Discovery of Orally Bioavailable 1,3,4-Trisubstituted 2-Oxopiperazine-Based Melanocortin-4 Receptor Agonists as Potential Antiobesity Agents

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A study that was designed to identify plausible replacements for highly basic guanidine moiety contained in potent MC4R agonists, as exemplified by **1**, led to the discovery of initial nonguanidine lead **5**. Propyl analog **23** was subsequently found to be equipotent to **5**, wherea analogs bearing smaller and branched alkyl groups at the 3 position of the oxopiperazine template demonstrated reduced binding affinity and agonist potency for MC4R. Acylation of the NH_2 group of the 4F-D-Phe residue of 3-propyl analog **23** significantly increased the binding affinity and the functional activity for MC4R. Analogs with neutral and weakly basic capping groups of the D-Phe residue exhibited excellent MC4R selectivity against MC1R whereas those with an amino acid had moderate MC4R/MC1R selectivity. We have also demonstrated that compound **35** showed promising oral bioavailability and a moderate oral half life and induced significant weight loss in a 28-day rat obesity model.

Introduction

Five melanocortin subtype receptors (MC1R−MC5R) have been identified and cloned. The endogenous peptide agonists of MCRs[a] α-, *β*-, and *γ*-melanocyte stimulating hormones (MSH) and adrenocorticotropic hormone (ACTH) are derived by post-translational cleavage from a common precursor protein, proopiomelanocortin (POMC).[1] The finding that MCRs are involved in the regulation of a wide range of physiological responses has stimulated intensive research interest in developing selective, nonpeptide small molecule ligands as potential therapeutic agents for melanocortin-mediated diseases.[2−5] The majority of research efforts in this area has been focused on the design of MC4R agonists and antagonists for the treatment of obesity, sexual dysfunction, and involuntary weight-loss associated diseases.[6−21]

We recently reported the discovery of a series of potent 1,3,4-trisubstituted 2-oxopiperazine based melanocortin-4 agonists in which the Arg-Nal dipeptide was conformationally constrained by a six-membered ring scaffold,[22] as exemplified by **1** (Table 1). All of these 2-oxopiperazine analogs contain a highly basic guanidine group that might be important for the high potency but detrimental for the cellular permeability and oral absorption, as indicated by the Caco-2 monolayer data (absorptive/exsorptive permeability coefficient of $0.2/0.2 \times 10^{-4}$ vs $1.0/1.3 \times 10^{-4}$ cm/min for **1** and mannitol, respectively). To develop orally bioavailable MC4R agonists, we thus set out to explore the replacement of the guanidine moiety of **1**. A similar strategy has been explored by Marsilje and coworkers to design MC4R antagonists with improved oral exposure, where basic amidine moiety was replaced with a series of imidazole ring systems.[23] The initial target compounds possessing neutral urea groups[22] or moieties with lower basicity (**2** and **3**, Scheme 1) exhibited significantly reduced MC4R agonist potency. However, during this study, the allyl tripeptidomimetic intermediate **5** was unexpectedly found to be a potent and selective MC4R agonist (Table 2). Herein we report the discovery of orally bioavailable 1,3,4-trisubstituted 2-oxopiperazine-based MC4R agonists on the basis of this new lead (**5**) through the modification of the C-3 side chain of the oxopiperazine template and the capping of the 4F-D-Phe residue of the top side chain.

Chemistry

The synthetic approach to **2** and **3** features a reductive amination of aldehyde **15**. The key ketopiperazine intermediate **12** was synthesized by the use of reaction sequences, as reported by Just[24] (Scheme 1). Allyl glycine **6** was coupled to L-2-naphthylalanine methylester **7** to produce dipeptide **8**, which was converted to 2-nitrophenylsulfonyl (Nos) derivative **10** in two steps. The heating of a mixture of **10** and 1,2-dibromoethane in the presence of potassium carbonate to 60 °C in DMF afforded 3-allyl 2-oxopiperazine **11**. The removal of the Nos group of **11**, followed by PyBOP-mediated coupling to 4F-D-Phe gave tripeptidomimetic **13**. Saponification of the ester of **13** and the subsequent coupling of the acid to methylamine furnished methylamide intermediate **14**. The oxidative cleavage of the olefin functionality of **14** with $NaIO_4$ and OsO_4 afforded aldehyde **15**, which was treated with the appropriate amines and $NaBH(OAc)_3$ to produce the target compounds **2** and **3**. We synthesized aminoguanidine analog **4** by coupling aldehyde **15** to α-aminoguanidine. The treatment of Boc intermediate **14** with trifluoroacetic acid (TFA) gave amino analog **5**.

The synthesis of 3-alkyl 2-oxopiperazine analogs was carried out by the use of reaction sequences that were similar to those that were delineated in Scheme 1 (Scheme 2). The key

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[a] Abbreviations: MCR, melanocortin receptor; ECDI, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride; PyBOP, benzotriazole-1-yl-oxy-tris-pyrrolidino-phosphonium hexafluorophosphate; HOBt, 1-hydroxybenzotriazole; NMM, 4-methylmorpholine; Aib, α-aminoisobutyric acid; Tic, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid; DMF, *N*,*N*-dimethylformamide.

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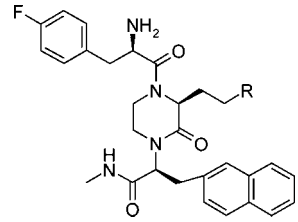
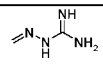
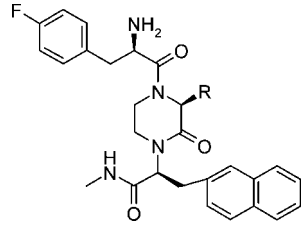
Table 1. Binding Affinity and Agonist Potency of Analogs Containing Groups with Lower Basicity[a]



Compound	R	MC1R Ki, nM	MC3R Ki, nM	MC4R Ki, nM	MC4R EC50, nM (Emax, %)
1		1120±151	470±50	11±1	2.2± 0.2(106)
2		16832±452	26323±3256	624±93	391±109(116)
3		4469±362	8734±416	556±89	167±09(102)
4		63±7	76±6	1.4±0.5	0.9±0.1(103)
45	NH_2	5820±514	4122±240	189±59	45±9(105)

[a] The data represent the mean of at least three experiments ± SEM, unless otherwise indicated.

Table 2. Binding Affinity and Agonist Activity of 3-Alkyl 2-Oxopiperazine Analogs[a]



		MC1R		MC3R		MC4R	
compd	R	K_i (nM)	EC50 (nM) (E_{max}, %)	K_i (nM)	EC50 (nM) (E_{max}, %)	K_i (nM)	EC50 (nM) (E_{max}, %)
5	allyl	4677 ± 274	(150)4 ± 163(59)	1080 ± 262	148 ± 28(66)	71 ± 12	34 ± 6(109)
23	propyl	10000 ± 0	1505 ± 94(59)	727 ± 66	149 ± 18(80)	76 ± 10	28 ± 7(92)
24	ethyl	10000 ± 0	1697 ± 54(64)	947 ± 121	237 ± 39(86)	180 ± 47	31 ± 8(100)
25	methyl	23400 ± 0	2300 ± 291(73)	2832 ± 307	300 ± 22(87)	98 ± 8	37 ± 9(85)
26	*i*-propyl	10000 ± 0	1523 ± 224(49)	1862 ± 467	271 ± 134(73)	714 ± 219	83 ± 2(90)

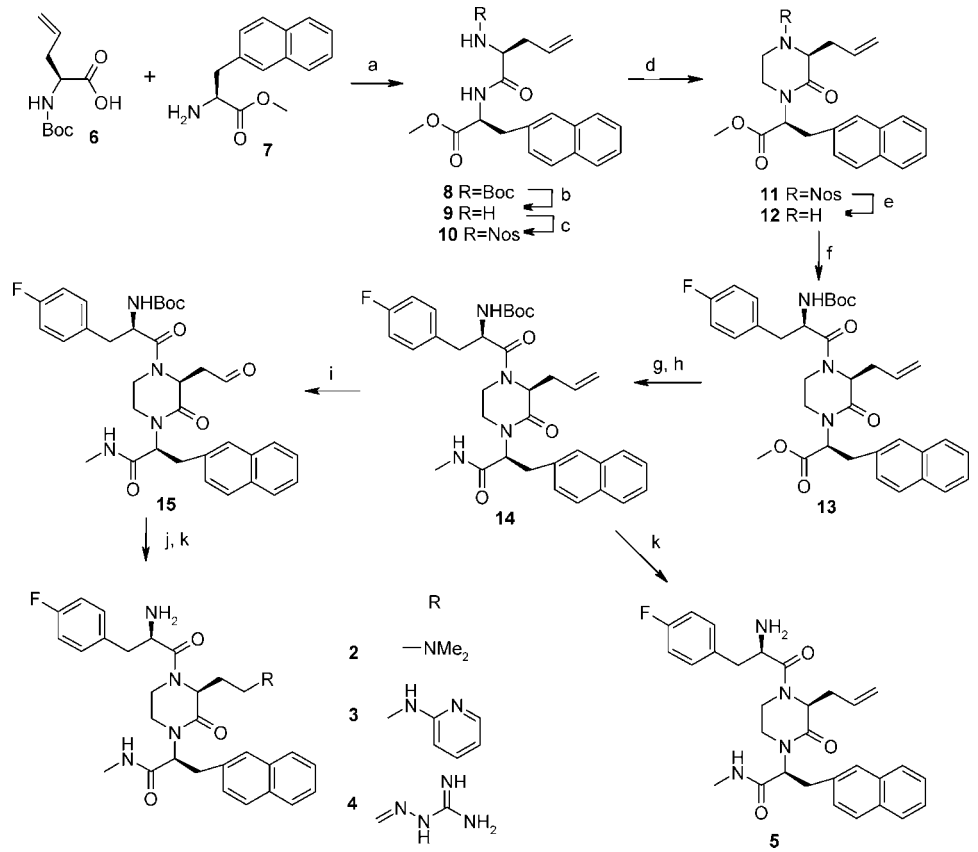
[a] The data represent the mean of at least three experiments ± SEM, unless otherwise indicated.

tripeptidomimetic intermediate **22** was prepared from appropriate amino acid **16** in six steps and was then treated with TFA to produce the target tripeptidomimetics **23**−**26**. For the synthesis of propyl analogs **27**−**44** bearing an acylated 4F-D-Phe residue, **23** was reacted with appropriate acids under EDCI activation. In the case of tetrapeptidomimetics (**35**−**44**), **23** was coupled to the Boc-protected amino acids, and the resulting products were treated with TFA.

Results and Discussion

The feasibility of replacing the basic guanidine functionality of **1** by groups with lower basicity was preliminarily explored through the synthesis and screening of **2** and **3.** Amino analog **45** was prepared by the use of another approach,[22] and its biological data were also included in Table 1 for comparison. As shown by the data that are listed in Table 1, the dimethylamino (**2**) and the aminopyridino (**3**) analogs showed 56- and 50-fold reduced binding affinities, respectively, as compared with **1**. Nevertheless, analog **45**, which contains a primary amine at the C-3 side chain, exhibited only 17-fold reduced affinity compared with guanidine **1**. All three compounds had significantly reduced agonist potencies as well. It should be noted that the weak activity that was seen with **2** might also be due to the nonoptimal location of the cation point charge as compared with the 3-methylene linked guanidine moiety. Aminoguanidine has been used as a guanidine replacement,[25] and therefore, analog **4** was synthesized from the common aldehyde intermediate **15**. Interestingly, **4** was found to have significantly improved binding affinity and agonist potency (EC50, 0.9 nM) for MC4R as well as improved potency for MC1R and MC3R. These results appear to suggest that a guanidine moiety was critical for achieving good MC4R agonist potency.

Scheme 1. Synthesis of 1,3,4-Trisubstituted 2-Oxopiperazine-Based Tripeptidomimetics[a]



[a] Reagents and conditions: (a) EDCI, HOBt, NMM, DMF; (b) TFA, CH_2Cl_2; (c) 2-nitrobenzenesulfonyl (Nos) chloride, Et_3N, $CHCl_3$; (d) 1,2-dibromoethane, K_2CO_3, DMF, 60 °C; (e) 4-mercaptophenol, K_2CO_3, CH_3CN; (f) BOC-D-Phe(4F)-OH, PyBOP, Et_3N, CH_2Cl_2; (g) LiOH, CH_3OH/H_2O; (h) NH_2CH_3, EDCI, HOBt, NMM, DMF; (i) OsO_4, $NaIO_4$, THF/H_2O; (j) **2** and **3**, amine (dimethylamine), 2-aminopyridine, $NaBH(OAc)_3$, 1,2-dichloroethane, **4**, α-aminoguanidine nitrate, ethanol/water (3/1), reflux; and (k) TFA, CH_2Cl_2.

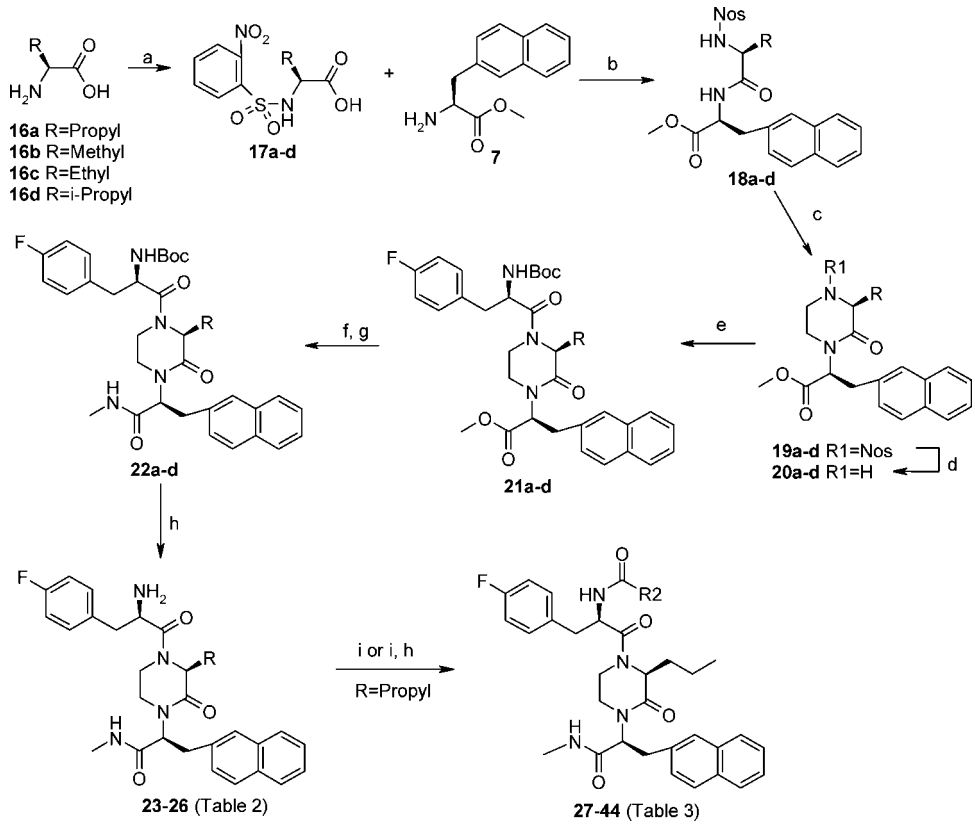
During this study, however, we became interested in allyl intermediate **14**, which was a tripeptidomimetic (D-Phe-(allyl)Gly-Nal) and was different than **1** in that it possessed a vinyl group rather than a guanidine group at the C-3 side chain. Therefore, **14** was treated with TFA to produce **5** for a direct comparison with **1** and was screened against MC1R, MC3R, and MC4R. Surprisingly, allyl analog **5** showed good binding (K_i, 71 nM) and agonist potency (EC50, 35 nM) for MC4R as well as good and moderate selectivity over MC1R and MC3R, respectively. In fact, **5** exhibited only 5-fold reduced affinity compared with guanidine analog **1** and 3-fold better affinity compared with primary amino analog **45**. Furthermore, **5** demonstrated significantly improved Caco-2 monolayer permeability (absorptive/exsorptive permeability coefficient of 3.9/9.1 $\times$ 10^{-4} vs 0.2/0.2 $\times$ 10^{-4} cm/min for **1**). This MC4R potency result was somewhat unexpected in that analog **5** lacked any heteroatom that would be anticipated to be required to mimic guanidine in terms of basicity or hydrogen-bond capacity.

We initially speculated that the vinyl group might play some kind of role in the observed activity by partially mimicking guanidine. To test this hypothesis, we subsequently synthesized and evaluated propyl analog **23**. Surprisingly, we found that **23** was equipotent to allyl analog **5** as a MC4R agonist with a K_i value of 76 nM and an EC50 value of 28 nM and it showed good selectivity for MC4R over MC1R as well (~100-fold on the basis of binding affinity). As in the case of allyl analog **5**, **23** also had significant binding and potency for MC3R. These results represent the first indication that the guanidine moiety could be completely removed from the lead compounds (**1**) while maintaining significant MC4R agonist potency and excellent selectivity relative to MC1R. Because of the good MC4R agonist potency and selectivity profiles and improved cellular permeability and lower molecular weights of **5** and **23**, these compounds served as new leads in the design of orally active MC4R agonists.

To gain a better understanding of the influence of the C-3 alkyl side chain on potency and selectivity profiles, we subsequently synthesized and evaluated a series of analogs containing a variety of alkyl groups at the C-3 position. As shown by the data that are listed in Table 2, the length of the alkyl substituent had an effect on the binding affinity and the functional potency. The shortening of the propyl side chain of **23** by one methylene (**24**) or two methylenes (**25**) resulted in a slight reduction in binding affinity as well as agonist potency for MC4R and MC3R. The analog containing branched isopropyl group (**26**) had 9-fold reduced affinity compared with **23**. These results suggest that a limited space is allowed for a hydrophobic group in which an alkyl side chain is occupied. It is worthy to note that all of these analogs demonstrated a good selectivity for MC4R over MC1R.

Having confirmed the activity of 3-alkyl 2-oxopiperazine based tripeptide mimetics, we then moved on to explore the acylation of the free amino (NH_2) group of the 4F-D-Phe side chain of **23** with an aim of further improving the potency and pharmacokinetic properties of analogs. Our previous efforts on guanidine-containing 2-oxopiperazine analogs have demonstrated that the acylation of the D-Phe residue led to a significant increase in the binding affinity and agonist potency for MC4R

Scheme 2. Synthesis of 3-Alkyl 2-Oxopiperazine Analogs[a]



[a] Reagents and conditions: (a) 2-nitrobenzenesulfonyl (Nos) chloride, Et_3N, THF/H_2O; (b) EDCI, HOBt, NMM, DMF; (c) 1,2-dibromoethane, K_2CO_3, 60 °C, DMF; (d) 4-mercapto-phenol, K_2CO_3, CH_3CN; (e) BOC-D-Phe(4F)-OH, PyBOP, NMM, DMF; (f) LiOH, CH_3OH/H_2O; (g) NH_2CH_3, EDCI, HOBt, NMM, DMF; (h) TFA, CH_2Cl_2; and (i) acid (R_2CO_2H), EDCI, HOBt, NMM, DMF.

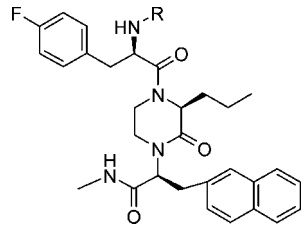
and MC1R.[22] It would be interesting to see whether a similar SAR trend would be followed within this nonguanidino 3-alkyl 2-oxopiperazine series when the same modification was implemented. Furthermore, the capping of the free amino group might also prove to be useful in modulating physicochemical parameters to improve PK profiles. Table 3 presents a series of *N*-acylated 4F-D-Phe analogs and their binding affinity and agonist potency for MC1R, MC3R, and MC4R. Consistent with the SAR that was observed with the guanidino 2-oxopiperazine series, all of the acylated analogs showed significantly enhanced binding affinities and functional potencies for MC4R as compared with nonacylated analog **23**, as shown by the biological data that are given in Table 3.

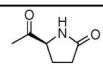
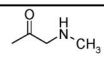
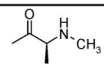
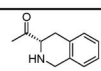
Acetylation of **23** led to analog **27**, which displayed single-nanomolar binding and functional potency as well as 170-fold selectivity for MC4R relative to MC1R. Compound **27** also had moderate selectivity for MC4R over MC3R (25-fold on the basis of affinity). The use of the more bulky pivaloyl **28** and methyl ether-containing **29** capping groups provided analogs with good potencies and selectivity for MC4R that were only slightly less potent than those of acetyl analog **27**. Analogs bearing hydrogen-bonding capacity, such as pyrrolidinone **30**, showed a K_i value of 4 nM and an EC50 value of 2 nM but were 2 times less selective for MC4R than they were for MC1R, as compared with **27**.

The enhancement in potency was also observed with heteroaromatic ring-containing acyl capping groups. For example, thiazole analog **31** showed 2-fold better binding affinity and similar agonist potency for MC4R as compared with **23**. The capping of **23** with the 4-pyridinylcarbonyl group afforded single-nanomolar MC4R agonist **32** with good and excellent selectivity over MC3R and MC1R, respectively. The moving of the basic nitrogen atom from the para position to the meta position (**33**) resulted in a slight loss of affinity and functional potency for MC4R but a ~2-fold increase in affinity and agonist potency for MC1R thus substantially reducing MC4R selectivity. Ortho isomer **34** showed a 9-fold reduced affinity and a 5-fold reduced functional potency for MC4R compared with para analog **29** as well as significantly decreased MC4R selectivity over MC1R. These data suggest that the orientation of the pyridine nitrogen might have an impact on how the analogs fit into and interact with the active binding sites of MC4R and MC1R.

Analogs that contain amino acids as the capping groups of the D-Phe residue demonstrated a slightly different SAR profile compared with those that contain neutral or weakly basic groups. In general, the capping of the D-Phe of **23** with an amino acid possessing a basic NH or NH_2 group substantially enhanced the binding affinity and the agonist potency for MC4R, but the resulting analogs exhibited lower selectivity for MC4R over MC1R than did those with neutral capping groups that were previously discussed (i.e., **27**−**29**) because of the simultaneous increases in affinity and functional activity for MC1R. For example, Aib analog **35** was equipotent to acetyl analog **27** as an MC4R agonist but had an 8-fold greater binding affinity and a 7-fold greater agonist potency for MC1R. The conformational rigidity at the α position of amino acids appeared to impact the binding affinity and the agonist potency. The tethering of two methyl groups of the Aib residue of **35** to form cyclopropyl ring **36** resulted in a 3-fold reduced affinity and a 39-fold reduced functional potency for MC4R as well as a 9-fold reduced affinity and a 5-fold reduced functional potency for

Table 3. Binding Affinity and Agonist Activity of 3-Propyl 2-Oxopiperazine Analogs Containing Acylated 4F-D-Phe[a]



Compound	R	MC1R		MC3R		MC4R	
		Ki nM	EC50 nM (Emax, %)	Ki nM	EC50 nM (Emax, %)	Ki nM	EC50 nM (Emax, %)
27		1389±290	1076±63(100)	201±23	113±22(62)	8±1	3±1(100)
28		994±104	796±161(114)	827±160	545± 82(82)	19±4	8±2(97)
29		889±99	308±20(98)	170±26	215±45(76)	14±2	5±1(99)
30		361±79	104±28(98)	128±14	25±5(92)	4±1	2±0.4(100)
31		1594±278	878± 20(119)	428±191	1100± 224(60)	36±9	37±3(100)
32		798±86	432±43(130)	309±90	103±23(91)	4±1	5±1.5(100)
33		364±3	193±33(119)	144±40	147±15(90)	6±1	12±2(100)
34		637±35	392± 4(112)	215±1	984± 115(66)	35±3	25±6(83)
35		174±19	145± 31(108)	322±28	44±4(104)	9±2	1.2±0.2(100)
36		1655±260	734±105(104)	434±120	848±240(56)	26±4	47±5(85)
37		144±8	48±5(122)	377±15	84±1(105)	11±1	10±3(119)
38		225±3	44±6(122)	471±168	58±3(113)	14±2	9±2(136)
39		271±57	98± 5(91)	282±32	52±13(91)	5±1	2.7±0.2(94)
40		101±16	50± 4(78)	207±32	51±16(93)	6±1	1.7± 0.5(92)
41		299±63	170±46(99)	165±15	40±3(107)	12±2	0.9±0.1(109)
42		100±31	69±19(79)	155±6	44±8(82)	5±1	0.9± 0.1(99)
43		17±1	10±1(111)	127±18	108±25(91)	5.2±1.3	1.3±0.3(109)
44		194±19	80±16(82)	80±15	12±1(81)	5.5±1.4	0.8±0.1(94)

[a] The data represent the mean of at least three experiments ± SEM, unless otherwise indicated.

MC1R. However, a more conformationally flexible four-membered (**37**) or five-membered (**38**) ring produced compounds that show a 2-fold better binding affinity and a 5-fold better agonist potency for MC4R as compared with cyclopropyl analog **36** and an improved affinity and agonist potency for MC1R and MC3R.

Table 4. Summary PK Parameters Following Intravenous Infusion and Oral Capsule Administration of **35** to Male Beagle Dogs (Mean (% CV))

compd, no. animals	dose (mg/kg)	route of admin	$AUC_{0\rightarrow\infty}$ (h·ng/mL)	Cl (mL/min/kg)	Vss (mL/kg)	$T_{1/2}$ (h)	MRT (h)	C_{max} (ng/mL)	T_{max} (h)	%F
35, $n = 3$	0.73	iv[a]	1132.9 (25.4)	11.2 (24.6)	941 (56.8)	3.35 (13.9)	1.32 (37.2)	4353 (35.4)	0.23 (0)	
35, $n = 3$	10	po[a]	3222.5 (61.8)			4.66 (22)	4.39 (8)	968 (42)	0.83 (17.3)	20.6

[a] iv is intravenous infusion; po is oral capsule.

Table 5. Summary of Serum Concentration Analysis Following 28 Days of Dosing in Dietary-Induced Obesity Rat Model

group	compd	BID dose (mg/kg)	sample	time (h)	concn ± SD (ng/mL)	pseudo $T_{1/2}$ (h)
3	**35**	10	C_{max}	2.00	68.7 ± (20.3)	7.30
	po		C_{min}	18.2	14.7 ± (3.4)	
4	**35**	30	C_{max}	2.16	161 ± (36.5)	9.34
	po		C_{min}	18.1	49.1 ± (7.3)	

Secondary amine-containing *N*-methyl glycine **39** and *N*-methyl alanine **40** analogs showed single-nanomolar binding affinity and functional potency for MC4R. The overall binding affinity and agonist potency profiles across three MCRs of these two analogs was similar to that of Aib **35**. Analog **41**, which bears a cyclic amino acid, proline, had a K_i value of 12 nM and subnanomolar agonist potency for MC4R as well as moderate selectivity for MC4R over MC1R and MC3R. A more conformationally flexible piperidine analog **42** exhibited similar agonist potency and a 2-fold better binding affinity for MC4R but exhibited a 3-fold better binding affinity and a 2-fold better functional potency for MC1R. The transposition of basic nitrogen of the piperidine ring to the para position (**43**) further enhanced the binding affinity and agonist potency for MC1R while retaining the functional potency for MC4R and the binding affinity for MC3R thus significantly reducing the selectivity for MC4R over MC1R. The size of the hydrophobic portion of the capping group did not appear to have significant influence on the binding affinity and functional potency for MC4R. For instance, Tic analog **44** was equipotent to piperidine analog **42** as a MC4R agonist, although it showed a 2-fold better binding affinity and a 4-fold better agonist potency for MC3R and a 2-fold reduced binding affinity for MC1R as compared with **42**.

Analogs **35** and **41** have been evaluated for intrinsic permeability. Both compounds were found to be efflux substrates, as demonstrated by Caco-2 data. Compound **35** exhibited *p*-glycoprotein-mediated efflux behavior with an absorptive/exsorptive permeability coefficient of $(0.9/8.6) \times 10^{-4}$ cm/min. For compound **41**, the efflux potential was even greater, as measured by a coefficient of $(0.2/8.0) \times 10^{-4}$ cm/min, which suggests that the replacement of the Aib group with a proline moiety resulted in a worse absorptive capability.

When administered by intravenous infusion in male beagles, **35** had moderate clearance and a high volume of distribution. The clearance was slightly lower than the hepatic plasma flow in the dog. The half life of **35** following intravenous infusion was short (~3.5 h). The bioavailability following oral gavage administration was moderate (~20%). The half life following oral gavage was intermediate (~5 h). A worthy observation is that all animals that were dosed orally with **35** lost between 0.2 and 0.5 kg between receiving the oral dose and being weighed the following week. The animals subsequently gained weight following the intravenous administration, which had a much lower plasma profile (Table 4).

In addition, in 28-day diet-induced obesity efficacy studies in rats, we found significant exposure of compound **35** at the 30 mg/kg dose, which correlated well with the weight loss that was seen over the course of the study (Table 5). Although we believe that CNS exposure is minimal with compound **35** on the basis of the Caco-2 data we did not measure brain concentrations in the study and therefore cannot rule out some CNS penetration. Compound **35** showed a significant decrease in percent weight change (14%) relative to the vehicle when dosed over 28 days and a corresponding loss of fat mass and a retention of lean mass (Figure 1).

Conclusions

We have described the design, synthesis, and structure−activity relationships of a series of potent and selective 1,3,4-trisubstituted 2-oxopiperazine based MC4R agonists. The initial non-guanidino lead emerged from the screening of an allyl intermediate, which was utilized to synthesize weakly basic group-containing 2-oxopiperazine analogs. The capping of the NH_2 group of the D-Phe residue of 3-propyl analog **23** with neutral and weakly basic acyl groups and amino acids significantly increased the binding affinity and functional activity for MC4R to afford a number of compounds that showed single- and subnanomolar potency. Analogs with neutral and weakly basic groups showed excellent MC4R selectivity against MC1R whereas those with an amino acid had moderate MC4R/MC1R selectivity. We have also demonstrated that compound **35** showed promising oral bioavailability and a moderate oral half life and induced significant weight loss in a long-term rodent obesity model. These data suggest that the MC4R pathway remains an attractive target of study for generating therapeutically useful weight-loss agents to combat the current obesity pandemic.

Experimental Section

General. Unless otherwise indicated, all reagents were purchased from commercial suppliers and were used without further purification. TLC analyses were carried out on precoated silica gel plates (Diamond MK6F). Flash column chromatography was conducted on Merck silica gel 60A (230−400) mesh. Reversed-phase preparative HPLC purification was carried out by the use of a Varian 320 and a Varian-A 10 μm (250 × 500 mm^2) column. We conducted analytical HPLC by using an Agilent polaris C18-A 3 μm column with a 15 min linear gradient from 95:5 to 1:99 0.1% H_3PO_4/CH_3CN at a flow rate of 1 mL/min with UV detection at 215 and 254 nm. ^{1}H NMR spectra were recorded on a Varian INOVA-300 NMR spectrometer and were reported as parts per million (ppm) relative to Me_4Si as the internal reference. Mass spectra data were determined on a Micromass ZMD-4000 apparatus. Elemental analyses (C, H, N) were conducted on a LECO CHNS-932 elemental analyzer.

Binding and Functional Assays. We measured the binding affinity and agonist activity of compounds at each subtype of MCR (MC1R, MC3R, MC4R) by using the previously described procedures.[26]

In Vivo Assays. A qualitative observational assessment of illness behavior was employed in an attempt to differentiate between appetite suppression and toxicity as a basis for the food-intake

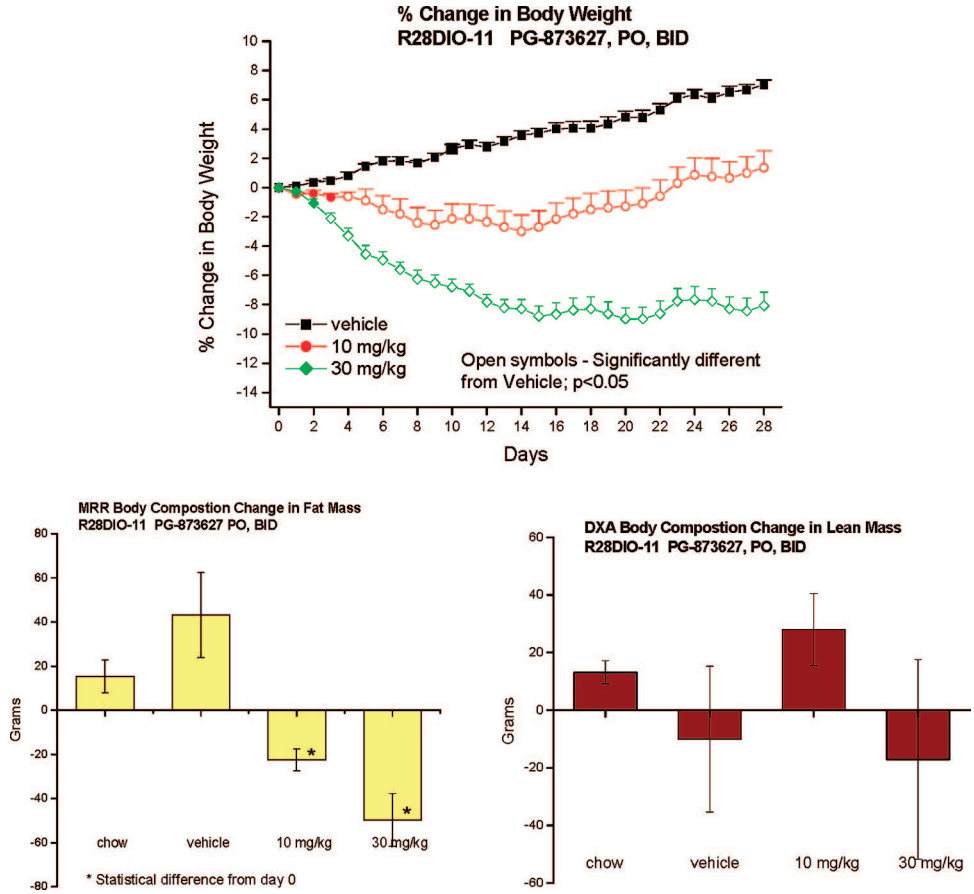


Figure 1. In vivo efficacy of compound **35** in a 28-day diet-induced rat obesity model.

reduction and body weight loss that were induced by MC4-R agonists. In this regard, animals were examined for comorbid behaviors that are observed with stress and toxicity (i.e., reduced ambulation, unkempt coats, porphyria, reduced socialization, altered defecation) at various time points over the time course of the compound administration. Such behaviors were not observed with any compound at doses that were given in these studies.

2-(2-*tert*-Butoxycarbonylamino-pent-4-enoylamino)-3-naphthalen-2-yl-propionic Acid Methyl Ester (8). To a solution of L-2-naphthylalanine methyl ester (4.1 g, 18 mmol) in DMF (50 mL) were added 2-*tert*-butoxycarbonylamino-pent-4-*R*-enoic acid (3.8 g, 18 mmol), 4-methylmorpholine (9.8 mL, 90 mmol), EDCI (4.5 g, 23.4 mmol), and 1-hydroxybenzotriazole hydrate (3.1 g, 23.4 mmol), and the reaction mixture was stirred overnight. The reaction was quenched with water and extracted with ethyl acetate (3 × 50 mL). The extracts were combined, were washed with brine, were dried over Na_2SO_4, and were concentrated. The residue was purified by flash column chromatography (silica gel, hexane/ethyl acetate 8:2 to 1:1) to produce **8** (6.4 g, 84% yield). ^{1}H NMR (300 MHz, CD_3OD, δ): 7.80 (m, 3H), 7.59 (s, 1H), 7.48 (m, 2H), 7.26 (m, 1H), 6.65 (m, 1H), 5.61 (s, 1H), 4.99 (m, 4H), 4.14 (m, 1H), 3.72 (s, 3H), 3.26 (m, 2H), 2.43 (m, 2H), 1.41 (s, 9H). MS (ESI) *m*/*z*: 427 [M + 1].

3-Naphthalen-2-yl-2-[2-(2-nitro-benzenesulfonylamino)-pent-4-enoylamino]-propionic Acid Methyl Ester (9). 2-(2-*tert*-Butoxycarbonylamino-pent-4-enoylamino)-3-naphthalen-2-yl-propionic acid methyl ester (**8**) (6.2 g, 14.6 mmol) was dissolved in a mixture of 1:1 TFA/dichloromethane (40 mL). The reaction mixture was stirred for 20 min. It was diluted with 1,2-dichloroethane and concentrated under reduced pressure to afford **9** in a quantitative yield. ^{1}H NMR (300 MHz, CD_3OD, δ): 8.58 (d, J = 8.1 Hz, 1H), 8.2 (s, 1H), 7.51 (m, 4H), 7.16 (m, 3H), 5.47 (m, 1H), 4.84 (m, 2H), 4.59 (m, 1H), 3.83 (m, 1H), 3.43 (s, 3H), 3.03 (ddd, J = 13.9, 8.1, 5.9 Hz, 2H), 2.41 (m, 2H). MS (ESI) *m*/*z*: 327 [M + 1].

3-Naphthalen-2-yl-2-[2-(2-nitro-benzenesulfonylamino)-pent-4-enoylamino]-propionic Acid Methyl Ester (10). To a solution of **9** (4.2 g, 9.5 mmol) in chloroform (12 mL) were added triethylamine (5.3 mL, 38 mmol) and 2-nitrobenzenesulfonyl chloride (2.5 g, 11.5 mmol) at 0 °C, and the reaction mixture was stirred for 3 h. It was quenched with 1 N HCl (15 mL) and diluted further with chloroform (15 mL). The organic layer was separated, was washed with saturated bicarbonate solution and brine, was dried over Na_2SO_4, and was concentrated. The residue was chromatographed on silica gel by eluting with 7:3 hexane/ethyl acetate followed by 1:1 hexane/ethyl acetate to produce **10** (3.8 g, 80% yield). ^{1}H NMR (300 MHz, CD_3OD, δ): 8.04 (d, J = 7.7 Hz, 1H), 7.83 (m, 1H), 7.73 (m, 4H), 7.57 (m, 2H), 7.26 (d, J = 8.4 Hz, 1H), 6.93 (d, J = 8.1 Hz, 1H), 5.9 (s, 1H), 5.19 (m, 1H), 4.87 (m, 3H), 4.02 (s, 1H), 3.74 (s, 2H), 3.74 (s, 3H), 3.32 (dd, J = 13.9, 5.1 Hz, 1H), 3.14 (dd, J = 13.9, 7.7 Hz, 1H), 2.44 (m, 1H), 2.26 (m, 1H). MS (ESI) *m*/*z*: 512 [M + 1].

2-[3-Allyl-4-(2-nitro-benzenesulfonyl)-2-oxo-piperazin-1-yl]-3-naphthalen-2-yl-propionic Acid Methyl Ester (11). To a solution of **10** (3.6 g, 7 mmol) in DMF (40 mL) were added 1,2-dibromoethane (13.3 g, 70 mmol) and K_2CO_3 (9.6 g, 70 mmol), and the reaction mixture was stirred at 60 °C for 15 h. It was quenched with 1 N HCl, and the resulting solution was extracted with ethyl acetate (3 × 50 mL). The extract was washed with brine, was dried with Na_2SO_4, and was concentrated to produce **11** (3.7 g, 97% yield). ^{1}H NMR (300 MHz, CD_3OD, δ): 8.03 (s, 1H), 7.92 (m, 1H), 7.79 (m, 3H), 7.56 (m, 5H), 7.21 (m, 1H), 5.43 (dd, J = 11.7, 5.1 Hz, 1H), 4.99 (m, 1H), 4.5 (m, 3H), 3.78 (d, J = 9.5 Hz, 1H), 3.07 (s, 3H), 3.57 (dd, J = 14.6, 5.5 Hz, 1H), 3.21 (m, 4H), 2.17 (m, 2H). MS (ESI) *m*/*z*: 538 [M + 1].

2-(3-Allyl-2-oxo-piperazin-1-yl)-3-naphthalen-2-yl-propionic Acid Methyl Ester (12). To a solution of nosyl-protected 2-oxopiperazine **11** (4.8 g, 8.9 mmol) in acetonitrile (40 mL) were added 4-thiolphenol (4.5 g, 35.7 mmol) and K_2CO_3 (7.4 g, 53.4 mmol), and the reaction mixture was stirred for 4 h. It was cooled in an ice bath and was treated with 1 M aqueous HCl to adjust the pH to

3. The mixture was extracted with Et_2O (3 × 100 mL). The ether extracts were combined and were extracted with 1 M aqueous HCl (100 mL). All acidic aqueous solutions were combined, were cooled in an ice bath, and were basified to pH 10 with K_2CO_3. The solution was extracted with ethyl acetate (3 × 100 mL). The organics were combined and washed with brine, were dried over Na_2SO_4, and were concentrated. The residue was purified by flash column chromatography on silica gel by an elution with 3:2 hexane/ethyl acetate (100% ethyl acetate), followed by 9:1 ethyl acetate/methanol to produce **12** (2.45 g, 79% yield). ^{1}H NMR (300 MHz, CD_3OD, δ): 8.02 (s, 1H), 7.80 (m, 1H), 7.66 (s, 1H), 7. 46 (m, 2H), 7.38 (d, J = 8.4 Hz, 2H), 5.33 (dd, J = 11.4, 4.8 Hz, 1H), 5.13 (m, 1H), 4.85 (d, J = 17.2 Hz, 1H), 4.60 (d, J = 10.2 Hz, 1H), 3.57 (dd, J = 14.6, 5.1 Hz, 1H), 3.49 (dd, J = 10.6, 5.4 Hz, 1H), 3.30 (m, 2H), 2.91 (m, 6H), 2.37 (dd, J = 11.4, 5.5 Hz, 2H). MS (ESI) *m*/*z*: 353 [M + 1].

2-{3-Allyl-4-[2-*tert*-butoxycarbonylamino-3-(4-fluoro-phenyl)-propionyl]-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic Acid Methyl Ester (13). To a solution of piperazine **12** (500 mg, 1.4 mmol) in dichloromethane (5.0 mL) were added triethylamine (232 μL, 167 mmol), PyBOP (960 mg, 1.85 mmol), and Boc-4-fluoro-D-phenylalanine (473 mg, 1.67 mmol) at 0 °C, and the reaction mixture was stirred overnight. It was quenched with saturated $NaHCO_3$ and was extracted with ethyl acetate (3 × 20 mL). The combined extracts were washed with brine, were dried over Na_2SO_4, and were concentrated. The residue was purified by the use of flash chromatography on silica gel by a first elution with 8:2 hexane/ethyl acetate, followed by 3:2 hexane/ethyl acetate to afford **13** (745 mg, 85%). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.75−7.83 (m, 3H), 7.50−7.54 (m, 4H), 7.06−7.09 (m, 2H), 6.88−6.93 (m, 2H), 5.44−5.62 (m, 1H), 4.82−5.07 (m, 2H), 4.31−4.64 (m, 3H), 3.56−3.82 (m, 4H), 3.51−3.56 (m, 1H), 3.05−3.26 (m, 3H); 2.56−2.96 (m, 3H), 2.24−2.14 (m, 2H), 1.37−1.78 (m, 9H). MS (ESI) *m*/*z*: 618 [M + 1].

[2-[2-Allyl-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-3-oxo-piperazin-1-yl]-1-(4-fluoro-benzyl)-2-oxo-ethyl]-carbamic Acid *tert*-Butyl Ester (14). To a solution of methyl ester **13** (200 mg, 0.32 mmol) in methanol (5 mL) were added LiOH (43 mg, 1.78 mmol) and water (1 mL). The reaction mixture was stirred for 4 h. It was then acidified with 1 N HCl and was concentrated to remove methanol. The aqueous phase was extracted with ethyl acetate (3 × 15 mL). The extract was washed with brine, was dried over Na_2SO_4 and was concentrated to produce 2-{3-allyl-4-[2-*tert*-butoxycarbonylamino-3-(4-fluoro-phenyl)-propionyl]-2-oxo-piperazin-1-yl}-3-naphthalen-2-yl-propionic acid in a nearly quantitative yield.

The crude acid (440 mg, 0.73 mmol) that was obtained above was dissolved in DMF (6.0 mL) and *N*-methylmorpholine (400 μL), and EDCI (181 mg, 0.95 mmol), methylamine (2 M solution in THF, 0.36 mL, 0.72 mmol), and 1-hydroxybenzotriazole hydrate (129 mg, 0.95 mmol) were added. The reaction mixture was stirred for 3 h at 0 °C. It was quenched with saturated ammonium chloride solution and was extracted with ethyl acetate (3 × 20 mL). The extract was washed with brine, was dried over Na_2SO_4 and was concentrated. The residue was purified by the use of flash column chromatography on silica gel by an elution with 8:2 hexane/ethyl acetate, followed by 1:1 hexane/ethyl acetate, and then 100% ethyl acetate afforded **14** (425 mg, 88% yield). ^{1}H NMR (300 MHz, CD_3OD, δ): 7.78−7.83 (m, 3H), 7.59 (s, 1H), 7.42−7.53 (m, 3H), 7.23−7.39 (m, 2H), 6.79−7.28 (m, 3H), 5.51−5.56 (m, 1H), 5.36−5.41 (m, 1H), 4.32−5.03 (m, 5H), 3.83−4.12 (m, 1H), 3.21−3.47 (m, 4H), 2.62−2.99 (m, 6H), 2.08−2.52 (m, 2H), 1.31−1.43 (m, 9H). MS (ESI) *m*/*z*: 617 [M + 1].

{1-(4-Fluoro-benzyl)-2-[4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-3-oxo-2-(2-oxo-ethyl)-piperazin-1-yl]-2-oxo-ethyl}-carbamic Acid *tert*-Butyl Ester (15). To a solution of **14** (120 mg, 0.19 mmol) in THF/water (4:1, 7.5 mL) was added a 4% aqueous solution of OsO_4 (300 μL) over a 5 min period to produce a bronze solution that was stirred at room temperature for 10 min. The solution was then treated with $NaIO_4$ (234 mg, 1.1 mmol) in portions, and the mixture was stirred for 3 h. The reaction mixture was diluted with water (20 mL) and was extracted with EtOAc (3 × 30 mL). The extract was dried over Na_2SO_4 and was concentrated. The residue was purified by flash column chromatography on silica gel by an elution with 2:1 ethyl acetate/hexane, followed by 100% ethyl acetate to afford **15** (96 mg, 80% yield). ^{1}H NMR (300 MHz, CD_3OD, δ): 9.48 (s, 1H), 7.36−7.83 (m, 3H), 7.41−7.59 (m, 3H), 7.28−7.31 (m, 1H), 6.88−7.16 (m, 4H), 6.40 (d, J = 4.8 Hz, 1H), 4.97−5.18 (m, 3H), 4.61−4.66 (m, 1H), 3.8 (d, J = 13.5 Hz, 2H), 3.17−3.77 (m, 4H), 2.73−2.93 (m, 2H), 2.48−2.61 (m, 2H), 1.38 (s, 9H). MS (ESI) *m*/*z*: 619 [M + 1].

2-[4-[2-Amino-3-(4-fluoro-phenyl)-propionyl]-3-(2-dimethylamino-ethyl)-2-oxo-piperazin-1-yl]-*N*-methyl-3-naphthalen-2-yl-propionamide (2). To a solution of aldehyde **15** (160 mg, 0.35 mmol) in 1,2-dichloroethane (2.0 mL) were added dimethylamine (18 mg, 0.19 mmol) and acetic acid (33 mg, 0.52 mmol), and the reaction mixture was stirred for 2 h. The reaction mixture was then treated with $NaBH(OAc)_3$ (64 mg, 0.40 mmol) and was stirred for an additional 2 h. It was quenched with brine (7 mL) and was extracted with ethyl acetate (3 × 10 mL). The extract was dried over Na_2SO_4 and was concentrated. The residue was subjected to purification by the use of reversed-phase HPLC to produce [2-[2-(2-dimethylamino-ethyl)-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-3-oxo-piperazin-1-yl]-1-(4-fluoro-benzyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester (151 mg, 89% yield). ^{1}H NMR (300 MHz, CD_3OD, δ): 7.77−7.85 (m, 3H), 7.64 (s, 1H), 7.39−7.52 (m, 4H), 7.26−7.28 (m, 2H), 7.02−7.08 (m, 2H), 5.52−5.85 (m, 1H), 4.57−4.66 (m, 2H), 4.25−4.36 (m, 1H), 2.76−3.59 (m, 13H), 1.48 (s, 9H), 0.82−1.04 (m, 2H), 0.25−0.77 (m, 4H). MS (ESI) *m*/*z*: 649 [M + 1].

The dimethylamino product that was obtained above (62 mg, 0.1 mmol) was dissolved in a 1:1 mixture of TFA/dichloromethane (1 mL), and the solution was stirred for 20 min. The reaction was diluted with 1,2-dichloroethane and was concentrated under reduced pressure. The residue was purified by the use of reversed-phase HPLC to produce pure **2** (32 mg, 61% yield). ^{1}H NMR (300 MHz, CD_3OD, δ): 7.77−7.91 (m, 4H), 7.43−7.57 (m, 3H), 7.29−7.34 (m, 3H), 7.12−7.17 (m, 2H), 5.62−5.67 (m, 1H), 4.46−4.71 (m, 2H), 3.10−3.79 (m, 9H), 2.78 (s, 3H), 2.51 (s, 6H), 1.42−1.47 (m, 1H), 0.99−1.04 (m, 1H). MS (ESI) *m*/*z*: 549 [M + 1]. Anal. Calcd for ($C_{31}H_{38}FN_5O_3 \cdot 2.5CF_3CO_2H$): C, H, N.

2-{4-[2-Amino-3-(4-fluoro-phenyl)-propionyl]-3-[2-(pyridin-2-ylamino)-ethyl]-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide (3). Compound **3** was prepared from aldehyde **15** and 2-aminopyridine as described for **2** in 23% yield over two steps. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.84−7.94 (m, 2H), 7.63−7.77 (m, 3H), 7.29−7.44 (m, 5H), 7.12−7.17 (m, 2H), 6.92−6.97 (m, 2H), 6.81 (d, J = 8.8 Hz, 1H), 5.69−5.74 (m, 2H), 4.58−4.67 (m, 2H), 2.79−3.62 (m, 12H), 1.46−1.48 (m, 1H), 0.98−1.02 (m, 1H). MS (ESI) *m*/*z*: 598 [M + 1]. Anal. Calcd for ($C_{34}H_{37}FN_6O_3 \cdot 3.5CF_3CO_2H \cdot 0.2H_2O$): C, H, N.

2-{3-(2-Amino-ethyl-guanidino)-4-[2-amino-3-(4-fluoro-phenyl)-propionyl]-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide (4). To a solution of aldehyde **15** (85 mg, 0.14 mmol) in ethanol/water (3:1, 3 mL) was added α-aminoguanidine nitrate (19 mg, 0.19 mmol), and the reaction mixture was heated at reflux for 1 h. The reaction was then quenched with brine (7 mL) and was extracted with ethyl acetate (3 × 10 mL). The extracts were combined, were washed with brine, were dried over Na_2SO_4 and were concentrated. The residue was subjected to reversed-phase HPLC purification to produce [2-[2-(2-amino-ethyl-guanidino)-4-(1-methylcarbamoyl-2-naphthalen-2-yl-ethyl)-3-oxo-piperazin-1-yl]-1-(4-fluoro-benzyl)-2-oxo-ethyl]-carbamic acid *tert*-butyl ester (73 mg). ^{1}H NMR (300 MHz, CD_3OD, δ): 7.75−7.84 (m, 2H), 7.43−7.64 (m, 2H), 7.29−7.31 (m, 3H), 6.86−7.25 (m, 4H), 5.39 (m, 2H), 5.04−5.15 (m, 1H), 4.48−4.61 (m, 1H), 2.69−3.76 (m, 8H), 2.06 (m, 1H), 1.45 (s, 9H). MS (ESI) *m*/*z*: 675 [M + 1].

The aminoguanidine product that was obtained in the last step (73 mg) was dissolved ina 1:1 TFA/dichloromethane mixture (1.0 mL). The mixture was stirred for 20 min and was then diluted with 1,2-dichloroethane and was concentrated under reduced pressure. The residue was purified by the use of reversed-phase HPLC to

produce **4** (26 mg) as a TFA salt. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.81−7.84 (m, 3H), 7.71 (s, 1H), 7.40−7.53 (m, 3H), 7.26−7.30 (m, 2H), 7.01−7.12 (m, 3H), 5.57−5.62 (m, 1H), 3.69−3.74 (m, 1H), 2.74−3.67 (m, 11H), 2.01−2.15 (m, 3H). MS (ESI) *m/z*: 576 [M + 1]. Anal. Calcd for ($C_{30}H_{35}FN_8O_3 \cdot 2.5CF_3CO_2H$): C, H, N.

2-{3-Allyl-4-[2-amino-3-(4-fluoro-phenyl)-propionyl]-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide (5). Boc intermediate **14** (350 mg, 0.57 mmol) was dissolved in 1:1 TFA/dichloromethane (1.0 mL). The solution was stirred for 20 min, was diluted with 1,2-dichloroethane, and was concentrated under reduced pressure to afford **5** in a quantitative yield. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.75−7.85 (m, 4H), 7.66−7.68 (m, 1H), 7.39−7.52 (m, 3H), 7.16−7.29 (m, 2H), 7.07 (m, 2H), 5.50−5.71 (m, 1H), 4.22−4.81 (m, 7H), 3.24−3.67 (m, 6H), 2.57−3.19 (m, 4H), 1.85−1.91 (m, 2H). MS (ESI) *m/z*: 517 [M + 1]. Anal. Calcd for ($C_{30}H_{33}FN_4O_3 \cdot 1.5CF_3CO_2H$): C, H, N.

2-(2-Nitro-benzenesulfonylamino)-pentanoic Acid (17a). Norvaline **16a** (7.5 g, 64.1 mmol) was dissolved in a mixture of H_2O (65 mL) and THF (20 mL), and triethylamine (20.7 g, 205 mmol) was added. The solution was cooled in an ice/water bath, and 2-nitrobenzenesulfonyl chloride (18 g, 81.4 mmol) was added in portions. The reaction mixture was stirred at room temperature for 18 h. It was concentrated in vacuo until approximately half of the original volume remained, it was acidified with concentrated HCl to a pH of ∼3, and it was extracted with EtOAc (3 × 150 mL). The organic layers were combined, were washed with brine, were dried over Na_2SO_4, were filtered, and were concentrated to yield **17a** as a yellow solid in quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.06−8.15 (m, 1H), 7.81−7.89 (m, 1H), 7.68−7.79 (m, 2H), 6.37 (bs, 1H), 3.95−4.08 (m, 1H), 1.56−1.85 (m, 2H), 1.15−1.40 (m, 2H), 0.81 (t, J = 7.2 Hz, 3H). MS (ESI) *m/z*: 303 [M + H].

(*S*)-Methyl 3-(Naphthalen-2-yl)-2-((*S*)-2-(2-nitrophenylsulfonamido)pentanamido)propanoate (18a). To a solution of **17a** (24.5 g, 81 mmol) in DMF (400 mL) were added L-β−2-napthylalanine methyl ester (21.6 g, 81 mmol), 4-methylmorpholine (26.7 mL, 240 mmol), EDCI (20.2 g, 110 mmol), and 1-hydroxybenzotriazole hydrate (24.1 g, 180 mmol), and the reaction mixture was stirred overnight. It was diluted with water and extracted with ethyl acetate (3 × 50 mL). The extract was washed with brine, was dried over Na_2SO_4, was filtered, and was concentrated. The residue was purified by flash chromatography (silica gel, hexane/ethyl acetate 8:2 to 1:1) to produce **18a** (30 g, 72% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.76−7.80 (m, 5H), 7.44−7.70 (m, 5H), 7.27 (d, J = 8.4 Hz, 1H), 4.35 (dd, J = 8.4, 5.5 Hz, 1H), 3.87−3.98 (m, 1H), 3.54 (s, 3H), 2.99−3.08 (m, 2H), 1.43−1.48 (m, 2H), 1.14−1.22 (m, 2H); 0.72 (t, J = 7.3 Hz, 3H). MS (ESI) *m/z*: 514 [M + 1].

(*S*)-Methyl 3-(Naphthalen-2-yl)-2-((*S*)-4-(2-nitrophenylsulfonyl)-2-oxo-3-propylpiperazin-1-yl)propanoate (19a). To a solution of dipeptide **18a** (30 g, 58.5 mmol) in DMF (350 mL) were added 1,2-dibromoethane (45 mL, 520 mmol) and K_2CO_3 (80 g, 580 mmol), and the reaction mixture was stirred at 60 °C for 15 h. It was slowly quenched with 1 N HCl, and the mixture was extracted with ethyl acetate (3 × 50 mL). The extract was washed with brine, was dried with Na_2SO_4, and was concentrated to produce **19a** (25.6 g, 82% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.96 (m, 1H), 7.50−7.80 (m, 3H), 7.55−7.60 (m, 4H), 7.45 (m, 2H), 7.26 (m, 1H), 5.50 (m, 1H), 4.30 (m, 1H), 3.77 (m, 1H), 3.69 (s, 3H), 3.56 (m, 1H), 3.10−3.40 (m, 4H), 1.10−1.40 (m, 2H), 0.83 (m, 2H), 0.42 (t, J = 8.0 Hz, 3H). MS (ESI) *m/z*: 540 [M + 1].

(*S*)-Methyl 3-(Naphthalen-2-yl)-2-((*S*)-2-oxo-3-propylpiperazin-1-yl)propanoate (20a). To a solution of **19a** (1.5 g, 2.8 mmol) in acetonitrile (20 mL) were added 4-mercaptophenol (0.70 g, 5.6 mmol) and K_2CO_3 (1.5 g, 11.1 mmol), and the reaction mixture was stirred for 18 h. It was then concentrated and water was added, and the aqueous layer was extracted with EtOAc (3 × 15 mL). The extract was washed with brine, was dried over Na_2SO_4, was filtered, and was concentrated. The crude product was purified by column chromatography (silica gel, 4:6 hexane/EtOAc, followed by 2:8 MeOH/EtOAc) to yield **20a** (0.99 g, 100%) as a yellow oil. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.75−7.90 (m, 3H), 7.64 (s, 1H), 7.40−7.50 (m, 2H), 7.36 (m, 1H), 5.30 (m, 1H), 3.77 (s, 3H), 3.56 (m, 1H), 3.43 (m, 1H), 3.20−3.35 (m, 2H), 2.75−3.10 (m, 3H), 1.35−1.70 (m, 3H), 0.90−1.10 (m, 2H), 0.69 (t, J = 7.4 Hz, 3H). MS (ESI) *m/z*: 355 [M + H].

(*S*)-Methyl 2-((*S*)-4-((*R*)-2-(*tert*-Butoxycarbonyl)-3-(4-fluorophenyl)propanoyl)-2-oxo-3-propylpiperazin-1-yl)-3-(naphthalen-2-yl-)propanoate (21a). To a solution of **20a** (0.42 g, 1.2 mmol) in dichloromethane (15 mL) were added Boc-D-Phe(4F)-OH (0.43 g, 1.5 mmol), *N*-methylmorpholine (180 mg, 1.8 mmol), and PyBOP (0.92 g, 1.8 mmol), and the reaction mixture was stirred at 0 °C for 16 h. The reaction was quenched with saturated aqueous $NaHCO_3$ solution (20 mL) and was extracted with $CHCl_3$ (3 × 10 mL). The organic layers were combined, wre washed with brine, were dried over Na_2SO_4, were filtered, and were concentrated. The residue was subjected to column chromatography (silica gel, hexane/EtOAc 6:4) to afford **21a** (0.69 g, 93%) as a white solid. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.69−7.85 (m, 3H), 7.40−7.60 (m, 3H), 7.09 (m, 1H), 7.08 (m, 2H), 6.91 (m, 2H), 5.25−5.70 (m, 1H), 4.50−5.10 (m, 2H), 3.75 −3.85 (m, 3H), 3.50−3.70 (m, 2H), 2.95−2.40 (m, 4H), 2.70−2.90 (m, 2H), 1.30−1.40 (m, 9H), 0.50−1.20 (m, 4H), 0.41 (m, 3H). MS (ESI) *m/z*: 642 [M + Na].

***tert*-Butyl (*R*)-3-(4-Fluorophenyl)-1-((*S*)-4-((*S*)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-3-oxo-2-propylpiperazin-1-yl)-1-oxopropan-2-yl)carbamate (22a).** Methyl ester **21a** (2.0 g, 3.2 mmol) was dissolved in methanol (10 mL), and LiOH (92 mg, 3.8 mmol) and water (1 mL) were added. The reaction mixture was stirred for 4 h and was then quenched with 1 N aqueous HCl and was concentrated to remove methanol. The aqueous layer was extracted with ethyl acetate (3 × 50 mL). The extract was washed with brine, was dried over Na_2SO_4, was filtered, and was concentrated to produce (*S*)-2-((*S*)-4-((*R*)-2-(*tert*-butoxycarbonyl)-3-(4-fluorophenyl)propanoyl)-2-oxo-3-propylpiperazin-1-yl)-3-(naphthalen-2-yl)propanoic acid in a quantitative yield. MS (ESI) *m/z*: 606 [M + 1].

To a solution of the acid (500 mg, 0.82 mmol) that was obtained above in DMF (3.0 mL) were added EDCI (219 mg, 1.15 mmol), methylamine (41 mg, 1.32 mmol), and 1-hydroxybenzotriazole hydrate (223 mg, 1.64 mmol), and the resulting mixture was stirred for 3 h. It was quenched with a saturated ammonium chloride solution (10 mL) and was extracted with ethyl acetate (3 × 10 mL). The extracts were combined, were washed with brine, were dried over Na_2SO_4, were filtered, and were concentrated. The residue was subjected to flash column chromatography (silica gel, 8:2 hexane/ethyl acetate, followed by 1:1 hexane/ethyl acetate and then 100% ethyl acetate) to afford **22a** (450 mg, 88% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.70−7.82 (m, 3H), 7.40−7.60 (m, 3H), 7.30 (m, 1H), 7.09 (m, 2H), 6.89 (m, 2H), 5.23−5.45 (m, 2H), 4.69 (m, 1H), 2.60−3.75 (m, 12H), 1.37 (s, 9H), 0.82−1.20 (m, 3H), 0.58 (m, 1H), 0.43 (m, 3H). MS (ESI) *m/z*: 619 [M + 1].

(*S*)-2-((*S*)-4-((*R*)-2-Amino-3-(4-fluorophenyl)propanoyl)-2-oxo-3-propylpiperazin-1-yl)-*N*-methyl-3-(naphthalen-2-yl)propanamide (23). Boc analog **22a** (1.8 g, 2.9 mmol) was dissolved in 1:1 TFA/dichloromethane (1.0 mL), and the reaction mixture was stirred for 20 min. It was diluted with 1,2-dichloroethane and was concentrated under reduced pressure to afford **23** in a quantitative yield. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.60−7.90 (m, 4H), 7.35−7.55 (m, 3H), 7.15−7.30 (m, 2H), 6.90−7.10 (m, 2H), 5.50−5.67 (m, 1H), 4.59 (m, 1H), 2.70−3.60 (m, 12H), 0.80−1.05 (m, 2H), 0.38 (m, 2H), 0.25 (m, 3H). MS (ESI) *m/z*: 519 [M + 1]. Anal. Calcd for ($C_{30}H_{35}FN_4O_3 \cdot 0.9CF_3CO_2H$): C, H, N.

(*S*)-2-((*S*)-4-((*R*)-2-Amino-3-(4-fluorophenyl)propanoyl)-3-ethyl-2-oxopiperazin-1-yl)-*N*-methyl-3-(naphthalen-2-yl)propanamide (24). Compound **24** synthesized from 2-aminobutanoic acid, as described for **23**. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.75−7.89 (m, 3H), 7.64−7.73 (m, 1H), 7.37−7.58 (m, 3H), 7.16−7.35 (m, 2H), 6.92−7.14 (m, 2H), 5.50−5.63 (m,1H), 4.61 (t, J = 7.6 Hz, 1H); 4.52 (t, J = 6.6 Hz, 1H), 4.21−4.37 (m, 1H), 2.92−3.71 (m, 7H), 2.74−2.89 (m, 4H), 0.88−1.30 (m, 2H), 0.18−0.31 (m, 3H). MS (ESI) *m/z*: 505 [M + H]. Anal. Calcd for ($C_{29}H_{33}FN_4O_3 \cdot 1.4CF_3CO_2H$): C, H, N.

2-{4-[2-Amino-3-(4-fluoro-phenyl)-propionyl]-3-methyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide (25). Compound **25** was synthesized from alanine, as described for **23**. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.75−7.85 (m, 3H), 7.64 (m, 1H), 7.30−7.52 (m, 3H), 7.18 (m, 2H), 6.98 (m, 2H), 5.43−5.59 (m, 1H), 4.25−4.65 (m, 1H), 2.40−3.50 (m, 12H), 0.55−0.76 (m, 3H). MS (ESI) *m*/*z*: 491 [M + H]. Anal. Calcd for ($C_{28}H_{31}FN_4O_3 \cdot 1.2CF_3CO_2H$): C, H, N.

2-{4-[2-Amino-3-(4-fluoro-phenyl)-propionyl]-3-isopropyl-2-oxo-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide (26). Compound **26** was synthesized from valine, as described for **23**. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.69−7.81 (m, 4H), 7.33−7.51 (m, 5H), 6.97−7.21 (m, 2H), 5.50−5.66 (m, 1H), 4.64 (t, J = 7.3 Hz, 1H), 4.50 (d, J = 6.9 Hz, 1H), 4.10−4.19 (m, 1H), 3.56−3.83 (m, 2H), 3.00−3.52 (m, 6H), 2.77−2.84 (m, 3H), 1.29−1.47 (m, 1H), 0.43−0.59 (m, 3H), 0.12−0.16 (m, 3H). MS (ESI) *m*/*z*: 519 [M + 1]. Anal. Calcd for ($C_{30}H_{35}FN_4O_3 \cdot 1.7CF_3CO_2H$): C, H, N.

2-{4-[2-Acetylamino-3-(4-fluoro-phenyl)-propionyl]-2-oxo-3-propyl-piperazin-1-yl}-*N*-methyl-3-naphthalen-2-yl-propionamide (27). To a solution of **23** (386 mg, 0.75 mmol) in DMF (6.0 mL) were added *N*-methylmorpholine (490 μL), EDCI (181 mg, 0.95 mmol), acetic acid (58 mg, 0.97 mmol), and 1-hydroxybenzotriazole hydrate (224 mg, 1.65 mmol), and the reaction mixture was stirred at 0 °C for 3 h. The reaction was then quenched with saturated ammonium chloride solution (10 mL) and was extracted with ethyl acetate (3 × 10 mL). The extracts were combined and washed with brine, were dried over Na_2SO_4, and were concentrated. Purification of the residue by flash chromatography (silica gel, eluting with 8:2 hexane/ethyl acetate, followed by 1:1 hexane/ethyl acetate and then 100% ethyl acetate) afforded **27** (210 mg, 50% yield). ^{1}H NMR (300 MHz, CD_3OD, δ): 7.63−7.90 (m, 4H), 7.35−7.48 (m, 3H), 7.20 (m, 2H), 6.94 (m, 2H), 5.58 (m, 1H), 4.56 (m, 1H), 2.70−4.00 (m, 12H), 1.88 (m, 3H), 0.85 (m, 2H), 0.15−0.35 (m, 5H). MS (ESI) *m*/*z*: 561 [M + 1]. Anal. Calcd for ($C_{32}H_{37}FN_4O_4$): C, H, N.

***N*-((1*R*)-1-[(4-Fluorophenyl)methyl]-2-{(2*S*)-4-[(1*S*)-2-(methylamino)-1-(2-naphthalenylmethyl)-2-oxoethyl]-3-oxo-2-propyl-1-piperazinyl}-2-oxoethyl)-2,2-dimethylpropanamide (28).** Compound **28** was synthesized from **23** and 2,2-dimethylpropanoic acid, as described for **27**, and was purified by the use of reversed-phase HPLC. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.60−7.85 (m, 4H), 7.35−7.50 (m, 3H), 7.20 (m, 2H), 6.95 (m, 2H), 5.50−5.65 (m, 1H), 4.80−5.05 (m, 1H), 3.90 (m, 1H), 2.65−3.60 (m, 12H), 1.00−1.15 (m, 9H), 0.87 (m, 2H), 0.20−0.40 (m, 5H). MS (ESI) *m*/*z*: 572 [M + 1]. Anal. Calcd for ($C_{35}H_{43}FN_4O_4 \cdot 0.7CF_3CO_2H$): C, H, N.

(2*S*)-2-((3*S*)-4-{4-Fluoro-*N*-[(methyloxy)acetyl]-D-phenylalanyl}-2-oxo-3-propyl-1-piperazinyl)-*N*-methyl-3-(2-naphthalenyl)propanamide (29). Compound **29** was synthesized from **23** and (methyloxy) acetic acid, as described for **27**, and was purified by the use of reversed-phase HPLC. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.60−7.90 (m, 4H), 7.35−7.55 (m, 3H), 7.10−7.25 (m, 2H), 6.95 (m, 2H), 5.50−5.65 (m, 1H), 5.05 (m, 1H), 4.57 (m, 1H), 2.85−4.15 (m, 17H), 0.80−1.00 (m, 2H), 0.20−0.40 (m, 5H). MS (ESI) *m*/*z*: 591 [M + 1]. Anal. Calcd for ($C_{33}H_{39}FN_4O_5 \cdot 0.3CF_3CO_2H$): C, H, N.

***N*-((*R*)-3-(4-Fluorophenyl)-1-((*S*)-4-((*S*)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-3-oxo-2-propylpiperazin-1-yl)-1-oxopropan-2-yl)-5-oxopyrrolidine-2-carboxamide (30).** Compound **30** was synthesized from **23** and pyroglutamic acid, as described for **27**, and was purified by the use of reversed-phase HPLC. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.42−7.81 (m, 6H), 7.30−7.32 (m, 2H), 7.10−7.12 (m, 2H), 6.90−6.94 (m, 2H), 5.42−5.67 (m, 1H), 4.58−5.05 (m, 3H), 4.09−4.12 (m, 1H), 3.08−3.82 (m, 4H), 2.71−2.95 (m, 4H), 2.04−2.44 (m, 3H), 0.30−1.05 (m, 9H). MS (ESI) *m*/*z*: 630 [M + 1]. Anal. Calcd for ($C_{35}H_{40}FN_5O_5 \cdot 0.5CF_3CO_2H$): C, H, N.

***N*-((*R*)-3-(4-Fluorophenyl)-1-((*S*)-4-((*S*)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-3-oxo-2-propylpiperazin-1-yl)-1-oxopropan-2-yl)thiazole-4-carboxamide (31).** Compound **31** was synthesized from **23** and 2-carboxylic acid thiazole, as described for **27**, and was purified by the use of reversed-phase HPLC. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 8.85−8.90 (m, 1H), 8.15−8.35 (m, 1H), 7.13−7.79 (m, 10H), 6.83−6.94 (m, 2H), 5.44−5.58 (m, 1H), 5.01−5.19 (m, 1H), 4.61−4.66 (m, 2H), 3.62−4.22 (m, 1H), 2.70−3.46 (m, 11H), 0.85−1.03 (m, 2H), 0.27−0.49 (m, 4H). MS (ESI) *m*/*z*: 630 [M + 1]. Anal. Calcd for ($C_{34}H_{36}FN_5O_4S \cdot 0.05CF_3CO_2H$): C, H, N.

***N*-((*R*)-3-(4-Fluorophenyl)-1-((*S*)-4-((*S*)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-3-oxo-2-propylpiperazin-1-yl)-1-oxopropan-2-yl)isonicotinamide (32).** Compound **32** was synthesized from **23** and isonicotinic acid, as described for **27**, and was purified by the use of reversed-phase HPLC. ^{1}H NMR (300 MHz, CD_3OD, δ): 8.64−8.91 (m, 1H), 7.65−7.90 (m, 2H), 7.36−7.79 (m, 8H), 7.15−7.27 (m, 2H), 6.93−7.01 (m, 2H), 5.85 (dd, J = 11.3, 4.9 Hz, 1H), 5.04−5.26 (m, 1H), 4.64 (t, J = 6.2 Hz, 1H), 3.78−4.22 (m, 1H), 2.69−3.51 (m, 11H), 0.91−1.02 (m, 2H), 0.21−0.45 (m, 4H). MS (ESI) *m*/*z*: 624 [M + 1]. Anal. Calcd for ($C_{36}H_{38}FN_5O_4 \cdot 0.1\ CF_3CO_2H$): C, H, N.

***N*-((*R*)-3-(4-Fluorophenyl)-1-((*S*)-4-((*S*)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-3-oxo-2-propylpiperazin-1-yl)-1-oxopropan-2-yl)nicotinamide (33).** was synthesized from **23** and nicotinic acid as described for **27** and purified by the use of reversed-phase HPLC. ^{1}H NMR (300 MHz, CD_3OD, δ): 8.64−8.96 (m, 1H), 7.70−7.90 (m, 2H), 7.40−7.79 (m, 8H), 7.15−7.27 (m, 2H), 6.93−7.01 (m, 2H), 5.85 (dd, J = 11.3, 4.9 Hz, 1H), 5.04−5.26 (m, 1H), 4.64 (t, J = 6.2 Hz, 1H), 3.80−4.22 (m, 1H), 2.72−3.51 (m, 11H), 0.91−1.02 (m, 2H), 0.21−0.45 (m, 4H). MS (ESI) *m*/*z*: 624 [M + 1]. Anal. Calcd for ($C_{36}H_{38}FN_5O_4 \cdot 0.1CF_3CO_2H$): C, H, N.

***N*-((*R*)-3-(4-Fluorophenyl)-1-((*S*)-4-((*S*)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-3-oxo-2-propylpiperazin-1-yl)-1-oxopropan-2-yl)picolinamide (34).** Compound **34** was synthesized from **23** and picolinic acid, as described for **27**, and was purified by the use of reversed-phase HPLC. ^{1}H NMR (300 MHz, CD_3OD, δ): 8.61−8.63 (m, 1H), 7.92−8.06 (m, 2H), 7.36−7.79 (m, 8H), 7.15−7.27 (m, 2H), 6.92−6.97 (m, 2H), 5.85 (dd, J = 11.3, 4.9 Hz, 1H), 5.04−5.26 (m, 1H), 4.64 (t, J = 6.2 Hz, 1H), 3.78−4.22 (m, 1H), 2.69−3.51 (m, 11H), 0.91−1.02 (m, 2H), 0.21−0.45 (m, 4H). MS (ESI) *m*/*z*: 624 [M + 1]. Anal. Calcd for ($C_{36}H_{38}FN_5O_4 \cdot 0.15CF_3CO_2H$): C, H, N.

(*S*)-2-((*S*)-4-((*R*)-2-Acetamido-3-amino propan-(4-fluorophenyl)-propanoyl)-2-oxo-3-propylpiperazin-1-yl)-*N*-methyl-3-(naphthalen-2-yl)propanamide (35). To a solution of **23** (300 mg, 0.47 mmol) in DMF (3.0 mL) were added *N*-methylmorpholine (258 μL, 2.35 mmol), 2-(*tert*-butoxycarbonyl)-2-methylpropanoic acid (165 mg, 0.57 mmol), 1-hydroxybenzotriazole hydrate (141 mg, 1.03 mmol), and EDCI (117 mg, 0.61 mmol), and the reaction mixture was stirred for 3 h. The reaction was quenched with saturated ammonium chloride solution (7 mL) and was extracted with ethyl acetate (3 × 10 mL). The extracts were combined, were washed with brine, were dried over Na_2SO_4, and were concentrated. The residue was purified by flash column chromatography (silica gel, 8:2 hexane/ethyl acetate, followed by 1:1 hexane/ethyl acetate and then 100% ethyl acetate) to afford *tert*-butyl (*R*)-3-(4-fluorophenyl)-1-((*S*)-4-((*S*)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-3-oxo-2-propylpiperazin-1-yl)-1-oxopropan-2-ylcarbamate (250 mg, 75% yield). ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.70−7.81 (m, 4H), 7.39−7.48 (m, 3H), 7.25 (m, 2H), 6.98 (m, 2H), 5.56−5.67 (m, 1H), 4.57−5.06 (m, 2H), 3.96−4.23 (m, 1H), 3.63−3.82 (m, 1H), 3.16−3.44 (m, 4H), 2.76−3.00 (m, 6 H), 1.54 (s, 3H), 1.5 (s, 9H), 1.47 (s, 3H), 0.92−1.35 (m, 2H), 0.27−0.41 (m, 5H). MS (ESI) *m*/*z*: 704 [M + 1].

The Boc intermediate (302 mg, 0.43 mmol) that was obtained above was dissolved in 1:1 TFA/dichloromethane (2.0 mL). The reaction mixture was stirred for 20 min, was diluted with 1,2-dichloroethane, and was concentrated under reduced pressure. The residue was purified by the use of reversed-phase HPLC to afford **35** (238 mg) as a TFA salt. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.70−7.81 (m, 4H), 7.39−7.48 (m, 3H), 7.25 (bs, 2H), 6.98 (m, 2H), 5.56−5.67 (m, 1H), 4.57−5.06 (m, 2H), 3.96−4.23 (m, 1H), 3.63−3.82 (m, 1H), 3.16−3.44 (m, 4H), 2.76−3.00 (m, 6H), 1.54 (s, 3H), 1.47 (s, 3H), 0.92−1.35 (m, 2H), 0.27−0.41 (m, 5H). MS

(ESI) *m/z*: 604 [M + 1]. Anal. Calcd for ($C_{34}H_{42}FN_5O_4 \cdot 0.9CF_3CO_2H$): C, H, N.

1-Amino-*N*-((1*R*)-1-[(4-fluorophenyl)methyl]-2-{(2*S*)-4-[(1*S*)-2-(methylamino)-1-(2-naphthalenylmethyl)-2-oxoethyl]-3-oxo-2-propyl-1-piperazinyl}−2-oxoethyl)cyclopropanecarboxamide (36). Compound **36** was synthesized from **23** and 1-({[(1,1-dimethylethyl)oxy]carbonyl}amino)cyclopropanecarboxylic acid, as described for **35**. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.65−7.82 (m, 4H), 7.35−7.50 (m, 3H), 7.20 (m, 2H), 6.96 (m, 2H), 5.51−5.66 (m, 1H), 5.02 (m, 1H), 4.23−3.93 (m, 1H), 2.65−3.70 (m, 12H), 0.75−1.65 (m, 6H), 0.20−0.58 (m, 5H). MS (ESI) *m/z*: 602 [M + 1]. Anal. Calcd for ($C_{34}H_{40}FN_5O_4 \cdot 2.3CF_3CO_2H$): C, H, N.

1-Amino-*N*-((*R*)-3-(4-fluorophenyl)-1-((*S*)-4-((*S*)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-propylpiperazin-1-yl)-1-oxopropan-2-yl)cyclobutanecarboxamide (37). Compound **37** was synthesized from **23** and *N*-Boc-1-aminocyclobutane carboxylic acid, as described for **35**. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.68−7.85 (m, 4H), 7.39−7.52 (m, 3H), 7.20−7.30 (m, 2H), 6.96−7.02 (m, 2H), 5.53−5.69 (m, 1H), 4.55−5.12 (m, 3H), 2.12−4.17 (m, 18H), 0.25−1.35 (m, 7H). MS (ESI) *m/z*: 602 [M + 1]. Anal. Calcd for ($C_{35}H_{44}FN_5O_4 \cdot 1.7CF_3CO_2H$): C, H, N.

1-Amino-*N*-((*R*)-3-(4-fluorophenyl)-1-((*S*)-4-((*S*)-1-(methylamino)-3-(naphthalen-2-yl)-1-oxopropan-2-yl)-2-propylpiperazin-1-yl)-1-oxopropan-2-yl)cyclopentanecarboxamide (38). Compound **38** was synthesized from **23** and Boc-1-amino-1-cyclopentanecarboxylic acid, as described for **35**. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.70−7.85 (m, 4H), 7.40−7.54 (m, 3H), 7.19−7.28 (m, 2H), 6.95−7.02 (m, 2H), 5.53−5.68 (m, 1H), 4.54−5.11 (m, 2H), 2.77−3.70 (m, 12H), 0.25−2.29 (m, 15H). MS (ESI) *m/z*: 630 [M + 1]. Anal. Calcd for ($C_{36}H_{44}FN_5O_4 \cdot 2.1CF_3CO_2H$): C, H, N.

(*S*)-2-((*S*)-4-((*R*)-3-(4-Fluorophenyl)-2-(2-(methylamino)acetamido)propanoyl)-2-oxo-3-propylpiperazin-1-yl)-*N*-methyl-3-(naphthalen-2-yl)propanamide (39). was synthesized from **23** and Boc-Sar-OH, as described for **35**. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.66−7.84 (m, 4H), 7.38−7.52 (m, 3H), 7.18−7.26 (m, 2H), 6.95−7.00 (m, 2H), 5.52−5.67 (m, 1H), 5.08−4.83 (m, 2H), 2.64−4.16 (m, 16H), 0.86−1.23 (m, 2H), 0.24−0.64 (m, 5H). MS (ESI) *m/z*: 590 [M + 1]. Anal. Calcd for ($C_{33}H_{40}FN_5O_4 \cdot 1.2CF_3CO_2H$): C, H, N.

(2*S*)-*N*-Methyl-2-[(3*S*)-4-(*N*-methyl-L-alanyl-4-fluoro-D-phenylalanyl)-2-oxo-3-propyl-1-piperazinyl]-3-(2-naphthalenyl)propanamide (40). Compound **40** was synthesized from **23** and Boc-*N*-methyl alanine, as described for **35**. ^{1}H NMR (300 MHz, $CDCl_3$, δ): 7.67−7.84 (m, 4H), 7.38−7.53 (m, 3H), 7.18−7.28 (m, 2H), 6.96−7.02 (m, 2H), 5.52−5.68 (m, 1H), 5.10 (t, J = 7.5 Hz, 1H), 4.58 (t, J = 6.4 Hz, 1H), 3.94−4.18 (m, 1H), 3.15−3.84 (m, 6H), 2.76−3.04 (m, 6H), 2.50−2.54 (m, 3H), 1.41−1.48 (m, 3H), 0.23−1.12 (m, 7H). MS (ESI) *m/e*: 604 [M + 1]. Anal. Calcd for ($C_{34}H_{42}FN_5O_4 \cdot 1.5CF_3CO_2H$): C, H, N.

(2*S*)-*N*-((1*R*)-1-[(4-Fluorophenyl)methyl]-2-{(2*S*)-4-[(1*S*)-2-(methylamino)-1-(2-naphthalenylmethyl)-2-oxoethyl]-3-oxo-2-propyl-1-piperazinyl}-2-oxoethyl)-2-pyrrolidinecarboxamide (41). Compound **41** was synthesized from **23** and BOC-Pro-OH, as described for **35**. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.75−7.81 (m, 4H), 7.35−7.49 (m, 3H), 7.14−7.24 (m, 2H), 6.92−6.98 (m, 2H), 5.40−5.64 (m, 1H), 5.06 (t, J = 7.6 Hz, 1H), 4.54 (t, J = 6.4 Hz, 1H), 4.07−4.21 (m, 1H), 3.94−3.98 (m, 1H), 3.55−3.67 (m, 1H), 3.50−3.17 (m, 6H), 2.73−3.05(m, 6H), 2.24−2.35 (m, 1H), 1.65−2.02 (m, 3H), 0.57−1.15 (m, 2H), 0.23−0.39 (m, 4H). MS (ESI) *m/z*: 616 [M + 1]. Anal. Calcd for ($C_{35}H_{42}FN_5O_4 \cdot 1.8CF_3CO_2H$): C, H, N.

(2*S*)-*N*-((1*R*)-1-[(4-Fluorophenyl)methyl]-2-{(2*S*)-4-[(1*S*)-2-(methylamino)-1-(2-naphthalenylmethyl)-2-oxoethyl]-3-oxo-2-propyl-1-piperazinyl}-2-oxoethyl)-2-piperidinecarboxamide (42). Compound **42** was synthesized from **23** and Boc-Pip-OH, as described for compound **35**. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.65−7.85 (m, 4H), 7.35−7.50 (m, 3H), 7.10−7.25 (m, 2H), 6.97 (m, 2H), 5.50−5.70 (m, 1H), 4.50−5.10 (m, 2H), 2.65−4.00 (m, 15H), 2.02 (m, 1H), 1.83 (m, 2H), 1.45−1.60 (m, 3H), 0.90 (m, 2H), 0.20−0.40 (m, 5H). MS (ESI) *m/z*: 599 [M + 1]. Anal. Calcd for ($C_{36}H_{44}FN_5O_4 \cdot 1.2CF_3CO_2H$): C, H, N.

***N*-((1*R*)-1-[(4-Fluorophenyl)methyl]-2-{(2*S*)-4-[(1*S*)-2-(methylamino)-1-(2-naphthalenylmethyl)-2-oxoethyl]-3-oxo-2-propyl-1-piperazinyl}-2-oxoethyl)-4-piperidinecarboxamide (43).** Compound **43** was synthesized from **23** and Boc-Inp-OH, as described for **35**. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.60−7.90 (m, 4H), 7.35−7.50 (m, 3H), 7.10−7.25 (m, 2H), 6.90−7.00 (m, 2H), 5.50−5.70 (m, 1H), 4.56 (m, 1H), 3.90 (m, 1H), 2.60−4.95 (m, 16H), 2.50 (m, 1H), 1.65−2.00 (m, 4H), 0.80−1.15 (m, 2H), 0.20−0.50 (m, 5H). MS (ESI) *m/z*: 599 [M + 1]. Anal. Calcd for ($C_{36}H_{44}FN_5O_4 \cdot 1.9CF_3CO_2H$): C, H, N.

(3*S*)-*N*-((1*R*)-1-[(4-Fluorophenyl)methyl]-2-{(2*S*)-4-[(1*S*)-2-(methylamino)-1-(2-naphthalenylmethyl)-2-oxoethyl]-3-oxo-2-propyl-1-piperazinyl}-2-oxoethyl)-1,2,3,4-tetrahydro-3-isoquinolinecarboxamide (44). Compound **44** was synthesized from **23** and Boc-Tic-OH, as described for **35**. ^{1}H NMR (300 MHz, CD_3OD, δ): 7.60−7.85 (m, 4H), 7.40−7.52 (m, 3H), 7.20−7.35 (m, 6H), 7.01 (m, 2H), 5.63 (m, 1H), 5.13 (m, 1H), 4.39 (m, 2H), 3.90−4.15 (m, 2H), 3.71 (m, 1H), 2.60−3.55 (m, 12H), 0.85−1.15 (m, 2H), 0.20−0.60 (m, 5H). MS (ESI) *m/z*: 678 [M + 1]. Anal. Calcd for ($C_{40}H_{44}FN_5O_4 \cdot 1.6CF_3CO_2H$): C, H, N.

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Supporting Information Available: Elemental analysis results for final compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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