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Synthesis and structure–activity studies of benzyl ester meperidine and normeperidine derivatives as selective serotonin transporter ligands

Xiaobo Gu [a], Sari Izenwasser [b], Dean Wade [b], Amy Housman [b], Gerard Gulasey [b], Jill B. Rhoden [a], Christopher D. Savoie [a], David L. Mobley [a], Stacey A. Lomenzo [a], Mark L. Trudell [a,*]

[a] Department of Chemistry, University of New Orleans, New Orleans, LA 70148, USA
[b] Department of Psychiatry and Behavioral Sciences, University of Miami Miller School of Medicine, Miami, FL 33136, USA

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ABSTRACT

A series of benzyl esters of meperidine and normeperidine were synthesized and evaluated for binding affinity at serotonin, dopamine and norepinephrine transporters. The 4-methoxybenzyl ester **8b** and 4-nitrobenzyl ester **8c** in the meperidine series and 4-methoxybenzyl ester **14a** in the normeperidine series exhibited low nanomolar binding affinities at the SERT (K_i values <2 nM) and high SERT selectivity (DAT/SERT >1500 and NET/SERT >1500).

1. Introduction

The serotonin transporter has been a therapeutic target for depression and anxiety for several decades.[1–3] Selective serotonin reuptake inhibitors (SSRIs, e.g., citalopram, fluoxetine and paroxetine) have widely been prescribed for patients suffering from this common psychiatric disorder (Fig. 1). However, despite the success of these drugs they suffer from significant side effects and thus there remains a need for new medications.[4] Within the past decade, the rationale for the development of new pharmacotherapies has expanded to target molecules that exhibit potent serontonin reuptake inhibition as well as to affect the function of other monoamine transporters or serotonin receptors. This approach has led to the development of dual serotonin/norepinephrine reuptake inhibitors (SNRIs, e.g., venlafaxine and duloxetine).[5,6] These dual inhibitors have been accepted as more efficacious than SSRIs for the treatment of depression with reduced side effects.[7,8]

More recently, pharmacological evidence suggests that triple monoamine uptake inhibitors (TUIs), targeting dopamine transporters (DAT) as well as serotonin transporters (SERT) and norepinephrine transporters (NET) may be even more efficacious and exhibit improved safety profiles as antidepressants.[9] The prototypical TUI, DOV 216,303 was found to be both safe and effective in

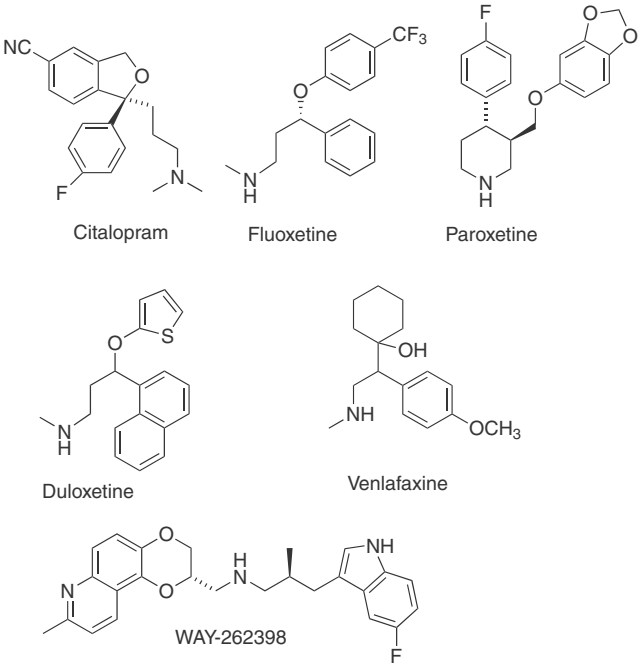

Figure 1. SSRIs, SNRIs TUIs and SSRI/5-HT_{1A} antagonsits.

* Corresponding author. Tel.: +1 504 280 7337; fax: +1 504 280 6860.
E-mail addresses: mtrudell@uno.edu, MLTCM@jazz.ucc.uno.edu (M.L. Trudell).

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Phase II clinical studies on depression, however, recently has been dropped from further development due to concerns about the patent lifetime.[10,11] While a balanced profile of inhibition at the three monoamine transporters has been suggested as desirable for the development of new antideressant therapeutics, compounds that inhibit serotonin reuptake as well as block 5-HT_{1A} autoreceptors,[12] which inhibit serotonergic neuronal firing in the presence of serotonin (5-HT_{1A} antagonism) have also been the focus of numerous studies.[3,13–17] It is believed that dual SSRI/5-HT_{1A} antagonists (e.g., WAY-262398)[18] may lead to medications with improved therapeutic utility. Despite these advances in depression/anxiety therapy, SSRIs remain among the most widely prescribed drugs for the treatment of depression and anxiety related disorders. Moreover, the modulation of the serotonin transporter remains an important focus in the development of new medications targeting depression.[19]

Our efforts to develop novel molecular scaffolds targeting monoamine transporter systems have led to the development of several classes of selective DAT ligands and selective SERT ligands.[20–23] Previously, we have reported on a series of derivatives of meperidine (**1**) that exhibited modest potency and selectivity for the SERT (Fig. 2).[21,22] However, unlike the prototypical SSRIs fluoxetine and paroxetine, the meperidine analogues **2** lack a secondary amine and two aromatic moieties common to the SERT pharmacophore.[24,25] In light of these deficiencies it was of interest to examine this class of meperidine-based SERT ligands to determine if SERT potency could be improved and the monoamine transporter selectivity influenced by the addition of a second strategically placed aryl ring system. To this end, we envisaged a series of benzyl ester normeperidine derivatives **3** that would be similar to the SERT pharmacophore. As illustrated in Figure 3, the alignment of predicted favorable solvated conformers of benzyl normeperidine **3**, fluoxetine and paroxetine suggested that appropriately substituted normeperidine benzyl esters should exhibit high affinity for the SERT.[26] A normeperidine benzyl ester **3** that exhibited potent

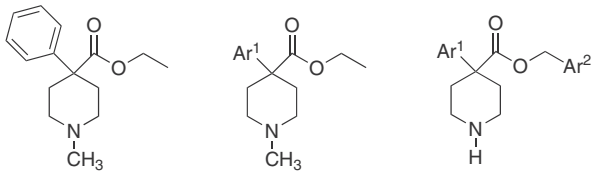


Figure 2. Meperidine derivatives

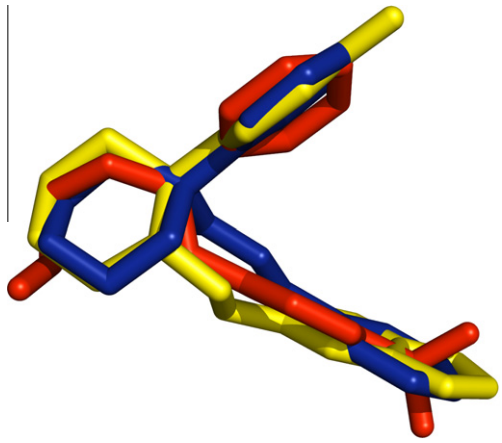


Figure 3. Superimposed predicted favorable solvated conformers of **3** (blue), fluoxetine (red) and paroxetine (yellow).

SERT affinity could then be evaluated at other monoamine transporters or serotonin receptors to determine the potential focus for medication development (e.g., SSRI, TUI, duel SSRI/5-HT_{1A} antagonists). Herein we report the synthesis and monoamine transporter affinity of novel benzyl ester meperidine and normeperidine derivatives.

2. Chemistry

Based upon previous structure–activity studies of meperidine analogues,[21] we focused on four 4-aryl (Ar^1) piperidine scaffolds (Ar^1 = 3,4-dichlorophenyl, 4-Ph-Ph, 4-I-Ph and 2-naphthyl). Previous studies had shown these aryl groups to contribute to the high potency and selectivity at SERT observed for the meperidine ethyl ester derivatives **2a–d** (Table 1) as well as a variety of piperidine and tropane derivatives.[27–30] As illustrated in Scheme 1, an initial series of normeperidine derivatives **4** were prepared from the corresponding ethyl esters **2** using 1-chloroethyl chloroformate (ACE-Cl). This two-step one-pot process typically afforded the normeperidine derivatives **4** in 59–73% yield. The benzyl ester derivatives were prepared from the corresponding nitriles **5** (Scheme 1) that were readily available using synthetic methods previously reported from our laboratory.[21] Hydrolysis of the nitrile moiety of **5** was achieved in a methanolic solution of sodium hydroxide (25% wt) at reflux, followed by an acidic work-up (2 N HCl) to afford the carboxylic acids **6** as the hydrochloride salts in >90% yield. Without purification, the carboxylic acids **6** were converted into the acid chlorides **7** with thionyl chloride and then treated with the appropriately substituted benzyl alcohol under phase-transfer conditions. This furnished the benzyl esters **8–11** in 25–62% yield for the two-step process. The normeperidine analogues **12–15** were then prepared in 70–85% yield using ACE-Cl procedure described above.

3. Biology

Binding affinities for the serotonin, dopamine and norepinephrine transporters were determined by the ability of the drug to displace the transporter selective radiolabeled ligands [^{3}H]citalopram, [^{3}H]WIN 35,428 and [^{3}H]nisoxetine, respectively, from the monoamine transporters in rat brain tissue. The binding affinities of all compounds listed in Table 1 initially were determined for the SERT and DAT. Typically selected compounds that exhibited either SERT binding affinities with K_i values <10 nM or that exhibited DAT/SERT selectivity >100 were then evaluated at norepinephrine transporters to determine a monoamine transporter selectivity profile. Although meperidine exhibits sub-micromolar affinity for μ-opioid receptors (K_i = 0.92 μM), previous structure–activity studies with substituted aryl analogues revealed that the 3,4-dichlorophenyl, 4-iodophenyl and 2-naphthyl meperidines exhibited reduced affinity at μ-opioid receptors.[21] Therefore evaluation of μ-opioid receptor affinity was deemed unnecessary at this time.

4. Results and discussion

Our initial expectation of improved SERT potency by the introduction of a secondary amine group into the meperidine skeleton was readily validated upon evaluation of the normeperidines **4** at the SERT. In general, a six-to-ten-fold improvement in SERT affinity was observed for the normeperidines **4** (e.g., **4c**, K_i = 2.5 nM) over the corresponding meperidine derivatives **2** (e.g., **2c**, K_i = 21.1 nM). Furthermore, the benzyl ester **8a** (K_i = 3.9 nM) exhibited significantly improved binding affinity for the SERT relative to meperidine (**1**, K_i = 414 nM) and the corresponding ethyl ester **2a** (K_i = 18.7 nM). The nearly six to ten-fold increase in SERT affinity

Table 1
Monoamine transporter affinity and selectivity

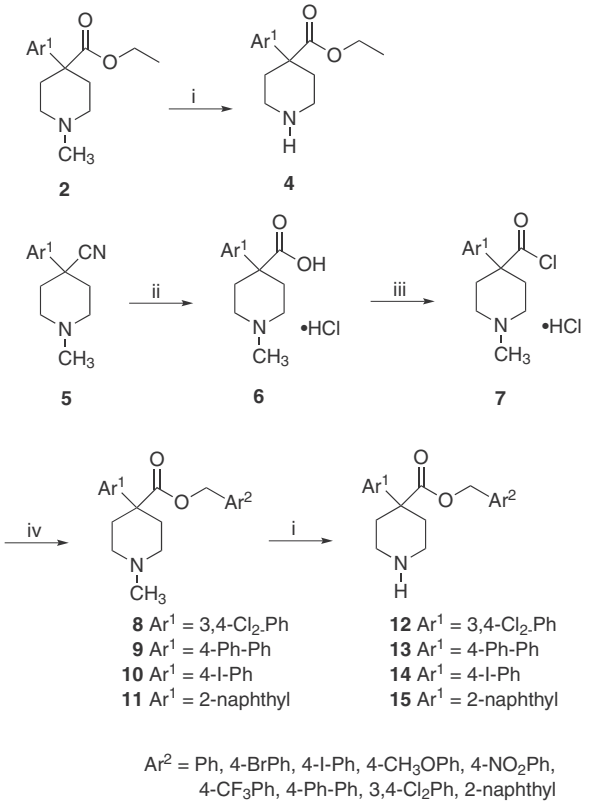
Compound[a]	Ar[1]	Ar[2]	SERT (K_i, nM)[b]	DAT (K_i, nM)[b]	NET (K_i, nM)[b]	DAT/SERT	NET/DAT	NET/SERT
Fluoxetine			2.0 ± 0.1[c]	784 ± 39[d]	473 ± 11[c]	392	0.60	240
Paroxetine			0.05 ± 0.0003[c]	98 ± 1.7[d]	59 ± 0.7[c]	2000	0.59	1200
1	Ph		413 ± 44[e]	17,800 ± 2700[e]	NT	43		
2a	3,4-Cl_2-Ph		18.7 ± 2.6[e]	125 ± 15[e]	74,500 ± 5100[e]	6.7	600	4000
2b	4-Ph		47.7 ± 4.1[e]	6801 ± 3060[e]	4824 ± 633[e]	160	0.71	110
2c	4-I-Ph		21.1 ± 2.4[e]	3250 ± 200[e]	519,000 ± 51,000[e]	150	160	25,000
2d	2-Naphthyl		7.2 ± 0.10[e]	1140 ± 380[e]	71,000 ± 9700[e]	160	62	9900
4a	3,4-Cl_2-Ph		21.6 ± 1.6	321 ± 58	NT	159		
4b	4-Ph-Ph		3.3 ± 1.0	3209 ± 388	NT	980		
4c	4-I-Ph		2.5 ± 0.8	3500 ± 321	NT	1400		
4d	2-Naphthyl		14.1 ± 2.1	710 ± 138	NT	51		
8a	3,4-Cl_2-Ph	Ph	3.9 ± 0.5	2970 ± 297	901 ± 122	760	3.3	230
8b	3,4-Cl_2-Ph	4-CH_3O-Ph	1.7 ± 0.2	2792 ± 626	300 ± 29	1600	0.11	180
8c	3,4-Cl_2-Ph	4-NO_2-Ph	1.0 ± 0.1	1530 ± 334	333 ± 54	1500	0.22	330
8d	3,4-Cl_2-Ph	3,4-Cl_2-Ph	4.3 ± 0.5	5226 ± 152	NT	1200		
8e	3,4-Cl_2-Ph	4-Br-Ph	7.0 ± 0.9	2563 ± 48	580 ± 52	370	0.23	83
8f	3,4-Cl_2-Ph	4-I-Ph	13.2 ± 1.8	3471 ± 238	NT	260		
8g	3,4-Cl_2-Ph	4-Ph-Ph	10.9 ± 2.1	5629 ± 508	NT	520		
8h	3,4-Cl_2-Ph	2-Naphthyl	9.9 ± 3.7	4913 ± 525	2549 ± 77	500	0.52	260
9	4-Ph-Ph	Ph	49.5 ± 7.4	2312 ± 334	NT	47		
12a	3,4-Cl_2-Ph	Ph	9.2 ± 3.1	919 ± 138	NT	100		
12b[f]	3,4-Cl_2-Ph	4-CH_3O-Ph	10.2 ± 2.7	1264 ± 142	3133 ± 578	110	2.5	307
12c[f]	3,4-Cl_2-Ph	4-NO_2-Ph	6.4 ± 1.9	1295 ± 263	1444 ± 415	227	1.1	226
12d[f]	3,4-Cl_2-Ph	3,4-Cl_2-Ph	30.2 ± 4.9	2892 ± 1539	11,930 ± 1060	96	4.1	400
12e	3,4-Cl_2-Ph	4-CF_3-Ph	46.7 ± 17	2244 ± 200	7902 ± 869	48	3.5	170
13	4-Ph-Ph	Ph	2.0 ± 0.3	1109 ± 84	NT	560		
14a[f]	4-I-Ph	4-CH_3O-Ph	0.6 ± 0.2	2925 ± 715	2731 ± 698	4900	0.93	4600
14b[f]	4-I-Ph	4-NO_2-Ph	5.9 ± 2.0	1777 ± 265	2069 ± 322	300	1.2	350
14c[f]	4-I-Ph	3,4-Cl_2-Ph	5.9 ± 2.7	4342 ± 1090	6059 ± 1598	740	1.4	1000
15a[f]	2-Naphthyl	4-CH_3O-Ph	2.9 ± 0.2	889 ± 463	2349 ± 127	310	2.6	810
15b[f]	2-Naphthyl	4-NO_2-Ph	2.0 ± 0.5	732 ± 132	937 ± 7	370	1.3	470
15c[f]	2-Naphthyl	3,4-Cl_2-Ph	26.5 ± 2.4	3212 ± 311	16,557 ± 4034	120	5.2	630

[a] All compounds were tested as the hydrochloride salt, unless noted otherwise. NT: Not tested.
[b] All values are the mean ± SEM of three or four experiments preformed in triplicate.
[c] Value taken from Ref. 31.
[d] Value taken from Ref. 32.
[e] Value taken from Ref. 21 and based upon inhibition of [^{3}H]paroxetine.
[f] Tested as the oxalate salt.

was accompanied by a significant decrease in DAT affinity. Thus the benzyl ester **8a** was not only more potent than the corresponding ethyl ester **2a** at the SERT, it was more SERT selective as well.

A series of substituted benzyl ester 4-(3,4-dichlorophenyl)-meperidine derivatives **8** were evaluated at the SERT and the DAT, since the 4-(3,4-dichlorophenyl)-meperidine scaffold was the most readily available of the meperidine derivatives from previous studies.[21] In general, all of the benzyl esters **8a**–**8h** exhibited high affinity for the SERT (K_i values $\leq$10 nM) and good DAT/SERT selectivity (DAT/SERT >100). It was noteworthy, that the 4-methoxybenzyl ester **8b** (K_i = 1.7 nM) and the 4-nitrobenzyl ester **8c** (K_i = 1.0 nM) were the most potent compounds at the SERT of the meperidine series and were equally DAT/SERT selective. The similarity in potency and selectivity of these two compounds was consistent with the SERT pharmacophore, which favors a H-bond acceptor group on the benzyl group (Ar^2) of **8**.[24,25] The NET binding affinity also was determined for selected derivatives of **8** and was found to increase relative to the corresponding ethyl esters **2**. However, the NET affinity of the benzyl esters (e.g., **8b** K_i = 300 nM) was significantly lower than that exhibited for the SERT and resulted in NET/SERT selectivity >100, (e.g., **8b**, NET/SERT = 180) albeit less selective than the corresponding ethyl ester (e.g., **2a**, NET/SERT = 4000). Alternatively, the 4-phenyl meperidine derivative **9** exhibited potency at the SERT (K_i = 49.5 nM) and the DAT (K_i = 2312 nM) that was not significantly different than that of the ethyl ester **2c**. It was interesting to note that the 4-phenyl congenor **9** was the only compound of the benzyl ester series that did not exhibit significantly improved SERT affinity over the corresponding ethyl esters. Overall, the results of the normeperidine ethyl esters **4** and the meperidine benzyl esters **8** were very satisfying and supported our rationale for the ligand design.

The affinity and selectivity of the benzyl esters **8b** and **8c** was very similar to fluoxetine and suggested that the meperidine derivatives were binding to the SERT in a similar motif. Since fluoxetine is a secondary amine it was of interest to explore a potential synergistic effect of the N–H group with the benzyl ester moiety on SERT affinity. A series of normeperidine benzyl ester analogues **12–15** were evaluated at monoamine transporters. The normeperidine congenors **12** of the 4-(3,4-dichlorophenyl) analogues were slightly less potent than the corresponding *N*-methyl derivatives. This was not surprising since a similar result was observed in the ethyl ester series where the *N*-methyl derivative **2b** was more potent at the SERT than **4a**. However, the 4-phenylnormeperidine benzyl ester **13** did exhibit a substantial increase in SERT affinity and a modest increase in DAT affinity. This supported our rationale for incorporation of both the N–H and benzyl ester moieties into the meperidine scaffold. Based upon the improved SERT affinity of **13**, we were encouraged to further investigate the structure–activity of the highly potent and SERT selective 4-(4-iodophenyl) (**14**) and 4-(2-naphthyl) (**15**) normeperidine scaffolds with the most potent substituted benzyl esters of the meperidine series (Ar^2 = 4-CH_3OPh, 4-NO_2Ph and 3,4-Cl_2Ph). As envisaged the iodo and naphthyl analogues, **14** and **15**, exhibited improved potency and selectivity for the SERT relative to that of the corresponding dichloro derivatives. The 4-(4-iodophenyl) normeperidine 4-methoxybenzyl ester **14a** was found possess subnanomolar potency at the SERT and was the most potent ligand of the study for the SERT (K_i = 0.6 nM). In addition, **14a** was also the most selec-



Scheme 1. General synthetic procedures. Reagents and conditions: (i) ACE-Cl, $NaHCO_3$, $ClCH_2CH_2Cl$, reflux; then CH_3OH, reflux, 3 h; (ii) NaOH, CH_3OH, reflux; then 2 N HCl; (iii) $SOCl_2$, reflux; (iv) Ar^2CH_2OH, Bu_4NHSO_4, 5% NaOH (aq), CH_2Cl_2.

tive compound for SERT (DAT/SERT = 4900; NET/SERT = 4600) and exhibited SERT selectivity that exceeded that of fluoxetine and paroxetine (Table 1). The 2-naphthyl derivatives **15a** and **15b** also exhibited high affinity and high selectivity for the SERT relative to the DAT and NET but were greater than 10-fold less selective for the SERT than **14a**.

5. Conclusion

In conclusion, we have synthesized a series of benzyl ester derivatives of meperidine and normeperidine as SERT selective compounds based upon the SERT pharmacophore. In general, the benzyl esters were significantly more potent at monoamine transporters than the corresponding ethyl esters and exhibited low nanomolar binding affinity for the SERT. The 4-methoxybenzyl esters **8b**, **14a** and 4-nitrobenzyl ester **8c** were the most SERT selective ligands of the study. Based upon these results, both the meperidine benzyl ester scaffold and the normeperidine benzyl ester scaffold seem to be well suited for the development of new compounds that display high potency and selectivity for the SERT. Studies to further characterize these compounds at serotonin receptors and in vivo are under way and will be reported in due course.

6. Experimental section

All chemicals were purchased from Aldrich Chemical Co., Milwaukee, WI. Unless otherwise noted. Anhydrous THF, CH_2Cl_2 and CH_3OH were purchased from Mallinkrodt Baker. Toluene and Et_2O (Drisolv®, EMD Chemicals) were purchased from VWR International. Chromatography refers to flash column chromatography on silica gel (Sorbent Technologies Silica Gel 60 Å, 230–400 mesh, 32–63 μm Standard Grade). Petroleum ether refers to pentanes with a boiling point range of 30–60 °C. 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. The compounds were characterized by NMR as the free base then converted into the corresponding salt. Melting points were determined for the salts and are uncorrected. Elemental analyses were obtained from Atlantic Microlabs, Inc., Norcross, GA.

6.1. General procedure for the preparation of hydrochloride salts

The base (50–100 mg) was dissolved in a minimum amount of diethyl ether (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 trituration 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 mm Hg). All compounds were homogeneous on thin-layer chromatography ($CHCl_3/CH_3OH/NH_4OH$, 90:9:1).

6.2. General procedure for the preparation of oxalate salts

The base (50–100 mg) was dissolved in a minimum amount of anhydrous THF (1–2 mL) and added to a THF solution (10 mL) of anhydrous oxalic acid (1 equiv). The salts crystallized and were washed with anhydrous THF (1 × 2 mL) and then washed with Et_2O (3 × 2 mL) and purified by trituration 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 mm Hg). All compounds were homogeneous by thin-layer chromatography ($CHCl_3/CH_3OH/NH_4OH$, 90:9:1).

6.3. General procedure for the preparation of normeperidine derivatives 4

A solution of **2** (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 and 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 and washed with 1.8 N NaOH (30 mL) and water (30 mL) 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 analogues **4** as waxy solids in 58–73% yield.

6.3.1. Ethyl 4-(3,4-dichlorophenyl)-piperidine-4-carboxylate (4a)

Tan solid (830 mg, 65% yield) ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (d, J = 2.0 Hz, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.21 (dd, J = 2.8,8.8 Hz, 1H), 5.76 (s, 1H), 4.16 (q, J = 7.2 Hz, 2H), 3.25 (d, J = 12.8 Hz, 2H), 2.90 (t, J = 12.0 Hz, 2H), 2.59 (d, J = 13.2 Hz, 2H), 2.02 (m, 2H), 1.20 (t, J = 6.8 Hz, 3H). ^{13}C NMR: (101 MHz, $CDCl_3$) δ 172.8, 142.1, 132.8, 131.6, 130.5, 127.9, 125.1, 61.6, 48.4, 42.9(2), 32.7(2), 13.9. Mp 203–205 °C (HCl salt). Anal. Calcd for $C_{14}H_{17}NO_2Cl_2 \cdot HCl$: C, 49.65; H, 5.36; N, 4.14. Found: C, 49.77; H, 5.42; N, 4.08.

6.3.2. Ethyl 4-biphenyl-4-yl-piperidine-4-carboxylate (4b)

Tan solid (1.4 g, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.58–7.31 (m, 9H), 4.17 (q, J = 6.8 Hz, 2H), 3.36 (d, J = 12.8 Hz, 2H), 3.01 (t, J = 11.2 Hz, 2H), 2.69 (d, J = 14.0 Hz, 2H), 2.25 (m, 2H), 1.20 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 140.3, 140.2, 140.1, 128.7(2), 127.4(3), 126.9(2), 125.9(2), 61.4, 48.3, 42.5(2), 31.8(2), 13.9. Mp 148–151 °C (HCl salt). Anal. Calcd for $C_{20}H_{23}NO_2 \cdot HCl \cdot H_2O$: C, 66.01; H, 7.20; N, 3.85. Found: C, 66.35; H, 7.04; N, 3.75.

6.3.3. Ethyl 4-(4-iodophenyl)-piperidine-4-carboxylate (4c)

Yellow solid (430 mg, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.67 (d, J = 8.4 Hz, 2H), 7.11 (d, J = 8.8 Hz, 2H), 4.14 (q, J = 7.2 Hz, 2H), 3.31 (d, J = 13.2 Hz, 2H), 2.88 (t, J = 11.2 Hz, 2H), 2.58 (d, J = 13.6 Hz, 2H), 1.99 (m, 2H), 1.18 (t, J = 11.6 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 173.4, 143.5, 142.0, 132.9, 137.7, 127.7, 93.0, 61.4, 48.9, 43.3, 33.2, 14.0. Mp 220–222 °C (HCl salt). Anal. Calcd for $C_{14}H_{18}NO_2I{\cdot}HCl{\cdot}1/4H_2O$: C, 42.02; H, 4.91; N, 3.50. Found: C, 42.01; H, 4.09; N, 3.50.

6.3.4. Ethyl 4-naphthalen-2-yl-piperidine-4-carboxylate (4d)

White solid (136 mg, 58% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.98–7.46 (m, 7H), 4.19 (q, J = 7.6 Hz, 2H), 3.49 (d, J = 13.2 Hz, 2H), 3.12 (t, J = 11.2 Hz, 2H), 2.80 (d, J = 14.4 Hz, 2H), 2.45 (m, 2H), 1.16 (t, J = 6.8 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$): δ 8 172.8, 137.7, 133.1, 132.4, 128.6, 128.0(2), 127.3, 126.3(2), 124.5, 123.2, 61.6, 48.2 42.0(2), 30.7(2), 13.9. Mp 223–225 °C (HCl salt). Anal. Calcd for $C_{18}H_{21}NO_2{\cdot}HCl$: C, 67.60; H, 6.93; N, 4.38. Found: C, 67.25; H, 6.89; N, 4.45.

6.4. General procedure for the preparation of carboxylic acids 6

A solution of the nitrile (**5**, 5.2 mmol) and 25% (wt) NaOH (34 mL) in methanol (100 mL) was stirred at reflux overnight, then cooled down to room temperature. The mixture was reduced to half the volume under reduced pressure and extracted with Et_2O (3 × 30 mL). The aqueous layer was cooled to 0 °C, then acidified to pH 2 with 1 M HCl solution and then extracted with ethyl acetate (3 × 75 mL). A white suspension was formed and the white solid was filtered by vacuum filtration. The solid was recrystallized from H_2O/MeOH (4:1, v/v) to afford the carboxylic acid hydrochloride salts **6** as white crystals. The salts were then carried on to the next step without characterization or further purification.

6.5. General procedure for the preparation of benzyl esters 8a–i, 9, 10a–c and 11a–c

Thionyl chloride (20 mL) was transferred to a 100 mL round-bottom flask fitted with a condenser and charged with the carboxylic acid **6** (1.85 mmol). The mixture was heated to reflux overnight with stirring under N_2. Excess thionyl chloride was removed by distillation to afford the crude acid chloride **7**. A solution of alcohol (1.85 mmol) and Bu_4NHSO_4 (0.36 mmol) in CH_2Cl_2 (20 mL) was transferred to the residue. The mixtures were cooled to −5 °C then 5% NaOH (3 mL) was added. Stirring was continued at −5 °C for 1 h and then the mixture was allowed to warm room temperature. The reaction mixture was monitored by TLC every 30 min until the starting material was consumed. The organic layer was separated, washed with water, dried (Na_2SO_4), filtered and concentrated under reduced pressure. Purification by column chromatography (MeOH/$CHCl_3$, 2:98) gave the benzyl esters **8**–**11** as waxy solids or oils in 25–62% yield.

6.5.1. Benzyl 4-(3,4-dichlorophenyl)-1-methylpiperidine-4-carboxylate (8a)

White solid (356 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) 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 (d, J = 8.4, 2.4 Hz, 1H), 5.10 (s, 2H), 2.76 (d, J = 8.8 Hz, 2H), 2.58 (d, J = 12.4 Hz, 2H), 2.24 (s, 3H), 2.12 (m, 2H), 1.92 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 135.4, 132.7, 131.3, 130.4, 129.5, 128.5, 128.3(2), 127.6(2), 127.1, 125.4, 67.0, 53.1(2), 48.4, 46.1, 33.6(2). Mp 186–188 °C (HCl salt). Anal. Calcd for $C_{20}H_{21}Cl_2NO_2{\cdot}HCl{\cdot}1/2H_2O$: C, 56.68; H, 5.47; N, 3.31. Found: C, 56.54; H, 5.53; N, 3.29.

6.5.2. 4-Methoxylbenzyl 4-(3,4-dichlorophenyl)-1-methylpiperidine-4-carboxylate (8b)

White solid (385 mg, 51% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 2.3, 1H), 7.34 (dd, J = 8.4, 4.1 Hz, 1H), 7.20 (m, 1H), 7.13 (m, 2H), 6.91–6.77 (m, 2H), 5.04 (s, 2H), 3.80 (s, 3H), 2.74 (d, J = 9.2 Hz, 2H), 2.53 (d, J = 12.6 Hz, 2H), 2.23 (s, 3H), 2.12–2.10 (m, 2H), 1.92 (d, J = 10.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 159.6, 132.9, 131.5, 130.6, 130.2(2), 128.5(2), 127.8, 125.6, 118.7, 114.1, 67.1, 55.9, 55.5, 53.4, 48.6, 46.3, 33.9(2). Mp 162–165 °C (HCl salt). Anal. Calcd for $C_{21}H_{23}Cl_2NO_3{\cdot}HCl{\cdot}H_2O$: C, 54.50; H, 5.66; N, 3.03. Found: C, 52.37; H, 5.60; N, 3.03.

6.5.3. 4-Nitrobenzyl 4-(3,4-dichlorophenyl)-1-methylpiperidine-4-carboxylate (8c)

Yellow solid (370 mg, 47% yield) ^{1}H NMR (free base): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (d, J = 8.8 Hz, 2H), 7.40 (dd, J = 2.4, 8.4 Hz, 2H), 7.29 (d, J = 8.8 Hz, 2H), 7.13 (dd, J = 2.4, 2.4 Hz, 1H), 5.17 (s, 2H), 2.74 (s, 2H), 2.56–2.53 (d, J = 12.4 Hz, 2H), 2.24 (s, 3H), 2.15–2.10 (dt, J = 10.8 Hz, 2H), 2.00–1.98 (d, J = 11.2 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 147.9, 142.8, 135.5, 133.1, 131.9(2), 130.8(2), 128.6(2), 125.6, 124.0, 65.7, 53.3(2), 48.6, 46.3, 33.7(2). Mp 187–189 °C (HCl salt). Anal. Calcd for $C_{20}H_{20}N_2O_4Cl_2{\cdot}HCl{\cdot}1/4H_2O$: C, 51.74; H, 4.67; N, 6.03. Found: C, 51.74; H, 4.75; N, 5.83.

6.5.4. 3,4-Dichlorobenzyl 4-(3,4-dichlorophenyl)-1-methylpiperidine-4-carboxylate (8d)

Tan solid (438 mg, 50% yield) ^{1}H NMR (free base): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (dd, J = 2.4, 8.4 Hz, 2H), 7.36 (s, 1H), 7.18 (dd, J = 2.0, 2.1 Hz, 2H), 7.00 (dd, J = 2.0, 2.0 Hz, 1H), 5.04 (s, 2H), 2.83 (s, 2H), 2.57 (d, J = 12.8 Hz, 2H), 2.30 (s, 3H), 2.19 (dt, J = 8.0 Hz, 2H), 2.05 (d, J = 10.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 141.3, 135.9, 133.1, 132.7, 132.6, 131.8, 130.8, 130.0, 128.5(2), 127.3, 125.6, 65.5, 53.3(2), 48.6, 46.3, 33.7(2). Mp 182–183 °C (HCl salt). Anal. Calcd for $C_{20}H_{19}NO_2Cl_4{\cdot}HCl$: C, 49.67; H, 4.17; N, 2.90. Found: C, 49.44; H, 4.27; N, 2.84.

6.5.5. 4-Bromobenzyl 4-(3,4-dichlorophenyl)-1-methylpiperidine-4-carboxylate (8e)

White solid (411 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45–7.41 (m, 3H), 7.37 (d, J = 8.0 Hz, 1H), 7.18–7.15 (m, 2H), 7.07 (d, J = 8.0 Hz, 1H), 5.04 (s, 2H), 2.76 (d, J = 8.4 Hz, 2H), 2.53 (d, J = 12.0 Hz, 2H), 2.24 (s, 3H), 2.13 (t, J = 12.0 Hz, 2H), 1.94 (t, J = 10.0 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 138.6, 134.9, 131.8(2), 131.5, 130.6, 130.2, 129.5, 128.5(2), 127.8, 122.6, 67.1, 55.5, 53.4, 48.5, 46.5, 32.1(2). Mp 140–142 °C (HCl salt). Anal. Calcd for $C_{20}H_{20}BrCl_2NO_2{\cdot}HCl{\cdot}1/2H_2O$: C, 47.78; H, 4.41; N, 2.79. Found: C, 47.70; H, 4.47; N, 2.73.

6.5.6. 4-Iodobenzyl 4-(3,4-dichlorophenyl)-1-methylpiperidine-4-carboxylate (8f)

White solid (466 mg, 50% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (m, 2H), 7.38 (m, 2H), 7.18 (m, 1H), 6.93 (d, J = 8.0 Hz, 2H), 5.03 (s, 2H), 2.75 (d, J = 8.8, 2H), 2.53 (d, J = 12.0 Hz, 2H), 2.24 (s, 3H), 2.11 (t, J = 10.4 Hz, 2H), 1.94 (t, J = 10.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.6, 138.6, 137.6(2), 135.0, 131.5, 130.6, 130.2, 130.1, 129.5(2), 127.8, 93.8, 67.1, 55.5, 53.4, 48.5, 46.5, 32.1(2). Mp 150–151 °C (HCl salt). Anal. Calcd for $C_{20}H_{20}Cl_2INO_2{\cdot}HCl{\cdot}H_2O$: C, 43.00; H, 4.15; N, 2.51. Found: C, 43.01; H, 4.02; N, 2.39.

6.5.7. Biphenylmethyl 4-(3,4-dichlorophenyl)-1-methylpiperidine-4-carboxylate (8g)

White solid (428 mg, 51% yield). ^{1}H NMR (free base): δ 7.59– 7.53 (m, 4H), 7.44 (dd, J = 6.8, 2.0 Hz, 3H), 7.37 (d, J = 8.8 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.20 (dd, J = 2.4, 6.4 Hz,

1H), 5.15 (s, 2H), 2.77 (d, J = 8.0 Hz, 2H), 2.57 (d, J = 12.8 Hz, 2H), 2.25 (s, 3H), 2.15 (t, J = 10.8 Hz, 2H), 1.96 (t, J = 10.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 140.5, 139.7, 138.4, 135.0, 132.1, 130.9, 130.7, 129.4(3), 128.2(2), 127.9(2), 127.7(2), 127.6, 127.5, 67.1, 53.2, 53.0, 47.0, 43.6, 32.7, 32.4. Mp 169–170 °C (HCl salt). Anal. Calcd for $C_{26}H_{25}Cl_2NO_2{\cdot}HCl{\cdot}H_2O$: C, 61.32; H, 5.55; N, 2.75. Found: C, 61.33; H, 5.48; N, 2.84.

6.5.8. 2-Naphthylmethyl-4-(3,4-dichlorophenyl)-1-methylpiperidine-4-carboxylate (8h)

White solid (403 mg, 51% yield). ^{1}H NMR (free base): δ 7.84–7.74 (m, 2H), 7.40–7.36 (m, 2H), 7.60 (s, 1H), 7.51–7.45 (m, 2H), 7.34 (d, J = 8.0 Hz,1H) 7.27 (s, 1H) 7.18 (m,1H), 5.27 (s, 2H), 2.75 (d, J = 5.6 Hz, 2H), 2.57 (d, J = 12.0 Hz, 2H), 2.23 (s, 3H), 2.14 (t, J = 10.8 Hz, 2H), 1.95 (t, J = 10.8 Hz, 2H). Mp 200–204 °C (HCl salt). Anal. Calcd for $C_{24}H_{23}Cl_2NO_2{\cdot}HCl{\cdot}1.5H_2O$: C, 58.61; H, 5.53; N, 2.85. Found: C, 58.37; H, 5.50; N, 2.83.

6.5.9. 4-Trifluoromethyl-4-(3,4-dichlorophenyl)-1-methylpiperidine-4-carboxylate (8i)

Colorless oil (400 mg, 48% yield). ^{1}H NMR (free base): (400 MHz, $CDCl_3$) δ 7.57 (d, J = 8.0 Hz, 2H), 7.39 (m, 2H), 7.29 (d, J = 8.4 Hz, 2H), 7.18 (dd, J = 2.0 Hz 1H), 5.15 (s, 2H), 2.80 (s, 2H), 2.56 (d, J = 12.8 Hz, 2H), 2.28 (s, 3H), 2.17 (t, J = 10.8 Hz 2H), 2.01 (t, J = 10.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 139.5, 135.4, 133.1, 130.8, 128.5, 128.3(2), 125.8(2), 125.7(2), 125.6, 122.8, 66.3, 53.2(2), 48.5, 46.2, 33.6(2). Anal. Calcd for $C_{21}H_{20}Cl_2F_3NO_2$: C, 56.52; H, 4.52; N, 3.14. Found: C, 56.33; H, 4.71; N, 3.08.

6.5.10. Benzyl 4-(4-phenyl-phenyl)-1-methylpiperidine-4-carboxylate (9)

Yellow solid (256 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 4H), 7.42 (m, 4H), 7.33–7.17 (m, 6H), 5.13 (s, 2H), 2.83 (br s, 2H), 2.65 (d, J = 12.8 Hz, 2H), 2.28 (s, 3H), 2.19 (t, J = 10.8 Hz 2H), 2.09 (t, J = 10.8 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 140.5, 139.8, 135.8, 128.7(2), 128.3(2), 128.0(2), 127.8(2), 127.2, 127.1, 126.9(2), 126.3(2), 66.5, 53.3(2), 48.4, 46.1, 33.6(2). Mp 201–202 °C (HCl salt). Anal. Calcd for $C_{26}H_{27}NO_2{\cdot}HCl{\cdot}H_2O$: C, 70.98; H, 6.87; N, 3.18. Found: C, 70.71; H, 7.00; N, 3.01.

6.5.11. 4-Methoxylbenzyl 4-(4-iodophenyl)-1-methylpiperidine-4-carboxylate (10a)

Colorless oil (215 mg, 25% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.8 Hz, 2H), 7.13–7.06 (m, 4H), 6.82 (d, J = 8.8 Hz, 2H), 5.08 (m 2H), 3.80 (s, 3H), 2.73 (br s, 2H), 2.54 (d, J = 12.8 Hz, 2H), 2.20 (s, 3H), 2.12 (m, 2H), 1.94 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.2, 159.9, 138.0, 137.8(2), 130.1(2), 128.2, 127.9, 127.5, 114.0(2), 93.0, 66.9, 55.5, 53.4(2), 48.7, 46.3, 33.7(2). Anal. Calcd for $C_{21}H_{24}INO_3$: C, 54.20; H, 5.20; N, 3.01. Found: C, 54.00; H, 5.30; N, 2.92.

6.5.12. 4-Nitrobenzyl 4-(4-iodophenyl)-1-methylpiperidine-4-carboxylate (10b)

Yellow oil (300 mg, 34% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.2 (d, J = 8.8 Hz, 2H), 7.66 (d, J = 8.4 Hz, 2H), 7.33 (d, J = 8.8 Hz, 2H), 7.17 (d, J = 8.8 Hz, 2H), 5.16 (s, 2H), 2.75 (s, 2H), 2.58 (m, 2H), 2.30 (s, 3H), 2.19–2.06 (m, 2H), 2.01 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 155.4, 143.1, 138.0(2), 134.8, 128.3(2), 123.9(2), 123.3(2), 93.2, 65.4, 53.4(2), 48.8, 46.4, 36.5(2). Anal. Calcd for $C_{20}H_{21}IN_2O_4$: C, 50.01; H, 4.41; N, 5.83. Found: C, 49.88; H, 4.51; N, 5.72.

6.5.13. 3,4-Dichlorobenzyl 4-(4-iodophenyl)-1-methylpiperidine-4-carboxylate (10c)

Yellow oil (447 mg, 48% yield). ^{1}H NMR (free base): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (d, J = 8.8 Hz, 2H), 7.35 (d, J = 8.0 Hz, 1H), 7.11–7.08 (m, 3H), 6.96 (dd, J = 4.8, 1.6 Hz, 1H), 5.03 (s, 2H), 2.74 (br s, 2H), 2.55 (d, J = 12.9 Hz, 2H), 2.25 (s, 3H), 2.09 (m, 2H), 2.0 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 155.4, 142.3, 138.0(2), 136.1, 130.7, 129.7, 128.0(2), 127.1(2), 93.4, 65.4, 53.4(2), 49.5, 44.4, 35.5(2). Anal. Calcd for $C_{20}H_{20}Cl_2INO_2$: C, 47.64; H, 4.00; N, 4.06. Found: C, 47.30; H, 4.29; N, 3.87.

6.5.14. 4-Methoxylbenzyl 4-(naphthalen-2-yl)-1-methylpiperidine-4-carboxylate (11a)

Colorless oil (209 mg, 29% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.74 (m, 4H), 7.50–7.45 (m, 3H), 7.12 (d, J = 8.0 Hz, 2H), 6.77 (d, J = 8.0 Hz, 2H), 5.06 (s, 2H), 3.75 (s, 3H), 2.80 (br s, 2H), 2.71 (d, J = 12.0 Hz, 2H), 2.26 (s, 3H), 2.18–2.12 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 159.8, 133.5, 132.6, 130.2(2), 128.5(2), 128.4, 128.0, 127.6, 126.4, 126.3, 125.1, 124.1, 114.0(2), 66.9, 55.5, 53.3(2), 48.9, 45.8, 33.4(2). Anal. Calcd for $C_{25}H_{27}NO_3$: C, 77.09; H, 6.99; N, 3.60. Found: C, 76.89; H, 7.03; N, 3.44.

6.5.15. 4-Nitrobenzyl 4-(naphthalen-2-yl)-1-methylpiperidine-4-carboxylate (11b)

Yellow oil (276 mg, 37% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.8 Hz, 2H), 7.83–7.75 (m, 4H), 7.50–7.46 (m, 3H), 7.18 (d, J = 8.6 Hz, 2H), 5.16 (m, 2H), 2.82 (br s, 2H), 2.73 (m, 2H), 2.27 (s, 3H), 2.26–2.17 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 147.7, 143.2, 133.5, 132.6, 128.6(2), 128.2(2), 127.7(2), 126.6(2), 125.2, 124.1, 123.8(2), 65.3, 53.6(2), 49.2, 46.5, 33.9(2). Anal. Calcd for $C_{24}H_{24}N_2O_4$: C, 71.27; H, 5.98; N, 6.93. Found: C, 71.00; H, 6.01; N, 6.87.

6.5.16. 3,4-Dichlorobenzyl 4-(naphthalen-2-yl)-1-methylpiperidine-4-carboxylate (11c)

Yellow oil (316 mg, 40% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.76 (m, 4H), 7.55–7.43 (m, 2H), 7.29–7.19 (m, 2H), 7.14 (d, J = 1.9 Hz, 1H), 7.00–6.86 (m, 1H), 5.03 (s, 2H), 2.89 (br s, 2H), 2.72 (m, 2H), 2.32 (s, 3H), 2.18 (m, 4H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.0, 140.2, 135.1, 133.5, 133.0, 132.7, 131.1(2), 130.9(2), 130.0(2), 128.0(2), 127.5(2), 125.2, 66.2, 56.0(2), 48.9, 42.1, 30.4, 29.7. Anal. Calcd for $C_{24}H_{23}Cl_2NO_2$: C, 67.29; H, 5.41; N, 3.27. Found: C, 67.19; H, 5.43; N, 3.10.

6.6. General procedure for the preparation of normeperidine analogues 12a–e, 13, 14a–c and 15

A solution of the meperidine benzyl ester (0.60 mmol), sodium bicarbonate (9.1 mmol) and 1-chloro-ethyl chloroformate (5.0 mmol) in 1,2-dichloroethane (20 mL) was heated to reflux under an atmosphere of nitrogen for 48 h. The mixture was filtered to remove any solids and the solvent was removed under reduced pressure. Methanol (50 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 analogues **12–15** as waxy solids.

6.6.1. Benzyl 4-(3,4-dichlorophenyl) piperidine-4-carboxylate (12a)

White solid (125 mg, 57% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 2.4 Hz, 1H), 7.36 (d, J = 8.0 Hz, 1H), 7.32–7.29 (m, 3H), 7.20–7.17 (m, 3H), 5.11 (s, 2H), 3.07 (d, J = 12.0 Hz, 2H), 2.77 (t, J = 10.8 Hz, 2H), 2.55 (d, J = 12.8 Hz, 2H), 2.40 (br s, 1H), 1.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 143.2, 135.7, 133.0, 131.6, 130.7(2), 128.6, 128.8, 128.6, 128.4, 128.3, 125.6, 67.3, 49.5, 44.0(2), 34.7(2). Mp 177–179 °C (HCl salt). Anal. Calcd for

$C_{19}H_{19}Cl_2NO_2$·HCl: C, 56.95; H, 5.03; N, 3.50. Found: C, 56.60; H, 4.95; N, 3.33.

6.6.2. 4-Methoxylbenzyl 4-(3,4-dichlorophenyl) piperidine-4-carboxylate (12b)

White solid (167 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.38–7.29 (m, 2H), 7.16–7.13 (m, 3H), 6.83 (d, J = 8.5 Hz, 2H), 5.05 (s, 2H), 3.80 (s, 3H), 3.06 (m, 2H), 2.77 (t, J = 11.2 Hz, 2H), 2.72 (br s, 1H), 2.50 (d, J = 12.0 Hz, 2H), 1.81 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.6, 159.9, 143.2, 132.9, 131.5, 130.6, 130.2, 128.4(2), 127.7, 125.5(2), 114.0, 67.1, 55.5, 49.4, 44.0(2), 34.6(2). Mp 182–183 °C (oxalate salt). Anal. Calcd for $C_{20}H_{21}Cl_2NO_3·C_2H_2O_4·0.1H_2O$: C, 54.36; H, 4.81; N, 2.88. Found: C, 54.70; H, 4.91; N, 2.87.

6.6.3. 4-Nitrobenzyl 4-(3,4-dichlorophenyl) piperidine-4-carboxylate (12c)

Yellow solid (169 mg, 69% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (d, J = 8.5 Hz, 2H), 7.45–7.36 (m, 3H), 7.32 (m, 2H), 7.19 (d, J = 8.0 Hz, 1H), 5.19 (s, 2H), 3.07 (d, J = 12.7 Hz, 2H), 2.77 (t, J = 11.5 Hz, 2H), 2.54 (d, J = 13.1 Hz, 2H), 2.39 (br s, 1H), 1.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.4, 147.9, 142.8(2), 133.1, 131.8, 130.8(2), 128.6, 128.4, 125.5, 123.9(2), 65.7, 49.5, 43.9(2), 34.6(2). Mp 175–178 °C (oxalate salt). Anal. Calcd for $C_{19}H_{18}Cl_2N_2O_4·C_2H_2O_4$: C, 50.52; H, 4.04; N, 5.61. Found: C, 50.60; H, 4.15; N, 5.33.

6.6.4. 3,4-Dichlorobenzyl 4-(3,4-dichlorophenyl) piperidine-4-carboxylate (12d)

Tan solid (182 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.40 (d, J = 8.3, 2H), 7.32 (d, J = 1.9 Hz, 1H), 7.17–7.06 (m, 2H), 6.98 (dd, J = 8.2, 1.6 Hz, 1H), 5.06 (s, 2H), 3.44 (d, J = 12.8 Hz, 2H), 3.04 (t, J = 11.7 Hz, 2H), 2.68 (d, J = 14.4 Hz, 2H), 2.42–2.21 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.5, 159.9, 139.9, 143.2, 132.9(2), 131.4, 130.7, 130.2, 128.0(2), 127.5, 125.1, 67.1, 49.0, 44.0(2), 34.6(2). Mp 142–143 °C (oxalate salt). Anal. Calcd for $C_{19}H_{17}Cl_4NO_2·C_2H_2O_4·1/2H_2O$: C, 47.39; H, 3.79; N, 2.63. Found: C, 47.60; H, 3.83; N, 2.74.

6.6.5. 4-Trifluoromethylbenzyl 4-(3,4-dichlorophenyl) piperidine-4-carboxylate (12e)

White solid (188 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (d, J = 8.0 Hz, 2H), 7.42 (d, J = 2.4 Hz, 1H), 7.27 (d, J = 8.4 Hz, 1H), 7.28 (d, J = 8.0 Hz, 2H), 7.18 (dd, J = 8.4, 2.4 Hz, 1H), 5.14 (s, 2H), 3.06 (m, 2H), 2.78 (m, 2H), 2.53 (d, J = 13.2 Hz, 2H), 2.23 (br s, 1H), 1.85 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.5, 142.9, 139.6, 133.0, 131.7, 130.9, 128.4, 128.3, 125.8(2), 125.7(2), 125.5, 122.8, 66.2, 49.5, 44.1(2), 34.7(2). Mp 112–113 °C (HCl salt). Anal. Calcd for $C_{20}H_{18}Cl_2F_3NO_2$·HCl·1/3H_2O: C, 50.60; H, 4.18; N, 2.95. Found: C, 50.65; H, 4.27; N, 2.92.

6.6.6. Benzyl 4-(4-phenyl-phenyl) piperidine-4-carboxylate (13)

Tan solid (100 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.55 (m, 4H), 7.42 (m, 4H), 7.33 (t, J = 7.5 Hz, 1H), 7.25 (m, 3H), 7.17 (m, 2H), 5.12 (s, 2H), 3.08 (dt, J = 12.9, 3.3 Hz, 2H), 2.80 (m, 2H), 2.69 (s, 1H), 2.62 (d, J = 13.2 Hz, 2H), 1.94 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.1, 141.7, 140.5, 139.9, 135.8, 128.7(2), 128.4(2), 128.0(2), 127.8(2), 127.3, 127.2, 126.9(2), 126.2(2), 66.6, 49.4, 43.9(2), 34.5(2). Mp 201–202 °C (HCl salt). Anal. Calcd for $C_{25}H_{25}NO_2$·HCl·1/4H_2O: C, 72.81; H, 6.48; N, 3.40. Found: C, 72.77; H, 6.43; N, 3.48.

6.6.7. 4-Methoxylbenzyl 4-(4-iodophenyl) piperidine-4-carboxylate (14a)

White solid (198 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, J = 8.6 Hz, 2H), 7.11 (d, J = 8.6 Hz, 2H), 7.03 (d, J = 8.6 Hz, 2H), 6.82 (d, J = 8.7 Hz, 2H), 5.03 (s, 2H), 3.80 (s, 3H), 3.21 (m, 2H), 2.80 (m, 2H), 2.58 (m, 3H), 2.07 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.3, 159.9, 138.0(2), 137.7, 130.2(2), 128.0, 127.9, 127.5, 114.2(2), 93.4, 67.3, 55.5, 49.8, 44.1(2), 33.7(2). Mp 205–206 °C (oxalate salt). Anal. Calcd for $C_{20}H_{22}INO_3·C_2H_2O_4$: C, 48.81; H, 4.47; N, 2.59. Found: C, 49.50; H, 4.71; N, 2.52.

6.6.8. 4-Nitrobenzyl 4-(4-iodophenyl) piperidine-4-carboxylate (14b)

Yellow solid (201 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.14 (d, J = 8.6 Hz, 2H), 7.66 (t, J = 8.0 Hz, 2H), 7.26 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.6 Hz, 2H), 5.17 (s, 2H), 3.06 (d, J = 12.5 Hz, 2H), 2.77 (t, J = 11.6 Hz, 2H), 2.54 (d, J = 12.6 Hz, 2H), 1.91–1.84 (m, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.9, 155.3, 143.1, 138.0(2), 133.7, 128.4(2), 128.1(2), 123.9(2), 93.2, 65.4, 49.7, 44.1(2), 34.6(2). Mp 207–209 °C (oxalate salt). Anal. Calcd for $C_{19}H_{19}IN_2O_4·C_2H_2O_4$: C, 45.34; H, 3.80; N, 5.04. Found: C, 46.44; H, 4.15; N, 4.69.

6.6.9. 3,4-Dichlorobenzyl 4-(4-iodophenyl) piperidine-4-carboxylate (14c)

White solid (206 mg, 70% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, J = 8.5 Hz, 2H), 7.35 (d, J = 8.2 Hz, 1H), 7.13 (d, J = 1.8 Hz, 1H), 7.09 (d, J = 8.5 Hz, 2H), 6.96 (dd, J = 8.2, 1.8 Hz, 1H), 5.02 (s, 2H), 3.07 (m, 2H), 2.79 (m, 2H), 2.53 (m, 3H), 1.87 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 173.8, 142.3, 138.0(2), 136.1, 132.9, 132.5, 131.1, 130.7, 129.8, 128.1, 127.2, 93.4, 65.3, 49.6, 44.0(2), 30.6(2). Mp 198–200 °C (oxalate salt). Anal. Calcd for $C_{19}H_{18}Cl_2INO_2·C_2H_2O_4$: C, 43.47; H, 3.47; N, 2.41. Found: C, 43.92; H, 3.59; N, 2.39.

6.6.10. 4-Methoxylbenzyl 4-(naphthalen-2-yl) piperidine-4-carboxylate (15a)

White solid (162 mg, 72% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88–7.66 (m, 4H), 7.54–7.40 (m, 3H), 7.09 (d, J = 8.8 Hz, 2H), 6.76 (d, J = 8.8 Hz, 2H), 5.05 (s, 2H), 3.75 (s, 3H), 3.15 (m, 3H), 2.84 (m, 2H), 2.67 (m, 2H), 2.03 (t, J = 10.4 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.5, 159.8, 140.3, 133.5, 132.6, 130.1, 128.5, 128.4(2), 128.1, 127.6, 126.4, 126.2, 124.9, 124.2, 114.0(2), 66.8, 55.4, 49.9, 44.2(2), 34.8(2). Mp 197–198 °C (oxalate salt). Anal. Calcd for $C_{24}H_{25}NO_3·C_2H_2O_4·1/3H_2O$: C, 66.32; H, 5.91; N, 2.97. Found: C, 66.34; H, 5.95; N, 2.93.

6.6.11. 4-Nitrobenzyl 4-(naphthalen-2-yl) piperidine-4-carboxylate (15b)

White solid (170 mg, 73% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.97 (d, J = 8.0 Hz, 2H), 7.85–7.77 (m, 4H), 7.48 (m, 2H), 7.17 (d, J = 8.4 Hz, 2H), 5.16 (s, 2H), 3.14 (m, 2H), 2.86 (m, 2H), 2.80 (m 2H), 2.67 (br s, 1H), 2.06 (t, J = 10.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 172.7, 147.9, 142.3, 133.4, 132.8, 129.2, 128.6, 128.4, 128.3(2), 127.7, 127.1(2), 127.0, 125.2, 123.9, 123.2, 65.9, 48.6, 42.0(2), 30.5(2). Mp 182–185 °C (oxalate salt). Anal. Calcd for $C_{23}H_{22}N_2O_4·C_2H_2O_4·1/2H_2O$: C, 61.34; H, 5.15; N, 5.72. Found: C, 61.85; H, 5.04; N, 5.68.

6.6.12. 3,4-Dichlorobenzyl 4-(naphthalen-2-yl) piperidine-4-carboxylate (15c)

White solid (177 mg, 71% yield). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83–7.75 (m, 4H), 7.54–7.47 (m, 3H), 7.24 (d, J = 8.0 Hz, 1H), 7.20 (d, J = 2.0 Hz,1H), 7.89 (dd, J = 8.0, 2.0 Hz, 1H), 5.02 (s, 2H), 3.12 (m, 2H), 2.93 (s, 1H), 2.87 (t J = 11.2 Hz, 2H), 2.68 (d, J = 11.2 Hz, 2H), 2.05 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 174.2, 139.7, 136.2, 133.5, 132.8, 132.7, 132.4, 130.6, 129.8, 128.7, 128.4, 127.7, 127.2, 126.6, 126.5, 125.1, 123.9, 65.2, 49.9, 44.1(2), 34.6(2). Mp 207–208 °C (oxalate salt). Anal. Calcd for $C_{23}H_{21}Cl_2NO_2·C_2H_2O_4$: C, 59.53; H, 4.60; N, 2.78. Found: C, 59.53; H, 5.02; N, 2.60.

6.7. [^{3}H]Citalopram binding assay

Brains from male Sprague–Dawley rats weighing 200–225 g (Taconic Labs) were removed, midbrain dissected and rapidly frozen. Membranes were prepared by homogenizing tissues in 25 volumes (w/v) of 50 mM Tris containing 120 mM NaCl and 5 mM KCl, (pH 7.4 at 25 °C), using a Brinkman Polytron (setting 6 for 20 s) and centrifuged at 20,000*g* for 10 min at 4 °C. The resulting pellet was resuspended in buffer, recentrifuged and resuspended in buffer to a concentration of 7.5 mg/mL. Ligand binding experiments were conducted in assay tubes containing 0.5 mL buffer for 60 min at room temperature. Each tube contained 1.4 nM [^{3}H]citalopram (Perkin Elmer, MA) and 1.5 mg midbrain tissue (original wet weight). Nonspecific binding was determined using 10 μM fluoxetine. Incubations were terminated by rapid filtration through Whatman GF/B filters, presoaked in 0.3% 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 liquid scintillation counter (Beckman Coulter Instruments, Fullerton, California). Data were analyzed by using GraphPad Prism software (San Diego, California).

6.8. [^{3}H]WIN 35,428 binding assay

Male Sprague–Dawley rats (200–250 g, Taconic, Germantown, NY) were decapitated and their brains removed to an ice-cooled dish for dissection of the caudate-putamen. The tissue was homogenized in 30 volumes 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, 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. 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 of protein/sample. Increasing concentrations of the drug being tested were added to triplicate samples of membrane suspension. Five minutes later, [^{3}H]WIN 35,428 (final concentration 1.5 nM) was added and the incubation was continued for 1 h on ice. The incubation was terminated by the addition of 5 mL of 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. Nonspecific binding was defined as binding in the presence of 100 μM cocaine. The 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).

6.9. [^{3}H]Nisoxetine binding assay

Frontal cortex of male Sprague–Dawley rats was removed and frozen. Membranes were prepared by homogenizing tissues in 50 mM Tris (120 mM NaCl, 5 mM KCl; pH 7.4 at 25 °C) and centrifuging (50,000*g* for 10 min at 4 °C). The resulting pellet was then washed and centrifuged two more times. The final pellet was resuspended to a concentration of 80 mg/ml (original wet weight). Assays were conducted in the above Tris buffer with volume totaled to 0.5 mL and a tissue concentration of 8 mg/tube. [^{3}H]Nisoxetine (specific activity 80 Ci/mmol; final concn 0.5 nM, Perkin Elmer, MA) was added and the incubation continued for 1 h on ice. Incubations were terminated by rapid filtration through Whatman GF/B filters, presoaked in 0.05% polyethylenimine (PEI). Nonspecific binding was defined using 1 μM desipramine. For these assays, an initial screen was conducted to assess displacement of nisoxetine at a concentration of 1 and 10 μM of the unknown compound. If there was greater than 50% displacement of nisoxetine, a K_i value was determined in subsequent studies. Data were analyzed with GraphPad Prism software (San Diego, California).

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