A mild catalyzed Imino-Diels Alder reaction. Synthesis of *N*-(2-(*o*-tolyl)-1,2,3,4-tetrahydroquinoline-4-il)formamide derivatives as antimicrobial agents

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35º Congresso Latino-americano de Química e 61º Congresso Brasileiro de Química.

14-18 November 2022 in Centro de Convenções do Hotel Windsor Florida, Rio de Janeiro, BRASIL.

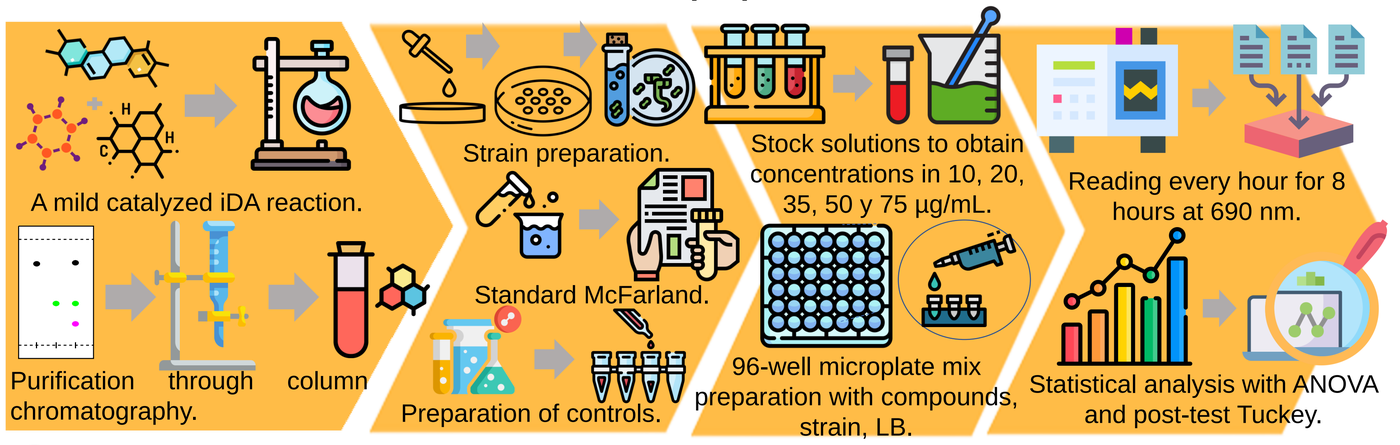
1 Introduction

Multidrug-resistant gram-negative pathogens have emerged as etiologic agents of infectious diseases such as *Escherichia coli* [1], and the microbial resistance to existing drug therapies reveals the need for new and efficient therapeutic agents [2]. Consequently, tetrahydroquinoline (THQ) alkaloids have appeared with remarkable pharmacological properties to develop novel antibacterial agents. The synthesis of THQs is described extensively in the literature through imino-Diels Alder reaction due to its simple, efficient, and low-cost preparation process[3,4].

This study aims to explore the versatility of the iDA process with synthetic THQ derivatives as antibacterial agents against *E. coli*.

2 Workflow

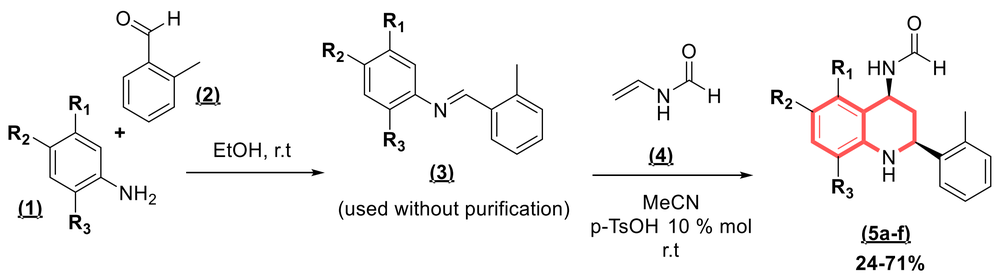
a Synthesis — **b** Biological media — **c** Test preparation — **d** Data and statistic



3 Results

Compound characterization

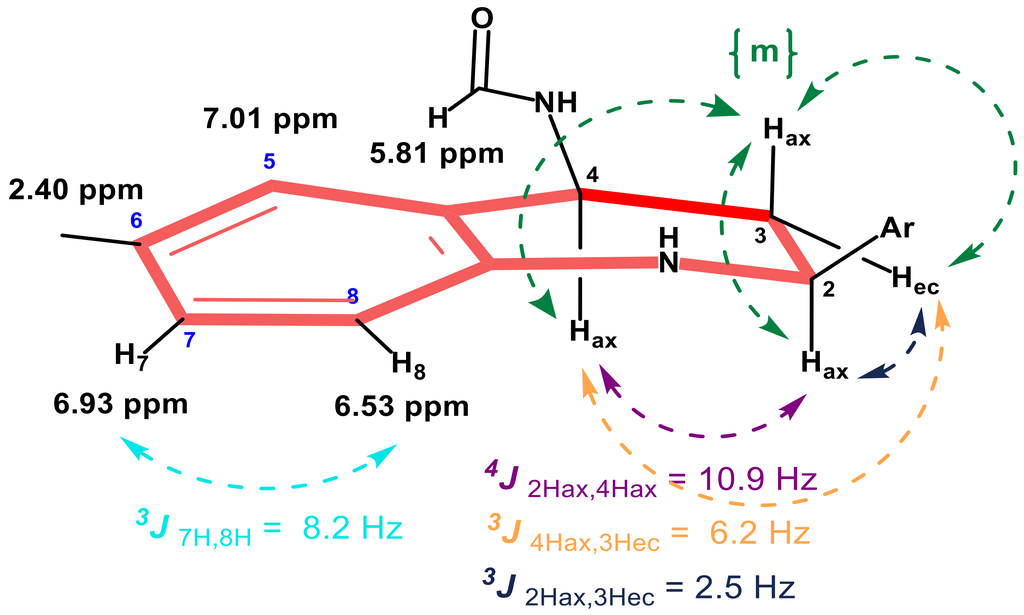
a ***N*-(2-(*o*-tolyl)-1,2,3,4-tetrahydroquinoline-4-il)formamide synthesis through imino-Diels Alder (iDA) process.**



5a: R_1= R_3= H; R_2= F. **5b**: R_1= R_2= H; R_3= C_3H_7. **5c**: R_1= R_3= H; R_2= Me. **5d**: R_1= R_3= H; R_2= Cl. **5e**: R_1= R_2= R_3= H. **5f**: R_1= R_3= H; R_2= I.

THQ	5a	5b	5c	5d	5e	5f
Rend. (%)	56	24	71	44	42	56

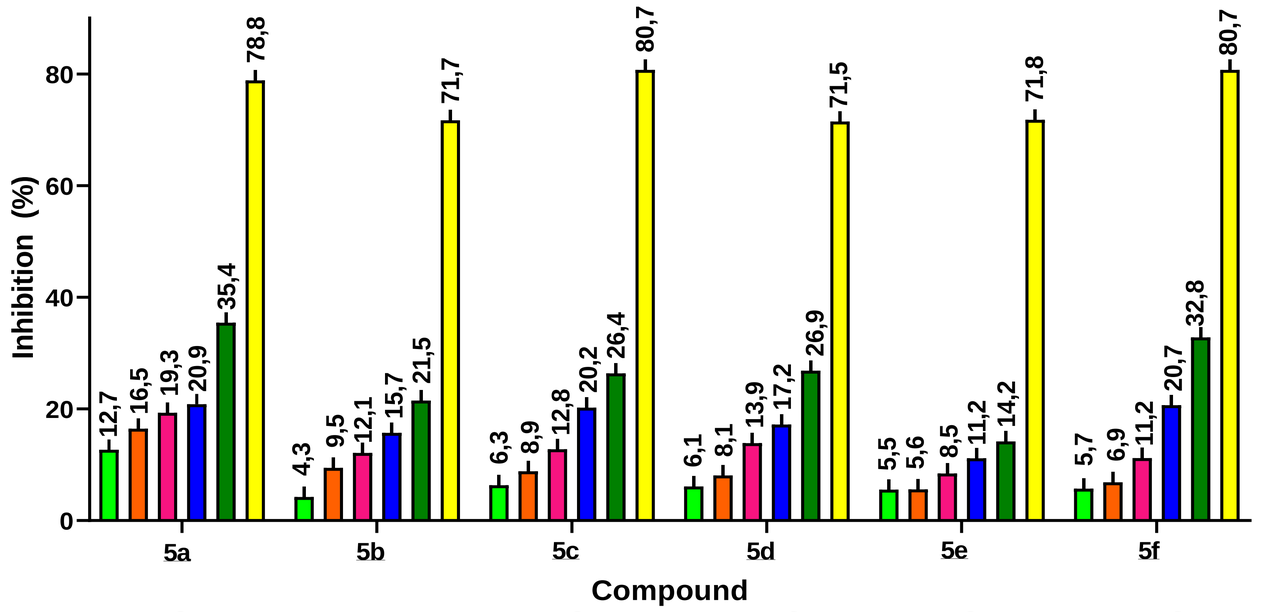
b **Coupling constants of ^{1}H-NMR.** All compounds were supported by ^{1}H-NMR, ^{13}C-NMR and two-dimensional NMR experiments.



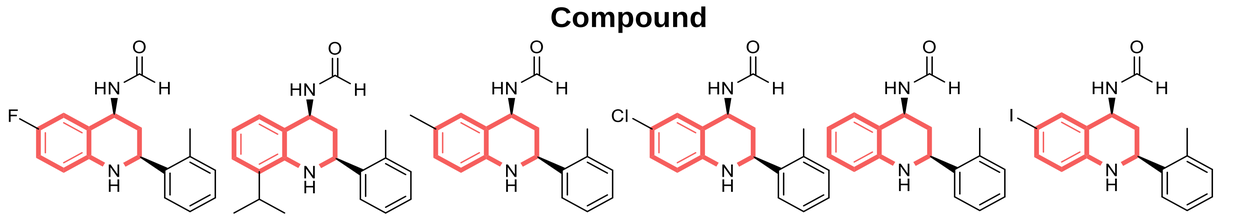
^{13}C NMR (101 MHz, $CDCl_3$): δ 161.13 (C=O), 143.24 (C4'), 140.90 (C1'), 135.18 (C2'), 130.81 (C6'), 129.30 (C5'), 127.74 (C4'), 127.53 (C3'), 127.39 (C8'), 126.55 (C5), 125.59 (C7), 120.73 (C6), 114.91 (C8), 51.89 (C4), 45.12 (C2), 37.18 (C3), 20.54 (6-Me), 19.16 (2'-Me) ppm. **^{13}C DEPT-135:** δ 161.13 (C=O), 130.79 (C6'), 129.30 (C5'), 127.74 (C4'), 127.49 (C3'), 126.55 (C5), 125.59 (C7), 114.91 (C8), 51.88 (C4), 45.12 (C2), **37.18 (C3)**, 20.54 (6-Me), 19.16 (2'-Me).

Growth inhibition

c **THQs inhibition percentage in *Escherichia coli* culture medium.**



THQs (5a-f)



10 µg/mL | 20 µg/mL | 35 µg/mL | 50 µg/mL | 75 µg/mL | C+ Gentamicin 20 µg/mL

d **MIC of evaluated molecules.**

THQ	5a	5b	5c	5d	5e	5f
CMI (µg/mL)	10	20	10	20	20	10

4 Conclusion

A series of 4-amide-THQ derivatives were obtained using an economical catalyst and under medium reaction conditions. In addition, compounds with electron-withdrawing groups could be considered growth inhibitors with MIC of 10 µg/mL, which deserves further investigation to explore the scope and limitation of their biological activities.

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Acknowledgements: L.J.G.M and *C.M.M.G. thank to MINISTERIO and "el fondo de Investigación en Salud" (FIS) (CTeI;519-2021 from 874-2020) for the financial support.