SYNTHESIS OF NEW INTERCALATED QUINONES AND THEIR CYTOTOXIC EFFECTS ON CANCER CELL LINES


Keywords: naphthoquinone; benzofuran; benzodioxine; antitumor activity; cytotoxicity

Naphthoquinones with benzofuran or benzodioxan ring were obtained from dichloronaphthoquinone and were fully characterized. The new benzodioxanes were tested on 4 cancer cells and one of them, a derivative from methyl pyrogallate was found very cytotoxic for cancer cells.

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Introduction

Quinones are one of the largest classes of antitumor agents.1 For example, among the drugs the most potent in cancer chemotherapy, there are the anthracycline antibiotics, Daunorubicin or Doxorubicin.2,3

DNA-intercalating molecules are usually aromatic, polycyclic and planar such as anthraquinones (as Doxorubicin, Saintopin),8,9 coumarins10 (as Elsamicin A11), or furanocoumarins (as Psoralen, Angelicin, Bergapten)12-15 and benzodioxins.16,17

Results and Discussion

We have chosen to study naphthoquinone derivatives containing a naphthobenzofuran or a benzodioxin ring. These molecules are easily available from the reaction of dichloronaphthoquinone with phenols according to Lieberman reaction18,19 and are well reported in literature.20

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Synthesis

The reactions between a wide range of structurally varied phenols and 2,3-dichloro-1,4-naphthoquinone (2,3-DCNQ) I led to the formation of C-O and C-C bonds affording the derivatives of a variety of polycyclic quinones in good yields (Scheme 1).
Synthesis and cytotoxicity of intercalated quinones

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Scheme 1. Formation of benzofuranonaphthoquinones from DCNQ 1 and phenols 2-4.

The products were obtained by the reaction of phenol derivatives with commercially available 2,3-DCNQ 1 under basic conditions. Resorcinol 2, phloroglucinol 3 and Sesamol 4, furnished [2,3]furano-4,9-dione (benzofuranonaphthoquinones) 8, 9 and 10 respectively. The compounds 8, 9 and 10 were previously prepared and described as cytotoxic for tumoral cells but not well characterised. In order to test in the future these compounds, we have fully characterised them by NMR (1H, 13C) and mass spectroscopy.

The reactions of 2,3-DCNQ 1 under basic conditions with catechol derivatives permit the formation of benzodioxin derivatives, through the formation of two C-O bonds.

Scheme 2. Formation of benzodioxins from DCNQ 1 and catechols 5-7.

With catechols like dihydroxycoumarin 5, pyrogallate derivates 6 and 7, we have obtained naphthoquinone benzodioxins respectively 11, 12 and 13. These compounds are not described in the literature. The reactions were simply performed by mixing reactants in the presence of potassium carbonate and acetone under reflux during several hours. All structures were fully characterized by standard spectroscopic methods (1H, 13C NMR, IR and MS data).

The results and the conditions of these reactions are reported in Table 1.

Scheme 3. Reaction of 2,3-DCNQ 1 with Umbelliferon 14.

With 7-hydroxycoumarin (Umbelliferon) 14, we are unable to obtain benzofuranonaphthoquinones but we have observed the formation of two products 15 and 16 (Scheme 3).

Clearly the phenol of Umbelliferon is desactivated and the formation of C-C bond does not occur. The attempts to obtain benzofuranonaphthoquinones with a Psoralen substructure, by ring closing of 15, in the presence of hard or soft Lewis acid (AlCl 3 or BiCl 3) or palladium acetate oxidative coupling conditions were unsuccessful.

Finally, in order to raise the Psoralen pattern, we have performed the reaction between the compound 9 and malic acid under acidic conditions, according to Pechmann conditions.21

Scheme 4. Reaction of 9 in the Pechmann conditions.

We have obtained a mixture of three lactone compounds which we were not able to break up (17, 18, 19).

Figure 3. Mixture of products obtained from 9 in the Pechmann conditions.

Cytotoxic effects

Compounds 8,22 923 and 1022 have been already synthetized and were evaluated in vitro by Cheng et al.22,24 for their inhibitory actions against cells line panel such as HL-60 (human promyelocytic leukemia) and SCLC (small cell lung cancer) cell lines. Compounds 8 and mainly 9 displayed the better cytotoxicity. The authors attributed this activity to the presence of hydroxyl group on aromatic cycle.

In this study, naphthoquinone benzodioxins were screened on a panel of four other cancer cell types corresponding to four types of cancer and isolated from four different cancer tissues.

The panel comprises human GBM cell line (U87MG); mouse melanoma cell line (B16F10); human epidermoid cell line (A431); human breast adenocarcinoma (pleural metastasis) cell line (MDAMB231). Throughout our goal to identify new compounds active against cancer cell, three new compounds were evaluated for their antiproliferative activity using a MTT test.
Table 1. Reactions of 2,3-dichloronaphthoquinone 1 with phenols 2-4 and catechols 5-7 under basic conditions

<table>
<thead>
<tr>
<th>DCNQ</th>
<th>Phenols, catechols</th>
<th>Reactions conditions</th>
<th>Products</th>
<th>Yielda %</th>
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<td><img src="image2.png" alt="Image" /></td>
<td>EtONa, RT, 12h</td>
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<td><img src="image5.png" alt="Image" /></td>
<td>KOH, MeOH 30°C, 3h</td>
<td><img src="image6.png" alt="Image" /></td>
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<tr>
<td><img src="image7.png" alt="Image" /></td>
<td><img src="image8.png" alt="Image" /></td>
<td>C₆H₅N, reflux 3h</td>
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<tr>
<td><img src="image10.png" alt="Image" /></td>
<td><img src="image11.png" alt="Image" /></td>
<td>K₂CO₃, acetone 60°C, 14h</td>
<td><img src="image12.png" alt="Image" /></td>
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<tr>
<td><img src="image13.png" alt="Image" /></td>
<td><img src="image14.png" alt="Image" /></td>
<td>K₂CO₃, acetone 60°C, 14h</td>
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<tr>
<td><img src="image16.png" alt="Image" /></td>
<td><img src="image17.png" alt="Image" /></td>
<td>K₂CO₃, acetone 60°C, 14h</td>
<td><img src="image18.png" alt="Image" /></td>
<td>90</td>
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</tbody>
</table>

Figure 4. Comparative effects of naphthoquinone benzodioxins on B16F10 cell proliferation (A), A431 cell proliferation (B), MDAMB231 cell proliferation (C) and U87MG cell proliferation (D). B16F10, A431, MDAMB231, U87MG cells were incubated with different concentrations of each compound. After 72 h, B16F10, A431, MDAMB231 and U87MG cell proliferation were assessed as described in “Experimental protocols”. Data represent the mean value ± SD of three independent experiments.
Naphthoquinone benzodioxins 11, 12, 13 were evaluated on the U87MG, B16F10, A431, and MDAMB 231 cell viability (Figure 3). Cells were treated at concentrations ranging from 0.01 µM to 100 µM. Two compounds 11, 13, (Table 2) were identified with EC50 inferior to 10 µM on the GBM cell line (U87MG) and the mouse melanoma cell line (B16F10). Among the compounds showing an extended antiproliferative activity 11 was the only one to be active against cancer cell lines derived from epidermoid cancer cell line (A431).

The differences of structure allowed us to establish structure activity relationships. Results showed that naphthoquinones benzodioxins have limited effect on MDAMB cell proliferation. In the other hand, the cytotoxicity is increased for the other cell models but depends on the structure of the heterocycles. The presence of free carboxylic group and hydroxyl group on the phenyl ring diminished drastically the cytotoxicity (compound 12). Replacement by an ester group increased significantly the biological activity for three cell lines such as human GBM cell line (U87MG), mouse melanoma cell line (B16F10), human epidermoid cell line (A431) (compound 11) and two cell lines human GBM cell line (U87MG); mouse melanoma cell line (B16F10) (compound 13). The nature of the ester function is an important factor to explain the biological activity differences. The presence of the ester with the free hydroxyl group on the phenyl ring did not increase the cytotoxicity. The lactone introduction led to the better results of cytotoxicity but the difference is weak.

<table>
<thead>
<tr>
<th>Compounds</th>
<th>U87MG</th>
<th>B16F10</th>
<th>A431</th>
<th>MDA-MB231</th>
</tr>
</thead>
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<tr>
<td>11</td>
<td>2 ± 0.9</td>
<td>0.4 ±0.2</td>
<td>9 ± 1</td>
<td>34 ±2</td>
</tr>
<tr>
<td>12</td>
<td>20 ± 5</td>
<td>22 ± 5</td>
<td>18 ± 2</td>
<td>34 ±5</td>
</tr>
<tr>
<td>13</td>
<td>2 ± 0.9</td>
<td>1 ±0.5</td>
<td>18 ± 2</td>
<td>35±2</td>
</tr>
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</table>

*Values are calculated from at least three independent experiments and for each set of experiments each point was repeated 3 times. **EC50 estimation was determined with XLSTAT software.

In conclusion, the compound 11 has given the best biological activity but the compound 13 could be interesting for in vivo biological evaluation. Naphthoquinones benzodioxins are very lipophilic. The presence of a free hydroxyl group should allow to increase the hydrophilicity and the solubilization in biocompatible medium.

**Experimental**

**General**

All commercial reagents were purchased from Acros, Aldrich, and Sigma and were used as received without further purification. Reaction times were monitored by TLC until no starting material remained. TLC was performed using Silica gel 60 F254 precoated aluminium sheets. Column chromatography was performed using Silica gel Si 60 (40-63 µm). $^{1}H$, $^{13}C$, HMBC and HSQC NMR spectra were recorded on a Bruker AC 400 or Bruker AC 500 spectrometers. Chemical shifts (δ) are expressed in parts per million (ppm) and are referenced to the internal deuterated solvents with tetramethylsilane as the internal standard. Data are reported as follows: multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, dd = doublet of doublet, dt = doublet of triplet, m = multiplet, br = broad signal). Coupling constants are expressed in Hertz (Hz). Mass spectra were recorded on a QTOF Micro (Waters) spectrometer with electrospray ionization (ESI, positive mode), lockspray orthophosphoric acid, infusion introduction at 10 µL/min, a source temperature of 80°C and desolvation temperature of 120 °C.

**Organic synthesis**

Synthesis of 3-hydroxybenzo[d]naphtho[2,3-b]furan-6,11-dione (8)

Sodium (1.6 g) is slowly added to ethanol (50 mL) into a 100 mL flask fitted with a reflux condenser, the mixture is stirred until total dissolution of sodium. The flask is then cooled to 0°C and 2,3-dichloro-1,4-naphthoquinone (M=227, 2.27 g, n=0.01 mol) is first introduced by small portions, followed by dropwise addition of resorcinol (M=110, 2.20 g, n = 0.02 mol) dissolved in 25 mL ethanol. The reaction is allowed to proceed under stirring overnight at room temperature. The next day, the mixture is acidified using a solution of HCl (1M). The formed precipitate is collected by suction filtration, washed successively with methanol and with diethylether affording the compound 8 as an orange solid. Yield = 65%. mp = 325°C (lit = 320°C [23]). IR ν (cm-1) = 1658, 1578, 1247, 993. NMR 1H (400 MHz, CDCl3) δ = 10.5 (s, 1H, OH), 8.09-8.13 (m, 2H, Hnapht), 7.99 (d, J = 8.5 Hz, 1H, CH-CH-COH), 7.87-7.91 (m, 2H, Hnapht), 7.19 (d, J = 2.0 Hz, 1H, CH-CO-COH), 7.07 (dd, J = 2.0 Hz and J = 8.5 Hz, 1H, CH-CH-COH). NMR 13C (125 MHz, CDCl3) δ = 181.4, 174.0, 160.1, 157.6, 152.3, 134.2, 134.1, 132.7, 132.2, 126.2, 126.1, 123.1, 123.7, 116.5, 114.1, 98.4. MS m/z (% relative abundance): 263 (M-H, 100), 235 (10), 219 (20), 191 (18). Exact mass (ESI-TOF) calculated for C13H10O2 [M-H] = 263.0344, found 263.0344.

Synthesis of 1,3-dihydroxybenzo[d]naphtho[2,3-b]furan-6,11-dione (9)

Potassium hydroxide (2.0 g; M = 56, n = 0.036 mol) is dissolved in methanol (50 mL) in a 100 mL flask fitted with a reflux condenser, the mixture is stirred under stirring until total dissolution of potassium hydroxide. The mixture is then heated under nitrogen to 30°C, 2,3-dichloro-1,4-naphthoquinone (M=227, 1.70 g, n = 7.5 10^{-3} mol) is introduced and the medium is slowly added to the mixture. The mixture is stirred under nitrogen to 30°C, 2,3-dichloro-1,4-naphthoquinone (M=227, 2.27 g, n=0.01 mol) is first introduced by small portions, followed by dropwise addition of resorcinol (M=110, 2.20 g, n = 0.02 mol) dissolved in 25 mL ethanol. The reaction is allowed to proceed under stirring overnight at room temperature. The next day, the mixture is acidified using a solution of HCl (1M). The formed precipitate is collected by suction filtration, washed successively with methanol and with diethylether affording the compound 8 as an orange solid. Yield = 65%. mp = 325°C (lit = 320°C [23]). IR ν (cm-1) = 1658, 1578, 1247, 993. NMR 1H (400 MHz, CDCl3) δ = 10.5 (s, 1H, OH), 8.09-8.13 (m, 2H, Hnapht), 7.99 (d, J = 8.5 Hz, 1H, CH-CH-COH), 7.87-7.91 (m, 2H, Hnapht), 7.19 (d, J = 2.0 Hz, 1H, CH-CO-COH), 7.07 (dd, J = 2.0 Hz and J = 8.5 Hz, 1H, CH-CH-COH). NMR 13C (125 MHz, CDCl3) δ = 181.4, 174.0, 160.1, 157.6, 152.3, 134.2, 134.1, 132.7, 132.2, 126.2, 126.1, 123.1, 123.7, 116.5, 114.1, 98.4. MS m/z (% relative abundance): 263 (M-H, 100), 235 (10), 219 (20), 191 (18). Exact mass (ESI-TOF) calculated for C13H10O2 [M-H] = 263.0344, found 263.0344.
Synthesis of 2-chloro-3-(2-oxo-2H-chromen-7-yloxy)naphtho-l,4-dione (15)

2,3-dichloro-1,4-naphthoquinone (0.5 g, M=227, n=2.2×10^{-3} mol), methyl gallic ester (0.37 g, M=184, n=2.10^{-3} mol), K$_2$CO$_3$ (0.61 g, M=138, n=4.4×10^{-2} mol) and 6 mL of anhydrous acetone are introduced in a 50 mL flask fitted with a reflux condenser and a CaCl$_2$ drying tube. The medium is under nitrogen stream and heated at 60°C using an oil bath during 14 hours. After cooling, the formed precipitate is collected by suction filtration, and then recrystallised in glacial acetic acid affording compound 13 as a red solid. Yield = 90 %. mp > 399°C. IR ν (cm$^{-1}$) = 3312, 1717, 1766, 1665, 1649, 1595, 1507, 1449, 1370, 1351, 1148, 1004. NMR $^1$H (500 MHz, DMSO-d$_6$, 60°C): δ = 8.03-8.00 (m, 2H, H$_{napht}$), 7.87-7.85 (m, 2H, H$_{napht}$), 7.31 (d, J = 2.0 Hz, 1H, CH-CO), 6.97 (d, J = 2.0 Hz, 1H, CH-C-CO$_2$Me), 3.83 (s, 3H, Me), 3.10 (s, 1H, OH). NMR $^{13}$C (125 MHz, DMSO-d$_6$, 60°C): δ = 176.7 (1), 176.6 (2), 164.7 (3), 146.3 (4), 141.3 (5), 138.9 (6), 138.8 (7), 134.8 (8), 134.2 (9), 133.0 (10), 129.8 (11-12), 126.3 (13-15), 115.2 (16), 117.7 (17), 52.2 (18). MS m/z (% relative abundance): 339 (M+H=100), 243 (8), 214 (15). Exact mass (ESI) calculated for C$_{18}$H$_{11}$O$_7$ [M+H] = 339.0505, found 339.0515.

Synthesis of methyl 4-hydroxy-6,11-dioxo-6,11-dihydrobenzof[b]dibenzo-1,4-dioxide (13)

2,3-dichloro-1,4-naphthoquinone (0.5 g, M=227, n=2.2×10^{-3} mol), methyl gallic ester (0.37 g, M=184, n=2.10^{-3} mol), K$_2$CO$_3$ (0.61 g, M=138, n=4.4×10^{-2} mol) and 6 mL of anhydrous acetone are introduced in a 50 mL flask fitted with a reflux condenser and a CaCl$_2$ drying tube. The medium is under nitrogen stream and heated at 60°C using an oil bath during 14 hours. After cooling, the formed precipitate is collected by suction filtration, and then recrystallised in glacial acetic acid affording compound 13 as a red solid. Yield = 90 %. mp > 399°C. IR ν (cm$^{-1}$) = 3312, 1717, 1766, 1665, 1649, 1595, 1507, 1449, 1370, 1351, 1148, 1004. NMR $^1$H (500 MHz, DMSO-d$_6$, 60°C): δ = 8.03-8.00 (m, 2H, H$_{napht}$), 7.87-7.85 (m, 2H, H$_{napht}$), 7.31 (d, J = 2.0 Hz, 1H, CH-CO), 6.97 (d, J = 2.0 Hz, 1H, CH-C-CO$_2$Me), 3.83 (s, 3H, Me), 3.10 (s, 1H, OH). NMR $^{13}$C (125 MHz, DMSO-d$_6$, 60°C): δ = 176.7 (1), 176.6 (2), 164.7 (3), 146.3 (4), 141.3 (5), 138.9 (6), 138.8 (7), 134.8 (8), 134.2 (9), 133.0 (10), 129.8 (11-12), 126.3 (13-15), 115.2 (16), 117.7 (17), 52.2 (18). MS m/z (% relative abundance): 339 (M+H=100), 243 (8), 214 (15). Exact mass (ESI) calculated for C$_{18}$H$_{11}$O$_7$ [M+H] = 339.0505, found 339.0515.

Synthesis of methyl 4-hydroxy-6,11-dioxo-6,11-dihydrobenzof[b]dibenzo-1,4-dioxide (13)

2,3-dichloro-1,4-naphthoquinone (0.5 g, M=227, n=2.2×10^{-3} mol), methyl gallic ester (0.37 g, M=184, n=2.10^{-3} mol), K$_2$CO$_3$ (0.61 g, M=138, n=4.4×10^{-2} mol) and 6 mL of anhydrous acetone are introduced in a 50 mL flask fitted with a reflux condenser and a CaCl$_2$ drying tube. The medium is under nitrogen stream and heated at 60°C using an oil bath during 14 hours. After cooling, the formed precipitate is collected by suction filtration, and then recrystallised in glacial acetic acid affording compound 13 as a red solid. Yield = 90 %. mp > 399°C. IR ν (cm$^{-1}$) = 3312, 1717, 1766, 1665, 1649, 1595, 1507, 1449, 1370, 1351, 1148, 1004. NMR $^1$H (500 MHz, DMSO-d$_6$, 60°C): δ = 8.03-8.00 (m, 2H, H$_{napht}$), 7.87-7.85 (m, 2H, H$_{napht}$), 7.31 (d, J = 2.0 Hz, 1H, CH-CO), 6.97 (d, J = 2.0 Hz, 1H, CH-C-CO$_2$Me), 3.83 (s, 3H, Me), 3.10 (s, 1H, OH). NMR $^{13}$C (125 MHz, DMSO-d$_6$, 60°C): δ = 176.7 (1), 176.6 (2), 164.7 (3), 146.3 (4), 141.3 (5), 138.9 (6), 138.8 (7), 134.8 (8), 134.2 (9), 133.0 (10), 129.8 (11-12), 126.3 (13-15), 115.2 (16), 117.7 (17), 52.2 (18). MS m/z (% relative abundance): 339 (M+H=100), 243 (8), 214 (15). Exact mass (ESI) calculated for C$_{18}$H$_{11}$O$_7$ [M+H] = 339.0505, found 339.0515.
Synthesis of 2,3-bis(2-oxo-2H-chromen-7-yl oxy)naphthalene-1,4-dione (16)

The compound 16 is isolated after chromatography as a second fraction. NMR $^1$H (400 MHz, CDCl3): $\delta = 8.12-8.16$ (m, 2H), 7.82-7.87 (m, 2H), 7.63 (d, $J = 9.6$ Hz, 2Hb), 7.41 (d, $J = 8.5$ Hz, 2Hc), 6.91 (dd, $J_1 = 2.4$ Hz, $J_2 = 8.5$ Hz, 2Hd), 6.87 (d, $J = 2.5$ Hz, 2He), 6.32 (d, $J = 9.6$ Hz, 2Ha). Exact mass (ESI-TOF) calculated for C$_{28}$H$_{14}$O$_8$Na$^+$ [M+Na] = 501.0586, found 501.0582.

MTT assay

Cell lines

A431, MDA-MB-231, B16F10, and U87MG cells were purchased from American Type Culture Collection (Rockville, MD, USA). The cells were routinely grown in DMEM (Life Technologies Inc., Gaithersburg, MD, USA), supplemented with 10% FCS, 2 mM L-glutamine, 1 mM sodium pyruvate, 50 U mL$^{-1}$ penicillin and 50 mL$^{-1}$ streptomycin (all obtained from Life Technologies Inc.), at 37°C in a 5% CO$_2$-humidified atmosphere.

Cell proliferation assay

Cell proliferation was assessed using a MTT-microculture assay$^{26}$ which is based on the ability of mitochondrial enzymes to reduce 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Sigma, LO, USA) into purple formazan crystals. Briefly, the cells were seeded in 10% FCS-DMEM at a density of 5x10$^3$ cells/well in 96-well tissue culture plates (Falcon, Strasbourg, France) and allowed to adhere for 24 h.

Cells were washed and incubated in DMEM-2% FCS with various concentrations of naphthoquinone benzodioxanes to reduce 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) (Sigma, LO, USA) into purple formazan crystals. Briefly, the cells were seeded in 10% FCS-DMEM at a density of 5x10$^3$ cells/well in 96-well tissue culture plates (Falcon, Strasbourg, France) and allowed to adhere for 24 h. Cells were washed and incubated in DMEM-2% FCS with various concentrations of naphthoquinone benzodioxins varying from 0.1 µM to 100 µM. After a 72 h incubation, cells were washed with PBS and incubated with 0.1 ml of MTT (2 mg mL$^{-1}$) for 4 h. Cells were lysed in 200 µL DMSO and absorbance corresponding to solubilized formazan pellet (which reflects the relative viable cell number) was measured in a Labsystem plate reader at 570 nm. Concentration-response curves were constructed and the EC$_{50}$ values (concentration of the compound inhibiting 50% of cell proliferation) were determined using the XL STAT software (Addinsoft).

Conclusions

Benzo[flu]naphthoquinones previously reported as cytotoxin on tumor cells were synthetized and fully characterized. The new benzo[flu]naphthoquinones were tested on 4 cancer cell lines, two of them displayed antiproliferative activity, and the ester 11 was found to be the most promising. According to our knowledge the cytotoxicity on cancer cells of benzodioxan naphthoquinones has not been reported in literature yet.

Acknowledgments

We gratefully acknowledge the CNRS (National Center for Scientific Research), the "Region Basse Normandie", the University of Boumerdes (Algeria), the Franco-Algerian program for the Superior Education (PROFS), and the Algerian-French cooperation for a BAF grant for Feyriel Dridi. Also the authors thank Rémy Legay and Baptiste Rigaud for ESI-MS and HRMS analysis.

References


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