Slow-Onset, Long-Duration, Alkyl Analogues of Methylphenidate with Enhanced Selectivity for the Dopamine Transporter

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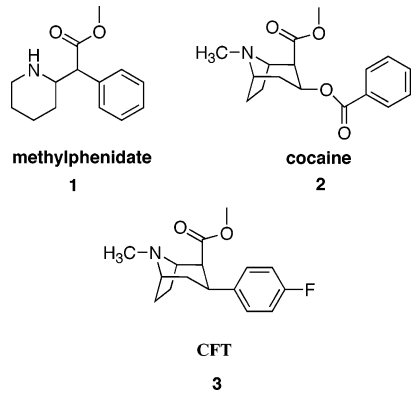
Methylphenidate analogues, in which the carbomethoxy has been replaced by an alkyl group and with different phenyl substituents, have been synthesized and tested in monoamine transporter assays. As predicted from a pharmacophore model, most of the *RR*/*SS* diastereomers showed high potency as dopamine reuptake inhibitors. Analogues with a 4-chlorophenyl group and an unbranched initial alkyl atom had consistently enhanced selectivity for the dopamine transporter. The most potent compounds were those with a three- or four-carbon chain. The "inactive" *RS*/*SR* diastereomers showed substantial activity when the phenyl substituent was 3,4-dichloro. On a locomotor assay, one compound was found to have a slow onset and a long duration of action. The activity of these compounds provides additional evidence for a conformational/superposition model of methylphenidate with cocaine-like structures. A ketone analogue, obtained by hydrogenating a previously described vinylogous amide, had activity similar to that of methylphenidate.

Introduction

Methylphenidate (Scheme 1), which was first synthesized 60 years ago,[1] is still commonly used for the treatment of attention-deficit hyperactivity disorder. The activity of the compound, whose primary pharmacological action is to block the reuptake of dopamine (DA) and norepinephrine (NE) by their respective transporters in the central nervous system, resides almost entirely in the threo isomer.[2−4] The absolute configuration of the active (+)-enantiomer has been determined to be *R*,*R* from chemical conversion to compounds with known absolute configuration,[5] and this has been confirmed more recently by X-ray crystallography.[6]

In cases where the three-dimensional structure of the binding site in a target protein is not well defined, as is the case for the monoamine transporters, one can perform ligand-based design to develop a pharmacophore. That is, by studying the conformational properties of a series of pharmacologically similar compounds, one can formulate hypotheses regarding the pharmacophore. To that end, conformational analyses were performed on a series of DA reuptake blockers, including cocaine and CFT (Scheme 1).[7] The preferred conformation of the tropane DA reuptake blockers was found to have an intramolecular hydrogen bond between the carbonyl oxygen and the *axial* ammonium hydrogen. On this basis, a pharmacophore model was proposed in which the key feature was the orientation of the ammonium hydrogen. The model could then explain why some DA reuptake inhibitors, such as 1-amino-4-phenyltetralins and 3-phenyl-1-aminoindanes, have optimal activity as secondary amines whereas others, such as cocaine, have optimal activity as tertiary amines. That is, an *N*-substituent in the tertiary amine of the former is in the position required for the ammonium hydrogen. This pharmacophore model has been tested by the synthesis of rigid analogues of cocaine with defined orientations

Scheme 1



of the ammonium hydrogen, and different transporter selectivities were demonstrated that were consistent with its predictions.[8] More recently, the pharmacophore model was extended to methylphenidate by a conformational analysis of the threo and erythro isomers using the molecular mechanics program MM2-87, and the preferred conformer of the threo isomer was found to have an intramolecular hydrogen bond between the carbonyl oxygen and the *equatorial* ammonium hydrogen.[6] Similar conformations were observed in a number of crystal structures of methylphenidate analogues with different phenyl substituents.[9] This model also correctly predicted a decrease of activity when the secondary amines of methylphenidate analogues were *N*-methylated.[10]

Using these preferred conformers of methylphenidate and CFT, the compounds were superimposed and an essentially perfect fit was found for the sequence of atoms from the amine atom through the ester group (Figure 1).[6] This suggests that methylphenidate and CFT should share similar structure activity relations with respect to the carbomethoxy side chain. It should be noted that an ester group is not required for the activity of tropane-containing DA reuptake blockers and compounds with a variety of other substitutions retain potent activity.[11−20] In

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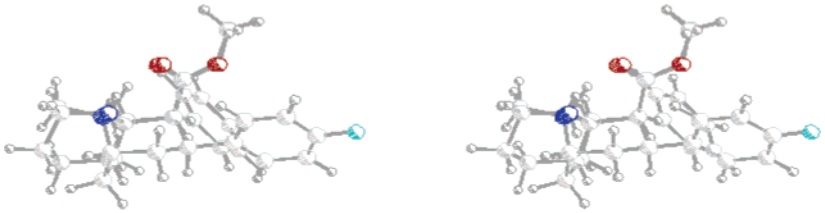
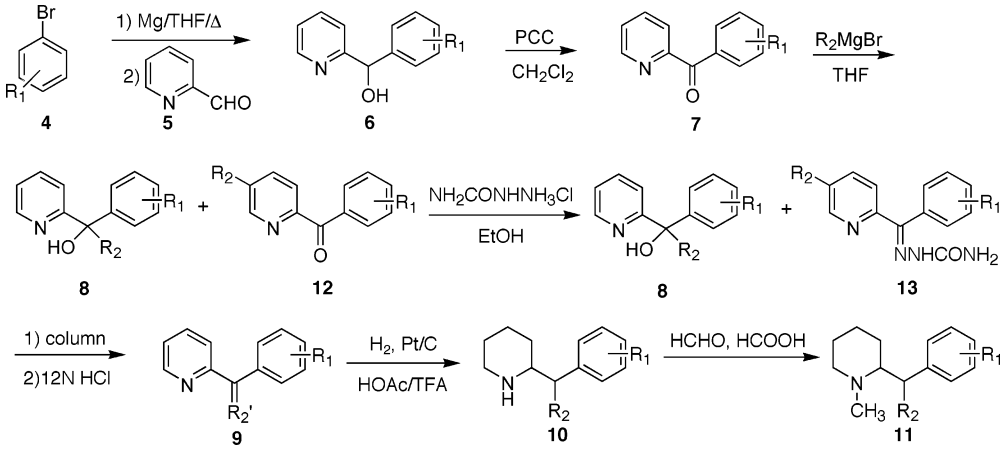


Figure 1. Stereoscopic images of the superposition of the atoms of (*R*,*R*)-methylphenidate and CFT from the nitrogen through the ester, showing an essentially perfect fit for that sequence of atoms.

Scheme 2



particular, replacing the carbomethoxy group in CFT and cocaine by a simple alkyl group can produce compounds with good potency in blocking the reuptake of dopamine.[8,13,15,18] If the superposition model of CFT and methylphenidate is correct, one would expect that similar substitutions in the latter should produce active compounds. On the basis of this ligand-based design, we have synthesized methylphenidate analogues in which the carbomethoxy group is replaced by various alkyl groups. There has been one previous limited report of alkyl analogues of methylphenidate from a half-century ago in which there was apparently no separation of diastereomers.[21] This was also prior to the development of binding and uptake assays so that it was impossible to determine any kind of selectivity, and in any case, virtually no in vivo pharmacological data were reported.

It should also be noted that the pharmacophore model for methylphenidate has been used by others to design novel methylphenidate analogues[22] and that the model has been successfully extended to the DA reuptake inhibitors bupropion[23] and BTCP.[24]

One less desirable aspect to the clinical use of methylphenidate is that it typically must be administered two or three times per day[25] since the ester moiety is rapidly metabolized to produce the inactive acid.[26] Methylphenidate, as a potent DA reuptake blocker, also has abuse potential. There is evidence that the abusability of a drug is correlated with a fast onset and a short duration of action.[27−31] Our goal is the synthesis of DA reuptake blockers with reduced abuse liability as possible maintenance pharmacotherapies for the treatment of cocaine dependence. Therefore, to obtain compounds with longer durations of action, we deemed it advantageous to replace the carbomethoxy with something more metabolically stable such as an alkyl group.

Because of the similar pharmacological profiles of cocaine and methylphenidate, there has been a revival of interest in the synthesis and testing of analogues of the latter as possible medications for treating cocaine abuse. Substitutions on the phenyl ring of methylphenidate were found to greatly enhance activity,[32,33] and as with other DA reuptake blockers, halogens such as chlorine and bromine in the meta and/or para positions provided the most potent compounds.[7] The addition of an *N*-methyl or *N*-allyl group to methylphenidate analogues, however, consistently reduced potency,[10,34] while an *N*-benzyl increased potency but appears to change the structure−activity relationships in the compound.[35] Similarly, changing the size of the nitrogen-containing ring led to less potent compounds, while replacement of the phenyl ring by a β-napthyl group enhanced potency.[35] More recently, it has been shown that the presence of the basic nitrogen is not always required for activity in methylphenidate since its replacement by oxygen or carbon, as with other dopamine uptake blockers,[36] still produces active compounds,[37] though this may require the presence of the potency-enhancing effect of the 3,4-dichloro group.

Synthesis

Most compounds were synthesized following Scheme 2. A bromobenzene (**4**) with the required phenyl substituent was converted into a Grignard reagent which was then allowed to react with pyridine-2-carboxaldehyde (**5**) to produce the secondary alcohol **6**. The alcohol **6** was oxidized with pyridinium chlorochromate to produce the ketone **7**, which was purified in a Kauffman column[38] (Ace Glass, Vineland, NJ). This was then allowed to react with a Grignard reagent that contains the required R_2 group to produce the tertiary alcohol **8**. After purification, alcohol **8** was dehydrated with refluxing HCl to produce alkene **9**, usually as a mixture of *Z* and *E* isomers. For a few compounds, it was necessary to use stronger HBr for the dehydration. Dehydration with HCl of alcohols **8** with methoxy groups on the phenyl ring resulted in considerable demethylation of the methoxy group. For these compounds, the dehydration was performed with $POCl_3$/pyridine.[39] The alkene mixture **9** was hydrogenated with 10% Pt/C in HOAc containing 3% CF_3-COOH to produce the final compounds **10** with a ratio of about 40:60 of the *RR*/*SS* and *RS*/*SR* diastereomers. The diastereomers

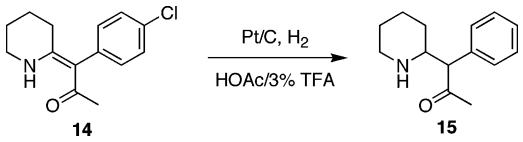
of **10** were generally separable by column chromatography. In the few instances where this was not easy, fractional crystallization was used to separate the diastereomers. Initially, many of the relative configurations of the diastereomers of **10** were determined by X-ray crystallography. However, it was also possible to distinguish the purified diastereomers by the NMR chemical shift of the benzylic methine proton. In the *RR*/*SS* diastereomers, that methine proton appeared as a broad doublet (J = ca. 12 Hz), usually at 3.2−3.0 ppm, which was 0.2−0.3 ppm downfield from the corresponding resonance in the *RS*/*SR* diastereomer. For the *N*-methyl analogues, the separated diastereomers were allowed to react with HCHO and HCOOH.

While the reactions in Scheme 2 used to prepare the methylphenidate analogues look deceptively simple, complications occurred with the use of the Grignard reagents to prepare the tertiary alcohols **8**. The addition of methyl and ethyl Grignard to ketone **7a** proceeded without difficulty, giving ∼90% yields of the desired tertiary alcohols **8a** and **8b**. However, with larger Grignard reagents, there was considerable reduction of ketones **7** back to the secondary alcohols **6** as is well-known to occur for some Grignard reactions. For example, the addition of ketone **7a** to a preformed solution of isobutyl Grignard at 0° gave 40% of the reduced secondary alcohol **6a** as an isolated side product. With a rapid, reverse addition of Grignard reagent at −10°, the yield of **6a** was again about 40%. Only when the Grignard reagent was added dropwise to a cooled (0°) solution of the ketones **7** did the desired tertiary alcohols **8** predominate over reduction products **6**. The reaction products were also accompanied by unexpected ketones **12**, resulting from the apparent 1,6-conjugate addition of the Grignard reagent to C-5 of the pyridine ring and subsequent oxidative loss of the C-5 hydrogen. We did not identify the oxidant in this addition. The amount of **12** produced in any reaction could be quantitated by integration of the proton NMR spectra of the crude product mixtures. The integrated area of the multiplets around δ 8.5 (H-6 on the pyridine rings of both alcohols and the byproduct ketone) can be compared with the integrated area around 8 ppm in which overlapping doublets due to three hydrogens deshielded by the ketone carbonyl appear in **12**. No other resonances appear near 8 ppm in either alcohol. Since we observed no evidence for the reaction of ketone **12** with a second molecule of Grignard reagent, we presumed that the ketone function was tied up, perhaps by chelation with magnesium ion until the Grignard reagent was consumed.

Workups of the Grignard additions for intermediates **8** generally produced mixtures with varying amounts of **6** and **12**. To aid in the purification of the tertiary alcohols **8**, it proved beneficial to reflux the crude mixture in ethanol with 1 equiv of semicarbazide hydrochloride. The fast-running **8** was then easily separated by silica gel chromatography from the polar semicarbazone derivatives of ketones **12** and the slow-running secondary alcohols **6**. On TLC, alcohols **8** had R_f values (with 10−25% ethyl acetate in hexanes) equal to or higher than those of the starting ketones. This unexpected mobility of tertiary alcohols **8** on silica gel can be explained by an intramolecular hydrogen bond between the hydroxyl group and pyridine nitrogen. In the NMR, the hydroxyl hydrogen in the tertiary alcohols **8** was always present as a sharp singlet at a chemical shift of 6.0 ± 0.2 ppm. In the secondary alcohols **6**, the OH resonance was broadened, and the compounds had very low R_f values.

We previously reported the synthesis of vinylogous amide analogues (compound **14**, Scheme 3) of methylphenidate.[40] We attempted to hydrogenate one of these compounds to the ketone

Scheme 3



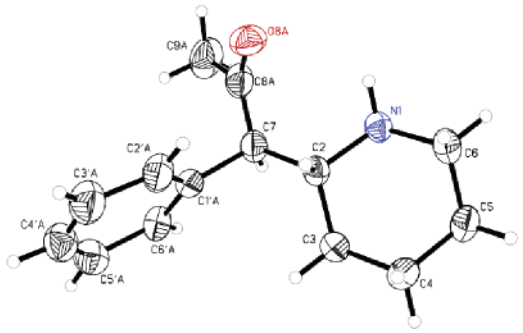


Figure 2. Crystal structure of the ketone analogue of methylphenidate (compound **15**). The structure shown is the major component in the crystal which contains some disorder.

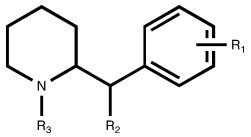
analogue of methylphenidate. However, because of the high stability of vinylogous amides, it was necessary to hydrogenate for 3 days, and the lengthy hydrogenation also removed the Cl from the phenyl ring (compound **15**). Upon making the HCl salt of a mixture of diastereomers, only a single isomer was found, and X-ray crystallography indicated that it was the *RR*/*SS* diastereomer (Figure 2). While this compound was stable enough to make a salt, to perform elemental analysis, to obtain a crystal structure, and for pharmacological testing, converting it back to the free base by treatment with a mild base was sufficient to cause it to decompose. This was assumed to be due to the highly acidic proton α to both the phenyl ring and the carbonyl group that is easily extracted by base. Because of this difficulty, no further synthetic work was performed on these kinds of compounds. The two methyl ester containing compounds with a 4-chloro- and 3,4-dichlorophenyl group were synthesized as before.[1,32]

Some comments must be made regarding the nomenclature for the diastereomers of **10**. In methylphenidate, the *RR*/*SS* diastereomers are designated as threo because the heteroatomic groups are on opposite sides when the protons on the two asymmetric carbons are eclipsed. In the methylphenidate analogues synthesized here, where an alkyl group replaces the carbomethoxy group, the diastereomers with the same relative configuration should be designated as erythro since the new alkyl chain is on the same side as the alkyl portion of the piperidine ring. However, due to the ambiguities inherent in the threo−erythro nomenclature, it is generally preferable to designate diastereomers using the Cahn−Ingold−Prelog system of *R* and *S*.[41] It should also be noted that, while a higher priority carbomethoxy group has been replaced by a lower priority alkyl group, the *R*,*R* enantiomer of methylphenidate still corresponds to the *R*,*R* enantiomer of the alkyl analogues.

Binding and Uptake Assays

The compounds were tested in binding and uptake assays utilizing recombinant human DA, NE, and 5HT transporters stably expressed in human embryonic kidney 293 cells (HEK-hDAT, -hNET, and -hSERT, respectively) as previously described.[42] The binding studies measured the potency of the test compounds in competition experiments with [^{125}I]RTI-55, while the uptake assays measured the potency in inhibiting the uptake of the respective tritiated monoamine neurotransmitters.

Table 1. Inhibition of [^{125}I]RTI-55 Binding (K_i, nM) and [^{3}H]Monoamine Uptake (IC_{50}, nM) by *RR*/*SS* Diastereomers



				dopamine		serotonin		norepinephrine			
	R1	R2	R3	[I^{125}]RTI-55 binding	DA uptake	[I^{125}]RTI-55 binding	5HT uptake	[I^{125}]RTI-55 binding	NE uptake	NE/DA binding	NE/DA uptake
1	H	$COOCH_3$	H	110 ± 9	79 ± 16	65000 ± 4000	5100 ± 7000	660 ± 50	61 ± 14	6.0	0.77
2	cocaine			500 ± 65	240 ± 15	340 ± 40	250 ± 40	500 ± 90	210 ± 30	1.0	0.88
	4-chloro	$COOCH_3$	H	25 ± 8	11 ± 2	6000 ± 100	>9800	110 ± 40	11 ± 3	4.4	1.0
10a	4-chloro	methyl	H	180 ± 70	22 ± 7	4900 ± 500	1900 ± 300	360 ± 140	35 ± 13	2.0	1.6
10b	4-chloro	ethyl	H	37 ± 10	23 ± 5	7800 ± 800	2400 ± 400	360 ± 60	210 ± 30	9.7	9.1
10c	4-chloro	propyl	H	11 ± 3	7.4 ± 0.4	2700 ± 600	2900 ± 1100	200 ± 80	50 ± 15	18	6.8
10d	4-chloro	isopropyl	H	46 ± 16	32 ± 6	5300 ± 1300	3300 ± 400	810 ± 170	51 ± 20	18	1.6
10e	4-chloro	butyl	H	7.8 ± 1.1	8.2 ± 2.1	4300 ± 400	4000 ± 400	230 ± 30	26 ± 7	29	3.2
10f	4-chloro	isobutyl	H	16 ± 4	8.6 ± 2.9	5900 ± 900	490 ± 80	840 ± 130	120 ± 40	53	14
10g	4-chloro	pentyl	H	23 ± 7	45 ± 14	2200 ± 100	1500 ± 300	160 ± 40	49 ± 16	7.0	1.1
10h	4-chloro	isopentyl	H	3.6 ± 1.2	14 ± 2	5000 ± 470	7300 ± 1400	830 ± 110	210 ± 40	230	15
10i	4-chloro	neopentyl	H	120 ± 40	60 ± 2	3900 ± 500	>8300	1400 ± 400	520 ± 110	12	8.7
10j	4-chloro	cyclopentylmethyl	H	9.4 ± 1.5	21 ± 1	2900 ± 80	2100 ± 900	1700 ± 600	310 ± 40	180	15
10k	4-chloro	cyclohexylmethyl	H	130 ± 40	230 ± 70	900 ± 400	1000 ± 200	4200 ± 200	940 ± 140	32	4.1
10l	4-chloro	benzyl	H	440 ± 110	370 ± 90	1100 ± 200	1100 ± 200	2900 ± 800	2900 ± 600	6.6	7.8
10m	4-chloro	phenethyl	H	24 ± 9	160 ± 20	640 ± 60	650 ± 210	1800 ± 600	680 ± 240	75	4.3
10n	4-chloro	phenpropyl	H	440 ± 150	290 ± 90	700 ± 200	1600 ± 300	490 ± 100	600 ± 140	1.1	2.1
10o	4-chloro	3-pentyl	H	400 ± 80	240 ± 60	3900 ± 300	>9400	970 ± 290	330 ± 80	2.4	1.4
10p	4-chloro	cyclopentyl	H	36 ± 10	27 ± 8.3	5700 ± 1100	4600 ± 800	380 ± 120	44 ± 18	11	1.6
10q	3-chloro	isobutyl	H	3.7 ± 1.1	2.8 ± 0.4	3200 ± 400	2100 ± 100	23 ± 6	14 ± 1	6.2	5.0
	3,4-dichloro	$COOCH_3$	H	1.4 ± 0.1	23 ± 3	1600 ± 150	540 ± 110	14 ± 6	10 ± 1	10	0.43
10r	3,4-dichloro	propyl	H	0.97 ± 0.31	4.5 ± 0.4	1800 ± 500	560 ± 120	3.9 ± 1.4	8.1 ± 3.8	4.0	1.8
10s	3,4-dichloro	butyl	H	2.3 ± 0.2	5.7 ± 0.5	1300 ± 300	1400 ± 300	12 ± 3	27 ± 10	5.2	4.7
10t	3,4-dichloro	isobutyl	H	1.0 ± 0.5	5.5 ± 1.3	1600 ± 100	1100 ± 300	25 ± 9	9.0 ± 1.2	25	1.6
11	3,4-dichloro	isobutyl	CH_3	6.6 ± 0.9	13 ± 4	1300 ± 200	1400 ± 500	190 ± 60	28 ± 3	29	2.2
10u	4-methoxy	isobutyl	H	52 ± 16	25 ± 9	2800 ± 600	3500 ± 500	3100 ± 200	410 ± 90	60	16
10v	3-methoxy	isobutyl	H	22 ± 5	35 ± 12	4200 ± 400	2700 ± 800	3800 ± 500	330 ± 40	170	9.4
10w	4-isopropyl	isobutyl	H	3300 ± 600	4000 ± 400	3300 ± 600	4700 ± 700	2500 ± 600	7100 ± 1800	0.76	1.8
15	H	$COCH_3$	H	370 ± 70	190 ± 50	7800 ± 1200	>9700	2700 ± 400	220 ± 30	7.3	1.2

Results

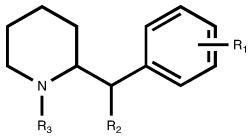
The binding affinity of the alkyl analogues of methylphenidate for the cloned human monoamine transporters and their potency at inhibiting the uptake of DA, 5HT, and NE at their respective transporters are shown in Table 1 for the *RR*/*SS* diastereomers and in Table 2 for the *RS*/*SR* diastereomers. Included in Table 1 are results for cocaine and methylphenidate under the same conditions. As is well-known, cocaine blocks all three monoamine transporter sites. The threo *RR*/*SS* diastereomer of methylphenidate, which contains the therapeutic activity, has considerable potency at the DA and NE transporters, but is much weaker at the 5HT transporter.

The greatest discrepancies between the binding and uptake results occur for the NE transporter, where there is a 10-fold or greater difference for a number of compounds. As a result, there are much larger differences in DA/NE selectivity based on the binding data than on the functional uptake data.

As found previously,[32] the addition of a chlorine atom to the meta and/or para position of the phenyl ring in methylphenidate increases potency significantly. The *RR*/*SS* diastereomer of the 4-chloro ester compound with a carbomethoxy group was 17-fold more potent than (*RR*/*SS*)-methylphenidate in blocking DA uptake and 3-fold more potent in blocking NE uptake. The ester compound with a 3,4-dichloro group was 8.3-fold more potent in blocking the uptake of DA and 3.8-fold in blocking the uptake of NE. Both compounds were approximately equipotent in blocking the uptake of DA and NE. As with methylphenidate itself, none of the synthesized compounds had significant binding affinity to the 5HT transporter or potency at blocking the uptake of 5HT, and the *RR*/*SS* diastereomers (Table 1) were considerably more potent in binding to the DA and NE transporters and in blocking uptake of those neurotransmitters than the equivalent *RS*/*SR* diastereomers (Table 2).

4-Chloro Compounds. A large number of analogues were made with a 4-chloro substituent, and most of the *RR*/*SS* diastereomers were considerably more potent than the equivalent ester-containing compound at binding to the DA transporter and blocking the uptake of DA, indicating that the ester group is not required for potent activity. The most potent compounds in blocking the uptake of DA were those where R_2 was three or four carbon atoms long. Branching at the second carbon, as in isobutyl ((*RR*/*SS*)-**10f**), and at the third carbon, as in isopentyl ((*RR*/*SS*)-**10h**), did not affect potency significantly as compared with that of the analogue without the additional methyl group. However, there was a significant decrease in potency with the neopentyl compound ((*RR*/*SS*)-**10i**). Compounds with phenyl rings in the side chain were considerably weaker, with the phenethyl compound appearing to be the optimal substitution. The most noteworthy aspect to these compounds, however, is the emergence of considerable selectivity for the DA transporter relative to the NE transporter in many of the compounds on the functional uptake assays. However, this only occurred for compounds with an unbranched first carbon atom since compounds in which the first atom was branched such as isopropyl ((*RR*/*SS*)-**10d**), 3-pentyl ((*RR*/*SS*)-**10o**), and cyclopentyl ((*RR*/*SS*)-**10p**) showed little selectivity. The compounds with the best selectivity are R_2 = isobutyl ((*RR*/*SS*)-**10f**), isopentyl ((*RR*/*SS*)-**10h**), and cyclopentylmethyl ((*RR*/*SS*)-**10j**), which are 53-, 230-,

Table 2. Inhibition of [^{125}I]RTI-55 Binding (K_i, nM) and [^{3}H]Monoamine Uptake (IC_{50}, nM) by *RS*/*SR* Diastereomers



				dopamine		serotonin		norepinephrine	
	R1	R2	R3	[I^{125}]RTI-55 binding	DA uptake	[I^{125}]RTI-55 binding	5HT uptake	[I^{125}]RTI-55 binding	NE uptake
	4-chloro	$COOCH_3$	H	2000 ± 600	2700 ± 1000	5900 ± 200	>10 mM	>6100	1400 ± 400
10a	4-chloro	methyl	H	>3900	1500 ± 700	>9100	4700 ± 800	>6300	3200 ± 800
10b	4-chloro	ethyl	H	1800 ± 300	2800 ± 700	4200 ± 400	4100 ± 1000	>9200	1300 ± 400
10c	4-chloro	propyl	H	380 ± 40	450 ± 60	3200 ± 1100	1300 ± 7	1400 ± 400	200 ± 50
10d	4-chloro	isopropyl	H	900 ± 320	990 ± 280	>10 mM		>10 mM	
10e	4-chloro	butyl	H	290 ± 70	170 ± 40	4800 ± 700	3300 ± 600	1600 ± 300	180 ± 60
10f	4-chloro	isobutyl	H	170 ± 50	380 ± 130	4300 ± 500	540 ± 150	4500 ± 1500	750 ± 170
10g	4-chloro	pentyl	H	870 ± 140	650 ± 20	3600 ± 1000	1700 ± 700	1500 ± 300	860 ± 330
10h	4-chloro	isopentyl	H	510 ± 170	680 ± 120	6700 ± 500	>8300	12000 ± 1400	3000 ± 540
10i	4-chloro	neopentyl	H	600 ± 40	670 ± 260	3500 ± 1000	1800 ± 600	>5500	730 ± 250
10j	4-chloro	cyclopentylmethyl	H	310 ± 80	180 ± 20	3200 ± 700	5600 ± 1400	2600 ± 800	730 ± 230
10k	4-chloro	cyclohexylmethyl	H	260 ± 30	410 ± 60	3700 ± 500	6400 ± 1300	4300 ± 200	1700 ± 600
10l	4-chloro	benzyl	H	550 ± 60	390 ± 60	4300 ± 800	4700 ± 500	4000 ± 800	>8800
10m	4-chloro	phenethyl	H	700 ± 90	420 ± 140	1800 ± 70	210 ± 900	2400 ± 700	610 ± 150
10n	4-chloro	phenpropyl	H	2900 ± 900	1400 ± 400	1500 ± 200	1200 ± 400	1500 ± 200	1700 ± 200
10o	4-chloro	3-pentyl	H	>5700	1200 ± 90	4800 ± 1100	>9600	4300 ± 200	3800 ± 30
10p	4-chloro	cyclopentyl	H	690 ± 140	240 ± 30	4600 ± 700	4200 ± 900	3300 ± 800	1000 ± 300
10q	3-chloro	isobutyl	H	140 ± 30	88 ± 12	3200 ± 400	870 ± 230	340 ± 50	73 ± 5
	3,4-dichloro	$COOCH_3$	H	90 ± 14	800 ± 110	2500 ± 420	1100 ± 90	4200 ± 1900	190 ± 50
10r	3,4-dichloro	propyl	H	43 ± 9	88 ± 32	450 ± 80	180 ± 60	30 ± 8	47 ± 22
10s	3,4-dichloro	butyl	H	29 ± 5	67 ± 13	1100 ± 200	550 ± 80	31 ± 11	63 ± 27
10t	3,4-dichloro	isobutyl	H	31 ± 11	13 ± 3	450 ± 40	290 ± 60	120 ± 30	19 ± 3
11	3,4-dichloro	isobutyl	CH_3	44 ± 12	45 ± 4	1500 ± 300	2400 ± 700	660 ± 130	100 ± 19
10u	4-methoxy	isobutyl	H	770 ± 220	400 ± 120	950 ± 190	1200 ± 300	16000 ± 2000	1600 ± 400
10v	3-methoxy	isobutyl	H	950 ± 190	140 ± 20	3800 ± 600	2600 ± 300	12000 ± 2300	1400 ± 90
10w	4-isopropyl	isobutyl	H	>6500	>9100	1700 ± 500	1700 ± 100	3200 ± 600	>8700

and 180-fold more selective in binding and 14-, 15-, and 15-fold more selective in blocking uptake at the DA transporter relative to the NE transporter, respectively. The cyclopentylmethyl analogue is closely related to the isobutyl compound in that the terminal methyl groups of the latter are tied into a cyclopentyl ring. The cyclohexylmethyl compound ((*RR*/*SS*)-**10k**), however, was about 10-fold weaker than the cyclopentylmethyl compound, presumably because the latter is smaller and more flexible. The selectivity for the DA transporter appears to be due to a decrease in potency at the NE transporter. The loss of potency as one lengthens the alkyl group parallels what has been found in methylphenidate analogues in which potency decreases as the size of the ester group is increased.[43]

3,4-Dichloro Compounds. These *RR*/*SS* diastereomers had somewhat higher binding affinity and potency at blocking the uptake of DA than the 4-chloro compounds with the same alkyl group (Table 1), in line with the previous finding that this phenyl substitution is optimal or close to optimal in all classes of DA reuptake blockers.[7] The most potent analogue was the propyl compound ((*RR*/*SS*)-**10r**). However, the selectivity for the DA transporter relative to the NE transporter has decreased. As in ester analogues of methylphenidate, an *N*-methyl substituent reduced potency.[10] However, one unexpected result with these compounds was that the *RS*/*SR* diastereomers that typically have weak activity at monoamine transporters now began to show decent potency at blocking uptake of monoamines, with the isobutyl compound ((*RS*/*SR*)-**10t**) having a potency of 13 nM in blocking the DA transporter and 19 nM in blocking the NE transporter (Table 2). This *RS*/*SR* compound even has a much higher potency in blocking the 5HT transporter than any other of the methylphenidate analogues reported here.

Other Phenyl Substituents. Chlorine and methoxy substituents in the 3- and 4-positions of the phenyl ring enhance potency in ester analogues of methylphenidate relative to that of the parent compound.[32] Single compounds were made with a 3-chloro, a 3-methoxy, or a 4-methoxy on the phenyl ring with the isobutyl side chain that is near optimal in the analogues with 4-chloro and 3,4-dichloro substituents. These halogen and methoxy substitutions also produced *RR*/*SS* diastereomers with low nanomolar potency. The 4-methoxy compound ((*RR*/*SS*)-**10u**) had the best selectivity for DA uptake inhibition with 16-fold selectivity in blocking uptake and 60-fold selectivity with respect to binding at the NE transporter. A compound with a 4-isopropyl substituent ((*RR*/*SS*)-**10w**) had little potency. The *RS*/*SR* diastereomers were weak inhibitors at all three monoamine transporter sites.

Ketone Analogue. The ketone analogue of methylphenidate (Figure 2) had activity comparable to that of methylphenidate. As was found previously in a number of crystal structures of ester analogues,[9] there was a hydrogen bond between the carbonyl oxygen and the equatorial ammonium proton in the crystal structure (Figure 2).

Locomotor Activity. The locomotor activities induced by various doses of cocaine, methylphenidate, and the 4-chloro, isobutyl compound ((*RR*/*SS*)-**10f**) over an 8 h period are shown in Figure 3. As can be seen, both cocaine and methylphenidate are active by the first 10 min data point and peak activity occurs during the first 30 min. In contrast, (*RR*/*SS*)-**10f** appears to have a slow onset of 20−30 min and peak activity occurs between 90 and 120 min. The compound also is active much longer and lasts for the entire 8 h period at the highest dose. Thus, the compound has the slow-onset, long-duration profile that is believed to reduce abuse potential. (*RR*/*SS*)-**10f** does not produce

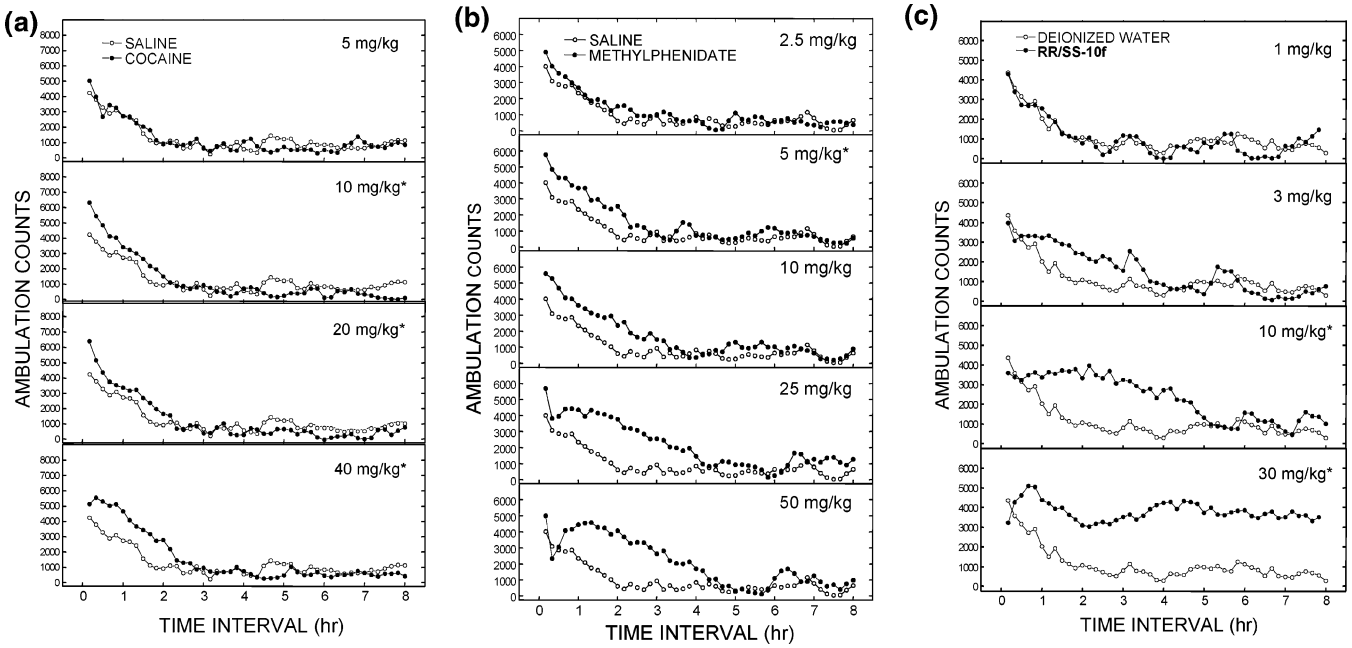


Figure 3. Effect of an ip injection of (a, left) cocaine, (b, middle) methylphenidate, and (c, right) (*RR*/*SS*)-**10f** on horizontal locomotor activity counts per 10 min in mice as a function of dose (top to bottom panels) and time during an 8 h session. Stimulant effects of doses of the compounds as compared with vehicle at (a) 0−30 min, (b) 0−30 min, and (c) 90−120 min that are statistically significant at $p < 0.05$ are indicated by an asterisk.

the maximum stimulation that occurs with cocaine or methylphenidate, presumably because it enters the brain more slowly so that its brain concentration increases more slowly.

Discussion

As with methylphenidate, the alkyl analogues were potent blockers at the DA and NE transporters and much weaker at the 5HT transporter. The optimal side chain substitutions were alkyl analogues that were three or four carbon atoms long. However, there were several unexpected structure−activity features of these compounds. First, the analogues with a 4-chlorophenyl group consistently showed enhanced selectivity for blocking the DA transporter relative to the NE transporter as compared with ester-containing compounds as long as the first carbon of the side chain was unbranched, due to lessened potency at the NE transporter. It should be noted that methylphenidate also is branched at this point due to the ester group. The compounds with a 3-chloro and a 3,4-dichloro group showed reduced DA transporter selectivity. The compounds with methoxy groups in the 3- and 4-positions of the phenyl ring also showed better selectivity for blocking uptake of DA, particularly when the group was in the 4-position. It seems that the 4-position is more critical for better DA transporter selectivity. A second, especially surprising result was the emergence of potent blocking activity in the "inactive" *RS*/*SR* diastereomers at all three monoamine transporters when the phenyl substitution was 3,4-dichloro.

The robust potency of these novel analogues of methylphenidate which were designed from a ligand-based analysis of methylphenidate and CFT provides additional evidence in favor of the conformation and superposition model of those compounds.[6] It also suggests that other substitutions that enhance blocking potency and selectivity in tropane-containing compounds should also produce potent compounds in analogues of methylphenidate.

As indicated above, methylphenidate must be taken two or three times per day due to the relatively quick in vivo metabolism of its ester to the pharmacologically inactive acid. As these novel alkyl analogues of methylphenidate are not esters, they would be expected to have longer in vivo half-lives, and this should make them more suitable as longer duration maintenance therapies for treating cocaine abuse. The longer duration of activity can be clearly seen in the locomotor activity of (*RR*/*SS*)-**10f** as compared with both cocaine and methylphenidate (Figure 3). The compound also appears to have an onset of activity of at least 20 min, whereas methylphenidate and cocaine have much faster onsets, suggesting that the compound would have reduced abuse potential (Figure 3). One can speculate that this is due to the absence of the ester group which appears to facilitate entry into the brain.

Experimental Section

General Information. New compounds were synthesized following Schemes 2 and 3. Reagents were purchased from Lancaster or Aldrich and used as is. ^{1}H and ^{13}C NMR spectra of most compounds were taken on a Varian 90 MHz spectrophotometer equipped with an Anasazi Instrument FT probe in $CDCl_3$ as a solvent (unless otherwise noted) with TMS as an internal standard. ^{1}H NMR spectra of some salts of compounds **10** were taken in D_2O at 270 MHz using a Jeol-FX-270 spectrometer, while other salts were taken in d_4-methanol at 90 MHz. Mass spectra were obtained from a Micromass LTC electrospray spectrophotometer. Catalytic hydrogenations were performed with a Parr shaker in a 500 mL bottle at 50−55 psi of H_2. Analytical thin layer chromatography was performed on Analtech 250 μm glass-backed silica gel plates. Flash chromatography was performed with silica gel 60 (70−230 mesh). HCl salts of the amines were obtained by dissolving the free base in EtOAc or a mixture of EtOAc and hexanes, adding HCl dissolved in ether, and filtering the solids. Recrystallizations to constant mp were from EtOAc that sometimes contained a little ethanol unless otherwise noted. Melting points were determined in a Mel-temp apparatus with a Hg thermometer and are uncorrected. The relative configurations of most of the final compounds were determined by crystallography of at least one of the diastereomeric pairs. The diastereomers of **10** could also be distinguished by ^{1}H NMR. On chromatography of free bases **10** with 0.5−1% Et_2NH in EtOAc/hexane, the *RS*/*SR* diastereomer always had a higher R_f value than the *RR*/*SS* diastereomer, except

in two cases where there was branching at the α-carbon (i.e., **10d** and **10p**). Elemental analyses of the final products as HCl salts were obtained from Atlantic Microlabs, Norcross, GA, and all were within ±0.4% of the theoretical values.

General Procedure for Secondary Alcohols 6. (4-Chlorophenyl)-2-pyridylmethanol (6a). A small crystal of iodine was added to Mg (7.07 g, 291 mmol) in THF (280 mL), and the slurry was heated. A solution of *p*-bromochlorobenzene **4** (53.6 g, 280 mmol) in THF (280 mL) was added slowly, and the mixture was refluxed for 2 h until almost all of the Mg had dissolved. The solution was cooled to 0 °C, pyridine-2-carboxaldehyde (**5**) (25 g, 233 mmol) in THF (22 mL) was added slowly, and the solution was allowed to warm to room temperature (rt) over 2 h. The reaction was diluted with saturated NH_4Cl, extracted with EtOAc (3×), washed with brine, dried ($MgSO_4$), and concentrated under reduced pressure to an oil. The oil was taken up in 300 mL of hexanes and allowed to crystallize. Filtration gave alcohol **6a** (49 g, 96%) as an off-white solid: mp 79−80 °C [lit. (*Bull. Chem. Soc. Jpn.* **1987**, *60*, 2651−2655) mp 82.5−84 °C]; ^{1}H NMR δ 8.53 (1H, d, br), 7.62 (1H, dt *J* = 2, 7 Hz), 7.30 (4H, s), 7.22 (1H, m), 7.15 (1H, apparent td, br), 6.00 (1H, s), 5.72 (1H, s); ^{13}C NMR δ 160.8, 147.4 (CH), 141.3, 136.5 (CH), 132.7, 128.0 (2C), 127.7 (2C), 122.0 (CH), 120.5 (CH), 74.1.

Data for (3-chlorophenyl)-2-pyridylmethanol (6b): ^{1}H NMR δ 8.34 (1H, ddd, *J* = 1, 2, 5 Hz), 7.50 (1H, dt *J* = 2, 7 Hz), 7.46−7.08 (5H, m), 7.02 (1H, ddd, *J* = 1, 5, 7 Hz), 5.73 (1H, s); ^{13}C NMR δ 161.2, 147.9, 145.3, 137.1, 134.2, 129.7, 127.6, 126.8, 125.0, 122.5, 121.0, 74.7.

Data for (3,4-dichlorophenyl)-2-pyridylmethanol (6c): ^{1}H NMR δ 8.44 (1H, dd, *J* = 2, 5 Hz), 7.62 (1H, dt, *J* = 2, 7 Hz), 7.59 (1H, d, *J* = 3 Hz), 7.55−7.07 (4H, m), 5.81 (1H, s, v br), 5.71 (1H, s); ^{13}C NMR δ 160.2, 148.0 (CH), 143.4, 137.2 (CH), 131.5, 130.4 128.8 (CH), 127.7, 126.2 (CH), 122.8 (CH), 121.1 (CH), 74.0 (CH).

(4-Methoxyphenyl)-2-pyridylmethanol (6d) and (3-Methoxyphenyl)-2-pyridylmethanol (6e). Crude alcohols 6d and 6e were not characterized, but oxidized directly to ketones **7d** and **7e**.

Data for (4-isopropylphenyl)-2-pyridylmethanol (6f): ^{1}H NMR δ 8.44 (1H, br), 7.6−6.9 (7H, m), 5.73 (1H, s), 2.85 (1H, septet), 1.10 (6H, d, *J* = 7 Hz); ^{13}C NMR δ 162.5, 147.8, 140.7, 138.7, 128.3, 127.0 (2C), 126.5 (2C), 122.2, 121.2, 75.1, 33.8, 24.0 (2C).

General Procedure for Synthesizing Ketones 7. (4-Chlorophenyl)-2-pyridylmethanone (7a). Pyridinium chlorochromate (67 g, 310 mmol) was dissolved in CH_2Cl_2 (∼600 mL), and 60 g of Celite was added with stirring. The alcohol **6a** (65 g, 296 mmol) was added and the slurry stirred at rt for 20 min. The solution was concentrated, 75 g of silica gel was added, and all solvents were removed. The preadsorbed product was placed atop dry silica gel (200 g) in a Kauffman column and was extracted with 700 mL of boiling heptane overnight. After being cooled to rt, the heptane solution deposited 46 g (71% yield) of crystalline ketone **7a** (mp 60−61 °C), which was collected by filtration: ^{1}H NMR δ 8.72 (1H, d, br), 8.02 (2H, d, *J* = 9 Hz, overlying 1H, m), 7.88 (1H, dt, *J* = 2, 7 Hz), 7.47 (2H, d, *J* = 7 Hz, overlying 1H, m); ^{13}C NMR δ 192.2, 154.6, 148.4 (CH), 139.2, 137.1(CH), 133.4, 132.4 (2CH), 128.3 (2C), 126.3(CH), 124.5(CH).

Data for (3-chlorophenyl)-2-pyridylmethanone (7b): ^{1}H NMR δ 8.69 (1H, ddd, *J* = 1, 2, 5 Hz), 8.11−7.77 (4H, m), 7.64−7.30 (3H, m); ^{13}C NMR δ 192.1, 154.3, 148.5, 137.9, 137.1, 134.2, 132.6, 130.9, 129.4, 129.2, 126.5, 124.6.

Data for (3,4-dichlorophenyl)-2-pyridylmethanone (7c): mp 81−2 °C; ^{1}H NMR δ 8.68 (1H, d, br), 8.25−7.77 (4H, m), 7.56−7.48 (2H, m); ^{13}C NMR δ 190.7, 154.1, 148.5, 137.2, 135.9, 133.0, 132.5, 130.2, 130.1, 126.7, 124.7.

Data for (4-methoxyphenyl)-2-pyridylmethanone (7d): ^{1}H NMR δ 8.69 (1H, d, br), 8.13 (2H, d, *J* = 9 Hz), 7.85 (1H, m), 7.82 (1H, dt, *J* = 2, 8 Hz), 7.42 (1H, ddd, *J* = 2, 5, 7 Hz), 6.95 (2H, d, *J* = 9 Hz); ^{13}C NMR δ 192.1, 163.6, 155.7, 148.3, 137.0, 133.5 (2C), 129.0, 125.8, 124.4, 113.5 (2C), 55.4.

Data for (3-methoxyphenyl)-2-pyridylmethanone (7e): ^{1}H NMR δ 8.64 (1H, d, br), 8.01−7.63 (4H, m), 7.44−7.03 (3H, m); ^{13}C NMR δ 193.1, 159.3, 155.1, 148.4, 137.6, 136.9, 129.1, 126.1, 124.4, 123.8, 119.0, 115.5, 55.2.

Data for (4-isopropylphenyl)-2-pyridylmethanone (7f): ^{1}H NMR δ 8.67 (1H, d, br), 8.08−7.94 (3H, m), 7.79 (1H, dt, *J* = 2, 5 Hz), 7.45−7.27 (3H, m), 2.94 (1H, septet, *J* = 7 Hz), 1.24 (6H, d, *J* = 7 Hz); ^{13}C NMR δ 193.2, 155.3, 154.3, 148.4, 136.9, 134.0, 131.3 (2C), 126.2 (2C), 125.9, 124.4, 34.2, 23.6 (2C).

General Procedure for Synthesizing Tertiary Alcohols 8. 1-(4-Chlorophenyl)-1-(2-pyridyl)-1-propanol (8b). Ketone **7a** (8.0 g, 36.8 mmol) was dissolved in THF (120 mL) and cooled to 0 °C, and a solution of 2 M EtMgBr (27 mL, 55.1 mmol) was slowly added via cannula over 2 h at 0 °C. During the addition, the solution took on a bright red color. The solution was diluted with saturated aqueous NH_4Cl, extracted 3× with EtOAc, washed with brine, and dried ($MgSO_4$). The EtOAc solution, one spot by TLC, was then concentrated to an oil (9.2 g, 99% recovery) of **8b**: ^{1}H NMR δ 8.48 (1H, d, br), 7.67 (1H, dt, *J* = 2,7 Hz), 7.52, (1H, m), 7.45 (2H, d, *J* = 9 Hz), 7.27 (2H, d, *J* = 9 Hz), 7.20 (1H, m), 5.91 (1H, s), 2.23 (2H, diastereotopic, 2 q, *J* = 7, Δδ = 2 Hz), 0.85 (3H, t, *J* = 7 Hz). Integration of the ^{1}H NMR spectrum from 8.1 to 7.9 ppm (two doublets) relative to the area of the δ 8.48 multiplet indicated the presence of about 6% **12b**.

Data for 1-(4-chlorophenyl)-1-(2-pyridyl)-1-butanol (8c): yield 85%; ^{1}H NMR δ 8.46 (1H, d, br), 7.57 (1H, td, *J* = 2, 7 Hz), 7.49 (2H, d, *J* = 8.7 Hz), 7.24 (2H, d, *J* = 8.7 Hz), overlapping 7.1−7.5 (2H, m), 5.84 (1H, s, br), 2.24 (2H, diastereotopic, 2 q, *J* = 7, Δδ = 2 Hz), 1.30 (m, 2H), 0.88 (3H, t, *J* = 7 Hz).

Data for 1-(4-chlorophenyl)-2-methyl-1-(2-pyridyl)-1-propanol (8d): ^{1}H NMR δ 8.45 (1H, d, br), 7.5−7.7 (3H, m), 7.2−7.4 (4H, 2 d, *J* = 9 Hz, overlying 1H, m), 6.05 (1H, s, br), 2.77 (1H, septet, *J* = 7 Hz), 0.94 (3H, d, *J* = 7 Hz), 0.72 (3H, d, *J* = 7 Hz).

Data for 1-(4-chlorophenyl)-1-(2-pyridyl)-1-pentanol (8e): oil; yield (after chromatography) 68%; ^{1}H NMR δ 8.46 (1H, d, br), 7.61 (1H, td, *J* = 2, 7 Hz), 7.48 (2H, d, *J* = 9 Hz), 7.24 (2H, d, *J* = 9 Hz), 7.0−7.4 (overlapping 2H, m), 5.94 (1H, s, br), 2.30−2.13 (2H, m), 1.43−1.13 (4H, m), 0.85 (3H, t, *J* = 7 Hz); ^{13}C NMR δ 163.3, 147.3 (CH), 145.3, 137.0 (CH), 132.6, 128.2 (2CH), 127.5 (2CH), 122.1 (CH), 120.2 (CH), 76.9, 41.0, 25.7, 23.0, 14.0.

Data for 1-(4-chlorophenyl)-3-methyl-1-(2-pyridyl)-1-butanol (8f): mp 69−71 °C (crystallized from pentane); yield 70%; ^{1}H NMR δ (8.48 1H, d, br), 7.54 (1H, td, *J* = 2, 7 Hz), 7.49 (2H, d, *J* = 9 Hz), 7.25 (2H, d, *J* = 9 Hz), overlapping 7.1−7.5 (2H, m), 5.98 (1H, s, br), 2.20 (1H, dd, *J* = 7, 14 Hz), 2.08 (1H, dd, *J* = 7, 14 Hz), 1.75 (1H, nonet, *J* = 7 Hz), 0.96 (3H, d, *J* = 7 Hz), 0.76 (3H, d, *J* = 7 Hz); ^{13}C NMR δ 163.7, 147.2 (CH), 146.0, 137.0 (CH), 132.6, 128.2 (2CH), 127.5 (2CH), 122.1 (CH), 120.5 (CH), 77.3, 49.6, 24.8, 24.4, 24.3.

Data for 1-(4-chlorophenyl)-1-(2-pyridyl)-1-hexanol (8g): yield 67%; ^{1}H NMR δ 8.42 (1H, ddd, *J* = 1, 2, 5 Hz), 7.54 (1H, td, *J* = 2, 7 Hz), 7.49 (2H, d, *J* = 9 Hz), 7.33 (1H, td, *J* = 2, 7 Hz), 7.22 (2H, d, *J* = 9 Hz), 7.04 (1H, ddd, *J* = 1, 5, 7 Hz), 5.97 (1H, s, br), 2.23 (2H, t, *J* = 7 Hz), 1.46−1.13 (6H, m), 0.82 (3H, t, *J* = 7 Hz); ^{13}C NMR δ 163.4, 147.2, 145.4, 137.0, 132.5, 128.2 (2C), 127.5 (2C), 122.0, 120.2, 76.9, 41.2, 32.1, 23.2, 22.5, 14.0.

Data for 1-(4-chlorophenyl)-4-methyl-1-(2-pyridyl)-1-pentanol (8h): yield 56%; ^{1}H NMR δ 8.42 (1H, ddd, *J* = 1, 2, 5 Hz), 7.64−7.43 (1H, m), 7.49 (2H, d, *J* = 9 Hz), 7.35−7.17 (1H, m), 7.22 (2H, d, *J* = 9 Hz), 7.04 (1H, ddd, *J* = 1, 5, 7 Hz), 5.98 (1H, s, br, OH), 2.36−2.16 (2H, m), 1.61−1.00 (3H, m), 0.85 (6H, d, *J* = 7 Hz); ^{13}C NMR δ 163.4, 147.2, 145.3, 137.0, 132.5, 128.2 (2C), 127.5 (2C), 122.0, 120.2, 76.9, 39.1, 32.4, 28.3, 22.6 (2C).

Data for 1-(4-chlorophenyl)-3,3-dimethyl-1-(2-pyridyl)-1-butanol (8i): yield (front-running component on silica column) 44%; ^{1}H NMR δ 8.37 (1H, d, br), 7.54 (2H, d, *J* = 9 Hz), 7.43−7.38 (2H, m), 7.19 (2H, d, *J* = 9 Hz), 6.98 (1H, td, *J* = 2, 7 Hz), 6.14 (1H, s, OH), 2.36 (1H, d, *J* = 15 Hz), 2.31 (1H, d, *J* = 15 Hz), 0.86 (9H, s); ^{13}C NMR δ 164.3, 147.5, 147.0 (CH), 136.9 (CH), 132.4, 128.2 (2CH), 127.3 (2CH), 121.9 (CH), 120.7 (CH), 78.7, 52.3, 32.1, 31.8 (3C).

The trailing component on a silica column was crystallized from hexane with a trace of diisopropyl ether to give (4-chlorophenyl)-[5-(2,2-dimethylpropyl)-2-pyridyl]methanone (**12i**): mp 70−71 °C; ^{1}H NMR δ 8.49 (1H, d, br), 8.05 (2H, d, J = 9 Hz), 8.01 (1H, d, J = 7 Hz), 7.68 (1H, dd, J = 2, 7), 7.47 (2H, d, J = 9 Hz), 2.60 (2H, s), 0.95 (9H, s); ^{13}C NMR δ 192.1, 152.3, 149.9 (CH), 139.0, 138.6 (2C, one a CH), 134.8, 132.4 (2CH), 128.3 (2CH), 123.9 (CH), 47.1, 31.6, 29.1 (3C); absolute mass calcd for $C_{17}H_{18}ClNaNO$ 310.0975, obsd 310.0979.

Data for 1-(4-chlorophenyl)-2-cyclopentyl-1-(2-pyridyl)ethanol (8j): yield 61%; ^{1}H NMR δ 8.45 (1H, d, br), 7.53 (2H, d, J = 9 Hz), 7.68−7.28 (2H, m), 7.23 (2H, d, J = 9 Hz), 7.10 (1H, td, J = 2, 7 Hz), 5.96 (1H, s, OH), 2.35 (2H, m), 1.87−1.02 (9H, m); ^{13}C NMR δ 163.7, 147.2, 145.8, 136.9, 132.6, 128.2 (2C), 127.6 (2C), 122.0, 120.6, 77.1, 47.0, 36.1, 34.4, 33.9, 24.9, 24.7.

Data for 1-(4-chlorophenyl)-2-cyclohexyl-1-(2-pyridyl)ethanol (8k): yield 63%; ^{1}H NMR δ 8.43 (1H, ddd, J = 1.0, 1.8, 4.8 Hz), 7.49 (2H, d, J = 9.0 Hz), 7.66−7.23 (2H, m), 7.22 (2H, d, J = 8.7 Hz), 7.07 (1H, ddd, J = 1.2, 4.9, 6.1 Hz), 6.02 (1H, s, OH), 2.16 (2H, m), 1.54−0.87 (11H, m); ^{13}C NMR δ 163.6, 147.0, 145.8, 136.8, 132.3, 128.0 (2C), 127.3 (2C), 121.8, 120.2, 77.0, 48.2, 35.0, 34.6, 33.4, 26.2 (3C).

Data for (4-chlorophenyl)[5-(cyclohexylmethyl)-2-pyridyl]-methanone (12k): ^{1}H NMR δ 8.47 (1H, d, J = 1.5 Hz, br), 8.07 (2H, d, J = 9 Hz), 7.98 (1H, d, J = 7 Hz), 7.72 (1H, dd, J = 2, 7 Hz), 7.42 (2H, d, J = 9 Hz), 2.55 (2H, d, J = 6.5 Hz), 1.85−1.5 (11H, m); ^{13}C NMR δ 191.7, 152.2, 149.0 (CH), 139.9, 138.8, 137.2 (CH), 134.8, 132.3 (2CH), 128.1 (2CH), 124.1 40.9, 39.3, 32.8 (2C) 26.1, 25.9 (2C); absolute mass calcd for $C_{19}H_{20}ClNaNO$ 336.1131, obsd 336.1122.

Data for 1-(4-chlorophenyl)-2-phenyl-1-(2-pyridyl)ethanol (8l): yield 70%; ^{1}H NMR δ 8.34 (1H, ddd, J = 1, 2, 5 Hz), 7.56 (2H, d, J = 9 Hz), 7.61−7.22 (2H, m), 7.27 (2H, d, J = 9 Hz), 7.20−6.88 (6H, m), 5.40 (1H, s, OH), 3.68 (1H, d, J = 13 Hz), 3.50 (1H, d, J = 13 Hz); ^{13}C NMR δ 162.6, 147.2, 144.7, 136.8, 136.1, 132.9, 130.7 (2C), 128.2 (2C), 127.7 (4C), 126.4, 122.1, 120.7, 77.2, 47.2.

Data for 1-(4-chlorophenyl)-3-phenyl-1-(2-pyridyl)-1-propanol (8m): yield 60%; ^{1}H NMR δ 8.37 (1H, dd, J = 2, 5 Hz), 7.50 (2H, d, J = 9 Hz), 7.61−7.07 (overlapping 8H, m), 7.23 (2H, d, J = 9 Hz), 6.10 (1H, s, OH), 2.63−2.47 (4H, m); ^{13}C NMR δ 162.9, 147.4, 144.8, 142.3, 137.2, 128.4 (6C), 127.5 (2C), 125.8, 122.3, 120.2, 76.7, 43.3, 30.1.

Data for 1-(4-chlorophenyl)-4-phenyl-1-(2-pyridyl)-1-butanol (8n): yield 69%; ^{1}H NMR δ 8.44 (1H, dd, J = 2, 5 Hz), 7.40 (2H, d, J = 9 Hz), 7.30−6.93 (overlapping 10H, m), 5.96 (1H, s, OH), 2.66−1.48 (6H, m); ^{13}C NMR δ 163.1, 147.2, 145.1, 142.1, 137.0, 132.6, 128.4 (2C), 128.2(4C), 127.4 (2C), 125.7, 122.0, 120.1, 76.8, 40.6, 35.9, 25.2.

Data for 1-(4-chlorophenyl)-2-ethyl-1-(2-pyridyl)-1-butananol (8o): yield 57%; ^{1}H NMR δ 8.40 (1H, dd, J = 2, 5 Hz), 7.60 (2H, d, J = 9 Hz), 7.59−7.33 (overlapping 2H, m), 7.24 (2H, d, J = 9 Hz), 7.04 (1H, ddd, J = 1, 2, 7 Hz), 6.13 (1H, s), 2.40−2.16 (1H, m), 1.65−1.07 (4H, m), 0.88 (3H, t, J = 7 Hz), 0.76 (3H, t, J = 7 Hz); ^{13}C NMR δ 163.2, 146.9, 145.5, 137.0, 132.3, 128.2 (2C), 127.5 (2C), 121.9, 120.4, 80.7, 49.3, 22.8, 22.3, 13.3, 13.1.

Data for 1-(4-chlorophenyl)-1-cyclopentyl-1-(2-pyridyl)methanol (8p): yield 63%; ^{1}H NMR δ 8.41 (1H, ddd, J = 1, 2, 5 Hz), 7.58 (2H, d, J = 9 Hz), 7.61−7.29 (2H, m), 7.24 (2H, d, J = 9 Hz), 7.07 (1H, ddd, J = 1, 2, 7 Hz), 6.18 (1H, s, OH), 3.05 (1H, pentet, J = 8 Hz), 1.62−1.19 (8H, m); ^{13}C NMR δ 163.4, 146.8, 145.6, 137.1, 132.4, 128.2 (2C), 127.7 (2C), 121.9, 120.4, 78.0, 48.0, 27.5, 26.8, 26.5, 26.4.

Data for 1-(3-chlorophenyl)-3-methyl-1-(2-pyridyl)-1-butanol (8q): yield 51%; ^{1}H NMR δ 8.43 (1H, d, br, J = 5 Hz), 7.60−7.00 (7H, m), 6.06 (1H, s, br), 2.41 (1H, dd, J = 7, 14 Hz), 2.06 (1H, dd, J = 7, 14 Hz), 1.77 (1H, octet, J = 7 Hz), 0.91 (3H, d, J = 7 Hz), 0.75 (3H, d, J = 7 Hz); ^{13}C NMR δ 163.3, 149.6, 147.1, 137.0, 134.1, 129.3, 126.8, 126.2, 124.1, 122.1, 120.4, 77.2, 49.4, 24.7, 24.3, 24.2.

Data for 1-(3,4-dichlorophenyl)-1-(2-pyridyl)-1-butanol (8r): yield 71%; ^{1}H NMR δ 8.44 (1H, ddd, J = 1, 2, 5 Hz), 7.72−7.50 (2H, m), 7.36−7.27 (3H, m), 7.09 (1H, ddd, J = 1, 5, 7 Hz), 6.00 (1H, s, br), 2.23 (2H, t, J = 7 Hz), 1.39−1.19 (2H, m), 0.87 (3H, t, J = 7 Hz); ^{13}C NMR δ 162.6 (2C), 147.4, 137.1, 132.2, 130.7, 130.0, 128.3, 125.6, 122.2, 120.1, 76.7, 43.4, 16.8, 14.3.

Data for 1-(3,4-dichlorophenyl)-1-(2-pyridyl)-1-pentanol (8s): yield 58%; ^{1}H NMR δ 8.43 (1H, ddd, J = 1, 2, 5 Hz), 7.72−7.49 (2H, m), 7.36−7.26 (3H, m), 7.08 (1H, ddd, J = 1, 5, 7 Hz), 6.07 (1H, s, br), 2.23 (2H, t, J = 7 Hz), 1.33−1.20 (4H, m), 0.83 (3H, t, J = 7 Hz); ^{13}C NMR δ 162.7, 147.4 (2C), 137.1, 132.2, 130.7, 130.0, 128.3, 125.6, 122.2, 120.1, 76.7, 40.9, 25.7, 23.0, 14.0.

Data for 1-(3,4-dichlorophenyl)-3-methyl-1-(2-pyridyl)-1-butanol (8t): yield 61%; ^{1}H NMR δ 8.43 (1H, dd, J = 2, 5 Hz), 7.71−7.34 (5H, m), 7.10 (1H, ddd, J = 1, 2, 7 Hz), 6.07 (1H, s, OH), 2.23−2.13 (2H, m), 1.76 (1H, septet, J = 6 Hz), 0.90 (3H, d, J = 6 Hz), 0.75 (3H, d, J = 6 Hz); ^{13}C NMR δ 162.8, 147.9, 147.2 (CH), 137.1 (CH), 132.2, 130.6, 129.9 (CH), 128.2 (CH), 125.4 (CH), 122.2 (CH), 120.3 (CH), 76.9, 49.3, 24.7, 24.3, 24.1.

Data for 1-(4-methoxyphenyl)-3-methyl-1-(2-pyridyl)-1-butanol (8u): ^{1}H NMR δ 8.39 (1H, ddd, J = 1, 2, 5 Hz), 7.65−7.22 (2H, m), 7.46 (2H, d, J = 9 Hz), 7.05, (1H, ddd, J = 1.3, 5, 6 Hz), 2.25 (1H, dd, J = 6, 14 Hz), 2.13 (1H, dd, J = 6, 14 Hz), 1.78 (1H, nonet, J = 6 Hz), 0.90 (3H, d, J = 6.9 Hz), 0.68 (3H, d, J = 6.9 Hz); ^{13}C NMR δ 164.4, 158.3, 147.0 (CH), 139.5, 136.7 (CH), 127.1 (2CH), 121.7 (CH), 120.6 (CH), 113.4 (2CH), 77.2, 55.0, 49.6, 24.8, 24.2.

Data for 1-(3-methoxyphenyl)-3-methyl-1-(2-pyridyl)-1-butanol (8v): ^{1}H NMR δ 8.40 (1H, d, br, J = 5 (Hz), 7.40 (2H, m), 7.20−6.90 (4H, m), 6.70 (1H, m), 6.05 (1H, s), 3.68 (3H, s), 2.25 (1H, dd, J = 6, 14 Hz), 2.17 (1H, dd, J = 6, 14), 1.88 (nonet, J = 6 Hz), 0.90 (3H, d, J = 6 Hz), 0.77 (3H, d, J = 6 Hz); ^{13}C NMR δ 164.0, 159.5, 149.0 147.0 136.8, 129.0, 121.8, 120.5, 118.3, 112.0, 111.8, 77.4, 54.9, 49.5, 24.8, 24.4, 24.2.

Data for 1-(4-isopropylphenyl)-3-methyl-1-(2-pyridyl)-1-butanol (8w): yield 60%; ^{1}H NMR δ 8.39 (1H, dd, J = 2, 5 Hz), 7.48 (2H, d, J = 9 Hz), 7.51−7.27 (2H, m), 7.13 (2H, d, J = 9 Hz), 6.98 (1H, dt, J = 2, 7 Hz), 6.01 (1H, s, OH), 2.83 (1H, septet, J = 7 Hz), 2.25 (1H, d, J = 6 Hz), 2.20 (1H, d, J = 6 Hz), 2.01−1.66 (1H, m), 1.17(6H, d, J = 7 Hz), 0.93 (3H, d, J = 6 Hz), 0.75 (3H, d, J = 6 Hz); ^{13}C NMR δ 164.3, 146.9, 144.8, 136.7, 126.1 (2C), 125.8 (2C), 121.7, 120.7, 77.4, 49.7, 33.6, 24.8, 24.3 (2C), 23.9 (2C).

Data for 2-[1-(4-chlorophenyl)ethenyl]pyridine (9a): yield 87%; ^{1}H NMR δ 8.56 (1H, ddd, J = 1, 2, 5 Hz), 7.50 (1H, dt, J = 2, 7 Hz), 7.32 (2H, d, J = 9 Hz), 7.17 (2H, d, J = 9 Hz), 7.22−6.98 (overlapping 2H, m), 5.97 (1H, d, J = 1.6 Hz), 5.50 (1H, d, J = 1.6 Hz); ^{13}C NMR δ 157.9, 149.3, 148.1, 138.9, 136.2, 133.6, 129.8 (2C), 128.4 (2C), 122.5 (2C), 118.0.

General Procedure for Synthesizing Intermediates 9. 2-[1-(4-Chlorophenyl)propenyl]pyridine (9b). Alcohol **8b** (9.2 g, 36.7 mmol) was dissolved in 12 N HCl (120 mL) and refluxed for 48 h. The acidic solution was concentrated and neutralized to pH 9 with NaOH. The alkaline solution was extracted 3× with EtOAc, washed with brine, dried ($MgSO_4$), filtered, and concentrated to an oil. After column chromatography with 10% EtOAc in hexanes as the eluent, 6.2 g (74% yield) of **9b** was obtained as a mixture of *Z* and *E* isomers. In some intermediates **9**, one isomer was preponderant; ^{1}H NMR (partial for major isomer) δ 8.67 (1H, dd, J = 2, 5 Hz), 7.68 (1H, dt, J = 2, 7 Hz), 7.27 (2H, d, J = 9 Hz), 7.13 (2H, d, J = 9 Hz), 6.25 (1H, q, J = 7 Hz), 1.80 (3H, d, J = 7 Hz).

Data for 2-[1-(4-chlorophenyl)-1-butenyl]pyridine (9c): yield 85%; ^{1}H NMR (partial for major isomer) δ 8.65 (1H, dd, J = 2, 5 Hz), 7.66 (1H, dt, J = 2, 7 Hz), 7.18, 7.16 (4H, central legs of aromatic doublets), overlapping 7.1−7.5 (2H, m), 6.14 (1H, t, J = 7 Hz), 2.16 (2H, pentet, J = 7 Hz), 1.04 (3H, t, J = 7 Hz).

Data for 2-[1-(4-chlorophenyl)-2-methylpropenyl]pyridine (9d): ^{1}H NMR δ 8.60 (1H, dd, J = 2, 5 Hz), 7.60 (1H, dt, J = 2, 7 Hz), 7.24 (2H, d, J = 9 Hz), 7.14 (2H, d, J = 9 Hz), 7.0−7.3 (2H, m), 1.83 (6H, s).

Data for 2-[1-(4-chlorophenyl)-1-pentenyl]pyridine (9e): yield (after chromatography) 81%; ^{1}H NMR (one isomer) δ 8.64 (1H, dd, J = 2, 5 Hz), 7.63 (1H, dt, J = 2, 7 Hz), 7.28−7.06 (6H, m), 6.25 (1H, t, J = 7 Hz), 2.14 (2H, q, J = 7 Hz), 1.42 (2H, sextet, J = 7 Hz), 0.87 (3H, t, J = 7 Hz); ^{13}C NMR δ 158.7, 149.6 (CH), 140.3, 136.1 (CH), 132.8 (CH), 132.5, 128.5 (2C), 128.3 (2C), 125.0 (CH), 121.9 (CH), 31.7, 22.9, 13.9 (1C overlapped).

Data for 2-[1-(4-chlorophenyl)-3-methyl-1-butenyl]pyridine (9f): oil; yield 79%; ^{1}H NMR (partial for major isomer) δ 8.65 (1H, dd, J = 2, 5 Hz, Py H-6), 7.68 (1H, td, 7,2 Hz, Py-H4), 7.19, 7.17 (4H, central legs of aromatic doublets), 5.95 (1H, d, J = 10 Hz, vinyl), 2.54 (1H, overlapping septets), 1.04 (6H, d, J = 8 Hz); ^{13}C NMR (protonated carbons of major isomer) δ 149.7, 139.6, 136.1, 128.4 (2C), 128.3 (2C), 124.8, 121.9, 28.6, 23.0 (2C).

Data for 2-[1-(4-chlorophenyl)-1-hexenyl]pyridine (9g): yield 93%; ^{1}H NMR (partial for major isomer) δ 8.64 (1H, dd, J = 2, 5 Hz), 7.60 (1H, dt, J = 2, 7 Hz), 7.28−7.03 (6H, m), 6.15 (1H, t, J = 7 Hz), 2.17 (2H, m), 1.52−1.25 (4H, m), 0.83 (3H, t, J = 7 Hz).

Data for 2-[1-(4-chlorophenyl)-4-methyl-1-pentenyl]pyridine (9h): yield 99%; ^{1}H NMR (partial for major isomer) δ 8.62 (1H, dd, J = 2, 5 Hz), 7.60 (1H, dt, J = 2, 7 Hz), 7.41−6.89 (6H, m), 6.18 (1H, t, J = 7 Hz), 2.03 (2H, t, J = 7 Hz), 1.99−1.58 (1H, m), 0.88 (6H, d, J = 7 Hz).

Data for 2-[1-(4-chlorophenyl)-3,3-dimethyl-1-butenyl]pyridine (9i): yield 95%; ^{1}H NMR (partial for major isomer) δ 8.65 (1H, dd, J = 2, 5 Hz), 7.64 (1H, dt, J = 2, 7 Hz), 7.25−7.04 (overlapping 2H, m), 7.20 (2H, d, J = 9 Hz), 7.09 (2H, d, J = 9 Hz), 6.21 (1H, s), 0.95 (9H, s); ^{13}C NMR (major isomer only) δ 159.3, 149.2, 142.0, 141.3, 137.4, 135.8, 132.7, 128.1 (4C), 125.6, 122.0, 30.9 (3C).

Data for 2-[1-(4-chlorophenyl)-2-cyclopentylvinyl]pyridine (9j): yield 97%; ^{1}H NMR (mostly one isomer) δ 8.62 (1H, d, br), 7.75−6.76 (7H, m), 6.06 (1H, d, J = 9 Hz), 2.52 (1H, m), 1.90−1.10 (8H, m); ^{13}C NMR δ 158.9, 149.7 (CH), 149.2, 138.7, 137.9 (CH), 136.0 (CH), 132.6, 128.5 (2CH), 128.3 (2CH), 125.0 (CH), 121.9 (CH), 40.3, 34.0 (2C), 25.6 (2C).

Data for 2-[1-(4-chlorophenyl)-2-cyclohexylvinyl]pyridine (9k): yield 99%; ^{1}H NMR (partial for major isomer) δ 8.66 (1H, dd, J = 2, 5 Hz), 7.65 (1H, ddd, J = 1 2, 7 Hz), 7.44−7.05 (overlapping 2H, m), 7.22 (2H, d, J = 9 Hz), 7.12 (2H, d, J = 9 Hz), 5.98 (1H, d, J = 10 Hz), 2.31 (1H, m), 1.90−0.98 (10H, m); ^{13}C NMR δ 158.8, 149.7 (CH), 149.1, 139.6, 138.2 (CH), 136.0 (CH), 132.6, 128.6 (2CH), 128.4 (2CH), 124.7 (CH), 121.9 (CH), 38.2, 33.1 (2C), 25.9, 25.5 (2C).

Data for 2-[1-(4-chlorophenyl)-2-phenylvinyl]pyridine (9l): yield 99%; ^{1}H NMR (partial for major isomer) δ 8.59 (1H, d, br), 7.83 (1H, s), 7.46−6.88 (12H, m).

Data for 2-[1-(4-chlorophenyl)-3-phenylpropenyl]pyridine (9m): yield 87%; ^{1}H NMR (one major isomer) δ 8.69 (1H, ddd, J = 1, 2, 5 Hz), 7.64 (1H, dt, J = 2, 7 Hz), 7.45−6.75 (11 H, m), 6.31 (1H, t, J = 7 Hz), 3.52 (2H, d, J = 7 Hz); ^{13}C NMR δ 158.2, 149.8, 140.7, 140.2, 139.9, 136.2, 133.1, 130.7, 128.6 (2C), 128.53 (2C), 128.48 (2C), 128.4 (2C), 126.2, 125.0, 122.2, 35.7.

Data for 2-[1-(4-chlorophenyl)-4-phenylbutenyl]pyridine (9n): yield 88%; ^{1}H NMR (60:40 mixture of isomers) δ 8.63 (0.6H, ddd, J = 1, 2, 5 Hz), 8.57 (0.4H, ddd, J = 1, 2, 5 Hz), 7.54 (0.6H, dt, J = 2, 5 Hz), 7.42−6.76 (11.4 H, m), 6.15 (0.6 H, t, J = 7 Hz), 2.75 (2H, t. J = 7 Hz), 2.44 (2H, q, J = 7 Hz).

Data for 2-[1-(4-chlorophenyl)-2-ethyl-1-butenyl]pyridine (9o): yield 97%; ^{1}H NMR δ 8.53 (1H, ddd, J = 1, 2, 5 Hz), 7.44 (1H, dt, J = 2, 7 Hz), 7.40−6.97 (5H, m), 2.18 (4H, q, J = 7 Hz), 2.15 (2H, q, J = 7 Hz), 1.00 (6H, t, J = 7 Hz); ^{13}C NMR δ 161.1, 149.3, 145.2, 140.6, 136.0, 132.4, 130.9 (2C), 128.3 (2C), 127.6, 124.2, 121.1, 24.9, 24.6, 13.2 (2C).

Data for 2-[(4-chlorophenyl)cyclopentylidenemethyl]pyridine (9p): yield 89%; ^{1}H NMR δ 8.58 (1H, dd, J = 2, 5 Hz), 7.52 (1H, dt, J = 2, 7 Hz), 7.28 (2H, d, J = 9 Hz), 7.21−6.98 (overlapping 2H, m), 7.14 (2H, d, J = 9 Hz), 2.56−2.31 (m, 4H), 1.75−1.59 (4H, m); ^{13}C NMR δ 160.7, 149.0, 148.2, 140.7, 135.9, 132.1, 131.5, 130.7 (2C), 128.3 (2C), 124.0, 120.9, 33.8, 33.2, 26.9, 26.5.

Data for 2-[1-(3-chlorophenyl)-3-methyl-1-butenyl]pyridine (9q): yield 86%; ^{1}H NMR (70:30 mixture of isomers) δ 8.64 (1H, m), 7.70−6.70 (6H, m), 6.78 (0.7H, d, J = 10 Hz), 5.99 (0.3H, d, J = 10 Hz), 2.63−2.28 (1H, m), 1.04 (6H, d, J = 7 Hz).

Data for 2-[1-(3,4-cichlorophenyl)butenyl]pyridine (9r): yield 85%; ^{1}H NMR (60:40 mixture of isomers) δ 8.60 (1H, br), 7.86−6.76 (6.6H, m), 6.17 (0.4H, t, J = 7 Hz), 2.15 (2H, q, J = 7 Hz), 1.04 (3H, t, J = 7 Hz).

Data for 2-[1-(3,4-dichlorophenyl)-1-pentenyl]pyridine (9s): yield 92%; ^{1}H NMR (ca. 60:40 mixture of isomers) δ 8.67 (1H, minor, dd, J = 2, 5 Hz), 8.55 (1H, major, ddd, J = 1, 2, 5 Hz) 7.69−6.98 (6H, m), 6.19 (1H, minor, t, J = 7 Hz), 2.11 (2H, m), 1.48 (2H, sextet, br), 0.89 (3H, t, J = 7 Hz).

Data for 2-[1-(3,4-dichlorophenyl)-3-methyl-1-butenyl]pyridine (9t): yield 99%; ^{1}H NMR (80:20 mixture of isomers) δ 8.67 (0.2H, m), 8.57 (0.8H, ddd, J = 1, 2, 5 Hz), 7.64−6.85 (6H, m), 6.71 (0.8H, d, J = 10 Hz), 5.99 (0.2H, d, J = 10 Hz), 2.42 (1H, m), 1.04 (6H, d, J = 7 Hz).

Data for 2-[1-(4-methoxyphenyl)-3-methyl-1-butenyl]pyridine (9u): ^{1}H NMR (ca. 60:40 mixture of isomers) δ 8.52 (1H, m), 7.54 (1H, m), 7.3−6.3 (6.6H, m), 5.89 (0.4H, d, J = 10 Hz), 3.75 (1.8H, s), 3.67 (1.2H, s), 2.46 (1H, m), 1.02 (6H, d, J = 7 Hz).

Data for 2-[1-(3-methoxyphenyl)-3-methyl-1-butenyl]pyridine (9v): ^{1}H NMR (ca. 60:40 mixture of isomers) δ 8.71 (1H, d, br), 7.84 (1H, t, br, J = 8 Hz), 7.55−6.70 (7.6H, m), 6.05 (0.4H, d, J = 10 Hz), 3.80 (1.8H, s), 3.74 (1.2H, s), 2.44 (1H, m), 1.10 (6H, 2 d, J = 7 Hz).

Data for 2-[1-(4-isopropylphenyl)-3-methyl-1-butenyl]pyridine (9w): yield 90%; ^{1}H NMR (60:40 mixture of isomers) δ 8.65 (1H, m), 7.64−7.02 (7H, m), 6.72 (0.4H, d, J = 10 Hz), 5.95 (0.6H, d, J = 10 Hz), 2.85 (1H, septet, J = 7 Hz), 2.62−2.25 (1H, m), 1.20 (6H, d, J = 7 Hz), 1.03 (6H, d, J = 7 Hz).

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)ethyl]piperidinium chloride ((*RS*/*SR*)-10a): yield 56%; ^{1}H NMR (free base) δ 7.24 (2H, d, J = 8.6 Hz), 7.13 (2H, d, J = 8.6 Hz), 2.98−2.80 (1H, m), 2.63−2.29 (3H, m), 2.00−1.01 (overlapping 6H, m), 1.19 (3H, d, J = 6.4 Hz); ^{13}C NMR (free base) δ 143.7, 132.0, 129.0 (2C), 128.6 (2C), 62.5, 47.4, 45.7, 30.4, 26.1, 25.0, 18.4. Anal. ($C_{13}H_{19}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)ethyl]piperidinium chloride ((*RR*/*SS*)-10a): yield 38%; ^{1}H NMR (free base) δ 7.24 (2H, d, J = 8.6 Hz), 7.08 (2H, d, J = 8.6 Hz), 3.16−2.99 (1H, m), 2.71−2.42 (3H, m), 1.91−1.10 (overlapping 6H, m), 1.26 (3H, d, J = 6.7 Hz); ^{13}C NMR (free base) δ 143.6, 131.9, 129.2 (2C), 128.5 (2C), 62.5, 47.5, 45.3, 30.9, 26.6, 25.1, 17.2. Anal. ($C_{13}H_{19}Cl_2N$) C, H, Cl, N.

General Procedure for Synthesizing Final Compounds 10. 2-[1-(4-Chlorophenyl)propyl]piperidine (10b). The *E*/*Z* mixture of alkene **9b** (8.0 g, 34.8 mmol) was dissolved in glacial acetic acid (110 mL) inside the Parr bottle. Trifluoroacetic acid (2.5 mL) was added, followed by the addition of 1.60 g of Pt/C. The reaction mixture was shaken for 24 h and determined to be complete by TLC. The reaction mixture was filtered through Celite and concentrated in vacuo. The crude residue was diluted with EtOAc (∼200 mL), and the organic phase was carefully washed 3× with saturated aqueous $NaHCO_3$ and 1× with brine. The organic phase was dried with Na_2SO_4, filtered, and concentrated in vacuo to yield a mixture of the *RS*/*SR* and *RR*/*SS* isomers **10a**, which were separable via SiO_2 chromatography using 99.5% EtOAc/0.5% Et_2NH → 10% MeOH/89.5% EtOAc/0.5% Et_2NH as the eluent, giving 2.9 g of (*RS*/*SR*)-**10b** (35%) eluting first followed by 2.0 g of (*RR*/*SS*)-**10b** (24%).

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)propyl]piperidinium chloride ((*RS*/*SR*)-10b): needle crystals; mp 239 °C; ^{1}H NMR (270 MHz, D_2O) δ 7.46 (2H, d, J = 8.3 Hz), 7.28 (2H, d, J = 8.3 Hz), 3.30 (1H, t, J = 9.5 Hz), 3.24 (1H, d, J = 11.7 Hz), 2.85 (1H, dt, J = 3.4, 8.0 Hz), 2.68 (1H, m), 2.30 (1H, d, br, J = 6.8 Hz), 2.00−1.75 (3H, m), 1.70−1.40 (4H, m), 0.65 (3H, t, J = 3.4 Hz); ^{13}C NMR (free base) δ 141.9, 132.7, 130.4 (2C), 129.1 (2C), 61.9, 54.3, 48.0, 31.4, 26.9, 25.6, 25.2, 12.6. Anal. ($C_{14}H_{21}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)propyl]piperidinium chloride ((*RR*/*SS*)-10b): mp 238−239 °C; ^{1}H NMR (270 MHz, D_2O) δ 7.42 (2H, d, J = 8.3 Hz), 7.23 (2H, d, J = 8.3 Hz), 3.37 (2H, t, br, J = 6.5 Hz), 3.05 (1H, t, J = 2.5 Hz), 2.80 (1H, m), 1.90−1.65 (4H, m), 1.58−1.20 (4H, m), 0.72 (3H, t, J = 7.0 Hz); ^{13}C NMR (free base) δ 138.5, 133.1, 129.9 (2C), 129.2 (2C), 61.6, 50.5, 45.9, 28.0, 25.5, 22.6, 22.3, 11.9. Anal. ($C_{14}H_{21}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)butyl]piperidinium chloride ((*RS*/*SR*)-10c): mp 211−2 °C; ^{1}H NMR (270 MHz, D_2O) δ 7.45 (2H, d, J = 8.3 Hz), 7.29 (2H, d, J = 8.3 Hz), 3.36−3.22 (2H, m), 2.89−2.75 (2H, m), 1.92−1.72 (4H, m), 1.67−1.45 (4H, m), 1.07−0.94 (2H, m), 0.78 (3H, t, J = 7.3 Hz). Anal. ($C_{15}H_{23}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)butyl]piperidinium chloride ((*RR*/*SS*)-10c): mp 234 °C; ^{1}H NMR (270 MHz, D_2O) δ 7.43 (2H, d, J = 8.3 Hz), 7.25 (2H, d, J = 8.3 Hz), 3.45−3.30 (2H, m), 3.07−2.85 (2H, m), 1.83−1.71 (4H, m), 1.50−1.32 (4H, m), 1.12−1.05 (2H, m), 0.82 (3H, t, J = 7.3 Hz). Anal. ($C_{15}H_{23}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)-2-methylpropyl]piperidinium chloride ((*RS*/*SR*)-10d): mp 305−306 °C; ^{1}H NMR (270 MHz, D_2O) δ 7.44 (2H, d, J = 8.3 Hz), 7.23 (2H, d, J = 8.3 Hz), 3.64−3.55 (1H, m), 3.30 (1H, dd, J = 1.6, 12.2 Hz), 3.05 (1H, dt, J = 3.0, 7.2 Hz), 2.65 (1H, dt, J = 2.4, 6.0 Hz), 2.15 (1H, septet, J = 7 Hz), 2.03 (1H, d, J = 12 Hz), 1.91−1.70 (2H, m), 1.61−1.24 (3H, m), 0.99 (3H, t, J = 6.6 Hz), 0.71 (3H, t, J = 6.6 Hz); ^{13}C NMR (free base) δ 138.9, 132.0, 131.1 (2C), 128.1 (2C), 57.7, 57.3, 47.4, 29.9, 27.4, 27.2, 25.0, 21.5, 18.9. Anal. ($C_{15}H_{23}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)-2-methylpropyl]piperidinium chloride ((*RR*/*SS*)-10d): mp 309 °C; ^{1}H NMR (270 MHz, D_2O) δ 7.46 (2H, d, J = 8.3 Hz), 7.27 (2H, d, J = 8.3 Hz), 3.68 (1H, m), 3.25 (1H, m), 2.95 (1H, m), 2.75 (1H, m), 2.24 (2H, m), 1.91 (2H, m), 1.70−1.32 (3H, m), 0.79 (3H, d, J = 6.6 Hz), 0.74 (3H, d, J = 6.6 Hz); ^{13}C NMR (free base) δ 138.8, 132.2, 131.1 (2C), 128.1 (2C), 57.6 (2C), 47.5, 31.1, 27.5, 26.5, 25.2, 21.8, 18.3. Anal. ($C_{15}H_{23}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)pentyl]piperidinium chloride ((*RS*/*SR*)-10e): ^{1}H NMR (free base) δ 7.26 (2H, d, J = 9 Hz), 7.13 (2H, d, J = 9 Hz), 2.90 (1H, d, J = 12 Hz, br), 2.65−2.3 (3H, m), 1.95−0.95 (12H, m), 0.79 (3H, t, J = 7 Hz); ^{13}C NMR (free base) δ 141.7, 132.1, 129.8 (2C), 128.6 (2C), 61.7, 51.9, 47.5, 31.5, 30.9, 29.7, 26.3, 25.1, 22.7, 13.9. Anal. ($C_{16}H_{25}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)pentyl]piperidinium chloride ((*RR*/*SS*)-10e): ^{1}H NMR (free base) δ 7.26 (2H, d, J = 8.6 Hz), 7.06 (2H, d, J = 8.6 Hz), 3.08 (1H, dd, br, J = 1, 12 Hz), 2.72−2.32 (3H, m), 2.00−1.9 (12H, m), 0.80 (3H, t, J = 7.5 Hz); ^{13}C NMR (free base) δ 141.6, 131.8, 129.9 (2C), 128.4 (2C), 61.6, 51.7, 47.5, 31.2, 30.8, 29.9, 26.8, 25.0, 22.7, 14.0. Anal. ($C_{16}H_{25}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)-3-methylbutyl]piperidinium chloride ((*RS*/*SR*)-10f): mp 276−7 °C; ^{1}H NMR (270 MHz, D_2O) δ 7.45 (2H, d, J = 8.3 Hz), 7.32 (2H, d, J = 8.3 Hz), 3.32−3.15 (2H, m), 2.94−2.76 (2H, m), 2.29 (1H, d, br, J = 8.8 Hz), 1.96−1.76 (2H, m), 1.74−1.40 (5H, m), 1.18−1.02 (1H, m), 0.79 (3H, d, J = 8.8 Hz), 0.77 (3H, d, J = 8.8 Hz); ^{13}C NMR (free base) δ 141.6, 132.0, 129.8 (2C), 128.6 (2C), 62.0, 49.5, 47.4, 41.1, 30.8, 26.3, 25.2, 25.0 24.1, 21.0. Anal. ($C_{16}H_{25}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)-3-methylbutyl]piperidinium chloride ((*RR*/*SS*)-10f): mp 296−7 °C; ^{1}H NMR (free base) δ 7.26 (2H, d, J = 8.3 Hz), 7.08 (2H, d, J = 8.3 Hz), 3.09 (1H, dd, br, J = 3, 12 Hz), 2.85−2.38 (3H, m), 1.75−0.98 (10H, m), 0.81 (3H, d, J = 7 Hz), 0.73 (3H, d, J = 7 Hz); ^{13}C NMR (free base) δ 141.4, 131.8, 129.9 (2C), 128.3 (2C), 61.9, 49.2, 47.4, 40.7, 30.8, 26.7, 25.3, 25.0, 24.4, 21.1. Anal. ($C_{16}H_{25}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)hexyl]piperidinium chloride ((*RS*/*SR*)-10g): yield 51%; ^{1}H NMR (free base) δ 7.27 (2H, d, J = 8.6 Hz), 7.11 (2H, d, J = 8.6 Hz), 3.03−2.78 (1H, d, br), 2.65−2.30 (3H, m), 1.96−1.03 (14H, m), 0.80 (3H, t, J = 7.2 Hz); ^{13}C NMR (free base) δ 141.7, 132.1, 129.8 (2C), 128.6 (2C), 61.7, 51.9, 47.4, 31.8 (2C), 30.9, 27.1, 26.3, 25.1, 22.5, 14.0. Anal. ($C_{17}H_{27}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)hexyl]piperidinium chloride ((*RR*/*SS*)-10g): yield 34%; ^{1}H NMR (free base) δ 7.20 (2H, d, J = 8.6 Hz), 7.04 (2H, d, J = 8.6 Hz), 3.20−2.95 (1H, d, br), 2.73−2.35 (3H, m), 1.97−0.99 (14H, m), 0.80 (3H, t, J = 7.2 Hz); ^{13}C NMR (free base) δ 141.7, 131.9, 129.9 (2C), 128.4 (2C), 61.6, 51.8, 47.5, 31.9, 31.5, 30.9, 27.3, 26.9, 25.1, 22.5, 14.1. Anal. ($C_{17}H_{27}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)-4-methylpentyl]piperidinium chloride ((*RS*/*SR*)-10h): yield 56%; mp 207−209 °C; ^{1}H NMR (free base) δ 7.23 (2H, d, J = 8.6 Hz), 7.12 (2H, d, J = 8.6 Hz), 3.03−2.78 (1H, d, br), 2.65−2.25 (3H, m), 1.99−1.04 (12H, m), 0.70 (6H, d, J = 7 Hz); ^{13}C NMR (free base) δ 141.7, 132.1, 129.8 (2C), 128.6 (2C), 61.7, 52.1, 47.5, 36.7, 30.9, 29.6, 28.0, 26.3, 25.1, 22.9, 22.1. Anal. ($C_{17}H_{27}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)-4-methylpentyl]piperidinium chloride ((*RR*/*SS*)-10h): yield 37%; ^{1}H NMR (free base) δ 7.24 (2H, d, J = 8.6 Hz), 7.05 (2H, d, J = 8.6 Hz), 3.20−2.96 (1H, d, br), 2.72−2.35 (3H, m), 1.99−1.06 (12H, m), 0.79 (6H, d, J = 7 Hz); ^{13}C NMR (free base) δ 141.5, 131.9, 129.9 (2C), 128.4 (2C), 61.7, 52.0, 47.5, 36.9, 30.8, 29.1, 28.1, 26.8, 25.0, 22.9, 22.3. Anal. ($C_{17}H_{27}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)-3,3-dimethylbutyl]-piperidinium chloride ((*RS*/*SR*)-10i): yield 56%; mp, sublimes above 270 °C; ^{1}H NMR (free base) δ 7.24 (2H, d, J = 8.6 Hz), 7.16 (2H, d, J = 8.6 Hz), 3.01−2.87 (1H, m), 2.59−2.28 (3H, m), 1.97−0.93 (8H, m), 0.74 (9H, s); ^{13}C NMR (free base) δ 143.5, 131.8, 130.3 (2C), 128.5 (2C), 62.6, 48.2, 47.5, 45.9, 31.2, 30.9, 30.1 (3C), 26.2, 25.2. Anal. ($C_{17}H_{27}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)-3,3-dimethylbutyl]-piperidinium chloride ((*RR*/*SS*)-10i): yield 36%; mp 319−320 °C; ^{1}H NMR (free base) δ 7.25 (2H, d, J = 8.6 Hz), 7.10 (2H, d, J = 8.6 Hz), 3.20−2.96 (1H, d, br), 2.67−2.37 (3H, m), 1.79−0.88 (8H, m), 0.75 (9H, s); ^{13}C NMR (free base) δ 143.1, 131.7, 130.3 (2C), 128.3 (2C), 62.8, 47.9, 47.5, 45.3, 31.6, 31.2, 30.2 (3C), 26.8, 25.1. Anal. ($C_{17}H_{27}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)-2-cyclopentylethyl]-piperidinium chloride ((*RS*/*SR*)-10j): yield 54%; ^{1}H NMR (free base) δ 7.25 (2H, d, J = 8.6 Hz), 7.16 (2H, d, J = 8.6 Hz), 3.04−2.78 (1H, m), 2.58−2.28 (3H, m), 1.97−0.95 (17H, m); ^{13}C NMR (free base) δ 141.8, 132.0, 129.9 (2C), 128.6 (2C), 61.9, 50.9, 47.4, 38.5, 37.5, 33.7, 31.7, 30.8, 26.2, 25.1 (3C). Anal. ($C_{18}H_{27}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)-2-cyclopentylethyl]-piperidinium chloride ((*RR*/*SS*)-10j): yield 36%; ^{1}H NMR (free base) δ 7.26 (2H, d, J = 8.6 Hz), 7.07 (2H, d, J = 8.6 Hz), 3.22−2.98 (1H, d, br), 2.71−2.40 (3H, m), 1.86−0.96 (17H, m); ^{13}C NMR (free base) δ 141.6, 131.8, 129.9 (2C), 128.3 (2C), 61.9, 50.6, 47.4, 38.1, 37.6, 33.6, 31.6, 30.8, 26.7, 25.1 (2C), 25.0. Anal. ($C_{18}H_{27}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)-2-cyclohexylethyl]-piperidinium chloride ((*RS*/*SR*)-10k): yield 55%; ^{1}H NMR (free base) δ 7.28 (2H, d, J = 8.6 Hz), 7.11 (2H, d, J = 8.6 Hz), 3.01−2.80 (1H, m), 2.61−2.35 (3H, m), 1.84−0.88 (19H, m); ^{13}C NMR (free base) δ 141.6, 132.0, 129.8 (2C), 128.6 (2C), 62.1, 48.4, 47.3, 39.5, 34.6 (2C), 32.0, 30.6, 26.6, 26.2, 26.0 (2C), 25.0. Anal. ($C_{19}H_{29}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)-2-cyclohexylethyl]-piperidinium chloride ((*RR*/*SS*)-10k): yield 37%; ^{1}H NMR (CD_3OD) δ 7.40 (2H, d, J = 9 Hz), 7.24 (2H, d, J = 9 Hz), 3.48−2.92 (4H, m), 1.86−0.77 (19H, m); ^{13}C NMR (CD_3OD) δ 139.2, 134.3, 131.5 (2C), 130.3 (2C), 62.5, 49.0 (2C), 40.1, 35.8, 35.5, 32.8, 28.0, 27.5, 27.2, 27.0, 23.34, 23.26. Anal. ($C_{19}H_{29}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)-2-phenylethyl]piperidinium chloride ((*RS*/*SR*)-10l): yield 56%; ^{1}H NMR (free base) δ 7.25−6.78 (9H, m), 3.25−2.33 (6H, m), 2.02−1.02 (6H, m); ^{13}C NMR (free base) δ 140.4, 140.0, 132.1, 130.0 (2C), 129.0 (2C),

128.4 (2C), 128.0 (2C), 125.7, 60.7, 53.8, 47.4, 38.6, 31.1, 26.3, 25.0. Anal. ($C_{19}H_{23}Cl_2N$) C, H, Cl, N.

Data for (RR/SS)-2-[1-(4-chlorophenyl)-2-phenylethyl]piperidinium chloride ((*RR*/*SS*)-10l): yield 36%; mp 250−2 °C; ^{1}H NMR (free base) δ 7.16−6.75 (9H, m), 3.27−2.45 (6H, m), 1.78−1.08 (6H, m); ^{13}C NMR (free base) δ 140.4, 140.0, 131.6, 129.8 (2C), 128.7 (2C), 127.9 (2C), 127.8 (2C), 125.5, 60.5, 53.3, 47.1, 38.0, 30.5, 26.6, 24.7. Anal. ($C_{19}H_{23}Cl_2N$) C, H, Cl, N.

Data for (RS/SR)-2-[1-(4-chlorophenyl)-3-phenylpropyl]piperidinium chloride ((*RS*/*SR*)-10m): yield 53%; ^{1}H NMR (CD_3OD) δ 7.48 (2H, d, J = 9 Hz), 7.31 (2H, d, J = 9 Hz), 7.29−7.00 (5H, m), 3.48−3.12 (2H, m), 3.01−2.68 (2H, m), 2.47−1.46 (10H, m); ^{13}C NMR (CD_3OD) δ 142.3, 138.6, 134.7, 131.6 (2C), 130.5 (2C), 129.4 (4C), 127.0, 62.6, 49.3, 46.9, 34.0, 33.4, 27.8, 23.3, 23.2. Anal. ($C_{20}H_{25}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)-3-phenylpropyl]piperidinium chloride ((*RR*/*SS*)-10m): yield 36%; ^{1}H NMR (CD_3OD) δ 7.43 (2H, d, J = 9 Hz), 7.26 (2H, d, J = 9 Hz), 7.22−7.04 (5H, m), 3.48−3.25 (2H, m), 3.18−2.81 (2H, m), 2.49−1.27 (10H, m); ^{13}C NMR (CD_3OD) δ 142.3, 138.7, 134.4, 131.6 (2C), 130.1 (2C), 129.4 (4C), 127.0, 62.1, 49.2, 46.7, 34.2 (2C), 27.9, 23.2 (2C). Anal. ($C_{20}H_{25}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)-4-phenylbutyl]piperidinium chloride ((*RS*/*SR*)-10n): yield 56%; ^{1}H NMR (free base) δ 7.30−6.99 (9H, m), 2.96−2.74 (1H, d, br), 2.67−2.23 (5H, m), 1.99−0.81 (10H, m); ^{13}C NMR (free base) δ 142.1, 141.3, 132.1, 129.8 (2C), 128.6 (2C), 128.3 (2C), 128.2 (2C), 125.7, 61.6, 51.6, 47.3, 35.8, 31.2, 30.7, 29.1, 26.2, 25.0. Anal. ($C_{21}H_{27}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)-4-phenylbutyl]piperidinium chloride ((*RR*/*SS*)-10n): yield 37%; ^{1}H NMR (free base) δ 7.27−6.96 (9H, m), 3.14−2.90 (1H, m), 2.69−2.28 (5H, m), 1.99−0.81 (10H, m); ^{13}C NMR (free base) δ 142.1, 141.2, 131.9, 129.8 (2C), 128.4 (2C), 128.3 (2C), 128.2 (2C), 125.6, 61.4, 51.6, 47.3, 35.8, 31.0, 30.7, 29.3, 26.6, 24.9. Anal. ($C_{21}H_{27}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-chlorophenyl)-2-ethylbutyl]piperidinium chloride ((*RS*/*SR*)-10o): yield 53%; ^{1}H NMR (free base) δ 7.25 (2H, d, J = 8.6 Hz), 7.12 (2H, d, J = 8.6 Hz), 3.05−2.78 (2H, m), 2.66−2.40 (2H, m), 1.82−1.06 (11H, m), 0.89 (3H, t, J = 6 Hz), 0.86 (3H, t, J = 6 Hz); ^{13}C NMR (free base) δ 139.3, 132.1, 131.0 (2C), 128.1 (2C), 57.6, 52.8, 47.5, 41.2, 31.3, 26.6, 25.2, 22.6 (2C), 11.9, 11.4. Anal. ($C_{17}H_{27}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-chlorophenyl)-2-ethylbutyl]piperidinium chloride ((*RR*/*SS*)-10o): yield 35%; ^{1}H NMR (free base) δ 7.24 (2H, d, J = 8.6 Hz), 7.06 (2H, d, J = 8.6 Hz), 3.20−2.51 (4H, m), 1.80−1.03 (11H, m), 0.90 (3H, t, J = 7 Hz), 0.84 (3H, t, J = 6 Hz); ^{13}C NMR (free base) δ 138.9, 131.6, 130.8 (2C), 127.6 (2C), 56.8, 52.5, 47.1, 40.0, 29.4, 26.8, 24.7, 22.0, 21.7, 11.0, 10.6. Anal. ($C_{17}H_{27}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[(4-chlorophenyl)cyclopentylmethyl]-piperidinium chloride (*RS*/*SR*)-10p): yield 57%; mp 233−4 °C (from CH_3CN); ^{1}H NMR (free base) δ 7.25 (2H, d, J = 8.6 Hz), 7.10 (2H, d, J = 8.6 Hz), 3.14−2.94 (1H, m), 2.89−2.68 (4H, m), 1.92−0.89 (14H, m); ^{13}C NMR (free base, $CDCl_3$) δ 140.4, 131.9, 130.8 (2C), 128.0 (2C), 59.4, 56.6, 47.6, 41.4, 32.0, 31.7, 30.9, 26.8, 25.3, 24.9, 24.7. Anal. ($C_{17}H_{25}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[(4-chlorophenyl)cyclopentylmethyl]-piperidinium chloride ((*RR*/*SS*)-10p): yield 32%; mp 250−1 °C (from CH_3CN); ^{1}H NMR (free base) δ 7.25 (2H, d, J = 8.6 Hz), 7.08 (2H, d, J = 8.6 Hz), 3.16−2.93 (1H, m), 2.92−2.43 (4H, m), 2.09−0.85 (14H, m); ^{13}C NMR (free base) δ 140.1, 131.9, 130.9 (2C), 128.0 (2C), 59.3, 56.8, 47.4, 41.4, 31.6 (2C), 28.4, 27.4, 25.2, 25.1, 24.6. Anal. ($C_{17}H_{25}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(3-chlorophenyl)-3-methylbutyl]piperidinium chloride ((*RS*/*SR*)-10q): yield 58%; ^{1}H NMR (free base) δ 7.32−7.02 (4H, m), 3.05−2.80 (1H, m), 2.63−2.30 (3H, m), 2.03−1.05 (9H, m), 0.80 (6H, d, J = 6 Hz); ^{13}C NMR (free base) δ 145.5, 134.4, 129.7, 128.4, 126.9, 126.7, 61.9, 50.0, 47.4, 41.0, 30.8, 26.3, 25.2, 25.0, 24.1, 21.1. Anal. ($C_{16}H_{25}Cl_2N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(3-chlorophenyl)-3-methylbutyl]piperidinium chloride ((*RR*/*SS*)-10q): yield 32%; ^{1}H NMR (free base) δ 7.32−6.96 (4H, m), 3.21−2.97 (1H, d, br, J = 2, 12), 2.73−2.45 (3H, m), 1.81−1.02 (9H, m), 0.81 (6H, d, J = 6 Hz); ^{13}C NMR (free base) δ 145.2, 134.1, 129.4, 128.6, 126.9, 126.4, 61.9, 49.7, 47.4, 40.7, 30.9, 26.7, 25.3, 25.0, 24.1, 21.1. Anal. ($C_{16}H_{25}Cl_2N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(3,4-dichlorophenyl)butyl]piperidinium chloride ((*RS*/*SR*)-10r): yield 53%; recrystallized from CH_3CN/EtOH, 9:1; ^{1}H NMR (free base) δ 7.36 (1H, d, J = 8.1 Hz), 7.30 (1H, d, J = 2.1 Hz), 7.05 (1H, dd, J = 2.1, 8.1 Hz), 3.03−2.80 (1H, d, br), 2.70−2.27 (3H, m), 2.01−0.93 (10H, m), 0.81 (3H, t, J = 7.2 Hz); ^{13}C NMR (free base) δ 143.8 (2C), 132.5, 130.3 (2C), 127.9, 61.4, 51.7, 47.4, 33.9, 30.9, 26.3, 25.1, 20.6, 14.0. Anal. ($C_{15}H_{22}Cl_3N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(3,4-dichlorophenyl)butyl]piperidinium chloride ((*RR*/*SS*)-10r): yield 36%; recrystallized from CH_3CN/EtOH, 6:1; ^{1}H NMR (free base) δ 7.34 (1H, d, J = 8.2 Hz), 7.24 (1H, d, J = 2.0 Hz), 6.98 (1H, dd, J = 2.0, 8.2 Hz), 3.21−2.98 (1H, d, br), 2.75−2.32 (3H, m), 1.95−0.96 (10H, m), 0.83 (3H, t, J = 7.2 Hz); ^{13}C NMR (free base) δ 143.6 (2C), 132.2, 130.4, 130.1, 128.0, 61.3, 51.5, 47.4, 33.6, 30.8, 26.7, 24.9, 20.7, 14.0. Anal. ($C_{15}H_{22}Cl_3N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(3,4-dichlorophenyl)pentyl]piperidinium chloride ((*RS*/*SR*)-10s): yield 55%; recrystallized from CH_3CN; ^{1}H NMR (free base) δ 7.37 (1H, d, J = 8.5 Hz), 7.30 (1H, d, J = 1.4 Hz), 7.04 (1H, dd, J = 1.4, 8.5 Hz), 3.05−2.72 (1H, m), 2.56−2.27 (3H, m), 2.02−0.99 (12H, m), 0.80 (3H, t, J = 7.2 Hz); ^{13}C NMR (free base) δ 143.7 (2C), 132.5, 130.4 (2C), 127.9, 61.5, 51.9, 47.4, 31.4, 30.8, 29.7, 26.3, 25.0, 22.7, 13.9. Anal. ($C_{16}H_{24}Cl_3N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(3,4-dichlorophenyl)pentyl]piperidinium chloride ((*RR*/*SS*)-10s): yield 37%; recrystallized from CH_3CN; ^{1}H NMR (free base) δ 7.35 (1H, d, J = 8.3 Hz), 7.24 (1H, d, J = 2.0 Hz), 6.98 (1H, dd, J = 2.0, 8.3 Hz), 3.21−2.98 (1H, m), 2.75−2.32 (3H, m), 1.95−0.96 (12H, m), 0.80 (3H, t, J = 7.2 Hz); ^{13}C NMR (free base) δ 143.6 (2C), 132.2, 130.4, 130.1, 128.0, 61.4, 51.7, 47.4, 31.1, 30.8, 29.8, 26.7, 24.9, 22.7, 14.0. Anal. ($C_{16}H_{24}Cl_3N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(3,4-dichlorophenyl)-3-methylbutyl]-piperidinium chloride ((*RS*/*SR*)-10t): recrystallized from CH_3CN/EtOH, 9:1; ^{1}H NMR (free base) δ 7.37 (1H, d, J = 8 Hz), 7.31 (1H, d, J = 2 Hz), 7.06 (1H, dd, J = 2, 7 Hz), 3.02−2.81 (1H, m), 2.60−2.32 (3H, m), 1.95−1.75 (2H, m), 1.60−1.13 (6H, m), 0.80 (6H, d, J = 6 Hz); ^{13}C NMR (free base) δ 143.7 (2C), 132.5, 130.3 (2C), 127.9, 61.8, 49.6, 47.4, 41.0, 30.8, 26.3, 25.3, 25.0, 24.0, 21.0. Anal. ($C_{16}H_{24}Cl_3N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(3,4-dichlorophenyl)-3-methylbutyl]-piperidinium chloride ((*RR*/*SS*)-10t): recrystallized from CH_3CN; ^{1}H NMR (free base) δ 7.36 (1H, d, J = 8 Hz), 7.24 (1H, d, J = 2 Hz), 6.99 (1H, dd, J = 2, 7 Hz), 3.21−2.97 (1H, m), 2.72−2.42 (3H, m), 1.74−1.01 (8H, m), 0.82 (3H, d, J = 6 Hz), 0.77 (3H, d, J = 6 Hz); ^{13}C NMR (free base) δ 143.5 (2C), 132.2, 130.4, 130.1, 128.0, 61.8, 49.2, 47.4, 40.6, 30.8, 26.6, 25.3, 24.9, 24.0, 21.1. Anal. ($C_{16}H_{24}Cl_3N$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-methoxyphenyl)-3-methylbutyl]piperidinium chloride ((*RS*/*SR*)-10u): the free base of this diastereomer could be selectively precipitated as an oxalate salt; ^{1}H NMR (free base) δ 7.12 (2H, d, J = 8 Hz), 6.84 (2H, d, J = 2 Hz), 3.78 (3H, s), 3.05−2.80 (1H, d, br), 2.64−2.28 (3H, m), 1.94−1.05 (10H, m), 0.80 (6H, d, J = 7 Hz). Anal. ($C_{17}H_{28}ClNO$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-methoxyphenyl)-3-methylbutyl]piperidinium chloride ((*RR*/*SS*)-10u): mp 238−40 °C; ^{1}H NMR (free base) δ 7.05 (2H, d, J = 8 Hz), 6.82 (2H, d, J = 2 Hz), 3.79 (3H, s), 3.23−3.01 (1H, d, br), 2.65−2.25 (3H, m), 1.90−0.98 (10H, m), 0.80 (6H, d, J = 7 Hz); ^{13}C NMR (free base) δ 157.4, 134.0, 128.8 (2C), 113.0 (2C), 61.6, 54.5, 48.0, 46.7, 40.2, 29.9, 25.8, 24.7, 24.3, 23.5, 20.5. Anal. ($C_{17}H_{28}ClNO$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(3-methoxyphenyl)-3-methylbutyl]piperidinium chloride ((*RS*/*SR*)-10v): ^{1}H NMR (salt in CD_3OD) δ 7.33 (1H, t, J = 9), 6.96−6.78 (3H, m), 4.82 (2H, s), 3.82 (3H, s),

3.5−3.1 (1H, m), 3.08−2.76 (2H, m). 2.35−2.1 (1H, m), 2.0−1.05 (9H, m), 0.84 (6H, d, $J = 7$ Hz); ^{13}C NMR (salt in CD_3OD) δ 161.9, 141.7, 131.4, 121.8, 115.5, 114.2, 62.2, 55.8, 48.5, 47.0, 41.0, 28.2, 26.2, 24.2, 23.4, 23.3, 21.3. Anal. ($C_{17}H_{28}ClNO$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(3-methoxyphenyl)-3-methylbutyl]piperidinium chloride ((*RR*/*SS*)-10v): ^{1}H NMR (salt in CD_3OD) δ 7.30 (1H, t, $J = 9$ Hz), 6.93−6.77 (3H, m), 4.83 (2H, s, br), 3.80 (3H, s), 3.5−2.8 (3H, m), 1.95−1.05 (12H, m), 0.88 (6H, d, br, $J = 6$ Hz); ^{13}C NMR (salt in CD_3OD) δ 161.6, 141.8, 131.0, 121.9, 115.8, 113.6, 62.6, 55.7, 48.2, 46.7, 41.6, 28.0, 26.3, 24.2, 23.4, 23.3, 21.3. Anal. ($C_{17}H_{28}ClNO$) C, H, Cl, N.

Data for (*RS*/*SR*)-2-[1-(4-isopropylphenyl)-3-methylbutyl]piperidinium chloride ((*RS*/*SR*)-10w): ^{1}H NMR (free base) δ 7.12 (4H, s), 3.03−2.72 (2H, m), 2.64−2.29 (3H, m), 1.98−1.07 (9H, m), 1.24 (6H, d, $J = 7$ Hz), 0.80 (6H, d, $J = 6$ Hz); ^{13}C NMR (free base) δ 146.6, 140.2, 128.3 (2C), 126.4 (2C), 62.2, 49.6, 47.5, 41.2, 33.6, 30.9, 26.4, 25.2 (2C), 24.2, 24.0 (2C), 21.1. Anal. ($C_{19}H_{32}ClN$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(4-isopropylphenyl)-3-methylbutyl]piperidinium chloride ((*RR*/*SS*)-10w): ^{1}H NMR (free base) δ 7.12 (2H, d, $J = 9$ Hz), 7.08 (2H, d, $J = 9$ Hz), 3.20−2.96 (1H, m), 2.88 (1H, heptet, $J = 7$ Hz), 2.68−2.45 (3H, m), 1.78−1.04 (9H, m), 1.24 (6H, d, $J = 7$ Hz), 0.81 (6H, d, $J = 6$ Hz); ^{13}C NMR (free base) δ 146.5, 140.0, 128.4 (2C), 126.1 (2C), 62.1, 49.2, 47.5, 40.7, 33.6, 30.8, 26.8, 25.3, 25.1, 24.1, 24.0 (2C), 21.2. Anal. ($C_{19}H_{32}ClN$) C, H, Cl, N.

(*RS*/*SR*)-2-[1-(3,4-Dichlorophenyl)-3-methylbutyl]-1-methylpiperidinium chloride ((*RS*/*SR*)-11). A solution of (*RS*/*SR*)-**10t** (0.18 g, 0.60 mmol) and HCHO (37% in H_2O, 0.14 mL) in formic acid (7 mL) was refluxed for 18 h. The reaction mixture was neutralized with 2 N NaOH to pH 8. The aqueous layer was extracted with CH_2Cl_2 (3×), and the organic layers were dried (Na_2SO_4) and concentrated to give 0.18 g (95%) of **11**: ^{1}H NMR (free base) δ 7.36 (1H, d, $J = 8$ Hz), 7.26 (1H, d, $J = 2$ Hz), 7.02 (1H, dd, $J = 2$, 7 Hz), 3.22 (1H, dt, $J = 12$, 6), 3.04−2.79 (1H, m), 2.35 (3H, s), 2.20−1.17 (11H, m), 0.85 (6H, pseudo-t, $J = 6$ Hz); ^{13}C NMR (free base) δ 143.2, 132.1, 131.2, 130.6, 129.9, 128.5, 70.1, 58.3, 43.2, 43.0, 33.4, 25.9, 25.4, 24.7, 24.4 (2C), 21.0. Anal. ($C_{17}H_{26}Cl_3N$) C, H, Cl, N.

Data for (*RR*/*SS*)-2-[1-(3,4-dichlorophenyl)-3-methylbutyl]-1-methylpiperidinium chloride ((*RR*/*SS*)-11): yield 95%; ^{1}H NMR (free base) δ 7.34 (1H, d, $J = 8$ Hz), 7.26 (1H, d, $J = 2$ Hz), 7.03 (1H, dd, $J = 2$, 8 Hz), 3.07−2.80 (2H, m), 2.52−2.05 (2H, m), 2.37 (3H, s), 1.64−1.12 (9H, m), 0.84 (6H, d, $J = 6$ Hz); ^{13}C NMR (free base) δ 143.5, 132.0, 131.2, 130.7, 129.9, 128.3, 67.5, 56.6, 43.7, 41.7, 39.8, 25.3, 24.6, 24.1, 23.8, 22.5, 21.4. Anal. ($C_{17}H_{26}Cl_3N$) C, H, Cl, N.

Data for (*RR*/*SS*)-1-Phenyl-1-(2-piperidinium)-2-propanone chloride ((*RR*/*SS*)-15): yield 79%; mp 171−3 °C; ^{13}C NMR ($CDOD_3$) δ 206.1, 133.1, 128.9 (2C), 128.4 (2C), 127.9, 60.3, 56.2, 44.7, 27.7, 25.5, 21.4, 21.1. Anal. ($C_{14}H_{20}ClNO$) C, H, Cl, N.

Binding and Uptake Assays. (a) Materials. Radioactive compounds were purchased from Perkin-Elmer Life Sciences (Boston, MA). Most other reagents were purchased from Sigma Chemical Co. (St. Louis, MO).

(b) Radioligand Binding Assays. As previously described,[42] HEK-hDAT and -hSERT cells were incubated in Dulbecco's modified Eagle's medium supplemented with 5% fetal bovine serum, 5% calf bovine serum, 0.05 U of penicillin/streptomycin, and puromycin (2 μg/mL). HEK-hNET cells were incubated in Dulbecco's modified Eagle's medium supplemented with 10% fetal bovine serum, 0.05 U of penicillin/streptomycin, and Geneticin (300 μg/mL). Cells were grown until confluent on 150 mm diameter tissue culture dishes in a humidified 10% CO_2 environment at 37 °C. The medium was removed from the plates, the cells were washed with 10 mL of PBS, lysis buffer (10 mL, 2 mM HEPES, 1 mM EDTA) was added, and the plates were placed on ice for 10 min. The cells were scraped from the plates and centrifuged for 20 min at 30000*g*. The pellet was resuspended in 6−24 mL of 0.32 M sucrose with a Polytron homogenizer at setting 7 for 5 s.

The assays contained an aliquot of membrane preparation (approximately 12−30 μg of protein, depending on the cell line, which resulted in binding <10% of the total radioactivity), drug, and [^{125}I]RTI-55 (40−80 pM final concentration) in a final volume of 250 μL. Krebs−HEPES assay buffer (25 mM HEPES, 122 mM NaCl, 5 mM KCl, 1.2 mM $MgSO_4$, 2.5 mM $CaCl_2$, 1 μM pargyline, 100 μM tropolone, 2 mg of glucose/mL, 0.2 mg of ascorbic acid/mL, pH 7.4) was used for all assays. Specific binding was defined as the difference in binding observed in the presence and absence of 5 μM mazindol (HEK-hDAT and -NET) or 5 μM imipramine (HEK-hSERT). The membranes were preincubated with the drugs at rt for 10 min before the addition of [^{125}I]RTI-55. The reaction was incubated for 90 min at rt in the dark and terminated by filtration through Wallac Filtermat A filters using a 96-well Tomtec cell harvester. Scintillation fluid (50 μL) was added to each filtered spot, and the radioactivity remaining on the filter was determined using a Wallac 1205 Betaplate or 1405 microBeta scintillation counter. Competition experiments were conducted with duplicate determinations of each point, and the experiments were repeated at least two additional times.

(c) Uptake Assays. As previously described,[42] HEK-hDAT, -hSERT, and -hNET cells were grown on 150 mm diameter tissue culture dishes. The medium was removed, and the plates were washed twice with Ca^{2+}- and Mg^{2+}-free PBS. Fresh Ca^{2+}- and Mg^{2+}-free PBS (2.5 mL) was then added, and the plates were placed in a 25 °C water bath for 5 min. The cells were gently scraped from the plates and were separated by trituration with a pipet for 5−10 aspirations and ejections. Aliquots (50 μL) of the suspended cells were added to assay tubes containing the drugs and Krebs−HEPES assay buffer in a final assay volume of 0.5 mL. After a 10 min preincubation in a 25 °C water bath, [^{3}H]neurotransmitter (20 nM final concentration; [^{3}H]DA, [^{3}H]5-HT, or [^{3}H]NE, 56, 26.9, or 60 Ci/mmol, respectively) was added, and the assay was incubated for 10 min. The reaction was terminated by filtration through Wallac Filtermat A filters, presoaked in 0.05% polyethylenimine, using a Tomtec cell harvester. Scintillation fluid was added to each filtered spot, and the radioactivity remaining on the filters was determined as described above. The specific uptake was defined as the difference in uptake observed in the absence and presence of 5 μM mazindol (hDAT and hNET) or 5 μM imipramine (hSERT). Competition experiments were run in triplicate for each point, and the experiments were repeated at least two additional times.

(d) Data Analysis. Prism software (GraphPad Software, San Diego, CA) was used to analyze all kinetic, saturation, and competition binding data. IC_{50} values were converted to K_i values using the Cheng−Prusoff equation.

Locomotor Assays. These were conducted using 40 Digiscan testing chambers (40.5 cm × 40.5 cm × 30.5 cm) housed in sets of two within sound-attenuating enclosures. A panel of 16 infrared beams and photodetectors were located in the horizontal direction of each activity chamber. A 7.5 W incandescent light above each chamber provided dim illumination, and fans provided an 80 dB ambient noise level. Separate groups of eight nonhabituated, male Swiss-Webster mice (Hsd:ND4, aged 2−3 months) were injected via the intraperitoneal route with vehicle, cocaine, methylphenidate, or the test compound immediately prior to locomotor testing. The vehicle was 0.9% saline for cocaine and methylphenidate and deionized water for (*RR*/*SS*)-**10f**. Horizontal activity (interruption of photocell beams) was measured for 8 h within 10 min periods beginning at 0800 h (2 h after lights on). Testing was conducted with one mouse per activity chamber. ED_{50} values, doses producing half-maximal stimulant activity ((maximum − mean control)/10 min), were estimated from a linear regression against log doses of the ascending portion of the dose−response curves.

X-ray Crystallography. Crystallographic data for the structural analysis have been deposited with the Cambridge Crystallographic Data Centre, CCDC deposition no. 615455.

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Supporting Information Available: X-ray crystallographic data and results from elemental analysis. This material is available free of charge via the Internet at http://pubs.acs.org.

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