http://dx.doi.org/10.21577/0103-5053.20190038

J. Braz. Chem. Soc., Vol. 00, No. 00, 1-12, 2019
Printed in Brazil - ©2019 Sociedade Brasileira de Química

Article

Synthesis and Biological Evaluation of New Eugenol-Derived 1,2,3-Triazoles as Antimycobacterial Agents

Thiago dos Santos,[a] Camila M. Coelho,[a] Thiago C. Elias,[b] Fallon S. Siqueira,[c] Eloísa S. S. D. Nora,[c] Marli M. A. de Campos,[c] Gabriel A. P. de Souza,[d] Luiz F. L. Coelho[d] and Diogo T. Carvalho[*,a]

[a]Departamento de Alimentos e Medicamentos, Faculdade de Ciências Farmacêuticas, Universidade Federal de Alfenas, 37130-001 Alfenas-MG, Brazil

[b]Laboratório de Modelagem Molecular e Simulação Computacional, Universidade Federal de Alfenas, 37130-001 Alfenas-MG, Brazil

[c]Departamento de Análises Clínicas e Toxicológicas, Universidade Federal de Santa Maria, 97105-900 Santa Maria-RS, Brazil

[d]Departamento de Microbiologia e Imunologia, Instituto de Ciências Biomédicas, Universidade Federal de Alfenas, 37130-001 Alfenas-MG, Brazil

Eugenol has diverse biological properties including antimycobacterial activity, and the triazole ring is an important heterocycle in antimycobacterial compounds. Therefore, this research aimed to synthesize novel eugenol-derived 1,2,3-triazole as antimycobacterial agents with interesting cytotoxic profile and pharmacological assets. Sixteen compounds were obtained and characterized by nuclear magnetic resonance (NMR), infrared (IR), and high-resolution mass spectrometry (HRMS). Among them, the best growth inhibition properties from a microdilution assay were observed for three derivatives: a benzylic ether (minimum inhibitory concentration (MIC) = 48.89 μM) against *Mycobacterium abscessus* (ATCC 19977), an *O*-galactosyde (MIC = 31.76 μM) against *Mycobacterium massiliense* (ATCC 48898) and a sulfonate (MIC = 88.64 μM) against *Mycobacterium fortuitum* (ATCC 6841). They can form biofilms, and the infection progression is challenging to control due to multi-drug resistance profiles against diverse antibiotics. In conclusion, the above-mentioned compounds represent starting points in the search of bioactive molecules against mycobacteria with low cytotoxicity and better pharmacological profiles.

Keywords: eugenol, rapid growing mycobacteria, 1,2,3-triazoles, mycobacterium

Introduction

Increasing bacterial resistance has been an emerging problem that can be correlated with the decline of investment in antibiotic research by the pharmaceutical industry. New antibiotics are usually reserved for the treatment of difficulty-manageable infections and are prescribed for a few days. Therefore, they are considered unprofitable in comparison with the drugs to treat chronic diseases.[1]

Additionally to this scenario, the antimicrobial consumption in animal breeding has been unequivocally linked to cases of multi-drug resistance.[2] Although bedaquiline was considered promising against *Mycobacterium tuberculosis* at its approval,[3] efflux-mediated bedaquiline resistance has already been identified in clinical management.[4]

Rapid growing mycobacteria (RGM) can form biofilms drastically affecting immunocompromised hosts, and the infection progression are challenging to control due to multi-drug resistance profiles against different antibiotics,[5] such as clarithromycin, imipenem,[6] rifampicin, isoniazid, ethambutol, pyrazinamide,[7] cefoxitin, and doxycycline.[8] *Mycobacterium fortuitum* is mainly present in skin, soft tissue and catheter associated infections,[9] while *Mycobacterium abscessus* noticeably accounts for pulmonary infections[10] and *Mycobacterium massiliense* for post-surgical ones.[11] Considering the reduced introduction of novel antibiotics in the market and the increasing resistance to the commonly used in mycobacterial infections, the urge

*e-mail: diogo.carvalho@unifal-mg.edu.br