N-[ω-(Tetralin-1-yl)alkyl] Derivatives of 3,3-Dimethylpiperidine Are Highly Potent and Selective σ_1 or σ_2 Ligands

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Several 3,3-dimethyl-*N*-[ω-(tetrahydronaphthalen-1-yl)alkyl]piperidine derivatives and some related compounds were prepared. Their affinities and σ-subtype selectivities were investigated by radioligand binding assays, labeling σ_1 receptors with [^{3}H]-SKF 10047 and σ_2 receptors with [^{3}H]-DTG. Many tested compounds bound σ_1 and/or σ_2 receptors with nanomolar or subnanomolar IC_{50} values. Compound (+)-**22**, (+)-3,3-dimethyl-1-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperidine, was the most potent (IC_{50} = 0.089 nM) and selective σ_1 ligand (1340-fold), showing a 10-fold enantioselectivity. Compounds **29** (3,3-dimethyl-1-[4-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-butyl]piperidine) and **31** (3,3-dimethyl-1-[5-(1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-pentyl]piperidine) were highly potent (IC_{50} = 0.016 nM and IC_{50} = 0.008 nM, respectively) and highly selective σ_2 ligands (more than 100 000-fold).

Interest around sigma (σ) receptors has been increased by the perspective of a potential use of σ agents in psychiatric disorders,[1−3] especially as atypical antipsychotics.[4−6] Further possible applications of σ ligands are supposed in cocaine abuse,[7,8] epilepsy,[9] neuroprotection,[10−12] and cognition enhancing,[13] as well as in tumor diagnosis.[14,15] Indeed, suggested functional roles of σ receptors in various tissues include dopamine[16] and NMDA receptor modulation,[17] interaction with neuropeptides and neurosteroids,[3] neurotoxicity in glial cells,[18] and involvement in the modulation of the biosynthesis of rat melatonine.[19] Nevertheless, σ ligands failed in clinical experimentations for schizophrenia,[2] and dystonic side effects of neuroleptics were ascribed to the σ activity.[20,21] Moreover, the individualization of a clear therapeutic target for σ ligands is complicated by the lack of any endogenous σ ligand and by the existence of multiple σ receptor subtypes.[22,23] Therefore the real significance of the enigmatic σ receptor has to be still disclosed.

However further new perspectives of interpretation for the action of σ ligands and for drug development were opened by the recent cloning and expression of the mammalian,[24] and then of the human, σ_1 receptor.[25] This latter possesses a single putative transmembrane domain and is homologue of the yeast sterol C_8-C_7 isomerase. Thus, sterol biosynthesis might be a σ_1 receptor function. When inhibited, it is supposed to produce changes in the lipid composition of cerebral membranes with alteration of the neuronal excitability.[26] It was speculated that the σ_2 receptor could also be an enzyme site. The development of highly selective σ_1 or σ_2 ligands may therefore provide new tools to investigate the functional and physiological role of σ receptors.

Up to now, several structurally unrelated σ ligands have been investigated[27] in structure−activity relationship studies, but few of them are known to be actually selective versus other central nervous system receptors and other σ subtypes. Potent and highly selective σ_1 ligands are (+)-pentazocine and related *N*-benzyl-6,7-benzomorphans[28] and some dextromethorphan analogues.[29] Only recently some selective σ_2 ligands were found by Lundbeck's researchers.[30]

In a previous work[31] we found potent and selective σ_1 ligands, such as some 3,3-dimethyl-*N*-(tetrahydronaphthalen-1-yl)piperidine derivatives, possessing a poor-affinity profile toward D2, 5-HT_{1A}, and PCP receptors. Furthermore, the same (tetralin-1-yl)alkyl moiety was present in some piperazine derivatives, which demonstrated[32] to bind the σ_2 receptor also but without adequate σ-subtype selectivity. Encouraged by such results we prepared a series of *N*-[ω-(1,2,3,4-tetrahydronaphthalen-1-yl)alkyl] and *N*-[ω-(indan-1-yl)alkyl] derivatives of 3,3-dimethylpiperidine and some related compounds (Table 1). In order to contribute to finding new potent and highly selective σ_1 or σ_2 ligands, our interest was focused on the structural features improving the affinity and the σ subtype selectivity. Thus, the 3,3-dimethylpiperidine moiety which is in agreement with Glennon's σ_1 receptorial model[33] was retained. The length of the intermediate alkyl chain and the size and the rigidity of the aliphatic ring were varied as well as the position of a methoxyl group on the aromatic ring. The possible enantioselectivities of σ_1 and σ_2 receptors were investigated preliminary on the enantiomers (+)-**22** and (−)-**22**.

Chemistry

The compounds here reported (Table 1) were mainly prepared from ω-haloalkyl derivatives (Scheme 1) with

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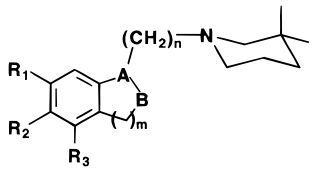
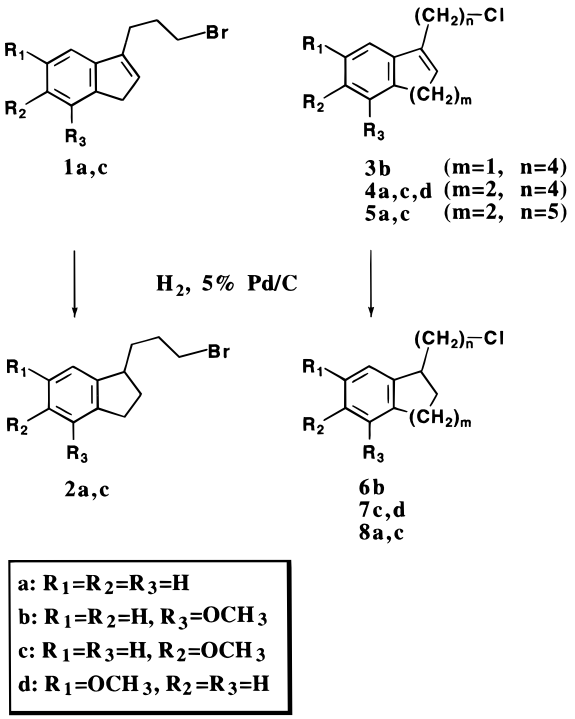
Table 1. Physical Properties



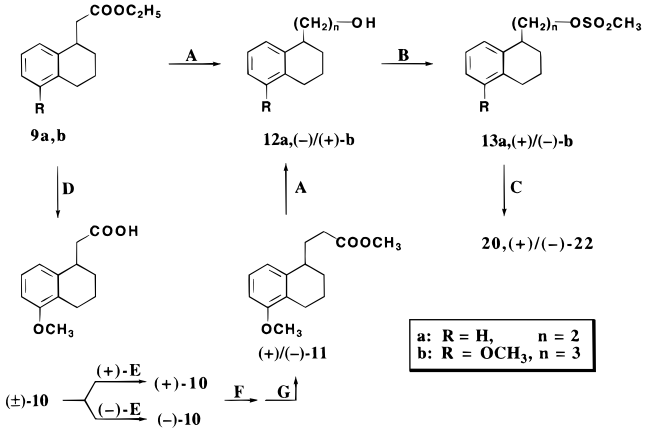
compd	R_1	R_2	R_3	A−B	*m*	*n*	formula[a]	mp (°C)	recryst solv[b]
16	H	H	H	C=CH	1	3	$C_{19}H_{27}N\cdot HCl\cdot H_2O$	189−190	A
17	H	H	H	CH−CH_2	1	3	$C_{19}H_{29}N\cdot HCl$[c]	162	A
18	H	OCH_3	H	CH−CH_2	1	3	$C_{20}H_{31}NO\cdot C_2O_4H_2$	151−152	A
19	H	H	OCH_3	CH−CH_2	1	4	$C_{21}H_{33}NO\cdot HCl\cdot {}^1/_5H_2O$	161−162	A
20	H	H	H	CH−CH_2	2	2	$C_{19}H_{29}N\cdot HCl$	191−192	A
21	H	H	H	CH−CH_2	2	3	$C_{20}H_{31}N\cdot HCl\cdot H_2O$	202−203	B
(±)-**22**[d]	H	H	OCH_3	CH−CH_2	2	3	$C_{21}H_{33}NO\cdot HCl\cdot {}^1/_3H_2O$	168−169	A
(+)-**22**	H	H	OCH_3	CH−CH_2	2	3	$C_{21}H_{33}NO\cdot HCl\cdot {}^1/_2H_2O$	183−184	A
(−)-**22**	H	H	OCH_3	CH−CH_2	2	3	$C_{21}H_{33}NO\cdot HCl$	183−184	A
23	H	H	OH	CH−CH_2	2	3	$C_{20}H_{31}NO\cdot HCl$	235−236	B
24	H	OCH_3	H	CH−CH_2	2	3	$C_{21}H_{33}NO\cdot HCl\cdot {}^1/_2H_2O$	185−187	A
25	OCH_3	H	H	CH−CH_2	2	3	$C_{21}H_{33}NO\cdot HCl\cdot {}^4/_5H_2O$	175−176	A
26	H	H	H	C=CH	2	4	$C_{21}H_{31}N\cdot C_2O_4H_2$	154−155	B
27[d]	H	H	H	CH−CH_2	2	4	$C_{21}H_{33}N\cdot HCl\cdot {}^1/_2H_2O$	175−176	A
28	H	H	OCH_3	CH−CH_2	2	4	$C_{22}H_{35}NO\cdot HCl$	177−178	A
29	H	OCH_3	H	CH−CH_2	2	4	$C_{22}H_{35}NO\cdot HCl$	166−167	A
30	OCH_3	H	H	CH−CH_2	2	4	$C_{22}H_{35}NO\cdot HCl$	181−182	A
31	H	H	H	CH−CH_2	2	5	$C_{22}H_{35}N\cdot HCl {}^1/_4H_2O$	168	A
32	H	OCH_3	H	CH−CH_2	2	5	$C_{23}H_{37}NO\cdot HCl$	175−176	A
33	H	H	H	CH_2−H[e]	0	4	$C_{18}H_{29}N\cdot HCl$	151−152	A

[a] White to ivory-colored (**16** and **22** are pale yellow, **17**, **23**, and **32** are beige-colored) crystalline powders, analyzed for C, H, N; results were within ±0.4% of the theoretical values for the formulas given. [b] A = methylene chloride/ethyl ether, B = methanol/ethyl ether. [c] H: calcd, 9.82; found, 10.32. [d] Compounds previously reported as hydrogen oxalate salts (see ref 31). [e] Phenylpentyl derivative (see Scheme 3).

Scheme 1



Scheme 2[a]

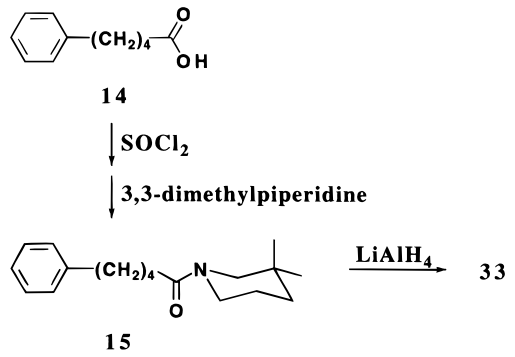


[a] Reagents: A = $LiAlH_4$; B = CH_3SO_2Cl; C = 3,3-dimethylpiperidine; D = NaOH; E = (*R*)-(+)- or (*S*)-(−)-1-phenylethylamine; F = $SOCl_2$; G = CH_2N_2, Ag^+.

3,3-dimethylpiperidine in acetonitrile according to the previously described procedure.[31] The indene intermediates **1a**,**c** and **3b** were prepared from 1-indanone and the appropriate Grignard's reagent.[34,35] 5-chloro-*n*-pentylmagnesium bromide was used to obtain the intermediates **5a**,**c**. Compounds **16** and **26** were prepared[31] from the indene **1a** and the 1,2-dihydronaphthalene **4a**, respectively. Target compounds **17**−**19**, **21**, **24**, **25**, and **28**−**32** were prepared from indanes **2** and **6** and tetrahydronaphthalenes **7** and **8**, which were obtained from the corresponding unsaturated intermediates **1** and **3**−**5** by catalytic hydrogenation.[31,35]

Following a previously reported[36] synthetic route, the ester **9a**[37] (Scheme 2) was prepared and reduced to 2-(1,2,3,4-tetrahydronaphthalen-1-yl)ethanol[38] (**12a**) with $LiAlH_4$. The alcohol **12a** was derivatized to the methylsulfonate **13a** with methanesulfonyl chloride,[39] and the latter was reacted with 3,3-dimethylpiperidine to yield the tetralinethyl compound **20**. The optically active compounds (+)-**22** and (−)-**22** were prepared in an analogous manner from (−)- and (+)-3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propanol, (−)-**12b** and (+)-**12b**, respectively, via the corresponding sul-

Scheme 3



fonates (+)-**13b** and (−)-**13b**. An alkaline hydrolysis of the ester **9b**[36] gave the racemic acid (±)-**10**.[40] Its salts, first with (*R*)-(+)-1-phenylethylamine and then with (*S*)-(−)-1-phenylethylamine, were resolved by fractional crystallization. (+)-**10** and (−)-**10** were individually derivatized to the corresponding acyl chlorides and then transformed to the methyl esters (+)-**11** and (−)-**11** with diazomethane in the presence of silver benzoate.[41] Reduction of (+)-**11** and (−)-**11** by $LiAlH_4$ gave (−)-**12b** and (+)-**12b**, respectively, which were treated in the above-mentioned way to yield the compounds (+)-**22** and (−)-**22**, respectively. The phenolic derivative **23** was obtained by demethylation of compound **22** with 48% HBr. Compound **33** (Scheme 3) was prepared from the corresponding acyl chloride of 5-phenylvaleric acid (**14**) and 3,3-dimethylpiperidine and by subsequent reduction of the derived amide **15** with $LiAlH_4$.

Pharmacology

All target compounds **16**−**33** as hydrochloride salts (compounds **18** and **26** as hydrogen oxalate salts) were evaluated for in vitro affinity on σ_1 and σ_2 receptors by radioreceptor binding assays. [^{3}H]-(+)-SKF 10047 (*N*-allylnormetazocine) was used as a specific radioligand for the σ_1 receptor because of the legal restrictions to the use of [^{3}H]-(+)-pentazocine. This assay was performed in the presence of unlabeled MK-801 ((+)-5-methyl-10,11-dihydro-5*H*-dibenzo-[*a*,*d*]cyclohepten-5,10-imine hydrogen maleate) to mask MK-801 sites (PCP binding sites) in the NMDA receptor. Whole rat brain membranes were used as tissue, and cold (+)-SKF 10047 was used to define the specific binding. σ total binding was performed using [^{3}H]-DTG as specific radioligand, guinea-pig brain cortex as tissue, and cold DTG to define the specific binding. The study of the responses of this preparation to specific σ_1 displacers such as (+)-SKF 10047 or dextromethorphan revealed that, using the adopted conditions, the measured binding was for over 2/3 of σ_2 type.

Concentrations required to inhibit 50% of radioligand specific binding (IC_{50}) were determined by three independent experiments with sample in duplicate or triplicate and six to nine different concentrations of the drug studied. Specific binding represented 75−88% of the total binding. The K_d values were calculated from saturation experiments using the latest version of the LIGAND computerized program as originally described by Munson and Rodbard.[42]

Table 2. Binding Affinities and Selectivities

	IC_{50}, nM[a]		IC_{50} ratio	
compd	[^{3}H]-(+)-SKF 10047	[^{3}H]-DTG	σ_2/σ_1	σ_1/σ_2
16	0.99 ± 0.05	1.09 ± 0.04	1	1
17	6.9 ± 0.5	4.5 ± 0.4	0.6	1.5
18	4660 ± 440	1.01 ± 0.03		4610
19	9.3 ± 0.5	4.6 ± 0.2	0.5	2
20	>10 000	1.10 ± 0.08		>9090
21	252 ± 9	135 ± 6	0.5	2
(±)-**22**	0.48 ± 0.03[b]	138 ± 6	287	
(+)-**22**	0.089 ± 0.008	119 ± 5	1340	
(−)-**22**	0.85 ± 0.11	111 ± 6	131	
23	41.0 ± 4.2	100 ± 6	2	0.4
24	>10 000	88 ± 7		>114
25	22.0 ± 2.1	109 ± 3	5	
26	9450 ± 960	1.1 ± 0.1		8590
27	0.69 ± 0.03[b]	5.5 ± 0.1	8	
28	978 ± 77	129 ± 7		8
29	2150 ± 110	0.016 ± 0.003		>100 000
30	25.6 ± 2.0	0.44 ± 0.04		58
31	1520 ± 150	0.008 ± 0.001		>100 000
32	0.62 ± 0.01	0.030 ± 0.001		21
33	5830 ± 840	10.0 ± 1.6		583
(+)-SKF 10047	92 ± 5			
DTG		45 ± 4		

[a] Data are expressed as mean values of three experiments with duplicate or triplicate samples. [b] Previously tested also as hydrogen oxalate salt in [^{3}H]-(+)-pentazocine binding on whole rat brain membranes (see ref 31).

Results and Discussion

Nearly all of the 3,3-dimethylpiperidine derivatives here reported showed a moderate to very high σ affinity (Table 2).

Structure−σ_1 Affinity. The potent ligands (±)-**22** and **27** confirmed the results of their previous[31] binding assay with [^{3}H]-(+)-pentazocine. Besides, (±)-**22** revealed a good σ_1 versus σ_2 selectivity (287-fold). The σ_1 affinity of its upper homologue **28** dropped (IC_{50} = 978 nM), suggesting that a four-methylene chain is incompatible with the 5-methoxyl substitution. On the other hand, when σ_1 binding data of the homologous series **20**, **21**, **27**, and **31** were compared, the best affinity was shown by the tetralin having a four-membered intermediate chain (**27**). In the series of the 6-MeO derivatives **24**, **29**, and **32**, only the latter reached a significant IC_{50} value (0.62 nM), but it showed a higher affinity toward the σ_2 receptor. A poor σ_1 affinity (IC_{50} = 5830 nM) was demonstrated by the phenylpentyl derivative **33**, where its intermediate chain has a greater conformational freedom than that of the related tetralin **27**. As far as the methoxyl substitution is concerned, the 5-methoxyl derivative (±)-**22** showed the highest σ_1 affinity and selectivity compared to its isomers and the corresponding phenolic derivative **23**. When the enantiomers of (±)-**22** were tested, the σ_1 affinity of (+)-**22** appeared almost 10-fold greater than that of (−)-**22**, whereas their σ_2 affinities were equivalent. Therefore the compound (+)-**22** was a highly potent (IC_{50} = 0.089 nM) and selective (1340-fold) σ_1 ligand.

Structure−σ_2 Affinity. Tested compounds were all σ_2 ligands to some extent. In the homologous series of the ω-(tetralin-1-yl)alkyl derivatives **20**, **21**, **27**, and **31**, an intermediate chain of five methylenes (**31**) gave the best results in terms of σ_2 affinity and selectivity (IC_{50} = 0.008 nM and >100 000-fold). Very high σ_2 affinities were found also for the 6-methoxytetralins **32** and **29**

(IC_{50} = 0.030 nM and IC_{50} = 0.016 nM, respectively). The first had a five-membered chain, the second a four-membered chain and was highly σ_2 selective (>100 000-fold). *N*-propyl derivatives **21**, **24**, and **25** demonstrated a lower σ_2 affinity compared to the respective *n*-butyl derivatives **27**, **29**, and **30**. Generally, highly potent σ_2 affinity seemed linked to a chain length of at least four methylenes. An adequate σ_2 affinity and a certain selectivity remained in the open derivative **33**. In the (tetrahydronaphthalen-1-yl)-*n*-propyl derivatives (**21**, (±)-**22**, **24**, **25**) the presence of the methoxyl group wherever positioned was unimportant, since their IC_{50} values ran around 100 nM. A similar affinity without enantioselectivity was maintained by (+)-**22** and (−)-**22**.

Conclusions. The above 3,3-dimethylpiperidines bind both σ_1 and σ_2 receptors, and 3,3-dimethylpiperidine is a moiety able to ingenerate a generic σ affinity. A clear structure−affinity relationship appears arduous to be defined, although the length of the intermediate chain and the bicyclic nucleus seem to be important structural requirements for σ subtype affinities and selectivites. Generally speaking, more strictly proper features appear to be required for a σ_1 selective binding in this series of compounds. Thus compound (+)-**22** can be considered a new, very specific σ_1 ligand. A wider array of structures seems to be tolerated by the σ_2 receptor. Therefore, compounds **29** and **31** are highly potent and quite selective σ_2 ligands.

Experimental Section

Chemistry. Column chromatography was carried out with 1:30 ICN silica gel 60A (63−200 μm) as the stationary phase. Melting points were determined in open capillaries using a Gallenkamp electrothermal apparatus. Elemental analyses of only solid samples were performed by the microanalytical section of our department with a Carlo Erba 1106 autoanalyzer; the analytical results (C, H, N) were within ±0.4% of the theoretical values, unless otherwise stated. ^{1}H-NMR spectra were recorded in $CDCl_3$ either on a Varian EM-390 (when 90 MHz is indicated) using tetramethylsilane as internal standard, or on a Bruker AM 300 WB instrument (300 MHz). Chemical shifts are reported in parts per million (ppm, δ). Recording of mass spectra was done on a Hewlett-Packard 5995 C gas chromatograph/mass spectrometer, electron impact 70 eV, equipped with a Hewlett-Packard 59970 A workstation; only significant *m*/*z* peaks, with their percent relative intensity indicated in parentheses, are reported herein. All compounds had NMR and mass spectra that were consistent with their structures. All of the spectral data of amines refer to their free bases. Optical rotations were measured with a Perkin-Elmer 241 MC polarimeter at room temperature (20 °C). HPLC was performed on a Waters chromatograph (Waters Assoc., Milford, MA) model 600 equipped with a U6K model injector and a 481 model variable wavelength detector.

3-(3-Bromo-*n*-propyl)-1*H*-indene (1a): pale yellow oil (44% overall yield); ^{1}H-NMR (90 MHz) δ 2.18 (m, 2H, J = 7 Hz, CH_2CH_2Br), 2.51−2.58 (br t, 2H, allylic), 3.20−3.29 (d, 2H, $J \sim 2$ Hz, benzylic), 3.40 (t, 2H, J = 6 Hz, CH_2Br), 6.25 (t, 1H, $J \sim 2$ Hz, vinylic), 7.10−7.55 (mm, 4H, aromatic); GC/MS *m*/*z* 269 (M^+ + 3, 2), 268 (M^+ + 2, 17), 266 (M^+, 18), 130 (88), 129 (100), 128 (67).

3-(3-Bromo-*n*-propyl)-1*H*,6-methoxyindene (1c): colorless oil (55% overall yield); ^{1}H-NMR 2.20 δ (m, 2H, J = 7 Hz), 2.65−2.71 (br t, 2H), 3.29 (br d, 2H), 3.47 (t, 2H, J = 7 Hz), 3.82 (s, 3H, OCH_3), 6.11 (br t, 1H), 6.83−7.25 (mm, 3H); GC/MS *m*/*z* 239 (M^+ + 3, 2), 238 (M^+ + 2, 12), 236 (M^+, 11), 159 (31), 160 (100), 115 (25).

1-(3-Bromo-*n*-propyl)indane (2a): pale yellow oil (quantitative yield); ^{1}H-NMR δ 1.51−1.75 (mm, 2H, 1 of chain $CHCH_2$ and 1 of *endo*-CH_2), 1.93−2.05 (mm, 3H, 1 of $CHCH_2$ and CH_2CH_2Br), 2.23−2.34 (m, 1H, 1 of *endo*-CH_2), 2.79−2.98 (mm, 2H, benzylic CH_2), 3.09−3.18 (m, 1H, benzylic CH), 3.45 (t, 2H, J = 6 Hz, CH_2Br), 7.14−7.22 (mm, 4H, aromatic); GC/MS *m*/*z* 241 (M^+ + 3, 1), 240 (M^+ + 2, 5), 239 (M^+ + 1, 1), 238 (M^+, 5), 117 (100), 115 (27).

1-(3-Bromo-*n*-propyl)-5-methoxyindane (2c): colorless oil (46% yield); ^{1}H-NMR δ 1.46−1.51 (m, 1H, 1 of chain $CHCH_2$), 1.53−1.77 (m, 1H, 1 of *endo*-CH_2), 1.84−2.01 (mm, 3H), 2.22−2.60 (m, 1H), 2.77−3.11 (mm, 3H), 3.43 (t, 2H, J = 7 Hz), 3.77 (s, 3H, OCH_3), 6.69−7.09 (mm, 3H); GC/MS *m*/*z* 271 (M^+ + 3, 1), 270 (M^+ + 2, 5), 269 (M^+ + 1, 1), 268 (M^+, 5), 147 (100), 115 (14).

3-(4-Chloro-*n*-butyl)-1*H*,7-methoxyindene (3b): colorless oil (34% overall yield); ^{1}H-NMR δ 1.75−1.94 (mm, 4H, $(CH_2)_2CH_2Cl$), 2.56−2.60 (br t, 2H, allylic), 3.30−3.31 (br d, 2H, benzylic), 3.58 (t, 2H, J = 6 Hz, CH_2Cl), 3.90 (s, 3H, OCH_3), 6.22 (br s, 1H, vinylic), 6.76−7.33 (mm, 3H, aromatic); GC/MS *m*/*z* 239 (M^+ + 3, 1), 238 (M^+ + 2, 9), 237 (M^+ + 1, 5), 236 (M^+, 26), 160 (52), 159 (100), 115 (60).

4-(4-Chloro-*n*-butyl)-1,2-dihydro-7-methoxynaphthalene (4c): colorless oil (48% overall yield); ^{1}H-NMR δ 1.60−1.94 (mm, 4H, $(CH_2)_2CH_2Cl$), 2.18−2.48 (mm, 4H, allylic), 2.70 (t, 2H, J = 8 Hz, benzylic), 3.54 (t, 2H, J = 7 Hz, CH_2Cl), 3.79 (s, 3H, OCH_3), 5.72 (br t, 1H, vinylic), 6.69−7.16 (mm, 3H, aromatic); GC/MS *m*/*z* 253 (M^+ + 3, 1), 252 (M^+ + 2, 9), 251 (M^+ + 1, 5), 250 (M^+, 26), 174 (100), 173 (22), 159 (68), 144 (28), 128 (32), 115 (41).

4-(5-Chloro-*n*-pentyl)-1,2-dihydronaphthalene (5a): colorless oil (34% overall yield); ^{1}H-NMR δ 1.42−1.89 (mm, 6H, $(CH_2)_3CH_2Cl$), 2.22−2.30 and 2.41−2.51 (mm, 4H, allylic), 2.76 (t, 2H, J = 8 Hz, benzylic), 3.55 (t, 2H, J = 7 Hz, CH_2Cl), 5.86−5.89 (br t, 1H, vinylic), 7.13−7.28 (mm, 4H, aromatic); GC/MS *m*/*z* 237 (M^+ + 3, 1), 236 (M^+ + 2, 5), 235 (M^+ + 1, 3), 234 (M^+, 14), 144 (100), 129 (99), 128 (60), 115 (30).

4-(5-Chloro-*n*-pentyl)-1,2-dihydro-7-methoxynaphthalene (5c): colorless oil (17% overall yield); ^{1}H-NMR δ 1.42−1.85 (mm, 6H), 2.17−2.24 and 2.39−2.43 (mm, 4H), 2.72 (t, 2H, J = 8 Hz), 3.52 (t, 2H, J = 7 Hz), 3.79 (s, 3H, OCH_3), 5.69−5.72 (br t, 1H, vinylic), 6.69−7.15 (mm, 3H); GC/MS *m*/*z* 267 (M^+ + 3, 1), 266 (M^+ + 2, 5), 265 (M^+ + 1, 3), 264 (M^+, 14), 174 (100), 129 (99), 159 (36).

1-(4-Chloro-*n*-butyl)-4-methoxyindane (6b): colorless oil (quantitative yield); ^{1}H-NMR δ 1.33−1.91 (mm, 7H, $(CH_2)_3CH_2Br$ and 1 of *endo*-CH_2), 2.25−2.36 (m, 1H, 1 of *endo*-CH_2), 2.71−2.97 (mm, 2H, benzylic CH_2), 3.08−3.18 (m, 1H, benzylic CH), 3.57 (t, 2H, J = 7 Hz, CH_2Br), 3.84 (s, 3H, OCH_3), 6.68−7.19 (mm, 3H, aromatic); GC/MS *m*/*z* 241 (M^+ + 3, 1), 240 (M^+ + 2, 4), 239 (M^+ + 1, 2), 238 (M^+, 12), 148 (23), 147 (100), 115 (18).

1-(4-Chloro-*n*-butyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (7c): colorless oil (quantitative yield); ^{1}H-NMR δ 1.43−1.92 (mm, 10H, $(CH_2)_2CH(CH_2)_3$), 2.72−2.75 (mm, 3H, benzylic), 3.55 (t, 2H, J = 7 Hz, CH_2Cl), 3.77 (s, 3H, OCH_3), 6.60−7.19 (mm, 3H, aromatic); GC/MS *m*/*z* 254 (M^+ + 2, 2), 253 (M^+ + 1, 1), 252 (M^+, 5), 161 (100).

1-(4-Chloro-*n*-butyl)-7-methoxy-1,2,3,4-tetrahydronaphthalene (7d): colorless oil (60% yield); ^{1}H-NMR δ 1.45−1.89 (mm, 10H), 2.63−2.76 (mm, 3H), 3.55 (t, 2H, J = 7 Hz), 3.77 (s, 3H), 6.65−7.00 (mm, 3H); GC/MS *m*/*z* 254 (M^+ + 2, 5), 253 (M^+ + 1, 2), 252 (M^+, 13), 162 (21), 161 (100), 115 (13).

1-(5-Chloro-*n*-pentyl)-1,2,3,4-tetrahydronaphthalene (8a): colorless oil (88% yield); ^{1}H-NMR δ 1.31−2.02 (mm, 12H, $(CH_2)_2CH(CH_2)_4$), 2.71−2.95 (mm, 3H, benzylic), 3.57 (t, 2H, J = 7 Hz, CH_2Cl), 7.10−7.22 (mm, 4H, aromatic); GC/MS *m*/*z* 239 (M^+ + 3, 1), 238 (M^+ + 2, 2), 237 (M^+ + 1, 1), 236 (M^+, 5), 132 (12), 131 (100), 115 (12).

1-(5-Chloro-*n*-pentyl)-6-methoxy-1,2,3,4-tetrahydronaphthalene (8c): colorless oil (quantitative yield); ^{1}H-NMR δ 1.31−1.89 (mm, 12H), 2.68−2.74 (mm, 3H), 3.52 (t, 2H, J = 7 Hz), 3.76 (s, 3H, OCH_3), 6.59−7.08 (mm, 3H); GC/MS *m*/*z* 268 (M^+ + 2, 2), 267 (M^+ + 1, 1), 266 (M^+, 4), 161 (100).

5-Methoxy-1,2,3,4-tetrahydro-1-naphthaleneacetic Acid (10): it was purified on silica gel column eluting with $CHCl_3$; ^{1}H-NMR (90 MHz) δ 1.60−1.96 (mm, 4H, *endo*-$(CH_2)_2$), 2.46−2.77 (mm, 4H, CH_2CO and benzylic CH_2), 3.13−3.50 (m, 1H, CH), 3.80 (s, 3H, OCH_3), 6.58−7.27 (mm, 3H, aromatic), 10.35−10.95 (br s, 1H, OH, D_2O exchanged); GC/MS *m*/*z* 221 ($M^+ + 1$, 10), 220 (M^+, 74), 174 (21), 161 (100), 160 (91), 159 (30), 158 (21), 145 (21), 129 (23), 128 (22), 115 (34).

Enantiomeric Resolution of (±)-10. A solution of carboxylic acid (±)-**10** (2.20 g, 10.0 mmol) and an equimolar amount of *R*-(+)-1-phenylethylamine (1.21 g) in $CHCl_3$ was concentrated under reduced pressure. Et_2O was added to precipitate the salt, which was filtered and recrystallized four times from $CHCl_3$/*n*-hexane as white needles. These were dissolved in $CHCl_3$, and the solution was washed three times with 3 N HCl, washed with H_2O, and then dried (Na_2SO_4). The removal of the solvent under reduced pressure gave (+)-**10**. Enantiomeric excess of (+)-**10** was determined by HPLC on Chiralcel OD column (25 × 0.46 cm, 0.8 mL/min, UV 254 nm) eluting solely with *n*-hexane/2-propanol/trifluoroacetic acid, 98:2:0.01; (+)-**10** was >99% ee. $[\alpha]_D = +8.8°$ (*c* 1.0, $CHCl_3$). The collected mother liquors were concentrated to dryness under reduced pressure, and the residue was solubilized in $CHCl_3$. This solution was washed (dil. HCl), dried (Na_2SO_4), and then concentrated to dryness in vacuo. The residual carboxylic acid was dissolved in $CHCl_3$ and mixed to an equimolar amount of *S*-(−)-1-phenylethylamine. The enantiomer (−)-**10** was obtained and analyzed for enantiomeric excess as previously described for the enantiomer (+)-**10**. Compound (−)-**10** displayed ee > 99% and $[\alpha]_D = -8.7°$ (*c* 1.0, $CHCl_3$).

(+)-3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-propanoic Acid Methyl Ester [(+)-11]. The carboxylic acid (+)-**10** (1.10 g, 5.0 mmol) in anhydrous Et_2O (15 mL) was stirred with freshly distilled $SOCl_2$ (10 mL) and with a few drops of pyridine for 30 min at room temperature. The mixture was concentrated under reduced pressure to give a pale yellow oil. The residue dissolved in anhydrous toluene (10 mL) was added to a cooled (−10 °C) diazomethane ethereal solution (prepared from 15 g of Diazald). The mixture was stirred for 1 h at the same temperature and then for 2 h at room temperature. Then it was concentrated under reduced pressure, and the residue was refluxed in anhydrous MeOH for 2 h in the presence of 10% silver benzoate in triethylamine (1 mL). The cooled mixture was filtered on Celite and concentrated under reduced pressure. The crude residue was chromatographed on a silica gel column (petroleum ether/ethyl acetate, 9:1, as eluent) to give (+)-**11** as a colorless oil (1.03 g, 83% yield): $[\alpha]_D = +11.8°$ (*c* 2.4, $CHCl_3$); ^{1}H-NMR (90 MHz) δ 1.55−2.20 (mm, 6H, $(CH_2)_2CHCH_2$), 2.31−2.56 (m, 2H, CH_2CO), 2.58−2.98 (mm, 3H, benzylic), 3.71 (s, 3H, $COOCH_3$), 3.82 (s, 3H, OCH_3), 6.60−7.33 (mm, 3H, aromatic); GC/MS *m*/*z* 249 ($M^+ + 1$, 6), 248 (M^+, 38), 175 (27), 174 (100), 162 (23), 161 (62), 159 (23), 115 (25).

(−)-3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-propanoic Acid Methyl Ester [(−)-11]. The enantiomer (−)-**11** was prepared as above starting from (−)-**10**. The compound (−)-**11** had $[\alpha]_D = -12.0°$ (*c* 3.0, $CHCl_3$).

(−)-3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-propanol [(−)-12b]. A solution of ester (+)-**11** (4.0 mmol) in anhydrous THF was added to a cooled (−10 °C) suspension of $LiAlH_4$ (0.16 g, 4.3 mmol) in the same solvent. The mixture was stirred overnight at room temperature and then cooled and treated with water. The solid was filtered, and the filtrate was concentrated under reduced pressure. The residue was chromatographed (CH_2Cl_2 as eluent) to give (−)-**12b** as a colorless oil (0.85 g, 90% yield): $[\alpha]_D = -2.8°$ (*c* 3.8, $CHCl_3$); ^{1}H-NMR (90 MHz) δ 1.50−1.91 (mm, 9H, $(CH_2)_2CH(CH_2)_2$ and OH, D_2O exchanged), 2.53−2.88 (mm, 3H, benzylic), 3.54−3.73 (m, 2H, CH_2OH), 3.80 (s, 3H, OCH_3), 6.57−7.26 (m, 3H, aromatic); GC/MS *m*/*z* 221 ($M^+ + 1$, 3), 220 (M^+, 23), 162 (19), 161 (100), 115 (20).

(+)-3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-propanol [(+)-12b]. The alcohol (+)-**12b** was prepared starting from (−)-**11**, as described for (−)-**12b**. (+)-**12b** had $[\alpha]_D = +3.0°$ (*c* 3.0, $CHCl_3$).

2-(1,2,3,4-Tetrahydronaphthalen-1-yl)ethyl Methanesulfonate (13a). Methanesulfonyl chloride (2.6 g, 23 mmol) was added to a solution of (1,2,3,4-tetrahydronaphthalen-1-yl)ethanol, **12a** (3.7 g, 21 mmol), and triethylamine (4.2 g, 42 mmol) in 50 mL of CH_2Cl_2. The reaction was worked up as described.[39] The crude oil was chromatographed (CH_2Cl_2 as eluent) to obtain compound **13a** (4.0 g, 75% yield): ^{1}H-NMR δ 1.64−2.23 (mm, 6H, $(CH_2)_2CHCH_2$), 2.70−2.87 (mm, 2H, benzylic CH_2), 2.94−3.01 (mm, 4H, SCH_3 and benzylic CH), 4.33 (t, 2H, $J = 6$ Hz, CH_2O), 7.04−7.15 (mm, 4H, aromatic); GC/MS *m*/*z* 256 ($M^+ + 2$, 1), 255 ($M^+ + 1$, 1), 254 (M^+, 2), 131 (59), 130 (100), 129 (56), 115 (27), 91 (26).

(+)-3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl Methanesulfonate [(+)-13b]. Mesylchloride (0.6 g, 5.0 mmol) and (−)-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propanol, (−)-**12b** (1.0 g, 4.6 mmol) were reacted in the presence of triethylamine (0.9 g, 9.0 mmol) according to the procedure described for **13a**, to afford 0.98 g of (+)-**13b** (75% yield): $[\alpha]_D = +2.8°$ (*c* 1.5, $CHCl_3$); ^{1}H-NMR δ 1.58−1.95 (mm, 8H, $(CH_2)_2CH(CH_2)_2$), 2.51−2.80 (mm, 3H, benzylic), 2.98 (s, 3H, SCH_3), 3.79 (s, 3H, OCH_3), 4.22 (t, 2H, $J = 6$ Hz, CH_2O), 6.58−7.15 (mm, 3H, aromatic); GC/MS *m*/*z* 301 ($M^+ + 3$, 1), 300 ($M^+ + 2$, 3), 299 ($M^+ + 1$, 9), 298 (M^+, 51), 174 (43), 161 (100), 159 (27).

(−)-3-(5-Methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl Methanesulfonate [(−)-13b]. According to the above procedure, (−)-**13b** was prepared from (+)-**12b** in 56% yield: $[\alpha]_D = -3.4°$ (*c* 1.0, $CHCl_3$).

5-Phenyl-*n*-pentanoic Acid 3,3-Dimethylpiperidine Amide (15). Freshly distilled $SOCl_2$ (10 mL) was added dropwise to a stirred and ice-cooled solution of 5-phenylvaleric acid, **14**, (10.0 g, 56 mmol) in CH_2Cl_2 (100 mL) under N_2. When the room temperature was reached, the solvent was evaporated under reduced pressure. The crude yellow oil was dissolved in CH_2Cl_2 (50 mL) and added dropwise to a stirred and ice-cooled solution of 3,3-dimethylpiperidine (7.0 g, 62 mmol) and triethylamine (excess) in CH_2Cl_2 (50 mL), under N_2. The mixture was stirred overnight at room temperature, and then it was washed twice (20 mL of 2N HCl), dried (Na_2SO_4), and concentrated under reduced pressure. The crude residue was purified by column chromatography (petroleum ether/ethyl acetate, 7:3 as eluent) to give pure amide **15** (8.3 g, 54% yield) as a yellow oil: ^{1}H-NMR[43] δ 0.87 and 0.89 (2s, 6H, 2 CH_3), 1.36 (t, 2H, $J = 6$ Hz, $CH_2C(CH_3)_2$), 1.52 (m, 2H, $NCH_2CH_2CH_2$); 1.60−1.73 (mm, 4H, chain CH_2CH_2), 2.27 and 2.34 (m, 2H, CH_2CO), 2.62 (br t, 2H, benzylic), 3.01 and 3.23 (2s, 2H, $NCH_2C(CH_3)_2$), 3.28 and 3.48 (2t, 2H, $J = 5.7$ Hz, NCH_2CH_2), 7.13−7.28 (mm, 5H, aromatic); GC/MS *m*/*z* 275 ($M^+ + 2$, 1), 274 ($M^+ + 1$, 7), 273 (M^+, 32), 168 (56), 155 (60), 154 (34), 140 (48), 98 (33), 91 (100).

Preparation of 3,3-Dimethylpiperidine Derivatives 16−22, 24−26, 28−32. Title compounds were prepared according to a reported reaction.[31] Unless otherwise stated, they were obtained as colorless oils after column chromatography (CH_2Cl_2/MeOH, 95:5, as eluent) with a 60−70% yield.

3,3-Dimethyl-1-[3-(1*H*-inden-3-yl)-*n*-propyl]piperidine (16): pale yellow oil, eluted with $CHCl_3$ (73% yield); ^{1}H-NMR δ 0.95 (s, 6H, 2 CH_3), 1.21 (t, 2H, $J = 6$ Hz, $CH_2C(CH_3)_2$), 1.55−1.61 (mm, 2H, piperidine CH_2), 1.78−1.88 (m, 2H, chain CH_2), 2.02 [s, 2H, $NCH_2C(CH_3)_2$], 2.32−2.36 (mm, 4H, CH_2NCH_2), 2.53−2.59 (mm, 2H, allylic), 3.30−3.31 (d, 2H, $J = 2$ Hz, benzylic), 7.13−7.45 (m, 1H, vinylic), 6.64−6.97 (mm, 4H, aromatic); GC/MS *m*/*z* 270 ($M^+ + 1$, 1), 269 (M^+, 2), 128 (22), 126 (100).

3,3-Dimethyl-1-[3-(indan-1-yl)-*n*-propyl]piperidine (17): eluted with $CHCl_3$ (45% yield); ^{1}H-NMR δ 0.92 (s, 6H, 2 CH_3), 1.19 (t, 2H, $J = 6$ Hz, $CH_2C(CH_3)_2$), 1.33−1.89 (mm, 7H, CH-$(CH_2)_2$, 1 of *endo*-CH_2 and piperidine CH_2), 1.98−2.00 (br d, 2H, $NCH_2C(CH_3)_2$), 2.21−2.32 (mm, 5H, CH_2NCH_2 and 1 of *endo*-CH_2), 2.74−3.13 (mm, 3H, benzylic), 7.08−7.21 (mm, 4H, aromatic); GC/MS *m*/*z* 272 ($M^+ + 1$, 2), 271 (M^+, 7), 126 (100).

3,3-Dimethyl-1-[3-(5-methoxyindan-1-yl)-*n*-propyl]piperidine (18): 89% yield; ^{1}H-NMR δ 0.93 (s, 6H), 1.20 (t, 2H, J = 6 Hz), 1.24−1.84 (mm, 7H), 2.03 (br d, 2H), 2.21−2.37 (mm, 5H), 2.72−3.07 (mm, 3H), 3.76 (s, 3H, OCH_3), 6.68−7.08 (mm, 3H); GC/MS m/z 302 ($M^+ + 1$, 3), 301 (M^+, 9), 126 (100).

3,3-Dimethyl-1-[4-(4-methoxyindan-1-yl)-*n*-butyl]piperidine (19): ^{1}H-NMR δ 0.92 (s, 6H), 1.19 (t, 2H, J = 6 Hz), 1.35−1.86 (mm, 9H, CH(CH_2)$_3$, 1 of *endo*-CH_2 and piperidine CH_2), 2.00 (br s, 2H), 2.21−2.32 (mm, 5H), 2.67−3.13 (m, 3H), 3.81 (s, 3H, OCH_3), 6.64−7.16 (mm, 3H); GC/MS m/z 316 ($M^+ + 1$, 2), 315 (M^+, 8), 126 (100).

3,3-Dimethyl-1-[2-(1,2,3,4-tetrahydronaphthalen-1-yl)-ethyl]piperidine (20): eluted with $CHCl_3$/MeOH, 9:1; ^{1}H-NMR δ 0.95 (s, 6 H, 2 CH_3), 1.23 (t, 2 H, J = 6 Hz, $CH_2C(CH_3)_2$), 1.56−2.11 (mm, 10 H, (CH_2)$_2$CH(CH_2)$_2$N and piperidine CH_2), 2.26−2.46 (m, 4H, CH_2NCH_2), 2.74−2.90 (mm, 3H, benzylic), 7.02−7.19 (m, 4H, aromatic); GC/MS m/z 273 ($M^+ + 2$, 1), 272 ($M^+ + 1$, 1), 271 (M^+, 10), 126 (100).

3,3-Dimethyl-1-[3-(1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperidine (21): 58% yield; ^{1}H-NMR δ 0.98 (s, 6H, 2 CH_3), 1.24−1.25 (m, 2H, $CH_2C(CH_3)_2$), 1.55−1.86 (mm, 10H, (CH_2)$_2$CH(CH_2)$_2$ and piperidine CH_2), 1.97−2.67 (mm, 6H, $NCH_2C(CH_3)_2$ and CH_2NCH_2), 2.71−2.74 (mm, 3H, benzylic), 7.02−7.16 (mm, 4H, aromatic); GC/MS m/z 286 ($M^+ + 1$, 2), 285 (M^+, 9), 126 (100).

(+)- and (−)-3,3-Dimethyl-1-[3-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperidine [(+)- and (−)-22]. Enantiomeric excess for (+)-**22** and (−)-**22** was determined by chiral HPLC in the same conditions as for (+)-**10** and (−)-**10**, eluting solely with *n*-hexane/2-propanol 98:2; both enantiomers displayed ee > 99%; $[\alpha]_D = +1.0°$ and $-1.0°$, respectively (c 1.0, $CHCl_3$).

3,3-Dimethyl-1-[3-(5-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperidine (23). Compound **22** (1.0 g, 3.2 mmol) was stirred in 80 mL of 48% HBr, and then the mixture was refluxed for 12 h. After cooling, it was made alkaline with conc. KOH, and then it was extracted three times with Et_2O. The collected organic layers were dried (Na_2SO_4) and evaporated to dryness, affording a residue which was purified by column chromatography ($CHCl_3$/CH_3OH, 9:1, as eluent). Pure **23** (0.91 g, 93% yield) was a pale yellow oil: ^{1}H-NMR δ 0.94 (s, 6H, 2 CH_3), 1.21 (t, 2H, J = 6 Hz, $CH_2C(CH_3)_2$), 1.50−1.91 (mm, 10H, (CH_2)$_2$CH(CH_2)$_2$ and piperidine CH_2), 2.00−2.10 (br s, 2H, $NCH_2C(CH_3)_2$), 2.25−2.35 (mm, 4H, CH_2NCH_2), 2.55−2.80 (mm, 3H, benzylic), 4.80−5.30 (br s, 1H, OH, D_2O exchanged), 6.56−7.01 (mm, 3H, aromatic); GC/MS m/z 302 ($M^+ + 1$, 4), 301 (M^+, 15), 126 (100).

3,3-Dimethyl-1-[3-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperidine (24): ^{1}H-NMR δ 0.99 (s, 6H, 2 CH_3), 1.26 (t, 2H, J = 6 Hz, $CH_2C(CH_3)_2$), 1.51−1.84 (mm, 10H, (CH_2)$_2$CH(CH_2)$_2$ and piperidine CH_2), 2.10−2.30 (br s, 2H, $NCH_2C(CH_3)_2$), 2.35−2.55 (mm, 4H, CH_2NCH_2), 2.60−2.75 (mm, 3H, benzylic), 3.74 (s, 3H, OCH_3), 6.56−7.06 (mm, 3H, aromatic); GC/MS m/z 316 ($M^+ + 1$, 2), 315 (M^+, 10), 126 (100).

3,3-Dimethyl-1-[3-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-propyl]piperidine (25): 96% yield; ^{1}H-NMR δ 0.95 (s, 6H), 1.21 (t, 2H, J = 6 Hz), 1.46−1.86 (mm, 10H), 1.93−2.15 (br d, 2H), 2.26−2.30 (mm, 4H), 2.66−2.73 (mm, 3H), 3.77 (s, 3H), 6.64−6.97 (mm, 3H); GC/MS m/z 316 ($M^+ + 1$, 2), 315 (M^+, 8), 126 (100).

3,3-Dimethyl-1-[4-(1,2-dihydronaphthalen-4-yl)-*n*-butyl]piperidine (26): pale yellow oil, eluted with $CHCl_3$; ^{1}H-NMR δ 0.92 (s, 6H, 2 CH_3), 1.17−1.22 (mm, 2H, $CH_2C(CH_3)_2$), 1.35−1.68 (mm, 6H, CH_2(CH_2)$_2$$CH_2$N and piperidine CH_2), 1.99 (s, 2H, $NCH_2C(CH_3)_2$), 2.20−2.50 (mm, 8H, 2 allyl CH_2 and CH_2NCH_2), 2.72 (t, 2H, J = 8 Hz, benzyl CH_2), 5.84 (br t, 1H, vinyl CH), 7.09−7.26 (mm, 4H, aromatic); GC/MS m/z 298 ($M^+ + 1$, 5), 297 (M^+, 21), 126 (100).

3,3-Dimethyl-1-[4-(5-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-butyl]piperidine (28): eluted with $CHCl_3$; ^{1}H-NMR δ 0.92 (s, 6H), 1.19 (t, 2H, J = 6 Hz), 1.28−1.83 (mm, 12H, (CH_2)$_2$CH(CH_2)$_3$ and piperidine CH_2), 1.99 (s, 2H), 2.21−2.26 (mm, 4H), 2.51−2.77 (mm, 3H), 3.80 (s, 3H) 6.63−7.12 (mm, 3H); GC/MS m/z 330 ($M^+ + 1$, 3), 329 (M^+, 11), 126 (100).

3,3-Dimethyl-1-[4-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-butyl]piperidine (29): ^{1}H-NMR δ 0.92 (s, 6H), 1.19 (t, 2H, J = 6 Hz), 1.27−1.88 (mm, 12H), 1.98 (s, 2H), 2.21−2.30 (mm, 4H), 2.65−2.73 (mm, 3H), 3.75 (s, 3H) 6.58−7.08 (m, 3H); GC/MS m/z 330 ($M^+ + 1$, 3), 329 (M^+, 14), 126 (100).

3,3-Dimethyl-1-[4-(7-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-butyl]piperidine (30): 36% yield; ^{1}H-NMR δ 0.92 (s, 6H), 1.19 (t, 2H, J = 6 Hz), 1.30−1.85 (mm, 12H), 1.99 (s, 2H), 2.24−2.26 (mm, 4H), 2.64−2.74 (mm, 3H), 3.77 (s, 3H) 6.63−6.99 (mm, 3H); GC/MS m/z 330 ($M^+ + 1$, 3), 329 (M^+, 12), 126 (100).

3,3-Dimethyl-1-[5-(1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-pentyl]piperidine (31): ^{1}H-NMR δ 0.92 (s, 6H), 1.19 (t, 2H, J = 6 Hz), 1.24−1.88 (mm, 14H, (CH_2)$_2$CH(CH_2)$_4$ and piperidine CH_2), 1.98 (s, 2H), 2.19−2.26 (mm, 4H), 2.67−2.76 (mm, 3H), 7.02−7.17 (mm, 4H); GC/MS m/z 314 ($M^+ + 1$, 1), 343 (M^+, 6), 126 (100).

3,3-Dimethyl-1-[5-(6-methoxy-1,2,3,4-tetrahydronaphthalen-1-yl)-*n*-pentyl]piperidine (32): eluted with $CHCl_3$; ^{1}H-NMR δ 0.93 (s, 6H), 1.20 (t, 2H, J = 6 Hz), 1.24−1.89 (mm, 14H), 2.02 (s, 2H), 2.15−2.27 (mm, 4H), 2.65−2.76 (mm, 3H), 3.75 (s, 3H, OCH_3) 6.57−7.08 (mm, 3H); GC/MS *m/z* 344 ($M^+ + 1$, 6), 343 (M^+, 23), 126 (100).

3,3-Dimethyl-1-(5-phenyl-*n*-pentyl)piperidine (33). $LiAlH_4$ (1.17 g) was added to a stirred solution of amide **15** (8.20 g, 30 mmol) in anhydrous THF (100 mL) under N_2. After 1 h, the reaction mixture was poured on ice, and the organic layer was dried (Na_2SO_4) and concentrated under reduced pressure. The residue was purified by column chromatography (CH_2Cl_2/MeOH, 95:5, as eluent) to afford **33** as a colorless oil in quantitative yield: ^{1}H-NMR δ 0.95 (s, 6H, 2 CH_3), 1.22 (t, 2H, J = 6 Hz, $CH_2C(CH_3)_2$), 1.31−1.39 (mm, 2H, piperidine CH_2), 1.41−1.71 (mm, 6H, $PhCH_2(CH_2)_3$), 2.01 (s, 2H, $NCH_2C(CH_3)_2$), 2.25−2.29 (mm, 4H, CH_2NCH_2), 2.63 (t, 2H, J = 8 Hz, benzylic), 7.16−7.32 (mm, 5H, aromatic); GC/MS m/z 260 ($M^+ + 1$, 1), 259 (M^+, 3), 126 (100).

Pharmacological Methods. Procedures involving use of small laboratory rodents and their care were conducted in conformity with institutional guidelines that are in compliance with national laws and policies (EEC Council Directive 86/609 and Italian government act 116/January 27, 1992).

σ_1 Receptor Binding Experiments: [^{3}H]-(+)-SKF 10047 Binding. The method adopted was originally described by McCann et al.[44] In brief, male Sprague Dawley rats (Charles River, Italy) were sacrificed by decapitation. The brains were rapidly removed, and whole fresh brain, minus the cerebellum and pons-medulla oblongata, was homogenized in 30 volumes of 5 mM Tris-HCl (pH = 8.0 at 25 °C) containing 10 mM K^+-EDTA with a Brinkmann Polytron (setting 5 for 3 × 15 s). The homogenate was centrifuged at 48000*g* for 15 min at 4 °C. The supernatant was discarded, and the pellets were washed once by resuspension in fresh buffer and then centrifuged. The final pellets were either resuspended in the incubation buffer or stored (for a maximum of 2 days) at −80 °C until assayed. For displacement experiments each sample received the following in a final volume of 0.5 mL: brain homogenate, equivalent of 8−10 mg of tissue based on the original w.w., 4−5 nM [^{3}H]-(+)-SKF 10047 (New England Nuclear, specific activity 60 Ci/mmol), 300 nM unlabeled MK-801 to block binding of (+)-SKF 10047 to PCP receptors, and various concentrations (10^{-10}−10^{-4} M) of the test substance. After incubation at 25 °C for 60 min, the reaction was ended by the addition of 5 mL of ice-cold Tris buffer and rapid filtration through Whatman GF/B filter paper presoaked in cold Tris buffer containing 0.5% polyethyleneimine to reduce nonspecific binding. Filters were then washed with 2 × 5 mL of cold buffer. Filters were then counted by liquid scintillation spectrometry using NEN Formula 989 as scintillation cocktail. Specific [^{3}H]-(+)-SKF 10047 binding was defined as the difference between binding in the absence or presence of 100 μM cold (+)-SKF 10047, a generous gift of SKB, Italy. The K_d

value for (+)-SKF 10047 was calculated from saturation experiments and was 3.8 nM.

***σ* Total Binding Experiments: [^{3}H]-DTG Binding.** These experiments were carried out with 7−8 nM [^{3}H]-DTG according to the method formerly followed[32] and originally described by Weber et al.[45] The K_d value for DTG was 54 nM.

References

(1) Walker, J. M.; Bowen, W. D.; Walker, F. O.; Matsumoto, R. R.; de Costa, B.; Rice, K. C. Sigma receptors: biology and function. *Pharmacol. Rev.* **1990**, *42*, 355−402.

(2) Gilligan, P. J.; Tam, S. W. Sigma receptor ligands: potential drugs for the treatment of CNS disorders? *Drugs News Perspect.* **1994**, *7*, 13−18.

(3) Debonnel, G.; de Montigny, C. Modulation of NMDA and dopaminergic neurotransmissions by sigma ligands: possible implications for the treatment of psychiatric disorders. *Life Sci.* **1996**, *58*, 721−734.

(4) Snyder, S. H.; Largent, B. L. Receptor mechanisms in antipsychotic drug action: Focus on sigma receptors. *J. Neuropsychiat.* **1989**, *1*, 7−15.

(5) Gewirtz, G. R.; Gorman, J. M.; Volavka, J.; Macaluso, J.; Gribkoff, G.; Taylor, D. P. BMY-14802, a sigma receptor ligand for the treatment of schizophrenia. *Neuropsychopharmacology* **1994**, *10*, 37−40.

(6) Frieboes, R. M.; Murck, H.; Wiedemann, K.; Holsboer, F.; Steiger, A. Open clinical trial on the sigma ligand panamesine in patients with schizophrenia. *Psychopharmacology* **1997**, *132*, 82−88.

(7) Izenwasser, S.; Hauck Newman, A.; Katz, J. L. Cocaine and several *σ* receptor ligands inhibit dopamine uptake in rat caudate-putamen. *Eur. J. Pharmacol.* **1993**, *243*, 201−205.

(8) Ujike, H.; Kuroda, S.; Otsuki, S. Sigma receptor antagonists block the development of sensitization to cocaine. *Eur. J. Pharmacol.* **1996**, *296*, 123−128.

(9) Lin, Z.; Kadaba, P. K. Molecular Targets for the Rational Design of Antiepileptic Drugs and Related Neuroprotective Agents. *Med. Res. Rev.* **1997**, *17*, 537−572.

(10) Taylor, D. P.; Yevich, J. P.; Dextraze, P.; Moon, S. L.; Behling, S. H.; Defnet, J.; Geissler, M. In *Multiple Sigma and PCP Receptor Ligands: Mechanism for Neuromodulation and Neuroprotection?* Kamenka, J.-M., Domino, E. F., Eds.; NPP Books: Ann Arbor, MI, 1992; pp 767−778.

(11) De Loore, K. L.; Lesage, A. S.; Peeters, L.; Leysen, J. E. Various sigma ligands exert long-term protection against glutamate toxicity in primary hippocampal neurones; apparent non involvement of identified sigma-2 sites. *Neurosci. Res. Comm.* **1994**, *14*, 43−52.

(12) Maurice, T.; Lockhart, B. P. Neuroprotective and anti-amnesic potentials of *σ* (sigma) receptor ligands. *Prog. Neuro-Psychopharmacol. Biol. Psychiat.* **1997**, *21*, 69−102.

(13) Matsuno, K.; Senda, T.; Kobayashi, T.; Okamoto, K.; Nakata, K.; Mita, S. SA4503, a novel cognitive enhancer, with sigma 1 receptor agonistic properties. *Behav. Brain Res.* **1997**, *83*, 221−224.

(14) Everaert, H.; Flamen, P.; Franken, P. R.; Verhaeghe, W.; Bossuyt, A. Sigma-receptor imaging by means of I-123-IDAB scintigraphy: clinical application in melanoma and non-small cell lung cancer. *Anticancer Res.* **1997**, *17*, 1577−1582.

(15) Vilner, B. J.; Bowen, W. D.; John, C. S.; Lim, B. B.; Geyer, B. C.; 99mTc-labeled sigma-receptor-binding complex: synthesis, characterization, and specific binding to human ductal breast carcinoma (T47D) cells. *Bioconjug. Chem.* **1997**, *8*, 304−309.

(16) Kobayashi, T.; Matsuno, K.; Murai, M.; Mita, S. Sigma 1 receptor subtype is involved in the facilitation of cortical dopaminergic transmission in the rat brain. *Neurochem. Res.* **1997**, *22*, 1105−1109.

(17) Klette, K. L.; Lin, Y.; Clapp, L. E.; De Coster, M. A.; Moreton, J. E.; Tortella, F. C.; Neuroprotective sigma ligands attenuate NMDA and trans-ACPD-induced calcium signaling in rat primary neurons. *Brain Res.* **1997**, *756*, 231−240.

(18) Vilner, B. J.; De Costa, B. R.; Bowen, W. D. Cytotoxicity of sigma ligands: Sigma receptor-mediated effects on cellular morphology and viability. *J. Neurosci.* **1995**, *15*, 117−134.

(19) Steardo, L.; Monteleone, P.; d'Istria, M.; Serino, I.; Maj, M.; Cuomo, V. Sigma receptor modulation of noradrenergic-stimulated pineal melatonin biosynthesis in rats. *J. Neurochem.* **1996**, *67*, 287−293.

(20) Bastianetto, S.; Perrault, G.; Sanger, D. J. Pharmacological evidence for the involvement of sigma sites in DTG-induced contralateral circling in rats. *Neuropharmacology* **1995**, *34*, 107−114.

(21) Jeanjean, A. P.; Laterre, E. C.; Maloteaux, J. M. Neuroleptic binding to sigma receptors: possible involvement in neuroleptic-induced acute dystonia. *Biol. Psychiatry* **1997**, *41*, 1010−1019.

(22) Quirion, R.; Bowen, W. D.; Itzhak, Y.; Junien, J. L.; Musacchio, J. M.; Rothman, R. B.; Su T.-P.; Tam, S. W.; Taylor, D. P. A proposal for the classification of sigma binding sites. *Trends Pharmacol. Sci.* **1992**, *13*, 85−86.

(23) Booth, R. G.; Wyrick, S. D. A novel brain receptor recognized by phenylaminotetralins may represent a sigma (σ_3) receptor subtype. *Med. Chem. Res.* **1994**, *4*, 225−237.

(24) Hanner, M.; Moebius, F. F.; Flandorfer, A.; Knaus, H.-G.; Striessnig, J.; Kempner, E.; Glossmann, H. Purification, molecular cloning, and expression of mammalian sigma$_1$-binding site. *Proc. Natl. Acad. Sci. U.S.A.* **1996**, *93*, 8072−8077.

(25) Kekuda, R.; Prasad, P. D.; Fei, Y.-J.; Leibach, F. H.; Ganapathy, V. Cloning and Functional Expression of the Human Type 1 Sigma Receptor (hSigmaR1). *Biochem. Biophys. Res. Comm.* **1996**, *229*, 553−558.

(26) Moebius, F. F.; Striessnig, J.; Glossmann, H. The mysteries of sigma receptors: new family members reveal a role in cholesterol synthesis. *Trends Pharmacol. Sci.* **1997**, *18*, 67−70.

(27) de Costa, B. R.; He, X.-S.; Dominguez, C.; Williams, W.; Rice, K. C.; Bowen, W. D. The role of novel ligands in biological characterization of sigma receptors. In *Perspective in Receptor Research;* Giardinà, D., Piergentili, A., Pigini, M., Eds.; Elsevier Science B. V.: Amsterdam, 1996; pp 313−320.

(28) Danso-Danquah, R.; Bai, X.; Zhang, X.; Mascarella, S. W.; Williams, W.; Sine, B.; Bowen, W. D.; Carroll, F. I. Synthesis and *σ* Binding Properties of 2′-Substituted 5,9a-Dimethyl-6,7-benzomorphans. *J. Med. Chem.* **1995**, *38*, 2978−2985.

(29) Newman, A. H.; Shah, J. H.; Izenwasser, S.; Heller, B.; Mattson, M.; Tortella, F. C. Highly selective σ_1 ligands based on dextromethorphan. *Med. Chem. Res.* **1996**, *6*, 102−117.

(30) Perregaard, J.; Moltzen, E. K.; Meier, E.; Sánchez, C. *σ* Ligands with Subnanomolar Affinity and Preference for the σ_2 Binding Site. 1. 3-(*ω*-Aminoalkyl)-1*H*-indoles. *J. Med. Chem.* **1995**, *38*, 1998−2008.

(31) Berardi, F.; Giudice, G.; Perrone, R.; Tortorella, V.; Govoni, S.; Lucchi, L. Novel Potent σ_1 Ligands: *N*-[*ω*-(Tetralin-1-yl)alkyl]-piperidine Derivatives. *J. Med. Chem.* **1996**, *39*, 4255−4260.

(32) Berardi, F.; Colabufo, N. A.; Giudice, G.; Perrone, R.; Tortorella, V.; Govoni, S.; Lucchi, L. New *σ* and 5-HT$_{1A}$ Receptor Ligands: *ω*-(Tetralin-1-yl)-*n*-alkylamine Derivatives. *J. Med. Chem.* **1996**, *39*, 176−182.

(33) Glennon, R. A.; Ablordeppey, S. Y.; Ismaiel A. M.; El-Ashmawy M. B.; Fischer, J. B.; Burke Howie, K. J. Structural Features important for σ_1 Receptor Binding. *J. Med. Chem.* **1994**, *37*, 1214−1219.

(34) Perrone, R.; Berardi, F.; Colabufo, N. A.; Tortorella, V.; Fiorentini, F.; Olgiati, V.; Vanotti, E.; Govoni, S. Mixed 5-HT$_{1A}$/D-2 Activity of a New Model of Arylpiperazine: 1-Aryl-4-[3-(1,2-dihydronaphthalen-4-yl)-n-propyl]piperazines. 1. Synthesis and Structure-Activity Relationships. *J. Med. Chem.* **1994**, *37*, 99−104.

(35) Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V.; Fiorentini, F.; Olgiati, V.; Ghiglieri, A.; Govoni, S. High Affinity and Selectivity on 5-HT$_{1A}$ Receptor of 1-Aryl-4-[(1-tetralin)alkyl]piperazines. 2. *J. Med. Chem.* **1995**, *38*, 942−949.

(36) Perrone, R.; Berardi, F.; Colabufo, N. A.; Leopoldo, M.; Tortorella, V.; Fornaretto, M. G.; Caccia, C.; McArthur, R. A. Structure-Activity Relationship Studies on the 5-HT$_{1A}$ Receptor Affinity of 1-Phenyl-4-[*ω*-(α- or *β*-tetralinyl)alkyl]piperazines. 4. *J. Med. Chem.* **1996**, *39*, 4928−4934.

(37) Reimann, E.; Voss, D. On the Synthesis of 3-(1-Tetralyl)- and 3-[5-(5,6,7,8-Tetrahydro)-quinolyl]alanine. *Arch. Pharm.* **1977**, *310*, 2−9.

(38) Taylor, S. K.; Hockerman, G. H.; Karrick, G. L.; Lyle, S. B.; Schramm, S. B. Friedel-Crafts Cyclialkylations of Some Epoxides. *J. Org. Chem.* **1983**, *48*, 2449−2452.

(39) Loiodice, F.; Longo, A.; Bianco, P.; Tortorella, V. 6-Chloro-2,3-Dihydro-4H-1-Benzopyran Carboxylic Acids: Synthesis, Optical Resolution and Absolute Configuration. *Tetrahedron: Asymmetry* **1995**, *6*, 1001−1011.

(40) Craig, J. C.; Dinner, A.; Mulligan, P. J. A Novel Variant of the Favorskii Reaction. *J. Org. Chem.* **1972**, *37*, 3539−3541.

(41) Bachmann, W. E.; Thomas, D. G. The Synthesis of the Sex Hormones. An Analog of Equilenin Lacking the Phenolic A Ring. *J. Am. Chem. Soc.* **1941**, *63*, 598−602.

(42) Munson, P. J.; Rodbard, D. Ligand: a versatile computerized approach for characterization of ligand binding systems. *Anal. Biochem.* **1980**, *107*, 220−239.

(43) An ^{1}H-NMR study at varying temperature was carried out in DMSO-d_6 (at 20 °C, δ): 0.80 and 0.85 (2s, 6H, 2 CH_3), 1.29−1.64 (mm, 8H, $CH_2CH_2C(CH_3)_2$ and chain CH_2CH_2), 2.25 and 2.31 (2t, 2H, J = 7.1 Hz, CH_2CO), 2.53−2.62 (2 overlapped t, 2H, benzylic), 3.06 and 3.12 (2s, 2H, $NCH_2C(CH_3)_2$), 3.26−3.39 (mm, 2H, NCH_2CH_2), 7.11−7.30 (mm, 5H, aromatic). The appearance of spectrum recorded at higher temperatures changed as detailed below. The two triplets at 2.25 and 2.31 δ began to merge at 40 °C and coalesced in a broad singlet (2.29 δ) at 80 °C; the signal at 2.53−2.62 δ began to become one triplet at 40

°C, better resolved on raising the temperature (2.59 δ, $J = 7.2$ Hz at 80 °C); the two singlets at 3.06 and 3.12 δ merged at 60 °C and coalesced in a broad singlet at 80 °C (3.10 δ); similarly, the signal at 3.26−3.39 coalesced in a broad signal at 60 °C and in a broad singlet at 80 °C (3.34 δ). Therefore there is evidence that the compound **23** presents nearly 50% of each of the two stable conformational isomers at room temperature.

(44) McCann, D. J.; Weissman, A. D.; Tsung-Ping, S. U. Sigma-1 and Sigma-2 Sites in Rat Brain; Comparison of Regional, Ontogenic and Subcellular Pattern. *Synapse* **1994**, *17*, 182−189.

(45) Weber E.; Sonders M.; Quarum, M.; Mc Lean, S.; Pou, S.; Keana, J. F. W. 1,3-Di(2-[5-^{3}H]tolyl)guanidine a selective ligand that labels σ-type receptors for psychotomimetic opiates and antipsychotic drugs. *Proc. Natl. Acad. Sci. U.S.A.* **1986**, *83*, 8784−8788.

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