

Synthesis and Structure–Activity Relationship Studies of Cytotoxic Anhydrovinblastine Amide Derivatives

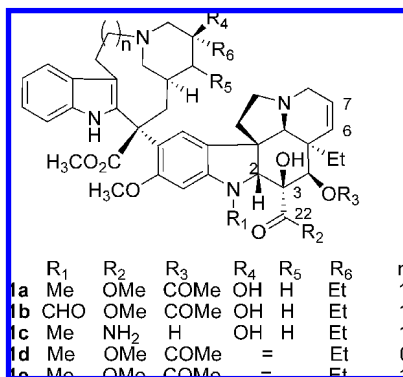
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A series of 3-demethoxycarbonyl-3-amide methyl anhydrovinblastine derivatives (**5b–24b**) was designed, synthesized, and evaluated for their proliferation inhibition activities against two tumor cell lines (A549 and HeLa). Most of the amide anhydrovinblastine derivatives exhibited potent cytotoxicity, with the size of the introduced substituents being the foremost factor in determining the resultant cytotoxic activity. Test results *in vivo* against sarcoma 180 of three potent compounds (**6b**, **12b**, and **24b**) indicated that the introduction of an amide group at the 22-position of anhydrovinblastine (**1e**) improved both potency and toxicity.

Vinblastine (**1a**) and vincristine (**1b**), dimeric indole alkaloids isolated from *Catharanthus roseus* (L.) G. Don (Apocynaceae),¹ have been used widely as clinically important antitumor agents in cancer chemotherapy for more than 40 years.² These two alkaloids, although structurally almost identical, differ markedly in the type of tumors that they affect and in their toxic properties.³ From the 1970s, extensive chemical research has been undertaken in an effort to yield more active and less toxic analogues exhibiting a wider spectrum of anticancer efficacy. Most of the research had mainly focused on the semisynthesis or total synthesis of vinblastine analogues from the two parts of the dimeric structure, the vindoline and velbenamine portions, by carbon skeleton modification and functional group transformation.⁴ To date, these efforts have led to only two approved drugs, vindesine (**1c**)⁵ and vinorelbine (**1d**).⁶ Therefore, new ideas and approaches are needed to extend investigations of the use of these alkaloids as anticancer agents. Anhydrovinblastine (**1e**), a synthetic precursor of vinorelbine, is currently in phase II clinical trials.⁷ Compared with **1b** and **1d**, anhydrovinblastine has shown superior antitumor activity to human tumor xenografts of non-small-cell lung cancer and cervical cancer at equitoxic doses.⁸ Although having poor cytotoxicity *in vitro*, **1e** shows advantages in terms of efficacy, tolerability, and range of activity over vinorelbine (**1d**) *in vivo*. These successful developments inspired us to design new derivatives for searching novel promising dimeric indole alkaloid antitumor agents with better therapeutic indices.



Structure–activity relationship studies on the vindoline portion of **1a** have demonstrated that the substitution at the C-22 position

is sensitive to the overall biological properties, including the potency, toxicity, and tumor spectrum.^{9–12} In particular, vindesine (**1c**) differs slightly from vinblastine (**1a**) by having an amide group instead of an ester group at the C-22 position and possesses an experimental antitumor spectrum that resembles that of vincristine (**1b**) rather than that of the parent alkaloid vinblastine, while its toxicological profile has suggested a potential for reduced neurotoxicity relative to that of **1b**.¹³ Additionally, there has been a lack of research in directly exploiting the C-22 position of the lead compound, **1e**. Hence, we are interested in exploring the effect of different amino groups at the C-22 position of anhydrovinblastine (**1e**), on the resultant antitumor activity. In our earlier publications a variety of carbamates and ether and ester anhydrovinblastine analogues were prepared for antitumor activity evaluation, and a candidate was obtained for preclinical trials.^{14,15} Herein, a total of 20 anhydrovinblastine derivatives (**5b–24b**) with different amide groups were designed for biological evaluation *in vitro* and *in vivo*, in order to gain a better understanding of the SAR of nitrogen-linked analogues at C-22 of compound **1e**.

Results and Discussion

The synthesis of targeted amide anhydrovinblastine analogues was achieved using vindoline as starting material, following the route as shown in Scheme 1. The key intermediate amine **4** was prepared easily in four steps from vindoline according to a previously reported procedure.¹⁴ *N*-Acylation of amine **4** was obtained with sodium hydride and complex BtCOR, which was prepared using a different acyl chloride or acid anhydride reacted with benzotriazole. Subsequently, the *N*-acylated compounds were further acetylated at C-4 OH to afford the amide vindoline derivatives **5a–24a**, which, upon coupling with catharanthine (**3**) by the modified Polonovski–Potier reaction, produced targeted amide anhydrovinblastine analogues (**5b–24b**).¹⁶

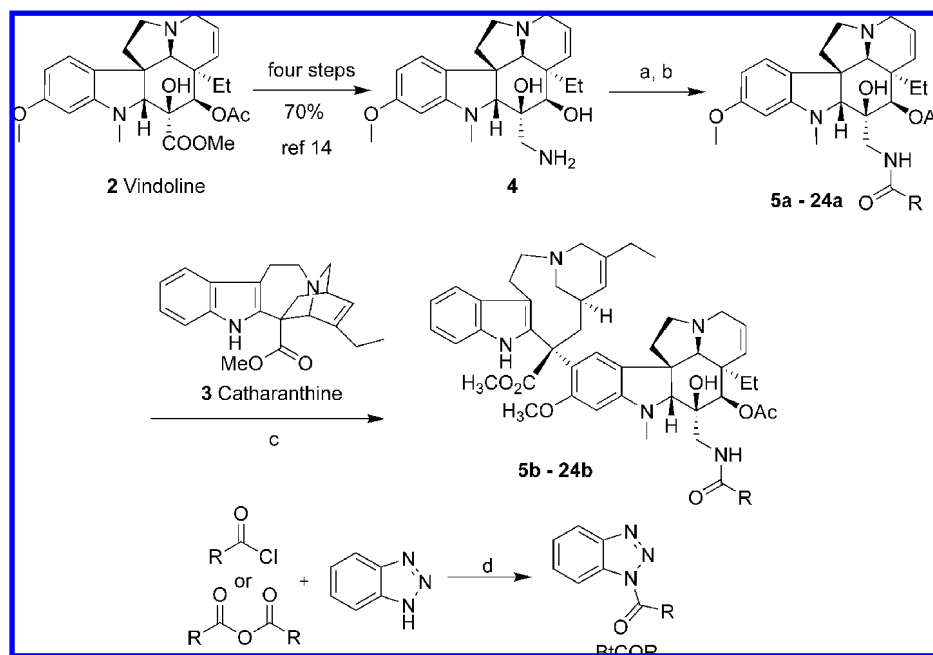
All the amide compounds (**5b–24b**) were evaluated *in vitro* for their cytotoxicity against human non-small-cell lung cancer (A549) and cervical epithelial adenocarcinoma (HeLa) cell lines using a sulforhodamine B (SRB) assay,¹⁷ employing **1d** and **1e** as the standard for comparison purposes. The IC₅₀ values for the inhibition of proliferation of the A549 and HeLa cell lines are shown in Table 1. In the aliphatic-substituted series, the acetamide compound **5b** showed comparable cytotoxicity against the A549 cell line to the positive control **1e** (IC₅₀ 22 nM for **5b** and 30 nM for **1e**). However, the activity of compound **5b** against the HeLa cell line decreased 16-fold when compared with **1e** (IC₅₀ 444 nM for **5b** vs 27 nM for **1e**). The propionamide derivative **6b** (IC₅₀ 43 and 57 nM) displayed only slightly lower activity than **1e** against both cell lines. With

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Scheme 1^a

^a Reagents and conditions: (a) NaH, THF, 0 °C to rt, 6 h; (b) Ac₂O, pyridine, 12 h; (c) (i) FeCl₃, HCl–H₂O buffer (pH = 2), 8 h; (ii) NaBH₄, NH₄OH, 0 °C, 15 min; (d) Et₃N, DCM, 0 °C to rt, 3 h.

the increasing size of alkyl groups by one additional carbon (**7b**, **8b**, **9b**, **10b**, and **11b**), a significant loss of cytotoxicity against the two cell lines used was observed. This indicated that small alkyl groups are tolerated to maintain the cytotoxicity. In addition, the cytotoxicity data of compounds **9b**, **10b**, and **11b** showed that the size of groups at the β -position of the ketone has no effect on activity. In particular, a cyclopropane (**12b**) and a cyclobutane carboxamide (**13b**) also demonstrated an equally potent cytotoxic activity to **1e** against the A549 cell line (IC₅₀ 26 vs 34 vs 30 nM, respectively), whereas compound **13b** displayed about 2-fold lower activity against the HeLa cell line than **12b** and **1e** (IC₅₀ 68 vs 35 vs 27 nM, respectively).

Among 11 aromatic-substituted amide analogues, the phenyl amide **14b** (IC₅₀ 27, 26 nM) showed equally potent cytotoxic activity to **1e**, whereas a benzyl-substituted derivative (**23b**) had less potent activity (IC₅₀ 39, 78 nM) (Table 1). This showed that a phenyl group was more suitable than a benzyl group to maintain such activity. Introduction of electron-withdrawing (F, Cl, and NO₂) or electron-donating (OMe) groups at the 4-position of the phenyl group afforded compounds **15b**, **18b**, **20b**, and **22b**, with no significant effects on cytotoxic activity against the A549 cell line. The derivatives with electron-withdrawing groups on the phenyl substituent exhibited better cytotoxic activities against the HeLa cell line than the compound with an electron-donating group. A 2-methoxy phenyl amide (**21b**) and a 3,4-methylenedioxy phenyl amide (**24b**) showed approximately 3-fold better activity against the A549 cell line than **1e** (IC₅₀ 10 vs 8 vs 30 nM), comparable to **1d** (IC₅₀ 9 nM). No distinct effect on cytotoxic activity against the A549 cell line was observed due to the positions of Cl in the phenyl ring (IC₅₀ 24 nM for **16b** vs 26 nM for **17b** vs 25 nM for **18b**). A 4-pyridine carboxylic amide (**19b**, IC₅₀ 27, 24 nM) had similar activity against both cell lines to 4-nitrophenyl (**20b**, IC₅₀ 33, 23 nM).

In an effort to further evaluate the antitumor activity of the novel amide anhydrovinblastine derivatives, three potent cytotoxic compounds, **6b**, **12b**, and **24b**, were selected for testing of their efficacy in the murine sarcoma 180 model (Table 2). For evaluation of the influence of the schedule of administration of these amide analogues on their activities and on the dose that could be injected without

resulting in undue toxicity, in addition to the single-dose schedules, a multiple-dose schedule was used. The results of two schedules of administration both indicated that these compounds showed remarkable *in vivo* antitumor activities when compared with the positive controls, **1d** and **1e**. The effects of single-dose administration (20 mg/kg) of these three compounds (**6b**, **12b**, **24b**) produced similar efficacy, but some mice died after day 1 because of the toxicity. However, the intermittent treatments (days 1, 4, 10 mg/kg) greatly increased the efficacy with tolerable toxicity (**6b**, **12b**). Therefore, the amide group at C-22 improved compound antitumor activity *in vivo*. These amide anhydrovinblastine derivatives might be promising leads for the development of new antitumor agents.

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 CDCl₃ (¹H NMR) and the δ 77.23 signal of CDCl₃ (¹³C 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 was distilled from sodium/benzophenone under nitrogen. Dichloromethane was distilled from calcium hydride. Compounds **1d** and **1e** were purchased from Shanghai Kang'ai Biological Products Company, Ltd. Catharanthine tartrate (**3**) was purchased from Shanghai AnTiKang-Sheng Plant Chemistry Company, Ltd.

3-Demethoxycarbonyl-3-aminomethyl-4-deacetylvindoline (4). Compound **4** was obtained using the method in a previous report¹⁴ in four steps: $[\alpha]_D^{20} +38$ (*c* 0.09, CHCl₃); ¹H NMR (400 MHz, CDCl₃) δ 8.64 (1H, s), 6.87 (1H, d, *J* = 8.0 Hz), 6.28 (1H, dd, *J* = 8.0, 2.4 Hz), 6.06 (1H, d, *J* = 2.4 Hz), 5.87–5.79 (2H, m), 3.78 (4H, s), 3.45 (1H, dd, *J* = 15.6, 4.4 Hz), 3.36–3.32 (1H, m), 3.24 (1H, s), 3.20 (1H, d, *J* = 11.6 Hz), 3.16 (1H, d, *J* = 11.6 Hz), 2.92 (3H, s), 2.83 (1H, dt, *J* =

Table 1. Cytotoxic Activity of Anhydrovinblastine Amide Analogues^a

compound	R	IC ₅₀ (μM)	
		A549	HeLa
1d		0.009 ± 0.004	0.009 ± 0.001
1e	3-COOCH ₃	0.030 ± 0.002	0.027 ± 0.001
5b		0.022 ± 0.001	0.444 ± 0.086
6b		0.043 ± 0.002	0.057 ± 0.006
7b		0.101 ± 0.007	0.132 ± 0.015
8b		0.095 ± 0.007	0.061 ± 0.006
9b		0.096 ± 0.005	0.097 ± 0.004
10b		0.152 ± 0.005	0.085 ± 0.003
11b		0.115 ± 0.007	0.093 ± 0.003
12b		0.026 ± 0.002	0.035 ± 0.003
13b		0.034 ± 0.004	0.068 ± 0.003
14b		0.027 ± 0.002	0.026 ± 0.003
15b		0.020 ± 0.009	0.025 ± 0.002
16b		0.024 ± 0.008	0.089 ± 0.003
17b		0.026 ± 0.003	0.067 ± 0.013
18b		0.025 ± 0.008	0.047 ± 0.003
19b		0.027 ± 0.009	0.024 ± 0.001
20b		0.033 ± 0.002	0.023 ± 0.007
21b		0.010 ± 0.001	0.021 ± 0.004
22b		0.030 ± 0.001	0.139 ± 0.027
23b		0.039 ± 0.004	0.078 ± 0.008
24b		0.008 ± 0.001	0.033 ± 0.004

^a Ditartrate of all compounds used in bioassays.

15.6, 2.0 Hz), 2.59 (1H, s), 2.52–2.47 (1H, m), 2.21–2.15 (2H, m), 1.42–1.37 (1H, m), 0.94–0.88 (1H, m), 0.65 (3H, t, *J* = 7.6 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 160.8, 154.4, 131.9, 126.5, 122.9, 122.8, 104.2, 96.1, 84.5, 78.4, 75.8, 68.1, 55.4, 52.5, 51.5, 51.3, 49.7, 45.2, 43.6, 41.5, 32.4, 7.9; EIMS *m/z* 385 [M⁺], 368, 355, 297, 194, 174, 162, 152, 135, 122, 93.

3-Demethoxycarbonyl-3-(acetamino)methylindoline (5a). Compound **4** (385 mg, 1 mmol) was dissolved in pyridine (1 mL) and Ac₂O (1 mL), and the resulting mixture was stirred for 8 h at room temperature. Saturated aqueous NaHCO₃ (10 mL) and EtOAc (50 mL) were added. The organic phase was washed with water (3 × 10 mL) and brine (10 mL), dried, and concentrated. The residue was purified

by column chromatography (silica gel; hexane–acetone, 3:1) to give the desired compound **5a** (417 mg, 89%) as a white solid: ¹H NMR (300 MHz, CDCl₃) δ 6.81 (1H, d, *J* = 8.1 Hz), 6.24 (1H, d, *J* = 8.1 Hz), 6.17 (1H, d, *J* = 7.2 Hz), 6.08 (1H, s), 5.82 (1H, dd, *J* = 10.2, 4.5 Hz), 5.35 (1H, d, *J* = 10.2 Hz), 4.92 (1H, s), 3.78 (3H, s), 3.65 (2H, m), 3.41 (2H, m), 3.33 (1H, s), 3.28 (1H, m), 2.98 (1H, d, *J* = 13.2 Hz), 2.79 (3H, s), 2.73 (1H, d, *J* = 4.8 Hz), 2.59 (1H, s), 2.47 (1H, m), 2.16 (2H, m), 2.09 (1H, s), 2.03 (3H, s), 1.92 (3H, s), 1.22 (1H, m), 0.94 (1H, m), 0.45 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 170.4, 170.3, 161.0, 154.3, 130.3, 125.5, 124.1, 122.6, 105.1, 96.6, 82.1, 77.0, 75.8, 67.3, 55.3, 52.2, 51.5, 50.8, 44.6, 43.7, 42.8, 40.6, 31.2, 23.3, 20.9, 7.5; ESIMS *m/z* 470.3 [M + 1]⁺.

General Procedure for the Preparation of Compounds 6a–24a.

To a solution of benzotriazole (238 mg, 2.0 mmol) in CH₂Cl₂ (10 mL) was added triethylamine (0.32 mL, 2.2 mmol). Then, a different acyl chloride (2.2 mmol) in CH₂Cl₂ (2 mL) was added dropwise at 0 °C. After being stirred at room temperature for 2 h, the mixture was diluted with water (50 mL) and extracted with CH₂Cl₂ (3 × 15 mL). The organic phase was combined, dried with anhydrous Na₂SO₄, and concentrated under vacuum pressure to give an intermediate *N*-acyl benzotriazole (BtCOR). Then, to a solution of BtCOR (1.1 mmol) and compound **4** (386 mg, 1 mmol) in THF (10 mL) was added NaH (60% in oil, 44 mg, 1.1 mmol). The mixture was stirred for 3 h at room temperature and quenched with saturated aqueous NH₄Cl (1 mL). The resulting solution was partitioned between EtOAc (3 × 15 mL) and water (50 mL). The EtOAc phases were combined, dried, and concentrated to dryness. The residue was purified by column chromatography (silica gel; hexane–acetone, 3:1–1:1) to give the *N*-acyl compound **4** as a white solid. This was added to pyridine (1 mL) and Ac₂O (1 mL) and stirred for 8 h at room temperature. Saturated aqueous NaHCO₃ (10 mL) and EtOAc (50 mL) were added. The organic phase was washed with water (3 × 10 mL) and brine (10 mL), dried, and concentrated. The residue was purified by column chromatography (silica gel; hexane–acetone, 4:1–2:1) to give the desired compounds **6a–24a**, each as a white solid.

3-Demethoxycarbonyl-3-(propionylamino)methylindoline (6a). Compound **6a** was prepared using propionyl chloride as starting material in 72% yield: ¹H NMR (300 MHz, CDCl₃) δ 9.20 (1H, s), 6.88 (1H, d, *J* = 8.1 Hz), 6.32 (1H, dd, *J* = 8.1, 2.1 Hz), 6.16 (1H, d, *J* = 5.7 Hz), 6.15 (1H, d, *J* = 2.1 Hz), 5.89 (1H, dd, *J* = 10.2, 4.2 Hz), 5.36 (1H, d, *J* = 10.2 Hz), 4.99 (1H, s), 3.79 (3H, s), 3.74 (1H, m), 3.50 (1H, dd, *J* = 15.9, 4.5 Hz), 3.39 (1H, m), 3.39 (1H, s), 3.03 (1H, d, *J* = 13.2 Hz), 2.86 (3H, s), 2.83 (1H, d, *J* = 15.9 Hz), 2.66 (1H, s), 2.53 (1H, dd, *J* = 18.0, 9.6 Hz), 2.33–2.19 (2H, m), 2.22 (2H, q, *J* = 7.5 Hz), 2.11 (3H, s), 1.36–1.29 (1H, m), 1.15 (3H, t, *J* = 7.5 Hz), 1.04–0.98 (1H, m), 0.52 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 173.9, 170.5, 161.0, 154.3, 130.4, 125.6, 124.1, 122.7, 105.2, 96.7, 82.2, 76.9, 75.9, 67.2, 55.4, 52.2, 51.5, 50.8, 44.8, 43.4, 42.8, 40.7, 31.3, 29.8, 21.0, 10.0, 7.5; ESIMS *m/z* 484.4 [M + 1]⁺.

3-Demethoxycarbonyl-3-(isobutyrylamino)methylindoline (7a). Compound **7a** was prepared using isobutyryl chloride as starting material in 75% yield: ¹H NMR (300 MHz, CDCl₃) δ 9.20 (1H, br s), 6.88 (1H, d, *J* = 8.4 Hz), 6.32 (1H, dd, *J* = 8.4, 2.1 Hz), 6.19 (1H, d, *J* = 8.1 Hz), 6.15 (1H, d, *J* = 2.1 Hz), 5.89 (1H, dd, *J* = 10.2, 3.6 Hz), 5.36 (1H, d, *J* = 10.2 Hz), 4.98 (1H, s), 3.79 (3H, s), 3.74 (1H, m), 3.48 (1H, dd, *J* = 15.9, 5.4 Hz), 3.38 (1H, m), 3.38 (1H, s), 2.99 (1H, d, *J* = 13.2 Hz), 2.84 (3H, s), 2.83 (1H, d, *J* = 15.9 Hz), 2.66 (1H, s), 2.54–2.48 (1H, m), 2.42–2.33 (1H, m), 2.29–2.18 (2H, m), 2.11 (3H, s), 1.37–1.27 (1H, m), 1.15 (3H, d, *J* = 2.1 Hz), 1.13 (3H, d, *J* = 2.1 Hz), 1.07–0.98 (1H, m), 0.52 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 171.2, 170.7, 161.2, 154.5, 130.5, 125.8, 124.2, 122.8, 105.4, 96.9, 82.2, 77.0, 76.1, 67.4, 55.5, 52.4, 51.7, 51.0, 45.0, 43.2, 43.0, 40.7, 35.9, 31.4, 21.1, 19.9, 19.7, 7.7; ESIMS *m/z* 498.3 [M + 1]⁺.

3-Demethoxycarbonyl-3-(pivaloylamino)methylindoline (8a). Compound **8a** was prepared using pivaloyl chloride as starting material in 68% yield: ¹H NMR (300 MHz, CDCl₃) δ 6.85 (1H, d, *J* = 8.4 Hz), 6.44 (1H, d, *J* = 8.1 Hz), 6.29 (1H, d, *J* = 8.1 Hz), 6.08 (1H, s), 5.84 (1H, dd, *J* = 9.9, 4.2 Hz), 5.61 (1H, d, *J* = 9.9 Hz), 4.97 (1H, s), 3.74 (3H, s), 3.65 (2H, m), 3.41 (2H, m), 3.33 (1H, s), 3.28 (1H, m), 2.98 (1H, d, *J* = 13.2 Hz), 2.84 (3H, s), 2.73 (1H, d, *J* = 4.8 Hz), 2.59 (1H, s), 2.47 (1H, m), 2.16 (2H, m), 2.09 (1H, s), 2.05 (3H, s), 1.92 (3H, s), 1.30 (1H, m), 1.17 (9H, s), 0.90 (1H, m), 0.57 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 178.7, 170.3, 161.0, 154.6, 130.8, 126.6, 124.5, 123.0, 105.1, 96.9, 82.4, 76.6, 75.3, 68.5, 55.5, 52.1, 52.0, 51.3,

Table 2. In Vivo Antitumor Efficacy of **6b**, **12b**, **24b**, **1d**, and **1e** against Sarcoma 180^a

group	dosage (mg/kg)	route and schedule	mice (n)		body weight (g)		tumor weight (X ± SD)	inhibition rate (%)
			initial/end	initial	end			
NS			16/16	21.6	31.9	1.60 ± 0.27		
6b	10	iv d 1, 4	8/8	20.6	21.4	0.25 ± 0.06	84.4 ^b	
	20	iv d 1	8/5	20.5	20.7	0.16 ± 0.03	90.0 ^b	
12b	10	iv d 1, 4	8/7	20.4	22.2	0.30 ± 0.05	81.3 ^b	
	20	iv d 1	8/5	20.5	23.9	0.18 ± 0.02	88.8 ^b	
24b	10	iv d 1, 4	8/8	20.5	25.3	0.67 ± 0.07	58.1 ^b	
	20	iv d 1	8/6	20.8	23.3	0.54 ± 0.17	66.3 ^b	
1d	10	iv, d 1, 4	8/8	24.1	27.5	0.60 ± 0.23	62.5 ^b	
1e	10	iv, d 1, 4	8/8	24.3	27.9	0.49 ± 0.10	69.4 ^b	

^a The in vivo experiment was carried out in Kunming mice bearing sarcoma 180 cells, and the compounds were given intravenously. Ditartrate of all compounds used in bioassays. ^b *p* < 0.01 versus control group.

44.9, 44.0, 43.6, 41.2, 38.9, 32.6, 27.7 (3 C), 20.9, 7.8; ESIMS *m/z* 512.4 [M + 1]⁺.

3-Demethoxycarbonyl-3-(butyrylamino)methylvindoline (9a). Compound **9a** was prepared using butyryl chloride as starting material in 68% yield: ¹H NMR (300 MHz, CDCl₃) δ 9.23 (1H, br s), 6.88 (1H, d, *J* = 8.4 Hz), 6.32 (1H, d, *J* = 8.4 Hz), 6.16 (1H, d, *J* = 8.1 Hz), 6.15 (1H, s), 5.89 (1H, dd, *J* = 10.2, 4.8 Hz), 5.37 (1H, d, *J* = 10.2 Hz), 5.01 (1H, s), 3.79 (3H, s), 3.74 (1H, m), 3.48 (1H, dd, *J* = 15.9, 5.4 Hz), 3.38 (1H, m), 3.41 (1H, s), 3.04 (1H, d, *J* = 14.4 Hz), 2.86 (3H, s), 2.83 (1H, d, *J* = 15.9 Hz), 2.67 (1H, s), 2.61–2.52 (1H, m), 2.34–2.16 (2H, m), 2.19 (2H, t, *J* = 7.2 Hz), 2.11 (3H, s), 1.70–1.63 (2H, m), 1.37–1.27 (1H, m), 0.91 (3H, t, *J* = 7.2 Hz), 1.03–0.85 (1H, m), 0.51 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 173.2, 170.5, 161.0, 154.3, 130.4, 125.6, 124.1, 122.7, 105.2, 96.7, 82.0, 77.0, 75.9, 67.4, 55.3, 52.2, 51.6, 50.8, 44.8, 43.3, 42.9, 40.6, 38.8, 31.3, 20.9, 19.2, 13.9, 7.5; ESIMS *m/z* 498.3 [M + 1]⁺.

3-Demethoxycarbonyl-3-(3'-methylbutyramino)methylvindoline (10a). Compound **10a** was prepared using 3-methylbutyryl chloride as starting material in 65% yield: ¹H NMR (300 MHz, CDCl₃) δ 9.25 (1H, br s), 6.87 (1H, d, *J* = 8.1 Hz), 6.31 (1H, dd, *J* = 8.1, 2.1 Hz), 6.15 (1H, d, *J* = 2.1 Hz), 6.10 (1H, d, *J* = 8.1 Hz), 5.89 (1H, dd, *J* = 10.5, 3.6 Hz), 5.36 (1H, d, *J* = 10.5 Hz), 5.00 (1H, s), 3.79 (3H, s), 3.79–3.72 (1H, m), 3.48 (1H, dd, *J* = 15.9, 5.1 Hz), 3.42–3.34 (1H, m), 3.39 (1H, s), 3.03 (1H, d, *J* = 13.2 Hz), 2.86 (3H, s), 2.83 (1H, d, *J* = 15.9 Hz), 2.63 (1H, s), 2.57–2.48 (1H, m), 2.35–2.16 (3H, m), 2.11 (3H, s), 2.10 (2H, d, *J* = 9.9 Hz), 1.37–1.27 (1H, m), 0.94 (6H, d, *J* = 6.3 Hz), 1.03–0.85 (1H, m), 0.51 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 172.7, 170.4, 160.9, 154.2, 130.2, 125.5, 124.0, 122.6, 105.1, 96.5, 81.8, 76.8, 75.8, 67.4, 55.2, 52.1, 51.6, 50.7, 46.1, 44.7, 43.2, 42.8, 40.4, 31.2, 26.0, 22.5, 22.4, 20.9, 7.5; ESIMS *m/z* 512.4 [M + 1]⁺.

3-Demethoxycarbonyl-3-(3',3'-dimethylbutyramino)methylvindoline (11a). Compound **11a** was prepared using 3,3-dimethylbutyryl chloride as starting material in 65% yield: ¹H NMR (300 MHz, CDCl₃) δ 9.25 (1H, br s), 6.88 (1H, d, *J* = 8.1 Hz), 6.32 (1H, dd, *J* = 8.1, 2.1 Hz), 6.15 (1H, d, *J* = 2.1 Hz), 6.10 (1H, d, *J* = 8.1 Hz), 5.89 (1H, dd, *J* = 9.9, 3.3 Hz), 5.36 (1H, d, *J* = 9.9 Hz), 5.02 (1H, s), 3.79 (3H, s), 3.79–3.72 (1H, m), 3.48 (1H, dd, *J* = 15.9, 5.1 Hz), 3.42–3.34 (1H, m), 3.42 (1H, s), 3.03 (1H, d, *J* = 13.2 Hz), 2.87 (3H, s), 2.83 (1H, d, *J* = 15.9 Hz), 2.64 (1H, s), 2.57–2.48 (1H, m), 2.35–2.16 (2H, m), 2.12 (3H, s), 2.10 (2H, s), 1.37–1.27 (1H, m), 0.94 (6H, d, *J* = 6.3 Hz), 1.03 (9H, s), 0.87–0.80 (1H, m), 0.50 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 171.9, 170.3, 160.9, 154.2, 130.2, 125.6, 124.0, 122.5, 105.0, 96.5, 81.7, 76.9, 75.7, 67.4, 55.2, 52.0, 51.6, 50.7, 50.5, 44.7, 43.1, 42.7, 40.4, 31.2, 30.8, 29.7 (3 C), 20.8, 7.4; ESIMS *m/z* 526.3 [M + 1]⁺.

3-Demethoxycarbonyl-3-(cyclopropanecarbonylamino)methylvindoline (12a). Compound **12a** was prepared using cyclopropanecarbonyl chloride as starting material in 62% yield: ¹H NMR (300 MHz, CDCl₃) δ 9.02 (1H, s), 6.87 (1H, d, *J* = 8.1 Hz), 6.31 (2H, dd, *J* = 8.1, 2.4 Hz), 6.14 (1H, d, *J* = 2.4 Hz), 5.89 (1H, d, *J* = 10.2, 3.6 Hz), 5.37 (1H, d, *J* = 10.2 Hz), 5.01 (1H, s), 3.75 (3H, s), 3.75–3.70 (1H, m), 3.51 (1H, dd, *J* = 15.9, 4.5 Hz), 3.43 (1H, s), 3.43–3.35 (1H, m), 3.09 (1H, d, *J* = 13.5 Hz), 2.86 (3H, s), 2.82 (1H, d, *J* = 15.9 Hz), 2.65 (1H, s), 2.58–2.49 (1H, m), 2.34–2.20 (2H, m), 2.10 (3H, s), 1.44–1.29 (2H, m), 1.18–1.07 (1H, m), 1.00–0.91 (2H, m), 0.76–0.67 (2H, m), 0.52 (3H, t, *J* = 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 173.6, 170.5, 161.1, 154.5, 130.5, 125.7, 124.2, 122.7, 105.2, 96.7, 82.3, 77.2,

76.0, 67.5, 55.4, 52.3, 51.7, 51.0, 44.8, 44.0, 43.0, 40.7, 31.4, 21.0, 14.8, 7.6, 7.0, 6.9; ESIMS *m/z* 496.4 [M + 1]⁺.

3-Demethoxycarbonyl-3-(cyclobutanecarbonylamino)methylvindoline (13a). Compound **13a** was prepared using cyclobutanecarbonyl chloride as starting material in 66% yield: ¹H NMR (300 MHz, CDCl₃) δ 9.17 (1H, s), 6.87 (1H, d, *J* = 8.1 Hz), 6.32 (1H, dd, *J* = 8.1, 2.1 Hz), 6.14 (1H, d, *J* = 2.1 Hz), 6.07 (1H, d, *J* = 7.8 Hz), 5.89 (1H, dd, *J* = 10.5, 3.6 Hz), 5.36 (1H, d, *J* = 10.5 Hz), 4.98 (1H, s), 3.80–3.73 (1H, m), 3.79 (3H, s), 3.47 (1H, dd, *J* = 15.9, 4.8 Hz), 3.42–3.34 (1H, m), 3.37 (1H, s), 3.05–3.00 (2H, m), 2.85 (3H, s), 2.81 (1H, d, *J* = 15.9 Hz), 2.66 (1H, s), 2.54–2.48 (1H, m), 2.32–2.12 (6H, m), 2.10 (3H, s), 1.98–1.87 (2H, m), 1.36–1.25 (1H, m), 1.05–0.98 (1H, m), 0.52 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 175.1, 170.6, 161.1, 154.4, 130.4, 125.7, 124.2, 122.8, 105.3, 96.8, 82.3, 77.0, 76.0, 67.3, 55.4, 52.3, 51.6, 50.9, 44.9, 43.3, 42.9, 40.8, 40.1, 31.3, 25.4, 25.4, 21.0, 7.6; ESIMS *m/z* 510.5 [M + 1]⁺.

3-Demethoxycarbonyl-3-(benzoylamino)methylvindoline (14a). Compound **14a** was prepared using benzoyl chloride as starting material in 73% yield: ¹H NMR (300 MHz, CDCl₃) δ 9.28 (1H, br s), 7.79 (2H, d, *J* = 6.9 Hz), 7.44 (3H, m), 6.91 (1H, s), 6.89 (1H, d, *J* = 8.1 Hz), 6.33 (1H, d, *J* = 8.1 Hz), 6.17 (1H, s), 5.91 (1H, m), 5.40 (1H, d, *J* = 10.5 Hz), 5.06 (1H, s), 3.93 (1H, m), 3.79 (3H, s), 3.55–3.41 (3H, m), 3.25 (1H, d, *J* = 12.9 Hz), 2.91 (3H, s), 2.83 (1H, m), 2.70 (1H, s), 2.55 (1H, m), 2.25 (1H, m), 2.10 (3H, m), 2.09 (3H, s), 1.08–1.01 (1H, m), 0.90–0.84 (1H, m), 0.54 (3H, t, *J* = 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 170.3, 167.6, 161.5, 154.6, 135.4, 132.2, 130.7, 128.6 (2 C), 127.5 (2 C), 125.9, 124.5, 123.1, 105.8, 97.2, 83.1, 77.1, 76.4, 67.5, 55.7, 52.4, 51.5, 51.0, 45.2, 44.2, 43.2, 41.3, 31.6, 21.1, 7.8; ESIMS *m/z* 532.3 [M + 1]⁺.

3-Demethoxycarbonyl-3-(4'-fluorobenzoylamino)methylvindoline (15a). Compound **15a** was prepared using 4-fluorobenzoyl chloride as starting material in 73% yield: ¹H NMR (300 MHz, CDCl₃) δ 9.28 (1H, s), 7.79 (2H, t, *J* = 8.1 Hz), 7.11 (2H, t, *J* = 8.1 Hz), 6.89 (1H, d, *J* = 8.4 Hz), 6.34 (1H, d, *J* = 8.4 Hz), 6.17 (1H, s), 5.91 (1H, dd, *J* = 10.2, 2.4 Hz), 5.40 (1H, d, *J* = 10.2 Hz), 5.05 (1H, s), 3.97–3.90 (1H, m), 3.79 (3H, s), 3.53–3.41 (2H, m), 3.45 (1H, s), 3.24 (1H, d, *J* = 13.2 Hz), 2.90 (3H, s), 2.85 (1H, d, *J* = 15.9 Hz), 2.70 (1H, s), 2.60–2.51 (1H, m), 2.30–2.17 (2H, m), 2.09 (3H, s), 1.37–1.30 (1H, m), 1.08–1.01 (1H, m), 0.55 (3H, t, *J* = 7.5 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 170.7, 166.4 (2 C), 161.1, 154.4, 131.0, 130.5, 129.3, 129.2, 125.6, 124.3, 122.8, 115.8, 115.5, 105.5, 97.0, 82.8, 77.0, 76.1, 67.2, 55.5, 52.5, 51.5, 50.9, 44.9, 44.1, 43.0, 41.1, 31.4, 21.0, 7.6; ESIMS *m/z* 550.3 [M + 1]⁺.

3-Demethoxycarbonyl-3-(2'-chlorobenzoylamino)methylvindoline (16a). Compound **16a** was prepared using 2-chlorobenzoyl chloride as starting material in 80% yield: ¹H NMR (300 MHz, CDCl₃) δ 9.16 (1H, s), 7.51 (1H, d, *J* = 6.6 Hz), 7.30–7.17 (3H, m), 6.83 (1H, d, *J* = 9.0 Hz), 6.80 (1H, d, *J* = 9.9 Hz), 6.23 (1H, d, *J* = 9.9 Hz, 1 H), 6.07 (1H, s), 5.79 (1H, dd, *J* = 10.2, 4.8 Hz), 5.30 (1H, d, *J* = 10.2 Hz), 4.98 (1H, s, 1 H), 3.94–3.87 (1H, m), 3.67 (3H, s), 3.42 (1H, s), 3.37 (1H, dd, *J* = 15.9, 4.8 Hz), 3.27–3.23 (1H, m), 3.15 (1H, d, *J* = 13.5 Hz), 2.88 (3H, s), 2.74 (1H, d, *J* = 16.5 Hz), 2.57 (1H, s), 2.47–2.38 (1H, m), 2.24–2.07 (2H, m), 2.02 (3H, s), 1.31–1.19 (1H, m), 1.02–0.89 (1H, m), 0.44 (3H, t, *J* = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 170.3, 166.4, 160.9, 154.2, 135.4, 131.0, 130.5, 130.2, 130.0, 129.8, 126.9, 125.5, 124.3, 122.5, 105.1, 96.6, 81.8, 76.8, 75.8, 67.3, 55.1, 52.1, 51.4, 50.7, 44.6, 43.8, 42.7, 40.7, 31.2, 20.8, 7.4; ESIMS *m/z* 566.3 [M + 1]⁺.

3-Demethoxycarbonyl-3-(3'-chlorobenzoylamino)methylvindoline (17a). Compound **17a** was prepared using 3-chlorobenzoyl chloride as starting material in 81% yield: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.29 (1H, br s), 7.77 (1H, s), 7.65 (1H, d, $J = 7.5$ Hz), 7.47 (1H, d, $J = 7.5$ Hz), 7.37 (1H, t, $J = 7.5$ Hz), 6.95 (1H, d, $J = 6.6$ Hz), 6.89 (1H, d, $J = 8.1$ Hz), 6.34 (1H, d, $J = 8.1$ Hz), 6.18 (1H, s), 5.92 (1H, dd, $J = 10.5, 4.5$ Hz), 5.40 (1H, d, $J = 10.5$ Hz), 5.05 (1H, s), 3.95 (1H, dd, $J = 13.2, 7.5$ Hz), 3.80 (3H, s), 3.54–3.42 (2H, m), 3.44 (1H, s), 3.24 (1H, d, $J = 13.5$ Hz), 2.91 (3H, s), 2.84 (1H, d, $J = 16.5$ Hz), 2.71 (1H, s), 2.58–2.53 (1H, m), 2.29–2.23 (2H, m), 2.10 (3H, s), 1.37–1.30 (1H, m), 1.08–1.01 (1H, m), 0.55 (3H, t, $J = 7.5$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 170.7, 166.1, 161.2, 154.4, 136.6, 134.8, 131.5, 130.5, 130.0, 127.4, 125.6, 125.1, 124.3, 122.9, 105.7, 97.0, 82.9, 76.9, 76.1, 67.2, 55.5, 52.5, 51.4, 51.0, 44.9, 44.1, 43.0, 41.2, 31.4, 21.1, 7.6; ESIMS m/z 566.4 $[\text{M} + 1]^+$.

3-Demethoxycarbonyl-3-(4'-chlorobenzoylamino)methylvindoline (18a). Compound **18a** was prepared using 4-chlorobenzoyl chloride as starting material in 78% yield: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.21 (1H, br s), 7.64 (2H, d, $J = 8.7$ Hz), 7.28 (1H, d, $J = 8.7$ Hz), 6.89 (1H, d, $J = 7.2$ Hz), 6.81 (1H, d, $J = 8.1$ Hz), 6.25 (1H, d, $J = 8.1$ Hz), 6.08 (1H, s), 5.83 (1H, dd, $J = 9.9, 4.5$ Hz), 5.31 (1H, d, $J = 9.9$ Hz), 4.97 (1H, s), 3.88–3.80 (1H, m), 3.68 (3H, s), 3.43–3.31 (2H, m), 3.37 (1H, s), 3.18 (1H, d, $J = 13.5$ Hz), 2.81 (3H, s), 2.76 (1H, d, $J = 16.5$ Hz), 2.62 (1H, s), 2.47 (1H, q, $J = 9.3$ Hz), 2.24–2.13 (2H, m), 1.97 (3H, s), 1.28–1.19 (1H, m), 1.02–0.93 (1H, m), 0.46 (3H, t, $J = 7.2$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 170.5, 166.1, 161.1, 154.2, 137.4, 133.1, 130.3, 128.7 (2 C), 128.3 (2 C), 125.5, 124.1, 122.7, 105.4, 96.9, 82.9, 76.9, 75.9, 67.1, 55.2, 52.4, 51.4, 50.8, 44.7, 44.1, 42.8, 41.0, 31.2, 20.9, 7.5; ESIMS m/z 566.4 $[\text{M} + 1]^+$.

3-Demethoxycarbonyl-3-(pyridine-4'-carbonylamino)methylvindoline (19a). Compound **19a** was prepared using pyridine-4-carbonyl chloride as starting material in 82% yield: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.37 (1H, br s), 8.74 (2H, d, $J = 3.9$ Hz), 7.62 (2H, d, $J = 3.9$ Hz), 7.10 (1H, d, $J = 5.4$ Hz), 6.90 (1H, d, $J = 8.4$ Hz), 6.35 (1H, d, $J = 8.4$ Hz), 6.18 (1H, s), 5.91 (1H, dd, $J = 10.2, 4.5$ Hz), 5.40 (1H, d, $J = 10.2$ Hz), 5.05 (1H, s), 3.99–3.92 (1H, m), 3.80 (3H, s), 3.52–3.42 (2H, m), 3.42 (1H, s), 3.26 (1H, d, $J = 13.5$ Hz), 2.90 (3H, s), 2.86 (1H, d, $J = 16.5$ Hz), 2.72 (1H, s), 2.57 (1H, q, $J = 9.6$ Hz), 2.26–2.17 (2H, m), 2.09 (3H, s), 1.31–1.25 (1H, m), 1.08–1.03 (1H, m), 0.56 (3H, t, $J = 7.2$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 170.7, 165.4, 161.2, 154.3, 150.7 (2 C), 141.9, 130.4, 125.5, 124.4, 122.9, 120.9 (2 C), 105.8, 97.2, 83.1, 76.8, 76.0, 67.1, 55.5, 52.6, 51.4, 50.9, 44.9, 44.2, 43.0, 41.4, 31.4, 21.1, 7.6; ESIMS m/z 533.4 $[\text{M} + 1]^+$.

3-Demethoxycarbonyl-3-(4'-nitrobenzoylamino)methylvindoline (20a). Compound **20a** was prepared using 4-nitrobenzoyl chloride as starting material in 80% yield: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.37 (1H, s), 8.29 (2H, d, $J = 8.7$ Hz), 7.93 (2H, d, $J = 8.7$ Hz), 7.11 (1H, d, $J = 5.4$ Hz), 6.90 (1H, d, $J = 7.8$ Hz), 6.36 (1H, d, $J = 7.8$ Hz), 6.18 (1H, s), 5.91 (1H, dd, $J = 10.2, 4.5$ Hz), 5.40 (1H, d, $J = 10.2$ Hz), 5.05 (1H, s), 4.01–3.94 (1H, m), 3.80 (3H, s), 3.53–3.42 (2H, m), 3.43 (1H, s), 3.27 (1H, d, $J = 13.5$ Hz), 2.91 (3H, s), 2.86 (1H, d, $J = 16.5$ Hz), 2.73 (1H, s), 2.62–2.53 (1H, m), 2.33–2.17 (2H, m), 2.09 (3H, s), 1.36–1.25 (1H, m), 1.08–1.01 (1H, m), 0.56 (3H, t, $J = 7.2$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 170.3, 164.9, 160.9, 153.9, 149.2, 140.1, 130.0, 127.9 (2 C), 125.3, 124.0, 123.4 (2 C), 120.6, 105.3, 96.8, 82.8, 76.5, 75.6, 66.8, 55.0, 52.3, 51.0, 50.5, 44.5, 44.1, 42.6, 41.0, 31.0, 20.6, 7.2; ESIMS m/z 577.3 $[\text{M} + 1]^+$.

3-Demethoxycarbonyl-3-(2'-methoxybenzoylamino)methylvindoline (21a). Compound **21a** was prepared using 2-methoxybenzoyl chloride as starting material in 82% yield: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.09 (1H, s), 8.45 (1H, d, $J = 7.8$ Hz), 8.15 (1H, d, $J = 7.5$ Hz), 7.43 (1H, t, $J = 7.8$ Hz), 7.06 (1H, t, $J = 7.8$ Hz), 6.97 (1H, d, $J = 7.8$ Hz), 6.88 (1H, d, $J = 8.4$ Hz), 6.30 (1H, d, $J = 8.4$ Hz), 6.14 (1H, s), 5.88 (1H, dd, $J = 10.2, 4.8$ Hz), 5.37 (1H, d, $J = 10.2$ Hz), 5.07 (1H, s), 4.01–3.93 (1H, m), 3.94 (3H, s), 3.79 (3H, s), 3.54–3.30 (2H, m), 3.49 (1H, s), 3.26 (1H, d, $J = 13.5$ Hz), 2.88 (3H, s), 2.83 (1H, d, $J = 16.5$ Hz), 2.65 (1H, s), 2.58–2.49 (1H, m), 2.35–2.16 (2H, m), 2.01 (3H, s), 1.42–1.35 (1H, m), 1.08–1.01 (1H, m), 0.52 (3H, t, $J = 7.2$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 170.1, 164.8, 160.6, 157.3, 154.1, 132.2, 131.4, 130.0, 125.5, 123.7, 122.3, 121.6, 120.6, 111.2, 104.5, 96.2, 81.8, 76.8, 75.6, 67.2, 55.7, 54.8, 51.8, 51.3, 50.4, 44.5, 43.7, 42.5, 40.1, 31.1, 20.4, 7.2; ESIMS m/z 562.3 $[\text{M} + 1]^+$.

3-Demethoxycarbonyl-3-(4'-methoxybenzoylamino)methylvindoline (22a). Compound **22a** was prepared using 4-methoxybenzoyl

chloride as starting material in 80% yield: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.04 (1H, br s), 7.19 (2H, d, $J = 8.4$ Hz), 6.87 (2H, d, $J = 8.4$ Hz), 6.85 (1H, d, $J = 8.1$ Hz), 6.32 (1H, dd, $J = 8.1, 2.1$ Hz), 6.16 (1H, d, $J = 8.1$ Hz), 6.02 (1H, s), 5.87 (1H, dd, $J = 10.2, 3.6$ Hz), 5.32 (1H, d, $J = 10.2$ Hz), 4.89 (1H, s), 3.86–3.82 (1H, m), 3.81 (3H, s), 3.79 (3H, s), 3.48 (1H, s), 3.48–3.41 (1H, m), 3.35–3.27 (1H, m), 3.16 (1H, s), 2.92 (1H, d, $J = 13.5$ Hz), 2.80 (1H, d, $J = 15.9$ Hz), 2.64 (3H, s), 2.53–2.44 (1H, m), 2.26–2.00 (2H, m), 2.09 (3H, s), 1.39–1.27 (1H, m), 1.03–0.91 (1H, m), 0.51 (3H, t, $J = 7.2$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 171.5, 170.9, 161.0, 158.8, 154.3, 130.7, 130.4, 127.3, 125.8, 124.2, 122.7, 114.4, 105.4, 97.5, 82.9, 76.4, 75.7, 67.1, 55.5, 55.3, 52.3, 51.5, 50.8, 45.0, 43.5, 43.2, 41.1, 31.2, 21.1, 7.6; ESIMS m/z 562.3 $[\text{M} + 1]^+$.

3-Demethoxycarbonyl-3-(phenylacetylamino)methylvindoline (23a). Compound **23a** was prepared using phenylacetyl chloride as starting material in 76% yield: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 7.26–7.20 (5H, m), 6.79 (1H, d, $J = 8.4$ Hz), 6.25 (1H, d, $J = 8.4$ Hz), 6.10 (1H, d, $J = 9.0$ Hz), 5.95 (1H, s), 5.81 (1H, dd, $J = 10.2, 4.2$ Hz), 5.26 (1H, d, $J = 10.2$ Hz), 4.83 (1H, s), 3.79–3.73 (1H, m), 3.73 (3H, s), 3.48 (2H, s), 3.38 (1H, dd, $J = 15.9, 5.1$ Hz), 3.30–3.20 (1H, m), 3.08 (1H, s), 2.86 (1H, d, $J = 13.8$ Hz), 2.74 (1H, d, $J = 15.9$ Hz), 2.55 (3H, s), 2.47–2.38 (1H, m), 2.20–1.93 (2H, m), 2.02 (1H, s), 1.30–1.19 (1H, m), 0.94–0.89 (1H, m), 0.45 (3H, t, $J = 7.2$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 171.0, 170.8, 161.0, 154.3, 135.4, 130.4, 129.6 (2 C), 129.0 (2 C), 127.2, 125.8, 124.2, 122.8, 105.5, 97.4, 82.9, 76.4, 75.8, 67.1, 55.5, 52.3, 51.4, 50.8, 45.0, 44.1, 43.6, 42.9, 41.0, 31.3, 21.1, 7.6; ESIMS m/z 546.4 $[\text{M} + 1]^+$.

3-Demethoxycarbonyl-3-(3',4'-methyleneedioxybenzoylamino)methylvindoline (24a). Compound **24a** was prepared using 3,4-methylene-dioxybenzoyl chloride as starting material in 74% yield: $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.26 (1H, br s), 7.32 (1H, d, $J = 8.1$ Hz), 7.28 (1H, s), 6.88 (1H, d, $J = 8.4$ Hz), 6.83 (1H, d, $J = 8.1$ Hz), 6.82 (1H, s), 6.33 (1H, d, $J = 8.4$ Hz), 6.16 (1H, d, $J = 2.1$ Hz), 6.02 (2H, s), 5.91 (1H, dd, $J = 10.2, 3.6$ Hz), 5.39 (1H, d, $J = 10.2$ Hz), 5.04 (1H, s), 3.89 (1H, dd, $J = 13.5, 8.1$ Hz), 3.79 (3H, s), 3.54–3.42 (2H, m), 3.45 (1H, s), 3.22 (1H, d, $J = 13.5$ Hz), 2.89 (3H, s), 2.83 (1H, d, $J = 15.9$ Hz), 2.69 (1H, s), 2.60–2.51 (1H, m), 2.33–2.10 (2H, m), 2.09 (3H, s), 1.37–1.25 (1H, m), 1.07–1.00 (1H, m), 0.54 (3H, t, $J = 7.5$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 170.2, 166.3, 160.7, 153.9, 149.9, 147.6, 130.0, 128.5, 125.3, 123.9, 122.5, 121.1, 107.7, 107.2, 105.0, 101.4, 96.4, 82.3, 76.6, 75.7, 66.8, 55.0, 52.0, 51.1, 50.5, 44.5, 43.7, 42.5, 40.6, 30.9, 20.6, 7.3; ESIMS m/z 576.4 $[\text{M} + 1]^+$.

General Procedure for the Preparation of 5b–24b. 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) and hydrochloric acid (40 mL, 0.1 N) under a nitrogen atmosphere. After 10 min of stirring at room temperature, compounds **5a–24a** (1 mmol) were added. After 8 h of stirring at room temperature, sodium borohydride (80 mg) in ammonium hydroxide (8 mL) was added dropwise at 0 °C, and it was left to react for 15 min. The reaction mixture was extracted with CH_2Cl_2 (4 \times 20 mL), and the organic phase was filtered through Celite and concentrated at reduced pressure. Then each residue was purified by column chromatography on silica gel (100:1–80:1, CHCl_3 –MeOH) to afford each compound (**5b–24b**) as a white solid in over 50% yield.

3-Demethoxycarbonyl-3-(acetamino)methylanhdrovinblastine (5b): $[\alpha]_{\text{D}}^{20} +63.4$ (c 0.30, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.33 (1H, s), 7.95 (1H, s), 7.45 (1H, d, $J = 7.2$ Hz), 7.06 (3H, m), 6.52 (1H, s), 6.13 (1H, s), 6.10 (1H, d, $J = 8.7$ Hz), 5.81 (1H, dd, $J = 10.2, 4.5$ Hz), 5.42 (1H, d, $J = 4.8$ Hz), 5.35 (1H, d, $J = 10.2$ Hz), 4.96 (1H, s), 3.76 (3H, s), 3.55 (3H, s), 2.82 (3H, s), 2.55 (1H, s), 2.07 (3H, s), 1.93 (3H, s), 1.43 (1H, m), 0.93 (3H, t, $J = 7.2$ Hz), 0.73 (3H, t, $J = 6.9$ Hz); $^{13}\text{C NMR}$ (75 MHz, CDCl_3) δ 174.9, 170.9, 170.5, 158.1, 153.7, 139.9, 135.2, 131.1, 130.1, 129.6, 124.7, 124.0, 123.7, 123.7, 122.5, 121.8, 119.1, 118.5, 117.4, 110.7, 95.3, 82.4, 76.8, 76.0, 66.2, 56.0, 55.6, 54.7, 52.8, 52.6, 52.2, 50.3 (2 C), 46.0, 45.3, 43.5, 42.9, 40.9, 34.5, 32.9, 31.6, 28.0, 25.6, 23.5, 21.1, 12.4, 8.4; ESIMS m/z 806.5 $[\text{M} + 1]^+$; HRESIMS m/z $\text{C}_{47}\text{H}_{60}\text{N}_5\text{O}_7$ $[\text{M} + \text{H}]^+$ calcd for 806.4493, found 806.4495.

3-Demethoxycarbonyl-3-(propionylamino)methylanhdrovinblastine (6b): $[\alpha]_{\text{D}}^{20} +65.1$ (c 0.28, CHCl_3); $^1\text{H NMR}$ (300 MHz, CDCl_3) δ 9.40 (1H, s), 8.00 (1H, s), 7.45 (1H, d, $J = 7.5$ Hz), 7.13 (3H, m), 6.53 (1H, s), 6.18 (1H, d, $J = 7.8$ Hz), 6.14 (1H, s),

5.81 (1H, dd, $J = 10.2, 3.9$ Hz), 5.43 (1H, d, $J = 6.3$ Hz), 5.35 (1H, d, $J = 10.2$ Hz), 4.95 (1H, s), 3.76 (3H, s), 3.55 (3H, s), 3.28 (1H, s), 2.81 (3H, s), 2.56 (1H, s), 2.16 (2H, q, $J = 7.8$ Hz), 2.08 (3H, s), 1.87 (2H, q, $J = 7.8$ Hz), 1.41 (1H, m), 1.08 (3H, t, $J = 7.8$ Hz), 0.93 (3H, t, $J = 7.8$ Hz), 0.74 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 174.9, 174.3, 170.9, 158.0, 153.6, 139.8, 135.0, 130.9, 130.0, 129.5, 124.6, 123.8, 123.6, 123.6, 122.4, 121.7, 120.0, 118.4, 117.4, 110.7, 95.2, 82.2, 77.0, 76.0, 65.9, 56.0, 55.5, 54.6, 52.7, 52.5, 51.9, 50.1 (2 C), 45.8, 45.3, 43.1, 42.8, 40.7, 34.3, 32.8, 31.5, 29.9, 28.0, 25.3, 21.0, 12.3, 10.1, 8.4; ESIMS m/z 820.4 [M + 1] $^+$; HRESIMS m/z $\text{C}_{48}\text{H}_{62}\text{N}_5\text{O}_7$ [M + H] $^+$ calcd for 820.4649, found 806.4650.

3-Demethoxycarbonyl-3-(isobutylamino)methylanhydrovinblastine (7b): [α] $^{20}_{\text{D}}$ +64.0 (c 0.30, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 9.43 (1H, s), 8.01 (1H, s), 7.52 (1H, d, $J = 7.5$ Hz), 7.16 (3H, m), 6.61 (1H, s), 6.21 (1H, s), 6.19 (1H, s), 5.88 (1H, dd, $J = 10.2, 3.6$ Hz), 5.47 (1H, d, $J = 6.0$ Hz), 5.42 (1H, d, $J = 10.2$ Hz), 5.02 (1H, s), 3.82 (3H, s), 3.62 (3H, s), 3.34 (1H, s), 2.86 (3H, s), 2.62 (1H, s), 2.15 (3H, s), 1.96 (2H, q, $J = 7.5$ Hz), 1.49 (1H, m), 1.15 (3H, d, $J = 1.8$ Hz), 1.14 (3H, d, $J = 1.8$ Hz), 0.99 (3H, t, $J = 7.5$ Hz), 0.80 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 177.3, 174.3, 170.9, 158.0, 153.6, 139.8, 135.1, 131.0, 130.0, 129.5, 124.7, 123.9, 123.7, 123.7, 122.5, 121.7, 119.1, 118.5, 117.2, 110.7, 95.2, 82.1, 77.0, 76.0, 66.0, 56.0, 55.5, 54.6, 52.7, 52.6, 51.9, 50.8, 50.2, 45.8, 45.4, 42.8, 42.8, 40.6, 35.8, 34.4, 32.7, 31.5, 28.0, 25.3, 21.0, 19.8, 19.7, 12.3, 8.4; ESIMS m/z 834.4 [M + 1] $^+$; HRESIMS m/z $\text{C}_{49}\text{H}_{64}\text{N}_5\text{O}_7$ [M + H] $^+$ calcd for 834.4806, found 834.4805.

3-Demethoxycarbonyl-3-(pivaloylamino)methylanhydrovinblastine (8b): [α] $^{20}_{\text{D}}$ +64.1 (c 0.34, CHCl_3); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.93 (1H, s), 8.56 (1H, s), 7.44 (1H, d, $J = 8.1$ Hz), 7.29 (1H, d, $J = 8.1$ Hz), 6.98 (2H, m), 6.62 (2H, s), 6.55 (1H, s), 5.79 (1H, m), 5.50 (1H, d, $J = 5.7$ Hz), 5.43 (1H, d, $J = 10.2$ Hz), 4.78 (1H, s), 3.78 (3H, s), 3.58 (3H, s), 2.86 (3H, s), 2.08 (3H, s), 1.43 (1H, m), 1.10 (9H, s), 0.96 (3H, t, $J = 7.2$ Hz), 0.65 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 176.8, 174.2, 170.5, 157.4, 153.2, 139.9, 135.5, 131.3, 130.4, 128.6, 124.3, 123.8, 123.6, 121.9, 121.1, 118.1, 117.6, 115.2, 111.7, 95.5, 81.9, 76.1, 75.5, 64.1, 56.2, 55.0, 54.2, 52.6, 52.5, 52.0, 49.4, 48.7, 46.0, 45.4, 42.5, 42.0, 40.5, 40.3, 38.2, 35.2, 32.9, 31.4, 27.2 (3 C), 27.1, 26.6, 20.8, 12.2, 7.9; ESIMS m/z 848.4 [M + 1] $^+$; HRESIMS m/z $\text{C}_{50}\text{H}_{66}\text{N}_5\text{O}_7$ [M + H] $^+$ calcd for 848.4962, found 848.4965.

3-Demethoxycarbonyl-3-(butylamino)methylanhydrovinblastine (9b): [α] $^{20}_{\text{D}}$ +63.6 (c 0.30, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 9.41 (1H, s), 8.02 (1H, s), 7.52 (1H, d, $J = 7.8$ Hz), 7.19–7.09 (3H, m), 6.59 (1H, s), 6.19 (1H, s), 6.15 (1H, d, $J = 7.8$ Hz), 5.89 (1H, dd, $J = 10.2, 6.0$ Hz), 5.49 (1H, d, $J = 5.7$ Hz), 5.41 (1H, d, $J = 10.2$ Hz), 5.02 (1H, s), 3.83 (3H, s), 3.79–3.70 (1H, m), 3.62 (3H, s), 3.55 (1H, d, $J = 16.5$ Hz), 3.35 (1H, s), 2.88 (3H, s), 2.62 (1H, s), 2.18 (2H, t, $J = 7.5$ Hz), 2.15 (3H, s), 1.94 (2H, q, $J = 7.2$ Hz), 1.70–1.60 (2H, m), 1.53–1.45 (1H, m), 1.30–1.20 (1H, m), 1.00 (3H, t, $J = 7.5$ Hz), 0.94 (3H, t, $J = 7.5$ Hz), 0.80 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 174.9, 173.4, 170.8, 158.0, 153.6, 140.0, 135.1, 131.0, 130.0, 129.6, 124.7, 123.9, 123.7, 123.7, 122.4, 121.7, 119.0, 118.5, 117.5, 110.6, 95.2, 82.1, 77.0, 76.0, 66.0, 56.0, 55.6, 54.7, 52.7, 52.5, 52.2, 50.2 (2 C), 45.9, 45.4, 43.0, 42.8, 40.7, 39.0, 34.4, 33.0, 31.5, 27.9, 25.7, 21.2, 19.4, 14.0, 12.4, 8.4; ESIMS m/z 834.4 [M + 1] $^+$; HRESIMS m/z $\text{C}_{49}\text{H}_{64}\text{N}_5\text{O}_7$ [M + H] $^+$ calcd for 834.4806, found 834.4807.

3-Demethoxycarbonyl-3-(3'-methylbutylamino)methylanhydrovinblastine (10b): [α] $^{20}_{\text{D}}$ +66.0 (c 0.27, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 9.40 (1H, s), 8.03 (1H, s), 7.53 (1H, d, $J = 7.8$ Hz), 7.19–7.09 (3H, m), 6.58 (1H, s), 6.19 (1H, s), 6.15 (1H, d, $J = 7.8$ Hz), 5.89 (1H, dd, $J = 10.2, 6.0$ Hz), 5.49 (1H, d, $J = 5.7$ Hz), 5.41 (1H, d, $J = 10.2$ Hz), 5.02 (1H, s), 3.83 (3H, s), 3.79–3.72 (1H, m), 3.62 (3H, s), 3.55 (1H, d, $J = 16.5$ Hz), 3.35 (1H, s), 2.88 (3H, s), 2.62 (1H, s), 2.15 (3H, s), 2.10 (2H, d, $J = 9.9$ Hz), 1.95 (2H, q, $J = 7.2$ Hz), 1.69–1.59 (2H, m), 1.53–1.45 (1H, m), 1.31–1.21 (1H, m), 0.99 (3H, t, $J = 7.5$ Hz), 0.94 (6H, d, $J = 6.3$ Hz), 0.80 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 174.8, 172.8, 170.7, 158.0, 153.5, 140.1, 135.1, 131.1, 130.0, 129.5, 124.5, 123.9, 123.6, 123.6, 122.3, 121.8, 118.9, 118.4, 117.5, 110.5, 95.1, 82.0, 77.0, 75.9, 66.2, 55.9, 55.5, 54.6, 52.6, 52.4, 52.4, 50.3, 50.2, 46.2, 46.0, 45.3, 43.0, 42.8, 40.6, 34.4, 33.0, 31.5, 27.9, 26.2, 26.0, 22.6, 22.5, 21.0, 12.4, 8.3; ESIMS m/z 848.4 [M + 1] $^+$; HRESIMS m/z $\text{C}_{50}\text{H}_{66}\text{N}_5\text{O}_7$ [M + H] $^+$ calcd for 848.4962, found 848.4960.

3-Demethoxycarbonyl-3-(3',3'-dimethylbutylamino)methylanhydrovinblastine (11b): [α] $^{20}_{\text{D}}$ +68.1 (c 0.30, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 9.42 (1H, s), 8.01 (1H, s), 7.52 (1H, d, $J = 7.8$ Hz), 7.17–7.09 (3H, m), 6.58 (1H, s), 6.19 (1H, s), 6.07 (1H, d, $J = 7.8$ Hz), 5.88 (1H, dd, $J = 10.2, 3.6$ Hz), 5.49 (1H, d, $J = 6.0$ Hz), 5.41 (1H, d, $J = 10.2$ Hz), 5.02 (1H, s), 3.83 (3H, s), 3.79–3.69 (1H, m), 3.62 (3H, s), 3.32 (1H, s), 2.89 (3H, s), 2.81 (1H, d, $J = 14.1$ Hz), 2.59 (1H, s), 2.15 (3H, s), 2.10 (2H, s), 1.94 (2H, q, $J = 7.2$ Hz), 1.53–1.46 (1H, m), 1.49 (1H, m), 1.30–1.19 (1H, m), 1.02 (9H, s), 0.99 (3H, t, $J = 7.5$ Hz), 0.80 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 174.7, 172.1, 170.6, 158.0, 153.5, 140.1, 135.0, 131.0, 130.0, 129.5, 124.5, 123.9, 123.7, 123.6, 122.3, 121.7, 118.9, 118.4, 117.4, 110.5, 95.1, 81.9, 77.0, 75.9, 66.2, 55.9, 55.5, 54.6, 52.5, 52.4, 52.3, 50.6, 50.4, 50.1, 45.9, 45.3, 42.9, 42.8, 40.5, 34.4, 33.0, 31.4, 31.0, 29.9 (3 C), 29.7, 25.8, 21.0, 12.3, 8.3; ESIMS m/z 862.4 [M + 1] $^+$; HRESIMS m/z $\text{C}_{51}\text{H}_{68}\text{N}_5\text{O}_7$ [M + H] $^+$ calcd for 862.5119, found 862.5114.

3-Demethoxycarbonyl-3-(cyclopropanecarbonylamino)methylanhydrovinblastine (12b): [α] $^{20}_{\text{D}}$ +65.0 (c 0.20, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 9.38 (1H, s), 8.01 (1H, s), 7.52 (1H, d, $J = 7.5$ Hz), 7.19–7.09 (3H, m), 6.61 (1H, s), 6.31 (1H, d, $J = 7.2$ Hz), 6.19 (1H, s), 5.88 (1H, dd, $J = 10.2, 3.6$ Hz), 5.48 (1H, d, $J = 6.0$ Hz), 5.42 (1H, d, $J = 10.2$ Hz), 5.04 (1H, s), 3.83 (3H, s), 3.77–3.70 (1H, m), 3.62 (3H, s), 3.54 (1H, d, $J = 16.5$ Hz), 3.40 (1H, s), 2.89 (3H, s), 2.62 (1H, s), 2.15 (3H, s), 1.93 (2H, q, $J = 7.5$ Hz), 1.49 (1H, m), 1.00 (3H, t, $J = 7.5$ Hz), 0.93 (2H, m), 0.81 (3H, t, $J = 7.2$ Hz), 0.71 (2H, m); ^{13}C NMR (75 MHz, CDCl_3) δ 174.9, 173.6, 170.7, 158.0, 153.6, 140.1, 135.1, 131.1, 130.1, 129.5, 124.5, 123.9, 123.6, 123.6, 122.3, 121.8, 118.9, 118.4, 117.5, 110.5, 95.1, 82.4, 77.2, 76.0, 66.1, 56.0, 55.5, 54.6, 52.7, 52.4, 52.4, 50.2 (2 C), 46.0, 45.2, 43.7, 42.8, 40.7, 34.4, 33.1, 31.5, 27.9, 26.0, 21.0, 14.8, 12.4, 8.4, 7.0, 6.9; ESIMS m/z 832.3 [M + 1] $^+$; HRESIMS m/z $\text{C}_{49}\text{H}_{62}\text{N}_5\text{O}_7$ [M + H] $^+$ calcd for 832.4649, found 832.4651.

3-Demethoxycarbonyl-3-(cyclobutanecarbonylamino)methylanhydrovinblastine (13b): [α] $^{20}_{\text{D}}$ +68.0 (c 0.35, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 9.38 (1H, s), 8.01 (1H, s), 7.52 (1H, d, $J = 7.8$ Hz), 7.16–7.08 (3H, m), 6.60 (1H, s), 6.19 (1H, s), 6.08 (1H, d, $J = 7.8$ Hz), 5.87 (1H, dd, $J = 10.2, 3.6$ Hz), 5.47 (1H, d, $J = 6.0$ Hz), 5.41 (1H, d, $J = 10.2$ Hz), 5.01 (1H, s), 3.82 (3H, s), 3.62 (3H, s), 3.31 (1H, s), 2.87 (3H, s), 2.62 (1H, s), 2.14 (3H, s), 1.98–1.87 (2H, m), 1.48 (1H, m), 0.99 (3H, t, $J = 7.5$ Hz), 0.80 (3H, t, $J = 7.5$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 175.1, 174.7, 170.7, 158.0, 153.5, 140.0, 135.0, 131.0, 130.0, 129.5, 124.5, 123.9, 123.6, 123.6, 122.3, 121.7, 118.9, 118.4, 117.3, 110.5, 95.1, 82.2, 76.9, 75.9, 66.0, 55.9, 55.5, 54.5, 52.6, 52.4, 52.2, 50.1 (2 C), 45.9, 45.2, 43.0, 42.7, 40.6, 40.0, 34.3, 32.9, 31.4, 27.8, 25.7, 25.3 (2 C), 21.0, 18.2, 12.3, 8.3; ESIMS m/z 846.4 [M + 1] $^+$; HRESIMS m/z $\text{C}_{50}\text{H}_{64}\text{N}_5\text{O}_7$ [M + H] $^+$ calcd for 846.4806, found 846.4809.

3-Demethoxycarbonyl-3-(benzoylamino)methylanhydrovinblastine (14b): [α] $^{20}_{\text{D}}$ +60.0 (c 0.30, CHCl_3); ^1H NMR (300 MHz, $\text{DMSO}-d_6$) δ 9.90 (1H, s), 8.64 (1H, s), 7.78 (2H, d, $J = 7.8$ Hz), 7.49 (3H, m), 7.29 (1H, d, $J = 7.8$ Hz), 6.98 (3H, m), 6.62 (1H, s), 6.56 (1H, s), 5.75 (1H, dd, $J = 10.2, 4.5$ Hz), 5.47 (2H, m), 4.86 (1H, s), 3.80 (3H, s), 3.58 (3H, s), 2.90 (3H, s), 2.09 (3H, s), 0.95 (3H, t, $J = 7.2$ Hz), 0.66 (3H, t, $J = 6.9$ Hz); ^{13}C NMR (75 MHz, $\text{DMSO}-d_6$) δ 173.9, 173.6, 170.6, 166.38, 157.3, 153.6, 137.6, 137.0, 135.6, 134.6, 131.3 (2 C), 130.6, 128.5 (2 C), 127.0 (2 C), 124.4, 123.8 (2 C), 121.4, 121.0, 118.4, 117.7, 113.2, 112.7, 111.9, 95.3, 81.2, 76.6, 75.8, 63.8, 56.3, 55.0, 53.8, 52.6, 52.2, 49.5 (2 C), 48.7, 45.2 (2 C), 43.1, 42.1, 38.7, 34.8, 31.4, 31.4, 30.7, 27.2, 20.8, 11.8, 7.9; ESIMS m/z 868.3 [M + 1] $^+$; HRESIMS m/z $\text{C}_{52}\text{H}_{62}\text{N}_5\text{O}_7$ [M + H] $^+$ calcd for 868.4649, found 868.4645.

3-Demethoxycarbonyl-3-(4'-fluorobenzoylamino)methylanhydrovinblastine (15b): [α] $^{20}_{\text{D}}$ +66.4 (c 0.20, CHCl_3); ^1H NMR (300 MHz, CDCl_3) δ 9.51 (1H, s), 8.03 (1H, s), 7.80 (2H, dd, $J = 8.4, 5.4$ Hz), 7.53 (1H, d, $J = 7.5$ Hz), 7.19–7.08 (5H, m), 6.90 (1H, d, $J = 7.5$ Hz), 6.63 (1H, s), 6.21 (1H, s), 5.90 (1H, dd, $J = 10.2, 3.9$ Hz), 5.46 (1H, s), 5.44 (1H, d, $J = 10.2$ Hz), 5.09 (1H, s), 3.95–3.88 (1H, m), 3.83 (3H, s), 3.63 (3H, s), 3.53 (1H, d, $J = 16.8$ Hz), 3.41 (1H, s), 2.91 (3H, s), 2.85 (1H, d, $J = 16.2$ Hz), 2.66 (1H, s), 2.14 (3H, s), 1.93 (2H, q, $J = 7.5$ Hz), 1.54–1.49 (1H, m), 0.99 (3H, t, $J = 7.5$ Hz), 0.82 (3H, t, $J = 7.2$ Hz); ^{13}C NMR (75 MHz, CDCl_3) δ 174.9, 171.0, 166.6, 166.5 (d), 158.0, 153.6, 139.9, 135.1, 130.9 (2 C), 130.0, 129.5, 129.3 (d, 2 C), 124.7, 123.9, 123.7, 123.6, 122.5, 121.9, 119.0,

118.5, 117.5, 115.7 (d, 2 C), 110.7, 95.3, 82.7, 77.0, 76.1, 65.9, 56.0, 55.6, 54.7, 52.9, 52.6, 52.0, 50.2, 50.1, 45.8, 45.4, 43.8, 42.8, 41.0, 34.4, 32.8, 31.6, 28.0, 25.5, 21.1, 12.3, 8.4; ESIMS m/z 886.4 [M + 1]⁺; HRESIMS m/z C₅₂H₆₁FN₅O₇ [M + H]⁺ calcd for 886.4555, found 886.4551.

3-Demethoxycarbonyl-3-(2'-chlorobenzoylamino)methylanhydrovinblastine (16b): [α]_D²⁰ +65.1 (c 0.30, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.44 (1H, s), 8.04 (1H, s), 7.60 (1H, dd, J = 6.6, 2.1 Hz), 7.52 (1H, d, J = 7.8 Hz), 7.32 (3H, m), 7.13 (3H, m), 6.90 (1H, d, J = 7.5 Hz), 6.61 (1H, s), 6.23 (1H, s), 5.88 (1H, dd, J = 10.2, 4.2 Hz), 5.47 (1H, s), 5.44 (1H, d, J = 10.2 Hz), 5.09 (1H, s), 3.98 (1H, m), 3.83 (3H, s), 3.62 (3H, s), 3.46 (1H, s), 3.00 (3H, s), 2.81 (2H, d, J = 15.6 Hz), 2.62 (1H, s), 2.18 (3H, s), 1.93 (2H, q, J = 7.5 Hz), 1.51 (1H, m), 1.26 (1H, m), 0.99 (3H, t, J = 7.5 Hz), 0.82 (3H, t, J = 6.9 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 174.9, 170.9, 166.9, 158.1, 153.7, 140.0, 135.6, 135.1, 131.3, 130.8, 130.3, 130.0 (2 C), 130.0, 129.6, 127.2, 124.6, 124.0, 123.7, 123.7, 122.4, 121.8, 119.0, 118.5, 117.5, 110.6, 94.7, 82.1, 77.0, 76.1, 66.2, 56.0, 55.6, 54.7, 52.7, 52.5, 52.2, 50.3, 50.2, 46.0, 45.4, 43.8, 42.9, 41.0, 34.5, 33.0, 31.6, 28.0, 25.8, 21.2, 12.4, 8.4; ESIMS m/z 902.5 [M + 1]⁺; HRESIMS m/z C₅₂H₆₁ClN₅O₇ [M + H]⁺ calcd for 902.4260, found 902.4263.

3-Demethoxycarbonyl-3-(3'-chlorobenzoylamino)methylanhydrovinblastine (17b): [α]_D²⁰ +65.8 (c 0.32, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.48 (1H, s), 8.03 (1H, s), 7.77 (1H, s), 7.66 (1H, d, J = 7.8 Hz), 7.53 (1H, d, J = 7.8 Hz), 7.47 (1H, d, J = 7.8 Hz), 7.36 (1H, t, J = 7.8 Hz), 7.19–7.09 (3H, m), 6.95 (1H, d, J = 7.8 Hz), 6.63 (1H, s), 6.22 (1H, s), 5.90 (1H, dd, J = 9.6, 4.5 Hz), 5.47–5.43 (2H, m), 5.08 (1H, s), 3.93 (1H, dd, J = 13.5, 7.5 Hz), 3.83 (3H, s), 3.63 (3H, s), 3.53 (1H, d, J = 16.5 Hz), 3.40 (1H, s), 2.92 (3H, s), 2.85 (1H, d, J = 15.9 Hz), 2.66 (1H, s), 2.14 (3H, s), 1.93 (2H, q, J = 7.2 Hz), 1.54–1.47 (1H, m), 1.31–1.25 (1H, m), 0.99 (3H, t, J = 7.5 Hz), 0.82 (3H, t, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 174.8, 170.9, 166.1, 158.1, 153.5, 140.0, 136.6, 135.1, 134.7, 131.5, 131.0, 130.0 (2 C), 129.5, 127.3, 125.1, 124.7, 123.9, 122.7, 123.6, 122.4, 122.1, 119.0, 118.5, 117.5, 110.6, 95.4, 82.8, 76.8, 76.0, 65.9, 56.0, 55.6, 54.6, 52.9, 52.5, 52.2, 50.1 (2 C), 45.9, 45.3, 43.8, 42.8, 41.1, 34.4, 33.0, 31.5, 27.9, 25.8, 21.1, 12.4, 8.4; ESIMS m/z 902.5 [M + 1]⁺; HRESIMS m/z C₅₂H₆₁ClN₅O₇ [M + H]⁺ calcd for 902.4260, found 902.4262.

3-Demethoxycarbonyl-3-(4'-chlorobenzoylamino)methylanhydrovinblastine (18b): [α]_D²⁰ +64.9 (c 0.30, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.48 (1H, s), 8.04 (1H, s), 7.73 (2H, d, J = 8.7 Hz), 7.52 (1H, d, J = 7.5 Hz), 7.39 (1H, d, J = 8.7 Hz), 7.13 (3H, m), 6.93 (1H, d, J = 6.9 Hz), 6.63 (1H, s), 6.21 (1H, s), 5.89 (1H, dd, J = 10.2, 4.2 Hz), 5.46 (1H, s), 5.46 (1H, d, J = 10.2 Hz), 5.09 (1H, s), 3.91 (1H, m), 3.83 (3H, s), 3.62 (3H, s), 3.40 (1H, s), 2.91 (3H, s), 2.84 (2H, d, J = 16.5 Hz), 2.65 (1H, s), 2.12 (3H, s), 1.93 (2H, q, J = 7.2 Hz), 1.51 (1H, m), 1.28 (1H, m), 0.99 (3H, t, J = 7.5 Hz), 0.82 (3H, t, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 174.9, 171.0, 166.5, 158.1, 153.6, 140.0, 137.8, 135.2, 131.2, 130.1, 130.1, 129.6, 129.0 (2 C), 128.5 (2 C), 124.7, 124.0, 123.8, 123.7, 122.5, 122.1, 119.1, 118.6, 117.5, 110.7, 95.4, 82.9, 77.0, 76.1, 66.0, 56.0, 55.7, 54.7, 52.9, 52.6, 52.3, 50.3 (2 C), 46.0, 45.4, 43.9, 42.9, 41.1, 34.5, 33.0, 31.6, 28.0, 25.8, 21.1, 12.4, 8.4; ESIMS m/z 902.5 [M + 1]⁺; HRESIMS m/z C₅₂H₆₁ClN₅O₇ [M + H]⁺ calcd for 902.4260, found 902.4263.

3-Demethoxycarbonyl-3-(pyridine-4'-carbonylamino)methylanhydrovinblastine (19b): [α]_D²⁰ +65.0 (c 0.30, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.57 (1H, s), 8.73 (2H, d, J = 6.0 Hz), 8.03 (1H, s), 7.62 (2H, d, J = 6.0 Hz), 7.52 (1H, d, J = 7.5 Hz), 7.20–7.09 (3H, m), 6.63 (1H, s), 6.22 (1H, s), 5.90 (1H, dd, J = 10.2, 3.9 Hz), 5.46 (1H, d, J = 10.2 Hz), 5.43 (1H, s), 5.09 (1H, s), 3.97–3.90 (1H, m), 3.83 (3H, s), 3.63 (3H, s), 3.52 (1H, d, J = 16.5 Hz), 3.38 (1H, s), 2.91 (3H, s), 2.67 (1H, s), 2.13 (3H, s), 1.92 (2H, q, J = 7.5 Hz), 1.53–1.48 (1H, m), 0.99 (3H, t, J = 7.5 Hz), 0.82 (3H, t, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 174.7, 170.9, 165.4, 158.0, 153.4, 150.6 (2 C), 141.7, 140.0, 135.1, 130.9, 129.9, 129.5, 124.7, 123.8, 123.7, 123.5, 122.5, 122.1, 120.9 (2 C), 119.0, 118.5, 117.3, 110.6, 95.3, 82.8, 76.8, 75.9, 65.8, 56.0, 55.6, 54.6, 52.9, 52.5, 52.0, 50.2, 50.0, 45.8, 45.3, 43.8, 42.8, 41.2, 34.3, 32.7, 31.5, 27.9, 25.4, 21.1, 12.3, 8.4; ESIMS m/z 869.5 [M + 1]⁺; HRESIMS m/z C₅₁H₆₁N₆O₇ [M + H]⁺ calcd for 869.4602, found 869.4601.

3-Demethoxycarbonyl-3-(4'-nitrobenzoylamino)methylanhydrovinblastine (20b): [α]_D²⁰ +64.3 (c 0.20, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.58 (1H, s), 8.28 (2H, d, J = 8.7 Hz), 8.04 (1H, s),

7.94 (2H, d, J = 8.7 Hz), 7.53 (1H, d, J = 7.5 Hz), 7.13 (4H, m), 6.64 (1H, s), 6.23 (1H, s), 5.91 (1H, dd, J = 10.2, 4.2 Hz), 5.47 (1H, s), 5.45 (1H, d, J = 10.2 Hz), 5.09 (1H, s), 3.91 (1H, m), 3.84 (3H, s), 3.63 (3H, s), 3.43 (1H, s), 2.93 (3H, s), 2.84 (2H, d, J = 16.5 Hz), 2.68 (1H, s), 2.13 (3H, s), 1.93 (2H, q, J = 7.2 Hz), 1.51 (1H, m), 1.28 (1H, m), 0.99 (3H, t, J = 7.5 Hz), 0.82 (3H, t, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 174.8, 171.0, 165.4, 158.1, 153.4, 149.6, 140.3, 140.0, 135.1, 130.9, 130.0, 129.6, 128.2 (2 C), 124.8, 124.0 (2 C), 123.8 (2 C), 123.5, 122.5, 122.3, 119.1, 118.5, 117.6, 110.7, 95.4, 83.0, 76.8, 76.0, 65.8, 56.0, 55.6, 54.5, 53.0, 52.6, 52.2, 50.2, 50.1, 45.9, 45.4, 44.0, 42.9, 41.4, 34.4, 33.0, 31.6, 28.0, 25.7, 21.2, 12.4, 8.4; ESIMS m/z 913.4 [M + 1]⁺; HRESIMS m/z C₅₂H₆₁N₆O₉ [M + H]⁺ calcd for 913.4500, found 913.4503.

3-Demethoxycarbonyl-3-(2'-methoxybenzoylamino)methylanhydrovinblastine (21b): [α]_D²⁰ +62.1 (c 0.20, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.27 (1H, s), 8.47 (1H, d, J = 7.2 Hz), 8.14 (1H, d, J = 7.5 Hz), 8.05 (1H, s), 7.52 (1H, d, J = 7.5 Hz), 7.42 (1H, t, J = 7.5 Hz), 7.14 (3H, m), 7.08 (1H, t, J = 7.5 Hz), 6.96 (1H, d, J = 7.5 Hz), 6.61 (1H, s), 6.20 (1H, s), 5.88 (1H, dd, J = 10.2, 4.2 Hz), 5.49 (1H, s), 5.45 (1H, d, J = 10.2 Hz), 5.09 (1H, s), 3.93 (1H, m), 3.90 (3H, s), 3.82 (3H, s), 3.61 (3H, s), 3.44 (1H, s), 2.91 (3H, s), 2.83 (2H, d, J = 15.6 Hz), 2.63 (1H, s), 2.13 (3H, s), 1.93 (2H, q, J = 7.5 Hz), 1.51 (1H, m), 1.26 (1H, m), 0.99 (3H, t, J = 7.5 Hz), 0.82 (3H, t, J = 6.9 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 174.9, 170.9, 165.5, 158.1, 157.7, 153.8, 140.0, 135.1, 132.6, 132.0, 131.3, 130.2, 129.6, 124.6, 124.0, 123.8, 123.7, 122.4, 122.3, 121.5, 121.2, 119.0, 118.5, 117.5, 111.6, 110.6, 95.1, 82.2, 77.3, 76.1, 66.3, 56.1, 56.0, 55.6, 54.7, 52.7, 52.5, 52.3, 50.4, 50.3, 46.0, 45.4, 43.8, 42.9, 40.6, 34.5, 33.0, 31.6, 28.0, 25.8, 21.1, 12.4, 8.4; ESIMS m/z 898.5 [M + 1]⁺; HRESIMS m/z C₅₃H₆₄N₅O₈ [M + H]⁺ calcd for 898.4755, found 898.4751.

3-Demethoxycarbonyl-3-(4'-methoxybenzoylamino)methylanhydrovinblastine (22b): [α]_D²⁰ +63.1 (c 0.17, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.24 (1H, s), 8.00 (1H, s), 7.52 (1H, d, J = 7.8 Hz), 7.20 (2H, d, J = 8.7 Hz), 7.14–7.08 (3H, m), 6.87 (2H, d, J = 8.7 Hz), 6.58 (1H, s), 6.17 (1H, d, J = 8.4 Hz), 6.10 (1H, s), 5.85 (1H, dd, J = 10.2, 4.2 Hz), 5.46 (1H, s), 5.38 (1H, d, J = 10.2 Hz), 4.95 (1H, s), 3.84 (3H, s), 3.79 (3H, s), 3.63 (1H, s), 3.12 (1H, s), 2.91 (1H, d, J = 13.5 Hz), 2.80 (1H, d, J = 15.9 Hz), 2.68 (3H, s), 2.59 (1H, s), 2.13 (3H, s), 1.93 (2H, q, J = 7.2 Hz), 1.45 (1H, m), 1.00 (3H, t, J = 7.5 Hz), 0.79 (3H, t, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 174.7, 171.5, 171.0, 158.8, 158.0, 153.5, 139.8, 135.1, 131.0, 130.6 (2 C), 130.0, 129.5, 127.4, 124.6, 123.9, 123.9, 123.7, 122.4, 122.3, 119.0, 118.4, 117.2, 114.4 (2 C), 110.6, 95.6, 82.8, 76.6, 75.7, 65.9, 56.0, 55.6, 55.4, 54.6, 52.7, 52.5, 52.1, 50.1 (2 C), 45.9, 45.5, 43.2, 42.8, 40.9, 34.4, 32.8, 31.5, 27.9, 25.6, 21.1, 12.4, 8.4; ESIMS m/z 898.5 [M + 1]⁺; HRESIMS m/z C₅₃H₆₄N₅O₈ [M + H]⁺ calcd for 898.4755, found 898.4752.

3-Demethoxycarbonyl-3-(phenylacetylaminomethyl)anhydrovinblastine (23b): [α]_D²⁰ +58.7 (c 0.15, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.25 (1H, s), 7.99 (1H, s), 7.52 (1H, d, J = 7.5 Hz), 7.37–7.27 (5H, m), 7.19–7.11 (3H, m), 6.59 (1H, s), 6.18 (1H, d, J = 8.7 Hz), 6.09 (1H, s), 5.84 (1H, dd, J = 10.2, 4.2 Hz), 5.45 (1H, s), 5.38 (1H, d, J = 10.2 Hz), 4.95 (1H, s), 3.84 (3H, s), 3.79–3.77 (1H, m), 3.63 (3H, s), 3.56 (2H, s), 3.10 (1H, s), 2.91 (1H, d, J = 13.8 Hz), 2.80 (1H, d, J = 15.9 Hz), 2.65 (3H, s), 2.59 (1H, s), 2.13 (3H, s), 1.92 (2H, q, J = 7.5 Hz), 1.51–1.44 (1H, m), 1.25–1.20 (1H, m), 1.00 (3H, t, J = 7.5 Hz), 0.79 (3H, t, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 174.7, 171.1, 171.0, 158.0, 153.7, 135.5, 135.1, 131.0, 130.0, 129.6 (2 C), 129.4, 129.0 (2 C), 127.2, 126.3, 124.7, 124.0, 123.7, 122.7, 121.8, 119.3, 118.4, 116.8, 110.7, 95.6, 82.7, 76.8, 75.8, 66.0, 56.0, 55.6, 54.6, 52.7, 52.6, 51.8, 50.1 (2 C), 45.8, 45.5, 44.2, 43.3, 42.9, 40.9, 34.4, 32.4, 31.5, 27.9, 24.8, 21.1, 12.4, 8.4; ESIMS m/z 882.5 [M + 1]⁺; HRESIMS m/z C₅₃H₆₄N₅O₇ [M + H]⁺ calcd for 882.4806, found 882.4805.

3-Demethoxycarbonyl-3-(3',4'-methylenedioxybenzoylamino)methylanhydrovinblastine (24b): [α]_D²⁰ +69.1 (c 0.20, CHCl₃); ¹H NMR (300 MHz, CDCl₃) δ 9.45 (1H, s), 8.03 (1H, s), 7.53 (1H, d, J = 8.1 Hz), 7.32 (1H, d, J = 8.1 Hz), 7.29 (1H, s), 7.18–7.09 (3H, m), 6.83 (2H, m), 6.62 (1H, s), 6.20 (1H, s), 6.02 (2H, s), 5.90 (1H, dd, J = 10.2, 3.9 Hz), 5.46 (2H, m), 5.08 (1H, s), 3.93–3.86 (1H, m), 3.83 (3H, s), 3.63 (3H, s), 3.52 (1H, d, J = 16.5 Hz), 3.40 (1H, s), 2.91 (3H, s), 2.65 (1H, s), 2.58 (1H, d, J = 12.9 Hz), 2.14 (3H, s), 1.97–1.89 (2H, m), 1.54–1.47 (1H, m), 1.31–1.25 (1H, m), 0.99 (3H, t, J = 7.5 Hz), 0.82 (3H, t, J = 7.2 Hz); ¹³C NMR (75 MHz, CDCl₃) δ 174.6,

170.8, 166.7, 158.0, 153.6, 150.3, 148.0, 139.8, 135.0, 131.0, 130.0, 129.4, 129.0, 124.7, 123.9, 123.7, 123.6, 122.9, 122.6, 121.6, 119.3, 118.5, 117.3, 110.6, 108.2, 107.7, 101.7, 95.2, 82.6, 76.9, 76.0, 66.0, 55.9, 55.5, 54.7, 52.8, 52.5, 51.7, 50.2 (2 C), 45.7, 45.4, 43.6, 42.8, 40.8, 34.4, 32.4, 31.5, 27.8, 24.9, 21.1, 12.3, 8.5; ESIMS m/z 912.4 $[M + 1]^+$; HRESIMS m/z C₅₃H₆₂N₅O₉ $[M + H]^+$ calcd for 912.4548, found 912.4551.

General Procedure for the Preparation of 5b–24b Tartrate. To a solution of tartaric acid (150 mg, 1 mmol) in acetone (20 mL) was added dropwise a solution of compounds **5b–24b** (0.5 mmol) in acetone (10 mL). After 10 min of stirring at room temperature, the reaction mixture was concentrated at reduced pressure to afford each compound (**5b–24b**) tartrate as a white solid.

Cytotoxicity Assays. The cytotoxicity testing was carried out according to a previously reported procedure.¹⁵

Antitumor Activity against Scarcoma 180 in Vivo. The antitumor activity evaluation was carried out according to a previously reported procedure.¹⁸

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Supporting Information Available: NMR spectra for compounds **5b–24b**. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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