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Novel isoquinoline derivatives as antimicrobial agents

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ABSTRACT

The wide variety of potent biological activities of natural and synthetic isoquinoline alkaloids encouraged us to develop novel antimicrobial isoquinoline compounds. We synthesized a variety of differently functionalized 1-pentyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines (THIQs), including dihydroisoquinolinium salts (**2** and **5**), methyl pentanoate-THIQ (**6**), 1-pentanol-THIQ (**7**), ester derivatives (**8**–**15**) and carbamate derivatives (**16**–**23**). We employed classic intramolecular Bischler–Napieralski cyclodehydration to generate the isoquinoline core. All the structures were characterized by nuclear magnetic resonance and mass spectrometry. The bactericide and fungicide activities were evaluated for all the synthesized compounds and structure-activity relationships were established. Many compounds exhibited high and broad-range bactericidal activity. Fluorophenylpropanoate ester **13** and the halogenated phenyl- (**17**, **18**) and phenethyl carbamates (**21**, **22**) exerted the most remarkable bactericidal activity. However, few compounds displayed antifungal activity against most of the fungi tested. Among them, chlorinated derivatives like chlorobenzoate and chlorophenylpropanoate esters (**10** and **14**, respectively) and chlorophenethyl carbamate **22**, exhibited the greatest antifungal activity.

1. Introduction

Isoquinoline alkaloids are natural and synthetic products with a wide variety of potent biological activities,[1,2] including inhibition of cell proliferation,[3,4] β-adrenergic receptor antagonism,[5] and inhibition of enzymes related to the metabolism of catecholamines and indoleamines, such as monoamino oxidase.[6] In the last few decades, many natural tetrahydroisoquinolines (THIQs) with potent antitumor and antimicrobial activities have been isolated.[7,8] Recently, some potent antifungal THIQs have been synthesized based on the structure of lanosterol 14α-demethylase (CYP51), a fungal key enzyme involved in sterol biosynthesis.[9,10] In addition, some potent antibacterial 1-aryl-6,7-dimethoxy-1,2,3,4-THIQs have been synthesized in recent years.[11]

Our research group has long since focused on isolating and synthesizing isoquinoline-containing compounds with dopaminergic[12–15] and antitumor[4] activity. However, since the development of resistance to classic antibiotics is a cause for concern for both agricultural pest control and human health, we have recently devoted our research efforts to find new antimicrobial agents. Therefore, we studied the bactericidal and fungicidal effects of new synthetic antimicrobial pyrrolo[2,1-*a*]isoquinolin-3-ones.[16] Given this background, we decided to synthesize sixteen new *N*-methyl-6,7-dimethoxy-1,2,3,4-THIQs with a functionalized pentyl chain at the 1-position, containing functionalized esters or carbamates. Among all the methods described for synthesizing the isoquinoline core, we decided to apply Bischler–Napieralski cyclodehydration.[2,17,18] Then, we performed an *N*-alkylation of the unstable imine and a subsequent reduction to obtain *N*-methyl-1-substituted-1,2,3,4-THIQs. Once synthesized, we next investigated the potential antibacterial and antifungal activities of these *N*-methyl-1-substituted-THIQs, including the new 1-pentyl-THIQs (eight esters and eight carbamates), as well as some of their precursors. Taken into account the results obtained in the biological assays, we analyzed the relevance of carbamate, ester or alcohol groups at the end of the alkyl chain at the 1-position of the THIQ nucleus. Therefore, we have been able to establish a structure–antimicrobial activity relationship among all the synthesized THIQs.

2. Results and discussion

2.1. Chemistry

The approach used to synthesize 1-butyl-THIQ, and the differently functionalized 1-pentyl-THIQs, was based on the preparation of *N*-(3,4-dimethoxy-phenthyl)pentanamide **1** and

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N-(3,4-dimethoxyphenethylamino)-6-oxohexanoate **4**, respectively. Both amides were obtained under Schotten–Baumann conditions with subsequent Bischler–Napieralski cyclodehydration to generate the isoquinoline core (Schemes 1 and 2). Then, β-(3,4-dimethoxyphenyl)ethylamine was condensed with valeryl chloride or methyl adipoyl chloride to give the corresponding amide **1** or **4**, respectively. These amides were next treated with $POCl_3$ to generate the appropriate dihydroisoquinoline **1′** or **4′**. These unstable imines **1′** and **4′** were N-alkylated with MeI to obtain the expected 3,4-dihydroisoquinolinium salt **2** and **5**, respectively. Finally, these imoniums were reduced with $NaBH_4$ to give the corresponding THIQs **3** and **6**. Subsequently, the terminal methyl ester of THIQ **6** was reduced to a primary alcohol with $LiAlH_4$ to generate 1-pentanol-THIQ **7**.

Owing to the chemical versatility of the terminal alcohol of THIQ **7**, we decided to synthesize the 1-pentyl-THIQs functionalized with esters (**8**–**15**) and carbamates (**16**–**23**) (Schemes 3 and 4). 1-Pentanol-THIQ **7** was reacted with acid chlorides in the presence of 4-DMAP and triethylamine to obtain the new esters compounds (**8**–**15**). Moreover, 1-pentanol-THIQ **7** reacted with the corresponding isocyanates to yield the corresponding carbamates (**16**–**23**). All the compounds' structures were elucidated by NMR spectra and ESMS spectrometry data. It should be emphasized that, to the best of our knowledge, products **2**–**23** are reported for the first time. Furthermore, we decided to explore the influence of a variety of functionalized substituents at the 1-position in the THIQ skeleton, including carbamate and ester groups on antimicrobial activity.

2.2. Antimicrobial activity

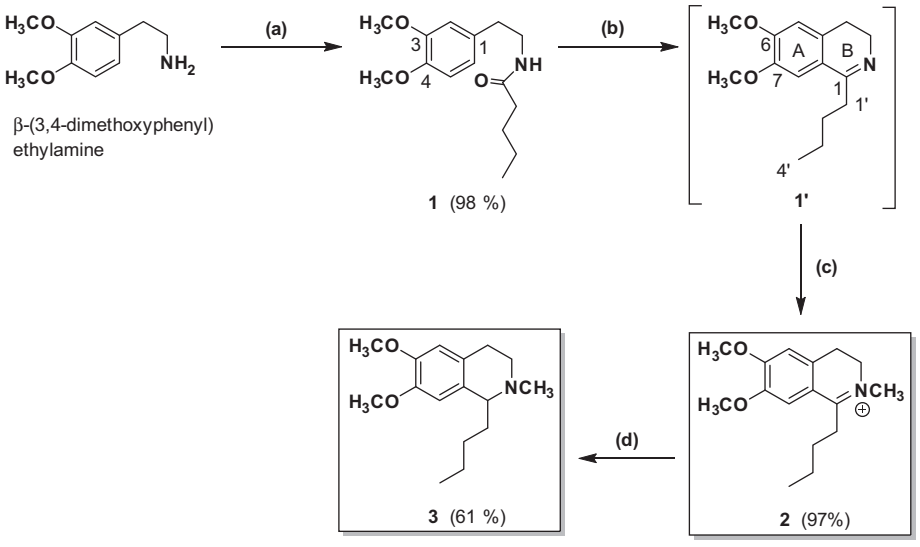
All the THIQs (**2**, **3**, **5**–**23**) were tested in vitro for their antimicrobial activity against several human pathogenic bacteria and economically relevant phytopathogenic fungi. The inhibition zones of bacterial and fungal growth caused by the synthesized compounds are outlined in Tables 1–5.

The bacterial strains used in the antibacterial assay were three Gram-positive (*Bacillus cereus*, *Staphylococcus aureus* and *Enterococcus faecalis*) and four Gram-negative (*Salmonella typhi*, *Escherichia coli* 100, *E. coli* 405 and *Erwinia carotovora*). The following phytopathogenic fungal strains were used to evaluate the antifungal activity: *Fusarium culmorum*, *Geotrichum candidum*, *Trichoderma viride*, *Phytophthora citrophthora* and *Aspergillus parasiticus*.

2.2.1. Structure–bactericidal activity relationships

Initially, we examined 1-alkyl-isoquinolines with DHIQ and THIQ nucleus, resulting both 1-butyl-3,4-dihydroisoquinolinium salt **2** and 1-butyl-THIQ **3** active against all the bacterial strains tested, except for *E. coli* 100. The introduction of a methyl ester in the alkyl chain at 1-position gave the DHIQ **5** and its analogous THIQ **6** that were active against few bacterial strains, however THIQ **6** displayed bactericidal effects against *S. aureus* and *E. coli 100*. In view of these results, the presence of a methyl ester group reduced the bactericidal spectrum. Interestingly, the common precursor 1-pentanol-THIQ **7** exhibited the highest activity against all the strains tested showing remarkable effects against *E. coli* 100 (62% inhibition). Despite these findings, it lacked of any relevant activity against *B. cereus*.

Next, to find more potent bactericidal THIQs, we examined the introduction of ester and carbamate functions in the alkyl chain at 1-position as well as substituent effects at the *para*-position of the phenyl group of these ester and carbamate THIQs. All the benzoate esters of the 1-pentyl-THIQs bearing different substituents in the phenyl group (**8**–**15**) exhibited relevant activity against all the bacteria tested. In general, they showed the following activity-growing trend: Ph (**8**) < PhOMe (**11**) < PhCl (**10**) < PhF (**9**), emphasizing that THIQ **9** with a fluorinated benzoate exhibited the highest activity against *S. typhi* (61%). Furthermore, phenylpropanoate derivatives **12**–**15**, in which two methylenes were placed between the ester group and the substituted aromatic ring, displayed broad antibacterial activity being effective against all the strains tested. Therefore, the conformational flexibility provided by the two additional carbons did not significantly improve the bactericidal activity of these compounds. Similarly to its analogs, the fluorinated compound **13** showed the strongest bactericidal activity against most of the strains tested. Its activity against *B. cereus* and *E. coli* 100 was noteworthy (49% and 46%, respectively). Regarding the carbamate series, all the 1-pentyl-THIQs **16**–**23**, showed wide broad-range of bactericidal activity (Table 3). In this context, THIQ **16** exhibited 59% of antibacterial activity against *E. coli* 100, while the fluorinated analog **17** showed 64% activity against *E. faecalis* and *E. carotovora*. Methoxylated THIQ **19** exhibited 51% activity against *S. aureus* and 52% activity against *E. coli* 405, while the chlorinated compound **18** displayed greater antibacterial activity against *S. typhi* and *E. coli* 405 (67% and 68%, respectively). Compared with analogs **16**–**19**, the THIQs **20**–**23** possessing two carbon



Scheme 1. Synthesis of *N*-methyl-1-butyl-6,7-dimethoxy-1,2,3,4-THIQ (**3**). Reagents and conditions: (a) β-(3,4-dimethoxyphenyl)ethylamine, valeryl chloride, NaOH 5%, CH_2Cl_2, rt, 2 h; (b) $POCl_3$, CH_3CN, reflux, 1 h; (c) MeI, acetone, reflux, 3 h; (d) $NaBH_4$, MeOH, rt, 2 h.