Synthesis and Structure−Activity Relationships of Novel Arylpiperazines as Potent and Selective Agonists of the Melanocortin Subtype-4 Receptor

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The melanocortin receptors have been implicated as potential targets for a number of important therapeutic indications, including inflammation, sexual dysfunction, and obesity. We identified compound **1**, an arylpiperazine attached to the dipeptide H-D-Tic-D-*p*-Cl-Phe-OH, as a novel melanocortin subtype-4 receptor (MC4R) agonist through iterative directed screening of nonpeptidyl G-protein-coupled receptor biased libraries. Structure−activity relationship (SAR) studies demonstrated that substitutions at the ortho position of the aryl ring improved binding and functional potency. For example, the *o*-isopropyl-substituted compound **29** (K_i = 720 nM) possessed 9-fold better binding affinity compared to the unsubstituted aryl ring (K_i = 6600 nM). Sulfonamide **39** (K_i = 220 nM) fills this space with a polar substituent, resulting in a further 2-fold improvement in binding affinity. The most potent compounds such as the diethylamine **44** (K_i = 60 nM) contain a basic group at this position. Basic heterocycles such as the imidazole **50** (K_i = 110 nM) were similarly effective. We also demonstrated good oral bioavailability for sulfonamide **39**.

Introduction

The melanocortin receptors form a family of G-protein-coupled receptors (GPCRs) that are activated by the melanocortin peptides: adrenocorticotropin (ACTH) and α-, *β*-, and *γ*-melanocyte-stimulating hormones (MSH). These peptide hormones are derived from post-translational processing of a precursor protein, pro-opiomelanocortin (POMC), which also gives rise to *β*-lipotropin and *β*-endorphin. They have a wide range of physiological effects on mammalian reproductive, immune, and central nervous systems.[1]

Five members of the melanocortin receptor family have been cloned and characterized.[2] MC1R is expressed in melanocytes and plays a key role in pigmentation and coat color. MC2R is expressed in the adrenal cortex and adipose tissues and, in response to ACTH, controls production of mineralcorticoid and glucocorticoid. MC3R is expressed in the brain, heart, gut, and placenta. Its physiological function is not well-defined, but based on a knock-out model, it is believed to be involved in nutrient partitioning.[3] MC4R is expressed in the hypothalamus and plays a critical role in regulating metabolism, feeding, and reproductive behavior. MC5R is expressed in the lung, gut, spleen, and skin and is involved in exocrine gland secretion. The involvement of the melanocortin receptors in a wide range of mammalian physiology has driven several research groups to identify selective, non-peptide agonists as possible drug treatments for melanocortin-mediated diseases.[4]

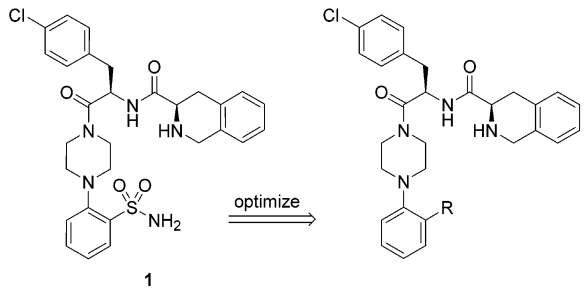

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Figure 1.

We identified arylpiperazine **1** through iterative directed screening of nonpeptidyl GPCR-biased libraries.[5] It is a full agonist at the human MC4 receptor (K_i = 900 ± 170 nM, EC_{50} = 120 ± 1 nM; 98% relative efficacy, $n \geq 2$). A key feature of this compound is the [(aminosulfonyl)phenyl]piperazine, which was a conserved element of these libraries. As a result, we had limited structure−activity relationship (SAR) data in this area of the lead compound. Efforts to develop the SAR around the arylpiperazine are described below.

Results

Chemistry. The final compounds for biological testing were prepared as described in Scheme 1. The commercially available amino acids D-*p*-chlorophenylalanine methyl ester (D-*p*-Cl-Phe-OMe) and D-*N*-Boc-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (Boc-D-Tic-OH) were coupled using EDC-DMAP to give dipeptide **2**. The methyl ester was then cleaved with sodium hydroxide to give Boc-D-Tic-D-*p*-Cl-Phe-OH (**3**). The arylpiperazines **4** were coupled to dipeptide **3** with

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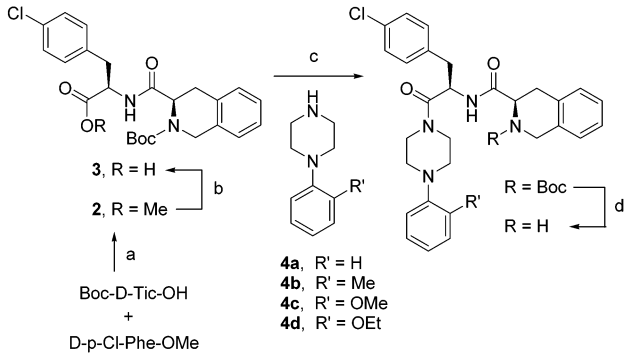
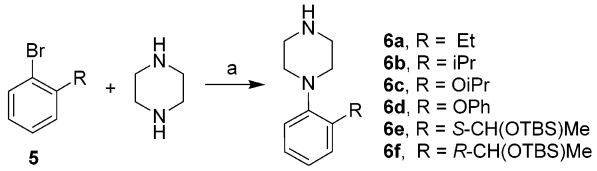
Scheme 1. Preparation of Boc-D-Tic-D-*p*-Cl-Phe-OH and Coupling to Arylpiperazines[a]



[a] Reagents: (a) EDC, DMAP, CH_2Cl_2; (b) NaOH, MeOH; (c) HATU, HOAt, $^iPr_2NEt$, CH_2Cl_2; (d) TFA, DMS, CH_2Cl_2.

Scheme 2. Pd Coupling of Aryl Bromides to Piperazine[a]



[a] Reagents: $Pd_2(dba)_3$, BINAP, NaO^{t}Bu, toluene.

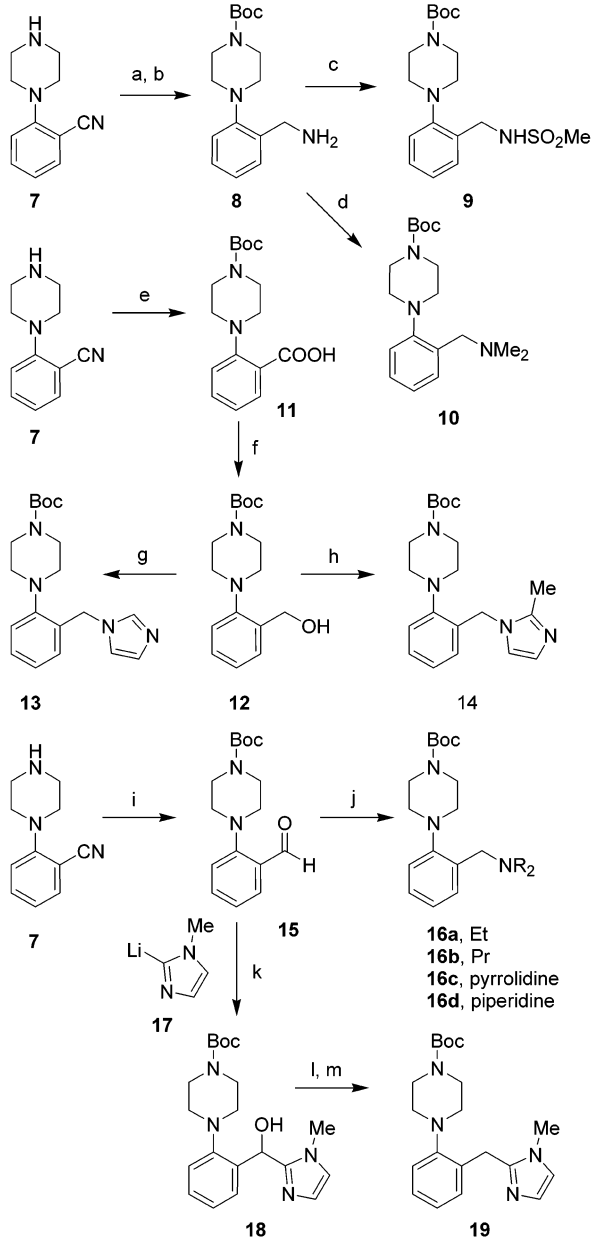
HATU−HOAt followed by TFA deprotection, purification, and HCl salt formation to give the final compounds for assay. The arylpiperazines **4a**−**d** were commercially available. Those arylpiperazines that were not commercially available were prepared as described in Schemes 2−5.

Many arylpiperazines were prepared by direct *N*-arylation of piperazine with readily available aryl bromides **5** (Scheme 2). The conditions of Buchwald,[6] palladium catalysis with BINAP as the ligand and sodium *tert*-butoxide as the base, provided the desired arylpiperazines **6a**−**f** in excellent yields.

Commercially available *N*-(2-cyanophenyl)piperazine (**7**) proved itself a versatile intermediate (Scheme 3). After protecting the piperazine of **7** with Boc_2O, the cyano group was reduced with sodium borohydride in the presence of TFA to give benzylamine **8**. Reaction of **8** with methanesulfonyl chloride gave **9**, while reductive amination with formaldehyde gave **10**. The cyano group of **7** was hydrolyzed to the acid followed by protection of the piperazine with Boc_2O in a one-pot procedure to give benzoic acid **11**. Benzoic acid **11** was reduced to alcohol **12** with borane. Alcohol **12** was reacted with imidazole under Mitsunobu conditions to give compound **13**. Alternatively, alcohol **12** was activated as the mesylate and reacted with 2-methylimidazole to give compound **14**. Finally, the cyano group of *N*-(2-cyanophenyl)piperazine (**7**) was easily reduced with DIBAL followed protection of the piperazine with Boc_2O in a one-pot procedure to give benzaldehyde **15**. Benzaldehyde **15** was further elaborated via reductive amination with various secondary amines to give arylpiperazines **16a**−**d**. Lithiated heterocycles such as 2-lithio-1-methylimidazole (**17**) were added to benzaldehyde **15** to give secondary alcohols such as **18**. Radical deoxygenation of **18** provided the C2-linked imidazole **19**.

Several desired arylpiperazines were derived from commercially available *N*-(2-nitrophenyl)piperazine (**20**)

Scheme 3. Derivatives of *N*-(2-Cyanophenyl)piperazine[a]

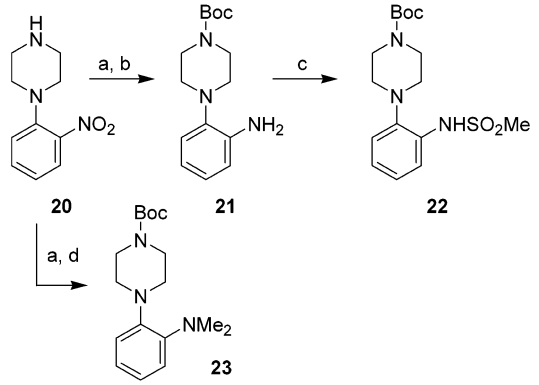


[a] Reagents: (a) Boc_2O, K_2CO_3, THF, H_2O; (b) $NaBH_4$, TFA, THF; (c) MsCl, Et_3N, CH_2Cl_2; (d) HCHO, $NaCNBH_3$, CH_3CN; (e) KOH, EtOH; then Boc_2O, $NaHCO_3$; (f) BH_3·THF, THF; (g) imidazole, PPh_3, DEAD, THF; (h) MsCl, DMAP, Et_3N, CH_2Cl_2; then 2-methylimidazole, THF; (i) DIBAL, dioxane; then Rochelle salt, H_2O; then $NaHCO_3$, Boc_2O; (j) R_2NH, $Ti(OiPr)_4$; then $NaBH_4$, EtOH; (k) ^{n}BuLi, 1-methylimidzole, THF; then **15**, THF; (l) NaH, CS_2, MeI; (m) Bu_3SnH, AIBN, toluene, 80 °C.

(Scheme 4). The piperazine was protected with Boc_2O and the aryl nitro group was then reduced via hydrogenation to give aniline **21**. Aniline **21** was reacted with methanesulfonyl chloride to give sulfonamide **22**. Hydrogenation of the aryl nitro group of **20** in the presence of formaldehyde gave dimethylaniline **23**.

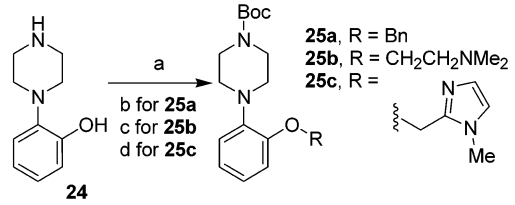
Finally, several arylpiperazines were prepared from commercially available *N*-(2-hydroxyphenyl)piperazine **24** (Scheme 5). The piperazine nitrogen was protected with Boc_2O. The phenol was alkylated with benzyl bromide to give **25a** and with 2-(dimethylamino)ethyl

Scheme 4. Derivatives of *N*-(2-Nitrophenyl)piperazine[a]



[a] Reagents: (a) Boc_2O, Et_3N, CH_2Cl_2; (b) H_2, Pd/C, EtOH; (c) MsCl, Et_3N, CH_2Cl_2; (d) HCHO, Pd/C, ^{i}PrOH.

Scheme 5. Derivatives of *N*-(2-Hydroxyphenyl)piperazine[a]



[a] Reagents: (a) Boc_2O, Et_3N, CH_2Cl_2; (b) BnBr, K_2CO_3, DMF; (c) $ClCH_2CH_2NMe_2$, K_2CO_3, KI, 18-crown-6, DMF; (d) ROH, PPh_3, DEAD, THF.

chloride to give **25b**. Alternatively, the phenol was alkylated under Mitsunobu conditions to give imidazole **25c**.

Pharmacology. Our initial efforts to optimize the arylpiperazine portion of lead compound **1** were guided by several primary assays. Affinities were determined by competitive inhibition of ^{125}I-NDP-α-MSH binding in HEK293 cells stably transfected with human MC1, MC3, MC4, or MC5 receptors. Agonist potencies were determined by measuring cAMP release in HEK293 cells stably transfected with human MC4 or MC3 receptors. The agonist relative efficacies as determined by the percentage of cAMP release relative to NDP-α-MSH were >80% for all compounds. Full concentration−response curves are provided in Figure 2 for select compounds. Further details of these assays are given in the Experimental Section.

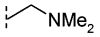
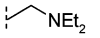
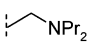
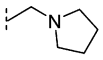
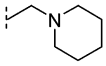
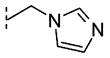
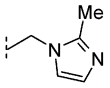
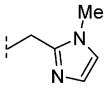
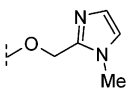
Various substitutions in the ortho position of the arylpiperazine were explored (Table 1). It was observed that increasing the size of the ortho substituent resulted in an increase in binding affinity and functional potency. For example, the isopropyl-substituted compound **29** possesses 9-fold better binding affinity than the unsubstituted compound **26**. In a similar manner, *O*-linked alkyl substitutions such as isopropoxide (**33**) have better binding affinity compared to phenol **30**. In general, aromatic groups such as phenyl (**34**) and benzyl (**35**) provided little benefit over the alkyl groups. The nitro (**36**), aniline (**37**), and dimethylaniline (**38**) compounds all possess binding affinities similar to the lead (**1**); however, sulfonamide **39**, the reversed sulfonamide of **1**, has 4-fold better binding affinity and 8-fold better functional potency. Extending the hydroxy functional group out by one carbon atom to give benzyl alcohol **40** resulted in a 3-fold increase in binding affinity relative to phenol **30**. The secondary alcohols **41** and **42** have 5-fold better binding affinity compared to **30**. Benzylmethanesulfonamide **43** is equipotent compared to sulfonamide **39**. However, *N*,*N*-dimethylbenzylamine **44** has 18-fold better binding affinity and 6-fold better functional potency than dimethylaniline **38**. *N*,*N*-Di-

Table 1. Initial Functional Group Exploration: Binding Affinity and Agonist Potency at HMC4[a]

compd	R	K_i[b] (nM)	EC_{50}[c] (nM)
α-MSH		26.6 ± 3.0	2.56 ± 0.48
26	H	6600 ± 400	360 ± 160
27	Me	1700 ± 360	1300 ± 33
28	Et	1300 ± 180	145 ± 1
29	^{i}Pr	720 ± 63	110 ± 6
30	OH	1900 ± 400	490 ± 120
31	OMe	1100 ± 25	71 ± 4
32	OEt	570 ± 180	40 ± 7
33	OiPr	460 ± 110	93 ± 45
34	OPh	640 ± 30	400 ± 50
35	OBn	640 ± 90	150 ± 51
36	NO_2	2400 ± 300	210 ± 26
37	NH_2	1700 ± 200	200 ± 32
38	NMe_2	1100 ± 250	44 ± 6
39	$NHSO_2Me$	220 ± 35	16 ± 3
40	CH_2OH	630 ± 230	150 ± 3
41	(*S*)-$CH(OH)CH_3$	350 ± 88	34.0 ± 0.8
42	(*R*)-$CH(OH)CH_3$	340 ± 30	44 ± 14
43	CH_2NHSO_2Me	210 ± 33	48 ± 7
44	CH_2NMe_2	60 ± 8	7.00 ± 0.02
45	$OCH_2CH_2NMe_2$	230 ± 17	98 ± 24

[a] Receptors expressed in HEK293 cells. [b] K_i values (n = 2 or 4) ± SEM determined by radioligand binding assay using ^{125}I-NDP-α-MSH. [c] EC_{50} values (n = 2 or 3) ± SEM determined by concentration of compound at 50% maximum cAMP release.

Table 2. Benzyl Amine SAR: Binding Affinity and Agonist Potency at HMC4[a]

compd	-R	Ki[b] (nM)	EC_{50}[c] (nM)
44		60 ± 8	7.00 ± 0.02
46		34 ± 5	14.0 ± 0.5
47		35 ± 4	8.0 ± 0.1
48		24 ± 1	39 ± 2
49		27 ± 1	37 ± 11
50		110 ± 23	14 ± 7
51		140 ± 31	21 ± 1
52		170 ± 11	44 ± 12
53		530 ± 18	140 ± 12

[a] Receptors expressed in HEK293 cells. [b] K_i values (n = 2 or 4) ± SEM determined by radioligand binding assay using ^{125}I-NDP-α-MSH. [c] EC_{50} values (n = 2) ± SEM determined by concentration of compound at 50% maximum cAMP release.

Table 3. Binding Affinity at hMC1, hMC3, hMC4, and hMC5 and Agonist Potency at hMC4 and MC5 for Key Compounds[a]

	K_i[b] (μM)				EC_{50}[c] (μM)	
compd	MC1R	MC3R	MC4R	MC5R	MC3R	MC4R
39	12 ± 3	8.8 ± 1.1	0.220 ± 0.035	1.2 ± 0.2	2.0 ± 0.6	0.016 ± 0.003
44	>20	7.0 ± 1.7	0.060 ± 0.008	1.4 ± 0.6	1.8 ± 0.7	0.00700 ± 0.00002
50	4.0 ± 0.7	3.6 ± 0.1	0.110 ± 0.023	0.7 ± 0.1	1.6 ± 0.6	0.014 ± 0.007

[a] Receptors expressed in HEK293 cells. [b] K_i values (n = 2 or 4) ± SEM determined by radioligand binding assay using ^{125}I-NDP-α-MSH. [c] EC_{50} values (n = 2) ± SEM determined by concentration of compound at 50% maximum cAMP release.

methylbenzylamine **44** compares favorably with the endogenous ligand α-MSH, having only 2-fold less binding affinity and functional potency. Ethanolamine **45** has 2-fold less binding affinity compared to **44** but is equipotent to sulfonamide **39**.

Structure−activity relationships around *N*,*N*-dimethylbenzylamine **44** were also explored (Table 2). Increasing the size of the alkyl groups resulted in a 2-fold increase in binding affinity: compare the dimethylamine (**44**) to the diethyl and dipropylamines (**46** and **47**). The cyclic amines pyrrolidine and piperidine (**48** and **49**) had affinities similar to the diethyl and dipropylamine (**46** and **47**). The tertiary amine was also replaced with basic heterocycles. The binding affinity of imidazole **50** was 5-fold less than that of **44**, but it maintained good functional potency. The *N*-linked and *C*-linked imidazoles **51** and **52** were similar to **50**. When the imidazole was extended out from the aryl ring by adding an oxygen linker, the resulting compound **53** was 3-fold less potent with 3-fold lower binding affinity than **52**.

Overall the compounds demonstrated good to excellent selectivity for MC4R over the other subtypes (Table 3). Sulfonamide **39** was >30-fold selective for MC4 over MC1 and MC3 based on affinity. The selectivity over MC5 was 5-fold. *N*,*N*-Dimethylbenzylamine **44** was 5-fold more selective than **39** at these receptors. The heterocyclic replacement for the benzylamine, imidazole **50**, was more similar in selectivity to sulfonamide **39**. Concentration−response curves for these compounds as well as the lead, arylpiperazine **1**, are presented in Figure 2a,b.

Sulfonamide **39** was chosen for bioavailability studies. It was dosed at 5 mg/kg iv (n = 3) and 30 mg/kg po (n = 3) in Fischer 344 rats in 10% acacia via gavage. Its oral bioavailability in rats was 30% with a volume of distribution of 4.5 ± 0.3 L/kg, while its clearance was 43 ± 1 mL/min/kg with a T_{max} of 3 ± 2 h and a $T_{1/2}$ of 1.7 ± 0.2 h.

Discussion

One successful strategy for the development of nonpeptidyl ligands for GPCR targets is the "privileged structure" approach.[7] Historically this approach has been largely empirical but it is now apparent that ligand binding chemical space is conserved across a range of evolutionarily related GPCRs. As a result, modification of a common scaffold that has proved itself successful at one receptor provides ligands that are selective for another. This approach appears to be most fruitful using conformationally rigid scaffolds such as benzodiazepines, biaryls, and spiropiperidines. In this example, we generated a series of libraries that were biased toward GPCR targets using the arylpiperazine as a conserved "privileged structure" scaffold that was modified by attaching a large number of dipeptides.[5] Iterative directed screening of these libraries against the MC4 receptor provided our lead compound **1**, in which the arylpiperazine nitrogen is attached to the dipeptide D-Tic-D-*p*-Cl-Phe. The same consensus dipeptide for MC4R has been reported by several other groups.[4b,8]

In the work described here, modification of the arylpiperazine portion resulted in further optimization of the lead series. A wide variety of functional groups at the position ortho to the piperazine were tolerated by the MC4 receptor. Binding was clearly improved as this space was filled; for example, in going from the unsubstituted compound **26** to the isopropyl-substituted compound **29**, we obtained a ligand with 9-fold better binding affinity. Sulfonamide **39**, which fills this space with a polar substituent, provides a further 2-fold improvement in binding affinity. Our most potent compounds filled this space with basic groups such as the dialkylamines **44**, **46**, and **47**. We found that we could also fill this space with basic heterocycles such as the imidazole **50**.

In summary, we have described the synthesis and structure−activity relationships of a novel series of arylpiperazines that are potent and selective agonists at the human MC4 receptor. Our efforts to optimize the arylpiperazine portion of the lead series successfully improved the binding affinity and functional potency at MC4. We have also demonstrated good oral bioavailability for sulfonamide **39**. Further improvement of this lead series and its potential use as a mediator of melanocortin physiology will be reported in due course.

Experimental Section

General. All reagents and solvents were used without further purification or drying. All reagents were purchased from Sigma-Aldrich, unless otherwise specified. Amino acids were purchased from Bachem, Novabiochem, or Midwest BioTech. Commercial grade anhydrous solvents were purchased from EMD chemicals or Mallinckrodt. All reactions were performed under an atmosphere of nitrogen, unless otherwise specified. Thin-layer chromatography (TLC) was conducted on precoated silica gel plates (Analtech or EM Science) and visualized with either short-wave UV light, 10% phosphomolybdic acid, or ceric ammonium molybdate. Flash column chromatography was carried out using prepacked silica gel columns from Biotage or Isco. Ion exchange chromatography was carried out using SCX BondElut columns from Varian. ^{1}H NMR spectra were collected on Varian 400 MHz or Bruker 300 MHz instruments and are recorded in parts per million (ppm) δ values, relative to $CHCl_3$ (δ 7.27), CHD_2OD (δ 3.30), or DMSO (δ 2.53) as the internal standard. Mass spectra were obtained on a Micromass QTOF-II, a Finnigen LCQ Duo Ion Trap or a PESciex API 150EX mass spectrometer, using electrospray ionization (ES) or atmospheric pressure chemical ionization (APCI). Abbreviations: Boc, *tert*-butoxycarbonyl; Boc_2O, di-*tert*-butyl dicarbonate; BINAP, 2,2′-bis(diphenylphosphino)-1,1′-binaphthyl; DMAP, 4-(dimethylamino)pyridine; DMS, dimethyl sulfide; EDC, 1-(3-(dimethylamino)propyl)-3-

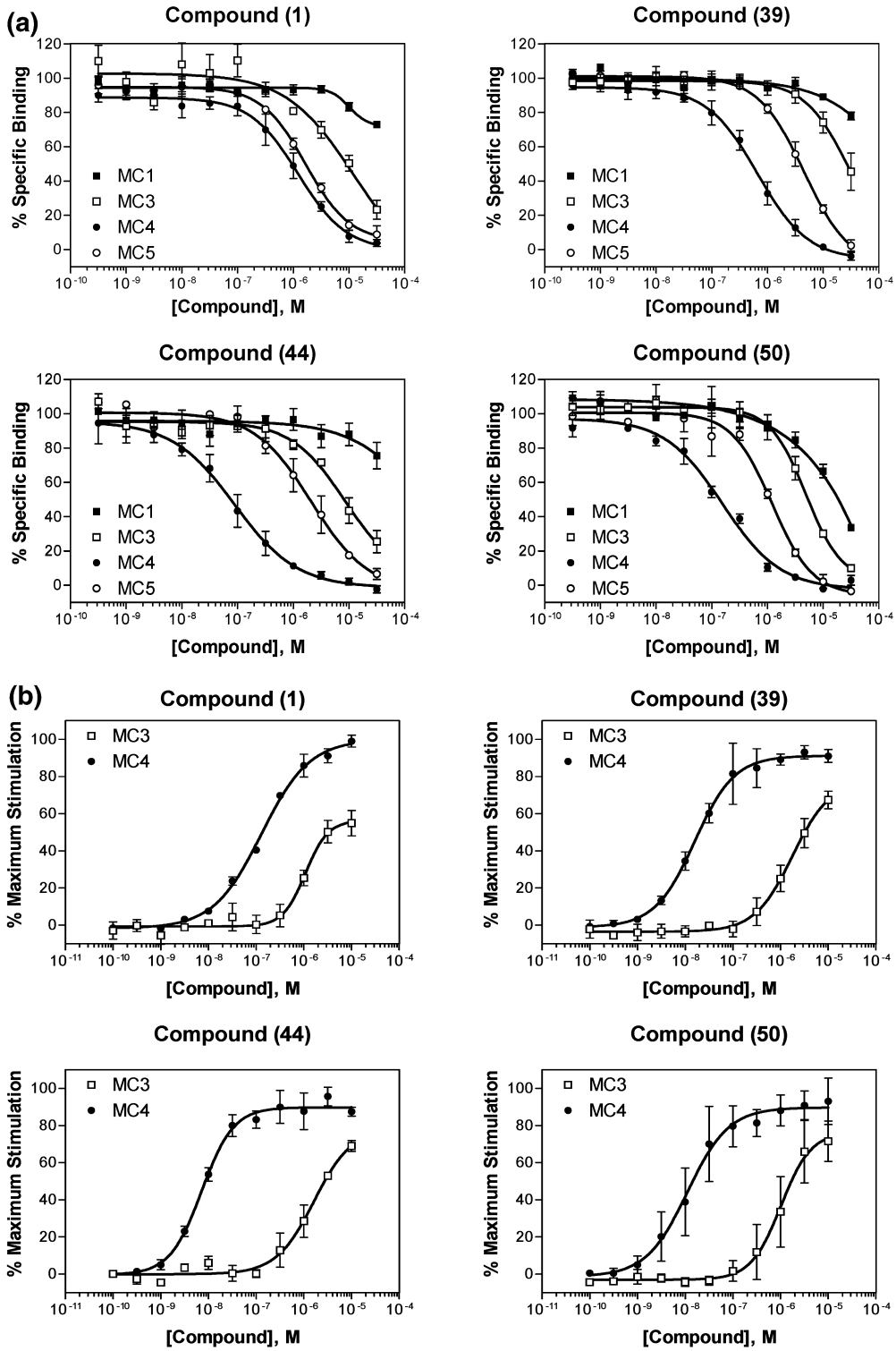


Figure 2. (a) Comparison of novel arylpiperazine compounds **1**, **39**, **44**, and **50** in MC1, MC3, MC4, and MC5 receptor binding profiles. The compounds shown have between 5- and >300-fold higher affinity for the MC4 receptor. Error bars indicate SEM for $n = 2$ or 4 independent determinations. (b) Agonist potencies for compounds **1**, **39**, **44**, and **50** were determined by measuring cAMP released from cells stably transfected with the MC3 or MC4 receptor. The compounds shown exhibit higher relative efficacies and agonist potencies for the MC4 receptor compared to the MC3 receptor. Percent maximum stimulation is relative to the cAMP release in the presence of NDP-αMSH. Error bars indicate SEM for $n = 2$ independent determinations.

ethylcarbodiimide hydrochloride; HOAt, 1-hydroxy-7-azabenzotriazole; HATU, *O*-(7-azobenzotriazol-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate; HEK, human embryonic kidney; $Pd_2(dba)_3$, tris(dibenzylideneacetone)dipalladium(0); TFA, trifluoroacetic acid; Tic, 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid.

Boc-D-Tic-D-*p*-Cl-Phe-OH (3). Step 1. The HCl salt of H-D-*p*-Cl-Phe-OMe (Midwest Biotech, 35.8 g, 129 mmol) was dissolved in water (200 mL). Ethyl acetate (200 mL) was added followed by addition of a saturated sodium bicarbonate solution. The mixture was stirred for about 5 min, and then the organic layer was separated, washed with water (200 mL), and dried over magnesium sulfate. Concentration of the mixture under reduced pressure produced a white solid (32.2 g). To the solid was added methylene chloride (200 mL), D-Boc-Tic-OH (35.8 g, 129 mmol), and 4-(dimethylamino)pyridine (75

mg). The mixture was cooled to 0 °C and EDC (24.7 g, 129 mmol) was added in two portions. After stirring for about 20 min, the ice bath was removed and the solution was allowed to warm to room temperature. The solution was stirred for about 4 h and then diluted with water (400 mL). The organic layer was washed with water (3×), dried over magnesium sulfate, and concentrated under reduced pressure to give a clear oil (70 g). Silica gel column chromatography (35% ethyl acetate/heptane) afforded about 55.6 g (85%) of the intermediate Boc-D-Tic-*p*-Cl-D-Phe-OMe (**2**). ^{1}H NMR (DMSO) (two rotomers observed): δ 8.26 (d, 1H), 8.19 (d, 0.5 H), 7.24 (d, 2H), 7.00−7.19 (m, 8H), 4.68 (m, 0.5H), 4.20−4.60 (m, 4.5H), 3.58 (s, 3H), 3.51 (s, 1.5H), 2.77−3.10 (m, 6H), 1.42 (s, 3H), 1.21 (s, 9H). LRMS (ES): 473.0 (M + 1), 471.1 (M − 1).

Step 2. The compound of step 1 (54.3 g, 114 mmol) was dissolved in methanol (170 mL). The solution was cooled to 0 °C with an ice bath and 1 N NaOH (290 mL) was added dropwise. After vigorous stirring for about 20 min, the mixture was warmed to about 25 °C. The solution was concentrated under reduced pressure to give a yellow oil. The oil was dissolved in water (200 mL) and the pH was adjusted to about 1. Ethyl acetate (200 mL) was added, and the organic layer was separated and dried over magnesium sulfate. The organic solution was filtered and concentrated to produce about 46.3 g of the title compound. ^{1}H NMR (DMSO) (two rotomers observed): δ 7.98 (d, 1H), 7.82 (d, 0.5 H), 6.90−7.41 (m, 16H), 4.20−4.70 (m, 8.5H), 2.60−3.20 (m, 8.5H), 1.32−1.41 (m, 19H). LRMS (ES): 459.1 (M + 1), 457.1 (M − 1).

***N*-(2-Ethylphenyl)piperazine (6a).** 2-Ethylbromobenzene (390 mg, 2.11 mmol), piperazine (280 mg, 3.25 mmol), $Pd_2(dba)_3$ (58 mg, 0.063 mmol), BINAP (60 mg, 0.096 mmol), sodium *t*-butoxide (285 mg, 2.97 mmol), and anhydrous toluene (4 mL) were combined in a 15 mL round-bottomed flask. The flask was evacuated and flushed with nitrogen (3×). The mixture was lowered into an oil bath and heated to 100 °C. After heating for about 2 h, the mixture was cooled, diluted with ethyl acetate (100 mL), filtered through Celite, and concentrated to a crude oil (432 mg). Purification by silica gel flash chromatography using a 99:1 to 85:15 gradient of dichloromethane:0.5 M ammonia/methanol gave the final product (225 mg, 1.18 mmol, 56%) as an oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (dd, J = 1.5, 7.3 Hz, 1H), 7.15 (dd, J = 1.8, 8.2 Hz, 1H), 7.21 (m, 2H), 2.98−3.02 (m, 4H), 2.82−2.86 (m, 4H), 2.69 (q, J = 7.6, 2H), 1.23 (t, J = 7.6, 3H). LRMS (ES+): 191.2 (M + 1).

***N*-(2-Isopropylphenyl)piperazine (6b).** The title compound was prepared from piperazine and 1-bromo-2-isopropylbenzene in a manner similar to that described for **6a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.27 (d, 1H, J = 8.6), 7.19−7.08 (m, 3H), 3.53 (septet, 1H, J = 7.0), 3.00−3.05 (m, 4H), 2.80−2.87 (m, 4H), 1.84 (bs, 1H), 1.22 (d, 6H, J = 7.0). LRMS (ES+): 205.4 (M + 1).

***N*-(2-Isopropoxyphenyl)piperazine (6c).** The title compound was prepared from piperazine and 1-bromo-2-isopropoxybenzene in a manner similar to that described for **6a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.96−6.84 (m, 4H), 4.60 (septet, 1H, J = 5.9 Hz), 3.05 (m, 8H), 2.01 (bs, 1H), 1.35 (d, 6H, J = 5.9 Hz). LRMS (ES+): 221.4 (M + 1).

***N*-(2-Phenoxyphenyl)piperazine (6d).** A mixture of phenylboronic acid (5.12 g, 42 mmol), 2-bromophenol (3.55 g, 21 mmol), $Cu(OAc)_2$ (7.63 g, 42 mmol), pyridine (8 mL, 103 mmol), and 4 Å molecular sieves (2.1 g) in CH_2Cl_2 was stirred at room temperature overnight. The mixture was diluted with CH_2Cl_2, filtered through Celite, washed with 1 M NaOH and brine, and dried. Removal of solvent gave 1-bromo-2-phenoxybenzene as crystals (1.40 g, 27%). LRMS (ES): 248 (M + 1). The title compound was prepared from piperazine and 1-bromo-2-phenoxybenzene in a manner similar to that described for **6a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.31−7.24 (m, 3H), 7.14−7.08 (m, 1H), 7.06−6.98 (m, 2H), 6.97−6.90 (m, 3H), 3.07−3.01 (m, 4H), 2.86−2.80 (m, 4H). LRMS (ES+): 255.1 (M + 1).

(*S*)-*N*-{2-[1-((*tert*-Butyldimethylsilanyl)oxy)ethyl]phenyl}piperazine (6e). To a 25 mL flask containing (*S*)-(−)-2-bromo-α-methylbenzyl alcohol (200 mg, 1.0 mmol), *tert*-butyldimethylsilyl chloride (165 mg, 1.1 mmol), and imidazole (203 mg, 3.0 mmol) flushed with nitrogen was added 5 mL of dimethylformamide. After stirring overnight, the mixture was quenched with saturated sodium bicarbonate; diluted with ethyl acetate; washed with NaH_2PO_4, saturated aqueous sodium bicarbonate, water, and brine; dried (Na_2SO_4); filtered; and concentrated. Purification by flash chromatography (10 g of SiO_2, linear gradient from 0 to 10% ethyl acetate/hexanes, 30 mL/min, over 30 min) gave 260 mg (0.82 mmol, 82%) of (*S*)-[1-(2-bromophenyl)ethoxy]-*tert*-butyldimethylsilane as a colorless oil. GC/MS (EI): 315 (M). The title compound was prepared from piperazine and (*S*)-[1-(2-bromophenyl)ethoxy]-*tert*-butyldimethylsilane in a manner similar the that described for **6a**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, 1H, J = 1.5 Hz), 7.31 (dt, 1H, J = 1.5, 7.3 Hz), 7.26−7.20 (m, 2H), 5.51 (q, 1H, J = 6.3 Hz), 3.17−3.08 (m, 4H), 2.96−2.90 (m, 4H), 2.20 (bs, 1H), 1.51 (d, 3H, J = 6.3 Hz), 0.97 (s, 9H), 0.12 (s, 3H), 0.00 (s, 3H). LRMS (ES+): 321.5 (M + 1).

(*R*)-*N*-{2-[1-(*tert*-Butyldimethylsilanyloxy)ethyl]phenyl}piperazine (6f). The title compound was prepared from (*R*)-(−)-2-bromo-α-methylbenzyl alcohol in a manner similar to that described for **6e**. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.65 (dd, 1H, J = 1.5 Hz), 7.32 (dt, 1H, J = 1.5, 7.3 Hz), 7.26−7.20 (m, 2H), 5.51 (q, 1H, J = 6.3 Hz), 3.16−3.07 (m, 4H), 2.95−2.89 (m, 4H), 2.09 (bs, 1H), 1.51 (d, 3H, J = 5.9 Hz), 0.97 (s, 9H), 0.11 (s, 3H), 0.00 (s, 3H). LRMS (ES+): 321.5 (M + 1).

1-Boc-4-(2-(aminomethyl)phenyl)piperazine (8). To a solution of *N*-(2-cyanophenyl)piperazine **7** (2.4 g, 12.78 mmol) in THF and H_2O (25 mL, 1:1) was added K_2CO_3 (3.9 g, 28.12 mmol). The solution was allowed to stir for about 10 min at room temperature. Boc_2O (3.1 g, 14.06 mmol) was then added and the reaction was allowed to stir for 1 h. The reaction mixture was diluted with EtOAc (100 mL) and washed with saturated $NaHCO_3$ (100 mL) and brine (100 mL). The organic phase was concentrated to give 3.2 g of 1-Boc-4-(2-cyanophenyl)piperazine (88%). To a solution of sodium borohydride (2.1 g, 56.03 mmol) in THF (25 mL) at 0 °C was added TFA (4.3 mL, 56.03 mmol) dropwise. 1-Boc-4-(2-cyanophenyl)piperazine (3.2 g, 11.21 mmol) was then added slowly at room temperature. The reaction was allowed to stir for about 12 h at room temperature. The reaction was quenched with H_2O, diluted 5-fold with EtOAc, and washed with brine. The organic phase was concentrated to give 1.0 g (30%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.34 (dd, 1H, J = 7.5, 1.6 Hz), 7.25 (dt, 1H, J = 7.6, 1.6 Hz), 7.14−7.08 (m, 2H), 3.94 (s, 2H), 3.60−3.54 (m, 4H), 2.89−2.84 (m, 4H), 2.44 (bs, 2H), 1.48 (s, 9H). LRMS (ES+) 292.1 (M + 1).

1-Boc-4-[2-((methylsulfonyl)amino)methyl)phenyl]piperazine (9). 1-Boc-4-(2-(aminomethyl)phenyl)piperazine **8** (2.09 g, 7.18 mmol) was dissolved in methylene chloride (50 mL), cooled to 0 °C, and treated with triethylamine (1.5 mL, 10.8 mmol) followed by methanesulfonyl chloride (0.67 mL, 8.61 mmol). The resulting mixture was stirred for about 3 h at room temperature; diluted with ether (200 mL); washed with water (50 mL), saturated aqueous sodium bicarbonate (50 mL), and brine (50 mL); and then dried over anhydrous magnesium sulfate. Concentration under reduced pressure followed by silica gel chromatography (30% ethyl acetate in hexanes) afforded the title compound (2.07 g, 78%) as a clear oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.25−7.40 (m, 2H), 7.00−7.15 (m, 2H), 4.40 (s, 1H), 3.55−3.65 (m, 4H), 2.80−2.95 (m, 4H), 2.75 (s, 3H), 1.60 (s, 9H). LRMS (APCI): 370 (M + H).

1-Boc-4-[2-((dimethylamino)methyl)phenyl]piperazine (10). 1-Boc-4-((2-aminomethyl)phenyl)piperazine **8** (2.0 g, 6.86 mmol) was dissolved in CH_3CN (15 mL) and cooled to about 0 °C. Aqueous formaldehyde (7.56 mL of a 37 wt % aqueous solution) was added to the cold solution followed by the addition of sodium cyanoborohydride (2.15 g, 34.32 mmol). The reaction mixture was allowed to stir at 0 °C for about 5 min and then allowed to warm to room temperature. The mixture was then concentrated to dryness. The resulting residue was taken up in EtOAc (100 mL) and washed with saturated $NaHCO_3$ solution (100 mL) and brine (100 mL). The organic phase was concentrated to dryness to afford about 2.2

g of the title compound. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 7.3 Hz, 1H), 7.20−7.25 (m, 1H), 7.00−7.10 (m, 2H), 3.65 (s, 2H), 3.55 (t, J = 4.4 Hz, 4H), 2.90 (t, J = 4.6 Hz, 4H), 2.25 (s, 6H), 1.50 (s, 9H). LRMS (ES+): 320.2 (M + 1).

1-Boc-4-(2-carboxyphenyl)piperazine (11). To a solution of *N*-(2-cyanophenyl)piperazine **7** (37.45 g, 200 mmol) in 500 mL of absolute ethanol was added 1000 mL of 25% aqueous KOH. The solution was heated to reflux for about 72 h and then cooled to about 0 °C. The solution was acidified with 890 mL of 5 M HCl, and then solid $NaHCO_3$ was added to bring the pH of the solution to about 8. $NaHCO_3$ (12.7 g, 120 mmol) and Boc_2O (11.4 g, 52.2 mmol) were added, and the mixture was stirred overnight, which was then acidified with 5 M HCl to about pH 1. After addition of EtOAc and brine, the aqueous solution was separated and extracted with EtOAc (2×). The combined organic solutions were washed with water (2×) and brine, dried (Na_2SO_4), filtered, and concentrated. The material was purified by recrystallization from EtOAc/hexanes to afford about 49.8 g (162 mmol, 81%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 16.5 (bs, 1H), 8.30 (dd, 1H, J = 7.8, 1.7 Hz), 7.60 (dt, 1H, J = 7.6, 1.6 Hz), 7.45−7.37 (m, 2H), 4.40−4.80 (m, 4H), 3.06−2.98 (m, 4H), 1.49 (s, 9H). LRMS (ES−): 305.2 (M − 1).

1-Boc-4-(2-(hydroxymethyl)phenyl)piperazine (12). To a solution of 1-Boc-4-(2-carboxyphenyl)piperazine **11** (37.5 g, 123 mmol) in 1000 mL of THF at 0 °C was added BH_3−THF (369 mL of a 1 M solution in THF, 369 mmol). The cold bath was removed and the solution stirred overnight. Another 50 mL of BH_3−THF was added. After stirring for 9 h, the solution was cooled to about 0 °C and then 220 mL of 2 M NaOH was added followed by EtOAc and brine. After separation, the aqueous solution was extracted with EtOAc (2×). The combined organic solutions were washed with water (2×) and brine, dried (Na_2SO_4), filtered, and concentrated to give about 35.2 g (120 mmol, 98%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30−7.20 (m, 2H), 7.17−7.10 (m, 2H), 4.83 (s, 1H), 4.79 (s, 2H), 3.61−3.56 (m, 4H), 2.93−2.89 (m, 4H), 1.48 (s, 9H). LRMS (ES+): 293.2 (M + 1).

1-Boc-4-(2-(imidazol-1-ylmethyl)phenyl)piperazine (13). To a solution of 1-Boc-4-(2-(hydroxymethyl)phenyl)piperazine **12** (300 mg, 1.02 mmol, 1.0 equiv), imidazole (104 mg, 1.53 mmol, 1.5 equiv), triphenylphosphine (535 mg, 2.04 mmol, 2.0 equiv), and THF at 0 °C under nitrogen was added DEAD (0.321 mL, 2.04 mmol, 2.0 equiv) slowly so that the temperature of reaction did not rise above 10 °C. After addition was completed, the ice bath was removed and the reaction mixture was stirred at room temperature overnight. Methanol was added and the mixture was stirred for about 15 min. The mixture was then concentrated. Purification by flash chromatography (35 g of SiO_2, linear gradient from 50 to 70% EtOAc/hexane for 15 min and 70% EtOAc for 18 min) afforded the title compound (109 mg, 0.32 mmol, 31%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.62 (s, 1H), 7.34 (dt, 1H, J = 7.6, 1.5 Hz), 7.19 (dd, 1H, J = 8.1, 1.0 Hz), 7.13 (dt, 1H, J = 7.5, 1.1 Hz), 7.08 (s, 1H), 7.03 (dd, 1H, J = 7.6, 1.3 Hz), 6.92 (s, 1H), 5.23 (s, 2H), 3.59−3.51 (m, 4H), 2.82−2.69 (m, 4H), 1.48 (s, 9H). LRMS (ES+): 343.2 (M + 1).

1-Boc-4-[2-((2-methylimidazol-1-yl)methyl)phenyl]piperazine (14). To a solution of 1-Boc-4-(2-(hydroxymethyl)-phenyl)piperazine **12** (300 mg, 1.03 mmol, 1.0 equiv), triethylamine (0.17 mL, 1.2 mmol, 1.2 equiv), and DMAP (6 mg, 0.05 mmol, 0.05 equiv) in CH_2Cl_2 (10 mL) was added methanesulfonyl chloride (0.085 mL, 1.1 mmol, 1.1 equiv). The solution was stirred at room temperature under N_2 for about 2 h. A solution of 2-methylimidazole (410 mg, 5.0 mmol, 5.0 equiv) in THF (3 mL) was added, and the mixture was allowed to stir at room temperature overnight. The mixture was diluted with EtOAc (50 mL) and washed with saturated aqueous $NaHCO_3$ (15 mL) and brine (15 mL). The combined organic extracts were dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (35 g of SiO_2, 40 mL/min, linear gradient from 0 to 10% 0.2 M NH_3 in MeOH/CH_2Cl_2 for 25 min and 10% 2.0M NH_3 in MeOH/CH_2Cl_2 for 7 min) afforded the title compound as a white solid (192 mg, 0.54 mmol, 54%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.30 (dt, 1H, J = 1.4, 8.0 Hz), 7.17 (dd, 1H, J = 8.0, 0.9 Hz), 7.08 (dt, 1H, J = 1.2, 7.6 Hz), 6.95 (d, 1H, J = 1.4 Hz), 6.82 (d, 1H, J = 1.4 Hz), 6.79 (d, 1H, J = 7.6), 5.13 (s, 2H), 3.57 (m, 4H), 2.81 (m, 4H), 2.33 (s, 3H), 1.51 (s, 9H). LRMS (ES+): 357.2 (M + H).

2-(*N*-Boc-piperazin-1-yl)benzaldehyde (15). To a solution of *N*-(2-cyanophenyl)piperazine **7** (375 mg, 2.0 mmol) in 15 mL of dioxane was added DIBAL-H (6 mL of a 1 M solution in heptane, 6 mmol). After stirring at room temperature for about 48 h, the solution was transferred via cannula into 20 mL of 0.5 M Rochelle salt. After stirring for about 2 h, $NaHCO_3$ (636 mg, 6 mmol) and Boc_2O (567 mg, 2.6 mmol) were added. After stirring overnight, EtOAc and brine were added. After separation, the aqueous solution was extracted with EtOAc (3×). The combined organic layers were washed with water and brine, dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (35 g of SiO_2, linear gradient from 10 to 20% EtOAc/hexane over 30 min at 35 mL/min) afforded about 436 mg (1.50 mmol, 75%) of the title compound as a yellow oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.34 (s, 1H), 7.82 (dd, 1H, J = 7.7, 1.6 Hz), 7.54 (dt, 1H, J = 7.7, 1.7 Hz), 7.18−7.08 (m, 2H), 3.65−3.60 (m, 4H), 3.06−3.01 (m, 4H), 1.48 (s, 9H). LRMS (ES+): 291.1 (M + 1).

1-Boc-4-(2-(pyrrolidin-1-ylmethyl)phenyl)piperazine (16c). To a solution of 2-(*N*-Boc-piperazin-1-yl)benzaldehyde **15** (400 mg, 1.4 mmol) in pyrrolidine (0.33 mL, 4 mmol) was added titanium isopropoxide (1.2 mL, 4 mmol), and the mixture was stirred at room temperature under a nitrogen atmosphere. After about 30 min, the mixture was diluted with ethanol (4 mL). Sodium borohydride (106 mg, 2.8 mmol) was added and the mixture was stirred for about 16 h. Water (2 mL) was added, and the resulting suspension was filtered. The filter cake was washed with methanol (5 mL), and the filtrate was concentrated to dryness. Purification by flash chromatography (1:1 hexanes/ethyl acetate) gave the title compound (470 mg, 96%) as a colorless oil. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.40−7.44 (m, 1H), 7.19−7.26 (m, 1H), 7.01−7.08 (m, 2H), 3.68 (s, 2H), 3.55 (t, J = 4.5 Hz, 4H), 2.92−2.95 (m, 4H), 2.53 (m, 4H), 1.75 (m, 4H), 1.49 (s, 9H). LRMS (APCI): 346 (M + H).

1-Boc-4-(2-((diethylamino)methyl)phenyl)piperazine (16a). The title compound was prepared from 2-(*N*-Boc-piperazin-1-yl)benzaldehyde **15** and diethylamine in a manner similar to that described for **16c**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 7.3 Hz, 1H), 7.19−7.26 (m, 1H), 7.03−7.11 (m, 2H), 3.63 (s, 2H), 3.56 (t, J = 4.4 Hz, 4H), 2.88 (t, J = 4.6 Hz, 4H), 2.54 (q, J = 7.2 Hz, 4H), 1.49 (s, 9H), 1.03 (t, J = 7.2 Hz, 6H). LRMS (APCI): 348 (M + H).

1-Boc-4-(2-((dipropylamino)methyl)phenyl)piperazine (16b). The title compound was prepared from 2-(*N*-Boc-piperazin-1-yl)benzaldehyde **15** and dipropylamine in a manner similar to that described for **16c**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54−7.57 (m, 1H), 7.01−7.26 (m, 3H), 3.58 (s, 2H), 3.49−3.53 (m, 4H), 2.85−2.90 (m, 4H), 2.38 (t, J = 7.3 Hz, 4H), 1.40−1.50 (m, 13H), 0.84 (t, J = 7.3 Hz, 6H). LRMS (APCI): 376 (M + H).

1-Boc-4-(2-(piperidin-1-ylmethyl)phenyl)piperazine (16d). The title compound was prepared from 2-(*N*-Boc-piperazin-1-yl)benzaldehyde **15** and piperidine in a manner similar to that described for **16c**. ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.38 (d, J = 7.6 Hz, 1H), 7.20−7.26 (m, 1H), 7.03−7.08 (m, 2H), 3.54−3.57 (m, 4H), 3.50 (s, 2H), 2.92−2.95 (m, 4H), 2.40 (m, 4H), 1.23−1.59 (m, 15H). LRMS (APCI): 360 (M + H).

1-Boc-4-{2-[hydroxy(1-methyl-1*H*-imidazol-2-yl)methyl]-phenyl}piperazine (18). To a solution of 1-methylimidazole (350 μL, 4.4 mmol) in 15 mL of THF at −78 °C was added ^{n}BuLi (1.5 mL of a 1.6 M solution in hexane, 2.4 mmol). After stirring for about 30 min, the solution was warmed to about 0 °C and then stirred for about 15 min. The mixture was then cooled to about −78 °C. A solution of 2-(*N*-Boc-piperazin-1-yl)benzaldehyde **15** (580 mg, 1.0 mmol) in 5 mL of THF was added via cannula. The solution was allowed to warm slowly to room temperature overnight. After addition of saturated aqueous NH_4Cl and brine, the solution was extracted with EtOAc (2×). The combined organic solutions were dried (Na_2-

SO_4), filtered, and concentrated. Purification by silica gel chromatography (35 g of SiO_2, linear gradient from 0 to 10% 0.2 M NH_3 in MeOH/CH_2Cl_2 over 30 min at 35 mL/min) afforded about 592 mg (1.59 mmol, 79%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.29 (dt, 1H, J = 7.7, 1.5 Hz), 7.21 (dd, 1H, J = 8.0, 0.9 Hz), 7.11 (dt, 1H, J = 7.4, 1.1 Hz), 7.02 (dd, 1H, J = 7.7, 1.4 Hz), 6.92 (d, 1H, J = 1.1 Hz), 6.82 (d, 1H, J = 1.2 Hz), 6.20 (s, 1H), 3.65−3.40 (m, 2H), 3.49 (s, 3H), 3.13−3.02 (m, 2H), 2.87−2.76 (m, 2H), 1.47 (s, 9H). LRMS (ES+): 373.2 (M + 1).

1-Boc-4-[2-((1-methyl-1*H*-imidazol-2-yl)methyl)phenyl]-piperazine (19). To a solution of 1-Boc-4-{2-[hydroxy(1-methyl-1*H*-imidazol-2-yl)methyl]phenyl}piperazine **18** (93 mg, 0.25 mmol) in 5 mL of THF was added NaH (30 mg, 0.75 mmol). After stirring for about 45 min, CS_2 (75 μL, 1.25 mmol) was added. After stirring for about 30 min, 5 mL of THF was added, followed by MeI (78 μL, 1.25 mmol). After stirring for about 1 h, saturated aqueous NH_4Cl and brine were added. The solution was extracted EtOAc (2×). The combined organic solutions were dried (Na_2SO_4), filtered, and concentrated. Purification by silica gel chromatography (35 g of SiO_2, linear gradient from 0 to 5% MeOH/CH_2Cl_2 over 30 min at 35 mL/min) afforded about 97 mg (0.21 mmol, 84%) of the xanthate as a yellow oil. LRMS (ES+): 463.2 (M + 1).

To a solution of the xanthate (90 mg, 0.195 mmol) and Bu_3-SnH (260 μL, 0.967 mmol) in 2 mL of toluene at 80°C was added AIBN (50 μL of a 0.4 M solution in toluene, 0.02 mmol). Another 50 μL of the AIBN solution was added every 2−3 h for 8 h. After stirring overnight, another 50 μL of the AIBN solution was added. After stirring for about 8 h more, the solution was concentrated and filtered through Celite with CH_2Cl_2. Purification by silica gel chromatography (35 g of SiO_2, linear gradient from 0 to 5% 0.2 M NH_3 in MeOH/CH_2Cl_2 over 30 min at 35 mL/min) afforded about 46 mg (0.13 mmol, 66%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.21 (m, 1H), 7.08 (d, 1H, J = 7.6 Hz), 7.03−7.01 (m, 2H), 6.95 (d, 1H, J = 1.2 Hz), 6.79 (d, 1H, J = 1.2 Hz), 4.17 (s, 2H), 3.52−3.50 (m, 4H), 3.36 (s, 3H), 2.56−2.58 (m, 4H), 1.48 (s, 9H). LRMS (ES+): 357.2 (M + 1).

1-Boc-4-(2-aminophenyl)piperazine (21). To a solution of *N*-(2-nitrophenyl)piperazine **20** (30 g, 145 mmol) and triethylamine (28.3 mL, 203 mmol) in 600 mL of CH_2Cl_2 was added di-*tert*-butyl dicarbonate (38 g, 174 mmol). After stirring overnight, the solution was washed with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), filtered, and concentrated to afford 1-Boc-4-(2-nitrophenyl)piperazine as an orange oil. To a solution of the oil in 2 L of ethanol was added 6 g of 5% Pd/C. After shaking under an atmosphere of 60 psi hydrogen overnight, the solution was filtered and concentrated to afford about 39 g (140 mmol, 97%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.00−6.94 (m, 2H), 6.78−6.72 (m, 2H), 4.21 (s, 2H), 3.60 (s, 4H), 2.90 (s, 4H), 1.49 (s, 9H). LRMS: 278.1 (M + 1).

1-Boc-4-(2-((methylsulfonyl)amino)phenyl)piperazine (22). To a solution of 1-Boc-4-(2-aminophenyl)piperazine **21** (5.55 g, 20 mmol) and triethyamine (5.6 mL, 40 mmol) in 200 mL of CH_2Cl_2 was added methanesulfonyl chloride (1.55 mL, 20 mmol). After stirring for 4 h, the solution was concentrated and the residue dissolved in 200 mL of EtOAc. The solution was washed twice with 1 M HCl, water, and brine; dried (Na_2SO_4); filtered; and concentrated to afford 6.68 g (18.8 mmol, 94%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.51 (dd, 1H, J = 8.3, 1.5 Hz), 7.21−7.15 (m, 2H), 7.09 (dt, 1H, J = 1.4, 7.2 Hz), 3.63−3.53 (m, 4H), 3.08 (s, 3H), 2.85−2.75 (m, 4H), 1.49 (s, 9H). LRMS (ES+): 356.1 (M + H).

1-Boc-4-(2-(dimethylamino)phenyl)piperazine (23). To a solution of 1-Boc-4-(2-nitrophenyl)piperazine (500 mg, 1.63 mmol, 1.0 equiv), prepared as described above for 1-Boc-4-(2-aminophenyl)piperazine **21**, in IPA (20 mL) was added formaldehyde (3.3 mL of a 37% solution in H_2O, 4.07 mmol, 2.5 equiv) and 10% Pd/C (125 mg). The reaction mixture was shaken under an atmosphere of hydrogen at 60 psi overnight. The mixture was filtered and diluted with CH_2Cl_2. The aqueous solution was separated and the organic solution was dried (Na_2SO_4), filtered through a pad of Celite, and concentrated. Purification by flash chromatography (35 g of SiO_2, 40 mL/min, linear gradient from 0 to 15% EtOAc/hexane for 20 min and 15% EtOAc/hexane for 13 min) gave 480 mg (1.57 mmol, 97%) of the title compound as a solid. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.07−6.80 (m, 4H), 3.57 (s, 4H), 3.06 (s, 4H), 2.83 (s, 6H), 1.48 (s, 9H). LRMS (ES+): 306.2 (M + H).

1-Boc-4-(2-hydroxyphenyl)piperazine. To a solution of *N*-(2-hydroxyphenyl)piperazine **24** (2.8 g, 15.7 mmol) and $NaHCO_3$ (2.3 g, 21.9 mmol) in 50 mL of THF, 50 mL of dioxane, and 50 mL of water was added di-*tert*-butyl dicarbonate (4.1 g, 18.8 mmol). After stirring overnight, the solution was neutralized with 1 M HCl and extracted with CH_2Cl_2 (2 × 100 mL). The combined organic solutions were dried (Na_2SO_4), filtered, and concentrated to give 4.0 g (14.4 mmol, 92%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.17−7.08 (m, 2H), 6.98 (d, 1H, J = 8.0 Hz), 6.88 (t, 1H, J = 7.6 Hz), 3.66−3.59 (m, 4H), 2.93−2.82 (m, 4H), 1.49 (s, 9H). LRMS (ES+): 279.2 (M + 1).

1-Boc-4-(2-(benzyloxy)phenyl)piperazine (25a). To a solution of 1-Boc-4-(2-hydroxyphenyl)piperazine (500 mg, 1.79 mmol) in 15 mL of DMF was added K_2CO_3 (592 mg, 4.29 mmol). After stirring for 5 min benzyl bromide (260 μL, 2.16 mmol) was added. After stirring overnight at 60 °C, the solution was cooled to room temperature, diluted with EtOAc; washed with water twice, saturated sodium bicarbonate, and brine; dried (Na_2SO_4); filtered; and concentrated. Purification by silica gel chromatography (35 g of SiO_2, 40 mL/min, from 10 to 30% EtOAc/hexanes, over 20 min and 30% EtOAc/hexanes for 13 min) afforded 344 mg (0.93 mmol, 54%) of the title compound. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47−7.43 (m, 2H), 7.41−7.36 (m, 2H), 7.35−7.29 (m, 1H), 7.03−6.91 (m, 4H), 5.13 (s, 2H), 3.60−3.53 (m, 4H), 3.09−3.01 (m, 4H), 1.5 (s, 9H). LRMS (ES+): 269.1 (M + H).

1-Boc-4-[2-((1-methyl-1*H*-imidazol-2-yl)methoxy)phenyl]piperazine (25c). To a solution of 1-Boc-4-(2-hydroxyphenyl)piperazine (556 mg, 2.0 mmol, 1.0 equiv), (1-methyl-1*H*-imidazol-2-yl)-methanol (448 mg, 4.0 mmol, 2.0 equiv), triphenylphosphine (1.04 g, 4.0 mmol, 2.0 equiv), and THF at 0 °C under nitrogen was added DEAD (0.629 mL, 4.0 mmol, 2.0 equiv) slowly so that the temperature of the reaction did not rise above 10 °C. After addition was complete, the ice bath was removed and the reaction mixture was stirred at room temperature overnight. After this time, methanol was added and the reaction was stirred for 15 min. The reaction mixture was then concentrated. Purification by flash chromatography (35 g of SiO_2, 40 mL/min, linear gradient from 0 to 8% 2.0 M NH_3 in MeOH/CH_2Cl_2 for 25 min and 8% 2.0 M NH_3 in MeOH for 7 min) afforded the title compound (279 mg, 0.75 mmol, 37%). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.06 (td, 1H, J = 10.8, 3.9 Hz), 7.00 (d, 1H, J = 1.2 Hz), 6.98 (d, 1H, J = 1.6 Hz), 6.87 (d, 1H, J = 1.0 Hz), 6.81−6.71 (m, 2H), 4.35 (d, 2H, J = 5.4 Hz), 4.0−3.2 (s, br, 4H), 3.67 (s, 3H), 2.90−2.77 (s, br, 4H), 1.48 (s, 9H). LRMS (ES+): 373.3 (M + H).

1-(D-Tic-4-Cl-D-Phe)-4-phenylpiperazine (26). Step 1. To a solution of *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** (156 mg, 0.34 mmol, 1.1 equiv), phenylpiperazine **4a** (50 mg, 0.31 mmol, 1.0 equiv), HOAt (710 μL of a 0.5 M solution in DMF, 0.36 mmol, 1.15 equiv), diisopropylethylamine (160 μL, 0.92 mmol, 3.0 equiv), and CH_2Cl_2 (4 mL) was added HATU (135 mg, 0.36 mmol, 1.15 equiv). After stirring at room temperature overnight, the solution was diluted with ethyl acetate; washed with 1 M HCl, water, saturated sodium bicarbonate, and brine; dried over Na_2SO_4; filtered; and concentrated. Purification by flash chromatography (10 g of SiO_2, linear gradient from 0 to 100% EtOAc/CH_2Cl_2, 35 mL/min, over 30 min) gave about 152 mg (0.25 mmol, 81%) of 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-phenylpiperazine. LRMS (ES+): 603.2 (M + H).

Step 2. To a solution of 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-phenylpiperazine (53 mg, 0.078 mmol) in CH_2Cl_2 (2 mL) and DMS (0.2 mL) was added TFA (2 mL). After stirring for about 2 h, the solution was azeotroped with heptane (2×). The residue was loaded onto an SCX ion exchange column with MeOH and flushed with MeOH. The product was eluted with

2 M NH_3 in MeOH and concentrated. Purification by flash chromatography (10 g of SiO_2, linear gradient from 0 to 10% methanol/CH_2Cl_2, 30 mL/min, over 30 min) afforded a white solid. The solid is dissolved in CH_2Cl_2 and precipitated with 1 M HCl in Et_2O. The solution was concentrated to afford 68 mg (0.126 mmol, 55%) of the HCl salt of the title compound. ^{1}H NMR (400 MHz, CD_3OD): δ 8.96 (d, 1H, J = 7.0 Hz), 7.50−7.44 (m, 2H), 7.39−7.23 (m, 11H), 5.20 (dd, 1H, J = 15.2, 7.3 Hz), 4.43 (s, 2H), 4.23 (dd, 1H, J = 11.9, 4.8 Hz), 3.96−3.86 (m, 3H), 3.73 (m, 1H), 3.50−3.42 (m, 3H), 3.30 (m, 1H), 3.19−3.06 (m, 3H), 2.92 (m, 1H). LRMS (ES+): 503.2 (M + H).

1-(D-Tic-4-Cl-D-Phe)-4-(2-methylphenyl)piperazine (27). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and *N*-(2-methylphenyl)piperazine **4b** in a manner similar to that described for **26**. ^{1}H NMR (400 MHz, CD_3OD): δ 8.97 (d, 1H, J = 6.6 Hz), 7.38−7.20 (m, 12H), 5.20 (m, 1H), 4.43 (s, 2H), 4.23 (dd, 1H, J = 4.3, 11.7 Hz), 4.00−3.70 (m, 4H), 4.00−3.70 (m, 4H), 3.46 (dd, 1H, J = 3.9, 16.8 Hz), 3.30−3.05 (m, 6H), 2.70 (m, 1H), 2.44 (s, 3H). LRMS (ES+): 517.2 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-ethylphenyl)piperazine (28). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and *N*-(2-ethylphenyl)piperazine **6a** in a manner similar to that described for **26**. ^{1}H NMR (400 MHz, CD_3OD): δ 7.37−7.19 (m, 9H), 7.13 (dt, 1H, J = 1.8, 7.9 Hz), 7.04 (dt, 1H, J = 1.2, 7.3 Hz), 6.95 (d, 1H, J = 7.9 Hz), 5.20 (t, 1H, J = 7.9 Hz), 4.32 (s, 2H), 4.15 (m, 1H), 3.80 (m, 1H), 3.63−3.49 (m, 3H), 3.35 (m, 1H), 3.15−3.00 (m, 3H), 2.82−2.55 (m, 5H), 2.25 (m, 1H), 1.20 (t, 3H, J = 7.7 Hz). LRMS (ES+): 531.3 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-isopropylphenyl)piperazine (29). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and *N*-(2-isopropylphenyl)piperazine **6b** in a manner similar to that described for **26**. ^{1}H NMR (400 MHz, MeOD): δ 8.95 (d, 1H, J = 5.7 Hz), 7.6−7.19 (m, 12H), 5.2 (m, 1H), 4.42 (s, 2H), 4.24 (dd, 1H, J = 4.7, 12.1 Hz), 4.00−3.60 (m, 3H), 3.68−3.51 (m, 3H), 3.20−2.80 (m, 7H), 1.25 (d, 3H, J = 6.6 Hz), 1.24 (d, 3H, J = 6.6 Hz). LRMS (ES+): 545.2 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-hydroxyphenyl)piperazine (30). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and *N*-(2-hydroxyphenyl)piperazine **24** in a manner similar to that described for **26**. ^{1}H NMR (400 MHz, MeOD): δ 7.43−7.23 (m, 10H), 7.06−7.01 (m, 2H), 5.19 (t, 1H, J = 7.8 Hz), 4.42 (s, 2H), 4.24 (dd, 1H, J = 6.8, 4.9 Hz), 4.06−3.94 (m, 3H), 3.79 (bs, 1H), 3.70−3.60 (m, 2H), 3.50−3.42 (m, 3H), 3.19−3.06 (m, 3H). LRMS (ES+): 519.5 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-methoxyphenyl)piperazine (31). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and *N*-(2-methoxyphenyl)piperazine **4c** in a manner similar to that described for **26**. ^{1}H NMR (400 MHz, CD_3OD): δ 9.01 (d, 1H, J = 7.0 Hz), 7.46−7.23 (m, 11H), 7.12 (t, 1H, J = 7.4 Hz), 5.19 (m, 1H), 4.43 (s, 2H), 4.23 (dd, 1H, J = 4.7, 11.7 Hz), 3.99 (s, 3H), 4.02−3.88 (m, 3H), 3.76 (m, 1H), 3.60−3.50 (m, 2H), 3.45 (dd, 1H, J = 4.7, 18.4 Hz), 3.35 (m, 1H), 3.20−3.08 (m, 3H), 2.96 (m, 1H). LRMS (ES+): 533.2 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-ethoxyphenyl)piperazine (32). 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-ethoxyphenyl)piperazine was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and *N*-(2-ethoxyphenyl)piperazine **4d** in a manner similar to that described in step 1 for **26**. To a solution of 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-ethoxyphenyl)piperazine (180 mg, 028 mmol) and dimethyl sulfide (0.5 mL) in 2 mL of CH_2Cl_2 was added 2 mL of TFA. After stirring for 1 h the solution was concentrated. The residue was dissolved in methylene chloride and precipitated with ether to obtain 170 mg (0.26 mmol) of the TFA salt of the title compound. ^{1}H NMR (400 MHz, DMSO): δ 9.0 (d, 1H, J = 2.8 Hz), 7.36−7.25 (m, 4H), 7.24−7.19 (m, 4H), 6.92−6.77 (m, 4H), 5.20 (m, 1H), 4.39−4.22 (m, 2H), 4.14 (m, 1H), 4.01 (d, 1H, J = 6.6 Hz), 3.98 (d, 1H, J = 6.6 Hz), 3.64−3.42 (m, 4H), 3.04−2.74 (m, 7H), 2.64 (m, 1H), 1.32 (t, 3H, J = 7.0 Hz). LRMS (ES+): 547.1 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-isopropoxyphenyl)piperazine (33). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and *N*-(2-isopropoxyphenyl)piperazine **6c** in a manner similar to that described for **26**. ^{1}H NMR (400 MHz, MeOD): δ 7.51−7.47 (m, 2H), 7.38−7.24 (m, 9H), 7.12 (dt, 1H, J = 1.2, 7.8 Hz), 5.20 (m, 1H), 4.42 (s, 2H), 4.24 (dd, 1H, J = 4.7, 11.7 Hz), 4.16−4.03 (m, 3H), 3.82 (m, 1H), 3.79−3.60 (m, 3H), 3.49 (m, 1H), 3.47 (dd, 1H, J = 5.0, 16.8 Hz), 3.19−3.03 (m, 4H), 1.43 (d, 6H, J = 6.2 Hz). LRMS (ES+): 561.2 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-phenoxyphenyl)piperazine (34). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and *N*-(2-phenoxyphenyl)piperazine **6d** in a manner similar to that described for **26**. ^{1}H NMR (400 MHz, MeOD): δ 9.00 (d, 1H, J = 6.4 Hz), 7.60 (d, 1H, J = 7.8 Hz), 7.50−7.22 (m, 14H), 7.20−7.14 (m, 2H), 6.93 (d, 1H, J = 4.8 Hz), 5.19 (m, 1H), 4.42 (s, 2H), 4.23 (dd, 1H, J = 11.1, 3.9 Hz), 4.05−3.88 (m, 3H), 3.82−3.63 (m, 3H), 3.54 (m, 1H), 3.43 (dd 1H, J = 4.5, 17.5 Hz), 3.22−3.05 (m, 4H). LRMS (ES+): 595.2 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-(benzyloxy)phenyl)piperazine (35). Step 1. To a solution of 4-Boc-1-(2-benzyloxyphenyl)piperazine **25a** and dimethyl sulfide (0.25 mL) in 6 mL of CH_2Cl_2 was added 3 mL of TFA. After stirring for 30 min the solution was concentrated to give an oil. The oil was loaded onto a 10-g SCX ion exchange column with MeOH. The column was flushed with 20 mL of MeOH then and 20 mL of 2 M NH_3 in MeOH. The fractions containing desired product were combined and concentrated to give 230 mg of 1-(2-(benzyloxy)-phenyl)piperazine as an oil. LRMS (ES+): 269.1 (M+H).

Step 2. To a solution of *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** (307 mg, 0.67 mmol, 1.0 equiv), 1-(2-(benzyloxy)phenyl)piperazine (180 mg, 0.67 mmol, 1.0 equiv), diisopropylethylamine (300 μL, 1.67 mmol, 2.5 equiv), and CH_2Cl_2 (7 mL) was added HATU (254 mg, 0.67 mmol, 1.0 equiv). After stirring at room temperature overnight, the solution was diluted with ethyl acetate; washed with 1 M HCl, water, saturated sodium bicarbonate, and brine; dried over Na_2SO_4; filtered; and concentrated. Purification by flash chromatography (35 g of SiO_2, linear gradient from 30 to 80% EtOAc/hexanes for 20 min and then 80% EtOAc/hexanes for 13 min, 35 mL/min) gave about 327 mg (0.46 mmol, 69%) of 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-(benzyloxy)phenyl)piperazine. LRMS (ES+): 709.1 (M + H).

Step 3. To a solution of 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-(benzyloxy)phenyl)piperazine (315 mg, 0.44 mmol) in CH_2Cl_2 (5 mL) and DMS (0.25 mL) was added TFA (3 mL). After stirring for about 1 h, the solution was azeotroped from heptane (2×). The residue was loaded onto an SCX ion exchange column with MeOH and flushed with MeOH. The product was eluted with 2 M NH_3 in MeOH and concentrated. Purification by flash chromatography (35 g SiO_2, step gradient from 0 to 11% 2 M NH_3 in methanol/CH_2Cl_2, 40 mL/min, over 36 min) afforded a white solid. The solid was dissolved in CH_2Cl_2 and precipitated with 1 M HCl in Et_2O. The solution was concentrated to afford 253 mg (0.39 mmol, 89%) of the HCl salt of the title compound. ^{1}H NMR (400 MHz, MeOD): δ 9.00 (d, 1H, J = 6.6 Hz), 7.54−7.49 (m, 2H), 7.46−7.22 (m, 14H), 7.13 (t, 1H, J = 7.7 Hz), 5.30 (s, 2H), 5.16 (m, 1H), 4.42 (s, 2H), 4.22 (dd, 1H, J = 11.9, 4.6 Hz), 4.12−3.33 (m, 6H), 3.38 (m, 1H), 3.44 (dd, 1H, J = 16.9, 4.8 Hz), 3.24−2.91 (m, 4H). LRMS (ES+): 609.2 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-nitrophenyl)piperazine (36). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and *N*-(2-nitrophenyl)piperazine **20** in a manner similar to that described for **26**. ^{1}H NMR (400 MHz, MeOD): δ 7.76 (dd, 1H, J = 1.2, 7.8 Hz), 7.57 (dt, 1H, J = 1.6, 7.4 Hz), 7.37−7.17 (m, 10H), 5.19 (t, 1H, J = 7.8 Hz), 4.41 (s, 2H), 4.19 (dd, 1H, J = 4.7, 11.7 Hz), 3.82 (m, 1H), 3.60−3.40 (m, 4H), 3.18−2.90 (m, 5H), 2.81 (m, 1H), 2.42 (m, 1H). LRMS (ES+): 548.2 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-aminophenyl)piperazine (37). 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-nitrophenyl)piperazine was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and *N*-(2-nitrophenyl)piperazine **20** in a manner similar to that described in step 1 for **26**. A solution of 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-nitrophenyl)piperazine (260 mg, 0.4 mmol) and PtO_2 (70 mg) in 30

mL of 2-propanol was shaken in a Parr hydrogenation apparatus under 45 psi of H_2 for about 1 h. The solution was filtered through Celite and concentrated to yield about 263 mg (0.4 mmol, 100%) of 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-aminophenyl)piperazine, which was used without further purification. 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-aminophenyl)piperazine was deprotected with TFA in a manner similar to that described in step 2 for **26**. ^{1}H NMR (400 MHz, MeOD): δ 7.41−7.29 (m, 12H), 5.2 (dd, 1H, J = 4.7, 3.1 Hz), 4.43 (s, 2H), 4.24 (dd, 1H, J = 7.0, 4.7 Hz), 3.94 (m, 1H), 3.71−3.40 (m, 4H), 3.20−3.03 (m, 3H), 2.90−2.70 (m, 2H), 2.65 (m, 1H), 2.19 (m 1H). LRMS (ES+): 518.3 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-(dimethylamino)phenyl)piperazine (38). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and 1-Boc-4-(2-(dimethylamino)phenyl)-piperazine **23** in a manner similar to that described for **35**. ^{1}H NMR (400 MHz, MeOD): δ 7.85 (d, 1H, J = 8.1 Hz), 7.66−7.50 (m, 3H), 7.48−7.23 (m, 8H), 5.21 (m, 1H), 4.50 (m, 1H), 4.44 (s, 2H), 4.24 (dd, 1H, J = 12.0, 4.6 Hz), 3.94 (m, 1H), 3.62 (m, 1H), 3.43 (m, 1H), 3.29 (s, 6H) 3.22−3.00 (m, 4H), 2.92−2.81 (m, 2H), 2.70 (m, 1H), 2.50 (m, 1H). LRMS (ES+): 546.2 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-((methylsulfonyl)amino)phenyl)piperazine (39). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and 1-Boc-4-(2-((methylsulfonyl)-amino)phenyl)piperazine **22** in a manner similar to that described for **35**. ^{1}H NMR (400 MHz, MeOD): δ 8.91 (d, 1H, J = 7.3 Hz), 7.49−7.14 (m, 11H), 5.21 (m, 1H), 4.42 (s, 2H), 4.22 (dd, 1H, J = 11.7, 4.7 Hz), 3.90 (m, 1H), 3.60−3.58 (m, 3H), 3.45 (dd, 1H, J = 4.7, 17.2 Hz), 3.20−3.08 (m, 4H), 3.08 (s, 3H), 2.95−2.80 (m, 2H), 2.74 (m, 1H), 2.34 (m, 1H). LRMS (ES+): 596.2 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-(hydroxymethyl)phenyl)piperazine (40). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and 1-Boc-4-(2-(hydroxymethyl)phenyl)-piperazine **12** in a manner similar to that described for **35**. ^{1}H NMR (400 MHz, CD_3OD): δ 9.02 (d, 1H, J = 6.8 Hz), 7.50−7.22 (m, 12H), 5.20 (m, 1H), 5.00 (s, 2H), 4.43 (s, 2H), 4.24 (dd, 1H, J = 11.7, 4.9 Hz), 4.03−3.70 (m, 4H), 3.55−3.41 (m, 3H), 3.29 (m, 1H), 3.21−3.05 (m, 3H), 2.89 (m, 1H). LRMS (ES+): 533.2 (M + 1).

(*S*)-1-(D-Tic-4-Cl-D-Phe)-4-[2-(1-hydroxyethyl)phenyl]-piperazine (41). (*S*)-1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-{2-[1-((*tert*-butyldimethylsilanyl)oxy)ethyl]phenyl}piperazine was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and (*S*)-*N*-{2-[1-((*tert*-butyldimethylsilanyl)oxy)ethyl]phenyl}piperazine **6e** in a manner similar to that described in step 1 for **26**. To a solution of (*S*)-1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-{2-[1-((*tert*-butyldimethylsilanyl)oxy)ethyl]phenyl}piperazine (100 mg, 0.13 mmol) in 2 mL of CH_2Cl_2 was added 1 drop of water and 1 mL of TFA. After stirring for 3 h, heptane was added and the solution concentrated to an oil. To a solution of the oil in a polypropylene tube in 2 mL of THF cooled to 0 °C was added 1 mL of HF−pyridine. The solution was allowed to warm slowly to room temperature with stirring overnight. The solution was diluted with CH_2Cl_2, washed twice with saturated aqueous sodium bicarbonate and brine, dried (Na_2SO_4), filtered, and concentrated. Purification by flash chromatography (10 g of SiO_2, linear gradient from 0 to 10% methanol/CH_2Cl_2, 30 mL/min, over 30 min) afforded a white solid. The solid was dissolved in CH_2Cl_2 and precipitated with 1 M HCl in Et_2O. The solution was concentrated to afford 63 mg (0.11 mmol, 82%) of the HCl salt of the title compound. ^{1}H NMR (400 MHz, CD_3OD): δ 7.47 (dd, 1H, J = 1.6, 7.8 Hz), 7.34−7.32 (m, 2H), 7.27−7.00 (m, 9H), 5.32 (q, 1H, J = 6.6 Hz), 5.17 (dd, 1H, J = 6.6, 8.2 Hz), 3.97 (s, 2H), 3.80 (m, 1H), 3.45−3.35 (m, 4H), 3.08−3.94 (m, 3H), 2.88 (m, 1H), 2.81 (dd, 1H, J = 10.2, 16.0 Hz), 2.65 (m, 1H), 2.52 (m, 1H), 2.28 (m, 1H), 1.41 (d, 3H, J = 6.6 Hz). LRMS (ES+): 547.3 (M + 1).

(*R*)-1-(D-Tic-4-Cl-D-Phe)-4-[2-(1-hydroxyethyl)phenyl]-piperazine (42). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and (*R*)-*N*-{2-[1-((*tert*-butyldimethylsilanyl)oxy)ethyl]phenyl}piperazine **6f** in a manner similar to that described for **41**. ^{1}H NMR (400 MHz, CD_3OD): δ 7.47 (d, 1H, J = 7.4 Hz), 7.34−7.30 (m, 2H), 7.27−7.01 (m, 9H), 5.33 (q, 1H, J = 6.3 Hz), 5.16 (t, 1H, J = 7.0 Hz), 3.97 (s, 2H), 3.80 (m, 1H), 3.62−3.35 (m, 4H), 3.08−2.95 (m, 4H), 2.85−2.80 (m, 2H), 2.78−2.65 (m 2H), 2.16 (m, 1H), 1.41 (d, 3H, J = 6.3 Hz). LRMS (ES+): 547.3 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-[2-(((methylsulfonyl)amino)methyl)phenyl]piperazine (43). 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-[2-(((methylsulfonyl)amino)methyl)phenyl]piperazine was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and 1-Boc-4-[2-(((methylsulfonyl)amino)methyl)phenyl]piperazine **9** in a manner similar to that described in steps 1 and 2 for **35**. The TFA salt of the title compound was prepared from 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-[2-(((methylsulfonyl)amino)methyl)phenyl]-piperazine in a manner similar to that described for **32**. ^{1}H NMR (300 MHz, DMSO): δ 9.30−9.60 (m, 2H), 9.00−9.10 (m, 1H), 7.20−7.60 (m, 11H), 6.85−7.10 (m, 2H), 4.80−5.10 (m, 1H), 4.10−4.50 (m, 5H), 2.35−3.85 (m, 9H), 2.50 (s, 3H). LRMS (APCI): 610 (M + H).

1-(D-Tic-4-Cl-D-Phe)-4-(2-((dimethylamino)methyl)phenyl)piperazine (44). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and 1-Boc-4-(2-((dimethylamino)-methyl)phenyl)piperazine **10** in a manner similar to that described for **35**. ^{1}H NMR (400 MHz, CD_3OD): δ 8.90 (d, 1H, J = 7.0 Hz), 7.52−7.47 (m, 2H), 7.39−7.22 (m, 10H), 5.21 (m, 1H), 4.44 (s, 2H), 4.43 (d, 1H, J = 13.2 Hz), 4.38 (d, 1H, J = 13.2 Hz), 4.24 (dd, 1H, J = 4.8, 12.3 Hz), 3.79−3.56 (m, 3H), 3.46 (dd, 1H, J = 4.8, 17.1 Hz), 3.26−3.04 (m, 4H), 2.92−2.76 (m, 3H), 2.88 (s, 3H), 2.87 (s, 3H), 2.64 (m, 1H). LRMS (ES+): 560.2 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-{2-[2-(dimethylamino)ethoxy]-phenyl}piperazine (45). To a solution of 1-Boc-4-(2-hydroxyphenyl)piperazine (300 mg, 1.08 mmol), 2-(dimethylamino)-ethyl chloride hydrochloride (233 mg, 1.62 mmol), K_2CO_3 (450 mg, 3.26 mmol), and KI (357 mg, 2.15 mmol) in DMF (10 mL) was added 18-crown-6 (1.42 g, 5.37 mmol). After stirring overnight, water was added and the solution extracted with CH_2Cl_2 (3×). The combined organic extracts were concentrated to an oil. The oil was loaded onto a 10 g SCX ion exchange column equilibrated with MeOH. The column was flushed with 20 mL of MeOH, 20 mL of 0.2 M NH_3 in MeOH, and 20 mL of 2 M NH_3 in MeOH. The fractions containing desired product were combined and concentrated to an oil. To a solution of the oil in MeOH (2 mL) was added 1 M HCl (6 mL) in Et_2O. After stirring overnight, the solution was concentrated to an oil to obtain *N*-{2-[2-(dimethylamino)ethoxy]phenyl}piperazine. LRMS: 250.2 (M + 1). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and *N*-{2-[2-(dimethylamino)-ethoxy]phenyl}piperazine in a manner similar to that described for **26**. NMR (400 MHz, CD_3OD): δ 8.99 (d, 1H, J = 6.8 Hz), 7.40−7.12 (m, 12H), 5.20 (m, 1H), 4.52−4.46 (m, 2H), 4.43 (s, 2H), 4.24 (dd, 1H, J = 12.0, 4.9 Hz), 4.14−3.74 (m, 4H), 3.72−3.66 (m, 2H), 3.55−3.20 (m, 3H), 3.45 (dd, 1H, J = 16.9, 4.9 Hz), 3.19−3.05 (m, 4H), 3.00 (s, 6H). LRMS (ES+): 590.3 (M + 1).

1-(D-Tic-4-Cl-D-Phe)-4-(2-((diethylamino)methyl)phenyl)-piperazine (46). 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-((diethylamino)methyl)phenyl)piperazine was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and 1-Boc-4-(2-((diethylamino)methyl)-phenyl)piperazine **16a** in a manner similar to that described in steps 1 and 2 for **35**. The TFA salt of the title compound was prepared from 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-((diethylamino)methyl)phenyl)piperazine in a manner similar to that described for **32**. ^{1}H NMR (300 MHz, CD_3OD): δ 7.47−7.53 (m, 2H), 7.21−7.39 (m, 10H), 5.20 (t, J = 7.4 Hz, 1H), 4.42 (s, 2H), 4.39 (s, 2H), 4.20−4.25 (m, 1H), 3.40−3.80 (m, 5H), 3.05−3.25 (m, 8H), 2.60−2.90 (m, 3H), 1.34 (t, J = 7.2 Hz, 6H). LRMS (APCI): 588 (M + H).

1-(D-Tic-4-Cl-D-Phe)-4-(2-((dipropylamino)methyl)phenyl)piperazine (47). 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-((dipropylamino)methyl)phenyl)piperazine was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and 1-Boc-4-(2-((dipropylamino)methyl)-phenyl)piperazine **16b** in a manner similar to that described in steps 1 and 2 for **35**. The TFA salt of the title compound was prepared from 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-((dipropyl-

amino)methyl)phenyl)piperazine in a manner similar to that described for **32**. ^{1}H NMR (300 MHz, CD_3OD): δ 7.47−7.53 (m, 2H), 7.21−7.39 (m, 10H), 5.20 (t, J = 7.5 Hz, 1H), 4.42 (s, 4H), 4.20−4.25 (m, 1H), 3.40−3.70 (m, 5H), 2.98−3.18 (m, 8H), 2.70−2.85 (m, 3H), 1.69−1.86 (m, 4H), 0.96 (t, J = 7.3 Hz, 6H). LRMS (APCI): 616 (M + H).

1-(D-Tic-4-Cl-D-Phe)-4-(2-(pyrrolidin-1-ylmethyl)phenyl)-piperazine (48). 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-(pyrrolidin-1-ylmethyl)phenyl)piperazine was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and 1-Boc-4-(2-(pyrrolidin-1-ylmethyl)-phenyl)piperazine **16c** in a manner similar to that described in steps 1 and 2 for **35**. The TFA salt of the title compound was prepared from 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-(pyrrolidin-1-ylmethyl)phenyl)piperazine in a manner similar to that described for **32**. ^{1}H NMR (300 MHz, CD_3OD): δ 7.45−7.50 (m, 2H), 7.19−7.39 (m, 10H), 5.20 (t, J = 7.2 Hz, 1H), 4.42 (s, 4H), 4.19−4.25 (m, 1H), 3.65−3.78 (m, 1H), 3.40−3.96 (m, 6H), 3.02−3.24 (m, 5H), 2.60−2.85 (m, 3H), 2.00−2.17 (m, 5H). LRMS (APCI): 586 (M + H).

1-(D-Tic-4-Cl-D-Phe)-4-(2-(piperidin-1-ylmethyl)phenyl)-piperazine (49). 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-(piperidin-1-ylmethyl)phenyl)piperazine was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and 1-Boc-4-(2-(piperidin-1-ylmethyl)-phenyl)piperazine **16d** in a manner similar to that described in steps 1 and 2 for **35**. The TFA salt of the title compound was prepared from 1-(*N*-Boc-D-Tic-4-Cl-D-Phe)-4-(2-(piperidin-1-ylmethyl)phenyl)piperazine in a manner similar to that described for **32**. ^{1}H NMR (300 MHz, CD_3OD): δ 7.47−7.52 (m, 2H), 7.21−7.39 (m, 10H), 5.21 (t, J = 7.1 Hz, 1H), 4.42 (s, 2H), 4.37 (s, 2H), 4.19−4.25 (m, 1H), 3.41−3.87 (m, 6H), 3.02−3.18 (m, 6H), 2.64−2.98 (m, 4H), 1.52−2.20 (m, 6H). LRMS (APCI): 600 (M + H).

1-(D-Tic-4-Cl-D-Phe)-4-(2-(imidazol-1-ylmethyl)phenyl)-piperazine (50). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and 1-Boc-4-(2-(imidazol-1-yl-methyl)phenyl)piperazine **13** in a manner similar to that described for **35**. ^{1}H NMR (400 MHz, MeOD): δ 8.98 (s, 1H), 7.55 (s, 2H), 7.46−7.16 (m, 12H), 5.53 (s, 2H), 5.21 (m, 1H), 4.43 (s, 2H), 4.23 (dd, 1H, J = 12.2, 4.9 Hz), 3.85 (m, 1H), 3.62−3.50 (m, 3H), 3.45 (dd, 1H, J = 5.1, 17.4 Hz), 3.18−3.03 (m, 3H), 2.80−2.52 (m, 3H), 2.18 (m, 1H). LRMS (ES+): 583.2 (M + H).

1-(D-Tic-4-Cl-D-Phe)-4-[2-((2-methylimidazol-1-yl)methyl)phenyl]piperazine (51). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and 1-Boc-4-[2-((2-methylimidazol-1-yl)methyl)phenyl]piperazine **14** in a manner similar to that described for **35**. ^{1}H NMR (400 MHz, MeOD): δ 8.93 (d, 1H, J = 7.3 Hz), 7.47−7.23 (m, 11H), 7.22−7.16 (m, 2H), 7.07 (dd, 1H, J = 7.6, 1.3 Hz), 5.45 (s, 2H), 5.22 (m, 1H), 4.43 (s, 2H), 4.23 (dd, 1H, J = 12.2, 4.6 Hz), 3.84 (m, 1H), 3.68−3.52 (m, 2H), 3.45 (dd, 1H, J = 4.6, 12.5 Hz), 3.19−3.02 (m, 4H), 2.84−2.69 (m, 2H), 2.62 (m, 1H), 2.56 (s, 3H), 2.22 (m, 1H). LRMS (ES+): 597.2 (M + H).

1-(D-Tic-4-Cl-D-Phe)-4-[2-((1-methyl-1*H*-imidazol-2-yl)-methyl)phenyl]piperazine (52). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and 1-Boc-4-[2-((1-methyl-1*H*-imidazol-2-yl)methyl)phenyl]piperazine **19** in a manner similar to that described for **35**. ^{1}H NMR (400 MHz, MeOD): δ 7.47 (d, 1H, J = 2.0 Hz), 7.41 (d, 1H, J = 2.0 Hz), 7.42−7.13 (m, 12H), 5.18 (m, 1H), 4.43 (s, 2H), 4.42 (s, 2H), 4.22 (dd, 1H, J = 12.1, 4.5 Hz), 3.70 (s, 3H), 3.44 (dd,1H, J = 4.4, 17.2 Hz), 3.53−3.35 (m, 2H), 3.18−3.01 (m, 4H), 2.76−2.49 (m, 4H), 2.13 (m, 1H). LRMS (ES+): 597.2 (M + H).

1-(D-Tic-4-Cl-D-Phe)-4-[2-((1-methyl-1*H*-imidazol-2-yl)-methoxy)phenyl]piperazine (53). The title compound was prepared from *N*-Boc-D-Tic-4-Cl-D-Phe-OH **3** and 1-Boc-4-[2-((1-methyl-1*H*-imidazol-2-yl)methoxy)phenyl]piperazine **25c** in a manner similar to that described for **35**. ^{1}H NMR (400 MHz, MeOD): δ 7.64 (d, 1H, J = 1.6 Hz), 7.60 (d, 1H, J = 1.6 Hz), 7.40−7.19 (m, 12H), 5.60 (s, 2H), 5.19 (m, 1H), 4.42 (s, 2H), 4.22 (dd, 1H, J = 11.6, 4.7 Hz), 3.95 (s, 3H), 4.05−3.71 (m, 4H), 3.44 (dd, 1H, J = 4.8, 17.2 Hz), 3.32−3.43 (m, 2H), 3.24−3.02 (m, 4H), 2.81 (m, 1H). LRMS (ES+): 613.2 (M + H).

Binding Assay. A radioligand binding assay was performed to identify competitive inhibitors of ^{125}I-NDP-α-MSH binding using membranes prepared from human embryonic kidney (HEK) 293 cells stably transfected with cloned human melanocortinin receptors. Cells are grown as adherent monolayers in roller bottle cultures at 37 °C and 5% CO_2/air atmosphere in a 3:1 mixture of Dulbecco's modified Eagle medium (DMEM) and Ham's F12 containing 25 mM L-glucose, 100 units/mL penicillin G, 100 μg/mL streptomyocin, 250 ng/mL amphoterin B, and 300 μg/mL genticin and supplemented with 5% fetal bovine serum. For large-scale production, monolayer cells are adapted to suspension culture (Berg et al. *Biotechniques* **1993**, *14*, no. 6) and are grown in either spinner or shaker flasks (37 °C and 7.5% CO_2/air overlay) in a modified DME/F12 medium containing 0.1 mM $CaCl_2$, 2% equine serum, and 100 μg/mL sodium heparin to prevent cell−cell aggregation. Cells are harvested by centrifugation and washed in PBS, and pellets are stored frozen at −80 °C until required for preparation of membranes.

For the preparation of membranes, frozen cell pellets are resuspended in 10 volumes of membrane prep buffer (10 mL buffer/g of cell paste) consisting of 50 mM Tris pH 7.5 at 4°C, 250 mM sucrose, 1 mM $MgCl_2$, Complete EDTA-free protease inhibitor tablet (Roche Applied Science, Indianapolis, IN), and 24 μg/mL DNase I (Sigma, St. Louis, MO). The cells are homogenized with a motor-driven Teflon−glass dounce homogenizer using 20 strokes, followed by centrifugation at 38000*g* at 4 °C for 40 min. The pellets are resuspended in membrane prep buffer at a concentration of 2.5−7.5 mg/mL, aliquoted, quick frozen in liquid nitrogen, and stored at −80 °C.

Standard competitive receptor/ligand binding experiments consisted of testing serial dilutions of test compound (30 μM to 300 pM) or unlabeled NDP-α-MSH (100 nM to 1 pM) in binding buffer (25 mM HEPES pH 7.5; 10 mM $CaCl_2$; 0.3% BSA) containing 0.5−5.0 μg membrane protein, 100 pM ^{125}I-NDP-α-MSH (Amersham Biosciences, Piscataway, NJ), and 0.25 mg of wheat germ agglutinin SPA beads. The resulting mixture is agitated briefly on a plate shaker and incubated for 10 h at room temperature. The radioactivity bound to the receptor is quantified in a PE Life Sciences Trilux microplate scintillation counter. Nonlinear regression analysis of competition binding data using a four-parameter logistic fit yields IC_{50} values which are converted to affinity constants (K_i values) using the Cheng−Prusoff equation, $K_i = IC_{50}/(1 + D/K_d)$, where D is the concentration of radioligand and K_d is the equilibrium dissociation constant determined from saturation binding anlaysis.

Functional Assay. Functional activity was determined using a standard cAMP assay testing serial dilutions of test compound (10 μM to 0.1 nM) or the control agonist NDP-α-MSH (100 nM to 1 pM). HEK 293 cells stably transfected with the human MC3 or MC4 receptor were grown in DMEM containing 10% FBS and 1% antibiotic/antimycotic solution. On the day of the assay, the cells were dislodged with enzyme-free cell dissociation solution and resuspended in cell buffer (Hank's balanced salt solution without phenol red HBSS-092, 0.1% BSA, 10 mM HEPES) at 1×10^6 cells/mL. Cell suspension (40 μL) was added to PET 96-well plates containing 20 μL of diluted compound or control agonist. Plates were incubated at 37 °C for 20 min, and the assay was stopped by the addition of 50 μL of quench buffer (50 mM sodium acetate, 0.25% Triton X-100).

cAMP was determined by an SPA-based competition assay using ^{125}I-cAMP (Amersham Biosciences), goat anti-cAMP antibody (ICN), and PVT anti-sheep antibody binding SPA beads as per manufacturer instructions (Amersham Biosciences). Assay buffer contained 50 mM sodium acetate and 0.1% BSA. A mixture containing SPA beads (1 mg/mL), antibody (0.65%), and radioligand (61 pM) was prepared in assay buffer, and 100 μL was added to each quenched well of the 96-well assay plate to yield a final volume of 210 μL. Following a 12 h incubation, the plates were counted in a PE Life Sciences Trilux microplate scintillation counter. The data were converted to picomoles of cAMP using a standard curve

assayed under the same conditions in the presence of varying concentrations of unlabeled cAMP. The data were analyzed using a four-parameter logistic nonlinear regression to generate agonist potencies (EC_{50}) and percent efficacy data relative to the maximum stimulation obtained with NDP-α-MSH.

Bioavailability Protocol. Fischer 344 rats (Harlan Laboratories) weighing between 200 and 250 g were used in the exposure studies ($n = 3$ per time point). Oral doses were administered at 30 mg/kg in a 10% acacia vehicle via gavage, and intravenous doses were administered at 5 mg/kg. Rats were bled via the retro-orbital route 0.5, 1, 2 and 6 h after oral dosing and 0.083, 1, 2, 4, 6, 8 and 24 h after intravenous dosing. All blood samples were collected into heparinized syringes. Plasma was harvested using centrifugation and stored at −70 °C until assayed. Plasma was assayed by electrospray LC/MS/MS on a Sciex API 3000 mass spectrometer using fast gradient elution on a 2 × 50 mm C18 HPLC column. Least squares regression of the standard concentrations was used for sample quantitation. Pharmacokinetic analysis using a model-independent analysis was used to generate pharmacokinetic parameter estimates.

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Supporting Information Available: HPLC and HRMS data for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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