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A Photochemical Approach to Pyridopyrroloquinoline Derivatives as New Potential Anticancer Agents

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Indoloquinoline alkaloid cryptolepine and pyridocarbazole alkaloid ellipticine are of great interest because in vitro and in vivo studies revealed their good cytotoxic properties. In order to obtain some biologically active analogs of these compounds, we developed a synthesis based on the photocyclisation of tertiary N-methylated enamines derived from cyclopentane-1,3-dione and 3 or 6-aminoquinoline. The angular cyclised compounds thus obtained were submitted to Beckmann rearrangement, preceded by the formation of a Z oxime. Finally, the 8-lactam ring was oxidised using 10% palladium/carbon in diphenylether and pyridopyrroloquinolines were obtained. These compounds and the intermediate lactams and cyclopentanopyrroloquinolines were tested in vitro on K 562 cells and A 2780 doxorubicine sensitive and resistant cells. All compounds were less effective than doxorubicine in sensitive cells but their activity wasn’t decreased by MDR resistance.

Key words photochemistry; pyridopyrroloquinoline; cytotoxicity; enamino; Beckmann

The pyridocarbazole alkaloid ellipticine is well known for its high cytotoxicity against several cancer cell lines due to its intercalating properties and its ability to inhibit DNA religation by topoisomerase II. A number of angular analogs have been prepared in order to obtain more active compounds. For example, one of the most promising products appeared to be intoplicine, synthesised firstly by Nguyen et al., which acts both as an intercalating agent and as a topoisomerase I and II inhibitor. So, considering the cytotoxic properties of angular nitrogenous heterocycles, other groups have elaborated several angular tetracyclic compounds derived from two or three nitrogenous heterocycles. Dalla Via et al. prepared indolopyrroloquinolines carrying a dialkylaminoalkyl side chain and different substituents. Linear flow dichroism studies demonstrated these compounds were able to intercalate into DNA and in vitro cytotoxicity studies showed IC50 on HL-60 cells varying between 0.5 and 1.6 μM. Furthermore, Da Settimo et al. prepared several derivatives of purinoquinazoline, pyridopyrimidopurine and pyridopyrimidobenzimidazole, all of them carrying a dialkylaminoalkyl side chain. Only purinoquinazolines could bind strongly to DNA and therefore could induce DNA double-strand breaks via inhibition of DNA religation by topoisomerase II. These compounds showed IC50 on HL-60 cells varying between 0.072 and 0.47 μM. Chart 1 represents some of the structures mentioned above.

Therefore, as a part of our studies related to the pharmacocchemistry of angular polynitrogenous tetracycles, we initiated a program in order to examine the synthesis of new pyridopyrroloquinolines and their antitumor activities against resistant cell lines (MDR phenotype +). Our synthetic methodology resides in the use of enamines derived from quinolines and cyclopentane-1,3-dione. Key steps of the synthesis are the photocyclisation of such enamines followed by Beckmann rearrangement to afford hydroxypyridine ring from 2-cyclopent-1-one ring, as shown in Chart 2. In this context, we have previously described the synthesis of indolopyrroloquinolines and pyridocarbazoles by photocyclisation of enamines derived from 3 or 6-aminoquinoline and cyclohexane-1,3-dione. This present work will allow us to study the photoreactivity of new enamines and to elaborate potentially cytotoxic compounds.

Results and Discussion

Chemistry
Firstly, we studied the reactivity of secondary halogenated enamines and. As shown in Chart 3, these compounds were obtained in two steps by con-

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densation of 3 or 6-aminoquinoline (8a, b) with cyclopentane-1,3-dione in toluene with paratoluenesulfonic acid, followed by α-iodination of 10 and 11 using BTMAICl₂, according to the procedures previously described.11,13)

Irradiation of enaminones 12 and 13 in acetonitrile with or without triethylamine gave a mixture of starting product and dehalogenated product, as shown in Table 1. Contrary to α-iodinated enaminones derived from 3 or 6-aminoquinoline and cyclohexane-1,3-dione, no cyclisation occurred.11)

Another attempt at photocyclisation was conducted according to the one-pot synthesis of pyridocarbazole and indoloquinoline previously described.11) Compounds 10 and 11 were irradiated in acetonitrile/H₂O/triethylamine in presence of iodine (2 eq) for 4 h. But only iodinated products 12 and 13 were obtained without any cyclised products, as shown in Table 2. So, when iodinated enaminones derived from aminooquinolines and cyclopentane-1,3-dione undergo irradiation, the competition between dehalogenation and cyclisation13) is clearly in favour of dehalogenation. As expected, this dehalogenation is enhanced by the presence of triethylamine, particularly in the case of 6-aminoquinoline derivatives. Chart 3 recapitulates these attempts.

Since secondary halogenated enaminones didn’t undergo photocyclisation, the reactivity of tertiary enaminones 14 and 15 was investigated (Chart 4). Previous works have been conducted by Gardette et al.14) who cyclised enaminones derived from N-methylaniline and cyclopentan-1,3-dione. These compounds were prepared by N-methylation of enaminones 10 and 11 using methyl iodide in toluene in presence of sodium hydride. Irradiation of such compounds under different conditions, as shown in Table 3, produced the best yield for cyclised compounds 16 and 17 when a mixture toluene/methanol (95/5) in a quartz reactor was being used, proving thus that photocyclisation requires much energy. The position of the intracyclic nitrogen atom seems to influence the reactivity of these compounds because photocyclisation yield is two fold smaller in the case of compound 15, derived from 6-aminoquinoline.

This photocyclisation appears to be regioselective, since we obtain only angular derivatives. The angular structure of these compounds is proven by the multiplet corresponding to H1, and whose shift in 1H-NMR spectrum appears at 8.77 ppm for compound 16 and 9.17 ppm for compound 17, due to the deshielding effect of the carbonyl group. Besides, compound 16 shows a characteristic singlet corresponding to H6 at 8.76 ppm and compound 17 shows a characteristic AB system corresponding to H5 and H6 at 7.57 ppm.

Thus, the cyclopentenone ring has been modified in three steps including Beckmann rearrangement in order both to introduce a third nitrogen atom and to obtain some totally aromatised compounds which can theoretically better inter-
First of all, the compounds 16 and 17 were treated by hydroxylamine hydrochloride, following the procedure described by Sekar et al.\(^\text{16,19}\) and Z oximes 18 and 19 were obtained. Configuration of C=N bond was determined by considering the \(^{13}\)C-NMR shift of the secondary carbon adjacent to the oxime function in our structures and in close compounds 20 and 21 synthesised by Scheiber et al.\(^\text{19}\) as shown in Chart 5.

The second step of this ring modification consisted in regioselective Beckmann rearrangement\(^\text{7}\) using polyphosphoric acid PPA, which gave lactams 22 (30%) and 23 (60%). The structure of the lactams was deduced from the configuration of the oximes, considering the mechanism of Beckmann transposition, and was confirmed by considering the \(^{13}\)C-NMR shift of the secondary carbon adjacent to the amide function in our structures and in close compounds 24 and 25 synthesised by Scheiber et al.\(^\text{19}\) as shown in Chart 6.

In order to obtain compounds 22 and 23 with better yields, compounds 16 and 17 were submitted to Schmidt transposition\(^\text{13}\) using sodium azide in refluxing sulfuric acid. But after 3 h, the starting material was recovered unchanged.

Finally, compounds 22 and 23 were treated by palladium/carbon 10% in diphenylether\(^\text{19}\) and underwent C=C bond oxydation to give the pyridopyrroloquinolines 26 and 27 with 30% and 32% yield respectively, as shown in Chart 7. This oxydation was expected to be more successful than previous attempts to oxydize cyclohexenone ring, since lactime tautomer in \(\delta\)-lactam ring is probably more easely formed than enol tautomer in cyclohexenone ring.

**Biological Results** In continuation of our previous works\(^\text{9,16}\) concerning the antiproliferative activity of tetracyclic nitrogenous heterocycles, and more precisely, their activity against MDR\(^+\) cancer cells lines, the cytotoxicity of the compounds 16, 17, 22, 23, 26 and 27 was evaluated by a cell growth inhibition assay against two human cell lines: K 562 (leukemia), and A 2780 (ovarian cancer) doxorubicine-sensitive and resistant (MDR\(^+\)) and was compared to the cytotoxicity of doxorubicine. The resistant subline A 2780 R was established by the continuous exposure of cells to gradually increasing concentrations of doxorubicine. The resistant subline K 562 R wasn’t tested because of the poor activity of our products against K 562 S cells. IC\(_{50}\) (concentration inhibiting 50% of the cell proliferation) expressed in mol/l and resistance factor (IC\(_{50}\) on A 2780 resistant cells/IC\(_{50}\) on A 2780 sensitive cells) of each compound are recapitulated in Table 4. IC\(_{50}\) of compound 22 couldn’t be determined exactly because of its poor solubility in the culture medium.

All the compounds were less effective than doxorubicine in all sensitive cells, whereas compounds 17, 23, 26 and 27 were as active as doxorubicine on A 2780 resistant cells with IC\(_{50}\) varying between 5 and 9.8×10\(^{-6}\) mol/l. The resistance factor of all those compounds (except 22, not determined) varies between 1.1 and 6.1 (doxorubicine: 121), which indicates that these compounds are not concerned by the multidrug resistance phenomenon.

Among these compounds, the less active ones are those which possess \(\delta\)-lactam ring. This can be due either to the poor solubility of these structures in the culture medium or to the structure of the compound itself. Besides, compounds derived from 6-aminoquinoline are globally more active than compounds derived from 3-aminoquinoline, proving the importance of the quinolinic nitrogen position in biological activity. But there’s only a little difference between the compounds 16 and 17 carrying a cyclopentenone ring and the compounds 26 and 27 carrying an hydroxyypyridine ring.

Compounds 16, 17, 26 and 27, which show the lowest IC\(_{50}\), are good candidates for further in vivo studies.

**Conclusion**

In this paper, we have reported the synthesis of tetracyclic nitrogen heterocycles: pyrido pyrroloquinolines obtained from cyclopentanopyrroloquinolines *via* a Beckmann rearrangement. The photochemical step which gives cyclopentanopyrroloquinolines from enamiones occurred with a total regioselectivity, since only angular compounds are obtained. The first *in vitro* studies reveal that the main interest of these

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**Table 4. IC\(_{50}\) and Resistance Factor of Tested Compounds and Doxorubicine**

<table>
<thead>
<tr>
<th>Compounds</th>
<th>K 562 cells (mol/l)</th>
<th>A 2780 cells sensitive (mol/l)</th>
<th>A 2780 cells resistant (mol/l)</th>
<th>Resistance factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>16</td>
<td>4.9×10(^{-5})±1.1×10(^{-5})</td>
<td>3.3×10(^{-5})±2.5×10(^{-5})</td>
<td>8.8×10(^{-5})±5.4×10(^{-5})</td>
<td>2.6</td>
</tr>
<tr>
<td>17</td>
<td>5.8×10(^{-5})±1.2×10(^{-5})</td>
<td>2.7×10(^{-5})±1.5×10(^{-5})</td>
<td>6.3×10(^{-5})±5.6×10(^{-5})</td>
<td>2.3</td>
</tr>
<tr>
<td>22</td>
<td>&gt;4.2×10(^{-4})</td>
<td>&gt;4.2×10(^{-4})</td>
<td>&gt;4.2×10(^{-4})</td>
<td>n.d.</td>
</tr>
<tr>
<td>23</td>
<td>7.7×10(^{-5})±1.9×10(^{-5})</td>
<td>1.6×10(^{-5})±7.9×10(^{-6})</td>
<td>9.8×10(^{-5})±9.4×10(^{-7})</td>
<td>6.1</td>
</tr>
<tr>
<td>26</td>
<td>5×10(^{-5})±10(^{-5})</td>
<td>4.5×10(^{-5})±1×10(^{-7})</td>
<td>5×10(^{-5})±6×10(^{-7})</td>
<td>1.1</td>
</tr>
<tr>
<td>27</td>
<td>1.1×10(^{-5})±3.8×10(^{-6})</td>
<td>5.7×10(^{-6})±7×10(^{-7})</td>
<td>8.5×10(^{-6})±3.8×10(^{-8})</td>
<td>1.5</td>
</tr>
<tr>
<td>Doxorubicine</td>
<td>1.6×10(^{-7})±3.3×10(^{-8})</td>
<td>2.4×10(^{-8})±4×10(^{-9})</td>
<td>2.9×10(^{-8})±4.9×10(^{-9})</td>
<td>121</td>
</tr>
</tbody>
</table>


3-[3'-Quinolinyl)methylamino]cyclopet-2-en-1-one 14 Compound 14 (600 mg, 2.7 mmol) was added to a suspension of sodium hydride (1.4 g, 25 mmol, 60% in mineral oil) in anhydrous toluene (50 ml). The mixture was refluxed under nitrogen for 2 h and cooled to room temperature. Methyl iodide (5 ml, 80 mmol) was then added and the mixture was refluxed for 4 h. After cooling, toluene was washed with water and the insoluble residue in the balloon flask was dissolved in dichloromethane and also washed with water. The organic layers were dried over sodium sulfate and evaporated in vacuo. The crude product was chromatographed on alumina gel with dichloromethane and a gradient of methanol as eluent to give 14 as a yellow oil. 1H-NMR (CDCl3, 100 MHz) δ 2.36 (2H, m, H5), 2.50 (2H, m, H4), 3.41 (3H, s, CH3), 5.16 (1H, s, H2), 7.56 (1H, m, H7'), 7.71 (1H, m, H6'), 7.78 (1H, d, J=8.1 Hz, H5'), 7.79 (1H, d, J=4.2 Hz, H4'), 8.07 (1H, d, J=8.4 Hz, H6'), 8.76 (1H, d, J=2.5 Hz, H2'); 13C-NMR (CDCl3, 100 MHz) δ 28.8, 32.6, 70.9, 121.1, 122.6, 126.9, 129.0, 130.9, 136.2, 136.7, 146.1, 150.6, 174.7, 199.8. Anal. Calc. for C16H12N2O: C, 75.63; H, 5.88; 11.76. Found: C, 75.75; H, 5.82; N, 11.81.

3-[6'-Quinolinyl)methylamino]cyclopet-2-en-1-one 15 This compound was obtained in 60% yield according to the procedure described for compound 14. Yellow oil. 1H-NMR (CDCl3, 100 MHz) δ 2.41 (2H, m, H5), 2.56 (2H, m, H4), 3.44 (3H, s, CH3), 7.46 (1H, m, H3'), 7.57 (1H, d, J=6.5 Hz, H7'), 7.67 (1H, m, H5'), 8.15 (2H, m, H4' and H6'), 8.95 (1H, d, J=2.6 Hz, H2'); 13C-NMR (CDCl3, 100 MHz) δ 30.1, 34.6, 41.7, 103.3, 122.4, 124.6, 128.2, 131.8, 136.3, 143.1, 147.1, 151.1, 171.2. Anal. Calc. for C15H11N2O2: C, 75.63; H, 5.88; N, 11.76. Found: C, 75.60; H, 5.81; N, 11.72.

Methylene-10-oxocyclopet-2-en-1-one [4]pyrrole[2,3-c]quinoline 16 Compound 14 (500 mg, 2.1 mmol) was then evaporated under reduced pressure. The crude product was chromatographed on alumina gel using dichloromethane as eluent to give 16 as a white powder, 50% (best yield). 1H-NMR (CDCl3, 100 MHz) δ 2.86 (2H, m, H5), 2.95 (2H, m, H4), 3.63 (3H, s, CH3), 7.60 (2H, m, H2 and H3), 8.10 (1H, m, H5), 8.76 (2H, m, H1 and H6); 13C-NMR (CDCl3, 100 MHz) δ 20.1, 31.4, 41.3, 121.1, 123.3, 124.2, 127.2, 127.6, 128.2, 129.1, 135.5, 135.6, 143.7, 167.9, 195.3. IR cm⁻¹ ν=1674. Anal. Calc. for C13H10NO2: C, 76.27; H, 5.08; N, 11.86. Found: C, 76.16; H, 5.11; N, 11.91.

Methylene-10-oxocyclopet-2-en-1-one [4]pyrrole[3,2-c]quinoline 17 This compound was obtained in 25% yield (best yield) according to the procedure described for compound 16. White powder, mp: 206—208 °C. 1H-NMR (CDCl3, 100 MHz) δ 2.71 (2H, m, H9), 2.81 (2H, m, H8), 3.42 (3H, s, CH3), 7.36 (1H, d, J=9.1 Hz, H6), 7.41 (1H, m, H7), 7.78 (1H, d, J=9.1 Hz, H5), 8.79 (1H, s, H3), 9.17 (1H, d, J=7.1 Hz, H1); 13C-NMR (CDCl3, 100 MHz) δ 21.3, 31.2, 41.4, 114.7, 119.9, 121.7, 121.8, 122.3, 123.7, 124.2, 127.2, 127.6, 128.2, 129.1, 135.5, 135.6, 143.7, 166.5, 195.7. IR cm⁻¹ ν=1674. Anal. Calc. for C14H10NO3: C, 76.27; H, 5.08; N, 11.86. Found: C, 76.32; H, 5.06; N, 11.90.

Hydroxyimino-10-oxocyclopet-2-en-1-one [4]pyrrole[4,5]pyrrole[3,2-c]quinoline 18 Compound 16 (180 mg, 0.76 mmol) and hydroxylamine hydrochloride (1g, 14.4 mmol) were dissolved in absolute ethanol (15 ml) and 2 ml of pyridine were added. The reaction mixture was refluxed under nitrogen for 3 h. After cooling, 30 ml of an aqueous solution of sodium carbonate10% were added. After extraction with dichloromethane, the organic layers were dried over sodium sulfate and evaporated in vacuo. The crude product was chromatographed on silica gel using dichloromethane and a gradient of methanol as eluent to give 18 as a white powder: 30%, mp: 154—156 °C. 1H-NMR (CDCl3, 100 MHz) δ 2.99 (2H, m, H9), 3.32 (2H, m, H8), 3.81 (3H, s, CH3), 7.52 (2H, m, H2 and H3), 8.0 (1H, d, J=8.0 Hz, H4), 8.78 (1H, s, H6), 8.98 (1H, d, J=8.0 Hz, H1); 13C-NMR (CDCl3, 100 MHz) δ 22.6, 31.2, 31.7, 116.9, 123.7, 123.7, 126.5, 127.4, 127.5, 128.2, 131.5, 135.6, 143.2, 158.0, 158.3. IR cm⁻¹ ν=1584, ν=1584, ν=2300—2400, MS=252 (35%), 251 (20%), 154 (100%), 136 (80%). Anal. Calc. for C15H10NO2: C, 71.71; H, 5.18; N, 16.73. Found: C, 71.83; H, 5.21; N, 16.67.

Hydroxyimino-10-oxocyclopet-2-en-1-one [4]pyrrole[3,2-f]quinoline 19 This compound was obtained in 33% yield according to the procedure described for compound 16. White powder, mp: 155—157 °C. 1H-NMR (CDCl3, 100 MHz) δ 3.09 (2H, m, H9), 3.27 (2H, m, H8), 3.85 (3H, s, CH3), 7.75 (1H, d, J=9.1 Hz, H6), 7.85 (1H, d, J=4.4 Hz, H4'), 8.16 (1H, m, H5'), 8.85 (1H, m, H2'), 13C-NMR (CDCl3, 100 MHz) δ 24.2, 31.5, 31.7, 113.9, 117.3, 118.6, 121.3, 121.8, 125.6, 136.6, 139.9, 141.7, 145.8, 158.1, 159.1. IR cm⁻¹ ν=1586, ν=2300—2400, MS=252 (5%), 250 (60%), 154 (40%), 149 (100%), 136 (40%). Anal. Calc. for C15H10NO2: C, 71.71; H, 5.18; N, 16.73. Found: C, 71.63; H, 5.20; N, 16.69.
8.9-Dihydro-7-methyl-11-oxopyrido[3’,4’-5]pyrrolo[2,3-]quinoline

22 Compound 18 (80 mg, 0.32 mmol) was added to phosphoric acid PPA (3 g) and phosphorus pentoxide (2 g) and the reaction mixture was stirred at 130 °C for 1 h. After cooling, 100 ml of ice cooled water were added. Then, sodium carbonate was added until pH became 7. After extraction with dichloromethane, the organic layers were dried over sodium sulfate and evaporated in vacuo. The crude product was chromatographed on silica gel using dichloromethane and a gradient of methanol to give 22 as a white powder: 30%, mp: 184—186 °C.

1H-NMR (CDCl 3, 400 MHz) δ: 3.37 (2H, J = 7.0 Hz, H8), 3.94 (2H, J = 7.0 Hz, H9), 4.14 (3H, s, CH 3), 7.97 (2H, m, H2 and H3), 8.23 (1H, J = 8.1 Hz, H4), 9.50 (1H, s, H6), 9.78 (1H, J = 8.4 Hz, H1). 13C-NMR (CDCl 3, 400 MHz) δ: 22.3, 32.1, 39.7, 109.02, 120.8, 122.3, 129.6, 129.0 (2C), 132.4, 133.5, 134.2, 156.1, 167.0. IR cm⁻¹v= 1645, MS = 252 (18%), 154 (96%), 136 (100%).

Anal. Calcd for C21H13N3O: C, 71.79; H, 5.18; N, 16.73. Found: C, 71.79; H, 5.22; N, 16.79.

8.9-Dihydro-7-methyl-11-oxopyrido[3’,4’-5]pyrrolo[3,2-]quinoline

23 This compound was obtained in 60% yield according to the procedure described for compound 22. White powder, mp: 198—200 °C. 1H-NMR (CDCl 3, 400 MHz) δ: 3.29 (2H, J = 7.1 Hz, H8), 3.89 (2H, J = 7.1 Hz, H9), 4.02 (3H, s, CH 3), 7.98 (1H, m, H2), 8.16 (1H, J = 9.2 Hz, H6), 8.26 (1H, J = 9.2 Hz, H5), 8.89 (1H, J = 5.0 Hz, H3), 10.81 (1H, J = 8.5 Hz, H1). 13C-NMR (CDCl 3, 400 MHz) δ: 21.9, 34.1, 40.2, 107.8, 116.3, 120.0, 120.3, 121.1, 124.7, 135.5, 136.5, 140.9, 147.3, 148.3, 168.1. IR cm⁻¹v= 1619, MS = 252 (100%), 149 (69%), 136 (8%).


References


