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Amino Acid Derivatives, Part 2: Synthesis, Antiviral, and Antitumor Activity of Simple Protected Amino Acids Functionalized at *N*-terminus with Naphthalene Side Chain

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ABSTRACT: *Coupling of various acylated amino acid derivatives with (naphthalen-2-lyloxy)acetic acid (***3***) in the presence of 1-hydroxy-benzoteriazole (HOBt) and DCC afforded the new amides* **6–12**. *Alternatively, the latter compounds were prepared from reaction of the corresponding hydrazide* **5**, *via the azide-coupling method, with the acylated amino acid derivatives. Treatment of* **6, 10–12** *with $N_2H_4 \cdot H_2O$ afforded the hydrazides* **13–16**, *respectively, as key intermediates for the synthesis of peptide derivatives. Reaction of* **12**, *as a acceptor, with the glycosyl-trichloroimidate* **18**, *as donors in the presence of TMSOTf gave the new glycoside* **19**. *The new compounds were evaluated for their anti-HIV-1, antibovine viral diarrhea virus (BVDV), and antitumor activity.* © 2005 Wiley Periodicals, Inc.

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INTRODUCTION

Recently, a major progress has been made in the treatment of HIV infection by the introduction of highly active antiretroviral therapy (HAART, a combination of nucleoside and nonnucleoside reverse transcriptase inhibitors (NNRTIs), and/or protease inhibitors, but the massive viral replication led to the emergence of drug-resistance strains and the urgent need for the new therapeutic approaches [1,2]. Kaletra, the first second-generation protease inhibitor to reach drug status, is a mixture of two protease inhibitors, lopnavir [3,4] and ritonavir [5]. New class of protease inhibitors incorporating amino acyl sulfonamide moieties was represented as an effective HIV isolates resistance

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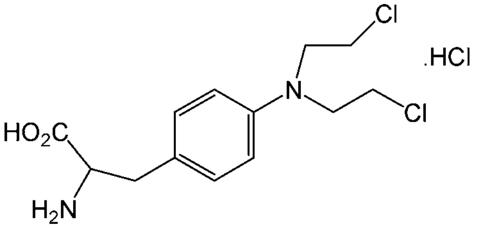
to the six clinically used drugs (saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, and lopinavir). Furthermore, amino acid derivatives such as lysyl amide prodrug of 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole [6], amino acid derivatives of paclitaxol [7], pyroglutamic acid [8], cysteine-modifying agents [9], and isoquinoline carboxylic acid derivative [10] are described as building block for HIV protease inhibitors [11]. On the other hand, difunctional enols of simple N-protected amino acids were reported as potential inhibitors of the HIV-1 protease [12]. Recently, De Clercq [13] has reviewed the new developments in the anti-HIV chemotherapy. On the other hand, several α-amino acids conjugated heterocyles reported as potential antitumor agents such as 4-toluensulfonylureido derivatives of amines, amino acids, dipeptides [14], and 2-(4-aminophenyl)benzothiazoles [15]. Some alkylating agents bearing amino acid residues showed highly cytotoxicity activity against various cancer cell lines, such as melphalan (L-phenylalanine mustard hydrochloride) **1** [16]. In connection with our recent attempts [17] to search for new protease inhibitors or nonnucleoside reverse transcriptase inhibitors, we report here the modification of protected amino acids ester by introduction of naphthalene residue via the coupling method.



1 Melphalan

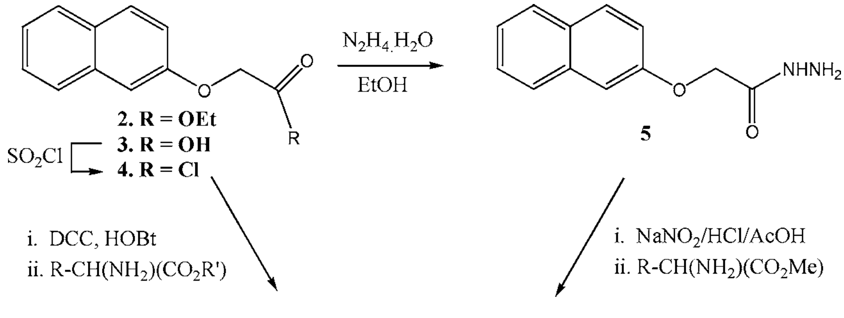
RESULTS AND DISCUSSION

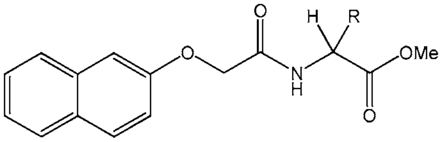
(Naphthalen-2-lyloxy)acetic acid (**3**) [18] has been selected as a starting material for coupling reaction with appropriate acylated amino acids. An convenient coupling method [19] was employed for the formation of peptides by reaction of the carboxylic acid group with acylated amino acid, using 1-hydroxy-benzotriazole (HOBt) [20,21] and *N*,*N*′-dicyclohexylcarbodiimide (DCC) [22], as coupling reagents. HOBt is widely used as additive to decrease racemization in the carbodiimide peptide coupling, since the alkylated proline is known as being chirally stable on "activation" for peptide coupling, and there are only few examples of reporting its racemization. One of the proposed mechanisms of racemization of amino acid derivatives is the direct ionization of α-hydrogen has been implicated in the racemization of derivatives of serine, tyrosine, phenylalanine, and cysteine [20]. Thus, treatment of **3** with the acylated amino acids (glycine, L-valine, L-tyrosine, L-leucine, L-alanine, L-methionine, and L-serine acetate hydrochloride) in the presence of coupling reagents afforded **6–12**, respectively, in 71–87% yield. Alternatively, **6–12** were prepared from the hydrazide derivative **5** via the azide-coupling method. The hydrazide **5** was prepared by two methods: direct treatment of the methyl (naphthalen-2-lyloxy)acetate (**2**) with $N_2H_4{\cdot}H_2O$ in EtOH [23], or treatment of acyl chloride **4**, prepared from chlorination of **3** by SO_2Cl, with $N_2H_4{\cdot}H_2O$ [24]. Treatment of **5**, in HOAc, with aq. $NaNO_2$ at low temperature afforded the unseparable azide derivative. The azide was reacted directly with the appropriate amino acid hydrochloride in ethyl acetate containing Et_3N at 0°C for 20 min gave, after neutralization, the desired amides **6–12** in 55–73% yield (Scheme 1).

Next, our target was the formation of peptide derivatives following the above procedure by treatment of hydrazide derivative as a starting precursor with amino acid ester, via the azide-coupling method. By following Sahin et al. method [23], the esters **6, 10–12** were boiled with $N_2H_4{\cdot}H_2O$ in EtOH to give the hydrazides **13–16** in 89, 81, 76, and 71% yield, respectively (Scheme 1).

An efficient anomeric stereocontrolled glycosylation method, with high yield of α-anomer, was reported recently [25,26], by using *O*-glycosyl trichloroacetoimidate as donor and alcohol as acceptor precursors in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as Lewis acid. Compound **12** was selected in our present work as alcohol acceptor for coupling with the protected D-mannofuranosyl-1-trichloroacetimidate **18**, as a donor precursor in the synthesis of new glycoamide derivative **19** (75%). The trichloroacetimidate **18** was prepared from reaction of **17** with trichloroacetonitrile in the presence of DBU as catalyst (Scheme 2).

The structures of the newly synthesized compounds **6–19** were determined from their ^1H-, ^{13}C NMR and mass spectra. The ^1H NMR spectra of **6–13** showed similar pattern of naphthalene aromatic protons. The C_{12}-NH, H-5, and H-8 were appeared as multiplets at δ 7.48–7.87, while H-7 and H-6 appeared as doublet of doublets of doublets (ddd) at the region δ 7.41–7.49 and δ 7.31–7.45 ($J_{5,7} = J_{6,8} \sim 1.2$ Hz; $J_{5,6} = J_{6,7} = J_{7,8} \sim 8.1$ Hz), respectively. The doublet of doublets at the region δ 7.19–7.30 ($J \sim 2.3$ Hz, 8.0 Hz) were attributed to H-3, while the doublets at δ 7.60–7.18 ($J \sim 2.5$ Hz) were assigned to

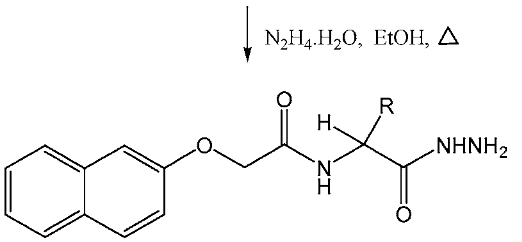




	R	amino acid
6	H	glycine
7	$CH(Me)_2$	L-valine
8	CH_2-*p*-OH-Ph	L-tyrosine
9	$CH_2CH(Me)_2$	L-leucine
10	Me	L-alanine
11	CH_2CH_2SMe	L-methionine
12	CH_2OH	L-serine

SCHEME 1

H-1. CH_2-10 protons were appeared as singlets at δ 4.60–4.73, except those of **10**, which appeared as doublet at δ 4.63 ($J = 2.7$ Hz). The protons of the amino acid residues were fully assigned. ^{13}C NMR spectra of the most new amides (Experimental section), showed similar pattern of naphthalene carbon resonances, meanwhile compound **11** was selected for this study. The carbonyl groups C-11 and C-14 resonated at δ 180.0 and δ 168.1, respectively. The naphthalene carbon resonated at relatively higher field. C-2 and C-8a appeared at δ 155.0 and 134.7, respectively, while C-1 to C-8 resonated in the region δ 108.2–129.9. C-10, acetyl, and C-13 were oriented at δ 67.0, 52.5, and 51.0. The resonances at δ 31.1 and δ 30.0 were attributed to C-15 and C-16, respectively, while SMe group appeared at lower field (δ 12.5). Similarly, compounds **13–16** and **19** were identified from their ^1H, ^{13}C NMR and mass spectra.



	R	amino acid
13	H	glycine
14	Me	L-alanine
15	CH_2CH_2SMe	L-methionine
16	CH_2OH	L-serine

BIOLOGICAL ACTIVITY

Antiviral Assay

Compounds **6–16** and **19** were tested for their anti-HIV-1 activity, in vitro, using III_B strain in human T-lymphocyte (MT-4) cells, and the results are summarized in Table 1 in which the data have been included for comparison purposes. Compound-induced cytotoxicity was also measured in MT-4 cells along with the antiviral activity.

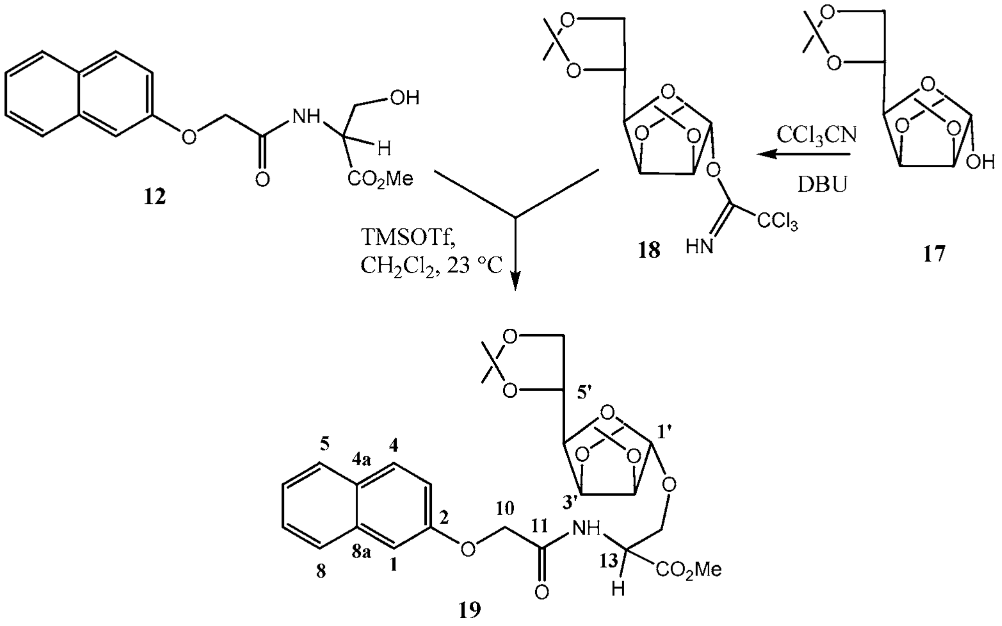
TABLE 1 In vitro Anti-HIV-1[a] From Some Naphthalene Compounds

	CC_{50} (μg/mL)[b] *MT-4*	*EC_{50} (μg/mL)[c]* *HIV-1*
6	>100	>100
7	42	>42
8	65	>65
9	>100	>100
10	59	>59
11	>100	>100
12	>100	>100
13	>100	>100
14	46	>46
15	>100	>100
14	>100	>100
EFV	40	0.003
AZT	63	0.02

[a] Anti-HIV-1 activity measured with strain III_B.

[b] Compound concentration required to reduce the viability of mock-infected MT-4 cells by 50%, as determined by the MTT method.

[c] Compound concentration required to achieve 50% protection of MT-4 cells from the HIV-1 induced cytopathogenicity, as determined by the MTT method.



SCHEME 2

The cavity on gp41 of the HIV plays an important role in the viral replication process, which could hold a small molecule inhibitor, and peptides containing D-amino acids that would fit this cavity have been identified and inhibit fusion. Accordingly, our synthetic strategy for synthesis of the new amino acids derivatives bearing naphthalene residue depends on this hypothesis. None of the new amino acid derivatives were found to inhibit HIV-1 replication, in vitro, at EC_{50} lower than the CC_{50} in comparison to the antiviral agent efavirenz (EFV) [27] and azidothymidine (AZT) [28]. In conclusion, the above data showed no selective anti-HIV activity.

The above compounds were screened against BVDV (bovine viral diarrhea virus) activity, and showed no inhibition at nontoxic concentrations, since the minimum inhibitory concentration required to reduce the virus-induced cytopathogenicity by 50% was higher than 19 or >100 μg/mL, as shown in Table 2. Compounds **9–16** and **19** showed CC_{50} and EC_{50} >100 μg/mL.

TABLE 2 In vitro Cytotoxicity and Anti-BVDV Activity of Some Naphthalene Compounds

Compound	*CC_{50} (μg/mL)*	*EC_{50} (μg/mL)*
6	>100	74
7	85	>85
8	>100	19

Anticancer Assay

Compounds **6–16** and **19** were evaluated for a preliminary estimation of the in vitro tumor-inhibiting activity against a panel of tumor cell lines consisting of CD4 human T-cells containing an integrated human T-leukemia virus type 1 (HTLV-1), CD4 human acute T-lymphoblastic leukemia, human splenic B-lymphoblastoid cells, human acute B-lymphoblastic leukemia, human skin melanoma, human breast adenocarcinoma, human lung squamous carcinoma, human hepatocellular carcinoma, human prostate carcinoma, human foreskin fibroblasts, and human lung fibroblasts, using the microculture tetrazolium assay (MTT) method [29]. This method is based on a metabolic reduction of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT), and the results are summarized in Table 3.

None of the new compounds were active against all tumor cell lines (CC_{50} = >100 μM), except compound **7** which showed marked activity against leukemia/lymphoma of MT4 cell line (CC_{50} = 42 μM). On the basis of the screened compounds, it is concluded that the side chain alkyl group of the L-valine might explain the cytotoxicity of **7** and causes a slight change in the antitumor activity, in comparison to the other amino acid derivatives.

EXPERIMENTAL

Melting points are uncorrected. NMR spectra were recorded on a 250 and 600 MHz (^1H), and 150.91

TABLE 3 In Vitro Antitumor Activity in Most Sensitive Tumor Cell Lines

Tumor	*Cell Lines*	*CC_{50}[a] (μM)*	*Tumor*	*Cell Lines*	*CC_{50}[a] (μM)*
Compound **7**			Compound **8**		
Leukemia/lymphoma	*MT4*[b]	42	Leukemia/lymphoma	*MT4*[b]	65
	CCRF-CEM[c]	60		*CCRF-CEM*[c]	80
	WIL-2NS[d]	70		*WIL-2NS*[d]	68
	CCRF-SB[e]	65		*CCRF-SB*[e]	80
MT-4		42	MT-4		65
MDBK		85	MDBK		>100
Solid tumor-derived cell lines	*SK-MEL-28*[f]	>100	Solid tumor-derived cell lines	*SK-MEL-28*[f]	>100
	MCF7[g]	>100		*MCF7*[g]	>100
	SKMES-1[h]	>100		*SKMES-1*[h]	>100
	HepG2[i]	>100		*HepG2*[i]	>100
	DU145[j]	>100		*DU145*[j]	>100
Normal-cell lines	CRL 7065[k]	>100	Normal-cell lines	CRL 7065[k]	>100
	MRC-5[l]	>100		MRC-5[l]	>100
Compound **10**			Compound **14**		
Leukemia/lymphoma	*MT4*[b]	59	Leukemia/lymphoma	*MT4*[b]	46
	CCRF-CEM[c]	64		*CCRF-CEM*[c]	67
	WIL-2NS[d]	58		*WIL-2NS*[d]	78
	CCRF-SB[e]	73		*CCRF-SB*[e]	85
MT-4		59	MT-4		46
MDBK		>100	MDBK		>100
Solid tumor-derived cell lines	*SK-MEL-28*[f]	>100	Solid tumor-derived cell lines	*SK-MEL-28*[f]	>100
	MCF7[g]	>100		*MCF7*[g]	>100
	SKMES-1[h]	>100		*SKMES-1*[h]	>100
	HepG2[i]	>100		*HepG2*[i]	>100
	DU145[j]	>100		*DU145*[j]	>100
Normal-cell lines	CRL 7065[k]	>100	Normal-cell lines	CRL 7065[k]	>100
	MRC-5[l]	>100		MRC-5[l]	>100

[a] Compound concentration required to reduce cell proliferation by 50% as determined by the MTT method, under condition allowing untreated controls to undergo at least three consecutive rounds of multiplication. Data represent mean values (±SD) for independent determinations.
[b] CD4 human T-cells containing an integrated HTLV-1.
[c] CD4 human acute T-lymphoblastic leukemia.
[d] Human splenic B-lymphoblastoid cells.
[e] Human acute B-lymphoblastic leukemia.
[f] Human skin melanoma.
[g] Human breast adenocarcinoma.
[h] Human lung squamous carcinoma.
[i] Human hepatocellular carcinoma.
[j] Human prostate carcinoma.
[k] Human foreskin fibroblasts.
[l] Human lung fibroblasts.

MHz (^{13}C) with TMS as internal standard on a δ scale in ppm. EI and FAB mass spectra were measured on MAT 8200 mass spectroscopy using 3-nitrophenol (NBOH) or glycerol as matrix.

*2-Naphthyloxy-acetic acid (**3**).* This compounds was prepared according to the literature [15] from 2-naphthol sodium salt (2.00 g, 12.04 mmol) and chloroacetic acid sodium salt (1.69 g, 14.45 mmol). Yield: 1.90 g (78%).

*2-Naphthyloxy-acetic acid hydrazide (**5**).* This compound was prepared by two reported methods: (a): From 2-naphthyloxy-acetic acid ethyl ester **2** (1.30 g, 3.63 mmol) and hydrazine hydrate (6.0 mmol). Yield: 0.59 g, 75% [21] (b): From naphthalene-2-carbonyl chloride **4** (1.5 g, 6.80 mmol) and hydrazine hydrate (9.0 mmol). Yield: 1.22 g, 83% [20].

General Procedure of Preparation of Amino Acid Esters Bearing Naphthalene

Method a. To a cold solution of the amino acid ester hydrochloride (10.0 mmol) at −5°C in MeCN (20 mL) and Et_3N (1 mL) were added **3** (2.02 g, 10.0 mmol), hydroxybenzotriazole (HOBT) (1.35 g, 10 mmol) and DCC (10.0 mmol), successively. The reaction mixture was stirred at 0°C for 1 h, 5°C for 1 h, and at 23°C for 16 h. The DCCU (dicyclohexylurea) was filtered, and the filtrate was evaporated to dryness and the residue was dissolved in ethyl acetate, filtered, washed successively with saturated NaCl solution, 5% $NaHCO_3$ solution, 1 N HCl, followed by washing with saturated NaCl solution and finally with water. The residue was dried (Na_2SO_4), filtered, evaporated to dryness and recrystallized from the appropriate solvent.

Method b. To a cold solution ($\sim -5^{\circ}C$) of **5** (173 mg, 0.80 mmol) in HOAc (6 mL), 1 N HCl (3 mL), and water (25 mL) was added a solution of $NaNO_2$ (870 mg, 1.0 mmol) in cold water (3 mL) After stirring at $-5^{\circ}C$ for 15 min, the yellow syrup was formed. The azide was taken in cold ethyl acetate (30 mL), washed with 3% solution of $NaHCO_3$, washed with water, and finally dried (Na_2SO_4). A solution of amino acid hydrochloride (0.90 mmol) in ethyl acetate (20 mL) containing 0.2 mL of Et_3N was stirred at $0^{\circ}C$ for 20 min, filtered and the filtrate was added to the azide solution. The mixture was kept at $-5^{\circ}C$ for 12 h, then at $23^{\circ}C$ for another 12 h, followed by washing with 0.5 N HCl, water, 3% solution of $NaHCO_3$ and finally dried (Na_2SO_4). The solution was evaporated to dryness, and the residue was recrystallized by ethyl acetate–petroleum ether to give the desired product.

*Methyl 2-naphthyloxy)acetamidoacetate (***6***).* From glycine acetate (1.25 g). Yield: *method a*, 2.13 g (78%); *method b*, 0.142 g (63%); oil. ^1H NMR ($CDCl_3$): δ 7.77–7.69 (m, 4H, NH, H-4, H-5, H-8); 7.47 (ddd, 1H, $J = 1.2$ Hz, 8.1 Hz, H-7); 7.44 (ddd, 1H, $J = 1.2$ Hz, 8.1 Hz, H-6); 7.22 (dd, 1H, $J = 2.8$ Hz, 7.8 Hz, H-3); 7.18 (d, 1H, $J = 2.8$ Hz, H-1); 4.62 (s, 2H, CH_2-10); 4.13 (d., 2H, $J = 5.6$ Hz, CH_2-13); 3.73 (s, 3H,OAc). ^{13}C NMR ($CDCl_3$): δ 170.0 (C-11); 168.7 (C-14); 155.1 (C-2); 134.4 (C-8a); 129.9 (C-4); 129.6 (C-4a); 127.7 (C-5); 127.1 (C-8); 126.6 (C-7); 124.4 (C-6); 118.2 (C-3); 107.9 (C-1); 67.4 (C-10); 52.4 (CO_2Me); 40.8. (C-13). MS: *m/z* (FAB) ($C_{15}H_{15}NO_4$) 274 $(M + H)^+$.

*Methyl 2-(2-naphthyloxyacetamido)-3-methylbutanoate (***7***).* From L-valine acetate hydrochloride (1.68 g). Yield: *method a*, 2.74 g (87%); *method b*, 0.174 g (69%); oil. ^1H NMR ($CDCl_3$): δ 7.78–7.65 (m, 4H, NH, H-4, H-5, H-8); 7.44 (ddd, 1H, $J = 1.3$ Hz, 8.1 Hz, H-7); 7.45 (ddd, 1H, $J = 1.2$ Hz, 8.1 Hz, H-6); 7.20 (dd, 1H, $J = 2.5$ Hz, 7.9 Hz, H-3); 7.13 (d, 1H, $J = 2.5$ Hz, H-1); 4.64 (m, 4H, CH_2-10, CH_2-13); 3.69 (s, 3H, OAc); 2.19 (m, 1H, H-15); 0.92, 0.87 (2 × d, 6H, $J = 6.9$ Hz, 2 × Me). ^{13}C NMR ($CDCl_3$): δ 172.0 (C-11); 168.2 (C-14); 155.1 (C-2); 134.3 (C-8a); 129.9 (C-4); 129.1 (C-4a); 127.7 (C-5); 127.0 (C-8); 126.7 (C-7); 124.4 (C-6); 118.1 (C-3); 107.9 (C-1); 67.5 (C-10); 56.8 (C-13); 52.1 (CO_2Me); 31.3 (C-15); 18.9, 17.7 (2 × Me). MS: *m/z* (FAB) ($C_{18}H_{21}NO_4$) 338 $(M + Na)^+$.

*Methyl 2-(2-naphthyloxyacetamido)-2-(4-hydroxyphenyl)acetate (***8***).* From L-tyrosine acetate hydrochloride (2.31 g). Yield: *method a*, 2.76 g (73%); *method b*, 0.166 g (55%); oil. ^1H NMR ($CDCl_3$): ^1H NMR ($CDCl_3$): δ 7.82–7.67 (m, 6H, NH, H-4, H-5, H-8, Ar-H); 7.49 (ddd, 1H, $J = 1.2$ Hz, 8.7 Hz, H-7); 7.36 (ddd, 1H, $J = 1.2$ Hz, 8.7 Hz, H-6); 7.22 (m, 4H, H-3, Ar-H); 7.06 (d, 1H, $J = 2.6$ Hz, H-1); 5.34 (s, 2H, CH_2Ph); 4.73 (br s, 4H, CH_2-10, CH_2-17); 4.68 (s., 1H, CH_2-13). MS: *m/z* (FAB) ($C_{22}H_{21}NO_5$) 380 $(M + H)^+$.

*Methyl 2-(2-naphthyloxyacetamido)-4-methylpentanoate (***9***).* From L-leucine acetate hydrochloride (1.81 g). Yield: *method a*, 2.40 g (76%); *method b*, 0.192 g (73%); oil. ^1H NMR ($CDCl_3$): δ 7.76–7.67 (m, 3H, H-4, H-5, H-8); 7.43 (dd, 1H, $J = 1.6$ Hz, 8.0 Hz, H-7); 7.31 (dd, 1H, $J = 1.6$ Hz, 8.1 Hz, H-6); 7.19 (dd, 1H, $J = 2.2$ Hz, 8.5 Hz, H-3); 7.15 (d, 1H, $J = 2.2$ Hz, H-1); 4.72 (m, 1H, H-13); 4.60 (s, 2H, CH_2-10); 3.69 (s, 3H, OAc); 1.77–1.52 (m, 4H, CH_2-15, CH_2-16); 0.92–0.85 (m, 6H, 2 × Me). MS: *m/z* (FAB) ($C_{19}H_{23}NO_4$) 352 $(M + Na)^+$.

*Methyl 2-(2-naphthyloxy)acetamido-propanoate (***10***).* From L-alanine acetate hydrochloride (1.39 g). Yield: *method a*, 2.32 g (81%); *method b*, 0.130 g (68%); oil. ^1H NMR ($CDCl_3$): ^1H NMR ($CDCl_3$): δ 7.78–7.69 (m, 4H, NH, H-4, H-5, H-8); 7.46 (ddd, 1H, $J = 1.2$ Hz, 8.5 Hz, H-7); 7.35 (ddd, 1H, $J = 1.2$ Hz, 8.5 Hz, H-6); 7.22 (dd, 1H, $J = 2.4$ Hz, 7.9 Hz, H-3); 7.18 (d, 1H, $J = 2.4$ Hz, H-1); 4.72 (m, 1H, CH_2-13); 4.63 (d, 2H, $J = 2.7$ Hz, CH_2-10); 3.73 (s, 3H, OAc); 1.47, 1.44 (d, 3H, $J = 7.1$ Hz, Me). ^{13}C NMR ($CDCl_3$): δ 173.0 (C-11); 167.8 (C-14); 155.1 (C-2); 134.3 (C-8a); 129.9 (C-4); 129.8 (C-4a); 127.7 (C-5); 127.0 (C-8); 126.7 (C-7); 124.3 (C-6); 117.8 (C-3); 107.9 (C-1); 67.4 (C-10); 52.1 (CO_2Me); 47.7 (C-13); 18.3.(C-15). MS: *m/z* (FAB) ($C_{16}H_{17}NO_4$) 310 $(M + Na)^+$.

*Methyl 2-(2-naphthyloxyacetamido)-4-(methylthio)butanoate (***11***).* From L-methionine acetate hydrochloride (2.0 g). Yield: *method a*, 2.58 g (71%); *method b*, 0.168 g (58%); mp 59–62°C. ^1H NMR ($CDCl_3$): δ 7.79–7.48 (m, 4H, NH, H-4, H-5, H-8); 7.41 (ddd, 1H, $J = 1.3$ Hz, 7.6 Hz, H-7); 7.37 (ddd, 1H, $J = 1.3$ Hz, 7.6 Hz, H-6); 7.22 (dd, 1H, $J = 2.3$ Hz, 8.4 Hz, H-3); 7.13 (d, 1H, $J = 2.3$ Hz, H-1); 4.85 (m, 1H, CH_2-13); 4.64 (s, 2H, CH_2-10); 3.73 (s, 3H, OAc); 2.61 (t, 2H, $J = 7.3$ Hz, CH_2-16); 2.46 (t, 2H, $J = 7.3$ Hz, CH_2-15); 2.00 (s, 3H, SMe). ^{13}C NMR ($CDCl_3$): δ 180.0 (C-11); 168.1 (C-14); 155.0 (C-2); 134.7 (C-8a); 129.9 (C-4); 129.8 (C-4a); 127.1 (C-5); 126.2 (C-8); 125.9 (C-7); 124.7 (C-6); 118.1 (C-3); 108.2 (C-1); 67.0 (C-10); 52.5 (CO_2Me); 51.0 (C-13); 31.1 (C-15); 30.0 (C-16); 12.5 (SMe). Anal.

Calcad. for $C_{18}H_{21}NO_4S$ (347.12): C, 62.23; H, 6.09; N, 4.03. Found: C, 61.94; H, 5.92; N, 3.89. MS: *m/z* (FAB) 348 $(M+H)^+$.

*Methyl 2-(2-naphthyloxyacetamido)-4-hydroxypropanoate (***12***).* From L-serine acetate hydrochloride (1.55 g). Yield: *method a*, 2.30 g (72%); *method b*, 0.170 g (65%); mp 145–147°C. ^{1}H NMR ($CDCl_3$): δ 7.73–7.61 (m, 4H, NH, H-4, H-5, H-8); 7.41 (ddd, 1H, $J = 1.3$ Hz, 8.0 Hz, H-7); 7.32 (ddd, 1H, $J = 1.2$ Hz, 8.0 Hz, H-6); 7.30 (dd, 1H, $J = 2.5$ Hz, 8.9 Hz, H-3); 7.09 (d, 1H, $J = 2.5$ Hz, H-1); 4.73 (dt, 1H, $J = 3.8$ Hz, 9.5 Hz, H-13); 4.60 (s, 2H, CH_2-10); 3.96 (2 × dd, 2H, J 3.8 Hz, 11.3 Hz, CH_2-15); 3.72 (br s, 3H, OAc, OH). ^{13}C NMR ($CDCl_3$): δ 172.9 (C-11); 169.1 (C-14); 150.7 (C-2); 132.9 (C-8a); 129.9 (C-4); 129.1 (C-4a); 127.7 (C-5); 127.0 (C-8); 126.7 (C-7); 124.4 (C-6); 118.2 (C-3); 107.9 (C-1); 67.4 (C-10); 62.9 (C-15); 52.7 (CO_2Me); 17.1 (C-17). Anal. Calcad. for $C_{17}H_{19}NO_5$ (317.33): C, 64.34; H, 6.03; N, 4.41. Found: C, 64.03; H, 5.89; N, 4.14. MS: *m/z* (FAB) ($C_{17}H_{19}NO_5$) 318 $(M+H)^+$.

General Procedure of Preparation of the Hydrazide Derivatives **13–16**

To a solution of the ester derivatives **6** and **10–12** (10 mmol) in EtOH (20 mL) was added $N_2H_4{\cdot}H_2O$ (15 mmol), and the reaction mixture was heated under reflux for 3 h. After cooling, the solution was evaporated to dryness and the residue was recrystallized from EtOH to give the desired hydrazide derivatives.

*2-Naphthyloxyacetamidoacetohydrazide (***13***).* From **6** (2.73 g). Yield: 2.57 g (89%); mp 228–230°C. ^{1}H NMR ($CDCl_3$): δ 9.13 (br s, 1H, NH); 8.39 (t, 1H, $J = 5.7$ Hz, NH); 7.84–7.77 (m, 3H, H-4, H-5, H-8); 7.45 (ddd, 1H, $J = 1.3$ Hz, 6.9 Hz, H-7); 7.34 (ddd, 1H, $J = 1.3$ Hz, 6.9 Hz, H-6); 7.29 (dd, 1H, $J = 2.6$ Hz, H-3); 7.23 (d, 1H, $J = 2.6$ Hz, H-1); 4.64 (s, 2H, CH_2-10); 4.20 (br s, 2H, NH_2); 3.78 (d, 2H, $J = 5.9$ Hz, CH_2-13). Anal. Calcad for $C_{14}H_{15}N_3O_3$ (273.28): C, 61.53; H, 5.53; N,15.38. Found: C, 61.21; H, 5.49; N, 14.95. MS: *m/z* (FAB) 296 $(M+Na)^+$.

*2-(2-Naphthyloxyacetamido)propanehydrazide (***14***).* From **10** (2.87 g). Yield: 2.58 g (81%); mp 175–178°C. ^{1}H NMR ($CDCl_3$): δ 8.05 (m, 1H, NH); 7.66–7.55 (m, 3H, H-4, H-5, H-8); 7.29–7.12 (m, 3H, H-3, H-6, H-7); 7.06 (d, 1H, $J = 2.5$ Hz, H-1); 4.44 (s, 2H, CH_2-10); 4.17 (m, 1H, H-13); 3.17 (br s, 2H, NH_2); 1.04 (t, 3H, $J = 3.6$ Hz, C_{13}-*Me*). Anal. Calcad for $C_{15}H_{17}N_3O_3$ (287.13): C, 62.71; H, 5.96; N, 14.63. Found: C, 62.47; H, 5.87; N, 14.42.. MS: *m/z* (FAB) 310 $(M+Na)^+$.

*2-(2-Naphthyloxyacetamido)-4-(methylthio)butanoylhydrazine (***15***).* From **11** (3.63 g). Yield: 2.98 g (76%); mp 185–188°C. ^{1}H NMR ($CDCl_3$): δ 8.37 (d, 1H, $J = 8.0$ Hz, NH); 7.92–7.80 (m, 3H, H-4, H-5, H-8); 7.48 (t, 1H, $J = 7.4$ Hz, H-7); 7.40 (t, 1H, $J = 7.6$ Hz, H-6); 7.30 (m, 2H, H-1, H-3); 4.70 (s, 2H, CH_2-10); 4.45 (m, 1H, H-13); 4.31 (br s, 2H, NH_2); 2.58 (br s, 2H, CH_2-16); 2.41 (m, 2H, CH_2-15); 2.00 (s, 3H, SMe). Anal. Calcad for $C_{17}H_{21}N_3O_3S$ (347.43): C, 58.77; H, 6.09; N, 12.09. Found: C, 58.52; H, 5.93; N, 11.84.. MS: *m/z* (FAB) 348 $(M+H)^+$.

*2-(2-Naphthyloxyacetamido)-3-hydroxypropanoylhydrazine (***16***).* From **12** (3.19 g). Yield: 2.15 g (71%); mp >250°C. ^{1}H NMR ($CDCl_3$): 9.02 (s, 1H, NH); 7.84 (d, 1H, $J = 8.2$ Hz, NH); 7.71–7.54 (m, 3H, H-4, H-5, H-8); 7.24 (t, 1H, $J = 7.5$ Hz, H-7); 7.13 (t, 1H, $J = 7.5$ Hz, H-6); 7.09 (d, 1H, $J = 2.2$ Hz, H-1); 7.03 (dd, 1H, $J = 2.2$ Hz, 8.9 Hz, H-3); 4.81 (8t, 1H, $J = 5.6$ Hz, OH); 4.45 (s, 2H, CH_2-10); 4.14 (m., 1H, H-13); 4.02 (br s, 2H, NH_2); 3.43 (m, 2H, CH_2-15). Anal. Calcad for $C_{15}H_{17}N_3O_4$ (303.31): C, 59.40; H, 5.65; N, 13.85. Found: C, 59.15; H, 7.73; N, 12.85.. MS: *m/z* (FAB) 304 $(M+H)^+$.

*Methyl(2-Naphthyloxy)-3-O-(2,3,5,6-di-O-isopropylidene-α-D-mannofuranos-1-yl) propanoate (***19***).* A solution of **12** (0.29 g, 0.90 mmol) and **18** (358 mg, 0.90 mmol) in dry CH_2Cl_2 (25 mL) was stirred under nitrogen at room temperature for 5 min, followed by the addition of TMSOTf (19.5 μL, 0.09 mmol). After stirring for 2 h, a solid $NaHCO_3$ was added slowly, filtered, and the filtrate was washed with water (30 mL), dried (Na_2SO_4), filtered and evaporated to dryness. The residue was purified by SiO_2 column (20 g), using ethyl acetate/petroleum ether as eluent to give **19** (0.36 g, 75%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.75–7.65 (m, 3H, H-4, H-5, H-8); 7.42–7.28 (m, 3H, NH, H-6, H-7); 7.19 (dd, 1H, $J = 2.3$ Hz, 8.8 Hz, H-3); 7.11 (d, 1H, $J = 2.3$ Hz, H-1); 4.81 (br s, 2H, H-1′, H-13); 4.61 (s, 2H, CH_2-10); 4.55 (dd, 1H, $J_{4',5'} = 3.5$ Hz, $J_{3',4'} = 4.8$ Hz, H-4′); 4.31 (m, 2H, CH_2-15); 4.03 (m, 1H, H-3′); 3.95 (dd, 1H, $J_{5',6'} = 4.2$ Hz, $J_{6',6''} = 9.0$ Hz, H-6′); 3.71 (s, 3H, OAc); 3.63 (dd, 1H, $J_{5',6''} = 3.3$ Hz, H-6″); 1.40 (2 × s, 6H, CMe_2); 1.34, 1.21 (2 × s, 6H, CMe_2). ^{13}C NMR ($CDCl_3$): δ 169.7 (C-11); 168.0 (C-14); 154.9 (C-2); 134.1 (C-8a); 129.6 (C-4); 129.4 (C-4a); 127.5 (C-5); 126.8 (C-8); 126.5 (C-7); 124.2 (C-6); 118.0 (C-3); 112.5 (C-7′); 108.9 (C-7″); 107.8 (C-1′); 105.9 (C-1); 84.6 (C-2′); 80.4 (C-4′), 79.1 (C-3′); 72.7 (C-5′), 67.3 (C-10); 66.6 (C-6′); 66.1 (C-15′); 62.6 (C-13);

51.8 (CO_2Me); 18.9, 18.5, 18.3, 17.6 ($2 \times CMe_2$). MS: m/z (FAB) $C_{27}H_{35}NO_{10}$ (533.57): MS: m/z (FAB) 556 $(M + Na)^+$.

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