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Design, Synthesis and Cytotoxicity Evaluation of 1-Chloromethyl-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (*seco*-CBI) Dimers

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Abstract—Three types of 1-chloromethyl-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (*seco*-CBI) dimers were designed, synthesized and evaluated in vitro by NCI against nine types of cancer cells. Biological results showed that the antitumor activities of these *seco*-CBI dimers were strongly related to the position and length of the linker and generally with potency increasing in the order of C7–C7 dimers (**22i**–**iv**) < C7–N3 dimers (**28i**–**iv**) < N3–N3 dimers (**25i**–**iv**). Compound **28iv** showed significant activity against CCRT-CEM, HL-60 (TB), MOLT-4, and SR leukemia cell lines and the MCF 7 breast cancer cell line with GI_{50} values < 0.01 μM. N3–N3 dimer **25i** displayed striking potency against leukemia, CNS cancer, melanoma and prostate cancer cell lines with GI_{50} values < 0.01 μM against all the cell lines and showed the highest overall potency of the agents examined (GMG = 0.0120 μM).

Introduction

Sequence-specific DNA alkylation has significant potential for use in molecular biology and human medicine. The cyclopropylindole class of antitumor antibiotics, exemplified by CC-1065 and duocarmycins (Fig. 1), are extremely potent cytotoxins that have engendered great interest both as potential anticancer drugs[1] and as targets for synthesis.[2] Studies on the mechanism of cytotoxic action show that these naturally occurring compounds bind to AT-rich sequences and selectively alkylate N3 of the 3′-adenine in the minor groove of B-DNA by their cyclopropylindole (CPI) subunits.[2a] Many synthetic analogues have been reported in the search for compounds with better antitumor selectivity and DNA sequence-specific binding properties.[3] As a successful example of modification, Boger first reported that the simplified moiety, 1,2,9,9a-tetrahydrocyclopropa[*c*]-benz[*e*]indole-4-one (CBI), and its analogues were more stable and more potent than the CPI counterparts.[4] In our group, attempts have been made to link CPI[5] and CBI[6] with pyrrole/imidazole polyamides, which are well-established DNA minor groove binders,[7] in attempts to improve their pharmacological properties and potencies. Studies have also shown that some synthetic compounds which contain two CPI moieties are significantly more potent than CC-1065 both in vitro and in vivo.[8] In fact, many active antitumor agents act by cross-linking DNA.[9] While to date some CPI dimers have been prepared to examine interstrand cross-linking of DNA,[8] to our knowledge, no attempt has been made to synthesize 1-chloromethyl-5-hydroxy-1,2-dihydro-3*H*-benz[*e*]indole (*seco*-CBI) dimers. It is well known that the activity of the dimeric drug is strongly related to the length and the position of the linker. In order to investigate the structure–activity relationships systematically, we have designed and synthesized three types of *seco*-CBI dimers (i.e., C7–C7, N3–N3 and N3–C7) which contain two racemic CBI moieties linked from two positions by a flexible methylene chain of variable length.

Results and Discussion

Chemistry

Our strategy of the synthesis of *seco*-CBI dimers requires a protected *seco*-CBI which possesses an active group at C8 or C7 position. The reports of the synthesis of 7-methoxy-CBI[10] and 7-cyano-CBI[11] encouraged us to design the synthetic methodology of 1-chloromethyl-5-benzoxy-1,2-dihydro-3*H*-benz[*e*]indole (**5**) shown in Scheme 1.

Condensation of 4-nitrobenzaldehyde (**6**) with the Wadswarth–Horner–Emmons reagent **7**[12] at low temperature provided **8** in 60% yield. Acid-catalyzed

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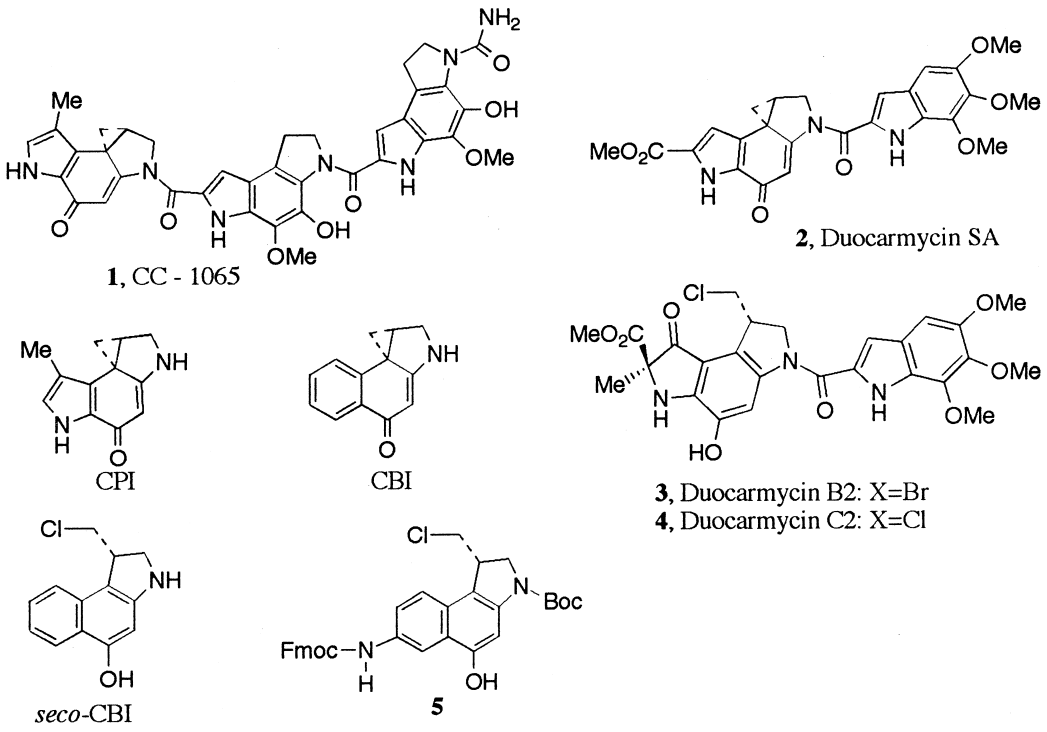
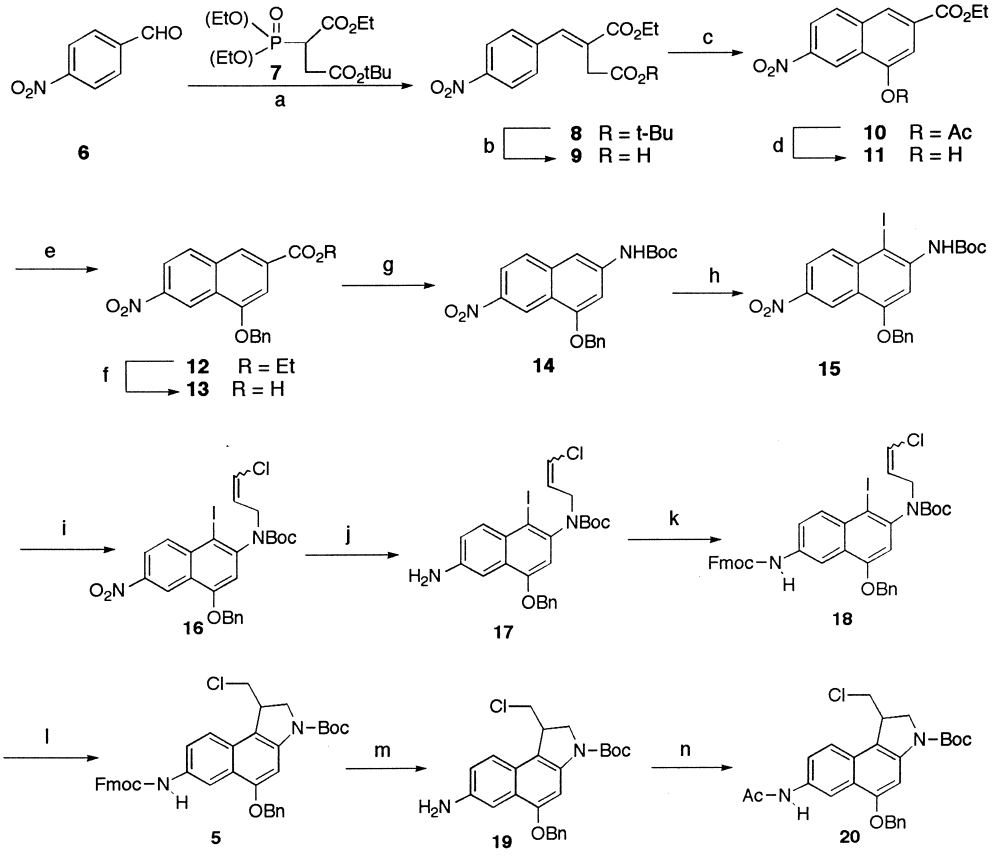


Figure 1. Structures.



Scheme 1. Reagents and conditions: (a) NaH, THF, 60%; (b) 9:1 TFA:H_2O, 23 °C, 91%; (c) Ac_2O–NaOAc; (d) K_2CO_3–EtOH, 77% from **9**; (e) BnBR, K_2CO_3, Cat. Bu_4NI, DMF; (f) LiOH, 3:1:1 THF:MeOH:H_2O, 99% from **11**; (g) DPPa, Et_3N, 4 Å molecular sieve, *t*-BuOH, 84%; (h) NIS, cat. TsOH, 1:1 THF:MeOH, 98%; (i) NaH, ClCH=$CHCH_2Cl$, cat. Bu_4NI, DMF, 83%; (j) $N_2H_4H_2O$, $FeCl_3$; (k) *F*moc-Cl, Et_3N, 86% from **16**; (l) Bu_3SnH, AIBN, 78%; (m) Bu_4NF, THF, 96%; (n) CH_3COCl, Et_3N, 92%.

deprotection of **8** afforded acid **9** in 91% yield. Although the nitro group is strongly electron-withdrawing, intramolecular Friedel–Crafts acylation of **9** effected by treatment with Ac_2O–NaOAc led to **10**. Hydrolysis of the *O*-acetate **10** afforded the free phenol **11** (77% overall yield from **9**). Protection of the phenol **11** followed by hydrolysis of the ethyl ester **12** cleanly provided **13** (99% overall yield). Curtius rearrangement of carboxylic acid **13** employing the Shioiri–Yamada reagent diphenyl phosphorazidate (DPPA) gave the carbamate **14**, also in good yield (84%). Acid-catalyzed C4 iodination at room temperature cleanly provided **15**[13] whose structure was confirmed by single crystal X-ray diffraction analysis (Fig. 2). Deprotonation of carbamate **15**, using NaH, followed by alkylation of the resulting anion with (*Z*:*E*)-1,3-dichloropropene in the presence of phase transfer catalyst Bu_4NI gave a mixture of *Z*:*E* isomers of vinyl chloride **16**. Selective reduction of the nitro group of **16** using hydrazine,[14] followed by protection of the amino group, provided **18** (86% yield from **16**), the desired precursor for the intramolecular aryl radical cyclization onto a tethered vinyl chloride.[13,15] A deoxygenated solution of **18** in fresh distilled dry benzene was heated at reflux for 15 h in the presence of tri-*n*-butyltin hydride and a catalytic amount of 2,2′-azobis(isobutyronitrile) (AIBN) to give the fully protected bifunctionalized racemic *seco*-CBI **5** in 78% yield. Although not investigated in detail, no reaction occurred when nitro compound **16** was treated under the same conditions as amine **18**. Deprotection of the *F*moc group followed immediately by reaction with acetyl chloride afforded **20** almost quantitatively.

Coupling **19** with 0.5 equiv of the appropriate di-acid chloride (glutaryl dichloride, adipoyl chloride, pimeloyl chloride, or suberoyl chloride) produced benzyl protected *seco*-CBI dimers **21i–iv** in high yield (80–89%). Treatment of **21i–iv** with ammonium formate in the presence of Pd/C[13] for about 15 min provided C7–C7 *seco*-CBI dimers **22i–iv** in 86–97% yield (Scheme 2).

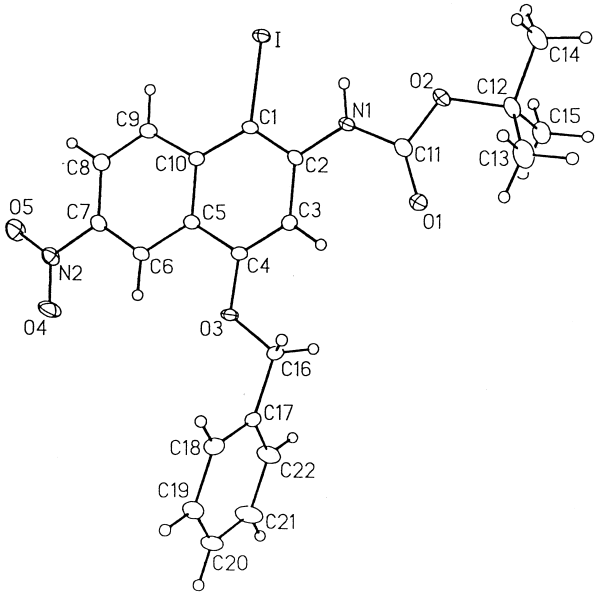


Figure 2. ORTEP diagram of compound **15**.

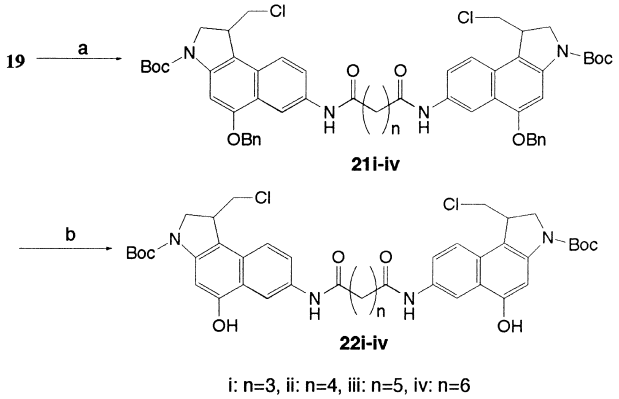
Detachment of the Boc group from **20** followed by coupling with 0.5 molar amount of the appropriate di-acid chloride (glutaryl dichloride, adipoyl chloride, pimeloyl chloride, or suberoyl chloride) afforded **24i–iv** in good yield (66–76%). Hydrogenolysis of **24i–iv** served to remove the benzyl group and provided N3–N3 *seco*-CBI dimers **25i–iv** (HCO_2NH_4, Pd/C, 72–76%) (Scheme 3).

Treatment of **23** with glutaric anhydride in the presence of triethylamine provided acid **26i** in good yield (89%) (Scheme 4). Condensation of agent **23** in the presence of EDCI with excess amount of the appropriate di-acid (adipic acid, pimelic acid, or suberic acid) gave acids **26ii–iv** in 67–68% yield. Notably, treatment of **23** with excess di-acid chloride led to a complex mixture, probably arising from the high activity of the acid chlorides. Coupling acids **26i–iv** with **19** (4 equiv of EDCI, DMF, 23 °C) produced protected *seco*-CBI dimers **27i–iv** in fair yield (48–62%). Deprotection of benzyl group from **27i–iv** afforded N3–C7 dimers **28i–iv** in good yield (71–77%).

Biological evaluation

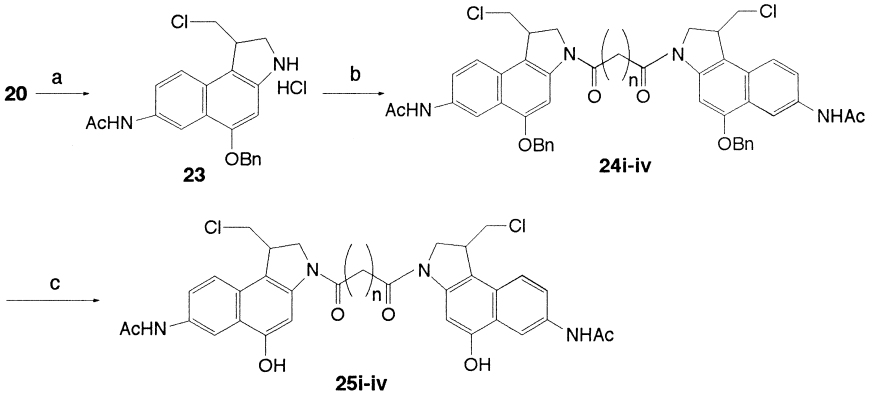
Compounds **22i–iv**, **25i–iv** and **28i–iv** were selected by the US National Cancer Institute (NCI) for evaluation in an in vitro preclinical antitumor screening program[16] against 60 human tumor cell lines derived from leukemia, non-small cell lung cancers, colon cancer, CNS cancer, melanoma, ovarian cancer, renal cancer, prostate cancer and breast cancer. Selected biological evaluation results of compounds **22i–iv**, **28i–iv** and **25i–iv** are presented in Tables 1–3, respectively, as GI_{50} values (the concentration of drug resulting in inhibition of cell growth to 50% of controls, equivalent to IC_{50}), together with MGM (the mean graph midpoint).

All compounds were active against almost all cell lines with MGM value from 41.6 μM (**22iii**) to 0.0120 μM (**25i**) (activity is defined as $GI_{50} < 100$ μM). In general, the activity sequence is C7–C7 dimers < C7–N3 dimers < N3–N3 dimers. Studies have shown that removal of the linking amide from the CC-1065 analogues would render the agents incapable of alkylating DNA.[17] The

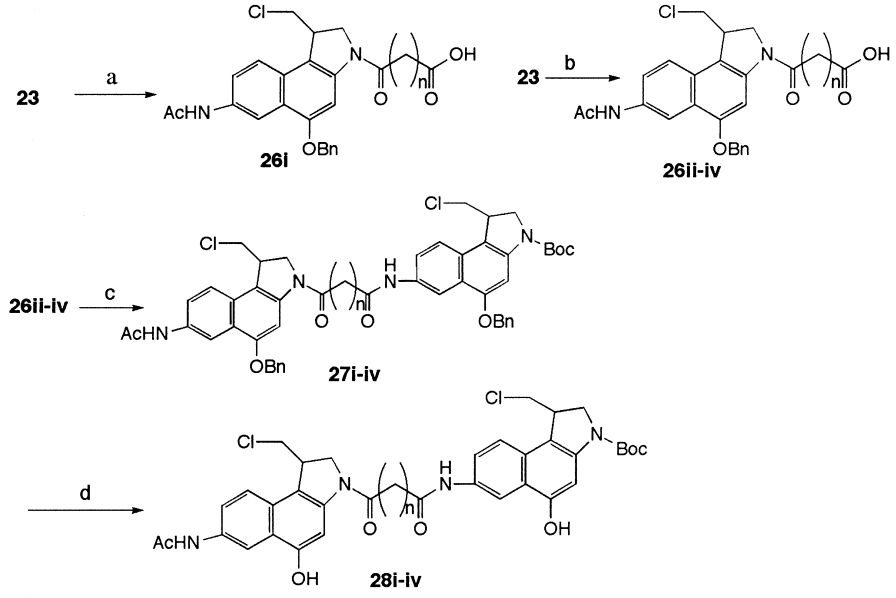


i: n=3, ii: n=4, iii: n=5, iv: n=6

Scheme 2. Reagents and conditions: (a) $ClCO(CH_2)_3COCl$, $ClCO(CH_2)_4COCl$, $ClCO(CH_2)_5COCl$, or $ClCO(CH_2)_6CO$, $ClEt_3N$, THF, 80–89%; (b) HCO_2NH_4, Pd/C, THF, 86–97%.



Scheme 3. Reagents and conditions: (a) 4 M HCl in dioxane; (b) $ClCO(CH_2)_3COCl$, $ClCO(CH_2)_4COCl$, $ClCO(CH_2)_5COCl$ or $ClCO(CH_2)_6COCl$, Et_3N, DMF, 66–76%; (c) HCO_2NH_4, Pd/C, DMF, 72–76%.



Scheme 4. Reagents and conditions: (a) glutaric anhydride, Et_3N, THF, 89%; (b) $ClCO(CH_2)_4COCl$, $ClCO(CH_2)_5COCl$, or $ClCO(CH_2)_6COCl$, Et_3N, EDCl, DMF, 67–68%; (c) **19**, EDCI, DMF, 48–62%; (d) HCO_2NH_4, Pd/C, THF, 71–77%.

cytotoxic sequence of these *seco*-CBI dimers also implies that the linking N3 amide plays a critically important role in DNA alkylation.

Among the C7–C7 dimers, **22i** is the most potent compound and the potency decreases with the increasing length of the linker (**22iii** and **22iv** have almost the same activities). For the C7–N3 dimers (**28i–iv**), compound **28iv**, which possesses the longest linker ($n=6$) in the series, proved to be the most potent with potency decreasing in the order of **28iv** ($n=6$) > **28i** ($n=3$) > **28ii** ($n=4$) > **28iii** ($n=5$). Interestingly, compound **28iv** ($n=6$, GMG = 0.0891 μM) was 30× as potent as compound **28iii** ($n=5$, GMG = 2.63 μM) with the only structural difference of one carbon decrease in the linkers.

Turning to the N3–N3 dimers, it is evident that this series of compounds is the most potent set investigated, with MGM values ranging from 0.116 μM for **25ii** to 0.0120 μM for **25i**. Compound **25i** displayed striking potency in the leukemia, CNS cancer, melanoma, prostate, and breast cancer cell panels with GI_{50} values lower than 0.01 μM in all the cell lines. Compound **25iii** and **25iv** selectively inhibited leukemia, CNS cancer and melanoma with the GI_{50} values lower than 0.01 μM in all the cell lines.

It was reported that the IC_{50}s of CPI[8a] and CBI[10] monomers against L1210 leukemia cell line were 0.06 and 0.08 μM, respectively. The substituted CBIs, 7-methoxy-CBI[10] and 7-cyano-CBI,[11] inhibit L1210 with the IC_{50} values of 2000 and 0.09 μM, respectively. While it is hard to compare the data of dimeric *seco*-CBI **28iv** and **25i–iv** from NCI with the reported data of these CBI monomers because none of the NCI's cell lines resembles L1210, the remarkable potencies for

Table 1. In vitro cytotoxic potencies (GI_{50}s) of C7–C7 dimers **22i–iv**

	GI_{50} (μM)[a]			
Panels/cancer cell lines	**22i**	**22ii**	**22iii**	**22iv**
Leukemia				
CCEF-CEM	1.53	9.94	1.24	28.8
HL-60 (TB)	3.00	—	—	–
MOLT-4	0.900	0.27	0.562	1.42
SR	2.20	0.306	0.404	0.678
Non-small cell lung cancer				
HOP-62	11.6	35.5	> 100	> 100
NCI-H23	4.67	2.95	13.1	24.4
NCI-H460	2.39	1.96	2.39	3.43
NCI-H522	5.42	12.3	> 100	> 100
Colon cancer				
COLO 205	7.64	12.9	37.8	22.9
HCC-2998	2.80	23.7	65.8	3.43
HCT-116	5.74	7.85	7.38	40.4
HT 29	11.0	22.3	22.8	32.6
CNS cancer				
SF-268	5.49	17.4	> 100	> 100
SNB-19	20.4	31.1	> 100	57.7
U 251	3.30	1.95	6.76	13.4
Melanoma				
LOX IMVI	4.85	5.34	3.98	57.7
MALME-3M	11.7	15.1	> 100	59.6
SK-MEL-2	3.33	7.31	72.1	31.0
SK-MEL-5	4.81	8.39	17.3	15.0
UACC-257	5.54	69.6	> 100	> 100
UACC-62	6.48	15.9	65.3	31.6
Ovarian cancer				
IGROV1	16.1	27.4	> 100	92.1
OVCAR-3	6.48	3.88	> 100	35.2
OVCAR-4	6.39	3.94	> 100	43.1
SK-OV-3	27.4	> 100	> 100	> 100
Renal cancer				
786-0	2.97	0.543	1.43	1.42
A498	8.08	10.1	24.0	15.7
SN12C	15.1	> 100	> 100	> 100
Prostate cancer				
PC-3	8.99	10.9	> 100	> 100
Breast cancer				
MCF 7	2.23	2.29	2.36	> 100
MDA-MB231/ATCC	12.9	33.8	> 100	39.9
MDA-MB-435	4.95	14.2	> 100	> 100
MDA-N	10.9	19.3	47.7	36.0
BT-549	7.15	17.4	> 100	> 100
T 47D	4.02	12.2	> 100	12.1
MGM[b]	8.71	13.2	41.6	33.1

[a]The cytotoxicity GI_{50} values are the concentrations corresponding to 50% growth inhibition.
[b]Mean graph midpoint (μM) for growth inhibition against all human cancer cell lines tested.

Table 2. In vitro cytotoxic potencies (GI_{50}s) of C7–N3 dimers **28i–iv**

	GI_{50} (μM)[a]			
Panels/cancer cell lines	**28i**	**28ii**	**28iii**	**28iv**
Leukemia				
CCEF-CEM	0.111	0.193	0.128	< 0.0100
HL-60 (TB)	0.0945	0.303	0.313	< 0.0100
MOLT-4	0.0724	0.190	0.0423	< 0.0100
SR	0.0204	0.0875	0.0587	< 0.0100
Non-small cell lung cancer				
HOP-62	2.20	2.84	1.57	0.0935
NCI-H23	1.42	1.37	1.01	0.0469
NCI-H460	1.71	2.26	0.665	0.0234
NCI-H522	0.371	0.740	1.05	0.0387
Colon cancer				
COLO 205	1.38	1.57	1.60	0.0928
HCC-2998	1.08	1.74	1.35	0.0551
HCT-116	0.996	2.45	1.65	0.0371
HT 29	1.36	2.69	2.98	0.143
CNS cancer				
SF-268	0.518	1.43	1.30	0.0399
SNB-19	1.13	1.81	1.33	0.0210
U 251	1.01	1.49	0.722	0.0169
Melanoma				
LOX IMVI	1.14	1.95	1.89	0.0420
MALME-3M	0.780	1.57	2.38	0.103
SK-MEL-2	0.996	1.68	1.54	0.0276
SK-MEL-5	0.966	1.64	1.36	0.0246
UACC-257	1.19	1.74	2.22	0.136
UACC-62	1.07	1.56	1.30	0.0675
Ovarian cancer				
IGROV1	1.19	1.42	7.65	0.0505
OVCAR-3	1.05	2.37	1.42	0.0520
OVCAR-4	1.89	3.08	3.61	0.232
SK-OV-3	1.36	4.39	3.52	0.0557
Renal cancer				
786-0	1.52	2.49	1.84	0.0578
A498	0.993	2.01	1.56	0.0248
SN12C	2.29	2.52	5.54	0.129
Prostate cancer				
PC-3	1.61	2.85	2.77	0.0816
Breast cancer				
MCF 7	0.162	0.378	0.191	0.0100
MDA-MB231/ATCC	1.67	2.89	2.76	< 0.215
MDA-MB-435	1.01	2.10	1.70	0.138
MDA-N	1.38	1.61	1.84	0.134
BT-549	1.33	1.87	1.91	0.158
T 47D	4.04	1.12	0.735	0.0946
MGM[b]	1.74	2.34	2.63	0.0891

[a]The cytotoxicity GI_{50} values are the concentrations corresponding to 50% growth inhibition.
[b]Mean graph midpoint (μM) for growth inhibition against 60 human cancer cell lines tested.

these *seco*-CBI dimers against leukemia lines as well as the other cancer cell lines have clear implications for the success of our design strategy.

Conclusions

We have designed and prepared three types of *seco*-CBI dimers and all the dimers were selected by the NCI for evaluation in an in vitro preclinical screening program against 60 human tumor cell lines. The results showed that the antitumor activities of these *seco*-CBI dimers were strongly related to the length of the linker and generally with potency increasing in the order of C7–C7 dimers (**22i–iv**) < C7–N3 dimers (**28i–iv**) < N3–N3 dimers (**25i–iv**). Compound **28iv** showed significant activity against CCRT-CEM, HL-60 (TB), MOLT-4, and SR leukemia cell lines and MCF 7 breast cancer cell line with GI_{50} values < 0.01 μM. N3–N3 dimer **25i** displayed striking potency in leukemia, CNS cancer, melanoma and prostate with GI_{50} values < 0.01 μM against all the cell lines and showed the highest overall potency

Table 3. In vitro cytotoxic potencies (GI_{50}s) of N3–N3 dimers **25i–iv**

	GI_{50} (μM)[a]			
Panels/cancer cell lines	**25i**	**25ii**	**25iii**	**25iv**
Leukemia				
CCEF-CEM	<0.0100	<0.0100	<0.0100	<0.0100
HL-60 (TB)	<0.0100	<0.0100	<0.0100	<0.0100
MOLT-4	<0.0100	<0.0100	<0.0100	<0.0100
SR	<0.0100	<0.0100	<0.0100	<0.0100
Non-small cell lung cancer				
HOP-62	<0.0100	0.201	<0.0100	<0.0100
NCI-H23	<0.0100	0.0259	<0.0100	<0.0100
NCI-H460	<0.0100	<0.0100	<0.0100	<0.0100
NCI-H522	<0.0100	0.0576	<0.0100	<0.0100
Colon cancer				
COLO 205	<0.0100	0.116	<0.0100	<0.0100
HCC-2998	0.0166	0.190	0.136	<0.0100
HCT-116	<0.0100	0.136	<0.0100	<0.0100
HT 29	0.0109	0.334	0.0176	0.0154
CNS cancer				
SF-268	<0.0100	0.0198	<0.0100	<0.0100
SNB-19	<0.0100	0.0184	<0.0100	<0.0100
U 251	<0.0100	0.0299	<0.0100	<0.0100
Melanoma				
LOX IMVI	<0.0100	0.0481	<0.0100	<0.0100
MALME-3M	<0.0100	0.205	<0.0100	<0.0100
SK-MEL-2	<0.0100	0.152	<0.0100	<0.0100
SK-MEL-5	<0.0100	0.137	<0.0100	<0.0100
UACC-257	<0.0100	0.146	<0.0100	<0.0100
UACC-62	<0.0100	0.0125	<0.0100	<0.0100
Ovarian cancer				
IGROV1	<0.0100	0.407	0.0192	<0.0100
OVCAR-3	<0.0100	0.249	0.0123	<0.0100
OVCAR-4	0.0234	2.61	0.150	0.0524
SK-OV-3	<0.0100	0.351	0.0102	<0.0100
Renal cancer				
786-0	<0.0100	0.0471	<0.0100	<0.0100
A498	<0.0100	0.138	<0.0100	<0.0100
SN12C	<0.0100	0.182	<0.0100	<0.0100
Prostate cancer				
PC-3	<0.0100	0.462	0.0193	<0.0100
Breast cancer				
MCF 7	<0.0100	<0.0100	<0.0100	<0.0100
MDA-MB231/ATCC	<0.0100	0.299	0.0215	0.0161
MDA-MB-435	<0.0100	0.240	0.0129	0.0120
MDA-N	<0.0100	0.193	0.0142	<0.0100
BT-549	0.0104	0.281	0.0108	<0.0100
T 47D	<0.0100	0.0166	<0.0100	<0.0100
MGM[b]	0.0120	0.166	0.0173	0.0151

[a]The cytotoxicity GI_{50} values are the concentrations corresponding to 50% growth inhibition.
[b]Mean graph midpoint (μM) for growth inhibition against 60 human cancer cell lines tested.

(GMG = 0.0120 μM). Some of these *seco*-CBI dimers are the most promising candidates and have been selected for further in vivo testing by the NCI.

Experimental

Melting points were determined using an Electrohome apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Bruker WH-360 spectrometer. High resolution mass spectra (HR–MS) were recorded on a modified MS-50 mass spectrometer equipped with a VG11-250J data system and on a Micromass Zabspec Hybrid Sector TOF by electrospray. Analytical thin layer chromatography was performed on silica-coated plastic plates (silica gel 60 F0254, Merck) and visualized under UV light. Preparative separations were performed by flash chromatography on silica gel (Merck, 70–230 or 230–400 mesh). All other solvents were used as received and were reagent grade where available.

***tert*-Butyl (*E*)-3-(ethoxycarbonyl)-4-(4-nitrophenyl)-3-butenoate (8).** To a solution of **7** (32.472 g, 96 mmol) in 20 mL of THF was added NaH (2.451 g, 97 mmol) at 0 °C, and the reaction mixture was stirred for 3 h. The solution was cooled to −40 °C, **6** (13.59 g, 90 mmol) in 70 mL of THF was added and the mixture was warmed to 23 °C and stirred for 10 h. The majority of THF was removed under reduced pressure, and saturated aqueous $NaHCO_3$ (100 mL) was added. The aqueous layer was extracted with EtOAc, and the organic layers were combined, washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 20% EtOAc:hexane) provided **8** (18.09 g, 60% yield) as a pale yellow powder. Mp 116–118 °C. ^{1}H NMR ($CDCl_3$), δ 8.23 (d, J = 8.9 Hz, 2H), 7.83 (s, 1H), 7.50 (d, J = 8.9 Hz, 2H), 4.28 (q, J = 7.2 Hz, 2H), 3.37 (s, 2H), 1.33 (t, J = 7.2 Hz, 3H). HR–MS m/z calcd for $C_{17}H_{21}NO_6$ 335.1369, found 335.1372.

(*E*)-3-(Ethoxycarbonyl)-4-(4-nitrophenyl)-3-butenic acid (9). A 9:1 mixture of CF_3CO_2H:H_2O (250 mL) at 0 °C was added to **8** (16.017 g, 47.8 mmol), and the reaction mixture was warmed to 23 °C and stirred for 4 h. The reaction mixture was concentrated in vacuo to provide **9** (12.138 g, 91% yield) as a pale yellow powder. Mp 142–143 °C. ^{1}H NMR (DMSO-d_6), δ 12.60 (br, 1H), 8.28 (d, J = 9.0 Hz, 2H), 7.82 (s, 1H), 7.67 (d, J = 9.0 Hz, 2H), 4.35 (q, J = 10.2 Hz, 2H), 3.53 (s, 2H), 1.39 (t, J = 10.2 Hz, 3H). HR–MS m/z calcd for $C_{13}H_{13}NO_6$ 279.0743, found 279.0732.

Ethyl 4-hydroxy-6-nitro-2-naphthalenecarboxylate (11). A mixture of **9** (13.395 g, 48 mmol) and NaOAc (4.252 g) in 300 mL of Ac_2O was warmed at 70 °C for 12 h. The volatiles were removed in vacuo, and a solution of the crude (**10**) and K_2CO_3 in 300 mL of EtOH was heated at reflux for 4 h. The reaction mixture was cooled to 0 °C, acidified with the addition of 1 M HCl (pH 6), and extracted with ether. The organic layers were combined, washed with saturated aqueous NaCl, dried (Na_2SO_4), and concentrated under reduced pressure. Chromatography (SiO_2, 25% EtOAc:hexane) provided **11** (11.206 g, 77% yield) as a yellow powder. Mp 189–191 °C. ^{1}H NMR ($CDCl_3$), δ 9.23 (d, J = 3.8 Hz, 1H), 8.32 (dd, J = 3.8, 15.6 Hz, 1H), 8.28 (s, 1H), 8.05 (d, J = 15.6 Hz, 1H), 7.63 (s, 1H), 6.16 (s, 1H), 4.60 (q, J = 10.1 Hz, 2H), 1.48 (t, J = 10.1 Hz, 3H). HR–MS m/z calcd for $C_{13}H_{11}NO_4$ 261.0637, found 261.0635.

4-Benzyloxy-6-nitro-2-naphthalenecarboxylic acid (13). A solution of **11** (8.70 g, 33.3 mmol) in dried DMF (150 mL) under Ar was treated with anhydrous K_2CO_3 (6.91 g), benzyl bromide (6.84 g, 40 mmol), and Bu_4NI

(0.5 g). The mixture was stirred at 23 °C for 10 h then ice-water was added. The solid that precipitated was collected and the solution of the crude product in THF: CH_3OH:H_2O (4:1:1, 290 mL) was treated with LiOH–H_2O (5.544 g, 132 mmol). The suspension was stirred at 23 °C for 4 h before water was added. The solution was acidified with the addition of 10% aqueous HCl, and the precipitate was collected and dried to afforded **13** (10.648 g, 99% yield) as a yellow powder. Mp 157–159 °C. ^{1}H NMR (DMSO-d_6), δ 8.97 (m, 1H), 8.35–8.29 (m, 3H), 7.63–7.36 (m, 6H), 5.42 (s, 2H). HR–MS *m*/*z* calcd for $C_{18}H_{13}NO_5$ 323.0794, found 323.0792.

***N*-(*tert*-Butyloxycarbonyl)-4-benzyloxy-6-nitro-2-naphthylamine (14).** A solution of **13** (8.250 g, 22.5 mmol) in freshly distilled dry *t*-BuOH (800 mL) was treated with Et_3N (2.760 g, 27.3 mmol) and 15 g of activated 4 Å molecular sieves. Diphenyl phosphorazidate (7.726 g, 28.1 mmol) was added, and the reaction mixture was heated at reflux for 15 h. The mixture was cooled to 23 °C, and the solvent was removed under vacuum. The residue was dissolved in EtOAc, and the organic phase was washed with 10% aqueous HCl, dried (Na_2SO_4), and concentrated in vacuo. Chromatography (SiO_2, 20% acetone:hexane) afforded **14** (8.439 g, 84% yield) as a yellow powder. Mp 185–186 °C. ^{1}H NMR ($CDCl_3$), δ 9.15 (d, J = 4.2 Hz, 1H), 8.21 (dd, J = 4.2, 16.2 Hz, 1H), 7.75 (d, J = 16.2 Hz, 1H), 7.56–7.39 (m, 6H), 7.18 (d, J = 3.6 Hz, 1H), 6.75 (br, 1H), 5.30 (s, 2H), 1.56 (s, 9H). HR–MS *m*/*z* calcd for $C_{22}H_{22}N_2O_5$ 349.1529, found 349.1528.

***N*-(*tert*-Butyloxycarbonyl)-4-benzyloxy-1-iodo-6-nitro-2-naphthylamine (15).** A solution of **14** (4.620 g, 11.7 mmol) in THF (90 mL) and MeOH (90 mL) was treated with TsOH–H_2O (0.135 g) and NIS (2.770 g, 12.3 mmol) at −40 °C under Ar, and the reaction mixture was stirred for 4 h before Et_2O (15 mL) was added. The organic phase was washed with 5% aqueous $NaHCO_3$ and saturated aqueous NaCl, dried (Na_2SO_4), and concentrated in vacuo to provide **15** (5.973 g, 98% yield) as yellow crystals. Mp 186–188 °C. ^{1}H NMR ($CDCl_3$), δ 9.15 (d, J = 4.5 Hz, 1H), 8.28 (s, 1H), 8.26 (dd, J = 4.5, 16.2 Hz, 1H), 8.13 (d, J = 16.2 Hz, 1H), 7.62–7.43 (m, 5H), 1.56 (s, 9H). HR–MS *m*/*z* calcd for $C_{22}H_{21}IN_2O_5$ 520.0495, found 520.0496.

***N*-(*tert*-Butyloxycarbonyl)-*N*-(3-chloro-2-propen-1-yl)-4-benzyloxy-1-iodo-6-nitro-2-naphthylamine (16).** A solution of **15** (3.180 g, 6.11 mmol) in anhydrous DMF (90 mL) under Ar was treated with NaH (0.232 g, 95%, 9.65 mmol), and the reaction mixture was stirred for 1 h. The mixture was cooled to 0 °C, and 1,3-dichloropropene (2.832 mL, 80%, 24.4 mmol) was added dropwise. The solution was stirred overnight. Water was added, and the aqueous phase was extracted with EtOAc. The combined organic phases were washed with saturated aqueous NaCl and dried (Na_2SO_4), and the solvent was removed under vacuum. Chromatography (SiO_2, 30% acetone:hexane) afforded **16** (3.017 g, 83% yield) as a yellow powder. Mp 181–183 °C. ^{1}H NMR (acetone-d_6), δ 9.17 (d, J = 2.4 Hz, 1H), 8.46 (d, J = 9.3 Hz, 1H), 8.39 (dd, J = 2.4, 9.3 Hz, 1H), 7.61–7.35 (m, 6H), 6.22–6.14 (m, 1H), 5.50 (s, 2H), 4.65–4.59 (m, 1H), 4.36–4.30 (m, 1H), 1.29 (s, 9H). HR–MS *m*/*z* calcd for $C_{25}H_{24}ClIN_2O_5$ 594.0419, found 594.0413.

***N*-(*tert*-Butyloxycarbonyl)-*N*-(3-chloro-2-propen-1-yl)-6-(9-fluorenylmethyloxy-carbonylamino)-4-benzyloxy-1-iodo-2-naphthylamine (18).** To a solution of **16** (3.208 g, 5.39 mmol) in MeOH (110 mL) and THF (90 mL) under Ar, 2.9 g of actived carbon, 0.9 g of $FeCl_3$–$6H_2O$ and 1.647 g of N_2H_4–H_2O (95%) were added. The mixture was heated at reflux for 7 h before it was cooled to 23 °C and filtered through Celite. The solvent was removed in vacuo and afforded unstable crude amine **17**. A solution of crude **17** in dry THF (50 mL) was treated with *F*moc-Cl (1.514 g, 5.85 mmol) and DMAP (0.647 g, 5.30 mmol) at 0 °C. After being stirred for 2 h, the reaction mixture was concentrated in vacuo. Chromatography (SiO_2, 20% EtOAc:hexane) afforded **18** (3.660 g, 86% yield) as a white powder. Mp 136–137 °C. ^{1}H NMR (acetone-d_6), δ 9.25 (s, 1H), 8.50 (s, 1H), 8.13 (d, J = 9.0 Hz, 1H), 7.93–7.86 (m, 3H), 7.78–7.74 (m, 2H), 7.60–7.56 (m, 2H), 7.46–7.28 (m, 7H), 7.02 (s, 1H), 6.28–6.14 (m, 2H), 5.38 (s, 1H), 4.52 (d, J = 6.7 Hz, 2H), 4.48–4.39 (m, 1H), 4.32 (t, J = 6.7 Hz, 1H), 4.02–3.94 (m, 1H), 1.29 (s, 9H). HR–ESMS *m*/*z* calcd for $C_{40}H_{36}N_2O_5ClINa$ 809.1255, found 809.1255 ($M + Na^+$).

5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-chloromethyl-7-(9-fluorenyl-methyloxycarbonylamino)-1,2-dihydro-3*H*-benz[*e*]indole (5). To a solution of **18** (12.100 g 15.4 mmol) in dry benzene (1000 mL) were added tri-*n*-butyltin hydride (4.55 mL, 18.4 mmol) and AIBN (0.126 g). After deoxygenation, the reaction mixture was heated at reflux for 4 h and concentrated in vacuo to give an oily residue. Trituration of the crude oil with hexanes provided a solid which was collected and washed with hexanes to give **5** (7.928 g, 78% yield) as a white powder. Mp 113–115 °C. ^{1}H NMR (acetone-d_6), δ 9.02 (s, 1H), 8.38 (s, 1H), 7.88–7.30 (m, 16H), 5.30 (s, 2H), 4.50 (d, J = 6.9 Hz, 2H), 4.30 (t, J = 6.9 Hz, 1H), 4.22–4.05 (m, 3H), 4.01 (dd, J = 3.1, 11.1 Hz, 1H), 3.70 (dd, J = 8.4,11.0 Hz, 1H), 1.58 (s, 9H). HR–MS *m*/*z* calcd for $C_{40}H_{37}N_2O_5{}^{35}Cl$ 660.23907, found 660.23920.

5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-chloromethyl-7-amino-1,2-dihydro-3*H*-benz[*e*]indole (19). To a solution of **5** (2.500 g, 3.78 mmol) in THF (130 mL) was added tetrabutylammonium fluoride (2.82 mL, 1.0 M in THF) and the mixture stirred at 23 °C for 1 h. The solvent was removed in vacuo. Chromatography (SiO_2, 50% EtOAc:hexane) afforded **19** (1.593 g, 96%) as a white powder. Mp 77–78 °C. ^{1}H NMR (acetone-d_6), δ 7.61–7.56 (m, 4H), 7.46–7.37 (m, 4H), 7.07 (dd, J = 2.4, 8.8 Hz, 1H), 5.23 (s, 2H), 4.82 (br, 2H), 4.19–3.95 (m, 4H), 3.64–3.59 (m, 1H), 1.57 (s, 9H). HR–MS *m*/*z* calcd for $C_{25}H_{27}N_2O_3Cl$ 438.1710, found 438.1708.

5-(Benzyloxy)-3-(*tert*-butyloxycarbonyl)-1-chloromethyl-7-acetylamino-1,2-dihydro-3*H*-benz[*e*]indole (20). To a solution of **19** (0.255 g, 0.582 mmol) in dry THF (30 mL) were added Et_3N (70.6 mg, 0.698 mmol) and AcCl (50.2 mg, 0.640 mmol) at 0 °C, and the reaction mixture was stirred for 3 h. The solvent was removed in vacuo.

Chromatography (SiO_2, 60% EtOAc:hexane) afforded **20** (0.257 g, 92% yield) as a white powder. Mp 101–103 °C. ^{1}H NMR (DMSO-d_6), δ 10.09 (s, 1H), 8.33 (s, 1H), 7.84–7.76 (m, 3H), 7.57–7.37 (m, 5H), 5.26 (s, 2H), 4.11–3.97 (m, 4H), 3.82–3.78 (m, 1H), 2.05 (s, 3H), 1.53 (s, 9H). HR–MS *m*/*z* calcd for $C_{27}H_{29}N_2O_4Cl$ 480.1816, found 480.1813.

General procedure A (preparation of compounds 21i–iv). A solution of **19** and Et_3N in anhydrous THF was cooled to 0 °C and the di-acid chloride was added dropwise. The reaction mixture was stirred at 23 °C for 2 h and then evaporated to removed THF. The residue was purified by flash chromatography (SiO_2, hexane–acetone) to give compounds **21i**–**iv**.

Compound 21i. Prepared according to general procedure A using 0.2549 g (0.581 mmol) of **19**, 0.0617 g (0.610 mmol) of Et_3N, 0.0491 g (0.291 mmol) of glutaryl dichloride, and 5 mL of THF to give 0.2347 g of **21i** (83% yield) as a white powder. Mp 146–148 °C. ^{1}H NMR (acetone-d_6), δ 9.36 (s, 2H), 8.44 (s, 2H), 7.96 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H), 7.61–7.36 (m, 12H), 5.28 (s, 4H), 4.19–4.07 (m, 6H), 4.02–3.98 (m, 2H), 3.72–3.67 (m, 12H), 2.50 (t, J = 7.1 Hz, 4H), 2.10–2.05 (m, 2H), 1.58 (s, 18H). HR–ESMS *m*/*z* calcd for $C_{55}H_{59}N_4O_8Cl_2$ 973.3710, found 973.3705 ($M+H^+$).

Compound 21ii. Prepared according to general procedure A using 0.2549 g (0.581 mmol) of **19**, 0.0617 g (0.610 mmol) of Et_3N, 0.0533 g (0.291 mmol) of adipoyl chloride, and 5 mL of THF to give 0.2287 g of **21ii** (80% yield) as a white powder. Mp 133–134 °C. ^{1}H NMR (DMSO-d_6), δ 10.04 (s, 2H), 8.33 (s, 2H), 7.82 (d, J = 9.0 Hz, 2H), 7.69 (d, J = 9.0 Hz, 2H), 7.54–7.34 (m, 12H), 5.24 (s, 4H), 4.11–3.94 (m, 8H), 3.78–3.69 (m, 2H), 2.38–2.32 (m, 4H), 1.70–1.62 (m, 2H), 1.52 (s, 18H). HR–ESMS *m*/*z* calcd for $C_{56}H_{61}N_4O_8Cl_2$ 987.3866, found 987.3877 ($M+H^+$).

Compound 21iii. Prepared according to general procedure A using 0.1905 g (0.434 mmol) of **19**, 0.0460 g (0.456 mmol) of Et_3N, 0.0428 g (0.217 mmol) of pimeloyl chloride, and 5 mL of THF to give 0.1935 g of **21iii** (89% yield) as a white powder. Mp 130–132 °C. ^{1}H NMR (DMSO-d_6), δ 10.04 (s, 2H), 8.32 (s, 2H), 7.83 (d, J = 9.0 Hz, 2H), 7.74 (d, J = 9.0 Hz, 2H), 7.54–7.33 (m, 12H), 5.25 (s, 4H), 4.13–3.96 (m, 8H), 3.81–3.78 (m, 2H), 2.34–2.30 (m, 4H), 1.65–1.56 (m, 6H), 1.53 (s, 18H). HR–ESMS *m*/*z* calcd for $C_{57}H_{63}N_4O_8Cl_2$ 1001.4023, found 1001.4019 ($M+H^+$).

Compound 21iv. Prepared according to general procedure A using 0.1994 g (0.454 mmol) of **19**, 0.0482 g (0.477 mmol) of Et_3N, 0.0479 g (0.227 mmol) of suberoyl chloride, and 5 mL of THF to give 0.1892 g of **21iv** (82% yield) as a white powder. Mp 129–131 °C. ^{1}H NMR (DMSO-d_6), δ 10.03 (s, 2H), 8.33 (s, 2H), 7.84 (d, J = 9.0 Hz, 2H), 7.75 (d, J = 9.0 Hz, 2H), 7.54–7.33 (m, 12H), 5.25 (s, 4H), 4.13–3.96 (m, 8H), 3.83–3.78 (m, 2H), 2.33–2.29 (m, 4H), 1.60–1.45 (m, 22H). HR–ESMS *m*/*z* calcd for $C_{58}H_{65}N_4O_8Cl_2$ 1015.4179, found 1015.4179 ($M+H^+$).

General procedure B (preparation of compounds 24i–iv). Compound **20** was treated with 4 N HCl in dioxane at 0 °C and stirred for 5 h slowly reaching 23 °C. Solvent was removed and the residue was dried for 1 h in vacuo. The residue was dissolved in anhydrous DMF, treated with Et_3N and di-acid chloride at 0 °C. After the reaction mixture was stirred at 23 °C for 4 h, the solvent was removed in vacuo. Flash chromatography (SiO_2, hexane–THF) afforded compounds **24i**–**iv**.

Compound 24i. Prepared according to general procedure B using 0.2000 g (0.416 mmol) of **20**, 8 mL of 4 N HCl in dioxane, 0.0351 g (0.208 mmol) of glutaryl dichloride, 0.0841 g (0.832 mmol) of Et_3N, and 8 mL of DMF to give 0.1172 g of **24i** (66% yield) as a white powder. Mp 186–187 °C. ^{1}H NMR (DMSO-d_6), δ 10.10 (s, 2H), 8.36 (s, 2H), 8.14 (s, 2H), 7.80–7.88 (m, 4H), 7.56–7.33 (m, 10H), 5.24 (s, 4H), 4.38–4.34 (m, 2H), 4.20–4.15 (m, 4H), 4.00–3.96 (m, 2H), 3.85–3.81 (m, 2H), 2.58–2.54 (m, 4H), 2.05 (s, 6H), 1.72–1.71 (m, 2H). ES–MS *m*/*z* calcd for $C_{49}H_{47}N_4O_6Cl_2$ 857.3, found 857.3 ($M+H^+$, 100), 859.2 (70).

Compound 24ii. Prepared according to general procedure B using 0.2000 g (0.416 mmol) of **20**, 8 mL of 4 N HCl in dioxane, 0.0381 g (0.208 mmol) of adipoyl chloride, 0.0841 g (0.832 mmol) of Et_3N, and 8 mL of DMF to give 0.1233 g of **24ii** (68% yield) as a white powder. Mp 183–185 °C. ^{1}H NMR (DMSO-d_6), δ 10.11 (s, 2H), 8.36 (s, 2H), 8.15 (s, 2H), 7.82–7.79 (m, 4H), 7.56–7.35 (m, 10H), 5.24 (s, 4H), 4.37–4.34 (m, 2H), 4.20–4.16 (m, 4H), 4.01–3.98 (m, 2H), 3.85–3.82 (m, 2H), 2.59–2.54 (m, 4H), 2.05 (s, 6H), 1.74–1.72 (m, 4H). ES–MS *m*/*z* calcd for $C_{50}H_{48}N_4O_6Cl_2Na$ 893.3, found 893.3 ($M+Na^+$, 70), 859.2 (50).

Compound 24iii. Prepared according to general procedure B using 0.2000 g (0.416 mmol) of **20**, 8 L of 4 N HCl in dioxane, 0.0410 g (0.208 mmol) of pimeloyl chloride, 0.0841 g (0.832 mmol) of Et_3N, and 8 mL of DMF to give 0.1227 g of **24iii** (67% yield) as a white powder. Mp 182–183 °C. ^{1}H NMR (DMSO-d_6), δ 10.11 (s, 2H), 8.36 (s, 2H), 8.15 (s, 2H), 7.83–7.79 (m, 4H), 7.57–7.36 (m, 10H), 5.24 (s, 4H), 4.36–4.34 (m, 2H), 4.20–4.16 (m, 4H), 4.00–3.97 (m, 2H), 3.85–3.83 (m, 2H), 2.57–2.53 (m, 4H), 2.05 (s, 6H), 1.75–1.71 (m, 6H). ES–MS *m*/*z* calcd for $C_{51}H_{51}N_4O_6Cl_2$ 885.3, found 885.3 ($M+H^+$, 100), 887.3 (75).

Compound 24iv. Prepared according to general procedure B using 0.2000 g (0.416 mmol) of **20**, 8 mL of 4 N HCl in dioxane, 0.0439 g (0.208 mmol) of suberoyl chloride, 0.0841 g (0.832 mmol) of Et_3N, and 8 mL of DMF to give 0.1423 g of **24iv** (76% yield) as a white powder. Mp 184–186 °C. ^{1}H NMR (DMSO-d_6), δ 10.08 (s, 2H), 8.36 (s, 2H), 8.16 (s, 2H), 7.83–7.78 (m, 4H), 7.56–7.34 (m, 10H), 5.24 (s, 4H), 4.36–4.34 (m, 2H), 4.19–4.16 (m, 4H), 4.02–3.96 (m, 2H), 3.86–3.83 (m, 2H), 2.58–2.53 (m, 4H), 2.06 (s, 6H), 1.76–1.70 (m, 8H). ES–MS *m*/*z* calcd for $C_{52}H_{52}N_4O_6Cl_2Na$ 921.3, found 921.3 ($M+Na^+$, 100), 923.3 (75).

Compound 26i. Compound **20** (0.5141 g, 1.069 mmol) was added to a solution of 4 N HCl in dioxane (20 mL)

at 0 °C under Ar. The reaction mixture was stirred at 23 °C for 5 h before the solvent was removed. After being dried in vacuo, the residue, Et_3N (0.2162 g, 2.138 mmol) and glutaric anhydride (0.1224 g, 1.069 mmol) were dissolved in anhydrous THF (20 mL), and the reaction mixture was stirred at 23 °C for 12 h then the solvent was removed in vacuo. Chromatography (SiO_2, 5% MeOH–CH_2Cl_2) afforded **26i** (0.4722 g, 89% yield) as a white powder. Mp 213–216 °C. ^{1}H NMR (DMSO-d_6), δ 10.12 (s, 1H), 8.37 (s, 1H), 8.14 (s, 1H), 7.82–7.78 (m, 2H), 7.57–7.36 (m, 5H), 5.25 (s, 2H), 4.32–4.30 (m, 1H), 4.15–4.12 (m, 2H), 4.00–3.97 (m, 1H), 3.85–3.82 (m, 1H), 2.57–2.54 (m, 2H), 2.35–2.31 (m, 2H), 2.05 (m, 3H), 1.86–1.80 (m, 2H). ES–MS *m*/*z* calcd for $C_{27}H_{28}N_2O_5Cl$ 495.2, found 495.2 ($M+H^+$, 100), 497.2 (40).

General procedure C (preparation of compounds 26ii–iv). Compound **20** was treated with 4 N HCl in dioxane at 0 °C and stirred for 5 h slowly reaching 23 °C. The solvent was removed and the residue was dried for 1 h in vacuo. The residue was dissolved in anhydrous DMF, treated with Et_3N and di-acid and EDCI at 23 °C. After the reaction mixture was stirred at 23 °C for 12 h, the solvent was removed in vacuo. Flash chromatography (SiO_2, hexane–acetone) afforded compounds **26ii**–**iv**.

Compound 26ii. Prepared according to general procedure C using 0.1619 g (0.336 mmol) of **20**, 5 mL of 4 N HCl in dioxane, 0.0374 g (0.370 mmol) of Et_3N, 0.1476 g (1.01 mmol) of adipic acid, 0.1936 g (1.01 mmol) of EDCI, and 4 mL of DMF to give 0.1172 g of **26ii** (68% yield) as a white powder. Mp 217–220 °C. ^{1}H NMR (DMSO-d_6), δ 12.02 (br, 1H), 10.11 (s, 1H), 8.36 (s, 1H), 8.14 (s, 1H), 7.84–7.78 (m, 2H), 7.57–7.34 (m, 5H), 5.24 (s, 2H), 4.33–4.29 (m, 1H), 4.14–4.13 (m, 2H), 4.01–3.97 (m, 1H), 3.84–3.79 (m, 1H), 2.58–2.53 (m, 2H), 2.28–2.24 (m, 2H), 2.05 (m, 3H), 1.62–1.58 (m, 4H). ES–MS *m*/*z* calcd for $C_{28}H_{30}N_2O_5Cl$ 509.2, found 509.2 ($M+H^+$, 100), 511.2 (35).

Compound 26iii. Prepared according to general procedure C using 0.2000 g (0.416 mmol) of **20**, 6 mL of 4 N HCl in dioxane, 0.0462 g (0.458 mmol) of Et_3N, 0.1998 g (1.25 mmol) of pimelic acid, 0.2390 g (1.25 mmol) of EDCI, and 4 mL of DMF to give 0.1447 g of **26iii** (68% yield) as a white powder. Mp 199–201 °C. ^{1}H NMR (DMSO-d_6), δ 11.98 (br, 1H), 10.11 (s, 1H), 8.37 (s, 1H), 8.14 (s, 1H), 7.82–7.78 (m, 2H), 7.58–7.36 (m, 5H), 5.24 (s, 2H), 4.33–4.29 (m, 1H), 4.16–4.13 (m, 2H), 4.01–3.98 (m, 1H), 3.84–3.81 (m, 1H), 2.54–2.51 (m, 2H), 2.24–2.20 (m, 2H), 2.05 (m, 3H), 1.63–1.53 (m, 4H), 1.38–1.34 (m, 2H). ES–MS *m*/*z* calcd for $C_{29}H_{32}N_2O_5Cl$ 523.2, found 523.2 ($M+H^+$, 100), 525.2 (35).

Compound 26iv. Prepared according to general procedure C using 0.1910 g (0.397 mmol) of **20**, 6 mL of 4 N HCl in dioxane, 0.0441 g (0.437 mmol) of Et_3N, 0.208 g (1.19 mmol) of suberic acid, 0.239 g (1.25 mmol) of EDCI, and 4 mL of DMF to give 0.1400 g of **26iv** (67% yield) as a white powder. Mp 201–203 °C. ^{1}H NMR (DMSO-d_6), δ 11.89 (br, 1H), 10.11 (s, 1H), 8.37 (s, 1H), 8.13 (s, 1H), 7.83–7.78 (m, 2H), 7.58–7.34 (m, 5H), 5.24 (s, 2H), 4.34–4.29 (m, 1H), 4.14–4.15 (m, 2H), 4.00–3.98 (m, 1H), 3.83–3.82 (m, 1H), 2.55–2.51 (m, 2H), 2.24–2.20 (m, 2H), 2.05 (m, 3H), 1.64–1.37 (m, 8H). ES–MS *m*/*z* calcd for $C_{30}H_{33}N_2O_5ClNa$ 559.3, found 559.3 ($M+Na^+$, 100), 561.3 (34).

General procedure D (preparation of compounds 27i–iv). A mixture of **26i**–**iv**, **19** and EDCI in DMF was stirred at 23 °C for 18 h. After DMF was removed in vacuo, the residue was purified by flash chromatography (SiO_2, hexane–acetone) to afford compounds **27i**–**iv**.

Compound 27i. Prepared according to general procedure D using 0.1000 g (0.202 mmol) of **26i**, 0.1419 g (0.323 mmol) of **19**, 0.155 g (0.808 mmol) of EDCI, and 4 mL of DMF to give 0.1147 g of **27i** (62% yield) as a white powder. Mp 155–157 °C. ^{1}H NMR (DMSO-d_6), δ 10.12 (s, 1H), 10.09 (s, 1H), 8.36 (s, 2H), 8.13 (s, 1H), 7.88–7.74 (m, 5H), 7.56–7.35 (m, 10H), 5.24 (s, 2H), 5.21 (s, 2H), 4.46–4.31 (m, 1H), 4.16–3.96 (m, 7H), 3.84–3.78 (m, 2H), 2.46–2.43 (m, 4H), 2.05 (s, 3H), 1.97–1.93 (m, 2H), 1.53 (s, 9H). ES–MS *m*/*z* calcd for $C_{52}H_{53}N_4O_7Cl_2$ 915.3, found 915.3 ($M+H^+$, 30), 917.3 (20).

Compound 27ii. Prepared according to general procedure D using 0.0915 g (0.180 mmol) of **26ii**, 0.1263 g (0.288 mmol) of **19**, 0.1379 g (0.719 mmol) of EDCI, and 3 mL of DMF to give 0.0929 g of **27ii** (56% yield) as a white powder. Mp 150–153 °C. ^{1}H NMR (DMSO-d_6), δ 10.11 (s, 1H), 10.08 (s, 1H), 8.36 (s, 2H), 8.13 (s, 1H), 7.85–7.76 (m, 5H), 7.56–7.34 (m, 10H), 5.25 (s, 2H), 5.23 (s, 2H), 4.38–4.25 (m, 1H), 4.16–3.95 (m, 7H), 3.85–3.77 (m, 2H), 2.46–2.43 (m, 4H), 2.05 (s, 3H), 1.74–1.65 (m, 4H), 1.53 (s, 9H). HR–ESMS *m*/*z* calcd for $C_{53}H_{55}N_4O_7Cl_2$ 929.3448, found 929.3464 ($M+H^+$).

Compound 27iii. Prepared according to general procedure D using 0.1098 g (0.210 mmol) of **26iii**, 0.1474 g (0.336 mmol) of **19**, 0.1610 g (0.839 mmol) of EDCI, and 3 mL of DMF to give 0.1023 g of **27iii** (52% yield) as a white powder. Mp 149–151 °C. ^{1}H NMR (DMSO-d_6), δ 10.11 (s, 1H), 10.05 (s, 1H), 8.36 (s, 1H), 8.34 (s, 1H), 8.13 (s, 1H), 7.86–7.74 (m, 5H), 7.56–7.35 (m, 10H), 5.24 (s, 2H), 5.22 (s, 2H), 4.36–4.28 (m, 1H), 4.17–3.95 (m, 7H), 3.83–3.75 (m, 2H), 2.42–2.40 (m, 4H), 2.08 (s, 3H), 1.72–1.63 (m, 6H), 1.53 (s, 9H). ES–MS *m*/*z* calcd for $C_{54}H_{57}N_4O_7Cl_2$ 943.3, found 943.3 ($M+H^+$, 100), 945.3 (70).

Compound 27iv. Prepared according to general procedure D using 0.1206 g (0.224 mmol) of **26iv**, 0.1577 g (0.358 mmol) of **19**, 0.1722 g (0.896 mmol) of EDCI, and 3 mL of DMF to give 0.1181 g of **27iv** (48% yield) as a white powder. Mp 152–154 °C. ^{1}H NMR (acetone-d_6), δ 9.36 (s, 2H), 8.44 (s, 2H), 7.97–7.94 (m, 2H), 7.75–7.73 (m, 2H), 7.60–7.35 (m, 12H), 5.28 (s, 4H), 4.19–3.97 (m, 8H), 3.70–3.67 (m, 2H), 2.52–2.48 (m, 4H), 2.05 (s, 3H), 1.59–1.32 (m, 17H). ES–MS *m*/*z* calcd for $C_{55}H_{59}N_4O_7Cl_2$ 943.4, found 957.4 ($M+H^+$, 30), 959.4 (20).

General procedure E (deprotection of benzyl group). To a solution of **21i**–**iv**, **24i**–**iv**, or **27i**–**iv** in THF or DMF was added 10% Pd/C under Ar. The mixture was cooled

to 0 °C and 10% aqueous ammonium formate was added. The mixture was stirred at 23 °C until the reaction was complete (TLC). The mixture was then filtered through a pad of Celite, and concentrated in vacuo. Flash chromatography (SiO_2, CH_2Cl_2–MeOH) afforded the final pure compounds.

Compound 22i. Prepared according to general procedure E using 0.1768 g (0.182 mmol) of **21i**, 0.826 mL of 10% aqueous ammonium formate, 0.11 g of 10% Pd/C, and 8 mL of THF to give 0.1279 g of **22i** (89% yield) as a white powder. Mp 162 °C (dec.). ^{1}H NMR (DMSO-d_6) δ: 10.26 (s, 2H), 10.01 (s, 2H), 8.41 (s, 2H), 7.70–7.62 (m, 6H), 4.09–3.65 (m, 10H), 2.42 (t, J = 7.2 Hz, 4H), 1.98–1.93 (m, 2H), 1.49 (s, 18H). HR–ESMS m/z calcd for $C_{41}H_{47}N_4O_8Cl_2$ 793.2771, found 793.2771 ($M+H^+$).

Compound 22ii. Prepared according to general procedure E using 0.2241 g (0.227 mmol) of **21ii**, 1.03 mL of 10% aqueous ammonium formate, 0.15 g of 10% Pd/C, and 10 mL of THF to give 0.1579 g of **22ii** (86% yield) as a white powder. Mp 159 °C (dec.). ^{1}H NMR (DMSO-d_6) δ: 10.25 (s, 2H), 9.98 (s, 2H), 8.34 (s, 2H), 7.70–7.62 (m, 6H), 4.07–3.59 (m, 10H), 2.41–2.36 (m, 4H), 1.69–1.65 (m, 4H), 1.52 (s, 18H). HR–ESMS m/z calcd for $C_{42}H_{48}N_4O_8Cl_2Na$ 829.2748, found 829.2755 ($M+Na^+$).

Compound 22iii. Prepared according to general procedure E using 0.1605 g (0.160 mmol) of **21iii**, 0.727 mL of 10% aqueous ammonium formate, 0.10 g of 10% Pd/C, and 8 mL of THF to give 0.1278 g of **22iii** (97% yield) as a white powder. Mp 158 °C (dec.). ^{1}H NMR (DMSO-d_6) δ: 10.26 (s, 2H), 9.96 (s, 2H), 8.38 (s, 2H), 7.68–7.61 (m, 6H), 4.08–3.65 (m, 10H), 2.34 (t, J = 7.2Hz, 4H), 1.68–1.63 (m, 4H), 1.52 (s, 18H), 1.43–1.37 (m, 2H). HR–ESMS m/z calcd for $C_{43}H_{51}N_4O_8Cl_2$ 821.3084, found 821.3082 ($M+H^+$).

Compound 22iv. Prepared according to general procedure E using 0.1783 g (0.176 mmol) of **21iv**, 0.798 mL of 10% aqueous ammonium formate, 0.10 g of 10% Pd/C, and 8 mL of THF to give 0.1249 g of **22iv** (85% yield) as a white powder. Mp 165 °C (dec.). ^{1}H NMR (DMSO-d_6) δ: 10.25 (s, 2H), 9.94 (s, 2H), 8.38 (s, 2H), 7.69–7.61 (m, 6H), 4.08–3.69 (m, 10H), 2.33 (t, J = 7.3 Hz, 4H), 1.68–1.60 (m, 4H), 1.52 (s, 18H), 1.38–1.34 (m, 4H). HR–ESMS m/z calcd for $C_{44}H_{53}N_4O_8Cl_2$ 835.3240, found 835.3244 ($M+H^+$).

Compound 25i. Prepared according to general procedure E using 0.0700 g (0.080 mmol) of **24i**, 0.206 mL of 10% aqueous ammonium formate, 0.04 g of 10% Pd/C, and 10 mL of DMF to give 0.0414 g of **25i** (75% yield) as a white powder. Mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ: 10.23 (s, 2H), 10.02 (s, 2H), 8.36 (s, 2H), 7.97 (s, 2H), 7.72–7.66 (m, 4H), 4.34–4.26 (m, 2H), 4.18–4.08 (m, 4H), 4.01–3.94 (m, 2H), 3.80–3.72 (m, 2H), 2.70–2.54 (m, 4H), 2.06 (s, 6H), 1.68–1.60 (m, 2H). HR–ESMS m/z calcd for $C_{35}H_{35}N_4O_6Cl_2$ 677.1934, found 677.1938 ($M+H^+$).

Compound 25ii. Prepared according to general procedure E using 0.1043 g (0.120 mmol) of **24ii**, 0.302 mL of 10% aqueous ammonium formate, 0.06 g of 10% Pd/C, and 10 mL of DMF to give 0.0624 g of **25ii** (76% yield) as a white powder. Mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ: 10.24 (s, 2H), 10.02 (s, 2H), 8.35 (s, 2H), 7.94 (s, 2H), 7.72 (d, J = 8.9 Hz, 2H), 7.64 (d, J = 8.9 Hz, 2H), 4.34–4.29 (m, 2H), 4.16–4.10 (m, 4H), 3.98–3.96 (m, 2H), 3.79–3.73 (m, 2H), 2.62–2.53 (m, 4H), 2.06 (s, 6H), 1.65–1.61 (m, 4H). HR–ESMS m/z calcd for $C_{36}H_{37}N_4O_6{}^{37}Cl_2$ 695.2031, found 695.2045 ($M+H^+$).

Compound 25iii. Prepared according to general procedure E using 0.0877 g (0.099 mmol) of **24iii**, 0.250 mL of 10% aqueous ammonium formate, 0.05 g of 10% Pd/C, and 10 mL of DMF to give 0.0510 g of **25iii** (73% yield) as a white powder. Mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ: 10.24 (s, 2H), 10.03 (s, 2H), 8.35 (s, 2H), 7.96 (s, 2H), 7.72 (d, J = 9.0 Hz, 2H), 7.65 (d, J = 9.0 Hz, 2H), 4.35–4.30 (m, 2H), 4.15–4.04 (m, 4H), 3.98–3.95 (m, 2H), 3.74–3.72 (m, 2H), 2.63–2.53 (m, 4H), 2.06 (s, 6H), 1.60–1.55 (m, 4H), 1.48–1.42 (m, 2H). HR–ESMS m/z calcd for $C_{37}H_{39}N_4O_6Cl_2$ 705.2247, found 705.2264 ($M+H^+$).

Compound 25iv. Prepared according to general procedure E using 0.0523 g (0.058 mmol) of **24iv**, 0.146 mL of 10% aqueous ammonium formate, 0.03 g of 10% Pd/C, and 10 mL of DMF to give 0.0301 g of **25iv** (72% yield) as a white powder. Mp > 250 °C. ^{1}H NMR (DMSO-d_6) δ: 10.24 (s, 2H), 10.03 (s, 2H), 8.35 (s, 2H), 7.95 (s, 2H), 7.72 (d, J = 8.7 Hz, 2H), 7.64 (d, J = 8.7 Hz, 2H), 4.32–4.26 (m, 2H), 4.14–4.05 (m, 4H), 3.99–3.94 (m, 2H), 3.76–3.72 (m, 2H), 2.63–2.52 (m, 4H), 2.07 (s, 6H), 1.66–1.62 (m, 4H), 1.45–1.38 (m, 4H). HR–ESMS m/z calcd for $C_{38}H_{40}N_4O_6Cl_2Na$ 741.2223, found 741.2239 ($M+H^+$).

Compound 28i. Prepared according to general procedure E using 0.0249 g (0.0272 mmol) of **27i**, 0.072 mL of 10% aqueous ammonium formate, 0.01 g of 10% Pd/C, and 2 mL of THF to give 0.0153 g of **28i** (77% yield) as a white powder. Mp 189 °C (dec.). ^{1}H NMR (DMSO-d_6) δ: 10.26 (s, 2H), 10.02 (s, 1H), 10.01 (s, 1H), 8.40 (s, 1H), 8.36 (s, 1H), 7.96 (s, 1H), 7.73–7.63 (m, 5H), 4.33–4.28 (m, 1H), 4.14–3.90 (m, 7H), 3.78–3.71 (m, 2H), 2.46–2.43 (m, 4H), 2.06 (s, 3H), 1.98–1.93 (m, 2H), 1.53 (s, 9H). HR–ESMS m/z calcd for $C_{38}H_{41}N_4O_7Cl^{37}Cl$ 737.2323, found 737.2330 ($M+H^+$).

Compound 28ii. Prepared according to general procedure E using 0.0889 g (0.0956 mmol) of **27ii**, 0.241 mL of 10% aqueous ammonium formate, 0.05 g of 10% Pd/C, and 8 mL of THF to give 0.0510 g of **28ii** (71% yield) as a white powder. Mp 212 °C (dec.). ^{1}H NMR (DMSO-d_6) δ: 10.25 (s, 1H), 10.23 (s, 1H), 10.01 (s, 1H), 9.98 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 7.94 (s, 1H), 7.71–7.63 (m, 5H), 4.34–4.27 (m, 1H), 4.14–3.94 (m, 7H), 3.78–3.72 (m, 2H, 2.45–2.32 (m, 4H), 2.06 (s, 3H), 1.78–1.64 (m, 4H), 1.53 (s, 9H). HR–ESMS m/z calcd for $C_{39}H_{43}N_4O_7Cl_2$ 749.2509, found 749.2496 ($M+H^+$).

Compound 28iii. Prepared according to general procedure E using 0.0986 g (0.104 mmol) of **27iii**, 0.263 mL of 10% aqueous ammonium formate, 0.05 g of 10% Pd/C,

and 8 mL of THF to give 0.0598 g of **28iii** (75% yield) as a white powder. Mp 196 °C (dec.). ^{1}H NMR (DMSO-d_6) δ: 10.25 (s, 1H), 10.23 (s, 1H), 10.02 (s, 1H), 9.96 (s, 1H), 8.38 (s, 1H), 8.35 (s, 1H), 7.94 (s, 1H), 7.72–7.62 (m, 5H), 4.33–4.27 (m, 1H), 4.13–3.95 (m, 7H), 3.78–3.72 (m, 2H), 2.44–2.33 (m, 4H), 2.06 (s, 3H), 1.70–1.62 (m, 4H), 1.53 (s, 9H), 1.47–1.41 (m, 2H). HR–ESMS m/z calcd for $C_{40}H_{45}N_4O_7Cl^{37}Cl$ 765.2636, found 765.2621 ($M+H^+$).

Compound 28iv. Prepared according to general procedure E using 0.0975 g (0.102 mmol) of **27iv**, 0.257 mL of 10% aqueous ammonium formate, 0.05 g of 10% Pd/C, and 10 mL of THF to give 0.0559 g of **28iv** (71% yield) as a white powder. Mp 194 °C (dec.). ^{1}H NMR (DMSO-d_6) δ: 10.25 (s, 1H), 10.22 (s, 1H), 10.01 (s, 1H), 9.94 (s, 1H), 8.38 (s, 1H), 8.34 (s, 1H), 7.94 (s, 1H), 7.72–7.63 (m, 5H), 4.30–4.25 (m, 1H), 4.12–3.93 (m, 7H), 3.76–3.72 (m, 2H), 2.45–2.32 (m, 4H), 2.06 (s, 3H), 1.66–1.58 (m, 4H), 1.53 (s, 9H), 1.40–1.34 (m, 4H). HR–ESMS m/z calcd for $C_{41}H_{47}N_4O_7Cl^{37}Cl$ 779.2792, found 779.2792 ($M+H^+$).

X-ray crystallographic analysis

Yellow crystals of **15** were obtained from ethyl acetate. They were stable without the mother liquor in air and were selected at room atmosphere for X-ray crystallography. Formula $C_{22}H_{21}IN_2O_5$, monoclinic, space group $C2/c$, $a=16.1690(6)$, $b=19.7813(6)$, $c=14.9515(7)$ Å, $\beta=116.755(4)$, $V=4270.2(3)$Å^3, $Z=8$, graphite-monochromated Cu K_α radiation ($\lambda=1.54178$Å), $\mu=12.09\,mm^{-1}$, $T=-60$ °C. Data were collected on a Siemens P4/RA diffractometer. Calculations were carried out with the use of programs in the SHELXTL (Version 5.0) package.

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