Synthesis and Structure−Activity Relationship Studies of Cytotoxic Ester and Ether Anhydrovinblastine Derivatives

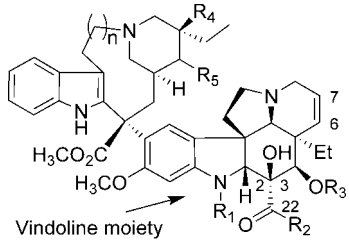
Han-Kun Zhang,[†,‡] Yong Shao,[†,‡] Hong Ding,[§] and Li-Hong Hu*[,†]

Shanghai Research Center for the Modernization of Traditional Chinese Medicine, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, People's Republic of China, and Department of Molecular Pharmacology, Shanghai Institute of Materia Medica, Chinese Academy of Sciences, Shanghai 201203, People's Republic of China

Received May 9, 2008

Two new series of 3-demethoxycarbonyl-3-ester and 3-demethoxycarbonyl-3-ether methyl anhydrovinblastine derivatives were designed, synthesized, and evaluated for their inhibitory activities against human non-small-cell lung cancer (A549) and cervical epithelial adenocarcinoma (HeLa) cell lines. Ester anhydrovinblastine derivatives exhibited potent cytotoxicity, whereas the ether analogues were much less active. The size of the introduced substituents was the foremost factor in determining the resultant cytotoxic activity. Compound **12b** showed a similar cytotoxic potency to the positive control, anhydrovinblastine (**1a**).

Vinca (*Catharanthus*) alkaloids are used widely in human cancer chemotherapy.[1] The discovery of the antitumor properties of these compounds was followed by extensive chemical research in this area with the aim of discovering new bisindole alkaloids with superior therapeutic activity. Anhydrovinblastine (**1a**)[2] is a new semisynthetic alkaloid that differs from vinblastine (**1b**) in having a 3′,4′-double bond in the catharanthine moiety, a property it shares with vinorelbine (**1c**).[3] Compound **1a** was found to be more active than **1b** and **1c** against human tumor xenografts of H460 non-small-cell lung cancer and of C4 cervical carcinoma in nude mice at equitoxic doses.[2] The improved efficacy resulted from a combination of increased antitumor potency and the ability to administer increased doses of **1a** compared to **1c**.



	R_1	R_2	R_3	R_4	R_5	n
1a	Me	OMe	COMe	=		1
1b	Me	OMe	COMe	OH	H	1
1c	Me	OMe	COMe	=		0

Functional group reversal is a common strategy in medicinal chemistry.[4,5] In previous investigations of the structural requirements for cytotoxic activity of **1a**,[6] an acetyloxymethyl group was introduced instead of methyl carboxylate at the C-22 position to afford a "reverse ester" derivative termed BM6 (**5b**).[7] Although its cytotoxic activity against a wide spectrum of tumor cell lines decreased about 10-fold when compared with **1c**, **5b** showed superior antitumor activities in vivo to **1c** in preclinical tumor models.[2] Accordingly, in the present study, 3-demethoxycarbonyl-3-ester methyl anhydrovinblastine derivatives, with inverted ester groups at the C-22 position of **1a**, were designed, synthesized, and tested for cytotoxic activity against the A549 and HeLa cell lines. In addition, 3-demethoxycarbonyl-3-methyl ether derivatives were also produced and tested in order to gain a better understanding of the SAR of oxygen-linked analogues at C-22 of compound **1a**.

Results and Discussion

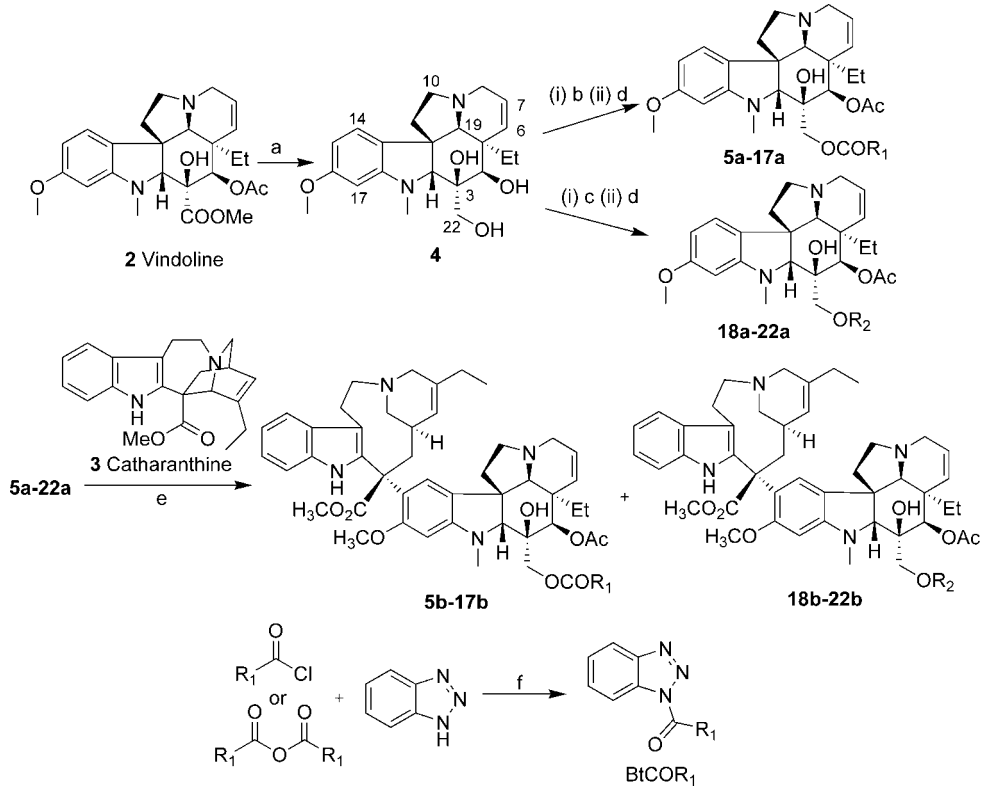
The synthetic strategy that allowed the preparation of anhydrovinblastine derivatives utilized the modified Polonovski−Potier reaction[8] as a key step to form dimer vinca alkaloids. Vindoline (**2**), the major alkaloid in whole plants of *Catharanthus roseus*, is readily obtained and so was chosen as the starting material. A total of 18 semisynthetic anhydrovinblastine derivatives (**5b**−**22b**) were prepared, as outlined in Scheme 1. The crucial intermediate triol **4** was prepared by reduction of **2** with $LiAlH_4$. The triol **4** was stirred with $BtCOR_1$ and sodium hydride in anhydrous THF at room temperature, then acetylated at C-4 OH to furnish compounds **5a**−**17a**, which were subsequently coupled with **3** to produce ester anhydrovinblastine derivatives (**5b**−**17b**). The $BtCOR_1$ derivatives could be prepared using a different acyl chloride or acid anhydride reacted with benzotriazole in the presence of diisopropylethylamine (DIPEA) in dichloromethane (DCM). By replacing the $BtCOR_1$ with different alkyl halides, the triol **4** was treated with diverse alkyl bromides in THF including 50% sodium hydroxide solution at 60 °C. This was acetylated at the C-4 OH to furnish compounds **18a**−**22a,** which were then coupled with catharanthine (**3**) to produce the ether anhydrovinblastine derivatives (**18b**−**22b**). Alkyl bromides were obtained from commercial suppliers.

The cytotoxic activities of all these anhydrovinblastine derivatives were evaluated against human non-small-cell lung cancer (A549) and cervical epithelial adenocarcinoma (HeLa) cell lines using a sulforhodamine B (SRB) assay,[9] employing **1a** as positive control. The IC_{50} values for the inhibition of proliferation of the A549 and HeLa cell lines are shown in Table 1. Among six alkyl-substituted ester analogues (**5b**−**10b**), a marked loss of cytotoxicity was observed against both cell lines with the increasing size of the alkyl groups. Similar conclusions also could be obtained from ester analogues substituted with aromatic groups (**11b** and **12b**). The benzyl ester **11b** (IC_{50} = 67.4, 272.0 nM), with an aromatic group having one more carbon atom than the phenyl ester **12b** (IC_{50} = 25.4, 35.6 nM), exhibited decreased cytotoxicity against both cell lines. This showed that a phenyl group is more suitable than a benzyl group to maintain activity. Introduction of electron-donating (OMe) or electron-withdrawing groups (Cl and NO_2) in the phenyl group greatly decreased the cytotoxicity against the HeLa cell line. However, the derivatives with electron-donating groups at the C-2 or C-4 position of the phenyl group (**13b**, **14b**) exhibited better cytotoxic activities against the A549 cell line than **1a**. 2-Substituted

* To whom correspondence should be addressed. Tel: 86-21-50272221. Fax: 86-21-50272221. E-mail: simmhulh@mail.shcnc.ac.cn.
† Shanghai Research Center for the Modernization of Traditional Chinese Medicine.
‡ These two authors contributed equally to this work.
§ Shanghai Institute of Materia Medica.

10.1021/np800284h CCC: $40.75
Published on Web 09/04/2008

Scheme 1[a]



[a] Reagents and conditions: (a) $LiAlH_4$, THF, 0 °C to rt, 4 h, 98%; (b) $BtCOR_1$, NaH, THF, rt, 3 h; (c) R_2Br, THF, 50% NaOH−H_2O, $Bu_4N^+I^-$, 60 °C, 6 h; (d) Ac_2O, pyridine; (e) (i) $FeCl_3$, HCl−H_2O buffer (pH = 2), 8 h; (ii) $NaBH_4$, NH_4OH, 0 °C, 15 min; (f) DCM, Et_3N, rt, 3 h.

phenyl esters showed higher activity than their 4-substituted counterparts against the A549 cell line. Compared with other ester derivatives, compound **12b** exhibited the best cytotoxic activity against both cell lines and showed an eqully cytotoxic potency to the **1a**.

As shown in Table 1, it was observed that the five ether derivatives (**18b**−**22b**) were much less active than **1a**. Thus, introducing an ether group at C-22 of the vindoline moiety is unsuitable for improving the cytotoxic activities of anhydrovinblastine derivatives. In comparison with **1a**, these ether analogues have a lack of a carbonyl group at C-22. As a hydrogen acceptor, the carbonyl group appears to be important for maintaining the cytotoxic potency.

In summary, the structure−activity relationships of two classes of derivatives of anhydrovinblastine (**1a**) as cytotoxic agents have been described. The size of the substituents at the C-22 position is a crucial factor for improving cytotoxic activity. Ester anhydrovinblastine derivatives are more promising than ether derivatives, with **12b** found to be equivalent in potency to **1a** in the biological assays used.

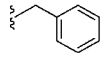
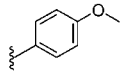
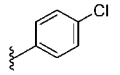
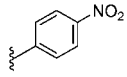
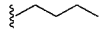
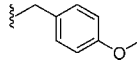
Experimental Section

General Experimental Procedures. Optical rotations were determined on a Perkin-Elmer 341 polarimeter. IR spectra were recorded on a Perkin-Elmer 577 spectrometer. NMR spectra were recorded on a Varian Mercury-VX300 Fourier transform spectrometer or a Bruker AM-400 spectrometer. The chemical shifts are reported in (ppm) using the δ 7.26 signal of $CDCl_3$ (^{1}H NMR) and the δ 77.23 signal of $CDCl_3$ (^{13}C NMR) as internal standards. EIMS were obtained on a Shimadzu GCMS-QP5050A spectrometer. ESIMS were run on a Bruker Esquire 3000 plus spectrometer in MeOH. Thin-layer chromatographic (TLC) plates (silica gel 60 GF, with glass support) from Yantai Jiangyou Company were used for monitoring the progress of a reaction and visualized with 254 nm UV light and/or sprayed with a 10% solution of ceric ammonium sulfate (CAS) in phosphoric acid. Unless otherwise mentioned, all chemicals and materials were used as received from commercial suppliers without further purification. Tetrahydrofuran (THF) was distilled from sodium benzophenone under nitrogen. Dichloromethane (DCM) was distilled from calcium hydride. Compounds **1a** and **1c** were purchased from Shanghai Kang'ai Biological Products Company, Ltd.

3,4,22-Triol-3-demethoxycarbonyl-3-hydroxymethyl-4-deacetylvindoline (4). To a suspension of $LiAlH_4$ (114 mg, 3.00 mmol) in dry THF (10 mL) at 0 °C was added slowly a solution of vindoline (486 mg, 1.00 mmol) in dry THF (10 mL). The reaction mixture was stirred at room temperature for 4 h and then quenched cautiously by the subsequent addition of water (114 μL), 15% NaOH(aq) (114 μL), and water (342 μL). The resulting suspension was warmed to room temperature and stirred for 10 min. The suspension was filtered through a fritted funnel, and the filtrate was concentrated in vacuo to give a crude triol. The product was used in the next step without purification. $[\alpha]^{20}_D$ +45 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.73 (1H, brs), 6.82 (1H, d, J = 8.0 Hz), 6.30 (1H, dd, J = 8.0, 2.4 Hz), 6.12 (1H, d, J = 2.4 Hz), 5.88 (1H, dd, J = 10.0, 4.8 Hz), 5.60 (1H, d, J = 10.0 Hz), 3.93 (1H, d, J = 11.2 Hz), 3.78 (3H, s), 3.72 (1H, d, J = 11.2 Hz), 3.52 (2H, s), 3.45 (1H, dd, J = 15.6, 4.4 Hz), 3.35 (1H, td, J = 9.2, 4.4 Hz), 3.00 (3H, s), 2.83 (1H, dt, J = 15.6, 2.0 Hz), 2.57 (1H, s), 2.53−2.50 (2H, m), 2.25−2.16 (3H, m), 1.36−1.31 (1H, m), 0.94−0.88 (1H, m), 0.62 (3H, t, J = 7.6 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 160.9 (C), 154.6 (C), 130.8 (CH), 126.5 (C), 124.3 (CH), 122.9 (CH), 104.6 (CH), 96.3 (CH), 81.0 (CH), 77.4 (CH), 75.2 (C), 68.3 (CH), 65.7 (CH_2), 55.4 (OCH_3), 51.8 (C), 51.7 (CH_2), 51.3 (CH_2), 44.8 (CH_2), 43.5 (C), 40.4 (CH_3), 32.5 (CH_2), 7.9 (CH_3); EIMS *m*/*z* 386 $[M]^+$ 368, 355, 297, 212, 188, 174, 162, 135, 93.

General Procedure for the Preparation of 5a−17a. A solution of the benzotriazole (2 mmol) in dry CH_2Cl_2 (10 mL) was treated with diisopropylethylamine (0.43 mL, 2.5 mmol) followed by the dropwise addition of a solution of a different acyl chloride or acid anhydride (2.2 mmol) in CH_2Cl_2 (2 mL) at 0 °C. This was allowed to warm to room temperature and stirred a further 2 h. Then, the reaction mixture was quenched with H_2O (20 mL) and extracted with EtOAc (2 × 20 mL). The combined organic phase was washed with brine (10 mL)

Table 1. Cytotoxic Activity of Anhydrovinblastine (**1a**) Analogues[a]

Compound	R_1 or R_2	IC_{50} (nM)	
		A549	HeLa
AVLB		36.9 ± 1.8	26.9 ± 0.9
5b		38.2 ± 5.7	35.3 ± 1.4
6b		39.1 ± 3.7	62.1 ± 1.7
7b		59.9 ± 3.6	87.5 ± 4.9
8b		181.0 ± 9.0	96.0 ± 8.0
9b		70.3 ± 5.7	175.0 ± 6.0
10b		47.9 ± 5.9	38.1± 1.5
11b		67.4 ± 3.7	272.0 ± 17.0
12b		25.4 ± 4.3	35.6 ± 1.1
13b		14.2 ± 4.2	154.0 ± 13.0
14b		29.7 ± 6.4	151.0 ± 11.0
15b		40.5 ± 3.1	147.0 ± 7.0
16b		56.7 ± 5.3	102.0 ± 8.0
17b		52.3 ± 2.4	169.0 ± 12.0
18b		98.0 ± 4.0	220.0 ± 9.0
19b		124 .0± 5.0	162.0 ± 10.0
20b		401.0 ± 21.0	398.0 ± 14.0
21b		422.0 ± 18.0	422.0 ± 17.0
22b		702.0 ± 23.0	409.0 ± 15.0

[a] Ditartrate of each compound used for bioassay.

and dried over anhydrous Na_2SO_4. Concentration gave a $BtCOR_1$ product, which was used in the next step without purification.

To a solution of **4** (1 mmol) and $BtCOR_1$ (1.1 mmol) in anhydrous THF (10 mL) was added sodium hydride (60%, 1 mmol) under N_2. After being stirred at room temperature for 3 h, the reaction mixture was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. Concentration followed by purification by flash chromatography (4:1, hexanes−acetone) provided a crude product, which was added to pyridine (1.0 mL) and Ac_2O (1.0 mL) at room temperature. After stirring the reaction mixture for 8 h, saturated $NaHCO_3$ (5 mL) and EtOAc (20 mL) were added, and the organic phase was washed with H_2O (3 × 10 mL) and brine (10 mL), dried, concentrated, and purified by flash chromatography (6:1, hexanes−acetone) to provide a white solid (**5a**−**17a**).

3-Demethoxycarbonyl-3-(methylcarbonyloxy)methylvindoline (5a). Compound **5a** was prepared using acetate anhydride as starting material. Yield: 85%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (1H, brs), 6.86 (1H, d, J = 8.1 Hz), 6.28 (1H, d, J = 8.1 Hz), 6.11 (1H, s), 5.87 (1H, dd, J = 9.9, 3.3 Hz), 5.35 (1H, d, J = 9.9 Hz), 5.00 (1H, s), 4.08 (2H, d, J = 10.8 Hz), 3.76 (3H, s), 3.62 (1H, s), 3.40 (2H, m), 2.84 (3H, s), 2.81 (1H, m), 2.61 (1H, s), 2.47 (1H, m), 2.25 (1H, m), 2.16 (1H, m), 2.11 (6H, s), 1.27 (1H, m), 0.96 (1H, m), 0.49 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (C), 170.8 (C), 161.1 (C), 154.4 (C), 130.2 (CH), 125.9 (C), 124.3 (CH), 122.8 (CH), 104.9 (CH), 96.4 (CH), 81.6 (CH), 76.8 (CH), 76.2 (C), 67.8 (CH), 66.9 (CH_2), 55.4 (OCH_3), 52.2 (C), 51.8 (CH_2), 50.9 (CH_2), 44.7 (CH_2), 42.7 (C), 40.1 (CH_3), 31.5 (CH_2), 21.2 (CH_3), 21.1 (CH_3), 7.6 (CH_3); ESIMS m/z 471.3 [M + 1]$^+$.

3-Demethoxycarbonyl-3-(ethylcarbonyloxy)methylvindoline (6a). Compound **6a** was prepared using propionyl chloride as starting material. Yield: 55%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.96 (1H, brs), 6.89 (1H, d, J = 8.1 Hz), 6.31 (1H, d, J = 8.1 Hz), 6.14 (1H, s), 5.87 (1H, dd, J = 10.2, 3.6 Hz), 5.37 (1H, d, J = 10.2 Hz), 5.04 (1H, s), 4.23 (1H, d, J = 11.4 Hz), 4.03 (1H, d, J = 11.4 Hz), 3.80 (3H, s), 3.64 (1H, s), 3.46 (2H, m), 2.87 (3H, s), 2.81 (1H, d, J = 15.9 Hz), 2.64 (1H, s), 2.51 (1H, m), 2.44 (2H, q, J = 7.2 Hz), 2.29 (2H, m), 2.15 (3H, s), 1.32 (1H, m), 1.16 (3H, t, J = 7.2 Hz), 1.03 (1H, m), 0.53 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.9 (C), 170.5 (C), 160.8 (C), 154.2 (C), 129.9 (CH), 125.7 (C), 124.0 (CH), 122.5 (CH), 104.6 (CH), 96.1 (CH), 81.4 (CH), 76.6 (CH), 76.0 (C), 67.6 (CH), 66.3 (CH_2), 55.1 (OCH_3), 51.9 (C), 51.6 (CH_2), 50.6 (CH_2), 44.4 (CH_2), 42.4 (C), 39.7 (CH_3), 31.3 (CH_2), 27.3 (CH_2), 20.7 (CH_3), 9.0 (CH_3), 7.4 (CH_3); ESIMS m/z 485.3 [M + 1]$^+$.

3-Demethoxycarbonyl-3-(isopropylcarbonyloxy)methylvindoline (7a). Compound **7a** was prepared using isobutyryl chloride as starting material. Yield: 58%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (1H, brs), 6.89 (1H, d, J = 8.1 Hz), 6.31 (1H, dd, J = 8.1, 2.4 Hz), 6.13 (1H, d, J = 2.4 Hz), 5.87 (1H, dd, J = 10.2, 3.6 Hz), 5.36 (1H, d, J = 10.2 Hz), 5.03 (1H, s), 4.25 (1H, d, J = 11.7 Hz), 4.01 (1H, d, J = 11.7 Hz), 3.79 (3H, s), 3.62 (1H, s), 3.45 (2H, m), 2.88 (3H, s), 2.80 (1H, d, J = 15.9 Hz), 2.69 (1H, m), 2.62 (1H, s), 2.51 (1H, m), 2.29 (2H, m), 2.13 (3H, s), 1.32 (1H, m), 1.19 (6H, dd, J = 6.6, 1.2 Hz), 1.03 (1H, m), 0.52 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.3 (C), 170.4 (C), 160.8 (C), 154.1 (C), 129.9 (CH), 125.7 (C), 123.9 (CH), 122.5 (CH), 104.5 (CH), 96.0 (CH), 81.4 (CH), 76.4 (CH), 76.0 (C), 67.6 (CH), 65.9 (CH_2), 55.0 (OCH_3), 51.8 (C), 51.6 (CH_2), 50.6 (CH_2), 44.4 (CH_2), 42.4 (C), 39.6 (CH_3), 33.6 (CH), 31.2 (CH_2), 20.6 (CH_3), 18.9 (CH_3), 18.7 (CH_3), 7.3 (CH_3); ESIMS m/z 499.2 [M + 1]$^+$.

3-Demethoxycarbonyl-3-(*tert*-butylcarbonyloxy)methylvindoline (8a). Compound **8a** was prepared using pivaloyl chloride as starting material. Yield: 56%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (1H, brs), 6.89 (1H, d, J = 8.1 Hz), 6.30 (1H, d, J = 8.1 Hz), 6.12 (1H, s), 5.84 (1H, dd, J = 9.3, 3.3 Hz), 5.33 (1H, d, J = 9.3 Hz), 5.01 (1H, s), 4.32 (1H, d, J = 11.4 Hz), 3.94 (1H, d, J = 11.4 Hz), 3.79 (3H, s), 3.60 (1H, s), 3.48 (2H, m), 2.89 (3H, s), 2.81 (1H, m), 2.63 (1H, s), 2.50 (1H, m), 2.25 (1H, m), 2.16 (1H, m), 2.06 (3H, s), 1.27 (1H, m), 1.24 (9H, s), 0.96 (1H, m), 0.50 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C), 170.8 (C), 161.0 (C), 154.4 (C), 130.2 (CH), 125.9 (C), 124.3 (CH), 122.8 (CH), 104.9 (CH), 96.4 (CH), 81.6 (CH), 76.8 (CH), 76.2 (C), 67.8 (CH), 66.9 (CH_2), 55.4 (OCH_3), 52.2 (C), 51.8 (CH_2), 50.9 (CH_2), 44.9 (CH_2), 42.7 (C), 40.1 (CH_3), 38.9 (C), 31.5 (CH_2), 27.7 ($3CH_3$), 21.2 (CH_3), 7.6 (CH_3); ESIMS m/z 513.3 [M + 1]$^+$.

3-Demethoxycarbonyl-3-(isobutylcarbonyloxy)methylvindoline (9a). Compound **9a** was prepared using isovaleryl chloride as starting material. Yield: 56%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.83 (1H, brs), 6.89 (1H, d, J = 8.1 Hz), 6.31 (1H, dd, J = 8.1, 2.4 Hz), 6.13 (1H, d, J = 2.1 Hz), 5.88 (1H, dd, J = 10.5, 3.6 Hz), 5.37 (1H, d, J = 10.5 Hz), 5.03 (1H, s), 4.26 (1H, d, J = 11.4 Hz), 4.00 (1H, d, J = 11.4 Hz), 3.80 (3H, s), 3.64 (1H, s), 3.48 (2H, m), 2.89 (3H, s), 2.81 (1H, d, J = 15.9 Hz), 2.64 (1H, s), 2.51 (1H, m), 2.29 (4H, m), 2.15 (3H, s), 1.32 (1H, m), 1.03 (1H, m), 0.97 (6H, d, J = 6.6 Hz), 0.89 (1H, m), 0.52 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.4 (C), 170.5 (C), 160.8 (C), 154.1 (C), 129.9 (CH), 125.7 (C), 123.9 (CH), 122.5 (CH), 104.6 (CH), 96.1 (CH), 81.2 (CH), 76.5 (CH), 76.0 (C), 67.6 (CH), 66.0 (CH_2), 55.0 (OCH_3), 51.8 (C), 51.5 (CH_2), 50.6 (CH_2), 44.4 (CH_2), 43.1 (CH_2), 42.4 (C), 39.7 (CH_3), 31.3 (CH_2), 25.3 (CH), 22.2 ($2CH_3$), 20.7 (CH_3), 7.3 (CH_3); ESIMS m/z 513.3 [M + 1]$^+$.

3-Demethoxycarbonyl-3-(cyclopropylcarbonyloxy)methylvindoline (10a). Compound **10a** was prepared using cyclopropanecarbonyl chloride as starting material. Yield: 52%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.95 (1H, brs), 6.90 (1H, d, J = 8.1 Hz), 6.32 (1H, dd, J = 8.1, 2.4 Hz), 6.14 (1H, d, J = 2.4 Hz), 5.89 (1H, dd, J = 10.2, 3.6 Hz), 5.38 (1H, d, J = 10.2 Hz), 5.04 (1H, s), 4.24 (1H, d, J = 11.7 Hz), 4.03 (1H, d, J = 11.7 Hz), 3.80 (3H, s), 3.68 (1H, s), 3.45 (2H, m), 2.90 (3H, s), 2.81 (1H, d, J = 14.1 Hz), 2.65 (1H, s), 2.50 (1H, m), 2.51

(1H, m), 2.30 (2H, m), 2.14 (3H, s), 1.74 (1H, m), 1.32 (2H, m), 1.01 (2H, m), 0.86 (2H, m), 0.53 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.5 (C), 170.6 (C), 160.9 (C), 154.3 (C), 130.0 (CH), 125.7 (C), 124.1 (CH), 122.6 (CH), 104.7 (CH), 96.2 (CH), 81.5 (CH), 76.7 (CH), 76.1 (C), 67.6 (CH), 66.6 (CH_2), 55.2 (OCH_3), 52.0 (C), 51.7 (CH_2), 50.7 (CH_2), 44.6 (CH_2), 42.5 (C), 39.9 (CH_3), 31.3 (CH_2), 20.8 (CH_3), 12.7 (CH), 8.5 ($2CH_2$), 7.4 (CH_3); ESIMS *m/z* 497.3 $[M + 1]^+$.

3-Demethoxycarbonyl-3-(benzylcarbonyloxy)methylvindoline (11a). Compound **11a** was prepared using phenylacetyl chloride as starting material. Yield: 61%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.02 (1H, brs), 7.22 (5H, m), 6.86 (1H, d, $J = 8.4$ Hz), 6.29 (1H, d, $J = 8.4$ Hz), 6.05 (1H, s), 5.87 (1H, dd, $J = 10.2$, 3.9 Hz), 5.37 (1H, d, $J = 10.2$ Hz), 4.99 (1H, s), 4.30 (1H, d, $J = 11.1$ Hz), 3.95 (1H, d, $J = 11.1$ Hz), 3.78 (3H, s), 3.72 (2H, s), 3.48 (2H, m), 2.81 (1H, m), 2.63 (1H, s), 2.56 (3H, s), 2.47 (1H, m), 2.25 (1H, m), 2.16 (2H, m), 2.12 (3H, s), 1.27 (1H, m), 0.96 (1H, m), 0.48 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C), 170.8 (C), 161.0 (C), 154.3 (C), 135.4 (C), 130.4 (CH), 129.6 (2 CH), 129.0 (2 CH), 127.2 (CH), 125.9 (C), 124.3 (CH), 122.8 (CH), 105.5 (CH), 97.4 (CH), 82.9 (CH), 76.5 (C), 75.8 (CH), 67.1 (CH), 66.9 (CH_2), 55.5 (OCH_3), 52.3 (C), 51.5 (CH_2), 50.9 (CH_2), 45.0 (CH_2), 43.6 (CH_2), 42.9 (C), 41.0 (CH_3), 31.3 (CH_2), 21.1 (CH_3), 7.6 (CH_3); ESIMS *m/z* 547.3 $[M + 1]^+$.

3-Demethoxycarbonyl-3-(phenylcarbonyloxy)methylvindoline (12a). Compound **12a** was prepared using benzoyl chloride as starting material. Yield: 63%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.94 (1H, brs), 8.08 (2H, d, $J = 7.5$ Hz), 7.56 (1H, t, $J = 7.5$ Hz), 7.44 (2H, t, $J = 7.5$ Hz), 6.91 (1H, d, $J = 8.4$ Hz), 6.32 (1H, d, $J = 8.4$ Hz), 6.11 (1H, s), 5.89 (1H, dd, $J = 10.2$, 3.9 Hz), 5.39 (1H, d, $J = 10.2$ Hz), 5.13 (1H, s), 4.57(1H, d, $J = 11.4$ Hz), 4.20 (1H, d, $J = 11.4$ Hz), 3.79 (3H, s), 3.74 (1H, s), 3.51−3.38 (2H, m), 2.92 (3H, s), 2.82 (1H, d, $J = 15.6$ Hz), 2.67 (1H, s), 2.51 (1H, m), 2.31 (2H, m), 2.14 (3H, s), 1.32 (1H, m), 0.79 (1H, m), 0.54 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.3 (C), 165.7 (C), 160.8 (C), 154.0 (C), 132.7 (CH), 129.9 (CH), 129.9 (C), 129.4 (2 CH), 128.1 (2 CH), 125.5 (C), 123.9 (CH), 122.5 (CH), 104.5 (CH), 96.0 (CH), 82.8 (CH), 76.4 (CH), 76.1 (C), 67.4 (CH), 66.5 (CH_2), 54.9 (OCH_3), 52.3 (C), 51.4 (CH_2), 50.5 (CH_2), 44.5 (CH_2), 42.4 (C), 39.7 (CH_3), 31.2 (CH_2), 20.6 (CH_3), 7.3 (CH_3); ESIMS *m/z* 533.4 $[M + 1]^+$.

3-Demethoxycarbonyl-3-(2-methoxylphenylcarbonyloxy)methylvindoline (13a). Compound **13a** was prepared using 2-methoxybenzoyl chloride as starting material. Yield: 63%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (1H, brs), 7.86 (1H, d, $J = 7.5$ Hz), 7.47 (1H, t, $J = 7.5$ Hz), 6.97 (1H, t, $J = 7.5$ Hz), 6.97 (1H, d, $J = 7.5$ Hz), 6.90 (1H, d, $J = 8.4$ Hz), 6.31 (1H, d, $J = 8.4$ Hz), 6.12 (1H, s), 5.88 (1H, dd, $J = 10.5$, 3.6 Hz), 5.38 (1H, d, $J = 10.5$ Hz), 5.12 (1H, s), 4.49 (1H, d, $J = 11.4$ Hz), 4.19 (1H, d, $J = 11.4$ Hz), 3.87 (3H, s), 3.79 (3H, s), 3.74 (1H, s), 3.50−3.36 (2H, m), 2.95 (3H, s), 2.80 (1H, d, $J = 15.6$ Hz), 2.66 (1H, s), 2.54 (1H, m), 2.31 (2H, m), 2.14 (3H, s), 1.36 (1H, m), 1.03 (1H, m), 0.53 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.2 (C), 165.5 (C), 160.6 (C), 158.7 (C), 154.0 (C), 133.1 (CH), 131.4 (CH), 129.6 (CH), 125.5 (C), 123.7 (CH), 122.3 (CH), 119.6 (CH), 119.5 (C), 111.5 (CH), 104.2 (CH), 95.7 (CH), 81.0 (CH), 76.3 (CH), 75.9 (C), 67.4 (CH), 66.3 (CH_2), 55.2 (OCH_3), 54.8 (OCH_3), 51.6 (C), 51.3 (CH_2), 50.3 (CH_2), 44.2 (CH_2), 42.2 (C), 39.1 (CH_3), 31.1 (CH_2), 20.4 (CH_3), 7.1 (CH_3); ESIMS *m/z* 563.3 $[M + 1]^+$.

3-Demethoxycarbonyl-3-(4-methoxylphenylcarbonyloxy)methylvindoline (14a). Compound **14a** was prepared using 4-methoxybenzoyl chloride as starting material. Yield: 62%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.86 (1H, brs), 7.97 (1H, d, $J = 8.7$ Hz), 6.84 (3H, d, $J = 8.7$ Hz), 6.24 (1H, d, $J = 8.7$ Hz), 6.04 (1H, s), 5.81 (1H, dd, $J = 10.5$, 4.5 Hz), 5.32 (1H, d, $J = 10.5$ Hz), 5.07 (1H, s), 4.46 (1H, d, $J = 11.7$ Hz), 4.11 (1H, d, $J = 11.7$ Hz), 3.74 (3H, s), 3.69 (3H, s), 3.66 (1H, s), 3.42−3.30 (2H, m), 2.84 (3H, s), 2.73 (1H, d, $J = 16.2$ Hz), 2.60 (1H, s), 2.43 (1H, m), 2.24 (2H, m), 2.05 (3H, s), 1.28 (1H, m), 1.00 (1H, m), 0.48 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.6 (C), 165.7 (C), 163.2 (C), 160.9 (C), 154.2 (C), 131.5 (2 CH), 130.5 (CH), 125.7 (C), 124.0 (CH), 122.6 (CH), 122.3 (C), 113.5 (2 CH), 104.5 (CH), 96.0 (CH), 82.0 (CH), 76.5 (CH), 76.2 (C), 67.5 (CH), 66.4 (CH_2), 55.1 (2 OCH_3), 52.0 (C), 51.5 (CH_2), 50.5 (CH_2), 44.6 (CH_2), 42.6 (C), 39.7 (CH_3), 31.3 (CH_2), 20.7 (CH_3), 7.4 (CH_3); ESIMS *m/z* 563.3 $[M + 1]^+$.

3-Demethoxycarbonyl-3-(2-chlorophenylcarbonyloxy)methylvindoline (15a). Compound **15a** was prepared using 2-chlorobenzoyl chloride as starting material. Yield: 63%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.79 (1H, brs), 7.79 (1H, d, $J = 7.2$ Hz), 7.29 (2H, m), 7.20 (1H, m), 6.79 (1H, t, $J = 8.1$ Hz), 6.20 (1H, d, $J = 8.1$ Hz), 6.02 (1H, s), 5.78 (1H, dd, $J = 10.5$, 3.6 Hz), 5.29 (1H, d, $J = 10.5$ Hz), 5.01 (1H, s), 4.44(1H, d, $J = 11.4$ Hz), 4.16 (1H, d, $J = 11.4$ Hz), 3.63 (3H, s), 3.61 (1H, s), 3.37−3.24 (2H, m), 2.89 (3H, s), 2.69 (1H, d, $J = 15.9$ Hz), 2.54 (1H, s), 2.39 (1H, m), 2.16 (2H, m), 2.01 (3H, s), 1.25 (1H, m), 0.95 (1H, m), 0.43 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (C), 164.8 (C), 160.8 (C), 154.0 (C), 133.3 (C), 132.3 (CH), 131.3 (CH), 130.7 (CH), 129.8 (CH), 129.7 (C), 126.4 (CH), 125.6 (C), 123.9 (CH), 122.5 (CH), 104.6 (CH), 96.0 (CH), 81.4 (CH), 76.3 (CH), 76.0 (C), 67.5 (CH), 67.0 (CH_2), 54.9 (OCH_3), 51.8 (C), 51.5 (CH_2), 50.6 (CH_2), 44.4 (CH_2), 42.4 (C), 39.8 (CH_3), 31.2 (CH_2), 20.6 (CH_3), 7.3 (CH_3); ESIMS *m/z* 567.3 $[M + 1]^+$.

3-Demethoxycarbonyl-3-(4-chlorophenylcarbonyloxy)methylvindoline (16a). Compound **16a** was prepared using 4-chlorobenzoyl chloride as starting material. Yield: 60%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.85 (1H, brs), 7.92 (2H, d, $J = 7.2$ Hz), 7.29 (2H, d, $J = 7.2$ Hz), 6.82 (1H, d, $J = 8.4$ Hz), 6.22 (1H, d, $J = 8.4$ Hz), 6.02 (1H, s), 5.78 (1H, dd, $J = 10.5$, 3.6 Hz), 5.30 (1H, d, $J = 10.5$ Hz), 5.04 (1H, s), 4.47(1H, d, $J = 11.4$ Hz), 4.13 (1H, d, $J = 11.4$ Hz), 3.65 (3H, s), 3.61 (1H, s), 3.38−3.27 (2H, m), 2.82 (3H, s), 2.71 (1H, d, $J = 15.9$ Hz), 2.59 (1H, s), 2.43 (1H, m), 2.19 (2H, m), 2.02 (3H, s), 1.26 (1H, m), 0.97 (1H, m), 0.46 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (C), 164.9 (C), 160.8 (C), 154.0 (C), 139.0 (C), 130.8 (2 CH), 129.9 (CH), 128.4 (2 CH), 128.4 (C), 125.5 (C), 124.0 (CH), 122.5 (CH), 104.5 (CH), 96.0 (CH), 82.0 (CH), 76.3 (CH), 76.0 (C), 67.4 (CH), 67.0 (CH_2), 55.0 (OCH_3), 52.0 (C), 51.4 (CH_2), 50.7 (CH_2), 44.5 (CH_2), 42.4 (C), 39.8 (CH_3), 31.2 (CH_2), 20.6 (CH_3), 7.3 (CH_3); ESIMS *m/z* 567.3 $[M + 1]^+$.

3-Demethoxycarbonyl-3-(4-nitrophenylcarbonyloxy)methylvindoline (17a). Compound **17a** was prepared using 4-nitrobenzoyl chloride as starting material. Yield: 60%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.88 (1H, brs), 8.14 (4H, s), 6.83 (1H, d, $J = 8.1$ Hz), 6.22 (1H, d, $J = 8.4$ Hz), 6.02 (1H, s), 5.80 (1H, dd, $J = 9.9$, 3.6 Hz), 5.31 (1H, d, $J = 9.9$ Hz), 5.03 (1H, s), 4.51 (1H, d, $J = 11.1$ Hz), 4.18 (1H, d, $J = 11.1$ Hz), 3.65 (3H, s), 3.61 (1H, s), 3.41−3.28 (2H, m), 2.84 (3H, s), 2.74 (1H, d, $J = 16.2$ Hz), 2.61 (1H, s), 2.43 (1H, m), 2.20 (2H, m), 2.02 (3H, s), 1.23 (1H, m), 0.95 (1H, m), 0.45 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (C), 164.0 (C), 160.8 (C), 154.0 (C), 150.2 (C), 135.2 (C), 130.5 (2 CH), 129.8 (CH), 125.4 (C), 124.0 (CH), 123.3 (2 CH), 122.5 (CH), 104.6 (CH), 96.1 (CH), 82.0 (CH), 76.2 (CH), 76.0 (C), 67.3 (CH), 67.2 (CH_2), 55.0 (OCH_3), 52.0 (C), 51.3 (CH_2), 50.5 (CH_2), 44.4 (CH_2), 42.4 (C), 39.9 (CH_3), 31.2 (CH_2), 20.6 (CH_3), 7.2 (CH_3); ESIMS *m/z* 578.3 $[M + 1]^+$.

General Procedure for the Preparation of 18a−22a. A solution of compound **4** (1 mmol) in THF (10 mL) was added to 50% sodium hydroxide solution (2 g) and *n*-$Bu_4N^+I^-$ (36.9 mg, 0.1 mmol). After being stirred at 60 °C for 0.5 h, diverse alkyl halides (2 mmol) were added slowly. The reaction mixture continued stirring for 6 h and was then cooled to room temperature. The mixture was quenched with H_2O (20 mL) and extracted with CH_2Cl_2 (2 × 25 mL). The combined organic extracts were washed with brine and dried over anhydrous Na_2SO_4. Concentration gave a residue that was added to pyridine (1.0 mL) and Ac_2O (1.0 mL) at room temperature. After stirring the reaction mixture for 8 h, saturated $NaHCO_3$ (5 mL) and EtOAc (20 mL) were added, and the organic phase was washed with H_2O (3 × 10 mL) and brine (10 mL), dried, concentrated, and purified by flash chromatography (6:1, hexanes−acetone) to provide a white solid (**18a**−**22a**).

3-Demethoxycarbonyl-3-(ethoxy)methylvindoline (18a). Compound **18a** was prepared using bromoethane as starting material. Yield: 58%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (1H, brs), 6.84 (1H, d, $J = 8.1$ Hz), 6.24 (1H, dd, $J = 8.1$, 2.1 Hz), 6.08 (1H, d, $J = 2.1$ Hz), 5.84 (1H, dd, $J = 10.2$, 4.8 Hz), 5.37 (1H, d, $J = 10.2$ Hz), 4.97 (1H, s), 3.76 (3H, s), 3.71 (1H, s), 2.93 (3H, s), 2.76 (1H, d, $J = 15.9$ Hz), 2.58 (1H, s), 2.40 (1H, m), 2.11 (3H, s), 1.22 (1H, m), 1.20 (3H, t, $J = 7.2$ Hz), 0.96 (1H, m), 0.50 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C), 161.1 (C), 154.8 (C), 130.4 (CH), 126.2 (C), 124.2 (CH), 122.7 (CH), 104.3 (CH), 96.0 (CH), 80.9 (CH), 77.6 (C), 77.6 (CH), 72.7 (CH_2), 68.0 (CH), 66.8 (CH_2), 55.4 (OCH_3), 52.0 (C), 52.0 (CH_2), 50.9 (CH_2), 44.8 (CH_2), 42.6 (C), 39.1 (CH_3), 31.7 (CH_2), 21.1 (CH_3), 15.1 (CH_3), 7.6 (CH_3); ESIMS *m/z* 457.3 $[M + 1]^+$.

3-Demethoxycarbonyl-3-(allyloxy)methylvindoline (19a). Compound **19a** was prepared using allyl bromide as starting material. Yield: 61%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (1H, brs), 6.79 (1H, d, $J =$

8.1 Hz), 6.19 (1H, dd, J = 8.1, 2.1 Hz), 6.03 (1H, d, J = 2.1 Hz), 5.85 (1H, m), 5.79 (1H, dd, J = 10.2, 4.5 Hz), 5.31 (1H, d, J = 10.2 Hz), 5.17 (1H, d, J = 17.1 Hz), 5.07 (1H, d, J = 10.2 Hz), 4.92 (1H, s), 3.96 (2H, m), 3.70 (3H, s), 3.64 (1H, s), 2.89 (3H, s), 2.72 (1H, d, J = 15.0 Hz), 2.52(1H, s), 2.40 (1H, m), 2.04 (3H, s), 1.15 (1H, m), 0.91 (1H, m), 0.45 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 171.0 (C), 161.1 (C), 154.8 (C), 135.0 (CH), 130.4 (CH), 126.2 (C), 124.3 (CH), 122.8 (CH), 117.3 (CH_2), 104.5 (CH), 96.1 (CH), 81.0 (CH), 78.0 (C), 77.6 (CH), 72.8 (CH_2), 72.5 (CH_2), 68.1 (CH), 55.4 (OCH_3), 52.0 (C), 52.0 (CH_2), 51.0 (CH_2), 44.8 (CH_2), 42.7 (C), 39.4 (CH_3), 31.7 (CH_2), 21.1 (CH_3), 7.7 (CH_3); ESIMS m/z 469.3 [M + 1]$^+$.

3-Demethoxycarbonyl-3-(propyloxy)methylvindoline (20a). Compound **20a** was prepared using 1-bromopropane as starting material. Yield: 51%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (1H, brs), 6.86 (1H, d, J = 8.1 Hz), 6.26 (1H, dd, J = 8.1, 2.1 Hz), 6.10 (1H, d, J = 2.1 Hz), 5.87 (1H, dd, J = 10.5, 4.8 Hz), 5.38 (1H, d, J = 10.5 Hz), 5.00 (1H, s), 3.79 (3H, s), 3.72 (1H, s), 3.52−3.26 (6H, m), 2.95 (3H, s), 2.77 (1H, d, J = 15.9 Hz), 2.58 (1H, s), 2.50−2.40 (1H, m), 2.31−2.19 (2H, m), 2.12 (3H, s), 1.73−1.55 (2H, m), 1.32−1.20 (1H, m), 1.05−0.95 (1H, m), 0.89 (3H, t, J = 7.2 Hz), 0.51 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.4 (C), 160.7 (C), 154.3 (C), 130.0 (CH), 125.9 (C), 123.7 (CH), 122.3 (CH), 103.9 (CH), 95.6 (CH), 80.5 (CH), 77.1 (CH), 76.9 (C), 73.1 (CH_2), 72.7 (CH_2), 67.7 (CH), 54.9 (OCH_3), 51.6 (CH_2), 51.5 (C), 50.5 (CH_2), 44.4 (CH_2), 42.2 (C), 38.7 (CH_3), 31.3 (CH_2), 22.4 (CH_2), 20.7 (CH_3), 10.5 (CH_3), 7.2 (CH_3); ESIMS m/z 471.2 [M + 1]$^+$.

3-Demethoxycarbonyl-3-(butyloxy)methylvindoline (21a). Compound **21a** was prepared using 1-bromobutane as starting material. Yield: 56%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.80 (1H, brs), 6.83 (1H, d, J = 8.1 Hz), 6.22 (1H, dd, J = 8.1, 2.4 Hz), 6.06 (1H, d, J = 2.4 Hz), 5.81 (1H, dd, J = 10.2, 4.8 Hz), 5.37 (1H, d, J = 10.2 Hz), 4.96 (1H, s), 3.74 (3H, s), 3.68 (1H, s), 2.90 (3H, s), 2.74 (1H, d, J = 16.2 Hz), 2.54 (1H, s), 2.40 (1H, m), 2.09 (3H, s), 1.54 (1H, m), 0.92 (1H, m), 0.85 (3H, t, J = 7.2 Hz), 0.48 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (C), 161.0 (C), 154.6 (C), 130.3 (CH), 126.2 (C), 124.1 (CH), 122.6 (CH), 104.2 (CH), 95.9 (CH), 80.8 (CH), 77.5 (C), 77.3 (CH), 73.0 (CH_2), 71.6 (CH_2), 68.1 (CH), 53.3 (OCH_3), 52.0 (CH_2), 52.9 (C), 50.8 (CH_2), 44.7 (CH_2), 42.5 (C), 39.0 (CH_3), 31.6 (CH_2), 21.0 (CH_3), 19.5 (CH_2), 14.0(CH_2), 15.1 (CH_3), 7.6 (CH_3); ESIMS m/z 485.4 [M + 1]$^+$.

3-Demethoxycarbonyl-3-(4-methoxylbenzyloxy)methylvindoline (22a). Compound **22a** was prepared using 4-methoxybenzyl bromide as starting material. Yield: 65%; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (2H, d, J = 8.1 Hz), 6.85 (1H, d, J = 8.1 Hz), 6.70 (2H, d, J = 8.1 Hz), 6.25 (1H, d, J = 8.1 Hz), 6.09 (1H, s), 5.51 (1H, dd, J = 10.2, 4.2 Hz), 5.36 (1H, d, J = 10.2 Hz), 4.98 (1H, s), 4.58 (2H, q, J = 11.7 Hz), 3.74 (6H, s), 3.54 (1H, s), 3.51−3.32 (4H, m), 2.93 (3H, s), 2.77 (1H, d, J = 16.2 Hz), 2.58 (1H, s), 2.44 (1H, m), 2.26 (2H, m), 2.04 (3H, s), 1.25 (1H, m), 0.93 (1H, m), 0.50 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 170.9 (C), 161.1 (C), 160.0 (C), 154.6 (C), 130.7 (CH), 130.1 (C), 128.5 (2 CH), 125.9 (C), 124.5 (CH), 123.1 (CH), 114.2 (2CH), 105.8 (CH), 97.2 (CH), 81.0 (CH), 78.0 (C), 77.6 (CH), 72.8 (CH_2), 72.5 (CH_2), 67.5 (CH), 55.7 (2OCH_3), 52.0 (C), 51.8 (CH_2), 45.2 (CH_2), 44.3 (CH_2), 43.2 (C), 40.3 (CH_3), 31.6 (CH_2), 21.3 (CH_3), 7.8 (CH_3); ESIMS m/z 549.3 [M + 1]$^+$.

General Procedure for the Preparation of 5b−22b. Catharanthine tartrate (486 mg, 1 mmol) and anhydrous ferric chloride (486 mg, 3 mmol) were combined in a mixture of glycine buffer (containing 320 mg of glycine and 250 mg of sodium chloride in 40 mL of water), along with hydrochloride acid (40 mL, 0.1 N), under a nitrogen atmosphere. After 10 min of stirring at room temperature, compounds **5a**−**22a** (1 mmol) were added individually. After 8 h of stirring at room temperature, sodium borohydride (80 mg) in ammonium hydroxide (8 mL) was added dropwise at 0 °C and left to react for 15 min. The reaction mixture was extracted with CH_2Cl_2 (4 × 20 mL), and the organic phase was filtered with Celite and concentrated at reduced pressure, then the residue was followed by column chromatography on silica gel (100:1, $CHCl_3$−MeOH) to afford each compound (**5b**−**22b**) as a white solid in over 50% yield.

3-Demethoxycarbonyl-3-(methylcarbonyloxy)methylanhydrovinblastine (5b): $[\alpha]^{20}_D$ +54.0 (c 0.10, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.25 (1H, s), 8.06 (1H, s), 7.48 (1H, d, J = 7.2 Hz), 7.10 (3H, m), 6.59 (1H, s), 6.17 (1H, s), 5.86 (1H, dd, J = 10.2, 4.5 Hz), 5.41 (1H, d, J = 10.2 Hz), 5.40 (1H, s), 5.02 (1H, s), 4.16 (1H, d, J = 11.7 Hz), 4.12 (1H, d, J = 11.7 Hz), 3.79 (3H, s), 3.58 (3H, s), 2.89 (3H, s), 2.59 (1H, s), 2.15 (3H, s), 2.10 (3H, s), 1.43 (1H, m), 1.21 (1H, m), 0.96 (3H, t, J = 7.5 Hz), 0.79 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.7 (C), 170.9 (C), 170.7 (C), 157.7 (C), 153.3 (C), 139.7 (C), 134.9 (C), 130.8 (C), 129.5 (CH), 129.3 (C), 124.6 (CH), 123.8 (CH), 123.5 (CH), 123.5 (C), 122.2 (CH), 121.3 (C), 118.8 (CH), 118.3 (CH), 117.2 (C), 110.4 (CH), 94.6 (CH), 81.5 (CH), 76.6 (CH), 76.0 (C), 66.3 (CH_2), 66.0 (CH), 55.7 (OCH_3), 55.3 (C), 54.4 (CH_2), 52.4 (OCH_3), 52.3 (CH_2), 51.9 (C), 50.1 (CH_2), 49.9 (CH_2), 45.7 (CH_2), 44.9 (CH_2), 42.3 (C), 39.9 (CH_3), 34.2 (CH_2), 32.8 (CH), 31.4 (CH_2), 27.7 (CH_2), 25.4 (CH_2), 21.0 (CH_3), 20.9 (CH_3), 12.2 (CH_3), 8.2 (CH_3); ESIMS m/z 807.5 [M + 1]$^+$; HRESIMS m/z 807.4337 (calcd for $C_{47}H_{58}N_4O_8$, 807.4333).

3-Demethoxycarbonyl-3-(ethylcarbonyloxy)methylanhydrovinblastine (6b): $[\alpha]^{20}_D$ +55.1 (c 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.13 (1H, s), 8.03 (1H, s), 7.53 (1H, d, J = 7.5 Hz), 7.14 (3H, m), 6.61 (1H, s), 6.18 (1H, s), 5.89 (1H, dd, J = 10.5, 4.5 Hz), 5.51 (1H, d, J = 6.0 Hz), 5.43 (1H, d, J = 10.5 Hz), 5.06 (1H, s), 4.23 (1H, d, J = 11.4 Hz), 4.02 (1H, d, J = 11.4 Hz), 3.83 (3H, s), 3.65 (3H, s), 2.92 (3H, s), 2.64 (1H, s), 2.42 (2H, q, J = 7.8 Hz), 2.19 (3H, s), 1.95 (2H, q, J = 7.5 Hz), 1.43 (1H, m), 1.21 (1H, m), 1.16 (3H, t, J = 7.8 Hz), 1.01 (3H, t, J = 7.5 Hz), 0.82 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (C), 174.2 (C), 171.1 (C), 158.0 (C), 153.5 (C), 140.0 (C), 135.1 (C), 131.1 (C), 129.7 (CH), 129.5 (C), 124.7 (CH), 124.0 (CH), 123.8 (C), 123.7 (CH), 122.4 (CH), 121.5 (C), 119.0 (CH), 118.4 (CH), 117.4 (C), 110.5 (CH), 94.8 (CH), 81.8 (CH), 76.9 (CH), 76.2 (C), 66.4 (CH), 66.3 (CH_2), 55.9 (OCH_3), 55.6 (C), 54.6 (CH_2), 52.6 (C), 52.4 (OCH_3), 52.3 (CH_2), 50.4 (CH_2), 50.2 (CH_2), 46.0 (CH_2), 45.1 (CH_2), 42.6 (C), 40.0 (CH_3), 34.5 (CH_2), 33.0 (CH), 31.6 (CH_2), 27.9 (CH_2), 27.6 (CH_2), 25.8 (CH_2), 21.1 (CH_3), 12.4 (CH_3), 9.2 (CH_3), 8.4 (CH_3); ESIMS m/z 821.5 [M + 1]$^+$; HRESIMS m/z 821.4484 (calcd for $C_{48}H_{60}N_4O_8$, 821.4489).

3-Demethoxycarbonyl-3-(isopropylcarbonyloxy)methylanhydrovinblastine (7b): $[\alpha]^{20}_D$ +60.0 (c 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.00 (1H, s), 8.02 (1H, s), 7.52 (1H, d, J = 7.5 Hz), 7.13 (3H, m), 6.61 (1H, s), 6.17 (1H, s), 5.85 (1H, dd, J = 10.2, 6.3 Hz), 5.49 (1H, d, J = 6.0 Hz), 5.41 (1H, d, J = 10.2 Hz), 5.05 (1H, s), 4.24 (1H, d, J = 11.4 Hz), 3.99 (1H, d, J = 11.4 Hz), 3.82 (3H, s), 3.64 (3H, s), 2.92 (3H, s), 2.59 (1H, s), 2.17 (3H, s), 1.94 (2H, q, J = 7.5 Hz), 1.47 (1H, m), 1.21 (1H, m), 1.19 (6H, d, J = 5.1 Hz), 1.00 (3H, t, J = 7.5 Hz), 0.81 (3H, t, J = 7.2 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 176.8 (C), 174.5 (C), 171.1 (C), 157.8 (C), 153.7 (C), 137.9 (C), 135.0 (C), 130.9 (C), 129.6 (CH), 129.0 (C), 124.7 (CH), 124.1 (C), 124.0 (CH), 123.5 (CH), 122.8 (CH), 120.5 (C), 119.4 (CH), 118.2 (CH), 115.6 (C), 110.6 (CH), 94.6 (CH), 81.6 (CH), 76.7 (CH), 76.1 (C), 66.4 (CH), 65.9 (CH_2), 55.8 (OCH_3), 55.3 (C), 54.4 (CH_2), 52.5 (OCH_3), 52.4 (C), 51.0 (CH_2), 50.4 (CH_2), 50.2 (CH_2), 45.5 (CH_2), 45.2 (CH_2), 42.5 (C), 39.7 (CH_3), 34.2 (CH_2), 33.9 (CH), 31.6 (CH), 31.5 (CH_2), 27.8 (CH_2), 23.4 (CH_2), 21.0 (CH_3), 19.1 (CH_3), 18.9 (CH_3), 11.9 (CH_3), 8.3 (CH_3); ESIMS m/z 835.5 [M + 1]$^+$; HRESIMS m/z 835.4653 (calcd for $C_{49}H_{62}N_4O_8$, 835.4646).

3-Demethoxycarbonyl-3-(*tert*-butylcarbonyloxy)methylanhydrovinblastine (8b): $[\alpha]^{20}_D$ +58.1 (c 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.86 (1H, s), 8.21 (1H, s), 7.44 (1H, d, J = 7.8 Hz), 7.28 (1H, d, J = 7.8 Hz), 6.99 (3H, m), 6.47 (1H, s), 6.30 (1H, s), 5.73 (1H, dd, J = 10.2, 4.5 Hz), 5.45 (2H, m), 4.82 (1H, s), 4.11 (1H, d, J = 11.4 Hz), 3.78 (3H, s), 3.70 (1H, d, J = 11.4 Hz), 3.57 (3H, s), 2.93 (3H, s), 2.70 (1H, s), 2.08 (3H, s), 1.15 (9H, s), 0.96 (3H, t, J = 7.5 Hz), 0.66 (3H, t, J = 6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 177.1 (C), 173.9 (C), 170.7 (C), 157.4 (C), 153.5 (C), 137.1 (C), 135.7 (C), 131.3 (C), 130.5 (CH), 128.4 (C), 124.5 (CH), 123.7 (CH), 123.7 (CH), 123.7 (C), 121.2 (CH), 120.3 (C), 118.5 (CH), 117.7 (CH), 113.2 (C), 112.0 (CH), 94.6 (CH), 81.5 (CH), 76.2 (CH), 75.9 (C), 64.5 (CH_2), 64.0 (CH), 56.2 (OCH_3), 55.0 (C), 53.7 (CH_2), 52.4 (OCH_3), 52.3 (CH_2), 52.3 (C), 49.6 (CH_2), 48.9 (CH_2), 45.5 (CH_2), 45.2 (CH_2), 42.0 (C), 39.9 (CH_3), 38.5 (C), 34.7 (CH_2), 31.5 (CH), 30.5 (CH_2), 27.2 (CH_2), 27.0 (3CH_3), 21.1 (CH_2), 20.8 (CH_3), 11.6 (CH_3), 7.9 (CH_3); ESIMS m/z 849.5 [M + 1]$^+$; HRESIMS m/z 849.4809 (calcd for $C_{50}H_{64}N_4O_8$, 849.4802).

3-Demethoxycarbonyl-3-(isobutylcarbonyloxy)methylanhydrovinblastine (9b): $[\alpha]^{20}_D$ +62.1 (c 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (1H, s), 8.02 (1H, s), 7.53 (1H, d, J = 7.5 Hz), 7.14 (3H, m), 6.62 (1H, s), 6.18 (1H, s), 5.88 (1H, dd, J = 10.2, 6.3 Hz),

5.48 (1H, d, $J = 6.0$ Hz), 5.43 (1H, d, $J = 10.2$ Hz), 5.06 (1H, s), 4.25 (1H, d, $J = 11.7$ Hz), 4.00 (1H, d, $J = 11.7$ Hz), 3.83 (3H, s), 3.62 (3H, s), 2.92 (3H, s), 2.60 (1H, s), 2.19 (3H, s), 1.94 (2H, q, $J = 7.5$ Hz), 1.47 (1H, m), 1.21 (1H, m), 1.01 (3H, t, $J = 7.5$ Hz), 0.97 (6H, d, $J = 6.6$ Hz), 0.82 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.6 (C), 172.7 (C), 171.0 (C), 157.8 (C), 153.5 (C), 139.3 (C), 135.0 (C), 130.9 (C), 129.6 (CH), 129.3 (C), 124.6 (CH), 123.9 (C), 123.9 (CH), 123.6 (CH), 122.4 (CH), 121.1 (C), 119.0 (CH), 118.3 (CH), 116.7 (C), 110.4 (CH), 94.6 (CH), 81.6 (CH), 76.7 (CH), 76.1 (C), 66.3 (CH), 65.9 (CH_2), 55.8 (OCH_3), 55.4 (C), 54.4 (CH_2), 52.4 (OCH_3), 52.4 (C), 51.8 (CH_2), 50.3 (CH_2), 50.1 (CH_2), 45.8 (CH_2), 45.1 (CH_2), 43.2 (CH_2), 42.5 (C), 39.9 (CH_3), 34.3 (CH_2), 32.5 (CH), 31.5 (CH_2), 27.8 (CH_2), 25.5 (CH), 25.0 (CH_2), 22.4 (CH_3), 22.3 (CH_3), 21.0 (CH_3), 12.2 (CH_3), 8.2 (CH_3); ESIMS *m/z* 849.5 $[M + 1]^+$; HRESIMS *m/z* 849.4807 (calcd for $C_{50}H_{64}N_4O_8$, 849.4802).

3-Demethoxycarbonyl-3-(cyclopropylcarbonyloxy)methylanhydrovinblastine (10b): $[\alpha]^{20}_D$ +60.0 (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.14 (1H, s), 8.03 (1H, s), 7.53 (1H, d, $J = 7.8$ Hz), 7.14 (3H, m), 6.62 (1H, s), 6.19 (1H, s), 5.89 (1H, dd, $J = 10.2$, 3.9 Hz), 5.51 (1H, d, $J = 6.0$ Hz), 5.44 (1H, d, $J = 10.2$ Hz), 5.06 (1H, s), 4.24 (1H, d, $J = 11.4$ Hz), 4.02 (1H, d, $J = 11.4$ Hz), 3.84 (3H, s), 3.65 (1H, s), 3.63 (3H, s), 2.94 (3H, s), 2.62 (1H, s), 2.18 (3H, s), 1.94 (2H, q, $J = 7.5$ Hz), 1.47 (1H, m), 1.21 (1H, m), 1.01 (5H, t, $J = 7.5$ Hz), 0.86 (2H, t, $J = 7.5$ Hz), 0.82 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (C), 174.8 (C), 171.8 (C), 157.9 (C), 153.5 (C), 139.8 (C), 135.0 (C), 130.9 (C), 129.7 (CH), 129.4 (C), 124.6 (CH), 123.9 (CH), 123.7 (CH), 123.6 (C), 122.3 (CH), 121.3 (C), 118.9 (CH), 118.4 (CH), 117.3 (C), 110.5 (CH), 94.7 (CH), 81.7 (CH), 76.8 (CH), 76.0 (C), 66.4 (CH_2), 66.3 (CH), 55.8 (OCH_3), 55.5 (C), 54.5 (CH_2), 52.5 (C), 52.4 (OCH_3), 52.0 (CH_2), 50.3 (CH_2), 50.1 (CH_2), 45.8 (CH_2), 45.1 (CH_2), 42.5 (C), 40.0 (CH_3), 34.4 (CH_2), 32.9 (CH), 31.5 (CH_2), 27.9 (CH_2), 25.4 (CH_2), 20.9 (CH_3), 12.8 (CH), 12.3 (CH_3), 8.7 (CH_2), 8.6 (CH_2), 8.3 (CH_3); ESIMS *m/z* 833.5 $[M + 1]^+$; HRESIMS *m/z* 833.4483 (calcd for $C_{49}H_{60}N_4O_8$, 833.4489).

3-Demethoxycarbonyl-3-(benzylcarbonyloxy)methylanhydrovinblastine (11b): $[\alpha]^{20}_D$ +63.1 (*c* 0.21, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.11 (1H, s), 8.03 (1H, s), 7.53 (1H, d, $J = 7.5$ Hz), 7.29 (5H, m), 7.14 (3H, m, 3 H), 6.62 (1H, s), 6.11 (1H, s), 5.88 (1H, dd, $J = 10.2$, 4.5 Hz), 5.46 (2H, m), 5.04 (1H, s), 4.32 (1H, d, $J = 11.4$ Hz), 3.96 (1H, d, $J = 11.4$ Hz), 3.82 (3H, s), 3.72 (2H, s), 3.61 (3H, s), 3.44 (1H, s), 2.60 (3H, s), 2.59 (1H, s), 2.17 (3H, s), 1.94 (2H, q, $J = 7.5$ Hz), 1.43 (1H, m), 1.21 (1H, m), 1.01 (3H, t, $J = 7.5$ Hz), 0.83 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (C), 171.1 (C), 171.0 (C), 157.9 (C), 153.5 (C), 140.1 (C), 135.0 (C), 134.0 (C), 131.0 (C), 129.7 (CH), 129.5 (2CH), 128.5 (2CH), 127.0 (CH), 127.0 (C), 124.7 (CH), 123.9 (CH), 123.6 (CH), 123.6 (C), 122.3 (CH), 121.4 (C), 118.9 (CH), 118.4 (CH), 117.4 (C), 110.5 (CH), 94.7 (CH), 81.6 (CH), 76.7 (CH), 76.2 (C), 66.4 (CH_2), 66.2 (CH), 55.8 (OCH_3), 55.5 (C), 54.5 (CH_2), 52.5 (OCH_3), 52.4 (CH_2), 52.3 (C), 50.2 (CH_2), 50.1 (CH_2), 46.0 (CH_2), 45.1 (CH_2), 42.5 (C), 41.4 (CH_2), 39.7 (CH_3), 34.4 (CH_2), 33.0 (CH), 31.6 (CH_2), 27.8 (CH_2), 25.9 (CH_2), 21.0 (CH_3), 12.4 (CH_3), 8.3 (CH_3); ESIMS *m/z* 883.5 $[M + 1]^+$; HRESIMS *m/z* 883.4642 (calcd for $C_{53}H_{62}N_4O_8$, 883.4646).

3-Demethoxycarbonyl-3-(phenylcarbonyloxy)methylanhydrovinblastine (12b): $[\alpha]^{20}_D$ +57.1 (*c* 0.20, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.12 (1H, s), 8.09 (2H, d, $J = 6.9$ Hz), 8.06 (1H, s), 7.55 (2H, m), 7.45 (1H, d, $J = 7.2$ Hz), 7.44 (1H, t, $J = 7.2$ Hz), 7.15 (3H, m), 6.65 (1H, s), 6.17 (1H, s), 5.90 (1H, dd, $J = 10.2$, 4.5 Hz), 5.48 (1H, d, $J = 9.6$ Hz), 5.45 (1H, d, $J = 10.2$ Hz), 5.18 (1H, s), 4.56 (1H, d, $J = 11.4$ Hz), 4.20 (1H, d, $J = 11.4$ Hz), 3.88 (3H, s), 3.73 (1H, s), 3.65 (3H, s), 2.96 (3H, s), 2.65 (1H, s), 2.18 (3H, s), 1.94 (2H, q, $J = 7.5$ Hz), 1.43 (1H, m), 1.21 (1H, m), 1.00 (3H, t, $J = 7.5$ Hz), 0.84 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (C), 171.2 (C), 166.3 (C), 158.0 (C), 153.6 (C), 140.0 (C), 135.2 (C), 133.2 (CH), 131.1 (C), 131.0 (C), 130.2 (C), 129.9 (3CH), 129.6 (C), 128.5 (2CH), 124.8 (CH), 124.0 (CH), 123.9 (CH), 122.4 (CH), 121.5 (C), 119.0 (CH), 118.5 (CH), 117.5 (C), 110.6 (CH), 94.6 (CH), 82.4 (CH), 76.9 (CH), 76.4 (C), 66.7 (CH_2), 66.4 (CH), 56.0 (OCH_3), 55.6 (C), 54.6 (CH_2), 52.5 (OCH_3), 52.2 (CH_2), 52.2 (C), 50.4 (CH_2), 50.3 (CH_2), 46.0 (CH_2), 45.4 (CH_2), 42.7 (C), 40.1 (CH_3), 34.5 (CH_2), 33.0 (CH), 31.7 (CH_2), 28.0 (CH_2), 25.7 (CH_2), 21.2 (CH_3), 12.4 (CH_3), 8.4 (CH_3); ESIMS *m/z* 869.5 $[M + 1]^+$; HRESIMS *m/z* 869.4485 (calcd for $C_{52}H_{60}N_4O_8$, 869.4489).

3-Demethoxycarbonyl-3-(2-methoxylphenylcarbonyloxy)methylanhydrovinblastine (13b): $[\alpha]^{20}_D$ +63.0 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.07 (1H, s), 8.05 (1H, s), 7.87 (1H, d, $J = 7.8$ Hz), 7.53 (1H, d, $J = 7.2$ Hz), 7.46 (1H, t, $J = 7.8$ Hz), 7.14 (3H, m), 7.00 (1H, t, $J = 7.8$ Hz), 6.95 (1H, d, $J = 7.8$ Hz), 6.63 (1H, s), 6.17 (1H, s), 5.88 (1H, dd, $J = 10.2$, 4.5 Hz), 5.48 (1H, d, $J = 9.3$ Hz), 5.44 (1H, d, $J = 10.2$ Hz), 5.14 (1H, s), 4.50 (1H, d, $J = 11.4$ Hz), 4.18 (1H, d, $J = 11.4$ Hz), 3.85 (3H, s), 3.82 (3H, s), 3.71 (1H, s), 3.62 (3H, s), 2.99 (3H, s), 2.62 (1H, s), 2.18 (3H, s), 1.95 (2H, q, $J = 7.5$ Hz), 1.43 (1H, m), 1.21 (1H, m), 1.00 (3H, t, $J = 7.5$ Hz), 0.83 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (C), 171.2 (C), 166.0 (C), 159.3 (C), 158.0 (C), 153.7 (C), 140.1 (C), 135.1 (C), 133.7 (CH), 132.1 (CH), 131.1 (2 C), 129.8 (CH), 129.6 (C), 124.7 (CH), 124.0 (CH), 123.8 (CH), 122.4 (CH), 121.3 (C), 120.2 (CH), 120.0 (C), 119.0 (CH), 118.5 (CH), 117.4 (C), 112.0 (CH), 110.6 (CH), 94.6 (CH), 82.0 (CH), 76.9 (CH), 76.4 (C), 66.5 (CH_2), 66.5 (CH), 56.0 (OCH_3), 55.9 (OCH_3), 55.6 (C), 54.6 (CH_2), 52.6 (C), 52.5 (OCH_3), 52.3 (CH_2), 50.4 (CH_2), 50.2 (CH_2), 46.0 (CH_2), 45.3 (CH_2), 42.7 (C), 39.7 (CH_3), 34.5 (CH_2), 33.0 (CH), 31.7 (CH_2), 28.0 (CH_2), 25.8 (CH_2), 21.2 (CH_3), 12.4 (CH_3), 8.4 (CH_3); ESIMS *m/z* 899.5 $[M + 1]^+$; HRESIMS *m/z* 899.4591 (calcd for $C_{53}H_{62}N_4O_9$, 899.4595).

3-Demethoxycarbonyl-3-(4-methoxylphenylcarbonyloxy)methylanhydrovinblastine (14b): $[\alpha]^{20}_D$ +60.1 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (1H, s), 8.06 (1H, s), 8.04 (2H, d, $J = 8.7$ Hz), 7.53 (1H, d, $J = 7.8$ Hz), 7.14 (3H, m), 6.92 (2H, d, $J = 8.7$ Hz), 6.64 (1H, s), 6.15 (1H, s), 5.89 (1H, dd, $J = 10.5$, 4.5 Hz), 5.47 (1H, d, $J = 9.6$ Hz), 5.44 (1H, d, $J = 10.5$ Hz), 5.18 (1H, s), 4.51 (1H, d, $J = 11.4$ Hz), 4.16 (1H, d, $J = 11.4$ Hz), 3.85 (3H, s), 3.82 (3H, s), 3.69 (1H, s), 3.63 (3H, s), 2.93 (3H, s), 2.64 (1H, s), 2.17 (3H, s), 1.94 (2H, q, $J = 7.5$ Hz), 1.43 (1H, m), 1.21 (1H, m), 1.00 (3H, t, $J = 7.5$ Hz), 0.83 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.9 (C), 171.2 (C), 166.0 (C), 163.6 (C), 158.0 (C), 153.6 (C), 140.0 (C), 135.1 (C), 132.0 (2 CH), 132.0 (C), 131.4 (C), 129.9 (CH), 129.6 (C), 124.8 (CH), 124.0 (CH), 123.9 (CH), 122.6 (C), 122.4 (CH), 121.4 (C), 119.0 (CH), 118.5 (CH), 117.4 (C), 113.8 (2 CH), 110.6 (CH), 94.6 (CH), 82.5 (CH), 76.9 (CH), 76.4 (C), 66.5 (CH_2), 66.4 (CH), 56.0 (OCH_3), 55.6 (C), 55.5 (OCH_3), 54.6 (CH_2), 52.8 (C), 52.5 (OCH_3), 52.3 (CH_2), 50.5 (CH_2), 50.3 (CH_2), 46.0 (CH_2), 45.4 (CH_2), 42.8 (C), 40.0 (CH_3), 34.5 (CH_2), 33.0 (CH), 31.7 (CH_2), 28.0 (CH_2), 25.8 (CH_2), 21.2 (CH_3), 12.4 (CH_3), 8.5 (CH_3); ESIMS *m/z* 899.5 $[M + 1]^+$; HRESIMS *m/z* 899.4597 (calcd for $C_{53}H_{62}N_4O_9$, 899.4595).

3-Demethoxycarbonyl-3-(2-chlorophenylcarbonyloxy)methylanhydrovinblastine (15b): $[\alpha]^{20}_D$ +64.1 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.10 (1H, s), 8.05 (1H, s), 7.89 (1H, d, $J = 6.6$ Hz), 7.53 (1H, d, $J = 7.2$ Hz), 7.42 (2H, d, $J = 7.8$ Hz), 7.31 (1H, t, $J = 7.8$ Hz), 7.14 (3H, m), 6.63 (1H, s), 6.18 (1H, s), 5.89 (1H, dd, $J = 10.2$, 4.5 Hz), 5.48 (1H, d, $J = 9.3$ Hz), 5.45 (1H, d, $J = 10.2$ Hz), 5.14 (1H, s), 4.52 (1H, d, $J = 11.4$ Hz), 4.26 (1H, d, $J = 11.4$ Hz), 3.82 (3H, s), 3.68 (1H, s), 3.62 (3H, s), 3.00 (3H, s), 2.62 (1H, s), 2.19 (3H, s), 1.94 (2H, q, $J = 7.5$ Hz), 1.50 (1H, m), 1.29 (1H, m), 1.00 (3H, t, $J = 7.5$ Hz), 0.83 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$)δ 174.9 (C), 171.2 (C), 165.3 (C), 158.0 (C), 153.6 (C), 140.1 (C), 135.1 (C), 133.9 (C), 132.7 (CH), 131.7 (CH), 131.2 (CH), 131.1 (C), 130.1 (C), 129.8 (CH), 129.6 (C), 126.7 (CH), 124.8 (CH), 124.0 (CH), 123.8 (CH), 122.4 (CH), 121.5 (2C), 119.0 (CH), 118.5 (CH), 117.4 (C), 110.6 (CH), 94.7 (CH), 82.0 (CH), 76.8 (CH), 76.3 (C), 67.2 (CH_2), 66.4 (CH), 56.0 (OCH_3), 55.6 (C), 54.6 (CH_2), 52.7 (C), 52.5 (OCH_3), 52.2 (CH_2), 50.4 (CH_2), 50.2 (CH_2), 46.0 (CH_2), 45.3 (CH_2), 42.7 (C), 40.2 (CH_3), 34.5 (CH_2), 33.0 (CH), 31.7 (CH_2), 28.0 (CH_2), 25.7 (CH_2), 21.2 (CH_3), 12.4 (CH_3), 8.4 (CH_3); ESIMS *m/z* 903.5 $[M + 1]^+$; HRESIMS *m/z* 903.4106 (calcd for $C_{52}H_{60}ClN_4O_8$, 903.4100).

3-Demethoxycarbonyl-3-(2-chlorophenylcarbonyloxy)methylanhydrovinblastine (16b): $[\alpha]^{20}_D$ +64.0 (*c* 0.30, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.15 (1H, s), 8.06 (1H, s), 8.02 (2H, d, $J = 8.4$ Hz), 7.53 (1H, d, $J = 7.5$ Hz), 7.41 (2H, d, $J = 8.4$ Hz), 7.14 (3H, m), 6.65 (1H, s), 6.16 (1H, s), 5.89 (1H, dd, $J = 10.2$, 4.5 Hz), 5.48 (1H, d, $J = 8.4$ Hz), 5.44 (1H, d, $J = 10.2$ Hz), 5.17 (1H, s), 4.54 (1H, d, $J = 11.7$ Hz), 4.20 (1H, d, $J = 11.7$ Hz), 3.82 (3H, s), 3.66 (1H, s), 3.64 (3H, s), 2.93 (3H, s), 2.65 (1H, s), 2.17 (3H, s), 1.94 (2H, q, $J = 7.5$ Hz), 1.53 (1H, m), 1.29 (1H, m), 0.98 (3H, t, $J = 7.5$ Hz), 0.84 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$)δ 174.9 (C), 171.2 (C), 165.5 (C), 158.1 (C), 153.5 (C), 140.1 (C), 139.6 (C), 135.2 (C), 131.3 (2 CH), 131.3 (C), 131.1 (C), 129.8 (CH), 129.6 (C), 128.9 (2 CH), 128.6 (C), 124.8 (CH), 124.0 (CH), 123.9 (CH), 122.4 (CH), 121.6

(C), 119.0 (CH), 118.5 (CH), 117.5 (C), 110.6 (CH), 94.6 (CH), 82.6 (CH), 76.8 (CH), 76.4 (C), 67.8 (CH_2), 66.3 (CH), 56.0 (OCH_3), 55.6 (C), 54.6 (CH_2), 52.8 (C), 52.5 (OCH_3), 52.2 (CH_2), 50.4 (CH_2), 50.2 (CH_2), 46.0 (CH_2), 45.4 (CH_2), 42.7 (C), 40.2 (CH_3), 34.5 (CH_2), 33.0 (CH), 31.7 (CH_2), 28.0 (CH_2), 25.8 (CH_2), 21.2 (CH_3), 12.4 (CH_3), 8.4 (CH_3); ESIMS *m/z* 903.5 $[M + 1]^+$; HRESIMS *m/z* 903.4104 (calcd for $C_{52}H_{60}ClN_4O_8$, 903.4100).

3-Demethoxycarbonyl-3-(4-nitrophenylcarbonyloxy)methylanhydrovinblastine (17b): $[\alpha]^{20}_D$ +62.5 (*c* 0.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.18 (1H, s), 8.28 (4H, d, $J = 6.0$ Hz), 8.04 (1H, s), 7.52 (1H, d, $J = 7.5$ Hz), 7.14 (3H, m), 6.61 (1H, s), 6.17 (1H, s), 5.89 (1H, dd, $J = 10.2$, 4.5 Hz), 5.53 (1H, s), 5.44 (1H, d, $J = 10.2$ Hz), 5.17 (1H, s), 4.59 (1H, d, $J = 11.4$ Hz), 4.26 (1H, d, $J = 11.4$ Hz), 3.83 (3H, s), 3.71 (1H, s), 3.65 (3H, s), 2.95 (3H, s), 2.65 (1H, s), 2.18 (3H, s), 1.96 (2H, q, $J = 7.5$ Hz), 1.53 (1H, m), 1.29 (1H, m), 1.01 (3H, t, $J = 7.5$ Hz), 0.83 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 174.8 (C), 171.3 (C), 164.5 (C), 158.1 (C), 153.6 (C), 150.7 (C), 135.6 (C), 135.2 (C), 131.0 (2CH), 131.0 (C), 130.4 (C), 129.7 (CH), 129.7 (C), 129.5 (C), 125.0 (CH), 123.9 (2 CH), 123.8 (2 CH), 122.7 (CH), 121.6 (C), 119.3 (CH), 118.5 (CH), 117.5 (C), 110.7 (CH), 94.8 (CH), 82.6 (CH), 76.7 (CH), 76.4 (C), 67.3 (CH_2), 66.3 (CH), 56.1 (OCH_3), 55.6 (C), 54.6 (CH_2), 54.3 (C), 52.7 (OCH_3), 51.8 (CH_2), 50.4 (CH_2), 50.4 (CH_2), 45.7 (CH_2), 45.4 (CH_2), 42.8 (C), 40.3 (CH_3), 34.4 (CH_2), 32.5 (CH), 31.7 (CH_2), 28.0 (CH_2), 25.8 (CH_2), 21.2 (CH_3), 12.3 (CH_3), 8.5 (CH_3); ESIMS *m/z* 914.5 $[M + 1]^+$; HRESIMS *m/z* 914.4344 (calcd for $C_{52}H_{60}N_5O_{10}$, 914.4340).

3-Demethoxycarbonyl-3-(ethoxy)methylanhydrovinblastine (18b): $[\alpha]^{20}_D$ +53.2 (*c* 0.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.03 (1H, s), 8.02 (1H, s), 7.51 (1H, d, $J = 7.8$ Hz), 7.10 (3H, m), 6.60 (1H, s), 6.16 (1H, s), 5.86 (1H, dd, $J = 10.5$, 4.2 Hz), 5.46 (1H, d, $J = 6.0$ Hz), 5.45 (1H, d, $J = 10.5$ Hz), 5.01 (1H, s), 3.82 (3H, s), 3.70 (1H, s), 3.60 (3H, s), 3.00 (3H, s), 2.58 (1H, s), 2.17 (3H, s), 1.43 (1H, m), 1.22 (3H, t, $J = 6.9$ Hz), 0.99 (3H, t, $J = 7.8$ Hz), 0.81 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1 (C), 171.3 (C), 158.0 (C), 153.9 (C), 140.1 (C), 135.1 (C), 131.3 (C), 129.9 (CH), 129.6 (C), 124.7 (CH), 124.1 (CH), 123.8 (CH), 123.8 (C), 122.4 (CH), 121.3 (C), 119.0 (CH), 118.5 (CH), 117.2 (C), 110.6 (CH), 94.5 (CH), 81.0 (CH), 77.7 (C), 76.8 (CH), 72.4 (CH_2), 66.9 (CH_2), 66.5 (CH), 56.0 (OCH_3), 55.6 (C), 54.6 (CH_2), 52.5 (OCH_3), 52.4 (CH_2), 52.3 (C), 50.5 (CH_2), 50.2 (CH_2), 46.1 (CH_2), 45.2 (CH_2), 42.3 (C), 39.1 (CH_3), 34.6 (CH_2), 33.1 (CH), 31.8 (CH_2), 28.0 (CH_2), 25.8 (CH_2), 21.2 (CH_3), 15.1 (CH_3), 12.4 (CH_3), 8.4 (CH_3); ESIMS *m/z* 793.5 $[M + 1]^+$; HRESIMS *m/z* 793.4538 (calcd for $C_{47}H_{60}N_4O_7$, 793.4540).

3-Demethoxycarbonyl-3-(allyloxy)methylanhydrovinblastine (19b): $[\alpha]^{20}_D$ +57.5 (*c* 0.35, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.01 (1H, s), 8.01 (1H, s), 7.52 (1H, d, $J = 7.8$ Hz), 7.10 (3H, m), 6.60 (1H, s), 6.16 (1H, s), 5.97 (1H, m), 5.86 (1H, dd, $J = 10.2$, 4.5 Hz), 5.46 (1H, d, $J = 6.0$ Hz), 5.45 (1H, d, $J = 10.2$ Hz), 5.24 (1H, d, $J = 17.1$ Hz), 5.14 (1H, d, $J = 10.2$ Hz), 5.02 (1H, s), 4.04 (2H, m), 3.84 (3H, s), 3.61(3H, s), 3.00 (3H, s), 2.59 (1H, s), 2.15 (3H, s), 1.43 (1H, m), 1.21 (1H, m), 1.00 (3H, t, $J = 7.5$ Hz), 0.82 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1 (C), 171.3 (C), 158.0 (C), 154.0 (C), 140.1 (C), 135.2 (C), 135.0 (CH), 131.4 (C), 130.0 (CH), 129.6 (C), 124.8 (CH), 124.2 (CH), 123.9 (CH), 123.9 (C), 122.5 (CH), 121.1 (C), 119.0 (CH), 118.6 (CH), 117.2 (CH_2), 117.2 (C), 110.7 (CH), 94.6 (CH), 81.2 (CH), 77.4 (CH), 77.4 (C), 72.9 (CH_2), 72.2 (CH_2), 66.7 (CH), 56.1 (OCH_3), 55.7 (C), 54.7 (CH_2), 52.5 (OCH_3), 52.5 (CH_2), 52.5 (C), 50.6 (CH_2), 50.3 (CH_2), 46.2 (CH_2), 45.3 (CH_2), 42.6 (C), 39.4 (CH_3), 34.7 (CH_2), 33.2 (CH), 31.9 (CH_2), 28.0 (CH_2), 26.1 (CH_2), 21.2 (CH_3), 12.6 (CH_3), 8.5 (CH_3); ESIMS *m/z* 805.4 $[M + 1]^+$; HRESIMS *m/z* 805.4537 (calcd for $C_{48}H_{60}N_4O_7$, 805.4540).

3-Demethoxycarbonyl-3-(propyloxy)methylanhydrovinblastine (20b): $[\alpha]^{20}_D$ +60.2 (*c* 0.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.00 (1H, s), 8.02 (1H, s), 7.52 (1H, d, $J = 7.5$ Hz), 7.14 (3H, m), 6.58 (1H, s), 6.16 (1H, s), 5.88 (1H, m), 5.86 (1H, dd, $J = 9.6$, 4.5 Hz), 5.51 (1H, d, $J = 6.0$ Hz), 5.45 (1H, d, $J = 9.6$ Hz), 5.03 (1H, s), 3.83 (3H, s), 3.62 (3H, s), 3.01 (3H, s), 2.57 (1H, s), 2.18 (3H, s), 1.96 (2H, q, $J = 7.5$ Hz), 1.43 (1H, m), 1.21 (1H, m), 1.01 (3H, t, $J = 7.5$ Hz), 0.91 (3H, t, $J = 7.2$ Hz), 0.82 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.1 (C), 171.3 (C), 158.0 (C), 153.9 (C), 140.1 (C), 135.2 (C), 131.3 (C), 129.9 (CH), 129.6 (C), 124.7 (CH), 124.1 (CH), 123.9 (CH), 123.8 (C), 122.4 (CH), 121.3 (C), 119.0 (CH), 118.5 (CH), 117.2 (C), 110.6 (CH), 94.5 (CH), 81.0 (CH), 77.7 (C), 76.8 (CH), 72.4 (CH_2), 68.9 (CH_2), 66.5 (CH), 56.0 (OCH_3), 55.6 (C), 54.6 (CH_2), 52.5 (OCH_3), 52.4 (CH_2), 52.3 (C), 50.5 (CH_2), 50.2 (CH_2), 46.1 (CH_2), 45.2 (CH_2), 42.3 (C), 39.1 (CH_3), 34.6 (CH_2), 33.1 (CH), 31.8 (CH_2), 28.0 (CH_2), 25.8 (CH_2), 23.0 (CH_2), 21.2 (CH_3), 12.4 (CH_3), 10.4 (CH_3), 8.4 (CH_3); ESIMS *m/z* 807.5 $[M + 1]^+$; HRESIMS *m/z* 807.4699 (calcd for $C_{48}H_{62}N_4O_7$, 807.4697).

3-Demethoxycarbonyl-3-(butyloxy)methylanhydrovinblastine (21b): $[\alpha]^{20}_D$ +58.0 (*c* 0.30, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$) δ 9.04 (1H, s), 8.01 (1H, s), 7.51 (1H, d, $J = 7.8$ Hz), 7.10 (3H, m), 6.60 (1H, s), 6.16 (1H, s), 5.86 (1H, dd, $J = 10.5$, 4.2 Hz), 5.46 (1H, d, $J = 6$ Hz), 5.45 (1H, d, $J = 10.5$ Hz), 5.02 (1H, s), 3.82 (3H, s), 3.74 (1H, s), 3.60 (3H, s), 3.00 (3H, s), 2.58 (1H, s), 2.17 (3H, s), 1.00 (3H, t, $J = 7.5$ Hz), 0.89 (3H, t, $J = 7.2$ Hz), 0.82 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.0 (C), 171.2 (C), 157.8 (C), 153.8 (C), 140.0 (C), 135.0 (C), 131.2 (C), 129.8 (CH), 129.5 (C), 124.7 (CH), 124.1 (C), 124.0 (CH), 123.7 (CH), 122.3 (CH), 120.8 (C), 118.9 (CH), 118.5 (CH), 117.4 (C), 110.5 (CH), 94.3 (CH), 80.9 (CH), 77.7 (CH), 77.2 (C), 72.6 (CH_2), 71.6 (CH_2), 66.4 (CH), 55.9 (OCH_3), 55.5 (C), 54.5 (CH_2), 52.4 (OCH_3), 52.3 (C), 52.2 (CH_2), 50.5 (CH_2), 50.1 (CH_2), 46.0 (CH_2), 45.2 (CH_2), 42.4 (C), 39.0 (CH_3), 34.5 (CH_2), 33.1 (CH), 31.7 (2 × CH_2), 27.9 (CH_2), 25.8 (CH_2), 21.2 (CH_3), 19.5 (CH_2), 14.0 (CH_3), 12.4 (CH_3), 8.4 (CH_3); ESIMS *m/z* 821.5 $[M + 1]^+$; HRESIMS *m/z* 821.4849 (calcd for $C_{49}H_{64}N_4O_7$, 821.4853).

3-Demethoxycarbonyl-3-(4-methoxylbenzyloxy)methylanhydrovinblastine (22b): $[\alpha]^{20}_D$ +60.1 (*c* 0.30, $CHCl_3$); ^1H NMR (300 MHz, DMSO-d_6) δ 9.76 (1H, s), 8.08 (1H, s), 7.43 (1H, d, $J = 7.2$ Hz), 7.24 (2H, d, $J = 7.8$ Hz), 7.00 (3H, m), 6.91 (2H, d, $J = 7.8$ Hz), 6.56 (1H, s), 6.42 (1H, s), 5.78 (1H, dd, $J = 10.2$, 4.5 Hz), 5.44 (2H, m), 4.77 (1H, s), 4.41 (2H, q, $J = 11.7$ Hz), 3.79 (3H, s), 3.74 (3H, s), 3.58 (3H, s), 2.96 (3H, s), 2.06 (3H, s), 1.43 (1H, m), 1.21 (1H, m), 0.95 (3H, t, $J = 7.5$ Hz), 0.65 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 173.9 (C), 170.7 (C), 158.8 (C), 157.3 (C), 153.7 (C), 137.1 (C), 135.7 (C), 131.4 (C), 130.7 (C), 130.4 (CH), 129.5 (2 CH), 128.5 (C), 124.4 (CH), 123.9 (CH), 123.9 (CH), 123.9 (C), 121.7 (CH), 120.0 (C), 118.6 (CH), 117.8 (CH), 113.7 (2 CH), 113.2 (C), 112.0 (CH), 94.3 (CH), 80.7 (CH), 77.2 (CH), 76.9 (CH_2), 72.6 (CH_2), 71.4 (C), 64.4 (CH), 56.2 (OCH_3), 55.1 (OCH_3), 55.1 (2 C), 53.7 (CH_2), 52.3 (OCH_3), 52.2 (CH_2), 49.6 (CH_2), 48.9 (CH_2), 45.6 (CH_2), 45.2 (CH_2), 42.0 (C), 39.9 (CH_3), 34.7 (CH_2), 31.6 (CH), 30.8 (CH_2), 30.5 (CH_2), 27.2 (CH_2), 20.8 (CH_3), 11.6 (CH_3), 7.9 (CH_3); ESIMS *m/z* 885.5 $[M + 1]^+$; HRESIMS *m/z* 885.4805 (calcd for $C_{53}H_{64}N_4O_8$, 885.4802).

Cytotoxicity Testing. The ditartrates of all compounds were used for bioassays. The human non-small-cell lung cancer (A549) and the cervical epithelial adenocarcinoma (HeLa) cell lines, obtained from American Type Culture Collection (Rockville, MD), were used for the determination of cytotoxicity with a sulforhodamine B (SRB)[9] assay. Briefly, cells were seeded at 6000 cells/well in 96-well plates (Falcon, CA) and allowed to attach overnight. Cells were treated in triplicate with graded concentrations of compounds at 37 °C for 72 h. Then, they were fixed with 10% trichloroacetic acid and incubated for 60 min at 4 °C. Next, the plates were washed and dried. SRB solution (0.4% w/v in 1% acetic acid) was added and the cultures incubated for an additional 15 min. After the plates were washed and dried, bound stain was solubilized with Tris buffer, and the optical densities were read on a plate reader (model Versa Max, Molecular Devices) at 515 nm (A_{515}). The results were expressed as IC_{50} (the compound concentration required for 50% growth inhibition of tumor cells) values, which were calculated by the Logit method. The mean IC_{50} was determined from the results of three independent tests.

Acknowledgment. Financial support by the Chinese National Natural Science Foundation of China (NNSF; No. 30772638) and Chinese National High-tech R&D Program (2006AA020602) is gratefully acknowledged.

Supporting Information Available: ^1H NMR spectra for compounds **5b**−**22b**. This material is available free of charge via the Internet at http://pubs.acs.org.

References and Notes

(1) Neuss, N.; Neuss, M. N. In *The Alkaloids*; Brossi, A., Suffness, M., Eds.; Academic Press: New York, 1990; Vol *37*, p 229.
(2) Ramnath, N.; Schwartz, G. N.; Smith, P.; Bong, D.; Kanter, P.; Berdzik, J.; Creaven, P. J. *Cancer Chemother. Pharmacol.* **2003**, *51*, 227–230.

(3) (a) Langlois, N.; Gueritte, F.; Langlois, Y.; Potier, P. *J. Am. Chem. Soc.* **1976**, *98*, 7017–7024. (b) Mangency, P.; Andriamialisoa, R. Z.; Lallemand, J.-Y.; Langlois, N.; Langlois, Y.; Potier, P. *Tetrahedron* **1979**, *35*, 2175–2179.
(4) Fauch, J. L. In *Advances in Drug Research*; Testa, B., Ed.; Academic Press: London, 1986; pp 29−69.
(5) Roy, P.; Day, L.; Sowton, E. *Br. Med. J.* **1975**, *3*, 195–197.
(6) Shao, Y.; Ding, H.; Tang, W. D.; Lou, L. G.; Hu, L. H. *Bioorg. Med. Chem.* **2007**, *15*, 5061–5075.
(7) Li, W. H.; Shao, Y.; Hu, L. H.; Zhang, X. W.; Chen, Y.; Tong, L. J.; Li, C.; Shen, X.; Ding, J. *Cancer Biol. Ther.* **2007**, *6*, e1–e8.
(8) Sundberg, R. J.; Hong, J.; Smith, S. Q.; Sabat, M. *Tetrahedron* **1998**, *54*, 6259–6292.
(9) Skehan, P.; Storeng, R.; Scudiero, D.; Monks, A.; McMahon, J.; Vistica, D.; Warren, J. T.; Bokesch, H.; Kenney, S.; Boyd, M. R. *J. Natl. Cancer Inst.* **1990**, *82*, 1107–1112.

NP800284H