ECMC 2023

MDPI

Abstract

Natural Product Analogues as Antibacterial Agents: The Case of Cinnamaldehyde and Colupulone†

Angeliki Kokkali [1], Anna-Maria Kostaki [2,3], Georgia Athanassopoulou [2,3] Apostolia Makri [4], Marina Sagnou [5] Veroniki P. Vidali [2*] and Georgia Kythreoti [1*]

[1] School of Liberal Arts and Sciences, The American College of Greece, 6 Gravias Street, 15342 Athens, Greece; gkythreoti@acg.edu (G.K.); a.kokkali@acg.edu (A.K.)
[2] Natural Products Synthesis & Bioorganic Chemistry Laboratory, Institute of Nanoscience & Nanotechnology, National Center for Scientific Research "Demokritos", Patr. Grigoriou & Neapoleos 27, 153 41 Athens, Greece; v.vidali@inn.demokritos.gr (V.P.V.); annamarkwst@gmail.com (A-M.K.); gathanasopoulou97@gmail.com (G.D.A.); oliamakri@hotmail.com (A.M.)
[3] School of Health Sciences, Department of Pharmacy, Division of Pharmaceutical Chemistry, National and Kapodistrian University of Athens, Greece; annamarkwst@gmail.com (A-M.K.); gathanasopoulou97@gmail.com (G.D.A.)
[4] Department of Food Science and Human Nutrition, Agricultural University of Athens, Iera Odos 75, 118 55 Athens, Greece; oliamakri@hotmail.com (A.M.)
[5] Institute of Biosciences & Applications, National Centre for Scientific Research "Demokritos", Patr. Grigoriou & Neapoleos 27, 153 41 Athens, Greece; sagnou@bio.demokritos.gr (M.S.)

† Athens, September 2023

Abstract: The ever-growing antibiotic resistance to currently prescribed antibiotics constitutes a main reason for investigating natural compounds for antibacterial action. Natural products can be used as leads for new synthetic antibacterial agents or as a source of novel bioactive compounds. Cinnamaldehyde and colupulone were selected as lead compounds for the purposes of this study. Cinnamaldehyde, a byproduct of the stem bark of *Cinnamomum cassia*, was isolated in 1834 by Jean-Baptiste Dumas, with uses ranging from the food and cosmetics to pharmaceutical industries. Colupulone, is a known hop *β*-acid found in *Humulus lupulus*, a plant also used in the pharmaceutical and food industry. Previous studies have shown that both compounds exhibit antibacterial properties. In order to investigate essential structures responsible for enhanced action, some functionalities on the selected parental compounds, cinnamaldehyde and colupulone, were preserved while others altered. Synthesis of these analogues was based on short synthetic routes, including efficient methods like Wittig reaction, Friedel-Crafts and C-alkylation of phloroglucinol derivatives. Subsequent testing for their antibacterial action against gram-positive and gram-negative microorganisms *Escherichia coli*, *Staphylococcus aureus* and *Pseudomonas aeruginosa* revealed important functionalities required for increased activities. The prospective development of a ligand-based pharmacophore was also investigated, by analyzing the structural-activity relationship of their bacterial growth inhibitory potencies. Enhance inhibitory action was observed for the para-methoxy analogue of *trans*-cinnamaldehyde against *E.coli*. In addition, all tested colupulone analogues exhibited enhanced activities for both *E. coli* and *S.aureus*. These results set the base for designing new compounds to better understand structure-activity relationship and improve activity.

Keywords: cinnamaldehyde analogues; colupulone analogues; antibacterial activity; structure-activity relationship.

Citation: Lastname, F.; Lastname, F.; Lastname, F. Title. *Med. Sci. Forum* **2023**, *2*, x. https://doi.org/10.3390/xxxxx

Academic Editor: Firstname Lastname

Published: date

Supplementary Materials:

Author Contributions: Conceptualization, V.P.V. and G.K.; methodology, V.P.V., G.K., A.M., ; software, V.P.V., G.K., M.S., A.K., A.M., A-M.K. and G.A.; validation, A.K., G.K., M.S., A.K., A-M.K., A.M., and G.A; formal analysis, A.K., A-M.K., A.M., and G.A.; investigation, V.P.V., G.K., M.S., A.K., A.M., A-M.K., and G.A.; resources, V.P.V., G.K., M.S.; data curation, V.P.V., G.K.; writing—original draft preparation, A.K.; writing—review and editing, V.P.V., G.K.; visualization, G.K.; supervision, V.P.V., G.K.; project administration, V.P.V., G.K.; funding acquisition, G.K. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Data Availability Statement: All data presented in this study will be available in future publications.

Acknowledgments: This study was supported by the Department of Science and Mathematics of Deree – The American College of Greece and the ACG 150 initiatives for supporting research and/or curriculum development.

Conflicts of Interest: The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.