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Structure–activity studies of 3′-4′-dichloro-meperidine analogues at dopamine and serotonin transporters

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Abstract—The structure–activity relationships of 3′,4′-dichloro-meperidine were investigated at dopamine (DAT) and serotonin transporters (SERT). Large ester substituents and lipophilic groups at the 4-position favored molecular recognition at the SERT. The benzyl ester of 3′,4′-dichloro-meperidine exhibited high potency and high selectivity for the SERT (DAT/SERT = 760). Chemical modification of the ester group and N-substitution generally led to compounds with decreased DAT affinity. Only small esters and alkyl groups were tolerated at the 4-position of the meperidine ring system by the DAT. Overall, the meperidine analogues were generally more selective for the SERT than for the DAT.

1. Introduction

Recent studies in our laboratory have focused upon the structure–activity relationships (SAR) of meperidine, **1**, an atypical μ-opioid agonist, at monoamine transporters.[1,2] Meperidine was initially found to be selective for the serotonin transporter (SERT) over the dopamine transporter (DAT) (SERT/DAT = 43).[1] Further exploration of various aryl-substituted meperidine analogues **2** revealed that although the DAT affinity of these compounds could be enhanced, high SERT affinity and selectivity predominated throughout the series.[2] Effects of the aryl substituent on the DAT affinity of meperidine analogues paralleled the SAR previously reported for 2β-carbomethoxy-3β-aryl tropanes **3**,[3–5] and *cis*-3-carbomethoxy-4-aryl piperidines, **4**.[6,7] From the SAR of the meperidine analogues, the 3,4-dichlorophenyl group was identified as an important moiety for molecular recognition at the DAT. Similar effects of the 3,4-dichlorophenyl group on DAT affinity have been reported for other tropane derivatives,[8–10] non-nitrogen tropane analogues,[11,12] and piperidine derivatives.[13] However, unlike these tropane, tropane-related, and piperidine ligands that are DAT selective, 3′,4′-dichloromeperidine, **5**, exhibited high potency at the SERT(K_i = 19 nM) and was slightly SERT-selective (DAT/SERT = 6.7) (see Fig. 1).

The inherent SERT selectivity of the meperidine analogues **2** warranted an investigation of the SAR at monoamine transporters to elucidate further the pharmacophore requirements at both the DAT and the SERT. To this end, it was of interest to explore the structural modification of meperidine and evaluate the effects on DAT and SERT affinities. The modestly SERT selective ligand **5** was selected as a molecular scaffold for these studies since it exhibited good affinity at

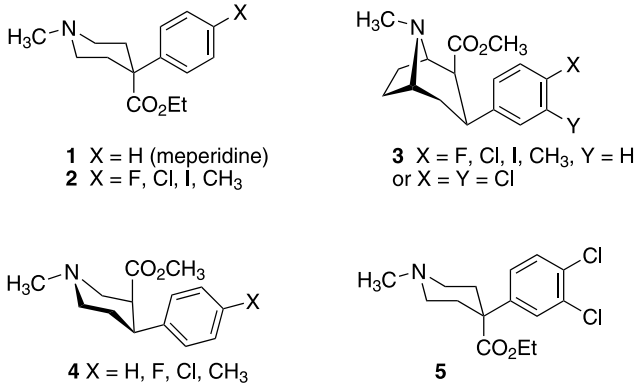

Figure 1.

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both the DAT and the SERT. Herein, we report the synthesis and biological evaluation of a series of modified ester and *N*-substituted analogues of 3′,4′-dichloromeperidine, **5**, at the dopamine and serotonin transporters.

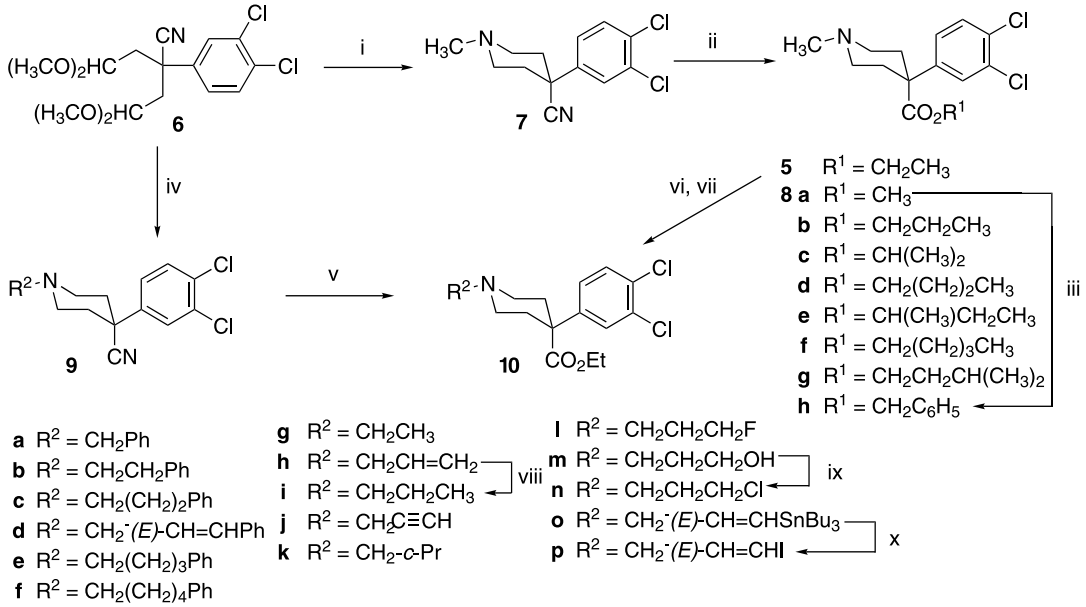
2. Results

In an attempt to specifically increase potency and selectivity for either the DAT or the SERT, various substitutions on the ester group and on the nitrogen atom as well as modifications of the ester moiety were considered. As illustrated in Scheme 1, ester analogues of **5** were prepared from the diacetal **6** using a synthetic approach that was previously developed in our laboratories.[2] Hydrolysis of **6** and concomitant reductive amination with methylamine furnished the piperidine nitrile **7**. The ester derivatives **8** were then obtained using a one-pot hydrolysis/esterification process. Hydrolysis of the nitrile **7** with aqueous sulfuric acid at 120 °C was followed by the addition of an appropriate alcohol in excess. Azeotropic distillation of the alcohol/water afforded the desired ester substitutions **8a**–**g** in good overall yield. However, this process was not amenable to high boiling alcohols. To this end, the benzyl ester **8h** was obtained in 51% yield from the methyl ester **8a** using the 1,3-bis(mesityl)imidazol-2-ylidene (IMes) carbene catalyzed transesterification method.[14]

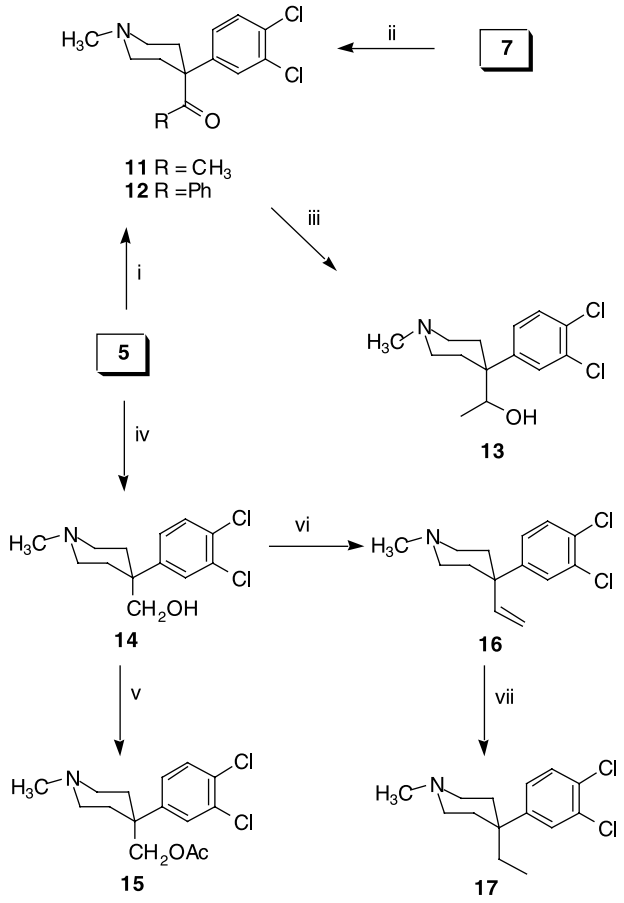
The *N*-substituted 3′,4′-dichloro meperidine derivatives were synthesized using two different methods (Scheme 1). The *N*-alkylaryl congeners **10a**–**c** were synthesized by a reductive amination sequence in which the *N*-alkylaryl group was introduced during construction of the piperidine ring system. The diacetal **6** was converted into the *N*-alkylaryl piperidine nitriles **9a**–**c** by hydrolysis of the acetal moieties, followed by reductive amination with the corresponding arylaldehyde. Subsequent transformation of the nitrile group of **9a**–**c** into the desired ethyl esters **10a**–**c** took place with a one-pot hydrolysis/ ethanol esterification process. Alternatively, the remaining *N*-alkylaryl (**10d**–**f**), *N*-alkyl, *N*-alkenyl, and *N*-alkynyl congeners (**10g**–**p**) were prepared from **5** via a demethylation/N-alkylation sequence. The *N*-3-chloropropyl derivative **10n** was prepared from the hydroxy derivative **10m** via the corresponding mesylate. Attempts to directly prepare **10n** from the 1,3-dichloropropane or 1-bromo-3-chloropropane afforded an intractable mixture. Finally, the *N*-(*E*)-3-iodo-2-propenyl analogue **10p** was prepared from the corresponding stannane **10o**.[15]

As illustrated in Scheme 2, functional group transformation at the 4-position took place in a straightforward fashion. Treatment of **5** or **7** with 1 equiv of a Grignard reagent (methyl magnesium bromide and phenyl magnesium bromide) afforded the corresponding ketones **11** and **12**, respectively. Sodium borohydride reduction of **11** gave the alcohol **13** in 90% yield. Lithium aluminum hydride reduction of **5** furnished the alcohol **14** in 95% yield. Subsequent conversion of **14** into the acetate **15,** the vinyl derivative **16**, and ethyl analogue **17** was effected using standard synthetic methods.

The transporter binding affinities were determined for the 3′,4′-dichloro meperidine analogues by their ability to displace bound radiolabeled ligands from rat caudate-putamen tissue.[2] The K_i values that are reported in Tables 1–3 are inhibition constants derived for the unlabeled ligands. The binding affinities of the meperidine analogues were determined at DAT by inhibition of [^{3}H]WIN 35,428 binding. For compounds that were equipotent with **5** at the DAT, the SERT affinity was also determined by inhi-



Scheme 1. Reagents and conditions: (i) 3 N HCl, 50 °C, then CH_3NH_2·HCl, CH_3OH, $NaBH_3CN$; (ii) H_2SO_4/H_2O, 120 °C, then R^1OH, azeotropic distillation; (iii) BnOH, IMes·HCl, *t*-BuOK, THF; (iv) 3 N HCl, 50 °C, then R^2NH_2·HCl, CH_3OH, $NaBH_3CN$; (v) H_2SO_4/H_2O, 120 °C, then EtOH, azeotropic distillation; (vi) ACE-Cl, $ClCH_2CH_2Cl$, reflux; then CH_3OH; (vii) R^2X (X=Cl or Br), KI, Et_3N, EtOH, reflux; (viii) H_2, 10% Pd/C, EtOH; (ix) MsCl, Et_3N, CH_2Cl_2, 48 h; (x) I_2, $CHCl_3$, 0 °C.



Scheme 2. Reagents and conditions: (i) CH_3MgBr, Et_2O, 0 °C; (ii) PhMgBr, Et_2O, 0 °C; (iii) $NaBH_4$, CH_3OH; (iv) $LiAlH_4$, Et_2O; (v) CH_3COCl, DMAP, ET_3N, CH_2Cl_2; (vi) $(COCl)_2$, DMSO, *i*-Pr_2NEt, CH_2Cl_2, then CH_3PPh_3Br, BuLi, THF; (vii) H_2, 10% Pd/C, CH_3OH.

bition of [^{3}H]paroxetine binding using assay methods previously reported.[2]

In general, the ester analogues **8a**–**h** (Table 1) exhibited equipotent-binding affinity at the SERT relative to **5**. In addition, all of the esters **8a**–**h** were more selective for the SERT than the DAT. Only the branched short-chain esters **8c** (*i*-Pr, K_i = 271 nM) and **8e** (*sec*-Bu, K_i = 283 nM) exhibited similar DAT potency. Once the ester chain exceeded four carbon atoms in length, the binding affinity at the DAT dropped into the micromolar range, while the SERT affinity was not significantly affected. It is noteworthy that the benzyl ester **8h** exhibited very high affinity for the SERT (K_i = 3.9 nM) and was the most potent analogue of the series. In addition, the transporter selectivity (DAT/SERT = 760) was nearly 3 orders of magnitude greater for the SERT than the DAT.

For the *N*-substituted series (Table 2), the esters (**10a**–**c**) were more potent than the corresponding nitriles (**9a**–**c**). This was consistent with the previous SAR of the aryl-substituted meperidine derivatives.[2] Overall, the *N*-alkyl substituted meperidine analogues were less potent at the DAT than the corresponding *N*-methyl derivative **5**. The most potent compounds of the *N*-substituted series were the *N*-propargyl **10j** (K_i = 504 nM) and the *N*-phenylpropyl ester **10c** (K_i = 515 nM) and *N*-propylchloro **10n** (K_i = 573 nM) derivatives, whereas the least potent compounds were the *N*-benzyl **10a** and the *N*-iodopropenyl **10n** derivatives.

The binding affinities of the modified ester derivatives **11**–**17** at the DAT and SERT are summarized in Table 3. Conversion of the ester moiety of **5** into the ketones **11** (K_i = 367 nM) and **12** (K_i = 253 nM) resulted in a slightly decreased affinity for both the DAT and the SERT. The alcohol derivatives **13** and **14** exhibited significant decreases in DAT affinity, while the SERT affinity was only modestly affected. As a result, the SERT selectivity of **13** and **14** increased significantly (DAT/SERT ≈ 40). Conversion of the alcohol **14** into the acetate **15** improved the DAT affinity (K_i = 633 nM) but remained SERT selective (K_i = 38 nM, DAT/SERT = 17). The 4-vinyl (**16**, K_i = 9 nM) and 4-ethyl (**17**, K_i = 11 nM) analogues exhibited potent SERT affinity and were nearly equipotent with **5** at the DAT but exhibited enhanced selectivity for the SERT (DAT/SERT ≈ 18).

3. Discussion

Despite similarities between the substituted aryltropanes and the aryl-substituted meperidine analogues relative to SAR trends at the DAT, the SAR of the ester moiety of the two classes of compounds was significantly different. Unlike the phenyltropanes that can tolerate a wide variety of esters and functionality at the 2-position of the tropane system and maintain high DAT affinity,[16–21] a slight modification of the ester group at the 4-position of the piperidine ring of **5** resulted in significant loss of

Table 1. In vitro binding data at the DAT and the SERT for the 3′,4′-dichloro meperidine ester derivatives **8**

Compound[a]	R^1	[^{3}H]WIN 35,428 (DAT) K_i (nM)[b]	[^{3}H]Paroxetine (SERT) K_i (nM)[b]	DAT/SERT
5	$-CH_2CH_3$	125 ± 15	18.7 ± 2.6	6.7
8a	$-CH_3$	383 ± 32	15.4 ± 1.1	25
8b	$-CH_2CH_2CH_3$	449 ± 94	16.4 ± 0.7	27
8c	$-CH(CH_3)_2$	271 ± 51	43.3 ± 7.0	6.3
8d	$-CH_2(CH_2)_2CH_3$	864 ± 110	16.0 ± 2.5	54
8e	$-CH(CH_3)CH_2CH_3$	283 ± 11	44.3 ± 4.7	6.4
8f	$-(CH_2)_4CH_3$	1580 ± 190	ND	ND
8g	$-CH_2CH_2CH(CH_3)_2$	1810 ± 230	ND	ND
8h	$-CH_2C_6H_5$	2970 ± 300	3.9 ± 0.5	760

ND, not determined.

[a] All compounds were tested as the HCl salt.

[b] All values are means ± SEM of three experiments performed in triplicate.

Table 2. In vitro binding data at DAT for the *N*-substituted 3′,4′-dichloro meperidine derivatives **9** and **10**

Compound[a]	R^2	[^{3}H]WIN 35,428 (DAT) K_i (nM)
4		2670 ± 240
9a	CH_2Ph	4180 ± 990
9b	CH_2CH_2Ph	1790 ± 120
9c	$CH_2(CH_2)_2Ph$	1500 ± 300
10a	CH_2Ph	1860 ± 230
10b	CH_2CH_2Ph	1100 ± 370
10c	$CH_2(CH_2)_2Ph$	514 ± 30
10d	*t*-$CH_2CH{=}CHPh$	1500 ± 110
10e	$CH_2(CH_2)_3Ph$	1110 ± 130
10f	$CH_2(CH_2)_4Ph$	625 ± 110
10g	CH_2CH_3	894 ± 460
10h	$CH_2CH{=}CH_2$	1140 ± 130
10i	$CH_2CH_2CH_3$	1170 ± 150
10j	$CH_2C{\equiv}CH$	504 ± 46
10k	CH_2-cycloPr	1510 ± 180
10l	$CH_2CH_2CH_2F$	825 ± 160
10m	$CH_2CH_2CH_2Cl$	573 ± 84
10n	*t*-$CH_2CH{=}CHI$	2000 ± 250

All values are means ± SEM of three experiments performed in triplicate.
[a] All compounds were tested as the HCl salt.

Table 3. In vitro binding data at DAT and SERT for the 3′,4′-dichloro meperidine derivatives **11**–**17**

Compound[a]	K_i (nM)		DAT/SERT
	DAT	SERT	
5	125 ± 15	19 ± 2.6	6.7
11	367 ± 35	35 ± 13	10
12	253 ± 21	200 ± 18	1.3
13	670 ± 39	17 ± 1	36
14	3310 ± 210	83 ± 3	40
15	633 ± 91	38 ± 6	17
16	192 ± 31	9 ± 2	17
17	163 ± 38	11 ± 1	18

All values are means ± SEM of three experiments performed in triplicate.
[a] All compounds were tested as the HCl salt.

affinity at the DAT. While small-branched esters (**8c** and **8e**) exhibited comparable affinity to the ethyl ester **5**, long-chain esters (**8d** and **8f**), as well as more sterically demanding esters (**8g** and **8h**), were not tolerated at the binding site on the DAT. Alternatly, an increase in the size of the ester chain of **5** led to increased affinity at the SERT. Most notably, the benzyl ester **8h** was the most potent ligand of the series at the SERT. In addition, **8h** exhibited high selectivity for the SERT over the DAT and is the most SERT selective meperidine analogue reported to date. From these data, it appears that it is the position of the ester moiety in the meperidine system, relative to that of the 2β-carbomethoxy-3β-aryltropanes, that leads to an observed reversal of transporter selectivity favoring the SERT. While the SERT can tolerate fairly large lipophilic ester residues at the 4-position, the DAT can only accommodate the small-ester chains. In addition, the hydroxyl group at the 4-position led to a greatly reduced affinity for the DAT, while the SERT affinity was unaffected. This represents a significant divergence in the SAR of the meperidines from the *cis*-3-substituted-4-arylpiperidines[22] and 2-substituted-3β-aryltropanes.

Substitution of the *N*-methyl group of **5** led to a greatly diminished affinity, of the ester analogues **10** at the DAT. Since N-substitution among the *cis*-3-carbomethoxy-4-arylpiperidines and 2β-carbomethoxy-3β-aryltropanes does not generally lead to increased SERT binding affinity these compounds were not evaluated in SERT assays.[23,24] In general, the various *N*-substituted derivatives **10** exhibited DAT affinity that was much less than the *N*-methyl analogue **5**. The *N*-alkylaryl analogues **10a**–**c** exhibited reduced affinity, relative to the *N*-methyl ester **5**, similar to that reported for the 3-carbomethoxy-4-arylpiperidines.[24] Likewise, *N*-alkyl (**10g**, **10i**, **10k**, **10l**, and **10m**), *N*-alkenyl (**10d**, **10h**, and **10n**), and *N*-alkynyl (**10j**) substitution led to decreased affinity of **5** at the DAT. Similar substitution effects have been reported for the 2β-carbomethoxy-3β-aryltropanes on DAT affinity with mixed effects on DAT/SERT selectivity.[15,23]

In general, the ester-modified derivatives **11**–**17** exhibited similar potency at SERT to that of the ester **5**. The 4-vinyl (**16**) and 4-ethyl (**17**) analogues were the most potent ligands of this series at the SERT and were equipotent with benzyl ester **8h**. However, the SERT selectivity of **16** and **17** over the DAT was only modestly increased, relative to **5**, due to only slightly diminished DAT affinities of the compounds. It is noteworthy that the electronic character of the functional group at the 4-position of the meperidine ring system did not significantly affect the binding affinity at the SERT. Only the alcohol **14** exhibited a significant reduction in affinity for the DAT relative to **5**. This is similar to the SAR of the 2β-substituted-3β-aryltropanes and *cis*-3-substituted 4-arylpiperidines in that an ester moiety is not required for high affinity binding and that a variety of functional groups can be tolerated at this position.[16–21,24,25]

In conclusion, the results of this study clearly demonstrate that meperidine and its analogues are selective ligands for the SERT over the DAT. Chemical modification of the ester group generally led to compounds with increased SERT affinity. The long-chain ester substituents and lipophilic groups at the 4-position favored molecular recognition at the SERT. In addition, hydrophilic groups did not affect SERT affinity but greatly reduced DAT affinity and led to enhanced SERT selectivity. The benzyl ester **8h** was found to be the most potent and most selective ligand of this study. Despite some structural similarities and common trends in SAR to the *cis*-3-substituted-4-arylpiperidines and 2-substituted-3β-aryltropanes, the meperidine derivatives exhibited more potent affinity for the SERT and were significantly less potent at the DAT than the corresponding *cis*-3-substituted-4-arylpiperidines and 2β-substituted-3β-aryltropanes. Overall, this investigation suggests that the ester moiety at the 4-position is a key structural feature of the meperidine-related compounds for molecular recognition at the SERT as well as differentiation between the SERT and the DAT. This suggests that analogues of meperidine could be developed as potential selective serotonin reuptake inhibitors (SSRIs). Structure–activity studies directed toward the optimiz-

ation of SERT selectivity are currently under investigation and will be reported in due course.

4. Experimental

All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI, unless otherwise noted. THF, CH_2Cl_2, and CH_3OH were dried under the argon system. Toluene and Et_2O were dried by distillation over Na/benzophenone. Chromatography refers to column chromatography on silica gel (Silica Gel 60, 230–400 mesh). Petroleum ether refers to pentanes with a boiling point range of 30–60 °C. Reported melting points are uncorrected. NMR spectra were recorded on a Varian-Gemini 400 MHz spectrometer. Chemical shifts are reported as δ values with tetramethylsilane (TMS), employed as the internal standard. Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA.

4.1. General procedure A. Preparation of hydrochloride salts

All of the compounds were converted into the hydrochloride salts for biological testing, as well as for storage and handling purposes. The base (50–100 mg) was dissolved in a minimum amount of Et_2O (1–2 mL) and added to a saturated ethereal solution (10 mL) of anhydrous hydrogen chloride. The hydrochloride salts crystallized and were washed with Et_2O (3× 2 mL) and purified by titration with Et_2O and ethyl acetate. Fractional moles of water could not be prevented, despite vigorous drying (110 °C, 1 h) under vacuum (0.01 mmHg). All compounds were homogeneous by thin-layer chromatography ($CHCl_3/CH_3OH/NH_4OH$, 90:9:1).

4.2. General procedure B. Esterification of nitriles

The nitrile **7** or **9** (5.2 mmol) in an aqueous solution of sulfuric acid (6.5 mL H_2SO_4/H_2O, 1:1) was heated in an oil bath at 120 °C for 1.5 h. The flask was then equipped with a Dean Stark Trap and excess alcohol was added. The water was azeotropically removed over 4 h and alcohol was added as needed. The reaction was heated to reflux overnight, then the reaction mixture was allowed to come to room temperature and excess alcohol was removed under reduced pressure. The flask was then cooled in an ice bath and the acid was neutralized to a pH of 10 with 1 N NaOH. The aqueous layer was extracted with Et_2O (3× 75 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by flash chromatography ($CHCl_3/CH_3OH/NH_4OH$, 90:9:1) to afford the esters **8a**–**g** and **10a**–**c**.

4.3. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid methyl ester (8a)

General procedure B. This compound was obtained as a yellow solid (150 mg, 56% yield) and converted into a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 196–198 °C. ^{1}H NMR (free base): δ 7.45 (d, 1H, J = 2.4 Hz), 7.40 (d, 1H, J = 8.4 Hz), 7.21 (dd, 1H, J = 2.4, 8.4 Hz), 3.67 (s, 3H), 2.81 (br s, 2H), 2.55 (d, 2H, J = 12.8 Hz), 2.30 (s, 3H), 2.18 (t, 2H, J = 10.8 Hz), 1.98 (t, 2H, J = 10.8 Hz). ^{13}C NMR (free base): δ 173.8, 142.9, 132.5, 131.1, 130.3, 128.1, 125.3, 53.2, 52.3, 48.3, 46.1, 33.7. Anal. Calcd for $C_{14}H_{17}NO_2Cl_2 \cdot HCl \cdot 0.5H_2O$: C, 48.36; H, 5.51; N, 4.03. Found: C, 48.28; H, 5.46; N, 4.09.

4.4. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid propyl ester (8b)

General procedure B. This compound was obtained as an orange oil (210 mg, 58% yield) and converted into a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 202–204 °C. ^{1}H NMR (free base): δ 7.47 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 2.0 Hz, J = 8.4 Hz, 1H), 4.04 (t, J = 6.6 Hz, 2H), 2.79 (br s, 2H), 2.56 (d, J = 13.2 Hz, 2H), 2.28 (s, 3H), 2.16 (m, 2H), 1.96 (m, 2H), 1.59 (m, 2H), 0.86 (t, J = 7.6 Hz, 3H). ^{13}C NMR (free base): δ 173.5, 136.6, 131.2, 130.4, 128.2, 125.4, 66.8, 53.2, 48.3, 46.1, 33.6, 21.8, 10.3. Anal. Calcd for $C_{16}H_{21}NO_2Cl_2 \cdot HCl \cdot H_2O$: C, 49.95; H, 6.29; N, 3.64. Found: C, 50.19; H, 6.00; N, 3.70.

4.5. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid isopropyl ester (8c)

General procedure B. This compound was obtained as an orange oil (134 mg, 39% yield) and converted into a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 221–223 °C. ^{1}H NMR (free base): δ 7.47 (d, J = 2.0 Hz, 1H), 7.40 (d, J = 8.8 Hz, 1H), 7.22 (dd, J = 2.0 Hz, J = 8.2 Hz, 1H), 5.02 (m, 1H), 2.82 (br s, 2H), 2.54 (d, J = 12.8 Hz, 2H), 2.30 (s, 3H), 2.16 (m, 2H), 1.96 (m, 2H), 1.17 (d, J = 6.0 Hz, 6H). ^{13}C NMR (free base): δ 172.8, 132.6, 131.2, 130.4, 128.2, 125.3, 66.7, 53.2, 48.2, 46.0, 33.5, 21.5. Anal. Calcd for $C_{16}H_{21}NO_2Cl_2 \cdot HCl \cdot H_2O$: C, 49.95; H, 6.29; N, 3.64. Found: C, 49.81; H, 6.20; N, 3.65.

4.6. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid butyl ester (8d)

General procedure B. This compound was obtained as an orange oil (200 mg, 54% yield) and converted into a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 177–179 °C. ^{1}H NMR (free base): δ 7.47 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.22 (dd, J = 2.4, 8.8 Hz, 1H), 4.07 (t, J = 6.4 Hz, 1H), 2.77 (br s, 2H), 2.54 (d, J = 13.2 Hz, 2H), 2.27 (s, 3H), 2.15 (t, J = 10.8 Hz, 2H), 1.94 (t, J = 11.2 Hz, 2H), 1.55 (m, J = 6.8 Hz, 2H), 1.28 (m, J = 7.2 Hz, 2H), 0.878 (t, J = 7.6 Hz, 3H). ^{13}C NMR (free base): δ 173.4, 143.1, 132.6, 131.1, 130.3, 128.2, 125.3, 65.0, 53.2, 48.3, 46.1, 33.6, 30.4, 19.0, 13.5. Anal. Calcd for $C_{17}H_{23}NO_2Cl_2 \cdot HCl \cdot H_2O$: C, 51.20; H, 6.57; N, 3.51. Found: C, 51.23; H, 6.54; N, 3.52.

4.7. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid *sec*-butyl ester (8e)

General procedure B. This compound was obtained as an orange oil (140 mg, 35% yield) and converted into

a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 198–200 °C. ^{1}H NMR (free base): δ 7.48 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 2.4, 8.4 Hz, 1H), 4.84 (m, 1H), 2.80 (br s, 2H), 2.56 (d, J = 12.8 Hz, 2H), 2.30 (s, 3H), 2.21 (m, 2H), 1.96 (m, 2H), 1.50 (m, 2H), 1.13 (d, J = 6.4 Hz, 3H), 0.78 (t, J = 7.6 Hz, 3H). ^{13}C NMR (free base): δ 173.0, 132.6, 131.1, 130.3, 128.2, 125.3, 53.2, 48.2, 46.1, 33.5, 28.6, 19.2, 9.6. Anal. Calcd for $C_{17}H_{23}NO_2Cl_2$·HCl: C, 53.63; H, 6.35; N, 3.68. Found: C, 53.51; H, 6.27; N, 3.68.

4.8. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid pentyl ester (8f)

General procedure B. This compound was obtained ($CHCl_3$/CH_3OH, 19:1) as an orange oil (56 mg, 17% yield) and converted into a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 158–160 °C. ^{1}H NMR (free base): δ 7.30 (d, J = 2.8 Hz, 1H), 7.35 (d, J = 11.6 Hz, 1H), 7.18 (dd, J = 2.8, 11.4 Hz, 1H), 4.03 (t, J = 8.8 Hz, 2H), 2.76 (d, J = 14.4 Hz, 2H), 2.51 (d, J = 16.8 Hz, 2H), 2.24 (s, 3H), 2.13 (t, J = 15.2 Hz, 2H), 1.91 (t, J = 14 Hz, 2H), 1.52 (m, J = 9.2 Hz, 2H), 1.21 (m, 4H), 0.82 (t, J = 9.2 Hz, 3H). ^{13}C NMR (free base): δ 173.1, 142.4, 132.6, 131.3, 130.3, 128.1, 125.2, 65.4, 53.0, 48.1, 45.6, 33.0, 28.1, 28.0, 22.1, 13.9. Anal. Calcd for $C_{18}H_{25}NO_2Cl_2$· HCl·H_2O: C, 52.37; H, 6.84; N, 3.39. Found: C, 51.95; H, 6.52; N, 3.21.

4.9. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid 3-methyl-butyl ester (8g)

General procedure B. This compound was obtained as an orange oil (250 mg, 70% yield) and converted into a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 176–178 °C. ^{1}H NMR (free base): δ 7.47 (d, J = 2.8 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.22 (dd, J = 2.2 Hz, J = 8.6 Hz, 1H), 4.10 (t, J = 6.6 Hz, 2H), 2.76 (br s, 2H), 2.54 (d, J = 12.8 Hz, 2H), 2.26 (s, 3H), 2.13 (m, 2H), 1.93 (m, 2H), 1.45 (m, 2H), 0.90 (m, 1H), 0.86 (d, J = 8.6 Hz, 6H). ^{13}C NMR (free base): δ 173.6, 132.6, 131.2, 130.3, 128.3, 125.4, 63.8, 53.2, 48.3, 46.1, 37.1, 33.7, 25.0, 22.3. Anal. Calcd for $C_{18}H_{25}NO_2Cl_2$·HCl: C, 54.77; H, 6.64; N, 3.55. Found: C, 54.83; H, 6.65; N, 3.59.

4.10. 4-(3,4-Dichlorophenyl)-1-methyl-piperidine-4-carboxylic acid benzyl ester (8h)

A flask containing oven-dried 4 A molecular sieves (500 mg) was charged with IMesHCl (10 mol %), potassium *t*-butoxide (9.5 mol %), and THF (1 mL). The mixture was allowed to stir under an atmosphere of nitrogen for 15 min. The methyl ester (1 mmol) and benzyl alcohol (1.5 mmol) were dissolved in THF (0.5 mL) and added to the reaction mixture via cannula. The reaction was allowed to stir at room temperature and was monitored by TLC ($CHCl_3$/CH_3OH, 19:1). The mixture was filtered and the solvent was removed under reduced pressure. The crude product was purified using column chromatography ($CHCl_3$/CH_3OH, 19:1) and obtained as a pale yellow solid (97 mg, 51% yield). The base was converted into a hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 186–188 °C. ^{1}H NMR (free base): δ 7.43 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.30 (m, 3H), 7.19 (m, 2H), 7.18 (dd, J = 2.4, 8.4 Hz, 1H), 5.10 (s, 2H), 2.76 (d, J = 8.8 Hz, 2H), 2.56 (d, J = 12.4 Hz, 2H), 2.24 (s, 3H), 2.12 (t, J = 10.8 Hz, 2H), 1.95 (t, J = 10.8 Hz, 2H). ^{13}C NMR (free base): δ 173.3, 135.4, 132.7, 131.3, 130.4, 128.5, 128.3, 128.1, 125.4, 67.0, 53.1, 48.4, 46.1, 33.6. Anal. Calcd for $C_{20}H_{21}NO_2Cl_2$·HCl· 0.5H_2O: C, 56.68; H, 5.47; N, 3.31. Found: C, 56.54; H, 5.53; N, 3.29.

4.11. General procedure C. Reductive amination of 6 with alkylaryl amines

To a three-necked round-bottomed flask containing 3 N HCl (160 mL) at 50 °C was added the diacetal **6** (10 mmol) and the mixture was allowed to stir overnight. The acid mixture was allowed to cool to room temperature and then extracted with Et_2O (300 mL). The ethereal layer was washed with saturated $NaHCO_3$ (150 mL) and dried (Na_2SO_4). The Et_2O was removed under reduced pressure. The resulting residue was dissolved in dry methanol (52 mL), and then the alkylaryl amine hydrochloride (21 mmol) was added, followed by the addition of $NaBH_3CN$ (9.4 mmol), and the mixture was allowed to stir for 48 h under an atmosphere of nitrogen. The methanol was removed under reduced pressure and the residue was treated with saturated $NaHCO_3$ (160 mL) and extracted with Et_2O (3× 100 mL). The combined organic fractions were dried (Na_2SO_4) and the solvent was removed under reduced pressure. The residue was purified by chromatography ($CHCl_3$/CH_3OH, 39:1) to afford **9a**–**c**, respectively.

4.12. 1-Benzyl-4-(3,4-dichlorophenyl)-piperidine-4-carbonitrile (9a)

General procedure C. This compound was obtained as a yellow oil (2.0 g, 56% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 271–274 °C (dec.). ^{1}H NMR (free base): δ 7.59 (d, J = 2.0 Hz, 1H), 7.47 (d, J = 8.0 Hz, 1H), 7.36 (d, J = 2.4 Hz, 1H), 7.34 (m, 4H), 7.29 (t, J = 4.4 Hz, 1H), 3.61 (s, 2H), 3.02 (d, J = 10.8 Hz, 2H), 2.51 (s, 2H), 2.08 (s, 4H). ^{13}C NMR (free base): δ 140.4, 137.7, 133.1, 132.2, 130.8, 128.9, 128.2, 127.8, 127.2, 125.1, 121.1, 62.6, 50.3, 42.2, 36.3. Anal. Calcd for $C_{19}H_{18}N_2Cl_2$·HCl·0.5H_2O: C, 58.40; H, 5.16; N, 7.17. Found: C, 58.24; H, 4.94; N, 7.08.

4.13. 4-(3,4-Dichlorophenyl)-1-phenethyl-piperidine-4-carbonitrile (9b)

General procedure C. This compound was obtained ($CHCl_3$) as a white solid (320 mg, 32% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 244–250 °C (dec.). ^{1}H NMR (free base): δ 7.60 (d, J = 2.4 Hz, 1H), 7.47 (d, J = 8.4 Hz, 1H), 7.35 (dd, J = 2.4, 8.6 Hz, 1H), 7.30 (m, 2H), 7.21 (m, 1H), 3.11 (d, J = 12.8 Hz, 2H), 2.83 (m, 2H), 2.71 (m, 2H), 2.55 (m, 2H), 2.10 (d, J = 8.6 Hz, 2H), 2.08 (m, 2H). ^{13}C NMR (free base): δ

140.2, 139.8, 133.2, 132.4, 130.9, 128.5, 128.4, 127.8, 126.1, 125.0, 121.0, 60.0, 50.5, 42.3, 36.4, 33.6. Anal. Calcd for $C_{20}H_{20}N_2Cl_2$·HCl: C, 60.70; H, 5.35; N, 7.08. Found: C, 60.66; H, 5.45; N, 6.99.

4.14. 4-(3,4-Dichlorophenyl)-1-(3-phenyl-propyl)-piperidine-4-carbonitrile (9c)

General procedure C. This compound was obtained ($CHCl_3$) as an orange oil (370 mg, 36% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 230–234 °C (dec.). ^{1}H NMR (free base): δ 7.60 (d, J = 2.0 Hz, 1H), 7.48 (d, J = 8.8 Hz, 1H), 7.35 (dd, J 2.4, 8.8 Hz, 1H), 7.29 (m, 2H), 7.20 (m, 3H), 3.05 (d, J = 12.0 Hz, 1H), 2.66 (t, J = 7.6 Hz, 2H), 2.49 (t, J = 7.6 Hz, 2H), 2.45 (d, J = 7.6 Hz, 2H), 2.09 (d, J = 4.0 Hz, 4H), 1.87 (m, J = 8.0 Hz, 2H); ^{13}C NMR (free base): δ 141.8, 140.4, 133.1, 132.3, 130.8, 128.3, 128.3, 127.8, 125.8, 125.0, 121.1, 57.5, 50.4, 42.3, 36.4, 33.5, 28.5. Anal. Calcd for $C_{21}H_{22}N_2Cl_2$·HCl: C, 61.55; H, 5.66; N, 6.84. Found: C, 61.67; H, 5.64; N, 6.82.

4.15. 1-Benzyl-4-(3,4-dichlorophenyl)-piperidine-4-carboxylic acid ethyl ester (10a)

General procedure B. This compound was obtained as a pale yellow solid (1.2 g, 55% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 246–249 °C. ^{1}H NMR (free base): δ 7.47 (d, J = 2.0 Hz, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.28 (m, 3H), 7.23 (m, 2H), 7.21 (dd, J = 2.0, 8.6 Hz, 1H), 4.12 (m, J = 7.2 Hz, 2H), 3.46 (s, 2H), 2.80 (d, J = 11.6 Hz, 2H), 2.51 (d, J = 12.8 Hz, 2H), 2.17 (t, J = 11.6 Hz, 2H), 1.90 (t, J = 11.2 Hz, 2H), 1.17 (t, J = 6.8 Hz, 3H). ^{13}C NMR (free base): δ 173.5, 143.3, 138.2, 132.5, 131.0, 130.3, 129.0, 128.1, 127.0, 125.4, 63.0, 61.1, 51.1, 48.7, 33.7, 14.0. Anal. Calcd for $C_{21}H_{23}NO_2Cl_2$·HCl: C, 58.82; H, 5.64; N, 3.27. Found: C, 58.78; H, 5.67; N, 3.23.

4.16. 4-(3,4-Dichlorophenyl)-1-phenethyl-piperidine-4-carboxylic acid ethyl ester (10b)

General procedure B. This compound was obtained as a light yellow solid (180 g, 50% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 206–208 °C. ^{1}H NMR (free base): δ 7.48 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.27 (m, 2H), 7.23 (dd, J = 2.0, 8.6 Hz, 1H), 7.19 (m, 3H), 4.14 (m, J = 7.2 Hz, 2H), 2.92 (d, J = 11.2 Hz, 2H), 2.80 (m, 2H), 2.58 (m, 4H), 2.22 (t, J = 10.8 Hz, 2H), 1.94 (m, 2H), 1.19 (t, J = 6.8 Hz, 3H). ^{13}C NMR (free base): δ 173.5, 143.1, 140.2, 132.6, 131.1, 130.3, 128.6, 128.3, 128.2, 126.0, 125.4, 61.2, 60.5, 51.2, 48.8, 33.7, 14.0. Anal. Calcd for $C_{22}H_{25}NO_2Cl_2$·HCl: C, 59.67; H, 5.92; N, 3.16. Found: C, 59.76; H, 5.96; N, 3.17.

4.17. 4-(3,4-Dichlorophenyl)-1-(3-phenylpropyl)-piperidine-4-carboxylic acid ethyl ester (10c)

General procedure B. This compound was obtained as a light yellow oil (140 mg, 47% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 179–180 °C. ^{1}H NMR (free base): δ 7.47 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.4 Hz, 1H), 7.27 (m, 2H), 7.21 (dd, J = 2.4, 8.6 Hz, 1H), 7.17 (m, 3H), 4.12 (m, J = 7.2 Hz, 2H), 2.83 (d, J = 10.4 Hz, 2H), 2.62 (t, J = 7.6 Hz, 2H), 2.53 (d, J = 13.2 Hz, 2H), 2.34 (t, J = 7.2 Hz, 2H), 2.12 (t, J = 10.8 Hz, 2H), 1.91 (t, J = 10.8 Hz, 2H), 1.81 (m, J = 7.6 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR (free base): δ 173.5, 143.2, 142.0, 132.5, 131.0, 130.3, 128.3, 128.2, 128.2, 128.1, 125.7, 125.4, 61.1, 57.9, 51.2, 48.8, 33.7, 33.6, 28.6, 14.0. Anal. Calcd for $C_{23}H_{27}NO_2Cl_2$·HCl: C, 60.47; H, 6.18; N, 3.07. Found: C, 60.36; H, 6.14; N, 3.09.

4.18. General procedure D. N-Demethylation N-alkylation of 5

A solution of **5** (6.1 mmol), sodium bicarbonate (9.1 mmol) and 1-chloro-ethylchloroformate (52 mmol) in 1,2-dichloroethane (27 mL) was heated to reflux under an atmosphere of nitrogen for 48 h. The product was filtered to remove the sodium bicarbonate and the solvent was removed under reduced pressure. Methanol (155 mL) was added and the mixture was heated to reflux for 3 h. The solvent was removed under reduced pressure. Chloroform was added, washed with 1.8 N NaOH (30 mL) and water (30 mL), and then dried (Na_2SO_4). The crude product was purified by column chromatography (SiO_2, $CHCl_3$/CH_3OH, 12:1) to afford the normeperidine analogue. To the N–H compound (0.33 mmol) and potassium iodide (0.1 mol %) in triethylamine (140 μL/mmol) and ethanol (10 mL/mmol), the appropriate alkylbromide or alkylchloride (0.50 mmol) was added. The mixture was heated to reflux under an atmosphere of nitrogen for 16 h. The solvent was removed under reduced pressure and the crude products were purified by column chromatography to afford the products **10d**–**p**.

4.19. 4-(3,4-Dichlorophenyl)-1-(cinnamyl)-piperidine-4-carboxylic acid ethyl ester (10d)

General procedure D. This compound was obtained as an orange solid (39 mg, 38% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 217–219 °C (dec.). ^{1}H NMR (free base): δ 7.47 (d, J = 2.4 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.37 (d, J = 6.8 Hz, 2H), 7.30 (t, J = 7.2 Hz, 2H), 7.23 (m, 1H), 7.22 (dd, J = 2.4, 8.6 Hz, 1H), 6.51 (d, J = 16.0 Hz, 1H), 6.26 (tt, J = 6.8 15.6 Hz, 1H), 4.14 (q, J = 6.8 Hz, 2H), 3.13 (d, J = 6.8 Hz, 2H), 2.91 (d, J = 9.6 Hz, 2H), 2.55 (d, J = 12.8 Hz, 2H), 2.19 (t, J = 10.8 Hz, 2H), 1.94 (t, J = 10.8 Hz, 2H), 1.19 (t, J = 6.8 Hz, 3H). ^{13}C NMR (free base): δ 173.5, 143.1, 136.8, 133.1, 132.6, 131.1, 130.3, 128.5, 128.2, 127.5, 126.5, 126.3, 125.4, 95.4, 61.2, 61.1, 51.2, 48.7, 33.7, 14.0. Anal. Calcd for $C_{23}H_{25}NO_2Cl_2$·HCl: C, 60.74; H, 5.76; N, 3.08. Found: C, 60.61; H, 5.62; N, 3.05.

4.20. 4-(3,4-Dichlorophenyl)-1-(4-phenylbutyl)-piperidine-4-carboxylic acid ethyl ester (10e)

General procedure D. This compound was obtained as a yellow solid (97 mg, 67%) and converted into the hydro-

chloride salt (Section 4.1), which was obtained as a white solid, mp 148–150 °C (HCl salt). ^{1}H NMR (free base): δ 7.46 (d, J = 2.0 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.26 (m, 2H), 7.21 (dd, J = 2.4, 8.2 Hz, 1H), 7.16 (m, 3H), 4.12 (q, J = 7.2 Hz, 2H), 2.83 (d, J = 10.4 Hz, 2H), 2.62 (t, J = 6.8 Hz, 2H), 2.53 (d, J = 12.8 Hz, 2H), 2.33 (t, J = 7.2 Hz, 2H), 2.12 (t, J = 10.8 Hz, 2H), 1.92 (t, J = 10.4 Hz, 2H), 1.63 (m, J = 8.4 Hz, 2H), 1.53 (m, J = 6.8 Hz, 2H), 1.18 (t, J = 7.2 Hz, 3H). ^{13}C NMR (free base): δ 173.4, 143.1, 142.3, 132.5, 131.2, 130.3, 128.3, 128.2, 128.1, 125.6, 125.3, 61.1, 58.4, 51.2, 48.7, 35.7, 33.5, 29.7, 26.5, 14.0. Anal. Calcd for $C_{24}H_{29}NO_2Cl_2 \cdot HCl \cdot 0.5H_2O$: C, 60.64; H, 6.46; N, 2.95. Found: C, 60.95; H, 6.36; N, 2.92.

4.21. 4-(3,4-Dichlorophenyl)-1-(5-phenylpentyl)-piperidine-4-carboxylic acid ethyl ester (10f)

General procedure D. This compound was obtained as an orange oil (55 mg, 37% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 157–158 °C. ^{1}H NMR (free base): δ 7.46 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.27 (m, 2H), 7.22 (dd, J = 2.4, 8.4 Hz, 1H), 7.17 (m, 3H), 4.13 (q, J = 6.8 Hz, 2H), 2.84 (d, J = 10.0 Hz, 2H), 2.61 (t, J = 7.6 Hz, 2H), 2.54 (d, J = 12.8 Hz, 2H), 2.32 (t, J = 7.6 Hz, 2H), 2.14 (t, J = 9.6 Hz, 2H), 1.94 (t, J = 10.4 Hz, 2H), 1.64 (m, J = 7.2 Hz, 2H), 1.54 (m, J = 7.6 Hz, 2H), 1.34 (m, J = 7.6 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR (free base): δ 173.5, 143.2, 142.5, 132.5, 131.1, 130.3, 128.3, 128.2, 128.2, 125.6, 125.4, 61.1, 58.6, 51.2, 48.8, 35.8, 33.6, 31.3, 27.2, 26.8, 14.0. Anal. Calcd for $C_{25}H_{31}NO_2Cl_2 \cdot HCl$: C, 61.93; H, 6.65; N, 2.89. Found: C, 61.87; H, 6.65; N, 2.88.

4.22. 4-(3,4-Dichlorophenyl)-1-ethyl-piperidine-4-carboxylic acid ethyl ester (10g)

General procedure D. This compound was obtained ($CHCl_3/CH_3OH$, 19:1) as an off-white solid (95 mg, 87% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 203–205 °C. ^{1}H NMR (free base): δ 7.45 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.23 (dd, J = 2.0, 8.6 Hz, 1H), 4.16 (q, J = 6.8 Hz, 2H), 3.11 (br s, 2H), 2.65 (q, J = 7.2 Hz, 2H), 2.62 (d, J = 8.8 Hz, 2H), 2.41 (t, J = 11.2 Hz, 2H), 2.22 (t, J = 10.8 Hz, 2H), 1.24 (t, J = 7.2 Hz, 3H), 1.20 (t, J = 6.8 Hz, 3H). ^{13}C NMR (free base): δ 172.7, 141.8, 132.5, 131.3, 130.3, 127.8, 125.1, 61.4, 52.1, 50.1, 48.1, 32.0, 13.7, 10.7.

4.23. 1-(Prop-2-enyl)-4-(3,4-dichlorophenyl)-piperidine-4-carboxylic acid ethyl ester (10h)

General procedure D. This compound was obtained as an orange oil (136 mg, 60% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 217–220 °C (dec.). ^{1}H NMR (free base): δ 7.47 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 8.4 Hz, 1H), 7.23 (dd, J = 2.0, 8.4 Hz, 1H), 5.85 (m, 1H), 5.16 (d, J = 25.6, 1H), 5.16 (s, 1H), 4.14 (q, J = 6.8 Hz, 2H), 2.97 (d, J = 6.0 Hz, 2H), 2.85 (d, J = 9.6 Hz, 2H), 2.55 (d, J = 12.8 Hz, 2H), 2.14 (t, J = 11.2 Hz, 2H), 1.92 (t, J = 10.8 Hz, 2H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR (free base): δ 173.4, 143.2, 134.9, 132.5, 131.1, 130.3, 128.1, 125.3, 118.0, 61.7, 61.1, 51.0, 48.7, 33.6, 13.9. Anal. Calcd for $C_{17}H_{21}NO_2Cl_2 \cdot HCl$: C, 53.91; H, 5.86; N, 3.70. Found: C, 54.13; H, 5.85; N, 3.69.

4.24. 4-(3,4-Dichlorophenyl)-1-propyl-piperidine-4-carboxylic acid ethyl ester (10i)

To a slurry of 10% Pd/C (4 mg) in ethanol (3.1 mL) under an atmosphere of nitrogen was added a solution of the alkene **10h** (39 mg, 0.11 mmol) in ethanol (3.1 mL). The mixture was hydrogenated at 1 atm overnight. The catalyst was removed by filtration through a pad of Celite. The filter cake was rinsed with methanol (25 mL) and the filtrate was concentrated under reduced pressure. The crude product was purified using column chromatography ($CHCl_3/CH_3OH$, 13:1) to furnish **10i** as an orange oil (22 mg, 56% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 205–208 °C. ^{1}H NMR (free base): δ 7.47 (d, J = 1.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.22 (dd, J = 2.0, 8.8 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 2.90 (d, 10.0 Hz, 2H), 2.55 (d, J = 13.2 Hz, 2H), 2.31 (m, 2H), 2.18 (t, J = 11.2 Hz, 2H), 1.97 (t, J = 10.8 Hz, 2H), 1.53 (m, J = 7.2 Hz, 2H), 1.20 (t, J = 6.8 Hz, 3H), 0.90 (t, J = 7.6 Hz, 3H). ^{13}C NMR (free base): δ 173.5, 143.0, 132.6, 131.2, 130.4, 128.2, 125.4, 61.2, 60.5, 51.1, 48.7, 33.4, 19.9, 14.0, 11.9. Anal. Calcd for $C_{17}H_{23}NO_2Cl_2 \cdot HCl$: C, 53.63; H, 6.35; N, 3.68. Found: C, 53.45; H, 6.28; N, 3.62.

4.25. 4-(3,4-Dichlorophenyl)-1-prop-2-ynyl-piperidine-4-carboxylic acid ethyl ester (10j)

General procedure D. This compound was obtained as a yellow solid (104 mg, 90% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 193–195 °C (dec.). ^{1}H NMR (free base): δ 7.46 (d, J = 1.6 Hz, 1H), 7.38 (d, J = 8.4 Hz, 1H), 7.21 (dd, J = 2.0, 8.6 Hz, 1H), 4.14 (q, J = 6.8 Hz, 2H), 3.27 (d, J = 2.4 Hz, 2H), 2.85 (d, J = 11.2 Hz, 2H), 2.57 (d, J = 12.4 Hz, 2H), 2.37 (t, J = 12.0, 2H), 2.23 (t, J = 2.4 Hz, 1H), 1.92 (t, J = 10.4 Hz, 2H), 1.19 (t, J = 6.8 Hz, 3H). ^{13}C NMR (free base): δ 173.3, 143.1, 132.6, 131.2, 130.4, 128.1, 125.3, 78.7, 73.1, 61.2, 50.0, 48.4, 46.9, 33.6, 14.0. Anal. Calcd for $C_{17}H_{19}NO_2Cl_2 \cdot HCl$: C, 54.20; H, 5.35; N, 3.72. Found: C, 54.17; H, 5.29; N, 3.69.

4.26. 1-Cyclopropylmethyl-4-(3,4-dichlorophenyl)-piperidine-4-carboxylic acid ethyl ester (10k)

General procedure D. This compound was obtained as a yellow solid (96 mg, 81% yield by NMR) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 199–201 °C (dec.). ^{1}H NMR (free base): δ 7.47 (d, J = 2.0 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.23 (dd, J = 2.4, 8.6 Hz, 1H), 4.14 (q, J = 7.2 Hz, 2H), 3.05 (br s, 2H), 2.57 (d, J = 12.4 Hz, 2H), 2.29 (d, J = 6.8 Hz, 2H), 2.23 (t, J = 11.2 Hz, 2H), 2.02 (t, J = 10.8 Hz, 2H), 1.20 (t, J = 6.8 Hz, 3H),

0.90 (m, 1H), 0.54 (m, 2H), 0.13 (m, 2H). ^{13}C NMR (free base): δ 173.5, 143.0, 132.6, 131.2, 130.4, 128.1, 125.3, 63.6, 61.2, 51.1, 48.7, 33.3, 14.0, 8.1, 4.0 (2C). Anal. Calcd for $C_{18}H_{23}NO_2Cl_2 \cdot HCl \cdot 1/4H_2O$: C, 54.42; H, 6.22; N, 3.53. Found: C, 54.12; H, 6.03; N, 3.51.

4.27. 4-(3,4-Dichlorophenyl)-1-(3-fluoropropyl)-piperidine-4-carboxylic acid ethyl ester (10l)

General procedure D. This compound was obtained as an orange/brown solid (95 mg, 79% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 209–211 °C. ^{1}H NMR (free base): δ 7.47 (d, J = 2.0 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.22 (dd, J = 2.0, 8.4 Hz, 1H), 4.50 (dt, J_{C-F} = 47.6 Hz, J = 6.0 Hz, 2H), 4.14 (q, J = 7.6 Hz, 2H), 2.85 (d, 10.8 Hz, 2H), 2.55 (d, J = 13.2 Hz, 2H), 2.47 (t, J = 7.6 Hz, 2H), 2.18 (t, J = 11.2 Hz, 2H), 1.90 (m, 4H), 1.20 (t, J = 7.6 Hz, 3H). ^{13}C NMR (free base): δ 173.4, 143.1, 132.5, 131.0, 130.3, 128.1, 125.3, 82.3 (J_{C-F} = 652 Hz), 61.1, 54.2, 54.1, 51.1, 48.6, 33.5, 28.0, 27.8, 13.9. Anal. Calcd for $C_{17}H_{22}NO_2Cl_2F \cdot HCl \cdot 0.5H_2O$: C, 50.64; H, 5.87; N, 3.47. Found: C, 50.62; H, 5.84; N, 3.44.

4.28. 4-(3,4-Dichlorophenyl)-1-(3-hydroxypropyl)-piperidine-4-carboxylic acid ethyl ester (10m)

General procedure D. This compound was obtained as a yellow oil (120 mg, 79%) and was converted into the hydrochloride salt (Section 4.1), which was obtained as an orange solid, mp 184–186 °C. ^{1}H NMR (free base): δ 7.45 (d, J = 2.4 Hz, 1H), 7.40 (d, J = 8.4 Hz, 1H), 7.21 (dd, J = 2.4, 8.8 Hz, 1H), 4.36 (s, 1H), 4.14 (q, J = 6.8 Hz, 2H), 3.81 (t, J = 5.2 Hz, 2H), 3.06 (br s, 2H), 2.67 (t, J = 6.0 Hz, 2H), 2.57 (d, J = 13.2 Hz, 2H), 2.27 (m, 2H), 1.95 (t, J = 9.2 Hz, 2H), 1.77 (m, J = 7.2 Hz, 2H), 1.19 (t, J = 6.8 Hz, 3H). ^{13}C NMR (free base): δ 173.2, 142.7, 132.7, 131.4, 130.5, 128.1, 125.3, 64.0, 61.4, 58.6, 51.3, 48.6, 33.3, 27.0, 14.0. Anal. Calcd for $C_{17}H_{23}NO_3Cl_2 \cdot HCl$: C, 51.47; H, 6.10; N, 3.53. Found: C, 51.31; H, 6.15; N, 3.56.

4.29. 1-(3-Chloropropyl)-4-(3,4-dichlorophenyl)-piperidine-4-carboxylic acid ethyl ester (10n)

The alcohol **10m** (150 mg, 0.42 mmol) was dissolved in CH_2Cl_2 (3.2 mL) and cooled to 0 °C under an atmosphere of nitrogen. Methanesulfonyl chloride (30 μL, 0.44 mmol) was added, followed by the addition of triethylamine (90 μL, 0.62 mmol). The reaction mixture was allowed to stir for 2 h. The mixture was then allowed to warm to room temperature and stirred for an additional 48 h. The crude product was purified using column chromatography ($CHCl_3/CH_3OH$, 13:1) to afford a yellow oil (97 mg, 61%). This compound was converted to the hydrochloride salt to afford a white solid, mp 205–207 °C. ^{1}H NMR (free base): δ 7.47 (d, J = 1.6 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.22 (dd, J = 2.0, 8.4 Hz, 1H), 4.13 (q, J = 7.6 Hz, 2H), 3.59 (t, J = 6.4 Hz, 2H), 2.81 (d, J = 11.2 Hz, 2H), 2.53 (d, J = 12.8 Hz, 2H), 2.45 (t, J = 6.8 Hz, 2H), 2.16 (t, J = 11.2 Hz, 2H), 1.92 (m, 4H), 1.19 (t, J = 7.2 Hz, 3H). ^{13}C NMR (free base): δ 173.5, 143.2, 132.6, 131.1, 130.3, 128.2, 125.4, 95.4, 61.1, 55.4, 51.3, 48.7, 43.1, 33.7, 30.0, 14.0. Anal. Calcd for $C_{17}H_{22}NO_2Cl_3 \cdot HCl$: C, 49.18; H, 5.58; N, 3.37. Found: C, 49.21; H, 5.56; N, 3.35.

4.30. 4-(3,4-Dichlorophenyl)-1-[(3-tri-*n*-butylstannanyl)-prop-(2*E*)-enyl]-piperidine-4-carboxylic acid ethyl ester (10o)

General procedure D with 3-(tri-*n*-butylstannyl)prop-(2*E*)-enyl chloride.[15,26] This compound was obtained (SiO_2, $CHCl_3$) as a yellow oil (85 mg, 54% yield). ^{1}H NMR: δ 7.48 (d, J = 2.4 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 7.22 (dd, J = 2.4, 8.6 Hz, 1H), 6.11 (d, J = 19.2 Hz, 1H), 5.99 (dt, J = 18.8, 6.0 Hz, 1H), 4.13 (q, J = 6.8 Hz, 2H), 3.03 (d, J = 5.6 Hz, 2H), 2.85 (d, J = 8.8 Hz, 2H), 2.55 (d, J = 13.2 Hz, 2H), 2.12 (t, J = 10.8 Hz, 2H), 1.93 (t, J = 11.2 Hz, 2H), 1.50 (m, 6H), 1.30 (m, 6H), 1.19 (t, J = 7.2 Hz, 3H), 0.910–0.866 (m, 15H). ^{13}C NMR: δ 173.5, 145.0, 143.2, 132.6, 132.3, 131.1, 130.3, 128.2, 125.3, 65.5, 61.1, 51.0, 48.7, 33.7, 29.0, 27.2, 13.9, 13.6, 9.4.

4.31. 4-(3,4-Dichlorophenyl)-1-[(3-tri-*n*-butylstannanyl)prop-(2*E*)-enyl]-piperidine-4-carboxylic acid ethyl ester (10p)

The stannyl derivative **10o** (60 mg, 0.10 mmol) was dissolved in $CHCl_3$ (0.6 mL) and the resulting mixture was cooled to 0 °C. A solution of iodine in $CHCl_3$ (0.1 N) was then added dropwise to the stirred mixture until a color change resulted. The solution was allowed to come to room temperature and stirred for an additional 4 h. The reaction mixture was washed with brine (5 mL) and dried (Na_2SO_4). The solvent was removed under reduced pressure and the crude product was purified by column chromatography (Et_2O/hexanes, 1:1) to give the product as a yellow oil (21 mg, 44% yield). This compound was converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 219–221 °C (dec.). ^{1}H NMR (free base): δ 7.46 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 8.8 Hz, 1H), 7.21 (dd, J = 2.8, 8.4 Hz, 1H), 6.57 (dt, J = 6.8, 14.8 Hz, 1H), 6.25 (d, J = 14.4 Hz, 1H), 4.13 (q, J = 6.8 Hz, 2H), 2.93 (dd, J = 1.6, 6.8 Hz, 2H), 2.81 (d, J = 11.2 Hz, 2H), 2.54 (d, J = 13.2 Hz, 2H), 2.15 (t, J = 11.2 Hz, 2H), 1.90 (m, 2H), 1.19 (t, J = 7.6 Hz, 3H). ^{13}C NMR (free base): δ 173.4, 142.8, 132.7, 131.2, 130.4, 128.2, 125.3, 78.6, 62.7, 61.2, 50.9, 48.6, 33.6, 14.0. Anal. Calcd for $C_{17}H_{20}NO_2Cl_2I \cdot HCl$: C, 40.26; H, 4.19; N, 2.78. Found: C, 40.42; H, 4.18; N, 2.75.

4.32. 1-[4-(3,4-Dichlorophenyl)-1-methyl-piperidin-4-yl]-ethanone (11)

To a solution of methyl magnesium bromide (0.37 mL, 1.1 mmol) in dry ether (0.21 mL) stirring under an atmosphere of nitrogen at 0 °C was added a solution of the ester **5** (120 mg, 0.37 mmol) in dry ether that had been cooled to 0 °C under an atmosphere of nitrogen. The mixture was allowed to stir for 20 min, and then allowed to return to room temperature and continue to stir overnight. Wet ether was added to the solution, followed by a deionized

water wash. The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by chromatography ($CHCl_3/CH_3OH$, 12:1) to give a yellow oil (68 mg, 65% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 254–256 °C (dec.). ^{1}H NMR (free base): δ 7.43 (d, J = 8.4 Hz, 1H), 7.40 (d, J = 2.4 Hz, 1H), 7.15 (dd, J = 2.4, 8.4 Hz, 1H), 2.66 (br s, 2H), 2.45 (d, J = 12.8 Hz, 2H), 2.25 (s, 3H), 2.21 (t, J = 10.8 Hz, 2H), 1.95 (s, 3H). ^{13}C NMR (free base): δ 208.1, 141.9, 133.0, 131.3, 130.7, 128.4, 125.7, 53.7, 52.6, 46.0, 32.7, 25.6. Anal. Calcd for $C_{14}H_{17}NOCl_2 \cdot HCl \cdot 3H_2O$: C, 44.64; H, 6.15; N, 3.72. Found: C, 44.94; H, 5.78; N, 3.68.

4.33. 4-(3,4-Dichlorophenyl)-1-methyl-piperidin-4-yl]-phenylmethanone (12)

To a stirred solution of phenyl magnesium bromide (0.39 mL, 1.2 mmol) in dry ether (0.19 mL) under an atmosphere of nitrogen at 0 °C was added a solution of the nitrile **7** (160 mg, 0.59 mmol) in dry ether that had been cooled to 0 °C under an atmosphere of nitrogen. The mixture was allowed to stir for 20 min, and then allowed to return to room temperature and stirred overnight. Wet ether was added to the solution, followed by a deionized water wash. The organic layer was dried (Na_2SO_4), and the solvent was removed under reduced pressure. The residue was purified by chromatography ($CHCl_3/CH_3OH$, 24:1) to give a yellow oil (114 mg, 56% yield). This compound was converted to the hydrochloride salt (Section 4.1), which was obtained as a white solid mp 244–246 °C (dec.). ^{1}H NMR (free base, 300 MHz): δ 7.51 (d, J = 2.1 Hz, 1H), 7.46 (d, J = 8.4 Hz, 1H), 7.44–7.22 (m, 5H), 7.25 (dd, J = 2.1, 8.6 Hz, 1H), 2.72 (m, 2H), 2.55 (m, J = 2.7, 8.9 Hz, 2H), 2.25 (s, 3H), 2.15–2.07 (m, 4H). ^{13}C NMR (free base): δ 203.0, 143.5, 137.4, 133.4, 131.7, 131.5, 131.0, 128.7, 128.3, 128.2, 125.6, 52.9, 52.8, 46.0, 35.1. Anal. Calcd for $C_{19}H_{19}NOCl_2 \cdot HCl \cdot 1/2H_2O$: C, 57.95; H, 5.38; N, 3.55. Found: C, 57.98; H, 5.34; N, 3.47.

4.34. 1-[4-(3,4-Dichlorophenyl)-1-methyl-piperidin-4-yl]-ethanol (13)

To a stirred solution of the ketone **8** (100 mg, 0.35 mmol) in methanol (1.7 mL) was added sodium borohydride (13 mg, 0.35 mmol). The mixture was stirred at room temperature under an atmosphere of nitrogen for 2 h. The solvent was removed under reduced pressure, and water was added to the resulting residue, followed by extraction with Et_2O (3× 5 mL), and the organic extracts were dried (Na_2SO_4). The crude product was purified using chromatography ($CHCl_3/CH_3OH$, 13:1) to give an off-white solid (80 mg, 80% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 185–187 °C. ^{1}H NMR (free base): δ 7.44 (d, J = 8.4 Hz, 1H), 7.42 (d, J = 2.4 Hz, 1H), 7.18 (dd, J = 2.4, 8.4 Hz, 1H), 3.70 (m, J = 6.8 Hz, 1H), 2.86 (d, J = 7.6 Hz, 2H), 2.45 (m, 1H), 2.28 (s, 3H), 2.15 (m, 2H), 2.05 (m, 4H), 0.925 (d, J = 6.4 Hz, 3H). ^{13}C NMR (free base): δ 140.6, 132.6, 130.7, 130.6, 130.1, 128.1, 55.6, 51.7, 51.5, 45.4, 44.7, 31.3, 30.9, 18.0. Anal. Calcd for $C_{14}H_{18}NOCl_2 \cdot HCl \cdot 0.5H_2O$: C, 50.54; H, 6.06; N, 4.21. Found: C, 50.35; H, 6.32; N, 4.26.

4.35. 4-(3,4-Dichlorophenyl)-1-methyl-piperidin-4-yl-methanol (14)

To a suspension of $LiAlH_4$ (250 mg, 6.5 mmol) in dry Et_2O (33 mL) under an atmosphere of nitrogen was added a solution of the ethyl ester **5** (1.0 g, 3.3 mmol) in dry Et_2O (33 mL). The reaction mixture was stirred at room temperature for 3 h. Wet ether (33 mL) and 1 M NaOH (0.2 mL) were added slowly. A white precipitate began to form and the mixture was allowed to stir for 1 h. The resulting suspension was filtered through Celite washing with Et_2O and EtOAc. The filtrate was filtered and dried to give a white solid (740 mg, 83% yield). This compound was converted to the hydrochloride salt (Section 4.1) to afford a white solid, mp 224–226 °C. ^{1}H NMR (free base): δ 7.44 (d, J = 10 Hz, 1H), 7.43 (d, J = 0.4 Hz, 1H), 7.19 (dd, J = 2.4, 8.6 Hz, 1H), 3.57 (s, 2H), 2.58 (m, 2H), 2.18 (s, 3H), 2.12 (t, J = 14.0 Hz, 2H), 1.96 (m, 2H), 1.81 (s, 2H). ^{13}C NMR (free base): δ 144.0, 132.5, 130.3, 130.2, 129.6, 126.8, 71.1, 51.5, 45.9, 41.5, 31.4. Anal. Calcd for $C_{13}H_{17}NOCl_2 \cdot HCl$: C, 50.26; H, 5.84; N, 4.51. Found: C, 50.01; H, 5.83; N, 4.46.

4.36. Acetic acid 4-(3,4-dichlorophenyl)-1-methyl-piperidin-4-yl methyl ester (15)

The alcohol **14** (190 mg, 0.700 mmol) was dried under vacuum and 4-(dimethylamino) pyridine (9 mg, 0.0697 mmol) was added to the flask and flushed with nitrogen. Dry CH_2Cl_2 (12 mL), fresh triethylamine (370 μL, 2.7 mmol), and acetyl chloride (70 μL, 1.04 mmol) were added dropwise at 0 °C. The mixture was allowed to stir on ice for 30 min, and then overnight at room temperature. To the mixture 1 N NaOH was added dropwise to adjust the pH to 10–11, followed by the addition of deionized water (10 mL). The mixture was extracted with CH_2Cl_2 (3× 15 mL) and the organic layers were dried (Na_2SO_4). The crude product was purified using chromatography ($CHCl_3/CH_3OH$, 13:1) to give a white solid (140 mg, 65% yield). This compound was converted into the hydrochloride salt (Section 4.1) to afford a white foam. ^{1}H NMR (free base): δ 7.43 (d, J = 2.4 Hz, 1H), 7.41 (d, J = 6.0 Hz, 1H), 7.18 (dd, J = 3.2, 11.4 Hz, 1H), 4.03 (s, 2H), 2.60 (m, 2H), 2.24 (s, 3H), 2.17 (m, 4H), 1.97 (m, 2H), 1.97 (s, 3H). ^{13}C NMR (free base): δ 170.5, 143.3, 132.4, 130.4, 130.2, 129.4, 126.5, 71.2, 51.4, 46.0, 39.6, 32.0, 20.7. Anal. Calcd for $C_{15}H_{19}NO_2Cl_2 \cdot HCl \cdot 1.5H_2O$: C, 47.44; H, 6.11; N, 3.69. Found: C, 47.11; H, 5.72; N, 3.35.

4.37. 4-(3,4-Dichlorophenyl)-1-methyl-4-vinyl-piperidine (16)

To a two-necked round-bottom-flask under an atmosphere of nitrogen was added a solution of oxalyl chloride (280 μL, 3.2 mmol) in dichloromethane (4.9 mL). The solution was cooled to −78 °C. A solution of dimethylsulfoxide (450 μL, 6.3 mmol) in dichlorometh-

ane (0.58 mL) was then added dropwise for over 5 min. The temperature rose to −70 °C and was allowed to continue to rise to −60 °C for over 10 min. The alcohol **14** (580 mg, 2.10 mmol) was dissolved in dichloromethane (3.5 mL) and added dropwise to the reaction mixture for over a 10 min period. The temperature rose to −55 °C and was allowed to continue to rise to −45 °C at which time diisopropylethyl amine (2.1 mL, 12 mmol) dissolved in dichloromethane (0.29 mL) was added and the solution was allowed to warm to 0 °C. The reaction mixture was added to ice-cold 1 M HCl and extracted with dichloromethane (3× 5 mL). The combined organic layers were washed with a pH 7 aqueous phosphate buffer (3× 5 mL) and dried over Na_2SO_4. The solvent was concentrated under reduced pressure and the crude product was purified by chromatography ($CHCl_3$/CH_3OH, 40:1) to give the aldehyde as a yellow oil (330 mg, 57% yield). ^{1}H NMR: δ 9.37 (s, 1H), 7.45 (d, J = 8.4 Hz, 1H), 7.38 (d, J = 2.4 Hz, 1H), 7.13 (dd, J = 2.0, 8.6, Hz, 1H), 2.72 (d, J = 11.2 Hz, 2H), 2.43 (d, J = 13.6 Hz, 2H), 2.27 (s, 3H), 2.20 (t, J = 2.2, 2H), 2.05 (m, 2H). A solution of 1.6 M *n*-butyl lithium (2.0 mL, 3.2 mmol) dissolved in THF (5.5 mL) was cooled to 0 °C with stirring under nitrogen. Methyl triphenyl phosphonium bromide (1.1 g, 3.2 mmol) was slowly added to the mixture. The resulting orange mixture was allowed to stir at 0 °C for 30 min and became milky in consistency. The reaction mixture was removed from the ice and the aldehyde (290 mg, 1.1 mmol) dissolved in THF (1.2 mL) was added and allowed to stir overnight at room temperature. The mixture was diluted with ethyl acetate (10 mL) and washed with saturated ammonium chloride (2× 15 mL). The organic phase was extracted with 10% HCl (3× 5 mL). The combined aqueous layers were washed with EtOAc (15 mL), neutralized with saturated $NaHCO_3$, and extracted with CH_2Cl_2 (3× 15 mL). The combined organic layers were dried over Na_2SO_4 and the solvent was removed under reduced pressure. The mixture was purified by chromatography ($CHCl_3$/CH_3OH, 13:1) to give a yellow oil (130 mg, 44% yield) and converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 211–214 °C (dec.). ^{1}H NMR (free base): δ 7.40 (d, J = 2.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 7.16 (dd, J = 2.0, 8.4 Hz, 1H), 5.77 (dd, J = 10.8, 17.6 Hz, 1H), 5.17 (d, J = 10.4 Hz, 1H), 4.91 (d, J = 17.6 Hz, 1H), 2.46 (br s, 4H), 2.25 (s, 3H), 2.13 (m, 2H), 2.01 (dt, J = 4.4, 14.0 Hz, 2H). ^{13}C NMR (free base): δ 146.8, 144.9, 132.3, 130.1, 129.9, 129.1, 126.3, 114.7, 51.9, 46.1, 42.3, 35.2. Anal. Calcd for $C_{14}H_{17}NCl_2 \cdot HCl \cdot 1.5H_2O$: C, 54.04; H, 5.99; N, 4.50. Found: C, 54.15; H, 5.94; N, 4.47.

4.38. 4-(3,4-Dichlorophenyl)-4-ethyl-1-methyl-piperidine (17)

To a slurry of 10% Pd/C (10 mg) in methanol (10 mL) under an atmosphere of nitrogen was added a solution of the alkene **16** (100 mg, 0.37 mmol) in methanol (10 mL). The mixture was hydrogenated at 1 atm overnight. The catalyst was removed by filtration through a pad of Celite. The filter cake was rinsed with methanol (30 mL) and the filtrate was concentrated under reduced pressure to give the product in sufficient purity as an orange oil (71 mg, 81% yield). This compound was converted into the hydrochloride salt (Section 4.1), which was obtained as a white solid, mp 200–204 °C (dec.). ^{1}H NMR (free base): δ 7.38 (d, J = 8.4 Hz, 1H), 7.34 (d, J = 2.0 Hz, 1H), 7.10 (dd, J = 2.0, 8.6 Hz, 1H), 2.55 (br s, 2H), 2.22 (s, 3H), 2.19–2.10 (m, 4H), 1.81 (m, 2H), 1.57 (q, J = 7.6 Hz, 2H), 0.563 (t, J = 7.6 Hz, 3H). ^{13}C NMR (free base): δ 146.3, 132.2, 130.0, 129.4, 129.2, 126.5, 51.8, 45.9, 39.2, 34.7, 29.6, 7.67. Anal. Calcd for $C_{14}H_{19}NCl_2 \cdot HCl$: C, 54.48; H, 6.53; N, 4.54. Found: C, 54.45; H, 6.47; N, 4.55.

4.39. [^{3}H]WIN 35,428 binding assay

Male Sprague–Dawley rats (200–250 g, Taconic, Germantown, NY) were decapitated and their brains were removed to an ice-cooled dish for dissection of the caudate putamen. The tissue was homogenized in 30 volumes of ice-cold modified Krebs–HEPES buffer (15 mM HEPES, 127 mM NaCl, 5 mM KCl, 1.2 mM $MgSO_4$, 2.5 mM $CaCl_2$, 1.3 mM NaH_2PO_4, and 10 mM glucose, pH adjusted to 7.4) using a Teflon/glass homogenizer and centrifuged at 20,000*g* for 10 min at 4 °C. The resulting pellet was then washed two more times by resuspension in ice-cold buffer and centrifugation at 20,000*g* for 10 min at 4 °C. Fresh homogenates were used in all experiments. Binding assays were conducted in modified Krebs–HEPES buffer on ice, essentially as previously described.[27] The total volume in each tube was 0.5 mL and the final concentration of membrane after all additions was approximately 0.3% (w/v) corresponding to 150–300 μg protein/sample. Increasing concentrations of the drug being tested were added to triplicate samples of the membrane suspension. Five minutes later, [^{3}H]WIN 35,428 (final concentration of 1.5 nM) was added and the incubation was continued for 1 h on ice. The incubation was terminated by the addition of 3 mL ice-cold buffer and rapid filtration through Whatman GF/B glass fiber filter paper (presoaked in 0.1% BSA in water to reduce non-specific binding) using a Brandel Cell Harvester (Gaithersburg, MD). After filtration, the filters were washed with three additional 3 mL washes and transferred to scintillation vials. Absolute ethanol (0.5 mL) and Beckman Ready Value Scintillation Cocktail (2.75 mL) were added to the vials, which were counted the next day at an efficiency of about 36%. Under these assay conditions, an average experiment yielded approximately 6000 dpm total binding per sample and approximately 250 dpm non-specific binding. Non-specific binding was defined as binding in the presence of 100 μM cocaine. K_i values were derived from 14 point competition assays using increasing concentrations of unlabeled compounds (0.05 nM to 100 μM) against 1.5 nM [^{3}H]WIN 35,428. Data were analyzed with GraphPad Prism software (San Diego, California).

4.40. [^{3}H]Paroxeting binding assay

Brains from male Sprague–Dawley rats weighing 200–225 g (Taconic Labs) were removed, and midbrain was dissected and rapidly frozen. Membranes were

prepared by homogenizing tissues in 20 volumes (w/v) of 50 mM Tris containing 120 mM NaCl and 5 mM KCl (pH7.4 at 25 °C), using a Brinkman Polytron (setting 6 for 20 s), and centrifuged at 50,000*g* for 10 min at 4 °C. The resulting pellet was resuspended in buffer, recentrifuged, and resuspended in buffer to a concentration of 15 mg/ml. Ligand-binding experiments were conducted in assay tubes containing 4.0 ml buffer for 90 min at room temperature. Each tube contained 0.2 nM [^{3}H]paroxetine (NEN) and 1.5 mg midbrain tissue (original wet weight). Non-specific binding was determined using 1 μM citalopram. Incubations were terminated by rapid filtration through Whatman GF/B filters, presoaked in 0.05% polyethylenimine, using a Brandel R48 filtering manifold (Brandel Instruments, Gaithersburg, Maryland). The filters were washed twice with 5 ml cold buffer and transferred to scintillation vials. Beckman Ready Safe (3.0 ml) was added and the vials were counted the next day using a Beckman 6000 liquid scintillation counter (Beckman Coulter Instruments, Fullerton, California). Data were analyzed by using GraphPad Prism software (San Diego, California).

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