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RESEARCH ARTICLE

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Abstract

The Diels-Alder reaction of vindoline and methyl vinyl ketone resulted in a Friedel-Crafts reaction product. In the reaction between the ortho-quinone derivative of vindoline and *N*-phenylmaleimide, two anomalous products were obtained, a vindoline dimer, and a condensed vindoline derivative.

Keywords

vindoline, Friedel-Crafts reaction, *N*-phenylmaleimide, condensation, rearrangement

1 Introduction

The “dimeric” alkaloids vinblastine (**1**) and vincristine (**2**) (Fig. 1), which comprise the “monomeric” units catharanthine (**3**) and vindoline (**4**) were isolated from the Madagascar periwinkle, *Catharanthus roseus*. These types of compounds have been known as anticancer agents for more than forty years [1, 2].

Vinblastine (**1**) has an antimicrotubule effect used for treating certain kinds of cancer, including Hodgkin’s lymphoma, non-small-cell lung cancer, breast cancer, head and neck cancer and testicular cancer. Vincristine (**2**), the *N*-formyl derivative of vinblastine (**1**) can be used in various types of chemotherapy. Its main uses are in the treatment of non-Hodgkin’s and Hodgkin’s lymphoma, acute lymphoblastic leukaemia, and neuroblastoma.

In the course of the synthetic investigations of dimeric *Vinca* alkaloids, various methods have been elaborated to synthesize new derivatives of vinblastine (**1**) and vincristine (**2**) with improved therapeutic effect exhibiting a higher selectivity and a lower toxicity [3, 4].

The Diels-Alder reaction was applied in the total synthesis of vinblastine analogues [5], in the enantioselective total synthesis of the akuammiline alkaloid (-)-vincorine [6], and the Strychnos alkaloid (+)-minfiensine [7], as well as in the synthesis of some *Aspidosperma* alkaloids [8]. Rearrangement through a retro Diels-Alder reaction was observed during the investigations of (-)-criocerine [9].

In our research project, we intended to investigate the Diels-Alder reaction of vindoline (**4**) and its newly synthesized ortho-quinone derivative [10].

2 Results and discussion

In spite of the fact that the C=C double bond in the 14,15-position of vindoline (**4**) is not a dienophilic electron deficient structural part, based on the analogy that acrolein also exhibits this type of reactivity [10], we carried out its Diels-Alder reaction with methyl vinyl ketone as a “diene” in an attempt to obtain compound **5**. However, a Friedel-Crafts reaction was observed to take place (Scheme 1) affording the alkylated adduct (**6**) in good yield (57%).

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Next, the *ortho*-quinone derivative of vindoline (**7**) was treated with *N*-phenylmaleimide in toluene in order to obtain adduct **8** via the usual cycloaddition reaction. However, instead of this adduct two by-products were isolated in low yields, a dimeric derivative (**9**) in a yield of 3%, and a vindoline condensed with *N*-phenylmaleimide (**10**) in a yield of 2% (Scheme 2).

In the course of the reaction, the expected adduct (**8**) is probably formed as an intermediate, as suggested by the relevant MS peak ($M+H = 630$). Compound **8** is probably

unstable under the conditions of the reaction (at 110°C) and reacts further. On the one hand, the (O)C-C(O) bond in compound **8** is opened, a partial decarbonylation takes place to furnish intermediate **C**, and species **7** is acylated by the monoacyl intermediate (**C**), resulting in compound **9**. On the other hand, the breaking of the (O)C-C(O) bond in compound **8** may be followed by a double decarbonylation to provide species **B**, as well as re-aromatization to form compound **10** (Scheme 3).

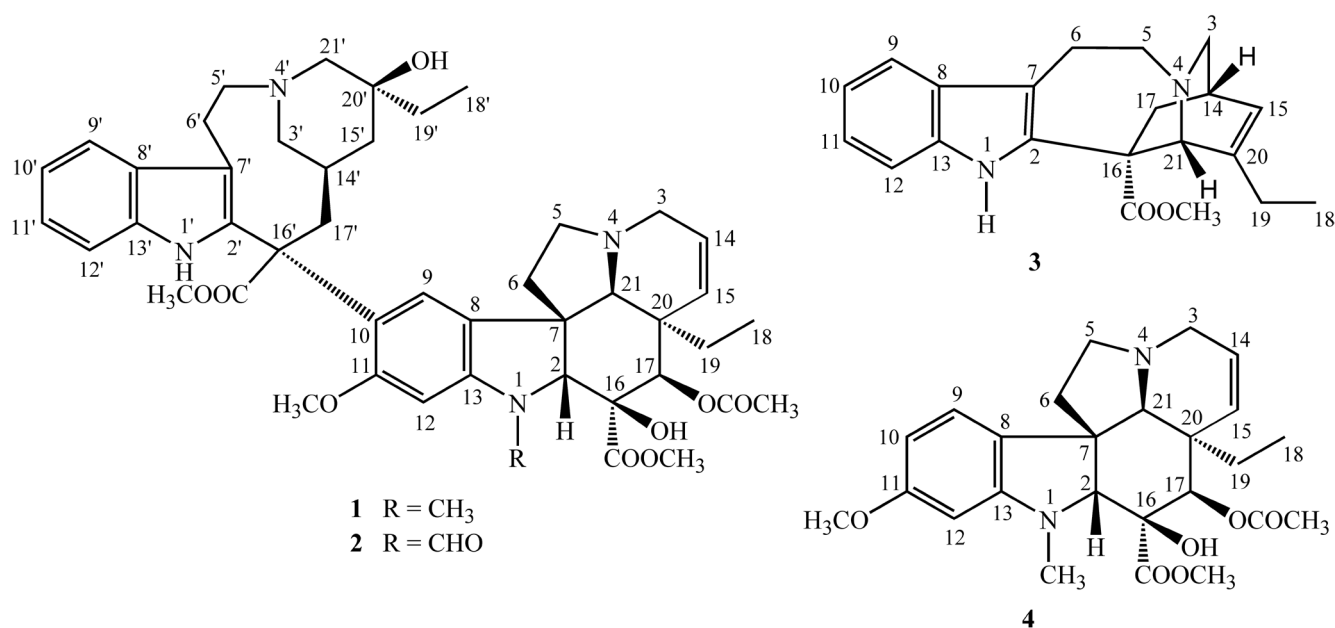
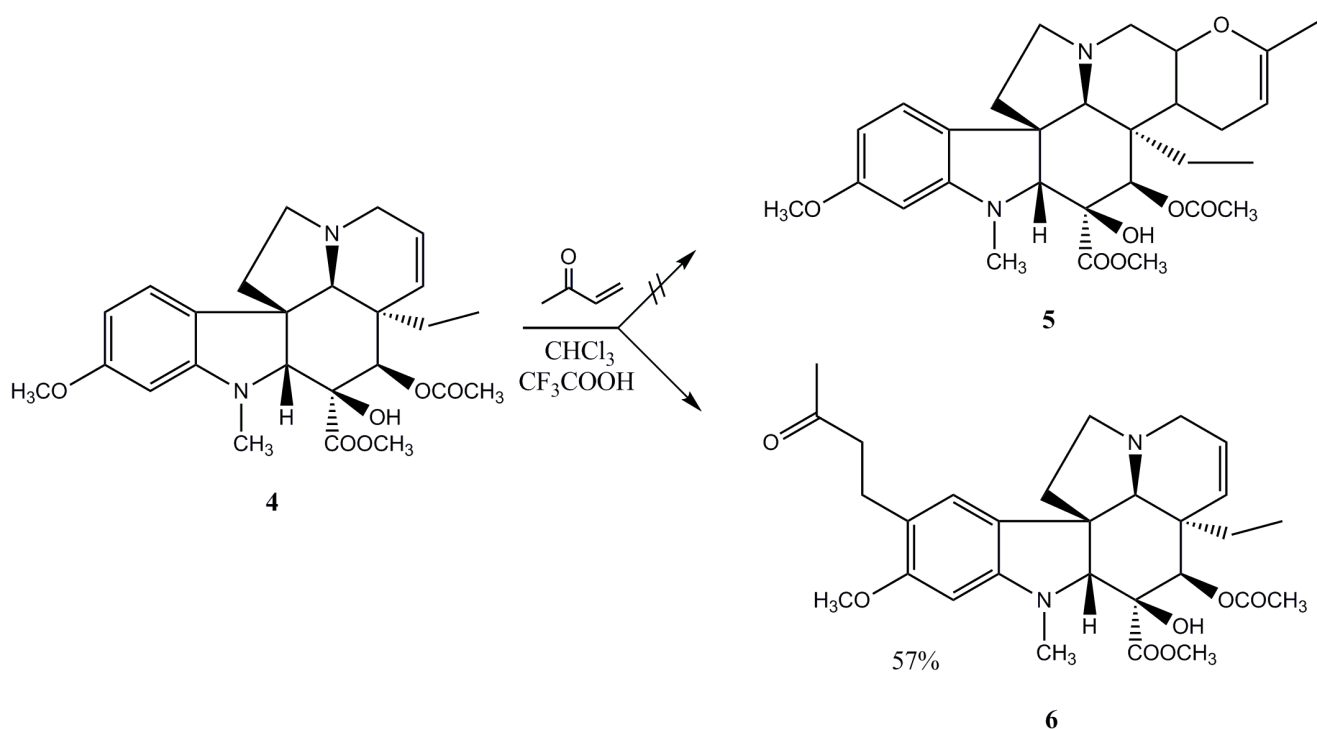
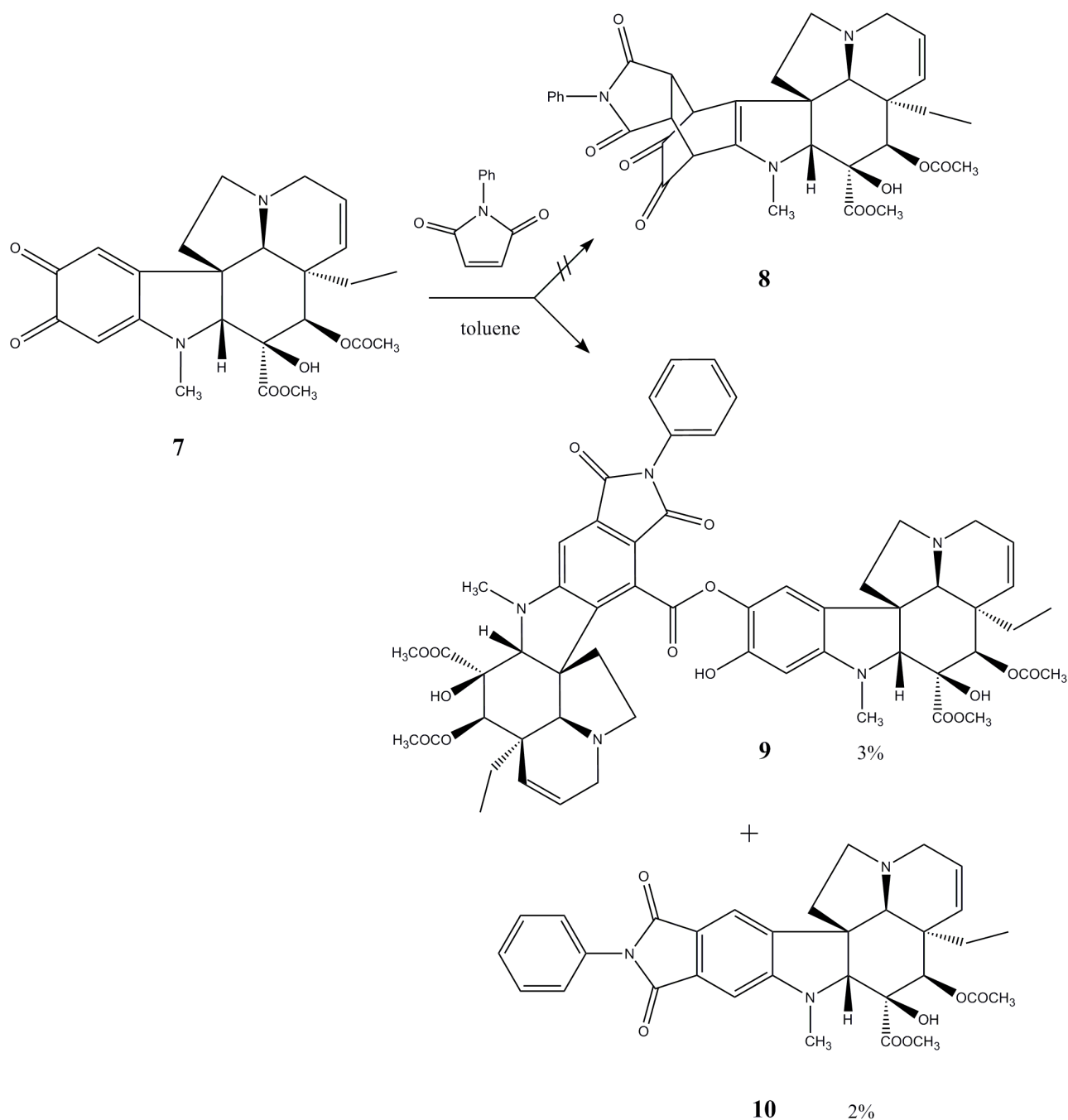


Fig. 1 The structure of *Vinca* alkaloids.



Scheme 1 The Friedel-Crafts reaction observed.



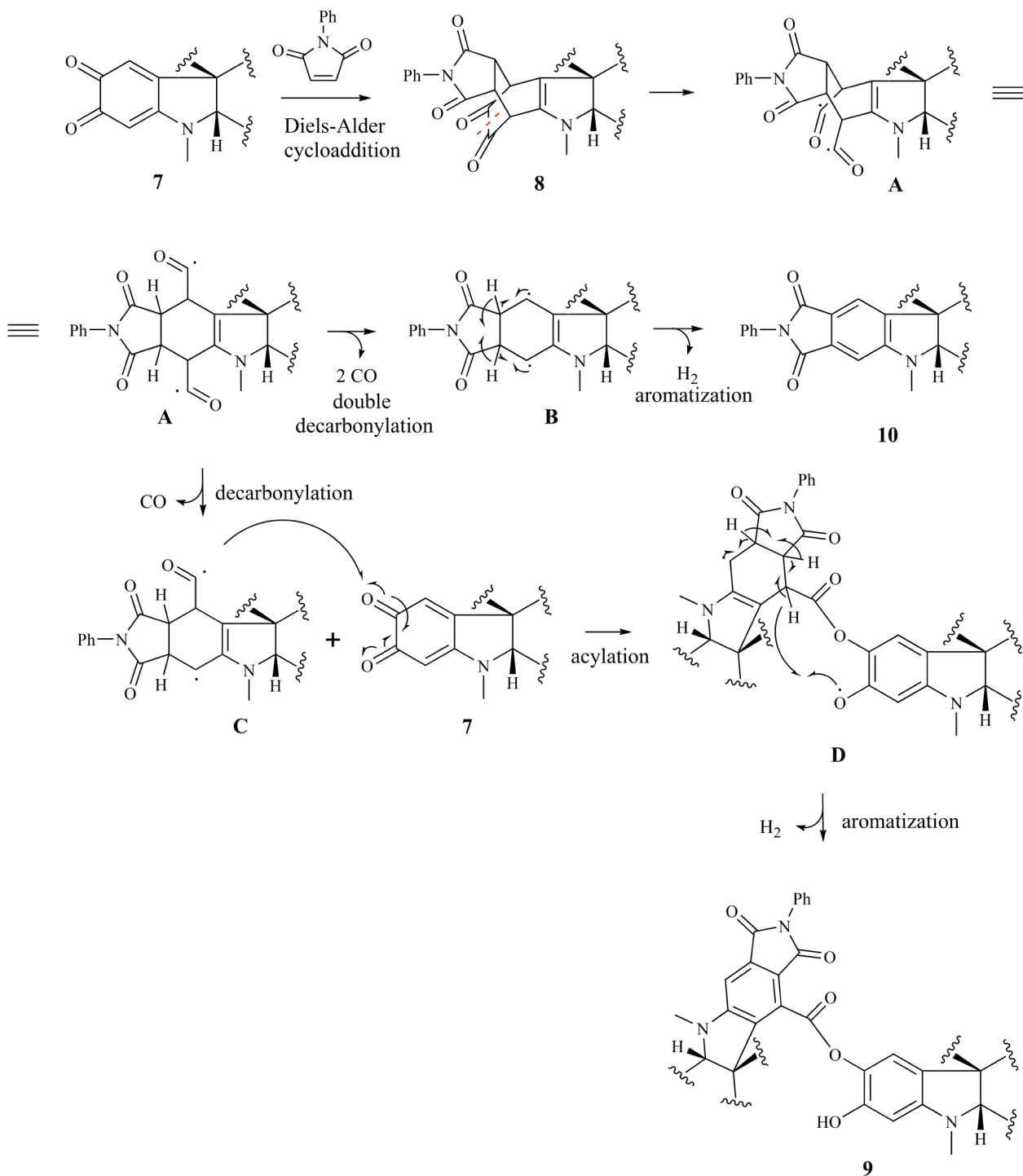
Scheme 2 Outcome of the reaction between the *ortho*-quinone derivative of vindoline and *N*-phenylmaleimide

3 Experimental

3.1 General

Melting points were measured on a VEB Analytik Dresden PHMK-77/1328 apparatus and are uncorrected. IR spectra were recorded on Zeiss IR 75 and 80 instruments. NMR measurements were performed on a Varian 800 MHz NMR spectrometer equipped with a $^1\text{H}\{^{13}\text{C}/^{15}\text{N}\}$ Triple Resonance ^{13}C Enhanced Salt Tolerant Cold Probe operating at 799.7 MHz for ^1H and 201.1 MHz for ^{13}C , and a Varian 500 MHz NMR spectrometer equipped with a $^1\text{H}\{^{13}\text{C}/^{15}\text{N}\}$ 5 mm PFG Triple Resonance ^{13}C Enhanced Cold Probe operating at 499.9 MHz for ^1H and 125.7 MHz for ^{13}C . Chemical shifts are given on the

delta scale as parts per million (ppm) with tetramethylsilane (TMS) (0.00 ppm for ^1H and ^{13}C). ^1H - ^1H , direct ^1H - ^{13}C , and long-range ^1H - ^{13}C scalar spin-spin connectivities were established from 2D zTOCSY, gHSQCAD, and gHMBCAD experiments, respectively. All pulse sequences were applied by using the standard spectrometer software package. All experiments were performed at 298 K. HRMS and MS-MS analyses were performed on an LTQ FT Ultra (Thermo Fisher Scientific) system. The ionization method was ESI, operated in positive ion mode. The protonated molecular ion peaks were fragmented by CID at a normalized collision energy of 35%. For the CID experiment helium was used as the collision gas.



Scheme 3 The proposed mechanism for the reaction.

The samples were dissolved in methanol. Data acquisition and analysis were accomplished with Xcalibur software version 2.0 (Thermo Fisher Scientific). TLC was carried out using Kieselgel 60F₂₅₄ (Merck) glass plates.

3.2 Friedel-Crafts reaction of vindoline (4)

Vindoline (4) (400 mg, 0.876 mmol) was dissolved in dichloromethane (40 ml), and methyl vinyl ketone (0.7 ml, 8.76 mmol) and trifluoroacetic acid (2.8 ml, 36.8 mmol) were added at room temperature under stirring. After 24 h the reaction mixture was washed with 5% aqueous sodium

bicarbonate (40 ml) and the aqueous phase was extracted with dichloromethane (2x30 ml). The combined organic phase was dried (magnesium sulfate) and evaporated to dryness. The crude product was purified by preparative TLC (dichloromethane-methanol 15:1), and 264 mg (57%) of adduct 6 was obtained. Mp. 68 °C.

TLC: dichloromethane-methanol 20:1, R_f = 0.52.

IR (KBr): 3469, 2934, 1713, 1369, 1241, 1042 cm^{-1} .

¹H NMR (799.7 MHz, DMSO-*d*₆) δ (ppm) 0.40 (3H, t, J = 7.5 Hz, H₃-18), 0.89 (1H, dq, J = 15.0, 7.5 Hz, H_x-19), 1.46 (1H, dq, J = 15.0, 7.5 Hz, H_y-19), 1.93 (3H, s, C(17)-OC(O)CH₃),

2.06 (3H, s, $\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{CH}_2$), 2.15–2.24 (2H, m, H_2 -6), 2.53–2.69 (9H, m, $\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{CH}_2$, N(1)- CH_3 , H-21, H_x -5), 2.79 (1H, ddd, $J = 16.2, 2.3, 1.7$ Hz, H_x -3), 3.26–3.30 (1H, m, H_y -5), 3.42 (1H, ddd, $J = 16.2, 4.9, 1.6$ Hz, H_y -3), 3.49 (1H, s, H-2), 3.65 (3H, s, C(16)- COOCH_3), 3.75 (3H, s, C(11)- OCH_3), 5.08 (1H, ddd, $J = 10.1, 2.3, 1.6$ Hz, H-15), 5.19 (1H, s, H-17), 5.82 (1H, ddd, $J = 10.1, 4.9, 1.7$ Hz, H-14), 6.29 (1H, s, H-12), 6.92 (1H, s, H-9), 8.80 (1H, br, C(16)- OH), ^{13}C NMR (201.1 MHz, $\text{DMSO}-d_6$) δ (ppm) 7.4 (C-18), 20.6 (C(17)- $\text{OC}(\text{O})\text{CH}_3$), 23.9 ($\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{CH}_2$), 29.5 ($\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{CH}_2$), 30.3 (C-19), 38.7 (N(1)- CH_3), 42.3 (C-20), 43.4 ($\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{CH}_2$), 43.6 (C-6), 50.4 (C-3), 51.2 (C-5), 51.6 (C(16)- COOCH_3), 52.2 (C-7), 55.3 (C(11)- OCH_3), 66.0 (C-21), 75.9 (C-17), 78.6 (C-16), 83.0 (C-2), 93.6 (C-12), 119.5 (C-10), 123.4 (C-9), 124.0 (C-8), 124.3 (C-14), 129.9 (C-15), 151.7 (C-13), 157.7 (C-11), 170.0 (C(17)- $\text{OC}(\text{O})\text{CH}_3$), 171.6 (C(16)- COOCH_3), 208.0 ($\text{CH}_3\text{C}(\text{O})\text{CH}_2\text{CH}_2$).

HRMS: $\text{M}+\text{H}=527.27615$ ($\text{C}_{29}\text{H}_{39}\text{N}_2\text{O}_7$; $\delta=1.8$ ppm); HR-ESI-MS-MS (CID=35%; rel. int. %): 509(13); 467(100); 435(3); 407(2); 258(9).

3.3 Reaction of *ortho*-quinone derivative of vindoline (7) and *N*-phenylmaleimide

The quinone derivative **7** (102 mg, 0.223 mmol) was dissolved in toluene (10 ml), then *N*-phenylmaleimide (43 mg, 0.248 mmol) was added. The reaction mixture was refluxed for 42 h. The solvent was evaporated, and the residue was separated by preparative TLC (dichloromethane-methanol 20:1). Two products were isolated, dimer **9** (6 mg, 3%) and the condensed monomer **10** (3 mg, 2%).

Dimer derivative **9**: Mp. 195 °C (decomp.).

TLC: dichloromethane-methanol 20:1, $R_f = 0.39$.

IR (KBr): 3401, 2929, 1747, 1715, 1587, 1385, 1234 cm^{-1} .

^1H NMR (499.9 MHz, CDCl_3) δ (ppm) 0.47 (3H, t, $J = 7.4$ Hz, H_3 -18'), 0.58 (3H, t, $J = 7.4$ Hz, H_3 -18), 1.17–1.25 (2H, m, H_x -19', H_x -19), 1.69–1.77 (1H, m, H_y -19'), 1.79–1.88 (1H, m, H_y -19), 2.07 (3H, s, C(17')- $\text{OC}(\text{O})\text{CH}_3$), 2.10 (3H, s, C(17)- $\text{OC}(\text{O})\text{CH}_3$), 2.15–2.20 (1H, m, H_x -6'), 2.38–2.61 (5H, m, H_x -5', H_y -6', H-21', H_x -5, H_x -6), 2.66 (3H, s, N(1')- CH_3), 2.75–2.82 (1H, m, H_x -3'), 2.84–2.88 (1H, m, H_y -6), 2.88 (3H, s, N(1)- CH_3), 2.91–2.97 (1H, m, H_x -3), 3.35–3.58 (5H, m, H_y -5, H_y -5', H-21, H_y -3, H_y -3'), 3.77 (1H, s, H-2'), 3.80 (3H, s, C(16')- COOCH_3), 3.85 (3H, s, C(16)- COOCH_3), 4.15 (1H, s, H-2), 5.19–5.23 (2H, m, H-15, H-15'), 5.48 (1H, s, H-17), 5.50 (1H, s, H-17'), 5.82–5.86 (2H, m, H-14, H-14'), 6.23 (1H, s, H-12'), 6.51 (1H, br s, H-9'), 7.07 (1H, s, H-12), 7.39–7.45 (3H, m, H-4'', H-2'', H-6''), 8.44 (1H, br s, C(11')- OH), 9.0–10.2 (2H, br, C(16)- OH), C(16')- OH). ^{13}C NMR (201.1 MHz, CDCl_3) δ (ppm) 8.0 (C-18'), 8.1 (C-18), 20.97 (C(17)- $\text{OC}(\text{O})\text{CH}_3$), 21.04 (C(17')- $\text{OC}(\text{O})\text{CH}_3$), 31.0 (C-19'), 32.0 (C-19), 36.7 (N(1)- CH_3), 38.2 (N(1')- CH_3), 43.1 (C-20'), 43.2 (br, C-6), 43.5 (C-20), 44.1 (br, C-6'), 51.2 (C-3), 51.3 (C-3'), 52.4

(C(16')- COOCH_3), 52.5 (C-5), 52.6 (C-5'), 52.7 (C-7'), 52.8 (C(16)- COOCH_3), 53.6 (C-7), 66.5 (br, C-21), 67.9 (br, C-21'), 75.3 (br, C-17), 76.1 (br, C-17'), 78.4 (C-16), 79.3 (C-16'), 83.2 (br, C-2'), 83.4 (br, C-2), 99.2 (C-12'), 104.0 (C-12), 114.7 (C-9'), 117.3 (br, C-10), 123.9 (br, C-14), 124.0 (br, C-14'), 124.9 (C-8'), 125.8 (C-9), 126.6 (C-2'', C-6''), 128.4 (C-4''), 129.1 (C-3'', C-5''), 129.9 (C-10'), 130.0 (C-15), 130.4 (C-15'), 131.1 (C-1''), 135.2 (C-11), 136.6 (br, C-8), 149.9 (C-11'), 152.4 (C-13'), 159.2 (C-13), 164.9* (C(9)- COOAr), 165.9 (C(11)-CO), 167.6* (C(10)-CO), 170.8 (C(17)- $\text{OC}(\text{O})\text{CH}_3$), C(17')- $\text{OC}(\text{O})\text{CH}_3$), 171.7 (C(16)- COOCH_3), 171.9 (C(16')- COOCH_3). *: uncertain assignment

HRMS: $\text{M}+\text{H}=1056.42448$ ($\delta=0.8$ ppm; $\text{C}_{57}\text{H}_{62}\text{O}_{15}\text{N}_3$). HR-ESI-MS-MS (CID=35%, rel. int. %): 1038(12); 996(100); 978(3); 894(10); 787(8); 598(53).

Condensed monomer **10**: Mp. 120 °C.

TLC: dichloromethane-methanol 20:1, $R_f = 0.58$.

IR (KBr): 3468, 2929, 1745, 1713, 1372, 1236, 754 cm^{-1} .

^1H NMR (499.9 MHz, CDCl_3) δ (ppm) 0.56 (3H, t, $J = 7.4$ Hz, H_3 -18), 1.11 (1H, dq, $J = 14.4, 7.4$ Hz, H_x -19), 1.71 (1H, dq, $J = 14.4, 7.4$ Hz, H_y -19), 2.09 (3H, s, C(17)- $\text{OC}(\text{O})\text{CH}_3$), 2.31–2.39 (1H, m, H_x -6), 2.40–2.50 (1H, m, H_y -6), 2.63–2.68 (1H, m, H_x -5), 2.85 (1H, br s, H-21), 2.86 (3H, s, N(1)- CH_3), 2.87–2.93 (1H, m, H_x -3), 3.48–3.61 (2H, m, H_y -3, H_y -5), 3.83 (3H, s, C(16)- COOCH_3), 4.04 (1H, br s, H-2), 5.27–5.31 (1H, m, H-15), 5.39 (1H, s, H-17), 5.91 (1H, ddd, $J = 10.3, 5.0, 1.4$ Hz, H-14), 6.94 (1H, s, H-12), 7.36–7.40 (1H, m, H-4'), 7.41–7.45 (2H, m, H-2', H-6'), 7.47–7.52 (2H, m, H-3', H-5'), 7.56 (1H, s, H-9), 9.35 (1H, br, C(16)- OH). ^{13}C NMR (125.7 MHz, CDCl_3) δ (ppm) 7.7 (C-18), 20.9 (C(17)- $\text{OC}(\text{O})\text{CH}_3$), 31.2 (C-19), 36.6 (N(1)- CH_3), 43.0 (C-20), 44.4 (C-6), 50.9 (C-3), 51.8 (C-5), 52.6 (C(16)- COOCH_3), 52.9 (C-7), 67.4 (C-21), 75.7 (C-17), 79.1 (C-16), 82.6 (br, C-2), 102.4 (C-12), 118.2 (C-9), 121.5 (C-10), 124.3 (br, C-14), 126.5 (C-2', C-6'), 127.8 (C-4'), 129.1 (C-3', C-5'), 129.9 (C-15), 132.0 (C-1'), 135.0 (C-11), 139.1 (C-8), 157.5 (C-13), 167.26 (C(11)-CO), 167.30 (C(10)-CO), 170.6 (C(17)- $\text{OC}(\text{O})\text{CH}_3$), 171.4 (C(16)- COOCH_3).

HRMS: $\text{M}+\text{H}=572.23887$ ($\delta=-0.5$ ppm; $\text{C}_{32}\text{H}_{34}\text{O}_7\text{N}_3$). HR-ESI-MS-MS (CID=35%, rel. int. %): 554(10); 530(3); 512(100); 480(23); 452(6); 424(3); 303(9).

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