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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

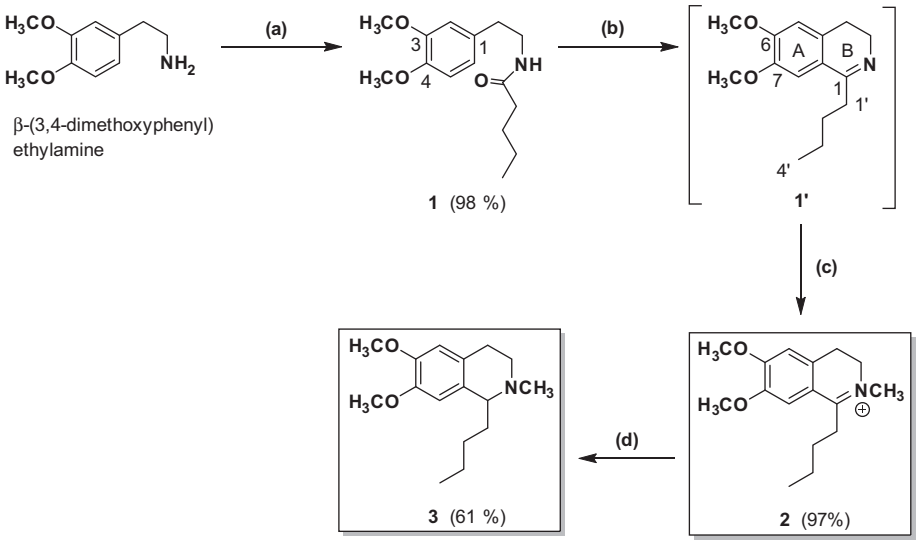
All the THIQs (**2**, **3**, **5**–**23**) were tested in vitro for their antimicrobial activity against several human pathogenic bacteria and economically relevant phytopathogenic fungi. The inhibition zones of bacterial and fungal growth caused by the synthesized compounds are outlined in Tables 1–5.

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*.

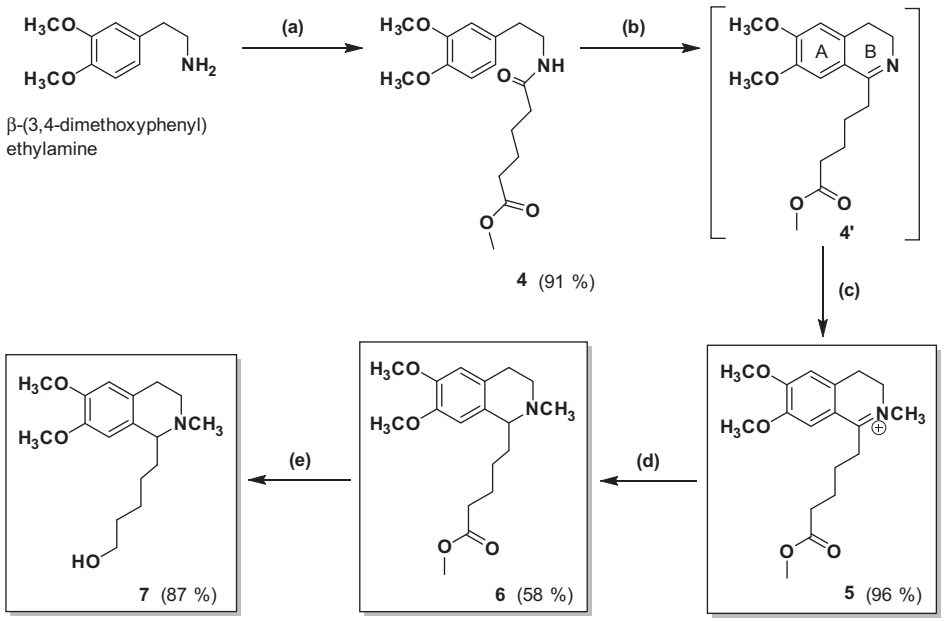
2.2.1. Structure–bactericidal activity relationships

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*.

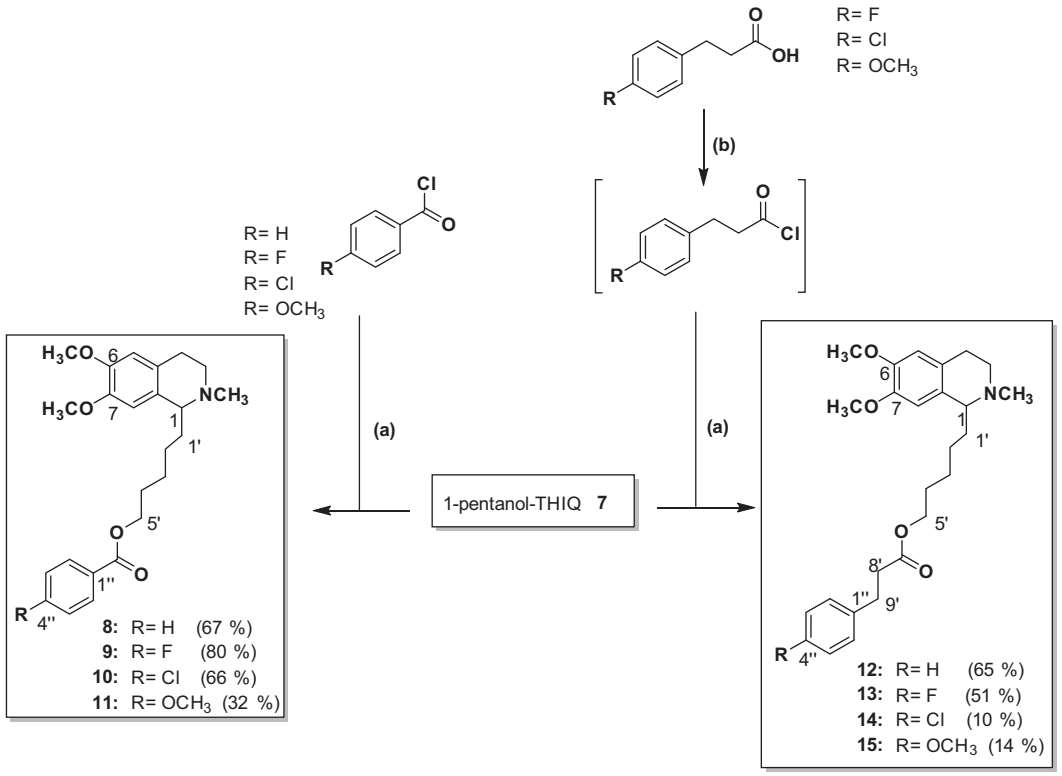
Next, to find more potent bactericidal THIQs, we examined the introduction of ester and carbamate functions in the alkyl chain at 1-position as well as substituent effects at the *para*-position of the phenyl group of these ester and carbamate THIQs. All the benzoate esters of the 1-pentyl-THIQs bearing 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.



Scheme 2. Synthesis of *N*-methyl-1-pentanol-6,7-dimethoxy-1,2,3,4-THIQ (**7**). Reagents and conditions: (a) β-(3,4-dimethoxyphenyl)ethylamine, methyl adipoyl 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; (e) $LiAlH_4$, Et_2O, THF, reflux, 2 h.

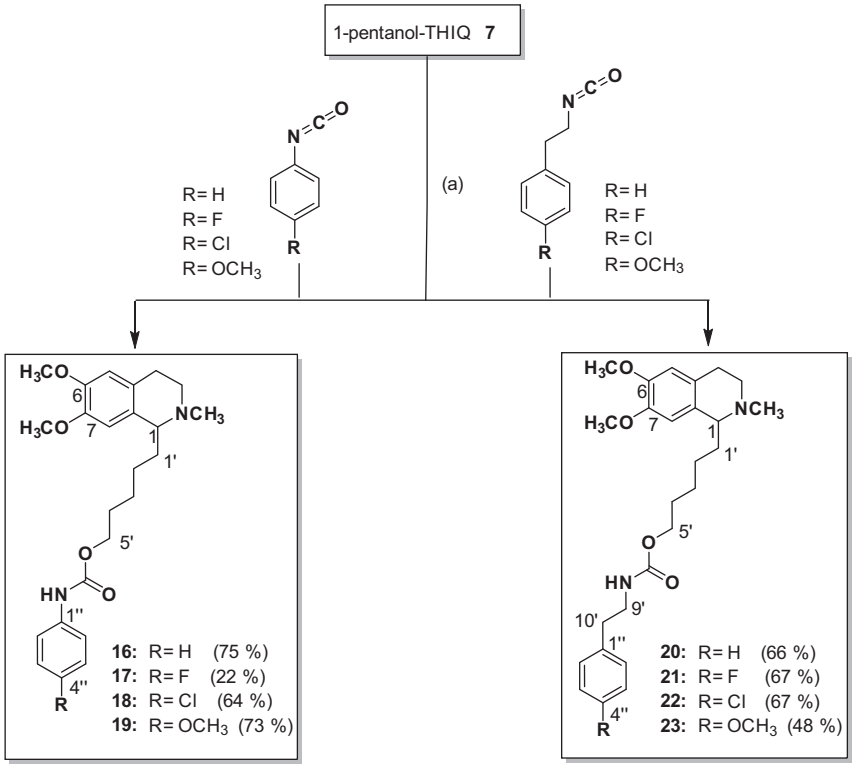


Scheme 3. Synthesis of esters *N*-methyl-1-pentyl-6,7-dimethoxy-1,2,3,4-THIQs (**8**–**15**). Reagents and conditions: (a) 4-DMAP, Et_3N, CH_2Cl_2, rt, 5 h; (b) $SOCl_2$, CH_2Cl_2, reflux, 3 h.

atom units linking the carbamate group and the corresponding phenyl substituent, displayed similar bactericidal activity trends. Of note, the halogenated phenyl derivatives including the fluorinated **21**, and the mainly chlorinated **22**, displayed the largest inhibition zones against most of the strains tested with remarkable results. In regard to this, the fluorinated phenyl derivative **21** was active by 61% and 62% against *S. typhi* and *E. coli* 405, respectively, and its chlorinated analog **22** exhibited a higher bactericidal activity against the same bacteria (75%).

2.2.2. Structure–fungicidal activity relationships

SAR studies were carried out against several phytopathogenic fungi. In this case, we observed that 1-butyl-tetrahydroisoquinoline **3** was only slightly active against *F. culmorum* and 3,



Scheme 4. Synthesis of carbamates *N*-methyl-1-pentyl-6,7-dimethoxy-1,2,3,4-THIQs (**16**–**23**). Reagents and condition: (a) CH_2Cl_2, reflux, 24 h.

Table 1

Strains	Bactericidal activity Inhibition zone (mm) 24 h (means ± SE)[a]					
	2[b]	**3**[b]	**5**[b]	**6**[b]	**7**[b]	Tetracycline[b]
B. cereus	7.0 ± 0^{A}	6.0 ± 0.5^{A}	6.33 ± 0.41^{A}	6.33 ± 0.41^{A}	0 ± 0	23.33 ± 0.41^{B}
S. aureus	7.0 ± 0^{A}	6.0 ± 0^{AB}	0 ± 0	5.50 ± 0^{B}	10.67 ± 1.08^{C}	27.0 ± 0.71^{D}
E. faecalis	7.0 ± 0^{A}	7.0 ± 0^{A}	0 ± 0	0 ± 0	10.33 ± 1.08^{B}	31.17 ± 0.89^{C}
S. typhi	6.75 ± 0.25^{A}	6.25 ± 0.25^{A}	0 ± 0	0 ± 0	12.33 ± 0.82^{B}	24.33 ± 0.41^{C}
E. coli 405	7.0 ± 0^{A}	6.0 ± 0^{A}	0 ± 0	0 ± 0	11.33 ± 1.08^{B}	25.67 ± 0.41^{C}
E. carotovora	7.0 ± 0^{A}	6.0 ± 0^{A}	5.50 ± 0^{A}	0 ± 0	8.0 ± 0.71^{A}	34.67 ± 1.45^{B}
E. coli 100	0 ± 0	0 ± 0	0 ± 0	5.83 ± 0.20^{A}	16.0 ± 0^{B}	25.67 ± 0.41^{C}

[a] Each value represents the average and the standard error of three independent experiments. Within each line, the mean values labelled with a different superscript (A–D) show statistically significant differences ($P < 0.05$).
[b] Dose: 0.2 mg/disk.

4-dihydroisoquinolinium salts **2** and **5** didn't show any antifungal activity neither at 10 μg/mm^2 nor at 20 μg/mm^2. Similarly, THIQs **6** and **7**, with methyl ester and alcohol groups, respectively, did not display antifungal activity at the doses tested. The introduction of an aromatic lipophilic group in the alkyl chain at 1-position such as benzoate and phenylpropanoate esters and phenyl and phenethyl-carbamates was essential to develop active THIQs. Results showed that all the 1-pentyl-THIQs bearing phenyl esters (**8**–**15**) showed antifungal activity against some of the strains. The unhalogenated THIQ **8**, the fluorinated THIQ **9** and the methoxylated THIQ **11** were all active against *F. culmorum*, *T. viride* and *G. candidum*. Interestingly, the chlorinated THIQ **10** displayed the highest antifungal activity against all the fungi tested, except for *A. parasiticus.* Additionally, phenylpropanoate THIQs **12**–**15** were more active than their corresponding benzoate analogs (**8**–**11**). These results suggest that conformational flexibility with a lengthened structure was, in general, beneficial for fungicidal activity. Regarding the carbamate series, all the 1-pentyl-THIQs (**16**–**23**) exhibited antifungal activity, except the fluorinated THIQ **17**, which was inactive for all the fungal strains tested. Finally, the presence of two-carbons between the carbamate and aromatic ring seemed to be detrimental for antifungal activity with the exception of the chlorinated THIQ **22**, which showed a wider fungicidal spectrum.

In conclusion, most of these 1-substituted-THIQs displayed both fungicidal and (mostly) bactericidal activity. Structure–bactericidal activity relationships revealed that 1-butyl-isoquinolines with DHIQ and THIQ nucleus (**2** and **3**, respectively), possessed moderate bactericidal activity. The introduction of a methyl ester group in the alkyl chain at 1-position such as DHIQ **5** and THIQ **6**, seemed to reduce the bactericidal spectrum. However, different substituents affording an alcohol function such as 1-pentanol-THIQ **7** and also several lipophilic 1-pentyl-THIQs with the phenyl ester (**8**–**15**) and phenyl carbamate (**16**–**23**) moieties, displayed significant bioactivity against all the bacteria tested. Structure–fungicidal activity relationships showed that the introduction in the alkyl chain at 1-position of ester and carbamate functions attached to

Table 2

Strains	Bactericidal activity Inhibition zone (mm) 24 h (means ± SE)[a]								
	8[b]	**9**[b]	**10**[b]	**11**[b]	**12**[b]	**13**[b]	**14**[b]	**15**[b]	Tetracycline[b]
B. cereus	10.83 ± 1.59^{A}	13.0 ± 0.71^{B}	13.0 ± 0^{B}	10.33 ± 0.41^{A}	10.33 ± 0.41^{A}	11.33 ± 0.41^{AB}	11.0 ± 0^{A}	8.50 ± 0.71^{C}	23.33 ± 0.41^{D}
S. aureus	10.67 ± 0.82^{AB}	13.67 ± 1.08^{C}	12.67 ± 0.41^{CD}	11.33 ± 0.41^{BC}	9.67 ± 0.41^{AE}	10.33 ± 0.41^{AB}	8.67 ± 0.41^{EF}	7.83 ± 0.20^{F}	27.0 ± 0.71^{G}
E. faecalis	9.83 ± 0.73^{A}	13.67 ± 0.41^{B}	11.67 ± 0.41^{C}	11.33 ± 0.41^{C}	8.67 ± 0.41^{DE}	9.33 ± 0.41^{AD}	8.33 ± 0.20^{E}	7.0 ± 0^{F}	31.17 ± 0.89^{G}
S. typhi	9.67 ± 0.41^{A}	14.83 ± 0.20^{B}	11.50 ± 0.35^{C}	11.33 ± 0.41^{C}	8.67 ± 0.41^{DE}	9.17 ± 0.20^{AD}	8.17 ± 0.41^{E}	8.0 ± 0.35^{E}	24.33 ± 0.41^{F}
E. coli 405	9.83 ± 0.54^{A}	13.67 ± 0.41^{B}	11.50 ± 0.35^{C}	11.33 ± 0.41^{C}	8.67 ± 0.41^{D}	8.83 ± 0.54^{D}	9.17 ± 0.54^{AD}	7.33 ± 0.20^{E}	25.67 ± 0.41^{F}
E. carotovora	12.17 ± 1.14^{A}	13.50 ± 0.35^{AB}	12.67 ± 0.41^{A}	10.33 ± 1.08^{A}	10.67 ± 0.41^{A}	11.67 ± 0.41^{A}	11.0 ± 0^{A}	11.33 ± 0.82^{A}	34.67 ± 1.45^{B}
E. coli 100	11.0 ± 0.71^{AB}	14.0 ± 0.71^{C}	13.67 ± 0.20^{C}	10.83 ± 0.20^{A}	11.33 ± 0.41^{AB}	11.83 ± 0.20^{B}	8.67 ± 0.20^{D}	7.0 ± 0^{E}	25.67 ± 0.41^{F}

[a] Each value represents the average and the standard error of three independent experiments. Within each line, the mean values labelled with a different superscript (A–G) show statistically significant differences ($P < 0.05$).
[b] Dose: 0.2 mg/disk.

Table 3

Strains	Bactericidal activity Inhibition zone (mm) 24 h (means ± SE)[a]								
	16[b]	**17**[b]	**18**[b]	**19**[b]	**20**[b]	**21**[b]	**22**[b]	**23**[b]	Tetracycline[b]
B. cereus	12.67 ± 1.08^{A}	14.33 ± 0.41^{B}	14.33 ± 0.41^{B}	10.33 ± 0.41^{CD}	10.17 ± 0.20^{C}	11.33 ± 0.41^{DE}	14.67 ± 0.41^{B}	12.0 ± 0^{AE}	23.33 ± 0.41^{F}
S. aureus	15.0 ± 0.93^{ABC}	14.0 ± 1.41^{AB}	17.33 ± 0.41^{C}	13.67 ± 0.41^{A}	14.0 ± 0.71^{AB}	15.33 ± 0.41^{ABC}	16.33 ± 0.41^{BC}	9.0 ± 1.41^{D}	27.0 ± 0.71^{E}
E. faecalis	14.17 ± 0.89^{A}	20.0 ± 1.87^{B}	18.0 ± 0.71^{BC}	14.67 ± 0.41^{A}	13.67 ± 0.82^{A}	15.0 ± 0.71^{AD}	17.0 ± 0.71^{CD}	11.0 ± 0.71^{E}	31.17 ± 0.89^{F}
S. typhi	12.0 ± 1.87^{AB}	14.67 ± 0.82^{CD}	16.33 ± 0.41^{CE}	11.33 ± 0.41^{A}	13.50 ± 0.35^{BC}	14.83 ± 0.20^{CD}	18.33 ± 0.41^{E}	13.33 ± 0.82^{BC}	24.33 ± 0.41^{F}
E. coli 405	12.33 ± 1.74^{AB}	12.0 ± 0.71^{A}	17.33 ± 0.41^{C}	13.33 ± 0.41^{AB}	14.0 ± 0.71^{BD}	16.0 ± 0.71^{CD}	17.67 ± 0.41^{C}	13.33 ± 0.41^{AB}	25.67 ± 0.41^{E}
E. carotovora	10.67 ± 0.41^{A}	22.33 ± 0.82^{B}	12.50 ± 0.35^{AC}	9.67 ± 0.41^{A}	11.0 ± 0^{A}	11.67 ± 0.41^{A}	18.33 ± 0.82^{B}	17.0 ± 1.22^{BC}	34.67 ± 1.45^{B}
E. coli 100	15.17 ± 0.20^{A}	12.33 ± 0.41^{BC}	13.17 ± 0.54^{B}	11.67 ± 0.41^{CD}	10.67 ± 0.41^{E}	11.33 ± 0.41^{DE}	12.33 ± 0.41^{BC}	10.67 ± 0.41^{E}	25.67 ± 0.41^{F}

[a] Each value represents the average and the standard error of three independent experiments. Within each line, the mean values labelled with a different superscript (A–F) show statistically significant differences ($P < 0.05$).
[b] Dose: 0.2 mg/disk.

Table 4

Strains	Antifungal activity Inhibition zone (mm) 72 h (means ± SE)[a]									
	3[b]	**8**[b]	**9**[b]	**10**[b]	**11**[b]	**12**[b]	**13**[b]	**14**[b]	**15**[b]	Benomyl
F. culmorum	5.50 ± 0^{A}	7.0 ± 0^{BC}	8.0 ± 0^{D}	6.67 ± 0.41^{B}	5.50 ± 0.25^{A}	6.33 ± 0.41^{B}	7.67 ± 0.41^{CD}	9.5 ± 0.5^{E}	6.5 ± 0.5^{B}	$18.0 \pm 0^{F,c}$
G. candidum	0 ± 0	6.75 ± 0.25^{A}	7.0 ± 0^{A}	12.33 ± 0^{B}	7.33 ± 0.25^{AC}	7.83 ± 0.20^{CD}	8.33 ± 0.82^{D}	8.5 ± 0.5^{D}	5.75 ± 0.25^{E}	0 ± 0
T. viride	0 ± 0	7.25 ± 0.25^{AB}	7.0 ± 0^{A}	9.0 ± 0.50^{C}	5.50 ± 0.61^{D}	8.0 ± 0.71^{ABC}	8.33 ± 0.41^{BC}	9.0 ± 0^{C}	6.0 ± 0^{D}	$22.0 \pm 1.0^{E,d}$
P. citrophthora	0 ± 0	0 ± 0	0 ± 0	10.33 ± 0^{A}	0 ± 0	6.67 ± 0.41^{B}	6.0 ± 0^{B}	8.5 ± 0.5^{C}	0 ± 0	$24.5 \pm 1.5^{D,e}$
Parasiticus	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	18.0 ± 1.0^{d}

Compounds **2** and **5**–**7** did not exert antifungal activity.
[a] Each value represents the average and the standard error of three independent experiments. Within each line, the mean values labeled with a different superscript (A–F) show statistically significant differences ($P < 0.05$).
[b] Dose: 0.2 mg/disk.
[c] Dose: 10 μg/disk.
[d] Dose: 1 μg/disk.
[e] Dose: 1.5 μg/disk.

different phenyl moieties was essential to develop new antifungal THIQs. In addition and on a regular basis, 1-pentyl-THIQs bearing esters (**8**–**15**) displayed generally more antifungal activity than the corresponding THIQs with carbamates (**16**–**23**).

3. Materials and methods

3.1. Synthetic procedures

3.1.1. General

Reagents were purchased from Sigma–Aldrich Chemical Company (St. Louis, MO, USA) and solvents from Scharlab (Barcelona, Spain). All the reactions were monitored by analytical thin layer chromatography with silica gel 60 F_{254} (Merck 5554). Residues were purified by silica gel 60 (40–63 μm, Merck 9385) column chromatography. Quoted yields were of purified compounds. Electrospray mass spectrometry (ESMS) was recorded in a Esquire 3000 Plus spectrometer instrument (Bruker). Nuclear magnetic resonance (^{1}H and ^{13}C NMR) spectra were recorded with $CDCl_3$ as solvent in a Bruker DPX-500 spectrometer. Multiplicities of ^{13}C NMR resonances were assigned by DEPT experiments. ^{1}H and ^{13}C assignments were realized by mono and bidimensional techniques (COSY 45, HMQC, HSQC and HMBC).

3.1.2. General procedure for the synthesis of amides (1 and 4)

Corresponding alkyl chloride (16.6 mmol) was added dropwise at 0 °C to a solution of β-(3,4-dimethoxyphenyl)ethylamine (3.0 g, 16.6 mmol) in CH_2Cl_2 (30 mL) and 5% aqueous NaOH (15 mL). The reaction was stirred at room temperature for 2 h. After extraction with CH_2Cl_2, the combined organic phases were washed with brine

Table 5

Strains	Antifungal activity Inhibition zone (mm) 72 h (means ± SE)[a]							
	16[b]	**18**[b]	**19**[b]	**20**[b]	**21**[b]	**22**[b]	**23**[b]	Benomyl
F. culmorum	7.0 ± 0[A]	7.33 ± 0.41[A]	0 ± 0	0 ± 0	0 ± 0	15.0 ± 3.0[B]	0 ± 0	18.0 ± 0[B,c]
G. candidum	6.25 ± 0.25[A]	10.33 ± 0.41[B]	6.67 ± 0.41[A]	7.67 ± 0.41[C]	7.67 ± 0.41[C]	10.0 ± 0.0[B]	7.0 ± 0[AC]	0 ± 0
T. viride	5.75 ± 0.25[A]	8.67 ± 0.82[B]	6.17 ± 0.54[A]	0 ± 0	0 ± 0	7.0 ± 0[AB]	0 ± 0	22.0 ± 1.0[C,d]
P. citrophthora	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	6.25 ± 0.25[A]	0 ± 0	24.5 ± 1.5[B,e]
Parasiticus	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	0 ± 0	18.0 ± 1.0[d]

Compound **17** did not display antifungal activity.

[a] Each value represents the average and the standard error of three independent experiments. Within each line, the mean values labeled with a different superscript (A–D) show statistically significant differences (P <0.05).

[b] Dose: 0.2 mg/disk.

[c] Dose: 10 μg/disk.

[d] Dose: 1 μg/disk.

[e] Dose: 1.5 μg/disk.

and H_2O, dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified (CH_2Cl_2/MeOH 95:5) to obtain the corresponding amide.

3.1.2.1. *N*-(3,4-Dimethoxyphenethyl)pentanamide (1). Under the conditions depicted above and using valeryl chloride (2.0 mL, 16.6 mmol), 4.3 g of amide **1** as a white powder (98%) were obtained. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.80–6.77 (m, 1H, H-5), 6.72–6.68 (m, 2H, H-2, H-6), 5.55 (brs, 1H, CONH), 3.84 (s, 6H, OCH_3-3, OCH_3-4), 3.47 (dd, J = 6.9, 12.9 Hz, 2H, H-α), 2.74 (t, J = 6.9 Hz, 2H, H-β), 2.10 (t, J = 6.9 Hz, 2H, H-1′), 1.60–1.51 (m, 2H, H-2′), 1.34–1.24 (m, 2H, H-3′), 0.87 (t, J = 7.5 Hz, 3H, H-4′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.1 (CONH), 149.0 (C-3), 147.6 (C-4), 131.4 (C-1), 120.6 (CH-6), 111.9 (CH-2), 111.3 (CH-5), 55.9 (OCH_3-3), 55.8 (OCH_3-4), 40.5 (CH_2-α), 36.5 (CH_2-1′), 35.2 (CH_2-β), 27.8 (CH_2-2′), 22.3 (CH_2-3′), 13.7 (CH_2-4′); ESMS m/z (%) 266 $[M+H]^+$ (5).

3.1.2.2. Methyl *N*-(3,4-dimethoxyphenethylamino)-6-oxohexanoate (4). Under the same conditions described in the general procedure and using methyl adipoyl chloride (2.6 mL, 16.6 mmol), 4.9 g of amide **4** as a yellow powder (91%) were obtained. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.77 (d, J = 8.0 Hz, 1H, H-5), 6.72–6.67 (m, 2H, H-2, H-6), 5.71 (s, 1H, CONH), 3.82 and 3.80 (2s, 6H, OCH_3-3 and OCH_3-4), 3.62 (s, 3H, $COOCH_3$), 3.46 (q, J = 7.1 Hz, 2H, H-α), 2.72 (t, J = 7.1 Hz, 2H, H-β), 2.28 (t, J = 6.9 Hz, 2H, H-4′), 2.11 (t, J = 6.0 Hz, 2H, H-1′), 1.65–1.53 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.8 (CO), 172.4 (CONH), 148.9 (C-3), 147.6 (C-4), 131.3 (C-1), 120.5 (CH-6), 111.8 (CH-5), 111.3 (CH-2), 55.8 (OCH_3-3, OCH_3-4), 51.4 ($COOCH_3$), 40.6 (CH_2-α), 36.1 (CH_2-1′), 35.2 (CH_2-β), 33.5 (CH_2-4′), 25.0 (CH_2-2′), 24.3 (CH_2-3′); ESMS m/z (%) 324 $[M+H]^+$ (5).

3.1.3. General procedure for the synthesis of *N*-methyl-1-substituted-6,7-dimethoxy-3,4-dihydroisoquinolinium (2 and 5)

A solution of the corresponding amide (7.5 mmol) in dry acetonitrile (30 mL) was treated with $POCl_3$ (3.5 mL, 37.7 mmol) and refluxed for 1 h under a N_2 atmosphere. Then, the reaction mixture was evaporated to dryness. The residue was dissolved in H_2O (10 mL), basified to pH ≈ 9 and extracted with CH_2Cl_2. The organic phase was washed with brine and H_2O, dried over anhydrous $NaSO_4$, filtered and evaporated to dryness. A reddish oil, corresponding to an imine, was obtained and directly used in the next reaction. The imine was dissolved in dry acetone (30 mL) and treated with MeI (1.7 mL, 26.6 mmol). The reaction mixture was stirred and refluxed for 3 h under a N_2 atmosphere. Then, the solvent was evaporated to dryness and the residue was purified (CH_2Cl_2/MeOH 9:1) to obtain the corresponding dihydroisoquinolinium salt.

3.1.3.1. *N*-Methyl-1-butyl-6,7-dimethoxy-3,4-dihydroisoquinolinium (2). Under the same conditions described above and using amide **1** (2.0 g, 7.5 mmol) as starting material, 1.9 g of a yellow powder **2** (97%) were obtained. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.18 (s, 1H, H-8), 6.91 (s, 1H, H-5), 4.14 (t, J = 7.8 Hz, 2H, H-3), 3.99 and 3.91 (2s, 6H, OCH_3-6 and OCH_3-7), 3.91 (s, 3H, NCH_3), 3.27 (t, J = 7.8 Hz, 2H, H-4), 3.21–3.16 (m, 2H, H-1′), 1.72–1.63 (m, 2H, H-2′), 1.56–1.47 (m, 2H, H-3′), 1.00–0.95 (m, 3H, H-4′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 177.1 (C-1), 156.4 (C-6), 148.7 (C-7), 133.4 (C-4a), 118.6 (C-8a), 112.0 (CH-8), 111.1 (CH-5), 56.9 (OCH_3-6), 56.6 (OCH_3-7), 53.3 (CH_2-3), 45.9 (NCH_3), 31.7 (CH_2-1′), 29.7 (CH_2-2′), 26.0 (CH_2-4), 22.8 (CH_2-3′), 13.6 (CH_2-4′); ESMS m/z (%) 263 $[M+H]^+$ (31).

3.1.3.2. *N*-Methyl-1-(methylpentanoate)-6,7-dimethoxy-3,4-dihydroisoquinolinium (5). Under the same conditions described in the general procedure and using **4** (2.0 g, 6.2 mmol) as starting material, 1.9 g of a yellow oil **5** (96%) were obtained. ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.22 (s, 1H, H-8), 6.90 (s, 1H, H-5), 4.11 (t, J = 7.3 Hz, 2H, H-3), 3.96 and 3.93 (2s, 6H, OCH_3-6 and OCH_3-7), 3.91 (s, 3H, NCH_3), 3.60 (s, 3H, $COOCH_3$), 3.30–3.20 (m, 4H, H-4, H-1′), 2.38 (t, J = 6.3 Hz, 2H, H-4′), 1.84–1.72 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 176.6 (C-1), 173.2 (CO), 156.3 (C-6), 148.7 (C-7), 133.3 (C-4a), 118.5 (C-8a), 111.9 (CH-8), 111.0 (CH-5), 56.9 (OCH_3-7), 56.7 (OCH_3-6), 53.2 (CH_2-3), 51.6 ($COOCH_3$), 46.0 (NCH_3), 32.7 (CH_2-4′), 31.7 (CH_2-1′), 26.8 (CH_2-2′), 25.9 (CH_2-4), 24.6 (CH_2-3′); ESMS m/z (%) 320 $[M]^+$ (11).

3.1.4. General procedure for the synthesis of *N*-methyl-1-substituted-6,7-dimethoxy-1,2,3,4-THIQs (3 and 6)

A solution of the corresponding dihydroisoquinolinium (1.9 mmol) in MeOH (30 mL) at 0 °C was treated with $NaBH_4$ (216 mg, 5.7 mmol). The reaction mixture was stirred at room temperature for 2 h. Then, H_2O (15 mL) was added dropwise and the organic solvent was removed under reduced pressure. The aqueous mixture was extracted with CH_2Cl_2 and washed with brine and H_2O. A combination of the organic phases was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified (CH_2Cl_2/MeOH 93:7) to obtain the corresponding THIQ.

3.1.4.1. *N*-Methyl-1-butyl-6,7-dimethoxy-1,2,3,4-THIQ (3). Under the same conditions described above and using **2** (0.5 g, 1.9 mmol) as starting material, 303 mg of a translucent oil **3** (61%) were obtained. ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.52 (s, 1H, H-8), 6.49 (s, 1H, H-5), 3.77 and 3.76 (2s, 6H, OCH_3-6 and OCH_3-7), 3.30 (t, J = 5.4 Hz, 1H, H-1), 3.08–3.00 (m, 1H, Ha-3), 2.71–2.54 (m, 3H, Hb-3, H-4), 2.37 (s, 3H, NCH_3), 1.71–1.64 (m, 2H, H-1′), 1.38–1.15 (m, 4H, H-2′, H-3′), 0.82 (t, J = 7.1 Hz, 3H, H-4′); ^{13}C

NMR (125 MHz, $CDCl_3$): δ 146.9 (C-6, C-7), 130.1 (C-8a), 126.3 (C-4a), 111.0 (CH-5), 110.0 (CH-8), 63.11 (CH-1), 55.6 (OCH_3-6), 55.4 (OCH_3-7), 48.0 (CH_2-3), 42.5 (NCH_3), 34.4 (CH_2-1′), 27.5 (CH_2-2′), 25.3 (CH_2-4), 22.7 (CH_2-3′), 13.8 (CH_2-4′); ESMS *m*/*z* (%) 264 $[M+H]^+$ (39).

3.1.4.2. *N*-Methyl-1-(methylpentanoate)-6,7-dimethoxy-1,2,3,4-THIQ (6). Under the same conditions described in the general procedure and using **5** (1.0 g, 3.1 mmol) as starting material, 576 mg of a translucent oil **6** (58%) were obtained. ^1H NMR (500 MHz, $CDCl_3$): δ 6.55 (s, 1H, H-5), 6.54 (s, 1H, H-8), 3.83 (s, 6H, OCH_3-6, OCH_3-7), 3.63 (s, 3H, $COOCH_3$), 3.35 (t, *J* = 5.5 Hz, 1H, H-1), 3.11–3.04 (m, 1H, Ha-3), 2.76–2.69 (m, 1H, Ha-4), 2.68–2.60 (m, 2H, Hb-3, Hb-4), 2.46 (s, 3H, NCH_3), 2.28 (t, *J* = 7.6 Hz, 2H, H-4′), 1.76–1.71 (m, 2H, H-1′), 1.66–1.56 (m, 2H, H-3′), 1.46–1.39 (m, 1H, Ha-2′), 1.31–1.24 (m, 1H, Hb-2′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 174.2 (CO), 147.2 (C- 6), 147.1 (C-7), 130.0 (C-8a), 126.6 (C-4a), 111.2 (CH-5), 110.1 (CH-8), 63.1 CH-1), 55.9 OCH_3-7), 55.7 (OCH_3-6), 51.4 ($COOCH_3$), 48.2 (CH_2-3), 42.7 (NCH_3), 34.6 (CH_2-1′), 34.0 (CH_2-4′), 25.5 (CH_2-4), 25.2 (CH_2-3′), 25.0 (CH_2-2′); ESMS *m*/*z* (%) 322 $[M+H]^+$ (2).

3.1.5. Synthesis of *N*-methyl-1-pentanol-6,7-dimethoxy-1,2,3,4-THIQ (7)

A solution of *N*-methyl-1-(methylpentanoate)-6,7-dimethoxy-1,2,3,4-THIQ **6** (545 mg, 1.7 mmol) in dry THF (30 mL) was added to a stirred suspension of $LiAlH_4$ (69 mg; 1.8 mmol) in anhydrous Et_2O (6 mL) under a N_2 atmosphere and the mixture was refluxed for 2 h. Thereafter, the reaction mixture was cooled and H_2O (15 mL) was added dropwise to destroy the excess of $LiAlH_4$. The solvent was evaporated to obtain 431 mg of a pink oil **7** (87%). ^1H NMR (500 MHz, $CDCl_3$): δ 6.55 (s, 1H, H-5), 6.54 (s, 1H, H-8), 3.83 (s, 6H, OCH_3-6, OCH_3-7), 3.59 (t, *J* = 6.6 Hz, 2H, H-5′), 3.37 (t, *J* = 5.5 Hz, 1H, H-1), 3.13–3.05 (m, 1H, Ha-3), 2.77–2.69 (m, 1H, Ha-4), 2.68–2.61 (m, 2H, Hb-3, Hb-4), 2.42 (s, 3H, NCH_3), 1.77-1.70 (m, 2H, H-1′), 1.58–1.50 (m, 2H, H-4′), 1.47–1.26 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 147.2 (C-6), 147.1 (C-7), 130.1 (C-8a), 126.5 (C-4a), 111.2 (CH-5), 110.2 (CH-8), 63.25 (CH-1), 62.7 (CH_2-5′), 56.0 (OCH_3-7), 55.8 (OCH_3-6), 48.0 (CH_2-3), 42.7 (NCH_3), 34.9 (CH_2-1′), 32.5 (CH_2-4′), 25.9 (CH_2-4), 25.3 (CH_2-3′), 25.2 (CH_2-2′); ESMS *m*/*z* (%) 294 $[M+H]^+$ (14).

3.1.6. General procedure for the synthesis of esters *N*-methyl-1-pentyl-6,7-dimethoxy-1,2,3,4-THIQ (8–15)

A solution of the corresponding benzoyl chloride (0.3 mmol) in dry CH_2Cl_2 (5 mL) was added dropwise at 0 °C to a stirred solution of *N*-methyl-1-pentanol-6,7-dimethoxy-1,2,3,4-THIQ **7** (88 mg, 0.3 mmol), 4-(dimethylamino)pyridine (12 mg, 0.1 mmol) and triethylamine (42 μL, 0.3 mmol) in dry CH_2Cl_2 (20 mL). The reaction mixture was stirred at room temperature under a N_2 atmosphere for 5 h. Next, the reaction mixture was extracted with CH_2Cl_2 and washed with H_2O. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified (toluene/AcOEt/MeOH 6:3:1) to obtain the corresponding THIQ ester.

3.1.6.1. *N*-Methyl-1-(pentylbenzoate)-6,7-dimethoxy-1,2,3,4-THIQ (8). Under the same conditions described above, **7** and benzoyl chloride (35.0 μL, 0.3 mmol) reacted to obtain 80 mg of a yellow oil **8** (67%). ^1H NMR (500 MHz, $CDCl_3$): δ 8.04–8.00 (m, 2H, H-2″, H-6″), 7.57–7.50 m, 1H, H-4″), 7.46–7.39 (m, 2H, H-3″, H-5″), 6.58 (s, 1H, H-5), 6.56 (s, 1H, H-8), 4.28 (t, *J* = 6.6 Hz, 2H, H-5′), 3.85 and 3.84 (2s, 6H, OCH_3-6 and OCH_3-7), 3.58 (t, *J* = 5.7 Hz, 2H, H-1), 3.30–3.20 (m, 1H, Ha-3), 2.91–2.85 (m, 1H, Hb-3), 2.85–2.78 (m, 1H, Ha-4), 2.78–2.70 (m, 1H, Hb-4), 2.54 (s, 3H, NCH_3), 1.97–1.85 (m, 1H, Ha-1′), 1.80–1.71 (m, 3H, Hb-1′, H-4′), 1.54–1.39 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.6 (CO), 147.7 (C-6), 147.4 (C-7), 132.8 (C-4″), 130.5 (C-1″), 129.5 (CH-2″, CH-6″), 128.4 (C-8a), 128.3 (CH-3″, CH-5″), 125.3 (C-4a), 111.4 (CH-8), 110.3 (CH-5), 65.0 (CH_2-5′), 63.2 (CH-1), 56.0 (OCH_3-6), 55.8 (OCH_3-7), 46.9 (CH_2-3), 41.7 (NCH_3), 34.8 (CH_2-1′), 28.7 (CH_2-4′), 26.3 (CH_2-3′), 25.6 (CH_2-2′), 24.5 (CH_2-4); ESMS *m*/*z* (%) 398 $[M+H]^+$ (29).

3.1.6.2. *N*-Methyl-1-[(4″-fluorobenzoate)pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (9). Under the same conditions described in the general procedure, **7** and 4-fluorobenzoyl chloride (60 μL, 0.5 mmol) reacted to obtain 166 mg of the yellow oil **9** (80%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.98–7.90 (m, 2H, H-2″, H-6″), 7.05–7.00 (m, 2H, H-3″, H-5″), 6.51 (s, 1H, H-5), 6.49 (s, 1H, H-8), 4.18 (t, *J* = 6.6 Hz, 2H, H-5′), 3.55 and 3.54 (2s, 6H, OCH_3-6 and OCH_3-7), 3.49 (t, *J* = 5.7 Hz, 1H, H-1), 3.20–3.11 (m, 1H, Ha-3), 2.81–2.70 (m, 1H, Hb-3), 2.70–2.62 (m, 2H, H-4), 2.44 (s, 3H, NCH_3), 1.86–1.77 (m, 1H, Ha-1′), 1.72–1.62 (m, 3H, Hb-1′, H-4′), 1.45–1.30 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.2 (C-4″, d, *J* = 251 Hz), 165.2 (CO), 147.3 (C-6), 147.0 (C-7), 131.5 (CH-2″, CH-6″, d, *J* = 9 Hz), 128.1 (C-8a), 126.4 (C-4a), 125.1 (C-1″), 114.6 (CH-3″, CH-5″, d, *J* = 21 Hz), 111.1 (CH-8), 110.1 (CH-5), 64.8 (CH_2-5′), 62.8 (CH-1), 55.7 (OCH_3-6), 55.5 (OCH_3-7), 46.7 (CH_2-3), 41.4 (NCH_3), 34.3 (CH_2-1′), 28.3 (CH_2-4′), 25.9 (CH_2-2′), 25.2 (CH_2-3′), 24.2 (CH_2-4); ESMS *m*/*z* (%) 416 $[M+H]^+$ (17).

3.1.6.3. *N*-Methyl-1-[(4″-chlorobenzoate)pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (10). Under the same conditions described above, **7** and 4-chlorobenzoyl chloride (0.1 mL, 0.8 mmol) reacted to obtain 143.3 mg of yellow oil **10** (66%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.97–7.91 (m, 2H, H-2″, H-6″), 7.42–7.35 (m, 2H, H-3″, H-5″), 6.56 (s, 1H, H-8), 6.55 (s, 1H, H-5), 4.28 (t, *J* = 6.7 Hz, 2H, H-5′), 3.83 and 3.82 (2s, 6H, OCH_3-6 and OCH_3-7), 3.38 (t, *J* = 5.4 Hz, 1H, H-1), 3.15–3.04 (m, 1H, Ha-3), 2.77–2.61 (m, 3H, Hb-3, H-4), 2.43 (s, 3H, NCH_3), 1.79–1.69 (m, 4H, H-1′, H-4′), 1.51–1.30 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 165.7 (CO), 147.2 (C-6, C-7), 139.2 (C-1″), 130.9 (CH-2″, CH-6″), 129.9 (C-8a), 128.9 (C-4″), 128.6 (CH-3″, CH-5″), 126.5 (C-4a), 111.2 (CH-5), 110.1 (CH-8), 65.3 (CH_2-5′), 63.3 (CH-1), 56.0 (OCH_3-6), 55.7 (OCH_3-7), 48.2 (CH_2-3), 42.7 (NCH_3), 34.9 (CH_2-1′), 28.7 (CH_2-4′), 26.3 (CH_2-3′), 25.5 (CH_2-4), 25.2 (CH_2-2′); ESMS *m*/*z* (%) 432 $[M+H]^+$ (12).

3.1.6.4. *N*-Methyl-1-[(4″-methoxybenzoate)pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (11). Under the same conditions described in the general procedure, **7** and 4-methoxybenzoyl chloride (0.1 mL, 0.8 mmol) reacted to obtain 68 mg of the yellow oil **11** (32%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.98–7.92 (m, 2H, H-3″, H-5″), 6.91–6.86 (m, 2H, H-2″, H-6″), 6.56 (s, 1H, H-5), 6.55 (s, 1H, H-8), 4.24 (t, *J* = 6.6 Hz, 2H, H-5′), 3.83 (s, 9H, OCH_3-6, OCH_3-7, OCH_3-4″), 3.51 (t, *J* = 5.7 Hz, 1H, H-1), 3.24–3.14 (m, 1H, Ha-3), 2.84–2.64 (m, 3H, Hb-3, H-4), 2.49 (s, 3H, NCH_3), 1.91–1.82 (m, 1H, Ha-1′), 1.79–1.68 (m, 3H, Hb-1′, H-4′), 1.53–1.37 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 166.3 (CO), 163.2 (C-4″), 147.5 (C-6), 147.3 (C-7), 131.4 (CH-3″, CH-5″), 128.9 (C-8a), 125.6 (C-4a), 122.9 (C-1″), 113.2 (CH-2″, CH-6″), 111.3 (CH-5), 110.3 (CH-8), 64.6 (CH_2-5′), 63.1 (CH-1), 56.0 (OCH_3-6), 55.8 (OCH_3-7), 47.1 (CH_2-3), 41.9 (NCH_3), 34.8 (CH_2-1′), 28.7 (CH_2-4′), 26.3 (CH_2-3′), 25.5 (CH_2-2′), 24.6 (CH_2-4); ESMS *m*/*z* (%) 428 $[M+H]^+$ (14).

3.1.6.5. *N*-Methyl-1-[(phenylpropanoate)pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (12). Under the same conditions described above, **7** and hydrocinnamoyl chloride (0.1 mL, 0.8 mmol) reacted to obtain 139 mg of yellow oil **12** (65%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.30–7.23 (m, 2H, H-2″, H-6″), 7.21–7.15 (m, 3H, H-3″, H-4″, H-5″), 6.56 (s, 1H, H-5), 6.55 (s, 1H, H-8), 4.03 (t, *J* = 6.7 Hz, 2H, H-5′), 3.83 (s, 6H, OCH_3-6, OCH_3-7), 3.37 (t,

J = 5.4 Hz, 1H, H-1), 3.14–3.05 (m, 1H, Ha-3), 2.93 (t, *J* = 7.8 Hz, 2H, H-9′), 2.78–2.63 (m, 3H, Hb-3, H-4), 2.60 (t, *J* = 7.8 Hz, 2H, H-8′), 2.44 (s, 3H, NCH_3), 1.77–1.69 (m, 2H, H-1′), 1.63–1.53 (m, 2H, H-4′), 1.47–1.24 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.8 (CO), 147.1 (C-6, C-7), 140.4 (C-1″), 129.9 (C-8a), 128.3 (CH-2″, CH-6″), 128.1 (CH-3″, CH-5″), 126.5 (C-4a), 126.2 (CH-4″), 111.2 (CH-5), 110.1 (CH-8), 64.5 (CH_2-5′), 63.2 (CH-1), 55.9 (OCH_3-6), 55.7 (OCH_3-7), 48.1 (CH_2-3), 42.6 (NCH_3), 35.8 (CH_2-8′), 34.8 (CH_2-1′), 30.8 (CH_2-9′), 28.5 (CH_2-4′), 26.1 (CH_2-3′), 25.4 (CH_2-4), 25.1 (CH_2-2′); ESMS *m*/*z* (%) 426 $[M+H]^+$ (14).

3.1.6.6. *N*-Methyl-1-[(4″-fluorophenylpropanoate)pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (13). A solution of 3-(4-fluorophenyl)propionic acid (300 mg, 1.8 mmol) in dry CH_2Cl_2 (20 mL) was treated with thionyl chloride (2.2 mL, 30.2 mmol). The reaction mixture was refluxed for 3 h and the solvent was then removed until dryness. A translucent oil, corresponding to 3-(4-fluorophenyl)propanoyl chloride, was obtained and used directly in the next reaction under the same conditions described in the general procedure. Therefore, **7** (314.5 mg, 1.1 mmol) and 3-(4-fluorophenyl)propanoyl chloride (300 mg, 1.6 mmol) reacted to obtain 251 mg of a yellow oil **13** (51%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.15–7.09 (m, 2H, H-2″, H-6″), 6.95–6.89 (m, 2H, H-3″, H-5″), 6.55 (s, 1H, H-5), 6.53 (s, 1H, H-8), 4.01 (t, *J* = 6.7 Hz, 2H, H-5′), 3.82 and 3.81 (2s, 6H, OCH_3-6 and OCH_3-7), 3.35 (t, *J* = 5.4 Hz, 1H, H-1), 3.12–3.03 (m, 1H, Ha-3), 2.88 (t, *J* = 7.7 Hz, 2H, H-9′), 2.74–2.60 (m, 3H, Hb-3, H-4), 2.56 (t, *J* = 7.7 Hz, 2H, H-8′), 2.41 (s, 3H, NCH_3), 1.75–1.67 (m, 2H, H-1′), 1.59–1.52 (m, 2H, H-4′), 1.44–1.21 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.6 (CO), 161.3 (C-4″, d, *J* = 242 Hz), 147.1 (C-6, C-7), 136.1 (C-1″), 130 (CH-2″, CH-6″, d, *J* = 8 Hz), 126.5 (C-8a, C-4a), 115.0 (CH-3″, CH-5″, d, *J* = 21 Hz), 111.2 (CH-8), 110.0 (CH-5), 64.5 (CH_2-5′), 63.2 (CH-1), 55.9 (OCH_3-6), 55.6 (OCH_3-7), 48.1 (CH_2-3), 42.6 (NCH_3), 35.8 (CH_2-8′), 34.7 (CH_2-1′), 30.0 (CH_2-9′), 28.5 (CH_2-4′), 26.1 (CH_2-4), 25.4 (CH_2-2′), 25.0 (CH_2-3′); ESMS *m*/*z* (%) 444 $[M+H]^+$ (19).

3.1.6.7. *N*-Methyl-1-[(4″-chlorophenylpropanoate)pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (14). A solution of 3-(4-chlorophenyl)propionic acid (111 mg, 0.6 mmol) was treated with thionyl chloride (0.7 mL, 9.6 mmol), as described for **13**. Then, a solution of 3-(4-chlorophenyl)propanoyl chloride (102 mg, 0.5 mmol) and **7** (118 mg, 0.4 mmol) reacted under the same conditions described in the general procedure to obtain 19 mg of a yellow oil **14** (10%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.23 (d, *J* = 8.3 Hz, 2H, H-3″, H-5″), 7.12 (d, *J* = 8.3 Hz, 2H, H-2″, H-6″), 6.56 (s, 1H, H-5), 6.55 (s, 1H, H-8), 4.02 (t, *J* = 6.7 Hz, 2H, H-5′), 3.84 (s, 6H, OCH_3-6, OCH_3-7), 3.40 (t, *J* = 5.1 Hz, 1H, H-1), 3.17–3.08 (m, 1H, Ha-3), 2.90 (t, *J* = 7.7 Hz, 2H, H-9′), 2.80–2.64 (m, 3H, Hb-3, H-4), 2.58 (t, *J* = 7.7 Hz, 2H, H-8′), 2.45 (s, 3H, NCH_3), 1.80–1.68 (m, 2H, H-1′), 1.62–1.53 (m, 2H, H-4′), 1.36–1.22 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 172.7 (CO), 147.3 (C-6), 147.2 (C-7), 139.0 (C-1″), 132.0 (C-8a, C-4″), 129.7 (CH-2″, CH-6″), 128.6 (CH-3″, CH-5″), 126.6 (C-4a), 111.3 (CH-5), 110.2 (CH-8), 64.7 (CH_2-5′), 63.3 (CH-1), 56.0 (OCH_3-6), 55.8 (OCH_3-7), 48.0 (CH_2-3), 42.6 (NCH_3), 35.7 (CH_2-8′), 34.9 (CH_2-1′), 30.3 (CH_2-9′), 28.6 (CH_2-4′), 26.2 (CH_2-2′, CH_2-3′), 25.3 (CH_2-4); ESMS *m*/*z* (%) 460 $[M+H]^+$ (32).

3.1.6.8. *N*-Methyl-1-[(4″-methoxyphenylpropanoate)-pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (15). A solution of 3-(4-methoxyphenyl)propionic acid (198 mg, 1.1 mmol) in dry CH_2Cl_2 (20 mL) was treated with thionyl chloride (1.4 mL, 19.2 mmol), as described for **13**. Then, a solution of 3-(4-methoxyphenyl)propanoyl chloride (198.7 mg, 1.0 mmol) and **7** reacted under the same conditions described in the general procedure to obtain 46 mg of the yellow oil **15** (14%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.13–7.07 (m, 2H, H-2″, H-6″), 6.84–6.78 (m, 2H, H-3″, H-5″), 6.56 (s, 1H, H-5), 6.55 (s, 1H, H-8), 4.03 (t, *J* = 6.7 Hz, 2H, H-5′), 3.84 (s, 6H, OCH_3-6, OCH_3-7), 3.77 (s, 3H, OCH_3-4″), 3.38 (t, *J* = 5.4 Hz, 1H, H-1), 3.15–3.06 (m, 1H, Ha-3), 2.87 (t, *J* = 7.8 Hz, 2H, H-9′), 2.79–2.71 (m, 1H, Ha-4), 2.71–2.63 (m, 2H, Hb-3, Hb-4), 2.57 (t, *J* = 7.8 Hz, 2H, H-8′), 2.44 (s, 3H, NCH_3), 1.78–1.69 (m, 2H, H-1′), 1.62–1.53 (m, 2H, H-4′), 1.47–1.23 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 173.0 (CO), 158.0 (C-4″), 147.2 (C-6, C-7), 132.6 (C-1″), 129.9 (C-8a), 129.2 (CH-2″, CH-6″), 126.4 (C-4a,) 113.8 (CH-3″, CH-5″), 111.3 (CH-5), 110.2 (CH-8), 64.5 (CH_2-5′), 63.3 (CH-1), 56.0 (OCH_3-6), 55.8 (OCH_3-7), 55.2 (OCH_3-4″), 48.1 (CH_2-3), 42.7 (NCH_3), 36.1 (CH_2-8′), 34.9 (CH_2-1′), 30.1 (CH_2-9′), 28.6 (CH_2-4′), 26.2 (CH_2-2′), 25.4 (CH_2-3′), 25.2 (CH_2-4); ESMS *m*/*z* (%) 456 $[M+H]^+$ (15).

3.1.7. General procedure for the synthesis of carbamates *N*-methyl-1-[(substituted carbamate)pentyl]-6,7-dimethoxy-1,2,3,4-THIQs (16–23)

A mixture of *N*-methyl-1-pentanol-6,7-dimethoxy-1,2,3,4-THIQ (**7**, 0.4 mmol) and the corresponding isocyanate (1.2 mmol) in CH_2Cl_2 (20 mL) was refluxed under a N_2 atmosphere for 24 h. The reaction mixture was extracted with CH_2Cl_2 and washed with brine and H_2O. The organic phase was dried over anhydrous Na_2SO_4, filtered and evaporated to dryness. The residue was purified (CH_2Cl_2/MeOH 97:3) to obtain the corresponding THIQ carbamate.

3.1.7.1. *N*-Methyl-1-[(phenylcarbamate)-pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (16). A mixture of **7** (118 mg, 0.4 mmol) and phenyl isocyanate (0.13 mL, 1.2 mmol) was subjected to similar conditions to those above described to obtain 124 mg of a dark yellow oil **16** (75%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.41–7.35 (m, 2H, H-3″, H-5″), 7.30–7.25 (m, 2H, H-2″, H-6″), 7.05–7.00 (m, 1H, H-4″), 6.86 (s, 1H, NH), 6.56 (s, 1H, H-5), 6.55 (s, 1H, H-8), 4.12 (t, *J* = 6.6 Hz, 2H, H-5′), 3.83 (s, 6H, OCH_3-6, OCH_3-7), 3.41 (t, *J* = 5.4 Hz, 1H, H-1), 3.17–3.08 (m, 1H, Ha-3), 2.79–2.63 (m, 3H, Hb-3, H-4), 2.45 (s, 3H, NCH_3), 1.83–1.70 (m, 2H, H-1′), 1.65 (qt, *J* = 6.9 Hz, 2H, H-4′), 1.49–1.30 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.7 (CO), 147.3 (C-6), 147.2 (C-7), 138.0 (C-1″), 129.6 (C-8a), 128.9 (CH-2″, CH-6″), 126.3 (C-4a), 123.2 (CH-4″), 118.6 (CH-3″, CH-5″), 111.3 (CH-8), 110.2 (CH-5), 65.3 (CH_2-5′), 63.3 (CH-1), 56.0 (OCH_3-6), 55.8 (OCH_3-7), 48.0 (CH_2-3), 42.5 (NCH_3), 34.8 (CH_2-1′), 28.8 (CH_2-4′), 26.2 (CH_2-3′), 25.3 (CH_2-4), 25.2 (CH_2-2′); ESMS *m*/*z* (%) 413 $[M+H]^+$ (36).

3.1.7.2. *N*-Methyl-1-[(4″-fluorophenylcarbamate)pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (17). A mixture of **7** (84 mg, 0.3 mmol) and 4-fluorophenyl isocyanate (0.1 mL, 0.9 mmol) was subjected to similar conditions to those described in the general procedure to obtain 28 mg of a dark yellow oil **17** (22%). ^1H NMR (500 MHz, $CDCl_3$): δ 7.34–7.24 (m, 2H, H-2″, H-6″), 6.94–6.88 (m, 2H, H-3″, H-5″), 6.50 (s, 1H, H-5), 6.49 (s, 1H, H-8), 4.05 (t, *J* = 6.5 Hz, 2H, H-5′), 3.77 (s, 6H, OCH_3-6, OCH_3-7), 3.50–3.43 (m, 1H, H-1), 3.18–3.10 (m, 1H, Ha-3), 2.77–2.66 (m, 3H, Hb-3, H-4), 2.45 (s, 3H, NCH_3), 1.83–1.74 (m, 1H, Ha-1′), 1.73–1.65 (m, 1H, Hb-1′), 1.62–1.55 (m, 2H, H-4′), 1.46–1.27 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 163.0 (C-4″, d, *J* = 243 Hz), 153.9 (CO), 147.6 (C-6), 147.4 (C-7), 134.1 (C-1″), 129.4 (C-8a), 125.5 (C-4a), 120.3 (CH-2″, CH-6″, d, *J* = 8 Hz), 115.5 (CH-3″, CH-5″, d, *J* = 23 Hz), 111.3 (CH-5), 110.2 (CH-8), 65.4 (CH_2-5′), 63.5 (CH-1), 56.0 (OCH_3-7), 55.8 (OCH_3-6), 47.6 (CH_2-3), 42.1 (NCH_3), 34.8 (CH_2-1′), 28.7 (CH_2-4′), 26.3 (CH_2-3′), 25.3 (CH_2-2′), 24.8 (CH_2-4); ESMS *m*/*z* (%) 431 $[M+H]^+$ (45).

3.1.7.3. *N*-Methyl-1-[(4″-chlorophenylcarbamate)-pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (18). A mixture of **7** (150 mg, 0.5 mmol) and 4-chlorophenyl isocyanate (0.2 mL, 1.5 mmol) was

subjected to similar conditions to those above described to obtain 144 mg of a yellow oil **18** (64%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.32 (d, J = 8.4 Hz, 2H, H-3″, H-5″), 7.23 (d, J = 8.4 Hz, 2H, H-2″, H-6″), 6.92 (s, 1H, NH), 6.56 (s, 1H, H-5), 6.55 (s, 1H, H-8), 4.11 (t, J = 6.6 Hz, 2H, H-5′), 3.83 and 3.82 (2s, 6H, OCH_3-6 and OCH_3-7), 3.37 (t, J = 5.3 Hz, 1H, H-1), 3.13–3.06 (m, 1H, Ha-3), 2.77–2.62 (m, 3H, Hb-3, H-4), 2.43 (s, 3H, NCH_3), 1.78–1.71 (m, 2H, H-1′), 1.67–1.59 (m, 2H, H-4′), 1.47–1.27 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 153.6 (CO), 147.2 (C-6), 147.1 (C-7), 136.7 (C-1″), 129.9 (C-8a), 128.9 (CH-2″, CH-6″), 128.1 (C-4″), 126.6 (C-4a), 119.8 (CH-3″, CH-5″), 111.3 (CH-5), 110.2 (CH-8), 65.5 (CH_2-5′), 63.3 (CH-1), 56.0 (OCH_3-6), 55.7 (OCH_3-7), 48.2 (CH_2-3), 42.7 (NCH_3), 34.8 (CH_2-1′), 28.8 (CH_2-4′), 26.2 (CH_2-4), 25.3 (CH_2-2′, CH_2-3′); ESMS m/z (%) 447 $[M+H]^+$ (100).

3.1.7.4. *N*-Methyl-1-[(4″-methoxyphenylcarbamate)pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (19). A mixture of **7** (150 mg, 0.5 mmol) and 4-methoxyphenyl isocyanate (0.2 mL, 1.5 mmol) was subjected to similar conditions to those above described to obtain 160 mg of a yellow oil **19** (73%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.30–7.23 (m, 2H, H-2″, H-6″), 6.83–6.79 (m, 2H, H-3″, H-5″), 6.55 (s, 1H, H-5), 6.54 (s, 1H, H-8), 4.09 (t, J = 6.6 Hz, 2H, H-5′), 3.82 (s, 6H, OCH_3-6, OCH_3-7), 3.75 (s, 3H, OCH_3-4″), 3.37 (t, J = 5.4 Hz, 1H, H-1), 3.13–3.05 (m, 1H, Ha-3), 2.77–2.61 (m, 3H, Hb-3, H-4), 2.42 (s, 3H, NCH_3), 1.77–1.70 (m, 2H, H-1′), 1.62 (p, J = 6.63 Hz, 2H, H-4′), 1.48–1.27 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 155.7 (C-4″), 154.1 (CO), 147.1 (C-6, C-7), 131.1 (C-1″), 129.9 (C-8a), 128.5 (C-4a), 120.5 (CH-2″, CH-6″), 114.1 (CH-3″, CH-5″), 111.2 (CH-5), 110.1 (CH-8), 65.1 (CH_2-5′), 63.2 (CH-1), 56.0 (OCH_3-6), 55.7 (OCH_3-7), 48.1 (CH_2-3), 42.7 (NCH_3), 34.7 (CH_2-1′), 28.8 (CH_2-4′), 26.2 (CH_2-4), 25.2 (CH_2-2′, CH_2-3′); ESMS m/z (%) 443 $[M+H]^+$ (100).

3.1.7.5. *N*-Methyl-1-[(phenethylcarbamate)pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (20). A mixture of **7** (150 mg, 0.5 mmol) and phenethyl isocyanate (0.2 mL, 1.5 mmol) was subjected to similar conditions to those described in the general procedure to obtain 146 mg of a yellow oil **20** (66%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.31–7.25 (m, 2H, H-2″, H-6″), 7.24–7.14 (m, 3H, H-3″, H-4″, H-5″), 6.56 (s, 1H, H-5), 6.55 (s, 1H, H-8), 4.71 (s, 1H, NH), 4.01 (t, J = 6.3 Hz, 2H, H-5′), 3.84 and 3.83 (2s, 6H, OCH_3-6 and OCH_3-7), 3.45–3.39 (m, 2H, H-9′), 3.37 (t, J = 5.4 Hz, 1H, H-1), 3.13–3.05 (m, 1H, Ha-3), 2.83–2.76 (m, 2H, H-10′), 2.77–2.62 (m, 3H, Hb-3, H-4), 2.43 (s, 3H, NCH_3), 1.78–1.69 (m, 2H, H-1′), 1.64–1.52 (m, 2H, H-4′), 1.46–1.25 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.6 (CO), 147.2 (C-6, C-7), 138.8 (C-1″), 130.1 (C-8a), 128.8 (CH-2″, CH-6″), 128.5 (CH-3″, CH-5″), 126.5 (CH-4″), 126.3 (C-4a), 111.2 (CH-5), 110.2 (CH-8), 64.9 (CH_2-5′), 63.3 (CH-1), 56.0 (OCH_3-6), 55.7 (OCH_3-7), 48.1 (CH_2-3), 42.7 (NCH_3), 42.1 (CH_2-9′), 36.1 (CH_2-10′), 34.9 (CH_2-1′), 29.0 (CH_2-4′), 26.2 (CH_2-4), 25.3 (CH_2-2′, CH_2-3′); ESMS m/z (%) 441 $[M+H]^+$ (100).

3.1.7.6. *N*-Methyl-1-[(4″-fluorophenethylcarbamate)-pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (21). A mixture of **7** (150 mg, 0.5 mmol) and 4-fluorophenethyl isocyanate (0.2 mL, 1.5 mmol) was subjected to similar conditions to those above described to obtain 153 mg of a yellow oil **21** (67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.17–7.08 (m, 2H, H-2″, H-6″), 7.00–6.94 (m, 2H, H-3″, H-5″), 6.55 (s, 1H, H-5), 6.54 (s, 1H, H-8), 4.72 (s, 1H, NH), 4.00 (t, J = 6.4 Hz, 2H, H-5′), 3.83 and 3.81 (2s, 6H, OCH_3-6 and OCH_3-7), 3.41–3.31 (m, 3H, H-1, H-9′), 3.13–3.04 (m, 1H, Ha-3), 2.81–2.60 (m, 5H, Hb-3, H-4, H-10′), 2.42 (s, 3H, NCH_3), 1.76–1.68 (m, 2H, H-1′), 1.62–1.52 (m, 2H, H-4′), 1.45–1.23 (m, 4H, H-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 161.6 (C-4″, d, J = 243 Hz), 156.6 (CO), 147.2 (C-6, C-7), 134.4 (C-1″), 130.1 (CH-2″, CH-6″, d, J = 8 Hz), 130.0 (C-8a), 126.5 (C-4a), 115.3 (CH-3″, CH-5″, d, J = 21 Hz), 111.2 (CH-8), 110.2 (CH-5), 64.9 (CH_2-5′), 63.3 (CH-1), 56.0 (OCH_3-7), 55.7 (OCH_3-6), 48.1 (CH_2-3), 42.7 (NCH_3), 42.1 (CH_2-9′), 35.3 (CH_2-10′), 34.9 (CH_2-1′), 29.0 (CH_2-4′), 26.2 (CH_2-4), 25.3 (CH_2-2′, CH_2-3′); ESMS m/z (%) 459 $[M+H]^+$ (100).

3.1.7.7. *N*-Methyl-1-[(4″-chlorophenethylcarbamate)pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (22). Finally, 244 mg of **7** (0.8 mmol) was subjected to similar conditions to those above described, using 4-chlorophenethyl isocyanate (0.4 mL, 2.5 mmol), to obtain 253 mg of the yellow oil **22** (67%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.27 (d, J = 8.3 Hz, 2H, H-3″, H-5″), 7.12 (d, J = 8.3 Hz, 2H, H-2″, H-6″), 6.56 (s, 2H, H-5, H-8), 4.70 (s, 1H, NH), 4.02 (t, J = 6.5 Hz, 2H, H-5′), 3.85 and 3.84 (2s, 6H, OCH_3-6 and OCH_3-7), 3.43–3.34 (m, 3H, H-1, H-9′), 3.15–3.07 (m, 1H, Ha-3), 2.80–2.75 (m, 2H, H-10′), 2.75–2.64 (m, 3H, Hb-3, H-4), 2.45 (s, 3H, NCH_3), 1.80–1.69 (m, 2H, H-1′), 1.62–1.53 (m, 2H, H-4′), 1.49–1.38 (m, 1H, Ha-2′), 1.38–1.23 (m, 3H, Hb-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 156.6 (CO), 147.2 (C-6, C-7), 137.3 (C-1″), 132.2 (C-4″), 130.1 (CH-2″, CH-6″), 129.9 (C-8a), 128.7 (CH-3″, CH-5″), 126.5 (C-4a), 111.3 (CH-5), 110.2 (CH-8), 65.0 (CH_2-5′), 63.3 (CH-1), 56.0 (OCH_3-7), 55.8 (OCH_3-6), 48.1 (CH_2-3), 42.7 (NCH_3), 41.9 (CH_2-9′), 35.5 (CH_2-10′), 34.9 (CH_2-1′), 29.0 (CH_2-4′), 26.2 (CH_2-3′), 25.4 (CH_2-2′), 25.2 (CH_2-4); ESMS m/z (%) 475 $[M+H]^+$ (7).

3.1.7.8. *N*-Methyl-1-[(4″-methoxyphenethylcarbamate)pentyl]-6,7-dimethoxy-1,2,3,4-THIQ (23). Finally, 162 mg of **7** (0.6 mmol) was subjected to similar conditions to those described in the general procedure, using 4-methoxyphenethyl isocyanate (0.3 mL, 1.7 mmol), to obtain 136 mg of the yellow oil **23** (48%). ^{1}H NMR (500 MHz, $CDCl_3$): δ 7.09 (d, J = 8.5 Hz, 2H, H-2″, H-6″), 6.84 (d, J = 8.5 Hz, 2H, H-3″, H-5″), 6.55 (s, 2H, H-5, H-8), 4.68 (s, 1H, NH), 4.01 (t, J = 6.2 Hz, 2H, H-5′), 3.84 and 3.83 (2s, 6H, OCH_3-6 and OCH_3-7), 3.77 (s, 3H, OCH_3-4″), 3.43–3.33 (m, 3H, H-1, H-9′), 3.15–3.08 (m, 1H, Ha-3), 2.78–2.63 (m, 5H, Hb-3, H-4, H-10′), 2.45 (s, 3H, NCH_3), 1.81–1.68 (m, 2H, H-1′), 1.64–1.53 (m, 2H, H-4′), 1.47–1.37 (m, 1H, Ha-2′), 1.37- 1.23 (m, 3H, Hb-2′, H-3′); ^{13}C NMR (125 MHz, $CDCl_3$): δ 158.2 (C-4″), 156.6 (CO), 147.3 (C-6), 147.2 (C-7), 130.8 (C-1″), 129.7 (C-8a, CH-3″, CH-5″), 126.3 (C-4a,), 114.0 (CH-2″, CH-6″), 111.3 (CH-5), 110.2 (CH-8), 64.9 (CH_2-5′), 63.4 (CH-1), 56.0 (OCH_3-6), 55.8 (OCH_3-7), 55.2 (OCH_3-4″), 48.0 (CH_2-3), 42.6 (NCH_3), 42.3 (CH_2-9′), 35.2 (CH_2-10′), 34.9 (CH_2-1′), 29.0 (CH_2-4′), 26.2 (CH_2-2′), 25.3 (CH_2-4, CH_2-3′); ESMS m/z (%) 471 $[M+H]^+$ (8).

3.2. Antimicrobial activities

3.2.1. Target microorganisms

Antifungal activity was measured against five phytopathogenic fungi: *Aspergillus parasiticus* (CECT 2681), *Trichoderma viride* (CECT 2423), *Fusarium culmorum* (CCM 172), *Phytophthora citrophthora* (CECT 2353) and *Geotrichum candidum* (CCM 245). Antibacterial activity was determined against seven human pathogenic bacteria: *Bacillus cereus* (CECT 148), *Staphylococcus aureus* (CECT 86), *Enterococcus faecalis* (CECT 481), *Salmonella typhi* (CECT 409), *Escherichia coli* (CECT 405), *Escherichia coli* (CECT 100) and *Erwinia carotovora* (CECT 225). The species were provided by the Spanish Type Culture Collection (CECT) or by the Cathedra Collection of Microbiology (CCM) of the Biotechnology Department (Polytechnic University of Valencia).

3.2.2. Antimicrobial assays

The assays were carried out in triplicate. Each compound was assayed against each microorganism using the paper disk-agar diffusion method as previously described.[19] The doses used in the assays for all compounds with the isoquinoline core (**2**, **3**, **5**–**23**) were 10 and 20 μg/mm^2 (0.2 and 0.4 mg/disk, respectively). Fungal

species were seeded in sterile Petri dishes containing Potato Dextrose Agar culture medium (Difco) and were incubated for 7 days at 28 °C. To obtain suspensions of $\sim 10^6$ conidia/mL, tween 80 (0.05%) in sterile distilled water solution was used. Then, 1 mL of conidia suspensions were added to 15 mL of PDA in sterile Petri dishes. Whatmann disks (No. 113, 0.5 cm diameter) were impregnated with the products to test at appropriate concentrations. After medium's solidification, four impregnated Whatmann disks were placed in the Petri dishes. Disks impregnated just with the vehicle were used as negative controls and those with benomyl (methyl-1-[butylcarbamoyl]-2-benzimidazolecarbamate) (Sigma) at different concentrations based on the fungal species assayed, were used as positive controls. Antifungal activity was determined by measuring the inhibition zone developed around the paper disk. For evaluation of the bactericidal activity, 24-h cultures of each bacterium (maintained in inclined tubes on solid culture medium) were reactivated with Nutrient Broth (Difco) and then incubated for a further 24 h at 28 or 37 °C, depending on the bacteria investigated. Next, 1 mL of each bacterial suspension was placed in sterile Petri plates and 15 mL of Plate Count Agar (Difco) culture medium added. After solidification of the medium, four Whatmann paper disks (No. 113, 0.5 cm diameter), previously impregnated with the products to test were placed in the dishes. The plates were incubated for 24 h in the dark at 28 or 37 °C, based on the bacteria investigated. Disks impregnated just with the vehicle were used as negative controls. A positive control with tetracycline hydrochloride (10 μg/mm^2) was also performed. This activity was determined by measuring the inhibition halo developed around the paper disk.

3.3. Statistical analysis

Variance analysis (one-way ANOVA) was performed for the antifungal and antibacterial results (Tables 1–5). Least significant difference (LSD) test was used to compare means and *F* test was performed to determine statistically significant differences ($P < 0.05$) by Statgraphics Centurion XVI version.

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