pharmaceuticals

Article

Exploring Probenecid Derived 1,3,4-Oxadiazole-Phthalimide Hybrid as α-Amylase Inhibitor: Synthesis, Structural Investigation, and Molecular Modeling

Bilal Ahmad Khan [1], Syeda Shamila Hamdani [1], Muhammad Khalid [2,3,*], Muhammad Ashfaq [4], Khurram Shahzad Munawar [5,6], Muhammad Nawaz Tahir [4], Ataualpa A. C. Braga [7], Ahmed M. Shawky [8], Alaa M. Alqahtani [9], Mohammed A. S. Abourehab [10], Gamal A. Gabr [11,12], Mahmoud A. A. Ibrahim [13,14,*] and Peter A. Sidhom [15]

1 Department of Chemistry, The University of Azad Jammu and Kashmir, Muzaffarabad 13100, Pakistan
2 Institute of Chemistry, Khwaja Fareed University of Engineering & Information Technology, Rahim Yar Khan 64200, Pakistan
3 Centre for Theoretical and Computational Research, Khwaja Fareed University of Engineering & Information Technology, Rahim Yar Khan 64200, Pakistan
4 Department of Physics, University of Sargodha, Punjab 40100, Pakistan
5 Institute of Chemistry, University of Sargodha, Sargodha 40100, Pakistan
6 Department of Chemistry, University of Mianwali, Mianwali 42200, Pakistan
7 Departamento de Química Fundamental, Instituto de Química, Universidade de São Paulo, Av. Prof. Lineu Prestes 748, São Paulo 05508-000, Brazil
8 Science and Technology Unit (STU), Umm Al-Qura University, Makkah 21955, Saudi Arabia
9 Pharmaceutical Chemistry Department, College of Pharmacy, Umm Al-Qura University, Makkah 21955, Saudi Arabia
10 Department of Pharmaceutics, College of Pharmacy, Umm Al-Qura University, Makkah 21955, Saudi Arabia
11 Department of Pharmacology and Toxicology, College of Pharmacy, Prince Sattam Bin Abdulaziz University, Al-Kharj 11942, Saudi Arabia
12 Agricultural Genetic Engineering Research Institute (AGERI), Agricultural Research Center, Giza 12619, Egypt
13 Computational Chemistry Laboratory, Chemistry Department, Faculty of Science, Minia University, Minia 61519, Egypt
14 School of Health Sciences, University of KwaZulu-Natal, Durban 4000, South Africa
15 Department of Pharmaceutical Chemistry, Faculty of Pharmacy, Tanta University, Tanta 31527, Egypt
* Correspondence: muhammad.khalid@kfueit.edu.pk (M.K.); m.ibrahim@compchem.net (M.A.A.I.)

Citation: Khan, B.A.; Hamdani, S.S.; Khalid, M.; Ashfaq, M.; Munawar, K.S.; Tahir, M.N.; Braga, A.A.C.; Shawky, A.M.; Alqahtani, A.M.; Abourehab, M.A.S.; et al. Exploring Probenecid Derived 1,3,4-Oxadiazole-Phthalimide Hybrid as α-Amylase Inhibitor: Synthesis, Structural Investigation, and Molecular Modeling. *Pharmaceuticals* **2023**, *16*, 424. https://doi.org/10.3390/ph16030424

Academic Editor: Phaedra Eleftheriou

Received: 12 December 2022
Revised: 2 March 2023
Accepted: 6 March 2023
Published: 10 March 2023

Abstract: 1,3,4-Oxadiazole moiety is a crucial pharmacophore in many biologically active compounds. In a typical synthesis, probenecid was subjected to a sequence of reactions to obtain a 1,3,4-oxadiazole–phthalimide hybrid (**PESMP**) in high yields. The NMR (^{1}H and ^{13}C) spectroscopic analysis initially confirmed the structure of **PESMP**. Further spectral aspects were validated based on a single-crystal XRD analysis. Experimental findings were confirmed afterwards by executing a Hirshfeld surface (HS) analysis and quantum mechanical computations. The HS analysis showed the role of the π···π stacking interactions in **PESMP**. **PESMP** was found to have a high stability and lower reactivity in terms of global reactivity parameters. α-Amylase inhibition studies revealed that the **PESMP** was a good inhibitor of α-amylase with an s value of 10.60 ± 0.16 µg/mL compared with that of standard acarbose (IC_{50} = 8.80 ± 0.21 µg/mL). Molecular docking was also utilized to reveal the binding pose and features of **PESMP** against the α-amylase enzyme. Via docking computations, the high potency of **PESMP** and acarbose towards the α-amylase enzyme was unveiled and confirmed by docking scores of −7.4 and −9.4 kcal/mol, respectively. These findings shine a new light on the potential of **PESMP** compounds as α-amylase inhibitors.

Keywords: oxadiazole; α-amylase inhibition; X-ray diffraction; molecular docking; DFT calculations

within SZYBKI software [69,70]. The Gasteiger method was utilized to assign the atomic charges of **PESMP** and acarbose compound [71]. In this work, docking computation was conducted utilizing AutoDock4.2.6 software [72]. The genetic algorithm number (*GA*) was adjusted to 250. The maximum number of energy evaluations (*eval*) was set to 25,000,000. Other docking parameters were set to default values. The grid box was tailored to involve the binding pocket of the α-amylase enzyme, with a grid size of 60 Å × 60 Å × 60 Å. The coordinates of the grid center were x = 32.644, y = 38.464, and z = −3.166. The AutoGrid program was employed to extract the grid maps with a spacing of 0.375 Å. All molecular interactions were represented using BIOVIA Materials Studio [73].

4. Conclusions

An efficient, multistep synthetic approach was followed to synthesize good yields of 4-(5-((1,3-dioxoisoindolin-2-yl)methylthio)-1,3,4-oxadiazol-2-yl)-N,N-dipropylbenzenesulfonamide (**PESMP**). Its synthesis was confirmed via structural validation using NMR (^{1}H, ^{13}C), FT-IR, and single-crystal X-ray diffraction analyses. The purity of **PESMP** was established on the basis of thin-layer chromatography. To obtain further insight into the features of the entitled compound, various DFT calculations were executed accordingly. The band gap value of the **PESMP** compound (0.1732 a.u.) for the HOMO-LUMO orbital was smaller than the band gap values of HOMO-LUMO ±1 and HOMO-LUMO ±2. The testing of **PESMP** against α-amylase revealed an IC_{50} = 10.60 ±0.16 µg/mL using acarbose (IC_{50}= 8.80 ±0.21 µg/mL) as a standard drug. Molecular docking revealed the binding mode of the **PESMP** compound against the active site of α-amylase. **PESMP** and acarbose showed docking scores of −7.4 and −9.4 kcal/mol against the α-amylase enzyme, respectively. These findings shine new light on the potential of the **PESMP** compound as an α-amylase inhibitor.

Supplementary Materials: The following supporting information can be downloaded at: https://www.mdpi.com/article/10.3390/ph16030424/s1, Figure S1: ^{1}H NMR spectrum of **PESMP**; Figure S2: ^{13}C NMR spectrum of **PESMP**; Figure S3: 2D fingerprint plots of the remaining contacts; Figure S4: Graphical representation of voids, (a) 1st view, and (b) 2nd view along the a-axis; Figure S5: 3D superimposition of the resolved experimental structure (in gray) and the portended binding mode (in cyan) of acarbose complexed with α-amylase enzyme; Table S1: Selected bond lengths and bond angles in the **PESMP** compound; Table S2: Interaction energies (kJ/mol); Table S3: Cartesian coordinates of the selected atoms that are involved in interaction energy calculations.

Author Contributions: Author Contributions: Conceptualization, B.A.K.; Data curation, S.S.H., M.K. and M.A.; Formal analysis, S.S.H. and K.S.M.; Investigation, B.A.K., M.N.T., A.A.C.B. and P.A.S.; Methodology, B.A.K. and P.A.S.; Project administration, B.A.K. and P.A.S.; Resources, B.A.K. and M.A.S.A.; Software, M.K. and M.A.A.I.; Supervision, B.A.K.; Visualization, A.M.S. and P.A.S.; Writing—original draft, S.S.H., M.K., M.A. and P.A.S.; Writing—review and editing, B.A.K., K.S.M., M.N.T., A.A.C.B., A.M.S., A.M.A., M.A.S.A., G.A.G. and M.A.A.I. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Data is contained within the article and Supplementary Materials.

Acknowledgments: Bilal Ahmad Khan is thankful to HEC Pakistan for its financial support (NRPU-6455). Muhammad Khalid gratefully acknowledges the financial support of HEC Pakistan (project no. 20-14703/NRPU/R&D/HEC/2021). Ataualpa A. C. Braga (grant 2015/01491-3) is highly thankful to Fundação de Amparo á Pesquisa do Estado de São Paulo for the cooperation and financial assistance. Ataualpa A. C. Braga (grant 312550/2020-0) also thanks the Brazilian National Research Council (CNPq) for financial support and fellowship. Mohammed A. S. Abourehab would like to thank the Deanship of Scientific Research at Umm Al-Qura University for supporting this work (Grant Code: (22UQU4290565DSR11)).