

## SYNTHESIS AND ANTIBACTERIAL EVALUATION OF NEW PYRROLO[3',4':3,4]PYRROLO[1,2-a]QUINOLINE AND PYRROLO[3',4':3,4]PYRROLO[2,1-a]ISOQUINOLINE DERIVATIVES

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**ABSTRACT.** Two series of new fused pyrrolo[3',4':3,4]pyrrolo[1,2-a]quinoline and pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline derivatives were synthesized and evaluated for the antimicrobial activity. The synthetic approach involves cycloimmonium ylides as 1,3-dipol intermediates. The structures of all synthesized compounds were proved by analytical and spectroscopic data. Crystal structure of compound **11a** has been also determined by single crystal XRD. The synthesized compounds were evaluated for their expected antimicrobial activity against *Staphylococcus aureus* ATCC25923, *Escherichia coli* ATCC25922 and *Candida albicans* ATCC10231, but no one showed activity against all the reference strains.

**Keywords:** heterocycles, cycloaddition, quinolines, isoquinolines, antibacterial

### INTRODUCTION

In recent years, medicinal chemistry has been focused on the development of new potent antimicrobial agents, to overcome the problem of bacterial resistance, which became a very serious medical problem for health care systems in the entire world [1,2].

In this respect, fused N-heterocyclic systems attracted an important interest, since their molecules contain two or more widely known pharmacophoric fragments [3].

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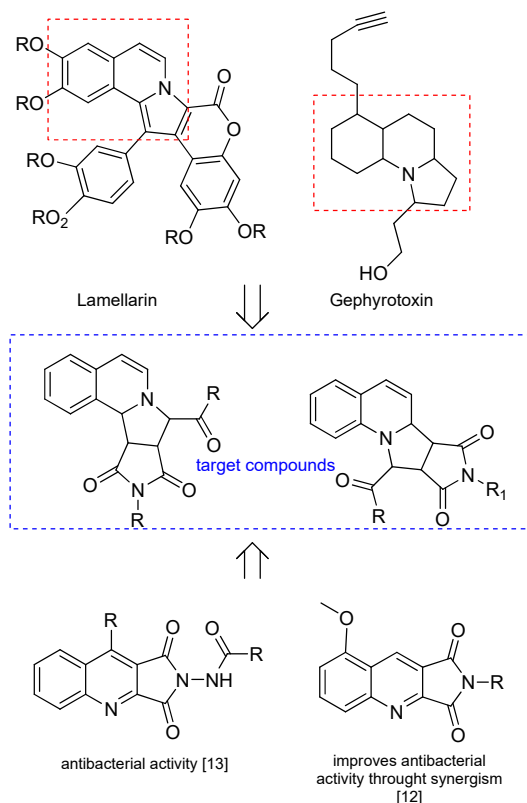
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Pyrrolo[2,1-a]isoquinolines are particular structural units in the heterocycle class, some of them occurring in biologically active compounds, the best known being lamellarine and gephyrotoxin groups of alkaloids (fig. 1). Some representatives of the group are known for their inhibitory properties of topoisomerase or HIV-1 integrase enzymes, while others showed anticancer activity, anti-inflammatory or cardiovascular properties [4].



**Figure 1.** Design of the target compounds

Pyrrolo[1,2-a]quinolines are also present in marine alkaloids as gephyrotoxin (fig. 1) that is reported as a muscarinic antagonist and presents interesting neurological activities [5,6].

For these reasons, the synthesis of pyrrolo[1,2-a]quinolines and pyrrolo[2,1-a] isoquinolines has drawn much recent research interest. Several synthetic methods for these fused N-heterocycles have been reported, including the reactions of 2-alkylpyridine with aldehydes or  $\alpha$ -haloketone [7], 1,3-dipolar

cycloadditions of quinolinium or isoquinolinium methylides to electron deficient dipolarofiles [8], 1,5-electrocyclizations and metal-catalyzed intramolecular C–N bond formation of alkynyl pyridines or propargylic pyridines [9].

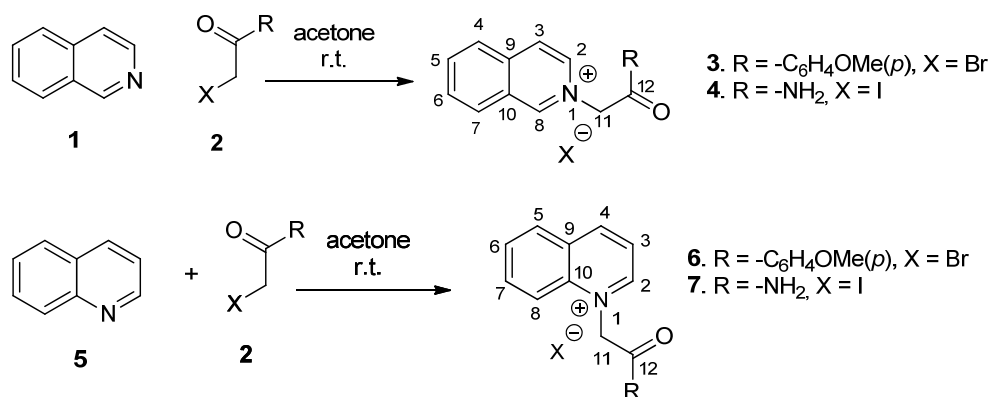
In the same time, cyclic imides and their N-derivatives are reported to exhibit valuable biological effects including antifungal [10] and antibacterial [11-13] (fig. 1).

In this context, as part of our ongoing research aiming at the design and synthesis of new fused N-heterocyclic compounds with biological activities [14-18], we present here the synthesis, structure and the antimicrobial evaluation of two series of compounds with pyrrolo-pyrrolo[2,1-a]isoquinoline and pyrrolo-pyrrolo[1,2-a]quinoline structures (fig. 1), both series having the end pyrrole cycle as N-substituted cyclic imide.

## RESULTS AND DISCUSSION

We decided to synthesize the pyrrolo-pyrrolo(iso)quinolone skeleton through the 3+2 cycloaddition of azomethineylide as the 1,3-dipole. This strategy has been used widely to construct complex cyclic systems from relatively simple precursors [19-22].

First step of our synthetic strategy was the synthesis of (iso)quinolinium monoquaternary salts **3-4** and **6-7** by an N-alkylation reaction with reactive halide type **2**, of isoquinoline and quinoline, respectively (Scheme 1). Reactions took place at room temperature with good to excellent yields. The structure of the new salts (**4** and **7**) was assigned by elemental and spectroscopic analysis: IR,  $^1\text{H}$  and  $^{13}\text{C}$  NMR.



Scheme 1. Synthesis of monoquaternary salts **3-4** and **5-6**

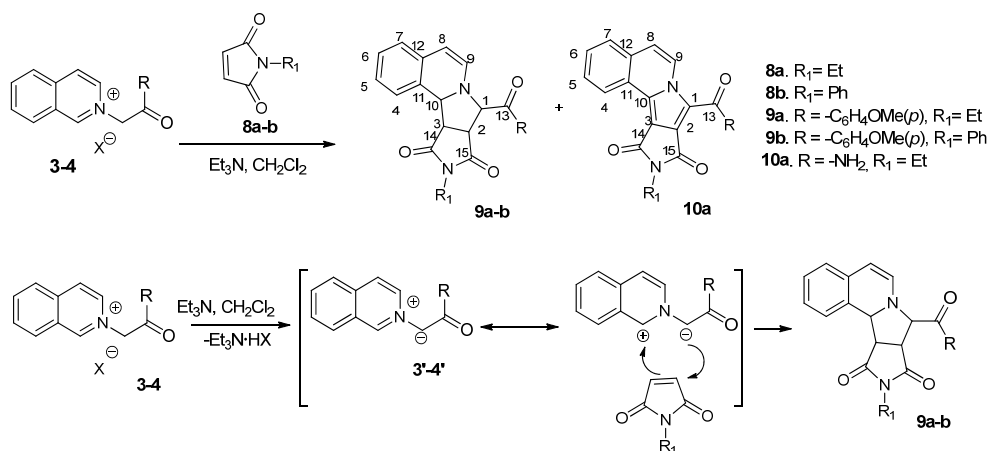
Next, the synthesis of pyrrolo[1,2-*a*]quinoline and pyrrolo[2,1-*a*]isoquinoline derivatives took place by 3+2 cycloaddition of N-ylides generated *in situ* from salts **3-4** and **6-7** to N-ethyl or N-phenylmaleimide as symmetrically substituted electron deficient alkenes.

Thus, by deprotonation of salts **3-4** and **6-7** under triethylamine treatment, the resonance stabilized N-ylides were *in situ* generated and reacted with N-ethyl or N-phenylmaleimide giving tetrahydropyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline derivatives **9a-b** or pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline derivatives **10a** (Scheme 2) and tetrahydropyrrolo[3',4':3,4]pyrrolo[1,2-*a*]quinolines **11a-b** and **12a**, respectively (Scheme 3). The cycloaddition reactions with N-ethyl or N-phenylmaleimide occur highly stereoselective, a single isomer being obtained in all cases.

The formation of compound **10a** could be explained by an oxidative dehydrogenation of the initial formed corresponding type **9** derivative, leading to the thermodynamically more stable product.

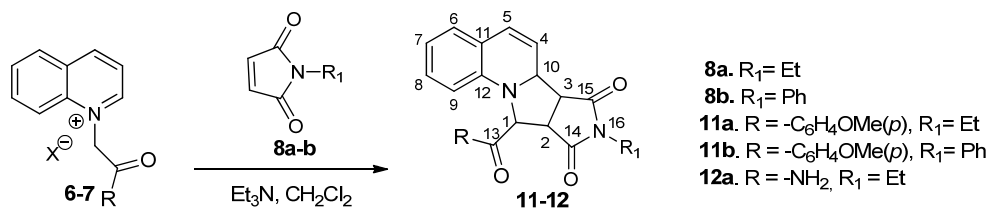
Interesting, the reaction of salts **4** and **7** with N-phenylmaleimide **8b** proved to be very difficult, complex and inseparable mixtures of compounds being obtained.

The structures of the new compounds **9a-b**, **10a**, **11a-b** and **12a** were assigned by elemental and spectroscopic analysis (IR, <sup>1</sup>H and <sup>13</sup>C-NMR).



*Scheme 2.* Synthesis pathway for the tetrahydropyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline derivatives **9a-b** and the pyrrolo[3',4':3,4]pyrrolo[2,1-*a*]isoquinoline derivative **10a** and the proposed reaction mechanism

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**Scheme 3.** Synthesis of tetrahydropyrrolo[3',4':3,4]pyrrolo[1,2-a]quinolines **11a-b** and **12a**

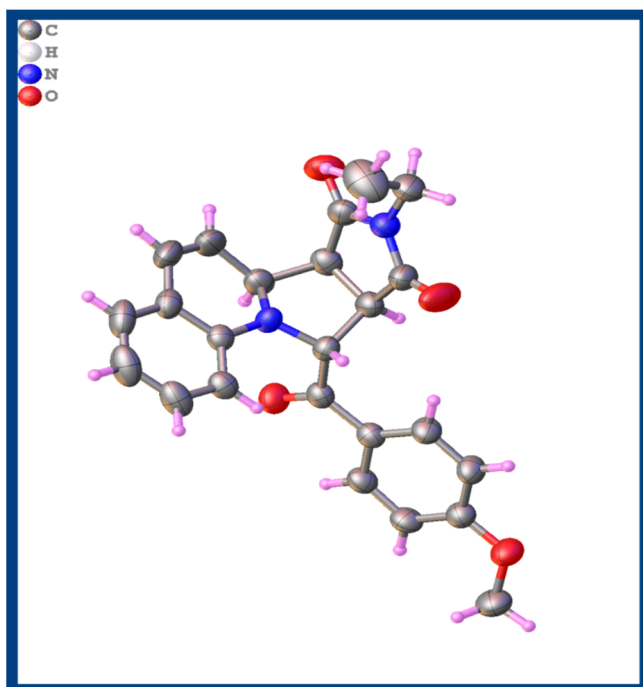
The IR spectra of polycyclic compounds type **9a-b** show absorption bands between 1774-1761 cm<sup>-1</sup> characteristic for in phase stretching vibrations of C=O imide groups and between 1696-1692 cm<sup>-1</sup> for out of phase vibrations of the same C=O imide group in some cases overlapped with ketone or amide carbonyl group absorption. In <sup>1</sup>H NMR spectrum of compounds **9a-b**, the signals at δ= 3.28-3.59 ppm have been assigned to H3 atom, the most shielded proton of the tetrahydropyrrole cycle. Protons 2 and 10 supply signals at δ= 3.76-4.15 ppm and δ=4.70-4.89 ppm, respectively. The signal delivered by H1 appears as singlet at weak fields (δ= 5.25-5.51 ppm) because of its electron withdrawing neighbours. The lack of coupling for H1 proton is a proof for a *trans* position relative to proton 2. The big values for the coupling constants *J*<sub>2,3</sub> (7.5-8.0 Hz) and *J*<sub>3,10</sub> (8.0 Hz) show us that hydrogen atoms H2, H3 and H10 lay on the same side of the tetrahydropyrrole ring, but on the opposite side of H1. <sup>13</sup>C-NMR spectra show two different signals for the two carbonyl imide carbon atoms at 174.1-174.6 ppm and 177.6-177.7 ppm respectively, while the carbonyl C13 furnishes signals at 192.0-192.3 ppm.

Compound **10a** furnishes a much simpler NMR spectrum with only two signals in the aliphatic region supplied by the ethyl group. Also the singlet signals of two amidic NH distinguish from the spectrum at 5.62 ppm and 8.71 ppm, respectively.

In <sup>1</sup>H NMR of compounds **11-12**, there are also four distinct signals in the aliphatic region corresponding to the four hydrogen atoms on the tetrahydropyrrole ring. The signals delivered by H1 appear as broad singlets, the small coupling (*J*<sub>1,2</sub>= 1.0 Hz) with H2 proton being a proof for a *trans* position relative to proton 1. On the other hand, the big values for the coupling constants *J*<sub>2,3</sub> (8.0 Hz) and *J*<sub>3,10</sub> (8.0 Hz) show us that hydrogen atoms H2, H3 and H10 lay on the same side of the pyrrole ring, but on the opposite side of H1.

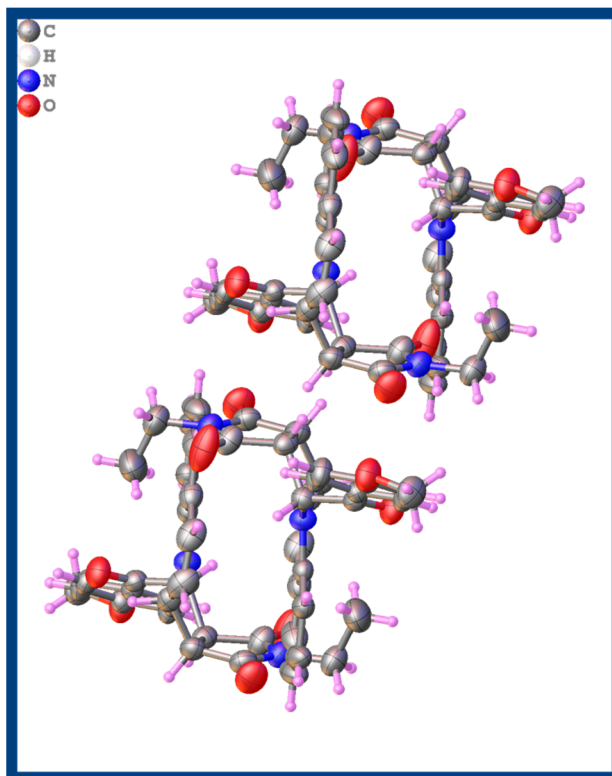
The above-mentioned conclusions for compounds type **11-12** were fully sustained by the structure obtained by single-crystal X-ray diffraction. Thus, the X-ray crystal structure of compound **11a**, is depicted in Figure 2.

Concerning the space disposal of the four fused rings we may notice that the end pyrrole cycle (former N-ethylmaleimide) is almost perpendicular to the quinoline plane. Full information concerning X-ray structure could be found in the Cambridge Crystallographic Data Centre (CCDC 1936035).



**Figure 2.** X-ray crystal structure of compound **11a** with thermal ellipsoids at 50% probability level

A perspective view of the **11a** compound is shown in Figure 3. From the analysis of molecules packing we can conclude that the crystals are stabilized mainly by rather weak H-bonds (H-O length 2.43 Å, C-O length 3.17 Å and C-H...O angle 136.4°). Also, we noticed the absence of  $\pi$ - $\pi$  interactions which is probably a consequence of the nonplanar character of those molecules. Despite those facts the crystal structure is rather compact, the voids size being too small to accommodate solvent molecules.



**Figure 3.** Packing (view along the c axis) of the molecules in the case of compound **11a**

### Antimicrobial activity

Our group has previously reported several 1,10-phenanthroline monoquaternary salts [23] possessing antibacterial and antifungal activities. Thus, we decided to evaluate the antimicrobial activity for all synthesized compounds, including isoquinolinium salts **3-4** and quinolinium salts **6-7** (excepting salt **7** whose antibacterial evaluation was already reported. [24]. The antimicrobial activity of compounds **3, 4, 6, 7, 9-10** and **11-12** was measured by the agar disk diffusion method [25] which consists of addition of the sterile disks containing the compounds on the culture medium pre-inoculated with the microbial suspension, and measuring of the clear zone caused by the growth inhibition around the disks after 24 h of incubation. Unfortunately, all tested compounds showed no antimicrobial activity against all the reference strains.

## CONCLUSIONS

The synthesis of new fused polycyclic indolizines derived from quinoline and isoquinoline is presented. The strategy adopted for construction of new pyrrolo[1,2-*a*]quinoline and pyrrolo[2,1-*a*]isoquinoline derivatives, including a typical Huisgen [3+2] dipolar cycloaddition of the corresponding isoquinolinium and quinolinium N-methylides to N-ethyl and N-phenylmaleimide proved to be straightforward and efficient. The cycloaddition reactions occur highly stereoselective (a single isomer being obtained). X-ray diffraction of compound **11a** proved unambiguously the compounds structure and brings information concerning lattice structure. The antibacterial activity of the synthesized compounds was measured, but all the investigated compounds showed no antimicrobial activity against the three reference strains.

## EXPERIMENTAL SECTION

### Chemistry

Melting points were recorded on an A. KrüssOptronic Melting Point Meter KSPI and are uncorrected. Proton and carbon nuclear magnetic resonance ( $\delta_H$ ,  $\delta_C$ ) spectra were recorded on a Bruker Avance III (500 MHz). All chemical shifts are quoted on the  $\delta$ -scale in ppm. Coupling constants are given in Hz. IR spectra were recorded on a FTIR Shimadzu or Jasco 660 *plus* FTIR spectrophotometer. Thin layer chromatography (TLC) was carried out on Merck silica gel 60F<sub>254</sub> plates. Column chromatography was carried out on silica gel (Roth 60, 0.04-0.063mm). Visualisation of the plates was achieved using a UV lamp ( $\lambda_{max}$ = 254 or 365 nm). All commercially available products were used without further purification unless otherwise specified.

### General procedure for synthesis of isoquinolinium and quinolinium salts **3** and **5**

1 mmol of quinoline or isoquinoline was dissolved in 5 mL acetone. Then 1.1 mmol of reactive halide was added and the resulted mixture was stirred at room temperature for 24 hours. The formed precipitate was filtered and washed with acetone to give the desired product.



### General procedure for synthesis of isoquinoline and quinoline derivatives 7 and 8

The cycloimmonium salt (1 mmol, 1 equiv.) and dipolarophile (NEMI or NFMI), (1.1 mmol, 1.1 equiv), were added to 5 mL of dichloromethane and the obtained suspension was stirred at room temperature (rt) under N<sub>2</sub> atmosphere. Triethylamine (TEA) (3 mmol, 3 equiv.) was added drop-wise over 1 hour (magnetic stirring) and the resulting mixture was then stirred for 24 hours at rt. Methanol (5 mL) was added and the resulting mixture is kept for 24 hours without stirring. The formed precipitate was collected by filtration to give a solid which was washed with methanol. The product was crystallized from dichloromethane/methanol (1/1, v/v).

### Spectral data

**2-(2-(4-methoxyphenyl)-2-oxoethyl)isoquinolin-2-ium bromide (3).** Grey solid,  $\eta = 95\%$ , m.p. = 215-217°C, IR (KBr, cm<sup>-1</sup>): 3009, 2947, 1684, 1604, 1237, 1162, 974. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 500 MHz):  $\delta = 3.91$  (s, 3H, OMe), 6.61 (s, 2H, H<sub>11</sub>), 7.20 (d,  $J = 8.0$  Hz, 2H, 2 x Ph-H), 8.09-8.13 (overlapped signals, 3H, H<sub>6</sub>, 2 x Ph-H), 8.33 (t,  $J = 7.5$  Hz, 1H, H<sub>5</sub>), 8.42 (d,  $J = 8.5$  Hz, 1H, H<sub>4</sub>), 8.55 (d,  $J = 8.0$  Hz, 1H, H<sub>7</sub>), 8.68 (d,  $J = 7.0$  Hz, 1H, H<sub>3</sub>), 8.75 (d,  $J = 6.5$  Hz, 1H, H<sub>2</sub>), 10.05 (s, 1H, H<sub>8</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 125 MHz):  $\delta = 55.9$  (OMe), 65.8 C<sub>11</sub>, 114.5 (2 x CH-Ph), 125.4 C<sub>3</sub>, 126.4 C<sub>q</sub>-Ph, 126.9 C<sub>10</sub>, 127.4 C<sub>4</sub>, 130.6 C<sub>7</sub>, 130.8 (2 x CH-Ph), 131.4 C<sub>6</sub>, 136.4 C<sub>2</sub>, 137.2 C<sub>5</sub>, 137.4 C<sub>9</sub>, 151.7 C<sub>8</sub>, 164.4 C<sub>q</sub>-Ph, 189.2 C<sub>12</sub>.

**2-(2-amino-2-oxoethyl)isoquinolin-2-ium iodide (4).** Yellow solid,  $\eta = 97\%$ , m.p. = 199-201°C, IR (KBr, cm<sup>-1</sup>): 3334, 3147, 2927, 1691, 1649, 1393, 1292 823. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 500 MHz):  $\delta = 5.53$  (s, 2H, H<sub>11</sub>), 7.77 (s, 1H, NH), 8.10 (as, 2H, H<sub>6</sub>, NH), 8.30-8.37 (overlapped signals, 2H, H<sub>5</sub>, H<sub>4</sub>), 8.52-8.70 (overlapped signals, 3H, H<sub>2</sub>, H<sub>3</sub>, H<sub>7</sub>), 10.01 (s, 1H, H<sub>8</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 125 MHz):  $\delta = 61.5$  C<sub>11</sub>, 125.1 C<sub>3</sub>, 126.7 C<sub>10</sub>, 127.3 C<sub>4</sub>, 130.5 C<sub>7</sub>, 131.3 C<sub>6</sub>, 136.4 C<sub>2</sub>, 137.1 C<sub>9</sub>, 137.3 C<sub>5</sub>, 151.6 C<sub>8</sub>, 166.2 C<sub>12</sub>.

**1-(2-(4-methoxyphenyl)-2-oxoethyl)quinolin-1-ium bromide (6).** Grey solid,  $\eta = 89\%$ , m.p. = 221-223 °C; IR (KBr, cm<sup>-1</sup>): 3024, 2956, 1673, 1598, 1519, 1359, 1240, 1175. <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>, 500 MHz):  $\delta = 3.92$  (s, 3H, OMe), 7.00 (s, 2H, H<sub>11</sub>), 7.22 (d,  $J = 8.5$  Hz, 2H, 2 x Ph-H), 8.13 (d,  $J = 8.5$  Hz, 2H, 2 x Ph-H), 8.06 (t,  $J = 7.5$  Hz, H<sub>6</sub>), 1H, 8.22 (t,  $J = 7.5$  Hz, 1H, H<sub>7</sub>), 8.33 (dd,  $J = 8.5; 5.5$  Hz, 1H, H<sub>3</sub>), 8.40 (d,  $J = 8.5$  Hz, 1H, H<sub>5</sub>), 8.55 (d,  $J = 8.5$  Hz, 1H, H<sub>8</sub>), 9.45 (d,  $J = 8.5$  Hz, 1H, H<sub>4</sub>), 9.55 (d,  $J = 5.5$  Hz, 1H, H<sub>2</sub>). <sup>13</sup>C-NMR (DMSO-d<sub>6</sub>, 125 MHz):  $\delta = 55.9$  (OMe), 62.9 C<sub>11</sub>, 114.4 (2 x CH-Ph), 119.1 C<sub>5</sub>, 122.2 C<sub>3</sub>, 126.4 C<sub>q</sub>-Ph, 129.4 C<sub>9</sub>, 130.0 C<sub>6</sub>, 130.6 C<sub>8</sub>, 131.2 (2 x CH-Ph), 135.9 C<sub>7</sub>, 138.6 C<sub>10</sub>, 148.5 C<sub>4</sub>, 151.0 C<sub>2</sub>, 164.5 C<sub>q</sub>-Ph, 189.0 C<sub>12</sub>.

**1-(2-amino-2-oxoethyl)quinolin-1-ium iodide (7).** Yellow solid,  $\eta = 68\%$ , m.p. = 236-239°C, IR (KBr,  $\text{cm}^{-1}$ ): 3361, 3154, 2980, 1678, 1620, 1523, 1356, 778.  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ , 500 MHz):  $\delta = 5.85$  (s, 2H,  $\text{H}_{11}$ ), 7.84 (s, 1H, NH), 8.05 (dt,  $J = 8.0 ; 2.0$  Hz, 1H,  $\text{H}_6$ ), 8.17 (s, 1H, NH), 8.25-8.31 (m, 3H,  $\text{H}_3$ ,  $\text{H}_7$ ,  $\text{H}_5$ ), 8.51 (d,  $J = 8.0$  Hz, 1H,  $\text{H}_8$ ), 9.38 (d,  $J = 8.0$  Hz, 1H,  $\text{H}_4$ ), 9.52 (d,  $J = 5.5$  Hz, 1H,  $\text{H}_2$ ).  $^{13}\text{C-NMR}$  ( $\text{DMSO-d}_6$ , 125 MHz):  $\delta = 58.8$   $\text{C}_{11}$ , 118.4  $\text{C}_5$ , 122.0  $\text{C}_3$ , 129.3  $\text{C}_9$ , 129.9  $\text{C}_6$ , 130.6  $\text{C}_8$ , 135.9  $\text{C}_7$ , 138.2  $\text{C}_{10}$ , 148.2  $\text{C}_4$ , 151.1  $\text{C}_2$ , 165.8  $\text{C}_{12}$ .

**10-ethyl-8-(4-methoxybenzoyl)-8,8a,11a,11b-tetrahydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-9,11(10H)-dione (9a).** Yellow crystals,  $\eta = 60\%$ , m.p. = 208-210°C; IR (KBr),  $\nu(\text{cm}^{-1})$ : 2978, 1774, 1696, 1670, 1600, 1399, 1225.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 500 MHz):  $\delta = 0.90$  (t,  $J = 7.0$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ), 3.25 (q,  $J = 7.0$  Hz, 2H,  $\text{CH}_2\text{CH}_3$ ), 3.28 (t,  $J = 8.0$  Hz, 1H,  $\text{H}_3$ ), 3.73 (1H, s, OMe), 3.76 (d,  $J = 7.5$  Hz, 1H,  $\text{H}_2$ ), 4.70 (d,  $J = 8.0$  Hz, 1H,  $\text{H}_{10}$ ), 5.16 (d,  $J = 7.5$  Hz, 1H,  $\text{H}_8$ ), 5.29 (s, 1H,  $\text{H}_1$ ), 6.05 (d,  $J = 7.5$  Hz, 1H,  $\text{H}_9$ ), 6.77 (d,  $J = 7.5$  Hz, 1H,  $\text{H}_4$ ), 6.83 (d,  $J = 8.5$  Hz, 2H, 2 x Ph-H), 7.00 (as, 2H,  $\text{H}_5$ ,  $\text{H}_6$ ), 7.03 (dd,  $J = 7.5 ; 4.0$  Hz, 1H,  $\text{H}_7$ ), 7.95 (d,  $J = 8.5$  Hz, 2H, 2 x Ph-H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 125 MHz):  $\delta = 11.4$  ( $\text{CH}_2\text{CH}_3$ ), 33.8 ( $\text{CH}_2\text{CH}_3$ ), 45.8  $\text{C}_2$ , 51.3  $\text{C}_3$ , 55.4 (OMe), 61.7  $\text{C}_{10}$ , 72.1  $\text{C}_1$ , 102.5  $\text{C}_8$ , 113.8 (2 x CH-Ph), 124.2  $\text{C}_4$ , 125.7  $\text{C}_6$ , 125.8  $\text{C}_{11}$ , 126.5 Cq-Ph, 127.3  $\text{C}_5$ , 128.2  $\text{C}_7$ , 130.8  $\text{C}_{12}$ , 131.4 (2 x CH-Ph), 134.9  $\text{C}_9$ , 163.9 Cq-Ph, 174.6  $\text{C}_{14}$ , 177.7  $\text{C}_{15}$ , 192.0  $\text{C}_{13}$ .

**8-(4-methoxybenzoyl)-10-phenyl-8,8a,11a,11b-tetrahydro-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-9,11(10H)-dione (9b).** Yellow solid,  $\eta = 90\%$ , m.p. = 208-210°C; IR (KBr),  $\nu(\text{cm}^{-1})$ : 1761, 1692, 1671, 1595, 1507, 1394, 1240, 1167.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 500 MHz):  $\delta = 3.59$  (t,  $J = 8.0$  Hz, 1H,  $\text{H}_3$ ), 3.86 (1H, s, OMe), 4.15 (d,  $J = 8.0$  Hz, 1H,  $\text{H}_2$ ), 4.89 (d,  $J = 8.0$  Hz, 1H,  $\text{H}_{10}$ ), 5.49 (d,  $J = 7.5$  Hz, 1H,  $\text{H}_8$ ), 5.51 (s, 1H,  $\text{H}_1$ ), 6.25 (d,  $J = 7.5$  Hz, 1H,  $\text{H}_9$ ), 7.12-7.20 (m, 3H,  $\text{H}_4$ ,  $\text{H}_6$ ,  $\text{H}_5$ ), 6.96 (ad,  $J = 8.5$  Hz, 3H, 2 x Ph-H,  $\text{H}_7$ ), 7.09 (d,  $J = 7.5$  Hz, 2H, 2 x Ph-H), 7.33 (t,  $J = 7.5$  Hz, 1H, Ph-H), 7.40 (t,  $J = 7.5$  Hz, 2H, 2 x Ph-H), 8.09 (d,  $J = 8.5$  Hz, 2H, 2 x Ph-H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 125 MHz):  $\delta = 46.5$   $\text{C}_2$ , 51.9  $\text{C}_3$ , 55.7 (OMe), 62.5  $\text{C}_{10}$ , 73.3  $\text{C}_1$ , 103.1  $\text{C}_8$ , 114.2 (2 x CH-Ph), 124.8  $\text{C}_7$ , 126.0 (2 x Ph-CH,  $\text{C}_{11}$ ), 126.5  $\text{C}_6$ , 126.9  $\text{C}_{14}$ , 127.8  $\text{C}_4$ , 128.6 (Ph-CH), 128.9  $\text{C}_5$ , 129.2 (2 x Ph-CH), 130.9  $\text{C}_{12}$ , 131.8 (2 x CH-Ph), 132.1 Cq-Ph, 135.3  $\text{C}_9$ , 164.4  $\text{C}_{17}$ , 174.1  $\text{C}_{14}$ , 177.6  $\text{C}_{15}$ , 192.3  $\text{C}_{13}$ .

**10-ethyl-8-(4-methoxybenzoyl)-9H-pyrrolo[3',4':3,4]pyrrolo[2,1-a]isoquinoline-9,11(10H)-dione (10a).** Brown solid,  $\eta = 60\%$ , m.p. = 239-240°C. IR (KBr,  $\text{cm}^{-1}$ ): 3394, 3182, 1741, 1687, 1618, 1408, 1221, 1018.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 500 MHz):  $\delta = 1.33$  (t,  $J = 7.0$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ), 3.79 (q,  $J = 7.0$  Hz, 2H,  $\text{CH}_2\text{CH}_3$ ), 5.62 (s, 1H, NH), 7.22 (d,  $J = 7.5$  Hz, 1H,  $\text{H}_8$ ), 7.67-7.76 (overlapped signals, 3H,  $\text{H}_5$ ,  $\text{H}_6$ ,  $\text{H}_7$ ), 8.71 (s, 1H, NH), 9.11 (d,  $J = 7.5$  Hz, 1H,  $\text{H}_4$ ), 9.64 (d,  $J = 7.5$  Hz, 1H,  $\text{H}_9$ ).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 125 MHz):  $\delta = 14.3$  ( $\text{CH}_2\text{CH}_3$ ), 33.7 ( $\text{CH}_2\text{CH}_3$ ), 111.0  $\text{C}_3$ , 114.8  $\text{C}_1$ , 115.9  $\text{C}_8$ , 124.0  $\text{C}_{11}$ , 125.8  $\text{C}_9$ , 126.8  $\text{C}_7$ , 127.4  $\text{C}_4$ , 129.0  $\text{C}_5$ , 129.5  $\text{C}_2$ , 130.4  $\text{C}_6$ , 131.6  $\text{C}_{12}$ , 151.8  $\text{C}_{10}$ , 161.2  $\text{C}_{14}$ , 163.7  $\text{C}_{13}$ , 166.2  $\text{C}_{15}$ .

**8-ethyl-10-(4-methoxybenzoyl)-6a,6b,9a,10-tetrahydro-7H-pyrrolo[3',4':3,4]pyrrolo[1,2-a]quinoline-7,9(8H)-dione (11a).** Yellow crystals,  $\eta = 70\%$ , m.p. = 190-192°C; IR (KBr),  $\nu(\text{cm}^{-1})$ : 3056, 2974; 2930, 2827, 1783, 1698, 1598, 1491, 1446, 1397, 1233, 1166, 759.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 500 MHz):  $\delta = 1.03$  (t,  $J = 7.0$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ), 3.41 (t,  $J = 8.0$  Hz, 1H,  $\text{H}_3$ ), 3.52 (q,  $J = 7.0$  Hz, 2H,  $\text{CH}_2\text{CH}_3$ ), 3.57 (dd,  $J = 8.0, 1.0$  Hz, 1H,  $\text{H}_2$ ), 3.91 (1H, s, OMe), 5.20 (td,  $J = 8.0, 2.0$  Hz, 1H,  $\text{H}_{10}$ ), 5.63 (s, 1H,  $\text{H}_1$ ), 6.05 (dd,  $J = 10.0, 2.0$  Hz, 1H,  $\text{H}_4$ ), 6.18 (d,  $J = 8.0$  Hz, 1H,  $\text{H}_9$ ), 6.40 (dd,  $J = 10.0, 2.0$  Hz, 1H,  $\text{H}_5$ ), 6.65 (t,  $J = 7.5$  Hz, 1H,  $\text{H}_7$ ), 6.92 (d,  $J = 7.0$  Hz, 1H,  $\text{H}_6$ ), 6.96 (t,  $J = 8.5$  Hz, 2H,  $\text{H}_8$ ), 7.04 (d,  $J = 8.5$  Hz, 2H, 2 x Ph-H), 8.28 (d,  $J = 8.5$  Hz, 2H, 2 x Ph-H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 125 MHz):  $\delta = 12.9$  ( $\text{CH}_2\text{CH}_3$ ), 34.5 ( $\text{CH}_2\text{CH}_3$ ), 47.0  $\text{C}_2$ , 48.2  $\text{C}_3$ , 55.7 (OMe), 60.7  $\text{C}_{10}$ , 63.8  $\text{C}_1$ , 110.7  $\text{C}_9$ , 114.5 (2 x CH-Ph), 118.8  $\text{C}_7$ , 121.1  $\text{C}_4$ , 122.2  $\text{C}_{11}$ , 126.6 Cq-Ph, 126.7  $\text{C}_5$ , 127.5  $\text{C}_6$ , 129.2  $\text{C}_8$ , 131.6 (2 x CH-Ph), 141.8  $\text{C}_{12}$ , 164.5 Cq-Ph, 175.7  $\text{C}_{14}$ , 177.6  $\text{C}_{15}$ , 194.2  $\text{C}_{13}$ .

**10-(4-methoxybenzoyl)-8-phenyl-6a,6b,9a,10-tetrahydro-7H-pyrrolo[3',4':3,4]pyrrolo[1,2-a]quinoline-7,9(8H)-dione (11b).** Yellow crystals,  $\eta = 80\%$ , m.p. = 198-199°C; IR (KBr),  $\nu(\text{cm}^{-1})$ : 3042, 2962, 2909, 1779, 1715, 1676, 1599, 1489, 1379, 1172, 746.  $^1\text{H-NMR}$  ( $\text{CDCl}_3$ , 500 MHz):  $\delta = 3.59$  (t,  $J = 8.0$  Hz, 1H,  $\text{H}_3$ ), 3.82 (d,  $J = 8.0$  Hz, 1H,  $\text{H}_2$ ), 3.91 (1H, s, OMe), 5.24 (td,  $J = 8.0, 2.0$  Hz, 1H,  $\text{H}_{10}$ ), 5.80 (s, 1H,  $\text{H}_1$ ), 6.09 (dd,  $J = 10.0, 2.5$  Hz, 1H,  $\text{H}_4$ ), 6.31 (d,  $J = 8.0$  Hz, 1H,  $\text{H}_9$ ), 6.46 (dd,  $J = 10.0, 2.0$  Hz, 1H,  $\text{H}_5$ ), 6.71 (t,  $J = 7.5$  Hz, 1H,  $\text{H}_7$ ), 6.97 (d,  $J = 7.5$  Hz, 1H,  $\text{H}_6$ ), 7.01 (t,  $J = 8.0$  Hz, 2H,  $\text{H}_8$ ), 7.03 (d,  $J = 8.5$  Hz, 2H, 2 x Ph-H), 7.10 (d,  $J = 7.5$  Hz, 2H, 2 x Ph-H), 7.35-7.43 (m, 3H, 3 x Ph-H), 8.29 (d,  $J = 8.5$  Hz, 2H, 2 x Ph-H).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 125 MHz):  $\delta = 47.1$   $\text{C}_2$ , 48.7  $\text{C}_3$ , 55.8 (OMe), 61.0  $\text{C}_{10}$ , 64.6  $\text{C}_1$ , 110.9  $\text{C}_9$ , 114.5 (2 x CH-Ph), 119.1  $\text{C}_7$ , 121.0  $\text{C}_4$ , 122.2  $\text{C}_{11}$ , 126.5 (2 x Ph-CH), 126.6 Cq-Ph, 127.0  $\text{C}_5$ , 127.7  $\text{C}_6$ , 129.0 (CH-Ph), 129.3 (2 x Ph-CH), 129.4  $\text{C}_8$ , 131.6 ( $\text{C}_{15}$ ,  $\text{C}_{19}$ , Ph-Cq), 141.7  $\text{C}_{12}$ , 164.6 Cq-Ph<sub>17</sub>, 175.0  $\text{C}_{14}$ , 177.0  $\text{C}_{15}$ , 194.1  $\text{C}_{13}$ .

**8-ethyl-7,9-dioxo-6b,7,8,9,9a,10-hexahydro-6aH-pyrrolo[3',4':3,4]pyrrolo[1,2-a]quinoline-10-carboxamide (12a).** Brown solid,  $\eta = 70\%$ , m.p. = 213-217°C. IR (KBr,  $\text{cm}^{-1}$ ): 3401, 3259, 2984, 1762, 1690, 1600, 1406, 1218, 1125, 759, 614.  $^1\text{H-NMR}$  ( $\text{DMSO-d}_6$ , 500 MHz):  $\delta = 0.81$  (t,  $J = 7.0$  Hz, 3H,  $\text{CH}_2\text{CH}_3$ ), 3.3 (q,  $J = 7.0$  Hz, 2H,  $\text{CH}_2\text{CH}_3$ ), 3.55 (overlapped signals, 2H,  $\text{H}_3, \text{H}_2$ ), 4.59 (s, 1H,  $\text{H}_1$ ), 5.11 (m, 1H,  $\text{H}_{10}$ ), 5.88 (dd,  $J = 10.0, 2.5$  Hz, 1H,  $\text{H}_4$ ), 6.34 (dd,  $J = 10.0, 2.0$  Hz, 1H,  $\text{H}_5$ ), 6.52 (d,  $J = 8.0$  Hz, 1H,  $\text{H}_9$ ), 6.58 (t,  $J = 7.0$  Hz, 1H,  $\text{H}_7$ ), 6.89 (dd,  $J = 7.5; 1.0$  Hz, 1H,  $\text{H}_6$ ), 6.98 (dt,  $J = 8.5; 1.0$  Hz, 1H,  $\text{H}_8$ ), 7.39 (s, 1H, NH), 7.92 (s, 1H, NH).  $^{13}\text{C-NMR}$  ( $\text{CDCl}_3$ , 125 MHz):  $\delta = 12.4$  ( $\text{CH}_2\text{CH}_3$ ), 33.2 ( $\text{CH}_2\text{CH}_3$ ), 47.3  $\text{C}_2$ , 48.5  $\text{C}_3$ , 59.4  $\text{C}_{10}$ , 62.0  $\text{C}_1$ , 110.5  $\text{C}_9$ , 117.8  $\text{C}_7$ , 121.1  $\text{C}_{11}$ , 121.6  $\text{C}_4$ , 125.4  $\text{C}_5$ , 126.9  $\text{C}_6$ , 128.9  $\text{C}_8$ , 142.1  $\text{C}_{12}$ , 172.1  $\text{C}_{13}$ , 175.9  $\text{C}_{14}$ , 177.4  $\text{C}_{15}$ .

## X-Ray Crystallography

Crystallographic measurements for compound  $C_{24}H_{22}N_2O_4$  were carried out on a SuperNova, Dual, Cu at zero, Eos diffractometer. The crystal was kept at 294 K during data collection. The unit cell determination and data integration were carried out using the CrysAlisPro package of Oxford Diffraction. Using Olex2 [26], the structure was solved with the Superflip [27] structure solution program using Charge Flipping and refined with the ShelXL [28] refinement package using Least Squares minimisation.

**Table 1.** Crystal data and structure refinement for **11a**

Identification code	<b>11a</b>
Empirical formula	$C_{24}H_{22}N_2O_4$
Formula weight	402.45
Temperature/K	294
Crystal system	triclinic
Space group	P-1
a/Å	8.9438(5)
b/Å	9.4257(4)
c/Å	13.1464(6)
$\alpha/^\circ$	92.456(3)
$\beta/^\circ$	107.620(4)
$\gamma/^\circ$	106.925(4)
Volume/Å <sup>3</sup>	1000.05(9)
Z	2
$\rho_{\text{calc}}/\text{mg}/\text{mm}^3$	1.3364
m/mm <sup>-1</sup>	0.747
F(000)	425.4
Crystal size/mm <sup>3</sup>	0.3200 × 0.2800 × 0.2200
Radiation	Cu K $\alpha$ ( $\lambda = 1.54184$ )
2 $\theta$ range for data collection	7.12 to 140.88°
Index ranges	-10 ≤ h ≤ 10, -11 ≤ k ≤ 9, -16 ≤ l ≤ 15
Reflections collected	6411
Independent reflections	3732[R(int) = 0.0124]
Data/restraints/parameters	3732/0/272
Goodness-of-fit on F <sup>2</sup>	1.059
Final R indexes [ $I \geq 2\sigma(I)$ ]	R <sub>1</sub> = 0.0426, wR <sub>2</sub> = N/A
Final R indexes [all data]	R <sub>1</sub> = 0.0456, wR <sub>2</sub> = 0.1136
Largest diff. peak/hole / e Å <sup>-3</sup>	0.17/-0.20

The main crystallographic data together with refinement details are summarized in Table 1. CCDC 1936035 contains the full crystallographic data. Those data can be obtained free of charge from the Cambridge Crystallographic Data Centre via [www.ccdc.cam.ac.uk/data\\_request/cif](http://www.ccdc.cam.ac.uk/data_request/cif).

### Antimicrobial activity

The antimicrobial activity was determined by disk diffusion assay against three different reference strains: *Staphylococcus aureus* ATCC25923, *Escherichia coli* ATCC25922 and *Candida albicans* ATCC10231. All microorganisms were stored at -80°C in 20% glycerol. The bacterial strains (*S. aureus* and *E. coli*) were refreshed in Mueller-Hinton broth at 36±1°C and the yeast strain (*C. albicans*) was refreshed on Sabouraud dextrose broth at 36±1°C. Microbial suspensions were prepared with these cultures in sterile solution to obtain turbidity optically comparable to that of 0.5 McFarland standards (yielding a suspension containing 1x10<sup>8</sup>CFU ml<sup>-1</sup> for all the microorganisms).

Volumes of 0.4 ml from each inoculum were spread onto Mueller-Hinton agar and Sabouraud dextrose agar and all the tested samples were added after the medium surface dried. The sterilized paper discs (6 mm) were placed on the plate and an aliquot (100 µl) of the tested compounds (concentration 10mg/ml, dissolved in DMSO) was added on the paper discs. To evaluate the antimicrobial properties, the growth inhibition was measured under standard conditions after 24 hours of incubation at 36±1 °C. After incubation, the diameters of inhibition zones were measured by using Image J software.

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