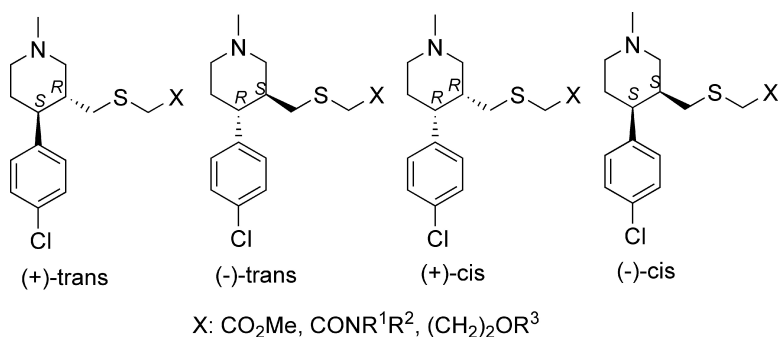## Article

Further Structure–Activity Relationship Studies of Piperidine-Based Monoamine Transporter Inhibitors: Effects of Piperidine Ring Stereochemistry on Potency. Identification of Norepinephrine Transporter Selective Ligands and Broad-Spectrum Transporter Inhibitors

Rong He, Toru Kurome, Kelly M. Giberson, Kenneth M. Johnson, and Alan P. Kozikowski

X: CO_2Me, $CONR^1R^2$, $(CH_2)_2OR^3$

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Further Structure−Activity Relationship Studies of Piperidine-Based Monoamine Transporter Inhibitors: Effects of Piperidine Ring Stereochemistry on Potency. Identification of Norepinephrine Transporter Selective Ligands and Broad-Spectrum Transporter Inhibitors

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4-(4-Chlorophenyl)piperidine analogues each bearing a thioacetamide side chain appendage similar to that found in the wake-promoting drug modafinil have been synthesized. The transporter inhibitory activity of both the *cis* and *trans* isomers of these 3,4-disubstituted piperidines in both their (+)- and (−)-enantiomeric forms was determined. These studies reveal that the (−)-*cis* analogues exhibit dopamine transporter/norepinephrine transporter (DAT/NET) selectivity as was previously reported for the (+)-*trans* analogues. On the other hand, the (−)-*trans* and the (+)-*cis* isomers show serotonin transporter (SERT) or SERT/NET selectivity. Among them, (+)-*cis*-**5b** shows a low nanomolar K_i for the NET with 39-fold and 321-fold lower potency at the DAT and SERT, respectively, thus making it a useful pharmacological research tool for exploring NET-associated behavioral signatures. On the other hand, several of the compounds described herein, such as (+)-*trans*-**5c**, show comparable activity at all three transporters. Because broad-spectrum transporter inhibitors have been hypothesized to exhibit a more rapid onset of action and/or a greater efficacy as antidepressant agents than those selective for SERT or SERT + NET, some of the present compounds will be valuable to study in animal models of depression.

Introduction

The biogenic amine neurotransmitters dopamine (DA), 5-hydroxytryptamine (5-HT), and norepinephrine (NE) are involved inter alia in the regulation of emotions, reactions to stress, and the physiological drives of appetite and sleep.[1] Chemical imbalances in these neurotransmitters result in pathological conditions such as depression, Parkinson's disease, bipolar disorder, and attention deficit hyperactivity disorder (ADHD).[2] The reuptake of these monoamine transmitters into nerve terminals through neuronal plasma membrane monoamine dopamine, norepinephrine, and serotonin transporters (DAT, SERT, and NET) provides a mechanism for modulating the intensity and duration of monoamine signaling at synapses. The design of agents capable of inhibiting these transporters continues to represent an important approach to the treatment of neuropsychiatric disorders and drug addiction.[3]

While cocaine, a major drug of abuse, is able to inhibit all three transporters, its effect at the DAT is believed to play the major role in its addictive properties. The dopamine hypothesis of cocaine's behavior-reinforcing effects has thus served as a major motivation for research efforts aimed at the discovery of DAT-selective inhibitors (GBR 12935, WIN35,428).[4] On the other hand, knowledge of serotonin's role in mood led to the discovery of serotonin-selective reuptake inhibitors (SSRIs) such as fluoxetine, citalopram, paroxetine, and setraline in the treatment of depression.[5] In contrast, despite the important role of NE in a number of disorders of the central nervous system (CNS) including depression and ADHD, a relatively smaller number of NET selective inhibitors have been developed to date (e.g., nisoxetine and reboxetine).[6] Although a variety of approaches have been explored to gain insights into the nature and site of interaction of the transporter inhibitors with their target proteins including binding and functional analysis using site directed mutagenesis,[7] homology-based molecular modeling, and photoaffinity/electrophile labeling of the binding site,[8] precise topographical details of the inhibitor−transporter complex are still lacking.

In the course of our studies aimed at identifying molecules for use in the treatment of cocaine addiction,[9] hybrid molecules combining structural features of (+)-methyl 4β-(4-chlorophenyl)-1-methylpiperidine-3α-carboxylate [nocaine, (+)-CPCA, (+)-*trans*-**1**], a piperidine-based analogue of cocaine lacking its tropane skeleton,[10] and modafinil,[11] a popular non-amphetamine-like wake-promoting agent, were prepared (Figure 1). The chemical synthesis and transporter activity of the (+)-*trans* isomers in this series were reported recently, and these compounds were shown to exhibit largely a mixed DAT/NET selectivity.[12] Moreover, comparative molecular field analysis (CoMFA) contour maps have been generated for analogues of (+)-*trans*-CPCA at the DAT.[13] These contour maps provide a visual representation of
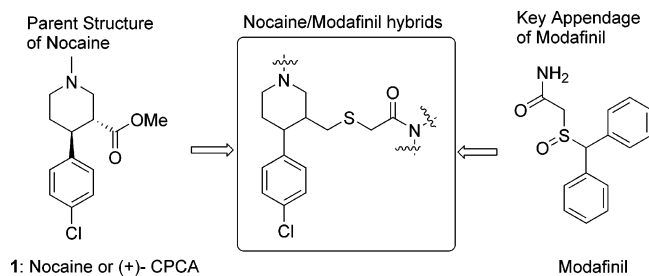
Figure 1. Rational design of nocaine/modafinil hybrid ligands.

the possible binding modes of members in this series bearing various substituents at the 3-position of the piperidine ring. The CoMFA analysis facilitates a pharmacophore-based approach to the design of additional analogues in the piperidine series. Because most of the modeling, chemistry, and pharmacology efforts have been directed to compounds derived from (+)-*trans*-CPCA, the effect of alterations in the relative and absolute stereochemistry of these 3,4-disubstituted piperidines on transporter inhibitory activity has yet to be fully elucidated. Comparison of the SAR of the four stereoisomeric series will provide additional information of use in the CoMFA analysis while potentially identifying other ligands of therapeutic value. Transporter selective ligands of high potency are also in considerable demand for study as diagnostic tools using positron emission tomography (PET).[14] Accordingly, in the present research all four stereoisomeric piperidines comprising a sulfur-bearing side chain containing an ester, amide, or alcohol group were prepared and their transporter activities were measured.

Chemistry

In reference to the druglike properties of the compounds selected for synthesis, most of the analogues were designed to have a suitable ClogP value (1 < ClogP < 5) and molecular weight (MW < 500) for penetration of the blood−brain barrier.[15] Scheme 1 shows the chemical synthesis of our target structures starting from each pure stereoisomer of CPCA **1**, which were prepared using the known literature procedure.[10a] These methods are similar to those we have reported previously.[12] Briefly, each isomer of **1** was converted to its corresponding alcohol **2** by lithium aluminum hydride (LiAlH$_4$) reduction, and the alcohol in turn was transformed to the iodide **3** by reaction with iodine in the presence of triphenylphosphine and imidazole. The key intermediate **4** was then obtained by coupling of **3** with methyl thioglycolate in the presence of cesium carbonate. Treatment of the ester **4** with either liquid ammonia or various alkylamines afforded the corresponding amides **5a**−**e**. On the other hand, the arylamines **5f**−**i** were obtained by reacting the acid **6** with the corresponding arylamines in the presence of *N*-(3-dimethylaminopropyl)-*N'*-ethylcarbodiimide hydrochloride (EDCI) and 1-hydroxybenzotriazole (HOBt). The inverse esters **8a** and **8b** were prepared from the alcohol **7** by conventional methods employing acetic anhydride/pyridine and benzoyl chloride/dimethylaminopyridine (DMAP), respectively.

To avoid complications from introduction of a new stereocenter, the sulfur atom was left unoxidized in these analogues. In the case of the drug modafinil,

which inspired the present series of ligands, the sulfur atom is present as the sulfoxide.

Biological Results and Discussion

The newly synthesized compounds (−)-*trans* **4**, **5a**−**e,g,h**, **7**, **8a,b**, (+)-*cis* **1**, **4**, **5b**−**i**, **7**, **8a,b**, (−)-*cis* **4**, **5a**−**e,g**, **7**, and **8a** were tested for the abilities to inhibit uptake of [³H]DA, [³H]5-HT, and [³H]NE through the corresponding transporters using rat synaptosomal nerve endings.[9a] The ClogP, uptake data, and selectivity profiles (based on the K_i values) of these compounds are shown in Table 1. Compounds synthesized from the (+)-*trans* isomer were tested earlier.[12] For comparison purposes, data for (+)-, (−)-*trans*-, and (−)-*cis*-CPCA from the previous papers[10,12] and for (−)-cocaine[12] and modafinil[12] are also listed.

A small set of analogues of each stereoisomer was prepared using the ester **4** as a common intermediate. These analogues include the unsubstituted amides, alkyl- and arylamides, alcohols, and their inverse ester derivatives. As was found to be the case for the various analogues prepared in the (+)-*trans* series, overall, most of the analogues prepared from the other three stereoisomers of **1** also exhibited good inhibitory activities at the NET. On the other hand, the nature of the stereochemistry of these piperidines did, however, exert a distinct influence on their DAT and SERT activity, leading to their overall transporter selectivity profile. Introduction of the thioacetate group into the side chain of each of the CPCA isomers led to the esters **4** generally possessing an improved activity relative to the starting compounds **1**. The (−)-*trans*-**4** isomer exhibits an improved potency at the SERT and the NET with little change in its DAT activity compared to the (−)-*trans*-**1**. The (−)-*cis*-**4**, on the other hand, shows a combined DAT/NET selectivity. In the case of the (+)-*cis*-**4**, NET selectivity was found, while the (+)-*cis*-**1** exhibits the best SERT selectivity in this series of analogues. An improvement in potency at all three transporters is observed for (+)-*trans*-**4**. Conversion of (+)- and (−)-*trans*-**4** into their unsubstituted amides (+)- and (−)-*trans*-**5a** was not particularly favorable, leading to a reduction in SERT activity in both cases. Examination of the data for the amide (−)-*cis*-**5a** shows that it is fairly active at all three transporters but shows little discrimination among them (K_i = 21−69 nM).

Among the (+)-*trans* isomers bearing an N-substituted amide side chain,[12] the monoalkylamides (+)-*trans*-**5b** and -**5c** show a much improved potency (12- to 159-fold) at the DAT relative to (+)-*trans*-**5a**. Both compounds are more active than the N,N-disubstituted amides (+)-*trans*-**5d** and -**5e** at the DAT. For these amides, a larger N-substitutent appears to favor heightened potency at both the SERT and the NET. The isopropylamide (+)-*trans*-**5c** and the piperidinylamide (+)-*trans*-**5e**, having groups bulkier than those present in either the methylamide (+)-*trans*-**5b** or the dimethylamide (+)-*trans*-**5d**, respectively, have K_i values less than 10 nM for both the SERT and the NET. In the case of the sterically smaller alcohol (+)-*trans*-**7**, the presence of the free OH group appears to be particularly advantageous for interaction with the NET because a K_i of 0.9 nM was found.

In the (−)-*trans*-amide series, the ligand (−)-*trans*-**5a** is similar in activity to (+)-*trans*-**5a** at the SERT and

Scheme 1[a]

X: CO_2Me, $CONR^1R^2$, CH_2OR^3
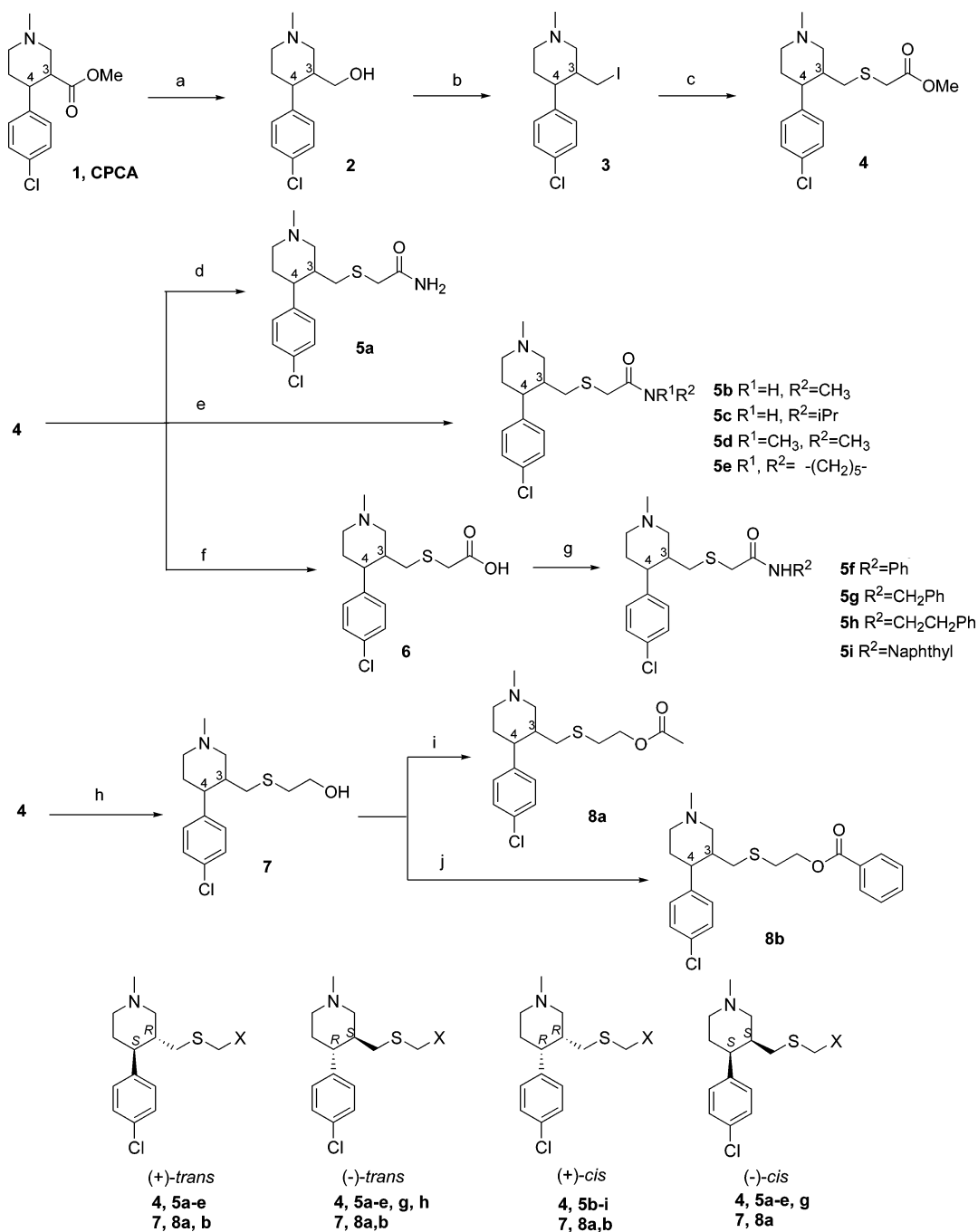
[a] Reagents and conditions: (a) $LiAlH_4$; (b) Ph_3P/I_2/imidazole; (c) methyl thioglycolate, Cs_2CO_3; (d) NH_3 (liquid), t-BuOH; (e) (for **5b−e**) HNR^1R^2 in MeOH; (f) LiOH, MeOH; (g) (for **5f−i**) H_2NR^2, EDCI; (h) $LiAlH_4$; (i) Ac_2O/pyridine; (j) benzoyl chloride, Et_3N, DMAP.

the NET, with the best activity being displayed at the NET. The *N*-alkyl-substituted amides (−)-*trans*-**5b−e** show a different transporter potency as found for the corresponding enantiomeric (+)-*trans*-amides. They exhibit moderate potency at the SERT and the NET with little discrimination among them and low potency at the DAT. The dialkyl-substituted amides (−)-*trans*-**5d** and -**5e** show strongly diminished activity at the DAT. The benzylamide (−)-*trans*-**5g** also has low activity at the DAT and the SERT, while it maintains activity at the NET. In going from (−)-*trans*-**5g** to the phenylethylamide (−)-*trans*-**5h**, the simple elongation of the side chain provides an improvement in both the DAT and

the SERT potencies (68-fold and 11-fold, respectively). This result may support the presence of a specific π-interaction between the ligand and the DAT and the SERT. Among the (−)-*trans*-amides, **5a** and **5g** had good NET selectivity over DAT and SERT.

In the (+)-*cis*-amide series, the monoalkylamides (+)-*cis*-**5b** and -**5c** show high potency at the NET. The methylamide **5b** exhibits poor activity at the SERT, while the amide (+)-*cis*-**5c** containing the larger isopropylamide group exhibits an improved SERT potency (49-fold more potent than **5b**). The NET activity of the phenylamide (+)-*cis*-**5f** ($K_i = 1060$ nM) was the weakest among the (+)-*cis*-amide ligands tested. Introduction of

Table 1. Activity at Monoamine Transporters

compd	ClogP[f]	reuptake $K_i \pm$ SEM (nM)[a]			uptake ratio (based on K_i)		
		[³H]DA	[³H]5HT	[³H]NE	5HT/DA	NE/DA	NE/5HT
cocaine[b]		423 ± 147	155 ± 1	108 ± 4			
modafinil[c]		3800		>10000			
(+)-*trans*-**1**[b] CPCA	3.22	233 ± 62	8490 ± 1430	252 ± 43	36.4	1.08	0.03
(+)-*trans*-**4**	3.15	80 ± 23	208 ± 47	25 ± 6	2.59	0.31	0.12
(+)-*trans*-**5a**	2.19	159 ± 19	557 ± 150	39 ± 5	3.5	0.24	0.07
(+)-*trans*-**5b**	2.29	13 ± 3	110 ± 45	25 ± 2	8.5	2.0	0.2
(+)-*trans*-**5c**	3.13	1.0 ± 0.2	1.1 ± 0.4	0.8 ± 0.1	1.11	0.8	0.72
(+)-*trans*-**5d**	2.89	116 ± 46	88 ± 22	27 ± 7	0.76	0.23	0.31
(+)-*trans*-**5e**	3.8	83 ± 1	4.5 ± 0.7	0.7 ± 0.3	0.05	0.008	0.15
(+)-*trans*-**7**	2.81	16 ± 5	158 ± 5	0.9 ± 0.3	9.81	0.06	0.005
(+)-*trans*-**8a**	3.71	35 ± 11	57 ± 18	3.6 ± 1.5	1.63	0.1	0.06
(+)-*trans*-**8b**	5.45	68 ± 22	6.7 ± 1.5	4.5 ± 1.2	0.1	0.07	0.67
(−)-*trans*-**1**[d]	3.22	2930 ± 580	930 ± 10	386 ± 112	0.32	0.14	0.43
(−)-*trans*-**4**	3.15	2620 ± 390	69 ± 15	57 ± 1	0.03	0.02	0.83
(−)-*trans*-**5a**	2.19	1100 ± 270	545 ± 167	53 ± 1	0.49	0.05	0.09
(−)-*trans*-**5b**	2.29	164 ± 6	116 ± 26	44 ± 2	0.71	0.27	0.38
(−)-*trans*-**5c**	3.13	663 ± 42	138 ± 19	67 ± 2	0.21	0.1	0.49
(−)-*trans*-**5d**	2.89	> 3000	186 ± 8	218 ± 35	0.06	0.07	1.17
(−)-*trans*-**5e**	3.8	> 3000	190 ± 29	82 ± 1	0.06	0.03	0.43
(−)-*trans*-**5g**	4.34	1570 ± 110	753 ± 81	32 ± 1	0.48	0.02	0.04
(−)-*trans*-**5h**	4.56	23 ± 3	68 ± 18	178 ± 27	2.97	7.81	2.63
(−)-*trans*-**7**	2.81	185 ± 62	129 ± 2	123 ± 29	0.69	0.66	0.95
(−)-*trans*-**8a**	3.71	536 ± 126	130 ± 14	52 ± 6	0.24	0.09	0.4
(−)-*trans*-**8b**	5.45	378 ± 75	71 ± 6	56 ± 14	0.19	0.15	0.79
(+)-*cis*-**1**	3.22	1560 ± 370	56 ± 10	415 ± 37	0.04	0.27	7.45
(+)-*cis*-**4**	3.15	598 ± 32	403 ± 9	98 ± 6	0.67	0.16	0.24
(+)-*cis*-**5b**	2.29	215 ± 15	1770 ± 240	5.5 ± 1.6	8.23	0.03	0.003
(+)-*cis*-**5c**	3.13	142 ± 5	36 ± 4	11 ± 1	0.25	0.07	0.3
(+)-*cis*-**5d**	2.89	176 ± 6	173 ± 45	47 ± 8	0.98	0.27	0.27
(+)-*cis*-**5e**	3.8	>3000	572 ± 46	134 ± 14	0.19	0.04	0.23
(+)-*cis*-**5f**	4.31	80 ± 5	91 ± 1	1060 ± 190	1.13	13.3	11.7
(+)-*cis*-**5g**	4.34	302 ± 9	22 ± 1	54 ± 8	0.07	0.18	2.49
(+)-*cis*-**5h**	4.56	112 ± 18	121 ± 19	100 ± 26	1.08	0.89	0.83
(+)-*cis*-**5i**	5.49	102 ± 9	108 ± 6	101 ± 18	1.06	0.99	0.94
(+)-*cis*-**7**	2.81	160 ± 5	305 ± 30	>3000	1.91	19	9.8
(+)-*cis*-**8a**	3.71	177 ± 55	125 ± 17	610 ± 9	0.71	3.49	4.88
(+)-*cis*-**8b**	5.45	1470 ± 430	270 ± 5	143 ± 6	0.18	0.09	0.53
(−)-*cis*-**1**[e]	3.22	69 ± 8	391 ± 27	88 ± 3	5.67	1.28	0.23
(−)-*cis*-**4**	3.15	38 ± 4	182 ± 24	22 ± 1	4.88	0.59	0.12
(−)-*cis*-**5a**	2.19	54 ± 1.9	21 ± 4	69 ± 14	0.39	1.29	3.34
(−)-*cis*-**5b**	2.29	311 ± 4	347 ± 52	18 ± 1	1.12	0.06	0.05
(−)-*cis*-**5c**	3.13	13 ± 5	154 ± 14	16 ± 2	11.5	1.19	0.1
(−)-*cis*-**5d**	2.89	17 ± 3	8.8 ± 2.1	63 ± 6	0.53	3.75	7.08
(−)-*cis*-**5e**	3.8	34 ± 5	42 ± 2	13 ± 1	1.22	0.38	0.32
(−)-*cis*-**5g**	4.34	3.9 ± 0.8	23 ± 5	85 ± 4	5.81	21.9	3.76
(−)-*cis*-**7**	2.81	37 ± 5	185 ± 16	26 ± 4	5.0	0.7	0.14
(−)-*cis*-**8a**	3.71	46 ± 5	469 ± 85	30 ± 7	10.1	0.65	0.06

[a] Data are mean values ± SEM from two to four independent experiments, each consisting of six drug concentrations in triplicate, as described in ref 9a. [b] Data for (+)-*trans* analogues were taken from ref 12. [c] Data taken from ref 11b. [d] Data taken from ref 10d. [e] Data taken from ref 10c. [f] ClogP calculated by using the program available at the Web site: http://www.daycgi.com/daycgi/clogp.

the slightly larger benzyl group into the amide to give (+)-*cis*-**5g** was found to be favorable and led to a recovery of activity at the NET relative to the *N*-phenylamide (20-fold more potent than **5f**). In comparison to (+)-*cis*-**5g**, analogues (+)-*cis*-**5h** and -**5i** failed to show any discrimination among the three transporters. Of considerable interest is the activity displayed by the methylamide (+)-*cis*-**5b** because this compound has a NET inhibitory activity of 5.5 nM while exhibiting 39-fold and 321-fold lower activity at the DAT and the SERT, respectively.

In the (−)-*cis* series, the majority of the compounds again show reasonably good activity for the DAT and the NET. The alkylamides (−)-*cis*-**5b**−**e** show good potency at the DAT except **5b**; all of these analogues show double-digit activity at the NET. The dialkyl-amides (−)-*cis*-**5d** and -**5e** were more potent than their monoalkylamide counterparts (−)-*cis*-**5b** and -**5c** at the SERT. The dimethylamide (−)-*cis*-**5d** shows low nano-

molar affinity for the SERT, although its selectivity is only 2- to 7-fold over those of the other transporters. The monomethylamide (−)-*cis*-**5b** showed a reasonable potency of 18 nM at the NET and is 19-fold and 17-fold selective over the SERT and the DAT, respectively.

Among the alcohols tested, (+)-*trans*-**7** shows excellent potency ($K_i = 0.9$ nM) and reasonably good selectivity (18- to 175-fold) at the NET, while the (+)-*cis*-**7** shows no activity at the concentration tested ($K_i > 3000$ nM) at the NET. Because the two alcohols (+)-*trans*-**7**, which maintains good activity at the NET, and (+)-*cis*-**7** differ only in the stereochemistry of the sulfur-bearing side chain, these compounds should be valuable in the elaboration of a CoMFA map for the NET.

For the inverse esters derived from the isomeric alcohols **7**, the only ones showing low nanomolar affinity were (+)-*trans*-**8a** and -**8b**. The former compound showed some NET selectivity, while the latter was more active at both the SERT and the NET. Derivatization of the
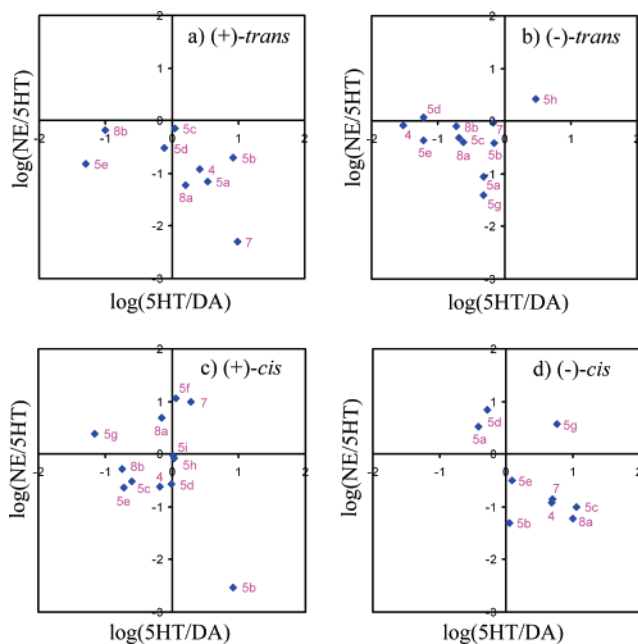
Figure 2. The log–log plots of the transporter activity shown by the four stereoisomeric series of piperidine analogues. For compounds showing a K_i value greater than 3000, "3000" was used for the calculation of the uptake ratio (see Table 1).

alcohol group of (+)-*cis*-**7** was effective in restoring NET activity as in the case of (+)-*cis*-**8a** and -**8b**. Introduction of the benzoyl group provided the largest effect on the activity of the (+)-*cis* alcohol **7** because its conversion to (+)-*cis*-**8b** led to more than a 21-fold increase in potency at the NET, while this change caused a 9-fold decrease in DAT potency.

Overall, the (+)-*trans* and (−)-*cis* series of compounds are more potent than the (−)-*trans* and the (+)-*cis* series at both the DAT and the SERT. The (+)-*trans* and (−)-*cis* series possess the 4S configuration at the 4-position of the piperidine ring, while the (−)-*trans* and the (+)-*cis* series have the 4R configuration at this position. The stereochemistry of this ring position thus influences the overall transporter selectivity profile of this group of ligands.

Many of the analogues from all four stereoisomeric series are reasonably well tolerated at the NET. The improved NET activity of these ligands relative to the methyl esters **1** may stem in part from the greater flexibility of the sulfur-bearing side chain in the vicinity of the piperidine ring as opposed to the sp²-hybridized carbomethoxy group present in **1**.[16]

Perhaps the best way to view the transporter selectivity profiles for members of each of these four isomeric series can be seen from the log(NET/5HT) − log(5HT/DAT) plots shown in Figure 2. In Figure, compounds showing the same potency at the two transporters under comparison (K_i ratio of 1.0) will fall on the zero line, whereas those falling at 1 or −1 would show a 10-fold difference in potency (K_i ratio of 10 or 0.1). Visual inspection of these plots reveals that the (−)-*cis* analogues (Figure 2d) and the (+)-*trans* analogues show a trend toward DAT/NET selectivity (Figure 2a) because more of the compounds occupy the lower right quadrant. On the other hand, the plots of the (−)-*trans* analogues (Figure 2b) and (+)-*cis* analogues (Figure 2c) reveal a trend toward SERT/NET selectivity because these com-

pounds occupy the two left quadrants clustering near the ordinate at 0. Also, as is apparent from Figure 2c, one of the (+)-*cis* compounds shows the best NET selectivity, namely, (+)-*cis*-**5b**.

Conclusions

In summary, the present study was undertaken in order to examine the influence of the stereochemistry of the piperidine ligands containing a sulfur side chain on their transporter selectivity. Many of the members of each of the three new stereoisomeric series reported herein exhibit reasonably good transporter inhibitory activity especially at the NET, much like that of the previously reported (+)-*trans* isomers. Of some interest in this study is the 68-fold change in DAT activity that is observed in going from the benzylamide (−)-*trans*-**5g** to the phenylethylamide (−)-*trans*-**5h** and the 20-fold increase in NET activity that is observed in going from the phenylamide (+)-*cis*-**5f** to the benzylamide (+)-*cis*-**5g**. Moreover, replacement of the monomethylamide groups of (+)-*trans*-**5b** and (+)-*cis*-**5b** by the larger, more hydrophobic isopropylamides as in (+)-*trans*-**5c** and (+)-*cis*-**5c** was found to lead to a valuable improvement in inhibitory potency at the SERT. Of the analogues studied herein, one of the most NET selective compounds was the alcohol (+)-*trans*-**7**. In contrast, the alcohol (+)-*cis*-**7**, which differs from (+)-*trans*-**7** only in the stereochemistry of the sulfur-bearing side chain, lacks both potency and selectivity.

In general, the (+)-*trans* and the (−)-*cis* analogues were found to exhibit a mixed DAT/NET selectivity. The (−)-*trans* and the (+)-*cis* analogues show a trend toward SERT or SERT/NET selectivity. Among the analogues newly explored in this study, (−)-*trans*-**5g**, (+)-*cis*-**5b**, and (−)-*cis*-**5b** show relatively good potency and selectivity at the NET. Because the K_i value of (+)-*cis*-**5b** at the NET is 5.5 nM and its selectivity for the NET is the best among those tested in this study, 321-fold over the SERT and 39-fold over the DAT, this compound will be valuable for exploration in animal models to gain a better understanding of NET-associated behavioral signatures.[17] Because broad-spectrum transporter inhibitors have been hypothesized to exhibit a more rapid onset of action and/or greater efficacy as antidepressant agents than those selective for SERT or SERT + NET, some of the present compounds will be valuable for study in animal models of depression.[18]

Experimental Section

¹H and ¹³C NMR spectra were obtained with a Bruker Avance spectrometer at 300 and 75 MHz, respectively. ¹H chemical shifts (δ) were reported in ppm downfield from internal Me₄Si. ¹³C chemical shifts (δ) are referenced to CDCl₃ (central peak, $\delta = 77.00$ ppm) as the internal standard. Mass spectra were measured using positive mode electrospray ionization (ESI). The HRMS data were obtained on a Micromass Q-TOF-2™ instrument. Optical rotations were measured with an AUTOPOL IV (Rudolph Research Analytical) instrument. TLC was performed on silica gel 60F₂₅₄ glass plates; column chromatography was performed using Merck silica gel (230−400 mesh). Analytical HPLC was performed using a Shimadzu LC-10AD system, equipped with a Waters 484 tunable absorbance detector set at 220 nm. Waters μ-Bondapak C₁₈ column (3.9 mm × 300 mm, 5 μm) and ACE 5 AQ C₁₈ UltraInert column (4.6 mm × 250 mm, 5 μm) were used. The HPLC data of tested compounds including the conditions can be seen in the Supporting Information. Starting

materials were obtained from Aldrich, Alfa Aesar, or Acros. Solvents were obtained from Fisher Scientific or Aldrich and were used without further purification unless noted otherwise.

(3*S*,4*R*)-4-(4-Chlorophenyl)-3-(hydroxymethyl)-1-methylpiperidine ((−)-*trans*-2). To a solution of (3*S*,4*R*)-4-(4-chlorophenyl)-1-methylpiperidine-3-carboxylic acid methyl ester (2.0 g, 7.5 mmol) in anhydrous THF (40 mL) that was cooled to 0 °C was added LiAlH$_4$ (425 mg, 11.25 mmol). The resulting mixture was warmed to room temperature and stirred overnight, then the reaction was quenched with a saturated solution of NH$_4$Cl (30 mL). The mixed solution was extracted with CH$_2$Cl$_2$ (3 × 25 mL). The combined organic extract was dried over Na$_2$SO$_4$, concentrated, and purified by column chromatography with EtOAc/MeOH/Et$_3$N (8/1/1) as the eluent to yield (−)-*trans*-2 as a white solid (1.61 g, 90%). [α]$^{25}_D$ −28° (*c* 0.49, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.22 (d, *J* = 8.4 Hz, 2H), 7.09 (d, *J* = 8.4 Hz, 2H), 3.50 (br s, 1H), 3.34 (dd, *J* = 2.7, 11 Hz, 1H), 3.14 (dd, *J* = 7.2, 11.1 Hz, 2H), 2.94−2.84 (m, 1H), 2.29 (s, 3H), 2.24 (td, *J* = 6.3, 10.1 Hz, 1H), 2.03−1.90 (m, 2H), 1.87 (dd, *J* = 10.8, 10.5 Hz, 1H), 1.82−1.69 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 142.9, 132.1, 128.9, 128.8, 63.3, 59.5, 56.2, 46.6, 44.1, 43.9, 34.4.

Compounds (+)-*cis*-2 and (−)-*cis*-2 were prepared by the general procedure described for (−)-*trans*-2.

(3*R*,4*R*)-4-(4-Chlorophenyl)-3-(hydroxymethyl)-1-methylpiperidine ((+)-*cis*-2). Yield 92%; white solid; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 3.76−3.50 (m, 2H), 3.15(br.d, *J* = 11 Hz, 1H), 3.10−3.00 (m, 1H), 2.84 (dt, *J* = 12, 4.4 Hz, 1H), 2.65−2.45 (m, 2H), 2.29 (s, 3H), 2.13 (td, *J* = 11, 3.0 Hz, 1H), 1.86−1.69 (m, 3H).

(3*S*,4*S*)-4-(4-Chlorophenyl)-3-(hydroxymethyl)-1-methylpiperidine ((−)-*cis*-2). Yield 100%; white solid; ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.5 Hz, 2H), 3.76−3.50 (m, 2H), 3.15 (br.d, *J* = 11 Hz, 1H), 3.10−3.00 (m, 1H), 2.84 (dt, *J* = 12, 4.4 Hz, 1H), 2.65−2.45 (m, 2H), 2.29 (s, 3H), 2.13 (td, *J* = 11, 3.0 Hz, 1H), 1.86−1.69 (m, 3H).

(3*S*,4*R*)-4-(4-Chlorophenyl)-3-(iodomethyl)-1-methylpiperidine ((−)-*trans*-3). To a solution of PPh$_3$ (2.41 g, 9.18 mmol) in anhydrous CH$_2$Cl$_2$ (60 mL) was added iodine (2.33 g, 9.18 mmol) under nitrogen at room temperature. After the mixture was stirred at room temperature for 15 min, imidazole (0.71 g, 10.43 mmol) was added in one portion, followed by the addition of a solution of (−)- *trans*-2 (1.0 g, 4.17 mmol) in 20 mL of CH$_2$Cl$_2$ at room temperature. The resulting mixture was refluxed for 3 h and then washed with a 5% aqueous solution of sodium thiosulfate to remove the excess iodine. The organic phase was dried over Na$_2$SO$_4$, concentrated, and purified by column chromatography first with EtOAc as the eluent to remove all the formed triphenylphosphine oxide and then with EtOAc/Et$_3$N (98/2 to 95/5) as the eluent to provide (−)-*trans*-3 as a colorless oil (1.25 g, 86%). [α]$^{25}_D$ −55° (*c* 0.83, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.28 (d, *J* = 8.7 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 3.17−3.08 (m, 1H), 3.04 (dd, *J* = 2.7 and 12.9 Hz, 1H), 2.98−2.90 (m, 1H), 2.75 (dd, *J* = 6.9 and 10.1 Hz, 1H), 2.38 (s, 3H), 2.29 (td, *J* = 4.5 and 11.3 Hz, 1H), 2.08 (td, *J* = 3.0, 13.2 Hz, 1H), 2.01−1.84 (m, 2H), 1.82−1.66 (m, 2H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 141.4, 132.2, 128.8 (2C), 61.9, 55.9, 46.6, 46.1, 41.4, 33.8, 10.7; MS (ESI) 350.1 [MH$^+$]; HRMS (ESI) calculated for C$_{13}$H$_{18}$ClIN$^+$ [MH$^+$] 350.0172, found 350.0164.

Compounds (+)-*cis*-3 and (−)-*cis*-3 were prepared by the general procedure described for (−)-*trans*-3.

(3*R*,4*R*)-4-(4-Chlorophenyl)-3-(iodomethyl)-1-methylpiperidine ((+)-*cis*-3). Yield 86%; colorless oil; [α]$^{25}_D$ −14° (*c* 0.55, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.30 (dd, *J* = 8.45 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 3.58−3.50 (m, 1H), 3.27−3.20 (m, 1H), 2.92−3.04 (m, 1H), 2.81−2.92 (m, 2H), 2.31 (s, 3H), 2.22 (m, 2H), 2.10−1.90 (m, 2H), 1.66−1.82 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 141.7, 132.5, 128.9, 128.8, 59.8, 56.8, 46.7, 44.4, 44.0, 25.1, 6.9; MS (ESI) 350.1 [MH$^+$]; HRMS (ESI) calculated for C$_{13}$H$_{18}$ClIN$^+$ [MH$^+$] 350.0172, found 350.0175.

(3*S*,4*S*)-4-(4-Chlorophenyl)-3-(iodomethyl)-1-methylpiperidine ((−)-*cis*-3). Yield 69%; colorless oil; [α]$^{25}_D$ +18°

(*c* 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.30 (dd, *J* = 8.45 Hz, 2H), 7.11 (d, *J* = 8.4 Hz, 2H), 3.58−3.50 (m, 1H), 3.27−3.20 (m, 1H), 3.00−2.97 (m, 1H), 2.97−2.83 (m, 2H), 2.30 (s, 3H), 2.22 (d, *J* = 10.6 Hz, 2H), 2.10−1.90 (m, 2H), 1.69−1.64 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 141.4, 132.5, 128.9, 128.8, 59.6, 56.8, 46.7, 44.1, 43.8, 25.1, 6.7; MS (ESI) 350.3 [MH$^+$]; HRMS (ESI) calculated for C$_{13}$H$_{18}$ClIN$^+$ [MH$^+$] 350.0172, found 350.0168.

[(3*S*,4*R*)-4-(4-Chlorophenyl)-1-methylpiperidine-3-ylmethylsulfanyl]acetic Acid Methyl Ester ((−)-*trans*-4). To a solution of (−)-*trans*-3 (617 mg, 1.76 mmol) in anhydrous MeCN (20 mL) was added 316 μL of methyl thioglycolate (374 mg, 3.52 mmol) under nitrogen at room temperature, followed by the addition of cesium carbonate (1.43 g, 4.40 mmol). After the mixture was stirred at room temperature overnight, the solvent was evaporated and the residue was partitioned with CH$_2$Cl$_2$/H$_2$O (1/1, 40 mL). The aqueous layer was extracted with CH$_2$Cl$_2$ (3 × 25 mL), and the combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by column chromatography using the mixture EtOAc/Et$_3$N (98/2 to 10/1) as the eluent to afford (−)-*trans*-4 as a colorless oil (505 mg, 88%). [α]$^{25}_D$ −98.2° (*c* 0.72, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.27 (d, *J* = 8.7 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 3.60 (s, 3H), 3.28−3.22 (m, 1H), 3.06 (q, *J* = 14.7 and 18.0 Hz, 2H), 2.97−2.92 (m, 1H), 2.50 (dd, *J* = 2.4 and 7.5 Hz, 1H), 2.34 (s, 3H), 2.28−1.96 (m, 4H), 1.84−1.74 (m, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 171.0, 142.8, 132.6, 129.3, 129.2, 61.1, 56.6, 52.7, 47.5, 46.8, 41.6, 35.3, 35.0, 34.3; MS (ESI) 328.2 [MH$^+$]; HRMS (ESI) calculated for C$_{16}$H$_{23}$ClNO$_2$S$^+$ [MH$^+$] 328.1138, found 328.1136.

Compounds (+)-*cis*-4 and (−)-*cis*-4 were prepared by the general procedure described for (−)-*trans*-4.

[(3*R*,4*R*)-4-(4-Chlorophenyl)-1-methylpiperidine-3-ylmethylsulfanyl]acetic acid Methyl Ester ((+)-*cis*-4). Yield 88%; colorless oil; [α]$^{25}_D$ +70.8° (*c* 0.72, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.30 (d, *J* = 8.48 Hz, 2H), 7.11 (d, *J* = 8.41 Hz, 2H), 3.58 (s, 3H), 3.24−3.17 (m, 1H), 3.08−2.90 (m, 3H), 2.79−2.90 (m, 2H), 2.29 (s, 3H), 2.25−1.98 (m, 5H), 1.78−1.65 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 171.0, 142.0, 132.2, 128.9, 128.7, 58.3, 56.5, 52.4, 46.7, 43.6, 40.7, 33.9, 30.1, 25.4; MS (ESI) 328.2 [MH$^+$]; HRMS (ESI) calculated for C$_{16}$H$_{23}$ClNO$_2$S$^+$ [MH$^+$] 328.1138, found 328.1142.

[(3*S*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidine-3-ylmethylsulfanyl]acetic acid Methyl Ester ((−)-*cis*-4). Yield 74%; colorless oil; [α]$^{25}_D$ −70.6° (*c* 0.5, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29 (d, *J* = 8.4 Hz, 2H), 7.11 (d, *J* = 8.3 Hz, 2H), 3.58 (s, 3H), 3.20−3.17 (m, 1H), 3.08−2.90 (m, 3H), 2.90−2.81 (m, 2H), 2.27 (s, 3H), 2.21−1.95(m, 5H), 1.74−1.68 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 171.0, 142.0, 132.2, 128.9, 128.7, 58.3, 56.5, 52.4, 46.7, 43.6, 40.7, 33.9, 30.1, 25.4; MS (ESI) 328.3 [MH$^+$]; HRMS (ESI) calculated for C$_{16}$H$_{23}$ClNO$_2$S$^+$ [MH$^+$] 328.1138, found 328.1134.

2-[[(3*S*,4*R*)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]acetamide ((−)-*trans*-5a). To a solution of (−)-*trans*-4 (176 mg, 0.54 mmol) in *t*-BuOH (3 mL), which was contained in a tube that was cooled with a dry ice/acetone bath, was introduced an excess of ammonia gas. The tube was capped, and the reaction mixture was stirred at room temperature for 72 h (Caution! Use adequate shielding.). The tube was recooled and opened, and the solvent was evaporated under vacuum. The residue was purified by column chromatography using EtOAc/MeOH/Et$_3$N (8/1/1) as the eluent to give (−)-*trans*-5a as a white solid (160 mg, 95%). [α]$^{25}_D$ −105° (*c* 0.53, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.28 (d, *J* = 8.1 Hz, 2 H), 7.11 (d, *J* = 8.7 Hz, 2 H), 6.46 (brs, 1H), 5.63 (brs, 1H), 3.27−3.22 (m, 1H), 3.07 (dd, *J* = 14.4 and 14.7 Hz, 2H), 2.98−2.84 (m, 1H), 2.44 (d, *J* = 10.2 Hz, 1H), 2.36 (s, 3H), 2.24−2.06 (m, 4H), 1.87−1.80 (m, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 171.4, 142.5, 132.8, 129.3, 129.2, 61.1, 56.5, 47.4, 46.8, 41.6, 36.7, 35.8, 35.1; MS (ESI) 313.1 [MH$^+$]; HRMS (ESI) calculated for C$_{15}$H$_{22}$ClN$_2$OS$^+$ [MH$^+$] 313.1141, found 313.1156.

2-[(3*S*,4*S*)-4-(4-Chlorophenyl)-1-methylpiperidine-3-yl]-methylsulfanyl]acetamide ((−)-*cis*-5a). Compound (−)-*cis*-

5a was prepared by the general procedure described for (−)-*trans*-**5a**. Yield:100%; white solid; [α]^{25}$_D$ −82.6° (*c* 1.0, CHCl$_3$); ^{1}HNMR (CDCl$_3$, 300 MHz) δ 7.29 (d, *J* = 8.3 Hz, 2H), 7.10 (d, *J* = 8.3 Hz, 2H), 6.89 (brs, 1H), 6.23 (brs, 1H), 3.22 (m, 1H), 3.10−2.98 (m, 3H), 2.90−2.80 (m, 2H), 2.29 (s, 3H), 2.21−1.96 (m, 5H), 1.72−1.69 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 171.9, 141.4, 132.3, 128.8, 58.2, 56.2, 46.5, 43.3, 40.9, 36.2, 30.2, 25.0; MS (ESI) 313.3 [MH$^+$]; HRMS (ESI) calculated for C$_{15}$H$_{22}$ClN$_2$-OS$^+$ [MH$^+$] 313.1141, found 313.1136.

2-[[(3S,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N-methylacetamide ((−)-trans-5b). (−)-*trans*-**4** (124 mg, 0.378 mmol) was dissolved in a 2.0 M solution of methylamine in MeOH (5.0 mL). The resulting mixture was stirred at room temperature for 24 h. The solvent was then evaporated under vacuum. The residue was purified by preparative TLC using EtOAc/Et$_3$N (10/1) as the developing solvent to afford (−)-*trans*-**5b** as a white solid (88.5 mg, 72%). [α]^{25}$_D$ −75.7° (*c* 0.66, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.2 Hz, 2H), 6.48 (brs, 1H), 3.22−3.16 (m, 1H), 3.15−2.95 (m, 2H), 2.94−2.82 (m, 1H), 2.70 (d, *J* = 5.1 Hz, 3H), 2.34 (s, 3H), 2.32−1.90 (m, 5H), 1.82−1.65 (m, 3H); ^{13}C NMR δ (CDCl$_3$, 75 MHz) 168.9, 142.4, 132.5, 129.1, 60.9, 56.3, 47.1, 46.6, 41.4, 36.8, 35.5, 34.8, 26.6; MS (ESI) 327.2 [MH$^+$]; HRMS (ESI) calculated for C$_{16}$H$_{24}$ClN$_2$OS$^+$ [MH$^+$] 327.1298, found 327.1307.

Compounds (+)-*cis*-**5b** and (−)-*cis*-**5b** were prepared by the same general procedure described for (−)-*trans*-**5b**.

2-[(3R,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N-methylacetamide ((+)-cis-5b). Yield 90%; colorless oil; [α]^{25}$_D$ +81°(*c* 0.35, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.30 (d, *J* = 8.31 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 6.90 (s, 1H), 3.21−3.16 (m, 1H), 3.05−2.99 (m, 3H), 2.90−2.82 (m, 1H), 2.78−2.67 (m, 4H), 2.29 (s, 3H), 2.05−1.85 (m, 5H), 1.73−1.61 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 168.0, 142.4, 132.5, 128.7, 58.3, 56.4, 46.5, 43.2, 40.5, 36.3, 30.1, 26.8, 25.1; MS (ESI) 327.1 [MH$^+$]; HRMS calculated for C$_{16}$H$_{24}$ClN$_2$-OS$^+$ [MH$^+$] 327.1298, found 327.1295.

2-[(3S,4S)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N-methylacetamide ((−)-cis-5b). Yield 84%; colorless oil; [α]^{25}$_D$ −88.7° (*c* 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29 (d, *J* = 8.3 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 6.90 (br.s, 1H), 3.20−3.16 (m, 1H), 3.05−2.98 (m, 3H), 2.90−2.82 (m, 1H), 2.79−2.72 (m, 4H), 2.29 (s, 3H), 2.17−1.97 (m, 5H), 1.72−1.68 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 169.0, 141.6, 132.3, 128.7, 58.3, 56.4, 46.5, 43.2, 40.5, 36.3, 30.1, 26.5, 25.1; MS (ESI) 327.4 [MH$^+$]; HRMS calculated for C$_{16}$H$_{24}$ClN$_2$-OS$^+$ [MH$^+$] 327.1298, found 327.1294.

2-[[(3S,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N-isopropylacetamide ((−)-trans-5c). (−)-*trans*-**4** (116 mg, 0.354 mmol) was dissolved in a mixture of 1.0 mL of MeOH and 2.0 mL of isopropylamine. The resulting solution was stirred at room temperature until TLC indicated that the starting material had almost disappeared. The solvent was then evaporated under vacuum. The crude product was purified by preparative TLC using EtOAc/Et$_3$N (10/1) as the developing solvent to afford (−)-*trans*-**5c** as a white solid (103 mg, 82%). [α]^{25}$_D$ −72.7° (*c*, 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.28 (d, *J* = 8.1 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 6.40 (d, *J* = 7.8 Hz, 1H), 4.02−3.85 (m, 1H), 3.25−3.19 (m, 1H), 3.05 and 2.98 (ABq, *J* = 8.4 Hz, 2H), 2.90−2.84 (m, 1H), 2.34 (s, 3H), 2.25−1.90 (m, 5H), 1.80−1.75 (m, 3H), 0.98 (d, *J* = 6.6 Hz, 3H), 0.94 (d, *J* = 6.6 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 167.1, 142.3, 132.6, 129.1, 129.0, 61.0, 56.3, 47.3, 46.5, 41.7, 41.2, 36.8, 35.3, 34.8, 22.6; MS (ESI) 355.3 [MH$^+$]; HRMS (ESI) calculated for C$_{18}$H$_{28}$ClN$_2$OS$^+$ [MH$^+$] 355.1611, found 355.1612.

Compounds (+)-*cis*-**5c** and (−)-*cis*-**5c** were prepared by the general procedure described for (−)-*trans*-**5c**.

2-[(3R,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N-isopropylacetamide ((+)-cis-5c). Yield 82%; white solid; [α]^{25}$_D$ +72° (*c* 0.41, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.28 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 7.0 Hz, 1H), 3.97 (m, 1H), 3.19 (d, *J* = 11.5 Hz, 1H), 3.02 (s, 2H), 2.89−2.75 (m, 2H), 2.28 (s, 3H), 2.05−1.95

(m, 5H), 1.69 (br.d, 1H), 1.07 (d, *J* = 6.3 Hz, 3H), 1.05 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 167.4, 141.6, 132.4, 128.8, 128.7, 67.1, 58.3, 56.4, 46.6, 43.4, 41.6, 40.5, 36.3, 29.7, 25.1, 22.7; MS (ESI) 355.1 [MH$^+$]; HRMS (ESI) calculated for C$_{18}$H$_{28}$ClN$_2$OS$^+$ [MH$^+$] 355.1611, found 355.1614.

2-[(3S,4S)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N-isopropylacetamide ((−)-cis-5c). Yield 90%; white solid; [α]^{25}$_D$ −81.3° (*c* 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.28 (d, *J* = 8.3 Hz, 2H), 7.08 (d, *J* = 8.3 Hz, 2H), 6.78 (d, *J* = 7.0 Hz, 1H), 3.97 (m, 1H), 3.19 (d, *J* = 11.5 Hz, 1H), 3.02 (s, 2H), 2.89−2.75 (m, 2H), 2.28 (s, 3H), 2.05−1.95 (m, 5H), 1.69 (br.d, 1H), 1.07 (d, *J* = 6.3 Hz, 3H), 1.05 (d, *J* = 6.3 Hz, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 167.4, 141.6, 132.4, 128.8, 128.7, 58.3, 56.4, 46.6, 43.4, 41.6, 40.5, 36.3, 29.7, 25.1, 22.7; MS (ESI) 355.5 [MH$^+$]; HRMS (ESI) calculated for C$_{18}$H$_{28}$ClN$_2$OS$^+$ [MH$^+$] 355.1611, found 355.1614.

2-[[(3S,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N,N-dimethylacetamide ((−)-trans-5d). (−)-*trans*-**4** (92.0 mg, 0.281 mmol) was dissolved in a 2.0 M solution of dimethylamine in MeOH (4.0 mL). The resulting mixture was stirred at room temperature until TLC analysis showed that the starting material had almost disappeared. The solvent was then evaporated under vacuum. The crude product was purified by preparative TLC using EtOAc/Et$_3$N (10/1) as the developing solvent to afford (−)-*trans*-**5d** as a colorless oil (87 mg, 91%). [α]^{25}$_D$ −72° (*c* 0.47, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.26 (d, *J* = 8.4 Hz, 2H), 7.12 (d, *J* = 8.4 Hz, 2H), 3.28−3.20 (m, 1H), 3.18 and 3.12 (ABq, *J* = 13.5 Hz, 2H), 2.98 (s, 3H), 2.97−2.88 (m, 1H), 2.87 (s, 3H), 2.49 (dd, *J* = 2.7, 12.8 Hz, 1H), 2.34 (s, 3H), 2.28−2.20 (m, 2H), 2.16−2.04 (m, 1H), 2.03−1.97 (m, 1H), 1.87−1.75 (m, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 168.9, 142.5, 132.1, 129.0, 128.8, 60.7, 56.2, 47.0, 46.5, 41.4, 37.9, 35.8, 34.7, 34.6, 34.5; MS(ESI) 341.2 [MH$^+$]; HRMS (ESI) C$_{17}$H$_{26}$ClN$_2$OS$^+$ [MH$^+$] 341.1454, found 341.1446.

Compounds (+)-*cis*-**5d** and (−)-*cis*-**5d** were prepared by the general procedure described for (−)-*trans*-**5d**.

2-[(3R,4S)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N,N-dimethylacetamide ((+)-cis-5d). Yield 82%; colorless oil; [α]^{25}$_D$ +68° (*c* 0.75, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.28 (d, *J* = 8.33 Hz, 2H), 7.13 (d, *J* = 8.32 Hz, 2H), 3.22−3.18 (m, 1H), 3.11 (q, *J* = 2.7 Hz, 14 Hz, 2H), 3.00−2.96 (m, 1H), 2.94 (s, 3H), 2.93−2.89 (m, 2H), 2.87 (s, 3H), 2.27 (s, 3H), 2.20−2.11 (m, 2H), 2.05−1.80 (m, 3H), 1.71−1.67 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 169.5, 142.2, 132.3, 129.2, 128.8, 58.6, 56.6, 46.8, 43.7, 41.0, 38.1, 36.1, 34.9, 30.5, 25.6; MS (ESI) 341.2 [MH$^+$]; HRMS (ESI) C$_{17}$H$_{26}$ClN$_2$OS$^+$ [MH$^+$] 341.1454, found 341.1445.

2-[(3S,4S)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N,N-dimethylacetamide ((−)-cis-5d). Yield 70%; colorless oil; [α]^{25}$_D$ −76.2° (*c* 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29 (d, *J* = 8.1 Hz, 2H), 7.13 (d, *J* = 8.3 Hz, 2H), 3.22−3.18 (m, 1H), 3.11 (d, *J* = 2.9 Hz, 2H), 3.00−2.96 (m, 1H), 2.95 (s, 3H), 2.88 (s, 3H), 2.28 (s, 3H), 2.21−1.99 (m, 5H), 1.70−1.68 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 169.5, 142.2, 132.3, 129.2, 128.8, 58.6, 56.6, 46.8, 43.7, 41.0, 38.1, 36.1, 34.9, 30.5, 25.6; MS (ESI) 341.2 [MH$^+$]; HRMS (ESI) C$_{17}$H$_{26}$ClN$_2$-OS$^+$ [MH$^+$] 341.1454, found 341.1455.

2-[[(3S,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-1-(piperidin-1-yl)ethanone ((−)-trans-5e). (−)-*trans*-**4** (117 mg, 0.357 mmol) was dissolved in a mixture of 1.0 mL of MeOH and 2.0 mL of piperidine. The resulting solution was stirred at room temperature until TLC analysis indicated that the starting material had been consumed. The solvent was then evaporated under vacuum. The crude product was purified by preparative TLC using EtOAc/Et$_3$N (10/1) as the developing solvent to afford (−)-*trans*-**5e** as a pale-yellow oil (125 mg, 92%). [α]^{25}$_D$ −75.2° (*c* 0.43, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.26 (d, *J* = 8.4 Hz, 2 H), 7.28 (d, *J* = 8.4 Hz, 2H), 7.14 (d, *J* = 8.4 Hz, 2H), 3.46 (m, 2H), 3.38−3.25 (m, 2H), 3.24−3.20 (m, 1H), 3.16 (ABq, *J* = 13.8 Hz, 2H), 2.93−2.85 (m, 1H), 2.50 (dd, *J* = 2.7, 12.6 Hz, 1H), 2.34 (s, 3H), 2.28−2.20 (m, 2H), 2.16−1.95 (m, 2H), 1.88−1.70 (m, 3H), 1.66−1.40 (m, 6H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 167.2, 142.7, 132.3, 129.2, 128.9, 61.0, 56.2, 47.6, 47.2, 46.6,

43.1, 41.4, 34.9, 34.7, 26.5, 25.6, 24.5; MS (ESI) 381.3 [MH$^+$]; HRMS (ESI) calculated for C$_{20}$H$_{30}$ClN$_2$OS$^+$ [MH$^+$] 381.1767, found 381.1768.

Compounds (+)-*cis*-**5e** and (−)-*cis*-**5e** were prepared by the general procedure described for (−)-*trans*-**5e**.

2-[(3R,4R)-4-(Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-1-(piperidne-1-yl)ethanone ((+)-cis-5e). Yield 87%; white solid; [α]$^{25}_D$ +77° (*c* 0.875, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) *δ* 7.30 (d, *J* = 8.1 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 3.45 (t, *J* = 5.39 Hz, 2H), 3.32 (t, *J* = 5.3 Hz, 2H), 3.24−3.08 (m, 3H), 3.01−2.94 (m, 1H), 2.90−2.75 (m, 2H), 2.28 (s, 3H), 2.20−1.98 (m, 5H), 1.74−1.31 (m, 7H); ^{13}C NMR (CDCl$_3$, 75 MHz) *δ* 167.5, 142.0, 132.1, 129.0, 128.6, 67.1, 58.4, 56.5, 47.6, 46.7, 43.5, 43.1, 40.6, 34.7, 30.2, 26.5, 25.7, 25.4, 24.6; MS (ESI) 381.2 [MH$^+$]; HRMS (ESI) calculated for C$_{20}$H$_{30}$ClN$_2$OS$^+$ [MH$^+$] 381.1767, found 381.1778.

2-[(3S,4S)-4-(Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-1-(piperidne-1-yl)ethanone ((−)-cis-5e). Yield 90%; white solid; [α]$^{25}_D$ −83.7° (*c* 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) *δ* 7.27 (d, *J* = 8.3 Hz, 2H), 7.14 (d, *J* = 8.3 Hz, 2H), 3.43 (t, *J* = 5.3 Hz, 2H), 3.29 (t, *J* = 5.2 Hz, 2H), 3.22−3.12 (m, 3H), 3.06−2.97 (m, 1H), 2.88−2.80 (m, 2H), 2.26 (s, 3H), 2.17−1.99 (m, 5H), 1.69−1.44 (m, 7H); ^{13}C NMR (CDCl$_3$, 75 MHz) *δ* 167.5, 142.0, 132.1, 129.0, 128.6, 58.4, 56.5, 47.6, 46.7, 43.5, 43.1, 40.6, 34.7, 30.2, 26.5, 25.7, 25.4, 24.6; MS (ESI) 381.4 [MH$^+$]; HRMS (ESI) calculated for C$_{20}$H$_{30}$ClN$_2$OS$^+$ [MH$^+$] 381.1767, found 381.1760.

(3S,4R)-[4-Chlorophenyl]-1-methylpieridin-3-ylmethylsulfanyl]acetic Acid ((−)-trans-6). To a solution of (−)-*trans*-**2** (400 mg, 1.22 mmol) in THF/H$_2$O (1/1, 20 mL) was added LiOH·2H$_2$O (100 mg, 2.38 mmol) under nitrogen at room temperature. After being stirred at room temperature until the reaction was complete, as judged by TLC analysis, the mixture was neutralized with 10% aqueous HCl solution and then extracted with CH$_2$Cl$_2$ (3 × 25 mL). The combined extracts were dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum to give (−)-*trans*-**6** as a yellow oil (352 mg, 92%). [α]$^{25}_D$ −72° (*c* 1.1, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) *δ* 7.32 (d, *J* = 8.1 Hz, 2H), 7.20 (d, *J* = 8.2 Hz, 2H), 3.99 (br d, *J* = 10 Hz, 1H), 3.58 (br d, *J* = 11 Hz, 1H), 3.13 (q, *J* = 15, 15 Hz, 2H), 2.88 (s, 3H), 2.88−2.70 (m, 3H), 2.69−2.45 (m, 3H), 2.24 (m, 1H), 2.00−1.96 (m, 1H);

(3R,4R)-[4-Chlorophenyl]-1-methylpieridin-3-ylmethylsulfanyl]acetic Acid HCl Salt ((+)-cis-6). Compound (+)-*cis*-**6** was prepared by the general procedure described for (−)-*trans*-**6**. Yield 90%; white solid; [α]$^{25}_D$ +125.8 ° (*c* 0.80, MeOH); ^{1}H NMR (CDCl$_3$, 300 MHz) *δ* 7.35 (d, *J* = 8.5 Hz, 2H), 7.24 (d, *J* = 8.4 Hz, 2H), 4.00 (br d, *J* = 11 Hz, 1H), 3.61 (br d, *J* = 11.5 Hz, 1H), 3.17−3.02 (m, 5H), 2.89 (s, 3H), 2.60−2.52 (m, 1H), 2.44−2.32 (m, 3H), 2.02−1.96 (m, 1H);

2-[[(3R,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N-phenylacetamide ((+)-cis-5f). To a solution of (+)-*cis*-**6** (30 mg, 0.10 mmol) in anhydrous CH$_2$Cl$_2$ (4 mL) was added aniline (18 mg, 0.15 mmol) under nitrogen at room temperature, followed by the addition of EDCI (28 mg, 0.15 mmol) and HOBt (5 mg, 0.01 mmol). After the mixture was stirred at room temperature overnight, the solvent was evaporated and the residue was diluted with ethyl acetate and washed with a saturated NaCl solution. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by TLC using the mixture EtOAc/Et$_3$N/MeOH (8/1/1) as the developing solvent to afford (+)-*cis*-**5f** as a colorless oil (30 mg, 73%). [α]$^{25}_D$ +70° (*c* 0.72, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) *δ* 7.53−7.21 (m, 6H), 7.20−7.10 (m, 1H), 7.08 (d, *J* = 8.3 Hz, 2H), 3.30−3.21 (m, 3H), 3.15−3.00 (m, 1H), 2.94−2.86 (m, 2H), 2.34 (s, 3H), 2.26−2.00 (m, 5H), 1.88−1.67 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) *δ* 166.8, 141.3, 137.7, 132.4, 129.3, 128.8, 128.7, 124.7, 120.1, 58.5, 56.6, 46.5, 43.4, 41.1, 37.4, 29.8, 25.0; MS (ESI) 389.2 [MH$^+$]; HRMS (ESI) C$_{21}$H$_{26}$ClN$_2$OS$^+$ [MH$^+$] 389.1454, found 389.1452.

2-[[(3S,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N-benzylacetamide ((−)-trans-5g). To a solution of (−)-*trans*-**6** (30 mg, 0.10 mmol) in anhydrous CH$_2$-

Cl$_2$ (4 mL) was added benzylamine (11 mg, 0.10 mmol) under nitrogen at room temperature, followed by the addition of EDCI (28 mg, 0.15 mmol) and HOBt (5 mg, 0.01 mmol). After the mixture was stirred at room temperature overnight, the solvent was evaporated and the residue was diluted with ethyl acetate and washed with a saturated NaCl solution. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by preparative TLC using the mixture EtOAc/Et$_3$N/MeOH (8/1/1) as the developing solvent to afford (−)-*trans*-**5g** as a white solid (25.4 mg, 63%). [α]$^{25}_D$ −74° (*c* 0.55, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) *δ* 7.34−7.19 (m, 7H), 7.10 (d, *J* = 7.5 Hz, 2H), 6.95−6.82 (brs, 1H), 4.35 (d, *J* = 5.52 Hz, 2H), 3.19−3.12 (m, 3H), 2.83−2.99 (m, 1H), 2.39−2.35 (m, 1H), 2.33 (s, 3H), 2.28−1.95 (m, 4H), 1.90−1.70 (m, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) *δ* 168.2, 142.0, 138.1, 132.3, 129.1, 129.0, 128.9, 127.8, 127.8, 60.8, 56.2, 47.2, 46.5, 43.9, 41.1, 36.8, 35.5, 34.8; MS (ESI) 403.1 [MH$^+$]; HRMS (ESI) calculated for C$_{22}$H$_{28}$ClN$_2$OS$^+$ [MH$^+$] 403.1611, found 403.1606.

Compounds (+)-*cis*-**5g** and (−)-*cis*-**5g** were prepared by the general procedure described for (−)-*trans*-**5g**.

2-[[(3R,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N-benzylacetamide ((+)-cis-5g). Yield 62%; white solid; [α]$^{25}_D$ +76° (*c* 0.60, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) *δ* 7.50 (brs, 1H), 7.38−7.25 (m, 6H), 7.01 (d, *J* = 8.32 Hz, 2H), 4.45 (ABq, *J* = 5.8, 14.6 Hz, 1H), 4.33 (ABq, *J* = 5.5, 14.6 Hz, 1H), 3.18−3.10 (m, 3H), 2.83−2.71 (m, 3H), 2.19 (s, 3H), 2.11−1.88 (m, 5H), 1.87−1.79 (m, 1H), 1.60−1.55 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) *δ* 168.5, 141.6, 138.2, 132.4, 128.9, 128.8, 128.7, 128.1, 127.8, 58.4, 56.4, 46.4, 43.4, 41.0, 36.5, 29.7, 24.9; MS (ESI) 403.1 [MH$^+$]; HRMS (ESI) calculated for C$_{22}$H$_{28}$ClN$_2$OS$^+$ [MH$^+$] 403.1611, found 403.1616.

2-[[(3S,4S)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N-benzylacetamide ((−)-cis-5g). Yield 58%; white solid; [α]$^{25}_D$ −71.4° (*c* 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) *δ* 7.51 (brs, 1H), 7.37−7.27 (m, 6H), 7.02 (d, *J* = 8.2 Hz, 2H), 4.47 (ABq, *J* = 5.9, 14.6 Hz, 1H), 4.34 (ABq, *J* = 5.4, 14.6 Hz, 1H), 3.18−3.12 (m, 3H), 2.85−2.72 (m, 3H), 2.20 (s, 3H), 2.11−1.88 (m, 5H), 1.87−1.76 (m, 1H), 1.60−1.56 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) *δ* 168.5, 141.5, 138.3, 132.3, 128.9, 128.7, 128.7, 128.1, 127.8, 58.4, 56.3, 46.4, 43.9, 43.4, 41.0, 36.5, 29.7, 24.9; MS (ESI) 403.1 [MH$^+$]; HRMS (ESI) calculated for C$_{22}$H$_{28}$ClN$_2$OS$^+$ [MH$^+$] 403.1611, found 403.1615.

2-[[(3S,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N-(2-phenylethyl)acetamide ((−)-cis-5h). To a solution of (−)-*trans*-**6** (30 mg, 0.10 mmol) in anhydrous CH$_2$Cl$_2$ (4 mL) was added 2-phenylethylamine (13 mg, 0.10 mmol) under nitrogen at room temperature, followed by the addition of EDCI (28 mg, 0.15 mmol) and HOBt (5 mg, 0.01 mmol). After the mixture was stirred at roomtemperature overnight, the solvent was evaporated and the residue was diluted with ethyl acetate and washed with a saturated NaCl solution. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by TLC using the mixture EtOAc/Et$_3$N/MeOH (8/1/1) as the developing solvent to afford (−)-*trans*-**5h** as a colorless oil (23 mg, 56%). [α]$^{25}_D$ −68° (*c* 0.42, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) *δ* 7.34−7.22 (m, 5H), 7.16 (d, *J* = 7.0 Hz, 2H), 7.09 (d, *J* = 8.3 Hz, 2H), 6.65−6.58 (m, 1H), 3.44 (dd, *J* = 13.1, 6.7 Hz, 2H), 3.21−3.19 (m, 1H), 3.11 (dd, *J* = 11.4, 16 Hz, 2H), 2.99−2.94 (m, 1H), 2.72 (t, *J* = 7.42 Hz, 2H), 2.35 (s, 3H), 2.30−2.08 (m, 2H), 2.05−1.98 (m, 3H), 1.80−1.75 (m, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) *δ* 168.2, 142.3, 138.8, 132.6, 129.1, 129.0, 128.9, 128.8, 126.8, 60.7, 56.2, 47.1, 46.5, 41.2, 40.9, 36.9, 35.7, 35.4, 34.7; MS (ESI) 417.3 [MH$^+$]; HRMS (ESI) calculated for C$_{23}$H$_{30}$ClN$_2$OS$^+$ [MH$^+$] 417.1767, found 417.1776.

2-[[(3R,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N-(2-phenylethyl)acetamide ((+)-cis-5h). Compound (+)-*cis*-**5h** was prepared by the general procedure described for (−)-*trans*-**5h**. Yield 58%; colorless oil; [α]$^{25}_D$ +65° (*c* 0.63, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) *δ* 7.35−7.23 (m, 5H), 7.18 (d, *J* = 7.13 Hz, 2H), 7.07 (d, *J* = 8.3 Hz, 2H), 6.93 (brs, 1H), 3.49−3.44 (m, 2H), 3.17−3.13 (m, 1H), 3.04 (s, 2H), 2.98−2.95 (m, 1H), 2.88−2.84 (m, 1H), 2.77−2.72 (m,

3H), 2.25 (s, 3H), 2.14−1.93 (m, 5H), 1.72−1.66 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 168.4, 141.6, 139.0, 132.3, 128.9, 128.8, 128.78, 128.7, 126.7,58.3, 56.5, 46.6, 43.3, 41.0, 40.7, 36.4, 35.8, 30.0, 25.2; MS (ESI) 417.1 [MH$^+$]; HRMS (ESI) calculated for C$_{23}$H$_{30}$ClN$_2$OS$^+$ [MH$^+$] 417.1767, found 417.1776.

2-[[(3R,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]-N-naphthylacetamide ((+)-cis-5i). To a solution of (+)-cis-**6** (30 mg, 0.10 mmol) in anhydrous CH$_2$Cl$_2$ (4 mL) was added β-naphthylamine (22 mg, 0.15 mmol) under nitrogen at room temperature, followed by the addition of EDCI (28 mg, 0.15 mmol) and HOBt (5 mg, 0.01 mmol). After the mixture was stirred at room temperature overnight, the solvent was evaporated and the residue was diluted with ethyl acetate and washed with a saturated NaCl solution. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by TLC using the mixture EtOAc/Et$_3$N/MeOH (8/1/1) as the developing solvent to afford (+)-cis-**5i** as a white solid (29 mg, 65%). [α]$^{25}_D$ +70° (c 0.47, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 9.16 (s, 1H), 8.19 (s, 1H), 7.86−7.81 (m, 3H), 7.52−7.40 (m, 3H), 7.28−7.23 (m, 1H), 7.07 (d, 2H), 3.33−3.26 (m, 3H), 3.09 (d, 1H), 2.98−2.90 (m, 2H), 2.37 (s, 3H), 2.28−1.99 (m, 5H), 1.71 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 167.1, 141.2, 135.2, 134.0, 132.5, 131.0, 129.0, 128.8, 128.7, 127.9, 127.8, 126.7, 125.3, 119.9, 116.9, 77.7, 77.2, 76.8, 58.5, 56.6, 46.6, 43.4, 41.2, 37.5, 29.8, 25.0; MS (ESI) 439.1 [MH$^+$]; HRMS (ESI) calculated for C$_{25}$H$_{28}$ClN$_2$OS$^+$ [MH$^+$] 439.1611, found 439.1613.

2-[[(3S,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]ethanol ((−)-trans-7). To a solution of [(3S,4R)-4-(4-chlorophenyl)-1-methylpiperidin-3-ylmethyl-sulfanyl]acetic acid methyl ester (271 mg, 0.827 mmol) in anhydrous THF (10 mL) that was cooled to 0 °C was added LiAlH$_4$ (47.1 mg, 1.24 mmol). The resulting mixture was warmed to room temperature and stirred overnight, and then the reaction was quenched with a saturated solution of NH$_4$-Cl (10 mL). The solution was extracted with CH$_2$Cl$_2$ (3 × 25 mL). The combined organic extracts were dried over Na$_2$SO$_4$, concentrated, and purified by column chromatography on silica gel with EtOAc/Et$_3$N (10:1) to EtOAc/MeOH/Et$_3$N (8:1:1) as the eluent to yield (−)-trans-**7** as a colorless oil (203 mg, 82%). [α]$^{25}_D$ −80.5° (c 0.65, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.28 (d, J = 8.3 Hz, 2 H), 7.13 (d, J = 8.3 Hz, 2H), 3.57−3.40 (m, 3H), 3.35−3.24 (m, 1H), 2.98−2.88 (m, 1H), 2.54 (t, J = 5.4 Hz, 2H), 2.35 (s, 3H), 2.31−2.20 (m, 2H), 2.08−2.04 (m, 3H), 1.81−1.70 (m, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 142.7, 132.7, 129.2 (2), 61.0, 60.5, 56.4, 47.3, 46.6, 41.8, 36.2, 34.7, 34.3; MS(ESI) 300.2 [MH$^+$]; HRMS (ESI) calculated for C$_{15}$H$_{23}$-ClNOS$^+$ [MH$^+$] 300.1189, found 300.1186.

Compounds (+)-cis-**7** and (−)-cis-**7** were prepared by the general procedure described for (−)-trans-**7**.

2-[[(3R,4R)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]ethanol ((+)-cis-7). Yield 78%; colorless oil; [α]$^{25}_D$ +85.5° (c 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29 (d, J = 8.5 Hz, 2H), 7.10 (d, J = 8.4 Hz, 2H), 3.68−3.63 (m, 2H), 3.48−3.40 (m, 1H), 3.07−2.98 (m, 1H), 2.96−2.82 (m, 2H), 2.69−2.42 (m, 2H), 2.31 (s, 3H), 2.23−1.95 (m, 6H), 1.76−1.62 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 141.8, 132.2, 128.8, 128.7, 62.6, 58.1, 56.4, 46.5, 43.4, 41.0, 36.0, 28.5, 24.9; MS (ESI) 300.2 [MH$^+$]; HRMS (ESI) calculated for C$_{15}$H$_{23}$ClNOS$^+$ [MH$^+$] 300.1189, found 300.1190.

2-[[(3S,4S)-4-(4-Chlorophenyl)-1-methylpiperidin-3-yl]-methylsulfanyl]ethanol ((−)-cis-7). Yield 68%; colorless oil; [α]$^{25}_D$ −87.3° (c 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29 (d, J = 8.4 Hz, 2H), 7.09 (d, J = 8.3 Hz, 2H), 3.68−3.63 (m, 2H), 3.46−3.41 (m, 1H), 3.07−2.98 (m, 1H), 3.03−2.83 (m, 2H), 2.64−2.45 (m, 2H), 2.30 (s, 3H), 2.23−1.95 (m, 6H), 1.69−1.67 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 141.8, 132.2, 128.8, 128.7, 62.6, 58.1, 56.4, 46.5, 43.5, 41.0, 35.9, 28.5, 24.9; MS (ESI) 300.3 [MH$^+$]; HRMS (ESI) calculated for C$_{15}$H$_{23}$ClNOS$^+$ [MH$^+$] 300.1189, found 300.1189.

Acetic Acid 2-[[(3S,4R)-4-(4-Chlorophenyl)-1-methyl-piperidin-3-yl]methylsulfanyl]ethyl Ester ((−)-trans-8a). To a solution of (−)-trans-**7** (92.0 mg, 0.307 mmol) in pyridine

(8 mL) was added 2.0 mL of Ac$_2$O under nitrogen at room temperature, followed by 1.0 mg of 4-(dimethylamino)pyridine (DMAP). After the mixture was stirred at room temperature for 2 h, the solvent was evaporated and the residue was diluted with ethyl acetate and washed with saturated NaHCO$_3$ aqueous solution (2 × 15 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by preparative TLC using EtOAc/Et$_3$N (10/1) as the developing solvent to afford (−)-trans-**8a** as a colorless oil (74 mg, 70%). [α]$^{25}_D$ −83.0° (c 1.05, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29 (d, J = 8.3 Hz, 2H), 7.14 (d, J = 8.4 Hz, 2H), 4.04−4.03 (m, 2H), 3.24−3.30 (m, 1H), 2.98−2.92 (m, 1H), 2.57 (t, J = 6.9 Hz, 2H), 2.43 (dd, J = 1.5, 10.2 Hz, 1H), 2.35 (s, 3H), 2.31−2.19 (m, 1H), 2.17−2.05 (m, 3H), 2.01 (s, 3H), 1.81−1.78 (m, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 171.1, 142.9, 132.6, 129.3, 129.2, 63.7, 61.2, 56.6, 47.4, 46.8, 42.0, 35.1, 31.4, 21.2; MS (ESI) 342.3 [MH$^+$]; HRMS (ESI) calculated for C$_{17}$H$_{25}$ClNO$_2$S$^+$ [MH$^+$] 342.1295, found 342.1287.

Compounds (+)-cis-**8a** and (−)-cis-**8a** were prepared by the general procedure described for (−)-trans-**8a**.

Acetic Acid 2-[[(3R,4R)-4-(4-Chlorophenyl)-1-methyl-piperidin-3-yl]methylsulfanyl]ethyl Ester ((+)-cis-8a). Yield 64%; colorless oil; [α]$^{25}_D$ +73° (c 1.1, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29 (d, J = 8.4 Hz, 2H), 7.12 (d, J = 8.31 Hz, 2H), 4.02−3.95 (m, 2H), 3.22−3.18 (m, 1H), 3.00−2.97 (m, 1H), 2.88−2.74 (m, 2H), 2.54−2.48 (m, 2H), 2.28 (s, 3H), 2.20−1.80 (m, 5H), 2.00 (s, 3H), 1.70−1.67 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 170.9, 142.0, 132.2, 128.8, 128.7, 63.6, 58.3, 56.5, 46.6, 43.6, 41.4, 30.8, 29.5, 25.3, 21.0; MS (ESI) 342.1 [MH$^+$]; HRMS (ESI) calculated for C$_{17}$H$_{25}$ClNO$_2$S$^+$ [MH$^+$] 342.1295, found 342.1289 [MH$^+$].

Acetic Acid 2-[[(3S,4S)-4-(4-Chlorophenyl)-1-methyl-piperidin-3-yl]methylsulfanyl]ethyl Ester ((−)-cis-8a). Yield 92%; [α]$^{25}_D$ −66.9° (c 1.0, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.29 (d, J = 8.3 Hz, 2H), 7.11 (d, J = 8.3 Hz, 2H), 4.05−3.91 (m, 2H), 3.21−3.17 (m, 1H), 3.00−2.97 (m, 1H), 2.88−2.74 (m, 2H), 2.54−2.48 (m, 2H), 2.27 (s, 3H), 2.13−2.00 (m, 5H), 2.00 (s, 3H), 1.70−1.67 (m, 1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 170.9, 142.0, 132.2, 128.8, 128.7, 63.6, 58.3, 56.5, 46.6, 43.6, 41.4, 30.8, 29.5, 25.3, 21.0; MS (ESI) 342.4 [MH$^+$]; HRMS (ESI) calculated for C$_{17}$H$_{25}$ClNO$_2$S$^+$ [MH$^+$] 342.1295, found 342.1288 [MH$^+$].

Benzoic Acid 2-[[(3S,4R)-4-(4-Chlorophenyl)-1-meth-ylpiperidin-3-yl]methylsulfanyl]ethyl Ester ((−)-trans-8b). To a solution of (−)-trans-**7** (89.0 mg, 0.297 mmol) in anhydrous THF (8 mL) were added Et$_3$N (83 µL) and DMAP (1.0 mg) under nitrogen at 0 °C, followed by benzoyl chloride (52 µL, 63 mg, 0.45 mmol). After the mixture was stirred at 0 °C to room temperature overnight, the solvent was evaporated and the residue was diluted with ethyl acetate and washed with saturated aqueous NaHCO$_3$ solution (2 × 10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated under vacuum. The crude product was purified by preparative TLC using EtOAc/Et$_3$N (10/1) as the developing solvent to afford (−)-trans-**8b** as a colorless oil (81 mg, 68%). [α]$^{25}_D$ −63.7° (c 0.72, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 7.96−7.91 (m, 2H), 7.52−7.46 (m, 1H), 7.39−7.34 (m, 2H), 7.18 (d, J = 8.1 Hz, 2H), 7.05 (d, J = 8.7 Hz, 2H), 4.28−4.16 (m, 2H), 3.22−3.17 (m, 1H), 2.87−2.84 (m, 1H), 2.63 (t, J = 6.6 Hz, 2H), 2.52−2.40 (m, 1H), 2.27 (s, 3H), 2.20−1.88 (m, 4H), 1.81−1.68 (m, 3H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 166.4, 142.6, 133.2, 132.3, 129.8, 129.1, 128.6, 63.8, 61.1, 56.3, 47.2, 46.4, 41.8, 35.0, 34.9, 31.5; MS (ESI) 404.2 [MH$^+$]; HRMS (ESI) calculated for C$_{22}$H$_{27}$ClNO$_2$S$^+$ [MH$^+$] 404.1446, found 404.1459.

Benzoic Acid 2-[[(3R,4R)-4-(4-Chlorophenyl)-1-meth-ylpiperidin-3-yl]methylsulfanyl]ethyl Ester ((+)-cis-8b). Compound (+)-cis-**8b** was prepared by the general procedure described for (−)-trans-**8b**. Yield 68%; colorless oil; [α]$^{25}_D$ +62° (c 0.33, CHCl$_3$); ^{1}H NMR (CDCl$_3$, 300 MHz) δ 8.04 (d, J = 7.34 Hz, 2H), 7.61−7.56 (m, 1H), 7.49−7.44 (m, 2H), 7.29 (d, J = 8.3 Hz, 2H), 7.13 (d, J = 8.3 Hz, 2H), 4.34−4.22 (m, 2H), 3.26−3.22 (m, 1H), 3.02−2.99 (m, 1H), 2.90−2.82 (m, 2H), 2.76−2.63 (m, 2H), 2.30 (s, 3H), 2.20−1.96 (m, 5H), 1.72−1.69 (m,

1H); ^{13}C NMR (CDCl$_3$, 75 MHz) δ 166.5, 142.0, 133.2, 132.1, 130.2, 129.9, 128.8, 128.7, 128.6, 64.1, 58.3, 56.5, 46.6, 43.6, 41.5, 31.1, 29.6, 25.4; MS (ESI) 404.2 [MH$^+$]; HRMS (ESI) calculated for C$_{22}$H$_{27}$ClNO$_2$S$^+$ [MH$^+$] 404.1446, found 404.1463.

Supporting Information Available: HPLC analysis data and NMR charts (^{1}H and ^{13}C) for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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