rate data are missing from Table 1.
• Page 16: Although the pharmacological data are described in this section, there is no structure-activity relationship (SAR) discussion. Please consider adding a brief SAR and logical explanation for the structures and their activities.
• Page 17, Docking Section: Please include the number of replicates for the animal study. Is n equal to 3?

2

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.

Dear Editor

Thanks a lot for sending the valuable reviewer's comments. I considered all their comments and arranged the text as the suggestions.

Please find the following point related to their comments. All the corrections have been highlighted in the text. I hope you find the new version of manuscript for publication in Iranian Journal of Pharmaceutical Research.

Sincerely Yours

Corresponding Author

Reviewer 1:

No comment

Review 2:

A more discussion was provided in the end of Pharmacology part (4.2).

A new docking study related to the validation study was performed.

The title of paper was changed as the suggestion of reviewer 4.

Reviewer 3:

The text was polished for any and typo and grammatical errors.

All specific comments were considered and the text was corrected.

Additionally; a more detailed rational for designing of compounds was provided and was added to the end part of introduction.

A new docking study related to the validation study was performed and added in the text.

The calculated log P was carried out by software. (Experimental part, general section)

The mortality rate data was added to table 1.

A more discussion about SAR was provided in the end of Pharmacology part.

The number of replicates for the animal study was 6 rats for all groups. (Section 3.3)

Reviewer 4:

1- The title was changed as the comment.
2- The text was polished for any and typo and grammatical errors.
3- The source of the compound was given. (section 3.1)
4- The numbering format was added.
5- (and 6) More details about specific aim and rationality of the work were provided in the end part of introduction.
7- The mentioned sentence was rewritten.
8- (and 9) The required items were provided in section 3.3.
10- The required items were provided in section 4.2.
11- The suggestions were considered and the text was corrected.
12- The quality of figure 2 was increased.
13- The conclusion part was added.

2 Revision 1

0 comments

No public comments in this round.