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Novel and Potent Anti-malarial Agents

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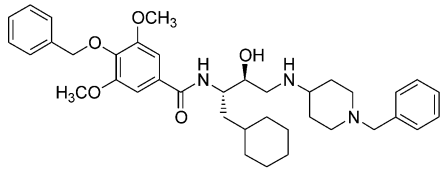
Abstract—Readily accessible, novel, and potent anti-malarial compounds have been developed. Optimization of the initial lead structure resulted in derivatives with IC_{50} values from 7 to 35 nM against chloroquine-sensitive and 70–350 nM against chloroquine-resistant strains of *Plasmodium falciparum*.

Introduction

Malaria continues to be a major health crisis, infecting approximately 400 million people and resulting in 1–3 million deaths every year.[1] The rapid spread of resistance to the currently used therapeutics presents an even more serious threat.[2] Unfortunately, new, effective, and inexpensive drugs are not being aggresively developed because the disease is prevalent in areas of the world that lack substantial economic resources.[3]

Recently, using a combination of structure-based design, mechanism-based design and combinatorial chemistry, we identified single digit nanomolar, low molecular weight inhibitors of the plasmodial aspartyl proteases plasmepsins I and II.[4] These enzymes are new potential therapeutic targets that degrade hemoglobin in the parasite food vacuole providing essential nutrients for parasite survival.[5]

During the screening of plasmepsin inhibitor libraries, compound **1** was identified to have potent activity in cell culture. This compound shows high levels of inhibition of parasite growth in cultured chloroquine sensitive (3D7) parasite-infected human erythrocytes ($IC_{50} = 70$ nM),[6] whereas its activity is approximately 300-fold lower ($IC_{50} = 20$ μM) in in vitro plasmepsin assays.[4,7] Although these results suggest that compound **1** is acting upon an alternative target, many of the quinoline-based anti-malarial drugs, such as chloroquine, show similar effects.[8]



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These drugs are hypothesized to exhibit heightened activity in cell culture (IC_{50} for chloroquine = 6 nM, 3D7) despite having poor activity in in vitro enzyme inhibition assays (IC_{50} for chloroquine ~100 μM for heme polymerization) because of their accumulation in the digestive vacuole. Like quinoline antimalarials, compound **1** contains basic amines. This functional group is thought to be important for the uptake and concentration of chloroquine in the acidic digestive vacuole. To confirm that this compound is not acting as a plasmepsin inhibitor, compound **2** was prepared since it is devoid of the secondary hydroxyl and P_1 side chain that are obligate functional groups of mechanism-based aspartyl protease inhibitors.[9] As expected, compound **2** showed extremely poor inhibitory activity against the plasmepsins (IC_{50} for plm II ≥ 250 μM). In contrast, in cell culture compound **2** is only 2-fold less potent ($IC_{50} = 150$ nM) than compound **1**, arguing strongly that compound **2** targets an alternative pathway. The unknown mechanism of action, high activity, and simple yet novel structure of **2** warrants further investigation.

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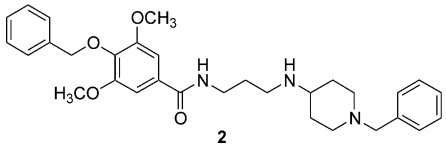

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Herein, we report structure–activity relationships that define the key structural determinants required for activity of this new class of antimalarial compounds. We further report potent compounds with activity superior to that of compound **2**, which are active against both drug sensitive and resistant parasite strains in cell culture.

Results and Discussion

Structure–activity relationships (SAR)

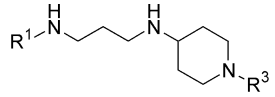
We first chose to define the key structural determinants for activity by variation of individual substituents in lead structure **2**. The SAR provided in Table 1 indicates that extended aromatic functionality at R^1 is essential for good activity. However, critical binding determinants beyond the extended aromatic functionality are not apparent. Note also that the cyclohexylmethyl group provides greater potency than the benzyl group at R^3 as illustrated by comparison of compounds **2** and **10**. More detailed SAR at the R^3 position is provided in Table 4. Finally, note that the 3- and 5-methoxy groups in the most potent compound, **10**, can be removed to provide compound **11** with only a very modest reduction in activity.

A number of analogues were prepared with modification of the linker region to establish the key determinants for activity in the central portion of the compound (Table 2). First, as shown for the compound series **2**, **16**, and **17**, and for the compound series **18**, **19**, and **20**, change in linker length does not greatly impact potency. In contrast, substitution of heteroatoms in the linker has a significant effect on activity. In particular, as shown for compounds **18**, **19**, and **20**, the presence of a basic amine provides a significant increase in potency. The SAR in Table 2 corroborates the SAR in Table 1 where the 3- and 5- methoxy groups may be replaced with hydrogens without significantly effecting activity (see compounds **21** and **22**).

As shown in Table 3, substitutions at the R^2 position are not accommodated. Introduction of an alkyl substituent whether small, such as a methyl group in compound **29**, or large, such as isobutyl and benzyl groups in compounds **31** and **32** respectively, results in a significant drop in potency. Interestingly, acylation of the amine to provide compound **30** completely abolishes activity.

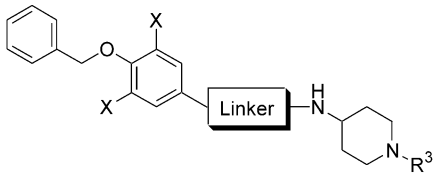
A number of substituents were next explored at R^3 as illustrated in Table 4. In particular, large hydrophobic groups at this position are critical for achieving good

Table 1. SAR data at the R^1 site



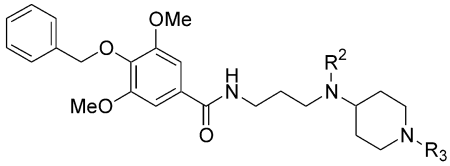
Compd	R^1	R^3	IC_{50} (nM) 3D7
2	[4-(OBn)-3,5-$(OMe)_2$]C_6H_2CO	$CH_2C_6H_5$	150
3	$C_6H_5CH_2C_6H_4CO$	$CH_2C_6H_5$	250
4	[1-Naphthyl}OCH_2CO	$CH_2C_6H_5$	350
5	$C_6H_5OCH_2CO$	$CH_2C_6H_5$	> 5000
6	3-Pyridyl-CO	$CH_2C_6H_5$	> 5000
7	$MeSO_2C_6H_4CO$	$CH_2C_6H_5$	> 5000
8	C_6H_5CO	$CH_2C_6H_5$	> 5000
9	H	$CH_2C_6H_5$	> 5000
10	[4-(OBn)-3,5-$(OMe)_2$]C_6H_2CO	$CH_2C_6H_{11}$	35
11	[4-(OBn)]C_6H_4CO	$CH_2C_6H_{11}$	50
12	C_6H_5-*E*-$CHCHC_6H_4CO$	$CH_2C_6H_{11}$	40
13	$C_6H_5CH_2CH_2C_6H_4CO$	$CH_2C_6C_{11}$	100
14	[4-(OC_6H_5)]C_6H_4CO	$CH_2C_6H_{11}$	150
15	$C_6H_5CH_2C_6H_4CO$	$CH_2C_6H_{11}$	600

Table 2. SAR in the linker region



Compd	X	Linker	R^3	IC_{50} (nM) 3D7
2	OMe	$CONH(CH_2)_3$	$CH_2C_6H_5$	200
16	OMe	$CONH(CH_2)_2$	$CH_2C_6H_5$	150
17	OMe	$CONH(CH_2)_4$	$CH_2C_6H_5$	300
18	OMe	$CH_2NH(CH_2)_2$	$CH_3C_6H_5$	40
19	OMe	$CH_2NH(CH_2)_3$	$CH_2C_6H_5$	30
20	OMe	$CH_2NH(CH_2)_4$	$CH_2C_6H_5$	35
21	OMe	$CH_2O(CH_2)_3$	$CH_2C_6H_5$	500
22	H	$CH_2O(CH_2)_3$	$CH_2C_6H_5$	500
23	H	$NHCO(CH_2)_2$	$CH_2C_6H_5$	75
24	H	$NHCO(CH_2)_3$	$CH_2C_6H_5$	70
10	OMe	$CONH(CH_2)_3$	$CH_2C_6H_{11}$	35
11	H	$CONH(CH_2)_3$	$CH_2C_6H_{11}$	50
25	H	$CH_2NH(CH_2)_2CO$	$CH_2C_6H_{11}$	> 300
26	H	$CH_2NH(CH_2)_3CO$	$CH_2C_6H_{11}$	> 200
27	H	$SO_2NH(CH_2)_3$	$CH_2C_6H_{11}$	90
28	H	$CON[C_2H_5](CH_2)_3$	$CH_2C_6H_{11}$	130

Table 3. SAR in the R^2 site

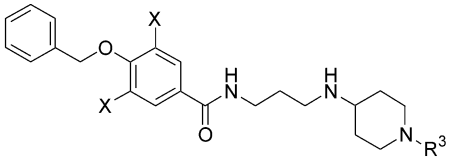


Compd	R^2	R^3	IC_{50} (nM) 3D7
2	H	$CH_2C_6H_5$	150
29	Me	$CH_2C_6H_5$	600
30	COMe	$CH_2C_6H_5$	> 5000
10	H	$CH_2C_6H_{11}$	30
31	Isobutyl	$CH_2C_6H_{11}$	75
32	Benzyl	$CH_2C_6H_{11}$	100

activity. Notably, as shown for compound **10**, the substituent at R^3 does not have to be aromatic. Finally, in preliminary data shown for compound **44** as compared to compound **10**, acyl groups provide reduced activity relative to alkyl groups at this position.

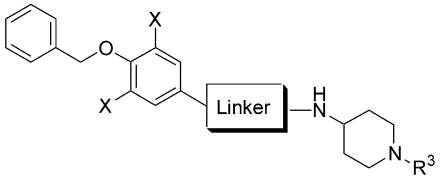
Based upon the SAR provided in Tables 1–4, compounds containing the optimal substitutions at each site were then tested both against the chloroquine sensitive strain, 3D7, and the chloroquine resistant strain, W2 (Table 5). Compounds **45** to **47**, which combine a basic amine within the linker and the cyclohexylmethyl or 2,2-phenylethyl groups at R^3, show the highest potency of any derivatives based upon lead **2**. The compounds remain quite active against the chloroquine resistant strain W2, although a 5- to 10-fold reduction in activity is observed. Notably, compounds **45**–**47** are of comparable potency to chloroquine against the drug-sensitive strain 3D7 ($IC_{50} = 6$ nM), and are more potent than chloroquine against the drug-resistant strain W2 ($IC_{50} = 190$ nM).

Table 4. SAR in the R^3 site



Compd	X	R^3	IC_{50} (nM) 3D7
10	OMe	$CH_2C_6H_{11}$	35
33	OMe	$CH_2CH(C_6H_5)_2$	30
34	OMe	$CH_2CH_2C_6H_5$	35
35	OMe	CH_2(1-Me-3-indole)	35
36	OMe	CH_2(2-naphthyl)	40
37	OMe	$CH_2C_6H_4C_6H_5$	50
38	OMe	$CH_2C_6H_3$-3,4-(methylenedioxy)	75
39	OMe	CH_2-3-Me-C_6H_4	75
40	OMe	$CH_2CH_2OCH_2C_6H_5$	75
41	OMe	CH_2(3-pyrazoyl)	200
42	OMe	CH_3	2000
11	H	$CH_2C_6H_{11}$	50
43	H	$CH_2CH(C_6H_5)_2$	25
44	H	COC_6H_{11}	500

Table 5. IC_{50} values for select compounds against W2

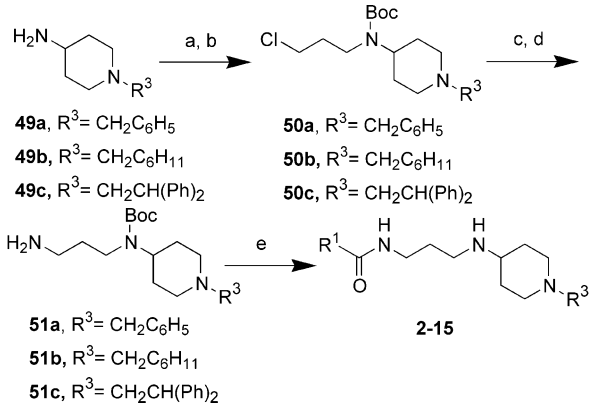


Compd	X	Linker	R^3	IC_{50} (nM)	
				3D7	W2
33	OMe	$CONH(CH_2)_3$	$CH_2CH(C_6H_5)_2$	30	200
43	H	$CONH(CH_2)_3$	$CH_2CH(C_6H_5)_2$	25	160
10	OMe	$CONH(CH_2)_3$	$CH_2C_6H_{11}$	35	350
20	OMe	$CH_2NH(CH_2)_3$	$CH_2C_6H_5$	30	150
45	OMe	$CH_2NH(CH_2)_3$	$CH_2C_6H_{11}$	15	180
46	OMe	$CH_2NH(CH_2)_3$	$CH_2CH(C_6H_5)_2$	12	100
47	H	$CH_2NH(CH_2)_3$	$CH_2CH(C_6H_5)_2$	7	70
48	H	$NHCO(CH_2)_2$	$CH_2CH(C_6H_5)_2$	18	130

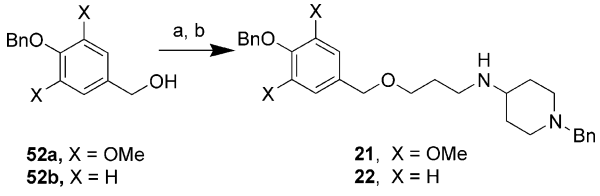
Chemistry

The aforementioned compounds were prepared according to the synthetic sequences illustrated in Schemes 1–8 .

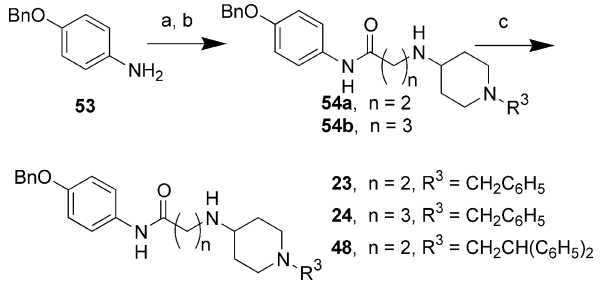
To introduce diversity at the R^1 site, amines **49a** and **49b** were alkylated with 3-chloropropyl bromide and the resulting secondary amine products were reacted with *tert*-butyl pyrocarbonate to provide intermediates **50a** and **50b**, respectively. The chloride substituents in **50a** and **50b** were then displaced with sodium azide, which was subsequently reduced to provide the primary amines **51a** and **51b**.[10] Diversity at the R^1 site was then introduced by treating the amines **51a** and **51b** with a variety of acids in a parallel format (Scheme 1). Solid supported EDC (P-EDC) was used for amide bond formation. Removal of the Boc group and purification of the products were achieved simultaneously by addition of a strongly acidic ion exchange resin (P-SO_3H)



Scheme 1. Reagents: (a) $Cl(CH_2)_3Br$, CH_3CN; (b) Boc_2O, THF; (c) NaN_3, NaI, DMF; (d) PhSH, $SnCl_2$, Et_3N, THF; (e) (1) R^1CO_2H, P-EDC, $CHCl_3$, (2) P-SO_3H, $CHCl_3$, (3) NH_3/MeOH.



Scheme 2. Reagents: (a) **50a**, NaH, DMF; (b) 4 N HCl/dioxane.



Scheme 3. Reagents: (a) $BocNH(CH_2)_nCO_2H$, TBTU, iPr_2EtN, DMF; (b) 4 N HCl/dioxane; (c) *N*-R^3-piperidone, $NaBH(OAc)_3$, DCE.

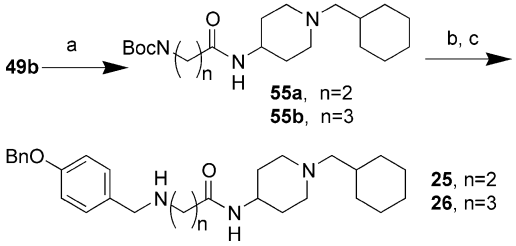
followed by rinsing with CH_2Cl_2 and methanol.[11] The free amine was then isolated by elution from the sulfonic acid resin with NH_3/MeOH.

Compounds **16** and **17** were prepared in a similar manner to **2**–**15** as shown in Scheme 1, except that 1-bromo-2-chloropropane was replaced with 1-bromo-2-chloroethane and 1-bromo-4-chlorobutane, respectively. Reduction of the amides **2**, **16**, and **17** with $LiAlH_4$ in THF then provided the corresponding amines **18**–**20**.

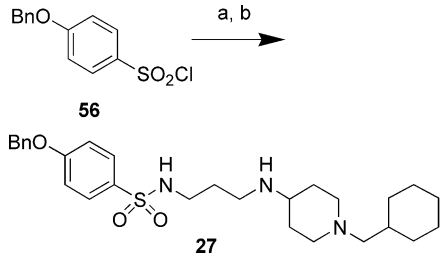
The ether functionality was incorporated in the linker by treating the alcohols **52a** and **52b** with NaH followed by addition of alkyl chloride **50a** followed by Boc removal to afford compounds **21** and **22**, respectively (Scheme 2).

The reversed amides **23**, **24**, and **48** were prepared by coupling 4-benzyloxyaniline **53** with *N*-Boc-β-alanine and *N*-Boc-4-aminobutyric acid followed by Boc deprotection to provide **54a** and **54b**, respectively (Scheme 3). Reductive alkylation with the appropriately *N*-substituted piperidone then provided **23**, **24**, and **48**.

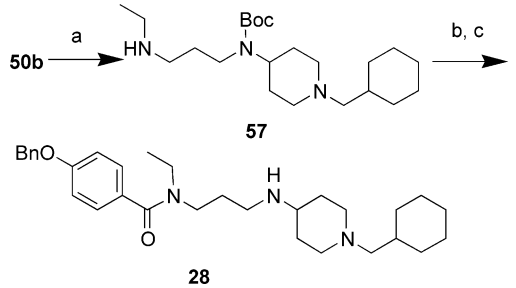
Compounds **25** and **26**, where the relative positions of the amide and amine displayed in **2** have been reversed,



Scheme 4. Reagents: (a) $BocNH(CH_2)_nCO_2H$, DCC, *N*-hydroxysuccinimide, iPr_2EtN; (b) 4 N HCl/dioxane; (c) *p*-benzyloxybenzaldehyde, AcOH, $NaBH(OAc)_3$, THF.



Scheme 5. Reagents: (a) **51b**, Et_3N, 1:1:1 H_2O/THF/dioxane; (b) 4 N HCl/dioxane.



Scheme 6. Reagents: (a) $EtNH_2$, H_2O, NaI, DMF, 60 °C; (b) 4-benzyloxybenzoic acid, HATU, $iPrEt_2N$, DMF; (c) 4 N HCl/dioxane.

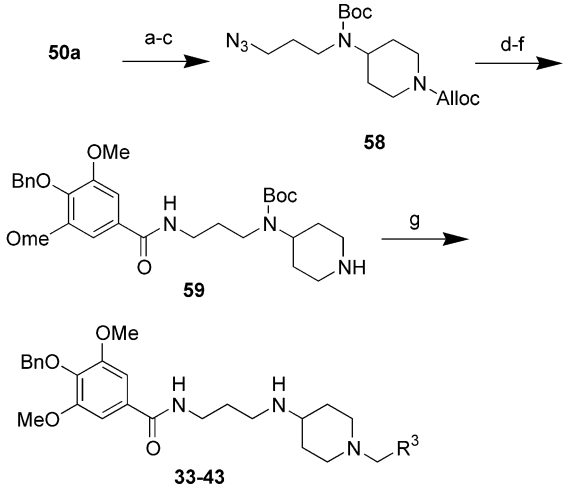
were prepared by acylating **49b** with *N*-Boc-β-alanine and *N*-Boc-4-aminobutyric acid to provide **55a** and **55b**, respectively. Removal of the Boc groups followed by reductive alkylation with 4-benzyloxybenzaldehyde provided **25** and **26**, respectively (Scheme 4).

Sulfonamide analogue **27** was prepared through treatment of sulfonyl chloride **56** with **51b** followed by deprotection of the Boc group (Scheme 5). Tertiary amide **28** was prepared by treating alkyl chloride **50b** with ethylamine, followed by acylation with 4-benzyloxybenzoic acid and subsequent Boc deprotection (Scheme 6).

The compounds incorporating substituents at R^2 (Table 3) were prepared by straightforward modification of the procedures to prepare the previous compounds. The *N*-methylated derivative **29** was prepared according to the sequence illustrated in Scheme 1 with the exception that 4-methylamino-1-benzylpiperidine was used in place of 4-amino-1-benzylpiperidine. The acetyl group in compound **30** was introduced by treating **2** with acetyl chloride in CH_2Cl_2. Compounds **31** and **32** were prepared by reductive alkylation of **10** with sodium cyanoborohydrde and isobutyraldehyde or benzaldehyde, respectively.

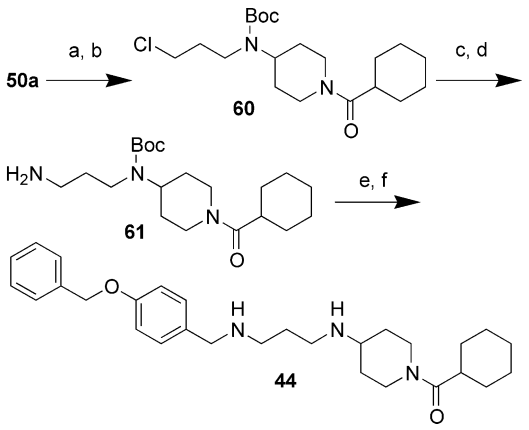
As shown in Scheme 7, diversity at the R^3 site was introduced in a parallel format by treating the amine precursor **59** with aldehydes under reductive conditions ($NaBH_3CN$, AcOH, MeOH). When the amine **59** was consumed, the reaction mixture was diluted with CH_2Cl_2. Removal of the Boc-group and purification was accomplished simultaneously by addition of sulfonic acid ion exchange resin. The desired free amines were then obtained by elution from the sulfonic acid resin with ammonia in methanol.

Alternatively, an amide was introduced at the R^3 site by debenzylation of **50a** followed by acylation with cyclo-



Scheme 7. Reagents: (a) H_2, Pd/C, AcOH, EtOAc; (b) Alloc-Cl, iPr_2EtN, CH_2Cl_2; (c) NaI, NaN_3, DMF; (d) $SnCl_2$, PhSH, Et_3N, THF; (e) 4-benzyloxy-3,5-dimethoxybenzoic acid, HATU, iPr_2EtN, DMF; (f) TBAF xH_2O, $TMSN_3$, $Pd(PPh_3)_4$, CH_2Cl_2; (g) (1) R^3CHO, $NaBH_3CN$, AcOH, MeOH, (2) P-SO_3H, CH_2Cl_2, (3) NH_3/MeOH.

hexanecarboxylic acid to provide **60** (Scheme 8). Conversion of **60** to amine **61** was followed by reductive alkylation with 4-benzyloxy-1-benzaldehyde and subsequent Boc deprotection to provide **44**.



Scheme 8. Reagents: (a) H_2, Pd/C, AcOH, EtOAc; (b) RCO_2H, HATU, iPr$_2$EtN, DMF; (c) NaI, NaN_3, DMF; (d) $SnCl_2$, PhSH, Et_3N, THF; (e) 4-benzoyl-1-benzaldehyde, $NaBH(OAc)_3$, AcOH, DCE; (f) 4N HCl/dioxane.

Conclusions

The compounds derived from lead compound **2** show excellent activities in cell culture against both chloroquine sensitive and resistant strains of parasitic cell lines. In particular, compounds **45**–**47** are as potent as chloroquine against the drug-sensitive strain 3D7, and more potent than chloroquine against the drug-resistant strain W2. Further issues still to be addressed include establishing the mechanism of action of the most potent compounds, although recent studies suggest that these novel compounds may act as heme polymerization inhibitors.[12] In addition, further structure optimization and evaluation of the most promising compounds in animal models is underway.

Experimental

General

Materials were obtained from commercial suppliers and employed without further purification unless otherwise stated. Ion exchange resin (AG MP-50, Cat. No. 143–0841) was purchased from Bio-Rad (Hercules, CA, USA). Anhydrous *N*,*N*-dimethyformamide (DMF) was purchased from Aldrich (Milwaukee, WI, USA). Chloroform ($CHCl_3$) was passed through basic alumina prior to use. Flash column chromatography was carried out with Merck 60 230–400 mesh silica gel. ^{1}H and ^{13}C NMR spectra were recorded using UCB Bruker AMX-300, AM-400, and DRX-500 spectrometers. All spectra were obtained in $CDCl_3$ or CD_3OD, and chemical shifts are recorded in parts per million relative to the internal solvent peak. Coupling constants are reported in hertz (Hz). Elemental analyses were performed by M-H-W Laboratories (Phoenix, AZ, USA).

***Plasmodium falciparum*-infected erythrocyte assay.** Assays of inhibitory activity in cultured parasite-infected human erythrocytes were performed as previously described.[6]

Compound 50a. To a solution of 1-bromo-3-chloropropane (1.0 g, 6.35 mmol) in CH_3CN (5 mL) was added 4-amino-1-benzylpiperidine (3.6 g, 19.5 mmol). The reaction mixture was stirred at room temperature for 16 h. As the reaction proceeded, formation of a white precipitate was observed. The reaction mixture was brought to pH 9 with saturated $NaHCO_3$ (15 mL), then extracted with EtOAc (3×30 mL). The combined organic phase was dried over Na_2SO_4 and concentrated to afford a yellow oil. Silica gel column chromatography using 19:1 CH_2Cl_2/MeOH afforded 1.64 g the amine as a pale yellow solid (97%).

This compound (1.55 g, 5.82 mmol) was then dissolved in THF (5 mL) and di-*t*-butyl dicarbonate (1.52 g, 6.98 mmol) was added. The reaction mixture was stirred at room temperature for 2 h and concentrated. Silica gel column chromatography using 99:1 CH_2Cl_2/MeOH yielded 2.0 g of **50a** as a yellow solid. (94%) ^{1}H NMR ($CDCl_3$) δ 1.47 (s, 9H), 1.62–1.68 (m, 2H), 1.69–1.80 (m, 2H), 1.94–2.10 (m, 4H), 2.94 (d, 2H), 3.20–3.30 (m, 2H), 3.50 (s, 2H), 3.53 (t, J = 6.4 Hz, 2H), 4.00 (bs, 1H), 7.25–7.28 (m, 1H), 7.31–7.35 (m, 4H).

Compound 50b. 2.98 g (7.99 mmol, 97.0%) of **50b** was prepared as a yellow oil according to the procedure described for **50a**. IR (cm^{-1}) 2922, 2849, 1691, 1449. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.87 (m, 2H), 1.22 (m, 3H), 1.47 (s, 9H), 1.46 (m, 1H), 1.71 (m, 10H), 1.98 (m, 4H), 2.09 (d, 2H, J = 6.8), 2.91 (d, br, 2H, J = 10.4), 3.24 (m, br, 2H), 3.53 (t, 2H, J = 6.4); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 26.7, 27.3, 28.4, 31.0, 31.9, 35.3, 43.0, 52.1, 53.8, 65.5, 79.9, 85.1, 155.4. Anal. calcd for $C_{20}H_{37}ClN_2O_2$: C, 64.41; H, 10.00; N, 7.51. Found: C, 64.11; H, 9.92; N, 7.36.

Compound 51a. To a solution of **50a** (1.92 g, 5.24 mmol) in DMF (5 mL) were added NaN_3 (3.41 g, 52.4 mmol) and NaI (0.79 g, 5.24 mmol) and the reaction mixture was stirred at 75–80 °C for 15 h. The solvent was removed in vacuo and the resultant residue was dissolved in $CHCl_3$ (20 mL). The organic phase was washed with water (2×20 mL), dried over Na_2SO_4, and then concentrated. Silica gel column chromatography using 49:1 CH_2Cl_2/MeOH afforded 1.84 g of the azide derivative as a colorless oil (94%).

To a solution of $SnCl_2$ (76 mg, 0.40 mmol) in THF (3 mL) were added PhSH (0.18 g, 1.61 mmol) and Et_3N (0.20 g, 2.01 mmol). The mixture was added to a solution of the azide described above (0.10 g, 0.027 mmol) in THF (2 mL) and the reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated and the residue was diluted with CH_2Cl_2 (5 mL) and then 2 N NaOH (5 mL) was added to the solution. The aqueous phase was separated and extracted with CH_2Cl_2 (2×10 mL). The combined organic phase was dried over Na_2SO_4 and concentrated to provide 87 mg

of **51a** as a colorless oil (93%) ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.54–1.80 (m, 4H), 1.91–2.04 (m, 2H), 2.10–2.18 (bs, 2H), 2.68 (t, J = 6.8 Hz, 2H), 2.92 (d, J = 11.6 Hz, 2H), 3.05–3.28 (m, 2H), 3.47 (s, 2H), 7.20–7.26 (m, 1H), 7.28–7.31 (m, 4H).

Compound 51b. 1.85 g (4.85 mmol, 86.7%) of **51b** was prepared as a yellow oil according to the procedure described for **51a**. IR (cm^{-1}) 3385, 2919, 1681. ^{1}H NMR (300 MHz, MeOD) δ 0.83 (m, 2H), 1.22 (m, 3H), 1.45 (s, 9H), 1.68 (m, 10H), 1.90 (m, 2H), 2.07 (d, 2H, J = 7.2), 2.51 (s, br, 3H), 2.72 (s, br, 2H), 2.90 (d, br, 2H, J = 15.2), 3.16 (s, br, 2H); ^{13}C NMR (125 MHz, MeOD) δ 25.8, 26.4, 27.4, 27.5, 29.3, 31.7, 35.2, 38.5, 40.0, 53.6, 55.0, 65.3, 79.7, 155.7. Anal. calcd for $C_{20}H_{39}N_3O_2$: C, 67.94; H, 11.12; N, 11.89; found, C, 67.54; H, 10.84; N, 11.63.

Compound 2. A pre-mixed solution of 4-benzyloxy-3,5-dimethoxybenzoic acid (93 mg, 0.32 mmol), PyBOP (170 mg, 0.32 mmol), HOAt (44 mg, 0.32 mmol) and diisopropylethylamine (0.12 mL, 0.67 mmol) in DMF (3 mL) was added to a solution of **51a** (94 mg, 0.27 mmol) in DMF (1 mL). The reaction mixture was stirred at room temperature for 16 h under nitrogen, and the DMF was removed in vacuo. The residue was diluted with $CHCl_3$ (10 mL) and the solution was washed with saturated $NaHCO_3$ (2×5 mL), then water (1×5 mL). The organic phase was dried over Na_2SO_4 and concentrated. Silica gel column chromatography using 97:3 CH_2Cl_2/MeOH afforded 0.15 g (88%) of the Boc-protected product as a colorless oil. This precursor (0.78 g, 1.26 mmol) was treated with 20% TFA in CH_2Cl_2 (10 mL) and stirred for 2 h at 0 °C, and then an additional 2 h at room temperature. The reaction mixture was concentrated and the residual TFA was removed by adding toluene. Silica gel column chromatograph using 45:5:1 CH_2Cl_2/MeOH/NH_4OH provided 0.70 g of **2** as a colorless oil (94%). The compound was dissolved in MeOH (2 mL) and the solution was acidified by adding 1 M HCl/ether. The solution was concentrated to afford pure **2** as the HCl salt. ^{1}H NMR (CD_3OD) δ 1.82–1.93 (m, 2H), 1.94–2.05 (m, 2H), 2.39 (d, J = 13.6 Hz, 2H), 3.10–3.20 (m, 4H), 3.47 (t, J = 6.4 Hz, 2H), 3.48–3.52 (m, 1H), 3.65 (d, J = 13.2 Hz, 2H), 3.80 (s, 6H), 5.04 (s, 2H), 7.04 (s, 2H), 7.34–7.40 (m, 5H), 7.45–7.58 (m, 5H); MALDI calcd for $C_{31}H_{39}N_3O_4$ = 517.66, obsd = 516.44.

General procedure for the synthesis of compounds 3–15

Polymer-bound EDC (0.71 mmol/g, 0.30 g) was added to the solution of a carboxylic acid (86 μmol) in $CHCl_3$ (2 mL) in a screw cap vial and stirred for 5 min. A solution of amine **51a** or **51b** (29 μmol) in $CHCl_3$ (1 mL) was then added to the suspension of the resin and the mixture was shaken for 6 h at room temperature. The mixture was filtered and the resin was washed with $CHCl_3$ (3×1 mL). Approximately 300 mg of an ion exchange resin was added to the filtrate and the mixture was shaken for an additional 5 h. The resin was washed with CH_2Cl_2 (2×2 mL) and MeOH (2×2 mL). The resin was then treated with 2 M NH_3 in MeOH (5 mL) and shaken for 30 min. The solution was drained into a sample vial and the resin was resubjected to NH_3/MeOH (2 mL) for an additional 30 min. The combined filtrate was concentrated to afford an oily residue, which was treated with 2 N HCl in ether to afford the HCl salt.

Compound 3. 2.5 mg, 95% yield. ^{1}H NMR ($CDCl_3$) δ 1.38 (dd, J = 3.6, 11.6 Hz, 2H), 1.43 (dd, J = 3.6, 11.6 Hz, 2H), 1.52 (bs, 1H), 1.66 (d, J = 12.0 Hz, 2H), 1.68 (quintet, J = 6.4 Hz, 2H), 1.89 (dt, J = 2.4 Hz, J = 11.6 Hz, 2H), 2.28 (tt, J = 4.0, 10.4 Hz, 1H), 2.65 (t, J = 6.4 Hz, 2H), 2.73 (d, J = 12.0 Hz, 2H), 3.44 (s, 2H), 3.48 (q, J = 6.0 Hz, 2H), 4.70 (s, 2H), 6.80 (d, J = 7.2 Hz, 1H), 7.26–7.38 (m, 5H), 7.49–7.52 (m, 4H), 7.81–7.84 (m, 1H), 8.23–8.26 (m, 1H); MALDI calcd for $C_{29}H_{35}N_3O$ = 441.61, obsd = 440.26. Anal. calcd for $C_{29}H_{35}N_3O2HCl$ C, 67.60; H, 7.25; N, 8.17. Found C, 67.55; H, 7.37; N, 8.12.

Compound 4. 1.9 mg, 92% yield. ^{1}H NMR ($CDCl_3$) δ 1.22 (dd, J = 3.6, 11.6 Hz, 2H), 1.26 (dd, J = 3.6, 11.6 Hz, 2H), 1.52 (bs, 1H), 1.66 (d, J = 12.0 Hz, 2H), 1.68 (quintet, J = 6.4 Hz, 2H), 1.89 (dt, J = 2.4, 11.6 Hz, 2H), 2.28 (tt, J = 4.0, 10.4 Hz, 1H), 2.65 (t, J = 6.4 Hz, 2H), 2.73 (d, J = 12.0 Hz, 2H), 3.44 (s, 2H), 3.48 (q, J = 6..0 Hz, 2H), 4.70 (s, 2H), 6.80 (d, J = 7.2 Hz, 1H), 7.26–7.38 (m, 5H), 7.49–7.52 (m, 4H), 7.81–7.84 (m, 1H), 8.23–8.26 (m., 1H); MALDI calcd for $C_{27}H_{33}N_3O_2$ = 431.57, obsd = 429.74. Anal. calcd for $C_{27}H_{33}N_3O_22HCl$ C, 64.28; H, 6.99; N, 8.33. Found C, 64.31; H, 6.78; N, 8.18.

Compound 5. 2.1 mg, 96% yield. ^{1}H NMR ($CDCl_3$) δ 1.36, (dd, J = 3.6, 11.6 Hz, 2H), 1.40 (dd, J = 3.6, 11.6 Hz, 2H), 1.70 (quintet, J = 6.4 Hz, 2H), 1.83 (d, J = 12.4 Hz, 2H), 1.99 (dt, J = 2.0, 11.6 Hz, 2H), 2.42 (tt, J = 4.0, 10.8 Hz, 1H), 2.71 (t, J = 6.4 Hz, 2H), 2.84 (d, J = 12.0 Hz, 2H), 3.45 (q, J = 6.4 Hz, 2H), 3.54 (s, 2H), 4.49 (s, 2H), 6.93 (d, J = 8.8 Hz, 2H), 7.02 (t, J = 7.2 Hz, 1H), 7.23–7.27 (m, 1H), 7.29–7.36 (m, 6H), 7.60 (bs, 1H); MALDI calcd for $C_{23}H_{31}N_3O$ = 381.51, obsd = 381.69. Anal. calcd for $C_{23}H_{31}N_3O$ 2HCl: C, 60.79; H, 7.32; N, 9.25. Found: C, 60.60; H 7.49; N 9.12.

Compound 6. 2.1 mg, 53% yield. ^{1}H NMR ($CDCl_3$) δ 1.43 (dd, J = 3.6, 11.6 Hz, 2H), 1.47 (dd, J = 3.6, 11.6 Hz, 2H), 1.81 (quintet, J = 5.6 Hz, 2H), 1.91 (d, J = 12.0 Hz, 2H), 2.01 (t, J = 11.6 Hz, 2H), 2.42 (bs, 1H), 2.53 (tt, J = 4.0, 10.8 Hz, 1H), 2.86 (d, J = 11.6 Hz, 2H), 2.91 (t, J = 5.6 Hz, 2H), 3.48 (s, 2H), 3.60 (q, J = 5.2 Hz, 2H), 7.23–7.28 (m, 1H), 7.29–7.34 (m, 4H), 7.37 (dd, J = 8.0, 4.8 Hz, 1H), 8.16 (td, J = 2.0, 8.0 Hz, 1H), 8.70 (dd, J = 1.6, 4.8 Hz, 1H), 8.80 (bs, 1H), 9.01 (d, J = 2.0 Hz, 1H); MALDI calcd for $C_{21}H_{28}N_4O$ = 352.47, obsd = 350.84.

Compound 7. 2.1 mg, 59% yield. ^{1}H NMR ($CDCl_3$) δ 1.36 (dd, J = 3.6, 11.6 Hz, 2H), 1.40 (dd, J = 4.0, 12.0 Hz, 2H), 1.63 (bs, 1H), 1.77 (quintet, J = 5.6 Hz, 2H), 1.88 (d, J = 12.0 Hz, 2H), 2.01 (dt, J = 2.0, 9.6 Hz, 2H), 2.47 (tt, J = 4.0, 10.8 Hz, 1H), 2.86 (d, J = 12.0 Hz, 2H), 2.89 (t, J = 5.6 Hz, 2H), 3.07 (s, 3H), 3.49 (s, 2H), 3.59 (q, J = 6.0 Hz, 2H), 7.23–7.35 (m, 5H), 7.99 (s, 4H), 8.98 (bs, 1H); MALDI calcd for $C_{23}H_{31}N_3O_3S$ = 429.58, obsd = 428.32.

Compound 8. 2.8 mg, 88% yield. ^{1}H NMR ($CDCl_3$) δ 1.37 (dd, J = 3.6, 11.6 Hz, 2H), 1.42 (dd, J = 3.6, 11.6 Hz, 2H), 1.58 (bs, 1H), 1.75 (quintet, J = 6.0 Hz, 2H), 1.88 (d, J = 12.0 Hz, 2H), 2.01 (dt, J = 2.4, 12.0 Hz, 2H), 2.47 (tt, J = 4.4, 10.8 Hz, 1H), 2.84 (t, J = 5.6 Hz, 2H), 2.84 (d, J = 12.0 Hz, 2H), 3.48 (s, 2H), 3.57 (q, J = 5.2 Hz, 2H), 7.22–7.28 (m, 1H), 7.29–7.34 (m, 4H), 7.39–7.48 (m, 3H), 7.81 (dd, J = 1.6, 8.4 Hz, 2H), 8.35 (bs, 1H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{22}H_{30}N_3O_1$, 352.2389; found, 352.2389.

Compound 9. Quantitative yield. ^{1}H NMR (CD_3OD) δ 2.06–2.12 (m, 4H), 2.41 (d, J = 11.6 Hz, 2H), 3.07 (t, J = 6.8 Hz, 2H), 3.19–3.28 (m, 4H), 3.54–3.58 (m, 1H), 3.59 (d, J = 12.4 Hz, 2H), 4.36 (s, 2H), 7.43–7.49 (m, 3H), 7.52–7.58 (m, 2H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{15}H_{26}N_3$, 248.2132; found, 248.2128.

Compound 10. 0.43 g (0.82 mmol, 48.2%) as a white solid. Mp 151–152 °C. IR (cm^{-1}) 3292, 2917, 2848, 1633, 1236. ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.81 (m, 2H), 1.15 (m, 3H), 1.37 (m, 3H), 1.73 (m, 12H), 2.03 (d, 2H, J = 7.2), 2.40 (m, 1H), 2.75 (m, 4H), 3.46 (q, br, 2H, J = 5.6), 3.81 (s, 6H), 5.00 (s, 2H), 7.04 (s, 2H), 7.27 (m, 3H), 7.43 (m, 2H), 8.14 (t, br, 1H, J = 5.2); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.5, 27.5, 30.1, 32.2, 32.8, 36.1, 38.7, 44.5, 53.8, 55.9, 56.5, 66.5, 75.6, 105.6, 128.7, 128.9, 129.2, 130.7, 138.7, 140.5, 154.4, 168.9. Anal. calcd for $C_{31}H_{45}N_3O_4$: C, 71.10; H, 8.66; N, 8.02. Found: C, 70.98; H, 8.42; N, 7.69.

Compound 11. 248 mg (0.54 mmol, 81%) ^{1}H NMR (400 MHz, $CDCl_3$) δ 0.89 (m, 2H), 1.24 (m, 3H), 1.45 (m, 3H), 1.64 (m, 7H), 1.78 (m, 4H), 1.94 (m, 2H), 2.48 (m, 1H), 22.71 (m, 1H), 2.84 (m, 4H), 3.53 (q, 2H, J = 5.6), 4.75 (bs, 1H), 5.11 (s, 2H), 6.98 (m, 2H), 7.39–7.44 (m, 4H), 7.78 (m, 2H), 8.12 (m, 1H).

Compound 12. 27 mg, 78% yield. IR (cm^{-1}) 3338, 2921, 2846, 1629. ^{1}H NMR (400 MHz, MeOH) δ 0.91 (m, 2H), 1.23 (m, 4H), 1.46 (m, 3H), 1.74 (m, 5H), 1.83 (t, 2H, J = 7), 1.89 (d, br, 2H, J = 14), 1.97 (t, br, 2H, J = 12) 2.14 (d, 2H, J = 6.5), 2.53 (m, 1H), 2.73 (t, 2H, J = 7), 2.90 (d, br, 2H, J = 12.5), 3.46 (t, 2H, J = 6.5), 7.21–7.38 (m, 5H), 7.58 (d, 2H, J = 7.5), 7.65 (d, 2H, J = 8.5), 7.81 (d, 2H, J = 8); ^{13}C NMR (125 MHz, MeOD) δ 26.3, 26.7, 27.0, 27.8, 31.7, 34.0, 37.2, 43.7, 52.4, 53.5, 68.0, 127.4, 127.7, 128.2, 128.8, 129.0, 129.7, 132.0, 133.2, 139.2, 142.3, 170.6. ESI-MS (LR) (m/z) $[M+H]^+$ calcd for $C_{30}H_{41}N_3O$ 460; found 460.

Compound 13. 26 mg, 69% yield. IR (cm^{-1}) 3289, 2921, 2848, 1639. ^{1}H NMR (400 MHz, MeOH) δ 0.91 (m, 2H), 1.22 (m, 3H), 1.45 (m, 3H), 1.70–1.98 (m, 12H), 2.13 (d, 2H, J = 6.8), 2.49 (m, 1H), 2.70 (t, 2H, J = 10.8), 2.93 (m, 6H), 3.43 (t, 2H, J = 6.4), 7.13 (m, 3H), 7.23 (m, 4H), 7.69 (m, 2H); ^{13}C NMR (125 MHz, MeOD) δ 27.2, 27.8, 30.2, 32.3, 33.2, 36.5, 38.6, 38.8, 38.8, 44.7, 54.1, 56.2, 66.8, 127.0, 128.3, 129.3, 129.6, 129.8, 133.2, 142.6, 147.2, 170.3. ESI-MS (LR) (m/z) $[M+H]^+$ calcd for $C_{30}H_{43}N_3O$ 462; found 462.

Compound 14. 39 mg, 80% yield. IR (cm^{-1}) 3292, 2921, 2845, 1639. ^{1}H NMR (400 MHz, MeOH) δ 0.90 (dq, 2H, J = 12.5, 3), 1.25 (m, 3H), 1.43 (dq, 2H, J = 12, 3.5), 1.46 (m, 1H), 1.73 (m, 8H), 1.88 (d, br, 2H), 1.94 (m, br, 2H), 2.13 (d, 2H, J = 6.5), 2.49 (m, 1H), 2.69 (t, 2H, J = 7), 2.88 (m, 2H), 3.45 (t, 2H, J = 6.5), 7.00 (m, 2H), 7.05 (m, 2H), 7.19 (m, 1H), 7.40 (m, 2H), 7.81 (m, 2H); ^{13}C NMR (125 MHz, MeOD) δ 25.4, 25.8, 26.3, 28.8, 31.7, 35.0, 37.3, 43.3, 52.6, 54.7, 65.4, 117.1, 119.5, 124.0, 128.8, 129.7, 147.7, 155.9, 160.6, 168.1. ESI-MS (LR) (m/z) $[M+H]+$ calcd for $C_{28}H_{39}N_3O_2$ 450; found 450.

Compound 15. 48 mg, 82% yield. IR (cm^{-1}) 3288, 2921, 2848, 1639. ^{1}H NMR (400 MHz, MeOH) δ 0.87 (m, 2H), 1.21 (m, 3H), 1.42 (dq, 3H, J = 12, 3.2), 1.65–1.96 (m, 11H), 2.11 (d, 2H, J = 6.8), 2.47 (m, 1H), 2.68 (t, 2H, J = 7.2), 2.86 (d, br, 2H, J = 12), 3.42 (t, 2H, J = 6.8), 4.00 (s, 2H), 7.17 (m, 3H), 7.26 (m, 4H), 7.73 (m, 2H); ^{13}C NMR (125 MHz, MeOD) δ 27.2, 27.7, 30.2, 32.3, 33.2, 36.5, 38.8, 42.5, 44.7, 54.1, 56.2, 66.8, 127.3, 128.4, 129.6, 129.9, 130.0, 133.4, 141.9, 146.8, 170.2. ESI-MS (LR) (m/z) $[M+H]^+$ calcd for $C_{28}H_{41}N_3O$, 448; found, 448.

Compound 16. 85% yield. ^{1}H NMR ($CDCl_3$) δ 1.64 (dd, J = 3.6, 11.6 Hz, 2H), 1.68 (dd, J = 3.6, 11.2 Hz, 2H), 1.96 (d, J = 13. 6 Hz, 2H), 2.01 (t, J = 11. 6 Hz, 2H), 2.83 (tt, J = 4.0, 10.0 Hz, 1H), 2.90 (d, J = 12.0 Hz, 2H), 3.10 (t, J = 5.2 Hz, 2H), 3.49 (s, 2H), 3.66 (q, J = 4 Hz, 2H), 3.83 (s, 6H), 5.05 (s, 2H), 7.11 (s, 2H), 7.24–7.36 (m, 8H), 7.47 (d, J = 8.0 Hz, 2H), 8.07 (bs, 1H); MALDI calcd for $C_{30}H_{37}N_3O_4$ = 503.63, obsd = 502.25.

Compound 17. 93% yield. ^{1}H NMR ($CDCl_3$) δ 1.61–1.72 (m, 6H), 1.95 (d, J = 10.4 Hz, 2H), 1.96 (t, J = 12.4 Hz, 2H), 2.79 (tt, J = 4.0, 10.1 Hz, 2H), 2.86 (t, J = 7.6 Hz, 2H), 2.89 (d, J = 12.4 Hz, 2H), 3.36 (q, J = 6.0 Hz, 2H), 3.47 (s, 2H), 3.81 (s, 6H), 5.04 (s, 2H), 7.07 (s, 2H), 7.23–7.35 (m, 8H), 7.45 (d, J = 8.4 Hz, 2H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{32}H_{42}N_3O_4$ 532.3163; found 532.3175.

Procedure for synthesis of compounds 18–20

Compound 19. Compound **2** (0.10 g, 0.17 mmol) was dissolved in THF (5 mL) and the solution was cooled to 0 °C. $LiAlH_4$ (20 mg, 0.51 mmol) was added and the reaction mixture was heated at reflux for 8 h. The reaction mixture was then cooled to 0 °C and saturated aqueous Na_2SO_4 was added dropwise with stirring. The mixture was dried over $MgSO_4$ and filtered. The filtrate was concentrated and the resultant residue was purified using silica gel column chromatography using 45:5:1 CH_2Cl_2/MeOH/NH_4OH to afford 55 mg of **19** as a colorless oil (64%). The amine product was converted into the HCl salt by treatment with 1 M HCl/ether: ^{1}H NMR (CD_3OD) δ 2.06–2.08 (m, 2H), 2.46 (d, J = 13.3 Hz, 2H), 3.17 (t, J = 14.0 Hz, 2H), 3.48–3.52 (m, 3H), 3.64 (d, J = 18.0 Hz, 2H), 3,88 (s, 6H), 4.25 (s, 2H), 4.37 (s, 2H), 4.98 (s, 2H), 6.93 (s, 2H), 7.25–7.38 (m, 3H), 7.42–7.48 (m, 2H), 7.50–7.61 (m, 5H); MALDI calcd for $C_{30}H_{39}N_3O_3$ = 489.65, obsd = 486.55.

Compound 18. Reduction of **16** as described for the synthesis of compound **19** afforded **18** in 30% yield. ^{1}H NMR ($CDCl_3$) δ 1.35 (dd, $J=3.6$, 12.2 Hz, 2H), 1.39 ((2dd, $J=3.6$, 12.2 Hz, 2H), 1.63 (bs, 1H), 1.70 (quintet, $J=6.8$ Hz, 2H), 1.84 (d, $J=12.4$ Hz, 2H), 2.00 (dt, $J=2.0$, 11.6 Hz, 2H), 2.43 (tt, $J=4.0$, 10.0 Hz, 1H), 2.71 (t, $J=6.8$ Hz, 2H), 2.84 (d, $J=12.9$ Hz, 2H), 3.48 (s, 2H), 3.71 (s, 2H), 3.82 (s, 6H), 4.98 (s, 2H), 6.54 (s, 2H), 7.22–7.36 (m, 8H), 7.49 (d, $J=4.9$ Hz, 2H); MALDI calcd for $C_{31}H_{41}N_3O_3=503.68$, obsd = 502.12.

Compound 20. Reduction of **17** as described for the synthesis of compound **19**. ^{1}H NMR ($CDCl_3$) δ 1.36 (dd, $J=3.6$, 12.0 Hz, 2H), 1.40 (2dd, $J=3.6$, 12.0 Hz, 2H), 1.52–1.60 (m, 3H), 1.84 (d, $J=12.4$ Hz, 2H), 2.01 (t, $J=11.6$ Hz, 2H), 2.46 (tt, $J=4.0$, 10.4 Hz. 2H), 2.63–2.70 (m, 4H), 2.85 (d, $J=12.9$ Hz, 2H), 3.50 (s, 2H), 3.73 (s, 2H), 3.83 (s, 6H), 5.94 (s, 2H), 6.56 (s, 2H), 7.23–7.36 (m, 8H), 7.50 (d, $J=7.2$ Hz, 2H); MALDI calcd for $C_{32}H_{43}N_3O_3=517.70$, obsd = 516.47.

Compound 21. 4-Benzyloxy-3,5-dimethoxybenzyl alcohol (**52a**) (0.12 mg, 0.44 mmol) was added to a suspension of 60% NaH (20 mg, 0.48 mmol) in DMF (2 mL) under nitrogen. The mixture was stirred at room temperature for 4 h and **50a** (80 mg, 0.22 mmol) in DMF (1 mL) was added. The reaction mixture was stirred at room temperature for 48 h and concentrated in vacuo. Silica gel column chromatography of the residue using 19:1 CH_2Cl_2/EtOAc afforded 89 mg of Boc-protected precursor as a colorless oil (68%). The Boc-group was then removed following the general procedure described for the synthesis of compounds **3**–**15** to yield **21** (73%): ^{1}H NMR ($CDCl_3$) δ 1.82–1.92 (m, 2H), 1.93–2.05 (m, 2H), 2.06–2.15 (m, 2H), 2.18–2.28 (m, 2H), 2.88–3.92 (m, 3H), 3.94–3.13 (m, 2H), 3.44–3.52 (m, 2H), 3.83 (s, 6H), 4.41 (s, 2H), 4.99 (s, 2H), 6.55 (s, 2H), 7.21–7.40 (m, 8H), 7.49 (d, $J=6.8$ Hz, 2H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{31}H_{41}N_2O_4$ 505.3062; found 505.3066.

Compound 22. Synthesized from **52b** and **50a** as described for **21** to afford **22** in 78% yield. ^{1}H NMR (CD_3OD) δ 1.52 (dd, $J=3.6$, 11.6 Hz, 2H), 1.56 (dd, $J=3.6$, 12.0 Hz, 2H), 1.80–1.98 (m, 4H), 2.07 (t, $J=12.0$ Hz, 2H), 2.92–3.02 (m, 3H), 3.06 (t, $J=7.2$ Hz, 2H), 3.54 (s, 2H), 3.60 (t, $J=5.6$ Hz, 2H), 4.44 (s, 2H), 5.08 (s, 2H), 6.98 (d, $J=8.8$ Hz, 2H), 7.27 (d, $J=8.8$ Hz, 2H), 7.28–7.37 (m, 8H), 7.38–7.43 (m, 2H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{29}H_{37}N_2O_2$ 445.2865; found 445.2855.

General procedure for reductive amination to prepare 23, 24, and 48

A mixture of amine **54a** or **54b** (1 equiv) and ketone (1 equiv) in DCE (0.2 M) was treated with $NaBH(OAc)_3$ (1.5 equiv). The pH of the reaction mixture was adjusted to ~6 by adding AcOH. The mixture was stirred at room temperature for 12 h and then treated with saturated $NaHCO_3$. The aqueous phase was separated from the organic phase and re-extracted with CH_2Cl_2 (2×). The combined organic phase was dried over Na_2SO_4 and concentrated. The crude product was purified by silica gel column chromatography using 45:5:1 CH_2Cl_2/MeOH/NH4OH to afford products in 77–85% yield.

Compound 23. To a solution of 4-benzyloxyaniline·HCl (**53**) (1.83 g, 7.74 mmol) in DMF (3 mL) was added to a pre-mixed solution of *N*-Boc-4-aminobutyric acid (1.31 g, 6.45 mmol), TBTU (2.48 g, 7.74 mmol) and diisopropylethylamine (2.08 g, 16.1 mmol) in DMF (7 mL). The reaction mixture was stirred at room temperature for 18 h under nitrogen atmosphere. The mixture was concentrated in vacuo and the residue was diluted with CH_2Cl_2 (20 mL). The solution was washed with aq 1 N HCl (15 mL), saturated $NaHCO_3$ (15 mL) and then water (10 mL). The organic phase was dried over Na_2SO_4 and concentrated. Silica gel column chromatography of the crude product using 49:1 CH_2Cl_2/MeOH afforded 2.2 g of Boc-protected amine as a light brown solid (90%). The Boc-group was then removed according to the procedure for the synthesis of **3**–**15** (20% TFA, CH_2Cl_2) to afford **54a**. Reductive amination of **54a** following the general procedure afforded **23**. ^{1}H NMR ($CDCl_3$) δ 1.48 (dd, $J=3.6$, 11.6 Hz, 2H), 1.52 (dd, $J=3.6$, 11.2 Hz, 2H), 1.95 (d, $J=12.4$ Hz, 2H), 2.06 (t, $J=11.2$ Hz, 2H), 2.33 (bs, 1H), 2.52 (t, $J=6.0$ Hz, 2H), 2.57 (tt, $J=4.9$, 10.8 Hz, 1H), 2,90 (d, $J=12.0$ Hz, 2H), 3.00 (t, $J=6.0$ Hz, 2H), 3.53 (s, 2H), 5.04 (s, 2H), 6.92 (d, $J=6.8$ Hz, 2H), 7.22–7.47 (m, 12H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{28}H_{34}N_3O_2$ 444.2640; found 444.2651.

Compound 24. 54b was synthesized as described for the synthesis of **54a**. **54b** was reductively alkylated following the general procedure to afford **24** in 77% yield; ^{1}H NMR ($CDCl_3$) δ 1.38 (dd, $J=3.2$, 11.8 Hz, 2H), 1.42 (dd, $J=3.2$, 11.8 Hz, 2H), 1.75 (bs, 1H), 1.78–1.98 (m, 4H), 2.01 (dt, $J=2.0$, 11.6 Hz, 2H), 2.46 (t, $J=6.8$ Hz, 2H), 2.45–2.51 (m, 1H), 2.75 (t, $J=6.4$ Hz, 2H), 2.86 (d, $J=12.0$ Hz, 2H), 3.51 (s, 2H), 5.04 (s, 2H), 6.92 (d, $J=8.8$ Hz, 2H), 7.24–7.45 (m, 10H), 7.44 (d, $J=8.8$ Hz, 2H), 8.90 (s, 1H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{29}H_{36}N_3O_2$ 458.2797; found 458.2808.

Compound 48. 54a was reductively alkylated following the general procedure to afford **48**. ^{1}H NMR ($CDCl_3$) δ 1.36 (dd, $J=3.6$, 12.0 Hz, 2H), 1.40 (dd, $J=3.6$, 12.0 Hz, 2H), 1.88 (d, $J=11.2$ Hz, 2H), 2.05 (bs, 1H), 2.10 (t, $J=11.2$ Hz, 2H), 2.50 (t, $J=6.0$ Hz, 2H), 2.53 (tt, $J=4.0$, 10.0 Hz, 1H), 2.91 (d, $J=12.0$ Hz, 2H), 2.97 (t, $J=5.6$ Hz, 2H), 3.00 (d, $J=7.2$ Hz, 2H), 4.22 (t, $J=7.6$ Hz, 1H), 5.05 (s, 2H), 6.92 (d, $J=9.2$ Hz, 2H), 7.18–7.23 (m, 2H), 7.24–7.33 (m, 9H), 7.36–7.46 (m, 6H); MALDI calcd for $C_{35}H_{39}N_3O_2=533.70$, obsd = 532.07.

Compound 55a. To a solution of 95 mg (0.50 mmol) of Boc-β-alanine-OH in 1 mL of CH_2Cl_2 was added 124 mg (0.601 mmol, 1.2 equiv) of dicyclohexylcarbodiimde and 70 mg (0.60 mmol, 1.2 equiv) of *N*-hydroxysuccinimide. The reaction mixture was stirred at room temperature for 15 min. The mixture was filtered and added to a solution of 161 mg (0.599 mmol, 1.2 equiv) of **49b** and 0.45 mL (1.3 mmol, 2.6 equiv) of iPr$_2$EtN in 1 mL of DMF. The reaction mixture was then stirred at

room temperature for 4 h. The solvent was removed in vacuo (ca. 1 mm Hg, 30 °C) and the resultant residue brought up in 10 mL of saturated $NaHCO_{3(aq)}$ and extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were washed with water (4×15 mL), dried, concentrated in vacuo, and purified by column chromatography, eluting with 20:1 CH_2Cl_2/MeOH to afford 72 mg (0.19 mmol, 38%) **55a** as a clear oil. IR (cm^{-1}) 3314, 2920, 2845, 1702, 1640. ^1H NMR (400 MHz $CDCl_3$) 0.84 (m, 2H), 1.14 (m, 3H), 1.41 (s, 9H), 1.44 (m, 3H), 1.71 (m, 5H), 1.85 (d, br, 2H, $J=10.8$), 1.99 (t, br, 2H, $J=8$, 10), 2.07 (d, 2H, $J=7.2$), 2.36 (t, 2H, $J=6$), 2.75 (d, br, 2H, $J=12$), 3.36 (dd, 2H, $J=6$, 6.4), 3.72 (m, 1H), 5.28 (d, br, 1H, $J=5.2$), 5.86 (s, br, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.0, 26.6, 28.4, 29.8, 31.9, 35.1, 36.4, 36.7, 46.5, 52.7, 65.4, 79.2, 156.1, 170.6. ESI-MS (LR) $[M+H]^+$ calcd for $C_{20}H_{37}N_3O_3$, 368; found 368.

Compound 55b. To 1.00 g (9.70 mmol) of 4-aminobutyric acid in 3 mL of water was added 0.78 g (19 mmol, 2 equiv) of NaOH. To this solution was added 2.11 g (9.70 mmol, 1 equiv) of di-*tert*-butyl dicarbonate in 15 mL of CH_2Cl_2. The reaction mixture was stirred at room temperature for 32 h, monitoring progress of the reaction by NMR. Upon disappearance of 4-aminobutyric acid, the reaction mixture was brought to pH 5 with 1 M $HCl_{(aq)}$, and extracted with CH_2Cl_2 (2×20 mL). The combined organic layers were dried and concentrated in vacuo to afford 1.48 g (7.28 mmol, 75.1%) 4-*N*-Boc-aminobutyric acid as a clear oil. Spectra is in agreement with literature data. ^1H NMR (400 MHz, $CDCl_3$) δ 1.44 (s, 9H), 1.83 (p, 2H, $J=6.8$, 7.2), 2.40 (t, 2H, $J=7.2$), 3.19 (m, br, 2H) 4.70 (s, br, 1H); ^{13}C NMR (500 MHz, $CDCl_3$) δ 24.9, 27.4, 30.7, 39.3, 78.5, 157.1, 175.6.

55b was prepared as described for **55a** to afford 121 mg (0.318 mmol, 63.6%) as a white solid. IR (cm^{-1}) 3302, 2292, 2850, 1692, 1642. ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (m, 2H), 1.20 (m, 4H), 1.44 (s, 9H), 1.47 (m, 3H), 1.79 (m, 6H), 1.80 (p, 2H, $J=6.8$), 1.90 (m, br, 2H), 2.07 (t, br, 2H), 2.13 (d, 2H, $J=6.8$), 2.18 (t, 2H, $J=7.2$), 2.81 (d, br, 1H), 3.16 (m, br, 2H) 3.79 (m, 1H), 5.30 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 26.5, 26.6, 28.3, 28.4, 31.9, 33.8, 35.2, 39.6, 46.4, 52.7, 65.5, 79.2, 156.5, 171.9. Anal. calcd for $C_{21}H_{39}N_3O_3$: C, 66.10; H, 10.30; N, 11.01. Found C, 66.12; H, 10.10; N, 10.70.

Compound 25. To a solution of 5 mL of 4 M HCl in dioxane was added 37 mg (0.1 mmol) of **55a**. The reaction mixture was stirred at room temperature for 15 min, and the solvent was removed in vacuo. The resultant product was purified by column chromatography, eluting with a gradient of 10:1 CH_2Cl_2/MeOH to 90:10:2 CH_2Cl_2/MeOH/NH_4OH to afford 26 mg (0.096 mmol, 96%) of deprotected **55a** as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 0.83 (q, br, 2H), 1.17 (m, 4H), 1.44 (m, 3H), 1.67 (m, 6H), 1.87 (m, 2H), 2.03 (t, br, 2H), 2.08 (d, 2H $J=6.8$), 2.29 (t, 2H, $J=6$), 2.74 (d, br, 1H), 2.99 (s, br, 2H), 3.79 (m, 1H); ^{13}C NMR (125 MHz, MeOD) δ 25.7, 26.3, 30.9, 31.7, 35.0, 36.9, 37.4, 43.8, 52.7, 65.5, 172.4.

To a solution of 26 mg (0.096 mmol) of the compound described above in 1 mL of THF was added 26 mg (0.12 mmol, 1.2 equiv) of *p*-benzyloxybenzaldehyde, AcOH diluted in THF was added dropwise to bring the pH to approximately 6, and 26 mg (0.12 mmol, 1.2 equiv) of $NaBH(OAc)_3$ was added. The reaction mixture was stirred at room temperature for 22 h. The solvent was removed in vacuo, the resultant solids brought up in saturated $NaHCO_{3(aq)}$ (20 mL), and extracted with CH_2Cl_2 (3×20 mL). The combined organic layers were dried and purified by column chromatography, eluting with a gradient of 10:1 CH_2Cl_2/MeOH to 90:10:2 CH_2Cl_2MeOH/NH_4OH to afford 22 mg (0.048 mmol, 48%) of **25** as a white solid. IR (cm^{-1}) 3500, 2925, 2859, 1658. ^1H NMR (400 MHz, $CDCl_3$) δ 0.88 (m, 2H), 1.17 (m, 4H), 1.46 (m, 3H), 1.7 (m, 6H), 1.87 (m, 2H), 2.06 (t, br, 2H, $J=11.2$), 2.10 (d, 2H, $J=7.2$), 2.36 (t, 2H, $J=6$), 2.73 (d, br, 1H), 2.88 (t, 2H $J=6$), 3.73 (s, 2H), 3.76 (m, 1H), 5.07 (s, 2H), 6.95 (m, 2H), 7.21 (m, 2H), 7.40 (m, 5H), 7.60 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 26.7, 32.0, 32.1, 35.3, 35.6, 45.1, 52.6, 52.7, 53.0, 65.7, 70.1, 114.9, 127.4, 127.9, 128.5, 129.4, 131.7, 136.9, 158.0, 171.8. HRMS-FAB (*m*/*z*) $[M+H]^+$ calcd for $C_{29}H_{41}N_3O_2$ 464.3277; found 464.3285.

Compound 26. Boc cleavage from **55b** was performed as described for synthesis of **25** to afford 38 mg (0.14 mmol, 97%) of deprotected **55b** as a white solid. ^1H NMR (400 MHz, $CDCl_3$) δ 0.85 (q, b, 2H), 1.19 (m, 4H), 1.44 (m, 3H), 1.71 (m, 6H), 1.82 (m, 4H), 2.00 (t, br, 2H), 2.08 (d, 2H, $J=7.2$), 2.26 (t, 2H, $J=7.6$), 2.78 (s, b, 1H), 3.40 (m, 2H), 3.73 (m, 1H), 6.32 (d, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.8, 26.3, 27.1, 30.9, 31.7, 32.9, 35.0, 40.1, 46.6, 52.7, 65.5, 173.2.

Reductive amination of the compound described above was performed as described for the synthesis of **25** to afford 28 mg (0.058 mmol, 41%) of **26** as a white powder. IR (cm^{-1}) 3285, 2921, 2849, 1641. ^1H NMR (400 MHz, $CDCl_3$) δ 0.84 (m, 2H), 1.19 (m, 4H), 1.43 (m, 4H), 1.73 (m, 6H), 1.83 (m, 4H), 2.00 (t, br, 2H, $J=9.2$), 2.09 (d, 2H, $J=5.6$), 2.43 (t, 2H, $J=5.6$), 2.67 (t, 2H, $J=5.6$), 2.75 (d, br, 1H, $J=8.8$), 3.71 (s, 2H), 2.75 (br, 1H), 5.10 (s, 2H), 5.85 (s, br, 1H), 6.94 (d, 2H $J=7.2$), 7.32 (m, 1H), 7.39, (m, 2H), 7.44 (m, 2H); ^{13}C NMR (125 MHz, MeOD) δ 24.6, 25.8, 26.3, 30.9, 31.7, 33.3, 35.0, 46.6, 47.3, 51.9, 52.6, 65.5, 69.5, 114.5, 127.1, 127.4, 128.0, 129.6, 130.1, 137.2, 158.3, 173.3. HRMS-FAB (*m*/*z*) $[M+H]^+$ calcd for $C_{30}H_{43}N_3O_2$ 478.3434; found 478.3421.

Compound 47. Alkylation and Boc protection of **49c** was performed as described for **50a** and **50b** to afford **50c** in 80% yield. NaN_3 displacement and reduction to the amine were performed as described for **51a** and **51b** to afford **51c**. Reductive amination of **51c** with 4-benzyloxybenzaldehyde as described for **25** and **26**, followed by Boc deprotection with 4 M HCl afforded **47** in 60% yield. ^1H NMR (400 MHz, MeOD) δ 1.25 (m, 2H), 1.66 (p, 2H), 1.75 (m, 2H), 2.04 (t, 2H), 2.38 (m, 1H), 2.66 (t, 4H), 2.86 (m, 2H), 2.95 (d, 2H), 3.70 (s, 2H), 4.19 (t, 1H), 5.04 (s, 2H), 6.91 (d, 2H), 7.16–7.43 (m, 17H).

Compound 56. To a solution of 2.00 g (8.60 mmol) *p*-hydroxybenzenesulfonic acid in 80 mL of 15% 0.5 M $NaOH_{(aq)}$ in EtOH was added 2.21 g (12.9 mmol, 1.5 equiv) of benzyl bromide. The reaction mixture was refluxed for 20 h. After cooling to room temperature, white crystals formed, which were collected and washed with ice cold CH_2Cl_2. The filtrate was concentrated in vacuo, and the resultant white powder recrystallized from H_2O to afford, in combination with the first crystal crop, 765 mg (2.67 mmol, 31%) of *p*-benzyloxybenzenesulfonic acid as white crystals. IR (cm^{-1}) 3067, 1237, 23, 1010, 842. ^1H NMR (400 MHz, $(CD_3)_2SO$) δ 5.09 (s, 2H), 6.92 (d, 2H, $J=8.5$) 7.31 (m, 1H), 7.37 (t, 2H, $J=7.6$), 7.42 (m, 2H), 7.49 (d, br, 2H, $J=8.8$); ^{13}C NMR (125 MHz, $(CD_3)_2SO$) δ 69.6, 114.1, 127.5, 128.1, 128.2, 128.8, 137.4, 141.4, 158.7. ESI-MS (LR) $[M-Na^+]^-$ calcd for $C_{13}H_{11}O_4SNa$ 263; found 263.

To 250 mg (0.776 mmol) of the sulfonic acid described above in 10 mL of CH_2Cl_2 was added 244 mg (1.17 mmol, 1.5 equiv) of PCl_5. The reaction mixture was stirred at 40 °C for 24 h, brought to room temperature and the resultant solid collected to afford 265 mg (0.937 mmol) of **56** as a pink solid in quantitative yield, which was used without further purification. IR (cm^{-1}) 2920, 2857, 1368, 1263, 1167. ^1H NMR (500 MHz, $(CD_3)_2SO$) δ 5.09 (s, 2H), 6.92 (dt, 2H, $J=9$, 2.5), 7.31 (t, 1H, $J=7$), 7.37 (t, 2H, $J=7$), 7.42 (m, 2H), 7.49 (dt, 2H, $J=9$, 2). ESI-MS (LR) $[M+H]^+$ calcd for $C_{13}H_{11}ClO_3S$, 282, found 282.

Compound 27. To a solution of 281 mg (0.738 mmol) of **51b** in 9 mL of 1:1:1 H_2O/THF/dioxane was added 0.16 mL (1.1 mmol, 1.5 equiv) of NEt_3 and 220 mg (0.810 mmol, 1.1 equiv) of **56**. The reaction mixture was stirred at room temperature for 20 h. The solvent was removed in vacuo, the resultant oil brought up in 15 mL of CH_2Cl_2, extracted with saturated $NaHCO_{3(aq)}$ (2×20 mL), the organic layer dried, and the solvent removed in vacuo. The resultant oil was purified by column chromatography, eluting with 30:1 CH_2Cl_2/MeOH, to afford 260 mg (0.433 mmol, 58.7%) of the coupled sulfonamide product as a clear oil. IR (cm^{-1}) 3257, 2922, 2850, 1686, 1365, 1157. ^1H NMR (400 MHz, $CDCl_3$) δ 0.81 (m, 2H), 1.16 (m, 3H), 1.38 (s, 9H), 1.41 (m, 2H), 1.63 (m, 11H), 1.86 (s, br, 2H), 2.06 (d, br, 2H, $J=6.8$), 2.86 (s, br, 4H), 3.18 (br, 2H), 5.06 (s, 2H), 6.99 (d, 2H, $J=8.8$), 7.35 (m, 5H), 7.77 (d, 2H, $J=8.8$); ^{13}C NMR (125 MHz, $CDCl_3$) δ 25.7, 26.3, 27.4, 29.1, 29.2, 31.6, 35.0, 40.5, 40.6, 44.7, 53.4, 65.1, 69.9, 79.7, 114.8, 127.2, 127.7, 128.2, 128.8, 132.1, 136.3, 155.6, 161.8. Anal. calcd for $C_{33}H_{49}N_3O_5S$: C, 66.08; H 8.23; N, 7.01; found C, 66.44; H, 8.07; N, 6.62.

To a solution of 4.0 M HCl in dioxane was added 130 mg (0.217 mmol) of the sulfonamide described above. The reaction mixture was stirred for 2 h at room temperature, and the solvent was removed in vacuo to afford a yellow oil which was purified by column chromatography, eluting with a gradient of 10:1 CH_2Cl_2/MeOH to 90:10:2 CH_2Cl_2/MeOH/NH_4OH to afford 61 mg (0.12 mmol, 55%) **27** as a clear oil. ^1H NMR (500 MHz, MeOD) δ 0.88 (m, 2H), 1.28 (m, 6H), 1.48 (m, 1H), 1.72 (m, 12H), 2.09 (d, 2H, $J=6.9$), 2.34 (m, 1H), 2.54 (t, 2H, $J=7.2$), 2.85 (m, 4H), 5.15 (s, 2H), 7.12 (m, 2H), 7.34 (m, 5H), 7.77 (m, 2H); ^{13}C NMR (125 MHz, MeOD) δ 25.7, 26.2, 28.9, 31.0, 31.7, 35.0, 40.8, 43.2, 52.7, 54.6, 65.4, 69.8, 114.7, 127.1, 127.7, 128.1, 128.6, 120.1, 132.2, 136.4.

Compound 57. To a solution of 295 mg (0.791 mmol) of **50b** in 1 mL of 1:1 CH_3CN/DMF was added 650 mg (4.33 mmol, 5 equiv) of NaI and 0.50 mL (6.2 mmol, 13 equiv) of 70 wt% ethylamine in water. The reaction mixture was stirred at 40 °C for 24 h. The solvent was then removed in vacuo (ca. 1 mm Hg, 30 °C), and the resultant oil was brought up in 10 mL of saturated $NaHCO_{3(aq)}$, followed by extraction with CH_2Cl_2 (3×10 mL). The combined organic layers were dried, concentrated, and purified by column chromatography, eluting with a gradient of 30:1 CH_2Cl_2/MeOH to 90:10:2 CH_2Cl_2/MeOH/NH_4OH to afford 115 mg (0.302 mmol, 38.2%) of **57** as a yellow oil. IR (cm^{-1}) 3323, 2922, 2858, 2477, 1697. ^1H NMR (500 MHz, MeOD) δ 0.867 (m, 2H), 1.13 (t, 3H, $J=9.6$), 1.24 (m, 3H), 1.54 (s, 9H), 1.55 (m, 1H), 1.70 (m, 12H), 1.94 (m, 2H), 2.12 (d, 2H, $J=9.2$), 2.63 (m, 4H), 2.95 (d, br, 2H, $J=4.8$), 3.17 (s, br, 2H); ^{13}C NMR (125 MHz, MeOD) δ 11.3, 26.1, 26.7, 28.4, 28.5, 31.7, 31.9, 35.6, 51.0, 51.2, 53.5, 53.6, 65.4, 65.4, 79.2, 155.0. ESI-MS (LR) $[M+H]^+$ calcd for $C_{22}H_{43}N_3O_2$ 382; found 382.

Compound 28. To a solution of 115 mg (0.303 mmol) of **57** in 3 mL of DMF was added 138 mg (0.363 mg, 1.2 equiv) of *O*-(7-azabenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate, 59 mg (0.46 mmol, 1.5 equiv) of *i*Pr_2EtN, and 173 mg (0.758 mmol, 2.5 equiv) of *p*-benzyloxy-benzoic acid. The reaction mixture was stirred at room temperature for 18 h. The solvent was removed in vacuo (ca. 1 mm Hg, 30 C), and the residue was dissolved in 10 mL of saturated $NaHCO_{3(aq)}$, followed by extraction with CH_2Cl_2 (2×15 mL). The solvent was removed in vacuo, and the resultant oil purified by column chromatography, eluting with 30:1 CH_2Cl_2 to afford 44 mg (0.074 mmol, 24%) of the coupled product as a colorless oil. IR (cm^{-1}) 2921, 2849, 1625, 1609. ^1H NMR (400 MHz, MeOD) δ 0.81 (m, 2H), 1.17 (m, 6H), 1.43 (s, br, 11H), 1.66 (m, br, 13H), 2.07 (d, br, 2H, $J=6.8$), 2.78 (m, 2H), 3.13 (m, br, 6H), 5.06 (s, 2H), 6.94 (d, 2H, $J=8.8$), 7.37 (m, 7H). ESI-MS (LR) $[M+H]^+$ calcd for $C_{36}H_{53}N_3O_4$ 592; found 592.

To a solution of 2 mL of 4.0 M HCl in dioxane was added 44 mg (0.074 mmol) of the product described above. The reaction mixture was stirred at room temperature for 2 h, the solvent was removed in vacuo, and the resultant product was purified by column chromatography, eluting with a gradient of 10:1 CH_2Cl_2/MeOH to 90/10/2 CH_2Cl_2/MeOH/NH_4OH to afford 17 mg (0.035 mmol, 47%) of **28** as a colorless oil. ^1H NMR (300 MHz, 1:1 MeOD:CD_2Cl_2) δ 1.17 (m, br, 9H), 1.78 (m, br, 6H), 2.09 (m, br, 6H), 2.92 (d, 2H, $J=6.3$), 3.09 (m, 4H), 3.49 (m, 7H), 5.11 (s, 2H), 7.03 (d, 2H, $J=11.6$), 7.36 (m, 7H). HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{31}H_{45}N_3O_2$ 492.3590; found 429.3582.

Compound 29. Prepared according to general procedure outlined for compounds **3**–**15** to afford **29** in 80% yield. ^{1}H NMR ($CDCl_3$) δ 1.59 (dd, J = 3.6, 12.2 Hz, 2H), 1.63 (dd, J = 3.6, 12.2 Hz, 2H), 1.70 (d, J = 10.3 Hz, 2H), 1.79 (quintet, J = 5.6 Hz, 2H), 1.92 (dt, J = 2.0, 11.6 Hz, 2H), 2.35 (s, 3H), 2.47 (tt, J = 4.0, 11.6 Hz, 1H), 2.71 (t, J = 5.6 Hz, 2H), 2.92 (d, J = 12.0 Hz, 2H), 3.46 (s, 2H), 3.54 (dd, J = 5.2, 11.2 Hz, 2H), 3.84 (s, 6H), 5.04 (s, 2H), 7.02 (s, 2H), 7.22–7.34 (m, 8H), 7.46 (d, J = 8.4 Hz, 2H), 8.52 (t, J = 4.9 Hz, 1H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{32}H_{42}N_3O_4$, 532.3168; found, 532.3175.

Compound 30. Treatment of **2** with acetyl chloride in CH_2Cl_2 afforded **30** in 88% yield. ^{1}H NMR ($CDCl_3$) δ 1.68 (d, J = 10.4 Hz, 2H), 1.76 (quintet, J = 6.0 Hz, 2H), 1.84 (dd, J = 3.6, 12.2 Hz, 2H), 1.88 (2dd, J = 3.6, 12.2 Hz, 2H), 2.04 (t, J = 12.0 Hz, 2H), 2.15 (s, 3H), 3.00 (d, J = 12.0 Hz, 2H), 3.36–3.39 (m, 2H), 3.44 (t, J = 6.4 Hz, 2H), 3.52 (s, 2H), 3.50–3.54 (m, 1H), 3,89 (s, 6H), 5.05 (s, 2H), 7.25 (s, 2H), 7.27–7.35 (m, 8H), 7.45–7.48 (m, 2H), 8.17 (t, J = 5.1 Hz, 1H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{33}H_{42}N_3O_5$ 560.3141; found 560.3124.

Compound 31. To 100 mg (0.20 mmol) of **10** in 1 mL of THF was added 0.55 mL (0.60 mmol, 3 equiv) of distilled isobutyraldehyde. AcOH was added dropwise until the pH was approximately equal to 7. To this solution was added 85 mg (0.40 mmol, 2 equiv) of $NaBH(OAc)_3$. The reaction mixture was stirred at room temperature for 12 h. The solvent was removed in vacuo and the resultant product brought up in saturated $NaHCO_{3(aq)}$ (30 mL) and extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with water (1×30 mL), dried, concentrated in vacuo and purified by column chromatography, eluting with 30:1 CH_2Cl_2/MeOH to afford 30 mg (0.052 mmol, 26%) of **31** as a colorless oil. IR (cm^{-1}) 3305, 2921, 2849, 1632. ^{1}H NMR (500 MHz, $CDCl_3$) δ 0.818 (m, 2H), 0.86 (d, 6H, J = 6.5), 1.20 (m, 4H), 1.41 (m, 1H), 1.54 (m, 3H), 1.65 (m, 11H), 2.04 (d, 2H, J = 7), 2.17 (d, 2H, J = 7), 2.46 (m, 1H), 2.60 (t, 2H, J = 5.5), 2.87 (d, br, 1H, J = 12), 3.54 (q, 2H, J = 6), 3.84 (s, 6H), 5.04 (s, 2H), 6.96 (s, 2H), 7.32 (m, 3H), 7.37 (m, br, 1H), 7.45 (m, 2H). ^{13}C NMR (125 MHz, $CDCl_3$) δ 21.1, 26.1, 26.7, 27.2, 27.2, 32.0, 35.3, 40.3, 50.3, 54.1, 54.6, 56.2, 57.8, 59.3, 65.7, 74.9, 104.3, 127.9, 128.1, 128.5, 130.9, 137.4, 139.2, 153.3, 167.4. HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{35}H_{53}N_3O_4$ 580.4114; found 580.4118.

Compound 32. Prepared as described for **31** using benzaldehyde to afford 50 mg (0.082 mmol, 41%) of **32** as a colorless oil. IR (cm^{-1}) 3306, 2921, 2848, 1651. ^{1}H NMR (400 MHz, $CDCl_3$) 0.84 (m, 2H), 1.19 (m, 3H), 1.45 (m, 1H), 1.68 (m, 13H), 2.09 (d, br, 2H, J = 6.5), 2.56 (m, 1H), 2.70 (t, 2H, J = 5.50), 2.94 (d, br, 2H, J = 10), 3.49 (q, 2H, J = 5.5), 3.61 (s, 2H), 3.71 (s, 6H), 5.05 (s, 2H), 6.88 (s, 2H), 7.15–7.35 (m, 8H), 7.46 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 26.1, 26.3, 26.7, 27.2, 32.0, 35.3, 40.1, 48.9, 54.0, 54.7, 56.1, 57.0, 65.5, 75.9, 104.5, 127.1, 127.9, 128.1, 128.3, 128.5, 129.0, 130.4, 136.6, 137.5, 139.3, 153.2, 167.0. HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{38}H_{51}N_3O_4$ 614.3958; found 614.3951.

Compound 58. N-*Debenzylation*. Compound **50a** (5.42 g, 14.8 mmol) was dissolved in EtOAc (20 mL) and to the solution was added Pd/C (1.0 g) followed by AcOH (0.9 g, 14.8 mmol). The reaction vessel was flushed with H_2 and stirred at room temperature for 36 h. The reaction mixture was then filtered through a Celite pad and rinsed with MeOH. The filtrate was concentrated and purified by silica gel column chromatography using 45:5:1 CH_2Cl_2/MeOH/NH_4OH to afford 3.5 g of *N*-debenzylated product as an off-white solid (85%).

***N*-Alloc protection.** To a solution of the amine (0.30 g, 1.08 mmol) obtained above and Et_3N (0.16 g, 1.62 mmol) in CH_2Cl_2 (10 mL) was added dropwise a solution of allyl chloroformate (0.16 g, 1.30 mmol) in CH_2Cl_2 (5 mL) at 0 °C. The reaction mixture was stirred at 0 °C for 15 min. The reaction solution was washed with 1 N HCl (10 mL) and then saturated $NaHCO_3$ (10 mL). The organic layer was dried over Na_2SO_4 and concentrated. Silica gel column chromatography using 97:3 CH_2Cl_2/MeOH yielded 0.33 g of product as an off-white solid (85%).

Azide **58** was prepared according to the procedure described previously for compounds **51a** and **51b**: ^{1}H NMR ($CDCl_3$) δ 1.43 (s, 9H), 1.52–1.67 (m, 4H), 1.76 (quintet, J = 6.8 Hz, 2H), 2.77 (bs, 2H), 3.11 (bs, 2H), 3.29 (t, J = 6.4 Hz, 2H), 4.24 (bs, 2H), 4.57 (d, J = 5.2 Hz, 2H), 5.20 (dd, J = 1.2, 12.0 Hz, 1H), 5.28 (dd, J = 1.6, 17.2 Hz, 1H), 5.93 (ddd, J = 1.2, 12.0, 17.2 Hz, 1H).

Compound 59. Amide **59** was prepared by reduction of azide **58** (as for **51a** and **51b**) and acylated to afford **59** in 90% overall yield: ^{1}H NMR ($CDCl_3$) δ 1.48 (s, 9H), 1.62–1.80 (m, 6H), 2.63 (t, J = 9.6 Hz, 2H), 3.15 (d, J = 12.4 Hz, 2H), 3.44 (t, J = 6.0 Hz, 2H), 3.41–3.48 (m, 2H), 3.71 (bs, 1H), 3.89 (s, 6H), 5.06 (s, 2H), 7.22 (s, 2H), 7.29–7.36 (m, 3H), 7.48 (d, J = 6.8 Hz, 2H), 8.20 (bs, 1H).

General procedure of the synthesis of compounds 33–43

In a parallel format, a solution of the amine **59** (50 mg, 0.095 mmol) in MeOH (1 mL) was placed in a sample vial. To this solution was added aldehyde (0.47 mmol) in MeOH (1 mL) followed by $NaBH_3CN$ (930 mg, 0.47 mmol). The pH of the reaction was adjusted to ~6 by adding AcOH (50 μL). The reaction mixture was stirred at room temperature for 48 h and then diluted with CH_2Cl_2 (3 mL). A strongly acidic ion exchange resin (1 mL resin bed) was added to the solution and stirred for 20 h. The resin was filtered and rinsed with MeOH (2×3 mL). The resin was then eluted with 2 M NH_3 in MeOH (2×3 mL) and the filtrate was concentrated. Chromatograpy of the product on a short plug of using 45:5:1 CH_2Cl_2/MeOH/NH_4OH yielded pure compounds **33**–**43** (34–94% yield). Each compound was stored as the HCl salt which was obtained by treating the oily residue with 1 M HCl/ether followed by concentration.

Compound 33. ^{1}H NMR ($CDCl_3$) δ 1.27 (dd, J = 3.6, 12.2 Hz, 2H), 1.31 (dd, J = 3.6, 12.2 Hz, 2H), 1.64 (bs, 1H), 1.75 (quintet, J = 6.0 Hz, 2H), 1.82 (d, J = 12.8 Hz, 2H), 2.02 (t, J = 10.0 Hz, 2H), 2.40 (tt, J = 4.0, 10.0 Hz, 1H), 2.83 (t, J = 5.2 Hz, 2H), 2.90 (d, J = 12.0 Hz, 2H), 2.95 (d, J = 5.2 Hz, 2H), 3.55 (q, J = 5.6 Hz, 2H), 3.78 (s, 6H), 4.18 (t, J = 7.6 Hz, 1H), 5.05 (s, 2H), 7.00 (s, 2H), 7.16–7.37 (m, 13H), 7.48 (d, J = 6.8 Hz, 2H), 8.11 (bs, 1H); MALDI calcd for $C_{38}H_{45}N_3O_4$ = 607.78, obsd = 605.57.

Compound 34. ^{1}H NMR ($CDCl_3$) δ 1.39 (dd, J = 3.6, 12.2 Hz, 2H), 1.43 (dd, J = 3.6, 12.2 Hz, 2H), 1.79 (quintet, J = 6.0 Hz, 2H), 1.81 (bs, 1H), 1.93 (d, J = 12.0 Hz, 2H), 2.04 (t, J = 12.0 Hz, 2H), 2.45 (tt, J = 4.0, 10.0 Hz, 1H), 2.57 (dd, J = 6.0, 10.8 Hz, 2H), 2.79 (dd, J = 6.0, 10.8 Hz, 2H), 2.85 (t, J = 6.0 Hz, 2H), 2.96 (d, J = 11.6 Hz, 2H), 3.56 (q, J = 5.6 Hz, 2H), 3.86 (s, 6H), 5.05 (s, 2H), 7.02 (s, 2H), 7.19 (d, J = 5.6 Hz, 2H), 7.27–7.36 (m, 3H), 7.47 (d, J = 6.8 Hz, 2H), 7.98 (bs, 1H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{32}H_{42}N_3O_4$ 532.3176; found 532.3174.

Compound 35. ^{1}H NMR ($CDCl_3$) δ 1.35 (dd, J = 3.6, 12.2 Hz, 2H), 1.39 (dd, J = 3.6, 12.2 Hz, 2H), 1.75 (quintet, J = 5.6 Hz, 2H), 1.86 (d, J = 12.4 Hz, 2H), 2.03 (t, J = 11.6 Hz, 2H), 2.43 (tt, i = 4.0, 10.0 Hz, 1H), 2.82 (t, J = 5.6 Hz, 2H), 2.94 (d, J = 11.6 Hz, 2H), 3.55 (q, J = 5.6 Hz, 2H), 3.68 (s, 2H), 3.76 (s, 3H), 3.81 (s, 6H), 5.05 (s, 2H), 6.99 (s, 1H), 7.01 (s, 2H), 7.12 (dt, J = 1.2, 6.8 Hz, 1H), 7.23 (dt, J = 1.2, 6.8 Hz, 1H), 7.29–7.36 (m, 4H), 7.47 (d, J = 8.4 Hz, 2H), 7.68 (d, J = 7.6 Hz, 1H), 8.05 (bs, 1H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{34}H_{43}N_4O_4$ 571.3295; found 571.3284.

Compound 36. ^{1}H NMR ($CDCl_3$) δ 1.39 (dd, J = 3.6, 12.2 Hz, 2H), 1.43 (dd, J = 3.6, 12.2 Hz, 2H), 1.75 (quintet, J = 6.0 Hz, 2H), 1.87 (d, J = 11.2 Hz, 2H), 2.04 (t, J = 11.6 Hz, 2H), 2.45 (tt, J = 4.0, 10.0 Hz, 1H), 2.84 (t, J = 5.6 Hz, 2H), 2.88 (d, J = 11.6 Hz, 2H), 3.56 (q, J = 6.4 Hz, 2H), 3.63 (s, 2H), 3.87 (s, 6H), 5.06 (s, 2H), 7.03 (s, 2H), 7.28–7.36 (m, 3H), 7.45–7.49 (m, 5H), 7.71 (s, 1H), 7.79–7.84 (m, 3H), 8.14 (bs, 1H); MALDI calcd for $C_{35}H_{41}N_3O_4$ = 567.72, obsd = 565.43. Anal. calcd for $C_{35}H_{41}N_3O_4$2HCl: C, 65,62; H, 6.76; N, 6.56; Found: C, 65.48; H, 6.60; N, 6.52.

Compound 37. ^{1}H NMR ($CDCl_3$) δ 1.38 (dd, J = 3.0, 12.0 Hz, 2H), 1.42 (dd, J = 3.0, 12.0 Hz, 2H), 1.71 (bs, 1H), 1.76 (t, J = 5.6 Hz, 2H), 1.89 (d, J = 10.4 Hz, 2H), 2.05 (t, J = 11.2 Hz, 2H), 2.46 (tt, J = 4.0, 10.0 Hz, 1H), 2.86 (t, J = 5.6 Hz, 2H), 2.89 (d, J = 11.6 Hz, 2H), 3.51 (s, 2H), 3.57 (q, J = 6.0 Hz, 2H), 3.88 (s, 6H), 5.06 (s, 2H), 7.03 (s, 2H), 7.27–7.38 (m, 6H), 7.44–7.48 (m, 4H), 7.54–7.61 (m, 4H), 8.12 (bs, 1H); MALDI calcd for $C_{37}H_{43}N_3O_4$ = 593.76, obsd = 591.36. Anal. calcd for $C_{37}H_{43}N_3O_4$2HCl: C, 66.80; H, 6.80; N, 6.30; Found: C, 66.80; H, 7.00; N, 6.42.

Compound 38. ^{1}H NMR ($CDCl_3$) δ 1.35 (dd, J = 3.6, 12.2 Hz, 2H), 1.39 (dd, J = 3.6, 12.2 Hz, 2H), 1.77 (quintet, J = 6.0 Hz, 2H), 1.87 (d, J = 12.0 Hz, 2H), 1.95 (t, J = 12.0 Hz, 2H), 2.46 (tt, J = 4.0, 10.0 Hz, 1H), 2.81 (d, J = 12.0 Hz, 2H), 2.85 (t, J = 5.6 Hz, 2H), 3.37 (s, 2H), 3.56 (q, J = 4.0 Hz, 2H), 3.87 (s, 6H), 5.06 (s, 2H), 5.93 (s, 2H), 6.70 (dd, J = 1.2, 8.0 Hz, 1H), 6.74 (d, J = 7.6 Hz, 1H), 6.82 (d, J = 1.2 Hz, 1H), 7.02 (s, 2H), 7.28–7.36 (m, 3H), 7.47 (d, J = 7.2 Hz, 2H), 8.10 (bs, 1H); MALDI calcd for $C_{32}H_{39}N_3O_6$ = 561.67, obsd = 560.20. Anal. calcd for $C_{39}N_3O_6$2HCl: C, 60.57; H, 6.51; N, 6.62; Found: C, 60.46; H, 6.73; N, 6.65.

Compound 39. ^{1}H NMR ($CDCl_3$) δ 1.36 (dd, J = 3.6, 12.2 Hz, 2H), 1.41 (dd, J = 3.6, 12.2 Hz, 2H), 1.76 (quintet, J = 5.6 Hz, 2H), 1.87 (d, J = 11.6 Hz, 2H), 1.98 (t, J = 11.6 Hz, 2H), 2.35 (s, 3H), 2.46 (tt, J = 4.0, 10.0 Hz, 1H), 2.84 (t, J = 6.0 Hz, 2H), 2.85 (d, J = 11.6 Hz, 2H), 3.43 (s, 2H), 3.55 (q, J = 6.0 Hz, 2H), 3.86 (s, 6H), 5.06 (s, 2H), 7.03 (s, 2H), 7.08 (t, J = 7.2 Hz, 2H), 7.11 (s, 1H), 7.20 (t, J = 7.2 Hz, 1H), 7.27–7.39 (m, 3H), 7.47 (d, J = 6.8 Hz, 2H), 8.12 (bs, 1H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{32}H_{42}N_3O_4$ 532.3163; found 532.3175.

Compound 40. ^{1}H NMR ($CDCl_3$) δ 1.36 (dd, J = 3.6, 12.2 Hz, 2H), 1.41 (dd, J = 3.6, 12.2 Hz, 2H), 1.76 (quintet, J = 6.0 Hz, 2H), 1.87 (d, J = 12.4 Hz, 2H), 2.02 (t, J = 12.0 Hz, 2H), 2.44 (tt, J = 4.0, 10.0 Hz, 1H), 2.58 (t, J = 6.0 Hz, 2H), 2.83 (t, J = 6.4 Hz, 2H), 2.90 (d, J = 12.0 Hz, 2H), 3.55 (t, J = 6.0 Hz, 2H), 3.56 (t, J = 6.0 Hz, 2H), 3.86 (s, 6H), 4.53 (s, 2H), 5.05 (s, 2H), 7.01 (s, 2H), 7.28–7.36 (m, 8H), 7.47 (d, J = 6.8 Hz, 2H), 7.99 (bs, 1H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{33}H_{44}N_3O_5$, 562.3272; found, 562.3281.

Compound 41. ^{1}H NMR ($CDCl_3$) δ 1.32 (dd, J = 3.6, 12.2 Hz, 2H), 1.36 (dd, J = 3.6, 12.2 Hz, 2H), 1.76 (quintet, J = 6.0 Hz, 2H), 1.87 (d, J = 12.0 Hz, 2H), 1.97 (t, J = 11.6 Hz, 2H), 2.00 (bs, 1H), 2.46 (tt, J = 4.0, 10.0 Hz, 1H), 2.79 (d, J = 11.6 Hz, 2H), 2.82 (t, J = 6.0 Hz, 2H), 3.45 (s, 1H), 3.48 (s, 2H), 3.55 (q, J = 5.6 Hz, 2H), 3.86 (s, 6H), 5.06 (s, 2H), 6.00 (dd, J = 2.8, 5.6 Hz, 1H), 6.11 (dd, J = 2.8, 5.6 Hz, 1H), 6.74 (dd, J = 2.8, 4.2 Hz, 1H), 7.02 (s, 2H), 7.29–7.36 (m, 3H), 7.47 (d, J = 8.4 Hz, 2H), 7.93 (bs, 1H); MALDI calcd for $C_{29}H_{38}N_4O_4$ = 506.64, obsd = 504.45.

Compound 42. ^{1}H NMR ($CDCl_3$) δ 1.33 (dd, J = 3.6, 12.2 Hz, 2H), 1.38 (dd, J = 3.6, 12.4 Hz, 2H), 1.73 (quintet, J = 6.0 Hz, 2H), 1.86 (d, J = 12.4 Hz, 2H), 1.93 (t, J = 11.6 Hz, 2H), 2.22 (s, 3H), 2.41 (tt, J = 4.0, 10.4 Hz, 1H), 2.76 (d, J = 12. 0 Hz, 2H), 2.80 (t, J = 6.0 Hz, 2H), 3.52 (q, J = 6.4 Hz, 2H), 3.83 (s, 6H), 5.03 (s, 2H), 7.00 (s, 2H), 7.25–7.36 (m, 3H), 7.45 (d, J = 8.0 Hz, 2H), 7.97 (t, J = 4.8 Hz, 1H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{25}H_{36}N_3O_4$ 442.2706; found 442.2728.

Compound 43. ^{1}H NMR ($CDCl_3$) δ 1.35 (dd, J = 3.6, 12.0 Hz, 2H), 1.39 (dd, J = 3.6, 12.0 Hz, 2H), 1.79 (quintet, J = 5.6 Hz, 2H), 1.89 (d, J = 12.0 Hz, 2H), 2.06 (t, J = 11.6 Hz, 2H), 2.49 (tt, J = 4.0, 10.8 Hz, 1H), 2.82 (t, J = 6.0 Hz, 2H), 2.89 (d, J = 11.6 Hz, 2H), 2.97 (d, J = 7.2 Hz, 2H), 3.54 (q, J = 6.0 Hz, 2H), 4.20 (t, J = 7.6 Hz, 1H), 5.09 (s, 2H), 6.97 (d, J = 8.8 Hz, 2H), 7.16–7.20 (m, 2H), 7.24–7.30 (m, 8H), 7.35–7.46 (m, 5H), 7.80 (d, J = 8.8 Hz, 2H), 8.28 (t, J = 4.8 Hz, 1H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{36}H_{42}N_3O_2$ 548.3269; found 548.3277.

Compound 60. Debenzylation of **50a** according to the procedure for the synthesis of **58** followed by acylation with cyclohexane carboxylic acid using HATU provided compound **60**. ^{1}H NMR ($CDCl_3$) δ 1.14–1.30 (m, 4H), 1.50 (s, 9H), 1.51–1.60 (m, 3H), 1.61–1.80 (m, 8H), 1.90 (quintet, $J = 6.8$ Hz, 2H), 2.40–2.45 (m, 2H), 2.91–3.05 (m, 1H), 3.09–3.21 (m, 2H), 3.48 (t, $J = 6.4$ Hz, 2H), 3.93 (d, $J = 12.4$ Hz, 1H), 4.70 (d, $J = 12.0$ Hz, 1H).

Compound 44. Conversion of the chloro group in **60** to an amino group as described for the synthesis of compounds **51a** and **51b** afforded **61.** Reductive amination with 4-benzyloxybenzaldehyde as described for **23**, **24**, and **48**, afforded **44**. ^{1}H NMR ($CDCl_3$) δ 1.20–1.40 (m, 5H), 1.43–1.58 (m, 2H), 1.65–1.73 (m, 3H), 1.85–1.95 (m, 6H), 2.46 (tt, $J = 3.2$, 8.4 Hz, 1H), 2.64 (t, $J = 11.6$ Hz, 1H), 2.74 (tt, $J = 3.6$, 10.8 Hz, 1H), 2.79–2.90 (m, 4H), 3.03 (t, $J = 12.8$ Hz, 1H), 3.81 (d, $J = 4.0$ Hz, 2H), 3.88 (d, $J = 14.4$ Hz, 1H), 4.52 (d, $J = 13.2$ Hz, 1H), 5.06 (s, 2H), 6.95 (d, $J = 8.8$ Hz, 2H), 7.28 (d, $J = 8.8$ Hz, 2H), 7.31–7.44 (m, 5H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{29}H_{40}N_3O_3$ 478.3062; found 478.3070.

Compound 45. LAH reduction of **10** afforded **45** in 79% yield. ^{1}H NMR ($CDCl_3$) δ 0.83, 0.87 (2d, $J = 12.2$ Hz, 2H), 1.13–1.26 (m, 3H), 1.34 (dd, $J = 3.6$, 12.4 Hz, 2H), 1.38 (2dd, $J = 3.6$, 12.4 Hz, 2H), 1.42–1.50 (m, 1H), 1.64–1.80 (m, 9H), 1.81–1.92 (m, 4H), 2.08 (d, $J = 7.2$ Hz, 2H), 2.41 (tt, $J = 3.2$, 8.4 Hz, 1H), 2.72 (dt, $J = 1.6$, 6.8 Hz, 2H), 2.81 (d, $J = 12.0$ Hz, 2H), 3.72 (s, 2H), 3.83 (s, 6H), 4.99 (s, 2H), 6.5 (s, 2H), 7.28–7.49 (m, 3H), 7.50 (d, $J = 8.4$ Hz, 2H); HRMS-FAB (m/z) $[M+H]^+$ calcd for $C_{35}H_{40}N_3O_2$, 534.3118; found, 532.3121.

Compound 46. LAH reduction of compound **33** afforded **46** in 44% yield. ^{1}H NMR ($CDCl_3$) δ 1.24 (dd, $J = 3.6$, 12.2 Hz, 2H), 1.29 (2dd, $J = 3.6$, 12.2 Hz, 2H), 1.72 (quintet, $J = 6.8$ Hz, 2H), 1.79 (d, $J = 11.6$ Hz, 2H), 1.96 (bs, 1H), 2.05 (dt, $J = 2.0$, 9.6 Hz, 2H), 2.41 (tt, $J = 3.2$, 8.4 Hz, 1H), 2.71 (dt, $J = 2.0$, 6.8 Hz, 2H), 2.87 (d, $J = 11.6$ Hz, 2H), 2.96 (d, $J = 7.6$ Hz, 2H), 3.72 (s, 2H), 3.81 (s, 6H), 4.19 (t, $J = 8.0$ Hz, 1H), 4.99 (s, 2H), 6.54 (s, H), 7.19–7.20 (m, 2H), 7.23–7.31 (m, 9H), 7.33–7.37 (m, 2H), 7.51 (d, $J = 8.0$ Hz, 2H); MALDI calcd for $C_{38}H_{47}N_3O_3 = 593.80$, obsd = 590.09.

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