Selective κ-Opioid Agonists: Synthesis and Structure–Activity Relationships of Piperidines Incorporating an Oxo-Containing Acyl Group

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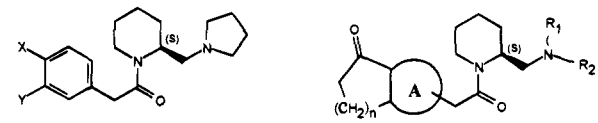
This study describes the synthesis and the structure–activity relationships (SARs) of the (*S*)-(−)-enantiomers of a novel class of 2-(aminomethyl)piperidine derivatives, using κ-opioid binding affinity and antinociceptive potency as the indices of biological activity. Compounds incorporating the 1-tetralon-6-ylacetyl residue (**30** and **34**–**45**) demonstrated an *in vivo* antinociceptive activity greater than predicted on the basis of their κ-binding affinities. In particular, (2*S*)-2-[(dimethylamino)methyl]-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthyl)acetyl]piperidine (**34**) was found to have a potency similar to spiradoline in animal models of antinociception after subcutaneous administration, with ED_{50}s of 0.47 and 0.73 μmol/kg in the mouse and in the rat abdominal constriction tests, respectively. Further *in vivo* studies in mice and/or rats revealed that compound **34**, compared to other selective κ-agonists, has a reduced propensity to cause a number of κ-related side effects, including locomotor impairment/sedation and diuresis, at antinociceptive doses. For example, it has an ED_{50} of 26.5 μmol/kg sc in the rat rotarod model, exhibiting a ratio of locomotor impairment/sedation *vs* analgesia of 36. Possible reasons for this differential activity and its clinical consequence are discussed.

Introduction

Selective κ-opioid agonists which produce antinociception in animals may have therapeutic utility as analgesics lacking the adverse side effects associated with morphine and other current opioid therapies.[1] However, κ-agonists identified to date also produce, at analgesic doses, a spectrum of side effects including locomotor impairment/sedation, motivational effects, CNS disturbances, and diuresis.[2–4]

Following the discovery of κ-opioid agonists from diverse chemical classes,[5–9] yet originating from modifications of the *trans*-3,4-dichloro-*N*-methyl-*N*-[2-(1-pyrrolidinyl)cyclohexyl]benzeneacetamide (U-50488)[10] and incorporating the κ-pharmacophore sequence N–C–C–N(sp_2),[11] considerable attention was focused on subtle modifications of some of the above mentioned chemical classes.[12–14]

The present study was undertaken to produce novel derivatives with safer biological profiles by incorporation of novel acyl groups in the 2-(1-pyrrolidinylmethyl)-piperidine framework, which is the diamine counterpart of the potent and κ-selective antinociceptive agents (2*S*)-1-[(3,4-dichlorophenyl)acetyl]-2-[(1-pyrrolidinyl)methyl]-piperidine (BRL 52537) and (2*S*)-1-[[4-(trifluoromethyl)-phenyl]acetyl]-2-[(1-pyrrolidinyl)methyl]piperidine (BRL 52656).[6] A common feature of the novel acyl groups should be the presence of an electron-withdrawing (EW) and lipophilic substituent in the *para* and/or *meta* position(s) of the arylacetyl moiety as demonstrated by previous QSAR analysis.[6] Thus, a series of piperidines of general formula **1**, featuring a benzylic ketone moiety in the acyl group,[15,16] has been synthesized and tested for its κ-binding affinity and antinociceptive activity. After identification of the most potent compound *in vivo*, optimization of the biological profile was obtained by incorporation in the basic side chain of a variety of linear and branched amines.



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X = Y = Cl BRL 52537

X = CF_3; Y = H BRL 52656

R_1R_2 = linear or cyclised alkyl

A = benzo,thieno; n = 1, 2, 3

This paper describes the synthesis and the structure–activity relationships (SARs) of the (*S*)-(−)-enantiomers of this novel class of compounds and discusses the antinociceptive, diuretic, and behavioral properties of the lead compound of the series.

The *in vivo* activities of the κ-agonists BRL 52656 and (±)-(5α,7α,8β)-3,4-dichloro-*N*-methyl-*N*-[7-(1-pyrrolidinyl)-1-oxaspiro[4.5]dec-8-yl]benzeneacetamide (spiradoline),[17] and of the μ-agonist morphine are also reported for comparative purposes.

Chemistry

(*S*)-(−)-Enantiomers **28**–**45** in Tables 2 and 3 of general formula **3** were synthesized according to Scheme 1.

The enantiomerically pure diamine moieties **2a**–**m** were synthesized as previously described[6] and acylated with the appropriate substituted arylacetyl chloride in the presence of anhydrous potassium carbonate to give the desired compounds **28**–**45** in high yields.

The syntheses of secondary amines **6j**, **6l**, **6m**, and **9** (intermediates of diamines **2j**–**m**) were accomplished according to Schemes 2 and 3. Thus, cycloalkylamines of general formula **4** were refluxed in HCOOEt and the resulting corresponding formyl derivatives **5** reduced with borane–methyl sulfide complex in refluxing THF. The hydrolysis of the amine–borane complex with 6 N

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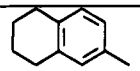
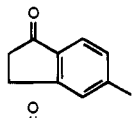
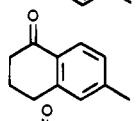
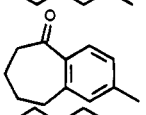
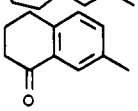
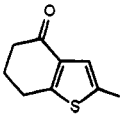
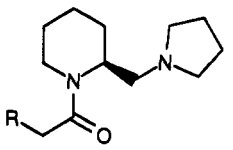
Table 1. Physical Properties of Cyclosubstituted Arylacetic Acids of Formula **13b**, **14**, **18a**, **18b**, **22**, and **27**

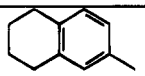
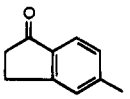
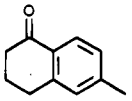
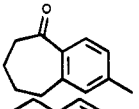
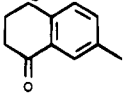
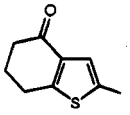
RCH_2COOH

compd	R	formula	mp,°C	anal.	recryst. solvent	80 MHz ^1H NMR, δ(ppm) $CDCl_3$
13b		$C_{12}H_{14}O_2$	93-95	C,H	C_6H_{12}	9.8 (s, br, COOH), 7.0 (s, 3H), 3.6 (s, 2H), 2.4-2.7 (m, 4H), 1.7-1.9 (m, 4H).
14		$C_{11}H_{10}O_3$	113-115	C,H	EtOAc-C_6H_{12}	8.0 (s, br, COOH), 7.7 (d, 1H), 7.2-7.4 (m, 2H), 3.7 (s, 2H), 3.1 (t, 2H), 2.6 (t, 2H).
18a		$C_{12}H_{12}O_3$	110-111	C,H	EtOAc-C_6H_{12}	9.6 (s, br, COOH), 8.0 (d, 1H), 7.1-7.3 (m, 2H), 3.7 (s, 2H), 2.9 (t, 2H), 2.6 (t,2H), 1.9-2.2 (m, 2H).
18b		$C_{13}H_{14}O_3$	oil	--	--	9.6 (s, br, COOH), 7.7 (d, 1H), 7.2-7.3 (m, 2H), 3.6 (s, 2H), 2.6-3.0 (m, 4H), 1.7-1.9 (m, 4H).
22		$C_{12}H_{12}O_3$	116-118	H;C[a]	EtOAc-C_6H_{12}	10.3 (s,br,COOH), 7.9 (s, 1H), 7.1-7.5 (m, 2H), 3.7 (s, 2H), 2.9 (t, 2H), 2.6 (t, 2H), 1.9-2.3 (m, 2H).
27		$C_{10}H_{10}O_3S$	130-132	C,H,S	EtOAc-C_6H_{12}	10.7 (s,br,COOH), 7.2 (s, 1H), 3.8 (s, 2H), 3.0 (t, 2H), 2.5 (t, 2H), 1.9-2.2 (m, 2H).

[a] C: calcd, 70.57; found, 69.97.

Table 2. Physical Properties of Compounds **28–33** of General Formula **3** in Which NR_1R_2 = Pyrrolidine

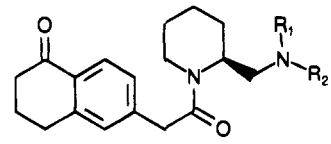


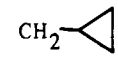
compd	R	formula	mp, °C	anal.	recryst. solvent	$[\alpha]_D^{20}$ (C=1, MeOH)
28		$C_{22}H_{32}N_2O\cdot HCl$	181-182	C,H,N,Cl	Me_2CO	- 46.9
29		$C_{21}H_{28}N_2O_2\cdot HCl$	187-189	H,N,Cl;C[a]	Me_2CO	- 48.3
30		$C_{22}H_{30}N_2O_2\cdot HCl$	179-180	C,H,N	Me_2CO-MeOH	- 49.2
31		$C_{23}H_{32}N_2O_2\cdot HCl$	180-182	C,H,N,Cl	Me_2CO-EtOAc	- 49.5
32		$C_{22}H_{30}N_2O_2$	oil	b	--	--
33		$C_{20}H_{28}N_2O_2S\cdot HCl$	hygroscopic	c	--	- 45.0

[a] C: calcd, 66.91; found, 65.61. [b] Purity >97% by ^1H NMR. [c] Purity >97% by HPLC.

HCl afforded the desired *N*-methyl-*N*-cycloalkylamines **6j**, **6l**, and **6m**. *N*-Methyl-*N*-cyclopropylmethylamine (**9**) was obtained by borane–methyl sulfide complex reduction of the tertiary amide **8**, readily available from cyclopropanecarboxylic acid (**7**) as described in Scheme 3.

Table 3. Physical Properties of Compounds **34–45** of General Formula **3** in Which R = 1-Tetralon-6-yl



compd	R_1	R_2	formula	mp, °C	anal.	recryst. solvent	$[\alpha]_D^{20}$ (C=1, MeOH)
34	Me	Me	$C_{20}H_{28}N_2O_2 \cdot HCl$	212-214	C,H,N,Cl	Me_2CO	- 60.7
35	Me	Et	$C_{21}H_{30}N_2O_2 \cdot HCl$	163-165	C,H,N,Cl	Me_2CO-EtOAc	- 62.3
36	Et	Et	$C_{22}H_{32}N_2O_2 \cdot HCl$	136-137	C,H,N,Cl	EtOAc-Me_2CO	- 61.6
37	Me	n-Pr	$C_{22}H_{32}N_2O_2 \cdot HCl$	155-158	H,N,Cl;C[a]	EtOAc	- 56.6
38	Me	i-Pr	$C_{22}H_{32}N_2O_2 \cdot HCl \cdot 0.5\ H_2O$	159-160	C,H,N,Cl	EtOAc-Et_2O	- 62.1
39	Me	t-Bu	$C_{23}H_{34}N_2O_2 \cdot HCl$	110-114	H,N;C,Cl[b]	EtOAc-Et_2O	nd
40	Me	$CH_2CH{=}CH_2$	$C_{22}H_{30}N_2O_2 \cdot HCl$	183-184	C,H,N,Cl	EtOAc	- 60.3
41	Me	$CH_2C{\equiv}CH$	$C_{22}H_{28}N_2O_2 \cdot HCl$	169-170	C,H,N	EtOAc-Et_2O	nd
42	Me		$C_{22}H_{30}N_2O_2 \cdot HCl$	172-174	C,H,N,Cl	EtOAc	- 55.6
43	Me		$C_{23}H_{32}N_2O_2 \cdot HCl$	148-150	C,H,N,Cl	EtOAc	- 54.9
44	Me		$C_{23}H_{32}N_2O_2 \cdot HCl$	184-186	C,H,N,Cl	EtOAc	- 58.8
45	Me		$C_{24}H_{34}N_2O_2 \cdot HCl \cdot 0.25\ H_2O$	126-129	C,H,N,Cl	EtOAc	- 62.1

[a] C: calcd, 67.24; found, 66.69. [b] C: calcd, 67.88; found, 66.92. Cl: calcd, 8.71; found, 8.22. nd = not determined.

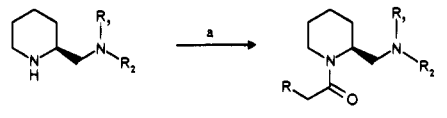
The variously substituted arylacetic acids **13b**, **14**, **18a**, **18b**, **22**, and **27** in Table 1, incorporated in compounds **28–33**, were synthesized according to Schemes 4–7.

5-Acetylindan and 6-acetyltetraline of formula **11a,b** (Scheme 4), readily available from the corresponding hydrocarbons, were submitted to Willgerodt[18] reaction (Kindler modification) in a refluxing morpholine–sulfur mixture.

The resulting thiomorpholide derivatives **12a,b** were hydrolyzed in refluxing basic medium to obtain the cyclosubstituted phenylacetic acids **13a,b** in high yields. Oxidation of **13a** with CrO_3–AcOH gave 1-oxoindan-5-acetic acid (**14**) and traces of an unisolated second product which might result from oxidation at position *meta*. After purification via dicyclohexylamine salt formation, a yield of 50% from **13a** was obtained. The same oxidative step applied to compound **13b** resulted in a 6:4 (by ^1H NMR) mixture of *para* and *meta* oxidation products, respectively. We were unable to separate this mixture either by standard crystallization techniques or by distillation of the corresponding ethyl esters.

Therefore, the synthesis of compounds **18a** and **22** was accomplished in an alternative manner as outlined in Schemes 5 and 6, respectively. 6-Acetamido-1-tetralone (**15a**, Scheme 5), prepared according to the method of Allinger and Jones[19] was hydrolyzed in 25%

Scheme 1[a]



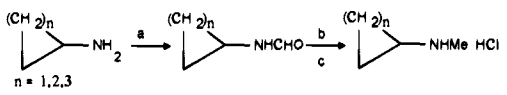
2 a-m 3

(BRL 52537, BRL 52656 and compounds 28-45)

	R_1	R_2		R_1	R_2
2a	-(CH_2)-		2h	Me	$CH_2CH{=}CH_2$
2b	Me	Me	2i	Me	$CH_2C{\equiv}CH$
2c	Me	Et	2j	Me	
2d	Et	Et	2k	Me	
2e	Me	n-Pr	2l	Me	
2f	Me	i-Pr	2m	Me	
2g	Me	t-Bu			

[a] Reagents: (a) RCH_2COCl, K_2CO_3, CH_2Cl_2.

Scheme 2[a]



n = 1,2,3

4 5 6j (n = 1) 6l (n = 2) 6m (n = 3)

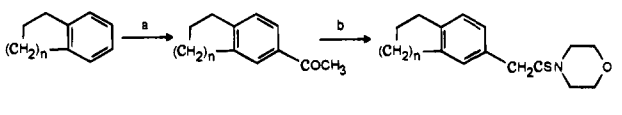
[a] Reagents: (a) HCOOEt, reflux, 3 h; (b) $Me_2S{\cdot}BH_3$, THF, 60 °C, 6 h; (c) HCl/H_2O, 80 °C, 3 h.

Scheme 3[a]

7 8 9

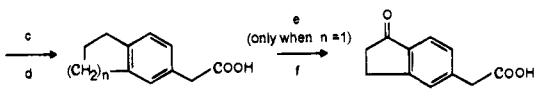
[a] Reagents: (a) $SOCl_2$, 60 °C, 3 h; (b) NH_2Me, H_2O; (c) $Me_2S{\cdot}BH_3$, THF, 60 °C, 6 h; (d) HCl/H_2O, 80 °C, 3 h.

Scheme 4[a]



10a (n = 1) 11a (n = 1) 12a (n = 1)

10b (n = 2) 11b (n = 2) 12b (n = 2)



13a (n = 1) 14

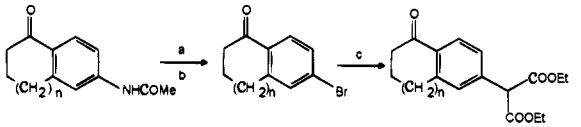
13b (n = 2)

[a] Reagents: (a) Ac_2O, $AlCl_3$, 0 °C; (b) S, morpholine, reflux, 24 h; (c) 10% KOH, 100 °C, 20 h; (d) dilute HCl; (e) CrO_3, AcOH, H_2O [only when n = 1]; (f) dicyclohexylamine, EtOH/EtOAc.

aqueous HBr and the resulting aniline derivative submitted to Sandmeyer reaction using CuBr as source of nucleophile. The copper-promoted coupling reaction[20] of **16a** with sodium diethyl malonate gave, after acidic hydrolysis and decarboxylation of the intermediate diester **17a**, the desired 5,6,7,8-tetrahydro-5-oxo-2-naphthaleneacetic acid [1-tetralone-6-acetic acid, **18a**] in about 20% yield from **16a**. Similarly, compound **18b** was obtained starting from 7-acetamido-1-benzosuberone.[19]

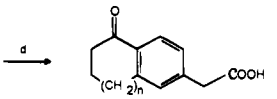
Phenylbutyric acid (**19**, Scheme 6) was converted into the corresponding ethyl ester, submitted to $AlCl_3$-

Scheme 5[a]



15a (n = 1) 16a (n = 1) 17a (n = 1)

15b (n = 2) 16b (n = 2) 17b (n = 2)

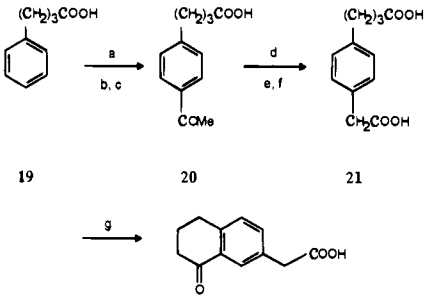


18a (n = 1)

18b (n = 2)

[a] Reagents: (a) 25% HBr, 60 °C, 2 h; (b) $NaNO_2$, CuBr, 48% HBr, 0 °C, 2 h; (c) $CH_2(COOEt)_2$, NaH, CuBr, 100 °C, 3 h; (d) 25% H_2SO_4, dioxane, 100 °C, 3 h.

Scheme 6[a]



19 20 21

22

[a] Reagents: (a) $SOCl_2$, EtOH, 60 °C, 4 h; (b) MeCOCl, $AlCl_3$, $CHCl_3$, 30 min; (c) dilute HCl, dioxane, 100 °C, 8 h; (d) S, morpholine, reflux, 3 h; (e) 10% KOH, 100 °C, 5 h; (f) dilute HCl; (g) PPA, xylene, 100 °C, 3 h.

catalized Friedel–Crafts reaction with MeCOCl, and refluxed in acidic medium to obtain the *p*-acetylphenylbutyric acid (**20**) in high yield, as described by Baddeley and Williamson.[21] This compound was submitted to the same reaction steps described for the synthesis of the homologous indanone derivative.[22] Thus, Willgerodt–Kindler reaction and subsequent hydrolysis afforded the diacid **21** which was cyclized in a refluxing PPA–xylene mixture to yield the desired 5,6,7,8-tetrahydro-8-oxo-2-naphthaleneacetic acid [1-tetralone-7-acetic acid, **22**].

Friedel–Crafts acylation of 2-thiopheneacetic acid ethyl ester with succinic anhydride (Scheme 7) followed by hydrolysis afforded the keto diacid **25** which was reduced in refluxing diethylene glycol with hydrazine to the diacid **26**. Intramolecular cyclization in Ac_2O–PPA afforded the 4-oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-acetic acid (**27**) in high yield.

Pharmacology

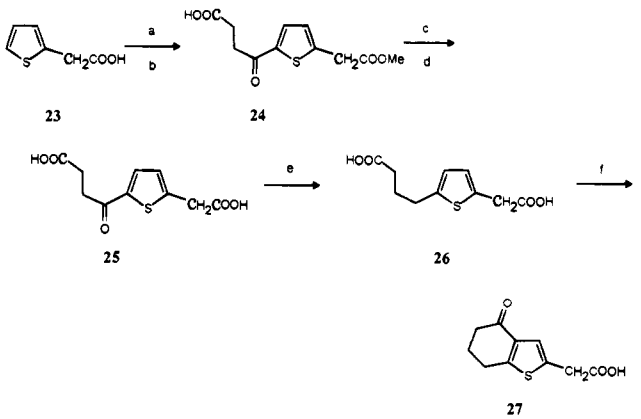
Binding affinities for the κ-opioid receptor and antinociceptive activities of (*S*)-(−)-enantiomers **28–45** following subcutaneous administration in the mouse phenyl-*p*-benzoquinone-induced abdominal constriction test (MAC) and in the mouse tail-flick test (MT-F) are shown in Table 4. In addition, locomotor impairment/sedative activities in the mouse rotarod model (MRR) of compounds **34–45** are reported. For comparative purposes, the κ-binding affinities and *in vivo* potencies of BRL 52656, spiradoline, and morphine are reported.

Table 4. Mouse Antinociceptive Activity, Locomotor Impairment/Sedation, and κ-Binding Affinity of Compounds **28–45** of General Formula **3**

	ED_{50},[a] μmol/kg sc			
	antinociception		locomotor	κ-binding
compd	MAC	MT-F	impairment/sedation, MRR	affinity, K_i,[b] nM
28	0.57 (0.44–0.75)	2.67 (1.78–4.00)	nd	0.81 ± 0.07
29	>1.5	>30	nd	7.93 ± 2.05
30	0.35 (0.23–0.55)	0.59 (0.39–0.90)	nd	7.60 ± 1.16
31	>1.5	>3	nd	5.44 ± 1.20
32	~1	>3	nd	5.61 ± 1.19
33	1.41 (0.96–2.08)	13.5 (8.1–22.5)	nd	6.54 ± 1.17
34	0.47 (0.32–0.69)	2.15 (1.31–3.52)	5.10 (3.42–7.61)	47.0 ± 4.5
35	0.18 (0.14–0.22)	1.77 (1.06–2.96)	2.30 (1.58–3.36)	10.3 ± 1.5
36	1.20 (0.88–1.62)	12.6 (7.5–21.1)	23.7 (17.6–31.8)	80.3 ± 5.9
37	0.62 (0.50–0.78)	6.81 (4.07–11.37)	7.99 (5.49–11.65)	22.2 ± 1.7
38	0.22 (0.18–0.26)	1.20 (0.79–1.83)	1.02 (0.83–1.26)	4.07 ± 0.62
39	nd	>30	nd	>100 (1)
40	0.37 (0.27–0.50)	3.42 (2.05–5.72)	8.66 (5.38–13.94)	19.2 ± 1.8
41	0.16 (0.11–0.22)	5.11 (3.05–8.51)	4.12 (2.71–6.26)	6.24 ± 0.76
42	0.40 (0.29–0.56)	7.85 (4.70–13.12)	13.7 (9.7–19.5)	52.1 ± 1.9
43	1.36 (1.14–1.62)	16.5 (10.2–26.5)	16.6 (12.6–21.9)	30.4 ± 1.1
44	0.34 (0.27–0.44)	1.45 (0.96–2.21)	3.32 (2.38–4.63)	34.8 ± 4.2
45	0.55 (0.41–0.73)	6.34 (3.79–10.60)	10.0 (6.7–15.0)	20.0 ± 0.9
BRL 52656	0.10 (0.06–0.15)	0.32 (0.21–0.48)	0.28 (0.18–0.42)	0.64 ± 0.05
spiradoline	0.18 (0.10–1.41)	0.50 (0.34–0.76)	0.65 (0.34–1.24)	1.13 ± 0.15
morphine	1.34 (0.98–1.82)	9.80 (5.89–12.85)		301 ± 30

[a] MAC = mouse abdominal constriction; MT-F = mouse tail-flick; MRR = mouse rotarod. nd = not determined. In pharmacological models *in vivo*, $n = 10$ animals for each dose tested. [b] Each value represents the mean ± SEM of independent experiments, each performed in triplicate ($n = 3$) unless otherwise indicated in parentheses. Binding affinity to μ-receptors for compounds **28–45** was found to be >1000 nM; for BRL 52656, 2340 nM; for spiradoline, 45.1 nM; for morphine, 3.30 nM.

Scheme 7[a]



[a] Reagents: (a) $SOCl_2$, MeOH, 60 °C, 4 h; (b) succinic anhydride, $AlCl_3$, $CHCl_3$, 0 °C; (c) 20% NaOH, 100 °C, 30 min; (d) dilute HCl; (e) NH_2NH_2, KOH, glycol, 195 °C, 2 h; (f) PPA, Ac_2O, 80 °C, 15 min.

The binding affinities of compound **34** at κ, μ, δ and σ sites are reported in Table 5.

The antinociceptive activities of **34**, BRL 52656, spiradoline and morphine following subcutaneous administration in the rat abdominal constriction test (RAC) are shown in Table 6, together with their locomotor impairment/sedative potentials in the rat rotarod model (RRR).

Table 5. Binding Affinities of Compound **34** at κ, μ, δ, and σ Sites

site	K_i,[a] nM	site	K_i,[a] nM
κ	47.0 ± 4.5	δ	>100.000
μ	6790 ± 640	σ	1210 ± 370

[a] Data represent the mean ± SEM of independent experiments, each performed in quadruplicate ($n = 4$).

The diuretic activity in normally hydrated rats (NHR) following subcutaneous administration of **34**, BRL 52656, and spiradoline is reported in Figure 1.

Results and Discussion

SAR Analysis. 1. Novel Oxo-Containing Acyl Groups (Compounds 28–33 in Table 2). Previous QSAR analysis[6] had demonstrated that the presence of an EW and lipophilic substituent in the *para* and/or *meta* position(s) of the arylacetyl moiety is required for optimization of antinociceptive potency (MT-F) and affinity for the κ-opioid receptor: *in vivo* and *in vitro* activities were correlated.

Following this QSAR indication, the tetralinyl derivative **28** (lipophilic only) and the tetralone analogue **30** (both lipophilic and EW) have been synthesized and

Table 6. Antinociceptive Activities and Locomotor Impairment/Sedative Potentials of **34**, BRL 52656, Spiradoline, and Morphine in Rat Models

	ED_{50},[a] μmol/kg sc			ED_{50},[a] μmol/kg sc	
compd	antinociception, RAC	locomotor impairment/sedation, RRR	compd	antinociception, RAC	locomotor impairment/sedation, RRR
34	0.73 (0.48–1.10)	26.5 (10.1–69.6)	spiradoline	0.47 (0.37–0.60)	1.55 (0.78–3.06)
BRL 52656	0.11 (0.09–0.15)	0.35 (0.12–0.97)	morphine	0.86 (0.51–1.44)	

[a] RAC = rat abdominal constriction; RRR = rat rotarod. In pharmacological models *in vivo*, $n = 10$ animals for each dose tested.

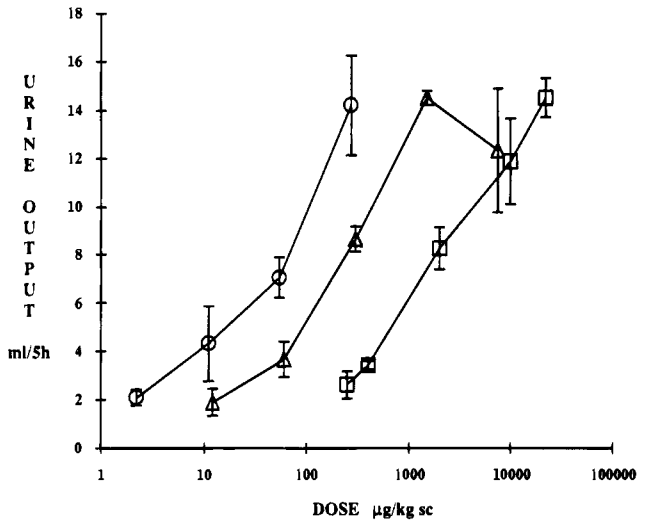


Figure 1. Diuretic activity in normally hydrated rats (NHR): dose–response curves of compound **34** (□, ED_{300} = 1533 μg/kg sc), BRL 52656 (○, ED_{300} = 35 μg/kg sc), and spiradoline (△, ED_{300} = 141 μg/kg sc).

tested. The results shown in Table 4 revealed that the *in vivo* activity of compound **30** was greater than that expected in view of its relatively poor κ-binding affinity. Changing the size of the condensed aliphatic ring—from a five- (the indanone derivative **29**) to a seven-membered ring (the benzosuberone derivative **31**)—produced compounds having similar κ-binding affinities to **30** but significantly lower analgesic activities in both MAC and MT-F tests.

A comparison of the antinociceptive potencies of compounds **30** and **32** revealed that *meta* oxo substitution is not well tolerated.

The replacement of the benzene ring with the thiophene (e.g. compound **33**) produced a decrease of the *in vivo* activity.

Overall, although the various novel oxo-containing acyl groups coupled with the 2-(1-pyrrolidinylmethyl)-piperidine framework confer to compounds **29–33** very similar κ-binding affinities (K_is in the range 5.44–7.93 nM), only (2*S*)-2-(1-pyrrolidinylmethyl)-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthyl)acetyl]piperidine (**30**) showed significant analgesic activity.

This finding prompted us to investigate in more detail the discrepancy seen between *in vitro* and *in vivo* data, by synthesizing a number of (2*S*)-2-[(dialkylamino)-methyl]-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthyl)acetyl]-piperidines with various tertiary basic moieties.

SAR Analysis. 2. Modification of the N-Substituents (Compounds 34–45 in Table 3). Since previous studies[6] had revealed a significant reduction in the antinociceptive activity upon shifting from the five- to the six-membered basic moiety, we decided to concentrate our attention on the linear substitution which offered a wider range of steric and electronic stepwise modifications.

First, the dimethylamino (**34**) and the diethylamino (**36**) derivatives were synthesized. The results shown in Table 4 revealed that dimethylamino derivative **34** was from 3 (MAC) to 6 (MT-F) times more potent than the diethylamino analogue **36** and suggested that, to maintain an adequate biological activity, at least one substituent should be a methyl group. Subsequently, compounds **35** and **37–45**, which feature a methyl group in the basic side chain, were synthesized and evaluated.

Overall, the isopropyl derivative **38** was the most potent compound *in vivo* (MAC ED_{50} = 0.22 μmol/kg sc, MT-F ED_{50} = 1.20 μmol/kg sc) and in the κ-receptor binding assay (K_i = 4.07 nM). The presence of a tetrasubstituted carbon atom adjacent to the basic nitrogen was not tolerated (compound **39**). However, compounds bearing sterically hindering substituents, such as cyclobutyl and cyclopentyl (compounds **44** and **45**, respectively) exhibited moderate affinity to κ-opioid receptors (K_is of 35 and 20 nM) and had good antinociceptive activities (MAC ED_{50}s of 0.34 and 0.55 μmol/kg sc, respectively).

Retrospective molecular modeling studies have been carried out to explain the inactivity of **39**. Calculation of the "excluded volume" between the active compounds **34**, **38**, and **42** and the inactive **39** revealed that, for all the low-energy conformations considered, at least one methyl group of the *tert*-butyl residue of **39** is outside from the total volume of the active compounds. Thus, the inactivity of the *tert*-butyl derivative **39** is probably due to the presence of the third methyl group, which may compete with the receptor for the available space.

With the exception of the most potent compound **38**, the ratios of locomotor impairment/sedation *vs* antinociception (MRR ED_{50}/MAC ED_{50}) for compounds **34–45** ranged from 10 to 35 compared to 2.8 (BRL 52656) and 3.6 (spiradoline), thus suggesting a reduced propensity to cause locomotor impairment/sedative side effects.

Overall, the lack of correlation between κ-opioid binding affinity and antinociceptive potency already noted with compound **30** is accentuated in compounds **34** and **44**, which showed good antinociceptive potency (similar to that of spiradoline and from 3 to 6 times higher than that of morphine) in spite of being weak—but very selective—κ-ligands (K_is = 47 and 35 nM, respectively).

The most interesting compound, (2*S*)-2-[(dimethylamino)methyl]-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthyl)-acetyl]piperidine (**34**), was selected for further evaluation to determine (a) its spectrum of binding affinities for a range of receptors and (b) its pharmacological profile in a second rodent species, the rat.

Biological Profile of (2*S*)-2-[(Dimethylamino)-methyl]-1-[(5,6,7,8-tetrahydro-5-oxo-2-naphthyl)-

acetyl]piperidine (34). 1. Binding Affinities (Table 5). Compound **34** showed a selective κ-binding profile with moderate affinity for the κ-opioid sites (K_i = 47.0 nM) and negligible affinity for μ, δ, and σ receptors (K_is > 1000 nM).

In addition, **34** did not bind to the following receptors: adenosine A_1 and A_2, adrenergic α_1 and α_2, benzodiazepine, CCK-A, CCK-B, dopamine D_1 and D_2, NMDA, and serotonin 5-HT_{1A}, 5-HT_2, and 5-HT_3 (K_is > 1000 nM).

2. Antinociceptive and Locomotor Impairment/Sedative Activities in the Rat (Table 6). Compound **34** produced dose-related effects in both the abdominal constriction model in rats (RAC) and in the rat rotarod model (RRR) of locomotor activity/sedation. In terms of its antinociceptive activity, **34** was equipotent to morphine and approximately 1.5- and 6.5-fold less potent than spiradoline and BRL 52656, respectively. However, compared to the other κ-agonists, compound **34** was much less potent in the rat rotarod model (17 and 76 times less potent than spiradoline and BRL 52656, respectively). Therefore, whereas BRL 52656 and spiradoline exhibited a ratio of locomotor impairment/sedation *vs* antinociception (RRR ED_{50}/RAC ED_{50}) of 3, **34** had a ratio of 36. In other words, at equivalent analgesic doses, **34** exhibited a far lower propensity than either BRL 52656 or spiradoline to produce unwanted locomotor impairment/sedative effects.

3. Diuretic Activity (Figure 1). Highly selective κ-opioid agonists produce diuresis in a number of species, including man.[23] In normally hydrated rats, **34** induced a dose-dependent diuresis and produced the same maximum effect as BRL 52656 and spiradoline (14−15 mL/5 h): this maximal effect was twice that of the partial κ-agonist butorphanol (data not shown). However, the diuretic activity of **34**—measured as the dose that produces a 300% increase in urine volume in 5 h compared to parallel control animals—was 1−2 orders of magnitude lower than that of BRL 52656 and spiradoline, as shown in Figure 1.

Conclusions

A novel class of 2-(aminomethyl)piperidine derivatives, incorporating the 1-tetralon-6-ylacetyl residue as acyl group (compounds **30** and **34**−**45**) have been discovered to possess an *in vivo* antinociceptive activity greater than expected in view of their relatively poor κ-binding affinity (K_is in a range from 7 to 80 nM). Incorporation of the dimethylamino basic moiety resulted in a compound (**34**) in which this biological anomaly was accentuated. Thus, **34** (K_i κ = 47 nM) was found to possess an *in vivo* subcutaneous antinociceptive activity, in MAC and RAC tests, similar to spiradoline which has, however, a κ-binding affinity of 1.13 nM.

Further investigation on **34** in rat models designed to assess the spectrum of possible κ-related side effects revealed that this compound, compared to other κ-opioid agonists like BRL 52656 and spiradoline, has a reduced propensity to cause locomotor impairment/sedation and diuresis.

Furthermore, studies on the aversive potential of **34** in a place preference model (used as an index of κ-mediated dysphoric activity) indicated that the compound was less active at equivalent antinociceptive doses than the other κ-agonists tested. This reduced activity, as well as the reduced propensity of **34** to cause locomotor impairment, may be related to the finding that **34**, compared to the other κ-agonists tested, has a lower potential to decrease dopamine levels in the dorsal caudate of conscious rats (monitored using a transcerebral brain microdialysis technique).[24]

To rule out the possibility that the lower sedative potential observed with **34** may simply be due to a limited brain penetration, lypophilicity measurements [Δ(log *P*) values][25] of **34** and BRL 52656 were determined and found to be 1.93 and 1.18, respectively. Such low Δ(log P) parameters strongly indicate a similar, high lipophilicity of the compounds and associated CNS penetration. This finding was in agreement with the remarkable potency of **34** (similar to that of spiradoline) in the abdominal constriction test of antinociception after subcutaneous administration, a test in which the action of κ-agonists appears to be, predominantly, centrally-mediated.

Therefore, the reason(s) for the analgesic selectivity of **34**, compared for example with BRL 52656 and spiradoline, is not known. One possibility is that it is due to a selective interaction with the κ_{1a}-, κ_{1b}-, κ_2-, or κ_3-receptor subtypes described recently.[26,27] This possibility is currently being investigated using a range of radioligand binding models.

Experimental Section

Binding Assays. κ-, μ-, and δ-receptor binding assays were performed as previously described.[7] The σ-receptor binding assay was performed according to the method of Sbacchi and Clarke.[28] The radioligand employed in the binding assays are as follows: for the κ-sites, [^{3}H] BRL 52537[28] (0.4 nM), in the presence of haloperidol (100 nM); for the μ-sites, [^{3}H][D-Ala^2,-MePhe^4,Gly-ol^5]enkephalin (DAMGO) (1 nM); for δ-sites, [^{3}H]-[D-Ala^2,D-Leu^5]enkephalin (1 nM), in the presence of DAMGO (40 nM); for σ-sites, [^{3}H]BRL 52537 (0.8 nM), in the presence of Naloxone (10 μM).

***In Vivo* Antinociceptive Studies.** Male CD-1 mice (Charles River; 20−35 g) and male SD rats (Charles River; 180−350 g) were used throughout these studies. The mouse phenyl-*p*-benzoquinone-induced abdominal constriction test (MAC) and mouse tail-flick test (MT-F) of antinociception were performed according to the procedure described by Siegmund et al.[29] and D'Amour and Smith.[30] The rat phenyl-*p*-benzoquinone-induced abdominal constriction test (RAC) was performed according to the procedure described by Blumberg et al.[31] ED_{50} values, and their 95% confidence intervals, were determined either by using the probit analysis method of Finney[32] (MT-F, RAC) or regression analysis (MAC).

Other *in Vivo* Studies. The locomotor impairment/sedative activity was assessed with the mouse and rat rotarod test according to the procedure described by Hayes[33] and Iwamoto.[34] The rat training period was six sessions of 5 min for 2 days, and the rotarod acceleration was 3−30 rpm in five sessions. ED_{50} values, and their 95% confidence intervals, were determined by using regression analysis method.

The diuretic activity was assessed in normally hydrated rats according to the procedure described by Leander.[35] The activity was expressed as milliliters of urine output in 5 h. ED_{300} values—the dose of testing drug which caused a 3-fold increase in urine output in comparison to urine amount of control animals—were determined by using regression analysis.

Chemistry. Melting points were determined with a Büchi 512 hot stage apparatus and are uncorrected. Proton NMR spectra were recorded on a Bruker AC80 or a Bruker CXP 300 spectrometer. Chemical shifts were recorded in parts per million downfield from tetramethylsilane. IR spectra were recorded as a liquid film on sodium chloride disks or in KBr with a Perkin-Elmer 1420 spectrophotometer. Optical rotations were determined in MeOH solution with a Perkin-Elmer 241 polarimeter at the sodium D-line. Silica gel used for flash column chromatography was Kiesegel 60 (230−400 mesh) (E.

Merck AG, Darmstadt, Germany). Evaporations were performed with reduced pressure and all oily products were dried at 0.1 mmHg for 16 h. Elemental analyses are indicated only by the symbols of the elements; analytical results were within 0.4% of the theoretical values unless otherwise indicated.

Synthesis of Known Intermediates. Diamines **2a–m** were obtained by reaction of (*S*)-(−)-pipecolic acid with the appropriate secondary amine and subsequent $LiAlH_4$ reduction of the intermediate amide as previously described.[6]

Compounds **15a,b** were obtained as described by Allinger and Jones.[19] Cyclosubstituted arylacetic acids were transformed into the corresponding acyl chlorides by using $(COCl)_2$ in refluxing CH_2Cl_2 as previously described.[6]

Pyrrolidine, dimethylamine, *N*-methylethylamine, diethylamine, *N*-methyl-*n*-propylamine, *N*-methylisopropylamine, *N*-methyl-*tert*-butylamine, *N*-methylallylamine, *N*-methylpropargylamine, cyclopropylamine, cyclobutylamine, cyclopentylamine, cyclopropanecarboxylic acid, indan, tetraline, phenylbutyric acid, and 2-thiopheneacetic acid were obtained from Aldrich Chemical Co. and were used without further purification.

General Method of Acylation of Diamines 2a–m To Obtain Compounds 28–45 of General Formula 3. A solution of the cyclosubstituted arylacetyl chloride (5 mmol) in CH_2Cl_2 (25 mL) was added dropwise to a stirred solution of the diamine (4.5 mmol) in the same solvent (40 mL) in the presence of anhydrous potassium carbonate (5 mmol) at 0 °C. After stirring at rt for 8 h, the reaction mixture was washed with 5% $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated in vacuo to yield the free bases, which were purified by silica gel flash column chromatography eluting with CH_2Cl_2 containing a small amount of MeOH (2–4%) and a trace of 28% NH_4OH (0.2–0.4%). The purified dissolved compounds were treated with a solution of HCl in Et_2O to give the HCl salts as white solids. The analytically pure samples were obtained by recrystallization (see Tables 2 and 3). As examples, the ^1H NMR, ^{13}C NMR (when available), and IR spectra of compounds **31**, **33**, and **34**, are reported.

Compound **31**: 80 MHz ^1H NMR (DMSO) δ 11.7 (s, br, H^+), 7.6 (d, 1H), 7.1–7.3 (m, 2H), 4.8–5.2 (m, 1H), 4.0–4.7 (m, 1H), 2.5–4.0 (m, 13H), 1.1–2.1 (m, 14H); IR (KBr) 3450, 2930, 2690, 1680, 1630, 1610, 1450, 1260 cm^{-1}.

Compound **33**: 80 MHz ^1H NMR ($CDCl_3$) δ 11.5 (s, br, H^+), 7.0 (s, 1H), 5.0–5.2 (m, 1H), 3.1–4.2 (m, 7H), 2.5–3.0 (m, 5H), 1.7–2.5 (m, 8H), 1.2–1.7 (m, 6H); IR (KBr) 3450, 2940, 2690, 1665, 1640, 1440, 1400 cm^{-1}.

Compound **34**: 80 MHz ^1H NMR ($CDCl_3$) δ 11.80 (s, br, H^+), 7.97 (d, J = 8 Hz, 1H), 7.10–7.35 (m, 2H), 5.10–5.45 (m, 1H), 3.95 (AB system, J = 16 Hz, 2H), 3.20–4.10 (m, 3H), 2.80–3.15 (m, 9H), 2.45–2.75 (t, J = 6 Hz, 2H), 1.90–2.30 (m, 2H), 1.10–1.85 (m, 6H); 300 MHz ^{13}C NMR ($CDCl_3$) δ 198.23 (*C*O), 171.27 (*N*CO), 131.22, 141.36, 144.70 (aromatic *C*), 127.29, 127.91, 129.88 (aromatic *C*H), 56.56 (CH_2NCO), 45.86 (*C*HNCO), 43.21 (CH_3N), 42.14 (CH_2N + CH_3N), 39.14, 41.11 (CH_2CO), 19.19, 23.23, 25.37, 26.79, 29.64 (CH_2); IR (KBr) 3450, 2940, 2700, 1680, 1640, 1610, 1410 cm^{-1}.

General Method of Formylation of Cycloalkylamines of General Formula 4 To Obtain Compounds of General Formula 5. Cycloalkylamines (0.2 mol) were refluxed for 4 h in HCOOEt (140 mL). Evaporation of the solvent and distillation of the residue yielded the desired *N*-formylcycloalkylamines in quantitative yield. As an example, *N*-formylcyclobutylamine was distilled at 82–87 °C/2 mmHg (purity > 97% by GC). IR (neat) 3260, 3010, 2860, 1670, 1540, 1380 cm^{-1}.

General Method of Reduction of Formyl Derivatives 5 To Obtain *N*-Methyl Cycloalkylamine Hydrochlorides 6j, 6l, and 6m. A 10 M solution of $Me_2S{\cdot}BH_3$ (0.4 mol) in THF (100 mL) was added dropwise to a solution of the *N*-formyl derivative (0.14 mol) in THF (140 mL) at 60 °C. The reaction mixture was refluxed for 14 h under nitrogen atmosphere, cooled to 0 °C, carefully treated with 6 N HCl, and heated again at 80 °C for 3 h. The solvent was evaporated and the residue treated with 40% NaOH solution and exhaustively extracted with Et_2O. The ethereal solution was dried over Na_2SO_4, treated with a saturated solution of HCl in Et_2O, and concentrated to dryness to yield the crude *N*-methylcycloalkylamine hydrochlorides as off-white hygroscopic materials. These salts were used without further purification in the subsequent reaction.

***N*-Methylcyclopropanecarboxamide (8).** Cyclopropanecarboxylic acid (0.30 mol) was added dropwise to a warm solution of $SOCl_2$ (0.32 mol) in toluene (120 mL) at such a rate as to maintain a temperature of 50 °C. After the addition, the reaction mixture was stirred at 80 °C for 2 h. The solution was then cooled to −5 °C and gaseous $MeNH_2$ (2 mol) bubbled into the reaction, the temperature being maintained below 10 °C. After evaporation of the solvent, the residue was taken up in CH_2Cl_2 and filtered to eliminate the excess of $MeNH_2{\cdot}HCl$. The organic solution was washed with 5% $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated to dryness. Crude **8** was recrystallized from hexane containing 10% Et_2O to yield 0.26 mol (87%) of the desired product, mp 56–57 °C.

***N*-Methyl-*N*-(cyclopropylmethyl)amine Hydrochloride (9).** *N*-methylcyclopropanecarboxamide (**8**) (0.10 mol) was reduced following the same procedure described above for the preparation of compounds **6j, 6l,** and **6m.** The obtained hydrochloride (0.09 mol) was used without further purification in the subsequent reaction.

General Method for Friedel–Crafts Acylation of Aromatic Hydrocarbons 10 To Obtain the Acetyl Derivatives of Formula 11. A mixture of indan (0.60 mol) and Ac_2O (0.72 mol) was added dropwise during 3 h to a slurry of $AlCl_3$ (1.44 mol) in CH_2Cl_2 (500 mL) cooled to 0 °C. The reaction mixture was stirred at room temperature under a nitrogen flux for 15 h and then poured into ice (500 g). The organic layer was separated, washed with 5 N HCl, H_2O, and 5% $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated to dryness. The residue was purified by distillation *in vacuo*. **11a** (n = 1): bp 90–94 °C/0.7 mmHg; **11b** (n = 2); bp 97–100 °C/0.3 mmHg. Typically, the yields of the distilled material were about 85% of the theoretical values.

General Procedure for Willgerodt Reaction (Kindler Modification) To Obtain Morpholides of General Formula 12. A mixture of compound 11 (0.30 mol), morpholine (0.50 mol), and S (0.45 mol) was refluxed for 24 h. During the subsequent cooling, EtOH (60 mL) was added and the precipitated material was filtered, washed with cold EtOH, and dried. Typically, the yields were about 80% of the theoretical values.

General Method for the Hydrolysis of Compounds 12 To Obtain Cyclosubstituted Arylacetic Acids 13a and 13b. Compounds **12** (0.23 mol) were refluxed for 20 h with 10% KOH (700 mL). Acidification with 5 N HCl to pH 1 and filtration afforded the crude acetic acids which were taken up in 5% $NaHCO_3$ solution, and the insoluble material was filtered off. The basic acqueous solution was acidified, filtered, washed with H_2O until the pH was neutral and dried. Typically, yields were about 75% of the theoretical values. **13a**: mp 109–111 °C (cyclohexane). **13b**: mp 93–95 °C (cyclohexane). See Table 1 for the ^1H NMR spectroscopic data.

1-Oxoindan-5-acetic Acid (14). A mixture of CrO_3 (0.063 mol), AcOH (54 mL), and H_2O (9 mL) was added dropwise at room temperature to a solution of **13a** (0.017 mol) in AcOH (200 mL). After 3 h, i-PrOH (60 mL) was added and the solution evaporated to dryness. The residue was dissolved in Et_2O and the ethereal solution extracted with 5% $NaHCO_3$ solution. The aqueous solution was then acidified with dilute HCl to pH 1, extracted with CH_2Cl_2, dried over Na_2SO_4, and evaporated to dryness. The residue was dissolved in EtOAc, dicyclohexylamine (0.020 mol) was added, and the corresponding salt was allowed to crystallize on standing. The salt was recrystallized from EtOH/EtOAc 1:3 to yield 0.75 g of a compound which was treated with dilute HCl and extracted with EtOAc. The organic solution was washed with H_2O, dried, and evaporated to dryness. The residue was recrystallized from a mixture of EtOAc/cyclohexane (35% overall yield): mp 113–115 °C; IR (KBr) 3440, 2940, 1730, 1670, 1610, 1440 cm^{-1}. See Table 1 for the ^1H NMR spectroscopic data.

General Method for the Preparation of Bromo Derivatives 16a and 16b. Acetamido derivatives **15a** and **15b**[19] (0.65 mol) were refluxed for 2 h in 25% HBr, and the solution was cooled to 0 °C. A solution of $NaNO_2$ (0.80 mol) in H_2O (260 mL) was added dropwise at such a rate as to maintain

the temperature below 3 °C. The reaction mixture was therefore added dropwise, under mechanical stirring, to a cooled solution of CuBr (0.67 mol) in 48% HBr (500 mL). After the addition was completed, the reaction was stirred at 0 °C for 1 h and then allowed to reach room temperature. H_2O (1000 mL) was added and the product extracted with a mixture of Et_2O/EtOAc 8:2. After removal of the solvent, the residue was distilled *in vacuo*. Typically, the yield of the distilled material was 78% of the theoretical value. **16a**: bp 123–125 °C/1 mmHg; 80 MHz ^1H NMR ($CDCl_3$) δ 7.3–7.7 (m, 3H), 2.6–3.0 (m, 4H), 1.7–2.0 (m, 2H); IR (neat) 2960, 1685, 1585 cm^{-1}. **16b**: bp 126–129 °C/0.4 mmHg; 80 MHz ^1H NMR ($CDCl_3$) δ 7.2–7.7 (m, 3H), 2.7–3.1 (m, 4H), 1.6–2.0 (m, 4H).

General Procedure for the Preparation of Diesters 17a and 17b.[20] A solution of diethyl malonate (0.032 mol) in dry dioxane (25 mL) was added dropwise to a stirred suspension of 60–65% NaH (0.040 mol) in dry dioxane (100 mL) at 0 °C under a nitrogen athmosphere. CuBr (0.054 mol) was added and the suspension was stirred at room temperature for 1 h. Compounds **16a** and **16b** (0.022 mol) dissolved in dry dioxane (25 mL) were added dropwise, and the reaction mixture was refluxed under nitrogen for 6 h, cooled, filtered, diluted with EtOAc (250 mL), washed twice with 5% HCl, dried over Na_2SO_4, and evaporated to dryness. The oily material thus obtained was purified by silica gel column chromatography by elution with hexane/Et_2O 1:1 to afford compounds **17a** and **17b** in 19 and 25% yield, respectively. **17a**: IR (neat) 1755, 1740, 1650, 1590, 1275, 1035 cm^{-1}; 80 MHz ^1H NMR ($CDCl_3$) δ 8.0 (d, 1H), 7.4 (m, 2H), 4.7 (s, 1H), 4.2 (q, 4H), 2.9 (t, 2H), 2.6 (t, 2H), 2.2 (m, 2H), 1.3 (t, 6H).

General Procedure of Hydrolysis To Obtain the Cyclosubstituted Arylacetic Acids 18a and 18b. The purified diesters **17a,b** (0.004 mol) were dissolved in dioxane (6 mL) and added to 25% H_2SO_4 (40 mL). The solution was refluxed for 3 h, cooled, diluted with H_2O (20 mL), and exhaustively extracted with Et_2O. The ethereal solution was dried over Na_2SO_4 and evaporated to dryness to obtain a dark oil which was dissolved in a small amount of EtOAc and diluted with cyclohexane for crystallization. **18a**: mp 110–111 °C; IR (KBr) 3420, 3010, 2960, 1740, 1660, 1605, 1290, cm^{-1}. **18b**: yellow oil, IR (neat) 3130, 2940, 1735, 1715, 1675, 1605 cm^{-1}. See Table 1 for the ^1H NMR spectroscopic data.

4-(4-Acetylphenyl)butyric Acid (20).[21] Redistilled $SOCl_2$ (0.33 mol) was added dropwise at −10 °C to a solution of 4-phenylbutyric acid (0.30 mol) in EtOH (400 mL). The solution was refluxed for 4 h and evaporated to dryness to give ethyl 4-phenylbutyrate in quantitative yield. This intermediate (0.15 mol) was added dropwise to a mixture of MeCOCl (0.30 mol) and $AlCl_3$ (0.60 mol) in $CHCl_3$ (440 mL) at room temperature. After 15 min, the reaction was poured into a mixture of ice (700 g) and 37% HCl (10 mL); the separated organic layer was wahsed with 5% $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated to dryness. The residue was distilled at 130–136 °C/0.4 mmHg to give ethyl 4-(4-acetylphenyl)butyrate in 67% yield. This compound (0.10 mol) was refluxed for 8 h in 18% HCl (180 mL) and dioxane (25 mL). After evaporation of the solvent, the product was extracted with Et_2O which was dried over Na_2SO_4 and evaporated. The residue was crystallized from cyclohexane in 83% yield: mp 54–56 °C; 80 MHz ^1H NMR ($CDCl_3$) δ 10.7 (s, br, COOH), 7.9 (d, 2H), 7.3 (d, 2H), 2.8 (t, 2H), 2.6 (s, 3H), 1.8–2.5 (m, 4H).

4-[4-(Carboxymethyl)phenyl]butyric Acid (21). A mixture of compound **20** (0.08 mol), morpholine (0.28 mol), and S (0.28 mol) was refluxed for 3 h. The reaction mixture was worked up as described in the preparation of compounds **12**. The thiomorpholide intermediate was refluxed for 3 h in 10% KOH (70 mL) and the reaction worked up as described in the preparation of compounds **13a,b** to yield compound **21** in 35% overall yield after crystallization from EtOAc: mp 132–134 °C; 80 MHz ^1H NMR ($CDCl_3$) δ 11.3 (s, br, COOH), 7.1 (s, 4H), 3.5 (s, 2H), 1.6–2.8 (m, 6H).

8-Oxo-5,6,7,8-tetrahydro-2-naphthaleneacetic Acid (1-Tetralone-7-acetic Acid) (22). A suspension of **21** (0.014 mol) in xylene (8 mL) was added portionwise to a mixture of polyphosphoric acid (PPA) (9 g) and dry xylene (20 mL) maintained at 100 °C. The reaction was heated for 3 h and poured into ice (100 g); Et_2O (50 mL) was added and the separated organic layer was concentrated to half-volume and extracted with 5% $NaHCO_3$ solution. The basic acqueous solution was acidified with concentrated HCl and exhaustively extracted with Et_2O which was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from EtOAc/cyclohexane: mp 116–118 °C; IR (KBr) 3450, 3100, 2940, 1730, 1660, 1610, 1175 cm^{-1}. See Table 1 for the ^1H NMR spectroscopic data.

5-[(Methoxycarbonyl)methyl]-γ-oxo-2-thiophenebutyric Acid (24). To a mechanically stirred solution of methyl 2-thiopheneacetate (0.26 mol) (obtained from 2-thiopheneacetic acid, MeOH, and $SOCl_2$ as described for the preparation of compound **20**) and succinic anhydride (0.28 mol) in CH_2Cl_2 (400 mL) maintained at 0 °C was added portionwise $AlCl_3$ (0.56 mol) in 45 min. After the addition was completed, the reaction mixture was allowed to reach room temperature and poured into ice (500 g). The separated organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to dryness. This product was used without further purification in the subsequent reaction.

5-(Carboxymethyl)-γ-oxo-2-thiophenebutyric Acid (25). The crude compound **24** was dissolved in 20% NaOH (300 mL) and refluxed for 30 min. After concentration, the acqueous solution was acidified with 18% HCl up to pH 1 and cooled overnight. The precipitated product was collected by filtration, washed with cold H_2O, and recrystallized from a mixture of EtOAc/cyclohexane 7:3 (80% overall yield from compound **23**): IR (KBr) 3450, 3100, 2910, 1710, 1660, 1460, 1390, 1245 cm^{-1}; 80 MHz ^1H NMR (CD_3OD) δ 7.7 (d, 1H), 7.0 (d, 1H), 3.8 (s, 2H), 3.2 (t, 2H), 2.7 (t, 2H).

5-(Carboxymethyl)-2-thiophenebutyric Acid (26). Compound **25** (0.10 mol), 85% KOH (0.34 mol), and 85% NH_2NH_2 (50 g) were heated at 195 °C in diethylene glycol (150 mL) for 2 h. After cooling, concentrated HCl was carefully added up to pH 1 and the product extracted with Et_2O. The dried ethereal solution was evaporated and the residue crystallized twice from H_2O (60% of the theoretical value): 80 MHz ^1H NMR ($CDCl_3$ + CD_3OD) δ 6.7 (d, 1H), 6.6 (d, 1H), 3.7 (s, 2H), 2.8 (t, 2H), 2.2–2.5 (m, 2H), 1.8–2.1 (m, 2H).

4-Oxo-4,5,6,7-tetrahydrobenzo[*b*]thiophene-2-acetic Acid (27). A mixture of diacid **26** (0.044 mol), Ac_2O (100 mL), and PPA (4 g) was heated at 80 °C for 15 min. After cooling, the reaction was poured into ice (200 g) and exhaustively extracted with Et_2O. The ethereal solution was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was purified by silica gel flash column chromatography eluting with CH_2Cl_2/MeOH/HCOOH 100:2:0.25 to obtain **27** (55% of the theoretical value), which was recrystallized from EtOAc/cyclohexane: mp 130–132 °C; IR (KBr) 3450, 2940, 1730, 1625, 1230 cm^{-1}. See Table 1 for the ^1H NMR spectroscopic data.

Δ(log P) Determinations. Partition coefficients measured in *n*-octanol/water have been used primarily as an assessment of the lypophilicity of drugs; however, it is recognized that in some cases this does not provide a good prediction for brain penetration. More recently, a good correlation has been found between the brain penetration and the differences of partition coefficients in two different solvent systems [Δ(log *P*)].[25] Thus, in the present study, we measured this value in the manner described herein. Partition coefficients were measured using the conventional shake-flask technique,[36] at 25 °C. The concentrations of the compounds after partitioning were determined spectrophotometrically. The measurements were carried out at pH 7.6, where the compounds are extensively ionized and concentrations of the species sufficiently high to be measured directly. The buffer system used to control the pH of the aqueous phase had the following composition: KH_2PO_4, 0.85 nM, and Na_2HPO_4, 3.05 nM. Δ(log *P*) was determined as the difference between the partition coefficients (log *P*) measured in *n*-octanol/aqueous buffer (log P_{oct}) and cyclohexane/aqueous buffer (log P_{cyh}) systems [i.e., $\Delta(\log P) = \log P_{oct} - \log P_{cyh}$].

Computer Modeling Studies. Structures of compounds **34, 38, 39,** and **42** were constructed with standard bond lengths and angles of the fragment database in MacroModel software,[37] using a Silicon Graphics workstation (Personal Iris). All the compounds were assumed to be protonated species (at physiological pH the concentration of the free base

is calculated to be less than 5%) and minimized by the MacroModel/BatchMin V3.5 program[37] using the MM2 force field. To optimize the geometry of such molecular models, MonteCarlo/Energy Minimization conformational searches[38] were performed ($E_i - E_{min} \leq 40$ kJ/mol). For the compounds studied, several low-energy conformers obtained with the above procedure, agreed favorably with previously reported ^{1}H NMR findings[6] and the ^{1}H NMR spectroscopic data of **34** [i.e. chair conformation of the piperidine ring and axial geometry of the (dialkylamino)methyl substituent]. Such results validated the computational method described herein.

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