Bioorganic & Medicinal Chemistry 20 (2012) 6589–6597

Contents lists available at SciVerse ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

# Synthesis of new antimicrobial pyrrolo[2,1-*a*]isoquinolin-3-ones

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ARTICLE INFO

*Article history:*
Received 21 April 2012
Revised 13 September 2012
Accepted 15 September 2012
Available online 24 September 2012

*Keywords:*
Pyrrolo[2,1-*a*]isoquinolin-3-ones
Bischler-Napieralski cyclodehydration
Bactericide
Fungicide

ABSTRACT

The attractive structure of the pyrroloisoquinoline moiety, together with its potential antimicrobial activity, encouraged us to prepare six 8-substituted and seven 8,9-disubstituted-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-ones in a few steps with good yields. We applied a convenient methodology via double intramolecular cyclization conducted by a Bischler-Napieralski cyclodehydration-imine reduction sequence, which is widely employed in the synthesis of isoquinoline alkaloids. Therefore, we synthesized three series of these pyrrolo[2,1-*a*]isoquinolin-3-ones characterized by the substituent at the 8-position or 8,9-positions of the aromatic ring: (a) different side chains are attached to an 8-OH group (series 1); (b) a chlorine atom is attached to the 8-position (series 2); and (c) 8- and 9-carbons are bearing an identical group (series 3). The compounds bearing a benzylic moiety at the 8-position, for example, 8-benzyloxy-pyrrolo[2,1-*a*]isoquinolin-3-one (**1a**) and 8-(4-fluorobenzyloxy)-pyrrolo[2,1-*a*]isoquinolin-3-one (**1e**), as well as, a 8-chloro-9-methoxy moiety including the 8-chloro-9-methoxy-pyrrolo[2,1-*a*]isoquinolin-3-one (**2a**), provided the most fungicide and bactericide agents, respectively.



## 1. Introduction

Isoquinoline alkaloids are a large family of natural products with a variety of powerful biological activities,[1] including inhibition of cellular proliferation.[2] Within the isoquinoline family, pyrroloisoquinoline alkaloids have been paid considerable attention in recent years because they display interesting biological activities such as antidepressant,[3] muscarinic agonist,[4] antiplatelet[5] and antitumor activity.[6] In 1968, the first natural pyrroloisoquinoline alkaloids were isolated from the peyote cactus and were identified as peyoglutam and mescalotam.[7] Since then, the pyrrolo[2,1-*a*]isoquinoline ring system is the main core of a wide variety of biologically active alkaloids, including antitumor crispine A, isolated from *Carduus crispus*,[8] tetracyclic compounds such as antiglycemic jamtine, isolated from the climbing shrub *Cocculus hirsutus*,[9] and erythrina type alkaloids with curare-like neuromuscular blocking activities.[10,11] In 1984, a tetracyclic framework bearing a pyrroloisoquinoline lactam was found in nuevamine[12] which displayed anti-inflammatory, antimicrobial, anti-leukemic and antitumor properties.[13] In 2004, tricyclic lactam trolline was isolated from *Trollius chinensis*. This alkaloid exhibited in vitro significant antibacterial activity against some strains of *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *Haemophilus influenza*, *Staphylococcus aureus*, *Streptococcus pneumonia*, *S. pyogenes*, and moderate antiviral activity against influenza viruses A and B.[14]

Actually, pyrrolo[2,1-*a*]isoquinolines were synthesized long before they were isolated as natural products, and were incorporated into larger ring systems; for example, in the lamellarins skeleton.[15] Nevertheless, given their attractive biological activities, the synthesis of new compounds bearing this structural framework has greatly increased in recent years.[16] One representative synthetic strategy involves the annulation of the pyrrole ring by intramolecular reaction of a 1,3-difunctionalized three-carbon building block with a 3,4-dihydroisoquinoline.[17–19] Other strategies proceed principally via phenethyl succinimides, in which a *N*-acyliminium ion undergoes different types of intramolecular aromatic π-cyclization reactions to provide the C10a–C10b bond formation. In this case, some broadly used approaches involve: (1) tandem carbophilic addition of the organolithium reagent-*N*-acyliminium ion cyclization sequence to obtain the isoquinolone skeleton;[20] (2) application of Parham-type cyclization to halogenated imides, giving the corresponding enamides;[21,22] and (3) the Pummerer/Mannich induced cyclization cascade, which involves a thionium-*N*-acyliminium ion cyclization to give the azabicyclic ring system.[23]

Our research group is focusing since a long time on isolating and synthesizing isoquinoline-containing compounds to obtain a variety of chemically diverse structures with dopaminergic activity.[24–28] However, the discovery of new antimicrobial agents in the last few years has become a need since some microorganisms develop resistance to classic drugs due to their extensive use. As mentioned above, previous works have shown the antimicrobial properties of pyrroloisoquinolines, including the nuevamine-type and trolline-type alkaloids.[13,14] The attractive structure of the

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http://dx.doi.org/10.1016/j.bmc.2012.09.033

pyrroloisoquinoline moiety, together with its potential antimicrobial activity, encouraged us to synthesize trolline analogs containing a lactam-ring pharmacophore similar to antibiotic β-lactams. Although several methods have been portrayed for the synthesis of this framework, we applied a typical methodology that we widely employed in the course of our research into isoquinoline synthesis. It is based on double intramolecular cyclization, conducted by Bischler-Napieralski cyclodehydration from an ester β-phenylethylamide and involves the subsequent reduction of the imine intermediate. Therefore, we prepared six 8-substituted and seven 8,9-disubstituted-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-ones, including the known alkaloid (±)-trolline, in a few steps with good yields for the purpose of exploring their antimicrobial activities. Specifically, we followed the same approach to synthesize three series of these pyrrolo[2,1-*a*]isoquinolinones characterized by the substituent at the 8-position of the aromatic ring. In these series: (a) different side chains are attached to an 8-OH group (series 1); (b) a chlorine atom is attached to the 8-position (series 2); and (c) 8- and 9-carbons are bearing an identical group (series 3). The biological results of these thirteen compounds have enabled us to draw conclusions on these groups' influence on antimicrobial activity.

## 2. Results and discussion

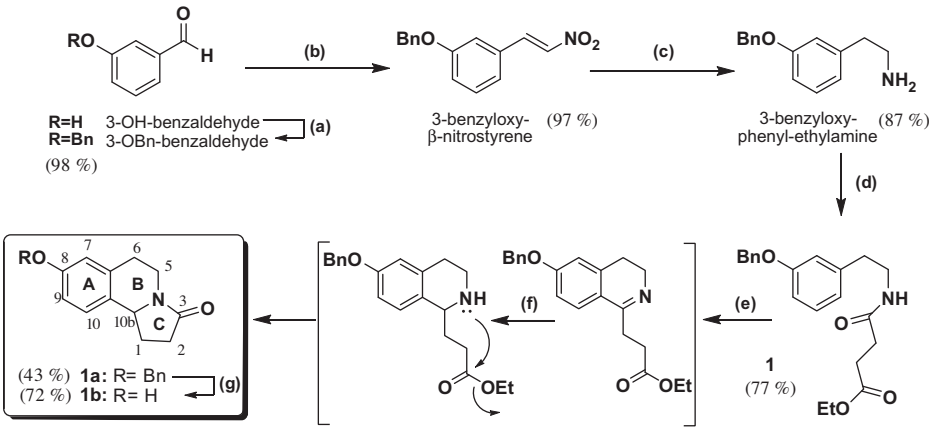
### 2.1. Chemistry

The general synthetic plan for these compounds focused on preparing the appropriate β-phenyl acetamides (**1**–**3**) by standard methods[25,26] to be cyclized by Bischler-Napieralski cyclodehydration. Firstly, these were prepared by starting with benzaldehyde derivatives: 3-hydroxybenzaldehyde (series 1, Scheme 1) and 3-chloro-4-methoxy-benzaldehyde (series 2, Scheme 2); and from the 3,4-dimethoxy-β-phenyl-ethylamine (series 3, Scheme 3). Therefore, by commencing with these benzaldehydes, and by a successive nitromethane-reduction sequence, β-phenylethylamine intermediates were obtained and then condensed with the ethyl succinyl chloride under Shotten-Bauman conditions to give the β-(3-benzyloxy-phenyl)acetamide (**1**), β-(3-chloro-4-methoxy-phenyl)acetamide (**2**) and β-(3,4-dimethoxy-phenyl)-acetamide (**3**), as outlined in Schemes 1–3, respectively. These amides **1**–**3** were treated with a $POCl_3$ reagent to lead us to the expected dihydroisoquinolines by Bischler-Napieralski cyclization. The obtained imine was reduced with $NaBH_4$ to give the tetrahydroisoquinoline skeleton and, simultaneously, the formed nucleophilic amine quickly attacked the carbonyl ester leading to C ring closure by a second intramolecular cyclization to give 8-benzyloxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**1a**), 8-chloro-9-methoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**2a**) and 8,9-dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**3a**) for series 1–3, respectively. In order to obtain different substitutions at the 8 and 9-positions to explore their influence on antimicrobial activity, the benzylic and the methoxy groups of **1a** (series 1) and **2a** (series 2) were deprotected under acid medium to give 8-hydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**1b**), and by $BBr_3$ to obtain 8-chloro-9-hydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**2b**) (Schemes 1 and 2). In addition, those substituents that seemed to enhance the antimicrobial activity were placed in both 8 and 9-positions on the aromatic A-ring (series 3), also by previous deprotection of **3a** by $BBr_3$ to obtain (±)-trolline (**3b**) (Scheme 3).

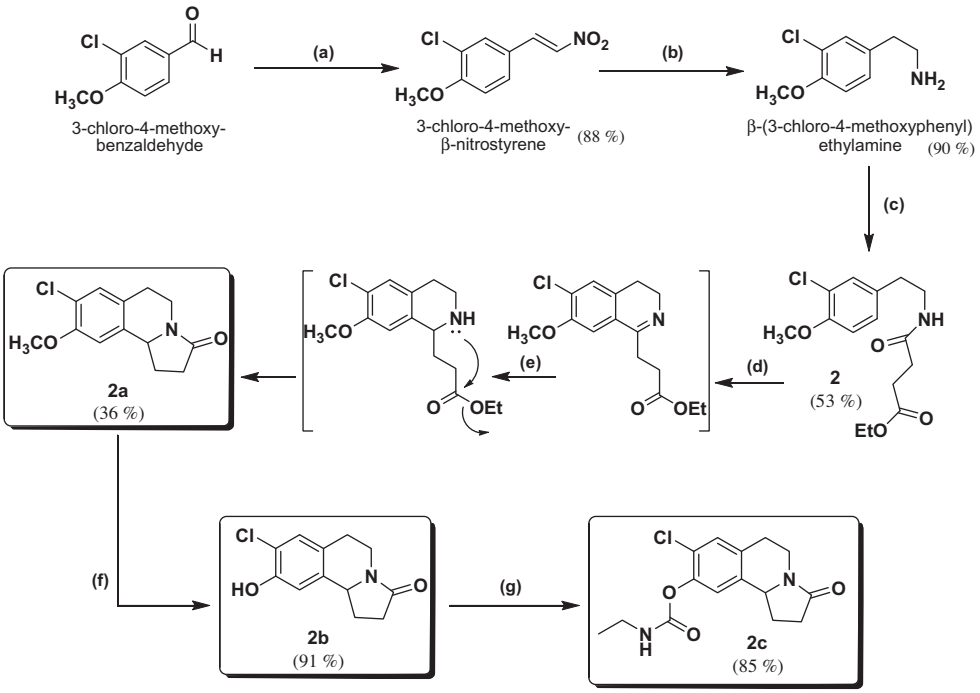
Secondly, in series 1, one carbamate and three O-alkylated derivatives were prepared from 8-hydroxy-pyrroloisoquinolone **1b** (Scheme 4) to give: 8-ethylcarbamate- (**1c**), 8-(1-piperidinethoxy)- (**1d**), 8-(4-fluorobenzyloxy)- (**1e**) and 8-phenylacetamide-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-ones (**1f**). In series 2, one carbamate derivative was prepared from 8-chloro-9-hydroxy-pyrroloisoquinolone **2b** to obtain 8-chloro-9-ethylcarbamate-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**2c**) (Scheme 2). In series 3, one 8,9-bis(4-fluorobenzyloxy)- (**3c**) and one 8,9-bis(phenylacetamide)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-ones (**3d**), were prepared from (±)-trolline (**3b**) (Scheme 3). All the target compounds were synthesized using a short approach with good yields. In addition, and to our knowledge, compounds **1a**–**1f**, **2a**–**2c**, **3c** and **3d** are reported for the first time. Their structures were confirmed by NMR spectral data and MS spectrometry.

### 2.2. Antimicrobial activity

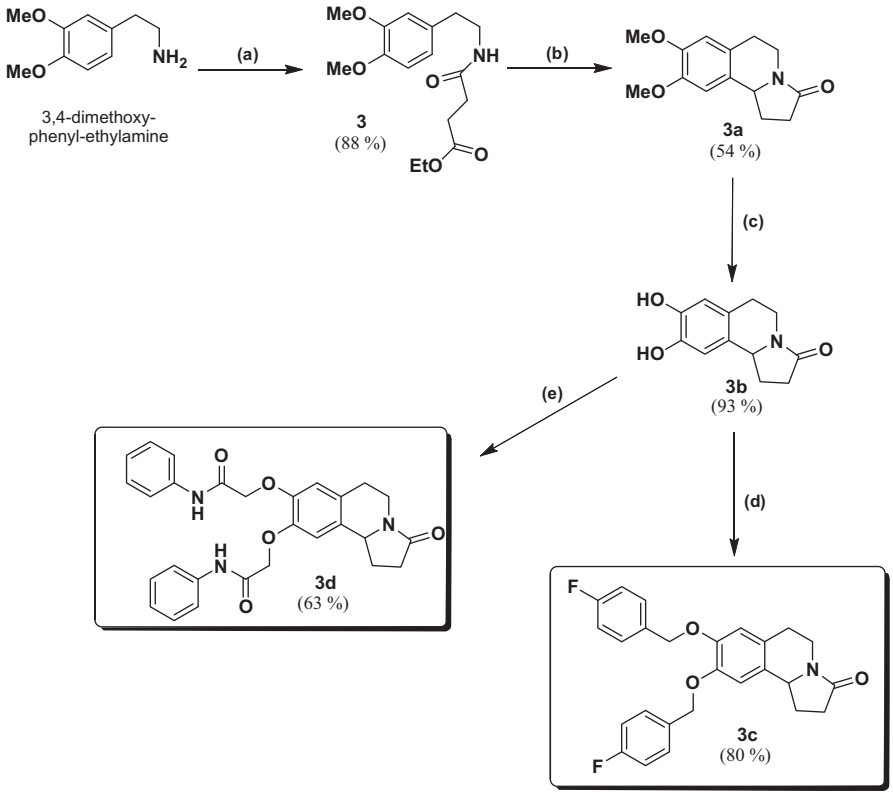
All the synthesized pyrrolo[2,1-*a*]isoquinolines were assayed in vitro for their ability to inhibit bacterial and fungal growth. In the antimicrobial assays, our compounds were tested against several human pathogenic and economically important phytopathogenic bacteria and/or fungi. The bacterial agents were distributed over Gram(+) and Gram(−) bacteria: *B. cereus*, *S. aureus*, and *E. faecalis* as Gram(+) and *S. typhii*, *E. coli* and *E. carotovora* as Gram(−) (Table 1). The inhibition zones exhibited by compounds **1a**–**1f**, **2a**–**2c** and **3a**–**3c** are summarized in Tables 1 and 2 for




**Scheme 1.** Synthesis of pyrroloisoquinolin-3-ones **1a,1b** (series 1). Reagents and conditions: (a) Benzyl chloride, $K_2CO_3$, EtOH, reflux, 6 h; (b) Nitromethane, $NH_4OAc$, AcOH, reflux, overnight; (c) $LiAlH_4$, THF/$Et_2O$, $N_2$, reflux, 2 h; (d) Ethyl succinyl chloride, NaOH 5%, $CH_2Cl_2$, rt, overnight; **(e)** $POCl_3$, $CH_2Cl_2$, $N_2$, reflux, 6 h; (f) $NaBH_4$; MeOH, rt, 2 h; (g) concd HCl–EtOH 1:1, reflux, 3 h.

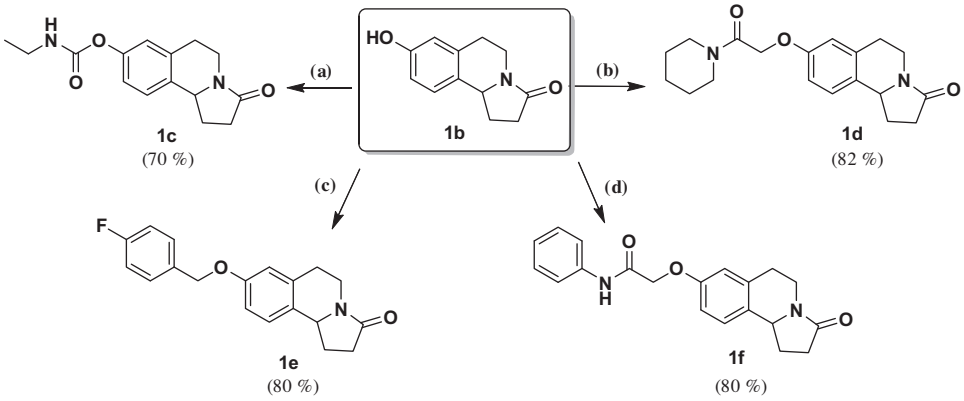



**Scheme 2.** Synthesis of pyrroloisoquinolin-3-one **2a–2c** (series 2). Reagents and conditions: (a) Nitromethane, $NH_4OAc$, AcOH, reflux, 6 h; (b) $LiAlH_4$, THF/$Et_2O$, $N_2$, reflux, 2 h; (c) Ethyl succinyl chloride, NaOH 5%, $CH_2Cl_2$, rt, overnight; (d) $POCl_3$, $CH_3CN$, $N_2$, reflux, 4 h; (e) $NaBH_4$; MeOH, rt, 2 h; (f) $BBr_3$, $CH_2Cl_2$, rt, 2 h; (g) Ethyl isocyanate, acetone, reflux, 3 h.




**Scheme 3.** Synthesis of pyrroloisoquinolin-3-ones **3a–3d** (series 3). Reagents and conditions: (a) Ethyl succinyl chloride, NaOH 5%, $CH_2Cl_2$, rt, overnight; (b) $POCl_3$, $CH_2Cl_2$, $N_2$, reflux, 3 h; and $NaBH_4$; MeOH, rt, 2 h; (c) $BBr_3$, $CH_2Cl_2$, rt, 2 h; (d) *p*-fluorobenzyl chloride, $K_2CO_3$, EtOH, reflux, overnight; (e) 2-bromo-*N*-phenylacetamide, $K_2CO_3$, EtOH, reflux, 6 h.

bactericidal and antifungal activity, respectively. In general, a lipophilic group at the 8- and/or 9-position seemed to provide moderate activity if compared with a free hydroxyl group such as **1b** and (±)-trolline (**3b**). The introduction of the *O*-benzyl group (**1a**) was adequate for activity, and a halogen atom (**1e**) over the benzyl moiety or even two *p*-fluorobenzyloxy groups (**3c**), did




**Scheme 4.** Synthesis of pyrroloisoquinolin-3-ones **1c–1f**. Reagents and conditions: (a) Ethyl isocyanate, acetone, reflux, 3 h; (b) 2-bromo-1-(piperidin-1-yl)ethanone, $K_2CO_3$, EtOH, reflux, 6 h; (c) *p*-fluorobenzyl chloride, $K_2CO_3$, EtOH, reflux, overnight; (d) 2-bromo-N-phenylacetamide, $K_2CO_3$, EtOH, reflux, 6 h.

**Table 1**

| Strains | Bactericidal activity Inhibition zone (mm) 24 h (means ± SE)[a] | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | **1a**[b] | **1b**[b] | **2a**[b] | **1c**[b] | **1e**[b] | **1f**[b] | **3b**[b] | **3c**[b] | Tetracycline[b] |
| *B. cereus* | $8.66 \pm 0.20^{A}$ | $7.50 \pm 0.35^{B}$ | $7.33 \pm 0.41^{BC}$ | $6.50 \pm 0.35^{C}$ | $7.50 \pm 0.61^{B}$ | $8.83 \pm 0.20^{A}$ | $6.66 \pm 0.41^{BC}$ | $7.33 \pm 0.41^{BC}$ | $24.33 \pm 0.41^{D}$ |
| *S. aureus* | $0 \pm 0$ | $0 \pm 0$ | $7.83 \pm 0.20^{A}$ | $0 \pm 0$ | $6.33 \pm 0.20^{B}$ | $0 \pm 0$ | $0 \pm 0$ | $0 \pm 0$ | $27.0 \pm 0.71^{C}$ |
| *E. faecalis* | $6.83 \pm 0.20^{AB}$ | $0 \pm 0$ | $6.83 \pm 0.20^{AB}$ | $8.50 \pm 0.35^{C}$ | $0 \pm 0$ | $7.33 \pm 0.41^{B}$ | $0 \pm 0$ | $6.33 \pm 0.20^{A}$ | $26.0 \pm 0.71^{D}$ |
| *S. typhii* | $6.0 \pm 0^{A}$ | $0 \pm 0$ | $7.33 \pm 0.73^{B}$ | $7.50 \pm 0.35^{B}$ | $0 \pm 0$ | $7.33 \pm 0.20^{B}$ | $0 \pm 0$ | $5.83 \pm 0.20^{A}$ | $24.33 \pm 0.41^{C}$ |
| *E. coli* 405 | $6.33 \pm 0.20^{A}$ | $0 \pm 0$ | $6.83 \pm 0.20^{AB}$ | $6.83 \pm 0.54^{AB}$ | $6.16 \pm 0.20^{A}$ | $7.50 \pm 0.35^{B}$ | $0 \pm 0$ | $6.83 \pm 0.20^{AB}$ | $25.66 \pm 0.41^{C}$ |
| *E. carotovora* | $7.26 \pm 0.18^{AB}$ | $0 \pm 0$ | $10.33 \pm 0.41^{C}$ | $8.83 \pm 0.20^{D}$ | $8.0 \pm 0.61^{B}$ | $8.0 \pm 0.35^{BD}$ | $0 \pm 0$ | $7 \pm 0^{A}$ | $13.33 \pm 0.41^{E}$ |
| *E. coli* 100 | $0 \pm 0$ | $0 \pm 0$ | $6.16 \pm 0.20^{A}$ | 6.33 ± 0.41A | $0 \pm 0$ | $0 \pm 0$ | $0 \pm 0$ | $0 \pm 0$ | $25.66 \pm 0.41^{B}$ |

[a] Each value represents the average and the standard error of three independent experiments. Within each line, the mean values labeled with the same superscript (A–E) do not present statistically significant differences ($P > 0.05$).

[b] Dose: 0.2 mg/disk. Compounds **1d, 2b, 2c** and **3d** did not show bactericidal activity. Compound **3a** showed bactericidal activity at 0.3 mg/disk for *S. aureus*, *E. faecalis*, *E. coli 405* and *E. carotovora*.

**Table 2**

| Strains | Antifungal activity Inhibition zone (mm) 72 h (means ± SE)[a] | | | | |
|---|---|---|---|---|---|
| | **1a**[b] | **2a**[b] | **1c**[b] | **1e**[b] | Benomyl |
| *A. parasiticus* | $6.83 \pm 0.20^{A}$ | $7.50 \pm 0.35^{B}$ | $0 \pm 0$ | $7.83 \pm 0.20^{B}$ | $29.33 \pm 0.41^{C,c1}$ |
| *T. viride* | $6.0 \pm 0^{A}$ | $0 \pm 0$ | $0 \pm 0$ | $8.10 \pm 0.25^{B}$ | $29.33 \pm 0.81^{C,c1}$ |
| *F. culmorum* | $12.0 \pm 0.71^{A}$ | $7.50 \pm 0.35^{B}$ | $0 \pm 0$ | $10.50 \pm 0.35^{C}$ | $27.66 \pm 1.08^{D,c2}$ |
| *G. candidum* | $6.16 \pm 0.20^{A}$ | $6.33 \pm 0.41^{A}$ | $0 \pm 0$ | $7.0 \pm 0.35^{A}$ | $0 \pm 0$ |
| *P. citrophthora* | $11.33 \pm 0.41^{A}$ | $6.83 \pm 0.20^{B}$ | $9.66 \pm 0.41^{C}$ | $10.66 \pm 0.41^{A}$ | $44.33 \pm 0.41^{D,c3}$ |

[a] Each value represents the average and the standard error of three independent experiments. Within each line, the mean values labeled with the same superscript (A–D) do not present statistically significant differences ($P > 0.05$).

[b] Dose: 0.2 mg/disk.

[c1] Dose: 20 μg/disk.

[c2] Dose: 0.2 mg/disk.

[c3] Dose: 30 μg/disk. Compounds **1b**, **1d, 1f** did not show antifungal activity.

not significantly improve it. Moreover, a carbamate bond at the 8-position (**1c**) also provided activity against most of the tested strains but not at 9-position (**2c**) on the aromatic A-ring. A similar effect was observed for **1f** and **3d** with one and two aromatic amide side chains, respectively. However, saturated amide **1d** at 8-position did not display any bactericidal activity. The most noteworthy compound was **2a**, which possessed both a chlorine atom which draws electron density away from the π system and an electron donating methoxyl group at the 8- and 9-position, respectively. This compound displayed bactericidal activity against all the tested strains. However, the presence of two methoxyl groups (**3a**) at 8 and 9-positions was detrimental to the activity of the compound and doses of 0.3 mg/disk were required to get a moderate bactericidal effect. Furthermore, **2a** showed the highest inhibition zone against *S. aureus* and *E. carotovora* among all the tested pyrroloisoquinolines. For this latter microorganism, **2a** possessed a potency that almost fell in the same range as the reference compound (tetracycline), suggesting that it could be a potential alternative bactericidal agent to this ubiquitous plant pathogen with a wide host range. Thus, the presence in **2a** of a chlorine atom and a methoxyl group at the 8-position and the 9-position, respectively, appeared to enhance activity.

Fungicide activity was tested against some phytopathogen fungi strains: *A. parasiticus, T. viridae, F. culmorum, G. candidum* and *P. citrophthora* (Table 2). Compounds **1a**, **2a**, **1c** and **1e** inhibited fungal growth in vitro. Compounds **1d** and **1f**, in which the substitution at the 8-position was an amide side chain, did not display growth inhibition of the selected fungi at 0.2 mg/disk, unlike

the bactericidal test. In series 1, the most active compounds were **1a** and their fluorinated analog **1e**, which showed similar potency. Consequently, it seems that the benzylic moiety located at the 8-position on the pyrroloisoquinoline structure contributed positively to its antifungal properties, even if there was, or was not, a halogen atom. Compound **2a,** which was seen to be the most potent bactericidal agent among the tested pyrroloisoquinolines, had a moderate antifungal effect. Its derivatives **2b** and **2c** did not display any antifungal activity even at 0.4 mg/disk. Surprisingly, other disubstituted series 3 analogous (**3a**–**3d**) also showed no fungicidal effect at the highest dose tested (0.4 mg/disk).

In conclusion, we prepared new eleven 8-substituted pyrrolo[2,1-*a*]isoquinolinones together with the known **3a** and trolline (**3b**) via a double cyclization unleashed by Bischler-Napieralski cyclodehydration and an imine reduction sequence in a few steps with good yields. The SAR studies reveal that the benzylic moiety at the 8-position, as in compounds **1a** (*O*-benzyl group) and **1e** (*O*-*p*-fluoro-benzyl group), and the 8-chloro-9-methoxy substitution as in **2a**, provide the most fungicide and bactericide agents, respectively.

## 3. Material and methods

### 3.1. General instrumentation

Melting points were taken on a Cambridge microscope instrument coupled with a Reichert-Jung. EIMS was recorded in a VG Auto Spec Fisons spectrometer instrument (Fisons, Manchester, United Kingdom). $^1$H NMR and $^{13}$C NMR spectra were recorded with $CDCl_3$ as a solvent in a Bruker AC-300, AC-400 or AC-500. Multiplicities of $^{13}$C NMR resonances were assigned by DEPT experiments. COSY, HSQC and HMBC correlations were recorded at 400 and 500 MHz (Bruker AC-400 or AC-500). The assignments of all compounds were made by COSY, DEPT, HSQC and HMBC. All the reactions were monitored by analytical TLC with silica gel 60 $F_{254}$ (Merck 5554). Residues were purified by silica gel 60 (40–63 μm, Merck 9385) column chromatography. Solvents and reagents were purchased from commercial sources. Quoted yields are of purified material.

### 3.2. General procedure for the synthesis of amides (1–3)

#### 3.2.1. 3-Benzyloxy-benzaldehyde

A mixture of 3-hydroxybenzaldehyde (3 g, 24.59 mmol), benzyl chloride (4.1 mL, 35.79 mmol) and anhydrous $K_2CO_3$ (2.4 g, 17.39 mmol) in absolute EtOH (30 mL) was refluxed for 6 h. Then the reaction mixture was concentrated to dryness, redissolved in 10 mL of $CH_2Cl_2$ and washed with 5% aqueous NaOH (3 × 10 mL). The organic layer was dried with anhydrous $Na_2SO_4$ and evaporated to dryness. The residue was purified by silica gel column chromatography (hexane/EtOAc, 8:2) to afford 5.1 g of 3-benzyloxy-benzaldehyde (98%) as a white solid. Mp: 54–56 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 9.85 (s, 1H, CHO), 7.32 (m, 9H, H-2, H-4, H-5, H-6, Ph), 5.11 (s, 2H, $OCH_2Ph$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ 192.5 (CHO), 159.7 (C-3), 138.2 (C-1), 136.7 (C-1′), 130.5 (CH-5), 129.1 (CH-3′, CH-5′), 128.6 (CH-4′), 127.9 (CH-2′, CH-6′), 124.1 (CH-6), 122.6 (CH-4), 113.6 (CH-2), 70.6 ($OCH_2Ph$); ESMS *m*/*z* (%): 213 (100) $[M+1]^+$.

#### 3.2.2. 3-Benxyloxy-β-nitrostyrene

A mixture of 3-benzyloxy-benzaldehyde (1 g, 4.71 mmol), nitromethane (0.7 mL, 12.89 mmol) and $NH_4OAc$ (0.8 g, 10.41 mmol) in AcOH (12.5 mL) was refluxed overnight. After cooling, the mixture was diluted with water and extracted with $CH_2Cl_2$ (3 × 10 mL). The organic solution was washed with brine (2 × 10 mL) and water (2 × 10 mL), dried with anhydrous $Na_2SO_4$ and evaporated to dryness to obtain the 3-benzyloxy-β-nitrostyrene (1.2 g, 97%) as yellow needles, which was used in the following step with no further purification. Mp: 80–83 °C; $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.88 (d, *J* = 13.8 Hz, 1H, H-β), 7.48 (d, *J* = 13.8 Hz, 1H, H-α), 7.40 (m, 7H, H-2, H-5, Ph), 7.01 (m, 2H, H-4, H-6), 5.11 (s, 2H, $OCH_2Ph$); $^{13}$C NMR (75 MHz, $CDCl_3$) $\delta$ = 159.6 (C-3), 139.4 (CH-β), 137.8 (C-1), 136.7 (C-1′), 130.9 (CH-α), 129.1-127.9 (6C, CH-5, CH2′-CH-6′), 122.4 (CH-6), 119.2 (CH-4), 115.5 (CH-2), 70.6 ($OCH_2Ph$); ESMS *m*/*z* (%): 256 (100) $[M+1]^+$.

#### 3.2.3. 3-Chloro-4-methoxy-β-nitrostyrene

3-Chloro-4-methoxy-benzaldehyde (1.0 g, 5.87 mmol) was submitted to the same conditions depicted above to obtain the 3-chloro-4-methoxy-β-nitrostyrene (1.1 g, 88%) as yellow needles, which was used in the following step with no further purification.[26] Mp: 143–145 °C; $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.91 (d, *J* = 13.7 Hz, 1H, H-β), 7.59 (d, *J* = 2.2 Hz, 1H, H-2), 7.52 (d, *J* = 13.7 Hz, 1H, H-α), 7.44 (dd, *J* = 8.6, 2.2 Hz, 1H, H-6), 6.97 (d, *J* = 8.6 Hz, 1H, H-5), 3.90 (s, 3H, $OCH_3$-4); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ = 158.4 (C-4), 138.4 (CH-β), 136.4 (CH-α), 130.9 (CH-2), 130.1 (CH-6), 124.2 (C-1), 123.7 (C-3), 112.7 (CH-5), 56.8 ($OCH_3$); MS (EI) *m*/*z* (%): 213.5 (55) $[M]^+$, 185 (100).

#### 3.2.4. β-(3-Benzyloxy-phenyl)ethylamine

A mixture of 3-benzyloxy-β-nitrostyrene (600 mg, 2.35 mmol) in 10 mL of anhydrous THF was added dropwise to a well-stirred suspension of $LiAlH_4$ (0.3 g, 8.7 mmol) in 13 mL of anhydrous $Et_2O$ under nitrogen atmosphere, and was refluxed for 2 h. Then the reaction mixture was cooled and the excess of reagent destroyed by a dropwise addition of $H_2O$. After a partial evaporation of the filtered portion, the aqueous solution was extracted with $CH_2Cl_2$ (3 × 10 mL). The organic layers were washed with brine, dried over $Na_2SO_4$ and the solvent was removed to give the β-(3-benzyloxy-phenyl)ethylamine (465 mg, 87%) as a yellow oil. $^1$H NMR (300 MHz, $CDCl_3$): $\delta$ = 7.20 (m, 6H, H-5, Ph), 6.83 (m, 3H, H-2, H-4, H-6), 5.03 (s, 2H, $OCH_2Ph$), 2.88 (t, *J* = 13.5 Hz, 2H, $CH_2$-β), 2.65 (t, *J* = 13.5 Hz, 2H, $CH_2$-α); $^{13}$C NMR (75 MHz, $CDCl_3$): $\delta$ = 159.3 (C-3), 140.1 (C-1′), 137.4 (C-1), 130.0 (CH-5), 129.9 (CH-3′, CH-5′), 128.3 (CH-4′), 127.9 (CH-2′, CH-6′), 121.9 (CH-6), 116.0 (CH-2), 112.8 (CH-4), 70.3 ($OCH_2Ph$), 43.7 ($CH_2$-β), 40.3 ($CH_2$-α); ESMS *m*/*z* (%): 228 (100) $[M+1]^+$.

#### 3.2.5. β-(3-Chloro-4-methoxyphenyl)ethylamine

3-Chloro-4-methoxy-β-nitrostyrene (1.0 g, 4.70 mmol) was submitted to the same conditions depicted above to obtain the 2-(3-chloro-4-methoxyphenyl)ethylamine (905 mg, 90%) as a yellow oil. The compound was used in further reaction without purification.[26] $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ = 7.30 (d, *J* = 2.2 Hz, 1H, H-2), 7.20 (dd, *J* = 8.5, 2.2 Hz, 1H, H-6), 6.80 (d, *J* = 8.5 Hz, 1H, H-5), 3.90 (s, 3H, $OCH_3$-4), 3.10 (m, 2H, H-β), 2.80 (m, 2H, H-α); $^{13}$C NMR (100 MHz, $CDCl_3$): $\delta$ = 153.8 (C-4), 133.3 (C-1), 130.8 (CH-2), 128.4 (CH-6), 122.6 (C-3), 112.5 (CH-5), 56.5 ($OCH_3$), 43.8 ($CH_2$-α), 39.1 ($CH_2$-β); MS (EI) *m*/*z* (%): 185 (45) $[M]^+$.

#### 3.2.6. Ethyl [β-(3-benzyloxy)phenethylamino]-oxobutanoate (1)

An amount of 0.47 mL of ethyl succinyl chloride (3.31 mmol) was added dropwise at 0 °C to a solution of β-(3-benzyloxy-phenyl)ethylamine (446 mg, 2.12 mmol) in $CH_2Cl_2$ and 5% aqueous NaOH (4 mL). The reaction was stirred at room temperature overnight to be then extracted with $CH_2Cl_2$ (3 × 10 mL). The combination of the organic phases was washed with brine (2 × 10 mL) and $H_2O$ (2 × 10 mL), dried over $Na_2SO_4$ and evaporated to dryness. The residue was purified by silica gel column chromatography (hexane/EtOAc 6:4) to afford 540 mg of amide **1** (77%) as a yellow powder. Mp: 68–71 °C; $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.22 (m, 6H, H-5, Ph), 6.76 (m, 3H, H-2, H-4, H-6), 5.09 (s, 2H, $OCH_2Ph$), 4.01 (q, *J* = 7.9 Hz,

2H, $CO_2C\underline{H_2}CH_3$), 3.40 (q, $J$ = 6.3 Hz, 2H, $CH_2$-α), 2.81 (t, $J$ = 6.3 Hz, 2H, $CH_2$-β), 2.65 (t, $J$ = 6.5 Hz, 2H, $C\underline{H_2}CO$), 2.37 (t, $J$ = 6.5 Hz, $C\underline{H_2}CONH$), 1.10 (t, $J$ = 7.9 Hz, 3H, $CO_2CH_2C\underline{H_3}$); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 172.9 ($\underline{C}O_2CH_2CH_3$), 171.3 (CONH), 159.0 (C-3), 140.5 (C-1′), 136.9 (C-1), 129.6 (CH-5), 128.5 (CH-3′, CH-5′), 127.9 (CH-4′), 127.4 (CH-2′, CH-6′), 121.3 (CH-6), 115.3 (CH-2), 112.8 (CH-4), 69.8 ($O\underline{CH_2}Ph$), 60.6 ($CO_2\underline{CH_2}CH_3$), 40.5 ($CH_2$-α), 35.6 ($CH_2$-β), 31.0 ($\underline{CH_2}CONH$), 29.5 ($\underline{CH_2}CO$), 14.1 ($CO_2CH_2\underline{CH_3}$); ESMS $m/z$ (%): 356 (100) $[M+1]^+$.

### 3.2.7. Ethyl [β-(3-chloro-4-methoxy)phenethylamino]-oxobutanoate (2)

β-(3-Chloro-4-methoxyphenyl)ethylamine (1 g, 5.39 mmol) was submitted to the same conditions depicted above. The residue was purified by silica gel column chromatography (hexane/EtOAc 5:5) to afford 900 mg of amide **2** (53%) as a yellow powder. Mp: 109–112 °C; $^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.17 (d, $J$ = 2.1 Hz, 1H, H-2), 7.04 (dd, $J$ = 8.3, 2.1 Hz, 1H, H-6), 6.84 (d, $J$ = 8.3 Hz, 1H, H-5), 4.11 (q, $J$ = 7.9 Hz, 2H, $CO_2C\underline{H_2}CH_3$), 3.85 (s, 3H, $OCH_3$_4), 3.43 (q, $J$ = 6.3 Hz, 2H, $CH_2$-α), 2.70 (t, $J$ = 6.3, 2H, $CH_2$-β), 2.60 (t, $J$ = 6.5 Hz, 2H, $C\underline{H_2}CO$), 2.41 (t, $J$ = 6.5 Hz, $C\underline{H_2}CONH$), 1.22 (t, $J$ = 7.9 Hz, 3H, $CO_2CH_2C\underline{H_3}$); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 173.1 ($\underline{C}O_2CH_2CH_3$), 171.8 (CONH), 153.5 (C-4), 131.9 (C-1), 130.3 (CH-2), 127.8 (CH-6), 122.2 (CH-3), 112.1 (CH-5), 60.7 ($CO_2\underline{CH_2}CH_3$), 56.1 ($OCH_3$), 40.6 ($CH_2$-α), 34.3 ($CH_2$-β), 30.9 ($\underline{CH_2}CONH$), 29.5 ($\underline{CH_2}CO$), 14.0 ($CO_2CH_2\underline{CH_3}$); ESMS $m/z$ (%): 314.5 (100) $[M+1]^+$.

### 3.2.8. Ethyl [β-(3,4-dimethoxy)phenethylamino]-oxobutanoate (3)

β-(3,4-Dimethoxyphenyl)ethylamine (1 g, 5.52 mmol) was submitted to the same conditions depicted above. The residue was purified by silica gel column chromatography (hexane/EtOAc 5:5) to afford 1.5 g of amide **3** (88%) as a white powder. Mp: 48–51 °C. $^1H$ NMR (500 MHz, $CDCl_3$): δ = 6.81 (d, $J$ = 2.1 Hz, 1H, H-5), 6.70 (m, 2H, H-2, H-6), 4.11 (q, $J$ = 7.9 Hz, 2H, $CO_2CH_2CH_3$), 3.85 (s, 3H, $OCH_3$-4), 3.84 (s, 3H, $OCH_3$-3), 3.43 (q, $J$ = 6.3 Hz, 2H, $CH_2$-α), 2.70 (t, $J$ = 6.3, 2H, $CH_2$-β), 2.60 (t, $J$ = 6.5 Hz, 2H, $CH_2CO$), 2.41 (t, $J$ = 6.5 Hz, $CH_2CONH$), 1.22 (t, $J$ = 7.9 Hz, 3H, $CO_2CH_2CH_3$); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 173.4 ($CO_2CH_2CH_3$), 171.9 (CONH), 149.4 (C-3), 148.0 (C-4), 131.9 (C-1), 121.1 (CH-6), 112.4 (CH-5), 111.8 (CH-2), 61.0 ($CO_2CH_2CH_3$), 56.2 (2× $OCH_3$), 41.2 ($CH_2$-α), 35.6 ($CH_2$-β), 31.4 ($CH_2CONH$), 29.8 ($CH_2CO$), 14.5 ($CO_2CH_2CH_3$); ESMS $m/z$ (%): 310 (100) $[M+1]^+$.

## 3.3. General procedure for the synthesis of 1,2,3,5,6,10b-pyrrolo[2,1-*a*]isoquinolin-3-ones (1a–3a)

### 3.3.1. 8-Benzyloxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (1a)

A solution of ethyl 4-[β-(3-benzyloxyphenyl)ethylamino]-4-oxobutanoate (**1**) (300 mg, 0.84 mmol) in dry $CH_2Cl_2$ (30 mL) was treated with $POCl_3$ (0.39 mL, 4.20 mmol) and was refluxed for 6 h in a nitrogen atmosphere. The reaction mixture was diluted with $H_2O$ (10 mL) and extracted with $CH_2Cl_2$ (3 × 10 mL). The organic solution was dried over $Na_2SO_4$ and evaporated to dryness. The residue was dissolved in MeOH (25 mL) and treated with $NaBH_4$ (400 mg, 10.57 mmol) at room temperature. The reaction mixture was stirred for 2 h. Afterward, $H_2O$ (5 mL) was added and the organic solvent was removed under reduced pressure. The aqueous mixture was made basic and extracted with $CH_2Cl_2$ (3 × 10 mL), dried over $Na_2SO_4$ and concentrated. The residue was purified by silica gel column chromatography (toluene/EtOAc/MeOH/$Et_3N$, 6:3:1:0.1) to obtain 105 mg of the 8-benzyloxy-pyrrolo[2,1-*a*]isoquinolin-3-one **1a** (43%) as a yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.36 (m, 5H, Ph), 7.02 (d, $J$ = 8.5 Hz, 1H, H-10), 6.87 (dd, $J$ = 8.5, 2.5 Hz, 1H, H-9), 6.75 (d, $J$ = 2.5 Hz, 1H, H-7), 5.04 (s, 2H, $OCH_2Ph$), 4.71 (t, $J$ = 8 Hz, 1H, H-10b), 4.23 (ddd, $J$ = 12.4, 5.8, 2.7 Hz, 1H, H-5α), 3.05 (m, 1H, H-5β), 2.91 (m, 1H, H-6α), 2.71 (m, 1H, H-6β), 2.61 (m, 1H, H-1α), 2.54 (m, 1H, H-2α), 2.45 (m, 1H, H-2β), 1.82 (m, 1H, H-1β); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 173.2 (NCO), 157.4 (C-8), 136.7 (C-1′), 134.8 (C-6a), 130.0 (C-10a), 128.5 (CH-3′, CH-5′), 127.9 (CH-4′), 127.3 (CH-2′, CH-6′), 125.8 (CH-10), 114.6 (CH-7), 113.8 (CH-9), 69.9 ($OCH_2Ph$), 56.3 (CH-10b), 36.8 ($CH_2$-5), 31.6 ($CH_2$-2), 28.7 ($CH_2$-6), 27.5 ($CH_2$-1); ESMS $m/z$ (%): 293 (100) $[M]^+$.

### 3.3.2. 8-Chloro-9-methoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (2a)

Ethyl β-(3-chloro-4-methoxy-phenethylamino)-4-oxobutanoate (**2**) (100 mg, 0.31 mmol) was submitted to the same conditions depicted above. The residue was purified by silica gel column chromatography (toluene/EtOAc/MeOH/$Et_3N$, 6:3:1:0.1) to obtain 28 mg of 8-chloro-9-methoxy-pyrrolo[2,1-*a*]isoquinolin-3-one **2a** (36%) as a yellow oil. $^1H$ NMR (500 MHz, $CDCl_3$): δ = 7.15 (s, 1H, H-7), 6.62 (s, 1H, H-10), 4.72 (t, $J$ = 8.0 Hz, 1H, H-10b), 4.28 (ddd, $J$ = 12.9, 6.2, 2.7 Hz, 1H, H-5α), 3.86 (s, 3H, $OCH_3$), 2.99 (m, 1H, H-5β), 2.84 (m, 1H, H-6α), 2.68 (m, 1H, H-6β), 2.66 (m, 1H, H-1α), 2.56 (m, 1H, H-2α), 2.48 (m, 1H, H-2β), 1.85 (m, 1H, H-1β); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 173.0 (NCO), 153.6 (C-9), 136.9 (C-10a), 130.5 (CH-7), 127.8 (C-6a), 121.1 (C-8), 108.3 (CH-10), 56.2 (CH-10b), 56.1 ($OCH_3$), 36.9 ($CH_2$-5), 31.6 ($CH_2$-2), 27.5 ($CH_2$-6), 27.4 ($CH_2$-1); ESMS $m/z$ (%): 251 (100) $[M]^+$.

### 3.3.3. 8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (3a)

Ethyl β-(3,4-dimethoxy-phenethylamino)-4-oxobutanoate (**3**) (1.2 g, 3.88 mmol) was submitted to the same conditions depicted above. The residue was purified by silica gel column chromatography ($CH_2Cl_2$/MeOH/$NN_4OH$, 95:5:0.1) to obtain 520 mg of 8, 9-dimethoxy-pyrrolo[2,1-*a*]isoquinolin-3-one **3a** (54%) as a green oil. $^1H$ NMR (500 MHz, CDCl3): δ = 6.59 (s, 1H, H-7), 6.54 (s, 1H, H-10), 4.70 (t, $J$ = 8.0 Hz, 1H, H-10b), 4.26 (ddd, $J$ = 12.9, 6.2, 2.7 Hz, 1H, H-5α), 3.83 (s, 3H, $OCH_3$-9), 3.82 (s, 3H, $OCH_3$-8), 2.99 (m, 1H, H-5β), 2.85 (m, 1H, H-6α), 2.65 (m, 1H, H-6β), 2.60 (m, 1H, H-1α), 2.55 (m, 1H, H-2α), 2.44 (m, 1H, H-2β), 1.80 (m, 1H, H-1β); $^{13}C$ NMR (125 MHz, CDCl3): δ = 173.1 (NCO), 148.0 (C-8), 147.8 (C-9), 129.2 (C-10a), 125.4 (C-6a), 111.6 (CH-7), 107.6 (CH-10), 56.5 (CH-10b), 55.9 ($OCH_3$-8), 55.8 ($OCH_3$-9), 36.9 ($CH_2$-5), 31.6 ($CH_2$-2), 27.9 ($CH_2$-6), 27.6 ($CH_2$-1); ESMS $m/z$ (%): 247 (100) $[M]^+$.

## 3.4. General procedure for the synthesis of 1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-ones (1b–1f)

### 3.4.1. 8-Hydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (1b)

8-benzyloxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**1a**) (200 mg, 0.68 mmol) was refluxed for 3 h in a mixture of equal volumes of ethanol and concentrated HCl (50 mL). The reaction mixture was evaporated to dryness and the residue purified by silica gel column cromatography ($CH_2Cl_2$/MeOH 94:6) to give 101 mg of 8-hydroxy-pyrrolo[2,1-*a*]isoquinolin-3-one **1b** (72%) as a white oil. $^1H$ NMR (500 MHz, $CDCl_3$): δ = 6.76 (d, $J$ = 8.3 Hz, 1H, H-10), 6.53 (dd, $J$ = 8.3, 2.0 Hz, 1H, H-9), 6.42 (d, $J$ = 2.0 Hz, 1H, H-7), 4.56 (t, $J$ = 8 Hz, 1H, H-10b), 3.90 (m, 1H, H-5α), 2.91 (m, 1H, H-5β), 2.67 (m, 1H, H-6α), 2.56 (m, 1H, H-6β), 2.45 (m, 1H, H-1α), 2.37 (m, 1H, H-2α), 2.22 (m, 1H, H-2β), 1.65 (m, 1H, H-1β); $^{13}C$ NMR (125 MHz, $CDCl_3$): δ = 174.0 (NCO), 155.3 (C-8), 134.2 (C-6a), 128.0 (C-10a), 125.4 (CH-10), 114.7 (CH-7), 113.9 (CH-9), 56.5 (CH-10b), 36.9 ($CH_2$-5), 31.3 ($CH_2$-2), 28.1 ($CH_2$-6), 27.1 ($CH_2$-1); ESMS $m/z$ (%): 203 (100) $[M]^+$.

#### 3.4.2. 8-Ethylcarbamate-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (1c)

A solution of 8-hydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]-isoquinolin-3-one (**1b**) (35 mg, 0.17 mmol) in dry acetone (10 mL) was treated with ethyl isocyanate (0.34 mmol, 0.03 mL). After refluxing for 3 h, the reaction mixture was concentrated to dryness, redissolved in 10 mL of $CH_2Cl_2$ and washed with $H_2O$ (3 × 10 mL). The organic layer was dried with anhydrous $Na_2SO_4$, filtered and evaporated under reduced pressure. The residue was purified through a silica gel column ($CH_2Cl_2$/MeOH 97:3) to afford 8-ethylcarbamate-pyrrolo[2,1-*a*]isoquinolin-3-one **1c** (34 mg, 70%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.09 (d, $J$ = 8.3 Hz, 1H, H-10), 7.00 (dd, $J$ = 8.3, 2.0 Hz, 1H, H-9), 6.91 (d, $J$ = 2.0 Hz, 1H, H-7), 4.71 (t, $J$ = 8.0 Hz, 1H, H-10b), 4.26 (m, 1H, H-5α), 3.30 (m, 2H, $CH_3C\underline{H_2}NHCO$), 3.07 (m, 1H, H-5β), 2.92 (m, 1H, H-6α), 2.77 (m, 1H, H-6β), 2.63 (m, 1H, H-1α), 2.53 (m, 1H, H-2α), 2.45 (m, 1H, H-2β), 1.86 (m, 1H, H-1β), 1.20 (m, 3H, $\underline{CH_3}CH_2NHCO$); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 173.2 (NCO), 154.4 (C-8), 149.6 (NHCO), 134.8 (C-6a), 134.4 (C-10a), 128.7 (CH-10), 125.1 (CH-7), 120.3 (CH-9), 56.5 (CH-10b), 36.8 ($CH_2$-5), 36.7 ($CH_3\underline{CH_2}NHCO$), 31.3 ($CH_2$-2), 28.5 ($CH_2$-6), 27.5 ($CH_2$-1), 15.0 ($\underline{CH_3}CH_2NHCO$); ESMS $m/z$ (%): 297 (100) $[M+Na]^+$.

#### 3.4.3. 8-(1-Piperidinethoxy)-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (1d)

A mixture of 8-hydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**1b**) (30 mg, 0.14 mmol), 2-bromo-1-(piperidin-1-yl)ethanone (19 mg, 0.14 mmol) and anhydrous $K_2CO_3$ (19 mg, 0.14 mmol) in absolute EtOH (10 mL) was refluxed for 6 h. Afterward, the reaction mixture was concentrated to dryness, redissolved in 10 mL of $CH_2Cl_2$ and washed with 5% aqueous NaOH (3 × 10 mL). The organic layer was dried with anhydrous $Na_2SO_4$, filtered and evaporated to dryness. The residue was purified by silica gel column chromatography (toluene/EtOAc/MeOH/$Et_3N$, 6:3:1:0.1) to afford 40 mg of 8-(1-piperidinethoxy)-pyrrolo[2,1-*a*]isoquinolin-3-one **1d** (82%) as a green oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.02 (d, $J$ = 8.5 Hz, 1H, H-10), 6.84 (dd, $J$ = 8.5, 2.6 Hz, 1H, H-9), 6.70 (d, $J$ = 2.6 Hz, 1H, H-7), 4.71 (t, $J$ = 6.7 Hz, 1H, H-10b), 4.65 (s, 2H, $OC\underline{H_2}CO$), 4.23 (m, 1H, H-5α), 3.55 (t, $J$ = 5.3 Hz, 2H, $C\underline{H_2}N$), 3.46 (t, $J$ = 5.3 Hz, 2H, $C\underline{H_2}N$), 3.04 (m, 1H, H-5β), 2.89 (m, 1H, H-6α), 2.73 (m, 1H, H-6β), 2.56 (m, 1H, H-1α), 2.52 (m, 1H, H-2α), 2.44 (m, 1H, H-2β), 1.82 (m, 1H, H-1β), 1.64–1.54 (m, 6H, $(C\underline{H_2})_3N$); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 173.2 (NCO-3), 166.0 ($N\underline{C}OCH_2O$), 156.7 (C-8), 135.0 (C-6a), 130.6 (C-10a), 125.9 (CH-10), 114.5 (CH-7), 113.6 (CH-9), 67.5 ($O\underline{CH_2}CO$), 56.4 (CH-10b), 46.3 and 43.2 (2 × $\underline{CH_2}N$), 36.9 ($CH_2$-5), 31.7 ($CH_2$-2), 28.6 ($CH_2$-6), 27.5 ($CH_2$-1), 26.4 and 25.4 (2 × $\underline{CH_2}CH_2N$), 24.3 ($\underline{CH_2}(CH_2)_2N$); ESMS $m/z$ (%): 328 (100) $[M]^+$.

#### 3.4.4. 8-(4-Fluorobenzyloxy)-1,2,3,5,6,10a-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (1e)

A mixture of 8-hydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**1b**) (20 mg, 0.10 mmol), *p*-fluorobenzyl chloride (0.01 mL) and anhydrous $K_2CO_3$ (10 mg) in absolute ethanol (10 mL) was refluxed overnight. Afterward, the reaction mixture was concentrated to dryness, redissolved in 10 mL of $CH_2Cl_2$ and washed with 5% aqueous NaOH (3 × 10 mL). The organic layer was dried with anhydrous $Na_2SO_4$, filtered and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography ($CH_2Cl_2$/MeOH 97:3) to afford 25 mg of 8-(4-fluorobenzyloxy)-pyrrolo[2,1-*a*]isoquinolin-3-one **1e** (80%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.38 (m, 2H, PhF), 7.07 (m, 3H, PhF, CH-10), 6.86 (dd, $J$ = 8.5, 2.5 Hz, 1H, H-9), 6.74 (d, $J$ = 2.5 Hz, 1H, H-7), 5.00 (s, 2H, $OC\underline{H_2}Ph$), 4.73 (t, $J$ = 7.8 Hz, 1H, H-10b), 4.25 (m, 1H, H-5α), 3.04 (m, 1H, H-5β), 2.91 (m, 1H, H-6α), 2.75 (m, 1H, H-6β), 2.63 (m, 1H, H-1α), 2.56 (m, 1H, H-2α), 2.46 (m, 1H, H-2β), 1.82 (m, 1H, H-1β); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 173.4 (NCO), 162.5 (C-4′, $^1J_{CF}$ = 246 Hz), 157.3 (C-8), 135.0 (C-1′), 132.5 (C-6a), 130.2 (C-10a), 129.3 (2CH, CH-2′, CH-6′), 125.9 (CH-10), 115.5 (2CH, CH-3′, CH-5′, $^2J_{CF}$ = 21.7 Hz), 114.5 (CH-7), 113.9 (CH-9), 69.3 ($OCH_2Ph$), 56.4 (CH-10b), 36.9 ($CH_2$-5), 31.7 ($CH_2$-2), 28.7 ($CH_2$-6), 27.6 ($CH_2$-1); ESMS $m/z$ (%): 311 (100) $[M]^+$.

#### 3.4.5. 8-Phenylacetamide-1,2,3,5,6,10a-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (1f)

A mixture of 8-hydroxy-1,2,3,5,6,10a-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**1b**) (30 mg, 0.14 mmol), 2-bromo-*N*-phenylacetamide (29 mg, 0.14 mmol) and anhydrous $K_2CO_3$ (19 mg, 0.14 mmol) in EtOH (10 mL) was refluxed for 6 h. Then the reaction mixture was concentrated to dryness, redissolved in 10 mL of $CH_2Cl_2$ and washed with 5% aqueous NaOH (3 × 10 mL). The organic layer was dried with anhydrous $Na_2SO_4$ and evaporated to dryness. The residue was purified by silica gel column chromatography (toluene/EtOAc/MeOH/$Et_3N$, 6:3:1:0.1) to afford 40 mg of 8-phenylacetamide-pyrrolo[2,1-*a*]isoquinolin-3-one **1f** (80%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.58 (d, 2H, $J$ = 7.6 Hz, H-2′, H-6′), 7.36 (t, 2H, $J$ = 7.5 Hz, H-3′, H-5′), 7.16 (t, 1H, $J$ = 7.5 Hz, H-4′), 7.10 (d, $J$ = 8.5 Hz, 1H, H-10), 6.90 (dd, $J$ = 8.5, 2.5 Hz, 1H, H-9), 6.78 (d, $J$ = 2.5 Hz, 1H, H-7), 4.74 (t, $J$ = 7.9 Hz, 1H, H-10b), 4.60 (s, 2H, $OC\underline{H_2}CO$), 4.28 (ddd, $J$ = 12.9, 6.2, 2.7 Hz, 1H, H-5α), 3.06 (m, 1H, H-5β), 2.93 (m, 1H, H-6α), 2.87 (m, 1H, H-6β), 2.65 (m, 1H, H-1α), 2.57 (m, 1H, H-2α), 2.47 (m, 1H, H-2β), 1.84 (m, 1H, H-1β); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 173.2 ($PhN\underline{C}O$), 166.0 (NCO-3), 155.7 (C-8), 136.7 (C-1′), 135.6 (C-6a), 131.8 (C-10a), 129.1 (2CH, CH-2′, CH-6′), 126.3 (CH-10), 124.9 (CH-4′), 120.1 (2CH, CH-3′, CH-5′), 114.9 (CH-7), 113.7 (CH-9), 67.7 ($O\underline{CH_2}CO$), 56.3 (CH-10b), 36.8 ($CH_2$-5), 31.7 ($CH_2$-2), 28.7 ($CH_2$-6), 27.6 ($CH_2$-1); ESMS $m/z$ (%): 336 (100) $[M]^+$.

### 3.5. General procedure for the synthesis of 1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-ones (2b and 3b)

#### 3.5.1. 8-Chloro-9-hydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (2b)

8-Chloro-9-methoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**2a**, 0.23 mmol, 60 mg) in dry $CH_2Cl_2$ was stirred at −78 °C. Then, 0.10 mL of $BBr_3$ were added under nitrogen atmosphere and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was evaporated to dryness and purified by silica gel column chromatography ($CH_2Cl_2$/MeOH 90:10) to afford 50 mg of 8-chloro-9-hydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one **2b** (91%) as a colorless oil. $^1$H NMR (500 MHz, CDCl3): $\delta$ = 7.18 (s, 1H, H-7), 6.97 (s, 1H, H-10), 4.48 (t, $J$ = 8.0 Hz, 1H, H-10b), 4.30 (ddd, $J$ = 12.9, 6.2, 2.7 Hz, 1H, H-5α), 2.87 (m, 1H, H-5β), 2.67 (m, 1H, H-6α), 2.51 (m, 1H, H-6β), 2.42 (m, 1H, H-1α), 2.35 (m, 1H, H-2α), 2.31 (m, 1H, H-2β), 1.62 (m, 1H, H-1β); $^{13}$C NMR (125 MHz, CDCl3): $\delta$ = 172.5 (NCO), 149.3 (C-9), 138.1 (C-10a), 131.3 (CH-7), 130.3 (C-6a), 119.9 (C-8), 113.6 (CH-10), 56.2 (CH-10b), 37.0 ($CH_2$-5), 31.7 ($CH_2$-2), 27.5 ($CH_2$-6), 27.4 ($CH_2$-1); ESMS $m/z$ (%): 237.5 (100) $[M]^+$.

#### 3.5.2. (±)-Trolline (3b)

8,9-Dimethoxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**3a**, 0.80 mmol, 200 mg) in dry $CH_2Cl_2$ was stirred at −78 °C. Then, 0.25 mL of $BBr_3$ were added under nitrogen atmosphere and the resulting mixture was stirred for 2 h at room temperature. The reaction mixture was evaporated to dryness and purified by silica gel column chromatography ($CH_2Cl_2$/MeOH 85:15) to afford 165 mg of 8,9-dihydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one **3b** (93%) as a white powder. Mp: 245–247 °C; $^1$H NMR (500 MHz, CDCl3): $\delta$ = 6.99 (s, 1H, H-7),

6.98 (s, 1H, H-10), 4.54 (t, $J$ = 8.0 Hz, 1H, H-10b), 4.32 (ddd, $J$ = 12.9, 6.2, 2.7 Hz, 1H, H-5α), 2.89 (m, 1H, H-5β), 2.74 (m, 1H, H-6α), 2.48 (m, 1H, H-6β), 2.43 (m, 1H, H-2α), 2.35 (m, 1H, H-2β), 2.33 (m, 1H, H-1α) 1.66 (m, 1H, H-1β); $^{13}$C NMR (125 MHz, CDCl3): $\delta$ = 172.6 (NCO), 146.3 (C-8), 146.1 (C-9), 129.3 (C-10a), 124.7 (C-6a), 118.7 (CH-10), 116.5 (CH-7), 56.4 (CH-10b), 37.4 ($CH_2$-5), 31.9 ($CH_2$-2), 28.1 ($CH_2$-6), 28.0 ($CH_2$-1); ESMS $m/z$ (%): 219 (100) $[M]^+$.

### 3.6. General procedure for the synthesis of 9-substituted-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-ones (2c, 3c and 3d)

#### 3.6.1. 8-Chloro-9-ethylcarbamate-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinoline-3-one (2c)

A solution of 8-chloro-9-hydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one **2b** (20 mg, 0.084 mmol) in dry acetone (10 mL) was treated with ethyl isocyanate (0.17 mmol, 0.01 mL). After refluxing for 3 h, the reaction mixture was concentrated to dryness, redissolved in 10 mL of $CH_2Cl_2$ and washed with $H_2O$ (3 × 10 mL). The organic layer was dried with anhydrous $Na_2SO_4$, filtered and evaporated under reduced pressure. The residue was purified through a silica gel column ($CH_2Cl_2$/MeOH 95:5) to afford 8-chloro-9-ethylcarbamate-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one **2c**. (85%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.10 (s, 1H, H-7), 6.78 (s, 1H, H-10), 4.68 (t, $J$ = 8.0 Hz, 1H, H-10b), 4.42 (ddd, $J$ = 12.9, 6.2, 2.7 Hz, 1H, H-5α), 3.72 (m, 2H, $CH_3CH_2NHCO$), 3.01 (m, 1H, H-5β), 2.83 (m, 1H, H-6α), 2.63 (m, 1H, H-6β), 2.61 (m, 1H, H-1α), 2.55 (m, 1H, H-2α), 2.46 (m, 1H, H-2β), 1.80 (m, 1H, H-1β), 1.20 (m, 3H, $CH_3CH_2NHCO$); 13C NMR (125 MHz, $CDCl_3$): $\delta$ = 173.3 (NCO), 158.5 (C-9), 150.5 (NHCO), 137.4 (C-10a), 130.6 (CH-7), 126.0 (C-6a), 119.3 (C-8), 112.5 (CH-10), 56.5 (CH-10b), 37.4 ($CH_3CH_2NHCO$), 37.0 ($CH_2$-5), 31.7 ($CH_2$-2), 27.4 ($CH_2$-6), 27.3 ($CH_2$-1), 15.4 ($CH_3CH_2NHCO$); ESMS $m/z$ (%): 308.5 (100) $[M]^+$.

#### 3.6.2. 8,9-Bis(4-fluorobenzyloxy)-1,2,3,5,6,10a-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (3c)

A mixture of 8, 9-dihydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**3b**) (50 mg, 0.22 mmol), *p*-fluorobenzyl chloride (0.04 mL) and anhydrous $K_2CO_3$ (40 mg) in absolute ethanol (20 mL) was refluxed overnight. Afterward, the reaction mixture was concentrated to dryness, redissolved in 10 mL of $CH_2Cl_2$ and washed with 5% aqueous NaOH (3 × 10 mL). The organic layer was dried with anhydrous $Na_2SO_4$, filtered and evaporated to dryness under reduced pressure. The residue was purified by silica gel column chromatography ($CH_2Cl_2$/MeOH 97:3) to afford 70 mg of 8-(4-fluorobenzyloxy)-pyrrolo[2,1-*a*]isoquinolin-3-one **1e** (80%) as a yellow oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.38 (m, 4H, PhF), 7.04 (m, 4H, PhF, CH-10), 6.69 (s, 1H, H-7), 6.64 (s, 1H, H-10), 5.05 (s, 4H, $OCH_2Ph$), 4.66 (t, $J$ = 7.8 Hz, 1H, H-10b), 4.26 (m, 1H, H-5α), 2.99 (m, 1H, H-5β), 2.84 (m, 1H, H-6α), 2.65 (m, 1H, H-6β), 2.56 (m, 1H, H-1α), 2.51 (m, 1H, H-2α), 2.42 (m, 1H, H-2β), 1.76 (m, 1H, H-1β); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 173.1 (NCO), 163.4 (C-4′, $^1J_{CF}$ = 246 Hz), 161.4 (C-4″, $^1J_{CF}$ = 246 Hz), 147.9 (C-8), 147.7 (C-9), 132.8 (C-1′, C-1″), 130.4 (C-10a), 129.2 (4CH, CH-3′, CH-5′, CH-3″, CH-5″), 126.9 (C-6a), 115.4 (4CH, CH-2′, CH-6′, CH-2″, CH-6″), 115.2 (CH-7), 112.2 (CH-10), 71.2 ($OCH_2Ph$), 70.7 ($OCH_2Ph$), 56.4 (CH-10b), 36.9 ($CH_2$-5), 31.7 ($CH_2$-2), 28.0 ($CH_2$-6), 27.5 ($CH_2$-1); ESMS $m/z$ (%): 435 (100) $[M]^+$.

#### 3.6.3. 8,9-Bis(phenylacetamide)-1,2,3,5,6,10a-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (3d)

A mixture of 8, 9-dihydroxy-1,2,3,5,6,10b-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one (**3b**) (30 mg, 0.13 mmol), 2-bromo-*N*-phenylacetamide (61 mg, 0.26 mmol) and anhydrous $K_2CO_3$ (30 mg, 0.22 mmol) in EtOH (10 mL) was refluxed for 6 h. Then the reaction mixture was concentrated to dryness, redissolved in 10 mL of $CH_2Cl_2$ and washed with 5% aqueous NaOH (3 × 10 mL). The organic layer was dried with anhydrous $Na_2SO_4$ and evaporated to dryness. The residue was purified by silica gel column chromatography ($CH_2Cl_2$/MeOH, 98:2) to afford 40 mg of 8,9-bis(phenylacetamide)-1,2,3,5,6,10a-hexahydropyrrolo[2,1-*a*]isoquinolin-3-one **3d** (63%) as a brown oil. $^1$H NMR (500 MHz, $CDCl_3$): $\delta$ = 7.52 (m, 4H, H-2′, H-6′, H-2″, H-6″), 7.26 (m, 4H, H-3′, H-5′, H-3″, H-5″), 7.10 (m, 2H, H-4′, H-4″), 6.75 (s, 1H, H-7), 6.72 (s, 1H, H-10), 4.68 (s, 2H,$OCH_2CO$), 4.67 (t, $J$ = 7.9 Hz, 1H, H-10b), 4.25 (ddd, $J$ = 12.9, 6.2, 2.7 Hz, 1H, H-5α), 2.98 (m, 1H, H-5β), 2.82 (m, 1H, H-6α), 2.66 (m, 1H, H-6β), 2.62 (m, 1H, H-2α), 2.53 (m, 1H, H-2β), 2.43 (m, 1H, H-1α), 1.74 (m, 1H, H-1β); $^{13}$C NMR (125 MHz, $CDCl_3$): $\delta$ = 173.0 (NCO-3), 165.9 (PhNCO), 146.9 (C-9), 146.2 (C-8), 136.6 (C-1′), 132.4 (C-10a), 128.9 (C-3′, C-5′, C-3″, C-5″), 124.9 (CH-4′, CH-4″), 128.7 (C-6a), 120.0 (4CH, CH-2′, CH-6′, CH-2″, CH-6″), 115.7 (CH-7), 111.9 (CH-10), 69.6 ($OCH_2CO$), 56.2 (CH-10b), 36.7 ($CH_2$-5), 31.6 ($CH_2$-6), 27.9 ($CH_2$-2), 27.4 ($CH_2$-1); ESMS $m/z$ (%): 485 (100) $[M]^+$.

### 3.7. Pharmacological assays

#### 3.7.1. Target microorganisms

Fungicidal activity was measured against 5 phytopathogens: *Aspergillus parasiticus* (CECT 2681), *Trichoderma* V*iride* (CECT 2423), *Fusarium culmorum* (CCM 172), *Phytophthora citrophthora* (CECT 2353) and *Geotrichum candidum* (CCM 245). Seven different bacterial strains were used to determine bactericidal activity: *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 strains were provided by the Colección Española de Cultivos Tipo (CECT) or by the Colección de la Cátedra de Microbiología (CMM) of the Biotechnology Department (Universidad Politécnica de Valencia).

#### 3.7.2. Antifungal and antibacterial activities

These assays were determined in triplicate by the paper disk-agar diffusion assay according to Cole.[29] The doses used in the assays were 10, 15 or 20 μg/mm$^2$ (0.2, 0.3 or 0.4 mg/disk). Fungal strains were seeded in Petri dishes containing PDA culture medium and were incubated for 7 days at 28 °C. Then, a Tween 80 solution (0.05%) in sterile distilled water was used to obtain a suspension containing ~106 conidia/mL. Next 1 mL of this conidia suspension was added to 15 mL of PDA in a Petri dish. After solidification, four Whatman disks (No. 113, 0.5 cm diameter) impregnated with the tested products, at appropriate doses, were added to these Petri dishes. The PDA plates containing disks impregnated with only the solvent used to dissolve the tested compounds were used as negative controls, and the disks with benomyl (methyl-1-[butylcarbamoyl]-2-benzimidazolecarbamate) (Sigma), at different concentrations according to the fungal species assayed, were used as positive controls. Fungicidal activity was determined by measuring the inhibition zone developed around the paper disk, indicating a zone of no growth.

In the bactericidal tests, 24-h cultures of each bacterium, maintained in inclined tubes on solid culture medium, were reactivated with a Nutrient Broth (Difco) and were incubated for 24 h at 28 or 37 °C according to the bacterium. Then, 1 mL of this suspension was inoculated in a Petri plate, and 15 mL of the culture medium Plate Count Agar (Difco) was added. When the medium was completely solidified, five paper disks loaded with the tested products were placed in the dish. These plates were incubated for 24 h in the dark at 28 or 37 °C, according to the bacterium. The plate Count Agar plates containing disks impregnated with only the solvent used to dissolve the tested compounds were used as negative

controls, and a positive control with tetracycline chlorhydrate (0.2 mg/disk) was performed to appraise the level of activities. Bactericidal activity was determined by measuring the halo developed around the paper disk.

### 3.8. Statistical analysis

Analysis of variance (ANOVA) was performed for the fungicidal and bactericidal data (Tables 1 and 2), and the least significant difference (LSD) test was used to compare means (Statgraphics centurion XVI version).

## References and notes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