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Amino Acid Derivatives, Part 3: New Peptide and Glycopeptide Derivatives Conjugated Naphthalene. Synthesis, Antitumor, Anti-HIV, and BVDV Evaluation

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ABSTRACT: *A series of peptide derivatives conjugated naphthalene residue* **11–25**, *the glycoside* **27** *as well as the 7-glycoside* **30**, *and the 2-(2-hydroxy-3-(N-benzyl-N-isopropylamino)propoxy)naphthalene bearing methionine* **31** *were synthesized. The new compounds were evaluated in vitro for cytotoxicity against HIV-1 and bovine viral diarrhea virus (BVDV), where* **31** *showed remarkable activity against HIV-1. The cytotoxicity, in vitro, of* **11–25** *and* **27** *was assayed against a panel of tumor cell lines consisting of CD4 human T-cells containing an integrated T-leukemia virus type 1 (HTLV-1), CD4 human acute T-lymphoblastic leukemia, splenic B-lymphoblastoid cells, acute B-lymphoblastic leukemia, melanoma, breast adenocarcinoma, lung squamous carcinoma, hepatocellular carcinoma, prostate carcinoma, foreskin fibroblasts, and lung fibroblasts.* © 2005 Wiley Periodicals, Inc. Heteroatom Chem 16:576–586, 2005; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20149

INTRODUCTION

The global spread and fatal prognosis of human immunodeficiency virus (HIV) infection emphasize the urgent need for effective antiretroviral therapies. The introduction of highly active antiretroviral therapy (HAART) involving the use of drug combinations to treat AIDS has had a dramatic impact on the morbidity and mortality of individuals infected by the HIV [1–3]. Kaletra, the first second-generation protease inhibitor to reach drug status, is a mixture of two protease inhibitors, lopinavir **1** [4,5], and ritonavir [6]. Lopinavir, which constitutes a peptide backbone, was originally designed to diminish the interactions of inhibitor with Val82 of HIV-1 PR, a residue that is often mutated in the

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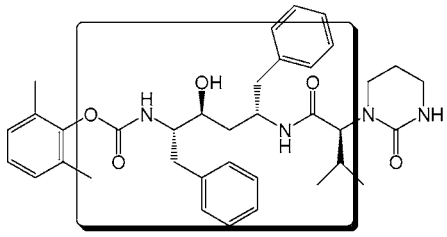
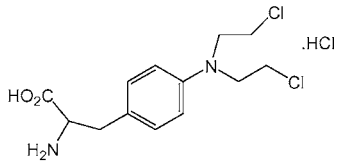
drug-resistance strains of the virus [3]. The core of lopinavir is identical to that of ritonavir, by replacement of the 2-thiazolyl end group in the latter by a modified substituted valine residue. Some amino acid derivatives such as lysyl amide prodrug of 2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole [7], amino acid derivatives of paclitaxol [8], pyroglutamic acid [9], cysteine-modifying agents [10], and isoquinoline carboxylic acid derivative [11] are reported as potential HIV protease inhibitors [12]. Furthermore, difunctional enols of simple N-protected amino acids were reported as potential inhibitors of the HIV-1 protease [13]. However, in spite of using the protease inhibitors for treatment of AIDS, but there are continuing problems of dose-limiting toxicities, the selection of resistant mutants [14], and the inability to adequately suppress viral replication including the emergence of multidrug-resistance strains of HIV-1 [15,16]. It is thus important to continually develop more potent and less aggressive drugs for the treatment of HIV. Recently, De Clercq [17] has reviewed the new developments in the anti-HIV chemotherapy. On the other hand, several α-amino acids conjugated heterocycles reported as potential antitumor agents such as 4-toluensulfonylureido derivatives of amines, amino acids, dipeptides [19], whereas some alkylating agents bearing amino acid residues showed highly cytotoxicity activity against various cancer cell lines, such as melphalan (L-phenylalanine mustard hydrochloride) **2** [19].

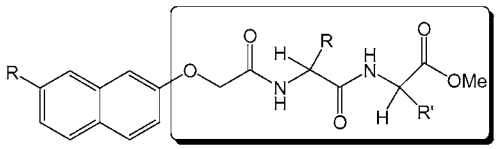
With respect to the fatal viruses, BVDV (bovine viral diarrhea virus) is considered as one of the classical examples of *Flaviviridae*, and studies with this virus are attractive due to its marked similarity with HCV the availability of infections cell cultures systems (which are lacking for HCV) and because BVDV replicates significantly most efficient than HCV, since Cleland et al. [20] used BVDV as an internal control for amplification of HCV. Only few examples are reported for the treatment of BVDV such as acridones [21] ribavirin and mycophenolic acid (MPA) [22], and iminosugars [23]. In connection with our strategy in synthesis of new amino acid derivatives [24,25], we report here the synthesis of new peptides bearing naphthalene residue as potential antiviral and antitumor candidates.



1. Liponavir



2. Melphalan

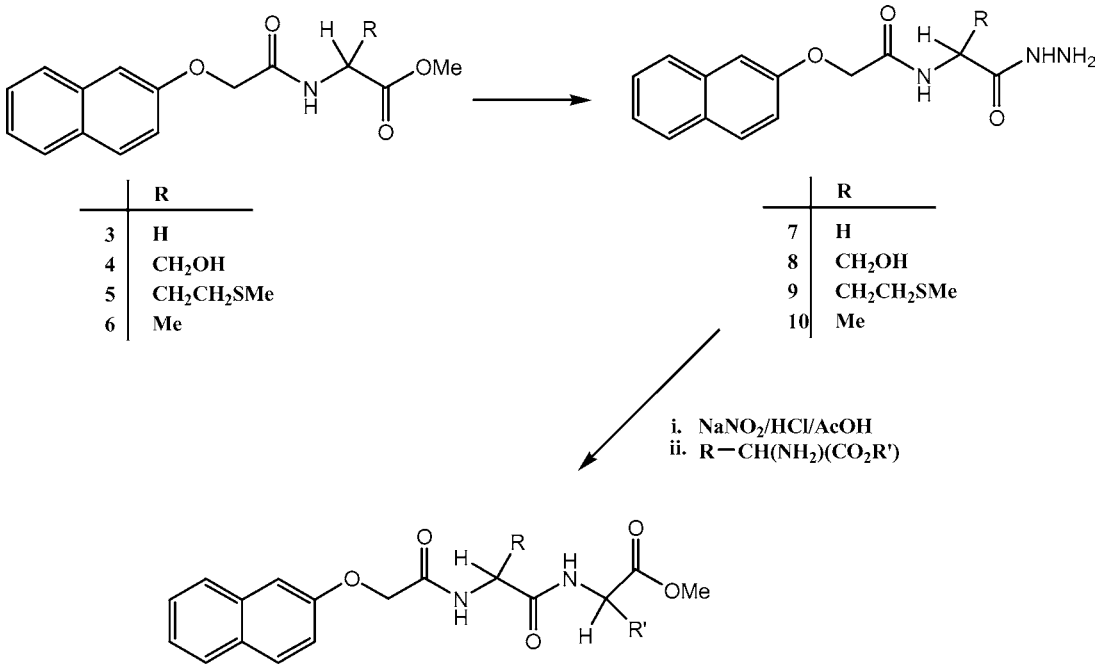


Our Target molecules

RESULTS AND DISCUSSION

The synthesis of the target compounds **11–25** and **27** are outlined in Schemes 1 and 2, respectively. The hydrazides **7–10** were prepared from the corresponding ester derivatives **3–6**, by applying the reported procedure [25,26]. These compounds have been selected as starting materials for coupling reaction with the appropriate acylated amino acids, via the azide-coupling method. Thus, treatment of compounds **7–10** at −5°C in HOAc and 1 N HCl with $NaNO_2$ afforded the inseparable azide derivatives. The yellow syrupy azide compounds were treated, in situ, with the acylated amino acid derivatives (L-methionine, L-valine, L-alanine, glycine, L-leucine, and L-serine acetates hydrochloride) in ethyl acetate containing Et_3N at 0°C gave, after neutralization, the desired peptides **11–25** in 51–72% yield (Scheme 1).

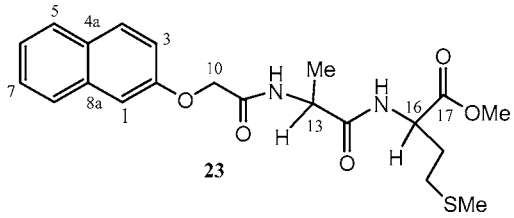
The structures of **11–25** were assigned from their ^1H, ^{13}C NMR, and mass spectra. The ^1H NMR spectra of **7–25** showed similar pattern of naphthalene aromatic protons. The multiplet at higher field (δ 7.93–7.54) were mostly attributed to NH, H-4, H-5, and H-5, whereas H-8 of compounds **17, 20**, and **25** was appeared as doublet of doublets at δ 8.13, 8.56, and 8.38, respectively. H-7 and H-6 appeared as



	R
3	H
4	CH_2OH
5	CH_2CH_2SMe
6	Me

	R
7	H
8	CH_2OH
9	CH_2CH_2SMe
10	Me

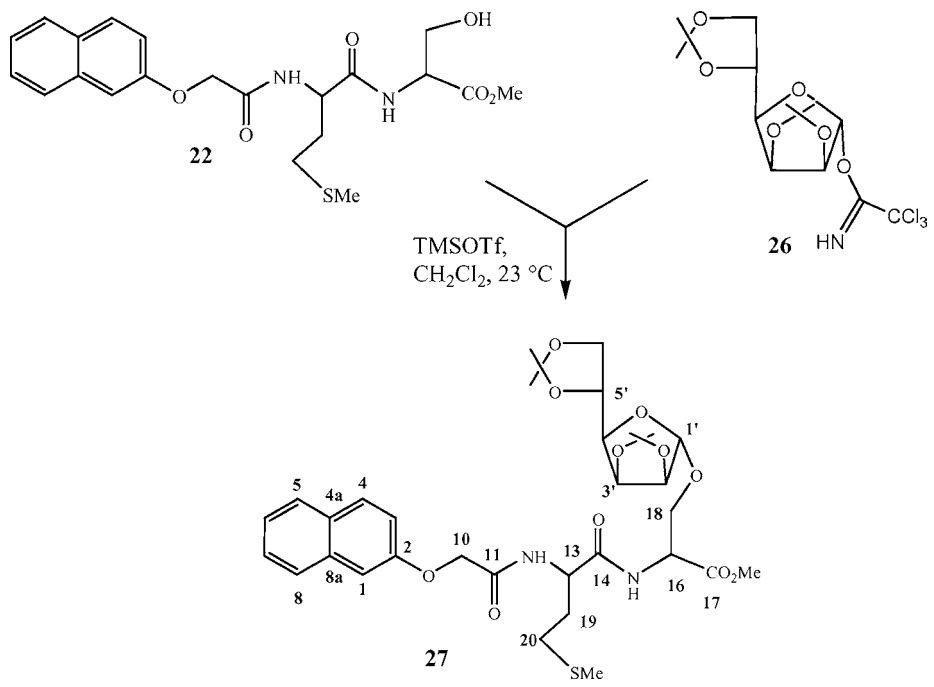
	R	R'	(amino acids)
11	H	CH_2CH_2SMe	Glycine-L-methionine
12	H	$CH(Me)_2$	Glycine-L-valine
13	H	Me	Glycine-L-alanine
14	H	H	Glycine-glycine
15	H	$CH_2CH(Me)_2$	Glycine-L-leucine
16	H	CH_2OH	Glycine-L-serine
17	CH_2OH	H	L-serine--glycine
18	CH_2OH	CH_2OH	L-serine-L-serine
19	CH_2OH	CH_2CH_2SMe	L-serine-L-mthionine
20	CH_2CH_2SMe	CH_2CH_2SMe	L-methionine-L-methionine
21	CH_2CH_2SMe	H	L-methionine-glycine
22	CH_2CH_2SMe	CH_2OH	L-methionine-L-serine
23	Me	CH_2CH_2SMe	L-alanine-L-methionine
24	Me	H	L-alanine-glycine
25	Me	CH_2OH	L-alanine-L-serine



23

SCHEME 1

multiplets in the region δ 7.84–7.24, except those of compounds **14, 15, 20, 21–23**, and **25** which appeared as doublet of doublets (did) at the region δ 7.54–7.39 and δ 42–7.30 ($J_{5,7} = J_{6,8} \sim 2.2$ Hz; $J_{5,6} = J_{6,7} = J_{7,8} \sim 7.5$ Hz), respectively. The doublet of doublets, the multiplets or broad singlets at the region δ 7.04–7.34 were assigned to H-3, while H-1 was appeared as singlet or broad singlet. CH_2-10, CH_2-13, and CH_2-16 were fully analyzed as well as the rest protons. The ^{13}C NMR spectra of **11–25** were

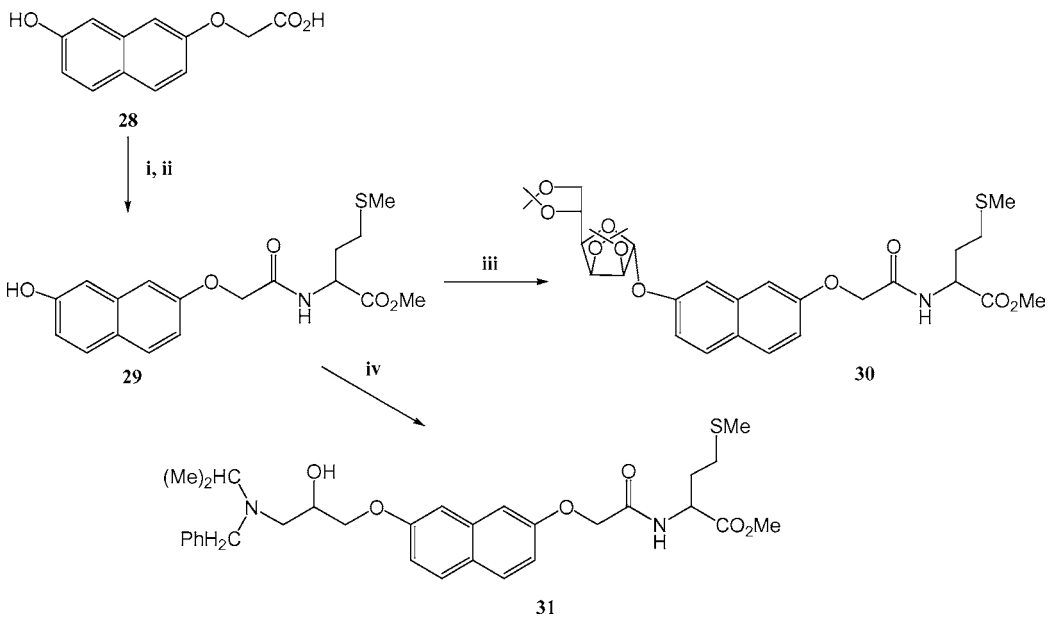


SCHEME 2

fully analyzed (Experimental section). Compound **23** was selected for the ^{1}H and ^{13}C NMR analysis. The ^{1}H NMR spectrum showed broad signal at δ 6.89, characterized by D_2O exchange as NH group. The multiplets at δ 4.78 and δ 4.73 were identified by the irradiation experiment as H-13 and H-16, respectively, while the singlets at δ 4.54, and δ 3.67 were attributed to CH_2-10 and CO_2Me, respectively. Irradiation of H-13 at δ 4.78, causing enhancement of the quartet at δ 2.10 into *pseudo*-doublet, indicating that the latter resonance is attributed to methylene protons of CH_2CH_2SMe group. Therefore, the methylene protons (CH_2SMe) at δ 2.48 were identified from irradiation of the above adjacent methylene group, while the singlet at δ 1.97 was assigned to same group. The ^{13}C NMR spectrum demonstrated three higher field signals at δ 172.2, 172.1, and 168.1 were assigned to (C_{17}=O), (C_{14}=O), (C_{11}=O), respectively. The aromatic protons from C-1 to C-8a were identified in comparison to the previously identified protons [20]. The resonances at δ 67.2, 52.5, and 51.6 were assigned to C-10, C-16, and CO_2Me, respectively. C-13, and C-16 were resonated at δ 48.4 and δ 41.2, respectively. The two signals at δ 31.2, and δ 30.0 were identified as (CH_2CH_2-SMe) and CH_2-SMe, respectively, while the lower field signals at δ 18.8 and δ 15.4 were assigned as C_{13}-*Me* and SMe group, respectively.

Next, our target was the synthesis of the glycopeptide **27** by following procedure reported by Schmidt et al. [27,28]. Thus, glycosylation of **22** as an alcohol-acceptor precursor, with glycosyltrichloroacetoimidate **26** as donor precursor in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonate (TMSOTf) as Lewis acid afforded **27** in 65% yield. The *o*-glycopyranosyl-trichloroacetoimidate **26** is characterized by its stability at room temperature for long periods of time without any decomposition, and described as an acceptor precursor that gives an efficient anomeric stereo-controlled glycosylation product with a high yield of α-anomer (Scheme 2).

The structure of **27** was identified from the ^{1}H NMR and mass spectra. The assignment of sugar proton resonances was identified by irradiation experiment. H-1′ appeared as a broad singlet at δ 4.85, confirming the α-anomer of the glycoside **27**. The doublet at δ 4.45 ($J_{2',3'}$ = 5.9 Hz) was attributed to H-2′, while H-3′ was oriented together with H-18 as multiplet at δ 4.03. H-4′ appeared as a doublet of doublets at δ 4.13 ($J_{3',4'}$ = 7.0 Hz, $J_{4',5'}$ = 3.0 Hz). The singlet at δ 4.72 was assigned to CH_2-10, while the two multiplets at δ 4.63 and δ 4.35 were attributed to H-16 and H-13, respectively. The multiplet and quartet at δ 2.17 and δ 2.07 (J = 7.1 Hz) were identified as the four methylene protons of CH_2CH_2SMe and CH_2CH_2SMe groups, respectively. The aromatic protons were identified in comparison to those of compound **20**.



SCHEME 3 *Reagents and conditions*. (i) DCC, HOBT, MeCN, −5°C; (ii) $NH_2CH[(CH_2)_2SMe]CO_2Me$ (iii) TMSOTf, CH_2Cl_2, 23°C, **26**; (iv) $ClCH_2CH(OH)CH_2N[CH(Me)_2](CH_2Ph)$, K_2CO_3, MeEtCO, 100°C, 5 days.

The discouraging biological results of the above compounds led us to turn our synthetic strategy to prepare new naphthalene derivatives such as **30** and **31**, in which the protected sugar moiety or the potentially active 2-hydroxy-3-alkyl-aminopropoxy group [29], respectively, was substituted at peri position. By applying the glycosylation method [27,28], **30** was prepared in 58% yield, using the protected D-mannofuranosyl-1-trichloroacetimidate **26** as donor and **29** as acceptor precursors in the presence of catalytic amounts of trimethylsilyl trifluoromethanesulfonate (TMSOTf). On the other hand, coupling of the acid derivative **28** [30] with methyl L-methionine carboxylate hydrochloride in the presence of HOBT and DCC as coupling reagents [31–33] afforded **29** (54%). Reaction of **29** with *N*-benzyl-*N*-isopropyl-2-hydroxy-3-chloropropylamine afforded **31** in low yield (20%), presumably due to the decomposition of the amino acid group at high temperature under reduced pressure (Scheme 3). The structures of **29–31** were identified from their ^{1}H NMR and mass spectra, in comparison to those of derivatives prepared previously [26].

In vitro Anti-HIV Assay

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 [34]. Accordingly, our synthetic strategy for synthesis of the new amino acids derivatives bearing naphthalene residue depends on this hypothesis. Compounds **11–25** and **27** 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. Compounds-induced cytotoxicity was also measured in MT-4 cells parallel with the antiviral activity. 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) [35] and azidothymidine (AZT) [36]. In conclusion, the above data showed no selective anti-HIV activity.

On the other hand, compounds **30** and **31** were tested against HIV-1 (III_B strain) with EC_{50} (μg/mL): >32; >1.20, respectively, and against HIV-2 (ROD strain) with EC_{50} (μg/mL): >45; >2.67, respectively, induced cytopathicity in human MT-4 lymphocyte cells at nontoxic concentrations. The above data showed no selective anti-HIV activity, although **31** showed remarkable inhibitory activity with C_{50} value (>1.20 μg/mL), but with low Si = 10. In conclusion, the structure-activity relationship suggested that the substitution of naphthalene bearing amino acid precursors carrying various potential β-adrenergic blocking group showed higher activity than those of the corresponding substituted derivatives bearing amino acids only.

TABLE 1 In vitro anti-HIV-1[a] of Some Naphthalene-Amino Acid Compounds

	CC_{50} (μg/mL)[b] MT-4	EC_{50} (μg/mL)[c] HIV-1
11	>100	>100
12	82	>82
13	59	>59
14	>100	>100
15	16	>16
16	58	>58
17	>100	>100
18	>100	>100
19	49	>49
20	>100	>100
21	>100	>100
22	>100	>100
23	48	>48
24	79	>79
25	>100	>100
27	75	>75
30[a]		>32
30[d]		>45
31[a]		>1.20 (Si = 10)
31[d]		>2.67
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.
[d]Anti-HIV-2 activity measured with strain ROD.

In vitro anti-BVDV

Compounds **11–25** and **27** 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 57 μg/mL, as shown by compound **27** (Table 2).

In vitro Cytotoxicity Assay

Compounds **11–25** and **27** 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 micro culture tetrazolium assay (MTT) method [37]. 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 **15** which showed marked activity against leukemia/lymphoma (*MT4* cell line, $CC_{50} = 16$ μM; *CCRF-CEM*, $CC_{50} = 20$ μM).

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

	CC_{50}(μg/mL)	EC_{50}(μg/mL)
13	>100	74
14	>100	61
16	>100	88
27	57	>57

In conclusion, the glycine–leucine peptide type of linkage can play a remarkable activity in the treatment of leukemia by modification of the conjugated functional groups attached this type of peptide derivative.

EXPERIMENTAL

General. Melting points are uncorrected. NMR spectra were recorded on a 250 and 600 MHz (^{1}H), and 150.91 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 spectrometery using 3-nitrophenol or glycerol as matrix.

General Procedure of Preparation of Peptides-Bearing Naphthalene

To a cold solution ($\sim -5^\circ$C) of **7–10** (3.0 mmol) in HOAc (22 mL), 1 N HCl (11 mL), and water (80 mL) was added a solution of $NaNO_2$ (mg, 3.5 mmol) in cold water (11 mL). After stirring at –5°C for 15 min, the yellow syrup was formed. The azide was taken in cold ethyl acetate (100 mL), washed with 3% solution of $NaHCO_3$, washed with water, and finally dried (Na_2SO_4). A solution of amino acid hydrochloride (3.33 mmol) in ethyl acetate (70 mL) containing 7.5 mL of Et_3N was stirred at 0°C for 20 min, filtered and the filtrate was added to the acid solution. The mixture was kept at −5°C for 12 h, then at 23°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 either oil, purified on SiO_2 column or solid, recrystallized by ethyl acetate-petroleum ether to give the desired product.

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)
12			**13**		
Leukemia/ lymphoma	*MT4*[b]	82	Leukemia/ lymphoma	MT4[b]	59
	CCRF-CEM[c]	85		*CCRF-CEM*[c]	68
	WIL-2NS[d]	>100		*WIL-2NS*[d]	97
	CCRF-SB[e]	>100		*CCRF-SB*[e]	90
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
15			***16***		
Leukemia/ lymphoma	*MT4*[b]	16	Leukemia/ lymphoma	*MT4*[b]	46
	CCRF-CEM[c]	20		*CCRF-CEM*[c]	67
	WIL-2NS[d]	34		*WIL-2NS*[d]	78
	CCRF-SB[e]	44		*CCRF-SB*[e]	85
Solid tumor-derived cell lines	*SK-MEL-28*[f]	40	Solid tumor-derived cell lines	*SK-MEL-28*[f]	>100
	MCF7[g]	60		*MCF7*[g]	>100
	SKMES-1[h]	53		*SKMES-1*[h]	>100
	HepG2[i]	74		*HepG2*[i]	>100
	DU145[j]	55		*DU145*[j]	>100
19			***24***		
Leukemia/ lymphoma	*MT4*[b]	49	Leukemia/ lymphoma	*MT4*[b]	79
	CCRF-CEM[c]	58		*CCRF-CEM*[c]	90
	WIL-2NS[d]	63		*WIL-2NS*[d]	>100
	CCRF-SB[e]	66		*CCRF-SB*[e]	>100
	DU145[j]	55		*DU145*[j]	>100

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.
[a]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.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-acetamido)-acetamido]-4-(methylthio)butanoate (**11**).* From **7** (0.82 g). Yield: 0.80 g (66%); oil. ^{1}H NMR ($CDCl_3$): δ 7.78–7.61 (m, 4H, NH, H-4, H-5, H-8); 7.48–7.32 (m, 2H, H-6, H-7); 7.13 (dd, 1H, $J = 2.2$ Hz, 6.8 Hz, H-3); 7.09 (d, 1H, $J = 2.2$ Hz, H-1); 4.55 (s, 1H, H-10); 4.52 (m, 1H, H-16); 4.10 (d, 1H, $J = 7.2$ Hz, H-13); 3.66 (s, 3H, CO_2Me); 2.14 (m, 1H, CH_2-18); 0.93 (d, 6H, $J = 1.9$ Hz, 7.2 Hz, C_{18}-Me_2). ^{13}C NMR ($CDCl_3$): δ 172.0 (C_{17}=O); 168.7 (C_{14}=O); 168.3 (C_{11}=O), 154.8 (C-2); 134.0 (C-8a); 129.7 (C-4); 129.3 (C-4a); 126.8 (C-5); 126.5 (C-8); 126.5 (C-7); 124.1 (C-6); 118.0 (C-3); 107.3 (C-1); 67.0 (C-10); 52.4 (CO_2Me); 51.4 (C-16); 42.3 (C-13); 31.1 (C-18); 29.8 (C-19); 15.2 (SMe). MS: m/z (FAB) ($C_{20}H_{24}N_2O_5S$) 427 $(M + Na)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-acetamido)-acetamido]-3-methylbutanoate (**12**).* From **7** (0.82 g). Yield: 0.64 g (57%); oil. ^{1}H NMR ($CDCl_3$): δ 7.82–7.72 (m, 4H, NH, H-4, H-5, H-8); 7.55–7.37 (m, 2H, H-6, H-7); 7.18 (dd, 1H, $J = 2.2$ Hz, 7.0 Hz, H-3); 7.14 (d, 1H, $J = 2.2$ Hz, H-1); 4.65 (s, 1H, H-10); 4.62 (m, 1H, H-16); 4.16 (d, 1H, $J = 7.4$ Hz, H-13); 3.75 (s, 3H, CO_2Me); 2.56 (q., 2H, $J = 7.4$ Hz, CH_2-19); 2.50 (q, 2H, $J = 7.4$ Hz, CH_2-18). ^{13}C NMR ($CDCl_3$): δ 172.1 (C_{17}=O); 168.7 (C_{14}=O); 168.0 (C_{11}=O), 154.9 (C-2); 134.1 (C-8a); 129.7 (C-4); 129.4 (C-4a); 127.5 (C-5); 126.5 (C-8); 126.5 (C-7); 124.1 (C-6); 118.0 (C-3); 107.5 (C-1); 67.1 (C-10); 57.3 (C-16); 51.9 (CO_2Me); 42.5 (C-13); 31.1 (C-18); 18.8 17.7 (CMe_2). MS: m/z (FAB) ($C_{20}H_{24}N_2O_5$) 395 $(M + Na)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-acetamido)-acetamido]propanoate (**13**).* From **7** (0.82 g). Yield: 0.69 g (67%); oil. ^{1}H NMR ($CDCl_3$): δ 7.93–7.62 (m, 4H, NH, H-4, H-5, H-8); 7.51–7.31 (m, 2H, H-6, H-7); 7.17 (dd, 1H, $J = 2.4$ Hz, 7.0 Hz, H-3); 7.17 (d, 1H, $J = 2.4$ Hz, H-1); 4.54 (s, 1H, H-10); 4.51 (m, 1H, H-16); 4.13 (d, 1H, $J = 5.0$ Hz, H-13); 3.75 (s, 3H, CO_2Me); 1.37 (d, 3H, $J = 7.2$ Hz, C_{16}-Me). MS: *m/z* (FAB) ($C_{18}H_{20}N_2O_5$) 367 $(M + Na)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-acetamido)-acetamido]acetate (**14**).* From **7** (0.82 g). Yield: 0.64 g (65%); oil. ^{1}H NMR ($CDCl_3$): δ 7.78–7.62 (m, 3H, H-4, H-5, H-8); 7.54 (dd, 1H, $J = 1.4$ Hz, 7.5 Hz, H-7); 7.38 (dd, 1H, $J = 1.4$ Hz, H-6); 7.26 (m, 1H, H-3); 7.02 (d, 1H, $J = 2.5$ Hz, H-1); 6.68 (br s, 1H, NH); 6.56 (br s, 1H, NH); 4.68 (s, 1H, H-10); 4.59 (m, 1H, H-16); 4.11 (d, 1H, $J = 6.0$ Hz, H-13); 3.65 (s, 3H, CO_2Me). MS: *m/z* (FAB) ($C_{17}H_{18}N_2O_5$) 353 $(M + Na)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-acetamido)-acetamido]-4-methylpentanoate (**15**).* From **7** (0.82 g). Yield: 0.82 g (71%); oil. ^{1}H NMR ($CDCl_3$): δ 7.81–7.67 (m, 4H, NH, H-4, H-5, H-8); 7.45 (ddd, 1H, $J = 1.2$ Hz, 2.3 Hz, 7.0 Hz, H-7); 7.35 (ddd, 1H, $J = 1.2$ Hz, 2.3 Hz, 7.0 Hz, H-6); 7.16 (dd, 1H, $J = 2.5$ Hz, 7.0 Hz, H-3); 7.10 (d, 1H, $J = 2.5$ Hz, H-1); 4.59 (s, 1H, H-10); 4.57 (m, 1H, H-16); 4.14 (d, 1H, $J = 5.2$ Hz, H-13); 3.70 (s, 3H, CO_2Me); 1.61 (m, 1H, CH_2-18); 1.25 (m, 1H, H-19); 0.93 (d, 6H, $J = 4.5$ Hz, $CHMe_2$). ^{13}C NMR ($CDCl_3$): δ 173.4 (C_{17}=O); 168.8 (C_{14}=O); 168.6 (C_{11}=O), 155.1 (C-2); 134.2 (C-8a); 129.8 (C-4); 129.5 (C-4a); 127.6 (C-5); 127.0 (C-8); 126.7 (C-7); 124.3 (C-6); 118.2 (C-3); 107.5 (C-1); 67.2 (C-10); 52.3 (C-16); 50.1 (CO_2Me); 42.5 (C-18); 24.8, 22.79 (CMe_2); 21.8 (C-16). MS: *m/z* (FAB) ($C_{21}H_{26}N_2O_5$) 387 $(M + H)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-acetamido)-acetamido]-3-hydroxypropanoate (**16**).* From **7** (0.82 g). Yield: 0.58 g (54%); oil. ^{1}H NMR ($CDCl_3$): δ 7.86–7.68 (m, 3H, H-4, H-5, H-8); 7.39–7.24 (m, 2H, H-6, H-7); 7.14 (dd, 1H, $J = 2.3$ Hz, 7.0 Hz, H-3); 7.01 (d, 1H, $J = 2.3$ Hz, H-1); 6.91, (br s, 1H, NH); 6.84 (br s, 1H, NH); 4.53 (s, 1H, H-10); 4.28–3.90 (m, 2H, H-13, H-18); 3.69 (8s, 3H, OAc); 2.00 (br s, 1H, OH). ^{13}C NMR ($CDCl_3$): δ 171.4 (C_{17}=O); 170.6 (C_{14}=O); 168.7 (C_{11}=O), 154.9 (C-2); 134.1 (C-8a); 129.7 (C-4); 129.4 (C-4a); 127.5 (C-5); 126.6 (C-8); 126.7 (C-7); 124.2 (C-6); 118.0 (C-3); 107.5 (C-1); 67.3 (C-10); 67.0 (C-18); 54.8 (C-16); 52.5 (CO_2Me); 42.3 (C-13). MS: *m/z* (FAB) ($C_{18}H_{20}N_2O_6$) 383 $(M + Na)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-3-hydroxy-propylamido)-acetamido]acetate (**17**).* From **8** (0.91 g). Yield: 0.60 g (56%); mp 145–148°C. ^{1}H NMR (DMSO-d_6) δ 8.45 (t, 1H, $J = 5.0$ Hz, NH); 8.13 (dd, 1H, $J = 1.6$ Hz, 8.0 Hz, H-8); 7.88–7.78 (m, 3H, NH, H-4, H-5); 7.44 (dd, 1H, $J = 2.3$ Hz, 7.8 Hz, H-7); 7.40–7.34 (m, 2H, H-1, H-6); 7.27 (d, 1H, $J = 2.3$ Hz, 8.8 Hz, H-3); 5.04 (t, 1H, $J = 5.2$ Hz, OH); 4.69 (s, 1H, H-10); 4.46 (dd, 1H, $J = 5.5$ Hz, 12.1 Hz, H-13); 3.86 (d, 1H, $J = 5.5$ Hz, H-18); 3.67 (t, 2H, $J = 5.0$ Hz, CH_2-16); 3.62 (s, 3H, CO_2Me). Anal Calcd for $C_{18}H_{20}N_2O_6$ (360.36): C, 59.99; H, 5.59; N, 7.77. Found: C, 59.72; H, 5.47; N, 7.43. MS: *m/z* (FAB) 361 $(M + H)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-3-hydroxy-propylamido)-acetamido]-3-hydroxypropanoate (**18**).* From **8** (0.91 g). Yield: 0.68 g (58%); oil. ^{1}H NMR (DMSO-d_6): δ 8.32 (d, 1H, $J = 7.6$ Hz, NH); 8.13 (d, 1H, $J = 8.0$ Hz, NH); 7.86–7.77 (m, 3H, H-4, H-5, H-8); 7.46 (dd, 1H, $J = 2.1$ Hz, 6.9 Hz, H-7); 7.42–7.32 (m, 2H, H-1, H-6); 7.24 (d, 1H, $J = 2.3$ Hz, 8.8 Hz, H-3); 5.03 (br s, 2H, 2 × OH); 4.68 (s, 1H, H-10); 4.53 (dd, 1H, $J = 5.5$ Hz, 10.5 Hz, H-13); 4.40 (dd, 1H, $J = 5.3$ Hz, 7.5 Hz, H-16); 3.75–3.65 (m, 4H, CH_2-18, CH_2-19); 3.59 (s, 3H, CO_2Me). MS: *m/z* (FAB) ($C_{19}H_{22}N_2O_7$) 413 $(M + Na)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-3-hydroxy-propylamido)-acetamido]-4-(methylthio)butanoate (**19**).* From **9** (1.04 g). Yield: 0.92 g (71%); oil. ^{1}H NMR ($CDCl_3$): δ 7.80–7.63 (m, 5H, 2×NH, H-4, H-5, H-8); 7.39 (dd, 1H, $J = 1.1$ Hz, 6.8 Hz, H-7); 7.30 (dd, 2H, $J = 1.3$ Hz, 6.8 Hz, H-6); 7.17 (dd, 1H, $J = 2.3$ Hz, 7.3 Hz, H-3); 7.05 (d, 1H, $J = 2.3$ Hz, H-1); 4.73–4.61 (m, 2H, H-13, OH); 4.57 (s, 1H, H-10); 4.01 (m, 1H, H-16); 3.73 (m, 2H, CH_2-OH); 3.65 (s, 3H, CO_2Me). 2.54 (m, 2H, CH_2CH_2SMe); 2.08 (m, 2H, CH_2CH_2SMe); 1.99 (s, 3H, SMe). ^{13}C NMR (DMSO-d_6): δ 170.1 (C_{17}=O); 169.0 (C_{14}=O); 168.8 (C_{11}=O), 154.8 (C-2); 134.1 (C-8a); 129.7 (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); 107.6 (C-1); 67.1 (C-10); 62.6 (CH_2OH); 54.1 (C-13); 51.9 (C-16); 51.6 (CO_2Me); 31.0 (CH_2CH_2SMe); 29.8 (CH_2CH_2SMe); 15.2 (SMe). MS: *m/z* (FAB) ($C_{21}H_{26}N_2O_6S$) 457 $(M + Na)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-4-(methylthio)-butylamido)-acetamido]-4-(methylthio)-butanoate (**20**).* From **9** (1.04 g). Yield: 0.84 g (59%); mp 67–71°C. ^{1}H NMR (DMSO-d_6): δ 8.56 (dd, 1H, $J = 2.3$ Hz, 7.0 Hz, H-8); 7.90–7.62 (m, 2H, H-4, H-5); 7.47 (dd, 1H, $J = 1.2$ Hz, 6.9 Hz, H-7); 7.35 (dd, 2H, $J = 1.2$ Hz, 6.9 Hz, H-6); 7.22 (m, 2H, H-1, H-3); 6.70 (br s, 1H, NH); 6.52 (br s, 1H, NH); 4.40 (m, 1H, H-13); 4.64 (s,

1H, H-10); 4.29 (m, 1H, H-16); 3.67 (s, 3H, CO_2Me). 2.60–2.31 (m, 4H, CH_2-19, CH_2CH_2SMe); 2.12–1.90 (m, 7H, CH_2-18, CH_2CH_2SMe, SMe). Anal Calcd for $C_{23}H_{30}N_2O_5S_2$ (478.62): C, 57.72; H, 6.32; N, 5.85. Found: C, 57.50; H, 6.21; N, 5.62. MS: *m/z* (FAB) 479 $(M+H)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-4-(methylthio)-butylamido)-acetamido]acetate (***21***).* From **9** (1.04 g). Yield: 0.76 g (63%); mp 71–75°C. ^{1}H NMR ($CDCl_3$): δ 7.73–7.62 (m, 3H, H-4, H-5, H-8); 7.39 (ddd, 1H, $J = 1.3$ Hz, 2.2 Hz, 8.0 Hz, H-7); 7.30 (ddd, 2H, $J = 1.3$ Hz, 2.2 Hz, 8.0 Hz, H-6); 7.17 (dd, 1H, $J = 2.3$ Hz, 8.8 Hz, H-3); 7.05 (d, 1H, $J = 2.3$ Hz, H-1); 6.88 (br s, 1H, NH); 6.56 (bra s, 1H, NH); 4.82 (m, 1H, H-13); 4.56 (s, 1H, H-10); 3.95 (m, 1H, H-16); 3.66 (s, 3H, CO_2Me). 2.50 (q, 2H, $J = 7.2$ Hz, CH_2CH_2SMe); 2.11 (q, 2H, $J = 7.2$ Hz, CH_2CH_2SMe); 1.98 (s, 3H, SMe). ^{13}C NMR ($CDCl_3$): δ 171.3 (C_{17}=O); 170.1 (C_{14}=O); 168.6 (C_{11}=O), 155.0 (C-2); 134.2 (C-8a); 129.9 (C-4); 129.5 (C-4a); 127.6 (C-5); 126.9 (C-8); 126.7 (C-7); 124.3 (C-6); 118.2 (C-3); 107.5 (C-1); 67.2 (C-10); 52.3 (CO_2Me); 51.7 (C-13); 41.2 (C-16); 31.6 (CH_2CH_2SMe); 29.9 (CH_2CH_2SMe); 15.2 (SMe). Anal Calcd for $C_{20}H_{24}N_2O_5S$ (404.40): C, 59.39; H, 5.98; N, 6.93. Found: C, 59.18; H, 5.89; N, 6.71. MS: *m/z* (FAB) 405 $(M+H)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-4-(methylthio)-butylamido)-acetamido]-3-hydroxypropanoate (***22***).* From **9** (1.04 g). Yield: 0.69 g (53%); mp 91–94°C. ^{1}H NMR (DMSO-d_6): δ 8.43 (d, 1H, $J = 7.8$ Hz, NH); 8.34 (d, 1H, $J = 8.3$ Hz, NH); 7.92–7.81 (m, 3H, H-4, H-5, H-8); 7.50 (did, 1H, $J = 2.2$ Hz, 7.5 Hz, H-7); 7.42 (did, 2H, $J = 2.2$ Hz, 7.5 Hz, H-6); 7.34 (bra s, 1H, H-3); 7.30 (d, 1H, $J = 2.4$ Hz, H-1); 5.17 (t, 1H, $J = 5.5$ Hz, OH); 4.76 (s, 1H, H-10); 4.64 (m, 1H, H-13); 4.44 (m, 1H, H-16); 3.82–3.68 (m, 2H, CH_2OH); 3.43 (s, 3H, CO_2Me). 2.46 (q, 2H, $J = 6.7$ Hz, CH_2CH_2SMe); 2.14–1.21 (m, 5H, CH_2CH_2SMe, SMe). Anal Calcd for $C_{21}H_{26}N_2O_6S$ (434.50): C, 58.05; H, 6.03; N, 6.45. Found: C, 57.86; H, 5.93; N, 6.21. MS: *m/z* (FAB) 435 $(M+H)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-propylamido)-acetamido]-4-(methylthio)butanoate (***23***).* From **10** (0.86 g). Yield: 0.85 g (68%); mp 68–71°C. ^{1}H NMR ($CDCl_3$): δ 7.73–7.54 (m, 4H, NH, H-4, H-5 H-8), 7.42 (dd, 1H, $J = 2.3$ Hz, 8.4 Hz, H-7), 7.30 (dd, $J = 2.3$ Hz, 8.4 Hz, H-6); 7.14 (dd, 1H, $J = 2.1$ Hz, 6.0 Hz, H-3); 7.08 (d, 1H, $J = 2.1$ Hz, H-1); 6.89 (bra s, 1H, NH), 4.78 (m, 1H, H-13); 4.73 (m, 1H, H-16); 4.54 (s, 1H, H-10); 3.67 (s, 3H, CO_2Me). 2.48 (q, 2H, $J = 7.3$ Hz, CH_2CH_2SMe); 2.10 (q, 2H, $J = 7.3$ Hz, CH_2CH_2SMe); 1.97 (s, 3H, SMe); 1.46 (d, 3H, $J = 7.1$ Hz, C_{13}-Me). ^{13}C NMR ($CDCl_3$): δ 172.2 (C_{17}=O); 172.1 (C_{14}=O); 168.1 (C_{11}=O), 155.0 (C-2); 134.2 (C-8a); 129.9 (C-4); 129.5 (C-4a); 127.7 (C-5); 126.9 (C-8); 126.6 (C-7); 124.3 (C-6); 118.2 (C-3); 107.6 (C-1); 67.2 (C-10); 52.5 (C-16); 51.6 (CO_2Me); 48.4 (C-13); 41.2 (C-16); 31.2 (CH_2CH_2SMe); 30.0 (CH_2CH_2SMe); 18.8 (C_{13}-*Me*); 15.4 (SMe). Anal Calcd for $C_{21}H_{26}N_2O_5S$ (418.50): C, 60.27; H, 6.26; N, 6.69. Found: C, 60.02; H, 6.13; N, 6.43. MS: *m/z* (FAB) 419 $(M+H)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-propylamido)-acetamido]acetate (***24***).* From **10** (0.86 g). Yield: 0.74 g (72%); oil. ^{1}H NMR ($CDCl_3$): δ 7.81–7.61 (m, 3H, NH, H-5, H-8); 7.55–7.30 (m, 3H, H-4, H-6, H-7); 7.18–7.04 (m, 2H, H-1, H-3); 6.75 (bra s, 1H, NH); 4.79 (m, 1H, H-13); 4.56 (br s, 1H, H-10); 3.94 (m, 1H, H-16); 3.59 (s, 3H, CO_2Me); 1.45 (d, 3H, $J = 7.1$ Hz, C_{13}-Me). ^{13}C NMR ($CDCl_3$): δ 172.5 (C_{17}=O); 170.2 (C_{14}=O); 168.2 (C_{11}=O), 155.1 (C-2); 134.2 (C-8a); 129.8 (C-4); 129.4 (C-4a); 127.7 (C-5); 126.9 (C-8); 126.6 (C-7); 124.3 (C-6); 118.2 (C-3); 107.6 (C-1); 67.2 (C-10); 52.3 (CO_2Me); 48.3 (C-13); 41.2 (C-16); 18.5 (C_{13}-*Me*). MS: *m/z* (FAB) ($C_{18}H_{20}N_2O_5$) 367 $(M+Na)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-propylamido)-acetamido]-3-hydroxypropanoate (***25***).* From **10** (0.86 g). Yield: 0.57 g (51%); mp. 128–132°C. ^{1}H NMR (DMSO-d_6): δ 8.38 (d, 1H, $J = 7.5$ Hz, H-8), 7.85–7.74 (m, 2H, H-4, H-5); 7.45 (ddd, 1H, $J = 1.5$, Hz, 2.2 Hz, 7.5 Hz, H-7); 7.34 (ddd, 1H, $J = 1.5$ Hz, 2.2 Hz, 7.5 Hz, H-6); 7.25 (bra s, 2H, H-1, H-3); 6.68 (br s, 1H, NH); 6.49 (br s, 1H, NH); 5.43 (q, 1H, $J = 7.6$ Hz, H-13); 5.07 (t, 1H, $J = 5.1$ Hz, OH), 4.51 (s, 1H, H-10); 4.70 8 (m, 1H, H-16); 3.68 (m, 1H, CH_2OH); 3.61 (s, 3H, $COMe_2$); 3.47 (m, 1H, CH_2OH); 1.28 (d, 3H, $J = 6.5$ HZ, C_{13}-Me). ^{13}C NMR (DMOS-d_6): δ 172.2 (C_{17}=O); 170.9 (C_{14}=O); 168.7 (C_{11}=O), 154.9 (C-2); 134.2 (C-8a); 129.9 (C-4); 129.5 (C-4a); 127.6 (C-5); 127.0 (C-8); 126.7 (C-7); 124.3 (C-6); 118.2 (C-3); 107.7 (C-1); 67.1 (C-10); 67.0 (CH_2OH); 54.9 (C-16); 52.6 (CO_2Me); 48.6 (C-13); 18.5 (C_{13}-Me). Anal Calcd for $C_{19}H_{22}N_2O_6$ (374.15): C, 60.95; H, 5.92; N, 7.48. Found: C, 60.72; H, 5.81; N, 7.25. MS: *m/z* (FAB) 375 $(M+H)^+$.

*Methyl 2-[2-(2-(naphthalen-6-yloxy)-4-(methylthio)-butylamido)-3-(2,3,4,5-di-O-isopropylidene-α-D-mannofuranos-1-yloxy)-acetamido]propanoate (***27***).* A solution of **22** (0.65 g, 1.50 mmol) and **26** (0.60 g, 1.50 mmol) in dry CH_2Cl_2 (30 mL) was stirred under nitrogen at room temperature for 5 min, followed by the addition of TMSOTf (1.50 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 **27** (0.65 g, 65%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.73–7.69 (m, 2H, NH, H-5); 7.57 (d, 1H, $J = 8.2$ Hz, H-4); 6.93 (m, 2H, H-3; H-8); 6.89 (m, 2H, H-1, H-6); 4.70 (s, 2H, CH_2-10); 4.59 (m, 2H, CH_2-13); 4.33 (m, 1H, H-14); 2.52 (m, 2H, CH_2CH_2SMe); 2.38 (m, 2H, CH_2CH_2SMe); 2.05 (s, 3H, SMe). Ms: *m/z* (FAB) ($C_{33}H_{44}N_2O_{11}S$) 699 $(M + Na)^+$.

*Methyl 2-[2-(2-hydroxynaphthyl-2-yloxy)-acetamido)-4-(methylthio)butanoate (***29***).* To a cold solution of methyl L-methionine carboxylate hydrochloride (10.0 mmol) at −5°C in MeCN (20 mL) and Et_3N (1 mL) were added **28** (2.18 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 (dicyclohexyl urea) 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. The residue was poured onto SiO_2 column, using CH_2Cl_2-MeOH (95:5) to give **29** (1.96 g, 54%), mp 77–81°C. ^{1}H 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_2CH_2SMe); 2.46 (t, 2H, $J = 7.3$ Hz, CH_2CH_2SMe); 2.00 (s, 3H, SMe). Anal Calcd for $C_{18}H_{21}NO_5S$ (363.43): C, 59.49; H, 5.82; N, 3.85. Found: C, 59.18; H, 4.93; N, 3.62. MS: *m/z* (FAB) 364 $(M + H)^+$.

*Methyl 2-[2-(2-O-(2,3,4,5-di-O-isopropylidene-α-D-mannofuranos-1-yloxy)napthyl-2-yloxy)-acetamido]-4-(methylthio)butanoate (***30***).* A solution of **29** (0.50 g, 1.37 mmol) and **26** (0.54 mg, 1.37 mmol) in dry CH_2Cl_2 (35 mL) was stirred under nitrogen at room temperature for 5 min, followed by the addition of TMSOTf (30 μL). After stirring for 2 h, a solid $NaHCO_3$ was added slowly, filtered, and the filtrate was washed with water (40 mL), dried (Na_2SO_4), filtered, and evaporated to dryness. The residue was purified by SiO_2 column (30 g), using ethyl acetate/petroleum ether as eluent to give **30** (0.17 g, 58%) as an oil. ^{1}H NMR ($CDCl_3$): δ δ 7.59–7.42 (m, 3H, NH, H-4, H-5); 7.20–6.95 (m, 7H, H-3, H-6, CH_2Ph); 6.95–6.90 (m, 2H, H-1; H-8); 4.80 (br s, 1H, H-1′), 4.77 (m, 1H, H-13); 4. 57 (s, 1H, H-10); 4.53 (dd, 1H, $J_{4',5'} = 3.5$ Hz, $J_{3',4'} = 4.6$ Hz, H-4′); 4.01 (m, 1H, H-3′); 3.95 (dd, 1H, $J_{5',6''} = 4.0$ Hz, $J_{6',6''} = 9.0$ Hz, H-6′); 3.73 (s, 3H, OAc); 3.62 (dd, 1H, $J_{5',6''} = 3.1$ Hz, H-6′); 2.61 (t, 2H, $J = 7.1$ Hz, CH_2CH_2SMe); 2.42 (t, 2H, $J = 7.1$ Hz, CH_2CH_2SMe); 1.37 (2 × s, 6H, CMe_2); 1.32, 1.22 (2 × s, 6H, CMe_2). MS: *m/z* (FAB) ($C_{30}H_{39}NO_{10}S$) 628 $(M + Na)^+$.

*Methyl 2-[2-(2-(3-N-benzyl-N-isopropylamino)-2-hydroxypropoxy)naphthalen-7-yloxy)-acetamido]-4-(methylthio)butanoate (***31***).* A mixture of **29** (1.10 g, 3.02 mmol) *N*-benzyl-*N*-ispropyl-2-hydroxy-3-chloropropylamine (4.95 g, 20.53 mmol), K_2CO_3 (6.42 g, 46.55 mmol), and EtMeCO (50 mL) was heated at 100°C for 5 days in a sealed tube. The reaction mixture was filtered, and the filtrate was evaporated to dryness. The residue was poured onto SiO_2 column (25 g) and eluted, in gradient with MeOH (0–5%) and CH_2Cl_2 to give **31** (0.34 g, 20%) as an oil. ^{1}H NMR ($CDCl_3$): δ 7.61–7.48 (m, 3H, NH, H-4, H-5); 7.22–7.00 (m, 7H, H-3, H-6, CH_2Ph); 6.95–6.90 (m, 2H, H-1; H-8); 4.80 (m, 1H, H-13); 4.59 (s, 2H, CH_2-10); 4.16 (m, 2H, CH_2-2′); 3.97 (m, 1H, H-3′); 3.70 (s, 3H, OAc); 3.61 (s, 2H, CH_2Ph); 2.96 (m, 1H, H-14); 2.06 (d, 1H, $J = 6.5$ Hz, NCHMe$_2$); 2.60 (t, 2H, $J = 7.2$ Hz, CH_2CH_2SMe); 2.50 (t, 2H, $J = 7.0$ Hz, CH_2-4′); 2.44 (t, 2H, $J = 7.2$ Hz, CH_2CH_2SMe); 2.00 (s, 3H, SMe); 1.07, 1.04 (2 × s, 6H, NCHMe_2). Ms: *m/z* (FAB) ($C_{31}H_{40}N_2O_6S$) 591 $(M + Na)^+$.

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