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Design, Synthesis, and Evaluation of Cytotoxic Effects of Functional Fatty Acid Derivatives as Potential Antineoplastic Agents for Breast Cancer

Maryam Hosseini, Farzad Kobarfard, Salimeh Amidi, Shaya Mokhtari, Anna Sedaghat, Soraya Shahhosseini

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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

2 comments · 5 Feb 2025 – 10 Feb 2025

Referee 1 Reviewer

MAJOR REVISION 5 Feb 2025

Include the EC50 values in the abstract for a comprehensive overview.

Specify the concentration range for each group of materials in the method section.

Justify the selection of the number of cells cultured in 96-well plates for the MTT assay.

Address the omission of toxicity data for compounds L5, L6, and L8 in Table 2. Clarify whether the error rate reported is standard deviation (SD) or standard error of the mean (SEM).

Detail the conditions under which flow cytometry was performed. Confirm whether the same number of cells was studied in Figure 5.

Note that approximately 30% of cells in the control group experienced necrosis, with up to 60% necrosis observed in other groups, as illustrated in Figure 5. The data suggest a combination of necrosis and apoptosis as the cell death mechanisms; thus, interpreting the data using total death rates would be more appropriate.

Enhance the discussion section by comparing your findings with similar studies. Review and reference more relevant literature to strengthen the analysis.

Referee 2 Reviewer

MAJOR REVISION 10 Feb 2025

The present manuscript investigates the design, synthesis, and cytotoxic evaluation of functional fatty acid derivatives as potential antineoplastic agents for breast cancer and aims to develop more potent and selective analogs. The study employs synthetic methods and presents findings that the novel fatty acid derivatives are potent antineoplastic agents. The topic is relevant and aligns well with the journal's scope. Overall, the manuscript needs to be revised and corrected substantially before it can be considered for further assessment. Some of the main concerns are as follows:

1. Provide a more accurate abstract of the manuscript, including its main objectives, methodology, key findings, and significance.

2. Check the manuscript's writing again. There are many grammatical and writing errors in the manuscript.

3. All of the spectral data must be rechecked. Much of the data is missing. For instance, the signals corresponding to NH and OH in D1 are missing from the IR spectral data.
Moreover, there are no CNMR or elemental analysis data.

4. Where is the table of docking scores?

4. The discussion does not adequately compare findings with previous literature. Give us more concise data. Provide a comprehensive structure–activity relationship discussion.

5. Some conclusions are not fully supported by the presented data. Give a more comprehensive and decisive conclusion.

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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.

Dear Editor,

We appreciate you and the reviewers for your precious time in reviewing our manuscript titled "Design, Synthesis, and Evaluation of Cytotoxic Effects of Functional Fatty Acid Derivatives as Potential Antineoplastic Agents for Breast Cancer" and providing valuable comments. It was your valuable and insightful comments that led to possible improvements in the current version. The authors have carefully considered the comments and tried their best to address every one of them. We hope the manuscript after careful revisions meet your high standards.
Below we provide the point-by-point responses. All modifications in the manuscript have been highlighted.

Reviewer 1:
Thank you for your comments. Corrections have been made according to your valuable comments and highlighted in yellow in the revised manuscript.

Comment: The manuscript needs minor corrections (shown in the uploaded relative file).
Response: Corrections have been made.

Reviewer 2:
Thank you for your valuable comments. Corrections have been made according to your valuable comments and highlighted in green in the revised manuscript.

Comment 1: Include the EC50 values in the abstract for a comprehensive overview.
Response: The EC50 values are inserted in the abstract section.

Comment 2: Specify the concentration range for each group of materials in the method section.
Response: In the method section the concentration range for each group of materials is added.

Comment 3: Justify the selection of the number of cells cultured in 96-well plates for MTT assay.
Response: The number of cells was selected as 15,000 according to previous articles and studies and considering the growth rate of existing cells.

Comment 4: Address the omission of toxicity data for compounds L5, L6, and L8 in Table 2. Clarify whether the error rate reported is Standard Deviation (SD) or Standard Error of Mean (SEM).
Response: The compounds in each group were screened and the cut-offs were selected according to the available references: Compounds with less than or equal to 50% viability for both groups were selected to determine EC50. Since compounds L5, L6, and L8 showed higher than 50% viability in the screening, they were not evaluated in the EC50 determination stage. Standard Error (SE) is reported.

Comment 5: Detail the conditions under which flow cytometry was performed. Confirm whether the same number of cells was studied in Figure 5.
Response: After three stages of cell passage in the flask, depending on the cell growth rate, 200,000 cells were seeded in each well of 6-well plates until a total of at least three replicates of each well reached one million cells for analysis with a flow cytometer. Figure 5 is presented as a percentage of mechanisms and is the result of readings of one million cells with the device.

Comment 6: Note that approximately 30% of cells in the control group experienced necrosis, with up to 60% necrosis observed in other groups, as illustrated in Figure 5. The data suggests a combination of necrosis and apoptosis as the cell death mechanisms, thus interpreting the data using total death rates would be more appropriate.
Response: In the text, the meaning of this part was modified by adding additional content.

Comment 7: Enhance the discussion section by comparing your findings with similar studies. Review and reference more relevant literature to strengthen the analysis.
Response: The requested changes were made to the manuscript.

Reviewer 3:
Thank you for your insightful comments on the manuscript. Corrections have been made according to your valuable comments and highlighted in pink in the revised manuscript.

Comment 1: Provide a more accurate abstract of the manuscript, including its main objectives, methodology, key findings, and significance.
Response: The abstract has been revised. Because it was similar to the other reviewers' comments, it was highlighted in other colors

Comment 2: Check the manuscript's writing language again. There are many grammatical and writing errors in the manuscript.
Response: The manuscript has been reviewed, and necessary corrections have been made. Because it was similar to the other reviewers' comments, it was highlighted in other colors.

Comment 3: All of the spectral data must be rechecked. There are many data losses. For instance, the corresponding signals of NH and OH in D1 disappeared from the IR spectral data. Moreover, there is no CNMR, or elemental analysis data.
Response: All spectral data were rechecked, and the corrections were applied to some spectra. In the case of compound D1, the OH peak was added to the assigned section. Elemental analysis has also been added. Due to the identification of the synthesized derivatives by elemental analysis, IR, MASS, and ^{1}H-NMR, and a match to the product structure, the ^{13}C-NMR spectrum was not obtained. All spectra are included in the Supporting Information.

Comment 4: Where is the table of docking scores?!!!
Response: In the manuscript, according to other articles, we preferred to present the results of the two compounds that had better results in the evaluation section, and the Binding affinity of these compounds was added. The requested table has been added in the supporting section.

Comment 5: The discussion does not adequately compare findings with previous literature. Give us more concise data. Provide a comprehensive structure-activity relationship discussion.
Response: In the results and discussion section, changes have been added and highlighted in green color.

Comment 6: Some conclusions are not fully supported by the presented data. Give a more comprehensive and decisive conclusion.
Response: Changes have been made to the text.

Reviewer 4:

Thank you for your insightful comments on the manuscript. Corrections have been made according to your valuable comments. The track changes are followed and the text is reviewed again. The changes are highlighted in blue color in the revised manuscript.

Abstract:
Comment 1: Please avoid mentioning the abbreviations in the abstract.
Response: DHA and LA abbreviation are transformed to the full name.

Comment 2: please add a sentence about synthesized compounds in the method section.
Response: In the abstract method section, a sentence about synthesized compounds is added.

Comment 3: The conclusion section was written poorly.
Response: The conclusion section in the abstract is corrected.

Introduction:
Comment 4: Please add references for lines 3 and 4 of paragraph 4.
Response: The references are added and highlighted in blue color.

Methods:
Comment 5: What is the grade of used solvents?
Response: The synthesis grade solvents were used and mentioned in the text.

Comment 6: In the “General Experimental Approach”, line 6, what do you mean by organic layer? If you mean solvent, please change it to organic solvent or solvent.
Response: The organic layer is changed to the organic solvent in the main text. We separated the two-phase solution obtained in the workup step with a separatory funnel. Then we evaporated the solvent of the organic layer.

Comment 7: In Figure 2, please draw the substrates; in the Figure caption, please explain what L and D are.
Response: Due to the compounds in this reaction having long chains, we did not draw the structures of the reagents. However, appropriate changes have been made in figure 2 for better understanding.

Results and Discussion

Comment 8: in the docking study section, please add the distance of important interactions in the text or Figures 3 and 4.

Response: The distances were placed in the text for each amino acid.

Comment 9: In the docking study, it is suggested that a table of docking scores of synthesized compounds and Cisplatin, as a reference compound, be added.

Response: The docking table was prepared and included in the supporting information section, in the docking section, the DHA compound was the standard, which was also included, and cisplatin was selected as the only standard in the evaluation section according to previous studies on cellular evaluation.

Comment 10: Please discuss the reasons for the effectiveness of compounds L3 and D3.

Response: It is explained in the manuscript.

Conclusion

Comment 11: The conclusion was written poorly. Please re-write this section.

Response: The conclusion was checked and this section has been rewritten.

2 Revision 1

0 comments

No public comments in this round.