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SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW "GRAMINE" OPENED DERIVATIVES OF VINORELBINE

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Abstract

New "gramine" opened derivatives was synthesized from an ammonium salt of vinorelbine or simplified analogues. Their structures were elucidated by NMR, MS or compared with the known similar analogues. Compound **8** exhibits a good cytotoxicity on the KB cell line as well as a good inhibiting activity toward the polymerisation of tubulin.

Keywords. vinorelbine, tubulin, gramine, vinca alkaloid.

1. INTRODUCTION

The first semisynthesis of a natural dimeric Vinca alkaloid, anhydrovinblastine **3**, was achieved in 1974 through a biomimetic coupling reaction of catharanthine **1** and vindoline (Fig. 1) [1, 2]. Vinorelbine **5** was then invented by the Potier team from anhydrovinblastine and leads to a cycle C 'shortened by one carbon (transformation from a tryptamine pattern to gramine pattern) [3]. This compound has very good anti-tumor activity and induces little side effects. Its synthesis is fast and extrapolated widely. It was developed and marketed by Pierre Fabre (Navelbine) in the 80's for the treatment of lung cancer and breast cancer.

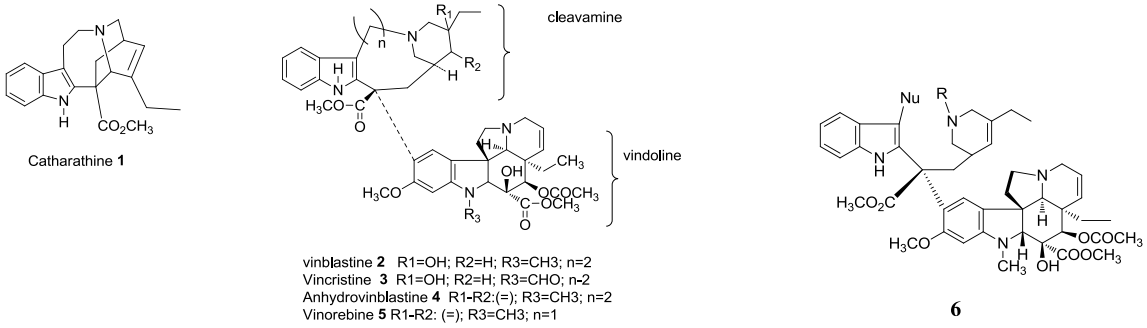


Figure 1: The natural and semisynthesis dimeric Vinca alkaloid

Further chemistry on this new type of tubulin interacting agent was undertaken with the aim of obtaining new compounds and of studying its mechanism of action. Starting either from anhydrovinblastine **3** or from vinorelbine **5** in the presence of various nucleophiles, a series of open-ring derivatives have been synthesized and isolated [4]. In the same manner, quaternary ammonium derivatives of vinorelbine were reacted with nucleophiles, leading to the corresponding «open» compounds **6** (Fig. 1). Such a fragmentation reaction is typically observed with «gramine» derivatives, and illustrates the possibility of introducing a reversible covalent bond between vinorelbine **5** and a nucleophilic residue during the interaction with tubulin, which can not occur with natural products such as vinblastine **1**, including the «tryptamine» moiety [5]. This original hypothesis might contribute to explain the different pharmacological properties of vinorelbine observed both in vitro and in vivo relative to vinblastine. However, there is as yet no confirmation of such a mode of action. Furthermore, none of the «open» derivatives exerted any activities in terms of cytotoxicity or

inhibition in the tubulin polymerization assay.

We report herein synthesis and biological activities of new "gramine" opened analogues from an ammonium salt of vinorelbine or its simply derivative.

2. EXPERIMENTAL

2.1. Method for preparation of opened compound seco C7 '-C8' with lithium dimethylamide

In a dry flask, a mixture of *n*-butyllithium (*n*-BuLi, 2.6 eq.) Dimethylamine (DMA; 3.0 eq) were dissolved in anhydrous THF (1.5 ml) and the reaction medium is stirred at 0 °C for 15 minutes under argon. A solution of the compounds **7** or **15** (1 eq.) in anhydrous THF (200 µL) is added to medium. After three hours of reaction under argon at room temperature, the mixture is washed once with saturated NaCl solution, dried and concentrated. The resulting crude residue was dissolved in heptane/ethyl acetate: 7/3 and filtered through Celite. After concentration of the solvent it gave the desired products **8** or **16** as translucent oils.

Compound **7**. ^{1}H NMR (500 MHz, $CDCl_3$) d (ppm) 0.68 (t, *J* = 7.8 Hz, 3H-H_{21}); 1.09 (t, *J* = 7.4 Hz, 3H-$H_{20'}$); 1.13 (m, 1H-H_{20b}); 1.69 (m, 1H-H_{20a}) ; 1.76 (m, 1H-H_{11b}) ; 2.02 (s, 3H-H_{27}); 2.08 (m, 2H-$H_{19'}$); 2.15 (m, 1H-$H_{2'}$); 2.16 (m, 1H-H_{11a}); 2.38 (m, 2H-$H_{1'b,10b}$); 2.51 (s, 1H-H_{19}); 2.67 (s, 3H-H_{23}); 2.78 (d, *J* = 16.0 Hz, 1H-H_{8b}); 3.22 (m, 2H-$H_{1'a,10a}$); 3.30 (dd, *J* = 16.0 Hz/3.8 Hz, 1H-H_{8a}); 3.39 (m, 1H-$H_{18'b}$); 3.66 (s, 3H-$H_{23'}$); 3.71 (s, 1H-H_2); 3.72 (s, 3H-$H_{25'}$); 3.73 (s, 3H-H_{25}); 3.80 (m, 4H-$H_{18'a,22}$); 4.80 (m, 1H-$H_{5'b}$); 4.84 (m, 1H-$H_{7'b}$); 4.82 (s, 2H-$H_{21'}$); 4.99 (d, *J* = 17.5 Hz, 1H-$H_{5'a}$); 5.21 (d, *J* = 10.5 Hz, 1H-H_6); 5.31 (s, 1H-H_4); 5.69 (m, 1H-$H_{7'a}$); 5.76 (s, 1H-$H_{3'}$); 5.80 (dd, *J* = 10.5 Hz/4.7 Hz, 1H-H_7); 6.05 (s, 2H-$H_{14,17}$); 7.18-7.32 (m, 3H-$H_{11',12',13'}$); 7.99 (d, *J* = 7.9 Hz, 1H-$H_{10'}$); 8.83 (s, 1H-$H_{15'}$). RMN ^{13}C (75 MHz, $CDCl_3$) d (ppm) 8.0 (C_{21}); 11.8 ($C_{20'}$); 21.1 (C_{27}); 26.9 ($C_{19'}$); 28.8 ($C_{2'}$); 30.5 (C_{20}); 33.5 ($C_{1'}$); 38.1 (C_{23}); 42.5 (C_5) ; 44.6 (C_{11}); 50.1 (C_8); 50.3 (C_{10}); 52.2 (C_{25}); 52.6 ($C_{23'}$); 53.0 (C_{12}); 53.3 ($C_{25'}$); 53.6 ($C_{18'}$); 54.3 ($C_{17'}$); 54.8 ($C_{7'}$); 55.8 (C_{22}); 59.6 ($C_{21'}$); 60.3 ($C_{5'}$); 65.2 (C_{19}); 76.3 (C_4); 79.6 (C_3); 82.9 (C_2); 94.1 (C_{17}); 101.7 ($C_{8'}$); 111.2 ($C_{13'}$); 117.5 (C_{15}); 118.9 ($C_{10'}$); 121.4 ($C_{3'}$); 121.9 (C_{14}); 122.3 ($C_{11'}$); 123.6 (C_{13}); 124.5 ($C_{12'}$); 124.8 (C_7); 129.2 ($C_{9'}$); 129.8 (C_6); 132.2 ($C_{4'}$); 134.3 ($C_{14'}$); 136.6 ($C_{16'}$); 153.6 (C_{18}); 158.4 (C_{16}); 166.2 ($C_{22'}$); 170.9 (C_{24}); 171.5 (C_{26}); 173.7 ($C_{24'}$). IR (cm^{-1}): 1741; 1233. $[\alpha]_D$ = 48 ($CHCl_3$, c = 0.78). ESIMS (MeOH) : 851.4 [M^+].

Compound **8**. ^{1}H NMR (500 MHz, $CDCl_3$) d (ppm) 0.49 (t, *J* = 7.3 Hz, 3H-H_{21}); 0.77 (m, 3H-$H_{20'}$); 1.23 (m, 1H-H_{20b}); 1.57 (m, 1H-H_{20a}); 1.73 (m, 2H-$H_{19'}$); 2.01 (s, 3H-H_{27}); 2.05 (s, 6H-$H_{24',25'}$); 2.11 (m, 1H-$H_{2'}$); 2.13 (m, 1H-$H_{1'b}$); 2.22 (m, 1H-H_{11b}); 2.29 (m, 1H-H_{11a}); 2.46 (m, 3H-$H_{1'a,10b,18'b}$); 2.52 (s, 1H-H_{19}); 2.57 (s, 3H-H_{23}); 2.72 (d, *J* = 16.6 Hz, 1H-H_{8b}); 2.84 (d, *J* = 15.5 Hz, 1H-$H_{5'b}$); 2.93 (d, *J* = 15.5 Hz, 1H-$H_{5'a}$); 2.95 (m, 1H-$H_{18'a}$); 3.11 (m, 1H-$H_{7'b}$); 3.28 (s, 2H-$H_{21'}$); 3.31 (m, 2H-$H_{7'a,10a}$); 3.40 (dd, *J* = 16.6 Hz/ 4.8 Hz, 1H-H_{8a}); 3.43 (s, 3H-H_{22}); 3.56 (s, 3H-$H_{23'}$); 3.69 (s, 3H-$H_{27'}$); 3.71 (s, 3H-H_{25}); 3.76 (s, 1H-H_2); 4.97 (s, 1H-$H_{3'}$); 5.23 (d, *J* = 10.0 Hz, 1H-H_6); 5.45 (s, 1H-H_4); 5.76 (dd, *J* = 10.0 Hz/4.1 Hz, 1H-H_7); 5.89 (s, 1H-H_{17}); 6.95 (t, *J* = 7.5 Hz, 1H-$H_{11'}$); 7.02 (s, 1H-H_{14}); 7.03 (t, *J* = 7.5 Hz, 1H-$H_{12'}$); 7.23 (d, *J* = 8.0 Hz, 1H-$H_{13'}$); 7.62 (d, *J* = 8.0 Hz, 1H-$H_{10'}$); 10.07 (s, 1H-$H_{15'}$). ^{13}C NMR (75 MHz, $CDCl_3$) d (ppm) 8.3 (C_{21}); 11.9 ($C_{20'}$); 21.1 (C_{27}); 27.5 ($C_{19'}$); 31.4 (C_{20}); 32.6 ($C_{2'}$); 38.0 (C_{23}); 40.9 ($C_{1'}$); 42.5 (C_5); 43.3 (C_{12}); 43.9 (C_{11}); 45.3 ($C_{24,25}$); 51.2 (C_8); 52.1 (C_{10}); 52.2 ($C_{23'}$); 52.3 ($C_{22,25}$); 53.6 ($C_{7'}$); 54.3 ($C_{17'}$); 54.6 ($C_{5'}$); 55.5 ($C_{18'}$); 55.9 ($C_{27'}$); 58.4 ($C_{21'}$) ; 67.9 (C_{19}); 75.9 (C_4); 79.6 (C_3); 83.1 (C_2); 94.0 (C_{17}); 105.7 ($C_{8'}$); 110.6 ($C_{13'}$); 118.7 ($C_{11'}$); 119.3 ($C_{10'}$); 121.0 ($C_{12'}$); 121.7 (C_{15}); 122.1 (C_{14}); 123.0 ($C_{3'}$); 123.8 (C_7); 124.4 (C_{13}); 129.5 ($C_{9'}$); 130.3 (C_6); 133.9 ($C_{14'}$); 136.2 ($C_{4'}$); 136.6 ($C_{16'}$); 153.1 (C_{18}); 158.6 (C_{16}); 169.2 ($C_{22'}$); 170.6 (C_{26}); 172.0 (C_{24}); 175.9 ($C_{26'}$). IR (cm^{-1}): 3410; 2809; 2359; 1744; 1460; 1234. $[\alpha]_D$ = -8 ($CHCl_3$, c = 1.03). ESIMS (MeOH): 851.4 [M^+].

Compound **16**. ^{1}H NMR (500 MHz, $CDCl_3$) d (ppm) 0.58/0.60 (t, *J* = 7.4 Hz, 3H-$H_{20'}$); 1.34 (d, *J* = 6.3 Hz, 3H-H_{10}); 1.62 (m, 2H-$H_{19'}$); 1.85 (s, 3H-$H_{24'}$); 1.92 (s, 3H-$H_{25'}$); 2.10 (m, 1H-$H_{18'b}$); 2.30 (m, 1H-$H_{2'}$); 2.49 (dd, *J* = 14.2 Hz/4.0 Hz, 1H-$H_{1'b}$); 2.64 (m, 1H-$H_{18'a}$); 2.80 (m, 1H- $H_{1'a}$); 2.82 (m, 2H-$H_{5'}$); 2.90/2.99 (s, 2H-$H_{7'}$); 3.31 (s, 2H-$H_{21'}$); 3.58 (m, 1H-H_3); 3.60/3.61 (s, 3H-$H_{23'}$); 3.69 (s, 3H-$H_{27'}$); 3.77/3.81 (s, 6H-$H_{11,12}$); 4.17 (m, 1H-H_{2b}); 4.48/4.53 (s, 1H-$H_{3'}$); 4.65 (m, 1H-H_{2a}); 6.94 (m, 1H- $H_{11'}$); 7.04 (t, *J* = 7.5 Hz, 1H-$H_{12'}$); 7.29 (d, *J* = 8.0 Hz, 1H-$H_{13'}$); 7.66/7.72 (d, *J* = 8.0 Hz, 1H-$H_{10'}$); 10.88/10.94 (s, 1H-$NH_{15'}$). ^{13}C-NMR (75 MHz, $CDCl_3$) d (ppm) 11.3 ($C_{20'}$); 19.1 (C_{10}); 27.2 ($C_{19'}$); 32.6 ($C_{2'}$); 35.3 (C_3); 42.9 ($C_{1'}$); 45.9 ($C_{24',25'}$); 52.0 ($C_{23'}$); 52.3 ($C_{17'}$); 52.6 ($C_{27'}$); 54.6 ($C_{5'}$); 56.3 ($C_{18'}$); 58.3 ($C_{21'}$); 60.5 ($C_{7'}$); 60.8 ($C_{11,12}$); 78.8 (C_2); 100.0 ($C_{8'}$); 106.4 (C_6); 110.7 ($C_{13'}$); 118.8 ($C_{11'}$); 119.8 ($C_{10'}$); 121.2 ($C_{12'}$); 121.5 (C_4); 122.8 ($C_{3'}$); 128.8 ($C_{9'}$); 133.6 ($C_{14'}$); 136.0 ($C_{4'}$); 135.9 ($C_{16'}$); 153.5 ($C_{5,7}$); 158.2 (C_9); 170.0 ($C_{22'}$); 176.1 ($C_{26'}$). IR (cm^{-1}): 2360; 1742; 1233; 1059. ESIMS (MeOH): 667.2 [M^+].

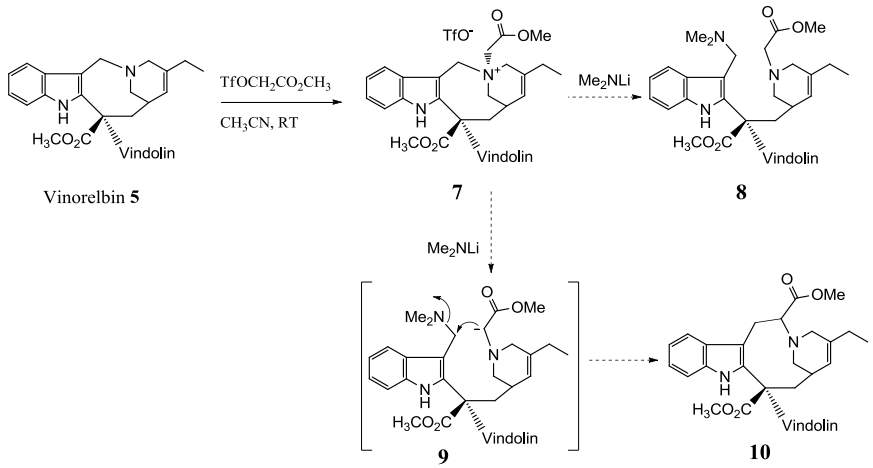
2.2. Method for preparation of opened compound seco C7 '-C8' with sodium methylate

In a dry flask, under argon, compound **7** (20 mg, 0.02 mmol) was dissolved in anhydrous methanol (2 mL). Sodium methoxide (0.02 mmol; 1 eq) was added at 0 °C. The reaction mixture was stirred at room temperature for 1 hour then concentrated. The crude residue was dissolved in ethyl acetate and the organic phase is washed with saturated NaCl solution, dried and concentrated. It gave quantitatively desired pure product **16** as clear oil.

Compound **15**. ^{1}H NMR (500 MHz, $CDCl_3$) d (ppm) 0.64 (t, *J* = 7.5 Hz, 3H-H_{21}); 0.69/0.72 (t, *J* = 7.3 Hz, 3H-$H_{20'}$); 1.30 (m, 1H-H_{20b}); 1.63 (m, 1H-H_{20a}); 1.70 (m, 2H-$H_{19'}$); 2.01 (s, 3H-H_{27}); 2.12 (m, 2H-$H_{2',18'b}$); 2.16 (m, 1H-H_{11b}); 2.26 (m, 1H-H_{11a}); 2.45 (m, 2H-$H_{1'b,18'a}$); 2.55 (m, 1H-$H_{1'a}$); 2.60 (s, 3H-H_{23}); 2.62 (m, 1H-H_{10b}); 2.73/2.84 (s, 1H-H_{19}); 2.76 (d, *J* = 14.9 Hz, 1H-$H_{5'b}$); 2.84 (m, 1H-H_{8b}); 2.90 (d, *J* = 14.9 Hz, 1H-$H_{5'a}$); 2.97/2.98 (s, 3H-$H_{24'}$); 3.17 (s, 2H-$H_{21'}$)/3.19 (d, *J* = 4.7 Hz, 1H-$H_{21'}$); 3.03/3.33 (s, 3H-H_{22}); 3.39 (m, 2H-$H_{8a,10a}$); 3.56/3.59 (s, 3H-$H_{23'}$); 3.64 (s, 3H-H_{25}); 3.66/3.67 (s, 1H-H_2); 3.71 (s, 3H-$H_{26'}$); 4.10 (dd, *J* = 12.2 Hz/2.2 Hz, 1H-$H_{7'b}$); 4.21 (dd, *J* = 12.2 Hz/3.9 Hz, 1H-$H_{7'a}$); 4.71/4.79 (s, 1H-$H_{3'}$); 5.31/5.37 (d, *J* = 10.2 Hz, 1H-H_6); 5.32/5.43 (s, 1H-H_4); 5.82/5.86 (dd, *J* = 10.2 Hz/ 4.5 Hz, 1H-H_7); 5.90 (s, 1H-H_{17}); 6.99 (dd, *J* = 15.7 Hz/7.9 Hz, 1H-$H_{11'}$); 7.07 (m, 2H-$H_{12',14}$); 7.28/7.33 (d, *J* = 8.2 Hz, 1H-$H_{13'}$); 7.54 (dd, *J* = 7.9 Hz/2.2 Hz, 1H-$H_{10'}$); 10.55/10.78 (s, 1H-$H_{15'}$). ^{13}C-NMR (75 MHz, $CDCl_3$) d (ppm) 7.9 (C_{21}); 11.7 ($C_{20'}$); 21.2 (C_{27}); 27.3 ($C_{19'}$); 31.1 (C_{20}); 32.1 ($C_{2'}$); 38.1 (C_{23}); 42.4 (C_5); 43.1 ($C_{1'}$) ; 43.3 (C_{12}) ; 44.8 (C_{11}); 50.4 (C_8); 50.8 (C_{10}); 51.6 (C_{25}); 52.3 ($C_{26'}$); 52.6 ($C_{23'}$); 54.7 ($C_{5'}$); 55.1 ($C_{18'}$); 56.0 ($C_{17'}$); 56.1 (C_{22}); 56.7 ($C_{24'}$); 58.8 ($C_{21'}$); 64.5 ($C_{7'}$); 66.9 (C_{19}); 76.0 (C_4); 79.9 (C_3); 83.5 (C_2); 94.0 (C_{17}); 105.7 ($C_{8'}$); 110.6 ($C_{13'}$); 118.8 ($C_{10'}$) ; 119.3 ($C_{11'}$); 121.1 ($C_{12'}$); 122.1 (C_{14}); 122.4 (C_{15}); 122.6 ($C_{3'}$); 123.8 (C_7); 124.4 (C_{13}); 128.8 ($C_{9'}$); 130.3 (C_6); 133.5 ($C_{14'}$); 136.5 ($C_{4'}$); 137.4 ($C_{16'}$); 152.8 (C_{18}); 158.9 (C_{16}) ; 170.6 ($C_{24,26}$); 171.8 ($C_{25'}$); 176.1 ($C_{22'}$). IR (cm^{-1}): 2356; 1744; 1460; 1248. ESIMS (MeOH): 905.4 [M+Na].

3. RESULTS AND DISCUSSION

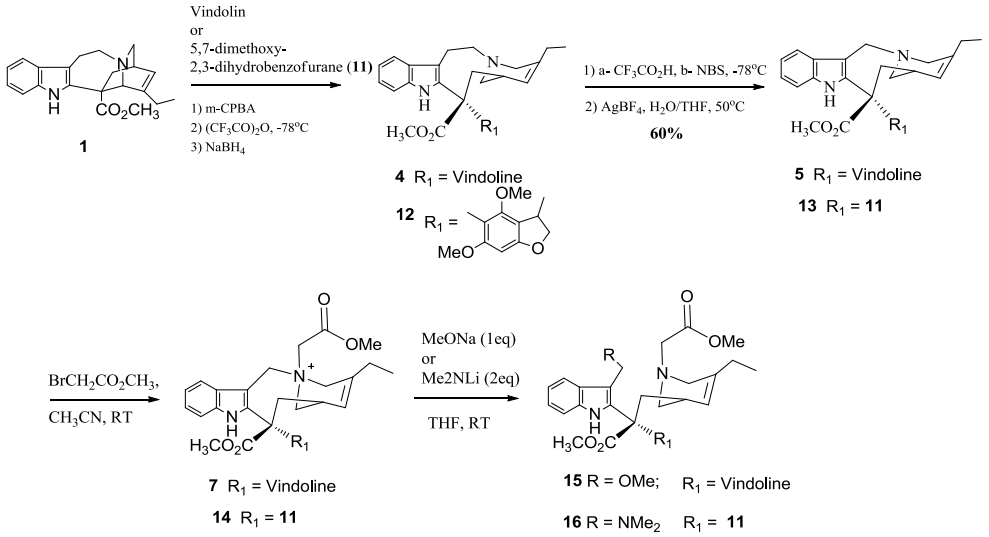
A reaction was performed on the vinorelbine methyl ester **7** with lithium dimethylamide in THF at room temperature. The reaction is complete if two equivalents of base are used: the new product is quantitatively obtained as a single diastereomer.



Scheme 1: Synthesis of compounds **8** and **10**

Theoretically, two products may be obtained under these experimental conditions (scheme 1). Either it forms the opening product 8 or it forms the insertion product **10**. A mass experiment in Electrospray negative mode (ESI^-) of the arriving product showed the absence of anion triflate which is synonym of neutral molecule. The value of the molecular peak in positive mode (ESI^+) is identical to that of the starting product that is equal to the molecular weight [M^+] of starting quaternary ammonium cation. In this case, it suggests that the insertion product might be formed. To determine this structure, its NMR spectra had been made a comparison of with those of closely related compounds: two newly synthesized compounds **15** and **16** (scheme 2). Compound **15** was obtained by adding sodium methoxide to **7**. The reaction is complete with one equivalent of sodium methoxide

in THF at RT and led quantitatively to product 16. Analysis of the mass spectrum obtained in electrospray positive mode (ESI^+) confirms the presence of a molecular ion peak corresponding to the "gramine" opened product.

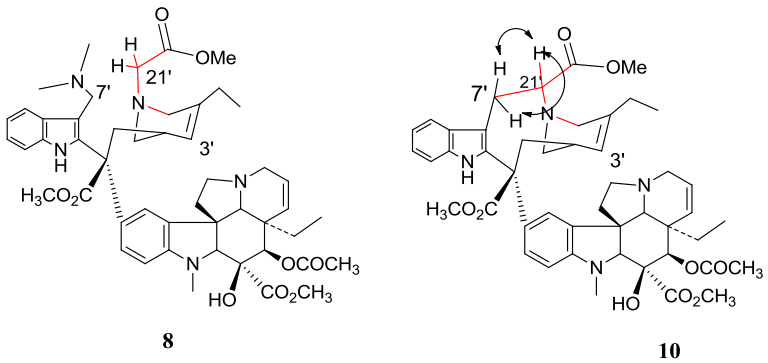


Scheme 2: Synthesis of compounds **15** and **16**

We also considered using 5,7-dimethoxy-2,3-dihydrobenzofurane **11** as a bioisostere of indol moiety. It was synthesized in a three-steps sequence from commercial 3,5-dimethoxyphenol [6]. Compound **11** was then coupled with catharanthine by Polonovski - Potier reaction and transformed to a simplified substrate **13** by method of the Potier team [3]. We also open the gramine bridge of the simplified ammonium salt **14** with lithium dimethylamide (2 equivalents in THF at RT). A new product **16** was obtained in the form of two diastereomers in ratio 1:1.

Table 1: Comparison of the spectra of ^{1}H-NMR between **8**, **10**, **15** and **16**

Proton	Compound **7** (δ ppm)	Compound **15** (δ ppm)		Compound **16** (δ ppm)		Compound **8** or **10** (δ ppm)
$H_{3'}$	5,76 (s)	4,71 (s)	4,79 (s)	4,48 (s)	4,53 (s)	4,97(s)
2 $H_{21'}$	4,82 (s)	3,17 (s)	3,19 (d)	3,30 (s)		3,28 (s)



8 **10**

Figure 2: Compounds **8** and **10**

The comparison of the spectra of ^{1}H-NMR between **8**, **10**, **15** and **16** is summarized in table 1. In fact:

- There is a shielding of all allylic protons H3' from 5.76 (starting material) to 5 ppm.

- Both protons H21' of **15** and **16** are much more shielded than the starting material (3.2 versus 4.8 ppm). The HSQC and HMBC spectra of compound **8** shown at 3.28 ppm, two protons as a singlet presence a correlation with a carbon CH_2 and a long-

range correlation with a carbonyl. It was concluded that these protons were consistent with H21' of "gramine" opened product. In the case of an insertion product **10**, it should have a single proton H21' (figure 2).

- We were able to demonstrate the presence of a singlet for integrating 6H at 2.05 ppm for **17** and at 1.92 ppm for **8**, close to shift values from those of the N-methyl (2.00 ppm) of vindoline moiety. These correspond to the six methyl protons of dimethylamine.

Analysis of NMR spectra finally allowed us to conclude that the finish product structure corresponds to the opened compound seco C7 '-C8' **8** and not to the insertion product **10**.

4. BIOLOGICAL ASSAY

The activity in inhibiting the assembly of tubulin and cytotoxicity against a cell line KB were evaluated for two "gramine" opened compounds **8** and **16**. The results are reported in table 2. Compound **16** is completely inactive while compound **8** has good cytotoxicity (0.2 µM) and relative activity on tubulin. This result is significant because the compounds seco **7'**-**8'** are presented in the literature as inactive [7].

Table 2: Biological activity of analogues **8** and **16**

Compounds	Inhibiting activity of the tubulin assembly IC_{50} [a] (µM) (IC_{50}/IC_{50VLB})	Cytotoxicity against a cell line KB/IC_{50} [b] (µM) (IC_{50}/IC_{50VLB})
8	39 (20)	0.195 (139)
16	inactive	inactive
VLB	1.6/2.6	1.16/1.60 nM

(a) The IC50 is the concentration of compound inhibiting 50 % of the assembly of tubulin. The report IC50 / IC50VLB reflects the activity of the analog relative to that of vinblastine; (b) the IC50 gives neccessary concentration of drug to inhibit 50 % of cell proliferation after 72 h of incubation. The ratio IC50 / IC50VLB reflects the cytotoxicity of the analog relative to that of vinblastine.

5. CONCLUSION

New "gramine" opened derivatives was synthesized from an ammonium salt of vinorelbine of simplified analogues. Its structure was elucidated by NMR, MS or compared with the known similar analogues. Compound **8** exhibits a good cytotoxicity on the KB cell line as well as a good inhibiting activity toward the polymerisation of tubulin.

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