Zahedan Journal of Research in Medical Sciences
Volume 28 · Issue 1 · e165680

OPEN PEER REVIEW

Molecular Docking Comparison of Icotinib and Erlotinib as EGFR Inhibitors

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SUBMITTED	REVISED	ACCEPTED	DOI
23 Aug 2025	21 Sep 2025	23 Sep 2025	10.5812/zjrms-165680

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

3 comments · 15 Sep 2025 – 15 Sep 2025

Referee 1 Reviewer

MAJOR REVISION 15 Sep 2025

The abstract lacks key figures. Instead of "the bond becomes stronger", it is necessary to state the exact values of the bond energies (-7.3 and -8.7 kcal/mol).
- Rewrite the abstract to include a summary of the objectives, the main method, the key results (with figures), and the main conclusion.
- The methods section is too brief, and important details are omitted.
- State whether the ligand and receptor structures were minimized before docking.
- The reason for choosing the specific dimensions of the GridBox (50*50*50) and its center location should be explained. Were these parameters chosen based on the position of the crystallized ligand in the 1M17 structure?
- The number of docking runs for each ligand and the criterion for selecting the best pose should be stated (usually several poses are calculated and the pose with the lowest energy is reported).
- To strengthen the results, it is suggested that other analyses such as molecular dynamics (MD) simulations or interaction energy calculations by other methods (MM-GBSA/PBSA) be performed in the future.
- The description of the structural difference between the two drugs ("they differ only in two hydrogen atoms") is incorrect. As is clear from Figure 1 and the chemical formula, Icotinib has an additional ring (furan ring) that results in the removal of two hydrogen atoms and the creation of a larger aromatic system. This is a major structural difference, not simply the removal of two hydrogens.
- Modify this section: "Icotinib has a furan ring that is an open chain in Erlotinib. This structural change could affect the flexibility of the molecule and its interaction pattern with the receptor."
- In Table 1, the list of amino acids in hydrophobic interactions for Icotinib is incomplete and ends with "...". This list should be complete.
- Provide a complete list of amino acids in the table.
- The discussion merely repeats the results and does not provide an in-depth analysis. The main question is: Why does Icotinib have a better binding energy?
- Enrich the discussion by analyzing this question. Does the formation of the ring in Icotinib reduce its flexibility and make it more suitable for active site placement? Could a different pattern of hydrophobic interactions (mentioned in Table 1) be the reason for this energy difference (e.g., interactions with additional amino acids such as Glu738, Thr830, Met742, Val702, Gly772 in the case of Icotinib)? This analysis elevates the article from a report of a number to an analytical study.
- The article contains typographical and grammatical errors (e.g., "AutoDocVina" instead of "AutoDock Vina", "InSilico" instead of "In silico", sometimes inconsistent capitalization of drug names).
- The page numbering and ID at the top of each page are not in order.
- Some sentences are long and need to be rewritten for clarity.
- The article should be carefully edited scientifically and linguistically. Use grammar software such as Grammarly and have it reviewed by a native English speaker. Ensure consistency in writing proper nouns.
- The statement "Please provide a way to send this zip file to the journal" in the Data Availability section is not professional.
- Rewrite this section in a standard way, for example: "The data supporting the findings of this study are available from the corresponding author upon reasonable request."

Associate Editor MAJOR REVISION 15 Sep 2025

Major Revision

Editor-in-Chief MAJOR REVISION 15 Sep 2025

Major Revision

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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.

Manuscript ID: 165680

Manuscript Title: Molecular docking comparison of Icotinib and Erlotinib as EGFR inhibitors

Dear Dr Saeedeh Yaghoubi

Associate Editor Manager

Zahedan Journal of Research in Medical Sciences

I want to thank the reviewers for their careful evaluation of the manuscript and their constructive critiques. I have revised the manuscript according to the reviewers' comments. Below is my point-by-point response to the reviewers' critiques/suggestions: Modified items in the article are highlighted in green.

Reviewer #1:

Question 1:

The abstract lacks key figures. Instead of "the bond becomes stronger", it is necessary to state the exact values of the bond energies (-7.3 and -8.7 kcal/mol).

Response 1:

Thanks for mentioning this important point about presenting results in the abstract. These points have been corrected in the abstract.

Question 2:

- Rewrite the abstract to include the objectives in summary, the main method, the key results (with figures), and the main conclusion.

Response 2:

Thank you for evaluating the Abstract and essential points. The points mentioned have been completely corrected.

Question 3:

- The methods section is too brief, and important details are omitted and not written.

Response 3:

Thank you for evaluating the method section. Based on your valuable suggestion, the method section has been rewritten with more details.

Question 4:

- State whether the ligand and receptor structures were minimized before docking.

Response 4:

Ligand and receptor minimization was not performed for this study.

Question 5:

- The reason for choosing the specific dimensions of the GridBox (50*50*50) and its center location should be explained. Were these parameters chosen based on the position of the crystallized ligand in the 1M17 structure?

Response 5:

The coordinates of the center of the Grid Box and the size of the Grid Box dimension were determined using the crystallization site of the erlotinib ligand in the PDB file in 1M17 (receptor). These items were added in the method section.

Question 6:

- The number of docking runs for each ligand and the criterion for selecting the best pose should be stated (usually several poses are calculated and the pose with the lowest energy is reported).

Response 6:

In this study, AutoDock Vina was configured to perform eight independent docking runs for each ligand. the pose with the strongest predicted binding affinity reported in this study reflects the optimal ligand-receptor interaction identified through these repeated docking simulations.

These items were also rewritten in the method section.

Question 7:

- To strengthen the results, it is suggested that other analyses, such as molecular dynamics (MD) simulations or interaction

energy calculations by other methods (MM-GBSA/PBSA) be performed in the future.

Response 7:

I appreciated the valuable suggestion on improving docking studies. As a researcher, I will definitely use your valuable suggestions in future studies.

Question 8:

- The description of the structural difference between the two drugs ("they differ only in two hydrogen atoms") is incorrect. As is clear from Figure 1 and the chemical formula, Icotinib has an additional ring (furan ring) that results in the removal of two hydrogen atoms and the creation of a larger aromatic system. This is a major structural difference, not simply the removal of two hydrogens.

Response 8:

Thanks for evaluating the results section. The mentioned section has been removed and replaced with the following:

The key structural features of icotinib include a quinazoline core similar to erlotinib but with a distinctive closed-ring side chain, which contributes to its unique pharmacological properties such as enhanced hydrophobicity. In contrast, erlotinib also contains the quinazoline core but features an open side chain, which affects its binding and pharmacokinetic profile differently. These differences in side-chain structure are crucial in defining their respective interaction with the epidermal growth factor receptor and influence their effectiveness and drug behaviours(13-16).

Question 9:

- Modify this section: "Icotinib has a furan ring that is an open chain in Erlotinib. This structural change could affect the flexibility of the molecule and its interaction pattern with the receptor."

Response 9:

This section was modified simultaneously with the modification of the sentence mentioned in the previous question.

The key structural features of icotinib include a quinazoline core similar to erlotinib but with a distinctive closed-ring side chain, which contributes to its unique pharmacological properties such as enhanced hydrophobicity. In contrast, erlotinib also contains the quinazoline core but features an open side chain, which affects its binding and pharmacokinetic profile differently. These differences in side-chain structure are crucial in defining their respective interaction with the epidermal growth factor receptor and influence their effectiveness and drug behaviours(13-16).

Question10:

- In Table 1, the list of amino acids in hydrophobic interactions for Icotinib is incomplete and ends with "...". This list should be complete.

Response 10:

According to the results of the analysis of the ligand binding site with the receptor, all the hydrophobic bonds involved in the binding of ligands to the receptor are listed in Table 1. According

to this table, erlotinib and Icotinib have established hydrophobic bonds with 11 and 12 amino acids, respectively. All these cases are also modified in the results section.

Question11:

- Provide a complete list of amino acids in the table.

Response 11:

According to the results of the analysis of the ligand binding site with the receptor, all the hydrophobic bonds involved in the binding of ligands to the receptor are listed in Table 1. According to this table, erlotinib and Icotinib have established hydrophobic bonds with 11 and 12 amino acids, respectively. All these cases are also modified in the results section.

Question12:

- The discussion merely repeats the results and does not provide an in-depth analysis. The main question is: Why does Icotinib have a better binding energy?

Response 12:

All the mentioned duplicate parts were removed, and the text of the discussion was rewritten.

One plausible explanation for this superior binding affinity is the increased number of hydrophobic interactions that icotinib forms (twelve residues) relative to erlotinib (eleven residues). Structural analysis attributes this to the presence of a 12-crown-4 cycle in icotinib's molecular structure, which stabilizes its engagement with the receptor kinase domain.

Another contributing factor to the superior binding affinity of icotinib compared to erlotinib could be the distinct types of amino acid residues with which icotinib interacts within the EGFR active site. As depicted in Figure 4, icotinib establishes hydrophobic interactions with several amino acids, specifically Glu738, Thr830, Met742, and Gly772, that are not involved in erlotinib’s interaction profile. These unique contacts may enhance icotinib’s binding stability and contribute to its stronger overall affinity for EGFR.

This observation aligns with previous reports showing that minor chemical modifications can significantly alter the binding interactions and affinities of tyrosine kinase inhibitors, influencing both their potency and selectivity profiles.

The cumulative effect of these interactions potentially translates into increased efficacy in inhibiting EGFR-driven oncogenic signalling pathways.

Question13:

- Enrich the discussion by analyzing this question. Does the formation of the ring in Icotinib reduce its flexibility and make it more suitable for active site placement? Could a different pattern of hydrophobic interactions (mentioned in Table 1) be the reason for this energy difference? (e.g., interactions with additional amino acids such as Glu738, Thr830, Met742, Val702, Gly772 in

the case of Icotinib). This analysis elevates the article from a report of a number to an analytical study.

Response 13:

I appreciate your valuable suggestions. The points you mentioned were implemented in the discussion section.

Question14:

- The article contains typographical and grammatical errors (e.g., "AutoDocVina" instead of "AutoDock Vina", "InSilico" instead of "In silico", sometimes inconsistent capitalization of drug names).

Response 14:

Thank you for reviewing and pointing out these errors. All typographical and grammatical errors have been corrected in the revised file.

Question15:

- The page numbering and ID at the top of each page are not in order.

Response 15:

Page numbering has been corrected in the new revised file.

Question16:

- Some sentences are long and need to be rewritten for clarity.

Long sentences were rewritten and modified to be more understandable in the revised file.

Question17:

- The article should be carefully edited scientifically and linguistically. Use grammar software such as Grammarly and have it reviewed by a native English speaker. Ensure consistency in writing proper nouns.

Response 17:

Based on valuable suggestions, linguistic and grammatical errors and mistakes were corrected using Grammarly software.

Question 18:

- The statement "Please provide a way to send this zip file to the journal" in the Data Availability section is not professional.

- Rewrite this section in a standard way, for example: "The data supporting the findings of this study are available from the corresponding author upon reasonable request."

Response 18:

I appreciate your valuable suggestion regarding the correction of this sentence. This sentence has been corrected according to the suggestion provided.

2 Revision 1

2 comments · 23 Sep 2025 – 23 Sep 2025

Associate Editor

ACCEPT 23 Sep 2025

- The exact binding energy values (-7.3 and -8.7 kcal/mol) have been added.
- The abstract structure has been improved to include the objectives, methods, key results and conclusions.
- More details have been added (e.g., how to determine the GridBox, number of docking runs, criteria for selecting the best pose).
- It has been explained that the GridBox coordinates were chosen based on the crystal structure of Erlotinib in PDB:1M17.
- The previous incorrect description ("only two hydrogen atoms differ") has been removed and a more detailed explanation of the structural differences (furan ring in Icotinib vs. open chain in Erlotinib) has been provided.
- The full list of amino acids for both ligands has been provided (11 for Erlotinib and 12 for Icotinib).
- The discussion is no longer a mere repetition of the results; a good analysis of the possible reasons for the superior binding energy of Icotinib is provided (more hydrophobic interactions, unique amino acids like Glu738, Thr830, etc.).
- Spelling and grammar errors have been corrected (e.g., AutoDock Vina instead of AutoDocVina).
- Long sentences have been rewritten.
- The author explicitly states that the minimization was not performed on the ligand and receptor. This could be a methodological weakness, but is acceptable if the goal is to directly compare the two ligands and both are processed under the same conditions.
- Although the discussion has been improved, the role of the "reduced flexibility due to looping" in Icotinib and its impact on active site occupancy could still be addressed. This section could be even stronger.
- Molecular dynamics (MD) simulations or energy calculations (MM-GBSA/PBSA):
- The author admits that these analyses were not performed, but promises that they will be included in future studies. This is a reasonable limitation for a basic docking paper.

Overall, the paper has been significantly improved and most of the serious shortcomings have been addressed.
The author has responded well to the comments of the reviewers and has made significant changes to the structure, content, and writing.
Although some methodological limitations remain, the paper as a whole now appears more scientifically and linguistically acceptable.

Editor-in-Chief

ACCEPT 23 Sep 2025

Accept