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Synthesis and In-Vivo Evaluation of Benzoxazole Derivatives as Promising Anti-Psoriatic Drugs for Clinical Use

Authored by:

Rami Ayoub; Jamal Jilani; Qais Jarrar; Raad Alani; Chrismawan Ardianto; Khang Wen Goh; Dalia Ali; Said Moshawih

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Article Information Overview

Manuscript ID	**molecules-1655347**
Status	Website online
DOI	10.3390/molecules27093023
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Article type	Article
Title	Synthesis and In-Vivo Evaluation of Benzoxazole Derivatives as Promising Anti-Psoriatic Drugs for Clinical Use
Journal	*Molecules* (https://www.mdpi.com/journal/molecules)
Volume	27
Issue	9
Section	Medicinal Chemistry (https://www.mdpi.com/journal/molecules/sections/medicinal_chemistry)
Special Issue	Biofunctional Molecule Exploratory Research on Application in Food and Health (https://www.mdpi.com/journal/molecules/special_issues/Bio_food_health)
Abstract	2-(4-Chlorophenyl)-5-benzoxazoleacetic acid (CBA) and its ester, methyl-2-(4-chloro-phenyl)-5-benzoxazoleacetate (MCBA), were synthesized, and their structures were confirmed by ^{1}HNMR, IR, and mass spectrophotometry. The anti-psoriatic activities of CBA and MCBA were tested using an imiquimod (IMQ)-induced psoriatic mouse model, in which mice were treated both topically (1% *w/w*) and orally (125 mg/kg) for 14 days. The erythema intensity, thickness, and desquamation of psoriasis were scored by calculating the psoriasis area severity index (PASI). The study also included the determination of histopathological alterations in the skin tissues of treated mice. Topical and oral administration of CBA and MCBA led to a reduction in erythema intensity, thickness, and desquamation, which was demonstrated by a significant decrease in the PASI value. In addition, skin tissues of mice treated with CBA and MCBA showed less evidence of psoriatic alterations, such as hyperkeratosis, parakeratosis, scale crust, edema, psoriasiform, and hyperplasia. After administration of either topical or oral dosing, the anti-psoriatic effects were found to be stronger in MCBA-treated than in CBA-treated mice. These effects were comparable to those produced by Clobetasol propionate, the reference drug. This drug discovery could be translated into a potential new drug for future clinical use in psoriasis treatment.
Keywords	synthesis; arylbenzoxazole; psoriasis; imiquimod; in vivo; prodrug

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Editor Decision

Decision	Accept after minor revision
Comments	The authors should correct the molecular formula of both compounds in page#9 including one hydrogen because is [M+H]+: where says "C16H12ClNO3 [M+H]+" should say "C16H13ClNO3 [M+H]+" where says "C15H10ClNO3 [M+H]+" should say "C15H11ClNO3 [M+H]+"
Decision Date	4 May 2022

Review Report

Reviewer 1	Review Report (Round 1) (/user/manuscripts/review/25360784?report=18383722) Review Report (Round 2) (/user/manuscripts/review/25360784?report=19279311)
Reviewer 2	Review Report (Round 1) (/user/manuscripts/review/25506214?report=18511677) Review Report (Round 2) (/user/manuscripts/review/25506214?report=19279318)

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Previously Published Papers

Khotib, J.; Gani, M.A.; Budiatin, A.S.; Lestari, M.L.A.D.; Rahadiansyah, E.; Ardianto, C. Signaling Pathway and Transcriptional Regulation in Osteoblasts during Bone Healing: Direct Involvement of Hydroxyapatite as a Biomaterial. *Pharmaceuticals* **2021**, *14*, 615. doi: 10.3390/ph14070615 (https://doi.org/10.3390/ph14070615)

Gani, M.A.; Budiatin, A.S.; Lestari, M.L.A.D.; Rantam, F.A.; Ardianto, C.; Khotib, J. Fabrication and Characterization of Submicron-Scale Bovine Hydroxyapatite: A Top-Down Approach for a Natural Biomaterial. *Materials* **2022**, *15*, 2324. doi: 10.3390/ma15062324 (https://doi.org/10.3390/ma15062324)

Khirfan, F.; Jarrar, Y.; Al-Qirim, T.; Goh, K.W.; Jarrar, Q.; Ardianto, C.; Awad, M.; Al-Ameer, H.J.; Al-Awaida, W.; Moshawih, S.; Ming, L.C. Analgesics Induce Alterations in the Expression of SARS-CoV-2 Entry and Arachidonic-Acid-Metabolizing Genes in the Mouse Lungs. *Pharmaceuticals* **2022**, *15*, 696. doi: 10.3390/ph15060696 (https://doi.org/10.3390/ph15060696)

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Lai, N.J.-Y.; Ngu, E.-L.; Pang, J.-R.; Wong, K.-H.; Ardianto, C.; Ming, L.C.; Lim, S.-H.; Walvekar, S.G.; Anwar, A.; Yow, Y.-Y. Carrageenophyte *Kappaphycus malesianus* Inhibits Microglia-Mediated Neuroinflammation via Suppression of AKT/NF-*κ*B and ERK Signaling Pathways. *Mar. Drugs* **2022**, *20*, 534. doi: 10.3390/md20080534 (https://doi.org/10.3390/md20080534)

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Ling, S.P.; Ming, L.C.; Dhaliwal, J.S.; Gupta, M.; Ardianto, C.; Goh, K.W.; Hussain, Z.; Shafqat, N. Role of Immunotherapy in the Treatment of Cancer: A Systematic Review. *Cancers* **2022**, *14*, 5205. doi: 10.3390/cancers14215205 (https://doi.org/10.3390/cancers14215205)

Budiatin, A.S.; Khotib, J.; Samirah, S.; Ardianto, C.; Gani, M.A.; Putri, B.R.K.H.; Arofik, H.; Sadiwa, R.N.; Lestari, I.; Pratama, Y.A.; Rahadiansyah, E.; Susilo, I. Acceleration of Bone Fracture Healing through the Use of Bovine Hydroxyapatite or Calcium Lactate Oral and Implant Bovine Hydroxyapatite–Gelatin on Bone Defect Animal Model. *Polymers* **2022**, *14*, 4812. doi: 10.3390/polym14224812 (https://doi.org/10.3390/polym14224812)

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Khan, F.B.; Singh, P.; Jamous, Y.F.; Ali, S.A.; Abdullah; Uddin, S.; Zia, Q.; Jena, M.K.; Khan, M.; Owais, M.; Huang, C.Y.; Chanukuppa, V.; Ardianto, C.; Ming, L.C.; Alam, W.; Khan, H.; Ayoub, M.A. Multifaceted Pharmacological Potentials of Curcumin, Genistein, and Tanshinone IIA through Proteomic Approaches: An In-Depth Review. *Cancers* **2023**, *15*, 249. doi: 10.3390/cancers15010249 (https://doi.org/10.3390/cancers15010249)

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Kocsis, D.; Horváth, S.; Kemény, Á.; Varga-Medveczky, Z.; Pongor, C.; Molnár, R.; Mihály, A.; Farkas, D.; Naszlady, B.M.; Fülöp, A.; Horváth, A.; Rózsa, B.; Pintér, E.; Gyulai, R.; Erdő, F. Drug Delivery through the Psoriatic Epidermal Barrier—A “Skin-On-A-Chip” Permeability Study and Ex Vivo Optical Imaging. *Int. J. Mol. Sci.* **2022**, *23*, 4237. doi: 10.3390/ijms23084237 (https://doi.org/10.3390/ijms23084237)

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Journal: Molecules (https://www.mdpi.com/journal/molecules) (ISSN 1420-3049)
Manuscript ID: molecules-1655347
Type: Article

Title: Synthesis and In-vivo Evaluation of Benzoxazole Derivatives as Promising Anti-Psoriatic Drugs (https://www.mdpi.com/1420-3049/27/9/3023)

Authors: Rami Ayoub * , Jamal Jilani , Qais Jarrar , Raad Alani , Chrismawan Ardianto * , Khang Wen Goh * , Dalia Ali , Said Moshawih

Section: Medicinal Chemistry (https://www.mdpi.com/journal/molecules/sections/medicinal_chemistry)
Special Issue: Biofunctional Molecule Exploratory Research on Application in Food and Health (https://www.mdpi.com/journal/molecules/special_issues/Bio_food_health)

Abstract: Benzoxazole derivatives are aromatic nitrogen compounds possessing a variety of pharmacological properties, including analgesic, anti-inflammatory, and immunosuppressive. However, anti-psoriatic effects of these compounds have not been yet investigated. In this study, novel benzoxazole derivatives, including 2-(2-(4-chlorophenyl) benzoxazol-5-yl) acetic acid (CBA) and its ester, methyl 2-(2-(4-chlorophenyl) benzoxazol-5-yl) acetate (MCBA) were synthesized, and their anti-psoriatic effects in mice were evaluated. The anti-psoriatic activities of CBA and MCBA were tested using an imiquimod (IMQ)-induced psoriatic mouse model in which mice were treated both topically (1% w/w) and orally (125 mg/kg) for 14 days. The erythema intensity, thickness, and desquamation of psoriasis was scored by calculating Psoriasis Area Severity Index (PASI). The study also included the determination of histopathological alterations on the skin tissues of treated mice. Topical and oral administration of CBA and MCBA led to a reduction in erythema intensity, thickness, and desquamation, which was demonstrated by a significant decrease of PASI values. In addition, skin tissues of mice treated with CBA and MCBA showed less evidence of psoriatic alterations, such as hyperkeratosis, parakeratosis, scale crust, edema, psoriasiform, and hyperplasia. After administration of either topical or oral dosing, the anti-psoriatic effects were found to be stronger in MCBA-treated than in CBA-treated mice. These effects were comparable to that produced by Clobetasol propionate (Clob), the reference drug. CBA and MCBA may be promising drugs for treating psoriasis disorders. However, more research is needed to support these results.

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Authors' Responses to Reviewer's Comments (Reviewer 1)

Author's Notes

Dear reviwer,

" Synthesis and In-vivo Evaluation of Benzoxazole Derivatives as Promising Anti-Psoriatic Drugs ".

Manuscript ID: molecules-1655347

Thank you for your email of March 29, 2022 informing me that the above manuscript needs revisions. We (the authors) did revise the manuscript according to the reviewer comments. Herein our response to the Reviewers comments:

Reviewer A - Comments

Comment 1: The abstract should be shortened (max 200 words, see rules of journal).

The answer: Thank you for your comment. We have revised the abstract as suggested. (Line 18-31)

Comment 2: The choice of a chemical route for the preparation of two benzoxazole derivatives should be explained based on an analysis of the relevant references and presented in the "Discussion" section.

The answer: **This is an excellent suggestion.** The chemical route for the preparation of two benzoxazole derivatives are included in the "Discussion" section in the revised manuscript. (Line 128-163)

Comment 3: A description of the synthesis of two benzoxazole derivatives should also be presented at the beginning of the "Results" section.

The answer: Yes, we agree with you. A description of the synthesis of two benzoxazole derivatives are included at the "Results" section in the revised manuscript. (Line 68-79)

Comment 4: CBA is known compound (Journal of Medicinal Chemistry (1975), 18(1), 53-8; DE2324443 A1 1973; DE2449990 A1 1975; Synthetic Communications (1985), 15(12), 1075-80) and the relevant references should be added and discussed in the "Discussion" section.

The answer: Thank you for your comment. You can refer to the corrected part as indicated. (Line 135)

Comment 5: Authors should once again carefully check the references in accordance with the examples reference style.

The answer: We appreciate your kind suggestion. All references have been crossed checked now.

Review Report Form

Quality of English Language
( ) English very difficult to understand/incomprehensible
( ) Extensive editing of English language and style required
( ) Moderate English changes required
( ) English language and style are fine/minor spell check required
(x) I am not qualified to assess the quality of English in this paper

	Yes	Can be improved	Must be improved	Not applicable
Does the introduction provide sufficient background and include all relevant references?	( )	( )	(x)	( )
Is the research design appropriate?	( )	( )	(x)	( )
Are the methods adequately described?	( )	(x)	( )	( )
Are the results clearly presented?	( )	(x)	( )	( )
Are the conclusions supported by the results?	( )	(x)	( )	( )

Comments and Suggestions for Authors

The manuscript entitled “Synthesis and In-vivo Evaluation of Benzoxazole Derivatives as Promising Anti-Psoriatic Drugs” by Rami Ayoub et al. described an approach for the synthesis of two benzoxazole derivatives and study their anti-psoriatic activity. The manuscript may be of general interest to the researchers of this field, but the manuscript lacks some information that the author should consider and incorporate in the present form of the manuscript. Here are a few concerns that need to be addressed in the present form of the manuscript.

1. The abstract should be shortened (max 200 words, see rules of journal).
2. The choice of a chemical route for the preparation of two benzoxazole derivatives should be explained based on an analysis of the relevant references and presented in the "Discussion" section.
3. A description of the synthesis of two benzoxazole derivatives should also be presented at the beginning of the "Results" section.
4. CBA is known compound (Journal of Medicinal Chemistry (1975), 18(1), 53-8; DE2324443 A1 1973; DE2449990 A1 1975; Synthetic Communications (1985), 15(12), 1075-80) and the relevant references should be added and discussed in the "Discussion" section.
5. Authors should once again carefully check the references in accordance with the examples reference style.

Submission Date 11 March 2022

Date of this review 14 Mar 2022 12:26:21

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Authors: Rami Ayoub * , Jamal Jilani , Qais Jarrar , Raad Alani , Chrismawan Ardianto * , Khang Wen Goh * , Dalia Ali , Said Moshawih

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Special Issue: Biofunctional Molecule Exploratory Research on Application in Food and Health (https://www.mdpi.com/journal/molecules/special_issues/Bio_food_health)

Abstract: Benzoxazole derivatives are aromatic nitrogen compounds possessing a variety of pharmacological properties, including analgesic, anti-inflammatory, and immunosuppressive. However, anti-psoriatic effects of these compounds have not been yet investigated. In this study, novel benzoxazole derivatives, including 2-(2-(4-chlorophenyl) benzoxazol-5-yl) acetic acid (CBA) and its ester, methyl 2-(2-(4-chlorophenyl) benzoxazol-5-yl) acetate (MCBA) were synthesized, and their anti-psoriatic effects in mice were evaluated. The anti-psoriatic activities of CBA and MCBA were tested using an imiquimod (IMQ)-induced psoriatic mouse model in which mice were treated both topically (1% w/w) and orally (125 mg/kg) for 14 days. The erythema intensity, thickness, and desquamation of psoriasis was scored by calculating Psoriasis Area Severity Index (PASI). The study also included the determination of histopathological alterations on the skin tissues of treated mice. Topical and oral administration of CBA and MCBA led to a reduction in erythema intensity, thickness, and desquamation, which was demonstrated by a significant decrease of PASI values. In addition, skin tissues of mice treated with CBA and MCBA showed less evidence of psoriatic alterations, such as hyperkeratosis, parakeratosis, scale crust, edema, psoriasiform, and hyperplasia. After administration of either topical or oral dosing, the anti-psoriatic effects were found to be stronger in MCBA-treated than in CBA-treated mice. These effects were comparable to that produced by Clobetasol propionate (Clob), the reference drug. CBA and MCBA may be promising drugs for treating psoriasis disorders. However, more research is needed to support these results.

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Authors' Responses to Reviewer's Comments (Reviewer 1)

Author's Notes

Dear Reviewer,

Thank you for your endorsement of our revised manuscript. Much appreciation.

Review Report Form

Quality of English Language

( ) English very difficult to understand/incomprehensible
( ) Extensive editing of English language and style required
( ) Moderate English changes required
( ) English language and style are fine/minor spell check required
(x) I am not qualified to assess the quality of English in this paper

	Yes	Can be improved	Must be improved	Not applicable
Does the introduction provide sufficient background and include all relevant references?	( )	(x)	( )	( )
Are all the cited references relevant to the research?	( )	(x)	( )	( )
Is the research design appropriate?	( )	(x)	( )	( )
Are the methods adequately described?	( )	(x)	( )	( )
Are the results clearly presented?	( )	(x)	( )	( )
Are the conclusions supported by the results?	( )	(x)	( )	( )

Comments and Suggestions for Authors

Dear colleagues,

many thanks for your respond to the suggestions from my side. I agree with your answers.

Submission Date 11 March 2022
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Section: Medicinal Chemistry (https://www.mdpi.com/journal/molecules/sections/medicinal_chemistry)
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Authors' Responses to Reviewer's Comments (Reviewer 2)

Author's Notes

Dear Editor,

" Synthesis and In-vivo Evaluation of Benzoxazole Derivatives as Promising Anti-Psoriatic Drugs ".

Manuscript ID: molecules-1655347

Thank you for your email of March 29, 2022 informing me that the above manuscript needs revisions. We (the authors) did revise the manuscript according to the reviewer comments. Herein our response to the Reviewers comments:

Reviewer B- Comments

Comment 1: The English language needs revising. The compounds characterization is very poor and needs more solid evidence

The Answer: We appreciate your kind suggestion. The English language was revised, and the compounds characterization was discussed in details in the revised manuscript.

Comment 2: Row 43 references should be expressed as [2, 3] instead of [2], [3]

The Answer: Thank you for your suggestion. We have revised it now. (Line 39)

Comment 3: Row 55 references the same -> [10-12]

The Answer: Thank you for your suggestion. We have revised it now. (Line 51)

Comment 4: Row 57 references [3, 13, 14]

The answer: Thank you for your suggestion. We have revised it now. (Line 53)

Comment 5: Row 62 remove the bracket before the reference

The answer: The bracket was removed as seen in the revised manuscript. Thank you for pointing it out (Line 57)

Comment 6: Row 124 [24], [25] -> [24, 25]

The answer: Thank you for your suggestion. We have revised it now. (Line 135)

Comment 7: Row 180 please correct 1H to ^{1}H (superscript)

The answer: It was corrected accordingly. Thank you (Line 220)

Comment 8: Row 184 Please give the full name of the compound and then give in brackets the abbreviation - methyl 2-(2-(4-chlorophenyl)benzo[d]oxazol-5-yl)acetate (MCBA)

The answer: Thank you for your suggestion. We have revised it now. (Line 224)

Comment 9: Row 185-196 Please make sure you correct all numbers in the molecular formulas to subscript and superscript where necessary.

The answer: The numbers of molecular formulas were corrected in the revise manuscript. Thank you for your suggestions (Line 225-236)

Comment 10: ^{1}H NMR is not described correctly. Please give the frequency at which the spectrum is recorded, next to the solvent used. In addition, the J constant is missing. Moreover, the aromatic protons are seven at the structure, but eight in the description. Could you please explain this extra proton?

The answer: Excellent points. The frequency and J constant are included in the revised manuscript. In addition, the description of aromatic protons was corrected. (Line 234-236)

Comment 11: The information for the MS analysis is missing in general. What apparatus? What source of ionization? The MS result is not accurate enough. See example: HR-MS ESI: calc. for $[C_{22}H_{16}N_4 + H]^+$ 337.14477, found 337.14436. Then calculate the mass error in ppm.

The answer: The missing data are included in revised manuscript and MS results are presented with more details in the revised manuscript as indicated by the reviewer. We are grateful for your comments (Line 236)

Comment 12: In Figure 4 please add the reaction conditions, and rename the title as Synthesis of MCBA

The answer: The reaction conditions were added in Figure 4 and the title was renamed as indicated. (Please see scheme 1) (Line 74)

Comment 13: Row 200 Please give the full name of the synthesized compound: 2-(2-(4-chlorophenyl)benzo[d]oxazol-5-yl)acetic acid (CBA)

The answer: Thank you for your suggestion. We have revised it now. (Line 237)

Comment 14: Row 201-209 Please make sure you correct all numbers in the molecular formulas to subscript and superscript where necessary.

The answer: Thank you. All numbers in the molecular formulas were corrected as seen as revised manuscript. (Line 238-247)

Comment 15: ^{1}H NMR is not described correctly. Its looks like a mess. Please check the journal requirements for NMR interpretation and correct them. Please give the frequency at which the spectrum is recorded, next to the solvent used. In addition, the J constants are missing again. Also, three of the protons are missing. Your product has 10 hydrogen atoms and only seven are described**.**

The answer: The frequency and J constant are included in the revised manuscript. In addition, the description of aromatic protons was corrected. Thank you for the kind comment. (Line 224-246)

Comment 16: The MS here is the same: please see the upper comment for the MS analysis**.**

The answer Thank you for the kind comment.: The missing information for the MS analysis of CBA are included in revised manuscript and MS results are presented with more details as indicated by the reviewer. (Line 246)

Comment 17: The IR also needs clarification. Please check on the journal's recommendations for IR interpretation and presenting**.**

The answer: Thank you for the kind comment.FTIR analysis are clarified in the revised manuscript. (Line 233, 243, 244)

Comment 18: In figure 5 please change the title: Synthesis of CBA

The answer: The title of Figure 5 was renamed as seen in the revised manuscript. (Please see scheme 2) Thank you for the kind comment. (Line 79)

Review Report Form

Quality of English Language

( ) English very difficult to understand/incomprehensible
( ) Extensive editing of English language and style required
(x) Moderate English changes required
( ) English language and style are fine/minor spell check required
( ) I am not qualified to assess the quality of English in this paper

	Yes	Can be improved	Must be improved	Not applicable
Does the introduction provide sufficient background and include all relevant references?	( )	(x)	( )	( )
Is the research design appropriate?	( )	(x)	( )	( )
Are the methods adequately described?	( )	( )	(x)	( )
Are the results clearly presented?	( )	( )	(x)	( )
Are the conclusions supported by the results?	( )	(x)	( )	( )

Comments and Suggestions for Authors

The presented manuscript “Synthesis and In-vivo Evaluation of Benzoxazole Derivatives as Promising Anti-Psoriatic Drugs” describes the in vivo results of two known compounds obtained, using old and known procedures, but are interesting in order to be found new psoriatic drugs for psoriasis treatment.

The English language needs revising. The compounds characterization is very poor and needs more solid evidence.

The manuscript needs major revision.

Here are some comments and suggestions that need to be taken into account:

Row 43 references should be expressed as [2, 3] instead of [2], [3]

Row 55 references the same -> [10-12]

Row 57 references [3, 13, 14]

Row 62 remove the bracket before the reference

Row 124 [24], [25] -> [24, 25]

Row 180 please correct 1H to ^{1}H (superscript)

Row 184 Please give the full name of the compound and then give in brackets the abbreviation - methyl 2-(2-(4-chlorophenyl)benzo[d]oxazol-5-yl)acetate (MCBA)

Row 185-196 Please make sure you correct all numbers in the molecular formulas to subscript and superscript where necessary.

^{1}H NMR is not described correctly. Please give the frequency at which the spectrum is recorded, next to the solvent used. In addition, the J constant is missing. Moreover, the aromatic protons are seven at the structure, but eight in the description. Could you please explain this extra proton?

The information for the MS analysis is missing in general. What apparatus? What source of ionization? The MS result is not accurate enough. See example: HR-MS ESI: calc. for $[C_{22}H_{16}N_4 + H]^+$ 337.14477, found 337.14436. Then calculate the mass error in ppm.

In Figure 4 please add the reaction conditions, and rename the title as Synthesis of MCBA

Row 200 Please give the full name of the synthesized compound: 2-(2-(4-chlorophenyl)benzo[d]oxazol-5-yl)acetic acid (CBA)

Row 201-209 Please make sure you correct all numbers in the molecular formulas to subscript and superscript where necessary.

^{1}H NMR is not described correctly. Its looks like a mess. Please check the journal requirements for NMR interpretation and correct them. Please give the frequency at which the spectrum is recorded, next to the solvent used. In addition, the J constants are missing again…Also three of the protons are missing. Your product has 10 hydrogen atoms and only seven are described.

The MS here is the same: please see the upper comment for the MS analysis.

The IR also needs clarification. Please check on the journal's recommendations for IR interpretation and presenting.

In figure 5 please change the title: Synthesis of CBA

Submission Date	11 March 2022
Date of this review	26 Mar 2022 13:04:06

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Journal: Molecules (https://www.mdpi.com/journal/molecules) (ISSN 1420-3049)
Manuscript ID: molecules-1655347
Type: Article

Title: Synthesis and In-vivo Evaluation of Benzoxazole Derivatives as Promising Anti-Psoriatic Drugs (https://www.mdpi.com/1420-3049/27/9/3023)

Authors: Rami Ayoub * , Jamal Jilani , Qais Jarrar , Raad Alani , Chrismawan Ardianto * , Khang Wen Goh * , Dalia Ali , Said Moshawih

Section: Medicinal Chemistry (https://www.mdpi.com/journal/molecules/sections/medicinal_chemistry)
Special Issue: Biofunctional Molecule Exploratory Research on Application in Food and Health (https://www.mdpi.com/journal/molecules/special_issues/Bio_food_health)

Abstract: Benzoxazole derivatives are aromatic nitrogen compounds possessing a variety of pharmacological properties, including analgesic, anti-inflammatory, and immunosuppressive. However, anti-psoriatic effects of these compounds have not been yet investigated. In this study, novel benzoxazole derivatives, including 2-(2-(4-chlorophenyl) benzoxazol-5-yl) acetic acid (CBA) and its ester, methyl 2-(2-(4-chlorophenyl) benzoxazol-5-yl) acetate (MCBA) were synthesized, and their anti-psoriatic effects in mice were evaluated. The anti-psoriatic activities of CBA and MCBA were tested using an imiquimod (IMQ)-induced psoriatic mouse model in which mice were treated both topically (1% w/w) and orally (125 mg/kg) for 14 days. The erythema intensity, thickness, and desquamation of psoriasis was scored by calculating Psoriasis Area Severity Index (PASI). The study also included the determination of histopathological alterations on the skin tissues of treated mice. Topical and oral administration of CBA and MCBA led to a reduction in erythema intensity, thickness, and desquamation, which was demonstrated by a significant decrease of PASI values. In addition, skin tissues of mice treated with CBA and MCBA showed less evidence of psoriatic alterations, such as hyperkeratosis, parakeratosis, scale crust, edema, psoriasiform, and hyperplasia. After administration of either topical or oral dosing, the anti-psoriatic effects were found to be stronger in MCBA-treated than in CBA-treated mice. These effects were comparable to that produced by Clobetasol propionate (Clob), the reference drug. CBA and MCBA may be promising drugs for treating psoriasis disorders. However, more research is needed to support these results.

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Authors' Responses to Reviewer's Comments (Reviewer 2)

Author's Notes: Dear reviewer

Pls see attached. Thank you so much for your suggestions, it really improved the standard of the paper.

Appreciate it!

Author's Notes File: Report Notes (/user/review/displayFile/25506214/VQ39WO4X?file=author-coverletter&report=19279318)

Review Report Form

Quality of English Language
( ) English very difficult to understand/incomprehensible
( ) Extensive editing of English language and style required
( ) Moderate English changes required
(x) English language and style are fine/minor spell check required
( ) I am not qualified to assess the quality of English in this paper

	Yes	Can be improved	Must be improved	Not applicable
Does the introduction provide sufficient background and include all relevant references?	(x)	( )	( )	( )
Are all the cited references relevant to the research?	(x)	( )	( )	( )
Is the research design appropriate?	(x)	( )	( )	( )
Are the methods adequately described?	(x)	( )	( )	( )
Are the results clearly presented?	(x)	( )	( )	( )

Are the conclusions supported by the results?	(x)	( )	( )	( )

Comments and Suggestions for Authors	Dear Authors, thank you for providing the revised version of your manuscript. I have carefully examined your revised version and I see that you have taken into account all my suggestions. Now your manuscript looks much better. One thing I would like you to correct is the MS data for both compounds. As you give [M+H]+ result please write down the correct mass. Also for the second compound (the acid), the molecular formula does not match the molecular weight (row 245). I suppose you copied the formula for the above and you didn't change it. Please correct the molecular formula. Kind Regards,
Submission Date	11 March 2022
Date of this review	26 Apr 2022 17:24:27